GLC-EUROPE MONITORING MISSION TO 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
ECDC – European Center for Disease Control and Prevention
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
NSP – National Strategic Plan to Control TB in Romania, 2015-2020
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 progress of implementation of the National M/XDR-TB Response Plan;
- to assess the current M/XDR–TB Control project supported by the Global Fund or any other donor.

Key issues to be elaborated and reviewed:

1) Implementation of the 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) Identify the need of technical assistance on any aspect of Program management of drug-resistant TB to fulfil the National M/XDR-TB Response Plan;
3) 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;
4) Assess case finding strategies and identify barriers to timely start of M/XDR-TB treatment, including TB in children;
5) Assess the county's readiness to introduce Bedaquiline
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.
- Identify areas of technical assistance from the WHO-Europe and GLC-Europe.
- Europe monitoring mission in 2015 to evaluate the progress of program performance.

2. Background information

GLC/Europe is supporting the implementation and scale up of the M/XDR-TB Response Plan in Romania. Since the launch of the GFATM project, GLC conducted yearly monitoring missions with the last one in March 2014, which was conducted as a part of the National Tuberculosis Review Program led by the WHO-Europe and ECDC.

Romania received several approvals from the GLC to access quality-assured SLD for a total of 850 MDR-TB patients. During 2004-2011 a total of 884 MDR-TB patients were enrolled into GLC-approved program with funding available from the GFATM grant. An average treatment success rate for the first three cohorts of a total of 364 MDR-TB patients (2004-2005, 2006-2007, 2009) is 66.8%. The treatment success rate of 2011 cohort was 73.6%. Despite the good program performance of GFATM grants in Romania, the treatment effectiveness of non-GLC cohorts of patients was showing extremely poor outcomes over the years due to series of structural, financial and organizational constrains. In early 2013 the GFATM approved financing through TFM of a new cohort of 300 patients to be enrolled in 2013-2014, which started in October 2013 and included regimens for 19 patients with XDR-TB. Additional 1,460 patients with M/XDR-TB will receive access to quality-assured second-line drugs (SLD), as well as new and other Group 5 drugs with funding available from the Norwegian Fund and the GFATM for the period until March 2018.

Political commitment in Romania has been increased recently, especially after continuous political and technical support from the WHO, ECDC and other international organizations, focused on strengthening the National Tuberculosis Program (NTP). In March 2015, the Government of Romania endorsed the National Strategic Plan for Control of Tuberculosis in Romania for 2015-2020, which presents the country's priorities to address the public health challenge of tuberculosis. The National Strategic Plan (NSP) was developed in close partnership with the MOH, the NTP and WHO, and other government and non-government organizations. The NSP outlines the national strategies to respond the unmet needs and build sustainability of the system, as well as presents the long-term vision, and identifies innovative approaches targeted on achieving dramatic decline in TB incidence and mortality in Romania by 2020.

Still, there are various bottlenecks require attention from the Government and International authorities in order to strengthen the capacity and performance of Romanian TB Program, but majority of them will be covered within the implementation of the NSP for 2015-2020 and two international donor-funded projects (GFATM and Norwegian Fund).

3. Follow up of the previous mission recommendations.

In compare with previous GLC-Europe monitoring mission the Romanian National Tuberculosis Program is showing significant progress in the scale up and management of drug resistant tuberculosis. Some of the key recommendations from the previous mission remain under progress and implementation. Out of 17 key recommendations to the Ministry of Health, 5 have been fully completed, and 12 were under implementation and progress. Out of 22 recommendations to the National Tuberculosis Program of Romania, three have been fully completed and 19 were under implementation and progress, and require joined efforts from the NTP and international donor organizations for successful completion. Several recommendations are repeated in the current report.

Priority recommendations from previous GLC monitoring mission	Status/Comments
Recommendations to the MOH	

Support and monitor the implementation of the National M/XDR-TB Response Plan.	The National M/XDR-TB Response Plan was included under the National Strategic Plan 2015-2020
Consider prevention and control of TB and M/XDR-TB as a public health priority; consequently, ensure sufficient and sustainable funding and the required changes in the health system. Finalize and approve the "National strategic plan for TB control 2013-2017" in line with the recommendations of this review. Ensure that no delays will occur in the approval of future norms (secondary legislation) necessary to implement consistently the National TB Programme.	In 2014, MoH increased the budget for NTP from 14,6 mil LEI up to 29,8 mil LEI. Additionally for the following years, around 20 mil EUROs are secured for TB control activities from GFATM and Norway grants. The National Strategic Plan 2015-2020 was developed and by the end of February will be approved through Gov decision.
Revise the second TB project under the Norwegian Financial Mechanism in line with the recommendations of this review and in supporting their effective implementation, considering also the technical assistance required. Establish, as soon as possible, a working group for drafting the concept note required to access the further support of The Global Fund. Revise the current composition of the country coordinating mechanism (CCM) to ensure the direct involvement of the Ministry of Health.	The second project for Norway grants stated on 4th of December, the CN was submitted on 15th of October and the CCM chair is the representatives of the MOH. Both grants received approvals for funding.
Revise the payment system under the National Health Insurance House in order to prevent unnecessary hospitalization of patients, promote administrative measures for TB infection control, ensure an appropriate distribution of laboratories and provide TB outcome-based incentives to family doctors under the package of minimum services currently under discussion.	All the activities are included under the NSP and will be implemented during the next 3 years with the technical support of WHO and national experts.
NTP Central Unit team should have a clear mandate (SOP) to act as the actual National Tuberculosis Program Unit and be enforced with capacity to perform coordination of activities, monitoring and supervision, planning and analysis, capacity building required for successful implementation of TB and DR-TB Control.	NTP team has a clear mandate as National TB Program.
NTP Central Unit team should be enforced by allocating adequate funding for monitoring and supervision visits to the counties.	MOH increased budget starting 2015.
Support the application preparation to the New Funding Mechanisms to the GFATM from Romania.	Concept Note submitted to GFATM on 15th of October.
Endorse the updated National Guidelines on PMDT and make it mandatory for implementation at all inpatient and outpatient institutions nationwide involved in the management of TB and DR-TB, including penitentiary sector.	This activity is included under the National Strategic Plan and will be implemented during the following period.
Ciprofloxacin should be withdrawn from the essential drug list (C2, section on tuberculosis) and not be used as fluoroquinolone in the treatment of patients with DR-TB and should be withdrawn from	NTP officially requested the MOH to withdraw Ciprofloxacin from the EDL (C2 list). Starting 2015, procurement of Ciprofloxacin under the national tender is

the essential drug list (section for tuberculosis).	not taking place.
Consider options for reallocating funds and finding additional financing to strengthen the ambulatory treatment; provide strict DOT, especially at ambulatory settings and personnel motivation, especially for PHC level. 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.	The activities were included under the National Strategic Plan and will be implemented gradually during the next years (a pilot will be implemented with the financial support from GFATM new TB grant).
Consider adequate financing of the culture testing (at least) using the liquid culture media.	The budget for NTP was increased and it was possible for the TB labs to procure liquid culture and DST. The liquid testing was included under the NSP and is planned to replace the solid media testing by 2018.
Consider allocating sustainable financing to perform the regular (at least twice per year) monitoring visits to the regional laboratories by the members of the Laboratory Working Group.	As the budget of the NTP was increased, last year one supervisory visit was performed at the level of each TB laboratories.
Ensure adequate financing and uninterrupted supply of drug procurement for FLD and SLD, especially with the upcoming change in financing of the National TB Program from the National Insurance House.	MoH ensure 100% of the budget for the TB FLD and cover partially the need for SLD. For the next 3 years, the needs will be covered with the financial support of the GFATM and Norway grants.
Centralize the drug procurement system for first and second-line anti-TB medications as an urgent measure. Consider creating the Central Supply Office for FLD and SLD procurement and nominate company/companies to perform distribution of drugs to the counties on a regular basis to avoid stock-outs and treatment interruptions.	The centralised drug procurement system is in place from February 2014. The system will be reviewed during 2015-2016.
Urgently endorse the National Infection Control Plan for 2013-2017 and ensure adequate financing of infection control activities.	The activities included under the National IC plan were included under the NSP but the Plan is not endorsed yet.
Urgently introduce TB infection control measures in diagnostic and treatment facilities and in congregate settings by revising the Ministry of Health's Order N°916 (26 July 2006) and the current system of health facility accreditation and including specific measures for the prevention of airborne TB transmission.	The activities were included under the NSP.
Address the issue of excessive hospitalization at TB inpatient facilities by creating criteria for admission to the hospital and strengthening the ambulatory care program, including aspects of adherence to treatment.	The activities are included under the NSP and will be addressed during the implementation of GFATM project. TA from International experts is expected.
Recommendations to the NTP	
Ensure complete 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 confirmed HR	The DST for the FLD was included under the NSP and will gradually reach 100% during the following period.

resistance, to define the exact reservoir of M/XDR-TB.	
Strengthen the coordination of activities, monitoring and supervision at county level. Clear ToR and SOP should be developed for the county coordinators. Adequate financing to perform monitoring visits to the treatment sites should be considered by the MOH and NIH.	The activity was included under the NSP and will be implemented during the following period.
Finalize the update the National Guidelines for Program Management of Drug-resistant Tuberculosis (PMDT) in alignment with the recent recommendations of the WHO (2008 and 2011 editions). Ensure that once endorsed, copies of the National Guidelines should be distributed among all TB specialists involved in PMDT.	The National Guidelines for PMDT was updated in 2013, however due to the availability of the drugs from group 5 (including BDQ) additional updates are required, including pharmacovigilance.
Any use of second-line drugs should be only authorized by DR-TB Committee to avoid improper management of patients and further amplification of drug resistance. Regimens for patients diagnosed with DR-TB (Mono-DR, PDR, MDR and XDR) should be designed in accordance with updated version of the National Guidelines.	Mono- and PDR-TB cases are discussed by the local commissions. However, no protocol available for mono and PDR-TB. M/XDR TB cases are submitted to the MDR-TB commissions for regimen design and outcomes. As part of the Norway grant, all DR-TB patients will be mapped and the regimens will be reviewed.
NTP should consider intense capacity building on PMDT for at minimum TB County Unit coordinators in alliance with updated National Guidelines on PMDT. Consider clinical rotation rounds for county TB coordinators at two MDR-TB Centers to improve their capacity to manage MDR-TB. Further cascade trainings on clinical and program aspects for the rest of doctors, nurses and PHC physicians involved in the management of patients with TB and DR-TB is highly recommended. Separate training for TB hospital/TB dispensary administration at all counties is essential to increase the level of support of the National TB Program implementation.	In progress, several training sessions were implemented with GFATM financial support and the training will be continued under the Norway grant (PMDT, IC TB, etc).
Strictly prohibit the use of Streptomycin in the regimens for patients with DR-TB.	
In the management of patients with any resistance to FQ (MDR-TB + FQ, XDR-TB), Moxifloxacin should serve as FQ of choice. Consider including the list of Group 5 agents used in the management of XDR-TB as an annex (Linezolid, Clofazimine, Imipenem/Cilastatin). Levofloxacin should serve as FQ of choice in the management of patients with MDR-TB	Updated version of the National guidelines is not yet endorsed by the MOH. Partially implemented, as Moxifloxacin is 3 times more expensive than Ofloxacin. No Moxifloxacin was available until February 2015 (from GFATM). During next three years Moxifloxacin will be available both from GFATM and Norway grant.
If considered to expand participation in Compassionate Use Program, the regimens containing bedaquiline should match the WHO Policy Guidance "The use of bedaquiline in the treatment of drug-resistant tuberculosis", 2013.	Not the case anymore, as the BDQ is officially registered in Romania and funds are available to procure the BDQ with Norway and GFATM funding.

