Section: Microbiology

Original Research Article

ENHANCING MULTIDRUG RESISTANT TUBERCULOSIS DETECTION: DIAGNOSTIC VALUE OF COMBINED SOLID CULTURE AND CBNAAT IN DRUG RESISTANT FOLLOWUP CASES

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Abstract

Background: Tuberculosis (TB) remains a major public health challenge, particularly in smear-negative, extrapulmonary, and drug-resistant cases where delayed diagnosis contributes to ongoing transmission and poor outcomes. Conventional solid culture, though cost-effective and widely available, suffers from prolonged turnaround time due to slow growth and additional biochemical confirmation steps. The integration of Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) with solid culture may significantly enhance diagnostic efficiency. **Aim:** To evaluate the diagnostic value of combining solid culture with CBNAAT in improving detection efficiency and reducing turnaround time in drug-resistant tuberculosis follow-up cases. **Materials and Methods:** This prospective laboratory-based study included 100 follow-up samples from patients on second-line anti-tubercular therapy for drug-resistant TB. Samples were processed using Lowenstein–Jensen (LJ) solid culture. Positive cultures were identified using both conventional biochemical methods and CBNAAT. Turnaround times were compared using Student's t-test. **Results:** Of the 100 follow-up samples, 9% showed culture positivity. Smear microscopy demonstrated a sensitivity of 55.5% and specificity of 100% when compared to culture. The mean turnaround time for identification using biochemical methods was 64 days, while CBNAAT reduced this to 34 days, achieving a statistically significant reduction of approximately 28-30 days ($p < 0.00001$). **Conclusion:** The combined use of solid culture and CBNAAT significantly improves diagnostic efficiency by reducing turnaround time without compromising accuracy, making it a valuable strategy for drug-resistant TB follow-up cases, particularly in resource-limited settings.

INTRODUCTION

Tuberculosis (TB) continues to be one of the leading causes of morbidity and mortality due to infectious diseases worldwide. According to the World Health Organization (WHO), TB remains a major public health concern, particularly in high-burden countries such as India, which accounts for a significant proportion of global TB and multidrug-resistant TB (MDR-TB) cases.[1] Despite substantial progress achieved under the Revised National Tuberculosis Control Programme (RNTCP), a considerable number of TB cases remain undiagnosed or are diagnosed late, especially among smear-negative and extrapulmonary cases. This diagnostic delay contributes to ongoing transmission, increased disease severity, and the emergence of drug resistance.[2]

The diagnosis of TB traditionally relies on sputum smear microscopy and culture. While smear microscopy is rapid and inexpensive, its sensitivity is limited, particularly in smear-negative, extrapulmonary, pediatric, and HIV-associated TB cases.[3] Culture remains the gold standard for TB diagnosis and drug susceptibility testing, as it allows for the detection of viable Mycobacterium tuberculosis bacilli and assessment of treatment response. Solid culture using Lowenstein–Jensen (LJ) medium is widely used in resource-limited settings due to its lower cost and biosafety requirements compared to liquid culture systems. However, the major limitation of solid culture is the prolonged turnaround time, often extending to several weeks, further delayed by the need for biochemical confirmation of the isolate.[4]

The introduction of molecular diagnostic techniques, particularly Cartridge-Based Nucleic Acid Amplification Test (CBNAAT), also known as Xpert MTB/RIF, has revolutionized TB diagnosis. CBNAAT enables rapid detection of Mycobacterium tuberculosis complex and simultaneous identification of rifampicin resistance within a few hours. WHO and RNTCP recommend CBNAAT as an initial diagnostic test for presumptive drug-resistant TB, HIV-associated TB, and extrapulmonary TB. However, CBNAAT cannot differentiate between live and dead bacilli and therefore is not recommended directly for follow-up samples, as it may yield false-positive results after treatment initiation.[5]

In follow-up of drug-resistant TB patients, culture remains essential to assess treatment response and detect treatment failure. Although liquid culture systems offer faster results, they require sophisticated infrastructure, higher biosafety levels, and increased operational costs, limiting their widespread use. In contrast, solid culture is more feasible in peripheral laboratories but suffers from delayed identification. Integrating CBNAAT for rapid identification of growth obtained on solid culture can bridge this gap by significantly reducing the time required for confirmation and resistance detection.[6]

The present study was undertaken to evaluate the diagnostic value of combining solid culture with CBNAAT for early identification of Mycobacterium tuberculosis in drug-resistant TB follow-up cases, with a focus on reducing turnaround time while maintaining diagnostic accuracy.[7]

Aims and Objectives

Aim

To enhance the efficiency of solid culture by reducing turnaround time through the use of CBNAAT for identification of Mycobacterium tuberculosis in follow-up cases of drug-resistant TB.

