

SEA-TB-304
Distribution: General

Management of Drug-resistant Tuberculosis

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Abbreviations

AIDS	Acquired immuno-deficiency syndrome
DOT	Directly observed treatment
DOTS	The internationally recommended strategy for TB control
DRS	Drug resistance surveillance or survey
DST	Drug susceptibility testing
EQA	External quality assurance
GDF	Global TB Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
MDR-TB	Multidrug-resistant tuberculosis (resistance to at least isoniazid and rifampicin)
NGOs	Non-governmental organizations
NIDCH	National Institute of Diseases of Chest and Hospital
NRL	National reference laboratory
NTP	National TB Control Programme
PHC	Primary health care
SEA	South-East Asia
SLD	Second-line drugs
SNRLs	Supra national reference laboratories
XDR-TB	Extensively drug-resistant tuberculosis

1. Background

The emergence of multidrug-resistant tuberculosis (MDR-TB) poses a significant threat to TB control activities in the World Health Organization's (WHO) South-East Asia (SEA) Region. While the first priority in dealing with MDR-TB remains the prevention of acquired drug resistance through effective DOTS directly observed treatment, short-course (DOTS) programmes, national tuberculosis control programmes are faced with the challenge of a growing pool of persons infected with MDR-TB who cannot be treated successfully with first-line drugs.

The new Stop TB strategy launched in 2006 calls for the comprehensive treatment of all TB patients, including those with drug resistance. The complexity of MDR-TB management makes it essential to transfer new skills to design, plan, implement and monitor interventions for the management of MDR-TB under programme conditions. In response to this felt need, an intercountry workshop was organized to impart the necessary skills on MDR-TB management.

2. Inaugural session

The workshop was opened by Dr Jai P. Narain, Director, Communicable Diseases, World Health Organization, Regional Office for South-East Asia, who delivered the keynote address on behalf of Dr Samlee Plianbangchang, WHO Regional Director for South-East Asia. In his keynote address the Regional Director said while almost all countries convened had made significant progress with DOTS implementation and expansion over the last decade, emerging MDR-TB, and more recently, extensively drug-resistant TB (XDR-TB), threatened to reverse the hard-won gains achieved in TB control in the Region. This regional workshop on the management of drug-resistant forms of tuberculosis was therefore, timely. being held. The Regional Director highlighted the priorities in addressing MDR- and XDR-TB, namely, sustaining the quality of DOTS to prevent MDR-TB, strengthening surveillance capacity for laboratory diagnosis of drug-resistant forms of TB, and forging partnerships with the private sector and unlinked hospitals to further reduce the pool of existing drug-resistant TB through effective management. Dr Samlee concluded by urging participants through

his message to develop country-specific action plans, including plans for resource mobilization, in order to effectively address multidrug-resistance in their respective countries.

After the introduction of the participants, Dr Pushpa Malla, National TB Programme Manager, Nepal, was elected as the Chair for the workshop and Dr D. Behara, Director, Lala Ram Swarup Institute as Co-chair. Dr Bo Myint, Assistant National TB Programme Manager, Myanmar, and Dr Hans Kluge, Medical Officer-TB, WHO, Myanmar, were nominated as rapporteurs.

Objectives of the workshop

Dr Puneet Dewan, Medical Officer-TB, WHO Regional Office for South-East Asia, then presented the objectives of the workshop. The specific objectives were to:

- Review the status of the management of drug-resistant TB in countries of the Region.
- Impart knowledge on the standardized approach for the management of multidrug-resistant TB.
- Impart skills to effectively plan, implement, and monitor activities to address multidrug-resistant TB under the National Programmes.
- Identify technical needs to facilitate the establishment of proven interventions for MDR-TB management under National TB programmes.

3. Introduction to MDR-TB control and DOTS-Plus planning

3.1 Overview of MDR-TB epidemiology in the South East-Asia Region

South-East Asia contributes 27% of the estimated global burden of MDR-TB¹. These estimates are based on population-based surveys available from

¹ Global TB Control WHO Report 2007, WHO Geneva

three countries of the Region – Myanmar, Nepal and Thailand and from sub-national surveys from India. The estimates for the other seven countries are based on mathematical modeling based on limited data. Currently most patients with drug-resistant forms of TB are diagnosed and treated outside national programmes largely by private sector providers and at large medical teaching facilities or tertiary care centres. Making quality assured laboratory and treatment services for MDR-TB widely accessible are major hurdles. Only India and Nepal have so far established projects to manage MDR-TB under the national programmes. There is very little information on XDR-TB from the Region, though its existence has been documented in Thailand, India and Bangladesh.

It was stressed that the wide confidence intervals regarding the estimates of MDR-TB, especially among previously treated cases basing treatment regimens or drug requirements for MDR-TB on these estimates would not be realistic. Due to the complexities in conducting drug-resistance surveys (DRS), countries were cautioned to conduct baseline surveys initially and build in other operational or additional components later.

3.2 MDR-TB: The political, technical and financial context

The emergence of extensively drug-resistant tuberculosis (XDR-TB) had also served to focus global attention on the disease and to mobilize additional resources to combat drug-resistant TB. The presentation reviewed the actions being taken at the global level to estimate the burden of drug-resistant TB, develop guidelines on the programmatic management of drug-resistant tuberculosis and efforts being made to mobilize resources through collaboration with the Global Fund, Green Light Committee (GLC), (UNITAID), and Presidents' Emergency Plan for AIDS Relief (PEPFAR). The presentation also summarized the progress in addressing MDR-TB, with more than 44 countries using the GLC mechanism, increasing numbers of trained consultants working in countries, expansion of the supranational reference laboratory network, ongoing drug resistance surveys of second-line drugs and efforts towards building laboratory capacity to ensure better access to patients.

It was clarified that the direct funding from the Global Funding could be utilized by individual institutions provided the project had been

approved by the national TB programme (NTP) of the country covered. Only GLC-approved sites in select countries — Myanmar, Nepal and Timor-Leste being from the South-East Asia Region — are currently eligible for funding support through UNITAID. Second-line drugs are procured by the Global Drug Facility (GDF) for the GLC.

