

Epidemiology of *Mycobacterium tuberculosis* infection in Pavia province, Lombardy, Northern Italy, 1998-2013

Elisa Fronti¹, Marco Vecchia², Luigia Scudeller³, Liliana Praticò⁴, Piero Marone⁵, Alba Muzzi⁶, Lorenzo Minoli², Elena Seminari²

¹UO Malattie Infettive, Ospedale Guglielmo da Saliceto, Piacenza, Italy;

²Clinica di Malattie Infettive, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;

³Direzione Scientifica, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy;

⁴Divisione Universitaria di Malattie Infettive e Medicina Tropicale, Spedali Civili di Brescia, Italy;

⁵SC Virologia e Microbiologia, Fondazione IRCCS Policlinico San Matteo, Pavia Italy;

⁶Direzione Medica di Presidio, Fondazione IRCCS Policlinico San Matteo, Pavia Italy

SUMMARY

This study investigated the epidemiology of tuberculosis in the last 16 years in the province of Pavia, Lombardy, Northern Italy. The objective was to evaluate the clinical pattern of tuberculosis in immigrant groups compared with Italians in an observational retrospective study conducted from 1998 to 2013.

In all, 615 tuberculosis cases were admitted, 354 males (57.3%), median age 47-years, 425 (69.1%) Italian-born patients, 190 (30.9%) immigrants. The ratio between the immigrant group and the Italian-born group of patients increased from 1.7% to 54.5% in the study period ($p=0.001$). HIV was the most common comorbidity, affecting 48 patients (7.8%), followed by diabetes in 35 (5.7%) and COPD in 30 (4.9%). The overall admission-associated mortality was 5.5%. Italian-born patients were older than non-Italian born subjects and had at least one comorbidity, 162 (38.1%) and 22 (11.6%), respectively ($p<0.0001$). Mortality was increased among Italian-born compared with non-Italian-born patients (7.3% versus 1.6%, $p=0.004$). No significant variation in extra-pulmonary tuberculosis (EPTB) prevalence occurred. Considering specific form of EPTB, HIV infection was associated with an increased risk of EPTB (RR 2.02, 95%CI 1.09-3.74, $p=0.026$). There was a high risk of tuberculosis among immigrants, whereas a decreasing trend was consistently observed among Italian-born patients. Italian-born patients show a higher tuberculosis-associated mortality risk due to older age and comorbidities.

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INTRODUCTION

The prevalence of tubercular disease in Italy has been declining over the last few decades, but this trend could change in the near future (La tubercolosi in Italia Rapporto 2008). On the one hand, immigration is growing fast in Italy and immigrants usually come from high-incidence countries where the clinical presentation of tuberculosis does not overlapping the European one (Sandgren *et al.*, 2013). On the other hand, longer life expectancy has led to an increased number of older people, often with chronic diseases associated with a variable degree of immunodeficiency (García-Rodríguez *et al.*, 2011).

While the trend in the incidence of pulmonary tuberculosis (PTB) is decreasing in western countries, the incidence of extrapulmonary (EPTB) forms is stable, producing a relative rise in the latter form (García-Rodríguez *et al.*, 2011; Kruijshaar *et al.*, 2009). In recent literature, some authors compared a population living in a northern Eu-

ropean country or North America with non-Caucasian groups, finding a higher incidence of EPTB among the latter (Peto *et al.*, 2009; te Beek *et al.*, 2006).

The Italian population is characterised by geographical and historical features of a genetic pedigree closer to the Mediterranean population than the population living in central or northern Europe. In addition, immigration in Pavia province, located in Northern Italy, mainly comprises people coming from eastern Europe where the Caucasian race is highly represented.

The aim of this study was to analyse the epidemiology of tuberculosis in the last 16 years in the province of Pavia, highlighting the clinical picture of the disease among immigrant groups compared with Italian-born subjects.

STUDY POPULATION AND METHODS

This is an observational retrospective study designed to evaluate the epidemiology, clinical pictures and risk factors of tuberculosis in patients who were admitted to the Fondazione IRCCS Policlinico San Matteo Hospital in Pavia between 1st January 1998 and 31st December 2013.

According to local ethical review board instructions, on hospital admission all patients signed an informed consent form for inclusion in observational studies, with anonymised data extraction, carried out at Fondazione IRCCS Policlinico San Matteo.

Key words:

Pulmonary infection, Immigrants, Extra-pulmonary tuberculosis, Diabetes, HIV coinfection.

