# Tuberculosis Incidence in Elderly in Serbia: Key Trends in Socioeconomic Transition

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**Aim** To examine tuberculosis incidence rates among the elderly in Central Serbia in 1992-2006 period, which was characterized by socioeconomic crisis and migration of population.

**Methods** We analyzed all reported active tuberculosis cases in a 15-year period, especially among patients aged ≥65, according to the Annual Reports of the 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** Total tuberculosis incidence rates showed a slight but non-significant decreasing trend ($P = 0.535$), and no significant increase was found in patients aged ≥65 years ($P = 0.064$), with an average age-specific incidence rate for the elderly of 64.0 (95% confidence interval, 60.7-67.4). The increase was significant in patients aged ≥70 years ($y = 49.3549 + 2.1186x$; $P = 0.001$), both in men ($y = 62.8666 + 2.3977x$; $P = 0.005$) and even more prominently in women ($y = 39.8240 + 1.9150x$; $P < 0.001$). The proportion of tuberculosis cases in the elderly peaked in 2005, with 35% of all tuberculosis cases.

**Conclusion** High incidence rates and increasing time trend of tuberculosis in the elderly in Central Serbia is a serious problem, especially among those aged 70 years and over, who might present a target group for active case-finding of the disease.

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Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis complex*. It can affect persons of any age and involve any site in the body. The risk of developing tuberculosis depends both on the risk of being infected and the risk of developing the active form of the disease. The former depends on the tuberculosis prevalence in the community, whereas the latter depends on many genetic and environmental factors (1-3). A total of 8-10 million people worldwide develop active tuberculosis per year, while at least 1.7 million people die from this disease (4,5). In 1993, the World Health Organization declared tuberculosis a global problem. The main reasons for this are the dramatically increasing number of immune-deficient people in the world and the problem of multi-drug resistant tuberculosis (5,6). In Europe, two tuberculosis trends can be observed, one being a declining epidemic in the west and the other an increasing one in the east (4).

While human immunodeficiency virus (HIV) infection presents the greatest single risk factor for developing active tuberculosis, in countries with low HIV prevalence, other factors that decrease human immunity are of higher importance. All tuberculosis risk factors are more pronounced and even multiplied in patients belonging to tuberculosis risk groups, such as immigrants/refugees, prisoners, elderly in old-age homes, people with disabilities in asylums, and Roma populations in slums (3,7-9). Tuberculosis in the elderly is an increasing problem in many countries (4), because of age-related decline in immunity (1) and increasing longevity (10). While the latter happens predominantly in developed countries, the elderly in developing countries suffer from poverty, malnutrition and tobacco smoking, which are proven risk factors for tuberculosis (1,11,12). Thus, tuberculosis in the elderly is likely to be a lasting and even an increasing problem worldwide.

Serbia is a country with intermediate tuberculosis incidence rate (4,13,14). A molecular epidemiologic analysis, performed in Belgrade, showed a recent frequent transmission of tuberculosis (15). The national tuberculosis mortality data show peak numbers in the elderly (16,17). In the 1990s, Serbia faced socioeconomic crisis, civil war, and mass migration of population following disintegration of former Yugoslavia. We investigated whether tuberculosis in the elderly in Serbia increased in the 1992-2006 period.

## Methods

In this descriptive study, we analyzed annual data on diagnosed cases of active tuberculosis categorized by sex and age for the 15-year period. In the analysis, we used the proportion of notifications by age group and sex and notification rate of tuberculosis per population by age group.

We obtained age- and sex-specific morbidity figures from annual reports of the Research and Epidemiology Department of the Institute of Lung Diseases and Tuberculosis in Belgrade, which is the national referral institution for lung diseases, Central Tuberculosis Register, and National Report on Tuberculosis for the years 2005 and 2006 (13,14). The cases were divided into five-year intervals, and patients in 65-69 and ≥70 age groups were considered elderly.

Population estimates based on 1991 and 2002 census data with extrapolation were used for the calculations of tuberculosis incidence rates in the observed period.

