REVIEW ARTICLE

CURRENT CONCEPTS

MDR Tuberculosis — Critical Steps for Prevention and Control

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Multidrug-resistant (MDR) tuberculosis is defined as disease caused by strains of *Mycobacterium tuberculosis* that are at least resistant to treatment with isoniazid and rifampicin; extensively drug-resistant (XDR) tuberculosis refers to disease caused by multidrug-resistant strains that are also resistant to treatment with any fluoroquinolone and any of the injectable drugs used in treatment with second-line anti-tuberculosis drugs (amikacin, capreomycin, and kanamycin). MDR tuberculosis and XDR tuberculosis are serious threats to the progress that has been made in the control of tuberculosis worldwide over the past decade.[1,2]

In 2008, an estimated 440,000 cases of MDR tuberculosis emerged globally.[1] India and China carry the greatest estimated burden of MDR tuberculosis, together accounting for almost 50% of the world's total cases. More than three quarters of the estimated cases of MDR tuberculosis occur in previously untreated patients. The proportion of MDR cases among new cases and previously treated cases of tuberculosis reported globally from 1994 through 2009 ranged from 0 to 28.3% and from 0 to 61.6%, respectively (Fig. 1). The highest proportions of MDR cases, and the most severe drug-resistance patterns, appear in the countries of the former Soviet Union. By 2009, a total of 58 countries had reported at least one case of XDR tuberculosis. In eight countries, reported cases of XDR tuberculosis account for more than 10% of all cases of MDR tuberculosis, and six of these countries were part of the former Soviet Union. By far the largest number of cases of XDR tuberculosis has been reported from South Africa (10.5% of all cases of MDR tuberculosis in that country), owing to rapid spread among people infected with the human immunodeficiency virus (HIV).

National programs are failing to diagnose and treat MDR tuberculosis. Globally, just under 30,000 cases of MDR tuberculosis were reported to the World Health Organization (WHO) in 2008 (7% of the estimated total), of which less than one fifth were managed according to international guidelines. The 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 tuberculosis is cost-effective[3] and that treatment of MDR tuberculosis, and even treatment of XDR tuberculosis, is feasible in persons who are not infected with HIV.[4,5]

In some countries, the incidence of tuberculosis is rising, and the incidence of MDR tuberculosis appears to be rising even faster (e.g., in Botswana and South Korea).[6] However, in Estonia, Hong Kong, the United States, and Orel and Tomsk Oblasts (in the Russian Federation), the incidence of tuberculosis is falling, and the incidence of MDR tuberculosis appears to be falling even faster.[1,6] This trend is

