# UNIVERSITY OF MEDICINE AND PHARMACY CRAIOVA

# DOCTORAL SCHOOL


# PhD THESIS


# ABSTRACT


## ASSESSMENT AND MONITORING PROGRESS IN THE TREATMENT OF MULTIDRUG- RESISTANT TUBERCULOSIS CASES IN ROMANIA UNDER DIFFERENT CONDITIONS OF TREATMENT (EXCELLENCE CENTERS VERSUS TERRITORIAL PROFILE UNITS)

PHD SUPERVISOR,

*PROFESSOR: VALENTIN CÎRLIG*


PHD STUDENT,

*Mihaela-Emilia TĂNĂSESCU*

Craiova

**Contents:**

**Introduction**

**I. MULTIDRUG- RESISTANT TUBERCULOSIS**

**I.1.MDR TB in the world**

  The establishment of drug resistance during tuberculosis therapy was a phenomenon identified shortly after the introduction of streptomycin in 1946-1947 [64]. Acquiring drug resistance in patients with TB is to a large extent an iatrogenic phenomenon, as a result of the artificial selection of spontaneous drug resistance mutations of Mycobacterium tuberculosis during inadequate or incomplete treatments [5,12,79]. These drug resistance strains can then be transmitted to other individuals, decreasing the effectiveness of treatment regimens used in treatment programs [72, 74, 76]

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampicin, two of the most effective first-line anti-TB drugs, considered major drugs, requires the use of second-line anti-TB drugs that are less more potent, more toxic, more expensive, and requires a longer duration of treatment [75,76].

XDR-TB is defined as MDR-TB plus resistance to any fluoroquinolone as well as to any second-line injectable drug (parenteral agents: kanamycin, amikacin or capreomycin), two of the most effective drug from the second line therapy [88].

The diagnosis, treatment and management of MDR-TB and XDR-TB cases require considerably more financial and human resources, and treatment outcomes are much weaker, increasing the risk of subsequent transmission of resistant strains [20,77,85].

**I. 2.MDR TB in Romania**

  In Romania after 2008 through implementation of the projects financed by the Global Fund and subsequently by the Norwegian Financial Mechanism have been treated as many cases with MDR TB. [83]. However it seems that the number of cases treated is still far below the estimated number of cases.

  Respecting the downward trend of the other major tuberculosis indicators (incidence, mortality, incidence in children), the number of new MDR TB cases recorded in Romania in recent years seems to decrease slowly but steadily, but there is a slight

increase in the number of cases of XDR, probably due to the testing of as many strains as resistance to second-line drugs [57,84].

## II. The substantiation of the project

Developing resistance to the first-line drugs and, in particular, those of the line II, has become a redundant problem for public health systems in a large number of countries, but also an obstacle to the fight for global control of tuberculosis. Although WHO experts have been discussing drug resistance for a long time, and scientific guides and publications have broad notions, in many countries the spread of antibiotic resistance is unknown, and the management of patients with multidrug-resistant tuberculosis is inadequate [41,79].

The management of drug- resistant TB is complex and often difficult, and at national level there must be an appropriate strategy for the prevention and dissemination of drug resistance (included in the National Control Program). That is why in Romania, expert committees have been set up for the treatment of chemically resistant cases that make up or suggest to the pneumologist, appropriate therapeutic regimens, in accordance with the recommendations of the updated WHO guidelines.

Chemoresistance to antituberculous drugs is a phenomenon with a negative effect on the effectiveness of TB treatment and on the evolution of TB endemic. Therefore, the epidemiological surveillance of resistance to anti - TB drugs is an essential component of monitoring the effectiveness of TB control measures. The epidemiological surveillance program, integrating national data, signals the dynamics of resistance in the territory.

For cases with chemosensitivity, therapeutic successes are obtained in over 85% of new cases of TB, in MDR-TB treatment is successful in 40-70% (in optimal conditions) and those with XDR-TB in proportion below 30%.

