

Technical Support to Second-line TB Drug Management, Moldova, June 14-16, 2006: Trip Report

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About RPM Plus

RPM Plus works in more than 20 developing and transitional countries to provide technical assistance to strengthen drug and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning and in promoting the appropriate use of health commodities in the public and private sectors.

Abstract

RPM Plus and in-country partners, the Ministry of Health and Social Protection (MoHSP), National Tuberculosis Control Program (NTP) and the Phtisiology and Pneumology Institute “Chiril Draganiuc”(PPI) are focusing their efforts on strengthening the drug management information system for the NTP. During the trip, an evaluation of the context and conditions was conducted with the NTP and main stakeholders for the potential implementation of a new Drug Management Information System (DMIS) developed by RPM Plus for second-line TB drug management. Preliminary conclusions are highly favorable to the relevance of this project for RPM Plus programming future planned funding with the USAID mission and counterparts in Moldova. Contacts for coordination of activities and initiatives in the field of information for TB were also conducted with other partners and stakeholders like GFATM. A working group of all stakeholders involved in the program was created, activities defined and a matrix of responsibilities agreed among all partners for the process of design and implementation of this new DMIS.

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Key Words

Tuberculosis, TB, MDR-TB, DMIS, Second-line Drugs Management, GLC

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ACRONYMS

AFB	Acid-fast bacilli microscopy
AIHA	American International Health Alliance
Am	Amikacin
Amx/Clv	Amoxicillin/clavulanic acid
Cfx	Ciprofloxacin
Cm	Capreomycin
Cs	Cycloserine
GP	General Practice Medicine Office
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
DIP	Penitentiary Information Department
DMIS	Drug Management Information System
DOT	Directly Observed Therapy
DOTS	Directly Observed Therapy Short-course [WHO TB Control Strategy]
DOTS Plus	DOTS strategy for MDR-TB
DST	Drug Sensitivity Test
E&E	Bureau for Europe and Eurasia [USAID]
FDC	Fixed Dose Combination
FY	Fiscal Year
GFATM	The Global Fund to Fight AIDS, Tuberculosis & Malaria
IPP	Individual Patient Package
IPPS	Individual Patient Package Scheme
MDR-TB	Multi-Drug Resistant Tuberculosis
MOHSP	Ministry of Health and Social Protection
MOJ	Ministry of Justice
MOIA	Ministry of Internal Affairs
MSH	Management Sciences for Health
NTP	National Tuberculosis Control Program
PCU	Project Coordination Unit
PHC	Primary Health Care
PPI	Phtisio-Pneumology Institute “ <i>Chiril Draganiuc</i> ”
RPM Plus	Rational Pharmaceutical Management Plus Program [MSH]
SPCPHSM	Public Health and Sanitary Management Scientific Practical Center
SYMETA	TB/AIDS/STI Programs Monitoring and Evaluation System
TA	Technical Assistance
TB	Tuberculosis
TOT	Training of Trainers

USAID United States Agency for International Development
WHO World Health Organization
WG Working Group

BACKGROUND

By definition, Multi-Drug Resistant Tuberculosis (MDR-TB) patients have developed resistance to at least isoniazid and rifampicin, currently the most powerful anti-TB medicines. The number of multidrug-resistant tuberculosis cases in many parts of the world is increasing due to poor treatment, noncompliance of patients, and poor access to pharmaceuticals. Moreover, the growing incidence of HIV/AIDS is expected to further impact the increasing number of MDR-TB patients. If MDR-TB continues to spread, treatment costs will increase, additional global health resources will be required to combat TB, and patients will suffer for longer periods, or worse, die.

To confront this growing public health menace, the World Health Organization (WHO) and its partners have established the DOTS Plus strategy which provides technical support to countries and regions to build on existing DOTS programs (for primary TB). The WHO DOTS Plus strategy provides technical support through the Green Light Committee (GLC) and concessionary prices for second-line medicines needed to treat MDR-TB. Medicines to treat one MDR-TB patient can cost upwards of US\$ 10,000 or more per treatment if purchased on the open market. By purchasing through the GLC procurement agent, a country program can reduce costs to as little as US\$ 2,000 per patient.

Management Sciences for Health (MSH) and its Rational Pharmaceutical Management Plus Program (RPM Plus) are partners with the WHO Stop TB program and the GLC. One of the RPM Plus streams of activities is to provide support in pharmaceutical management of MDR-TB medicines in collaboration with the GLC and its partners.

In the coming years, 2007-2009, the Moldova National Tuberculosis Program (NTP), responsible for ensuring the continuous supply of drugs, plans to extend the number of multi-drug resistant tuberculosis (MDR-TB) patients to be treated within the DOTS Plus program from 200 patients to 600.

The Public Health drug distribution system will be used to supply prescribed medicines, augmented where necessary to ensure full and complete tracking of second-line anti-TB pharmaceuticals. The current DOTS Plus pilot project is being implemented according to the new distribution of second-line anti-TB - Individual Patient Package Scheme (IPPS). The purpose of the new scheme is to strengthen the drug management of the tuberculosis (TB) control program. The IPP scheme aims to individualize drug management required by each MDR-TB patient in both phases of treatment. The scheme is relevant for this pilot project which was predicted to recruit a small cohort of patients. Since the number of MDR-TB patients recruited will increase, the current IPP scheme of drug distribution will be updated to a sustainable model and thus continue to be implemented for MDR-TB patient treatment in the years to come.

Administrative division of the health system consists of 37 “raions,” or counties, including the Eastern Region (five “raions” and three towns) and the Chisinau and Balti municipalities. Strict recruitment criteria will be used to enroll patients on treatment with second-line drugs in the DOTS-Plus project.

Since 2002, RPM Plus has been providing technical assistance (TA) to the NTP concerning the drug management for DOTS and DOTS-Plus program. In collaboration with the NTP Manager, RPM Plus has drafted a management system for first- and second-line anti-TB drugs, which was used already for planning and distribution of the GDF drugs, and RPM Plus has worked to strengthen the capacity of the NTP through several workshops, the latest of which took place in May and June 2006.

For the period 2006-2007, RPM Plus and in-country partners, the Ministry of Health and Social Protection (MOHSP), the NTP and the Phtisio-Pneumology Institute “*Chiril Draganiuc*”(PPI) will be focused on strengthening the second-line drug management information system (DMIS) to support the extension of the DOTS Plus project in Moldova. For a better coordination of all activities undertaken in the information field to strengthen diagnosis, treatment and MDR-TB cases management, this new applicative for Drugs Management Information will be developed and harmonized with other DMIS initiatives like the SYMETA (TB/AIDS/STI Programs Monitoring and Evaluation System), which may be currently developed with other key stakeholders and supported by partners such as the GFATM.

Purpose of Trip

Activity monitoring and workplan definition with NTP and counterparts for implementation of a new MDR-TB information system (DMIS) for diagnostic, treatment case management, provision and distribution of second-line drugs.

Scope of Work

Scope of work for Joël Keravec is as follows:

- Introduction of Senior Program Associate, Joel Keravec to USAID and in-country partners
- Review progress with on-going activity for the management of first-line anti-TB medicines
- Activity review and workplan definition for further strengthening of the pharmaceutical management of MDR-TB
- Present and demonstrate RPM Plus second-line TB Drug Management Information System to the NTP
- Initiate discussion on current initiatives undertaken in the information field with counterparts and harmonize a program of activities to be supported with current funding from USAID for strengthening the national tuberculosis control program
- Establish a workplan for the implementation of the system in Moldova
- Brief/debrief the USAID Mission on the RPM Plus programming future planned funding with the USAID mission and counterparts in Moldova

During his visit, Dr Joel Keravec was accompanied by Rita Seicas, Pharmacist and RPM Plus local consultant (based in Chisinau, Moldova). Rita Seicas is currently providing technical assistance to the NTP in Moldova for this program.

