rGLC Europe

TECHNICAL SUPPORT MISSION on IMPLEMENTATION OF THE NATIONAL TB PROGRAM, ROMANIA.

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In May 2018, a regional Green Light Committee (rGLC) mission went to Romania to give support and technical assistance to the National Tuberculosis Programme (NTP) with the management of drug-resistant tuberculosis (DR-TB). TB is a significant public health threat in Romania, even though the country is not on WHO's list of high-burden countries for TB and/or MDR-TB. Even so, there has been a steady decrease in the main TB indicators over the past decade due to progress in implementing the NTP. Recommendations from previous rGLC missions on scaling up access to rapid molecular diagnosis of TB and therapy for DR-TB (including new TB drugs) have been taken seriously by the Ministry of Health and the NTP. Political commitment has increased recently, especially following political and technical support from the WHO Regional Office for Europe. Several aspects still, however, require attention and continuing support from the government and technical assistance from the Regional Office in order to strengthen the NTP's capacity and performance in eliminating the burden of TB and DR-TB in Romania.

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Clearance of the report (transparency)

This report has been fully cleared by the National Tuberculosis Program, Romania, for publication and circulation.

Contents

Abbreviations

aDSM	active TB drug-safety monitoring and management
Amx/Clv	amoxicillin-clavulanate
Bdq	bedaquiline
Cfz	clofazimine
Cm	capreomycin
Dlm	delamanid
DOT	directly observed treatment
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
E	ethambutol
Eto	ethionamide
FLD	first-line anti-tuberculosis drug
FQ	fluoroquinolone
H	isoniazid
Imp-cls	imipenem-cilastatin
Km	kanamycin
LPA	line probe assay
Lzd	linezolid
LWG	Laboratory working group
MDR-TB	multidrug-resistant tuberculosis
Mfx	moxifloxacin
MGIT	mycobacteria growth indicator tube
MNI	Marius Nasta Pneumology Institute
MTB/RIF	*Mycobacterium tuberculosis* complex and resistance to rifampin
NRL	National reference laboratory
NIH	National insurance house
NTP	National Tuberculosis Programme
Ofx	ofloxacin
PAS	para-aminosalicylic acid
PCR	polymerase chain reaction
PHC	primary health care
Pto	prothionamide
rGLC	regional Green Light Committee
R	rifampicin
RR	rifampicin resistance/rifampicin-resistant
RRL	regional reference laboratory
S	streptomycin
SLD	second-line anti-tuberculosis drug
SS+, SS-	smear-positive, smear-negative
TB	tuberculosis
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

Executive summary

Tuberculosis (TB) has remained a significant public health threat over the past two decades in Romania, even though the country is not included in the WHO list of high-burden countries for TB and/or multidrug-resistant (MDR) TB. Data provided by the National Tuberculosis Programme (NTP) show a steady decrease in the main TB indicators over the past decade, with incidence declining from 122.2 per 100 000 people in 2002 to 54.4 per 100 000 in 2017. The mortality rate for TB (excluding those with HIV co-infection) was reported to be 5.1% in 2016 (down from 5.9% in 2012); the corresponding figure for HIV-positive cases is assumed to be higher.

Romania has received several approvals from the regional Green Light Committee (rGLC) of the WHO European Region to access quality-assured second-line drugs (SLDs) for a total of 2715 M/XDR-TB patients (cohorts 1–7). Between 2004 and 2018, a total of 2715 MDR-TB patients were enrolled in the rGLC-approved programme, with funding available from the grant from the Global Fund to Fight AIDS, Tuberculosis and Malaria for 1713 patients (cohorts 1–5 and 7) and a grant from the Government of Norway for 1002 patients (cohort 6). The average treatment success rate was 68.2% (cohorts 1–4) and 72.8% (cohort 5). Treatment outcomes for cohorts 6 and 7 will start becoming available from 2019. Despite the good performance under the Global Fund 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. In total, 96 patients were enrolled in treatment with individualized regimens containing bedaquiline (Bdq) during 2015–2018 under the Global Fund and Norwegian grants. In 2018 the Ministry of Health endorsed the inclusion of Bdq, delamanid (Dlm) and linezolid (Lzd) but not clofazimine (Cfz) in the national list of essential medicines eligible for government funding, so that procurement could start in 2019. The NTP estimates that a total of 214 patients could access treatment with individualized regimens containing new TB drugs in 2019 (164 on Bdq and 50 on Dlm), which were approved by the Ministry of Health for funding and procurement. A way has been found to procure Cfz with special permission from the Ministry of Health. In addition, with a forthcoming European Economic Area grant from the government of Norway for 2019–2021, an additional 600 patients with multidrug/extensively drug-resistant (M/XDR) TB will access the full range of SLD, of whom up to 100 will be treated with new TB drugs. Drug susceptibility testing (DST) for first- and second-line drugs has improved as a result of increased availability and access to rapid molecular diagnosis of TB and drug-resistant (DR) TB (GeneXpert and line probe assay (LPA)) with 44 GeneXpert modules to become available by the end of 2018. Taking into account that starting 2019 the Ministry of Health is taking over the funding and procurement of consumables for all laboratory diagnosis of TB, including GeneXpert cartridges and kits for LPA testing, a substantial level of programme sustainability was noted during the mission.

Political commitment 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 Government endorsed the National Strategic Plan for Tuberculosis 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 Ministry of Health, 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 for TB care and identifies innovative approaches targeted at achieving a dramatic decline in TB incidence and mortality in Romania by 2020.

Several aspects require attention and continuous support from the Government and technical assistance from WHO in order to strengthen the capacity and performance of the NTP. Most of these

will be addressed with the implementation of the NSP. The rGLC missions have reported on progress by the NTP in implementing the Programme over several years and the majority of the missions' recommendations have been adopted. The scope of the current mission has moved from monitoring to support; it contains information on findings and a summary of discussions concerning most aspects of the programmatic management of DR-TB, in which the major focus has been on use of new drugs for the treatment of DR-TB in Romania.

Key recommendations

No.	Recommendation	Timeframe	Responsible (institution)
1	The NTP central unit should be strengthened and sustained so as to carry out the operations required for monitoring, coordination, management and supervision of the implementation of the NTP.	2018 and onward	Ministry of Health
2	Eight regional NTP units/teams should be established and supported with clear terms of reference to carry out monitoring, coordination, management and supervision of the implementation of the NTP in several counties.	2018 and onward	Ministry of Health, NTP
3	Access and complete coverage with rapid diagnosis of TB and rifampicin resistance (RR) (GeneXpert) for presumptive TB cases should be ensured.	2018 and onward	Ministry of Health, NTP, national reference laboratories (NRLs)
4	Access to rapid molecular diagnosis of DR-TB should be expanded through the creation of a network of interregional TB laboratories empowered to perform DST for first- and second-line anti-TB medications (phenotypic and molecular). The procurement of supplies should be facilitated for rapid molecular diagnosis of TB and DR-TB and their uninterrupted supply to the regional TB laboratories. Adequate financing of and support for regional TB laboratories should be ensured, including but not limited to human resources, capacity-building, monitoring and supervision, transport of specimens and quality assurance. The necessary amendments should be made to existing legislation to ensure the smooth expansion of access to Geno Type MTBDR*sl*.	2018 Q3-Q4 and onward	Ministry of Health, NTP
5	Coverage with SLD DST (preferably SLD LPA) should be increased to all patients diagnosed with RR so as to ensure appropriate design of individualized regimens.	2018 and onward	NTP
6	Consideration should be given to introducing DST to	2018–2019	NTP, NRLs,

	Bdq, Dlm, Lzd and Cfz at the level of national reference laboratories, and support sought from the supranational reference laboratory in Stockholm and the rGLC.		supranational reference laboratory
7	The uninterrupted procurement of a minimum of 45 000–55 000 GeneXpert cartridges should be ensured for 2019.	2018	Ministry of Health
8	The procurement of consumables for molecular diagnosis (GeneXpert, HAIN Test) should be facilitated to avoid stockouts and delays in diagnosis of TB and DR-TB. Consideration should be given to signing procurement contracts for one fiscal year. Approval should be given to split shipments of consumables as part of the national orders.	2018 and onward	Ministry of Health, regional municipalities, hospital administrations, NTP
9	The national guidelines for management of DR-TB should be endorsed, with the possibility of introducing updates from the forthcoming revision of the WHO guidelines on DR-TB.	2018 Q3	Ministry of Health
10	For all patients with M/XDR-TB who require therapy with new TB drugs, procurement should be organized, finalized and ensured (estimates provided to Ministry of Health by NTP for 2019–2020).	2018 Q3-Q4	Ministry of Health, NTP
11	Adequate management of M/XDR-TB in counties should be ensured, including but not limited to capacity-building for regional TB teams, active drug safety management and monitoring (aDSM), and introduction of methods to strengthen adherence.	2018 and onward	NTP
12	Consideration should be given to the step-by-step scale-up of introduction of treatment with new anti-TB drugs at regional MDR-TB treatment centres (university hospitals with sufficient capacity and infrastructure).	2018 Q3-Q4	NTP
13	Decisions about the off-label use of Bdq and Dlm should be taken on a case-by-case basis according to the WHO statement of September 2017.	2018 and onward	NTP
14	The possibility of introducing a shorter treatment regimen for MDR-TB after release of the revised WHO guidelines on treatment of DR-TB should be discussed.	2019	NTP
15	For patients who require TB retreatment, the category II regimen should no longer be prescribed. DST should be conducted to inform the choice of treatment	2018	NTP

	regimen (good practice statement). The TB guideline should be reviewed accordingly.		
16	The capacity of ambulatory care for TB and DR-TB should be strengthened by the introduction of and support for patient-centred models of care as alternatives to hospitalization as well as methods to strengthen adherence.	2018 and onward	NTP
17	Video-observed therapy as an alternative method of DOT should be considered for patients with drug-susceptible and drug-resistant TB. Consideration should be given to using video-observed therapy in real time or recorded via Skype or messenger service applications (such as WhatsApp, Viber).	2018	NTP
18	Universal coverage with regimens containing new anti-TB drugs for management of M/XDR-TB (Bdq, Dlm, Lzd, Cfz and imipenem-cilastatin+amoxicillin-clavulanate) should be ensured, including in the prison sector.	2018 Q1	Ministry of Health, NTP, Prison sector
19	Adequate financing and an uninterrupted supply of SLDs should be ensured, including Groups A (FQs), B (second-line injectable agents), C (Eto/ Pto, cycloserine, Lzd, Cfz) and D2 (Bdq, Dlm) for all patients diagnosed with DR-TB..	2018 and onward	Ministry of Health, NTP
20	The following revision should be considered to the national list of essential medicines, TB component (C2 list),: • remove Ofx and consider levofloxacin (Group 1) as first choice FQs for MDR-TB; • include PAS (Group D3) in the C2 list only upon release of the updated WHO guidelines; revise the national drug orders accordingly, as savings can be made if the revised guidelines do not recognize PAS for wide use in treating MDR-TB; • include Cfz (Group C) in the C2 list once it is registered in Romania; meanwhile, ensure an uninterrupted supply of Cfz, as the core MDR-TB drug, for patients with DR-TB; • include Cm (Group B) in the C2 list.	2018	Ministry of Health, NTP
21	The use of one of the WHO-recommended tools for quantification and forecasting of TB drugs, such as QuanTB, should be considered.	2018	NTP

22	Consideration should be given to revising the current system of drug distribution and to rationalizing the delivery system for TB drugs to user points to improve drug management, reporting and avoid possible stockouts as well as interruptions to treatment.	2018–2019	Ministry of Health, NTP
23	The core level, at least, of aDSM should be introduced into the NTP when managing: • patients with MDR-TB on treatment with Bdq, Dlm and other new medicines; • all XDR-TB patients on second-line treatment, as these regimens include repurposed companion drugs (Lzd and Cfz); • MDR-TB patients enrolled in treatment with novel MDR-TB regimens (including a shorter MDR-TB regimen).	2018	Ministry of Health, NTP, National Drug Regulatory Authority
24	Consideration should be given to procuring paediatric formulations of drugs for MDR-TB, and technical assistance should be sought from the Global Drug Facility.	2018	NTP
25	For patients who require TB retreatment, the category II regimen should no longer be prescribed. The national procurement plan for 2019 should be reviewed accordingly.	2018 Q3-Q4	NTP, Ministry of Health
26	Technical assistance from the Regional Office and rGLC should be considered with the choice of package and introduction of aDSM into the NT.	2018–2019	NTP
27	The updated version of the National Infection Control Plan should be endorsed and adequate financing of infection control measures ensured.	2018	Ministry of Health
28	The legislative base regulating health facility accreditation and prevention of TB transmission should be revised to include appropriate infection control 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.	2018 Q3-Q4	Ministry of Health, NTP
29	The F-A-S-T strategy/approach should be expanded and routinely implemented 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.	2018 and onward	NTP

30	Consideration should be given to revising the treatment recording and reporting forms on DR-TB and including them in the revised national guidelines for DR-TB.	2018 Q3-Q4	NTP

[a] Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely, and Treat effectively based on rapid DST.

