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
DR-TB – Drug-resistant tuberculosis
DST – Drug susceptibility testing
ECDC – European Center for Disease Control and Prevention
EQC – External Quality Control
FLD – First-line anti-tuberculosis drugs
FQ – Fluoroquinolone
GDF – Global Drug Facility
GFATM – Global Fund to Fight AIDS, Tuberculosis and Malaria
rGLC – Regional Green Light Committee
HIV – Human immune deficiency virus
IC – Infection control
MDR-TB – Multi drug-resistant tuberculosis
M&E – Monitoring and Evaluation
MNI – Marius Nasta Institute
MOH – Ministry of Health
MOJ – Ministry of Justice
NG – Norwegian Grant
NFM – New Funding Model
NIH – National Institute of Health
NSP – National Strategic Plan to Control TB in Romania, 2015-2020
NRL – National reference laboratory
NTP – National Tuberculosis Programme
PIU – Project implementation unit
PMDT – Programme management of drug-resistant tuberculosis
POCU – Financial mechanism from the European Structure Fund
RR – Resistance to rifampicin
RAA – Romanian Angel Appeal
R&R – Recording and Reporting
RRL – Regional reference laboratory
SAT – Self-administered treatment
SLD – Second-line anti-tuberculosis drugs
SLDST – Drug susceptibility testing to second-line drugs
SNRL – Supra-National reference laboratory
SS (+/-) – Smear (positive/negative)
TA – Technical Assistance

TB – Tuberculosis
TFM – Transitional Funding Mechanism
WHO – World Health Organization
XDR-TB – Extensively drug-resistant tuberculosis

1. Terms of Reference

Objectives:

- to assess the implementation of the programme, evaluate current achievements and sustainability of the programme and to 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 for technical assistance on any aspect of the Programme 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 systems; 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 country'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 in the ambulatory sector); childhood TB case management; TB care delivery ethics and other relevant aspects of the programme with a focus on vulnerable groups (e.g. 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 paediatric dosages and formulations; collaboration with the first and second-line drug procurement agency;
11) Information system (including availability of a database and recording and reporting forms) and data management (routine collection and cohort analysis); existence of separate MDR-TB register or user-friendly platform for separate data management/analysis from the general TB register. Existence of laboratory information management section/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 that can be provided by WHO-Europe and GLC-Europe.

2. Background information

The rGLC/Europe is supporting the implementation and scale up of the M/XDR-TB Response Plan in Romania. Since the launch of the GFATM project, the rGLC has conducted yearly monitoring missions, with the last one in March 2015.

Romania received several approvals from the GLC to access quality-assured SLD for a total of 850 MDR-TB patients. From 2004-2011 a total of 884 MDR-TB patients were enrolled into the GLC-approved programme with funding available from the GFATM grant. The average treatment success rate for the first three cohorts of a total of 364 MDR-TB patients (2004-2005, 2006-2007, 2009) was 66.8%. The treatment success rate of the 2011 cohort was 73.6%. Despite good performance of GFATM grants related to the TB Programme in Romania, the treatment effectiveness of non-GLC cohorts of patients has showed extremely poor outcomes over the years due to a series of structural, financial and organizational constraints. In early 2013 the GFATM approved financing through TFM of a new cohort of 300 patients to be enrolled in 2013-2014; this started in October 2013 and included regimens for 19 patients with XDR-TB. An 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-Europe, ECDC and other international organizations focused on strengthening the National Tuberculosis Programme (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, WHO and other governmental and non-governmental organizations. The NSP outlines the national strategies to respond unmet needs and to build sustainability of the system, as well as presenting the long-term vision of TB care and identifying innovative approaches targeted on achieving a dramatic decline in TB incidence and mortality in Romania by 2020.

Still, there are various bottlenecks that require attention from the Government and International authorities in order to strengthen the capacity and performance of the Romanian TB Programme. The majority of them will be addressed with 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.

The Romanian National Tuberculosis Programme (NTP) is showing significant progress in the scale up and management of drug resistant tuberculosis. The majority of key recommendations from the previous mission are in progress; it is acknowledged that the complexity of the tasks require significant effort and time. Out of 17 key recommendations to the Ministry of Health, 1 has been fully completed and 16 were in progress. Out of 27 recommendations to the NTP, five have been fully completed and 22 were in progress; success will require joint efforts from the NTP and international donor organizations. Several recommendations are repeated throughout the current report.

Priority recommendations from previous GLC monitoring mission	**Status/Comments**
Recommendations to the MOH	
Prevention and control of TB and M/XDR-TB should	Implementation of the National Strategy is

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.	in progress. For the period 2015-2016, approximately 90% of the budget for MDR-TB drugs and laboratory consumables for rapid molecular diagnosis was from internationally funded projects. As stated within the National Strategy, from 2017 the government will cover the costs of diagnosis and treatment of TB. The last 1-2 years were transitional to advocate for amendments in existing legislation.
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).	Generally, the National Strategic Plan for TB Control for 2016-2020 matches the TB Action Plan for the WHO European Region for 2016-2020. Also, as the document was approved by the government it will not be easy to change.
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).	Completed.
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.	In progress. As part of the TA from WHO-EURO (data collection for cost analysis).
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.	The National guideline on PMDT is included within the national implementation plan for group 5 drugs. After finalisation the document will be printed and distributed among specialists.
Consider creation of the multi-sectorial National TB Coordination Committee as a National Task Force 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.	The National TB Coordination Committee is included within an Order of the Ministry of Health. Status: pending. The Technical Working Group is composed of 5 experts from the Marius Nasta Institute (MNI).
Consider options for reallocating funds and finding additional financing to strengthen the ambulatory treatment; provide strict DOT, especially at	At the moment, funds are allocated from internationally funded projects. However, from 2017 the funds will be ensured

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.	through nationally funded projects (POCU). After a project is finalised an assessment will be performed in order to ensure the sustainability of funding from the government.
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 mechanism focusing on availability of ancillary drugs is under development with report to be presented to the MOH by the end of May 2016.
Support the on-going rationalization of laboratory network, ensuring adequate financing of laboratory services and developing strategic approaches to ensure adequate financing past donor funding in 2018.	International experts have prepared several strategic documents for review, with subsequent submission to the MOH planned for endorsement.
Urgently endorse the updated version of the National Infection Control Plan in Romania and ensure adequate financing of infection control activities.	In progress. The national infection control plan was updated and submitted for approval to the MOH. The MOH requested minor changes to be made. Expected to be endorsed by the end of 2016.
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.	Will be up for consideration after the approval of the National Infection control plan.
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.	In progress. As part of the TA from WHO-EURO (data collection for cost analysis).
Ensure adequate financing and uninterrupted supply of drug procurement for FLD and SLD at all treatment sites through the government sources.	100% of FLD are procured from the government budget. SLD procurement is partially ensured from the government budget. In 2016, all diagnosed MDR cases will be covered from the Norwegian and GFATM grants. It is expected that later in 2016 the MOH will accept necessary legislative changes, which will approve funding of SLD and Group 5 drugs (missing from C2 list) from government sources.
Develop strategy to ensure allocation of adequate financing of drug procurement past 2018 for the management of M/XDR-TB.	After the inclusion of all necessary drugs into the C2 list of essential medicines, centralised procurement will be performed, which will allow requesting of additional funding based on the needs of

	the programme.
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.	Same as above.
Revise conditions of the National tender to avoid possible stock outs of TB medicines.	No stock-outs for FLD. Unknown for SLD.
The Essential drug list should include only those medications, which are included into the regimens of updated National Guidelines on PMDT for Romania.	Same as above.
Recommendations to the NTP	
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.	In progress. Included in National Implementation Plan for new TB drugs.
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.	In progress.
Introduce and perform thorough pharmacovigilance system as a part of introduction of Bedaquiline and other Group 5 agents.	In place through the National Drugs Agency. However, the NTP will perform strict monitoring of adverse events, and recording and reporting during therapy with new TB drugs. Requires improvement.
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).	The prescription of the drugs for new TB and companion drugs is done only at the level of MDR-TB Commissions (Bucharest and Bisericani).
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	Completed.

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.	
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 mechanism of availability and distribution of ancillary drugs is under revision.
Develop strategies to perform palliative care of patients who failed treatment	TB Hospital in Laemna will become the 3rd MDR-TB center for patients in social need and those who have failed therapy.
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.	In progress.
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.	In progress.
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.	In progress.
Develop standard operating procedures for processing and managing specimens for the new rapid molecular diagnostic and liquid media methods.	In progress.
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.	In progress.
Ensure allocation of adequate financing for personal protection measures for health and administrative personnel at all treatment sites involved in program	Procurement is still decentralized even with availability of funds. Requires improvement.

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.	
Continue the risk assessment of the county TB facilities and make any necessary updates of the National IC Plans.	National IC Plan already updated. Risk assessment has not been completed at all TB institutions. In progress.
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.	As part of the Norwegian grant, 44 biosafety cabinets had been procured and will be delivered in June 2016. 2000 UVGI lamps were procured and will be installed in TB laboratories and TB hospitals.
The Essential drug list should include only those medications, which are included into the regimens of updated National Guidelines on PMDT for Romania.	See above.
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.	MOH is planning to develop an electronic tool for drug consumption and forecasting.
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.	In progress.
Develop the Implementation Plan for Introduction of new TB drugs in Romania.	In progress.
Consider using the QuanTB – Tuberculosis Medicines Quantification Tool (http://siapsprogram.org/quantb/) for TB drugs quantification and forecasting at National level.	To be considered. Drug requests are created at county level with further centralization at NTP.
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.	Regular monitoring is taking place but with limited capacity (2 specialists at the level of NTP Central Unit). Requires improvement.
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.	In progress.
Ensure that the National registry contains information on all TB and DR-TB cases registered in the country, not only those registered for treatment.	In progress.
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.	In progress.

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.	In progress.
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.	In progress.
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.	In progress but requires expansion. 6 counties are implementing the pilot under a GFATM grant for psychosocial support of vulnerable patients. Also, within the Norwegian grant all patients at high risk of defaulting from treatment are provided with the social support to improve adherence to therapy.

