Preparing for uninterrupted supply of TB drugs after the end of the GF grant to Romania

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5 March 2018

List of Acronyms and Abbreviations

C2	List of products eligible for reimbursement by the government
EMEA	European Medicines Agency
EXW	ExWorks (Inco term)
FDC	Fixed Dose Combination tablet
FLD	First Line Drug
GDF	Global Drug Facility
GF	Global Fund
GLC	Green Light Committee
IDA	International Dispensary Association
MDR	Multiple Drug Resistant (TB)
MoH	Ministry of Health
NAMMD	National Agency for Medicines and Medical Devices
NFM	Norwegian Financial Mechanism
NHIH	National Health Insurance House
PNPSCT	Programului Național de Prevenire, Supraveghere și Control al Tuberculozei (The Romanian NTP)
PR	Principal Recipient
PSM	Procurement and Supply Chain Management
RAAF	Romanian Angel Appeal Foundation
SNA	Special Needs Authorisation
SLD	Second Line Drug
STR	Standardized shorter MDR-TB regimen
UNOPS	United Nations Organisation for Project Services
WHO	World Health Organisation
XDR	Xtreme Drug Resistant TB

1. Background

1.1 Aim of the visit

The aim of this visit was to provide assistance to the Romanian Angel Appeal Foundation (RAAF), the National TB Program and the Ministry of Health of Romania with planning for an uninterrupted supply of quality-assured TB drugs after the end of the GF grant.

The objectives were to:

1. Establish which TB pharmaceuticals and key commodities the country will need to procured. *(Due to time limitations we focussed on MDR and XDR medicines)*
2. Estimate the quantities of these products.
3. Using market benchmark prices, estimate the budget required.
4. Analyse the national procurement regulations for pharmaceutical products and possible obstacles if these products are being procured in accordance with them; the analysis shall include, but not be limited to: (1) registration requirements (2) guarantee of the assured quality of the products; (3) identification of the suppliers (4) possibility to procure through GDF.
5. Provide solutions to overcome any procurement hurdles identified and discuss these with the key stakeholders and decision makers.

1.2 Report "The Crisis of Anti-TB Medicines in Romania"

In October 2017, shortly prior to this visit, the NGO Romanian Health Observatory, in collaboration with the StopTBpartnership Romania, published the alert report "The Crisis of Anti-TB Medicines in Romania". This report called for action to overcome several acute challenges that would prevent access to needed TB medicines in Romania once the Global Fund financing for TB drug procurement ends in March 2018.

The report identified the following types of challenges:

- Legal (bureaucracy, contradictory legislation)
- Some TB medicines are not included in the C2 list which is the basis for reimbursement by the Romanian State.
- Some medicines have not been assigned a reimbursement price making it impossible for public institutions to purchase them legally.
- Lack of centralised procurement (due to lack of funds or other reasons)
- Lengthy special needs import authorisation procedures.
- Lack of interest by the manufacturers to request marketing authorisation in Romania.

The report "The Crisis of Anti-TB Medicines in Romania" has been very helpful for this mission and can be found online via this shortened link: http://bit.ly/2gSMGfC.

2. Current MDR TB Guidelines, Regimen and Patient numbers

2.1 TB Guidelines

The latest officially approved National TB Guidelines are from 2005. These were the basis for the successful application in 2004 for GLC approval which allowed the start of treating the 1st cohort of MDR patients in Romania in 2005.

Although specialists are working on updating the 2005 national guidelines, this has not yet been completed (amongst others due to changing WHO guidelines). However, in practice the program follows the latest WHO guidelines.

2.2 Regimens used

All patients enrolled in the donor cohorts are placed on a regimen by the national MDR commission. To a large extent, patients receive individualized regimen but for planning purposes, the PNPSCT assumes that the following standard regimen are applied

MDR:

- 10-Km-Cs-Lfx-Pto / 14-Cs-Lfx-Pto
- 10-Cm-Cs-Lfx-Pto / 14-Cs-Lfx-Pto

Pre-XDR and XDR:

- 12-Km-Cs-Mfx-Pto-Lzd / 12-Cs-Mfx-Pto-Lzd
- 6-Cm-Cs-Lfx-Pto-Cfz-Lzd-BDQ / 6-Cm-Cs-Lfx-Pto-Cfz-Lzd / 12-Cs-Lfx-Pto-Cfz-Lzd

(In addition, first line drugs Z, E and H may be used in these regimen but these are not shown as these are supposed to be adequately available)

In principle, patients treated with domestically funded medicines should also be started by the MDR commission but at times these patients are started on a regimen decided in the periphery.

In addition, some patients will be treated with Delamanid which has been included in the quantification for the procurement with national funding.

We enquired whether the country intends to roll out the new Shorter TB Regimen (STR) but were informed that this is not likely to happen in 2018/9 so we will not consider STR in this report.

2.3 Available medicines

All medicines required for the above mentioned regimen have been financed by Global Fund and Norwegian grants. Patient cohorts, 1, 2, 3, 4, 5 and 7 have been treated using MDR medicines procured from Global Fund grants while cohort 6 (which was the largest cohort and included 1000 patients) was treated with MDR medicines procured from the Norwegian Financial Mechanism grant.

In parallel, there have also been cohorts treated with medicines procured with national budget. These follow the same guidelines but most medicines required have not been available. Drugs available via national procurement and thus for use in the national cohorts were the following:

- Amikacine (the only injectable drug procured with domestic funding but even this one is subject to availability challenges)
- Ofloxacin and Moxifloxacin
- Cycloserine
- Prothionamide

Using additional first line drugs, these can be combined into a WHO compliant MDR regimen: 10-Am-Cs-Mfx-Pto / 14-Cs-Mfx-Pto

(Again, first line drugs Z, E and H may be included in this regimen but these are not shown as these are supposed to be adequately available)

However, there is no room for variations (for example in case of side effects or resistance) and the medicines are not suitable to make regimens to treat (pre) XDR cases.

Treatment outcomes for the cohorts with donor medicines show cure-rates well above 70% which is much better than the national cohorts in which less than 30% of patients get cured. This could be due to several reasons including drug quality, options to adjust in case of side effects or resistance or other factors such as availability of social patient support in the donor grants.

2.4 Patient enrolment

For 2018, the PNPSCT anticipates to enrol a total of 600 new patients (Both in the donor and in the national cohorts).

