MULTIDRUG RESISTANT TUBERCULOSIS (MDR-TB) IN COMMUNITY SETTING OF BANGLADESH

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MBBS, MASTERS IN HEALTH ECONOMICS

A thesis submitted for the degree of Doctor of Philosophy

At the University of Newcastle, Newcastle, Australia

AUGUST, 2015

Statement of Originality

I, solemnly and sincerely declare, in relation to the thesis entitled Multidrug resistant tuberculosis (MDR-TB) in community settings of Bangladesh, that:

The thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository.

Mahfuza Rifat

Date:

Acknowledgement

I wish to thank a number of people who were part of my PhD journey.

I am grateful to my supervisors; their support means a lot to me to complete my study. My Principal supervisor Milton Hasnat was very supportive throughout my PhD. He guided me to accomplish the challenging works. I am very grateful to John Hall, who provided valuable inputs and encouragement, always. I am also thankful to Christopher Oldmeadow for his guidance.

My PhD was supported by the Australian Leadership Award scholarship, and I am grateful to Australian Government for this Leadership development initiative under the Australian Award programme.

I am grateful to BRAC, a non-government organization with extensive experience in tuberculosis control in Bangladesh. I have received intense support from BRAC in collecting such a big number of data from all over the country. Thanks to all my BRAC colleagues for supporting my field work in Bangladesh including Md. Akramul Islam from BRAC. I have also received encouragement from Jalaluddin Ahmed, Faruque Ahmed, Kawsar Afsana and Ahmed Mushtaque Raza Chowdhury of BRAC. The national tuberculosis control programmes, other partner NGOs in Bangladesh were very supportive during my field works; I am pleased to acknowledge the organizations. I am also thankful to the colleagues from WHO for providing me current updates. Thanks to CHAD, another non-government organization in Bangladesh to facilitate field works.

I am thankful to my parents, mother Syeda Zinat Ara Khanam, brother and sisters, and uncle Syed Abul Mokarrum, for encouraging me, although they were staying far away.

List of publications and papers contributing to this thesis

Paper published

1. **Rifat M**, Milton AH, Hall J, Oldmeadow C, Islam MA, Husain A, Akhanda MW, Siddiquea BN: Development of multidrug resistant tuberculosis in Bangladesh: a case-control study on risk factors. PLoS One 2014, 9(8):e105214.

2. **Rifat M**, Hall J, Oldmeadow C, Husain A, Hinderaker SG, Milton AH: Factors related to previous tuberculosis treatment of Multidrug resistant Tuberculosis patients in Bangladesh. BMJ Open 5(9) · September 2015.

3. **Rifat M**, Rusen ID, Islam MA, Enarson DA, Ahmed F, Ahmed SM, Karim F: Why are tuberculosis patients not treated earlier? A study of informal health practitioners in Bangladesh. International Journal of Tuberculosis & Lung Disease 2011, 15(5):647-651.

4. **Rifat M**, Hall J, Oldmeadow C, Husain A, Milton AH: Health system delays in treatment of Multidrug resistant tuberculosis patients in Bangladesh. BMC Infectious Diseases 15(1):526 · November 2015.

Copies of the four published papers are provided in Appendix A, B, C and D

Statement of Authorship (thesis by publication)

I hereby certify that this thesis is in the form of a series of published papers of which I am a joint author. I have included as part of the thesis a written statement from each co-author, endorsed by the Faculty Assistant Dean (Research Training), attesting to my contribution to the joint publications.

Statement of the co-authors' with the endorsement by the Assistant Dean (Research Training), are provided in Appendix E

Mahfuza Rifat

Date:

Candidate's Contributions to the Study

Activities	Primary role	Others involved
Overall study	MR, AHM, JH, CO	MAI, BNS
Ethics application to the University of Newcastle and Government of Bangladesh	MR, AHM, JH	BNS
Study design	MR, AHM, JH	MAI, IR
Logistic procurement	MR, AHM	
Staff recruitment and training	MR, AHM, BNS	BRAC
Development of questionnaire	MR, AHM, JH	
Pretesting of the questionnaire	MR, BNS	
Recruitment of the study participants	MR, BNS	BRAC
Data collection	BRAC	
Supervision of field work	MR, MWA, BNS	CHAD
Data entry screen design, data entry	MR	BRAC
Data cleaning and editing	MR, CO	
Data analysis	MR,CO	
Scientific write-up and publication	MR, AHM, JH, CO	SGH, SMA, FK, FA, IR, MAH, DA

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List of abstracts for conference presentation

1. Characteristics of MDR-TB patients in Bangladesh

   Rifat M, Hall J, Hasnat MA, Islam MA, Siddiquea B, Akhanda MW, Husain A.

   Published in the Abstract book of 44th World Conference on Lung Health of International Union against Tuberculosis and Lung Diseases. Volume 17, Number 12, December 2013, Supplement 2.

   2. Previous TB treatment in MDR-TB patients in Bangladesh and health system factors

   Rifat M, Hall J, Hasnat MA, Islam MA, Siddiquea B.

   Published in the Abstract book of 44th World Conference on Lung Health of International Union against Tuberculosis and Lung Diseases. Volume 17, Number 12, December 2013, Supplement 2.

   3. Delay in treatment of Multidrug resistant tuberculosis (MDR-TB) patients in Bangladesh.

   Rifat M, Milton AH, Hall J, Oldmeadow C, Husain A.

   Published in the abstract book of the Asian Pacific Region Conference of IUTALD (The Union) to be held from August 31to September 2, 2015.

Other published abstract

1. Community Based Management of Multidrug Resistance TB in Bangladesh

   Rifat M, Alam J, Rana M, Husain A, Islam A, Sultana S, Akandha W, Siddiqui M, Hall J, Milton AH.

   Published in the Abstract book of 4th Asia Pacific Region Conference of the International Union against Tuberculosis and Lung Diseases. Hanoi, Vietnam. April, 2013. The poster was awarded as the best poster presentation award of the conference.

Copies of the 4 abstracts are presented in Appendix F.

Glossary

AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BCG	Bacille-Calmette-Guérin; vaccine for tuberculosis
BMRC	Bangladesh Medical Research Council
DOT	Directly-observed therapy
DOTS	Directly observed treatment strategy; core approach of the Stop TB strategy for TB control
DRS	Drug resistant surveillance
DR-TB	Drug-resistant tuberculosis
DST	Drug-susceptibility testing
EQA	External quality assurance
FNAC	Fine needle aspiration biopsy
HIV	Human Immuno-deficiency virus
HREC	Human research ethics committee
IUTLD	International Union against Tuberculosis and Lung Diseases (The Union)
LPA	Line-probe assay
MDG	Millennium Development Goal
MDR-TB	Multidrug-resistant tuberculosis, defined as resistance to at least isoniazid and rifampicin, the two most powerful anti-TB drugs
NGO	Non-government organization
NTP	National tuberculosis control programme
PCR	Polymerase chain reaction
PMDT	Programmatic Management of Drug resistant tuberculosis
RR-TB	Rifampicin-resistant tuberculosis

TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis, defined as MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable
Xpert MTB/ RIF	An automated, cartridge-based nucleic amplification assay for the simultaneous detection of TB and rifampicin resistance

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Abstract

Background: Bangladesh is one of the high burden countries for tuberculosis (TB) as well as for multi-drug resistant tuberculosis (MDR-TB). Research projects presented in this thesis addressed the following areas: risk factors for development of MDR-TB; factors related to previous tuberculosis treatment of MDR-TB patients; delays in treatment of drug sensitive tuberculosis patients; and the health system delay in the treatment of MDR-TB patients, in Bangladesh.

Method: This thesis by publication consists of four papers. A case control study of 250 MDR-TB patients as cases and 750 drug sensitive TB patients as controls was conducted to determine the risk factors of MDR-TB in Bangladesh. A total 293 patients of the same dataset, who had history of previous tuberculosis treatment, were included in the second study to identify the factors related to previous tuberculosis treatment. MDR-TB patients who were diagnosed using the rapid diagnostic tests (n=207), were included in our fourth study, to determine the health system delay in MDR-TB treatment. We had conducted another cross sectional study (n=7280) to determine the delay in drug sensitive TB patient which has also been included in this thesis.

Key findings: Our first study suggests that previous tuberculosis treatment is the major contributing factor to MDR-TB (OR 716.6, 95% CI 282.1–1820.8). Other factors found to be associated with MDR-TB are age group “18-25” (OR 1.8, CI 1.1-2.9) and “26-45” (OR 1.7, CI 1.1-2.7), compared to the age-group “ >45 years”; patient’s education up to secondary level (OR 1.9, CI 1.32.8), as opposed to the “no education” group; service and business as occupation (OR 2.9, CI 1.3-6.4; OR 3.7, CI 1.6-8.7, respectively); smoking history (OR 1.6, CI 0.99-2.5); and type 2 diabetes (OR 2.6 CI 1.5-4.3).

Incomplete treatment (4.3; 95% CI 1.7-10.6), hospitalization for tuberculosis treatment (OR 16.9; CI 1.8-156.2), and adverse reaction (OR 8.2; 95% CI 3.2-20.7), are the factors related to previous tuberculosis treatment most likely to result in MDR-TB. Drug sensitive TB patients, who are seeking care from informal practitioners access care more promptly, but experience prolonged delay in initiating treatment, compared to those visiting qualified practitioners ($p<0.05$). Health system delay (time between visiting a provider and start of treatment) of MDR-TB patient was associated with the visit to private practitioners for first consultation, compared to visiting a DOTS centre (mean difference (days): 37.7; 95%; CI 15.0-60.4.1; p 0.003). Introduction of rapid diagnostic methods for MDR-TB has reduced the diagnosis time although some degree of delay was present in treatment initiation (median 5 and 10 days, respectively). Conclusion and recommendation: National Tuberculosis programmes should address identified risk factors in MDR-TB control strategy including previous tuberculosis treatment. Socio-demographic groups such as specific age-groups and people with some levels of education, who were associated with development of MDR-TB, could be addressed by the national TB control programme, through effective communication approach in preventing drug resistance. The integration of MDR-TB control activities with diabetes and tobacco control; engaging the private practitioners in MDR-TB control; and continued involvement of informal practitioners for early referral for diagnosis and treatment of TB, are needed in Bangladesh.

Structure of the thesis

This thesis by publication is composed of background, objectives, brief literature review, four papers, and a final chapter providing a conclusion and recommendations. At the time of submission, two papers have been published, one has been accepted for publication and one paper has been submitted to peer reviewed journal.

Chapter 1 provides an overview of multidrug resistant tuberculosis, a brief literature review of multidrug resistant tuberculosis, associated risk factors and delay in treatment of tuberculosis patients including the multidrug resistant tuberculosis. It also describes the rationale for studying risk factors of multidrug resistant tuberculosis and the delay in tuberculosis treatment in Bangladesh; presents research questions, objectives, and a statement regarding ethical approval.

Chapter 2 (Paper 1), presents a case control study on risk factors for multidrug resistant tuberculosis in Bangladesh. The title of the paper is "Development of multidrug resistant tuberculosis in Bangladesh: a case-control study on risk factors", have been published in *PLoS One*.

Chapter 3 (Paper 2), focuses on previously treated tuberculosis patients in Bangladesh. The resulting manuscript titled "Factors related to previous tuberculosis treatment of multidrug resistant tuberculosis patients in Bangladesh" was published in *BMJ Open*.

Chapter 4 (Paper 3), reports a study on treatment delay among drug-sensitive tuberculosis patients in Bangladesh, focusing on the role of informal health practitioners. The title of the paper is "Why are tuberculosis patients not treated earlier? A study of informal health practitioners in Bangladesh" has been published in the International Journal on Tuberculosis and Lung Diseases (*IJTLD*) journal.

Chapter 5 (Paper 4), explores the health system delay in treatment of multidrug resistant tuberculosis in Bangladesh. The study titled "Health System delay in treatment of

Multidrug resistant tuberculosis patients in Bangladesh" was published in *BMC Infectious diseases* journal.

Chapter 6 provides a conclusion and recommendations.

Chapter 1 Overview of Multidrug resistant tuberculosis

1.1. Introduction

Globally, tuberculosis (TB) is the second largest cause of death from infectious diseases after the Human Immuno-Deficiency Virus (HIV) [1]. Tuberculosis became a forgotten disease as the technically advanced countries had achieved good control of TB; however, it persisted in developing countries [2]. Recurrence of TB in western countries and the spread of HIV during the 1980s brought TB back on to the international health agenda [2]. The World Health Organization declared TB as a global public health emergency in 1993 [3]. TB is a major global health problem and TB related deaths occur mostly in poor countries, the poorest of the poor are the more affected [4, 5].

National control programmes at country level adopted a TB control strategy, widely known as the "DOTS strategy" and later, the "Stop TB strategy", following the global call announced by the World Health Organization [6]. Globally, the TB mortality rate and the TB prevalence rate fell by an estimated 45% and 41% respectively, between 1990 and 2013 [1]. The incidence rate for TB has also been reducing each year since 2000 [1]. Despite these achievements, TB control programmes are facing the new challenge posed by multidrug-resistant TB (MDR-TB) and extensive drug-resistant TB (XDR-TB) [7]. Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* [8]. Multidrug-resistant TB (MDR-TB) is caused by bacteria that are resistant to at least isoniazid and rifampicin, the most effective anti-TB drugs for treating TB [9]. MDR-TB cannot be treated with first line anti-TB medicine and needs a longer treatment with second line anti-TB medicines, which are more expensive and more toxic. XDR-TB is a form of drug resistant TB that does not respond to first-line as well as key second-line drugs. The bacteria are resistant to isoniazid and rifampicin as

well as to any fluoroquinolone and any of the second-line anti-TB injectable agents (amikacin, kanamycin and/or capreomycin) [9]. The cure rate of MDR-TB is comparatively lower than for drug susceptible TB [10-12].

Diagnosis and appropriate treatment of MDR-TB and XDR-TB remain a major challenge in controlling TB [13]. Globally a total of 300,000 MDR-TB patients were estimated to have MDR-TB with 45% having been notified in the same year [1]. In 2011, the overall treatment success rates for MDR-TB and drug sensitive TB patients were 48% and 86% respectively, according to WHO [1]. Failure to control MDR-TB effectively may lead to another era with TB being regarded as a untreatable disease. Effective TB control strategies and implementation of priority research are essential to prevent and control MDR-TB.

The WHO has identified 27 high burden countries for MDR-TB; of these, four countries including Bangladesh are in South-East Asian region [14]. MDR-TB is an emerging public health problem as 1.4% new TB patients and 29% of the retreatment patients have MDR-TB in Bangladesh [15, 16]. Although the rate of MDR-TB is still relatively low, due to the overall high TB burden in Bangladesh the absolute number of MDR-TB cases is quite large, with an estimated 2100 new TB patients and 2600 previously treated TB patients in 2013 [1]. Bangladesh has one of the highest population densities in the world, is one of the high burden countries for TB, but has a low prevalence of HIV [17].

Once an individual is exposed to TB, various factors (i.e. time since infection, HIV, untreated or poorly treated previous TB, age, gender, malnutrition, diabetes, silicosis, delay in diagnosis and treatment) determine the risk of becoming infected, the probability that an infected individual will develop tuberculosis, and whether a diseased

individual will die from tuberculosis [8]. Similarly, the development of MDR-TB is also affected by several risk factors. Drug resistance may result from inadequate, incomplete or poor treatment quality, which allows the development of mutant, resistant strains [18]. Poor treatment outcomes can be caused by inappropriate treatment; inadequate drug quality and supply; and patient factors related to non-adherence and treatment responses, which could be further influenced by health system, social and individual determinants [18]. Patients who have been treated for TB previously are more likely to develop MDR-TB [19-25]. 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 [1]. Identifying the population at risk of MDR-TB is essential to developing appropriate case finding strategies [21]. To understand the development of drug resistance it is essential to know the management approach during the previous tuberculosis treatment. Early detection and effective treatment of TB and MDR-TB are key to prevent development and transmission of MDR-TB [18]. Delay in TB treatment may result in disease progression, transmission of TB to the community and poor treatment outcome including increased risk of death [26]. Tuberculosis treatment delay among drug sensitive TB patients has been reported in previous studies [27]. Delays in treatment initiation for MDR-TB patients also have been reported in some studies, although the context and the definition of delay were variable [28-34]. Information related to delay in drug-sensitive TB and MDR-TB treatment is important to identify where the focus in the implementation of the early diagnosis and treatment approach should be in a TB control programme.

The research presented in this thesis addresses the knowledge gaps in the following areas:

- Risk factors for development of multidrug resistant tuberculosis in Bangladesh
- Factors related to previous tuberculosis treatment of multidrug resistant tuberculosis patients in Bangladesh
- Delay in drug sensitive tuberculosis treatment and associated factors
- Health system delay in multidrug resistant tuberculosis treatment and associated factors.

1.2 Literature Review

1.2.1 Search strategy

A literature review was conducted to locate studies on risk factors for contracting MDR-TB, previous tuberculosis treatment of MDR-TB and delay in tuberculosis treatment through searches in MEDLINE and PubMed. Furthermore, some important web sites such as Google-scholar were searched for more information on MDR-TB. The literature search was conducted using the key words: “Tuberculosis”; “Multidrug resistant tuberculosis” OR MDR-TB”; “Multidrug resistant tuberculosis” OR”MDR TB” AND “risk factors”; “Multidrug resistant tuberculosis” OR ”MDR TB” AND “predictors”; “Previous tuberculosis treatment” AND “MDR-TB”; “Retreatment” AND “MDR-TB”; “Delay in drug sensitive tuberculosis treatment”; “Delay” AND “MDR-TB” and “Time to treatment” AND “MDR-TB”. Endnote X7 has been used for reference library.

1.2.2 General information about Tuberculosis

Tuberculosis (TB) is an infectious disease caused predominantly by a bacterium called *Mycobacterium tuberculosis.* TB usually affects the lungs causing pulmonary tuberculosis, but can also affect other sites of the body and is then known as extra-pulmonary TB [8]. The disease is usually transmitted through the air, when pulmonary TB patients expel the bacteria, mainly by coughing [8]. A relatively small proportion of

people infected with *M. tuberculosis* will develop TB disease. People infected with the human immunodeficiency virus (HIV) are more prone to develop the disease [8, 9] and women are less commonly affected, although it is also an important factor for women's death globally [35].

1.2.3 Global Tuberculosis Scenario

Tuberculosis has been a major public health problem for centuries [2]. Despite the availability of affordable, effective treatment, a total 9 million people developed TB disease and 1.5 million died from the disease in 2013, which included 0.36 million among people infected with HIV representing an intolerable burden of human suffering and an unacceptable barrier to socio-economic development [1]. About 60% of TB disease and deaths occur among men, although the disease among the women is also high, represented by 0.5 million TB deaths among the women in 2013 [1]. A total 80,000 HIV negative children died from TB in the same year [1].

HIV infection increases the risk of active TB disease among individuals infected both with HIV and TB [9]. HIV and TB co-infected people represented 13% of the TB patients in 2013 [1]. The African region constituted 78% of global HIV-positive new TB cases patients, in 2013 [1]. The South-East Asia and the Western pacific region carry more than half (56%) of the TB burden [1]. WHO identified 22 high burden countries for TB which includes Bangladesh [1].

Globally, 3.5% (95% CI: 2.2-4.7%) of new TB patients and 20.5% (95% CI: 13.6-27.5%) of previously treated TB patients are estimated to have MDR-TB. An estimated 48,000 (range: 35,000- 61,000) MDR-TB emerged and 21,000 (range: 130,000-290,000) deaths, in 2013. An estimated 9.0% (95% CI: 6.5-11.5%) of people with MDR-TB have XDR-TB which was present in 100 countries. India, China and Russian

federation represented more than the half of the global burden of MDR-TB [1]. WHO have listed 27 high burden countries for MDR-TB those accounts for 85% of global burden of MDR-TB [7].

1.2.4 Global response to tuberculosis including multidrug-resistant tuberculosis

The World Health Assembly acknowledged TB as a major public health problem in 1991 [5]. Following the declaration of TB as a global emergency by the WHO, the internationally recommended DOTS strategy for treating TB was launched in 1994; this is based on five components: government commitment; case detection through passive case finding; standardized short-course chemotherapy at least for sputum smear-positive cases; a system of regular drug supply; and a monitoring system for programme supervision and evaluation [5]. This strategy was adopted by countries all over the world and improved case detection and treatment success rates [1]. In spite of these improvements there were emerging challenges that required enhancement of the DOTS strategy. The Stop TB Partnership was established in 2000 as a global response [5]. In 2006, the Global Plan to Stop TB 2006-2015 was launched in Davos, Switzerland at the World Economic Forum [5]. The targets of that Global Plan were revisited in the new Global Plan 2011-2015 [10].

In 2006 the WHO recommended the Stop TB Strategy as an enhancement of the DOTS strategy [10]. Drug resistant TB was also included in this new strategy. The components of the Stop TB Strategy highlight the need to address the challenge of drug-resistant TB and TB-HIV co-infections, engaging all care providers in TB care and control, and contributing to strengthening of health systems, the role of communities and people with TB, and the research and development for new diagnostics, new drugs and new

vaccines [10]. The targets of the Stop TB Strategy are in line with the global targets of TB control such as the Millennium Development Goals (MDGs).

The WHO conducted a ministerial meeting with high burden countries for MDR-TB in Beijing, China, to address the need of MDR-TB management. The 62nd World Health Assembly adopted resolution WHA 62.15 on prevention and control of MDR-TB and XDR-TB. The resolution urges member states towards achieving universal access to diagnosis and treatment of MDR-TB or XDR-TB by 2015 [48].

The recent post-2015 strategy for TB control "Global strategy and targets for tuberculosis prevention, care and control after 2015" was adopted at the 67th World Health Assembly in 2014 [49]. The post-2015 strategy has a vision of making the world free of TB, with zero deaths, disease, and suffering due to TB. This strategy will be supported by three main pillars: integrated patient-centred care and prevention; bold policy and a supportive system; and intensified research and innovation [49].

Figure 1.1 Goals, targets and indicators for tuberculosis (TB) control

Source: World Health organization. Global Tuberculosis report, 2014

Millennium Development Goals: Combat HIV/AIDS, malaria and other disease

Target 6.C: Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases

Indicator 6.9: Incidence, prevalence and death rates associated with TB

Indicator 6.10: Proportion of tuberculosis cases detected and cured under DOTS

Stop TB partnership targets (2015-2050)

MDG 6, Target 6c: Halt and begin to reverse the incidence of TB by 2015

By 2015: Reduce prevalence of and deaths due to TB by 50% (compared with 1990)

By 2050: Eliminate TB as a public health problem, defined as a global incidence of active TB of less than one case per 1 million

The post-2015 global TB strategy

Vision: A TB-free world. Zero deaths, disease and suffering due to TB

Goal: End the global tuberculosis epidemic

Milestones for 2025:

-75% reduction in TB deaths (compared with 2015)

-50% reduction in TB incidence rate (less than 55 TB cases per 100,000)

-No affected families facing catastrophic costs due to TB

Targets for 2035:

-95% reduction in TB deaths (compared with 2015)

-90% reduction in TB incidence rate (less than 10 TB cases per 100,000)

-No affected families facing catastrophic costs due to TB

1.2.5 Management approach of Tuberculosis in Bangladesh

In Bangladesh, TB services which were initiated in 1965 were mainly curative; it did not include other components of DOTS strategies in a comprehensive way. The services were available in 44 TB clinics, eight chest disease hospitals and five TB hospitals [36]. The NTP started field implementation of the DOTS strategy in 1993, and progressively expanded to cover all sub-districts and metropolitan cities of the country, in collaboration with NGO partners. Bangladesh has a dynamic NGO sector providing TB control services in collaboration with NTP through a partnership approach [36, 38]. TB control services are integrated in the basic health care service [36, 39]. The standard regimen for drug sensitive TB comprises four drugs for new TB patients and five drugs for previously treated TB patients (isoniazid, rifampicin, pyrazinamide and ethambutol, for new TB patients; streptomycin is additional for previously treated patients) [40]. Community health volunteers such as *Shasthya Shebika* (female community health volunteer of the major partner NGO, BRAC), village doctors and other field level workers identify individuals with symptoms of TB and refer them for sputum examination at NTP designated government or NGO facilities commonly known as DOTS centres. Symptomatic patients also seek care directly from the DOTS centres. Community involvement in Bangladesh has enhanced the referral of symptomatic patients for diagnosis and increased the case notification of TB [41]. Directly observed treatment (DOT), which refers to the taking of TB medication in front of a health worker or volunteer, is provided. In Bangladesh, DOT is commonly provided at the community level by *Shasthya Shebikas*, village doctors or other community volunteers to ensure treatment compliance; some patients also receive DOT from a health facility if close by [41-43]. Treatment progress of the patients is followed up at recommended intervals, according to the national treatment guideline [40]. TB medicines are provided

by the NTP free of cost. The community based management of drug susceptible tuberculosis has been found to be cost effective [44].

NTP started the DOTS plus project for treating MDR-TB with patients with standardized regimen, in 2008. Before the DOTS Plus project MDR-TB patients were being treated by individualized regimen by one NGO, in a specialized hospital or by private practitioners. The NTP has been implementing community based ambulatory treatment of MDR-TB since June, 2009. After completing the intensive phase (which usually takes 8 months) of treatment at hospital, MDR-TB patients were being treated at home. According to the recent guideline recommended period for hospitalization is the time taken for two consecutive smear conversions. Currently, one national and four regional level government hospitals are providing MDR-TB diagnosis and treatment services. Presumptive MDR-TB cases who are identified at the district, sub-district or lower level are referred to these central and regional level hospitals for diagnosis and treatment initiation, according to the national guideline [45].

Duration of current treatment regimen for MDR-TB in Bangladesh is a minimum of 20-22 months and includes pyrazinamide, kanamycin, ofloxacin, ethionamide and cycloserine [45]. Another regimen of 9 months duration has been implemented in two divisions of Bangladesh by an NGO the Damien Foundation, in collaboration with NTP [46]. The nine month regimen for MDR-TB (comprised of high-dose gatifloxacin, ethambutol, pyrazinamide and clofazimine, kanamicin, prothionamide, and isoniazid) has recently shown promising results with 84.4% treatment success [46].

The private health sector remains important in Bangladesh with some TB patients preferring to seek care from private practitioners [47]. However, the NTP does not have strong links with the private sector, and TB patients treated by private practitioners are

not always reported under the NTP system. As in many other countries, TB services provided by the private sector are poor, with use of inappropriate treatment and poor case holding, leading to incomplete treatment and drug resistance [47].

1.2.6 Tuberculosis scenario in Bangladesh

Tuberculosis is a major public health problem and one of the leading causes of adult mortality and preventable deaths in Bangladesh [15]. Bangladesh is listed among the world's 22 high burden countries for TB. Although the HIV prevalence is still low, which is less than 1%, the HIV/AIDS is a potential threat to TB control as increasing trend of HIV prevalence have been observed in some high risk groups [17]. Bangladesh adopted the WHO recommended TB control strategy in 1994 and achieved 70% case detection and 90% treatment success rate, in 2006 [36].