Early diagnosis with a quality reliable DST for both I-st and II-nd line drugs for which there are standardised methods of testing (quinolones and injectables) is an effective case approach of MDR / XDR TB as recommended by WHO / ECDC.
To improve diagnosis, WHO recommends culture and DST in a liquid medium, a method that greatly reduces the delay in achieving the results and increases the sensitivity of the method by 10% [144, 147]. In the case of molecular testing, approved by WHO for MTB

detection and resistance to RMP, the GeneXpert automated system and the LPA method used for HIN and / or RMP detection, respectively, LPA for II-nd line drugs [153,154].

Just as important as ensuring uninterrupted provision of medicines and building appropriate schemes is to ensure the best patient compliance and the correct management of drug side effects. The psychological support to the MDR TB patient is an integral part of the treatment, without which the outcome of the therapy is sometimes compromised.
The prolonged duration of therapy, drug toxicity, isolation, lack of working capacity, social stigma are factors as important as the lack of therapy in the failure of treatment or abandonment.

## III. The objectives of the survey/ study hypothesis:

Results obtained in treatment of MDR-TB cases under uninterrupted treatment and appropriate treatment regimes (MDR Excellence Centers between 2004 and 2008) compared to those treated in the relevant territorial network. During 2004-2008, within the DOTS Plus project in Romania, the Global Fund ensured the financing of the project to *ensure uninterrupted supplies of high-quality second-line anti-tuberculosis drugs (MDRTB : T1A5.5 Round 2.)* in the value of USD 1.856.152.

### III.1 Material and method:

An observational (retrospective) analytical study was carried out on patients with MDR-TB admitted to the Centers of Excellence in Romania between 2004-2008 (400 patients representing cohort I and II GLC), with definitive results at the time of analysis and those from the territorial network (provided by the computer system).

Patient evaluation was performed according to the therapeutic protocols developed under the National Tuberculosis Control Program and the DOTS Plus Program.

The 400 patients from the two Centers of Excellence (170 in Bucharest and 230 from the Bisericani) were included in two equal cohorts of 200 patients corresponding to the two initial phases of the project over the years 2004-2008.

From patient observation sheets, MDR-TB registries and the computer system were provided demographic data, length of hospitalization, PNCT category, radiological lesions, results of bacteriological examinations in dynamics and results of treatment of patients with MDR-TB. The accuracy of the laboratory methods was verified by repeated quality assurance tests developed by the WHO and IUATLD TB reference laboratory network.

## III.2. Assessment:

**The results were targeted by:**

I have followed in this study the distribution of cases by age, gender, medium of provenance; bacteriological confirmation rate by microscopic examination; sensitivity to antibiotics; treatment outcomes obtained in patients treated in the two centers of excellence, in optimal conditions compared to tuberculosis network (under conditions of inconsistent supply with medicines), the presence of adverse reactions to antituberculous drugs.

All of these were aimed at establishing a correlation between the optimal treatment conditions that patients had in the project (hospitalization until sputum conversion, continuous medication according to expert schemes, management of adverse reactions) and good treatment results ( well above the country average).

This is all the more so since the WHO's recent recommendations (the WHO Regional Office for Europe in 2016) suggest treating as many MDR TB cases ambulatory cases in order to prevent the transmission of resistant strains in the hospital.

I think that this solution is applicable to countries that have a relatively small number of MDR cases and optimal conditions to make correct circuits in ambulatory units.

In Romania's current socio-economic conditions, with a rather low level of health education (and we should not forget that a good part of the cases of tuberculosis come from vulnerable environments), I do not think this is yet a feasible solution for our country and this is also demonstrated by the results of the analysis below.

Perhaps not the knowledge about the disease and disease management lack of doctors and personnel involved in the care of MDR / XDR TB cases (let's not forget that in the Global Fund projects staff training has also been carried out: 11 trainers and 438 MDR case managers TB and also many national MDR practice guidelines have been developed), but primarily sub-funded healthcare is responsible for suboptimal outcomes in this segment of patients: sometimes expensive drugs that can not be secured by annual budgets offered to pneumophysiology units

And for a good grip to treatment, informing and educating the patient are essential [33]. I think that are not sufficient in this respect the action they can do doctors pneumoftiziologi (for patient and contactii thereof), but it is imperative and participation of the network of primary medicine.

