



Assessment of Pattern of Drug-resistant TB and Associated Factors in Rewa, Madhya Pradesh, India

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Abstract

Background and aims: The emergence and spread of drug-resistant strains of *Mycobacterium tuberculosis* are greatly complicating tuberculosis (TB) control efforts in many countries. In India, in 2018, out of 2.4 million notified cases of TB, there were an estimated 66 359 and 3,882 laboratory-confirmed cases of multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant TB (XDR-TB) respectively. The main objective of this study was to assess pattern of drug-resistant tuberculosis (DR-TB) and factors associated with it in Rewa district of Madhya Pradesh, India.

Methods: This descriptive-analytical cross-sectional study was carried out at a tertiary care center in Rewa district from March 1, 2019, to February 29, 2020 (12 months). Taking the census method into account, all of 186 DR-TB cases registered at District Tuberculosis Centre (DTC), Rewa district, with the age of 18 years and above were included in the study. All the patients were interviewed thoroughly using a pre-tested, pre-validated, and reliable pro forma which included information regarding socio-demographic profile and history of TB. For statistical analysis, chi-square test (with/without Yate's correction) was applied and a *P* value less than 0.05 was considered statistically significant.

Results: In the present study, 71.6% and 28.4% of the cases were reported to be male and female, respectively. Additionally, 78.4% of the study subjects belonged to the age group of less than 45 years. Besides, rifampicin-resistant TB (RR-TB) was found to be the most prevalent type (56.4%), followed by isoniazid-resistant TB (HR-TB) (13.4%), and mixed pattern (12.4%) of DR-TB.

Conclusion: DR-TB was more commonly observed in males of the economically productive age group (45 years and below), which can affect the social and economic development of individual, society, and nation.

Keywords: Drug-resistant tuberculosis, Epidemiology of DR-TB, Factors of DR-TB

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Introduction

Tuberculosis (TB) is a chronic, common, infectious disease caused by *Mycobacterium tuberculosis*, mainly affecting the lungs besides brain, kidneys, or spine.¹ The resistance of *M. tuberculosis* to drugs manifests when there is a growth of new resistant mutants among the actively multiplying bacillary population in the presence of drugs. The genetic mutation makes the drug ineffective against the mutant bacilli.¹ The emergence and spread of drug-resistant strains of *M. tuberculosis* are greatly complicating TB control efforts in many countries.²

In 2018, there were approximately 500 000 (417 000–556 000) new cases of resistance to Rifampicin (first-line anti-TB drug) globally, of which 78% had multi-drug resistant tuberculosis (MDR-TB). The three countries with the largest share of the global burden were India (27%), China (14%) and the Russian Federation (9%).²

In India, out of 2.4 million notified cases of TB, there were 66 359 and 3882 laboratory confirmed cases of MDR-TB and extreme drug resistant tuberculosis (XDR-TB) respectively.³ India as a current hotspot of this silent

pandemic, in terms of morbidity and mortality, is bearing direct and indirect socio-economic burden of about \$23.7 billion annually.¹ With this background, further research activities regarding DR-TB need to be conducted, which will help achieve the goal of “TB Elimination by 2025”. Hence, the present study entitled “Assessment of pattern of drug-resistant TB (DR-TB) and factors associated with it in Rewa, Madhya Pradesh, India” was conducted in Rewa district of Madhya Pradesh state (Central India), which was perhaps the first study in the district taking DR-TB into consideration.

Materials and Methods

Type of Study

This descriptive-analytical cross-sectional study was conducted from March 1, 2019, to February 29, 2020 (12 months).

Study Population

This study was carried out in Rewa district of Madhya Pradesh state (India), with a population of about 2.37

million (2011 Census, the fifth most populous district in the state) and a population density of 375 people per km² (the seventh most densely populated district in the state). It has 9 Community Development Blocks and 12 Tehsils.

Sampling and Sample Size

Using census method, all of 186 DR-TB cases registered at District Tuberculosis Centre (DTC), Rewa district with the age of 18 years and above were included in the study.

Study Tool

To develop the questionnaire, different relevant studies regarding DR-TB were reviewed thoroughly and only factors pertaining to the study were taken into consideration. All the patients were interviewed thoroughly using this pre-tested pre-validated (I-CVI=0.8) and reliable (Cronbach's alpha=0.8) questionnaire which included information regarding socio-demographic information such as age, gender, marital status, type of family, education, occupation, location of residence, family income per month, and history of TB. All the preventive measures against TB were adopted during the interview. To evaluate the pattern of resistance, results of drug-susceptibility testing [CBNAAT (Cartridge Based Nucleic Acid Amplification Test)/LPA (Line Probe Assay)] were used. In our study, overcrowding was said to occur if the number of persons living in the room exceeds four.⁴

Modified B.G. Prasad Scale (March 2020) was used for categorization of the socio-economic status of patients. For classification of type, pattern of resistance, and history of TB, standard NTEP (National Tuberculosis Elimination Program) definitions² given below were implemented.

