

EPIDEMIOLOGICAL AND ECONOMIC ASPECTS OF TUBERCULOSIS IN CHILDREN. A COMPARATIVE ANALYSIS: ROMANIA VS. THE REPUBLIC OF MOLDOVA

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Manuscript received: September 2015

Abstract

In the present paper there are reviewed some issues concerning tuberculosis (TB) in children in Romania comparative to The Republic of Moldova. The data information came from specialized literature, national reports and statistics on TB management and monitoring, incidence in children and budget expenditure. The obtained results showed the existence of a large number of TB cases in children, even if this disease is considered eradicated in most European countries, but also a downward trend for the new TB cases diagnosed in children between 2010 and 2014 in both countries.

Rezumat

În lucrare sunt prezentate câteva aspecte principale care privesc tuberculoza la copiii, în România, comparativ cu Republica Moldova. Datele utilizate provin din literatura de specialitate, rapoarte naționale și statistici referitoare la managementul și monitorizarea tuberculozei, incidența la copii și cheltuielile bugetare. Rezultatele obținute au evidențiat existența unui număr mare de cazuri de tuberculoză la copii, chiar în condițiile în care această patologie este considerată a fi eradicată în majoritatea statelor europene, dar și o tendință descrescătoare în ceea ce privește noile cazuri de tuberculoză diagnosticate la copii, în perioada 2010-2014, în ambele țări.

Keywords: tuberculosis, children, epidemiological, economic

Introduction

In 2015, despite the advances in science and medicine and even though nearly all cases can be cured, tuberculosis (TB) remains one of the world's biggest threats. According to statistics, 1.5 million people died in 2014 of TB [21, 22] among which 1.1 million were HIV-negative and 0.4 million HIV-positive. It is estimated that tuberculosis will no longer exist in the EU/EEA by 2050, if Europe continues to decrease the number of cases. There is a need for tailored interventions for each country's conditions. The proposed goal in strategies like "The end of TB strategy" is the use of current tools and interventions more efficiently, with reference to the ever-changing market dynamics.

Tuberculosis is a pathology caused by one of the following two types of bacteria - *Mycobacterium tuberculosis* complex or *Mycobacterium bovis*. The former includes the agent bearing the same name, considered by specialists as the most widespread and the most important disease agent in humans, whereas the latter, just like other *Mycobacterium*

species, is transmitted by ingestion of unpasteurized milk [1, 4].

Tuberculosis Prophylaxis

Literature [1-4] mentions that Tuberculosis can be prevented by BCG (Bacillus Calmette-Guérin) vaccination, chemo-prophylaxis and TB infection control.

BCG Vaccination

BCG vaccination (with a strain of attenuated *Mycobacterium bovis* bacillus) is an active immunization method used only for new-born children (aged 4-7 days), upon their discharge from hospital and without tuberculin testing (the immune response to tuberculin intradermal reaction (IDR) is used for identifying delayed hypersensitivity and immunity to Koch bacillus). Positive IDR does not indicate for certain that the presence of bacteria; it shows only that previous infection or BCG vaccination occurred. Vaccination is used to prevent serious and aggressive forms of the disease (military tuberculosis or tuberculous meningitis in infants and small children).

After 5 months, the family doctor checks if the post-BCG vaccine scar is present, and/or vaccinates the infant, if, for various reasons, he/she could not be vaccinated as a new-born.

Intradermal inoculation of a small amount of tuberculin (a substance extracted from tuberculosis bacilli culture) and a positive response after 72 hours indicates the presence of the bacterium. To confirm the diagnosis, a thoracic X-ray is required in order to confirm the presence of nodules cavities caused by bacteria, or the presence of bacteria surrounded by macrophages, which create opaque areas on the X-ray.

The level of protection against tuberculosis (vaccine efficacy) is controversial, since the protection degree reported in various studies varies from 20% to 60% [3]. This variation, which is extremely important in assessing vaccine effectiveness, has led to different attitudes towards vaccination, from the global indication for vaccination (mass vaccination), to a non-discriminating basis, to abstaining from the indication of "mass" vaccination (the USA, the Netherlands) [2]. Vaccine efficacy also varies depending on the geographical position, with higher rates in temperate climate areas and lower or even null ones in equatorial areas. Differences concerning the lack of efficacy in countries with high incidence (India) and also in countries with low incidence (UK) exist.

The vaccine does not provide any natural protection against tuberculosis infection; vaccinated children can be infected if they come into contact with people who are infected with tuberculosis. Generally, the protection lasts 15-20 years.