ACTIVITIES

RPM Plus Senior Program Associate Joël Keravec and RPM Plus Pharmaceutical Consultant Rita Seicas met all stakeholders and counterparts involved in MDR-TB case management to review on-going activities and propose new activities for strengthening second-line TB drug management.

The detailed list of contacts met and the agenda of the meetings is presented in annex 1. The information presented below was obtained after extended discussions with Dr. Silviu Sofronie, Director of the Institute of Phtisio-pneumology “Chiril Draganiuc”(PPI), Dr. Dumitru Sain, NTP Coordinator, Liuba Nepoliuc, Chief of the MDR-TB ward at the PPI, Anghelina Djugostran, Chief of the Hospital Pharmacy, PPI, Dr. Victor Burinschi, TB/AIDS Coordinator, Mihai Ciocanu, Director of the Public Health and Sanitary Management Scientific Practical Center (SPCPHSM), Otilia Scutelnicu, Chief of the Monitoring and Evaluation Department for National Programs, Valeriu Plesca, IT Specialist of the SPCPHSM.

In July 2004 the NTP submitted application to the GLC for the DOTS-Plus project on MDR-TB. The DOTS Plan was to enroll 100 patients over one year which was approved by the GLC in March 2005. The diagnosis, treatment and follow-up of patients with drug resistant TB are free of charge in the DOTS Plus project. Funding was provided through a GFATM Round 1 grant.

A current application to the GLC is requesting the approval of another DOT Plus project covering 600 patients over a 3 year period, 2007-2009, and the expenses of diagnosis, treatment and follow-up, including ancillary tests and medications as well as incentives and enablers will be funded by grants from Rounds 1 and 6 of the GFATM.

The Government of Moldova will be covering the salaries of the staff and operational costs of the TB facilities. In addition, the government is partially covering the renovation costs for better infection control in the Vorniceni TB hospital.

The first 17 patients were enrolled in December 2005, and today a total of 92 patients have been enrolled with 82 patients from the civil services, mainly from Chisinau, and 10 from the penitentiary system. Exclusion criteria for enrollment are:

1. Patients who refuse MDR treatment;
2. Return after default and “old-chronic” patients¹
3. Patients with laboratory confirmed co-morbidities, which can be considered contra-indications for MDR-TB treatment (based on decision of the DOTS-Plus Recruitment Committee).

The patients are treated during the intensive phase in the Institute of Phtisio-pulmonology, where 30 beds are available for smear positive MDR-TB patients. An additional 16 beds are made available in another department of the same institute for smear negative MDR-TB cases. In the

¹ The new definition of “chronic” is a failure of Category II treatment whereas the previous definition of a “chronic” applied to a mixture of usually highly irregular patients. The previous definition will be applied.

penitentiary system there are separate rooms for MDR-TB patients in one of the departments of Pruncul Prison Hospital in Chisinau.

First patients started ambulatory treatment in June 2006. The direct observed therapy (DOT) is done 6 times per week in the primary health care system (PHC) or TB dispensary close to the home of the patient. Social support (food packages) is provided once per month. The doctors/nurses where DOT is practiced have received individual training as well as have attended a training course for management of MDR-TB patients. The patients are seen monthly by the coordinating TB doctor (2 sputum smear microcopies monthly, 1 culture and 1 DST every 2 months, 1 Chest X-ray every 6 months) and presented once per three months to the “DOTS-Plus Enrollment Committee” in the PPI.

Out of 92 enrolled:

- 24 are new MDR-TB patients: MDR-TB patients who have never received anti-TB treatment, or who have received anti-TB treatment less than one month
- 59 are MDR-TB patients treated previously only with first-line anti-TB drugs: MDR-TB patients who were previously treated for one month or longer only with first-line anti-TB drugs
- 9 are MDR-TB patients treated previously with second-line anti-TB drugs: MDR-TB patients who were previously treated for one month or longer with at least one second-line anti-TB drug (with or without first-line anti-TB drugs)

As of now, one never previously treated patient defaulted within the first 3 months and the other had severe side effects (hepatotoxicity) and had to discontinue treatment.

In May 2006 the GLC monitoring mission found the progress of the DOTS-Plus pilot project satisfactory and recommended expansion of the project to 1300 patients (approximately 350 diagnosed per year with a 600 backlog needing treatment) over 3 years, including MDR-TB and polyresistant cases. The National Tuberculosis Program (NTP) is currently finalizing its second application for this DOTS Plus project extension.

The monitoring and evaluation of the National Program for TB control by the Ministry of Health and Social Protection (MOHSP) and NTP with the support of international partners is being implemented through the system SYMETA. A more detailed description on second-line drugs management issues is presented in annex 2.

The current practice of data collection concerning MDR-TB patients is based on a systematic data collection providing general data on recruited MDR-TB patients, previous history of treatment, and current status as well as laboratory data. However, information on drug management is not included in this system. Data on second-line anti-TB drug management is collected and maintained at different departments (pharmacy level, monitoring and evaluation department, warehouse, etc.), but it is not integrated in one system, which would be useful for the Public Health and Sanitary Management Scientific Practical Center. To respond to NTP and MOHSP needs, RPM Plus technical assistance will be focusing on developing a specific module for a Drug Management Information System (DMIS) which will be able to provide basic data and reports on all aspects of management of Multi-drug Tuberculosis at all levels.

During meetings with Moldovan counterparts, RPM Plus Senior Program Associate Joël Keravec presented and discussed the DMIS currently used in Brazil, where RPM Plus has recently developed, field tested, and implemented a comprehensive drug management information system for improving diagnosis, treatment, and management of MDR-TB cases.

The DMIS consists of a computer application accessible through the Internet which could be used by designated “raion” level MDR-TB reference centers or local treatment facility to register new patients and regularly report on case management throughout the treatment course. The monitoring of medicine stocks is incorporated within the system, allowing the central administration of the program to track existing quantities of drugs, quantities consumed, and quantities needed for the next re-order period.

Following the discussions with key stakeholders involved in the implementation of DOTS Plus strategy along with the visit of the MSH RPM Plus Technical Assistance in Moldova, it was decided to form a Working Group (WG) to build on the Brazilian experience and adapt this logical framework to the Moldovan context for MDR-TB drug management.

The purpose of the WG is to:

- coordinate the development and implementation of DMIS for MDR-TB,
- rationalize and optimize all counterparts initiatives and efforts undertaken in the TB information field
- avoid duplication/conflicts in the strategies to be followed and in the information templates used for data collection and regular reporting on first-line TB and MDR-TB.

