PROGRESS IN DOTS-PLUS AND THE MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB)

Proceedings of the Meeting
of the Stop TB Working Group on DOTS-Plus for MDR-TB

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EXECUTIVE SUMMARY

Tuberculosis (TB) is a leading cause of adult deaths due to infectious diseases. The DOTS strategy for TB control has been hailed as one of the most cost-effective health interventions to date. However, in some areas, the success of DOTS is threatened by the rise of multidrug-resistant TB (MDR-TB). To address the problem of MDR-TB, the World Health Organization (WHO) in collaboration with its international partners is testing a strategy, known as “DOTS-Plus”, for the management of MDR-TB. Convened by WHO, the Stop TB Working Group on DOTS-Plus for MDR-TB was established in 1999 to ensure that efforts directed towards establishing DOTS-Plus pilot projects are coordinated. As part of the activities of the Working Group, a three-day annual meeting was held to discuss the progress in DOTS-Plus. This document summarizes the presentations, discussions, conclusions and recommendations of this meeting.

The first day of the meeting was devoted to reviewing the progress achieved by DOTS-Plus pilot projects by the national TB programmes (NTPs) and other institutions involved in the management of MDR-TB. The first half of the second day of the meeting focused on drug access issues, including the concept, functions and preliminary results of the Green Light Committee and the advances made with the pooled procurement of second-line anti-TB drugs. The second half of the second day concentrated on research issues around MDR-TB. The third day focused on site visits of TB control areas in Peru including DOTS-Plus sites [those of NTP – Peru and Partners in Health (PIH)] and a training session for preparing applications to the Green Light Committee.

The meeting concluded with the following recommendations:

- emphasize that the priority for NTPs is DOTS expansion, and DOTS-Plus when it is justified,
- ensure standard methods are used across all DOTS-Plus pilot projects,
- provide technical support to DOTS-Plus pilot projects as needed,
- increase the visibility and the awareness of the Green Light Committee,
- continue monitoring progress in drug procurement activities,
- further develop and promote a research agenda for MDR-TB, and
- redistribute the terms of reference for the Working Group to inform all parties and revisit the roles of the Working Group and its subgroups.

The next meeting of the Working Group will be held in the Baltic Region in mid-2002.
BACKGROUND

Two global surveys conducted by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) published in 1997 and 2000 found MDR-TB in nearly every country surveyed, and determined that levels of MDR-TB are disproportionately high in some settings. Coordination of efforts to address MDR-TB was seen as a priority during a series of meetings of international TB experts in 1998. In 1999, the WHO Working Group on DOTS-Plus for MDR-TB (later renamed the Stop TB Working Group on DOTS-Plus for MDR-TB) was established to advise WHO in developing policy recommendations for Member States regarding the management of MDR-TB. Four subgroups are created under the Working Group:

- a Scientific Panel on clinical/programmatic issues to develop guidelines for establishing DOTS-Plus pilot projects and to offer guidance on such issues,
- the Subgroup on Drug Procurement Issues to increase access to second-line anti-TB drugs,
- the Subgroup on Laboratory Issues to develop guidelines for drug-susceptibility testing (DST) to second-line anti-TB drugs, and
- the Green Light Committee to foster access to concessionally priced second-line anti-TB drugs to those projects adherent to the guidelines developed by the Scientific Panel.

On 25-27 January 2001, WHO, the Pan American Health Organization (PAHO), and the NTP of the Ministry of Health of Peru hosted the second meeting of the Working Group to review the progress achieved thus far, and to discuss new directions for the future. The meeting was sponsored by WHO, the Rockefeller Foundation, the United States Agency on International Development, and Harvard Medical School.

AIMS OF THE MEETING

The meeting was structured to achieve the following objectives:

1. to present and discuss progress of the various methodological approaches NTPs and other organizations are using to manage MDR-TB under DOTS-Plus,

2. to discuss the progress and next steps in the procurement of high-quality, concessionally-priced second-line anti-TB drugs,

3. to prepare a research agenda for DOTS-Plus pilot projects,

4. to perform site visits to the TB control service of Peru, including DOTS-Plus by the NTP - Peru and PIH, and

5. to conduct a training session in developing applications to the Green Light Committee.
OPENING REMARKS

The meeting was opened by Dr Eduardo Pretell Zarate (Minister of Health of Peru). He expressed the continued commitment of the government of Peru to TB control including management of MDR-TB. Dr Andrée Marie Diouf (WHO Representative of the Director-General in Peru) acknowledged the excellent work of the NTP in Peru. WHO targets of 70% case detection and 85% cure rate have been achieved, and WHO has estimated a rate decline of 7.4% per year of new pulmonary cases since 1993. Dr J.W. Lee (Director of Stop TB, WHO) delivered a welcoming message from the WHO Director-General and thanked the government of Peru for kindly hosting the meeting. Finally, on behalf of all attending members of the Working Group, Dr Howard Hiatt (Harvard Medical School) expressed the commitment of the partners to continue working to address MDR-TB within the aegis of the Working Group.

PROGRESS OF MDR-TB MANAGEMENT

Progress of the Stop TB Working Group on DOTS-Plus for MDR-TB

Dr Mario Raviglione (WHO) outlined the history of DOTS-Plus and the progress of the Working Group to date. The WHO working definition of DOTS-Plus is as follows:

"DOTS-Plus is a case management strategy under development designed to manage MDR-TB using second-line drugs within the DOTS strategy in low- and middle-income countries."

The Working Group was established in 1999 as a result of the need to coordinate international efforts to manage MDR-TB. The Working Group and its subgroups have had several meetings since then and much progress has been achieved. Necessary actions for control of MDR-TB include increasing access to second-line anti-TB drugs, building technical capacity for DOTS-Plus, building adequate laboratory components, and increasing advocacy (for example, via public-private partnerships). Several research issues remain unresolved, e.g., measuring the transmissibility of MDR-TB strains, developing rapid detection methods of MDR-TB, determining the best approach to treatment (standardised or individualised) for a given setting, and evaluating the overall feasibility of DOTS-Plus using economic analyses. It is perceived that future DOTS-Plus activities will be mainstreamed within the DOTS expansion movement.

