EPIDEMIOLOGICAL ASPECTS OF TUBERCULOSIS IN ADULTS IN ROMANIA *VERSUS* THE REPUBLIC OF MOLDOVA

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Abstract

The purpose of this paper was to monitor the epidemiological aspects of tuberculosis in adult patients in Romania vs. the Republic of Moldova between 2000 and 2015. For the appropriate analysis of data obtained, we used comparative statistical methods, we determined primary statistical indicators and we applied the similarity metric method. The study showed a clear improvement of the specific indicators which however are insufficient in terms of the World Health Organisation (WHO) strategies requirements.

Rezumat

Această lucrare a avut ca scop urmărirea aspectelor epidemiologice privind tuberculoza la adulți în România, comparativ cu Republica Moldova în perioada 2000-2015. Pentru analiza optimă a datelor obținute am folosit metode statistice comparative, am determinat indicatori statistici primari și am aplicat metoda metricilor de similaritate. Din studiu a reieșit o îmbunătățire evidentă a indicatorilor specifici dar insuficientă față de cerințele stabilite prin strategiile Organizației Mondiale a Sănătății (OMS).

Keywords: tuberculosis, multidrug-resistant tuberculosis, epidemiological indicators

Introduction

Tuberculosis is a widely and globally spread infectious and contagious disease which represents a public health priority. Since 1997, the World Health Organization (WHO) has published global reports presenting informations concerning the tuberculosis epidemics and the progress made, as well as the financing, therapeutic schemes and main indicators based on the data reported by more than 200 countries [1, 2]. The declared purpose of this monitoring is to decrease by 2030 the tuberculosis infection incidence by 80% and the deaths caused by it by 90%, so as to completely eradicate it by 2050.

The number of Romanian patients diagnosed with a form of tuberculosis is approximately 25% of the total number of cases in the European Union (EU) Member States. A significant number of patients has the new form of multidrug-resistant tuberculosis (MDR-TB), caused by incomplete and incorrect treatments, while also increasing the possibility of disease transmission.

In 2015, the Romanian Government approved the National Strategy for Tuberculosis Control, an essential programmatic document with the purpose of obtaining a more thorough and efficient approach for fighting this pathology (by rapid diagnosis, correct and complete monitoring of patient-centred therapy in order to ensure a proper treatment adherence) and increasing the funding (by mobilizing resources from structural funds and other non-refundable European funds) [3]. The main objectives were to reduce the incidence and the mortality of tuberculosis by providing prevention, early identification, diagnosis, treatment services and by increasing treatment adherence in alignment with the WHO recommendation.

As shown by the statistical data provided by the existing literature [4, 5, 8] Romania has recorded progress in the last 12 years, in spite of the fact that the tuberculosis incidence rate is still four times higher than the European average, the healing rate is insufficient and the number of infected people is increasing each year. Among objectives proposed in the National Strategy, we note the following: an universal access to rapid diagnosis methods, the diagnose of more than 85% of estimated drug-sensitive TB and MDR-TB cases; a successful treatment of at least 90% of new cases, more than 85% of retreatments and 75% of MDR-TB cases; reducing the general rate of mortality caused by tuberculosis to less than $4.3^0/_{000}$ in the inhabitants; a general reduction of pathology incidence; a more

efficient tuberculosis control by the health system; reaching a global disease incidence rate of $50^0/_{000}$ inhabitants by 2020; decreasing the number of deaths to less than $5^0/_{000}$ inhabitants in 2020; reducing the total number of patients to less than 10,000 cases in 2020.

Funding will be ensured from the following sources: structural funds in the programming phase 2014-2020 - 145 million RON (32 mil EUR); funds from the Norwegian Government - 46 million RON (10.2 mil EUR); resources from the Global Fund to Fight AIDS, Tuberculosis and Malaria - 37 million RON (8.2 mil EUR); State Budget revenues, refundable and non- refundable funding.

The total budget for the 2015 - 2020 Strategy is 1.571 billion RON (349 mil EUR), for diagnose and treatment activities, equipment of laboratories, surveillance and human resources.

In 2014, the budget for programs associated to communicable diseases was 426,500 RON (94,777.7 EUR), out of which 69,806 RON (15,512.4 EUR) was assigned to the National Immunization Program and the amount of 14,921 RON (3,315.7 EUR) was assigned to the program for the Surveillance and Control of Tuberculosis.

