Original Article

To investigate the impact of revised diagnostic algorithm on presentation of multidrug-resistant tuberculosis cases at a referral centre in India

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Abstract

Introduction: A shift in policy has occurred with the introduction of molecular diagnostic tools for the upfront diagnosis of all cases of tuberculosis, including drug-resistant tuberculosis. The impact of this shift in policy on severity of disease was studied, and comparisons were drawn between the year 2015 and 2020. **Study Type and Design:** This was an observational study conducted between 2020 and 2021. Seventy patients of MDR-TB with or without additional drug resistance, hospitalized in the year 2015 and 2020, were studied. **Results:** The study reveals a substantial reduction in the median time from the onset of symptoms to diagnosis between 2015 and 2020. Specifically, the median duration decreased from 12 weeks in 2015 to 8 weeks in 2020. Moreover, we found that in 2015, all cases under study had a history of tuberculosis in comparison to 2020. Additionally, there was a higher incidence of anemia in 2015 compared to 2020. In the radiological examination, it was observed that in 2015, a higher frequency of cases exhibited cavitations, bronchiectasis, and fibrosis on chest X-rays compared to the findings in 2020. The mean cavity size in 2015 measured 6.73 cm, while in 2020, it averaged 4.06 cm. Additionally, we noticed a higher occurrence of significantly advanced cases in 2015 in contrast to 2020. **Conclusion:** The implementation of the new policy of upfront DST was noted to decrease the time required for diagnosis and bacterial load as ascertained from degree of sputum smear positivity, radiological lesions, and severity of anemia.

Keywords: Early diagnosis, MDR-TB, molecular testing, upfront DST

Introduction

Drug resistance in mycobacterium tuberculosis (MTB) is one among the most important hurdles in controlling the mortality and morbidity of tuberculosis (TB). As per the national anti-tuberculosis drug resistance survey conducted in India, 6.19% of cases of TB (2.84% among new and 11.60% among previously treated cases) were MDR cases.[1] According to WHO in 2023, rifampicin sensitivity testing was performed in 73% (2.9/4.0 million) of the patients who confirmed bacteriological TB. Testing has increased comparatively from 2021 (69%) to 2019 (62%). In 2022 among those who were tested, 0.149 million were rifampicin-resistant/multidrug-resistant and 27075 cases were pre-XDR-TB or XDR-TB.[2] It is estimated

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that national TB elimination program of India (NTEP) misses 50% of drug-resistant TB cases.[3]

There have been significant changes in the guidelines for the management of tuberculosis in India from 2015 to 2020. Earlier, Category II or treatment failure in previously treated cases were advised DST; thus, the program would miss the cases of primary MDR-TB.[4] The mainstay of diagnosis of drug resistance was culture and phenotypic DST. As this was a time-consuming procedure, there would be a delay in diagnosis of drug resistance and thus delay in appropriate therapy. Thus, they had more chances of developing more severe disease which would be associated with higher morbidity and mortality. From a public health point of view, these cases continued to be the sources of spread of DRTB as they were on an ineffective regimen.

In the current guidelines, the use of rapid molecular diagnostics like cartridge-based nucleic acid amplification test (CBNAAT) and line probe assay (LPA) has also been advocated. Now, upfront DST by at least CBNAAT, compulsory notification, and thereby programmatic management of cases has been advocated. Also, DST is performed for a much wider group including all TB cases, presumptive TB cases, suspect children, people with HIV infection, and contacts of MDR-TB.[5] The use of faster molecular method for DST has led to earlier diagnosis of drug resistance and earlier initiation of appropriate regimen. This would imply earlier detection, earlier treatment initiation, and less severe disease and thus better treatment outcomes.

Emphasizing on understanding the effectiveness of this revised algorithm is also crucial for primary care physicians, as it could potentially streamline the diagnostic process, leading to earlier detection and appropriate management of MDR-TB cases at the primary care level. By doing so, the study aims to improve patient outcomes and reduce the spread of MDR-TB within communities, which directly impacts the daily practice of primary care physicians.

Based on this, the current study was planned. No such study has been conducted in the past, which could assess if there is any change in the clinicoradiological and microbiological profile at presentation since these new changes have been brought.