4. Current mission recommendations (summary)

	Recommendations to the MOH	Responsibility
1	Prevention and control of TB and M/XDR-TB should be considered a public health priority. The Government of Romania should support the implementation of the National Strategic Plan for TB Control for 2015-2020. Sufficient and sustainable funding should be ensured to sustain National TB Programme implementation. Aspects requiring particular support are: access to adequate treatment regimens and uninterrupted supply of TB drugs, including new TB drugs; ambulatory treatment and social support of patients; diagnosis; and infection control.	MOH
2	Support implementation of the new GFATM and Norwegian grants. MNI Pulmonology Institute (NTP) should play a leading role in the management and implementation of this and upcoming grants (European Structure Fund - POCU).	MOH
3	Consider endorsement of the multi-sectorial National TB Coordination Committee as a National Task Force mechanism to oversee the preparation, planning, implementation and evaluation of new TB drugs (Bedaquiline, Delamanid and other TB drugs recommended for therapy of M/XDR-TB).	MOH
4	Consider endorsement of the National Implementation Plan for Introduction of new TB drugs for the management of M/XDR-TB.	MOH
5	To endorse the updated version of the National Infection Control Plan in Romania and ensure adequate financing of infection control activities.	MOH
6	To revise the existing legislative base regulating health facility accreditation and prevention of TB transmission to include appropriate measures of TB infection control at all healthcare	MOH

	institutions involved in TB control and prevention, especially in settings with a high density of TB patients, such as TB inpatient facilities.	
7	Ensure adequate financing and uninterrupted supply of drug procurement for FLD and SLD at all treatment sites (continuous recommendation).	MOH
8	Develop a strategy to ensure allocation of adequate financing of second-line drug procurement beyond 2018 for the management of M/XDR-TB (continuous recommendation).	MOH
9	Update the National Essential Drug List (C2 list) to include the following medicines: Capreomycin, Levofloxacin, Moxiflixacin, PAS, Bedaquiline, Linezolid and Imipenium/Cilastatin). Consider update of the C2 list with Delamanid and Clofazimine once the drugs are registered in Romania.	MOH
10	Revise conditions of the National tender to avoid possible stock outs of TB medicines (continuous recommendation).	MOH
11	The Essential drug list (C2) should include only those medications that are included in the regimens of the updated National Guidelines on PMDT for Romania (continuous recommendation).	MOH NTP
12	Endorse the Implementation Plan for Introduction of new TB drugs in Romania.	MOH
	Recommendations to the NTP	**Responsibility**
1	Consider introducing an update of the National Guidelines for Programme Management of Drug-resistant Tuberculosis (PMDT) in line with recently released recommendations by the WHO on PMDT, especially on new groups of TB drugs and regimen design for M/XDR-TB.	NTP
2	Besides the use of Bedaquiline, consider procurement and use of Delamanid treatment of patients with M/XDR-TB according to the WHO Guidelines on PMDT (2016).	NTP
3	Expand indications for the use of new TB drugs in accordance with the new groups of TB medicines recommended by the WHO (2016).	NTP
4	Ensure distribution of the updated version of the National Guidelines on PMDT and training of all healthcare providers involved in management of patients with M/XDR-TB.	NTP
5	Introduce and implement main aspects of active drug safety and monitoring (aDSM) as a part of scaling up access to new TB drugs. Ensure implementation of the minimum requirements for laboratory diagnosis in outpatient settings. If this is not done, it may affect adherence to therapy and lead to development of serious adverse events.	NTP
6	Ensure introduction and strict implementation of diagnostic algorithms on drug-susceptibility testing, as part of updated National Guidelines on PMDT adhering to the following principles (continued recommendation): • DST to FLD (at least to H and R) should be performed for all SS+ and CC+ patients regardless of patient type. • DST to SLD should be performed in all cases diagnosed with H and R resistance, or R resistance alone. • Repeat DST on second-line anti-TB drugs for MDR-TB patients who remain smear/culture positive after 3-4 months of	NTP

	treatment or who become smear/culture positive after conversion at a later stage of treatment.	
7	Consider collaborating with SNRL on DST to new TB drugs. Consider either storing samples of positive cultures from baseline until culture conversion for patients on therapy with new TB drugs in laboratory refrigerators or send the sample to SNRL for DST. This will facilitate understanding of the trends of amplification of drug resistance.	NTP
8	Once diagnosed Gx+/RIF+ the standardized MDR-TB regimen should be initiated with a minimum of 5 effective drugs from groups A, B, C and D1 followed by conventional DST to H and other FLD using rapid molecular diagnostic tests (LPA) and/or MGIT.	NTP
9	In patients with rifampicin-resistant or multidrug-resistant TB, a regimen with at least five effective TB medicines is recommended during the intensive phase, including pyrazinamide and four core SLD – one chosen from group A, one from group B, and at least two from group C. If the minimum effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five.	NTP
10	Ensure daily directly observed therapy of patients, in particular for those who receive therapy with new TB drugs, especially delamanid, linezolid, clofazimine and carbapenems.	NTP
11	Consider revising the National policy on the management of DS-TB to align it with the WHO Treatment of Tuberculosis Guidelines (4th edition, 2009): • 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.	NTP
12	Ensure 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.	NTP
13	Increase coverage with DST to second-line drugs (at least an injectable agent and FQ) to all Rifampicin-positive cases across country, especially in high-burden counties using rapid molecular diagnosis testing (LPA) or liquid media systems (MGIT). Consider expanding access to MTBDR*sl* in other parts of Romania (Iasi).	NTP
14	Improve monitoring of implementation of the diagnostic algorithm at county level to ensure timely use of rapid molecular testing for TB and DR-TB.	NTP
15	Update the national laboratory reporting forms with information on rapid molecular diagnosis (Xpert MTB/RIF, MTBDRPlus, MTBDRPlus-sl). Incorporate the updated forms into National Guidelines on DR-TB and National Laboratory Guidelines (continuous recommendation).	NTP
16	Introduce F-A-S-T strategy/approach in all TB inpatient facilities, which is focused on finding cases actively, safely separating patients according to smear/DST status and initiate appropriate therapy for TB or DR-TB.	NTP
17	Perform rapid molecular diagnosis of TB and resistance to at least H and/or R (Xpert MTB/RIF and MTBDR*Plus*) prior to admission to TB inpatient facilities (continuous recommendation).	NTP

18	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 TB inpatient facilities that house all TB types. Early diagnosis of TB and identification of resistance to at least rifampicin should serve as an essential element for timely and safe separation of patients and initiation of appropriate treatment under direct observation in order to decrease the level of nosocomial transmission of infection in congested settings, including the prison sector (continuous recommendation).	NTP
19	Ensure allocation of adequate financing for personal protection measures for health and administrative personnel at all treatment sites involved in the management of TB and DR-TB. Respirators for health personnel should be no less than FFP2 level of protection. “Fit testing” is mandatory before purchasing respirators for health personnel in each inpatient facility.	NTP
20	Ensure adequate financing for purchasing surgical masks for infectious patients and suspects.	NTP
21	Update the National Essential Drug List (C2 list) to include the following medicines: Capreomycin, Levofloxacin, Moxiflixacin, PAS, Bedaquiline, Linezolid and Imipenium/Cilastatin). Consider update of the C2 list with Delamanid and Clofazimine once the drugs are registered in Romania.	MOH
22	Finalize the development of an electronic system specifically designed for drug management.	NTP
23	Conduct regular monitoring of recording and reporting (R&R), 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
24	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
25	Complete the development of an electronic laboratory section / module for the National TB Registry by the end of 2016 and perform regular monitoring of laboratory data entry at all regional level laboratories.	NTP

5. General country/region profile

Findings and summary of discussion:

Romania is a country located at the crossroads of Central and South-Eastern Europe, on the Lower Danube, both within and outside the Carpathian arch, bordering Hungary, Serbia, Bulgaria, Moldova and Ukraine, with access to the Black Sea. At 238,391 square kilometres, Romania is the ninth largest country of the European Union (EU) by area, and has the seventh largest population of the EU with 20,121,641 people according to the 2011 census (19,511,000 – 2015 estimate). This population size is lower than that recorded in the 2004 census (22,063,996). The country's capital and largest city is Bucharest; it is the tenth largest city in the EU, with about 1,883,425 inhabitants (Romanian 2011 census, INSSE). Romania is divided into 41 counties and the municipality of Bucharest. Each county is administered by a county council, which is responsible for local affairs. Counties are further subdivided 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 special status as it is considered 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 World Bank estimates from 2015, Romania's total GDP (PPP) is US $435,454 billion ($21,916 per capita) which defines the country as an upper-middle income economy. The actual unemployment rate has been relatively low in recent years and stands at 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 effect of the global economic recession on the country's economy resulted in state salary cuts of up to 25% over the last five years. In the late 2000s nearly 10% of the population was in absolute poverty – of these 90% live in rural areas. A set of reform programmes, commenced in 1999, introduced a private health insurance system. The state-run healthcare system is free, but suffers from neglect and has deteriorated in recent years due to a lack of funding and underpaid staff. Romania has a 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 Programme in Romania has national coverage and solid infrastructure of both clinical and diagnostic facilities, as well as trained personnel at all levels to carry out the existing programme. Financing of TB Control and Prevention in Romania comes from the government, through the Ministry of Health (MOH).

6. Epidemiology, Case finding and Programme performance data

Findings and summary of discussion:

In Romania Tuberculosis has remained a significant public health threat over the past two decades, even though it is not included in the WHO list of high-burden countries for TB and/or MDR-TB. Data provided by the NTP shows a steady decrease in main TB indicators over the past decade, with TB incidence declining from 142.2 per 100,000 people in 2002 (30,985 new cases and relapses) to 71.7 per 100,000 in 2015. The mortality rate of TB (excluding those with HIV co-infection) was reported at low levels of 5.7% in 2014 (down from 5.9% in 2012) – the corresponding figure is assumed to be higher in HIV positive cases. The absolute number of TB

deaths in 2014 was 1,109. Data on TB mortality in the civilian sector were not available for 2015 (Table 1.1).

Table 1.1. Incidence, prevalence and mortality rates of TB, 2013-2015, Civilian sector (data by NTP)

Year	Incidence	Prevalence	Mortality
2013	77.6	127.8	5.7
2014	74.6	121.4	5.7 (1,109)
2015 (19,908,574)	71.7	116.8	N/A

Table 1.2 Incidence, prevalence and mortality rates of TB, 2013-2015, Prison sector (data provided by NTP)

Year	Incidence	Prevalence	Mortality
2013	425.7	805.7	9.1
2014	695.7	1,087.0	6.7
2015	567.8	1,110.9	7.1

Table 2. TB case notification 2013-2015, Civilian sector (data by NTP)

Case notifications	2013		2014		2015	
	abs	%	abs	%	abs	%
New cases	**12,846**	**100**	**12,482**	**100**	**12,029**	**100**
Smear-positive	6,251	48.7	6,008	48.1	5,774	48.0
Smear-negative	4,187	32.6	4,167	33.4	3,994	33.2
Smear unknown	111	0.9	103	0.8	108	0.9
Extrapulmonary TB	2,297	17.9	2,204	17.7	2,153	17.9
Other	0	0	0	0	0	0
Total new	12,846	100.1	12,482	100	12,029	100
Retreatment cases	**3,843**	**100**	**3,397**	**100**		
Relapse	2,659	69.2	2,352	69.2	2,240	69.0
Treatment after failure	582	15.1	513	15.1	506	15.6
Treatment after default	602	15.7	532	15.7	500	15.4
Other	0	0	0	0	0	0
Total retreatment	3,843	100	3,397	100	3,246	100

Table 3. TB case notification 2013-2015, Prison sector (data by NTP)

Case notifications	2013		2014		2015	
	abs	%	abs	%	abs	%
New cases	**121**	**1006%**	**180**	**100%**	**146**	**100**
Smear-positive	**40**	33.1%	**55**	30.6%	46	31.4
Smear-negative	**60**	49.6%	**88**	48.9%	72	49.3
Smear unknown	**0**	0.0%	**0**	0.0%	0	0
Extrapulmonary TB	**21**	17.4%	**37**	20.6%	28	19.3
Other	**0**	0.0%	**0**	0.0%	0	0
Total new	**121**	100.0%	**180**	100.0%	146	100
Retreatment cases						

Relapse	**19**	73.1%	**26**	83.9%	15	65.2
Treatment after failure	**2**	7.7%	**0**	0.0%	0	
Treatment after default	**5**	19.2%	**5**	16.1%	8	34.8
Other	**0**	0.0%	**0**	0.0%	0	
Total retreatment	**26**	100.0%	**31**	100.0%	23	100

Table 4. TB case notifications, 2014 (WHO)

New cases	**Abs.**	**Retreatment cases**	
Pulmonary, bacteriologically confirmed	7,874	Pulmonary, bacteriologically confirmed	1,899
Pulmonary, clinically diagnosed	2,421	Pulmonary, clinically diagnosed	356
Extrapulmonary	2,209	Extrapulmonary	102
Total new and relapse	**14,861**		
Previously treated, excluding relapses	1,045		
Total cases notified	**15,906**		

The incidence of TB varied 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 regions and lower rates in the Central and Northwest regions. The absolute number of TB patients with active disease at the end of the year in Romania remains high (around 23,259 in 2015). The main TB indices are declining mostly due to the access to treatment for the 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 Programme in Romania. Even though not recognized as a high-burden country for TB and MDR-TB by the WHO, MDR-TB is one of the major obstacles for the successful implementation of the National TB Control and Prevention Programme in Romania. The number and proportion of MDR-TB cases in the country remains high, with improvements in laboratory diagnosis of drug resistance one of major contributing factors. According to the DRS conducted in 2003-2004, MDR-TB was found in 2.9% of 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 support from the SNRL.