DOTS-Plus in Peru: Experience with a Standard Treatment Regimen

Dr Pedro Suarez (NTP-Peru) presented progress achieved in Peru on the management of chronic patients with a history of more than two treatment regimens (relapses of Category I who failed Category II, consecutive failures of Category I and Category II) with MDR-TB using a standardized second-line drug treatment regimen. Two key components have made possible the administration of therapy countrywide to chronic MDR-TB patients:

1) the establishment of a special committee of 12 local experts to review applications from the health institution throughout the country to enrol patients, and
2) the creation of an MDR-TB unit under the aegis of the NTP to monitor and assess the progress of this initiative.

The coordinators of the 34 health departments are linked to this unit in order to ensure coordination. Preliminary results show cure rates of 48% in the first 466 patients evaluated. This rate increases to 63% when only patients that completed therapy are evaluated. Peru has implemented this service as a national policy. In collaboration with WHO, NTP Peru has undertaken full analysis of the available data in order to strengthen its DOTS-Plus strategy.

**DOTS-Plus in Peru: Experience with a Tailored Treatment Regimen**

Dr Jaime Bayona [Socion en Salud (SES)] presented the progress achieved under an individualized second-line drug treatment regimen in three districts of Lima, under the aegis of the NTP. This approach uses community health workers to directly observe administration of therapy, and susceptibility testing to second-line anti-TB drugs (provided by Massachusetts State Laboratory). Overall, 87 patients were admitted up to 30 December 2000. Analysis was limited to 58 patients with more than 4 months of treatment. Of the 58 patients, 81% are still on treatment but have converted from culture positive to negative, 10% are still on treatment and are culture positive, 5% have died, and 1.7% have defaulted. The presentation highlighted the success of this collaboration.

**DOTS-Plus in the Philippines: A Multi-district Approach**

Dr Thelma Tupasi (Tropical Disease Foundation) described the situation of TB in the Philippines in the form of determining the magnitude of MDR-TB and what the private sector can do to help the NTP. DOTS expansion in the Philippines has been rapid, reaching 43% population coverage in 1999 compared with 17% in 1998. The 1997 nationwide TB prevalence survey showed 4.3% MDR-TB in 188 M. tuberculosis strains tested. Data from the Makati Medical Center suggest an increase in resistance to ciprofloxacin and ofloxacin. The DOTS-Plus pilot project at the Makati Medical Center is part of a three step process whereby the Makati Medical Center will serve as a focal point for the development of local expertise in MDR-TB management in an attempt to expand MDR-TB treatment centers countrywide. Individualised regimens based on culture and DST are utilised in this project. This project represents an integrated effort from the private sector and the NTP to manage MDR-TB cases, but concern remains in reducing the source of cases in the private sector.

**Management of Chronic Patients in Morocco**

Dr Salah Ottmani (WHO) described the experience of the NTP in MDR-TB management in Morocco, which focuses on chronic cases of TB. In the past, clear recommendations existed for new cases, relapses, failures, and treatment interruptions. However, relapses to Category II, failures of Category II, smear positive cases after interruption on Category II, and repeated failures, relapses, and defaulters still remained an issue for the NTP. Each year this group totalled approximately 240 cases (representing 0.5% to 0.7% of all TB cases), with 50% of those cases being new chronics entering and 50% of those cases exiting the pool of total cases due to cure or death. This defined pool of chronics is identified at the provincial level and then reported to one of two national hospitals for management. These two hospitals prescribe one of three intensive phase regimens (standard Category II, standard MDR-TB, or individualised) based upon case history. However, patients undergo the intensive phase of treatment at the provincial hospital. Upon completion of the intensive
phase of treatment, patients are referred to the national hospital for reassessment. Treatment is then completed at the primary health care facility in the province. Second-line anti-TB drugs became affordable to the NTP when the costs of first-line anti-TB drugs decreased dramatically.

**MDR-TB Management in Latvia: A Countrywide Approach**

Dr Vaira Leimane (NTP - Latvia) presented data from four years of experience of managing MDR-TB at the national level. The NTP of Latvia was established in 1995 and began treatment of MDR-TB patients in 1997. DOTS is now implemented countrywide. Drug resistance surveillance results from 1999 indicate levels of MDR-TB were 9.5% and 27% in new and previously treated cases, respectively, and some patients are resistant to first- and second-line anti-TB drugs. The Latvia NTP utilises a consilium of MDR-TB experts that makes decisions in the management of patients, including designing individualised treatment regimens. Patients are evaluated by the consilium at three to four month intervals, and decisions are made on wilful defaulters, surgical treatment, duration of treatment courses, and the termination of treatment for non-effective treatment. For each patient, local physicians evaluate adherence to treatment and smear and culture conversions on a monthly basis. Culture conversion rate for MDR-TB patients was between 62% - 74% in 1997-2000. While the programme has been able to maintain a stable rate of primary MDR-TB cases from 1997-2000 and decrease the number of acquired MDR-TB cases, many obstacles have emerged including patients who refuse hospitalisation or treatment, patients who are lost due to lack of a permanent living place, discrepant results for DST to second-line anti-TB drugs, and treatment alteration due to interruption, drug intolerance, and shortage of anti-TB drugs.

**MDR-TB Management in Estonia: A Countrywide Approach**

Dr Kai Vink (NTP - Estonia) reported on the progress of MDR-TB activities in Estonia. By 2000, the DOTS strategy had been implemented countrywide including DOTS-Plus in the prison system. This includes DOT, an established structure for a laboratory network, and a standard system for recording and reporting. Treatment of patients is individualised according to DST results. Two hospitals participate in diagnosis of cases and start the treatment, and one hospital is used for treatment. The NTP also utilises a consilium of TB experts that evaluates cases every three months and modifies treatment regimens as needed. Specific registers at the district level are used for MDR-TB cases and these registers are linked with national registers. National register is linked separately to the TB laboratory network that supplies districts with culture data. Cohort analysis for new MDR-TB cases notified in 1999 demonstrated 4.9% failures, 20.6% deaths, and 20.6% defaulters. Supplies of second-line anti-TB drugs and limited funds have been two major problems for the NTP.