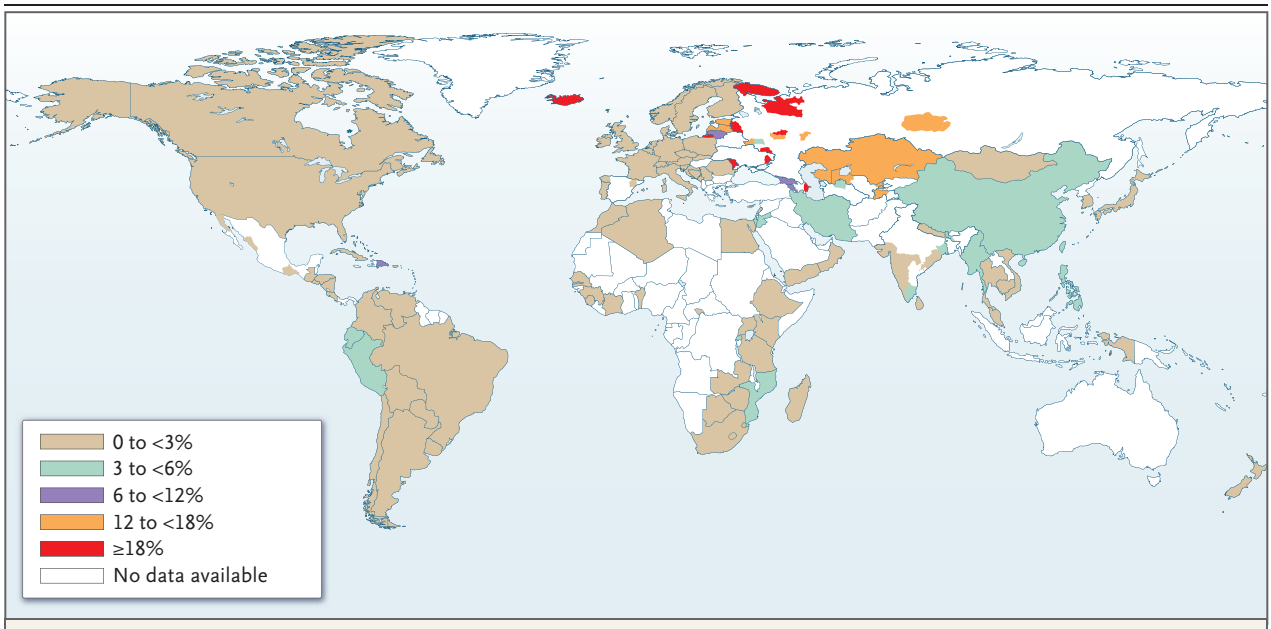

Figure 1. Distribution of the Proportion of Cases of MDR Tuberculosis among New Cases of Tuberculosis, 1994–2009.

The following 27 countries are responsible for 85% of the world's estimated cases of MDR tuberculosis and are classified as countries with a high burden of MDR tuberculosis: China, India, Russia, Pakistan, Bangladesh, South Africa, Ukraine, Indonesia, Philippines, Nigeria, Uzbekistan, Democratic Republic of Congo, Kazakhstan, Vietnam, Ethiopia, Myanmar, Tajikistan, Azerbaijan, Moldova, Kyrgyzstan, Belarus, Georgia, Bulgaria, Lithuania, Armenia, Latvia, and Estonia. Adapted from the 2010 report on MDR and XDR tuberculosis from the WHO.[1]

the result of high-quality care and control practices that result in high rates of case detection and cure, drug-susceptibility testing for all patients, and the provision of appropriate treatment for all patients carrying drug-resistant strains. In short, preventing initial infection with MDR tuberculosis and managing the treatment of existing cases appropriately are the keys to containing the spread of this disease.

The WHO-recommended Stop TB Strategy[7] provides the framework for treating and caring for those who are sick and controlling the epidemic of drug-susceptible and drug-resistant disease. The DOTS approach, which underpins the Stop TB Strategy, calls for political commitment to national programs designed to control disease by means of early diagnosis with the use of bacteriologic testing, standardized treatment with supervision and patient support, and provision and management of the drugs used in treatment; the approach also includes the monitoring of treatment and evaluation of its effectiveness. Between 1995 and 2008, a total of 36 million people were treated successfully with the use of the DOTS approach, and 6 million lives were saved.[8] Specific guidelines for controlling drug-susceptible and drug-resistant disease already exist,[9,10] and the Global Plan to Stop TB, 2006 through 2015, developed by the Stop TB Partnership, specifies the scale at which these interventions need to be funded and implemented to achieve global targets.[11] However, to date, planning, funding, and implementation are falling far behind the milestones that have been set.

Prompted by concern that political support for the management of MDR tuberculosis is insufficient, WHO, the Bill and Melinda Gates Foundation, and the Chinese Ministry of Health organized a ministerial conference in Beijing in April 2009.[12] The report from the conference in Beijing and the subsequent resolution (number 62.15) approved by the World Health Assembly in May 2009 state that significant changes in several components of the health care system must be made if MDR tuberculosis is to be eliminated.[13,14] This review assesses the critical factors impeding control and discusses the solutions required to address them.

CRITICAL WEAKNESSES AND HOW TO ADDRESS THEM

Prevention is better than cure. Thus, the top priority for the control and, ultimately, elimination of MDR tuberculosis is prevention of its emergence.[15] Once MDR tuberculosis has emerged, however, urgent measures are required to curb its effects on efforts to control the disease. The major obstacles and approaches to controlling MDR tuberculosis are described below and summarized in Table 1. Three topics of great importance — the global shortage of health care workers,[16] the need for improvements in surveillance systems,[1] and the urgent need for intensified research on new diagnostic tests, drugs, and vaccines[17] — have been well described elsewhere and are beyond the scope of this article.

