REVIEW

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Tuberculosis and its particularities in Romania and worldwide

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Abstract

Tuberculosis (TB) is a global health issue, with a rising incidence since the beginning of this century. It poses a severe mortality risk and also poses a serious economic risk as it reduces the working capacity of an individual in the most productive part of life. Developing countries face widespread tuberculosis infection – up to 95% of all cases and 98% of deaths, respectively. It is a highly contagious infectious disease caused by *Mycobacterium tuberculosis* (the Koch bacillus) that can be contracted from either humans or animal hosts. Infection is also associated with immunodepressive conditions and can be contacted through airborne, digestive, cutaneous or other routes of transmission. Pulmonary TB can be either primary – when events follow a first contact between the organism and the bacillus, and secondary – in case of a reactivation of a latent primary infection. One of the aims of this review is to present the current epidemiological data of TB infections in Romania, compared to the rest of the world, with an analysis of associated conditions and extra-respiratory TB infections. One of the main conclusions of our review is that optimal management of this complex disease can only be achieved through a coherent national prevention and treatment program, with centralized financing and sufficient epidemiological, imaging and laboratory support, in conjunction with good patient compliance.

Keywords: primary pulmonary tuberculosis, extra-respiratory tuberculosis, incidence, prevalence, co-infection.

Introduction

Tuberculosis (TB) is a contagious infectious disease with chronic evolution, widespread in the population, which, untreated or improperly treated, has a significant fatality. It more commonly affects the adult population in their most productive years of life, thus having economic and social consequences [1].

In the last two decades, there has been a progressive increase in the number of cases of tuberculosis across the globe due to increasing human immunodeficiency virus (HIV) incidence, low economic status of nations, migration and emergence of resistant strains of tuberculosis bacillus [2].

Each year 8–9 million persons develop the disease and approximately two million people die of TB or its complications [3].

Currently, about a third of the world population is infected with the tuberculosis bacillus, 47% of the infected population living in Southeast Asia [3–5]. Among people infected with Koch's bacillus, a percentage between 5% and 10% develop the disease [6].

Although almost all countries are confronted with this disease, tuberculosis remains a serious problem of the developing countries who accumulate about 95% of cases and 98% of deaths.

The epidemiological process in tuberculosis

Tuberculosis is a chronic inflammation caused by infection with the *Mycobacterium tuberculosis* (Koch bacillus) – either the human or bovine type. It can be located in any organ in the body, lung being the preferred location due to its structure.

Sources of infection

The main sources of tuberculosis infection are:

▪ Patients with pulmonary tuberculosis bacilli that eliminate them, especially those with detectable bacilli in sputum smear microscopy;

▪ Patients with extra-respiratory tuberculosis, presenting with open or fistulising active injuries through contact with the product originated from the pathological lesion

(node tuberculosis, urogenital, osteoarticular, skin, etc.);

▪ Animals sick with TB (more commonly bovine tuberculosis mastitis lesions) spreading the *M. bovis* infection through their natural and pathological products (milk, urine or feces). Occasional contamination from wild animals (badgers), pets (dogs, cats) or laboratory animals sick with tuberculosis may also occur [7].

The routes of transmission of tuberculosis infection

The main route of transmission of TB is the air (95% of cases) through droplets containing bacilli ("Pflüge's drops"). By inhaling these droplets, healthy individuals are infected from diseased persons (that eliminate bacilli). The most contagious forms of tuberculosis are endobronchial and laryngeal.

Digestive transmission requires a higher concentration of bacilli and is less frequent than the air-borne transmission. This usually happens through unsterilized milk or milk products originating from bovines having tuberculosis, in this case *M. bovis* being the incriminated agent.

Cutaneous transmission occurs in those that work with pathological products originating from the tuberculosis-infected persons (laboratory technicians or pathologists).

Other very rare routes of transmission are conjunctival path (infectious particles are projected on the conjunctiva), the trans-placental route, intrapartum (aspiration of amniotic fluid to the fetus) and instrumental [1, 7].

TB infection represents the status of an organism with viable tuberculosis bacilli present, without signs or symptoms of disease. This is a latent infection with tuberculosis bacillus. In Romania, the majority of the population is infected with *M. tuberculosis*. In about 10% of cases, the infection progresses to disease in the first two years of exposure (6–24 months).

Extra-respiratory tuberculosis represents the form that is localized outside the lung.