The National tuberculosis control programme completed a nationwide prevalence survey of smear positive TB cases among person aged more than 15 years in 2009 [37]. According to this survey, overall crude prevalence of new smear-positive TB in persons aged more than 15 years was 63.3 per 100,000 (95% CI 43.6–88.9) and the adjusted prevalence was 79.4 per 100,000 (95% CI 47.1–133.8) [37]. The prevalence was significantly lower than the previous nationwide survey findings for Bangladesh held in 1987-1988 which was 870 per 100,000 populations [37].

MDR-TB is an emerging public health problem in Bangladesh and the country is also one of the 27 high burden countries for MDR-TB identified by WHO [7]. According to the recent drug resistant survey, 1.4% of new cases and 29% of the retreatment cases in Bangladesh have MDR-TB [16]. Although the rate of MDR-TB is still relatively low, due to the overall high TB burden in Bangladesh the absolute number of MDR-TB

cases was quite large, with 2100 among new TB patients and 2600 among the previously treated TB patients, in 2013 [1].

Table 1.1 presents the WHO estimates on Bangladesh TB status.

Table 1.1 Current estimates of Tuberculosis in Bangladesh

Source: World Health organization. Global Tuberculosis report, 2014

Population (2013)	157 millions
Incidence of all types of TB, per 100,000 [a]	224 (199-253)
Prevalence of all types of TB per 100,000 [a]	402 (210-656)
Mortality per 100,000 (excluding HIV)	51 (33-69)
Mortality per 100,000 (HIV positive TB only)	0.26 (0.12-0.3)
TB patients with known HIV status (%)	1
MDR-TB among the new patients (%)	1.4 (0.7–2.5)
MDR-TB among the retreatment patients (%)	29 (24–34)
All types of TB notified cases	190,891
MDR-TB cases among the new pulmonary TB	2100 (1000-3700)
MDR-TB cases among the retreated pulmonary TB	2600 (2200-3200)
Treatment success rate of new and relapse TB (%) [b]	92
Treatment success rate of previously treated TB (excluding relapse) (%) [b]	82
Treatment success rate of Rifampicin-resistance/MDR-TB (%) [c]	68

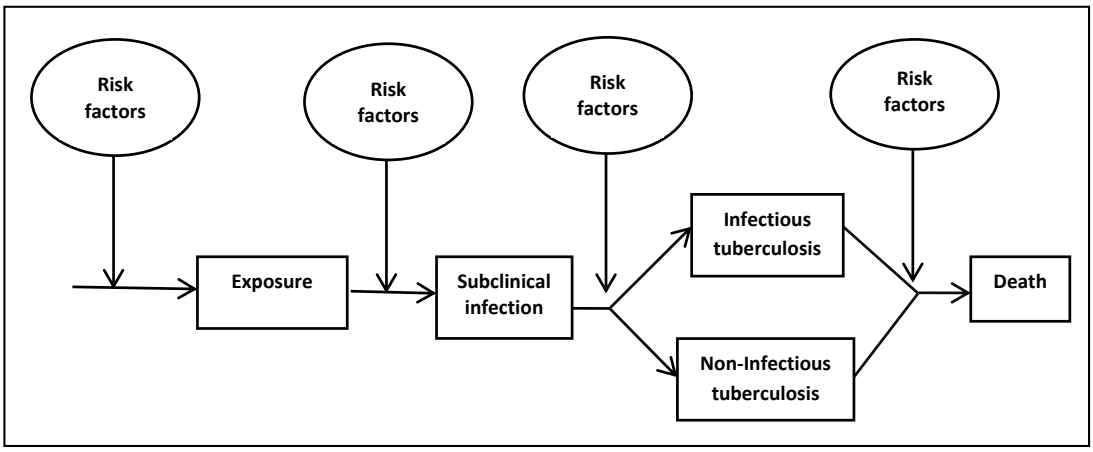
[a] HIV positive TB included
[b] Enrolled in 2012
[c] Registered in 2011

1.2.7 Risk factors for MDR-TB

Rieder (1999) presents a model on the epidemiological basis of TB, which demonstrates the pathogenesis of TB from the exposure to death (Figure-1.2) [8]. Once an individual is exposed to an infectious agent, there are factors that determine the risk of becoming infected, risk factors which determine the probability that an infected individual will develop TB, and risk factors which determine the probability that a diseased individual will die from TB [8]. Similarly, the two main pathways that lead to the development of the acquired (secondary) drug resistance and the primary drug resistance are also affected by presence or absence of several factors (Figure-1.3) [18]. Resistance developed within the patient because of sub-therapeutic doses for any reason, such as inappropriate and inadequate treatment or poor quality of medicine, is referred to as acquired resistance [50]. Subsequent transmission of the drug-resistant

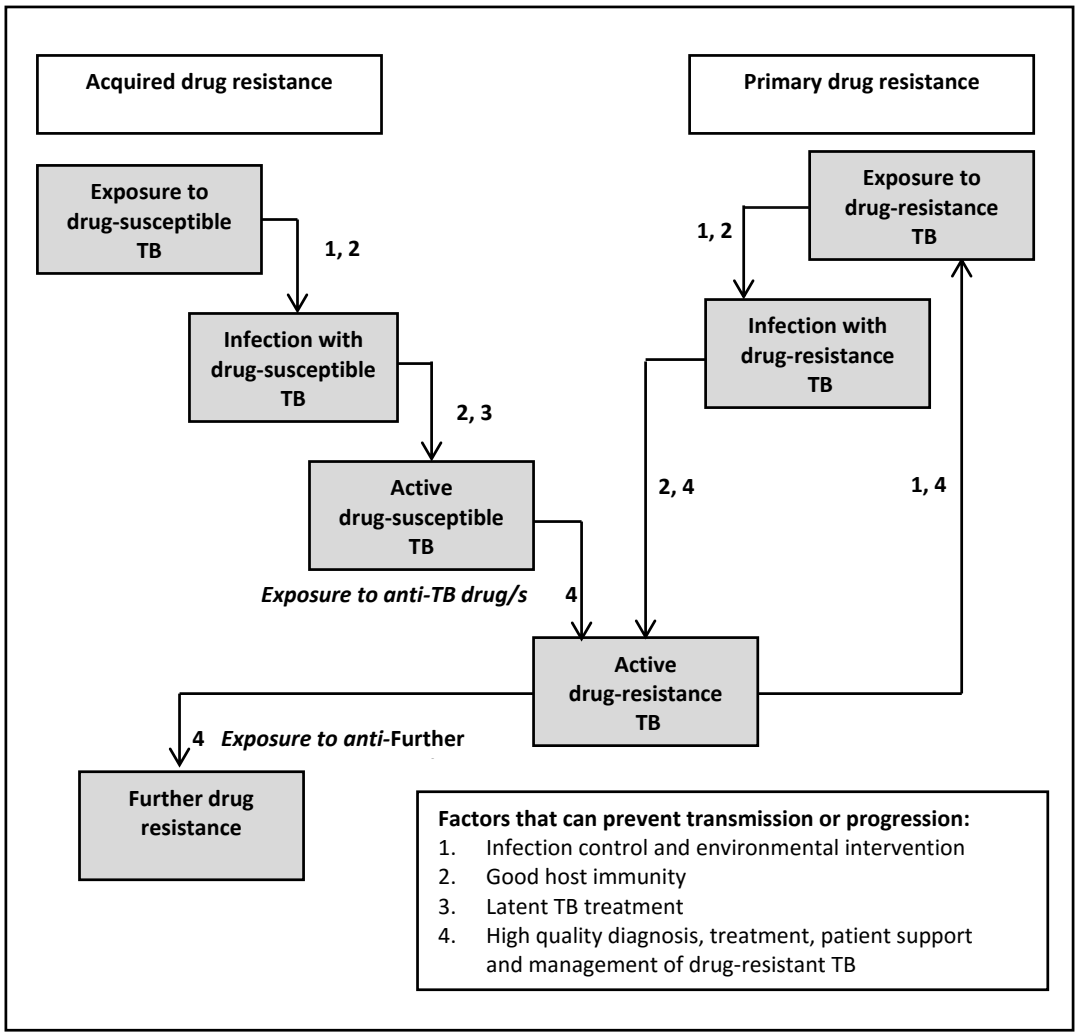
infection to other persons may lead to a disease that is drug resistant from the outset, which is known as primary resistance [50].

Figure 1.2 A model of tuberculosis epidemiology following the pathogenesis of tuberculosis.



Source: Rieder HL. Epidemiologic Basis of Tuberculosis Control. First ed. Paris: International Union Against Tuberculosis and Lung Disease; 1999.

Figure 1.3 Two pathways leading to drug resistance tuberculosis



Source: World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis; 2014

Previous studies identified some risk factors associated with MDR-TB, namely previous TB treatment [19, 20, 23, 24, 51], poor past compliance with treatment [24, 52], HIV infection [20, 53], younger age-group [20, 22, 54], gender [20, 52], foreign-born [20, 22, 55], living in an urban area [54], working in health care [53], type by bacteriology and pulmonary site of TB [53], presence of cavitation in lungs [24, 56], contact with a TB patient [51], smoking or other substance misuse [53, 57], chronic renal failure [58],

diabetes [59], use of other anti-microbial medicine [58], being an asylum seeker [53], living in a nursing home [53], being a prisoner [53], and hospitalization history [60]. Inappropriate medical management, absence of directly observed treatment, lack of uniformity between public and private sectors, limited or interrupted drug supply, poor quality and unregulated and widespread availability of anti-tuberculosis drugs, were also reported as important causes associated with MDR-TB [19, 24, 51]. Many studies attempted to identify the risk factors in different settings, however, findings related to some risk-factors such as HIV status [19, 61], age-group [19] and gender of the patients [20, 23, 52] differed. Moreover, study designs varied widely, some findings were based on small sample sizes and some came from drug resistance surveys.

Previous TB treatment

A previous history of anti-tuberculosis treatment has been found as a risk factor for MDR-TB [23, 24, 51, 57, 62, 63]. A systematic review of risk factors conducted in Europe lists previous treatment history for TB as the strongest determinant of MDR-TB, with the pooled risk of MDR-TB being 10.2 times higher in previously treated patients than in new patients [20]. Incomplete or inadequate previous TB treatment is also found to be the associated with MDR-TB [19, 52, 64, 65]. Incomplete treatment for more than 3 months increased the likelihood of developing MDR-TB in a descriptive prospective study of 299 TB patients conducted in the Philippine (OR 2.44, 95% CI 1.49-4.01) [66]. A drug resistance survey conducted in eleven countries by the WHO and the International Union against TB and Lung Diseases (IUATLD) studied the determinants of MDR-TB regarding demographic, previous TB treatment and HIV status. They found that longer treatment duration (12 months or more) due to failure of prior treatment was a risk factor for MDR-TB (OR 13.7, 95% CI 4.5-41.6; P< 0.001) [19].

MDR-TB was found to be associated with a history of failed treatment for TB (adjusted OR 51.7, 95% CI: 6.6-403.7) in a case-control study conducted on 116 drug susceptible, 123 MDR-TB and 139 XDR-TB patients in South Africa [60]. Hospitalization of more than 14 days was associated with MDR-TB and XDR-TB in the same study (adjusted OR 3.8; 95% CI 1.1-13.3 and adjusted OR 6.1; 95% CI: 1.8-21.0, respectively) [60].

HIV status and other co morbidities

Studies on the impact of HIV status as a risk factor for MDR-TB showed variable results. A retrospective cohort study conducted in a specialized treatment unit in Madrid, Spain, included 30 MDR-TB and 666 non-MDR-TB patients through medical record review [57]. This study did not find any relationship of HIV status with MDR-TB. The same result was found in another case-control study conducted in India with 47, 30 and 117 patients who had MDR-TB, XDR-TB and non-MDR -TB, respectively (OR 0.19; 95% CI 0.024-1.56) [67]. Moreover, the WHO-IUATLD conducted multi-country study showed that HIV infection is not an independent risk factor for MDR-TB (OR 0.75; 95% CI 0.43-1.3) [19]. However, some other studies reported different results for the association between HIV and MDR-TB. Another systematic review and meta-analysis of MDR-TB in Europe included 29 eligible studies found that HIV was as a risk factor for MDR-TB (OR 3.52; 95% CI 2.48-5.01) [20]. In contrast, another systematic review and meta-analysis of 32 eligible studies could not demonstrate any association between HIV status and MDR-TB, but they suggested some association with primary MDR-TB and HIV (pooled prevalence ratio 2.72; 95% CI 2.03-3.66) [61]. Another study conducted in the high burden HIV settings of South Africa, where 85% of the participants were HIV-infected, found that HIV is a risk factor for XDR-TB (adjusted OR 8.2, 95% CI: 1.3-52.6), but not for MDR-TB [60]. Chronic renal failure as a co-morbid illness (adjusted OR 4.96; 95% CI: 1.37-18.01) and use of antimicrobials

other than anti-TB medicine (adjusted OR 4.37; 95% CI: 1.74-10.95) was also reported as risk factors in a case-control study [58].

Socio-demographic factors

Socio-demographic factors have been explored in different studies. Faustini et al. (2006), in their systematic review on risk factors, found that males are more likely to be MDR-TB than females (OR 1.38; 95% CI: 1.16-1.65) [20]. However, some other studies reported female sex as risk factor. A cross-sectional study in Pakistan with 640 TB patients including 32 with MDR-TB, found that being female was associated with MDR-TB (OR 3.12; CI 95%: 1.40-6.91) [52]. Another cross-sectional study in Georgia conducted on 1314 TB patients, which included 195 MDR patients, also found an association with female sex (OR 1.58; CI 95%: 1.02-2.32) [23]. Younger age was found to be a risk factor (OR 3.12; CI 95%: 1.40-6.91) in a case-control study of 156 MDR-TB patients and 322 non-MDR controls conducted in Hong Kong [22]. Faustini et al. found that the age group less than 65 years was more likely to have MDR-TB [20]. Another study showed that compared to the age-group 15 to 29, the 30-59 year age-group was at increased risk (OR 1.5; CI 95%: 1.1-2.0) for MDR-TB [54]. The age group 45-65 years was identified as being most likely to be infected with MDR-TB in one study in Spain (OR3.24; 95% CI: 1.34-7.81) [57]. Using a specific age group as a predictor for MDR-TB world-wide cannot be recommended from these findings. Occupation of the patient as a health care worker was found to be associated with MDR-TB in one study (OR 1.69, 95% CI: OR 0.5-5.6) [53].

Clinical factors

Clinical factors associated with MDR-TB have been explored in several studies. The site of TB manifestation showed that MDR-TB patients contract mostly pulmonary TB

and are smear-positive in bacteriological examination [62]. Similarly, one study reported that extra-pulmonary TB was less likely in MDR-TB patients (OR 0.14; 95% CI 0.017-1.04) [67]. Few studies examined the genetic susceptibility of MDR-TB patients. Presence of specific alleles HLA-DRB1*14 allele (OR 8.2; 95% CI: 2.1-31.3) as a risk factor for MDR-TB was found in one case-control study conducted on 130 MDR-TB and 130 drug sensitive TB patients in India [24]. This study also noted a higher number of cavities (OR 6; 95% CI: 2.1-17.3) in chest radiographs as a risk factor. Cavitation of lungs was mentioned as more common in MDR-TB patients in another study, although this was not associated significantly with MDR-TB status [62]. Another study similarly did not find any influence of cavitation on MDR-TB [67].

MDR-TB in special groups of people

Casal et al. (2005) conducted a case-control study on 138 MDR-TB and 276 non-MDR-TB patients in high income settings of four European countries, namely France, Germany, Italy and Spain [53]. They found that intravenous drug users (OR 4.68; 95% CI: 1.7-12.6), asylum seekers (OR 2.55; 95% CI: 1.3-4.9), nursing home residents (OR 2.05; 95% CI: 0.7-5.9), and prisoners (OR 2.02; 95% CI: 0.4-10.1) are the high-risk groups for MDR-TB [53]. However another study conducted in Madrid, Spain, did not find a strong association with intravenous drug use and imprisonment [57]. Ethnic groups were also found to be at increased risk in one study [52]. Homosexual contacts, prior antiretroviral therapy and prophylaxis against *Pneumocystis carinii* were associated with the MDR-TB among patients infected with HIV [68].

Contact of TB patient

Contact with TB patients was found to be associated with MDR-TB compared to individuals without a contact history, as found in a case control study of 60 MDR-TB

patients, 80 controls with drug sensitive TB and 80 community controls (OR 4.66; 95% CI: 1.56-13.87) [69]. This study conducted in Lima, Peru, also found that recent TB household contact, but not contact with an MDR-TB case, was a predictor of MDR-TB (OR 7.47; 95% CI: 1.91-29.3). However, this study included only new patients as case and control [22]. Contact with TB patients as a risk of developing MDR-TB was also mentioned in other studies [51, 65].

Residence status

In Hong Kong, residence status of patients was found to be a risk factor associated with MDR-TB. Non-permanent residents (OR 6.85; 95% CI: 1.38-34.09) and frequent travelers (OR 2.48, 95% CI 1.07-5.74) were found to be at higher risk in Hong Kong [22]. Similarly, foreign-born persons (OR 2.46; 95% CI: 1.86-3.24) were also at greater risk to contract MDR-TB [20]. Urban migrant (OR 1.4; 95% CI 1.1-1.8) or residing in urban area (OR 1.8; 95% CI: 1.4-2.2), in Shanghai, China was risk factors in a cross-sectional study conducted on 8419 TB patients, including 4% with MDR-TB [54].

Health system factors

Camerino (2010) classified the risk factors into two categories: the first category includes some of the factors facilitating the selection of resistance in the community and the other category includes factors that are related to individual patients' vulnerability to developing MDR-TB [21]. The first category is closely linked with the health system. Health system-related factors such as non-compliance, absence of supervised treatment, influence of private providers or non-availability of medicine during previous treatment are related to MDR-TB [21].

Inadequate treatment during a previous TB episode leads to treatment failure with increased risk of developing MDR-TB [21]. Prevention of drug resistance depends

largely on the control effort of the underlying health system. The role of both public and private sectors are important [48]. Patients treated by the private sector without following the national guideline are more likely to experience interruption of treatment [70]. Countries in Eastern Europe who have a high rate of failure also have a high level of drug resistant TB cases [48]. 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-tuberculosis 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 (NTP) were mentioned to be factors related to the development of drug resistance [71, 72].

Risk factors for MDR-TB in Bangladesh

Flora et al. conducted a study in 2010 on risk factors of MDR-TB in Bangladesh, that recruited a small number of selected participants (136 MDR-TB and 152 drug sensitive TB) [73], making it impossible to generalize the findings of the study. There were also discrepancies between the presented results and the conclusions drawn. The authors reported that only 30 (22.1%) MDR-TB patients and seven (4.6%) drug-sensitive TB patients had a previous history of tuberculosis. However, they included the total sample in the analysis to test the factors related to past illness, such as “Course of treatment” and “Directly observed treatment” [73]. It is not clear whether they were looking for the effects of current or previous treatment episodes. The NTP in Bangladesh started the MDR-TB programme in 2008 and gradually expanded its services in subsequent years [15]. At the time of the previously conducted study the MDR-TB programme was still evolving.

1.2.8 Delay in tuberculosis treatment

The impact of a delay in TB treatment has been explored in many settings [27, 74-76]. It may result in disease progression, transmission of TB to the community, and poor treatment outcome including increased risk of death [26]. A systematic review showed a total delay of 25 days in China up to 185 days in Tanzania [27], with a total delay of 60 days in Nepal, 62 days in India and 97 days in Pakistan [74, 75, 77]. Different types of health care providers administer TB services in Bangladesh, including both qualified and informal practitioners. In Bangladesh, informal practitioners are the providers of curative care for many people and diseases; in one survey, 60% of people chose informal practitioners, 63% among the poorest 25% of population [78]. A previous study of 1,000 patients from Bangladesh reported a total delay of 61 days for men and 53 days for women, although the study did not evaluate the type of service providers sought for TB treatment [77]. Total delay and delay in treatment initiation after diagnosis of drug-sensitive TB patients of Bangladesh have been reported in two recent studies [79, 80]. Mean total delay in the treatment of TB patients was 31 days in one study [79]; treatment initiation delay (range 2-17 days) at the peripheral centers after being referred from one tertiary hospital was explored in the later study [80].

A cross-sectional study conducted in China found an association between delay in initiating treatment and MDR-TB status [81]. The study stated that patient diagnosed and treated after 60 days from the onset of symptoms were more likely to develop MDR-TB than those treated more promptly (OR 264; 95% CI: 1.61-4.30) [81]. Another study in Kwazulu-Natal of South Africa found a mean delay of 12.4 weeks for MDR-TB patients, starting from collection of sputum for diagnosis to treatment initiation [31]. Diagnostic delay was inherent in MDR-TB management while the diagnosis of MDR-TB relied on culture methods, which require longer time [82]. Delay in commencing

treatment for MDR-TB has been reported in some studies, although the context and the definition of delay were variable [28-34]. Diagnostic and treatment initiation delays were frequently reported in these studies

1.3 Rationale

Multidrug-resistant TB poses a serious challenge to the TB control efforts at national and global level. Characteristics of MDR-TB patients have not yet been systematically explored in Bangladesh. Although having received previous TB treatment is a known risk factor for MDR-TB, adequate information on factors related to the previous TB treatment is not available in Bangladesh. Identifying the population at risk of MDR-TB is essential for the development of appropriate case finding strategies. Factors related to previous management of TB need to be identified for effective control. Information on delay in treatment of TB and associated factors are crucial to enhance the implementation of early diagnosis and the evaluation of an effective treatment approach to aid TB control. The research conducted to determine the characteristics of MDR-TB patients in Bangladesh focused on factors related to previous treatment of MDR-TB. This study included information regarding the treatment delay in MDR-TB patients, which is not yet known in Bangladesh. Research on treatment delay in drug-sensitive patients and its relation to different health providers was also conducted.

Findings of this study will not only be of great benefit to Bangladesh, but will also benefit the TB control programme in Australia. Although the incidence of TB is low at around 5.5 cases per 100,000 population and proportion of MDR-TB among the TB patients is approximately 2%, patients with MDR-TB are being reported in people living in Australia who were born in high-burden TB countries within the Western Pacific and South East Asian regions [83].

1.4 Research Questions

1. What are the risk factors associated with MDR-TB patients of Bangladesh?
2. What are the previous TB treatment factors associated with MDR-TB?
3. What are the total delay, patient delay and health system delay among the drug sensitive TB treatment and what are the factors related to these delays?
4. What is the health system delay in MDR-TB diagnosis and treatment, and what are the factors related to the health system delay?

1.5 Objectives

1. To determine the risk factors associated with MDR-TB.
2. To determine the factors related to the previous TB management of MDR-TB patients
3. To determine the length of time between start of symptoms and start of TB treatment and document the factors related to delay in treatment initiation, focusing on the role of informal health practitioners.

   To identify the time needed for MDR-TB diagnosis and treatment initiation, and the factors associated with the health system delay.

1.6 Ethics approval

The research was approved by the Human Research Ethics Committee (HREC) of the University of Newcastle, Australia (H-2012-0107) and the Bangladesh Medical Research Council (BMRC), Dhaka, Bangladesh. 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 interviewers read out

the information sheet. 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 National TB Control Programme (NTP), Bangladesh.

1.7 Limitation

In the main case control study, we recruited hospital based cases, as a population-based risk study was not feasible for MDR-TB. However, our cases are likely to be representative of MDR-TB patients in Bangladesh as we recruited from all three Government TB hospitals which treat most of the MDR-TB patients in the country. We recruited the controls from the population rather than from MDR-TB hospitals to ensure they were representative of non-MDR patients. We could not assess HIV status as a risk factor in our study. However, Bangladesh is a low burden country for HIV. It was not feasible to confirm drug susceptibility using Drug Sensitivity Testing (DST) of the controls, as only high-risk patients are routinely tested. We did not have the funds for DST and HIV testing.

In our second study, most patients have more than one episode of previous tuberculosis factor treatment. These findings were extracted based on the most recent episode of previous treatment of MDR-TB patients to avoid recall bias. Our third study on treatment delay among the drug sensitive TB patients was limited by the fact that the information obtained was based on the patient's statement and could not be verified. The fourth study on health system delay among the MDR-TB patients included only patients who were already enrolled in MDR-TB treatment. We do not have information about patients who did not start treatment after diagnosis. Unlike with the delay in drug-sensitive TB patients, it is difficult to determine the date for the onset of symptoms that prompted a visit to a clinician among the MDR-TB patients and the provider delay was based on patient's recalled information.

Chapter 2 Development of multidrug resistant tuberculosis in Bangladesh: A case-control study on risk factors

2.1 Abstract

Objective: To determine the risk factors for developing multidrug resistant tuberculosis in Bangladesh.

Methods: This case-control study was set in central, district and sub-district level hospitals of rural and urban Bangladesh. Included were 250 multidrug resistant tuberculosis (MDR-TB) patients as cases and 750 drug susceptible tuberculosis patients as controls. We recruited cases from all three government hospitals treating MDR-TB in Bangladesh during the study period. Controls were selected randomly from those local treatment units that had referred the cases. Information was collected through face-to-face interviews and record reviews. Unadjusted and multivariable logistic regression was used to analyse the data.

Results: Previous treatment history was shown to be the major contributing factor to MDR-TB in univariate analysis. After adjusting for other factors in multivariable analysis, age group “18-25” (OR 1.77, CI 1.07-2.93) and “26-45” (OR 1.72, CI 1.12-2.66), compared to the age group “more than 45”, some level of education (OR 1.94, CI 1.32-2.85) ,as opposed to no education, service and business as occupation (OR 2.88, CI 1.29-6.44; OR 3.71, CI 1.59-8.66, respectively),compared to the unemployed, smoking history (OR 1.58, CI 0.99-2.5), and type 2 diabetes (OR 2.56 CI 1.51-4.34) were associated with MDR-TB. Previous treatment was not included in the multivariable analysis as it was correlated with multiple predictors.

Conclusion: Previous tuberculosis treatment was found to be the major risk factor for MDR-TB. This study also identified age 18 to 45 years, some education up to secondary level, service and business as occupation, past smoking status, and type 2 diabetes as comorbid illness as risk factors. National Tuberculosis programme should address these risk factors in MDR-TB control strategy. The integration of MDR-TB control activities with diabetes and tobacco control programmes is needed in Bangladesh.

2.2 Introduction

Despite an overall decreasing incidence and mortality rate for tuberculosis (TB), multidrug resistance tuberculosis (MDR-TB) continues to be a serious threat to the current global tuberculosis control effort [48, 84]. MDR-TB is caused by bacteria that are resistant to at least isoniazid and rifampicin, the most effective anti-TB drugs for treating TB [85]. MDR-TB does not respond to standard six-month treatment with first-line anti-TB drugs; extended treatment is required involving drugs that are more toxic and more expensive [85]. Cure rate of MDR-TB is 50 to 70% which is lower than the drug-susceptible TB [10]. Failure to control MDR-TB may lead to another era with TB being regarded as a fatal disease.

