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Factors related to previous tuberculosis treatment of patients with multidrug-resistant tuberculosis in Bangladesh

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ABSTRACT

Objective: Previous tuberculosis (TB) treatment status is an established risk factor for multidrug-resistant TB (MDR-TB). This study explores which factors related to previous TB treatment may lead to the development of multidrug resistant in Bangladesh.

Design: We previously conducted a large case–control study to identify risk factors for developing MDR-TB in Bangladesh. Patients who had a history of previous TB treatment, either MDR-TB or non-MDR-TB, were interviewed about their previous treatment episode. This study restricts analysis to the strata of patients who have been previously treated for TB. Information was collected through face-to-face interviews and record reviews. Unadjusted and multivariable logistic regression was used for data analysis.

Setting: Central-level, district-level and subdistrict-level hospitals in rural and urban Bangladesh.

Results: The strata of previously treated patients include a total of 293 patients (245 current MDR-TB; 48 non-MDR-TB). Overall, 54% of patients received previous TB treatment more than once, and all of these patients were multidrug resistant. Patients with MDR-TB were more likely to have experienced the following factors: incomplete treatment (OR 4.3; 95% CI 1.7 to 10.6), adverse reactions due to TB treatment (OR 8.2; 95% CI 3.2 to 20.7), hospitalisation for symptoms associated with TB (OR 16.9; CI 1.8 to 156.2), DOTS (directly observed treatment, short-course) centre as treatment unit (OR 6.4; CI 1.8 to 22.8), supervised treatment (OR 3.8; CI 1.6 to 9.5); time-to-treatment centre (OR 0.984; CI 0.974 to 0.993).

Conclusions: Incomplete treatment, hospitalisation for TB treatment and adverse reaction are the factors related to previous TB treatment of patients with MDR-TB. Although the presence of supervised treatment (DOT), less time-to-treatment centres and being treated in DOTS centres were relatively higher among the patients with MDR-TB compared with patients without MDR-TB, these findings include information of their most recent TB treatment episode only. Most (64.5%) of the patients with MDR-TB had received TB treatment more than once.

Strengths and limitations of this study

- Previous tuberculosis (TB) treatment is an important risk factor for patients with multidrug-resistant TB (MDR-TB). Information regarding the previous TB treatment of MDR-TB is not available in Bangladesh.
- Strata of previously treated patients have been taken from a previously conducted large case–control study with adequate sample size and power.
- Information regarding the recent episode of the previous TB treatment were collected to minimise the recall bias. A majority of the patients with MDR-TB were treated more than once but we do not have information on other treatment episodes.

INTRODUCTION

Global tuberculosis (TB) control efforts are facing the additional challenge of multidrug-resistant TB (MDR-TB).[1] MDR-TB is caused by bacteria that are resistant to at least isoniazid and rifampicin, the most effective anti-TB drugs for treating TB.[2] MDR-TB cannot be treated with first-line anti-TB medicines and needs a longer treatment period with stronger second-line medicines.[3] A total of 0.14 million cases of drug-resistant TB were reported worldwide in 2013; however, the estimate for MDR-TB incidence is at least five times higher than the reported cases.[4] The number of reported MDR-TB cases has been increasing in recent years.[4] Globally, 20.5% (13.6–27.5%) of previously treated cases and 3.5% (2.2–4.7%) of new cases are estimated to have MDR-TB.[4] Previous TB treatment is a known risk factor for MDR-TB.[5–11] Patients with previous TB treatment are difficult to manage and might be infectious for a longer period of time. 'Previous treatment' may mean a relapse after a successful treatment, a return after treatment discontinuation, a treatment

failure, or any other types (other types include patients with an unknown previous history; with unknown outcome of that previous treatment; and/or who have returned to treatment with smear-negative pulmonary TB or bacteriologically negative extrapulmonary TB).[12] Previously treated recurrent TB is no longer a neglected area; rather, it is considered to be an important factor for TB control.[13 14] Programmatic factors such as poor management of the patient, lack of directly observed treatment, limited or interrupted drug supplies, poor drug quality, widespread availability of anti-TB drugs without prescription, lack of uniformity between the public and private health sectors regarding the treatment regimens, and poorly managed and supported National TB Control Programmes (NTPs) were cited to be the factors related to development of drug resistance.[15 16]