With funding available from GFATM TFM management of patients with XDR-TB should be initiated at DR-TB centers. Ensure strict implementation of all program and medical requirements of PMDT for all GLC cohort patients on XDR-TB regimens especially.	The XDR TB patients will be enrolled only in the MDR TB centers and patients will be included under the projects for social and psychological support.
Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-TB drugs, irrespective of CD4-cell-count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment (strong recommendation). Conduct an in-depth analysis of the incidence and prevalence of viral hepatitis C and/or B among TB and DR-TB patients and develop tools towards management of co-infection. Technical assistance from the WHO-Europe should be considered.	
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. Consider developing mechanisms for covering the ancillary medicines for side effect management through the new mechanism of financing through the MOH, especially for ambulatory sector.	The data base will be updated with the financial support of the Norway grants and the side effects will be added. Cost of the drugs for side effect management for ambulatory care were included under the NSP.
Develop strategies aimed on improving patients' adherence to treatment using the principles of patient-centered approach to address the problem of high rate of default from treatment. Alternatives for hospitalization should be developed by the NTP and presented to the MOH for financial support. Strict DOT should be performed at all levels and stages of TB and DR-TB management.	The activities were included under the NSP and will be gradually implemented with the financial support of GFATM, ESF, Government of Romania.
Ensure the universal access to rapid diagnosis of TB and MDR-TB by using cartridge-based Nucleic Acid Amplification Techniques at selected lower level laboratories and/or sputum collection points with high rates of TB and/or MDR-TB (e.g. prisons, selected hospitals, HIV centres) and Line Probe Assay in geographically-representative regional laboratories. Accordingly, redesign the TB laboratory network and complete its rationalization by the end of 2015.	Under implementation.
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.	Under implementation.
Continue performing regular external quality assurance of LPA in SNRL (at least once per year) once equipment is installed.	
Update the National Guidelines on Laboratory Diagnosis for Tuberculosis with rapid molecular	Included under the Norway grant.

diagnosis used in the country.	
Consider creating TB Infection Control Committee at National level and empower it to monitor the implementation of the plan.	To be implemented with WHO/ECDC/EUCOM.
Complete the comprehensive assessment on IC at each inpatient facility using the TB Infection control generic templates.	To be implemented with WHO/ECDC/EUCOM.
Update the Essential Drug List for 2013 to exclude Cirpofloxacin as it is considered as weak regimen to exclude the possibility of purchasing weak fluoroquinolone. The Essential drug list should include only those medications, which are included into the regimens of updated National Guidelines on PMDT for Romania.	Under implementation.
Rationalize the recording and reporting system, revise the national TB database to better process patients' data and ensure their analysis and use for policy decisions.	Under implementation with the financial support of Norway grant.
Ensure that the National registry contains information on all TB and DR-TB cases registered in the country, not only those registered for treatment.	Under implementation with the financial support of Norway grant.
Address the issues of improving equal access to TB and DR-TB patients' adherence to treatment, especially at those groups with high risk to default.	Under implementation with the financial support of Norway grant, GFATM grant.

4. Current mission recommendations (summary)

	Recommendations to the MOH
1	Prevention and control of TB and M/XDR-TB should be considered as a public health priority. The implementation of the National Strategic Plan for TB Control for 2015-2020 should be supported by the Government of Romania with sufficient and sustainable funding, and necessary changes in the health system. Aspects requiring support include access to adequate treatment regimens and uninterrupted supply of TB drugs, ambulatory treatment and social support of patients, diagnosis and infection control.
2	Consider an update of the National Strategic Plan for TB Control for 2016-2020 with upcoming release of the TB Action Plan for the WHO European Region (possibly in 2017).
3	Support the implementation of the new GFATM and Norwegian grants. MNI Pulmonology Institute (NTP) should play the leading role in the management and implementation of this and upcoming grants (European Structure Fund).
4	Revise the payment system under the National Health Insurance House in order to prevent unnecessary hospitalization of patients, promote administrative measures for TB infection control, ensure an appropriate distribution of laboratories and provide TB outcome-based incentives to family doctors under the package of minimum services currently under discussion.
5	Support the update and endorse the updated National Guidelines on PMDT and make it mandatory for implementation at all inpatient and outpatient institutions nationwide involved in the management of TB and DR-TB, including penitentiary sector. Ensure that once endorsed, copies of the National Guidelines should be distributed among all TB specialists involved in PMDT.
6	Consider creation of the multi-sectorial National TB Coordination Committee as a National Task Forse mechanism to oversee the preparation, planning, implementation and evaluation of new TB drugs (Bedaquiline, Delamanid and Group 5 agents), as well as other new TB drugs/regimens as appropriate to access management of M/XDR-TB. A Technical Working Group should be created as an advisory board to the National TB Coordination Committee to oversee any technical aspects related to access to new TB and Group 5 drugs.
7	Consider options for reallocating funds and finding additional financing to strengthen the ambulatory treatment; provide strict DOT, especially at ambulatory settings and personnel motivation, especially for PHC level. 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.
8	Consider developing mechanisms for covering the ancillary medicines for side effect management through the new mechanism of financing through the MOH, especially for ambulatory sector.
9	Support the ongoing rationalization of laboratory network, ensuring adequate financing of laboratory services and developing strategic approaches to ensure adequate financing past donor funding in 2018.
10	Urgently endorse the updated version of the National Infection Control Plan in Romania and ensure adequate financing of infection control activities.
11	Urgently introduce TB infection control measures in diagnostic and treatment facilities and in congregate settings by revising the Ministry of Health's Order N°916 (26 July 2006) and the current system of health facility accreditation and including specific measures for the prevention of airborne TB transmission.
12	Develop mechanisms to address the issue of excessive hospitalization at TB inpatient facilities using the opportunity of international donor funding by creating criteria for admission to the hospital and strengthening the ambulatory care program, including aspects

	of adherence to treatment.
13	Ensure adequate financing and uninterrupted supply of drug procurement for FLD and SLD at all treatment sites through the government sources.
14	Develop strategy to ensure allocation of adequate financing of drug procurement past 2018 for the management of M/XDR-TB.
15	Update the National Essential Drug List (C2 list) to include the following medicines: Capreomycin, Levofloxacin, PAS, Bedaquiline, Linezolid and Imipenium/Cilastatin). Consider update of the C2 list with Delamanid and Clofazimine once the drugs are registered in Romania.
16	Revise conditions of the National tender to avoid possible stock outs of TB medicines.
17	The Essential drug list should include only those medications, which are included into the regimens of updated National Guidelines on PMDT for Romania.
	Recommendations to the NTP
1	Finalize the update the National Guidelines for Program Management of Drug-resistant Tuberculosis (PMDT) in alignment with the recent recommendations of the WHO (Companion Handbook to the WHO Guidelines on PMDT, 2015 edition), especially with parts on new TB and companion drugs, pharmacovigilance, management of cases with mono- and poly-resistant TB.
2	Develop the National Implementation Plan for Introduction of Bedaquiline and other new TB and companion drugs (Group 5 drugs) according the WHO Interim Policy Guidance on Bedaquiline and Delamanid.
3	Introduce and perform thorough pharmacovigilance system as a part of introduction of Bedaquiline and other Group 5 agents.
4	Any use of second-line drugs, as well as new TB and companion drugs, should be only authorized by DR-TB Committee to avoid improper management of patients and further amplification of drug resistance. Regimens for patients diagnosed with DR-TB (Mono-DR, PDR, MDR and XDR) should be designed in accordance with updated version of the National Guidelines (continuous recommendation).
5	Consider revising the National policy on the management of DS-TB to be in the alignment with the WHO Treatment of Tuberculosis Guidelines (4th edition, 2009): 1. New patients with pulmonary TB should receive a regimen containing 6 months of Rifampicin: 2HREZ/4HR; 2. Category III regimen should be phased out from the treatment protocol, and replaced by Category I regimen; 3. Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy, provided that each dose is directly observed; 4. In patients treated with regimen containing Rifampicin throughout treatment, if a positive sputum smear is found at completion of intensive phase, the extension of intensive phase is not recommended. Sputum culture and DST should be performed; 5. Consider not using the retreatment regimen (Category II) for patients with high likelihood of MDR-TB.
6	Develop the list of possible ancillary medicines used in the management of DR-TB. The list to be updated on a regular basis. Consider developing mechanisms for covering the ancillary medicines for side effect management through the new mechanism of financing through the MOH, especially for ambulatory sector.
7	Develop strategies to perform palliative care of patients who failed treatment
8	Ensure the universal access to rapid diagnosis of TB and MDR-TB by using cartridge-based Nucleic Acid Amplification Techniques at selected lower level laboratories and/or sputum collection points with high rates of TB and/or MDR-TB (e.g. prisons, selected hospitals, HIV centres) and Line Probe Assay in geographically-representative regional laboratories by the end of 2015.
9	Update the National algorithm for diagnosing DR-TB with liquid media testing (culture and

	DST using MGIT-960 and VersaTrek). Include the updated version of diagnostic algorithm into National Guidelines on DR-TB and National Laboratory Guidelines accordingly.
10	Update the National laboratory reporting forms with information on rapid molecular diagnosis (Xpert MTB/RIF, MTBDRPlus, MTBDRPlus-sl). Include the updated forms into National Guidelines on DR-TB and National Laboratory Guidelines accordingly.
11	Develop standard operating procedures for processing and managing specimens for the new rapid molecular diagnostic and liquid media methods.
12	Perform rapid molecular diagnosis of TB and resistance to at least H and/or R (Xpert MTB/RIF and MTBDRPlus) prior hospitalization to TB inpatient facilities.
13	Ensure allocation of adequate financing for personal protection measures for health and administrative personnel at all treatment sites involved in program and medical management of TB and DR-TB. Also ensure adequate financing for purchasing surgical masks for infectious patients and suspects. Fit testing is mandatory before purchasing respirators for health personnel in each inpatient facility.
14	Continue the risk assessment of the county TB facilities and make any necessary updates of the National IC Plans.
15	Ensure appropriate biosafety measures in all laboratories performing culture and DST, including rapid molecular diagnosis. Ensure adequate financing for maintenance of biosafety cabinets and replacement of filters, as well as personal protection of all laboratory personnel.
16	The Essential drug list should include only those medications, which are included into the regimens of updated National Guidelines on PMDT for Romania.
17	Improve the capacity of NTP to conduct regular monitoring over the drug consumption at county-level. Consider developing an electronic system specifically designed for drug management.
18	Support the introduction of new TB drugs (Bedaquiline and Delamanide) for the management of drug-resistant TB according to the WHO Interim Policy Guidance. Ensure proper pharmacovigilance while introducing the use of new TB and companion drugs into practice.
19	Develop the Implementation Plan for Introduction of new TB drugs in Romania.
20	Consider using the QuanTB – Tuberculosis Medicines Quantification Tool (http://siapsprogram.org/quantb/) for TB drugs quantification and forecasting at National level.
21	Conduct regular monitoring over recording and reporting, data collection and entry at county level TB dispensaries and laboratories. Perform “snapshots” of 5-6 counties every month and address the issues of missing data and R&R to the county TB coordinators.
22	Continue rationalizing the recording and reporting system and revising the national TB database to better process patients’ data and ensure their analysis and use for policy decisions.
23	Ensure that the National registry contains information on all TB and DR-TB cases registered in the country, not only those registered for treatment.
24	Update the National Guidelines on PMDT, section on R&R in alignment with the WHO 2013 Revised definitions and reporting framework for tuberculosis or latest ECDC definitions.
25	Revise the existing R&R forms for DR-TB and make appropriate updates in accordance with Part 4 “Forms for drug-resistant TB programs” of the WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Include the updated forms into the updated version of the National Guidelines for PMDT in Romania.
26	Complete the development of electronic Laboratory module for the National TB Registry and perform regular monitoring over laboratory data entry at all regional level laboratories.
27	Address the issues of improving equal access to TB and DR-TB patients’ adherence to treatment, especially at those groups with high risk to default.

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 20,121,641 people according to the 2011 census (19,942,642 – 2014 estimate), 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 1,883,425 people (Romanian 2011 census, INSSE). 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).

According to the World Bank 2015 estimate, Romania's total GDP (PPP) is $403.579 billion, per capita is $20,355, which places country to the upper-middle income category. Actual unemployment rate is relatively low in recent years and stands about 6.5% in March 2015 as reported by Institutul National de Statistica. Unemployment aid is granted on a time-limited, individually determined basis. 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 five 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. Romania has the universal healthcare system, which covers medical examinations, emergency care and treatment of a range of diseases for free, including tuberculosis and HIV/AIDS. Most common causes of death are cardiovascular diseases, cancer and tuberculosis.

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. Financing of TB Control and Prevention in Romania comes from the government sources through the Ministry of Health (MOH).

6. Epidemiology, Case finding and Program performance data

Findings and summary of discussion:

In Romania Tuberculosis remains an important public health threat over the past two decades, placing the country in the list of 18 high-priority countries in the WHO European Region. Data provided by the NTP shows the steady decrease in TB main TB indices over the past decade, with TB incidence declining from 142.2 per 100,000 people in 2002 (30,985 new cases and relapses) to 70.2 per 100,000 people in 2014. Mortality rate of TB (excluding HIV) was reported at low levels of

5.2% in 2014, assuming to be higher with HIV positive cases, and is also declining from 5.9% in 2012, with absolute number of 1,109 people died of TB in 2014 (Table 1).

