rGLC/EUROPE
TEECHNICAL ASSISTANCE MISSION
TO ROMANIA

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Contents

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List of acronyms

aDSM	Active Tuberculosis Drug drug safety monitoring and management
AE	Adverse event
Am	Amikacin
Amx-Clv	Amoxicillin-clavulanate
Bdq	Bedaquiline
C2 list	National Essential Drug List
CC (+/-)	Culture (positive/negative)
Cfz	Clofazimine
Cm	Capreomycin
Cs	Cycloserine
CU	Compassionate use
Dlm	Delamanid
DOT	Directly observed therapy
DRS	Drug resistance survey
DR-TB	Drug-resistant tuberculosis
DS-TB	Drug-susceptible tuberculosis
DST	Drug susceptibility testing
E	Ethambutol
EEA	European Economic Area
EQC	External quality control
ESIF	European Structural and Investment Funds
Eto	Ethionamide
FLD	First-line drug
FQ	Fluoroquinolone
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
H	Isoniazid
IC	Infection control
Imp-Cls	Imipenem-cilastatin
IQE	Injectable, fluoroquinolone and Ethionamide for LPA
Km	Kanamycin
Lfx	Levofloxacin
LPA	Line probe assay
LWG	Laboratory working group
Lzd	Linezolid
M&E	Monitoring and Evaluation
MDR-TB	Multidrug-resistant tuberculosis
Mfx	Moxifloxacin
MGIT	Mycobacteria growth indicator tube
MNI	Marius Nasta Pneumophysiology Institute
MoH	Ministry of Health
NCP	National Commission of Pneumology
NIH	National Insurance House
NRL	National reference laboratory
NSP	National Strategic Plan for TB Control in Romania, 2015–2020
NTP	National Tuberculosis Programme
Ofx	Ofloxacin
PAS	Para-aminosalicylic acid
PHC	Primary health care
PMDT	Programmatic management of drug-resistant tuberculosis

Pto	Prothionamide
PV	Pharmacovigilance
R	Rifampicin
R&R	Recording and reporting
RAA	Romanian Angel Appeal
rGLC	Regional Green Light Committee
RR	Rifampicin-resistant
RRL	Regional reference laboratory
S	Streptomycin
SLD	Second-line drug
SLI	Second-line injectable
SRL	Supranational Reference Laboratory
SS (+/–)	Smear (positive/negative)
STR	Shorter treatment regimen
TB	Tuberculosis
VOT	Video-observed therapy
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

1. Terms of reference

Objectives

- To assess the progress of the implementation of the National Strategic Plan (NSP), including its M/XDR-TB component, and to develop recommendations for future activities.
- To assess progress made by the National Tuberculosis Programme (NTP) and its readiness for effective introduction of new drugs.
- To assess the effectiveness of implementing the current drug-resistant TB (DR-TB) control project supported by the Global Fund, including TB drug management.
- To advise on the estimated number of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) patients for 2017–2018.
- To assess the readiness for an effective start-up of a shorter (nine-month) treatment regimen (STR) for suitable patients.

Key issues to be elaborated and reviewed

- To identify the need for technical assistance and recommended actions with any aspect of the programmatic management of DR-TB in order to fulfil the NSP.
- To assess case-finding strategies and identify barriers to the timely start of DR-TB treatment, including TB in children.
- To review and provide recommendations on the existing guidelines on DR-TB.
- To assess medical/clinical aspects of the management and treatment of MDR-TB and XDR-TB.
- To assess the status of the introduction of new TB drugs.
- To assess active drug safety monitoring and management (aDSM).
- To ensure follow-up of TB and DR-TB patients; adherence to treatment; and a patient-centred approach and social support.

Expected outcomes of the mission

- Produce rGLC/Europe monitoring mission report with recommendations.
- Identify areas of technical assistance that can be provided by the WHO Regional Office for Europe and rGLC/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, the last of which took place in May 2016.

Romania received several approvals from the rGLC to access quality-assured second-line drugs (SLDs) for a total of 2715 M/XDR-TB patients (cohorts 1–7). Between 2004 and 2014 a total of 1253 MDR-TB patients were enrolled in the rGLC-approved programme, with funding available from the GFATM grant (cohorts 1–5). The average treatment success rate was 68.2% (cohorts 1–4) and 72.8% (cohort 5); 17 patients were still on treatment). Despite good performance of GFATM grants related to the NTP in Romania, the treatment effectiveness of non-rGLC cohorts of patients has shown extremely poor outcomes over the years on account of a series of structural, financial and organizational constraints. An additional 1460 patients with M/XDR-TB will gain access to quality-assured SLDs, as well as new and other Group 5 drugs, with funding available from the Norway Grant and the GFATM for the period until March 2018. A total of 1002 patients with M/XDR-TB have been already enrolled with the support of the NG, including 70 on a regimen containing bedaquiline (Bdq). Another 460 M/XDR-TB patients, including 80 on a Bdq-containing regimen, will be enrolled by August 2018 within the GFATM grant.

Political commitment in Romania has increased recently, especially following continuous political and technical support from the WHO Regional Office for Europe, the European Centre for Disease Prevention and Control and other international organizations focused on strengthening the NTP. In March 2015, the Romanian government endorsed the National Strategic Plan for TB Control in Romania, 2015–2020 (NSP), which presents the country's priorities in addressing the public health challenge of TB. The NSP was developed in close partnership with the Romanian Ministry of Health (MoH), the NTP, WHO, and other governmental and nongovernmental organizations. The NSP outlines national strategies to meet needs that are not currently satisfied and to build the sustainability of the system; it also presents a long-term vision of TB care and identifies innovative approaches targeted at achieving a dramatic decline in TB incidence and mortality in Romania by 2020.

There are various bottlenecks that require attention from the government and international authorities in order to strengthen the capacity and performance of the Romanian NTP. Most of these will be addressed with the implementation of the NSP for 2015–2020 and support from external donor and technical assistance agencies.

3. Follow-up of the previous mission recommendations

The Romanian NTP is showing significant progress in the scale-up and management of DR-TB. The majority of key recommendations from the previous mission were either completed or in progress; it was acknowledged that some recommendations required significant effort from the NTP. Of 13 key recommendations to the MoH, eight have been fully completed and five were in progress or required improvement. Of 25 recommendations to the NTP, only one has not been completed (as a result of insufficient funding), six have been fully completed, and 18 were in progress; success will require joint efforts from the NTP and international donor organizations. Several recommendations were classed as continuous/ongoing, and were repeated in the current report.

Recommendations to the MoH	Responsibility
Prevention and control of TB and M/XDR-TB should be considered a public health priority. The Romanian government should support the implementation of the NSP for 2015–2020. Sufficient and sustainable funding should be ensured to sustain NTP 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.	Significant support from the MoH has been witnessed, with increased political commitment and trends towards sustainability.
Support implementation of the new GFATM and Norway Grants. The Marius Nasta Pneumophysiology Institute (MNI) should play a leading role in the management and implementation of this and upcoming grants (POCU, from the European Structural and Investment Funds (ESIF)).	In addition, the MoH appointed MNI to become Principal Recipient of the ESIF grant.
Consider endorsement of the multisectoral National TB Coordination Committee as a National Task Force mechanism to oversee the preparation, planning, implementation and evaluation of new TB drugs – Bdq, delamanid (Dlm) and other TB drugs recommended for therapy of M/XDR-TB).	The National Commission of Pneumology (NCP) will serve as the National Task Force mechanism to scale up access to the new TB drugs. The recently recommended changes to the National Essential Drug List (C2 list) should include addition of the new TB drugs.
Consider endorsement of the National Implementation Plan for introduction of new TB drugs for the management of M/XDR-TB.	Under development; due to be submitted to the MoH for endorsement, along with other guidelines developed by the NTP and approved by the NCP.
Endorse the updated version of the National Infection Control Plan in Romania and ensure adequate financing of infection control (IC) measures.	In progress.
Revise the existing legislative base regulating health facility accreditation and prevention of TB transmission; to include appropriate IC measures at all health care institutions involved in TB control and prevention, especially in settings with a high density of TB patients, such as TB inpatient facilities.	In progress.

Ensure adequate financing and uninterrupted supply/procurement of first-line drugs (FLDs) and SLDs at all treatment sites (ongoing recommendation).	Uninterrupted supply has been ensured with external donor funding (Norway Grant and GFATM). Funding from the MoH was available and national tender took place. No available distributor for amikacin (Am) and combination of FLDs.
Develop a strategy to ensure allocation of adequate funding for SLD procurement beyond 2018, for the management of M/XDR-TB (ongoing recommendation).	The NTP budgeted funding for 500 M/XDR-TB patients through EEA grant. C2 list was approved for update with new and other TB drugs.
Update the National Essential Drug List (C2 list) to include the following medicines: capreomycin (Cm), levofloxacin (Lfx), moxifloxacin (Mfx), para-aminosalicylic acid (PAS), Bdq, Linezolid (Lzd) and imipenem-cilastatin (Imp-Cls). Consider update of the C2 list with Dlm and Clofazimine (Cfz) once the drugs are registered in Romania.	The MoH issued a decree which allowed update of C2 list with new and other SLDs.
Revise conditions of the national tender to avoid possible stock-outs of TB medicines (ongoing recommendation).	
The C2 list should include only those medications that are included in the regimens of the updated national guidelines on the programmatic management of drug-resistant tuberculosis (PMDT) for Romania (ongoing recommendation).	
Endorse the National Implementation Plan for introduction of new TB drugs in Romania.	Under development; the plan will be submitted to the MoH for endorsement, along with other guidelines developed by the NTP and approved by the NCP.
Recommendations to the NTP	**Responsibility**
Consider updating the national guidelines on PMDT in line with recently released recommendations by WHO on PMDT, especially on new groups of TB drugs and regimen design for M/XDR-TB.	A new National Clinical Guide on the use of new TB drugs has been developed, but it is still to be endorsed by the MoH.
In addition to use of Bdq, consider procurement and use of Dlm in treatment of patients with M/XDR-TB, according to the WHO guidelines on PMDT (2016).	In progress. Dlm was approved for inclusion in the C2 list.
Expand indications for the use of new TB drugs in accordance with the new groups of TB medicines recommended by WHO (2016).	In progress. New drugs are now available only through external funds, and their use is limited to those with XDR-TB or pre-XDR-TB.
Ensure distribution of the updated version of the national guidelines on PMDT and training of all health care providers involved in management of patients with M/XDR-TB.	In progress.