Extra-respiratory tuberculosis as an epidemiologic phenomenon is rarely addressed in the medical literature. There are articles describing various forms of extra-respiratory tuberculosis [8–10], in which it is perceived more as a clinical feature and less as a public health problem (with epidemiological potential). One of the likely reasons for extra-respiratory TB not being on the list of priorities of public health is that due to location, disease transmission is reduced [11, 12].

At the end of the twentieth century, there was a significant increase in prevalence and, therefore, the number of extra-respiratory localizations increased worldwide [13–15].

The main factors that contributed to the increasing the number of extra-respiratory tuberculosis cases are the increased number of immunocompromised persons, the increase worldwide population (especially the elderly segments) and the increasing number of medical personnel exposed to TB infection. [16]. Extra-respiratory TB is more common in children than in adults. [16]

Tubercle bacilli are often located in well-vascularized areas such as the meninges, kidneys, spine or the epiphysis of long bones [17].

Morphology

Pulmonary tuberculosis can be of two types, depending on the evolution of tuberculosis infection in the body: primary and secondary.

Primary pulmonary tuberculosis

It is defined as all bacteriological, clinical, radiological and biological events that follow the first contact between the body and the TB bacillus.

The Ghon's complex is the pathognomonic lesion of primary pulmonary tuberculosis resulting from the initial infection with *M. tuberculosis*. Macroscopically, it comprises three elements.

Ghon's complex is a small nodular formation (approximately 1 cm in diameter), yellow-white in color, with central necrosis, encapsulated, and medio-pulmonary located under the pleura (at either the base of the upper lobe or in the superior portion of the lower lobe). Lymphadenitis (inflammation of the lymph node) is determined by lymphatic dissemination of Koch bacilli in the hilar ganglia, which become enlarged, with increased consistency, yellow-white color with or without central necrosis of cazeification. Lymphangitis (inflammation of lymphatic vessels) is only visible radiographically and takes the form of an opaque strip with its contour wiped out, low intensity between hilar lymph nodes and the Ghon's complex. At times, miliary nodules can be identified along the lymphatic vessel, as a "string of pearls" [18, 19].

Primary pulmonary tuberculosis may have a favorable evolution, with resolution in 95% of cases, leaving scar fibrosis or calcification, thus resulting the Ranke complex. Otherwise, primary progressive tuberculosis is installed with a number of entities entities. Primary cazeous pneumonia can occur through local outbreak by extension of the Ghon's complex to a segment or lobe, the area affected gaining a compact appearance, yellow-gray, low consistency (necrosis). It can have a severe evolution with its liquefaction and drainage, resulting in a tuberculous primary cavern.

TB bronchopneumonia fistulation and drainage occurs through the primary bronchi complex elements, throughout the entire lung parenchyma. The resulting condensation circumscribed lesions with a diameter of 0.5 to 1 cm, white-yellow, uneven contour, centered by a bronchiolitis and separated by normal lung parenchyma [18]. Miliary TB – dissemination occurs through hematogenous or lymphatic dissemination of Koch bacilli, both locally (miliary pulmonary) or remote (most common: kidney, liver, spleen or meninges). This takes the form of multiple small nodular lesions (2–3 mm), well defined, yellowish, like millet seeds, spread over the entire affected organ (miliary TB).

Secondary pulmonary tuberculosis

Approximately 90–95% of secondary tuberculosis cases in adults occur after reactivation of latent primary infection, other cases appearing after reinfection with *M. tuberculosis* [20].

Morphological substrate of secondary tuberculosis at the beginning is the apical node, which has macroscopic appearance of a solid nodular lesion situated in one or

both lungs, small size (max. 3 cm), yellowish-gray, low consistency (necrosis caseosa). After anti-TB treatment, it heals with scarring and calcium salt impregnation. In the absence of treatment, the lesions are slowly progressive, destructive, being accompanied by an intense process of perilesional fibrosis [20, 21].