Objectives

1. To identify Mycobacterium tuberculosis from positive solid culture isolates using CBNAAT immediately after growth detection.
2. To identify acid-fast bacilli (AFB) isolates using conventional biochemical tests including niacin test, nitrate reduction test, and para-nitrobenzoic acid (PNB) susceptibility test.
3. To compare the turnaround time between CBNAAT-based identification and conventional biochemical methods.

MATERIALS AND METHODS

Study Design

Prospective laboratory-based observational study.

Study Setting

The study was conducted in an RNTCP-certified laboratory for solid culture in the Department of Microbiology, K.A.P.V. Government Medical College, Tiruchirappalli, India.

Study Period

January 2019 to December 2019.

Sample Size

A total of 100 follow-up samples from patients receiving second-line treatment for drug-resistant tuberculosis.

Inclusion Criteria

- Follow-up samples from patients diagnosed with MDR-TB and receiving second-line anti-tubercular therapy.

Ethical Considerations

Ethical clearance was obtained from the Institutional Ethics Committee of K.A.P.V. Government Medical College, Tiruchirappalli. Informed consent was obtained from all participants prior to sample collection.

Specimen Processing and Biosafety

All specimens were processed in a certified Class II Type A1 biosafety cabinet. Standard biosafety precautions, including use of N95 masks and personal protective equipment, were strictly followed.

Culture Method

Processed specimens were inoculated onto Lowenstein–Jensen (LJ) medium and incubated at 37°C. Cultures were examined daily for the first week and weekly thereafter for up to eight weeks.

Identification of Isolates

Positive cultures were identified using:

- Conventional biochemical tests (niacin test, nitrate reduction test, and PNB susceptibility)
- CBNAAT performed directly on culture growth

Statistical Analysis

Data were analyzed using Epi Info version 7. Turnaround times were compared using Student's t-test, with $p < 0.05$ considered statistically significant.

RESULTS

Table 1: Age-wise Distribution of Drug-Resistant TB Cases

Age Group (years)	Frequency	Percentage
1–15	2	2%
15–30	24	24%

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31–45	35	35%
46–60	27	27%
61–75	12	12%

Table 1 shows the age-wise distribution of drug-resistant tuberculosis cases. The majority of patients belonged to the 31–45-year age group (35%), followed by those aged 46–60 years (27%) and 15–30 years (24%). Elderly patients aged 61–75 years accounted for 12% of cases, while the lowest proportion was observed in the pediatric age group of 1–15 years (2%). This indicates that drug-resistant TB predominantly affects individuals in the economically productive age group.

Table 2: Gender-wise Distribution

Gender	Frequency	Percentage
Male	68	68%
Female	32	32%

Table 2 depicts the gender-wise distribution of cases. A clear male predominance was observed, with males constituting 68% of the study population, while females accounted for 32% of cases.

Table 3: Types of Drug Resistance

Type	Number	Percentage
INH mono-resistant	34	34%
Rifampicin-resistant	29	29%
MDR-TB	36	36%
XDR-TB	1	1%

Table 3 illustrates the pattern of drug resistance. Multidrug-resistant TB (MDR-TB) was the most common type (36%), followed closely by isoniazid (INH) mono-resistance (34%) and rifampicin resistance (29%). Extensively drug-resistant TB (XDR-TB) was rare, observed in only 1% of cases.

Table 4: HIV Status of Drug-Resistant TB Cases

HIV Status	Number	Percentage
Positive	2	2%
Negative	98	98%

Table 4 presents the HIV status of drug-resistant TB patients. The vast majority (98%) were HIV-negative, while only 2% of patients were HIV-positive.

