Assessment of Molecular and Traditional Diagnostic Methods for Tuberculosis in Tribal Belt of Western India

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ABSTRACT:
Tuberculosis (TB) remains a significant public health challenge in the tribal regions of Western India owing to limited healthcare infrastructure and resource constraints. This study evaluated the effectiveness of TB diagnostic techniques, including Ziehl-Neelsen (ZN) staining, the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), Truenat, culture testing, Xpert Ultra, and the Tuberculin Skin Test (TST). ZN staining showed limited sensitivity with a positivity rate of 1.63%. CBNAAT and Truenat demonstrated higher sensitivities, detecting 8.74% and 8.34% of the cases, respectively, making them more reliable for early detection. Culture testing, although the gold standard, had a lower positivity rate of 6.66% owing to its dependence on viable bacilli and longer processing times. Xpert Ultra detected multidrug-resistant TB (MDR-TB) and identified resistance to isoniazid (INH), fluoroquinolones (FLQ), and amikacin (AMK) in a subset of cases, highlighting the need for advanced molecular diagnostics to guide treatment. The TST showed a high prevalence of latent TB (58.69%), indicating widespread exposure in the tribal population. Demographic analysis revealed a higher prevalence of TB in males and older individuals. These findings emphasize the need for advanced molecular diagnostics, such as CBNAAT, Truenat, and Xpert Ultra, to improve TB detection and management in resource-limited settings. Expanding access to these tools is crucial for effective TB control and for achieving global elimination goals.

Introduction

Tuberculosis (TB) is one of the most serious infectious diseases globally, causing major health issues, particularly in countries such as India. Despite improvements in diagnosis and treatment, India reported approximately 2.82 million TB cases by 2022, representing 27% of the global TB burden (Bhadauria et al., 2023). These numbers highlight the severity of the epidemic, especially in vulnerable groups, such as those living in the tribal areas of Western India, where healthcare access is often limited. The Indian government, through initiatives such as the National Tuberculosis Elimination Program (NTEP), has set ambitious goals to eliminate TB by 2025 in line with the World Health Organization's (WHO) target to end TB globally by 2030 (Razak et al., 2022). However, achieving these goals is difficult due to socioeconomic

challenges, healthcare inequalities, and the ongoing emergence of drug-resistant strains (Grace G & P, 2024).

Tuberculosis is caused by *Mycobacterium tuberculosis* (M.tb), an airborne bacterium that mainly affects the lungs but can also infect other organs, leading to serious illness and death (Nickerson, 2000). TB spreads through tiny droplets released into the air when an infected person coughs or sneezes, making it highly contagious, especially for people with prolonged exposure. Despite the availability of diagnostic tools, early detection and treatment of TB in areas with limited resources are hindered by poor infrastructure and reliance on older diagnostic methods.

Diagnostic methods for TB have come a long way, from traditional Ziehl-Neelsen staining to more advanced molecular techniques (Balaji et al., 2024). However, in the tribal regions of Western India, where access to modern healthcare facilities is limited, traditional methods such as Acid-Fast Bacilli (AFB) smear microscopy are still commonly used. Although affordable, these methods have limitations in accuracy, which makes timely detection and treatment challenging. Recently, molecular diagnostic tools such as the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), Truenat, and UltraNat have been recognized for their ability to provide quick and reliable results (Karigoudar et al., 2021). Introducing these technologies in remote healthcare centers is essential for closing the gap between diagnosis and treatment, ultimately helping reduce TB transmission in underserved areas.

Another major challenge in controlling TB in these regions is the rise of drug-resistant TB, including multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) (Seung et al., 2015). MDR-TB, which is resistant to isoniazid and rifampicin, makes treatment more difficult, making timely diagnosis even more important (Lange et al., 2019). Tribal areas, with their unique socio-cultural factors, face additional challenges, such as low awareness of TB symptoms, social stigma, and difficulties in accessing healthcare. These factors lead to delayed diagnosis, incomplete treatment, and ongoing spread of TB in the community.

This study aimed to evaluate and compare different diagnostic methods, including Ziehl-Neelsen staining, CBNAAT, Truenat, and UltraNat, for diagnosing TB in the tribal regions of Western India. By identifying the most effective diagnostic approach for these underserved areas, this study hopes to provide important insights for improving TB control strategies and supporting the national goal of eliminating TB. Closing the gaps in diagnostic ability, healthcare services, and community awareness will be crucial for reducing the burden of TB, especially in marginalized populations where the disease is most persistent.

