

# Epidemiological Patterns of Tuberculosis in Croatia in the Period 1996–2005

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## ABSTRACT

*The last comprehensive publication on tuberculosis in Croatia and the earliest impact of war, besides the yearly routine reports, was done in 1996 in Croatian. We were, therefore, interested to explore incidence trends and to highlight the early post-war tuberculosis epidemiological patterns in the next ten years period (1996–2005). A retrospective analysis of epidemiological data on all registered tuberculosis cases in Croatia searching the databases of 21 Croatian Public Health Institutes and the National Tuberculosis Registry was made. During the study period, the total tuberculosis incidence rates in Croatia dropped from 45 to 25.8/100 000 inhabitants. The average highest age-specific rates were recorded in the age group  $\geq 65$  years being in decrease in all age groups. Paediatric cases (0–14 years) represented 4.5% of all cases. Tuberculosis cases among males were recorded in 64% cases, and 83.6% were indigenous population. Tuberculosis was bacteriologically confirmed in 67.7% cases. A low proportion of drug resistance (3.3%) was recorded. During 1985–2005, 56 tuberculosis cases among 242 AIDS cases were reported. Tuberculosis mortality showed a decreasing trend ( $p < 0.001$ ). However, tuberculosis has still had the highest mortality rates among infectious diseases in Croatia. Despite the War chain of events and tuberculosis programmatic changes, tuberculosis incidence rates in Croatia have been decreasing but they are still far away from national target, incidence rate of 10/100 000 declared in 1998 and much higher than in European Union and Western Europe. Tuberculosis among children, resistance to tuberculosis drugs and HIV prevalence, significant problems in many European countries, have not caused problems in tuberculosis control in Croatia. This favourable epidemiological situation must be kept and improved through strengthened tuberculosis control measures.*

**Key words:** Croatia, tuberculosis, epidemiology, incidence

## Introduction

Tuberculosis (TB), a disease estimated to be as old as the humanity, even today in the third millennium, represents an important global public health problem. We all face the devastating statistics related to tuberculosis impact on the human well-being<sup>1</sup>. More than ever, the mankind has been united to stop TB today.

Croatia, a TB middle incidence country, has been included in international efforts for successful global TB control. Croatia is an European Union (EU) candidate member state with 4.4 million inhabitants, divided in 21 counties. At the beginning of the 1990s, the disintegra-

tion of the former Yugoslavia lead to a war in the region, especially in Croatia, with consequences in lives lost, migration, damaged economy and political changes. Under these difficult circumstances, antituberculosis dispensaries were shut down in 1993 and the National TB Control Programme (NTP) was created. It has been based on primary health care physicians at the first level, hospital physicians at the second level and the National Council for TB control at the third level. It was a dramatic programmatic change during grave war chain of events and many actors were not adequately prepared to take new

responsibilities. In order to facilitate the implementation of NTP, new National guidelines on TB control were published in 1998<sup>2</sup>.

The last comprehensive publication on TB in Croatia and the earliest impact of war, besides the yearly routine reports, was done in 1996 in Croatian<sup>3</sup>. We were, therefore, interested to explore incidence trends and to highlight the early post-war TB epidemiological patterns in the next ten years.

### Subjects and Methods

The data of all registered TB cases in Croatia were collected from Epidemiology Services of 21 county Public Health Institutes and from the National TB Registry. The study period was January 1<sup>st</sup> 1996 to December 31<sup>st</sup> 2005. According to the Code of Infection Diseases Population Protection, all TB cases are subject to mandatory reporting to the Epidemiology Units of Public Health Institutes. Accompanying this notification is a supplemental questionnaire with additional data on each patient. We evaluated both sources of TB data covering demographic data, type of TB case, precise localisation, medical risk factors, bacteriology results, and drug susceptibility testing results. Since 1998, a mandatory notification system has included a dual- physician and laboratory notification. A TB case was defined according to the national guidelines based on the WHO case definition<sup>2</sup>.

The official death statistics was the source of mortality<sup>4</sup>. The incidence and mortality rates were calculated based on 1991 and 2001 census data<sup>5</sup>. Annual percentage changes in incidence rates were calculated as the percentage difference between the rates of two successive years and as the mean of changes over the period observed. Expected trends of decrease of annual incidence and mortality rates were investigated using regression analysis. A p value of less than 0.05 was accepted as indicating statistical significance.

Analysis was performed using Epi-Info version 5.0, 1990 (Centres for Diseases Control, Atlanta, GA) and SAS procedure PROC REG, 2007 (SAS Institute IncCary, NC).