Methods

Study setting and population

It was an observational study conducted between September 2020 and September 2021 at the National Institute of Tuberculosis and Respiratory Diseases (NITRD), New Delhi, after obtaining ethical approval from Institutional Research and Ethics Committee (Office letter no: Acad.Sec/PGEC/2021/5232 and NITRD/RC/2020/1929), respectively. Cases with MDR-TB and MDR-TB with additional drug resistance, hospitalized in the year 2015 and 2020 each, were included.

Study sample size

The sample size was calculated based on the prevalence of MDR-TB cases in India. Previously reported MDR-TB cases in the NDRS survey are 6.19%, and the error is 6%.

Hence sample size,

$$N = \frac{(Z_{\alpha/2})^2 \, P \, (1 - P)}{E^2} = \frac{(1.96)^2 \, 0.0619 \, (1 - 0.0619)}{(0.06)^2} = 62$$

$Z_{\alpha/2}$ = Z statistic at 95% confidence interval = 1.96.

P = Prevalence.

E = Precision assumed to be 0.06.

The calculated sample size was 62. Hence, we included 70 cases in each group for the study.

Study subjects

Adult patients suffering from multidrug-resistant tuberculosis admitted in NITRD in year 2015 and 2020 were included in the study. The study excluded patients with drug-sensitive tuberculosis and MDR-TB patients who were admitted to hospitals after commencement of the study and those who refused to participate or give consent.

Data collection

DRTB patients admitted during the study period were explained about the study after obtaining a signed informed consent. For cases hospitalised in 2015 and for cases hospitalised in 2020 before the study period, data were collected from the medical records department (MRD). A detailed clinical history was taken, and clinical examination was performed. All the findings were entered in a data collection sheet that included: blood samples were sent for complete blood count, blood glucose, liver function test, urea, creatinine, serum electrolytes, and other tests as deemed necessary. Anemia was classified as mild, moderate, or severe as per the WHO classification.[6] Chest radiographs (CXR) were obtained. The extent of lung involvement was graded as mild, moderate, and severe as per the National Tuberculosis Association, New York, diagnostic standard and classification of tuberculosis.[7] Appropriate biological samples were sent for analysis of drug resistance by CBNAAT, LPA, or liquid culture (LC) and drug susceptibility testing (DST) by MGIT 960 system. These were performed at the Department of Microbiology, NITRD. In the year 2015, the main method for diagnosis of DRTB at NITRD was first-line LPA and culture and DST. In the year 2020, the major method for diagnosis of drug resistance was CBNAAT, first-line and second-line LPA, and LC-DST.

Statistical analysis

Data were entered into a Microsoft Excel spreadsheet. These data were then analysed using SPSS software (version 27; SPSS Inc., Chicago, IL, USA). Data were summarised as mean and standard deviation or median and interquartile range for numerical variables and counts and percentages for categorical variables. For numerical variables, tests for normality like Shapiro-Wilk test were performed. Depending on the data, Mann-Whitney *U* test, Student *t*-test, ANOVA, Chi-square tests were performed to look for any significant difference in findings between the two groups.

Results

A total of 70 patients were enrolled during the defined study period. In the 2015 (earlier policy) and 2020 (current policy) study group, the numbers of males were 49 (70%) and 36 (51.4%). The median and interquartile range of age of 2015 group was 29.5 and 12 years and of 2020 group was 26 and 11 years. Age distribution was similar in the groups. In the 2015, 22 (31.4%) patients were from rural area and 48 (68.6%) from urban area, while in 2020, this number was 07 (10%) and 63 (90%), respectively. There were more people from rural area in 2015 compared to 2020 ($P = 0.002$).

The most common comorbidity in both the groups was diabetes mellitus (DM); other comorbidities included chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), hypertension, and asthma. These were similar in the two groups ($P = 0.49$). In both the groups, the common symptoms included cough, breathlessness, fever, weight loss, loss of appetite, chest pain, and hemoptysis. The cases in the 2020 study group had lower median duration from the onset of symptoms until diagnosis. It was 12 weeks in 2015 and 8 weeks in 2020. This difference was statistically significant ($P = 0.01$). All the cases (100%) in the 2015 study group had a history of tuberculosis at least once in the past, while 15 cases (21.4%) in the 2020 study group had no history of tuberculosis, and 55 cases (78.6%) had a history of tuberculosis. This difference was statistically significant ($P = 0.0002$).

