



A MINISTERIAL MEETING OF HIGH M/XDR-TB BURDEN COUNTRIES

1-3 April 2009 – Beijing, China

**Addressing
the key bottlenecks hampering the prevention
and scale-up of M/XDR-TB control and patient care**



World Health
Organization



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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is a life-threatening form of TB affecting half a million people every year that causes much higher rates of mortality than drug-susceptible TB. MDR-TB is on the rise in some countries, yet only some 3% of cases are being treated according to standards set by the World Health Organization (WHO). If MDR-TB is not vigorously addressed, it stands to replace the mainly drug-susceptible strains causing 95% of the world's TB today. An urgent response is therefore called for at political and technical levels. It is for this reason that the meeting in Beijing has been convened.

The meeting is organized by the WHO, the Ministry of Health of the People's Republic of China and the Bill & Melinda Gates Foundation.

Objectives of the meeting

1. To build consensus and political commitment in the 27 countries with a high burden of MDR-TB¹ to act immediately in scaling up the prevention and management of MDR-TB, overcoming common bottlenecks and ensuring effective engagement of partners who can assist in these efforts, with the emerging economies at the forefront.
2. To scale up the management of MDR-TB and enable the 27 high MDR-TB burden countries to develop five-year national strategic plans for MDR-TB, incorporated in national TB strategic plans and embedded within national health plans and systems.

Participants

Participants will include Ministers of Health and senior decision-makers from the high MDR-TB burden countries, and those countries with informative experience in MDR-TB; senior representatives of global and regional health and development agencies involved in MDR-TB; affected communities; bilateral development agencies; development banks; foundations, nongovernmental organizations; private pharmaceutical and diagnostic enterprises; research institutions; and technical agencies.

¹ Armenia, Azerbaijan, Bangladesh, Belarus, Bulgaria, China, Democratic Republic of Congo, Estonia, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Myanmar, Nigeria, Philippines, Russian Federation, Pakistan, South Africa, Tajikistan, Ukraine, Uzbekistan, Viet Nam.



Current situation of global TB control

Global control of TB has advanced enormously in the past 15 years. Since 1995, 37 million TB cases have been treated under DOTS programmes and, partly as a result, the global incidence of the disease has fallen since 2003. However, unresolved constraints, principally outside the control of national TB programmes (NTPs) but within the health system, have hampered efforts to advance TB control. Moreover, these same constraints are fuelling the emergence of MDR-TB and extensively drug-resistant TB (M/XDR-TB).

Using surveillance data from WHO and partners generated since 1994, it is estimated that about 510 000 cases of MDR-TB occur every year, of whom tens of thousands are XDR-TB. In some countries, MDR-TB rates are rising, while in others they are falling. For most countries, the data are not yet good enough to predict trends.

M/XDR TB is more difficult and costly to treat than drug-susceptible TB, with significantly higher rates of mortality. People living with HIV are especially vulnerable to M/XDR-TB; and the epidemics of HIV and MDR-TB are already overlapping in Eastern Europe and Southern Africa, leading to fatality rates as high as 98% in one hospital in South Africa. Moreover, very few of the half a million people with MDR-TB are receiving treatment. Countries report that some 5% were expected to have been treated within NTPs in 2008, while around 3% of the total number will have received treatment through the Green Light Committee (an initiative established in 2000 by WHO and partners to support MDR-TB treatment programmes in providing low-priced medicines of assured quality that meet WHO standards).

Background to the meeting

The framework for addressing drug-susceptible and drug-resistant disease already exists and is familiar to most countries, through the Stop TB Strategy, the Global Plan to Stop TB, 2006–2015, and WHO guidelines for the programmatic management of drug-resistant TB.

The second meeting of the WHO Global Task Force on XDR-TB (April 2008) identified slow progress in preventing and managing drug resistance that fell significantly behind the milestones of the Global Plan. It therefore recommended that WHO convene a meeting of the 27 high MDR-TB burden countries as part of a strategy to significantly raise political commitment and country-level involvement and thus scale up the response to MDR-TB. A ministerial meeting was called for because the solutions that are needed necessitate high-level political actions within the broader health system. In fact, the solutions do not lie solely within the authority of the NTP.



Preparatory work at political and technical levels

To raise the awareness and profile of MDR-TB, several meetings were organized in 2008 with officials from ministries of health and NTPs of 10 high MDR-TB burden countries at the Union's World Conference on Lung Health (Paris, France, October), with four central Asian countries (Tashkent, Uzbekistan, November) and with countries of the South-East Asia Region (Malé, Maldives, December). The conclusions of a strategic discussion on TB held at the board meeting of the Global Fund to Fight AIDS, Tuberculosis and Malaria (New Delhi, India, November) included a request for countries to submit sufficiently ambitious proposals to address MDR-TB in the upcoming rounds.

In October 2008, the members and networks of the Stop TB Partnership were informed of the ministerial meeting, and many have been working with countries, including assisting in the development of MDR-TB strategic plans. The Stop TB Partnership is organizing high-level missions to countries with a significant MDR-TB problem. The first mission, to India, was led by Jorge Sampaio (United Nations Secretary-General's Special Envoy to Stop TB and the former President of Portugal). The delegation met with the Minister of Health to discuss the country's needs. Missions to Azerbaijan and South Africa are under discussion.

After Beijing – planning for country-level action

The meeting in Beijing aims to help countries in better responding to the burden of TB and, in particular, to the expanding epidemic of drug-resistant TB. After the meeting, countries are expected to fill in their current gaps in TB control and accelerate the scale up of prevention and management of M/XDR-TB. Ways of achieving this will be discussed on the second and third days of the meeting. WHO and its partners stand ready to provide any technical support that may be needed. In particular, the Green Light Committee and its secretariat are available to support the development of proposals to scale up the management of M/XDR-TB and the procurement of quality-assured medicines, through the Stop TB Partnership's Global Drug Facility (GDF) or quality-assured national suppliers.

To support this process, planning tools are available, or under development, for scaling up MDR-TB control. Some tools have already been used by countries and partners in preparation for the meeting and will be available afterwards. The tools are based on the six components of the Stop TB Strategy (see *Table on page 8*), including the prevention and programmatic management of M/XDR-TB, and will support countries in identifying gaps and needs as well as in guiding their public health response based on cost-effectiveness and priority criteria. The tools are all available through WHO.



After Beijing – global-level action

The Executive Board of WHO agreed to a request from the People’s Republic of China to discuss the item “Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis” at the World Health Assembly in May 2009. A report has been prepared and a resolution will be drafted.

- MDR-TB will be the main theme of the Pacific Health Summit (Seattle, WA, USA, June 2009).
- A meeting of Chief Executive Officers of the diagnostics industry will discuss the development of diagnostics (Annecy, France, June 2009).
- Some of the WHO regional committees will discuss the problem of M/XDR-TB (August and November 2009).
- M/XDR-TB will feature on the agenda of the Union World Conference on Lung Health (Cancun, Mexico, November 2009).



KEY BOTTLENECKS IN M/XDR-TB CONTROL AND PATIENT CARE - EXECUTIVE SUMMARY

In preparation for this meeting, WHO has prepared a series of briefing papers that describe the key bottlenecks to controlling M/XDR-TB and providing care to M/XDR-TB patients, and how they can be addressed. The 10 papers are incorporated in this document and conclude with tables summarizing for each bottleneck the actions required and by whom.

Surveillance data on TB provided by WHO and partners enable the future epidemic to be modelled. These data show, in **Paper 1: Forecasting the control of MDR-TB epidemics**, that both prevention of MDR-TB (“turning off the tap” through improving basic TB control) and diagnosis and effective treatment of MDR-TB cases (reducing transmission in the community of drug-resistant strains) are necessary to reducing rates of MDR-TB in countries where MDR-TB is already established and the rate is high. This can be achieved with existing diagnostics and treatment regimens, but new technology and approaches to diagnosis and treatment are needed to reduce cases and deaths more quickly. There are at least four reasons to intensify case finding and treatment for MDR-TB in all countries: to give the best possible chance of cure to all patients, whether they have drug-susceptible or drug-resistant TB; to accelerate TB decline, and move as quickly as possible towards elimination; to prevent the build-up in populations of drug-resistant, latent infection; and to plan for worst outcomes in the face of uncertainty (be risk averse).

Significant gaps remain in basic TB control. Three of the key ones are outlined in **Paper 2: Addressing the gaps in TB control**. Too often hospitals are a barrier to patients in accessing proper care for TB; a wide array of providers exists, in both private and public sectors, and many give substandard care, while the potential to enlist patients and communities in the provision of proper care is ignored. Mechanisms are laid out to harness the potential of patients and communities, as well as identify all care providers and link hospitals and providers of care of all kinds with NTPs.

Paper 3: Providing M/XDR-TB management and care reflects the complexity of the steps needed to manage, that is diagnose, treat and care for, people with MDR-TB. The paper is not prescriptive but lays out the issues that need to be considered to facilitate decision-making on the best mix of sites to care for patients, whether in hospital or in the community. The ethical dimension of provision of care is addressed because in managing MDR-TB it is imperative to ensure that the rights and duties of patients are assured as well as those of the community. Collaboration in delivery of care for MDR-TB is recommended with all non-governmental structures, including the private sector. HIV is a



major problem for people with MDR-TB, and the collaborative engagement of AIDS control programmes with their TB counterparts, in the problem of MDR-TB, is essential.

Paper 4: Addressing the health workforce crisis calls for countries to develop strategic and operational plans for health workforce development to both strengthen basic TB control and scale up management of M/XDR-TB. Plans need to go beyond traditional training activities and address staffing, motivation, retention and support systems issues. NTPs need to collaborate and coordinate with other health programmes to ensure that health workforce needs for TB control are included in overall health workforce development.

Until WHO's Stop TB Strategy was launched in 2006, global TB control efforts underplayed the need for laboratories. **Paper 5: Responding to the laboratory bottleneck** addresses the gap which has built up and calls for TB laboratory needs to be addressed in strategic plans for the national health laboratory system as a whole. Meeting this gap will require an additional 2000 new or revitalized laboratories capable of culture and drug sensitivity testing to be established and more than 20,000 new laboratory technicians to be trained and deployed. A systematic approach at country level to planning of laboratory costs is essential, starting with clear policies for screening of patients at risk of MDR-TB and applying appropriate diagnostic algorithms using the different modalities available.

Not all countries are insisting on anti-TB medicines that are of proven quality based on WHO standards, or stringent regulatory authority standards according to **Paper 6: Ensuring access to quality-assured anti-TB medicines**. Fixed-dose combinations of first-line medicines are insufficiently used given that they are proven to be at least as effective as loose pills in curing patients of TB and in addition they offer significant practical and logistic advantages. If countries were truly averse to the risk of creation of resistance they would use them much more. WHO and the GDF offer several services to help national drug procurement. With respect to the second-line medicines, insufficient amounts are being produced, even for the relatively few patients enrolled for treatment. Pharmaceutical companies are not yet convinced that there is a return to be made from investing in this market. To break this cycle, governments should commit to scaling up treatment for MDR-TB, thus creating greater demand, enabling more accurate forecasts, and bringing more companies into the supply network.

The unregulated availability of anti-TB medicines, whether first-line or second-line, is fuelling the development of MDR and XDR-TB. **Paper 7: Restricting the availability of anti-TB medicines** calls for governments to ban immediately "over-the-counter" sales of such products. It further advises the accreditation of practitioners in the public and private sectors to prescribe anti-TB medicines and restrictions in the right to carry out prescribing practices to accredited practitioners.



Neglected until outbreaks of MDR-TB and XDR-TB forced the issue of infection control onto the agendas of public health and TB control, **Paper 8: Prioritizing TB infection control** calls for urgent development of national plans, in line with the new WHO policy on TB infection control, to upgrade all health-care facilities to make them safe for patients and health-care workers. This requires a national approach which can be based on existing infection control structures, and administrative, environmental and personal protection measures in all facilities.

Against the backdrop of static research funding for TB, **Paper 9: Maximizing research opportunities to address M/XDR-TB** calls for greater involvement of all governments, especially those of the emerging economies, and funding agencies in research on MDR-TB. Multi-agency and country coordination is recommended to develop new rapid methods for detection of M/XDR-TB and field test them. Similarly, new medicines are urgently needed, as well as the design and funding of randomized controlled trials for treatment and prevention of MDR-TB using both new and available compounds. In addition, opportunities are clearly being missed, to make full use of the funds available for operational research within existing Global Fund grants. One essential area where such funds could be used is in investigating the causes of drug resistance in different settings.

To achieve the target set out in the Global Plan to Stop TB 2006–2015, 1.4 million cases of M/XDR-TB will need to be treated in the 27 countries with the highest burden in the seven years 2009–2015, according to **Paper 10: Financing M/XDR-TB control and care**. The total cost of diagnosing and treating 1.4 million cases (including infection control) amounts to US\$ 16.9 billion over seven years, rising from US\$ 0.7 billion in 2009 to US\$ 4.4 billion in 2015; the latter figure is 61 times the funding available in 2009. Most funding is required in the European Region (US\$ 8.9 billion), followed by Asia (US\$ 7.1 billion). The first step, in order to mobilize the required funding, is the preparation of country-specific budgets as part of national strategic plans for TB control. 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, UNITAID, and other donor agencies and financial mechanisms.



Table. The Stop TB Strategy at a glance, 2009

VISION	A world free of TB
GOAL	To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets
OBJECTIVES	<ul style="list-style-type: none"> • Achieve universal access to quality diagnosis and patient-centred treatment • Reduce the human suffering and socioeconomic burden associated with TB • Protect vulnerable populations from TB, TB/HIV and drug-resistant TB • Support development of new tools and enable their timely and effective use
TARGETS	<ul style="list-style-type: none"> • MDG 6, Target 8: Halt and begin to reverse the incidence of TB by 2015 • Targets linked to the MDGs and endorsed by Stop TB Partnership: <ul style="list-style-type: none"> – 2005: detect at least 70% of infectious TB cases and cure at least 85% of them – 2015: reduce prevalence of and deaths due to TB by 50% – 2050: eliminate TB as a public health problem
COMPONENTS OF THE STRATEGY AND IMPLEMENTATION APPROACHES	
<ol style="list-style-type: none"> 1. Pursue high-quality DOTS expansion and enhancement <ol style="list-style-type: none"> a. Secure political commitment, with adequate and sustained financing b. Ensure early case detection, and diagnosis through quality-assured bacteriology c. Provide standardized treatment with supervision, and patient support d. Ensure effective drug supply and management e. Monitor and evaluate performance and impact 2. Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations <ol style="list-style-type: none"> a. Scale-up collaborative TB/HIV activities b. Scale-up prevention and management of multidrug-resistant TB (MDR-TB) c. Address the needs of TB contacts, and of poor and vulnerable populations 3. Contribute to health system strengthening based on primary health care <ol style="list-style-type: none"> a. Help improve health policies, human resource development, financing, supplies, service delivery, and information b. Strengthen infection control in health services, other congregate settings and households c. Upgrade laboratory networks, and implement the Practical Approach to Lung Health (PAL) d. Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health 4. Engage all care providers <ol style="list-style-type: none"> a. Involve all public, voluntary, corporate and private providers through Public-Private Mix (PPM) approaches b. Promote use of the International Standards for Tuberculosis Care 5. Empower people with TB, and communities through partnership <ol style="list-style-type: none"> a. Pursue advocacy, communication and social mobilization b. Foster community participation in TB care, prevention and health promotion c. Promote use of the Patients' Charter for Tuberculosis Care 6. Enable and promote research <ol style="list-style-type: none"> a. Conduct programme-based operational research b. Advocate for and participate in research to develop new diagnostics, medicines and vaccines 	



1. FORECASTING THE CONTROL OF MDR-TB EPIDEMICS¹

The problem

Treatment for TB, using combinations of four or more medicines, is highly efficacious until some bacteria develop resistance to one or more of these medicines. Then transmission, treatment failure and deaths all rise. A minimum requirement for the elimination of TB is that each case infected with a drug-sensitive or a drug-resistant strain must generate, on average, less than one further case. This paper summarizes work carried out by WHO to (a) determine the scale of the drug-resistance problem worldwide, (b) assess the conditions under which the spread of drug-resistant TB (especially MDR-TB) can be reversed, and (c) set out a plan of action that can meet those conditions. Further details are available from Dr Chris Dye on request.