Patients enrolled on treatment before the end of March 2018 can still receive treatment with GF and Norwegian funded medicines for the full 2 years of their regimen. At the time of the visit, it was still unknown what will happen with patients enrolled after March as it was not yet assured that all the required medicines will still be available. However, on 5th March 2018 (at the final revision of this report), we were informed that an agreement had been reached that would mean that the Norwegian grant would cover the medicines for another 600 MDR and (pre)XDR treatments.

3. Procurement of MDR medicines

In most countries, procurement of TB medicines is notoriously challenging due to lack of interest by suppliers, monopolistic market situations, quality concerns and often very long lead times. These factors are also experienced by Romania and even for 1st line TB medicines that are locally produced in Romania (Produced by Antibiotice SA), the country experienced delays and stock outs in 2017.

3.1 Procurement with donor funding

The MDR and XDR medicines for the cohorts 1-7 were all financed with donor money (Global Fund and Norwegian Financial Mechanism) and procurement was done by the Romanian Angel Appeal Foundation via the Global Drug Facility GDF, a one stop supply mechanism for all TB medicines and diagnostics. GDF is housed by UNOPS. This channel has worked out well.

However, during our visit, we were informed that from March 2018 onwards, there would l be no more funding for MDR medicines from Global Fund or Norwegian Financial Mechanism. There will be an application for a GF transitional fund but this will not include a budget for drug procurement.

It was furthermore anticipated that by the end of 2018, there will be another grant of around Euro 12.6 million from the Norwegian Financial Mechanism but this would not include budget for TB drug procurement. MoH will be the Project Operator while Marinus Nasta will be the Project Promotor.

As per January 2018, the last outstanding orders paid with donor funds had been received and the country would thus have to plan to cover the entire future needs with domestic funding.

On 5 March 2018, (at the final draft of this report), we were informed that the NTP succeded to include drugs for 600 patients in the budget of the new Norwegian Financial Mechanism Grant. This would thus cover most of the MDR and XDR drug needs for 2019.

3.2 Procurement with domestic funding

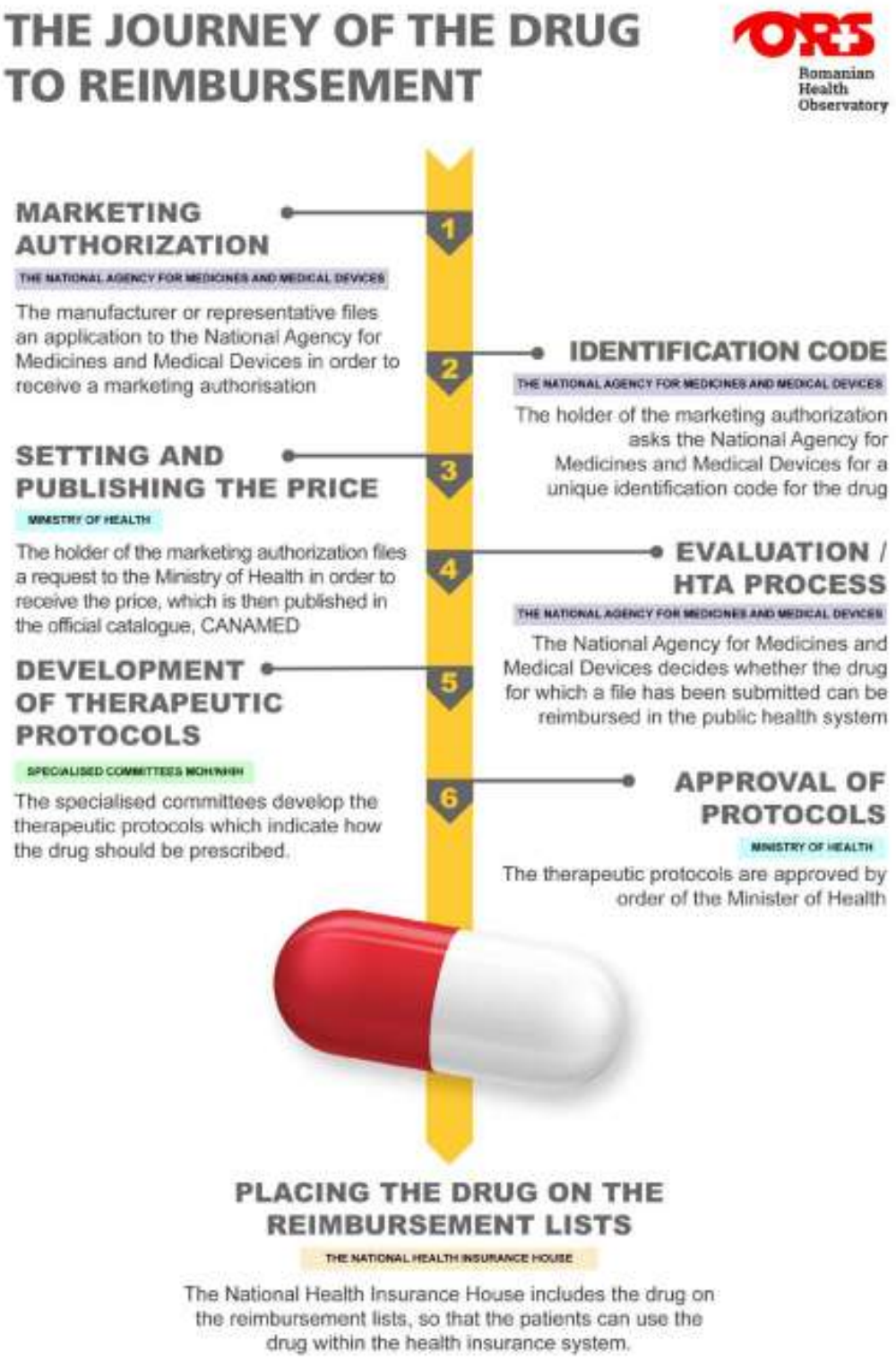
Procurement of drugs with domestic funds for the national programs (such as TB and the national vaccination program) is done by the procurement Department in the MoH, in line with EU legislation. As per EU regulations, even medicines and vaccines that are locally produced must be procured via competitive bidding.

We were unable to meet with the MoH procurement team as we were informed by the Minister of Health that the team would be in position to share any information, especially in the current tense political environment (the Romanian Prime Minister resigned on the first day of the visit).

The approach used by the MoH is central level negotiation via competitive bidding for framework contracts for medicines included on the “C2 reimbursement list”.

The steps to get a medicines on the C2 reimbursement list is shown in the illustration below (taken from the Romania Health Observatory report) and described in further detail in 5.2.