**Management of Anti-TB Drug Resistance in Russia: Experience in Orel Oblast**

Dr Charles Wells [Centers for Disease Control and Prevention (CDC)] described the TB situation in Orel Oblast (Russian Federation) by showing the increasing number of infectious TB cases since 1991, coinciding with the political and economic transition of the former Soviet Union. A representative survey of drug resistance was conducted by CDC in 1997 and 2000. The magnitude of MDR-TB is 4.3% among new cases and 16.7% among previously treated cases. The approach in Orel Oblast focuses on modification of the standard Category II regimen to a new regimen containing isoniazid, rifampicin, pyrazinamide, ethambutol, capreomycin, and ofloxacin in the initial phase and a continuation phase based upon DST results. Resistance to second-line anti-TB drugs was only identified for kanamycin. Preliminary results for the first two completed cohorts of new smear positive TB cases indicated 75% completion/cures, 13% deaths, 7% failures, and 5% treatment
interruptions. Full DOTS-Plus implementation is anticipated by June 2001. It was underscored that the high number of TB/HIV co-infections would only compound the TB epidemic in the future. From two cases in 1996, the numbers of co-infected patients jumped to 111 in 1999.

**MDR-TB Management in Tomsk Oblast: Integration of Prison and Civilian Programmes**

Dr Alexander Trusov [Public Health Research Institute (PHRI)] presented surveillance data from Tomsk Oblast (Russian Federation) indicating MDR-TB comprises 9.7% of new cases in the civilian sector and 25.1% of new cases in the prison sector. Programme management is a three-step process that places priority on the treatment of drug-susceptible patients and, then, in the management of MDR-TB cases. For the direct management of cases, the programme uses a project manual and routine examination by specialists. Poly-resistant cases are also a concern for the programme.

Dr Tim Cullinan [(Medical Emergency Relief International (MERLIN)] further described the approach used in Tomsk Oblast. MDR-TB cases resistant to three and four drugs comprise a large proportion of resistant cases among new and all cases, in addition to cases resistant only to isoniazid and rifampicin. For all new cases of TB in 1999, the Tomsk project has achieved a 78% cure rate, 7% failure rate, 6% death rate, and 2% defaulter rate.

**ACCESS TO SECOND-LINE ANTI-TB DRUGS**

**Green Light Committee: Is This the Correct Approach to Control Access to Drugs?**

Mr Rajesh Gupta (WHO) explained the three problems associated with second-line anti-TB drugs: cost (up to USD 15000 for a MDR-TB regimen vs. up to USD 50 for a standard DOTS regimen), treatment delivery (ensuring second-line anti-TB drugs are administered in the proper context to prevent their misuse and emergence of resistance to these drugs), and quality (ensuring that high-quality second-line anti-TB drugs are being used). These problems were addressed by using a pooled-procurement system [led by Médecins Sans Frontières (MSF)/Transfer and the International Dispensary Association (IDA) Foundation] and the concept of the Green Light Committee. Preliminary data were presented demonstrating how the pooled procurement process could have saved some countries 51% to 94% of their expenditures on MDR-TB drugs during 1998 – 2000. The Green Light Committee reviews projects in reference to the Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB and releases access to the pooled-procurement process to those projects adhering to the standards outlined in the guidelines. In addition, the Green Light Committee offers technical assistance, via members of the Working Group, to potential DOTS-Plus pilot projects and continual monitoring of such projects once approved. It was emphasised that the problem is not only access to drugs, but also access to effective treatment programmes.

**Drug Procurement: Where Are We?**

Mr Pierre Poivre (MSF/Transfer) described the role of MSF/Transfer in the drug procurement process. MSF/Transfer responds to the humanitarian efforts by managing and procuring supplies on a cost recovery basis. Having invested a large amount of finances to engage in negotiations for concessional prices, MSF/Transfer are leading the short-term procurement process to provide complete treatment courses of for 2000 patients in DOTS-Plus projects approved by the Green Light Committee. Problems in the procurement process have included patent restrictions, registration, packaging, labelling, and logistics. Programmes can best assist procurement agents by identifying
problems and special needs well in advance so that the procurement agents can prepare accordingly and have better leverage to negotiate with manufacturers.

Prospects for a Long-term Drug Procurement

Mr Guido Bakker (IDA Foundation) described the role of the IDA Foundation in the procurement process. The IDA Foundation's mission statement is to provide high quality essential drugs and medical supplies at the lowest possible price to non-profit health organizations in developing countries. Non-profit organizations in the pharmaceutical industry are possible when sales price calculations are transparent. The IDA Foundation calculates its sale price from the total of the following variables: purchasing price, 8% overhead cost recovery, and a 1% future investment cost. The IDA Foundation intends to undertake procurement responsibilities when MSF/Transfer has reached its 2000 patient capacity. In terms of continued procurement, the IDA Foundation will focus on four tasks: generic availability, quality assurance, affordability, and sustainability.

DEFINING A RESEARCH AGENDA FOR MDR-TB

Diagnostic Research Tools Priorities

Dr Marcos Espinal (WHO) presented priority research questions related to the diagnosis of drug-resistant TB on behalf of Dr Mark Perkins (TDR/WHO). Given the number of potential new technologies available, including MGIT, RedoxMB, MTT, Alamar blue, MODS, phage replication assay, gene amplification and mutation detection, Luciferase reporter phage, E test, flow cytometry, and microcolony inspection and their various costs, the following questions were cited as part of a list of priority questions:

- What are the performance characteristics of these tests?
- Which tests have the most favourable profiles for routine use in low- to middle-income countries?
- Do cheaper, non-commercial methods have important disadvantages?
- How will performance of in-vitro diagnostics be monitored given the lack of regulation in many countries?
- Are there specimen requirements to some of these assays that impact their performance?
- What are the clinical applications in terms of patient selection and treatment outcomes for timing of various diagnostic results?

Working Group Summary:

The primary objective is to have DST available in all high prevalence MDR-TB countries for surveillance and for patient management. DST methods must be accurate, easy to perform, and inexpensive. The group developed five specific points of action:

1. determine the minimum infrastructure necessary to perform accurate and rapid DST in high prevalence MDR-TB countries,
2. evaluate and compare the accuracy, specificity, sensitivity, predictive value for resistance and susceptibility, turnaround time, and cost of rapid DST methods for rifampicin,

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1 It is noted that WHO has a special arrangement with the IDA Foundation to lower the IDA Foundation's standard overhead cost-recovery and future investment cost percentages for DOTS-Plus pilot projects.
3. evaluate the accuracy, specificity, sensitivity, predictive value for resistance and susceptibility, cost, and turnaround time for the direct DST sputum Lowenstein-Jensen method compared to the conventional method,

4. evaluate and compare the accuracy, specificity, sensitivity, predictive value for resistance and susceptibility, turnaround time, and cost of DST for first and second-line anti-TB drugs using new rapid methods, and

5. design and implement collaborative studies to evaluate treatment outcomes for different DST methods with varying turnaround times and in different patient populations.