Isoniazid Resistance (HR-TB): Resistance to Isoniazid Only

RR-TB/MDR-TB: Resistance to rifampicin only or at least both isoniazid and rifampicin.

RR-TB/MDR with other drug resistance: Resistance to rifampicin only or at least both isoniazid and rifampicin along with other second line injectable drugs (SLIDs). This includes resistance to fluoroquinolones and other second-line injectable drugs.

Resistance in cultures from patients for which treatment had been administered for <1 month or not at all is known as primary drug resistance while resistance in cultures from patients with one or more previous TB treatment episodes (for at least one or more than one month), including those with treatment failures and relapse, is called acquired drug resistance.

Statistical Analysis

Collected data were entered in a Microsoft Excel spreadsheet, coded appropriately, and analyzed using SPSS version 18.0. Chi-square test (with/without Yate's correction) was applied and a *P* value of less than 0.05 was considered statistically significant.

Results

Table 1 depicts that there were 133 (71.6%) male and 53 (28.4%) female participants in the study. Additionally, 146 (78.4%) patients belonged to the age group of less than 45 years. Among all the patients, 18 (9.6%) cases were illiterate and 81 (43.6%) were educated up to 8th standard. It also illustrates that the majority of patients belonged to the lower socio-economic class (38.9%), followed by the lower-middle class (31.7%). Moreover, 65% of the patients belonged to joint family and 41.3% of the patients were residing in overcrowded households. More than three-fourths of the patients came from rural regions of Rewa district. The highest proportion (31.5%) of cases were reported from Huzur block, followed by Sirmour. Additionally, 30 (66%) DR-TB cases were referred from a nearby district (Satna, 55 km) for further management. Additionally, 179 (96.2%) patients had pulmonary DR-TB. Table 2 depicts that rifampicin-resistant TB (RR-TB) was found to be the most common type (56.4%), followed by isoniazid-resistant TB (HR-TB) (13.4%), and mixed pattern (12.4%) of DR-TB. Out of 46 study subjects with MDR + Other drugs resistance, 7 subjects had pre-extensively drug resistance (XDR), 9 had XDR, 23 had mixed and 7 had mixed + bedaquiline resistance. According to Tables 3, 4, patients with acquired type of DR-TB had MDR with other drug resistance pattern whereas patients with primary type more commonly had RR and HR-TB. The mean duration of previous treatment and relapse were found to be 7.3 ± 6.3 and 14 ± 12.3 months, respectively.

There was a statistically significant association ($P=0.0011$) between the age below 45 years and drug resistance. Besides, laborers were more prone to the occurrence and increase in drug resistance compared to others. Occurrence of DR-TB was more common in married subjects ($P=0.001$). However, drug resistance was significantly associated with living in joint family ($P=0.033$). Moreover, drug resistance was more common in patients from rural areas and belonging to (70.4%) lower-middle and lower socio-economic classes.

Discussion

In our study, 186 DR-TB patients were included, out of which 133 (71.5%) were male and 53 (28.5%) were female. In a similar study done by Kumari et al,⁵ it was found that 76% of the patients were male and 24% were female. Lu et al⁶ also reported that out of 1154 DR-TB patients, 67.3% were male and 32.6% were female.

Considering the age of the subjects, out of 133 male DR-TB patients, 105 (78.9%) belonged to the 18-45 years age group and 12 (9%) aged more than 60 years. In a similar study conducted by Uike et al⁷ in Yavatmal, almost half (46.67%) of the patients belonged to the productive age group (i.e., 30-45 years) and one-third (35.00%) were in the age group of 15-30 years.

A major proportion (43.6%) of the patients had education level up to middle school, 32.2% were educated

Table 1. Association of Patterns of Drug-resistance with Different Socio-demographic Variables

