DOTS-PLUS: PRELIMINARY RESULTS AND EMERGING ISSUES

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

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This document was written by Rajesh Gupta, Ernesto Jaramillo, and Marcos Espinal on behalf of the Stop TB Working Group on DOTS-Plus for MDR-TB.

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SUMMARY

Tuberculosis (TB) is a leading cause of adult deaths from infectious diseases. The DOTS strategy for TB control recommended by the World Health Organization (WHO) is hailed as one of the most cost-effective of all health interventions to date. In some areas, however, its success is threatened by the rise of multidrug-resistant TB (MDR-TB). To address the problem of MDR-TB, WHO in collaboration with its international partners is piloting a strategy known as DOTS-Plus. The Stop TB Working Group on DOTS-Plus for MDR-TB (convened by WHO) was created in 1999 to ensure that efforts directed towards establishing DOTS-Plus pilot projects are coordinated. Several pilot projects through the Green Light Committee (GLC), which grants access to high-quality, concessionally-priced second-line anti-TB drugs, have been established. The Working Group held its annual meeting in Tallinn, Estonia, on 10 – 12 April 2002 to discuss progress in DOTS-Plus. This document summarises the presentations, discussions, conclusions, and recommendations of the meeting.

Over 40 organizations and over 25 countries were represented by more than 150 participants at the meeting. The morning session of the first day was devoted to reviewing governance issues of the Working Group and the progress achieved by current GLC-approved DOTS-Plus pilot projects. Of the parallel sessions in the afternoon, one was devoted to convergence prospects for the GLC and the Global Drug Facility (GDF) and the other to programmatic, clinical and laboratory issues related to DOTS-Plus. The second day focused on discussions surrounding cohort definitions for the management of MDR-TB, fitness of MDR strains, best treatment strategies for MDR-TB, and next steps for the Working Group. The third day involved site visits to TB control areas in Estonia and a training session for preparing applications to the GLC.

The meeting concluded with the following recommendations:

- use MDR-TB and the GLC as tools for promoting DOTS expansion;
- continue supporting new pilot projects via the GLC;
- establish a Core Group to help manage the activities of the Working Group;
- finalize and operationalize standard cohort definitions;
- support the harmonization process of the GLC and the GDF;
- finalize a priority research agenda for DOTS-Plus;
- establish a database to catalogue MDR-TB research activities globally; and
- redistribute the terms of reference for the Working Group and its subgroups.

The next meeting of the Working Group will be held in south-east Asia in mid 2003.
BACKGROUND

Two global surveys conducted by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) published in 1997 and 2000 found multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampicin, in nearly every country. These surveys found that the prevalence of MDR-TB is disproportionately high in some settings. In 1999, the WHO Working Group on DOTS-Plus for MDR-TB (later renamed the Stop TB Working Group on DOTS-Plus for MDR-TB) was established to advise WHO in developing policy recommendations for Member States regarding the management of MDR-TB. Four subgroups were created under the Working Group, whose duties are modified as needed:

- the Green Light Committee (GLC) to foster access to and rational use of concessionally priced second-line anti-TB drugs;
- a Subgroup on Drug Procurement Issues to address issues related to increasing access to second-line anti-TB drugs;
- a Scientific Panel on clinical, laboratory and programmatic issues to offer guidance on such issues to the GLC; and
- a Subgroup on Laboratory Issues to standardize drug-susceptibility testing (DST) methods to second-line anti-TB drugs.

On 10 – 12 April 2002, WHO and the National TB Programme (NTP) of Estonia hosted the third meeting of the Working Group to review progress thus far, and to discuss new directions for the future.

AIMS OF THE MEETING

The meeting was structured to achieve the following objectives:

1. to present the current progress of GLC approved DOTS-Plus pilot projects;
2. to discuss the harmonization of the GLC and the Global Drug Facility (GDF);
3. to discuss clinical, programmatic, and laboratory issues related to DOTS-Plus;
4. to discuss research issues related to DOTS-Plus;
5. to perform site visits to the TB control service of Estonia; and
6. to conduct a training session in developing applications to the GLC.
OPENING REMARKS

Dr Kai Vink (NTP Manager of Estonia) opened the meeting by welcoming participants to Estonia and introducing a video documentary depicting the TB epidemic in Eastern Europe during the late 1990s. The video, produced by WHO, focused on cases of MDR-TB that had already emerged. Following the video presentation was Dr Ani Aaviksoo (Ministry of Social Affairs of Estonia), who expressed how international support from the GLC and the Nordic countries was very important to Estonia. Dr Aaviksoo highlighted the link between poverty and TB, and indicated that striving for equity in health is only possible if basic issues such as improving education and alleviating poverty are also addressed. Dr Mario Raviglione (Coordinator, WHO) delivered a welcoming address on behalf of WHO, and conveyed how the activities of the Working Group relate to the activities of the Stop TB Partnership as a whole, how DOTS-Plus is integrated into the DOTS expansion movement, and how DOTS-Plus in Estonia is an example of effective international cooperation. Dr Richard Zaleskis (TB Regional Advisor, WHO-European Region) explained the situation of TB control in Eastern Europe, emphasizing that DOTS Expansion in Eastern Europe involves a joint vision including examination of the financial, clinical, epidemiological, and social issues related to TB. Dr Jim Kim (Harvard Medical School; Chair, Working Group) outlined an expanded vision of DOTS that encompasses MDR-TB and TB-HIV. Dr Kim concluded the session by stressing the importance of using DOTS-Plus, MDR-TB, and the GLC as tools to promote DOTS expansion. He highlighted examples of two countries (Estonia and Peru) where continued commitment to DOTS expansion and sustaining the NTPs resulted from the activities of the GLC.

GOVERNANCE ISSUES

From Lima to Tallinn: Progress and Governance Issues

Dr Jim Kim reported on the progress of the Working Group since the January 2001 meeting in Lima, Peru. Five new projects had been approved by the GLC, seven monitoring missions had taken place, and four pre-application assessment missions were completed. Thanks to efforts by Médecins Sans Frontières, Harvard Medical School, and WHO, the cost of second-line anti-TB drugs had fallen by up to 99%. Eli Lilly and Company had agreed to continue their support of DOTS-Plus by extending their concessional pricing agreement and doubling the quantities of drugs provided. A long-term procurement arrangement between the International Dispensary Association and WHO was finalized. Future activities for the Working Group include establishing more pilot projects, expanding the role of the laboratory to support MDR diagnosis, optimizing GLC operations, facilitating technology transfer of drugs, conducting economic analyses of pilot projects, increasing research activities according to a prioritized research agenda, and promoting advocacy of a comprehensive TB control strategy. Lastly, the concept of a Core Group was proposed. This Core Group would improve the efficiency of the Working Group by overseeing the activities of the Working Group, liaising between the various parties (Working Group members, Secretariat, and other Stop TB Working Groups), and the Secretariat of the Working Group.
PROGRESS IN DOTS-PLUS PILOT PROJECTS

DOTS-Plus in Estonia

Dr Kai Vink presented DOTS-Plus in the context of the TB epidemic in Estonia. The NTP was established in 1998 and country-wide coverage with DOTS was achieved in May 2000. Case notification has steadily increased since 1990, with decreases occurring in 1999 (potentially attributable to change in notification due to DOTS) and 2001 (representing an actual decrease in TB incidence). In 2001, MDR-TB levels were 14.2% in new and 42.1% in previously treated cases. DOTS-Plus officially started in August 2001, although Estonia has managed its MDR-TB patients since 1996. Nearly 80% of patients are resistant to greater than five drugs in the “DOTS-Plus” cohort of 80 patients. Since GLC approval, 103 patients have been enrolled on treatment. Treatment is individualized, and current conversion rate at six months is 61%. High levels of alcoholism in MDR-TB patients is one of the main problems faced by the NTP.

DOTS-Plus in Latvia

Dr Vaira Leimane (NTP Latvia) presented the MDR-TB situation in Latvia. From 1997 – 2001, the levels of primary and acquired MDR-TB have remained high but fairly stable, at 9 – 10% and 29 – 35%, respectively. Cumulative data from Latvia indicates that 348 (44%) patients are on treatment, 181 (23%) were cured, 101 (12.5%) died, 64 (8%) were lost from follow-up, and 101 (12.5%) are under symptomatic treatment. Of the new MDR-TB cases diagnosed in 2001, 6% were co-infected with HIV, and there was an average of three to four risk factors per patient. In 2001, a new and more aggressive treatment strategy was implemented. A full cohort evaluation from 1999 showed that 64% of patients were cured, 24% failed treatment (of which 30% died), 3% died, and 9% defaulted (of which 23% were recovered and began new treatment). Of note is that only two patients (1.3%) relapsed after being declared “cured” (one year follow-up data). Interim outcomes from the 2001 cohort show that 67% of patients are likely cures, 8% are defaulters, 9% are failures, 3% died, and 13% did not yet convert. Delays in the flow of funds for the purchase of second-line anti-TB drugs is the main difficulty faced by the NTP.

DOTS-Plus in Tomsk

Dr Gennady Peremetin (Tomsk Oblast TB Dispensary) described the DOTS-Plus pilot project in Tomsk Oblast, Russian Federation. From 1994 – 1999, DOTS was implemented in the prison and civilian sectors of Tomsk. In late 2000, DOTS-Plus was implemented in the prison sector and, subsequently, in the civilian sector in early 2001. Since 1996, TB incidence has remained fairly stable at 107.7 – 117.6 per 100,000. In 2001, MDR-TB among new cases in the civilian and prison sectors was 10.2% and 15.6%, respectively. To date, 177 patients are enrolled of which 160 (90.4%) are still on treatment. Culture conversion rate is 71% for patients on treatment. Patient motivation is a strong component of this programme and includes incorporation of social workers into TB services, consultation of inmates being released, procurement of clothes, identifying contact relatives in the civilian sector, nutritional support, and payment of transportation expenses. Current constraints include lack of drug supply due to the limited number of suppliers registered in the Russian Federation.
**DOTS-Plus in Manila**

Dr Thelma Tupasi (Tropical Disease Foundation/Makati Medical Center) presented the DOTS-Plus pilot project in Manila, Philippines. The project is a collaboration between the public and private sectors in Manila. Although management of MDR-TB patients began in April 1999, the accrual of the majority of patients did not occur until the project was approved by the GLC in October 2000. Most MDR-TB patients (84.2%) are referred from the private sector. For data available on 100 MDR-TB patients, 70 (70%) are resistant to four or five first-line anti-TB drugs. In addition, resistance to ciprofloxacin among MDR-TB patients has increased from 10.3% in 1989 – 1994 to 51.4% in 1995 – 2000. In the same patients, resistance to ofloxacin increased from 24.0% to 51.4%. Under programmatic conditions, treatment outcome data for 117 patients are as follows: approximately 70% of patients are cures or likely cures, 9% failed treatment or are likely failures, 9% defaulted, 2% transferred out, and 11% died. Severe adverse drug reactions were reported in 8.7% of patients. Overall problems include lack of consistent funding for the programme, lack of standard drug resistance surveillance (DRS) data in the Philippines, and the need for increased incorporation of the private sector into the DOTS programme.