Key Objectives of WG:

- **Strategic objective:** Develop and implement an appropriate Drug Management Information Systems for MDR-TB drugs management.
- **Technical objectives:**
 - Optimize the current MDR-TB notification system
 - Define and test a model of MDR-TB health surveillance for patient management and appropriate data transfer at all levels (NTP, MOHSP, raions, reference centers)
 - Maintain a MDR-TB case management data base at central level
 - Define follow-up indicators for case management and standardized epidemiological and operational reports
 - Provide data for monitoring and operations research
 - Record and store data on distribution and use of medicines

Scope of work of WG

- Evaluate diagnostic procedures, standard treatment guidelines (STGs) and practices for MDR-TB patient management

- Revise diagnostic, STGs, notification procedures and practices for MDR-TB case management
- Examine the current practice of data collection
- Identify needs of the NTP and MOHSP for the new DMIS
- Develop data sheets for patient follow-up
- Define information flows and indicators for monitoring and standardized reporting
- Develop a DMIS logical framework for MDR-TB patient management harmonized with existing public health surveillance systems
- Undertake training workshops to implement the new model of MDR-TB patient management

Composition of Working Group:

- WG is a multidisciplinary group whose members are representatives of the organizations and institutions from different levels of the public and non-governmental sectors involved in implementation of the DOTS Plus strategy.
- Members of the WG are:
 1. **Liviu Vovc**, Chief of the General Department of the MOHSP
 2. **Mihai Ciocanu**, Director, Public Health and Sanitary Management Scientific Practical Center
 3. **Otilia Scutelnicuic**, Chief, Monitoring and Evaluation of the National Program Department, Public Health and Sanitary Management Scientific Practical Center
 4. **Valeriu Plesca**, IT specialist, Monitoring and Evaluation of the National Program Department, Public Health and Sanitary Management Scientific Practical Center
 5. **Silviu Sofronie**, Director, PPI (Phtisio-Pneumology Institute “*Chiril Draganiuc*”)
 6. **Dumitru Sain**, NTP coordinator
 7. **Victoria Vulpe**, TB specialist, Drug Management team, Phtisio-Pneumology Institute “*Chiril Draganiuc*”
 8. **Liubovi Nepoliuc**, Chief, MDR-TB ward, PPI Ftiziopneumology Institute “*Chiril Draganiuc*”
 9. **Moraru Nicolae**, Chief, NRL, Ftiziopneumology Institute “*Chiril Draganiuc*”
 10. **Victor Burinschi**, TB/AIDS Coordinator PCU “TB/AIDS Program”
 11. **Rita Seicaș**, Consultant, Management Science for Health
 12. **Joël Keravec**, Senior Program Associate, Management Science for Health
 13. **Viorel Soltan**, Director of the project, American International Health Alliance (AIHA)
 14. **Valeriu Crudu**, Laboratory and surveillance specialist, AIHA

Other participants may be invited to the team’s meetings as needed.

Matrix of Responsibilities - Role of members:

Representatives of MOHSP

- Follow-up for all steps of the development of the DMIS in close collaboration with the WG coordinator, RPM Plus
- Approve all modules for the newly developed DMIS and all drug management procedures
- Validate the strategies for DMIS use at all levels and validate all training materials
- Coordinate the implementation of the system at all levels

Representatives of the Institute of Phthisiopneumology “Chiril Draganiuc” and Coordinators of DOTS Plus project

- Evaluate diagnosis, standard treatment guidelines (STGs) and practices for MDR-TB patient management
- Revise diagnosis, STGs and practices for MDR-TB patient management and notification
- Defining the necessity of the DMIS according to the recommendations of GLC, WHO and other international partners
- Revise the current system of data collection bases of MDR-TB
- Determine the needed data focusing on all aspects of the management of MDR-TB: Diagnosis, Recruitment, Treatment, Laboratory management, Drug supply management, Reports
- Define indicators and reports formats for management of MDR-TB
- Develop data collection and reporting flow
- Contribute to the development and validation of the training materials
- Monitor implementation of the new DMIS
- Maintain and update the system with data

Representatives of the Scientific Practice Center of Public Health and Sanitary Management

- Examine draft model of software for management of MDR-TB Patients
- Evaluate the compatibility with needs of the NTP and MOHSP
- Evaluate the possibility of integration with the current system for TB-SYMETA
- Develop Terms of Reference for updating and integration of MDR-TB software with SYMETA
- Coordinate the development of updated MDR-TB software
- Coordinate approval and implementation of updated MDR-TB software
- Develop training materials
- Conduct training for beneficiaries

AIHA:

- Provide technical assistance in updating and integration of MDR-TB software with SYMETA
- Support development of Laboratory data management component
- Support development of training materials
- Support in conducting trainings

PCU “TB/AIDS Program”

- Provide assistance for development and implementation of new MDR-TB software
- Support in maintaining the DMIS
- Support in developing training materials

RPM Plus - MSH

- Coordinate and facilitate the activity of the WG for all steps needed by the program
- Define and monitor workplans and activities
- Provide a model software for management of MDR-TB Patients
- Provide support in updating and integrating MDR-TB software with current systems
- Provide assistance in elaboration of drug management component
- Coordinate development of the DMIS
- Support development of training materials
- Support in conducting training

Collaborators and Partners

- **Liviu Vovc**, Chief of the General Department of the MOHSP
- **Mihai Ciocanu**, Director, Scientific Practical Center of Public Health and Sanitary Management
- **Otilia Scutelnicuic**, Chief, Monitoring and Evaluation of the National Program Department, Scientific Practical Center of Public Health and Sanitary Management
- **Valeriu Plesca**, IT specialist Monitoring and Evaluation of the National Program Department, Scientific Practical Center of Public Health and Sanitary Management
- **Silviu Sofronie**, Director, Ftiziopneumology Institute “*Chiril Draganiuc*”
- **Dumitru Sain**, NTP coordinator
- **Victoria Vulpe**, TB specialist, Drug Management team, Ftiziopneumology Institute “*Chiril Draganiuc*”
- **Liubovi Nepoliuc**, Chief, MDRTB ward, Ftiziopneumology Institute “*Chiril Draganiuc*”
- **Moraru Nicolae**, Chief, NRL, Ftiziopneumology Institute “*Chiril Draganiuc*”
- **Victor Burinschi**, TB/AIDS Coordinator PCU “TB/AIDS Program”
- **Viorel Soltan**, Director of the project, American International Health Alliance (AIHA)
- **Valeriu Crudu**, Laboratory and surveillance specialist, AIHA
- **Rita Seicaș**, Consultant, MSH
- **Joël Keravec**, Senior Program Associate, Management Science for Health

NEXT STEPS

Immediate Follow-up Activities

1. Officially nominate the members of the WG with all local counterparts (the principle responsibilities of the WG have been fully accepted by all stakeholders including the NTP and MoHSP)
2. Organize the first meeting of the WG according to the Scope of Work presented in this report
3. Follow-up on RPM Plus proposed DMIS model to study relevance of templates, harmonize with current templates in use and translate data collection tools
4. Test the RPM Plus DMIS model by designing a new data base in Romanian language first and upload it to the Web for access by local counterparts

Recommendations

To gain time on scheduled activities, RPM Plus suggests to articulate a task force using the current developers who were responsible for the design and realization of the DMIS in Brazil with the local technical counterparts and Moldovan developers already involved in the SYMETA project for better efficiency in the development process.

Agreement or Understandings with Counterparts

The principle responsibilities of the WG have been fully accepted by all stakeholders for the implementation steps of the new DMIS for second-line TB drug management. According to the WG scope of work, institutional agreements have been assured for the continuation of the workplan, in accordance with the defined strategic and technical objectives.

Important Upcoming Activities or Benchmarks in Program

RPM Plus is also providing support to the Romania NTP for strengthening second-line drug management on a GLC approved project. Both Romania and Moldova programs and workplans will benefit from all activities and synergies carried out in the region, especially during the design and testing phases of the new DMIS in the Romanian language.