And for optimal adherence to treatment, information and education of the patient are essential [33]. I believe that the actions that can be made by pneumophtysiologists (for the patient and his / her contacts) are not sufficient, but action of the primary medicine network is also imperative.

## IV. Results:

- In the center of excellence MDR-TB Bucharest were admitted in this retrospective study 170 patients with MDR-TB between 2004 and 2008: 99 men and 71 women; of which 102 patients in urban areas and 68 of the rural environment.
- At the Center of Excellence at Bisericani 230 patients with MDR-TB were admitted in the study between 2004 and 2008: 123 males and 107 women; of which 84 urban and 146 rural patients.

- In both of the centers, on the batches of patients admitted in the period 2004-2008 it is found admitting a greater number of men than of women: 58% to 52% in Bucharest and Bisericani, and depending on the environment of origin in the center of Bucharest, most patients have derived from the urban environment, while at Bisericani most came from rural areas.

- The average duration of hospitalization was similar in the two centers: 117 days-Bucharest and 121 days- Bisericani.

- The largest group was represented by the chronic patients - **47,7% in Bucharest,** and Bisericani **22**% of the total number of patients with MDR-TB register.

- Relapses were more frequent in Bisericani (40%) than in Bucharest (17%).

- Most new cases were recorded in Bucharest (22.4%) compared to Bisericani (17%).

- The therapeutic failures were most frequent in the center of the Bisericani (21%) compared with the Center in Bucharest (12.9%) .

- The radiological lesions were polymorphic, most of them having bilateral localizations (76% of patients from Bisericani and 47% in Bucharest) and a significant number of them with cavitary lesions (66.6% in the patients from Bisericani and 77 , 6% in patients in Bucharest).

- The number of patients with bacteriological confirmation and culture was predominant in the two enrollment centers (84.6% in Bucharest and 84.4% in the Bisericani), while MDR-TB cases with negative smear and positive cultures were in a higher percentage in Bisericani (9.1%) than in Bucharest (7.1%).

- Most of the cases enrolled in the GLC cohort had only HR resistance (60.5%), in the remaining cases plus other resistances: HR+1 (E/S/K/CS/Ptm), HR+2 (ES/SK/KA/KE, a.s), HR+3 (QSK,ska/ESK,s.a), HR+4 (QSKPtm, CsSQPtm,ESKCs,s.a), HR (QSKCsPtm+5).

- Resistance to HIN, SM, RMP and EMB was more common in the previously treated cases, the proportion of cases resistant to 3 or 4 drugs being significantly higher

in the latter than in new cases, indicating a progressive accumulation of resistance along treatments.

- Of the total number of MDR-TB cases included in cohort I, at Bisericani most patients were resistant to HR and other 2 drugs (34.73%), while in Bucharest the highest share was patients with resistance to HR and one other drug.

- For cohort II, the resistance spectrum was more extensive. In Bucharest: HR + 2 other drugs predominated (29.3%), followed in similar proportions by those with HR resistance, HR + 1 and HR + 3 drugs.

- Among the patients from Bisericani, the most prevalent were those with only HR resistance (53.6%). Equal proportions were those with HR + 2 or 3 drugs.

- Surgery was a therapeutic option in 17 patients (10%) in the center of Bucharest: 16 resection surgery (11 lobectomies, 5 pneumonectomies) and 1 thoracoplasty were performed. In the center Bisericani - surgery - 15 patients (6.52%): 9 lobectomies, 3 pneumonectomies and 3 thoracoplasty.

- The conversion rate in microscopy and culture for the two centers was: Bucharest reference center: Negative M and C (mean duration 3-4 months) at 72.5% of the patients, and at Bisericani: Negative M and C (average duration 3-4 months) to 64% of the patients.

