

The Global MDR-TB & XDR-TB Response Plan 2007–2008



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The Global MDR-TB & XDR-TB Response Plan 2007–2008

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Abbreviations

ACSM

advocacy, communication and social mobilization

ARV

antiretroviral (drugs)

CDC

United States Centers for Disease Control and Prevention

DRS

drug resistance surveillance

DST

drug susceptibility testing

FIND

Foundation for Innovative New Diagnostics

GDF

Global Drug Facility

GLC

Green Light Committee

Global Fund

Global Fund to Fight AIDS, Tuberculosis and Malaria

HIV

human immunodeficiency virus

KNCV

KNCV Tuberculosis Foundation

MDR-TB

multidrug-resistant tuberculosis

NACP

national AIDS control programme

NRL

national TB reference laboratory

NTP

national TB control programme

PIH

Partners In Health

SADC

Southern African Development Community

SRL

supranational TB reference laboratory

TB

tuberculosis

Union

International Union Against Tuberculosis and Lung Disease

USAID

United States Agency for International Development

WHO

World Health Organization

XDR-TB

extensively drug-resistant tuberculosis

1. Executive summary

This document details the activities required between 2007 and 2008 at the global, regional and national levels by the World Health Organization (WHO), members of the Stop TB Partnership and countries/areas to address the growing problem of drug-resistant tuberculosis (TB).

More than 400 000 cases of multidrug-resistant TB (MDR-TB¹) emerge every year as a result of under investments in basic activities to control TB, poor management of anti-TB drugs and transmission of drug-resistant strains. MDR-TB is much more difficult and costly to treat than drug-susceptible TB, but recent work has shown that treatment is feasible and cost-effective even in settings of limited resources.

In 2006, extensively drug-resistant TB (XDR-TB²) was reported in all regions of the world and was rapidly classified by WHO as a serious emerging threat to global public health, especially, in countries with a high prevalence of the human immunodeficiency virus (HIV). XDR-TB raises the possibility that the current TB epidemic of mostly drug-susceptible TB will be replaced with a form of TB with severely restricted treatment options. This phenomenon would jeopardize the progress made in recent years to control TB globally and would also put at risk the plans to progress towards universal access to HIV prevention and treatment. Patients with XDR-TB would have to be managed in the same way as TB patients before the antibiotic era. The economic, social and health security of countries and communities with a high prevalence of TB would be threatened by virtually untreatable TB among the breadwinners, parents and economically productive age groups.

1 MDR-TB is defined as TB resistant to the two main first-line drugs (isoniazid and rifampicin).

2 XDR-TB is defined as TB resistant to multiple drugs as well as to any one of the fluoroquinolone drugs and to at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin).

To combat this threat, WHO convened a Global Task Force on XDR-TB on 17 October 2006 in Geneva, Switzerland. Its members urged the implementation of additional measures to scale-up control of TB to prevent the emergence of new MDR-TB and XDR-TB cases as well as the acceleration of treatment for patients with drug-resistant forms of the disease. WHO was asked to update its *Guidelines for the programmatic management of drug-resistant tuberculosis* to incorporate the diagnosis and treatment of XDR-TB. Because *The Global Plan to Stop TB, 2006–2015* (the Global Plan),³ had been launched in January 2006, immediate revision of the component on MDR-TB was strongly recommended in order to reach universal access⁴ to sound management of MDR-TB and XDR-TB by 2015 in all countries; and near-to universal access in the 25 countries with high burdens of MDR-TB and XDR-TB by 2010. The revised plan will include the treatment of 1.6 million MDR-TB and XDR-TB patients by 2015, instead of 800 000 MDR-TB patients as stated in the original Global Plan.

The successful implementation of this plan demands accelerated diagnosis of and treatment for drug-susceptible TB. Strengthening the coverage and quality of basic TB control services is the first and most important measure to prevent MDR-TB and is the fundamental platform for deploying management of drug-resistant TB.

This document does not discuss the rationale or technical aspects of the global response to drug-resistant TB; rather, it details the main activities to be conducted at global, regional and country levels in 2007 and 2008 to operationalize the drug-resistance component of the Global Plan. It also marks the beginning of the integration of MDR-TB

3 *The Global Plan to Stop TB, 2006–2015*. Geneva, World Health Organization, 2006 (WHO/HTM/STB/2006.35).

4 Universal access is defined as access to diagnosis and treatment for 80% of the population.

and XDR-TB activities into general TB control activities. Urgent priorities include the gathering of information on the magnitude, distribution, trends, treatment practices and outcomes of XDR-TB; a significant expansion of TB laboratory services; development of sound TB infection control policies and their implementation; advocacy, communication and social mobilization (ACSM) to sustain political commitment; resource mobilization; and the promotion of research and development for new tools.

Full implementation of this Response Plan will save the lives of 134 000 people affected by MDR-TB and XDR-TB by the end of 2008. The global budget necessary to respond to MDR-TB and XDR-TB in 2007–2008 is estimated at US\$ 2.15 billion.

This plan has been reviewed and endorsed by the Working Group on MDR-TB of the Stop TB Partnership, and will be the blueprint for the Working Group to operationalize the drug-resistant TB component of the Global Plan. It has also been reviewed and endorsed by the WHO Strategic and Technical Advisory Group for TB at its meeting in 2007.

2. Background

While the definition of MDR-TB has been long established and is now widely accepted, the definition of XDR-TB is more recent. In 2005, the United States Centers for Disease Control and Prevention (CDC), WHO and 14 supranational TB reference laboratories (SRLs) initiated a study to determine the extent to which resistance to second-line anti-TB drugs had emerged among MDR-TB isolates. The data were published by WHO and CDC in March 2006 in an article⁵ in which XDR-TB was first defined.⁶ The study, which analysed 17 690 isolates from 49 countries, showed that 20% of all isolates collected were MDR-TB and that 2% were XDR-TB. XDR-TB was identified in all regions. Latvia and the United States were able to provide data on drug susceptibility for their entire TB populations, showing that 4% and 19% of their MDR-TB cases had XDR-TB, respectively. The Republic of Korea reported on the majority of its TB cases, to show that 15% of MDR-TB cases had XDR-TB. The total number and proportion of XDR-TB isolates observed in this study increased from 5% of MDR-TB isolates in 2000 to 7% of MDR-TB isolates in 2004.⁷

During its fifth meeting in May 2006, the Stop TB Working Group on MDR-TB⁸ dis-

5 Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs – worldwide, 2000–2004. *Morbidity and Mortality Weekly Report*, 2006, 55(11):301–305.

6 XDR-TB was initially defined as MDR-TB with further resistance to three or more of the six main classes of second-line anti-TB drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine and para-aminosalicylic acid).

7 Using the initial XDR-TB definition.

8 *Report of the Fifth annual meeting of the Stop TB Working Group on MDR-TB (formerly DOTS-Plus for MDR-TB)*. Atlanta, GA, USA, 12 May 2006 (WHO/HTM/STB/2006.XXX; available at: http://www.stoptb.org/wg/dots_plus/assets/documents/Atlanta%20meeting%20report.pdf).

cussed the emergence of XDR-TB and defined it as a major threat to progress in controlling MDR-TB. It recommended further analysis of the data collected by the SRL network, which had been set up by WHO in 1994 (and subsequently enlarged) as part of the WHO anti-TB drug resistance surveillance project. It also examined the results of a study being conducted in South Africa, which were published later that year.⁹

This was an outbreak of HIV-associated XDR-TB in Tugela Ferry, KwaZulu-Natal Province, South Africa. From January 2005 to March 2006, 221 MDR-TB cases were identified in Tugela Ferry, of whom 53 (23%) were also resistant to kanamycin and ciprofloxacin. Half of the patients had never previously received anti-TB treatment. Of the 53 patients, 44 were tested for HIV and all were found to be HIV-positive. Mortality was extremely high: 52 (98%) of the patients died within a median range of 16 days of initial sputum collection, of whom 15 (28%) were receiving treatment with antiretroviral drugs (ARVs).

By 2006, XDR-TB had been reported as a serious, emerging threat to public health and TB control, raising concerns of TB epidemics with severely restricted treatment options that could jeopardize the progress made in global TB control. Furthermore, XDR-TB poses specific challenges to global control of HIV/AIDS and could compromise the progress already made in many countries towards universal access to HIV treatment and prevention.

In June 2006, WHO's Strategic and Technical Advisory Group for Tuberculosis urged WHO to take immediate and effective action to address MDR-TB and XDR-TB in the WHO African Region. Subsequently, in August 2006, the outbreak in Tugela Ferry was

9 Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Gandhi NR et al. *Lancet*, 2006; 368: 1575–1580.

discussed at the XVI International AIDS Conference in Toronto, Canada.

In October 2006, the WHO Stop TB and HIV departments organized a meeting of the Global Task Force on XDR-TB at WHO headquarters in Geneva, Switzerland, in response to the XDR-TB emergency. During this meeting, eight recommendations were put forward to the international TB community, outlining key areas of response, beginning with strengthening of basic TB and HIV/AIDS control and proper management of MDR-TB following WHO guidelines.¹⁰ In addition, the XDR-TB definition was revised.¹¹ In February 2007, WHO reported on the initial achievements in addressing XDR-TB, outlining more than 80 activities carried out by WHO and Stop TB Partnership members following the recommendations issued by the Task Force.¹²

10 *Report of the Meeting of the WHO Global Task Force on XDR-TB* (available at: http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.375_eng.pdf).

11 XDR-TB is defined as resistance to at least rifampicin and isoniazid (which is the definition of MDR-TB), in addition to any fluoroquinolone, and to at least one of the three injectable drugs used in anti-TB treatment: capreomycin, kanamycin and amikacin.

12 *Control of XDR-TB – Update on progress since the Global XDR-TB Task Force Meeting, 9–10 October 2006* (available at: http://www.who.int/tb/xdr/globaltaskforce_update_feb07.pdf).

Objectives for the response to MDR-TB and XDR-TB in 2007 and 2008

1. Strengthen basic activities to control TB and HIV/AIDS, as detailed in the Stop TB Strategy and the Global Plan, to avoid additional emergence of MDR-TB and XDR-TB

In pursuit of Objective One, WHO and members of the Stop TB Partnership will seek to carry out the following activities:

- a. Mobilize expert teams to review basic activities for control of TB and HIV/AIDS in countries likely to have a high prevalence of XDR-TB; to accelerate improvements in control measures and; to gain political commitment to implement the Stop TB Strategy.
- b. Deploy international staff in priority MDR-TB countries, especially in those with high or increasing levels of HIV infection, to assist national TB control programmes (NTPs) in improving control of TB, TB/HIV, MDR-TB and XDR-TB.
- c. Employ two additional staff at WHO headquarters: one for overall coordination of XDR-TB activities, and one for coordination of measures to strengthen laboratories.
- d. Under the leadership of the Secretariat of the Working Group on MDR-TB, revise the Global Plan to link new actions and needs in light of XDR-TB emergence, devoting particular attention to scaling-up the laboratory strengthening component and the number of MDR-TB patients to be treated. The costs of treating XDR-TB and of infection control measures to be reflected in the budget of the revised Global Plan.
- e. Assist countries in applying for new rounds of funding from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and reprogramming existing grants to reflect actions needed to prevent and control MDR-TB and XDR-TB.
- f. Under WHO leadership, define appropriate responses to MDR-TB and XDR-TB in HIV policy and practice from global to local level, and begin the process of implementation at country level.

