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

Geneva, Switzerland
9–10 October 2006
Report of the meeting of the WHO Global Task Force on XDR-TB

Geneva, Switzerland
9–10 October 2006
© World Health Organization 2006

All rights reserved.

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either express or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.
Contents

1. BACKGROUND ................................................................................................................................. 1

2. CURRENTLY AVAILABLE DATA ON XDR-TB AND THEIR IMPLICATIONS FOR TB AND HIV/AIDS CONTROL PROGRAMMES................................................................................................. 3


4. SUMMARY OF BREAKOUT SESSIONS ......................................................................................... 6

5. STRENGTHENING LABORATORIES TO PROVIDE RAPID DRUG SUSCEPTIBILITY TESTING IN RESOURCE-LIMITED SETTINGS ......................................................................................................................... 9

6. COORDINATION, COLLABORATION WITH NATIONAL AUTHORITIES, INTERNATIONAL PARTNERS AND WHO, AND PROPOSED PLAN OF ACTION TO FIGHT MDR-TB AND XDR-TB .................................................................................................................. 10

7. RECOMMENDATIONS AND NEXT STEPS ............................................................................. 11

ANNEX 1 AGENDA .............................................................................................................................. 15

ANNEX 2 LIST OF PARTICIPANTS ............................................................................................. 18

ANNEX 3. ALGORITHM FOR INITIAL MANAGEMENT OF PATIENTS AT RISK OF DRUG-RESISTANT TUBERCULOSIS AND HIV INFECTION ........................................................................... 23

ANNEX 4. PROGRAMMATIC MANAGEMENT OF XDR-TB AND TREATMENT DESIGN IN HIV-NEGATIVE AND HIV-POSITIVE INDIVIDUALS .................................................................................. 24
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 PARTNERS\(^2\) 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 South 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

---

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 developed 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 architectured 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). 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.

---

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 isolation 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.

---

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.

---


\(^2\) *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

<table>
<thead>
<tr>
<th>TIME</th>
<th>TITLE/ACTIVITY</th>
<th>SPEAKER</th>
</tr>
</thead>
</table>
| 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) | M. Letsie  
                 |                                                                                | R. Green-Thompson  
<pre><code>             |                                                                                | R. Mukasa                                                |
</code></pre>
<p>| 11:30 – 12:00  | Discussion                                                                    | Chairperson                                                                                 |
| 12:00 – 13:00  | Lunch                                                                         |                                                                                             |</p>
<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Speakers</th>
</tr>
</thead>
</table>
| 13:00 – 13:40| 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)* | • V. Leimane  
• T. Tupasi  
• J. Bayona  
• M. Danilovits |
|              | • Latvia  
• The Philippines  
• Peru  
• Estonia |
| 13:40 – 14:20| Discussion                                                               | Chairperson                                                              |
| 14:20 – 17:30| Six breakout sessions:                                                   | Chair/Co-Chairperson:  
R. O’Brien/M. Harrington  
K. Lambregts/P. Salif Sow  
F. Drobniewski/J. Nkengasong  
E. Nardell  
C. Dye/R. Granich  
J. Deane/A. Winter |
|              | • 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                        |                                                                         |
|              | **Working tea/coffee break included**                                   |                                                                         |
| 17:30 – 18:00| Plenary session with WHO Acting Director-General, Dr Anders Nordström     |                                                                         |
| 18:00 – 19:00| **Meeting of rapporteurs and communication staff**                       |                                                                         |
**Tuesday, 10 October 2006**