The present study did not require the approval of an Ethics Committee.

### Results

In total, 16 654 TB cases were identified during the 10-year period. Total TB incidence rates in Croatia decreased significantly, with estimated yearly decrease of 2 *per* 100 000 ( $p < 0.001$ ) and it dropped from 45 to 25.8. An overall incidence of TB was 36 *per* 100 000. The mean percentage of annual changes was -5.7%. Cases among males represented 64% of all TB cases (overall M:F ratio was 1.8). Average TB incidence rates in males and females were 48 and 25 *per* 100 000, respectively.

Lung was the most common disease site (nearly 90% of cases). Decreasing trend in the incidence of TB cases

with a pulmonary site was observed ( $b = -1.939$ ,  $p < 0.001$ ), as well as in the incidence of extrapulmonary cases ( $b = -0.116$ ,  $p = 0.04$ , Figure 1).

The most common site of extrapulmonary tuberculosis (EPTB) was pleura (55%) with other sites being less frequent.

The highest percentage of all TB cases (28.4%) and the average highest age-specific rates (77 *per* 100 000) were recorded in the age group  $\geq 65$  years (Table 1).

Over the period observed, age-specific rates have been decreasing in all age groups, especially in the age group  $\geq 65$  years (Figure 2).

Paediatric cases (0–14 years) represented 4.5% of all TB cases. BCG vaccine coverage of newborns in Croatia was 95.8–98.9%, on average 97.7%. With mandatory im-

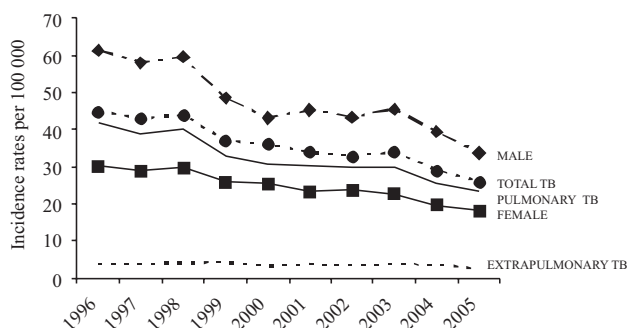


Fig. 1. TB incidence rates total, by sex and disease site in Croatia, 1996–2005; T – tuberculosis.

TABLE 1  
SELECTED CHARACTERISTICS OF PATIENTS WITH TUBERCULOSIS (N=16 654)

Sex:	N (%)
Female	5 944 (35.7)
Male	10 710 (64.3)
Age group (years) :	
≤14	753 (4.5)
15–24	1 241 (7.4)
25–34	1 708 (10.3)
35–44	2 875 (17.3)
45–54	2 924 (17.5)
55–64	2 425 (14.6)
≥65	4 728 (28.4)
Origin total :	10 624
Native	8 886 (83.6)
Foreign born	1 738 (16.4)
Type of case:	
New	15 261 (91.6)
Retreated	1 393 (8.4)
Disease site:	
Pulmonary	14 985 (90)
Extrapulmonary	1 669 (10)

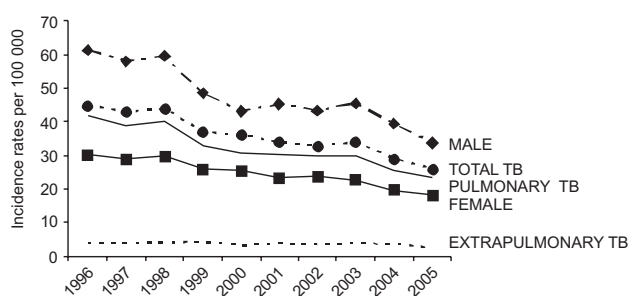


Fig. 2. Age-specific tuberculosis incidence rates in Croatia, 1996–2005.

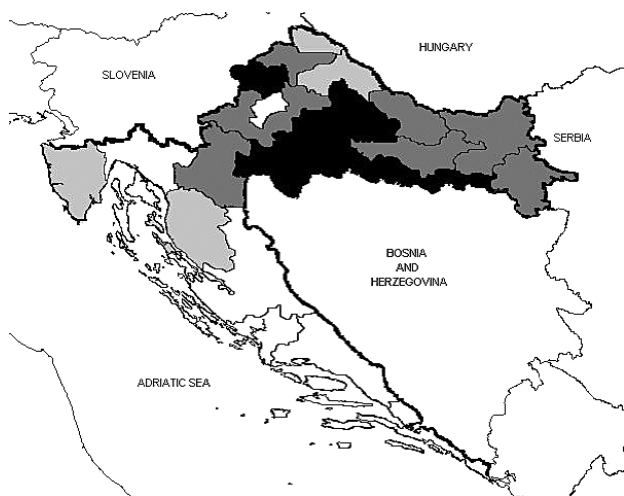


Fig. 3. Average tuberculosis incidence rates among counties in Croatia, 1996–2005. White – incidence rates <30/100 000, Light gray – incidence rates 31–40/100 000, Dark gray – incidence rates 41–50/100 000, Black – incidence rates >51/100 000.