Introduce and implement the main aspects of active drug safety monitoring and management (aDSM) as part of a scaling-up of 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 the development of serious adverse events.	In progress; requires improvement. aDSM started as an operational research, but is not used completely or routinely.
Ensure introduction and strict implementation of diagnostic algorithms on drug susceptibility testing (DST), as part of updated national guidelines on PMDT, adhering to the following principles (ongoing recommendation): • DST to FLDs (at least to H and R) should be performed for all SS+ and CC+ patients regardless of patient type. • DST to SLDs should be performed in all cases diagnosed with HR-resistance, or R-resistance alone. • Repeat DST on SLDs for MDR-TB patients who remain SS/CC+ after three to four months of treatment or who become SS/CC+ after conversion at a later stage of treatment.	National TB laboratory guidelines have been developed and approved by WHO; still to be endorsed by the NCP and further submitted to the MoH.
Consider collaborating with the Supranational Reference Laboratory (SRL) on DST to new TB drugs. Consider (i) storing in laboratory refrigerators samples of positive cultures from baseline until culture conversion for patients on therapy with new TB drugs; or (ii) sending samples to SRL for DST. This will facilitate understanding of the trends of amplification of drug resistance.	In progress. Strategy for storing isolates from patients on new TB drugs and sending to SRL for DST to be discussed.
Once diagnosed as Xpert MTB/RIF-positive, the standardized MDR-TB regimen should be initiated with a minimum of five effective drugs from groups A, B, C and D1, followed by conventional DST to H and other FLDs using rapid molecular diagnostic tests (LPA) and/or MGIT.	Completed.
In patients with rifampicin-resistant (RR) or MDR-TB, a regimen with at least five effective TB medicines is recommended during the intensive phase, including pyrazinamide (Z) and four core SLDs – 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 group D3 may be added to bring the total to five.	Described in the new National Clinical Guide on the use of new TB drugs, but access is not nationwide as drugs are only available to a limited number of patients (80 through the GFATM grant).
Ensure daily directly observed therapy (DOT) of patients, in particular those who receive treatment with new TB drugs, especially Dlm, Lzd, Cfz and carbapenems.	Requires improvement.
Consider revising the national policy on the management of drug-susceptible tuberculosis (DS-TB) to align it with 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	In progress.

therapy, provided that each dose is directly observed."	
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 LPA in geographically representative regional laboratories.	In progress.
Increase coverage of DST to SLDs (at least an injectable agent and FQ) to all R-positive cases across the country, especially in high-burden counties, using rapid molecular diagnosis testing (LPA) or liquid media systems (MGIT). Consider expanding access to MTBDR*sl* to other parts of Romania (e.g. Iași).	In progress; requires improvement.
Improve monitoring of implementation of the diagnostic algorithm at county level to ensure timely use of rapid molecular testing for TB and DR-TB.	In progress; requires improvement.
Update the national laboratory reporting forms with information on rapid molecular diagnosis (Xpert MTB/RIF, MTBDR*plus*, MTBDR*plus-sl*). Incorporate the updated forms in the national guidelines on DR-TB and the National Laboratory Guidelines (ongoing recommendation).	
Introduce F-A-S-T strategy/approach in all TB inpatient facilities; this is focused on finding cases actively, safely separating patients according to smear/DST status, and initiating appropriate therapy for TB or DR-TB.	In progress; requires improvement.
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 (ongoing recommendation).	In progress; requires improvement.
Introduce essential administrative measures to separate TB from non-TB patients; SS/CC+ drug-susceptible patients from SS/CC+ drug-resistant patients; MDR-TB from XDR-TB patients – especially at TB inpatient facilities that house all TB types. Early diagnosis of TB and identification of resistance to at least R should serve as an essential element in the 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 (ongoing recommendation).	In progress; requires improvement.
Ensure allocation of adequate funding 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.	In progress; requires improvement.
Ensure adequate funding for purchasing surgical masks for infectious patients and suspects.	In progress; requires improvement.
Update the C2 list to include the following medicines: Cm, Lfx,	The MoH issued a decree which

Mfx, PAS, Bdq, Lzd and Imp-Cls. Consider update of the C2 list to include Dlm and Cfz once these drugs are registered in Romania.	allowed update of C2 list with new and other SLDs.
Finalize the development of an electronic system specifically designed for drug management.	Requires additional funding not available from current grants.
Conduct regular monitoring of recording and reporting (R&R) and of data collection and entry at county level (TB dispensaries and laboratories). Take "snapshots" of five or six counties every month and address issues of missing data and R&R to the county TB coordinators.	Requires improvement.
Ensure that the national registry contains information on all TB and DR-TB cases registered in the country, not only those registered for treatment.	Requires improvement.
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.	Requires improvement.

4. Current mission recommendations (summary)

	Recommendations to the Ministry of Health (MoH)	Responsibility	Timeframe
1	Support the implementation of the National Strategic Plan for TB Control, 2015–2020 (NSP) and ensure sufficient and sustainable funding for implementation of the National TB Programme (NTP).	MoH	Q3 2017
2	Support application for possible funding from external donor organizations (European Structural and Investment Funds – POCU).	MoH	Q3-Q4 2017
3	Ensure that the delegated mandate of the NTP to operate as the central management unit is supported with adequate funding.	MoH	Q4 2017
4	Ensure uninterrupted and sufficient funding of consumables and reagents for rapid molecular and liquid conventional DST after the end of external donor funding.	MoH	Q3– Q4 2017
5	Endorse the updated version of the National Infection Control Plan in Romania and ensure adequate financing of infection control (IC) activities.	MoH	Q3 2017
6	Ensure adequate funding and uninterrupted supply/procurement of FLDs and SLDs, including new TB drugs recommended for treatment of M/XDR-TB.	MoH	2017
7	Ensure fast update and inclusion of the following drugs in the C2 list, according to the National Clinical Guide for MDR-TB: Bdq, Dlm, Cfz, Lzd, Imp-Cls, Amx-Clv, Mfx, Cm,	MoH	Q3-Q4 2017

	Km, Lfx and PAS.		
8	Revise conditions of the national tender to avoid possible stock-outs of TB medicines (ongoing recommendation).	MoH	2017

	Recommendation to the National TB Programme (NTP)	Responsibility	Timeframe
1	Consider updating the National Methodological Guide on TB (2015) with the latest WHO *Guidelines for treatment of drug-susceptible tuberculosis and patient care* (2017 update), especially: "In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug-susceptibility testing should be conducted to inform the choice of treatment regimen."	NTP	2017
2	Consider updating the National Methodological Guide on TB (2015) with the latest WHO recommendations highlighted in the new Clinical Guide on the use of new TB drugs in Romania (2016) and submit to the National Commission of Pneumology for endorsement.	NTP	Q3-Q4 2017
3	DR-TB Central Committee should finalize and systematize the standard set of documents to be used for referral of a patient on new TB drugs when discharged from MDR-TB centres for treatment continuation.	NTP	Q3-Q4 2017
4	Dlm may be added to the WHO-recommended longer regimen in children and adolescents (6–17 years).	NTP	Q3-Q4 2017
5	Introduce and implement the main aspects of active drug safety monitoring and management (aDSM) as part of a scaling-up of access to new TB drugs. Ensure implementation of the minimum requirements for laboratory diagnosis in outpatient settings as required by the new Clinical Guide on the use of new TB drugs.	NTP	Q3-Q4 2017
6	Consider collaborating with the SRL on DST to new TB drugs. Consider (i) storing in laboratory refrigerators samples of positive cultures from baseline until culture conversion for patients on therapy with new TB drugs; or (ii) sending samples to SRL for DST. This will facilitate understanding of the trends of amplification of drug resistance.	NTP	Q3-Q4 2017
7	Prepare a plan for step-by-step training on the new national DR-TB guidelines, first including counties with larger numbers of patients on new TB drugs. Strengthen the capacity of the county-level teams to manage patients on new TB drugs. Consider rotation of doctors from counties in Bucharest – building capacity and institutional memory (not on personal time of county-level doctors, formally approved and funded by the MoH).	NTP	Q4 2017

8	Define the responsibilities for all levels of patient care and management and map the flow of recording and reporting (R&R) forms: • DR-TB Central Committee • pneumologist • primary health care (PHC) doctor • DOT provider/community health worker • patient • multidisciplinary team (their responsibilities should be mapped and focused on supervisory work rather than covering the work of doctors and DOT providers).	NTP	Q4 2017
9	Consider using modern technology to enhance programme monitoring and evaluation (M&E), between national and county levels, at county level and between counties (regional level): Skype video conferences, WhatsApp, Viber, etc.	NTP	Q4 2017
10	Consider clinical in-site training/rotation of county TB coordinators in MDR-TB centres in Bucharest and Bisericani, as part of capacity-building measures to increase knowledge of the use of new TB drugs. Funding of rotation should be considered from either national or county-level budgets.	MoH NTP	Q4 2017
11	Ensure daily directly observed therapy (DOT) of patients, in particular those who receive treatment with new TB drugs, especially Dlm, Lzd, Cfz and carbapenems.	NTP	Q4 2017
12	Video-observed therapy (VOT) may replace DOT when video communication technology is available and can be appropriately organized and operated by health care providers and patients. VOT is needed to decrease the level of self-administration of TB and DR-TB treatment.	NTP	2017 - 2018
13	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 LPA in geographically representative regional laboratories (ongoing recommendation).	NTP	2017
14	Consider revision of the laboratory reorganization plan based on TB burden, capacity and infrastructure (roads) in counties, to ensure universal and uninterrupted access to rapid molecular diagnosis of TB and DR-TB.	NTP	2017
15	Ensure universal coverage of DST to SLDs (at least an injectable agent and FQ) to all RR/MDR-TB cases, especially in high-burden counties using rapid molecular diagnosis testing (LPA) or liquid media systems (MGIT).	NTP	2017

16	Monitor the implementation of TB and DR-TB diagnostic algorithms at county level to ensure timely use of rapid molecular testing for TB and DR-TB.	NTP	2017
17	Revise the existing legislative base regulating health facility accreditation and prevention of TB transmission; to include appropriate IC measures at all health care institutions involved in TB control and prevention, especially in settings with a high density of TB patients, such as TB inpatient facilities.	MoH NTP	2017 -2018
18	Expand and routinely implement the F-A-S-T strategy/approach across all health institutions involved in TB control – to find cases actively, safely separate patients according to smear/DST status, and initiate appropriate therapy for TB or DR-TB.	NTP	2017-2018
19	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 (ongoing recommendation).	NTP	2017
20	Ensure allocation of adequate funding for personal protection measures for health and administrative personnel at all treatment sites involved in the management of TB and DR-TB (ongoing recommendation).	NTP	2017
21	Calculate the actual needs for the new TB drugs, taking into account the eligibility criteria described in the National Clinical Guide on the use of new TB drugs. This measure is required to scale up access to the new TB drugs for a larger cohort of patients. Consider technical assistance from the WHO Regional Office for Europe or Global Drug Facility (GDF).	NTP	Q3-Q4 2017
22	Finalize the development of an electronic system specifically designed for drug management.	NTP	Q3-Q4 2017
23	Ensure that the national registry contains information on all TB and DR-TB cases registered in the country, not only those registered for treatment (ongoing recommendation).	NTP	Q4 2017
24	Include RR cases in cohort reporting and analysis.	NTP	Q4 2017
25	Revise and update treatment registration forms to bring into alignment with Part 4 of the WHO *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (2015), especially in light of the use of new TB drugs. Updated forms to be institutionalized and brought into routine practice.	NTP	Q4 2017
26	Map the flow of case registration and treatment forms for MDR-TB to ensure adequate R&R.	NTP	Q4 2017
27	Consider separate reporting on treatment outcomes for	NTP	Q3-Q4 2017

	rGLC and non-rGLC cohorts.		

5. General country/region profile

Romania is a country located at the crossroads of central and south-eastern Europe, on the Lower Danube; it lies both within and outside the Carpathian arch, bordering Hungary, Serbia, Bulgaria, the Republic of Moldova and Ukraine, and has 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). The country's capital and largest city is Bucharest; it is the tenth-largest city in the EU, with about 2 106 144 inhabitants (Romanian 2011 census, INSSEa and Eurostat statistics of 30 July 2015). 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 is a total of 319 cities and 2686 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 larger regions: North-eastern (Iași), Western (Timișoara), North-western (Cluj-Napoca), Central (Brașov), South-eastern (Constanța), Southern (Ploiești), Bucharest-Ilfov (Bucharest) and South-western (Craiova).