The WHO has identified 27 high burden countries for MDR-TB. Four of these countries, including Bangladesh, belong to the South-East Asian region.[17] In Bangladesh, MDR-TB is an emerging public health problem.[18] According to the recent drug-resistant survey (DRS), 1.4% of new cases and 29% of the retreatment cases in Bangladesh have MDR-TB.[19] Although the rate of MDR-TB is still relatively low, owing to the overall high TB burden in Bangladesh the absolute number of MDR-TB cases was quite large, with 2100 among the new patients with TB and 2600 among the previously treated patients with TB, in 2013.[4] Recent studies in Bangladesh suggest that previous TB treatment is an important risk factor for MDR-TB.[19 20] Retreatment patients constitute approximately 3% of all patients with TB in the national data collection which corresponded to 6385 patients in 2013.[4] However, the detailed information regarding the previous TB treatment has not yet been collected. Factors related to previous management of TB need to be identified to develop control strategies. The main objective of this study is to explore the factors related to the previous TB treatment of patients with current MDR-TB compared with TB patients without MDR-TB in Bangladesh.

METHODS

We previously conducted a case–control study to identify the risk factors of MDR-TB in Bangladesh.[21] The study included 250 patients with MDR-TB and 750 TB patients without MDR-TB, and the sample size demonstrated sufficient power (80%) to detect at least a 10% difference in the prevalence of any of the exposure variables at the 5% significance threshold.[21] We found that 293 patients (29.3%) (245 MDR-TB and 48 non-MDR-TB) had previously received treatment for TB. All patients with a history of previous TB treatment were interviewed about parameters related to their treatment history. This study restricts analysis to the strata of patients who had previously received treatment for TB.

The setting, definition, and the inclusion and exclusion criteria of the study have been previously described in detail.[21] The setting was central-level, district-level and subdistrict-level hospitals in rural and urban Bangladesh. Patients with MDR-TB aged between 18 and 65 years who gave their informed consent were included in the study. History of TB treatment and number of episodes of previous TB treatment were based on the patient's statement. Patients, who received treatment for MDR-TB following the diagnostic criteria of the NTP guidelines, were classified as MDR-TB. The NTP has adopted automated real-time PCR (Xpert MTB/RIF) as the diagnostic tool of patients with MDR-TB. Culture and drug-sensitivity testing (DST) and line probe assays were also used.[22] Xpert MTB/RIF diagnoses only rifampicin resistance. Patients who are resistant to rifampicin are generally also resistant to isoniazid (another first-line drug). Monoresistance to rifampicin is fairly uncommon (0.2% and 0.4% among new and previously treated patients, respectively), as shown by a recent DRS conducted in Bangladesh.[19] Patients with drug-susceptible TB aged 18–65 years, who gave their informed consent, were diagnosed through sputum smear microscopy or other investigations (X-ray, fine-needle aspiration cytology or biopsy) as per NTP guidelines and expected to respond to the standard combination of drugs. In this paper, we will refer to those as non-MDR-TB patients. We excluded patients who were not within the eligible age group or had any serious illness requiring admission to the intensive care unit, recent surgery or any medical emergency that needed continuous observation.

As the patients might have had more than one previous treatment episode, we collected detailed information based on their most recent episode, to aid the accuracy of the recalled information. According to the national TB guidelines, the recommended duration of TB treatment is 6 and 8 months for new and retreatment types of drug-sensitive patients, respectively.[23]

The presence or absence of incomplete treatment during the previous TB treatment was based on the patient's statement, which refers to any discontinuation of treatment during the latest episode of previous TB treatment. Treatment discontinuation due to treatment failure is also included under 'incomplete treatment'.

