

# **Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis**

## **Report by the Secretariat**

1. In 2007, the Health Assembly in resolution WHA60.19 noted considerable progress made in tuberculosis control globally since 1991 and acknowledged the WHO Stop TB strategy, which incorporates the internationally recommended DOTS strategy, as a comprehensive approach to global control. Recognizing the alarming emergence and transmission of drug-resistant tuberculosis,<sup>1</sup> Member States were urged to develop and implement plans for prevention and control in line with the Stop TB Partnership's Global Plan to Stop TB 2006–2015 as part of their national health development plans. However, data suggest the problem of multidrug resistance is worsening: in 2008, WHO's fourth global report on anti-tuberculosis drug resistance<sup>2</sup> noted the highest levels of multidrug resistance ever recorded in a general population, with an estimated half a million cases occurring globally, including 50 000 cases of extensively drug-resistant tuberculosis. Recognizing its relevance for global security, the Executive Board agreed that an item on the prevention and control of multidrug and extensively drug-resistant tuberculosis should be added to the provisional agenda of the World Health Assembly.<sup>3</sup> Notwithstanding the achievements over the past decade, prevention and management of drug-resistant tuberculosis require much stronger control which, in turn, requires resolving of weaknesses of health systems. The challenges posed by drug-resistant tuberculosis offer important opportunities to strengthen health systems with the goal of achieving universal coverage for health care.

2. The care and control of tuberculosis have progressed significantly during the past decade and the incidence of new cases is estimated to have fallen slightly each year since 2003. In 2007, 9.3 million new cases are estimated to have occurred and 63% were treated under programmes using the Stop TB strategy, with over 85% treatment success. An estimated 37% of cases worldwide, however, remain un-notified, with patients receiving either no treatment or treatment that is unlikely to reach internationally recommended standards.

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<sup>1</sup> Multidrug-resistant tuberculosis is defined as resistance to at least rifampicin and isoniazid, the two most powerful anti-tuberculosis medicines. Extensively drug resistant-tuberculosis is defined as multidrug-resistant tuberculosis that is also resistant to any one of the fluoroquinolones and to at least one of three injectable second-line antibiotics (amikacin, capreomycin or kanamycin).

<sup>2</sup> Document WHO/HTM/TB/2008.394.

<sup>3</sup> Document EB124/2009/REC/2, summary record of the eleventh meeting, section 3, and the twelfth meeting, section 1.

3. Emergence and spread of multidrug- and extensively drug-resistant tuberculosis are facilitated by inadequate case detection and inappropriate treatment. While country-level data collection and reporting need further improvements, several countries have reported increasing levels of anti-tuberculosis drug resistance. Twenty-seven countries,<sup>1</sup> 15 of which are in eastern Europe and central Asia, account for 85% of the total burden of multidrug-resistant tuberculosis. China, India and the Russian Federation together constitute over half the burden but the problem of multidrug- and extensively drug-resistant tuberculosis is global and present in almost all countries surveyed. Fifty-five countries have, at the time of writing, reported at least one case of extensively drug-resistant tuberculosis, but in most low-income countries the magnitude of the problem is unknown.

4. Altogether countries, in their planning for 2008, expected a total of about only 25 000 patients with multidrug-resistant tuberculosis to be detected and treated, of which about half would have been treated according to internationally recommended standards, representing only about 3% of the 500 000 estimated new cases of multidrug-resistant tuberculosis. Yet treatment is feasible and cost-effective if WHO guidelines are followed, with cure rates of up to 80% among multidrug-resistant cases and up to 60% among extensively drug-resistant cases in low-resource settings. Inappropriate treatment that is not in line with the recommended guidelines runs the risk of raising mortality, increasing resistance and spreading resistance even further.

5. Well-functioning national control programmes with high cure and detection rates are detecting only low levels of multidrug-resistant tuberculosis. Conversely, multidrug-resistant tuberculosis emerges as a result of underinvestment in the Stop TB strategy.<sup>2</sup> The emphasis for action therefore needs to be both on strengthening basic control to prevent the emergence of drug resistance and on diagnosing and treating the cases of multidrug- and extensively drug-resistant tuberculosis effectively in order to prevent transmission. The frameworks for controlling both drug-susceptible and drug-resistant disease exist in the Stop TB strategy and in the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Nevertheless, major obstacles persist, which include: weak general health systems, with consequent gaps in basic tuberculosis control; health workforce crisis; inadequate laboratory capacity; insufficient expansion of programmes to treat drug-resistant tuberculosis; non-engagement of private-care providers; inadequate collaboration between HIV and tuberculosis programmes; problems with production, supply and rational use of anti-tuberculosis medicines; inattention to infection control; insufficient funding for research and development; and inadequate financial resources.