- g. Make assessments on the availability and patterns of use of second-line anti-TB drugs in the public and private sectors in selected countries, in order to ensure the use of these drugs according to WHO guidelines and to encourage best practices.
- h. Advocate for and encourage the involvement of all health-care providers in sound TB, MDR-TB and XDR-TB control, including the private sector and prison services.
- i. Foster the use of quality-assured first- and second-line anti-TB drugs, according to WHO guidelines, by Member States to avoid additional development of MDR-TB and XDR-TB. Encourage strong regulation of second-line drugs, particularly by national governments.

2. Scale-up the programmatic management of MDR-TB and XDR-TB to reach the targets set forth in the Global Plan

In pursuit of Objective Two, WHO and members of the Stop TB Partnership will seek to carry out the following activities:

- a. Expand and establish coordination between partners; and review global implementation of sound MDR-TB and XDR-TB control activities vis-à-vis the Global Plan through the meetings of the Stop TB Working Group on MDR-TB and its subgroups and the annual WHO report on global TB control.
- b. Under the leadership of WHO headquarters (both HIV and Stop TB departments), update the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* by commissioning a group of experts to revise in particular the chapter on co-management of HIV infection and MDR-TB, including concomitant treatment with ARVs. The revised version should incorporate guidance on human rights, enforced quarantine and involuntary treatment for XDR-TB as well as address the early use of anti-TB drugs under development on compassion-

ate grounds. The guidelines should promote the standards set forth in the *Patients' charter for tuberculosis care*¹³ as well as the ambulatory management of MDR-TB patients during the full course of treatment, to make it more convenient to patients and their families; to accelerate the scale up of treatment provision as per the Global Plan, save costs, reduce risk of nosocomial infection; and to strengthen community involvement in TB control. In addition, the guidelines and their revisions should be translated into priority languages, printed and widely disseminated.

- c. Strengthen technical assistance on MDR-TB management to countries, and expand the capacity of the Green Light Committee (GLC) mechanism to promote access to quality-assured second-line anti-TB drugs. Enhance the capacity of technical assistance on MDR-TB management available through WHO and technical agencies by expanding the pool of adequately trained MDR-TB consultants.
- d. WHO and technical partners to ensure the dissemination and implementation at country level of the new recording and reporting system for routine management of drug-resistant cases.
- e. Continue discussion of the importance of limiting the spread of XDR-TB under the new International Health Regulations¹⁴ and provide information to Member States on the management

13 Patients' charter for tuberculosis care available at http://www.who.int/tb/publications/2006/istc_charter.pdf

14 The International Health Regulations (IHR) provide for a new communication mechanism for any event with the potential to cause a public health emergency of international concern. The IHR provide a framework for establishing what exactly national authorities are expected to do in order to identify an emergency concerning XDR-TB, notify the international community and provide an effective response.

of XDR-TB patients and their close contacts. In addition, define the required steps needed in case of an XDR-TB event at national and international levels.

- f. Develop generic training modules to accompany the revised WHO *Guidelines for the programmatic management of drug-resistant tuberculosis*.
- g. WHO and partners to expand the training workshops on MDR-TB and XDR-TB management for NTP staff organized at regional level.
- h. Accelerate the prequalification of quality-assured second-line anti-TB drug manufacturers and continue to advocate for reduction in prices of second-line anti-TB drugs.
- i. The Global Drug Facility (GDF) to address the current constraints resulting in long delays in procuring second-line anti-TB drugs to GLC-approved programmes. GDF to create and manage a buffer stock of these drugs with funding sought from UNITAID.
- j. Encourage NTPs with established GLC-approved MDR-TB control programmes to publish data on the programmatic management of XDR-TB and treatment outcomes.
- k. Plan for introduction of new drugs once they become available, through coordination with the Stop TB Partnership research and development working groups.

3. Strengthen laboratory services for adequate and timely diagnosis of MDR-TB and XDR-TB

In pursuit of Objective Three, WHO and members of the Stop TB Partnership will seek to carry out the following activities:

- a. Develop a strategic, budgeted plan for strengthening laboratory services, including the deployment of rapid diagnostic tests, led by the laboratory strengthening subgroup of the DOTS Expansion Working Group.
- b. Accelerate access to rapid rifampicin testing to improve case detection of all patients suspected of MDR-TB and XDR-TB, and in particular in high HIV

- prevalence settings, in collaboration with the Foundation for Innovative New Diagnostics (FIND).
- c. Continue to expand the capacity for, and ensure the quality of, first- and second-line drug susceptibility testing (DST), mainly of the aminoglycosides and fluoroquinolones, since DST of most second-line anti-TB drugs is not yet standardized, through additional training courses, technical assistance and strategic laboratory network planning.
 - d. Expand the WHO SRL network with additional laboratories, particularly those in low-resource regions, and continue the annual meetings.

4. Expand surveillance of MDR-TB and XDR-TB to better understand the magnitude and trends of drug resistance and the links with HIV

In pursuit of Objective Four, WHO and members of the Stop TB Partnership will seek to carry out the following activities:

- a. Incorporate second-line DST (mainly of the aminoglycosides and the fluoroquinolones) into the ongoing round of routine drug resistance surveys by SRLs to obtain a better picture of the magnitude and trends of XDR-TB globally.
- b. Conduct rapid drug resistance surveys in priority countries of the Southern African Development Community (SADC) in collaboration with the SRLs in South Africa (Medical Research Council) and the United Kingdom (Health Protection Agency, Mycobacterium Reference Unit).
- c. Strengthen and expand the SRL network, particularly in the WHO African Region.
- d. WHO and the International Union Against Tuberculosis and Lung Disease (Union) to publish the fourth drug resistance surveillance report by the end of 2007. Additionally, analyse and publish data from XDR-TB rapid surveys on failure cases and gather and analyse information on the epidemiological relationship between MDR-TB and HIV.

- e. Develop technical policy guidelines for the proper conduct of second-line DST through a meeting convened by WHO with technical partners.
- f. Accelerate efforts to conduct drug resistance surveys and surveillance, particularly in African countries that have not yet reported data on drug resistance trends, and in countries where standardized second-line regimens have been implemented.

5. Foster sound infection control measures to avoid MDR-TB and XDR-TB transmission to protect patients, health workers, others working in congregate settings, and the broader community, especially in high HIV prevalence settings

In pursuit of Objective Five, WHO and members of the Stop TB Partnership will seek to carry out the following activities:

- a. CDC to assist WHO with updating the *WHO Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings* published in 1999.
- b. Ensure publication and wide dissemination of the guidelines *Tuberculosis infection control in the era of expanding HIV care and treatment*.
- c. WHO to develop, through a global consultation of appropriate experts, guidelines for programme managers of NTPs and national AIDS control programmes (NACPs) to implement infection control measures nationwide. This guidance needs to be followed by a plan to support implementation of the infection control guidelines at country level, with appropriate indicators, and mechanisms to monitor implementation over time. This work to be coordinated by the subgroup on infection control, recently established under the TB/HIV Working Group of the Stop TB Partnership.
- d. Expand the pool of infection control consultants by organizing training sessions and on-the-job training of potential consultants.

6. Strengthen ACSM for sustained political commitment and a patient-centred approach to treatment

In pursuit of Objective Six, WHO and members of the Stop TB Partnership will seek to carry out the following activities:

- a. Encourage all health-care providers to follow the *International standards for tuberculosis care*¹⁵ to curb further development of MDR-TB and XDR-TB.
- b. Update the WHO and Stop TB Partnership web sites on XDR-TB to contain monthly activity updates, frequently-asked questions, press releases, articles and meeting reports.
- c. Prepare a generic advocacy pack containing information materials for patients, health-care workers, employers, donors and civil society, which promotes health education and communication activities that help to reduce stigma attached to TB, coordinated by the Advocacy and Resource Mobilization Subgroup of the MDR-TB Working Group of the Stop TB Partnership.
- d. Strengthen communication with key country and global advocacy groups on XDR-TB, develop and distribute treatment literacy materials and the *Patient's Charter*.¹⁶
- e. Deliver technical assistance to countries aimed at improving their communications on TB, MDR-TB and XDR-TB.
- f. Add an XDR-TB component to the current Advocacy Communication and Social Mobilization Working Group training materials for consultants.
- g. Advocate for the XDR-TB emergency and response needs at the following important events:
 - i. World TB Day, 24 March;
 - ii. Release of the Global report on drug resistance surveillance containing data on XDR-TB and MDR-TB/HIV, October 2007;
 - iii. Meeting of the Stop TB Working Group on MDR-TB, Tbilisi, Georgia, 20-22 September 2007;
 - iv. European high-level ministerial forum on TB control, Berlin, 22 October 2007;
 - v. Union World Conference on Lung Health, Cape Town, South Africa, November 2007;
 - vi. International AIDS Society conferences in Sydney (2007) and Mexico (2008).

15 International standards for tuberculosis care Available at http://www.who.int/tb/publications/2006/istc_report_shortversion.pdf

16 Patient's Charter Available at http://www.stoptb.org/globalplan/assets/documents/IP_OMS_Charte_GB_Epreuve.pdf

7. Pursue resource mobilization at global, regional and country levels to ensure that necessary resources are available

In pursuit of Objective Seven, WHO and members of the Stop TB Partnership will seek to carry out the following activities:

- a. Assist countries with developing plans for activities in response to MDR-TB and XDR-TB, in particular through assistance, where needed, in preparing proposals for the Global Fund.
- b. Seek funding for a sustainable approach at the global level to control MDR-TB and XDR-TB.
- c. Initiate scale-up of access to second-line anti-TB drugs to GLC-approved countries by negotiating financial support from UNITAID, the innovative funding mechanism established by the governments of Brazil, France, Chile, Norway and the United Kingdom, to accelerate access to high-quality drugs and diagnostics for HIV/AIDS, malaria and TB in countries with a high burden of these diseases.
- d. Responsible authorities for trials of new anti-TB drugs should consider the evaluation in parallel of new drugs for both susceptible and resistant TB cases.

8. Promote research and development into new diagnostics, drugs, vaccines, and operational research on MDR-TB management to shorten the length of treatment,

In pursuit of Objective Eight, WHO and members of the Stop TB Partnership will seek to carry out the following activities:

- a. Encourage the private sector and academia to commit more human and financial resources into research, in collaboration with the Stop TB Partnership secretariat and Working Groups on new tools.
- b. Advocate for additional funding for clinical trials and for a policy on rapid access to new drugs, once approved by stringent drug regulatory authorities.
- c. Define priority areas of operational research for MDR-TB and XDR-TB; encourage research activities at country level; and coordinate partners to avoid duplication of work and ensure

optimal use of resources, according to WHO guidelines, through the research subgroup of the Stop TB Working Group on MDR-TB. Strengthening of the recording and reporting system for MDR-TB is important to conduct operational research activities (See 2.d. above).



4. Milestones

In order to assess progress in implementing this Response Plan, specific indicators and milestones have been developed to reflect the priorities of the Stop TB Strategy and the revised MDR-TB component of the Global Plan (Table 1).

The Stop TB Working Group on MDR-TB will regularly monitor the milestones of the Response Plan and will report annually on its implementation.

Table 1. Milestones for implementation of the Global MDR-TB and XDR-TB Response Plan 2007–2008

Indicator	2007	2008
Number of cultures performed	1 800 000	2 200 000
Number of drugs susceptibility tests performed	750 000	900 000
Number of new national or provincial reference laboratories established	21	22
Number of MDR-TB patients enrolled on treatment (excluding XDR-TB)	60 000	100 000
Number of XDR-TB patients enrolled on treatment	6 000	10 000
% of MDR-TB cases enrolled on treatment of those estimated (excluding XDR-TB)	16%	28%
% of XDR-TB patients enrolled on treatment of those estimated	25%	43%

It is expected that implementing the Response Plan and reaching the milestones indicated in Section 4 above will have a profound impact on the response to MDR-TB and XDR-TB at the global level in both the short and longer term. The expected impact is summarized below

- The international and regional coordination that is necessary to enable all countries to provide universal access to diagnosis and treatment of MDR-TB by the year 2015 will have been established.
- The capacity to scale-up the MDR-TB component of the Global Plan will be solidly established at country level by the end of 2008.
- In 2007, 49 000 lives will be saved and 85 000 in 2008, paving the way to achieve the goal of saving 1.2 million lives by 2015.