Therefore, the secondary progressive TB appears with five main entities. Apical cavitary fibrocaseosus TB occurs by the draining of the caseum from the apical nodule through the bronchial wall and then eliminating it by cough. The caseum can be aspirated, resulting bronchogenic dissemination in the lung territories causing TB bronchopneumonia. This progresses to one or more incompletely evacuated cavities (TB bronchopneumonia) with thin anfractuos wall, lined with caseous debris (recent cavitation). Cavity wall gets thinner after complete evacuation of the caseum. Old caverns have thicker walls, with perilesional fibrosis and smooth internal surface that may include fibro-vascular bands with Rasmussen microaneurysmal dilatation [22]. Advanced cavitary fibrocaseous tuberculosis with large lesions extended to one or more pulmonary lobes in different evolutionary stages: large areas of caseous necrosis, cavities, fibrosis and thickened pleura with multiple adhesions. Tuberculous bronchopneumonia presenting with multiple patchy circumscribed condensated foci with a diameter of 0.5–1 cm, white to yellowish, irregular shape, centered by a bronchi and separated by normal lung parenchyma (polycyclic tubercles). It is considered as an acute complication of secondary tuberculosis. Miliary tuberculosis appears by lymphatic dissemination exclusively in lung, and by blood dissemination resulting in systemic miliary tuberculosis, affecting the bone, spleen, liver, adrenal, kidneys, serous, etc. Macroscopically, it has the same aspect as in primary miliary TB. Caseous pneumonia is an acute complication that presents as a diffuse yellowish area of consolidation accompanied by multiple small sized cavities with irregular walls and caseous debris [20, 21, 23].

Microscopically, the characteristic lesion in TB is the tuberculous granuloma, constituted of central necrosis area surrounded by giant multinucleated cell (Langhans type) with epithelioid cell sand a collar of lymphocytes in the periphery of the granuloma.

Tuberculosis – a major public health problem in Romania

Today, the value of the global incidence (new cases and relapses) of tuberculosis in our country is the highest in the European Union and one of the highest in the *World Health Organization* (WHO) European Region (5th place after Kazakhstan, Moldova, Georgia and Kyrgyzstan).

After 1985, the incidence of tuberculosis began to register a gradual increase. This growth was faster after 1990, peaking in 2002 (142.2%000), 2003 being the first year after 1985 there has been decline in TB incidence (135.7%000). The downward trend continued, and in 2011 reached a level of 82.8%000, in 2013 was 73%000 and in 2014 was 70.2%000 (Figure 1) [22, 24–29]; 2014 represented the 12th consecutive year of decrease in the incidence of tuberculosis in Romania.

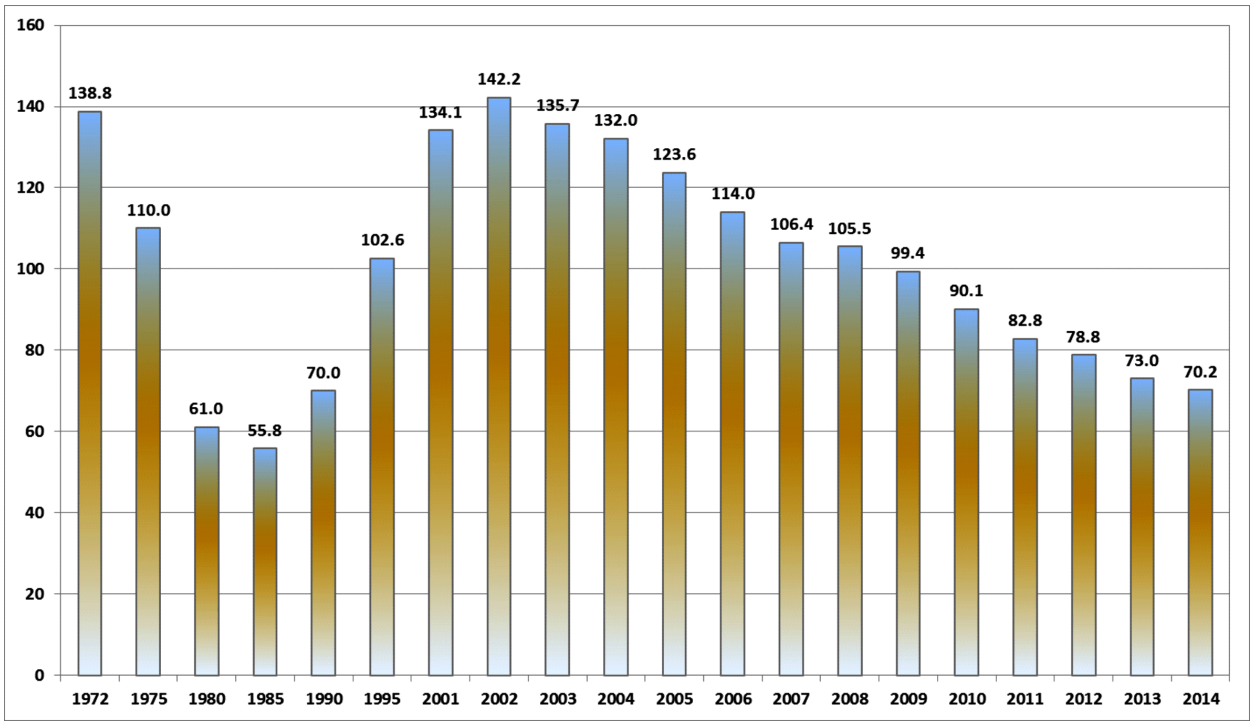

Figure 1 – ***Global incidence of TB in Romania, between 1972 and 2014 (UATM PNPSCT National Database).***

