Short Term Assessment TB Supply Chain, Romania

Date March 3-March 7, 2016

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2. Executive Summary

For mainly historical reasons the rates of TB in Romania are much higher than they should be. Because of missing medicines, treatment failure rates and cases of MDR TB, are twice as high as European norms. The treatment failure rate of MDR TB cases are four times higher when government funded than when donor funded. New medicines for the treatment of MDR TB are urgently needed and are currently being paid for by the Global Fund and Norway. Despite some of these medicines being considered as having received a Special Needs approval, release has been delayed.

Romania has a strong legal system which is respected and effective. The legislative changes necessary are well understood and apparently unopposed. Changes already have the support, in principle, of the MOH, NAMMD, Central Procurement, NTP, RAA, WHO, WB, Global Fund and Norway, and are under review prior to implementation.

Frame contract process has sufficient safeguards to ensure good prices, good practice and transparency. The costs for first line TB medicines were reduced and became uniform throughout Romania. Prices of TB treatments remain higher than necessary and several important TB medicines still cannot be purchased.

Some procedural changes are also needed. Variable payments represent an expense and a risk to the supplier, making goods more expensive. Because stock level information is not shared within the supply chain, it is impossible for the NTP to know the extent to which treatments are being interrupted because of lack of medicines. There are two main data systems in use within the TB program and they operate independently and in parallel. Information needed by the TB managers is not made available to them. Market research to seek out and engage companies able to provide more cost effective treatments is not performed.

It is therefore recommended to;

1. Facilitate through legal support, the well understood legislative adjustments necessary to allow medicines, which are urgently needed and cannot currently be approved, to be approved under a revised set of conditions. These conditions would include following WHO recommendations.
2. Expand the frame contract process can to eventually include all TB medicines; as well as many other major medical products.
3. Evaluate treatments used by countries with similar TB burden, to understand their safety and efficacy oversight process and see the level of savings achieved.
4. Create supply chain and market research responsibilities; enhancing the responsibilities of the Health Technology Assessment Group, procurement, wholesaling and program management.

3. Acronyms and Abbreviations

C2 list	List of products eligible for government reimbursement.
DOTs	Directly observed treatment, short-course.
EU	European Union
FDC	Fixed dose combination
GLC	Green Light Committee
IDA	IDA Foundation to supply medicines
MA	Market Authorization
MDR	Multi-drug resistance
MOH	Ministry of Health
NAMMD	National Agency for Medicines and Medical Devices
NHIH	National Health Insurance House
NTP	National-Tuberculosis-programme.
PICS	Pharmaceutical Inspection Co-operation Scheme
RAA	Romanian Angel Appeal
TB	Tuberculosis
USA	United States of America
WHO	World Health Organization
XDR	Extensively drug-resistant

4. Acknowledgements

Gratitude is expressed to the Ministry of Health and the National Tuberculosis Program of Romania, the WHO Regional Office for Europe, the WHO Country Office in Romania, Romanian Angel Appeal as the Principal Recipient of the GFATM in Romania, who together with WHO made possible to conduct this short term assessment. During the assessment, the following people gave generously of their time and knowledge. This report is a compilation of their thoughts and wisdom, though errors and omissions are entirely due to the author.

Marius Nasta Institute:
Dr. Victor Spinu – NTP manager, MDR department coordinator
Dr. Cristi Popa – pulmonologist, Romanian expert on centralized procurement
Dr. Domnica Chiotan – researcher, pulmonologist,
Dr. Adriana Moisoiu – laboratory coordinator,
Otilia Petrescu – Pharmacy department coordinator,
Marina Gontariu – coordinator of the procurement department, economist,
Irina Nicolae – economist, accountability department,
Daniela Toma – legal adviser,
Alina Degeratu – legal adviser,

Ministry of Health:
Dr. Victor Strambu – Secretary of State
Carmen Comandasu – procurement manager,
Mihaela Bardos – director of the National Agency for Programs,

National Agency for Medicines and Medical Devices:
Dr. Nicolae Fotin – president,
Dr. Marius Tanasa – vice-president,

Romanian Angel Appeal
Nicoleta Manescu - Coordonator asistenta tehnica

World Bank:
Adriana Ivama - Brunel, consultant
Marcelo Bortman – task leader of the health sector reform project

World Health Organization
Cassandra Butu.

Particular thanks are due to Dr. Cristi Poppa who participated in almost every meeting, while still managing his TB patient load and Nicoleta Manescu RAA who provided coordination, translation, valuable insights, fact checking and 101 services which made the consultancy pleasant and easy.

5. Terms of Reference

Assessment of the legal and regulatory framework for centralized procurement, current barriers and develop recommendations and strategies

Aim and objectives

The aim of the WHO assistance is to create in Romania a legislative environment that supports the management supply of anti-TB medicines and other relevant commodities that is effective to cover all TB needs, cost-efficient, ensuring high-quality products, in line with the international and European Union standards and sustainable in long-terms by the Ministry of Health without external funding.

The objectives are:

1. Analyze the current system of procurement of anti-TB medicines and other relevant commodities, its function and problems.

2. Analyze the existing legal and regulatory framework supporting the central procurement of anti-TB medicines and other relevant commodities and its problems.

3. Develop a detail report on how the legal/regulatory framework should be revised, with recommendations for immediate action and/or medium-term reform.