**DOTS-Plus in Lima**

Dr Jaime Bayona (Socios en Salud) described the DOTS-Plus project in Lima, Peru. Established in 1996, the project uses individualized treatment regimens for patients failing the standard MDR-TB treatment regimen provided by the NTP in Peru. As of 2001, the project also places select Category I treatment failures (i.e. those from Lima) directly onto individualized regimens. Data from 154 patients revealed that 79% were cured, 12% failed, 8% died, 1% transferred out, and zero defaulted. In Category I failures, the standard Category II re-treatment regimen yielded only a 40% cure rate in this setting. However, for defaulters and relapses of Category I, cure rates were 74% and 80%, respectively. Cohort analysis of the standard MDR-TB treatment regimen showed that 46.7% of patients were cured, 33.7% failed treatment, 13.4% abandoned treatment, and 16.4% died. The main challenge for the project is further expansion in Peru.

**Feasibility and Cost-effectiveness of DOTS-Plus in Peru**

Drs Marcos Espinal (WHO) and Katherine Floyd (WHO) presented an evaluation of the feasibility and cost-effectiveness of the DOTS-plus programme in Peru. This evaluation was undertaken for the cohort of 466 patients enrolled between the start of the programme in October 1997 and March 1999, who were treated with a standardized 18-month regimen. Overall, 225 (48%) patients were cured, 57 (12%) died, 131 (28%) failed, and 53 (11%) defaulted. Almost 90% of patients complied with treatment. Among MDR patients, resistance to five or more drugs was significantly associated with poor treatment outcome (death, failure, default). Among patients who were declared cured, 96% had a negative smear after six months of treatment and 86% had a negative culture after six months of treatment. The total annual cost of the programme was about US$ 0.6 million per year, equivalent to 8% of the NTP budget. The cost per patient treated was US$ 2381. The cost per disability-adjusted life-year (DALY) gained was US$ 211, and US$ 165 at drug prices projected (at the time of analysis) for 2002.

Further analysis was also presented for two other treatment strategies, using data for the existing standardized programme and data from the published literature. These strategies
were: 1) implementation of the existing standardized programme, plus individualized treatment for those who failed the standardized drug regimen, and 2) implementation of the existing standardized programme, plus individualized treatment for failures of the standardized programme, and in addition enrolment in the standardized programme of Category I failures found to have MDR (i.e. the re-treatment regimen is bypassed for Category I failures with MDR). Results showed that the use of these strategies would increase effectiveness in terms of both the cure rate and DALYs gained, with total annual costs ranging from US$ 0.7 to 0.9 million (8-12% of the NTP budget) in an optimistic cost scenario (individualised treatment cost per patient of US$ 2500) and US$ 1.2 – 2.0 million (25-34% of the NTP budget) in a high-cost scenario (individualised treatment cost per patient of US$ 10,000). The cost per DALY gained would range from a mean of around US$ 200 in the optimistic cost scenario to US$ 300-400 (depending on the strategy) in the high-cost scenario.

The main conclusions of the study were:
• Delivery of second-line anti-TB drugs under programme conditions is feasible, provided a strong TB control programme is already in place.
• It is important to make efforts to increase cure rates – for example by using stronger drugs and individualised treatment for some patients.
• All three strategies assessed are cost-effective in middle-income countries when compared with standard benchmarks."

GREEN LIGHT COMMITTEE AND GLOBAL DRUG FACILITY:
PROSPECTS FOR CONVERGENCE

Quality Assurance for the Procurement of Anti-TB Drugs

Dr Souly Phanouvong (WHO) presented quality assurance issues related to anti-TB drugs. Quality assurance is needed especially for anti-TB drugs as low-quality drugs can lead to discrediting of the NTP and to the emergence of MDR-TB. In a survey performed by WHO, only 7% of drugs (for several diseases, including TB) contained the correct ingredients. Quality assurance has technical and regulatory elements nested in a legal framework for each country. Three practical approaches were presented: ensuring only drugs that meet set standards for quality are purchased, verifying that shipped goods meet specifications, and monitoring and maintaining the quality of the drugs purchased.

Green Light Committee (GLC): From Theory to Reality

As Chair of the GLC, Dr Kitty Lambregts-van Weezenbeek [Royal Netherlands Tuberculosis Association (KNCV)] presented the history, current activities, and future prospects of the GLC. DOTS-Plus is programmatically more complicated than DOTS and there are several obstacles to its implementation. Accordingly, implementation of DOTS-Plus needs to proceed in a rational manner. At the same time access to second-line anti-TB drugs is currently increasing as a result of activities of the Working Group. The GLC was established to ensure that projects receiving these drugs were in line with the Guidelines for

Establishing *DOTS-Plus Pilot Projects for the Management of MDR-TB*. In addition, the GLC performs continuous monitoring of these projects, coordinates and facilitates technical assistance to potential projects, and, ultimately, participates in the policy development process for MDR-TB. Outcomes of the process include approval of eight projects for a total of 2370 patients and promotion DOTS expansion. Future issues include linking and harmonizing with the Global Drug Facility and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (GFATM), increasing DRS activities globally, and monitoring the effect of further reductions in prices and increases in suppliers of second-line anti-TB drugs.

**Global Drug Facility (GDF): Improving Access to First-Line Anti-TB Drugs**

Dr Jacob Kumaresan (Executive Secretary, Stop TB Partnership), presented the activities of the GDF. The GDF is managed by the Stop TB Partnership secretariat and is a novel approach to securing access to high-quality first-line anti-TB drugs. The GDF is currently focusing on standardizing products. GDF operations involve an application and review process, country visits, drug procurement, and monitoring. Through the GDF, first-line anti-TB drug costs have been reduced by up to 30%. Applications are approved for 17 countries, with drugs being secured for 643,013 patients.

**Harmonization of the Global Drug Facility and the Green Light Committee**

Ms Gini Arnold (WHO) and Mr Rajesh Gupta (WHO) presented a potential plan of harmonization of the GDF and the GLC. Harmonization was discussed in the context of six topics: scope, governance, procurement, administration, applications and review, and financing. While the scope of the two projects are different (with the GLC more focused on policy development), it is possible for the GDF, via the GLC process, to include second-line anti-TB drugs within its mandate. In terms of governance, accountability may need to remain separate for legal reasons, but both processes could provide reports to all relevant institutions in order to increase transparency. The review processes could be streamlined via a joint application form, standard review cycle, having observers from each process attend the meetings of the other, and combining monitoring missions. Funding could be channelled to cover all activities of both processes and to provide grants for second-line anti-TB drugs, but should be done so under a clear and transparent process. While some risks exist (such as dilution of identity of each process and potential choices in priority setting), harmonization appears to be beneficial to both.

Participants supported the notion of convergence and suggested that the respective secretariats develop details of the harmonization plan based upon the presentations. It was emphasized that harmonization should occur in a manner and with a product that is advantageous to both processes. Quality of drugs provided by the GLC and GDF should not suffer, and should be guaranteed via a process similar to the scheme used to prequalify suppliers of anti-retrovirals. Further discussion of the harmonisation plan indicated the need for linking the GDF and GLC to the GFATM. Participants expressed concern that if the Global Fund were to finance projects without GLC review, procurement of drugs outside the scope of the GLC may disrupt the market for second-line anti-TB drugs and costs of treatment regimens would increase. In addition, such projects would not be monitored and may contribute to resistance to second-line anti-TB drugs.
Defaulting Treatment and Side-effects: Obstacles to Managing Patients?

Dr Manfred Danilovits (NTP Estonia) opened the presentation with cohort data from 1999 for 112 MDR-TB cases: 57% treatment success, 21% defaulters, 6% failures, and 16% deaths. For drug-susceptible TB patients, the rate of treatment success and default in 1999 was 74.9% and 10.0%, respectively. In 2000, the rate of treatment success and default improved to 83.1% and 7.7%, respectively. High default rates in Estonia are primarily attributed to alcohol abuse and prior imprisonment. Socioeconomic and health education problems, drug abuse, and co-infection with HIV are also contributing to default. The introduction of several administrative measures, a case management team, enablers and incentives, psychological support, and overall good communication (all specifically tailored for the high-risk defaulter populations) are key to improving adherence. Although a specific management algorithm exists for management of adverse reactions, most patients present with only mild symptoms and can be managed without alteration in therapy. Dose reduction or drug elimination are last options for management of adverse reactions.

Adherence to Treatment: Role of Social Support

Dr Ernesto Jaramillo (WHO) began the presentation by indicating that adherence to treatment is one of the biggest challenges facing both TB patients and the NTP. It is commonly accepted by many health care workers that poor adherence to treatment is mainly a problem arising from misconceptions of the patient about the disease and its treatment. Health education is therefore usually seen as the most powerful tool to overcome defaulting in treatment. However, human behaviour is complex and there is no single psychosocial construct for health behaviour that is reliable and accurate in predicting treatment adherence, including TB. Human social behaviour is the result of factors under the control of the individual (agency) as well as forces that are mostly beyond its control (structure). There is increasing evidence that default rates decrease once the structural forces impinging on adherence to TB treatment are improved (by the provision of social support). Social support can be delivered to TB patients in various ways: top-down versus bottom-up approaches; tailored versus generic interventions; community-based versus donor-driven packages; and interventions targeting patients as subjects of their own social development. There is still a lack of research on the efficacy and feasibility of these different approaches in the context of low-income countries.