Background

Romania is located at the crossroads of central and south-eastern Europe. It is the ninth largest country with the seventh largest population in the European Union (EU): 19 638 000 in 2017. The capital and largest city is Bucharest with 20 121 643 inhabitants in 2011 (Romanian 2011 census,[1] National Institute of Statistics[2]). 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) – 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 mayors and local administrations. There is a total of 319 cities and 2686 communities. The capital is divided into six sectors, and has special status as it is considered a part of a county.

Against the background of the continuing threat to public health from TB in Romania, a regional Green Light Committee (rGLC) mission went to the country from 20 to 26 May 2018 in order to:

- assess the progress of the implementation of the National Strategic Plan for Tuberculosis for 2015–2020 (NSP), including its M/XDR-TB component, and develop recommendations for future activities;
- assess the progress made and readiness for effective introduction of new drugs by the NTP;
- assess the effectiveness of implementing the current drug-resistant (DR) TB control project supported by the Global Fund, including TB drug management;
- advise on the estimated number of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB patients for 2017–2018;
- assess the readiness for an effective start-up of a nine-month short course of treatment for suitable patients.

The full terms of reference of the mission are at Annex 1 and the programme with people met at Annex 2.

Tuberculosis in Romania

Tuberculosis (TB) has remained a significant public health threat over the past two decades in Romania, even though the country is not included in the WHO list of high-burden countries for TB and/or multidrug-resistant (MDR) TB. Data provided by the National Tuberculosis Programme (NTP) show a steady decrease in the main TB indicators over the past decade, with incidence declining from 122.2 per 100 000 people in 2002 to 54.4 per 100 000 in 2017 (Table 1). The mortality rate for TB (excluding those with HIV co-infection) was reported to be 5.1% in 2016 (down from 5.9% in 2012); the corresponding figure for HIV-positive cases is assumed to be higher. Overall, there has been a decline in the number of TB cases, especially of those previously treated. This indicates that the NTP is performing well.

[1] The usually resident population on 1st January 2017 down 122.0 thousand persons [press release]. Bucharest: National Institute of Statistics; 2017 (http://www.insse.ro/cms/sites/default/files/com_presa/com_pdf/poprez_ian2017e.pdf, accessed 24 July 2018).

[2] Rezultate definitive ale Recensământului Populaţiei şi al Locuinţelor – 2011 (caracteristici demografice ale populaţiei [Final results of population and housing census – 2011 (Demographic characteristics of population]. Bucharest: National Institute of Statistics (https://web.archive.org/web/20130717125951/http:/www.recensamantromania.ro/wp-content/uploads/2013/07/REZULTATE-DEFINITIVE-RPL_2011.pdf, accessed 24 July 2018).

Table 1. TB case notifications, 2000–2016

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
New cases	23897	25847	26567	25166	24305	22348	20371	18909	18716	17771	15941	14535	13874	12846	12482	11995	10727
Previously treated cases	-	-	-	-	-	6940	6229	5928	5964	5393	5118	4667	4316	3843	3397	3188	2874
All TB cases	-	-	-	-	-	29288	26600	24837	24680	23164	21059	19202	18190	16689	15879	15183	13601
New cases per 100 000 population	-	-	122.6	116.6	113.3	104.8	96.1	90.5	91.1	87.3	78.7	72.1	69.2	64.3	62.7	60.5	54.4
All TB cases per 100 000	-	-	-	143.9	148.8	137.4	125.5	118.9	120.2	113.7	104.0	95.3	90.7	83.5	79.7	76.6	69.0
Incident (new and relapse) cases in children (0–14 years)[a]	-	-	-	-	-	-	-	-	-	-	-	-	-	695	639	655	596

[a] Data for 2000–2004 not available.
Source: NTP.

In 2017, 67% of the notified cases were new pulmonary laboratory-confirmed and 15% new pulmonary clinically diagnosed (Table 2). Of previously treated patients, 60% of relapse cases were laboratory-confirmed and 18% clinically diagnosed. This can probably be attributed to poor utilization of the rapid diagnostic tools available on the market. In 2016, only 5% of cases (new and relapse) were tested with rapid diagnosis at the time of diagnosis (Annex 3).

Table 2. TB case notifications by category, 2013–2017

	2013	2014	2015	2016	2017
New cases (total)	**12 846**	**12 482**	**11 995**	**10 727**	**10 377**
New pulmonary, laboratory-confirmed	8 112	7 904	7 711	7 099	6 952
New pulmonary, clinically diagnosed	2 437	2 374	1 977	1 651	1 561
New extrapulmonary	2 297	2 204	2 307	1 977	1 864
Previously treated cases (total)	**3 843**	**3 397**	**3 188**	**2 874**	**2 627**
Relapses pulmonary, laboratory-confirmed	2 203	1 897	1 840	1 679	1 567
Relapses pulmonary, clinically diagnosed	335	353	259	265	282
Relapses extrapulmonary	121	102	121	103	84
Other previously treated	1 184	1 045	968	827	694
Other TB cases	0	0	0	0	0
All TB cases	**16 689**	**15 879**	**15 183**	**13 601**	**13 004**

Source: NTP.

In recent years, the treatment success rate for new and relapse TB cases has been over 85%, with a low rate of treatment failure and treatment failure, but death (8% in 2016) (Table 3). Treatment outcomes among previously treated cases (other than relapses) showed a significantly lower treatment success rate not exceeding 50% and with high rates of treatment failures (13.3%), death (11.7%) and lost to follow-up (25.2%) (Table 4). Generally, a major impediment to improving treatment outcomes, among all TB cases, including MDR-TB, is an increasing rate of those lost to

follow-up in TB treatment. Romania has been facing issues of labour migration in recent decades, mostly to Western Europe, with patients often interrupting therapy to take up work in other countries.

Table 3. TB treatment outcomes, new and relapse cases, 2012–2016 cohorts

	2012		2013		2014		2015		2016[a]	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
New and relapse cohort size	**16 339**		**15 084**		**14 582**		**13 908**		**12 459**	
Treatment success	13 892	85.0	12 849	85.2	12 418	85.2	11 854	85.2	10 708	85.9
Treatment failed	411	2.5	320	2.1	289	2.0	234	1.7	193	1.5
Death	1 110	6.8	1 035	6.9	1 084	7.4	1 071	7.7	1 002	8.0
Lost to follow-up	880	5.4	832	5.5	782	5.4	733	5.3	522	4.2
Still on treatment + transfer	46	0.3	48	0.3	9	0.1	16	0.1	34	0.3

[a] Final outcomes to be available in 2018.
Source: NTP (national TB database).

Table 4. TB treatment outcomes, previously treated cases (other than relapse), 2012–2016 cohorts

	2012		2013		2014		2015*		2016*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Previously treated cohort size	**1 070**		**925**		**765**		**680**		**592**	
Treatment success	488	45.6	414	44.8	352	46.0	326	47.9	290	49.0
Treatment failed	154	14.4	130	14.1	132	17.3	113	16.6	79	13.3
Death	126	11.8	115	12.4	81	10.6	67	9.9	69	11.7
lost to follow-up	286	26.7	261	28.2	200	26.1	173	25.4	149	25.2
Still on treatment + transfer	16	1.5	5	0.5	0	0.0	1	0.1	5	0.8

[a] Final outcomes to be available in 2018.
Source: NTP (national TB database).

According to the latest WHO data, in 2016 the estimated proportion of TB cases with rifampicin-resistant (RR)/MDR-TB was 2.8% (2.4–3.3%) among new cases and 17% (16–19%) among previously treated cases (Table 5) (Annex 3). In 2016, the total absolute number of registered RR/MDR-TB cases was 550, less than in the previous year. A total of 336 tests were reported as MTB+/RR+ in 2017. However, taking into account that coverage with rapid molecular testing requires improvement, the totals of RR/MDR-TB among new and previously treated cases might be higher than officially reported.

Table 5. RR/MDR-TB prevalence among new and previously treated TB cases with first-line drug (FLD) DST results, 2012–2016 (%)

	2012	2013	2014	2015	2016
New cases	207	211	168	166	181
Previously treated cases	575	452	434	429	369

Source: NTP (national TB database).

The proportion of patients, both new and previously treated, covered by DST to FLDs is increasing but is still not enough. In particular, it is critical among previously treated patients: in 2016, only 76.1% of these patients had DST results and almost 17% of these were diagnosed with RR/MDR-TB. Thus, efforts should be made to increase the routine use of DST (preferably using molecular methods) to improve the guidance of designing effective treatment regimens. RR/MDR-TB has remained the same among new laboratory-confirmed cases in recent years but has been decreasing among previously treated cases (Tables 6, 7).

Table 6. FLD resistance profile among new TB cases, 2014–2016

	2014		**2015**		**2016**	
	N	*%*	*N*	*%*	*N*	*%*
Total number of new cases notified	12 482		11 995		10 727	
Number of cases with FLD DST results	6 035	48.3	6 628	55.3	6 370	59.4
Susceptible to isoniazid (H) or rifampicin (R)	5 622	93.2	6 186	93.3	5 985	94.0
H ± other resistance (polydrug-resistant tuberculosis)	245	4.1	276	4.2	204	3.2
R ± other resistance (RR/MDR-TB)	168	2.8	166	2.5	181	2.8

Source: NTP (national TB database).