Table 1.1. Incidence, prevalence and mortality rates of TB, 2012-2014, Civilian sector (data provided by NTP)

Year	Incidence	Prevalence	Mortality
2012	78.8	133.7	5.9
2013	73.0	125.0	5.3
2014 (21,267,165)	70.2	113.7 (Abs. 24,273)	5.2 (Abs. 1,109)

Table 1.2 Incidence, prevalence and mortality rates of TB, 2012-2014, Prison sector (data provided by NTP)

Year	Incidence	Prevalence	Mortality
2012 population = 31720	129 (406,7)	207 (652.6)	2 (6.3)
2013 population = 32890	141 (444.5)	237 (747.2)	3 (9.1)
2014 Population = 29899	211 (705.7)	316 (1,056.9)	2 (6.7)

Romania reported TB case notification of 57.5% among new smear positive cases and 63.7% among relapses in 2014 (Table 2) in civilian sector, and 37.8% and 81.3% in prison sector respectively. However, the data submitted to the WHO in 2013 shows case notification among new smear positive cases of 50% (6,987) and 51% among relapses (2,219) as of 2012 (Table 4). Data slightly differs from what is officially reported to the WHO and what was presented by the NTP during the current mission.

Table 2. TB case notification 2012-2014, Civilian sector (NTP)

Case notifications	2012		2013		2014	
	Abs.	%	Abs.	%	Abs.	%
New cases						
Smear-positive	7,111	62.3	6,252	59.2	5,937	57.5
Smear-negative	4,176	36.6	4,187	39.7	4,214	40.8
Smear-negative/Culture-positive	1,799		1,852		1,674	
Smear-unknown	118	1.0	114	1.1	170	1.6
Smear-unknown/Culture-positive	1		0		2	
Extrapumonary TB	2,469	17.8	2,298	17.9	2,240	17.8
Other	-	-	-	-	-	-
Total new	13,874	100.0	12,851	100.0	12,561	100.0
Retreatment cases						
Relapse	2,890	67.0	2,660	69.1	2,379	63.7
Treatment after failure	738	17.1	586	15.2	402	10.8
Treatment after default	688	15.9	603	15.7	647	17.3
Other (chronic)	0	0	0	0	309	8.3
Total retreatment	4,316	100.0	3,849	100.0	3,737	100.0

Table 3. TB case notification 2012-2014, Prison sector (NTP)

Case notifications	2012		2013*		2014**	
	abs	%	abs	%	abs	%
New cases pulmonary	**97**	**85.8**	**101**	**82.8**	**148**	**80.0**
Smear-positive	46	47.4	40	39.6	56	37.8
Smear-negative	51	52.6	61	60.4	91	61.5
Smear-negative and C pos.	*25*		*29*		*47*	
Smear unknown	0	0	0	0	1	0.7
Smear unknown and C pos	*0*	*0*	*0*	*0*	*0*	*0*
Extrapumonary TB	**16**	**14.2**	**21**	**17.2**	**37**	**20.0**
Other	0	0	0	0	0	0
Total new	**113**	**100**	**122**	**100**	**185**	**100**
Retreatment cases						
Relapse	16	76.2	19	73.1	26	81.3
Treatment after failure	0	0	2	7.7	0	0
Treatment after default	5	23.8	5	19.2	6	18.8
Other	0	0	0	0	0	0
Total retreatment	**21**	**100**	**26**	**100**	**32**	**100**

Table 4. TB case notifications, 2012 (WHO)

New cases	Abs.	%	Retreatment cases	Abs.	%
Smear positive	6,987	50	Relapse	2,219	51
Smear negative	4,224	30	Treatment after failure	663	15
Smear unknown/not done	205	1	Treatment after default	570	13
Extrapulmonary	2,472	18	Other	857	20
Other	0	0			
Total new	13,888		Total retreatment	4,309	
Other (history unknown)	0				
Total new and relapses	**16,107**		**Total cases notified**	**18,197**	

Incidence of TB varies across the country and is more or less related to the socio-economic status of the regions with higher rates in Eastern, Western and Southern parts and lower in the Central part and the North-West. Absolute number of all cases registered with TB remains high and was around 24,000 in 2014. Main TB indices are declining mostly due to the access to treatment for majority of TB cases diagnosed, as well as the availability of FLD for drug-susceptible TB.

M/XDR-TB

Despite the successes in managing drug-susceptible TB, drug-resistant tuberculosis is a major challenge to the effectiveness of National Tuberculosis Program in Romania. Even not recognized as high-burden country for MDR-TB by the WHO, MDR-TB is one of the major public health obstacles for the successful implementation of the National TB Control and Prevention Program in Romania. Number and proportion of MDR-TB in the country is high mostly due to several factors contributing to the growth of the reservoir of DR-TB patients in the country, and improvements in laboratory diagnosis of drug resistance. According to the DRS conducted a decade ago, 2003-2004, MDR-TB was found in 2.9% among new pulmonary cases and 10.7% among retreatment cases.

Any resistance was found in 19.9%. On March 1, 2014 Romania launched the second national DRS with results to be available in later in 2015.

In 2013 the WHO estimated 2.8% among new (1.8-4.2) and 11 (8-15) among retreatment cases in Romania, and around 1,110 MDR-TB cases annually (320 (210-480) new and 470 (350-630) retreatment cases). However, in 2012 out of 5,966 cases tested for MDR-TB (3,944 new and 2,022 retreatment) MDR-TB was diagnosed in 530 cases. NTP data show slight decrease in absolute number of MDR-TB cases among the new and retreatment cases over the past three years (Table 5). However, number of reported cases does not reflect the actual situation if not every culture positive pulmonary TB new and retreatment cases are being tested for drug-susceptibility. With upcoming funding from the GFATM and Norwegian Fund and increased access to rapid molecular diagnosis of DR-TB, as well as liquid media testing to perform conventional DST to FLD and SLD, coverage with DST will be significantly improved. As of January 1, 2015, there were 1,021 MDR-TB cases registered in the country (Table 6.1. and Table 6.2.).

Table 5. Registered MDR-TB cases in civilian and prison sectors, 2011-2013 (9 months)

Type	2011	2012	2013 (9 months)
New	124	114	70
Re-treatment	423	416	231
TOTAL	**547**	**530**	**301**

Table 6.1. Prevalence of MDR-TB, 2012-2014, Civilian sector

	TB-TOTAL	TB without MDR	MDR-TB	%
2012	28,454	27,287	1,167	4.1
2013	26,584	25,302	1,282	4.8
2014	24,172	23,158	1,014	4.2

Table 6.2 Prevalence of MDR-TB, 2012-2014, Prison sector

	TB TOTAL	TB without MDR	MDR-TB	%
2012	153	144	9	5.9
2013	219	209	10	4.6
2014	316	309	7	2.1

Coverage with DST to SLD is also not complete, as not every R-resistant case had been tested for conventional DST to the rest of first-line and all second-line drugs (Table 7). However, the arrival of new laboratory equipment (Xpert and LPA, and MGIT), as well as creation of a functional laboratory network will significantly increase coverage and provide true data on the number of patients with resistance to second-line drugs.

Table 7. DST to SLD performed among MDR-TB, 2011 – 2014, Civilian and prison sectors

Year/No	2011	2012	2013*	2014 (9 month)**
MDR-TB	547	684	575	389
SLD	259	369	332	201
Pre-XDR (MDR Q res)	27	48	35	35
XDR	34	41	58	35

Prospective study of drug resistance performed for 756 MDR-TB cases collected during 4 months (October 2009 and January 2010) in Romania, revealed 9.9% of XDR-TB in new MDR-TB and 11.6% in retreatment MDR-TB cases. Over the past three years percentage of XDR-TB remains around 10% out of all MDR-TB cases (Table 8). However, the number of XDR-TB seems to be underdiagnosed due to the fact that not every diagnosed case with any resistance to Rifampicin is being tested to SLDST. Assuming an average of 10% of all MDR-TB cases to have resistance to an injectable agent and fluoroquinolone, it makes up a reservoir of around 150 patients XDR-TB, whose treatment currently is almost impossible due to poor access to adequate XDR-TB regimen with later generation fluoroquinolones, Capreomycin and Group 5 drugs.

Table 8. Registered XDR-TB cases in civilian and prison sectors, 2011-2013 (9 months)

Type	2011	2012	2013 (9 months)
Pre XDR-TB (INJECTABLE)	61	64	34
Pre XDR-TB (FQ)	1	9	8
XDR-TB	34	30	20

Previous shortages of SLD, especially injectable agents and adequate FQ had already led to creation of reservoir of XDR-TB, especially at county level TB facilities. Currently, absence of adequate range of SLD and Group 5 agents, unregulated approach to diagnose and manage patients with pre-XDR-TB (resistance to either FQ or injectable agent alone), as well as nosocomial transmission of strains in congregated settings with poor infection control (TB hospitals), serve as major obstacles to the effectiveness of the National DR-TB Program. During previous years the number of MDR-TB patients registered for treatment with Category IV regimen does not reflect the actual number of patients started on adequate MDR-TB regimen due to problems with drug procurement. Totals of 622 for 2011, 601 for 2012 and 357 for 2013 also include those patients, whose regimens were lacking appropriate fluoroquinolone and injectable agent (Table 9). However, starting October 2013, the proportion of adequately designed MDR-TB regimens increased because of changes in drug procurement system and enrolment of 302 patients with quality-assured SLD through GDF mechanism (TFM GFATM).

Table 9. MDR-TB and XDR-TB patients registered for treatment with Category IV regimens, 2011-2013

Cohort/year	2011	2012	2013
MDR-TB patients	622	601	357
XDR-TB patients with Moxifloxacin	1	9	8

Treatment outcomes of GLC cohorts enrolled to the MDR-TB treatment program with Rounds 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) (Table 10). In 2013 Romania received an approval from GFATM for enrolment of 300 patients (302 – actual enrolment) with 19 of them with XDR-TB, out of 44 XDR-TB patients registered in 2013. Enrolment was finished in October 2014.

Table 10.1. Enrolment and treatment outcomes of GLC approved cohorts, 2004-2011

Cohort	# enrolled	Still on treatment	Success	Lost to follow up	Failure	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	0	96 (66.2%)	10 (6.9%)	17 (11.7%)	1 (0.7%)	21 (14.5%)
Cohort 4 (2010-2011)	339	205	46	23	28	3*	27
TOTAL	**884**	**217**	**406**	**71**	**95**	**9**	**86**

Table 10.2. Enrolment and treatment outcomes of GLC approved cohorts, 2011-2014

Cohort	# enrolled	Still on treatment	Success	Lost to follow up	Failure	Excluded	Died
Cohort 4 (2011)	91 (100%)	0	67 (73.6%)	8 (8.8%)	10 (11%)	1 (1.1%)	5 (5.5%)
Cohort 5 (2012)	42	0	35	2	3	0	2
Cohort 6 (2013)	138	126	0	4	0	1	7
Cohort 7 (2014)	164	158	0	0	0	0	6
TOTAL	**435**	**284**	**102**	**14**	**13**	**2**	**20**

Treatment outcomes for the non-GLC cohorts are extremely poor. Similar to 2008 and 2009, data of 2010 cohort analysis show treatment success rate of 20.0% (17.9% cured and 2.1% treatment completed), 17.1% died, 40.2% failure, 18.5% default and 4.2% not evaluated in comparison with the GLC cohort. Total percentage of unfavourable outcomes for 2010 non-GLC cohort was 80.0%. Similarly, treatment outcomes for 2011 show extremely low treatment success rate of 16%, and high rates of patients who failed therapy (39.6%) and died (22.1%), Table 11. Poor treatment outcomes for non-GLC cohort were due to several factors, especially delays in diagnosis and initiation of therapy (lack of access to rapid diagnostic methods), improper treatment and patient management. During several years the decentralized system of drug procurement and unavailability of full range of second-line anti-TB medications for non-GLC MDR-TB patients served as the major contributor to aggravating the situation with drug-resistant tuberculosis and growth of M/XDR-TB reservoir. Medical management of non-GLC MDR-TB patients was negatively affected by stock outs of injectable agents (aminoglycosides and Capreomycin) and fluoroquinolones (Ofloxacin and Levofloxacin), and use of Ciprofloxacin. Lack of strategies and possibilities to address patients' adherence to treatment still remain as threat to successful implementation of the Program. Factors contributing to the growth of DR-TB reservoir (defaults and failures) prevailed those influencing its decrease (cured + treatment completed + died + transferred out), which along with delays in diagnosis of DR-TB, prolonged hospitalization and poor infection control at inpatient facilities, significantly aggravated the burden with drug resistance in Romania over the past years.