6. Partnerships

Prevention and control of MDR-TB and XDR-TB require coordinated input from all the technical and financial agencies involved. The Stop TB Partnership Secretariat, which coordinates over 400 international organizations, countries, funding agencies from the public and private sector, governmental and nongovernmental organizations and people representing the affected TB community and its working groups; the GLC and the GDF; the SRL network; and TB and HIV/AIDS civil societies, are all crucial to fighting this emergency.

All seven working groups of the Stop TB Partnership: MDR-TB; DOTS Expansion; TB/HIV; Advocacy, Communication and Social Mobilization; and the three groups for new TB diagnostics, drugs and vaccines are already working on the threat of MDR-TB and XDR-TB. The MDR-TB Working Group is highly involved in policy recommendations and the implementation and scale-up of sound MDR-TB and XDR-TB control practices. The DOTS Expansion Working Group is facilitating work, especially in the 22 high TB burden countries, in the areas of health systems and laboratory strengthening, involvement of all health-care providers, and Global Fund collaboration and support. The TB/HIV Working Group has established a subgroup on infection control as a result of XDR-TB. The ACSM Working Group has set up a task force on XDR-TB advocacy and communication. The new tools working groups are all involved in coordinated approaches to enhance research and development through the Task Force on Retooling, which coordinates research plans and efforts with those of the implementation working groups.

The GDF of the Stop TB Partnership provides countries with the drugs and supplies needed to diagnose and treat adults and children with both drug-susceptible and drug-resistant TB.¹⁷ Along with drug provision, it provides direct technical assistance on drug management. The GDF provides more

anti-TB drugs – free of charge – to countries unable to pay for them than any other group. It also procures anti-TB drugs for countries that have the means to buy them and can ship drugs at short notice in the event of a humanitarian or natural disaster, armed conflict, or other situation where life-saving anti-TB drugs are unavailable.¹⁸

The main technical partners in TB have been working for many years with WHO, such as the Union, KNCV Tuberculosis Foundation (KNCV) and CDC, and are of vital importance for the delivery of technical assistance and for strengthening capacity. Consultants for different elements of TB control, and mainly MDR-TB control, have been trained at different consultant courses. An important and underused source for strengthening control of MDR-TB and XDR-TB is also staff working in ongoing GLC-approved MDR-TB control programmes. The Lilly MDR-TB Partnership plays an important role by involving professional health-care organizations in the response to MDR-TB and XDR-TB, and has been also for a number of years providing a limited quantity of two important second-line anti-TB drugs at concessional prices as well as technology transfer for the production of these drugs in middle- and low-income countries.

WHO will, through its headquarters and regional and country offices, provide leadership and coordination to the global response to MDR-TB and XDR-TB. Within WHO, the lead will be taken by the Stop TB Department and the Secretariat of the Working Group on MDR-TB of the Stop TB Partnership in close collaboration with the HIV Department. Outside WHO, the chief partners will coordinate through the MDR-TB Working Group. Several departments within WHO will also contribute to the work including:

- Medicines Policy and Standards of the Health Technology and Pharmaceuticals cluster – for use of anti-TB drugs

17 <http://www.stoptb.org/gdf/>

18 http://www.stoptb.org/gdf/assets/documents/GDF_10in6.pdf

- according to WHO guidelines, and quality assurance of anti-TB drugs.
- Epidemic and Pandemic Alert and Response of the Communicable Diseases cluster – for the implications of XDR-TB on the new International Health Regulations.
 - Ethics, Trade, Human Rights and Law of the Sustainable Development and Health Environments cluster – for policy recommendations on involuntary treatment, use of drugs under development, and human rights of TB patients, including those with MDR-TB and XDR-TB.
 - Equity, Poverty and Social Determinants of Health of the Evidence and Information for Policy cluster – for poverty and social determinants of TB, including XDR-TB.

7.

Regional MDR-TB and XDR-TB response activities

For each WHO region, the following information is provided in Annex 1:

- epidemiology of MDR-TB and XDR-TB;
- status of SRLs and national TB reference laboratories (NRLs);
- GLC-approved MDR-TB control projects;
- Global Fund status for drug resistance surveillance and MDR-TB control;
- human resource development;
- priority countries for MDR-TB and XDR-TB response activities;
- MDR-TB and XDR-TB response activities in 2007–2008;
- milestones for 2007–2008.

On 1 November 2006, global leaders in TB control called for US\$95 million emergency funding to address the XDR-TB problem, with focus on the SADC countries most in need in 2007.¹⁹ This budget request was broken down into US\$80 million for the following country needs:

- US\$35 million for strengthening TB control activities and preventing anti-TB drug resistance through in-country operations, including infection control measures and laboratory capacity building;
- US\$40 million for accessing high-quality second-line anti-TB drugs;
- US\$5 million for developing rapid TB diagnostic tests.

It is not possible at this time accurately to quantify how much has been granted or pledged to countries for these needs, but the section below details the needs for specific support.

In addition, the emergency request asked for US\$15 million for technical assistance in affected countries (focusing again on the SADC countries) provided by international agencies. This has, to date (June 2007), resulted in the contributions of approximately US\$8 million to WHO and partners.

- The UK Department for International Development has granted US\$3 million to WHO for the XDR-TB response, with focus on SADC countries – a major contribution that is allowing WHO and partners to update policy documents and plans to reflect the XDR-TB threat, measure the magnitude of XDR-TB in Southern African countries, employ national and international staff to key countries to coordinate the XDR-TB response, train national TB staff in sound MDR-TB management and infection control, expand

- laboratory capacities in Southern Africa and support activities at country level.
- The Italian Cooperation has granted emergency funds to WHO to support the XDR-TB response, with focus on South Africa (US\$305 000).
- The Open Society Institute has committed financial resources to Partners In Health (PIH) to support TB control efforts in Lesotho. These funds will also support a WHO international officer to be based in the country.
- The United States Agency for International Development (USAID) has agreed to support significant activities in South Africa, including an international WHO staff member to be based in Pretoria (US\$1.3 million).
- FIND has committed to undertake large-scale evaluation and demonstration projects of tests for rapid MDR-TB diagnosis in South Africa and neighbouring countries.
- USAID, through its Tuberculosis Control Assistance Program, has agreed to fund MDR-TB and XDR-TB activities, including capacity-building activities.

In addition to specific funds on XDR-TB, a number of initiatives and donors are supporting MDR-TB activities, including:

- UNITAID has agreed to provide US\$20 million towards second-line anti-TB drugs to GLC-approved projects in 17 mainly low-income countries. This will contribute significantly to scaling-up control of MDR-TB using quality-assured drugs, as outlined in the Global Plan. UNITAID will also support the WHO prequalification project on HIV, TB and malaria drugs and is considering supporting MDR-TB diagnostics.
- USAID, which is supporting WHO (at headquarters, regional and country levels) and partners, with MDR-TB surveillance and control activities for several years.
- Eli Lilly, in addition to supplying two second-line anti-TB drugs at concessional prices to the GLC, will transfer technology to manufacture two sec-

¹⁹ For further information see: http://www.who.int/tb/xdr/news_release_01nov06/en/index.html.

ond-line anti-TB drugs, supporting WHO and a number of partner organizations working on MDR-TB control (including the International Council of Nurses, World Medical Association, PIH, International Hospital Federation, International Federation of Red Cross and Red Crescent Societies).

- The Bill & Melinda Gates Foundation, which has funded WHO and partners for MDR-TB activities since 2000 (funding will end summer 2007).
- The United States Global AIDS Coordinator through USAID, has contributed US\$2 million to support GLC costs associated with providing technical assistance and monitoring for Global Fund grant recipients.

Another important source of funds for the GLC is the Global Fund, which agreed at its 13th board meeting that countries requesting funds for MDR-TB control must include a cost-sharing element for GLC services corresponding to a flat rate per grant per year that will not exceed US\$50 000. A memorandum of understanding between the Global Fund and the Stop TB Partnership is expected to be signed in the final quarter of 2007 to formalize the flow of funds.

9. Budget requirements

The additional budget requirements for the global MDR-TB and XDR-TB response plan for 2007–2008 are divided into four parts:

1. Resource needs in 25 priority MDR-TB and XDR-TB countries.
2. Resource needs in non-high MDR-TB burden countries.
3. Technical assistance: resource needs and gaps for technical cooperation by WHO and members of the Stop TB Partnership at global and regional levels.
4. Research and development for new drugs, diagnostics and vaccines, and operational research.

1. Resource needs in 25 priority MDR-TB and XDR-TB countries

Priority MDR-TB and XDR-TB countries have been chosen based on estimated MDR-TB burden, estimated proportion of MDR-TB (>10% among both new and re-treatment cases combined) and, for some countries, data on XDR-TB. The selected countries constitute 85% of the estimated global burden of MDR-TB (Table 2).

Table 2. The 25 priority MDR-TB and XDR-TB countries

WHO region	Country	Estimated total number of MDR-TB cases	Estimated proportion of MDR-TB among combined* cases (%)
WPR	China	139 894	8.9
SEAR	India	87 413	4.1
EEUR	Russian Federation	34 055	16.8
AFR	South Africa	10 348	2.6
SEAR	Indonesia	10 024	1.8
EMR	Pakistan	9 306	3.2
AFR	Nigeria	7 969	2.0
EEUR	Ukraine	7 854	13.6
SEAR	Bangladesh	7 216	2.2
EEUR	Uzbekistan	7 043	18.5
EEUR	Kazakhstan	6 718	23.4
AFR	Ethiopia	5 102	1.9
WPR	Viet Nam	5 033	3.2
AFR	Democratic Republic of the Congo	4 941	2.3
SEAR	Myanmar	4 756	5.2
WPR	Philippines	4 469	1.8
EEUR	Azerbaijan	1 579	18.8
EEUR	Republic of Moldova	1 459	18.9
EEUR	Tajikistan	1 394	10.9
EEUR	Georgia	980	19.5
EEUR	Kyrgyzstan	766	10.6
EEUR	Belarus	707	10.4
EEUR	Lithuania	422	16.4
EEUR	Latvia	208	11.5
EEUR	Estonia	147	20.1
TOTAL		359 802	5.1

*New MDR-TB cases plus previously treated MDR-TB patients.

Data to calculate the resource needs and available funds by country are taken from the Global Plan II and the 2007 WHO report on global tuberculosis control.²⁰

The current Global Plan estimates that from 2006 to 2015 almost 800 000 MDR-TB cases should receive adequate treatment. In the proposed revised version, the corresponding number is estimated at 1.6 million MDR-TB cases. The revised Global Plan aims for 61% of the burden of MDR-TB and XDR-TB cases in the 25 high MDR-TB burden countries to be properly treated, from 2006 to 2015, compared with 23% of MDR-TB cases in the current Global Plan. These estimates are derived from country-by-country calculations.