Data collection

TB patients with and without MDR-TB were identified as part of a previously conducted case–control study on risk factors of MDR-TB.[21] Patients with MDR-TB from all over Bangladesh are referred to one of the three government hospitals, the national hospital in Dhaka or a regional hospital in either Chittagong or Rajshahi. All eligible patients with MDR-TB who were admitted from September 2012 to mid-April 2013 were recruited from these hospitals under the previously conducted study. The hospitals that were providing MDR-TB treatment were receiving patients referred by the various treatment units from rural and urban Bangladesh. Each patient

with TB is assigned a unique TB registration number as a routine practice. Treatment registration numbers of patients with TB, who were diagnosed during the specified period that is, during the same month that MDR-TB was diagnosed, were listed. Three patients without MDR-TB per patient with MDR-TB, from the local TB treatment unit from where the case was referred, were recruited under the previous study.

All patients who had a history of previous TB treatment were subsequently interviewed about parameters related to their previous treatment; these findings are reported in this study. Site of previous treatment, treatment regimen and treatment outcome-related information were collected from the patient record review.

Trained investigators collected information from the study participants by face-to-face interview using a pretested questionnaire and by review of records. All the investigators received training on data collection procedures for one week. Diagnosis of TB through microscopy is under an external quality assessment (EQA) network at country level. The NTP has its inbuilt quality control mechanism for diagnosis of patients with MDR-TB through a laboratory based in Antwerp, Belgium.

Statistical analysis

We compared participant characteristics between patients with (245) and without MDR-TB (48) using Student t-tests for continuous measures, and χ^2 tests for categorical measures. Unadjusted and multivariable logistic regression models were used to estimate ORs (and 95% CIs) for MDR-TB status with the following variables: site of previous TB, adverse reaction due to TB treatment, hospitalisation due to TB, type of centre for treatment initiation and follow-up, presence of supervised treatment (directly observed treatment, DOT), time-to-treatment centre, incomplete treatment. We initially included all variables in the adjusted model, but later excluded variables that had insufficient frequencies or may have collinear relationships with the variables included in the model. The excluded variables from the multivariable model were: treatment regimen, treatment outcome, treatment extension, type of provider, and cost-to-treatment and distance-to-treatment centres. Cost-to-treatment and distance-to-treatment centres were excluded from the model for possible collinearity with the variable 'time-to-treatment centre'.

We assessed statistical significance of ORs using the likelihood ratio tests, and we had sufficient patients to include the variables in the multivariable model without risk of overfitting. The ORs derived from these models correspond to effects specific to the strata of patients who have been previously treated for TB. Data analysis was carried out using Stata statistical software V.12 (StataCorp LP).

Ethics considerations

An information sheet describing the purpose of the study and the individuals' rights as study participants was handed to the participants to read. For individuals with inadequate literacy, the information sheet was read out by the interviewers. All participants consented by signing the consent form or, if unable to do so, by adding their thumb impression. All patients had been treated through the NTP, Bangladesh.

RESULTS

Among the previously treated patients with MDR-TB, 64.5% had been treated more than once and all patients without MDR-TB had only one episode of treatment previously. The mean age of previously treated patients with MDR-TB was lower than that of patients without MDR-TB. The majority of patients were male and had pulmonary TB. Detailed demographic and clinical characteristics are presented in table 1.

For some patients, it was not possible to get information regarding the previous treatment outcome (19%), treatment extension (9%) and previous treatment regimen (11%) from the records. Among the patients with MDR-TB, 63.7% received a retreatment regimen commonly known as category 2, consisting of five drugs including injectable streptomycin. On the basis of the available records, all non-MDR-TB patients were treated with the regimen for new patients with TB that consists of a combination of four oral drugs. The most frequent category for duration of previous treatment was 5 months (59.6%). The majority (64.6%) of patients with drug-sensitive TB discontinued their treatment at 3 months or less. Treatment failure was higher among the patients with MDR-TB compared with patients without MDR-TB (68.4% and 28.6%, respectively) during their previous treatment. Of the patients with MDR-TB, 32.6% reported having an extended treatment period since their sputum remained positive after the intended period of treatment. This treatment extension was only reported by 5.4% of the patients without MDR-TB. Hospitalisation for TB-related problems during their previous TB treatment mostly occurred for patients with MDR-TB (13.5%). The three main causes of hospitalisation during previous TB treatment were massive haemoptysis (33.3%), severe weakness (33.3%) and pleural effusion (15.2%) (these results are not shown in table).