Table 11. Number of patients started treatment with second-line drugs, non-GLC cohort, 2011

Cohort/Year	# enrolled	Still on treatment	Success	Lost to follow up	Failure	Died	Not evaluated
2011 TOTAL	547	20	140	90	191	106	0
2011 NON-GLC	***457***	***20***	***73***	***82***	***181***	***101***	***0***
2011 % NON-GLC	***457(100%)***	***4.4%***	***16%***	***17.9%***	***39.6%***	***22.1%***	***0***

However, considering the endorsement of the National Strategic Plan for TB Control in Romania for 2015-2020, increased financing from the Government of Romania and availability of adequate financing from the international donor sources, the Romanian NTP will be able to achieve rapid decline in main TB indices, including DR-TB over the next few years. Mapping of patients with M/XDR-TB will be performed by the end of 2015. It was discussed with the NTP to perform mapping of patients with DR-TB at county level using the assistance from county MDR-TB Coordinators.

7. Coordination of the program and financing

Findings and summary of discussion:

Ministry of Health of Romania (MOH) is the main responsible government body for overall management, coordination and supervision over health programs in the country including TB. Implementation of National TB Control and Prevention is performed through the NTP Central Unit responsible for coordination of activities, monitoring and supervision over program in counties. The organizational structure of TB services in Romania has not significantly changed since the previous GLC monitoring mission, but the level of financial commitment from the Government. Starting 2015 the budget allocations on National TB Program of Romania from the MOH increased from 3.3 million Euros (2014) to 6.7 million Euros, and is reflected in the National Strategic Plan. Also, there are changes in the financing system of TB Program with NIH is now responsible for covering costs related to hospitalization.

The previous year recommendation "NTP Central Unit team should have a clear mandate (SOP) to act as the actual National Tuberculosis Program Unit and be enforced with capacity to perform coordination of activities, monitoring and supervision, planning and analysis, capacity building required for successful implementation of TB and DR-TB Control" is completely fulfilled by the MOH. The NTP Central Unit comprises a group of specialists, each responsible for specific aspect of TB control (Annex 6); all specialists are officially contracted. Dr. Gilda Popescu, who succeeded in managing of the National TB Program for the past three years, leads the NTP Central Unit, who is in charge of coordinating all activities within the National TB Program and supporting donor grants. As a part of Norwegian Fund grant the NTP Units in counties will be empowered with MDR-TB Coordinators selected from regional specialists, who will be responsible for coordinating of activities on PMDT in responsible county.

In compare with the previous missions there is a significantly increased level of political commitment noted from the Government of Romania, and especially the Ministry of Health. In March 2015, the Government of Romania endorsed the National Strategic Plan for Control of Tuberculosis in Romania for 2015-2020, which presents the country's priorities to address the public health challenge of tuberculosis (Annex 3). The National Strategic Plan (NSP) was developed in close partnership with the MOH, the NTP and WHO, and other government and non-government organizations. The NSP outlines the national strategies to respond the unmet needs and build sustainability of the system, as well as presents the long-term vision, and identifies innovative approaches targeted on achieving dramatic decline in TB incidence and mortality in Romania by 2020. The document presents the goal and objectives for diagnosis, treatment and prevention of TB in the country. There are 8 strategic objectives in the NSP, including ensuring universal access to rapid diagnostic methods for TB and DR-TB, coverage with appropriate therapy of all diagnosed TB and DR-TB cases, and achieving high treatment success rates both for TB and DR-TB, which suppose to result in sharp decline of TB incidence and mortality. To ensure these actions are effective, the NSP for 2015-2020 will be based upon three pillars and pursue a series of key intervention areas: (1) Integrated patient-centered care and prevention, (2) Bold policies and supportive systems, (3) Innovative research and evidence-based strategies. The earlier endorsed National M/XDR-TB Response Plan for 2012-2015 with six areas of interventions and detailed budget, developed with the technical assistance from the WHO-Europe, was successfully endorsed in October 2012, but its implementation was delayed due to financial constrains. However, the National M/XDR-TB Response Plan had been successfully incorporated into NSP for 2016-2020 for further implementation. The budget of the NSP for 2015-2020 is consolidated, and include budgets from the Government of Romania, Norwegian grant, the GFATM, European Structure Fund, the World Bank and other (279,029,902.7 Euros). With majority of funding coming from the

Government of Romania, the NSP acts as very important step towards building the sustainability of the National Tuberculosis Program of Romania.

One of the major components of the NSP is conducting a reform with the purpose to reduce the unnecessary hospitalization through implementation of ambulatory based treatment of TB cases. The reform will be supported by the new GFATM grant for 2015-2018 and will be implemented in 6 counties with burden of TB and MDR-TB. The reform will include revision of financial mechanism of reimbursement to health providers involved in TB control, and reallocation of funds from inpatient to outpatient care, and establishing legal framework for reform. It is expected that through implementation of reform, the cost of hospitalization for TB will significantly decrease through progressive decrease in the number of hospitalizations for TB and MDR-TB, as well as development of alternatives for inpatient treatment.

In 2014 Romania submitted a concept note to the GFATM with request to receive funding of 8.4 million Euros to address the gaps and challenges in TB control in the country for the period of 04/2015 – 03/2018 (Annex 5). The goal of the grant was to contribute to achievement of reduction in TB incidence and mortality in Romania through involved high impact interventions (diagnosis, treatment, care and prevention) with special focus on key affected population through the following objectives:

- Early and quality-assured TB diagnosis through strengthening of TB laboratory capacity;
- Implementation of patient-centered interventions in 6 high-burden counties of Romania;
- Improvement of treatment outcomes for M/XDR-TB patients by provision of complete, non-interrupted drug regimens;
- Strengthening the national legal framework to regulate TB control in Romania.

The application included 5 program modules: (1) Case detection and diagnosis, (2) Interventions for key affected populations, (3) MDR-TB, (4) Health Systems Strengthening and (5) Program Management. In addition, the NTP also added a separate component on TB-HIV focused on diagnosing TB among HIV-infected people.

The funding request from Romania was successfully approved by the GFATM starting April 1, 2015. Under the new GFATM grant the Romanian NTP was planning to ensure access to quality-assured SLD for 460 M/XDR-TB patients using the GDF mechanism and procure series of equipment to increase access to rapid molecular diagnosis of TB and DR-TB (Xpert MTB/RIF, LPA, MGIT-960). Similarly to the previous grants funded by the GFATM, the Romanian Angel Appeal Foundation (RAA) will act as the Principal Recipient of the new grant, in order to fulfil country's obligations and reach the indicators of both grants. Besides, RAA provide continuous assistance to the NTP Central Unit on implementing the grant objectives and improve program performance at all levels. More detailed description of activities of the new GFATM grant is presented below in relevant chapters of current report.

In 2014 the Romanian NTP received an approval from the Norwegian government for the total amount of 10.7 million Euros for 20 months (August 2014 – April 2016). The grant is focused on consolidating efforts on TB control activities especially on MDR-TB, and poor and vulnerable populations, and is considered as an extension of previously funded activities. Marius Nasta Pneumology Institute acts as the Principal Recipient of the grant, which will be managed by the NTP Central Unit and partnered with RAA, Center for Health Policies and Services and LHL International Tuberculosis Foundation. The grant includes thirteen Workpackages/objectives, focused on early diagnosis of TB and DR-TB, treatment of M/XDR-TB with quality-assured drugs, including new drugs, building integrated community support, infection control, and various capacity building activities. With funding from the Norwegian grant it will become possible to provide treatment for 1,000 patients with M/XDR-TB, and provide social support for them, significantly improve the laboratory capacity and increase access to rapid molecular diagnosis of

TB and DR-TB, create functional network of 8 regional reference laboratories, and invest into procurement of equipment to decrease the risk of nosocomial transmission of infection. More detailed description of activities of the grant is presented below in relevant chapters of current report.

Starting 2015 the National TB Program will receive funding from the United States Embassy in Romania, which will be allocated on renovation and reconstruction of ventilation system of MDR-TB ward at MNI. Funding is conditional with the MOH guarantee maintenance and utility costs for running the ventilation system, as well as replacement of HEPA filters. Also, the US Embassy will support training on Infection Control by specialists from the US Department of Defence, and some financial support will be allocated on diagnosis of drug resistance.

Infrastructure of TB Services in Romania is well developed and presented with wide network of TB Dispensaries (174) and additional 93 TB hospitals and TB Units with 5,625 TB beds countrywide. Recently 11 TB dispensaries were closed because of the change in administrative profile, however, 4 will be reopened. Marius Nasta Pneumology Institute in Bucharest is the leading institution in the country on TB Control and serves as headquarters for the NTP Central Unit and is one of two MDR-TB Centers in Romania. 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 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.

There is an evidence of good level of collaboration with the WHO-Europe, who initiated the joined technical assistance to scale up the PMDT in Romania in collaboration with ECDC and other organizations.

Recommendations:

	Recommendation	**Responsibility**
1	Prevention and control of TB and M/XDR-TB should be considered as a public health priority. The implementation of the National Strategic Plan for TB Control for 2015-2020 should be supported by the Government of Romania with sufficient and sustainable funding, and necessary changes in the health system. Aspects requiring support include access to adequate treatment regimens and uninterrupted supply of TB drugs, ambulatory treatment and social support of patients, diagnosis and infection control.	MOH
2	Consider an update of the National Strategic Plan for TB Control for 2016-2020 with upcoming release of the TB Action Plan for the WHO European Region (possibly in 2017).	MOH
3	Support the implementation of the new GFATM and Norwegian grants. MNI Pulmonology Institute (NTP) should play the leading role in the management and implementation of this and upcoming grants (European Structure Fund).	MOH
4	Revise the payment system under the National Health Insurance House in order to prevent unnecessary hospitalization of patients, promote administrative measures for TB infection control, ensure an appropriate distribution of laboratories and provide TB outcome-based incentives to family doctors under the package of minimum services currently under	MOH

	discussion.	
5	Strengthen the coordination of activities, monitoring and supervision at county level. Clear ToR and SOP should be developed for the county coordinators. Adequate financing to perform monitoring visits to the treatment sites should be considered by the MOH and NIH.	NTP

8. Treatment strategies and administration

Findings and summary of discussion:

Treatment of drug-sensitive TB patients 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. Treatment success rates shows good results with treatment success rate among new smear/culture positive cases of 85% in 2012 cohort and 65.4% among retreatment cases, which is slightly higher than previous year, even with majority of patients treated under self-administration due to lack of strategies and financing to ensure adherence to therapy. Preliminary data from 2013 showed treatment success rate among smear-positive pulmonary new cases of 82.3% and 63.8% among all retreatment cases (Table 12). The coverage with DST supposed to be improved since the past year mission because of the increased access to rapid molecular diagnosis of TB and drug-resistance (LPA and Xpert MTB/RIF), and data on drug resistance submitted to NTP are accurate. Also, the situation supposes to improve significantly taking into account the ongoing drug-resistance surveillance (DRS), which will be over on March 31, 2015, which will shed the light on the level of DR-TB in Romania, including resistance to SLD.

The National approach to the management of patients with drug-susceptible TB had not been changed in accordance with the WHO Treatment of Tuberculosis Guidelines 4th edition of 2009 as it was recommended during previous missions. Thus, Category III regimen was not phased out from the treatment protocol, and recommended optimal daily dosing of frequency throughout the course of therapy for new patients with pulmonary TB is not happening.

Table 12. Treatment outcomes of regular TB, Romania, 2012 and 2013, *without MDR.* Civilian sector.

