

**DRUG RESISTANCE PATTERN OF *M. TUBERCULOSIS* IN CATEGORY II TREATMENT FAILURE PULMONARY TUBERCULOSIS PATIENTS**

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Abstract

This study was designed to determine the extent of drug resistance of *M. tuberculosis* (MTB) isolated from category II treatment failure pulmonary tuberculosis (PTB) patients. A total of 100 Ziehl-Neelsen (Z-N) smear positive category II failure PTB patients were included in this study. Sputum culture was done in Lowenstein-Jensen (L-J) media. Conventional proportion method on Lowenstein-Jensen (L-J) media was used to determine the drug susceptibility of *M. tuberculosis* to isoniazid (INH), rifampicin (RMP), ofloxacin (OFX) and kanamycin (KA). Out of 100 sputum samples, a total of 87 samples were positive by culture. Drug susceptibility test (DST) revealed that 82 (94.25%) isolates were resistant to one or more anti-TB drugs. Resistance to isoniazide (INH), rifampicin (RMP), ofloxacin (OFX) and kanamycin (KA) was 94.25%, 82.75%, 29.90% and 3.45% respectively. Among these isolates, 79.31% and 3.45% isolates were multi-drug resistant (MDR) and extended drug resistant (XDR) *M. tuberculosis* respectively. High rate of anti-tubercular drug resistance was observed among the category II treatment failure TB patients.

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**Key Words:** MDR-TB, XDR-TB, Category II treatment failure tuberculosis.

**Introduction**

Globally tuberculosis (TB) is among the top ten killer infectious diseases, second only to HIV.<sup>1</sup> One third of the world's population is harboring tuberculosis infection. In 2011, about 5.8 million new TB cases and 1.4 million deaths due to TB occurred worldwide.<sup>2</sup> The prevalence and incidence of TB gradually declined over the last 100 years with the improvement of socio-economic conditions and introduction of anti-tubercular drugs. But the emergence of drug resistance in TB has changed the scenario. The emergence of drug resistant *M. tuberculosis strain* has greatly complicated the TB control effort in many countries including Bangladesh. Bangladesh ranks 6<sup>th</sup> among the twenty two TB high-burden countries of the world and 9<sup>th</sup> among the 25 high priority multi-drug resistance TB (MDR-TB) countries.<sup>3</sup> In present days, multi drug and extensive

drug resistant TB is the main problem in its effective control. *M. tuberculosis strains* that are resistant to the two most potent anti-TB drugs, isoniazid and rifampicin, are termed as multidrug-resistant TB (MDR-TB) strains. Extensively drug-resistant TB (XDR-TB) is a form of TB caused by bacteria that are resistant to isoniazid and rifampicin (ie MDR-TB), as well as to any fluoroquinolone and any of the second-line anti-TB injectable drugs like amikacin, kanamycin or capreomycin. These forms of TB do not respond to the standard six-month treatment with the first line anti-TB drugs and can take up to two years or more to treat with drugs that are less potent, more toxic and much more expensive.<sup>4</sup> The magnitude of drug resistance is not yet known in many areas of the world including high TB burden countries. Evidences from

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half of the world's nations confirm that drug resistance is a serious global problem. A worldwide estimated emergence of 310,000 cases of MDR-TB was reported in 2011.<sup>2</sup> In Bangladesh, a few studies on the rate of drug resistant *M. tuberculosis* were conducted. As per 2011 WHO report, estimated MDR-TB rate in Bangladesh is 1.4% among the new cases and 29% among previously treated TB cases.<sup>5</sup> In addition, XDR-TB have been reported from 58 countries.<sup>6,7</sup> Three cases of XDR were also detected in Bangladesh.<sup>3</sup>

Both MDR-TB and XDR-TB are the emerging threats to the success of tuberculosis control programs. Although treatable, MDR-TB cases are difficult and costly. On the other hand, XDR-TB cases are virtually untreatable since none of the standard or reserve drugs is effective. To prevent the transmission of these strains, early identification of this type of resistant strain is important. Such early detection could optimize treatment, improve the outcome and prevent the transmission of MDR-TB.

In view of the above, the present study was carried out in a tertiary referral hospital of Dhaka city to determine the resistance pattern of *M. tuberculosis* (MTB) isolated from first and selected second line anti-TB drugs among category II treatment failure tuberculosis patients.

### Materials and Methods

A total of 100 Z-N smear positive category II treatment failure pulmonary tuberculosis patients of different age and sex were enrolled in this study. Sample collection and laboratory works were done in the National Tuberculosis Referral Laboratory (NTRL) and National Institute of Disease of Chest and Hospital (NIDCH), during the period of January to December 2010. Drug susceptibility was done only on culture positive isolates.