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

<table>
<thead>
<tr>
<th>TIME</th>
<th>TITLE/ACTIVITY</th>
<th>SPEAKER</th>
</tr>
</thead>
<tbody>
<tr>
<td>09:00 – 10:30</td>
<td>Plenary reports:</td>
<td>Rapporteurs</td>
</tr>
<tr>
<td></td>
<td>• Management of XDR-TB suspects in high and low HIV prevalence settings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Programmatic management of XDR-TB and treatment design in HIV negative and positive people</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Laboratory XDR-TB definitions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Infection control and protection of health-care workers, with emphasis on high HIV prevalence settings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Immediate XDR-TB surveillance activities and needs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Advocacy, communication and social mobilization</td>
<td></td>
</tr>
<tr>
<td>10:30 – 11:00</td>
<td>Tea/Coffee Break</td>
<td></td>
</tr>
<tr>
<td>11:00 – 11:30</td>
<td>Strengthening laboratories to provide rapid drug susceptibility testing in resource poor settings (15 minutes presentation followed by discussion)</td>
<td>A. van Deun, Institute of Tropical Medicine, Belgium, and the UNION</td>
</tr>
<tr>
<td>11:30 – 12:00</td>
<td>The urgent need for new diagnostic tests, drugs and vaccines (15 minutes presentation followed by discussion)</td>
<td>R. O’Brien, Foundation for Innovative New Diagnostics</td>
</tr>
<tr>
<td>12:00 – 13:30</td>
<td>Lunch</td>
<td></td>
</tr>
<tr>
<td>13:30 – 14:30</td>
<td>Coordination, collaboration with national authorities, international partners and WHO in the fight against MDR-TB and XDR-TB and proposed budget needs and gaps (20 minutes presentation followed by discussion)</td>
<td>P. Nunn, Coordinator, Stop TB Department, WHO</td>
</tr>
<tr>
<td>14:30 – 16:00</td>
<td>Proposed outlined plan of action on MDR-TB and XDR-TB prevention and control measures to be taken at national and global levels (20 minutes presentation followed by discussion)</td>
<td>T. Tupasi, Chair, Stop TB Working Group on MDR-TB, Tropical Disease Foundation, the Philippines</td>
</tr>
<tr>
<td>16:00 – 16:30</td>
<td>Tea/coffee break</td>
<td></td>
</tr>
<tr>
<td>16:30 – 17:00</td>
<td>Conclusions and next steps</td>
<td>Chairperson</td>
</tr>
<tr>
<td>17:00 – 17:15</td>
<td>Closure of the Global XDR-TB Task Force meeting</td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 2  LIST OF PARTICIPANTS

1. Sabine Beckmann  
Senior Technical Officer  
Global Programme on HIV/AIDS  
International Labour Organization  
4 route des Morillons  
1211 Geneva 22, Switzerland

2. Amy Bloom  
Senior Technical Advisor  
Office of HIV/AIDS Bureau for Global Health  
US Agency for International Development  
1300 Pennsylvania Avenue, NW  
Washington, DC  20523–3700, USA

3. François Bonnici  
Global Health Initiative  
World Economic Forum  
Route de la Capite 91–93  
1223 Cologny, Switzerland

4. Martina Casenghi  
Campaign for Access to Essential Medicines  
Médecins Sans Frontières  
78 Rue de Lausanne  
1211 Geneva 21, Switzerland

5. Kenneth Castro  
Director  
Division of TB Elimination  
National Center for HIV, STD and TB  
Centers for Disease Control and Prevention  
1600 Clifton Road, NE, Mailstop E-10  
Corporate Square Building, Bldg 10  
Atlanta, GA  30333, USA

6. Peter Cegielski  
Team Leader, MDR-TB  
International Programs and Research Branch  
Division of Tuberculosis Elimination  
Centers for Disease Control and Prevention  
1600 Clifton Road, NE, Mailstop E-10  
Atlanta, GA  30333, USA

7. Timothy Chonde  
National TB Programme Manager  
National TB and Leprosy Programme  
Ministry of Health and Social Welfare  
P.O. Box 9083  
Dar es Salaam, United Republic of Tanzania

8. Gavin Churchyard  
Chief Executive  
Aurum Institute  
6th Floor, 47 Main Street  
Ferreiradsorp, Johannesburg 2001  
Gauteng, South Africa

9. Gerrit Coetzee  
Head  
National Tuberculosis Reference Laboratory  
National Health Laboratory Service  
P.O. Box 1038  
Johannesburg, South Africa

10. William Coggin  
Senior Public Health Advisor  
Global AIDS Program  
Centers for Diseases Control and Prevention  
1600 Clifton Road, NE, Mailstop E-10  
Corporate Square Building, Bldg.10  
Atlanta, GA  30333, USA

11. Manfred Danilovits  
Head, Department of Tuberculosis  
Tartu University, Lung Clinic  
Riia 167, Tartu 51014, Estonia

12. James Deane  
Managing Director  
Communication for Social Change Consortium  
56 Southbrook Road  
London SE12 8LL, England

