



Time trend and clinical pattern of extrapulmonary tuberculosis in Serbia, 1993–2007

Tendencije učestalosti i klinički oblici vanplućne tuberkuloze u Srbiji u periodu 1993–2007.

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Abstract

Background/Aim. Increased incidence of extrapulmonary tuberculosis (XPTB) is reported worldwide. Serbia is a country in socio-economic transition period with low-middle HIV prevalence and intermediate-to-low tuberculosis (TB) incidence rate, 100% directly observed treatment (DOT) coverage, and mandatory BCG vaccination at birth. The aim of the study was to examine the incidence trend and clinical features of XPTB in Serbia during a 15-year period. **Methods.** This retrospective observational study included XPTB cases diagnosed in the period between 1st January 1993 and 31st December 2007, according to the reports of the National Referral Institute of Lung Diseases and Tuberculosis in Belgrade and Central Tuberculosis Register. Population estimates with extrapolations were based on 1991 and 2002 census data. **Results.** While the overall TB incidence rate showed a slight, not significant decreasing trend ($p = 0.535$), a significant increase was found for XPTB ($y = 1.7996 + 0.089x$; $R^2 = 0.4141$; $p =$

0.01). A total of 2,858 XPTB cases (newly diagnosed and 10% relapses) gave an average age specific incidence rate of 2.51/100,000 population (95% confidence interval, SD = 0.6182) with 8.9% annual increase. The male-to-female ratio was 0.54. Lymph nodes were most frequently affected site (48.5%) followed by genitourinary (20.5%), pleural (12%), and osseo-articular (10.3%) TB. Treatment outcome was successful in 88.29% of patients (cured and completed), 3.64% died, 5.18% interrupted, 0.57% displaced, and 2.3% unknown. **Conclusion.** Increasing trend of XPTB incidence rate may be a result of increased morbidity due to still present risk factors, possible higher detection rate in Serbia and better notification. A high coverage of newborns with BCG vaccination at birth might contribute to a decreased number and rare XPTB cases in children.

Key words:

tuberculosis, urogenital; tuberculosis, miliary; tuberculosis, lymph node; tuberculosis, meningeal; tuberculosis, osteoarthicular; serbia; incidence.

Apstrakt

Uvod/Cilj. Incidencija vanplućne tuberkuloze (VPTB) je u porastu širom sveta. Srbija, koja se nalazi u periodu socioekonomske tranzicije je zemlja niske-srednje prevalencije infekcije HIV i srednje-niske stope incidencije tuberkuloze (TB) sa 100% primenjenom strategijom neposredno nadzirane terapije (DOT) i obaveznom BCG vakcinacijom po rođenju. Cilj našeg rada bio je da se ispita incidencija i klinički oblici VPTB u Srbiji tokom 15 godina. **Metode.** Retrospektivna opservaciona studija obuhvatila je sve slučajeve VPTB dijagnostikovane u periodu od 1. januara 1993. do 31. decembra 2007. godine, prema Godišnjim izveštajima Instituta za plućne bolesti i tuberkulozu u Beogradu (nacionalna referentna ustanova) i Centralnog registra za tuber-

kulozu. Procena broja stanovnika izvršena je na osnovu popisa stanovništva od 1991. i 2002. godine. **Rezultati.** Dok je ukupna stopa incidencije TB pokazala blagu neznatnu tendenciju opadanja ($p = 0,535$), našli smo značajan porast stope incidencije VPTB ($y = 1,7996 + 0,089x$; $R^2 = 0,4141$; $p = 0,01$). Ukupno 2 858 bolesnika sa VPTB (novodijagnostikovani i 10% recidiva) dalo je prosečnu starosno specifičnu stopu incidencije od 2,51/100 000 stanovnika (interval poverenja 95%, SD = 0,6182) sa godišnjim porastom od 8,9%. Odnos broja obolelih osoba muškog i ženskog pola bilo je 0,54. Najčešće su bile zahvaćene limfne žlezde (48,5%), potom urogenitalni organi (20,5%), pleura (12%) i koštanozglobni sistem (10,3%). Kod 88,29% bolesnika lečenje je uspešno završeno, 3,64% bolesnika je umrlo, 5,18% prekinulo lečenje, 0,57% premešteno, dok je za 2,3% ishod leče-