According to World Bank estimates (2017), Romania's total GDP (PPP) is US$ 470.312 billion (US$ 23 957 per capita), which defines the country as an upper-middle-income economy. The actual unemployment rate has been relatively low in recent years and stood at about 6.5% in March 2015, as reported by the Romanian National Institute of Statistics. Unemployment aid is granted on a time-limited, individually determined basis. At the same time, the effects of the global economic recession on the country's economy have 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% lived in rural areas. A set of reform programmes, commenced in 1999, introduced a private health insurance system. The state-run health care system is free, but suffers from neglect and has deteriorated in recent years as a result of inadequate funding and underpaid staff. Romania has a universal health care system, which covers medical examinations, emergency care and free treatment of a range of diseases, including TB and HIV/AIDS. The most common causes of death are cardiovascular diseases, cancer and TB.

The National TB Programme (NTP) in Romania has national coverage and a 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

In Romania TB 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 show a steady decrease in the 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 64.5 per 100 000 in 2016. The mortality rate of TB (excluding those with HIV coinfection) was reported at the low level of 5.3% in 2015 (down from 5.9% in 2012); the corresponding figure for HIV-positive cases is assumed to be higher. Data on TB mortality in the civilian sector were not available for 2016 (Table 1). See also Annex 2 for incidence rates officially reported to WHO (2015).

Table 1. Incidence, prevalence and mortality rates of TB, 2014–2016, civilian sector (data provided by NTP)

Year	Incidence	Prevalence	Mortality
2014	74.6	121.4	5.6
2015	71.7	116.2	5.3
2016	64.5	105.2	NA

Table 2. TB case notification, 2014–2016, civilian sector (data provided by NTP)

Case notifications	2014		2015		2016	
	abs	%	abs	%	abs	%
New cases	**12 846**	**100**	**12 482**	**100**	**12 029**	**100**
Smear-positive (SS+)	6251	48.7	6008	48.1	5774	48.0
Smear-negative (SS–)	4187	32.6	4167	33.4	3994	33.2
Smear unknown	111	0.9	103	0.8	108	0.9
Extrapulmonary TB	2297	17.9	2204	17.7	2153	17.9
Other	0	0	0	0	0	0
Total new	12 846	100	12 482	100	12 029	100
Retreatment cases	**3843**	**100**	**3397**	**100**	**3246**	**100**
Relapse	2659	69.2	2352	69.2	2240	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	3843	100	3397	100	3246	100
TOTAL: new + retreatment	**16 689**		**15 879**		**15 275**	

The incidence of TB varied across the country and was quite closely related to the socioeconomic status of the regions, with higher rates in the Eastern, Western and Southern regions and lower rates in the Central and North-western regions. The absolute number of TB patients with active disease at the end of 2016 in Romania remains high (around 20 854 at the end of 2016). The main TB indices are declining, mostly as a result of access to treatment for the majority of diagnosed TB cases, as well as the availability of FLDs for DS-TB.

M/XDR-TB

Despite the successes in managing DS-TB, DR-TB is a major challenge to the effectiveness of the NTP in Romania. Even though Romania is not recognized by WHO as a high-burden country for TB and MDR-TB, MDR-TB is one of the major obstacles to the successful implementation of the National TB Programme in the country. The number and proportion of MDR-TB cases in Romania remain high, although this is partly explained by significant improvements in laboratory diagnosis of drug resistance. According to the drug resistance survey (DRS) conducted in 2014–2015, resistance to H and R together was found in 2.5% of new pulmonary cases and 10.8% of retreatment cases. XDR-TB was identified in 15.8% of new cases and 13.5% of previously treated cases (see Annex 3 for more information).

In 2015, WHO estimated a rate of 3.0% (2.1–3.9) for MDR-TB among new cases and 12.0% (9.3–15.0) among retreatment cases in Romania. This estimated of 670 MDR-TB cases among notified pulmonary TB cases in 2015 (540–790), which is lower than in previous years. According to reports of 2015 data submitted to WHO, in laboratory testing of 7748 cases, RR/MDR-TB was confirmed in 576, and the number of patients who started therapy for MDR-TB was 591. Of these 7748, only 330 were tested with DST to SLDs, with 53 XDR-TB patients diagnosed. The situation has changed

significantly over the past year, with an increased number of RR/MDR-TB cases tested with DST to SLDs (for more detailed information, see Section 9 below).

The number of patients with active MDR-TB at the end of the year was falling slightly in the civilian sector; this is explained both by good treatment success rate of DS-TB and increased treatment coverage of patients with a full range of SLDs for MDR-TB, achieved through government and donor funding sources. A total of 960 MDR-TB patients had been registered in Romania by the end of 2016 (Table 3); most of these were from the Eastern and Southern historical regions of Romania (Tables 4 and 5). With the arrival of new TB drugs for treatment of patients with resistance to FQs and those whose treatment of MDR-TB was ineffective, there is an opportunity to reduce 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, implementation of the diagnostic algorithm for screening TB suspects will increase the number of RR pulmonary TB cases detected, and detection of FQ-resistant cases will rise when LPA to SLDs is widely accessible.

Table 3. Absolute number of MDR-TB cases registered by the end of year, civilian sector, 2014–2016 (data provided by NTP)

	Total TB	TB without MDR	MDR-TB	%
2014	24 172	22 995	1177	4.9
2015	23 040	22 010	1030	4.5
2016	20 854	19 894	960	4.6

Table 4. Absolute number of patients diagnosed with MDR-TB by county, civilian sector, 2016

County	Abs. number of cases MDR, 2016	New	Relapse	Other retreatment cases
A	***1***	***2***	***3***	***4***
TOTAL	**419**	**122**	**114**	**183**
Alba	2	1	0	1
Arad	4	1	2	1
Argeș	11	3	5	3
Bacău	16	3	5	8
Bihor	7	3	1	3
Bistrița-Năsăud	2	0	0	2
Botoșani	7	2	2	3
Brașov	6	3	0	3
Brăila	5	0	1	4
Buzău	6	2	1	3
Caraș-Severin	8	3	1	4
Călărași	17	2	6	9
Cluj	3	3	0	0
Constanța	19	4	9	6
Covasna	6	4	1	1
Dâmbovița	13	8	3	2
Dolj	18	3	6	9

Galați	10	1	4	5
Giurgiu	9	4	0	5
Gorj	12	1	5	6
Harghita	0	0	0	0
Hunedoara	13	2	6	5
Ialomița	7	2	2	3
Iași	11	4	4	3
Ilfov	10	1	3	6
Maramureș	10	0	2	8
Mehedinți	7	1	3	3
Mureș	10	6	2	2
Neamț	11	2	4	5
Olt	11	3	1	7
Prahova	19	5	3	11
Satu Mare	13	4	2	7
Sălaj	1	0	0	1
Sibiu	15	5	2	8
Suceava	8	4	1	3
Teleorman	13	5	3	5
Timiș	18	2	6	10
Tulcea	1	0	0	1
Vaslui	6	3	1	2
Vâlcea	8	2	3	3
Vrancea	5	1	0	4
Bucharest	41	19	14	8

Table 5. Absolute number of patients diagnosed with XDR-TB by county, civilian sector, 2015–2016

County	2015	2016
TOTAL	**58**	**70**
Alba	1	0
Arad	0	0
Argeș	1	1
Bacău	1	2
Bihor	1	3
Bistrița-Năsăud	0	1
Botoșani	2	0
Brașov	1	0
Brăila	0	3
Buzău	0	1
Caraș-Severin	0	3
Călărași	1	6

Cluj	1	0
Constanța	1	3
Covasna	0	0
Dâmbovița	2	0
Dolj	4	0
Galați	1	2
Giurgiu	1	0
Gorj	1	2
Harghita	0	0
Hunedoara	3	4
Ialomița	1	0
Iași	5	3
Ilfov	1	6
Maramureș	0	1
Mehedinți	0	0
Mureș	1	0
Neamț	3	5
Olt	3	2
Prahova	0	2
Satu Mare	2	1
Sălaj	0	0
Sibiu	2	2
Suceava	2	1
Teleorman	0	1
Timiș	3	3
Tulcea	2	1
Vaslui	0	0
Vâlcea	0	1
Vrancea	2	2
Bucharest	9	8

The latest DRS report puts the proportion of XDR-TB cases among MDR-TB cases at 14.4%; in view of this, the approximate number (out of 960 registered patients) requiring treatment with new TB drugs (Bdq-containing regimen) should be 138 by the end of 2016. In fact, only 70 have been diagnosed with XDR-TB. Pre-XDR-TB patients with resistance to FQs would result in further patients being identified, and all of these would be candidates for therapy with new TB drugs. The underdiagnosis of XDR-TB cases seems to be due to the fact that not every case diagnosed with any resistance to R is being tested with DST to SLDs. Only 80 of these cases will receive therapy in 2017–2018 (through the GFATM grant). This estimate does not include an additional number of patients with pre-XDR-TB (MDR + FQ-resistance and MDR + SLI-resistance); nor those patients with MDR-TB who could benefit from access to new TB drugs (Bdq and Dlm) and other Group C core MDR-TB drugs (Lzd and Cfz).

Although it is improving, coverage with DST to SLDs is not complete, as not every R-resistant case has been tested with conventional DST to the remaining FLDs and all SLDs (see Section 9 below).

However, the arrival of new laboratory equipment (LPA and MGIT), as well as the creation of a functional laboratory network, will significantly increase coverage and provide true data on the number of patients with resistance to SLDs.

Previous shortages of SLDs – especially injectable agents and FQs – 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 SLDs through government funding and two external grants (GFATM and Norway Grant). Appropriate use of this funding guarantees that 1460 patients will have access to quality-assured SLDs by the end of 2018 (1002 patients have already been enrolled); and that 150 patients resistant to FQs will have access to new TB drugs (80 + 70 patients, respectively, with 80 patients already enrolled). The NTP hoped that it would be possible to get additional funding for new TB drugs from government sources in future (for 500 M/XDR-TB patients, through an EEA grant). Both the GFATM and the Norway grants served as catalysts for increasing access to new TB drugs; this allowed the NTP to work closely with the MoH to scale up access to new TB drugs and make the system sustainable (for more on treatment and drug procurement, see Sections 8 and 11 below).

Treatment outcomes of rGLC cohorts enrolled in the MDR-TB treatment programme in Rounds 2 and 6 of GFATM funding show comparatively good programme performance (Table 6). It also shows the ongoing enrolment of patients with external funding from the GFATM grant.

Table 6. Enrolment and treatment outcomes of rGLC-approved cohorts, 2004 to present

Cohort	No. 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 (68.2%)	37 (9.7%)	44 (11.5%)	3 (0.8%)	37 (9.7%)
Cohort 5 (GFATM NFM)[a]	327	17	238 (72.8%)	13 (4.0%)	21 (6.4%)	2 (0.6%)	36 (11.0%)
Cohort 6 (Norway Grant)	1002	869	11 (1.1%)	11 (1.1%)	16 (1.6%)	14 + 36[b]	45 (4.5%)
Cohort 7 (GFATM TFM)[c]	460	10	0	0	0	0	0
TOTAL	**2715**	**988**	**797**	**71**	**95**	**9**	**86**

[a] NFM = New Funding Mechanism.

[b] 14 excluded; 36 transferred out.

[c] TFM = Transitional Funding Mechanism.