munization, the number of TB meningitis and millitary TB among children younger than 14, was reduced to only 5 and 4 cases in 10 years.

Indigenous population accounted for the majority of our TB cases (83.6%) while 16.4% were foreign born.

Of all cases, 91.6% were new cases (Table 1). The incidence rates of retreated cases were stable during the overall period ( $p=0.28$ ), while the incidence of new TB cases decreased from 43 to 23 *per* 100 000 ( $b=-1.996$ ,  $p<0.001$ ).

Sizeable variations in incidence were clearly evident between northern and southern Croatian counties. The geographical distribution of tuberculosis in Croatia showed considerably higher morbidity rates in the northern parts of the country, ranging from 18 in Dubrovacko-Neretvanska County in the South to 62 *per* 100 000 in Brodsko-Posavska County in the North (Figure 3).

According to the data from 11380 (68% of total TB cases) collected supplemental questionnaires, 27.7% of those TB cases had suffered from some additional disease or medical condition.

Sputum smear positivity was recorded in 43.9% cases with the average case notification rate of 10.8 *per* 100 000. Bacteriological tests were performed for 98% of all cases and 67.7% or 11 280 cases were bacteriologically confirmed. Drug Susceptibility Test (DST) was requested in all patients with a positive culture and it is recorded in supplemental questionnaires. According to the data from supplemental questionnaires, we notified 8023 DST results. During the period 1996–2005, Croatia had a low proportion of drug resistance (3.3%), and 60 cases (0.7%) were multidrug resistant (defined as resistance to at least isoniazid and rifampicin).

During 1986–2005, 56 TB cases among 242 AIDS cases were reported in Croatia. During the study period, TB mortality showed a decreasing trend ( $b=0.164$ ,  $p<0.001$ ). Registered TB mortality rates were in the range 2.5–4.7, with the average rate of 3.7/100 000. The average ratio of TB deaths to TB notification was 0.1.

## Discussion

The TB incidence and mortality rates showed a permanent decline during the period 1996–2005. TB notification system and official death statistics, as well as the quality of data remained relatively stable during the study period. The trends observed in this study reflected an objective situation in Croatia. As opposed to other European countries, the epidemiological patterns of tuberculosis in Croatia showed some distinctive features.

The annual incidence in Croatia decreased progressively, but is still higher than in EU and countries from Western Europe (WE). An incidence rate of 25.8/100 000 and 1114 cases were notified in 2005. In that year, the incidence rates in the Scandinavian countries, as well in many EU countries (Luxembourg, Italy, France, Germany), were 6–8 *per* 100 000<sup>1</sup>. The reason for this higher incidence, in comparison with selected developed European countries, and despite a favourable regression trend, probably lies in the fact that TB epidemic in Croatia started at the beginning of 19<sup>th</sup> century – one hundred years later than in WE – with the peak at the turn of 19<sup>th</sup> century. Age groups with the highest incidence rates (over 65 years) were born in the period from 1920 to 1940 when TB incidence rates were 508 *per* 100 000. The same age groups are still an important reservoir of infection and the reason for relatively high morbidity nowadays. In addition, Croatia had after World War II intensive immigration from other parts of the former Yugoslavia, where TB incidence was very high<sup>2,6</sup>. After 1955, when 20 000 new cases were registered in Croatia, the number of TB cases has been in decrease<sup>3</sup>. However, the War in Croatia stopped the regression trend of TB, although the incidence rate was not increased<sup>3</sup>. Since 1999, for the first time after stagnation, till today incidence rates have been dropping despite the war in the region and the problems related to the implementation of NTP.