13. Isabelle Devaux  
Epidemiologist, Euro TB  
Institut de Veille Sanitaire  
12 rue du Val d’Osne  
94415 St Maurice-Cedex, France

14. Susan Dorman  
Assistant Professor of Medicine  
Johns Hopkins University School of Medicine  
Center for Medical Research  
1503 East Jefferson Street, Room 105  
Baltimore, MD  21231, USA

15. Beatrice Dlamini  
National AIDS Programme Manager  
Ministry of Health and Social Welfare  
P.O. Box 5, Mbabane, Swaziland
16. Professor Francis Drobniewski  
Director, Health Protection Agency  
National Mycobacterium Reference Unit  
Head, Clinical TB and HIV Group  
Center for Infectious Diseases, Institute for  
Cell and Molecular Sciences,  
Barts and the London School of Medicine  
Clinical Sciences Research Center  
2 Newark Street, London E1 2AT, England

17. Katherine Fielding  
Lecturer  
London School of Hygiene & Tropical Medicine  
Keppel Street, London WC1E 7HT, England

18. Jennifer Furin  
Country Director, Partners In Health  
Private Bag A391, Maseru 100, Lesotho

19. Jaime N. Bayona Garcia  
Director, Socios En Salud – Sucursal Perú  
Av. Merino Reyna 575  
Raúl Porras B. Carabayllo  
Lima 06, Peru

20. Lawrence Geiter  
Senior Director, Epidemiology and Field Studies  
Aeras Global Tuberculosis Vaccine Foundation  
7500 Old Georgetown Road, Suite 800  
Bethesda, MD  20814, USA

21. Neel Gandhi  
Assistant Professor, Department of Medicine  
Albert Einstein College of Medicine  
111 E. 210th Street, Bronx  
New York, NY  10467, USA

22. Case Gordon  
World Care Council  
Place Pepin  
Viols en Laval, 34380 France

23. Reuben Granich  
Technical Advisor and Program Officer  
Program Services  
Office of the US Global AIDS Coordinator  
2100 Pennsylvania Avenue, NW  
Washington DC, USA

24. Ronald Green-Thompson  
Advisor to the Minister of Health  
Department of Health  
Private Bag X828  
Pretoria 001, South Africa

25. Mark Harrington  
Executive Director  
Treatment Action Group  
611 Broadway, Suite 612  
New York, NY  10002, USA

26. Sven Hoffner  
Associate Professor, Department of Bacteriology  
Swedish Institute for Infectious Disease Control  
Nobels väg 18, Solna, SE-171 82, Sweden

27. Paul Jensen  
Centers for Disease Control and Prevention  
1600 Clifton Road, NE, Mailstop E-10  
Corporate Square Building, Bldg 10  
Atlanta, GA  30333, USA

28. Neeraj Kak  
Senior Technical Advisor  
Quality Assurance Project  
University Research Cooperation  
7200 Wisconsin Avenue, Suite 600  
Bethesda, MD  20814, USA

29. Gladys Khumalo  
Chief Nursing Officer  
Ministry of Health and Social Welfare  
P.O. Box 5, Mbabane, Swaziland

30. Michael Kimerling  
Director, Gorgas TB Initiative  
University of Alabama at Birmingham  
Bevill Biomedical Research Building 206 D  
1530 3rd Avenue S  
Birmingham, AL  35294–2170, USA

31. Sophia Kisting  
Director, Global Programme on HIV/AIDS  
International Labour Organization  
4 route des Morillons  
1211 Geneva 22, Switzerland

32. Catharina (Kitty) Lambregts-van  
Weezenbeek  
KNCV Tuberculosis Foundation  
PO Box 146  
2501 CC The Hague, The Netherlands

33. Vaira Leimane  
MDR-TB Programme Manager  
Chief of Ward Training Centre of Excellence  
Programme, State Centre of TB and Lung  
Disease - p/o Cekule  
LV 2118, Riga District, Latvia
34. Moselinyane Letsie  
Head, Disease Control Unit  
Ministry of Health and Social Welfare  
P. O. Box A212  
Maseru 100, Lesotho

35. Tsebo Litheko  
Project Manager, TB Crisis Plan  
Department of Health  
Private Bag X828, Pretoria 001, South Africa