The new budget requirements for drug resistance management also include the more costly management of XDR-TB, which has been estimated to account for 13% of global MDR-TB costs, with regional variations depending on estimated regional XDR-TB patterns. The additional costs estimated for managing XDR-TB cases lie predominantly in the more costly second- and so-called third-line drug regimens, DST to second-line anti-TB drugs, prolonged hospitalization, additional budget requirements for management of adverse events and strengthened infection control measures. While the costs of treatment of MDR-TB range from US\$1 979 to US\$8 196 per patient treated, those of XDR-TB have been estimated to range from US\$6 843 to US\$15 579, also depending on regional differences in second-line drug resistance patterns that influence the drug costs, and other cost differences, mainly for hospitalization. It includes as well the costs for laboratory strengthening (see Annex 2).

20 *Global tuberculosis control: surveillance, planning, financing. WHO report 2007.* Geneva, World Health Organization, 2007 (WHO/HTM/TB/2007.376); available at http://www.who.int/entity/tb/publications/global_report/2007/pdf/full.pdf.

Based on the revised Global Plan, the total resource needs for the 25 high MDR-TB and XDR-TB burden countries in 2007 are estimated at US\$566 million. In these calculations, approximately 60 000 MDR-TB and 6000 XDR-TB cases will receive adequate treatment in 2007. In 2008, US\$891 million is estimated to be needed to treat approximately 100 000 MDR-TB and 10 000 XDR-TB patients. A detailed budget is shown in Annex 2. Annex 3 shows MDR and XDR-TB patients expected to be treated in 2007 and 2008 by country.

The Global Fund, the newly established UNITAID (which will support the global scale up of second-line anti-TB drugs, mainly in countries classified as low-income by the World Bank), bilateral agencies, foundations and multilateral agencies are key partners for funding urgent needs at country levels.

2. Resource needs in non-high MDR-TB burden countries

While the revised MDR-TB component of the Global Plan calls for universal access to MDR-TB diagnosis and treatment by 2015, other countries also need support to scale-up MDR-TB management in this biennium. The costs for this need are estimated to be US\$107 million for 2007 and US\$155 million for 2008. These estimates are calculated on the assumption that these non-high MDR-TB burden countries will require 15% of total global costs.

3. Technical assistance: resource needs and gaps for technical cooperation by WHO and members of the Stop TB Partnership at global and regional levels

Technical assistance includes activities by WHO and partners on strategic and technical support; capacity building; surveillance; monitoring and evaluation; ACSM; operational research; and research and development.

Following the meeting of the Global Task Force on XDR-TB, and as mentioned above, WHO estimated the financial needs for technical cooperation to tackle the XDR-TB emergency, with focus on SADC countries at US\$15 million. This budget also included funds needed at global level, particularly for

revision of TB, HIV and MDR-TB policy documents in light of XDR-TB, and approximately US\$8 million has been received thus far by WHO and partners.

The total resource needs estimated to be needed for technical cooperation by WHO and members of the Stop TB Partnership in 2007–2008 amount to US\$102 million. Considering that US\$8 million has been received in 2007, the funding gap for technical cooperation is **94 million** (US\$34 million in 2007 and US\$60 million in 2008).

4. Research and development for new drugs, diagnostics, vaccines and operational research

The Stop TB research working groups have confirmed that research and development associated with XDR-TB is US\$314 million for 2007 and 2008 (US\$157 million each year). This includes diagnostics, drugs and vaccines research. However, it does not include costs of operational research, as per the research agenda on MDR-TB, estimated at US\$20 millions for 2007–2008 (US\$10 million each year). A total of **US\$334 million** is the total estimated cost of research for the MDR-TB and XDR-TB response.

To summarize, the total resource needs at country level in 2007–2008 are estimated at US\$1.72 billion, of which US\$163 million is estimated as available in 2007, leaving a funding gap of US\$1.56 billion at country level. For technical cooperation by WHO and members of the Stop TB Partnership, US\$102 million is needed, of which US\$8 million has been pledged in 2007. In total, the funding gap of the Response Plan to MDR-TB and XDR-TB is US\$1.65 billion, excluding research and development.

Adding the needs for research and development, i.e. US\$334 million, the total global needs to scale-up to the levels of diagnosis and treatment of MDR-TB and XDR-TB required in 2007–2008 to accelerate progress to reach universal access by 2015, amount to US\$2.15 billion (see Table 3).

Of note is that the budget requirements at country level are based on calculations from a provisionally updated Global Plan. The costs are based on MDR-TB and XDR-TB management per patient from a provider perspective, with appropriate adjustments for income level and, sometimes, to the drug regimen, to reflect the regional drug resistance pattern. All relevant costs are incorporated, including items such as the drug regimen (including both first- and second-line anti-TB drugs), hospitalization, DOT visits, establishing and sustaining culture and DST laboratories, laboratory tests (smear, culture, DST), X-rays, training, programme and data management, food parcels and management of adverse events.²¹ As such, these costs include all laboratory tests needed to be performed on MDR-TB and XDR-TB patients for diagnosis and treatment monitoring. The calculated costs for laboratory consider two components: capital investments (equipment, refurbishment and/or construction of laboratories) and running costs (including culture, and rapid and conventional DST methods). Estimated unit costs are based on the current catalogue prices. A reduction of the unit costs is foreseen because a large amount of equipment and consumables will be procured. Higher costs are estimated in the first year of implementation due to the greater component of capital investment needed to build and equip the pool of laboratories sufficient to process all culture and DST tests.

21 For further information see: http://whqlibdoc.who.int/publications/2006/924159487X_eng.pdf

Table 3. Estimated costs of the global response to MDR-TB and XDR-TB, 2007–2008

Items	2007	2008	Total	Funding gap
Resources needed at country level	673	1046	1719	1557
Technical assistance	42	60	102	94
Research and development	167	167	334	334
Total	882	1273	2155	1985

Regional MDR-TB and XDR-TB response activities WHO African Region

Epidemiology of MDR-TB and XDR-TB

By 2002, 37% of African countries had conducted baseline drug resistance surveys. The region has made good progress in expanding baseline surveys since 2002 and data will shortly be available from Ethiopia, Madagascar, Namibia, Rwanda and the United Republic of Tanzania, with several other countries planning baseline or repeat surveys (Lesotho, Malawi, Mozambique, Uganda, Zambia and Zimbabwe). WHO estimates a 2% prevalence of MDR-TB for the region as a whole but there are variations, with Côte D'Ivoire, Democratic Republic of the Congo (Kinshasa) and Mozambique showing much higher rates of resistance. There are few trends in the region, but those available from Botswana show a significant upward trend in prevalence of resistance. Another survey due to take place in 2007 in Botswana will help to further establish trends that may be indicative of the situation in other countries in the region. The low prevalence of resistance in the region has been fairly consistent in surveys; however it is likely that many smaller epidemics of MDR-TB and even XDR-TB, where second-line anti-TB drugs have been extensively used, are likely going undetected due to poor laboratory capacity. Rapid surveys of failure cases in several African countries will provide a better picture of the situation with regard to XDR-TB, and second-line testing of MDR-TB isolates collected in 2006 surveys will also take place. In addition, a low prevalence of MDR-TB translates to an enormous number of cases in some of the high-burden countries.

Status of SRLs and NRLs linked to international laboratories

There are currently only two SRLs for the entire WHO African Region, one in Algeria and one in South Africa. At this time, SRLs in Australia, Europe and USA fill some of the gaps. However, plans are under way to expand the number of SRLs in the region.

GLC-approved MDR-TB control projects

Until the end of 2006, the GLC had approved five countries in the African Region: Burkina Faso, Democratic Republic of the Congo, Guinea, Kenya and Rwanda. Lesotho and Uganda currently have applications under review. Benin, Ethiopia, Malawi, Mali, Namibia and Mozambique are expected to apply in 2007.

Global Fund status for drug resistance surveillance and MDR-TB control

The following countries have financial resources from the Global Fund for MDR-TB control: Benin, Democratic Republic of the Congo, Ethiopia, Kenya, Mozambique, Namibia, Rwanda, United Republic of Tanzania, Uganda and Zambia.

Human resource development

The first regional training course for the WHO African Region on the programmatic management of MDR-TB was organized in Dar es Salaam, United Republic of Tanzania, on 16-20 October 2006. 35 staff from NTPs in Kenya, United Republic of Tanzania, Ethiopia, Burkina Faso, Benin, Nigeria, Democratic Republic of Congo, Mozambique, Namibia, Guinea and Rwanda attended the course. By the end of the course each delegation developed a plan for concrete next steps to address MDR-TB surveillance, diagnosis, and treatment in their own country.

Priority countries for MDR-TB and XDR-TB response

The key countries in the region are the following SADC countries: Botswana, Democratic Republic of the Congo, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland and Zimbabwe, and also Côte d'Ivoire, Ethiopia, Ghana, Kenya, Nigeria, Rwanda, Senegal and Uganda. These countries have been chosen due to a high estimated MDR-TB burden, relatively high HIV prevalence, proximity to South Africa where XDR-TB cases have been confirmed and/or poor performing NTPs with high default rates.

Regarding the priority SADC countries, the following country activities took place in 2006:

Botswana

- A rapid XDR-TB survey was planned for and will be launched in early 2007

Lesotho

- A mission was conducted by CDC, PIH and WHO to assist the NTP to respond to the XDR-TB threat
- A rapid XDR-TB survey was initiated
- An application to treat MDR-TB patients was submitted to the GLC
- PIH was granted funds from the Open Society Institute to assist national authorities to improve TB control, including a WHO international staff member
- FIND committed staff for six months to build TB laboratory capacity in the context of a demonstration project of rapid culture and DST

Malawi

- A national MDR-TB control plan was developed, highlighting needs to strengthen laboratory services and revitalize collaboration with the GLC for MDR-TB treatment

Mozambique

- An XDR-TB emergency plan was developed and a rapid XDR-TB survey was planned

Namibia

- An XDR-TB plan was elaborated indicating urgent needs for technical assistance to improve the capacities of the NRL, to conduct a rapid XDR-TB survey and to address infection control

South Africa

- Two XDR-TB emergency meetings were organized
- Funds were raised to place a WHO international staff member and national programme officers in South Africa for two years

- A review of the laboratories is under way to establish the magnitude of MDR-TB and XDR-TB in the country

Swaziland

- An XDR-TB emergency plan was developed
- A WHO review was conducted in March 2007
- Funds have been raised (June 2007) from the Italian Cooperation for an international staff to support the NTP

Zimbabwe

- A draft XDR-TB emergency budget was developed

Milestones for 2007–2008

- Expansion of WHO African Region staff with one MDR-TB coordinator, a laboratory staff member and surveillance officers in the subregional offices in Burkina Faso, Gabon and Zimbabwe
- Employment of WHO international staff in South Africa, for Lesotho and Swaziland, as well as for additional WHO national staff in South Africa
- Country missions conducted to at least Botswana, Democratic Republic of the Congo, Lesotho, Malawi, Mozambique, Namibia, South Africa, Swaziland and Zimbabwe, and also Ethiopia, Kenya, Rwanda and Uganda
- Four workshops on MDR-TB and XDR-TB control conducted for Central, East, South and Western Africa
- Laboratory strengthening and infection control training conducted for SADC countries
- Finalization and publication of rapid XDR-TB surveys in priority SADC countries
- Identification of two additional SRLs in the region

Regional MDR-TB and XDR-TB response activities WHO Region of the Americas

Epidemiology of MDR-TB and XDR-TB

By 2002, 41% of countries in the Americas had conducted baseline drug resistance surveys, representing areas covering over 90% of smear-positive TB cases. The region has made good progress in coverage and trends for the highest burden countries. WHO estimates a 2.9% prevalence of MDR-TB in Latin America as a whole, but there are important variations in the region; Dominican Republic, Ecuador and Peru show much higher rates of resistance. Canada, Cuba and the USA show approximately 1% MDR-TB as well as steady or downward trends over time. Data from surveys in Argentina, Brazil and Peru will be important in better understanding trends and relationships between drug resistance and HIV. Second-line anti-TB drugs have been available in the region, and it is likely that XDR-TB is present in the countries with high prevalence of MDR-TB such as Ecuador and Peru, as well as in the few MDR-TB cases identified by some of the higher resource countries such as Argentina. Laboratory capacity in the region is very well established and all SRLs conduct DST for second-line drugs, therefore new surveys will incorporate second-line testing for MDR-TB isolates collected in surveys.

