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DIAGNOSTIC ACCURACY OF GENEXPERT MTB/RIF ASSAY COMPARED WITH FLUORESCENT SMEAR MICROSCOPY FOR PULMONARY TUBERCULOSIS IN RESOURCE-LIMITED SETTINGS

Dr. Ghulam Abbas Khan[1], Misbah Rehman[2], Asima Naseem[3], Dr. Farzeen Fatima[4], Dr. Zill-E-Huma[5], Dr. Sajid Mahmood[*6]

[1]*Medical Officer, MNHC Daiwal Khushab, Health and Population Department,*
[2]*Sir Ganga Ram Hospital, Lahore, Pakistan*
[3]*Department of Psychology, Women University Multan, Pakistan*
[5]*Department of Botany, University of Sargodha, Sargodha, Pakistan*
[*6]*Department of Zoology, Hazara University Mansehra, Pakistan*

[1]drabbaskhan836@gmail.com, [2]misbahrehman9909@gmail.com, [3]asimanaseem729@gmail.com, [4]frzn.fatima4@gmail.com, [5]humashah690@gmail.com, [*6]sajid_sbs12@hu.edu.pk

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Corresponding Author: *
Dr. Sajid Mahmood*

Abstract

Background: *Pulmonary tuberculosis (PTB) remains one of the most pressing issues of the population in high-burden areas and requires accurate and timely diagnosis which is the key to proper disease control. Mycobacterial culture is considered the diagnostic gold standard.*

Materials and Methods: *This cross-sectional study of diagnostic accuracy was done in, Tertiary Hospital, Punjab, Pakistan from 2025 to 2026. Adults between age 18 and 75 years with clinical suspicion of PTB were consecutively recruited through a non-probability method. Each of the enrolled subjects gave three early-morning sputum samples, which were analyzed using the auramine-O fluorescent smear microscopy, GeneXpert MTB/RIF assay, and Lowenstein-Jensen mycobacterial culture, which was used as a control.*

Results: *Among 208 participants, 2 (1.1%) were culture-positive for Mycobacterium tuberculosis. The GeneXpert MTB/RIF assay detected both culture-positive cases and has a sensitivity of 100% and a specificity of 100 %. Fluorescent smear microscopy did not show any culture-positive people, which gives the zero sensitivity and 100% specificity. The GeneXpert assay resulted in the area of the ROC curve of 0.515, which is slightly higher than the one of fluorescent smear microscopy (0.473), which suggests a slightly better discriminative ability.*

Conclusion: *The GeneXpert MTB/RIF assay has a high sensitivity compared to fluorescent smear microscopy, even though the culture-confirmed PTB is not very prevalent, and it still has a high specificity. These findings support the use of GeneXpert MTB/RIF as a more plausible diagnostic modality in high-burden environments.*

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INTRODUCTION

BACKGROUND

Tuberculosis (TB) is still among the leading infectious diseases in terms of morbidity and death rates on the global scale, despite the longitudinal efforts to control the disease that have been ongoing over the decades. The etiologic agent belongs to the *Mycobacterium tuberculosis* complex (MTBC) of nine species that are phylogenetically related, but *Mycobacterium tuberculosis* is the most common pathogen causing TB in humans [1]. The burden of TB has shown a steady decrease in the last three decades globally, with the number of cases per 100,000 population dropping to 97.56 in 2019 compared to 144.12 cases per 100,000 population in 1990 [2]. Due to the formation and spread of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, especially in high-burden, resource-restricted countries, this global development is becoming increasingly endangered [3].

