

Editorial

TACKLING EXTENSIVELY DRUG RESISTANT TUBERCULOSIS (XDR-TB)

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Tuberculosis remains a major cause of morbidity and mortality worldwide. The rise and spread of drug resistance is threatening global efforts of tuberculosis control. Extensively drug-resistant tuberculosis (XDR-TB) is a severe form of drug-resistant TB, defined as tuberculosis caused by a *Mycobacterium tuberculosis* strain that is resistant to isoniazid and rifampicin among the first-line antitubercular drugs (multidrug-resistant tuberculosis; MDR-TB) in addition to resistance to any fluoroquinolone and at least one of the three injectable second-line drugs (SLDs), namely amikacin, kanamycin and/or capreomycin. The first reports of XDR-TB appeared in 2006.^{1,2} Since then, a total of 84 countries have reported cases of XDR-TB. The true scale of XDR-TB is unknown as many countries lack the necessary equipment and capacity to accurately diagnose it. An estimated number of 630,000 cases of MDR TB (460,000-790,000 out of ~12 million prevalent TB cases) were reported in the world in 2011 as per the 2012 WHO global tuberculosis report.³ There were an estimated 310000 (range, 220 000–400 000) MDR-TB cases among notified TB patients with pulmonary TB in 2011. Almost 60% of these cases were in India, China and the Russian Federation. XDR-TB has been identified in 84 countries; the average proportion of MDR-TB cases with XDR-TB is 9.0% (6.7–11.2%). Levels of MDR-TB remain worryingly high in some parts of the world, notably countries in eastern Europe and central Asia. In several of these countries, 9–32% of new cases have MDR-TB and more than 50% of previously treated cases have MDR-TB.³ By far, the largest number of cases of XDR-TB has been reported from South Africa (10.5% of all cases of MDR-TB in that country), owing to rapid spread among people infected with the human immunodeficiency virus.⁴

XDR-TB strains have arisen due to the mismanagement of individuals with MDR-TB. The global epidemic of drug-resistant tuberculosis is due to a combination of acquired resistance and primary transmission. Because XDR-TB is resistant to the most powerful first-line and second-line drugs, patients are left with treatment options that are much less effective and often have worse treatment outcomes. National programmes are failing to diagnose and treat MDR and XDR tuberculosis. Only 7% of estimated 440,000 cases of MDR-TB cases were reported to WHO and only a fifth were treated according to WHO recommended regimens.³ A vast majority of the remaining cases probably are not diagnosed or, if diagnosed, are mismanaged. This problem remains despite the evidence that management of MDR and XDR tuberculosis is cost-effective.⁵

Within a year of the first reports of XDR-TB in 2006, isolated cases were reported in Italy that had resistance to all first-line anti-TB drugs and second-line anti-TB drugs that were tested.⁶⁻⁸ In 2009, a cohort of 15 patients in Iran was reported who were resistant to all anti-TB drugs tested.⁹ The terms 'extremely drug resistant' (XXDR-TB) and 'totally drug-resistant TB' (TDR-TB) were given by the authors reporting this group of patients. In 2012, Dr Udawadia reported four patients from Mumbai with TDR-TB¹⁰, with subsequent media reports of a further eight cases which got lot of media publicity.¹¹ However, within a couple of weeks, the health authorities had rejected these claims, saying that all the cases were in fact XDR-TB infections. While the concept of TDR-TB is

easily understood in general terms, in practice, *in vitro* drug susceptibility testing (DST) is technically challenging and got limitations on its use. Conventional DST for the primary antitubercular drugs has been thoroughly studied and consensus reached on appropriate methods, critical drug concentrations that define resistance, and reliability and reproducibility of testing.¹² Reproducibility and reliability of DST for the SLDs are limited or have not been established. The correlation of DST results with clinical response to treatment has not yet been adequately established. Thus, a strain of TB with *in vitro* DST results showing resistance could, in fact, in the patient, be susceptible to these drugs. Lastly, new drugs are under development, and their effectiveness against these “totally drug resistant” strains has not yet been reported. For these reasons, the term “totally drug resistant” tuberculosis is not yet recognized by the WHO. For now, these cases are defined as XDR-TB, according to WHO definitions.¹³