The mean hemoglobin level of participants in the 2015 study group (9.73 ± 1.91 g/dl) was lower than the participants of the 2020 study group (10.79 ± 2.47 g/dl) ($P = 0.008$). More cases (63, 90%) among the 2015 group had anemia as compared to the 2020 group (n = 49, 70%) ($P = 0.0013$). Total leucocyte count, platelet count, and other laboratory parameters were similar in both the groups ($P > 0.05$). It is shown in Table 1.

A greater number of cases of 2015 had cavities (n = 63, 90%) ($P = 0.040$), bronchiectasis (n = 63, 90%) ($P = 0.023$), and fibrosis/volume loss (n = 65, 92.8%) ($P = 0.026$) as compared to 2020. More cases of 2015 (n = 58, 82.8%) had far advanced involvement of lungs, as compared to the 2020 study group (n = 34) ($P = 0.0002$). The mean total size of cavities in the year 2015 was larger (6.73 cm) as compared to the 2020 study group (4.06 cm) ($P < 0.001$). Chest X-ray findings of the study participants are shown in Table 1, and comparison of size of the cavity is presented in Table 2.

Scanty and 1+ smear microscopy results were more common in the 2020 group ($P = 0.041$), and 2+ and 3+ smear microscopy results were more in the 2015 group ($P = 0.0289$). This is shown in Table 3. Seven cases each in the 2015 and 2020 group were XDR-TB cases. The total number of pre-XDR, pre-XDR (FQ), and pre-XDR (SLI) cases were 19, 28, and 15, 24 and 4,4 in the 2015 and 2020 group respectively as shown in Figure 1. These findings were similar in both the groups.

Additional resistance to at least one first-line or second-line drugs was seen in 64.3% cases (n = 45) of 2015 and 75.7% cases (n = 53) of 2020. Thirty (42.86%) cases of the 2015 study group and 28 (40%) cases of the 2020 study group had additional resistance to one antitubercular drug (ATD). Seven (10%) and 18 (25.7%) cases of the 2015 and 2020 groups, respectively, had additional resistance to two ATDs. Five (7.1%) and 4 (5.7%) cases

Table 1: Comparison of chest X-ray findings among the study group

Chest X-ray Findings	2015 No. (%)	2020 No. (%)	*P*
Cavity	63 (90%)	54 (77.1%)	0.040
Unilateral Cavity	22 (31.4%)	23 (32.8%)	0.860
Bilateral Cavities	41 (58.6%)	31 (45.7%)	0.091
Consolidation/Infiltrates	69 (98.6%)	66 (94.3%)	0.172
Pleural Effusion	24 (34.3%)	18 (25.7%)	0.268
Lymphadenopathy	12 (17.1%)	9 (12.9%)	0.478
Fibrosis/volume loss	65 (92.8%)	56 (80%)	0.026
Bronchiectasis	63 (90%)	45 (64.3%)	0.023
Pneumothorax	5 (7.1%)	4 (5.7%)	0.7304
Hydropneumothorax	8 (11.4%)	6 (8.6%)	0.5731
Overall radiographic Extent of Involvement			
Nil	0	01 (1.4%)	-
Minimal and moderately advanced	12 (17.14%)	35 (50%)	<0.0001
Far advanced cases	58 (82.8%)	34 (48.6%)	0.0002

Table 2: Comparison of size of cavities among the study group

Size of cavities (in cm)		
Year	**Mean Size±SD**	***P***
2015	6.73±4.04	<0.001
2020	4.06±3.27	

Table 3: Comparison of AFB smear microscopy status

AFB smear microscopy			
Sputum smear status	**2015**	**2020**	***P***
Smear negative	1	3	0.3102
Scanty and 1+	15	26	0.041
2+ & 3+	54	42	0.0289

of the 2015 and 2020 study groups had additional resistance to three other ATDs. One (1.4%) case each in both the groups had additional resistance to 4 other ATDs. Two (2.9%) cases in the 2015 study group and 4 (5.7%) in the 2020 study group had additional resistance to five other ATDs. Additional resistance to ATDs among study participants between two groups is shown in Figure 2.

