World Health Organization
REGIONAL OFFICE FOR Europe

GLC/EUROPE MISSION

FOR MONITORING OF THE IMPLEMENTATION

OF THE NATIONAL M/XDR-TB RESPONSE PLAN

IN ROMANIA

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List of acronyms

AIDS – Acquired immune deficiency syndrome
ART – Antiretroviral treatment
CC (+/-)- Culture (positive/negative)
DOT – directly observed treatment
DRS – Drug resistance surveillance
DST – Drug susceptibility testing
FLD – First-line anti-tuberculosis drugs
GDF – Global Drug Facility
GFATM – Global Fund to Fight AIDS, Tuberculosis and Malaria
GLC – Green Light Committee
HIV – Human immune deficiency
IC – Infection control
MDR-TB – Multi drug-resistant tuberculosis
MNI – Marius Nasta Institute
MOH – Ministry of Health
MOJ – Ministry of Justice
NRL – National reference laboratory
NTP – National Tuberculosis Program
PIU – Project implementation unit
PMDT – Program management of drug-resistant tuberculosis
RAA – Romanian Angel Appeal
SAT – Self-administered treatment
SLD – Second-line anti-tuberculosis drugs
SNRL – Supra-National reference laboratory
SS (+/-) – Smear (positive/negative)
TB – Tuberculosis
UNDP – United Nations Development Program
WHO – World Health Organization
XDR-TB – Extensively drug-resistant tuberculosis

1. Terms of Reference

Objectives:

- to assess the implementation of the program, evaluate current achievements and sustainability of the program; and develop recommendations for future activities;
- to assess the National M/XDR-TB Response Plan and ensure that it complies with the European M/XDR-TB Response Plan;
- to assess the progress of the implementation of the National M/XDR-TB Response Plan (if available);
- to assess the current M/XDR–TB Control project supported by the Global Fund or any other donor (if applicable).

Key issues to be elaborated and reviewed:

1) Availability of the National M/XDR-TB Response Plan, which includes coverage of all patients including children and adolescents, prisoners and migrants, homeless and etc.;
2) Alignment of the National M/XDR-TB Response Plan to the *"Consolidated Action Plan to Prevent and Combat M/XDR-TB in WHO European Region 2011 – 2015"*;
3) Identify the need of technical assistance to elaborate and modify the National M/XDR-TB Response Plan;
4) Assess the level of the governmental support and coordination between government and internal and external partners (donors, implementers); the project and the community; civilian and penitentiary system; M/XDR-TB and HIV interventions; human resources management and training;
5) Assess case finding strategies and identify barriers to timely start of M/XDR-TB treatment, including TB in children;
6) Case management and treatment strategies and approaches (clinical protocols and guidelines, side effect management and availability of diagnostics and ancillary drugs at all levels, especially at ambulatory sector); TB children case management; TB care delivery ethics and other relevant aspects of the program with the focus on vulnerable groups (prisoners, former prisoners, migrants and children);
7) Follow up of TB and M/XDR-TB patients; patient-centered approach and social support;
8) Infection control strategies at inpatient and outpatient settings;
9) Current status of laboratory services, diagnostics, accessibility for the patients, including children; collaboration with the supranational reference laboratory;
10) Drug management system for first and second-line TB drugs in terms of quantification method, procurement, importation, storage, distribution and delivery to the patients, availability of children dosages formulation; collaboration with the first and second-line drug procurement agency;
11) Information system (including availability of recording and reporting forms, and data base) and data management (routine collection and cohort analysis); existence of separate MDR-TB register or user-friendly platform for separate data management from the all TB register. Existence of the laboratory information management module linked to MDR-TB and/or TB register.
12) Identify the need, frequency and duration of technical assistance to implement the National M/XDR-TB Response Plan.

Expected outcome of the mission

- GLC-Europe monitoring mission report with recommendations.
- Updated M/XDR-TB Response Plan revised and submitted to the Ministry of Health.
- Request the WHO-Europe for the follow-up GLC-Europe monitoring mission in six months to evaluate the progress of program performance.
- Request the WHO-Europe for the possibility to negotiate with the MOH of Romania on conducting the comprehensive WHO TB Program Review Mission.

2. Background information

GLC/Europe is supporting the scaling up of the M/XDR-TB Response Plan in Romania. The last monitoring mission was conducted by Dr. Einar Heldal on July 7-14, 2011. This year the mission is conducted by Dr. Askar Yedilbayev, the GLC Consultant, to assess the TB Program activities and provide assistance in developing/update the Romanian M/XDR-TB Response Plan on behalf of the GLC-Europe.

The NTP Central Unit has developed the Country M/XDR-TB Response Plan for 2012-2015, which was reviewed by the GLC Consultant together with the NTP Central Unit team. General recommendations for the plan was to make it SMART (specific, measurable, achievable, realistic and time-bound), prioritise the objectives with activities to be supported by the Government and external funding, and cover all areas required improvement. The plan was supposed to be submitted for approval to the MOH of Romania in May-June 2012. Technical assistance was offered to the NTP Central Unit on finalizing the Plan by the GLC Consultant. Taking into consideration the available infrastructure and human resources, as well as possible approval of the TFM of the GFATM Round 6 application later in 2012, the Plan is considered to be adequate when objectives prioritised, but with lack of financing from the Government sources major objectives are doubtful to be achieved. A strong political will and support is crucial to perform additional reform in changing the health system of drug procurement, infection control, laboratory, ambulatory care treatment and capacity building.

3. Follow up of the previous mission recommendations.

Romanian National Tuberculosis Program is showing some progress in the management of drug resistant tuberculosis but generally the majority of recommendations from the previous GLC monitoring mission remain unchanged. Out of 36 recommendations from the previous GLC monitoring mission only 7 had been completed, for 16 there was some progress and require improvement, and 13 have no change. Several recommendations are repeated in the current report. Lack of progress is mainly explained by lack of political and financial support from the MOH. Complete list of recommendations from the previous GLC monitoring mission together with the comments from the NTP and former NTP Coordinator, Dr. Elmira Ibraim, are also provided to the current report (Annex 6).

The progress of implementing majority of recommendation is slow, and mostly related to health and financial challenges, adequate use of available resources, capacity and infrastructure. Funding allocated to combat tuberculosis and its drug-resistant strains in Romania should be considered for reallocation to support and strengthen those parts, which require significant improvement (drug management and procurement, infection control, laboratory, coordination and management of the NTP, ambulatory treatment and patients' adherence to treatment).

Priority recommendations from previous GLC monitoring mission	Status/Comments
MOH should strengthen the central unit, ensuring sufficient staff with clear ToR, salaries and budget to carry out its functions.	ToR developed, salary support allocated starting January 2012
MOH should consider establishing an intermediate regional level, similar to the 8 regions for lab and AIDS, which is more manageable for the central unit. These regional levels would then supervise a limited number of counties.	Not completed due to budget shortages
MOH/NTP should update MDR guidelines, including criteria for treatment in centres of excellence, reporting, function of the two MDR commissions, treatment regimens.	External TA is required
NTP/MOH should ensure that smear and culture is done in all TB cases, that DST is done in all culture confirmed cases and that the coverage by county and dispensary is monitored through the R&R system. High coverage of DST should be ensured immediately in groups where NTP defines that it is especially indicated: in all previously treated cases and in groups of new cases with increased risk.	Not completed due to budget shortages
The MOH/NTP should introduce rapid tests for RH resistance, with clear algorithm for its use.	No funding available
The MOH/NTP should strengthen the reference function of the reference laboratories, ensure sufficient funding for laboratories to do all recommended tests, ensure that adequate routines for infection control are followed in all laboratories, ensure that the recording and reporting system is implemented. The MOH/NTP should continue the process of centralizing the laboratory network.	In progress but very slow due to limited availability of funds from the government sources
MOH/NTP should ensure social support to patients who need it, including travel cost (bus tickets) and food.	No funding available
MOH/Insurance house should implement the decision to centralize procurement of 1.and 2.line TB drugs.	Explanation in the Drug management section
MOH/Insurance house should ensure procurement of 1.and 2.line drugs for all TB patients not covered by GF. Drugs for 840 patients can be immediately procured through the GLC mechanism with governmental funding. The price is estimated to be 5,5 mill euro lower for full 2 year	Explanation in the Drug management section

treatment of 1000 MDR-TB patients with GLC mechanism than purchased from local providers.	
MOH/NTP should revise the national guidelines for infection control and ensure that practices are in line with international recommendations in laboratories doing culture and DST, in wards and outpatient areas.	

