

**Report of the meeting of the
WHO Global Task Force on XDR-TB**

**Geneva, Switzerland
9–10 October 2006**



**World Health
Organization**

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1. Background

In March 2006, the World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) reported extensively drug-resistant tuberculosis (XDR-TB)¹ 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 gains 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 May 2006, the results of an outbreak of HIV-associated XDR-TB in Tugela Ferry, KwaZulu-Natal Province, South Africa, were presented at the PARTNERS² meeting in Atlanta, Georgia, USA.

In June 2006, WHO's strategic and technical advisory group for tuberculosis urged WHO to take immediate and effective action to address multidrug-resistant TB (MDR-TB) and XDR-TB in the African Region. Subsequently, in August 2006, the outbreak in Tugela Ferry was discussed at the XVI International AIDS Conference in Toronto, Canada.

From 7 to 8 September 2006, at an expert consultation meeting organized jointly by the South African Medical Research Council (MRC), WHO and CDC in Johannesburg, South Africa, international concerns about the emergence of XDR-TB were heightened by reports from KwaZulu-Natal Province of very high mortality rates in people co-infected with HIV and XDR-TB, beyond Tugela Ferry.

From 9 to 10 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 and as a follow up to the expert consultation (Annex 1).

More than 110 participants representing the most affected countries attended the meeting, together with global experts in TB control and MDR-TB management; HIV prevention, care and control; infection control and occupational health; communicable disease preparedness and response; advocacy, communication and social mobilization (ACSM); and representatives from bilateral and multilateral agencies and organizations (Annex 2).

¹ 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).

² The PARTNERS project was funded by the Bill & Melinda Gates Foundation in 2000 to develop a replicable model for controlling MDR-TB in resource-limited settings. The grant supported a five-year collaborative effort between the Harvard Medical School, CDC, Partners In Health, the Task Force for Child Survival and Development, and WHO.

The objectives of the meeting were:

- To define key issues, make recommendations and propose urgent actions required in the next three to six months in the following areas:
 1. Management of XDR-TB suspects in settings of high and low HIV prevalence
 2. Programmatic management of XDR-TB and design of treatment regimens in HIV-negative and HIV-positive individuals
 3. The laboratory XDR-TB definition
 4. Infection control and protection of health-care workers, with emphasis on settings with high HIV prevalence
 5. Immediate activities and needs for surveillance of XDR-TB
 6. Advocacy, communication and social mobilization
- To develop plans for an appropriate response at the global level, and within countries, including designation of roles and responsibilities.

Dr Kenneth Castro, Director, Division of TB Elimination, CDC, USA, and Miss M.K. Matsau, Deputy Director-General, Strategic Health Programmes, Department of Health, South Africa, chaired the meeting. Dr Mario Raviglione, Director, Stop TB Department, WHO, opened the meeting by emphasizing that the management of drug-resistant TB is no longer an optional activity for countries but part of basic TB control, as outlined in the new Stop TB Strategy. XDR-TB has been identified in all regions of the world. Although a major concern in Eastern Europe, XDR-TB is now emerging in Africa among people living with HIV.

Mr Case Gordon, World Care Council, France, welcomed the participants on behalf of civil society and urged them to work with the global community and patients in the fight against XDR-TB.

The WHO Acting Director-General, Dr Anders Nordström, in addressing the meeting, stressed the urgency of critical actions to address the XDR-TB crisis. Such efforts are needed particularly in areas of high HIV prevalence. However, XDR-TB is a reminder of the longstanding need to strengthen TB control, and to build the necessary capacity in health services to respond to drug-resistant TB.

The first part of the meeting focused on the currently available data on XDR-TB and their implications for TB and HIV/AIDS control programmes. Following this introduction, representatives from three Southern African countries and four countries in Asia, Eastern Europe and Latin America presented their available data on MDR-TB and XDR-TB, MDR-TB management practices and availability of second-line anti-TB drugs. During the second part of the meeting, discussions were held in six working groups addressing each of the key issues listed above under the meeting objectives.

Discussions were held on the need for strengthening laboratory services to provide rapid drug susceptibility testing (DST) in resource-limited settings and on the urgent need for accelerated research and development of new tools. Finally, the meeting considered coordination with and collaboration among national authorities and international partners to fight MDR-TB and XDR-TB, and a proposed emergency plan of action to control XDR-TB.

2. Currently available data on XDR-TB and their implications for TB and HIV/AIDS control programmes

New WHO estimates suggest that 424 000 MDR-TB cases occurred in 2004 (95% confidence interval 376 000–620 000), or 4.3% of all new and previously treated TB cases.¹ In 2000, the Green Light Committee (GLC) was created to improve access to, and rational use of, second-line drugs. At the same time, GLC-approved pilot projects were launched to evaluate the feasibility and cost-effectiveness of managing MDR-TB in resource-constrained settings. At the beginning of 2006, the new *Stop TB Strategy*² and the *Global Plan to Stop TB, 2006–2015*³ were launched. Both documents include MDR-TB management as a basic component of TB control; following their launch in May 2006, WHO published *Guidelines for the programmatic management of drug-resistant tuberculosis*.⁴

Dr Sarita Shah, Albert Einstein College of Medicine, USA, presented the first global compilation of XDR-TB data. In 2005, CDC, WHO and 25 supranational TB reference laboratories (SRLs) initiated a study to determine the extent to which resistance to second-line drugs had emerged among MDR-TB isolates. The data were published by WHO and CDC in March 2006 in an article in which XDR-TB was first defined.⁵ The study analysed 17 690 isolates from 49 countries to reveal a prevalence of MDR-TB and XDR-TB of 20% and 2%, respectively. XDR-TB was identified in all regions but was most common in the Republic of Korea (15% of all MDR-TB isolates) and countries of Eastern Europe/western Asia (14% of all MDR-TB isolates). The total number and proportion of XDR-TB isolates observed worldwide increased from 5% of MDR-TB isolates in 2000 to 7% of MDR-TB isolates in 2004. The limitations of the study included variations in second-line DST by SRLs, concerns with the XDR-TB definition and significant sample biases. Prospective and population-based XDR-TB surveys are urgently needed.