nja bio nepoznat. **Zaključak.** Tendencija porasta incidencije VPTB u Srbiji može da bude rezultat porasta morbiditeta usled još uvek prisutnih faktora rizika, moguće veće stope otkrivanja slučajeva i boljeg prijavljivanja. Visoki obuhvat novorođenčadi BCG vakcinacijom može da objasni što je VPTB u Srbiji kod dece retka.

Introduction

Although TB usually affects lungs, it can be spread through the blood stream and involve other sites leading to extrapulmonary TB (XPTB) ¹. This latter usually happens easier in immune compromised host ^{2, 3}. Thus, increasing number of XPTB cases worldwide is due to increasing number of immunodeficient persons, predominantly human immunodeficiency virus (HIV)-positive ones ²⁻⁴. Nowadays, Serbia is an intermediate-low TB incidence country ⁴. It ranks among HIV/AIDS low-middle prevalence countries and both HIV infection and drug resistance seem not to be major problems in current TB control ⁴. Some other risk factors are of higher importance in developing TB such as stress and malnutrition, diabetes mellitus, chronic alcohol and tobacco abuse, and coexisting malignant disease, which are especially prominent in the existed and newly appeared risk groups ⁵⁻⁷. Despite a slight decreasing trend of reported overall cases of TB in Serbia in recent years, we observed an increasing trend in some selected age groups and reported rare forms of XPTB in the setting ^{5,8-14}.

Among all forms of XPTB, only pleural TB is equally likely to develop in male and female TB patients (adjusted for age, race/ethnicity and country of origin). All the other extrapulmonary forms (lymphatic, osteo-articular, peritoneal, pericardial, meningeal, and rarer forms) are consistently more likely to develop in female than in male patients ¹⁵.

The aim of our study was to examine the time trend of XPTB incidence rate in Serbia from 1993 to 2007 and to analyze the clinical pattern of the disease.

Methods

In this retrospective descriptive study, we analyzed annual data on diagnosed active TB cases for a 15-year-period, 1993–2007, categorized by sex and age. In the analysis, we used the proportion of notifications by age group and sex, and notification rate of TB per population by age-group as the main indicators over time.

The sources of data were Annual Summaries of the Research and Epidemiology Department of the National Referral Institute of Lung Diseases and Tuberculosis in Belgrade, and Central TB register ⁹⁻¹².

The setting characteristics: South-East European country in socioeconomic transition period with population of 7,481,579 and TB incidence rate 27/100,000 population in 2007 ⁹. Since 1952, the Serbian national TB reporting system provided age- and sex-specific morbidity figures for the year the cases were reported (cross-sectional reports). The age groups were defined as five-year intervals except

Ključne reči:

tuberkuloza, urogenitalna; tuberkuloza, milijarna; tuberkuloza limfnih žlezda; tuberkuloza moždanica; tuberkuloza, osteoartikularna; srbija; incidenca.

for the first two intervals (0 years and 1–4 years) with 65–69 and ≥ 70 available age intervals for the elderly. According to the number and distribution of the XPTB cases notified, as well as the importance of the first years of age in TB pathogenesis and control, we used the age interval 0–4 years followed by the next three 20-year intervals (5–24, 25–44, 45–64), and the ≥ 65 years, to present the data most effectively.

Population estimates based on 1991 and 2002 census data with extrapolation were used for the calculations of TB incidence rates in the observed period. Incidence rates were expressed as the number of TB patients per 100,000 (No/100,000) population.

A regression line was fitted to the annual age specific incidence rates to ascertain the *p* value. For the estimation of regression coefficients, Statistical Package for the Social Sciences (SPSS) for Windows version 16.0 was used. We used the following formula for linear regression to test the trends: value on vertical axis = intercept +/- slope multiplied by value on horizontal-axis ($y = a + bx$). Trendline was fitted by the sum of least squares.