ANNEX 1: AGENDA

Management Sciences for Health Rational Pharmaceutical Program Plus

Mission to Moldova – Final Agenda June 14-16, 2006

Participants:

Dr. Joël Keravec *Senior Program Associate, Management Sciences for Health/RPM Plus*
Ph. Rita Seicas, *Consultant, Management Sciences for Health /RPM Plus, Moldova.*

<i>June 15, Thursday</i>		
<i>Institution, program</i>	<i>Name and position</i>	<i>Suggested duration- Topics discussed</i>
NTP Institute of Phthisiopneumology “Chiril Draganiuc”	Dr. Silviu Sofronie, Director Dr. Dumitru Sain, NTP Coordinator Liuba Nepoliuc Chief of the MDR-TB ward	09.30 -2.20.00 p.m. Briefing Presentation of RPM Plus DMIS Evaluation of the relevance of the DMIS model in the Moldova context Strategic discussion for workplans and activities First conclusions and next steps for stakeholders support and participation to the WG
Institute of Phthisiopneumology “Chiril Draganiuc”	Anghelina Djugostran Chief of the Hospital Pharmacy	02.50.-03.40pm Presentation of RPM Plus DMIS Current practice of DMIS
USAID Mission Chisinau Office	Diana Cazacu Project Management Assistant,	04.30-05.00 pm Briefing-debriefing Strategic discussion for workplans and activities on RPM Plus continuing support for strengthening 2 nd line drugs management RPM Plus programming future planned funding with the USAID mission and counterparts in Moldova

June 16, Friday

<i>Institution, program</i>	<i>Name and position</i>	<i>Suggested duration</i>
PCU “TB/AIDS Program”	Victor Burinschi TB/AIDS Coordinator	8.45 -9.45 a.m. Presentation of RPM Plus DMIS Evaluation of the relevance of the DMIS model in the Moldova
Scientific Practical Center of Public Health and Sanitary Management	Mihai Ciocanu Director Otilia Scutelnicuic Chief National Programs Monitoring and Evaluation Department Valeriu Plesca Specialist IT	10.10-12.30 a.m. Presentation of RPM Plus DMIS Evaluation of the relevance of the DMIS model in the Moldova and integration with SYMETA
NTP	Dr. Dumitru Sain, NTP Coordinator	12.50 -01.30 p.m. Final debriefing on mission and conclusions and next steps for stakeholders support and participation to the WG

ANNEX 2: TB AND MDR-TB DRUGS MANAGEMENT CONTEXT IN MOLDOVA ¹

¹ *Source:* Draft for the second application to the GLC for DOTS plus project extension, *NTP*

I. General Background for TB and MDR-TB in Moldova

The Republic of Moldova is landlocked and is bordered by Romania to the west and Ukraine to the north, east and south. As of January 1, 2006 the population consisted of 3.9 million people. Official net migration rate is –0.23 per 1000 population, but it is estimated that migrant workers constitute as much as 10% of the total population or as much as 25% of the adult population (≥ 15 years). The actual figure may be even higher. Migrant workers, males and females, primarily go to Russia, Germany, Italy, Portugal, Spain, and Israel.

The country covers a territory of 33.7 thousand km² and is administratively divided into 32 “raions,” three municipalities (Balti, Bender and Chisinau), Gagauzia autonomous territorial unit and 1 territorial unit Transnistria. The decentralized “raion” structure was adopted in 2001 and implemented in 2003 replacing the former more centralized structure based on “judets.”

The anti-TB drugs were freely available on the open market until 2002 after which the centralized drug procurement limited the opportunities to sell anti-TB drugs because they were available for patients without any charge. In 2005 the government passed a law prohibiting the sale of anti-TB drugs. Currently, first-line anti-TB drugs are available only through the NTP. Some of the second-line anti-TB drugs such as aminoglycosides and fluoroquinolones are available by prescription from a doctor in the pharmacies.

1) TB related Health System Structure:

TB services are free of charge for all patients.

The health care system in Moldova is divided into three levels:

- Republican institutions at the national level;
- Raion and municipal institutions at the intermediate level;
- Primary health care (PHC) at the local level.

Most services are governmental along with some private specialty services, clinical laboratories, and a private pharmacy sector.

In 2005 the PHC sector consisted of 48 PHC centers, 383 health centers, 554 General Practice offices (GP) and 329 medical units. The number of GPs in Moldova in 2005 was 6000, up from 2136 in 2001. The number of nurses is somewhat higher. The number of GPs is estimated to cover 90% of requirements and the number of nurses 92% of requirements.

2) Main particularities of TB Health Services Organization:

Tuberculosis control is integrated into the overall health system, with PHC services, Phtisiology and Pneumology services, the *Center for Preventive Medicine*, the *Center for Public Health and Sanitary Management*, and the *Phtisio-pneumology Institute “Chiril Draganiuc”* (PPI) in Chisinau which has principal responsibility and houses the central Unit of the NTP. The current National Program on Prophylaxis and Control of Tuberculosis was approved by the government in December 2005 for four years, 2006-2010 (*Decision of the Government of Republic of Moldova No. 1409; 30 December, 2005*).

The NTP uses a multi-sectoral approach involving the Ministry of Health and Social Protection, (MOHSP), the Ministry of Justice (MOJ), and the Ministry of Internal Affairs (MOIA) and collaborates with nongovernmental organizations (NGOs) and international partners.

The NTP is responsible for inter-sectoral and within-sectoral coordination of the TB control activities on all levels and clinical management of TB cases. Diagnosis and treatment of TB is done at the federal level (PPI), rayon, municipality, and primary care levels. The PHC system and general hospitals refer patients to the specialized TB service.

Epidemiologists, working in the Center for Preventive Medicine, are responsible for contact tracing and infection control and cooperating closely with the PHC and TB services.

The unified surveillance system, SYMETA, managed by the *Center for Public Health and Sanitary Management* oversees the reporting and recording of infectious diseases, including TB. The Monitoring Unit of the NTP Central Unit is closely cooperating with the SYMETA.

A person with signs and/or symptoms of TB is exempted from payment at the peripheral level, i.e. for consultation, acid-fast bacilli (AFB) microscopy, and x-ray examination. A payment is requested from the patient for additional examinations such as tomography, bronchoscopy, etc, if these are indicated. When a patient has been diagnosed with TB, treatment and follow-up are free of charge except that it has not been possible to guarantee treatment with second-line drugs for all patients in need. The international partners are covering the cost of culture and drug susceptibility testing (DST) through the GFATM grant.

Private sector is underdeveloped as of now and does not participate in TB control. Only few services are private, such as some specialty services, clinical laboratories, and a private pharmacy sector.

Ministry of Internal Affairs. The Ministry of Internal Affairs (MOIA) has its own staff. A doctor, who functions as a TB coordinator, is stationed at the MOIA, and 17 TB nurses stationed at police stations are involved in case finding and continuity of anti-TB treatment on arrest and after release from custody. There is a plan to increase the number of nurses to 32. TB cases from this sector are managed by MOHSP services.

Security Forces and Railway workers. Security Forces and Railway workers have access to special health facilities, but when found to be suspect for tuberculosis, are referred to the phtisio-pulmonologist.

Medical service in the Army. The army has its own medical services. When a conscript is found to have tuberculosis he will be discharged from the service and is referred to the phtisio-pulmonologist.