Status of SRLs and NRLs linked to international laboratories

There are five SRLs in the region: Argentina, Chile, Mexico and two in the USA. These SRLs are the mainstay of the laboratory strengthening functions in the region, and nearly all countries in the region are linked to an SRL. Annual proficiency testing is carried out for the majority of NRLs.

GLC-approved MDR-TB control projects

In the region, there are currently 12 countries with GLC-approved programmes: Belize, Bolivia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Haiti, Honduras, Mexico, Nicaragua, Paraguay and Peru.

Global Fund status for drug resistance surveillance and MDR-TB control

The following countries have funding from the Global Fund for MDR-TB management: Bolivia, Dominican Republic, Ecuador, El Salvador, Honduras, Nicaragua, Paraguay and Peru.

Human resource development

WHO and the Union have supported regional training courses which have been conducted in the Dominican Republic in 2005 and in Mexico in 2006. Several national courses have been held in GLC-approved countries. The Peruvian MDR-TB control programme has been visited by a number of NTP staff from other countries for on-the-job training.

Priority countries for MDR-TB and XDR-TB response

The following countries have been prioritized for the MDR-TB and XDR-TB action plan: Argentina, Brazil, Colombia, Dominican Republic, Ecuador, Guatemala, Guyana, Haiti, Honduras, Mexico, Paraguay and Peru. The criteria for prioritization were the high prevalence of primary MDR-TB in accordance with national surveys (Dominican Republic, Ecuador, Guatemala and Peru), high prevalence of HIV/AIDS in the general population (Guyana, Haiti and Honduras), existence of XDR-TB in accordance with the initial study conducted by the CDC and WHO (Argentina, Brazil and Mexico) and two countries were added (Colombia and Paraguay) upon existing evidence of indiscriminate utilization of second-line anti-TB drugs.

MDR-TB and XDR-TB response activities in 2007–2008

1. Strengthen basic TB and HIV/AIDS control

The strengthening of DOTS, the progress of implementation of collaborative TB/HIV activities and the management of MDR-TB will be done through external evaluation missions to countries and the realization of national and international evaluation workshops.

2. Scale-up the programmatic management of MDR-TB and XDR-TB to reach the targets set forth in the Global Plan to Stop TB, 2006–2015, and the Regional Plan

Programmatic management of MDR-TB and XDR-TB will be implemented and/or expanded in countries according to WHO guidelines. Training of national and sub-national staff will be conducted. Drug management capacity will be strengthened and use of first-line anti-TB drug fixed-dose-combinations will be fostered. Programming for TB/HIV collaborative activities will be included in management plans for MDR-TB.

3. Strengthen laboratory services for adequate and timely diagnosis of MDR-TB and XDR-TB

National laboratory networks will increase their capacities to introduce second-line DST and also new diagnostic tools for rapid rifampicin testing. National laboratory networks will further develop and implement bio-safety plans. The SRLs in Argentina, Chile and Mexico will support training of national laboratory staff and strengthen activities of external quality control and monitoring.

4. Expand MDR-TB and XDR-TB surveillance to better understand the magnitude and trends of drug resistance and links with HIV

Routine MDR-TB and XDR-TB surveillance will be implemented in accordance with the Regional Plan for TB Control, 2006-2015. In addition, a regional study will be conducted to measure the XDR-TB magnitude.

5. Foster sound infection control measures to avoid MDR-TB and XDR-TB transmission to protect patients, health workers, others working in congregate settings, and the broader community, especially in high HIV prevalence settings

Training on infection control will be conducted and countries will develop and

implement guidelines and national plans on infection control.

6. Strengthen advocacy, communication and social mobilization

Advocacy and communication plans will be developed to maintain the momentum for MDR-TB and XDR-TB. Information documents will be widely disseminated.

7. Pursue resource mobilization at regional and country levels

Support will be provided to countries to apply for funding for MDR-TB and XDR-TB, from the Global Fund and other donors. Fundraising will be conducted to obtain resources for regional level activities.

8. Promote research and development into new diagnostics, drugs and vaccines

Operational research activities will be incorporated into national drug resistance control plans.

Milestones for 2007–2008

- Priority countries should have developed strategic plans for the prevention and control of MDR-TB and XDR-TB, with technical support from WHO and partners.
- Regional infection control guidelines should have been developed and implemented according to strategic plans.
- Priority countries should have set up expert committees on MDR-TB and XDR-TB.
- National and international training workshops should have been held.
- With support from SRLs, bio-safety measures should have been implemented in national laboratory networks.
- Data should be available on the regional XDR-TB magnitude.

- Countries should have developed routine MDR-TB surveillance systems:
 - 2007: Argentina, Brazil, Chile, Colombia, Mexico, Peru and Paraguay;
 - 2008: Dominican Republic, Ecuador, Guyana and Haiti.
- Countries should have developed routine DST to second-line anti-TB drugs:
 - 2007: Argentina, Brazil, Chile, Colombia, Mexico and Peru;
 - 2008: Dominican Republic, Ecuador and Paraguay.
- Colombia, Guyana and Paraguay should have applied to the Global Fund for MDR-TB and XDR-TB resources. During 2007, Argentina and Guatemala should apply to the GLC. Colombia and Guyana should apply during 2008. The GLC-approved programmes in Ecuador and Mexico should have expanded their geographical coverage, and the number of MDR-TB patients to be treated should have increased in the Dominican Republic, Ecuador, Honduras, Mexico and Paraguay.
- The countries should have advocacy strategies to alert decision-makers on the need to prevent and control MDR-TB and XDR-TB through the proper application of the Stop TB Strategy in each country.

Epidemiology of MDR-TB and XDR-TB

By 2002, 22% of countries in the Eastern Mediterranean Region had conducted baseline drug resistance surveys. Since then, the region has made excellent progress in establishing coverage, and data will be available from Jordan, Lebanon, Morocco and the Syrian Arab Republic. Many of the countries in the region are affected by conflict, making expansion of survey coverage difficult. WHO estimates a 3.3% prevalence of MDR-TB in the Eastern Mediterranean region as a whole, but some recent surveys have reflected a higher prevalence of around 5%. There is concern that some of the higher burden countries such as Afghanistan and Pakistan have high prevalence of resistance. There are few trends available in the region with the exception of selected Gulf countries where epidemiology relies in large part on annual immigration and does not accurately reflect the picture in the region. Laboratory capacity must be strengthened in order to improve capacity to determine trends. XDR-TB has been reported from the Islamic Republic of Iran. Yemen has also tested XDR-TB through the drug resistance survey in collaboration with Japan and results will be available soon. XDR-TB is likely present in many countries in the region, but the extent of the problem is unknown.

Status of SRLs and NRLs linked to international laboratories

One SRL was confirmed in 2005 in Egypt, though there is demonstrated need for additional SRLs in the region given the planned expansion of laboratory capacity. All countries that have conducted drug resistance surveys are linked to an SRL; others are not.

GLC-approved MDR-TB control projects

Five countries have GLC approval in the Eastern Mediterranean region: Egypt, Jordan, Lebanon, the Syrian Arab Republic and Tunisia.

Global Fund status for drug resistance surveillance and MDR-TB control

Egypt was approved by the Global Fund in Round 2 for MDR-TB management, Sudan in Round 5 and Djibouti, Egypt, Iraq, Morocco and the Syrian Arab Republic in Round 6.

Human resource development

A training workshop on MDR-TB management was held for country representatives from Jordan, Lebanon and the Syrian Arab Republic in 2005. Three consultants from the region have been trained at WHO international MDR-TB consultant courses.

Priority countries for MDR-TB and XDR-TB response

Supranational TB reference laboratories: The SRL network has to expand in the region with the NRLs in the Islamic Republic of Iran and Oman being the strongest candidates.

Drug resistance surveillance: the Islamic Republic of Iran and Morocco are expected to finalize ongoing surveys. The Libyan Arab Jamahiriya, Saudi Arabia, Somalia and Sudan will start preparation for and implementation of drug-resistance surveys in 2007.

MDR-TB management: Egypt is planning to expand its MDR-TB management project, and the Syrian Arab Republic and Tunisia are planning to initiate implementation during the second quarter of 2007.

In 2007–2008, it is expected that the Islamic Republic of Iran, Morocco and Yemen will apply to the GLC. Gulf countries such as Bahrain, Kuwait, Oman and Qatar should be encouraged to apply to the GLC since they are already providing MDR-TB care that is not fully in line with WHO guidelines.

XDR-TB: In addition to Yemen, rapid XDR-TB surveys are needed in Egypt, the Islamic Republic of Iran, Jordan and Morocco. Lebanon, Sudan and the Syrian Arab Republic are also potential countries where the XDR-TB burden could be studied.

MDR-TB and XDR-TB response activities in 2007–2008

- Identification and support to two new SRLs in the Islamic Republic of Iran and Oman, in addition to strengthening of the available SRL in Egypt.
- The NRLs in Iraq, Jordan, Lebanon, the Libyan Arab Jamahiriya, the Syrian Arab Republic and the West Bank and Gaza Strip should be strengthened through linking with the SRL in Egypt.
- A regional training workshop will be conducted for 11 countries on laboratory strengthening.
- A regional course on the programmatic management of MDR-TB will be held for the five GLC-approved countries and eight countries that are planning to apply to the GLC (Bahrain, Islamic Republic of Iran, Kuwait, Morocco, Oman, Saudi Arabia, Qatar and Yemen).
- Technical and financial support will be provided for national training to strengthen laboratory capacities.
- Priority countries should be supported with laboratory equipment and supplies.
- Technical and financial assistance should be provided for drug resistance surveys in the Islamic Republic of Iran, the Libyan Arab Republic, Sudan and the Syrian Arab Republic.
- Technical support should be provided for MDR-TB management in Egypt, Jordan, Lebanon, Tunisia and the Syrian Arab Republic.
- Assistance should be provided to develop GLC applications for Bahrain, the Islamic Republic of Iran, Kuwait, Morocco, Oman, Qatar, Yemen and, possibly, Sudan.
- Technical and financial support for rapid XDR-TB surveys should be provided to Egypt, the Islamic Republic of Iran, Jordan, Lebanon, Morocco, Sudan and the Syrian Arab Republic.
- The WHO regional office should be strengthened by the recruitment of one international staff member for MDR-TB control.

Milestones for 2007–2008

- Additional SRLs should have been designated in the Islamic Republic of Iran and Oman.
- The NRLs in Iraq, Jordan, Lebanon, the Libyan Arab Jamahiriya, the Syrian Arab Republic and the West Bank and Gaza Strip should have established links and collaboration with the SRL in Egypt.
- Regional MDR-TB management workshop and laboratory strengthening workshop should have been held.
- Results should be available from rapid XDR-TB surveys from Egypt, the Islamic Republic of Iran, Jordan, Lebanon, Morocco, Sudan and the Syrian Arab Republic.
- The regional office should have been strengthened by an additional staff member for MDR-TB control.
- MDR-TB treatment should have been started and scaled-up in Egypt, Jordan, Lebanon, the Syrian Arab Republic and Tunisia.
- GLC proposals should have been submitted by Bahrain, the Islamic Republic of Iran, Kuwait, Morocco, Oman, Qatar, Yemen and, possibly, Sudan.
- Drug resistance surveys should have been launched in the Islamic Republic of Iran, the Libyan Arab Jamahiriya, Saudi Arabia and Sudan.