Incidence rates were expressed as the number of tuberculosis patients per 100 000 population as generally accepted form in tuberculosis reporting (4). A regression line was fitted to the annual age specific incidence rates for ≥65-year- and ≥70- year-old population to determine the *P* value. We used the following for-

mula for linear regression to test trends: value on vertical axis = intercept +/− slope multiplied by value on horizontal-axis (y = a + bx). The trendline was fitted by the sum of least squares. For the estimation of regression coefficients, Statistical Package for the Social Sciences for Windows, version 16.0 (SPSS Inc., Chicago, IL, USA) was used.

## Results

The total average age-specific tuberculosis incidence rate for the elderly aged ≥65 during 1992-2006 in Central Serbia was 64.05/100 000 population (95% confidence interval [CI], 60.65-67.44): 79.87 (95% CI, 75.27-84.47) in men and 52.05 (95% CI, 48.91-55.19) in women (Figure 1).

The total tuberculosis incidence rate showed a slight, non-significant decrease in the observed period (y = 34.519-0.0882x; $R^2 = 0.030$, $P = 0.535$), and the rate in patients aged ≥65 years showed an increase, but without statistical significance, both overall ($P = 0.064$) and according to sex ($P = 0.137$ for men; $P = 0.079$ for women).

However, we found a significant increase in tuberculosis incidence rate in patients aged ≥70 (y = 49.3549 + 2.1186x; $P = 0.001$) (Figures 2 and 3). Total average age-specific tuberculosis incidence rate for the elderly aged ≥70 years in the period 1992-2006 was 66.30 (95% CI, 59.55-73.05) with average value of 82.05 (95% CI, 73.41-90.69) in men and 55.14 (95% CI, 49.13-61.16) in women.

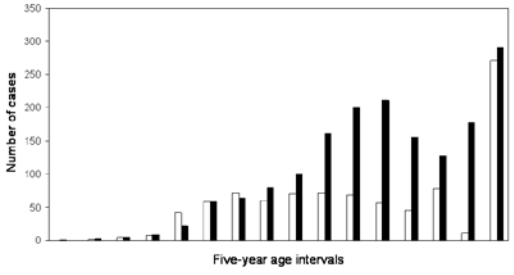


**Figure 1.** Tuberculosis distribution in Serbia in 2003 by sex and 5-year age intervals. Majority of tuberculosis patients were men in their 4th-6th decade of life. Closed bars – men; open bars – women.

The proportion of tuberculosis cases in patients aged ≥65 amounted to more than one-third of all tuberculosis cases in the observed period (peak value 34.8% in 2005). The increase in patients aged ≥70 ranged from 9.5% in 1992 to 30.7% in 2005 and 26% in 2006.

Tuberculosis incidence doubled in patients aged ≥70 years from 1992 to 2006 (Figure 4). Male-to-female ratio slightly decreased, being the highest in 1995 (1.81) and equal in the last year of the analysis. In three of 15 years of analysis (1997, 1999, and 2000), we found more female tuberculosis patients among patients aged ≥70 (Figure 5).

The comparison between time trends of tuberculosis incidence rates in men and wom-

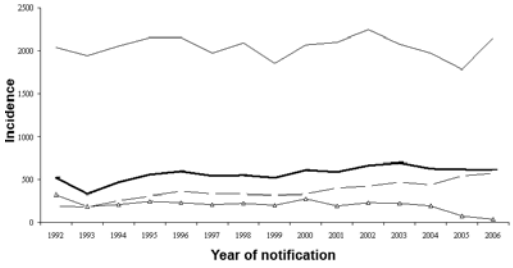


**Figure 2.** Incidence of tuberculosis in Central Serbia in all age groups and in the elderly, 1992-2006. Linear distribution of tuberculosis incidence showed a slight decrease in the number of all tuberculosis cases and patients aged 65-69, while there was an evident increase in patients aged ≥65, and especially in patients aged ≥70 (see Figure 3 for incidence rates). Thin line – all ages; thick line –≥65 years; dashed line –≥70 years; open triangles line – 65-69 years.