Previously, Romania reported treatment outcomes for joint cohorts of rGLC and non-rGLC patients. The cohorts of patients were not similar, which seems not appropriate; the need to provide separate reporting was discussed with the NTP and recommended to consult the WHO Regional Office for Europe. Treatment outcomes for non-rGLC cohorts were extremely poor until significant changes in the drug procurement mechanism were made in 2015, when an almost complete range of SLDs became available countrywide. Similar to the situation in 2008 and 2009, analysis of the data from the 2010 cohort shows a treatment success rate of 20.0% (17.9% cured and 2.1% completed treatment), 17.1% died, 40.2% failed, 18.5% defaulted, and 4.2% were not evaluated, and include data for both GLC and non-GLC cohorts (Table 7). The total percentage of unfavourable outcomes reaches up to 80.0%. Similarly, treatment outcomes for 2011 show an extremely low treatment success rate of 16% and high rates of patients who failed therapy (39.6%) and died (22.1%). Poor treatment outcomes were the result of several factors, especially

delays in diagnosis and initiation of therapy (due to lack of access to rapid diagnostic methods) and lack of SLD to design adequate treatment regimens.

Table 7. Treatment outcomes for MDR-TB cohort (GLC and non-GLC), 2010, civilian and prison sectors

Registration group	Cured	Completed treatment	Died	Failed	Defaulted	Not evaluated[a]	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 Category II treatment	18	2	17	29	17	3	86
Other retreatment, or unknown retreatment[b]	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%**

[a] "Not evaluated" = total cases registered, minus the sum of all treatment outcomes. This category includes "transferred out", "still on treatment", and any other registered cases where the treatment outcome has not been evaluated.

[b] "Unknown retreatment" is a previously treated case but without information on the outcome of the previous treatment.

In the years leading up to 2015, the decentralized system of drug procurement and the fact that a full range of SLDs was not available to non-rGLC MDR-TB patients were the major factors contributing to the deteriorating situation with regard to DR-TB and the growth of the M/XDR-TB reservoir. Before the drug procurement system was reformed, the factors contributing to the growth of the DR-TB reservoir (defaults and failures) outweighed those influencing its decrease (patients cured, completing treatment, dying and transferring out). 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, the National Strategic Plan for TB Control in Romania, 2015–2020 (NSP) has now been endorsed, funding from the Romanian government has increased, and adequate funding from international donor sources is available. For all these reasons, the Romanian NTP should be in a position to bring about a rapid decline in the main TB indices – including DR-TB – over the next few years.

7. Coordination of the programme and financing

The Romanian Ministry of Health (MoH) is the main government body responsible for overall management, coordination and supervision of health programmes in the country, including TB. Implementation of TB control and prevention is performed through the NTP Central Unit, which is responsible for coordination, monitoring and supervision of programme activities in the 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. Budget allocations from the MoH to the Romanian NTP have increased from €3.3 million in 2014 to €6.7 million (this was reflected in the NSP, which had already been endorsed). The MoH supported the implementation of both the GFATM grant and the Norway Grant, and recognized the role of the Marius Nasta Pneumophysiology Institute (MNI) as the Central Unit for management of the NTP. Significant support was received from the MoH in endorsement of the

new decree which authorized the inclusion of all new TB drugs (except Bdq, which was already included) in the C2 list, making them eligible for further ordering and government funding.

The NTP Central Unit team received a mandate from the MoH to act as the official NTP control unit, but it still required improvement. The MoH supported the NTP Central Unit by empowering it 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 comprised a group of specialists, each responsible for a specific aspect of TB control. Earlier in 2015–2016, as part of the Norway Grant, the NTP units at county level were given MDR-TB coordinators, who were themselves regional specialists; they were made responsible for coordinating activities on PMDT in each county.

In 2015 the Romanian government endorsed the National Strategic Plan for TB Control in Romania, 2015–2020 (NSP), which sets forth the country's priorities in addressing the public health challenge of TB. The NSP was developed in close partnership with the MoH, the NTP and WHO, as well as other government and nongovernmental organizations. The NSP outlines national strategies to meet needs that are not currently satisfied and to build the sustainability of the system; it also presents a long-term vision and identifies innovative approaches targeted at achieving a dramatic decline in TB incidence and mortality in Romania by 2020. The document presents goals and objectives for the diagnosis, treatment and prevention of TB in the country. There are eight strategic objectives in the NSP, the aim of which is to bring about a sharp decline in TB incidence and mortality; these objectives include ensuring universal access to rapid diagnostic methods for TB and DR-TB; providing coverage with appropriate therapy for all diagnosed TB and DR-TB cases; and achieving high treatment success rates for both TB and DR-TB.

To ensure that these measures are effective, the NSP for 2015–2020 is based on three pillars and outlines a series of key intervention areas: (1) integrated patient-centred care and prevention; (2) bold policies and supportive systems; and (3) innovative research and evidence-based strategies. The National M/XDR-TB Response Plan has been successfully incorporated in the NSP for 2016–2020 and has a key role in implementing the programme across the country. The NSP's budget for 2015–2020 has been consolidated and includes funding from the Romanian government, the Norway Grant, the GFATM, the European Structural and Investment Funds, the World Bank and other organizations (€279 029 902). With the majority of funding coming from the government, the NSP serves a very important function in building the sustainability of the NTP in Romania. It is assumed that once new funding opportunities become available in the country, the NSP will be updated accordingly.

One of the major components of the NSP is to reform the financing of TB services with a view to reducing unnecessary hospitalization through implementation of ambulatory-based treatment of TB. This reform, supported by the new GFATM grant for 2015–2018, is to be implemented in six counties with a high burden of TB and MDR-TB. The reform includes revision of the financial mechanism by which health providers involved in TB control are reimbursed, reallocation of funds from inpatient to outpatient care, and establishing the required legal framework. It is expected that implementation of this reform will significantly reduce the cost of hospitalization for TB (by progressively reducing the number of hospitalizations for TB and MDR-TB) and lead to the development of alternatives to inpatient treatment.

In 2015 Romania received approval from the GFATM to implement an €8.4 million grant to fill gaps and address challenges in TB control in the country for the period from April 2015 to March 2018. The goal of the grant is to contribute to a reduction in TB incidence and mortality in Romania through high-impact interventions (in the areas of diagnosis, treatment, care and

prevention), with a special focus on key affected populations. The following objectives are defined:

- early and quality-assured TB diagnosis by strengthening TB laboratory capacity;
- implementation of patient-centred interventions in six high-burden counties of Romania;
- improvement of treatment outcomes for M/XDR-TB patients by provision of complete drug regimens and uninterrupted treatment; and
- strengthening of the national legal framework regulating TB control in Romania.

The grant application included five 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 added a separate component on TB–HIV coinfection, focused on diagnosing TB among HIV-infected individuals.

Under the new GFATM grant, the NTP has been able to ensure access to quality-assured SLDs, including new TB drugs, for 460 M/XDR-TB patients (80 on Bdq, 120 on Lzd, 120 on Cfz) and to scale up access to rapid molecular diagnosis of TB and DR-TB (Xpert MTB/RIF, LPA, MGIT 960). As it was for previous grants made by the GFATM, the Romanian Angel Appeal (RAA) foundation will act as the Principal Recipient of the new grant, in order to fulfil the country's obligations and achieve the indicators. In addition, the RAA will provide continuous assistance to the NTP Central Unit in implementing grant objectives and improving programme performance at all levels. A more detailed description of the activities associated with the new GFATM grant is given below in Sections 8–11.

In 2014 the Romanian NTP received approval from the Norwegian government for a €10.7 million grant, which was initially to extend over 20 months (August 2014–April 2016) and was then successfully extended until March 2017. The grant was focused on efforts to consolidate TB control activities, especially in relation to MDR-TB and poor and vulnerable populations. The MNI acted as the Principal Recipient of the grant and managed by the NTP Central Unit. The grant included 13 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 Norway Grant, it became possible to provide treatment for 1002 patients with M/XDR-TB, including 70 on new TB drugs, and to provide them with social support (for further details, see Section 8 below). Also significant investments were made to improve laboratory capacity and scale up access to rapid molecular diagnosis of TB and DR-TB; to create a functional network of eight regional reference laboratories (RRLs); and to invest in procurement of equipment to decrease the risk of nosocomial transmission of infection.

It was noted that there was a good level of collaboration with the WHO Regional Office for Europe, as well as with other international organizations and funds.

	Recommendation	**Responsibility**
1	Support the implementation of the National Strategic Plan for TB Control, 2015–2020 (NSP) and ensure sufficient and sustainable funding for implementation of the National TB Programme (NTP).	MoH
2	Support application for possible funding from external donor organizations (European Structural and Investment Funds – POCU).	MoH
3	Ensure that the delegated mandate of the NTP to operate as the central management unit is supported with adequate funding.	MoH

8. Treatment strategies and administration

Starting in 2016, the Romanian NTP introduced the use of new TB drugs under programmatic conditions. By the time of the visit, Romania had received 70 treatments with Bdq, Lzd and Cfz, including the cohort of six patients who started therapy under compassionate use (CU) conditions. Dlm was not available, but was considered by the NTP for treatment of M/XDR-TB with future donor or government funding.

With funding available from the Norway Grant (August 2014–April 2017), the NTP enrolled the first cohort of DR-TB patients on new TB drugs (100). Mostly with confirmed resistance to either FQs and/or SLIs, treatment regimens included the following drugs: Bdq (70, including seven on CU), Lzd (100), Cfz (45), and Imp-Cls + Amx-Clv (30). Forty-five regimens contained three drugs, Bdq–Lzd–Cfz, and specialists from the MNI considered it the backbone regimen for patients with XDR-TB. Dlm was not available and accordingly was not used for DR-TB treatment regimens. Enrolment targets for the Norway Grant were 1000 M/XDR-TB patients, including 100 on new TB drugs; this was achieved and completed in April 2017, when a total of 1002 M/XDR-TB patients had started therapy. Seven patients had already received Bdq and other companion drugs under the CU programme; all were considered cured. Within the GFATM grant (April 2015–March 2018), the enrolment target was 460 M/XDR-TB patients, including 80 patients to initiate therapy on new TB drugs (Bdq – 80; Lzd – 120; Cfz – 120). At the time of the mission, 10 patients with confirmed FQ-resistance had already started therapy on a Bdq-containing regimen, bringing the total of patients treated with Bdq in Romania to 80. Lzd and Cfz were considered core drugs for MDR-TB and assumed to be part of a conventional MDR-TB regimen when it is not possible to build a regimen with fewer than four effective drugs.

Treatment regimens for all DR-TB patients, including polydrug-resistant TB (PDR-TB) cases and those on new TB drugs, were designed by two national DR-TB committees (MNI and Bisericani TB Hospital). Each DR-TB committee was responsible for supervision of DR-TB control and prevention in 50% of the country and served as a national referral centre for DR-TB. Members of the DR-TB committees were trained in PMDT at international or local training sessions. The DR-TB committees ensured equal access to treatment regardless of the source of the drugs. The role of a DR-TB committee included discussion of the treatment strategy, regimen design, management of adverse reactions and serious adverse reactions, causality assessment, referrals between inpatient and outpatient settings, and outcome definition. Approaches to case definitions matched the WHO criteria (*Definitions and reporting framework for tuberculosis*, updated 2014) and were based on the site of the disease, prior treatment history, and type of drug resistance. Treatment regimens for DR-TB were standardized, with further individualization aimed at having the maximum number of effective drugs in the regimen. The presence of R-resistance, identified by rapid molecular diagnosis, or confirmed resistance to a minimum of H and R together, was identified as an indication for initiation of therapy with standardized or individualized regimen for MDR-TB, mostly designed in accordance with the WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* (2011 update).