36. Jose Francisco Duda Macera  
Medical Coordinator for TB/HIV control programmes in prisons  
International Committee of the Red Cross  
19, avenue de la Paix  
1202 Geneva, Switzerland

37. Davide Manissero  
Expert, Unit of Scientific Advice  
European Centre for Disease Prevention and Control  
Tomtebodavägen 11A  
Stockholm, S 171 83, Sweden

38. Refiloe Matji  
Regional Director, University Research Council  
Postnet Suite No. 391  
Elarduspark, Pretoria, South Africa

39. M. K. Matsau  
Deputy Director-General  
Strategic Health Programmes  
Department of Health  
Private Bag X828, Pretoria 001, South Africa

40. Bess Miller  
Associate Director, TB/HIV Prevention and Care Global AIDS Program  
Centers for Diseases Control and Prevention  
1600 Clifton Road, NE, Mailstop E-10  
Corporate Square Building, Bldg.10  
Atlanta, GA 30333, USA

41. Carolyn Mohan  
TB Advisor  
Office of HIV/AIDS Bureau for Global Health US Agency for International Development  
1300 Pennsylvania Avenue, NW  
Washington, DC 20523–3700, USA

42. Anthony Peter Moll  
Principal Medical Officer  
Church of Scotland Hospital  
Private Bag X502  
Tugela Ferry 3010, South Africa

43. Lebohang Moqhali  
Counsellor  
Permanent Mission of Kingdom of Lesotho to the United Nations and other International Organizations in Geneva  
Chemin de Ruches 21  
1292 Chambésy, Geneva, Switzerland

44. Kekeletso Mosisili  
Director  
Health Research and Laboratory Services  
Central Laboratory  
Queen Elizabeth II Hospital, Kingsway Road  
Maseru 100, Lesotho

45. Rosemary Mukasa  
Senior Medical Officer  
National TB Control Programme  
Ministry of Health, P.O. Box 54  
Manzini, Swaziland

46. Megan Murray  
Assistant Professor of Epidemiology  
Department of Epidemiology  
Kresge Building, Room 809  
677 Huntington Avenue  
Boston, MA 02115, USA

47. Edward Nardell  
Associate Professor, Harvard Medical School  
Brigham and Women’s Hospital  
Office of Public Affairs, 75 Francis Street  
Boston, MA 02115, USA

48. John Nkengasong  
Chief International Laboratory Branch  
Global AIDS Program  
Centers for Diseases Control and Prevention  
1600 Clifton Road, NE, Mailstop E-10  
Corporate Square Building, Bldg.10  
Atlanta, GA 30333, USA

49. Rick O’Brien  
Foundation for Innovative New Diagnostics  
P.O. Box 93  
71, avenue Louis Casaï  
1216 Cointrin, Geneva, Switzerland
50. C. Paramasivan  
Foundation for Innovative New Diagnostics  
P.O. Box 93  
71, avenue Louis Csaï  
1216 Cointrin, Geneva, Switzerland

51. Alasdair Reid  
HIV/TB Adviser  
Epidemic Monitoring and Prevention Policy, Evidence and Partnerships  
UNAIDS  
20, avenue Appia  
1211 Geneva 27, Switzerland

52. John Ridderhof  
Centers for Disease Control and Prevention  
Centers for Diseases Control and Prevention  
1600 Clifton Road, NE, Mailstop E-10  
Corporate Square Building, Bldg.10  
Atlanta, GA 30333, USA

53. Sabine Rüsch-Gerdes  
Head  
National Reference Center for Mycobacteria  
Forschungszentrum Borstel  
Parkallee 18, Borstel 23845, Germany

54. Bernard Schwartlander  
Director, Performance Evaluation & Policy  
Global Fund to Fight AIDS, Tuberculosis and Malaria  
Blandonnet International Business Center  
8, chemin de Blandonnet  
1214 Vernier, Geneva, Switzerland

55. Sharita Shah  
Assistant Professor  
Division of General Medicine  
Albert Einstein College of Medicine  
Montefiore Medical Center  
111 E. 210th Street, Bronx  
New York, NY 10467, USA

56. Thomas M. Shinnick  
Chief, Mycobacteriology Laboratory Branch  
Division of TB Elimination  
Centers for Disease Control and Prevention  
1600 Clifton Road, NE, Mailstop E-10  
Corporate Square Building, Bldg.10  
Atlanta, GA 30333, USA