During the study period, other ex-Yugoslavia countries faced increased or levelled off incidence, except Slovenia<sup>1,6,7</sup>. In the countries in Eastern Europe, which

have been facing similar socioeconomic and political changes after the break-up of the former Soviet Union (FSU), TB incidence showed an increasing trend<sup>1</sup>. It was explained by poor TB control, socioeconomic decline and substandard health services<sup>8</sup>. On the contrary, after initial adaptation to new NTP in Croatia during the war and early post-war period, TB control activities have been developed, continuing anti-tuberculosis dispensary activities, in terms of both prevention and treatment. Croatian NTP has been marked by widely available TB laboratory services, free of charge TB drugs with uninterrupted supply of first line drugs, high obligatory BCG vaccination coverage and longstanding and reliable TB notification system. DOTS (directly observed treatment short-course) implementation has been the highest NTP priority, as well as advocacy, communication and social mobilisation, an integral part of the new WHO Stop TB Strategy<sup>9–13</sup>.

The age patterns of Croatia's TB cases corresponded to that of developed countries, with the incidence being the highest at the oldest age, resulting probably from a reactivation of an old infection. In more than 28% of all TB cases patients were aged over 65, which is significantly different from the Central and Eastern European region (15% vs. 7%)<sup>14</sup>.

A low proportion of drug-resistant and multidrug resistant tuberculosis (MDR-TB) was notified during the period observed (3.3% and 0.7%). According to the last WHO survey, the estimated proportion of MDR-TB is 5% of all new cases worldwide, with the highest proportion in the countries of FSU (up to 22.3%)<sup>15</sup>. No case of extensively resistant tuberculosis (defined as resistance to isoniazid, rifampicin, any fluoroquinolone, and at least one of three injectable second-line drugs: amikacin, kanamycin, or capreomycin), estimated to be a global emergency, has been reported in Croatia so far. Opposite to other countries, drug resistance has not been a significant threat to tuberculosis control in Croatia.

Croatian Laboratory Tuberculosis Network has been based in 14 laboratories, 8 of which have been performing DST, a mandatory test for each positive culture. All TB laboratories have been from 1995 participating in the external quality control scheme of the sensitivity test to antituberculars. Croatian Mycobacterium Reference Laboratory (NRL) has been supervised by Mycobacteria Reference Laboratory from Borstel, Germany, and in 2007 the NRL was nominated as one of the WHO controlled TB Supranational Reference Laboratory Network. The national external quality assurance scheme covered all laboratories performing DST. However, the data on DST applied only to 71.1% of bacteriologically confirmed TB cases, due to incomplete data aggregation from supplemental questionnaires with DST results.

HIV/AIDS situation has been monitored in Croatia since 1986 when the first AIDS cases were documented. During 1986–2005, TB was reported in, on average, 1.1% of AIDS cases, annually. Opposite to Croatia, the proportion of HIV-positive TB cases showed considerably higher rates in the EU and WE (15.4% Portugal, 6.4%

France, 5.3% The Netherlands) as well as in Estonia and Latvia, where the spread of HIV is more recent than in the WE<sup>13</sup>. Croatia had a low-level HIV epidemic with 8.4% HIV-infected patients per 1 million, partly as a result of many years of primary and secondary prevention efforts. It is estimated that the relatively low number of HIV-positive patients probably has no significant impact on tuberculosis epidemiology in Croatia<sup>2</sup>.

Differences in TB incidence rates among regions in Croatia are long-standing. It has been postulated that climatic conditions during cold months could facilitate TB transmission, particularly in overcrowded and poorly ventilated conditions. The higher incidence in northern parts of the country may be attributed to continental climate with cold winters and increase of indoor activities in opposite to southern counties with mediterranean climate with very mild and sunny winters<sup>16</sup>. Another explanation probably came from recent war and post-war migration, more common in the counties across the border with Bosnia and Herzegovina which had the highest TB incidence rates in ex-Yugoslavia<sup>2,7</sup>.

Furthermore, in the EU and WE, 20% cases were of foreign origin. Croatia's TB cases of foreign origin were represented in a similar proportion of cases (16%) in the period observed. In contrast to the EU and WE, where immigrants came from Africa and Asia<sup>14,17–19</sup>, TB cases of foreign origin in Croatia came mainly from one neighbouring country, Bosnia and Herzegovina, which had the highest incidence rates in the former Yugoslavia<sup>7</sup>. During the recent wartime in Croatia, TB cases among the refugees from the neighbouring countries were added to total Croatian TB cases. However, because the portion of the refugees and foreign nationals become Croatian citizens, it was no longer possible to monitor TB morbidity among them at a national level. Consequently, in order to somehow register TB in this population category, »born outside Croatia« was introduced into the TB surveillance system.