2012		Treatment completed	Cured	Death	Lost to follow up	Failure	Not evaluated	Total
New	Pulm. SS+	**1,052 (15%)**	**4,879 (70%)**	**486 (7%)**	**316 (4.5%)**	**232 (3.3%)**	**18 (0.2%)**	**6,983 (100%)**
	Pulm. SS-	**2,391**	**1,268**	**281**	**194**	**14**	**3**	**4,151**
	EP	**2,252**	**0**	**108**	**98**	**4**	**5**	**2,467**
	Total new							
Retreatment Retreatment	Pulm. Relapse SS+	**252**	**1054**	**176**	**193**	**149**	**5**	**1,829**
	Pulm. Relapse SS-	**303**	**287**	**75**	**72**	**10**	**5**	**752**
	Pulm. Default SS+	**63**	**130**	**49**	**186**	**40**	**0**	**468**
	Pulm. Default SS-	**43**	**16**	**9**	**37**	**1**	**0**	**106**
	Pulm.	**86**	**155**	**68**	**65**	**114**	**3**	**491**

	Failure+Chr							
	Total relapse	**747 (20.4%)**	**1,642 (45%)**	**377 (10.3%)**	**553 (15.2%)**	**314 (8.7%)**	**13 (0.4%)**	**3,646 (100%)**
	EP	**99**	**0**	**7**	**11**	**2**	**1**	**120**
2013*		**Treatment completed**	**Cured**	**Death**	**Lost to follow up**	**Failure**	**Not evaluated**	**Total**
New	Pulm. SS+	**759 (12.4%)**	**4,271 (69.9%)**	**471 (7.6%)**	**279 (4.5%)**	**174 (2.7%)**	**177 (2.9%)**	**6,131 (100%)**
	Pulm. SS-	**2,242**	**1,341**	**249**	**187**	**16**	**122**	**4,157**
	EP	**2,009**	**0**	**104**	**87**	**9**	**84**	**2,293**
	Total new							**,**
5 RetreatmentTotal relapse	Pulm. Relapse SS+	**218**	**930**	**171**	**180**	**114**	**43**	**1,656**
	Pulm. Relapse SS-	**305**	**255**	**71**	**67**	**9**	**11**	**718**
	Pulm. Default SS+	**57**	**123**	**38**	**149**	**27**	**15**	**409**
	Pulm. Default SS-	**32**	**12**	**9**	**45**	**1**	**4**	**103**
	Pulm. Failure	**24**	**92**	**15**	**33**	**35**	**11**	**210**
	Pulm. Other = Chronics	**9**	**43**	**43**	**22**	**70**	**10**	**197**
	Total relapse	**645 (19.7%)**	**1,455 (44.1%)**	**347 (10.6%)**	**496 (15.1%)**	**256 (7.9%)**	**94 (2.6%)**	**3,293 (100%)**
	EP	**96**	**0**	**8**	**12**	**4**	**9**	**129**

***Provisory evaluations for 2013, at 15.02.2015**

Management of patients with MDR-TB is performed in accordance with the National Guidelines on PMDT, which was updated by the NTP with recent WHO Guidelines in 2013 but not yet endorsed by the MOH. Endorsement of updated version of the National Guidelines will be done once the NTP makes corresponding changes in line with the latest WHO Companion Handbook to the WHO guidelines for the PMDT, 2015 edition, especially on following chapters:

- Treatment strategies for mono- and poly-resistant TB (drug-resistant TB other than MDR-TB)
- Treatment strategies for MDR-TB and XDR-TB (new TB and companion drugs)
- Management of contacts of MDR-TB patients
- Pharmacovigilance

The guidelines also include required diagnostic algorithms, protocols on side effect management, and required registration and treatment forms. Thus, by the time of the current rGLC mission there were no clear formal regulatory document on medical management DR-TB available.

Regimens for MDR-TB are designed by two DR-TB Committees: at Marius Nasta Pneumology Institute (MNI) and Bisericani TB Hospital, who are responsible for patient enrolment, treatment regimen design, management of severe side effects, surgical care and patients' referral. Each of DR-TB Committee is covering 50% of the country and serves as referral centers for MDR-TB treatment initiation. Members of the MDR-TB commissions are trained on PMDT at either international or local trainings. DR-TB Committees are ensuring equal access to MDR-TB treatment with no respect to the source of SLD. Criteria for duration of intensive phase and of the whole course of chemotherapy match the WHO recommendations of 2011 with minimum duration of intensive phase no less than 8 months, and minimum duration of the whole course of treatment no less than 20 months for patients never treated before for MDR-TB. For patients already treated for DR-TB and for those with massive pulmonary damage the whole duration of treatment exceed 20 months. Criteria for stopping the injectable agent are based on strong evidence of culture

conversion – up to 4 consecutive negative cultures – and clinical response to treatment. There are no limitations for prolonging the duration of intensive phase and the whole duration of treatment. Coverage with FLD DST is performed according to DR-TB Diagnostic algorithm, but its introduction requires strengthening. There is an increased access to DST to SLD in compare with previous missions by rGLC, especially with upcoming funding from GFATM and Norwegian Fund.

MDR-TB regimens include an injectable agent (Aminoglycoside or Cm), fluoroquinolone (Lfx), Group 4 agents (Pto, Cs, PAS) and Z with maximum dosages according to patient's weight and tolerance. Frequency of treatment is 7 days per week at inpatient and 5-6 days per week at outpatient settings with no matter of the phase of treatment. Ethambutol is used in M/XDR-TB regimens only if it is susceptible by DST results. Pyrazinamide is used for the whole duration of therapy. Minimum duration of the use of an injectable agent is 8 months for MDR-TB, and 12 for XDR-TB. Kanamycin is an injectable of first choice for if susceptible (in the GLC cohort), as believed as more potent agents than Cm. Levofloxacin serves as fluoroquinolone of choice for all MDR-TB patients in maximum dosages (750 mg <=70 kg, 1,000 => 71 kg). Moxifloxacin is used in when DST shows resistance to Fq. In certain circumstances Mfx is used for strengthening the regimen: diabetes mellitus, HIV co-infection, massive pulmonary damage, other. PAS is not routinely added to an MDR-TB regimen, but as additional drug in pre-XDR and XDR-TB regimens. Group 4 agents are present in majority of MDR-TB regimens. Strategy for including Ethionamide is based on strong evidence of susceptibility by DST.

Treatment regimens for mono and poly-resistant TB had not been included into the updated version of the National Guidelines of Romania (2013), which had not been submitted to the MOH yet, and are scheduled for update in line with the latest WHO guidelines (2015). The guidelines need to be revised with the presence of access to rapid molecular diagnosis of drug resistance (Xpert MTB/RIF, LPA). According to newly released Companion Handbook to the WHO guidelines for the PMDT (April 2015) "All TB patients infected with strains resistant to Rifampicin should be treated using a full MDR-TB regimen, with Isoniazid being added to/included in the regimen until DST results to Isoniazid are available and appropriate adjustments to the regimen can be made. If DST results to Isoniazid shows susceptibility, Isoniazid can be continued in the MDR-TB regimen". Thus, following updates are required in the new version of the National Guidelines.

Approaches to the management of XDR-TB are similar to the MDR-TB with regimens based on DST pattern and history of previous treatments. As of the time of the visit, XDR-TB regimens include longer use of injectable agents, fluoroquinolone of later generation (Mfx) and the rest of SLD with Z. Group 5 drugs are not yet available in Romania, except 2 cases treated with Bedaquiline under Compassionate Use Program. Delamanid and companion drugs from Group 5 (Clofazimine, Linezolid, Imipenium/Cilastatin and Amoxicillin-Clavulanic acid) are not yet available in Romania, but had been ordered to the GDF within GFATM and Norwegian grants. It was discussed with the NTP that regimens for XDR-TB should be based on the latest recommendations of the WHO Companion Handbook (2015), chapter 5.15.

As noted earlier, the recent Romanian funding request to the GFATM was approved for the total funding of 8.4 million Euros for three year starting April 2015. Under the new GFATM grant the Romanian NTP is planning to ensure access to quality-assured SLD for 460 M/XDR-TB patients through the GDF mechanism. With funding from the Norwegian government of a total of 10.7 million Euros, the Romanian NTP will be able to enrol up to 1,000 patients with M/XDR-TB over the period of 20 months, which seems ambitious, but possible, considering the number of patients require access to adequate therapy with quality-assured drugs. Currently, there is no other way to access Group 5 agents (new TB and companion drugs) to treat patients with pre-XDR, certain XDR-TB, or severe MDR-TB when conditions require novel approaches to therapy, than the international donor funding. Even if Bedaquiline was recently registered in the country it is still yet

not included into Essential Drug List of Medicines (EDL or C2 list) to be purchased with government funding. With funding available from GFATM and Norwegian government the NTP is planning to treat 172 pre-XDR and XDR-TB patients with SLD and Group 5 drugs within the next three years (70 with Norwegian fund, and 102 with GFATM, including 22 with TFM). It was discussed, that the NTP should consider purchasing implantable venous access systems, like porth-a-cath, designed for longer use of Imipenium-cilastatin.

In November 2014 the RAA (PR of GFATM grant) had submitted the first drug order to the GDF within two upcoming grants to receive medicines for 1,022 M/XDR-TB patients to be enrolled over 2015, and those 288 patients already on treatment (TFM GFATM grant). Regimens listed in the order were intended for the treatment of patients with MDR-TB, pre-XDR-TB (MDR-TB + resistance to either FQ or Injectable agent but not together) and XDR-TB. Order for the regimens for pre-XDR-TB and XDR-TB included Moxifloxacin, Linezolid, Clofazimine, Imipenium/Cilastatin and Bedaquiline. The order was submitted for a joined cohort of patients (GFATM and Norwegian grant).

The NTP is planning to develop the Implementation Plan for Introduction of Bedaquiline, while the new TB drug will become available through the new funding sources and is also supported by Janssen Pharmaceuticals. There is a desperate need for new TB and companion drugs in Romania, as current possibilities for the management of patients with drug-resistant TB, especially those suffering from pre-XDR-TB and XDR-TB, are extremely limited. The latest drug order to GDF included regimens containing Bedaquiline, Linezolid, Clofazimine and Imipenium/Cilastatin (70 patients on Bedaquiline). It was discussed with the MOH, that there is a need to create the multi-sectorial National TB Coordination Committee as a National Task Forse mechanism to oversee the preparation, planning, implementation and evaluation of new TB drugs (Bedaquiline, Delamanid and Group 5 agents), as well as other new TB drugs/regimens as appropriate to access management of M/XDR-TB. A Technical Working Group should be created as an advisory board to the National TB Coordination Committee to oversee any technical aspects related to access to new TB and Group 5 drugs. It was discussed at the meeting with the MOH, that there would be a support for introduction of new TB drugs, as well as companion drugs, into the management of DR-TB in Romania.

Requirements for clinical monitoring over DR-TB patient's dynamic are clear and include sputum smear microscopy and culture at the start of treatment, and further repeated on a monthly basis during the intensive and continuation phase. Time of smear and culture conversion is not monitored, but is strongly recommended to evaluate the effectiveness of the intensive phase treatment. Clinical examinations include general blood and urine tests, biochemical analysis (bilirubin, LFT, urea, uric acid, electrolytes, creatinine, 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 mostly when patients are hospitalized and include psychiatrists, ENT, ophthalmologists, dentists, and internists, especially at MDR-TB Centres. However, range of specialists varies from county to county. Surgical management is available also mostly at major treatment facilities, with prevailing resection surgeries not palliative. Options for palliative treatments are limited as in majority of countries in the WHO European Region due to absence of practice and facilities to provide patient management. Pharmacovigilance exists as a State required system, but is spontaneous.

Management of adverse reactions requires improvement and should be supported by increased knowledge of doctors and nurses, as well as adequate supply of ancillary medicines. System of pharmacovigilance is well developed and introduced into daily practice; however, recording of adverse reactions is being performed only upon temporary/permanent withdrawal of medicine from the regimen, which is a common practice, in government approved yellow forms. Any

adverse reaction on therapy, including TB, is being encouraged by government point system, used for future accreditation of physicians. However, the system of pharmacovigilance is monitored by MOH, thus, decreases chances of false reporting. Other forms allowing registration of adverse reactions are not available. It was not possible to identify the frequency of adverse events even at DR-TB center in Bisericani (Marius Nasta Institute was not visited during current mission). Doctors are noticing GI side effects, arthralgies and depression as most common adverse reactions. At the same a lot of complains were related to the pain after use of Amikacin, thus, certain number of patients were refusing the injectable agent, which increases the risk of unfavourable outcome. 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. At MDR-TB Centers majority of patients are getting Pyridoxine (Vitamin B6) to decrease the risks of side effects on Cycloserine and Ethionamide. Dosages for Pyridoxine are adequate, at maximum daily dose of 300 mg.

Enrolment of the GLC cohort within GFATM TFM had finished in October 2014 with cohort of 302 patients started treatment during 2013-2014. Treatment initiation was performed at either one of DR-TB Center with further referral for treatment continuation to the county of residence. MDR-TB Regimens designed by DR-TB Committees are adequate and include Z, injectable agent, FQ (Levofloxacin or Moxifloxacin), Eto/Pto, Cs and/or PAS, and are based on recommendations by the WHO from 2011. Since then, all diagnosed DR-TB patients are being treated with SLD secured through the government sources. It was noted that the MDR-TB regimens were lacking fluoroquinolone due to the stock out of Ofloxacin (Levofloxacin cannot be purchased because it is not included into C2 list, so as PAS). Capreomycin was also not available for the same reason as Levofloxacin, but MDR-TB regimens contained Amikacin as an injectable of first choice. Even if Ciprofloxacin is no longer in use, as weak fluoroquinolone, that regimens lacking FQ are at a high risk to aquire additional resistance to FQ, lead to unfavourable outcome and further spread of infection in society. The MOH should revise the EDL list (C2 list) according to recommendations from previous rGLC missions, and include Cm, Lfx, PAS, and Group 5 drugs, for further procurement from the government sources.

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 but require to be regulated in the annex form in the updated version of the National Guidelines on PMDT. 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. Some outpatient facilities at PHC level are providing patients with one-two week supply of drugs for self-administration, which is completely unacceptable and increase the risk of developing unfavourable treatment outcome and contribute to continuous infectiousness of patients.