Role of Training in DOTS-Plus

Mrs Karin Bergstrom (WHO) described the role of training in the implementation of DOTS-Plus. In-service training enhances the competence of the health care providers and managers in implementing the case strategy. Competence can be ensured via a systematic approach to training management, clear definitions of tasks, assignment of responsibilities, competency-based training programmes, and a systematic evaluation of competencies at the end of training. Constraints to maintaining compliance include the stringent requirements for training versus the low case-load (relative to drug-susceptible TB), and the additional components of training needed for DOTS-Plus. However, since competence does not necessarily guarantee performance, in-service training does not ensure that health care workers perform according to standards. In addition, pilot projects are often well-funded and may not represent the conditions appropriate for large-scale implementation.
**Surveillance and Laboratory Issues**

1. **Drug Resistance in Eastern Europe: Do We Know the Magnitude of the Problem?**

Dr Mohammed Aziz (WHO) presented the progress of DRS in Eastern Europe. The WHO/IUATLD global project on DRS began in 1994 with reports published in 1997, 2000, and 2003 (projected). Data for DRS is only available from 18% of Eastern and Central European countries. However, in these areas, the average level of MDR-TB and rifampicin-mono resistance is 2.5% and 5%, respectively. DRS should be a prerequisite for implementation of DOTS-Plus, and priority should be placed on expanding DRS activities in Central and Eastern Europe.

2. **Role of the Laboratory in the DOTS-Plus Strategy**

Dr Leonid Heifets (National Jewish Medical Research Center) described the dilemmas and options in identifying patients with drug-resistant TB. Two options were presented: to test the subset of patients that did not respond to the initial treatment or to test all new patients. Each option has its own advantages and disadvantages. In order for rapid turnaround time for laboratory reports to occur, a centralised laboratory system is needed with the following requirements: ability to process large volumes of specimens, equipped with biosafety requirements, use of agar medium for culture isolation and DST, and capability for direct DST (to at least isoniazid and rifampicin) on agar plates. The Ural model in Sverdlovsk is based on a centralized laboratory performing DST to all new patients. The return time for reports is as follows: smear - within 24 hours; 70% of culture results - within three weeks; DST (direct) - three to four weeks; DST (indirect) – six weeks; and confirmation of *Mycobacterium tuberculosis* – three weeks.

3. **Standardization and Quality Control to Improve Reliability of Drug-susceptibility Testing**

Dr Sven Hoffner (Swedish Institute for Infectious Disease Control) explained the problems with current DST methods. Three general types of DST are possible: solid medium [proportion method (reference technique), absolute concentration method (reference technique), and resistance ratio method (reference technique)], broth medium [Bactec 460 (reference technique), MGIT (alternative techniques), and BacT/ALERT (alternative technique)], and molecular methods [Line Probe Assay (LiPA), DNA Chip Technology, and Pyrosequencing]. The disadvantages include unreliable results with standardization and quality assurance, slow processes (especially for methods based on solid medium), need for laboratory safety, cost (especially for more rapid methods), and need for expert knowledge (especially for molecular techniques). Quality assurance is currently performed by the WHO/IUATLD Supranational TB Laboratory Network, which has improved the sensitivity and efficiency of its member laboratories. Standardization of methods, however, is still needed.
Cohort Analysis: The Need for Standards

Dr. Peter Cegielski [Centers for Disease Control and Prevention (CDC)] presented standard cohort definitions and a core data set of monitoring variables, which were developed in close collaboration with Latvian State Center for TB and Lung Disease, Medical Research Council of South Africa, Partners In Health, and WHO. The goal of the process was to develop definitions by using standard DOTS cohort definitions and monitoring variables as a template, and modifying those definitions to fit MDR-TB management as needed. Cohort definitions included case registration and outcome definitions. The core data set contained demographic data and social history, medical history, current TB information, follow-up information, and interim and final outcomes (as defined). The document will be distributed for comments to members of the Working Group, and finalized accordingly. It will be recommended that all DOTS-Plus pilot projects adhere to these definitions to ensure that data can be compared across projects.

Fitness of MDR-TB: Superbug or Not?

Dr. Marcos Burgos (Stanford University) began this session by explaining fitness can be inferred from four different type of studies: laboratory data, epidemiological and clinical studies, molecular epidemiology, and surveillance and modelling data. Previous data with different approaches from six studies indicated drug-resistant strains were from 0.16 to 3.00 times as fit as drug-susceptible strains. In San Francisco, data of ten years collected from a prospective molecular epidemiological study showed that isoniazid-resistant strains were 0.2 as fit as drug susceptible strains. Rifampicin-resistant strains were nearly three times as fit as drug-susceptible strains, but in 80% of the cases studied these strains were obtained from patients that were also HIV seropositive. No transmission of MDR-TB resulting in active cases of TB was observed. It was concluded that in San Francisco isoniazid-resistant strains and MDR-TB appeared to be less fit than drug-susceptible strains, but that this fitness may be offset by a decreased host response (i.e. HIV) and longer period of infectiousness.

Dr. Megan Murray (Harvard School of Public Health) followed by examining the relative strengths and weaknesses of different methodologies in measuring fitness. Laboratory studies have indicated that resistance can impose biological costs, but that subsequent mutations may compensate for the original loss in fitness. Cluster studies demonstrate that MDR-TB is between 0.09 and 7.84 times as fit as drug-susceptible TB, but cluster studies may not be accurate because of detection bias, confounding, and infection dynamics. Epidemiological studies indicate that drug-resistant TB is equally as fit as drug-susceptible TB, but only a few studies have been conducted using this methodology. Model-based estimates rely on average estimates and make several assumptions; however, since drug-resistant strains seem not to be homogeneous, the appropriateness of using estimates based on averages is questionable. Overall, the data appear to very heterogeneous, indicating that setting-specific analyses may be best given the setting-specific epidemiology of MDR-TB.

Best Treatment Strategies for Settings of High MDR-TB

Dr. Michael Kimerling (University of Alabama at Birmingham) presented a decision analysis to determine the impact of DOTS in a confined setting (Colony 33 prison setting
from the Russian Federation) with a high background rate of drug resistance. Three strategies for Category I failures were analysed: use of standard short-course chemotherapy (Category II), use of an empiric MDR treatment regimen, and use of an empiric MDR treatment regimen based upon risk stratification of patients. The analysis revealed that the empiric MDR strategy and the risk stratification strategy decreased the amplification of MDR-TB. With a 70% reduction in MDR-TB drug costs, the risk stratification strategy was less expensive and more effective than standardized short-course chemotherapy for this population. With a 90% reduction in MDR-TB drug costs, the risk stratification strategy and empiric MDR strategy were less expensive and more effective than standardized short-course chemotherapy for this population. Of note is that the model is conservative, static, and may not be applicable for conditions outside those for which it was created, and that several items were not addressed in the analysis.

**Prioritized Research Agenda for MDR-TB**

Dr Alan Hinman (Task Force for Child Survival and Development) presented a prioritized research agenda based upon the 14 research areas identified at the last meeting of the Working Group in Lima in January 2001. The proposed priority topics are as follows:

- define optimal standardised protocols to treat MDR-TB,
- identify threshold indicators for implementing DOTS-Plus,
- ascertain programmatic, laboratory, and resource requirements for DOTS-Plus,
- quantify the risk of MDR-TB in various populations,
- establish optimal timing for laboratory testing,
- assess programmatic utility of rapid diagnostics tests, and
- create standards and parameters for testing of second-line anti-TB drugs.

In addition, other non-research priority activities were presented. These activities are as follows:

- implement and operationalize cohort definitions,
- implement and operationalize core data set for programme evaluation,
- carry out surveillance for adverse events,
- evaluate MDR-TB training activities, and
- initiate and evaluate infection control procedures.

To ensure that research activities were prioritised appropriately, WHO would distribute a questionnaire to all Working Group members to rank the list of research topics presented. Based on the results of the questionnaire, a final priority research agenda would be created. In addition, WHO would begin the process of cataloguing all MDR-TB related research activities to ensure that the items listed in the priority research agenda were being addressed.

**TRAINING SESSION FOR APPLYING TO THE GREEN LIGHT COMMITTEE**

A workshop to introduce the process for applying to the GLC led by Dr Ernesto Jaramillo and Dr Kitty Lambregts was held after the meeting of the Working Group in Tallinn. The workshop was facilitated by the GLC Secretariat (WHO) and attended by 15 participants of
the Working Group meeting from Costa Rica, India, Kazakhstan, Malawi, Mexico, Russian Federation, and South Africa. Participants were briefed on the antecedents of the DOTS-Plus strategy, and the history and *modus operandi* of the GLC. The references *Instructions for Applying to the Green Light Committee and Guidelines for Establishing DOTS Plus Pilot projects for the Management of Multidrug-resistant Tuberculosis (MDR-TB)* were distributed, and a review of the main components of each document was made. The facilitator addressed questions raised by participants, and technical assistance in application development was offered to those countries interested in implementing a DOTS-Plus pilot project.

**SITE VISIT**

Visits to the prisons, MDR-TB hospital, and other health facilities were conducted to observe the implementation of DOTS and DOTS-Plus. Participants were impressed with the quality of the Estonian NTP, the rapid implementation and scaling up of DOTS and DOTS-Plus in the area, and the cooperation built with several international partners.

**CONCLUSIONS AND RECOMMENDATIONS**

In conclusion, participants re-emphasised that implementation of the DOTS strategy prevents the emergence of MDR-TB, and that priority should therefore be placed on DOTS implementation. However, as part of DOTS expansion activities, some countries need to consider now the implementation of DOTS-Plus to address their MDR-TB burden.

In addition, the following recommendations emerged from the meeting:

1) MDR-TB and the GLC should be used as a tool to promote DOTS expansion.

2) The prioritized research agenda should be distributed to the Working Group for comments and finalized as soon as possible.

3) WHO should implement its plan to catalogue all research activities related to MDR-TB into a research database to be made available to all Working Group members.

4) Cohort definitions and core data set should be distributed to the Working Group for comments, finalized, and operationalized as soon as possible.

5) Pilot projects reviewed by the GLC should continue to be implemented and supported by the international community.

6) Advocacy related to DOTS-Plus activities should be increased.

7) Activities related to access to drugs should be maintained, the drug procurement process should continue to be monitored, and ensuring quality of drugs provided by the GLC and GDF should remain a priority activity for WHO.