Table 7. FLD resistance profile among previously treated TB cases, 2014–2016

	2014		**2015**		**2016**	
	N	*%*	*N*	*%*	*N*	*%*
Total number of previously treated cases notified	3397		3188		2874	
Number of cases with FLD DST results	2238	*65.9%*	2342	*73.5*	2186	*76.1%*
Susceptible to isoniazid (H) or rifampicin (R)	1645	73.5%	1767	75.4%	1701	77.8%
H ± other resistance (polydrug-resistant tuberculosis)	159	7.1%	146	6.2%	116	5.3%
R ± other resistance (RR/MDR-TB)	33+401	19.4%	429	18.3%	369	16.9%

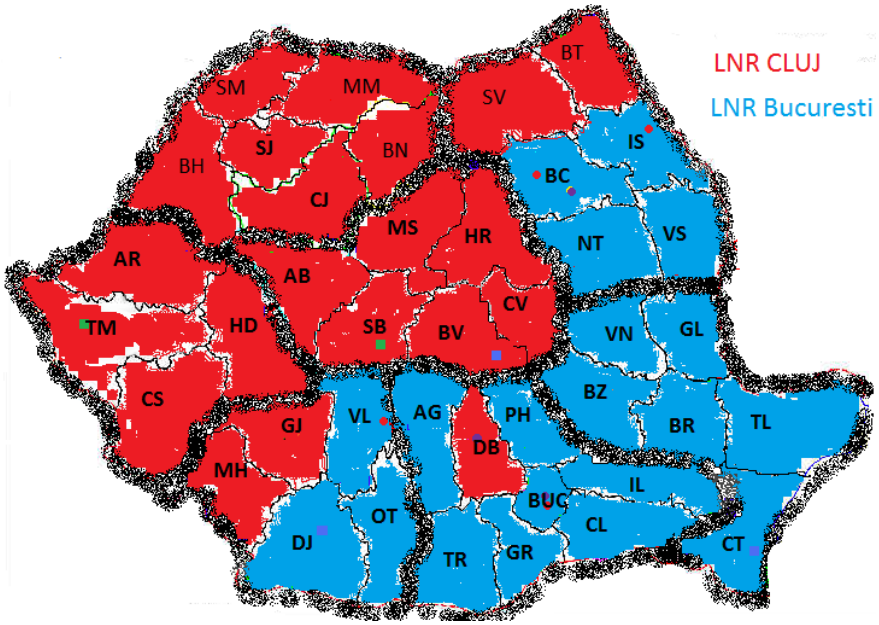
Source: NTP (national TB database).

DR-TB case finding and diagnosis

In recent years there has been progress in the laboratory diagnosis of TB and DR-TB in Romania. 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 Global Fund and a grant from Norway. Reorganization was considered one of the objectives of the NSP. The NTP has taken huge steps forward in establishing a functional laboratory network with the purpose of improving access to rapid molecular diagnosis of TB and drug resistance. The existing infrastructure and capacity of the laboratory services guarantee universal access to smear, culture and DST for diagnosis and follow-up across the country.

Two national reference laboratories (NRLs), in Bucharest and Cluj Napoca, coordinate the activities of, and give methodological assistance, supervision and mentorship to county-level laboratories while serving as the national referral centres for DST to second-line drugs (SLD) (Fig. 1). Coordination of activities at national level has been carried out by the Laboratory working group (LWG), which is nominated annually by the Ministry of Health with a national laboratory coordinator based in the Cluj Napoca NRL.

Fig. 1. Map of supervisory coverage by NRLs (Bucharest and Cluj Napoca), 2018



AB: Alba, AR: Arad, AG: Argeș, BC: Bacău, BH: Bihor, BN: Bistrița-Năsăud, BT: Botoșani, BR: Brăila, BV: Brașov, BUC: Bucharest, BZ: Buzău, CL: Călărași, CS: Caraș-Severin, CJ: Cluj, CT: Constanța, CV: Covasna, DB: Dâmbovița, DJ: Dolj, GL: Galați, GR: Giurgiu, GJ: Gorj, HR: Harghita, HD: Hunedoara, IL: Ialomița, IS: Iași, IF: Ilfov, MM: Maramureș, MH: Mehedinți, MS: Mureș, NT: Neamț, OT: Olt, PH: Prahova, SJ: Sălaj, SM: Satu Mare, SB: Sibiu, SV: Suceava, TR: Teleorman, TM: Timiș, TL: Tulcea, VL: Vâlcea, VS: Vaslui, VN: Vrancea.

The laboratory network consists of 94 laboratories across the country, including two in the penitentiary sector (Table 8). Forty-four level III laboratories (including the two NRLs) perform sputum smear microscopy, culture and DST to FLDs (short-line DST to H and R) on solid media. A smaller number of regional laboratories perform DST using liquid media and molecular diagnostic tests to SLD (Table 8).

Table 8. Structure of TB diagnostic/laboratory network and methods used

Region / sector	Number of TB diagnostic facilities *	Number of facilities performing:										
				solid media investigations (such as Löwenstein–Jensen medium)			*liquid media investigations (automated mycobacteria growth indicator tube (MGIT))*				*line probe assays (LPA)*	
		direct smear microscopy	GeneXpert MTB/ RIF	Culture	DST to FLDs	DST to SLDs	Culture	DST to SLDs	DST to FLDs S, H, R, E	DST to FLDs H, R, E	GenoType MTBDR*plus*	GenoType MTBDR*sl*
AB	3	3		3	1							
AR	1	1	1	1	1							
AG	4	4	1	4	1							
BC	4	4	1	4	2		1		1		1	
BT	2	2	1	2	1							
BH	1	1	1	1	1						1	
BN	1	1		1	1							

BV	1	1	1	1	1		1		1		1	
BR	1	1	1	1	1						1	
BZ	2	2		2	1							
CL	2	2	1	2	1		1			1		
CT	3	3	1	1	1		1		1		1	
CS	2	2		2	1							
CJ	**2**	2	1	2	1	1	1	1	1		1	1
CV	1	1		1								
DB	1	1	1	1	1							
DJ	4	4	1	4	2		1		1	1	1	
GR	3	3		3	1							
GJ	3	3	1	3	1							
GL	1	1	1	1	1		1			1		
HD	2	2		2	1							
HR	1	1		1								
IS	2	2	1	2	1		1		1		1	
IL	1	1	1	1	1		1					
MM	4	4	1	4	1							
MH	1	1	1	1	1							
MS	2	2	1	2	1							
NT	4	4	1	3	1	1						
OT	5	5	1	4	1							
PH	4	4		3	1		1					
SM	2	2		2	1							
SJ	1	1		1	1							
SB	1	1	1	1	1		1		1			
SV	4	4		3	1							
TM	3	3	1	3	1		1		1		1	
TL	2	2	1	2	1							
TR	1	1	1	1	1							
VS	2	2		2	1							
VN	1	1	1	1	1							
VL	3	3		3	1							
Bucharest	6	6	1	6	4	1	2	1	1	1	1	1
Civilian sector total	**92**	**92**	**27**	**86**	**42**	**3**	**14**	**2**	**9**	**4**	**10**	**2**
Penitentiary sector	**2**	**2**	**0**	**2**	**2**		**0**	**0**	**0**	**0**	**0**	**0**
Country total	**94**	**94**	**27**	**88**	**44**	**3**	**14**	**2**	**9**	**4**	**10**	**2**

S – streptomycin, H – isoniazid, R – rifampicin, E – ethambutol.

[a] Figures include laboratories as well as basic management units using GeneXpert only.

Source: NTP.

The NTP is in the process of building a network of interregional TB laboratories to be located in eight counties and serve as referral centres for neighbouring regions with the ultimate goal of increasing access to rapid molecular diagnosis of TB. The selection of interregional TB laboratories was made on the basis of disease burden, geographical proximity to other counties and capacity (equipment, infection control measures and trained personnel). The NTP is also planning to reduce the number of regional laboratories to 30–35, leaving only those with sufficient capacity (equipment and personnel) and showing a good level of performance. In 2018, the National Laboratory Working Group under the NTP developed the National Laboratory Guidelines.[3] These have three annexes covering TB diagnosis,

[3] Indaco Lege [5] [website]. Order no. 6/2018 regarding the modification and completion of the Order of the Minister of Health no. 1.171 / 2015 for the approval of the Methodological Guide for Implementation of the National Program for Prevention, Supervision and Control of Tuberculosis. Bucharest: Indaco Systems; 2018 (https://lege5.ro/en/Gratuit/gi3donzxgi3a/ordinul-nr-6-2018-privind-modificarea-si-completarea-ordinului-ministrului-sanatatii-nr-1171-2015-pentru-aprobarea-ghidului-metodologic-de-implementare-a-programului-national-de-prevenire-supraveghere, accessed 25 July 2018).

a centralized procurement plan and the procedure for evaluating laboratory standards, including information on the organizational restructuring of the national laboratory network, diagnostic algorithms and other technical aspects. The guidelines are available in Romanian and were recently endorsed by the Ministry of Health for national use. They describe the minimum requirements for three levels of laboratory: NRLs, interregional TB laboratories and regional laboratories.

In 2017, 245 802 presumptive TB cases and 98 321 TB contacts were screened for active TB (Tables 9, 10; data only available for the civilian sector), resulting in the notification of 10 727 cases. Most of the cases were tested with sputum smear microscopy and 18 149 were tested on GeneXpert. In view of the increasing access to rapid diagnostic tools and recently revised diagnostic algorithm (National Laboratory Guidelines, 2018), the case notification yield is expected to be significantly higher in future years. In addition, the Ministry of Health and the NTP should invest efforts in implementing the diagnostic algorithm, especially at primary health care (PHC) level, and ensure the availability of sufficient amounts and an uninterrupted supply of GeneXpert cartridges at national and regional levels.

Table 9. Number of TB suspects tested for active TB, 2013–2017

Region/sector	2013	2014	2015	2016	2017
Region 1	Unknown	Unknown	Unknown	Unknown	Unknown
Region 3	Unknown	Unknown	Unknown	Unknown	Unknown
Region 3	Unknown	Unknown	Unknown	Unknown	Unknown
Civilian sector total	308 671	295 313	282 990	254 302	245 802
Penitentiary sector	–	–	–	–	–
Country total	**308 671**	**295 313**	**282 990**	**254 302**	**245 802**

Source: NTP.

Table 10. Number of contacts of TB cases investigated for active TB, 2013–2017

Region/sector	2013	2014	2015	2016	2017
Region 1	Unknown	Unknown	Unknown	Unknown	Unknown
Region 3	Unknown	Unknown	Unknown	Unknown	Unknown
Region 3	Unknown	Unknown	Unknown	Unknown	Unknown
Civilian sector total	123 469	118 125	113 196	101 721	98 321
Penitentiary sector	Unknown	Unknown	Unknown	Unknown	Unknown
Country total	**123 469**	**118 125**	**113 196**	**101 721**	**98 321**

Source: NTP.

The NTP follows passive contact investigation practice, in which patients are asked to bring their family members to the health care facility for investigation. It is not known how many people living with HIV were screened for active TB between 2013 and 2017.

Coverage with DST to FLDs and SLDs has improved as a result of the increased availability of and access to rapid molecular diagnosis of TB and DR-TB (GeneXpert *Mycobacterium tuberculosis* complex and resistance to R (MTB/RIF) and LPA). Only 27 of the 47 counties are equipped with GeneXpert machines. As part of the Norwegian grant, the NTP is planning to procure an additional 17 GeneXpert machines which will bring the number up to a total of 44 and two for the prison sector. This will significantly increase access to rapid molecular diagnosis by making the method available almost at point of care, and will eventually shorten the time to initiation of appropriate therapy. The

diagnostic algorithm for GeneXpert includes the testing of new cases and presumptive TB cases with suspicion of RR-TB, including close contacts and relapses who should be tested at least once.

There was a significant increase in the number of GeneXpert tests from 13 743 in 2016 to 18 149 in 2017 (Table 11). Data on the results of GeneXpert testing provided by the NTP show a discrepancy between the totals of valid and invalid tests and MTB+ (Table 12). Taking into account the total number of 18 149 tests performed in 2017, of which 14 601 were MTB- and 309 had invalid results, the assumption is that a maximum of 3239 cases underwent GeneXpert testing. If the test was performed at least once per case, these cases should be assumed to be new or relapse according to the TB diagnostic algorithm. The total number of new and relapse cases in 2017 was 13 014, of which only 25% (3239) were tested using GeneXpert; this shows that there is a need to increase coverage with rapid molecular diagnosis to three times to ensure prompt diagnosis of TB and RR-TB. The Ministry of Health should, therefore, guarantee the procurement of around 50 000–55 000 GeneXpert cartridges for 2019 to ensure the implementation of the diagnostic algorithm, and facilitate the procedure for signing procurement contracts with county-level municipalities to avoid stockouts and delays in diagnosis. With 44 GeneXpert machines functioning by the end of 2018 and a minimum workload of 1250 tests/year or 6.25 tests/day, there will be a need to ensure the uninterrupted procurement of 55 000 GeneXpert cartridges annually. The NTP's estimate of the needs for GeneXpert cartridges in 2019 (minimum 40 000 and maximum 90 000) has been approved by the Ministry of Health and will be included in a national tender in the summer of 2018. The outcomes of the national tender will be valid for two years, and the cartridges can be procured in split shipments. In addition, the NTP included a budget for 10 000 cartridges to cover a temporary gap until the national tender takes place.