3) First Line Treatment Regimen and Procurement:

Empiric treatment regimen in new pulmonary and extrapulmonary TB cases (Category I) is a four-drug combination of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) administered on a daily basis in the intensive phase (in exceptional cases, intermittently three times per week). In cases of adverse reactions to Ethambutol, Streptomycin (S) is substituted for E.

As a rule, treatment in the intensive phase is delivered in the hospital. Exceptions to this are allowed for patients preferring ambulatory treatment. In this case, a health worker administers the direct observed therapy (DOT) at a health facility close to the patient's home. This is done in coordination with the corresponding raion health center.

The intensive phase of treatment is prolonged for a third month if smear conversion has not occurred at the end of two months. The continuation phase of treatment consists of RH administered on an ambulatory basis three times per week, with a total duration of treatment of six months.

S, as the fifth drug, is added in the intensive phase in cases classified as retreatment (Category II) and the treatment is prolonged, with a total duration of treatment of eight months.

Category 1 and Category 2 treatment regimes are consistent with the International Standards for Tuberculosis Care. FDC (H/R) is used from 2001. 100% of R use is in FDCs.

The culture and DST are done for all smear positive and smear negative cases from 2006. In case of multi-drug resistance or polyresistance the case is assessed for possible enrollment in the DOTS-Plus project for second-line treatment.

4) *Laboratory network:*

The TB laboratory network is developed based on the population to be served and geographical characteristics. It consists of 57 microscopy centers (level I), 3 Regional Reference Laboratories (RRL) (level II), and one National Reference Laboratories NRL (level III).

The microscopy centers are attached to TB cabinets, equipped with modern microscopes, and serve a population of 50,000 to 100,000 (average 77,000). The tasks of the microscopy centers are: reception of pathological specimens containing Mycobacterium tuberculosis (MBT), smear preparation, Ziehl-Nielsen (ZN) staining, microscopy investigation of TB symptomatic and TB patients during the continuation phase of treatment.

The microscopy centers participate in quality control of microscopy investigation, both internal and external (Lot Quality Assurance System –LQAS).

The RRLs are located in the TB departments and Republican TB Hospitals and serve territories with populations of about 1 million each. Their tasks are microscopy investigation, isolation and identification of *M.tuberculosis complex* by culture investigation, DST for first-line drugs; and quality control of microscopy centers.

The RRLs in Balti, Bender, and Vorniceni perform AFB microscopy, culture, and DST on first-line drugs, and participate in QA for culture and DST investigation.

The NRL is located at the PPI and functions as the coordinating body for the microbiological service for TB diagnosis. Its tasks are microscopy investigation; isolation and identification of *M.tuberculosis complex*; DST of MBT cultures for first- and second-line drugs; training of laboratory network staff; internal quality control of microscopy, culture, and DST; participating in elaboration of legislative decrees; standardization of laboratory methods; epidemiological survey of anti-TB drug resistance; and external quality control of MBT DST.

As the designated NRL, the Chisinau laboratory is the only laboratory performing DST on second-line drugs in Moldova.

Penitentiary system. There are 4 for smear microscopy labs within the penitentiary system (including Transnistria). In addition the labs in civil services, close to the prison, provide services for the smear microscopy. Culture and DST are performed in the NRL.

In December 2005, an official relationship was established with the Reference Center for Mycobacteria, Forschungszentrum in Borstel, Germany, to serve as the Supra-National Reference Laboratory (SNRL) for Moldova.

Quality control procedures have been initiated with an exchange of a panel of 20 strains between the NRL and the SNRL. Every quarter, the NRL from Chisinau sends a panel of 20 strains of *M.tuberculosis* for quality control procedures in SNRL, Borstel.

With funding and technical assistance from USAID/AIHA and GFATM, the RRLs and NRL facilities were renovated and equipped with modern bio-safety cabinets, centrifuges, incubators, refrigerators, and a BACTEC/MGIT.

Training of key laboratory personnel -Training of Trainers (TOT) - was conducted at the WHO Center of Excellence in Latvia in September 2004, followed by training of 35% of laboratory staff in the network.

5) DOTS coverage and patients adherence to treatment:

DOT is done in all hospitals daily throughout the stay (during the intensive phase). It is estimated that nearly 60% of the patients receive DOT in the continuation phase on an ambulatory basis, close to their home. Patients who do not receive fully supervised therapy in the continuation phase attend a health facility once per week. DOT cabinets are attached to microscopy centers or outpatient departments.

The tracing of defaulters is done by the PHC in cooperation with TB services. In case a patient is receiving DOT three times per week in the ambulatory phase and does not turn up 2 times, the health care worker is making an effort to find the patient by using the information received before regarding his/her habits, place of living, friends, relatives, etc. The HCW is calling the home of the patient or going there if needed. Due to high migration to neighboring countries (labor migrants) the defaulter is often connected with temporary migration. In these cases it is almost impossible to find the case.

6) TB and MDR-TB Epidemiological Data:

With a deterioration in socio-economic conditions and inadequate financing of disease control, the number of notified TB cases increased sharply in Moldova from 1990-2000. In late 2001, Moldova adopted the WHO-recommended DOTS strategy and rapidly expanded DOTS to cover the entire country by January 2004. Moldova has undertaken a concerted effort in controlling TB in recent years, instituting international standards and strengthening diagnosis, treatment, surveillance, and public communications for TB. *Please see Table 1 Indicators of TB control in Moldova, 1998-2005*

Table 1. Indicators of TB control in Moldova, 1998-2005

N	Indicators	1998	1999	2000	2001	2002	2003	2004	2005
1	Notification rate, per 100000 population	67	68,6	68,5	89,4	97,3	108,4	121,7	133,4
2	Incidence new cases, per 100000 population	59,2	61,8	59,7	80,0	80,5	85,7	93,1	107,3
3	Incidence bacillary forms, per 100000 population	17,3	17,8	19,5	27,6	29,5	30,1	37,3	42,2
4	Mortality rate, per 100000 population	11,4	15,5	17,2	15,5	15,6	16,9	17,1	19,1

Beginning in 2001, a break in the previous stable plateau in notified cases with a yearly progressive increase during 2001-2005 occurred, probably due to increased DOTS coverage and the rise in health care seeking behavior of the population. There was a larger increase in new cases notified in rural areas than in urban areas and the rate per 100,000 population in rural areas is approaching the rate in urban areas. This is due to the intensification of case finding in rural areas as DOTS was expanded and new regulations concerning the national insurance system and primary health care (PHC) were put into effect under Order 180, issued in August 2001.

In 2005, 5,632 “new cases” and “relapses” of TB were notified in the civil and prison sectors, which means a 9.3% increase from 2004 (5,154). This comes up to 133.4 cases per 100,000 population versus 121.7 per 100,000 population in 2004.

During the same period, new cases increased from 3,941 to 4,518 and the rate per 100,000 population increased from 93.1 to 107. Increase in the incidence rate was higher than in case notification rate (14.9% versus 9.6%), which is probably due to the improved detection and treatment during recent years.

Among new cases, the male to female ratio was 2.7 in 2005. The increase in cases is faster for males than for females. Adults over age 18 comprised 94% of new cases in 2005, increasing from 91% in 2004.

The reservoir of relapse cases is diminishing as drug supply shortages and inadequate treatment of the previous 5-10 years is being reversed. At the same time, capacity for diagnosis and surveillance are improving, resulting in higher numbers of cases notified and started on treatment.

