Original Research

Factors Associated with the Development of Secondary Multidrug-resistant Tuberculosis

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Abstract

Background: Spread of multidrug-resistant tuberculosis (TB) is a threat to India's TB control program. We conducted this study with the objective to determine the risk factors for the development of secondary multidrug-resistant TB. **Methods:** We conducted an unmatched case–control study involving 247 multidrug-resistant TB patients as "cases" and 494 individuals who were declared as "cured" after category I DOTS treatment as "controls." Data were collected through face-to-face interviews and review of treatment records. Multivariable logistic regressions were used to analyze the collected data. **Results:** The mean duration for which cases took first-line anti-TB drug was 19.7 months. The mean duration between initial diagnosis of TB and diagnosis of multi-drug resistant TB (MDR-TB) was 28.3 months. In our study, 26.7%, 50.2%, and 23.1% of MDR-TB cases had one, two, or more previous episodes of TB before being diagnosed as MDR-TB. In multivariable analysis, low or no formal education (album-oriented rock [AOR] =1.63 [confidence interval (CI) = 1.03–3.11]), labor occupation (AOR = 2.15 [CI = 1.18–3.90]), smoking (AOR = 2.56 [CI = 1.19–3.26]), having HIV (AOR = 9.45 [CI = 6.80–15.9]), migration for job (AOR = 3.70 [CI = 1.96–5.67]), stopping TB treatment due to comorbid conditions (AOR = 8.86 [CI = 5.45–11.2]), and having type 2 diabetes (AOR = 3.4 [CI = 1.96–5.16]) were associated with MDR-TB. **Conclusions:** Government of India should devise strategy to prevent interruption of treatment to stop the emergence and spread of MDR-TB. We need to better integrate TB control activities with diabetes and tobacco control programs for better health outcome among patients.

Keywords: *India, multidrug resistance, risk factors, tuberculosis*

Introduction

Achievements of India's revised national tuberculosis (TB) control program (RNTCP) have been remarkable; it has succeeded in increasing case detection and cure rate, thus reducing the mortality due to TB.[1] The treatment for TB is lengthy, especially for category II DOTS patient, making adherence to treatment an inherent problem in ensuring cure.[2] Lack of adherence to standard treatment has accelerated the emergence of drug resistance in *Mycobacterium tuberculosis*.[3,4] Today, we have a complete spectrum of drug resistance pattern among *M. tuberculosis* ranging from monoresistance against rifampicin and isoniazid to totally drug-resistant *M. tuberculosis*.[5,6] However, the one form which is most widespread and possesses the greatest challenge to TB control program is the multidrug-resistant TB (MDR-TB). MDR-TB bacteria just like drug-sensitive form spread in all types of settings; in fact, it had spread from patients to health workers, caregivers, and family members.[5,7] Studies have found that similar to drug-sensitive form, MDR-TB causes both active and latent disease among contacts.[7,8] Thus, over time, it is theoretically possible that MDR-TB might become equally prevalent as drug-sensitive *M. tuberculosis*.[1]

Annual TB report for the year 2017 highlights the increasing caseload as well as interstate variations in the total burden of MDR-TB cases in India.[9] In India, during the year 2013, there were a total of 19,298 MDR-TB cases which increased to 33,280 cases by the year 2016.[9] In Madhya Pradesh, the number of MDR-TB cases increased from 588 in 2013 to 1794 by the year 2016.[9] These figures tell us why it is so urgent to devise a strategy to stop the emergence and spread of MDR-TB. MDR-TB is more difficult to control than its drug-sensitive counterpart because the diagnosis of MDR-TB is

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difficult, its treatment is both costlier and longer, and the drugs used in its treatment have severe adverse effect thus making adherence to treatment even more difficult.[6,8] To reduce the emergence of MDR-TB, we need to ensure 100.0% adherence to treatment among patients currently receiving treatment for non-MDR-TB. In addition, we need to identify at the earliest all possible patients who might be harboring MDR-TB bacilli and ensure they receive correct and complete treatment so as to reduce the spread of resistant bacilli among contacts.

The risk factors responsible for the development of MDR-TB are categorized as treatment-related (direct) factors and other (indirect) factors such as biological, social, economic, and health system related.[10-17] All these factors need to be mapped in detail so as to develop an effective counterstrategy against MDR-TB. Many studies have been conducted in different parts of world including South Asian countries to determine the risk factors of MDR-TB.[10-18] Since the social, cultural, programmatic, and economic factors differ from country to country, we carried out this study with the objective to determine the risk factor for the development of secondary multidrug-resistant TB.