FINANCING CONTROL AND CARE

To achieve the goal of universal access to diagnosis and treatment described in the Global Plan to Stop TB, 1.3 million cases of MDR tuberculosis in the 27 countries with the highest burden of MDR disease will need to be treated between 2010 and 2015.[1] The total estimated cost of such treatment is several billion U.S. dollars, an amount far in excess of the existing level of funding. The national strategic plans in these countries must incorporate the preparation of ambitious budgets for the prevention and control of MDR tuberculosis. These plans must be consistent with policies on health care financing, including social-protection schemes (the delivery of commodities to reduce the social vulnerability of poor populations), and with broader planning and financing frameworks. These countries — especially the middle-income countries among them — must mobilize their domestic resources. In 2001, the WHO Commission on Macroeconomics and Health indicated that these middle-income countries could finance all, or almost all, of their health care needs.[18] While maximizing the use of domestic resources, they should also target resources available from international financing organizations, such as the Global Fund to Fight AIDS (Acquired Immunodeficiency Syndrome), Tuberculosis, and Malaria and UNITAID, an organization that provides grants allowing countries to purchase diagnostic tests and drugs used in the treatment of HIV–AIDS, malaria, and tuberculosis. The failure to adequately fund a response to MDR tuberculosis would have catastrophic consequences in terms of both human lives and tuberculosis control in general.

ABOLISHING FINANCIAL BARRIERS

Health expenditures that account for more than 40% of household income (after deducting the cost of basic subsistence) have been defined as catastrophic.[19] In virtually all countries with a high burden of MDR tuberculosis, treatment costs (per course of treatment) for one person are more than 100% of the gross national income per capita (the cost of second-line anti-tuberculosis drugs alone is typically $2,000 to $4,000 per patient).[1] Collective financing mechanisms are therefore required to guarantee universal access to health care. The main source of funding should be domestic resources, such as contributions from taxes, payroll deductions, or mandatory insurance premiums.[20,21] Most countries in Africa, Asia, and the Middle East have not attained universal health coverage,[22] although there are exceptions. Lessons need to be drawn from universal health-financing schemes applied in such diverse settings as Mexico, Rwanda, and Thailand, where access to care may facilitate early detection and treatment of all tuberculosis cases.

Even before universal health coverage is achieved, immediate steps can be taken to reduce catastrophic health expenditures for patients with tuberculosis and their households.[23] These steps include decentralization of services to reduce the indirect costs that patients seeking care incur, provision of patient incentives and social support to promote adherence to treatment, and subsidization of care provided in the private sector that is in line with guidelines from national tuberculosis programs.

ENGAGING ALL CARE PROVIDERS

A substantial proportion of patients with tuberculosis or MDR tuberculosis seek care with providers who are not linked to national tuberculosis programs.[24,25] In five countries with a high burden of MDR tuberculosis, more than half of all sales of first-line anti-tuberculosis drugs occur in the private sector, and the proportion is even higher for sales of second-line drugs.[26] Many physicians in the private sector and some in the public sector do not follow internationally recommended treatment regimens for tuberculosis, use medicines of questionable quality, and ne-

Table 1. Critical Challenges in the Control of MDR Tuberculosis and XDR Tuberculosis and Potential Solutions Supported by the WHO.*