Number and distribution of drug-resistant TB cases worldwide

There were an estimated 289,000 new MDR-TB cases (3.1% of all new TB patients) in 2007, and 221,000 (19%) among previously treated patients. The number of MDR-TB cases among new and previously treated TB patients is greatest in the South-East Asia and Western Pacific Regions, the most populous areas of the world, followed by Eastern Europe (former Soviet republics). Eastern Europe has by far the highest frequencies of MDR-TB among new (13%) and previously treated patients (47%). Twenty-seven most-affected countries, 15 in Eastern Europe, accounted for 85% of all MDR-TB cases arising worldwide in 2007. China, India and Russia together account for half of all new cases.

Trends in drug-resistant TB and their implications

In the majority of 60 settings examined in 55 countries, there were no discernible time trends – either up or down – in MDR-TB cases. These data come mostly from low-incidence countries, consist of relatively few repeat observations, and include only 5 of the 27 most-affected countries. Because the data are limited, we cannot yet determine regional or global trends in MDR-TB.

In 10 of 13 settings (parts or groups of countries)² where changes in TB incidence have been measured over several years, these time trends show that drug-sensitive and drug-resistant TB are declining under current conditions of TB control. MDR-TB strains are not self-sustaining, and MDR-TB would die out if new cases were not created by

¹ This paper was prepared by C Dye, BG Williams, M Zignol, P Glaziou, A Wright, A Pantoja and W Jakubowiak. It is an abbreviation of a fuller technical paper.

² The 13 settings are three Baltic States, Botswana, Germany, Hong Kong (Special Administrative Region of China), three Russian oblasts, the United Kingdom, United States, a group of five Central European countries and a group of 15 additional Western European countries.



amplification. This means that all strains of TB will continue to decline if control programmes remain at least as good as they are at present. However, many patients unnecessarily fail treatment, and the decline in incidence is slower than it could be.

In 2 settings, MDR-TB incidence was increasing up to 2006, and MDR-TB appears to be self-sustaining under present (or recent) conditions of control. Under these circumstances, it is vital to detect TB patients earlier, and increase the chance of cure for each patient, in order to reverse the spread of resistance.

The remaining country is unique among the 13 because the numbers of cases of drug-sensitive, isoniazid resistant and MDR-TB were all increasing up to 2002, probably due to co-infection with HIV. The most recent case reports (up to 2007) indicate that the total number of TB cases is now falling in this country too, but we do not know whether this is true of drug-resistant TB.

“Universal access” and its potential impact

Where MDR-TB is self-sustaining, the number of resistant cases could go on increasing for decades if control is not improved. In these settings, it is not sufficient to treat drug-sensitive patients successfully in a good, basic DOTS programme. That will have little impact on the spread of resistance, and will increase the proportion of cases that is resistant. The best way to control TB is to diagnose promptly and cure both sensitive and resistant cases. Then, where MDR-TB is increasing, it will be forced into decline; where MDR-TB is already in decline, the number of cases will fall more quickly.

WHO's future planning for the MDR-TB response aims to achieve "universal access" which is the diagnosis and treatment, by 2015, of at least 80% of patients with smear-positive MDR-TB in the 27 countries most-affected. Based on our evaluation of trends, full implementation of such a plan would almost certainly ensure that the spread of MDR-TB will be reversed by 2015, even in those settings where resistant cases have been increasing most rapidly.

Conclusion

In our assessment, it is possible to reverse the spread of MDR-TB with currently available treatment regimens and by improved case finding, even in settings where MDR-TB incidence is high and increasing. "Universal access", if fully implemented, can achieve this.

There are at least four reasons to intensify case finding and treatment for MDR-TB in all countries: to plan for worst outcomes in the face of uncertainty (be risk averse); to accelerate TB decline and move as quickly as possible towards elimination; to prevent the



build-up in populations of drug-resistant, latent infection; and to give the best possible chance of cure to all patients, whether they have drug-sensitive or drug-resistant TB. Even where drug-resistant strains of TB are not self-sustaining, application of the best possible treatments for all patients will promote the fastest possible decline in TB. But with current control techniques and technologies, even the fastest decline will not lead to TB elimination (<1 case per million population) by the target date of 2050. Elimination by mid-century requires a new approach to TB control, including a new combination of diagnostics, medicines and vaccines.



2. ADDRESSING THE GAPS IN TB CONTROL

The common causes of drug resistance are well known. Treating TB with only a single effective drug (monotherapy) was identified as the chief cause of drug-resistant TB 60 years ago. Use of more than one drug may also be tantamount to monotherapy due to poor drug quality, poor drug management practices, wrong prescribing, consuming wrong treatment and poor adherence to treatment. All these causes may be addressed only if sound basic TB control is in place.

Bottlenecks to TB control vary from country to country. **This paper presents some of the major gaps in basic TB control: continuing substandard TB care in hospitals, inadequate engagement of the private sector, and insufficient involvement of TB patients and affected communities.** Addressing these gaps should help both: basic TB control and prevention of MDR-TB. The paragraphs below define each of the bottlenecks separately, discuss possible solutions to address them and outline the actions that need to be undertaken swiftly.

2.1 Strengthening involvement of hospitals in TB control

The problem

Programmatic TB diagnosis and treatment services in most countries are health centre based. However, evidence shows that significant numbers of TB patients continue to present to hospitals. For example, an assessment of case detection in Indonesia showed that private and public hospitals detected three times as many cases as government health centres although none of them were notified to the NTP.¹ According to the national TB prevalence survey in China, 91% of TB suspects who consulted health-care providers first went to a general hospital.²

A recent assessment of a large, one thousand bed hospital in a high TB-burden country in Africa sums up a representative picture of how hospitals provide perfect conditions for generating M/XDR-TB:

Only 18% of those diagnosed with smear positive pulmonary TB in the hospital laboratory completed their treatment and 11% were cured. Clinicians did not

¹ Irawati SR et al. Hospital DOTS linkage in Indonesia: a model for DOTS expansion into government and private hospitals. *International Journal of Tuberculosis and Lung Disease*, 2007, 11(1):33–39.

² *Report on the nationwide random survey for the epidemiology of tuberculosis in 2000*. Beijing, Ministry of Health of the People's Republic of China, 2002.



adhere to the diagnostic guidelines of the NTP. In the TB register, 85% of PTB cases were diagnosed in the absence of sputum microscopy. Chest X-rays alone were used to diagnose pulmonary TB in 45% of the records reviewed. In addition, clinicians failed to document a clinical history suggestive of TB. Only 66 (29%) of the hospital's 225 smear positive pulmonary TB patients reached the clinics for completion of their treatment.¹

Hospitals thus remain the weakest link in the NTP.

For NTPs setting up collaboration is beset with barriers both inside and outside hospitals. Health centres and hospitals are often under different departments within the ministries of health (MoH). Making the more powerful departments responsible for hospitals cooperate in TB control requires serious commitment and coordination. Inside hospitals, interacting with busy, high-profile, specialist clinicians, often indifferent to public health importance of TB management, is problematic and outside the hospitals, establishing referral links with peripheral health centers to achieve the continuum of care for patients from distant regions requires establishing working networks and effective communication among facilities.²

The solution

Some countries have begun addressing the challenge of involving hospitals in TB control. China's well-functioning internet-based disease information system that requires hospitals to report details of all TB suspects and patients presenting to them for TB dispensaries to follow up has contributed to the country achieving the 70% case detection target.³ Hospital linkage within the NTP network in Indonesia tripled case detection in some areas while engagement of medical colleges in India almost doubled case detection in some cities. PhilHealth, the governmental health insurance organization in the Philippines has, in collaboration with the NTP, developed a package of financial incentives for health facilities, public and private, available only to those who are certified and accredited for TB management. While all these efforts have produced results, leakage of patients does occur before and after diagnosis.

Hospital involvement in TB control requires special efforts at all levels. Countries have been addressing the issue by creating special task forces for the purpose at the national

¹ Loveday M et al. A health systems assessment of the Kwazulu-Natal tuberculosis programme in the context of increasing drug resistance. *International Journal of Tuberculosis and Lung Disease*, 2008, 12(9):1042–1047.

² Uplekar M. Stopping tuberculosis: time to turn urgent attention to hospitals [editorial]. *International Journal of Tuberculosis and Lung Disease*, 2008, 12(9):986.

³ Wang L et al. Strengthening involvement of hospitals in TB control in China using Internet-based communicable disease information system [in preparation].



and provincial levels and leading groups or committees within hospitals. Until commitment is obtained, MoH authorities should be faced with evidence on how hospitals complicate rather than contain the problem of TB. Involving specialists, clinicians and nurses in TB control efforts should be possible through promotion of the International Standards for TB Care (ISTC). To create peer pressure so that the standards are put into practice, national associations of health professionals should be mobilized. Once clinicians and nurses are convinced, achieving internal coordination among hospital departments and external networking with peripheral-level health facilities may remain mainly managerial issues.

Urgent actions needed

- Recognize the importance of hospitals in TB control and especially in preventing MDR-TB and commit adequate resources, human and financial, for the purpose.
- Set up a national mechanism to ensure coordination at the highest levels among departments responsible for health centres, general hospitals and specialist hospitals/ medical colleges.
- Prepare an inventory of all hospitals and designate hospitals responsible for provision of TB services through certification / accreditation schemes
- Develop, disseminate and implement guidelines on establishing linkages between hospitals and health centres as well as measures to be implemented within hospitals to ensure seamless care provision for TB suspects and cases, in line with the ISTC.
- In order to make the collaboration sustainable, ensure adequate compensation to hospitals for their input to TB control.

2.2 Scaling up public–private mix for TB care and control

The problem

Steady progress in basic TB control over the last decade notwithstanding, close to 40% of all sputum smear positive TB cases and about a half of all sputum smear negative TB cases do not get notified globally.¹ In absolute numbers, this amounts to around a staggering 4 million sputum smear positive TB cases alone. Do these patients get diagnosed and treated at all? What proportion is diagnosed? Who diagnoses and treats them? Are they managed properly? Who ensures their adherence to treatment? What are their treatment outcomes?

¹ *Global tuberculosis control: epidemiology, planning, financing. WHO report 2009.* Geneva, World Health Organization, 2009 (WHO/HTM/TB/2009.411).



There is enough evidence that a substantial proportion of patients with TB do present themselves to a wide array of health-care providers not linked in any way to the NTPs.^{1,2} Evidence also indicates that many of these patients are managed in inappropriate, non-standardized ways with anti-TB medicines of questionable quality.³ This is further corroborated by available data on sale of anti-TB medicines in the retail private market in HBCs.⁴ Most of these patients are neither notified to the NTPs nor are their treatment outcomes known. There are reasons to believe that mismanaged TB patients unknown to NTPs could be an important source for emergence and spread of MDR-TB.⁵

The solution

A comprehensive, health systems approach to strengthen the supply side of TB care provision is among the most important solutions to turning off the tap of MDR-TB. This should be possible through a rapid scale up of PPM interventions to engage all relevant care providers – private, voluntary, corporate and public – in basic TB care and control. While strengthening their own services, NTPs should also help strengthen other institutions offering TB care by providing overall stewardship, financing, guidance, training, supervision and quality assurance. Appropriate TB control tasks may be assigned to every care provider. Working with hundreds of individual practitioners or health facilities may be beyond the capacity of NTPs. In such circumstances, NTPs should collaborate with professional associations for engaging their networks of practitioners.

Health professionals' associations may require assistance to strengthen their own capacity which NTPs should try and offer. In places where such associations do not exist or are fragmented, it may be worthwhile, from a long term perspective, to encourage and assist in establishing professional associations, or coalitions thereof, for the purpose of TB care and control.

Attention needs also to be paid to laboratories offering TB diagnostic services to help improve access to quality diagnosis. At the same time, NTPs also need to work with relevant national authorities to address two very important issues: ensuring the quality and supply of medicines and enforcing their rational use.

¹ *Assessing tuberculosis prevalence through population-based surveys*. Manila, World Health Organization Regional Office for the Western Pacific, 2007.

² Dewan PK et al. Public-private mix in India: improving tuberculosis control through intersectoral partnerships. *British Medical Journal*, 2006, 332:574–578.

³ Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. *Lancet*, 2001, 358(9285):912–916.

⁴ *Pathway to patients: charting the dynamics of the global TB drug market*. New York, NY, Global Alliance for TB Drug Development, 2007.

⁵ Uplekar M, Lönnroth K. MDR and XDR: price of delaying engagement with all care providers for control of TB and TB/HIV. *Tropical Medicine and International Health*, 2007, 12(4):473–474.



Urgent actions needed

- Intensify efforts to identify TB service providers outside the scope of NTPs and engage them to ensure that all TB patients receive care in line with the ISTC.
- Formulate/modify policies to enable securing and providing human and financial resources, support and supervision for scaling up PPM programmes.
- Make professional associations close partners in TB care and control investing in strengthening their capacity if required.
- Engage private laboratories to improve access to diagnosis, providing them with support, training and quality assurance services.
- Measure contribution of diverse care providers to TB control and adapt policies and strategies to optimize it.
- Ensure quality and enforce rational use of anti-TB medicines available in the private market (see background paper: “Stop wasting precious drugs!..”).

2.3 Increasing involvement and empowerment of patients and communities

The problem

Today, too few people with TB and affected communities are empowered to express their needs, engage actively in TB control and prevent infection and disease. Without ways to expand their access to and involvement in quality care and prevention, they are at high risk of facing conditions that contribute to the spread of drug-resistant TB. They may not have access to information about TB and related services; they often have misconceptions about the disease that influence their health-related behavior; and, they nearly always face barriers to care -- physical, financial, social, and/or cultural.

There is sufficient evidence in support of effectiveness and cost-effectiveness of community involvement. Some countries do also have interventions in place to involve communities in TB control. However, the scarcity of information on the scope and nature of community interventions seem to indicate that this may not be a priority. Too often, over-burdened control programmes and health workers lack the capacity and impetus to stimulate and support partnerships with patients and communities. This may result from prioritizing medical services, shortages of workers, and limited training to reach out from health services and into communities.

The solution

The Stop TB Strategy calls for empowerment of people with TB, and communities, through: advocacy, communication and social mobilization (ACSM); community participation in TB care; and use of the Patients’ Charter for Tuberculosis Care, which lays out the rights and responsibilities of TB patients. The Strategy also calls for



measures to improve access to treatment. It explicitly includes patient support as essential to effective treatment. Provision of incentives and enablers (food, transport vouchers, etc.) has helped address obstacles to care seeking among some vulnerable populations – these require careful thinking in order to ensure impact and sustainability.

