Communicable Diseases Cluster
Prevention and Control Department

WHO Meeting to co-ordinate the DOTS-plus workplan on pilot projects for the management of multidrug resistant (MDR) tuberculosis (TB)
29 January 1999

Conference Room B, WHO/HQ Geneva

Edited by
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Mario C. Raviglione, MD
Executive Summary

In October 1997, the World Health Organization (WHO) released a global survey of resistance to antituberculosis drugs, identifying “hot spots” of multidrug-resistant tuberculosis (MDR-TB) in some countries that potentially could spread to neighbouring countries. This report described that high rates of MDR-TB exist in Latvia (22%), Estonia (12%), Delhi State, India (13%), Dominican Republic (9%), and Ivanovo Oblast in Russia (7%). The current information is that the situation of MDR-TB in some settings of the former Soviet Union countries is particularly critical.

There is increasing evidence from a number of settings in countries with poor TB control programmes (due to insufficient implementation of DOTS) that rates of treatment failure and death are unacceptably high. Subsequent laboratory studies of patients who have failed DOTS regimens reveal that large numbers of these patients have MDR-TB. Many have become chronic excretors of MDR strains in their communities. At the same time, in recent years, there has been heartening evidence that many patients with MDR-TB - estimates have ranged from 60 to 80% - can be cured with appropriate management based on second-line drugs. Considering the serious risk of continued spread of MDR-TB, WHO has decided to establish a global coalition of experts and institutions committed to the provision of technical support and training to “hot spots” in which unacceptably high levels of drug resistance threaten to compromise TB control efforts.

On January 29th, 1999, WHO convened a meeting to plan and coordinate a rational, evidence-based approach to this emerging issue. Participants in the meeting reported particularly disturbing trends of increased drug resistance in the former Soviet Union, even though advances have been made in implementing DOTS-based programmes. The meeting served as a forum for the presentation and review of major efforts currently underway.

WHO recommended that participating organizations commit resources in order to develop evidence-based policy guidelines for the management of MDR-TB. WHO supported the efforts of these institutions to implement and expand “DOTS-PLUS” pilot projects to progressively cover larger populations affected by drug-resistant tuberculosis, while ensuring that the basic elements of DOTS are fully and effectively implemented to prevent creation of new MDR-TB cases.

The Meeting concluded the following:
Participants agreed to strengthen collaboration on MDR-TB work between the various institutions, the communities affected, and WHO.

1. WHO is committed to address effectively MDR-TB as a threat to current TB control efforts. This will be achieved with “DOTS-PLUS” pilot projects in countries/settings where MDR-TB is confirmed through quality-controlled representative data. These data will be obtained, as in the past, through the WHO/IUATLD Global DRS Project.

2. There was general agreement that pilot projects of “DOTS-PLUS” to manage MDR-TB should be launched only in countries/settings implementing the DOTS strategy. In non-DOTS countries/settings with high levels of MDR-TB, launching of pilot projects is recommended only if the DOTS strategy is to be rapidly and simultaneously implemented. In addition, in certain settings where prisons are targeted for action, control interventions should encompass both the civil and the prison populations.

3. Protocols should be prepared and adapted to the local conditions following the generic guidelines contained in the documents “Basis for the development of an evidence-based case-management strategy for MDR-TB within the WHO’s DOTS strategy” (WHO/TB/99.260) and “Guidelines for the Management of Drug-Resistant Tuberculosis” (WHO/TB/96.210).

4. It is recommended that protocols to address MDR-TB be circulated and reviewed by members of the Working Group through WHO before they are implemented, in order to ensure the international comparability of methodology.

5. WHO is committed to build a global coalition of experts and interested parties
to address MDR-TB and serve as coordinating institution to provide technical resources for its control. In addition, WHO will take the role of a negotiator or broker, facilitating implementation of “DOTS-PLUS” pilot projects. Results of these projects will be fundamental to provide evidence for policy recommendations to WHO Member States.

