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ORIGINAL ARTICLE

Drug resistance of Mycobacterium tuberculosis in selected urban and rural areas in Bangladesh

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Abstract

The magnitude of anti-tuberculosis drug resistance in Bangladesh is not precisely known. We studied the drug resistance patterns of Mycobacterium tuberculosis in an urban and a rural area of Bangladesh. A tuberculosis (TB) surveillance system has been set up in a population of 106,000 in rural Matlab and in a TB clinic in urban Dhaka. Trained field workers interviewed all persons ≥15 y at Matlab to detect suspected cases of tuberculosis (cough >21 d) and sputum samples were examined for acid-fast bacilli (AFB). The first 3 AFB positive patients daily from the urban clinic were included. AFB positive cases diagnosed between June 2001 and June 2003 from both settings were cultured and drug susceptibility tests were performed. Of 657 isolates, resistance to 1 or more drugs was observed in 48.4% of isolates. Resistance to streptomycin, isoniazid, ethambutol and rifampicin was observed in 45.2%, 14.2%, 7.9% and 6.4% of isolates, respectively. Multidrug resistance was observed in 5.5% of isolates. It was significantly higher among persons who previously had received tuberculosis treatment of ≥1 month (15.4% vs 3.0%, adjusted OR: 6.12, 95% CI: 3.03–12.34). The magnitude of anti-tuberculosis drug resistance in Bangladesh is high. Further evaluation is needed to explain the high proportion of streptomycin resistant M. tuberculosis. Appropriate measures to control and prevent drug resistant tuberculosis in Bangladesh to reduce mortality and transmission are warranted.

Introduction

Drug resistant and multidrug resistant tuberculosis (MDR-TB) are emerging and growing problems worldwide [1–3]. Better understanding of the prevalence of anti-tuberculosis drug resistance is 1 of the key elements in the control of tuberculosis. Alternative drugs for treating resistant cases currently available are less effective, more costly, more likely to cause adverse reactions and require longer duration of treatment and follow-up than first line drugs [4]. Studies have shown that the prevalence of resistance of M. tuberculosis to any anti-tuberculosis drug ranged from 2% to 41% (median 10.4%) [2]. Primary MDR-TB, defined as resistance to both isoniazid and rifampicin, was found with a median prevalence of 1.4% (range 0–14.4%). The prevalence of acquired resistance to any drug ranged from 5.3% to 100% and the median prevalence of acquired MDR-TB was 13% (range 0–54%). MDR-TB is associated with a death rate of 50 to 80% and often with short disease span (4–16 weeks) from diagnosis to death [5,6].

The factors associated with the emergence of MDR-TB and their effects on the epidemiology of TB are complex and multi-faceted. In a recent meta analysis of determinants of MDR-TB in 11 countries several programmatic factors have been identified such as poor medical management, lack of direct observed treatment, limited or interrupted drug supplies, poor drug quality, widespread availability of anti-TB drugs without prescription, dissociation between public and private sector, and poorly managed national control programmes [7,8].

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Bangladesh is the most densely populated country in the world; extreme poverty, malnutrition, and overcrowding create a substantial risk for infection with M. tuberculosis among its population of 135 million people. Among 212 countries, Bangladesh ranks as the fourth highest TB disease burden in 2001 [9], having 300,000 new cases and around 70,000 deaths annually. Despite efforts by the government to control TB in the country through directly observed treatment, short-course (DOTS), only 32% of cases are detected [10]. An impending threat of human immunodeficiency virus (HIV) epidemic [11] and increase in MDR-TB in Bangladesh further complicates the situation. However, the magnitude of anti-tuberculosis drug resistance in Bangladesh is not precisely known. A rural-based study reported the prevalence of resistance as 10.9% to any anti-tuberculosis drugs (isoniazid, rifampicin, ethambutol, streptomycin) and MDR in 0.23% in new cases and 5.6% in previously treated cases [12]. An urban study of 101 untreated patients of pulmonary tuberculosis revealed 29.7% resistance to 1 or more anti-tuberculosis drugs and 4.9% were cases of MDR [13]. The sample size of this study was limited and patients were included only from 1 urban clinic in Dhaka. We carried out a study to reassess the problem using a systematic sampling technique from a reference tuberculosis clinic in Dhaka and tuberculosis surveillance system from a rural area in Bangladesh.

Material and methods

Study site and population

This study was carried out in an urban population among patients attending at Shyamoli Chest Clinic, Dhaka and in the rural area of Matlab.

Shyamoli Chest Clinic. This is the only tuberculosis reference clinic in Bangladesh. About 100–150 patients attend the clinic with chest diseases daily; most present with cough and purulent sputum. About 10–15% of samples are sputum smear positive TB cases. The first 3 patients daily with positive AFB specimens were included in the study.