Preventing initial infection with MDR and XDR tuberculosis and managing the treatment of existing cases appropriately are the keys to containing the spread of this disease. The discovery of patients with MDR or XDR-TB emphasizes the importance of ensuring that all care for tuberculosis, whether in the public or private sector, must conform to international standards in order to prevent the emergence of drug resistance.¹⁴ Almost all countries must ensure appropriate diagnosis and treatment of cases of MDR-TB. National regulations for the quality and dispensing of anti-TB drugs, particularly of the second-line drugs, need to be strictly enforced. To achieve this, most countries require simultaneous scale-up of the diagnostic and treatment services for drug-resistant TB, and the provision of adequate and continuous supplies of quality-assured second line drugs for both MDR- and XDR-TB to meet the increased demand. XDR and TDR-TB raise many difficult issues concerning the management of patients, for example, whether to isolate patients, the need for institutional, palliative or end-of-life care, and the compassionate use of new drugs to prevent transmission of infection.¹⁵

Molecular diagnostics have made earlier and improved diagnosis of active disease possible. Laboratory expertise and resources are required for these tests to become available throughout the developing world. Globally in 2010, only 4% of new and 6% of previously treated TB patients were tested for susceptibility to isoniazid and rifampicin, while the Global Plan targets are 20% or more, and 100%, respectively. The number of reported cases of MDR-TB was only 18% of the estimated number of cases among TB patients notified in 2010.¹⁵ And only around one quarter of them were treated in accordance with recommended international guidelines.

Tuberculosis control efforts are complicated by weak programmes with poor access to laboratory diagnosis and effective treatment. Investment in laboratory capacity and staff and the introduction of new rapid diagnostic tests are crucial. The World Health Organization (WHO) recommends that standard drug-susceptibility testing be performed at the same time that the Xpert MTB/RIF assay is performed to confirm rifampicin resistance and the susceptibility of the *M. tuberculosis* isolate to other drugs. Other screening tests for drug resistance include the microscopic-observation drug-susceptibility (MODS) assay, the nitrate reductase assay, and colorimetric reductase methods. The MODS assay simultaneously detects *M. tuberculosis* bacilli, on the basis of cording formation, and isoniazid and rifampicin resistance. Since most of these methods are not currently available in countries where tuberculosis is highly endemic, it is estimated that only 10% of cases of MDR-TB are currently diagnosed worldwide and only half of them receive appropriate treatment.¹⁵ XDR-TB is extremely difficult to diagnose and treat in countries where the disease is endemic.

A review on 13 recent studies of XDR-TB show that XDR-TB can be successfully treated in up to 65% of patients, particularly those who are not co-infected with HIV. However, treatment

duration is longer and outcomes are, in general, poorer than for non-XDR TB patients. Early diagnosis and aggressive management of XDR-TB provide the best chance of positive outcome, but prevention is still paramount. Several new drugs belonging to new classes of anti-mycobacterial agents are under development, but until they are shown to be effective in properly conducted clinical trials, WHO cannot recommend their routine use.

Newer antituberculosis drugs offer the promise of shortened treatment regimens for drug-sensitive disease and more effective treatment for drug-resistant disease and latent infection. New vaccines against tuberculosis in advanced clinical trials offer hope for future tuberculosis control. Although these scientific developments are promising, the global economic crises continue to hinder tuberculosis control programmes. Strong political and financial commitments will be required to achieve global control of tuberculosis and avert millions of unnecessary deaths.

The WHO recommended Stop TB Strategy provides the framework for the effective large-scale treatment and control of both drug-susceptible and drug-resistant disease.¹⁶ The Global Plan to Stop TB, 2011 – 2015, developed by the Stop TB Partnership, including WHO, estimates funding needs for implementation levels needed to achieve global targets.¹⁷

XDR-TB raises concerns of a future TB epidemic with restricted treatment options, and jeopardizes the major gains made in TB control. It is therefore vital that TB control be managed properly and new tools developed to prevent, treat and diagnose these patients. Preventing initial infection with MDR and XDR tuberculosis and managing the treatment of existing cases appropriately are the keys to containing the spread of this disease. Recent advances in diagnostics, drugs and vaccines and enhanced implementation of existing interventions have increased the prospects for improved clinical care and global tuberculosis control.

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TB SUPERVISOR COURSE

The Tuberculosis Association of India is going to start a “TB Supervisor Course” of three month duration to be conducted at the New Delhi Tuberculosis Centre, New Delhi.

This will be a certificate course comprising two months' class room (theory) training followed by one month field training at various DTOs and other TB institutions.

For details regarding eligibility, commencement date, etc. kindly keep a track on our website: www.tbassnindia.org.

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