6. A Working Group named “DOTS-PLUS for MDR-TB” should be established immediately. The Working Group will derive policy recommendations for WHO Member States on the management of MDR-TB, after feasibility and cost-effectiveness data generated through pilot projects are fully evaluated in a 2-3 year period. Sub-groups within the Working Group will be formed to address the issue of “drug procurement system” and “laboratory network for drug susceptibility testing of second-line drugs”.

7. Six projects which could provide important information for policy development, and therefore, should be implemented as soon as possible, were proposed: 1) The two projects in Peru proposed in close collaboration by the NTP Peru and by Harvard/Partners in Health; 2) The project in Tomsk Oblast, Russia, proposed by MERLIN/PHRI; 3) The project in Estonia proposed by IUATLD; 4) The project in Ivanovo Oblast, Russia, proposed by CDC; 5) The project in Latvia, proposed by CDC; 6) The project in Baku, Azerbaijan (in the prison system), proposed by ICRC. Identification of funds will be actively pursued to allow implementation of these pilot projects.

<table>
<thead>
<tr>
<th>Summary of WHO current position on MDR-TB</th>
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<tr>
<td>To achieve TB control worldwide, WHO continues to consider implementation of sound TB control programmes following the DOTS strategy as a top priority for action.</td>
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<tr>
<td>Recognizing that MDR-TB is a considerable threat to the effectiveness of DOTS in some areas of the world, WHO strongly supports pilot projects to assess the feasibility of DOTS-PLUS* interventions in a variety of settings, provided DOTS is in place or being simultaneously introduced.</td>
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<td>Based on the results of these pilot projects, WHO and its partners of the newly established Working Group on “DOTS-PLUS for MDR-TB” will formulate international policy recommendations on MDR-TB management.</td>
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* A working definition of DOTS-PLUS is the following: “DOTS-PLUS is a case-management strategy designed to manage MDR-TB using 2nd line drugs within the DOTS strategy in low-and middle-income countries”.
Background

The WHO/IUATLD Global Project on Drug Resistance Surveillance (DRS) has shown that Multidrug-Resistant Tuberculosis (MDR-TB) is present in almost all countries surveyed and that a few “hot spots” with very high MDR-TB rates exist today. 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.

As a result of the worldwide awareness of this potential epidemic, there has been an increasing call for action to prevent and contain the spread of MDR-TB. Following the 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 co-sponsored a meeting at Harvard University, Cambridge, United States, to discuss potential initiatives to address this issue in developing countries. Later in July 1998, a second meeting at WHO headquarters brought together recognized worldwide technical experts to discuss two generic protocols for the management of MDR TB. More recently, in a meeting hosted by the First Lady of the United States, Mrs. Hillary Clinton, at the White House, in the presence of the WHO Director General Dr Gro Brundtland, the President of the World Bank Mr J Wolfensohn, and Mr G. Soros, the need to contain the threat of MDR-TB worldwide was emphasized.

Since in resource-limited settings drug susceptibility testing (DST) is not widely available and second-line drugs are, in most cases, not affordable, potential management strategies for MDR-TB will need to be adapted and carefully tested before international recommendations are issued. Two pilot initiatives to manage MDR-TB are ongoing in Peru. One, at the district level, is funded by Partners in Health, an NGO associated with Harvard University, and uses individualized regimens based on second-line drugs. The other, countrywide, is led by the National TB Control Programme, and uses standardized regimens based on second-line drugs. Preliminary results of the above pilot projects are encouraging. However, both projects need to be widely replicated in different settings in order to generate sufficient data toward international policy recommendations. Therefore, at this moment, what is needed is a concrete plan of action during the next 2-3 years, which will result in the implementation of a number of pilot projects (feasibility studies) in a variety of settings.

Aims of the meeting

In order to prepare this plan of action, a meeting was convened at WHO headquarter in Geneva on 29 January 1999 to establish a coordinated initiative on MDR-TB. The immediate aim of the initiative will be to provide evidence from testing in the field the feasibility of using standardized or individualized regimens; to establish drug supply systems for second-line drugs; to monitor treatment and its outcomes; and to evaluate costs and cost-effectiveness of these interventions. In essence, to find the most appropriate solution to the problem. Ultimately, WHO will produce policy recommendations for use by all Member States based on the joint review with other institutions and experts of the results of pilot studies. At the same time, they will continue to raise awareness of the issue of MDR-TB and channel donors and funds where they are needed. If sufficient funds are allocated to address the issue (especially the drug procurement component is addressed appropriately), if DOTS is in place to prevent onset of new MDR-TB, and if the interventions of treatment of existing MDR-TB cases are successful, MDR-TB could be drastically reduced as a public health problem in many areas within years. To achieve these objectives, efforts need to be coordinated and work in partnership with other institutions of recognized experience and prestige promoted.