4. Current mission recommendations (summary).

Organization	Action / Recommendation	Time frame
MoH	• Endorse the National M/XDR-TB Response Plan for 2012-2015 and consider adequate financial support for the program implementation.	ASAP
	• NTP Central Unit team should have a clear mandate to act as the actual National Tuberculosis Program Unit and be enforced by specialists free of work responsibilities as doctors to perform coordination over National Tuberculosis Control Program in Romania, supported with adequate salaries, and fulfil obligations described in current ToRs.	ASAP
	• Consider optimization and structural reorganization of laboratory network to reallocate funds for DST. Cost analysis, performance evaluation, capacity and infection control of each laboratory is requested (quality control for DST concordance of each lab).	By January 1, 2013
	• Centralize the drug procurement system for first and second-line anti-TB medications as an urgent measure.	ASAP
	• Consider direct purchasing of SLD through the GDF mechanism with government funding to ensure treatment of MDR-TB patients.	To be considered
	• Review the Essential Drug List to include Capreomycin and PAS when registered, exclude Ciprofloxacin as an urgent need. Provide most possible assistance for importing at least Capreomycin by special order of the MOH for all MDR-TB patients require.	ASAP
	• Provide adequate financial resources for the update of the National Electronic TB Register with MDR-TB.	By January 1, 2013
NTP (civilian sector and penitentiary sector)	• Provide coverage to DST to first line drugs to all SS+ and CC+ cases, as well as coverage to DST to second-line drugs to all cases with HR resistance, to define the exact reservoir of M/XDR-TB.	On regular basis
	• NTP Regional Units at counties should be created and enforced with coordinators on drug management, TB/DR-TB, M&E and surveillance with clear terms of reference.	By October 1, 2012
	• Update the National Guidelines for Program Management of Drug-resistant Tuberculosis (PMDT) with the recent recommendations of the WHO (June 2011).	By October 1, 2012
	• Ensure adequate infection control measures in all TB inpatient settings, mostly administrative separation of non-TB from TB, TB from DR-TB, MDR-TB from XDR-TB and FQ resistant patients. Installation of adequate amount of UVGIs is crucial for all TB inpatient facilities (if possible).	ASAP
	• Develop mechanisms for strengthening TB patients' adherence to treatment and address the problem of high rate of default using the resources available. Strict DOT should be performed at all levels and stages of TB and DR-TB management.	ASAP
	• Strengthen the capacity building in the management of M/XDR-TB for all TB and PHC specialists involved, including penitentiary sector.	Timeline to be considered
	• Introduce rapid tests for HR resistance, or at least R resistance. An algorithm for rapid molecular diagnosis should be developed with certain criteria for patient groups – with the TA from SNRL. Training of laboratory personnel is required to perform rapid molecular diagnosis.	To be considered

Partners (SNRL)	• Conduct quality assurance on FLD and SLD on a regular basis, to be performed by NRLs.	On regular basis
Donors (GFATM)	• Support the approval of the TFM application	To be considered
WHO/EURO	• Provide technical assistance in updating the National Guidelines on Program management of DR-TB • Provide technical assistance on updating the National laboratory guidelines • Provide the policy dialogue with the MOH to endorse the National M/XDR-TB Response Plan	By the end of 2012 By the end of 2012 By the end of 2012

5. General country/region profile

Findings and summary of discussion:

Romania is a country located at the crossroads of the Central and South-eastern Europe, on the Lower Danube, within and outside the Carpathian arch, bordering Hungaria, Serbia, Bulgaria, Moldova and Ukraine, with an access to the Black Sea. At 238,391 square kilometres, Romania is the ninth largest country of the European Union by area, and has the seventh largest population of the EU with 21,275,000 people (2011 census), which decreased in compare with 2004 census from 22,063,996 people. Country's capital and largest city is Bucharest, the tenth largest city in the EU, with about 2 million people. Romania is divided into 41 counties and the municipality of Bucharest. Each county is administered by a country council, responsible for local affairs, and further subdivision into cities and communities with their own mayor and local administration. There are total of 319 cities and 2,686 communities in Romania. The capital is divided into six sectors, and has a special status as it is considered as a part of a county. Historically the country is divided into eight bigger regions: North-eastern (Iasi), Western (Timisoara), North-western (Cluj-Napoca), Central (Brasov), South-eastern (Constanta), Southern (Ploiesti), Bucharest-Ilfov (Bucharest) and South-western (Craiova).

Romania's total GDP (PPP) is $267.151 billion, per capita - $13,380, which places country to the upper-middle income category according to the World Bank ranking. Unemployment rate is relatively low in recent years and stand about 5% in 2011. At the same time the country's economy is affected by the global economic recession resulted in state salary cuts up to 25% during last two years. In the late 2000s nearly 10% of population was in absolute poverty and of these 90% live in rural areas. A set of reforming programs has been started in 1999 introducing private health insurance system. The state-run healthcare system is free, but suffers from neglect and has been deteriorated in recent years due to lack funding and underpaid staff. Life expectancy at birth is 70 for male, 77 for female, and 73 in average for both sexes. The fertility rate is decreasing with 1.4 births per woman recorded in 2009. The birth rate (10.61% in 2008) is slightly lower than the mortality rate (11.84% in 2008) resulting in shrinking and aging of population. The number of Romanians abroad is estimated from 4-12 million people (including mixed origin). After the 1989 revolution and in 1990s, a significant number of people emigrated to the EU countries and North America, for better labour conditions and education.

The National TB Program in Romania is having national coverage and a solid infrastructure of both clinical and diagnostic facilities, as well as trained personnel at all levels to perform the existing program. The financial system of health services is having two flows both covering certain areas of the program, making Ministry of Health (MOH) responsible for financing of TB prevention and National Insurance House responsible for financing drug procurement, TB hospitals and dispensaries through its branches in counties.

Infrastructure of TB Services in Romania is well developed and presented with wide network of TB Dispensaries (184) and additional 94 facilities with 5,981 hospital beds countrywide. Number of TB dispensaries and TB hospitals may vary from county to county. Annual bed occupancy is around 80%, with majority of TB and MDR-TB patients being hospitalized at least for the start of the treatment. Hospital stay is being regulated and monitored by the NIH with certain number of bed days for drug-susceptible and drug-resistant tuberculosis. With decentralized system of health services, health financing through the NIH and health procurement including drugs, the county level TB facilities have their own responsibility on performing coordination over TB control, drug management, supervision and reporting. With regulated duration of hospital stay for TB and DR-TB, patients are being referred for ambulatory sector for treatment continuation, mostly performed by TB dispensaries and Primary Healthcare facilities. Unfortunately, DOT is not in fully complied at all outpatient settings, which worsens the situation with growing number of DR-TB.

Table 1. Structure of TB Services (visited facilities only)

Facility		Total No of beds	TB beds	Out of TB - X/MDR-TB beds	TB out-patient unit attached	comments
Civilian TB services						
Hospital with TB services						
1	MNI	N/A	N/A	48	Yes	Good IC
2	Laemna Pneumology Hospital	154	80	10	No	Poor IC, mixed department for TB, DR-TB and Pulmonary patients
	TOTAL					
TB outpatient departments/units						
1	TB Dispensaries	-	-	-	Yes	-
2	PHC clinics	-	-	-	Yes	-
	TOTAL					
Prison system						
Hospital with TB services						
1	TB Hospital in Bucharest	-	-	9	-	-
	TOTAL					

6. Epidemiology, Case finding and Program performance data

Findings and summary of discussion:

Burden of tuberculosis still remain as one of the main public health threats to the country with the prevalence (including HIV) of 143.6 per 100,000 population (2011). The incidence of TB reported 82.8 per 100,000 people in 2011 with total of 17,749 new cases, and is declining in compare with previous years (99.4 – 2009, 90.0 – 2010). Mortality rate of TB (excluding HIV) was reported at low levels of 6.0%, assuming to be higher with HIV positive cases, and is also declining from 7.1% in 2009. The country reported the case notification of 61.3% among new smear positive cases and 67.3% among relapses in 2011. Absolute number of all cases with TB remains high and is around 30,000 in 2011. Main TB indices are declining mostly due to the increased diagnosis and access to treatment for majority of TB cases diagnosed, as well as the availability of FLD for drug-susceptible TB through the government funding. Treatment success rates shows good results with treatment success rate of new smear positive cases of 85% in 2007 cohort (72% cured and 13% treatment completed), default rate of 5%, failure- 4.0 and died of 4.0%, even with notified cases of self-administered treatment especially in rural areas.

Table 2a. Incidence, prevalence and mortality rates of TB 2009-2011, Civilian sector

	Incidence		Prevalence		Mortality	
Year	Abs.	Per 100,000	Abs.	Per 100,000	Abs.	Per 100,000
2009 (population 21,469,959)	21,342	99.4	34,777	161.9	1,523	7.1
2010 (population 21,431,298)	19,294	90.0	31,794	148.4	1,482	6.9
2011 (population 21,431,298)	17,749	82.8	30,769	143.6	1,283	6.0

Table 2b. Incidence, prevalence and mortality rates of TB 2009-2011, Prison sector

	Incidence		Prevalence		Mortality	
Year	Abs.	Per 100,000	Abs.	Per 100,000	Abs.	Per 100,000
2009 (population 21,469,959)	168	630.4	393	1,474	4	15.0
2010 (population 21,431,298)	152	551.5	293	1,063	1	3.6
2011 (population 21,431,298)	143	488.7	304	1,038	0	0.0

Table 3a. TB case notification 2009-2011, Civilian sector

Case notifications	2009		2010		2011	
	abs	%	Abs	%	abs	%
New cases						
Smear-positive	9,111	62.4	8,016	61.4	7,327	61.3
Smear-negative	5,360	36.7	4,906	37.6	4,441	37.2
Smear unknown	129	0.9	133	1.0	183	1.5
Extrapumonary TB	3,171	17.8	2,889	18.1	2,656	18.2
Other	0	0	0	0	0	0
Total new	17,771	100	15,944	100	14,607	100
Retreatment cases						
Relapse	3,571	66.2	3,350	65.7	3,142	67.3
Treatment after failure	477	8.8	452	8.9	401	8.6
Treatment after default	841	15.6	825	16.1	731	15.7
Other	504	9.4	476	9.3	394	8.4
Total retreatment	5,393	100	5,103	100	4,668	100