In November 2017, MoH informed in a press release that the number of MDR medicines in the C2 list would be expanded and in December 2017, a proposed new C2 list was published to which 9 MDR medicines had indeed been added. At the time of this visit, the expanded C2 list was published online and open for the public to react. The list was not yet officially approved but we were assured by the MoH and AMDDS that this would be done in February 2018.



Once a medicine gets officially confirmed on the C2 list, the MoH team will start the tender procedures for the framework contracts. This may take many months to complete and in some cases no bidders may come forward or no agreement can be reached and the process needs to be repeated. In case the attempt fails again, the MoH will request Unifarma to procure the product directly from the international market.

Some of the current framework contracts will end in September 2018 (others in 2019) and we were informed that MoH has started the process to tender for new contracts. However, during our discussions we received conflicting information as to whether the process had indeed been started and if so, to which stage it had currently proceeded.

Recommendation 1: MoH to check whether processes are on track to timely replace or extend the framework contracts for TB medicines that will end in 2018. (There is no longer a parallel supply channel with Global Fund funded procurement so the framework contracts have become of vital importance now).

Once framework contracts have been established, the hospitals can procure the needed quantities from the awarded companies at the centrally agreed prices. The quantities are thus decided by the programs. MoH will pay the costs of these orders.

Various interviewees informed that the framework contract approach works but that it takes around 1 year to complete the tendering, that some products are still not available and that if a product is for some reason not available from the awarded supplier, it effectively becomes impossible to obtain the medicines from another source.

For example there is a challenging situation regarding the 3 injectable MDR drugs:

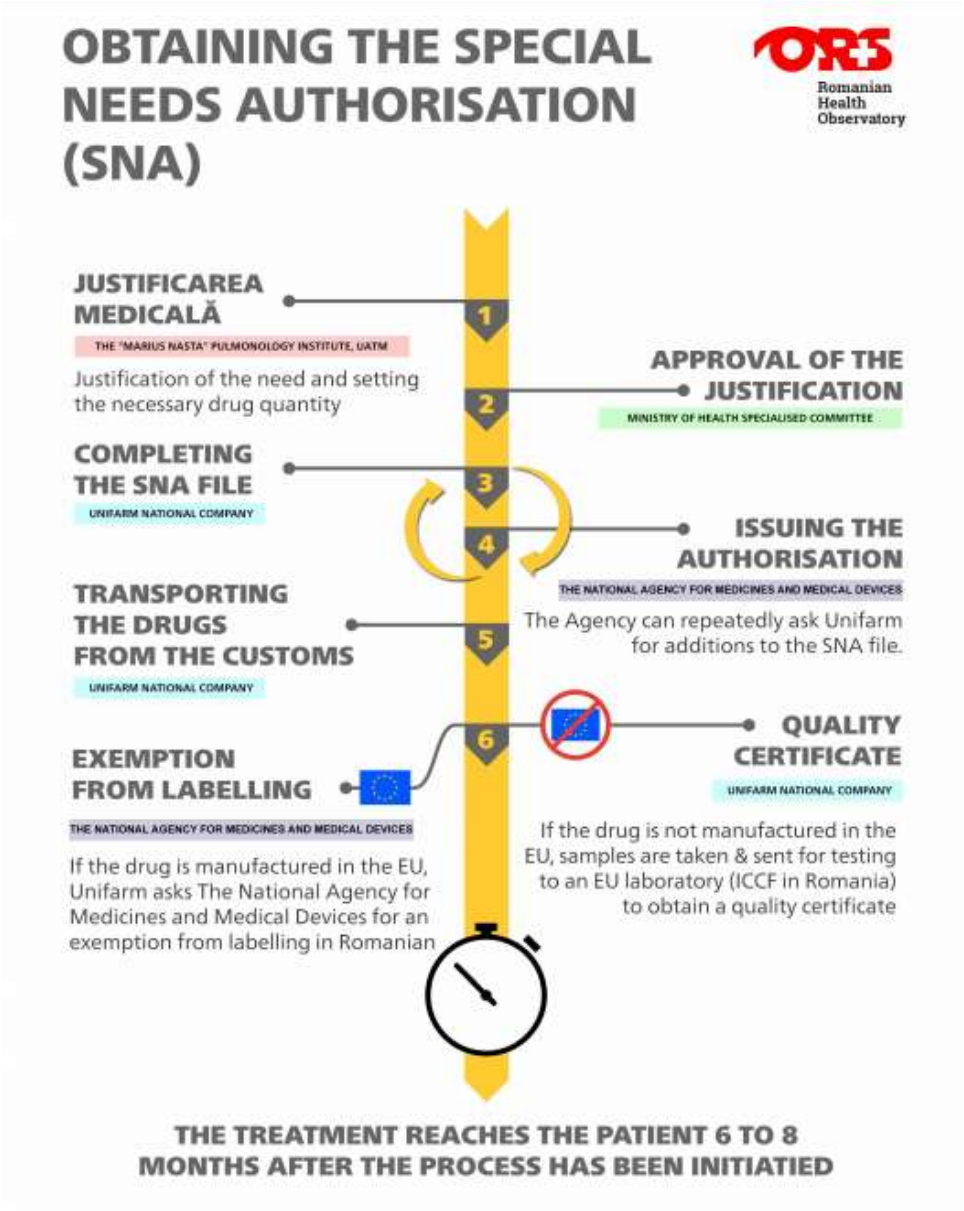
- Amikacin: Is on the C2 list but the tender to establish a framework contract failed twice and hence the product is not available.
- Kanamycin: Manufacturers Panpharma and Antibiotic SA have registered but in practice, their products are not available.
- Capreomycin: the product is not registered in Romania.

Even though these 3 products will all be on the expanded C2 list, it must be anticipated that it will still take at least 1 year to establish framework contracts.

Recommendation 2: MoH to make extra efforts to ensure availability of the injectable MDR medicines (Kanamycin, Capreomycin, Amikacin) as these are the backbone of all MDR regimen but are known to be hard to source.

Once framework contracts are in place, hospitals need to get permission from the PNPSCT before they can sign a contract with the framework companies. There is no coordination of hospital procurements and neither is there a fixed time schedule to guide when orders can be placed. Basically, whenever a hospital has need for a product and on condition that budget is available, they can initiate procurement. In total 190 facilities (170 hospitals and some extra pharmacies) need to request permission from PNPSCT whenever they wish to use the framework contract. We witnessed how facilities called and emailed during the interview with the PNPSCT person responsible for drug management with questions about quantification and procurement.