Even though MDR and XDR-TB presented challenges, there was a need to balance this with the much more pressing need to implement sound TB control and strengthen national reference laboratories for quality assured smear microscopy and culture, followed by first drug susceptibility testing.

3.3 DOTS-Plus projects: Country experiences

The experiences with DOTS-Plus programme planning and process were presented by participants from Nepal, Bangladesh and India. The presenters discussed country-specific experiences in planning MDR-TB treatment initiation. The main experiences in common were the complexity of planning and the long gap between the preparation and submission of a GLC application and the actual commencement of treatment of patients. The reasons cited for the same were the time required to obtain local and national government commitment to reconcile GLC procurement policies with national policy, the multiple rounds of clarifications requested by GLC, and time taken by countries to respond to it. Accreditation of the national reference laboratory, which is a pre-condition to begin activities, and suboptimal drug procurement and management procedures were additional factors delaying the status of activities.

Country presentations

Bangladesh

Bangladesh has achieved 100% DOTS coverage, with 71% case detection and a 92% treatment success rate. The treatment of MDR-TB patients will be supported through the Global Fund for a period of five years. Bangladesh had applied to GLC in March 2006 and the same was approved in June 2006. MDR-TB guidelines have been developed and are being printed and distributed. Patient recruitment has been initiated.

Limited studies to date suggest that the prevalence of MDR-TB is around 3% among newly diagnosed cases and 15% among previously treated patients. Drug-resistant survey (DRS) conducted by the Damien Foundation in 1995 and 2001 suggest a fall in the prevalence of MDR-TB from 0.7% to 0.4% among new and from 6.8% to 3.0% among previously treated patients. The NTP proposes to conduct a drug susceptibility test (DST) for all category II and I failures. The DST will be done at the NRL at the National Institute of Diseases of Chest and Hospital (NIDCH) for all first-line drugs and linked with the Bangkok SRL for DST proficiency testing. The treatment plan is to admit Category II failures to the hospital at NIDCH and administer a standardized DOTS-Plus regimen (Km Z Ofx Eto Cs) while awaiting DST results. If the patient has poly-resistant or MDR-TB based on DST results, the same regimen will be continued. If mono-resistance is detected, the patient will be restarted on a Category II regimen. Daily DOT at NIDCH is continued till DST results are available and at least one culture is negative. After discharge, daily DOT will be the responsibility of NGO workers or field workers at the upazilla level. Treatment will be monitored by monthly sputum smears and cultures till four consecutive cultures are negative followed by smears and cultures done quarterly. Liver function and renal function tests will be done at the beginning and once in six months at the NIDCH. Adverse reactions will be managed as necessary.

Another site where MDR-TB is being managed in Bangladesh since 1997 is the area covered by the Damien Foundation. Patients failing on Category II regimens, with proved resistance to H and R or rifampicin resistance on lipa test are eligible provided they agree to stay in the hospital for the intensive phase of treatment. Treatment regimens have been designed based on the history of drug use and drug resistance pattern from surveys undertaken by the Damien Foundation. Initial regimens of 21 months, duration have been subsequently revised based on the evidence of over three years of follow-up of these patients. Varying durations of treatment are currently being investigated; it has been observed that response and relapse was similar with 21 and 15 months of treatment and a nine month regimen is being investigated.

Nepal

Nepal has carried out four rounds of national drug resistance surveillance and DOTS-Plus was initiated in 2005 with the establishment of five DOTS-Plus centres and 16 sub-centres. The national reference laboratory (GENETUP) in

Nepal is linked with the supranational reference laboratory (SNRL), Gaoting, in Germany. MDR-TB among chronic cases (failures of Category II) is known to be around 88%. Between 2005 and 2007, 350 patients have been initiated on DOTS-Plus treatment. The process of approval from the GLC was quite complex and took almost three years from the GLC application to the time the drugs were delivered. DOTS-Plus was implemented in a phased manner after training staff and ensuring logistics. Patients who fail on a Category II regimen and any smear- positive patient with MDR-TB confirmed at the National DOTS-Plus Reference Laboratory are eligible to be treated. Empiric MDR-TB treatment is initiated for all Category II failures since more than 90% of these patients are found to have MDR-TB. The regimen used includes eight to twelve months of administering Km Z Ofx Eto Cs in the intensive phase followed by Z Ofx Eto Cs for ten to twenty months. Drugs are supplied in drug boxes allotted to each patient in two weight bands for the entire course of treatment. Injectables are supplied in a separate box. Patient support is provided through local initiatives. The main problems encountered are logistic issues (establishing a separate supply system for second-line drugs, given the short life of these drugs and related storage problems), laboratory issues (transportation of sputa, apprehension on the part of staff to handle these specimens), clinical and sociological challenges (stigma, extra work on staff, providing social and financial support to patients etc.) and a more difficult monitoring and evaluation system. Identifying a DOT provider who can ensure patient adherence for at least 24 months, especially when DOT is decentralized, poses a challenge. Patients are advised to stay within the DOTS- Plus area thus posing socioeconomic problem for them. For expanding DOTS- Plus services, additional facilities need to be established and the services decentralized. At the implementation level, there is shortage of trained manpower and expert physicians to deal with common side effects of second-line anti-TB drugs.

India

India has participated in the three rounds of global drug resistance surveillance. The prevalence of MDR-TB among newly diagnosed TB cases is <3% and 12% among patients with prior anti-TB treatment.

India has one urban site where GLC supported MDR-TB management is in place. The site is a DOT centre under the national TB control programme and has culture and accredited DST facilities. Patients failing Category II regimen (smear-positive at five months or later on Category II treatment) have their sputum specimens sent for culture and DST. A total of

105 patients were admitted for MDR-TB treatment between January 2002 and March 2006. The treatment regimen used was standardized one (6-9 KmOfxEtoCsZ/18OfxEto). Patients are hospitalized for a minimum duration of one month and this period is utilized to build linkages with the TB health visitor in the field and to ascertain the tolerance to drugs. Subsequently, on discharge DOT is provided at one of the 16 DOT centres under the hospital. Patients attend the hospital every month and are seen by the specialist at the time of changing the regimen from intensive to continuation phase, in the event of any adverse drug reaction and at the time of declaring treatment outcome. For reports received until July 2007, 68% of patients had converted to a sputum smear-negative status, 15% had defaulted, 17% died and 3% had failed treatment. The main issues identified by this project was the burden of daily DOT; the long duration of treatment on the patient and the provider; the need for training the DOT provider especially to identify adverse drug reaction; strengthening the links between hospital and the programme, maintaining the drug flow and ensuring proper storage in view of the limited shelf-life of the products, and the need to further simplify recording and reporting formats. The delegates visited the laboratory and imparted treatment services at this site.

