

PREVALENCE OF TUBERCULOSIS IN SOUTH-WEST ROMANIA AND THE DIRECT COSTS BURDEN

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Manuscript received: May 2020

Abstract

Antituberculous treatment has the purpose to rapidly stop transmission and to prevent relapse, in order to further reduce the tuberculosis (TB) burden and development of resistant bacterial strains. Romania had the highest TB incidence among EU countries and since 2018, an active TB screening program has been introduced among vulnerable populations. The aim of this study was to identify all the patients diagnosed with TB in Dolj County, Romania, in 2018 and to evaluate their characteristics, as well as to estimate the amounts reimbursed by the National Health Insurance Fund, based on the data reported by the hospitals from Dolj, Romania. The treatment was analysed through descriptive statistics for hospitalized cases based on a principal diagnosis of TB which received continuous care in 2018. In Dolj County, 6378 people, with a mean age of 39 ± 30.42 years, were infected with *Mycobacterium tuberculosis* in 2018. More than a half were males (3,723 - 58%) and 2,655 - 42% were females. The prevalence of TB in Dolj County in 2018 was 1.01%. The treatment outcomes of TB patients were: 1,441 (22.6%) cured, 5,036 (78.9%) treatment completed, 25 (0.4%) died, 47 (0.7%) failed and 163 (2.6%) interrupted. The number of those with treatment failed and treatment interrupted represents an unfavourable treatment outcome and it was less than 210 patients (3.3%) in 2018, which is a very good indicator compared with the 85% World Health Organization (WHO) target of TB treatment success. In order to evaluate TB control strategies, it is essential to trace TB incidence, prevalence and mortality, but also to comprehend treatment outcomes.

Rezumat

Tratamentul antituberculos are scopul de opri rapid transmiterea bacteriană și de a preveni recidiva, astfel încât povara tuberculozei (TB) să fie diminuată, iar dezvoltarea tulpinilor bacteriene rezistente să fie încetinită. România a avut cea mai mare incidență a TB dintre țările din UE, iar din 2018 a fost introdus un program activ de *screening* pentru monitorizarea și identificarea cazurilor de TB în rândul populațiilor vulnerabile. Studiul a avut ca scop identificarea tuturor pacienților diagnosticați cu TB la nivelul județului Dolj în 2018 și evaluarea caracteristicilor acestora, precum și estimarea sumelor rambursate de Fondul Național de Asigurări de Sănătate, pe baza datelor raportate de spitalele din Dolj. Tratamentul a fost analizat prin statistici descriptive, pentru cazurile internate pe baza unui diagnostic principal de TB, care au primit îngrijiri continue în anul 2018. În Dolj, în 2018, 6378 persoane, au fost infectate cu *Mycobacterium tuberculosis*. Mai mult de jumătate (3723) dintre acestea erau bărbați (adică 58%) și 2655 (42%) erau femei. Rezultatele tratamentului administrat pacienților cu TB au fost: 1441 (22,6%) au fost vindecați, 5036 (78,9%) au finalizat tratamentul, 25 (0,4%) au murit, 47 (0,7%) au eșuat tratamentul și 163 (2,6%) au întrerupt tratamentul. Numărul persoanelor care au avut un tratament eșuat și al celor care au întrerupt tratamentul reprezintă un rezultat nefavorabil cu privire la administrarea farmacoterapiei antituberculoase și a fost mai mic de 210 pacienți (3,3%) în 2018, ceea ce reprezintă un indicator foarte bun în comparație cu obiectivul OMS de a avea 85% dintre pacienți care finalizează cu succes tratamentul pentru TB.

Keywords: *Mycobacterium tuberculosis*, isoniazid, rifampicin, pyridoxine, direct costs

Introduction

Mycobacterium tuberculosis (*M.tb.*) is one of the most insidious and slow-growing bacilli, which enters human organisms through cough and expelled air droplets derived from sputum and saliva, and initiates

tuberculosis (TB), a communicable airborne and challenging disease [12, 33, 35]. Infectious patients, with sputum-smear positive pulmonary disease, are able to transmit *M.tb.* to other individuals who might present three different outcomes: immediate and

immunological bacterial removal, primary active TB or latent infection, without clinical manifestations, but which can reactivate after 5 years [5, 22].