Operational Research Priorities

Dr Kitty Lambregts-van Weezenbeek [Royal Netherlands TB Association (KNCV)] presented two basic operational questions that set the foundation for operational research priorities:

- What are the times frames involved in development/management of MDR-TB (in relation to MDR-TB prevalence and programme performance)?
- What factors are responsible for the emergence of MDR-TB?

Operational research priorities related to diagnosis include evaluating the relevance of second-line anti-TB DST for clinical decision making, standardising approaches for DST of second-line anti-TB drugs, and determining a method for routing application of rapid DSTs. Treatment issues fall into three categories: strategy (risk of amplification of drug resistance by DOTS regimens in relation to the drug resistance pattern, effectiveness of a standardised versus individualised regimen, and the need for alternative DOTS regimens in relation to the prevalence of drug resistance), regimens (efficacy of various regimens, minimal amount of DOT required, duration of intensive/continuation phases, efficacy of intermittent therapy in the continuation phase, use of isoniazid in low-level isoniazid-resistant patients, and frequency of various types of bacteriological monitoring), and delivery/case-holding (centralised versus decentralised treatment and behavioural issues associated with patients and providers). Infection control issues require the options for management of MDR-TB patients in the absence of MDR-TB treatment facilities or given a limited availability of second-line anti-TB drugs, minimal infection control measures needed for a DOTS-Plus pilot project, and safety measures necessary for handling large quantities of MDR-TB sputa. For laboratory issues, the minimal requirements for adequate supervision of laboratory performance are needed. Recording and reporting systems require applicable definitions, a minimal data set (beyond the pilot phase), and the optimal frequency and methodology of routine analysis of programme data by different levels of programme management. With reference to the private sectors, focus should be placed upon determining the contribution of the private sector to the problem of MDR-TB, and the relation of the availability of anti-TB drugs for other diseases and the prevalence of resistance to these drugs in TB patients.

Working Group Summary:

Five topics were addressed: reporting and recording, programmatic factors, clinical issues, infection control, and cost-effectiveness analysis. Important issues to be addressed for recording and reporting included establishing case definitions, developing standard methods for evaluation of outcomes, and collecting a standard core set of data. Programmatic factors identified as priority areas of research were minimal amount of human resources needed to conduct a pilot project, utility of active case finding, feasibility of implementing a standardised approach versus an individualised approach, adherence/behavioural issues for patients, implementation of DST and drug resistance surveillance,
and coordination of laboratory services with a reference laboratory. Clinical issues included monitoring of side effects, developing strategies to manage HIV-infected patients that are co-infected with MDR-TB, and elucidating factors affecting treatment outcomes and/or data collection. Infection control issues were related to the implementation by rapid diagnostic technology, monitoring and surveillance of staff with TB infection and disease, and use of molecular techniques for investigations of transmission. To perform cost-effectiveness analyses, a collection of comprehensive cost data and appropriate outcomes for measuring effectiveness is needed.

\textbf{Epidemiological/Clinical Research Priorities}

Dr Philip Hopewell [University of California, San Francisco (UCSF)] highlighted five categories where research is needed: clinical care, epidemiological impact, operational aspects, financial requirements, and ethical considerations. Clinical care issues to investigate were tailored versus empiric regimens, indicators of risk for MDR-TB, and optimum laboratory research/techniques. Epidemiological issues highlighted were transmission/infectivity of strains of MDR-TB, predictors of infection with MDR-TB, and treatment of latent infection with MDR organisms. Operational questions were related to access to laboratories, organization of treatment, and enhancing/coordinating external donor support. Cost-effectiveness analysis was pointed out as the most pressing financial question. Finally, ethical questions posed were if it is ethical not to treat patients under certain conditions and if it is ethical to divert limited resources from basic TB control.

\textbf{Working Group Summary:}

The Working Group divided the topic into four categories: infection control issues, understanding the causes of treatment failure, TB dynamics, and treatment of children. Infection control issues focused on identifying the factors that will facilitate early diagnosis of MDR-TB, the duration of infectiousness of MDR-TB, the risk factors for the acquisition of MDR-TB, and the methods to implement and assess effective control measures. To better comprehend the nature of treatment failures, the group proposed to investigate disease factors, adverse reactions, and pharmaceutical integrity (quality and supply) associated with treatment failure of patients enrolled in DOTS-Plus pilot projects. Two major issues arose with studying TB dynamics: the impact and/or burden of MDR-TB in a given community, and the risk and rate of super-infection of MDR-TB in a patient with drug-susceptible TB. In reference to children the major concerns were how to treat children infected with MDR-TB and the effects of second-line anti-TB drugs on children.

\textbf{Management: Is a Clinical Trial For MDR-TB Feasible and Even Necessary?}

Dr Nils Billo (IUATLD), provided three categories of evidence needed for the treatment of MDR-TB: clinical evidence, clinical trials, and community-based evaluation. It was proposed that a potential clinical trial could involve a comparison of the various regimens outlined in the WHO publication \textit{Guidelines for the Management of MDR-TB}. Data were presented comparing the similarity between the clinical outcomes of various approaches to treating MDR-TB and the natural history of TB. Justification for clinical trials included the need to evaluate the recommendations in the \textit{Guidelines for the Management of MDR-TB} and to determine the optimal treatment approach for developing countries. Another proposal could involve determining the feasibility of using an individualised regimen versus a standardised regimen in isoniazid and rifampicin resistant patients. Such a trial was estimated to cost USD 7 million. It was highlighted that any clinical trial would have to strongly take ethical issues into account.
Working Group Summary:

Overall, the group determined that conducting a clinical trial would be very difficult. Comparison of a standardised approach versus an individualised approach (in the context of a clinical trial) pose problems in terms of defining the standard regimen, and ethical problems associated with giving a suboptimal regimen for a known resistance pattern or to unnecessarily expose patients to toxic medicines. It was determined that such a trial would ultimately be comparing the clinical efficacy of two different regimens. In terms of determining an ideal treatment regimen for a given resistant pattern, cost and sample size pose problems. A potential clinical trial could compare the effectiveness of different standardised regimens where only one drug would be different between the regimens (for example, ciprofloxacin versus ofloxacin versus levofloxacin). Animal models were proposed, but limitations in terms of generalisability were recognised. Clinical trials may only be possible via a multi-agency partnership. It is key to ensure that such results will be worth the investment (in terms of time and money) and will adhere to ethical standards.