Bangladesh is one of the 27 high burden countries for MDR-TB [14]. In Bangladesh, 1.4% of new tuberculosis patients, and 29% of previously treated tuberculosis patients are estimated to be MDR-TB [85]. Although the proportion of MDR-TB is still low, due to the overall high TB burden in Bangladesh the absolute number of MDR cases is quite large (estimated 1900 for new and 2300 for previously treated patients) [84]. Bangladesh is unique in that it has one of the highest population densities in the world, is one of the high burden countries for TB, but has a low prevalence of HIV [17].

Identifying the population at risk of MDR-TB is essential and may help in developing appropriate case finding strategies [86]. Previous studies identified some risk factors associated with MDR-TB, namely previous TB treatment [19, 20, 23, 24, 51], poor past compliance with treatment [24, 52], HIV infection [20, 53], younger age-group [20, 22, 54], gender [20, 52], foreign born people [20, 22], living in an urban area [54], working in health care [53], type by bacteriology and pulmonary site of TB [53], presence of cavitation in lungs [24], contact with a TB patient [51], smoking or other substance misuse [53, 57], chronic renal failure [58], diabetes [59], use of other anti-microbial medicine [58], being an asylum seeker [53], living in a nursing home [53], being a prisoner [53], and hospitalization history [60]. Inappropriate medical management, absence of directly observed treatment, lack of uniformity between public and private sectors, limited or interrupted drug supply, poor quality and widespread availability of anti-tuberculosis drugs, were also reported as important causes associated with MDR-TB [19, 24, 51]. However, findings related to some risk-factors such as HIV status [19, 61], age-group [19] and gender of the patients [20, 23, 52] differed. Moreover, study designs varied widely, some findings were based on small sample sizes and some came from drug resistance surveys.

Characteristics of MDR-TB patients have not been systematically explored in Bangladesh. Flora et al. conducted a study in 2010 that recruited a small number of purposively selected participants [73], making it impossible to generalise the findings of the study. There were also a few discrepancies between the presented results and the conclusions drawn. The authors reported that only 30 (22.1%) MDR-TB patients and seven (4.6%) drug sensitive TB patients had a previous history of tuberculosis. However, they included the total sample in the analysis to test the factors related to past illness, such as “Course of treatment” and “Directly observed treatment” [73]. It is not

clear whether they were looking for the effects of current or previous treatment episodes. The National Tuberculosis Control Programme (NTP) Bangladesh started the MDR-TB programme in 2008 and gradually expanded its services in subsequent years [15]. At the time of the previously conducted study the MDR-TB programme was still evolving.

This is the context for our case-control study that explores the factors associated with MDR-TB. We compared the backgrounds and histories of MDR and drug-susceptible TB patients. All consenting MDR-TB patients aged between 18 and 65 years who were treated at one of the three government hospitals responsible for MDR-TB treatment in the country during the study period between September 2012 and April 2013 were included in the study. Controls were selected randomly from those local treatment units that had referred the cases.

2.3 Methods

2.3.1. Ethics considerations

The study was approved by the Human Research Ethics Committee (HREC) of the University of Newcastle (UoN), Australia and the Bangladesh Medical Research Council (BMRC), Dhaka, Bangladesh. 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. Written informed consent was then obtained from each person. A thumb impression was obtained from those who were unable to sign the consent form. All patients had been treated through the National TB Control Programme (NTP).

2.3.2 Study population and design

Patients were recruited from central, district and sub-district level government hospitals and Non-governmental organization (NGO) clinics in rural and urban Bangladesh. This case-control study includes 250 MDR-TB patients as cases and 750 drug-sensitive TB patients as controls. We designed the study to have 80% power to detect at least a 10% difference in the prevalence of any of our exposure variables at 5% significance threshold, assuming prevalence in the controls of 40% (with greater power and smaller effects detectable for exposures with lower control prevalence). This sample allowed us to accommodate the multivariate analysis for multiple factors.

MDR-TB patients aged between 18 to 65 years who gave their informed consent were included in the study. Patients who received treatment for MDR-TB following the criteria of the national guidelines of the National Tuberculosis Control Programme (NTP) were classified as MDR-TB. The NTP has recently adopted automated real time PCR (Xpert MTB/RIF) as the diagnostic tool of MDR-TB patients. Culture and Drug Sensitivity Testing (DST) and Line probe assays were also used [45]. Xpert MTB/RIF diagnoses only Rifampicin resistance. Patients who are resistant to Rifampicin are generally also resistant to Isoniazid (another first-line drug) as well. Mono-resistance to Rifampicin is fairly uncommon (0.2% and 0.4% among new and previously treated patients, respectively), as shown by a recent drug resistance survey (DRS) conducted in Bangladesh [87]. Controls were drug susceptible TB patients aged 18 to 65 years, diagnosed through sputum smear microscopy or other investigations (X-ray, FNAC, and Biopsy) as per national guidelines who would 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 (ICU), recent surgery or any medical emergency that needs continuous observation.

2.3.3 Data collection

MDR-TB patients from all over Bangladesh are referred to one of the three government hospitals (to the national hospital in Dhaka or a regional hospital in either Chittagong or Rajshahi). We consecutively recruited all eligible MDR-TB patients who were admitted in all three Government hospitals providing MDR-TB diagnosis and treatment services, from September 2012 ; recruitment ceased in April 2013 when the target of 250 cases was reached. We had considered 10% non-response rate in the sample size calculation. However, only seven TB patients (two cases and five controls) did not participate in the study. We recruited three controls per case from the local tuberculosis treatment unit from where the case was referred. The hospitals that were providing MDR-TB treatment were receiving patients referred by the various treatment units from rural and urban Bangladesh. Each TB patient is assigned a unique TB registration number as a routine practice. Treatment registration numbers of the tuberculosis patients, who were diagnosed during the specified period i.e. during the same month that MDR-TB was diagnosed, were listed. The controls were selected concurrently to avoid any seasonal bias. Three controls per MDR-TB case were randomly selected from this list at the treatment unit. (From the list of treatment registration number we derived serial interval by dividing the total number of patients of that month by three. First control was selected using an assigned random number; subsequent two controls were selected adding up the serial interval with the treatment registration number of first and second controls).Trained investigators collected information from the study participants using a pretested questionnaire through a face-to-face interview and review of records. All the

investigators received training on data collection procedures for one week. The NTP has its inbuilt quality control mechanism for diagnosis of MDR-TB patients through a laboratory based in Antwerp, Belgium. Diagnosis of drug-sensitive tuberculosis through microscopy is under an external quality assessment (EQA) network at country level.

2.3.4 Statistical analysis

A data entry template was used and data was validated by a series of logical checks. Summary statistics and tables were produced from cleaned and acceptable data. We compared participant characteristics between MDR-TB cases and controls using Student t-tests for continuous measures, and Chi-square (χ^2) tests for categorical measures. Associations between participant characteristics and MDR-TB status were assessed using both unadjusted and multivariable logistic regression models. We had sufficient MDR-TB cases to include the following variables in the multivariable model without risk of over-fitting: age, gender, educational status, occupation, history of health care related work, monthly household income, living conditions (number of persons per room), BCG vaccination status, contact with other TB patients, smoking, substance misuse (alcohol or drug addiction), type 2 diabetes as co-morbidity, and hospitalization history (within 7 months for any reason). We included all variables to the initial multivariable model and variables were removed from this model if the Likelihood ratio test was not significant at 5% and the coefficients of the remaining variables did not change by more than 15% (indicating no evidence of confounding). Collineartiy was assessed through inspecting variance inflation factors and assessing pair-wise Chi-Square tests. Data analysis was carried out using Stata statistical software version 12 (StataCorp LP, TX, USA).

2.4 Results

2.4.1 Socio-demographic and clinical characteristics

The study included 250 MDR-TB and 750 non-MDR-TB patients representing all seven divisions of Bangladesh. Mean age of participants was 37 years and 61% were male. About half of the participants had some education at secondary level or below and a median monthly income of 10000 Bangladeshi taka (129 USD approximately).

Details of Socio-demographic and clinical characteristics are shown in Table 2.1.

2.4.2 Risk factors for MDR-TB

2.4.2.1 Univariate analysis

Previous history of tuberculosis treatment was a major contributing factor to MDR-TB (OR 716.6, 95% CI 282.1-1820.8). In total, 29.3 % of participants had a history of previous tuberculosis treatment that was 98% of the MDR-TB and 6.4% of non-MDR-TB patients. MDR-TB patients were more likely to be male, aged between 18 and 45, educational level of secondary and below or higher secondary and above, have an occupation in service or business or transport work, are a smoker, have a history of substance misuse or type 2 diabetes (Table 2.2).

2.4.2.2 Multivariate analysis

We removed previous treatment form the multivariable model since the variance inflation factors were high and it had a high degree of association with many of the variables in the model. The variables showing strong association with previous treatment included age (Chi-square 7.2,df 2; p 0.027), educational status (Chi-square 15.3, df 2; p <0.0001), occupation (Chi-square 22.4, df 4; p <0.0001), history of health care related work (Chi-square 6.3, df 1; p 0.01), monthly household income (Chi-square

15.0, df 4; p 0.005), smoking (Chi-square 29.2, df 2; $p < 0.0001$), substance misuse (Chi-square 7.3, df 1; p 0.007) and type 2 diabetes as co-morbidity (Chi-square 8.7, df 1; p 0.003).

For the final multivariable model, we found that age group, educational status, occupation, smoking status, and type 2 diabetes were significantly associated with MDR-TB (Table 2.3).

Table 2.1 Socio-demographic and clinical characteristics of the study participants

Variables	Case	Control	Total	p[a]
Age				0.0001
Mean	33.9	37.9	36.9	
Median	30	35	35	
SD	12.3	14.1	13.8	
Sex				0.027
Male	167 (66.8%)	442 (58.9%)	609 (60.9 %)	
Female	83 (33.2%)	308 (41.1%)	391 (39.1%)	
Education				<0.0001
None	55(22%)	298 (39.7%)	353 (35.3%)	
Secondary and below	175 (70%)	398 (53.1%)	573 (57.3%)	
Higher secondary and above	20 (8%)	54 (7.2%)	74 (7.4%)	
Occupation				
None	9 (3.6%)	58 (7.7%)	67 (6.7%)	<0.0001
Service	74 (29.6%)	135 (18%)	209 (20.9%)	
Others [b]	108 (43.2%)	447 (59.6%)	555 (55.5%)	
Business	46 (18.4%)	79 (10.5%)	125 (12.5%)	
Transport worker	13 (5.2%)	31 (4.1%)	44 (4.4%)	
Income (BDT)[c]				
Mean	13066.0	11820.2	12132.0	0.1206
Median	10000	10000	10000	
SD	11016.3	10965.8	13.8	
Person living per room				0.069
Four or less	215 (86%)	676 (90.1%)	891 (89.1%)	
More than four	35 (14%)	74 (9.9%)	109 (10.9%)	
Weight (kilogram)				
Mean	42.5	44.6	44.0	0.002
Median	41.0	44.0	43.0	
SD	9.7	9.1	9.3	
BCG vaccination status				0.056
Absent	123 (49.2%)	317 (42.3%)	440 (44%)	
Present	127 (50.8%)	433 (57.7%)	560 (56%)	
Previous history of TB treatment				<0.0001
No	5 (2%)	702 (93.6%)	707 (70.7%)	
Yes	245 (98%)	48 (6.4%)	293 (29.3%)	
Cavitation in chest X-ray [d]				<0.0001
Absent	136 (90.7%)	330 (98.2%)	466 (95.9%)	
Present	14 (9.3%)	6 (1.8%)	20 (4.1%)	
History of Health care work				0.144
Absent	246 (98.4%)	722 (96.3%)	968 (96.8%)	
Present	4 (1.6%)	28 (3.7%)	32 (3.2%)	
Contact of TB patient				0.496
Absent	153 (61.2%)	477 (63.6%)	630 (63%)	
Present	97 (38.8%)	273 (36.4%)	370 (37%)	

Table 2.1 Continued.

Variables	Case	Control	Total	pa
Smoking status				<0.0001
Never smoked	125 (50%)	409 (54.5%)	534(53.4%)	
Current smoker	1(0.4%)	82 (10.9%)	83 (8.3%)	
Past smoker	124 (49.6%)	259 (34.5%)	383 (38.3%)	
Substance misuse*				0.013
Absent	213(85.2%)	681 (90.8%)	894 (89.4%)	
Present	37 (14.8%)	69 (9.2%)	106 (10.6%)	
Type-2 Diabetes				<0.0001
Absent	216 (86.4%)	701 (93.5%)	917 (91.7%)	
Present	34 (13.6%)	49 (6.5%)	83 (8.3%)	
Kidney disease				1.000
Absent	248 (99.2%)	745 (99.3%)	993 (99.3%)	
Present	2 (0.8%)	5 (0.7%)	7 (0.7%)	
Other disease [e]				0.831
Absent	242 (96.8%)	728 (97.1%)	970 (97%)	
Present	8 (3.2%)	22 (2.9%)	30 (3%)	
Hospitalization history [f]				0.194
Absent	246 (98.4%)	724 (96.7%)	970 (97.1%)	
Present	4 (1.6%)	25 (3.3%)	29 (2.9%)	

[a] P is the Probability of t-test or Chi-square ($\chi^{2)}$ tests. Fisher's exact Chi-square ($\chi^{2)}$ test was used for history of health care work, kidney disease, other disease, smoking status and hospitalization history.
[b] 'Others' subgroup under 'Occupation' includes housewife and self-employed small works.
[c] BDT: Bangladeshi currency.
[d] Cavitation related information was not available in 51% of the participants.
[e] Other disease included hypertension, heart diseases, asthma, chronic obstructive pulmonary diseases and chronic dysentery.
[f] Hospitalization history (within last seven months due to any reason) had one missing value
*Substance misuse refers to alcohol, cannabis and injectable drugs.

Table 2.2 Univariate logistic regression analysis on factors related to multidrug resistant tuberculosis (MDR-TB).

Variables	Odds ratio	Confidence Interval [a]	p [b]
Previous history of TB Treatment			
No	1.00		
Yes	716.63	282.1-1820.8	<0.0001
Gender			
Female	1.00		
Male	1.4	1.0-1.9	0.028
Age-group			
More than 45 years	1.00		
18 to 25 years	1.97	1.3-3.0	0.001
26 to 45 years	2.06	1.4-3.0	<0.0001
Education			
None	1.00		
Secondary and below	2.38	1.7-3.3	<0.0001
Higher secondary and above	2.01	1.1-3.6	0.02
Occupation			
None	1.00		
Service	3.53	1.7-7.5	0.001
Others [c]	1.56	0.7-3.2	0.236
Business	3.75	1.7-8.3	0.001
Transport worker	2.70	1.0-7.0	0.041
Smoking status			
Never smoked	1.00		
Current smoker	0.04	0.05-0.3	0.001
Past smoker	1.57	1.2-2.1	0.003
Substance misuse*			
No	1.00		
Yes	1.71	1.1-2.6	0.014
Type-2 Diabetes			
No	1.00		
Yes	2.25	1.4-3.6	0.001

[a] Confidence interval at 95% level

[b] p is the p value of Wald test statistic.

[c] 'Others' subgroup under 'Occupation' includes housewife and self-employed small works

Only the significant variables are shown in the table (significance level at 0.05)

*Substance misuse refers to alcohol, cannabis and injectable drugs.

Table 2.3 Multivariable analysis on factors related to multidrug resistant tuberculosis (MDR-TB)

Predictor	Adjusted Odds ratio	Confidence Interval [a]	p[b] (Wald)	p[c] (lrt)
Age group				0.0325
More than 45 years	1.00			
18 to 25 years	1.77	1.07-2.93	0.027	
26 to 45 years	1.72	1.12-2.66	0.013	
Education				0.0026
None	1.00			
Secondary and below	1.94	1.32-2.85	0.001	
Higher secondary and above	1.83	0.92-3.65	0.086	
Occupation				
None	1.00			0.002
Service	2.88	1.29-6.44	0.010	
Others [d]	1.65	0.76-3.55	0.203	
Business	3.71	1.59-8.66	0.002	
Transport worker	2.71	0.95-7.72	0.063	
Smoking status				<0.0001
Never smoked	1.00			
Current smoker	0.04	0.005-0.29	0.002	
Past smoker	1.58	0.99-2.50	0.053	
Type-2 Diabetes				0.0006
Absent	1.00			
Present	2.56	1.51-4.34	0.001	

[a] Confidence interval at 95% level.
[b] p (Wald) is the p value of Wald test statistic..
[c] p (lrt) is the p value corresponding to the Likelihood ratio test statistic
[d] "Others" subgroup under "Occupation" includes housewife and self-employed small works.
Only the significant variables in multivariate model are shown in the table (significance level 0.05).

2.5 Discussion

Multidrug resistance is more commonly reported among previously treated tuberculosis patients than in new tuberculosis patients, globally as well as in Bangladesh [84]. Our study showed that most MDR-TB patients (98%) had a history of previous tuberculosis treatment, in line with other studies [19, 20, 23, 24, 51, 57]. In a systematic review of risk factors conducted in Europe, previous treatment history of TB was the strongest determinant of MDR-TB in Europe and the pooled risk of MDR-TB was 10.23 times higher in previously treated patients than in patients without prior treatment [20]. Previous treatment as a risk factor helped in developing the MDR-TB case finding strategy during the introduction of MDR-TB programmes [86]. Drug sensitivity testing is not routinely done on all TB patients in Bangladesh due to the large number of patients diagnosed each year [45]. Recent national guidelines recommend that previously treated patients, new TB patients with treatment failure, and people in contact with MDR-TB patients, are referred for MDR-TB testing. In addition, patients with delayed response in treatment, or with smear-negative or extra-pulmonary TB that does not improve clinically, with relapse or who receive treatment after default, or who have HIV, are tested for MDR-TB in Bangladesh [45].

In our study, being between 18 and 45 years of age was associated with an increased risk for MDR-TB compared to the age group more than 45 years; similar to what was reported in another study conducted in Hong Kong [22]. Another study conducted in Bangladesh found that patients under 40 years are more likely to develop MDR-TB, based on univariate findings, although this association could not be established in the multivariate model (OR 0.87; 95% CI 0.40- 1.93 and OR 0.87 CI 0.33-2.33 for age-groups 21 to 30 years and 31 to 40 years, respectively) [73]. Other studies conducted in Shanghai and Spain found that the greatest risk of MDR-TB was associated with age 35

to 59 [54] and 45 to 65 years [57], respectively. Although the range varies, being below 65 years is associated with developing MDR-TB, as reported in multi-country reviews [19, 20]. Younger people are more likely to come in contact with MDR-TB as they are more mobile and active compared to the older age group through their involvement in work or study [22]. They may also find it difficult to take regular supervised medicine due to conflicting work times, which results in poor treatment adherence. Another explanation for the greater risk in younger age groups may be that Rifampicin was introduced in recent decades and many elderly people may not have been exposed to it [22]. These explanations may not be applicable to primary drug resistance that is transmitted. In our study only five (2%) MDR-TB patients did not have any history of previous treatment, in line with the low level of primary resistance in a recent drug resistance survey, where 1.4% of MDR-TB patients did not have a previous diagnosis, compared to 28% of previously treated patients [87].

A number of occupations such as those associated with services and business were more likely to be linked with MDR-TB compared to non-working individuals. Occupation as transport workers, another highly mobile group, was associated with MDR-TB if examined alone, although we did not observe any difference after adjusting for other factors. This study did not show any association with health care as an occupation, which was found to be associated with MDR-TB in another study [53]. Patients with some educational qualification were more likely to develop MDR-TB than patients with no formal education or from the highest educational group.

Type 2 Diabetes is known to be a risk factor for TB [88] and is linked to MDR-TB in our and other studies [59]. It may affect TB treatment outcome and disease presentation [88], leading to failed treatment, although this is not always the case [89]. Impaired

immunity due to diabetes may increase susceptibility to infection with drug resistant strains [59]. Bangladesh is facing the dual burden of communicable and non-communicable diseases. The prevalence of Diabetes mellitus has increased from 2.3% in 1999 to 7.9% in 2009 [90]. The relationship between MDR-TB and diabetes could be addressed by treating diabetic patients with tuberculosis within a collaborative framework [91]. In our study, the diabetes status was self-reported by the patients. Further studies using a screening method for diabetes status need to be conducted.

MDR-TB patients were more likely to be past tobacco smokers in our study. Although current smokers were less likely to have MDR-TB compared to non-smokers, this may be a result of MDR-TB patients quitting smoking on diagnosis. Smoking is one of the main determinants for TB and some studies showed an association with acquired drug resistance [92]. Another study showed that smoking is a predictor for delayed response to treatment [93]. Tobacco control efforts have been initiated in Bangladesh in recent years, including some piloting of its integration with tuberculosis services [94]. Our finding suggests that TB and tobacco control efforts need to be sustained to control TB overall as well as MDR-TB. Intravenous drug use was a risk factor for MDR-TB in another study [53]. Drug or alcohol misuse was not a significant cause of MDR-TB in our study, after adjusting for other factors.

Males were more likely to have MDR-TB than females in some settings [20] whereas the opposite was true in others [23, 52]. Gender was not a risk factor in our study. Although contact with TB patients was found to be associated with MDR-TB in other studies [51, 70, 95], we did not observe any association. Neither did we observe any effect of income, crowding status expressed as persons per room, vaccination status (BCG), history of hospitalization within seven months, and kidney disease. Overall,

56% of our participants were BCG vaccinated in their childhood. Recent BCG coverage among children has increased remarkably in Bangladesh and has reached almost 98% [96].

In this study we focused on hospital based cases, as a population-based risk factor study was not feasible for MDR-TB. However, our cases are likely to be representative of MDR-TB patients in Bangladesh as we recruited from all three Government TB hospitals which treat most of the MDR-TB patients in the country. We recruited the controls from the population rather than from MDR-TB hospitals to ensure they were representative of non-MDR patients. In Bangladesh, most TB patients are treated within the NTP designated DOTS centres, and current case notification rate in Bangladesh is 68% [84]. We could not assess HIV status as a risk factor in our study. However, Bangladesh is a low burden country for HIV [6]. It was not feasible to confirm drug susceptibility using Drug Sensitivity Testing (DST) of the controls, as only high-risk patients are routinely tested, and we did not have the funds for this.

2.6 Conclusion

Previous tuberculosis treatment was found to be the major risk factor for MDR-TB. This study also identified the following as risk factors for MDR-TB: age 18 to 45 years, some education up to secondary level, service and business as occupation, past smoking status, and type 2 diabetes as comorbid illness. These risk factors should be addressed in the strategy for MDR-TB control. The NTP of Bangladesh is reliant on multi-sectoral involvement to address all risk factors and can advocate for these issues in order to improve control of MDR-TB. The integration of MDR-TB control activities with diabetes and tobacco control programmes would be a good place to start these collaborative efforts.

Chapter 3 Factors related to previous tuberculosis treatment of Multidrug resistant Tuberculosis patients in Bangladesh

3.1 Abstract

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

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

Setting: Central, district 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 patients). Overall, 54% of patients received previous tuberculosis treatment more than once, and all of these patients were multidrug resistant. MDR-TB patients were more likely to have experienced the following factors: incomplete treatment (4.3; 95% CI 1.7-10.6), adverse reactions due to TB treatment (OR 8.2; 95% CI 3.2-20.7), hospitalization for symptoms associated with tuberculosis (OR 16.9; CI 1.8-156.2), DOTS centre as treatment unit (OR 6.4; CI 1.8-22.8),

supervised treatment (OR 3.8; CI 1.6-9.5); time to treatment centre (OR 0.984; CI 0.974-0.993).

Conclusion: Incomplete treatment, hospitalization for tuberculosis treatment and adverse reaction are the factors related to previous tuberculosis treatment of MDR-TB patients. Although the presence of supervised treatment (DOT), less time to treatment centres and being treated in DOTS centres were relatively higher among the MDR-TB patients compared to non-MDR-TB patients, these findings include information of their most recent TB treatment episode only. Most (64.5%) of the MDR-TB patients had received tuberculosis treatment more than once.

3.2 Introduction

Global tuberculosis (TB) control efforts are facing the additional challenge of Multidrug Resistant tuberculosis (MDR-TB) [7]. MDR-TB is caused by bacteria that are resistant to at least isoniazid and rifampicin, the most effective anti-TB drugs for treating TB [85]. MDR-TB cannot be treated with first line anti-tuberculosis medicines and needs a longer treatment period with stronger second-line medicines [48]. 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 [97]. The number of reported MDR-TB cases has been increasing in recent years [97]. 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 [97]. Previous tuberculosis treatment is a known risk factor for MDR-TB [19-25]. Patients with previous TB treatment are difficult to manage and might be infectious for a longer period. ‘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 extra-pulmonary TB) [98]. Previously treated recurrent TB is no longer a neglected area; rather it is considered to be an important factor to be considered for TB control [10, 99]. 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-tuberculosis 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 (NTP) were cited to be the factors related to development of drug resistance [71, 72].

The World Health Organization (WHO) has identified 27 high burden countries for MDR-TB. Four of these countries, including Bangladesh, belong to the South-East Asian region [14]. In Bangladesh, MDR-TB is an emerging public health problem [100]. According to the recent drug resistant survey, 1.4% of new cases and 29% of the retreatment cases in Bangladesh have MDR-TB [16]. Although the rate of MDR-TB is still relatively low, due to the overall high TB burden in Bangladesh the absolute number of MDR-TB cases was quite large, with 2100 among new TB patients and 2600 among the previously treated TB patients, in 2013 [97]. Recent studies in Bangladesh suggest that previous tuberculosis treatment is an important risk factor for MDR-TB [16, 73]. Re-treatment patients constitute approximately 3% of all tuberculosis patients in the national data collection which corresponded to 6385 patients in 2013 [100]. However, the detailed information regarding the previous tuberculosis treatment has not yet been collected. Factors related to previous management of tuberculosis need to be identified to develop control strategies. The main objective of this study is to explore

the factors related to the previous tuberculosis treatment of current MDR-TB patients compared to the non-MDR-TB patients of Bangladesh.

3.3 Methods

We previously conducted a case-control study to identify the risk factors of multidrug resistant tuberculosis in Bangladesh [101]. The study included 250 MDR-TB and 750 non-MDR-TB tuberculosis patients, 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 5% significance threshold [101]. We found that 293 patients (29.3%) (245 MDR-TB and 48 non-MDR-TB) had previously received treatment for tuberculosis. All patients with a history of previous tuberculosis treatment were interviewed about parameters related to their previous treatment history. This study restricts analysis to the strata of patients that have previously treated for tuberculosis.

