Prevalence of Multi-Drug Resistant (MDR) pulmonary tuberculosis in a tertiary care hospital of Narshingdi, Bangladesh

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Abstract
Tuberculosis is a chronic, communicable, granulomatous disease. Most infections in humans result in an asymptomatic, latent infection and about one in ten latent infections eventually progresses to active disease, which, if left untreated, kills more than 50% of those infected. In 2011, an anti-tuberculosis (TB) drug resistance survey in Narshingdi, Bangladesh, enrolled new and retreatment patients. In the study, a number of villages were randomly selected and 264 pulmonary tuberculosis (PTB) patients were identified. All the patients received treatment with standardized first-line drug (FLD) regimens and were investigated to document treatment efficiency. Among the patients, 130 were reported in lower income, 117 in medium income and only 17 in higher income group. Farmers (95%) in low income group, and female housewives (68%) in medium income group were mostly infected. Silicosis and malnutrition were assumed responsible for high PTB cases in farmers and housewives respectively. Males were more prone to PTB and the ratios of male to female patients were found to increase with increasing age. The working youth group (25-34) and older people (above 64) were found most vulnerable. Multi-drug resistant (MDR) TB was detected in both new and retreatment patients. Patients with MDR-TB who had been declared cured with first-line anti-TB treatment had a high rate of TB recurrence and death. The rate of TB recurrence and death was high four years after MDR-TB patients were judged to have been cured. PTB patients in Bangladesh had high recurrence and death rates even after treatment with standardized FLD regimens, reinforcing the need for early survey, diagnosis and treatment, including assessment of treatment outcomes.

Keywords: Tuberculosis, Drug resistant, Treatment, Recurrent, Bangladesh

1. Introduction
Tuberculosis is a common and in many cases lethal infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis. Tuberculosis usually attacks the lungs but can also affect other parts of the body. Most infections in humans result in an asymptomatic, latent infection and about one in ten latent infections eventually progresses to active disease. The mortality rate for untreated tuberculosis is more than 50%.

One third of the world's population is thought to be infected with M. tuberculosis and new infections occur at a rate of about one per second. In 2007, an estimated 13.7 million chronic active cases, 9.3 million new cases, and 1.8 million deaths were reported and mostly in developing countries. With over 9 million cases and nearly 2 million deaths annually, tuberculosis (TB) remains a major cause of morbidity and mortality worldwide.
Diagnosis of TB relies on radiology, tuberculin test, blood tests, as well as microscopic examination and microbiological culture of infected bodily fluids. Treatment is difficult and requires long courses of multiple antibiotics. One of the important challenges for TB control is drug resistance, particularly multidrug resistant (MDR) and extensively drug-resistant (XDR) TB. Effective TB treatment is difficult, due to the unusual structure and chemical composition of the mycobacterial cell wall, which makes many antibiotics ineffective and hinders the entry of drugs. TB requires much longer periods of treatment (around 6 to 24 months) to entirely eliminate mycobacteria from the body instead of the short course of antibiotics typically used. Latent TB treatment usually uses a single antibiotic, while active TB disease is best treated with combinations of several antibiotics, to reduce the risk of the bacteria developing antibiotic resistance. Drug-resistant TB is a public health issue in many developing countries, as treatment is longer and requires more expensive drugs. MDR-TB and XDR-TB treatment relies on regimens with less effective and more toxic second-line drugs (SLD). Failure rates of MDR-TB patients treated with standard World Health Organization (WHO) FLD treatment regimens ranged 4%–47% among new cases and 21%–50% among retreatment cases.

Considering the above facts, the aim of this study was to assess the prevalence of pulmonary tuberculosis in Palash, Narsingdi, Bangladesh. The study also aims at evaluation of drug resistant pattern and treatment outcome with standard drugs.

2. Materials and Methods

2.1 Ethics Statement: The study was approved by the Upazilla Health Complex, Palash, Narsingdi Ethical Committee for TB Operational Research. Written informed consent was obtained from individuals before an interview was conducted and sputum samples were collected. If the individual had died, written informed consent was obtained from the family member before they were interviewed. Patients and TB hospitals were informed of the sputum smear, culture, and DST test result. MDR-TB patients identified during follow-up were requested to go to the TB hospital for treatment, including with second-line drugs.