Although *M.tb.* commonly enters the respiratory system, there can be other damaged sites (lymph nodes, skeletal sites, pleural and abdominal sites, central nervous system) where the bacteria can determine fewer, but more severe symptoms than in pulmonary TB, therefore commencing extrapulmonary disease forms [2, 5, 16, 22]. Cases of extrapulmonary TB are more difficult to diagnose and often present delayed signs such as low-grade constant fever, sterile pyuria, haematuria (genitourinary TB), cervical and sub-clavicular nodes (lymphadenitis), spinal constitutional modifications (Pott's disease), abnormal behaviour, headaches or convulsions (meningeal TB) [2, 16, 24]. The histopathological structures which define TB and allow *M.tb.* to persist for decades, under a low metabolic rate, are granulomas observed in both latent and active infection [2, 16, 22]. The disease outcomes depend on the interaction of the host with the bacilli; therefore, granulomas are involved not only in control of infection, but also in pathogenesis [2, 22]. In order to prevent dissemination, macrophages encounter *M.tb.* and create an immunologic host-protective environment, by recruiting phagocytic cells such as monocytes, lymphocytes, neutrophils and more uninfected macrophages [2]. An inflammatory response is further initiated through cytokine production and chemokine secretion, leading to tissue remodelling [2, 16]. Calcified granulomas, with fewer inflammatory cells, appear as hallmarks in latent TB, whereas in active TB, the host often presents high granulomatous inflammation, disruption of immunoregulatory mechanism and macrophage necrosis [16, 24].

The granuloma is actually a dynamic lesion, because it involves multiple cell interaction and proliferation, and can easily shift from bacilli containment to bacilli release [2]. In the absence of antituberculous treatment, the lesions are slowly progressive, destructive, being accompanied by an intense process of perilesional fibrosis [2, 16, 24]. On the other hand, after long-term pharmacotherapy, the caseating granulomas may be replaced by fibrosis, through collagen accumulation and calcification, therefore early diagnosis and clinical research could lead to better antituberculous treatment outcomes [2, 18].

According to World Health Organisation (WHO), one of every three TB patients, especially from high-burden countries such as South Africa, India, China, Russian Federation, is not included in special TB surveillance international health programs [5, 34]. Patients who had TB once have an increased risk of disease relapse, even shortly after completing anti-TB treatment [1, 13]. Furthermore, recent trials have shown that 5 - 8% of patients fail treatment and also, that patients with high smear grade (3+) at baseline are more likely to interrupt treatment compared to

patients with lower smear grades [15, 20]. In fact, it has been shown that even a small number of missed doses and non-adherence increase the risk for poor outcomes and resistant *M.tb.* strains, which further lead to multi-drug resistant TB (MDR-TB) and to the impossibility of public health systems to truly stop the TB evolution and transmission [5, 20, 26].

Assessing the burden of TB is a topic of permanent interest of public health researchers and health-care decision-makers to measure the cost of illness (COI) and to evaluate the potential costs and benefits of public health interventions. COI analysis may include direct costs (medical costs, non-medical costs), productivity losses, and intangible costs of the TB and can quantify the magnitude of the problem [17].

The aim of this study was to identify all the patients diagnosed with TB in Dolj County, Romania, in 2018 and to evaluate their characteristics, as well as to estimate the amounts reimbursed by the National Health Insurance Fund, based on the data reported by the hospitals from Dolj County.

Materials and Methods

The study was approved by The Ethic Committee of The University of Medicine and Pharmacy of Craiova, Romania (Nr.5/17.01.2019).

We used anonymized individual patient data reported by hospitals from Dolj County, Romania, at the Health Insurance House of Dolj, following the legal requirements on personal data protection. The patients' dataset extracted from Health Insurance House of Dolj for 2018 included the following demographic and clinical information: patient gender, age, hospital, treatment and outcome (cured, completed, died, failed, interrupted – from WHO definitions [36, 37]), length of stay (hospital days), results of laboratory analysis. Data were collected from the patients' records at the healthcare hospitals from South-west Romania (Craiova, Calafat, Filiași, Dăbuleni, Băilești and Leamna). The treatment could be analysed only for those cases admitted in the hospital with continuous care and diagnosed with TB as principal diagnosis in 2018. We investigated service burden and costs in association with TB.