Corresponding author:

Elena Seminari

E-mail: e.seminari@smatteo.pv.it

Diagnosis codes obtained through administrative data (international classification of disease ICD-10) were utilized to identify patients with PTB (010-011-012) and EPTB (013-014-015-016-017). Risk factors associated with tuberculosis were identified with the diagnosis code. Data on age, gender, country of origin, resistance to anti-tuberculosis drugs, duration of hospital stay and disease localization were also collected. All cases were microbiologically confirmed. Outcome was divided into two categories: discharged alive or deceased.

Since all the patients were admitted to San Matteo Hospital, a third-level facility and referral centre for tuberculosis diagnosis and treatment, we can assume that the analysis includes the vast majority of the cases in the province of Pavia. Using the data available on the ISTAT (Italian National Statistics Institute) website, the incidence of tuberculosis in the Italian population and in the immigrant population living in Pavia province was estimated.

Immigrants were subsequently divided according to the WHO world region map (definition of region grouping) into six world regions: African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region.

Analysis

Data are reported as medians (1-3 IQR). Student's t-test or ANOVA test were used to analyse normally distributed variables (2 groups or more than 2 groups, respectively), Mann-Whitney test or Kruskal-Wallis test were used to analyse variables with asymmetrical distribution (2 groups or more than 2 groups, respectively). Chi-square test and Fisher's exact test were used to compare categorical variables. Features of the Italian patients and the immigrant patients were compared. The chi-square test was used to evaluate the incidence trend of tuberculosis in the years. Two-sided tests were used, a P-value was considered significant if less than 0.05. Logistic regression was used to evaluate variables associated with mortality (Italian origin versus non-Italian origin and number of comorbidities) and differences in clinical presentations (PTB was considered an independent variable, while age, gender and ethnic group -according to WHO world region map- dependent variables). Analyses were performed using STATA 13.

RESULTS

In the study period, 615 cases of tuberculosis were admitted to our Hospital, 354 patients were male (57.3%), median age was 47.3 years (30.3-67.2), 425 (69.1%) were Italian-born patients, 190 (30.9%) were immigrants.

The average population in Pavia province between 2001 and 2013 (ISTAT) was 525,351 citizens, with an average number of 37,933 immigrants.

The cumulative incidence of tuberculosis in the population of Pavia province was 7.42 cases/100,000 inhabitants per year. These data were confirmed by the Italian epidemiology database (<http://www.salute.gov>) where the cumulative incidence of tuberculosis was estimated at 7.41 cases/100,000 people per year. The cumulative incidence in the Italian group was 5.4 cases/100,000 per year and the incidence among the immigrant group was 33.4 cases/100,000 people per year. The ratio between the immigrant group and the Italian-born group of patients increased from 1.7% to 54.5% in the 16 years of analysis ($p=0.001$) (Fig. 1).

In the immigrant group of patients, 85 (44.7%) were from Europe, 39 (20.5%) from Africa, 27 (14.2%) were from Central or South America, 19 (10%) from the Eastern Mediterranean region, 10 (5.3%) from South-East Asia and 10 (5.3%) from the Western Pacific area (Fig. 2).

The incidence of the comorbidities showed that HIV was the most common, observed in 48 patients (7.8%), followed by diabetes in 35 patients (5.7%), COPD in 30 patients (4.9%), solid organ cancer in 22 patients (3.6%), chronic liver disease in 21 (3.4%), CKD in 15 (2.4%), hematological malignancies in 7 (1.1%) and rheumatic diseases in 5 (0.8%) patients.

Overall admission-associated mortality was 5.5%.

Resistance to at least one drug was detected in 138 patients (22.4%) (99 of them were Italians and 38 were immigrants), the difference between the two groups was not significant (20.5% versus 23.3% $p=0.5$). In particular, resistance to streptomycin was detected in 63 cases (33.2%), to isoniazid in 46 (24.2%), rifampin in 18 cases (9.5%), ethambutol in 10 (5.3%), and pyrazinamide in 59 (31.1%). During the study period 9 cases of MDR tuberculosis (resistance to isoniazid and rifampin) were diagnosed and 3 XDR cases (resistance to isoniazid, rifampin, fluoroquinolones and aminoglycosides). Six MDR strains were from

