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Research Article

Prevalence of Rifampicin Resistance among Pulmonary Tuberculosis Patients in Bangladesh and Strategic Priorities

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Abstract

Background: The resistance to rifampicin which is the most effective drug for TB treatment has increased at an alarming rate and is already a big threat to the global effort to eliminate the disease. This study investigates the distribution of rifampicin resistance among new and previously treated sputum smear-positive pulmonary patients with MDR-TB and risk factors associated with developing drug resistance in Bangladesh program setting. Such information is useful for estimating the extent of drug resistance and for developing targeted strategies to prevent the transmission of MDR-TB.

Methods and Findings: This is a retrospective analysis of the GeneXpert MTB/RIF usage data to estimate prevalence of rifampicin resistance among different groups of pulmonary TB patients. Routine data of all patients tested with GeneXpert installed in all 39 National TB Control Program laboratories were collected and analyzed for this study. Data collected for 61,836 presumptive TB patients including 42,223 (68.3%) male and 19,613 (31.7%) female. Most of the patients (57.02%) were new TB presumptive cases who are progressively sputum smear negative, other category (14.32%) who do not fall in any standard category, and failure after category 2 treatment (12.25%). Of the presumptive cases tested, 41% were diagnosed as MTB positive and 2.47% were diagnosed as rifampicin resistant. The highest rate of rifampicin resistance (15.49%) was found among the Category 2 failure presumptive patients and lowest (0.66%) among new TB presumptive patients.

Conclusion: Despite increased access to GeneXpert in most high burden TB countries, a large proportion of MDR-TB cases remain undetected or detected after considerable delay causing new transmission. The study shows that GeneXpert usage data is a potential counterpoint to costly Drug Resistant Surveys (DRS) to understand the magnitude and distribution of MDR-TB among pulmonary TB patients. Routine monitoring and analysis of GeneXpert data will immensely benefit countries to develop targeted strategies for accelerating detection, management and transmission control of MDR-TB.

Keywords: *GeneXpert MTB/RIF; Rifampicin Resistance; Prevalence; Drug Resistance Survey*

Introduction

Multidrug-resistant tuberculosis (MDR-TB) has emerged as a significant global health concern [1,2]. There are alarming reports of increasing drug resistance from various parts of the world which potentially threaten to disrupt the gains achieved in tuberculosis (TB) control over the last decade [3] and global progress towards achieving the targets of End TB strategy. In 2016, there were 600,000 new cases with resistance to rifampicin (Rif), the most effective first-line drug, of which 490,000 had multidrug-resistant TB (MDR-TB) [4]. Rifampicin-resistant TB (RR-TB) is defined as resistance to rifampicin detected using genotypic or phenotypic methods with or without resistance to other first-line anti-TB drugs. MDR-TB is essentially a man-made phenomenon and arises due to inadequate treatment of drug-sensitive TB [5]. The prevalence of MDR-TB mirrors the functional state and efficacy of tuberculosis control programs in the country.

The emergence of MDR-TB, i.e. resistance to at least rifampicin and isoniazid associated with treatment failure, relapse, complications and mortality, presents additional challenges to TB control. Rifampicin remains one of the most important drugs in the treatment of drug-sensitive tuberculosis and has been used increasingly in fixed-dose combinations (FDCs) [6]. The World Health Organization (WHO) and International Union Against Tuberculosis and Lung Diseases (IUATLD) recommend use of FDCs because they improve patient adherence, simplify prescribing and management of drug supplies, and reduce prescription errors [7]. Despite high efficacy of FDCs, there are several risk factors for developing drug resistance including previous anti-TB treatment, presence of co-morbidities, non-compliance with drug, physician's error and patient's living conditions [8-10]. A case-control study found that respondents with previous history of TB treatment were 21 times more likely to develop MDR-TB compared to those without previous TB treatment [11]. The risk of reducing bioavailability (BA) of rifampicin in FDCs contributing to drug resistance also remains a concern. Several research studies, surveys and field experiences indicate that the BA of rifampicin may be reduced due to many factors, potentially including quality of therapeutic substances, drug formulation, storage conditions and meal intake [12-17].