- The 400 patients from the two centers (170 from Bucharest and 230 from Bisericani) were divided into two equal lots of 200 patients (within the cohorts treated with medication externally financed by GLC) from the end of 2004 to the first months of 2008.

- The success rate (cured + treatment completed) of cohort I was 58% (116 patients). The highest number of patients treated successfully was in the new cases category (14 + 17 = 31), relapsed (22 + 13 = 35) and chronic (11 + 12 = 23).

- It is worth noting the significant number of deaths (25 = 12.5%) and the number of patients registered as failure (31 = 15.5%), which indicates the severity of the cases. The highest number of deaths was in the category of chronic patients (11) and relapses (10).

- The rate of default, although increased when enrollment was made by signing informed consent, was nevertheless lower than the national average in this category of patients.

- The cohort II success rate is 75%, higher than the first cohort (150 patients). The highest number of successfully treated patients was recorded in this category of relapses (24 + 32 = 56), new cases (27 + 12 = 39), after abandonment (13 + 4 = 17) and failure of treatment with regime 1 (11 + 6 = 17).

- The number of deaths in cohort II (13 = 6.5%) was much lower than in the first cohort (by half) and the number of patients registered as failure (20 = 10%).

- The highest number of deaths is also recorded in the category of relapses (7).

- The abandon rate, although still higher, is lower than in the first cohort (8%).

- The cumulative success rate (calculated on the total number of patients in the cohorts) was 66.5%, lower than in the developed countries (where it is 70% pasta), but much higher than the rest of the patients in the network (nonGLC ) in the 2008 evaluation year (which was 19.3%).

- Treatment outcomes for the 2008 non-GLC analyzed cohort were alarming: 19.3% success rate, 23.2% mortality, 34.7% failure and 21.5% dropout (cohort non-GLC, 2008, 792 patients).

-  The number of failures predominated (275 = 34.7%) and abandonment (170 = 21.5%). It should be noted the high number of deaths (184= 23,2 %)

- For a similar cohort as enrollment categories in 2009, the treatment outcomes were similar to the previous year, with a success rate of 15.1%, 18.9% mortality, 36.7% failure, 19% deaths and abandonment 20.2% (in a total of 624 patients).

- The prevalence of failures, abandonment and deaths over the two years (2008-2009) is evident. All of these patients feed the case pool for the following years, with the selection of new resistances over time through multiple abandonment and treatment retreats. It is very likely that this is the reason why the number of cases preXDR and XDR TB has increased in recent years.

- The total percentage of patients who are eliminated from the total burden of resistant cases (cured, completed treatment, death, leaving the country) is lower than those who continuously increase the burden of MDR-TB cases (failures,

abandonment, lost) - 43 % compared to 56.2% in 2008 and 34.1% compared to 56.9% in 2009.

# V. Discussions:

○ The results of the study highlight the fact that therapeutic success rates close to the WHO recommendations and those registered in some EU countries (70%) can only be achieved by following the recommendations of the guidelines.

○ This requires uninterrupted treatment provided at the appropriate dose and administration duration, which can only be provided with adequate funding (for the analyzed lots being provided by Green Light Committees with Global Fund funding).

○ For similar patient profiles treated in TB network units, although the therapeutic regimens were built under the guidance of the MDR Commission, the results were far more disappointing (below 35% success rate) due to the continued non-insurance of medication in the absence of sufficient funds for its procurement.

○ Patients treated in excellence centers for a long period of time (3-6 months) have benefited from a period of special psychological support.

○ The management of adverse reactions has been properly what has contributed to the improvement of the tolerance of the treatment.

○ More recent WHO recommendations (WHO Regional Office for Europe in 2016) suggest treating as many cases of MDR TB as ambulatory care to prevent the transmission of resistant strains in the hospital environment.

○ It has also been suggested to use part of the funds saved by reducing hospitalizations as an incentive for patients with tuberculosis to increase adherence to treatment.