According to WHO, case detection increased by nearly 50% between 2003 and 2004. In 2003, only 39% of new smear positive cases were being detected, increasing to 59% in 2004. Although this rate is below the global target of 70%, the increase is an indication of the success of interventions in enhancing diagnostic infrastructure and skills, raising public awareness, and revamping recording and reporting systems.

MDR-TB

The resistance to anti-TB drugs is worryingly high in the country. According to the data from the National Reference Lab (NRL), multi-drug resistance in never previously treated patients has risen from 5.0% in 2000 to 9.9 % and in previously treated cases from 33.2% to 38.6 %. If the prison system is included the drug resistance among never previously treated was as high as 12.7% and in previously treated cases from 41.4% in 2004. Total resistance was 28.5% and any resistance in never previously treated cases was 24.9% and in previously treated cases 53.7%.

Prison

Prisoners are the most severely affected by TB. In 2005, the case notification rate for new cases was a staggering 1,902.9 (1,020 cases) per 100,000, nearly 18 times the countrywide rate. Currently about 13% of patients with active TB are having MDR-TB in penitentiary system. To address this significant part of the epidemic, the National Program on Prophylaxis and Control of Tuberculosis for 2006-2010 calls for strengthening diagnosis and treatment and improving detention and maintenance conditions in penitentiaries.

7) Procurement and, Storage and Distribution for First Line Drugs:

A three-year GDF grant guaranteed drug supply for the DOTS program for the years 2001 – 2004. A sound drug management system has been established within the NTP. First-line anti-TB drugs are stored in the semi-governmental agency, “San Farm Prim,” and distributed on a quarterly basis, based on the

case notification. Even though the GDF funding for drugs has ended in 2004, the republic has started direct procurement from the GDF (2005 and 2006).

The funds needed for procurement of first- and second-line anti-TB drugs for the entire country, including Transnistria and the penitentiary system, are requested from the GFATM Round 6 for the years 2008 – 2012. A recent GDF monitoring report (March 2006) recommended that NTP increase the buffer stock from 50% to 100% of requirements.

The Government is expected to increasingly take over the responsibility of financing first-line drugs for the NTP.

There have been neither stock-outs nor distribution problems within the last 3 years in Moldova.

The private market for anti-TB drugs is virtually non-existent in Moldova. The government has passed a law prohibiting the sale of anti-TB drugs on the open market in the country in 2005. The first-line anti-TB drugs are available only through the NTP. Some of the second-line anti-TB drugs are available (specifically aminoglycosides and fluoroquinolones) by prescription of a doctor in the pharmacies.

II. Second line TB Drugs Management for MDR-TB in Moldova

1. National Context for MDR-TB Drug management:

Treatment of MDR-TB patients will be ensured by health facilities at two levels:

1. The *intensive phase* will be undertaken at the:

1. Public Health Facilities Ftiziopneumology Institute, MDR-TB wards of the Clinic nr.1 from Chisinau (with 50 beds) and Clinic nr. 2 from Vorniceni (with 80 beds);
2. Public Health Facilities Ftiziopneumology Municipality Hospital from Chisinau, MDR-TB wards (with 25 beds);
3. Penitentiary Wide Profile Republican Hospital Pruncul MDR-TB wards (with 50 beds) (both phases of treatment).

2. The *continuous phase* will be provided at the TB ambulatory facility with the support of primary health care for those outpatients that are in the rural area, with strong monitoring of the TB coordinators from the rayon. Distribution of drugs for outpatients will be done by the pharmacy of the Ftiziopneumology Institute from Chisinau.

Drugs from the San Farm Prim will be distributed every two months to the pharmacy, based on approval of the NTP.

GLC procured products will be labeled distinctively (or uniquely) to facilitate their control by the use of pre-printed, adhesive labels (or a specially designed ink stamp).

The non-governmental organization Management Sciences for Health (MSH), with an external consultant and a local consultant in Chisinau, has advised the NTP concerning the drug management for DOTS and DOTS-Plus program. MSH, in collaboration with the NTP Manager, has drafted a management system

for first- and second-line anti-TB drugs, which was used already for planning and distribution of the GDF drugs.

To strengthen the capacity of the NTP several trainings on drug management, with international participation were organized (in 2004) jointly with MSH and the NTP. The NTP and MSH provided local training in drug management of second-line drugs for the DOTS Plus Project in May and June 2006.

2. Treatment regimens:

The treatment scheme for the next cohorts will be based on the standard regimen, with the same pharmaceutical products which were in the treatment regimen for the first cohort, namely: Capreomycin, Ethionamide, Ofloxacin, Cycloserine and Pyrazinamide.

The total length of treatment is 24 months, in which the intensive phase consists of 6 months and the continuous phase is for 18 months. The treatment scheme for the intensive phase is based on 5 drugs, while the continuous phase is based on 4 drugs (excludes Capreomycin injection from the continuation phase).

Para-aminosalicylic acid (PAS) will be used as a reserve drug in case of severe adverse reactions or absolute contra-indications.

Quantities for full treatment for one patient (7Cm6(O-Et-Cs-Z)(PASER)/18 O-Et-Cs-Z(PASER) (maximum weights used):

	Unit (mg, tab, cap)	Daily doses	Days intensive phase	Days continuous phase	Total days of treatment	Total units	Price/unit	Cost/Rx
Capreomycin	1000	1	196	0	196	196	3,68	721,28
Ofloxacin	200	4	168	504	672	2688	0,046	123,65
Ethionamide	250	3	168	504	672	2016	0,102	205,63
Cycloserine	250	3	168	504	672	2016	0,525	1058,40
Pyrazinamide	500	4	168	504	672	2688	0,013	34,94
Total								2143.90

3. Procurement of drugs:

The Ministry of Health and Social Protection (MOHSP) will procure these drugs through the grant from the Global Fund to Fight AIDS, TB and Malaria (GFTAM), with the approval of the Green Light Committee (GLC) mechanism.

The estimated quantity is based on a number of predicted MDR-TB patients for treatment and approved treatment regimen. The 2007-2009 orders were included in the estimation as well as the 10 % of buffer stock.

The quality of second-line drugs for the DOTS-Plus project will be assured through procurement process of the International Agency selected and approved by the GLC to supply drugs and by usual, mandatory, testing on arrival of the consignment in Moldova by the Drug Quality Control Laboratory of the

Medicines Agency. Existing storage capacity and practices in the health system will ensure that the quality does not deteriorate during the period between receipt by the NTP and consumption by the patient.

Drugs for supportive or ancillary therapy for MDR-TB patients will be provided through the budget of the MOHSP and the local budget of health facilities.

4. Drug registration:

The leading role in import and registration of the drugs in Moldova is with the Medicines Agency (MA) formed in 2005 (Government Decision Nr.617 from 28 June 2005 “Strengthen the pharmaceutical situation in the R. Moldova”). The main purpose of the MA is to implement the state drugs policy and coordinate and control pharmaceutical activities.

The main activities include:

- Marketing authorization (evaluation, homologation and registration) of drugs;
- Supervise the drugs quality;
- Supervise and control over pharmaceutical activities;
- Monitoring and coordination of drug supply and pharmaceutical assistance at the national level;
- Regulation of the field of medicinal products and pharmaceutical activities;
- Information on drugs;
- Methodic and organizational activities and consultation of the pharmaceutical units.