Rapid diagnosis and detection of drug resistance is critical for TB control, as transmission and emergence of MDR-TB cause serious health problems. In 2010, World Health Organization (WHO) endorsed the GeneXpert MTB/RIF, a cartridge-based fully automated molecular diagnostic assay that uses real time Polymerase Chain Reaction (PCR) to identify M. tuberculosis complex DNA and the mutations associated with rifampicin resistance directly from sputum specimens, in less than two hours [7] Use of this technology has significantly increased detection of RR-TB in the past few years. In most settings, particularly where FDC first-line anti-TB drugs are used, resistance to rifampicin is strongly associated with resistance to isoniazid. Since 90% of the people resistant to rifampicin are also resistant to isoniazid, GeneXpert MTB/RIF positive cases are considered a surrogate marker for multi-drug resistant TB [18].

Bangladesh is a high TB and MDR-TB burden country with annual occurrence of 362,000 new drug sensitive TB, 5,800 DR-TB among notified pulmonary cases, and approximately 59, 000 deaths annually due to this disease [19]. The first nationwide Drug Resistant Survey (DRS) 2010-11 estimated 7% overall prevalence of MDR-TB; 1.4% in new patients and 28.5% in previously treated TB patients. A sentinel survey conducted in 2011-14 covering 14 selected hospitals estimated 3.2% overall prevalence including 2.3% among new and 13.8% among previously treated patients [20]. The purpose of this study is to complement the body of evidence with more recent data to understand the drug resistance trend, patterns, distribution from programmatic perspectives. Such information would be useful not only to estimate the extent of the problem in high-risk population, but also for reviewing the tuberculosis control program and for developing targeted strategies to prevent the transmission of MDR-TB in Bangladesh and other similar settings.

Method

Setting

Bangladesh initiated the routine use of GeneXpert MTB/Rif in 2012 and has progressively scaled up access to GeneXpert platforms across the country with technical and financial assistance from donors including the US Agency for International Development (USAID), notably through the TB CARE II project which provided technical support to introducing and scaling up GeneXpert. Located at the district level public sector TB laboratories and hospitals, GeneXpert is used for screening presumptive drug resistant cases among failures, non-converters, relapses and return after default of Category I and II, close contacts of MDR-TB patients, all TB/HIV infected patients at the start of TB therapy and smear negative cases with persistent TB symptoms. Each GeneXpert site was required to collect usage data monthly for performance tracking and supervision.

Data collection and analysis

This is a retrospective analysis of the GeneXpert usage data to obtain an indirect measure of the prevalence of rifampicin resistance among different groups of pulmonary TB patients based on routine service delivery data. For study purpose, routine demographic and clinical data and treatment history of all patients tested with GeneXpert were collected from all GeneXpert sites for analysis of the prevalence of rifampicin resistance among different groups of pulmonary TB patients. Data were collected for 18 months from January 2014 to June 2015 during which period all the GeneXpert machines were fully functioning in the selected 35 districts with referral network linking the eligible patients for GeneXpert screening from the remaining areas of the country. Primary data collected from the GeneXpert sites were downloaded into an Excel spreadsheet maintained by the TB CARE II project. Univariate analyses were performed

to calculate aggregate number of patients screened with GeneXpert and test results, distribution of rifampicin resistant cases by new and different retreatment categories of pulmonary TB patients based on their treatment background, sex and age groups. The study team strictly maintained data quality and completeness through cross-checking and verification of primary data. The study team visited selected GeneXpert sites to update incomplete or missing data as identified during the data quality assurance process.

All data collection and analysis were conducted according to international principles of maintaining privacy and confidentiality of personal information.

Results

Data was collected for 61,836 presumptive TB patients including 68.3% male and 31.7% female. The mean age of patients tested in GeneXpert was 31 years. Of those 61,836 patients, 16,185 (26%) were retreatment cases including category 1 and 2 failure, delayed converters, relapse and loss to follow-up. Total number of new patients (who were progressively sputum smear negative) tested with GeneXpert were 35,257 (57%). Close contacts of MDR-TB, defined as presumptive MDR-TB, are grouped separately. includes sputum smear negative, close contacts of MDR-TB, HIV positive, and other. Patients under 'Other' kept separate as they do not fit into any of the above categories and includes sputum smear-positive patients with unknown previous treatment outcome, sputum smear-positive patients who received treatment other than Category I or II (possibly in the private sector), patients who have received several unsuccessful treatments and were considered incurable by health staff and who have lived with active TB disease with no or inadequate treatment (e.g. "chronic" patients), etc. General characteristics of all patients are given in the table 1.