Management of patients with DR-TB was performed in accordance with the National Methodological Guide on TB (2015), which included PMDT and served as the national protocol for both DS-TB and DR-TB. While the Guide was in alignment with the WHO 2011 *Guidelines for PMDT*, it had not been amended with the updated WHO 2016 recommendations, especially on the use of new TB drugs, however, it did not contradict the current WHO recommendations and approaches to DR-TB patient management and care. The Methodological Guide omitted minimum requirements for the use of new TB drugs, but it included necessary diagnostic algorithms, regimen design and treatment principles for DS-TB and DR-TB, protocols on side-effect management, and treatment forms. Treatment initiation for RR/MDR-TB cases with standardized

regimens became possible at the county level (through the county DR-TB coordinators); this involved delegation of decision-making to the lower level and was considered a significant achievement. Once registered for treatment, every case had to be submitted to a relevant national DR-TB committee for confirmation, so as for regimen change upon arrival of conventional DST.

All standardized MDR-TB regimens were based on DST and included at least four SLDs considered effective: a second-line injectable agent (aminoglycoside or Cm), fluoroquinolone (Lfx), prothionamide (Pto), Cs/PAS and pyrazinamide (Z), with maximum dosages according to the patient's weight and tolerance. Frequency of treatment was seven days a week in inpatient settings and five to six days a week in outpatient settings, regardless of the phase of treatment. Ethambutol (E) was used if shown susceptible by DST. Z was used during the entire therapy. For detailed information on management of RR/MDR-TB, please refer to the previous rGLC mission report, as the details have not changed. During 2016–2017, the majority of patients who were diagnosed with RR/MDR-TB were enrolled in a treatment programme within the Norway Grant, with a complete set of SLDs and new TB drugs only for those with confirmed XDR-TB (Km, Lfx, Pto, Cs, PAS, Lzd, Cfz and Bdq). Standardized regimens for RR/MDR-TB patients outside the rGLC cohort contained Am–Ofx–Pto–Cs–Z–E, with Mfx available for regimen reinforcement.

To ensure alignment of the NTP with the latest WHO recommendations and to scale up access to new TB drugs, the NTP developed a detailed Clinical Guide on the use of new TB drugs, which was mostly used by clinicians at the MNI. The new Clinical Guide was reviewed during the mission and found to be in alignment with the latest *WHO treatment guidelines for drug-resistant tuberculosis* (2016 update). The new Clinical Guide did not include the new grouping of TB drugs, but was based on the classification of TB drugs described in the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (2015). The new TB drugs – Bdq, Dlm, Lzd, Cfz and carbapenems – were all listed and presented as Group 5 agents in the national classification of TB drugs. The new document contained information on regimen design for DR-TB based on the 2015 grouping of TB drugs, dosages, and drug-to-drug interactions, especially with antiretroviral medicines; it also included a schedule of events for clinical monitoring, protocols on adverse event management, and required treatment and consent forms. Off-label use of the new TB drugs was described in a separate chapter. The new Clinical Guide did not contradict any of the latest WHO recommendations on the management of patients with DR-TB. The consultant's recommendation to the NTP was that the new Clinical Guide should be used at the DR-TB committee level only and that the National Methodological Guide on TB should be updated with the minimum information on treatment with new TB drugs and aDSM required at county level.

As described in the new Clinical Guide, the following categories of patients with DR-TB were eligible for treatment initiation with new TB drugs:

1. Patients for whom construction of a regimen with four probably effective SLDs (from Groups 2 to 4) including an FQ and an injectable is not possible:
   (a) XDR-TB (resistance to an FQ and at least one injectable);
   (b) pre-XDR-TB (resistance to an FQ or to at least one SLI, but not both);
   (c) patients with two or more Group 4 drugs (Eto/Pto, Cs, PAS) compromised;
   (d) contact with a patient with a strain with resistance pattern of (a), (b) or (c);
   (e) patients unable to tolerate MDR-TB drugs necessary for construction of the regimen (e.g. ototoxicity due to an injectable agent);
   (f) patients who are a "failure" on an MDR-TB regimen by WHO 2013 definitions.

2. Other patients who have a high risk of an unfavourable 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 an extensive SLD resistance background).

According to the new Clinical Guide, the factors taken into account when building the regimen with new TB drugs included: DST, history of previous use of FLDs and SLDs, information on contacts, co-morbid and pre-existing conditions, and information on adherence. All patients were required to have a sputum sample collected for second-line DST at the time of starting treatment with new TB drugs. The total number of Group 5 drugs in the regimen was influenced by the number of Group 4 drugs considered to be effective. The ultimate goal of the regimen with new TB drugs, especially for XDR-TB patients, was to have at least four probably effective SLDs in the regimen. Criteria for duration of the intensive phase and of the whole course of chemotherapy matched the WHO recommendations, with minimum duration of the intensive phase no less than eight months and minimum duration of the whole course of treatment no less than 20 months, for patients never previously treated for MDR-TB. Extension beyond 20 months was possible for previously treated patients with DR-TB and others with massive pulmonary destruction. Criteria for stopping the injectable agent were based on strong evidence of culture conversion – up to four consecutive negative cultures – and clinical response to treatment. There were no limitations on prolonging the duration of the intensive phase and the whole duration of treatment.

The new Clinical Guide regulated duration of the use of Bdq and Dlm at 24 weeks, with dosages and frequency described in the WHO interim policy guidance. Lzd was recommended for use throughout the entire course of therapy with 600 mg dose daily. Pyridoxine (50 mg daily) was included as accompaniment to Lzd, as prophylaxis against peripheral neuropathy. Cfz was available only within the GFATM or Norway Grant and was mostly used in combination with Bdq and Lzd in 100 mg daily dose over the entire course of treatment, mostly for patients with confirmed resistance to FQ (XDR-TB and pre-XDR-TB), as stipulated by the new Clinical Guide. No plans had been drawn up by the NTP to introduce the shorter treatment regimen (STR) for MDR-TB, and Cfz was available only for conventional M/XDR-TB individualized regimens. Imp-Cls was included in the new Clinical Guide, but there were no plans to use any of the grants to purchase it; when it became available, it was supposed to be used for patients with severe DR-TB as a reinforcing agent, 1000 mg twice daily for seven days week. The NTP was aware of the complex administration of Imp-Cls, which requires twice daily infusions, each 40–60 minutes long, and frequent access to central veins with implantable access systems, such as portacath. Amx-Clv will be added to regimens including Imp-Cls (carbapenem). Dosing of Amx-Clv was based on the clavulanic acid component: 125 mg 30 minutes orally before IV infusion of Imp-Cls. Off-label use of the medicines – according to the 2016 WHO guidelines, extended use of Bdq or Dlm, concomitant use of Bdq and Dlm, use of new drugs in patients under 18 years of age, during pregnancy or lactation – had not previously been done in Romania, but it was possible by decision of the DR-TB committees, according to the new Clinical Guide.

There is a desperate need for new TB and companion drugs in Romania, as the current options for management of patients with DR-TB, especially those suffering from pre-XDR-TB and XDR-TB, are still limited. Compared to previous missions, access to new TB drugs has significantly improved,

but national scale-up is required, as a sufficient level of institutional and infrastructural capacity exists in both the national and the county-level TB programmes. Treatment initiation with new TB drugs was possible only at the level of the two national DR-TB centres – the MNI and Bisericani TB Hospital – with outpatient treatment following discharge continued under the supervision of the county TB coordinators. There were several reports of patients who, for various reasons, refused to be hospitalized for initiation of therapy with new TB drugs at either of the national DR-TB centres; thus they remained either untreated or on therapy with a weak regimen. Following the example of decentralizing initiation of therapy with standardized longer regimens for RR/MDR-TB, the NTP should consider strengthening the capacity of some regional TB hospitals to initiate therapy with new TB drugs.

The requirements for clinical monitoring of MDR-TB therapy were clear and included routine performance of bacteriological and clinical investigations, as required by the National Methodological Guide on TB. The recommendation made by the previous mission to introduce aDSM for patients on new TB drugs had been partially completed. The NTP team performed a retrospective analysis of the first 44 patients who started therapy with a Bdq-containing regimen at the MNI in 2015–2016. The retrospective research showed that monitoring of patients on new TB drugs had been performed regularly, with capture of values associated with the most common adverse events: blood tests (RBC, platelets), ECG (HR and QT), liver and kidney function tests. Some of the baseline screening and follow-up monitoring tests have not been performed, but are included as mandatory tests in the new Clinical Guide on the use of new TB drugs. Common Terminology Criteria for Adverse Events (CTCAE) (version 4.0, published 2009 by US Department of Health and Human Services) was used to provide descriptive terminology for adverse event (AE) reporting, with a grading (severity) scale provided for each AE.

For clinical examinations available at the national MDR-TB centre at the MNI, there was a minimum requirement for aDSM for patients on therapy with new TB drugs; the examinations included general blood and urine tests, biochemical analysis (bilirubin, LFT, urea, uric acid, electrolytes, creatinine, glucose), chest radiography and ECG. Baseline and follow-up screening for peripheral neuropathy, visual acuity and colour-blindness were not performed, but they were part of the new Clinical Guide on the use of new TB drugs. At the MDR-TB centre at the MNI, all patients with Lzd in their regimen were given pyridoxine (Vitamin B6) to decrease the risk of peripheral neuropathy. There was a state system of pharmacovigilance (PV) present but it was not mandatory. Thus, it was recommended that, in addition to routine monitoring requirements, the NTP should introduce active recording and reporting (R&R) of serious adverse reactions to the National PV Unit.

Management of adverse reactions requires improvement and should be supported by increased knowledge on the part of doctors and nurses, and there should also be an adequate supply of ancillary medicines. The PV system was in place as 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. Recording of any adverse reaction in the course of therapy, including TB care, is encouraged by the government point system, which is used for future accreditation of physicians. The PV system was monitored by the MoH by performing a causality assessment of every single serious adverse event, which decreased the chances of false reporting. Such approaches to aDSM are essential when the NTP is expanding access to new TB drugs. A full range of clinical monitoring techniques was not performed at the outpatient settings visited, and varied from county to county. It was discussed with the NTP that a standard set of documents and forms should be prepared for outpatient settings, which county TB coordinators would receive prior to discharge of a patient from an inpatient facility. This would ensure proper implementation of clinical monitoring and aDSM requirements.

Outpatient facilities

Extensive infrastructure (93 TB hospitals, sanatoria and TB units), with a capacity of 5625 TB beds, has made inpatient treatment available throughout the country. As noted earlier, once evidence of strong clinical and bacteriological response to therapy had been found, patients with DR-TB, including those on new TB drugs, were discharged from DR-TB centres and referred for further treatment at TB dispensaries. It was also noted above that treatment of RR cases was initiated at regional-level facilities. Duration of hospitalization for MDR-TB patients was still regulated by the National Insurance House (NIH) and was, on average, around three months countrywide, including at the MDR-TB centres in Bucharest and Bisericani. Patients were usually discharged from MDR-TB centres during the intensive phase, once the first negative culture result had arrived. The existing financing of TB hospitals based on bed occupancy incentivizes them to keep patients as inpatients (see Section 10 below).