In 2013, compared to 2002, the global incidence of tuberculosis decreased by 48.7%, while the incidence of new cases decreased by 44% (from 26 567 to 12 866 cases) and relapses by 33% (from 4418 to 2664 cases) [22, 24, 25].

In 2014, compared to the same year, 2002, the global incidence of TB has declined by 51%; the incidence of new cases fell by 53% (from 26567 cases to 12562) and that of relapses by 46% (from 4418 cases to 2376 cases).

The number of new cases and relapses registered annually decreased from 30 985 in 2002 to 17 672 in 2011, reaching 14 938 cases in 2014 (Figure 2) [28].

The incidence of tuberculosis in children followed the same downward trend as the global incidence, with the remark that between 2011 and 2013 this indicator registered the same value. In 2013, compared to 2002, the incidence of TB in children has decreased by 54%. In 2014, this indicator reached 20.3%000 (Figure 3).

Tuberculosis mortality in Romania was 10.8%000 in 2002, dropping to 8.3%000 in 2005. Further declines were very small from one year to another, reaching 5.3%000 in 2014 (down 51% between 2002 and 2014) (Figure 4). The global incidence of TB in Romania continues its downward trend during last years dropping to 1.7% in 2015 and 64.8% in 2016 [25–29].

The global incidence of TB among children, an indicator that defines epidemic severity in a region, decreases from 21.3% in 2015 to 19.4% in 2016. The global incidence of TB among children is represented in the last years by new cases of disease, relapse of TB in 2016 being registered only in five counties.

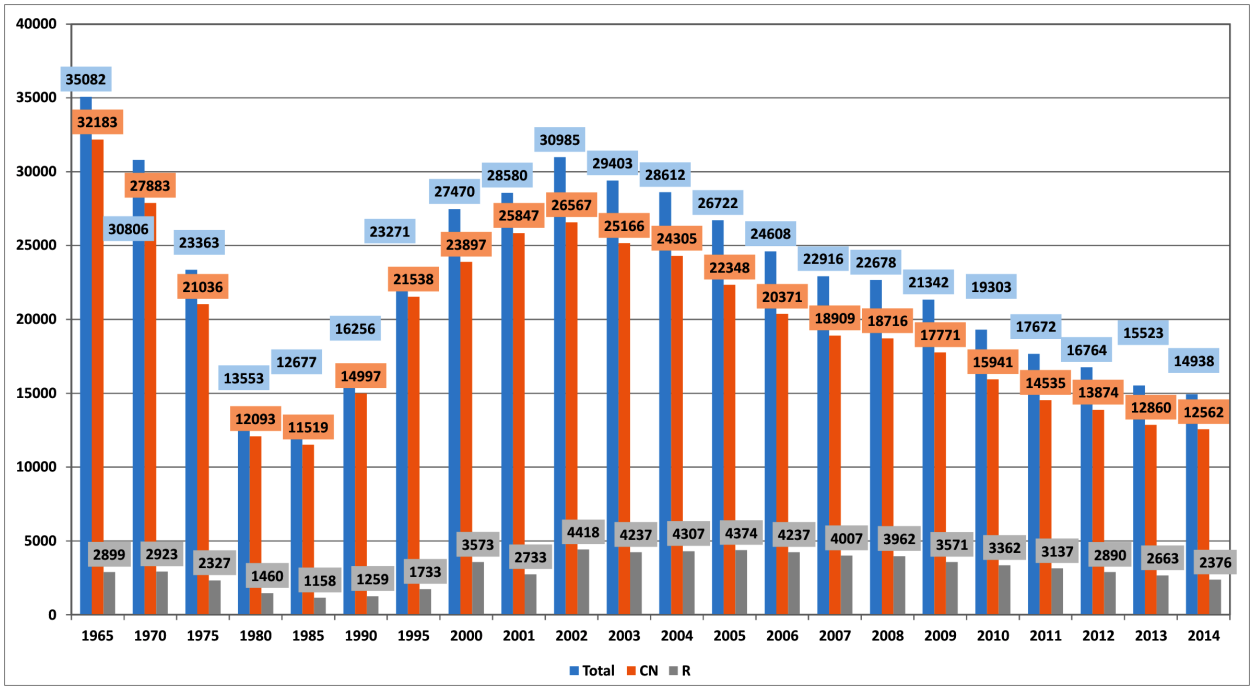

Figure 2 – ***Number of new cases and recurrences of TB in Romania between 1965 and 2014.***