Starting 2009, 13 indicators were proposed [2, 3]: *5 physical indicators:* 84,000 examined contacts (optimum number – 4/newly-identified TB case), 210,000 potential cases (optimum number 10/newly-identified TB case), 21,000 cases receiving chemoprophylaxis (1 case of chemoprophylaxis/identified TB case), 8,800 supervision visits in the field made by specialized doctors (80% of the general practitioner were visited at least once a year), 310 supervision visits in counties (80% TB clinics were visited at least once a year by the county/regional/national coordinator); *4 efficiency indicators:* 60 RON (13.3 EUR) - average cost of active identification of tuberculosis patients by the control of contacts and other risk groups, 60 RON (13.3 EUR) - average cost of active identification of tuberculosis patients by the control of symptomatic patients, 16 RON (3.5 EUR) - average cost of chemoprophylaxis, 800 RON (177.77 EUR) - average cost of supervision visit in the field; *4 result indicators (optimum value):* 80% of the total number of registered contacts was examined, 10% of the examined suspects were found as sick, 90% of the total number of people for whom chemoprophylaxis was recommended received chemoprophylaxis, 80% of the scheduled visits were performed.

During the period 2011 - 2013, the following 5 types of activities were carried out, in compliance with the approved budget for the National Programs for Communicable Diseases - Tuberculosis Surveillance and Control: *activities carried out by the National Public Health Institute* through National Centre for Surveillance and Control of Communicable Diseases (NCSCCD) and its regional structures; *activities*

carried out at the level of "Marius Nasta" Pneumology Institute of Bucharest, Romania, such as: consistent and efficient access for the surveillance and control of specific morbidity and of multidrug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) cases, national coordination for the identification, evaluation and treatment administration in MDR/XDR-TB cases; *activities performed in pneumoftiziology clinics*; *activities performed in family medicine offices*; *activities performed by public health directorates* at county level and in Bucharest.

The 6 evaluation indicators monitored are classified into 3 types: *physical*: the number of people examined for the identification of tuberculosis infection/TB cases (suspects, symptomatic patients, contacts, high-risk groups): 200,000, number of people to whom chemoprophylaxis was initiated: 10,000; *efficiency*: average cost/tuberculin skin test (TST)/tuberculin purified protein (TPP) derivative – 20 RON (4.4 EUR), average monthly cost/chemoprophylaxis treatment – 10 RON (2.2 EUR); *result*: percentage of new tuberculosis cases for which an epidemiological investigation was performed, out of the total number of newly-identified cases: 90%, percentage of people with chemoprophylaxis out of the number of people for whom chemoprophylaxis was recommended: 90%.

For the same purposes, in the Republic of Moldova, the National Program for Tuberculosis Control includes the following activities for 2011 - 2015 [6]: ensuring a quality diagnose, with a detection rate of smear-positive pulmonary tuberculosis cases of more than 70% in 2015; obtaining and maintaining universal access to efficient treatment of all forms of tuberculosis by 2015, and achieving a success rate for the treatment of new cases of smear-positive pulmonary tuberculosis of at least 78% and a success rate for the treatment of multidrug-resistant tuberculosis cases of at least 60%; ensuring social support for at least 90% of socially-vulnerable tuberculosis patients in 2015; ensuring an efficient control of TB/HIV co-infection, while reducing the TB/HIV co-infection rate in the tuberculosis cases to less than 3% by 2015; increasing in 2015 the population's knowledge of tuberculosis to at least 80% and maintaining a BCG vaccination rate at birth of at least 98% and a revaccination rate of 85%; developing and applying in 2014 the scientific research and operational results in the field of tuberculosis control with the performance of at least 7 research studies; consolidation in 2015 of an efficient system for the Program management, coordination, monitoring and evaluation.