Modus operandi

The objectives will be achieved through the close collaboration with two local experts, i.e. an expert on legal issues already hired by RAA and another expert working in the NTP central management unit. *(n.b. The legal expert was recruited but had not yet taken up the position and so was unavailable for the period of the assessment.)*

It is foreseen a comprehensive desk review of all relevant documents and one mission in the country where to visit few facilities relevant to anti-TB drug supply management and meet all most important national and international stakeholders (e.g., the National Regulatory Drug Authority, the National Health Insurance House, the Ministry of Health, the NTP, etc.). Before and after the country mission, the work with local experts will be done through means for distance communication.

Deliverables

Report to the Ministry of Health with the analysis of the current procurement of anti-TB medicines and other relevant commodities and recommendations for immediate action and/or medium-term reform of the legal/regulatory framework.

6. Background Information

Romania is listed among the 18 high-priority countries to fight tuberculosis (TB) in the WHO European Region. Last WHO estimates of TB incidence and mortality are respectively 81 (7191) cases and 5.5 deaths per 100 000 population in 2014. These rates have been decreasing slowly by steadily during the last years. Multidrug resistant (MDR) TB is estimated in 2.8% (1.8-4.2%) of the newly-diagnosed and 11% (8-15%) of the previously-treated TB patients. In 2014, HIV was found in 2.9% of the TB patients tested (69% of the total detected). In 2014, the National TB Programme (NTP) detected 94% (83-110%) of the estimated incident TB cases. The treatment success in 2012 was of 85% among new smear positive cases but only 45% among the retreatment cases, 58% among the TB/HIV patients and 34% among the MDR-TB patients.

WHO – ECDC jointly performed a NTP review in March 2014. Based on its recommendations, a national strategic plan to control TB in 2015-2020 was developed, as well as a TB Concept Note for submission to the Global Fund. The National Strategic Plan to Prevent and Control M/XDR-TB 2015-2020 was officially approved, including its budget, by the Government in February 2015. Most recently, Romania was approved for a USD 8.9 million grant under by the Global Fund (April 2015-March 2018) with the local nongovernmental organization (NGO) Romanian Angel Appeal (RAA) Foundation as principal recipient. The technical assistance described in these terms of reference is delivered under a donor agreement between the RAA and the WHO Regional Office for Europe.

Romania has an elevated number of TB cases and taking care of the medical needs of its population requires a strategy which is not followed or needed by Western Europe. Existing legislation to ensure safety and efficacy of medicines is well described and is followed but does not allow for access to all the medicines needed for TB control.

The supply chain for essential medicines is working well and, to a large extent, does what the country requests of it. While it is always easy to identify ways to improve any supply situation, note should be taken that medicines are being provided and people are being treated, policy is well described and procedures are followed, staff is well trained and highly professional.

For TB medicines, the Ministry introduced centralized contracting two years ago resulting in considerable cost savings while maintaining the regular function of the supply chain. Despite many positive elements, TB, including MDR and XDR TB, are at alarming levels. The information concerning the supply chain is not available centrally and the supply chain is not getting all of the needed medicines to where they are needed, when they are needed and does not allow for the tight control in the use of medicines combatting multi drug resistance.

7. Observations of the Current Supply System

For the purpose of this report, the services supporting the supply chain, including centralized frame contracts, are examined and then the flow of medicines from the supplier to the patient is documented, to determine if there are impediments in the way goods, funds and data move from place to place. A focus is made on the selection and approval of goods that allow frame contracts, because this is where the barriers to the use of TB medicines are most apparent.

Services Supporting the Supply Chain

Legislation, Data Management, Finances, Acquisition

Legislation

While not part of the day to day operations, the legal office establishes the legislation and provides oversight to ensure that all of the rules and regulations are followed.

The procurement process surrounding the tendering, award and contracting for medicines is sound, for all goods on the C2 list. This certainly includes the centralized Frame Contracting process. There are sufficient checks and balances and transparency to ensure the process is fair and equitable.

The civil servants of Romania have a reputation of following the rules that the law provides. This means that when changes are made, implementation will follow rapidly.

The MOH has good authority and history of creating new legislation that enables more health care. The legal framework has been amended through numerous pieces of lawmaking introduced to address specific problems but the ad hoc nature of such actions has led to complicated and sometimes conflicting legislation.

Regulation of medicines has two aspects;

1) ensuring the safety and efficacy of medicines authorized for use within Romania
2) determination of affordability and cost effectiveness.

The AAMDM, part of the MOH, has a key role is determining safety and efficacy. Apart from its own panel of experts, it maintains a roster of external consultants who are invited to participate in discussions when specific expertise is needed. When TB medicines are under discussion, Dr. Spinu of the NTP is called upon for his expertise.

The AAMDM uses a point system to determine if the new medicines under consideration should be approved for use within Romania and then to what extent should its use be covered by some level of government reimbursement. Because of existing legislation, the AAMDM is currently unable to approve the use of TB medicines

for off label use or if they have not been produced within Western Europe or the USA, no matter how safe, effective or affordable they are. This legislation not only blocks access to medicines urgently needed for MDR TB but blocks access to external sources of medicines such as the WHO created STOP TB Global Drug Facility for TB Drugs as a source of high quality safe, effective and affordable medicines.

Medicines are approved for use in Romania thorough a Market Authorization and then by a review to determine the level of government reimbursement. In the absence of government reimbursement there has been no reason to go through a Market Authorization process. With the advent of large external donations of some products, gaps in the Market Authorization process have become apparent. Some medicines not produced in Europe or the USA but known to be safe and effective and urgently needed in Romania.