According to the Law, the MA is prohibited from using drugs, pharmaceuticals and medical supplies without the authorization of the Ministry of Health and Social Protection. The authorization of drugs is carried out in the order of the following priorities:

- essential and/or vital necessary drugs, according to the list approved by the MHSP;
- drugs elaborated according to GLP and GCP, products according to GMP and registered by US Food and Drug Administration (FDA), European Medicines Evaluation Agency (EMA) or Collaborator Agreement of Drug Regulatory Authorities of European Associated Countries (CADREAC);
- drugs authorized in at least three neighboring countries of the Republic of Moldova;
- drugs manufactured observing the rules of GMP and authorized in at least three countries.

The procedure of authorization for the essential, generic, important drugs is the same.

Registration of anti-TB drugs is based on requirements of the regulations in the marketing authorization of medicinal products with technical advice by specialist from NTP and IPP. The Registration Certificate is valid for 5 years from the date of issue by the Medicine Agency and can be renewed after this period at the request of its holder. *Please see the Annex 3. List of second-line anti-TB drugs registered in Moldova.*

5. Importation and Customs Clearance:

The MOHSP and Project Coordination Unit will enter into an agreement with the para-statal importer/distributor, San Farm Prim, to handle the importation of the second-line drug consignment, convey the consignment to the San Farm Prim warehouse in Chisinau, arrange quality testing, and store the drugs. San Farm Prim has been managing the importation and issue of the GDF first-line anti-TB drugs on behalf of the NTP. The San Farm Prim also manages the importation, storage, and issue of first- and second-line anti-TB drugs procured by the Project Coordination Unit (PCU), funded by GFTAM.

The San Farm Prim is therefore fully conversant with governmental requirements and procedures. Any customs charges will be financed by the Government or waived.

The main stock will be kept by the para-statal importer/distributor San Farm Prim. The San Farm Prim will release drugs following the official decision of the MOHSP and NTP.

The supply is based on data from registered cases in the DOTS Plus program. Following recent reports on drug management, the supply will be adjusted according to the real needs of health facilities.

According to the provisions of the Law of pharmaceutical activity all drugs should be registered in the country. In special cases (cataclysms, catastrophes, epidemics, epizooties, systemic poisoning, other cases that threaten the health of people, absence of analogues or substitutes on the pharmaceutical market, and in case if drugs are requested for clinical study), the Ministry of Health and Social Protection may authorize the drug import from other countries into the Republic of Moldova and issue drugs to population and medical-sanitary institutions, not registered in the country but registered in the country of origin.

Of the 25 products listed in the GLC Product Information Sheets¹, as available through the GLC mechanism, those currently registered in Moldova are listed at the end of this annex. As explained above, in case a drug is needed which is not registered, this situation will be managed by the MOHSP through the convocation of a Commission for the authorization to import unregistered drugs (to issue a special authorization for the importation of vital unregistered drugs needed for health programs). This arrangement is in line with steps undertaken by the MOHSP in order to import drugs for first-line treatment of TB for the DOTS program and second-line drugs for DOTS Plus pilot project funded by GFATM.

6. Central storage and transfer of stock to health facilities:

The second line anti-TB drugs are stored in the PPI pharmacy and dispensed to the PPI MDR-TB ward on a weekly basis and to those peripheral units managing individual patients in continuation phase on a quarterly basis. For the continuation phase the drugs are pre-packed by patient and released only on authorization of the coordinator of the DOTS-plus project.

Drugs will be stocked at the pharmacy according to the principles of the drug storage instruction. Separate records in the pharmacy stock register will be maintained for the GLC sourced second-line drugs to document receipts, issues to the MDR department and other TB cabinets, stock levels, and facilitate reporting to the Drug Management Team (DMT) of the NTP. Specifically, each two months, reports will be prepared by the pharmacists and submitted to the Coordinator of DOTS-plus Project and chief of the Drug Management Team indicating current stocks, quantities issued (to recipient department and “rayon”), expiry dates, etc. These reports will be reviewed in conjunction with patient records to validate the movement of stock.

7. Delivery to Patient and Use:

¹ Procurement Manual for the DOTS-Plus Projects Approved by the Green Light Committee (WHO/HTM/TB/2003.328), WHO, October 2003.

All doses are given supervised for MDR-TB cases. The incentives and enablers scheme (food packages and reimbursement of transportation in amount of 30 USD per month) is supporting the MDR-TB patients to adhere to the treatment. The funds for this are available in the GFATM grant.

Treatment of the intensive phase for all cases in the cohorts will take place within the MDR-TB departments of the TB Ftiziopneumology Institute, Clinic no.1 from Chisinau and Clinic no. 2 from Vorniceni; Ftiziopneumology Municipality Hospital from Chisinau; and Penitentiary Wide Profile Republican Hospital Pruncul.

When the MDR-TB patients are discharged from the hospital the information is forwarded from the PPI to the ambulatory or polyclinic setting (and vice versa if necessary) using the current NTP form (TB09). The personnel in ambulatory settings have received overall training in treatment adherence within the current DOTS-Plus project. In addition case-by-case practical training is provided to the person, who will be providing DOT to the MDR-TB patient.

Issues of second-line drugs by the pharmacists will only be made on the basis of appropriate authorization of the DOTS-plus Project Coordinator, chief of the MDR-TB ward (for intensive phase) and chief of the DMT (for continuous phase).

Drug related issues will be made on a weekly basis for the MDR departments and regularly every two months for the health facility of the penitentiary system and Ftiziopneumology Municipality Hospital from Chisinau and for the peripheral health services which have patients in the continuation phase.

The NTP introduced an innovative system for the individualized management of drugs required by each MDR-TB patient for both phases of the treatment. The pharmacist, following the instructions of the Recruitment Committee and chief of the MDR-TB ward, which determined the exact regimen for each case, assembles the second-line drugs needed for each patient for one week for inpatients and two months for outpatients into a *patient pack*, labeling the package individually and specifically for each patient.

The *patient pack* for the patients in the continuation phase is transferred to the “rayon” level each two month. Handling of drugs is minimized and accountability simplified through the implementation of the *patient pack* system and monitoring of DOT compliance is facilitated by direct review of the contents of the pack.

The recording of administered drug doses at both levels is based on individual principles using specially developed forms in order to ensure the tracing of each dose from procurement to patients.

The recording of DOT administered drugs will be carried out using a monitoring form based on the principles of, and adapted from the standard TB01 form.

The introduced new scheme of distribution of second-line drugs - Individual Patient Package - assists the NTP in strengthening the distribution, evidence, and reporting practice of the drugs. Furthermore, it improves the monitoring of drug use and treatment outcome. The NTP has developed, with the assistance of MSH, the Standard Operating Procedures for the implementation of the patient package scheme for the management of drugs for the treatment of MDR-TB.

For the next cohorts, the NTP plans to update the current scheme of distribution based on the system for the individualized management of drugs required by each MDR-TB patient in the both phases. The pharmacists will follow the Recruitment Committee and chief of MDR-TB ward instructions determining

the exact required regimen, assemble the second-line drugs needed for each patient, and label the accumulated package according to the patient identification.