3.4 Perspectives and plans for MDR-TB in the SAARC Region

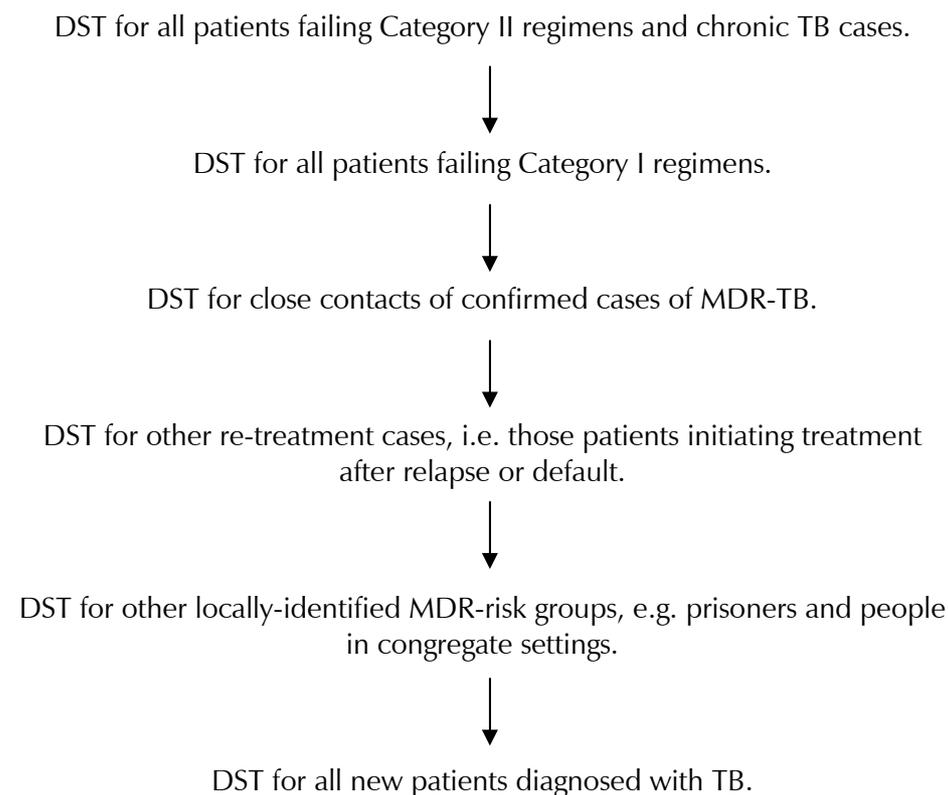
The MDR-TB situation in the SAARC Region and actions taken by the SAARC TB and HIV/AIDS centre were presented. The major barriers in initiating DOTS-Plus projects for the management of MDR-TB in the Region were highlighted and the importance of quality DOTS implementation in preventing MDR-TB was stressed. The SAARC centre had conducted seven workshops in the Region to assist Member countries to develop protocols for DRS; establish quality-assured for culture and drug susceptibility testing (DST); and develop guidelines for the management of TB/HIV and MDR-TB, drug management and cross-border interventions. The need to prevent MDR-TB from developing by ensuring quality DOTS programmes was stressed as an approach that was much more cost-effective than DOTS-Plus.

4. Case-finding strategies

The presentation on case-finding strategies identified the need for carefully selecting patients for culture and drug susceptibility testing. This selection

largely depends on the country-specific epidemiological situation, the local capacity for culture and DST in terms of quality assured laboratories, and human and financial resources available. Based on the results published so far, patient groups identified to have high probability of MDR-TB are those failing to be cured through category II treatment or Category I treatment regimens, and close contacts of MDR-TB cases. The importance of getting culture and DST results from a quality-assured laboratory was re-emphasized.

The discussion that followed again focused on the challenge of establishing quality-assured laboratories and effectively working with the available supra-national reference laboratories (SNRLs). It was felt that each country should develop an action plan with functional linkage to an accredited supranational reference laboratory for the necessary technical assistance and external quality assurance (EQA). A logical step-wise approach for the selection of patients for testing through culture and DST was suggested. The following order of prioritization was proposed:



4.1 Drug resistance surveillance (DRS)

The principles of DRS, methodology for planning, and the importance of a clear and well-defined protocol were discussed. The need for national quality-assured laboratories for culture and drug susceptibility testing, and the need for external quality assurance were stressed. Another important consideration was a plan for the utilization of the data generated. Logistics for laboratory consumables needed to be considered while planning surveys. It was emphasized that quality should not be compromised in order to include larger samples.

Discussions focused on the availability of quality assured laboratories and the need for expanding the supranational laboratory network, especially for the high TB-burden countries. It was felt that surveillance should be undertaken in parallel with the development of treatment capacity. Second-line DST is not yet adequately standardized, though much attention is being paid to this issue. High-burden countries needed more assistance from SNRLs, but the inherent structure of the network and the lack of an adequate number of laboratory experts made technical assistance on a large scale difficult to manage. SNRLs required means of sustainable financing for their reference laboratory functions, particularly as national reference laboratories (NRLs) are increasingly taking on functions previously reserved for SNRLs.

4.2 Challenges in MDR-TB case-finding

Nepal and Bangladesh were undertaking culture and DST for all TB patients failing Category I and II regimens, patients being started on category II regimens, and contacts of MDR-TB cases, while India has opted to do culture and DST only for category II patients remaining smear-positive at four months or later during treatment. The main problems faced by the countries were to get an adequate number of laboratories quality assured for DST, resulting in delays in getting the DST results. Patients were likely to be lost, while waiting for the DST results. Difficulties in transportation of sputum specimens to the accredited laboratories was another major constraint. Bangladesh and Nepal initiate MDR-TB treatment for failures of Category II regimens while India does so only once patients are confirmed to be MDR-TB cases.