Patients were asked if they had stopped their treatment at any point of their previous TB treatment, and in this paper we refer to it as incomplete treatment. Incomplete treatment during previous TB treatment was reported by 63.3% and 29.2% of patients with and without MDR-TB, respectively, as stated by the patients. Reasons for incomplete treatment among the patients with and without MDR-TB are presented in table 2.

Patients who do not complete their treatment are supposed to be followed up by one of their healthcare providers, according to the national TB guideline.[23] A high proportion (91.6%) of patients with MDR-TB reported that they had been followed up during

Table 1 Demographic and clinical characteristics of previously treated patients with TB

Variable	Non-MDR-TB (n=48)	MDR-TB (n=245)	Total	p Value
Age				0.0001*
Mean	41	33.8	35	
SD	15.8	12.3	13.2	
Age group (years)				0.002†
18–25	11 (22.9%)	79 (32.2%)	90 (30.7%)	
26–45	17 (35.4%)	121 (49.4%)	138 (47.1%)	
>45	20 (41.7%)	45 (18.4%)	65 (22.2%)	
Sex				0.027†
Male	28 (58.3%)	163 (66.5%)	191 (65.2%)	
Female	20 (41.7%)	82 (33.5%)	102 (34.8%)	
Site of previous TB				<0.0001†
Extrapulmonary	7 (14.6%)	5 (2.0%)	12 (4.1%)	
Pulmonary	41 (85.4%)	240 (98.0%)	281 (95.9%)	
Treatment regimen‡				<0.0001†
Category 1	16 (100%)	86 (35.1%)	102 (39.0%)	
Category 2	0 (0%)	156 (63.7%)	156 (59.8%)	
MDR-NTP	0 (0%)	2 (0.8%)	2 (0.8%)	
Non-standardised	0 (0%)	1 (0.4%)	1 (0.0%)	
Duration of treatment (months)				<0.0001†
6–8	3 (6.3%)	15 (6.1%)	18 (6.1%)	
4–5	14 (29.1%)	146 (59.6%)	160 (54.6%)	
3 or less	31 (64.6%)	84 (34.3%)	115 (39.3%)	
Treatment outcome‡				0.001†
Cured	6 (42.8%)	20 (9.2%)	26 (11.2%)	
Completed	4 (28.6%)	43 (19.7%)	47 (20.3%)	
Default	0 (0%)	6 (2.8%)	6 (2.6%)	
Failure	4 (28.6%)	149 (68.3%)	153 (65.9%)	
Adverse reaction				<0.0001†
Absent	34 (70.8%)	57 (23.3%)	91 (31.1%)	
Present	14 (29.2%)	188 (76.7%)	202 (68.9%)	
Treatment extension‡				0.001†
Absent	35 (94.6%)	155 (67.4%)	190 (71.2%)	
Present	2 (5.4%)	75 (32.6%)	77 (28.8%)	
Hospitalisation due to TB				0.069†
Absent	46 (95.8%)	212 (86.5%)	258 (88.1%)	
Present	2 (4.2%)	33 (13.5%)	35 (11.9%)	

*Probability of Student t-test.
†Probability of χ^2 test.
‡Treatment regimen, treatment outcome and treatment extension had a total of 261, 231 and 267 observations, respectively.
MDR-TB, multidrug-resistant tuberculosis; NTP, National TB Control Programme.

previous TB treatment, although follow-up was quite low (14.3%) among patients without MDR-TB.