BCG vaccination is used especially in countries with high incidence of the disease, immediately after birth, to avoid developing more serious forms of the disease at very young ages.

Chemoprophylaxis of Tuberculosis

Chemoprophylaxis (isoniazid monotherapy in doses of 10 mg/kg b.w./day or 200 mg/m² body surface area – not recommended in cases of active liver disease [4]) is used for children, teenagers (aged 12 to 16) and young people and aims to prevent the development of an active form of tuberculosis in individuals who came into contact with an infection source (pulmonary TB with positive smear).

If the contact is with an isoniazid-resistant source, rifampicin is used for prophylactic purposes in doses of 10 mg/kg b.w./day, for a period of 6-12 months. According to guidelines, double chemoprophylaxis and multi-chemoprophylaxis are forbidden [1]. The association of pyridoxine (B₆) in doses of 250 mg/day is recommended for the following groups: infants, individuals with low dietary protein intake, HIV-infected individuals, and individuals with neuropathy predisposition

diseases. A special group is formed by negative HIV patients who came into contact with patients diagnosed with multidrug resistance tuberculosis (MDR-TB), for whom there is no international consensus concerning the therapeutic indications and schemes for chemoprophylaxis [29].

Chemoprophylaxis is recommended for people with high risk of progression from latent multidrug-resistant infection to disease (immunodeficiency), while for immunocompetent contacts, surveillance can be considered without treatment, for at least two years. Doctors may choose the regimen of chemotherapy from the extended range of novel therapeutic means and decide on the most suitable treatment for their individual patients [5]. There are two therapies recommended for chemoprophylaxis which should be used for 12 months, for immunodeficient patients and at least 6 months for immunocompetent ones:

- pyrazinamide (25-30mg/kg b.w./day) taken together with ethambutol (15-25 mg/day);
- pyrazinamide (25-30mg/kg b.w./day) taken together with a quinolone with therapeutical indication for tuberculosis (ciprofloxacin, ofloxacin or levofloxacin).

Monitoring the Transmission of Tuberculosis

TB infection control is made by general preventive actions (treatment of diagnosed patients, hygiene, filtering bacilli in the air – appropriate ventilation, natural light, UV radiation) and by actions taken in healthcare facilities for tuberculosis patients (special actions):

- hospitalization of individuals diagnosed with smear-positive pulmonary TB in intensive phase;
- isolating and/or providing patients with surgical masks, if they walk in shared areas;
- avoiding any contact between HIV-infected patients and TB patients;
- sputum sampling in specially-equipped areas and in recipients that are incinerated afterwards;
- ensuring the appropriate natural or artificial ventilation in all the areas where TB patients are hospitalized; guided airflow and HEPA filter in the areas where MDR TB patients are hospitalized;
- appointing people in charge with designing and maintaining a TB control program for the unit;
- chemical disinfection of potentially-contaminated areas.

The aim of this paper is to highlight issues debated in Romania and The Republic of Moldova, concerning the management and monitoring of tuberculosis in children.

Materials and Methods

Materials used were 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.

Results and Discussion

The dynamics of live births to the population of Romania in the period 2010 – 2014 is presented in Table I, in accordance with the data published in Health Statistics Yearbook (*Anuarul de Statistică Sanitară*), in 2015 [6].

Table I

Number of live births in the total population of Romania and the Republic of Moldova (RM)

Population / Year		2010	2011	2012	2013	2014
Population	Romania (01.07)	22,492,083	22,441,740	22,401,865	22,359,849	22,299,730
	RM (31.12)	3,560,430	3,559,541	3,559,497	3,557,634	3,555,159
Live births	Romania	212,199	196,242	201,104	198,216	185,322
	RM	40,474	39,182	39,435	37,871	38,616
Per 1,000 population	Romania	9.4	8.7	9	8.9	8.3
	RM	11.4	11.0	11.1	10.6	10.9

The presented data in the table that, with the decrease in the Romanian population in 2014 (by almost 200,000 people), the number of live births also decreased by 12.66%.

According to the data of the National Statistics Office of the Republic of Moldova [25], the dynamics of live births of the population from the Republic of Moldova in the period 2010-2014 show a slows decrease in 2011 and 2013 and an insignificant increase in 2012 and 2014, thus ensuring an average of 1.2% for these years.