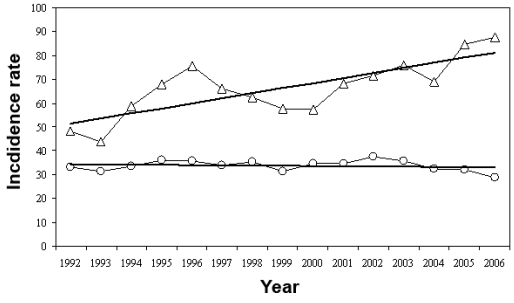


**Figure 3.** Comparison of time trends of tuberculosis incidence rates (No./100 000 population) in Central Serbia in all patients and patients aged ≥70 years in the period 1992-2006. Trend lines show a slightly decreasing time trend of tuberculosis incidence rates in all tuberculosis cases (y = 34.519–0.0882x; $R^2 = 0.030$; $P = 0.535$) and a significantly increasing trend in patients aged ≥70 (y = 49.3549 + 2.1186x; $P = 0.001$). In the elderly, incidence rate increased in the period 1993-1996 and 2000-2003 and decreased in the period 1996-1999, which correlated well with intensity of risk factors for tuberculosis infection and tuberculosis disease; open triangles – tuberculosis in aged ≥70 years; open circles – all tuberculosis cases.

en aged ≥70 showed that the increasing trend in women had higher significance level than in men ($y = 39.8240 + 1.9150x$; $R^2$: 0.622; $P < 0.001$ and $y = 62.867 + 2.3977x$; $R^2$: 0.473; $P = 0.005$, respectively; Figure 6).

## Discussion

The results of our study showed that total tuberculosis incidence rate in Serbia slightly decreased in the 1992-2006 period. Although the majority of patients with tuberculosis in Serbia were in the 40-60 age group, the peak incidence rate was in the oldest segment of the population. This is not surprising because many of co-morbidities that are risk factors for developing tuberculosis, such as diabetes mellitus and renal failure, occur more frequently in older than in younger patients and contribute to increased tuberculosis incidence in the elderly (1). Our results may also present an indicator of a successful national tuberculosis control program over decades (1,3,9). The most important risk factor for developing active tuberculosis in the elderly is considered to be the reactivation of the disease that had been acquired earlier (10). Thus, when tuberculosis is in decline, higher tuberculosis rates in the elderly reflect more intense transmission in these patients during their childhood and early adulthood (1,10). While in low-income countries tuberculosis notification rates still peak in young adults (1,18), industrialized countries usually report higher tuberculosis rates in the older population as a tail end of the past epidemic (10).

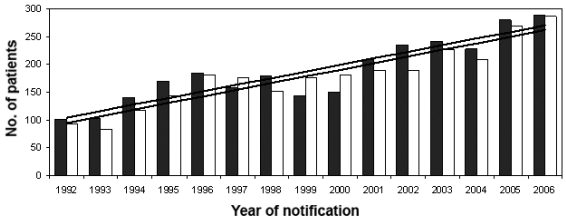


**Figure 4.** Tuberculosis incidence in Central Serbia in patients aged ≥70 by sex in the period 1992-2006. Tuberculosis incidence more than doubled over the 15-year study period in both men and women aged ≥70 (see Figure 5 for incidence rates). The number of affected women prevailed in 1997, 1999, and 2000. Closed bars – men; open bars – women.

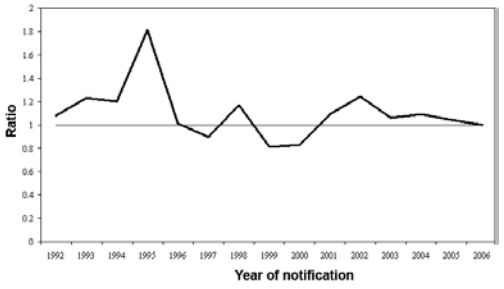


**Figure 5.** Male-to-female ratio in tuberculosis patients aged ≥70. The ratio showed slightly decreasing tendency being 1 (equal) in the last year of analysis. Thin line – value 1; thick line – male-to-female ratio.