Dr Paul Nunn, Coordinator, WHO TB/HIV and drug resistance team, presented XDR-TB as an emerging global threat. MDR-TB is the basis for XDR-TB. The highest rates of MDR-TB have been reported from countries of the former Soviet Union, where many countries report that 10% of new and 50% of previously treated TB cases have MDR-TB.⁶ MDR-TB data are lacking from many parts of the world, including many countries in Africa, but several outbreaks of MDR-TB associated with HIV have been reported since 1990 in several locations including London, Milan and New York. The threat of XDR-TB is now present in all regions of the world, and people living with HIV are particularly vulnerable. XDR-TB is found in a number of different TB strains, indicating systematic failures in TB control. However, only a few countries have

¹ Zignol M et al. Global incidence of multidrug-resistant tuberculosis. *Journal of Infectious Diseases*, 2006, 194:479–485.

² *The Stop TB Strategy*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.368).

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

⁴ *Guidelines for the programmatic management of drug-resistant tuberculosis*. Geneva, World Health Organization 2006 (WHO/HTM/2006.361).

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 *Anti-tuberculosis drug resistance in the world. Report no. 3*. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.343).

capacity for its diagnosis. Cure rates of 50–60% have been reported, but they were predominately in HIV-negative people and only in well equipped and soundly managed TB control programmes.

In response to concerns about drug resistance, an international MDR-TB control policy has been developed and is being implemented. WHO and partners have organized several regional workshops on MDR-TB management (the first course for the WHO African Region will be held in the United Republic of Tanzania on 16–20 October 2006) and courses for TB consultants on MDR-TB control. The network of SRLs is expanding. More countries, including China, India and the Russian Federation, are benefiting from support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) for MDR-TB control. The GLC has approved more than 40 countries for access to quality-assured second-line anti-TB drugs at reduced prices, and technical support. The initial GLC projects have demonstrated that MDR-TB control in resource-constrained settings is feasible and cost effective. The WHO prequalification project on second-line anti-TB drugs is proceeding, with meetings held in China, India and the Russian Federation to encourage manufacturers to apply for prequalification. The seven-point action plan developed¹ at the expert XDR-TB consultation in South Africa organized by the South African MRC, CDC and WHO was presented.

Dr Charles Gilks, Coordinator, WHO HIV Department, reported that XDR-TB poses specific challenges in the fight against HIV/AIDS and can compromise the progress made in countries towards universal access to antiretroviral drugs (ARVs). Alarmist messages on XDR-TB can readily arouse fear and stigma and could hamper HIV health-seeking behaviours. The rapid identification and treatment of XDR-TB may be significantly compromised by HIV. Underlying HIV will add significant challenges to the clinical management of XDR-TB. The treatment, protection and retention of health-care workers are an urgent priority. Dr Gilks concluded that the XDR-TB problem in many parts of the world cannot be solved unless HIV is properly considered and appropriately included in the evolving responses.

Dr Anthony Moll, Church of Scotland Hospital, Tugela Ferry, KwaZulu-Natal, South Africa, presented details of the HIV-associated XDR-TB outbreak in Tugela Ferry, where up to 80% of all TB cases are co-infected with HIV. From January 2005 to March 2006, 221 MDR-TB cases were identified in Tugela Ferry, of which 53 were also resistant to kanamycin and ciprofloxacin. Half of the patients had never previously received anti-TB treatment. Out of the 53 patients, 44 were tested for HIV and found to be HIV-positive. Mortality was high: 52 of the patients died within a median range of 16 days of initial sputum collection. Fifteen of the patients who died were receiving ARV treatment. ARV treatment success is thus threatened by MDR-TB and XDR-TB. The transmission of MDR-TB and XDR-TB must be urgently addressed if survival of HIV patients is to be improved.

¹ On a foundation of quality-assured basic TB control, countries should (i) conduct rapid surveys of XDR-TB; (ii) enhance laboratory capacity; (iii) improve technical capacity of clinical and public health managers to effectively respond to XDR-TB outbreaks; (iv) implement infection control precautions; (v) increase research support for anti-TB drug development; (vi) increase research support for development of rapid diagnostic tests; and (vii) promote universal access to ARVs as part of joint TB/HIV control activities. For full report of the meeting please see <http://www.mrc.ac.za/operationaltb/expert.htm>.

Dr Ernesto Jaramillo, WHO Medical Officer, WHO TB/HIV and drug resistance team, reminded the participants of the major achievements in management of MDR-TB during the past six years. The vision of MDR-TB control as put forward in the Global Plan is to have drug resistance surveillance and management of MDR-TB integrated as routine components of TB control, providing access to diagnosis and treatment for all TB patients and by all health-care providers by 2015. An increasing number of countries are using the GLC mechanism for access to second-line drugs. The public health problem is acknowledged, and the strategy and plans for addressing drug resistance are developed.

3. MDR-TB and XDR-TB data from seven countries worldwide: current control practices and availability of second-line anti-TB drugs

Lesotho, South Africa and Swaziland

In 2004, Lesotho, South Africa and Swaziland had TB case notification rates of 634, 560 and 780 cases per 100 000 population, respectively. The estimated HIV prevalence among adult incident TB cases ranged from 60% to 81%. Treatment success among new TB cases is reported at 70% in Lesotho, 66% in South Africa and 42% in Swaziland. Drug resistance surveys have been conducted in the three countries, but the studies were conducted 4–10 years ago. The results ranged from 1% MDR-TB among new TB patients to 14% MDR-TB among previously treated cases.