Epidemiology of MDR-TB and XDR-TB

By 2002, approximately 71% of countries in the European Region had conducted baseline drug resistance surveys. This group is largely composed of countries in Western and Central Europe that conduct routine and continuous drug resistance surveillance. Countries of Eastern Europe and Central Asia provide culture and DST services to the majority of TB patients, yet the quality assurance mechanisms need to be expanded for both laboratory and for reporting systems in order to ensure reliable surveillance data. In the meantime, surveys are taking place in many of these countries to generate a baseline picture of resistance, and good progress has been made. Baseline data will be available from Armenia, Azerbaijan, Georgia, Moldova, Kyrgyzstan (Bishkek), Ukraine (Donetsk Oblast) and Uzbekistan (Tashkent) shortly. The Russian Federation has made exceptional progress in establishing proficiency testing of DST for regional laboratories.

Prevalence of resistance is relatively low in Western and Central Europe, while estimated rates of MDR-TB in countries of the former Soviet Union are the highest in the world, at 16%. Moreover, subgroups of population (e.g. prisoners and injecting drug users) share risks for MDR-TB and for HIV infection, which is reported to be growing at the highest rates in the world. Trends in Western Europe are greatly affected by immigration but generally remain steady and low. This is largely also true of the Central European countries. Latvia has shown decreases in resistance over time, but Tomsk Oblast, Russian Federation, has shown increasing trends. It is likely that where good TB control is in place trends will begin to gradually decrease, but this will take time, and where TB control remains poor trends will increase. WHO expects that XDR-TB, like MDR-TB, will be of greatest concern in the countries of the former Soviet Union, given the prevalence of MDR-TB and the extensive use of second-line anti-TB drugs. If Latvia is an indication, then it is likely that at least 15% of MDR-TB will be XDR-TB. Moreover, anecdotal evidence suggests that some XDR-TB strains in the European Region may, in fact, be totally drug re-

sistant and incurable with the anti-TB drugs available today. The actual magnitude and trend of MDR-TB, XDR-TB and HIV coinfection are not known with certainty in the European Region, and it is essential to establish representative anti-TB drug resistance, to be merged with HIV surveillance in all countries, based on quality assured systems and standardized methodology for second-line DST.

Status of SRLs and NRLs linked to international laboratories

Currently 11 SRLs are based in Europe, and six are extremely active and conduct proficiency testing for all the countries from the region. The European Laboratory Strengthening Task Force (LSTF), with members selected among the heads of SRL and NRLs, was established in January 2005 and is responsible for the overall strengthening of the laboratory networks in the region, which is instrumental for properly and timely addressing the MDR-TB epidemic. The European LSTF will be involved in the development of a strategic, budgeted plan for strengthening laboratory services, including deployment of rapid diagnostic tests. 17 of the 18 priority countries are linked to SRLs (with the exception of Turkmenistan) and are already involved in quality control and proficiency testing activities. However, most of the NRLs need further strengthening and empowering within countries. Each of the countries request technical assistance and financial support in order to increase the capacity of their reference laboratory and laboratory network in identifying the MDR-TB and XDR-TB strains, in participating in the quality assurance systems with SRLs and in participating in second-line DST by the SRL. It is very important to establish two additional SRLs in the European Region, possibly located in former Soviet Union countries. Main international organizations, besides WHO, are involved in strengthening the laboratory services in the European Region, such as CDC, KNCV, Kreditanstalt für Wiederaufbau (KfW) and Project Hope. Proper communication and coordination among all these players, based on countries' needs and opportunities, will ensure more effective and efficient actions.

GLC-approved MDR-TB control projects

The European Region has currently 24 MDR-TB and XDR-TB projects in 12 countries approved by the GLC: Armenia, Azerbaijan, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Romania, Russian Federation (12 oblasts) and Uzbekistan. The increasing support of the Global Fund in the region and capacity of GLC to provide technical assistance are fostering the scaling-up of MDR-TB and XDR-TB control projects, whose number are expected to increase exponentially and become an integral part of the implementation of the Stop TB Strategy in all countries. Increasing further the capacity of providing GLC assistance from regional level, organizing the deployment of external consultants and the coordination with all partners involved is of paramount importance to ensure the scaling-up of GLC-approved MDR-TB and XDR-TB control interventions in the region, financed by countries and/or external resources.

Global Fund status for drug resistance surveillance and MDR-TB control

The European Region has currently 15 countries granted by the Global Fund in Round 1 (Republic of Moldova), Round 2 (Kyrgyzstan, Romania), Round 3 (Russian Federation, Serbia and Tajikistan), Round 4 (Georgia, Russian Federation, Serbia-Kosovo and Uzbekistan), Round 5 (Albania, Armenia, Azerbaijan and the Former Yugoslav Republic of Macedonia) and Round 6 (Belarus, Bosnia & Herzegovina, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Republic of Moldova, Romania, Montenegro and Tajikistan). With the exception of the Former Yugoslav Republic of Macedonia, all grants have MDR-TB and XDR-TB components. Some countries were approved for a second grant with the main aim of expanding their pilot cohort of MDR-TB and XDR-TB patients (Georgia, Kyrgyzstan, Republic of Moldova, Russian Federation and Tajikistan), a path which is expected to be followed by more countries in future. Some countries are most likely to apply to Global Fund Round 7, such as Ukraine, Uzbekistan and Turkmenistan. Moreover, UNITAID is already recognized as an additional and important financing opportunity,

and four countries in the region already applied to it for second-line anti-TB drugs: Azerbaijan, Kyrgyzstan, Republic of Moldova and Uzbekistan. Countries among those with high MDR-TB and XDR-TB burden in the region, such as Estonia, Latvia and Lithuania, are appropriately addressing MDR-TB with national resources. In all countries granted by the Global Fund, support is given to running a first or second survey on first-line anti-TB drug resistance, which should be expanded to second-line drugs in order to understand the extent and distribution of XDR-TB. Moreover, HIV surveillance should be also linked.

Human resource development

To address the needs of the WHO European region challenged by the highest MDR-TB and XDR-TB levels in the world, a WHO Collaborating Centre was established in Riga, Latvia, for Research and Training in Management of MDR-TB. For many years, it has ensured global and regional training courses on MDR-TB and XDR-TB for clinicians, paramedics, managers and consultants. Two global courses for MDR-TB consultants were organized by WHO headquarters in 2005 and 2007, and 14 specialists from the European Region were trained. Three regional MDR-TB courses were organized by WHO EURO and attended by specialists from countries of the former Soviet Union. National MDR-TB courses were also held in all GLC-approved countries. A global course for training laboratory consultants was held in Cairo, Egypt in 2006 and was attended by three specialists from the European region, while senior laboratory consultants were trained during a regional course organized in 2006 in Romania. Scaling-up interventions to adequately address MDR-TB and XDR-TB requires significant investments in human resources development, including staffing and training at many levels and for several tasks. While maintaining current regional courses, mainly covering MDR-TB programmatic management and laboratory, additional areas for training need to be covered in future, such as clinical management of MDR-TB and XDR-TB and HIV, TB infection control in health settings, management of second-line anti-TB drugs and support to MDR-TB and HIV patients.

Priority countries for MDR-TB and XDR-TB response

In the WHO European region, 18 countries grouped under the WHO epidemiological region of Eastern Europe, and as described in the Global Plan to Stop TB, 2006–2015, are considered at high-priority for TB control: Armenia, Azerbaijan, Belarus, Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Republic of Moldova, Romania, Russian Federation, Tajikistan, Turkey, Turkmenistan, Ukraine and Uzbekistan. These countries, mostly from the former Soviet Union, have extensive use of second-line anti-TB drugs, high prevalence of MDR-TB, likely of XDR-TB, and HIV infection. Some countries are already on their way to properly address MDR-TB. Many other countries are less effective. The 18 high-priority countries for TB in the European Region differ in needs to respond to MDR-TB and XDR-TB and can be grouped according to priority areas:

Priority area	Priority country
Expanding and strengthening basic TB and HIV control as detailed in the Stop TB Strategy	Armenia, Azerbaijan, Kazakhstan, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan, all other countries
Strengthening TB drug (first and second-line) resistance surveillance	Belarus, Bulgaria, Tajikistan, Turkmenistan, all other countries
Linking HIV surveillance to TB drug resistance surveillance	Azerbaijan, Estonia, Latvia, Lithuania, Kazakhstan, Russian Federation, Ukraine
Starting a MDR-TB pilot project	Armenia, Azerbaijan, Belarus, Bulgaria, Tajikistan, Turkey, Turkmenistan, Ukraine
Expanding and strengthening existing MDR-TB interventions	Georgia, Kazakhstan, Kyrgyzstan, Lithuania, Moldova, Romania, Uzbekistan, Russian Federation
Strengthening national network of laboratories	Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Romania, Russian Federation, Ukraine, Tajikistan, Turkmenistan, Turkey, Uzbekistan
Implementing MDR-TB infection control measures	Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Romania, Russian Federation, Ukraine, Tajikistan, Turkmenistan, Turkey, Uzbekistan.
Enhancing quality of locally-produced first and second-line anti-TB drugs	Belarus, Bulgaria, Kazakhstan, Romania, Russian Federation, Turkey
Enhancing implementation of Stop TB Strategy in prisons	Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Russian Federation, Tajikistan, Turkmenistan, Ukraine, Uzbekistan
Enhancing ACSM for MDR-TB and XDR-TB	Azerbaijan, Moldova, Kazakhstan, Romania, Russian Federation, Ukraine, all other countries

MDR-TB and XDR-TB response activities in 2007–2008

The main activities that are planned for 2007–2008 to address MDR-TB, XDR-TB and HIV coinfection in the 18 high-priority countries for TB in the WHO European region are:

- 1. Strengthen basic TB and HIV control**
 - 1.1. Strengthen the full implementation of the Stop TB Strategy in all 18 countries with intensified coordination and technical assistance by employing at country level seven WHO national professional officers (Armenia, Azerbaijan, Belarus, Bulgaria, Georgia, Republic of Moldova and Romania) and eight WHO international professional officers (Kazakhstan, Kyrgyzstan, Tajikistan, Turkey, Turkmenistan, Uzbekistan and two officers in both the Russian Federation and Ukraine).
 - 1.2. Undertake a systematic review of basic TB and HIV control activities in all 18 TB high-priority countries and identify needs and opportunities for addressing MDR-TB and XDR-TB, including HIV coinfection.
 - 1.3. Prepare the “Plan to Stop TB in the high-priority countries of the WHO European Region 2007–2015” for advocacy and guide for countries in preparing national plans. Creating consensus through consultancy meeting, translation into Russian, printing and dissemination.
 - 1.4. Undertake an external review of the NTP in Azerbaijan, Bulgaria, Kazakhstan and Georgia.
 - 1.5. Organize TB high-level missions aimed at raising political commitment on prevention and control of MDR-TB and XDR-TB in Azerbaijan, Belarus, Kazakhstan, Romania, Turkey, Turkmenistan and Ukraine.
 - 1.6. Continue the assistance to at least three countries applying to the Global Fund Round 7 (priority in Ukraine, Turkmenistan), to at least five countries applying to UNITAID and to at least 10 countries in their process of
- Global Fund grant negotiation and re-negotiation.
- 2. Scale-up programmatic management of MDR/XDR-TB and HIV coinfection**
 - 2.1. Establish close coordination within EURO and among partners to support and advise countries reporting XDR-TB cases and in need of international contact tracing.
 - 2.2. Ensure Russian translation of the WHO guidelines for the programmatic management of drug-resistant TB as revised by WHO headquarters, and other relevant new publications.
 - 2.3. Prepare and disseminate an updated stand-alone clinical protocol for TB/HIV that includes MDR-TB and XDR-TB management in HIV-positive cases.
 - 2.4. Ensure adequate MDR-TB and XDR-TB technical assistance (project proposal, GLC assessments, local training) to projects/countries, with or without Global Fund granting, including training and employing four additional GLC consultants.
 - 2.5. Ensure coordination of MDR-TB related assistance to countries by employing one international professional and administrative WHO staff in the WHO Regional Office and one international professional and administrative WHO staff in the Russian Federation.
 - 2.6. Promote coordination and capacity building among GLC-approved projects by organizing one workshop with all concerned institutions and organizations in the region.
 - 2.7. Organize two MDR-TB management courses for countries of the former Soviet Union at the WHO Collaborating Centre in Riga, Latvia.
 - 2.8. Organize two TB and TB/HIV training courses for countries of the former Soviet Union at the WHO Collaborating Centre in Sondalo, Italy.
 - 2.9. Organize four subregional training courses on management of second-line TB drugs.
 - 2.10. Organize four subregional training courses on support of MDR-TB and HIV patients.