Tuberculosis is one of the main infectious and parasitic diseases in Romania (Table II) together

with: syphilis, *Chlamydia*, angina caused by haemorrhagic streptococcus, diarrheic diseases, botulism, dysenteries, leptospirosis, viral hepatitis (A, B), hepatitis C, cerebrospinal meningitis, epidemic parotitis, measles, rubella, trichinosis, tetanus, whooping cough, food poisoning, salmonellosis, scarlet fever, chicken pox, malaria, Lyme disease, West-Nyle infection, nosocomial infections.

In Romania, the total number of new TB cases decreased in these 5 years by approx. 21.6% and 22.2% in children respectively, as shown in Table II and Figure 1.

Table II

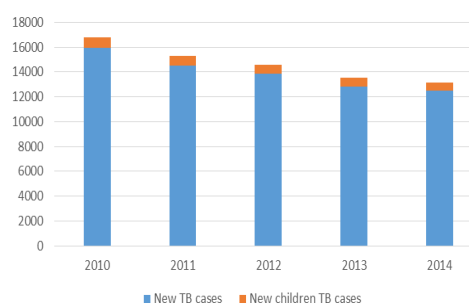
New TB cases registered in Romania and Republic of Moldova in the period 2010-2014

Year	2010	2011	2012	2013	2014
ROMANIA					
New TB cases	15,941	14,535	13,874	12,846	12,498
New TB cases in children	811	759	712	689	631
REPUBLIC OF MOLDOVA					
New TB cases*	3,109	3,179	3,167	3,050	2,747
Per 100,000 population*	87.3	89.3	89.0	85.7	77.2
New pulmonary TB cases in children*	71	80	41	55	54
New respiratory TB cases in children*	167	196	166	158	137

*For the Republic of Moldova, statistical data are presented excluding Transnistria and the town of Tighina

In the same period, the Republic of Moldova shows a decrease in new TB cases in the years 2012 – 2014 and an insignificant increase in 2011 (Figure 3). The declining trend was approx. 3% in average and the basic trend – 11.6%. Also, the new TB cases in children are decreasing, both for pulmonary TB (-23.9%), and for respiratory TB (-18.0%).

The figure (Figure 1) shows that the decrease in the number of TB cases was slow, but steady, both in children and in uninfected adults.

**Figure 1.**

Number of new TB cases in adults and children from Romania

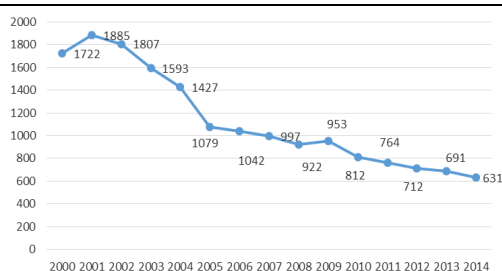


Figure 2.

Trends for new TB cases in Romanian children

In Romania the number of infected children with Koch bacillus decreased by 66 %, from 2001 until 2014 (Figure 2).

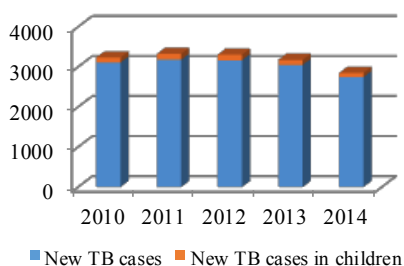


Figure 3.

Number of newly-diagnosed TB cases in adults and children in the Republic of Moldova

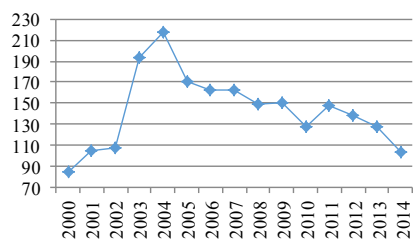


Figure 4.

Trends of new cases of TB in children from the Republic of Moldova

In the Republic of Moldova the percentage of infected children was 52 % from 2004 until 2014 (Figure 4).

Distribution of Funds Allocated to the National Health Programs for Tuberculosis

The national health programs implemented in the period between 2010 and 2014 were designed, implemented and coordinated by the Ministry of Health. Their objectives were established with the support of the National Health Insurance House, the Romanian College of Physicians, Romanian Federative Chamber of Physicians' Trade Unions, representatives of scientific medical associations, teaching clinics, research units, non-governmental organizations, trade unions, employers' associations, ministries and central institutions with own healthcare systems as well as representatives of the population [7-12].

They consist in a set of activities and services for the prevention and treatment of diseases with serious consequences on population health, sometimes with high epidemiological risks. They are funded by the State Budget and the Single National Health Insurance Fund within annual limits.