57. Tileman-Dothias von Schoen-Angerer  
Executive Director  
Campaign for Access to Essential Medicines  
Médecins Sans Frontières  
78 rue de Lausanne  
CP 116, 1211 Geneva 21, Switzerland

58. Paul Sommerfeld  
Chair, TB ALERT  
22 Tiverton Road  
London NW10 3HL, England

59. Papa Salif Sow  
Dakar University Hospital  
Fann Hospital BP  
5035 Dakar, Senegal

60. Thelma Tupasi  
Executive Director  
Tropical Disease Foundation, Inc.  
Makati Medical Center  
No. 2 Corner Amorsolo and dela Rosa Street  
1200 Makati City, Philippines

61. Armand Van Deun  
Bacteriology Consultant  
Mycobacteriology Unit  
Institute of Tropical Medicine  
Nationalestraat 155  
B-2000 Antwerpen, Belgium

62. Cristo van Nierkerk  
Clinical Research Scientist  
Global Alliance TB Drug Development  
P.O. Box 92127, Mookloof 0059, South Africa

63. Francis Varaine  
International Medical Coordinator  
Médecins sans Frontières  
rue Dupre 94, B1090 Brussels, Belgium

64. Richard Walwelma  
Laboratory Supervisor  
National Referral Laboratory  
Ministry of Health and Social Welfare  
P.O. Box 8, Mbabane, Swaziland

65. Charles Wells  
Chief  
International Research & Programmes Branch  
Division of TB Elimination  
Centers for Disease Control and Prevention  
1600 Clifton Road, NE, Mailstop E-10  
Corporate Square Building, Bldg.10  
Atlanta, GA 30333, USA
66. Karin Weyer  
Director, TB Research Programme  
Operational and Policy Research  
Medical Research Council  
Cnr Theodore Ave. & Southpansberg Road  
Private Bag X385  
0001 Arcadia, Pretoria, South Africa

67. Paul Zintl  
Chief Operating Officer  
Partners In Health  
641 Huntington Avenue, 1st Floor  
Boston, MA 02115, USA

WHO headquarters, Task Force  
Secretariat
74. Anders Nordström, Acting Director-General
75. Anarfi Asamoah-Baah, Assistant Director-General, HIV/AIDS, TB and Malaria
76. Mario Raviglione, Director, Stop TB Department
77. Mohamed Aziz, Stop TB Department
78. Louise Baker, Stop TB Partnership
79. Léopold Blanc, Coordinator, Tuberculosis, Strategy and Health Systems, Stop TB Department
80. Jesus Garcia Calleja, HIV Department
81. Francesca Celletti, HIV Department
82. Chris Dye, Coordinator, Tuberculosis, Monitoring and Evaluation, Stop TB Department
83. Sarah England, Stop TB Partnership
84. Marcos Espinal-Fuentes, Executive Secretary, Stop TB Partnership
85. Giuliano Gargioni, Stop TB Department
86. Charles Gilks, Coordinator, ART and HIV Care, HIV Department
87. Haileyesus Getahun, Stop TB Department
88. Max Hardiman, Epidemic and Pandemic Alert and Response
89. Ernesto Jaramillo, Stop TB Department
90. Fabienne Jouberton, Stop TB Partnership
91. Thomas Kanyok, Tropical Disease Research
92. Ted Karpf, HIV Department
93. Fuad Mirzayev, Tropical Disease Research
94. Eva Nathanson, Stop TB Department
95. Paul Nunn, Coordinator, TB/HIV and Drug Resistance, Stop TB Department
96. Salah Ottmani, Stop TB Department
97. Piero Olliaro, Tropical Disease Research
98. Amy Piatek, Stop TB Department
99. Fabio Scano, Stop TB Department
100. George Schmid, HIV Department
101. Iain Simpson, Director-General's Office
102. Donald Sutherland, HIV Department
103. Glenn Thomas, Stop TB Department
104. Dick Thompson, Communicable Diseases
105. Mukund Uplekar, Stop TB Department
106. Véronique Vincent, Stop TB Department
107. Marco Vitoria, HIV Department
108. Diana Weil, Stop TB Department
109. Susan Wilburn, Occupational and Environmental Health
110. Brian Williams, Stop TB Department
111. Anne Winter, HIV Department
112. Abigail Wright, Stop TB Department
113. Matteo Zignol, Stop TB Department