Data have been extracted and processed in Excel. Data were analysed using the GraphPad Prism 9 software (GraphPad Software, LLC, San Diego, CA, USA). Descriptive statistics were used to summarize patients and their characteristics using percentages for categorical variables and mean $\pm$ standard deviation for continuous variables. We used the T-test (for normal distributed variables) and nonparametric Mann-Whitney U test (for variables without normal distribution). Categorical variables were compared using Chi-square test. It was considered statistically significant at the 5% level (two-tailed).

Results and Discussion

In 2018, 6,378 people have been reported to be infected with *M.tb.* in Dolj County, Romania. More than a half were males (3,723 patients, 58%) and 2,655 patients (42%) were females. The mean age was 39 ± 30.42 years. The prevalence of TB in the Dolj County, Romania, was 1.01% in 2018.

The treatment outcomes of TB patients were: 1,441 (22.6%) cured, 5,036 (78.9%) treatment completed, 25 (0.4%) died, 47 (0.7%) failed, 163 (2.6%) interrupted. The treatment success is the number of patients cured and treatment completed, but some of the cured patients were also treatment completed in the same year, 2018. The unfavourable treatment outcome is the number of patients with treatment failed and treatment interrupted less than 210 patients (3.3%). It is a very good indicator compared with 85% target of TB treatment success.

With 25 cases of fatal TB, for a population of 630,911 in the Dolj County, we found a TB death rate of 3.96 (*per* 100,000 people). Of the 25 patients who died of TB in 2018, two (approximately 8%) were females. The mean age was 60.2 (SD = 11.12). The youngest patient had 38 years old and the oldest was 78 years old.

1,099 cases have been reported to receive treatment in hospitals from Dolj County in 2018, of which 308 patients (28%) were females and 791 patients (72%) were males. The number of patients with continuous care in hospitals from Dolj County is presented in Figure 1. Patients from Craiova hospital constitute the largest population, 714 cases (52%), followed by Leamna hospital with 313 patients (23%).

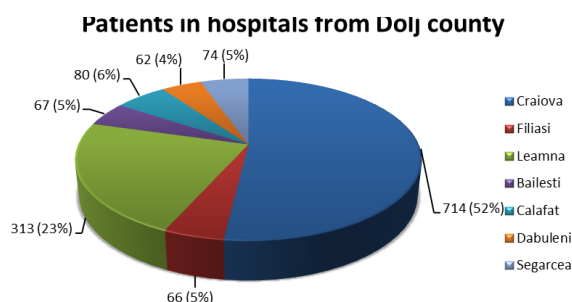


Figure 1.
Distribution of tuberculosis patients with continuous care in hospitals from Dolj County, Romania, in 2018

The use of TB treatment and their dimension were extracted and presented in Table I.

Table I

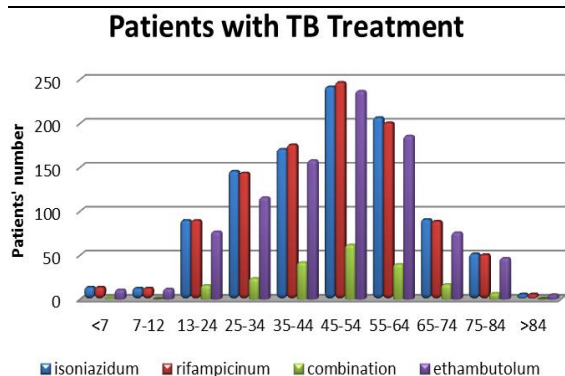
Number of patients with tuberculosis for each treatment

		Number of patients (%)					
		Isoniazidum (n = 1032)	Rifampicinum (n = 1031)	Combination Rifampicinum + isoniazidum (n = 209)	Ethambutolum (n = 925)	Pyrazinamidum (n = 878)	Streptomycinum (n = 59)
Gender	Male	966 (94%)	733 (71%)	163 (78%)	680 (74%)	644 (73%)	49 (83%)
	Female	66 (6%)	298 (29%)	46 (22%)	245 (26%)	234 (27%)	10 (17%)
Age	< 7	14 (1%)	14 (1%)	1 (< 1%)	11 (1%)	11 (1%)	0
	7 - 12	13 (1%)	13 (1%)	0	12 (1%)	12 (1%)	0
	13 - 24	90 (9%)	90 (9%)	16 (7%)	77 (8%)	75 (9%)	1 (1.7%)
	25 - 34	146 (14%)	144 (14%)	24 (11%)	116 (13%)	114 (13%)	2 (3.4%)
	35 - 44	171 (17%)	176 (17%)	42 (20%)	158 (17%)	152 (17%)	9 (15.3%)
	45 - 54	242 (23%)	247 (24%)	62 (29%)	237 (26%)	218 (25%)	19 (32%)
	55 - 64	207 (20%)	201 (19%)	40 (19%)	186 (20%)	171 (19%)	14 (24%)
	65 - 74	91 (9%)	89 (9%)	17 (8%)	76 (8%)	76 (9%)	10 (17%)
	75 - 84	52 (5%)	51 (5%)	7 (3%)	47 (5%)	45 (5%)	4 (7%)
	> 84	6 (1%)	6 (1%)	0	5 (1%)	4 (0.5%)	0