In 2014 the WHO estimated 2.8% (1.8-4.2) MDR among new and 11% (8-15) among retreatment cases in Romania. This amounted to approximately 900 MDR-TB cases amongst notified pulmonary TB cases annually (290 (190-430) new and 360 (270-480) retreatment cases), which is significantly less compared to previous years. According to reports of 2014 data submitted to the WHO, RR/MDR-TB was confirmed on laboratory testing in 578 out of 7,922 cases tested for RR/MDR-TB (5,751 new and 2,171 retreatment). The number of patients started on MDR-TB therapy in 2014 was 648.

The number of patients with active MDR-TB at the end of the year was slightly decreasing in both civilian and penitentiary sectors (Tables 5.1 and 5.2), which is explained both by good treatment success rate of DS-TB and increased treatment coverage of patients with a full range of SLD for MDR-TB from government and donor funding sources. With the arrival of new TB drugs to Romania for use in treatment of patients with resistance to FQ and those whose treatment of

MDR-TB was ineffective, there is a chance to decrease the prevalence of M/XDR-TB in the country. It is assumed that even with increased access to rapid molecular diagnosis of drug resistance, the number of reported cases does not reflect the actual prevalence of MDR-TB in Romania. However, thorough implementation of diagnostic algorithms for screening TB suspects will increase the yield of detection of rifampicin-resistant pulmonary TB cases. As of January 1, 2016, there were 1,091 MDR-TB cases registered in the country (Table 5.1).

Table 5.1. Absolute number of MDR-TB cases registered by the end of year, 2013-2015. Civilian sector (data provided by NTP).

	TB-TOTAL	TB without MDR	MDR-TB	%
2013	25,543	24,261	1,282	5,0
2014	24,172	22,995	1,177	4,2
2015	23,259	22,168	1,091	4,7

Table 5.2 Absolute number of MDR-TB cases registered by the end of year, 2013-2015. Prison sector (data provided by NTP).

	TB TOTAL	TB without MDR	MDR-TB	%
2012	153	144	9	5.9
2013	265	255	10	3.8
2014	329	322	7	2.1
2015	315	311	4	1.3

Coverage with DST to SLD is not complete, as not every R-resistant case has been tested with conventional DST to the rest of the first-line and all second-line drugs (Table 6). However, the arrival of new laboratory equipment (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. According to the NTP, as of January 1 2016 there were 58 new XDR-TB cases registered in Romania. Data on the number of patients with FQ-resistance (incidence and prevalence) was difficult to extract but will become possible once the laboratory network is fully integrated into the national TB registry.

Table 6. 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 (6.21%)	41 (6.0%)	58 (10.1%)	35 (9.0%)

Over the past three years the percentage of XDR-TB has remained steady at around 10% of all MDR-TB cases (Tables 7, 9.1 and 9.2). However, the number of XDR-TB cases seems to be underdiagnosed due to the fact that not every diagnosed case with any resistance to Rifampicin is being tested with 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 110 patients with XDR-TB, whose treatment requires therapy with new TB drugs.

Table 7. Registered XDR-TB cases in civilian and prison sectors, 2011-2013 (9 months)

Type	2011	2012	2013 (9 months)
Pre XDR-TB	61	64	34

(INJECTABLE)			
Pre XDR-TB (FQ)	1	9	8
XDR-TB	34	30	20

Previous shortages of SLD – especially injectable agents and adequate supplies of FQ – had already led to the creation of a reservoir of XDR-TB, especially at county level TB facilities. Currently, access to MDR-TB therapy has significantly improved with increased availability of SLD from government funding and two external grants (GFATM and Norwegian grant (NG)). The appropriate use of this funding guarantees access to quality assured SLD for more than 1,000 patients in the coming two years (see below) and 150 FQ-R patients will get access to new TB drugs (80+70 patients). The NTP hoped that there would be the possibility of additional funding for new TB drugs available from government sources in future. Thus, both GFATM and NG served as catalysers for increasing access to new TB drugs. Note: both applications to external donor funding had been developed back in 2013. Thus, they do not include Delamanid and have only a limited number of patients (150) that can be enrolled to new therapies over 3 years.

Table 9.1. MDR-TB patients in specific counties by type, civilian sector, 2015.

County	Abs. number of cases MDR, 2015	New	Relapse	Failure	After default	Chronic
A	***1***	***2***	***3***	***4***	***5***	***6***
TOTAL	**490**	**128**	**123**	**59**	**64**	**116**
Alba	6	2	2	2	0	0
Arad	2	0	1	0	0	1
Argeș	11	4	3	0	1	3
Bacău	16	4	3	0	4	5
Bihor	8	1	2	1	0	4
Bistrița-Năsăud	2	1	1	0	0	0
Botoșani	9	4	2	2	1	0
Brașov	7	3	3	0	0	1
Brăila	5	1	1	1	0	2
Buzău	0	0	0	0	0	0
Caraș-Severin	7	1	1	0	5	0
Călărași	13	2	2	0	2	7
Cluj	13	5	3	2	1	2
Constanța	17	6	3	3	0	5
Covasna	1	0	1	0	0	0
Dâmbovița	20	5	4	4	4	3
Dolj	30	3	10	3	5	9
Galați	8	0	1	0	2	5
Giurgiu	4	2	2	0	0	0
Gorj	6	0	2	1	1	2
Harghita	0	0	0	0	0	0

Hunedoara	17	3	2	2	4	6
Ialomița	13	3	2	6	0	2
Iași	22	9	3	0	2	8
Ilfov	5	0	3	0	0	2
Maramureș	13	3	3	3	3	1
Mehedinți	9	1	1	2	4	1
Mureș	12	3	5	1	1	2
Neamț	18	4	4	1	2	7
Olt	17	5	5	3	4	0
Prahova	19	4	7	1	2	5
Satu Mare	16	4	5	3	2	2
Sălaj	0	0	0	0	0	0
Sibiu	26	7	8	6	1	4
Suceava	5	0	3	0	0	2
Teleorman	5	2	1	0	0	2
Timiș	20	3	6	4	1	6
Tulcea	5	1	0	3	0	1
Vaslui	11	5	1	1	4	0
Vâlcea	10	1	2	2	1	4
Vrancea	5	0	2	1	0	2
București	57	26	12	2	7	10

Table 9.2. XDR-TB patients in specific counties by type, civilian sector, 2015.

County	Abs. number of cases MDR, 2015	New	Relapse	Failure	After default	Chronic
A	***1***	***2***	***3***	***4***	***5***	***6***
TOTAL	**58**	**9**	**3**	**10**	**5**	**31**
Alba	1	1	0	0	0	0
Arad	0	0	0	0	0	0
Argeș	1	1	0	0	0	0
Bacău	1	0	0	0	0	1
Bihor	1	0	0	0	0	1
Bistrița-Năsăud	0	0	0	0	0	0
Botoșani	2	1	0	1	0	0
Brașov	1	0	0	0	0	1
Brăila	0	0	0	0	0	0
Buzău	0	0	0	0	0	0
Caraș-Severin	0	0	0	0	0	0
Călărași	1	0	0	0	0	1

Cluj	1	0	0	0	0	1
Constanța	1	0	0	0	0	1
Covasna	0	0	0	0	0	0
Dâmbovița	2	0	0	0	1	1
Dolj	4	1	0	0	1	2
Galați	1	0	0	0	0	1
Giurgiu	1	1	0	0	0	0
Gorj	1	0	0	0	0	1
Harghita	0	0	0	0	0	0
Hunedoara	3	0	0	0	0	3
Ialomița	1	1	0	0	0	0
Iași	5	1	0	0	1	3
Ilfov	1	0	0	0	0	1
Maramureș	0	0	0	0	0	0
Mehedinți	0	0	0	0	0	0
Mureș	1	0	0	0	0	1
Neamț	3	0	0	0	0	3
Olt	3	1	0	1	1	0
Prahova	0	0	0	0	0	0
Satu Mare	2	0	0	1	0	1
Sălaj	0	0	0	0	0	0
Sibiu	2	0	0	2	0	0
Suceava	2	0	1	1	0	0
Teleorman	0	0	0	0	0	0
Timiș	3	0	0	2	0	1
Tulcea	2	0	0	1	0	1
Vaslui	0	0	0	0	0	0
Vâlcea	0	0	0	0	0	0
Vrancea	2	0	0	0	0	2
București	9	1	2	1	1	4

Treatment outcomes of GLC cohorts enrolled to the MDR-TB treatment programme in Rounds 2 and 6 of GFATM funding shows comparatively good programme performance with the total number of patients enrolled from 2004-2011 of total of 884 patients (percentage for final treatment outcomes given for Cohorts 1, 2 and 3 in Table 10). Table 10 also shows ongoing enrolment of patients with two external funding sources – GFATM NFM and the Norwegian Fund.

Table 10. Enrolment and treatment outcomes of GLC approved cohorts, 2004-present

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)	381	0	260	37 (9.7%)	44 (11.5%)	3 (0.8%)	37 (9.7%)

			(68.2%)				
Cohort 5 (GFATM NFM)	327	109 (33.3%)	162 (49.5%)	11 (3.4%)	12 (3.7%)	1 (0.3%)	32 (9.8%)
Cohort 6 (NG)	460	423 (92%)	0 (0%)	6 (1.3%)	1 (0.2%)	11 (2.4%)	19 (4.1%)
TOTAL	**884**	**217**	**406**	**71**	**95**	**9**	**86**

Treatment outcomes for the non-GLC cohorts were extremely poor until significant changes in the drug procurement mechanism were made in 2015, when an almost complete range of SLD became available countrywide. Similar to 2008 and 2009, data from the 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 to the non-GLC cohort (Table 11). The total percentage of unfavourable outcomes for the 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 the 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.

Table 11. Treatment outcomes for non-GLC MDR-TB cohort, 2010, Civilian and Prison sectors

Registration group	Cured	Treatment completed	Died	Failed	Defaulted	Not evaluated [1]	Total
New	30	4	15	46	16	5	116
Relapse	32	3	24	50	24	7	140
After default	6	2	14	26	32	3	83
After failure of Category I and II treatment	18	2	17	29	17	3	86
Other retreatment, or unknown retreatment[2]	17	1	28	80	17	6	149
Total	**103**	**12**	**98**	**231**	**106**	**24**	**574**
Percentage	**17.9%**	**2.1%**	**17.1%**	**40.2%**	**18.5%**	**4.2%**	**100%**

In the years leading up to 2015 the decentralized system of drug procurement and lack of availability of a full range of second-line anti-TB medications for non-GLC MDR-TB patients served as the major contributing factors aggravating the situation with DR-TB and growth of the M/XDR-TB reservoir. Before reforming the drug procurement system, the factors contributing to the growth of the DR-TB reservoir (defaults and failures) outweighed those influencing its decrease

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

(cured + treatment completed + died + transferred out). The growth of the DR-TB reservoir was also exacerbated by delays in diagnosis of DR-TB, prolonged hospitalization and poor infection control at inpatient facilities. 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 the availability of adequate financing from international donor sources, the Romanian NTP will be able to achieve a rapid decline in main TB indices – including DR-TB – over the next few years.