A decrease was noticed in the proportion of cases of foreign origin from 18 to 8.8% during the study period, reflecting, probably, a downward trend of migration due to the War. This trend in notification over time differed markedly from EU countries where the proportion of cases of foreign origin has been increasing<sup>17–19</sup>. Other countries from the Central or Eastern Europe showed no foreign-born or foreign citizen TB cases<sup>14</sup>.

The low frequency of extrapulmonary tuberculosis (EPTB) in Croatia (less than 10%), compared to the EU and WE (20%) could be attributed to the low frequency of HIV/AIDS cases in Croatia. Serbia also reported a low frequency of EPTB (6%)<sup>6</sup> but unlike the Serbian notification system, pleura, the most common site of EPTB in Croatia, was registered within the EPTB according to national case definitions.

A decline and low levels in notification rates in paediatric cases in the study period suggested a decreasing level of transmission in the general population, as notified in the EU and WE<sup>14</sup>. Low incidence rates of disseminated forms and tuberculous meningitis in children un-



der 14, reflected a longstanding and successful mandatory immunization with the BCG vaccine, introduced in 1948.

As opposed to numerous Eastern European countries, which faced increasing TB mortality since 1990, TB mortality in Croatia continuously decreased during the period observed, with a low death-to-notification ratio. It may be explained by early treatment, uninterrupted supply of TB drugs, low drug resistance or low effect of HIV co-morbidity. However, tuberculosis has still had the highest mortality rates among infectious diseases in Croatia<sup>4</sup>.

## Conclusions

Despite the War chain of events and TB programmatic changes, TB incidence rates in Croatia have been

decreasing but they are still far away from national target, incidence rate of 10/ 100 000 declared in 1998 and much higher than in EU and WE. TB among children, resistance to TB drugs and HIV prevalence, significant problems in many European countries, has not been the problems in TB control in Croatia. This favourable epidemiological situation must be kept and improved through strengthened TB control measures.

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## EPIDEMIOLOŠKE OSOBITOSTI TUBERKULOZE U HRVATSKOJ OD 1996. DO 2005. GODINE

### SAŽETAK

Zadnji iscrpni rad o tuberkulozi u Hrvatskoj i najranijim posljedicama rata, osim rutinskih godišnjih izvješća, je objavljen 1996. godine na hrvatskom jeziku. Stoga je cilj ovog rada bio pokazati kretanje incidencije tuberkuloze i procijeliti njenu epidemiološku pojavnost u slijedećem desetogodišnjem razdoblju (1996.–2005.). Napravljena je retrospektivna analiza svih slučajeva tuberkuloze u Hrvatskoj koji su registrirani u županijskim Zavodima za javno zdravstvo kao i Nacionalnom registru tuberkuloze. Za vrijeme razdoblja istraživanja, ukupna incidencija tuberkuloze u Hrvatskoj je pala sa 45 na 28,5 na 100 000 stanovnika. Najviše dobnog specifične stope incidencije zabilježene su u u skupini  $\geq 65$  godina i bile su u opadanju u svim dobnim skupinama. Tuberkuloza među djecom (0–14 godina) je prijavljena u 4,5 % slučajeva. Od ukupnog broja oboljelih, 64% su bili muškarci. Većina slučajeva tuberkuloze (83,6%) zabilježena je među autohtonim stanovništvom. Tuberkuloza je bila bakteriološki potvrđena u 67,7 % oboljelih. Zabilježen je nizak udio tuberkuloze rezistentne na antituberkulotike (3,3% oboljelih). U razdoblju od 1986. do 2005. godine, među 242 oboljelih od AIDS-a, prijavljeno je 56 oboljelih od tuberkuloze. Bez obzira što je u promatranom razdoblju smrtnost od tuberkulo-

ze imala silazni trend ( $p < 0,001$ ), ona je imala najveću smrtnost među oboljelima od zaraznih bolesti u Hrvatskoj. Usprkos ratnim događanjima i promjenama sustava nadzora nad tuberkulozom u Hrvatskoj, stope incidencije od tuberkuloze su bile u padu, ali su bile daleko od nacionalnog cilja postavljenog još 1998. godine (stope incidencije od 10/100 000 stanovnika) i daleko više nego u Europskoj zajednici i zemljama zapadne Europe. Tuberkuloza među djecom, rezistencija na antituberkulotike i prevalencija zaraženih HIV-om, značajni problemi u mnogim europskim zemljama, nisu predstavljali problem u nadzoru nad tuberkulozom u Hrvatskoj. Takva povoljna epidemiološka situacija mora se očuvati i dalje unaprijeđivati kroz pojačane mjere nadzora nad tuberkulozom.