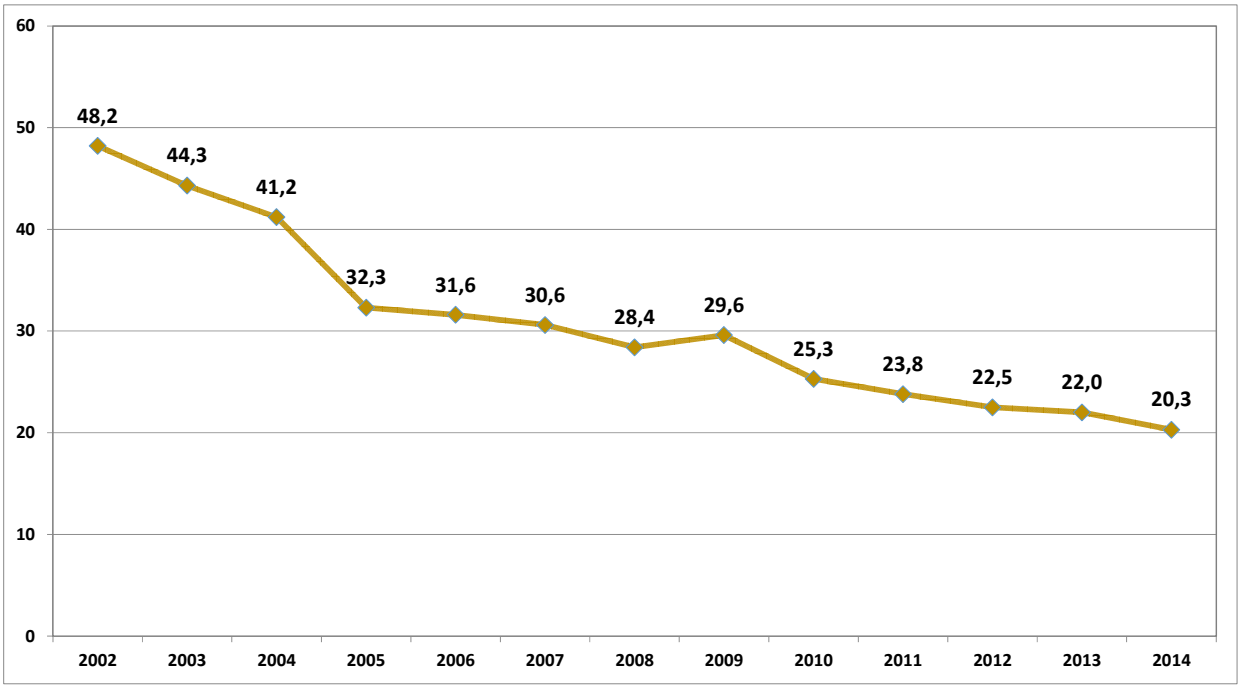

Figure 3 – ***Global incidence of TB in Romanian children between 2002 and 2014. We can see a decrease by 57.9% within the timeframe. Numbers were not significantly altered by the Eurostat adjustment that occurred in August 2014.***