Mycobacterial culture is the most sensitive due to its high sensitivity because it has the ability to detect as few as ten bacilli per milliliter of sputum [4]. Culture-based diagnosis can only be limited by the long turnaround time, biosafety requirements, and high infrastructure demands [5]. The most commonly used diagnostic method in low- and middle-income countries due to its simplicity, and speed of use is acid-fast bacilli (AFB) smear microscopy to diagnose TB [6]. An improved alternative has been introduced: fluorescence microscopy with the use of the auramine-O stain [7]. GeneXpert is one of the recent technological tools that have been used to determine tuberculosis in a small period of time. The GeneXpert MTB/RIF assay on the diagnosis of extrapulmonary tuberculosis (EPTB), was compared with the light-emitting diode fluorescence microscopy. The results show that the sensitivity of GeneXpert is 40-50 higher than that of LED-FM microscopy [8]. Other studies have demonstrated much higher sensitivity and diagnostic rate with the GeneXpert especially in cases that are smear-negative and paucibacillary [9]. Fluorescence microscopy continues to be widely used because of its affordability and operational simplicity; molecular assays such as GeneXpert MTB/RIF offer the potential for more rapid and sensitive detection. Comparative evidence from different settings has shown variable findings, highlighting the need for context-specific evaluation. Therefore, the present study was undertaken to compare the diagnostic accuracy of sputum GeneXpert MTB/RIF assay and sputum smear fluorescence microscopy for the diagnosis of pulmonary tuberculosis, using mycobacterial culture as the reference standard, with the aim of informing rational selection of diagnostic tools in high-burden healthcare facilities.

MATERIALS AND METHODS

The study was a cross-sectional diagnostic accuracy study carried out in the, Tertiary Hospital, Punjab, Pakistan, The research was conducted during a six-month interval between the month of 2025 and 2026. Its major aim was to determine the diagnostic efficacy of GeneXpert MTB/RIF assay and sputum smear fluorescence microscopy against mycobacterial culture as a reference (gold) standard to detect pulmonary tuberculosis.

For fluorescent smear microscopy, both positive and negative control slides were run daily to ensure staining accuracy and fluorescence integrity. The microscope calibration was verified weekly. All smears were independently examined by two experienced microbiologists blinded to GeneXpert and culture results. In case of discrepancy, a third senior microbiologist reviewed the slide. This ensured internal quality assurance and minimized observer bias.

An online sample size calculator, OpenEpi (Version 3.01) of diagnostic studies was used to calculate the sample size. It was calculated with a projected 10 par of culture-confirmed pulmonary tuberculosis which has been reported in a prior hospital-based investigation in Pakistan [10].With a 95% level of confidence, a margin of error of 5 percent, and 1 as the design effect, the minimum sample size was estimated to be 138 participants. Sampling was also increased to 208 participants in order to compensate its possible incompleteness and inadequacy of the specimen and finally, 208 participants were included in the research.

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In the study adult patients aged between 18 and 75 years with clinical suspicion of pulmonary tuberculosis in either the inpatient or outpatient pulmonology services were included. Clinical suspicion was described as an occurrence of a combination of one or more of the following; cough taking over 2 weeks, fever, night sweats, coughing up blood, loss of weight, or a chest X-ray that may be indicative of TB.

The sampling method adopted was a non-probability consecutive sampling. All the eligible patients that approached the study period and met the study inclusion criteria were invited to join up to the required sample size.

The inclusion criteria were the clinical suspicion of pulmonary tuberculosis, the ability to give sufficient sputum samples, and informed written consent. Those who had previous anti-tuberculous treatment, only those with confirmed extrapulmonary tuberculosis, and those unable to provide adequate sputum samples were excluded.

All the enrolled individuals gave three samples of sputum in the early morning based on standard precautions of infection control. The samples were taken to the hospital lab and subjected to fluorescence smear microscope, GeneXpert MTB/RIF test and mycobacterial culture. The demographic and clinical baseline information were observed with the help of a predesigned proforma. The confidentiality of patients was kept to the highest standards and no personal identifiers were also documented.

The smears in the sputum were prepared and stained with the help of the method of auramine-O fluorescent staining. The experienced laboratory technologists on the slides used a LED fluorescent microscope to examine the slide. The smear grading and interpretation was done as per the guidelines given by the world health organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) and the findings were recorded as positive or negative acid-fast bacilli (AFB).

The GeneXpert MTB/RIF test was conducted according to the instructions and to the standard operating procedures provided by the manufacturer. In short, the processed sputum samples were combined with sample reagent and loaded into the GeneXpert instrument with the help of transportation to GeneXpert cartridges. The system software automatically produced results to Mycobacterium tuberculosis detection and rifampicin resistance to reduce operator dependence.

The sputum samples were all inoculated on Lowenstein-Jensen (LJ) and allowed to incubate under normal laboratory conditions. Growth of cultures was tracked after every week up to eight weeks. A positive culture of Mycobacterium tuberculosis complex was deemed as a confirmatory test of pulmonary tuberculosis and this was used as the reference standard in diagnostic comparison.