Matlab. This rural area is situated 55 km southeast of Dhaka, capital of Bangladesh. Matlab is broadly representative of most aspects of rural Bangladesh. Since 1966 a health and demographic surveillance system (HDSS), which consists of the recording of vital events, has been maintained prospectively in the area by the ICDDR,B (International Centre for Diarrhoeal Disease Research, Bangladesh): Centre for Health and Population Research [14]. A maternal, child health and family planning programme (MCH-FP) has been in operation for half of the population of the HDSS area (current population of HDSS is about 220,000) since 1978 and an intensive research has been conducted in this population [15]. The study was conducted in the MCH-FP intervention area. A tuberculosis surveillance system was set up in July 2001 in the area. Each community health research worker (CHRW) in the intervention area covers a population of about 1800. She visits all households in the HDSS area monthly and enquires if any member in the household aged 15 y and above has had symptoms of cough for more than 21 d. These cases are referred to the government Matlab Upa-zila Health Complex (UHC) for sputum examination and necessary treatment. Three sputum specimens (2 spot and 1 morning specimen) were collected from each suspected TB patient consecutively for 2 d.

All sputum specimens were examined for AFB smear microscopy at the Matlab UHC and appropriate treatment was ensured in each case. Portions of pre-treatment sample from all AFB positive specimens were routinely transported to Shaymoli Chest Clinic in Dhaka for culture and sensitivity testing. Transportation was made on a daily basis in a standardized silicon tube.

Antimicrobial resistance pattern was monitored in urban Dhaka by collecting sputum specimens from the first 3 AFB positive cases daily attending Shyamoli Chest Clinic. Informed consent was obtained from each case.

All suspected TB patients at Matlab, and patients included in Dhaka, were interviewed by trained field workers to record any previous treatment, chemotherapy, compliance, risk factors and some socio-demographic factors by administering a pre-tested standardized questionnaire. Suspects at Shaymoli Chest Clinic were interviewed after sputum microscopy results were available.

A total of 657 smear positive pulmonary tuberculosis cases diagnosed between June 2001 and June 2003 from these settings were cultured on Lowenstein-Jensen medium and drug susceptibility tests were performed using standard techniques.

Sample size

A total of 415 specimens was required to estimate the prevalence of 10.9% ($\pm$3% precision) resistance to any anti-tuberculosis drugs [12] and 450 specimens for the prevalence of MDR (4.95% prevalence and precision of $\pm$2.0% with 95% confidence limit) [13].

Culture and susceptibility testing methods

At Shyamoli Chest Clinic, specimens were taken between Sunday and Thursday during office hours. The first 3 Ziehl Neelsen (ZN) stained AFB smear positive sputum specimens of patients aged 15 y and above were included. All sputum positive AFB specimens from Matlab were transported to Shyamoli Chest Clinic. Five ml ZN stained smear positive sputum specimens contained in 50 ml falcon tubes were transported. All patients were asked to give sputum for ZN smear staining and the slides were examined under oil immersion. Sputum specimens were decontaminated following the standard procedure of Petroff [16]. The supernatant was discarded and 2 loopfuls of palette were inoculated on 2 Lowenstein-Jensen (L-J) slants. Inoculated L-J slants were incubated at 37°C for 8 weeks and the inoculated slants were examined once every week for contamination as well for growth of visible mycobacterial colony. Sputum was considered culture negative when no visible mycobaacterial colony was grown on either of the L-J slants within 8 weeks of incubation at 37°C.

Standard proportion susceptibility testing method of Canetti et al. [17] was followed for susceptibility testing of isolates to isoniazid (0.2 mg/l), rifampicin (40 mg/l), ethambutol (2 mg/l) and streptomycin (4 mg/l). To calculate the susceptibility of an isolate to a particular antibiotic, the number of mycobacterial colonies grown on the drug containing L-J slant was divided by the number grown on drug free L-J slant multiplied by 100. When the outcome was less than 1, the mycobacterial culture was considered sensitive to a particular antibiotic, and resistant when the outcome was 1 and above.

Definitions

Smear positive pulmonary tuberculosis. At least 2 sputum specimens positive for AFB or 1 sputum positive for AFB and radiological abnormalities consistent with tuberculosis [18].

Drug resistant tuberculosis. Mycobacterium tuberculosis bacilli resistance to 1 or more antituberculosis drugs [19].

Primary resistance. The presence of resistant strains in the sputum sample of a patient who had no history of previous TB treatment or received treatment of TB for less than 1 month [2].

Acquired resistance. The presence of drug resistant strains in the sputum sample of a patient who had at least 1 month of previous history of anti-tuberculosis treatment [2].