Materials and Methods

Study Setting

This study was conducted in the tribal regions of Western India, an area characterized by limited healthcare infrastructure and significant challenges in accessing modern diagnostic facilities. This study aimed to evaluate various diagnostic methods for tuberculosis (TB), focusing on the detection of *Mycobacterium tuberculosis* in clinical specimens from patients in this underserved region. The diagnostic methods included traditional Ziehl-Neelsen (ZN) staining, the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), Truenat, and the Tuberculin Skin Test (TST).

Study Population

This study involved patients presenting with clinical symptoms suggestive of pulmonary tuberculosis, including chronic cough, hemoptysis, chest pain, and fever. Participants were recruited from various community health centers across the tribal belt. The inclusion criteria were Individuals suspected of having TB, aged > 18 years, and willing to provide written informed consent were included. Patients on anti-tuberculosis treatment and those unable to provide a clinical specimen were excluded.

Sample Collection

Clinical specimens, primarily sputum, were collected from the participants under aseptic conditions. In cases where sputum was not available, other biological samples, such as cerebrospinal fluid or tissue biopsies, were collected as per clinical indications. Samples were collected following biosafety protocols to prevent the spread of infection and contamination.

Ziehl-Neelsen Staining

Ziehl-Neelsen staining was used as the initial screening method for the detection of acid-fast bacilli (AFB). Sputum smears were prepared by spreading the sample onto a clean glass slide, which was then air-dried and heat-fixed. The smear was flooded with carbol fuchsin, gently heated, and stained for 5-10 minutes. After cooling, the smear was decolorized with acid–acid acid-alcohol for one minute and counterstained with methylene blue. The stained slides were examined under an oil immersion microscope at 1000x magnification. Acid-fast bacilli appeared as bright red rods on a blue or colorless background.

Cartridge-Based Nucleic Acid Amplification Test (CBNAAT)

The CBNAAT (GeneXpert MTB/RIF) test was used to detect *Mycobacterium tuberculosis* complex DNA and rifampicin resistance. This method involves the use of automated cartridges, which purify and concentrate bacilli from sputum samples, followed by sonication to isolate genomic material. Real-time PCR was performed to detect the TB-specific DNA and mutations associated with rifampicin resistance. Results were obtained within 90 min, enabling rapid identification of both TB and MDR-TB cases.

Truenat Testing

Truenat, a chip-based Real-Time Polymerase Chain Reaction (PCR) test, has also been used to detect *Mycobacterium tuberculosis*. This portable test allows molecular diagnostics in a point-of-care setting, making it particularly suitable for remote tribal areas. A small volume (6 μL) of purified DNA was used

and the results were available within 30 min. The test was performed using the Truelab Real-Time Micro PCR Analyzer, which amplified the target DNA sequences and provided qualitative results indicating the presence or absence of *M. tuberculosis*.

Tuberculin Skin Test (TST)

The Tuberculin Skin Test, also known as the Mantoux test, is used to assess latent TB infections. A tuberculin-purified protein derivative (PPD) was injected intradermally on the forearm, and induration was measured after 48–72 h. The presence and size of induration were used to classify the results as positive, negative, or doubtful. This test was primarily used to determine previous exposure to *M. tuberculosis*.

Quality Control and Biosafety

Quality control measures were implemented throughout the study to ensure reliability of the results. Positive and negative control slides were included in each Ziehl-Neelsen staining batch. The CBNAAT and Truenat assays were performed according to the manufacturer's instructions, with internal quality checks. Biosafety protocols were strictly followed, including the use of personal protective equipment (PPE), decontamination of work surfaces, and proper disposal of biological waste to prevent cross-contamination and ensure safety.

Data Analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each diagnostic method were calculated using culture-based methods as gold standard. Statistical analysis was performed to compare the diagnostic accuracy of Ziehl-Neelsen staining, CBNAAT, Truenat, and TST. The results were analyzed using SPSS software, and a p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

Ethical approval for the study was obtained from the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to sample collection. The study was conducted in compliance with ethical standards for research involving human subjects, ensuring confidentiality and the right to withdraw at any point during the study.