Socio-demographic Characteristics	Pattern of Resistance			P Value
	HR-TB (%)	RR/MDR- TB (%)	MDR + OTHER DRUGS (%)	
	n=25	n=115	n=46	
Gender				
Male	16 (64)	88 (76.5)	29 (63)	0.155
Female	9 (36)	27 (23.5)	17 (37)	
Age group				
≤45 years	19 (76)	86 (74.7)	41 (89.1)	0.001
>45 years	6 (24)	29 (25.3)	40 (10.9)	
Education				
Illiterate	2 (8)	11 (9.5)	5 (10.8)	0.960
Up to middle school	13 (52)	50 (43.5)	18 (39.1)	
Up to higher secondary	6 (24)	38 (33)	16 (34.7)	
Above higher secondary	4 (16)	16 (14)	7 (15.4)	
Occupation				
Labourers	4 (16)	49 (42.6)	17 (36.9)	0.436*
Farmers	2 (8)	11 (9.7)	3 (6.6)	
Students	3 (12)	13 (11.3)	8 (17.3)	
Drivers	5 (20)	6 (5.2)	4 (8.6)	
Factory workers	2 (8)	9 (7.8)	1 (2.2)	
Professionals	4 (16)	6 (5.2)	3 (6.6)	
Housewives	4 (16)	15 (13)	10 (21.8)	
Pensioners	1 (4)	6 (5.2)	0	
Marital status				
Married	22 (88)	88 (76.5)	7 (15.2)	≤0.001
Unmarried	3 (12)	27 (23.4)	39 (84)	
Location of residence				
Rural	16 (64)	91 (79.1)	35 (76)	0.271
Urban	9 (36)	24 (20.9)	11 (24)	
Socio-economic status (Modified BG Prasad Scale)				
Upper (Class-I)	0	3 (2.6)	1 (2.1)	0.997*
Upper middle (Class-II)	4 (16)	15 (13)	7 (15.2)	
Middle (Class-III)	4 (16)	15 (13)	6 (13)	
Lower middle (Class-IV)	6 (24)	40 (34.8)	13 (28.3)	
Lower (Class-V)	11 (44)	42 (36.6)	19 (41.4)	
Types of family				
Nuclear	4 (16)	46 (40)	15 (32.6)	0.033
Joint	21 (80)	69 (60)	41 (67.4)	
Overcrowding				
Present	7 (28)	47 (40.8)	23 (50)	0.195
Absent	18 (72)	68 (59.2)	23 (50)	

*With Yate's correction.

up to higher secondary, and 9.6% were illiterate. Similar results were reported by Sharma et al⁸ in Central Madhya Pradesh, according to which 44.6% of the patients had education level up to 12th standard and 11.7% of the patients were illiterate. In contrast to our study, Gaude et al⁹ in Belgaum, Karnataka, reported that illiteracy was significantly associated with the development of MDR.

In our study, the majority (37.7%) of the patients were

labourers, followed by housewives (15.6%) and students (12.9%). In concordance to our study, Sharma et al¹⁰ also reported that 28.2% of the patients were housewives, 14.5% were students, and 18.9% were labourers.

Considering the marital status of the patients, we found out that 138 (74.1%) out of 186 subjects were married. The findings of Sharma et al,⁸ Morris et al,¹¹ and Mulisa et al¹² were in agreement with our study, which also reported that

Table 2. Prevalence of Patterns of Resistance among Subjects (N = 186)

Pattern of Resistance	No. (%)
1. HR-TB (N = 25)	25 (13.4)
2. RR/MDR-TB (N = 115)	
RR-TB	105 (56.4)
MDR-TB	10 (5.5)
3. MDR with other drug-resistance (N = 46)	
Pre-XDR	7 (3.8)
XDR	9 (4.8)
Mixed*	23 (12.4)
Mixed + Bedaquiline resistance	7 (3.7)

*HR/RR-TB with fluoroquinolone resistance and/or SLIDs and/or linezolid.

more than 70% of the patients were married.

Considering the subject's location of residence, out of 186 study subjects, 142 (76.3%) belonged to rural areas and 44 (23.7%) belonged to urban areas. Similar findings were reported in studies done by Jangid et al,¹³ Uike et al,⁷ and Venkatesh,¹⁴ according to which more than 70% of the patients belonged to rural areas.

Based on the results, 38.9% and 31.7% of the patients from Rewa belonged to lower and lower-middle socio-economic classes. A similar pattern was also reported in studies conducted by Nagpal et al,¹⁵ and Gaude et al,⁹ where more than 70% of the patients belonged to either lower or lower-middle socio-economic class.

Considering overcrowding as one of the major determinants of transmission of TB, we found that 77 (41.3%) of the patients were living in overcrowded households. The prevalence of overcrowding was found to be higher (44.4%) in the joint family than in the nuclear family (35.4%)(Table 5). Similar findings were reported by Adane et al,¹⁶ according to which overcrowding was present in 37% of the households of the patients.