Options for directly observed therapy (DOT) during ambulatory treatment were still limited, with patients actively coming to TB dispensaries and PHC clinics for treatment. The PHC clinics and TB dispensaries offered DOT on weekdays, with Saturday treatment mostly self-administered. Treatment during the continuation phase was delegated to PHC services, but absence of financial incentives from the MoH meant that family doctors were not motivated or interested in providing strict DOT for TB and DR-TB patients. Options for a patient-centred approach and use of hospital-replacement mechanisms, such as home-based treatment or video-observed therapy (VOT), were still very limited as a result of insufficient capacity and management. Vehicles were available at most TB dispensaries, but there were restrictions on purchase of fuel (100 litres a month). Home patronage nurses were not available, while lack of financial incentives and absence of transportation (or reimbursement for it) also meant that nurses from PHC services were not motivated to perform daily DOT. Social support was also lacking and restricted to salary disability allowance for those patients who were employed prior to the start of treatment. In the case of the unemployed or homeless, no social support or transportation reimbursement was available from government sources. Another option considered by TB doctors was to delegate responsibilities for DOT to trustworthy family members, but this clearly offered no guarantee of quality.

In summary, the recently approved NSP for 2015–2020 has reform of ambulatory care as one of its major components, with the overall goal of reducing unnecessary hospitalization. Reform will start under the new GFATM grant in six pilot counties with a high burden of TB and DR-TB, with the ultimate aim of disseminating experience gained in these regions countrywide. With the arrival of new funding from the GFATM and Norway Grant, it has become possible to strengthen ambulatory care. Within the GFATM grant, six multidisciplinary teams (including one doctor, one psychologist and one social worker) were set up and placed in TB hospitals, with the principal task of assessing and referring TB patients to the ambulatory sector. The target group was identified as patients who have more than four months until the end of treatment. Such multidisciplinary teams were created in Neamț, Argeș, Maramureș, Constanța, Dolj counties and Bucharest. In addition to this, DOT and social support vouchers were organized in most counties for MDR-TB patients enrolled in the GFATM project. Activities within the GFATM grant will also focus on developing the national policy documents aimed at strengthening outpatient treatment of TB and reducing unnecessary hospitalization. The grant will allow the existing laws and reimbursement practices that contribute to hospitalization to be reviewed 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 centres for treatment and care of socially disadvantaged TB and M/XDR-TB patients during their course of treatment.

One of the main objectives of the Norway Grant was to develop an integrated model of support for TB treatment and prevention at community level among poor and vulnerable groups. Thus,

patients enrolled within the Norway Grant from poor communities, including the Roma population, received DOT and social support during the outpatient stage of therapy. Community health providers (health mediators and community nurses) performed DOT.

	Recommendation	Responsibility
1	Consider updating the National Methodological Guide on TB (2015) with the latest WHO *Guidelines for treatment of drug-susceptible tuberculosis and patient care* (2017 update), especially: "In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug-susceptibility testing should be conducted to inform the choice of treatment regimen."	NTP
2	Consider updating the National Methodological Guide on TB (2015) with the latest WHO recommendations highlighted in the new Clinical Guide on the use of new TB drugs in Romania (2016) and submit to the National Commission of Pneumology for endorsement.	NTP
3	DR-TB Central Committee should finalize and systematize the standard set of documents to be used for referral of a patient on new TB drugs when discharged from MDR-TB centres for treatment continuation.	NTP
4	Dlm may be added to the WHO-recommended longer regimen in children and adolescents (6–17 years).	NTP
5	Introduce and implement the main aspects of active drug safety monitoring and management (aDSM) as part of a scaling-up of access to new TB drugs. Ensure implementation of the minimum requirements for laboratory diagnosis in outpatient settings as required by the new Clinical Guide on the use of new TB drugs.	NTP
6	Consider collaborating with the SRL on DST to new TB drugs. Consider (i) storing in laboratory refrigerators samples of positive cultures from baseline until culture conversion for patients on therapy with new TB drugs; or (ii) sending samples to SRL for DST. This will facilitate understanding of the trends of amplification of drug resistance.	NTP
7	Prepare a plan for step-by-step training on the new national DR-TB guidelines, first including counties with larger numbers of patients on new TB drugs. Strengthen the capacity of the county-level teams to manage patients on new TB drugs. Consider rotation of doctors from counties in Bucharest – building capacity and institutional memory (not on personal time of county-level doctors, formally approved and funded by the MoH).	NTP
8	Define the responsibilities for all levels of patient care and management and map the flow of recording and reporting (R&R) forms: • DR-TB Central Committee • pneumologist • primary health care (PHC) doctor • DOT provider/community health worker • patient • multidisciplinary team (their responsibilities should be mapped and	NTP

	focused on supervisory work rather than covering the work of doctors and DOT providers).	
9	Consider using modern technology to enhance programme monitoring and evaluation (M&E), between national and county levels, at county level and between counties (regional level): Skype video conferences, WhatsApp, Viber, etc.	NTP
10	Consider clinical in-site training/rotation of county TB coordinators in MDR-TB centres in Bucharest and Bisericani, as part of capacity-building measures to increase knowledge of the use of new TB drugs. Funding of rotation should be considered from either national or county-level budgets.	MoH NTP
11	Ensure daily directly observed therapy (DOT) of patients, in particular those who receive treatment with new TB drugs, especially Dlm, Lzd, Cfz and carbapenems.	NTP
12	Video-observed therapy (VOT) may replace DOT when video communication technology is available and can be appropriately organized and operated by health care providers and patients. VOT is needed to decrease the level of self-administration of TB and DR-TB treatment.	NTP

9. TB laboratories

Coordination of activities at national level has been performed by the Laboratory Working Group (LWG), which is nominated annually by the MoH; the LWG has the option of performing regular monitoring visits to county-level laboratories at least once a year. The NTP laboratory coordinator is based in the national reference laboratory (NRL) in Cluj-Napoca. Following reorganization of the laboratory network, two grants have made supervisory visits by the LWG possible; they have not been performed on a regular basis, however, and only occur during personal vacation time of LWG members. It is highly recommended to the MoH to make a commitment and ensure that, if a clear mandate is granted to the LWG, supervisory monitoring visits happen on a regular basis, with the financial support of the government.

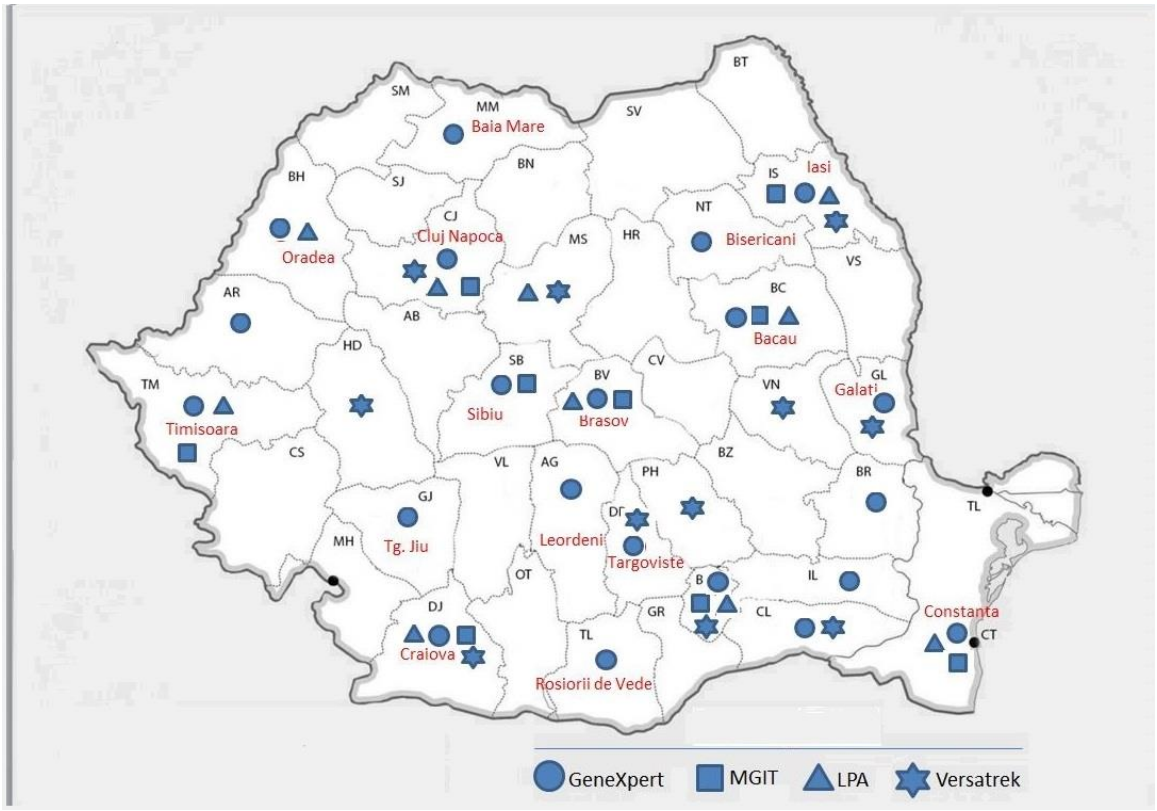
Structurally, the laboratory network remains unchanged, but it underwent a process of reorganization and strengthening to improve access to rapid molecular diagnosis of drug resistance, with financial support from the GFATM and the Norway Grant. Reorganization was considered one of the objectives of the National Strategic Plan for TB for 2015–2020 (NSP), which was endorsed by the Romanian government in March 2015. The NTP has taken huge forward steps in establishing a functional laboratory network with the purpose of improving access to rapid molecular diagnosis of TB and drug resistance. Strengthening the laboratory network was made possible by strong political support from the MoH and funding available from the GFATM and Norway Grant.

Having undergone strengthening and reorganization over the past few years, the laboratory network now consists of 170 laboratories across Romania. There are 14 Level 1 laboratories for sputum smear microscopy only; 40 Level 2 laboratories performing sputum smear microscopy and culture; 43 Level 3 laboratories performing sputum smear microscopy, culture and DST to FLDs (short-line DST to H and R); and two NRLs performing DST to FLDs and SLDs (the MNI in Bucharest and Cluj-Napoca). Reorganization was in progress with the goal to create a wide but functional

laboratory network: two NRLs and six regional reference laboratories (RRLs) to serve as reference centres for eight geographical regions. It is expected that reorganization will significantly improve access to rapid diagnosis of TB and RR, as well as DST to SLDs. Selection of RRLs had been made on the basis of 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 transportation of samples from counties to RRLs, as well as supervision and monitoring of laboratory performance (within the Norway Grant, nine vehicles have already been purchased).

Coverage with DST to FLDs and SLDs has improved as a result of increased availability and access to rapid molecular diagnosis of TB and DR-TB (Xpert MTB/RIF and LPA). The current laboratory capacity includes 21 GeneXpert MTB/RIF machines, 10 LPA MTBDR*plus* complexes, nine BACTEC MGIT 960 complexes and 10 VersaTREK machines (Fig. 1).

Figure 1. Distribution of rapid molecular and liquid media systems in Romania, 2017



While the majority of Level 3 laboratories in the counties still perform short-line DST to FLDs using solid media, the already ongoing reorganization of laboratory infrastructure had significantly increased access to rapid molecular diagnosis of TB and drug resistance, and hence timely initiation of therapy. With adequate financing coming from external funding, the Romanian NTP had sufficient coverage with rapid DST to FLDs, which improved early diagnosis of R- or HR-resistant cases: a total of 15 000 DST to HR using LPA equipment and 34 100 tests using Xpert MTB/RIF beyond 2018. Geographically, all regions of Romania, including those with a high burden of TB and DR-TB, had access to a full range of diagnosis of TB and DR-TB, including rapid molecular diagnosis of R-resistance and second-line LPA. Both grants served as catalysts to scale up access to rapid diagnosis of TB and R-resistance, and brought substantial financial investment into improvement of laboratory infrastructure, performance and biosafety. Forty-two biosafety cabinets were procured with the Norway Grant, to ensure laboratory biosecurity and meet the international requirements for biosafety.