4.3 Choosing a case-finding strategy

The participants worked in small groups to discuss and review case-finding strategies appropriate for each of their countries. Following the group work, participants presented the strategies they felt would be best to adopt in their respective countries to identify patients suspected to have MDR-TB, also taking into consideration the available facilities in the country for DST. Bangladesh, DPR Korea, India, Maldives, Bhutan and Timor-Leste identified Category II failures as the patient group that should undergo DST. Indonesia, Myanmar, Nepal, Sri Lanka and Thailand identified in addition to Category II failures, Category I failure, chronic cases and contacts of MDR-TB cases as the patient group that should undergo DST. Bhutan and Maldives opted to test all smear-positive cases once their own laboratories were established in order to maintain a basic number of cultures for quality culture and DST, and to extend culture as a modality for diagnosis of all forms of TB.

5. Organization of a national TB laboratory network

5.1 Minimal laboratory requirements for mycobacterial culture and DST

The minimal requirement for establishing mycobacterial culture and DST are first, to formulate and establish a national policy for culture and DST, and then the documentation of the programmatic and laboratory processes and work instructions for the staff undertaking the work. Linking the NRL to an SNRL would be essential to facilitate the process of building the technical capacity of laboratory technicians and for the purpose of external quality assurance (EQA). Minimal bio-safety requirements as spelt out in the biosafety guidelines from WHO need to be in place to conduct various mycobacteriology tasks. Staff should be systematically trained on basic safety precautions and good laboratory practice. The relative merits of the different culture and DST techniques were discussed. It was emphasized that it is essential before considering the use of liquid media or any other technique that the laboratory be proficient in the use of solid media and DST using standard methods, such as the proportion, resistance ratio, and absolute concentration methods. The procedures to be adopted for quality assurance such as proficiency testing and blinded cross-checking between NRLs and the designated SNRL were also discussed. Molecular technologies offer considerable hope for early detection of Rifampicin resistance but still need considerable validation.

The need to establish more reference laboratories which could serve the high-burden countries was expressed in the discussions, as well as the need for sustainable financing for the designated SNRLs to provide technical support and undertake external quality assurance for the NRLs linked to them.

The participants visited the laboratory facility available at the Lala Ram Swarup Hospital (LRSH) in New Delhi as a field exercise.

5.2 National laboratory networks and quality assurance

Participants worked in groups to map culture and DST facilities available in their respective countries and to identify gaps and requirements to strengthen their national networks. Bhutan, Maldives, Timor-Leste and DPR Korea do not have an accredited laboratory for culture and DST though the respective ministries of health plan to set up these facilities in the near future. Until then, these countries will continue to liaise with national reference laboratories in other countries in the Region for culture and DST. Bangladesh, Nepal, India, Indonesia, Sri Lanka and Myanmar have established reference laboratories at the central level. However, these countries also needed to expand their national laboratory networks to ensure greater access to their services. Participants then visited the reference laboratory at the LRS Institute in New Delhi on a field visit to observe the management and functioning of this centre.

6. Recording and reporting

The aim of the MDR-TB data information system was to allow the managers at different levels of the programme to monitor overall activities and programme performance. The reporting system in use was based on the DOTS recording and reporting system. The records to be maintained include a treatment card with details of previous treatment, requests for sputum culture and DST examination, laboratory registers, Category IV patient identity cards and Category IV registers. Quarterly reports are generated and entered in the Category IV register.

Reporting on MDR-TB needs to be integrated within the NTP's overall recording and reporting systems, and the data set required to be reported

on, simplified to the extent possible, so as to retain the robustness of the DOTS reporting system. The routine reporting includes quarterly reports on case-finding, DOTS-Plus six months interim report, DOTS-Plus 12-month culture conversion reports and quarterly reports on treatment outcomes of MDR-TB patients on category IV regimens initiated on 31 to 33 treatment months earlier.

It should be clear that data are collected primarily for the purpose of programme management, rather than for case-based clinical management or research. Hence information that may be important to clinicians, but not relevant for monitoring and evaluation, could perhaps be left out, to be included only in the treatment cards for clinical decision-making.

It was felt that it would be advantageous to pursue integration into the routine TB programme recording and reporting system, rather than creating a separate system. Simplicity and compatibility with international reporting standards and WHO guidelines needs to be taken into account when designing a recording and reporting system. Substantial training and ongoing supervision is essential.

There was a strong consensus among the participants on the importance of collecting only a minimum set of indicators useful for programme management, evaluation and improvement.

7. Management of MDR–TB

7.1 Principles of MDR management

This presentation covered the available second-line drug regimens for managing MDR-TB, the mechanism of action of the drugs available and the main principles in designing the regimen for MDR-TB management. It was stressed that there were no clinical trials comparing the efficacy of different regimens and drugs and that the existing international recommendations were mainly based on expert opinion and experience in clinical medicine, as opposed to programmatic management. The five important principles for designing an MDR-TB regimen highlighted were to: 1) use at least four reliable drugs; 2) not to use drugs which are known to have cross-resistance; 3) to use drugs that are safe; 4) to include drugs in the hierarchical order of efficacy and 5) to be prepared to monitor and manage the adverse reactions. The duration of treatment should be guided by both

smear and culture conversion. The minimum duration recommended was at least six months of an intensive phase followed by an 18-month continuation phase. The current recommendations for injectable drugs is to use these for at least six months, ensuring four consecutive negative cultures during this period. DST results need to be interpreted cautiously: while in vitro and in vivo correlation of DST is very reliable for Isoniazid and Rifampicin, this is considerably less reliable for streptomycin and ethambutol, and quite poor for other second-line drugs. However, DST to kanamycin, ofloxacin and ciprofloxacin may be useful, but this has to be interpreted carefully. All DST results have to be interpreted taking the history of drug use by the patient into consideration.