The Special Needs legislation was almost certainly created to allow for circumstances that allowed for actions outside of the standard procedures. Because of the way it was written, it ends up requiring a similar set of approvals as medicines within the government reimbursed systems, though the approvals are viewed perhaps more sympathetically and cost effectiveness is not considered as the central government does not pay. Currently all medicines including those authorized as Special Needs require an MA valid for Romania. Medicines used within Romania must either be produced in Romania or produced and approved for use in Western Europe or the USA. This effectively blocks use of some important TB medicines as they will never get an MA for Romania, nor would the producer wish to obtain one.

Western European norms form the basis of some of the legislation and these legal requirements do not meet all of the current needs of the TB program because, in the case of TB, Romania is not like the Western Europe. For mainly technical historical reasons TB is at a level not seen in other EU countries for decades. Because cases are so few, the EU simply has no priority on TB treatment and the funds spent on treatments are a very small percentage of each national budget; using EU norms as a guideline to acquire TB medicines is inappropriate. Until TB falls to levels similar to the rest of the EU, models from outside Europe, where TB is endemic and an appreciable percentage of the budget are consumed, are more applicable..

Each hospital has its own legal office and, when requested by a prescribing physician and supported by the hospital manger, may authorize, using funds other than those provided by the MOH, the purchase of medicines needed for individual patients intended to bypass most of the centralized procedures. However, current interpretation requires the same processes to be followed that are normally required to purchase any unapproved product. It is being interpreted as only allowing for the purchase of products that have been approved for use within Romania but which the government has declined to reimburse. The hospital would fund from whatever resources are available to it. The law is not clear and it is possible that the law could be clarified so that under Special Needs requests, most of the normal procedures could be waived. In practice

outside of external donations, few funds are available for such purchases and would be insufficient to meet the level of funding needed to treat MDR TB.

Consequences Legislation

Some medicines needed to treat MDR TB including XDR TB are being blocked from national use from any source, even when received as a donation, because of interpretations of the existing legislation.

Low cost TB products from well-respected sources such as the GDF are unable to be considered.

Medicines produced in Romania but indicated for treatments of diseases other than TB, cannot be used for TB as there is no indication for TB use. Ways must be found to acquire and approve additional needed medicines even though they do not have an indication for use in TB in the EU or USA and, in some cases, from any authority.

Dispensing less than the full required set of medicines increases the risk of MDR TB and is the most common reason for the development of XDR TB. This means that the medicines need to become available as a group or not at all and the use of the group of medicines needs to be limited and tightly controlled. Medicines which must only be used in regimens concurrently or in combination are being approved on an ad hoc basis. Use of such products will exacerbate the serious MDR problem rather than alleviate them. Medicines which must be administered in combination or concurrently with other medicines require new legislation to prevent them being acquired and used independently.

Dispensing of medicines for XDR TB needs to be tightly controlled so that the problems of XDR TB are not exacerbated. However MoH Order No. 388/186/2015 allows doctors who work in TB dispensaries the right to prescribe medicines for patients in ambulatory system.

The law recognizes the need for a Special Needs approval and the provision gives considerable latitude in accepting the physicians determination that medicines without an indication for TB in Romania may be still be brought into the country for use in TB treatment. For most circumstances these rules are suitable but they are not suitable for TB medicines used to treat MDR TB. Currently Special Needs approval needs to have an indication for TB from selected Western European countries but TB is a minor problem in Western Europe and some of the medicines necessary to treat TB do not have such an indication in any European country. Because the total number of patients with MDR and XDR TB is so low globally, manufacturers have not performed the clinical studies and other procedures to extend their use to get such an indication in any country and will probably never do so. Countries using such medicines do so under Special Needs legislation of the using countries and such countries include the USA and European countries.

The WHO has recommended the use of such medicines for TB for more than ten years and their use is closely monitored to confirm safety and efficacy. The use of medicines to combat MDR is limited and it is crucial that control and use of such medicines for TB remain in the hands of a few experienced and authorized physicians.

Data Management

Effective management of the supply chain and the provision of services to provide and pay for medicines require the accumulation and availability of data. Data is required for stock management and financial purposes:

1) Data needed to understand the demand (patient use), Data needed to understand supply (products and producers) and data to show how the supply chain is operating (stock flows).

2) Data needed to ensure that expenditures are within available funds, at every level.

There are two main data systems in use within the TB program and they operate independently and in parallel.

The NHIH system captures data from the pharmacies about patients, treatments, goods and expenditures. The financial data are consolidated and reported to intermediate and central levels. The data appears to be sufficient to allow all managers along the financial flow chain to make informed decisions and manage budgets effectively. Data related to patients and goods are not passed along.

The TB Ambulatory system captures patient data which includes medicine regimens. These data are available to intermediate and central level and are used to determine prevalence and effectiveness of treatment. The data is sufficient for all managers to understand the prevalence and effectiveness of their area of responsibility but is insufficient to monitor medicines usage or product flow.

The medicine regimen data is available centrally but is not in a usable format and is therefore unused. From a medicine use perspective, the data is inaccurate in that it only records regimens not levels of active ingredients and because it is unused, there is no follow up to obtain missing information or correct errors.

There are numerous desk based systems where operators are collecting data in hard copy format and manually consolidating. Reports from such efforts are not widely available

Consequences Data Management

Perhaps the saddest observation of all during this consultancy, two systems running in parallel with significant overlap but much of the needed data is not being made available to the decision makers. The program must either

a) Gain access to the NHIH data to enable the program to be managed or

b) Expand the NTP system to capture the data that is missing.

