**Editorial**

# MDR / XDR-TB: where do we stand?

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Tuberculosis (TB) is one of the leading causes of death due to an infectious disease, second only to HIV/AIDS worldwide[1]. It is estimated that approximately one third of the world's population is infected with *Mycobacterium tuberculosis,* and 10% of infected individuals will develop active TB at some point in their lives. MDR-TB or multidrug-resistant tuberculosis is a specific form of drug resistant TB that occurs when bacteria are resistant to at least isoniazid and rifampicin, the two most powerful anti-TB drugs. While XDR-TB or extensively drug-resistant tuberculosis is a MDR-TB that is also resistant to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs (capreomycin, kanamycin and amikacin). The concept and term XDR-TB as a distinct nosological entity were first developed by the Centers for Disease Control and Prevention (CDC) in March 2005 and were introduced into public use in October 2005 at the 36th World Conference on Lung Health in Paris, France[2]. For some years, isolated cases of very highly resistant TB have been seen around the world that we would today call XDR-TB. In 2008, an estimated 500,000 individuals throughout the world developed MDR- TB with 150,000 deaths. According to World Health Organization (WHO), XDR-TB cases have been detected from at least 58 countries as of March 2010 and 5.4% of MDR-TB cases have XDR-TB with 25,000 new cases of XDR-TB emerging every year[3]. However, the true global prevalence of XDR TB and MDR TB is unknown, because drug susceptibility testing, even for first line drugs, is not routinely performed in most TB endemic countries, and many cases likely are undetected[4]. Incidentally, India and China cover the 50% of world's burden of MDR-TB and Bangladesh ranks 9th in the list of 25 high priority MDR/XDR-TB countries as prepared by Stop TB partnership.

Drug resistance in TB may be broadly classified as primary and acquired. When drug resistance is demonstrated in patient who has never received anti-TB treatment previously, it is termed as primary resistance or better called drug-resistance among new cases. While acquired resistance refers to drug resistance among previously treated cases. Tuberculosis can usually be treated with a course of four standard or first-line anti-TB drugs. If these drugs are misused or mismanaged, MDR-TB can develop. MDR-TB takes longer to treat with second line of drugs which are more expensive and have more side effects. Similarly, XDR-TB can also develop when these second-line drugs are misused or mismanaged and therefore also become ineffective. Because XDR-TB is resistant to both first and second line of drugs, treatment options become seriously limited. In general, poorly managed TB control programmes, for example, when patients are not properly supported to complete their full course of treatment; when health care-providers prescribe the wrong treatment, or the wrong dose, or for too short a period of time, when the supply of drugs is erratic, or when the drugs are of poor quality are reasons when anti-TB drugs are misused or mismanaged. Although the initial development of drug resistance in patients receiving anti-TB therapy is often due to multiple factors but suboptimal drug concentrations and varying degrees of nonadherence to therapy are the leading factors for drug-resistant observed in countries with high numbers of patients co infected with HIV.

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In fact, TB is one of the most common infections in people living with HIV/AIDS because of their compromised immunity and existing control programs for TB have been seriously compromised in the setting of widespread HIV infection. Fortunately because of the still less number of XDR-TB, HIV/AIDS patients are mostly infected with drug-susceptible TB that can be effectively treated with standard first line anti-TB drugs[5].

There is probably no difference between the route and speed of transmission of XDR-TB and any other forms of TB. The spread of TB bacteria depends on factors such as the number and concentration of infectious people in any one place together with presence of people with a higher risk of being infected. It is generally stated that 90% of the immunocompetent people after being infected with TB bacilli do not develop ordinary TB and this is also true or even less for MDR/XDR-TB because still the number of resistant cases is very low. It is very vital that the clinicians caring the TB patients are aware of the possibility of drug resistance and have access to laboratories that can provide early and accurate diagnosis. Besides, all six classes of second line drugs must be available to clinicians to provide effective treatment. It is still not known whether strains of MDR and XDR-TB are more transmissible or more virulent than their drug susceptible counterparts.

Antibiogram or drug-susceptibility testing for *M. tuberculosis* is of paramount importance for any attempt to combat MDR/XDR-TB. Conventional drug-susceptibility testing (DST) has limitations. Solid media-based techniques, such as Löwenstein–Jensen and Middlebrook 7H10/11 using the proportion, absolute concentration and resistance ratio methods, take up to 8–12 weeks. Liquid media-based methods, such as the BACTEC and BacT/ALERT systems, are faster and sensitive, but more expensive and complex[6]. Although rapid, sensitive and specific detection of isoniazid and rifampicin resistance is currently possible, further research is necessary to identify new tools able to diagnose resistance to second-line anti-TB drugs in a simple, economical and reproducible manner[7]. Rapid tests can provide results within days (even without culture, *i.e.* directly on specimens) and thus enable prompt and appropriate treatment, decrease morbidity and mortality, and interrupt transmission. Line probe assays (based on reverse-hybridization DNA strip technology) could potentially address this urgent need. A notable advantage of molecular tests is their rapid (6 h to 2 days) turn-around time, which may have implications for patient management and transmission of drug-resistant TB[8].