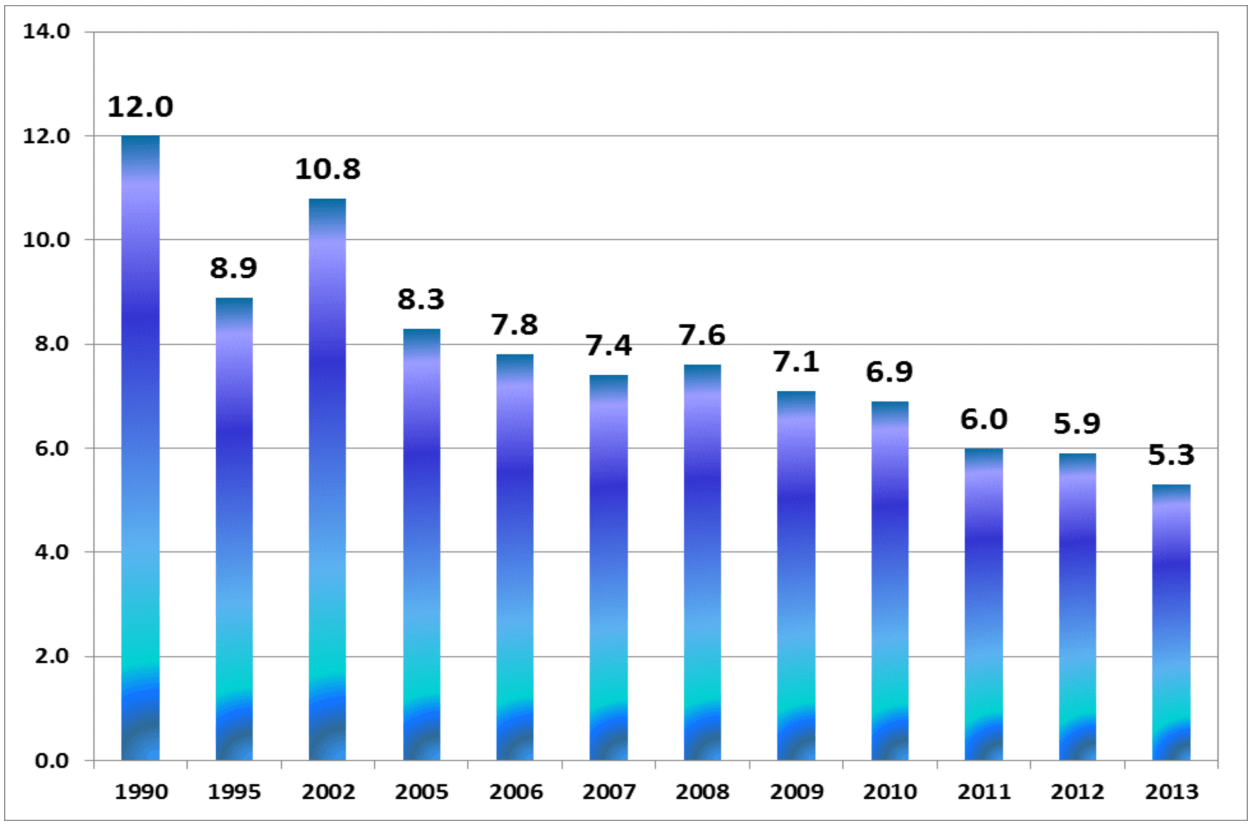

Figure 4 – ***TB mortality in Romania between 1990 and 2013.***

Tuberculosis in the world

Despite the availability of effective treatment, TB remains a major health problem worldwide. In 1993, WHO declared TB a public health emergency in the world, when it was estimated a total of 7–8 million illnesses and 1.3–1.6 million deaths annually. The newest WHO Reports show a gradual decline in the absolute number of TB cases in 2006 and of the incidence rates of TB since 2002. In 2013, WHO has reported a total of 6.1 million cases of disease of which 5.7 million new cases and 0.4 million relapses [30–32].

The death rate decreased in 2013 compared to 1990 by 45%; however, the 50% target proposed to be achieved by 2015, according to the *Stop TB Partnership*, has not been achieved yet. India and Nigeria report 1/3 of deaths worldwide. India and China have 24% of cases of TB and 11% of deaths caused by TB and 60% of cases of illness and death belong to men. Therapeutic success rate recorded reported to new cases was 86% and in the WHO European Region maintained at 75% (with constant values). Comparing indicators in highly developed countries in Europe, it was found that all countries that were analyzed had smaller indicators than EU except Spain and Portugal (with higher values than the average) possibly due to the influx of population from Eastern European countries [32–34].

Epidemiology of extra-respiratory tuberculosis

Extra-respiratory tuberculosis represented about 15–20% of all cases of tuberculosis before the appearance of HIV infection [35–38].

HIV infection has increased the number of TB cases in the world.

Extra-respiratory percentage of TB cases in 1993 in the United States represented 15.7% of all TB cases, and in 2006, the proportion of these cases represented about 21% [35]. Today, extra-respiratory tuberculosis represents 15% of all cases of tuberculosis [37].

In 2010, in the WHO European Region, 388 875 cases of tuberculosis were registered, of which 65 783 (17%) were cases of extra-respiratory TB. Extra-respiratory proportion of tuberculosis cases has remained relatively stable in the last four years [35–37].

It has been noticed that in the European Union countries and Economic European Area, it is a higher percentage of extra-respiratory TB cases from all TB in comparison with other countries from Europe that do not belong to this area, 22% to 16%. Five countries reported a percentage higher than 40% for extra-respiratory TB cases: Great Britain (47%), Netherlands (45%), Norway (41%) and Malta (41%) [10, 38].