Excessive infrastructure (93 TB hospitals, sanatoriums and TB units) with capacity of 5,625 TB beds had made inpatient treatment available all around the country. As noted earlier, once evidence of strong clinical and bacteriological response to therapy is achieved, patients with DR-TB are being discharged from DR-TB centers and referred for treatment continuation to TB dispensaries. However, NTP noticed that there is small number of patients who initiate treatment at regional level facilities, but this is considered as exception. Duration of hospitalization for MDR-TB patients is still regulated by the NIH and is in average around 3 months countrywide, including the MDR-TB Centers in Bucharest and Bisericani. Usually patients are being discharged from MDR-TB Centers during the intensive phase once the first negative culture result arrive. At the same time the existing financing of TB hospitals, which is based on bed occupancy, makes TB hospitals motivated in keeping patients hospitalized (see part on Infection Control).

Options for DOT at ambulatory treatment are still limited and remained the same as past year with patients coming actively for treatment to TB dispensaries and PHC clinics. Currently, PHC level clinics and TB dispensaries offer DOT during the weekdays with Saturday treatment mostly performed as self-administered. With treatment during continuation phase is delegated to PHC, family doctors are not motivated and interested in providing strict DOT for TB and DR-TB patients because of absence of financial incentives from MOH. Possibilities for patient-centered approach and use of hospital-replacement mechanisms like home-based treatment are very limited due to the insufficient capacity and management. Vehicles available at majority of TB dispensaries but have restrictions on financing of gasoline. Positions of home patronage nurses are not available, and those nurses, especially from PHC Services are also not motivated to perform daily DOT due to lack of financial incentive and absence of transportation or its reimbursement. 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, even for the GFATM patients enrolled during 2013-2014 (TFM cohort). 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 is not available through the GFATM grant as in previous years as GFATM TFM does not consider funding of social support initiatives.

However, with the arrival of new funding from the GFATM and Norwegian Fund it will become possible strengthen the ambulatory care through introduction of patient-centered approaches, social support and DOT. One of the main objectives of the Norwegian Fund grant is to develop an integrated model of support at community level for TB treatment and prevention among poor and vulnerable groups. Thus, it is planned that 1,000 TB and M/XDR-TB patients from poor communities, including Roma population, will receive DOT and social support during outpatient stage of therapy offered by the community health providers (health mediators and community nurses). It is planned that a group of 240 community health workers will be selected and trained to perform activities within the GFATM grant. Besides, the grant will focus on training health mediators and community nurses from 50 poor rural communities on TB education and DOT. The new GFATM grant has a whole component focused on provision of patient education on treatment and adherence to therapy (social and psychological support).

In summary, the recently approved NSP for 2015-2020 has ambulatory reform as one of the major components for implementation with the overall goal to reduce unnecessary hospitalization. The reform will start under new GFATM grant in 6 pilot counties with high burden of TB and DR-TB for further dissemination of experience country-wide. Activities will include establishment of multidisciplinary teams, who will provide medical, social and psychological care for patients, including patient education on treatment and adherence. For detailed description please refer to Annex 5. Also, members of multidisciplinary groups will be responsible for performing risk assessment for default for every DR-TB patient starting therapy with SLD. The new GFATM grant will mostly focus on developing the national policy documents focused on strengthening the outpatient treatment of TB and reducing the unnecessary hospitalization. The grant will allow to review the existing laws and reimbursement practices that contribute to hospitalization and research models of ambulatory care; and develop protocols and guidelines for outpatient and inpatient treatment, including criteria for hospitalization and outpatient care. It is also planned to create two centers for treatment and care of socially-disadvantaged TB/M/XDR-TB patients during the course of therapy.

Recommendations:

	Recommendation	Responsibility
1	Finalize the update the National Guidelines for Program Management of Drug-resistant Tuberculosis (PMDT) in alignment with the recent recommendations of the WHO (Companion Handbook to the WHO Guidelines on PMDT, 2015 edition), especially with parts on new TB and companion drugs, pharmacovigilance, management of cases with mono- and poly-resistant TB.	NTP
2	Support the update and endorse the updated National Guidelines on PMDT and make it mandatory for implementation at all inpatient and outpatient institutions nationwide involved in the management of TB and DR-TB, including penitentiary sector. Ensure that once endorsed, copies of the National Guidelines should be distributed among all TB specialists involved in PMDT.	MOH
3	Consider creation of the multi-sectorial National TB Coordination Committee as a National Task Forse mechanism to oversee the preparation, planning, implementation and evaluation of new TB drugs (Bedaquiline, Delamanid and Group 5 agents), as well as other new TB drugs/regimens as appropriate to access management of M/XDR-TB. A Technical Working Group should be created as an advisory board to the National TB Coordination Committee to oversee any technical aspects related to access to new TB and Group 5 drugs.	MOH
4	Develop the National Implementation Plan for Introduction of Bedaquiline and other new TB and companion drugs (Group 5 drugs) according the WHO Interim Policy Guidance on Bedaquiline and Delamanid.	NTP
5	Introduce and perform thorough pharmacovigilance system as a part of introduction of Bedaquiline and other Group 5 agents.	NTP
6	Any use of second-line drugs, as well as new TB and companion drugs, should be only authorized by DR-TB Committee to avoid improper management of patients and further amplification of drug resistance. Regimens for patients diagnosed with DR-TB (Mono-DR, PDR, MDR and XDR) should be designed in accordance with updated version of the National Guidelines (continuous recommendation).	NTP
7	Ensure introduction and strict implementation of diagnostic algorithms on drug-susceptibility testing, as part of updated National Guidelines on PMDT with following principles: • 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, or R resistance alone. • 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
8	Consider revising the National policy on the management of DS-TB to be in the alignment with the WHO Treatment of Tuberculosis Guidelines (4th edition, 2009): 6. New patients with pulmonary TB should receive a regimen	NTP

	containing 6 months of Rifampicin: 2HREZ/4HR; 7. Category III regimen should be phased out from the treatment protocol, and replaced by Category I regimen; 8. Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy, provided that each dose is directly observed; 9. In patients treated with regimen containing Rifampicin throughout treatment, if a positive sputum smear is found at completion of intensive phase, the extension of intensive phase is not recommended. Sputum culture and DST should be performed; 10. Consider not using the retreatment regimen (Category II) for patients with high likelihood of MDR-TB.	
9	Develop the list of possible ancillary medicines used in the management of DR-TB. The list to be updated on a regular basis. Consider developing mechanisms for covering the ancillary medicines for side effect management through the new mechanism of financing through the MOH, especially for ambulatory sector.	NTP
10	Consider options for reallocating funds and finding additional financing to strengthen the ambulatory treatment; provide strict DOT, especially at ambulatory settings and personnel motivation, especially for PHC level. 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
11	Consider developing mechanisms for covering the ancillary medicines for side effect management through the new mechanism of financing through the MOH, especially for ambulatory sector.	MOH
12	Develop strategies to perform palliative care of patients who failed treatment	NTP

9. TB Laboratory

Findings and summary of discussion:

Laboratory network is under strengthening and reorganization over the past years, and still widely presented by 83 laboratories in each county of Romania, with 14 level I laboratories for sputum smear microscopy only, 47 level II laboratories performing sputum smear microscopy and culture, 44 level III laboratories performing sputum smear microscopy, culture and DST to FLD (short-line DST to Isoniazid and Rifampicin) and 2 National reference laboratories, included in the number of level III laboratories, performing DST to FLD and SLD (MNI in Bucharest and Cluj Napoca). The workloads vary tremendously among the laboratories with microscopy analysis in level 1 facilities ranging from 39 to 2707 specimens a year. In level III laboratories, the number of smears analyzed ranged from 1689-20,442 while the number of cultures processed on solid media ranged from 248 to 20,442. The workload in some laboratories falls short of expected levels needed to maintain capacity and ensure quality of diagnosis. Structurally, the laboratory network remained the same as in previous year, but with plans to establish a functional network to improve access to rapid molecular diagnosis of drug resistance with financial support from the donor funding (GFATM and Norwegian government). Also, the reorganization was considered as one of the objectives of the

National Strategic Plan for TB for 2015-2020, which was endorsed by the Government of Romania in March 2015.

While the majority of level III laboratories in counties still perform the short-line DST to FLD using solid media, the reorganization will significantly improve early diagnosis of DR-TB and timely initiation of adequate therapy. Currently, it usually takes up to three months in average to receive the DST results from the county-level laboratories to further initiate therapy. As of previous year visit access to rapid molecular diagnosis was limited to two LPA modules installed in two NRLs in Bucharest and Cluj Napoka, and no Xpert MTB/RIF equipment available. Coverage with DST to SLD was even lower, available only at two NRLs equipped with LPA (MTBDRPlus-sl), and no access to liquid media DST. Also, the diagnostic algorithm was only updated in early 2014 and became available for use only less than a year ago. Lack of access to rapid diagnosis of R-resistant cases as well as diagnosis of resistance to SLD, had been one of the leading factors to worsening of the burden with M/XDR-TB in the country.

However, currently the Romanian NTP is performing a huge step forward to establish a functional laboratory network with the purpose to improve access to rapid molecular diagnosis of drug resistance. Starting early 2015 the financial assistance will be provided from the GFATM and Norwegian government. Reorganization will result in creating a network of 8 national and regional reference laboratories (NRLs and RRLs), who will serve as reference centers in 8 key geographical regions of the country in order improve access to rapid diagnosis of resistance to rifampicin and second-line drugs (IQE) for all counties. Selection of RRLs was made based on the burden of disease, geographical proximity to other counties and capacity (equipment, infection control measures and trained personnel). The NTP is planning to ensure transportation of samples from counties to RRLs and supervision and monitoring within Norwegian grant through procurement of 9 vehicles (8 for RRLs and 1 for NTP). Even if the size of M/XDR-TB reservoir is not yet known completely, but based only on WHO estimates, the ongoing reorganization of laboratory network and capacity improvements to increase access to rapid molecular diagnosis of drug-resistant TB will significantly improve knowledge on the actual burden of disease, strengthen PMDT and call for further actions.

Two laboratories recognized as National Reference laboratories in Bucharest at MNI and Cluj-Napoca (north and south) performing quality assurance for the whole country. The NTP Coordinator on Laboratory is based in NRL in Cluj Napoca. By the time of the visit only three laboratories performed DST to SLD (Km, Am, Cm, Fq, Eto): two NRL, and one partially in Bisericani (Bisericani lab performed culture and DST to FLD and SLD only for Neamt county and patients from other counties only if they are hospitalized at Bisericani MDR-TB Center). Two NRLs served as reference laboratories for 50% of the county each for DST to SLD to ensure geographical accessibility. Starting spring 2015 with upcoming reorganization and creation of a functional laboratory network it will become possible to decentralize access to rapid DST through regional reference laboratories.

By the time of the visit, the culture testing on liquid media was possible with 7 MB/BACT, the Middlebrook 7H10 medium, with machines available for isolation of MTB and 5 BACTEC MGIT-960 machines from previous years. None of BACTEC MGIT-960 machines were performing DST, but for culture only for selected specimens (Brasov, Constanta, Craiova, Timisoara, Sibiu). However, with donor funding available the NTP is planning to purchase 5 MGIT-960 machines (3 with Norwegian and 2 with GFATM) for instalment in 2 NRLs (Bucharest and Cluj Napoka), and 3 level III laboratories (Iasi, Bakau and Timisoara). It was discussed with the NTP to reconsider instalment of one MGIT-960 from laboratory in Iasi to Bisericani, the second main DR-TB treatment site with well-functioning level III laboratory. Starting 2015 with funding available from GFATM it will be possible to perform 5,000 culture tests, 2,000 DST to first- and 1,000 to second-line drugs over

three years (2015-2018). Similarly, within Norwegian grant, the NTP is planning to use the capacity of three MGIT-960 to perform 19,250 liquid culture testing, 10,700 DST to first- and 1,350 DST to second-line drugs during 20 months (April 2014 – August 2016). Besides MGIT, the NTP will receive three VersaTREK System for liquid DST to first-line drugs (HRESZ), which will be installed in Craiova, Constanta, Coloraj or Leorden laboratories, but currently available only in NRL (Bucharest). The assumptions for installation will be based on geographical coverage of the laboratory, and capacity (space, availability of biosafety cabinets, human resources and workload based on burden of disease). Availability of VersaTrek modules will also improve time for culture confirmation (up to 14 days) and DST (up to one week), as well as ensure high sensitivity.