Results

A total of 2,858 XPTB cases were registered in Serbia from 1993 to 2007. They presented the proportion of overall TB cases that ranged from 7–11.5% being 8% on average over the observed 15-year-period. While the overall TB incidence rate showed a slight, not significant decreasing trend ($y = 35.241 - 0.2643x$; $R^2 = 0.1712$; $p = 0.535$), a significant increase was found in patients with XPTB ($y = 1.7996 + 0.089x$; $R^2 = 0.4141$; $p = 0.01$). An average age specific incidence rate of XPTB was 2.51/100,000 population (95% confidence interval, SD = 0.6182) with annual increase of 8.9% (Figure 1).

Distribution of XPTB cases by sex and age showed peak number in the 45–64-year age interval for male and female cases (Figure 2). Only two cases were recorded in the age interval 0–4 years over the observed period and both were girls. The female cases have prevailed in all the other ages with the average male-to-female ratio 0.54, being 0.6, 0.45, 0.59 and 0.55 for the age intervals 5–24, 25–44, 45–64, and 65 years and over, respectively (Figure 2).

The most frequently affected sites were lymph nodes (48.5%), and the next three ranked genitourinary (20.5%), pleural (12%), and osteo-articular TB (10.1%) (Figure 3). Only three XPTB patients have been reported to be HIV-positive. Individual data for the last three years of the analysis showed that the treatment of XPTB was successful in 88.29%, 3.64% of the patients died, 5.18% interrupted treat-

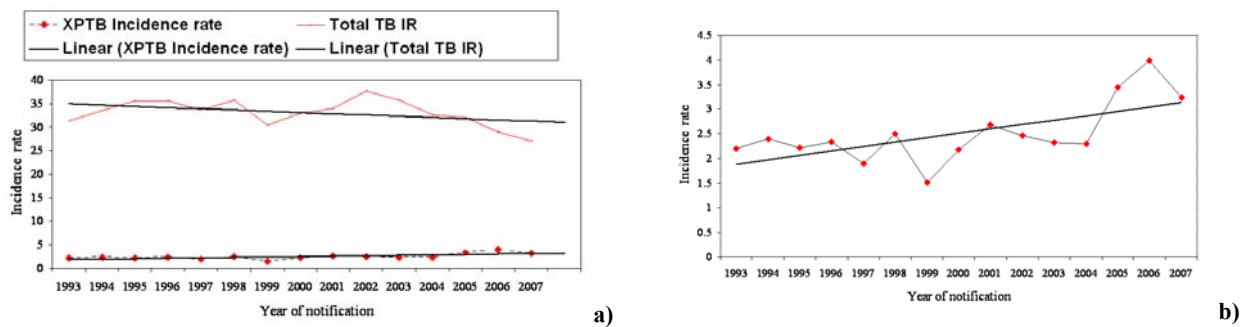


Fig. 1 – Time trends of the overall tuberculosis (TB) (a) and extrapulmonary tuberculosis (XPTB) (b) incidence rates in Serbia (1993–2007)

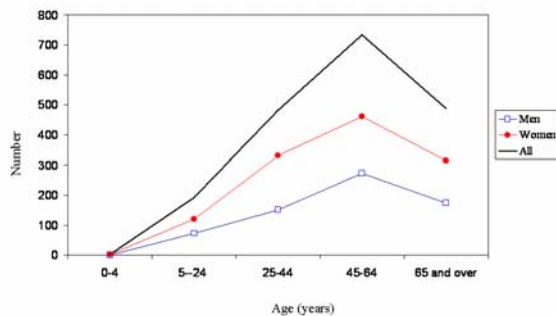


Fig. 2 – Distribution of extrapulmonary tuberculosis cases in Serbia by sex and age