The expected outcomes of the meeting were the following:

A clear notion of who will be doing what in assessing feasibility of MDR-TB management at programme level, trying to target the known “hot spots,” and a proposed budget for launching DOTS-PLUS feasibility projects in various locations, as well as a list of available sources of financing and remaining needs.
Establishment of a global WHO Working Group “DOTS-PLUS” addressing MDR-TB formed by all interested partners (agencies, institutions, governmental and non-governmental organizations) which will discuss, recommend and implement future steps as well as serve as a coordinating body for this initiative.

Agreement for implementation of comparable intervention studies in the field using two generic protocols as discussed in previous meetings (see WHO/TB/99.260).

Support for the continuation of the Global WHO/IUATLD DRS, in collaboration with the dozens of institutions taking part in the Project, to expand knowledge on drug resistance worldwide, assess trends, and identify new hot spots. In addition, support for the production of mathematical models of MDR-TB elimination to help guide future programmatic interventions.

Proceedings
The meeting agenda is presented in Annex 1. The morning section was chaired by Dr Lee Reichman, National Tuberculosis Center, United States, and the afternoon session by Dr Nancy Binkin, Centers for Disease Control, United States. Dr David Heymann, Executive Director of WHO Communicable Diseases (CDS), and Dr Arata Kochi, Director of CDS Prevention and Control (WHO/ CDS/ CPC), opened the meeting by highlighting the commitment of WHO to address MDR-TB management. Following these interventions, Dr Mario Raviglione, Acting Team Coordinator, Operational and Epidemiological Research, WHO/CDS/ CPC, discussed the agenda and the objectives of the meeting, making special emphasis on the fact that more data are needed on the feasibility and cost-effectiveness of potential interventions to manage MDR-TB. Dr Raviglione made it clear that the available data from the novel approaches under implementation in Peru are not sufficient for international policy guidelines. Thus, the main goal of this meeting was to produce a clear plan to coordinate the launch of several projects in different resource-limited settings.

Dr Paul Farmer from Partners in Health/ Harvard University briefly reviewed the protocol to manage MDR-TB cases based on the administration of a tailored regimen with second-line drugs (WHO/TB/99.260). Methodological issues of this protocol which is currently being tested in two districts of Lima, Peru, in collaboration with the National Tuberculosis Programme (NTP), were provided to the audience. Dr Hans Rieder from IUATLD reviewed the generic guidelines for protocol development of a standard third-line treatment regimen for tuberculosis patients (likely MDR-TB cases) failing treatment on a standard WHO/IUATLD retreatment regimen, (WHO/TB/99.260). This protocol is based on the administration of a standardized regimen with second-line drugs.

These two generic guidelines are aimed to serve as the basis for protocol development and they should be adapted to the appropriate settings.

Dr Pedro G. Suarez, programme manager of NTP Peru, brought into considerations the importance of managing MDR-TB on a countrywide basis within the framework of the NTP. In Peru, the NTP is now in a consolidated phase showing a decrease of the incidence and morbidity rates of TB by 34% and 24.6% respectively between 1993 and 1997. For the management of MDR-TB, Peru is implementing a standardized approach using second-line drugs countrywide, following the recommendations of the WHO Guidelines for the management of drug-resistant tuberculosis (WHO/TB/96.210). This project is overseen by a special committee of local experts under the aegis of NTP. Medical records of patients who fail standard WHO retreatment regimen are sent to Lima, where the committee evaluates each case individually and recommends enrolment into the project. A technical unit runs the logistics and administration of the project.