Within this program, 17 indicators are considered: *3 impact indicators*: tuberculosis mortality *per* 100,000 inhabitants, global incidence of tuberculosis *per* 100,000 inhabitants, % of TB/HIV co-infection rate among tuberculosis cases; *9 result indicators*:

success rate of the treatment of new cases of smear-positive pulmonary tuberculosis, %, success rate of the treatment of multidrug-resistant tuberculosis cases, %, rate of new cases of smear-positive pulmonary tuberculosis, %, rate multidrug-resistant tuberculosis cases in new cases, %, rate of multidrug-resistant tuberculosis cases in previously-treated cases, %, BCG vaccination rate at birth, %, coverage rate for tuberculosis patients for whom HIV testing was performed, %, percentage of socially vulnerable tuberculosis patients to whom social services were provided, %, percentage of population aware of at least three basic symptoms of tuberculosis, %, *5 product indicators*: number of scientific research studies performed, number of operational research studies performed, number of scientific research results put into practice, number of methodical instructions and recommendations developed by the unit coordinating the Program implementation, number of monitoring reports developed by the unit coordinating the Program implementation.

According to the National Clinical Protocol [7], the global incidence of tuberculosis in the Republic of Moldova decreased by 9.2% between 2005 - 2009 (from $116.0^0/_{000}$ to $106.9^0/_{000}$ inhabitants); in cities, the decrease was 33.4% (from $142.3^0/_{000}$ to $109.0^0/_{000}$ cases) whereas at county level, a slow trend was observed for the stabilization of the process ($105.90^0/_{000}$ cases in 2005 and $106.10^0/_{000}$ cases in 2009, respectively).

It was observed a decrease in the number of new cases by 9% (with an incidence of $80^0/_{000}$ in population) compared to 2013 and by 13% compared to 2010. A high incidence of new cases still exists in the Eastern part of the country, i.e. $103^0/_{000}$ population, which exceeds by 1.3 times the rate of new cases identified in the counties on the right side of the Nistru River.

Concerning the mortality rate by tuberculosis progression, at the end of 2014, it was $12^0/_{000}$, 481 cases ($10^0/_{000}$ in the population on the right bank and $26^0/_{000}$ in the population on the left side of the Nistru River) i.e. a decrease by 34% *vs.* 2010 (727 cases).

The purpose of this paper was to present the main epidemiological aspects of tuberculosis in adult patients in Romania and the Republic of Moldova.

Materials and Methods

We performed a comparative statistical analysis of the main indicators: incidence, mortality rate, number of relapses, therapy success rate, adherence to treatment and the budget allocated in the two countries for TB and MDR-TB and applied the similarity metric method. *The materials* used included manuals, specific literature in this field, reports, national laws and information on TB treatment and prophylaxis, transmitting ways, its incidence and the distribution

of funds allocated to National Health Programs for Tuberculosis.

We analysed the evolution of indicators in the National Program for Tuberculosis Control in the period 2011 - 2014 in Moldova *vs.* Romania, calculating primary statistical indicators (mean, standard deviation, and coefficient of variation) and similarity factor f_2. The coefficient of variation is the percentage defined as the ratio of the standard deviation (stdev) to the arithmetic mean ($\bar{x}$) of the statistical series measuring variation irrespective of the unit of measurement of the characteristic size, which does not depend on the actual content of the characteristic or its size grade and always indicates the degree of homogeneity of the arithmetic mean [14]:

$$cv = \frac{stdev*100}{\bar{x}}.$$

When comparing sets of answers, the correlation coefficient is not sufficient to determine similarity and, for this reason, it is important to use a metric indicator that is sensitive both to correlations and to distances; this is f_2 which is also called the similarity factor [15]:

$$f_2 = 50\log\frac{100}{\sqrt{1+\frac{\sum_{i=1}^{n}(\mu_{ri}-\mu_{ti})^2}{n}}} = 38,$$

where μ_i represents the compared data and n - the number of entries.

If the compared data are identical, $f_2 = 100$; if the difference between the data is exactly 10%, corresponding to a distance value of 0.5, $f_2 = 50$; if the distance between the points is 20%, $f_2 = 35$. Generally, the value set by literature for similarity is 50.