The setting, definition and the inclusion and exclusion criteria of the study have been described in detail previously [101]. The setting was central, district and subdistrict level hospitals in rural and urban Bangladesh. MDR-TB patients aged between 18 and 65 years who gave their informed consent were included in the study. Previous history of TB treatment and number of episodes of previous TB treatment were based on patient's statement. Patients, who received treatment for MDR-TB following the 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 MDR-TB patients. Culture and Drug Sensitivity Testing (DST) and Line probe assays were also used [45]. Xpert MTB/RIF diagnoses only Rifampicin resistance. Patients who are resistant to Rifampicin are generally also resistant to Isoniazid (another first-line drug). Mono-resistance to Rifampicin is fairly uncommon (0.2% and 0.4% among new and

previously treated patients, respectively), as shown by a recent drug resistance survey (DRS) conducted in Bangladesh [16]. Drug susceptible TB patients aged 18 to 65 years, who gave their informed consent, were diagnosed through sputum smear microscopy or other investigations (X-ray, FNAC 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 (ICU), 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 tuberculosis treatment is six and eight months for new and retreatment types of drug-sensitive patients, respectively [40]. Presence or absence of incomplete treatment during the previous TB treatment was based on patient's statement, which refer 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".

3.3.1 Data collection

MDR-TB and non-MDR-TB patients were identified as part of a previously conducted case control study on risk factors of MDR-TB [101]. MDR-TB patients 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 MDR-TB patients 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 TB patient is assigned a unique TB registration number as a routine practice. Treatment registration numbers of tuberculosis patients, who were diagnosed during the specified period i.e. during the same month that MDR-TB was diagnosed, were listed. Three non-MDR-TB patients per MDR-TB patient, from the local tuberculosis treatment unit from where the case was referred, were recruited under the previous study.

All patients who had a history of previous tuberculosis 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 was collected from patient record review.

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

3.3.2 Statistical analysis

We compared participant characteristics between MDR-TB (245) and non-MDR-TB (48) patients using Student t-tests for continuous measures, and Chi-square (χ^2) tests for categorical measures. Unadjusted and multivariable logistic regression models were used to estimate odds ratios (and 95% confidence intervals) for MDR-TB status. Multivariable model included following variables: site of previous tuberculosis, adverse reaction due to tuberculosis treatment, hospitalization due to tuberculosis, type of centre

for treatment initiation and follow up, presence of supervised 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 and distance to treatment centre. Cost to treatment centre and distance to treatment centre were excluded from the model for possible colinearity with the variable "time to treatment centre".

We assessed statistical significance of odds ratios using the likelihood ratio tests, and we had sufficient patients to include the variables in the multivariable model without risk of over-fitting. The odds ratios derived from these models correspond to effects specific to the strata of patients that have been previously treated for tuberculosis. Data analysis was carried out using Stata statistical software version 12 (StataCorp LP, TX, USA).

3.3.3 Ethics considerations

The study was approved by the Human Research Ethics Committee (HREC) of the University of Newcastle (UoN), Australia and the Bangladesh Medical Research Council (BMRC), Dhaka, Bangladesh. 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 National TB Control Programme (NTP), Bangladesh.

3.4 Results

Among the previously treated MDR-TB patients, 64.5% had been treated more than once and all non-MDR-TB patients had only one episode of treatment previously. Mean age of previously treated MDR-TB patients was lower than non-MDR-TB patients. The majority of the patients were male and had pulmonary tuberculosis. Detailed demographic and clinical characteristics are presented in Table 3.1.

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 MDR-TB patients, 63.7% received a retreatment regimen commonly known as category-2, consisting of five drugs including injectable Streptomycin. Based on the available records, all non-MDR-TB patients were treated with the regimen for new tuberculosis patients that consist of a combination of four oral drugs. The most frequent category for duration of previous treatment was five months (59.6%). The majority (64.6%) of drug-sensitive TB patients discontinued their treatment at three months or less. Treatment failure was higher among the MDR-TB patients compared to non-MDR-TB patients (68.4% and 28.6%, respectively) during their previous treatment. Of the MDR-TB patients, 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 non-MDR-TB patients. Hospitalization for TB related problems during their previous TB treatment mostly occurred for MDR-TB patients (13.5%). The three main causes of hospitalization 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).

Table 3.1 Demographic and clinical characteristics of previously treated tuberculosis patients

Variable	Non-MDR-TB (n=48)	MDR-TB (n=245)	Total	P
Age (years)				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 to 45 years	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 [a]				<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-standardized	0 (0%)	1 (0.4%)	1 (0.0%)	
Duration of treatment				<0.0001*
6-8 months	3 (6.3%)	15(6.1%)	18 (6.1%)	
4- 5 months	14 (29.1%)	146 (59.6%)	160 (54.6%)	
3 months or less	31 (64.6%)	84 (34.3%)	115 (39.3%)	
Treatment outcome [a]				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 [a]				0.001*
Absent	35 (94.6%)	155 (67.4%)	190 (71.2%)	
Present	2 (5.4%)	75 (32.6%)	77 (28.8%)	
Hospitalization 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%)	

[a] Treatment regimen, treatment outcome and treatment extension had total 261, 231 and 267 observations respectively.

* Probability of χ^2

** Probability of t-test

Patients were asked if they had stopped their treatment at any point of their previous tuberculosis treatment and in this paper we refer it as incomplete treatment. Incomplete treatment during previous TB treatment was reported by 63.3% and 29.2% of MDR-TB and non-MDR-TB patients, respectively, as stated by the patients. Reasons for incomplete treatment among the MDR-TB and non-MDR-TB patients are presented in Table 3.2.

Table 3.2 Incomplete treatment and the reasons reported by previously treated tuberculosis patients

Variable	Non-MDR-TB (n=48) n (%)	MDR-TB (n=245) n (%)	P
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

Patients who do not complete their treatment are supposed to be followed up by one of their health care providers, according to the national TB guideline [40]. A high proportion (91.6%) of MDR-TB patients reported that they had been followed up during previous TB treatment, although among non-MDR-TB patients follow-up was quite low (14.3%).

Current MDR-TB patients had been treated for their previous tuberculosis mostly in designated centres for TB (DOTS centre) (95.9%); for non-MDR-TB patients the proportion was 70.8%. Rate of treatment in private centres during previous treatment episode was 4.1% and 29.2% for MDR-TB and non MDR-TB patients, respectively. Although majority of MDR-TB patients were treated in DOTS centre, supervised intake of medicine by Directly Observed Treatment (DOT) during their previous treatment was reported by 78.4% of MDR-TB patients and 41.7% of non MDR-TB patients, respectively, as reported by the patients.

We further explored who had supervised the medicine intake and found that 70.3% of MDR-TB and 80% of non-MDR-TB patients were given their medicine by trained providers (community health volunteers, health worker at facility or field level, village doctors). The rest of the patients were given their medicine by a family member, neighbours or other providers.

Median travel time to visit the previous treatment centre, which was the designated unit for treatment initiation and follow-up, was 20 minute for MDR-TB and 40 minutes for non-MDR-TB patients.

Details of health system factors are presented in Table 3.3.

Table 3.3 Health system related characteristics of previously treated tuberculosis patients

Variable	Non-MDR-TB n=48	MDR-TB n=245	Total	p
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 [a]	16 (80%)	135 (70.3%)	151 (71.2%)	
Family/other provider [b]	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 (minute)				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	

* Probability of χ^2 test
**Probability of t-test
[a] 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
[b] "Family and other providers" includes family members, neighbours and other volunteers supervising the treatment
BDT is Bangladesh taka (1 USD is 77 BDT approximately)
Time to treatment centre, cost to treatment centre and distance to treatment centre had total 286, 283 and 285 observations, respectively.

3.4.1 Logistic regression analysis

In the multivariable adjusted analysis, MDR-TB patients were shown to be more likely to be male (OR 5.1; CI 1.8-14), have a history of incomplete tuberculosis treatment (4.3; 95% CI 1.7-10.6), adverse reactions due to anti-tuberculosis medicines (OR 8.2; 95% CI 3.2-20.7), hospitalization due to tuberculosis (OR 16.9; CI 1.8-156.2), have been treated in a designated DOTS centre (OR 6.4; CI 1.8-22.8) and time to treatment centre (OR 0.984; CI 0.974-0.993).

Directly observed treatment (OR 3.8; 95% CI 1.6-9.5) was high among MDR-TB patients during their previous TB treatment compared to the non-MDR-TB patients. Site of previous TB (pulmonary or extrapulmonary) was no longer associated in the adjusted model. Findings of the logistic regression are shown in Table 3.4.

Table 3.4 Univariate and multivariable analyses on multidrug resistant tuberculosis status and previous treatment related factors

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

[*] Confidence interval at 95% level

[**] P is the value of Wald test statistic

3.5 Discussion

MDR-TB patients were found to be four times more likely to have a history of incomplete tuberculosis treatment than non-MDR-TB patients. Incomplete treatment refers to discontinuation at any phase of the previous treatment reported by patients. This finding has been supported by many studies [19, 24, 52, 64, 66]. The majority of MDR-TB patients (92.3%) stated that the reason for incomplete treatment was that they remained positive to tuberculosis bacteria in 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 the 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 [45]. However, half of the non-MDR-TB patients did not complete their treatment as they felt better after starting the treatment. The next cause after "feeling better" for treatment discontinuation reported by non-MDR-TB patients 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 mobilization activities [40]. Although the MDR-TB patients 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 MDR-TB patients had more than one episode of earlier TB treatment. The TB control programmes should address the reasons for incomplete treatment for all types of tuberculosis patients. Incomplete treatment may lead to development of drug resistance at any point of time irrespective of number of treatment episodes.

MDR-TB patients were more likely to have adverse reactions to anti-tuberculosis 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 explained as the use of second line drugs during their previous TB treatment, and these are commonly more toxic than first line anti-tuberculosis drugs [102]. In our study, we found most of the MDR-TB patients were treated previously 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 MDR-TB patients. However, the patients with adverse reactions to anti-tuberculosis medicine can be treated with special care. Patient education at the beginning of treatment can be strengthened by advice on adverse reactions.

Hospitalization for more than fourteen days associated with MDR-TB and XDR-TB was found in one study [60]. In our previous study, we did not find any association of MDR-TB status with hospitalization due to any other cause within the last seven months of current treatment [101]. Hospitalization 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 hospitalization 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 to be tested for MDR-TB: previously treated patients, current TB patients 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 MDR-TB patients [45].

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 [21]. The other category includes factors that are related to the individual patient's vulnerability to develop MDR-TB, such as clinical and demographic factors [21].

In our study, more MDR-TB patients reported supervised treatment (DOT) during their most recent TB treatment episode compared to the non-MDR-TB patients (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 [9]. 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 MDR-TB patients they might have been treated with a retreatment regimen which contains injectable Streptomycin which requires more supervised care as the injection must be administered by a provider. This could also explain the comparatively higher level of follow up among the MDR-TB patients by the providers after incomplete treatment. We found that more MDR-TB patients than non-MDR-TB patients 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 the MDR-TB patients 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 to the patients who had been treated on a new patient's regimen (category-1). However, new tuberculosis patients require the same effort as retreatment patients to prevent further development of drug resistance.

The national TB control programmes of high burden TB countries where a private sector is also present face difficulties to implement treatment guidelines, resulting in inadequate treatment or non-compliance [72]. In Bangladesh, designated DOTS centres are the centres managed by public and non-government organizations 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 TB control programme. Medicines for TB are also available in the private market in Bangladesh and the unregulated private sector is likely to treat tuberculosis patients using non-standardized regimen which may lead to development of drug resistance [79]. In our study, MDR-TB patients 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 MDR-TB patients are treated under these three Government hospitals. We do not have any information on MDR-TB patients treated by private physicians who are beyond national TB control programme. 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 rate of MDR-TB among patients treated by DOTS centre and by private providers [103]. Thorough review of medication given during previous treatment, regardless of its setting, was recommended [103].

The National Tuberculosis Control Programme (NTP) of Bangladesh provides services integrated into the basic health services [100]. Tuberculosis control through DOTS services has been expanded throughout the country in all sub-districts and metropolitan cities with the support of Non-Government Organizations such as BRAC, the Damien Foundation and other organizations such as UPHCSDP, NHSDP and BGMEA, or through public private partnerships [100]. 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 [104]. 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 minutes in MDR-TB and non-MDR-TB, respectively) among the MDR-TB patients compared to non-MDR-TB patients. We did not find any significant difference in cost 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 unstable living circumstances, such as the eviction of slum in some areas or losing a job. A detail

qualitative study needs to be conducted in future regarding other treatment access factors of tuberculosis patients.

This study is a stratified analysis of previously treated tuberculosis patients taken from a case control study which recruited the MDR-TB and non-MDR-TB patients representing the population. The sample size and power were calculated based on 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 of all previous treatment episodes for the patients as we had extracted the information based on the most recent episode, to aid the accuracy of the recalled information. It was not feasible to confirm drug susceptibility using Drug Sensitivity Testing (DST) of the non-MDR-TB patients, as only high-risk patients are routinely tested, and we did not have the funds for this.

3.6 Conclusion

In conclusion, we found that incomplete treatment which includes treatment discontinuation due to treatment failure, adverse reactions to anti tuberculosis medicine, and hospitalization for TB complications during previous tuberculosis treatment are the main factors leading up to MDR-TB. Although we found seemingly contradictory findings regarding supervised treatment, less time required to visit treatment centre and the designated DOTS centre, it does not necessarily mean that supervised treatment, accessibility or being treated in a designated DOTS centre contribute to MDR-TB. These findings are based on the most recent episode of previous treatment of MDR-TB patients, as most patients have more than one episode of previous tuberculosis 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 hospitalized for TB related causes could be tested for MDR-TB. Patient education could be strengthened for all TB patients regarding adverse effect and compliance related issues.

Chapter 4 Why are tuberculosis patients not treated earlier? A study of informal health practitioners in Bangladesh

4.1 Summary

Setting: Five districts and four cities of Bangladesh.

Objective: To study the role of informal health practitioners in delay in initiating tuberculosis TB treatment in new smear-positive TB patients.

Design: A cross-sectional study of all patients registered within specific projects in Bangladesh using routine records from projects. Definitions were as follows: 1) total delay: duration from onset of symptoms to initiation of treatment; 2) Patient delay: onset of symptoms to first visit to any practitioner; and 3) Health system delay- first visit to practitioner to treatment initiation.

Results: A total of 7280 cases were enrolled. Prolonged delay was calculated as ≥5 weeks for patient delay, ≥10 weeks for health system delay and ≥13 weeks for total delay. Prolonged patient delay was less frequent when patients first consulted informal as compared to qualified health practitioner (30% vs. 68%). Similar figures for prolonged health system delay were 52% and 16%, while those for total delay were 47% and 27%. The differences were statistically significant ($p<0.05$).

Conclusion: Patients seeking care from informal practitioners, access care more promptly but have prolonged delays in initiating treatment. Further investigation on how to involve these practitioners in the programme should be evaluated.

4.2 Introduction

Tuberculosis (TB) is a major public health problem in Bangladesh, which according to World Health Organization ranks sixth among high-burden countries [105]. The National Tuberculosis Control programme (NTP) started implementation of the internationally recommended DOTS strategy in 1993, and is now estimated to have reached the high treatment success (92 %) and case detection (72%) targets that are expected to reduce the transmission of infection in the community [36].
Delays often occur in initiating TB treatment [27, 76]. Such delays may lead to progression of disease, poor treatment outcomes, an increased risk of death and an increase in TB transmission in the community which represents a major obstacle to the control of a TB epidemic [26]. These adverse effects justify our interest in understanding factors behind the delays and finding possible solutions to the problem in Bangladesh.

Different types of health care providers administer TB services in Bangladesh, including both qualified and informal practitioners. A previous study in Bangladesh focused on the role of gender in increasing delays, but did not evaluate the type of service providers [76]. The objective of the current study was to determine the time between start of symptoms and start of TB treatment in selected urban and rural areas of Bangladesh, and document the factors related to delay in treatment initiation, focusing on the role of informal health practitioners.

4.3 Methods

4.3.1 Design

This cross-sectional study included all new smear positive pulmonary TB cases registered during the period of April, 2004 to September, 2005 within FIDELIS (Fund

for Innovative DOTS Expansion through Local Initiatives to Stop TB) projects in Bangladesh. The study is an analysis of information obtained from the routine reports from these projects.

4.3.2 Background

BRAC (formerly Bangladesh Rural Advancement Committee), a non-government organization (NGO) based in Bangladesh has been supporting the NTP for many years and provides TB services that cover about two thirds of the country's population. BRAC undertook these two projects, covering a total population of 23.7 million, as part of these services. The projects were carried out in five districts and four city corporation areas, selected for their low estimated case detection rates.

4.3.3 Study Population

The study focused on new smear positive pulmonary TB patients. According to the national guidelines, these are defined as patients who have never received anti-tuberculosis drugs or have received drugs for ≤1 month. Smear Positive pulmonary TB was defined as a patient with at least two sputum specimens positive for acid-fast bacilli (AFB) on smear microscopy, or one sputum specimen positive for AFB if supported by a chest radiograph consistent with active TB or a sputum culture positive for *M. tuberculosis* [106].

Based on the research question "Does seeking first level care from informal health practitioners result in delay in initiating treatment?" a sample size calculation was made using Open Epi software. Sufficient power was obtained using the assumption that 4200 (60%) of approximately 7000 cases registered, would visit informal practitioners and 36% would be found to have a delay in diagnosis.

4.3.4 Data sources, data collection and variables

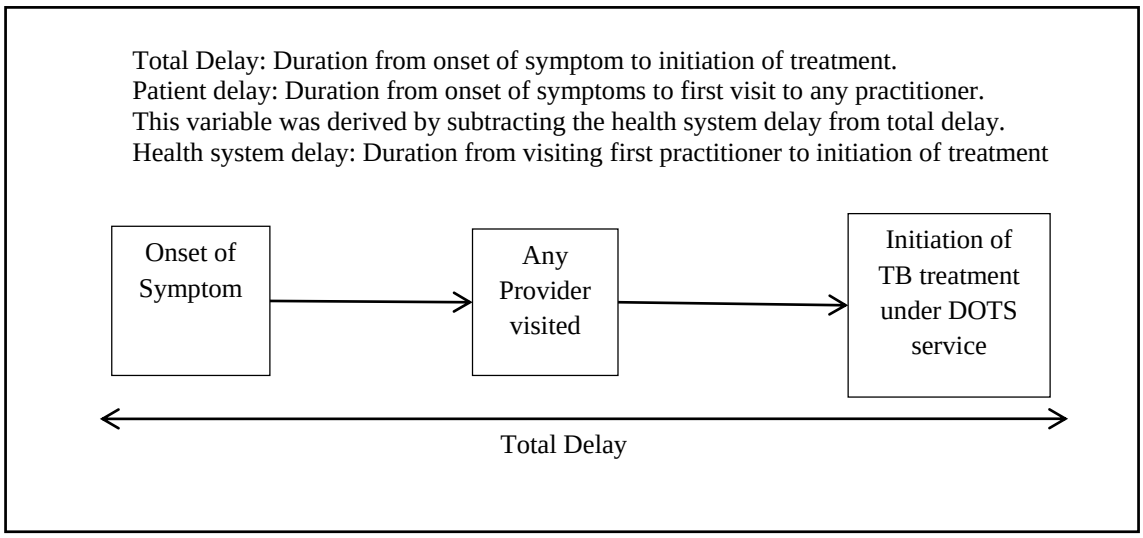
Data were collected routinely during treatment initiation as part of the provision of services, using a prescribed form required by the projects. The questionnaire included the following: 1) information on the total period of time from earliest onset of symptoms to initiation of treatment, expressed in weeks; 2) any visit made to a health care practitioner prior to start of treatment, and details about time and type of practitioner visited; and 3) information regarding the patient's demographic characteristics (age, sex, and project area) and symptoms present during the episode. Information on symptoms and type of practitioner was presented in multiple choice tick boxes.

Staff involved in the projects were trained on how to use the questionnaire. Periodic checking of questionnaires and feedback were part of routine programme activities and were used to monitor data quality.

Informal practitioners referred to as “traditional healer or equivalent” included village doctors, pharmacists, rural medical practitioners, and traditional healers, none of whom held a science or medicine degree. Qualified practitioners included all other personnel who had a medical degree including private practitioners not within the TB (DOTS) facility, medical doctors and public sector health care workers working in public sector TB (DOTS) facilities. Other variables that were collected from patients and analysed were age, sex, and urban-rural status. Urban status was defined as patients coming from urban projects and the Sadar subdistricts (which include the district town). Other areas were regarded as rural.

Key outcome variables and their definitions are shown in the Figure 4.1. In this study we considered cough as the main symptom for considering delay as most of the new smear-positive patients usually have cough.

Figure 4.1 Definition of key outcome variables



As the distribution of delay was expected to be non-normal, the overall distribution in the entire group of patients were divided into five parts (quintiles), by twenty per cent intervals in the distribution. Prolonged delay was defined by the two highest quintiles of the distribution of delay for all patients, the cut-off point being defined by taking the specific week that included 60% of the patients.

4.3.5 Data Analysis

Data were computer-entered with no personal identifiers and were analysed using SPSS 13(Statistical Package for Social Sciences, Chicago, IL, USA). Statistical analysis was carried out using chi-square for univariate analysis and logistic regression for multivariate analysis.

4.3.6 Ethical considerations

The project was approved by the NGO Affairs Bureau of Bangladesh. Ethical approval for the current study was obtained from the Bangladesh Medical and Research Council and the Ethics Advisory Group of The International Union Against Tuberculosis and Lung Disease.

4.4 Results

There were 7280 new smear positive pulmonary TB cases enrolled in the projects, whose socio-demographic characteristics are shown in Table 4.1. The median total delay of these patients was 12 weeks, with the median patient delay and health system delay being 4 and 8 weeks, respectively.

Table 4.1 Socio-demographic characteristics of patients under the study

Variable	n	%
Sex		
Male	5019	69
Female	2261	31
Residence		
Urban	3542	49
Rural	3738	51
Practitioners visited for first consultation		
Traditional healer or equivalent [a]	5023	69
Non DOTS [b]	1152	16
DOTS clinic [c]	84	1
No practitioner visited prior to this visit of treatment initiation	1021	14
Patient's age , years, mean ± SD	38.5± 16.3	

[a.] Includes traditional healer, pharmacists, and rural medical practitioners and village doctors.
[b] Private practitioners and gradate medical doctors.
[c] DOTS facility recognized by the national tuberculosis control programme (NTP).
SD= Standard Deviation

The quintile distribution for the entire group of patients in terms of weeks of delay corresponded to 0-7, 8-9, 10-12, 13-17 and ≥18, for total delay. For patient delay, the distribution was < 1, 1-2, 3-4, 5-7, and ≥8. For health system delay, it was 0- 2, 3-6, 7-9, 10-11, ≥12.

We then compared the distributions among patients who first consulted qualified practitioners with those who first consulted informal practitioners (Figures 4.2 and 4.3). We found that prolonged total delay (≥13 weeks) occurred in 47% of those first consulting an informal practitioner compared with 27% of those who first consulted a qualified practitioner. The corresponding figures for prolonged patient delay (≥5 weeks) were 30% and 68% for informal and qualified practitioners, respectively. Distributions for prolonged health system delay (≥10 weeks) were 52% for those consulting informal practitioners and 16% for those first consulting qualified practitioners. These differences were all statistically significant. (Pearson Chi-Square: $p < 0.05$; Table 4.2).

Figure 4.2 Total delay in starting tuberculosis treatment by status of health practitioners in selected areas of Bangladesh.

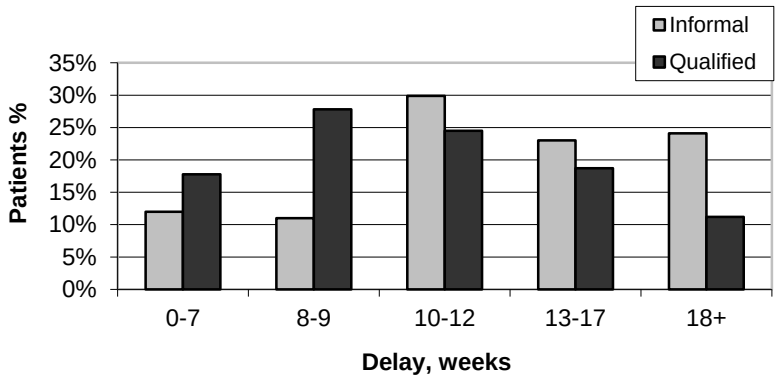


Figure 4.3 Tuberculosis patient delay in in selected area of Bangladesh by first visit to health practitioners.

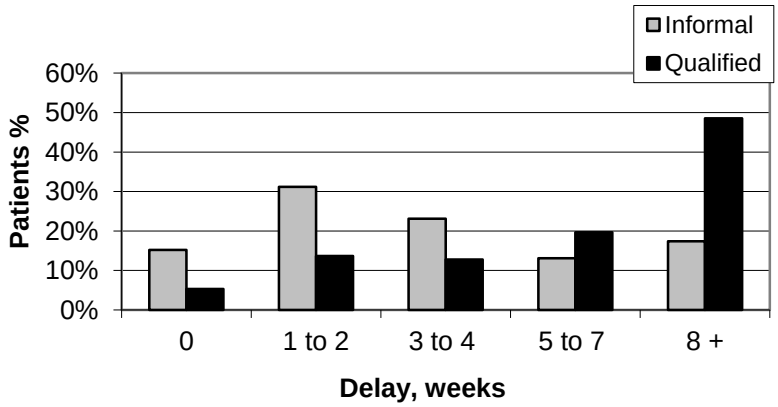


Table 4.2 Prolonged delays (total, patient and health system delays) comparing the first visits to informal providers and those to qualified and practitioners [a]

Variable	n	P value [b]
Total delay		
≤ 12 weeks		
Informal [c]	2656	
Qualified [d]	1643	
≥13 weeks		<0.001
Informal [c]	2367	
Qualified [d]	614	
Patient delay		
≤ 4 weeks		
Informal [c]	3434	
Qualified [d]	704	
≥5weeks		<0.001
Informal [c]	1506	
Qualified [d]	1512	
Health System Delay		
≤ 9 weeks		
Informal [c]	2404	
Qualified [d]	1895	
≥10 weeks		<0.001
Informal [c]	2619	
Qualified [d]	362	

[a] The cut off points for prolonged delay were taken by considering the two highest quintiles of distribution of all patients in the study in which 60% of the patients were included.

[b] P-values from chi-square

[c] Includes traditional healer, pharmacists, and rural medical practitioners and village doctors.

[d] Includes non-DOT clinic e.g. private practitioners and gradate medical doctors; public sector DOTS facility recognized by the national tuberculosis control programme (NTP) and those who made no visits before this visit.

Logistic regression analysis of prolonged total delay comparing those who first consulted informal and qualified practitioners, was carried out with age, sex and place of residence (urban or rural) as covariates. This analysis showed that prolonged delay was associated with greater age and with rural residence, as compared to urban residence. Adjusted by type of practitioner visited and age of patients, the difference in total delay between males and females was not statistically significant (Table 4.3). The same associations were found from logistic regression analysis for both patient and health system delays (Table 4.3).