The difference between extra-respiratory TB reports may vary because of different ways in diagnose, epidemiological factors, immigration and prevalence factors of different *M. tuberculosis* strains (some with extra-respiratory tropism) [10, 35–37].

Globally, *WHO* reported in 2011 a number of 6.2 million TB cases, from which 5.8 million were new and 0.8 million (15%) with extra-respiratory localization.

In the same year, in European Union, 16 116 extra-respiratory TB cases were mentioned. These represent 22% of the total declared TB cases from European Union [31]. Between 2002 and 2011, in this area, a number of 86 8726 TB cases were reported, from which 3696 (0.4%)

were not reported with a precise set, 167 652 (19.3%) were extra-respiratory cases, 648 225 (74.6%) were pulmonary TB and 49 153 (5.7%) were both respiratory and extra-respiratory TB. These last ones were registered as pulmonary TB cases. In this way, the number of TB pulmonary cases increased to 80.3%.

In 2011, WHO European Area registered 253 769 new TB cases, from which 42 489 (17%) were extra-respiratory [35–38]. The percentage of extra-respiratory TB vary between different countries of Europe, between 5.8% and 44.4%.

The WHO European Region gathered 26 countries that reported data about TB until 2007. From 2007, the number of countries increased to 30 [35].

These countries were divided in two parts. First part gathers countries with a low incidence of extra-respiratory TB, this means 20 cases for 100 000 inhabitants; joins 23 countries. The second part gathers countries with a higher incidence 20 cases for 100 000 inhabitants. The following countries have a higher incidence: Romania, Bulgaria, Estonia, Latvia, Lithuania, Portugal and Poland. The notification rate seems to be stable in the two groups [35–38].

In the same year, 2011, the percentage of extra-respiratory TB cases was higher ($p<0.01$) in the countries with low incidence (26.4% of all TB cases) in comparison with high incidence countries (13.2% of all TB cases) [35–38].

The tuberculosis diagnosis was confirmed in culture test in 33.7% cases of extra-respiratory TB and in 62.9% cases of pulmonary TB ($p<0.01$).

In 2011, in Romania, 2781 extra-respiratory TB cases were declared, that represents 14% of all TB. The notification rate was 13 cases for 100 000 inhabitants. Between 2002 and 2011, the percentage of extra-respiratory TB cases grew from 11% (2002) to 14% (2011) [35].

Anti-TB drug resistance was reported only in European Union countries for extra-respiratory cases. From 31 644 cases sensitive to anti-TB drug, 6933 were extra-respiratory patients. From extra-respiratory TB cases for which the drug sensitivity was tested, the rate of multidrug-resistant (MDR) TB was 2.3% (n=158) [37]. The success degree of therapy in the WHO European Region between 2002 and 2011 was 81.4% in extra-respiratory TB, in comparison with 73.5% in respiratory TB ($p<0.01$) [35–38].

Extra-respiratory TB can be located in different areas of the body. It can affect one organ or it can be localized simultaneously in different organs. TB can affect lungs, too. The usual organs touched by TB are lymphatic ganglions, lymphatic vessels, bones, pleural area, urogenital area, meninges, peritoneum and skin [38].

In the WHO European Region, from 167 652 extra-respiratory TB cases, only 108 345 (64.6%) had a precise localization. The most common localization of extra-respiratory TB were pleural area – 39 749 (36.7%) cases, followed by extrathoracic ganglions 21 812 (20.1%) cases. Among the pediatric population (0–14 years) from 9735 cases of extra-respiratory TB, 47.2% have intrathoracic localization and 18.5% were at the pleural area. Also, among the pediatric population 5.8% of the cases had bacillary meningitis in comparison to 2.9% of different group age. The pleural localization was the most common for the ones over 65 years old (22 778 cases of extra-respiratory TB), which means 29%, followed by extra-thoracic ganglionar localization [35].

In Romania, in 2011, the most frequent extra-respiratory TB localizations was pleural area with 1606 (58%) cases and ganglionic area with 535 (19%) cases, then TB of vertebral spine and TB of meningitis, the last two were 129 (5%) cases [35–38].

In the WHO European Area, between 2002 and 2011, the least culture confirmation were for pleural TB (15.1%), meningitis TB (20.7%) and spine TB (21.5%). The most culture confirmation were genito-urinary TB (40.8%) and miliary TB (46.1%) [38].