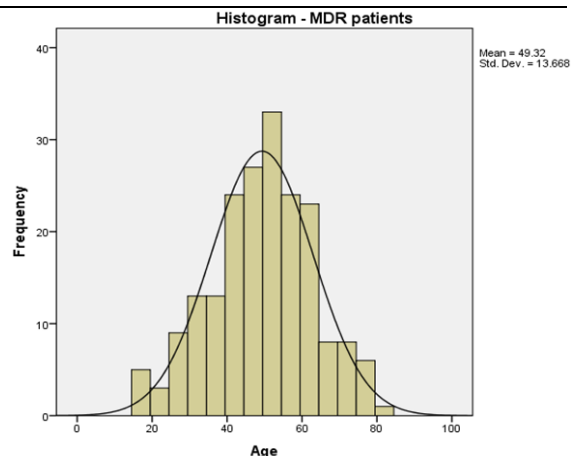
The highest percentage of patients from Dolj County received isoniazid (H) (1,032 patients from a total of 1,099 cases) and rifampicin (R) (1,031 patients from a total of 1,099 cases), the most effective bactericidal drugs. Streptomycin (S) was the least administered substance in 2018, especially in children and elderly. Most of TB cases appear in young adults, especially men (94%) between 45 and 54 years old. On the contrary, children (below 7 and 7 - 12 years old) and elderly (over 84 years old) represent a low proportion of the total cases reported in Dolj County in 2018. The number of new cases in 2018 could not be determined, but the number of patients with multi-

drug resistant TB (MDR-TB) was calculated according to the reported treatment. A number of 266 patients had MDR-TB, of which 218 were men (82%) and 48 were women (18%). The mean age was 49.32 ± 13.67 years, as reported in Figure 3.

The proportion of MDR-TB patients' treatment was: five patients treated with amikacin, 39 patients treated with cycloserine, four patients treated with levofloxacin, 176 patients treated with ofloxacin, 42 patients treated with protonamide, as reported in Table II.

**Figure 2.**

Distribution of patients for different anti-tuberculosis treatment in Dolj County, Romania, in 2018

**Figure 3.**

The normal distribution of age for the MDR-TB patients

Table II

Number of patients with MDR-TB for each treatment

		Number of patients (%)				
		Amikacinum (n = 5)	Cycloserinum (n = 39)	Levofloxacinum (n = 4)	Ofloxacinum (n = 176)	Protionamidum (n = 42)
Gender	Male	5 (100%)	32 (82%)	2 (50%)	147 (84%)	32 (76%)
	Female	0	7 (18%)	2 (50%)	29 (16%)	10 (24%)
Age	<7	0	0	0	0	0
	7-12	0	0	0	0	0
	13-24	0	2 (5%)	0	5 (3%)	2 (5%)
	25-34	2 (40%)	2 (5%)	3 (75%)	20 (11%)	4 (10%)
	35-44	0	8 (21%)	0	34 (19%)	6 (14%)
	45-54	3 (40%)	11 (28%)	0	57 (32%)	11 (26%)
	55-64	0	12 (31%)	1 (25%)	43 (24%)	12 (29%)
	65-74	0	3 (8%)	0	13 (7%)	4 (10%)
	75-84	0	1 (3%)	0	4 (2%)	3 (7%)
	>84	0	0	2 (50%)	0	0

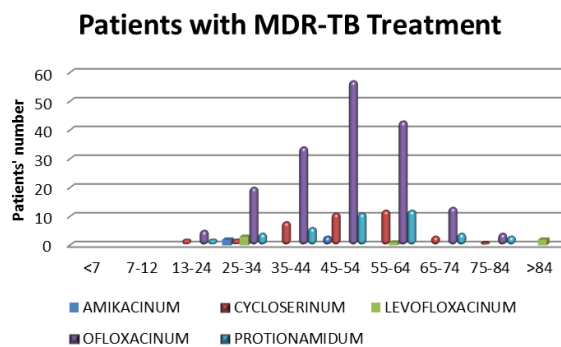
The number of complex drug resistance patients was high, 266 (24.2%), ofloxacin being the most used drug for treatment of MDR-TB patients, as shown in Figure 4.