GeneXpert

Access to Xpert MTB/RIF became available across the country in 2014; it was purchased with donor funding and leased from Cepheid with the obligation to perform no less than 100 tests a month (Bacău and Călărași). Fourteen Xpert MTB/RIF four-module machines were planned for procurement after 2015, with funding available from the GFATM (six machines to be procured, 5500 tests already performed) and the Norway Grant (eight machines to perform 28 600 tests, already partially performed, in Cluj, Iași, Constanța, Dolj, Timișoara, Brașov, Argeș and Maramureș counties). Xpert modules were installed in counties with a high burden of DR-TB and HIV, as well as in the NRLs. Two four-module machines were already available at the NRL in Bucharest (one is due to be procured in December 2017) and one in Bisericani (Neamț county). No shortages of cartridges were found in laboratories visited. The available stock at NRL in Bucharest was 500 cartridges with expiry date in August 2017, 350 in January 2018, 2180 in May 2018, and 950 in February 2018. The last shipment of cartridges arrived in March 2017, and the available stock will be used at the NRL in Bucharest (around 3000 cartridges, with the rest to be distributed between the counties). In 2016 the government approved the budget for procurement of TB consumables, which will require the MoH to issue a decree on centralized procurement and allow purchase of Xpert cartridges according to the request made by the NTP laboratory coordinator (a minimum of 20 000 and maximum of 45 000 cartridges per year). Starting in 2018, procurement of Xpert cartridges will be fully paid for with funding allocated by the MoH to the NTP. A total of 13 367 GeneXpert tests were performed in 2016 (3273 in 2015), according to the new diagnostic algorithm, which was developed with support from the SRL and included in the National Laboratory Guidelines.

LPA

Supported by external donor funding, the NTP was scaling up access to rapid diagnosis of drug resistance to FLDs and SLDs using the line probe assay (LPA). A total of 10 LPA systems were available in Romania, with two automatic Genotype machines recently procured within the Norway Grant and two within the GFATM grant. LPA machines were already functioning in two NRLs (Bucharest and Bisericani) performing MTBDR*plus* and MTBDR*sl*, and there were five in Level 3 RRLs in Brașov, Constanța, Timișoara, Bacău and Iași, for MTBDR*plus* only. Training for laboratory specialists was conducted with support from the European Centre for Disease Prevention and Control and the WHO Regional Office for Europe. Heads of NRLs were trained at the SRL in Stockholm and finalized the diagnostic algorithm for LPA. Within the GFATM grant, the NTP was planning to perform over 5000 DST to FLDs and 1000 DST to SLDs within a three-year period. Within the Norway Grant, the NTP was planning to perform 10 000 DST to HR at new Level 3 laboratories in Iași and Constanța to cover the eastern part of Romania. However, the planned 600 DST to SLDs (IQE) on LPA were only available at two NRLs (Bucharest and Cluj-Napoca), which were serving as referral centres for the whole country, thereby limiting access to diagnosis of resistance to SLDs. A total of 3379 DST to FLDs were performed in 2016, and 276 DST to SLDs, which was little changed from 2015. As in the previous year, DST to SLDs with LPA required scale-up by improving transportation of samples for testing and monitoring implementation of the updated diagnostic algorithm.

Conventional DST to FLDs and SLDs on liquid media

Access to conventional DST to FLDs and SLDs on liquid media had improved since the last rGLC mission. Two NRLs (Bucharest and Cluj-Napoca, north and south) were performing quality assurance, and to ensure geographical accessibility, each served as a reference laboratory for DST to SLDs for half of the country – which seemed insufficient, given the country's needs for this kind of testing. BACTEC MGIT 960 systems had been purchased with external funding and installed at two NRLs and several RRLs (Iași, Constanța, Timișoara, Bacău, Craiova, Brașov, Sibiu and Leorden). The automated systems in RRLs were performing only culture testing on liquid media and DST to

FLDs including Z, but those in NRLs were also performing DST to SLDs. DST on MGIT 960 was 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) and S (1.0), with results available after three to four weeks. At the same time, both NRLs and RRLs were performing DST on solid media to 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 they were carrying out repeat testing on automated liquid media systems (MGIT or VersaTREK). According to the diagnostic algorithm, DST to SLDs was performed only in cases with confirmed resistance to R and only upon a physician's request. Usually DST results were reported back to clinicians on the same day. Previous recommendations – to initiate a standardized MDR-TB regimen for all cases with diagnosed R- or HR-resistance until arrival of conventional DST to other FLDs and SLDs – had been carried out and introduced into routine practice.

Funding available from the GFATM and Norway Grant allowed the NTP to perform 5000 culture tests, 2000 DST to FLDs and 1000 to SLDs (GFATM); and 19 250 liquid culture tests, 10 700 DST to FLDs and 1350 DST to SLDs (Norway Grant) during 2015–2018. As well as MGIT 960, the NTP received three VersaTREK systems for liquid DST to FLDs (HRESZ), which were installed in the Craiova, Constanța, Coloraj or Leorden laboratories (in addition to the NRL in Bucharest). The choice of location for installation was based on geographical coverage, proximity to other counties and laboratory capacity (space, availability of biosafety cabinets, human resources and workload based on the burden of disease). It was assumed that availability of VersaTREK modules would improve time for confirmation of culture results (up to 14 days) and DST (up to one week), as well as ensuring 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. External quality control (EQC) for DST to FLDs and SLDs was performed by both NRLs. A total of 24 427 tests on liquid media was performed in 2016, which was higher than in earlier years (17 835 in 2015 and 3988 in 2014).

The Swedish Institute for Infectious Disease Control served as SRL for Romania and provided continuous technical assistance to laboratory services on DST, laboratory infection control, EQA and drug resistance surveys (DRS) (2008–2009 and 2014–2015). The SRL provided assistance in methodology and capacity-building of laboratory personnel, as well as helping with development of the protocol for rapid molecular DST. The most recent DRS took place between March 2014 and March 2015 with three laboratories participating: the NRLs in Bucharest and Cluj-Napoca and the Level 3 laboratory in Bisericani. DST was performed using the absolute concentration method to H, R, S and E; and using the proportion method to H, R, Ofx, Km, Am and Cm on solid media, as well as LPA. The survey was based on pulmonary smear-positive cases (the estimated number of new cases was 1520), with countrywide coverage of cluster-sampling. For the DRS, selected counties (50 clusters, including 41 counties and three from Bucharest) were supposed to submit 35 smear-positive samples from new cases and 35 smear-positive samples from relapses and retreatment cases. The survey was completed on 31 March 2015; the results are presented in Annex 3. None of the laboratories were performing DST to either the new TB drug and repurposed companion drugs used in the programme: Bdq, Lzd, Cfz, Imp-Cls.

	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 LPA in geographically representative regional laboratories (ongoing recommendation).	NTP

2	Consider revision of the laboratory reorganization plan based on TB burden, capacity and infrastructure (roads) in counties, to ensure universal and uninterrupted access to rapid molecular diagnosis of TB and DR-TB.	NTP
3	Ensure universal coverage of DST to SLDs (at least an injectable agent and FQ) to all RR/MDR-TB cases, especially in high-burden counties using rapid molecular diagnosis testing (LPA) or liquid media systems (MGIT).	NTP
4	Ensure uninterrupted and sufficient funding of consumables and reagents for rapid molecular and liquid conventional DST after the end of external donor funding.	MoH
5	Monitor the implementation of TB and DR-TB diagnostic algorithms at county level to ensure timely use of rapid molecular testing for TB and DR-TB.	NTP

10. TB infection control

During previous missions, the risk of TB transmission was high in most inpatient facilities, especially DR-TB wards, as a result of a lack of infection control (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 SLDs. The risk of transmission differed from one facility to another and was related to the availability and access to rapid molecular diagnosis, the administrative measures in place (number and type of patients hospitalized, length of hospitalization, measures for separating patients), and development of the ambulatory care sector. TB laboratories had 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 in outpatient settings was lower than in inpatient facilities as a result of excessive hospitalization, delays in diagnosis of drug resistance, poor IC measures and delays in treatment initiation. Often, extension of hospitalization resulted from social problems (homelessness, poor social status of patients, and the need for symptomatic therapy).

Improving IC was one of the priorities of the NTP in Romania and one of the key interventions in the recently approved National Strategic Plan (Intervention 2.5: “Establish IC standards and requirements for health care 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 included information on all relevant components of IC: 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. The document would serve as a guide for all TB institutions in Romania to develop and introduce IC plans.

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 5625 TB beds countrywide. In 2015–2016, 11

TB dispensaries were closed to streamline administrative costs. The number of TB dispensaries and TB hospitals varies from county to county, but almost every county has at least one TB ambulatory care facility and access to one TB hospital or TB laboratory. The Marius Nasta Pneumophysiology Institute (MNI) in Bucharest is the leading institution in the country on TB control and serves as headquarters for the NTP Central Unit; it is one of two MDR-TB centres in Romania. The other MDR-TB centre is based in Bisericani TB hospital and has 70 TB beds. Annual bed occupancy is 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 DS-TB and DR-TB. The duration of hospital stay was regulated for DS-TB and DR-TB, with patients getting referred for treatment continuation to the ambulatory sector, which was mostly performed by TB dispensaries and PHC facilities. The MoH has plans to organize eight regional MDR-TB centres in eight other historic locations of Romania: Brad (Hunedoara county), Valea Iașului (Argeș county), Moroieni (Prahova county), Năruja (Vrancea county), Leamna (Dolj county), Drajna (Prahova county), Bixad (Satu Mare county) and Agigea (Constanța county). The GFATM is supporting the renovation of some of the centres, including the MNI and Laemna TB hospital.

Since 2013 the NTP has been using a comprehensive tool to provide background information on current IC measures performed in a facility, with clear instructions for improvement. The template contains information on management of IC, M&E and budget tools. Each facility has been asked to develop and implement its own IC plan. Using the tool, the NTP has 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.

As in previous rGLC missions, it was witnessed that there were several positive improvements in IC in the majority of TB inpatient facilities. IC plans were available from almost every TB inpatient facility, but had not yet been implemented, pending a national decree regulating the national guidelines on IC and availability of funding. Fourteen TB institutions with extremely high risk of nosocomial transmission, including two leading MDR-TB centres in Bucharest and Bisericani, were identified during the assessment. The MDR-TB ward at the MNI had recently been renovated with GFATM grant funding. Some institutions, such as the TB hospital in Laemna (which was first visited by the rGLC in 2012, then in 2015, 2016 and 2017), 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 centres for hospitalization of vulnerable and homeless patients who require continuation of therapy in an inpatient facility. Laemna TB hospital will serve as an inpatient referral facility for MDR-TB for several counties in the southern region of Romania, which has a high TB burden. The renovation of one wing of the Laemna hospital has been completed, with ultraviolet germicidal irradiation (UVGI) lamps due to be installed in summer 2017. It was unclear whether renovation of other high-risk TB inpatient facilities is possible because of a lack of financial resources.