Table 11. Number of GeneXpert MTB/RIF instruments and investigations performed, 2013–2017

Region/sector	Number of GeneXpert MTB/RIF instruments	Number of GeneXpert MTB/RIF tests performed				
		2013	2014	2015	2016	2017
AR	1	NA	NA	50	120	620
BC	1	NA	NA	58	87	578
BR	1	NA	NA	NA	NA	104
MM	1	NA	NA	5	1407	987
MH	1	NA	NA	NA	NA	74
VN	1	NA	NA	NA	NA	66
GL	1	NA	NA	NA	273	546
CL	1	NA	1	219	566	566
BV	1	NA	NA	1	401	412
TM	2	NA	NA	173	584	1778
NT	1	NA	122	473	689	637
BT	1	NA	NA	NA	NA	13
CJ-LNR	1	NA	NA	3	1148	1075
CT	1	NA	6	427	1842	1430
TR	1	NA	NA	4	239	185
IL	1	NA	NA	36	123	119
GJ	1	NA	NA	6	48	121
AG	1	NA	NA	6	668	1021
DB	1	NA	NA	283	431	319
IS	1	NA	NA	1	1046	930
B-LNR	3	NA	747	1463	2988	5000
OT	1	NA	NA	NA	NA	47
DJ	1	NA	NA	52	439	532
SB	1	NA	NA	6	323	484
BH	1	NA	NA	3	312	334

MS	1	NA	NA	NA	NA	127
TL	1	NA	NA	NA	NA	34
Civilian sector total	**30**	**NA**	**876**	**3 271**	**13 743**	**18 149**
Penitentiary sector	**0**	**NA**	**0**	**0**	**0**	**0**
Country total	**30**	**NA**	**876**	**3 271**	**13 743**	**18 149**

Source: NTP/NRL database.

Table 12. GeneXpert MTB/RIF testing results, countrywide, 2013–2017

Year	Total number of GeneXpert MTB/RIF tests	Invalid test results				Valid test results					
		Total invalid tests	"Test invalid"	"Test error"	"Test No Result"	Total valid tests	MTB–	MTB(+)			
								MTB+ total	MTB+/R- susceptible	MTB+/RR	MTB+/R- indeterminate
2013	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2014	876	27	12	11	4	849	600	239	190	38	11
2015	3 269	94	63	31	1	3 174	2 432	784	674	89	21
2016	13 734	381	135	217	37	13 341	10 418	2 667	2 589	319	22
2017	18 139	309	84	207	44	18 573	14 601	3 443	3 559	336	97

Source: NTP/NRL database.

During the first and second quarters of 2018 at least 50% of counties experienced shortages of GeneXpert cartridges due to organizational constrains. The current process of transition from external donor funding to domestic funding, with the Government committed to taking over the procurement of GeneXpert cartridges, has led to significant delays in signing procurement contracts between county-level municipalities and the Ministry of Health and, as a result, in delays in diagnosis.

Number of conventional DST to FLDs and SLDs on liquid media was less than in the previous year, which is related to the transition from donor to government funding. BACTEC MGIT 960 systems have been purchased with external funding and installed at two NRLs and several regional reference laboratories (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 pyrazinamide (Z); those in NRLs were also performing DST to SLDs. DST on MGIT 960 was performed to capreomycin (Cm) (2.5), ethambutol (E) (5.0), H (0.1), kanamycin (Km) (2.5), moxifloxacin (Mfx) (0.5), ofloxacin (Ofx) (1.0), Z (100), R (1.0) and streptomycin (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), ethionamide (Eto) (30), Cm (40), Ofx (2.0) and Km (30), and repeat testing on automated liquid media systems (MGIT or VersaTREK). According to the diagnostic algorithm, DST to SLDs was performed only in cases with confirmed resistance to R and only at a physician's request. Usually DST results were reported back to clinicians on the same day. The previous recommendations to initiate a standardized MDR-TB regimen for all cases with diagnosed R- or HR-resistance until the arrival of conventional DST to other FLDs and SLDs had been carried out and introduced into routine practice.

Funding available from the Global Fund and Norway grants allowed the NTP to perform 5000 culture tests, 2000 DST to FLDs and 1000 to SLDs (Global Fund) as well as 19 250 liquid culture tests, 10 700 DST to FLDs and 1350 DST to SLDs (Norway Grant) during 2015–2018. In addition to 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 the availability of the VersaTREK modules would improve the time for confirmation of culture results (up to 14 days) and DST (up to one week) as well as ensure high sensitivity. According to the diagnostic algorithm, the VersaTREK system was supposed to be used for paediatric cases, HIV-positive cases and pleural fluid. External quality control for DST to FLDs and SLDs was performed by both NRLs. A total of 17 352 tests on liquid media were performed in 2017, fewer than in the previous year (Table 13).

Table 13. Number of microscopy, culture and DST investigations, countrywide, 2013–2017

Investigations	2013	2014	2015	2016	2017
Direct smear microscopy[a]	478 872	437 546	386 763	363 139	346 408
Culture on solid media	456 277	445 431	374 195	353 054	341 036
DST to FLDs on solid media	11 525	12 998	13 320	10 516	10 840
DST to SLDs on solid media	1 289	1 125	1 100	965	685
Culture in liquid media (automated MGIT)	4 633	4 088	17 835	24 427	17 352
DST to FLDs in liquid media (automated MGIT)	0	0	2 108	3 981	2 570
DST to SLDs in liquid media (automated MGIT)	0	0	0	36	36
LPA MTBDR*plus*	1 462	4 189	3 518	3 379	3 011
LPA MTBDR*sl*	222	491	110	276	322

Source: NTP/NRL database.

Other options for DST included rapid molecular diagnosis methods such as the polymerase chain reaction (PCR) LPA or (GenoType MTBDR*plus* and MTBDR*sl*). A total of 10 LPA systems are available: two automatic Genotype machines installed at two of the NRLs (Bucharest and Bisericani) performing the complete range of PCR LPA DST to H, R, and E, Km, Cm, and fluoroquinolones (FQ), and five installed in the level III RRLs in Brașov, Constanța, Timișoara, Bacău, Bihor, Braila, Dolj and Iași for MTBDR*plus* only. Two NRLs (Bucharest and Cluj-Napoca) serve as referral centres for the whole country for DST to SLD, which limits access to diagnosis of resistance to second-line injectable agents and FQ. A total of 3011 DST to FLDs and 322 DST to SLDs were performed in 2017, slightly more than in the previous year. As in 2016, DST to SLDs with LPA required scale-up by improving the transport of samples for testing and monitoring the implementation of the updated diagnostic algorithm. Indications for MTBDR*sl* are explained in revised algorithms and are in line with the generally accepted international approach. According to the algorithm, HAIN testing is performed for smear-positive (SS+) new and retreatment cases (category I and category II), smear-negative (SS-) and culture-positive cases, and SS+ cases with positive smear or culture results during the third month of therapy. LPA is performed in parallel with MGIT. Since MTBDR*sl* is only available at the NRLs and the number of tests remains low, it is recommended that the NTP empower regional TB laboratories with capacity to perform the test, which seems possible. The time from collection of sample to arrival of DST results to FLDs on PCR LPA is two to three days, or up to three weeks on MGIT, which is sufficient to initiate the appropriate treatment regimen once the results are available.

No genome sequencing is being done, although it might be helpful for designing the MDR-TB regimen. Genome sequencing provides comprehensive data on drug resistance, which would enable

proactive patient management based on accurate identification of mutations that are known to be associated with resistance to FLDs and SLDs. No testing for DST to bedaquiline (Bdq), delamanid (Dlm), Lzd or clofazimine (Cfz) was being done at the time of the mission, which the NTP should take into consideration and collaborate on with SNRL to organize appropriate training and technical assistance. The NTP should consider such testing and collaborate with the supranational reference laboratory (SNRL). Procurement of reagents and kits for MTBDR*plus* and MTBDR*sl* testing were covered with two external donor-funding sources.

The Public Health Agency of Sweden served as the SNRL for Romania and provided continuous technical assistance to laboratory services on DST, laboratory infection control, external quality assurance and drug resistance surveys (DRS) during 2008–2009 and 2014–2015. The Institute provided assistance in methodology and capacity-building for laboratory personnel and helped with the development of the protocol for rapid molecular DST.

Recommendations

No.	Recommendation	Timeframe	Responsible (institution)
1	Access and complete coverage with rapid diagnosis of TB and rifampicin resistance (RR) (GeneXpert) for presumptive TB cases should be ensured.	2018 and onward	Ministry of Health, NTP, NRLs
2	Access to rapid molecular diagnosis of DR-TB should be expanded through the creation of a network of interregional TB laboratories empowered to perform DST for first- and second-line anti-TB medications (phenotypic and molecular). The procurement of supplies should be facilitated for rapid molecular diagnosis of TB and DR-TB and their uninterrupted supply to the regional TB laboratories. Adequate financing of and support for regional TB laboratories should be ensured, including but not limited to human resources, capacity-building, monitoring and supervision, transport of specimens and quality assurance. The necessary amendments should be made to existing legislation to ensure the smooth expansion of access to Geno Type MTBDR*sl*.	2018 Q3-Q4 and onward	Ministry of Health, NTP
3	Consideration should be given to introducing DST to Bdq, Dlm, Lzd and Cfz at the level of national reference laboratories, and support sought from the supranational reference laboratory in Stockholm and the rGLC.	2018–2019	NTP, NRLs, SNRL
4	Consideration should be given to introducing genome sequencing for better identification of mutations known to be associated with FLDs and	2018–2019	NTP

	SLDs in the light of forthcoming plans to pilot shorter treatment regimens for MDR-TB.		
5	The uninterrupted procurement of a minimum of 45 000–55 000 GeneXpert cartridges should be ensured for 2019.	2018	Ministry of Health
6	The procurement of consumables for molecular diagnosis (GeneXpert, HAIN Test) should be facilitated to avoid stockouts and delays in diagnosis of TB and DR-TB. Consideration should be given to signing procurement contracts for one fiscal year. Approval should be given to split shipments of consumables as part of national orders.	2018 and onward	Ministry of Health, regional municipalities, hospital administrations, NTP

DR-TB treatment and case management

In the civilian section, patients with DR-TB are treated in inpatient and outpatient settings; in the prison sector, they are treated in the specialized TB ward. The prison sector was not visited during this mission, and no DR-TB patients were being treated with individualized Bdq-containing regimens. Access to treatment with new TB drugs and hospitalization in the DR-TB centre in the Marius Nasta Pneumology Institute (MNI) or Bisericani are mandatory for all patients with DR-TB, followed by discharge to an outpatient setting for continued treatment. Patients who refuse hospitalization for initiation of treatment with new TB drugs in either DR-TB centre remain in therapy with a standardized MDR-TB regimen at a county TB hospital. During 2018–2020, the NTP is planning to expand access to new TB drugs in up to eight interregional DR-TB centres located in the eight historic regions of the country. There is no legislation providing for forced treatment of TB and alternatives to hospitalization are not widely available. Nevertheless, as an alternative, PHC providers carry out directly observed therapy (DOT) against reimbursement by the National insurance house. The criteria for hospitalization remain the same and include initiation of therapy for DR-TB, including new TB drugs in cases of adverse drug reactions, co-morbid conditions and the need for surgery. Discharge from hospital is possible upon bacteriological conversion (two to three months of therapy) and confirmation of appropriate DOT established at the patient's place of residence. The mission noticed that some patients were being kept in hospital for longer treatment for socioeconomic reasons.