Presentation of plan of work by participating organizations
Several presentations followed in which the participant institutions outlined their approach to address MDR-TB, including the selected setting and type of protocol they intend to use for the management of this problem. In most of cases lack of funding was a major constraint preventing to launching of DOTS-PLUS protocols. The majority of speakers focused on areas
or countries from the former Soviet Union, where a major MDR-TB problem exists. Presentations are highlighted below.

International Union against Tuberculosis and Lung Diseases (IUATLD)

Dr Thuridur Arnadottir discussed IUATLD’s proposal which will target Estonia by using a combined approach that will allow the implementation of the DOTS strategy and the management of MDR-TB cases at the same time (see Annex 2 presenting a thoughtful flow-chart for recruitment of cases). The IUATLD participated with the NO-TB-BALTIC Initiative in a review conducted in Estonia in March 1997. Since then, a national tuberculosis programme has been established and DOTS demonstration projects are starting assisted by the Finnish Lung Health Association (FILHA). The IUATLD has, together with the Estonian NTP and the Swedish Institute for Infectious Disease Control (SIIDC), developed a protocol for intervention. Estonia is chosen as a middle income country, with increasing incidence of TB and a serious problem of MDR-TB. A definite advantage of this project is that it will use the reference laboratory in Tartu with existing quality control provided by one of the WHO/IUATLD SRL (Sweden). In addition, this project will be targeting a country with a small population and will have a comprehensive approach to TB control allowing monitoring of the epidemic.

The situation in Estonia, as in the other Baltic countries, is one of increasing incidence with a high prevalence of MDR-TB among previously untreated cases. This proportion is around 10% currently. Between 700 and 800 TB cases are reported annually in Estonia, and only half of these cases are bacteriologically confirmed. Thus, either the diagnostic work-up is insufficient or there is over-diagnosis of TB. Culture is performed in all cases and drug susceptibility testing (DST) is performed in all cases with a positive culture. Approximately 50 to 60 ‘fresh’ cases of MDR-TB are diagnosed every year. The current policy is to treat these patients with second line drugs using individualized case management. However, due to financial constraints only about 20% can be treated which draws attention to the futility of having such a policy in the case of Estonia today. Furthermore, one of the consequences of the policy in the present situation is that resistance to second line drugs is beginning to appear. Of great concern is the cumulative ‘back-log’ of MDR cases (acquired and primary MDR) which may be as much as 300 cases. If these estimations are correct, perhaps as much as one out of two TB infections in Estonia today may be with MDR strains. The DOTS strategy may not suffice in this situation. However, there is insufficient information to formulate a different policy. Thus, there is urgent need for policy research. The proposed intervention is: DOTS for all newly detected cases, improved infection control, standardized case management and standardized treatment of MDR-TB cases. This treatment will be organized as a randomized clinical trial. MDR-TB cases will be recruited for the clinical trial at the point of failure of first line treatment. It is expected to recruit roughly 1000 bacteriologically confirmed TB cases in a three year period, whereof approximately 200 will be MDR-TB cases. A protocol for the clinical trial component will be developed based on the generic guidelines (WHO/TB/99.260) with modifications to fit the setting. The cost of this project, which is not funded yet, is estimated as 1.5 US$ million. The SIIDC will partially, if not fully, cover laboratory costs and it is hoped that there will be cooperation with the NO-TB-BALTIC Initiative.

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<th>Main features of proposed project in Estonia</th>
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<td>- DOTS with strengthening of TB control in general and of surveillance in particular;</td>
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<td>- Improved infection control;</td>
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<td>- Standardized management of MDR cases;</td>
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<td>- Treatment of MDR cases when they fail (at four or five months of first-line regimen);</td>
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<td>- Standardized treatment of MDR cases in a randomized controlled clinical trial;</td>
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<td>- Monitoring of acquired resistance as a result of standardization;</td>
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<td>- 24-36 month follow-up of all MDR-cases for detection of disease recurrence, and an economic analysis.</td>
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Royal Netherlands Tuberculosis Association (KNCV)

Dr Peter Gondrie on behalf of KNCV pointed out that launching a DOTS-PLUS protocol was not an immediate priority for this institution. Defining other important methodological and logistical issues related to the new initiative was KNCV’s main priority. Among these issues, there was a need to define clearly when to use DOTS-PLUS; when to use standard versus individualized approach; when to stop the monitoring of cases; how to supervise the patients enrolled; and also the need to assess transmissibility of MDR strains in immunocompetent persons. Other remarks were on the type of system to use for drug supply, and the sustainability, and necessary training for the launching of DOTS-PLUS protocols. KNCV has a special department for procurement of drugs, which may be able to cut costs. A special committee from KNCV will later formulate a detailed position on DOTS-PLUS.