Patients with current MDR-TB had been treated for their previous TB mostly in designated centres for TB (DOTS (directly observed treatment strategy, short-course) centre) (95.9%); for patients without MDR-TB, the proportion was 70.8%. Rate of treatment in private centres was 4.1% and 29.2% for patients with MDR-TB and non-MDR-TB, respectively. Although the majority of patients with MDR-TB were treated in DOTS centres, supervised intake of medicine by DOT during their previous treatment was reported by 78.4% of patients with MDR-TB and 41.7% of patients without MDR-TB, respectively, as reported by the patients.

We further explored who had supervised the medicine intake and found that 70.3% of patients with MDR-TB and 80% of patients without MDR-TB were given their medicine by trained providers (community health volunteers, health workers at the facility or field level, village doctors). The rest of the patients were given their medicine by a family member, neighbours or other providers.

The median travel time to visit the previous treatment centre, which was the designated unit for treatment initiation and follow-up, was 20 min for patients with MDR-TB and 40min for patients without MDR-TB.

Details of health system factors are presented in table 3.

Logistic regression analysis

In the multivariable adjusted analysis, patients with MDR-TB were shown to be more likely to be male (OR 5.1; CI 1.8 to 14), have a history of incomplete TB

Table 2 Incomplete treatment and the reasons reported by previously treated patients with tuberculosis

Variable	Non-MDR-TB (n=48) n (%)	MDR-TB (n=245) n (%)	p Value
Treatment completion			<0.0001*
Completed treatment	34 (70.8)	90 (36.7)	
Incomplete treatment	14 (29.2)	155 (63.3)	
Reasons for incomplete treatment			
Felt better	7 (50.0)	7 (4.5)	
Remained positive in microscopy test	1 (7.1)	143 (92.3)	
Change of address	4 (28.7)	0 (0)	
Expense of treatment	1 (7.1)	1 (0.6)	
Adverse effect	0 (0)	2 (1.3)	
Lack of family support	1 (7.1)	0 (0)	
Others	0 (0)	2 (1.3)	

*Probability of χ^2 test.
MDR-TB, multidrug-resistant tuberculosis.

treatment (OR 4.3; 95% CI 1.7 to 10.6), adverse reactions due to anti-TB medicines (OR 8.2; 95% CI 3.2 to 20.7), hospitalisation due to TB (OR 16.9; CI 1.8 to 156.2), have been treated in a designated DOTS centre (OR 6.4; CI 1.8 to 22.8) and time-to-treatment centre (OR 0.984; CI 0.974 to 0.993).

Table 3 Health system-related characteristics of previously treated patients with tuberculosis

Variable	Non-MDR-TB n=48	MDR-TB n=245	Total	p Value
Supervised treatment (DOT)				<0.0001*
Unsupervised treatment	28 (58.3%)	53 (21.6%)	81 (27.6%)	
Supervised treatment	20 (41.7%)	192 (78.4%)	212 (72.4%)	
Type of DOT provider				0.36*
Trained provider†	16 (80%)	135 (70.3%)	151 (71.2%)	
Family/other provider‡	4 (20%)	57 (29.7%)	61 (28.8%)	
Type of treatment unit				<0.0001*
Private centre	14 (29.2%)	10 (4.1%)	24 (8.2%)	
Designated DOTS centre	34 (70.8%)	235 (95.9%)	269 (91.8%)	
Follow-up by the providers after incomplete treatment				<0.0001*
No follow-up	12 (85.7%)	13 (8.4%)	25 (14.8%)	
Follow-up done	2 (14.3%)	142 (91.6%)	144 (85.2%)	
Time-to-treatment centre (min)				0.0005§
Mean	49.8	29.7	32.9	
Median	40	20	30	
SD	34.7	35.5	36.1	
Range	5–150	1–420	1–420	
Cost-to-treatment centre (BDT)				0.46§
Mean	27.3	22.9	23.6	
Median	20	15	20	
SD	22	38.3	36.1	
Range	0–100	0–500	0–500	
Distance-to-treatment centre (miles)				0.91§
Mean	4.6	4.3	4.3	
Median	3	2	2	
SD	4	16.1	14.9	
Range	0.2–15	0–175	0–175	

US$1 is 77 BDT approximately.
Time-to-treatment, cost-to-treatment and distance-to-treatment centres had a total of 286, 283 and 285 observations, respectively.
*Probability of χ^2 test.
†Trained providers include providers trained on supervision on medicine intake (DOT) such as community health volunteers, health workers at facility and field level and village doctors.
‡'Family and other providers' include family members, neighbours and other volunteers supervising the treatment.
§Probability of Student t-test.
BDT, Bangladesh taka; DOT, directly observed treatment; DOTS, DOT, short-course; MDR-TB, multidrug-resistant tuberculosis.