The TB services infrastructure is well-developed: a countrywide network of 85 TB facilities (dispensaries and hospitals) is involved in TB control in the civilian sector, with 5048 adult and 288 paediatric TB beds (Tables 14, 15). In 2015–2016, 11 TB dispensaries were closed to streamline administrative costs and another seven have been closed since the mission took place. 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 average duration of hospital stay is 34.0 days for adults and 21.7 for paediatric TB patients (Table 15) with possible extension up to 90 days for patients with DR-TB. This is regulated by the Ministry of Health and monitored by the national insurance house (NIH). The total number of hospitalizations/discharges in 2017 was 35 374 for both adult and paediatric TB cases; a total of 13 004 new and previously treated cases were registered, leaving a substantial number of hospitalizations for other reasons. It is still the practice to hospitalize presumptive TB cases for differential diagnosis with TB in TB facilities, especially those for differential diagnosis of pulmonary diseases (chronic obstructive pulmonary disease, lung cancer) with TB. It was not in the mandate of this mission to identify the number of hospitalizations of non-TB patients in TB facilities or to check the status of administrative separation of TB patients at all facilities. However, in those TB facilities

visited the administrative separation of epidemiological flows was in place with non-TB patients hospitalized in separate buildings. Scaling up access to rapid molecular diagnosis of TB and DR-TB will improve the diagnosis of TB, help avoid the unnecessary hospitalization of non-TB patients in TB facilities and reduce the chances of nosocomial transmission of infection.

Table 14. Number of TB inpatient facilities, number and profile of TB hospital beds, by sector and level of care

Types of institution and bed	Country total	By sector		By level of care in the civilian sector		
		Civilian sector	Penitentiary sector	Central level	Regional level	District level
Facilities providing hospital treatment for patients with active TB	**87**	85	2	6	41	40
Total number of beds for treatment of active TB for: – DR-TB patients – children – extrapulmonary TB – surgery	**5493** **164** **288** **30** **157**	5443 164 288 30 157	50 – – – –	355 48 80 10 52	2850 116 208 20 105	2288 – – – –
Facilities providing palliative care for TB patients	–	–	–	–	–	–
Beds for palliative care	–	–	–	–	–	–
Facilities providing involuntary isolation of TB patients	–	–	–	–	–	–
Beds for involuntary isolation	–	–	–	–	–	–

Source: NTP.

Table 15. Main activity indicators for institutions providing inpatient treatment of active TB cases, countrywide, 2013–2017 (civilian sector)

Activity indicators	2013	2014	2015	2016	2017
Total number of beds for treatment of active TB – adults – children	Unknown	Unknown	Unknown	Unknown	5 048 288
Total number of hospitalizations (discharges) – adults – children	Unknown	Unknown	Unknown	Unknown	32 781 2,593
Total number of patient days (“bed days”)	Unknown	Unknown	Unknown	Unknown	Unknown
Average length of stay (days) – adults – children	Unknown	Unknown	Unknown	Unknown	34.0 21.7
Bed occupancy rate (%) – adults	Unknown	Unknown	Unknown	Unknown	60.6%

– children					53.6%
Number of surgical interventions, all types	Unknown	Unknown	Unknown	Unknown	Unknown
Surgical activity (%)	Unknown	Unknown	Unknown	Unknown	Unknown

Source: NTP.

Two leading clinical centres are responsible for initiating the treatment of patients with DR-TB: the MNI in Bucharest (which hosts the NTP central unit and NRL) and the DR-TB centre in Bisericani. The majority of MDR-TB patients on new TB drugs are hospitalized in one of two centres for baseline assessment and start of therapy, with follow-up in an ambulatory setting after discharge. The NTP is planning to assign eight county TB hospitals as interregional DR-TB centres: in 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).

Starting in 2016, the NTP introduced the use of new TB drugs under programmatic conditions, already having experience of treating patients with Bdq under the compassionate use programme (six patients). During 2015–2018, a total of 187 patients accessed new and repurposed companion drugs from two sources of funding (the Norway and Global Fund grants), including 85 patients enrolled in treatment with regimens containing Bdq. The rest of the cohort were treated with individualized regimens containing SLD with only Lzd and/or Cfz added, but counted as having accessed new therapies.

Enrolment under the Norway grant (August 2014–April 2017) was projected to be 1000 M/XDR-TB patients, including 100 on new TB drugs with a total of 1002 patients enrolled. Of that cohort, 100 started therapy with new TB drugs, of whom 63 patients enrolled with regimens containing Bdq and the remaining 37 were treated with individualized regimens containing Lzd and/or Cfz. Enrolment under the Global Fund grant (April 2015–March 2018) was projected to be 460 M/XDR-TB patients, including 80 patients to be treated with new TB drugs (Bdq, Lzd, Cfz). Of this cohort the NTP had managed to enrol 33 patients on a Bdq-containing regimen by the time of the mission. With savings from the grant, the NTP is planning to extend enrolment of patients beyond the target number of 460, making a total of 510–560 to be treated by September 2018. No exact estimate of savings from the Global Fund grant was made during the mission, but one will be provided by the NTP to the WHO Regional Office for Europe later in the summer.

In total, 96 patients were enrolled in treatment with Bdq-containing regimens under the two funding mechanisms during 2015–2018. Earlier in 2018, the Ministry of Health endorsed the inclusion of Bdq, Dlm, Lzd and Imp-cls, except Cfz, in the national list of essential medicines eligible for government funding, making it possible to start procuring these drugs next year bearing in mind that all of them are registered in the EU. The NTP has given estimates for 2019 to the Ministry of Health and is planning to receive 164 treatment courses of Bdq and 50 of Dlm. In addition, the NTP is planning to enrol 600 patients with M/XDR-TB under the forthcoming European Economic Area (EEA grant) for 2019–2021, of whom up to 100 will receive therapy with new TB drugs (see also the section on drug supply and management).

Table 16. Number of RR/MDR-TB patients enrolled in treatment, 2013–2017

Patients	**2013**	**2014**	**2015**	**2016**	**2017**
Total number of RR/MDR-TB patients enrolled in treatment:	662 (656 treated)	602 (597 treated)	595 (588 treated)	550 (546 treated)	449 (442treated)
– of which, in penitentiary sector	3	3	4	3	4
– of which, children (0–14 years)	2	4	4	1	1

– of which, on STRs	0	0	0	0	0
– of which, on regimens containing new drugs (Bdq, Dlm)	2*	2*	4*	54*	22*

Source: NTP.

* Bedaquiline-containing regimens

The NTP has developed an updated version of the national guidelines for TB and DR-TB, which has been submitted to the Ministry of Health for review and endorsement but not yet approved. The updated version matches the 2016 WHO guidelines on treatment of DR-TB and includes information on Bdq and Dlm. It does not include the new grouping of TB drugs; instead it uses the classification of TB drugs described in the WHO compendium handbook to the guidelines on programmatic management of DR-TB of 2015. The new TB drugs – Bdq, Dlm, Lzd, Cfz and carbapenems – are listed and presented as Group 5 agents in the national classification of TB drugs. The new document contains information on regimen design for DR-TB based on the 2015 grouping of TB drugs, dosages, diagnostic algorithms, protocols on the management of side-effects, and the required registration and treatment forms. It does not contradict any of the latest WHO recommendations and policy documents related to management of patients with DR-TB but helps clinicians design adequate treatment regimens. With the forthcoming revision of the WHO guidelines on DR-TB, some updates to the national guidelines might be possible in 2019.

Treatment regimens for DR-TB are individualized and take into account several factors to determine the appropriate minimum and combination of effective drugs in the regimen. As well as DST, a history of previous use of FLDs and SLDs, information on contacts, comorbidities and pre-existing conditions and information on adherence must be taken into account in building the regimen. The ultimate goal of the regimen with new TB drugs, especially in the case of XDR-TB, is to include at least four probably effective SLDs. The duration of the intensive phase of treatment is set at no less than eight months and duration of the whole course of chemotherapy at no less than 20 months, although an extension beyond 20 months is possible for previously treated patients with DR-TB and others with massive pulmonary destruction. Discontinuation or non-inclusion of the injectable agent in the MDR-TB regimen is possible but does not often happen, and takes into account the present or increasing toxicity to second-line injectables (hearing impairment, renal insufficiency, hypersensitivity, pain at site of injection).

All standardized MDR-TB regimens were based on DST and included at least four SLDs considered to be effective: a second-line injectable agent (aminoglycoside or Cm), FQ (Lfx), prothionamide (Pto), Cs/para-aminosalicylic acid (PAS) and 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. The NTP was advised to implement a minimum of six days a week dosing of SLDs at outpatient settings and ensure DOT. E was used if shown susceptible by DST. Z was used during the entire therapy. During 2016–2017, the majority of patients who were diagnosed with RR/MDR-TB were enrolled in a treatment programme under the Norway and Global Fund grants, 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/Lfx–Pto–Cs–Z–E, with Mfx available to reinforce the regimen. Similarly to previous missions, it was advised that Lfx should be considered as FQ of first choice in the management of patients with MDR-TB instead of Ofx.

In most cases the indications for treatment with new TB drugs were laboratory-confirmed resistance to FQ and/or second-line injectable (pre-XDR and XDR-TB). All XDR-TB regimens contained three drugs, Bdq–Lzd–Cfz, and the DR-TB committee considered it the backbone regimen for patients with resistance to FQ. Dlm had never been used before and was not available through any source of funding, but was considered as a potential drug by the NTP for treatment of M/XDR-TB and was

included in the national procurement plan. 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.

Bdq and Dlm have been used for 24 weeks, with dosages and frequency described in the WHO interim guidance and updated national guidelines. Lzd has been used for the entire treatment at a 600 mg dose daily, with pyridoxine (vitamin B6) 50 mg daily. Cfz only became available in Romania under the Norway and Global Fund grants and has mainly been used together with Bdq and Lzd to manage pre-XDR and XDR-TB, administered at 100 mg once daily throughout the entire course of treatment. Imipenem-cilastatin (Imp-cls) is used for a limited number of patients at a dose of 1000 mg twice daily: two vials administered as 40–60 minute infusions twice daily (four vials daily). Its use is limited to the inpatient phase and is mainly affected by administrative constraints in outpatient settings. Patients on Imp-cls require long-term access to their central veins because of the twice-daily intravenous infusions, which are not available for DR-TB patients in Romania. Amoxicillin-clavulanate (Amx/Clv) is added to regimens, which included Imp-cls (carbapenem), as recommended in the latest WHO guidelines. The dosage of Amx/Clv was based on the clavulanic acid component, 125 mg 30 minutes orally before the intravenous infusion of Imp-cls.

The off-label use of the new TB drugs was not recorded during the visit. However, the 2017 WHO *Best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of MDR-TB*[4] describes the extended use of Bdq and Dlm beyond 24 weeks and the use in patients from special categories (under 18 years of age for Bdq, during pregnancy or lactation), which can be considered by the NTP in individual cases. In addition, the NTP was informed that more evidence and possible new recommendations would be released after the July 2017 revision of the WHO guidelines. The concomitant use of Bdq and Dlm was not recorded, as Dlm was not available in Romania for treatment of DR-TB. When Dlm does become available for treatment of DR-TB, its use in combination with Bdq should not be considered as off-label as both drugs would be used upon indications. DR-TB committees might consider this combination of new TB drugs in individual cases for patients with extensive pulmonary damage who show a slow positive response to therapy with an extensive drug-resistance pattern and in whom bacteriological conversion had been achieved at later months. If considered for off-label use (such as an extension of Bdq and Dlm beyond 24 weeks), the treating physicians should obtain a patient's informed consent and provide thorough clinical monitoring throughout the entire course of therapy.