Perhaps most importantly, XDR-TB has been shown in the current literature to be a treatable as well as curable condition. While this is an encouraging finding, complacency is not appropriate. XDR-TB patients do more poorly in terms of smear and culture conversion, treatment duration, treatment failure and death. With clear indications that XDR-TB results from mismanaged cases of drug-susceptible and MDR-TB, the first imperative is to treat susceptible TB appropriately to completion and to provide rapid diagnosis and aggressive, appropriate treatment of MDR-TB to avoid the unnecessary development of additional cases of XDR-TB[9].

The WHO Global Task Force on XDR-TB developed seven main recommendations to prevent and control XDR, as follows[10]:

**1)** Prevention of XDR-TB through basic strengthening of TB and HIV control. The new Stop TB Strategy and the Global Plan to Stop TB are the essential reference documents to guide these priority interventions.

**2)** Improvement of management of XDR-TB suspects. These interventions will be based on accelerating the access to laboratory facilities, with DST including a rapid test for rifampicin resistance, and improving detection of cases suspected of harbouring MDR strains both in high and low HIV prevalence settings.

**3)** Strengthened management of XDR-TB and treatment design in HIV-negative and positive individuals. This intervention will be based on the adequate application of the new WHO guidelines for programmatic management of drug-resistant TB using second-line drugs properly and through a patient-centered approach to ensure adequate support and supervision.

**4)** Standardization of the definition of XDR-TB. The global adoption of the new definition will improve the comparability of data obtained through ongoing surveillance in low TB incidence and *ad hoc* surveys in high TB incidence countries.

**5)** An increase in HCW infection control and protection. This intervention, aimed at reducing the ongoing transmission of MDR-TB especially among HIV-positive individuals in congregate care settings, will be focused mainly (but not exclusively) on high HIV prevalence settings.

**6)** Implementation of immediate XDR-TB surveillance activities.

**7)** Initiation of advocacy, communication and social mobilization activities. There is an urgent need to inform and raise awareness about TB and XDR-TB.

Global tuberculosis control is facing major challenges today. In general, much effort is still required to make quality care accessible without barriers of gender, age, type of disease, social setting, and ability to pay. The most critical need for patients with drug-resistant TB is access to new drugs. Several new therapies are in clinical trials[11]. The National Institute of Allergy and Infectious Diseases (NIAID), USA has focused its drug discovery efforts on studies of the physiology of *M. tuberculosis* and its interaction with the host to identify suitable points of intervention against which new drug candidates can be developed. Unfortunately, new TB therapeutics are not expected to be widely available in the immediate future. In the interim, it has been recognized that even the current first and second line therapies for TB are likely not fully optimized and need to be reexamined to determine whether adequate drug levels are being achieved in patients with advanced disease, in children, in those receiving antiretroviral therapies, and in those with other co morbidities[12]. Furthermore, FDA-approved antibiotics not currently used for treatment of TB should be tested clinically to determine whether they can contribute to treatment approaches for drug-resistant and drug-susceptible TB; if this is the case, additional drugs with anti–*M. tuberculosis* activity might be made available in a timely manner to address the global threat of MDR/XDR TB[13]. Considering all the issues, WHO has developed a new six point Stop TB Strategy which builds on the successes of DOTS while also explicitly addressing the key challenges facing TB. Its goal is to dramatically reduce the global burden of tuberculosis by 2015.

Any attempt to combat drug-resistant-TB, research activities need to be directed to create a foundation of knowledge for the discovery of new diagnostics, drugs, and vaccines. The largest potential impact on TB control and the development of drug resistance would come from effective vaccines to prevent all forms of TB. The currently available vaccine, Bacille Calmette Guérin, does not provide adequate protection against pulmonary TB, particularly in adults, and therefore has limited utility for the control of TB

transmission. Development of new vaccines and vaccination strategies has been stymied by a lack of understanding of the nature and mechanisms of immune protection that would have to be elicited by an effective vaccine. Programs for the genetic sequencing of representative *M. tuberculosis* strains are ongoing, and drug resistance markers are beginning to be identified; it is also important to understand how host factors contribute to the development of drug resistance in TB. Answers to these research questions will not only improve our understanding of the pathogenesis of TB and provide additional drug targets and potential diagnostic and immunological markers but, hopefully, will also help to prevent development of drug resistance in the future.

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