7. Coordination of the programme and financing

Findings and summary of discussion:

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

The NTP Central Unit team had a clear mandate from the MOH to act as the actual National Tuberculosis Programme Unit. This was enforced by the capacity to perform coordination of activities, monitoring and supervision, planning and analysis and capacity building required for successful implementation of TB and DR-TB control. The NTP Central Unit comprises a group of specialists, each responsible for a specific aspect of TB control. Since the most recent visit the NTP manager has changed, which did not negatively affect the programme at all. Dr. Gilda Popescu, who succeeded in managing the National TB Programme for the past four years, became the manager of Marius Nasta Pneumology Institute with Dr. Victor Spinu, the leading MDR-TB expert in Romania, succeeding her as National TB Programme manager. As a part of the Norwegian Fund grant, the NTP Units at county level were empowered with MDR-TB Coordinators who were themselves regional specialists; they were made responsible for coordination of activities on PMDT in each respective county.

In 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 the WHO, and other government and non-governmental organizations. The NSP outlines the national strategies to respond to unmet needs and build sustainability of the system, as well as presents the long-term vision and identifies innovative approaches targeted on achieving a dramatic decline in TB incidence and mortality in Romania by 2020. The document presents the goals and objectives for diagnosis, treatment and prevention of TB in the country. There were 8 strategic objectives in the NSP, including ensuring universal access to rapid diagnostic methods for TB and DR-TB, coverage with appropriate therapy for all diagnosed TB and DR-TB cases, and achieving high treatment success rates for both TB and DR-TB, which have the intention of achieving a sharp decline in TB incidence and mortality. To ensure these actions were effective, the NSP for 2015-2020 was based on three pillars and follow 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 previously endorsed National M/XDR-TB Response Plan for 2012-2015, with its six areas of intervention and

detailed budget, developed with the technical assistance from WHO-Europe, was successfully endorsed in October 2012, but its implementation was delayed due to financial constraints. However, the National M/XDR-TB Response Plan has been successfully incorporated into NSP for 2016-2020 and was an integral part for implementation across the country. The budget of the NSP for 2015-2020 was consolidated, and includes funding from the Government of Romania, the Norwegian grant, the GFATM, the European Structure Fund, the World Bank and other organisations (279,029,902.7 Euros). With the majority of funding coming from the Government of Romania, the NSP acts as a very important step towards building the sustainability of the National Tuberculosis Programme of Romania.

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

In 2015 Romania received an approval from GFATM to implement an 8.4 million Euro grant to address the gaps and challenges in TB control in the country for the period from 04/2015 – 03/2018. The goal of the grant was to contribute to a reduction in TB incidence and mortality in Romania through high impact interventions (in the fields of diagnosis, treatment, care and prevention) with a special focus on key affected populations through the following objectives:

- Early and quality-assured TB diagnosis by strengthening 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 drug regimens and non-interrupted treatment;
- Strengthening the national legal framework to regulate TB control in Romania.

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

Under the new GFATM grant the Romanian NTP was planning to ensure access to quality-assured SLD including access to new TB drugs, for 460 M/XDR-TB patients using the GDF mechanism. The plan was also to procure 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 the country's obligations and reach the indicators of both grants. In addition, the RAA will provide continuous assistance to the NTP Central Unit on implementing grant objectives and improve programme performance at all levels. A more detailed description of activities of the new GFATM grant is presented below in relevant chapters of the current report ("Treatment strategies and administration, Laboratory, Infection Control, Drug Management).

In 2014 the Romanian NTP received approval from the Norwegian government for 10.7 million Euros for 20 months (August 2014 – April 2016), which was successfully extended until March 2017. The grant 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 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 to 1,000 patients with M/XDR-TB, including access to new TB drugs, and provide social support for them. It will also be possible to significantly improve laboratory capacity and increase access to rapid molecular diagnosis of TB and DR-TB, create a functional network of 8 regional reference laboratories, and to invest in procurement of equipment to decrease the risk of nosocomial transmission of infection. A more detailed description of activities of the grant is presented below in relevant chapters of current report (Laboratory, Infection Control).

In 2015 the National TB Programme received funding from the United States Embassy in Romania to renovate and reconstruct the ventilation system in the MDR-TB ward at MNI, which was in place by the time of the visit. Funding was conditional with on the MOH guaranteeing to meet the maintenance and utility costs for running the ventilation system, as well as replacement of HEPA filters. Also, the US Embassy agreed to support training on Infection Control by specialists from the US Department of Defence; some financial support will also be allocated for diagnosis of drug resistance.

There is evidence of a good level of collaboration with WHO-Europe, who initiated joint 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 a public health priority. The Government of Romania should support the implementation of the National Strategic Plan for TB Control for 2015-2020. Sufficient and sustainable funding should be ensured to sustain National TB Programme implementation. Aspects requiring particular support are: access to adequate treatment regimens and uninterrupted supply of TB drugs, including new TB drugs; ambulatory treatment and social support of patients; diagnosis; and infection control.	MOH
2	Support implementation of the new GFATM and Norwegian grants. MNI Pulmonology Institute (NTP) should play a leading role in the management and implementation of this and upcoming grants (European Structure Fund - POCU).	MOH

8. Treatment strategies and administration

Findings and summary of discussion:

The infrastructure of TB Services in Romania is well developed and has a wide network of TB Dispensaries (174), 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. The Marius Nasta Pneumology Institute in Bucharest was the leading institution in the country on TB Control and served as headquarters for the NTP Central Unit and was one of two MDR-TB Centers in Romania. The number of TB dispensaries and TB hospitals varies from county to county. Annual bed occupancy was around 80%, with the majority of TB and MDR-TB patients being hospitalized at least for the start of treatment. Hospital stay has been regulated by the MOH

and monitored by the NIH with a certain number of bed days for drug-susceptible and drug-resistant tuberculosis. With regulated by the duration of hospital stay for TB and DR-TB, patients had been referred for treatment continuation to ambulatory sector, mostly performed by TB dispensaries and Primary Healthcare facilities.

Treatment of drug-sensitive TB is performed according to the WHO recommendations. New cases start treatment with a 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 show good results with success among new smear/culture positive cases of 84% of treatment effectiveness in the 2013 cohort and 84.5% in the 2014 cohort, and 66.1% in 2013 and 2014 cohorts respectively as reported by the NTP (Table 12). Data officially reported to the WHO show a treatment success of new and relapse cases registered in 2013 of 85% and a treatment success rate of 45% for previously treated cases excluding relapses in the same year (Annex 2). Coverage with DST to FLD and SLD improved compared to the previous year due to increased availability and access to rapid molecular diagnosis of TB and DR-TB (Xpert MTB/RIF and LPA) – see the section 9 (TB Laboratory) for more details. The National approach to the management of patients with drug-susceptible TB has been updated in accordance with the WHO Treatment of Tuberculosis Guidelines 4th edition of 2009 as was recommended during previous missions. The Category III regimen was phased out from the treatment protocol, but optimal daily dosing throughout the course of therapy for new patients with pulmonary TB is not yet happening.

Table 12. Treatment outcomes of regular TB, Romania, 2013 and 2014, *without Rifampicin resistant cases.* Civilian sector.

2013		**Treatment completed**	**Cured**	**Death**	**Lost to follow up**	**Failure**	**No TB**	**Not evaluated**	**Total**
New	SS+	894	4,261	470	291	169		1 (ST*)	**6,086**
	SS-	2,365	1,320	250	198	15		0	**4,148**
	SS (Unk)	60	0	42	9	0		0	**111**
	EP	2086	0	107	88	9		0	**2290**
	Total new	**5,405**	**5,581**	**869**	**586**	**193**		**1**	**12,635**
Retreatment	Relapse SS+	271	904	170	176	110		1 (ST)	**1,632**
	Relapse SS-	311	259	70	67	9		0	**716**
	Default SS+	60	122	42	150	27		0	**401**
	Default SS-	36	12	10	45	0		0	**103**
	Failure	57	117	56	58	100		0	**388**
	Other (SS: Unk Rel+Def)	7	0	13	3	0		0	14+9+ = **23**
	EP	105	0	8	12	3		0	**128**
2014		**Treatment completed**	**Cured**	**Death**	**Lost to follow up**	**Failure**	**No TB**	**Not evaluated**	**Total**
New	SS+	805	4170	435	281	157		26+14(ST)	**5,888**
	SS-	2,282	1,338	270	186	22		17+10(ST)	**4125**
	SS (Unk)	47	0	48	6	1		1	**103**
	EP	1976	0	93	81	5		15+28(ST)	**2,198**
	Total new	**5,110**	**5,508**	**846**	**554**	**185**		**111**	**12,314**
Re	Relapse	217	835	141	137	92		6+10(ST)	**1,438**

	SS+Pulm								
	Relapse SS-Pulm	284	216	71	66	8		6+3(ST)	**654**
	Default SS+ Pulm	35	119	37	122	27		2+2(ST)	**344**
	Default SS-Pulm	28	14	9	39	1		0+1(ST)	**92**
	Failure Pulm	37	95	31	33	99		1+6(ST)	**302**
	Other (Pulm.R+Def SS:Unk)	0	5	12	1	0		0	**18**
	EP	100	0	7	6	0		0+1(ST)	**114**
	Total R	701	1,284	308	404	227		38	**2,962**

Management of patients with MDR-TB is performed in accordance with the National Methodological Guidelines on TB, which included PMDT and served as National protocol for TB and DR-TB – this was approved by the MOH in 2016 and published. The National Protocol is in alignment with the WHO 2011 Guidelines but had to be updated with the recent release of 2016 WHO Guidelines on PMDT, especially on the part on new grouping of drugs and approaches to regimen design. The national protocol included necessary diagnostic algorithms, protocols on side effect management, and required registration and treatment forms. At the time of the visit the national implementation plan on the introduction and use of new TB drugs was under development. This will include all recent recommendations on medical management of DR-TB with new TB drugs and is intended to serve as a guide for the use of new treatments for DR-TB.

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 DR-TB Committee covers 50% of the country and serve 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 ensure equal access to MDR-TB treatment regardless to the source of SLD. Compared to the previous mission, treatment of MDR-TB can be initiated at county level once Rifampicin resistance is confirmed, with further confirmation of regimen by National DR-TB Committee. Coverage with DST to FLD is performed according to the DR-TB diagnostic algorithm, but its introduction requires improvement. There is increased access to DST to SLD compared to previous missions by rGLC, especially with funding from GFATM and Norwegian Fund.

At the time of the mission, criteria for the duration of the intensive phase and of the whole course of chemotherapy match the WHO recommendations of 2011 with a minimum duration of the intensive phase being 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 exceeds 20 months. Criteria for stopping the injectable agent were based on strong evidence of culture conversion – up to 4 consecutive negative cultures – and clinical response to treatment. There were no limitations for prolonging the use of an injectable agent (Group B) or the whole duration of treatment.