Patient characteristics	Number	%
Sex		
Male	42,223	68.3%
Female	19,613	31.7%
Retreatment cases		
Failure after cat 1	1,330	2.15%
Failure after cat 2	381	0.62%
Delayed converters of cat 1	7,576	12.25%
Delayed converters of cat 2	340	0.55%
Relapse after cat 1	4,432	7.17%
Relapse after cat 2	585	0.95%
Loss to FU from cat1	1,220	1.97%
Loss to FU from cat2	321	0.52%
New TB presumptive (sputum smear negative)	35,257	57.02%
Close contacts of MDR TB	1,113	1.80%
HIV positive patients	426	0.69%
Other	8,855	14.32%

Table 1: *General characteristic of patients tested by GeneXpert MTB/RIF.*

Out of 61,836 presumptive TB cases tested by GeneXpert, 25,302 (41%) were diagnosed as MTB positive including 17,458 (69%) male and 7844 (31%) female. The mean age of all patients tested in GeneXpert was 33 years. Of the retreatment cases 16,185 tested, 100% of them were bacteriologically positive as expected. Bacteriologically positive cases among new presumptive smear negative patients and 'Other" were 26.12% and 8% respectively.

The proportion of RR-TB was 2.47% among all patients tested with GeneXpert and 6% among bacteriologically cases. The highest rate of RR was 16.67% found among bacteriologically positive HIV positive patients. Within retreatment cases, the highest rate of RR was 15.49% among the category 2 failure patients followed by relapse after category 2 (15.04%) and failure after category 1 (12.78%). RR

among close contacts of MDR-TB was 14.09%. Table 2 provides detail breakdown of bacteriologically positive and RR cases by different categories.

Patient Characteristics	Bacteriologically Positive (n = 25,302)		Rifampicin Resistant TB (n = 1,530)	
	Number	%	Number	%
Sex				
Male	17,458	69.00%	1,079	6.18
Female	7,844	31.00%	451	5.75
Retreatment cases				
Failure after cat 1	1,330	5.26%	170	12.78
Failure after cat 2	381	1.51%	59	15.49
Delayed converters of cat 1	7,576	29.94%	327	4.32
Delayed converters of cat 2	340	1.34%	30	8.82
Relapse after cat 1	4,432	17.52%	381	8.60
Relapse after cat 2	585	2.31%	88	15.04
Loss to FU from cat1	1,220	4.82%	65	5.33
Loss to FU from cat2	321	1.27%	19	5.92
New TB presumptive (sputum smear negative)	6,609	26.12%	231	3.50
Close contact of MDR TB	433	1.71%	61	14.09
HIV positive patients	60	0.24%	10	16.67
Other	2,015	7.96%	89	4.42

Table 2: *General characteristic of bacteriological positive and RIF resistant TB cases.*

The distribution of detected RR cases shows that the proportion was highest with 400 (26.1%) cases among 25 - 34 years age group following by 357 (23.3%) among 15 - 24 and 261 (17.1%) among 35 - 44 years old men and women. While the study found 26 (1.7%) among the 5 - 14 years children, there were no cases among under-5 children. Age and sex distribution of RR-TB patients are shown in the table 3.

Age group	Male	Female	Total
0 - 4 years	0 (0%)	0 (0%)	0 (0%)
5 - 14 years	11 (1%)	15 (3.3%)	26 (1.7%)
15 - 24 years	208 (19.3%)	159 (33%)	357 (23.3%)
25 - 34 years	264 (24.5%)	136 (30.2%)	400 (26.1%)
35 - 44 years	200 (19%)	61 (13.5%)	261 (17.1%)
45 - 54 years	173 (16%)	41 (9.1%)	214 (14%)
55 - 64 years	137 (12.7%)	31 (6.9%)	168 (11%)
65 and above	86 (8%)	18 (4%)	104 (6.8%)
Total	1079	451	1530

Table 3: *Age and sex distribution of all Rifampicin Resistant (RR) TB detected.*

All the patients were tested and diagnosed at 39 GeneXpert sites located in 34 district headquarters of Bangladesh. The study also looked into geographic distribution of the RR patients which shows concentration of cases in the largest urban cities led by Dhaka (21.11%), Chittagong (9.87%), Rajshahi (6.47%), Sylhet (5.95%), and Rangpur (5.06%).