Table 4.3 Results of logistic regression analysis: Prolong delays (total, health system and patient delay) in tuberculosis treatment among patients in Bangladesh with by sex, place of residence and type of first practitioner consulted [a]

Variables	Exp (B)	95% C.I. for Exp (B)	
		Lower	Upper
Prolonged Total treatment Delay (≥13 weeks) [b]			
Age	1.01	1.01	1.02
Sex (male vs. female)	1.05	0.94	1.17
Urban vs. rural status	0.58	0.53	0.64
Informal vs. qualified practitioner visited	2.26	2.02	2.52
Prolonged Health System Delay (≥10 weeks) [b]			
Age	1.01	1.00	1.01
Sex (male vs. female)	1.00	0.90	1.12
Urban vs. rural status	0.47	0.43	0.52
Informal vs. qualified practitioner visited	5.54	4.88	6.29
Prolonged Patient Delay (≥5 weeks) [b]			
Age	1.01	1.00	1.01
Sex (male vs. female)	1.10	0.98	1.23
Urban vs. rural status	0.88	0.80	0.98
Informal vs. qualified practitioner visited	0.20	0.18	0.22

[a] The cut off points for prolonged delay were taken by considering the two highest quintiles of distribution of all patients in the study in which 60% of the patients were included.

[b] Includes traditional healer, pharmacists, and rural medical practitioners and village doctors. Qualified includes non-DOT clinic e.g. private practitioners and gradate medical doctors; public sector DOTS facility recognized by the national tuberculosis control programme (NTP) and those who made no visits before this visit.

We excluded 124 cases from the analysis of patient delay. The main symptom used for calculating delay was cough, whereas these 124 cases (of 7280) had visited practitioners for other TB symptoms such as fever and other chest symptoms, which began before cough. As they had a negative patient delay, they were excluded from analysis.

4.5 Discussion

Delays in seeking care for TB have been observed in many settings. A systematic review indicated total delay ranging from 25 days in China to 185 days in Tanzania [27], delays were reported of 60 days in Nepal, 62 days in India and 97 days in Pakistan [74, 75, 77]. A previous study of 1000 patients from Bangladesh reported total delays of 61days for women and 53 days for men [76]. The median total delay documented in our study was 12 weeks.

While success may be achieved in detecting and curing a high proportion of cases in a country, this delay in care seeking may adversely affect our attempts to curb transmission of this infectious disease. These delays need to be understood to be improved.

This study specifically chose to focus on informal practitioners. In Bangladesh, informal practitioners are the providers of curative care for many people; in one survey, 60% of people chose informal practitioners, 63% among the poorest 25% of population [78]. Although the majority of these practitioners have no formal medical training, they are preferred by the poor because they are easily accessible and they render inexpensive services. Our study focused on the role informal health practitioners' play in delays to determine how to reduce these delays. While we found that informal practitioners appeared to provide more accessible services (patient delay was shorter when they first

consulted informal practitioners, whether in urban or rural areas), the total and health systems delays were greater when the first practitioner was from the informal sector. Delays associated with visits to informal practitioners were also found in Mwanza, Tanzania [107]. Visits to informal health practitioners were not evaluated in a previous study on delay in Bangladesh [76].

While in many settings patient delays contribute a major proportion of total delay [77, 107, 108], in the present study, we found that patient delay was comparatively shorter than health system delay. This was also observed in Ghana and Botswana though they had defined patient delay as start of symptoms to first visit to a health facility [109, 110].

Bangladesh provides TB services in collaboration with NGOs through community involvement [38, 111]. Much emphasis has been given to community involvement and enhanced awareness of the community in recent years [41], which may be one reason why patient delay contributes a lower proportion to total delay than in other locations.

The involvement of all care providers in TB control is much emphasized in the current international TB control strategy [5]. Study in Bangladesh showed that village doctors may contribute to referring TB suspects and provision of DOT [112]. This is important, as the national guidelines of Bangladesh allow treatment to be initiated only by qualified physicians; other practitioners can only refer suspects and cases to the DOTS facility [40]. Clearly, further efforts are needed to encourage informal practitioners to refer the suspects to service points promptly in order to reduce delay and they should have the access to the TB DOTS facilities. Further investigation on how to involve these practitioners in the programme should be undertaken.

Although we did not find any difference between men and women, a previous study in Bangladesh showed significant delay in females of higher age group [76]. More involvement of female community-based volunteers in the project areas where our study was undertaken may have contributed to the different finding in our study. The prolonged delay we found associated with rural residence could be due to lack of access to services and lower economic status of patients, as was found in Mwanza Tanzania [107].

This study covers a large population which includes all available records of the projects. It was based on an interview document of a routine project, illustrating the feasibility of routinely assessing delay. Incorporating routine evaluation as a part of routine practice would aid services in understanding and reducing delays, consequently improving TB control.

While the advantages of conducting such research within routine service and using programmatic documents are obvious, they are limited by the fact that the information obtained was based on the patient's statement and could not be verified.

We believe that this simple study, using information from routine services, will be beneficial in helping us understand and address this important problem.

Chapter 5 Health system delays in treatment of Multidrug resistant tuberculosis patients in Bangladesh

5.1 Abstract

Background: Bangladesh is one of the 27 high burden countries for multidrug resistant tuberculosis listed by the World Health Organization. Delay in multidrug resistant tuberculosis treatment may allow progression of the disease and affect the attempts to curb transmission of drug resistant tuberculosis. The main objective of this study was to investigate the health system delay in multidrug resistant tuberculosis treatment in Bangladesh and to explore the factors related to the delay.

Methods: Information related to the delay was collected as part of a previously conducted case-control study. The current study restricts analysis to patients with multidrug resistant tuberculosis who were diagnosed using rapid diagnostic methods (Xpert MTB/RIF or the line probe assay). Information was collected by face-to-face interviews and through record reviews from all three Government hospitals providing multidrug resistant tuberculosis services, from September 2012 to April 2013. Multivariable regression analysis was performed using Bootstrap variance estimators. Definitions were as follows: Provider delay: time between visiting a provider for first consultation on MDR-TB related symptom to visiting a designated diagnostic centre for testing; Diagnostic delay: time from date of diagnostic sample provided to date of result; Treatment initiation delay: time between the date of diagnosis and date of treatment initiation; Health system delay: time between visiting a provider to start of treatment. Health system delay was derived by adding provider delay, diagnostic delay and treatment initiation delay.

Results: The 207 multidrug resistant tuberculosis patients experienced a health system delay of median 7.1 weeks. The health system delay consists of provider delay (median 4 weeks), diagnostic delay (median 5 days) and treatment initiation delay (median 10 days). Health system delay (Coefficient: 37.7 days; 95%; CI 15.0-60.4; p 0.003) was associated with the visit to private practitioners for first consultation.

Conclusions: Diagnosis time for multidrug resistant tuberculosis was fast using the rapid tests. However, some degree of delay was present in treatment initiation, after diagnosis. The effective way to reduce health system delay would be through strategies such as engaging private practitioners in multidrug resistant tuberculosis control.

5.2 Background

Multidrug resistant tuberculosis (MDR-TB) is a major challenge to worldwide tuberculosis (TB) control [7]. Despite the progress in detection, in 2013 a total of 55% the estimated MDR-TB were under-detected and 29% of the diagnosed patients were not on treatment [97]. Delay in TB treatment may result in disease transmission, progression, and poor treatment outcome including increased risk of death [113]. Several studies have reported that delay in TB initiating treatment contributed to development of MDR-TB [81, 114, 115].

Bangladesh is one of the high burden countries for TB and has also been listed on the 27 high burden countries for MDR-TB by the World Health Organization (WHO) [97]. Due to the overall high TB burden in Bangladesh, the proportion of patients with MDR-TB (1.4% and 29%, among the new and previously treated TB patients, respectively) amounts to 4700 people (2100 and 2600 among new and previously treated TB patients, respectively), which provides a significant challenge for the national tuberculosis control programme [97].

Delay in MDR-TB treatment may cause more suffering to the affected patients as well as hinder the attempts to curb the spread of MDR-TB. Delay in initiation of tuberculosis treatment among the drug sensitive TB patients has been reported in many studies [27]. Some studies reported delay in commencing treatment of MDR-TB patients, although diagnostic and treatment initiation delays were frequently reported in these studies; the context and definition of delays were variable [28-34]. Some studies focused on rapid diagnostic methods for MDR-TB detection, reporting either the time taken for diagnosis or time from diagnosis to treatment initiation [28, 30, 34, 116]. We could only find one study on patient-related delay among the MDR-TB patients and its associated factors, a qualitative study carried out in Cape Town, South Africa [117]. The study reported inaccurate perception of their symptoms as an important factor in the delay in seeking care. Diagnostic delay was inherent in the MDR-TB management procedure while the diagnosis of MDR-TB relied on culture methods, which require longer time than the more advanced tests now routinely in use [82]. In 2012, the National TB control programme of Bangladesh (NTP) adopted rapid tests such as automated real time PCR (Xpert MTB/RIF) and Line probe assays to diagnose MDR-TB/Rifampicin resistant TB (RR-TB) as recommended by the World Health Organization; these methods reduce the time needed for diagnosis [118, 119].

In Bangladesh, TB service is integrated in the basic health care services and available in all hospitals at sub-district level and below, in chest disease clinics, in district and medical college hospitals and in urban health centres run by government and non-government organizations (NGOs) [15]. Bangladesh has a dynamic NGO sector providing TB control services in collaboration with NTP through a partnership approach [38]. Different types of health care providers administer TB services in Bangladesh, including both qualified private practitioners and informal providers [112, 120]. Private

practitioners are popular in Bangladesh irrespective of patients' income level and residence [47]. However, NTP does not have strong linkage with the private sector. As in many other countries, TB services provided by the private sector are poor, with use of inappropriate treatment and poor case holding, leading to incomplete treatment and drug resistance [47].

Delays in the treatment of drug-sensitive TB patients have been reported in several studies carried out in Bangladesh [76, 79, 80, 121]. Our study aims to explore delays related to the commencement of treatment for MDR-TB patients caused by the health system, namely provider delay, diagnostic delay and treatment initiation delay. Further, we aim to explore possible factors related to the health system delay, as well as to offer potential solutions.

5.3 Methods

5.3.1 Study population and setting

MDR-TB patients were identified as part of a previously conducted case-control study on risk factors associated with MDR-TB in Bangladesh when information related to treatment delay was also collected [101].The study included 250 MDR-TB and 750 non-MDR-TB tuberculosis patients. In the current study we restrict the analysis to data related to the delay in treatment of MDR-TB patients.

NTP Bangladesh adopted the standardized regimen for treating MDR-TB and started the DOTS Plus project, in 2008 [45]. Currently one hospital at national level and four at regional level are providing MDR-TB diagnosis and treatment services. These hospitals are equipped with reference laboratories and a MDR-TB treatment ward. Presumptive MDR-TB patients who are identified at the district, sub-district or lower level are

referred to these central and regional level hospitals for diagnosis and treatment initiation of MDR-TB, according to the national guideline [45].

At the time of our data collection, MDR-TB patients from all over Bangladesh (central, district and subdistrict level) were referred to one of three government hospitals, i.e. the national hospital in Dhaka or a regional hospital in either Chittagong or Rajshahi. All eligible MDR-TB patients from these hospitals who were admitted from September 2012 to mid-April 2013 were recruited. At that time the rapid diagnostic tests were still evolving in Bangladesh, and some of the MDR-TB patients were diagnosed through the conventional culture and DST method. We only included the MDR-TB patients diagnosed by rapid diagnosis tests to ensure valid comparisons.

Except for the diagnostic criteria, the inclusion and exclusion criteria of this study were similar to the previous study [101]. The NTP has adopted automated real time PCR (Xpert MTB/RIF) as the preferred rapid diagnostic tool of MDR-TB patients. Culture and Drug Sensitivity Testing (DST) and Line probe assays were also used by NTP [45]. Xpert MTB/RIF diagnoses only Rifampicin resistance. However, patients who are resistant to Rifampicin are generally also resistant to Isoniazid (another first-line drug). Mono-resistance to Rifampicin is fairly uncommon (0.2% and 0.4% among new and previously treated patients, respectively), as shown by a recent drug resistance survey (DRS) conducted in Bangladesh [122]. This study included 207 MDR-TB patients who were diagnosed by the rapid tests, i.e. Xpert MTB/RIF or Line probe assays, to maintain the consistency in overall delay related information. We had excluded 34 patients who were diagnosed by the conventional culture and DST method. Nine patients were excluded due to missing information. The NTP uses a laboratory based in Antwerp, Belgium as quality control for diagnosis of MDR-TB patients.

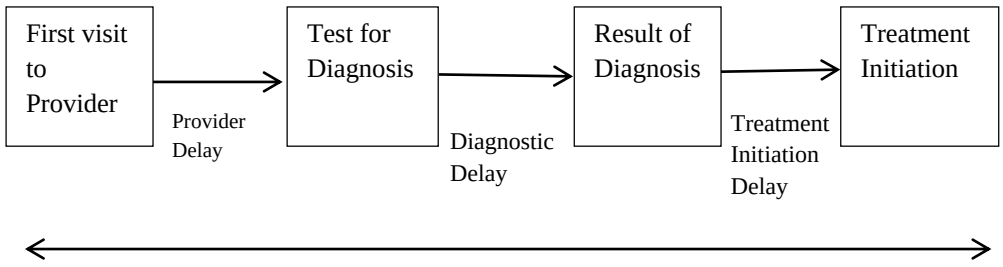
5.3.2 Data collection and definitions

Definitions used in this study are as follows: Provider delay: time between visiting a provider to visiting designated diagnostic centre for testing; Diagnostic delay: time between the diagnostic sample provided to date the result is available; Treatment initiation delay: time between the date of diagnosis and the date of treatment initiation; Health system delay: time between visiting a provider to start of treatment. Health system delay was derived by adding provider delay, diagnostic delay and treatment initiation delay (Figure 5.1). In this study, the term private practitioner refers to clinicians who are at least medical graduates; informal providers are the one without medical degree (MBBS), i.e. village doctors, medical assistants.

We tried to keep the definitions in line with a study conducted in Bangladesh that focused on treatment delay among drug sensitive TB patients due to health care providers [113]. Delay-related definitions used for drug-sensitive TB were not completely applicable to MDR-TB. As it is difficult to estimate patient delay (defined as the time between the onset of symptom to visiting a health care provider) for MDR-TB, as most of the patients had been treated previously, we focused our study on the delay due to the health system. We interviewed patients regarding their first visit to a health provider, assuming the patient would visit a provider when they perceived the symptoms as worsening or suspected a lack of response to their ongoing treatment. The provider delay in our study is based on patients' perceptions. Most of the participants (97%) were TB patients who had previously received treatment for TB. We asked the patients specifically how many weeks before the MDR-TB diagnosis they had visited a health provider for their current problem (i.e. worsening of TB symptoms, or feeling that the disease was not responding to treatment).

Trained investigators collected information from the study participants by face-to-face interview using a pre-tested questionnaire, and by review of records. Information related to the time frame of the patient's visit to the provider was collected through interview, and since their recall may not be accurate, it was expressed in weeks rather than days. The dates of diagnosis and treatment were taken from the hospital records, and the diagnostic and treatment delays were expressed in days.

Figure 5.1 Definition of delays used in this study



Adapted from: Rifat M, Rusen ID, Islam MA, Enarson DA, Ahmed F, Ahmed SM, Karim F: Why are tuberculosis patients not treated earlier? A study of informal health practitioners in Bangladesh. *International Journal of Tuberculosis & Lung Disease* 2011, 15(5):647-651.

5.3.3 Statistical analysis

Socio-demographic characteristics were summarised using means and standard deviations for continuous variables and counts/percentages for categorical variables. Multivariable regression models were used to estimate the effect of age, sex, education, occupation, residence status, type of TB the patient, and the provider visited for first consultation, on health system delay. We have included patient characteristics such as education, occupation, residence status and income in the multivariable analysis, assuming that these characteristics may influence the choice of provider and affect the health system delay. Since the distribution of delay was skewed, we used Bootstrap variance estimators for regression analysis. Regression coefficients are presented with 95% confidence intervals and associated p values for simple and Omnibus hypotheses. Data analysis was carried out using Stata statistical software version 12 (StataCorp LP, TX, USA).

5.3.4 Limitation of the study

This study includes only patients who were already enrolled in MDR-TB treatment. We do not have information about patients who did not start treatment after diagnosis. Unlike with the delay in drug-sensitive TB patients, it is difficult to determine the date for the onset of symptoms that prompted a visit to a clinician among the MDR-TB patients. Information related to provider delay was based on patients' information recalled during face-to-face interviews, and could not be verified.

5.3.5 Ethics considerations

The study was approved by the Human Research Ethics Committee (HREC) of the University of Newcastle (UoN), Australia, and the Bangladesh Medical Research Council (BMRC), Dhaka, Bangladesh. An information sheet describing the purpose of

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

5.4 Results

Socio-demographic characteristics of the patients are presented in Table 5.1. The median delay caused by health system factors was 7.1 weeks. Provider delay (median 4 weeks), diagnostic delay (median 5 days) and treatment initiation delay (median 10 days) make up the health system delay (Table 5.2).

Total 89 MDR-TB patients (43.8%) consulted a private practitioner first, for their MDR-TB related symptom (Table 5.1), which included 86 previously treated TB patients. Only 9.5% of the previously treated TB patients had been treated in the private sector for their previous TB disease and the rest (90.5%) were treated in a DOTS centre (not shown in table).

Multivariable regression analysis of health system and associated factors causing delay in the treatment of MDR-TB patients are shown in Table 5.3. Patients who visiting private practitioners for the first consultation experienced a greater health system delay compared to those visiting the NTP designated DOTS centre (mean difference, 37.7 days; 95% CI 15.0-60.4; p 0.003).

Table 5.1 Socio-demographic and clinical characteristics of the multidrug resistant tuberculosis (MDR-TB) patients in Bangladesh

Variables	Rapid tests (n=207) n (%)
Gender	
Male	138 (66.7)
Female	69 (33.3)
Education	
None	53 (22.0)
Secondary and below	169 (70.1)
Higher secondary and above	19 (7.9)
Provider visited for first consultation	
DOTS	91 (45.4)
Private	89 (43.8)
Informal	22 (10.8)
Rural-vs-Urban status	
Rural	102 (49.3)
Urban	105 (50.7)
Occupation	
None	8 (3.9)
Service	66 (31.9)
Farmer	16 (7.7)
Student	5 (2.4)
Homemaker	39 (18.8)
Factory worker	16 (7.7)
Business	36 (17.4)
Self employed	12 (5.8)
Transport worker	9 (4.4)
Smoking status	
Smoker	103 (49.8)
Non- smoker	104 (50.2)
Type of TB patient	
New	5 (2.4)
Previously treated	202 (97.6)
Treatment outcome of previously treated patients	
Cured	16 (7.9)
Completed	37 (18.3)
Default from treatment	5 (2.5)
Treatment failure	119 (58.9)
No record available	25 (12.4)
Age (mean ± SD)	34 ± 12.0
Income (mean ± SD)	13664.3 ±11521.7

Age and Income are expressed in the table is the mean ± Standard Deviation. All other variables are expressed as n (%).Income is in Bangladeshi taka (BDT), monthly. 1 USD =78 BDT approximately.
DOTS: National TB control programme designated centres for TB treatment; Smoking status includes current and past smokers.

Table 5.2 Delays in treatment among the multidrug resistant tuberculosis (MDR-TB) patients of Bangladesh (n=207)

	Median	IQR	Mean	SD
Health System delay (weeks)	7.1	8.6 (4.6-13.3)	10.5	11.25
Provider delay (weeks)	4	6 (2-8)	6.8	9.6
Diagnostic delay (days)	5	6 (1-7)	5.9	8.1
Treatment initiation delay (days)	10	17 (6-23)	20.5	28.9

Health system delay includes the provider delay, diagnostic delay and treatment initiation delay
Diagnostic delay includes the patients who had the rapid tests such as Gene Xpert and or LPA
Diagnostic delay, provider delay and health system delay had 3, 4 and 7 missing values, respectively.
Standard deviation (SD), Interquartile range (IQR)

Table 5.3 Factors related to health system delay of multidrug resistant tuberculosis (MDR-TB) patients of Bangladesh

		Univariate analysis (n=200)				Multivariable analysis (n=200)				
Variable	**Median Health system delay**	**Coefficient [a]**	**p***	**95% Confidence Interval**		**Coefficient [a]**	**p***	**p****	**95% Confidence Interval**	
				Lower	**Upper**				**Lower**	**Upper**
Gender										
Male	51.5	Reference				Reference				
Female	45	-21.9	0.01	-38.9	-4.9	-18.1	0.27		-50.4	14.2
Education								0.35		
No education	43	Reference				Reference				
Up to secondary level	50.5	4.1	0.70	-16.9	25.0	3.5	0.76		-18.7	25.7
Higher secondary and above	54.5	58.0	0.13	-17.6	133.5	58.1	0.15		-20.3	136.5
Provider visited								**0.003**		
DOTS centre [c]	45	Reference				Reference				
Private practitioners	53	33.6	0.01	10.2	57.0	37.7	**0.001**		15.0	60.4
Informal provider	59.5	23.4	0.12	-5.9	52.7	26.2	0.13		-8.0	60.5
Residence status										
Rural	51	Reference				Reference				
Urban	46	-1.3	0.89	-19.0	16.4	4.6	0.70		-19.1	28.2
Type of the patients								0.07		
New TB patient	57	Reference				Reference				
Cured, previously treated	45	-4.2	0.83	-41.4	33.0	21.8	0.40		-29.3	72.9
Completed, previously treated	40.5	2.0	0.90	-30.1	34.0	16.5	0.54		-36.5	69.4
Default, previously treated	51	2.0	0.91	-31.1	35.1	42.6	0.16		-16.7	101.9
Failure, previously treated	54	27.4	0.14	-9.3	64.1	51.7	0.08		-5.3	108.7
No outcome recorded, previously treated	56.5	5.1	0.79	-31.3	41.4	23.9	0.42		-34.0	81.7
Occupation								0.66		
None	41.5	Reference				Reference				
Service	51	34.7	0.02	5.4	64.0	17.1	0.34		-17.9	52.1
Farmer	54	25.0	0.10	-4.8	54.8	32.8	0.16		-12.8	78.4
Student	27	-15.3	0.14	-35.6	5.0	-21.7	0.56		-93.9	50.6
Homemaker	49	14.4	0.25	-9.9	38.7	26.2	0.12		-6.8	59.1
Factory worker	54	41.6	0.15	-15.0	98.2	36.6	0.32		-35.1	108.2
Business	48.5	31.8	0.03	2.7	60.8	8.8	0.72		-38.6	56.2
Self employed	70.5	43.9	0.07	-3.5	91.3	45.9	0.13		-13.7	105.4
Transport worker	45.5	51.0	0.24	-33.8	135.8	45.1	0.31		-41.7	131.8
Age (years)	-	-0.02	0.95	-0.5	0.5	-0.3	0.36		-1.0	0.4
Income (BDT)[b]	-	0.001	0.21	-0.001	0.003	0.0003	0.71		-0.001	0.002

[a] Regression coefficients reflect adjusted difference in mean delay (days), while all other factors remain constant.
[b] Income is in Bangladeshi taka (BDT), monthly. 1 USD =78 BDT approximately.
[c] DOTS centres are the NTP designated treatment centres for tuberculosis.
p* is the value that the regression coefficient is zero
p** is the value form the omnibus test that all coefficients for that variable are zero

5.5 Discussion

Our study found that time taken for diagnosis of MDR-TB is five days since the introduction of rapid tests in the programme; subsequently it took ten days to initiate treatment. A recent study on pre-diagnosis and pre-treatment attrition of MDR-TB patients of Bangladesh presented the median time for diagnosis and treatment initiation as four and five days, respectively [123]. The study included 163 MDR-TB patients diagnosed by Xpert MTB/RIF from selective areas which are supported by one NGO (BRAC) in Bangladesh. Whereas, our study included patients from all three government hospitals providing MDR-TB services at that time, which included patients referred from all areas of Bangladesh (including the area not supported by BRAC), during the study period. Laboratory turnaround time reported by another study conducted in Cape town, South Africa was less than one day using Xpert based algorithm and 24 days using Line probe assay based algorithm [30]. The study also reported time to initiate treatment after diagnosis as 10 and 14 days in Xpert and Line probe assay based algorithm, respectively [30]. Similar results were found in a multicounty study which reported median time to detect rifampicin resistant as one day for Xpert MTB/RIF test and 20 days for Line Probe Assay based test [28]. Another study on MTB-DR Plus showed reduction in laboratory processing time (median 22 days) compared to culture based DST which was 55 days; whereas it took 20 days of operational delay to start the treatment [34]. Diagnosis time using MTB-DR plus was also reported as 4.2 and 11 days in Georgia and India, respectively [116, 124]. In our study, time needed for diagnosis is satisfactory. However, there was a remarkable delay in treatment initiation before the diagnosis, which was also observed in other studies on rapid tests for MDR-TB diagnosis [30, 34].

Unlike most other studies on the delay to treatment of MDR-TB patients, the definition of health system delay in our study includes the delay related to the visit to the health care provider. Median health system delay is 7.1 weeks in our study, which is mainly due to provider delay (4 weeks). Those patients who visited a private practitioner after perceiving their symptom during their current MDR-TB episode, experienced longer health system delays than patients who visited a NTP designated DOTS centre. In another study on drug sensitive TB patients in Bangladesh, visiting informal providers was associated with longer health system delay [113]. In contrast; we did not find any association between delay in treatment and visiting informal providers. MDR-TB patients may prefer qualified practitioners to informal providers as treatment is more complicated. We also found that many of the MDR-TB patients, who consulted private practitioners first for their current problem, had been treated in DOTS centre during previous TB treatment and this group of patients were reliant on private practitioners for their current complicated problem. This finding indicates that the MDR-TB patients might have visited multiple providers during the course of previous and current TB disease. However our finding concludes those who had in touch with private practitioners had experienced greater health system delay.

The provider delay may be due to lack of awareness of referral services by private practitioners. A sputum result of drug-sensitive TB patients at 5^{th} month or 8^{th} month of treatment forms the basis for a decision on referral for MDR-TB diagnosis, according to the national guideline. Waiting for the scheduled sputum conversion result could be another factor for provider delay. However, the national guideline also allows clinicians to refer a patient for MDR-TB screening [45]. NTP and its NGO partners in Bangladesh are involved in linking the private practitioners to the national TB control programme [47], encouraging private practitioners to refer TB patients to NTP designated DOTS

centres where they receive tuberculosis treatment free of charge. However, many of the private practitioners who are not linked to the NTP often do not treat the TB patients according to the International Standards for Tuberculosis Care (ISTC) [47, 125, 126]. Strengthening the involvement of private practitioners in TB control with emphasis on MDR-TB is needed.

Delay in treatment initiation of MDR-TB, was also reported in a few other studies based on conventional DST methods. Two studies using conventional culture and DST for MDR-TB diagnosis reported a total time from diagnosis to treatment initiation of 12.4 weeks and 17 weeks in Kwazulu Natal, South Africa and Cameroon, respectively [31, 33]. Time for diagnosis and treatment initiation using conventional culture was 246 to 283 days, respectively among children, if the information of their MDR-TB contact was not one of the criteria for diagnosis [32]. Time taken at different stages of MDR-TB management using conventional culture and DST method, starting from sample collection to start of treatment, was also reported in another study which presents a total turnaround time of 5 months which was almost double of the bacteriological procedure [127]. To get a patient started on treatment after diagnosis took 12.8 days in Vietnam [29].