8) A plan for harmonization of the GLC and the GDF should be jointly drafted by the secretariats of each and submitted to the Stop TB Coordinating Board.
9) A Core Group should be established to help facilitate the activities of the Working Group and should begin its work as soon as possible.

10) Technology transfer of second-line anti-TB drug production is widely supported and should be facilitated by the Working Group as needed.

The meeting concluded with the formal appointment of selected members of the Working Group to the Core Group. The next meeting of the Working Group will be held in mid-2003 in south-east Asia.
### ANNEX 1: AGENDA FOR MEETING OF THE STOP TB WORKING GROUP ON DOTS-PLUS FOR MDR-TB

#### Day 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Opening Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 AM – 8:35 AM</td>
<td>Video</td>
</tr>
</tbody>
</table>
| 8:35 AM – 9:00 AM | Dr Siiri Oviir  
Minister of Social Affairs of Estonia  
Dr Mario Raviglione  
Stop TB Department, WHO  
Dr Richard Zaleskis, WHO  
European Region  
Dr Jim Kim  
Chairman of the Working Group |

*Chairperson: R. Zaleskis  
Rapporteur: Marcos Burgos*

#### Session 1: Governance Issues

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
</tr>
</thead>
</table>
| 9:00 AM – 9:15 AM | Governance of the Working Group  
Proposal for a Core Team  
J. Kim |
| 9:15 AM – 9:45 AM | Discussion and Recommendations |

#### Session 2: DOTS-Plus Progress

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
</tr>
</thead>
</table>
| 9:45 AM – 10:00 AM | DOTS-Plus in Estonia  
K. Vink |
| 10:00 AM – 10:15 AM | DOTS-Plus in Latvia  
V. Leimane |
| 10:15 AM – 10:30 AM | DOTS-Plus in Tomsk  
G. Peremitin |
| 10:30 AM – 11:00 AM | Discussion |
| 11:00 AM – 11:30 AM | Coffee Break |
| 11:30 AM – 11:45 AM | DOTS-Plus in Manila  
T. Tupasi |
| 11:45 AM – 12:00 M | DOTS-Plus in Lima  
J. Bayona |
| 12:00 M – 12:30 PM | Lessons Learned  
Panellists |
# Annex 1: Agenda for Meeting of the Stop TB Working Group on DOTS-Plus For MDR-TB

**12:30 PM – 12:50 PM**  
**Special Presentation**  
Feasibility and Cost-effectiveness of DOTS-Plus in Peru  
M. Espinal  
K. Floyd

**12:50 PM – 1:10 PM**  
**Discussion**

**1:10 PM – 2:30 PM**  
**Lunch – Restaurant Seasons at the Radisson**

## Session 3: Parallel Sessions

<table>
<thead>
<tr>
<th>GLC and GDF</th>
<th>Room</th>
<th>GDF</th>
<th>Rapporteur: M. Henkens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prospects for Convergence</strong></td>
<td>Hansa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Chairperson: Tim Healing**

- **2:30 PM – 2:45 PM**  
  Quality Assurance in the Procurement of Anti-tuberculosis Drugs  
  S. Phanouvong

- **2:45 PM – 3:00 PM**  
  Green Light Committee: From Theory to Reality  
  K. Lambregts

- **3:00 PM – 3:15 PM**  
  Global Drug Facility: Improving Access to First-line Anti-tuberculosis Drugs  
  J. Kumaresan

- **3:15 PM – 3:30 PM**  
  GLC/GDF Points of Convergence  
  R. Gupta  
  V. Arnold

- **3:30 PM – 4:00 PM**  
  Discussion

- **4:00 PM – 4:30 PM**  
  Coffee Break

- **4:30 PM – 5:30 PM**  
  Discussion and Recommendations to Stop TB Coordinating Board

**Programmatic, Clinical and Laboratory issues**  
Room Cuxhaven

**Chairperson: Thelma Tupasi**

- **2:30 PM – 2:45 PM**  
  Role of Surgery in the Management of MDR-TB  
  M. Perelman

- **2:45 PM – 3:00 PM**  
  Defaulting Treatment and Side-effects: Obstacle to Managing Patients?  
  M. Danilovits
### Annex 1: Agenda for Meeting of the Stop TB Working Group on DOTS-Plus For MDR-TB

<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda Item</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:00 PM – 3:15 PM</td>
<td>Adherence to Treatment: Role of Social Support</td>
<td>E. Jaramillo</td>
</tr>
<tr>
<td>3:15 PM – 3:30 PM</td>
<td>Role of Training in DOTS-Plus</td>
<td>K. Bergstrom</td>
</tr>
<tr>
<td>3:30 PM – 4:30 PM</td>
<td>Discussion</td>
<td></td>
</tr>
<tr>
<td>4:30 PM – 5:00 PM</td>
<td>Coffee Break</td>
<td></td>
</tr>
<tr>
<td>5:00 PM – 5:30 PM</td>
<td>Surveillance and Laboratory Issues (10 min each)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drug Resistance in Eastern Europe: Do We Know the Magnitude of the Problem?</td>
<td>M. Aziz</td>
</tr>
<tr>
<td></td>
<td>Role of the Laboratory in the DOTS-Plus Strategy</td>
<td>L. Heifets</td>
</tr>
<tr>
<td></td>
<td>Standardisation and Quality Control to Improve Reliability of DST</td>
<td>S. Hoffner</td>
</tr>
<tr>
<td>5:30 PM – 6:00 PM</td>
<td>Discussion</td>
<td></td>
</tr>
<tr>
<td>8:00 PM</td>
<td>Reception at Tallinn Town Hall</td>
<td></td>
</tr>
</tbody>
</table>

### Day 2  Session 4: Unfinished Business

**Chairperson: Pierre Chaulet**  **Rapporteur: Joia Mukherjee**

<table>
<thead>
<tr>
<th>Time</th>
<th>Agenda Item</th>
<th>Presenter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 AM – 8:45 AM</td>
<td>Cohort Analysis: The Need for Standards</td>
<td>P. Cegielski</td>
</tr>
<tr>
<td>8:45 AM – 9:30 AM</td>
<td>Discussion and Recommendations</td>
<td></td>
</tr>
<tr>
<td>9:30 AM – 10:00 AM</td>
<td>Roundtable Fitness of MDR-TB: “Superbug” or Not? (10 min each)</td>
<td>M. Murray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M. Burgos</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C. Dye</td>
</tr>
<tr>
<td>10:00 AM – 11:00 AM</td>
<td>Discussion</td>
<td></td>
</tr>
<tr>
<td>11:00 AM – 11:30 AM</td>
<td>Coffee Break</td>
<td></td>
</tr>
<tr>
<td>11:30 AM – 11:45 AM</td>
<td>Best Treatment Strategies for Settings of High MDR-TB</td>
<td>M. Kimerling</td>
</tr>
</tbody>
</table>
Annex 1: Agenda for Meeting of the Stop TB Working Group on DOTS-Plus For MDR-TB

11:45 AM – 12:00 PM Prioritised Research Agenda A. Hinman
12:00 PM – 1:00 PM Discussion
1:00 PM – 2:30 PM Lunch – Restaurant Seasons at the Radisson

Session 5: Next Steps

*Chairperson: Alan Hinman*  
*Rapporteur: M. Grzemska*

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Chairperson/Reporteur</th>
</tr>
</thead>
<tbody>
<tr>
<td>2:30 PM – 4:00 PM</td>
<td>Report of the Rapporteurs</td>
<td>All</td>
</tr>
<tr>
<td>4:00 PM – 4:30 PM</td>
<td>Coffee Break</td>
<td>All</td>
</tr>
<tr>
<td>4:30 PM – 5:30 PM</td>
<td>Administrative Issues of the WG: Structure, Next Meeting, Next Steps</td>
<td>All</td>
</tr>
<tr>
<td>5:30 PM – 5:40 PM</td>
<td>Closing Remarks M. Espinal</td>
<td></td>
</tr>
<tr>
<td>8:00 PM</td>
<td>Festive Dinner at Lillepaviljon</td>
<td></td>
</tr>
</tbody>
</table>

Day 3  
Site Visits and Training Session

**AM**  
Transportation, snack bags and lunch will be provided

**PM**  
Training Session on Applying to the GLC
ANNEX 2: LIST OF PARTICIPANTS

Dr Ain Aaviksoo
Head of Public Health Department
Ministry of Social Affairs
29 Gonsiori
15027 Tallinn
Estonia

Dr Yevgeny Andreyev
Head of Health Department
Tomsk TB Prison
U1 Energeticheskaya 6a, 3
634009 Tomsk
Russian Federation
Tel.: +7 382 276 7528

Dr Indira Aitmagambetova
Health Project management Specialist
Office of Health and Population
USAID / CAR
41 Kazybek Bi Street
480100 Almaty
Kazakhstan
Tel: +3272 50 76 12 ext 406
Fax: +3272 50 76 35/36
E-mail: indira@usaid.gov

Dr V.K. Arora
Director
LRS Institute of Tuberculosis and Allied Diseases
Sri Aurbondo Marg
110 030 New Delhi
India
Tel: + 91 11 685 4922 or 4929 or 5094
Fax: + 91 11 651 7834 or 656 8227
E-mail: vk_raksha@vsnl.in

Dr Taimi Alas
Economic Assistant
U.S. Embassy in Tallinn
20 Kentmanni
15099 Tallinn
Estonia
Tel.: +372 668 8127
Fax: +372 668 8266
E-mail: talas@online.ee

Ms Lea Avango
CFO
Quattromed OÜ
Estonia
Tel./Fax: +372 678 0419

Dr Alan Altraja
Head of the Department
Department of Pulmonary Medicine
University of Tartu
167 Riia
51014 Tartu
Estonia
Tel.: +372 731 8901
Fax: +372 731 8905
E-mail: ala@kliinikum.ee

Mr Guido Bakker
Project Coordinator, MDR - TB
IDA Foundation
PO Box 37098
1030 AB Amsterdam
The Netherlands
Tel: +31 20 403 3051
Fax: +31 20 403 1854
E-mail: guidobakker@planet.nl
Annex 2: List of Participants