In Lesotho, all MDR-TB cases receive a standardized regimen of amikacin, ciprofloxacin, ethionamide, pyrazinamide and ethambutol. Patients are treated on an ambulatory basis and direct observation of treatment is standard practice. Since 2004, second-line anti-TB drugs have been available only in the public sector. Lesotho has a national TB reference laboratory which is linked to the MRC SRL in South Africa. Currently, very few patients are tested for MDR-TB (80 DST tests were done in 2006). The country plans to conduct a rapid XDR-TB survey in two districts neighbouring KwaZulu-Natal.

Since 2001, South Africa has had a national policy on MDR-TB management whereby a standardized regimen of kanamycin, ofloxacin, ethionamide, pyrazinamide and ethambutol or cycloserine is given to all confirmed MDR-TB cases. Each province has an MDR-TB treatment centre. During the initial phase of treatment, all MDR-TB patients are hospitalized. Direct observation of MDR-TB treatment is challenging after discharge from the hospitals. The latest data on treatment outcomes show that 48.5% of MDR-TB patients are successfully treated. Second-line drugs are available in both public and private sectors. There is currently no national TB reference laboratory in South Africa, but 18 provincial laboratories perform culture and DST.

In Swaziland, MDR-TB patients are treated with the same standardized regimen as in South Africa. MDR-TB patients are being treated in hospitals and direct observation of treatment is standard care. Preliminary results indicate that 45% of MDR-TB cases are successfully treated. Second-line anti-TB drugs are available only through the

public sector. The national TB reference laboratory is linked to the MRC SRL in South Africa.

All three Southern African countries outlined their needs for technical assistance to control TB, MDR-TB and XDR-TB. Particular requests were made to improve TB laboratory services, conduct representative drug resistance surveillance activities, manage MDR-TB and XDR-TB cases, improve infection control measures and support second-line drug procurement and management.

Estonia, Latvia, Peru and the Philippines

All four countries have MDR-TB control programmes that are approved by the GLC. The national TB reference laboratories have their drug susceptibility tests quality assured by SRLs. All countries treat MDR-TB patients with individualized regimens based on DST of first- and (except for the Philippines) of second-line drugs, as well as history of second-line drug use. In Peru and the Philippines, MDR-TB patients are treated on an ambulatory basis; in Estonia and Latvia, patients are hospitalized during the intensive phase of treatment. Recently published data from these projects show a treatment success rate of 70% in MDR-TB cases.

Data from Latvia show treatment success rates ranging from 24% in MDR-TB patients with additional resistance to fluoroquinolones and aminoglycosides, 18% in MDR-TB patients with additional resistance to fluoroquinolones, aminoglycosides and capreomycin, and 58% in MDR-TB patients meeting the initial XDR-TB definition. Regarding HIV, Latvia successfully treated 74% of new HIV-associated TB patients compared with 56% HIV-associated MDR-TB cases. Among all MDR-TB cases in the Latvia cohort, 3% were co-infected with HIV. Of note is that 12% of the MDR-TB patients also resistant to fluoroquinolones and aminoglycosides were HIV positive. Data from Latvia are also showing that while the number of MDR-TB cases is falling, the proportion that has additional resistance to second-line anti-TB drugs is increasing. Regarding XDR-TB cases, data from Peru show that among 136 patients, 54% were successfully treated. HIV data were not presented for the XDR-TB cohort; however, among the MDR-TB cases, 1.5% had HIV. In Estonia, 85 XDR-TB patients have been identified during the past five years, however, treatment outcome data are still to be reported.

4. Summary of breakout sessions

4.1 Management of XDR-TB suspects in settings of high and low HIV prevalence

The high XDR-TB fatality rate among people living with HIV is a major concern. The group discussed the challenges associated with early and adequate identification of such individuals, emphasizing the importance of improving TB diagnosis among HIV-positive people and those living in high HIV prevalence settings. Rapid identification of rifampicin resistance is crucial. This could be done by either molecular tests, such as the nucleic acid amplification assays (NAAT) or liquid-based culture media. Access to these technologies needs to be urgently expanded to countries in need. Empirical treatment with a regimen comprising the likely most

effective second-line anti-TB drugs available should be given to all known or suspected cases of XDR-TB who are HIV infected (see Annex 3).

4.2 Programmatic management of XDR-TB and treatment design in HIV negative and positive individuals

Programmatic management of XDR-TB is a highly complex challenge for TB control in low-income countries (see Annex 4). The response to the XDR-TB crisis should include strengthening of basic TB control and delivery of timely diagnosis and adequate treatment with quality-assured second-line TB drugs to all cases. The principles contained in the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* are also valid for the management of XDR-TB. However, it is necessary to update the sections on case-finding and initial management of patients likely to harbour XDR-TB bacilli, as well as treatment design and case holding in settings with high HIV prevalence. Regimen design should be based on the history of previous exposure to drugs and the results of DST performed in quality-assured TB laboratories. Sound management of second-line drugs includes not only the registration of drugs quality assured by stringent drug regulatory authorities but also the delivery of treatment under appropriate conditions. Efforts to continue mobilizing second-line anti-TB drug manufacturers for prequalification should be pursued, as too few second-line anti-TB drug products are prequalified by the WHO prequalification project. Interaction of second-line anti-TB drugs with ARVs should be carefully assessed based on the best evidence available. The use of so-called "third-line" anti-TB drugs is not recommended given the lack of evidence on efficacy. However, "third-line" anti-TB drugs can be used in cases where adequate regimens are impossible to form with first and second-line anti-TB drugs. Similarly, the use of anti-TB drugs under development is not currently recommended but should be explored.