Results

Overview of Diagnostic Methods and Results

This study evaluated several diagnostic approaches for tuberculosis (TB) in a population from the tribal belt of Western India. The methods included Ziehl-Neelsen (ZN) staining, the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), Truenat, culture testing, Xpert Ultra, and the Tuberculin Skin Test (TST). The results varied across these methods, demonstrating different detection rates and highlighting key characteristics of TB detection in this population.

Ziehl-Neelsen (ZN) Staining

Of the total 1226 samples collected from patients suspected of TB, 20 (1.63%) tested positive by Ziehl-

Neelsen staining. Of these, sputum specimens showed a higher positivity rate than non-sputum specimens did. Specifically, for sputum samples collected in December 2023, January, and February 2024, positivity rates ranged from 1.24% to 2.20%. Among the non-sputum samples, only one cerebrospinal fluid (CSF) sample tested positive, resulting in a positivity rate of 0.48%. Although ZN staining is a useful screening tool, the overall positivity rate remains relatively low, underscoring its limited sensitivity.

TABLE 4: -Below given table represents the month wise segregation of collected samples.

ZN Staining (Sputum Samples)				
MONTH	TOTAL SAMPLES	TOTAL POSITIVE	TOTAL NEGATIVE	PERCENTAGE(%)
DECEMBER 2023	561	7	554	1.24%
JANUARY 2024	318	7	311	2.20%
FEBRUARY 2024	347	5	342	1.44%
ZN Staining (Non-Sputum Samples)				
JANUARY & FEBRUARY 2024	207	1(CSF)	206	0.48%
TOTAL	1226	20	1206	1.63%

Cartridge-Based Nucleic Acid Amplification Test (CBNAAT)

CBNAAT was performed on 1029 samples, and 90 samples (8.74%) were confirmed to be TB-positive. This positivity rate was significantly higher than that of ZN staining, suggesting that CBNAAT has a better sensitivity for detecting TB, particularly in tribal populations. The sex distribution showed that 27.8% of the positive cases were female and 72.2% were male. The age distribution indicated that TB cases were more prevalent among older individuals.

Truenat

Truenat testing was conducted on 1018 samples, with 85 samples (8.34%) testing positive. Similar to CBNAAT, Truenat staining demonstrated a higher positivity rate than ZN staining did. This method is particularly advantageous because of its portability and suitability for point-of-care testing in remote

areas. The gender-based analysis showed that males had a higher proportion of positive results than females, indicating the need for targeted interventions for this demographic.

Culture Testing

Culture testing was performed using Lowenstein-Jensen (LJ) slants for a subset of 150 samples, with 10 samples (6.66%) showing growth of Mycobacterium tuberculosis. The positivity rate was lower than that of CBNAAT and Truenat staining but higher than that of ZN staining. Although this method is considered the gold standard, it requires longer time to obtain results, limiting its applicability in urgent cases. Among the ten positive samples, 60% were male and 40% were female.

Xpert Ultra

Xpert Ultra, the next-generation version of CBNAAT, was used to assess multidrug-resistant TB (MDR-TB) in selected cases. Of the 50 samples tested, all tested positive for TB. Drug resistance to three main antibiotics was detected in a subset of these samples: isoniazid (INH), fluoroquinolones (FLQ), and amikacin (AMK). Among the positive samples, resistance to INH was observed in four samples, resistance to FLQ in three, and resistance to AMK in two. These results underscore the importance of using advanced molecular diagnostics to promptly identify drug resistance patterns and to effectively manage MDR-TB.

TABLE 5: -The table below represents 13 positive results of samples tested by Xpert Ultra and also indicates which sample exhibits resistance for which drug.