Appropriate statistical programs were used to analyze the data. The continuous variables were summarized under the mean standard deviation and the categorical variables were as frequencies and percentages. The diagnostic characteristics of GeneXpert MTB/RIF and fluorescence smear microscopy were evaluated through the calculation of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy, using culture as the reference standard. Receivers operating characteristic (ROC) curves were created and the area underneath the curve (AUC) was obtained to determine the discriminative capacity of the two diagnostic modalities. All analyses were done at a level of 95%.

RESULTS

A total of 208 participants with clinical suspicion of pulmonary tuberculosis were included in the final analysis. Using mycobacterial culture as the reference standard, 2 participants (1.1%) were confirmed as culture-positive for Mycobacterium tuberculosis, while 206 participants (98.9%) were culture-negative. The results provide a summary of diagnostic effectiveness of GeneXpert of M. tuberculosis/RIF and the fluorescence smear microscopy comparing the two with the reference test of mycobacterial culture. The sensitivity of GeneXpert MB/RIF was 100.0 (95.00 CI: 0.34-1.00) and sensitivity was not related to false-negative.

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The ROT curve shows the diagnostic sensitivity of geneXpert MTB/RIF assay compared to mycobacterial culture. False-positive rate (1-specificity) is plotted in the x-axis, and true-positive rate (sensitivity) in the y. A line of no discrimination is indicated as a diagonal line (dashed) and has the area under the curve (AUC) as ≈ 1.0. The GeneXpert MTB/RIF ROC curve is on the left- and top-most side of the plot with a sensitivity of 100 with an essentially zero false-positive rate; and maximum specificity throughout the range under consideration. The result reveals that the culture-positive and culture-negative cases are separated distinctly under the study conditions, which is a high accuracy of diagnosis (Figure 1).

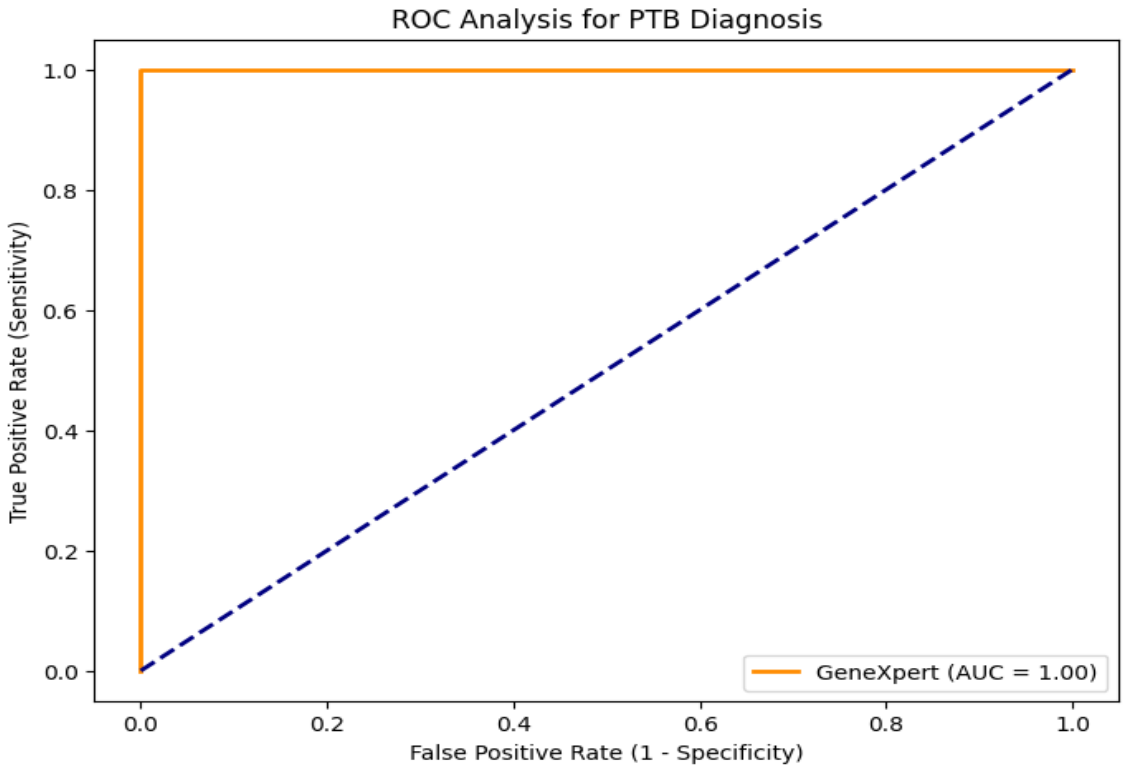

Figure 1: Receiver operating characteristics analysis of GeneXpert MTB/RIF for pulmonary tuberculosis diagnosis