The determinants for choosing a Category IV regimen for the treatment of MDR-TB cases are dependent the available national DRS data and usage of second-line drugs in the country. The relative merits of standardized as opposed to individualized treatment regimens were discussed, as also the merits and demerits of empiric treatment of Category II failures and other patients who are considered to be at high risk of having developed MDR-TB.

Issues that remain to be clarified globally are the duration of use of an injectable drug, and when to consider switching from intensive to continuation phase. Though a minimum of six months use of an injectable drug is currently recommended, the criteria for changing from the intensive to the continuation phase requires careful consideration, since the current WHO guideline that calls for three documented consecutive negative cultures has been found to be impractical and possibly unnecessary in some settings.

DST should, therefore, complement rather than invalidate other sources of data about the likely effectiveness of a drug, such as a detailed treatment history and clinical correlation. The prolonged use of aminoglycosides is complex due to audiometric side effects, especially in the elderly, necessitating intense patient counselling and, in some cases, a choice between deafness and optimal treatment for MDR-TB. The therapeutic use of newer-generation fluoroquinolones (sparfloxacin, gatifloxacin, and moxifloxacin), given that some facilities are using these drugs despite detection of resistance to ofloxacin/ciprofloxacin in vitro, was also discussed. However, this practice is not supported by any evidence, anecdotal or otherwise, and it was concluded that these drugs should therefore be reserved for very specific situations only.

7.2 Management of MDR-TB in special situations

Not much data are available on the management of MDR-TB during pregnancy. Management of MDR-TB may need to be modified in certain special clinical situations. If the patient is pregnant, it is preferable to postpone the initiation of treatment to the second trimester after this is agreed upon by the patient and the doctor, unless the clinical status is deemed to be severe and posing a threat to life. It is preferable in any case to avoid aminoglycosides, ethionamide and prothionamide during pregnancy. In a breastfeeding mother, the infant should be given infant formula and the mother and child should interact in a well-ventilated area. It is advisable for the mother to cover her mouth while handling her baby. The long-term effects of second-line drugs among children have not been studied. No drug is absolutely contra-indicated in children and MDR-TB therapy in children should follow the same principles as for adults, with the dosages adjusted to body weight. For patients with MDR-TB and diabetes, use of ethionamide/prothionamide may make it more difficult to control the blood sugar levels and may also require the monitoring of creatinine and potassium more frequently. The management of MDR-TB in patients with history of renal insufficiency requires dose adjustments, while those with liver disorder cannot be given pyrazinamide and those with seizure disorders be given anti-convulsants in addition. Cycloserine could be given for patients with psychiatric disorders, but with close monitoring.

7.3 Country presentations: Case studies and discussions on MDR-TB management strategies including regimen design

Nepal and Bangladesh start all category II failures on an empiric standardized category IV regimen while waiting for the DST results. The policy of empiric treatment in these two countries was guided by the fact that more than 80% of Category II failures had organisms resistant to isoniazid and rifampicin (MDR-TB). Nepal is using a four monthly patient-wise box for each patient. India starts MDR-TB treatment only when the diagnosis of MDR-TB is confirmed by the laboratory.

In Bangladesh, MDR-TB patients are hospitalized for the initial six month period while the in-patient stay was one month in India, and treatment ambulatory from the beginning, in Nepal. It was felt that the period of initial hospitalization would be helpful to monitor adverse drug

reactions which are more common in the first month of treatment, especially in areas with little specialized clinical capacity. Both Bangladesh and Nepal were changing to continuation phase when the third or fourth month cultures became negative while India was doing so if the fourth month culture was negative with smears negative at fifth and sixth month. It was felt that this practice would essentially require prolongation of the intensive phase, as experience has demonstrated that it was not feasible to have DST results back by the sixth month when the decision to move to the continuation phase needed to be made. The use of smear results to guide this decision needed to be considered, given the observed high correlation between smear and culture conversion. However, it was felt necessary to generate scientific evidence for the use of smears alone for follow-up, by analyzing the large volume of data derived from comparing follow-up smear and culture results available from other MDR-TB treatment sites.

7.4 Monitoring treatment adherence

The need for thorough pre-treatment evaluation and monitoring during treatment with follow-up through smears and cultures, and for monitoring for adverse reactions to drugs in addition to providing supervised therapy, counselling and social and emotional support to the patient and family were discussed. The challenges of securing administrative commitment to establish and sustain this costly and labour-intensive intervention, the need for daily supervision of the prolonged treatment, ensuring an uninterrupted supply chain for drugs which had a shorter shelf-life, and the importance of maintaining a uniform recording and reporting system were also discussed.

The main issues of the discussion related to the measures to be taken to ensure patient adherence considering the low therapeutic index of all second-line drugs other than fluoroquinolones and the relatively high frequency of spontaneous mutations at concentrations achieved in vivo, risking the amplification of second-line drug resistance. These included the need for a patient-centred approach with special consideration towards ensuring that they do not need to travel long distances, decentralized treatment after training health workers in MDR-TB treatment, and supervision and reporting. Ways to ensure access to care for side-effects, family support and involvement stressing the importance of treatment supervision and social, psychological and emotional support were also discussed. These were considered to be critical to maximize treatment

adherence and increase the likelihood of successful treatment outcomes. It was felt that there was also a need to involve nongovernmental organizations in planning and implementation since these are an important source of community-based social support. Psychosocial support also has to be provided by a dedicated psychosocial coordinator having a behavioural sciences background who could strictly monitor treatment adherence and screen for psychological side-effects that clinicians often tended to overlook.

7.5 Managing adverse reactions

The presentation highlighted the need for health workers to be aware of adverse reactions to various drugs able to recognize recognizing these early and manage them effectively, since numerous tablets and drugs are used. Going by the experience of the Lala Ram Swarup Institute, the adverse reactions encountered ranged from mild to moderate and could be managed effectively. No patient required a termination of the regimen or drugs used. The commonest adverse reactions observed were gastrointestinal upsets followed by arthralgia, giddiness and disturbances with hearing. The need to train treatment providers to identify these adverse reactions early and take necessary action was stressed. The programme should provide ancillary drugs and psychosocial support to the patients, it was stated.