6. Weak national health systems impede basic control and facilitate re-appearance and spread of drug-resistant tuberculosis. Effective control requires appropriate national policies, trained and motivated staff, and quality-assured laboratory- and medicine-supply systems supported by an adequately funded tuberculosis programme. All health-care facilities used by patients with symptoms of tuberculosis must be engaged with general and specialized hospitals, academic institutions and the array of diverse private-care providers need to be involved as a priority. A network of patient-friendly health clinics and staff is essential to ensure that treatment is supervised in a supportive manner and is quality-assured, free of cost, and easy to access. If patients discontinue their treatment, there must be

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<sup>1</sup> These are the countries with 4000 or more cases of multidrug-resistant tuberculosis estimated to occur annually: Armenia, Azerbaijan, Bangladesh, Belarus, Bulgaria, China, Democratic Republic of the Congo, Estonia, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Myanmar, Nigeria, Pakistan, Philippines, Republic of Moldova, Russian Federation, South Africa, Tajikistan, Ukraine, Uzbekistan, and Viet Nam.

<sup>2</sup> Document WHO/HTM/TB/2006.368.

mechanisms to trace them and re-establish treatment. Moreover, informed, motivated and resourced communities can contribute to case finding and adherence support especially in resource-poor settings.

7. WHO estimates that 57 countries, including 36 in sub-Saharan Africa, 15 of them with a high tuberculosis-burden, are facing a serious shortage of health-service providers.<sup>1</sup> Cases of detection and treatment success rates in these countries are generally low. Insufficient workforce, uneven distribution, weak capacity, high workload, frequent transfers, low motivation, and weak supervision are among the important deficiencies. There is no standard solution to resolve these problems, but effective strategies should focus on improving recruitment, helping the existing workforce to perform better, and slowing the rate at which health workers leave the workforce, all in line with a comprehensive strategic plan for human resources for health.

8. Presently, less than 5% of the estimated cases of multidrug-resistant tuberculosis are being diagnosed. Many countries, especially in Africa, lack laboratory capacity to culture *Mycobacterium tuberculosis* and do drug-susceptibility tests. Laboratory capacity, neglected for a long time, needs rapid expansion under international norms and standards, as part of the strengthening of a broader national public health laboratory system; the Global Laboratory Initiative of WHO and partners is helping to enhance coordination of the response. New technologies that can accelerate the diagnosis of drug-resistant tuberculosis are available, but not yet widely implemented, the main obstacle being lack of an adequate, safe laboratory infrastructure and appropriately trained staff.

9. National programmes need policies on where and how to treat drug-resistant tuberculosis cases. In some countries, patients are admitted to hospital for long periods of time, which is labour-intensive and costly, raises important ethical and social issues, and increases the risk of nosocomial transmission if infection control is weak. New models of care enabling safe and effective treatment supplemented by community-based support have proven to be feasible and effective in low-resource settings. To expand treatment services effectively and rapidly, countries will need centres of excellence to ensure adequate capacity building of health-care providers for tuberculosis management.

10. A large proportion of tuberculosis patients are diagnosed and treated in the private sector in many countries and the quality of management is uneven: the patients detected are not notified and their treatment outcomes are unknown. Models of collaboration with the private sector for care and control including management of multidrug-resistant tuberculosis, in which patients do not have to pay for costs of care, have proved effective in resource-poor settings and are necessary for rapid expansion of multidrug-resistant tuberculosis management. Health ministries should involve the private-care sector in ensuring provision of quality treatment through public-private mix approaches linked with the national tuberculosis programme.

11. People living with HIV are more susceptible to developing tuberculosis, including drug-resistant tuberculosis. Also, HIV infection greatly increases the fatality rate among multidrug- and extensively drug-resistant tuberculosis. Improved and strengthened collaboration between tuberculosis and HIV programmes is required to prevent rapid transmission of drug-resistant tuberculosis and resulting high mortality among communities heavily affected by HIV. To this end, WHO recommended that collaborative tuberculosis/HIV activities should be expanded.<sup>2</sup>

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<sup>1</sup> *The world health report 2006: working together for health*. Geneva, World Health Organization, 2006.