Unnecessary delays should be prevented to control further transmission of MDR-TB. The delay between diagnosis and initiating treatment might be due to the need for other necessary medical examinations such as clinical tests prior to initiation of treatment (e.g. liver function test, Xray, thyroid profile, blood sugar) [30]. Other operational issues adding to the delay might be sample transportation, laboratory-based diagnostic and patient notification, and admission to hospital, or may be due to the protocol for processing smear-negative samples [34, 127].

The reason for the delay in treatment initiation in Bangladesh could be due to the initial hospitalization requirement for MDR-TB treatment, according to the protocol that was usually 6 to 8 months. MDR-TB patients may require preparation time to get admitted to hospital for months. Again, those hospitals also had bed limitation to enrol all patients at a time and patient has to wait in queue. Need for shortening of hospital stay was felt by the programme to make a balance between the number of patients diagnosed by rapid tests and the number of beds available at MDR-TB hospitals.

A pilot project on shortening hospital stay is under way, i.e. to start ambulatory treatment after two consecutive negative sputum culture results. Patients were treated as ambulatory at community level after initial hospitalization. Ambulatory or community-based treatment for MDR-TB is also recommended by the WHO, whenever possible [97]. One study reported that the reason for treatment initiation delay was due to the need for a decision made by the Programmatic Management of Drug Resistant TB (PMDT) Council, and the time taken to assign the patient to the treatment support during the long preparation phase [29]. Another study reported that having a town address was associated with less delay among MDR-TB and we did not find any relationship with urban-rural status and time to treatment, in our study [34].

5.6 Conclusion

Introduction of rapid diagnostic methods have satisfactory time needed for MDR-TB diagnosis. Treatment initiation subsequent to diagnosis was delayed may be due to programmatic factors. This could be improved by identifying specific problems of implementation at programme level. Engaging private practitioners in national MDR-TB control programme should be enhanced to reduce the overall delay in MDR-TB management.

Chapter 6 Conclusion and recommendations

Multidrug-resistant tuberculosis (MDR-TB) is an increasing concern globally and a threat to disease-control efforts in many countries including Bangladesh. We have conducted our research to determine the risk factors of MDR-TB patients in Bangladesh. Our research also included the information regarding the time taken for diagnosis and treatment of MDR-TB patients and the factors associated with health system delay. Research on treatment delay in drug sensitive tuberculosis (TB) patients and its relation to different health providers was also conducted.

Prior TB treatment is a major risk factor for development of MDR-TB in Bangladesh. The case control study on risk factors of MDR-TB in Bangladesh also identified age: 18 to 45 years (OR 1.77, CI 1.07-2.93), compared to the age group more than 45 years; education: up to secondary level (OR 1.94, CI 1.32-2.85), as opposed to the "no education" group ; occupation: service and business (OR 2.88, CI 1.29-6.44; OR 3.71, CI 1.59-8.66, respectively), compared to the "unemployed" group; smoking history (OR 1.58, CI 0.99-2.5); and type 2 diabetes as comorbid illness (OR 2.56 CI 1.51-4.34), as risk factors for MDR-TB.

As the history of previous TB treatment is a known risk factor for MDR-TB, supported by many other studies, we further explored the factors related to previous tuberculosis treatment of MDR-TB patients. Most of the MDR-TB (64%) patients had been treated for tuberculosis previously and more than once. Incomplete treatment, which included treatment discontinuation due to treatment failure (4.3; 95% CI 1.7-10.6); adverse reactions to anti-tuberculosis medicine (OR 8.2; 95% CI 3.2-20.7); and hospitalization for TB complications (OR 16.9; CI 1.8-156.2) during previous tuberculosis treatment are the main factors leading up to MDR-TB.

The study on treatment delay among the drug sensitive TB patients showed that patients seeking care from informal practitioners experience prolonged health system delay in initiation of treatment compared to patients seeking care from qualified practitioners (52% and 16%; p 0.005), although the former access care more promptly (30% vs 68%; p 0.005). However, in the study among the multidrug resistant TB patients, health system delay was associated with visiting private practitioners (mean difference37.7 days longer compared to visiting NTP designated DOTS centre; 95%; CI 15.0-60.4; p 0.003). We did not find any association between health system delay among the MDR-TB patients and visiting the informal providers. We also found that since the introduction of rapid diagnostic methods, time to diagnosis has been reduced although some degree of delay was present in treatment initiation of MDR-TB patients.

The risk factors for MDR-TB should be addressed in the MDR-TB control strategy at country level and other equivalent health care settings. The findings could be used in policy and practices of MDR-TB programme. Specific socio-economic groups such as age-group, educational status and several occupations could be addressed for MDR-TB prevention and control through health education programmes. Patient education could also be strengthened regarding adverse effect and compliance related issues.

The national tuberculosis control programme of Bangladesh (NTP) is reliant on multi-sectoral involvement to address all risk factors, and can advocate for these issues in order to improve control of MDR-TB. The integration of MDR-TB control activities with diabetes and tobacco control programmes would be a good place to start these collaborative efforts.

Early diagnosis and adequate treatment of drug sensitive tuberculosis patients is the crucial approach to prevent development of drug resistance. Basic TB services should

be strengthened for new tuberculosis patients so that they do not transform to a "previously treated" patient in future. Patient education could be strengthened for all types of TB patients with emphasis on adverse effects and compliance related topics. Patients who are hospitalized for TB related problems could be routinely tested for MDR-TB to allow early diagnosis and treatment. Although we did not find any association of MDR-TB status with "history of hospitalization due to any other cause, within the last seven months of current treatment", "hospitalization due to TB-related causes during previous TB treatment" was associated with MDR-TB, in the second study. This group of patient already had TB and was hospitalized for complication. MDR-TB among the new TB patient was 14% in a recent drug resistant survey conducted in Bangladesh. We cannot conclude from our finding that the patients had been infected with MDR-TB from the hospitals. However, transmission of MDR-TB is an important issue in Bangladesh and infection prevention should be implemented as a basic requirement of disease prevention and control [129].

Delay in the treatment of patients with drug sensitive tuberculosis could be reduced by strengthening the involvement of informal providers with the national TB control programme. NTP has started training informal providers on TB guideline and referral services and it should be continued. Engaging the private practitioners with special focus on MDR-TB control is needed. Along with drug sensitive TB, private practitioner could be trained on MDR-TB and develop linkages with NTP to enhance referral of presumptive or diagnosed MDR-TB patients. NGOs working for TB control could be involved in engaging private practitioners at different levels. Treatment initiation delay subsequent to diagnosis could be improved by identifying specific problems at implementation level. Programmatic management of drug resistance TB (PMDT)

committee is already functional in Bangladesh; the committee should identify specific reason and start treatment without substantial treatment initiation delay.

Some potential areas for further research guided by the study findings could be: research on MDR-TB and diabetes status, involving private practitioners in reducing delay in MDR-TB, transmission of MDR-TB in health care settings. We also recommend research on MDR-TB among the children which was beyond the scope of our study.

In Bangladesh, the National TB control programme and its partner NGOs have been managing approximately 0.19 million of tuberculosis patients annually, with 92% treatment success, according to the WHO report [1]. We have conducted research for that specific portion of TB patients who are becoming drug resistance. We expect that the findings of our research will benefit the resource limited, high burden country Bangladesh, in controlling MDR-TB patients.

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Development of Multidrug Resistant Tuberculosis in Bangladesh: A Case-Control Study on Risk Factors

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Abstract

Objective: To determine the risk factors for developing multidrug resistant tuberculosis in Bangladesh.

Methods: This case-control study was set in central, district and sub-district level hospitals of rural and urban Bangladesh. Included were 250 multidrug resistant tuberculosis (MDR-TB) patients as cases and 750 drug susceptible tuberculosis patients as controls. We recruited cases from all three government hospitals treating MDR-TB in Bangladesh during the study period. Controls were selected randomly from those local treatment units that had referred the cases. Information was collected through face-to-face interviews and record reviews. Unadjusted and multivariable logistic regression were used to analyse the data.

Results: Previous treatment history was shown to be the major contributing factor to MDR-TB in univariate analysis. After adjusting for other factors in multivariable analysis, age group "18–25" (OR 1.77, CI 1.07–2.93) and "26–45" (OR 1.72, CI 1.12–2.66), some level of education (OR 1.94, CI 1.32–2.85), service and business as occupation (OR 2.88, CI 1.29–6.44; OR 3.71, CI 1.59–8.66, respectively), smoking history (OR 1.58, CI 0.99–2.5), and type 2 diabetes (OR 2.56 CI 1.51–4.34) were associated with MDR-TB. Previous treatment was not included in the multivariable analysis as it was correlated with multiple predictors.

Conclusion: Previous tuberculosis treatment was found to be the major risk factor for MDR-TB. This study also identified age 18 to 45 years, some education up to secondary level, service and business as occupation, past smoking status, and type 2 diabetes as comorbid illness as risk factors. National Tuberculosis programme should address these risk factors in MDR-TB control strategy. The integration of MDR-TB control activities with diabetes and tobacco control programmes is needed in Bangladesh.

Citation: Rifat M, Milton AH, Hall J, Oldmeadow C, Islam MA, et al. (2014) Development of Multidrug Resistant Tuberculosis in Bangladesh: A Case-Control Study on Risk Factors. PLoS ONE 9(8): e105214. doi:10.1371/journal.pone.0105214

Editor: Ulrike Gertrud Munderloh, University of Minnesota, United States of America

Received May 6, 2014; **Accepted** July 17, 2014; **Published** August 19, 2014

Data Availability: The authors confirm that, for approved reasons, some access restrictions apply to the data underlying the findings. 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 dataset. It will be provided upon request to anyone who is interested in the research topic. Interested readers may contact the corresponding author. The electronic version of the dataset is kept with University of Newcastle Australia, following the original research protocol, which has also been approved by Human Research Ethics Committee (HREC) of the University of Newcastle.

Funding: This research was supported by the Australian Respiratory Council, the University of Newcastle, Australia, and BRAC Bangladesh. The funders had no role in study design, data collection and analysis or decision to publish or preparation of manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

Despite an overall decreasing incidence and mortality rate for tuberculosis (TB), multidrug resistance tuberculosis (MDR-TB) continues to be a serious threat to the current global tuberculosis control effort [1,2]. MDR-TB is caused by bacteria that are resistant to at least isoniazid and rifampicin, the most effective anti-TB drugs for treating TB [3]. MDR-TB does not respond to standard six-month treatment with first-line anti-TB drugs; extended treatment is required involving drugs that are more toxic and more expensive [3]. Cure rate of MDR-TB is 50 to 70% which is lower than the drug-susceptible TB [4]. Failure to control MDR-TB may lead to another era with TB being regarded as a fatal disease.

Bangladesh is one of the 27 high burden countries for MDR-TB [5]. In Bangladesh, 1.4% of new tuberculosis patients, and 29% of previously treated tuberculosis patients are estimated to be MDR-TB [1]. Although the proportion of MDR-TB is still low, due to the overall high TB burden in Bangladesh the absolute number of MDR cases is quite large (estimated 1900 for new and 2300 for previously treated patients) [1]. Bangladesh is unique in that it has one of the highest population densities in the world, is one of the high burden countries for TB, but has a low prevalence of HIV [6].

Identifying the population at risk of MDR-TB is essential and may help in developing appropriate case finding strategies [7]. Previous studies identified some risk factors associated with MDR-TB, namely previous TB treatment [8,9,10,11,12], poor past

Table 1. Socio-demographic and clinical characteristics of the study participants.

Variables	Case	Control	Total	p[a]
Age				0.0001
Mean	33.9	37.9	36.9	
Median	30	35	35	
SD	12.3	14.1	13.8	
Sex				0.027
Male	167 (66.8%)	442 (58.9%)	609 (60.9%)	
Female	83 (33.2%)	308 (41.1%)	391 (39.1%)	
Education				<0.0001
None	55(22%)	298 (39.7%)	353 (35.3%)	
Secondary and below	175 (70%)	398 (53.1%)	573 (57.3%)	
Higher secondary and above	20 (8%)	54 (7.2%)	74 (7.4%)	
Occupation				
None	9 (3.6%)	58 (7.7%)	67 (6.7%)	<0.0001
Service	74 (29.6%)	135 (18%)	209 (20.9%)	
Others [b]	108 (43.2%)	447 (59.6%)	555 (55.5%)	
Business	46 (18.4%)	79 (10.5%)	125 (12.5%)	
Transport worker	13 (5.2%)	31 (4.1%)	44 (4.4%)	
Income (BDT)[c]				
Mean	13066.0	11820.2	12132.0	0.1206
Median	10000	10000	10000	
SD	11016.3	10965.8	13.8	
Person living per room				0.069
Four or less	215 (86%)	676 (90.1%)	891 (89.1%)	
More than four	35 (14%)	74 (9.9%)	109 (10.9%)	
Weight (killogram)				
Mean	42.5	44.6	44.0	0.002
Median	41.0	44.0	43.0	
SD	9.7	9.1	9.3	
BCG vaccination status				0.056
Absent	123 (49.2%)	317 (42.3%)	440 (44%)	
Present	127 (50.8%)	433 (57.7%)	560 (56%)	
Previous history of TB treatment				<0.0001
No	5 (2%)	702 (93.6%)	707 (70.7%)	
Yes	245 (98%)	48 (6.4%)	293 (29.3%)	
Cavitation in chest X-ray [d]				<0.0001
Absent	136 (90.7%)	330 (98.2%)	466 (95.9%)	
Present	14 (9.3%)	6 (1.8%)	20 (4.1%)	
History of Health care work				0.144
Absent	246 (98.4%)	722 (96.3%)	968 (96.8%)	
Present	4 (1.6%)	28 (3.7%)	32 (3.2%)	
Contact of TB patient				0.496
Absent	153 (61.2%)	477 (63.6%)	630 (63%)	
Present	97 (38.8%)	273 (36.4%)	370 (37%)	
Smoking status				<0.0001
Never smoked	125 (50%)	409 (54.5%)	534(53.4%)	
Current smoker	1(0.4%)	82 (10.9%)	83 (8.3%)	
Past smoker	124 (49.6%)	259 (34.5%)	383 (38.3%)	
Substance misuse				0.013
Absent	213(85.2%)	681 (90.8%)	894 (89.4%)	
Present	37 (14.8%)	69 (9.2%)	106 (10.6%)	

Table 1. Cont.

Variables	Case	Control	Total	p[a]
Type-2 Diabetes				<0.0001
Absent	216 (86.4%)	701 (93.5%)	917 (91.7%)	
Present	34 (13.6%)	49 (6.5%)	83 (8.3%)	
Kidney disease				1.000
Absent	248 (99.2%)	745 (99.3%)	993 (99.3%)	
Present	2 (0.8%)	5 (0.7%)	7 (0.7%)	
Other disease [e]				0.831
Absent	242 (96.8%)	728 (97.1%)	970 (97%)	
Present	8 (3.2%)	22 (2.9%)	30 (3%)	
Hospitalization history [f]				0.194
Absent	246 (98.4%)	724 (96.7%)	970 (97.1%)	
Present	4 (1.6%)	25 (3.3%)	29 (2.9%)	

[a]P is the Probability of t-test or Chi-square (χ^2) tests. Fisher's exact Chi-square (χ^2) test was used for history of health care work, kidney disease, other disease, smoking status and hospitalization history.
[b]'Others' subgroup under 'Occupation' includes housewife and self-employed small works.
[c]BDT: Bangladeshi currency.
[d]Cavitation related information was not available in 51% of the participants.
[e]Other disease included hypertension, heart diseases, asthma, chronic obstructive pulmonary diseases and chronic dysentery.
[f]Hospitalization history had one missing value.
doi:10.1371/journal.pone.0105214.t001

compliance with treatment [12,13], HIV infection [9,14], younger age-group [9,15,16], gender [9,13], foreign born people [9,16], living in an urban area [15], working in health care [14], type by bacteriology and pulmonary site of TB [14], presence of cavitation in lungs [12], contact with a TB patient [11], smoking or other substance misuse [14,17,18], chronic renal failure [19], diabetes [20], use of other anti-microbial medicine [19], being an asylum seeker [14], living in a nursing home [14], being a prisoner [14], and hospitalization history [21]. Inappropriate medical management, absence of directly observed treatment, lack of uniformity between public and private sectors, limited or interrupted drug supply, poor quality and widespread availability of anti-tuberculosis drugs, were also reported as important causes associated with MDR-TB [10,22,23]. However, findings related to some risk-factors such as HIV status [10,24], age group [10] and gender of the patients [8,9,13] differed. Moreover, study designs varied widely, some findings were based on small sample sizes and some came from drug resistance surveys.

Characteristics of MDR-TB patients have not been systematically explored in Bangladesh. Flora et al. conducted a study in 2010 that recruited a small number of purposively selected participants [25], making it impossible to generalise the findings of the study. There were also a few discrepancies between the presented results and the conclusions drawn. The authors reported that only 30 (22.1%) MDR-TB patients and seven (4.6%) drug sensitive TB patients had a previous history of tuberculosis. However, they included the total sample in the analysis to test the factors related to past illness, such as "Course of treatment" and "Directly observed treatment" [25]. It is not clear whether they were looking for the effects of current or previous treatment episodes. The National Tuberculosis Control Programme (NTP) Bangladesh started the MDR-TB programme in 2008 and gradually expanded its services in subsequent years [26]. At the time of the previously conducted study the MDR-TB programme was still evolving.

This is the context for our case-control study that explores the factors associated with MDR-TB. We compared the backgrounds and histories of MDR and drug-susceptible TB patients. All consenting MDR-TB patients aged between 18 and 65 years who were treated at one of the three government hospitals responsible for MDR-TB treatment in the country during the study period between September 2012 and April 2013 were included in the study.Controls were selected randomly from those local treatment units that had referred the cases.

Methods

Ethics considerations

The study was approved by the Human Research Ethics Committee (HREC) of the University of Newcastle (UoN), Australia and the Bangladesh Medical Research Council (BMRC), Dhaka, Bangladesh. 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. Written informed consent was then obtained from each person. A thumb impression was obtained from those who were unable to sign the consent form. All patients had been treated through the National TB Control Programme (NTP).

Study population and design

Patients were recruited from central, district and sub-district level government hospitals and Non-governmental organization (NGO) clinics in rural and urban Bangladesh. This case-control study includes 250 MDR-TB patients as cases and 750 drug-sensitive TB patients as controls. We designed the study to have 80% power to detect at least a 10% difference in the prevalence of any of our exposure variables at 5% significance threshold, assuming prevalence in the controls of 40% (with greater power and smaller effects detectable for exposures with lower control prevalence). This sample allowed us to accommodate the multivariable analysis for multiple factors.

MDR-TB patients aged between 18 to 65 years who gave their informed consent were included in the study. Patients who

Table 2. Univariate logistic regression analysis on factors related to Multidrug Resistant Tuberculosis (MDR-TB).

Variables	Odds ratio	Confidence Interval [a]	p [b]
Previous history of TB Treatment			
No	1.00		
Yes	716.63	282.1–1820.8	<0.0001
Gender			
Female	1.00		
Male	1.4	1.0–1.9	0.028
Age-group			
More than 45 years	1.00		
18 to 25 years	1.97	1.3–3.0	0.001
26 to 45 years	2.06	1.4–3.0	<0.0001
Education			
None	1.00		
Secondary and below	2.38	1.7–3.3	<0.0001
Higher secondary and above	2.01	1.1–3.6	0.02
Occupation			
None	1.00		
Service	3.53	1.7–7.5	0.001
Others [c]	1.56	0.7–3.2	0.236
Business	3.75	1.7–8.3	0.001
Transport worker	2.70	1.0–7.0	0.041
Smoking status			
Never smoked	1.00		
Current smoker	0.04	0.05–0.3	0.001
Past smoker	1.57	1.2–2.1	0.003
Substance misuse			
No	1.00		
Yes	1.71	1.1–2.6	0.014
Type-2 Diabetes			
No	1.00		
Yes	2.25	1.4–3.6	0.001

[a]Confidence interval at 95% level.
[b]p is the p value of Wald test statistic.
[c]'Others' subgroup under 'Occupation' includes housewife and self-employed small works.
Only the significant variables are shown in the table (significance level at 0.05).
doi:10.1371/journal.pone.0105214.t002

received treatment for MDR-TB following the criteria of the national guidelines of the National Tuberculosis Control Programme (NTP) were classified as MDR-TB. The NTP has recently adopted automated real time PCR (Xpert MTB/RIF) as the diagnostic tool of MDR-TB patients. Culture and Drug Sensitivity Testing (DST) and Line probe assays were also used [27]. Xpert MTB/RIF diagnoses only Rifampicin resistance. Patients who are resistant to Rifampicin are generally also resistant to Isoniazid (another first-line drug) as well. Mono-resistance to Rifampicin is fairly uncommon (0.2% and 0.4% among new and previously treated patients, respectively), as shown by a recent drug resistance survey (DRS) conducted in Bangladesh [28]. Controls were drug susceptible TB patients aged 18 to 65 years, diagnosed through sputum smear microscopy or other investigations (X-ray, FNAC, and Biopsy) as per national guidelines who would 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 (ICU), recent surgery or any medical emergency that needs continuous observation.

Data collection

MDR-TB patients from all over Bangladesh are referred to one of the three government hospitals (to the national hospital in Dhaka or a regional hospital in either Chittagong or Rajshahi). We consecutively recruited all eligible MDR-TB patients who were admitted from September 2012; recruitment ceased in April 2013 when the target of 250 cases was reached.

We recruited three controls per case from the local tuberculosis treatment unit from where the case was referred. The hospitals that were providing MDR-TB treatment were receiving patients referred by the various treatment units from rural and urban Bangladesh. Each TB patient is assigned a unique TB registration number as a routine practice. Treatment registration numbers of

Table 3. Multivariable analysis on factors related to Multidrug Resistance Tuberculosis (MDR-TB).

Predictor	Adjusted Odds ratio	Confidence Interval [a]	p[b] (Wald)	p[c] (lrt)
Age group				0.0325
More than 45 years	1.00			
18 to 25 years	1.77	1.07–2.93	0.027	
26 to 45 years	1.72	1.12–2.66	0.013	
Education				0.0026
None	1.00			
Secondary and below	1.94	1.32–2.85	0.001	
Higher secondary and above	1.83	0.92–3.65	0.086	
Occupation				
None	1.00			0.002
Service	2.88	1.29–6.44	0.010	
Others [d]	1.65	0.76–3.55	0.203	
Business	3.71	1.59–8.66	0.002	
Transport worker	2.71	0.95–7.72	0.063	
Smoking status				**<0.0001**
Never smoked	1.00			
Current smoker	0.04	0.005–0.29	0.002	
Past smoker	1.58	0.99–2.50	0.053	
Type-2 Diabetes				0.0006
Absent	1.00			
Present	2.56	1.51–4.34	0.001	

[a]Confidence interval at 95% level.
[b]p (Wald) is the p value of Wald test statistic.
[c]p (lrt) is the p value corresponding to the Likelihood ratio test statistic.
[d]"Others" subgroup under "Occupation" includes housewife and self-employed small works.
Only the significant variables in multivariable model are shown in the table (significance level 0.05).
doi:10.1371/journal.pone.0105214.t003

the tuberculosis patients, who were diagnosed during the specified period i.e. during the same month that MDR-TB was diagnosed, were listed. Three controls per MDR-TB case were randomly selected from this list at the treatment unit.

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

Statistical analysis

A data entry template was used and data was validated by a series of logical checks. Summary statistics and tables were produced from cleaned and acceptable data. We compared participant characteristics between MDR-TB cases and controls using Student t-tests for continuous measures, and Chi-square (χ^2) tests for categorical measures. Associations between participant characteristics and MDR-TB status were assessed using both unadjusted and multivariable logistic regression models. We had sufficient MDR-TB cases to include the following variables in the multivariable model without risk of over-fitting: age, gender, educational status, occupation, history of health care related work, monthly household income, living conditions (number of persons per room), BCG vaccination status, contact with other TB patients, smoking, substance misuse (alcohol or drug addiction), type 2 diabetes as co-morbidity, and hospitalization history. We included all variables to the initial multivariable model and variables were removed from this model if the Likelihood ratio test was not significant at 5% and the coefficients of the remaining variables did not change by more than 15% (indicating no evidence of confounding). Collineartiy was assessed through inspecting variance inflation factors and assessing pair-wise Chi-Square tests. Data analysis was carried out using Stata statistical software version 12 (StataCorp LP, TX, USA).

Results

Socio-demographic and clinical characteristics

The study included 250 MDR-TB and 750 non-MDR-TB patients representing all seven divisions of Bangladesh. Mean age of participants was 37 years and 61% were male. About half of the participants had some education at secondary level or below and a median monthly income of 10000 Bangladeshi taka (129 USD approximately).

Details of Socio-demographic and clinical characteristics are shown in Table 1.

Risk factors for MDR-TB

Univariate analysis. Previous history of tuberculosis treatment was a major contributing factor to MDR-TB (OR 716.6, 95% CI 282.1–1820.8). In total, 29.3% of participants had a

history of previous tuberculosis treatment that was 98% of the MDR-TB and 6.4% of non-MDR-TB patients. MDR-TB patients were more likely to be male, aged between 18 and 45, educational level of secondary and below or higher secondary and above, have an occupation in service or business or transport work, are a smoker, have a history of substance misuse or type 2 diabetes (Table-2).

Multivariable analysis. We removed previous treatment from the multivariable model since the variance inflation factors were high and it had a high degree of association with many of the variables in the model. The variables showing strong association with previous treatment included age (Chi-square 7.2,df 2; p 0.027), educational status (Chi-square 15.3, df 2; p <0.0001), occupation (Chi-square 22.4, df 4; p <0.0001), history of health care related work (Chi-square 6.3, df 1; p 0.01), monthly household income (Chi-square 15.0, df 4; p 0.005), smoking (Chi-square 29.2, df 2; p < 0.0001), substance misuse (Chi-square 7.3, df 1; p 0.007) and type 2 diabetes as co-morbidity (Chi-square 8.7, df 1; p 0.003).

For the final multivariable model, we found that age group, educational status, occupation, smoking status, and type 2 diabetes were significantly associated with MDR-TB (Table-3).

Discussion

Multidrug resistance is more commonly reported among previously treated tuberculosis patients than in new tuberculosis patients, globally as well as in Bangladesh [1]. Our study showed that most MDR-TB patients (98%) had a history of previous tuberculosis treatment, in line with other studies [8,9,10,11,12,17]. In a systematic review of risk factors conducted in Europe, previous treatment history of TB was the strongest determinant of MDR-TB in Europe and the pooled risk of MDR-TB was 10.23 times higher in previously treated patients than in patients without prior treatment [9]. Previous treatment as a risk factor helped in developing the MDR-TB case finding strategy during the introduction of MDR-TB programmes [7]. Drug sensitivity testing is not routinely done on all TB patients in Bangladesh due to the large number of patients diagnosed each year [27]. Recent national guidelines recommend that previously treated patients, new TB patients with treatment failure, and people in contact with MDR-TB patients, are referred for MDR-TB testing. In addition, patients with delayed response in treatment, or with smear-negative or extra-pulmonary TB that does not improve clinically, with relapse or who receive treatment after default, or who have HIV, are tested for MDR-TB in Bangladesh [27].