Advantages of patient packages

- Patient package assembled centrally by qualified, professional pharmacist under direction of senior NTP staff
- Drug needs in response to changes in regimen ensured centrally by supervising TB specialists
- MDR-TB patient is assured of continuity of supply from the commencement of the treatment course
- Patient package can move (between health facilities) if patient moves around the country
- Simplifies inventory control between the PPI pharmacy and peripheral health unit
- Incompletely consumed package (demise of patient, defaulter, emigration, etc.) is returned to the PPI pharmacy for other re-supply needs
- Does not rely on the periphery to quantify re-supply needs
- Second-line drugs are well protected in transit

Characteristics of system

- Pack contents assembled for one week (intensive phase) and two months (continuous phase) supply of second-line anti-TB drugs
- Pack identified for specific patient (and location of patient, health facility)
- On commencement of the ambulatory phase of treatment two month supply is transferred to patient location
- Subsequent re-supply is in pack containing 2 month requirements (providing re-supply is scheduled every two month)

Strategies for Ex-prisoners

The incentives and enablers (in the amount of 8 USD per month) are used to improve adherence to treatment for prisoners released still on first-line anti-TB treatment. This pilot project for ex-prisoners started with the support of Caritas Luxemburg and KNCV TF (financed by ICCO/CORDAID) from 2005. According to the data from the Penitentiary Information Department 57 prisoners with active drug sensitive TB have been transferred out of prisons in 2005. Only 26.3% (15) of released patients were lost for follow-up, compared to 41% during the pre-pilot project period in 2004, out of which 10.5 % (6) refused the treatment, 3.6% (2) were imprisoned again and 12.7% (7) gave wrong addresses. MDR-TB patients were not eligible for this project due to lack of second-line anti-TB drugs.

The ex-prisoners on MDR-TB treatment will receive similar support as the MDR-TB patients in civil services within the DOTS-Plus project.

8. Information Systems and Data Management

The development and implementation of a Data Management Information System tool for DOTS-Plus surveillance and monitoring is planned.

The data recording and reporting within *DOTS program* is done according to the WHO recommended forms, which are modified and translated into Romanian. The minimum set of the information

recommended by WHO is collected in addition to a few other variables agreed upon by the stakeholders in the country.

The forms are at the moment under revision due to the newly published *The Guidelines for The Programmatic Management of Drug-Resistant Tuberculosis (WHO-2006)* as well as due to the development of the unified electronic database, SYMETA, at the *Center for Public Health and Management* which oversees the reporting and recording for TB.

The individualized electronic database has been already developed for all TB cases. The link to the laboratory individualized database as well as to the individualized MDR-TB database is under development at the moment and should be ready by 2007.

All these in process developments and current systems in use are going to be integrated with the project of a new module for second-line TB drug information management to be developed with RPM Plus technical assistance.

Annex 3. List of second-line anti-TB drugs registered in the country

Nr. o/o	International Non-proprietary Name	Strength	Brand name of registered drugs	Manufacturer and country of origin
1	Amikacin	Liofil./sol. inj. 0.5 g	Amicil	Kievmedpreparat SAD, Ukraine
		Liofil./sol. inj. 1.0 g	Amicil	Kievmedpreparat SAD, Ukraine
		Pulb./sol. inj. 500 mg	Amikacin	Krasfarma SAD, Russian
		Inj. 250 mg	Amikacin-KMP	Kievmedpreparat SAD, Ukraine
		Inj. 100 mg	Amikacin-KMP	Kievmedpreparat SAD, Ukraine
2	Capreomicin	-	-	-
3	Ethionamid	250 mg tab.	Ethomid	Macleods Pharmaceuticals Ltd, India
4	Cycloserin	250 mg capsules	Coxerin	Macleods Pharmaceuticals Ltd, India
		250 mg capsules	Cicloserin	Vitaminic production facture Scelcovo SAD, Russia
5	Ofloxacin	200 mg tab.	Ofloxacin	Hau Giang Pharmaceutical Joint-Stock Company HG.PHARM, Vietnam
		200mg tab.	Fcin-200	West-Coast Pharmaceutical Works, India
		200 mg tab.	Floxwin-200	XL Laboratories Pvt Ltd, India

		200 mg tab.	OfloHexal	Hexal AG (producător Salutas Pharma GmbH), Germany
		400 mg tab.	OfloHexal	Hexal AG (producător Salutas Pharma GmbH), Germany
		200 mg tab.	Ofloxacin-FPO	"Obolenskoe" SAĀ, Russian
		200 mg tab.	Ofloxacin-ICN	ICN Leksredstva SAD, Russia
		200 mg tab.	Ofloxacin-KMP	Kievmedpreparat SAD, Ukraine
		200 mg tab.	Ofloxin	Zentiva a.s., Czech Republic
		200 mg tab.	Tariferid	Briņtalov-A SAI, Russia
		200 mg tab.	Zanocin 200	Ranbaxy Laboratories Ltd, India
		400 mg tab.	Zanocin OD	Ranbaxy Laboratories Ltd, India
		200mg	Ofloxacin	Sedico Pharmaceutical Co, Egipt
6	Para-aminosalicylic acid	-		-
7	Pyrazinamidum	500 mg tab.	Pirazinamid	Holden Medical, Holland (manufacture- Holden Medical Laboratories Pvt.Ltd, India)
			Pirazinamid	KRKA, Slovenia
			Pirazinamid	Imexpharm, Vietnam
			Pirazinamid	Antibiotice, Romania
			Pirazinamid	Ipca Laboratories Ltd, India
		300 mg tab.	Pirazinamid	Europarmaco, Moldova
8	Ciprofloxacin	250 mg tablets	Ciprinol	KRKA Slovenia
			Cifloxinal	Pro Med CS, Czech Republic
			Ceflox 250	Plethico Pharmaceuticals, India
			Ciprobin	Brintalov, Russia
			Ciprofloxacin, capsule	Tamus Pharm SRL, Moldova
			Cifran 250	Ranbaxy, India
			Ciprowin 250	Alembic, India
			Ultraflox-250	Bal Pharma, India
			Microflox	Micro Labs, India
			Cefan-250	Bombay Tablet, India
			Ciprofloxacin	Nature Product Europe, Holland

			Ciprol	Bosnalijek, Bosnia si Hertogovina
			Ciprofloxacin (in bulk)	LOK-Beta Parmaceuticals Ltd. India
			Ciprofloxacin	Technolog SAI Ucraina
			Ciprofloxacin	IM Vermodje SRL, Moldova
			Ciprofloxacin -FPO	“Obolenskoe”SAI , Russia
			Ciprox	ICS Eurofarmaco Moldova
9	Ciprofloxacin	500 mg tab.	Ciprinol	KRKA Slovenia
			Ciprofloxacin	Hau Giang United, Vietnam
			Ciprofloxacin, capsule	Tamus Pharm SRL, Moldova
			Ceflox 500	Plethico Pharmaceuticals, India
			Cifran OD prolong release	Ranbaxy, India
			Cifran 500	Ranbaxy, India
			Cifan 500	Bombay Tablet, India
			Ciprowin 500	Alembic, India
			Microflox	Micro lab, India
			Cirpofloxacin	Intermed, India
			Ciprofloxacin	Natur Product Europe, Holland
			Cirpodac 500	Cadila, India
			Ciprolox 500	Inter Pharma, India
			Ciprol	Bosnalijek, Bosnia and Hertogovina
			Ciprofloxacin (in bulk)	LOK-Beta Parmaceuticals Ltd. India
			Ciprofloxacin	Technolog SAI Ucraina
			Ciprofloxacin	IM Vermodje SRL, Moldova
	Ciprox	ICS Eurofarmaco Moldova		
	Siprobela	Nobel Ilac Sanayiive Ticaret, Turkey		
10	Kanamicina	powder for injection 1 g	Kanamycin-KMP	Kievmedpreparat SAD, Ukraine