2.2 Drug Resistance Survey: For the drug resistance survey (DRS), the “Guidelines for surveillance of drug resistance in tuberculosis” developed by WHO/IUATLD were followed. In the district Narsingdi, a number of villages were randomly selected under Palash Union council for the survey. All smear-positive cases in the survey area during the study period (From February to November, 2011) were diagnosed and positive samples were eligible for inclusion. Drug resistance was assessed against four anti-tuberculosis drugs such as isoniazid, rifampicin, streptomycin and ethambutol.

2.3 Treatment Regimen and Outcome assessment: The district Narsingdi followed the National Tuberculosis Programme (NTP) treatment guidelines for all TB patients. Treatment of new smear-positive patients consisted of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol followed by 4 months of isoniazid and rifampicin three times weekly (2H3R3Z3E3/4H3R3). Patients who had previously received at least one month of TB treatment (i.e. retreatment patients) received 2 months of isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol, followed by 6 months of isoniazid, rifampicin, and ethambutol three times weekly (2H3R3Z3E3S3/6H3R3E3). Drug intake was observed at the health facility throughout the treatment.

Treatment outcomes were assessed using international definitions and were recorded in routine treatment registers. Treatment success was defined as either cure or treatment completed. Cure was defined as a patient who was sputum smear-negative in the last month of treatment and on at least one previous occasion. Treatment completed was defined as a patient who had completed treatment but who did not meet the criteria to be classified as a cure or a failure. Treatment failure was defined as a patient who was sputum smear-positive at 5 months or later during treatment. Default was defined as a patient whose treatment had been interrupted for two consecutive months or more. Transfer out was defined as a patient who had been transferred to another recording and reporting unit and hence treatment outcome was unknown. Death was defined as a patient who died for any reason during the course of treatment. The cause of death during TB treatment was not recorded.

2.4 Follow up of TB Patients: Staffs from regional TB centers included in the DRS were instructed on how to follow-up the 264 patients included in the DRS. Regional staffs and one provincial staff member interviewed patients in their home in the period. During the interview, participants were asked about presence of common TB symptoms (i.e., cough, haemoptysis, chest pain, fever, fatigue, anorexia and night sweat). Three sputum samples were collected from all.
participants for microscopy, culture and DST using the same methods. Staff rechecked the smear examination results, diagnosis and dates with the medical files in the facility. If the patient had died, family members were interviewed about the time of death and its probable cause. Staff would recheck the cause with the death certificate provided by the hospital. Patients who had TB registered as a cause of death were assumed to have had recurrent TB.\textsuperscript{21}

2.5 Data Management and Analysis: Analysis was performed using SPSS 13.0 (SPSS Inc. Chicago, IL, USA). For the analysis of treatment outcome from initial TB treatment, we compared patients who were cured to those that failed, died, or defaulted in a multivariate logistic regression model. Variables available were living area, economic condition, sex, age, drug resistance pattern, bacillary load, and number of treatment episodes.

3. Results

3.1 Study population: A total of 264 TB patients were recorded within the population of randomly selected villages under Palash Union council under Narsingdi district of Bangladesh. The survey regions were developing rural and sub-urban areas.

3.2 Socio-economical condition of PTB patients: Among the 264 TB patients, 130 patients were from low income group mostly of farmer (124 patients) along with a few patients from other occupation like day labour, rickshaw puller, bus driver and tailor. Medium income group population was also reported to have higher TB cases. A total of 117 patients were recorded in this economic group and most of them were of female sex and were housewives (68%). The rest of the patients of this income group were either service holder (26%) or students (10%). TB cases from high income group were least reported and all those reported were business people (Figure 1).