Médecins Sans Frontières (MSF)

Dr Hans Kluge outlined the priorities of MSF in terms of MDR-TB. The main position of MSF is that in order to manage successfully MDR-TB in Russia, current obstacles to implement DOTS should be removed before DOTS-PLUS is launched. These shortcomings are high rates of defaulting, lack of direct observation, different TB control strategies, and poor laboratory reliability. Other important problems are related to human resources (motivation of local personnel and expatriates), lack of a national TB control policy (drug import, drug availability), and lack of financial support.

The TB programmes supported by MSF in former Soviet Union are in the penal systems of Kemerovo, the communities of Chimkent and Almaty in Kazakhstan, and the communities of Munyak and Kungrad in Uzbekistan. Other communities assisted are Karabagh, South Ossetia, and Abkhazia. At the moment there is not an immediate plan to launch DOTS-PLUS pilot projects.

International Committee of the Red Cross (ICRC)

Dr Rudy Coninx presented the activities of the ICRC in Baku where work in prisons is being done. The Ministry of Health of Baku recommends the DOTS strategy for the general population and in the prisons. The latter is implemented by ICRC. Cure rates among susceptible cases in the general population is 74%. The rate of MDR in prisons is 23% and cure rate using standardized first-line treatment is only 26%. ICRC proposes to expand DOTS in the community and to launch DOTS-PLUS in the prison system. However, strong support from WHO will be needed for this activity. A combined approach was suggested, consisting of WHO expanding DOTS in the community and ICRC launching DOTS-PLUS in the prisons.

International Federation of the Red Cross (IFRC)

Dr Michael Pelly represented the IFRC. This organization has carried out assessments in Belarus, Moldova, Russian Federation and Ukraine. The plan is to launch an appeal in March 1999 to develop a programme of TB assistance in the four countries. The approach of the programme will be to work through/with the MOH in the countries, supporting programmes that are utilising the internationally approved guidelines of care. The role of the Red Cross will include health education, nutritional and social support to patients and their families, support to laboratories and training to improve microscopic diagnostic capacity, use of Red Cross nurses to assist in ensuring treatment compliance as well as TB policy advocacy. The programme is planned to start in several oblasts in each country. It is hoped that collaborative programmes can be developed with WHO, CDC and other groups in some of the pilot areas, especially as it is felt that the style of the Federation’s programme will complement a purely medical programme. Therefore IFRC would welcome discussions from any group involved in this region.

Damien Foundation

Dr Francois Portaëls spoke on behalf of Damien Foundation. This institution collaborates with MSF and ICRC through
the Institute of Tropical Medicine in Antwerp. Strains sent from Mariinsk and Baku, are typed by restriction-fragment length polymorphism (RFLP). Also in Kazakhstan high levels of MDR-TB have been shown through the studies carried out by the Antwerp Laboratory. There is interest in working with failure cases in Bangladesh. There is no immediate plan to launch DOTS-PLUS pilot projects independently.

**Finnish Lung Health Association (FLHA)**

Several DOTS pilot projects are supported by FLHA in the regions of Murmansk, Leningrad, and Southern Estonia. Also in the planning phase are DOTS initiatives for the Karelia Republic (Russian Federation), specifically in the Karhumaki prison hospital. FLHA is also associated with the NO-TB Baltic project. The main priority at this moment is to concentrate on the implementation and strengthening of the on-going DOTS projects. Some of the conditions that FLHA suggested, as minimal requirements to launch DOTS-PLUS are i) sufficient and well-trained human resources, ii) availability of financial resources, and iii) achievement of adequate organizational and administrative standards in the target region.