At the time of the visit, standardized MDR-TB regimens are based on DST results and included at least four second-line drugs assumed to be effective: an injectable agent (Aminoglycoside or Cm), fluoroquinolone (Lfx), Pto, Cs/PAS and Z with maximum dosages according to the patient's weight and tolerance. Frequency of treatment was 7 days per week in inpatient and 5-6 days per week in

outpatient settings regardless of the phase of treatment. Ethambutol was used only if it is susceptible by DST results. Pyrazinamide was used for the whole duration of therapy. Minimum duration of the use of an injectable agent was 8 months for MDR-TB and 12 months for XDR-TB. In MDR-TB regimens of non-GLC cohort patients the regimen contained Am-Ofx/Mfx-Pto-Cs-Z-E, which was prescribed to the majority of patients in counties until arrival of conventional DST results. For patients starting therapy within GFATM or NG the spectrum of drugs was wider: Km, Lfx, Pto, Cs, PAS, Lzd, Cfz and Bdq. Taking into account the availability of the complete range of second-line drugs in both grants, the majority of patients in 2016 and 2017 will initiate therapy through external donor funding. Kanamycin was the injectable of first choice for susceptible TB (in the GLC cohort), as it is believed to be more potent than Cm. Levofloxacin served as the fluoroquinolone of choice for all MDR-TB patients in maximum dosages (750 mg <=70 kg, 1,000 => 71 kg) in GLC cohorts. Moxifloxacin is used when DST shows resistance to Fq. In certain circumstances Mfx was used for strengthening the regimen e.g. in patients with diabetes mellitus, HIV co-infection and massive pulmonary damage among others. PAS was not routinely added to the MDR-TB regimen, but as an additional drug in pre-XDR and XDR-TB regimens. Group 4 agents were present in the majority of MDR-TB regimens. Ethionamide was included based on strong evidence of susceptibility on DST.

Taking into account the recent release of the new version of WHO Guidelines on PMDT, it is recommended to the NTP to consider including new grouping of TB drugs as a tool to design of MDR-TB regimens in the National guidelines on DR-TB. Thus, according to new WHO guidelines “In patients with rifampicin-resistant or multidrug-resistant TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core SLD – one chosen from group A, one from group B, and at least two from group C. If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total of five”.

Approaches to the management of XDR-TB were similar to the MDR-TB with regimens based on DST pattern and history of previous treatment. At the time of the visit, XDR-TB regimens include longer use of injectable agents, a later generation fluoroquinolone (Mfx), and the rest of the SLD thought to be effective: Z and Group 5 drugs (old grouping of drugs by the WHO). The NTP started using Group 5 drugs under the compassionate use programme. Starting in 2016 the Romanian NTP introduced the use of new TB drugs under programmatic conditions. By the time of the visit Romania received 70 treatments with Bedaquiline, Linezolid and Clofazimine. Delamanid was not available in Romania at the time of the visit, but should be considered by the NTP for future drug orders with any external funding possible. Possible indications for the use of Group D2 drugs (Bedaquiline and Delamanid) has been discussed with the NTP:

1. Patients for whom the construction of a regimen with four likely effective second-line drugs (from Groups 2 to 4) including a fluoroquinolone and an injectable is not possible:
    a. XDR-TB (resistance to a fluoroquinolone and at least one injectable).
    b. Pre-XDR-TB (resistance to a fluoroquinolone or to at least one second-line injectable, but not both).
    c. Patients with two or more Group 4 drugs (by old WHO grouping) (Eto/Pto, Cs, PAS) compromised.
    d. Contact with a patient with a strain with resistance pattern a, b, or c.
    e. Patients unable to tolerate MDR-TB drugs necessary for construction of the regimen (for example, ototoxicity due to an injectable agent).
    f. Patients who are classed as a "failure" of an MDR-TB regimen by WHO 2013 definitions.
2. Other patients who have high risk of unfavorable outcome but do not fit one of the above categories:

a. Patients with extensive or advanced disease (X-ray demonstrating multiple cavities, bilateral lesions, or extensive parenchymal damage or multiple system involvement).
b. Patients with increased likelihood of acquisition of additional resistance, treatment failure, or death due to co-morbidities or other conditions (drug contraindication, patients with low body mass index (BMI), HIV, diabetes).
c. Patients coming from catchment areas that have poor MDR-TB treatment outcomes despite good programmatic conditions (e.g. sites with extensive background second-line drug resistance).

Treatment regimens for mono and poly-resistant TB had not been included in the updated version of the National Guidelines of Romania but are scheduled to be updated in line with Chapter 6 of the WHO Compendium to the guidelines to PMDT (2015), taking into account the recent release of the WHO Guidelines to PMDT (2016).

Romania received funding from the GFATM for NFM for a total of 8.4 million Euros for three years starting April 2015 and ending December 2017. Within the GFATM grant 460 M/XDR-TB patients will get access to quality-assured SLD through the GDF mechanism, including 80 patients to access new TB drugs (mostly Bedaquiline containing regimens). With funding from the Norwegian government of a total of 10.7 million Euros, the Romanian NTP was planning to enrol up to 1,000 patients with M/XDR-TB over a 20-month period (November 2014 – April 2016) but the enrolment was extended for another 12 months until March 2017. It seemed ambitious, but possible, considering the number of patients who require access to adequate therapy with quality-assured drugs. Within the Norwegian grant the NTP was planning to ensure access to new TB drugs for 70 patients (bedaquiline containing regimen), while before 2016 the new TB drugs were available under the Compassionate Use (CU) Programme only. At the time of the visit 7 patients had already received bedaquiline and other companion drugs under CU Programme, 6 of whom were considered to be cured and 1 patient was still on therapy; all regimens contained bedaquiline (6 months), linezolid (whole duration of therapy) and clofazimine (whole duration of therapy) and all 7 patients achieved culture conversion in the early months of therapy.

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. With external donor funding Romania has started using new TB drugs under programmatic conditions. 70 courses of Bedaquiline have already been procured, as well as by Linezolid and Clofazimine to form the backbone of treatment regimens. It was agreed that these three drugs would be used for patients with confirmed resistance to FQ (pre-XDR and XDR-TB). However, the country also HAS to consider access to Delamanid within existing donor funding as it BECOMES available through the international mechanisms. It also has to extend indications for the use of new TB drugs for other patients once there is more funding available for therapy under programmatic conditions (see the indications above). At the time of the visit 18 patients have been receiving therapy with a bedaquiline-containing regimen: 10 under GFATM grant and 8 under the NG. Treatment with new TB drugs was initiated in one of two MDR-TB centers – the DR-TB ward in Bisericani and the Marius Nasta Institute in Bucharest. Access to the new TB drugs in Romania has significantly improved. However, there were cases noted when patients were refusing to be hospitalized to one of the MDR-TB centers for initiation of therapy – various reasons, mainly social, were noted.

Even if Bedaquiline was registered in the country it was still yet not included in the Essential Drug List of Medicines (EDL or C2 list) to be purchased with government funding. Similar to Delamanid being registered by the European Medicine Association for the use in countries of the European Union, it should be considered for inclusion in the EDL/C2 list along with Linezolid and Clofazimine, for use in treatment of M/XDR-TB, as per the latest WHO guidelines (2016).

The NTP was finalizing the development of the Implementation Plan for the introduction of new TB drugs in Romania, which is supposed to serve as a programmatic and clinical guide and complement the national guidelines on PMDT. The document is to be finalized and released late in the summer of 2016. During the last mission it was discussed with the MOH that there is a need to create a multi-sectorial National TB Coordination Committee as a National Task Force 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 improve management of M/XDR-TB. The recommendation on setting up the Technical Working Group on technical aspects of MDR-TB management, especially related to the introduction of new TB drugs, was completed with five experts, including the NTP manager, as members of the committee. It is planned that the MOH will release the decree regulating the National TB Coordinating Committee – status was pending at the time of the visit.

Requirements for clinical monitoring of a DR-TB patient's condition were clear and included sputum smear microscopy and culture at the start of treatment and repeated on a monthly basis during the intensive and continuation phases. The time of smear and culture conversion was not monitored, but was strongly recommended to evaluate the effectiveness of the intensive phase of treatment. Clinical examinations included general blood and urine tests, biochemical analysis (bilirubin, LFT, urea, uric acid, electrolytes, creatinine, glucose). Chest radiography examinations were available at MDR-TB Centres and TB hospitals and were performed as a monitoring tool at the start of the treatment and then on a quarterly basis. Specialist doctors are available mostly when patients are hospitalized and include psychiatrists, ENT surgeons, ophthalmologists, dentists, and internists, especially at MDR-TB Centres. However, the range of specialists varied from county to county. Surgical management was available mostly at major treatment facilities, with prevailing resection type of surgeries not palliative methods. Options for palliative treatments were limited as in the majority of countries in the WHO European Region due to absence of practice and facilities to provide patient management. However, as described in the report the NTP was planning to set up a palliative care ward in one of the regional MDR-TB Centers in Laemna, Dolj county. Pharmacovigilance existed as a State requirement, but is spontaneous. Thus, it was recommended to introduce the key elements of active drug safety monitoring and management (aDSM) according to the latest WHO policy, especially while scaling up access to the new TB drugs.

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. The system of pharmacovigilance was in place as a part of daily general practice. However, recording of adverse reactions was made in government approved yellow forms only upon temporary/permanent withdrawal of a medicine from the regimen. Any adverse reaction on therapy, including TB care, is encouraged by the government point system, used for future accreditation of physicians. However, the system of pharmacovigilance was monitored by the MOH by causality assessment, thus decreasing the chances of false reporting. Other forms allowing registration of adverse reactions were not available. It was not possible to identify the frequency of adverse events at DR-TB center in Marius Nasta Institute. Doctors were noticing GI side effects, arthralgia and depression as the most common adverse reactions. At the same time, a lot of complains were related to pain after use of amikacin, thus a number of patients were refusing the injectable agent, which increases the risk of an unfavourable outcome. At county level there was still the common practice of withdrawing the agent(s) thought to be the cause of adverse reaction drug rather than keeping it/them in the regimen and and using ancillary medication to minimise side effects. However, it was noticed that almost every change in DR-TB regimen was confirmed with central DR-TB committees (MNI or Bisericani). At MDR-TB Centers, the majority of patients were receiving Pyridoxine (Vitamin B6) to decrease the risks of peripheral neuropathy. These

approaches of active drug safety monitoring and management are especially essential when the NTP is expanding access to new TB drugs.

During the inpatient phase SLD are taken 7 days a week, once or twice daily. Dosages were prescribed according to patient's weight and tolerance but required to be regulated in the annex to the updated version of the National Guidelines on PMDT. In ambulatory settings visited DR-TB patients were taking drugs 5 days a week at the healthcare facility with the Saturday dose self-administered. Some outpatient facilities at PHC level were providing patients with a one-to-two week supply of drugs for self-administration, which was increasing the risks of developing unfavourable treatment outcomes and contributing to prolonged or ongoing infectiousness of patients. It was discussed with the NTP that there is a desperate need to ensure 100% DOT using various methods, especially when the treatment regimen contains drugs prescribed daily, like delamanid, clofazimine and linezolid, as well as bedaquiline during the first two weeks of therapy.

Excessive infrastructure (93 TB hospitals, sanatoriums and TB units) with a capacity of 5,625 TB beds has made inpatient treatment available all around the country. As noted earlier, once evidence of strong clinical and bacteriological response to therapy was achieved, patients with DR-TB had been discharged from DR-TB centers and referred for treatment continuation by TB dispensaries. However, the NTP noticed that there was a tendency for treatment initiation at regional level facilities with later confirmation of the regimen by the DR-TB committee (described above). Duration of hospitalization for MDR-TB patients was still regulated by the NIH and was, on average, around 3 months countrywide, including in the MDR-TB Centers in Bucharest and Bisericani. Usually patients were discharged from MDR-TB Centers during the intensive phase once the first negative culture result arrived. The existing financing of TB hospitals based on bed occupancy incentivises TB hospitals to keep patients as inpatients (see part on Infection Control).