Results and Discussion

We have analysed the data [6-9] on the incidence and mortality rate and shown the evolution of TB cases in adult patients in Figures 1 and 2.
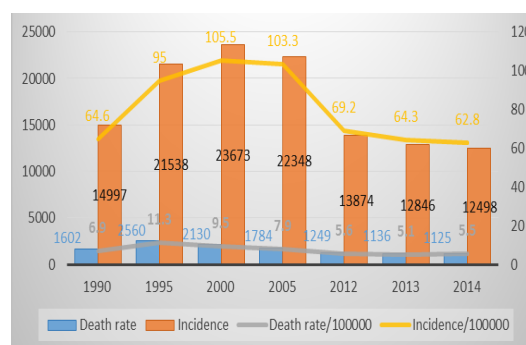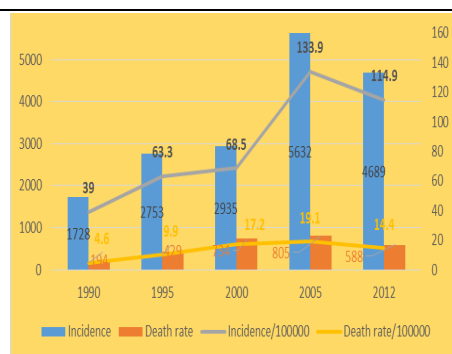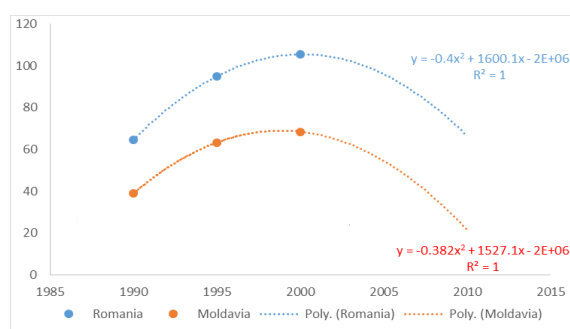

Figure 1.
TB Incidence and mortality rate in Romania
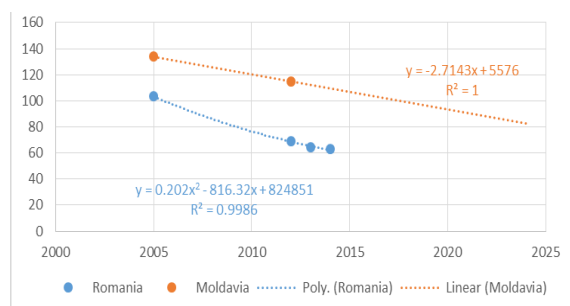
Figure 2.
TB Incidence and mortality rate in Moldova

The comparative analysis of the evolution of the incidence rate in Romania and the Republic of Moldova (Figures 1 and 2) shows an increasing trend in both countries between 1990-2000, the transition to the market economy, and focus of Romanian politics on the objective of becoming an European Union Member State.

Using the curve-fitting method as shown in Figure 3, the progress of tuberculosis incidence rate is almost identical for the two countries until 2005, with a similar decrease estimated after 2005.
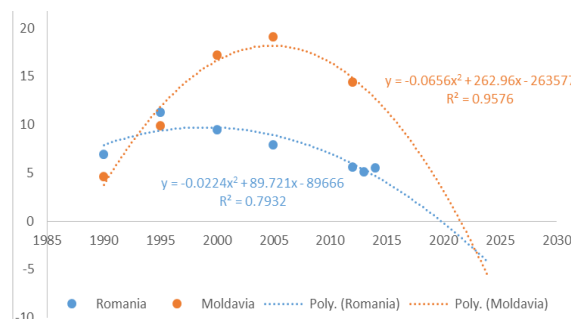

Figure 3.
Estimated incidence rate of TB in Romania and Moldova 1990 - 2010

Figure 4.
Real incidence rate of TB in Romania and Moldova 2005 - 2015

Unlike the estimate, the actual data showed a decrease in the incidence rate which occurred linearly for the Republic of Moldova, ($R^2 = 1$), while for Romania it followed a polynomial correlation model ($R^2 = 0.99$). The values obtained also suggest a significant decrease in the rate of mortality caused by tuberculosis in the two countries, from $12.3^0/_{000}$ (1995) to $5.5^0/_{000}$ (2014) in Romania, and from $19.1^0/_{000}$ (2005) to $14.4^0/_{000}$ (2012) in Moldova respectively, as shown in the equations that describe the polynomial regression [6, 7, 10, 11, 13].

Figure 5.
Forecast of TB mortality rate in Romania and Moldova

The data in Table I show that the values of the coefficient of variation are in the range 0.43 - 117.74, which means that the mean values of the observed indicators are not homogenous. Concerning f_2, the accepted value of 50% was exceeded only in 3 situations, which does not confirm the similarity assumption. We mention that data concerning the indicators verified by these methods were insufficient in the case of Romania.