Goal	Problem	Proposed Solution
Finance control and treatment for MDR-TB and XDR-TB	Estimated cost for 2010–2015 is $16.2 billion (in U.S $), increasing annually from <$1.3 billion in 2010 to $4.4 billion in 2015; funding needed is already in excess of the planned national MDR-TB budgets for 2010	Maximize use of domestic resources while targeting resources from the Global Fund to Fight AIDS, Tuberculosis, and Malaria, UNITAID, and other external funding mechanisms
Abolish financial barriers	In countries with a high burden of MDR-TB, treatment costs for a single patient constitute more than 100% of the gross national income per capita	Improve health care financing schemes to strive for universal access to prevention and control; decentralize services to reduce indirect costs; promote patient adherence to treatment; and subsidize care provided in the private sector
Engage all care providers in appropriate MDR-TB prevention and control	A substantial proportion of patients seek care from providers who do not follow internationally recommended standards of treatment	Engage diverse providers (public, voluntary, private, and corporate) to align TB-management practices with WHO International Standards for TB Care
Optimize MDR-TB and XDR-TB management and care	Persons with infectious MDR-TB and XDR-TB remain in the community for long periods of time because of delayed diagnosis and initiation of treatment with second-line anti-TB drugs; hospitalization of patients with MDR-TB or XDR-TB poses problem of nosocomial transmission and is costly and inconvenient for patients	Ensure timely diagnosis and treatment initiation for patients with MDR-TB or XDR-TB; implement appropriate models of care, preferably outpatient, to ensure patient-centered care, avoid disease transmission in health care facilities, and make rational use of financial resources
Address laboratory crisis	In 2008, in 27 countries with the highest burden of MDR-TB, only 1% of patients with newly diagnosed TB and 3% of patients with previously treated TB underwent drug-susceptibility testing	Strengthen laboratory services by using new molecular technologies
Ensure access to quality-assured anti-TB drugs	Use of counterfeit and poor-quality anti-TB drugs, which can lead to development and amplification of drug resistance, is well documented, but there is no accurate estimate of the scale of the problem	Secure affordable, quality-assured anti-TB drugs using national procurement mechanisms while building up a reliable second-line anti-TB drug market, with manufacturers investing in increased volumes and improved quality
Restrict availability of anti-TB drugs	Wide availability of anti-TB drugs over the counter in retail pharmacies encourages self-treatment and the purchase of inadequate quantities and combinations of medicines	Restrict drug availability to accredited providers by combining government policy, agreement with providers and industry on improved marketing practices, and optimization of the protocol for drug management and supply specified by the national TB program
Prioritize TB infection control	Ongoing transmission of MDR-TB and XDR-TB occurs in health care facilities and congregate settings because of inadequate infection control	Engage wide range of stakeholders across the health system (e.g., hospital administrators, architects, engineers, and health care workers), including those concerned with control of other infections with airborne potential, such as influenza, to implement infection-control policies
Address global health workforce crisis	Shortage of trained staff to effectively manage the 1.6 million MDR-TB cases expected by 2015 is exacerbated in many low-income countries by active recruitment of staff by industrialized countries	Revise or update strategic plans for increasing the TB health care workforce (including private health care providers) to improve basic TB control and to scale up MDR-TB control
Improve surveillance systems	Estimates of the burden of drug-resistant TB globally and by country remain incomplete and less than accurate	Establish or strengthen continuous surveillance systems for drug-resistant TB
Invest in research and development of new diagnostic tests, drugs, and vaccines	Tools for prevention, diagnosis, and treatment of TB and drug-resistant TB are obsolete	Ensure collaboration between development and technical agencies to facilitate development and field testing of new tools for prevention, diagnosis, and treatment of TB

* The international group known as UNITAID purchases and distributes diagnostic tests and drugs used in the treatment of HIV–AIDS, malaria, and tuberculosis. AIDS denotes acquired immunodeficiency syndrome, MDR-TB multidrug-resistant tuberculosis, TB tuberculosis, WHO World Health Organization, and XDR-TB extensively drug-resistant tuberculosis.

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glect essential principles of case management.[27,28] Such practices lead to the development, amplification, and spread of drug resistance. In addition, collaboration with public and private hospitals warrants special attention.[29]

Guidance on implementing a mix of public and private approaches to tuberculosis care is available,[30] and many national tuberculosis programs have begun to incorporate diverse sources of care, including public, voluntary, private, and corporate providers. Nonetheless, only a fraction of the tuberculosis cases diagnosed by practitioners outside the public sector are registered with or referred to national tuberculosis programs.[31,32] These approaches should therefore be scaled up and applied to the prevention and management of MDR tuberculosis as well. National tuberculosis programs need to play a stewardship role and provide guidelines, training, technical and financial support, and the supervision needed to align the practices of private providers with the International Standards for TB Care.[33] Effective engagement of diverse care providers will require national tuberculosis programs to both augment their own capacities and strengthen private provider networks to enable them to shoulder their responsibility for managing tuberculosis and MDR tuberculosis. Professional associations need to act as intermediaries between national tuberculosis programs and private providers. Nongovernmental organizations have introduced successful programs for the management of MDR tuberculosis in a number of countries and are key players in scaling up diagnosis and treatment.[34,35]

But collaborative approaches and appropriate incentives alone may not enlist the support of all relevant care providers — some regulation may be necessary. In some countries with a high burden of tuberculosis, providers are not required to notify the government when a new case of tuberculosis has been diagnosed. And even in countries where notification is required, systems have not been established to ensure that the requirement is met. Case notification for both tuberculosis and MDR tuberculosis must be made mandatory; providers who follow best practices should be certified and accredited and should be offered access to free supplies of quality-assured antituberculosis drugs for their patients.[30] Sustainable engagement of all care providers will require national tuberculosis programs to work in close partnership with health professionals, representatives of the pharmaceutical industry, pharmacists, and drug regulatory authorities, in addition to consumer and patient associations.