Options for DOT during ambulatory treatment were still limited with patients coming actively for treatment to TB dispensaries and PHC clinics. The PHC level clinics and TB dispensaries were offering DOT on weekdays with Saturday treatment mostly self-administered. With treatment during the continuation phase delegated to PHC, family doctors were not motivated or interested in providing strict DOT for TB and DR-TB patients because of the absence of financial incentives from the MOH. Possibilities for a patient-centered approach and the use of hospital replacement mechanisms, like home-based treatment, were still very limited due to insufficient capacity and management. Vehicles were available at the majority of TB dispensaries but had restrictions on financing of gasoline (100 l/month). Home patronage nurses were not available and those nurses from PHC Services were also not motivated to perform daily DOT due to lack of financial incentives and absence of transportation or its reimbursement. Social support was also lacking and restricted to salary disability allowance for those patients employed prior to the start of treatment. In the case of unemployment or homelessness, no social support or transportation reimbursement were available from government sources. Another option considered by TB doctors was delegating responsibilities for DOT to family members whom they trust, which assumed the quality was not guaranteed.

However, with the arrival of new funding from the GFATM and Norwegian Fund it became possible to strengthen ambulatory care. One of the main objectives of the Norwegian Fund grant was to develop an integrated model of support at community level for TB treatment and prevention among poor and vulnerable groups. Thus, 1,000 TB and M/XDR-TB patients from poor communities, including the Roma population, will receive DOT and social support during the outpatient stage of therapy. Community health providers (health mediators and community nurses) will offer this service. Also, within the GFATM NFM grant it was planned to train a group of 240 community health workers who would perform daily DOT for DR-TB patients. In addition, the grant will focus on training health mediators and community nurses from 50 poor rural

communities in TB education and DOT. The new GFATM grant has a whole section focused on provision of patient education with regards to treatment and adherence to therapy (social and psychological support).

In summary, the recently approved NSP for 2015-2020 has reform of ambulatory care as one of its major components with the overall goal to reduce unnecessary hospitalization. The reform will start under the new GFATM grant in 6 pilot counties with a high burden of TB and DR-TB with the aim of disseminating experience in these regions countrywide. Activities will include the establishment of multidisciplinary teams who will provide medical, social and psychological care for patients, including patient education on treatment and adherence. In addition, members of multidisciplinary groups will be responsible for assessing the risk of treatment defaulting for every DR-TB patient starting therapy with SLD. The new GFATM grant will mostly focus on developing the national policy documents aimed at strengthening outpatient treatment of TB and reducing unnecessary hospitalization. The grant will allow review of the existing laws and reimbursement practices that contribute to hospitalization and facilitate research into models of ambulatory care; it will also help to develop protocols and guidelines for outpatient and inpatient treatment, including criteria for hospitalization and outpatient care. It is planned to create two centers for treatment and care of socially disadvantaged TB/M/XDR-TB patients during their course of treatment.

Recommendations:

	Recommendation	**Responsibility**
1	Consider introducing an update of the National Guidelines for Program Management of Drug-resistant Tuberculosis (PMDT) in alignment with the recently released recommendations by the WHO on PMDT especially on new grouping of TB drugs and regimen design for M/XDR-TB.	NTP
2	indications for the use of new TB drugs in accordance with the new grouping of TB medicines recommended by the WHO (2016).	NTP
3	Ensure distribution of the updated version of the National Guidelines on PMDT and training of all healthcare providers involved in management of patients with M/XDR-TB.	NTP
4	Consider endorsement of the multi-sectorial National TB Coordination Committee as a National Task Force mechanism to oversee the preparation, planning, implementation and evaluation of new TB drugs (Bedaquiline, Delamanid and other TB drugs recommended for therapy of M/XDR-TB).	MOH
5	Consider endorsement of the National Implementation Plan for Introduction of new TB drugs for the management of M/XDR-TB.	MOH
6	Introduce and implement main aspects of active drug safety and monitoring (aDSM) as a part of scaling up access to new TB drugs. Ensure implementation of the minimum requirements for laboratory diagnosis in outpatient settings. If this is not done, it may affect adherence to therapy and lead to development of serious adverse events.	NTP
7	Ensure introduction and strict implementation of diagnostic algorithms on drug-susceptibility testing, as part of updated National Guidelines on PMDT adhering to the following principles (continued recommendation): • DST to FLD (at least to H and R) should be performed for all SS+	NTP

	and CC+ patients regardless of patient type. • DST to SLD should be performed in all cases diagnosed with H and R resistance, or R resistance alone. • Repeat DST on second-line anti-TB drugs for MDR-TB patients who remain smear/culture positive after 3-4 months of treatment or who become smear/culture positive after conversion at a later stage of treatment.	
8	Consider collaborating with SNRL on DST to new TB drugs. Consider either storing samples of positive cultures from baseline until culture conversion for patients on therapy with new TB drugs in laboratory refrigerators or send the sample to SNRL for DST. This will facilitate understanding of the trends of amplification of drug resistance.	NTP
9	Once diagnosed Gx+/RIF+ the standardized MDR-TB regimen should be initiated with a minimum of 5 effective drugs from groups A, B, C and D1 followed by conventional DST to H and other FLD using rapid molecular diagnostic tests (LPA) and/or MGIT.	NTP
10	In patients with rifampicin-resistant or multidrug-resistant TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core SLD – one chosen from group A, one from group B, and at least two from group C. If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total of five.	NTP
11	Ensure daily directly observed therapy of patients, in particular for those who receive therapy with new TB drugs, especially delamanid, linezolid, clofazimine and carbapenems.	NTP
12	Consider revising the National policy on the management of DS-TB to align it with the WHO Treatment of Tuberculosis Guidelines (4th edition, 2009): • 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.	NTP

9. TB Laboratory

Findings and summary of discussion:

The current rGLC mission was conducted in conjunction with the Laboratory mission by the WHO-Europe consultant. Thus, for more details on laboratory issues please refer to the Laboratory mission report. The laboratory network has undergone strengthening and reorganization over the past few years, and consists of 170 laboratories across Romania. There are 14 level I laboratories for sputum smear microscopy only, 40 level II laboratories performing sputum smear microscopy and culture, 43 level III laboratories performing sputum smear microscopy, culture and DST to FLD (short-line DST to Isoniazid and Rifampicin) and 2 National reference laboratories performing DST to FLD and SLD (MNI in Bucharest and Cluj Napoca).

Structurally, the laboratory network remains unchanged compared to the previous year, but there are plans to establish a functional network to improve access to rapid molecular diagnosis of drug resistance with financial support from the GFATM and the Norwegian government. The reorganization was considered 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. The NTP made huge steps forward performing a huge step forward in establishing a functional laboratory network with the purpose of improving access to rapid molecular diagnosis of TB and drug resistance. Strengthening of the laboratory network became possible due to strong political support from the MOH and funding available from GFATM and NG grants. It was expected that the reorganization would result in creating a network of 2 national and 6 regional reference laboratories, which will serve as reference centers in eight main geographical regions in order to improve access to rapid diagnosis of resistance to rifampicin and second-line drugs (IQE) for all counties. Selection of RRLs had been done based on disease burden, geographical proximity to other counties and capacity (equipment, infection control measures and trained personnel). Within both grants the NTP has committed to ensure the transportation of samples from counties to RRLs and supervision and monitoring of laboratory performance (within Norwegian Grant 9 vehicles have been procured). Even though the size of the M/XDR-TB reservoir is not yet completely known, based on WHO estimates the ongoing reorganization of the laboratory network and capacity improvements to increase access to rapid molecular diagnosis of drug-resistant TB will significantly improve the knowledge of the actual disease burden and provide better programme implementation.

Coordination of activities at National level has been performed by the Laboratory Working Group, which is nominated annually by the MOH, and has the option of performing regular monitoring visits to county level laboratories at least once per year. The NTP Laboratory Coordinator is based in the NRL in Cluj Napoca. With two grants and reorganization of the laboratory network, supervisory visits started being performed on a regular basis to ensure adequate performance and to conduct quality control. However, the MOH should consider supporting laboratory performance and adequate functioning of network beyond the withdrawal of external donor funding.

While the majority of level III laboratories in counties still perform short-line DST to FLD using solid media, the already ongoing reorganization of laboratory infrastructure had significantly increased access to rapid molecular diagnosis of TB and drug resistance, and as a result timely initiation of therapy. Still, the majority of county-level laboratories perform DST on solid media, which significantly affects treatment outcomes and contribute to nosocomial transmission of infection. With adequate financing coming from external funding, the Romanian NTP had 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 using LPA equipment and 34,100 tests using Xpert MTB/RIF until 2018. Geographically, all regions of Romania – including those with a high burden of TB and DR-TB – are supposed to have access to a full range of diagnosis of TB and DR-TB, including DST to SLD by the end of 2016. The NTP plans to perform centralized training for all laboratory personnel on rapid molecular diagnosis of drug resistance and use of liquid media testing. Both grants had solid investments in improving laboratory biosafety. Thus, 42 biosafety cabinets became available within from the NG to ensure laboratory biosecurity and meet the international requirements for biosafety.

Gene Xpert

Access to Xpert MTB/RIF became available in 2014 across the country; both were purchased with donor funding and leased from Cepheid with the obligation to perform no less than 100 tests/month (Bacau and Calarasi). Originally, 14 Xpert MTB/RIF four-module machines were to be purchased in 2015 with funding available from GFATM (6 machines to perform 5,500 tests, which were already used) and the Norwegian grant (8 machines to perform 28,600 tests). Xpert modules were planned for installment in counties with a high burden of DR-TB and HIV, as well as NRLs. Within the Norwegian grant 8 machines had been already purchased and installed in Cluj, Iasi, Constanta, Dolj, Timisoara, Brasov, Arges and Maramures counties. Two four-module machines

were already available at the NRL in Bucharest and one in Bisericani (Neamt county). No shortages in cartridges were found across the country (e.g. expiry date of 2017-07-02). The NTP will place the last order for the last set of Xpert cartridges in December 2016. In April 2016 the Government approved the budget for procurement of TB consumables, which will require the MOH to release a Decree on centralized procurement and allow purchase of Xpert cartridges according to the request prepared by the NTP laboratory coordinator (minimum of 20,000 and maximum of 45,000 cartridges per year). The new diagnostic algorithm was developed with the help of SNRL and included in an updated version of the National Guidelines on PMDT and the National Laboratory Guidelines.

LPA

The NTP was scaling up access to rapid diagnosis of drug resistance to FLD and SLD using the Line Probe Assay (LPA) with external donor funding. Two automatic Genotype machines were procured within the NG and two within GFATM grant. LPA machines had been already functioning in two NRLs (Bucharest and Bisericani) performing MTBDR*Plus* and MTBDR*sl*, and five in Level III RRLs in Brasov, Constanta, Timisoara, Bacau and Iasi (planned for later in 2016) for MTBDR*Plus* only. Training for laboratory specialists had been conducted with support from ECDC and WHO-Europe in 2014. Also, heads of NRLs were trained at the SNRL in Stockholm and finalized the diagnostic algorithm for LPA. Within the GFATM grant the NTP was planning to perform over 5,000 DST to first-line drugs and 1,000 DST to second-line drugs within a three-year period. Within the Norwegian Grant the NTP was planning to perform 10,000 DSTs to HR at new level III laboratories in Iasi and Constanta to cover the eastern part of Romania. However, the planned 600 DST to second-line drugs (IQE) on LPA were only available at two NRLs (Bucharest and Cluj Napoka) serving as referral centers for the whole country, limiting access to diagnosis of resistance to SLD. Still, DST to SLD coverage with LPA is low and requires significant improvement by both expanding access/geographical proximity to a Level III laboratory in another geographical region of Romania and improving transportation of samples for testing.