3. Strengthen laboratory services

- 3.1. Support the European Laboratory Strengthening Task Force (three meetings) activities, including the preparation of a detailed action plan addressing MDR-TB and XDR-TB.
- 3.2. Assist at least 10 countries to further strengthen their NRLs and national laboratory networks by organizing missions with teams of experts, including training of four additional laboratory consultants.
- 3.3. Ensure coordination of laboratory strengthening by employing one international professional WHO staff in the WHO Regional Office and one international professional WHO staff in the Russian Federation.
- 3.4. Organize four subregional workshops (Central Asian republics, South Caucasus, Balkan countries, and Russian Federation and Ukraine) to promote communication between NTP managers, NRL managers and SRLs.

4. Expand MDR/XDR-TB surveillance

- 4.1. Perform rapid XDR-TB surveys in Ukraine and Kazakhstan.
- 4.2. Assess two additional laboratories for their inclusion as SRLs in the European Region.
- 4.3. Ensure the Russian translation of the fourth report of the WHO/IUATLD global project on drug resistance surveillance and its dissemination.
- 4.4. Organize one training course on HIV surveillance among TB patients in Zagreb, Croatia.
- 4.5. Provide further assistance to at least four countries in planning and implementing MDR-TB and XDR-TB and HIV combined surveys.
- 4.6. Monitor the implementation of the Stop TB Strategy in countries and coordinate assistance to countries on MDR-TB and XDR-TB and HIV surveillance by employing one international professional WHO staff in the WHO Regional Office.
- 4.7. Enhance second-line DST in the Russian Federation through a national workshop.

5. Foster infection control measures

- 5.1. Finalize, print and distribute the European Guidelines for Infection control, including their translation into Russian.
- 5.2. Organize two training courses for 15 high-priority countries on infection control measures.
- 5.3. Provide technical assistance on adoption and implementation of TB infection control measures in 15 countries.

6. Strengthen advocacy, communication and social mobilization

- 6.1. Organize the "European High Level Ministerial Forum: TB – a regional emergency" on 22 October 2007 in Berlin, Germany, for advocacy and coordination among all partners.
- 6.2. Organize a regional workshop with TB/HIV representatives of communities and nongovernmental organizations on MDR-TB and XDR-TB.
- 6.3. Organize two training courses for TB/HIV activists on MDR-TB and XDR-TB.
- 6.4. Produce systematic evidence of the socioeconomic causes and impact of MDR-TB, and disseminate it for advocacy.
- 6.5. Strengthen ACSM in the WHO Regional Office by developing a regional strategy, designing and producing appropriate means of communication and updating current material.
- 6.6. Assist and support the activities of the European Stop TB Partnership through technical assistance.

Milestones for 2007–2008

First and second quarter 2007

- Recruitment of seven WHO national professional officers in countries
- Recruitment of eight WHO international professional officers in countries
- Recruitment of three international professional officers in WHO EURO
- Recruitment of one administrative assistant in WHO EURO
- Recruitment of two international professional officers in the Russian Federation
- ACSM services contracted out for one year
- Develop a report with a review of MDR-TB and HIV control activities in 18 countries
- Translate and disseminate the revised MDR-TB management guidelines
- European guidelines for infection control

Third and fourth quarter 2007

- Assistance provided to three countries in applying to Global Fund Round 7
- Updated TB/HIV clinical protocol printed and disseminated
- One regional workshop for GLC-approved projects held
- Results of rapid XDR-TB surveys available from two countries
- Two additional SRLs assessed and enrolled
- One course on HIV surveillance among TB patients organized in Zagreb, Croatia

First and second quarter 2008

- “Plan to Stop TB in the high-priority countries of the WHO European Region 2007–2015” printed and disseminated
- WHO/IUATLD global drug resistance 4th report translated and disseminated

Third and fourth quarter of 2008

- Reports with external review of NTPs in four countries
- TB high-level missions organized in seven countries

- Assistance provided to 15 countries in negotiating with the Global Fund and/or applying to UNITAID
- Establishment and scaling-up of MDR-TB interventions assisted in 30 sites/countries
- Two MDR-TB management training courses conducted in Riga, Latvia
- Two TB and TB/HIV training courses conducted in Sondalo, Italy
- Four subregional training courses on second-line anti-TB drug management conducted
- Four subregional training courses on MDR-TB/HIV patient support held
- Plan to strengthen laboratories prepared by the European Laboratory Task Force
- Assistance to strengthening NRLs and national laboratory network provided in 10 countries
- Four subregional workshops organized on laboratory strengthening
- MDR-TB combined with HIV surveillance established in four countries
- Workshop on second-line DST conducted in the Russian Federation
- Two regional workshops organized on infection control
- Fifteen countries assisted in establishing infection control measures
- Increased commitment to MDR-TB control gained following the High Level Ministerial Forum in Berlin
- Regional workshop conducted on TB/HIV
- Two training courses on MDR-TB for HIV activists carried out
- Evidence on socioeconomic causes and impact of MDR-TB produced and disseminated
- European Stop TB Partnership assisted and supported

Epidemiology of MDR-TB and XDR-TB

By 2002, 30% of countries in the South East Asia Region had conducted baseline drug resistance surveys. Since then, the Region has made excellent progress with national and sub-national drug resistance surveys ongoing or completed in two large states in India, Indonesia (central Java), Myanmar and Sri Lanka. Surveys are planned in Bangladesh, Bhutan, and in three previously unsurveyed states in India. Third and fourth surveys are ongoing in Nepal and Thailand as part of the continuing rounds of global drug resistance surveillance (DRS). WHO estimates a 3.5% prevalence of MDR-TB in the region as a whole; despite this low prevalence, given the large numbers of TB patients in the region, a very large burden of MDR-TB exists. Myanmar has shown higher prevalence of MDR-TB (4%), and Thailand much lower (1%). It is likely that XDR-TB is present in most countries, as elsewhere in the world, given the widespread availability of second-line anti-TB drugs. Preliminary data on second-line drug resistance prevalence will be available from India and possibly from Myanmar and Thailand by the end of 2007. Expanded drug resistance surveillance will be important in determining the extent of second-line anti-TB drug resistance in the region. Both surveillance and MDR-TB treatment activities in the region have not been adequately addressed by NTPs due to limited capacity for culture and DST and case management under programme conditions

Outside of a very small number of treatment programmes (both GLC-approved and unapproved), MDR-TB is diagnosed presumptively on clinical grounds or based on DST results from laboratories not covered by an adequate external quality assurance system. Medical colleges, TB hospitals and the private sector are the sites where patients are treated with second-line drugs. The widespread use of fluoroquinolones as adjuncts or substitutes in the first-line regimens, particularly in the private sector, has been reported by the 2006 programme monitoring mission in India.

Status of SRLs and NRLs linked to international laboratories

There are two SRLs in the region as well as supplemental support provided by four SRLs based in Europe, Australia and the United States. Further expansion of SRLs in the region is required given the expansion of laboratory capacity planned in countries.

GLC-approved MDR-TB control projects

Four GLC-approved projects are in place, including three conducted by the NTPs in Bangladesh, Nepal and Timor-Leste. India has a GLC-approved site at an institute in New Delhi. The Indian programme currently has a GLC application under review. Bhutan and Myanmar are expected to submit applications in 2007 and Indonesia in 2008.

Global Fund status for drug resistance surveillance and MDR-TB control

Bangladesh, Bhutan, India, Indonesia, Nepal, Sri Lanka and Timor-Leste have funds from the Global Fund for MDR-TB management obtained during Rounds 4–6 of Global fund grants.

Human resource development

A regional workshop for programme management of drug-resistant tuberculosis took place in March 2007.

In India, training on MDR-TB management has been conducted (January 2007) for programme officers in two states, which are beginning MDR-TB control activities in areas of the states of Gujarat and Rajasthan in March 2007.

A regional workshop on planning for laboratory strengthening was held in Chennai in July 2006. Consultancies with other SRLs are planned to build capacity for second-line drug resistance training in 2007. NRL staff from countries from the region will participate in the global laboratory workshop planned for March 2007. A regional laboratory workshop for hands-on training on culture and DST is planned for the second quarter of 2007.

In-country technical support missions to assist with country assessments and capacity building for MDR-TB management have been requested for Bhutan, Bangladesh, Indonesia, Sri Lanka and Timor-Leste during 2007.

Priority countries for MDR-TB and XDR-TB response

Priority countries are Bangladesh, India, Indonesia, Myanmar, Nepal and Thailand.

MDR-TB and XDR-TB response activities in 2007–2008

Country activities in priority countries for MDR TB and XDR TB response

Bangladesh

- Ongoing MDR-TB management in areas under the Damien Foundation
- National guidelines for MDR-TB to be finalized
- Approved GLC application; in-country technical support mission to follow
- MDR-TB treatment programme pilot to be set up under the NTP
- Survey of DST among Category II failures is ongoing with support from the Belgian SRL

India

- Prioritization of MDR-TB and XDR-TB prevention through improved DOTS implementation, initiation of MDR-TB treatment services, and increased engagement of medical colleges and the private sector
- National guidelines on MDR-TB management developed
- GLC application under review
- 1 GLC-approved MDR-TB site in New Delhi; community-based MDR-TB treatment starting in March 2007 in areas of 2 states, and in October / November 2007 in areas 2 additional states.
- Network of 3 NRLs established, with 1 additional NRL being quality-assured.
- Network of 24 state-level Intermediate Reference Laboratories being established for the provision of quality-assured culture and DST services.

- DRS recently completed in two large states; second line DST being conducted in all MDR-TB isolates for population-based estimate of XDR-TB prevalence; DRS surveys planned in two more states in 2007–2008.