Table 3b. TB case notification 2009-2011, Prison sector

Case notifications	2009		2010		2011	
	abs	%	Abs	%	abs	%
New cases						
Smear-positive	39	31.7	38	35.2	43	43.9
Smear-negative	84	68.3	69	63.9	54	55.1
Smear unknown	0	0	1	0.9	1	1
Extrapumonary TB	13	9.5	17	13.6	14	12.5
Other	0	0	0	0	0	0
Total new	136	100	125	100	112	100
Retreatment cases						
Relapse	32	84.2	27	84.4	31	83.8
Treatment after failure	1	2.65	0	0	1	2.7
Treatment after default	4	10.5	5	15.6	4	10.8
Other	1	2.65	0	0	1	2.7
Total retreatment	38	100	32	100	37	100

However, despite the fact of successes in managing drug-susceptible TB, drug-resistant tuberculosis is a major challenge to the effectiveness of National Tuberculosis Program in Romania, placing the country in the list of 18 high-burden countries for MDR-TB in the WHO European Region. DST results for 9 months of 2011 showed rates of primary MDR-TB of 3.0% and 19.5% among retreatment cases (3.2% and 17.9% respectively in 2010). The drug-resistance survey (DRS) conducted during four months of 2009-2010 with results collected of 756 MDR-TB cases defined the level of XDR-TB among MDR-TB cases of 11.37% (among new MDR-TB cases - 9.9%, among retreatment cases – 11.6%). DRS also showed extremely high level of any resistance to Cm (69.3%), to Km (57.3%) and Am (54.7%) among tested strains. Please refer for more detailed information on DRS to the previous GLC monitoring mission report of 2011.

The number and proportion of MDR-TB in the country is increasing mostly due to several factors contributing to the growth of the reservoir of DR-TB patients in the country. According to the WHO estimates, Romania has around 1,300 MDR-TB cases annually. In 2011 the country official statistics reports a total of 384 confirmed MDR-TB cases (93 new and 291 retreatment cases) and 161 MDR-TB suspects (30 new and 131 retreatment cases). Due to the fact of low DST coverage of all CC+ cases, the actual number of MDR-TB is underestimated. In 2009, 35.6% of all CC+ new cases were covered with DST, 53.2% of CC+ among relapses, and 59.3% among other retreatment cases. The situation has not

been improved over the past two years mostly because of the decreased financing and poor referral for DST by doctors (not every SS+ and CC+ covered with DST). DST to SLD is also not yet performed to all MDR-TB patients by the time of diagnosis HR resistance, which makes impossible to estimate the actual number of XDR-TB. Delays with diagnosis of drug resistance due to the absence of rapid diagnosis of drug resistance (LPA, Gene Xpert, BACTEC MGIT-960 System) and timely start of treatment also contributes to the poor treatment outcomes and as a result contribute to the growth of the MDR-TB reservoir.

Decentralized system of drug procurement and unavailability of full range of second-line anti-TB medications serves as the major contributor to the worsening of the situation of drug-resistant tuberculosis. As described in the Drug Management section of current report, medical management of MDR-TB patients is suffering from the stock outs of aminoglycosides (Kanamycin and Amikacin) and Capreomycin, insufficient amount of proper fluoroquinolones (Ofloxacin and Levofloxacin), making patients treated with weak Ciprofloxacin. Treatment outcomes for the recent non-GLC cohorts are frightening with treatment success rate of 19%, died 23.2%, failed 34.7% and default of 21.5% (2008 non GLC-cohort, absolute number 792 patients). Cohort analysis of treatment outcomes for 2009 are similar with treatment success of 15.1%, died of 18.9%, failed 36.7% and default rate of 20.2% (absolute number of 624 patients). Total percentage of patients decreasing reservoir (cured + treatment completed + died + transferred out of the country) is less than those possibly contributing to the continuous growth of MDR-TB reservoir (failures and defaulters assuming if abandoned treatment while being SS+/CC+) – 43% versus 56.2% in 2008 and 34.1% versus 56.9% in 2009. High rate of default is explained due to the lack of patient-centered approach and mechanisms targeting patients' adherence to treatment, such as lack of social support, psychological care, defaulter tracing, low motivation of personnel, resulting in poor DOT. Also, even with decentralized system of care provision including tuberculosis management and increased role of primary health care, family doctors and nurses are not providing 100% DOT to TB patients because of no financial stimulus to treat tuberculosis at ambulatory settings.

Treatment outcomes of GLC cohorts enrolled to the MDR-TB treatment program with Round 2 and 6 GFATM funding shows comparatively good program performance with the total number of patients enrolled over 2004-2011 of total of 884 patients (percentage for final treatment outcomes given for Cohorts 1 and 2):

Cohort	# enrolled	Still on treatment	Success	Default	Failure	Lost to follow up/excluded*	Died
Cohort 1 (2004-2005)	200	0	118 (59%)	22 (11%)	31 (15.5%)	4 (2%)	25 (12.5%)
Cohort 2 (2006-2007)	200	0	150 (75%)	16 (8%)	20 (10%)	1 (0.5%)	13 (6.5%)
Cohort 3 (2009)	145	5	92	10	16	1*	21
Cohort 4 (2010-2011)	339	205	46	23	28	3*	27
TOTAL	884	217	406	71	95	9	86

**Note: lost to follow-up or excluded from the program should be considered as default*

The country is planning to scale up coverage with MDR-TB treatment to achieve the target by 2015 to cover 80% of estimated 1,300 MDR-TB cases (610 in 2012, 770 in 2013, 880 in 2014 and 990 in 2015). With current system of decentralized drug procurement and low access to quality-assured second-line anti-TB medications it seems to be impossible, and if continued treatment with inadequate regimens,

Romania will continue facing major threat of DR-TB, including high level of resistance to injectable agents and fluoroquinolones.

On March 31, 2012 Romania applied to the Transitional Funding Mechanism for the Round 6 of the Global Fund. If approved by the GFATM the country will be able to continue enrolment of 300 patients with MDR-TB.

Table 4a. Treatment outcomes for non-GLC MDR-TB cohort, 2008, Civilian sector

Registration group	Cured	Treatment completed	Died	Failed	Defaulted	Not evaluated [1]	Total
New	38	5	12	43	19	0	117
Relapse	43	11	41	65	38	0	198
After default	4	4	28	18	51	0	105
After failure of Category I and II treatment	22	0	16	20	17	0	75
Other retreatment, or unknown retreatment[2]	20	6	87	129	45	10	297
Total	**127**	**26**	**184**	**275**	**170**	**10**	**792**
Percentage	**16.0%**	**3.3%**	**23.2%**	**34.7%**	**21.5%**	**1.3%**	**100%**

Table 4b. Treatment outcomes for non-GLC MDR-TB cohort, 2009, Civilian sector

Registration group	Cured	Treatment completed	Died	Failed	Defaulted	Not evaluated [3]	Total
New	29	4	14	63	27	11	148
Relapse	26	4	29	62	41	19	181
After default	4	1	20	19	28	4	76
After failure of Category I and II treatment	16	1	13	32	12	4	78
Other retreatment, or unknown retreatment[4]	7	3	42	53	18	18	141
Total	**82**	**13**	**118**	**229**	**126**	**56**	**624**
Percentage	**13.1%**	**2.1%**	**18.9%**	**36.7%**	**20.2%**	**9.0%**	**100%**

[1] Not evaluated = cases registered - sum of treatment outcomes
'Not evaluated' includes 'transferred out', 'still on treatment' and any other registered case where the treatment outcome has not been evaluated.
[2] Unknown retreatment is a previously treated cases but without information on outcome of previous treatment
[3] Not evaluated = cases registered - sum of treatment outcomes
'Not evaluated' includes 'transferred out', 'still on treatment' and any other registered case where the treatment outcome has not been evaluated.
[4] Unknown retreatment is a previously treated cases but without information on outcome of previous treatment

Table 4c. Treatment outcomes for non-GLC MDR-TB cohort, 2008, Prison sector

Registration group	Cured	Treatment completed	Died	Failed	Defaulted	Not evaluated [5]	Total
New	0	0	0	1	0	0	1
Relapse	1	0	0	0	0	0	1
After default	0	0	0	0	0	0	0
After failure of Category I and II treatment	0	0	0	0	1	0	1
Other retreatment, or unknown retreatment[6]	0	0	0	0	0	0	0
Total	**1**	**0**	**0**	**1**	**1**	**0**	**3**
Percentage	**33.3%**	**0%**	**0%**	**33.3%**	**33.3%**	**0%**	**100%**

Table 4d. Treatment outcomes for non-GLC MDR-TB cohort, 2009, Prison sector

Registration group	Cured	Treatment completed	Died	Failed	Defaulted	Not evaluated [7]	Total
New	0	0	0	0	0	0	0
Relapse	0	0	0	0	0	2	2
After default	1	0	0	0	1	1	3
After failure of Category I and II treatment	0	0	0	0	0	0	0
Other retreatment, or unknown retreatment[8]	0	0	0	0	0	0	0
Total	**1**	**0**	**0**	**0**	**1**	**3**	**5**
Percentage	**20.0%**	**0%**	**0%**	**0%**	**20.0%**	**60.0%**	**100%**