4.3 The laboratory XDR-TB definition

The group discussed possible options for the definition of XDR-TB, the role of laboratories in TB control and the scaling up of laboratory services to address new threats and challenges. A number of considerations were taken into account while discussing the revised XDR-TB definition, the most prominent being:

- technical feasibility and reproducibility of testing for second-line anti-TB drugs;
- efficacy and availability of second-line anti-TB drugs;
- the need for a definition with significant worse treatment outcome than MDR-TB alone.

Consensus was reached and a revised definition was presented to the task force during the meeting (see 7.4 below). In addition, the group discussed the short- and long-term needs to scale up and strengthen culture and DST, including the need for rapid diagnostic tests.

4.4 Infection control and protection of health-care workers, with emphasis on settings with high HIV prevalence

Guidelines on TB infection control have been in existence for a long time but rarely implemented because infection control is not seen as a priority for TB control programmes or the general health service. As a result, no one takes responsibility for enforcing good infection control procedures and there is no global or national monitoring and evaluation of infection control practice at country level. There is a need to re-brand or repackage and advocate for good infection control practices in health care and other important settings (especially high HIV prevalence settings) to make them more attractive and relevant to those responsible for their implementation, especially in light of increasing integration of TB and HIV control services. However, most TB transmission occurs outside the health-care setting, and a broader approach needs to be considered, including other aspects of TB prevention, intensified case-finding in affected communities, greater use of preventive therapy and contact tracing; and enforcing stricter criteria for architected design and planning to minimize opportunities for TB transmission in public buildings. Enabling staff, especially those who are HIV infected, to minimize their risk of TB infection must be a priority. Training on infection control must be expanded and include hospital administrators, engineers, laboratory staff and all health facility staff in contact with patients. The importance of rapid, high-quality diagnostic tests for effective infection control was also discussed.

4.5 Immediate activities and needs for surveillance of XDR-TB

The session on surveillance began with a summary of the ways in which WHO collects information on drug resistance. These are: (i) through the WHO/IUATLD (International Union Against Tuberculosis and Lung Disease) Global Project on drug resistance surveillance, which collects data from countries conducting continuous surveillance (i.e. countries that use culture and DST as a primary standard of diagnosis), or (ii) from countries conducting periodic surveys. WHO also collects information on a subset of drug resistance (laboratory confirmed MDR-TB) from all countries through annual reporting to the TB Monitoring and Evaluation unit.

Discussions following the summary focused on two main areas: how information on second-line anti-TB drug resistance could be collected through existing mechanisms, and the ways in which systems need to be enhanced to understand the extent and magnitude of second-line anti-TB drug resistance. Discussion of enhancing systems included a detailed exchange on implementing rapid surveys of XDR-TB in high-risk groups and in congregate settings. The role of rapid rifampicin susceptibility testing in such surveys was also discussed.

4.6 Advocacy, communication and social mobilization

There has been major and sustained media interest in XDR-TB, especially in Southern Africa. However, concern was expressed that while such attention spotlights issues around TB control, it could adversely impact affected populations by arousing stigma,

panic and fear. In this context, the group briefly discussed core messages that could be incorporated into a communication strategy at global and country levels. Reference was made to a previous TB emergency “outbreak” (MDR-TB in New York City) and how communication around this event succeeded in achieving a substantial and immediate increase in funding for improved TB control. Participants from the Stop TB new tools working groups and WHO HIV Department provided input on suitable communication strategies. The importance of considering the perspectives of patients and affected communities was noted.

A separate group discussion was held to map out procedures in costing the response to XDR-TB. These are: (i) immediate assessments in response to country demand; (ii) short-to-medium term responses in countries at high risk; (iii) the areas addressed by the Task Force subgroups; (iv) global normative and technical support by WHO and technical partners; (v) longer-term core TB and HIV prevention, care and control improvements; and (vi) research. The group discussed in-kind contributions, possibly via technical partners, and began mapping potential sources of financing for different needs.

5. Strengthening laboratories to provide rapid drug susceptibility testing in resource-limited settings

Dr Armand van Deun, the Union and Institute of Tropical Medicine, Antwerp, Belgium, proposed a way forward to accelerate DST in resource-constrained countries. The introduction of rapid tests requires not only financial resources but also proper infrastructure and skilled human resources. There is not yet consensus on which rapid test to use and which second-line anti-TB drugs should be tested.

WHO guidelines on both surveillance and management of drug resistant TB may be too ambitious for low-income countries without regular and consistent technical assistance to laboratories. It was proposed that countries with limited resources that cannot conduct DST of all anti-TB drugs focus on either rifampicin alone or, if facilities are more advanced, of rifampicin, isoniazid, kanamycin and ofloxacin. In addition, focused DST should begin with failure cases before expanding to other patient groups.

In view of the urgent need to scale up DST, alternative options should be made available for countries without a quality-assured national TB reference laboratory. Rapid molecular tests could be performed in an SRL or a national university or private laboratory. Simple and fast newer methods are available for DST of rifampicin and possibly also of kanamycin and ofloxacin, such as the MODS method (microscopic-observation drug susceptibility). Urgent priority needs include:

- development of consensus guidelines for rapid DST methods;
- pilot testing of molecular tests in referral laboratories in resource-limited settings;
- inclusion of second-line DST in the SRL proficiency testing system;
- mobilization of funding for laboratory strengthening.

Dr Rick O’Brien, Foundation for Innovative New Diagnostics (FIND), presented the work of FIND on new TB diagnostics, the Global Alliance for TB Drug Development,

and AERAS for the development of new and effective TB vaccines. FIND has contractual agreements with four companies, with the aim of providing useful diagnostic products at the lowest possible price for the public sector in developing countries. Immediate research priorities for the diagnosis of drug resistance include: (i) further evaluation of culture-based direct DST testing, including testing for fluoroquinolones; (ii) standardization of liquid-based second-line DST; (iii) large-scale demonstration projects of phage and NAAT assays; and (iv) inclusion of fluoroquinolones in the phage assay and detection of *gyrA* mutations in NAAT assays.