Methods

This was a community-based unmatched case–control study. This study was conducted in three districts of Madhya Pradesh, a central Indian state. Patients suspected of having MDR-TB are first counseled by microscopy technician, and then, sputum sample is collected.[5] Collected sample is sent to a government-accredited laboratory to confirm the diagnosis of MDR-TB.[5] When the presence of MDR-TB is confirmed and exact drug resistance pattern is identified, a patient is started on prescribed treatment. Drug resistance coordinator (DRC) posted in each district counsels the MDR-TB patient in detail about the nature, duration, and possible adverse effect of drugs used in the treatment. As a part of therapy, an initial assessment of the patient is carried out, and details of this evaluation are kept in the form of a medical record. The total duration of the study was 15 months (September 2015 to November 2016). The period of recruitment of cases and control and data collection was 11 months (November 2015 to September 2016). Patients who were diagnosed as having as MDR-TB and enrolled with DRC in selected districts during the period of data collection were included in the study. An individual aged ≥18 years of any gender who have been diagnosed as having multidrug-resistant TB are considered as cases. Diagnosis of MDR-TB was confirmed by government-accredited laboratory following nationally prescribed guidelines.[5] Exclusion criteria are as follows: (i) patients who cannot be traced during the period of data collection, (ii) excessively sick patients who were unable to complete interview, and (iii) patients who did not give consent for the study. Sputum positive, drug-susceptible category I DOTS patients of the same gender as case who completed treatment and was declared as cured are considered as controls. Inclusion criteria are as follows: (i) patients who completed treatment within 6 months of the date of interview and (ii) those who gave valid consent for the study. All individuals who were diagnosed as MDR-TB and enrolled with DRC (in the selected districts) were included in the study. Two gender-matched controls were selected per case. The study employed nonprobability purposive sampling to select study participants. A list of all MDR TB patients along with their address and phone number was obtained from DRC (all registered MDR-TB patients had mobile/telephone). Initially, all participants (cases and controls) were approached by means of telephone. An "approach" was defined as "one phone call made on two different days of the week for two successive weeks." Those who cannot be contacted after this approach were termed as "untraceable" and thus excluded from the study. Participants who refused to meet for interview and who were out of the station (of the selected districts) during the phone conversation were also excluded. All those who responded to telephone call were explained the nature and purpose of the study; thereafter, a date for the face-to-face interview was fixed with the case. Oral informed consent was obtained from each study participants before the interview. A thumb impression was obtained from those who were unable to sign after reading out the consent form for them to understand. Controls were selected from the same microscopy center where a particular case was enrolled for initial treatment. Data were collected by means of a questionnaire. For designing the questionnaire, a systematic search for related studies was carried out using PubMed.[10-17] The final version of the questionnaire had the reliability of $\alpha = 0.93$. The questionnaire was translated from English to Hindi (native language) with the help of DRC. The study questionnaire had three components. The first part of questionnaire collected information related to the demographic, social, and economical background. The second part of questionnaire collected data related to medical history of cases and controls. The third part collected data related to the past history of TB treatment among cases. Alcohol consumption was defined as "yes" if the consumption was at least once a week. A participant was categorized as a smoker if he/she smoked on two separate days in 1 week. There were two sources of data. Part of information was collected from the treatment record available with the DRC and part of information by face-to-face interview with cases and controls. The face-to-face interview was conducted at the home of cases and controls. The study was approved by the ethical board for human research CMC, Bhopal. Confidentiality of data was maintained throughout the study. Filled questionnaires were checked for completeness of data before entering into SPSS version 20.0 (IBM Corp., 2012, New York) for analysis. Continuous variables such as age and per capita income were converted into categorical variables for analysis. Statistical significance of all independent variables

was initially evaluated using univariate logistic regression analyses. Those independent variables which were significant ($P \leq 0.05$) in univariate regression model were then included in the final multivariable logistic regression model. Adjusted odds ratio along with their confidence interval and P value were calculated. For analytical consideration, $P = 0.05$ or less was considered statistically significant.

Results

During the period of data collection, a total of 14 cases did not respond to telephone call (untraceable) and 19 cases were excluded for other reasons. The final analysis was done on 247 cases and 494 controls. Sociodemographic characteristics of cases and controls are presented in Table 1. Mean age of cases and controls was 37.6 and 42.3 years, respectively (not shown in Table 1). Table 2 details the clinical profile of cases and controls. Table 3 shows the data related to the past history of TB among MDR-TB patients (cases). The mean duration for which cases took first-line anti-TB drugs was 19.7 months and the mean duration between first initiation of anti-TB treatment and the diagnosis of MDR-TB was 28.3 months. Table 4 shows all the independent variables which were found to be statistically significant ($P \leq 0.05$) in the multivariable regression model.