The NHIH is required under the existing legislation to collect most of the needed data and collects the rest. MOH Order No. 388/186/2015 NHIH has the following obligations in relation with TB dispensaries doctors: to keep separate records of issued electronic prescriptions. Numerous conversations between the NTP and the NIHH have proven fruitless as the NIHH declines to share any data other than financial. The legislation does not specify how it is to be shared and so only financial data, needed to control budgets and payments, are shared. Naturally there will be some cost in finding ways to share the data but the cost would be minimal and should be borne by the recipient of the data.

Financing

Even the richest countries have to limit the payment for health services available to its citizens. Public health consideration should take priority over individual health. Approval for medicines for use within Romania is based on a points system with significant points being awarded for cost and cost-effectiveness.

Data is collected on all medicines irrespective of the acquisition cost but information relating to prescribed medicines, not paid for the government, is not provided. Information on the value of medicines in-use is needed by many decision makers and information concerning medicines with zero government contribution is collected but not provided.

Payment against approved budgets is not certain, neither in amount nor payment period.

Consequences Financing

The inability to be confident that funds will be available when suppliers need to be paid reduces the number of companies willing to do business and raises the cost for those still willing.

Not being confident that all of the needed medicines will be available throughout treatment often results in poor dispensing practice. In times of medicines shortages efforts to encourage delinquent patients to come in for their medications diminish.

Failure to ensure that TB medicines are available, dispensed and taken by patients in need until cured, results in a higher rate of MDR TB currently estimated as 5% of cases. As the per patient treatment cost of MDR TB can be several hundred times higher than per patient treatment costs for regular TB , stock shortages, even for short periods of one or more of the medicines required for treatment, results in massive increase in per patient cost. Unless MDR TB is prevented or treated adequately the cost to the TB program may increase to exceed available funds.

Judging medicines on a point system which includes financial costs to the government unnecessarily impedes programs which use external funds.

Acquisition

Procurement for TB medicines is undertaken at two levels;

- the Central Level and
- By the Pharmacies.

Pharmacies undertake their own TB medicines procurements but within the frame contracts drawn up by the Ministry. Pharmacy procurement of TB medicines may be considered as requisitions against a fixed contract.

The creation of frame contracts centrally is handled well and has provided the results expected. Fundamentally the procurement department is the gate keeper making sure that the information provided, is correct. They are provided with the products needed, the specifications, the quantities, the time or time period, the availability of funds and the commitment to release funds. All this information is provided from the different responsible bodies and the unit goes through a detailed and professional ritual which results in the creation of a frame contract, covering a two year time period. The frame contract allows for two alternate suppliers should the first supplier fail to supply medicines when requested. There is an option at the first anniversary for the terms and conditions to be renegotiated. This is a well-controlled process.

Once the frame contract is in place the central Procurement office is not involved in any of the routine supply.

Donors providing TB medicines need similar information to arrive at contracts but the process is outside of Romanian norms and some aspects require waivers to allow the supply to proceed. Procedures to obtain waivers still have to be followed and the waivers are for a limited time period and only considered when the need is great and the funds are provided from external sources.

In the event that there are no government or donor provided medicines the physician may still prescribe additional medications but in such cases a source of payment must be found. There is ambiguity concerning the need to follow all of the requirements for government funded products, except for the funding. At the moment government staff is assuming that the requirements are the same and requesting all requirements to be met.

Consequences Acquisition

From brief observation, some needed TB medications such as Levofloxacin, linezolid, imipenem/cilastatin, PAS, capreomycin, clofazamine, amoxicillin/clavulanate, are not requested from the procurement section because they are not on the C2 list and

will be rejected. No one has the responsibility to undertake market research to see if other Producers not on the list should be encouraged to participate.

Quantities needed are based on estimated amounts made with inadequate or missing data and require no justification. The procurement office does not have any responsibility to undertake forecasts or to determine if forecasting has been done using suitable methodology.

Specifications are rigid and no one has the responsibility to consider variations even when they may result in greater cost effectiveness.

Terms and condition are known to vary during the period of the contract and payment is often delayed. The consequence of such actions is to scare off international suppliers and to increase the prices from national suppliers.

Flow of medicines

Producer/ Wholesaler→pharmacy→ambulatory→patient.

Producer/Wholesaler

To a very large extent, medicines used routinely to treat TB are produced within Romania. First line medicines have been produced for decades and the supply may be considered suitable to meet the needs of the patients. Contracts for first line TB medicines were established with the Producers/Wholesalers following standard government practices resulting in a two year frame contract against which pharmacies may requisition the needed medicines and the government will, eventually, pay for the delivery of authorized goods. All medicines included in the frame contracts are on the Essential Medicines list of Romania, have MA and are included on the C2 list for government reimbursement. For items not used to treat TB and/or not within centralized frame contracts, the 190 individual pharmacies go through an individual tender and award process.

Second-line medicines are more complicated, as many are imported. The Producers of second-line medicines have been selected by outside entities and the products are allowed into the country using special exemptions to the regular registration and authorization process. They could not be included in the frame contract as they are not on the C2 list and there was no money to pay for them. Currently second line medicines are purchased with funds from donors and against contracts that are not governed by Romania. This will change in the future and Romania must prepare to have all TB medicines included in routine supply.