○ In Romania's current socio-economic conditions, with a rather low level of health education (and not forgetting that much of the tuberculosis cases come from vulnerable environments), I do not think this is yet a feasible solution for our country.

- Sometimes precarious living conditions (houses overcrowded, unsanitary conditions) may favor more spread of resistant strains than in-hospital transmission (most of the tuberculosis treatment units having an infection control plan).

- Many of the outpatient units for tuberculosis treatment work in old buildings with an architecture that does not allow for proper circuits for patients with sensitive tuberculosis and those with resistance or with patients with nontuberculous lung disease.

- Travel expenses for ambulatory units can be a burden for some patients (daily travel is required to ensure treatment under direct observation !!).

- Community health services (including tuberculosis, especially DOTS insurance) should be provided by community health workers employed by municipalities with funds from the Ministry of Health. Currently, the number of these workers has fallen over the years due to the cuts of funds to municipalities and their need to redistribute such workers to other activities.

- Remodeling an existing patient care system based on hospital care requires modifications of legislation and, above all, financial changes (which can be burdensome for a sub-funded segment).

- In order to facilitate the adoption of the new treatment model, it will be necessary to invest in staff (medical and non-medical), the involvement of social workers and the primary care network.

- Therefore, I consider that it is not only advisable, but mandatory hospitalization of patients with multidrug-resistant tuberculosis (at least until microscopic conversion), and these patients can not be properly managed as outpatients.

- In order to ensure optimal adherence to treatment, significant efforts must be made in the sphere of health education through Information, Education, Communication [33], patient awareness of the dangers of the disease and its complications through lack of treatment, weighing more, in my opinion, than the incentives offered to the patient to begin and complete a treatment.

- The primary care network should be co-opted in PNSPCT actions for the treatment of patients with resistant tuberculosis by supervised outpatient treatment in isolated or immobilized areas and by careful medical surveillance of their contacts.

- Cannot be ensured early diagnosis without reliable and quickly methods of diagnosis.

- Thus, generalizing the testing of susceptibility to first-line drugs (HIN and RMP) in all confirmed TB cases in culture is essential in the early detection of chemoresistance and, to the same extent, in all county laboratories with GeneXpert assay kits (for rapid diagnosis of resistance to RMP).

- A close collaboration with psychiatrists, staff employed in Drug Treatment Centers and Psychosocial Rehabilitation Centers is essential to the growing number of patients nowadays (drug users).

- After healing, professional and social redevelopment should be encouraged (some patients abandon treatment, preferring retirement in the desire to prolong this minimal but stable source of income).

# VI. CONCLUSIONS:

The implementation of the DOTS Plus program at the national level becomes mandatory, both for the daily and supervised administration of the treatment and the provision of the necessary medication (which we should not forget, so far Romania has ensured it mainly through projects financed from external sources). The national program still functions as a donor-dependent program.

Regardless of the strictly medical considerations, the legislative, organizational and financial framework could ensure the implementation of disease control actions to make tuberculosis control in Romania a "success story".

Given the worrying results of current MDR / XDR TB cases in Romania (even with the current availability of bacteriological laboratories that can provide a rapid diagnosis), with new classes of second-line drugs recently in use, a study on patients treated about 10 years ago (but achieving comparable results to current ones in developed countries and a small number of chemically resistant cases, 60-70% success rate) draws attention to the need for specialized centers in the treatment of resistant cases and in the conditions of continuous administration, without medication interruptions, unlimited by poor financing. Over time, the healthcare system in Romania (the Ministry of Health, the National House of Health Insurance) will have to take over these expenditures (now secured from external financing projects), or we will witness a dramatic increase in the number of MDR / XDR TB cases.

In order to achieve comparable results to European countries in the control of MDR TB, Romania faces some major obstacles: legislative and procedural coherence issues (which are hoped to be corrected after the new legislative proposal) and limited, intermittent and unpredictable funding an important role in dealing with these cases, but this is unpredictable and limited in scope and duration).

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