OPTIMIZING DISEASE MANAGEMENT AND CARE

Transmission of drug-resistant tuberculosis occurs in the community,[36] as indicated by the high frequencies of MDR tuberculosis among previously untreated patients in some countries. In most countries with limited resources, patients with MDR or XDR tuberculosis must complete two unsuccessful courses of treatment with first-line anti-tuberculosis drugs before being eligible for treatment with second-line drugs.[37] Moreover, in many countries, treatment of MDR tuberculosis is started only after the diagnosis has been confirmed, a process that takes months when conventional methods are used. As a result, persons with infectious MDR or XDR tuberculosis remain in the community for long periods of time. Prompt diagnosis and treatment of tuberculosis and MDR tuberculosis can keep the case reproduction number of MDR strains below their replacement rate — and perhaps even below that of non-MDR strains.[6]

Outbreaks of MDR tuberculosis have occurred in hospitals, and patients with tuberculosis who are hospitalized have a higher risk of acquiring MDR tuberculosis than do those who are treated as outpatients.[38,39] Treating MDR tuberculosis in a hospital is more expensive than doing so on an ambulatory basis. Hospital treatment is also more socially and economically disruptive for most patients.[40] In addition, the number of hospital beds may become insufficient as countries expand treatment for MDR tuberculosis. Despite the complexities involved in caring for patients with MDR tuberculosis, including lengthy therapy with poorly tolerated drugs, clinic-based or community-based care has proved to be feasible and effective in several countries, including Nepal[41] and Peru.[42] However, the effectiveness of outpatient care depends on the availability of primary care facilities, qualified health care workers, and social support networks to promote adherence to treatment. Countries need to select the model of care that is right for them, taking into account the personal rights and needs of patients and communities,[43] the numbers of patients who have both MDR tuberculosis and

HIV–AIDS, the social circumstances of patients,[44] the health care infrastructure, and the ability of the country to mobilize resources.

RESPONDING TO THE LABORATORY CRISIS

Weak laboratory capacity remains a serious impediment to prompt diagnosis and better control of MDR tuberculosis.[1] The goal of universal access to drug-susceptibility testing has not yet been achieved. In 2008, drug-susceptibility testing was performed in only 1% of new tuberculosis cases and 3% of previously treated cases in the 27 countries with the highest burden of MDR tuberculosis.

Today, rapid molecular tests for MDR tuberculosis are available.[45] For instance, one new automated rapid test for rifampicin resistance holds promise for easier detection of MDR tuberculosis even in community settings.[46] The implementation of this and other rapid tests, especially in countries with a high prevalence of concurrent HIV infection and MDR tuberculosis, can prevent fatal delays in detection.[47] The establishment of quality-assured diagnostic capacity, including rapid diagnostic technologies to identify MDR tuberculosis, is feasible in resource-limited settings.[48] Use of the new molecular technologies offers one of the best avenues for improving overall diagnostic capacity in the laboratory.[49] At present, however, the adoption of the new rapid tests will not eliminate the need for conventional drug-susceptibility testing with the use of solid or liquid culture. Conventional susceptibility testing is required to determine susceptibility to drugs other than rifampicin and isoniazid.[9] While countries expand laboratory capacity and introduce the new rapid tests, targeted drug-susceptibility testing should be performed in specific groups of patients at risk for drug resistance. Expansion of diagnostic capacity for MDR tuberculosis must be coupled with access to second-line anti-tuberculosis drugs. Efforts to shorten the time required for diagnosis must occur in tandem with measures that minimize organizational delay to ensure prompt initiation of treatment.

ENSURING ACCESS TO QUALITY-ASSURED DRUGS

In 2007, only 15% of reported new cases of tuberculosis were treated with fixed-dose combinations of anti-tuberculosis drugs,[50] despite their logistic advantages and potential to reduce the risk of the development of drug resistance.[51] The use of counterfeit and poor-quality anti-tuberculosis drugs, which can lead to the development and amplification of drug resistance, is well documented, but there is no accurate estimate of the scale of the problem.[52,53] International quality standards have been developed but are often ignored, and an insufficient number of manufacturers have been approved under the WHO Prequalification Programme.[54]

To effectively prevent and manage MDR tuberculosis, countries need to secure affordable, quality-assured, anti-tuberculosis drugs through national procurement mechanisms. Affordable and quality-assured, second-line anti-tuberculosis drugs can also be accessed through the WHO Green Light Committee, which ensures management of MDR tuberculosis that is in line with international quality standards in 70 countries.[1] However, of particular concern for efforts to increase the scale of MDR tuberculosis management is the insufficient supply of quality-assured, second-line anti-tuberculosis drugs.[13] As of April 2010, only two manufacturers that produce three of the seven second-line anti-tuberculosis drugs on the WHO Model List of Essential Medicines had been approved by the WHO Prequalification Programme.[54] Building up a reliable market of second-line anti-tuberculosis drugs, with manufacturers investing in increased volumes and improved quality, requires more accurate forecasting of demand. In addition, national authorities need to expedite the enrollment of many more patients under proper management conditions.

