

INFORMATION NOTE: Management of multidrug-resistant tuberculosis

Introduction

Major progress has been made towards achieving global control of tuberculosis (TB) over the past two decades. During 1995–2009, a total of 49 million patients were treated in DOTS programmes worldwide, of whom 41 million were successfully treated, and up to 6 million lives were saved. Incidence rates have been declining globally and in all sub-regions except in certain African countries since 2004. This progress is being threatened by multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), forms of TB that are more difficult and costly to diagnose, treat and cure than drug-susceptible TB. M/XDR-TB is particularly lethal in people living with the human immunodeficiency virus (HIV). In 2008, the World Health Organization (WHO) estimated that 440 000 cases of MDR-TB emerged globally; 85% of its global burden occurs in 27 countries.

The World Health Organization (WHO) has recognized M/XDR-TB as a major challenge to be addressed as part of the Stop TB Strategy, launched in 2006. In April 2009, WHO convened a ministerial meeting of countries with a high burden of MDR-TB in Beijing, China, at which countries committed to tackling the epidemic with innovation and urgency. The Beijing "Call for Action" paved the way for the 62nd World Health Assembly in May 2009 to adopt resolution WHA62.15 on prevention and control of MDR-TB and XDR-TB, urging Member States to take action on multiple fronts towards achieving universal access to diagnosis and treatment of M/XDR-TB by 2015.

What is MDR-TB?

Multidrug-resistant TB (MDR-TB) is caused by bacteria that are resistant to at least isoniazid and rifampicin, the two most effective anti-TB drugs. MDR-TB results from either primary infection with resistant bacteria or may develop during the course of treatment, often due to mismanagement. Extensively drug-resistant TB (XDR-TB) is a form of TB caused by bacteria that are resistant to isoniazid and rifampicin (i.e. MDR-TB) as well as any fluoroquinolone and any of the second-line anti-TB injectable agents (amikacin, kanamycin and/or capreomycin). These forms of TB do not respond to the standard six-month treatment with 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.

Issues for consideration

Despite the important progress being made, severe bottlenecks are limiting the response to the M/XDR-TB epidemic. Indeed, only 10% (24,511 / 250,000) of the estimated MDR-TB cases among notified TB cases in 2009 in the high MDR-TB burden countries, and 11% (30,475 / 280,000) globally were enrolled on treatment. Some countries are making progress by implementing policy changes that rationalize the use of hospitals, such as South Africa, or treating patients through community-based models of care, such as the Philippines. However, diagnostic capacity remains limited. Furthermore, the price of some quality-assured second-line drugs has not fallen, and shortages of drugs still occur. Overall, there is recognition that the response to MDR-TB must be built across health systems, and corresponding plans have been made. It is well accepted that weak health-care systems are often at the root of M/XDR-TB, hampering progress on two major fronts: prevention of the M/XDR-TB epidemic and treatment of those affected. In many countries, both the human and financial resources are grossly insufficient and frequently inadequate.

The Global Fund at its Third Board Meeting (GF/B4/2 [January 2003]) recognized that the Green Light Committee (GLC) provides a package of services for MDR-TB control and determined that Principal Recipients of GF grants would be required to procure second-line anti-tuberculosis drugs through the GLC Initiative (via the Global TB Drug Facility [GDF]). At its Thirteenth Board Meeting (GF/B13/8 (27-28 April 2006)), the GF further determined that CCMs applying for funding of MDR-TB control activities in a proposal under Round 6 and subsequent rounds of funding or in a Request for Continued Funding, must include in such Proposal or Request for Continued Funding provision to share the cost of the GLC Initiative. Resultant to this decision a cost-sharing scheme was introduced in all grants with MDR-TB components to contribute to the efforts made

by the GLC initiative in countries receiving Global Fund grants. This scheme represents a USD 50 000 flat fee for GLC services per grant, per year of implementation of the MDR-TB component.

During 2009, key stakeholders supporting the expansion of MDR-TB services and care concluded that a revision of the global framework that addresses MDR-TB diagnosis and management was necessary. At retreats of partners convened by WHO in October 2009 and February 2010, it was agreed that a new model of coordination and support to countries was needed. The model should **emphasize support to countries rather than control, and advocacy to ensure countries honour the commitments made at the 62nd WHA**. In addition, the new model aims to **increase access to quality assured second line drugs, and provide more, better, and more extensive technical assistance** over the short, medium and long term. Three Task Forces were set up to look into: i) the provision of technical assistance; ii) availability of quality assured second-line TB drugs (SLDs); and iii) monitoring and evaluation, and the governance structure for MDR-TB management scale-up. The three Task Forces worked over 14 months to develop the new framework and presented their recommendations to a meeting of key stakeholders on the "way forward to achieve universal access to diagnosis, treatment and care of MDR-TB" held in Geneva, Switzerland, 22-23 February 2011.