<sup>2</sup> Documents WHO/HTM/TB/2004.330 and WHO/HTM/HIV/2004.1.

12. Quality-assured medicines are essential for successful treatment of tuberculosis. Manufacturing processes must meet international standards and the quality of the finished product must be assured. WHO standards for quality medicines are not always observed. Quality-assured fixed-dose combinations, developed as a tool to prevent the emergence of resistance, are not widely used. Inadequate supply of quality-assured second-line medicines has been a major issue. Since 2000, the Green Light Committee, established by WHO and partners, has provided access to medicines that are quality assured to WHO standards, and concessionally priced, for projects worldwide that apply WHO guidelines.<sup>1</sup> Concerted action on the part of governments, drug-regulatory authorities, the pharmaceutical industry, and WHO is required to ensure that adequate and uninterrupted supply of quality-assured anti-tuberculosis medicines are available and accessible to all those in need.

13. Availability of over-the-counter anti-tuberculosis medicines in retail pharmacies and irrational prescriptions by care providers in many countries have facilitated emergence of drug resistance. Some countries have successfully restricted prescribing and dispensing of anti-tuberculosis medicines to accredited facilities where full adherence to internationally recommended standards of treatment can be ensured. Such practices should be encouraged and supported. Countries should also undertake active promotion of rational use of medicines through comprehensive approaches involving drug regulatory authorities, national tuberculosis programmes, health-care providers, the pharmaceutical industry, pharmacists and consumers.

14. Infection control in health-care and institutional settings, essential to prevent disease transmission, has yet to receive adequate attention in the policy and practice of control of communicable diseases such as tuberculosis in resource-poor countries. Recent outbreaks of extensively drug-resistant tuberculosis with high mortality have stimulated activities to institute infection control in some settings. To better protect health-care workers and decrease the risk of tuberculosis transmission in institutional settings, such as correctional facilities and within households, infection control requires engagement with a wide range of stakeholders across the health system including hospital administrators, architects, engineers, as well as doctors, nurses and laboratory staff.

15. Research in tuberculosis has only recently been established on a reasonable scale, although research funding in 2007 showed little increase over 2006. Global control of multidrug-resistant tuberculosis will depend, ultimately, on wide availability of new, rapid diagnostic tests capable of providing results within hours without complex equipment or laboratory biosafety requirements; new medicines to shorten treatment and treat multidrug- and extensively drug-resistant tuberculosis within months rather than years; and a vaccine to prevent tuberculosis, be it drug-susceptible or resistant. Greater attention to and resources for, tuberculosis research are essential.

16. To achieve the target set out in the Global Plan to Stop TB 2006–2015, 1.5 million cases of multidrug- and extensively drug-resistant tuberculosis will need to be treated in the 27 countries with the highest burden in the seven years from 2009 to 2015. The projected number of treated cases increases from 70 000 in 2009 to 382 000 cases in 2015. Combined with a cost per patient treated that is usually in the range US\$ 3000–10 000,<sup>2</sup> the total cost of treating 1.5 million cases amounts to US\$ 11 500 million over seven years, rising from US\$ 500 million in 2009 to US\$ 3100 million in

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<sup>1</sup> By end 2008, the Green Light Committee had approved 60 countries for multidrug-resistant tuberculosis management and treatment for a total of 49 858 multidrug-resistant tuberculosis patients since 2000. Of the 27 priority multidrug-resistant tuberculosis countries, all have Green Light Committee approval, except Nigeria and South Africa.

<sup>2</sup> Costs vary according to the drug regimen, the model of care that is used, and prices of inputs (for example, higher costs for staff are expected in countries with higher incomes).

2015; the latter figure is 43 times the funding available in 2009 and 53% of the total funding required for tuberculosis control. Most funding is required in the European Region (US\$ 7800 million), followed by Asia (US\$ 2800 million). In order to mobilize the required funding for improved management of multidrug- and extensively drug-resistant tuberculosis, preparation of country-specific budgets as part of national strategic plans is the first step that needs to be taken. WHO has prepared a planning and budgeting tool for this purpose. Domestic resources need to be accessed especially in middle-income countries. If sufficient domestic funding cannot be mobilized, countries should make full use of resources available from the Global Fund to Fight AIDS, Tuberculosis and Malaria, the International Drug Purchase Facility (UNITAID), and other donor agencies and funding mechanisms.

### **ACTION BY THE HEALTH ASSEMBLY**

17. The Health Assembly is invited to note the report and provide guidance.

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