RESTRICTING DRUG AVAILABILITY

Anti-tuberculosis drugs are widely available over the counter in retail pharmacies in many countries.[55] This encourages self-treatment and the purchase of inadequate quantities and combinations of medicines. Even when the drugs are prescribed, those prescribing the drugs outside national tuberculosis programs may not abide by recommended regimens, and some patients may purchase only part of the prescription because of financial constraints.[56] Prescription and dispensing of medicines in general, and of antibiotics in particular, are poorly monitored and regulated in most countries.[57] Even when regulations exist, their enforcement is often insufficient.

An essential step toward improved prevention

of MDR tuberculosis is to encourage the engagement of private and public providers with national tuberculosis programs on a voluntary basis.[30] A more forceful approach would be to restrict the right to prescribe and dispense the drugs to the national tuberculosis program itself or to providers that have been accredited by the program. Either approach would require a combination of new government policy and dialogue with care providers, including pharmacists, and the pharmaceutical industry. Such measures undertaken by national tuberculosis programs to optimize drug management and supply have been successful in some countries, including Brazil, Ghana, Syria, and Tanzania. Consumers also need to be aware of the risks of poor prescribing practices and, as discussed above, the clinical and public health threats posed by substandard medicines.[52,57] Demand-driven efforts to push for more accountability and enforcement of regulations by national authorities may be highly effective. Further advances in social responsibility and improved marketing practices on the part of drug manufacturers are also essential, along with supportive government measures.

PRIORITIZING CONTROL OF TUBERCULOSIS INFECTION

As a result of inadequate measures of infection control, there is ongoing transmission of MDR tuberculosis and XDR tuberculosis in health care facilities and congregate settings (e.g., prisons).[38] To date, virtually no country with a high burden of tuberculosis has implemented systematic measures to reduce the risk of tuberculosis transmission in health facilities.[1] Health care workers, especially those working in tuberculosis hospitals and in resource-limited settings, are at substantially higher risk of contracting tuberculosis and MDR tuberculosis than the general population.[58,59]

All health care facilities that admit patients with tuberculosis or patients suspected of having tuberculosis should implement tuberculosis-control measures that complement general measures of infection control, especially those which target other airborne infections.[60] Home-based and community treatment of MDR tuberculosis should be promoted. To curb the increased risk of nosocomial tuberculosis and MDR tuberculosis among health care workers, some countries have added tuberculosis to the list of recognized occupational hazards.[59] Infection control requires engagement with a wide range of stakeholders across the health care system, including hospital administrators, architects, engineers, doctors, nurses, and laboratory staff. On the policy level, infection control requires collaborative action among those concerned with infections with airborne potential, such as influenza.

THE URGENT NEED FOR ACTION

Critical weaknesses in current approaches to the treatment and control of MDR tuberculosis and XDR tuberculosis have been identified and are being addressed at the global level. In 2009, the Beijing Call for Action[13] and the passage of World Health Assembly Resolution 62.15[14] signaled a major step forward in coordinated planning for the treatment and control of MDR tuberculosis and in the commitment to achieve universal access to diagnosis and treatment by 2015 for patients who have the disease. Resolutions, however, are useful only insofar as they stimulate the appropriate policymakers in governments to act on them. By October 2009, 20 of the 27 countries with the highest burden of MDR tuberculosis were updating their national tuberculosis-control plans to include a component addressing MDR tuberculosis, in compliance with the World Health Assembly resolution. Furthermore, for the countries that have received grants from the Global Fund in its ninth round of grants, funding requested for the management of MDR tuberculosis was by far the largest requested for all aspects of tuberculosis control: more than $500 million (in U.S. dollars) was requested for the management of MDR tuberculosis in 28 countries over a period of 5 years.

Every one of the recommendations in this article for improving the treatment and control of MDR tuberculosis requires action beyond national tuberculosis control programs, sometimes in the political environment outside the health care system. This is a highly ambitious but necessary agenda for health authorities in the affected countries and for the global health community. The steps involved in controlling MDR tuberculosis are also important steps toward strengthening health care systems, including progress in achieving universal health care coverage. If this

policy agenda is not pursued with urgency, the human and financial costs to societies will be profound.

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