Regarding new drugs, there are currently six compounds under clinical trials, four of which are novel compounds active against MDR-TB. Dr O'Brien stressed the urgent need for funding for clinical trials and for a policy on rapid access to new drugs once approved by stringent drug regulatory authorities.

Finally, regarding a new TB vaccine, it was stressed that despite the lack of animal models and immunological surrogates of vaccine-induced protection in humans, highly promising candidates for a vaccine have emerged. A moderately effective vaccine in combination with drug control could virtually eliminate the TB epidemic. A prime-boost vaccine could be licensed and available in 7–10 years. However, significant funding is needed for clinical development of TB vaccine candidates.

6. Coordination, collaboration with national authorities, international partners and WHO, and proposed plan of action to fight MDR-TB and XDR-TB

Dr Nunn stressed that prevention and control of XDR-TB requires a coordinated input from technical and financial agencies. The main technical partners are all working with WHO, and international partnerships such as the Stop TB Partnership working groups, the GLC, the SRL network, and TB and HIV/AIDS civil societies are crucial to fighting this emergency. The GFATM, the newly established UNITAID (which will support the global scale up of second-line anti-TB drugs), bilateral agencies, foundations and multilateral agencies are key partners for funding urgent needs at global and country levels.

In close collaboration with partners of the Global XDR-TB Task Force, WHO is ready to:

- take the recommendations of the meeting forward and develop a plan that identifies the resources required to implement the outcomes,
- mobilize teams of experts that can be deployed in the field, at the request of countries, to assist in strengthening control of TB and, where relevant, HIV.

Dr Thelma Tupasi, Chair of the Stop TB Working Group on MDR-TB, Tropical Disease Foundation, the Philippines, presented a proposed plan of action for MDR-TB and XDR-TB prevention and control. She stressed that existing groups and task forces should be employed to implement rapidly the meeting recommendations. There is, of course, full support from the MDR-TB Working Group, especially its subgroups; the GLC to support countries to access quality-assured second-line drugs and technical assistance; the subgroup on research to update relevant WHO guidelines and the

MDR-TB research agenda in light of new and emerging XDR-TB evidence; and the subgroup on advocacy and resource mobilization that will work closely with the XDR-TB task force on ACSM. The Working Group will also work in close contact with the subgroup on laboratory strengthening of the DOTS Expansion Working Group to develop the necessary laboratory strengthening policies and plans. Links will also be made with other working groups to ensure broad involvement in MDR-TB and XDR-TB control.

It was proposed that XDR-TB could be considered as a public health emergency of international concern under the renewed WHO International Health Regulations (IHR).¹ However, the new IHR will only come into force in June 2007 for conditions other than avian and pandemic influenza. The regulations apply particularly to situations where there is a significant risk of international spread, whereas the chief risk of XDR-TB is that it is independently created in countries. Under the regulations, WHO Member States would be required to notify the numbers of XDR-TB cases, and travel and trade restrictions might then follow. The IHR are really intended for outbreaks of acute disease rather than the acute-on-chronic situation of MDR-TB and XDR-TB. In addition, if the IHR are invoked they require to be rescinded within a relatively short period of time. However, should there be evidence of an international spread of XDR-TB, a standing recommendation could be issued under the IHR to address XDR-TB as a continuous risk rather than as a single event.

7. Recommendations and next steps

7.1 General recommendations

To prevent drug-resistant TB, the Task Force on XDR-TB underlined, as **its first priority, the need for immediate strengthening of TB control in countries**, as detailed in the new Stop TB Strategy and the Global Plan to Stop TB, 2006–2015. This should be done together with **scaling up universal access to HIV treatment and care**.

Task Force members recommended, and agreed to take part in, the mobilization of teams of experts that can be deployed in the field, at the request of countries, to assist in strengthening TB control.

The Global Plan should be reviewed by the Stop TB Partnership and, where necessary, revised to reflect the threat of XDR-TB. In particular, the laboratory strengthening component, and the number of MDR-TB cases treated, should be scaled up. The costs of treating XDR-TB and of infection control measures need to be reflected in the budgets.

¹ *International Health Regulations (2005)*. Geneva, World Health Organization, 2005.

7.2 Management of XDR-TB suspects in settings of high and low HIV prevalence

The algorithm for the management of patients at risk for MDR-TB and XDR-TB should be disseminated rapidly, evaluated in the field and refined as needed.

WHO and FIND should ensure that access to rapid tests for rifampicin resistance to improve case detection of all patients suspected of MDR-TB is swiftly enabled.

7.3 Programmatic management of XDR-TB and treatment design in HIV negative and positive individuals

The WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* should be implemented as swiftly as possible. All partners are responsible for assisting countries to do so. WHO will commission a group of experts to update parts of the guidelines to address the XDR-TB threat and improve the TB/HIV co-management component, including co-management of treatment with ARV. The same group will prepare guidelines for the treatment of known and suspected XDR-TB.

The GLC will facilitate access to high-quality second-line anti-TB drugs to avoid further development of XDR-TB.

WHO will disseminate the legal and ethical global guidelines that address the issue of compulsory medical treatment and isolation¹ and facilitate discussion at national level.

7.4 The laboratory XDR-TB definition and laboratory strengthening

The Task Force revised the definition of XDR-TB to facilitate surveillance, patient care, standardization of reporting and to reflect the seriousness of the condition.

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 following injectable drugs used in anti-TB treatment: capreomycin, kanamycin and amikacin. WHO will disseminate the revised definition.

A strategic, budgeted plan for strengthening laboratory services, including the deployment of rapid diagnostic tests, should be developed by the laboratory strengthening subgroup of the DOTS Expansion Working Group, in collaboration with the European Laboratory Strengthening Task Force.