According to the national data register in Romania, the culture rate confirmation of extra-respiratory TB is between 8% and 10%. In Romania, the diagnose of extra-respiratory TB is made by the "organ" specialist along with the pulmonologist, the treatment being prescribed by the respiratory physician [38, 39].

The global rate of therapeutic success for extra-respiratory TB with precise localization was 83.2%. According to the localization, the highest success rate was seen in ganglionic intrathoracic TB (82.4%) and pleural TB (86.7%). For miliary TB, the success therapeutic rate was just 48.9% [35–38].

Tuberculosis and HIV infection

HIV–TB co-infection is defined by the simultaneous HIV infection and latent TB or active TB. In 2011, 8.7 million active TB cases were reported worldwide, from which 1.1 million (13%) had HIV infection. Almost 79% of HIV infections were located in Africa [40–44].

Global estimates of 40 million HIV infections are reported in literature; about one third also have TB co-infection [44–48].

HIV patients are the ones with a higher risk for extra-respiratory TB, 50% higher risk from all TB [44–46]. Risk of extra-respiratory TB and microbacteriemia increases with a higher grade of immunosuppression [40, 41].

The TB characteristics associated with AIDS are: extra-respiratory localization, miliary disease, fast progression, lymphadenopathy, tissue abscess, negative cutaneous test for tuberculin. The drug TB therapy answer is positive and similar to the ones without HIV infection. Drugs side affects occur more often to HIV infected patients. It is not known if HIV-infected patients have a higher risk of TB reinfection.

Drug interactions might lead to a coloration between infectious disease doctors and respiratory doctors in HIV treatment and anti-TB treatment [44].

The most frequent localization of extra-respiratory TB at HIV-infected patients is the ganglionic area (35% of cases), followed by pleural infection (20%); the rest of localizations represent together approximately 45% [44–48].

In Eastern Europe, TB is the most common opportunistic infection present at the detection of HIV infection in adults and adolescents (32% pulmonary tuberculosis, 12% extrapulmonary tuberculosis).

Universal access to acquired immunodeficiency syndrome (AIDS) treatment and care has been introduced

in Romania in 2001. The program was based on the political commitment and partnership between public authorities, pharmaceutical companies, patients and other International Agencies [40–44].

High rate of HIV cases for children infected in late 1980s and at the beginning of 1990s (>90% of the cases are F1 subtype) configured a unique cohort of patients infected with HIV. Six thousand cases are still alive.

The number of patients benefiting from top quality antiretroviral treatment increased from 3500 in 2001 to 8809 at the end of 2013. In 2013, the Romanian government spent 65 082 067.99 USD for the treatment program.

In 2012, Romania reported to the *Joint ECDC–WHO Reporting TB Platform* that 9922 (54%) of 18 197 TB patients registered in that year were tested for HIV and 232 (2%) of them were found with HIV infection. For the same year, Romania reported that 90% of TB/HIV patients had been placed on antiretroviral therapy and 76% on co-trimoxazole preventive treatment.

In the Olt County, we obtained interesting data after a small retrospective descriptive study using records of patients infected with HIV, between 2005 and 2015. We analyzed patients registered with TB–HIV. We analyzed 256 medical charts, of which 76 (29.68%) had at least one treatment for TB. Only with minor difference predominated women (52.7%) and rural residence (54%). Majority is formed of those born between 1980 and 1990 (86.84%), with predominance of Romanians (93.4%) compared to the Roma people. Regarding all TB diagnoses (pulmonary and extra-pulmonary), 48 were new cases, other 28 presented relapses, two cases presented multidrug resistance. TB and HIV have been diagnosed at the same time in 25 (32.89%) cases. At the time of TB diagnosis, 40 (52.63%) patients had CD4+ lymphocytes count.

Because diagnosis of TB among people living with HIV (PLHIV) is particularly challenging, there is delay in detection of TB and subsequent treatment. As a result, HIV-related TB deaths are a significant public health problem in high HIV-prevalent settings PLHIV should be screened for TB symptoms at each visit to a health facility or each encounter with a health care worker.

Conclusions

Tuberculosis is a disease with increased factors that is very hard to control, eventually just through national applied programs. It is necessary to have numerous national interventions for an increase in economical and social level of population. Vulnerable groups are the "targets" that the national program for TB prevention and treatment has to focus on. Social protection program have a positive impact in decreasing the number of TB patients, especially among the vulnerable groups.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Floarea Mimi Niţu and Antigona-Carmen Trofor contributed equally to the manuscript and thus share main authorship.

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