Advocacy: What Needs to be Done

Dr Ian Smith (WHO) explained TB advocacy in the changing context of health by highlighting the new interest in TB as a disease of poverty and inequity, and renewed interest from the public sector donors. New avenues should be explored, including building partnerships for global public health goods, disbursing resources, delivering services through the private sector, and adapting DOTS for different scenarios. An interactive relationship exists between increasing DOTS coverage, adapting DOTS for issues like MDR-TB and HIV, and improving DOTS via new tools. Strategies for advocacy should include reducing the emergence of drug resistance by expanding DOTS, developing an effective treatment strategy to cure people who have drug-resistant TB (i.e. DOTS-Plus), increasing access, affordability, and control of the second-line anti-TB drugs needed to treat people with MDR-TB, and developing new tools for the management of MDR-TB.

Working Group Summary:

The Working Group emphasized that advocacy for MDR-TB must be in the broader context of advocacy for TB with an aim to bring unity and consistency among all parties. A clear need arose for a practical advocacy plan involving all the stakeholders, expert help in terms of social marketing, flexibility but concordance in approaches, country specific approaches and tools, and a potential relationship with HIV and malaria advocacy efforts. It was proposed that a cross-cutting advocacy group with representation from partners, countries, patients, NGOs, industry, media, and professionals from non-health related fields could be a solution. Goals of such a group would be to mobilise partners and build coalition, mobilise new resources, sustain interest and awareness, develop consistent but flexible messages, develop common vocabulary, and mainstream TB in the context of a reforming and developing health sector.

SPECIAL PRESENTATIONS

The PARTNERS Project Contribution of the Task Force for Child Survival and Development (TFCSD) to DOTS-Plus

Dr Mark Rosenberg (TFCSD) presented the potential contribution of PARTNERS (Partnership Against Resistant Tuberculosis: A Network for Equity Resource Strengthening) for TB Control to
the Working Group. The PARTNERS program, a collaborative effort between the NTP of Peru, PIH/SES, Massachusetts State Laboratory, WHO, CDC, and TFCSD has four specific goals: to demonstrate in Peru the success and sustainability of an integrated TB control programme for MDR-TB, to develop the infrastructure to support this programme and make it exportable, to export this approach to other countries, and to help develop a model for integrated TB control programme in order to support strategies for global TB elimination in collaboration with the efforts of the Working Group.

**Resistance to Second-line Drugs in Resource-limited Settings**

Dr Francois Portaels [Institute of Tropical Medicine (ITM)] presented on the potential problem of TB resistant to second-line anti-TB drugs. Using rapid DST methods (MGIT, MAB) and the proportion method as a gold standard, a 95% sensitivity for kanamycin resistance was achieved. Results were available in one week. The conclusion was that the above methods offer a promising opportunity to rapidly diagnose drug-resistant TB. Costs and feasibility, however, are major problems to overcome in order to have such diagnostic tests in place in resource-limited settings.

**Are Side-effects A Real Obstacle to DOTS-Plus?**

Dr Michael Iseman (National Jewish Medical and Research Centre) discussed the toxicity of second-line drugs. While there is no doubt that toxicity compromises ability to treat MDR-TB, it is also certain that there is no other option for the management of this ailment. Serious side-effects are observed when using ethionamide, cycloserine, and capreomycin. In order to discuss the negative impact of second-line drugs the approach used at the National Jewish Medical and Research Centre was presented. This approach is based on training clinical staff, educating patients, and establishing a very close staff-patient interaction. The experience observed in Peru shows that second-line anti-TB drugs can be used and that side-effects are not a justification to prevent patients with MDR-TB receiving treatment.

**Is MDR-TB the Priority of the Century? Finding the Balance in the Global Public Health Agenda**

Dr Paul Farmer (Harvard Medical School/PIH) focused the first half of this presentation on integrating community involvement with TB control. The clinical, social, and epidemiological importance of cases undetected by standard epidemiological methods and the continued transmission of strains of MDR-TB from lack of management of such cases serve as the basis for the community-based approach in northern Lima. Key factors listed for the success of this approach include involvement of community health workers, political will from various levels, and support from the family and community. Benefits cited include increased contact with at-risk families, identification of contacts for screening, and identification of other problems. The need for operational research in management of MDR-TB, especially in reference to improving adherence to therapy, the role of DOT, incentives, and in-patient versus out-patient care, was emphasised.

Dr Jim Kim (Harvard Medical School/PIH) continued the presentation by focusing on cost-effectiveness issues. Costing analysis included direct costs, programme costs and diagnostic costs. For a sample of 74 people in northern Lima whose average age at onset of treatment was 29.5 years, average costs per patient was USD 12,053. Anti-TB drugs comprised 90% of the these costs. Uncalculated costs were DST at the Massachusetts State Laboratory and the consultancy of the
Harvard Medical School/PIH team. Preliminary calculations of Disability Adjusted Life Years (DALYs) shows a cost-effectiveness ratio of USD 5392/DALY.

TRAINING SESSION

Mr Rajesh Gupta and Dr Marcos Espinal (WHO) conducted the training session for countries applying to the Green Light Committee. Participants were guided through a summary of each section of the Guidelines for Establishing DOTS-Plus Pilot Projects for Managing MDR-TB, and then through each section of the document Instructions for Applying to the Green Light Committee for Access to Second-line Anti-TB Drugs. This was followed by an open question and answer session. It was indicated that the Green Light Committee, at the present time, would not accommodate single-patient requests; NTPs do not have to have 100% DOTS coverage to apply to the Green Light Committee; pilot projects do not have to be country-wide but can be centralised to one area (which is preferred in some settings); and NGOs can apply to the Green Light Committee (although the pilot project must be supported by the NTP of that country). Participants suggested that the Green Light Committee should become a link to sources of funding as many DOTS-based TB control programmes are programmatically capable of conducting DOTS-Plus pilot projects but lack the funding (even with the concessional prices negotiated for second-line anti-TB drugs) to implement such projects.