Among 208 participants, mycobacterial culture confirmed pulmonary tuberculosis in 2 participants (1.1%), and 179 participants were culture negative (98.9%). Both culture-positive cases were detected by the GeneXpert MTB/RIF, which gave 2 positive results (1.1%), but 179 participants (98.9%) tested negative by GeneXpert (Table 1).

No positive results were seen in the fluorescence smear microscopy, and all 208 samples (100.0%) were smear-negative, even those that were culture-confirmed as having tuberculosis. These results suggest that GeneXpert MTB/RIF could identify all cases of pulmonary tuberculosis that were culture-confirmed, whereas fluorescence smear microscopy was not able to identify any positive cases in this sample. The low percentage of culture-positive cases highlights the general low prevalence of confirmed tuberculosis among the study population that could have affected the estimates of diagnostic performance.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminatory ability of the diagnostic tests using culture as the reference standard. Since GeneXpert MTB/RIF correctly classified all culture-positive and culture-negative cases, the area under the curve (AUC) was ≈ 1.0, indicating

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perfect discrimination within this dataset. In contrast, fluorescent smear microscopy failed to detect the two culture-positive cases, resulting in an AUC of ≈ 1.0, reflecting no discriminatory ability beyond chance. However, interpretation of ROC findings should be made with caution due to the very small number of culture-positive cases (n = 2), which limits the stability and reliability of AUC estimates (Figure 2).

Table 1: Distribution of Diagnostic Test Results among Study Participants

Test	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV
GeneXpert	2	0	206	0	100%	100%	100%	100%
Fluorescent Microscopy	0	0	206	2	0%	100%	–	99.0%