In our study, being between 18 and 45 years of age was associated with an increased risk for MDR-TB, similar to what was reported in another study conducted in Hong Kong [16]. Another study conducted in Bangladesh found that patients under 40 years are more likely to develop MDR-TB, based on univariate findings, although this association was weak in the multivariable model (OR 0.87; 95% CI 0.40–1.93 and OR 0.87 CI 0.33–2.33 for age-groups 21 to 30 years and 31 to 40 years, respectively) [25]. Other studies conducted in Shanghai and Spain found that the greatest risk of MDR-TB was associated with age 35 to 59 [15] and 45 to 65 years [17], respectively. Although the range varies, being below 65 years is associated with developing MDR-TB, as reported in multi-country reviews [9,10]. Younger people are more likely to come in contact with MDR-TB as they are more mobile and active compared to the older age group through their involvement in work or study [16]. They may also find it difficult to take regular supervised medicine due to conflicting work times, which results in poor treatment adherence. Another explanation for the greater risk in younger age groups may be that Rifampicin was introduced in recent decades and many elderly people may not have been exposed to it [16]. These explanations may not be applicable to primary drug resistance that is transmitted. In our study only five (2%) MDR-TB patients did not have any history of previous treatment, in line with the low level of primary resistance in a recent drug resistance survey, where 1.4% of MDR-TB patients did not have a previous diagnosis, compared to 28% of previously treated patients [28].

A number of occupations such as those associated with services and business were more likely to be linked with MDR-TB compared to non-working individuals. Occupation as transport workers, another highly mobile group, was associated with MDR-TB if examined alone, although we did not observe any difference after adjusting for other factors. This study did not show any association with health care as an occupation, which was found to be associated with MDR-TB in another study [14]. Patients with some educational qualification were more likely to develop MDR-TB than patients with no formal education or from the highest educational group.

Type 2 Diabetes is known to be a risk factor for TB [29] and is linked to MDR-TB in our and other studies [20]. It may affect TB treatment outcome and disease presentation [29], leading to failed treatment, although this is not always the case [30]. Impaired immunity due to diabetes may increase susceptibility to infection with drug resistant strains [20]. Bangladesh is facing the dual burden of communicable and non-communicable diseases. The prevalence of Diabetes mellitus has increased from 2.3% in 1999 to 7.9% in 2009 [31]. The relationship between MDR-TB and diabetes could be addressed by treating diabetic patients with tuberculosis within a collaborative framework [32]. In our study, the diabetes status was self-reported by the patients. Further studies using a screening method for diabetes status need to be conducted.

MDR-TB patients were more likely to be past tobacco smokers in our study. Although current smokers were less likely to have MDR-TB compared to non-smokers, this may be a result of MDR-TB patients quitting smoking on diagnosis. Smoking is one of the main determinants for TB and some studies showed an association with acquired drug resistance [18]. Another study showed that smoking is a predictor for delayed response to treatment [33]. Tobacco control efforts have been initiated in Bangladesh in recent years, including some piloting of its integration with tuberculosis services [34]. Our finding suggests that TB and tobacco control efforts need to be sustained to control TB overall as well as MDR-TB. Intravenous drug use was a risk factor for MDR-TB in another study [14]. Drug or alcohol misuse was not a significant cause of MDR-TB in our study, after adjusting for other factors.

Males were more likely to have MDR-TB than females in some settings [9] whereas the opposite was true in others [8,13]. Gender was not a risk factor in our study. Although contact with TB patients was found to be associated with MDR-TB in other studies [11,23,35], we did not observe any association. Neither did we observe any effect of income, crowding status expressed as persons per room, vaccination status (BCG), history of hospitalization within seven months, and kidney disease. Overall, 56% of our participants were BCG vaccinated in their childhood. Recent BCG coverage among children has increased remarkably in Bangladesh and has reached almost 98% [36].

In this study we focused on hospital based cases, as a population-based risk factor study was not feasible for MDR-TB. However, our cases are likely to be representative of MDR-TB patients in Bangladesh as we recruited from all three Government

TB hospitals which treat most of the MDR-TB patients in the country. We recruited the controls from the population rather than from MDR-TB hospitals to ensure they were representative of non-MDR patients. In Bangladesh, most TB patients are treated within the NTP designated DOTS centres, and current case notification rate in Bangladesh is 68% [1]. We could not assess HIV status as a risk factor in our study. However, Bangladesh is a low burden country for HIV [6]. It was not feasible to confirm drug susceptibility using Drug Sensitivity Testing (DST) of the controls, as only high-risk patients are routinely tested, and we did not have the funds for this.

Conclusion

Previous tuberculosis treatment was found to be the major risk factor for MDR-TB. This study also identified the following as risk factors for MDR-TB: age 18 to 45 years, some education up to secondary level, service and business as occupation, past smoking status, and type 2 diabetes as comorbid illness. These risk factors should be addressed in the strategy for MDR-TB control. The NTP of Bangladesh is reliant on multi-sectoral involvement to address all risk factors and can advocate for these issues in order to improve control of MDR-TB. The integration of MDR-TB control activities with diabetes and tobacco control programmes would be a good place to start these collaborative efforts.

Acknowledgments

We received cooperation from the National Tuberculosis Control Programme, Directorate General of Health Services and Damien Foundation, Bangladesh. We gratefully acknowledge the contribution of the research team who worked hard to collect quality data. The authors thank Claudia Koller for assistance with editing this manuscript. Finally, we are grateful to the study participants for their valuable time and assistance.

Author Contributions

Conceived and designed the experiments: MR AHM JH. Performed the experiments: MR BNS MAI. Analyzed the data: MR CO. Contributed reagents/materials/analysis tools: MR AHM JH AH MWA. Contributed to the writing of the manuscript: MR AHM JH CO MAI AH MWA BNS.

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BMJ Open

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

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To cite: Rifat M, Hall J, Oldmeadow C, *et al*. Factors related to previous tuberculosis treatment of patients with multidrug-resistant tuberculosis in Bangladesh. *BMJ Open* 2015;**5**:e008273. doi:10.1136/bmjopen-2015-008273

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-008273).

Received 22 March 2015
Revised 23 July 2015
Accepted 10 August 2015

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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.

Acknowledgements The authors received cooperation from the National Tuberculosis Control Programme, Directorate General of Health Services and Damien Foundation, Bangladesh and other partners including UPHCSDP, NHSDP and BGMEA. They gratefully acknowledge the contribution of Md. Akramul Islam, BRAC, for providing valuable inputs and extensive support to implement this study. They are thankful to Bodrun Naher Siddiquea, Muhammad Amzad Hossen, Md. Zaidur Rahman, Md. Momenul Islam and all other BRAC colleagues who worked hard to collect quality data. The authors also thank Claudia Koller for assistance with editing this manuscript. Finally, they are grateful to the study participants for their valuable time and assistance.

Contributors MR, AHM and JH contributed in designing and planning the study. MR collected and analysed the data and prepared the manuscript. CO provided input in data analysis and writing. All authors reviewed the document and provided their inputs.

Funding The study was based in Bangladesh and was partially supported by the Australian Respiratory Council, BRAC Bangladesh and University of Newcastle Australia.

Competing interests None declared.

Ethics approval Human Research Ethics Committee (HREC) of the University of Newcastle (UoN), Australia and the Bangladesh Medical Research Council (BMRC), Dhaka, Bangladesh.

Provenance and peer review Not commissioned; externally peer reviewed.

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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BMJ Open

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

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BMJ Open 2015 5:
doi: 10.1136/bmjopen-2015-008273

INT J TUBERC LUNG DIS 15(5):647–651

doi:10.5588/ijtld.10.0205

Why are tuberculosis patients not treated earlier? A study of informal health practitioners in Bangladesh

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SUMMARY

SETTING: Five districts and four cities of Bangladesh.

OBJECTIVE: To study the role of informal health practitioners in delays in initiating tuberculosis (TB) treatment in new smear-positive TB patients.

DESIGN: A cross-sectional study of all patients registered within specific projects in Bangladesh using routine records from projects. Definitions were as follows: 1) total delay: duration from onset of symptoms to initiation of treatment; 2) patient delay: onset of symptoms to first visit to any practitioner; and 3) health system delay: first visit to practitioner to treatment initiation.

RESULTS: A total of 7280 cases were enrolled. Prolonged delay was calculated as ⩾5 weeks for patient delay, ⩾10 weeks for health system delay and ⩾13 weeks for total delay. Prolonged patient delay was less frequent when patients first consulted informal as compared to qualified health practitioners (30% vs. 68%). Similar figures for prolonged health system delay were respectively 52% and 16%, while those for total delay were 47% and 27%. The differences were statistically significant ($P < 0.05$).

CONCLUSION: Patients seeking care from informal practitioners access care more promptly, but have prolonged delays in initiating treatment. Further investigation on how to involve these practitioners in the programme should be evaluated.

KEY WORDS: delay; informal practitioner; tuberculosis

TUBERCULOSIS (TB) is a major public health problem in Bangladesh, which according to the World Health Organization ranks sixth among high-burden countries.[1] The National Tuberculosis Control Programme (NTP) started implementation of the internationally recommended DOTS strategy in 1993, which is now estimated to have reached the high treatment success (92%) and case detection (72%) targets that are expected to reduce the transmission of infection in the community.[2]

Delays often occur in initiating TB treatment.[3,4] Such delays may lead to progression of disease, poor treatment outcomes, an increased risk of death and an increase in TB transmission in the community, which represents a major obstacle to the control of a TB epidemic.[5] These adverse effects justify our interest in understanding factors behind the delays and finding possible solutions to the problem in Bangladesh.

Different types of health care providers administer TB services in Bangladesh, including both qualified and informal practitioners. A previous study in Bangladesh focused on the role of gender in increasing delays, but did not evaluate the type of service providers.[3]

The objective of the present study was to determine the time between the start of symptoms and the start of TB treatment in selected urban and rural areas of Bangladesh, and to document the factors related to delay in treatment initiation, focusing on the role of informal health practitioners.

METHODS

Design

This cross-sectional study included all new smear-positive pulmonary TB cases registered during the period from April 2004 to September 2005 in FIDELIS (Fund for Innovative DOTS Expansion through Local Initiatives to Stop TB) projects in Bangladesh. The study is an analysis of information obtained from the routine reports from these projects.

Background

The Bangladesh Rural Advancement Committee (formerly BRAC), a non-governmental organisation (NGO) based in Bangladesh, has been supporting the NTP for many years and provides TB services that cover about two thirds of the country's population. BRAC undertook these two projects, covering a total population of 23.7 million, as part of these services. The projects were carried out in five districts and four

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Article submitted 30 March 2010. Final version accepted 20 October 2010.

city corporation areas, selected for their low estimated case detection rates.

Study population

The study focused on new smear-positive pulmonary TB patients. According to the national guidelines, these are defined as patients who have never received anti-tuberculosis drugs or have received drugs for <1 month. Smear-positive pulmonary TB was defined as a patient with at least two sputum specimens positive for acid-fast bacilli (AFB) on smear microscopy, or one sputum specimen positive for AFB if supported by a chest radiograph consistent with active TB or a sputum culture positive for *M. tuberculosis*.[6]

Based on the research question 'Does seeking first-level care from informal health practitioners result in delay in initiating treatment?' a sample size calculation was made using Open Epi software.[7] Sufficient power was obtained using the assumption that 4200 (60%) of approximately 7000 cases registered would visit informal practitioners, and 36% would be found to have a delay in diagnosis.

Data sources, data collection and variables

Data were collected routinely during treatment initiation as part of the provision of services, using a prescribed form required by the projects. The questionnaire included the following: 1) information on the total period of time from earliest onset of symptoms to initiation of treatment, expressed in weeks; 2) any visit made to a health care practitioner prior to start of treatment, and details about the time and the type of practitioner visited; and 3) information regarding the patient's demographic characteristics (age, sex and project area) and symptoms present during the episode. Information on symptoms and type of practitioner was presented in multiple choice tick boxes.

Staff involved in the projects were trained on how to use the questionnaire. Periodic checking of the questionnaires and feedback were part of routine programme activities and were used to monitor data quality.

Informal practitioners, referred to as 'traditional healer or equivalent', included village doctors, pharmacists, rural medical practitioners and traditional healers, none of whom held a science or medicine degree. Qualified practitioners included all other personnel who had a medical degree including private practitioners not within the TB (DOTS) facility, medical doctors and public sector health care workers working in public sector TB (DOTS) facilities. Other variables that were collected from patients and analysed were age, sex and urban/rural status. Urban status was defined as patients coming from urban projects and the Sadar subdistricts (which include the district town). Other areas were regarded as rural.

Key outcome variables and their definitions are shown in Figure 1. In this study, we considered cough as the main symptom for considering delay, as most new smear-positive patients usually have cough.

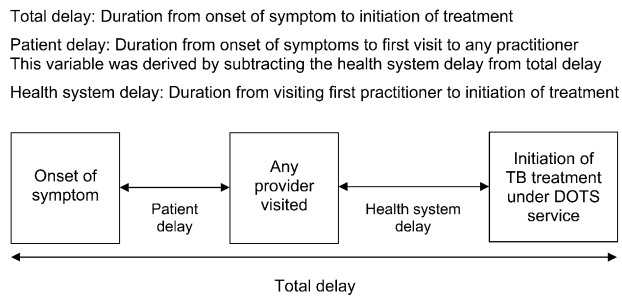

Figure 1 Definition of key outcome variables

As the distribution of delay was expected to be non-normal, the overall distribution in the entire group of patients was divided into five parts (quintiles), by 20% intervals in the distribution. Prolonged delay was defined by the two highest quintiles of the distribution of delay for all patients, the cut-off point being defined by taking the specific week that included 60% of the patients.

Data analysis

Data were computer-entered with no personal identifiers, and were analysed using SPSS 13 (Statistical Package for Social Sciences, Chicago, IL, USA). Statistical analysis was carried out using χ^2 for univariate analysis and logistic regression for multivariate analysis.

Ethical considerations

The project was approved by the NGO Affairs Bureau of Bangladesh. Ethical approval for the current study was obtained from the Bangladesh Medical and Research Council and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease.

RESULTS

There were 7280 new smear-positive pulmonary TB cases enrolled in the projects; their socio-demographic characteristics are shown in Table 1. The median total delay for these patients was 12 weeks, with the median patient delay and health system delay being 4 and 8 weeks, respectively.

The quintile distribution for the entire group of patients in terms of weeks of delay corresponded to 0–7, 8–9, 10–12, 13–17 and ⩾18, for total delay. For patient delay, the distribution was <1, 1–2, 3–4, 5–7, ⩾8. For health system delay, it was 0–2, 3–6, 7–9, 10–11, ⩾12.

We then compared the distributions among patients who first consulted qualified practitioners with those who first consulted informal practitioners (Figures 2 and 3). We found that prolonged total delay

Table 1 Socio-demographic characteristics of patients under the study

Variable	*n*	%
Sex		
Male	5019	69
Female	2261	31
Residence		
Urban	3542	49
Rural	3738	51
Practitioners visited for first consultation		
Traditional healer or equivalent*	5023	69
Non DOTS clinic †	1152	16
DOTS clinic‡	84	1
No practitioner visited prior to treatment initiation	1021	14
Patient age, years, mean ± SD	38.5 ± 16.3	

*Includes traditional healers, pharmacists, rural medical practitioners and village doctors.
†Private practitioners and graduate medical doctors.
‡DOTS facility recognised by the NTP.
SD = standard deviation; NTP = National TB Control Programme.

(⩾13 weeks) occurred in 47% of those first consulting an informal practitioner compared with 27% of those who first consulted a qualified practitioner. The corresponding figures for prolonged patient delay (⩾5 weeks) were 30% and 68% for informal and qualified practitioners, respectively. Distributions for prolonged health system delay (⩾10 weeks) were 52% for those consulting informal practitioners and 16% for those first consulting qualified practitioners. These differences were all statistically significant (Pearson χ^2 $P < 0.05$; Table 2).

Logistic regression analysis of prolonged total delay, comparing those who first consulted informal and qualified practitioners, was carried out with age, sex and place of residence (urban or rural) as covariates. This analysis showed that prolonged delay was associated with greater age and rural residence as compared to urban residence. Adjusted by type of practitioner visited and age of patients, the difference in total delay between males and females was not statistically significant (Table 3). The same associations were found from logistic regression analysis for both patient and health system delays (Table 3).

We excluded 124 cases from the analysis of patient delay. The main symptom used for calculating delay was cough, whereas these 124 cases (of 7280) had visited practitioners for other TB symptoms such as fever and other chest symptoms, which began before cough. As they had a negative patient delay, they were excluded from analysis.

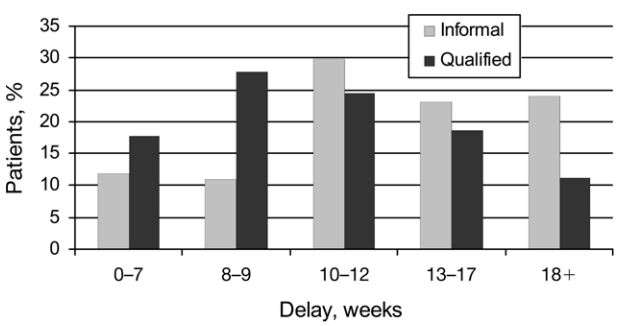

Figure 2 Total delay in starting tuberculosis treatment by status of health practitioners in selected areas of Bangladesh.

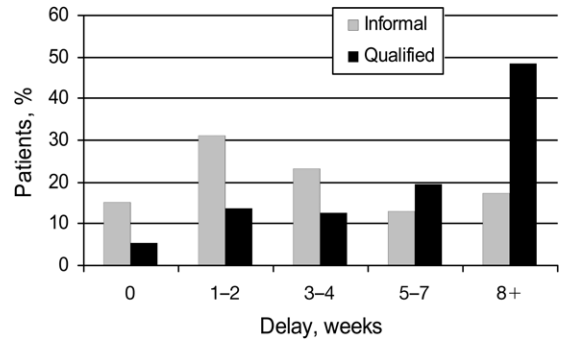

Figure 3 Tuberculosis patient delays in selected areas of Bangladesh by first visit to health practitioners.

DISCUSSION

Delays in seeking care for TB have been observed in many settings. A systematic review indicated total delays ranging from 25 days in China to 185 days in Tanzania,[4] while delays were reported of 60 days

Table 2 Prolonged delays (total, patient and health system delays) comparing first visits to informal practitioners and those to qualified practitioners*

		P value†
Total delay		
⩽12 weeks		
Informal‡	2656	
Qualified§	1643	
⩾13 weeks		
Informal‡	2367	
Qualified§	614	<0.001
Patient delay		
⩽4 weeks		
Informal	3434	
Qualified	704	
⩾5 weeks		
Informal	1506	
Qualified	1512	<0.001
Health system delay		
⩽9 weeks		
Informal	2404	
Qualified	1895	
⩾10 weeks		
Informal	2619	
Qualified	362	<0.001

*The cut-off points for prolonged delay were taken by considering the two highest quintiles of distribution of all patients in the study in which 60% of the patients were included.
†χ^2 test.
‡Includes traditional healers, pharmacists, rural medical practitioners, village doctors.
§Includes non-DOT clinics, e.g., private practitioners and graduate medical doctors; public sector DOTS facility recognised by the NTP and those who made no visits before this visit.
NTP = National Tuberculosis Control Programme.

Table 3 Results of logistic regression analysis: prolonged delays (total, health system and patient delays) in tuberculosis treatment among patients in Bangladesh by age, sex, place of residence and type of first practitioner consulted*

Variable	Exp (B)	95%CI for Exp (B) Lower	Upper
Prolonged total treatment delay (⩾13 weeks)*			
Age	1.01	1.01	1.02
Sex (male vs. female)	1.05	0.94	1.17
Urban vs. rural status	0.58	0.53	0.64
Informal vs. qualified practitioner visited†	2.26	2.02	2.52
Prolonged health system delay (⩾10 weeks)*			
Age	1.01	1.00	1.01
Sex (male vs. female)	1.00	0.90	1.12
Urban vs. rural status	0.47	0.43	0.52
Informal vs. qualified practitioner visited†	5.54	4.88	6.29
Prolonged patient delay (⩾5 weeks)*			
Age	1.01	1.00	1.01
Sex (male vs. female)	1.10	0.98	1.23
Urban vs. rural status	0.88	0.80	0.98
Informal vs. qualified practitioner visited†	0.20	0.18	0.22

*The cut-off points for prolonged delay were taken by considering the two highest quintiles of distribution of all patients in the study that included 60% of the patients.
†Informal practitioners include traditional healers, pharmacists, rural medical practitioners, village doctors. Qualified practitioners include non-DOT clinics, e.g., private practitioners and graduate medical doctors; public sector DOTS facility recognised by the NTP and those who made no visits before this visit.

in Nepal, 62 days in India and 97 days in Pakistan.[8–10] A previous study of 1000 patients from Bangladesh reported total delays of 61 days for women and 53 days for men.[3] The median total delay documented in our study was 12 weeks.

While success may be achieved in detecting and curing a high proportion of cases in a country, delays in care seeking may adversely affect attempts to curb transmission of this infectious disease. These delays need to be understood to be improved.

This study specifically chose to focus on informal practitioners. In Bangladesh, informal practitioners are the providers of curative care for many people; in one survey, 60% of people chose informal practitioners, 63% among the poorest 25% of the population.[11] Although the majority of these practitioners have no formal medical training, they are preferred by the poor because they are easily accessible and they render inexpensive services. Our study focused on the role informal health practitioners play in delays to determine how to reduce them. While we found that informal practitioners appeared to provide more accessible services (patient delay was shorter when they first consulted informal practitioners, whether in urban or rural areas), the total and health systems delays were greater when the first practitioner was from the informal sector. Delays associated with visits to informal practitioners were also observed in Mwanza, Tanzania.[12] Visits to informal health practitioners were not evaluated in a previous study on delay in Bangladesh.[3]

While in many settings patient delays contribute a major proportion of total delay,[9,12,13] in the present study we found that patient delay was comparatively shorter than health system delay. This was also observed in Ghana and Botswana, although in these studies patient delay had been defined as the time from onset of symptoms to first visit to a health facility, rather than to a health practitioner.[14,15]

Bangladesh provides TB services in collaboration with NGOs through community involvement.[16,17] Much emphasis has been given to community involvement and enhanced awareness of the community in recent years,[18] which may be one reason why patient delay contributes a lower proportion to total delay than in other locations.

The involvement of all care providers in TB control is much emphasised in the current international TB control strategy.[19] A study in Bangladesh showed that village doctors may contribute to referring TB suspects and provision of DOT.[20] This is important, as the national guidelines of Bangladesh allow treatment to be initiated only by qualified physicians; other practitioners can only refer suspects and cases to the DOTS facility.[21] Clearly, further efforts are needed to encourage informal practitioners to refer TB suspects to service points promptly to reduce delays; they should also have access to TB DOTS facilities. Further investigation on how to involve these practitioners in the NTP should be undertaken.

Although we did not find any differences between men and women, a previous study in Bangladesh showed significant patient delays among females of higher age group.[3] More involvement of female community-based volunteers in the project areas where our study was undertaken may have contributed to the difference in the findings in our study. The prolonged delay associated with rural residence could be due to lack of access to services and lower economic status of patients in these areas, as was found in Mwanza, Tanzania.[12]

This study covers a large population which includes all available records of the projects. It was based on an interview document of a routine project, illustrating the feasibility of routinely assessing delay. Incorporating routine evaluation as a part of routine practice would aid services in understanding and reducing delays, consequently improving TB control.

While the advantages of conducting such research within routine services and using programmatic documents are obvious, they are limited by the fact that the information obtained was based on patient statements and could not be verified.

We believe that this simple study, using information from routine services, will be beneficial in helping us understand and address this important problem.

Acknowledgements

The authors are grateful to all BRAC staff involved in these projects. This research was supported through an operational research

course jointly developed and run by the Centre for Operational Research, the International Union Against Tuberculosis and Lung Disease ([The Union], Paris, France), and the Operational Research Unit, Médecins sans Frontières, Brussels, Belgium. This field work was partially funded by the FIDELIS project, managed by The Union with funding from the Government of Canada through the Canadian International Development Agency.

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RÉSUMÉ

CONTEXTE : Cinq districts et quatre villes au Bangladesh.

OBJECTIF : Etudier le rôle des praticiens de santé « informels » dans le retard intervenant dans la mise en route du traitement de la tuberculose (TB) chez les nouveaux patients atteints de TB à bacilloscopie positive des frottis.

SCHÉMA : Etude transversale de l'ensemble des patients enregistrés au sein de projets spécifiques au Bangladesh en utilisant leurs dossiers de routine. Les définitions ont été les suivantes : 1) durée totale du retard entre le début des symptômes et la mise en route du traitement ; 2) retard-patient entre le début des symptômes et la première visite à n'importe quel type de praticien ; 3) retard du système de santé depuis la première visite au praticien jusqu'à la mise en route du traitement.

RÉSULTATS : On a enrôlé au total 7280 cas. On a calculé que la prolongation du retard-patient était de ⩾5 semaines, de ⩾10 semaines pour le retard-système de sante et de ⩾13 semaines pour le retard total. La prolongation du retard-patient a été moins fréquente lorsque les patients avaient consulté d'abord un praticien « informel » plutôt qu'un praticien qualifié (30% vs. 68%). Des donnés similaires ont concerné la prolongation du retard-système de santé rencontré dans 52% vs. 16%, alors que le retard total a été rencontré chez 47% pour les praticiens « informels » et chez 27% pour les praticiens qualifiés. Ces différences sont statistiquement significatives ($P < 0,05$).

CONCLUSION : Les patients recourant pour soins à des praticiens « informels » accèdent plus rapidement aux soins, mais subissent un retard prolongé dans la mise en route du traitement. Des investigations complémentaires sur la façon d'impliquer ces praticiens dans le programme devraient être réévaluées.

RESUMEN

MARCO DE REFERENCIA: Cinco distritos y cuatro ciudades de Bangladesh.

OBJETIVO: Estudiar la contribución de los proveedores tradicionales de atención sanitaria o del personal equivalente al retraso del comienzo del tratamiento antituberculoso en los casos nuevos de tuberculosis con baciloscopia positiva.

MÉTODOS: Se llevó a cabo un estudio transversal de todos los pacientes inscritos en proyectos específicos en Bangladesh, a partir de los registros sistemáticos de los proyectos. Las definiciones adoptadas fueron: 1) la duración total del retraso desde el inicio de los síntomas hasta el comienzo del tratamiento; 2) el retraso dependiente del paciente, entre el inicio de los síntomas hasta la primera consulta a algún proveedor de atención; y 3) el retraso dependiente del sistema de salud, entre la primera consulta al médico y el comienzo del tratamiento.