Discussion

Delay in diagnosis and initiation of treatment is one of the major causes of poor treatment outcome in MDR-TB. The new policies advocate upfront DST and use of molecular methods for diagnosis of DST which has led to earlier diagnosis and thus earlier initiation of treatment.[5] In the present study, there was male predominance (60.7%) similar to Global TB report 2023 (55%),[2] India TB report 2021 (61.7%),[3] and NDRS survey (72.01%).[1] The maximum number of cases (80.7%) belonged to the 18–45 years age group. Om Prakash Giri *et al.*[8] also reported that the age group 15–45 years had a maximum number of MDR-TB cases in their study. The number of cases from rural area decreased from 31.4% in 2015 to 10% in 2020. Most of the MDR-TB cases, with the current policy of decentralisation of DRTB services, were treated at the peripheral centres in 2020. Difficult to treat TB cases that required expert pulmonologist opinion or those requiring newer drugs were hospitalised in 2020 for treatment initiation.

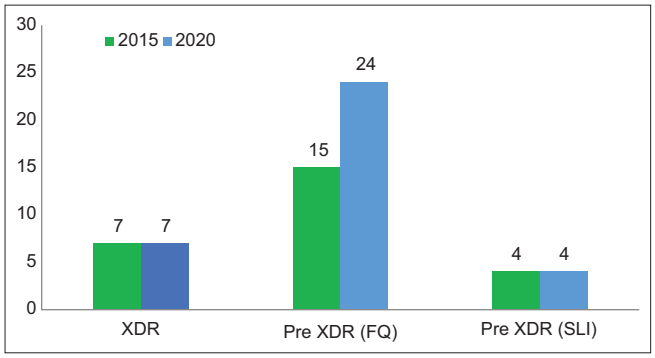

Figure 1: Prevalence of XDR and Pre-XDR tuberculosis in 2015 and 2020 group

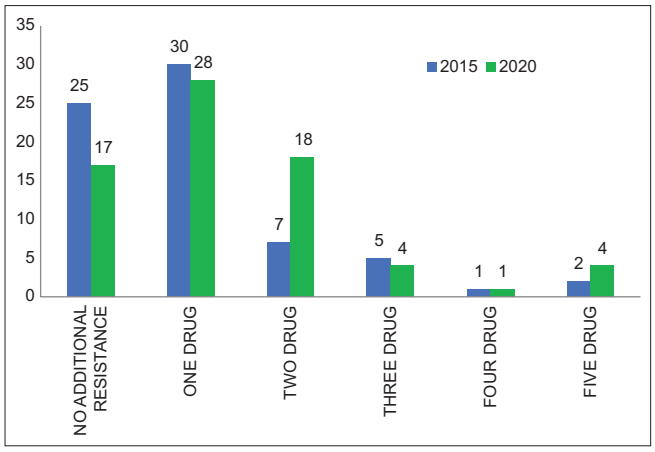

Figure 2: Details of additional drug resistance in the study group

The symptoms at presentation were similar in both the groups. The median and interquartile range for duration from symptom onset to diagnosis was lesser in the 2020 group (8 weeks) in comparison to the 2015 group (12 weeks). This was similar to studies by Xu Caihong *et al.*,[9] and X Zhang *et al.*,[10] where the median delay in diagnosis was 84 days and 102 days, respectively. However, despite extensive literature search, no study could be found comparing the diagnostic delay in 2015 and 2020. The policy of upfront DST for all TB cases and the use of rapid molecular diagnostic methods like CBNAAT, LPA has led to an earlier diagnosis. The number of cases with a history of TB in the past in relation to diagnosis was significant. Change in the guidelines including the use of upfront DST in all cases of tuberculosis is the reason behind this. Thus, cases with even primary drug resistance were being diagnosed in 2020.

The mean hemoglobin level was higher in the 2020 group. More cases in 2015 had anemia as compared to 2020. Diagnosis at an earlier stage of the disease is the reason for this. Although the cases with severe anemia was higher in 2015, this difference was not significant. The study by O. A. Adejumo *et al.*[11] found that 70.2% had anemia among MDR-TB patients in 2014, and 71% of the MDR-TB patients had anemia in a study by Magassouba AS *et al.* in 2016.[12] Similarly, Kiran B *et al.*[13] reported that 60% of the MDR-TB cases had anemia in their study. Again, there was no study comparing anemia among the two groups.