Medicines such as Capreomycin that are not registered in Romania, or Kanamycin which is registered but practically unavailable, may be imported after issuance of a Special Needs Authorisation (SNA). This is a lengthy procedure (see illustration below which is taken from the Romania Health Observatory report) but several interviewees confirmed that this route does work. Products procured via the SNA route do not have to comply with the maximum price level.



4. Storage and distribution of MDR medicines

4.1 Donor funded medicines

TB medicines that were procured with donor funds (GF or Norwegian Financial Mechanism) as well as those procured by Unifarm upon request by MoH (Because no framework contract could be established) are stored at Unifarm's warehouse in Bucharest. RAAF pays around Euro 2200-2600 per month for this service. This covers drugs needed for approximately 200 patients and includes:

- costs of storage (100 m2),
- administrative costs,
- Euro 4.40/first kg delivered and Euro 1 for every additional kg and
- Euro 1/km delivery.

Based on the requests received from the hospitals, the PNPSCT calculates which medicines are needed in which quantities and informs MoH and Unifarm. PNPSCT instructs Unifarm to make monthly or 2-monthly packs for each individual patient. Using their own vehicle fleet, Unifarm then delivers the patient packs with MDR medicines to the medical officers in charge at the hospitals.

The medicines are directly delivered to the hospitals based on their orders and there are no intermediate storage points at regional or county level. The donor funded medicines are thus distributed via a 2 level, "pull-based" distribution system.

Unifarm shares monthly stock reports with the Romania Angel Appeal Foundation and these impress as accurate and reliable. We did see the latest report which dated from end of December 2017 and will use this to comment on the current stock situation (See 4).

4.2 Domestically funded medicines

The storage and distribution of TB medicines under the MoH framework contracts is the responsibility of the companies that won the contracts. Hence there is no centrally managed stock and no assured safety stock for these medicines. It is entirely up to the 6 or 7 framework contracted companies to decide how they prepare for any orders from the hospitals.

In future, Unifarm will only stock items that failed in MoH's framework negotiations and are then procured by Unifarm via the SNA route.

5 Recent constructive decisions by MoH and NAMMD

Since the publication of the Romania Health Observatory Report in October 2017, the Romanian MoH has taken several constructive decisions:

5.1 Increased domestic budget support for the TB program

On 23 November 2017, MoH published a press release in which it announced to increase the 2018 budget for the PNPSCT to 41 million Lei (around Euro 10 million) in order to provide treatment for all TB patients. This was indeed a significant increase from the 19.875 million Lei (around Euro 5 million) budget that the TB program had in 2017. (However, since support from Global Fund will not provide for MDR medicines from 2018 onwards, the increase will largely be needed to ensure continued availability of MDR medicines).

http://www.ms.ro/2017/11/22/toti-pacientii-cu-afectiuni-tb-vor-fi-tratati-in-cadrul-programului-national-de-prevenire-supraveghere-si-control-al-tuberculozei/

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Toți pacienții cu afecțiuni TB vor fi tratați în cadrul Programului Național de Prevenire, Supraveghere și Control al Tuberculozei

22 noiembrie 2017

În 2018, Ministerul Sănătății (MS) va dubla bugetul Programului Național de Prevenire, Supraveghere și Control al Tuberculozei.

Astfel, MS va aloca peste 41 milioane de lei pentru derularea Programului Național de Prevenire, Supraveghere și Control al Tuberculozei în vederea asigurării accesului la diagnostic și tratament corect pentru toți pacienții afectați de tuberculoză, inclusiv tuberculoză multidrog rezistentă (MDR/XDR).

În prezent, sunt disponibile, în lista de medicamente compensate 100% care se acordă bolnavilor incluși în Programul național de tratament al bolnavilor cu tuberculoză, un număr de 21 denumiri comune internaționale (DCI), utilizate în tratamentul bolnavilor cu TB BK sensibilă sau multidrog – rezistentă.

(translation provided in Annex 1)

During our meeting with the Honourable Minister of Health, we were assured that the 41 million Lei were within the overall MoH budget that was approved by MoF on 12 Jan 2018. Although this budget does not earmark the amount for TB specifically, the Minister assured that the amount would indeed be available for TB in 2018. This amount is for general support for the TB programme and it has not yet been decided how much of it can be used for drug procurement. This was reportedly being worked out by the programs department and the national TB coordinator and it was expected that this would be finalized before the end of January 2018.

However, the Minister assured that hospitals can already undertake procurement as the funding is already guaranteed.

Despite these firm assurances, we found during the final revision of this report on 5th March 2018 that the actual approved 2018 budget for the NTP as shown on the MoH website (http://www.ms.ro/wp-content/uploads/2018/03/OMS-modificare4-buget-2018.pdf) had not doubled as the former Minister of Health – Bodog – announced in December. Instead the budget was shown to be 22.901.000 Lei which means a 15% increase compared to the 2017 budget which was 19.875.000 Lei.

2. Bugetul alocat programelor naționale de sănătate publică aprobate pentru anul 2018

mii lei

PROGRAMELE NAȚIONALE DE SĂNĂTATE PUBLICĂ	Buget de stat	Venituri proprii	Total
I. Programul național de boli transmisibile din care:	**231.553**	**176.983**	**408.536**
Programul național de vaccinare	129.194	23.726	**152.920**
Programul național de supraveghere și control al bolilor transmisibile prioritare		2.116	**2.116**
Programul național de supraveghere și control al infecției HIV	102.359	127.122	**229.481**
Programul național de supraveghere și control al tuberculozei		22.901	**22.901**
Programul național de supraveghere și control al			

We still recommend that MoH fulfills its commitment to double the TB program budget.

Even so, one hurdle that still needs to be overcome is to increase the allocated budget for each of the hospitals as they will from now on increasingly need to procure MDR medicines via the centrally negotiated framework contracts (these were previously provided to them free of charge via GF and Norwegian funds.) Without such an adjustment, hospitals will be allocated budgets similar to 2017 and will thus not be in position to utilise the additional (and needed) funding available.

Recommendation 3: MoH to uphold it's commitment to earmark the 41 million Lei for TB program and reserve around half of this amount for TB medicines. MoH to prepare for a similar budget to be available in 2019 and beyond.

Recommendation 4: MoH to increase the allocated budget for each of the hospitals as they will from now on increasingly need to procure MDR medicines via the centrally negotiated framework contracts Without such an adjustment, hospitals will be allocated budgets similar to 2017 and will thus not be in position to utilise the additional (and needed) funding available.