**Medical Emergency Relief International (MERLIN) / Public Health Research Institute (PHRI)**

Dr Tim Healing and Dr Michael Kimerling discussed MERLIN/PHRI collaborative activities. MERLIN has been working in Tomsk Oblast, the Russian Federation, since 1994. During this period a collaborative programme designed to adapt DOTS to Tomsk TB services has been undertaken. WHO standard short-course chemotherapy regimens have been introduced and laboratory services modernized. The Russian Ministry of Health has recognized this programme as an official pilot project. In 1998 PHRI joined MERLIN in the oblast by providing support and training for medical and laboratory services and by further stimulating the change process.

Whilst the rate of new TB cases has fallen in Tomsk by almost 6%, there has been a doubling of MDR from 3% in 1997 to 6% in 1998 and the rate of MDR in Tomsk prison now exceeds 25%. The joint MERLIN/PHRI initiative will involve in the future: i) lobbying the Russian Ministry of Health to support dissemination of the Tomsk pilot project, ii) consolidation of the reforms achieved and the implementation of the reforms outside Tomsk City (e.g. elsewhere in the oblast), iii) dissemination of pilot projects elsewhere in Russia using Tomsk TB service staff to advocate policy change and train staff in other oblasts, and iv) the development of a detailed MDR treatment programme in collaboration with the Tomsk TB service.

The goals of a DOTS-PLUS programme to be launched by MERLIN/PHRI are to stop further creation and spread of MDR, treat known cases of MDR, evaluate rapid detection methods for early identification of rifampicin-resistant cases, and establish a model programme and center of excellence in Siberia. It will cover the civil society, prisons, mental institutions, and shelters. DST to first-line drugs will be done at the TB laboratory in Tomsk, whilst to second-line drugs will be done in Moscow and Boston laboratories. Different scenarios are proposed. In the first one, DST results to first-line drugs will be awaited to start appropriate TB chemotherapy. This approach implies treatment delays, higher transmissibility of *Mycobacterium tuberculosis*, potential greater morbidity and mortality, and more hospital days. Therefore, this approach is not recommended. The second scenario will focus on a risk-assessment approach. It is being proposed to question patients on history of prior TB therapy and imprisonment. If the answer to both questions is "yes", the patient will be considered potential MDR and administered a 18-24 months second-line drug treatment regimen. On the other hand, if the answer is "yes/no" the patient will be considered at intermediate risk of resistance and he/she will be given a 12-18 months treatment regimen (to be defined). Finally, if the answer to both questions is "no", the patient will be considered susceptible and a standard 6-months regimen will be given. After DST results are available, treatment regimens will be adjusted accordingly. However, due to the extraordinarily high prevalence of MDR-TB in Tomsk prisons, a different initial treatment strategy may be required and will be considered separately from the approach proposed for the civilian
sector. The ability to quickly identify rifampin resistance will be especially important in the prison setting and in determining the most appropriate initial regimen.

This programme was initially proposed for two years and will include i) training of a civilian-based MDR team in the United States, ii) developing of Tomsk regional laboratory as a reference for the entire DOTS-PLUS programme, iii) treatment of both prisoners and civilians, iv) developing transition services (TB dispensary, community clinics, and shelters), and v) developing access to second-line drug testing and rapid detection method for rifampicin resistance. At present no funding is available to launch this programme, as the European Community (EC) has in principle declined financial support. The MERLIN/PHRI team will be looking actively for funding elsewhere and reconsider submission to EC.

Department for International Development (DFID) / Know How Fund

Dr Iain McDonald presented DFID activities. DFID supports the work of MERLIN in Tomsk and is involved in health sector reform in Kemerovo and elsewhere in Central and Eastern Europe. It is currently investigating the possibility of setting up new DOTS-based projects in Russia through its Know How Fund.

DFID recognises the seriousness of the threat of MDR-TB and intends to contribute to the development of a WHO-led strategy to tackle the problem.

Partners in Health/Harvard University

Dr Paul Farmer discussed the current activities. Partners in Health/Harvard University plans to continue the DOTS-PLUS project in Peru in close collaboration with Peruvian NTP. As part of a recent agreement, fellowships to train Peruvian health care workers on the management of MDR-TB and laboratory training will be offered to the NTP.