Table 5: Proportion of smear positivity with culture during follow up of MDR TB:

Smear	Culture positive	Culture negative
Smear positive	5	0
Smear negative	4	91

Sensitivity of microscopy = 5/9= 55.55%

Specificity of microscopy = 91/91= 100%

Among 100 follow-up cases, 9 showed culture positivity. Smear microscopy detected 5 of these cases, yielding a sensitivity of 55.5% and specificity of 100% compared to culture

Table 6: Difference in Turnaround time (TAT) by using conventional biochemical tests and CBNAAT as a method of identification:

Isolate S.No	Specimen receiving to initiation of culture	Duration of culture to get 2+ visible growth	Culture ID by Biochemical tests	Culture ID by CBNAAT	TOTAL TAT by Biochemical tests	TOTAL TAT by using CBNAAT	Difference
1.	1 day	28 days	28 days	2 hours	57 days	29 days	28 days
2.	1 day	28 days	28 days	2 hours	57 days	29 days	28 days
3.	1 day	49 days	28 days	2 hours	78 days	50 days	28 days
4.	1 day	28 days	28 days	2 hours	57 days	29 days	28 days
5.	1 day	35 days	28 days	2 hours	64 days	36 days	28 days
6.	1 day	35 days	28 days	2 hours	64 days	36 days	28 days
7.	1 day	35 days	28 days	2 hours	64 days	36 days	28 days
8.	1 day	28 days	28 days	2 hours	57 days	29 days	28 days
9.	1 day	35 days	28 days	2 hours	64 days	36 days	28 days

Followup positive cases were identified by using conventional biochemical tests such as Niacin test, Nitrate test and PNB susceptibility test. Simultaneously the positive cultures were identified by using CBNAAT.

It takes about an average of 64 days to identify as Mycobacterium tuberculosis by using biochemical tests as a method of choice for identification and an average of 34 days to identify as Mycobacterium tuberculosis by using CBNAAT with culture as a method of choice for identification. We compare this difference by using students t test.

Here t value =8.7 (p value< 0.00001) which indicates this study is most significant one.

Considerably CBNAAT reduces 28 days for final identification

Table 7: Resistant pattern in Positive cases:

S.no of isolate	At the time of initial diagnosis	At the time of follow up using Xpert MTB/RIF	At the time of followup using LPA (in IRL)
1	MDR	RR	MDR
2	RR	RR	MDR
3	MDR	RR	MDR
4	MDR	RR	MDR
5	RR	RR	RR
6	RR	RR	RR
7	MDR	RR	XDR
8	INH MONO	RR	MDR
9	MDR	RR	MDR

At the time of initial diagnosis, out of 9 positive cases 5 cases were MDR, 3 cases were RR and 1 case was INH mono resistant TB. But at the time of follow up culture using CBNAAT for the identification, all cases were found to be RR. 1 INH mono resistant case was also turned into RR. This was confirmed by sending those positive samples to IRL, Chennai. There 6 cases was found to be MDR, 2 RR and 1 XDR.