4042 new cases and relapses were identified and reported in the Republic of Moldova in 2014, which led to a year-end rate of 99 in 100 thousand population as global incidence, which is 10% lower than in 2013 and 13% lower than in 2010 [6, 7]. Similarly, in Romania, the percentage of new cases and relapses decrease from $98.1^0/_{000}$ (2010) to $77.5^0/_{000}$ in 2013 (ECDC 2015 report) but then increased again in 2014 to $84.6^0/_{000}$ [11, 13].

We analysed the results obtained following the treatment in TB cases and found that they depend not only on clinical and economic factors, but also on issues related to the service providers, such as patient management, monitoring quality and continuity, patients' knowledge of the disease and treatment. Thus, the success rate of tuberculosis treatment for the cases evaluated at the end of 2014 reached 76% in drug-sensitive TB patients and 58% in MDR-TB patients in Moldova; in Romania it reached 84.6% cured patients, and 32% of the MDR cases, respectively (2012 - 2013) [6, 7]. It is important to mention that the success rate is largely dependent on the accountability of attending physicians for the compliance with the therapeutic protocols [12, 13, 23].

Improvements were observed as concerns the adherence to treatment of tuberculosis patients, with a decrease of the abandon rate from 12% to 6% for drug-sensitive tuberculosis patients and from

28% to 20% for multidrug-resistant tuberculosis patients vs. the data recorded at the end of 2010, in the Republic of Moldova, [7], whereas in Romania (according to the ECDC 2016 Report [13]) after the

first treatment year, 373 patients abandoned the treatment, i.e. a rate of 4.8%, and 129 after 24 months, i.e. 18.9%.

Table I

Evolution of the monitoring indicators for the National Program for Tuberculosis Control for the period 2011 - 2014 in Moldova and Romania [6, 7, 11, 13]

No	Indicators Moldova/Romania	2011	2012	2013	2014	Mean	Stdev	CV%	f_2
	Impact indicators								
1.	Tuberculosis mortality, 100 thousand population[1, 2, 5, 7]	16.1 5.7	14.4 5.6	11.1 5.1	12.5 5	13.53 5.35	2.19 0.35	16.16 6.56	53.8
2.	Global incidence of tuberculosis, 100 thousand population[1, 2, 5, 7, 11]	114.5 39.4	114.7 50.5	110.3 43.7	99.8 38.6	109.83 43.05	6.98 5.45	6.36 12.66	8.7
3.	TB/HIV co-infection rate in tuberculosis cases, %[1, 2, 5, 8]	5.0 2.6	5.0 2.4	5.1 2.7	7.3 -	5.6 1.93	1.13 1.29	20.26 66.98	68.09
	Result indicators								
1.	The success rate of the treatment of new cases of smear-positive pulmonary tuberculosis, %[1, 2, 8, 9]	62 78.7	62 78.6	62 -	76 -	65.5 39.33	7 45.41	10.69 115.47	14.86
2.	The success rate of the treatment of cases of multidrug resistant tuberculosis, %[1, 2, 5, 8, 9]	54.3 25.6	58.9 34	- -	- -	28.3 14.9	32.73 17.54	115.66 117.74	36.03
3.	Rate of new cases of smear-positive pulmonary tuberculosis, %[1, 2, 5, 8, 9]	31.2 70.3	33.0 75.3	35.1 76	35.5 -	33.7 55.4	1.99 37.02	5.92 66.82	20.15
4.	Rate of multidrug resistant tuberculosis in new cases, %[1, 2, 5, 8, 9]	26 8.7	24 9	25 -	24 -	24.75 4.43	0.96 5.11	3.87 115.5	34.1
5.	Rate of multidrug-resistant tuberculosis in previously treated cases, %[1, 2, 5]	64	62	63	62	62.75	0.96	1.53	-
6.	Rate of BCG vaccination at birth, %[6, 10]	98.3 99	97.6 99	97.8 99	98.5 98	98.05 98.75	0.42 0.50	0.43 0.51	92.29
7.	Coverage rate of tuberculosis patients as concerns HIV testing, %[1, 2, 5]	94.0	94.6	95.3	95.4	94.83	0.66	0.69	-
8.	Percentage of socially vulnerable tuberculosis patients to whom social services were provided, %	-	-	-	72	-	-	-	-
9.	Percentage of population aware of at least three basic symptoms of tuberculosis, %[3]	-	63	-	-	-	-	-	-
	Product indicators								
1.	Number of scientific research studies performed[4, 5]	7	9	9	7	8	1.15	14.43	-
2.	Number of operational research studies made	2	2	1	-	1.25	0.96	76.59	-
3.	Number of scientific research results put into practice[4, 5]	7	12	9	8	9	2.16	24	-
4.	Number of methodical instructions and recommendations made by the unit coordinating the Program implementation[5]	5	4	5	6	5	0.82	16.33	-
5.	Number of monitoring reports prepared by the unit coordinating the Program implementation[5]	45	48	62	65	55	9.97	18.12	-