5.2 Expansion of the C2 list of drugs that will be reimbursed

The press release of 23 Nov 2017 announced that MoH would make all the TB medicines for treatment of 600 MDR/XDR patients available in 2018. In December 2017, this announcement was indeed followed by a proposed expansion of the C2 list with 9 additional TB drugs included (page 2, position from 22 to 30): http://www.ms.ro/wp-content/uploads/2017/12/HG.pdf

6. La SUBLISTA C ,,DCI-uri corespunzătoare medicamentelor de care beneficiază asiguraţii în regim de compensare 100%", SECŢIUNEA C2 ,,DCI-uri corespunzătoare medicamentelor de care beneficiază asiguraţii incluşi în programele naţionale de sănătate cu scop curativ în tratamentul ambulatoriu şi spitalicesc", la punctul "P1: Programul naţional de boli transmisibile", subpunctul "B. Subprogramul de tratament al bolnavilor cu tuberculoză", după poziția 21 se adaugă nouă noi poziții, pozițiile 22 - 30, cu următorul cuprins:

22.	Combinații (Amoxillinum + Acidum clavulanicum)	J01CR02
23.	Combinații (Imipenemum + Cilastatinum)	J01DH51
24.	Levofloxacinum	J01MA12
25.	Linezolidum	J01XX08
26.	Rifamycin	J04AB03
27.	Etionamidum	J04AD03
28.	Combinații (Rifampicinum + Pyrazinamidum + Izoniazidum)	J04AM05
29.	Combinații (Rifampicinum + Pyrazinamidum + Izoniazidum + Ethambutolum)	J04AM06
30.	Clofaziminum	J04BA01 "

The expanded C2 list is currently published for public consultation. The addition would bring the number of TB medicines on the C2 list to 30 and would allow reimbursement of all medicines needed to provide MDR and XDR regimen. We visited the NAMMD and were assured that the approval of the C2 additional 9 medicines is expected in February 2018 and will then be effected.

Recommendation 5: NAMMD to rapidly assess (and if positive, approve) the 9 added MDR medicines in the C2 list so that MoH can start the process of framework contract negotiations.

5.3 Fast track registration assessment for MDR and XDR medicines

NAMMD furthermore informed that MDR and XDR medicines have been submitted via a fast track assessment and that as of now, only 5 formulations (including Capreomycin and PAS) have not been registered because no manufacturer has expressed interest to apply for market authorisation in Romania. However, these 5 medicines can be imported via a Special Needs Authorisation (SNA).

The following link provides an up-to-date insight in the registered pharmaceutical products in Romania: https://www.anm.ro/nomenclator/medicamente

Recommendation 6: MoH to apply for special SNA for the 5 formulations that are currently not registered.

6 Current drug stock situation

6.1 Current drug stock situation

At the time of our visit, the majority of stock of MDR medicines was still financed by Global Fund and Norwegian grants and held at Unifarm warehouse. Unifarm and Romanian Angel Foundation informed that there are no more outstanding deliveries of GF or Norwegian funded orders.

We were informed that hospitals should only procure stock to cover a maximum of 3 months. For the sake of this forecast, we will not consider these stocks held at the hospitals.

Using the data in the stock report from Unifarm as of end of December 2017, we made the following estimation of number of patients that can be treated:

	Unifarma Stock end Dec 2017 (single tab/amps/sachets)	Per person per day	Days in a regimen	needed per patient	Patients that can be treated	
Capreomycin/UE 1g powder	79,075	1	300	300	264	471
Kanamycin 1g /UE powder for inj 50 vials	62,352	1	300	300	208	
Cycloserine/NONUE 250mg 100 cap blister	862,590	3	720	2160	399	415
PAS sodium 5.52g eq. to 4g PAS powder f oral sol., 25 sac	23,026	2	720	1440	16	
Levofloxacin/UE 250mg 100 tab blister	764,140	4	720	2880	265	286
Moxifloxacin/NONUE 400mg 100 tab blister	29,600	2	720	1440	21	
Prothionamide/UE 250 mg 100 tab blister	387,600	3	720	2160	179	
Rifabutin/NONUE 150mg 100 cap jar	8,600	2	720	1440	6	
Clofazimine 50mg 100 cap jar	18,700	2	720	1440	13	
Clofazimine 100mg 100 cap jar	30,943	2	720	1440	21	
Linezolid/NONUE 600mg 20 tab blister	72,199	1	720	720	100	

Expiry dates of the current stocks at Unifarm are generally good (with a few exceptions of small quantities that have an expiry date in 2018 but we do not expect that these will expire as the quantities can be utilised by current patients).

Most MDR and XDR patients receive regimen based on Capreomycin/Kanamycin with Cycloserine/PAS and with Levofloxacine/Moxifloxacin and Prothionamide. Only few patients will require Rifabutin, Clofazimine or Linezolid. The medicines with similar colours (e.g. Capreomycin and Kanamycin) can in most cases be used interchangeably. There is thus sufficient central level stock to enrol around half of the 600 patients that are foreseen for 2018. This provides some welcome safety stock to cover the period needed by MoH to establish framework contracts.

6.2 Drug Budget estimations

Estimate based on an average GDF price per regimen

At GDF prices, First Line regimen cost around Euro 35 per patient for new patients and around Euro 60 for retreatment patients. Romania has about 12,000 new cases per year and about 2,500 retreatment. The cost for first line drugs would thus be around Euro 600,000 or 2.4 million Lei (if procured at GDF prices).

Based on the MDR and XDR medicines procured by RAAF with GF funds in 2016 and 2017, we calculated that the average medicines costs per patient were as follows:

- Medicine cost of 1 MDR regimen: Euro 2,172
- Medicine cost of 1 XDR regimen: Euro 6,679

The prices are based on landed costs in Romania so including freight, insurance etc.

Based on 530 MDR and 70 XDR patients to be enrolled in 2018, the cost at GDF prices would thus be:

(530 x Euro 2,172) + (70 x Euro 6,679) = Euro 1,151,160 + Euro 467,530 = Euro 1,618,690

It should be noted that these medicines were procured from the Global Drug Facility GDF which is a non-profit organisation housed by UNOPS. Prices that MoH may achieve during the framework contract negotiations are likely to be considerably higher. Based on a comparison of the below 4 products, prices achieved by frameworks are double the GDF prices (unfortunately, the cost driving medicines such as Kanamycin, cycloserine, capreomycin are not yet under framework contracts so we could not compare prices at this stage):

	Frame work (Lei)	Frame work (Euro)	GDF ExW price Euro ($)	Price ratio Framework/(GDF+25% for freight & insurance)
Isoniazide 300mg	0.19	0.05	0.017 ($0.02)	2.4
Moxycyclin 400mg	3.75	0.94	0.29 ($0.35)	2.6
Ofloxacine 200mg	0.27	0.06	0.025 ($0.03)	1.9
Prothionamide 250mg	1.02	0.26	0.11 ($0.13)	1.9

Based on this rough price estimation, annual MDR and XDR medicine costs based on framework contracts may thus become around Euro 3-4 million or 12-16 million Lei.