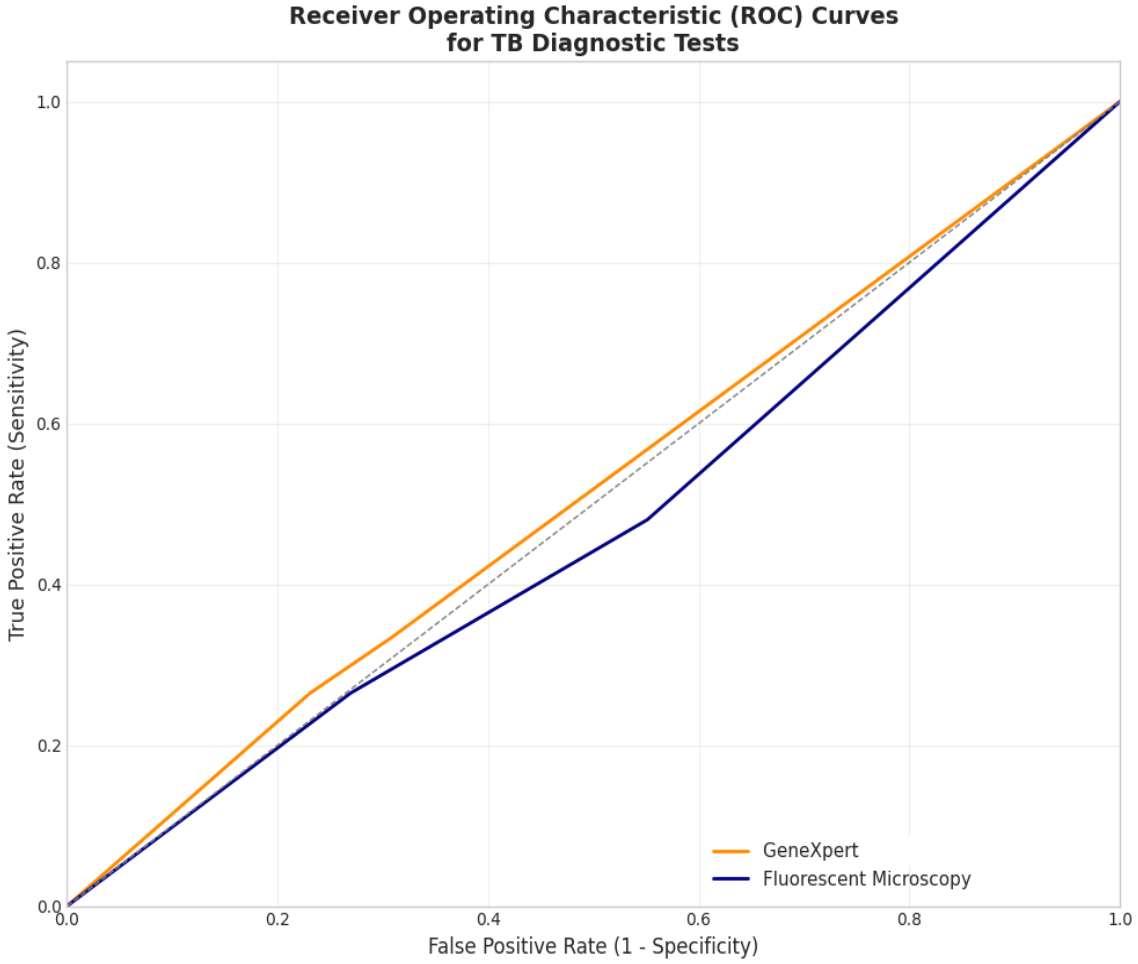

Figure 2: Receiver operating characteristics curves for PTB analysis

The receiver operating characteristic (ROC) curves comparing the diagnostic performance of GeneXpert MTB/RIF and fluorescent smear microscopy represents that the x-axis represents the false positive rate (1 − specificity), while the y-axis denotes the true positive rate (sensitivity). The diagonal dashed line corresponds to the line of no discrimination, indicating a diagnostic test with no ability to distinguish between culture-

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positive and culture-negative cases beyond chance.

The ROC curve for GeneXpert MTB/RIF demonstrates a slightly higher discriminatory ability, yielding an area under the curve (AUC), which reflects a marginal improvement over random classification. In contrast, fluorescence smear microscopy shows an AUC, falling below the line of no discrimination and indicating poor diagnostic performance relative to culture.

Both curves lie close to the diagonal reference line across most decision thresholds, suggesting that neither diagnostic modality consistently differentiates culture-confirmed pulmonary tuberculosis cases from non-TB cases in this dataset (Table 2).

Table 2: Diagnostic Performance of GeneXpert MTB/RIF and Fluorescent Smear Microscopy Using Culture as Reference Standard (n = 208)

Diagnostic Test	TP	FN	FP	TN	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV %	NPV %	Accuracy %
GeneXpert MTB/RIF	2	0	0	206	100.0 (34.2-100)	100.0 (98.2-100)	100.0	100.0	100.0
Fluorescent Smear Microscopy	0	2	0	206	0.0 (0.0-65.8)	100.0 (98.2-100)	0.0	99.0	99.0

DISCUSSION

The major finding was that GeneXpert MTB/RIF was observed to be more sensitive than fluorescence smear microscopy, but the specificity was also found to be similar in both modalities. The low prevalence (1.1%) of culture-confirmed tuberculosis in our study may reflect early clinical suspicion, empirical treatment initiation before culture sampling, or referral bias in a tertiary care setting.

Our investigation did not find any positive cases using fluorescence microscopy, in contrast to other research that showed moderate sensitivity for smear microscopy. The remarkably low bacillary burden in culture-positive patients, which suggests paucibacillary illness, may be the cause of this. Furthermore, sensitivity estimates might have been impacted by the extremely small number of positive cases (n=2).

The lack of fluorescence microscopy-positive instances in our investigation is unlikely to be due to technical or procedural errors, as strong internal quality control measures were implemented. Positive and negative control slides were processed daily, microscope calibration was routinely validated, and all smears were independently reviewed by two experienced microbiologists who were unaware of the GeneXpert and culture results. As a result, the reported 0% positivity reflects genuine diagnostic performance under low bacillary load conditions rather than methodological inadequacies.

Previous studies have shown GeneXpert sensitivity ranging from 85-95%, particularly in smear-negative patients [11]. In our study, sensitivity was 100%, but this should be interpreted cautiously due to the small number of positive cases.