SITE VISITS

Visits to the health departments of Lima North (including the PIH site), Lima South, Lima East, and Callao were conducted to observe the implementation of DOTS and DOTS-Plus in Peru. Participants were impressed with the quality of the Peruvian NTP well as with the coalition built with several international partners.

CONCLUSIONS AND RECOMMENDATIONS

Participants reiterated the priority for NTPs is the implementation of the DOTS strategy, and that the DOTS strategy prevents the emergence of MDR-TB in areas with little or no MDR-TB. However, in areas with significant levels of MDR-TB, DOTS-Plus may need to be implemented provided DOTS is in place and shown to be effective. Once evidence of feasibility and cost-effectiveness is gathered from various DOTS-Plus pilot projects over the next three years, WHO will evaluate evidence to develop policy recommendations for Member States.

Track 1: Progress of DOTS-Plus

1) Remarkable progress has been achieved in DOTS-Plus since the last meeting held in 1999. This includes the establishment of the Green Light Committee; availability of guidelines to establish DOTS-Plus pilot projects; reduction of the prices of second-line anti-TB drugs; and the implementation of DOTS-Plus pilot projects.

2) Management of MDR-TB can be done using different approaches:

- standardized treatment regimens countrywide - Peru and Morocco,
- tailored treatment regimens countrywide - Latvia, Estonia, and
- tailored treatment regimens regionwide - Tomsk, Orel, Manila, and Lima.
Flexibility is necessary without disregarding quality in order to integrate the use of second-line anti-TB drugs within TB control programme activities.

3) Work must continue to assess the cost-effectiveness of the different approaches. International support is needed, as resource-limited settings cannot cope along with this ailment.

4) Some countries need “emergency” intervention in order to reduce the high MDR-TB burden. Other countries need DOTS first, followed by DOTS-Plus when needed and when DOTS is shown to succeed.

5) The Working Group should continue its work in order to elaborate recommendations for policy guidelines regarding the management of MDR-TB.

6) WHO should distribute the terms of reference of the Working Group (See Annex 3) in order to improve clarity and transparency.

Track 2: Access to Drugs

1) The Green Light Committee is an additional advantage to address the problem of MDR-TB. The procurement agents need to continue working on price reduction and ensuring quality. The Green Light Committee should continue to monitor projects for proper utilisation of drugs and facilitate technical support (via the Working Group) where needed.

2) The Green Light Committee needs to communicate in detail its role, terms of reference, membership access, and decision-making process to all members of the Working Group.

3) The agreement between MSF/Transfer and WHO for short-term procurement of second-line anti-TB drugs for the first 2000 patients approved by the GLC should be closely linked with the long-term procurement strategy under negotiation between WHO and the IDA Foundation. Thus, shortages of drugs is prevented and the mechanism of access to drugs is assured.

4) The IDA Foundation and WHO arrangement for long-term procurement of second-line drugs (generic availability, quality assurance, affordability, and sustainability) should be supported in full and finalised as soon as possible.

Track 3: Defining a Research Agenda for MDR-TB

A detailed research agenda listing priorities is to be drafted by WHO following the recommendations of the five smaller, ad hoc Working Groups of the wider DOTS-Plus Working Group. Such a document will be circulated widely. Donor agencies will be approached by the partners for funding to conduct the proposed research.

Other Issues

The meeting concluded with the appointment by consensus of Dr Jim Kim (Harvard Medical School/PIH) as the new chairperson of the Working Group. Accordingly, Dr Kim resigned from his position as chairperson of the Green Light Committee. Kitty Lambregts van-Weezenbeek (KNCV) was appointed as the new chairperson of the Green Light Committee. The next meeting of the Working Group will be held in the Baltic region in mid-2002.
AGENDA FOR THE MEETING

Thursday, 25 January 2001

Opening Remarks

8:30 AM – 9:00 AM
Dr Marie Andree Diouf
WHO Representative Peru

Dr Howard Hiatt
Harvard University

Dr J.W. Lee
Director STOP TB, WHO

Dr Eduardo Pretell Zarate
Minister of Health of Peru

Chairperson: Edith Alarcon, NTP Peru
Rapporteur: Mercedes Becerra, PIH

Track 1

Progress of MDR-TB Management

9:00 AM – 9:15 AM
Progress of the Stop TB Working Group on DOTS-Plus for MDR-TB
M. Raviglione, WHO

9:15 AM – 9:45 AM
DOTS-Plus in Peru: Experience with a Standard Treatment Regimen
P.G. Suarez, NTP Peru

9:45 AM – 10:00 AM
DOTS-Plus in Peru: Experience with a Tailored Treatment regimen
J. Bayona, SES

10:00 AM – 11:00 AM
Discussion

11:00 AM – 11:30 AM
Coffee Break

11:30 AM – 11:45 AM
The PARTNERS Project Contribution of the Task Force for Child Survival and Development to DOTS-Plus
M. Rosenberg, TFCSD

11:45 AM – 12:00 M
DOTS-Plus in the Philippines: A Multi-district Approach
T. Tupasi, Tropical Disease Foundation, Phillipines
Thursday, 25 January 2001

12:00 AM – 12:15 PM Management of Chronic Patients in Morocco
S. Ottmani, WHO

12:15 PM – 1:00 PM Discussion

1:00 PM – 2:00 PM Lunch

Progress of MDR-TB Management

Chairperson: Lee Reichman, UMDNJ
Rapporteur: Kayla Laserson, CDC

2:00 PM – 2:15 PM MDR-TB Management in Latvia: A Countrywide Approach
V. Lemanis, NTP Latvia

2:15 PM – 2:30 PM MDR-TB Management in Estonia: A Countrywide Approach
K. Vink, NTP Estonia

2:30 PM – 2:45 PM MDR-TB Management in Tomsk Oblast: Integration of Prison and Civilian Programmes
T. Cullinan, MERLIN
A. Trusov, PHRI

2:45 PM – 3:00 PM MDR-TB Management in Orel Oblast: Modifying the Category II Regimen
C. Wells, CDC

3:00 PM – 4:00 PM Discussion

4:00 PM – 4:30 PM Coffee Break

Special Presentations

4:30 PM – 4:45 PM Resistance to Second-line Drugs in Resource-limited Settings
F. Portaels, ITM