Source: [1]SIME TB; [2]*Centrul Naţional de Management în Sănătate* (National Health Management Centre); [3]*Scurt raport al sondajului sociologic Tuberculoza în Moldova:cunoştinţe, atitudini şi practici ale populaţiei generale*, 2012, PAS Centre, Chisinau 2013 http://pas.md/ro/Studies; [4]The Academy of Science of Moldova; [5]"Chiril Draganiuc" Institute of Phthisiopneumology; [6]National Center for Public Health; [7]*Anuar Statistică sanitară* 2014, CNSISP, Bucharest 2015; [8]Eurostat 2015 (age ≥ 15), [9]ECDC –Tuberculosis 2011-2013; [10]WHO Immunization; [11]Global TB report

As concerns MDR-TB, Figure 6 shows the prevalence at world level.

We compared the MDR-TB prevalence in the two countries with the one at world level and found that, while the Republic of Moldova is close to the maximum general values (Belarus 35^0/$_{000}$, Russia 23^0/$_{000}$, and Azerbaijan 22^0/$_{000}$), Romania ranges among the countries with an average prevalence. Drug-resistant and, particularly, multidrug-(MDR-

TB) and extensively drug-resistant (XDR-TB) tuberculosis is a serious challenge for tuberculosis control programs in many countries, including Moldova; high level of resistance are reported both by Moldova and by many countries worldwide, especially in Asia, Africa and South-East Europe [6]. According to the statistical data reported by the Romanian Ministry of Health, the number of MDR-TB cases reported each year is as shown in Figure 7.
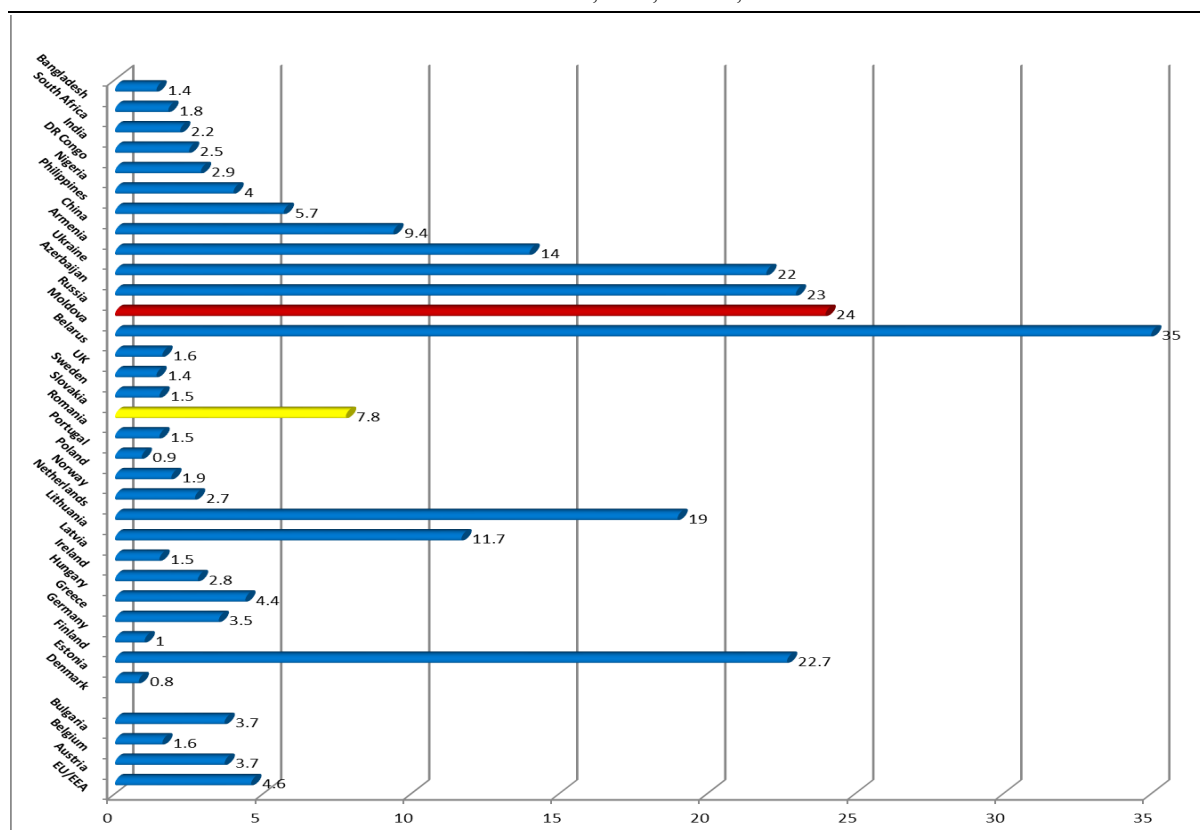
Figure 6.
MDR-TB prevalence in the new tuberculosis cases in countries with high burden of resistance to drugs
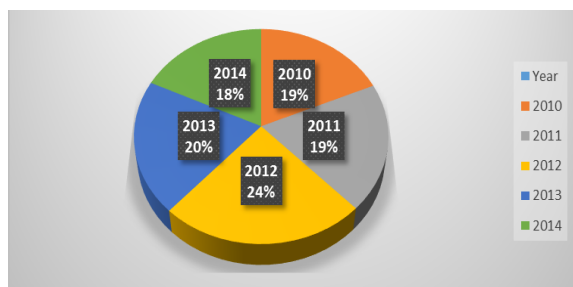