Discussion

The study is an attempt to understand the prevalence and distribution of rifampicin resistance among different groups of pulmonary TB patients over a period of 18 months based on retrospective analysis of GeneXpert usage data collected from 39 functioning GeneXpert sites under the national TB control program. In the study population, overall prevalence of rifampicin resistance, including multidrug resistance, was significantly higher among retreatment cases specifically category 2 failures and category 2 relapses as compared with other categories. The present study findings of higher resistance among previously treated cases is consistent with other studies conducted in Bangladesh [11,21] and national and global estimates [19]. These results underline the need for contact investigation of DR TB index cases, routing screening of HIV positive patients, timely identification of treatment failures and relapse cases by early referral for culture and sensitivity testing and early initiation of appropriate treatment with second-line drugs.

The RR rate for retreatment patients found in this study was much lower (7%) than that reported (28.5%) in the last DRS which had a different design with a sample of 27 new and all retreatment smear positive patients enrolled from each cluster. The DRS retreatment included already registered patients in whom treatment was failing, patients who relapsed immediately following treatment and patients who returned after loss to follow-up. Most of the previously treated cases enrolled in the DRS was from chest disease clinics, and thus represented more complicated cases who were failing treatment and were already at risk of developing MDR-TB. These differences in survey design might have contributed to a higher MDR-TB prevalence among retreatment patients in the national DRS. However, the findings from this study reinforces strategic priorities to target the previously treated patients for identification and treatment of RIF resistant cases.

The prevalence of RR found in this study among new patients who are MTB positive was much higher (3.5%) than the national DRS estimate (1.4%). That these new patients were presumptive smear negative cases referred for GeneXpert test is a plausible explanation for the high rate among this group. Although this rate cannot be generalized for all new patients, this finding has important programmatic implications for targeting smear negative cases for increased detection of RR TB. The high prevalence of RIF in this group is a sign of on-going infection adding new cases while diminishing program effectiveness. Effective strategies to expand GeneXpert testing of all presumptive smear negative patients will significantly increase early detection and reduce new disease transmission.

The high rates of RIF resistant cases among MTB positive close contacts of MDR-TB patients (14.09%) and HIV positive patients (16.67%) are important study findings that points to intensified case finding targeting these groups. Systematic contact tracing of all index MDR as well as drug-sensitive TB patients and testing them by GeneXpert have great potential to increase detection and halt transmission at an early stage. Around 50% of the detected RR patients are within the 15 - 34 age group which is considered the most active phase of life. The scenario is more prominent among the female group; 63% of female RR patients are within this age group. The high rate of RR TB among the young, active and mobile population is of high relevance to control disease transmission. The national program should consider supporting studies to develop a better understanding of the infection and resistance in this group for future strategic considerations.

Drug related factors including quality of drug substance, production process, packaging, storage and distribution, and environmental conditions can affect the BA of rifampicin. For that reason, quality assurance of the drug product throughout the manufacturing processes including its entire shelf-life is of utmost importance to prevent undesirable clinical consequences resulting from suboptimal quality of medications used in patients with drug sensitive (DS) tuberculosis. It is difficult to establish the root causes of poor BA of rifampicin in FDCs as many possible factors need to be considered. The national program may consider strengthening drug quality monitoring and support studies to generate additional evidence to inform policies on FDCs use at national, sub-national and individual levels.

Study Limitations

The study presented here has several limitations as it relied on the routine data collected from the GeneXpert sites. Since no population-based data was used, the study findings cannot be generalized to whole population. A significant number of presumptive cases were classified under 'Other' for lack of clarity in their clinical background information. Although RIF resistance was high in this group, no specific discussion of strategic priorities could be made to address this issue.

Conclusion

Drug resistant surveys are expensive and conducted once in several years. Use of data generated through continuous monitoring and surveillance is an important alternative to intermittent surveys; provides a reliable basis for developing interim prevalence estimates; observing trends in disease patterns, and performance gaps to support on-going program management decisions. The study is a unique attempt in this direction to demonstrate the importance of continuous monitoring of drug resistance trends, and how MDR-TB burden countries can utilize the date to build evidence for shaping future policies and priorities to address this public health challenge.

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