4:45 PM – 5:00 PM Are Side-effects of Second-line Drugs a Real Obstacle to DOTS-Plus?
M. Iseman, National Jewish Medical and Research Center

5:00 PM – 6:00 PM Discussion

7:00 PM Reception/Dinner
Annex 1 - Agenda

Friday, 26 January 2001

Chairperson: Daniel Kibuga, NTP Kenya        Rapporteur: Kai Vink, NTP Estonia

Track 2  Access to Drugs

8:30 AM – 8:45 AM  Green Light Committee: Is This the Correct Approach to Control Access to Drugs?  
                                      R. Gupta, WHO

8:45 AM – 9:30 AM  Discussion

9:30 AM – 9:45 AM  Drug Procurement Where Are We?  
                                      P. Poivre, MSF/Transfer

9:45 AM – 10:00 AM  Prospects for a Long-term Drug Procurement  
                                      G. Bakker, IDA Foundation

10:00 AM – 10:45 AM  Discussion

10:45 AM – 11:00 AM  Coffee Break

11:00 AM – 11:15 AM  Public-private Partnerships for MDR-TB: Perspective from Eli Lilly and Co  
                                      Eli Lilly (Cancelled)

11:15 AM – 12:00 M  Discussion

Special Presentation

12:00 PM – 12:30 PM  Is MDR-TB the Priority of the Century? Finding the Balance in the Global Public Health Agenda.  
                                      P. Farmer / J. Kim, Harvard Medical School

12:30 PM – 1:00 PM  Discussion

1:00 PM – 2:00 PM  Lunch
Annex I - Agenda

Friday, 26 January 2001

Chairperson: Marcos Espinal, WHO  Rapporteur: Rajesh Gupta, WHO

Track 3  Defining a Research Agenda for MDR-TB

2:00 PM – 2:15 PM  Diagnostic Tools Research Priorities
M. Perkins / M. Espinal, WHO

2:15 PM – 2:30 PM  Operational Research Priorities
K. Lambregts van-Weeenbeek, KNCV

2:30 PM – 2:45 PM  Epidemiological/Clinical Research Priorities
P. Hopewell, UCSF

2:45 PM – 3:00 PM  Management: Is a Clinical Trial for MDR-TB Feasible and Even Necessary?
N. Billo, IUATLD

3:00 PM – 3:15 PM  Advocacy: What Needs to be Done?
I. Smith, WHO

3:15 PM – 6:15 PM  Five Working Groups

Group Chairperson:
Portaels, Lambregts, Hopewell, Billo, Smith
Each group selects a rapporteur

Each group will select five research priorities or options for a clinical trial* using the speaker presentation as the starting point; other issues can be listed as “also of interest”

15 minutes coffee break at 4:30

* The clinical trial group should also discuss if it is feasible to conduct a formal clinical trial or programmatic trials are sufficient.

7:00 PM  Dinner
Annex 1 - Agenda

Saturday, 27 January 2001

Session 1: This session is only for countries or groups that intend to apply to the Green Light Committee

Chairperson: Rajesh Gupta, WHO

8:00 AM – 8:30 AM Applying to the Green Light Committee
R. Gupta / M. Espinal (WHO)

8:30 AM – 12:00 PM Training Session for Developing
Applications to the Green Light Committee
R. Gupta / M. Espinal (WHO)

Session 2: Those who are not attending Session 1 will visit health centers and hospitals to observe the implementation of DOTS and DOTS-Plus.

8:00 AM – 12:00 PM Site Visits (Groups of 10 people)
NTP Peru

12:00 M – 2:00 PM Return to the hotel for lunch and final plenary session

Chairpersons: Mario Raviglione, WHO and Jim Kim, PIH

Final Plenary Session

2:00 PM – 3:00 PM Report from the Working Groups on Research Issues
10 Minutes each
Rapporteurs
Annex 1 - Agenda

Saturday, 27 January 2001

3:00 PM – 3:45 PM  
Next Steps on Each Track

Each track will be summarized (progress and next steps) in a 5 minutes presentation followed by 10 minutes discussion

Track 1  
Progress of MDR-TB Management  
E. Alarcon

Track 2  
Access to Drugs  
K. Vink

Track 3  
Research Agenda  
M. Espinal

3:45 PM – 4:20 PM  
Other Issues (Selection of the next meeting’s chairperson of the Working Group and the Green Light Committee)

All

4:20 PM – 4:30 PM  
Closing Remarks

J.W. Lee, WHO
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TERMS OF REFERENCE FOR THE STOP TB WORKING GROUP ON DOTS-PLUS FOR MDR-TB

"DOTS-Plus for Multidrug-Resistant Tuberculosis"

A Stop TB Working Group Convened by WHO

Terms of Reference

The Working Group on “DOTS-Plus for MDR-TB” is an inter-institutional arrangement of many partners involved in the management of multidrug-resistant tuberculosis (MDR-TB) under the umbrella of Stop TB convened by WHO.

Rationale for the Working Group

The WHO/IUATLD Global Project on Drug Resistance Surveillance (DRS) has shown that MDR-TB is present in almost all countries surveyed and that a few “hot spots” with very high MDR-TB prevalence exist. The potential spread of MDR-TB could be a threat to the success of DOTS, the WHO strategy for TB control. DOTS is a five-component policy package acknowledged by the World Bank as one of the most cost-effective interventions in human health.

Following identification of such “hot spots,” there has been an increasing call for action to prevent and contain the spread of MDR-TB. After publication of the Global Report on DRS in 1997, WHO initiated a series of consultations to design a strategy to address MDR-TB as a potential public health problem. In April 1998, WHO and Harvard/PIH co-sponsored a meeting in Cambridge, USA, to discuss a potential approach to address this issue in developing countries. Later in July 1998, a second meeting at WHO headquarters (Geneva, Switzerland) brought together recognised worldwide technical experts to produce two generic protocols for the management of MDR-TB.