Among all 9 Community Development Blocks of Rewa district, 49 (31.5%) of the patients came from Huzur block followed by Sirmour block with 24 (15.3%) DR-TB cases. The reasons for this can be the larger population of these blocks and the shorter distance from DTC, Rewa, in comparison to other blocks. Additionally, 30 (16.1%) cases

were referred from nearby a district (Satna, n = 20) because most of the referred patients (56.6%) had either XDR-TB or mixed DR-TB and Bedaquiline was available only at DR-TB Centre located in Rewa.⁸

Considering the type of resistance, 73 (39.2%) patients had acquired type of drug resistance, among which 41 (56.1%) of the patients were of relapse type and 26 (35.6%) were defaulters. The mean duration of previous treatment and relapse was found to be 7.3±6.3 and 14±12.3 months, respectively. Figure 1 depicts reason-wise distribution of defaulter patients according to which the main reason for non-adherence to treatment was feeling of betterment due to improvement in the symptoms. Similar findings were reported by Sharma et al,¹⁰ Selvakumar et al,¹⁷ and Mukati et al,¹⁸ according to which the prevalence of acquired type of resistance was more than 35%.

In our study, out of 186 DR-TB patients, the prevalence of HR-TB, RR/MDR-TB, and MDR with other drug resistance was reported to be 16.8%, 69.9%, and 13.3% among 113 (60.8%) new patients. Among 73 (39.2%) previously treated patients, it was found to be 8.2%, 49.3%, and 13.3%. In concordance to our study, in National Anti-TB Drug Resistance Survey conducted in 2018, the prevalence of HR-TB, RR/MDR-TB, and MDR with other drug resistance was found to be 4.2%, 75.6%, and 20.2%, respectively. Besides, in a study done by Sinha et al,¹⁹ the prevalence of resistance to at least one anti-TB drug was 71.1% and that of MDR was 53.5%.

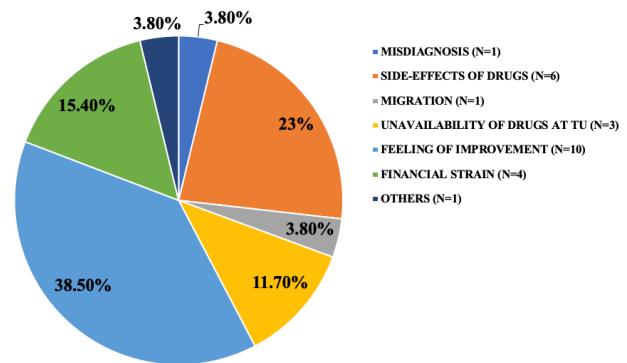


Figure 1. Reason-wise distribution of defaulters (%) [N=26]

Table 3. Association of Type of Drug Resistance with Patterns of Drug Resistance (N = 186)

	HR-TB (%)	RR/MDR-TB (%)	MDR + OTHER DRUGS (%)	P Value	Total
Acquired	6 (24)	36 (31.3)	31 (67.3)	≤0.001	73 (39.2)
Primary	19 (76)	79 (68.7)	15 (32.7)		113 (60.8)
Total	25	115	46		186

Table 4. Association of Patterns of Resistance WITH Acquired Type of Drug Resistance

	HR-TB (%)	RR/MDR- TB (%)	MDR + OTHER DRUGS (%)	P value	Total (%)
Defaulters	1 (16.7)	11 (30.6)	14 (45.1)	0.320	26 (35.6)
Failure	1 (16.7)	1 (2.8)	5 (16.1)		6 (8.2)
Relapse	4 (66.6)	24 (66.6)	12 (38.8)		41 (56.2)
Total	6	36	31		73

Table 5. Criteria for overcrowding in houses of DR-TB patients

Number of rooms	Standard number of persons
1	2
2	3 (additional 2 for each further room)

Limitations

More vital information could be achieved by taking a larger sample size. Since the present study was limited only to DR-TB cases and there was no comparison group, definite conclusions regarding the factors responsible for development of resistance and the relationship between social, behavioral, and environmental aspects and drug resistance need to be explored and hence, further research is recommended.

Conclusion

Based on the results of our study, it can be concluded that DR-TB was more commonly observed in males of the economically productive age group (45 years and below), which can affect the social and economic development of the individual, society, and nation. Besides, less educated subjects and those who belonged to low socio-economic status had a higher risk of contracting DR-TB. The acquired drug resistance was seen in 39.2% of the cases and the recurrence of previous TB was found to be the major contributor of DR-TB in Rewa.

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Authors' Contribution

GD contributed to conceptualization, methodology, and formal analysis of the manuscript. SN contributed to the literature search and data curation. AA contributed to the validation and interpretation of the data. TJ contributed to data collection and writing of the first draft of the manuscript. NM contributed to methodology and data acquisition. All authors participated in preparing, reviewing, and editing the manuscript.

Conflict of Interest Disclosures

None.

Ethical Approval

The study was approved by Institutional Ethical Committee of Shyam Shah Medical College and associated Sanjay Gandhi and Gandhi Memorial Hospital, Rewa, and was performed in accordance with the principles of the declaration of Helsinki. Written informed consent approved by IEC was obtained before the initiation of data collection.

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