The Stop TB Partnership should address needs of the SRL network for additional support and expansion, especially to areas outside established market economies.

¹ *Good practice in legislation and regulations for TB control: an indicator of political will.* Geneva, World Health Organization, 2001 (WHO/CDS/TB/2001.290).

Ultimately, all patients with known or suspected TB should have access to timely, quality-assured TB laboratory services, including smear microscopy, culture and DST.

7.5 Infection control and protection of health-care workers, with emphasis on settings with high HIV prevalence

The Task Force recommended that countries rapidly implement appropriate infection control measures in health-care settings and other risk areas, including prisons, in order to reduce ongoing transmission of drug-resistant TB, especially among HIV-positive individuals. Initially, CDC will assist with updating the WHO *Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings* (1999), and CDC and WHO will ensure their rapid dissemination together with the newly published addendum, *Tuberculosis infection control in the era of expanding HIV care and treatment*.

To ensure appropriate consideration of infection control issues necessary to protect patients, health-care workers and visitors and HIV-infected individuals in particular, a sub working group (SWG) on infection control should be established within the Stop TB Partnership. The position of the SWG and its terms of reference should be proposed at the forthcoming Stop TB Partnership Coordinating Board meeting in Jakarta, Indonesia, on 29–30 November 2006. In the meantime, WHO will establish a provisional secretariat and organize a first meeting in Paris, France, at the Union conference.

The SWG should urgently develop a plan to support implementation of the infection control guidelines at country level, develop indicators and monitor implementation over time. The pool of consultants capable of providing technical assistance on infection control must be rapidly expanded.

7.6 Immediate activities and needs for surveillance of XDR-TB

Surveillance of XDR-TB must be embedded in existing drug resistance surveillance systems to increase access to second-line DST. A task force of members of the surveillance group at the meeting should be set up, which WHO will coordinate.

A “quiver” of generic protocols should be prepared by the surveillance task force to determine rapidly the geographical distribution and extent of XDR-TB, its association with HIV and its genetic origins.

Future anti-TB drug resistance surveillance should include HIV testing wherever possible, and use of rapid rifampicin tests should be explored to expand the scope of drug resistance surveillance.

7.7 Advocacy, communication and social mobilization

The Stop TB Partnership should establish an XDR-TB task force on ACSM within existing structures. This task force should initiate information-sharing strategies that

promote effective prevention, treatment and control of XDR-TB at global and national levels and in high HIV prevalence settings. These strategies should develop a proactive media approach, place affected people at the heart of the response, mobilize existing supportive networks (e.g. the HIV community), provide clear information on the XDR-TB situation, promote public debate and provide space for people to tell their stories. The task force should also address the development of a strategy for increasing ACSM capacities and strengthening communication channels at global and country levels.

All Stop TB partners should actively promote the *International standards for TB care*¹ and the *Patients' charter for tuberculosis care*² as well as treatment literacy.

7.8 Resource mobilization

The Stop TB Partnership should develop a fully budgeted plan for raising the resources and funding required to address XDR-TB. Immediately, WHO should draw up costed plans for countries immediate needs, technical assistance, surveillance and global policy and coordination. Short- and medium-term needs should be addressed directly afterwards. The plan should include rapid briefing of development partners and agencies.

7.9 Research and development

WHO and the Stop TB Partnership should hold a focused meeting on research and development issues relating to XDR-TB as soon as possible.

¹ *International standards for TB care*. The Hague, Tuberculosis Coalition for Technical Assistance, 2006.

² *The patients' charter for tuberculosis care*. World Care Council, 2006.

ANNEX 1 AGENDA

Monday, 9 October 2006

Chairperson: K. Castro, Centers for Disease Control and Prevention (CDC), USA

Rapporteur: A. Piatek, Stop TB Department, WHO

TIME	TITLE/ACTIVITY	SPEAKER
09:00 – 09:15	Opening, welcoming remarks, objectives and expected outcomes of the meeting and introduction of participants	M. Raviglione, Director, Stop TB Department, WHO C. Gordon, World Care Council, France
09:15 – 09:25	XDR-TB definitions and global data	S. Shah, Albert Einstein College of Medicine, USA
09:25 – 09:40	The emerging global threat of XDR-TB	P. Nunn, Coordinator, Stop TB Department, WHO
09:40 – 09:55	XDR-TB – concerns for HIV/AIDS control programmes	C. Gilks, Coordinator, HIV Department, WHO
09:55 – 10:15	HIV-associated M(X)DR-TB in KwaZulu-Natal, South Africa	A. Moll, Church of Scotland Hospital, Tugela Ferry, South Africa
10:15 – 10:30	WHO-recommended MDR-TB surveillance and control practices	E. Jaramillo, Medical Officer, Stop TB Department, WHO
10:30 – 11:00	Tea/coffee break	
11:00 – 11:30	Available MDR-TB and XDR-TB data, current MDR-TB management practices and availability of second-line anti-TB drugs in three Southern African countries (10 minutes presentation per country) <ul style="list-style-type: none"> • Lesotho • South Africa • Swaziland 	<ul style="list-style-type: none"> • M. Letsie • R. Green-Thompson • R. Mukasa
11:30 – 12:00	Discussion	Chairperson
12:00 – 13:00	Lunch	

Monday, 9 October 2006 (continued)