[5] Not evaluated = cases registered - sum of treatment outcomes
'Not evaluated' includes 'transferred out', 'still on treatment' and any other registered case where the treatment outcome has not been evaluated.
[6] Unknown retreatment is a previously treated cases but without information on outcome of previous treatment
[7] Not evaluated = cases registered - sum of treatment outcomes
'Not evaluated' includes 'transferred out', 'still on treatment' and any other registered case where the treatment outcome has not been evaluated.
[8] Unknown retreatment is a previously treated cases but without information on outcome of previous treatment

Recommendations to be included into National M/XDR-TB Response Plan:

	Recommendation	Responsibility
1	Provide coverage to DST to first line drugs to all SS+ and CC+ cases, as well as coverage to DST to second-line drugs to all cases with HR resistance, to define the exact reservoir of M/XDR-TB.	NTP
2	Plans to scale up the enrolment of MDR-TB should be supported by changes in government system of drug management towards centralization and assurance of adequate provision of quality-assured second-line drugs.	MOH, NIH, NTP

7. Coordination of the program and financing

Findings and summary of discussion:

Organizational structure of TB services in Romania has not significantly changed since the previous GLC monitoring mission with the NTP Central Unit with coordinators responsible for coordination of activities, methodology, data collection and supervision. The NTP Central Unit is based in the Marius Nasta Pneumology Institute at Bucharest, and consists of a group of coordinators responsible for certain area of TB Control: Technical Coordinator (group leader), Drug Management and Infection Control Coordinator, MDR-TB Coordinator, M&E and Surveillance Coordinator, IEC Coordinator, Laboratory Coordinator, TB/HIV Coordinator and Coordinator on Operational Research. The NTP Central Unit relates to 41 counties plus Bucharest TB coordinators and is not yet supported by the NTP Regional Units, responsible for coordination at county level. Technical coordinator, or the Head of the NTP, is officially assigned by the MOH and provided with political support but limited authority, so as coordinators. Clear terms of references for the NTP Central Unit were developed and endorsed by the MOH. Starting from January 2012 each coordinator started being paid for the work performed as the part of the NTP. However, all coordinators continue performing regular work responsibilities as MOH employees (doctors, biologists, etc). Salaries of the NTP are low, which makes to continue the main job and use the NTP position as an additional payment. On the other hand the MOH is not able to recruit competent persons because of the low salary rate, therefore the agreement was to have doctors sharing two positions – the NTP and doctoral.

As recommended before NTP Regional coordinators at county level were also assigned by the MOH mostly from cohort of chief pulmonologists of TB dispensaries to be responsible for coordination of activities at respected area, which is endorsed in ToRs, but with no team of coordinators. Often times the NTP Central Unit does not have that opportunity to visit the counties on a regular basis for program monitoring, especially to remote areas. Thus, it seems that additional assistance to the NTP Central Unit from the county level would benefit to provide adequate monitoring and supervision over the TB control at regions. It was discussed with the NTP team that the Regional NTP groups should be created and reinforced with coordinators at least on drug management, M&E and surveillance. Moreover, this will provide the Regional NTP Coordinators with more supervisory and managerial power over TB Program in the county. Also, the Regional Coordinators are often time overloaded with main work as doctors, which affects the quality of coordination and program management. It seems impossible for them alone to provide adequate amount of time for reporting, surveillance, monitoring and data collection and analysis for the county. Another obstacle to program implementation at county level is the lack of financing from the NIH to perform supervision and monitoring over treatment of patients in counties, as TB dispensaries have limited funds for gasoline with no forecast to be improved due to financial recession (only 100 litres of gasoline per month).

NTP was reorganized in April 2012 with new NTP Manager and the team assigned by the MOH and new team of coordinators. The old team continue provide assistance to the newly assigned coordinators but it seems challenging at least for the first months to fulfil their obligations without the support from the previous NTP coordinators. Central Unit coordinators should be also free of their work responsibilities as doctors of MNI to perform the NTP coordination and supervision at high quality, build the system capacity and perform advocacy at National level.

NTP Central Unit has developed the series of regulatory and strategic documents to strengthen the TB Control, including program management of MDR-TB, in Romania (National Tuberculosis Strategy for 2012-2015, draft of the National M/XDRTB Response Plan for 2012-2015, etc). The development of all documents had been highly supported by the PIU of the GFATM grant, the Romanian Angel Appeal. The National M/XDR-TB Response Plan covers all areas of scaling up the program management of MDR-TB and includes reasonable tasks and activities with adequate timeline and approximate budget to be

allocated from Government and the GFATM (if TFM application approved). The GLC Consultant provided assistance in amending the draft M/XDR-TB Plan and discussed the majority of objectives and activities together with the NTP team to make it SMART (specific, measurable, achievable, realistic and time-bound). It was recommended to prioritize the activities from high to low importance in terms of reality and availability of financial resources and support from the Government. With current budget cuts due to global financial recession prioritization of activities is essential to complete the objectives of the plan and reach adequate results on PMDT. Rationalization of resources available (centralization of drug procurement system, limiting the number of laboratories performing DST, etc), along with strengthening coordination of activities at national and county levels will allow the government to reallocate funds on essential components described in the National M/XDR-TB Response Plan.

Recommendations to be included into National M/XDR-TB Response Plan:

	Recommendation	**Responsibility**
1	Endorse the National M/XDR-TB Response Plan for 2012-2015 and consider adequate financial support for the program implementation.	MOH
2	NTP Central Unit team should have a clear mandate to act as the actual National Tuberculosis Program Unit and be enforced by specialists free of work responsibilities as doctors to perform coordination over National Tuberculosis Control Program in Romania, supported with adequate salaries, and fulfil obligations described in current ToRs.	MOH
3	NTP Central Unit team should be enforced by allocating adequate funding for monitoring and supervision visits to the counties.	MOH
4	NTP Regional Units at counties should be created and enforced with coordinators on drug management, TB/DR-TB, M&E and surveillance with clear terms of reference.	MOH, NTP

8. Treatment strategies and administration

Findings and summary of discussion:

Treatment of drug-sensitive TB patients in both entities is performed according to the WHO recommendations with new cases start treatment with Category I regimen and retreatment cases with Category II. Cohort analysis is being performed and submitted to the WHO on a regular basis for drug sensitive TB, data collection from every treatment facility is centralized at the level of NTP at MNI.

Management of MDR-TB is performed in accordance with the National Guidelines on PMDT (2005), which was developed in accordance with the international recommendations. No changes had been performed to the guidelines since 2005, thus, it require urgent update in accordance with the recent WHO recommendations of 2008 and 2011, especially on the number of medicines, dosages, duration of intensive phase and total treatment course, requirements for clinical monitoring and management of co-infection with HIV. In the guidelines the regimens are based on DST result and include FLD (E and Z), Injectable agent for intensive phase (Km/Am/Cm), Fluoroquinolone, Cs, PAS. Regimen for HR resistance pattern includes Streptomycin, which is not in alliance with the WHO recommendations. Aminoglycosides (Km/Am) are used in the regimen for patients with confirmed drug susceptibility to either medicine; if resistant then Cm is recorded as an injectable agent of choice. NTP has established two MDR-TB commissions (Bucharest and Bisericani) responsible for decision making on patient enrolment, treatment regimen design, severe side effects management, surgical treatment and patients' referral. Majority of members of the MDR-TB commissions are trained on PMDT. The MDR-TB commissions are ensuring equal access to MDR-TB treatment. There are no clear criteria for enrolment of GLC or non-GLC patients, furthermore, as there are no SLDs for almost one year, then the enrolment criteria are not relevant.

Inpatient treatment of MDR-TB is being available countrywide, at each county mostly at TB Hospitals, but majority of patients are being hospitalized to specialized MDR-TB wards at MDR-TB Centres at MNI and Bisericani. Duration of hospitalization for MDR-TB patients is possible for 106 days and is regulated by the NIH.

Criteria for duration of intensive phase are based on strong bacteriological evidence and are at minimum of 6 months (180 dosages) and two consecutive negative cultures after last positive. According to the protocol all SS+ and CC+ cases have to be covered with DST at least to FLD. Unfortunately that is not being performed as doctors are not requesting DST, especially at counties. Those DST performed at county level is mostly to H and R, and called "short-line", which seems reasonable due to the lack of financing, but even though not covering 100% of cases needed (around 42% in average of new and retreatment cases covered, 2009). DST for SLD suppose to be performed to all cases diagnosed with H and R resistance pattern, but also is not covering even half of those required.

Majority of treatment regimens of non-GLC cohort for intensive and continuation phases include E, Z, Injectable agent (Am for limited number of patients), Fluoroquinolone (Ciprofloxacin, very rarely Ofloxacin and Moxifloxacin), Prothionamide and Cycloserine. During the hospital stay SLD are taken 7 days a week, BID or at single dose. Dosages prescribed are according to patient's weight and tolerance. At ambulatory settings visited DR-TB patients are taking drugs 5 days a week at healthcare facility with the Saturday dose taken under self administration. Due to the lack of injectable agents from the Government sources and not registered Capreomycin, weak fluoroquinolone (Ciprofloxacin), the treatment regimens for non-GLC cohort are extremely poor and ineffective, leaving patients remain smear/culture positive at late months of treatment. PAS is also not registered in Romania. Use of Streptomycin as an injectable agent was noticed at Laemna TB hospital. Moxifloxacin was available at MNI for patients with laboratory confirmed XDR-TB (3 patients) but due to the high cost is not covering all diagnosed XDR-TB cases. Group 5 drugs are not widely available but Clarythromycin used at 500 mg BID for patients with severe pulmonary damage and XDR-TB. Other agents such as Imipenem, Linezolid, Amoxicillin-Clavulanic Acid are registered but not available for treatment purposes.