In 2015, Chuchottaworn and colleagues documented that 83.7% of MDR-TB cases exhibited cavities on chest X-rays.[14] Additionally, Cheon and collaborators reported in a separate study that 79.1% of MDR-TB cases displayed pulmonary cavities.[15] In the current study, 83.5% cases had cavities on CXR. In our study, the average cavity size was 5.39 cm. This aligns with findings from Cheon,[15] as well as Kim Sanghyeon *et al.*,[16] where the reported mean cavity sizes were 3.6 cm and 3.77 cm, respectively. Earlier diagnosis of drug resistance, thus identification of disease at an earlier stage in the 2020 group compared to the 2015 group, was evident in the extent of radiological involvement and presence of cavities and bronchiectasis. These features were less in the 2020 group, as compared to the 2015 group. Besides, the average total size of cavities was smaller in the 2020 group. Due to the same reason, the number of cases with higher bacterial load denoted by smear microscopy was higher in 2015 as compared to 2020.

As per Global TB report, there was an increase in the reported cases of XDR-TB in the year 2019 as compared to the year 2015.[17,18] In the current study, the percentage of XDR-TB was same in both groups; small sample size may be the reason behind this.

The NDRS survey of India reported that additional resistance to any fluoroquinolones was 21.82% and 3.58% to any second-line

injectable drugs.[1] In this study, pre-XDR (FQ) cases were 21.42% and 34.28% in the 2015 and 2020 study groups, respectively. Pre-XDR (SLI) in both the groups was 5.71% each. The current study enrolled only hospitalised patients from a tertiary care centre, which is expected to have resistance to additional drugs; thus, there is some difference from the findings of NDRS survey. In our study, more cases in the 2020 (75.7%) were resistant to other ATDs. There has been policy change regarding hospitalisation in our institute; all MDR cases were hospitalised for treatment initiation in 2015; however, in 2020, the cases which were hospitalised were either critically ill or had multiple resistance (difficult to formulate a regimen) or needed newer drugs like bedaquiline (BDQ) or delaminid (DLM). Hence, the resistance profile in 2020 was worse as compared to 2015. There were no studies comparing resistance among the two groups.

Primary care physicians play a vital role in community TB control. Understanding the impact of revised diagnostic algorithms on MDR-TB cases helps them contribute better to public health initiatives. They can offer feedback to policymakers and healthcare administrators, advocating for improved laboratory facilities, rapid molecular diagnostic tests, and training programs at primary care centers. This knowledge also enhances diagnostic accuracy, leading to prompt treatment initiation, better treatment planning, reduced treatment failure risk, and prevention of drug-resistant strain spread, ultimately improving patient outcomes.

Our study had a few limitations: Due to time constraints, only 140 hospitalised cases from a referral hospital were included in the study. The multicentric study with larger sample size should be conducted to validate the results. The major impact of the change in guidelines might be better treatment outcomes, but due to time constrains, treatment outcome was not followed.

Conclusion

The current PMDT guidelines recommend immediate DST and the utilization of rapid molecular diagnostic methods for detecting drug resistance. In contrast, the 2015 policy limited DST to specific situations and primarily relied on time-consuming techniques (phenotypic DST) rather than molecular approaches. To assess the impact of this policy shift, our study was conducted. The findings indicate that the 2020 policy of implementing upfront DST for both confirmed and suspected TB patients resulted in earlier detection of MDR-TB. This is evident in the significantly reduced diagnostic delay in 2020, along with lower radiological disease severity, fewer cases exhibiting cavities, and a decreased degree of sputum positivity. Additionally, many MDR-TB patients in 2020 had either no previous treatment history or had undergone treatment only once in the past.

Abbreviations

MTB-Mycobacterium tuberculosis
TB-tuberculosis
NTEP-National TB elimination program of India
CBNAAT-Cartridge based nucleic acid amplification test
LPA-Line probe assay
MRD-medical records department
CXR-Chest radiograph
LC-Liquid culture
DST-Drug susceptibility testing
DM-Diabetes mellitus
COPD-Chronic obstructive pulmonary disease
CKD-chronic kidney disease
ATD-antitubercular drug
Pre-XDR-Pre-extensively drug-resistant TB
XDR-TB-extensively drug-resistant TB
FQ-Fluoroquinolone
SLI-Second line injectable
BDQ-Bedaquiline
DLM-Delaminid
PMDT-Programmatic management of drug resistant TB

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Nil.

Conflicts of interest

There are no conflicts of interest.

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