SAMPLE ID NO.	DATE	ASSAY NAME	TEST RESULT	INH RESISTANCE	FLQ RESISTANCE	AMK RESISTANCE	KAN RESISTANCE	CAP RESISTANCE	ETH RESISTANCE
1	13/5/2023	XPERT MTB-XRD	MTB DETECTED	DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
2	6/6/2023	XPERT MTB-XRD	MTB DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
3	13/6/2023	XPERT MTB-XRD	MTB DETECTED	NOT DETECTED	DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
4	13/6/2024	XPERT MTB-XRD	MTB DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
5	15/6/2023	XPERT MTB-XRD	MTB DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
6	16/6/2023	XPERT MTB-XRD	MTB DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
7	31/8/2023	XPERT MTB-XRD	MTB DETECTED	DETECTED	DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
8	8/9/2023	XPERT MTB-XRD	ERROR	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
9	8/9/2023	XPERT MTB-XRD	MTB DETECTED	DETECTED	DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	DETECTED
10	14/10/2023	XPERT MTB-XRD	MTB DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
11	16/12/2023	XPERT MTB-XRD	MTB DETECTED	NOT DETECTED	DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
12	16/12/2023	XPERT MTB-XRD	MTB DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED
13	16/12/2023	XPERT MTB-XRD	MTB DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED	NOT DETECTED

Tuberculin Skin Test (TST)

A total of 92 patients underwent the Tuberculin Skin Test (TST), and 54 (58.69%) tested positive, indicating latent TB infection. Sex analysis revealed a relatively balanced distribution of positive cases between males and females. The TST results indicated a high prevalence of latent TB, suggesting that TB exposure is widespread in the tribal population.

Comparative Analysis of Diagnostic Methods

Comparative analysis of ZN staining, CBNAAT, Truenat, and culture testing demonstrated significant differences in the sensitivity and positivity rates. ZN staining showed the lowest positivity rate (1.63%), whereas CBNAAT showed the highest detection rate (8.74%). Truenat, with a positivity rate of 8.34%, closely followed CBNAAT in terms of effectiveness. Culture testing, which has a lower positivity rate (6.66%) than that of molecular methods, remains a crucial tool for confirming TB. Xpert Ultra has provided valuable insights into drug resistance, which is particularly important for

managing MDR-TB cases.

Demographic Insights

Across all diagnostic methods, TB was more commonly detected among male patients compared to female patients. Age distribution analysis suggested that TB prevalence was higher in older age groups, highlighting the need for focused interventions in these individuals. The detection of MDR-TB by Xpert Ultra highlights the ongoing challenge of drug resistance in TB management.

Discussion

This study provides an important comparison of different tuberculosis (TB) diagnostic techniques, focusing on their effectiveness in the tribal regions of Western India, a setting characterized by limited healthcare infrastructure. By comparing Ziehl-Neelsen (ZN) staining, the Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), Truenat, culture testing, Xpert Ultra, and the Tuberculin Skin Test (TST), this study highlights both the strengths and limitations of these diagnostic methods in resource-constrained environments.

Ziehl-Neelsen (ZN) staining showed the lowest positivity rate (1.63%), reflecting its limited sensitivity. Although ZN staining remains a widely used method owing to its affordability and ease of use, the data emphasize its inadequacy for early and accurate TB detection, especially in cases where the bacterial load is low. In this context, the higher positivity rates observed with molecular methods such as CBNAAT and Truenat make them more favorable options for reliable TB diagnosis.

CBNAAT and Truenat demonstrated significantly better diagnostic performances than ZN staining, with positivity rates of 8.74% and 8.34%, respectively. These findings indicate that molecular diagnostic tools are more effective for detecting TB, particularly in patients with lower bacillary loads. The higher sensitivity of CBNAAT, which detects more positive cases than ZN staining, underscores its value for accurately identifying TB cases and rifampicin resistance in a timely manner. Truenat, with its portability and rapid diagnostic capabilities, is also particularly useful in field conditions, making it a viable option for remote and underserved areas. The close similarity in detection rates between CBNAAT and Truenat supports the notion that both can be effectively used to complement traditional diagnostics, especially in peripheral settings where advanced laboratory facilities are lacking.

Similar results have also been reported in other studies. Ziehl-Neelsen (ZN) staining generally showed lower positivity rates than other methods across multiple studies. The conventional ZN method detected acid-fast bacilli (AFB) in only 4.78% of specimens, whereas the GeneXpert assay showed positivity in 10.42% of specimens in one study (Hamal et al., 2022). Another study found that ZN staining detected AFB in only 12.5% of cases, whereas the modified bleach method detected AFB in 60.7% (Prayaga & Chandrasekhar, 2012). Similarly, routine ZN staining detected AFB in only 31.6% of samples, compared to 63.5% using the bleach method in another study (Rathi et al., 2015). Interestingly, modifications to the ZN method can affect its sensitivity. The use of 0.3% carbol

fuchsin in the ZN method resulted in significantly lower sensitivity (72%) than the standard ZN method (84%) (Selvakumar et al., 2002). Additionally, using a weaker acid concentration for decolorization can lead to false positives by making other organisms appear acid fast (Olson et al., 1998).