The shorter treatment regimen (STR) for MDR-TB has not yet been introduced in Romania, either as a pilot or for programmatic use. It was recommended that the NTP should consider introduction of the shorter treatment regimen only as a pilot and after the release of the WHO comprehensive review of the DR-TB guidelines, which will include the final results of the STREAM I Trial (July 2018). Any modification of the shorter treatment regimen should be carried out under operational research conditions and with guidance recently released by the Global Drug-resistant TB Initiative (GDI).[5]

Clinical and laboratory monitoring of DR-TB patients on new TB drugs is performed on a regular basis as required by national guidelines. A minimum of six months of monthly electrocardiogram monitoring is conducted for patients on Bdq-containing regimens. The remaining clinical investigations include baseline and monthly monitoring of electrolytes (at baseline and during hospitalization), complete blood count, liver and kidney function tests, and albumin, bacteriology and physical examinations. Chest X-rays are possible on a quarterly basis; more advanced methods of radiological investigations are possible at major hospitals, including the future interregional DR-TB

[4] *Best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of MDR-TB* Geneva: World Health Organization; 2017 (https://www.ghdonline.org/uploads/Best_practice_off-label_bdq_dlmFINAL11.08.2017.pdf, accessed 23 July 2018).

[5] Stop TB Partnership. Global Drug-resistant TB Initiative (GDI) [website]. Geneva: World Health Organization; 2018 (http://www.stoptb.org/wg/mdrtb/resources.asp, accessed 23 July 2018).

centres. A wide network of specialists, including cardiologists, neurologists, ear, nose and throat doctors and ophthalmologists are available in case of adverse reactions or clinical consultations at TB hospitals and major PHC clinics. However, clinical monitoring of patients at outpatient settings requires improvement because some of the tests are not done on a regular basis and there is a chance of missing adverse reactions after discharge from hospitals to outpatient settings, especially those located remotely. Thus, it is strongly recommended that the NTP should improve capacity at both central and regional levels to manage and monitor DR-TB patients on therapy with new TB drugs. For more details on pharmacovigilance please refer to the section on drug supply and management and pharmacovigilance below.

A shortage of access to SLDs (especially injectable agents and FQs) during 2010–2015 due to health system challenges had led to the creation of a reservoir of M/XDR-TB, especially at county-level TB facilities. Currently, access to MDR-TB therapy has significantly improved with the increased availability of SLDs through government funding and two external grants (the Global Fund and Norway grants). Both grants served as catalysts for scaling up access to DR-TB treatment, including the new TB drugs. 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 this reservoir (defaults and failures) outweighed those influencing its shrinkage (patients cured, completing treatment, dying and transferring out). The growth of the DR-TB reservoir was also exacerbated by delays in the diagnosis of DR-TB, prolonged hospitalization and poor infection control at inpatient facilities. However, the NSP regulates the universal access to diagnosis of and treatment for TB and DR-TB and the Government's commitment to sustainability of the NTP. For all these reasons, the NTP should be in a position to expect a rapid decline in the main TB indices (including DR-TB) over the next few years.

The latest treatment outcomes for RR/MDR-TB and XDR-TB are available for 2014 and 2015, when the treatment success rate for RR/MDR-TB stood at a maximum of 43.2% and the rates for treatment failure, death and loss to follow-up were high (Tables 17, 18). These treatment outcomes are presented for both GLC and non-GLC cohorts and should, therefore, be considered as less informative for evaluating performance of the NTP. The cohorts of patients were not similar, which does not seem appropriate; the need to provide separate reporting was discussed with the NTP with the recommendation to consult the Regional Office. 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. In addition, Bdq only became available for a limited number of patients under the compassionate use programme starting in 2015, which obviously cannot have influenced treatment outcomes. Table 19 presents the treatment outcomes of GLC cohorts of patients and shows significantly higher treatment success rates. Nevertheless, it is expected that with increased access to Bdq, Lzd, Cfz from both grants (2016 to the present) and government procurement from 2019 of Bdq, Dlm, Lzd and Imp-cls, as well as improvements in the provision of DOT, it will be possible to have achieved significantly better treatment outcomes for cohorts of patients with MDR-TB and XDR-TB starting in 2016 (final outcomes to be available 36 months after end of the year).

Table 17. TB treatment outcomes, RR/MDR-TB cases, 2011–2015 cohorts

	2011		**2012**		**2013**		**2014**		**2015**	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
RR/MDR-TB cohort size	**618**	**100**	**782**	**100**	**663**	**100**	**602**	**100**	**595**	**100**
Treatment succeeded	184	29.8	290	37.1	258	38.9	249	41.4	257	43.2

Treatment failed	204	33	204	26.1	168	25.3	164	27.2	162	27.2
Died	110	17.8	126	16.1	117	17.6	101	16.8	100	16.8
Lost to follow-up	101	16.3	143	18.3	107	16.1	88	14.6	70	11.8

Source: NTP.

Table 18. TB treatment outcomes, XDR-TB cases, 2011–2015 cohorts

	2011		2012		2013		2014 (36m)		2015 (24m)	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
XDR-TB cohort size	**34**	**100**	**41**	**100**	**56**	**100**	**58**	**100**	**71**	**100**
Treatment succeeded	6	17.6	5	12.2	11	19.6	9	15.5	28	39.4
Treatment failed	13	38.2	22	53.7	29	51.8	28	48.3	28	39.4
Died	10	29.4	10	24.4	12	21.4	15	25.9	10	14.1
Lost to follow-up	5	14.7	4	9.8	4	7.1	6	10.3	5	7.0

Source: NTP.

Table 19. TB treatment outcomes, MDR-TB cases, 2011–2015 cohorts

Cohort	No. enrolled	Still in treatment	Success	Lost to follow-up	Failure	Excluded	Death
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 (Global Fund new funding mechanism)	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[a]	45 (4.5%)
Cohort 7 (Global Fund transitional funding mechanism)	460	10	0	0	0	0	0
TOTAL	**2715**	**988**	**797**	**71**	**95**	**9**	**86**

[a] 14 excluded; 36 transferred out.

Options for DOT during ambulatory treatment are limited, with patients actively coming to TB dispensaries and PHC clinics for treatment. PHC clinics and TB dispensaries offer DOT on weekdays; on Saturdays treatment is mostly self-administered. With treatment during the continuation phase delegated to PHC, a significant improvement was observed during the mission, especially in view of the monetary incentives paid to PHC providers (family doctors) to provide DOT as part of the providers' contract, which will hopefully increase their commitment and improve treatment outcomes. Options for a patient-centred approach and use of hospital replacement mechanisms, such as home-based treatment or video-observed therapy, are still very limited.

The NSP for 2015–2020 has reform of ambulatory care as one of its major components, with the overall goal of reducing unnecessary hospitalization. Reform started in 2016 under the Global Fund 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. Under the Global Fund grant, six multidisciplinary teams (including one doctor, one psychologist and one social worker) were set up in TB hospitals in

Neamț, Argeș, Maramureș, Constanța, Dolj counties and Bucharest, with the principal task of assessing and referring TB patients to the ambulatory sector. The target group was identified as patients with more than four months until the end of treatment. In addition to this, DOT and social support vouchers were organized in most counties for MDR-TB patients enrolled in the Global Fund project. The NTP is using the experience from the Global Fund grant to develop national policy with a focus on strengthening the ambulatory care for TB and reducing unnecessary hospitalization. Changes in national legislation had already happened, with DOT added as a service to Ministry of Health contracts with family doctors, paid by the national health insurance.

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 under the 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.

Recommendations

No.	Recommendation	Timeframe	Responsible (institution)
1	Universal coverage with regimens containing new anti-TB drugs for management of M/XDR-TB (Bdq, Dlm, Lzd, Cfz and Imp-cls+Amx/Clv) should be ensured, including in the prison sector.	2018 Q1	Ministry of Health, NTP, Prison sector
2	The national guidelines for management of DR-TB should be endorsed, with the possibility of introducing updates from the forthcoming revision of the WHO guidelines on DR-TB.	2018 Q3	Ministry of Health
3	For all patients with M/XDR-TB who require therapy with new TB drugs, procurement should be organized, finalized and ensured (estimates provided to Ministry of Health by NTP for 2019–2020).	2018 Q3-Q4	Ministry of Health, NTP
4	Adequate management of M/XDR-TB in counties should be ensured, including but not limited to capacity-building for regional TB teams, active drug safety management and monitoring (aDSM), and introduction of methods to strengthen adherence.	2018 and onward	NTP
5	Consideration should be given to the step-by-step scale-up of introduction of treatment with new anti-TB drugs at regional MDR-TB treatment centres (university hospitals with sufficient capacity and infrastructure).	2018 Q3-Q4	NTP
6	Coverage with SLD DST (preferably SLD LPA)	2018 and	NTP

	should be increased to all patients diagnosed with RR to ensure the appropriate design of individualized regimens.	onward	
7	Decisions about the off-label use of Bdq and Dlm should be taken on a case-by-case basis according to the WHO statement of September 2017.	2018 and onward	NTP
8	The possibility of introducing a shorter treatment regimen for MDR-TB after release of the revised WHO guidelines on treatment of DR-TB should be discussed.	2019	NTP
9	For patients who require TB retreatment, the category II regimen should no longer be prescribed. DST should be conducted to inform the choice of treatment regimen (good practice statement). The TB guideline should be reviewed accordingly.	2018	NTP
10	The capacity of ambulatory care for TB and DR-TB should be strengthened by the introduction of and support for patient-centred models of care as alternatives to hospitalization as well as methods to strengthen adherence.	2018 and onward	NTP
11	Video-observed therapy as an alternative method of DOT should be considered for patients with drug-susceptible and drug-resistant TB. Consideration should be given to using video-observed therapy in real time or recorded via Skype or messenger service applications (such as WhatsApp, Viber).	2018	NTP

Other programme areas

Programmatic management of DR-TB in prisons

The prison sector was not visited during this mission. No DR-TB patients are being treated with individualized Bdq-containing regimens.

Recommendations

No.	Recommendation	Timeframe	Responsible (institution)
1	Universal coverage with regimens containing new anti-TB drugs for management of M/XDR-TB (Bdq, Dlm, Lzd, Cfz and Imp-cls+Amx/Clv) should be ensured, including in the prison sector.	2018 Q1	Ministry of Health, NTP, Prison sector

Drug supply and management, pharmacovigilance

The system of drug procurement is centralized and fully funded by the Ministry of Health. All anti-TB medications are purchased through the system of national tenders according to the list of essential medicines, TB component, approved and updated by the Ministry's annual national tenders (the C2 list). Several improvements in the national system of drug procurement have been observed since the last mission, including: increased access to anti-TB drugs for DR-TB at all treatment sites, no stockouts or shortages of drugs noted by the consultant or reported by the NTP, improved national list of essential medicines and better coordination between the NTP and counties in estimating drug needs and orders.

On 4 May 2017, the Ministry of Health signed a decree allowing the use of medicines effective against MTB and its drug-resistant strains, as recommended by the latest WHO guidelines, and authorizes their inclusion in the C2 list. As a result, the NTP revised the C2 list and included Bdq, Dlm, Lzd, Mfx, Lfx and Imp-cls, which made them eligible for purchase with government funding starting in 2019. In addition, the decree facilitates the import of these drugs even if registration is pending, as with Cfz and Dlm, to be procured in the first place with external funding. The consultant discussed some suggestions with the NTP for improving the C2 list of medicines: (i) Ofx should be removed from the C2 list and levofloxacin (Group 1) should serve as the FQ of choice in the management of DR-TB; (ii) consideration should be given to adding PAS (Group D3) to the list following the publication of the updated WHO guidelines, as savings can be made if PAS is not widely used in regimens for DR-TB; (iii) once Cfz is registered in the EU or Romania, it should be included in the C2 list as a core MDR-TB drug from Group C; and (iv) Cm should be included in the C2 list as a Group B drug.