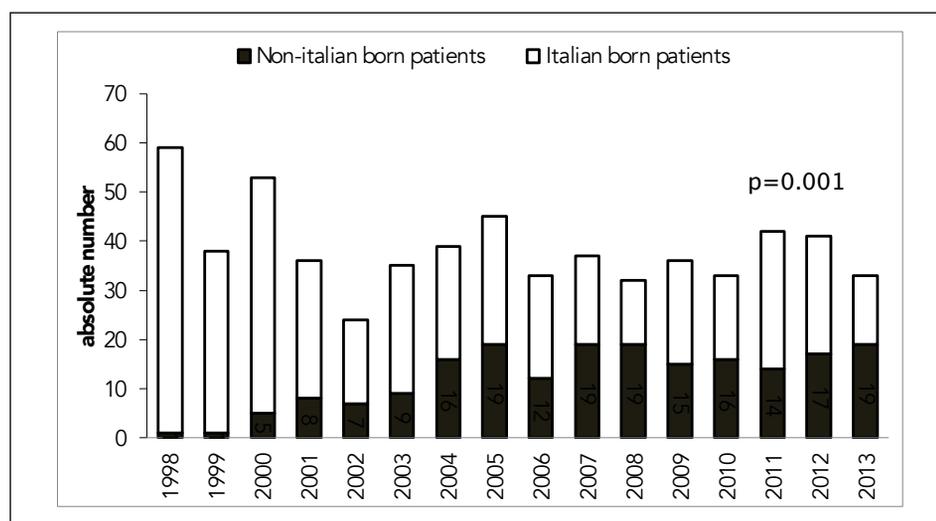


Figure 1 - Absolute cases of tuberculosis among Italian-born and non-Italian born patients in Pavia province.

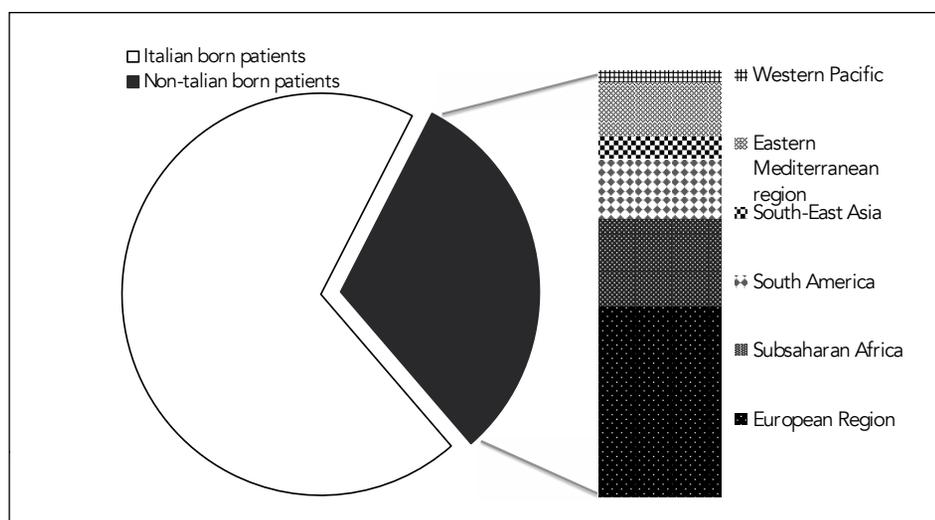


Figure 2 - Geographical provenience of immigrants with tuberculosis resident in Pavia province.

Italian patients, and 2 out of 3 XDR strains were from Italian patients.

Epidemiology of TB in the Italian-born patients and immigrant patients

The main characteristics of Italian-born and immigrant patients are shown in *Table 1*. The Italian-born patients were older than the immigrants ($p < 0.001$). Having at least one comorbidity was more common among Italian than immigrant patients, 162 (38.1%) and 22 (11.6%), respectively ($p < 0.0001$). In particular, diabetes, cancer, COPD, HIV and liver disease were the commonest pathologies associated with TB in Italian-born patients. This difference was statistically significant for each comorbidity analysed, except for HIV infection and rheumatic diseases. At multivariable analysis, mortality increased with the number of copathologies (RR 1.6, 95% CI 1.15-2.34, $p = 0.007$) and among Italian-born compared with immigrant patients (RR 3.8, 95% CI 1.1-12.9, $p = 0.032$).

Characteristics of TB localizations (PTB and EPTB) among patients belonging to WHO world regions

PTB was diagnosed in 450 (73.2%) cases and EPTB in 165 (26.7%) distributed as follows: 29 (17.6%) central nervous

system, 9 (5.5%) intestines, peritoneum and mesenteric glands, 30 (18.2%) bones and joints, 18 (10.9%) genitourinary system, 69 (41.8%) lymph nodes and 10 (6.1%) disseminated miliary tuberculosis (*Table 2*). In the time span between 1998 and 2013 no significant variation in EPTB prevalence occurred. A comparison between PTB and EPTB patients is shown in *Table 2*. Median age was 47 years for both groups, chronic comorbidities were uniform in both groups.