Table 1: Distribution of sociodemographic characteristics among cases and controls

Sociodemographic variable	Cases (*n*=247), *n* (%)	Control (*n*=494), *n* (%)
Gender		
Male	147 (59.5)	300 (60.7)
Female	96 (38.9)	194 (39.3)
Other	4 (1.6)	-
Age (years)		
<30	38 (15.4)	164 (33.2)
30-≤50	149 (60.3)	194 (39.3)
>50	60 (24.3)	136 (27.5)
Formal education		
None	48 (19.5)	58 (11.7)
Up to primary	93 (37.7)	112 (22.6)
Up to 12th standard	77 (31.1)	220 (44.6)
College or higher	29 (11.7)	104 (21.1)
Occupation status		
Student/part time job	58 (23.5)	119 (24.1)
Service/business	23 (9.3)	54 (10.9)
Labor	109 (44.1)	94 (19.0)
Agriculture	31 (12.6)	168 (34.0)
Homemaker	26 (10.5)	59 (12.0)
Number of family member		
<4	66 (26.7)	139 (28.1)
4-6	133 (53.8)	292 (59.1)
>6	48 (19.4)	63 (12.6)
Type of family		
Nuclear	104 (42.1)	219 (44.3)
Joint	143 (57.9)	275 (55.7)
Person per room		
2 or less	54 (21.8)	131 (26.5)
3-4	119 (48.2)	239 (48.4)
>4	74 (30.0)	124 (25.1)
Number of children (<10 years) living in same house		
<2	39 (15.8)	71 (14.4)
2-4	146 (59.1)	314 (63.6)
>4	62 (25.1)	109 (22.1)
Per capita income per month		
<2000	82 (33.2)	92 (18.6)
2000-4000	124 (50.2)	259 (52.4)
>4000	41 (16.6)	143 (29.0)
Marital status		
Married	189 (76.5)	382 (77.3)
Unmarried	31 (12.6)	100 (20.3)
Separated/divorced/ widowed	27 (10.9)	12 (2.4)

Discussion

Globally, as well as in India, secondary MDR-TB is much more common than acquiring primary resistance from an infected person.[19] In our study, 26.7%, 50.2%, and 23.1% of MDR-TB cases had one, two, or more previous episodes of TB before being diagnosed as MDR-TB. A study conducted in China reported that having a history of 3 or more previous episodes of TB treatment increased the odds of developing MDR-TB by 83.0%.[16] Another study conducted in Pakistan by Ahmad *et al*. found that 90% of the cases in comparison to 73% of the controls reportedly had a history of prior TB treatment.[18] Of the total 247 MDR-TB cases included in the study, 73.3% had a history of category II DOTS treatment. Similar to our observation, Flora *et al*. reported that 87.5% of all MDR-TB cases had a history of category II DOTS treatment.[13] Of the total 247 cases included in the study, 18.6% of patients were declared cured and 45.4% defaulted during their last episode of TB treatment. Similarly, Ahmad *et al*. noted that among those who had a history of prior TB treatment, 42% of the cases and 9% of the controls defaulted from TB treatment in the past.[18]

In our study, belonging to middle age group (between 30 and 50 years of age) increased the odds for developing MDR-TB by 41.0%; similar findings were reported by other studies conducted in Bangladesh, Hong-Kong, and Ethiopia.[11,12,17] Although the exact "range of age" varied in these studies, a common thread was that patient aged between 30 and 65 years had higher odds of developing MDR-TB. A middle-aged person is more mobile, more likely to migrate, and is more active as compared to both younger and older patients.

We noted that "labor" occupation was associated with higher odds of developing MDR-TB as compared to other

Table 2: Distribution of cases and controls on the basis on clinical characteristics