Now there are more opportunities and resources available for community and civil society initiated efforts, especially through Global Fund support as well as bilateral and national resources. Some national medium-term TB control plans now have explicit community-involvement strategies. However, to ensure that such strategies are more widely implemented, and yield desired results, more could be done at different levels. National Stop TB Partnerships and other community health networks can help. Collaborating with those working against other major disease pandemics and health problems can be a critical step forward. Communities working to expand access for HIV care have joined with those working on TB, thereby greatly increasing the voice, influence and impact of such efforts.

New approaches to health workforce development should help. These include the development of additional cadres of health workers based in the community and/or mobilized from the community, reinforced pre-service and in-service training of current staff to build their capacities, and new ways to retain health workers, especially in rural and per-urban areas. In addition, drawing other care providers in the private, and NGO sectors will help, and ensuring that the needs, ideas and concerns of communities and civil society are formally sought out and heard.

Urgent actions needed

- Ensure that health sector plans include active steps to increase the involvement of affected communities in the design, implementation, monitoring and evaluation of health promotion, preventive and curative services.
- Support efforts to improve the health workforce, and engage all available partners to help address TB and other public health priorities through primary health care.
- Identify and remove barriers to care for poor and other vulnerable communities.
- Mobilize resources to support community-level partnerships and local initiatives.
- Ensure communications that increase awareness of how to prevent the spread of TB, including its drug-resistant forms, through early detection of those who are ill and through quality care.



3. PROVIDING M/XDR-TB MANAGEMENT AND CARE

Countries are facing major challenges the management of M/XDR-TB. This paper will focus on the challenges related with the models of care (hospital-based vs. outpatient care) selected to treat patients with MDR-TB and the proposed measures to tackle those challenges, namely, the balance between hospital-based and out-patient care in the context of social support and community-based care, ethics of treatment and care, involvement of all health-care providers (including hospitals), and the needs of persons with HIV.

3.1 Hospital-based versus outpatient care

The problem

Treatment and care of MDR-TB is *demanding*, relatively *complex*, and *costly*. MOHs are quite often relying on models of care that are not suitable to the needs of patients, are not in line with WHO guidance, reduce the impact of treatment, and/or are not cost-effective. The chief *demands* come from the length of therapy (two years) and the need to deliver directly observed treatment (DOT) using a patient-centered approach. The *complexity* stems from the following facts:

- Second-line anti-TB drugs (SLDs) produce a higher frequency and more severe adverse reactions than first-line anti-TB drugs (FLDs), especially during the first six to twelve weeks of treatment. Poor management of adverse drug reactions contributes to high treatment default and extended period of transmission of M/XDR-TB
- Coinfection with HIV may require frequent or lengthy hospitalization
- Proper infection control measures should be available in hospitals whenever TB patients are hospitalized; and at the household level to reduce contamination of air with the bacilli; but these practices should not promote or increase stigma
- Monitoring of the response to treatment is based on culture and not only smears
- Public hospitals and the private health sector are quite often the initial, single or intermittent provider of M/XDR-TB care
- Protecting the community and health-care workers from infection while treating patients raise major ethical issues
- Case-holding is complicated when patients migrate to settings with uneven capacities in place to manage M/XDR-TB

The high cost of MDR-TB management is mostly the result of the cost of SLDs; use of hospitalization (up to 50% of the total cost of treatment in middle income countries); and the size of the workforce necessary to diagnose, treat and care.



The solution

Countries have been tackling *demands, complexity, and costs* of M/XDR-TB management by implementing one or two different models of care:

- *Out-patient care*, which consists of treating patients on ambulatory basis from the start of treatment and hospitalizing only for medical reasons. The chief advantage of this model is the social acceptability by patients; its lower cost; and the lower risk of nosocomial transmission. The successful implementation of this model depends, to a large extent, on i) the availability of a strong social support network to promote adherence to treatment through information and education on the disease, psychological counseling, and enablers to deal with socio-economic barriers; and ii) on the availability of a network of primary health-care facilities with health-care workers properly trained on M/XDR-TB management.
- *Hospital-based care*, which consists of hospitalizing patients until they become culture negative (usually during the first six months of treatment); followed by outpatient care. The main advantages of this model are the easier implementation of DOT; the probable lower transmission of infection to household contacts and community in general; and the easier training of health-care workers that are not familiar with SLDs. The successful implementation of this model depends on the availability of funds and beds to support hospitalization for long periods; proper infection control measures in hospital wards; and the implementation of basic ethics and legal principles that guarantee respect and promotion of human rights. The higher frequency of other medical conditions among those co-infected HIV makes more frequent the need to hospitalize these patients.

Out-patient care happens in both models since hospitalizing for two years is not an option for obvious reasons, ranging from costs to social acceptability. Despite the high costs, M/XDR-TB treatment is cost-effective compared to international benchmarks and measured in disability adjusted life years (DALYs) averted, both in settings using hospitalization during the initial phase of treatment and in those treating on out-patient care basis during the full course of treatment. However, there are no studies looking at the cost-effectiveness of hospital-based care in low resource settings. One model is not necessarily better than the other, and both may coexist. However, depending on the patient needs and the capacity in place, one model may be preferred over the other. In a small size country, for example, that plans to treat thousands of cases every year, it is very unlikely that there is hospital capacity ready available to properly treat these patients, making out-patient care the preferred option. However, hospitalization may be the preferred choice in the case of HIV infected patients during the initial phase of treatment; in the absence of social support networks that promote treatment adherence; or when



primary health-care workers properly trained in the management of adverse effects are lacking or insufficient.

Urgent actions needed

Overall, the countries should select models of care to manage M/XDR-TB after having conducted a thorough analysis of, at least, the following factors:

- Patient needs and his/her preferred options to adhere to treatment
- Local law and ethics standards
- Engagement of private sector and public hospitals in M/XDR-TB management
- Hospitals with infection control measures in place
- Estimated number of patients to treat and hospital-bed capacity
- Funding to guarantee the health-care workforce needed to deliver DOT
- Primary health-care workforce properly trained on MDR-TB management
- Burden of HIV among MDR-TB patients to be treated and level of collaboration established with HIV control programmes
- Laboratory capacity in place to monitor response to treatment
- Attitudes of caregivers to the different options of care
- Social support networks that facilitate a patient-centred approach to DOT
- Capacity to educate, and not only to train, patients on hygiene and infection control measures at household level
- Geographical access to points of M/XDR-TB care

WHO, Stop TB Partnership and technical agencies to assist countries in conducting the analysis to create models of care that meet the needs of the patients and are feasible and cost-effective in the health system.

The WHO Guidelines for the programmatic management of DR-TB define a framework for M/XDR-TB treatment drawing on the five components of the DOTS strategy.¹ The Green Light Committee Initiative of WHO and the Stop TB Partnership supports the piloting and scaling up of MDR-TB management, and promotes the best standards of care drawing on WHO guidelines.² In the next sections, we discuss in more depth some fundamental components of that framework that should be carefully examined when selecting and implementing a model of M/XDR-TB care and their respective challenges.

¹ *Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008.* Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402).

² http://www.who.int/tb/challenges/mdr/greenlightcommittee/faq1_initiative/en/index.html



3.2 Ensuring that TB treatment and care are consistent with ethics and human rights norms and promote social justice

The problem

In some circumstances, personal dignity and rights of patients have been compromised in the process of TB care and control, and fundamental ethical norms for public health and clinical practice may not have been applied. Steps taken by some Governments, service facilities and providers in the interest of protecting public safety may have included measures that have not effectively balanced the protection of the health and rights of the public and those of persons suspected to have TB or with confirmed TB. In the face of worries about M/XDR-TB, public emotions linked to poor information and stigma, severely strained manpower and resources, all may further complicate and compromise careful decision-making. In some instances this has led to severe restrictions on rights, such as broad rather than exceptional use of involuntary detention or isolation. Ethically-compromised practices may also be linked closely to inequitable access to, and quality of, prevention, care and health promotion related to TB and other health challenges. Poor, vulnerable and highly marginalized groups are most likely to become infected with TB and to suffer poor outcomes when illness occurs.

Many NTPs may currently have incomplete answers and policies to questions relevant to the ethical design and conduct of services, particularly in light of MDR-TB, for example: (a) what are best practices for care of patients and infection control if M/XDR-TB is suspected and diagnostic tests and second-line medicines are not yet readily available? (b) if adequate TB infection control practices are not yet in place in major hospitals where should infectious TB patients be initially treated? (c) what are the limits of health-care workers' "duty to treat", especially when proper infection control measures are absent? (d) what human rights principles and local laws are being applied in decision-making regarding the use of involuntary detention? (e) are the International Standards of TB Care, the Patients Charter for Tuberculosis Care, International Health Regulations, and ethical standards in TB research and surveillance being applied?^{1,2,3} Though the answers to some of these questions may vary with local context, capacity ready available to answer these questions under a sound ethical framework is weak or may even be absent in some countries.

¹ *The international standards for tuberculosis care*. The Hague, Tuberculosis Coalition for Technical Assistance, 2006.

² *The patients' charter for tuberculosis care*. World Care Council/Conseil Mondial de Soins, 2006 (www.worldcarecouncil.org/).

³ http://www.who.int/tb/features_archive/involuntary_treatment/en/index.html



The solution

To help prevent or address such problems, countries should:

- pursue overall aims of primary health care, universal health coverage, and the upholding of human rights, social justice and development;
- apply all six components of the Stop TB Strategy for effective TB detection, diagnosis, treatment and prevention, and with recognition of the need to address all forms of TB and to serve all persons in need, and especially the poor and vulnerable;
- strengthen capacities to develop and apply ethically-based TB care and control policies, drawing on all available guidance and best practices. This includes involving ethics advisory bodies at the national or facility level, seeking technical assistance.

Urgent actions needed

- NTPs should explicitly consider ethical issues related to policy and service provision.
- WHO, with the assistance of a WHO Task Force on Ethical Issues in TB Control and broad stakeholder consultation, to complete guidelines by early 2010 to help support sound ethical practice in TB control for use by NTPs, all stakeholders involved in TB prevention, treatment and care.
- Ministries of health and NTPs may wish to create their own task forces on ethical issues to consider key immediate questions as they develop MDR-TB response plans. Relevant legislation may also be required.

3.3 Involving all health-care providers, including public hospitals

NTPs in many high TB-burden countries have not had the capacity to treat M/XDR-TB patients. Many of these patients were managed, and continue to be managed, outside NTPs. Countries with a large burden of M/XDR-TB- do have the capacity to diagnose M/XDR-TB cases in the private sector. For example, a network of private laboratories in India diagnosed about a thousand MDR-TB cases in 2007. Laboratories in large hospitals in China and Indonesia are also equipped to diagnose drug-resistant TB. In the absence of any formal links with NTPs, the quality of diagnosis, treatment and care by these private providers remains questionable.



The market for SLDs in high M/XDR-TB burden countries is large. However, unlike FLDs, a large proportion of which are bulk-purchased by NTPs, most if not all SLDs are sold in the private retail market. The prescribers and the receivers of MDR-TB medicines are not known to NTPs and efforts are rarely made to identify them.

There are concrete examples of private institutions undertaking M/XDR-TB management. The Aga Khan University hospital in Karachi, Pakistan, has a good working programme on MDR-TB management. Indus hospital, a state-of-the-art, multi-speciality, philanthropic hospital in the same city, financed by expatriates, recently set up a community based MDR-TB management programme on the lines of that run by Partners in Health in Peru. A few NGO and private hospitals in India undertake proper management of MDR-TB patients. A remarkable example has been the Tropical Disease Foundation hosted by Makati Medical Centre -- a modern private multi-speciality hospital -- in the Philippines, which was the very first project approved by the Green Light Committee. Almost every care provider can play important role in the management of drug susceptible TB. However, in view of the complexities involved, treatment and care of M/DR-TB has to be undertaken by specialist care providers affiliated to institutions equipped to provide the support required. Treatment supervision may be community-based but it has to be backed up by expert support. Public-private mix initiatives need to be tailored to the requirements of programmatic management of MDR-TB.

The emergence and spread of M/XDR-TB is likely to be checked only through a rapid scale up of programmatic management of M/XDR-TB. This is unlikely to happen if NTPs focus their attention on public sector institutions alone. A sequential approach of waiting to first strengthen public sector laboratories and treatment centres and then begin supporting non-programme structures may not help achieve the necessary pace either. NTPs ought to take a more comprehensive approach of identifying, strengthening and making operational, an adequate number of selected facilities from all sectors: public, voluntary, private or corporate. For example, following the Philippines example, if addressing quality or other related issues in some NGO or private institutions is likely to take time or investment than setting up a public sector institution from the scratch, work must begin on both fronts simultaneously. If there is no capacity in the public sector to undertake both, capacity outside the programme must be harnessed at the same time to meet the requirements.



Urgent actions needed

- TB technical partners should help NTPs undertake a situation assessment of M/XDR-TB diagnosis, treatment and care in the country encompassing all public, private, corporate and voluntary sectors.
- NTPs should conduct a mapping to understand the sources of M/XDR-TB patients and the places where they are currently diagnosed and treated.
- NTPs should understand M/XDR-TB diagnosis and treatment practices among other laboratories and care providers and assess their appropriateness.
- NTPs should assess the strengths and weaknesses of non-programme laboratories and care providers and their potential to collaborate in scaling up M/XDR-TB management.
- NTPs should undertake phased involvement of willing non-programme laboratories and institutions in M/XDR-TB management by first establishing linkages with them and harnessing their capacity to deliver.

3.4 Collaborating with HIV programmes to strengthen both TB and HIV control

The problem

People living with HIV have a higher risk of M/XDR-TB, with an increased mortality up to 90% or more, and greatly reduced survival time. Early diagnosis and treatment of drug resistant TB is thus essential but complicated. Management of drug-drug interactions with antiretroviral therapy (ART) and anti-TB treatment is also a major challenge, due to frequent severe toxicities and adverse events experienced when combining SLDs and ART.

Of the 27 MDR-TB priority countries, 12 are also TB/HIV priority countries.¹ These countries contain $\frac{3}{4}$ million HIV related TB cases, 54% of all HIV related TB globally.²

HIV is probably accelerating the spread of M/XDR-TB, especially in countries where prevalence of infection with M/XDR-TB is high. New HIV infections are stable or on the rise in those countries with higher proportions of MDR-TB cases including China, the Russian Federation, Ukraine and Latvia necessitating urgent actions to address the overlapping epidemics.³ Although not well studied the problem is a public health concern in sub-Saharan Africa also.

¹ China, the Democratic Republic of the Congo, Estonia, Ethiopia, India, Indonesia, Myanmar, Nigeria, the Russian Federation, South Africa, Ukraine and Viet Nam.

² *Global tuberculosis control: epidemiology, planning, financing. WHO report 2009.* Geneva, World Health Organization, 2009 (WHO/HTM/TB/2009.411).

³ Report on the global HIV/AIDS epidemic 2008, UNAIDS.



The solution

In order to obtain a better understanding of the extent and magnitude of the overlap between HIV and TB drug resistance we must incorporate HIV status in drug resistance surveys. We must also explore synergies between HIV and TB drug resistance surveillance.