Dr Dirgh Singh Bam  
Director  
SAARC Tuberculosis Centre  
National Tuberculosis Centre  
Thimi, Bhakatpur  
Nepal  
Tel: +977 1 631 048  
Fax: + 977 1 630 061  
E-mail: saarctb@mos.com.np

Dr Steven Barid  
Deputy Coordinator  
Partners TB control program  
Task Force for Child Survival and Development  
750 Commerce Drive, Suite 400  
Decatur, GA 30030  
United States of America  
Tel.: +1 404 592 1403  
Fax: + 1 404 592 1448  
E-mail: sbaird@taskforce.org

Dr Donna Barry  
Russia Project Director  
Partners In Health  
641 Huntington Avenue  
Boston, MA 02115  
United States of America  
Tel.: +1 617 432 6020  
Fax: +1 617 432 6045  
E-mail: dbarry@pih.org

Dr Jaime Bayona García  
Director de Proyectos  
Socios En Salud - Sucursal Parú  
Avenida Merino Reyna 575  
Carabayllo, Lima 06  
Perú  
Tel: + 511 547 0891  
Fax: + 511 547 2121  
E-mail: jbayona@amauta.rcp.net.pe

Dr Mercedes Becerra  
Research Co-Director  
Harvard Medical School  
641 Huntington Avenue  
Boston, MA 02115  
United States of America  
Tel: +1 617 432 3734  
Fax: +1 617 432 2565  
E-mail: mbecerra@post.harvard.edu

Dr Steven Barid  
Deputy Coordinator  
Partners TB control program  
Task Force for Child Survival and Development  
750 Commerce Drive, Suite 400  
Decatur, GA 30030  
United States of America  
Tel.: +1 404 592 1403  
Fax: + 1 404 592 1448  
E-mail: sbaird@taskforce.org

Dr Donna Barry  
Russia Project Director  
Partners In Health  
641 Huntington Avenue  
Boston, MA 02115  
United States of America  
Tel.: +1 617 432 6020  
Fax: +1 617 432 6045  
E-mail: dbarry@pih.org

Dr Steven Barid  
Deputy Coordinator  
Partners TB control program  
Task Force for Child Survival and Development  
750 Commerce Drive, Suite 400  
Decatur, GA 30030  
United States of America  
Tel.: +1 404 592 1403  
Fax: + 1 404 592 1448  
E-mail: sbaird@taskforce.org

Dr Donna Barry  
Russia Project Director  
Partners In Health  
641 Huntington Avenue  
Boston, MA 02115  
United States of America  
Tel.: +1 617 432 6020  
Fax: +1 617 432 6045  
E-mail: dbarry@pih.org

Dr Mercedes Becerra  
Research Co-Director  
Harvard Medical School  
641 Huntington Avenue  
Boston, MA 02115  
United States of America  
Tel: +1 617 432 3734  
Fax: +1 617 432 2565  
E-mail: mbecerra@post.harvard.edu

Dr Ludmilla Blinova  
Laboratory Head  
Tomsk Oblast Penitentiary System  
Tomsk  
Russian Federation  
Tel.: +7 382 267 4438  
Fax: +7 382 241 8710  
E-mail: ism@pbtb.tomsk.ru

Dr Amy Bloom  
Global Programme for Health  
USAID  
Ronald Reagan Building  
3.07-75M, 3rd floor, RRB  
Washington D.C. 20523-3700  
United States of America  
Tel.: +1 202 712 0693  
Fax: +1 202 216 3046  
E-mail: abloom@usaid.gov

Dr Serguei Borisov  
Russian Research Institute of Phthisiopulmonology  
Dostoyevsky str.4  
103030 Moscow  
Russian Federation  
Tel: + 7 095 281 8422  
Fax: + 7 095 281 4537 or 095 971 1515

Dr Alexander Borodulin  
Deputy Chief  
Guin Ministry of Justice  
Medical Department  
Russian Federation
Annex 2: List of Participants

Dr Valentin Borstchevsky
Director
Scientific Research Institute for Pulmonology and Phthysiology
Novinki
223059 Minsk
Belarus
Tel: + 375 172 898795
Fax: +375 172 898950
E-mail: niipulm@bcsmi.minsk.by

Dr Lennart Brander
MDR-TB Program in Estonia
Finnish Lung Health Association
Sibeliuksenkatu 11 A1
00250 Helsinki
Finland
Tel: + 358 9 4542 1230
Fax: + 358 9 4542 1210

Dr Marcos Burgos
Division of Infectious Diseases and Geographic Medicine
Stanford University
School of Medicine
Medical Centre, RM S-156
94305 Stanford, CA
United States of America
Tel: + 1 505 272 5666
Fax: + 1 650 498 7011
E-mail: burgosm@yahoo.com

Dr Patrizia Carlevaro
Head of International Aid Unit
Eli Lilly Export S.A.
P.O. Box 580
16 chemin des Coquelicots
1214 Vernier
Switzerland
Tel: + 41 22 306 03 94 - direct
Fax: + 41 22 306 04 94
E-mail: carlevaro_patricia@lilly.com

Dr J. Peter Cegielski
Medical Epidemiologist
Centers for Disease Control & Prevention (CDC)
Mailstop E-10
1600 Clifton Road
30333 Atlanta, GA
United States of America
Tel: +1 404 639 5329
Fax: +1 404 639 8604
E-mail: gzc2@cdc.gov

Prof. Pierre Chaulet
Conseilen aupie de la Direction de la Prevention
Ministere de la Sante et de la Population
8 Rue du Hoggar, Hydra
16035 Alger
Algeria
Tel/Fax: + 213 21 60 0409
E-mail: chaulet.p@algeria.com

Dr Valentina Cherednichenko
Clinical Doctor/Pharmacologist
Tomsk TB Services
Ulitsa Luxemburg 17
634009 Tomsk
Russian Federation
Tel.: +7 382 251 3971

Dr Sang-Nae Cho
Professor
Department of Microbiology
Yonsei University College of Medicine
134 shinchon-dong
Seoul 120-752
Republic of Korea
Tel: +822 361 5282
Fax: +882 392 7088
E-mail: raycho@yumc.yonsei.ac.kr

Dr Philippe Creach
Head of Tuberculosis Programme in Georgia
International Committee of the Red Cross
Georgia
Tel.: +995 777 21 536
Fax: +995 532 93 5520
E-mail: pcreach.tbi@icrc.org
Annex 2: List of Participants

Dr Manfred Danilovits  
Head of Department of Tuberculosis  
Estonian National Tuberculosis Program  
Riia Street 167  
Tartu  
Estonia  
Tel: +372 7 449 940  
Fax: +372 7 449 943  
E-mail: manfred@cut.ee

Dr Edita Davidaviciene  
NTP Manager  
Lithuanian Centre of Pulmonology and Tuberculosis  
Antakalnio 77  
2040 Vilnius  
Lithuania  
Tel: + 370 2 342 232  
E-mail: edita.david@takas.lt

Dr Mirtha Del Granado  
National TB Control Program Manager  
Ministerio de Salud  
Av. Capital Ravelo No. 2199  
La Paz  
Bolivia  
Tel: + 591-2 442 006  
Fax: + 591-2 441 328  
E-mail: mdelgranado@yahoo.com

Prof. Inna R. Dorozhkova  
Head of Laboratory  
Research Institute of Phthisiopulmonology (RIPP)  
4, Dostoyevskogo str.  
127994 Moscow  
Russian Federation  
Tel.: +7 095 281 8422  
Fax: +7 095 971 1515  
E-mail: tbcripp@cityline.ru

Dr Francis Drobniewski  
Director  
PHLS Mycobacterium Reference Unit  
Dulwich Public Health Laboratory  
Dulwich Hospital, East Dulwich Grove  
SE22 8QF London  
United Kingdom of Great Britain and Northern Ireland  
Tel: + 44 208 693 1312  
Fax: + 44 208 346 6477  
E-mail: francis.drobniewski@kcl.ac.uk

Dr Alexandr Dronnikov  
Deputy Governor  
Tomsk Oblast Administration  
Pr Lenina 6  
634009 Tomsk  
Russian Federation  
Tel.: +7 382 251 0358

Dr Valery Dushkevich  
Head of Prisonery TB Department  
Prisonery Central Hospital  
Kalaranna tn 2  
10415 Tallinn  
Estonia  
Tel.: +372 6 663 840  
Fax: +372 6 448 867  
E-mail: tbc@keskv.just.ee

Prof. Vladislav Erokhin  
Director  
WHO Collaborating Centre for TB  
Central Tuberculosis Research Institute  
Russian Academy of Medical Sciences  
Yauzskaya Alley, 2  
107564 Moscow  
Russian Federation  
Tel: + 7 095 963 8013 or 268 1441  
Fax: + 7 095 963 8000  
E-mail: cniitram@online.ru
Annex 2: List of Participants

Dr Edith Elizabeth Ferreira
Directora del Programa de Tuberculosis
Secretaría de Salud
San Luis de Potosí 199 8vo piso
Col Roma
México D.F.
Tel: +52 55 844270 or 56717182
Fax: +52 55 847191
E-mail: micobacteriosis@mail.ssa.gob.mx

Dr Hamish Fraser
Partners In Health
Informatics in Telemedicine
641 Huntington Avenue
Boston, MA 02115
United States of America
Tel: +1 617 432 3930
E-mail: hamish@medg.lcs.mit.edu

Dr Dalija Gaidamoniene
Head of National TB and Lung Diseases Hospital
National TB and Lung Diseases Hospital
Antakalnio 77, 2040 Vilnius
Lithuania
Tel: +370 2 34 2507
Fax: +370 2 34 22 32
E-mail: gaidam@takas.lt

Dr Irina Gelmanova
Project Coordinator
Partners In Health
8 Ozerkovskayanaberezhnaya
113184 Moscow
Russian Federation
Tel: +7 095 787 8817
Fax: +7 095 787 8822
E-mail: irinapih@osi.ru

Dr Victor Gherasichev
Deputy Director of SIZO
Central SIZO TB Hospital
16, Svetayeva Str., Orel 203026
Russian Federation
Tel: +7 086 241 4600
Fax: +7 086 241 4600
E-mail: td@med.orel.ru

Prof. Valentina Golyschevskaya
Head, National Reference Laboratory
Central Tuberculosis Research Institute
Russian Academy of Medical Sciences
Yauzskaya Alley, 2
107564 Moscow
Russian Federation
Tel: +7 095 963 8013 or 268 1441
Fax: +7 095 963 8000
E-mail: cniitram@online.ru