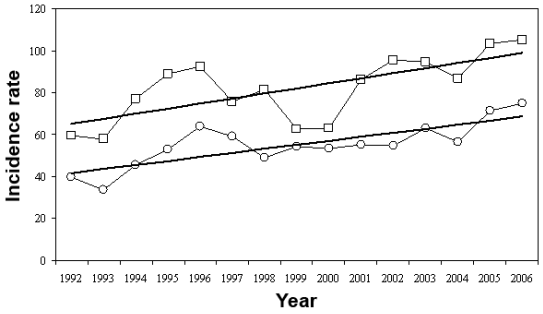


**Figure 6.** Time trend of tuberculosis incidence rates (No./100 000 population) in Central Serbia in patients aged ≥70 by sex,1992-2006. Comparison of increasing time trends of tuberculosis incidence rates between men and women aged ≥70 years showed higher level of significance in women ($P < 0.001$) than in men ($P = 0.005$). Open squares – men; open circles – women.

The results of our study also showed that tuberculosis incidence and incidence rate in the elderly in Central Serbia increased during 1992-2006 period, especially in the elderly aged 70 years and over. Increasing time trend in this age group suggests that the risk of disease is increasing in the cohort. Indeed, in the studied period Serbia went through a difficult socio-economic crisis, which created a fertile ground for the development of many tuberculosis risk factors, leading both to a higher risk of infection and a higher risk of developing the active form of the disease (9,12). Worsening of the economic crisis during the 1990s and widespread poverty, with the highest hyperinflation ever (12), mostly affected the elderly. Poverty is strongly associated with tuberculosis incidence (19,20), and stress and malnutri-

tion are also well known risk factors for developing tuberculosis (1).

In general, age-specific incidence of tuberculosis varies greatly over time within and between countries (1). In the United Kingdom, tuberculosis in population aged ≥65 increased from 13% to 16% between 1991 to 2001 and was projected to increase to 23% by 2031 (10), while in our population it was already 25% in 1992 and peaked to almost 35% in 2005. The increase in the proportion of tuberculosis in the aged ≥70 in our study was even more evident. In this group, the incidence rate in men was almost 3-fold higher than the total average incidence rate.

In Serbia and worldwide, tuberculosis notification rates are about twice higher among men than among women (1,13,14). However, patients aged ≥70 in our analysis were an exception. Male-to-female ratio in this age group was not only lower than expected, but showed a decrease over the 15-year period. Moreover, we found that in three of the 15 studied years female tuberculosis incidence prevailed, while the both sexes were equal represented in 2006. An explanation for this could be the traditional organization of family life in Serbia, which in times of economic crises placed greater responsibility and stress on women than on men (21). A possible impact of extrapulmonary tuberculosis cases, which are found to be more frequent in women, should not be completely neglected, although the rates of extrapulmonary tuberculosis in Serbia are actually small (13,14).

Cough is one of the most common symptoms of pulmonary tuberculosis (3,22). However, cough is also a common symptom in smokers and elderly patients with a variety of pulmonary and cardiac diseases. Undetected pulmonary tuberculosis patient, whose cough can be explained by other co-morbidities, may be a potent source of tuberculosis infection, especially for the close contacts (23). Education on tuberculosis symptoms in the population may greatly contribute to the prevention of tuberculosis spread within the community (24). A recent study has shown that knowledge about tuberculosis was not satisfactory in the general population of Serbia and that one of the strongest predictors of misconceptions was older age (25).

Our study had several limitations, including the possible underreporting of tuberculosis cases. Serbian national anti-tuberculosis program was established in 1952, following the recommendations of the World Health Organization and regularly improved thereafter. The recording and reporting system was its important part with a long-term tradition (3,9). This is why we assume the data were a good approximation of all active tuberculosis cases in Serbia. Although it is possible that there were unreported tuberculosis cases in the study period, there could not have been many of them and this could not have significantly affected the incidence values. However, the last two years of the analysis are based on individual data only and these showed a lower tuberculosis incidence compared with collective data over time. So, underreporting seems to be more probable in the last two years. Since we found constant increase of tuberculosis incidence in the elderly in the 15-year study period, possible underreporting in the last two years would make our results even more convincing.

Healthcare workers' continuous medical education and awareness on tuberculosis are necessary to increase tuberculosis detection rate and contribute to proper treatment (26). Active case-finding of tuberculosis in risk groups contribute to the global plan of stopping tuberculosis and the results of our study appoint to a possible target group, which might be included in such screening programs for tuberculosis.

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