7.6 Panel discussion: Treatment delivery and adherence

This discussion centred on the need for decentralizing treatment, following up patients for a minimum period of 24 months, and early recognition and prompt management of adverse reactions. In Nepal, MDR-TB patients are required to reside in the area close to the facilities for the entire duration of the treatment, necessitating a shifting of residence. This poses an enormous social and economic burden on the patient and his family. In India, patients have to travel to the DOTS-Plus clinic at least four times during treatment. The problems faced in supplying drugs to the peripheral treatment providers and of collecting sputum from specified pre-determined facilities for transportation to the nearest culture/DST laboratory were also discussed.

Participants visited the in-patient treatment facility of the LRS Institute, the state-of-the-art infection control ward under construction, and

peripheral treatment centres where patients were being provided treatment after discharge from the hospital. Participants also interviewed patients and providers.

7.7 Challenges in decentralization and integration of MDR-TB into general health services: Experiences from Nepal and India

The participants highlighted the importance of decentralizing MDR-TB treatment beyond tertiary care facilities and into the community if treatment targets were to be met. MDR-TB patients frequently accessed treatment in DOTS-Plus areas although they were situated too far away from the catchment areas of these DOTS-Plus project sites. The challenges that the national programme in Nepal faced when decentralizing treatment services are listed in Table 1.

Table 1: Challenges in Decentralization of DOTS-Plus implementation

National level	Regional/district level
Lack of technical human resources for: <ul style="list-style-type: none"> - Clinical management - Follow-up, monitoring and evaluation Lack of laboratory services Transportation systems for sputum Specimen monitoring system to be integrated or kept as separate? Logistics – delivery of drugs to be combined or kept separate? Need for procurement and delivery of drugs for side-effects Training of regional /district-level staff <ul style="list-style-type: none"> - Who needs to be trained? - How is turnover handled? 	Determination of level of services – PHC or district? Resistance from health professionals: <ul style="list-style-type: none"> - Extra workload - Fear of the contagious nature of diseases - Not wanting to allow MDR cases to mingle with regular patients Demands for : <ul style="list-style-type: none"> - Separate facilities such as isolation rooms and beds - Extra manpower - Incentives or stipends - Infection control measures

Suggested modalities to overcome these challenges were shared by the NTP Manager, Nepal, based on their experience. These approaches were to:

- develop simplified recording and reporting tools, i.e. a DOTS treatment card and a register
- simplify monitoring during treatment by limiting sputum smear examinations to the 2nd, 4th, 6th and 8th month, with culture examinations at 4th and 6th months during the intensive phase
- undertake smear examination every two months and cultures only in the 12th, 16th, 20th and 24th month during the continuation phase.
- revise the definition of “cure” to fit the simplified monitoring routine.
- consider alternative DOT arrangements, with periodic (e.g. weekly) observation for stable and adherent patients.
- plan to return unused second line drugs in case of default or death.
- keep records as simple as possible for field staff.
- consider some time of initial hospitalization, so that patients are as stable as possible when discharged for treatment at a lower level health facility.
- build in need-based training for those facilities with patients on MDR-TB treatment.

8. Infection control and protection of health-care workers

An overview of infection control measures was presented with the emphasis on developing and implementing an infection control plan that was practical, affordable and comprehensive. Flexibility, creativity and adaptability to the local situation were emphasized. The role of administrative control measures, environmental engineering measures and personal respiratory protection measures to minimize the risk of transmission and their relative merits and feasibility were discussed. Administrative measures to segregate patients with known drug-resistant TB, who were still in the early stages of treatment, from other patients and HIV-infected patients in particular, were highlighted. The importance of ensuring cross-ventilation for infection control was stressed. The need to

monitor and evaluate the infection control measures currently being implemented and of revising the plan for infection control as and when required was also emphasized.

The discussion highlighted out the following issues:

- Maximizing natural ventilation was deemed as being generally more effective and less expensive as opposed to mechanically-assisted ventilation.
- Programmes needed to select country-specific effective and affordable infection control approaches, replicable beyond pilot projects, to limit spread of infection within facilities and in the communities.
- A mix of counselling, maximizing treatment adherence, teaching cough etiquette, and segregating young children and HIV infected persons as far as possible was required.
- There must be an emphasis on the need for screening health workers regularly exposed to MDR-TB patients.

Some sites have considered additional incentives for staff exposed to MDR or XDR-TB patients, especially since the risk of transmission within the community, prior to diagnosis at health facilities, is largely unknown.

9. Procurement and management of second-line drugs

The Green Light Committee and Procurement of second-line drugs; practical considerations and estimation of needs

The Green Light Committee (GLC) was set up primarily with the purpose of assisting countries in the procurement of high-quality second-line drugs (SLD) at the best possible prices through a pooled procurement mechanism for GLC-approved MDR-TB programmes in countries. The GLC monitors the rational use of second-line drugs. The committee has several partners, and reviews project applications and determines whether a DOTS-Plus project in a country is in line with WHO guidelines before granting its approval. Projects financed by the Global Fund and UNITAID are provided second-line drugs only after approval by the GLC. The GLC has six review

cycles per year. Important documents to be submitted along with GLC applications are details of DOTS implementation in the country, the organizational set-up of the NTP including political commitment, and strategy and protocol for the management of the DOTS-Plus programme. The laboratory support components, such as the quality assurance mechanisms planned, and a description of laboratory facilities in the programme are required. The treatment regimen has to be in agreement with internationally recommended principles, with a rational justification for the choice of the regimen. Patient monitoring procedures need to be spelt out. The lead time for the supply of drug following GLC approval is around four to six months. The national programme should ensure import, customs clearance and registration of the products, or a waiver in advance. The main challenges in the procurement of SLD are the limited number of quality assured products and manufacturers and the short shelf-life of the drugs necessitating good storage practices, robust inventory mechanisms, and efficient drug distribution and management information systems. Calculations of the drug requirement poses a problem due to the different treatment regimens adopted and clinical adjustments in the regimens which is difficult to forecast. The GLC price list does not include cost of insurance, freight and possible taxation. The country is responsible for clearance of the drugs from the port and for in-country logistics.