Culture testing, which is considered the gold standard for TB diagnosis, showed a lower positivity rate of 6.66% than CBNAAT and Truenat. Chandrappa et al. (2018) reported that, among 74 CBNAAT-positive cases, 71 (95.94%) were positive by AFB culture, suggesting that CBNAAT detected a few additional cases. Sethumadhavan et al. (2021) found that CBNAAT was positive in 58 specimens, whereas culture was positive in 48. CBNAAT detected an additional 10 samples compared to the culture. This lower rate can be attributed to the requirement of viable bacilli for positive culture growth and the prolonged incubation period, which limit its utility in time-sensitive cases. However, culture remains essential for confirming TB and for assessing antimicrobial susceptibility, thereby providing critical information for the treatment of complex cases.

The Xpert MTB/RIF assay, including its Ultra version, has shown high sensitivity and specificity for detecting Mycobacterium tuberculosis (MTB) and rifampicin (RIF) resistance, which are key indicators of multidrug-resistant tuberculosis (MDR-TB) (Li et al., 2023; Lorent et al., 2015; Ullah et al., 2017). Studies have demonstrated that Xpert can rapidly diagnose MDR-TB, with results available in as little as two days compared to traditional culture methods (Lorent et al., 2015).

Xpert Ultra was used to evaluate multidrug-resistant TB (MDR-TB). Of the 50 samples tested, all were positive for TB, with a subset showing resistance to key antibiotics: isoniazid (INH), fluoroquinolones (FLQ), and amikacin (AMK). Specifically, resistance to INH, FLQ, and AMK was observed in four, three, and two samples, respectively. The identification of these resistant strains emphasizes the growing concerns regarding drug resistance in TB management. These findings also illustrate the importance of molecular diagnostics, such as Xpert Ultra, in promptly detecting drug resistance, which is crucial for guiding effective treatment regimens, especially in regions where MDR-TB prevalence is increasing. Early detection of drug-resistant strains helps in timely intervention, prevents the spread of resistant TB, and improves treatment outcomes.

The Tuberculin Skin Test (TST) showed a high positivity rate of 58.69%, indicating a significant prevalence of latent TB infections in the tribal population. This high rate suggests widespread exposure to Mycobacterium tuberculosis, which, in combination with socio-economic factors and limited access to healthcare, poses a considerable challenge to TB control in these regions. TST serves as a useful tool for identifying latent TB, especially in asymptomatic individuals, allowing for preventive interventions that could reduce the risk of active TB development.

Demographic insights from the study showed a higher TB prevalence in males across all diagnostic methods, with older individuals being more commonly affected. These findings align with the existing literature suggesting that men may have higher exposure to TB risk factors, such as occupational

exposure or lifestyle-related vulnerabilities, than women. The higher prevalence in older age groups also emphasizes the need for targeted interventions to protect vulnerable populations, particularly in settings with limited health care resources.

Comparative analysis of the various diagnostic methods clearly indicates that while traditional methods such as ZN staining and culture testing remain relevant, especially for confirmatory purposes, molecular diagnostics such as CBNAAT, Truenat, and Xpert Ultra are indispensable for improving TB detection rates and effectively managing MDR-TB. This study also underscores the importance of integrating multiple diagnostic tools to achieve a comprehensive understanding of TB prevalence, particularly in high-burden and underserved populations.

Conclusion

This study highlights the need for greater access to advanced molecular diagnostics in the tribal regions of Western India. The implementation of CBNAAT, Truenat, and Xpert Ultra in local healthcare facilities could significantly enhance the early detection and treatment of TB, ultimately reducing its transmission and improving patient outcomes. Addressing the gaps in diagnostic capacity, healthcare access, and awareness is crucial for achieving the national and global goals of TB elimination. Additionally, the growing challenge of drug-resistant TB demands the continuous surveillance and integration of molecular diagnostic techniques to ensure timely detection and effective treatment.

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