Directly observed treatment (OR 3.8; 95% CI 1.6 to 9.5) was high among patients with MDR-TB during their previous TB treatment compared to patients without MDR-TB. Site of previous TB (pulmonary or extrapulmonary) was no longer associated in the adjusted model. Findings of the logistic regression are shown in table 4.

DISCUSSION

Patients with MDR-TB were found to be four times more likely to have a history of incomplete TB treatment than patients without MDR-TB. Incomplete treatment refers to discontinuation at any phase of the previous treatment reported by patients. This finding has been supported by many studies.[5 10 24–26] The majority of patients with MDR-TB (92.3%) stated that the reason for incomplete treatment was that they remained positive to TB bacteria in the microscopy test and had stopped their previous treatment to initiate diagnosis and treatment for MDR-TB. Remaining positive for TB bacteria is an indication of treatment failure and thus 'incomplete treatment' in this study also includes treatment failure. This finding reflects the implementation of national guidelines that recommend that the patients who do not respond to the retreatment regimen should be referred for diagnosis of MDR-TB.[22] However, half of the patients without MDR-TB did not complete their treatment as they felt better after starting the treatment. The next cause after 'feeling better' for treatment discontinuation reported by patients without MDR-TB was change of their address. Although the NTP has a system in place to provide service to the patients transferred from one place to another, these figures show that patient education regarding discontinuation of treatment needs to be further strengthened through advocacy communication and social mobilisation activities.[23] Although the patients with MDR-TB reported that non-responsive previous treatment was the main cause of their incomplete treatment, these findings are based on their most recent episode of previous treatment and most of the patients with MDR-TB had more than one episode of earlier TB treatment. The TB control programmes should address the reasons for incomplete treatment for all types of patients with TB. Incomplete treatment may lead to development of drug resistance at any point of time irrespective of the number of treatment episodes.

Patients with MDR-TB were more likely to have adverse reactions to anti-TB medication during their previous TB treatment. Association of MDR-TB with adverse reaction during their previous TB treatment was found in another study and this association was

Table 4 Univariate and multivariable analyses on multidrug-resistant TB status and previous treatment-related factors

	Univariate analysis			Multivariable analysis		
Variable	**OR**	**95% CI**	**p Value***	**OR**	**95% CI**	**p Value***
Age (years)						
18–25	1			1		
26–45	0.99	0.44 to 2.23	0.983	1.3	0.45 to 3.9	0.613
>45	0.31	0.14 to 0.71	0.006	0.33	0.10 to 1.12	0.075
Sex						
Female	1			1		
Male	1.4	2.5 to 6.7	0.277	5.1	1.8 to 14	0.002
Site of previous TB						
Extrapulmonary	1			1		
Pulmonary	8.2	2.5 to 27.1	0.001	2.6	0.52 to 13.1	0.244
Adverse effect						
Absent	1			1		
Present	8	4.0 to 16.0	<0.0001	8.2	3.2 to 20.7	<0.0001
Hospitalisation due to TB						
Absent	1			1		
Present	3.6	0.8 to 15.5	0.087	16.9	1.8 to 156.2	0.013
Supervised treatment (DOT)						
Absent	1			1		
Present	5.1	2.6 to 9.7	<0.0001	3.8	1.6 to 9.5	0.004
Type of treatment unit						
Private	1			1		
DOTS centre	9.7	4.0 to 23.5	<0.0001	6.4	1.8 to 22.8	0.004
Treatment completion						
Completed treatment	1			1		
Incomplete treatment	4.2	2.1 to 8.2	<0.0001	4.3	1.7 to 10.6	0.002
Time-to-treatment centre (min)	0.988	0.979 to 0.997	0.007	0.984	0.974 to 0.993	0.001