By 2007, only 11% of all TB patients in the 27 MDR-TB priority countries were tested for HIV, which is up from 2% in 2004. One out of four (25%) of those tested for HIV were found to be positive and almost a third (29%) of these were placed on antiretroviral therapy (ART). Building further on this experience, nationwide scale up of collaborative TB/HIV activities through strengthened collaboration between national TB and AIDS control programmes need to ensure:

- HIV testing of all TB patients and suspects, including those with both drug susceptible and drug resistant strains;
- intensified and prompt TB case finding mainly by HIV service providers;
- early diagnosis and treatment of drug susceptible and drug resistant cases among people living with HIV;
- TB prevention once active disease has been excluded;
- the institution of TB infection control measures in all HIV care settings.

In settings where there is extensive overlap between drug resistance and HIV, and where early diagnosis is difficult, provisions to put patients on empirical treatment for drug resistant TB will avert unnecessary death of people living with HIV.

Enhanced access to better and quicker TB diagnosis (including culture technologies and molecular tests), particularly among people living with HIV, will identify drug susceptible and resistant strains for appropriate treatment. Exploring synergistic opportunities between HIV and TB laboratory initiatives will benefit both sides.

For all of this to happen there will need to be improved collaboration between TB and HIV stakeholders to include MDR-TB and XDR-TB in TB and HIV strategic planning and to generate the political commitment for action and resource allocation. Increased engagement of community groups will empower communities to act to prevent the spread of TB and generate demand for collaborative TB/HIV services, including prompt TB prevention, diagnosis and treatment.

Operational research on optimal models of care for people living with HIV, including clinical trials for shorter and more efficacious co-treatment (anti-TB medicines and ART), is also part of the solution.



Urgent actions needed

- To map extent of the problem by including HIV testing as a standard in national TB drug resistance surveys.
- Nationwide scale up collaborative TB/HIV activities.
- Scale up the access for better TB diagnostic capacity in PLHIV including culture technologies and molecular tests.
- Increased engagement of community groups.
- Improved collaboration between TB and HIV stakeholders and political commitment.
- Basic and operational research on optimal models of care in HIV related M/XDR TB.



4. ADDRESSING THE HEALTH WORKFORCE CRISIS

“We have to work together to ensure access to a motivated, skilled, and supported health worker by every person in every village everywhere.”

Dr LEE Jong-wook, Director-General, WHO (high-level forum, Paris, France, November 2005)¹

The problem

The Global Plan to Stop TB 2006–2015 urges a dramatic scale-up of MDR-TB diagnosis and treatment. A 2007 addendum calls for the treatment of 1.6 million MDR-TB patients by 2015. Currently, about 20,000 MDR-TB patients per year (less than 5% of the estimated incident MDR-TB cases) are being treated within NTPs.² To effectively manage and treat 1.6 million MDR-TB patients by 2015, a significant amount of additional skilled staff will be needed.

Not only the scale up of effective MDR-TB management, but also the effective prevention of MDR-TB, will depend on sufficient attention being given to human resource development (HRD). DOTS has been expanded rapidly in many countries. However, the expansion has not always been accompanied by adequate and continuous efforts to ensure sufficient training of staff, supervisory capacity and collection of essential human resource management information. This has had a severe effect on the quality of some programmes. In a survey of the 22 TB high burden countries (HBC), 17 out of 22 NTP managers identified inadequate human resources as the most important constraint for reaching TB control targets. Evidence from programme reviews in many HBC have shown that there is often inadequate central and peripheral level human resource capacity to ensure basic TB service quality, let alone capacity for expanding services into new interventions such as the diagnosis and management of MDR-TB.³

The additional threats to the workforce posed by the HIV/AIDS epidemic, the increased demands on already overstretched health systems, and the stigmatization of some health-care related occupations, have had a devastating effect on the availability of health workers in many countries. WHO estimates that 57 countries are facing a critical shortage

¹ *The world health report 2006 – working together for health*. Geneva, World Health Organization, 2006 (available at <http://www.who.int/whr/en/index.html>);

² *Global tuberculosis control: epidemiology, planning, financing. WHO report 2009*. Geneva, World Health Organization, 2009 (WHO/HTM/TB/2009.411).

³ TB Control in the South-East Asia Region. Report of the annual meeting of NTP managers 2005 and 2007. SEA-TB-276 and SEA-TB 310 resp
Fourth Review of the NTP in Thailand 2007 SEA-TB-306
Report of the Joint External TB Monitoring Mission, Indonesia, 16-27 April 2007, Bakati Husada and the Stop TB Partnership



of health service providers,¹ and 15 of those countries are TB HBCs. The health workforce crisis in TB control is therefore very clearly linked to wider health systems constraints.

The shortage of staff is exacerbated in many low-income countries by active recruitment for health-care workers on the part of the industrialized countries.

The solution

An imperative step to improve basic TB control and scale up of MDR-TB control is for ministries of health, NTPs and partners to urgently give the highest priority to HRD for the implementation of all components of the Stop TB strategy. An increased financing of HRD activities is a necessary part of that commitment. There are no simple solutions to the health workforce crisis. Whatever the circumstances however, effective short and long term workforce strategies to prevent MDR-TB and scale up MDR-TB control focus on addressing the three core challenges in HRD:

- improving recruitment;
- helping the existing workforce to perform better (including quality training);
- slowing the rate at which health workers leave the health workforce.²

Experience from a number of countries has shown that HRD is possible with determined and sustainable action and support from internal and external technical and financial partners:^{3,4}

- Indonesia, for example, used a strategic approach to HRD from 2000 onwards. It included assigning a dedicated focal point for HRD within the NTP, the systematic review of existing competences based on task analysis and functions, the revision of existing training programmes and training material and the development of task and level specific training material for skills development; regular supervision to identify staff turnovers and performance problems; and organization of continuous education. External funding was used to recruit additional staff at central and provincial levels. These HRD steps were associated with a more than three-fold increase in case notification of new smear positive TB, from 52,000 to 175,000 cases between 2000 and 2006. Treatment success rates were sustained at over 85% and reached 91% in 2005.^{5,1} Although it is not possible to determine how much of the incremental success

¹ *The world health report 2006 – working together for health*. Geneva, World Health Organization, 2006.

² *The world health report 2006 – working together for health*. Geneva, World Health Organization, 2006.

³ *Malawi's Emergency Human Resource Programme*, 2008

(http://www.who.int/workforcealliance/knowledge/case_studies/malawi.pdf).

⁴ Framework of the Indonesian Strategic Plan for Tuberculosis Control: 2006–2010.

⁵ *Annual TB Report 2005, Indonesia*. Jakarta, Ministry of Health of the Republic of Indonesia, 2006.



can be attributed to HRD, these key HRD steps were essential to ensure effective service delivery.

- Other countries (e.g. Bangladesh, Ethiopia, India, Kenya, Myanmar, Philippines, the United Republic of Tanzania) have used external funding to implement activities aimed at addressing key challenges. Resources have been allocated for: “top-up” of salaries; effective and increased supervision; organization of regular review meetings at all levels; strengthening collaboration with NGOs and the private sector; improving the working environment; and by contracting staff to fill critical gaps in the health system.
- Broader health-system wide HRD initiatives, such as the Emergency Human Resources Programme (EHRP) in Malawi, have been used as a basis for improved human resources for TB control. There is already evidence that the EHRP, which focuses on retention, deployment, recruitment, training and tutor incentives for 11 priority cadres, has resulted in a reduction in nurse emigration, increased enrolment in training programmes, and increased numbers of health staff: 40% more doctors, 50% more clinical officers and 30% more nurses in post in 2007 than in 2003.

Scaling up of pre-service training is a longer term goal, as the impact is not felt immediately due to training lag-time, and because expanding training capacity requires investment in people and infrastructure that itself takes time.

Urgent action needed

- Ensure that HRD needs for basic TB control and needs for scale up of MDR-TB control are included in overall health workforce planning and development.
- Revise/update strategic HRD plans (including private health-care providers) to improve basic TB control and to scale up of MDR-TB control.
- Collaborate and coordinate with other public health programmes, with other departments and services in the ministry of health (especially hospital and diagnostic services administration) and with other units in the provincial/district health services.
- Develop medium-term implementation plans to enable alignment with general HRD strategies and plans.
- Collaborate with HRH planning units/departments of MOH, donors and technical support agencies in long term HRD within health system development for staffing and retention.
- Include resources for technical assistance for revision/updating of the HRD in proposals to GF and other donors.

¹ *Report of the External Monitoring Mission, Indonesia, 7–18 March 2005.* New Delhi, World Health Organization (SEA-TB-280).



5. RESPONDING TO THE LABORATORY BOTTLENECK

The problem

Care of patients with drug-resistant TB starts with a quality assured diagnosis, obtained by growing and identifying *Mycobacterium tuberculosis* from clinical specimens and conducting drug susceptibility testing (DST) of the organism to confirm or exclude resistance. In reality, however, less than 5% of the estimated global burden of MDR-TB cases and an even smaller fraction of XDR-TB cases are being detected, the consequence of critical gaps in laboratory capacity for culture and DST, as outlined in Table 1.

Table 1. Coverage of laboratory services, high-burden countries, 2007

	Population thousands	National reference laboratory (NRL) ^a	Access to diagnostic services						Laboratories included in external quality assurance for sputum smear microscopy	
			Sputum smear		Culture		DST		number	%
			number of labs	per 100 000 pop	number of labs	per 5 million pop ^b	number of labs	per 10 million pop ^b		
1 India	1 169 016	Y	12 184	1.0	11	0.05	11	0.1	11 386	93
2 China	1 328 630	Y	3 294	0.2	327	1.2	187	1.4	3 294	100
3 Indonesia	231 627	N	4 855	2.1	41	0.9	11	0.5	4 855	100
4 Nigeria	148 093	Y	794	0.5	2	0.1	1	0.1	347	44
5 South Africa	48 577	Y	249	0.5	15	1.5	10	2.1	241	97
6 Bangladesh	158 665	Y	753	0.5	4	0.1	2	0.1	753	100
7 Ethiopia	83 099	Y	833	1.0	1	0.1	1	0.1	–	–
8 Pakistan	163 902	N	1 131	0.7	3	0.1	1	0.1	360	32
9 Philippines	87 960	Y	2 374	2.7	3	0.2	3	0.3	2 374	100
10 DR Congo	62 636	Y	1 205	1.9	1	0.1	1	0.2	1 023	85
11 Russian Federation	142 499	Y	4 048	2.8	965	34	280	20	–	–
12 Viet Nam	87 375	Y	737	0.8	17	1.0	2	0.2	–	–
13 Kenya	37 538	Y	930	2.5	5	0.7	1	0.3	37	4.0
14 Brazil	191 791	Y	4 044	2.1	193	5.0	38	2.0	1 819	45
15 UR Tanzania	40 454	Y	717	1.8	3	0.4	1	0.2	–	–
16 Uganda	30 884	Y	716	2.3	3	0.5	2	0.6	716	100
17 Zimbabwe	13 349	Y	180	1.3	1	0.4	1	0.7	0	0
18 Thailand	63 884	Y	1 023	1.6	65	5.1	14	2.2	1 023	100
19 Mozambique	21 397	Y	252	1.2	1	0.2	1	0.5	252	100
20 Myanmar	48 798	Y	324	0.7	2	0.2	1	0.2	54	17
21 Cambodia	14 444	Y	201	1.4	3	1.0	1	0.7	186	93
22 Afghanistan	27 145	Y	500	1.8	1	0.2	–	–	360	72
High-burden countries (22)	4 201 761	20	41 344	1.0	1 667	2.0	570	1.4	29 080	70
AFR	765 283	34	8 547	1.1	110	0.7	45	0.6	4 466	52
AMR	599 140	29	13 874	2.3	1 487	12	111	1.9	9 040	65
EMR	555 064	18	4 094	0.7	162	1.5	36	0.6	2 158	53
EUR	611 415	43	6 744	1.1	2 216	18	762	12	284	4.2
SEAR	1 745 394	10	20 090	1.2	129	0.4	43	0.2	18 372	91
WPR	1 648 205	27	7 997	0.5	463	1.4	224	1.4	6 262	78
Global	5 924 501	161	61 346	1.0	4 567	3.9	1 221	2.1	40 582	66

– Indicates information not provided; labs, laboratories; pop, population.

a In the lower part of the table the number of countries answering "yes" to this question is shown.

b To provide culture for diagnosis of paediatric, extrapulmonary and ss-/HV+ TB, as well as DST for re-treatment and failure cases, most countries will need one culture facility per 5 million population and one DST facility per 10 million population.



Arguably the weakest component of health systems, laboratory services have historically been grossly neglected and underfunded. Diagnostic capacity therefore constitutes a major bottleneck for scaling up management and control of MDR-TB and XDR-TB, largely as a result of:

- insufficient and underfunded laboratory strengthening plans;
- inadequate laboratory infrastructure and biosafety;
- vastly inadequate numbers of skilled staff;
- slow diagnostic tool development and technology transfer;
- insufficient and uncoordinated technical assistance.

Estimates based on epidemiological modelling indicate that 60 million culture investigations and five million DST investigations are required annually to meet the diagnostic goals of drug-resistant and HIV-associated TB by 2015, resulting in a current gap of 50 million cultures and 4.5 million DSTs per annum, 85% of these in the high-burden MDR-TB countries. Meeting the estimated global gap will require at least 2,000 new culture and DST laboratories to be established and more than 20,000 new laboratory technicians to be trained and deployed. A systematic approach at country level to planning of laboratory costs is essential, starting with clear policies for screening of patients at risk of MDR-TB and applying appropriate diagnostic algorithms using the different modalities available (solid culture, liquid culture, line probe assays).

Evidence from laboratory assessments shows that the majority of laboratories for culture and DST in resource-limited settings do not meet basic standards for laboratory biosafety or technical proficiency. Standardized operating procedures and quality assurance systems for culture and DST are largely absent or poorly implemented. The high infection risk associated with manipulation of live (and often drug resistant) cultures of *M. tuberculosis* necessitate renovation, construction and maintenance of laboratories according to biosafety level 3 standards, including appropriate laboratory design, negative air flow systems, and validation and maintenance of essential biosafety equipment.

One of the main reasons for the precarious state of laboratory services relates to oversight of and budgets for laboratories often falling outside the jurisdiction of national TB control programmes, thereby aggravating problems relating to laboratory infrastructure, forecasting and planning, and sustainability of technical competency. Human resource development is a particularly pressing problem, with more than 70% of countries reporting critical shortages in skilled laboratory staff. Poor skills distribution, poor compensation, low staff morale and motivation, and lack of career structure being key recurring themes.



Aside from human resources and infrastructure, a major additional impediment to improving and expanding laboratory services is the lack of dedicated, on-site, prolonged, external, experienced technical assistance. The specialized nature of laboratory administration, management and technical procedures dictate the need for specific knowledge and skills, training and mentoring, and ongoing monitoring of performance. Experience shows that training of staff in technical laboratory procedures is relatively easy; however, growing country experience also show that conventional approaches to technical assistance are inadequate, leading to inconsistent technical assistance provided during brief consultant visits, insufficient time devoted to the managerial and administrative components of laboratory strengthening, and poor accountability mechanisms to ensure sustainable quality.

The solution

Research into new TB diagnostic tools has been accelerated over the past few years and the diagnostic pipeline is now rapidly expanding.¹ Commercial liquid culture systems as well as molecular line probe assays for rapid detection of MDR-TB have been recently endorsed by WHO and policy recommendations on their use are available.² Technology transfer of these tools has, however, been slow in resource-limited settings as a direct consequence of laboratory services being ill-equipped to absorb these technologies. Robust, point-of-care diagnostic tests for TB are not expected before 2012; therefore, uptake of existing rapid technologies needs to be accelerated and will require adequate, safe laboratory infrastructure and clear policies at country level for their use in MDR-TB screening and diagnostic algorithms.

