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

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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

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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.

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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

Table of Contents

List of Tables

List of Figures

List of Appendices

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.