3.3 Age & Sex differentiation of PTB patients: The vulnerability to tuberculosis was found to vary between age and sex groups (Figure 2). Males were found more prone to the disease than female and the incidence of infection increased in male in older age (Fig. 2). In the younger population (aged below 24), patient’s sex were not a variable in their disease vulnerability. Males were reported to have higher TB incidence than female of aged above 25. In the survey, there were a few cases of TB reported in children. The most vulnerable age groups were the youth working age group between aged 25 and 34 years along with the oldster population (Fig. 2).
3.4 Drug resistance: Table-1 shows drug resistance pattern of 88 strains of *M. tuberculosis* to 4 anti-tuberculosis drugs. All strains were resistant to one or more drugs. Highest resistance was found against Isoniazid (INH) either alone or in combination with other drugs. From resistance pattern of 88 strains of *M tuberculosis* it appears that 31 (35.22%) were resistant to a single drug, 26 (29.54 %) were resistant to 2 drugs, 10 (21.50 %) resistant to 3 drugs, 12 (13.63 %) were resistant to all 4 drugs. MDR was found in 31 (35.22 %) cases.

| Number of drugs | Name of drug(s) | No of resistant strains |
|-----------------|-----------------|-------------------------|
| 1 drug          | Isoniazid (INH) | 13                      |
|                 | Rifampicin (RMP)| 9                       |
|                 | Streptomycin (SM)| 4                      |
|                 | Ethambutol (EMB)| 5                       |
| 2 drugs         | INH+RMP*        | 5                       |
|                 | INH+SM          | 3                       |
|                 | INH+EMB         | 4                       |
|                 | EMB+SM          | 6                       |
|                 | EMB+RMP         | 3                       |
|                 | SM+RMP          | 5                       |
| 3 drugs         | INH+RMP+SM*     | 8                       |
|                 | INH+RMP+EMB*    | 6                       |
|                 | RMP+SM+EMB      | 5                       |
| 4 drugs         | INH+RMP+EMB+SM* | 12                      |
| MDR*            |                 | 31                      |

3.5 Treatment follow up: In the survey, patients diagnosed to be TB positive were treated and follow up. All the patients were first administered with 2 months drug regime, for new cases the drug regime consisted of isoniazid, rifampicin, pyrazinamide, and ethambutol and for the patients who received at least one month TB treatment previously the drug regime consisted of isoniazid, rifampicin, pyrazinamide, streptomycin and ethambutol. Upon the regime, 86% patients were responded to the treatment and diagnosed to be cured. The treatment were completed with another drug regime; 4 months drug consisted of isoniazid and rifampicin for newly diagnosed patients and 6 months drug consisted of isoniazid, rifampicin, and ethambutol for previously treated patients. Drug intake and responses to drugs were observed at the health facility throughout the treatment. Within 6 months from starting treatment, all the 264 patients were reported to be cured. No cases of treatment failure, treatment default or death was reported among the TB patients in the study period.

| Age Group (years) of patients | 0-4 | 5-14 | 15-24 | 25-34 | 35-44 | 45-54 | 55-64 | Above 64 | Total |
|-------------------------------|-----|------|-------|-------|-------|-------|-------|----------|-------|
| Patients cured after 2 months of drug regimen | Male | -    | -     | -     | 16    | 25    | 22    | 29       | 17    | 41    | 150   |
|                                | Female | -    | -     | -     | 13    | 24    | 16    | 9        | 5     | 10    | 77    |
|                                | Sum up | -    | -     | -     | 29    | 49    | 38    | 38       | 22    | 51    | 227   |
| Patients cured after 5 months of drug regimen | Male | -    | -     | -     | 3     | 1     | 5     | 3        | 3     | 3     | 15    |
|                                | Female | -    | -     | -     | -     | -     | -     | -        | -     | -     | 2     |
|                                | Sum up | -    | -     | -     | 3     | 1     | 5     | 3        | 5     | 5     | 17    |
| Patients cured after 6 months of drug regimen | Male | -    | 2     | 1     | 4     | -     | -     | 2        | 1     | 2     | 10    |
|                                | Female | -    | 2     | 4     | 2     | 2     | -     | -        | -     | -     | 10    |
|                                | Sum up | -    | 4     | 5     | 6     | 2     | -     | 2        | 1     | 1     | 20    |
| Total                         | -    | 4    | 34    | 58    | 41    | 43    | 27    | 57       | 57    | 264   |

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4. Discussion

In Bangladesh, 300,000 new cases and 70,000 deaths reported per year due to PTB, hence the nationwide survey on its prevalence got importance in recent years. PTB patients in Bangladesh had already been reported to have high recurrence and death rates, which reinforced need for early survey, diagnosis, treatment and outcome assessment. Though, the study had given a scenario on the PTB prevalence in Bangladesh, regional and geographical impact could be assessed by long term countrywide investigation.