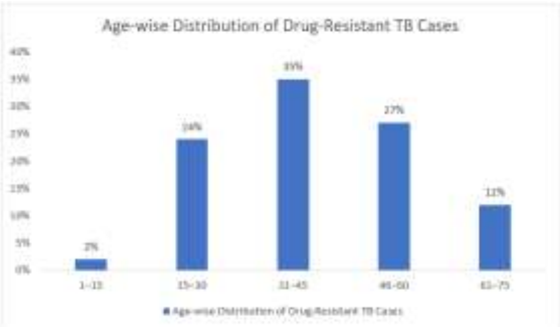

Figure 1: Age Distribution

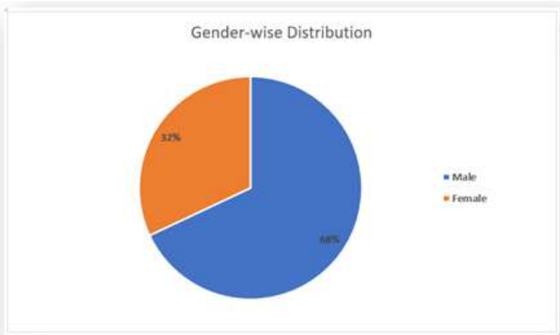

Figure 2: Gender-wise Distribution

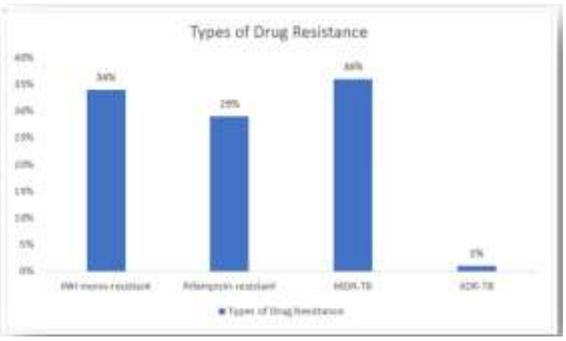

Figure 3: Type of Drug Resistance

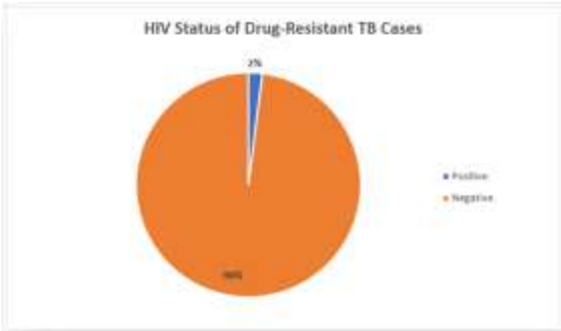

Figure 4: HIV Status of Drug- Resistant TB Cases

DISCUSSION

Drug-resistant tuberculosis (DR-TB) continues to pose a serious challenge to global tuberculosis (TB) control efforts. In 2016, an estimated 601,000 new cases of rifampicin-resistant TB were reported globally, of which approximately 490,000 were multidrug-resistant TB (MDR-TB). Nearly half of these cases were reported from India, China, and the Russian Federation, highlighting the disproportionate burden of DR-TB in high-incidence countries such as India. The emergence and persistence of DR-TB threaten the progress achieved by national TB control programs and remain a major obstacle to achieving the End TB targets. Strengthening systems for early detection, effective treatment, and sustained cure is therefore essential to prevent further emergence and transmission of resistant strains. Uplekar M et al. (2016).[8]

Inadequately treated patients harboring drug-resistant Mycobacterium tuberculosis serve as a continuous source of transmission in the community. Poor infection control practices in healthcare facilities and congregate settings further facilitate the spread of resistant strains. Hence, rapid diagnosis, prompt initiation of appropriate treatment regimens, and interruption of transmission are critical for effective DR-TB control. Measures aimed at reducing TB incidence overall also contribute significantly to preventing the development of drug resistance. Vishwakarma D et al. (2023).[9]

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As per RNTCP and PMDT guidelines, follow-up of DR-TB patients requires periodic sputum examination using smear microscopy and culture at predefined intervals during treatment. Sputum samples are examined from the third to seventh month of treatment at monthly intervals and subsequently at three-monthly intervals until treatment completion. Culture plays a pivotal role in monitoring treatment response and deciding the transition from intensive phase to continuation phase. Vaman RS et al. (2021).[10] Although liquid culture is preferred due to higher sensitivity and shorter turnaround time (TAT), its widespread implementation is limited by the need for biosafety level-3 infrastructure, automated systems, and higher costs. Consequently, solid culture using Lowenstein–Jensen (LJ) medium continues to be widely employed, particularly in resource-limited settings.

However, phenotypic drug susceptibility testing (DST) using solid culture, though considered the gold standard for first-line and important second-line drugs, is time-consuming. Culture positivity requires 4–6 weeks, followed by an additional 28 days for biochemical confirmation of Mycobacterium tuberculosis. This prolonged turnaround time delays identification of treatment failure and detection of emerging resistance. The present study aimed to reduce this diagnostic delay by incorporating CBNAAT for rapid identification of culture isolates, thereby improving the efficiency of solid culture-based follow-up.

In the present study, 100 follow-up samples from patients on second-line treatment were analyzed. As shown in Table 1, the majority of DR-TB cases were observed in the 31–45-year age group (35%), followed by 46–60 years (27%) and 15–30 years (24%). Only 2% of cases occurred in children below 15 years. This age distribution indicates that DR-TB predominantly affects individuals in their economically productive years, resulting in significant socioeconomic consequences. Similar age trends have been reported by Wright Aet al.(2009) and Goyal Vet al.(2017), supporting the consistency of these findings across different populations.[11,12]

Gender-wise distribution (Table 2) revealed a clear male predominance, with males accounting for 68% of cases. This finding is consistent with studies by Goyal V et al.(2017)and Singh Net al.(2025) which reported that more than two-thirds of DR-TB patients were male.[12,13] Factors such as increased occupational exposure, higher prevalence of risk behaviors, and differences in healthcare-seeking behavior may contribute to this observed gender disparity.