*Wald test statistic.
DOT, directly observed treatment; DOTS, directly observed treatment strategy; DOT, short-course; TB, tuberculosis.

explained as the use of second-line drugs during their previous TB treatment, and these are commonly more toxic than first-line anti-TB drugs.[27] In our study, we found that most of the patients with MDR-TB were previously treated with retreatment regimens that did not include any of the second-line drugs commonly used for MDR-TB treatment. The retreatment regimen included injectable streptomycin additional to the medicines used for new patients. Additionally, adverse reaction as a cause of incomplete treatment was reported by only 1.3% of patients with MDR-TB. However, the patients with adverse reactions to anti-TB medicine can be treated with special care. Patient education at the beginning of treatment can be strengthened by advice on adverse reactions.

Hospitalisation for more than 14 days associated with MDR-TB and extensively drug-resistant TB (XDR-TB) was found in one study.[28] In our previous study, we did not find any association of MDR-TB status with hospitalisation due to any other cause within the past 7 months of current treatment.[21] Hospitalisation due to TB-related causes during previous treatment was associated with MDR-TB in our current study. This finding indicates that patients may have experienced some difficulties and complicated TB disease. Another possibility is that these patients were not diagnosed properly as drug-resistant patients, and became sick enough for hospitalisation during their previous episode. The NTP may consider MDR-TB testing for patients admitted to hospitals for TB-specific problems. The recent national guideline recommends that the following groups be tested for MDR-TB: previously treated patients, patients with current TB with treatment failure, patients with delayed response in treatment or with smear-negative or extrapulmonary TB that does not improve clinically, patients with relapse or who receive treatment after default, patients who have HIV, and people in contact with patients with MDR-TB.[22]

Camerino classified the risk factors for the emergence of MDR-TB into two categories. The first category includes some of the factors facilitating the selection of resistance in the community and is closely linked to the health system; it includes non-compliance, absence of supervised treatment and the influence of private providers during previous treatment.[7] The other category includes factors that are related to the individual patient's vulnerability to develop MDR-TB, such as clinical and demographic factors.[7]

In our study, more patients with MDR-TB reported supervised treatment (DOT) during their most recent TB treatment episode compared to patients without MDR-TB (78.4% vs 41.7%). Absence of supervised treatment may lead to irregular intake and cause drug resistance, which is an established fact, but our finding looks contradictory.[29] However, this finding is based on the most recent episode of previous TB treatment and we do not have information on their other previous episodes, when they might have had irregular intake. Moreover, during the latest episode of previous TB treatment, the patients with MDR-TB might have been treated with a retreatment regimen which contains injectable streptomycin. Injection must be administered by a provider and require more supervised care. This could also explain the comparatively higher level of follow-up among patients with MDR-TB by the providers after incomplete treatment. We found that more patients with than without MDR-TB reported being followed up by a provider after treatment discontinuation during their previous episode. Another possible explanation of these findings could be that the health system approach is targeted towards retreatment patients, as 63.7% of patients with MDR-TB were receiving a retreatment regimen (category 2) during their latest episode. Retreatment regimens are complicated as patients have a higher chance to develop MDR-TB and might have taken more care compared with the patients who had been treated on a new patient's regimen (category 1). However, patients with new TB require the same effort as retreatment patients to prevent further development of drug resistance.