The consultant discussed several areas for improvement with the NTP focused on improving the tracking system for the consumption of TB drugs in the counties to facilitate forecasting and future orders. At present the NTP relies on approximate estimates of needs based on non-standardized reporting from counties. A national electronic system (software) should be created to address these gaps so as to provide regular reporting on the consumption of drugs and to estimate needs, which will eventually improve the system of TB drug management at county and national level and avoid any possible risks of stockouts and shortages. In addition, the recommendation for the NTP to consider using one of the WHO-recommended tools for quantification and forecasting, such as QuanTB, remains for consideration and is not mandatory. The distribution of anti-TB medicines to county-level TB hospitals and dispensaries still requires improvement to avoid possible stockouts, shortages and interruptions in treatment. Even with the national tender for selection of drugs, the distribution of drugs to user points (TB hospitals in counties) requires the participation of different distribution companies in the national tender, which is impossible to control at central level and poses risks of stockouts of drugs at the level of the TB hospitals. Consideration should be given to revising the current system of drug distribution and rationalizing the system of delivery of TB drugs to user points to improve drug management and reporting and avoid possible stockouts as well as interruptions in treatment.

In total, 96 patients were enrolled in treatment with regimens containing Bdq under the Norway and Global Fund grants during 2015–2018. Earlier in 2018 the Ministry of Health endorsed the inclusion of Bdq, Dlm, Lzd and Imp-cls, except Cfz, in the national list of essential medicines (C2 list), which made them eligible for government funding and procurement starting in 2019. The NTP has given the Ministry of Health estimates for 2019 and is planning to receive a minimum of 164 treatment courses of Bdq and 50 courses of Dlm. The consultant checked these estimates with the NTP during the mission and found them reasonable. The Ministry of Health has committed itself to support the budget allocation starting in 2019 for all SLD, including Bdq, Dlm, Lzd and Cfz. Unifarm, the major distributing company, will procure Cfz, taking into account that the drug is not yet registered in

Romania. In addition, the NTP is planning to enrol 600 patients with M/XDR-TB under the forthcoming EEA grant for 2019–2021, of whom up to 100 will receive therapy with new TB drugs.

At the time of the mission the NTP had no plans to introduce a shorter regimen for MDR-TB, so no drug estimates had been included in the national procurement plan for 2019. The consultant discussed with the NTP the introduction of a shorter regimen for MDR-TB after the release of the revised version of the WHO guidelines planned for mid-July 2018. In addition, the consultant recommended discontinuing the use of the category II regimen for patients who require TB retreatment, and the conduct of DST to inform the choice of treatment regimen. Generally, stopping the inclusion of the category II regimen in estimates of the national procurement plan will bring extra savings, which can be spent on covering more DR-TB patients with new TB drugs.

There is a national system of pharmacovigilance for DR-TB. The system of aDSM, as recommended by WHO, is incomplete and does not use systematic and standard recording and reporting of adverse events. Minimum clinical and laboratory examination of patients on therapy with new TB drugs is carried out in the two main DR-TB centres (MNI and Bisericani), which have the capacity for this task, including specialists such as cardiologists, neurologists, ear, nose and throat doctors and ophthalmologists. The capacity of the interregional DR-TB centres, which are currently being set up, is, however, questionable. Similarly, the capacity to perform the minimum of mandatory instrumental and laboratory clinical investigations at the level of PHC, including training of family doctors and coordination and supervision by the regional TB coordinator, will require thorough assessment and significant improvement. Currently, all DR-TB patients eligible for therapy with new TB drugs are hospitalized and treatment is initiated at the DR-TB centre, followed by discharge to a county TB dispensary or hospital or PHC facility for continuation of treatment. Regional TB coordinators are responsible for supervising and mentoring family doctors for the medical and programme management of DR-TB while patients receive therapy at the level of PHC clinics. The implementation of minimum requirements for clinical and laboratory monitoring, as defined by the new DR-TB guidelines and recommended by DR-TB committees, is incomplete and there is a high chance that adverse events will be missed, which will eventually affect treatment outcomes. For example, basic screening for peripheral neuropathy and optic neuritis (an adverse event of Lzd) is not carried out in the counties. Electrocardiogram monitoring is being done but interpretation of the results, including calculation of the QT interval, can only be done by cardiologists, who are not always available, rather than by TB treatment providers.

There is a significant need to introduce a standardized system of systematic laboratory and clinical assessments during treatment, which are happening more or less, to detect toxicity and adverse events. Discussions should take place at national level with representatives of the National Drug Regulatory Authority regarding the choice of level of aDSM package: core, intermediate or advanced. A core aDSM package with recording and reporting of adverse events could be introduced at least as a first stage, with an intermediate level package introduced later. Assistance from the Regional Office and rGLC should be considered with the introduction of an aDSM core package, and adequate efforts allocated to capacity-building in the NTP and among county-level health providers as the country scales up access to the new TB drugs. Once the level of aDSM is selected by the NTP, external technical assistance should include the development of forms and standard operating procedures for standard recording and reporting of adverse events, procedures for causality assessment and international reporting to WHO.

Recommendations

No.	Recommendation	Timeframe	Responsible (institution)

1	Adequate financing and an uninterrupted supply of SLDs should be ensured, including Groups A (FQs), B (second-line injectable agents), C (Eto/ Pto, cycloserine, Lzd, Cfz) and D2 (Bdq, Dlm) for all patients diagnosed with DR-TB.	2018 and onward	Ministry of Health, NTP
2	The following revision should be considered to the national list of essential medicines, TB component (C2 list),: • remove Ofx and consider levofloxacin (Group 1) as first choice FQs for MDR-TB; • include PAS (Group D3) in the C2 list only upon release of the updated WHO guidelines; revise the national drug orders accordingly, as savings can be made if the revised guidelines do not recognize PAS for wide use in treating MDR-TB; • include Cfz (Group C) in the C2 list once it is registered in Romania; meanwhile, ensure an uninterrupted supply of Cfz, as the core MDR-TB drug, for patients with DR-TB; • include Cm (Group B) in the C2 list.	2018	Ministry of Health, NTP
3	The use of one of the WHO-recommended tools for quantification and forecasting of TB drugs, such as QuanTB, should be considered.	2018	NTP
4	Consideration should be given to revising the current system of drug distribution and to rationalizing the delivery system for TB drugs to user points to improve drug management, reporting and avoid possible stockouts as well as interruptions to treatment.	2018–2019	Ministry of Health, NTP
5	The core level, at least, of aDSM should be introduced into the NTP when managing: • patients with MDR-TB in treatment with Bdq, Dlm and other new medicines; • all XDR-TB patients in second-line treatment, as these regimens include repurposed companion drugs (Lzd and Cfz); • MDR-TB patients enrolled in treatment with novel MDR-TB regimens (including a shorter MDR-TB regimen).	2018	Ministry of Health, NTP, National Drug Regulatory Authority
6	Consideration should be given to procuring paediatric formulations of drugs for MDR-TB, and technical assistance should be sought from the Global Drug Facility.	2018	NTP

7	For patients who require TB retreatment, the category II regimen should no longer be prescribed. The national procurement plan for 2019 should be reviewed accordingly.	2018 Q3-Q4	NTP, Ministry of Health
8	Technical assistance from the Regional Office and rGLC should be considered with the choice of package and introduction of aDSM into the NT.	2018–2019	NTP
9	Training on aDSM should be conducted for TB health providers at central and regional level.	2018	NTP, National Drug Regulatory Authority

Infection control

Improving infection control was a priority in the NTP, recognized by the Ministry of Health in its 2017 approval of the NSP (Intervention 2.5. Establish infection control standards and requirements for health care facilities). As part of the NSP, the Ministry of Health endorsed the earlier National Infection Control Plan for Tuberculosis Control, which is in line with the latest WHO recommendations. This Plan includes information on all relevant components of infection control: administrative, environmental and personal protection measures, and will serve as a guide for all facilities involved in TB control to develop and implement their own infection control plans. The purpose of the document is 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 recent years, the NTP has been using a comprehensive tool to provide background information on current infection control measures in facilities, with clear instructions for improvement. The template contains information on management of infection control, monitoring and evaluation and budget tools. Each facility has been asked to develop and implement its own infection control plan. Using the tool, the NTP has classified TB hospitals based on: (i) the risk of nosocomial transmission; (ii) TB incidence and the number of TB patients in the county; (iii) the number of beds for TB patients in the facility; (iv) types of patients diagnosed and treated in the facility; and (v) TB incidence among health personnel in the facility. The Plan will allow facility-level infection control plans to be implemented, mainly including the administrative separation of patient flows and personal protection measures for health facility personnel.

The administrative separation of patient flows was evident in all facilities visited during the mission. Positive improvements included (in Laemna and Pascani hospitals) separate wards allocated to patients with DR-TB. Infection control plans were available in almost every TB inpatient facility, although they had not been implemented in full as the funds were to be allocated from the Ministry of Health in accordance with the National Infection Control Plan. The TB hospital in Laemna, Craiova county (visited by the rGLC in 2012, 2015, 2016, 2017 and 2018), had made significant improvements in separating non-TB from TB and DR-TB patients. In Laemna, a new building for the MDR-TB ward was under construction and due to be ready by the autumn of 2018. This would make the hospital one of eight intercounty MDR-TB treatment centres for the hospitalization of vulnerable and homeless patients who need to continue their 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.

As well as the Global Fund grant, the NTP is committed to improving infection control 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, increased access to regimens with new TB drugs and early initiation of appropriate treatment seem to be the measures with the most potential which are aimed at decreasing the risk of nosocomial transmission of infection. Earlier in

2017 the NTP procured 2000 upper-level ultraviolet germicidal lamps, which were installed in 49 institutions across Romania (Philips, 30 m^2 coverage, 18 000 hours/lamp). Lamps were modern, reliable and user-friendly and recommended for use in institutions involved in TB control by an international consultant on infection control. Free Flight Phase 2 biosafety class respirators provide personal protection for health/administrative personnel at DR-TB centres (MNI and Bisericani) and are recommended to all inpatient TB facilities involved in the management of TB patients, including those in therapy for DR-TB.

Despite the availability of external funding (from the EEA) for the next three years, the absence of Government endorsement for the National Infection Control Plan makes the implementation of some measures problematic. The scheduled installation of ultraviolet germicidal lamps was not regulated by any of the national standards but carried out on the basis of international recommendations only. There is a need to urgently endorse the updated version of the National Infection Control Plan and ensure adequate financing for infection control activities. Furthermore, the Ministry of Health should introduce TB infection control measures in diagnostic and treatment facilities and in crowded settings by revising its Order No. 916 (26 July 2006) and the current system of health facility accreditation, including specific measures for the prevention of airborne TB transmission.

Recommendations

No.	Recommendation	Timeframe	Responsible (institution)
1	The updated version of the National Infection Control Plan should be endorsed and adequate financing of infection control measures ensured.	2018	Ministry of Health
2	The legislative base regulating health facility accreditation and prevention of TB transmission should be revised to include appropriate infection control 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.	2018 Q3-Q4	Ministry of Health, NTP
3	The F-A-S-T strategy/approach should be expanded and routinely implemented 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.[a]	2018 and onward	NTP
4	Rapid molecular diagnosis of TB and resistance to at least H and/or R (GeneXpert MTB/RIF and MTBDR*plus*) should be done prior to a patient being admitted to a TB inpatient facility (ongoing recommendation).	2018 and onward	NTP
5	The allocation of adequate funding for personal protection measures for health and administrative personnel should be ensured at all	2018 and onward	NTP

	treatment sites involved in the management of TB and DR-TB (ongoing recommendation).		

[a] Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely, and Treat effectively based on rapid DST.