Adequate laboratory capacity constitutes several essential elements which need to be addressed simultaneously, within comprehensive strategies and national laboratory strengthening plans. Strengthening TB laboratory services may offer one of the best avenues for financing overall laboratory improvement as an essential health systems component. Fundamental to this work is collaboration between TB control programmes and public health laboratory systems at country level, in the areas of:

- Infrastructure, biosafety and utilities
- Human resource development (including training and retention)
- Specimen referral, supply chain management and logistics
- Equipment and maintenance

¹ World Health Organization, Stop TB Partnership Retooling Task Force, Stop TB Partnership New Diagnostics Working Group. *New laboratory diagnostic tools for tuberculosis control*, 2009 (available at www.stoptb.org/retooling).

² 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) are available at www.who/tb/dots/laboratory/en.



- Technical procedures (disease-specific)
- Quality assurance
- Data management

Urgent actions needed

- Increased political commitment to strengthening laboratory capacity as an essential health systems component, preferably through a dedicated laboratory directorate or division within the Ministry of Health, with clear management structures, roles and responsibilities;
- National laboratory strategic plans, delineating different levels of laboratory service delivery within tiered laboratory networks and outlining the role of different technologies (including rapid diagnostic tests for drug resistant TB) in screening and diagnostic algorithms;
- National human resource development and training plans, outlining the different expertise required at each level of laboratory services, establishing career paths and appropriate remuneration, and developing strategies for human resource retention;
- Increased and sustained funding from bilateral and multilateral donors to support the essential elements of laboratory strengthening as a cross-cutting health systems component, linked to appropriate monitoring and evaluation mechanisms to avoid duplication and optimize synergies;
- Creation of novel mechanisms for long-term, on-site technical assistance to accelerate the capacity of countries to perform mycobacterial culture, DST and rapid molecular tests within quality assured laboratory systems, tied to a plan for development of sustained local capacity and leadership.
- Increased research on, and funding for, the development and rapid deployment of robust point-of-care diagnostic tests.



6. ENSURING ACCESS TO QUALITY-ASSURED ANTI-TB MEDICINES

This paper aims to promote (i) increased use of quality assured first-line fixed-dose combination anti-TB medicines (FDCs) as a means to help prevent the creation of drug resistant TB, (ii) increased demand for quality-assured SLDs to treat MDR-TB, (iii) widespread acceptance of international quality assurance standards for all anti-TB medicines, (iv) the acceleration of international prequalification of SLDs, (v) the strengthening of the capacity of national medicines regulatory authorities (NMRAs) to regulate the quality of anti-TB medicines produced in countries with the highest burden of MDR-TB.

6.1 Increasing access to quality-assured first-line FDCs

The Problem

An essential component of successful treatment of TB and the prevention of MDR-TB is the uninterrupted supply of quality assured medicines. The causes of MDR-TB include erratic medicine intake (particularly interruptions of treatment) and treatment with a single TB medicine.^{1,2} FDCs were developed primarily as a tool to mitigate the emergence of resistance by ensuring that all medicines were present in patients in effective concentrations at the same time. Use of FDCs significantly reduces the risk associated with monotherapy, i.e. the development of drug-resistant strains of *Mycobacterium tuberculosis*.³ Even though both WHO and the International Union against TB and Lung Disease recommend the use of FDCs,^{4,5} they are used in too few patients and their quality is not assured to WHO standards.

While many countries have adopted FDCs during the last decade, FDCs are still only used by approximately half of those reporting to WHO: out of 136 countries that reported to WHO in 2007, FDCs of 2, 3 or 4 medicines were used by 66 (50%) for the two-month intensive phase of treatment for new smear positive cases, while 61 countries (46%) used

¹ Mitchison DA. How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:10–15.

² Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax*, 1998, 53:536–548.

³ WHO Drug Information, 1999, 13:249–262.

⁴ *Operational guide for national tuberculosis control programmes on the introduction and use of fixed-dose combination drugs*. Geneva, World Health Organization, 2002 (WHO/CDS/TB/2002.308; WHO/EDM/PAR/2002.6).

⁵ The promise and reality of fixed-dose combinations with rifampicin. *International Journal of Tuberculosis and Lung Disease*, 1994, 75:180–181.



2-medicine FDCs in the continuation phase of treatment.¹ Globally, however, only about 15% of new patients receive FDCs.

Secondly, treatment with poor quality medicines can result in insufficient concentration of the drug, selection of drug resistant bacilli, and thus the creation of a case with drug resistance, resulting in failure to cure. Yet, the quality of anti-TB FDCs is not always assured by NMRAs, even in countries that are using them. Furthermore, there are particular concerns regarding the bioavailability of rifampicin in FDCs which is easily compromised if strict manufacturing procedures are not followed, or poor quality raw materials are used. If the bioavailability of rifampicin is inadequate, treatment failures and emergence of rifampicin resistant TB is possible. Thus, national procurement and regulatory bodies should be strongly encouraged to insist on obtaining data proving the bioavailability of rifampicin, in addition to other quality assurance data when purchasing and distributing FDCs. Unfortunately, bioavailability testing is expensive, and although dissolution testing is much cheaper, adequate results in the dissolution tests are no guarantee of acceptable bioavailability of rifampicin².

WHO has established strategies for quality assurance of FDCs under its Prequalification Programme. A simplified protocol for testing of rifampicin bioavailability, moreover, has been developed,³ and several laboratories now exist for quality assurance and rifampicin bioavailability testing for FDCs.

The solution

1. National commitment to scale-up the introduction and/or use of FDCs

Governments of high-burden MDR-TB countries could effectively increase their ability to prevent MDR-TB by committing to the introduction and/or scale up of use of quality assured FDCs (with proven rifampicin bioavailability), according to the WHO Stop TB Strategy. WHO has included FDCs in the Model List of Essential Medicines on the basis of the solid evidence that short-course chemotherapy is effective and the assumption that,

¹ Source: World Health Organization. Global tuberculosis control: surveillance, planning, financing. Geneva: WHO; 2008 - DRAFT.

² Acocella G. Human bioavailability studies (IUATLD Symposium Quality Control of Anti-tuberculosis Drugs Dubrovnik, 6 October 1988). *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1989, 64:38–40.

³ Ellard GA. Quality assurance: protocol for assessing the rifampicin bioavailability of combined formulations in healthy volunteers. *International Journal of Tuberculosis and Lung Disease*, 1999, 3 (Suppl.): S284-S285; Fourie PB et al. *WHO Model Protocol. Establishing the bioequivalence of rifampicin in fixed-dose formulations containing isoniazid with or without pyrazinamide and/or ethambutol, compared to the single medicine reference preparations administered in loose combination*. Geneva, World Health Organization, 1999 (unpublished document WHO/CDS/TB/99.274).



as long as the constituents of FDCs provide the same bioavailability as the individual constituent medicines, FDCs will be as efficacious as single-medicine formulations.¹

While the precise impact of FDCs on reducing the development of drug resistance is still under study, FDCs have several practical advantages. The 4 and 3-medicine FDCs provide greater reliability in the delivery of short-course chemotherapy.² Because of the large number of tablets that have to be taken every day, patients often default: use of FDCs reduces the number of pills that need to be taken. FDCs are therefore easier to dispense – fewer medicines are needed to be selected and counted. Prices of FDCs, especially the 4-drug FDC³ are the same as, or lower than, those of loose pills. Treatment is therefore easier to finance. FDCs are also easier to stock at all levels – just five medicines may be suitable for all categories and all patient weights; and they make it easier to assure quality - at the international level the few suppliers have been examined according to WHO standards and centrally monitored. Lastly, FDCs make it easier to adjust dosage by weight.

2. Commitment from high burden MDR-TB countries to buy and enforce the use of quality assured FDCs

Beyond committing to introduce and/or scale-up use of FDCs, governments would also need to commit to purchasing only FDCs that are quality-assured. Such a commitment could take a number of forms in practice:

- i. The Global Drug Facility (GDF), a supply mechanism set up by WHO and Stop TB partners, ensures that quality assured anti-TB medicines and diagnostics are available for implementation of the Stop TB Strategy. Its services fall into three areas: (i) grants of anti-TB medicines for eligible countries that are donor-dependent for some or all their medicine needs (ii) direct procurement services for countries that have sufficient finances but lack adequate procurement or quality assurance systems and (iii) a "white-list" of suppliers of medicines of known good quality for countries with sufficient finances and good procurement mechanisms but which lack a robust quality assurance system⁴.

¹ WHO Expert Committee on Pharmaceutical Preparations. *Thirty-fourth report*. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863): Annex 9.

² Norval PY et al. Estimate of the global market for rifampicin containing fixed-dose combination tablets. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:S292–S300; discussion S17–21.

³ Matiru R, Ryan T. The Global Drug Facility: a unique, holistic and pioneering approach to drug procurement and management. *Bulletin of the World Health Organization*, 2007, 85:348–353.

⁴ Matiru R, Ryan T. The Global Drug Facility: a unique, holistic and pioneering approach to medicine procurement and management. *Bull WHO* 2007; 85:348-353.



- ii. For countries with cost effective local manufacturing capacity for FDCs, this commitment could mean accessing FDCs in the short-term via any of the service options listed above, while developing their capacity to produce quality-assured FDCs locally. In the medium term, support can be obtained through WHO, in collaboration with the government, or interested donors, to provide, or broker, technical support to improve the manufacturing practices of select manufacturers to produce FDCs that reach WHO standards.

6.2 Increasing access to quality-assured medicines to treat MDR-TB

The problem

Lack of demand for quality assured SLDs

If countries are to rise to the challenge of treating all those in need, they will need access to sufficient supplies of affordable, SLDs produced to WHO standards. However, worldwide supply of such quality-assured SLDs is, as yet, small, and volumes are insufficient to treat the increasing numbers of patients being enrolled for care throughout the world. There are roughly three times as many MDR-TB patients being treated with medicines of uncertain quality than with quality-assured SLDs. There are robust sales of SLDs of uncertain quality in countries with high burdens of MDR-TB and they appear to be growing rapidly: the value of these SLDs sold last year, in China and Russia for example, was more than ten times higher than all the SLDs sold last year through the GDF.

Lack of quality-assurance of SLDs

Widespread use of SLDs of uncertain or sub-standard quality drives the production of XDR-TB, with its higher mortality and costs of treatment. Although international standards have been developed so that suppliers can ensure the quality of SLDs, these standards are not adhered to by most manufacturers involved in production. In fact, at present, only two SLDs have been successfully prequalified under the WHO Prequalification Programme.¹ Even where national quality standards exist, these standards are not often enforced by NMRAs. As a result, the majority of patients being treated for MDR-TB around the world are receiving medicines of uncertain quality. Compared to the estimated global incidence of ~500,000 MDR-TB patients per year, only 14,000 patients per year are expected to be enrolled in GLC approved programmes (in 52 countries) and receive medicines that are quality-assured.

¹ WHO Prequalification Programme. WHO, 2008. Available at <http://healthtech.who.int/pq/>



Poor forecasting of demand

A further major challenge to increased access to these medicines is that the global market for quality assured SLDs is fragmented and poorly-characterized. Moreover, demand is opaque, has always been difficult to forecast and is ineffectually communicated. Tapping this market will necessitate significantly improved forecasting of demand if manufacturers are going to be encouraged to invest in increased and improved quality of SLD production.

The solution

1. National commitment to more rapid scale-up and enrolment of MDR-TB Patients

If pharmaceutical suppliers are to produce adequate quantities of SLDs that are quality-assured, they must be able to see adequate market demand – from individual countries and at the global level. If countries make a commitment, in Beijing or thereafter, to significantly expand treatment of patients with MDR-TB and there is a significant expansion of government- or donor-sponsored purchase and procurement, this will help improve access to quality-assured SLDs. With relatively reliable and higher demand, governments and international purchasing facilities such as the GDF would be able to incentivize manufacturers via improved demand forecasting, to invest time and resources into improving the quality of their products. These changes in the market for quality assured anti-TB medicines will take some time to be understood by national and international market participants, but the sooner suppliers of SLDs understand the changing dynamics of the market, the more inclined they will be to incur the upfront expense of having their products quality-assured. And the more readily national governments and other purchasers of SLDs are able to access quality assured medicines, the more likely they will be to insist on them for their patients.

Such expansion of demand will only come if the governments of high-burden MDR-TB countries take the necessary measures to build and/or strengthen National TB control Programmes so that they are able to enrol many more patients under proper programmatic management conditions for MDR-TB. Moreover, such measures would need to include accurate and regular monitoring and reporting of patients enrolled and treated to national and international agencies so as to enable reliable demand forecasts to be prepared and communicated to industry.

2. Commitment from high burden MDR-TB countries to buy and enforce the use of quality-assured SLDs

In order to effectively confront the MDR-TB epidemic, governments of high burden MDR-TB countries would need to commit to purchasing only SLDs that are quality-assured.



Such a commitment could take a number of forms in practice: (1) Working through the Green Light Committee (GLC) Initiative, countries unable to secure affordable, quality assured SLDs from their own national or regional markets or via their own procurement mechanisms, could do so via the GDF. The GDF uses consolidated pooled procurement, competitive international tendering mechanisms, strategic stockpiling and reliance on WHO's Prequalification Programme or Stringent National Medicine Regulatory Authorities (SNRAs) to assure product quality. (2) Where governments have sufficient procurement capacity but are unable to identify sources of quality assured SLDs the GDF can assist them to identify these sources and share information on pricing.

These options, in order to be effective, would require: GDF and its partners to expand the number of sources of quality assured SLDs from its current baseline. (This is already under way through a tiered system of quality assurance involving WHO's Prequalification Programme and SNRAs, which is also embraced by major financing mechanisms such as the Global Fund and UNITAID); GDF and its partners to establish stable benchmark prices for quality assured SLDs sourced by countries through the GLC mechanism or directly from suppliers of quality assured SLDs identified by the GDF; Governments to provide conditional approval of waivers or fast-track mechanisms for importation of quality assured SLDs, even if only for an interim period while they develop their own capacity to produce and/or procure quality assured SLDs.

For some countries with comparative advantages for cost effective, local manufacturing of SLDs, this commitment could mean accessing quality assured SLDs in the short-term via options 1 or 2 above while developing their capacity to produce quality assured SLDs locally in the medium to long term.

Lastly, improving the capacity of NMRAs to ensure the production of anti-TB medicines of assured quality is a necessity. The responsibility for quality oversight ultimately lies with each country's NMRA and alternative approaches through international prequalification mechanisms are costly and time-consuming. These alternative procedures, moreover, ignore the capabilities of existing NMRAs and do not take the actions necessary to build the NMRAs' capacity to become stringent. This can undermine the authority that the NMRA currently has, increase dependence on external resources, and undermine the principle of sustainability at the national level. WHO, in collaboration with SNRAs and interested donors, could provide or broker technical support to high burden MDR-TB countries to strengthen the capacity of their NMRAs and, where appropriate, the capacity of their manufacturers.

Realistically, not all governments would be able to translate these commitments in the above areas into immediate practice. However, actions could certainly be taken in progressive phases accordingly to clear timelines and targets, with a willingness of governments to be monitored and report on their progress.