Indonesia

- National guidelines for MDR-TB management to be developed
- Country preparedness assessment for MDR-TB control to be undertaken
- The preparation of an application to the GLC to be initiated
- DRS ongoing in central Java

Myanmar

- National guidelines for MDR-TB to be developed
- Country assessment for MDR-TB to be undertaken
- GLC application to the GLC to be completed
- DRS completed in 2004; ongoing additional survey of DST of Category II failures in anticipation for future design of the MDR-TB control programme

Nepal

- National guidelines for MDR TB finalized
- GLC site in place; MDR-TB treatment programme expanded in 2007, based on an evaluation of the on going MDR-TB sites conducted in 2006
- Development of national reference laboratory planned
- DRS ongoing

Thailand

- SRL designated in late 2006; capacity for second-line DST present; capacity to support other countries in the region to be built
- DRS ongoing; second line DST to be included
- National guidelines for MDR-TB to be reviewed and updated

WHO Regional Office activities

In-country technical assistance

- Training of national programme staff and participating NGOs in the management of drug-resistant TB and MDR-TB
- Preparation of GLC applications (March 2007)
- Country preparedness missions for countries commencing MDR-TB component of TB control programmes (Bangladesh, Indonesia, Myanmar, Thailand, Sri Lanka)
- Supporting development of national guidelines for the treatment of drug-resistant TB.
- Assisting with cross-border TB control in the context of MDR-TB management (Myanmar–Thai cross-border disease control project)
- PPM-DOTS: promoting the International Standards for Tuberculosis Care (ISTC) at country level among private and un-linked public providers primarily to prevent drug resistance, and sensitization to prevent misuse of second-line drugs

Human resource development

- Support for country-level workshops for the management of drug-resistant TB, in association with the introduction of national guidelines for the diagnosis and management of drug-resistant TB, including infection control.
- Building SRL capacity to respond to the needs of Member States for laboratory strengthening via support of SRL-based laboratory coordinators
- Building capacity for drug procurement and supply management of second-line drugs in collaboration with GDF

Laboratory strengthening

- Regional workshop on laboratory strengthening
- Regional training on laboratory network management
- In-country training of laboratory staff on minimum laboratory requirements for the establishment of culture and

DST (including infection control) and quality assurance

- Training of SRL and NRL laboratory staff on second-line DST
- DRS protocol development, support for implementation in selected countries
- Support to SRLs to support NRLs in the region

Strengthening of Regional Office Capacity

- Establishment of an MDR-TB focal point in the regional office
- Development of a roster of laboratory experts for technical assistance to laboratory strengthening, and support ongoing technical assistance to national and regional laboratories

Monitoring, evaluation and operational research

- Assist countries to evaluate MDR-TB pilot project implementation
- Conduct intercountry meeting on MDR-TB management implementation, and dissemination of pilot experiences
- Evaluate the operational use of rapid rifampicin resistance testing as a means of speeding the detection and referral of patients eligible for MDR-TB treatment

Milestones for 2007–2008

- Regional costed plan in place for MDR-TB and XDR-TB developed
- GLC-approved MDR-TB pilots established in Bangladesh, Bhutan, Myanmar and Timor-Leste, scaling-up in India, Nepal
- The first regional workshop on MDR-TB management conducted
- Laboratory training on culture and DST
- Representative XDR-TB data available from the Indian NTP
- Preliminary data on XDR-TB from Bangladesh, Myanmar and Thailand

Regional MDR-TB and XDR-TB response activities WHO Western Pacific Region

Epidemiology of MDR-TB and XDR-TB

By 2002, 31% of countries in the Western Pacific Region had conducted baseline drug resistance surveys which represented areas covering over 50% of smear-positive TB cases. The region has made good progress in baseline coverage, but very few trends are available with the exception of countries conducting continuous surveillance (Australia, Hong Kong SAR, New Zealand and Singapore). China has an ambitious surveillance plan expanding survey coverage by a few provinces each year and has planned a nationwide survey to take place in 2007. The Philippines reports baseline data, and in the near future data from repeat surveys will be available from Cambodia, Japan, Republic of Korea and Viet Nam. WHO estimates a 7% prevalence of MDR-TB in the Western Pacific Region as a whole, but there are important variations in the region. Established market economies as well as Cambodia and Mongolia show low prevalence of resistance, while China and the Philippines have shown much higher rates of MDR-TB (estimated 8.9% and 4% respectively). XDR-TB has been documented in Hong Kong SAR and the Philippines and is likely to be widespread in China given the widespread use of second-line agents and underlying prevalence of MDR-TB. Second-line DST is being established at the NRL in China, which will greatly facilitate determination of XDR-TB in the country.

Status of SRLs and NRLs linked to international laboratories

Currently there are five SRLs in the region; two in Australia, Hong Kong SAR, Republic of Korea and Japan. The laboratory network in the region is well coordinated and most countries are linked to an SRL for the purpose of surveys and also receive additional technical support.

GLC-approved MDR-TB control projects

Three countries are approved by the GLC: Cambodia (as part of an operational research project), Mongolia and the Philippines. The NTP of China has an application under review and Viet Nam is expected to submit application in early 2007.

Global Fund status for drug resistance surveillance and MDR-TB control

China, Mongolia, the Philippines and Viet Nam have funding from the Global Fund for MDR-TB management.

Human resource development

Two regional MDR-TB training courses have been held at the WHO Collaborating Centre on MDR-TB control in Riga, Latvia, and at the Korean Institute of TB, Republic of Korea. WHO has supported several national courses in China, Mongolia and the Philippines.

Priority countries for MDR-TB and XDR-TB response

The regional priority countries are: Cambodia, China, Mongolia, the Philippines and Viet Nam.

MDR-TB and XDR-TB response activities in 2007–2008

Regarding DRS, any new survey will incorporate second-line DST for MDR-TB isolates collected and should include testing for at least aminoglycosides and fluoroquinolones. Testing for those two classes of drugs should also be included in surveillance efforts in GLC-approved programme areas, in particular, as part of initial assessments. Rapid surveys in some countries will be further discussed. A mechanism to notify confirmed XDR-TB cases will be considered, including a regular regional reporting system.

On laboratory strengthening, training activities on culture and DST need to be stepped up while work on policy development for the use of culture for diagnosis is pursued. Testing for second-line drugs should be introduced in NRLs in China, Mongolia, and then in the Philippines. A regional laboratory consultation meeting will provide an updated policy on culture, the use and implementation of second-line drugs testing at national levels, and a rational approach to regional technical assistance for laboratories.

A systematic approach to infection control needs to be developed, starting with the creation of a regional roster of infection con-

trol consultants to provide technical assistance to countries. National indicators on infection control will need to be implemented to monitor progress at national levels. Such indicators could include the proportion of infection control certified facilities (including TB laboratories) and the proportion of facilities with a designated officer in charge of infection control. Such issues will be discussed at the next NTP and laboratory managers meeting in Malaysia.

There is insufficient regional capacity to support GLC-approved programmes and to assess more areas for programmatic management of MDR-TB. More consultants need to be identified and trained. Regional training efforts were greatly stepped up in 2006, and training efforts will be further strengthened in 2007 and 2008.

Regarding HIV, work is under way in collaboration on a regional policy on provider initiated testing and counseling. Testing for HIV in TB will be promoted in settings with a concentrated or generalized epidemic. Recommended infection control policies need urgent implementation in countries such as Cambodia or Viet Nam, where TB cases regardless of their resistance status are referred to HIV clinics for testing and for care.

Milestones for 2007–2008

Regional activities

- The progress and plans for MDR-TB and XDR-TB prevention and control activities during 2007 and 2008 should be reviewed at the NTP and NRL meeting in Kuching, Malaysia, in April 2007
- A regional laboratory strengthening workshop should be carried out in Hanoi, Viet Nam
- Advanced TB courses should be held in Seoul, Korea, and Manila, the Philippines
- A four-country workshop on second-line anti-TB drug management should take place in the Philippines
- A training course on MDR-TB and XDR-TB management should be conducted for NTP staff from China and Viet Nam at the WHO Collaborating Centre in Riga, Latvia

- A regional laboratory consultation meeting

China

- Technical assistance should be provided for a national drug resistance survey, which should include second-line DST on all MDR-TB isolates
- XDR-TB assessments should be carried out in GLC-approved pilot provinces
- A course should be conducted for Chinese representatives on MDR-TB and XDR-TB management in Riga, Latvia

Mongolia

- Assistance should be provided for the country to apply for expansion of MDR-TB control activities for Global Fund round 7
- A national drug resistance survey including second-line DST should be started in 2007

Philippines

- A course on second-line anti-TB drug management should be held
- A review of the laboratory network performance with emphasis on culture and DST in the context of expansion of programmatic management of MDR-TB should take place
- The MDR-TB recording and reporting system should be reviewed

Cambodia

- A national workshop on MDR-TB prevention and control should be held and an initial assessment of a GLC programme should be undertaken
- Technical assistance should be provided to develop an application to the Global Fund Assistance to include MDR-TB and infection control in round 7 application

Viet Nam

- A workshop on MDR-TB management should be conducted
- Technical assistance should be provided for the development of a GLC application and the application should have been sent for GLC review

Budget breakdown for the 25 high-burden MDR-TB and XDR-TB countries (US\$ millions)

Year	2007	2008
Drugs for MDR-TB treatment	201	328
Programme costs for MDR-TB management	206	307
Hospitalization	54	80
DOT visits	31	46
X-rays and other laboratory tests	4	6
Training	15	23
Programme and data management	46	68
Food parcels	20	30
Management of adverse events	10	15
Other	26	39
Drugs for XDR-TB treatment	46	67
Programme costs for XDR-TB management	27	41
Hospitalization	15	23
DOT visits	3	4
X-rays and other laboratory tests	1	1
Training	1	2
Programme and data management	3	5
Food parcels	1	2
Adverse events	1	1
Other	2	3
Infection control costs for MDR-TB and XDR-TB management	33	58
Laboratory costs for MDR-TB and XDR-TB diagnosis	53	90
Capital investments ^a	23	44
Running costs ^b	30	46
Total^c	566	891
Technical assistance	36	51
Grand total	602	942

^a Capital investments include costs for laboratory construction, refurbishments and equipment.

^b Running costs include costs for culture and drug susceptibility testing.

^c May not total exactly owing to rounding of numbers.

MDR-TB and XDR-TB patients expected to be treated in 2007 and 2008, by WHO region

Country/area	2007		2008	
WHO region	MDR-TB patients on treatment (excluding XDR)	XDR-TB patients on treatment	MDR-TB patients on treatment (excluding XDR)	XDR-TB patients on treatment
African				
DR Congo	268	27	523	48
Ethiopia	343	34	669	61
Nigeria	173	17	337	31
South Africa	719	71	1 401	129
European				
Azerbaijan	614	72	737	86
Belarus	579	68	695	81
Estonia	60	7	72	8
Georgia	363	42	435	51
Kazakhstan	2 212	258	2 655	311
Kyrgyzstan	627	73	752	88
Latvia	155	18	186	22
Lithuania	335	39	425	50
Republic of Moldova	567	66	680	80
Russian Federation	16 393	1 915	19 675	2 306
Tajikistan	1 123	131	1 348	158
Ukraine	4 306	503	5 169	606
Uzbekistan	3 032	354	3 640	427
Eastern Medirerranean				
Pakistan	1 224	104	2 397	182
South-East Asia				
Bangladesh	1 741	150	3 115	260
India	9 873	853	27 176	2 266
Indonesia	2 937	254	8 084	674
Myanmar	461	40	1 269	106
Western Pacific				
China	8 142	669	14 423	1 120
Philippines	1 473	121	2 610	203
Viet Nam	899	74	1 593	124
TOTAL	58 619	5 960	100 066	9 478

DISCLAIMER

Annex 3 - South Africa:

The authors are aware that the figures from South Africa regarding the expected MDR-TB and XDR-TB patients on treatment are an underestimate. Revised combined figures for all cases of MDR and XDR-TB identified between 2004 and September 2007 will be released shortly by the South African Authorities.



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