Collaboration with the Tomsk project and further consultations with former Soviet Union countries will continue. Also, a modelling assessment of the epidemiological impact of MDR-TB is being planned.

Centers for Disease Control (CDC)

Dr Nancy Binkin outlined CDC priorities in the area of MDR-TB. CDC will launch a DOTS-PLUS project in Ivanovo Oblast, the Russian Federation. In this Oblast, there is a 15% failure rate and 15% death rate of TB cases treated by the WHO-established DOTS programme. Protocol development is underway. Regarding treatment, it is proposed to look at DST results and decide on the need to individualize the treatment regimen. Some components of the protocol will include finding elements predicting MDR and evaluation of nosocomial risk. This project will be funded through CDC/USAID.

The possibility of jointly work with the NO-TB Baltic project is also under evaluation. CDC will also sponsor a 3-day course on the management of MDR-TB in Ivanovo, Tomsk, Latvia, and Estonia.

United States Agency for International Development (USAID)

Dr Amy Bloom spoke on behalf of USAID. This agency will continue funding DRS and DOTS-PLUS projects through WHO/CDC. Drug procurement systems may be also assisted by this agency.

NO-TB BALTIC Initiative

Dr Tone Ringdal of the Norwegian National Health Association presented this project. The activities for 1999-2000 include launching/strengthening DOTS in Estonia, Latvia, and Lithuania. These include the support of training and supervision, upgrading the quality of microscopy services, and introduction of programme procedures in pilot areas with approximately 2000 new smear positive patients per year (2 areas in each country). Also, emphasis will be given to out-reach activities. Treatment for a limited number of MDR-TB patients will be initiated. Planning for improving facilities for isolation of MDR-TB patients will be considered.

Other presentations

Drug procurement

Dr Jim Yong Kim from Partners in Health discussed mechanism and approaches for a drug procurement central system that could be used by all partners implementing DOTS-PLUS pilot protocols.
Dr Kim explained that until recently it has been argued that high treatment costs for MDR-TB—particularly costs of medications—all but precluded the implementation of treatment in resource-poor settings. Indeed, treatment costs in some U.S. hospital settings have exceeded $100,000 per patient. He stated that such high costs were not inevitable, and a community-based project in Lima, Peru has shown MDR-TB to be treatable for a fraction of this figure. While innovative programme design can succeed in bringing down the cost of MDR-TB therapy significantly, efforts continue to be hampered by the high cost of medications. If the preliminary results of the Lima-based programme are to be replicated on a larger scale, it will be necessary to secure stable and affordable global access to medications suitable for combating drug-resistant TB strains. In fact, the price and availability of second-line TB drugs is extremely variable. Capreomycin, for example, has been proven to be a crucial drug for the treatment of highly resistant MDR-TB strains. Cost, it seems, has little to do with the actual expense of the drug production, but much to do with the negotiating strategies and leverage of groups working in different locations to obtain medicines from the manufacturers (Annex 3 presents prices and manufacturers of second-line drugs). This dynamic is underscored by the steadily declining price, since the widespread implementation of standardized drug regimens, of the first-line medications used to treat drug-susceptible tuberculosis. The true demand for MDR-TB drugs is not felt by the pharmaceutical industry, in large part because many of those ill with the disease are generally not able to pay for the drugs at current prices. A global, coordinated approach, one in which a central MDR-TB authority would help supply national tuberculosis control programmes with second-line drugs, would lead to the emergence of economies of scale which could lower drug prices dramatically.

**Establishing a DOTS-PLUS Working Group**

Finally, Dr Marcos Espinal, WHO/CDS/CPC, outlined the terms of reference to create the Working Group. The main activities of the Working Group will be to 1) assist WHO in deriving policy recommendations for WHO member states on the management of MDR-TB based on the assessment of the feasibility and cost-effectiveness of the pilot projects; 2) coordinate and monitor the implementation of internationally comparable pilot projects to manage MDR-TB using standardized or individualized regimens of second-line drugs; 3) review proposals for pilot projects and evaluate periodically the quality and quantity of the data gathered; 4) meet periodically to review progress achieved and delineate further activities; and 5) assist in the identification of resources to fund and implement pilot projects for the management of MDR-TB.