Following the stakeholders meeting, the transition plan was finalized and, with the new global framework to support scale-up of MDR-TB services and care, presented at the 20th Stop TB Partnership Co-ordinating Board meeting in Washington DC, USA, 31 March - 1 April 2011. The Board endorsed the plan and the new global support framework. The main points under the new global support framework to scale-up DR-TB services and care are:

- focus will be on building national capacity to scale-up MDR-TB services and care, via increased technical assistance
- no separate GLC application or approval process, but rather, review of national MDR-TB management expansion plans at time of grant negotiation
- programmes/projects can request directly to GDF for QA second-line drug procurement and supply
- MDR-TB related advocacy activities to be strengthened
- establishment of a strategic committee at the global level (gGLC) with dual role of advising WHO and Partners, with it's Secretariat to be hosted in WHO Geneva
- decentralised regional entities (rGLCs) to be established in a phased manner (Year 1 - AMRO, EURO and WPRO). The rGLC Secretariats are to be housed in a STP partner - in the first three regions this will be in the WHO Regional Offices.

The new framework, with the global and three regional GLCs, will be in place from 1 July 2011.

In light of the new framework for global support to the scale-up of MDR-TB services and care, applicants for Global Fund support for MDR-TB activities should therefore explain their plans for scaling up universal access to diagnosis and treatment of M/XDR-TB by 2015, including a detailed description of MDR-TB activities, the budget and indicators. Activities may include surveillance, prevention, diagnosis and treatment, and/or care and support interventions.

The submission of a National TB Strategic Plan incorporating a DR-TB component (preferable), and/or a specific MDR-TB management expansion implementation plan, is highly encouraged when submitting a proposal to the Global Fund Round 11 that includes DR-TB activities. If the proposal requests funding for MDR-TB, the applicant should click the "Yes" box in Section 6.3 of the application form indicating that USD \$50,000 per year over the full proposal term is to be included in the detailed budget and the funds must be reserved for payment to the GLC Secretariat support services over the period of the proposal. These funds cannot be used for any implementation activities

In its report on Round 10 proposals, the TRP noted that ".. that in many proposals the approach to screening and follow-up of MDR-TB patients was not sufficiently described and recommends that in the future Technical Partners work with applicants to ensure that these issues are

adequately addressed." Please contact the GLC secretariat at glc_secretariat@who.int in case you wish to receive technical assistance specifically to support the preparation of the DR-TB component of the National Strategic TB Plan and GF Round 11 application. In addition, it should be noted that applicants should include in the proposal budget any technical assistance that may be required to implement DR-TB related activities during the proposal timeframe.

Incorporating DR-TB activities in Global Fund proposals

The WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* and its update from 2011 provide guidance on recommended interventions that countries should implement.¹ Interventions are required to cover the diagnosing, treating and caring for people affected by M/XDR-TB, and also those aimed at preventing M/XDR-TB through basic TB control. The Global Fund encourages applicants to work with partners, including WHO, to determine which activities to prioritize to include in their DR TB proposals based on country context.

International guidelines promote integration of services for basic TB control and for MDR-TB within a framework approach, consisting of an essential core of five components based on fundamental principles of TB control and flexible options for country-specific implementation. The core components are comprehensive, ensuring that all essential elements of MDR-TB treatment are included. The design and implementation may vary from one country or region to another depending on the local situation. These core components are:

- 1. Sustained political commitment**
- 2. Appropriate case-finding strategy including quality-assured culture and DST**
- 3. Appropriate treatment strategies that use second-line drugs under proper case management conditions**
- 4. Uninterrupted supply of quality-assured second-line anti-tuberculosis drugs**
- 5. Recording and reporting system designed for DR-TB control programmes that enables monitoring of performance and evaluation of treatment outcomes**

The following DR-TB related activities/interventions are strongly recommended that build on the existing WHO policy and which countries are encouraged to consider:

- Addressing the factors leading to the emergence of MDR-TB
 - Strengthening of National Drug Regulatory Authorities to ensure proper registration, availability, quality, safety and distribution of second-line drugs
 - Strengthening of basic TB control activities, in both public and private sectors
 - Development of appropriate infection control measures and their implementation across all levels of health facilities
- Setting up national level expert DR-TB committee/advisory body to guide DR-TB related policy development and provide oversight of implementation of DR-TB related services
- Establishment of DR-TB management expertise within the NTP structure to ensure proper organization and coordination of DR-TB services with local institutions, the general medical and social services, and other relevant partners
- Conducting appropriate surveillance of DR-TB prevalence among tuberculosis patients
- Appropriate case finding activities based on the local epidemiological situation and local capacity for diagnosis of DR-TB cases

¹ WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008* (WHO/HTM/TB/2008.402). Geneva, Switzerland: WHO, 2008. and WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update* (WHO/HTM/STB/2011.XX). Geneva, Switzerland: WHO, 2011.

- Establishment and/or strengthening of appropriate laboratory services for the diagnosis of DR-TB patients (drug susceptibility testing for first and second line anti-TB drugs), including the introduction of newer and rapid diagnostic technologies.
- Establishment and/or strengthening of appropriate transportation systems of sputa samples for diagnosis and follow-up of DR-TB patients
- Implementation of appropriate models of care for DR-TB cases, including use of in-patient, ambulatory and community based care as required
- Consistent supply of quality assured second-line anti-TB drugs for the treatment of MDR-TB patients at all levels of the health system, with establishment and/or strengthening of stocking and distribution systems
- Mechanisms for the monitoring and management of adverse drug effects
- Increasing human resource capacity through the provision of appropriate standardized DR-TB related trainings for staff at all levels of health systems, adequate pay, motivation of staff and professional recognition, and the provision of supportive supervision activities
- Development and/or strengthening of support systems for DR-TB patients and their families, and staff/treatment providers
- Strengthening linkages with HIV programmes, to ensure appropriate services and care are provided to all HIV-infected DR-TB patients
- Provision of appropriate palliative care for those DR-TB patients who have failed all available curative treatment
- Implementation and/or updating of a, preferably electronic, comprehensive standardized recording and reporting system, which links laboratories, treatment sites, drug stores and programme management units

Further Reading / Resources

This factsheet has been prepared in collaboration with technical partners, using the key resources below. For details and discussions on the strength of the evidence on the above recommendations, applicants are strongly encouraged to review the following key resources:

World Health Organization (WHO). *Beijing "Call for Action" on tuberculosis control and patient care: Together addressing the global M/XDR-TB epidemic*. Beijing, 2009. Available at: http://www.who.int/tb_beijingmeeting/media/en_call_for_action.pdf

WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008* (WHO/HTM/TB/2008.402). Geneva, Switzerland: WHO, 2008.

WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update* (WHO/HTM/STB/2011.XX). Geneva, Switzerland: WHO, 2011.

WHO. 62nd World Health Assembly. *Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis*. WHA62.15. Eighth plenary meeting, 22 May 2009. A62/VR/8.

WHO. *Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response*. WHO/HTM/TB/2010.3. Geneva, Switzerland: WHO, 2010. Available at: <http://www.who.int/tb/publications/2010/en/index.html>.

WHO. *Policy recommendations on the use of liquid culture (2007), second-line drug susceptibility testing (2008), and the use of line probe assays for rapid MDR-TB screening (2008)*. Geneva, Switzerland: World Health Organization, 2007 & 2008. Available at: http://www.who.int/tb/laboratory/policy_statements/en/index.html.

WHO. *Guidance on ethics of tuberculosis prevention, care and control*. WHO/HTM/TB/2010.16. Geneva, Switzerland: WHO, 2010.. Available at: <http://www.who.int/tb/publications/2010/en/index.html>.

WHO. *Guidelines for surveillance of drug resistance in tuberculosis*, 4th ed. Geneva, Switzerland: WHO, 2009. Available at: http://whqlibdoc.who.int/publications/2009/9789241598675_eng.pdf.

WHO. *Antiretroviral therapy for HIV infection in adults and adolescents. Recommendations for a public health approach*. Geneva, Switzerland: WHO, 2006 revision. Available at: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf.

WHO. *Policy on TB Infection Control in Health-care facilities, Congregate Settings and Households*. Geneva, Switzerland: WHO, 2009 (WHO/HTM/TB/2009.419). Available at: <http://www.who.int/tb/publications/2009/en/index.html>.