The currently recommended PAS formulation being supplied through the GLC requires refrigeration for storing. Negotiations are underway with Lupin India to produce and supply the heat-stable Sodium PAS that manufactured by them.

Participants were also introduced to a standardized tool for estimating and forecasting drug requirements and were given time to practice using the tool. Short presentations on the various fields in the template were made and examples used to explain the forecasting and management of second-line drug requirements.

10. Country plans for MDR-TB management under national programmes

Participants teamed up in individual country groups to review their own country situations with regard to the facilities available and to develop a future plan of action. Table 2 summarizes the details of the country presentations on next stages proposed, following the group work.

Table 2: Country Plans for MDR-TB Management

Country	Laboratory set-up	Case-finding strategy	Treatment plan	Challenges
Bangladesh	National Institute of Disease and Chest Hospital: Functional for culture & DST. Propose to establish four DST laboratories in the country in the next five years.	DST for failures of Category II.	Standardized regimen of six months of KmZOfxEtocS/18OfxEtocS. Plan to start empiric MDR treatment for Category II failures. Hospitalize for Intensive phase, change to continuation phase after four consecutive cultures are negative. Initiate treatment for 50 patients in 2007, to be scaled up to 300 patients by 2010. Plan for decentralization, using existing community DOT providers.	Establishing quality assured laboratory services Securing long term funding.
Bhutan	To be established in the space provided in the National Referral Hospital under construction. Till then to coordinate with other laboratories in the Region.	Failures of Category II initially. When their facility is established for all smear- positive cases to maintain quality.	Confirmed MDR cases. Individualized regimen with hospitalization during IP plan to initiate treatment for five patients in 2008 and 15 by 2009.	Establishing a quality assured laboratory. Training of all concerned. Technical assistance
DPR Korea	NRL to be established and linked with SRL at Thailand	Failures of Category II. To test 100 Category II failures in 2009.	Standardized regimen. (to be decided) with six months intensive phase, change to CP if culture negative at four months.	Financial and technical support. Human resource development for culture & DST.
India	Four NRLs functioning. Two state-level IRLs established. Plan to establish 25 IRLs by 2010.	Failures of Category II. To initiate 100 patients on treatment in 2007, scale up to 1550 by 2009.	Standardized regimen of six to nine months of KmEtocOfxZCs(Emb) followed by 18-24 months of EtocOfxCs(Emb) with PAS as an alternate drug. Initial hospitalization up to one month. Change to CP if culture negative at four month with negative smears at five and six months.	Delayed installation of equipment at IRL and long accreditation process. Training and human resources. Loss of patients between determination of eligibility for culture/DST and starting of MDR treatment, due to delays and operational constraints

Country	Laboratory set-up	Case-finding strategy	Treatment plan	Challenges
Indonesia	Three functional laboratories having QA with IMVS.	From selected areas, failures of Category I and II, on admission to Category II and contacts of known MDR-TB patients. 100 patients to be initiated on treatment in 2008 and another 100 in 2009.	Standardized regimen: Six months of KmOxEtOZCs(Emb) followed by 12-18 months of OixEtOcs(Emb); PAS will be added if quinolone resistant, capreomycin if kanamycin resistant. Hospitalization for the initial one month. Change to CP if culture negative at four months. DST for second-line drugs done for all patients. The aminoglycoside to be used to be decided by DST results.	Funding not available in time. Human resources coordination between laboratory, treatment center, health center etc. is not adequate. Procurement of second-line drugs
Maldives	Not available; the government intends to establish one. To coordinate with other laboratories in the Region till then.	All Category II failures, once the laboratory is established for all smear negative cases to maintain quality	Individualized regimen with six months' hospitalization. Change from IP to CP at fourth month if culture negative.	Establishing a quality assured laboratory. Training for culture and DST. Need technical and financial assistance.
Myanmar	National Reference Laboratory Yangon. External quality assurance by SRL, Bangkok. Another laboratory being established in Upper Myanmar.	Category II failures, "old" chronic cases. To initiate 100 patients on treatment in 2008 and 2009.	Standardized regimen based on the results of the ongoing DST survey among Category II failures. Hospitalized during IP, change from IP to CP if consecutive smears and cultures are negative for three months.	Ensuring sufficient funding for all DOTS Plus components. Ensuring daily DOT and identifying early adverse reactions. Overall DOTS Plus programme management (logistics, recording and reporting, supervision, monitoring and evaluation).

Country	Laboratory set-up	Case-finding strategy	Treatment plan	Challenges
Nepal	National Reference Laboratory at GENETUP; functional EQA with Gauting, Germany. Laboratory being established at the National Tuberculosis Centre. Plan to establish three regional-level laboratories for culture and DST and at the central level.	All suspected MDR cases. To treat 350 patients by 2007, 150 in 2008 and 150 in 2009.	Standardized regimen: 8-12 months of KmOixEtoCsZ followed by 16-20 months of EtoCsZ Empiric MDR treatment for all Category II failures. Change to CP when two sputums become negative by smear and culture at three and three and a half months. Expand and decentralize to a total of eight DOTS-Plus centres and 31 sub-centres over the next three years Simplification of the regimen after reviewing the results in two years.	Financial support for training, programme management and socioeconomic support for patients. Limited technical and human resources.
Sri Lanka	National Reference Laboratory at Wellisara Chest Hospital. Establish one more culture/DST laboratory at Kandy. EQA with SRL at Chennai.	Category I smear-positive patients at the time of initiation of treatment for all Category II cases. Contacts of known MDR-TB cases, chronic defaulters, health-care workers. Plan to do DST for second-line drugs	Standardized regimen: six months of KmOixEtoZ/18 months of EtoCs. Mandatory hospitalization during IP, change over to CP if four consecutive cultures are negative.	GLC application process. EQA completion. Drug management issues.
Thailand	Two functional laboratories. EQA with Bangkok SRL. Culture/DST available in many Regions. Plans to establish culture/DST at all regional levels and culture laboratories at the provincial level.	Category I and II failures, contacts of MDR-TB cases, patients with recurrent TB, HIV infected TB cases, prisoners.	Empiric use of MDR-TB treatment possible. Two regimens are used currently. Propose to use a standardized regimen for confirmed MDR cases. Hospitalization only if clinically indicated. Change from IP to CP if 2 consecutive cultures are negative.	Establishment of laboratory capacity and EQA network. Human resources for supervision and monitoring Socio-psychological support for patients.