Urgent actions needed

- National commitment to increasingly (and in a phased manner if needed) buy quality assured FDCs.
- Willingness to accept targets for 1 and willingness to monitor and report on progress against targets.
- Provision of specific technical support and mechanisms to support WHO Prequalification of FDC suppliers in key priority countries (medium term) and/or to strengthen the capacity of NMRAs (long term).
- Commitment to expand the market for international sources of quality-assured FDCs and maintain low-cost benchmark prices.
- National commitment to rapidly enrol MDR-TB patients under proper programmatic conditions (as per realistic targets).
- National commitment to increasingly (and in a phased manner if needed) buy quality assured SLDs.
- National commitment to conditional approval of waivers or fast-track mechanisms for importation of quality assured SLDs, even if only for an interim period, while, where applicable, national capacities for production and/or procurement of quality assured SLDs are developed.



7. RESTRICTING THE AVAILABILITY OF ANTI-TB MEDICINES

The problem

1. Currently, only 62% of estimated drug-susceptible TB cases and less than 5% of the estimated MDR-TB cases are detected and treated within NTPs.¹ The majority of them have previously been visiting one or several health providers outside NTP. For example, studies have shown that the proportion of patients that had turned first to a private provider was 50% in Viet Nam,² 75% in India³ and 96% in Myanmar.⁴ Use of public sector providers that are not linked to NTP is also common.^{5,6}
2. In some settings, a considerable proportion of people with TB also receive TB treatment outside NTPs. For example, 75% of all TB patients were treated outside the NTP in a large city in Indonesia⁶; a study from a metropolitan area in Viet Nam estimated that 40% of patients on TB treatment were treated by private providers not linked to the NTP⁷; and among cases on TB treatment identified in the prevalence surveys in China in 2000⁸ and Myanmar in 2006⁹ (Yangon only), 88% and 48% respectively were treated outside the NTP. A recent estimate of the TB drug market in 10 countries found that about half of the total TB drug market was in the private sector. In some of the major high-TB-burden countries the share is even higher: 90% in the Philippines, 74% in India, 67% in Indonesia and 56% in China.¹⁰

¹ *Global tuberculosis control: epidemiology, strategy, financing. WHO report 2009.* Geneva, World Health Organization, 2009 (WHO/HTM/TB/2009.411).

² Lönnroth K et al. Utilisation of private and public health care providers among people with symptoms of tuberculosis in Ho Chi Minh City, Viet Nam. *Health Policy and Planning*, 2001, 16:47–54.

³ Pantoja A et al. Economic evaluation of PPM-DOTS in Bangalore, south India. Part I: Profile and costs of TB patients [accepted for publication]. *International Journal of Tuberculosis and Lung Disease*, 2009.

⁴ Lönnroth K et al. Social franchising of TB care through private general practitioners in Myanmar - an assessment of access, quality of care, equity, and financial protection. *Health Policy and Planning*, 2007, 22:156–166.

⁵ *Report on nationwide random survey for the epidemiology of tuberculosis 2000.* Beijing, Ministry of Health of the People's Republic of China, 2001.

⁶ Irawati SR et al. Hospital DOTS linkage in Indonesia: a model for DOTS expansion into government and private hospitals. *International Journal of Tuberculosis and Lung Disease*, 2007, 11:33–39.

⁷ Lönnroth K et al. Private pharmacies and TB control – a survey of case detection skills and reported anti-TB drug dispensing in private pharmacies in Ho Chi Minh City, Viet Nam. *International Journal of Tuberculosis and Lung Disease*, 2000; 4:1052–1059.

⁸ *Report on nationwide random survey for the epidemiology of tuberculosis in 2000.* Beijing, Ministry of Health of the People's Republic of China, 2001.

⁹ Lwin T et al. *TB prevalence survey in Yangon Division, Myanmar (2006).* Poster presented at the IUATLD World Conference on Lung Health, Cape Town, 2007.

¹⁰ *Pathway to patients – charting the dynamics of the global TB drug market.* New York, NY, the TB Alliance, 2007.



3. Unfortunately, private physicians, as well as public sector providers outside NTP, rarely follow recommended TB treatment regimens.¹ Treatment outcomes are poor in private and public facilities that operate outside NTP, often with a treatment success rate of less than 50%.^{2,1}
4. Many patients thus receive TB treatment of questionable quality at private and public facilities. Therefore, prevention of drug-resistance development and amplification needs to include efforts to minimize irrational use of anti-TB medicines across the whole health system.
5. Both FLDs and SLDs are widely available over-the-counter (OTC) in retail pharmacies. This encourages self-treatment and the purchase of inadequate quantities of medications - a recipe for encouraging the emergence of drug resistance. Even when anti-TB medicines are sold against a prescription, prescribers outside national programmes may not use recommended regimens, and patients may fill only part of the prescription due to financial constraints.
6. Prescription and dispensing of medicines in general, and antibiotics (including anti-TB medicines) in particular, is poorly monitored and regulated in most countries. When regulation exists, there is often not enough capacity to enforce it. Misuse of antibiotics is a huge problem world-wide, which is fuelling the rapidly increasing occurrence of antimicrobial resistance. The misuse of anti-TB medicines therefore need to be addressed as part of broader health systems strengthening efforts to limit misuse of antibiotics.

The solution

An essential step to prevent further development of MDR-TB is to continue to scale up public-private mix (PPM) approaches for TB care and control, which promotes rational use of anti-TB medicines among all health-care providers (see background paper on "Prevention of M/XDR-TB: Gaps in basic TB control"). PPM approaches have been successfully piloted in several countries and scaled up in a few. However, no country has been able to engage all relevant health-care providers, and most countries with PPM initiatives have still only engaged a fraction of the private providers. This is partly due to reluctance among some providers to engage in activities that may not have any clear financial benefit for them. The PPM approach builds on voluntary collaboration and has

¹ Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. *Lancet*, 2001, 358:912–916.

² Irawati SR et al. Hospital DOTS linkage in Indonesia: a model for DOTS expansion into government and private hospitals. *International Journal of Tuberculosis and Lung Disease*, 2007, 11:33–39.



rarely been supported by regulatory interventions to restrict availability of anti-TB medicines and/or prescription rights to quality-assured facilities. Complementary efforts to improve rational use of anti-TB medicines across the whole system may therefore involve:

1. ***Enforced prohibition of OTC dispensing of anti-TB medicines:*** Many countries have regulations in place, but they are rarely enforced, and penalties for violations are normally benign. Strengthened capacity for enforcing such regulation is needed. Similarly, dispensing of anti-TB medicines by prescribing physicians should be prohibited, as the direct financial incentive from drug sales may negatively affect prescribing behaviour. Obviously, such efforts need be done in collaboration with drug regulatory bodies and other relevant stakeholders.
2. ***Explore regulatory approaches to restrict prescription and dispensing rights to accredited facilities:*** One strategy to further limit misuse of anti-TB medicines is to restrict prescribing and dispensing rights to facilities where rational prescribing and dispensing can be assured and essential information on the patient and the provider can be monitored. A possible model is to completely ban TB drug sales and dispensing outside facilities that are directly affiliated with the NTP. Several countries (e.g. Brazil, Syrian Arab Republic, United Republic of Tanzania, and Zambia) have regulations that completely prohibit sales of FLDs in retail pharmacies, and give the NTP a monopoly for drug procurement and distribution. In at least some of these countries, this regulation seems to work in that anti-TB medicines are not available outside quality assured facilities designated to treat TB (public or private). Further documentation is needed to validate this and analyse how such regulation can effectively be put in place.

Restricting availability to SLDs may be more challenging than restricting sale of 1st line medicines since many of them are used for other indications than TB. However, it is in principle possible to restrict access to at least some of them (the ones most specific for TB, and the ones that are suitable only for treatment in special institutions) to accredited providers. Restricting prescription and/or dispensing rights would require classification of anti-TB medicines into a category of “controlled substances” (such as narcotics and psychotropic medicines or medicines that are made available on special license for specific projects or cases). This is easier for medicines that are being registered for the first time in a country. For, example, the Philippines has managed to restrict the availability of all SLDs, except amikacin and fluoroquinolones, to GLC-approved projects in selected facilities. They are not available in retail pharmacies.¹ There is very little experience of this approach globally, and it should be explored further, piloted, and evaluated.

¹ Lönnroth K. A PPM approach to scaling up programmatic management of drug-resistant TB – lessons from the Philippines [travel report]. Geneva, World Health Organization, 2008.



3. ***Develop guidelines and recommended practice:*** An alternative, “softer”, approach is to recommend (but not prohibit) pharmacies not to stock anti-TB medicines and refer all clients requesting anti-TB medicines to NTP-affiliated facilities. This has been tried in Cambodia, where the NTP in collaboration with the national pharmacy association, has instructed all pharmacies in selected areas not to stock anti-TB medicines, but refer TB suspects to the NTP. Simultaneously they requested all private providers to refer all TB suspects to the NTP. Preliminary investigations indicate that this approach has led to non-availability of anti-TB medicines in these pharmacies.¹ Similar approaches have been reported from Viet Nam.² In theory, such an approach could be considerably strengthened if both professional associations and pharmaceutical companies are engaged in efforts to make medicines available only at quality assured facilities as well as in the dissemination of information about the need to refer TB cases to these facilities.

Urgent actions needed

- Put in place and enforce regulation that prohibits the dispensing of anti-TB medicines without a prescription, and which prohibits physicians to sell such medicines directly to patients.
- In conjunction with PPM scale-up and the development of formal accreditation mechanisms, explore regulatory approaches that restrict prescription and dispensing rights to quality-assured facilities only.
- Regardless of existing regulation, develop recommendations and guidelines for all health-care providers, including pharmacies, stating that anti-TB medicines should be prescribed and dispensed only in facilities of assured quality.

¹ Travel report by Monica Diaz Yesudian, January 2009.

² Gebhard A. *Viet Nam National TB Programme – Review 2006*. KNCV and WHO, 2007.



8. PRIORITIZING TB INFECTION CONTROL

The problem

TB infection control in health-care and congregate settings has been largely neglected in the policy and practice of health system interventions until recent outbreaks of M/XDR-TB among patients with a high prevalence of HIV in a hospital setting in southern Africa stimulated belated activity.

TB infection control is comprised of a combination of controls aimed at minimizing the risk of TB transmission. The selection of the best combination of controls is informed by local programmatic, climatic and socioeconomic conditions.

Updated WHO policy on TB infection control¹ provides guidance to countries on what to do and how to prioritize the elements of TB infection control. While the focus of the recommendations is on health facilities, the document also provides guidance on preventing TB transmission in congregate settings and households. It is organized under four main categories: managerial activities, administrative (includes practices such as triage for coughers), environmental controls, and personal protective equipment. It encourages more home-based and community treatment of TB, including MDR-TB and emphasizes a patient-centered approach, with particular attention to minimizing stigma.

The literature review shows that implementation of the different kinds of controls as a combination reduces transmission of TB in health-care facilities, thus protecting health workers and averting TB cases and deaths among health staff.¹ Consequently, all facilities, public and private, caring for patients or suspects with TB should implement TB infection control measures. These should complement general infection control efforts and those targeting other airborne infections.²

To date, few countries have developed strategies to implement TB infection control interventions.³ Most have not engaged Ministries of Health or Justice or those responsible for infrastructure, for example, to take the necessary steps to establish a coordinated approach to implementation of TB infection control, including engagement of the multiple stakeholders in addition to the government, such as technical partners, and civil society.

¹ *WHO policy on infection control* [in press]. Geneva, World Health Organization, 2009.

² *Infection, prevention and control of epidemic and pandemic-prone acute respiratory diseases in health care: WHO interim guidelines*. Geneva, World Health Organization, 2007.

³ *Global tuberculosis control: epidemiology, strategy, financing. WHO report 2009*. Geneva, World Health Organization, 2009 (WHO/HTM/TB/2009.411).



The solution

To successfully initiate and rapidly scale-up TB infection control best practices and reduce transmission of TB including MDR-TB and XDR-TB in health facilities and congregate settings, three major aspects must be addressed at the highest political levels:

1. Leadership

TB infection control involves many disciplines (TB and HIV control programme staff, health workers, engineers, building maintenance) and ongoing encouragement of routine behaviors (covering cough, wearing respiratory protection, for example). Systems must be developed to provide direction, oversight, monitoring and evaluation.

2. Technical expertise

Improvement of ventilation systems, complemented by UVGI when needed, as well as implementation of all the elements of TB infection control require specific technical expertise for implementation. Health workers require leadership and training to reinforce behaviours necessary to initiate and maintain TB infection control measures.

3. Financial resources

The implementation of TB infection control requires a minimum level of infrastructure, including renovation and new construction of safe facilities, and assumes the rational design, construction or renovation and use of buildings. This has major financial and political implications at country level and requires a high level of political commitment.

Urgent actions needed

- Disseminate the 2009 WHO policy on TB infection control
- Define roles and responsibilities within the Ministry of Health, Ministry of Justice, Ministry of Infrastructure, and civil society to facilitate the implementation of the WHO Policy. This includes the following:
 - Identify and strengthen national coordinating bodies on TB infection control building on existing general infection control efforts. Coordination between TB, HIV, occupational health, correctional service and civil society is necessary.
 - Develop national plans, with designated budgets, to scale up TB infection control.
 - Mobilize and empower groups of people living with HIV to prevent the spread of TB and especially MDR-TB in their communities.



- Establish standard monitoring and evaluation systems for use by all stakeholders to ensure ongoing monitoring of TB infection control practices.
 - Avail existing and new resources to improve the implementation of the TB infection control in health facilities, congregate settings and household.
- Identify building infrastructure requirements and associated costs for the implementation of TB infection control.
- Assess needs and provide technical assistance required for initiation and scale-up of the TB infection control at the national level.
- Define and assess costs of human resource requirements (including need for engineers, building maintenance personnel, development of infection control staff) at country level.
- Develop and implement a research agenda to determine the effectiveness of the individual controls on the impact of reduction of TB transmission. More operational research is needed on the operationalization of the individual controls described in the policy.



9. MAXIMIZING RESEARCH OPPORTUNITIES TO ADDRESS M/XDR-TB

Although much has been learned on MDR-TB management in recent years, important knowledge gaps are contributing to the current high costs and complexity of case finding and treatment. For this reason, the Working Group on MDR-TB developed a research agenda that identifies the key research questions to be answered in order to strengthen the evidence-base of current guidelines, accelerate the scale-up, and simplify the management of drug-resistant TB programmes.¹ Other groups have arrived at similar conclusions.²

Governments, development agencies, research funding agencies, and technical agencies have a critical role to facilitate the implementation of research to improve the programmatic management of drug-resistant TB and make diagnosis and effective treatment available to all those in need.

The most urgent research questions are discussed in this document.

9.1 Diagnostic test development

The problems

DST of isoniazid and rifampicin gives reliable and reproducible results, conversely to susceptibility testing for second-line medicines,³ which currently compromises case finding of XDR-TB and clinical management of MDR-TB. More evidence is needed to illustrate the clinical relevance of second-line drug resistance, and also of cross-resistance, such as between newer and older generation fluoroquinolones. The turnaround time of DST is several weeks depending on the culture method used, causing delays in identifying patients in need of second-line treatment as well as in selecting effective medicines.

¹ Cobelens FGJ et al. Scaling up programmatic management of drug-resistant tuberculosis: a prioritized research agenda. *PLoS Medicine*, 2008, 5(7):e150.

² Fauci AS, NIAID Tuberculosis Working Group. Multidrug-resistant and extensively drug-resistant tuberculosis: the National Institute of Allergy and Infectious Diseases Research agenda and recommendations for priority research. *Journal of Infectious Diseases*, 2008, 197:1493–1498.

³ Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. *European Respiratory Journal*, 2005, 25:564–569.



The solutions

Several methods for rapid detection of drug resistance have been, or are being, developed. Line-probe assays for molecular resistance testing have been recently endorsed by WHO¹ and are expected to accelerate dramatically case finding and treatment of MDR-TB, thus reducing the period of infectiousness. Molecular assays also simplify decentralization of DST. They are however currently only available in commercial form for rifampicin (and to some extent isoniazid), and must be adapted to the programme setting. Development of rapid methods which can detect second-line drug resistance in the remote areas would accelerate the process of identifying a suitable treatment regimen in patients with XDR-TB.

Urgent actions needed

Governments, development agencies, and technical agencies should facilitate field-testing of available molecular resistance assays in order to adapt their utilization for screening and diagnostic purposes at local level. Researchers and research funding agencies should work towards the development of rapid methods for detection of resistance to first and second-line in the remote areas.

9.2 Treatment (including preventive therapy)

The problems

The currently recommended second-line treatment regimens are complex, of long duration, and require intensive monitoring of adverse events and treatment outcomes. Treatment efficacy is poor unless stringent approaches are taken to ensure treatment adherence. There is justifiable concern about the feasibility and success of these regimens when second-line treatment is scaled-up beyond the pilot project stage. Regimens are needed with shorter duration, fewer medicines, fewer adverse events, and which offer standardized approaches to treatment, with less intensive monitoring, yet without compromising effectiveness. However, well designed comparative studies, including randomized-controlled clinical trials of possible drug combinations have never been conducted; current guidelines are based on clinical experience only.

Highly promising new compounds, however, are being evaluated for safety and efficacy against TB in humans. Some of these medicines have the potential to significantly

¹ WHO policy statement. *Molecular line probe assays for rapid screening of patients at risk of MDR-TB*. Geneva, World Health Organization, 2008 (available at http://www.who.int/tb/features_archive/policy_statement.pdf).



improve treatment efficacy for MDR-TB when used in relatively simple and short regimens.

However, current funding is almost exclusively targeted on research and development of new medicines up until licensure, and no financial or technical mechanism covers the essential “Phase IV” step in which the optimum treatment duration and combination of currently available and new medicines are put to rigorous testing.

Similar problems exist with preventive treatment of infection with MDR-TB organisms. Standard isoniazid preventive therapy is ineffective, and pyrazinamide in combination with other medicines as preventive therapy has been associated with unacceptably high frequencies of liver toxicity and death. No large-scale controlled trials have been conducted of a preventive therapy regimen that could be used for contacts of patients with MDR-TB, and funding for such studies is very limited.

The solutions

Since large-scale use requires solid evidence, it is essential that these study questions be addressed in randomized-controlled clinical trials. These trials will need to be done in a coordinated fashion in several settings in order to take into account the enormous variability in host and bacillary populations as well as social and environmental conditions.

Urgent actions needed

Research funding agencies should consider investing in (i) clinical trials aiming at shortening, simplifying and improving efficacy of treatment regimens for drug-resistant TB using available medicines and also new compounds, and (ii) preventive therapy trials to define optimal treatment combinations and duration for preventive treatment of infected persons exposed to patients with drug-resistant TB.

9.3 Programmatic aspects

The problems

The pilot projects on management of drug-resistant TB have yielded best practices on a variety of operational issues that need to be translated into cost-effective strategies adapted to much larger, countrywide scale. This is particularly urgent with regard to identification of MDR-TB patients, treatment adherence, and infection control. Selection strategies of patients eligible for second-line treatment should target those most at risk of having MDR-TB, and include patients who live far from DST facilities and those treated in the private sector.



Adherence to treatment for MDR-TB is highly important for its success but complicated by its long duration and sometimes high frequency of adverse events. Strategies need to be developed that maximize treatment adherence in a sustainable way, and factors that affect adherence need to be studied.

Nosocomial transmission of MDR-TB is well documented, in particular in settings with high HIV infection prevalence.¹ The high cost of some of the infection control measures limits their application in resource-limited settings, and little is known about the effectiveness of less costly alternatives proposed in the current guidelines.

The Global Fund and other donor agencies encourage the inclusion of operations research (OR) in programs they support. In the case of the Global Fund the proportion of proposals including OR and the proportional budgets for OR increased from Rounds 1–5 to Round 6. Of note, over the total Global Fund portfolio, the budget allocated to OR increased from 0.4% to 3% but funding opportunities are not fully utilized yet.²

The solutions

For each of these three areas, strategies that optimize integration of management of drug-resistant TB into existing TB control programs need to be developed and evaluated for cost-effectiveness. This is possible through OR, which should be part of all TB programs in order to improve policy, programme implementation, and ultimately access to care. The challenges related to designing, planning, implementing and taking full advantage of OR in countries are well known. Instruments to support programs willing to take on OR activities are now available³ although more will need to be developed. At the moment technical assistance for OR is insufficient and needs to be strengthened.

Urgent actions needed

Governments, development agencies, and technical agencies should work in partnership to incorporate OR on drug-resistant TB into the activities of TB control programs. Governments and technical agencies should make full use of existing funding opportunities for OR.

¹ Wells CD et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *Journal of Infectious Diseases*, 2007, 196 Suppl 1:S86–107.

² Korenromp E et al. *Operational Research on HIV/AIDS, tuberculosis and malaria control in Global Fund-supported programs: Rounds 1–6 grants. Proceedings of the 5th European conference on Tropical Medicine and International Health*, 2007 (available at: http://www.theglobalfund.org/documents/performance/results/Rounds1-6_SIE_ReviewOfORInExistingGrants.pdf).

³ The Global Fund to Fight AIDS, Tuberculosis and Malaria and the Special Programme for Research and Training in Tropical Disease. *Framework for operations and implementation research in health and disease control programs*, 2008 (available at: <http://www.who.int/tdr/publications/training-guideline-publications/framework-operation-research/pdf/framework-operation-research.pdf>).



9.4 Prevention of drug resistance

The problems

Preventing development and transmission of drug-resistant TB requires knowledge about its causal factors. The conditions leading to drug resistance in TB are well described, yet the substantial variation in its worldwide distribution suggests that their relative importance may vary between settings.¹ Examples of such potential causal factors include type and quality of first-line treatment supervision; access to anti-TB medicines outside TB programs; use of fixed-dose combinations; the quality of medicines used, infection control practices, *M. tuberculosis* genotype; HIV prevalence; and level of use of antiretroviral treatment. Without knowledge of the most important contributing factors, a targeted, cost-effective control response to the problem of MDR-TB is not possible. This is still the case for many settings, partly due to the limited availability or quality of drug resistance data, as well as of the limited quality of routine statistics. In addition, investigation of the causes of drug resistance is an area of work that has been largely undervalued and neglected by the research community and donors. The Global Fund and other donors are encouraging countries to include operations research and monitoring and evaluation components in their grant applications, and yet these opportunities are frequently ignored.

The solutions

Understanding the role of risk factors to the development and transmission of drug resistance that are amenable to control interventions is the recipe for “turning off the tap”. Drug resistance surveillance of adequate quality is within reach for many countries now that molecular resistance testing is possible on a large scale. Combining this with targeted research activities that build on and complement routine monitoring and evaluation would provide a strong framework for identifying these risk factors.

Urgent actions to be taken

Governments, technical agencies and research funding agencies should consider investing in research aimed at understanding the causal factors for the development of drug resistance. Governments and technical agencies should make full use of existing funding opportunities for OR.

¹ *Anti-tuberculosis drug resistance in the world. Fourth global report.* Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.394).



Conclusions

Data from 2007 show that overall investments for TB research and development appear to be decelerating rather than accelerating. At this pace, less than half of the US\$ 9 billion recommended by the Global Plan to Stop TB, 2006–2015 will be spent on TB research and development by 2015.¹

Governments, in particular those of the BRICS economies (Brazil, Russia, India, China and South Africa), development agencies, research funding agencies and technical agencies have a critical role to play in facilitating research on drug-resistant TB, particularly in the areas of field-testing of diagnostic tests, clinical trials to shorten treatment regimens and to develop efficacious preventive regimens, operations research, and exploring the role of risk factors in the development of drug-resistant TB.

¹ Treatment Action Group. *Funding trends in TB research & development: 2005–2007. Preliminary report*. Paris, France, 2008 (available at: <http://www.treatmentactiongroup.org/publication.aspx?id=2486>).



10. FINANCING M/XDR-TB CONTROL AND CARE

The problem

An estimated 511 000 cases of MDR-TB occurred in 2007, of which 85% were in the 27 high MDR-TB burden countries. Less than 30 000 of these cases were diagnosed (just under 24 000 in the high MDR-TB burden countries) and only 3 681 were known to be treated according to international guidelines.¹ Funding for MDR-TB amounts to US\$ 72 million in the 27 high MDR-TB burden countries in 2009, most of which is from national governments (European countries and South Africa) or the Global Fund (other countries).

The Stop TB Partnership's Global Plan to Stop TB² has set out the interventions that need to be implemented from 2006 to 2015 to achieve global targets that have been set for 2015,³ and estimates of the funding requirements.⁴ The M/XDR-TB component of the plan (Table 10.1) is based on the target that 80% of estimated cases of M/XDR-TB should be diagnosed and treated according to international guidelines by 2015. To achieve this target, around 1.4 million cases of M/XDR-TB will need to be treated in the 27 high MDR-TB burden countries in the seven years 2009–2015, rising from 63 000 cases in 2009 to 357 000 cases in 2015. The total cost of diagnosing and treating these patients (including infection control) is estimated at US\$ 16.9 billion over seven years, rising from US\$ 0.7 billion in 2009 to US\$ 4.4 billion in 2015.^{5,6} The funding required in 2015 is 61 times higher than the funding available in 2009. Most funding is required in the European Region (US\$ 8.9 billion) (Figure 10.1), followed by Asia (US\$ 7.1 billion, mostly for China and India).

¹ *Global tuberculosis control: epidemiology, strategy, financing. WHO report 2009.* Geneva, World Health Organization, 2009 (WHO/HTM/TB/2009.411).

² *The Global Plan to Stop TB, 2006–2015: actions for life towards a world free of tuberculosis.* Geneva, Stop TB Partnership and World Health Organization, 2006 (WHO/HTM/STB/2006.35). The M/XDR component has been revised twice. The second revision in early 2009 accounted for updated estimates of the number of MDR cases that occur each year, and the number of patients that were actually diagnosed and treated in 2008.

³ The targets for reductions in the global burden of TB are that incidence should be falling by 2015 (MDG Target 6.c), and that the number of cases and deaths should be halved by 2015 compared with a baseline of 1990 (targets set by the Stop TB Partnership). Other targets include (i) detecting at least 70% of new smear-positive cases of TB and successfully treating at least 85% of such cases and (ii) achieving universal access to treatment for MDR-TB and universal access to ART for HIV-positive TB patients (with universal access defined as 80% of those in need accessing care).

⁴ Floyd K, Pantoja A. Financial resources required for tuberculosis control to achieve global targets set for 2015. *Bulletin of the World Health Organization*, 2008, 86(7):568–576.

⁵ The total cost per patient treated is usually in the range US\$ 3 000–10 000. 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).

⁶ The main cost drivers for laboratory tests are either (i) screening among HIV-positive TB cases (high HIV prevalence countries) or (ii) the number of previously treated cases (all other countries).



Table 10.1 Number of M/XDR-TB cases to be treated (in thousands) and associated funding requirements (in US\$ billions) in 27 high MDR-TB burden countries 2009–2015, Global Plan (second revision)

Cases/funding	2009	2010	2011	2012	2013	2014	2015	Total
Cases to be treated	63	100	141	186	237	294	357	1378
Funding required for laboratory <i>diagnosis and monitoring</i>	0.2	0.5	0.6	0.7	1.2	1.4	1.5	6.1
% funding for laboratory for running/capital costs	53/47	52/48	62/38	67/33	57/43	62/38	64/36	61/39
Funding required for <i>treatment</i>	0.4	0.7	1.0	1.3	1.7	2.2	2.8	10.1
% funding for <i>treatment</i> for drugs/hospitalization/other	51/24/25	53/22/25	53/22/25	53/22/25	53/22/25	53/23/24	53/23/24	53/22/25
Funding required for Infection Control (IC)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.7
Total funding required, <i>diagnosis, treatment and IC</i>	0.7	1.3	1.7	2.1	3.0	3.7	4.4	16.9

Full implementation of the M/XDR-TB component of the Global Plan requires a rapid and substantial scale-up in diagnostic and treatment services, and associated funding.

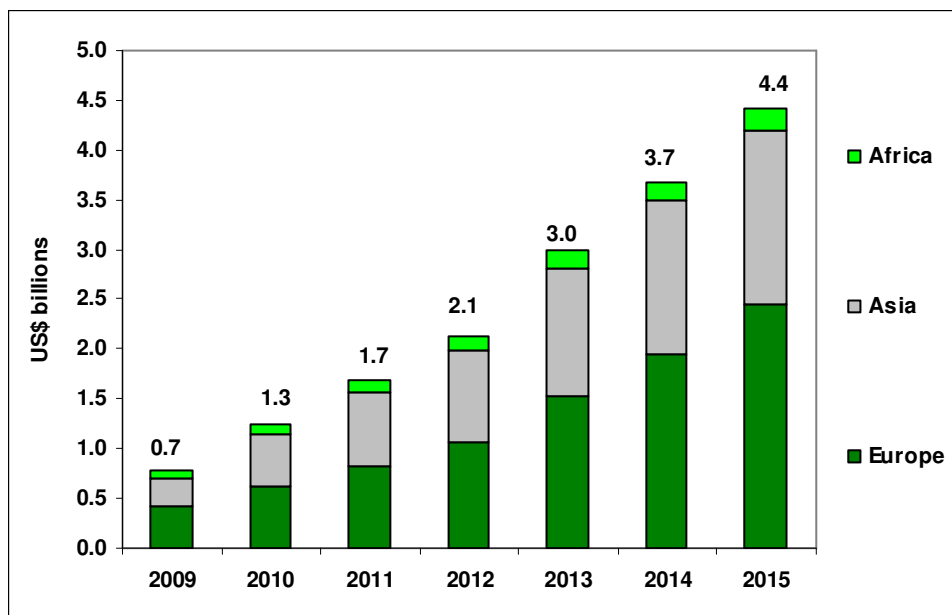
Possible solutions for mobilization of funding

- Patients/households.** The cost of treatment per patient for MDR-TB is higher than the average income per capita (measured as gross national income, or GNI, per capita) in all of the 27 high MDR-TB burden countries. Just the cost of second-line drugs per patient is also higher than GNI per capita in 20 of the 27 countries. With health expenditures of more than 40% of individual/household income after basic subsistence needs are met defined as "catastrophic", people with MDR-TB cannot be expected to finance their own treatment. Some form of collective financing mechanism is required.
- National governments.** There appears to be considerable potential to mobilize funding from domestic sources in high MDR-TB burden countries, including those with the largest number of cases. In 2001, the report of the Commission on Macroeconomics and Health to WHO suggested that 96–100% of the funding required for health care could be mobilized from domestic sources in middle-income countries. Of the US\$ 16.9 billion required for MDR-TB from 2009 to 2015, US\$ 7.0 billion (41%) is needed in upper-middle income countries (GNI per capita of US\$ 3706–11455) and US\$ 7.7 billion (46%) is needed in lower middle-income



countries (GNI per capita of US\$ 936–3705). Only 13% of the required funding is needed in low-income countries. By 2015, the funding required is equivalent to 3-5% of general government health expenditure (in 2005) in middle-income countries, and up to 16% in low-income countries.