Dr Ekaterina Goncharova
Medical Coordinator
Partners In Health
Ozerkovskaya Naberezhnaya 8
113184 Moscow
Russian Federation
Tel: +7 095 787 8817
Fax: +7 095 787 8822
E-mail: egucharova@pih.org

Dr Torunn Hasler
Consultant International Cooperation
The Norwegian heart and Lung Association
Post Box 4374
N-0402 Oslo
Norway
Tel: +47 22 79 9325
Fax: +47 22 22 3833
E-mail: th@lhl.no

Dr Tim Healing
Health Adviser
Medical Emergency Relief International (MERLIN)
5-13 Trinity Street, Borough
London SE1 1DB
United Kingdom of Great Britain and Northern Ireland
Tel: +44 0 207 378 4888
Fax: +44 0 207 378 4899
E-mail: tim.healing@merlin.org.uk
Dr Leonid Heifets  
Clinical Mycobacteriology National Jewish National Jewish Medical & Research Center  
1400 Jackson St.  
Denver, CO 80206  
United States of America  
Tel: + 1 303 398 1384  
Fax: + 1 303 398 1953  
E-mail: heifetsl@njc.org

Dr Myriam Henkens  
International Medical Co-ordinator  
International Office Médecins sans Frontières  
rue de la Tourelle 39  
1040 Brussels  
Belgium  
Tel: + 32 2 280 18 81  
Fax: + 32 2 280 01 73  
E-mail: myriam_henkens@bi.msf.org

Dr Alan Hinman  
Coordinator  
PARTNERS TB Control Program  
Task Force for Child Survival and Development  
750 Commerce Drive Suite 400  
400 Decatur, GA 30030  
United States of America  
Tel: + 1 404 371 0466 or 687 5636  
Fax: + 1 404 592 1448  
E-mail: ahinman@taskforce.org

Dr Marcus Hodge  
Medical Officer, Stop TB, WPRO Communicable Disease Prevention and Control  
P.O. Box 2932  
1099 Manila  
Philippines  
Tel: + 63 2 528 9720  
Fax: + 63 2 521 1036  
E-mail: hodgem@who.org.ph

Dr Sven Hoffner  
Swedish Institute for Infectious Disease Control  
Nobels väg 18  
171 82 Solna  
Sweden  
Tel: + 46 8 457 2431  
Fax: + 46 8 301 797  
E-mail: sven.hoffner@smi.ki.se

Dr Vahur Hollo  
Manager  
Estonian TB Registry  
Põllu 63  
11619 Tallinn  
Estonia  
Tel: +372 6 519 523  
Fax: +372 6 519 503  
E-mail: vahur@kivimaeh.ee

Dr Veronika Iljina  
Head of the TB Department  
Kohtla-Järve Lung Hospital  
Torujõe 13  
30321 Kohtla-Järve  
Estonia  
Tel: +372 33 73 218  
Fax: +372 33 73 218  
E-mail: viljina@hot.ee

Dr Myrzakhat Imanaliev  
Deputy Director on Methodical Work  
Research Institute of Tuberculosis  
Akhunbaev Street 90a  
Bishkek 720020  
Kyrgyz Republic  
Tel: + 996 312 47 09 36  
Fax: + 996 312 47 09 24  
E-mail: niit@uzerzkynret.kg

Dr Shahmurat Ismailov  
Head of Pulmonary MDR Treatment Department  
National TB Center  
5 Bekkhoshchina Street  
480100 Almaty  
Kazakhstan  
Tel: +7 327 190 0634
Annex 2: List of Participants

Dr Wieslaw Jakubowiak  
TB Co-ordinator  
Office of Special Representative of the Director General in Moscow  
World Health Organization  
28 Ostozhenka Street  
119034 Moscow  
Russian Federation  
Tel: +7 095 787 21 18  
Fax: +7 095 787 21 49  
E-mail: w.jakubowiak@who.org.ru

Dr Vytautas Jurkuvenas  
Project Technical Advisor  
TB Initiative  
Gorgas Memorial Institute  
University of Alabama at Birmingham  
RPHB 217, 1530 3rd Avenue South  
35294-0022 Birmingham  
Alabama  
United States of America  
Tel: +1 205 934 7047  
Fax: +1 205 975 3329  
Fax in Kemerovo: +7 384 2 37 81 51  
E-mail: vyta@kuzbass.net

Dr Oleg Nikolaevich Karataev  
Chief Medical Officer  
Donetsk Regional Clinical TB Hospital  
104-a, Ilyicha Av.  
83059 Donetsk  
Ukraine  
Tel: +380 622 94 0331  
Fax: +380 623 85 0950

Dr Marja-Leena Katila  
Consultant/Technical Expert  
Finnish Lung Health Association (FILHA)  
Isokaari 12  
70420 Kuopio  
Finland  
Tel: +358 17 17 3210  
Fax: +358 17 17 3202  
E-mail: marja-leena.katila@kuh.fi

Prof. George Khechinashvili  
NTP Manager  
50 Maruashvili Street  
Tbilisi 380001  
Georgia  
Fax: +99 532 955 836  
E-mail: tbinst@access.sanet.ge

Dr Tatiana Khorosheva  
Orel TB Dispensary  
16, Svetayeva Str.,  
203026 Orel  
Russian Federation  
Tel: +7 086 241 4600  
Fax: +7 086 241 4600  
E-mail: td@med.orel.ru

Dr Nina Khouriева  
WHO TB Programme National Professional Officer in Russian Federation  
28 Ostozhenka Street, Suite 300  
119034 Moscow  
Russian Federation  
Tel: +7 097 872 116  
Fax: +7 097 872 149  
E-mail: nkhourieva.r@who.org.ru

Dr Jim Yong Kim  
Program Director  
Program in Infectious Disease and Social Change  
Department of Social Medicine  
Harvard Medical School  
641 Huntington House  
Boston, MA 02115  
United States of America  
Tel: +1 617 432 2575  
Fax: +1 617 432 2565  
E-mail: jim@pih.org

Dr Sang Jae Kim  
Consultant (former Director)  
Korean Institute of Tuberculosis  
14, Woomyundon, Seochoku  
137-140 Seoul  
Republic of Korea  
Tel: +82 2 576 0357  
Fax: +82 2 573 1914  
E-mail: sangjkm@soback.kornet.nm.kr

25
Annex 2: List of Participants

Dr Michael Kimerling
Director
Gorgas Memorial Institute TB Initiat.
University of Alabama at Birmingham
RPHB 217, 1530 3rd Avenue South
35294-0022 Birmingham
Alabama
United States of America
Tel: +1 205 934 7047
Fax: +1 205 975 3329
E-mail: kimerlin@uab.edu

Dr Kersti Kloch
TB Program Assistant
Tartu University Lung Hospital
Riia 167
51014 Tartu
Estonia
Tel: +372 7 449 943
Fax: +372 7 449 943
E-mail: kersti.kloch@klinikum.ee

Mr Karostelyov Korostelev Nikolai
Head of TB Prison IK-1
TB Prison IK-1
Ul Suvordva 7
634009 Tomsk
Russian Federation
Tel: +7 382 266 6809
Fax: +7 095 384 751804

Dr Annika Krüüner
Estonian TB Reference Laboratory
Puusepa 1a
50406 Tartu
Estonia
Tel: +372 7 428 262
E-mail: Annika.Kryyner@klinikum.ee

Ms Rachel Kunigas
Scientist
Quattromed OÜ, Nooruse 9
50411 Tartu
Estonia
Tel: +372 7 380 276
Fax: +372 7 380 289
E-mail: rahel.kunigas@quattromed.ee

Dr Anu Kurve
Head of Outpatient Department
Kivimäe Lung Hospital
Põllu 61/63
11613 Tallinn
Estonia
Tel: +372 6 519 559
E-mail: anukurve@hotmail.com

Dr Irina Kuznetsova
Ivanovo TB Dispensary
17, Krutinskaya Str.
153000 Ivanovo
Russian Federation
Tel: +7 0932 32 76 88
Fax: +7 0932 412559
E-mail: ivfti@tpi.ru

Dr Dominique Lafontaine
Project Coordinator
Center of Excellence (COE) Project
Médecins Sans Frontières/Gorgas
Shmitovskyi proezd 3
Stroenie 3, 4th Floor
123 100 Moscow
Russian Federation
Tel: +7 095 256 6664
Fax: +7 095 253 2447
E-mail: msfbms@aha.ru

Dr Kitty Lambregts
Senior Consultant Tuberculosis Control
Royal Netherlands Tuberculosis Association (KNCV)
Riouwstraat 7
2501 CC The Hague
The Netherlands
Tel: +31 70 416 7222
Fax: +31 70 517 7656
E-mail: lambregtsk@kncvtbc.nl
Annex 2: List of Participants

Dr Piret Laur  
The WHO Liaison Officer  
WHO Liaison Office  
c/o Ministry of Social Affairs  
Gonsiori Str. 29  
EE-0104 Tallinn  
Tel: +372 699 9731 or 699 9736  
Fax: +372 626 2209 or 626 9731  
E-mail: piret.laur@sm.ee

Dr Duk-Hyung Lee  
Director  
National Masan Tuberculosis Hospital  
468 Gapo-dong, Hapo-ku  
Masan, Kyungsangnam-do 631-320  
Republic of Korea  
Tel: +82 55 242 7131  
Fax: +82 55 242 1135  
E-mail: leeduk0125@hanmail.net

Dr Vaira Leimane  
TB Programme Manager  
Medical School  
State Centre of Tuberculosis and Lung Disease of Latvia  
Darza 2 Gamkalnes pag  
LV 2137 Riga reg  
Latvia  
Tel: +371 7048241  
Fax: +371 7901014  
E-mail: tbcentrs@parks.lv

Ms Klavdia Levina  
Laboratory Chairman  
Kivimäe Hospital  
Põllu 61/62, Tallinn  
Estonia  
E-mail: klevina@hotmail.com

Dr Evija Livchane  
Medical Consultant  
Public Health Research Institute  
Representative Office  
in Russian Federation  
Trekhp rudny per., 11/13 build. 3  
13001 Moscow  
Russian Federation  
Tel: +7 095 974 17 91 or 92/93/94  
Fax: +7 095 974 17 89  
E-mail: www.tuberculosis.ru