Conventional DST to FLD and SLD

Access to conventional DST to other of FLD and SLD on liquid media has improved since the last rGLC mission. Two laboratories recognized as National Reference laboratories in Bucharest at MNI and Cluj-Napoca (north and south) perform quality assurance for the whole country. Two NRLs served as reference laboratories for DST to SLD for 50% of the country each to ensure geographical accessibility, which seemed insufficient taking into account the country's needs for SLDST. BACTEC MGIT-960 systems had been purchased with external funding and installed at 2 NRLs and several RRLs (in March 2016) – Iasi (planned for later 2016), Constanta, Timisoara, Bacau, Craiova, Brasov, Sibiu and Leorden. Automated systems in RRLs were performing only culture testing on liquid media and DST to FLD including Z, but those in NRLs were also performing DST to SLD. DST on MGIT-960 is performed to Cm (2.5), E (5.0), H (0.1), Km (2.5), Mfx (0.5), Ofx (1.0), Z (100), R (1.0), S (1.0) with results available after 3-4 weeks. At the same time, both NRLs and RRLs still perform DST on solid media for the following drugs: H (0.2), R (40), E (2.0), S (4.0), Eto (30), Cm (40), Ofx (2.0), and Km (30) and repeat testing on automated liquid media systems (MGIT or VersaTREK). According to the diagnostic algorithm DST to SLD is performed only in cases with confirmed resistance to R and only upon a physician's request. Usually DST results are reported back to clinicians on the same day. However, delays in treatment initiation with individualized regimens are clear given the poor implementation of the diagnostic algorithm for DST to SLD. Thus, it has been discussed with NTP to initiate a standardized MDR-TB regimen for all cases with diagnosed Rifampicin or HR-resistance until arrival of conventional DST to other FLD and SLD.

Starting in 2015 with funding available from GFATM it became 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 the Norwegian grant, the NTP had funding to support 19,250 liquid culture tests, 10,700 DST to first- and 1,350 DST to second-line drugs. Besides MGIT-960, the NTP received three VersaTREK Systems for liquid DST to first-line drugs (HRESZ) to be installed in Craiova, Constanta, Coloraj or Leorden laboratories besides the NRL in Bucharest, for which this was already in place. The reasons for installation were based on geographical coverage and proximity of the laboratory to other counties and laboratory capacity (space, availability of biosafety cabinets, human resources and workload based on the burden of disease). It is assumed that availability of VersaTrek modules will also improve time for confirmation of culture results (up to 14 days) and DST (up to one week), as well as ensure high sensitivity. According to the diagnostic algorithm, the VersaTREK system was supposed to be used for paediatric cases, HIV-positive cases and for pleural fluid. EQC for DST to FLD and SLD is performed by NRL in Cluj Napoka, and at the time of the rGLC mission had covered only 20 laboratories (out of 44), including regional reference laboratories.

The Swedish Institute for Infectious Disease Control served as SNRL for Romania and provided continuous technical assistance to laboratory services on DST, laboratory infection control, EQA and DRS (2008-2009 and 2014-2015). SNRL provided assistance in methodology and capacity building of laboratory personnel as well as helped with developing the protocol for rapid molecular DST. The DRS took place between 03/2014 – 03/2015 with three laboratories participating: NRLs (Bucharest and Cluj Napoka) and the 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. Selected counties (50 clusters, including 41 counties and 3 from Bucharest) were supposed to submit 35 smear-positive samples from new cases and 35 smear-positive samples from relapses and retreatment cases for the DRS. The survey was planned for completion on March 31, 2015 but the results were not available by the time of the mission. According to the design of the DRS, each H-resistant or R-resistant case would be tested for conventional DST to other 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	Ensure 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.	NTP
2	Increase coverage with DST to second-line drugs (at least an injectable agent and FQ) to all Rifampicin-positive cases across country, especially in high-burden counties using rapid molecular diagnosis testing (LPA) or liquid media systems (MGIT). Consider expanding access to MTBDR*s*/ in other parts of Romania (Iasi).	NTP
3	Improve monitoring of implementation of the diagnostic algorithm at county level to ensure timely use of rapid molecular testing for TB and DR-TB.	NTP
4	Update the national laboratory reporting forms with information on rapid molecular diagnosis (Xpert MTB/RIF, MTBDRPlus, MTBDRPlus-sl). Incorporate the updated forms into National Guidelines on DR-TB and National Laboratory Guidelines (continuous recommendation).	NTP

5	Ensure procurement and maintenance of laboratory biosafety cabinets, which perform culture testing and DST.	NTP

10. TB Infection Control

Findings and summary of discussion:

Improving infection control is one of the priorities of the National Tuberculosis Programme 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 the National IC Plan for Tuberculosis Control in Romania for 2013-2017 in line 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 crowded settings in Romania. The document was revised in 2013 and submitted to the MOH with approval still pending. When approved, the document will serve as a guide for all TB institutions in Romania to develop and introduce their IC plans. Still, at the time of the visit there was no national mechanism to regulate IC at TB facilities in Romania.

The TB network in Romania comprised of 87 inpatient facilities (hospitals with TB departments), 174 TB ambulatory care facilities and 113 TB laboratories. Each of the 41 counties had at least one TB ambulatory care facility and access to one TB hospital or TB laboratory. At the present time, two centers were recognized as National centers for MDR-TB (one in Bucharest with 50 beds and one in Bisericani with 70 beds). The MOH had plans to organize 8 regional MDR-TB centers in 8 other historic locations of Romania: 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 GF is supporting the renovation of some of the centers, including MNI and Laemna TB Hospital.

The risk of TB transmission was high in the majority of inpatient facilities, especially for DR-TB, due to a lack of IC measures such as proper ventilation, separation of patient flows, access to early diagnosis of TB and DR-TB, and the existing health financing system of TB hospitals. For several years the situation with DR-TB was aggravated by the lack of a complete range of SLD, resulting in stable high numbers of patients being treated with a failing regimen. The risk of transmission differed from one facility to another and was related to the number of patients hospitalized, types of patients and drug-resistance pattern, infection control measures and performance of the TB control programme in the county. TB laboratories have different risks of infection based on the procedures performed (microscopy, cultures, DST, molecular biology), work practices and adherence to IC measures. There was a certain level of risk of TB transmission in outpatient settings, especially in the case of referrals of TB suspects for diagnosis confirmation from PHC to TB dispensaries. However, the risk of transmission at outpatient settings was relatively low compared with TB inpatient facilities due to excessive and prolonged hospitalization, poor infection control measures and delays in treatment initiation. Often, extension of hospitalization resulted from social problems (homelessness, social cases, symptomatic therapy).

In 2013, with technical assistance from ECDC, the NTP developed a template of an IC Plan for the generic TB facility – a comprehensive tool to provide background information on current IC measures performed in a facility with clear instructions for improvement. The template contained information on management of IC, M&E and budget tools. Each facility developed their own IC plans, or was about to finish the assessment. Using the tool, the NTP had made a classification of

TB hospitals based on: (1) risk of nosocomial transmission; (2) TB incidence and the number of TB patients in county; (3) number of beds for TB patients in the facility; (4) type of patients diagnosed and treated in the facility; and (5) TB incidence among health personnel in the facility.

The IC assessment took place in 2014 and identified 14 TB institutions with extremely high risk of nosocomial transmission, including two leading MDR-TB centers in Bucharest and Bisericani. However, only one MDR-TB ward (at Marius Nasta Institute) had been scheduled for renovation within the GFATM grant. Earlier in 2015 the US Embassy in Romania had allocated funding for installation of a mechanical ventilation system and support the maintenance of equipment for negotiated period (2000 Euros/month) at MNI. It is unclear whether renovation of the other high-risk TB inpatient facilities is possible due to lack of financial resources. However, the GFATM grant will also support renovation of one wing of the Laemna TB Hospital for 30-35 beds, which will serve as the third national MDR-TB center, covering patients from 4-5 neighbouring counties.

Other than funding from the GFATM, the NTP is committed to improving IC measures in the majority of inpatient facilities involved in TB control with additional external and existing government funding. Activities of early diagnosis of TB cases and separation of patients according to drug resistance patterns seem to be the measures with the most potential, taking into account the existing availability of funding. Within the Norwegian grant the NTP has plans to procure 2,000 UVGI lamps for further instalment at 49 institutions across the country based on results of assessment and needs. The lamps were modern and recommended for use in institutions involved in TB control. In addition, the NTP had identified and trained 20 national coordinators on TB infection control, identified as medical personnel from county-level TB facilities to implement the National IC Plan across the country. Two IC coordinators had an engineering background and were identified to perform monitoring of the installation and maintenance of UVGI lamps and ventilation across the country. At the time of the mission around 150 medical personnel out of 960 involved in TB control had been trained in the basics of IC at TB facilities based on the National IC Plan. Furthermore, the GFATM grant was originally focused on development of the national policy documents focused on strengthening the outpatient treatment of TB and reducing unnecessary hospitalization. The grant was intended to review the existing laws and reimbursement practices contributing to unnecessary hospitalization and study different models of ambulatory care. The plan was also to develop protocols and guidelines for outpatient and inpatient treatment, including criteria for hospitalization and outpatient care.

Despite the availability of external funding for the next three years, the absence of a government-endorsed National IC Plan makes the implementation of some activities problematic. The scheduled installation of UVGIs was not regulated by any of the national standards but by 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. Furthermore, the MOH should introduce TB infection control measures in diagnostic and treatment facilities and in crowded settings by revising the Ministry of Health's Order N°916 (26 July 2006) and the current system of health facility accreditation, including specific measures for the prevention of airborne TB transmission.

Similarly to the previous GLC missions, it is assumed that there are some (but not many) significant positive improvements in infection control in the majority of TB inpatient facilities. IC plans were available from almost every TB inpatient facility, but these were not yet implemented due to an absence of a national decree regulating the national guidelines on IC. However, some institutions such as the TB Hospital in Laemna – which was first visited by the rGLC in 2012, then in 2015 – had made appropriate improvements in implementing separation of non-TB from TB and DR-TB patients. The Laemna TB hospital will become one of eight inter-county MDR-TB treatment centers for hospitalization of vulnerable and homeless patients who require continuation of

therapy in an inpatient facility. The scheduled renovation of one wing of Laemna hospital in 2016 will be enriched by installation of UVGI lamps and will enable better organisation of patient flows.