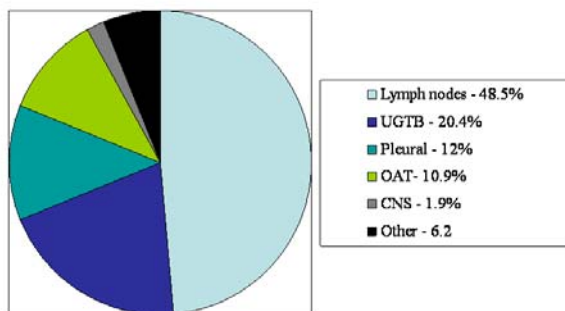


Fig. 3 – Distribution of extrapulmonary tuberculosis cases in Serbia by the sites involved

ment, 0.57% were displaced, and none was still on treatment at the time of the evaluation, 18 months from the treatment initiation. The disease outcome was unknown for the 2.3% of the cases⁹⁻¹¹.

Discussion

The results of our study showed a total of 2,858 cases of XPTB over 15 years giving an average incidence rate of 2.51/100,000 population, and a significant increase over the study period. In the United States of America, after a steady decline during several decades, there was an increase in the rate of TB in the 1980s that coincided with the acquired immunodeficiency syndrome (AIDS) epidemic. Disease patterns since have changed, and there is now a higher inci-

dence of disseminated and extrapulmonary disease¹⁶. In the American study, common extrapulmonary sites of TB included lymph nodes, pleura, and osseous areas while Sos et al.¹⁷ reported lymph nodes (42.6%), miliary and disseminated (19.5%), and pleura (12.8%) as the three first ranked sites. The lymph node affection is the first ranked XPTB site in many studies although the proportion may vary in different settings¹⁷⁻¹⁹. The proportion in our study is similar to the results of Parimon et al.¹⁸.

Although HIV infection is the greatest single risk factor for developing active TB in infected person, it is still not considered major problem of TB management in Serbia due to the overall low HIV infection prevalence by 2003⁴. Due to the lack of systematic HIV-testing of TB patients, it is uncertain were the three reported HIV-positive patients the only HIV-positive XPTB cases in the study period. However, we assume that some other risk factors, which have been proved to decrease human immunity, might be of higher importance for developing active TB²⁻⁴. The 1990s in the country were characterized by complex and unique socioeconomic crisis enriched with a wide spectrum of TB risk factors. These have led to both higher risk of infection and, in infected, higher risk of developing TB active disease. Worsening of economic crisis with the highest hyperinflation ever has brought poverty, which is strongly associated with TB incidence^{2, 20-22}. Stress and malnutrition are also well-known risk factors for developing TB². In the countries with low TB and HIV-infection prevalence, the data about foreign origin might indicate the possibility of TB disease especially if a patient belongs to any of the risk groups for developing TB^{23, 24}.

While the overall male-to-female ratio of pulmonary TB in Serbia accounts for 2 : 1, when it comes to XPTB, the two thirds of the patients are female. We found similar findings in some other studies on XPTB¹⁵. In the study of XPTB in Cambodian refugees in Thailand, lymphatic tuberculosis was equally frequent among male and female children, but it was much more common among adult females than among adult males²⁵, suggesting that underlying genetic and maturational factors may impact on the expression of TB².

The results of our study also showed that XPTB was rare in children over the observed 15-year-period. This could be explained by systematic Bacille Calmette-Guerin (BCG) vaccination, mandatory in Serbia at birth, which has been

proved to protect the youngest from the most serious forms of TB and the TB related death²⁶.

Although recording and reporting of both pulmonary and XPTB through the pulmonary facilities network has a long-term tradition in Serbia, a possible underreporting may present a limitation of our study, which might affect incidence values. The retrospective character of a study represents limitation. The other limitation originates from the disease itself. XPTB can be difficult to diagnose and requires a high index of suspicion. Thus, it is possible that some of the cases remained not diagnosed and/or not reported over the observed period. Despite the possible limitations, our study showed significant increasing trend of XPTB with 8.9% annual increase.

Conclusion

To prevent, diagnose and treat XPTB in a timely manner, physicians should be aware of TB epidemiological situation in the world and in the local setting. The knowledge on TB risk factors, existing risk groups for TB, as well as the importance of proper recording and reporting of all the cases may contribute to better TB control and decrease TB related death.

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