RESULTADOS: Se incluyeron en el estudio 7280 casos. Se calculó que el retraso dependiente de los pacientes fue de ⩾5 semanas, el retraso dependiente del sistema sanitario fue de ⩾10 semanas y el retraso total fue de ⩾13 semanas. El retraso prolongado dependiente del paciente fue menos frecuente cuando los pacientes consultaron en primera instancia a un proveedor tradicional de atención, en comparación con un médico calificado (30% contra 68%). Se observaron proporciones equivalentes en el retraso dependiente del sistema de salud (52% contra 16%); se observó un retraso total en 47% de los pacientes que consultaron inicialmente un proveedor tradicional y en 27% de los que acudieron primero a un médico calificado. Las diferencias fueron estadísticamente significativas ($P < 0,05$).

CONCLUSIÓN: Los pacientes que acuden a los proveedores tradicionales de atención de salud obtienen un acceso más rápido a la atención, pero presentan un retraso prolongado del comienzo del tratamiento. Es necesario investigar más el mecanismo óptimo que logre vincular a estos proveedores de atención al programa de salud.

Rifat et al. BMC Infectious Diseases (2015) 15:526
DOI 10.1186/s12879-015-1253-9

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Health system delay in treatment of multidrug resistant tuberculosis patients in Bangladesh

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Abstract

Background: Bangladesh is one of the 27 high burden countries for multidrug resistant tuberculosis listed by the World Health Organization. Delay in multidrug resistant tuberculosis treatment may allow progression of the disease and affect the attempts to curb transmission of drug resistant tuberculosis. The main objective of this study was to investigate the health system delay in multidrug resistant tuberculosis treatment in Bangladesh and to explore the factors related to the delay.

Methods: Information related to the delay was collected as part of a previously conducted case–control study. The current study restricts analysis to patients with multidrug resistant tuberculosis who were diagnosed using rapid diagnostic methods (Xpert MTB/RIF or the line probe assay). Information was collected by face-to-face interviews and through record reviews from all three Government hospitals providing multidrug resistant tuberculosis services, from September 2012 to April 2013. Multivariable regression analysis was performed using Bootstrap variance estimators. Definitions were as follows: Provider delay: time between visiting a provider for first consultation on MDR-TB related symptom to visiting a designated diagnostic centre for testing; Diagnostic delay: time from date of diagnostic sample provided to date of result; Treatment initiation delay: time between the date of diagnosis and date of treatment initiation; Health system delay: time between visiting a provider to start of treatment. Health system delay was derived by adding provider delay, diagnostic delay and treatment initiation delay.

Results: The 207 multidrug resistant tuberculosis patients experienced a health system delay of median 7.1 weeks. The health system delay consists of provider delay (median 4 weeks), diagnostic delay (median 5 days) and treatment initiation delay (median 10 days). Health system delay (Coefficient: 37.7; 95 %; CI 15.0–60.4; p 0.003) was associated with the visit to private practitioners for first consultation.

Conclusions: Diagnosis time for multidrug resistant tuberculosis was fast using the rapid tests. However, some degree of delay was present in treatment initiation, after diagnosis. The most effective way to reduce health system delay would be through strategies such as engaging private practitioners in multidrug resistant tuberculosis control.

Keywords: Delay, MDR-TB, Multidrug resistant tuberculosis, Barrier to treatment, Health system, Private practitioner

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Background

Multidrug resistant tuberculosis (MDR-TB) is a major challenge to worldwide tuberculosis (TB) control [1]. Despite the progress in detection, in 2013 a total of 55 % the estimated MDR-TB were under-detected and 29 % of the diagnosed patients were not on treatment [2]. Delay in TB treatment may result in disease transmission, progression, and poor treatment outcome including increased risk of death [3]. Several studies have reported that delay in TB initiating treatment contributed to development of MDR-TB [4–6].

Bangladesh is one of the high burden countries for TB and has also been listed on the 27 high burden countries for MDR-TB by the World Health Organization (WHO) [2]. Due to the overall high TB burden in Bangladesh, the proportion of patients with MDR-TB (1.4 % and 29 %, among the new and previously treated TB patients, respectively) amounts to 4700 people (2100 and 2600 among new and previously treated TB patients, respectively), which provides a significant challenge for the national tuberculosis control programme [2].

Delay in MDR-TB treatment may cause more suffering to the affected patients as well as hinder the attempts to curb the spread of MDR-TB. Delay in initiation of tuberculosis treatment among the drug sensitive TB patients has been reported in many studies [7]. Some studies reported delay in commencing treatment of MDR-TB patients, although diagnostic and treatment initiation delays were frequently reported in these studies; the context and definition of delays were variable [8–14]. Some studies focused on rapid diagnostic methods for MDR-TB detection, reporting either the time taken for diagnosis or time from diagnosis to treatment initiation [8, 10, 14, 15]. We could only find one study on patient-related delay among the MDR-TB patients and its associated factors, a qualitative study carried out in Cape Town, South Africa [16]. The study reported inaccurate perception of their symptoms as an important factor in the delay in seeking care. Diagnostic delay was inherent in the MDR-TB management procedure while the diagnosis of MDR-TB relied on culture methods, which require longer time than the more advanced tests now routinely in use [17]. In 2012, the National TB control programme of Bangladesh (NTP) adopted rapid tests such as automated real time PCR (Xpert MTB/RIF) and Line probe assays to diagnose MDR-TB/Rifampicin resistant TB (RR-TB) as recommended by the World Health Organization [18, 19]; these methods reduce the time needed for diagnosis.

In Bangladesh, TB service is integrated in the basic health care services and available in all hospitals at sub-district level and below, in chest disease clinics, in district and medical college hospitals and in urban health centres run by government and non-government organizations (NGOs) [20]. Bangladesh has a dynamic NGO sector providing TB control services in collaboration with NTP through a partnership approach [21]. Different types of health care providers administer TB services in Bangladesh, including both qualified private practitioners and informal providers [22, 23]. Private practitioners are popular in Bangladesh irrespective of patients' income level and residence [24]. However, NTP does not have strong linkage with the private sector. As in many other countries, TB services provided by the private sector are poor, with use of inappropriate treatment and poor case holding, leading to incomplete treatment and drug resistance [24].

Delays in the treatment of drug-sensitive TB patients have been reported in several studies carried out in Bangladesh [3, 25–27]. Our study aims to explore delays related to the commencement of treatment for MDR-TB patients caused by the health system, namely provider delay, diagnostic delay and treatment initiation delay. Further, we aim to explore possible factors related to the health system delay, as well as to offer potential solutions.

Methods

Study population and setting

MDR-TB patients were identified as part of a previously conducted case–control study on risk factors associated with MDR-TB in Bangladesh when information related to treatment delay was also collected [28]. The study included 250 MDR-TB and 750 non-MDR-TB tuberculosis patients. In the current study we restrict the analysis to data related to the delay in treatment of MDR-TB patients.

NTP Bangladesh adopted the standardized regimen for treating MDR-TB and started the DOTS Plus project, in 2008 [29]. Currently one hospital at national level and four at regional level are providing MDR-TB diagnosis and treatment services. These hospitals are equipped with reference laboratories and a MDR-TB treatment ward. Presumptive MDR-TB patients who are identified at the district, sub-district or lower level are referred to these central and regional level hospitals for diagnosis and treatment initiation of MDR-TB, according to the national guideline [29].

At the time of our data collection, MDR-TB patients from all over Bangladesh (central, district and subdistrict level) were referred to one of three government hospitals, i.e. the national hospital in Dhaka or a regional hospital in either Chittagong or Rajshahi. All eligible MDR-TB patients from these hospitals who were admitted from September 2012 to mid-April 2013 were recruited. At that time the rapid diagnostic tests were still evolving in Bangladesh, and some of the MDR-TB patients were diagnosed through the conventional

culture and DST method. We only included the MDR-TB patients diagnosed by rapid diagnosis tests to ensure valid comparisons.

Except for the diagnostic criteria, the inclusion and exclusion criteria of this study were similar to the previous study [28]. The NTP has adopted automated real time PCR (Xpert MTB/RIF) as the preferred rapid diagnostic tool of MDR-TB patients. Culture and Drug Sensitivity Testing (DST) and Line probe assays were also used by NTP [29]. Xpert MTB/RIF diagnoses only Rifampicin resistance. However, patients who are resistant to Rifampicin are generally also resistant to Isoniazid (another first-line drug). Mono-resistance to Rifampicin is fairly uncommon (0.2 % and 0.4 % among new and previously treated patients, respectively), as shown by a recent drug resistance survey (DRS) conducted in Bangladesh [30]. This study included 207 MDR-TB patients who were diagnosed by the rapid tests, i.e. Xpert MTB/RIF or Line probe assays, to maintain the consistency in overall delay related information. We had excluded 34 patients who were diagnosed by the conventional culture and DST method. Nine patients were excluded due to missing information. The NTP uses a laboratory based in Antwerp, Belgium as quality control for diagnosis of MDR-TB patients.

Data collection and definitions

Definitions used in this study are as follows: Provider delay: time between visiting a provider to visiting designated diagnostic centre for testing; Diagnostic delay: time between the diagnostic sample provided to date the result is available; Treatment initiation delay: time between the date of diagnosis and the date of treatment initiation; Health system delay: time between visiting a provider to start of treatment. Health system delay was derived by adding provider delay, diagnostic delay and treatment initiation delay (Fig. 1). In this study, the term private practitioner refers to clinicians who are at least medical graduates; informal providers are the one without medical degree (MBBS), i.e. village doctors, medical assistants.

We tried to keep the definitions in line with a study conducted in Bangladesh that focused on treatment delay among drug sensitive TB patients due to health care providers [3]. Delay-related definitions used for drug-sensitive TB were not completely applicable to MDR-TB. As it is difficult to estimate patient delay (defined as the time between the onset of symptom to visiting a health care provider) for MDR-TB, as most of the patients had been treated previously, we focused our study on the delay due to the health system. We interviewed patients regarding their first visit to a health provider, assuming the patient would visit a provider when they perceived the symptoms as worsening or suspected a lack of response to their ongoing treatment. The provider delay in our study is based on patients' perceptions. Most of the participants (97 %) were TB patients who had previously received treatment for TB. We asked the patients specifically how many weeks before the MDR-TB diagnosis they had visited a health provider for their current problem (i.e. worsening of TB symptoms, or feeling that the disease was not responding to treatment).

Trained investigators collected information from the study participants by face-to-face interview using a pre-tested questionnaire, and by review of records. Information related to the time frame of the patient's visit to the provider was collected through interview, and since their recall may not be accurate, it was expressed in weeks rather than days. The dates of diagnosis and treatment were taken from the hospital records, and the diagnostic and treatment delays were expressed in days.

Statistical analysis

Socio-demographic characteristics were summarised using means and standard deviations for continuous variables and counts/percentages for categorical variables. Multivariable regression models were used to estimate the effect of age, sex, education, occupation, residence status, type of TB the patient, and the provider visited for first consultation, on health system delay. We have included patient characteristics such

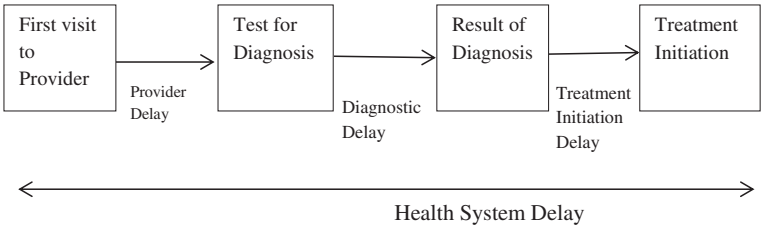

Fig. 1 Definition of delays used in this study. Adapted from: Rifat M, Rusen ID, Islam MA, Enarson DA, Ahmed F, Ahmed SM, Karim F: Why are tuberculosis patients not treated earlier? A study of informal health practitioners in Bangladesh. *International Journal of Tuberculosis & Lung Disease* 2011, 15(5):647–651

as education, occupation, residence status and income in the multivariable analysis, assuming that these characteristics may influence the choice of provider and affect the health system delay. Since the distribution of delay was skewed, we used Bootstrap variance estimators for regression analysis. Regression coefficients are presented with 95 % confidence intervals and associated p values for simple and Omnibus hypotheses. Data analysis was carried out using Stata statistical software version 12 (StataCorp LP, TX, USA).

Limitation of the study

This study includes only patients who were already enrolled in MDR-TB treatment. We do not have information about patients who did not start treatment after diagnosis. Unlike with the delay in drug-sensitive TB patients, it is difficult to determine the date for the onset of symptoms that prompted a visit to a clinician among the MDR-TB patients. Information related to provider delay was based on patients' information recalled during face-to-face interviews, and could not be verified.

Ethics considerations

The study was approved by the Human Research Ethics Committee (HREC) of the University of Newcastle (UoN), Australia, and the Bangladesh Medical Research Council (BMRC), Dhaka, Bangladesh. An information sheet describing the purpose of the study and the individuals' rights as study participants was handed to each participant to read. For individuals with inadequate literacy, the information sheet was read out by the interviewers. Participants consented by signing the consent form, or if unable to do so, by adding their thumb impression. All patients had been treated through NTP Bangladesh.

Results

Socio-demographic characteristics of the patients are presented in Table 1. The median delay caused by health system factors was 7.1 weeks. Provider delay (median 4 weeks), diagnostic delay (median 5 days) and treatment initiation delay (median 10 days) make up the health system delay (Table 2).

Total 89 MDR-TB patients (43.8 %) consulted a private practitioner first, for their MDR-TB related symptom (Table 1), which included 86 previously treated TB patients. Only 9.5 % of the previously treated TB patients had been treated in the private sector for their previous TB disease and the rest (90.5 %) were treated in a DOTS centre (not shown in table).

Multivariable regression analysis (Table 3) of health system and associated factors causing delay in the treatment of MDR-TB patients are shown in Table 3. Patients

Table 1 Socio-demographic and clinical characteristics of the multidrug resistant tuberculosis (MDR-TB) patients in Bangladesh

Variables	Rapid tests ($n = 207$)
	n (%)
Gender	
Male	138 (66.7)
Female	69 (33.3)
Education	
None	53 (22.0)
Secondary and below	169 (70.1)
Higher secondary and above	19 (7.9)
Provider visited for first consultation	
DOTS	91 (45.4)
Private	89 (43.8)
Informal	22 (10.8)
Residence status	
Rural	102 (49.3)
Urban	105 (50.7)
Occupation	
None	8 (3.9)
Service	66 (31.9)
Farmer	16 (7.7)
Student	5 (2.4)
Homemaker	39 (18.8)
Factory worker	16 (7.7)
Business	36 (17.4)
Self employed	12 (5.8)
Transport worker	9 (4.4)
Smoking status	
Smoker	103 (49.8)
Non- smoker	104 (50.2)
Type of TB patient	
New	5 (2.4)
Previously treated	202 (97.6)
Treatment outcome of previously treated patients	
Cured	16 (7.9)
Completed	37 (18.3)
Default from treatment	5 (2.5)
Treatment failure	119 (58.9)
No record available	25 (12.4)
Age (mean ± SD)	34 ± 12.0
Income (mean ± SD)	13664.3 ± 11521.7

Age and Income are expressed in the table is the mean ± Standard Deviation. All other variables are expressed as n (%)
Income is in Bangladeshi taka (BDT), monthly. 1 USD =78 BDT approximately
DOTS: National TB control programme designated centres for TB treatment

Table 2 Delays in treatment among the multidrug resistant tuberculosis (MDR-TB) patients of Bangladesh ($n = 207$)

	Median	IQR	Mean	SD
Health System delay (weeks)	7.1	8.6 (4.6–13.3)	10.5	11.25
Provider delay (weeks)	4	6 (2–8)	6.8	9.6
Diagnostic delay (days)	5	6 (1–7)	5.9	8.1
Treatment initiation delay (days)	10	17 (6–23)	20.5	28.9

Health system delay includes the provider delay, diagnostic delay and treatment initiation delay
Diagnostic delay includes the patients who had the rapid tests such as Gene Xpert and or LPA
Diagnostic delay, provider delay and health system delay had 3, 4 and 7 missing values, respectively
Standard deviation (SD), Interquartile range (IQR)

who visiting private practitioners for the first consultation experienced a greater health system delay compared to those visiting the NTP designated DOTS centre (mean difference, 37.7 days; 95 % CI 15.0–60.4; p 0.003).

Discussion

Our study found that time taken for diagnosis of MDR-TB is five days since the introduction of rapid tests in the programme; subsequently it took ten days to initiate treatment. A recent study on pre-diagnosis and pre-treatment attrition of MDR-TB patients of Bangladesh presented the median time for diagnosis and treatment initiation as four and five days, respectively [31]. The study included 163 MDR-TB patients diagnosed by Xpert MTB/RIF from selective areas which are supported by one NGO (BRAC) in Bangladesh. Whereas, our study included patients from all three government hospitals providing MDR-TB services at that time, which included patients referred from all areas of Bangladesh (including the area not supported by BRAC), during the study period. Laboratory turnaround time reported by another study conducted in Cape Town, South Africa was less than one day using Xpert based algorithm and 24 days using Line probe assay based algorithm [10]. The study also reported time to initiate treatment after diagnosis as 10 and 14 days in Xpert and Line probe assay based algorithm, respectively [10]. Similar results were found in a multicounty study which reported median time to detect rifampicin resistant as one day for Xpert MTB/RIF test and 20 days for Line Probe Assay based test [8]. Another study on MTB-DR Plus showed reduction in laboratory processing time (median 22 days) compared to culture based DST which was 55 days; whereas it took 20 days of operational delay to start the treatment [14]. Diagnosis time using MTB-DR plus was also reported as 4.2 and 11 days in Georgia and India, respectively [15, 32]. In our study, time needed for diagnosis is satisfactory. However, there was a remarkable delay in treatment initiation before the diagnosis, which was also observed in other studies on rapid tests for MDR-TB diagnosis [10, 14].

Unlike most other studies on the delay to treatment of MDR-TB patients, the definition of health system delay in our study includes the delay related to the visit to the health care provider. Median health system delay is 7.1 weeks in our study, which is mainly due to provider delay (4 weeks). Those patients who visited a private practitioner after perceiving their symptom during their current MDR-TB episode, experienced longer health system delays than patients who visited a NTP designated DOTS centre. In another study on drug sensitive TB patients in Bangladesh, visiting informal providers was associated with longer health system delay [3]. In contrast, we did not find any association between delay in treatment and visiting informal providers. MDR-TB patients may prefer qualified practitioners to informal providers as treatment is more complicated. We also found that many of the MDR-TB patients, who consulted private practitioners first for their current problem, had been treated in DOTS centre during previous TB treatment and this group of patients were reliant on private practitioners for their current complicated problem. This finding indicates that the MDR-TB patients might have visited multiple providers during the course of previous and current TB disease. However our finding concludes those who had in touch with private practitioners had experienced greater health system delay.

The provider delay may be due to lack of awareness of referral services by private practitioners. A sputum result of drug-sensitive TB patients at 5^{th} month or 8^{th} month of treatment forms the basis for a decision on referral for MDR-TB diagnosis, according to the national guideline. Waiting for the scheduled sputum conversion result could be another factor for provider delay. However, the national guideline also allows clinicians to refer a patient for MDR-TB screening [29]. NTP and its NGO partners in Bangladesh are involved in linking the private practitioners to the national TB control programme [24], encouraging private practitioners to refer TB patients to NTP designated DOTS centres where they receive tuberculosis treatment free of charge. However, many of the private practitioners who are not linked to the NTP often do not treat the TB patients according to the International Standards for Tuberculosis Care (ISTC) [24, 33, 34]. Strengthening the involvement of private practitioners in TB control with emphasis on MDR-TB is needed.

Delay in treatment initiation of MDR-TB, was also reported in a few other studies based on conventional DST methods. Two studies using conventional culture and DST for MDR-TB diagnosis reported a total time from diagnosis to treatment initiation of 12.4 weeks and 17 weeks in Kwazulu Natal, South Africa and Cameroon,

Table 3 Factors related to health system delay of multidrug resistant tuberculosis (MDR-TB) patients of Bangladesh

Variable	Median Health system delay	Univariate analysis ($n = 200$)				Multivariable analysis ($n = 200$)				
		Coefficient[a]	p*	95 % Confidence Interval		Coefficient[a]	p*	p**	95 % Confidence Interval	
				Lower	Upper				Lower	Upper
Gender										
Male	51.5	Reference				Reference				
Female	45	−21.9	0.01	−38.9	−4.9	−18.1	0.27		−50.4	14.2
Education								0.35		
No education	43	Reference				Reference				
Up to secondary level	50.5	4.1	0.70	−16.9	25.0	3.5	0.76		−18.7	25.7
Higher secondary and above	54.5	58.0	0.13	−17.6	133.5	58.1	0.15		−20.3	136.5
Provider visited								0.003		
DOTS centre[c]	45	Reference				Reference				
Private practitioners	53	33.6	0.01	10.2	57.0	37.7	0.001		15.0	60.4
Informal provider	59.5	23.4	0.12	−5.9	52.7	26.2	0.13		−8.0	60.5
Residence status										
Rural	51	Reference				Reference				
Urban	46	−1.3	0.89	−19.0	16.4	4.6	0.70		−19.1	28.2
Type of the patients								0.07		
New TB patient	57	Reference				Reference				
Cured, previously treated	45	−4.2	0.83	−41.4	33.0	21.8	0.40		−29.3	72.9
Completed, previously treated	40.5	2.0	0.90	−30.1	34.0	16.5	0.54		−36.5	69.4
Default, previously treated	51	2.0	0.91	−31.1	35.1	42.6	0.16		−16.7	101.9
Failure, previously treated	54	27.4	0.14	−9.3	64.1	51.7	0.08		−5.3	108.7
No outcome recorded, previously treated	56.5	5.1	0.79	−31.3	41.4	23.9	0.42		−34.0	81.7
Occupation								0.66		
None	41.5	Reference				Reference				
Service	51	34.7	0.02	5.4	64.0	17.1	0.34		−17.9	52.1
Farmer	54	25.0	0.10	−4.8	54.8	32.8	0.16		−12.8	78.4
Student	27	−15.3	0.14	−35.6	5.0	−21.7	0.56		−93.9	50.6
Homemaker	49	14.4	0.25	−9.9	38.7	26.2	0.12		−6.8	59.1
Factory worker	54	41.6	0.15	−15.0	98.2	36.6	0.32		−35.1	108.2
Business	48.5	31.8	0.03	2.7	60.8	8.8	0.72		−38.6	56.2
Self employed	70.5	43.9	0.07	−3.5	91.3	45.9	0.13		−13.7	105.4
Transport worker	45.5	51.0	0.24	−33.8	135.8	45.1	0.31		−41.7	131.8
Age (years)	-	−0.02	0.95	−0.5	0.5	−0.3	0.36		−1.0	0.4
Income (BDT)[b]	-	0.001	0.21	−0.001	0.003	0.0003	0.71		−0.001	0.002

[a]Regression coefficients reflect adjusted difference in mean delay (days), while all other factors remain constant
[b]Income is in Bangladeshi taka (BDT), monthly. 1 USD =78 BDT approximately
[c]DOTS centres are the NTP designated treatment centres for tuberculosis
p*is the value that the regression coefficient is zero
*p***is the value form the omnibus test that all coefficients for that variable are zero

respectively [11, 13]. Time for diagnosis and treatment initiation using conventional culture was 246 to 283 days, respectively among children, if the information of their MDR-TB contact was not one of the criteria for diagnosis [12]. Time taken at different stages of MDR-TB management using conventional culture and DST method, starting from sample collection to start of treatment, was also reported in another study which presents a total turnaround time of 5 months which was almost double of the bacteriological procedure [35]. To get a patient started on treatment after diagnosis took 12.8 days in Vietnam [9].

Unnecessary delays should be prevented to control further transmission of MDR-TB. The delay between diagnosis and initiating treatment might be due to the need for other necessary medical examinations such as clinical tests prior to initiation of treatment (e.g. liver function test, Xray, thyroid profile, blood sugar) [10]. Other operational issues adding to the delay might be sample transportation, laboratory-based diagnostic and patient notification, and admission to hospital, or may be due to the protocol for processing smear-negative samples [14, 35].

The reason for the delay in treatment initiation in Bangladesh could be due to the initial hospitalization requirement for MDR-TB treatment, according to the protocol that was usually 6 to 8 months. MDR-TB patients may require preparation time to get admitted to hospital for months. Again, those hospitals also had bed limitation to enrol all patients at a time and patient has to wait in queue. Need for shortening of hospital stay was felt by the programme to make a balance between the number of patients diagnosed by rapid tests and the number of beds available at MDR-TB hospitals.

A pilot project on shortening hospital stay is under way, i.e. to start ambulatory treatment after two consecutive negative sputum culture results. Patients were treated as ambulatory at community level after initial hospitalization. Ambulatory or community-based treatment for MDR-TB is also recommended by the WHO, whenever possible [2]. One study reported that the reason for treatment initiation delay was due to the need for a decision made by the Programmatic Management of Drug Resistant TB (PMDT) Council, and the time taken to assign the patient to the treatment support during the long preparation phase [9]. Another study reported that having a town address was associated with less delay among MDR-TB and we did not find any relationship with urban–rural status and time to treatment, in our study [14].

Conclusion

Introduction of rapid diagnostic methods have satisfactory time needed for MDR-TB diagnosis. Treatment initiation subsequent to diagnosis was delayed may be due to programmatic factors. This could be improved by identifying specific problems of implementation at programme level. Engaging private practitioners in national MDR-TB control programme should be enhanced to reduce the overall delay in MDR-TB management.

Abbreviations

DRS: Drug resistant surveillance; DST: Drug-susceptibility testing; ISTC: International standards for tuberculosis care; LPA: Line-probe assay; MDR-TB: Multidrug-resistant tuberculosis; NGO: Non-government organization; NTP: National tuberculosis control programme; PCR: Polymerase chain reaction; PMDT: Programmatic management of drug resistant tuberculosis; RR-TB: Rifampicin-resistant tuberculosis; TB: Tuberculosis; Xpert: Xpert MTB/ RIF.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MR contributed in designing and MR, AHM. JH and AH contributed in planning of the study. MR collected and analysed the data, and prepared the manuscript. CO provided input into data analysis and writing. MR, AHM, JH, CO and AH reviewed the document and provided their inputs in writing. All authors read and approved the final manuscript.

Acknowledgement

We received cooperation from the National Tuberculosis Control Programme, Directorate General of Health Services and Damien Foundation, Bangladesh and other partners including UPHCSDP, NHSDP and BGMEA. We gratefully acknowledge the contribution of Md. Akramul Islam and Bodrun Naher Siddiquea and all other BRAC colleagues who were involved in the project. The authors thank Claudia Koller for assistance with editing this manuscript. Finally, we are grateful to the study participants for their valuable time and assistance. This research was funded by the Australian Respiratory Council, BRAC Bangladesh and University of Newcastle Australia.

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Received: 21 July 2015 Accepted: 27 October 2015
Published online: 16 November 2015

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