In January 1999, a major meeting took place in WHO/HQ to define a strategy targeting MDR-TB. The main recommendations were to establish a Working Group on DOTS-Plus for MDR-TB, to focus on drug access, to negotiate with the pharmaceutical industry for a reduction in drug prices, and to elaborate guidelines for implementation of pilot projects and for drug susceptibility testing of second-line drugs.
Annex 3 - Terms of Reference

In industrialized countries, management of MDR-TB is based on the use of tailored treatment regimens with second-line anti-TB drugs according to the patient's drug susceptibility pattern. However, no conclusive evidence at programme level is yet available on how feasible this approach to designing regimens would be in low-and middle-income countries. In some of these settings drug-susceptibility testing (DST) is not widely available and second-line anti-TB drugs are not affordable so potential management strategies for MDR-TB must be adapted and carefully tested before recommendations are issued.

A Working Group was created in 1999 by WHO to assess the feasibility and cost-effectiveness of management strategies for MDR-TB, and to generate evidence-based policy on the management of MDR-TB in middle- and low-income countries. Several pilot projects have been established. The results of such pilot projects will, in turn, generate sufficient data from which WHO will be able to develop international policy recommendations. With the establishment of the Stop TB structure, the Working Group became the Stop TB Working Group on DOTS-Plus for MDR-TB.

Objectives of the Working Group

In order to address effectively the issue of MDR-TB care and control, efforts will be coordinated and collaborative work in partnership with other institutions of recognized experience and prestige promoted. The objectives of the Working Group are as follows:

1. To assist in producing policy recommendations for Member States on the management of MDR-TB, based on the assessment of the feasibility, effectiveness, and cost-effectiveness data generated by pilot projects implemented by the agencies/institutions participating in the Working Group, or by WHO;

2. To coordinate and monitor the implementation of internationally comparable pilot projects for the management of MDR-TB. In most cases, the representatives of participating agencies/institutions will be acting as principal investigators on behalf of the agency/institution they represent;

3. To establish a system that allows WHO Member States to have access to high-quality second-line drugs at reduced prices and, at the same time, prevents misuse of such drugs;

4. To review progress achieved within the DOTS-PLUS initiative; and

5. To identify resources to fund and implement DOTS-PLUS pilot projects and to assist with global coordination of the initiative.

Membership

Participation in the Working Group is open to any institution or technical expert (not affiliated with any institution) serving in a personal capacity and willing to help achieve the goals mentioned in the above listed terms of reference. The Working Group is composed of one representative of each participating agency/institution and technical experts in their personal capacity. Institutional representatives in the Working Group and its subgroups are designated at the discretion of the institution.
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The Working Group selects a chair from among the representatives of the Partners to preside over the meetings of the Working Group. The chair of the Working Group is selected for a period of two years and represents the Working Group during meetings of the Stop TB Coordinating Board. WHO will consult the chair for advice on when to convene meetings of the Working Group. Each subgroup of the Working Group will select its chair for the duration of the subgroup’s existence, to and preside over the meetings of the subgroup.

WHO will provide the secretariat functions for the meetings of the Working Group and its subgroups.

Progress to Date

The Working Group was established in 1999 prior to the creation of the Stop TB structure. Therefore, work began and is now under-way to address the above objectives. Several subgroups within the Working Group have been created:

1. The Subgroup on Laboratory Issues was created to make recommendations with regard to standard guidelines for DST for second-line anti-TB drugs. The resulting document has been finalized and is titled Guidelines for Drug-Susceptibility to Second-line Anti-TB Drugs for DOTS-Plus. Thus, this subgroup has satisfied its objective and has been dissolved.

2. The Scientific Panel on programmatic, laboratory, clinical issues was created with two objectives:

   - To prepare and review guidelines to implement DOTS-Plus pilot projects.
   - To assess the data generated by the pilot projects in order to, ultimately, advise WHO in developing policy recommendations for member states.

A third objective has been added:

   - To provide technical advice to the Green Light Committee and resolve programmatic and clinical issues (including establishing case definitions) regarding the management of MDR-TB.

The first objective of the Scientific Panel has been completed. The resulting document has been finalized and is entitled Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB. However, this document will be reviewed and revised periodically to reflect the most recent data available. The second objective will be addressed as data are generated and collected. The third objective is being addressed as the Scientific Panel advises WHO with regard to the work of the Green Light Committee.

3. The Subgroup on Drug Procurement Systems for second-line Anti-TB Drugs was created to make recommendations for increasing access (primarily in terms of lowering cost) to high-quality second-line anti-TB drugs. Activities of this subgroup have resulted in a large decrease in the price of second-line anti-TB drugs, and the establishment of two procurement arrangements that (combined) will supply complete treatment courses for DOTS-Plus pilot projects which the Green Light Committee finds to be in accordance with the Guidelines for
Annex 3 - Terms of Reference

Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB. Thus, this subgroup has satisfied its objective and has been dissolved.

4. The Green Light Committee, generated by the Subgroup on Drug Procurement Systems for second-line Anti-TB Drugs as its implementing arm and natural evolution, has the following tasks:

- To evaluate proposals from potential DOTS-Plus pilot projects to determine if those projects have adequately addressed all issues highlighted in the Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB so that such projects may benefit from concessional-priced second-line anti-TB drugs, as a result of the work of the Subgroup on Drugs Procurement Systems (see above).

- To promote technical assistance, through the Partners participating in the Working Group, in the submission of proposals to the Green Light Committee and in the implementation of the project protocols.

- To re-assess, periodically, pilot projects whose applications have been found to meet the requirements highlighted in the Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB, including through site visits as WHO may deem necessary and appropriate.

Financing

Financing of the Working Group, including its subgroups, will be the responsibility of all participant member institutions. Travel expenses for participation in meetings of the Working Group will be shared between the members, depending on the availability of funds. In terms of financing travel expenses, participants from resource-limited countries should be funded by members in industrialized countries.

Meetings

Meetings of the Working Group will be held at least once every two years and will be convened by WHO in agreement with sponsoring members. Decisions will be taken by consensus. Meetings of subgroups will be held on an ad hoc basis when needed (based on recommendations of each subgroup and according to a priority scale).
LIST OF WHO REFERENCE DOCUMENTS FOR MDR-TB


Coordination of DOTS-Plus Pilot Projects for the Management of MDR-TB. WHO/CDS/CPC/TB/99.262


Guidelines for the Management of Drug-resistant Tuberculosis. WHO/TB/96.210

Guidelines for Surveillance of Drug Resistance in Tuberculosis. WHO/TB/96.216


Treatment of Tuberculosis: Guidelines for National Programmes. WHO/TB/97.220 (rev.2)