While some Producers accept orders directly from any of the approximately 190 pharmacies, some Producers appoint, as an agent, a commercial Wholesaler to manage orders and make deliveries. As an agent, the Wholesaler is also responsible to obtain market authorizations, respond to tenders and obtain payment for goods

delivered. Under a frame contract for TB medicines, outlining the products, prices and terms and conditions, orders are accepted from any of the pharmacies and payment is received from the government. Because all of the first line medicines are purchased from Romanian producers, market authorizations are always in place.

UNIFARM is a specially designated Wholesaler and all imported goods, approved by the government but selected by outside entities, are received here. Imported goods may be held in quarantine and need to go through additional quality assurance procedures, depending on their origin.

Consequences-Producer/Wholesaler

To some extent the Producer and Wholesaler are protected from competition. Variable payments, months after the goods have been provided, represent an expense and a risk to the supplier. Expenses and risk have to be built into the price, making goods more expensive. Additionally such terms and conditions are not generally acceptable to international suppliers and so they do not compete. The absence of competition allows current suppliers to be less than the best they can be. Locally produced medicines are not only more expensive than internationally provided products but also have remained with the same specifications from past decades. WHO recommends the 4FDC and 2FDC for first line treatment because they are easier to use by the patient with less chances of error and in addition partial treatments cannot be given. They improve compliance and therefore the cure rate and reduce the risk of the development of MDR TB through treatment with incomplete regimes. The local market for FDCs is too small for Romania to consider production and getting market authorizations and it is doubtful that Romania could compete on price with India or China, with their huge local markets. FDCs are neither requested nor provided by local Producers. As only traditional products are available, per-patients costs are higher than prices available on the international market; market size is too small for local producers to go through the effort and expense to produce additional second line medicines for TB use. Inviting international suppliers to make offers against frame contracts is possible but requires manufacturers to have market authorizations for the use of the medicines for TB, in Romania, EU countries or the USA. Many of the needed medicines do not, and may never, meet these conditions.

Pharmacy

Each pharmacy acts independently in deciding what items to stock, reserve stock levels and order period, though there are national guidelines. Each pharmacy is responsible to tender and contract for products. For the centralized frame contracts, for first line and for other TB medicines, approval for the pharmacy to buy is requested of the Ministry, to make sure the demand is still within the pharmacy and the government's budget. The approval process takes about one week and once approval is received, then the goods are requisitioned from the supplier designated in the national frame contract. Delivery is made within 72 hours. Most Goods provided from sources outside of the country and ordered in cooperation with the donor are delivered to UNIFARM.

The pharmacy orders from UNIFARM in the same manner as other Wholesalers. For TB medicines for MDR TB approvals are necessary from the TB Commissions operating in Bucharest and Bisericani.

The pharmacy maintains a full data base of information concerning the management of medicines within the pharmacy. This information is used to manage the day to day stock levels of all commodities.

For TB medicines the pharmacy does not dispense directly to the patients but provides to the TB Ambulatory unit so they may provide to the patient. The pharmacy maintains records concerning medicines received and provided, as well as patient data. All data related to goods and patients is provided to the NHIH periodically. The pharmacy works within approved budgets but does not receive cash for goods provided nor pays directly for goods received.

Consequences Pharmacy

Tendering and contracting for medicines by each pharmacy, is an onerous task. Relying on centralized contracts reduces the workload and provides better prices and service.

Because stock level information at each pharmacy is not shared with other managers within the supply chain, it is impossible for the NTP to know the extent to which treatments are being interrupted because of lack of medicines. Additionally there is a probability that while some pharmacies are out of stock other pharmacies are overstocked. As this information is not made available to decision makers, there is no possibility to move stock around to better treat patients.

Obtaining government approval before requisitioning goods is impotent as information concerning patient burden and stocks on hand is not provided. The authorization is given on historical and incomplete data. The pharmacy has the data but does not provide it. There are more efficient ways to ensure medicines ordered are within budget. There is a mismatch between goods authorized for purchase and goods actually purchased.

The guidelines require TB medicines to be ordered quarterly to be similar to the way other medicines are ordered. - Emergency Government Ordinance 71/2012. All the orders are being limited by budget and do not respect the rule of drugs' management: "3 months + 1 buffer month ". (According with Art. 23(n) of HM Order 386/2015: stocks of medicines, sanitary materials and medical devices will be dimensioned at the average monthly consumption level of the previous year properly for a period of 3 months.) This does not follow international guidelines for stocking TB drugs. Because of the consequence on public health, should there be any interruption of supply, safety stocks are recommended to be 100% of the drugs used during an order period. Quarterly ordering will increase the probability of stock outs and therefore interruption of patient treatments. The frame contracts required the demands created by all of the pharmacies

to be pooled together rather than undertake 190 separate contract negotiations. The results of the coordinated tender was a success as prices obtained overall were lower and became uniform throughout the country.

Coordinating the data generated at each pharmacy would be an additional success and allow for more accurate estimates of demand and much better stock control. In the absence of real data, quantities of medicines approved this year are largely based on quantities of medicines purchased last year. If the demand is static then such a system works reasonably well. If the market is changing or if there have been stocks-outs, which has distorted offtake figures, then such a system only perpetuates problems. There are anomalies in the data, with authorizations from the ministry greatly exceeding goods ordered from the suppliers and number of patients being reported as being treated exceeding calculated prevalence rates.