Dr Helle-Mai Loit  
Head of the Department of Pulmonology  
Institute of Experimental and Clinical Medicine  
Hiiu 42, 11619 Tallinn  
Estonia  
Tel: +372 6 572 061  
Fax: +372 6 670 814  
E-mail: ekmipulmo@hot.ee

Dr Asif Mujtaba Mahmud  
Assistant Professor Respiratory Medicine  
Institute of Diseases of Chest and Hospital (IDCH)  
Dhaka, Bangladesh  
Tel: +880 2 881 5793  
Fax: +880 2 8613247  
E-mail: alina@bdcom.com

Dr Igor Malakhov  
Medical Head of Colony 33  
Kemerovo GUIN, Ministry of Justice  
Smitovsky Proezd 3, Building 3  
123100 Moscow  
Russian Federation  
Tel: +7 095 256 6664  
Fax: +7 095 253 2447  
E-mail: msfmos@aha.ru
Annex 2: List of Participants

Prof. Andrey Mariandyshev
Head of the Phtisiopulmonological Department of the Northern State Medical University Novgorodsky 28 Regional Tuberculosis Dispensary
163002 Arkhangelsk
Russian Federation
Tel: +7 818 2 – 209 360 or 660 564
Private tel: +7 818 2 – 655 564
Fax: +7 818 2 – 209 360 or 263 226
E mail: mao@arh.ru

Dr Zeidy Mata
National Tuberculosis Program Manager
Tres Ríos, Cartago 200 metros este y 50 norte Iglesia Católica
Residencial La Antigua
P.O. Box 320-2250
Tres Ríos Cartago
Costa Rica
Tel: + 506 223 1128 (Office)
E-mail: mbpzma@racsa.co.cr

Prof. Vasyl Mihailovich Melnyk
Deputy Director
Institute of Phthisiology and Pulmonology named by F.G.Yanovsky
7, Usvis Protasiv Yar
03680 Kiev-110
Ukraine
Tel/fax: + 380 44 277 21 18
E-mail: melnik@ifp.kiev.ua

Dr Vladimir Mishin
Central TB Research Institute
2, Yauzskaya Alley
107564 Moscow
Russian Federation
Tel: + 7 095 – 2681 441
Fax: + 7 095 – 9638 000
E-mail: citramn@online.ru

Dr Sergei Mishustin
Head
Tomsk Oblast Penitentiary System
Russian Federation
Tel: +7 382 267 4438
Fax: +7 382 241 8710
E-mail: ism@pbtb.tomsk.ru

Dr Kestutis Miskinis
WHO Officer for TB Control in Ukraine
1A, Olimpieva Street
83045 Donetsk
Ukraine
Tel/fax: + 380 062 385 0948
E-mail: kmi@who.donbass.com

Dr Joia Mukherjee
PIH / PIDSC / Socios en Salud Department of Social Medicine
Harvard University
641 Huntington Avenue
Boston, MA 02115
United States of America
Tel: + 1 617 432 5278
Fax: + 1 617 432 2565
E-mail: jmukher@attglobal.net

Dr Megan Murray
Assistant Professor
Department of Epidemiology
Harvard Medical School
Kresge Building, Room 809
677 Huntington Avenue
Boston, MA 02115
United States of America
Tel: + 1 617 432-2781
Fax: + 1 617 566-7805
E-mail: mmurray@hsph.harvard.edu

Dr Ed Nardell
Physician
Harvard Cambridge Hospital
1493 Cambridge, MA 02139
United States of America
Tel: + 1 617 665 1029
Fax: + 1 617 665 1672
E-mail: edward.nardell@state.ma.us
Dr Krista Nokkur  
Assistant-Resident  
North Estonia Regional Hospital  
Center of TB Disease  
Ravila mnt 29  
75101 Kose Harjumaa  
Estonia  
Tel: +372 603 6127  
Fax: +372 603 6434

Ms Nohelly Nombela  
Registration Officer  
IDA Foundation  
Slochterweg 35  
1027 AA Amsterdam  
The Netherlands  
Tel: +312 040 33 051  
Fax: +312 040 31 854  
E-mail: nnombela@ida.nl

Dr Knut Øvreberg  
LHL- IUATLD TB Consultant  
The Norwegian Heart and Lung Association  
P.B. 4375 Torshov  
Sandakerveien 99  
0402 Oslo 4  
Norway

Dr Domingo J. Palmero  
Pulmonologist  
Hospital Muñiz  
Nicolas Videla 559  
1424 Buenos Aires  
Argentina  
Tel/Fax: + 54 11 4432-6569  
E-mail: djpalmero@intramed.net.ar

Dr Seung-Kyu Park  
Chief  
Division of Pulmonary Surgery  
National Masan Tuberculosis Hospital  
468 Gapo-dong, Hapo-ku  
Masan, Kyungsangnam-do 631-320  
Republic of Korea  
Tel: + 82 55 246 1141  
Fax: +82 55 242 1135  
E-mail: pulmo@uniTelco.kr

Dr Alexander Passetchnikov  
Tomsk TB Project Director  
Partners In Health  
Belinski, 634029  
Tomsk  
Russian Federation  
Tel/Fax: +38 22 53 2625  
E-mail: alexander@phri.msk.ru

Dr Vera Pavlova  
Head of Laboratory  
Tomsk TB Polyclinic  
U1 Astnovskaja 9a-19  
634009 Tomsk  
Russian Federation  
Tel: +73 82 242 6072

Dr Irina Pechiorina  
Deputy Head  
Oblast TB Dispensary  
Kemerovo  
Russian Federation  
Tel: +7 005 256 6664  
Fax: + 7 095 253 2447  
E-mail: msfbmos@aha.ru

Dr Lea Pehme  
Pulmonologist  
Tartu University Clinics, Lung Clinic  
Riia 167, 51014 Tartu  
Estonia  
Tel.: +372 744 9942  
E-mail: leape@cut.ee

Prof. Mikhail I. Perelmann  
Director  
Russian Research Institute of Phthisiopulmonology  
Dostoyevsky str.4  
103030 Moscow  
Russian Federation  
Tel: + 7 095 281 8422  
Fax: + 7 095 281 4537 or 971 1515  
E-mail: tbrcripp@cityline.ru
Annex 2: List of Participants

Dr Gennady Peremitin
Tomsk Oblast TB Dispensary
Luxembourg Street 17
34009 Tomsk
Russian Federation
Tel.: +7 382 251 5207
Fax: +7 382 251 4298
E-mail: ftisiatria@mail.tomsknet.ru

Mr Pierre Poivre
General Manager
Transfer (Médecins Sans Frontières)
Rue Dupré 94
1090 Brussels
Belgium
Tel: +32 2 474 7500 or 477 487726
E-mail: pierre_poivre@msf.be

Dr Oksana Ponomarenko
Director of Representative Office on Russia
Public Health Research Institute
Malaya Trubetsnaya, 8 11th floor
103009 Moscow
Russian Federation
Tel: +7 095 974 1792
Fax: +7 095 974 1789
E-mail: oksana@phri.msk.ru

Dr Olga Popova
Lung Doctor
Kivimäe Hospital
Põllu 63
11619 Tallinn
Estonia
Tel.: +372 651 9527

Dr Jack Preger
Calcutta Rescue
85 Collin Street
Calcutta 700016
India
P.O. Box 9253
Middleton Row P.O.
Calcutta 700071
India
Tel: +91 33 246 1520
Fax: +91 33 21 75 675
E-mail: jpreger@vsnl.com

Dr Md Atiqur Rahman
Resident Physician
(Assistant Professor)
Institute of Disease of Chest and Hospital (IDCH)
Mohakhali, Dhaka
Bangladesh
Tel.: +880 2 882 9840
Fax: +880 2 988 3444
E-mail: alina@bdcom.com

Prof. Galymzhan Rakhishev
Director
Kazakh TB Research Institute
5, Bekhoshina Street
480100 Almaty
Kazakhstan
Tel: + 7 327 2 918 658
Fax: + 7 327 2 918 658
E-mail: tbrk@itte.kz

Dr Emilia Repina
Deputy Chief Doctor
Ivanovo TB Dispensary
17, Krutinskaya Street
Ivanovo 153000
Russian Federation
Tel: + 7 0932 32 76 88
Fax: + 7 0932 412559
E-mail: ivfti@tpi.ru

Dr Michael Rich
PIH / PIDSC / Socios en Salud
Harvard Medical School
641 Huntington Avenue
Boston, MA 02115
United States of America
Tel: +1 617 432 3734
Fax: +1 617 497 1640
E-mail: mlrich@attglobal.net

Dr Andrus Rumm
Head of TB Department
Kivimäe Lung Hospital
Põllu 61/63
11613 Tallinn
Estonia
Tel: +372 6 519 533
E-mail: a_rumm@hotmail.com
Dr Svetlana Safonova  
Chief TB Specialist  
Guin Ministry of Justice  
Medical Department  
Narvskaya 15a  
125130 Moscow  
Russian Federation  
Tel: +7 095 200 4690  
Fax: +7 095 200 5918  
E-mail: oksana@phri.msk.ru

Dr Kwonjune Seung  
Physician  
Partners In Health  
Harvard Medical School  
641 Huntington Avenue  
Boston 02115 MA  
United States of America  
Tel: +1 617 532 6492  
Fax: +1 617 532 5300  
E-mail: kjseung@pih.org

Dr Oleg Sheyanenko  
Head of Department for Chronic Patients and DOTS-Plus Coordinator  
Ministry of Justice  
Colony 33  
Kemerovo GUIN  
Russian Federation  
Tel: +7 095 256 6664  
Fax: +7 095 253 2447

Dr Heinart Sillastu  
Consulting Professor  
Tartu University Lung Hospital  
Riia 167  
Estonia  
51014 Tartu  
Tel: +372 7 422 385  
Fax: +372 7 422 385

Dr Andrei Slavuckij  
Medical Coordinator  
Center of Excellence (COE) Project  
Médecins Sans Frontières/Gorgas  
Shmitovskyi proezd 3 Stroenie 3, 4th Flr  
Moscow 123 100  
Russian Federation  
Tel: + 7 095 256 6660 or 6664  
Fax: + 7 095 253 2447