Multidrug resistance (MDR). Resistance to at least isoniazid and rifampicin, with or without resistance to other drugs [7].

Data analysis

Data were entered using the software package FoxPro (Microsoft Corporation) and analysed by the STATA statistical software (Release 5.0, Stata Corporation, College Station, Texas, 1997). Logistic regression analyses were performed to determine predictors of MDR-TB. Odds ratio (OR) with 95% confidence intervals (CI) were calculated.

Quality control

All positive and 10% of negative specimens at Matlab were rechecked in Dhaka by an experienced microbiologist (ZR). Systematically selected specimens from Shyamoli Chest Clinic in Dhaka were sent to the WHO Tuberculosis Reference Centre at Chennai, India for external quality control checking of our susceptibility data. The agreement of results between our tests and tests in the reference centre was 95%.

Results

A total of 657 culture positive isolates was tested for drug susceptibility; 600 from Dhaka and 57 from Matlab. More than two-thirds of patients were male; males were predominant in all age groups except among 15–24-y-old patients. 60% of the patients were below 35 y of age. Among females, 56% were <25 y old (Table I).

The overall resistance to streptomycin, isoniazid, ethambutol and rifampicin was 45.2%, 14.2%, 7.9%, and 6.4%, respectively. About 20% of patients had received treatment for tuberculosis for 1 month or more. About 48% of the isolates were resistant to any anti-tuberculosis drugs. MDR was detected in

Table I. Distribution of culture positive cases by age and gender, Dhaka and Matlab.

Age (y)	Male *n* (%)	Female *n* (%)	Total *n*
15–24	95 (44.2)	120 (55.8)	215
25–34	134 (74.9)	45 (25.1)	179
35–44	83 (76.9)	25 (23.1)	108
≥45	131 (84.5)	24 (15.5)	155
Total	443 (67.4)	214 (32.6)	657

Data in parenthesis are row percentages.

5.5% of isolates. MDR was significantly higher among persons who had received tuberculosis treatment for ≥1 month (15.4% vs 3.0%, $p < 0.0001$). There was no significant difference in overall resistance patterns between Dhaka and Matlab (Table II).

Resistance to any drug ranged from 45.1 to 54.2% in different age groups (Table III). Resistance to isoniazid was highest among persons aged >45 y, but resistance to rifampicin was lowest in that age group. There was no significant difference in the prevalence of MDR between different age groups.

Patients who received antituberculosis treatment of 1 month or more were more likely to have MDR-TB (OR: 6.12, 95% CI: 3.03–12.34) after adjusting for age and gender (Table IV). However, no significant difference was observed in MDR between different age groups and gender.

Discussion

The study documents substantial drug resistance to anti-tuberculosis drugs and the presence of MDR strains, representing an immense public health problem in Bangladesh. The rates of MDR are lower than reported rates of 22.1% in Lativa [2], 9% in Estonia [20], 10.2% in the Dominican Republic [3] and 19% in New York city [21], but higher than reported rates of 0% in Kenya [22], 0.5% from the Netherlands [23] and 2.5% from Florence, Italy [24]. Our study revealed that within a short period of time the prevalence of MDR has increased several-fold compared to the study by Deun et al. [12]. This study was conducted in a rural area in Bangladesh and MDR was found in 0.23% in new cases and 5.56% in retreatment cases. However, another study conducted in urban Dhaka was limited to only untreated patients with pulmonary tuberculosis [13]. This study revealed that 4.95% of the cases were MDR. The data of our study came from the tuberculosis surveillance system established in a defined rural population of Matlab, and from an urban reference tuberculosis clinic where ICDDR,B has recently established a quality controlled laboratory meeting biological safety standards for the isolation and culture of M. tuberculosis. Since 1996, culturing of M. tuberculosis has not been undertaken in any government setting in Bangladesh. ICDDR,B in collaboration with the National Tuberculosis Control Programme (NTP) in Bangladesh started culture of M. tuberculosis in the government laboratory in 2001. Due to logistics limitations we included only the first 3 smear positive AFB samples daily from the urban clinic, rather than all positive cases.

Our study finding of high-acquired MDR compared to primary MDR is consistent with findings from reports from other countries [4]. The high risk of developing MDR in patients with previous TB treatment has also been observed in other studies [7], and may have been acquired through inadequate prior chemotherapy. These patients are more likely than new patients to harbour and transmit bacilli resistant to at least isoniazid [18].