TB Ambulatory units

Because TB products are provided under a Directly Observed Therapy strategy, the pharmacy provided medicines to the TB Ambulatory units, on a patient by patient basis, responding to a physician's prescription. The patient presents periodically and is observed taking the medicines. In practice the patients comes once a week or month, confirms that all medications have been taken as prescribed and receives an additional period's supply. Medicines may be provided to another medical worker living closer to the patient, who would then provide to the patient in a similar manner. In the event a patient does not come for more medication then there is a follow up to determine what has happened. In a worst case scenario the patient may miss two months treatment before the TB Ambulatory follows up.

The TB Ambulatory units, record and report concerning patients treated and regimens prescribed. These data are used for prevalence estimates and the data is considered to be accurate and sufficient for such purposes.

Consequences TB Ambulatory Units

DOTS require each dose to be observed but it is common practice to provide the patient with one week or one month's worth of medicines and trust them to self-administer. It is well know that this does not work as well as necessary, which is why DOTS is recommended. Strategies to implement DOTS, as required by the NTP, require additional monitoring. Greater emphasis to seek out patients, who interrupt treatment, should be made. A strategy to seek out high risk patients to get them to a diagnosis is needed. Patients develop MDR TB at rates higher than normal. High failure rates indicate the patient is not taking the full dose of recommended treatments and this can be caused by non-compliance by the patient, prescribed medicines not following WHO recommended regimens or medicines not being available when needed. Shortage of medicines will inevitably lead to incomplete prescription and or patients receiving only partial treatments. Should stock control and data sharing methods be improved such that there are no stock outs at any time it may be expected that real

demand will be shown to be higher. If more attention to compliance is made or there is more success in treating patients currently not in the health system the demand will increase. This potential demand increase should be considered in any future tender or demand estimates

The Ambulatory units enter much of the data already entered by the pharmacy but add in information concerning prescribed regimens. Unfortunately the regimen is weight dependent but this detail is not captured, so the drug use information available is useful for determining patient burden and disease prevalence but incomplete from a medicine management perspective. Crucial data, which could help pinpoint the reasons for failures in the cure rates, is not made available to the decision makers.

Patient

At risk population have an expectation for their disease to be detected, and all patients have a right to be diagnosed, treated and perhaps isolated, in accordance with National protocols. The patient must present themselves to a physician. If the physician suspects TB then the patient is referred to a pulmonary specialist who will complete the diagnosis using standardized laboratory testing. The physician will prescribe the appropriate medicine regimen, which is weight dependent. The patient must come to the Ambulatory frequently and periodically to receive medication

Patients have a right to refuse medication and protocols involving counseling and perhaps isolation, must then be followed

Consequences patient

Case detection of TB regularly exceeds the international target of 75%; and treatment outcomes for TB are good. Treatment outcomes for the majority of MDR-TB patients remain unacceptable with around 20% treatment success rates (Source: NSP 2015-2020). Failure to be cured leads to premature death or increases the per-patient cost to the TB program, several hundred times over. Progression to XDR TB has costs which may be unaffordable. When patients fail to be cured, at the expected rate, or develop MDR TB at a rate much higher than expected, it could be that the medicines are provided but not taken, which is a failure of DOTS or the medicines were not provided. It should be possible from the entered data to determine which of these problems to address first, but the data is not made available to the decision makers.

The conversion rate for 40 patients receiving medicines provided through the GLC is cured at a rate corresponding to international norms. MDR patients being treated from government resource fail at a rate three times higher. Treatment failure is most often due to the unavailability of one or more needed medicines provided together in the same regimen. It should be possible to document which patients are receiving only a partial regimen due to shortage of medicines but the data is being withheld from the decision makers.

Funds for MDR and XDR TB are being provided by external donors but this is for a limited two year period. Preparations must be made to take over responsibility as interruption of supply during treatment will accelerate the development of MDR TB and risk exceeding any foreseeable financial allotment from the government.

8. Recommendations

Romania has a strong legal system which is respected and effective. The legislative changes necessary to allow new TB medicines urgently needed, into the country, are well described and are apparently unopposed. Proposed changes already have the support, in principle, of the MOH, NAMMD, Central Procurement unit, NTP, RAA, WHO, WB, Gates Foundation and Norway, and are currently under review prior to implementation. In this respect it is matter of supporting the progress towards working out the language and making sure that the changes are comprehensive , allowing for needed TB medicines now and in the future to be acquired, while at the same time putting in alternate methods of oversight, beyond Romania, EU and USA, to ensure safety and efficacy.

There are undoubtedly some other medications that are needed in Romania but not produced in the USA or EU, but TB is in a unique situation in that without rapid introduction of the needed medicines, development of more XDR TB patients could results in medicines cost of more than the entire TB budget; this must be prevented. In this respect it is a public health imperative.

It is not only legislative changes that are necessary to make use of these new medicines as effective as possible but also changes to the way medicines are acquired, approved, financed and monitored. The reality is that legislative changes must occur but once the medicines are received, other system changes must occur, at about the same time, for use of these medicines to be fully effective. Data is not available to make accurate calculations but it may be predicted that cure rates for MDR TB will improve threefold while per patient treatment costs would fall by more than 25%.