In this study, conventional proportion method on Lowenstein-Jensen (L-J) media was used to determine the drug susceptibility of *M. tuberculosis* to isoniazid (INH), rifampicin (RMP), ofloxacin (OFX) and kanamycin (KA). Required amounts of stock solutions of drugs were added to media to obtain critical concentration of drugs in each medium. Critical concentration of INH was- 0.2 µg/ml, RMP- 40 µg/ml, OFX- 2 µg/ml, and KA- 30 µg/ml. The critical concentration of drugs was the amount that inhibited

**Table 1:** Resistance pattern of *M. tuberculosis* isolated from category II treatment failure cases

Category of cases	Total cases	Overall resistant <sup>a</sup> to				Resistant to any drug no.(%)
		INH no. (%)	RIF no. (%)	OFX no. (%)	KA no. (%)	
Category II treatment failure cases	87	82 (94.25)	72 (82.75)	26 (29.90)	3 (3.45)	82 (94.25)

Note: a= Resistant to one or more drug

the growth of susceptible tubercle bacilli without affecting the growth of resistant mutants present.<sup>8</sup>

### Results

During the study period a total of 100 smear positive category II treatment failure pulmonary tuberculosis patients were enrolled. Out of the 100 patients, sputum samples from 87 (87%) were positive by culture. All were identified as *M. tuberculosis* complex. Out of 87 isolates, 82 (94.25%) were resistant to one or more drugs. Highest resistant was found against isoniazid (94.25%) followed by rifampicin (82.75%), ofloxacin (29.90%) and Kanamycin (3.45%) either alone or in combination with other drugs (Table-1). Sixty nine (79.31%) isolates were detected as MDR while three (3.45%) were XDR (Table-2). Ten (11.49%) isolates were detected as resistant to only INH while no RMP mono resistant isolate was detected in the present study. Out of 87 isolates, five were sensitive to all four drugs tested.

**Table 2:** Rate of MDR / XDR-TB of category II treatment failure cases

Categories	Total no	MDR no.(%)	MDR Pattern		XDR <sup>a</sup> no.(%)
			INH+RMP	INH+RMP+OFX	
Category II treatment failure cases	87	69 (79.31)	46 (52.87)	23 (26.44)	03 (3.45)

Note: a= All XDR isolates were resistant to INH+RMP+OFX+KA. MDR = Multi drug resistance; XDR= Extended drug resistance; INH = Isoniazid; RMP = Rifampicin; OFX = Ofloxacin; KA = Kanamycin;

## Discussion

The results of the present study showed that there were a very high rate of resistance to one or more drugs (94.25%) among the bacteria isolated from category II treatment failure cases. Other authors found 76% to 86% resistance to INH among Category II failure patients.<sup>9,10</sup> INH resistance was the most common form of anti-tuberculosis drug resistance encountered, whether alone or in combination with other drugs. In the present study, RMP resistant isolates were combined with resistance to other drugs. No RMP mono resistant isolate was found in the present study. RMP mono-resistant in *M. tuberculosis* is rare, except those associated with HIV patients.<sup>11</sup> Thus RMP resistance generally serves as a surrogate marker for dual resistance to RMP and INH.<sup>12</sup>

Among these culture positive isolates, 79.31% were diagnosed as MDR-TB. Previously in 2009, similar high rate of multi drug resistant *M. tuberculosis* (83% and 87%) was also reported in two different studies among category II failure Bangladeshi patients.<sup>9,10</sup> No national study has been conducted in Bangladesh to evaluate the current status of MDR/XDR-TB among the category II treatment failure cases. Recent national Drug Resistance Surveillance (DRS) data recorded the rate of MDR-TB as 1.4% among new cases and 29% among previously treated TB cases.<sup>5</sup> Therefore, routine bacteriological monitoring of category II failure cases is needed to detect and isolate MDR-TB cases to prevent transmission and mortality. Out of total 87 isolates, about 10% isolates showed resistance to ofloxacin. Fluoroquinolone is frequently used in respiratory tract as well as other types of community acquired infections. So, irrational and frequent short course use of fluoroquinolones for various other type infections may be restricted to prevent the development of fluoroquinolones resistance among *M. tuberculosis*. Three isolates (3.45%) were diagnosed as XDR-TB. This high rate of XDR *M. tuberculosis* could be due to the fact that our enrolled patients were category II treatment failure cases from a tertiary care centre where difficult cases were referred from all over the country. However, the overall prevalence of XDR-TB among all MDR-B isolates was 6.6% worldwide, 6.5% in industrialized countries, 13.6% in Russia, 1.5% in Asia and 0.6% in Africa.<sup>7</sup>

The high rate of MDR-TB among the Category II treatment failure cases is a serious threat for effective

TB control program in the country. Improvement is needed in the existing diagnostic laboratories. Better diagnostic tests for quick screening of drug resistant MTB should be developed and made available at the grass-root level. Infection control procedures also have to be improved in hospitals to stop spread of MDR/XDR-TB in the country.

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