Dr Ivan Solovic  
Head of the Department for MDR-TB  
Institute for TB, Lung Diseases and Thoracic Surgery  
059 84 Vysne Hagy  
Slovakia  
Tel: +421 52 44 14 413  
Fax: +421 52 44 97 715  
E-mail: solovic@hagy.sk

Dr Bertie Squire  
Senior Lecturer Tropical Medicine  
Liverpool School of Tropical Medicine  
Pembroke Place, Liverpool L3 5QA  
United Kingdom  
Tel: + 44 151 708 9393  
Fax: + 44 151 708 8733  
E-mail: sbsquire@liv.ac.uk

Dr Natalia Starchenkova  
Phthisiatrist  
Ministry of Justice, Guin  
Kemerovo GUIN  
Russian Federation  
Tel: +7 095 256 6664  
Fax: +7 095 253 2447  
E-mail: msfmos@aha.ru

Prof. Aivar Karlovich Strelis  
Regional Tuberculosis  
Tomsk Region  
26-4, Internationalist Street  
634057 Tomsk  
Russian Federation  
Tel: +7 382 291 1480  
Fax: +7 382 291 1260
Annex 2: List of Participants

Dr Jaak Tälli  
Member of the Managing Board  
North Estonia Regional Hospital  
Tallinn  
Estonia  
Tel: +372 50 15 242  
Fax: +372 5 971 200  
E-mail: jaak.talli@saperh.ee

Dr Tiit Talpsep  
Director of Development  
Quattromed Oü  
Nooruse 9  
50411 Tartu  
Estonia  
Tel: +372 7 380 276  
Fax: +372 7 380 284  
E-mail: tiit.talpsep@quattromed.ee

Ms Yolanda Tayler  
Senior procurement Specialist  
(Focal Point for Health)  
The World Bank  
1818 H Street, N.W.  
Washington, D.C. 20433  
United States of America  
Tel: +1 202 473 0810  
Fax: +1 202 522 3318  
E-mail: ytayler@worldbank.org

Dr Tamara Tonkel  
Deputy Head of Tomsk TB Services  
Tomsk TB Services  
U1 Luxembourg 17  
634009 Tomsk  
Russian Federation  
Tel: +7 382 251 3177  
Fax: +7 382 251 4508  
E-mail: tonkel1@mail2000.ru

Dr Tülay Törün  
Departments of Pulmonary Disease  
Sreyyapasa Center for Chest Diseases and Thoracic Surgery, No. 49/3  
81320 Kadıköy  
Istanbul  
Turkey  
E-mail: tulaytorun@superonline.com

Dr Thelma E.Tupasi  
Tropical Disease Foundation /  
Makati Medical Center  
2 Amorsolo St.  
Makati City 1200  
Philippines  
Tel: + 63 2 893 6066 or 817 8773  
Fax: + 63 2 810 2874  
E-mail: tdf@info.com.ph

Dr Leonid Viktorovich Turchenko  
Chief Doctor  
Kiev City Central TB Dispensary  
35, Vasilkovsky Street  
01022 Kiev  
Ukraine  
Tel/fax: + 380 44 263 51 73  
E-mail: cgcptd@health.kiev.ua

Dr Irina Vassilieva  
Central TB Research Institute  
2, Yauzskaya Alley,  
107564 Moscow, Russia  
Tel: + 7 095 2681441  
Fax: + 7 095 9638000  
E-mail: citramn@online.ru

Ms Natalia Vezhnina  
Administrator  
Center of Excellence (COE) Project Médecins Sans Frontières  
Nikiutsky Boulevard 12 KV 73  
Moscow  
Russian Federation

Dr Kai Vink  
Manager of NTP  
Tartu University Lung Clinic  
Riia 167  
51014 Tartu  
Estonia  
Tel: +372 744 9944  
Fax: +372 744 9943  
E-mail: kai.vink@kliinikum.ee
Annex 2: List of Participants

Dr Anatoly Vinokur  
WHO TB Programme Officer  
Office of the Special Representative of the WHO Director General in the Russian Federation  
28, Ostozhenka St., suite 300  
119034 Moscow  
Russian Federation  
Tel: +7 095 787-2116 (WHO TB office)  
Tel: +7 501 414-0825 (direct line)  
Fax.: +7 095 787-2149

Dr Erika Vitek  
Senior Service Fellow  
Centers for Disease Control & Prevention (CDC)  
Mailstop E-10  
1600 Clifton Road  
Atlanta, GA 30333  
United States of America

Ms Diana Weil  
Senior Public Health Specialist  
WHO-Secondee  
Health, Nutrition and Population Team  
Human Development Department  
World Bank  
G7-049  
1818 H Street, N.W  
Washington, D.C. 20433  
United States of America  
Tel: + 1 202 473 6782  
Fax: + 1 202 522 3489  
E-mail: dweil@worldbank.org

Dr Karin Weyer  
Unit for TB Operational Research and Policy  
Medical Research Council  
Private Bag X385  
1 Soutpansberg Road  
0001 Pretoria  
South Africa  
E-mail: karin.weyer@mrc.ac.za

Dr Galina Yanova  
Head Doctor of TB Hospital  
Tomsk TB Hospital  
Novaia Street 1  
634009 Tomsk  
Russian Federation  
Tel: +7 382 291 1260

Dr Richard Zaleskis  
WHO Regional Adviser for TB Control in Europe  
Scherfigsvej 8,  
2100 Copenhagen  
Denmark  
Tel: + 453 917 1335  
Fax: + 453 917 1851  
E-mail: rza@who.dk
Annex 2: List of Participants

**WHO Secretariat**

**Stop TB (STB)**
Dr J.W. Lee, Director

**TBS/STB**
Dr Mario Raviglione, Coordinator
Mrs Karin Bergström
Ms Corazon Dolores
Dr Marcos Espinal
Dr Katherine Floyd
Dr Malgorzata Grzemska
Mr Rajesh Gupta
Dr Ernesto Jaramillo

**TME/STB**
Dr Chris Dye, Coordinator

**TBP/STB**
Dr Jacob Kumaresan, Coordinator
Ms Gini Arnold
Dr Ian Smith

**EPH/CSR**
Dr Mohamed Abdel Aziz

**EDM/PAR**
Dr Souly Phanouvong

**ITT/AVT**
Ms Marion Lindsay
ANNEX 3: TERMS OF REFERENCE FOR THE STOP TB WORKING GROUP ON DOTS-PLUS FOR MDR-TB

“DOTS-Plus for Multidrug-Resistant Tuberculosis”

A Stop TB Working Group Convened by WHO

Terms of Reference

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

Rationale for the Working Group

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

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

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

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

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

**Objectives of the Working Group**

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

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

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

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

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

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

**Membership**

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

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

Progress to Date

The Working Group was established in 1999 before the creation of the Stop TB structure. Therefore, work began and is now underway to address the above objectives. In 2002, a Core Group was established to assist the Secretariat in rapidly implementing the recommendations of the Working Group and in pursuing its objectives and aims. Accordingly, the Core Group has the following tasks:

- To assist with the preparatory work for the (annual) Working Group meetings.
- To hold regular conferences to assist in faster decision-making related to Working Group activities.
- To oversee activities of the ad hoc or subgroups of the Working Group.
- To liaise with the Green Light Committee to assist countries in implementation of Green Light Committee recommendations as needed.
- To interact with other Stop TB Working Groups to coordinate activities.

In addition, several subgroups within the Working Group exist:

1. The Subgroup on Laboratory Issues was created to make recommendations concerning standard guidelines for DST for second-line anti-TB drugs. The resulting document *Guidelines for Drug-Susceptibility Testing to Second-line Anti-TB Drugs for DOTS-Plus* has been finalized. Although this subgroup was dissolved, it has been recreated and now focuses on setting the basis for determining standards for DST to second-line anti-TB drugs.

2. The Scientific Panel on Programmatic, Laboratory, Clinical Issues was created with two objectives:
   - To prepare and review guidelines to implement DOTS-Plus pilot projects.
   - To assess the data generated by DOTS-Plus pilot projects in order to, ultimately, advise WHO in developing policy recommendations for its Member States.
• To provide technical advice to the Green Light Committee and resolve programmatic and clinical issues (including establishing case definitions) regarding for management of MDR-TB.

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

3. The Subgroup on Drug Procurement Systems was recreated as the Subgroup on Procurement Issues. Originally, the Subgroup on Drug Procurement Systems was created to make recommendations for increasing access (primarily in terms of lowering cost) to high-quality second-line anti-TB drugs. The activities of this subgroup have resulted in a large decrease in the price of second-line anti-TB drugs, and the establishment of two procurement arrangements that (combined) will supply complete treatment courses for DOTS-Plus pilot projects which the Green Light Committee finds to be in accordance with the *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB*. This recreated subgroup has the following objectives:

• To resolve registration issues of capreomycin, cycloserine, and granular PAS in the Russian Federation.

• To identify potential partners for technology transfer of capreomycin and cycloserine.

• To develop a strategy for increasing access to diagnostics.

• To develop a strategy for increasing access to ancillary drugs for the management of adverse reactions.

• To perform a second survey of the global use of second-line anti-TB drugs.

As a special body of the Working Group, the Green Light Committee (created in 2000 by the Subgroup on Drug Procurement Systems for second-line anti-TB drugs as its implementing arm and natural evolution) has the following tasks:

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

• To promote technical assistance, through the partners participating in the Working Group, in the submission of proposals to the Green Light Committee, and in the implementation of the project protocols.
• To re-assess, periodically, pilot projects whose applications are found to meet the requirements highlighted in the *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB*, including through site visits as WHO may deem necessary and appropriate.

**Financing**

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

**Meetings**

Meetings of the Working Group will be held at least once every two years and will be convened by WHO in agreement with sponsoring members. Decisions will be taken by consensus. Meetings of subgroups will be held on an ad hoc basis when needed (based on recommendations of each subgroup and according to a priority scale).
ANNEX 4: LIST OF WHO REFERENCE DOCUMENTS FOR MDR-TB


ANNEX 5: STRUCTURE OF THE WORKING GROUP ON DOTS-PLUS FOR MDR-TB

Working Group on DOTS-Plus for MDR-TB

Core Group

Subgroup on Procurement Issues

Scientific Panel

Subgroup on Laboratory Issues

Green Light Committee