13:00 – 13:40	<p>Available MDR-TB and XDR-TB data, current MDR-TB management practices and availability of second-line anti-TB drugs in selected Eastern European, Latin American and Asian countries (10 minutes presentation per country)</p> <ul style="list-style-type: none"> • Latvia • The Philippines • Peru • Estonia 	<ul style="list-style-type: none"> • V. Leimane • T. Tupasi • J. Bayona • M. Danilovits
13:40 – 14:20	Discussion	Chairperson
14:20 – 17:30	<p><i>Six breakout sessions:</i></p> <ul style="list-style-type: none"> • Management of XDR-TB suspects in high and low HIV prevalence settings • Programmatic management of XDR-TB and treatment design in HIV negative and positive people • Laboratory XDR-TB definitions • Infection control and protection of health-care workers, with emphasis on high HIV prevalence settings • Immediate XDR-TB surveillance activities and needs • Advocacy, communication and social mobilization <p>Working tea/coffee break included</p>	<p><i>Chair/Co-Chairperson:</i></p> <p>R. O'Brien/M. Harrington</p> <p>K. Lambregts/P. Salif Sow</p> <p>F. Drobniewski/J. Nkengasong E. Nardell</p> <p>C. Dye/R. Granich</p> <p>J. Deane/A. Winter</p>
17:30 – 18:00	Plenary session with WHO Acting Director-General, Dr Anders Nordström	
18:00 – 19:00	<i>Meeting of rapporteurs and communication staff</i>	

Tuesday, 10 October 2006

Chairperson: M.K. Matsau, Deputy Director-General, Strategic Health Programmes, Department of Health, South Africa

TIME	TITLE/ACTIVITY	SPEAKER
09:00 – 10:30	Plenary reports: <ul style="list-style-type: none"> • Management of XDR-TB suspects in high and low HIV prevalence settings • Programmatic management of XDR-TB and treatment design in HIV negative and positive people • Laboratory XDR-TB definitions • Infection control and protection of health-care workers, with emphasis on high HIV prevalence settings • Immediate XDR-TB surveillance activities and needs • Advocacy, communication and social mobilization 	Rapporteurs
10:30 – 11:00	Tea/Coffee Break	
11:00 – 11:30	Strengthening laboratories to provide rapid drug susceptibility testing in resource poor settings <i>(15 minutes presentation followed by discussion)</i>	A. van Deun, Institute of Tropical Medicine, Belgium, and the UNION
11:30 – 12:00	The urgent need for new diagnostic tests, drugs and vaccines <i>(15 minutes presentation followed by discussion)</i>	R. O'Brien, Foundation for Innovative New Diagnostics
12:00 – 13:30	Lunch	
13:30 – 14:30	Coordination, collaboration with national authorities, international partners and WHO in the fight against MDR-TB and XDR-TB and proposed budget needs and gaps <i>(20 minutes presentation followed by discussion)</i>	P. Nunn, Coordinator, Stop TB Department, WHO
14:30 – 16:00	Proposed outlined plan of action on MDR-TB and XDR-TB prevention and control measures to be taken at national and global levels <i>(20 minutes presentation followed by discussion)</i>	T. Tupasi, Chair, Stop TB Working Group on MDR-TB, Tropical Disease Foundation, the Philippines
16:00 – 16:30	Tea/coffee break	
16:30 – 17:00	Conclusions and next steps	Chairperson
17:00 – 17:15	Closure of the Global XDR-TB Task Force meeting	

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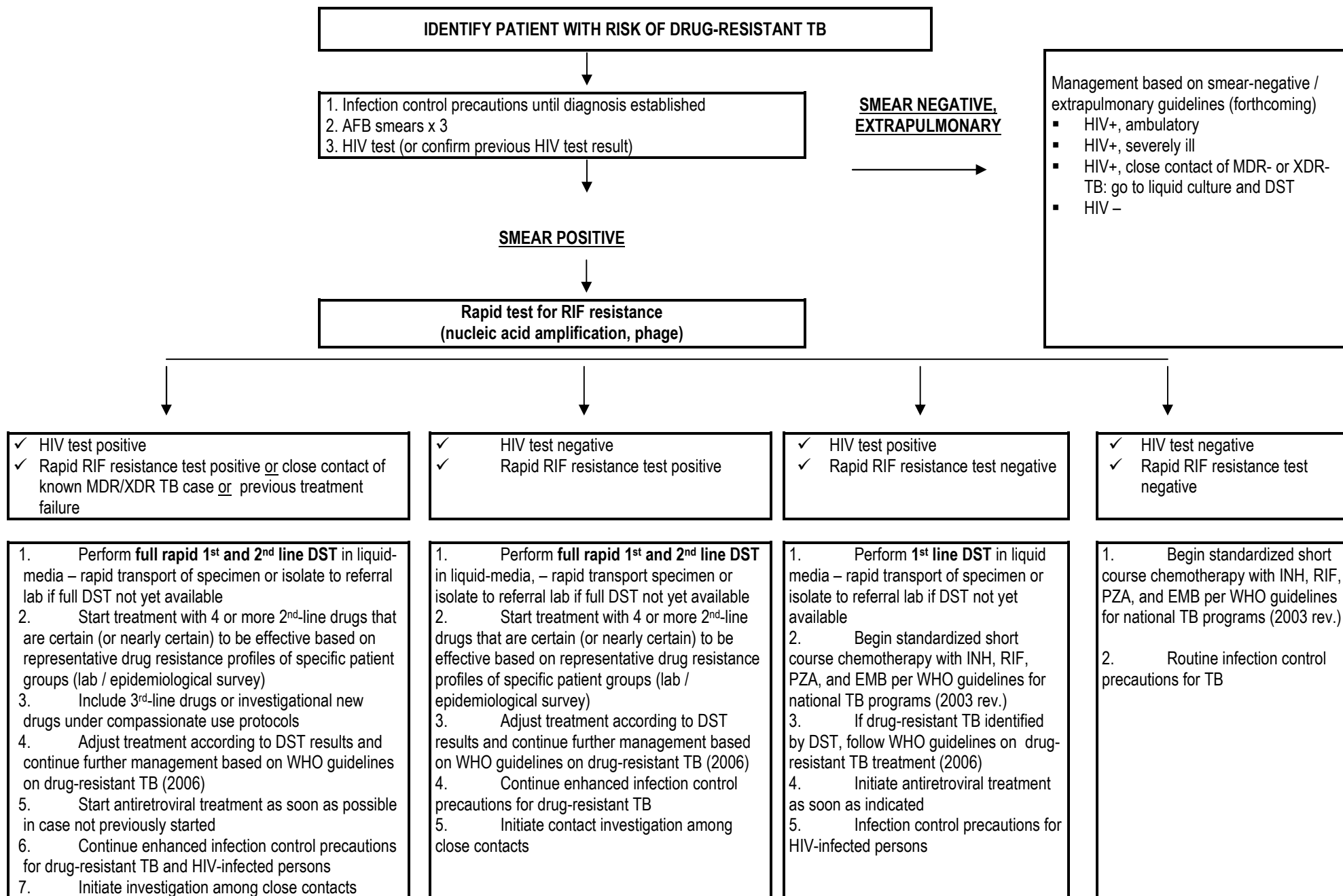
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ANNEX 3. ALGORITHM FOR INITIAL MANAGEMENT OF PATIENTS AT RISK OF DRUG-RESISTANT TUBERCULOSIS AND HIV INFECTION