The national programs concerning infectious diseases include programs and sub-programs out of which those concerning tuberculosis are the National Immunization Program (*Programul Național de Imunizare*) and the National Program for the Prevention and Control of Infectious Diseases (*Programul Național de Supraveghere și Control al Bolilor Transmisibile*), which includes the Subprogram for the Surveillance and Control of Tuberculosis.

The National Program for the Prevention, Surveillance and Control of Tuberculosis is presented in Table III.

Table III

Distribution of funds for National Health Program (NHP)-Tuberculosis in 2010 [8-11]

National programs	Total budget funding RON (Euro equivalent)
National Immunization Program	72,218 (17,153.91 €)
National Program for Transmissible Diseases (HIV, tuberculosis, sexually-transmitted diseases, other priority infectious diseases)	43,560 (10,346.79 €)
Subprogram for the Surveillance and Control of Tuberculosis	5,626 (1,336.34 €)

In 2010, budget funds amounting to RON 72,218 (17,153.91 €) were allocated to the national immunization program, and RON 43,560 (10,346.79 €) to the national program for infectious diseases, out of which 12.91% to the subprogram for the surveillance and control or tuberculosis.

The Ministry of Health allocated the amount of RON 258,877 (61,728.50 €) out of the funds for the National Programs for Infectious Diseases, for the purchase of 1,000,000 doses of BCG vaccine for the vaccination of all children born in the period

February - June 2010 (approximately 60,000 children), as well as the vaccination of all newborns in the following 6 months [8-20].

In 2011, the BCG vaccine was purchased through UNICEF in a total quantity of 664,000 doses; vaccination coverage that year being 98.3% (Table IV). This high number of doses explains the need to create a reserve for the following situations:

1. if, following scar reading (5 months), the scar is smaller than 3 mm, re-vaccination is

- necessary, because the expected result was not obtained (there are no antibodies);
2. up to the age of 6 months, vaccination is made directly, and, after this age, intradermal reaction to tuberculin (IDR) testing is necessary with 2 PPD (purified protein derivative) units; reading performed after 72 hours indicates whether antibodies are present or not and whether it is necessary or not to repeat the vaccination;

3. in the case of an epidemics, healthy individuals that come into contact with TB patients can be re-vaccinated;
4. vaccination is recommended for foreign nationals that visit countries with TB risk;
5. patients with HIV virus or AIDS are required to be vaccinated for TB, on a compulsory basis;
6. accidents, handling operations, transport, inappropriate storage of vaccine doses.

Table IV

Budget expenditure for BCG vaccination in Romania [19-20]

Year	Number of purchased BCG vaccine doses	Contract value (RON/Euro equivalent)	Approximate price per dose (RON/Euro equivalent)	Budget allocated to the Immunization Program (RON thousand/Euro equivalent)
2010	1,000,000	259,877.00 (61,728.50 €)	0.26 (0.06 €)	-
2011	664,000	172,640.00 (40,813.23 €)	0.26 (0.06 €)	-
2012	588,400	1,107,252.00 (248,820.67 €)	1.88 (0.42 €)	-
2013	418,400	2,125,137.28 (481,890.53 €)	5.08 (1.15 €)	8,121 (1,841.49 €)
2014	513,100	4,804,668.4 (1,082,132.52 €)	9.36 (2.10 €)	14,924 (3,361.26 €)

Table IV shows that, while the number of purchased vaccine doses decreased in the analyzed period, the value of contracts increased more than 20 times.

Between 2006 and 2010, the Republic of Moldova implemented the DOTS program for the prophylaxis and treatment against tuberculosis, which focused on:

- ✓ political support;
- ✓ identification of cases;
- ✓ treatment;
- ✓ provision of medicines;
- ✓ monitoring.

In the Republic of Moldova, according to the provisions of the National Program for the Control of Tuberculosis for the years 2011-2015 [28], financial resources amounting to MDL 1,957.7 million were allocated (44,370.88 €).

The use of these resources for TB patients in the last four years is presented in Table V.

Table V

Budget expenditure for TB patients in the Republic of Moldova

Year	Value MDL thousand (RON/Euro)
2011	148,620.78 (41,613.81 RON/9,884.51 €)
2012	165,319.95 (44,636.38 RON/10,030.64 €)
2013	172,200.50 (41,328.12 RON/9,371.45 €)
2014	186,358.34 (42,862.41 RON/9,653.69 €)

The table data show the increase in budget expenditure in 2012 vs. 2011 by 11.23% and by 8.22% in 2014 vs. 2013. For 2015, the amount of

MDL 222,361.2 (9,810.86 €) thousand is planned, that is 19.32% more than in 2014 (Figure 5).