Figure 7.
Percentage of MDR-TB patients in Romania
between 2010 and 2014

The analysis above clearly shows that the percentage of these patients remains rather unchanged, which indicates a problem in the therapeutic solution for these types of cases, a situation that also occurs in the case of infantile tuberculosis [16]. We also considered the number of TB cases with HIV co-infections which was 246 in 2014 and 301 in 2015.

We performed a comparative analysis of the budget allocated to the National Programs for the Prevention of Communicable Diseases, namely TB in Romania (Table II).

Table II

Budget allocated to the National Programs for Communicable Diseases in Romania [2-4, 17-22]

Year	Total budget for Communicable Diseases (RON) thousand)/Euro*	TB assured budget (RON thousand)/Euro*	%
2009	343,313/86,259.54	-	-
2010	228,946/54,252.60	12,100/2,867.29	5.28
2011	104,059/24,426.99	-	-
2012	110,100/25,486.11	14,600/3,379.62	13.26
2013	188,574/42,760.54	17,400/3,945.57	9.22
2014	233,007/52,010.49	29,400/6,562.5	12.61
2015	-	21,000/4,677.06	

*The NBR exchange rate for RON/EUR valid for 1 January each year was used for the calculation

The data presented in Table II show that the budget allocated to the National Programs for Communicable Diseases in Romania varied considerably in the period 2009 - 2014. The maximum limit was reached in 2009, and it was followed by a regression which, two years later, was almost 70%. In 2014, the total budget was 32% lower than the one approved in 2009, but 19% higher than in 2013. We calculated the percentage of the budget allocated for tuberculosis in the reviewed period. The data show

that the highest percentage was allocated in 2012. We noticed that, since the amount of 40 thousand RON was not used in 2014, the Ministry diminished it 21,000 RON for the following year.

Conclusions

The data resulted from this study indicate that tuberculosis is a major health issue for both countries, each one taking great efforts to harmonize their laws and management with the WHO indications. In both countries, the high costs determined by tuberculosis have the same causes: the low standard of living, non-rational diet, alcoholism, migration, increase in the number of homeless people, deteriorated ecology, harmful factors at the place of living, etc. However, we believe that the budget allocated to the Program for Prevention, Surveillance and Control is low in both countries and that this is an issue that requires further consideration. This study was significantly difficult due the insufficiency or even lack of reports for summarized statistical data at national level.

Acknowledgement

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