For the GLC cohort of patients treatment regimens are adequate and include Cm/Am, Ofx, Pto, Cs, PAS and Z. Ethambutol is used if susceptible mostly for intensive phase treatment. Levofloxacin is not available for the GLC cohort as FQ of choice but probably will be considered for the next cohort of 300 patients if the TFM application to be approved by the GFATM.

Requirements for clinical monitoring over DR-TB patient's dynamic are clear and include sputum smear microscopy and culture at the start of treatment, then further repeated on a monthly basis during the intensive and continuation phase. Clinical examinations include general blood and urine tests, biochemical analysis (bilirubin, LFT, urea, uric acid, electrolytes, creatinin, glucose). Chest radiography examinations available at MDR-TB Centres and TB hospitals and being performed as monitoring tool at the start of the treatment and then on a quarterly basis. Narrow specialists are available for inpatient stage and include psychiatrists, ENT, ophthalmologists, dentists, internists, especially at MDR-TB Centres (MNI). Surgical management is available also mostly at major treatment facilities, and usually performed for 10% of DR-TB patients (mostly resectional surgeries not palliative). Options for palliative treatments are limited as in majority of countries in the WHO European Region, but the NTP is planning to establish 2 hospices at former sanatoriums, required minor renovation.

Side effects are managed properly, but not recorded and monitored neither on paper nor electronic format. Ancillary medicines are available at inpatient treatment but not at outpatient, which increases the risks of default. Doctors are noticing GI side effects and arthralgies as most common adverse reactions. At county level there was a tendency defined to withdraw the most possible for adverse reaction drug rather than keeping it in the regimen and use of ancillary medicine. Vitamin B6 (Pyridoxine) was not widely used for non-GLC cohort, but for GLC cohort patients was available at tablet form and used as prophylactics measure against CNS and PNS adverse reactions. Dosages for Pyridoxine are adequate, at maximum daily dose of 300 mg.

Time of smear and culture conversion is not monitored, but as noted before, majority of non-GLC patients observed at Laemna TB Hospital remain positive at later months of treatment mostly due to weak regimens. Smear/culture conversion of GLC cohort patients and non-GLC cohort observed at MNI had Ofloxacin and an Injectable agent in the regimen (Am for non-GLC and Cm for GLC cohort), thus achieved culture conversion at earlier months from the start of treatment.

Options for DOT at ambulatory treatment is limited to TB dispensaries and PHC clinics at counties, and TB Dispensary departments at major TB-Pulmonology centres, with patients coming to the facilities for the drug intake themselves. PHC level clinics and TB dispensaries offer DOT during the weekdays with Saturday treatment mostly performed as self administered. Possibilities for patient-centered approach and use of hospital-replacement mechanisms are very limited due to the lack of vehicles specifically allocated for home patronage treatment. Those vehicles available have limited number of patients on treatment not covered with DOT on a regular daily basis, mostly because of the lack of financing for gasoline allocated to TB Dispensary from the NIH (100 litres per month). Moreover, positions of home patronage nurses are not available, and those nurses, especially from PHC Services are not motivated and interested in providing strict DOT for TB and DR-TB patients. Social support is also lacking and restricted to salary disability allowance for those patients employed prior to the start of treatment. In case of unemployment or homeless no social support is available. Transportation reimbursement is also not taking place from the Government sources. Another option considered by TB doctors was delegating responsibilities for DOT to family members, whom they might trust, but it seems to be not effective, as results for non-GLC cohort treatment is showing extremely poor treatment outcomes. Social support for GLC-cohort patients was available through the GFATM Round 2 and 6 grants with food baskets allocated to all patients on a monthly basis. With the TFM application submitted to the GFATM on March 31, 2012, the social support will not be covered if approved due to restrictions from the donor side, but SLD and trainings as capacity building.

Prison sector

Treatment of Tuberculosis and drug-resistant tuberculosis is performed in two specialized prison facilities with TB beds (130 and 60) and managed by the National Administration of Penitentiaries of the

Ministry of Justice of Romania. With the total population of 30,694 people, Romanian prison system is having high indices of tuberculosis infection (incidence of 588 per 100,000 population in 2011), and fortunately limited number of patients with confirmed MDR-TB. Totally, in absolute numbers there were around 130 patients over 2008-2010 both males and females registered as new cases and relapses for the prisons and around 40 patients registered as arrested. Around 40% were registered as smear positive, no reporting data available on those with culture positive results, as well as the coverage with DST at least to H and R.

Laboratory diagnosis of DR-TB including smear, culture and DST (only short-line to H and R) is available for all smear-positive patients and covered through the MoJ budget. The Consultant was told that every smear-positive case is tested for culture and DST. As of the time of the visit there were 60 TB patients including 8 with confirmed MDR-TB (6 males and 2 females), one male patient had monoresistance to H; and all 9 DR-TB patients were included into treatment program (non-GLC cohort). Patients with confirmed MDR-TB receive treatment in the specialized ward, each patient is being placed in separate and locked room with no access for contacting other patients. IC measures of administrative separation of TB patients with drug-resistant TB from those with confirmed susceptibility is clear. UVGIs were not available, natural ventilation was available with all windows open because of the warm time of the year. All smear/culture positive patients were using surgical masks, personnel were wearing respirators, but some were using surgical masks.

As of the time of the visit, MDR-TB regimens included mostly 4-5 anti-TB medications from the Government sources: Ciprofloxacin, Prothionamide, Cycloserine, Pyrazinamide, Ethambutol and Clarythromycin. None of the patients were on injectable agent. Out of 9 patients, four remained smear and culture positive even being on treatment for several drugs. Only 2 achieved culture conversion and 2 remained culture negative from the start of the treatment (one with monoresistance to H). Even treated under DOT, MDR-TB regimens are considered to be extremely weak with the lack of effective fluoroquinolones (at least Ofloxacin, better Levofloxacin) and injectable agent in addition to CS and Pto available.

Treatment outcomes of the MDR-TB non-GLC cohort in the prison sector are jeopardized and directly affected by the lack of full range of SLD. DST to SLD were not available for all DR-TB patients on treatment, especially for those remained smear-culture positive. Treatment results are similar to the ones in the civilian services, with approximately 1/3 failing in the cohort started treatment in 2008 (Tables 4). However, the number of patients is too low to draw any further conclusions. The proportion of failures and DST to SLD were not available for all DR-TB patients on treatment, especially for those remained smear-culture positive.

Recommendations to be included into National M/XDR-TB Response Plan:

	Recommendation	**Responsibility**
1	Update the National Guidelines for Program Management of Drug-resistant Tuberculosis (PMDT) with the recent recommendations of the WHO (June 2011). The National Guidelines on PMDT should be mandatory for use at all treatment sites including penitentiary sector. Consider technical assistance in updating the National Guidelines on PMDT from the GLC-Europe and the WHO-Euro.	NTP, MOH
1.1	In the treatment of patients with MDR-TB, a later fluoroquinolone rather than earlier-generation fluoroquinolone should be used. Levofloxacin should play the role of fluoroquinolones of first choice. Moxifloxacin should be used in all regimens of patients with confirmed drug resistance to Fq, including those with XDR-TB. Discontinue the use of Ciprofloxacin, due to the poor activity against strains resistant to Ofx.	NTP Penitentiary sector

1.2	In the treatment of patients with MDR-TB, regimens should include at least Pyrazinamide, a parenteral agent (Am/Km/Cm), a fluoroquinolones (Ofloxacin/Levofloxacin/Moxifloxacin), Ethionamide/Prothionamide and either Cycloserine and PAS, if Cycloserine cannot be used.	NTP Penitentiary sector
1.3	Streptomycin should not be used as an injectable agent for the treatment of patients with M/XDR-TB.	NTP Penitentiary sector
1.4	Ciprofloxacin should not be used as a potent fluoroquinolone in the treatment of patients with MDR-TB and should be withdrawn from the essential drug list (section for tuberculosis).	NTP Penitentiary sector
1.3	In the treatment of patients with MDR-TB, an intensive phase of at least 8 months's duration is recommended. The whole duration of treatment should be at least 20 months.	NTP Penitentiary sector
1.5	Follow Chapter 8 of the WHO Guidelines on Program Management of DR-TB (2008 emergency update) on managing the patients with polidrug-resistant TB.	NTP Penitentiary sector
1.6	DST to FLD (at least to H and R) should be performed to all SS+ and CC+ patients with no matter on patient type. DST to SLD should be performed to all cases diagnosed with H and R resistance.	NTP Penitentiary sector
2	Repeat DST on second-line anti-TB drugs for MDR-TB who remain smear/culture positive after 4 months of treatment or became smear/culture positive after conversion at later months of treatment.	NTP Penitentiary sector
3	Ensure adequate infection control measures in all TB inpatient settings, mostly administrative separation of non-TB from TB, TB from DR-TB, MDR-TB from XDR-TB and FQ resistant patients. Installation of adequate amount of UVGIs is crucial for all TB inpatient facilities.	NTP Penitentiary sector
4	Develop mechanisms for strengthening TB patients' adherence to treatment and address the problem of high rate of default using the resources available. Strict DOT should be performed at all levels and stages of TB and DR-TB management.	NTP Penitentiary sector
5	Consider options for reallocating funds and finding additional financing to strengthen the ambulatory treatment; provide strict DOT, especially at ambulatory settings and personnel motivation. Develop additional financial mechanisms and allocation of funds to provide social support for at least those TB and DR-TB patients needed, including variety of incentives and enablers. Consider developing mechanisms of allocating social support from municipal budget on a regular basis.	MOH
6	Perform recording of the frequency of adverse reactions to at least SLD and the use of ancillary medicines. Develop the list of possible ancillary medicines used in the management of DR-TB. The list to be updated on a regular basis.	NTP Penitentiary sector
7	Consider developing mechanisms for covering the ancillary medicines for side effect management through the NIH, especially for ambulatory sector.	NIH, MOH, NTP
8	Strengthen the capacity building in the management of M/XDR-TB for all TB and PHC specialists involved, including penitentiary sector.	NTP, MOH, partners