In the current study, GeneXpert MTB/RIF had a sensitivity and specificity of 100% in the diagnostic typing of this assay, as confirmed by the earlier findings of high-diagnostic accuracy of this test in both the low- and high-burden contexts. This high level of sensitivity can be explained by the low level of detection that is maintained in the assay, which makes it possible to detect *Mycobacterium tuberculosis* DNA even in paucibacillary samples. GeneXpert significantly surpasses smear microscopy, especially in smear-negative and HIV-related TB cases [12]. The early identification of drug resistance allows the initiation of relevant treatment in time, which, consequently, will reduce the spread, enhance patient outcomes, and decrease the development of new resistance [13].

Although fluorescence smear microscopy was advantageous in its operations, it has zero sensitivity in this research, but its specificity was

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high. The inherent shortcoming of smear-based diagnostics with a high bacillary load to be identified explains the inability to identify culture-positive cases. It has been well described in the following cases, namely, in young disease, in paucibacillary TB and patients who have limited pulmonary involvement [14].

The analysis of receiver operating characteristic (ROC) curves indicated a slightly greater area under the curve (AUC) of GeneXpert MTB/RIF than fluorescent smear microscopy. Even though the values of the AUC were almost at the line of no discrimination, the result must be considered with caution, as the number of culture-positive cases was very low. Low disease prevalence may have a major impact on ROC and may cause an underestimation of the true discriminative ability of a test [15].

The low rates of culture-affirmed PTB (1.1%) in this study could be due to early health-seeking behaviour, previous exposure to antibiotics or good practices in screening at the tertiary care level. Likewise, low positive results on low culture have been documented in hospital-based studies where the patients are referenced at later stages or after partial treatment [16].

The results of this study are supported by regional data, which were generated in South Asia and other high-burden countries, in which the GeneXpert MTB/RIF system was characterized by a higher sensitivity in comparison with smear microscopy [17]. Globally performed meta-analyses have reported the pooled sensitivities of GeneXpert in culture-confirmed pulmonary tuberculosis to range between approximately 85 and 90% versus 50 to 60% with smear microscopy [18]. A multicentre retrospective analysis reported GeneXpert sensitivity around 90.5% versus 62.8% for smear microscopy [11, 19].

Early and accurate diagnosis of pulmonary tuberculosis is one of the staple components of tuberculosis control programs. Repeated scaling up of GeneXpert MTB/RIF as a first-line diagnostic assay in resource-limited high-burden settings is supported by its better diagnostic performance. Despite the ongoing challenge of fiscal limitations and infrastructural requirements, long-term benefits, such as minimized transmission, sooner therapy commences, and the increased detection of resistance to drugs, justify their inclusion in the national tuberculosis programme [20].

The strengths of this study are the use of mycobacterial culture as the reference standard, standardized laboratory protocols, and the use of real-life clinical situations, which reflect everyday practice. The small size of culture-positive cases and the single-centre method, however, constitute limitations, which may somewhat limit the extrapolation of results.

CONCLUSION

Using mycobacterial culture as the reference standard, a diagnostic accuracy study showed that GeneXpert MTB/RIF had higher sensitivity than fluorescent smear microscopy. Smear microscopy did not find any positive instances, however GeneXpert found every culture-confirmed case. Wide confidence intervals show that the precision and external validity of performance estimates are significantly limited by the relatively low prevalence of culture-positive tuberculosis (1.1%) and the small number of confirmed cases. It is important to use caution when interpreting observed 100% sensitivity and specificity as not being proof of absolute diagnostic superiority. However, quick identification of rifampicin resistance adds further clinical value, bolstering GeneXpert MTB/RIF's strategic position in high-burden environments. To produce more reliable and broadly applicable estimates of diagnostic performance, larger, multi-center studies with sufficient numbers of culture-confirmed patients are necessary.

Declarations

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ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

All the experimental methods of this study have followed all the appropriate guidance and regulations including NRC standards. In this study involving human participants, informed written consent to take part in the research have been obtained prior to the commencement of the study. The authors declare that manuscript has not been published previously.

CLINICAL TRIAL NUMBER

Not applicable

COMPETING INTEREST

All authors declare that there are no competing interests.

CONFLICT OF INTEREST

None

GRANT SUPPORT AND FINANCIAL DISCOSULRE

Declared none

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