The highest percentage (24%) of patients receiving pyridoxine, as a supplement during H therapy, was between 45 and 54 years old, followed by those between 55 and 64 years old (21%) (Table III).

We compared the group of TB patients with MDR-TB treatment (who received second-line antituberculous agents) with the group of patients without MDR-TB treatment (who received first-line antituberculous agents). The results are shown in Table IV. No significant difference was found for age between the two groups. Instead, the gender was different between the two groups, with more men in the MDR-TB treatment group.

After we investigated the economic impact of TB and the service utilization pattern of patients with TB in the Dolj county, we obtained a value of direct costs of RON 45,390,457 (approximately \$ 10,531,429, with \$ 1 = RON 4.31). The direct costs associated with TB

were drug administration (RON 327,170.5 = \$ 75,910), hospitalization days (number = 100,961, value = RON 44,929,664 = \$ 10,424,516), the medical consultation (number = 8,787, value = RON 97,327.35 = \$ 22,582) and laboratory tests (number = 1,707, value = RON 36,295.64 = \$ 8,421).

**Figure 4.**

Distribution of patients for different MDR-TB treatment in Dolj County, Romania, in 2018

Table III

Number of patients with pyridoxine supplementation during therapy

		Number of patients receiving pyridoxinum (n = 921) (%)	Mean of the number of drugs given/patient
Gender	Male	675 (73%)	19
	Female	246 (27%)	16
Age	< 7	8 (0.9%)	6
	7 - 12	13 (1.4%)	9
	13 - 24	78 (8%)	10
	25 - 34	121 (13%)	13
	35 - 44	159 (17%)	22
	45 - 54	224 (24%)	21
	55 - 64	193 (21%)	19
	65 - 74	78 (8%)	22
	75 - 84	43 (5%)	12
	> 84	4 (0.4%)	10

Table IV

Characteristics of MDR-TB patients vs. non-MDR-TB patients

		MDR-TB patients	Non-MDR-TB patients	p-value
Gender	Male	162 (13%)	790 (61%)	0.0026
	Female	35 (3%)	308 (24%)	
Age	Mean (SD)	49.32 (13.67)	46.8 (17.2)	0.0658
	Median (IQR)	50 (18)	48 (24.75)	

SD = Standard Deviation; IQR = Interquartile Range

According to WHO, in 2018, more than 10 million people (5.8 million men, 3.2 million women and over 1.0 million children under 15 years old) proved non-specific and common TB symptoms such as chronic cough, night sweats, fever, weight loss, a general feeling of discomfort and 1.5 million died [5, 35]. Despite the fact that Europe counts less than 3% of TB cases worldwide, Romania presents the highest incidence [5, 12, 35]. Romania, with a 20 million population, notified in 2018 approximately 13.000 new TB cases (68%), with 3200 cases among HIV-positive patients (1.6%) and 7100 (3.6%) MDR-TB cases [35].

In the past years, our country has intensified efforts in order to increase notification of new cases, often associated with behavioural and demographic factors, but also to ensure a correct diagnosis and the most effective treatment, through national surveillance programs [12, 33]. The concerning number of deaths among HIV-negative people in Romania, in 2018 (8600), with a rate of 4.4%, claimed the importance to determine a report regarding the number of deaths, number of confirmed cases and number of relapse cases in order to reduce the incidence of active TB and MDR-TB [35].

Although, some studies reported no significant differences between men and women regarding any anti-TB drug resistance [11], MDR-TB prevalence has been noted with a higher rate in male patients [6, 10]. Our report noted three times more men with MDR-TB treatment in comparison with ones receiving first-line antituberculous agents. Unfortunately, we could not differentiate from our database if the MDR-cases

were relapses due to low first-line pharmacotherapy adherence or new cases.