Figure 10.1 Funding needs by region, Global Plan, US\$ billions



- The Global Fund** is the single biggest source of external funding for TB control. The total value of grants awarded in rounds 1–8 is US\$ 3.9 billion,¹ equivalent to 25% of total Global Fund commitments (US\$ 15.2 billion for HIV, TB and malaria) and about US\$ 320 million per year. If this level of funding is sustained and all Global Fund financing was used for MDR-TB management, regardless of the income level of the country, the Global Fund could provide 46% of the funding required in 2009, 15% in 2012 and 7% in 2015. Although the Global Fund could finance a large share of the costs of MDR-TB management in some low-income countries with a relatively small number of cases, it seems unlikely that it could finance most of the costs of MDR-TB management across all 27 countries.
- UNITAID** provides funding for drugs and diagnostics related to HIV, TB and malaria.² To date, it has committed US\$ 900 million for the three diseases, including US\$ 146 million for TB drugs and diagnostics. Funding for TB drugs and diagnostics includes US\$ 82 million for second-line drugs (for the treatment of 10

¹ *The Global Fund to fight AIDS, Tuberculosis and Malaria* [online database], (available at: <http://www.theglobalfund.org/en/commitmentsdisbursements/?lang=en>; accessed March 2009).

² <http://www.unitaid.eu/>



286 patients in approved projects plus a stockpile of drugs sufficient for around 15 000 additional patients) and US\$ 26 million for the diagnosis of MDR-TB (for a total of 74 000 patients, 2008–2011).

- **Other donors.** Various bilateral donors and foundations provide funding via mechanisms besides the Global Fund and UNITAID. In recent years, the total value of grants has been less than US\$ 100 million per year for TB overall.

Urgent actions required

- **Preparation of country-specific budgets, based on national strategic plans.** The Global Plan provides a broad indication only of the funding that is required for scaling up the management of M/XDR-TB. The first urgent action is to develop country-specific plans and to accurately assess the funding required to implement them, within the framework of the targets included in the Global Plan. The model of care (e.g. extensive use of hospitalization vs. outpatient care), the source of second-line drugs (e.g. GLC vs. other sources) and policy related to the patients to be screened for MDR-TB¹ are three examples of major issues that need to be carefully considered during the planning process: the choice will have a big influence on funding requirements. WHO has developed a TB planning and budgeting tool that can help countries to prepare comprehensive plans and budgets for MDR-TB as well as for all aspects of TB control, within the framework of the Global Plan. To date, the tool has been used by more than 50 countries. A good example of a country where the tool has been used to develop a precise budget for MDR-TB diagnosis and treatment is South Africa. The tool is available at http://www.who.int/tb/dots/planning_budgeting_tool/en/index.html.
- **Mobilize funding based on a fully-budgeted national strategic plan, with particular attention to domestic funding in middle-income countries.** Based on a fully-budgeted plan, explore the possibility of domestic funding - particularly in middle-income countries. Ensure that budgets for MDR-TB are consistent with policy on health-care financing and with broader planning and financing frameworks (such as Medium-Term Expenditure Frameworks and country compacts signed as part of the International Health Partnership²). Apply for funding from major donors if sufficient domestic financing cannot be mobilized. Consider the recommendations of the High Level Task Force on Innovative Financing, which was set up in September 2008 and is due to report in July 2009.

¹ Categories of case to be considered for laboratory screening for MDR include a) previously treated cases b) all new cases that have a positive sputum smear after three months of treatment and c) all cases that are both HIV-positive and smear-negative.

² <http://www.internationalhealthpartnership.net>



ANNEX 1: URGENT ACTIONS NEEDED TO PREVENT AND MANAGE M/XDR-TB

Addressing the gaps in TB control

1. Strengthening involvement of hospitals in TB control

Actions needed	Actors responsible
Recognize the importance of hospitals in TB control and especially in preventing MDR-TB and commit adequate resources, human and financial, for the purpose.	National TB Programme, Ministry of Health, Ministry of Finance
Set up a national mechanism to ensure coordination at the highest levels among departments responsible for health centres, general hospitals and specialist hospitals/medical colleges.	National TB Programme, Directorates responsible for health centres, hospitals, and academic institutions
Prepare an inventory of all hospitals and designate hospitals responsible for provision of TB services through certification / accreditation schemes.	National TB Programme, Directorates responsible for hospitals and medical colleges
Develop, disseminate and implement guidelines on establishing linkages between hospitals and health centres as well as measures to be implemented within hospitals to ensure seamless care provision for TB suspects and cases, in line with the ISTC.	National TB Programme along with the directorates responsible for hospitals and medical colleges
In order to make the collaboration sustainable, ensure adequate compensation to hospitals for their input to TB control.	National TB Programme with relevant authorities

2. Scaling up Public-Private Mix for TB care and control

Actions needed	Actors responsible
Intensify efforts to identify TB service providers outside the scope of National TB Programmes and engage them to ensure that all TB patients receive care in line with the ISTC.	National TB Programme
Formulate/modify policies to enable securing and providing human and financial resources, support and supervision for scaling up PPM programmes.	Ministry of Health



Make professional associations close partners in TB care and control investing in strengthening their capacity if required.	National TB Programme
Engage private laboratories to improve access to diagnosis, providing them with support, training and quality assurance services.	National TB Programme
Measure contribution of diverse care providers to TB control and adapt policies and strategies to optimize it.	National TB Programme
Ensure quality and enforce rational use of TB drugs available in the private market.	Ministry of Health, National Drug Authority

3. Increasing involvement and empowerment of patients and communities

Actions needed	Actors responsible
Ensure that health sector plans include active steps to increase the involvement of affected communities in the design, implementation, monitoring and evaluation of health promotion, preventive and curative services.	Ministry of Health supported by National TB Programme
Support efforts to improve the health workforce, and engage all available partners to help address TB and other public health priorities through primary health care.	National TB Programme
Identify and remove barriers to care for poor and other vulnerable communities.	National TB Programme with Ministry of Health and other relevant stakeholders
Mobilize resources to support community-level partnerships and local initiatives.	National TB Programme with Ministry of Health
Ensure communications that increase awareness of how to prevent the spread of tuberculosis, including its drug-resistant forms, through early detection of those who are ill and through quality care.	National TB Programme



Providing M/XDR-TB management and care

1. Hospital-based versus outpatient care

Actions needed	Actors responsible
To select models of M/XDR-TB management and care after a thorough analysis that takes into account social, ethical and health systems elements.	National TB Programme, Ministry of Health, Ministry of Finance
To assist NTPs in conducting the analysis required for selecting models of care.	WHO, Stop TB Partnership and technical agencies
To make use of the tools and resources available for piloting and scaling up MDR-TB management, including the GLC, GDF, and the Global Laboratory Initiative.	Donors, Ministry of Health, National TB Programme

2. Ensuring that TB treatment and care are consistent with ethics and human rights norms and promote social justice

Actions needed	Actors responsible
Explicit consideration of the ethical issues related to policy and service provision in management of M/XDR-TB and TB in general	Ministry of Health, National TB Programme, technical partners
Production, distribution and training on guidelines for ethical based management of M/XDR-TB	WHO
Establishing task forces as necessary to support an ethical based management of TB and M/XDR-TB.	Ministry of Health and other sectors as relevant

3. Involving all health care providers, including public hospitals

Actions needed	Actors responsible
Assessment of the current role of all public, private, corporate and voluntary sectors in M/XDR-TB diagnosis, treatment and care in the country.	National TB Programme
Phased involvement of institutions that outside the NTP are delivering diagnostic, treatment and care services to patients with M/XDR-TB to harness their capacity to deliver	National TB Programme



4. Collaborating with HIV programmes to strengthen both TB and HIV control

Actions needed	Actors responsible
To map extent of the problem by including HIV testing as a standard in national TB drug resistance surveys.	National TB and AIDS Programmes, Ministry of Health, technical partner agencies, HIV implementers
Nationwide scale up of collaborative TB/HIV activities.	National TB and AIDS Programmes, HIV implementers
Scale up the access for better TB diagnostic capacity in people living with HIV including culture technologies and molecular tests.	National TB Programme, Ministry of Health, National Laboratory services, HIV implementers
Increased engagement of community groups.	National TB and AIDS programmes, Ministry of Health, civil society, community leaders, HIV implementers
Improved collaboration between TB and HIV stakeholders and political commitment.	NTP and NAP, Ministry of Health, bilateral multilateral and NGO stakeholders and donors
Basic and operational research on optimal models of care in HIV related M/XDR-TB	Researchers, research organizations and funding agencies

Addressing the health workforce crisis

Actions needed	Actors responsible
Ensure that HRD needs for basic TB control and needs for scale up of M/XDR-TB control are included in overall health workforce development.	Ministry of Health, National TB Programme HRH departments, Ministry of Finance, Ministry of Planning
Revise/update strategic HRD plans (including private health care providers) to improve basic TB control and to scale up of M/XDR-TB control.	National TB Programme, HRH, partners; internal stakeholders
Collaborate and coordinate with other public health programmes, with other departments and services in the ministry of health (especially hospital and diagnostic services administration) and with other units in the provincial/district health services.	National TB Programme, HRH, relevant units and departments at all levels
Develop medium-term implementation plans to enable alignment with general HRD strategies and plans.	National TB Programme, HRH, partners, internal stakeholders
Collaborate with HRH planning units/departments of Ministry of Health, donors and technical support agencies in long term	National TB Programme, HRH, financial and technical support agencies



HRD within health system development for staffing and retention.	
Include resources for technical assistance for revision/updating of the HRD in proposals to Global Fund and other donors.	National TB Programme

Responding to the laboratory bottleneck

Actions needed	Actors responsible
Recognize and acknowledge the importance of laboratory systems in TB control and commit adequate human and financial resources.	Ministry of Health, Ministry of Finance
Set up a national mechanism to ensure coordination at all levels among departments responsible for laboratory services, disease-specific programmes, human resource development, and training.	Directorate responsible for Laboratory Services, National TB and AIDS Programmes, training and academic institutions
Ensure that health sector plans include adequately conceptualized and budgeted components for comprehensive laboratory capacity development.	Ministry of Health, supported by National TB Programme and Directorate of Laboratory Services
Identify and remove barriers to laboratory staff career development, remuneration, staff retention, and sustainability of technical competency.	Ministry of Health, supported by National TB Programme and Directorate of Laboratory Services
Prepare a national inventory of donor and technical partner efforts in laboratory strengthening and identify synergies and opportunities for optimization of resources.	National TB Programme, Directorate for Laboratory Services
Formulate/modify policies and screening algorithms to facilitate scale-up of rapid diagnostics for MDR- and XDR-TB control.	National TB Programme, Directorate for Laboratory Services
Engage private laboratories to improve access to TB diagnostic capacity, ensuring adequate support, training and quality assurance.	National TB Programme, Directorate responsible for Laboratory Services, training and academic institutions.



Ensuring access to quality-assured anti-TB medicines

Actions needed	Actors responsible
National commitment to increasingly (and in a phased manner if needed) buy quality assured FDCs.	Governments
Willingness to accept targets for 1 and willingness to monitor and report on progress against targets.	Governments
Provision of specific technical support and mechanisms to support WHO Prequalification of FDC suppliers in key priority countries (medium term) and/or to strengthen the capacity of NMRAs* (long term).	WHO, SMRAs,** donors, governments
Commitment to expand the market for international sources of quality assured FDCs and maintain low cost benchmark prices.	WHO/GDF and UNITAID
National commitment to rapidly enroll MDR-TB patients under proper programmatic conditions (as per realistic targets).	Governments
National commitment to increasingly (and in a phased manner if needed) buy quality assured SLDs.	Governments
National commitment to conditional approval of waivers or fast-track mechanisms for importation of quality assured SLDs, even if only for an interim period, while, where applicable, national capacities for production and/or procurement of quality assured SLDs are developed.	Governments
Willingness to accept targets for 5, 6 and 7 and willingness to monitor and report on progress against targets.	Governments
Provision of specific technical support and mechanisms to support the Prequalification of SLD suppliers in key priority countries (medium term) and/or to strengthen the capacity of NDRAs (long term)	WHO, SMRAs, donors, governments
Commitment to expand the market for international sources of quality assured SLDs and establish benchmark prices.	WHO/GDF and UNITAID

* Stringent National Medicine Regulatory Authorities

** National Medicine Regulatory Authorities



Restricting the availability of anti-TB medicines

Actions needed	Actors responsible
Put in place and enforce regulation that prohibits the dispensing of TB drugs without a prescription, and which prohibits physicians to sell TB drugs directly to patients.	Ministry of Health, drug regulatory body, National TB Programme
Explore regulatory approaches to restrict prescription and dispensing rights of all or selected TB drugs to quality-assured facilities only.	Ministry of Health, drug regulatory body, National TB Programme
Develop recommendations / guidelines for all health care providers, including pharmacies, stating that TB drugs should be prescribed and dispensed only in quality-assured facilities.	Ministry of Health, National TB Programme, partner organizations, drug regulatory body professional associations, pharmaceutical companies

Prioritizing TB infection control

Action needed	Actors responsible
Disseminate the 2009 WHO policy on TB infection control.	WHO and partners
Define roles and responsibilities within the Ministry of Health, Ministry of Justice, Ministry of Infrastructure, and civil society to facilitate the implementation of the WHO Policy.	Ministry of Health in collaboration with other ministries and civil society
Identify building infrastructure requirements and associated costs for the implementation of TB infection control.	Ministry of Health and other relevant ministries within government
Assess needs and provide technical assistance required for initiation and scale-up of the TB infection control at the national level.	Ministry of Health in collaboration with technical partners
Define and assess costs of human resource requirements (including need for engineers, building maintenance personnel, development of infection control staff) at country level.	Ministry of Health and Ministry of Finance
Develop and implement a research agenda to determine the effectiveness of the individual control on the impact of reduction of TB transmission. More operational research is needed on the operationalization of the individual controls described in the policy.	Ministry of Health and technical partners



Maximizing research opportunities to address M/XDR-TB

Action needed	Actors responsible
To facilitate field-testing of available molecular resistance assays.	Governments, development agencies, and technical agencies
To work towards the development of rapid methods for detection of resistance to second-line and other first-line drugs.	Researchers and research funding agencies
To consider investing in phase 4 clinical trials aiming at shortening, simplifying and improving efficacy of treatment regimens for drug-resistant TB.	Research funding agencies.
To consider investing in preventive therapy trials to define optimal treatment combinations and duration for preventive treatment of infected persons exposed to patients with drug-resistant TB.	Research funding agencies
To work in partnership to incorporate operations research on drug-resistant TB into the activities of TB control programmes.	Governments, development agencies, and technical agencies
To make full use of existing funding opportunities for operations research on drug-resistant TB.	Governments and technical agencies
To consider investing in research aimed at understanding the casual factors for the development of drug-resistant TB.	Governments, development agencies, and research funding agencies

Financing M/XDR-TB control and care

Action needed	Actors responsible
Preparation of country-specific budgets, based on national strategic plans.	National TB Programme, Ministry of Health, technical agencies
Mobilize funding based on a fully-budgeted national strategic plan, with particular attention to domestic funding in middle-income countries.	Ministry of Health, Ministry of Finance, bilateral donors, international organizations, development banks, Global Fund to Fight AIDS, Tuberculosis and Malaria, UNITAID