The first national drug resistance survey (DRS) in 2007 reported an overall MDR-TB prevalence of 8.3%, of which 8% were XDR-TB. In the global project on anti-tuberculosis drug resistance surveillance organized by the World Health Organization and the International Union against Tuberculosis and Lung Disease (WHO/IUATLD), the prevalence of any drug resistance was 36.1% among new cases and 67.5% among retreatment cases, i.e., TB patients who received at least one month of anti-TB treatment in the past. The MDR prevalence was 7.2% among new patients and 30.4% among retreatment patients.

Both the new and retreatment patients were included in this study. The study was based on the information collected from 264 pulmonary tuberculosis (PTB) patients, which were identified in a number of randomly selected villages among the survey area. The patients were diagnosed, received treatment with FLD regimens and treatment efficiency were investigated by follow up procedure. Living standard and economic conditions was found to influence the prevalence. PTB had also found to infect variably with gender and in different age groups. Farmers were mostly suffered from PTB among the low income group and female housewives among the medium income group. Males were more vulnerable than female to PTB and it increases with ageing. The working youth and elderly people were found the most vulnerable. In drug resistance assay, 35.22% TB isolates were resistant to a single drug, 29.54% were resistant to 2 drugs, 21.50% were resistant to 3 drugs & 13.63% were resistant to all 4 drugs (INH, RMP, SM, EMB). MDR was found in 35.22% cases.

Some previous studies conducted in Bangladesh has reported recurrence of TB and treatment failure in the long run with combination of drugs and increasing resistance of *M. tuberculosis* to first line drugs such as Isoniazid, rifampicin etc. In a previous study in Bangladesh by Banu et al., 88% patients had recurrent TB infection and 73.5% TB isolates were found to be multi-drug resistance. They also showed that Multi-drug resistance was significantly higher among patients with previous history of anti-tuberculosis treatment. Another study in Bangladesh by Rahman et al. showed resistance of TB isolates for INH, RMP, EMB and SM were 76.03%, 71.63%, 27.55% and 55.65% respectively. In another study by Zaman et al., it was found that 48.4% TB isolates in a rural and an urban area of Bangladesh were resistant to 1 or more drugs. 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. Their study also confirms that drug resistance was significantly higher among persons who previously had received tuberculosis treatment.

In a study by Hussain et al. in Rajshahi, Bangladesh showed that the percentage of MDR TB in total study population was 0.4%, the percentage of MDR TB among retreatment cases were 3.7% and some patients remained smear positive even after eight months of treatment. In a study conducted in Bogra district, Bangladesh registered a large number of PTB patients and 13% of them remain smear positive even after 2 years of treatment indicating rapid emergence of drug resistance in TB isolates. In another study in Sunamganj district, Bangladesh showed that total resistance among new cases to any drug was 31% and for SM it was 18%, INH 23%, RMP 2%, EMB 10% and 2% of the isolates were multidrug-resistant (MDR).

This study in concordance with previous studies and alarms us about high prevalence of pulmonary tuberculosis in Bangladesh and increasing drug resistance in *M. tuberculosis* isolates. MDR TB and XDR TB percentage as well as treatment failure and recurrent TB infection is increasing day by day. Based on our study results, we strongly suggest that Bangladesh rapidly scale-up access to MDR-TB diagnosis and treatment around the country, with priority for provinces with high anti-TB drug resistance prevalence.

5. Conclusion

In conclusion, MDR-PTB patients in Bangladesh had high recurrence and death rates four years after treatment with standardized FLD regimens. Documentation of cure based on conventional smear microscopy at the end of treatment was a poor predictor of long-term outcome. Adequate identification and treatment of MDR-TB patients is urgently needed.
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in order to improve long-term outcomes and to control the spread of MDR-PTB.

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