Legislation; immediate

The spirt of the Special Needs legislation authorizes physicians to take on responsibility for individual patient treatment which are not covered by current medicines policy or, in anticipation, for patients affected by epidemic. Law 95/2006 allows for temporary authorization when a physician requests a drug for a patient or patients directly under his/her care. In the case of an epidemic this is broadened to include patients which have not yet been identified but will come under the physicians care imminently

Given the rate of TB is so much higher than the rest of Europe, the incidence of MDR TB is double and treatment failures for MDR TB are triple European norms, legislation dealing with epidemic pathogens are appropriate.

While the Special Needs legislation normally allows physicians sufficient latitude to treat patients with medicines not supplied by the government, the current interpretation is still to require the medicines to go through a similar government approval process.

Some medicines crucial to treat TB and being requested under Special Needs may never be able to overcome the barriers imposed.

The National Strategic Plan 2015-2020 requests that Law 95/2006 and Order 85/2013 be amended in order to allow the urgent acquisition of medicines outside the normal public procurement process.

Recognizing that because of the special circumstances of TB infections, especially MDR TB infections, current legislation unnecessarily represents a barrier to effective treatment, and it is proposed:

Recommendation:

1. Allow TB medicines recommended by WHO, that are not indicated for TB use in Romania and acknowledging that some products may never have an indication for TB, to be brought into the country under the Special Needs legislation for use to control TB under the following, modified circumstances.

2. When the Special Needs medicines are not available from Romanian, USA or European Producers, then production and products from companies that have been approved by

    - a) any member of the PICS scheme, which include the USA and EU countries,
    - b) WHO,

    may also be considered.

3. The requesting physician shall make the determination as to the suitability of labelling and other aspects of presentation and packaging.

4. The approved and identified dispensing physician(s) may use such medicines for TB treatments, at their discretion, irrespective of their current indication.

In considering the request for Special Needs authorization the Health Technology Assessment panel may also require assurance that:

1. The request is supported by the NTP and is based on the published international recommendations of WHO.

2. In the event that the production of the medicine is not under the constant oversight of PICS, then additional quality assurance steps may be taken and could include batch release by a PICS approved laboratory.

3. There will be an independent, pre-release inspection, to ensure that quality assurance requirements have been met and the products meet the specifications approved by the requesting physician.

4. Medicines that must be used concurrently or in combination with others are to be submitted for consideration together and at the same time understanding that a Special Needs approval for use shall be made for all or none.

5. Approved products shall be made available only to a limited number of named prescribers and their use be restricted to follow WHO guidelines.

Modifications to the Special Needs approval are proposed, because the current legislation already acknowledges that there are special circumstances where the regular legislation may not meet the urgent needs of public health. By interpreting or clarifying, that the Special Needs approval can be granted by the ANMDM once they are convinced that safety and efficacy standards have been met, by means other than those described in the current legislation, then acquisition, distribution and use can be approved. This is a first step intended for rapid approval and implementation.

Legislation; Longer Term

The legislation concerning the creation of frame contracts at the centralized level appear sound, effective and suitable for what has been expected. Prices have been reduced and standardized throughout the country, availability of medicines has improved and the work load on the pharmacy has been reduced, even though there is an extra approval step to ensure requisitions remain within adjustable budget limitations. The performance of the suppliers has been satisfactory, so that the lowest priced supplier received almost all of the business. The time period of two years works well. The review process after one year works well. It is a good working model and could be expanded to other pharmaceutical commodities with expectations of similar positive results. (This information has been provided anecdotally as supporting data is not available centrally.)

The current legislation ensures that patients only receive medicines which are safe and effective. It also provides for a review process which ensures that only medicines which are cost effective and affordable are approved. Safety and efficacy standards rely on USA and EU standards. There is a need to expand the standards to include medicines which are needed In Romania but not needed and not produced in either the USA or EU. The global production market place is changing and some high quality, effective products are produced in countries like India; this is especially true of TB products. Romania needs to expand its approval process to include such products and producers to allow their use within the country, applying additional safeguards and oversight

Medicines for the treatment of MDR TB are being brought into Romania under procedures which are exceptional to the norm and are currently being funded by donors

outside of Romania. External donations will continue for a limited time and at some point the Romanian government shall take over responsibility for the acquisition and payment for such medicines. Some of the medicines will need to be imported and are not expected to able to comply with existing legislation.

Recommendations:

1. The frame contract process should be continued, and expanded to other TB medicines and other high value, high volume medical items.
2. Legislation should be expanded to allow for the approval of medicines which are not produced in Romania, EU or USA but have satisfactory oversight of quality and efficacy. Acceptable oversight needs definition. Additional safeguards need to be defined. Such approvals would be part of the NAMMD approval process through the Health Technology Assessment panels.
3. The NAMMD should be able to provide a market authorization for a product to be used in Romania without an application from the producer. Such approval should be subject to additional safeguards and oversight directed by the NAMMD.

Data Immediate

The barriers to data availability to the NTP managers, concerning patients, products and treatments must be overcome. The easiest way is to require the NHIH to release all of the data gathered, in real time or near real time, so that the NTP and other managers, may identify problems and make adjustments in areas of stock shortages, inappropriate dispensing or poor patient compliance. In addition the information will be used to balance stocks and to calculate purchase quantities with more precision. Collection of such data by the NHIH is required under existing legislation but the legislation does not specify manners of reporting. The use of such data is an imperative for centralized frame contracting.

While the TB program is moving in the right direction, its success is well below international norms. The reasons for this can be inferred from the available data but the data is not being made available in a timely manner with sufficient accuracy. Two data systems are currently used within the TB program and operate in parallel. The NHIH system collects all necessary data but only passes along consolidated financial data.