Including the estimated costs of the first line TB medicines (at least 2.4 million Lei if procured at GDF prices), drug costs could thus easily consume half of the promised 41 million Lei total annual budget for TB support.

Estimate based on Romania's maximum price per individual medicine

Dr Popa did a recent estimate in which he followed the following approach:

Expected number of patients that need each medicine	X	medicines quantities needed to provide the standard regimen	X	maximum Price

For example:

250 patients	X	240 ampules kanamycin	X	maximum price

In this way it was estimated that the total annual requirement for First line, MDR and XDR medicines of around 49M Lei or 10M Euro. The main items in terms of value were:

- 12.5 M Lei worth of Linezolid (Based on 270 patients in 2018)
- 6.0 M Lei worth of Delamanid (based on 60 patients in 2018)
- 4.4 M Lei worth of Bedaquiline (Based on 80 patients in 2018)

7 National TB drug management

7.1 Responsibility

In most countries, the national tuberculosis program is managed by a team of full time specialists. In Romania however, the PNPSCT is run by a team of technical consultants with part-time contracts. TB Drug management (including stock monitoring and quantification for procurement with donor funds as well as basis for MoH framework negotiations) is the responsibility of one person (Pulmonologist Dr Christi Popa). His job description includes amongst others the following tasks:

• *providing consultancy and technical assistance to specialized units that implement the PNPSCT (Programului Național de Prevenire, Supraveghere și Control al* Tuberculozei*) on:*

- establish the annual need for medicines

- developing drug orders

• *Analyze the request for an opinion from the specialized units implementing the PNPSCT*

• *estimate the quantities of drugs necessary for the implementation of the PNPSCT, based on the estimates made by the specialized units*

• *prepares the necessary medication based on the estimates made by the specialized units, for the implementation of the PNPSCT at national level*

Within the same contract, Dr Popa is furthermore responsible for Infection Control activities in the program. For Drug management and Infection control combined, he has a contract for just 42 hours per month (at a remuneration of Euro 200 per month). Apart from the low salary offered, we consider the 42 hours per month to be grossly inadequate considering the value and importance of the TB medicines to be managed.

7.2 Assessing the TB drug stock situation

Although the stock at Unifarm is easily assessed, drug management is complicated because there is no way to know the situation in the hospitals. There is no mechanism for the PNPSCT to know the hospital's remaining stocks, their consumption rates or the quantities that they procured under the framework contracts.

Hospitals must report stocks to MoH but this is only reflecting the stock value and the reports do not include quantities or expiry dates. And even IF hospitals send additional reports, there is no standard format and hence PNPSCT receives many different papers and Excel based reports which are impossible to aggregate.

7.3 Permission for procurement by the hospitals

Hospitals are obliged to request PNPSCT for procurement permission but there is no mechanism to confirm whether the hospitals then indeed proceed and buy the quantities approved. Neither is there reporting of remaining stock levels at the hospitals. The procurement permission task can not be done properly within the very limited time available (The 42 hours per month contract which also includes Infection Control activities).

We foresee that the reordering process will become even more complex and labour-intensive in the coming period as the supply of medicines will increasingly and ultimately entirely be financed by domestic funds and all medicines will then need to be sourced via decentralized procurement based on centrally negotiated framework contracts.

7.4 TB Drug Management Capacity

Global Fund support for TB drug procurement has already ended and Norwegian Finance Mechanism Funding is unlikely to continue for much longer. Thus, the Government of Romania will soon be the only source of finance for TB medicines. This will be a major change and present many challenges. It is of vital importance that the program as well as the individual hospitals have the capacity to make reliable forecasts and engage in continuous drug stock management. This will be needed for amongst others the following reasons:

- Financial: TB medicines will constitute a considerable amount of money which needs to be budgeted and adequately accounted for
- Logistics and lead time: Suppliers and manufacturers will require projections of quantities likely needed so they can prepare their own business processes.
- Assess whether requested quantities are reasonable: Hospitals place orders and request permission to procure from NTP but in order to assess these requests, the PNPSCT must have information about consumption, stocks and treatment at the hospital.
- Therapeutic: The consequences of stock out of one or more TB medicines will have grave consequences for the individual patient as well as for the community and society at large as it may result in additional infections and risk of development of resistant forms of TB.
- Reduce risk of expiry: If the PNPSTC knows the quantities and expiry dates of stock at the hospitals, it can organise redistribution in order to prevent expiry at places with excessive stock.

Recommendation 7: PNPSCT to create a full time position for a TB commodity management support officer. This person could work under direct supervision of Dr Cristi Popa and amongst others be involved with the following tasks:

- **Assessing whether the drug orders and procurement requests by the hospitals are rational and can be approved.**
- **Monitor stock levels at all levels to detect items at risk of stock out or expiry**
- **Initiate redistribution of stocks between hospitals to prevent stock outs or wastage**
- **Make forecasts of needed quantities and values for purposes of budgeting**

- **Training and supervision of staff responsible for drug management at the hospitals**
- **Liaise with the framework contract holders to exchange information about stock levels, projected needs etc.**

8 Possible sources of MDR drug management data

Drug management requires timely availability of reliable data. Here are some possible data sources that could be used by PNPSCT:

8.1 National Health Insurance House

Romania has mandatory health insurance via NHIH (There is no significant private health insurance coverage). NHIH is quite autonomous and not directly subordinated to MoH but do adhere to MoH's health policies. However, the NHIH is no longer involved in reimbursing of TB medicines anymore as these are now fully covered via MoH.

We were nevertheless interested in meeting with NHIH because previous consultants (e.g. Peter Evans WHO 2016 visit) proposed that the data from NHIH would be of use for the TB program.

NHIH does indeed receive monthly drug consumption reports from all hospitals. The purpose of these reporting is for clawback tax purposes. The reports provide insight in the actual quantity of medicines dispensed to each patient. We were informed that hospitals do indeed report for the drugs that are reimbursed by NHIH but that reports for other drugs (such as those for TB) may not be fully reported.