The NTP is planning to scale up the rapid diagnosis of drug resistance using the LPA with funding available from TFM GFATM and two automatic Genotype machines arrived in May 2013. Training for laboratory specialists had been conducted with support from ECDC and WHO-Europe in early 2014. Also, heads of NRLs had had been trained at SNRL in Stockholm and finalized the diagnostic algorithm for LPA. The rapid molecular diagnostic equipment (LPA) was installed in two NRLs to perform DST to HR and essential SLD (Amikacin only and FQ). SNRL provided assistance in methodology and capacity building of laboratory personnel as well as helped with developing protocol for rapid DST. With funding available from GFATM the NTP is planning to perform over 5,000 DST to first-line drugs and 1,000 DST to second-line drugs within three-year period. In addition two LPA machines will be purchased through Norwegian grant to perform 10,000 DSTs to HR and 600 DST to second-line drugs (IQE). The equipment will be installed in level III laboratories of Iasi and Constanta to cover the eastern part of Romania. Due to the current reconstruction of the laboratory in Iasi, the second LPA machine will be placed in the laboratory of Bakau county.

Access to Xpert MTB/RIF became available in Romania in compare with previous rGLC mission with 8 machines, 4-module each, already functioning (purchased - 2 in Bucharest, 1 in Bisericani; 5 installed in level III laboratories across the country under lease from Cepheid with obligation to perform no less than 100 tests per month). Fourteen Xpert MTB/RIF four-module machines will be purchased later in 2015 with funding available from GFATM (6 machines to perform 5,500 tests) and Norwegian grant (8 machines to perform 28,600 tests). Xpert modules will be installed in laboratories of counties, which have high burden of DR-TB and HIV. The new diagnostic algorithm was developed with the help of SNRL and planned to be included into updated version of the National Guidelines on PMDT and the National Laboratory Guidelines (Annex 4). However, the algorithm is missing the part on the use of liquid media testing (culture and DST). Training for personnel will be performed directly at workplace.

Considering adequate financing coming with external funding, the Romanian NTP has sufficient coverage with rapid DST to first-line drugs, which improves early diagnosis of R-resistant or HR-resistant cases – a total of 15,000 DST to HR for the next three years using LPA equipment and 34,100 of tests using Xpert MTB/RIF. Geographically, all regions of Romania, including those with high burden of TB and DR-TB, will have an access to rapid molecular diagnosis of TB and DR-TB by the end of 2015. Besides, within Norwegian grant, the NTP have planned to perform centralized training for all laboratory personnel on rapid molecular diagnosis of drug resistance and use of liquid media testing. Infection control in laboratories will be significantly improved with upcoming donor funding. Thus, 42 biosafety cabinets will be within Norwegian grant to ensure laboratory biosecurity and meet the international requirements for biosafety.

Coordination of activities at National level is being performed by Laboratory Working Group, which is yearly nominated by the MOH, with a possibility to perform regular monitoring visits to county level laboratories at least once per year. However, with upcoming donor funding and reorganization of laboratory network, supervisory visits will be performed on a more frequent basis to ensure adequate performance. 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 technical assistance on DRS (2008 and 2014). The latest DRS was taking place during the mission (03/2014 – 03/2015) with three laboratories participating: NRLs (Bucharest and Cluj Napoka), and level III laboratory in Bisericani. DST was performed using the absolute concentration method to H, R, S, E and the proportion method to H, R, Ofx, Km, Am, Cm on solid media, as well as LPA. The survey was based on pulmonary smear positive cases (estimated number of new cases was 1,520) with countrywide coverage of cluster sampling. The DRS was not completed yet due to unequal enrollment of samples, which started first from counties with low incidence of TB and only continued to high-burden sites in October 2014. Selected counties (50 clusters, including 41 counties and 3 from Bucharest) were supposed to submit for DRS 35 new smear-positive samples from new cases and 35 smear-positive samples from relapses and retreatment cases. The survey was planned for completion on March 31, 2015. According to the design of the DRS, each H-resistant or R-resistant case would be tested for conventional DST to the rest FLD and SLD. It was not possible to obtain preliminary results of the survey because enrollment started from low incidence parts of the country.

Recommendations:

	Recommendation	Responsibility
1	Support the ongoing rationalization of laboratory network, ensuring adequate financing of laboratory services and developing strategic approaches to ensure adequate financing past donor funding in 2018.	MOH
2	Ensure the universal access to rapid diagnosis of TB and MDR-TB by using cartridge-based Nucleic Acid Amplification Techniques at selected lower level laboratories and/or sputum collection points with high rates of TB and/or MDR-TB (e.g. prisons, selected hospitals, HIV centres) and Line Probe Assay in geographically-representative regional laboratories by the end of 2015.	MOH NTP
3	Update the National algorithm for diagnosing DR-TB with liquid media testing (culture and DST using MGIT-960 and VersaTrek). Include the updated version of diagnostic algorithm into National Guidelines on DR-TB and National Laboratory Guidelines accordingly.	NTP
4	Update the National laboratory reporting forms with information on rapid molecular diagnosis (Xpert MTB/RIF, MTBDRPlus, MTBDRPlus-sl). Include the updated forms into National Guidelines on DR-TB and National Laboratory Guidelines accordingly.	NTP
5	Develop standard operating procedures for processing and managing specimens for the new rapid molecular diagnostic and liquid media methods.	NTP

10. TB Infection Control

Findings and summary of discussion:

Improving infection control is one of the priorities of for the National Tuberculosis Program in Romania and one of the key interventions in the recently approved National TB Control Strategy (Intervention 2.5. Establish IC standards and requirements for healthcare facilities). In 2012 the NTP developed National IC Plan for Tuberculosis Control in Romania for 2013-2017 in alliance with the latest WHO recommendations, which includes information on all relevant components of

infection control: administrative, environmental and personal protection measures. The purpose of the document was to review the risk of TB transmission and make recommendations to reduce the risk of occupational exposure/transmission of TB within health care facilities and congregate settings in Romania. The document was revised in 2013, but was never approved by the MOH. If approved, the Plan will serve as guidance for all TB facilities in Romania to develop and introduce their IC plans. Thus, there is no national mechanism to regulate the IC at TB facilities in Romania.

The TB network in Romania is comprised of 87 inpatient facilities (hospitals with TB departments), 174 TB ambulatories and 113 TB laboratories. Each of the 41 counties has at least one TB ambulatory and access to one TB hospital or TB laboratory. At the moment, two MDR-TB centers are functioning (one in Bucharest with 50 beds and one in Bisericani, with 70 beds), but the MOH is planning to organize 8 regional MDR-TB centers in 8 other locations: Brad (Hunedoara county), Valea Iasului (Arges county), Moroieni (Prahova county), Naruja (Vrancea county), Leamna (Dolj county), Drajna (Prahova county), Bixad (Satu Mare county) and Agigea (Constanta county).

The risk of TB transmission is high in every facility, especially of drug-resistant TB, due to years of challenges mostly related to the availability of SLD and poor IC measures at hospitals. However, the risk of transmission differs from one facility to another, and is related to the number of cases treated, types of patients, infection control measures in place, and performance of the county TB control program. TB laboratories have different risks of infection based on the procedures performed inside (microscopy, cultures, DST, molecular biology), work practices in place and adherence to the IC measures. The risk for TB transmission in the ambulatories is important, as many suspects are investigated here, but it is relative low in comparison with the hospitals, where patients have long hospitalization period, delayed identification of drug resistance and sometimes with delay in starting proper treatment. Sometimes, hospitalization is prolonged for financial reasons (the TB case is paid based on the length of hospitalization) or for social reasons (homeless, social cases). Among the TB cases in staff registered over the last 5 years in the TB facilities, 115 cases were identified in the hospitals and 20 cases in the ambulatories.

In 2013 ECDC initiated the TB Infection Control Project in Romania for 2013-2014 with the purpose to improve IC at inpatient TB facilities. With technical assistance from ECDC consultant, the NTP developed a template of IC Plan for generic TB facility, a comprehensive tool to provide background information on current IC measures performed in a facility with clear instructions for improvement (Annex 2). The template contains information on management of IC, M&E and budget tools. Each facility developed their own IC plans, or about to finish the assessment. Using the tool, NTP had made a classification of TB hospitals based on several risk factors, like:

- Risk of nosocomial transmission
- TB incidence and the number of TB patients in county
- Number of beds for TB patients in facility
- Type of patients diagnosed and treated in the facility
- TB incidence among health personnel in the facility

The risk assessment and classification have helped determining the types of interventions for implementation at each facility involved in TB control. Based on the assessment, which took place in 2014, identified 14 TB institutions with extremely high risk of nosocomial transmission, including two MDR-TB centers in Bucharest and Bisericani. Thus, they, as well as other institutions with high risk of nosocomial transmission will become the first-grade target for IC interventions with upcoming donor funding starting 2015.

Considering the problems identified the NTP is planning to improve the capacity of facilities, involved in TB control in Romania with upcoming external funding. With Norwegian funding it will become possible to purchase 2,000 UVGI lamps for further instalment at 49 institutions across the

country based on prioritization performed by NTP. It was agreed with the NTP that installation of the upper-level UVGI lamps, monitoring over performance and maintenance should be performed by a trained technician. A ToT session will be organised in order to train 20 national trainers/coordinators in TB infection control, who will be identified as medical personnel from county-level TB facilities and perform National IC monitoring and implementation. Two of the national coordinators will be engineers responsible for all technical aspects related to mechanical engineering ventilation and upper-level germicidal lamps. Furthermore, the national trainers will train 960 TB providers, including doctors, nurses, and administrative personnel. In addition the US Embassy in Romania allocated funding for Installation of the mechanical ventilation system and will support maintenance of equipment for negotiated period (2000 Euros/month) at MNI. In terms of IC, the GFATM grant will mostly focus on developing the national policy documents focused on strengthening the outpatient treatment of TB and reducing the unnecessary hospitalization. The grant will allow to review the existing laws and reimbursement practices that contribute to hospitalization and research models of ambulatory care; and develop protocols and guidelines for outpatient and inpatient treatment, including criteria for hospitalization and outpatient care.

During 2013-2014 the NTP have identified specialists from each TB hospital around Romania who were considered as focal point responsible for coordination of Infection Control activities at their facilities. Selected specialists were trained on basics of IC, and further received refreshment trainings within ECDC IC project. Participants were provided with developed tools for IC assessment and contributed to provision of information for risk assessment, initiated by the NTP. Unfortunately, only 50% of all institutions involved in TB control were received refreshment training last year, but there will be an opportunity to be trained and monitored by identified national IC coordinators.

Despite the availability of external funding for the next three years, absence of the government-endorsed National IC Plan makes problematic the implementation of series of activities. The scheduled installation of UVGIs is not regulated by any of the national standards but international recommendations only. Thus, there is a need to urgently endorse the updated version of the National Infection Control Plan in Romania and ensure adequate financing of infection control activities. Also, the MOH should introduce TB infection control measures in diagnostic and treatment facilities and in congregate settings by revising the Ministry of Health's Order N°916 (26 July 2006) and the current system of health facility accreditation and including specific measures for the prevention of airborne TB transmission.

Similar to the previous GLC missions, it is assumed that there were no significant positive changes in improving the infection control in majority of TB inpatient facilities due to the transition to increased financing of National TB Program and upcoming donor funding (2015). IC plans are available from almost whole country, but monitoring system was still not yet in place established at national level, but expected for significant changes starting April 2015. However, the TB Hospital in Laemna, which was visited first by the rGLC in 2012 had made appropriate improvements in terms of separation of non-TB from TB patients, and those with MDR-TB from regular TB patients. The Laemna TB hospital will be one of eight inter-county MDR-TB treatment centers, because of the high burden for TB and DR-TB, and has a well-functioning laboratory, whose capacity will be improved with upcoming donor funding, as well as the capacity of the hospital (SLD and upper-level UVGI lamps).

Completion of recommendations is partial and majority are of slow progress. Considering the fact of low treatment success rate among MDR-TB patients, poor treatment regimens due to the unavailability of full range of SLD, incomplete coverage with DST to SLD and questionable DOT, hospitalization serves as one of the major ways for infection transmission. Administrative

separation of patients by DST and smear/culture positive status, as well as early diagnosis of TB and DR-TB, and timely start of treatment, is the most effective measure of Infection Control for Romania. This general statement is true taking into account current financial constrains and inability to fund the instalment and maintenance of engineering ventilation. Air exchange should be considered at all inpatient facilities, by regular opening windows in patients' rooms. Recommendations from previous missions to invest funding into rapid diagnosis of TB and DR-TB (LPA and GeneXpert) and increase access to rapid DST, will be completely fulfilled in spring-summer 2015 with arrival of international donor funding, as well as access to full range of quality-assured SLD. Similarly, the installation of upper-level UVGI lamps within Norwegian grant at inpatient facilities and those ambulatory setting at high risk of infection transmission will bring positive impact on reducing the burden of TB and DR-TB in Romania. Excessive hospitalization at TB inpatient facilities is another challenge to address. Decrease in the number of TB hospital beds in those facilities, who do not meet the standards of infection control might not be a bed solution, considering the existing approach of financing hospitals. It is the matter of reforming the health financing system for hospitals based on completed case with released funding reallocated on strengthening service delivery at outpatient sector, rather closing the improper functioning facilities. This might become possible with upcoming funding from the GFATM, which will allow the MOH to address the issue of excessive hospitalization and strengthen the ambulatory treatment for TB. In a long run these efforts will significantly improve the sustainability of the National TB Program in Romania.