There is good financial control for budgeting purposes but information necessary to measure the relationship between medicines availability and health impact is hidden. The NTP has installed its own parallel system to measure program performance but gathers insufficient data to helpful in medicine management or to identify problems in a timely fashion allowing for corrective actions to be taken.

Recommendation:

Release to the NTP managers, for analysis, all TB data currently collected by the NIHH but not shared, on patients, stock movements and treatments.

Data Longer Term

Because real time data has not been made routinely available there is little overall use of data in the management of the supply chain. Once the data is being made routinely available, every aspect of stock movement should be monitored centrally. Apart from a supply chain manager providing oversight of the stock movements, the individual pharmacies would continue to do what they do. With the flow of real data, problems will quickly become apparent and corrective actions proposed. Where there is a mismatch between patient burden and stock movements, a closer look at the operation should identify the problem. Where treatment rates are low or MDR is high, stock shortages can be identified or eliminated as the cause of the problem.

Recommendation:

1. Actively monitor all stock movements of TB medicines along the supply chain.
2. Use real data concerning stock movements for forecasting as opposed to disease burden estimates.
3. Establish warning signals through a dash board arrangement to show when there are anomalies in stock movements or health outcomes, which require investigation and correction.

Finances Immediate

Delayed or intermittent release of government funds increases the costs of all medicines but for TB there are other important considerations. From a public health standpoint it is unethical to start patients on a TB regimen unless the complete treatment can be assured. Funds for the medicine component should be committed before the patient starts treatment. In the absence of committed sufficient funds, the physician should tell the patient that treatment cannot be started; but this is an untenable position. Physicians will do the best they can for the patient but partial treatments are not as successful and have higher conversion rate to increased medicine resistance.

Recommendation:

Where uncertain funding can have a negative effect on public health or risk increasing public health cost dramatically in future years, make funding commitments for TB firm and make availability at the start of the year.

Finances Longer Term

The funds available from the government for TB control have been increased significantly in the recent past and this is to be applauded. However the slow and unpredictable release of funds has a negative effect on the TB program. By making payment terms for contract long and unpredictable many suppliers are unable to absorb the risk and extra cost this causes and so do not compete. This is especially true for international suppliers. Even for Romanian suppliers, there is a need for them to build in extra cost to cover worst case scenarios. Making payments reliable and in a timely fashion will attract more competition, especially low cost international competition and result in lower prices even for local suppliers

Recommendation*:*

Explore ways to have funds available to make payments to suppliers within 30 days after release of goods. This could be an internal revolving fund used when government release is delayed.

Health Technology

The market approval, finances and procurement are all handled competently within the centralized system. The legislation is sound and for the most part protects the citizens of Romania while allowing access to medicines of known good quality. The system of medicines acquisition, involving approval, contracting and wholesaling is passive, with no responsibility or authority to consider new products and sources that could provide treatments which are more user friendly reduced error in dispensing or cost effective.

What is missing is a product champion who works for the TB program and working within the current system, to seek ways to acquire more cost effective treatments. This champion would undertake market research, be in constant contact with potential suppliers and generally encourage new companies to qualify to compete for business. The role would primarily to understand the market and to find ways for new low cost products to be registered. Such a person would work closely with the Health Technology Panel, the procurement group and one or more wholesalers.

Recommendation: Create a new position to undertake market research with the intention to have more companies competing in Romanian tenders.

9. Strategy

There is almost universal support for the well-known changes needed to be made to the legislation to allow the import and use of urgently needed medicines for TB control and the process for change is already underway but could be accelerated. There is an urgent need to apply these changes to the Special Needs authorization, but such changes should carry over to normal registration. Changes in the approach to expanding the medicines acceptable for use in Romania are procedural as well as legislative. The frame contract process works well, the process of getting more products approved, to be included in the frame contract process, needs to be added.

- Step one is to request the legal advisors in the NTP to work with the legal advisors in the MOH to arrive at suitable wording for the new legislation. This should allow the Health Technology Assessment panel group within the ANMMD, to include, within defined circumstances,
    - an expansion of sources of medicines to include production outside of Europe and the USA and
    - approve the use of products for TB treatments in the absence of an indication for such and
    - define the extra controls necessary for such approvals.
- Step two is to undertake a quick market analysis of treatments used by countries with similar TB burden to see the extra steps they take to ensure safety and efficacy of products and the level of savings that are likely to be achieved by implementing similar changes. Savings, of more than 25% of the per-patient medicines cost, are anticipated. Once the significant savings are confirmed, without any compromise to safety and efficacy, then such data should be used to stimulate enthusiasm for other proposed changes.
- Step three is to create a new permanent position to undertake market research and to work closely with members of the NTP, the Health Technology Assessment Group, the procurement office and one or more wholesalers (UNIFARM?). Getting products needed by TB approved for use in Romania should be ongoing and well in advance of any tendering process and should be independent of any government intention to reimburse or not reimburse specific products. Priority should be made for the products which will result in the greatest savings but all TB products should be constantly researched. This person should overcome all barriers preventing suppliers participate in tenders. Occasional external support from international bodies such as WHO, WB, STOP TB, IDA etc. may be invited to participate during early strategy sessions.
- Step four can be taken once the data already collected is released to the NTP for management purposes Create a new responsibility for managing the supply chain through the use of data. Determine the reports that would be most useful and create an early warning system that would highlight anomalies allowing for further investigation or corrective actions to be taken.