Two sub-groups within the Working Group will be formed, for drug procurement and for laboratory issues (testing of second-line drugs). The former will be coordinated by Dr Jim Yong Kim and the latter by Dr Francois Portaëls and Dr Max Salfinger. Heads of relevant supranational reference laboratories (SRL) should be also part of the latter one.

All participants (see list in Annex 4) in the meeting, as well as NTP managers of pilot sites, relevant heads of SRLs, researchers, and other interested experts, will be formally invited to be members of the Working Group.
## Agenda

**Morning Chairperson:** Dr Lee Reichmann  
**Afternoon Chairperson:** Dr Nancy Binkin

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<th>Time</th>
<th>Event</th>
<th>Participant(s)</th>
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<tr>
<td>09.45</td>
<td>Registration</td>
<td>Participants</td>
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<tr>
<td>10.00</td>
<td>Welcoming Remarks</td>
<td>Dr. D. Heymann, WHO</td>
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<tr>
<td>10.05</td>
<td>Rationale and objectives of the meeting</td>
<td>Dr A. Kochi, WHO</td>
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<td>10.15</td>
<td>Adoption of the agenda</td>
<td>Dr M. Raviglione, WHO</td>
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<tr>
<td>10.30</td>
<td>Standardized protocol for MDR TB</td>
<td>Dr H. Rieder, IUATLD</td>
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<td>10.40</td>
<td>Individualized protocol for MDR TB</td>
<td>Dr P. Farmer, Harvard/PIH</td>
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<td>10.50</td>
<td>DOTS Plus project in Peru: outline</td>
<td>Dr P. Suarez, NTP, Peru</td>
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<tr>
<td>11.00</td>
<td>Discussion</td>
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<td>11.15</td>
<td>Coffee/Tea Break</td>
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<td>11.30</td>
<td>Workplan. 10 minutes per institution to present plans regarding DOTS-PLUS feasibility studies: country, timescale, approach, cost, drug procurement IUATLD, KNCV, MERLIN, MSF, ICRC, Damien</td>
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<td>12.30</td>
<td>Lunch</td>
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<tr>
<td>14.00</td>
<td>Workplan. 10 minutes per institution to present plans regarding DOTS-PLUS feasibility studies: country, timescale, approach, cost, drug procurement PHRI, Harvard/PIH, CDC/USAID, NOTBBALTIC, others</td>
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<td>15.30</td>
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<td>16.00</td>
<td>Drug facility for second-line drugs</td>
<td>Dr J. Kim, Harvard/PIH All</td>
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<td>16.45</td>
<td>Setting the DOTS-PLUS Working Group</td>
<td>Dr M. Espinal, WHO</td>
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<td>17.15</td>
<td>Next Steps and Concluding Remarks</td>
<td>Dr M. Raviglione and Dr S. Spinaci, WHO</td>
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Research protocol proposed by IUATLD

Title of project: The DOTS strategy and multi-drug resistant tuberculosis / Estonia

Flow chart of recruitment

consecutive tuberculosis cases in the study period

2100

bacteriologically confirmed

1050

included

"new"

900

first-line regimen sensitivity test

fully sensitive 650

other resist. 130

"MDR" resist. 120

failure 7

"relapses"

150

second-line regimen sensitivity test

fully sensitive 80

other resist. 20

"MDR" resist. 50

failure 1

(? study DST)

second-line regimen 22

third-line regimen 60

second-line regimen 5

third-line regimen 50

Estimated recruitment:
900 for first-line treatment
177 for second-line treatment (150+7+15+1+4)
110 for third-line treatment (60+50)
### 2nd line Anti-TB Drugs Prices/Manufacturers

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<th>Drug</th>
<th>Company</th>
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<td>300 mg/d/y</td>
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**Sources:**
Prices obtained through direct inquiry to drug manufacturers and Brigham and Women’s Hospital (BWH).


**Acquired by Partners In Health through Magnificat (1998).**
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