We did not find any significant difference in overall resistance patterns between urban and rural areas in Bangladesh, and in both places 80% of patients were either not treated or treated for less than 1 month with anti-tuberculosis drugs before sputum samples were taken for culture. In both rural and urban areas in Bangladesh drugs for TB treatment are sold without any prescription and this may lead to irregular and inadequate treatment. Although DOTS treatment through NTP is available in most of the district and sub-district hospitals in Bangladesh, the majority of the cases are not covered under the programme.

We observed that 45% of strains were resistant to streptomycin. Currently streptomycin is not recommended for use in uncomplicated tuberculosis and the drug is not widely available for its limited use. More than 2 decades ago, streptomycin combined

Table II. Percentages distribution of antimicrobial resistance pattern of Mycobacterium tuberculosis isolates.

	Dhaka			Matlab			
Drug	Primary* ($n = 481$)	Acquired+ (119)	Total (600)	Primary (46)	Acquired (11)	Total (57)	Overall (657)
Streptomycin	44.5	50.4	45.7	34.8	63.6	40.4	45.2
Isoniazid	12.3	24.4	14.7	2.2	36.4	8.8	14.2
Etambutol	4.6	18.5	7.3	13.1	18.2	14.0	7.9
Rifampicin	3.9	16.8	6.5	0	27.3	5.3	6.4
Multidrug resistant	3.3	14.3	5.5	0	27.3	5.3	5.5
Any drug	46.4	56.3	48.3	43.5	72.7	49.1	48.4

* No antituberculosis drugs or received antituberculosis drugs <1 month.
+ Antituberculosis drugs received previously for 1 month or more.

Table III. Distribution of drug resistance patterns by age groups.

	Resistance*					
Age groups (y)	Streptomycin	Isoniazid	Rifampicin	Ethambutol	Any drug	Multidrug resistant
15–24 ($n = 215$)	42.8	14.0	5.6	5.6	45.1	5.1
25–34 ($n = 179$)	49.2	11.8	7.8	10.1	52.0	5.6
35–44 ($n = 108$)	49.1	13.0	7.4	11.1	52.8	6.5
≥45 ($n = 155$)	41.3	18.1	5.2	6.5	54.2	5.2
Total ($n = 657$)	45.2	14.2	6.4	7.9	48.4	5.5

* Data expressed as percentages.

with penicillin was widely used in Bangladesh for the treatment of respiratory and other infections, but there is no evidence that it has been widely used in recent y. High resistance to streptomycin has also been reported from India [25]. Further investigation is needed to explain the high prevalence of streptomycin resistant M. tuberculosis.

The main causes of MDR are non-adherence to therapy and the use of inadequate treatment regimens. The magnitude of MDR in a country is a useful indicator of the performance of a national TB control programme. The cost of treating a case of MDR in a developing country can range from US$ 800 to $10,000 [26] and has been estimated at $180,000 in the USA [4]. Most developing countries cannot afford such costs. Our findings suggest that there could be about 10,000 MDR TB cases in Bangladesh. If these cases are not treated properly this will result in high mortality and an increased risk of transmitting resistant strains in the community [27]. Not only are drugs required for treating MDR cases unavailable in Bangladesh, but also provision for susceptibility testing and supervised management in a hospital setting is very limited. TB patients should be treated with a standard regimen and it needs to be ensured that patients complete the full course of treatment. Patients should also be aware of possible adverse reactions to the drugs and every effort should be made to manage these reactions.

Several limitations of the study should be noted. The findings may not be generalizable since specimens in the urban area were collected only from patients attending a reference tuberculosis clinic. Many of these cases were referred and may be more severe than other cases in the community. Furthermore, the number of samples from the rural area was limited.

The high prevalence of MDR in Bangladesh is a major threat to the NTP. There is an urgent need to detect and isolate MDR-TB cases in Bangladesh in order to prevent transmission and mortality. Coordinated efforts between NTP, and different NGOs based on agreed strategy are needed to address the challenge of MDR-TB cases in Bangladesh.

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Table IV. Logistic regression analyses to predict factors associated with multidrug resistant M. tuberculosis.

Variables	*n* (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Age (y)			
15–24	215 (32.7)	1.00	1.00
25–34	179 (27.2)	1.09 (0.45, 2.65)	1.14 (0.44, 2.91)
35–44	108 (16.4)	1.28 (0.48, 3.41)	1.33 (0.46, 3.79)
≥45	155 (23.6)	1.00 (0.40, 2.57)	0.83 (0.29, 2.31)
Gender			
Male	443 (67.4)	1.00	1.00
Female	214 (32.6)	1.33 (0.67, 2.67)	1.47 (0.69, 3.16)
Treatment duration			
<30 d	527 (80.2)	1.00	1.00
≥30 d	130 (19.8)	5.80 (2.92, 11.56)	6.12 (3.03, 12.34)

* Adjusted for age, gender and treatment duration.

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