WHO Regional Office for Africa
68. El Hadj Belabbes  
c/o WHO Gabon  
BP 820, Libreville, Gabon

69. Georges Alfred Ki-Zerbo  
Regional Adviser, HIV  
BP 6, Cité du Djoue, Brazzaville, Congo

70. Wilfred Nkoma  
Regional Adviser, TB  
Parirenyatwa Hospital  
P.O. Box BE 773, Harare, Zimbabwe

WHO Regional Office for the Americas
71. Mirtha del Granado  
Regional Adviser, TB  
Pan American Sanitary Bureau  
525, 23rd Street, N.W.  
Washington, DC 20037, USA

WHO Regional Office for the Eastern Mediterranean
72. Akihiro Seita  
Regional Adviser, TB  
P.O. Box 7608  
Abdul Razzak al Sanhouri Street  
Nasr City, Cairo 11371, Egypt

WHO Regional Office for Europe
73. Pierpao de Colombani  
Medical Officer, TB  
Scherfigsvej 8  
DK-2100 Copenhagen Ø  
Denmark
ANNEX 3. ALGORITHM FOR INITIAL MANAGEMENT OF PATIENTS AT RISK OF DRUG-RESISTANT TUBERCULOSIS AND HIV INFECTION

IDENTIFY PATIENT WITH RISK OF DRUG-RESISTANT TB

1. Infection control precautions until diagnosis established
2. AFB smears x 3
3. HIV test (or confirm previous HIV test result)

SMEAR NEGATIVE, EXTRAPULMONARY

Management based on smear-negative / extrapulmonary guidelines (forthcoming)
- HIV+, ambulatory
- HIV+, severely ill
- HIV+, close contact of MDR- or XDR-TB: go to liquid culture and DST
- HIV –

SMEAR POSITIVE

Rapid test for RIF resistance (nucleic acid amplification, phage)

✓ HIV test positive
✓ Rapid RIF resistance test positive or close contact of known MDR/XDR TB case or previous treatment failure

✓ HIV test negative
✓ Rapid RIF resistance test positive

✓ HIV test positive
✓ Rapid RIF resistance test negative

✓ HIV test negative
✓ Rapid RIF resistance test negative

1. Perform full rapid 1st and 2nd line DST in liquid-media – rapid transport of specimen or isolate to referral lab if full DST not yet available
2. Start treatment with 4 or more 2nd-line drugs that are certain (or nearly certain) to be effective based on representative drug resistance profiles of specific patient groups (lab / epidemiological survey)
3. Include 3rd-line drugs or investigational new drugs under compassionate use protocols
4. Adjust treatment according to DST results and continue further management based on WHO guidelines on drug-resistant TB (2006)
5. Start antiretroviral treatment as soon as possible in case not previously started
6. Continue enhanced infection control precautions for drug-resistant TB and HIV-infected persons
7. Initiate investigation among close contacts

1. Perform full rapid 1st and 2nd line DST in liquid-media – rapid transport of specimen or isolate to referral lab if full DST not yet available
2. Start treatment with 4 or more 2nd-line drugs that are certain (or nearly certain) to be effective based on representative drug resistance profiles of specific patient groups (lab / epidemiological survey)
3. Adjust treatment according to DST results and continue further management based on WHO guidelines on drug-resistant TB (2006)
4. Continue enhanced infection control precautions for drug-resistant TB
5. Initiate contact investigation among close contacts

1. Perform 1st line DST in liquid media – rapid transport of specimen or isolate to referral lab if DST not yet available
2. Begin standardized short course chemotherapy with INH, RIF, PZA, and EMB per WHO guidelines for national TB programs (2003 rev.)
3. If drug-resistant TB identified by DST, follow WHO guidelines on drug-resistant TB treatment (2006)
4. Initiate antiretroviral treatment as soon as indicated
5. Infection control precautions for HIV-infected persons

1. Begin standardized short course chemotherapy with INH, RIF, PZA, and EMB per WHO guidelines for national TB programs (2003 rev.)
2. Routine infection control precautions for TB
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 coinfected 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.