We furthermore learned that NHIH does not provide regular reporting to MoH but were assured that MoH can request data from NHIH whenever they wish. Even PNPSCT can request these data but would need to submit the request via MoH.

In fact, upon a request by the State Secretary for health, NHIH provided a report of all medicines dispensed in the period 2016 and first half 2017. This report was made on 18 Sep 2017. The report included financial info as well as number of patients and quantity of meds dispensed. It included all drugs, whether covered by NHIH or not but did not offer information about the source of the medicines (For example whether donor procured or bought by the hospital under MoH framework contract).

Upon our request, NHIH officer showed us the report (on screen) and we saw that it includes financial info as well as number of patients and quantity of meds dispensed. It even provides more detailed info like the product strength, brand name, manufacturer's name and country of manufacture. It included all drugs, whether covered by NHIH or not. NHIH cannot see the source of the medicine (for example GF or procured by the hospital). For some issued medicines, the therapeutic indication can be seen (e.g. 1B = TB) but we also noted that some typical TB medicines were recorded without any therapeutic code.

We zoomed into TB medicines and noted the following for the period 2016 and first half 2017:

- Kanamycin: In total around 15,000 vials were issued. However, only 5 patients were indicated as 1B (TB) and these 5 patients received a total of only 351 vials which equates to only 70 vials per patient while a patient would need around 300.
- Capreomycin: 3 patients received a total of 333 ampules (But these patients were not indicated as 1B). Thus only 111 amp per TB patient while 300 would have been required for an MDR regimen.

- Amikacin: In total 319,000 vials were used but only 69,000 vials were for 723 patients with indication 1B. (Others for HIV and other unknown indications). Thus only 95 vials per TB patient while around 300 would have been expected..
- Streptomycin: 3500 patients received 160,000 vials which means 45 vials per patient.
- Cycloserine: 1008 TB patients received 287,000 caps which is only 285 caps per patient.
- RH combination tab: 13,466 TB patients received 1.6 million tab which works out at only 118 tab per patient.
- H300: 19,000 TB patients received 1.5 million tab being only 79 tab per patient.
- Ofloxacin: 2000 TB patients received 660,000 tab or 330 tab per patient.
- Pyrazinamide: 20,000 TB patients received 5 million tab which is only 250 tab per patient.
- Ethambutol (250 and 400mg): 22,000 TB patients received 5.8 million tabs equal to only 264 tab per patient
- There were many more TB medicines (could not capture more data) but we noted there were no entries for the 4FDC, bedaquiline or delamanide.

We were pleased to meet with a positive and collaborative attitude at NHIH and appreciate that they did report to MoH and that this report allowed for a quick retrieval of TB drug data. However, the quantities of drugs issued per patient (for example 70 vials kanamycin) are very low (a typical patient on MDR regime would need around 300 vials) and the reported quantities may thus not reflect the full picture.

We conclude that unfortunately, the NHIH data are incomplete and not really useful for TB drug management by the program.

8.2 National TB database software

The National TB database is mostly used to collect programmatic data but is currently not suitable for collection of drug related data. At the central level, one can see patient data, type of TB, HIV status etc. One can also see the regimen but only as it was initially prescribed. It is not visible whether the regimen was adjusted, whether there were interruptions etc. The data are not derived from the pharmacy and hence do not show what was actually dispensed.

The software offers very limited report generation. It can for example not show an overview of all patients currently on MDR regimen.

Around 2015, an attempt was made to expand the software with a drug management component in the software. The development of the component was financed by Norwegian Financial Mechanism and the idea was that the database would also be used for re-ordering. Unfortunately it proved more complex than foreseen and the idea was abandoned.

The hospitals now use Excel forms to submit requests for new supply from the Unifarma warehouse.

We do not consider the national TB Database software a useful data source for TB drug management.

8.3 MOH SER

MoH has its own electronic patient reporting system which is called Sistemul Eelectronic de Raportare (SER). The SER reports include information about all medicines dispensed (at least in the public hospitals). Data go to MoH but NHIH can request reports if needed.

During this brief visit, we were unable to verify the quality, completeness and availability of this data source.

8.4 MoH Reimbursement records

As national funds will soon become the sole source of funding for TB medicines, the records linked to reimbursement of the hospital's procurement could become a valuable source of data to understand the quantities procured (and presumably used in the country.

Recommendation 8: PNPSCT to explore whether the MoH reimbursement records could be a possible source of drug management data.

8.5 Companies

Since there are usually only 6 or 7 framework holders which together provide all the TB medicines, it may be feasible to request these companies to share data about quantities delivered to each hospital and the remaining stock levels at the company warehouse. The request to share such data could be included in the framework contracts.

Recommendation 9: MoH to include in the framework contracts an obligation for the contract holders to provide MoH (and PNPSCT) with data about quantities of medicines delivered to each hospital as well as quantities in stock and in pipeline.

8.6 Hospitals via direct reporting to the PNPSCT

Following a dramatic stock out of vaccines in 2016, Romania introduced a system to monitor vaccines all the way down to the general practitioner level. In a similar vein, Hospitals could be asked to provide monthly or quarterly reports on number of patients, their regimen as well as the remaining drug stocks. This would be a new approach and the advantage would be that the report design can still be made in such a way that the key data such as quantities dispensed, quantities remaining and patient regimen are all reported in a standard format that will allow aggregation at the central level.

Requesting cooperation from the hospital should be easily enforced as they must always get permission to procure via the framework contracts from the PNPSCT. PNPSCT will only be in position to assess whether the request is justified on the basis of current stocks and needs at the hospital.

Recommendation 10: PNPSCT to develop a standard reporting tool (preferably in Excel) which can be used by the hospitals to provide data about quantities of MDR medicines consumed, left in stock and number of patients per regimen.

Summary of recommendations:

1. MoH to check whether processes are on track to timely replace or extend the framework contracts for TB medicines that will end in 2018.

2. MoH to make extra efforts to ensure availability of the injectable MDR medicines (Kanamycin, Capreomycin, Amikacin) as these are the backbone of all MDR regimen but are known to be hard to source.

3. MoH to uphold it's commitment to earmark the 41 million Lei for TB program and reserve around half of this amount for TB medicines. MoH to prepare for a similar budget to be available in 2019 and beyond.

4. MoH to increase the allocated budget for each of the hospitals as they will from now on increasingly need to procure MDR medicines via the centrally negotiated framework contracts Without such an adjustment, hospitals will be allocated budgets similar to 2017 and will thus not be in position to utilise the additional (and needed) funding available.