ANNEX 4. PROGRAMMATIC MANAGEMENT OF XDR-TB AND TREATMENT DESIGN IN HIV-NEGATIVE AND HIV-POSITIVE INDIVIDUALS

XDR-TB results from two sources:

1. Inappropriate use of first- and second-line anti-TB drugs, resulting in acquired drug resistance.
2. Transmission of XDR-TB strains within the community.

General challenges

Lack of tools for drug-resistant TB

(i) the lack of rapid and accurate diagnostic tests for drug susceptibility requires urgent development and strengthening of laboratory diagnostic and monitoring capacities; (ii) the limited efficacy and high toxicity of existing drugs is coupled with a lack of new effective drugs.

Programmatic challenges

The main programmatic challenges are:

- Weak health systems: inappropriate treatment regimens, mismanagement of first- and second-line anti-TB drugs, limited laboratory diagnostic capacities, lack of support for treatment adherence and counseling and poor infection control.
- Insufficient human resources and poorly developed capacities in number and quality, lack of technical monitoring and supervision and a need for further training and retraining.
- Lack of representative drug resistance surveillance data for all categories of patients.
- Ethical and legal issues regarding the use of compulsory treatment, when and how to stop treatment and the protection of the public's health.

Programmatic actions

The immediate issues to be addressed in developing an XDR-TB treatment programme are:

- installing a national coordination mechanism and legal framework for drug-resistant programmes;
- assessing and addressing the causes of MDR-TB and XDR-TB;
- implementing a sound drug-resistance programme based on the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis*;
- developing country-specific case management protocols, detection strategy and infection control policy;
- strengthening laboratory services and infrastructure to manage drug-resistant TB.

Challenges in XDR-TB patient management

The probability of MDR-TB patients having resistance to any fluoroquinolone and to at least one of the three following injectable drugs used in anti-TB treatment (amikacin, kanamycin and capreomycin) is directly related to whether the patient has been exposed to these drugs and/or was exposed to infectious XDR-TB patients. All TB patients at increased risk of MDR-TB and XDR-TB should have a drug susceptibility test conducted, covering first-line anti-TB drugs, and at least a fluoroquinolone and the aminoglycosides. Coinfection of XDR-TB with HIV is a particularly lethal combination. Given the need to build upon a patient-centered approach, the challenges are:

- access to timely and accurate diagnosis;
- availability of all second-line drugs (including capreomycin and PAS) of assured quality;
- access to HIV diagnosis and continuum of care;
- identification of, and measures to address, barriers to treatment adherence;
- management of adverse events and drug–drug interactions.

The challenges to managing XDR-TB patients also extend to their families and close contacts within the community.

Patient management

Treatment of XDR-TB follows the principles established in the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis*. However, evidence on the required duration of treatment in patients with resistance to the fluoroquinolones and/or both groups of injectable drugs (aminoglycosides and polypeptide) is lacking.

- Hierarchy of drug group use still applies.
- DST from a reliable laboratory can be used to guide the initial (empirical) design and changes in the treatment regimen. However, two issues may impede this approach: (i) the lack of standardization for DST for several key second-line anti-TB drugs, and (ii) the clinical relevance of second-line DST results.
- XDR-TB/HIV co-management:
 - HIV coinfection, once established, may require the urgent use of ARVs in addition to anti-TB drugs, which requires careful consideration of (i) appropriate timing in initiating both therapies, (ii) adequate management of possible drug–drug interactions and (iii) adequate management of immune reconstitution inflammatory syndrome.
 - For HIV coinfecting patients with rifampicin resistance: no evidence exists to support the use of third-line drugs or anti-TB drugs with unclear efficacy in place of second-line anti-TB drugs unless adequate regimens are impossible to form with second-line anti-TB drugs.
 - Compassionate use of newly developed drugs for XDR-TB should be considered only in the context that they cause no harm to the patient or compromise other drugs in use. As these drugs are still under development, indications for their use are not yet established.
 - Supportive and/or palliative care after suspending therapy should be in place for patients who fail XDR-TB treatment, as described in the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis*.

Recommendations

- Implement sound MDR-TB control programmes.
- Establish a Task Force to identify specific research questions related to XDR-TB.
- Update the WHO *Guidelines on the programmatic management of drug-resistant tuberculosis* to address XDR-TB and improve the TB/HIV component, including concomitant treatment with ARVs.
- WHO to coordinate discussions on the legal and ethical issues at global level that impact XDR-TB management.
- WHO to lead the push for the development of new tools (drugs and diagnostic tests).
- WHO to establish criteria and provide guidance for possible compassionate use of newly discovered anti-TB drugs.