9. TB Laboratory

Findings and summary of discussion:

Laboratory network is under strengthening and reorganization over the past years, and still widely presented by 113 laboratories in each county of Romania, with 17 level I laboratories performing only sputum smear microscopy, 51 culture points, 43 level III laboratories performing DST to FLD (H, R, S. E). None of the laboratories performs DST to Z. Number of laboratories was hardly reduced since the previous GLC mission. Two laboratories recognized as National Reference laboratories in Bucharest at MNI and Cluj-Napoca (north and south) performing quality assurance for the whole country. Only four laboratories perform DST to SLD (Km, Fq, Eto, Cs, PAS): two NRL, in Iasi and partially in Bisericani to ensure geographical accessibility to SLD DST and QA for all counties of Romania. Swedish Institute for Infectious Disease Control serves as SNRL for Romanian NTP, and provides continuous technical assistance to bacteriological laboratories in terms of methodology, drug susceptibility testing, EQA and lab infection control, as well as conducted the DRS in 2008. Financial assistance had been provided through the GFATM grant.

The draft of the National M/XDR-TB Response Plan before the current GLC mission suggested to keep at least one level III laboratory performing DST to FLD in each county, keep 25 level II laboratories in those counties with high incidence of TB (over 80 per 100,000), but it seems inappropriate due to the current financial recession and need for rational use of resources available. The plan also suggested strengthening eight laboratories who will serve as centres of excellence located in eight historically recognized geographic territories of the country.

Majority of level III laboratories in counties (41) perform so called short-line DST to FLD, to Isoniazid and Rifampicin only. Average time to get the DST result to FLD from the time of collection might take up to three months. The DST to SLD performed only by two NRL and laboratories at Iasi and Bisericani to Km, Ofx, Eto, Cs and PAS. None of them perform DST to Capreomycin, except laboratory in Iasi. All DST to FLD and SLD are performed using solid L-J media by absolute concentration method, no liquid media DST or rapid molecular diagnosis is available in the country due to the lack of financial resources. Additional financing either from government or international sources should be considered by the NTP to purchase the liquid media system (BACTEC MGIT-960) and/or rapid molecular diagnosis to fasten the diagnosis of drug resistance and ensure timely start of treatment. Number of level III laboratories performing DST to SLD is reasonable, but the NTP should revise the minimum of drugs to be tested to save additional costs, increase and ensure universal coverage to SLD of every DR-TB case. The SLD DST should be performed at minimum to two injectable agents (either to Km or Am, and Cm), fluoroquinolones (Ofx) and Eto, as these medicines are recognized by the WHO as most potent agents in the MDR-TB regimen. Rational procurement of pure substancies for SLD DST will provide with additional financing to perform DST to Capreomycin.

According to the National Guidelines on MDR-TB, DST to FLD (short-line to HR) should be performed to every C+ case. Confirmed resistance to HR should be followed by SLD DST. DST performance data showed that not every case resistant to HR was tested to SLD (at MNI). Also, it was not possible to differentiate the DST performed for diagnosis and monitoring.

Quality of DST to FLD performed in 41 level III laboratories including concordance of data should be performed by NRLs on a regular basis and were not available as a summary table by the time of the visit. Also, no information was available at NRL (MNI) on infection control, human resource and equipment capacity at each level III laboratory performing DST to FLD. The NRL perform the QA for short-line DST (HR only) at usually once a year on every level III laboratory, with an average concordance rate of 82%. The EQA for DST to FLD and SLD is being performed on an annual basis at SNRL in Stockholm. Recent EQA results showed high rate of concordance (data from four level III

laboratories performing DST to SLD) H – 100%, R – 100%, S – 100%, E – 100%, Am – 100% (Iasi), Km – 100%, Ofx – 94.4%, Cm (Iasi) – 100%. DST to Cs, Eto and PAS were not included into EQA.

It was agreed during the discussion of the M/XDR-TB Response Plan that there is an urgent need to perform the cost analysis, as long as performance evaluation of each of level III laboratory (41), because the exceeded number of level III laboratories performing DST to FLD with almost unknown program performance is cost ineffective and might affect the quality of results. The cost effectiveness and performance evaluation should include information on concordance of DST to FLD, workload, number of personnel, infection control and equipment, commodities and products (media, pure substances, biosafety cabinets, centrifuges, etc), as well as geographical proximity to one of the eight regional level III laboratory. Due to the existing financing system of laboratory network there is no need to close level III laboratories to keep personnel, but rather to delegate the DST to FLD to those laboratories meeting the requirements of program performance, capacity and infection control. Once cost analysis and performance evaluation completed, perform the discussion and amendments to the regulations and existing financial system of laboratories to ensure reallocation of funds for strengthening the capacity of NRL and those laboratories recognized as those performing DST to FLD. Reallocation of saved funds should also ensure proper and timely transportation of bacteriological materials to those limited number of laboratories performing DST to FLD.

DRS was done with the technical assistance from the SNRL (Sweden) over 2009-2010 for four laboratories performing DST to SLD with generally good performance. DRS defined the level of XDR-TB among MDR-TB cases of 11.37% (among new MDR-TB cases - 9.9%, among retreatment cases – 11.6%). DRS showed extremely high level of any resistance to Cm (69.3%), to Km (57.3%) and Am (54.7%) among tested strains. Please refer for more detailed information on DRS to the previous GLC monitoring mission report of 2011.

Laboratory in the prison sector performs smear/culture and DST to “short-line” drugs (H and R). Coverage with culture and “short-line” DST is available for all smear-positive patients. DST to SLD was not noticed to be performed at neither civilian sector lab nor SNRL. In 2011 the lab performed 2,044 culture tests, with 175 registered as CC+ (samples not patients). Contamination rate is relatively high of 4.5% mostly due to the lack of adequate IC measures. DST to “short-line” (H and R) was performed to 60 samples, as explained, all patients with culture positive result was covered with DST.

Recommendations to be included into National M/XDR-TB Response Plan:

	Recommendation	**Responsibility**
1	Consider optimization and structural reorganization of laboratory network to reallocate funds for DST. Cost analysis, performance evaluation, capacity and infection control of each laboratory is requested (quality control for DST concordance of each lab).	MOH/NTP
2	Consider performance of SLD DST at minimum to two injectable agents (Km or Am, and Cm), Fluoroquinolone (Ofx) and Eto at four level III laboratories (Bucharest, Cluj-Napoca, Iasi and partially Bisericani). Coverage with DST to SLD for the prison sector is strongly recommended.	MOH/NTP Penitentiary sector
3	Ensure adequate IC measures at level II and level III laboratories. Administrative separation of “clean” and “infectious” zones, as well as availability of Class 2 biosafety cabinets is essential to perform DST to FLD and SLD. Individual protection of personnel (3-M, N-95 or similar) is strongly recommended for all personnel working in level i, II and III laboratories. Consider installation of UVGIs in the corridors of the	MOH/NTP

	laboratories to decrease the risk of nosocomial transmission of infection to laboratory personnel.	
4	Ensure that DST to FLD at least to HR performed to each C+ patient. DST to SLD plus E should be performed once HR or any R resistance defined.	MOH/NTP Penitentiary sector
5	Introduce rapid tests for HR resistance, or at least R resistance. An algorithm for rapid molecular diagnosis should be developed with certain criteria for patient groups – with the TA from SNRL. Training of laboratory personnel is required to perform rapid molecular diagnosis.	MOH/NTP
6	Conduct quality assurance on FLD and SLD on a regular basis, to be performed by NRLs, including penitentiary sector.	MOH/NTP

10. TB Infection Control

Findings and summary of discussion:

Improving infection control is one of the priorities of Romanian NTP. The NTP has developed the National IC Plan for Tuberculosis for 2011-2015, which includes all relevant information on administrative, environmental measures and personal protection and are in alliance with the recent WHO recommendations. The plan is not yet adopted by the MOH. Coordination of IC activities is performed at the level of NTP by IC Coordinator. Due to the changes at the leadership of the NTP the new IC Coordinator has not yet assigned by the time of the visit. There is no adequate structural coordination at county level TB Units (county NTP) for infection control issues.
Due to the fact that treatment of patients with MDR-TB is decentralized to county level, the Category IV intensive phase is available only at so-called MDR-TB centres at MNI, Bisericani, and other TB hospitals in counties. Continuation phase is under the responsibility of county level TB dispensaries (ambulatory sector). Treatment of drug-susceptible TB during the intensive phase is available country wide at the level of TB hospitals.