5. NAMMD to rapidly assess (and if positive, approve) the 9 added MDR medicines in the C2 list so that MoH can start the process of framework contract negotiations.

6. MoH to apply for special SNA for the 5 formulations that are currently not registered.

7. The PNOPSCT needs to create a full time position for a TB commodity management support officer. This person could work under direct supervision of Dr Cristi Popa and amongst others be involved with the following tasks:

- Assessing whether the drug orders and procurement requests by the hospitals are rational and can be approved.
- Monitor stock levels at all levels to detect items at risk of stock out or expiry
- Initiate redistribution of stocks between hospitals to prevent stock outs or wastage
- Make forecasts of needed quantities and values for purposes of budgeting
- Training and supervision of staff responsible for drug management at the hospitals
- Liaise with the framework contract holders to exchange information about stock levels, projected needs etc.

8. PNPSCT to explore whether MoH reimbursement records can serve as a possible source of drug management data.

9. MoH to include in framework contracts an obligation for the contract holders to provide MoH (and PNPSCT) with data about quantities of medicines delivered to each hospital as well as quantities in stock and in pipeline.

10. PNPSCT to develop a standard reporting tool (preferably in Excel) which can be used by the hospitals to provide data about quantities of MDR medicines consumed, left in stock and number of patients per regimen.

Annex 1:

Translation (via Google Translate) of the MoH press release (23 November 2017) in which it announced to increase the 2018 budget for the PNPSCT to 41 million Lei (around Euro 10 million) in order to provide treatment for all TB patients. *(It appears that this commitment has not yet materialized as we noticed a budget of just 22.901 million Lei on the MoH website on 5 March 2018)*

In 2018, the Ministry of Health (MS) will double the budget of the National Program for Prevention, Supervision and Control of Tuberculosis.

Thus, the MS will allocate over 41 million lei for the implementation of the National Tuberculosis Prevention, Control and Control Program in order to ensure access to diagnosis and treatment for all patients affected by tuberculosis, including multidrug-resistant tuberculosis (MDR / XDR).

At present, a total of 21 common international names (ICDs) used in the treatment of patients with sensitive or multi-drug TB BK are available in the 100% compensation list for patients included in the National Program for the Treatment of Tuberculosis Patients..

By the end of this year, the Ministry of Health will develop a Government Decision whereby a number of 9 DCIs needed to treat tuberculosis, previously provided through external funding, will be included in the list of compensated and free medicines. For these medicines, at the request of the Ministry of Health, the National Agency for Medicines and Medical Devices has gone through the Health Technology Assessment (HTA) procedure.

This will fully cover the treatment necessary for patients with TB, including resistant multidrug tuberculosis, according to the national guidelines developed on the basis of WHO recommendations.

The Ministry of Health has completed the centralized public procurement procedure this year to provide the culture media needed to diagnose TB in the liquid environment, including genetic testing, and by the end of the year will initiate a centralized public procurement procedure for antituberculous drugs whose framework agreements expire in September 2018, as well as the medicines that will be included in the list of compensated and free medicines through the HG.

Until the completion of the centralized acquisition of the 9 DCIs, each healthcare unit providing treatment for MDR / XDR tuberculosis patients can purchase medicines from the 2018 budget allocated to the National Program for the Prevention, Control and Control of Tuberculosis.

In order to ensure access to diagnosis and treatment for all TB patients including TB MDR / XDR, in the absence of external funding, the Ministry of Health also envisages other measures:

- rapid testing for TB of 15,000 people at risk, and providing treatment and psychological and social support for 600 MDR / XDR TB patients in a Norwegian funding project with a budget of 10,000,000 Euro
- training of 1,320 pneumologists and nurses from the pneumophysiology network as well as family medicine doctors within a project financed by structural funds - "Improving the technical capacity of professionals in the identification, diagnosis and treatment of TB and lung diseases" 'worth € 3,000,000;
- active detection of TB and latent TB by screening 75,000 risk groups (homeless, injecting drug users, detained people, poor rural population with low access to health services), providing social support, psychological, peer support and

subsidies to increase adherence to treatment for 15,000 patients under another Structural Funds project worth EUR 15,000,000;

- accessing a transition grant from the Global Fund to fight HIV / AIDS, TB and Malaria in order to facilitate the take-up and implementation within the National Program of interventions and services funded so far by the Global Fund.

Tuberculosis (TB) is a public health priority for the Ministry of Health and for the Government of Romania.

The results of the last years show an improvement of disease-specific epidemiological indicators in our country, following the development of several programs to combat this disease.

The Ministry of Health approved a series of measures to improve tuberculosis control, among which the most important is ***the National Strategy for Tuberculosis Control in Romania 2015 - 2020*** and the assumption of funding from the ***Ministry of Health's*** budget ***for prevention, surveillance and control of tuberculosis*** at the level of the units sanitary facilities that implement the National Tuberculosis Plan.

The National Strategy for the Control of Tuberculosis in Romania 2015 - 2020 (document approved by the Government of Romania through GD.121 / 2015) aims to ***eliminate TB as a public health problem in Romania by 2050.***

The interventions included in the strategic document aim to provide services for the prevention, detection, treatment and increase of adherence to treatment for tuberculosis patients and, in particular, multidrug-resistant tuberculosis, in accordance with the recommendations of the World Health Organization.

In order to implement the measures and actions envisaged in the National Strategy for Tuberculosis Control, the state institutions, the Ministry of Health, the National Program for Prevention, Supervision and Control of Tuberculosis have partners of non-governmental organizations, national and international organizations.

In addition to the Ministry of Health budget and external non-reimbursable financing sources (Global Fund, Norwegian Funds), which have so far provided MDB / XDR resistant TB drug, the Ministry of Health has been used to implement the interventions foreseen in the Strategy developed by the Ministry of Health.

In recent years, significant progress has been made in controlling this disease:

- *The screening rate* is over 70% since 2009, and in 2014 it has risen to 94% for new cases and 85% for TB MDR cases;
- *Global Incidence (IG)* has fallen by **54.6%** in the last 14 years (from 142.2% in 2002 to 64.8% in 2016).
- *IG TB in children* decreased by **59.7%** (from 48.3% in 2002 to 19.4% in 2016);
- *The prevalence of TB* decreased by **41.7%** (from 200.2% in 2004 to 116.7% in 2015);
- *TB mortality* decreased by **50.9%** (from 10.8% in 2002 to 5.3% in 2015)