Htun *et al.* proved that female sex predisposes to longer treatment delay, which further leads to difficulty in controlling MDR-TB, but the retrospective study was conducted in a Regional TB Centre from Myanmar [14]. On the other hand, The European Surveillance System (TESSy) used a multivariable regression model for ten years (2002-2011) in a cohort study including 28 countries and underlined a higher proportion of men who died or failed completing antituberculous treatment, including second-line agents, therefore a lower treatment success rate for male sex [19]. Even more, Chaves Torres *et al.* emphasized that female sex speeds better anti-TB treatment outcomes [6]. Our study accentuates actual difficulties in controlling TB epidemic, sustained especially by the growing number of MDR-TB cases reported in the past years [19, 35]. TESSy reported Romania as one of the countries that showed an increasing treatment success rate throughout ten years in patients diagnosed with MDR-TB, even though Romania was also one of the top three countries that had surpassed more than 10% of unsatisfactory anti-TB treatment outcomes [19]. Glausser *et al.* ranked migrants born-cases in Romania as the 3rd place regarding antituberculous drug resistance, after Somalia and Eritrea, in a study conducted in Germany between 2008 and 2017, based on surveillance data [11]. Proportions of age groups and sex between MDR-TB-patients and TB-patients did not change in our study, consistent with TESSy trend analysis [19]. For countries within the European Union (EU) and European Economic Area (EEA), WHO and European

Centre for Disease Prevention and Control (ECDC) recommended a treatment success rate of 85% at 12 months for all new culture positive pulmonary TB cases and a treatment success rate of 90% for all new smear positive pulmonary TB cases [9]. In our report, we couldn't differentiate new culture positive pulmonary TB cases or new smear positive PTB cases, but we found a successful treatment rate for Dolj County which indicates that Romania could be able to meet WHO/ECDC targets for TB treatment success.

The number of TB patients showed age-specific differences with a higher proportion reported for 35 - 65 years. Our data confirm that most of TB cases appear in young adults, especially men (94%) of 45 - 54 years old, which is in line with other studies showing a higher susceptibility of men due to an X chromosome gene [40], consistent with WHO notification regarding men predisposition to develop TB with a higher rate than women [5, 35, 37]. Although TB in children remains rare in Dolj County, when present it can lead to severe disease, with common dissemination in meninges, bone marrow and urinary tract [8, 27]. Therefore, TB among children continues to demand special attention not only because of their treatment particularity, but also as an indicator of current transmission among the population. The low proportion of active TB cases in children (below 7 and 7 - 12 years old) and elderly (> 84 years old) reported in Dolj County, in 2018, underlined a promising result of all the efforts Romania has made in the last years in order to ease the TB burden.

This calls attention to the importance of keeping continued vigilance against TB for all age groups and the consideration for differential diagnosis also based on histopathological examinations. The reduction of TB prevalence can be realized by avoiding risk-factors such as: contact with other TB cases or foreign-born persons from endemic areas, smoking, heavy alcohol consumption and administration of immuno-compromising drugs [5, 33]. Furthermore, taking actions regarding life quality and poor nutrition in patients can decrease not only the local incidence of TB in Romania, but also the global number of deaths, estimated by WHO at almost 1.2 million among HIV-negative people in 2018 [5, 10, 31, 35]. TB mortality rate *per* 100,000 had a decreasing slope. In 2017, TB death rate for Romania was 4.7 cases *per* 100,000 people, which dropped from 10 cases *per* 100,000 people in 2003 and 7.7 in 2007 [31, 39]. TB death rate *per* 100,000 people in Romania in 2018 was reported at 4.4 and we found a very significant outcome (3.96) to this indicator for Dolj County. The TB mortality rate (ICD A15-19) of 3.96 cases *per* 100,000 is an indicator met only in Lithuania and Romania by all EU/EEA Member States being more than the target of 2.7% [37].

Early adopted anti-TB treatment can control the progression of the disease and can prevent drug

resistance [29, 34]. According to WHO, a cured patient is one who was initially sputum smear-positive, but after treatment or before completion of treatment, is sputum smear negative on at least two previous occasions, usually at the end of the second and fifth month [15, 35, 37]. The standard recommended anti-TB treatment represents a six months regimen containing a two months intensive phase with H, R, pyrazineamide (Z), ethambutol (E), followed by a continuous phase of four months [1, 5, 9, 15, 40]. Our data supports WHO guidelines recommendations, the highest percentage of patients from Dolj County receiving H and R which are also the most effective bactericidal drugs in preventing MDR-TB strains [3, 5, 15]. One of the reasons of high recommendation of H and R may highlight the efforts specialists from Dolj County have made in the last years in order to strengthen latent TB treatment surveillance. We underline that the most used treatment for latent TB represents a daily combination of these two drugs, orally administered, for three months [2, 28]. Treating latent TB is mandatory in order to eliminate the global TB burden [29].