Treatment of MDR-TB patients at Marius Nasta Institute is being performed in a separate building with 48 MDR-TB beds, no ventilation is available in the building. The MDR-TB department serves as one of two centres for MDR-TB treatment during the intensive phase. The MDR-TB ward is equipped with UVGIs but not at all patient rooms. Patients are being separated by smear/DST status, which is considered as an adequate measure of administrative separation of patients. Respirators available for personnel, patients are using surgical masks.

The Consultant visited the Laemna Pulmonology Hospital at Dolj County designated for treatment of pulmonology and TB patients. The hospital is located in two stored well renovated building with no modern ventilation, and was assumed to serve as one of the centres for MDR-TB treatment. By the time of the visit the hospital had 80 patients with TB, including 23 with DR-TB (10 with confirmed MDR-TB) and 74 pulmonology patients (COPD, acute pneumonia, acute bronchitis, etc). Average duration for hospitalization is regulated and monitored by NIH and is 40 days for drug-susceptible TB and 120 days for MDR-TB patients. Hospitalization might be increased if a patient will be discharged and hospitalized again, even the same day. Generally, patients were separated only by rooms by TB/MDR-TB/bacteriological S+/C+ status. At the same time, all patients were located in one ward and shared same corridor, bathrooms and toilets. No UVGIs available in the whole facility but basic UV lamps turned on when patients were out of their rooms. Personnel were using both respirators and surgical masks, but not all of them. Even if hospital administration was separating hours in cafeteria for breakfast, lunch and dinner for pulmonology and TB patients, as well as DOT provided in patients rooms there is an extremely high risk for nosocomial transmission of TB and its DR-TB strains to regular pulmonology patients. Health personnel and visitors are also at high risk to be infected with DR-TB. Consultant was informed that similar situation with IC with inadequate administrative separation of patients and poor IC is almost in every TB hospital in the country. None of the assessment of each TB facility for IC had been performed so far.

Table 6. Summary of Infection Control measures in TB facilities including laboratories.

Facility and type of infection control measure	Infection control measures in TB department(s)
Facility: Laemna Pulmonology TB Hospital	
Administrative control measures	1. Separation of patients by smear/DST status in rooms 2. TB and non-TB patients are sharing same floors and facilities 3. Separate time for dining for TB and non-TB patients
Environmental control measures	1. Basic UV lamps 2. General airflow (open windows) 3. Engineering ventilation is not available
Personal protection	1. Respirators available for personnel 2. Surgical masks available for patients 3. Cough etiquette is not prioritised
Facility: MDR-TB Ward, Marius Nasta Institute	
Administrative control measures	1. Separation of patients by smear/DST status in rooms 2. MDR-TB patients in separate MDR-TB ward 3. N/A
Environmental control measures	1. UVGIs available in MDR-TB ward 2. Engineering ventilation is not available 3. N/A
Personal protection	1. Respirators available for personnel 2. Surgical masks available for patients 3. N/A
Facility: Prison TB Hospital	
Administrative control measures	1. Patients are separated in rooms from each other by smear/culture/DST status 2. DOT and food delivery provided in rooms 3. No contact with other patients
Environmental control measures	1. Natural ventilation 2. No UVGIs available but basic UV lamps 3. N/A
Personal protection	1. Patients wearing surgical masks 2. Majority of personnel wearing respirators 3. N/A

Recommendations to be included into National M/XDR-TB Response Plan:

	Recommendation	Responsibility
1	Administrative measures of separating TB from non-TB patients, smear/culture positive drug susceptible patients from smear/culture positive drug resistant patients, MDR-TB from XDR-TB is essential, especially at all TB inpatient facilities.	NTP
2	UVGI lamps are recommended for use at patients' presence at least in all inpatient facilities (wards, corridors, procedure rooms, DOT points), including penitentiary sector.	MOH, NTP, Penitentiary sector
3	Health personnel at all treatment sites with presence of any infectious patient should wear respirators and patients at all inpatient sites at minimum should wear surgical masks.	NTP, Penitentiary sector

4	Conduct the comprehensive assessment on IC at each inpatient facility. Check list with certain criteria should be developed and used for assessment. Each facility should develop and implement the clear IC plan to fulfil the administrative separation of patients by MTB/smear/culture/DST status.	NTP
5	Ensure and support training on IC.	MOH, NTP, partners
6	Update the National Guidelines on IC. Technical assistance from the WHO-Europe should be considered.	NTP, WHO-Europe

11. Second line anti-TB drug management

Findings and summary of discussion:

The drug procurement system is financed through the NIH and county NIHs and totally decentralized to county level, making TB facilities responsible for forecasting, order, distribution and use of all TB medications. Each TB facility is being financed through the local NIH, and responsible to organize tenders with the list of medications needed. The legislation regulates the tenders to happen in up to two months since the place of the request. Facilities are able to purchase medications according to the essential drug list (EDL) of medications and providers approved on the annual basis by the MOH. The MOH list includes all essential medications used for the medical practice, including the majority of anti-TB drugs listed in the Section P1 "National Program of Infectious Diseases", Subprogram "Treatment of Tubeculosis": all first (H, R, E, Z, S) and second-line (Kanamycin, Amikacin, Ofloxacin, Ciprofloxacin, Moxifloxacin, Prothionamide, Cycloserine, Clarythromycin) but lacking Capreomycin and PAS. Majority of providers for FLD and SLD are from Romanian and other European pharmaceutical companies, which probably are prequalified by the WHO. However, the Romanian market of pharmaceutical companies producing SLD is not widely presented, making suppliers not interested in importing the SLD from outside Romania due to the smaller quantities in compare with other pharmaceutical markets.

The essential drug list includes information on maximum unit prices for each medication, which result in selecting positions of cheaper medications with no respect to potency and quality. Thus, it makes TB facilities selecting medications, which are more cost-inexpensive, due to existing financing mechanism and availability of funds allocated to each TB facility by the local NIH for average amount of patients treated per year. Also, the providers are not interested in participating in multiple tenders taking place at each TB facility level due to smaller quantities. As a result, the majority of TB facilities in Romania are purchasing Ciprofloxacin as fluoroquinolone of choice but not Ofloxacin for MDR-TB or Moxifloxacin for XDR-TB, as these medications are more expensive and TB dispensaries are interested in purchasing higher quantities of Ciprofloxacin to cover the majority of patients and provide buffer stock.

NTP drug orders and tenders for anti-TB drugs are mostly done once in two years, the process is unpredictable, which put in jeopardy the availability of adequate quantity of medications in case of inadequate forecast. Former NTP Coordinator on drug management was performing the data collection on stocks of first and second-line drugs in each county by submitting the requests on a regular basis, which should be continued by newly assigned Coordinator. The information is entered in MS Excel, no separate software is available. The tables show the analysis on average monthly consumption in each county and summary column for the whole country for each medication. At the same time, with decentralized drug procurement system it seems almost impossible to track drug orders and tenders taking place in each county, which severe the situation. According to the data, the current availability of NTP medications does not reflect the actual need for the following medications with major stock outs for Injectable agents (Km, Cm, Am), fluoroquinolones (Mfx for XDR-TB and FQ resistant patients) and PAS. The table below describes serves as summary table and does not reflect the situation by counties (41), which assumed to be more severe than the average National data with stock outs for major SLD. Also, due to decentralized system of procurement and autonomous status of county TB facilities it was impossible to verify the total number of MDR-TB patients on intensive phase to calculate the actual need for injectable agents.

Table 7a. Availability and stock out of SLD, National summary data, March 31, 2012

Drug	Average monthly consumption	National drug stock as of March 31, 2012	Availability and stock outs
Km	5,525	614	0.1 months
Am	6,159	6,224	1.0 months
Pto	81,503	185,744	2.3 months
Cs	75,724	133,318	1.8 months
Ofx	72,334	169,623	2.3 months
Lfx	2,440	345	0.2 months
Mfx	1,838	661	0.4 months
Cm	820	0	0.0 months
PAS	2,020	0	0.0 months
Clr	11,841	22,296	1.9 months
Z	654,541	1,390,818	2.1 months
Cipro	61,336	183,750	3.0 months

Availability of SLD at county level had been analyzed on the example of Craiova TB Dispensary at Dolj county. With 11 MDR-TB patients on treatment, the treatment regimens seems to be extremely weak having Ciprofloxacin as FQ, Pto, Cs, Z and E. Similar situation with availability of non-GLC SLD happens in all counties, which puts in jeopardy the effectiveness of the whole National Tuberculosis Program in Romania and contribute to the growth of the reservoir of patients with extreme drug-resistant tuberculosis.

