

Editorial

Extensively Drug Resistant Tuberculosis (XDR-TB)

One third of the world's population or nearly 2 billion people are infected with *Mycobacterium tuberculosis*, of which 75% sufferers are in the 15-54 year age group. Two million people die of tuberculosis (TB) each year. Bangladesh ranks 6th among the 22 TB high-burden countries in the world and 9th among 25 high priority multidrug resistant (MDR) and extensively drug resistant (XDR) TB countries.¹ The MDR-TB is defined as a case of TB resistant to the main first-line drugs namely Rifampicin and Isoniazid. Whereas, XDR-TB is defined as a case of TB with MDR as well as resistance to any of the fluoroquinolone drugs and to at least one of the three injectable second-line drugs, like Amikacin, Capreomycin or Kanamycin.

The MDR-TB cases are very difficult and costly to treat but yet manageable or treatable. But XDR-TB cases are virtually untreatable since none of the standard drugs or the reserves are effective, so this issue needs to be addressed before treating them like "TB patients before the antibiotic era". These MDR-TB and XDR-TB terms are undoubtedly frightening to Bangladesh where the incidence rate of sputum-positive pulmonary TB is 229 people per 100,000 population, and the bread-earning economically productive age group (15-45 years) has been found affected mostly.²

In a published report, 63 isolates of sputum samples from different areas of Bangladesh were studied in the National Institute of Diseases of Chest and Hospital (NIDCH) in 2005. Drug susceptibility testing was done on 42 of 63 isolates in a Supranational Reference Laboratory (SRL) at Antwerp, Belgium. Among 42 strains, 35 (83%) were found resistant to both Isoniazid and Rifampicin (MDR). Among these MDR strains, 40% were found resistant to any one of the 2nd line drugs (Kanamycin, Ofloxacin, Ethionamide, and Para Amino Salicylic acid). However, none of the strains were found to be XDR.³ Another study demonstrated that the prevalence of MDR-TB was 3% among new and 15.4% in previously treated patients in Bangladesh.⁴

During November, 2004 to November, 2005, the Center for Disease Control (CDC) and WHO surveyed the WHO/International Union against Tuberculosis and Lung Disease Global Supranational TB Reference Laboratory Network and found that new MDR-TB cases have been emerging every year all over the world and it is now estimated that more than 400,000 new cases occur annually. The SRL Network identified that XDR-TB was the most common in South Korea showing 15% of all MDR-TB cases. It has been estimated worldwide that other than South Korea, XDR-TB isolates increased from 14 (5% of MDR-TB isolates) in 2000 to 34 (7% of MDR-TB isolates) in 2004.⁵ Researchers have identified MDR-TB cases from 102 out of 109 countries in a survey in the past decade and outlined the underlying cause for this emergence of drug resistant strains as: (i) improper management of TB; (ii) low quality of anti-TB drugs; and (iii) incorrect use of drugs.⁶

A study in South Africa shows XDR-TB, identified in HIV/AIDS population, has a high mortality rate. Among 544 patients, 221 (40.63%) were MDR-TB and 53 (23.98%) of the MDR-TB cases were characterized as XDR-TB. Most of the XDR-TB were HIV positive (44.83%) and died in a very short time.⁷ Considering this high mortality in HIV/AIDS patients, XDR-TB also poses serious threat to public health. Realizing the crisis, an expert consultation meeting was hosted by South African Research council on Drug Resistant TB in Johannesburg in 2007, and was supported by WHO and CDC, USA.⁸ Based on available data and facts, certain recommendations were outlined in the "WHO Guidelines to prevent XDR-TB". The objectives were: to strengthen basic TB care, to increase collaboration between HIV and TB control programmes, and to increase investment in laboratory infrastructures for better detection. However, data is still scarce in many areas of the world leaving the vast field of research on TB, particularly when the XDR-TB is on the rise.⁸

If the guidelines are to be followed, we need to know the drug

resistance situation of *M. tuberculosis* clinical isolates in Bangladesh. Culture and susceptibility testing of the *M. tuberculosis* were started at Shaymoli TB clinic, Dhaka in 2001 and very recently in NIDCH. Since these centres cannot fulfill the demands of the whole country, the NTP (National TB Project) plans to establish regional reference laboratories at Chittagong, Rajshahi and Khulna. These regional laboratories will carry out culture only. Isolates will be sent to the National Tuberculosis Reference Laboratory (NTRL) at NIDCH for susceptibility testing. [personal communication with Professor PC Barua, Director, Mycobacterial Disease Control (MBDC), and Line Director, TB and Leprosy Control, Directorate General of Health Services, Bangladesh] Dots-plus project has been implementing by National TB Control Program (NTP) with funding from Global Fund against AIDS, TB, Malaria (GFATM) from July, 2008 at the NIDCH, Bangladesh, which targets to include 700 patients.⁹

South Africa constitutes 11% of African population and 2/3rd of their deaths were found due to TB in the continent, the reason were found linked with association of HIV infection. The first outbreak of XDR-TB was in Kwazulu-Natal Province of South Africa and the study was done on the samples obtained in 2005 to 2006, where HIV patients were also victims.⁷ Such highly resistant strains are thought to be less virulent to people who are immunologically competent and healthy. But even then the threat remains the same for healthy people as well, since there is no chemoprophylaxis right now and as American Chemical Society estimates that the first drugs of an entirely new class will not be ready for regular use until 2012.¹⁰

In an issue relating to immunotherapy, a strain named *Mycobacterium vaccae* has been used with TB therapy in several researches against MDR -TB has shown encouraging results. This *M. vaccae*, a rapidly growing pigment-producing strain, was first isolated from cow-dung in Austria, and the word was derived from Latin word *Vacca* meaning 'cow'. Intradermal injection of heat-killed suspension of *M. vaccae* (NCTC 11659) has been used to treat and prevent Leprosy across the globe and positive results were found. Thus this preparation has been produced and marketed by a small pharmaceutical company (SR Pharma) as 'SRL172' strain. It has been used in studies along with anti-TB therapy in South Africa and Uganda, and found to have beneficial effects in the treatment of Tuberculosis.¹¹

The WHO experts on HIV/AIDS expressed the XDR crisis as a severe one as it is thought to be emerging or occurred from re-infection of TB cases in HIV sufferers, when his/her immunity is diminished. Is it possible that TB cases in South Africa (also a prevalent zone for HIV) may have transformed into XDR-TB cases even after proper complete treatment in depressed immunity due to HIV infection? Questions arise whether it is possible that dormant bacilli in an immunocompromised person reemerge as a XDR strain. What possible outcome might Bangladesh have to bear where 50% of the population is supposed to be infected? So, it is obvious that HIV and TB programs must have a close link. Laboratories should be involved in early confirmation of TB cases and isolating strains for drug susceptibility testing. An HIV positive case must be tested for TB and a drug resistant TB case must be tested for HIV. The stigma of HIV should be removed to avoid any undetected case.

"This is not an individual's responsibility, also a public responsibility, a collective responsibility" as mentioned by an advisor in the WHO, Africa office.⁷ Therefore, close collaboration between Clinicians, Microbiologists and public health Officials under the agencies of the National Tuberculosis Control Program (NTP) is imperative for reaching the Millennium Development Goals (MDG) of halving the prevalence and mortality by 2010 and reducing the incidence of TB by 2015.¹²

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[Conflict of Interest: none declared]