Country	Laboratory set-up	Case-finding strategy	Treatment plan	Challenges
Timor Leste	National Reference Laboratory for culture, DST done at SRL at Adelaide.	Category II failures. To initiate treatment for 15 cases in 2007, scale up to 175 cases during a five year period.	Laboratory confirmed MDR cases treated with Standardized regimens with individualized use of first line drugs where susceptible. Six months of KmOxETOEmb(PAS)/18 months of ETOEmb(PAS). Mandatory hospitalization for IP and change over to CP when three consecutive smears and cultures are negative.	Technical assistance for developing national guidelines. Shipping of sputum specimens for DST; drug management-related issues.

11. Conclusions and recommendations

Member countries had already prepared or are in the process of preparing the DOTS-Plus guidelines. Establishing or expanding quality assured laboratories for culture and DST was the main challenge mentioned by most countries. Technical and financial support is required by most Member countries. In addition, technical assistance is required for preparing for the Global Fund grant and the GLC applications. The other issues that were raised were: organization and monitoring of treatment, problems in decentralizing beyond the health facility level for management, feasibility of monthly cultures during the intensive phase of treatment and bimonthly cultures subsequently and the lengthy reporting formats.

Recommendations

Participants provided the following consensus feedback to WHO and partners so that future MDR and XDR-TB treatment recommendations would reflect programmatic concerns and operational realities.

- (1) International guidelines should be revised in the light of limitations in programme capacity and more recent lessons learnt from the few resource-limited settings which are providing decentralized treatment for drug-resistant TB.
- (2) Guidelines should support flexibility in bacteriologic monitoring as per country capacity.
 - (a) Reduce the number and frequency of cultures recommended for switching from the intensive to the continuation phase of treatment
 - (b) Reduce the frequency of smears and cultures needed throughout the course of treatment for monitoring purposes.
- (3) Simplify and further clarify the outcome definition for cure:
 - (a) Reduce number of negative cultures needed for classification of cure, so that outcome definitions are better synchronized with the monitoring routines chosen by countries.

- (4) WHO, GLC, technical agencies and partners should increase availability of in-country technical assistance during preparation and early implementation phases.
- (5) The GLC should make available the Sodium-PAS formulation at the earliest.
- (6) Support resource mobilization efforts for countries without bilateral donor support.
- (7) Assist countries to build capacity for second-line DST in national reference laboratories.
- (8) Individual country targets for treatment of MDR/XDR TB should in the future be developed in consultation with countries.

It was suggested that an analysis on the correlation between smear and culture conversion be undertaken for the cohort of MDR-TB patients treated at the pilot sites and that information to be used to facilitate decision making on whether follow-up and monitoring of patients undergoing treatment can be based on smear results. If found suitable, this would reduce the burden of cost and work-load on the overstretched health facilities.

Annex 1

Programme

Monday, 6 August 2007

Registration

Inaugural session

Module 1: Introduction to MDR-TB control and DOTS-Plus Planning

Overview of MDR-TB in the South-East Asia Region (*P. Dewan, WHO/SEARO*)

MDR-TB: The political, financial and technical context (*A. Wright, WHO/HQ*)

DOTS-Plus projects: Country experiences (NTP representatives: Nepal, Bangladesh, India)

Perspectives and plans for MDR-TB in the SAARC Region (*K.K. Jha, SAARC TB and HIV/AIDS Centre*)

Module 2: Case-finding strategies

Case-finding strategies (*M. Quelapio, TDF, Manila*)

Drug-resistance surveillance (*A. Wright, WHO/HQ*)

Challenges in MDR-TB case-finding
(*LRS, India, Damien Foundation, Bangladesh*)

Introduction to preparing country plans (*P. Dewan, WHO/SEARO*)

Group work: Choosing a case-finding strategy

Tuesday, 7 August 2007

Module 3: Organization of a laboratory network

Minimal laboratory requirements for mycobacterial culture and DST –
(*Prof K. Feldmann, SRL Gauting*)

Group work: Laboratory networks and quality assurance

Field visit: Visit to Mycobacteriology Laboratory, (LRS, India)

Group work: Laboratory networks and quality assurance (contd...)

Recording and reporting (Part I): (*F. Wares, WHO-India*)

Wednesday, 8 August 2007

Group work presentations on case-finding and laboratory network

Module 4: Management of MDR-TB

Principles of MDR management (part I) (*M. Quelapio, TDF Manila*)

Principles of MDR management (part II) (*M. Quelapio, TDF Manila*)

Management of MDR-TB in special situations

Country presentations: Case studies and discussions on MDR TB management strategies including regimen design [Nepal, India, Damien Foundation (Bangladesh)]

Monitoring treatment adherence (*M. Quelapio, TDR Manila*)

Managing adverse reactions [LRS India]

Panel discussion: Treatment delivery and adherence
(Discussants: LRS, Nepal NTP, Damien, *M. Quelapio TDF Manila*)

Recording and reporting (part II): Case management and treatment outcomes
(*F Wares, WHO-India*)

Thursday, 9 August 2007

Field visit to treatment facility and infection control

Field visit to ambulatory MDR-TB treatment facility, with patient interactions [LRS, India]

Infection control and protection of health care workers (*H. Kluge, WHO-Myanmar*)

Challenges in decentralization and integration of MDR-TB treatment into general health services (Nepal, LRS India)

Group work: Country plans for MDR-TB management under national programmes

Friday, 10 August 2007

Module 5: Procurement and management of second-line anti-TB drugs

The Green Light Committee and Procurement of second-line drugs; practical considerations, and estimation of needs (*A. Wright, WHO/HQ*)

Practical exercise in the drug management and forecasting (*A. Wright, WHO/HQ*)

Presentation of Country Plans for MDR-TB management under national programmes

Conclusions and Recommendations

Closing session

Annex 2

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