Clinical parameter	Cases (*n*=247), *n* (%)	Control (*n*=494), *n* (%)
HIV status		
Positive	29 (11.7)	3 (0.6)
Negative	190 (76.9)	302 (61.1)
Not determined	28 (11.3)	189 (38.3)
Diabetes		
Yes	64 (25.9)	24 (4.9)
No	183 (74.1)	470 (95.1)
BMI		
Low	102 (41.3)	97 (19.6)
Normal	87 (35.2)	280 (56.7)
Overweight and obese	58 (23.5)	117 (23.7)
Smoking		
Yes	86 (34.8)	92 (18.6)
No	161 (65.1)	402 (81.4)
Chewing tobacco		
Yes	133 (53.8)	291 (58.9)
No	114 (46.2)	203 (41.1)
Alcohol consumption		
Yes	94 (38.1)	113 (22.9)
No	153 (61.9)	381 (77.1)
Other substance(s) abuse		
Yes	38 (15.4)	26 (5.3)
No	209 (84.6)	468 (94.7)
Close### contact with TB case		
Yes	102 (41.3)	188 (38.1)
No	145 (58.7)	306 (61.9)
Close### contact with TB defaulter		
Yes	63 (25.5)	13 (2.6)
No	184 (74.5)	481 (97.4)
Migrated during TB treatment		
Yes	71 (28.7)	23 (4.7)
No	176 (71.3)	471 (95.3)
Have suffered from other diseases during TB treatment^		
Yes	93 (37.7)	59 (11.9)
No	154 (62.3)	435 (88.1)
Ever stopped TB treatment due to other diseases		
Yes	63 (25.5)	12 (2.4)
No	184 (74.5)	482 (97.6)
Ever taken treatment for symptoms of TB from Ayush physician		
Yes	94 (38.1)	38 (7.7)
No	153 (61.9)	456 (92.3)
Ever stopped treatment due to drug's side effect		
Yes	98 (39.7)	53 (10.7)
No	149 (60.3)	441 (89.3)

###Close - either coworker, family member, or neighbor. ^- both infectious and non-infectious diseases. TB=Tuberculosis, BMI=Body mass index

occupations. In our study, migration during the earlier treatment episode(s) was associated with higher odds of developing MDR-TB. Rifat *et al*. in their study noted that "transport workers" had higher odds of acquiring MDR-TB.[11] Occupation such as migrant labor, transport workers (especially truck drivers), and nomads involve continuous migration causing frequent interruptions in treatment, thus paving way for development of drug resistance among *M. tuberculosis* bacilli. We noted that patients with "low to nil" educational qualification had higher odds (63.0%) of developing MDR-TB as compared to patients with higher education. Similar to our study, Zhang *et al*. noted that lower educational qualification was associated with 87.0% higher odds of developing TB.[16] Very similar to our finding, Ahmad *et al*. also noted that having low or no formal education increased the odds of MDR-TB.[18] However, Rifat *et al*. observed that patients with some educational qualification were more likely to develop MDR-TB than patients with either no formal education or higher education.[11] It is quite possible that patient with no or less education might not know the importance of adhering to treatment thus may prematurely stop treatment either when the symptoms disappear or when side effects appear thus facilitating the development of MDR-TB.

India along with many other developing countries is at the midriff of an epidemiological transition. With each passing year, the prevalence of diabetes is increasing in India, and very soon, India will be crowned as the diabetes capital of the world.[20] Type 2 diabetes is a known risk factor for TB and is even linked to the development of MDR-TB in some studies.[21] In our study, we observed that diabetes increased the odds of developing MDR-TB by more than three times. Similarly, Rifat *et al*. observed that patients with diabetes had more than two times higher odds of developing MDR-TB.[11] Because of continuously increasing the prevalence of both diabetes and MDR-TB in India, a collaborative framework of action is needed to jointly address this dual burden of morbidity.[22] In addition, we observed that patient who suffered from other comorbid conditions during their previous episode of TB treatment had more than eight times higher odds of developing MDR-TB. We also noted that both cases and controls with other comorbid conditions frequently interrupted the

Table 3: Distribution of cases based on past history of tuberculosis (*n*=247)

Treatment variable	*n* (%)
Number of previous episode(s) TB	
1	66 (26.7)
2	124 (50.2)
3 or more	57 (23.1)
Ever received category II DOTS treatment	
Yes	181 (73.3)
No	66 (26.7)
Type of enrollment in category II DOTS^^^	
Relapse	49 (27.1)
Default	98 (54.1)
Failure	34 (18.8)
Total duration for which TB drugs were taken (months)$	
<6	51 (20.6)
6-12	78 (31.6)
12-18	92 (37.3)
>18	26 (10.5)
Outcome of last TB treatment episode	
Cured	46 (18.6)
Failure	89 (36.0)
Default	112 (45.4)
Time between diagnosis of MDR-TB and first episode of TB (months)	
<12	32 (13.0)
12-18	49 (19.8)
19-24	72 (29.1)
>24	94 (38.1)

^^^For the last episode of TB treatment, $For all episodes of TB combined. TB=Tuberculosis, MDR=Multidrug resistant, DOTS= Directly Observed Treatment Short-course