Analysis of drug resistance patterns (Table 3) showed that MDR-TB was the most common form (36%), followed by INH mono-resistance (34%) and rifampicin-resistant TB (29%). XDR-TB was rare, accounting for only 1% of cases. The higher proportion of INH resistance compared to rifampicin resistance observed in this study is in agreement with reports by Chakraborty M et al. (2023) who also documented a higher prevalence of INH resistance in Indian settings.[14] Early detection of INH mono-resistance is crucial, as inappropriate treatment can lead to progression to MDR-TB.

HIV co-infection was detected in only 2% of cases (Table 4). This finding correlates with observations bySultana ZZ et al.(2021) who reported wide variability in MDR-TB prevalence among HIV-positive individuals across different studies.[15] The low HIV prevalence in the present cohort may reflect regional epidemiological patterns or effective HIV–TB collaborative interventions.

Among the 100 follow-up cases, nine were found to be culture-positive, indicating delayed conversion or treatment failure. Of these, five cases were both smear- and culture-positive, while four were smear-negative but culture-positive. Smear microscopy demonstrated a sensitivity of 55.55% and a specificity of 100% when compared with culture. These findings highlight the limited sensitivity of smear microscopy during follow-up, particularly in cases with low bacillary load. PMDT guidelines emphasize that culture conversion is a more reliable indicator of treatment response than smear conversion, as culture reflects the presence of viable bacilli even at very low concentrations. Vaman RS et al. (2021).[10]

All nine culture-positive cases were correctly identified as Mycobacterium tuberculosis using both conventional biochemical methods and CBNAAT. This finding is consistent with WHO reports indicating that Xpert MTB/RIF has high sensitivity and specificity for TB detection and is highly accurate in distinguishing TB from non-tuberculous mycobacteria.[5] The ability of CBNAAT to simultaneously detect rifampicin resistance further enhances its diagnostic value.

A key finding of this study is the significant reduction in turnaround time achieved by using CBNAAT for identification of solid culture isolates. Bir R et al. (2025) The mean time to identification using conventional biochemical methods was 64 days, whereas CBNAAT reduced this to 34 days, resulting in a reduction of nearly 28–30 days. This difference was statistically significant ($p < 0.00001$). Early identification of resistance facilitates timely modification of treatment regimens, reduces the risk of ongoing transmission, and improves patient outcomes.[6]

Changes in resistance patterns were also detected during follow-up. While initial diagnosis included 5 MDR-TB cases, 3 cases of rifampicin resistance, and 1 case of INH mono-resistance, all nine follow-up culture-positive cases were identified as rifampicin-resistant using CBNAAT. Further confirmation at the Intermediate Reference Laboratory revealed six MDR-TB cases, two rifampicin-resistant cases, and one XDR-TB case. Early detection of XDR-TB using CBNAAT, nearly one month earlier than conventional biochemical methods, underscores the potential of this approach in preventing further amplification of resistance and reducing community transmission. Mishra D et al. (2023).[5]

Interrupted or irregular TB treatment is a major determinant of acquired drug resistance and progression to MDR- and XDR-TB. These findings emphasize the need to strengthen laboratory capacity with rapid, reliable diagnostic tools. Pozo G et al. (2019),[16] Using CBNAAT for identification of solid culture isolates is particularly useful in smear-negative follow-up cases where line probe assays cannot be applied directly. This combined approach offers a practical and effective strategy to improve diagnostic efficiency and limit the spread of drug-resistant tuberculosis in resource-limited settings. Pai M et al. (2023).[17]

CONCLUSION

The introduction of cartridge-based nucleic acid amplification testing (CBNAAT/Xpert MTB-RIF) has markedly improved the early detection of Mycobacterium tuberculosis and rifampicin resistance, particularly in smear-negative and drug-resistant tuberculosis cases. The present study demonstrates that CBNAAT offers high sensitivity and specificity when compared with culture as the reference standard, while additionally providing semi-quantitative information on bacillary load. Although RNTCP guidelines recommend liquid culture for follow-up due to its higher sensitivity and shorter turnaround time, its widespread use is limited by the need for biosafety level-3 infrastructure, automated systems, and high operational costs. Solid culture, though more feasible and economical, is hindered by delayed identification due to prolonged biochemical confirmation. Integrating CBNAAT with solid culture significantly overcomes this limitation by reducing the identification and reporting time by nearly 28 days, while simultaneously detecting rifampicin resistance. Thus, the combined use of solid culture and CBNAAT represents a practical, accurate, and cost-effective strategy for the diagnosis and follow-up of tuberculosis in resource-limited settings.

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