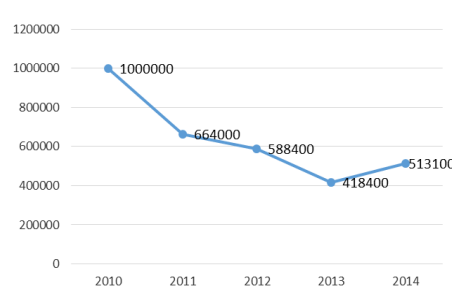


Figure 5.

The evolution of the number of BCG vaccine doses in Romania

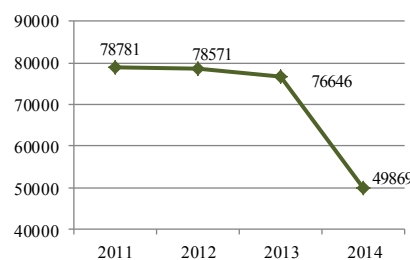


Figure 6.

The descending tendency of vaccine doses in the Republic of Moldova

The progress of the number of BCG vaccine doses purchased in Romania is presented in Figure 5, the downward trend being similar to that of new cases of tuberculosis in the period 2010-2014. The same descending trend of the administered BCG vaccine

doses is present in the Republic of Moldova (Figure 6). While, in 2012 the number of BCG doses decreased by only 0.21%, in 2014, the number of doses decreased by 34.93% as compared to 2013 [26].

In the period between 2011 and 2014, the adverse events following immunization in children in the Republic of Moldova are characterized by the following figures: 2011 – 0.11%; 2012 – 0.15%; 2013 – 0.13% and 2014 – 0.21%.

Primary BCG vaccination coverage of children aged between 1 and 7 in the Republic of Moldova is presented in Figure 7 [25].

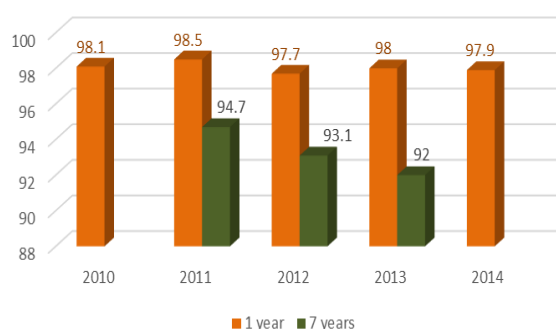


Figure 7.

Percentage of BCG vaccination coverage in children in the Republic of Moldova

In the European Union and the European Economic Area, the confirmed cases of tuberculosis in children vary between 20 and 30%. Out of these, in 80% of the countries, the pulmonary cases predominate.

The therapeutic success after 12 months of treatment ranged between 60 and 100%. Not all the states monitored or reported the progress of TB patients.

Following the 24-month monitoring of patients after the treatment for multi-drug resistant TB, most of the countries reported a 100% therapeutic success. According to WHO, not all states reported information concerning this aspect [24]. The responsible use of antibiotherapy in hospitals can improve the qualitative indicators and responsabilize doctors and patient in regards to respecting therapeutical protocols [23].

The World Health Organization published data (collected in 2012) regarding the European region which concerns children diagnosed with TB in the European region included two groups: 0-4 years of age and 5-15 years of age. New TB cases were reported in infants and small children (aged 4 or less) in seven states (Belgium, Cyprus, Denmark, Greece, Italy, Slovenia, Spain).

Conclusions

This paper, presents a comparative study (European reports, legislative regulations) approved both in Romania and the Republic of Moldova. These two independent states have many similarities, one of these being an increased number of cases of tuberculosis. During 2010-2014 in both countries, the number of births and the incidence of tuberculosis have decreased (in adult population but also in children).

The trend of infected children presents a decrease (up to 66% in Romania between 2001 and 2014, respectively up to 52% in Moldova during 2004-2014).

Moreover, a slight increase in the budget expenditure for TB patients has been shown in the past year.

With time and continuing enforcement of legislation, it is foreseen that TB will be eradicated from many other European countries.

Acknowledgements

This article was part of the research project "Epidemiological and Economic Aspects of Tuberculosis in Children. A Comparative Analysis: Romania vs. the Republic of Moldova". The study has been funded through the bilateral agreement Romania – Moldova No 12/23.12.2013., launched by the "N. Testemițanu" competition. The results have been partially presented at the National Congress of Pharmacy in Romania, XVth edition, in Iași, Romania, on September 24-27, 2014.

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