Table 4: Multivariable analysis on factors related to multidrug-resistant tuberculosis

Variable	Adjusted OR	CI	*P*
Age group			
30-≤50	1.41	1.01-1.92	0.04
<30->50	1.00		
Educational status			
Low (no education + primary schools)	1.63	1.03-3.11	0.01
High (12th standard and college)	1.00		
Occupation			
Labor	2.15	1.18-3.90	0.01
Other	1		
HIV status			
Positive	9.45	6.8-15.9	0.008
Negative	1		
History of close### contact with TB defaulter			
Yes	7.51	5.14-9.10	0.01
No	1		
Smoking status			
Yes	2.56	1.19-3.26	0.039
No	1		
Type 2 diabetes mellitus			
Yes	3.40	1.96-5.16	0.03
No	1		
Alcohol intake			
Yes	1.94	1.10-2.89	0.041
No	1.00		
Other substances abuse			
Yes	2.10	1.16-3.90	0.03
No	1.00		
Migration for job			
Yes	3.70	1.96-5.67	0.004
No	1.00		
Taking treatment from Ayush for symptoms of TB			
Yes	4.19	2.89-8.78	0.01
No	1		
Per capita income			
<2000	1.82	1.21-2.59	0.041
≥2000	1		
Ever stopped TB treatment due to other diseases			
Yes	8.86	5.45-11.2	<0.001
No	1		
Marital status			
Separated/divorced/widowed	1.68	1.29-2.09	0.021
Married + unmarried	1		

Only the significant variables in multivariable model are shown in the table. ###Close - either coworker, family member, or neighbor. CI=Confidence interval at 95% level, TB=Tuberculosis, OR=Odds ratio

treatment. It must be further investigated that for how long and for which all comorbid condition(s), a patient currently on DOTS therapy interrupts treatment.

In our study, we observed that patients who are smoking tobacco, consuming alcohol, and abusing other substances had higher odds of developing MDR-TB. Smoking is one of the main determinants for TB, and some studies suggest that smoking might even contribute to the development of drug resistance.[23] Given the huge number of tobacco consumer in India, we suggest that tobacco control efforts should be aligned with TB control program in a better way so as to reduce the consumption of tobacco in any form.[24] Contrary to our findings, studies conducted in Bangladesh and China did not find any significant association between alcohol consumption and development of MDR-TB.[11,16] This may be due to the difference in the amount, frequency, type of alcohol consumed, and definition of "alcoholism" adopted in these studies. In light of contradicting evidence, this issue needs further research. We observed that "contact" with a case of TB was not associated with the development of MDR-TB. Similar to our study, Rifat *et al*. did not observe any association between contact with TB patient and development of MDR-TB.[11] However, contrary to our findings, Ahmad *et al*. noted that MDR-TB cases were more

likely to have a TB patient in their home.[18] This difference can be possibly attributed to the fact that we considered all close family members, neighbor, and coworkers whereas Ahmad *et al*. only considered household contacts.[18]

In our study, "divorced/separated/widowed" patient had higher odds of developing MDR-TB as compared to the married or unmarried patient. Study conducted in Ethiopia also found that "unmarried/single" patient has higher odds of developing MDR-TB.[17] Divorced/separated/widowed persons are more likely to be depressed, lack social support, or get involved in unhealthy lifestyle such as consuming alcohol, making it difficult for them to adhere to treatment thus increasing their odds of developing MDR-TB. Income levels strongly influence the health behavior of an individual. We noted that patient who belonged to lowest per capita income group (INR <2000) had higher odds of developing MDR-TB. In contrast, the study conducted in Bangladesh did not find any association between income level and MDR-TB.[11] Poverty might hinder as well as delay seeking the correct treatment and adhering to it. In our study, we did not observe any significant association between degree of household overcrowding, body mass index, tobacco chewing, or any other household characteristics with the development of MDR-TB.

Conclusions

As a last note, we would like to stress on the fact that the current epidemic of multidrug-resistant TB in India is a system-made public health problem. The treatment for MDR-TB is longer, costlier, and more difficult to complete due to severe side effects associated with second-line drugs. We must remember that mishandling of current epidemic of MDR-TB will provide momentum for the materialization of even more severely resistant form(s) of TB which will be insuperable to control.[25,26] In the year 2016 itself, a total of 2456 cases of extensive drug-resistant TB have already been identified across India.[9] It is just a matter of time and some more mismanagement on our part, and very soon, this number will increase to 20,000.

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Conflicts of interest

There are no conflicts of interest.

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