On the other hand, streptomycin (S) can be administered as an alternative to E, but is not recommended in uncomplicated cases [5]. In 2018, S was the least administered substance in Dolj County, especially in children and elderly, because it requires parenteral injection and provides a risk of renal impairment, irreversible vestibular-cochlear nerve damage, deafness and neuromuscular blockade [4, 5]. WHO recommends using S and other aminoglycosides only in critical situations, without any alternative drugs [4, 15, 20]. The large number of patients with complex drug resistance, which contributes to a higher incidence of TB in population risk groups, as well as high proportions of infectious PTB demonstrate that TB is still a disease with significant public health relevance in Romania. The costs of treating MDR-TB and XDR-TB actually exceed the total budget for TB control in high-burden countries worldwide, so combating and preventing resistant strains has not only human consequences, but also economic ones [34, 40]. The most prescribed second-line anti-TB drug in 2018 was ofloxacin, a cost-effective fluoroquinolone, with increased adherence due to oral administration and low risk of adverse reactions [5, 40]. Though, common side effects such as increased hepatic enzymes, gastrointestinal disorders or even cardiovascular, by prolonging QT interval and by generating arrhythmias, could appear [3, 5].

Another analysed data regards the co-administration of pyridoxine (vitamin B6) and H, with the highest percentage in patients aged 45 - 64, included also in the highest proportion of TB cases. There are several recent studies that also noted more adverse reactions in patients over 35 years old [13, 21]. Risk groups such as malnourished, immunocompromised, diabetic patients, alcohol consumers and pregnant women

are recommended to orally administrate 10 - 50 mg pyridoxine in order to reduce H-induced neuropathy or other neurological disorders [4, 5, 8, 22]. Furthermore, the role of micronutrients and vitamins in TB prophylaxis and treatment is being widely discussed and it seems that vitamin C leads to a dormancy state of *M.tb*, stimulating the bacteriostatic effect of antituberculous drugs, while vitamin D has an immunomodulatory function and stimulates host immunity to rapidly kill the bacteria [13, 22, 29].

The strengths of the study include the population-wide approach with TB from Dolj for 1 year, with no missing patients to ensure complete reimbursements. One of the limitations of this study was the missing of some information that were not included in the database: other disease conditions (like HIV-infection or other viral co-infection or medical conditions), other treatments (with drugs that can interact with TB drugs [13, 22]) or other associated factors that could be important in disease progression and mortality among TB cases, as TB re-treatments or lack of therapy compliance [7, 23]. New strategies could be implemented for assessing [23, 32] and guarantee for a complete adherence to TB therapy.

Using data from the Health Insurance House of Dolj, it was important to estimate the TB burden among children or adolescents in the Dolj County, and for every segment of age. The average expenditure *per* notified TB patient (US\$ *per* patient) reported to WHO for Romania in 2018 was of approximately US\$ 450. We found a burden of US\$ 1651 *per* patient with TB in Dolj County [30, 36, 38], which is almost four times the national reported data. TB was associated with increased service use and costs in Dolj County. Future local plans to address the goal of TB elimination and minimization of financial burden [25, 36] will need to take this into account.

From all 12,205 TB case notifications in 2018 in Romania in WHO's global TB database [36, 38], 6,378 (52%) are only in Dolj County. This study indicates that the prevalence of tuberculosis in Dolj County is still high, but with more than 85% of treatment success.

Conclusions

Even though TB is the most prevalent contagious disease cause of death, determining more than 3 million deaths each year, the improvement of TB control strategies and progresses made in predicting new cases may lower future epidemics. The analysis of notified cases or treatment outcomes needs further exploration in order to predict prevalence rates in specific geographic areas, but could be a solution to obtain positive results. According to WHO End TB Strategy, these results should be translated through a percentage of treatment success rates higher than 90%.

Conflict of interest

The authors declare no conflict of interest.

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