Aside from the GFATM funding, the NTP is committed to improving IC measures in the majority of inpatient facilities involved in TB control through additional external and existing government funding. Given the current availability of funding, early diagnosis of TB cases and separation of patients according to drug resistance patterns seem to be the measures with the most potential. Within external donor funding, the NTP has procured 2000 UVGI lamps, which were installed in 49 institutions across Romania. The lamps were modern, user-friendly and recommended for use in institutions involved in TB control by an international consultant on IC.

Figure 2. Upper-level ultraviolet germicidal lamp (UVGI)

In addition, the NTP has identified 20 national coordinators on TB infection control – medical personnel from county-level TB facilities trained to implement the National IC Plan across the country. Two IC coordinators have an engineering background and were selected to perform monitoring of the installation and maintenance of UVGI lamps and ventilation across the country. The majority of specialists involved in TB control have been trained in the basics of IC at TB facilities, in accordance with the National IC Plan. One of the objectives of the GFATM grant was to improve the national policy on outpatient treatment of TB and to reduce unnecessary hospitalization, which was done in 2016 in accord with National Law 861 on community care. Within the grant it became possible to review existing legislation and reimbursement practices contributing to unnecessary hospitalization, and different models of ambulatory care were studied. Protocols and guidelines for outpatient and inpatient treatment will be developed, 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 measures problematic. The scheduled installation of UVGIs was not regulated by any of the national standards but carried out on the basis of international recommendations only. Thus, there is a need to urgently endorse the updated version of the National IC Plan in Romania and ensure adequate financing of IC activities. Furthermore, the MoH should introduce TB IC measures in diagnostic and treatment facilities and in crowded settings by revising the MoH's Order No. 916 (26 July 2006) and the current system of health facility accreditation, including specific measures for the prevention of airborne TB transmission.

There was some progress in completing the recommendations arising from the previous rGLC mission. However, some of the recommendations remain technically incomplete as

implementation is ongoing. There continue to be many causes of infection transmission, including the low treatment success rate among MDR-TB patients, suboptimal treatment regimens due to unavailability of a full range of SLDs, incomplete coverage with DST to SLDs, questionable DOT, excessive hospitalization, and poor separation of patients by smear/DST status. 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 in rapid diagnosis of TB and DR-TB (LPA and GeneXpert) and to increase access to rapid DST have been completed with the arrival of international donor funding (GFATM and Norway Grant); and there is now access to a full range of quality-assured SLDs. Similarly, the installation of upper-level UVGI lamps within the Norway Grant at inpatient facilities and ambulatory settings at high risk of infection transmission will bring a positive impact in reducing the burden of TB and DR-TB. A decrease in the number of TB hospital beds in facilities that do not meet IC standards might not be a bad solution, considering the existing approach to hospital financing. The plan to reform the hospital health financing system, with funds reallocated to strengthening service delivery in outpatient settings, was ongoing and seen as an improvement. The WHO Regional Office for Europe provided technical assistance in conducting an assessment of the existing financing system for TB services, including excessive hospitalization of TB patients.

	Recommendation	**Responsibility**
1	Endorse the updated version of the National Infection Control Plan in Romania and ensure adequate financing of IC measures.	MoH
2	Revise the existing legislative base regulating health facility accreditation and prevention of TB transmission; to include appropriate IC measures at all health care 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	Expand and routinely implement the F-A-S-T strategy/approach across all health institutions involved in TB control – to find cases actively, safely separate 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 (ongoing recommendation).	NTP
5	Ensure allocation of adequate funding for personal protection measures for health and administrative personnel at all treatment sites involved in the management of TB and DR-TB (ongoing recommendation).	NTP

11. Second-line drug management

Since 2013 the drug procurement system for TB has been centralized with a system of national tenders. Financing of drug procurement is performed by the MoH, which serves as a single funding source. National tenders usually happen once a year and are organized according to the list of essential medicines (TB component of the C2 list). The centralized tender at national level has led to a fall in prices for most TB medicines.

The C2 list has not been officially revised/changed as previously recommended by the rGLC and Global Drug Facility (GDF), but the NTP submitted a request to the MoH that drugs recommended by WHO be included in the list. On 4 May 2017, the MoH signed a decree which allowed use of medicines recommended by WHO as effective against MTB and its drug-resistant strains and authorized their inclusion in the C2 list. Once included, these drugs will be eligible for further funding from the MoH and available for use according to the national protocol: Lfx, Mfx, Cm and PAS, as well as other Group C and D2 drugs (Lzd, Cfz, Bdq, Dlm and Imp-Cls). Even if they are not registered in Romania, medicines such as Dlm can be used for therapy of DR-TB, as per the latest WHO recommendations, and can be legally procured by the government. Ciprofloxacin was excluded from the national tender, which made it impossible to purchase and use in TB therapy. This development is considered a significant move towards acceptance of WHO recommendations for management of DR-TB and scaling-up of universal access to new TB drugs across Romania. Also, the new decree will facilitate import and use of Cfz and Dlm, alongside Bdq and Lzd, within the GFATM grant or any other future funding.

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; absence of an effective centralized system for monitoring of orders, consumption and stocks of medicines; lack of flexibility in budget allocation and access to medication; lack of legislative provisions to allow 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 have to place orders and pay for TB medicines from their own budgets. Coordination between the NTP and TB facilities that were responsible for drug purchasing in counties still requires improvement. The NTP is aware of funding allocated by the MoH for TB medicines, but lacks information on drug orders and consumption in the counties. The NTP should have sufficient authority to monitor drug consumption at county level on a regular basis. There is still no unified electronic information system available at the level of the NTP for FLD and SLD management, and there is no system to monitor and track actual consumption of TB drugs. Thus, estimates of requirements and forecasting of national procurement appear to be approximate and hence suboptimal. According to the NTP, the software was developed for county-level pharmacies to place and track orders of certain quantities of TB drugs. Thus, the recommendation to the NTP that it should consider using one of the WHO-recommended tools for quantification and forecasting, such as QuanTB, is up for consideration but not mandatory.

The mechanism of distributing medicines to the counties requires significant improvement, such as identifying selected distributing companies responsible for timely delivery of drugs to the counties to avoid stock-outs and treatment interruptions. There is a need for the NTP to make recommendations to the MoH on improving the conditions of the national tender to avoid stock-outs and hence treatment interruptions.

As noted earlier, the GFATM grant to Romania for the three years starting April 2015 was €8.4 million. Under this grant, there are plans to ensure access to therapy with quality-assured SLDs for 460 M/XDR-TB patients through the GDF mechanism, including 80 patients with access to

new TB drugs. With funding from the Norwegian government of a total of €10.7 million, the Romanian NTP finished enrolment of 1002 patients with M/XDR-TB in April 2017 (after 32 months of grant implementation). Seventy patients, including six on the compassionate use (CU) programme, have been enrolled on therapy with new TB drugs (see Section 8 above). Drug orders to the GDF have been placed by the Romanian Angel Appeal (RAA), the Principal Recipient of the GFATM grant, the MNI or the Principal Recipient of the Norway Grant and cleared by the rGLC of the WHO Regional Office for Europe. Drug requests for both grants combined include M/XDR-TB treatment regimens and the number of patients to be enrolled during the calendar year. The last drug order for the joint cohort was received in September 2016. No significant shortages of drugs have been noted. 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 an injectable agent, but not both) and XDR-TB. Regimens for pre-XDR-TB and XDR-TB included Mfx, Lzd, Cfz, Imp-Cls and Bdq, but not Dlm. Even with the end of the Norway Grant, enrolment of patients for treatment with new TB drugs will continue, with 70 more patients due to be enrolled within the GFATM grant (10 have already started therapy).

	Recommendation	**Responsibility**
1	Calculate the actual needs for the new TB drugs, taking into account the eligibility criteria described in the National Clinical Guide on the use of new TB drugs. This measure is required to scale up access to the new TB drugs for a larger cohort of patients. Consider technical assistance from the WHO Regional Office for Europe or Global Drug Facility (GDF).	NTP
2	Ensure adequate funding and uninterrupted supply/procurement of FLDs and SLDs, including new TB drugs recommended for treatment of M/XDR-TB.	MoH
3	Ensure fast update and inclusion of the following drugs in the C2 list, according to the National Clinical Guide for MDR-TB: Bdq, Dlm, Cfz, Lzd, Imp-Cls, Amx-Clv, Mfx, Cm, Km, Lfx and PAS.	MoH
4	Revise conditions of the national tender to avoid possible stock-outs of TB medicines (ongoing recommendation).	MoH
5	Finalize the development of an electronic system specifically designed for drug management.	NTP

12. Information system and data management

The national recording and reporting (R&R) system is in line with WHO requirements. Data collection is 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 the MNI (Bucharest). Information is collected from TB institutions (hospitals and dispensaries) in the counties. TB surveillance is regulated and has been endorsed by the MoH as mandatory for all institutions involved in the TB programme. TB surveillance software is functioning at all TB dispensaries, with all cases registered at county level and then reported to the NTP (at national level). The information data flow has three levels: data are collected at TB clinics (primary level); compiled for the county by the TB coordinator and epidemiologist at county level (secondary level); then referred to the MNI (NTP coordinator)

(tertiary level). The current version of software still requires improvement so that it can aggregate cohort data, especially when stratification by drug-resistance pattern is requested. With support from the Norway Grant, this initiative is in the course of implementation.

A separate electronic MDR-TB registry is available within the national registry with data entered on patients registered for treatment with SLDs. All information on every MDR-TB case registered for treatment is first recorded in paper registers, available at MDR-TB centres, and then entered into the electronic register. Access to the MDR-TB registry is available at the level of the NTP and TB dispensary. The registry includes only those patients registered for MDR treatment and does not include those diagnosed with MDR-TB who are not on therapy for any reason. The registry contains 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. The county TB coordinators are responsible for case registration and data entry in the regions. All laboratory data are stored in paper registers in every laboratory and then reported quarterly to the level of the NTP (national laboratory coordinator). Progress on developing the TB laboratory component as part of the national electronic register was not personally witnessed during the mission. The NRL informed that development of the unified laboratory module of the national register was taking place and was under testing phase by the time of the mission.

It was discussed with the NTP that the treatment registration forms should be revised and updated 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* (2015) and included into the updated version of the national guidelines on PMDT in Romania.

	Recommendation	**Responsibility**
1	Ensure that the national registry contains information on all TB and DR-TB cases registered in the country, not only those registered for treatment (ongoing recommendation).	NTP
2	Include RR cases in cohort reporting and analysis.	NTP
3	Revise and update treatment registration forms to bring into alignment with Part 4 of the WHO *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (2015), especially in light of the use of new TB drugs. Updated forms to be institutionalized and brought into routine practice.	NTP
4	Map the flow of case registration and treatment forms for MDR-TB to ensure adequate recording and reporting (R&R).	NTP
5	Consider separate reporting on treatment outcomes for rGLC and non-rGLC cohorts.	NTP

13. Ethics of TB prevention, care and control

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 to work outside the country. Within the Norway Grant, the NTP has implemented a series of activities to address social challenges facing poor and vulnerable patients, including the Roma population, by ensuring access to appropriate diagnosis and treatment, as well as psychosocial support to ensure adherence to therapy. Within the GFATM grant, the NTP is due to create six multidisciplinary teams to provide psychosocial support for patients from vulnerable groups with a high risk of defaulting from treatment.

14. Attachments

- Annex 1: rGLC mission agenda
- Annex 2: WHO TB country profile, Romania, 2016
- Annex 3: Drug resistance surveys in Romania