The NTPs of high burden TB countries where a private sector is also present face difficulties in implementing treatment guidelines, resulting in inadequate treatment or non-compliance.[16] In Bangladesh, designated DOTS centres are the centres managed by public and non-government organisations that are linked with the NTP, which offers free services and medicine for TB treatment. These DOTS centres are the point of treatment initiation and follow-up. Private centres are for-profit private practitioners, clinics and hospitals where patients need to pay for TB treatment and these services are not commonly linked with the TB control programme. Medicines for TB are also available in the private market in Bangladesh and the unregulated private sector is likely to treat patients with TB using non-standardised regimen, which may lead to the development of drug resistance.[30] In our study, patients with MDR-TB had been enrolled mostly with the designated DOTS centres during their most recent episode of previous TB, rather than private centres. The possible explanation could be that retreatment patients are complicated cases that private practitioners prefer not to treat. This study is a hospital-based study and we assumed that most of the patients with MDR-TB are treated at these three government hospitals. We do not have any information on patients with MDR-TB treated by private physicians who are beyond NTP. However, we were not able to collect information on other episodes to evaluate if patients had been treated in the private sectors previously. Another study reported similar rates of MDR-TB among patients treated by DOTS centres and by private providers and thorough review of medication given during previous treatment, regardless of its setting, was recommended.[31]

The NTP of Bangladesh provides services integrated into the basic health services.[18] TB control through

DOTS services has been expanded throughout the country in all subdistricts and metropolitan cities with the support of non-government organisations such as BRAC, the Damien Foundation and other organisations such as UPHCSDP, NHSDP and BGMEA, or through public–private partnerships.[18] Accessing services from DOTS centres might reflect the expansion of DOTS services and their reach of more patients. Widespread deployment of community health workers and their involvement in high-priority health areas including TB has brought these services to the household level.[32] The community-based approach is adopted widely in Bangladesh, so patients do not have to travel to health centres for every administration of medicine; it can be given by community-level providers and the patient only visits the centre for diagnosis, follow-up and complications. Time-to-treatment centre was relatively lower (20 vs 40 min in MDR-TB and non-MDR-TB, respectively) among the patients with MDR-TB compared with patients without MDR-TB. We did not find any significant difference in cost-to-treatment and distance-to-treatment centres. Although access to treatment could be a factor for developing drug resistance, we could not make conclusions about this factor from our findings. Patients may be living in closer proximities, along with some other problems other than time, cost and distance, to access the treatment. We also found that the second major reason for incomplete treatment was change in address which might be due to unstable living circumstances, such as the eviction of slum-dwellers in some areas or losing a job. A detailed qualitative study needs to be conducted in future regarding other treatment access factors of patients with TB.

This study is a stratified analysis of all previously treated TB patients with TB taken from a case–control study which recruited patients with and without MDR-TB representing the population. The sample size and power were calculated on the basis of the initial risk factor study, and as such our analysis of the subset has less power than the full study, but the results still present important exploratory findings. We do not have information on all previous treatment episodes for the patients as we had extracted the information on the basis of the most recent episode, to aid the accuracy of the recalled information. It was not feasible to confirm drug susceptibility using DST of the patients with non-MDR-TB, as only high-risk patients are routinely tested, and we did not have the funds for this.

CONCLUSION

In conclusion, we found that incomplete treatment which includes treatment discontinuation due to treatment failure, adverse reactions to anti-TB medicine, and hospitalisation for TB complications during previous TB treatment are the main factors leading up to MDR-TB. Although we found seemingly contradictory findings regarding supervised treatment, less time required to visit the treatment centre and the designated DOTS centre, it does not necessarily mean that supervised treatment, accessibility or being treated in a designated DOTS centre contributes to MDR-TB. These findings are based on the most recent episode of previous treatment of patients with MDR-TB, as most patients have more than one episode of previous TB treatment. In addition, the health system may be better prepared for the retreatment of patients. Therefore, basic DOTS services should be strengthened for new patients to prevent development of drug resistance. Patients who are hospitalised for TB-related causes could be tested for MDR-TB. Patient education could be strengthened for all patients with TB regarding adverse effect and compliance-related issues.

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Data sharing statement All relevant data in this study are freely available in the manuscript as submitted and are included in summary tables and the results section of the manuscript. The author has full access to the data set. The electronic version of the data set is kept with the University of Newcastle Australia, following the original research protocol, which has also been approved by the Human Research Ethics Committee (HREC) of the University of Newcastle. It will be provided on request to anyone who is interested in the research topic. Interested readers may contact the corresponding author.

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