Human resources, capacity-building needs

A series of capacity-building initiatives for the management of patients with new TB drugs and aDSM are recommended for county-level TB coordinators and family doctors to ensure greater access to new TB drugs and adequate implementation of the NTP.

Recommendations

No.	Recommendation	Timeframe	Responsible (institution)
1	Training curricula on the NTP and medical management of DR-TB should be ensured for at least two levels of health provider: TB county coordinators and PHC providers.	2018 Q3–Q4	NTP
2	Assistance from the Regional Office and rGLC should be considered for the review of training materials.	2018 Q3-Q4	NTP
3	A series of capacity-building seminars should be conducted on programmatic management of DR-TB with a focus on the use of new TB drugs and aDSM.	2018–2019	NTP

Information system, programme monitoring and supervision

The national recording and reporting 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 Ministry of Health as mandatory for all institutions involved in the TB programme. TB surveillance software is functioning in all TB dispensaries, with all cases registered at county level and then reported to the NTP. 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) and then referred to the MNI (NTP coordinator) (tertiary level). The current software 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 is being done.

A separate electronic MDR-TB registry is available in 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 in therapy for any reason. The registry contains information on the patient's unique number, diagnosis, bacteriology results (smear, culture, DST and rapid molecular tests), treatment regimen and clinical testing. The central coordination unit at

national level monitors the collection of data 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 NTP (national laboratory coordinator).

The treatment registration forms should be revised and updated in accordance with the WHO *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis*, Part 4 (Forms for drug-resistant TB programmes)[6] and included in the updated version of the national guidelines on DR-TB. In addition, the NTP was advised to develop forms and standard operating procedures for implementation of aDSM and introduce them into routine practice.

Recommendations

No.	Recommendation	Timeframe	Responsible (institution)
1	Consideration should be given to revising the treatment recording and reporting forms on DR-TB and including them in the revised national guidelines for DR-TB.	2018 Q3-Q4	NTP

Legal and ethical issues

Treatment of TB and MDR-TB, including regimens with new TB drugs, is free irrespective of the patient's race, ethnicity, religion, age or gender. Access to treatment is equal for every patient diagnosed with DR-TB, irrespective of place of residence in the country. Patients can choose whether to start treatment in hospital or where they live. Palliative care for TB patients is not available in Romania.

In recent years Romania has faced issues connected with migration of labour, mostly to Western Europe, with patients often defaulting on treatment in order to take up work outside the country.

Recommendations

No.	Recommendation	Timeframe	Responsible (institution)
1	Access to diagnostics and treatment of DR-TB should be scaled up, including to new TB drugs.	2018	Ministry of Health

Strategic planning, funding of programmatic management of DR-TB interventions and partnerships

The NSP was developed in line with the WHO End TB Strategy to ensure the full impact of a complex of public health and programmatic actions on the burden of TB in the country. It outlines national strategies to meet needs that are not currently satisfied and to build sustainability in the system. It also presents a long-term vision and identifies innovative approaches targeted at achieving a

[6] Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014 (Part 4; http://apps.who.int/iris/bitstream/handle/10665/130918/9789241548809_eng.pdf?sequence=1, accessed 23 July 2018).

dramatic decline in TB incidence and mortality in Romania by 2020. The Plan presents goals and objectives for the diagnosis, treatment and prevention of TB. The aim of the eight strategic objectives is to bring about a sharp decline in TB incidence and mortality through 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 is based on three pillars and outlines a series of key intervention areas: (i) integrated patient-centred care and prevention; (ii) bold policies and supportive systems; and (iii) innovative research and evidence-based strategies. The National M/XDR-TB Response Plan has been successfully incorporated into the NSP for 2016–2020 and has a key role in implementing the NTP across the country. The NSP's budget for 2015–2020 has been consolidated and includes funding from the Government, the Norway grant, the Global Fund, 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 plays a very important role in building the sustainability of the NTP. 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 hospitalizations through implementation of ambulatory-based treatment of TB. This reform, supported by the Global Fund grant for 2015–2018, is being 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 establishment of 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 Global Fund to implement an €8.4 million grant to fill gaps and address challenges in TB control in the country for the period April 2015 to March 2018. The goal of the grant is to contribute to a reduction in TB incidence and mortality through high-impact interventions in the areas of diagnosis, treatment, care and prevention, with a special focus on the key affected populations. Under the new Global Fund grant, the NTP has been able to ensure access to quality-assured SLDs, including new TB drugs, for 460 M/XDR-TB patients and to scale up access to rapid molecular diagnosis of TB and DR-TB (GeneXpert MTB/RIF, LPA, MGIT 960).

From August 2014 to April 2017, the NTP implemented the grant received from the Norwegian Government for €10.7 million. The grant was focused on efforts to consolidate TB control activities, especially in relation to MDR-TB and poor and vulnerable populations. 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 on treatment delivery). Significant investments were also 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 RRLs and to invest in the procurement of equipment to reduce the risk of nosocomial transmission of infection.

The forthcoming external funding opportunities for 2018–2023 include the following.

1. Programul Operațional Capital Uman [Human Capital Operational Programme] – POCU 4.8, focused on strengthening the capacity of health providers involved in implementation of the NTP (2018–2021). Budget: €3 million; principal recipient: MNI; status: grant agreement signed.
2. POCU 4.9, focused on screening of TB and latent TB infection and measures to increase adherence to treatment (2018–2023). Budget: €15 million; principal recipient: MNI; status: grant agreement signed.

3. EEA grant, focused on diagnostic and treatment of TB, DR-TB and TB/HIV co-infection. Budget: €10 million; principal recipient: MNI; status: approved by Ministry of Health but not yet signed.
4. Global Fund grant, focused on supporting the implementation of TB health reform. Budget: €3 million; principal recipient: Romanian Angel Appeal; status: to be determined.

A series of activities to support and ensure the implementation of the NSP will require revisions to current policy, so the involvement of all country stakeholders and support from the Ministry of Health will be required. With most of the funding coming from the state budget, implementation of the NSP is guaranteed. External donor funding still, however, provides support for several components of the NTP for which coverage by the Ministry of Health currently seems problematic or impossible because it will require amendments to existing regulations and a reform of health financing. These components are critical and are highlighted in this report as requiring support and attention from the Ministry of Health and the NTP. Their implementation will require additional investments from external donor funding for at least three years, during which time the Government should gradually take over full financial responsibility.

Annex 1 Terms of reference

Objectives

The aim of the proposed mission is to support the lead clinical consultant in:

- assessing the progress of the implementation of the NSP, including its M/XDR-TB component, and develop recommendations for future activities;
- assessing the progress made and readiness for effective introduction of new drugs by the NTP;
- assessing the effectiveness of implementing the current DR-TB control project supported by the Global Fund, including TB drug management;
- advising on the estimated number of MDR-TB and XDR-TB patients for 2017–2018;
- assessing readiness for an effective start-up of a nine months short course treatment for suitable patients.

Key issues to be elaborated and reviewed

The key issues to be drawn up and reviewed are 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;
- assess case-finding strategies and identify barriers to the prompt start of DR-TB treatment, including TB in children;
- review and provide recommendations on the existing guidelines on DR-TB;
- assess medical/clinical aspects of management and treatment of MDR-TB and XDR-TB;
- assess the status of the introduction of new TB drugs;
- assess aDSM;
- ensure follow-up of TB and DR-TB patients, their adherence to treatment and the patient-centred approach and social support;
- assess the experience with paediatric fixed dose combinations received from the GLC, plans and readiness to introduce them;
- assess the implementation of the 2016 WHO recommendation for a shortened regimen (9–12 months) for treating clearly specified forms of DR-TB;
- assess the status of rapid diagnostics.

Description of work

It is proposed that the technical assistance mission is divided into five working days in the country and five working days outside the country, with a view to conducting the following activities:

- supporting the NTP in developing an initial draft of the DR-TB plan/guidelines (days 1–4);
- participating in meetings with the Ministry of Health, NTP and partners (day 5);
- assessing the current case-management system and finding the best solutions for patients placed on the WHO-recommended shorter treatment regimen (including monitoring and follow-up);
- supporting the NTP in finalizing the revised TB treatment guidelines and a transition plan (days 6–10, remotely).

Deliverables

- rGLC monitoring mission report with recommendations.
- Identification of areas of technical assistance from the Regional Office and rGLC.

Annex 2 Agenda

TIME	ACTIVITY	LOCATION	PARTICIPANTS
21 May 2018, Monday			
09:45–13:30	Meeting and initial briefing at the NTP office	MNI, Bucharest	Adriana Socaci, NTP Michaela Stefan, NTP Domnica Chiotan, NTP Nicoleta Cioran, NTP Mariana Andrei, NTP Victor Spinu, NTP Christina Popa, NTP Cristian Popa, NTP Askar Yedilbayev, rGLC
13:30–19:30	Travel to Iasi county		Adriana Socaci, NTP Michaela Stefan, NTP Askar Yedilbayev, rGLC
22 May 2018, Tuesday			
08:30–15:30	Meeting with NTP team of Iasi county Visit to Iasi TB dispensary, bacteriological and clinical laboratories Visit to MDR-TB ward at Pascani hospital	Iasi county	Adriana Socaci, NTP Michaela Stefan, NTP NTP team of Iasi county Askar Yedilbayev, rGLC
15:30–21:30	Travel to Bucharest		Adriana Socaci, NTP Michaela Stefan, NTP Askar Yedilbayev, rGLC
23 May 2018, Wednesday			
06:30–09:30	Travel to Craiova county		Adriana Socaci, NTP Michaela Stefan, NTP Askar Yedilbayev, rGLC
09:30–16:00	Meeting with NTP team of Craiova county Visit to Iasi TB dispensary, bacteriological and clinical laboratories Visit to MDR-TB ward at Laemna hospital	Craiova county	Adriana Socaci, NTP Michaela Stefan, NTP NTP team of Craiova county Askar Yedilbayev, rGLC
16:00 – 20:00	Travel to Bucharest		Adriana Socaci, NTP Michaela Stefan, NTP

			Askar Yedilbayev, rGLC
24 May 2018, Thursday			
09:00–17:00	Visit to TB dispensary in Bucharest (S4) Visit to MDR-TB centre at MNI Participation in DR-TB Committee Meetings with NTP: DR-TB case management, drug procurement, DR-TB case finding, laboratory, aDSM, infection control	Bucharest S4 MNI, Bucharest	Adriana Socaci, NTP Michaela Stefan, NTP Daniela Homorodan, NTP Domnica Chiotan, NTP Mariana Andrei, NTP Victor Spinu, NTP Christina Popa, NTP Cristian Popa, NTP Askar Yedilbayev, rGLC
25 May 2018, Friday			
09:00–12:00	Meetings with NTP: DR-TB case management, drug procurement, DR-TB case finding, laboratory, aDSM, infection control (continued)	MNI, Bucharest	Adriana Socaci, NTP Michaela Stefan, NTP Daniela Homorodan, NTP Domnica Chiotan, NTP Mariana Andrei, NTP Victor Spinu, NTP Christina Popa, NTP Askar Yedilbayev, rGLC
12:00 – 13:00	Meeting at Ministry of Health	Ministry of Health, Bucharest	Mihaela Bardos, Ministry of Health Amalia Serban, Ministry of Health Adriana Socaci, NTP Michaela Stefan, NTP Daniela Homorodan, NTP Cassandra Butu, WHO CO Askar Yedilbayev, rGLC
13:00 – 16:00	Debriefing at NTP	MNI, Bucharest	Adriana Socaci, NTP Michaela Stefan, NTP Daniela Homorodan, NTP Domnica Chiotan, NTP Mariana Andrei, NTP Victor Spinu, NTP Christina Popa, NTP Cristian Popa, NTP Askar Yedilbayev, rGLC

Annex 3 WHO TB country profile: Romania, 2016