Table 7b. Availability and stock out of SLD, Dolj county data, Craiova TB Dispensary, April 24, 2012

Drug	Average monthly consumption	National drug stock as of April 24, 2012	Availability and stock outs
Km	60	0	0.0 months
Am	0	0	0.0 months
Pto	3,100	10,936	3.5 months
Cs	2,943	6,010	2.0 months
Ofx	120	0	0.0 months
Lfx	0	0	0.0 months
Mfx	0	0	0 months
Cm	0	0	0 months
PAS	0	0	0 months
Clr	0	0	0 months
Z	31,600	71,238	2.3 months
Cipro	6,576	18,181	2.8 months

The SLD procurement for the GLC cohort is centralized and managed through the PIU of the GFATM grant through the GDF mechanism. UNIFARM, the National storage and distribution facility, serves as centralized distributor for the GLC medications, and has well established and reliable system of distribution to all territories of Romania. Within National TB Program the UNIFARM is now responsible for drug storage and distribution of GLC medicines, Am and Cm (imported by special decree of the MOH for the non-GLC cohort). In 2011 due to the fact of insufficient availability of Am at county level, the UNIFARM imported only 25,000 vials of Am (Biodacin, Poland) by special decree of the MOH and distributed to the several counties, which was sufficient only for 10 months of treatment with injectable agent for 83 patients (10% of the need). In 2012, the same mechanism used for import of 4,000 vials of Am, which is not enough for growing number of patients and will stock out soon (400 vials remained by the time of the visit).

As of March 31, 2012, 202 MDR-TB patients were on treatment in GLC cohort, with the last patient enrolled in April 2011 (10 patients were receiving the injectable agent). None of the drugs were at stock outs and expired, but close for Cycloserine (May 2012) and Ofloxacin (August 2012). Capreomycin has short expiration in September 2012, which will not affect treatment of 10 patients on treatment with injectable agent. In average, the PIU of GFATM grant was ordering the injectable agent up to 10 months of intensive phase, which seems adequate and matches the requirements of the recent WHO recommendations (2011).

The previous GLC monitoring mission together with the NTP Central Unit conducted the cost effectiveness analysis for the local versus GLC procurement (updated in October 2010), which showed the comparison in prices of 2.6 times higher for decentralized local system of procurement. Procurement through the GDF mechanism also seems challenging, as GDF cannot participate in State tenders even if cost-effective. Thus, there is a need for the Government (MOH) to include the WHO prequalification as requirement for tender documentation for State SLD procurement.

Recommendations to be included into National M/XDR-TB Response Plan:

	Recommendation	Responsibility
1	Consider direct purchasing of SLD through the GDF mechanism with government funding to ensure treatment of MDR-TB patients.	MOH
2	Centralize the drug procurement system for first and second-line anti-TB medications as an urgent measure. Joined decree of MOH and NIH should be performed as the first step.	MOH, NIH
3	Include the WHO prequalification as requirement for tender documentation for State procurement of anti-TB medications.	MOH, NTP
4	Review the Essential Drug List to include Capreomycin and PAS when registered, exclude Ciprofloxacin as an urgent need. Provide most possible assistance for importing at least Capreomycin by special order of the MOH for all MDR-TB patients require.	MOH, NTP
5	Improve coordination on drug management between National and county level. Assign County level coordinators on drug management responsible for tracking drug order, forecasting, monitoring at county level, data collection and coordination of activities with the NTP Coordinator on Drug Management.	MOH, NTP

12. Information system and data management

Findings and summary of discussion

National recording and reporting system generally corresponds to the WHO recommendations. Data collection for the whole country and international reporting is being performed by the NTP Central Unit on behalf of the MOH. All TB Dispensaries have established computerized web-based system with servers at TB Surveillance Unit at NTP level in MNI (Bucharest), and collect information from labs and hospitals in the county. TB Surveillance is regulated and had been endorsed by the MOH as mandatory for all institutions involved in TB program. TB Surveillance software is functioning at all TB dispensaries, with all cases registered and reported to the National level. The software has technical limitations with producing reports at both National and county levels. However, the decentralized system of information flow from each TB dispensary requires improvement.

Data information system on laboratory results is also centralized at NTP level (MNI) with the data including number of sputum smear microscopies, cultures and DST performed by each laboratory. However, culture and DST results are not complete due to the fact that data are not entered into system at county level labs on a regular basis.

Separate MDR-TB registry is available in MS Excel since January 2012 with essential information on DR-TB case registration. Forms for DR-TB had been developed and match the requirements of the WHO (Guidelines for PMDT, 2008) and institutionalized at the National level. Unfortunately, data operators at TB dispensary level do not often make the distinction between GLC and non-GLC cohort, which affect the cohort analysis. As discussed with the head of NTP and the team, there is an urgent need to update the National Electronic TB registry with the information required for Program management of DR-TB, which will include at least all essential information on case notification, lab data with smear/culture/DST results, patient type, treatment regimen in according to the latest WHO recommendations. DR-TB forms should also be filled in at a regular basis, and updated in direct consistency with the latest WHO recommendations, filled in at each county. System of centralized data collection should be improved.

All MDR-TB cases registered should be entered notified in TB03 to allow TB dispensaries perform cohort analysis on a quarterly/annual basis. In addition, there is a need to stratify cases by SS+/CC+, SS-/CC+, SS+/CC-, SS-/CC- status by the time of registration. Treatment outcomes for DR-TB patients should be performed in accordance to the recent WHO recommendations.

Recommendations to be included into National M/XDR-TB Response Plan:

	Recommendation	Responsibility
1	Update the National Electronic TB Register with essential information on MDR-TB. Develop the list of variables on DR-TB case registration and management. Penitentiary system should use similar register as in civilian sector.	NTP, Penitentiary sector
2	Provide adequate financial resources for the update of the National Electronic TB Register with MDR-TB.	MOH
3	Conduct regular monitoring over data collection and entry at county level TB dispensaries and laboratories.	NTP at county level
4	Ensure proper training on TB Surveillance at National level for all personnel responsible for surveillance and cohort analysis. Consider technical assistance in conducting training from the WHO-Europe.	NTP, Penitentiary sector

13. Ethics of TB prevention, care and control

Findings and summary of discussion

Treatment of TB and MDR-TB in Romania is free of charge with no respect to race, ethnicity, religion, age and gender. Minorities, especially Roma population, do have an access to basic health services including free diagnosis of TB and treatment. Over the past years Romania is facing the issues of outgoing labour migration, with often patients defaulting treatment for work outside of the country.

Please provide recommendations to be included into National M/XDR-TB Response Plan:

	Recommendation	Responsibility
1	Address the issues of improving TB and DR-TB patients' adherence to treatment, especially at those groups with high risk to default.	MOH, NTP, Penitentiary secor

14. List of people met in chronological order

- Dr. Elmira Ibraim – Head of NTP (former), MNI
- Dr. Mihaela Stefan – Program Manager, RAA
- Dr. Emilia Crisan – Medical Director of MNI
- Dr. Gilda Popescu – Head of NTP, MNI
- Dr. Mariana Andrei – DOTS-Plus Project Manager, MNI
- Dr. Ruxandra Spataru – DOTS-Plus Project MDR-TB Expert, MNI
- Dr. Nicoleta Cioran – M&E coordinator, NTP, MNI
- Dr. Cristina Popa – MDR-TB Coordinator (former), NTP, MNI
- Dr. Cristian Didilescu – NTP Consultant, MNI
- Mr. Horia Cocei – IT and Data Collection Specialist, NTP, MNI
- Dr. Cristian Popa – Drug Management and CITB Coordinator (former), NTP, MNI
- Dr. Lucia Mihailescu – NTPP Manager
- Dr. Victor Spinu – MDR-TB Bucharest Center Manager
- Dr. Adriana Moisoiu – Laboratory Coordinator, NTP, MNI
- Dr. Olga Moldovan – Coordinator for NRL, MNI
- Dr. Tudor Palaghianu – Drug Management Coordinator, NTP, MNI
- Mrs. Elena Ioan – OPPC, Sector 4, MNI
- Dr. Otilia Petrescu – Pharmacist, MNI
- Dr. Miu Cornelia – NTP Coordinator, Craiova TB Dispensary, Dolj County
- Dr. Voicu Maceseanu Alin – Respiratory Diseases Physician, Craiova TB Dispensary, Dolj County
- Dr. Mirela Corneanu - Respiratory Diseases Physician, Craiova TB Dispensary, Dolj County
- Dr. Victor Grecu - Respiratory Diseases Physician, Craiova TB Dispensary, Dolj County
- Mrs. Daniela Parvu – Surveillance specialist, Craiova TB Dispensary, Dolj County
- Dr. Adriana Florescu – Biolog, NTP Coordinator for Dolj County
- Dr. Cornelia Editoiu – Biolog, Craiova TB Dispensary for Dolj County
- Dr. Constantin Marica, Professor, MNI
- Dr. Elena Pascu – General Director, C.N. Unifarm S.A.
- Dr. Amalia Eechete – Deputy Director, Public Health Control in Public Health Department, Ministry of Health
- Mrs. Silvia Asandi – General Manager, RAA
- Dr. Lucia Mihailescu – PIU-TB NAP Coordinator
- Dr. Caliopi Franiseailu – Laboratory specialist, prison sector

- Dr. Maria Tirea – Medical manager, prison sector
- Dr. Mihaela Padut, Pneumologist, prison sector
- Mr. Dan Corbescu – TB Projects Implementation Unit, National Administration of Penitentiaries
- Mrs. Oana Constan – Director of Health Programs Department, NIH
- Mr. Ady Popescu – Secretary of Health Programs Department, NIH
- Mr. Iulian Petre – Executiv Director, UNOPA

15. Attachments

- Annex 1: GLC monitoring mission agenda
- Annex 2: DRS results of Romania (2009-2010)
- Annex 3: Laboratories performing smear/culture/DST
- Annex 4: Structure of laboratory network
- Annex 5: DST results of 2010 and 9 months of 2011
- Annex 6: Recommendations from the previous GLC monitoring mission with status of completion