The NTP is showing some progress in completing the recommendations from the previous rGLC mission. However, some of the recommendations remain technically incomplete due to ongoing implementation. Considering the low treatment success rate among MDR-TB patients, suboptimal treatment regimens due to the unavailability of a full range of SLD, incomplete coverage with DST to SLD, questionable DOT, excessive hospitalization and poor separation of patients by smear/DST status still serve as some of the many reasons for infection transmission. Access to rapid molecular diagnosis of TB and DR-TB has been scaled up since 2015, but requires further improvement and support from the government for sustainability beyond the end of external donor funding. Recommendations from previous missions to invest funding into rapid diagnosis of TB and DR-TB (LPA and GeneXpert) and increase access to rapid DST have been completed with the arrival of international donor funding (GFATM and Norwegian grant), as well as access to a full range of quality-assured SLD. Similarly, the installation of upper-level UVGI lamps within the Norwegian grant at inpatient facilities and those ambulatory settings at high risk of infection transmission will bring a positive impact in reducing the burden of TB and DR-TB in Romania. A decrease in the number of TB hospital beds in those facilities that do not meet the standards of infection control might not be a bad solution, considering the existing approach of financing hospitals. The intention is to reform the hospital health financing system with released funding reallocated to strengthening service delivery in the outpatient sector, rather than closing poorly functioning facilities. Assessment of the existing financing system of TB services, including excessive hospitalization of TB patients, was in progress at the time of the mission and is being implemented with the technical assistance of WHO-Europe. In the long run these efforts will significantly improve the sustainability of the National TB Programme in Romania.

Recommendations:

	Recommendation	**Responsibility**
1	To endorse the updated version of the National Infection Control Plan in Romania and ensure adequate financing of infection control activities.	MOH
2	To revise the existing legislative base regulating health facility accreditation and prevention of TB transmission to include appropriate measures of TB infection control at all healthcare institutions involved in TB control and prevention, especially in settings with a high density of TB patients, such as TB inpatient facilities.	MOH NTP
3	Introduce F-A-S-T strategy/approach in all TB inpatient facilities, which is focused on finding cases actively, safely separating patients according to smear/DST status and initiate appropriate therapy for TB or DR-TB.	NTP
4	Perform rapid molecular diagnosis of TB and resistance to at least H and/or R (Xpert MTB/RIF and MTBDR*Plus*) prior to admission to TB inpatient facilities (continuous recommendation).	NTP
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 TB inpatient facilities that house all TB types. Early diagnosis of TB and identification of resistance to at least rifampicin should serve as an essential element for timely and safe separation of patients and initiation of appropriate treatment under direct observation in order to decrease the level of nosocomial transmission of infection in congested settings, including the prison sector	NTP

	(continuous recommendation).	
6	Ensure allocation of adequate financing for personal protection measures for health and administrative personnel at all treatment sites involved in the management of TB and DR-TB. Respirators for health personnel should be no less than FFP2 level of protection. "Fit testing" is mandatory before purchasing respirators for health personnel in each inpatient facility.	NTP
7	Ensure adequate financing for purchasing surgical masks for infectious patients and suspects.	NTP

11. Second line anti-TB drug management

Findings and summary of discussion:

In 2013 the government of Romania made the decision to centralize the drug procurement system in the country and initiated the system of National tenders after decentralization. Financing of drug procurement was performed by the MOH, which serves as a single funding source. National tenders usually happen once per year and were organized according to the list of essential medicines (TB component C2 list). The C2 list had not been officially revised/changed as recommended earlier by rGLC and GDF but some improvements were noticed. The list still contained Ciprofloxacin and was lacking Levofloxacin, Moxiflixacin, Capreomycin and PAS, as well as other Group C and D2 drugs (Linezolid, Clofazimine, Bedquiline, Delamanid and Imipenem/Cilastatin) used for treatment of M/XDR-TB. However, Ciprofloxacin was excluded from the National tender, which made it impossible to purchase and use in TB. The centralized tender at national level led to a decrease in prices for the majority of TB medicines. At the time of the mission, the Government was responsible for procurement of all FLD for the management of drug-susceptible TB and certain SLD included in the C2 list (Am, Ofx, Cs, Pto). The recently endorsed National Strategic Plan (March 2015) ensures full implementation of a centralized procurement mechanism starting in 2018. Thus, with existing donor funding the Romanian NTP will be able to cover the needs of SLD to treat M/XDR-TB. Moreover, the MOH has to ensure establishment of a coordination mechanism and ensure allocation of adequate financing for drug procurement beyond 2018.

The system of centralized procurement has advantages (lower prices through a competitive selection of suppliers, ensuring access to medicines for all health facilities which run the programme) and disadvantages (excessive bureaucracy in the procedure for obtaining approvals, the absence of an effective centralized system for monitoring of orders, consumption and stocks of medicines, lack of flexibility in the distribution of the budget, access to medication, lack of legislative provisions to allow the purchase of drugs in the period between the conclusion of a framework agreement and signing of the next one, etc.). Even with a national tender taking place, TB institutions still had to place orders and pay for TB medicines from their own budget. Still, coordination between the NTP and TB facilities that are responsible for drug purchasing in counties requires improvement. The NTP was aware of funding allocated for TB medicines by the MOH, but lacked information on drug orders and consumption in counties. The NTP should have enough authority to monitor drug consumption at county-level on a regular basis. Still, there was no unified electronic information system available at the level of the NTP for FLD and SLD management. There was no system to monitor and track the actual consumption of anti-TB drugs. Thus, estimations of the needs and forecasting of national procurement seemed to be approximate and therefore suboptimal. According to the NTP the software was developed for county-level pharmacies to place and track orders on certain quantities of TB drugs. Thus, the

recommendation to the NTP to consider using one of the WHO recommended tools for quantification and forecasting, like QuanTB, are up for consideration but are not mandatory.

The mechanism of distribution of medicines to the counties require significant improvements, such as by identifying selected distributing companies responsible for timely delivery of drugs to the counties to avoid stock-outs and treatment interruptions. There was a need for the NTP to develop suggestions to the MOH on improving the conditions of the National tender to avoid stock-outs of medicines and, as a result, treatment interruptions. For more details on drug distribution and legal analysis around centralized drug procurement please refer to the report by the WHO consultant "Assessment of the legal and regulatory framework for centralized procurement of anti-TB drugs in Romania" of March 2016 (Attachment 2).

As noted earlier, the GFATM grant for Romania was 8.4 million Euros for the three years starting April 2015, under which there were plans to ensure access to therapy with 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 was planning to enrol up to 1,000 patients with M/XDR-TB over a 20-month period, which seemed ambitious. However, the enrolment was approved for extension because of the gap between 2014-2015 when it was stopped due to the lack of international funding to procure TB drugs. Thus, during 2016 the NTP plans to enrol 850 patients with MDR-TB into the treatment programme. Drug orders to the GDF have been placed by either RAA, the PR of the GFATM grant or by MNI, the PR of the NG and cleared by the rGLC of WHO-Europe. Drug requests combined for both grants included M/XDR-TB treatment regimens and the number of patients to be enrolled during the calendar year. 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 both) and XDR-TB. Regimens for pre-XDR-TB and XDR-TB included Moxifloxacin, Linezolid, Clofazimine, Imipenium/Cilastatin and Bedaquiline, but not Delamanid. In total, as a result of the two grants, 150 patients will initiate therapy with a Bedaquiline containing regimen until the end of 2017 (70 from GFATM and 80 from Norwegian grant).

It was agreed during the last mission that NTP was to prepare a comprehensive document to regulate the use of new TB drugs in Romania. Originally, the document was intended to be limited to the use of Bedaquiline, but taking into account the need for the use of other Group C and D2 medications it was recommended to develop a unified programmatic document. Clinical aspects of the use of new drugs required an update in the National guidelines for TB and DR-TB. 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. During the last and current missions it was discussed with the MOH that there is a need to create a multi-sectorial National TB Coordination Committee as a National Task Force mechanism to oversee the preparation, planning, implementation and evaluation of new TB drugs (Groups C and D2), as well as other new TB drugs/regimens in the 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 drugs.

Recommendations:

	Recommendation	**Responsibility**
1	Ensure adequate financing and uninterrupted supply of drug procurement for FLD and SLD at all treatment sites (continuous recommendation).	MOH
2	Develop a strategy to ensure allocation of adequate financing of second-line drug procurement beyond 2018 for the management of	MOH

	M/XDR-TB (continuous recommendation).	
3	Update the National Essential Drug List (C2 list) to include the following medicines: Capreomycin, Levofloxacin, Moxiflixacin, 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 (continuous recommendation).	MOH
5	The Essential drug list (C2) should include only those medications that are included in the regimens of the updated National Guidelines on PMDT for Romania (continuous recommendation).	MOH NTP
6	Finalize the development of an electronic system specifically designed for drug management.	NTP
7	Endorse the Implementation Plan for Introduction of new TB drugs in Romania.	MOH

12. Information system and data management

Findings and summary of discussion

The national recording and reporting system was in line with WHO recommendations. Data collection was centralized at the level of the NTP, with information collected from every county TB coordinator. All TB Dispensaries have established a computerized, web-based system with servers at the TB Surveillance Unit at NTP level in MNI (Bucharest). Information is collected from TB institutions (hospitals and dispensaries) in the county. TB Surveillance was regulated and had been endorsed by the MOH as mandatory for all institutions involved in the TB programme. TB Surveillance software was functioning at all TB dispensaries, with all cases registered and reported at the National level. As in the previous mission, the current software had experienced difficulties with providing the aggregated data at National and county levels. Furthermore, the laboratory component had not been fully integrated into the national registry at the time of the mission. However, with support from the Norwegian grant the software has been under development. The information data flow had three levels, with data collected at TB clinics (first level), compiled for the county at county level by the TB coordinator and epidemiologist (secondary level), and further referred to the tertiary level to the MNI (NTP Coordinator).

A separate electronic MDR-TB registry was available within the National Registry with data entered on patients registered for treatment with SLD. All information on every MDR-TB case registered for treatment was recorded in paper registers, available at MDR-TB centers. Access to the MDR-TB registry was available at the level of the NTP and TB dispensary. However, the registry included only those patients registered for Category IV treatment and did not include those diagnosed with MDR-TB who were not on therapy. The registry contained information on the patient's unique number, diagnosis, bacteriology results (smear, culture, DST), treatment regimen and clinical testing. The Central Coordination Unit at National level performs monitoring of data collection and reporting of information from the counties. County coordinators do the same for TB clinics. Still, there was no unified laboratory registry in electronic format; each laboratory has its own, and also kept records in paper registers. However, at the time of the mission, a unified laboratory module for the National register was under construction and is expected to be completed by the end of 2016. The existing R&R forms for DR-TB had been revised in accordance with Part 4 of the "Forms for drug-resistant TB programs" of the WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (2015) but they has not yet introduced to the updated version of the National Guidelines for PMDT in Romania.

Monitoring of the NTP Central Unit is performed at least twice per year and often based on results of programme performance and reporting. In 2014 the NTP Central Unit performed several snapshots of quality of data recording in the National Registry in each county and defined the range of missing data. Several counties where identified as recording data poorly, which made it apparent to county-level TB coordinators that this issue needed to be addressed.

Recommendations:

	Recommendation	Responsibility
1	Conduct regular monitoring of recording and reporting (R&R), 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	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
3	Complete the development of an electronic laboratory section / module for the National TB Registry by the end of 2016 and perform regular monitoring of 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 regardless of race, ethnicity, religion, age or gender. Often, minorities – especially the Roma population – have access to basic health services including free diagnosis and treatment of TB. In recent years Romania has faced issues of outgoing labour migration, with patients often defaulting from treatment as they move for work outside the country. Within the Norwegian grant the NTP is planning to address the social challenges of poor and vulnerable patients, including the Roma population, through ensuring access to appropriate diagnosis and treatment, as well as psychosocial support to ensure adherence to therapy. Within the GFATM grant it is planned to create six multidisciplinary teams who will provide psychosocial support for patients from vulnerable groups with a high risk of defaulting from treatment.

14. Attachments

- Annex 1: GLC monitoring mission agenda
- Annex 2: WHO TB Country Profile, Romania, 2014