Recommendations:

	Recommendation	**Responsibility**
1	Urgently endorse the updated version of the National Infection Control Plan in Romania and ensure adequate financing of infection control activities.	MOH
2	Urgently introduce TB infection control measures in diagnostic and treatment facilities and in congregate settings by revising the Ministry of Health's Order N°916 (26 July 2006) and the current system of health facility accreditation and including specific measures for the prevention of airborne TB transmission.	MOH
3	Develop mechanisms to address the issue of excessive hospitalization at TB inpatient facilities using the opportunity of international donor funding by creating criteria for admission to the hospital and strengthening the ambulatory care program, including aspects of adherence to treatment.	MOH
5	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. Early diagnosis of TB and drug resistance at least to rifampicin should serve as essential element for timely and safely separation of patients, initiation of appropriate treatment under direct observation, in order to decrease the level of nosocomial transmission of infection in congregated settings, including prison sector (continuous recommendation).	NTP
6	Perform rapid molecular diagnosis of TB and resistance to at least H and/or R (Xpert MTB/RIF and MTBDRPlus) prior hospitalization to TB inpatient facilities.	NTP
7	Ensure allocation of adequate financing for personal protection measures for health and administrative personnel at all treatment sites involved in program and medical management of TB and DR-TB. Also	NTP

	ensure adequate financing for purchasing surgical masks for infectious patients and suspects. Fit testing is mandatory before purchasing respirators for health personnel in each inpatient facility.	
8	Continue the risk assessment of the county TB facilities and make any necessary updates of the National IC Plans.	NTP
9	Ensure appropriate biosafety measures in all laboratories performing culture and DST, including rapid molecular diagnosis. Ensure adequate financing for maintenance of biosafety cabinets and replacement of filters, as well as personal protection of all laboratory personnel.	NTP

11. Second line anti-TB drug management

Findings and summary of discussion:

In 2013 the government of Romania made the decision to centralize drug procurement system in the country launched the system of National tenders since decentralization. Financing of drug procurement is performed by the MOH, who serves as single funding source. National tenders usually happen once per year, and are organized according to the list of essential medicines (TB component C2 list). The C2 list had not been revised according to the recommendations of the previous rGLC and GDF missions but some improvements are noticed. The list still contains Ciprofloxacin and lacking Levofloxacin, Capreomycin and PAS, as well as new and Group 5 drugs. However, Ciprofloxacin is excluded from the National tender, which makes it impssible for procurement. Centralized national tender allowed decreasing the prices through open competition for majority of TB medicines. However, even with one national tender taking place, TB institutions have to make the orders and pay for TB medicines themselves. There is a lack of coordination between the NTP and TB facilities, which are responsible for drug purchasing in counties. The NTP is aware of the actual funding allocated for TB medicines approved by the MOH, but is lacking the information on drug orders and consumption in counties. The NTP should have the capacity and consider improving monitoring over the drug consumption at county-level on a regular basis (monthly or quarterly). System to monitor and track the actual consumption of anti-TB drugs is not in place, thus, estimations on the needs and forecasting seems to be problematic. However, according to the NTP, software was developed for county-level pharmacies for ordering certain quantities of TB drugs and tracking the order. Also, there is no comprehensive electronic information system available especially for drug management of FLD and SLD. Thus, it was recommended to the NTP to consider using one of the WHO recommended tools for quantification and forecasting, like QuanTB.

Still, the mechanism of distribution of medicines to the counties require significant improvements, through identifying selected distributing companies responsible for timely delivery of drugs to the counties to avoid the stock-outs and treatment interruptions. It was found during the mission that currently Romania is experiencing the stock out of Ofloxacin, purchased through the MOH funding, because the producer of registered drug have not produced enough quantity of medicine, and is the only one selected for procurement by the National tender. It might take up to additional 3 months to contract another producer of registered Ofloxacin in Romania, also because the running contract is not yet finished, which aggravates treatment outcomes and put the current MDR-TB patients at risk of acquiring resistance to FQ. There is a need for the NTP to develop suggestions to the MOH on improving the conditions of the National tender to avoid the stock outs of medicines and, as a result, treatment interruptions.

The recently endorsed National Strategic Plan (March 2015) ensures a full implementation of centralized procurement mechanism only starting 2018, thus, with existing donor funding the Romanian NTP will be able to cover the needs in SLD to treat M/XDR-TB. Moreover, the MOH has to ensure establishing the mechanism of coordination and ensure allocation of adequate financing of drug procurement past 2018.

As noted earlier, the recent Romanian funding request to the GFATM was approved for the total funding of 8.4 million Euros for three year starting April 2015. Under the new GFATM grant the Romanian NTP is planning to ensure access to quality-assured SLD for 460 M/XDR-TB patients through GDF. With funding from the Norwegian government of a total of 10.7 million Euros, the Romanian NTP will be able to enrol up to 1,000 patients with M/XDR-TB over the period of 20 months, which seems ambitious, but possible, considering the number of patients require access to adequate therapy with quality-assured drugs.

The drug order to GDF was submitted by the RAA, the PR of the grant, in early November 2014, and was cleared by the rGLC. The order included 1022 patients with M/XDR-TB to be enrolled during 2015 and 288 patients already on treatment. Regimens listed in the order were intended for the treatment of patients with MDR-TB, pre-XDR-TB (MDR-TB + resistance to either FQ or Injectable agent but not together) and XDR-TB. Order for the regimens for pre-XDR-TB and XDR-TB included Moxifloxacin, Linezolid, Clofazimine, Imipenium/Cilastatin and Bedaquiline. The order was submitted to combined cohort of patients (GFATM and Norwegian grant).

The NTP is planning to develop the Implementation Plan for Introduction of Bedaquiline, while the new TB drug will become available through the new funding sources and is also supported by Janssen Pharmaceuticals. There is a desperate need for new TB and companion drugs in Romania, as current possibilities for the management of patients with drug-resistant TB, especially those suffering from pre-XDR-TB and XDR-TB, are extremely limited. The latest drug order to GDF included regimens containing Bedaquiline, Linezolid, Clofazimine and Imipenium/Cilastatin (70 patients on Bedaquiline). It was discussed with the MOH, that there is a need to create the multi-sectorial National TB Coordination Committee as a National Task Forse mechanism to oversee the preparation, planning, implementation and evaluation of new TB drugs (Bedaquiline, Delamanid and Group 5 agents), as well as other new TB drugs/regimens as appropriate to access management of M/XDR-TB. A Technical Working Group should be created as an advisory board to the National TB Coordination Committee to oversee any technical aspects related to access to new TB and Group 5 drugs. It was discussed at the meeting with the MOH, that there would be a support for introduction of new TB drugs, as well as companion drugs, into the management of DR-TB in Romania.

However, even with important positive changes with donor funding, the availability of medicines at treatment sites is not complete, except those sites with MDR-TB patients on treatment with GFATM drugs (TFM cohort). There are still budget limitations for procurement of anti-TB drugs; thus, coverage with adequate regimens from government sources is limited until the start of the grant. Tender process is time and resource consuming resulting in delays with procurement of drugs. Availability of SLD at MDR-TB Centers and in the rest of the country differs, with full range of medicines available in Bucharest and Bisericani, and missing some of the SLD at county level facilities, making patients treated with extremely weak regimens. Recommendation from previous missions to consider purchasing SLD with government funding through the GDF mechanism is not possible due to the absence of legal framework to procure TB medicines directly from the international procurement agency of medicines.

Recommendations:

	Recommendation	Responsibility
1	Ensure adequate financing and uninterrupted supply of drug procurement for FLD and SLD at all treatment sites.	MOH
2	Develop strategy to ensure allocation of adequate financing of drug procurement past 2018 for the management of M/XDR-TB.	MOH
3	Update the National Essential Drug List (C2 list) to include the following medicines: Capreomycin, Levofloxacin, PAS, Bedaquiline, Linezolid and Imipenium/Cilastatin). Consider update of the C2 list with Delamanid and Clofazimine once the drugs are registered in Romania.	MOH
4	Revise conditions of the National tender to avoid possible stock outs of TB medicines.	MOH
5	The Essential drug list should include only those medications, which are included into the regimens of updated National Guidelines on PMDT for Romania.	MOH NTP
6	Improve the capacity of NTP to conduct regular monitoring over the drug consumption at county-level. Consider developing an electronic system specifically designed for drug management.	NTP
7	Address the issues of Rational Drug Use (RDU) at all levels of TB and DR-TB care delivery.	MOH NTP
8	Support the introduction of new TB drugs (Bedaquiline and Delamanide) for the management of drug-resistant TB according to the WHO Interim Policy Guidance. Ensure proper pharmacovigilance while introducing the use of new TB and companion drugs into practice.	MOH NTP
9	Develop the Implementation Plan for Introduction of new TB drugs in Romania.	NTP
10	Consider using the QuanTB – Tuberculosis Medicines Quantification Tool (http://siapsprogram.org/quantb/) for TB drugs quantification and forecasting at National level.	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 is centralized at the level of NTP, with information collected from every county TB coordinator. 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 TB institutions (hospitals and dispensaries) 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. The information data flow has three levels, with data collected at TB clinics (first level), compiled for the county at county level by TB coordinator and TB epidemiologist (secondary level), and further referred to the tertiary level to the MNI (NTP Coordinator).

Separate electronic MDR-TB registry is available within the National Registry with data entered on patients registered for treatment with SLD. However, all information on every MDR-TB case registered for treatment is recorded in paper registrars, available at MDR-TB centers. Access to MDR-TB registry is available at central level (MDR-TB coordinator) and at each TB clinic. However,

the registry include only those patients registered for Category IV treatment and does not include those diagnosed with MDR-TB. The registry contains information on patient's unique number, diagnosis, bacteriology results (smear, culture, DST), treatment regimen and clinical testing. Monitoring over data collection and reporting is being performed by Central Coordination Unit from National level to the counties and by county coordinators to TB clinics. There is no unified laboratory registry in the electronic format, but each laboratory has its own, and also keeps the records in paper registers. However, currently the NTP is under the process of developing the unified laboratory module for the National register, which will be finished by 2016.

Monitoring is being performed at minimum twice per year and often based on results of program performance and reporting. In July 2014 the Central Coordination Unit performed several snapshots over quality of data recording into National Registry in each county and define the range of missing data. Several counties where identified with poor data recording, which made the issue to be addressed to county-level TB coordinators. With upcoming funding from the Norwegian government a series of activities planed to improve the National Information System for TB, including the upgrade of the National registry (Work package 3 of the grant).

Recommendations:

	Recommendation	Responsibility
1	Conduct regular monitoring over recording and reporting, data collection and entry at county level TB dispensaries and laboratories. Perform "snapshots" of 5-6 counties every month and address the issues of missing data and R&R to the county TB coordinators.	NTP
2	Continue rationalizing the recording and reporting system and revising the national TB database to better process patients' data and ensure their analysis and use for policy decisions.	NTP
3	Ensure that the National registry contains information on all TB and DR-TB cases registered in the country, not only those registered for treatment.	NTP
4	Update the National Guidelines on PMDT, section on R&R in alignment with the WHO 2013 Revised definitions and reporting framework for tuberculosis or latest ECDC definitions.	NTP
5	Revise the existing R&R forms for DR-TB and make appropriate updates in accordance with Part 4 "Forms for drug-resistant TB programs" of the WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Include the updated forms into the updated version of the National Guidelines for PMDT in Romania.	NTP
6	Complete the development of electronic Laboratory module for the National TB Registry and perform regular monitoring over laboratory data entry at all regional level laboratories.	NTP

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. Often times, 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. Within the new GFATM, the NTP will address social challenges of poor and vulnerable patients, including Roma population, through ensuring access to appropriate diagnosis and treatment, as well as socio-psychological support.

Recommendations:

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

14. Attachments

- Annex 1: GLC monitoring mission agenda
- Annex 2: Generic Infection Control Plan
- Annex 3: National Strategic Plan for TB Control in Romania, 2015-2020
- Annex 4: DR-TB diagnostic algorithm
- Annex 5: GFATM Concept note from Romania
- Annex 6: Structure of NTP Central Unit