Considering the specific form of EPTB, HIV infection was associated with an increased risk of EPTB (RR 2.02, 95% CI 1.09-3.74, $p = 0.026$). In particular, the risk of central nervous system TB was increased in HIV-positive patients (RR 6.3, 95% CI 2.7-14.8, $p < 0.0005$) as well the risk of abdominal TB (RR 6.2, 95% CI 1.5-25.8, $p = 0.01$). The risk of tuberculosis of the genitourinary system was increased in patients with CKD (RR 9.75, 95% CI 2.5-38.2, $p = 0.001$).

Mortality was not different for PTB and EPTB in general (4.7% vs 8.1%, $p = 0.115$), whereas it was increased in case of CNS TB (31%, $p < 0.0001$).

Patients from different regions were compared to evaluate differences in TB localizations. The risk of EPTB was considerably lower among the Non-Italian European than the Italian-born population (RR 0.34, 95% CI 0.16-0.7,

Table 1 - Patient characteristics.

	Total cases (%)	Italians (%)	Immigrants (%)	p-value
N	615	425 (69.1)	190 (30.9)	
Age (IQR)	47.3 (30.3-67.2)	50.7 (39.8-73.4)	31.2 (24-40.9)	<0.001
Male	354 (57.6)	247 (58.1)	107 (56.3)	0.7
PTB	450 (73.3)	307 (72.4)	143 (75.3)	0.5
Comorbidities:				
- At least one	184 (29.9)	162 (38.1)	22 (11.6)	<0.001
- Diabetes	35 (5.7)	33 (7.8)	2 (1)	0.001
- Solid tumour	22 (3.6)	22 (5.2)	0 (0)	0.001
- Haematologic tumour	7 (1.1)	7 (1.7)	0 (0)	0.008
- CKD	15 (2.4)	15 (3.5)	0 (0)	0.009
- Autoimmune diseases	5 (0.8)	5 (1.2)	0 (0)	0.1
- COPD	30 (4.9)	29 (6.8)	1 (0.5)	0.001
- HIV	48 (7.8)	36 (8.5)	12 (6.3)	0.4
- Chronic liver disease	21 (3.4)	21 (5)	0 (0)	0.002

Table 2 - Epidemiological characteristics of PTB and EPTB.

	TOTAL TB CASES 615	PTB 467 (75.9)	EPTB 148 (24.1)	p
Male (%)	354	277 (59,3)	77 (52)	0.1
Age (median, IQR)	47.3 (30.3-67.2)	47.1 (30.5-66.6)	47.7 (29.9-69.6)	0.5
Origin				
- Italians (%)	425	316 (74.4)	109 (25.6)	0.2
- Immigrants (%)	190	151 (79.5)	39 (20.5)	
WHO Region of origin for immigrants (%)				
- 1	85	76 (89.4)	9 (10.6)	0.007
- 2	39	23 (59)	16 (41)	
- 3	27	22 (81.5)	5 (19.5)	
- 4	10	7 (70)	3 (30)	
- 5	24	19 (79.2)	5 (20.8)	
- 6	5	4 (80)	1 (20)	
Comorbidities				
- Diabetes	35	31 (6.87)	4 (2.44)	0.04
- Solid tumour	22	18 (4)	4 (2.4)	0.4
- Haematologic tumour	7	5 (1.1)	2 (1.2)	0.9
- CKD	15	8 (1.8)	7 (4.3)	0.08
- Autoimmune diseases	5	3 (0.7)	2 (1.2)	0.2
- COPD	30	27 (6)	3 (1.8)	0.03
- HIV	48	28 (6.2)	20 (12.2)	0.01
- Liver disease	21	13 (2.9)	8 (4.9)	0.2

p=0.004), whereas it was increased in Africa-born patients (RR 2, 95% CI 1.02-3.96, p=0.041). No difference in the risk of EPTB was observed for patients from other regions of the world. In particular, Africa-born patients were at risk for CNS TB (RR 5.6% CI 2.03-14.86, p=0.001). At multivariable analysis HIV infection and African origin remained associated with an increased risk of CNS tuberculosis (RR 5.1, 95% CI 2.1-12.3, p<0.0001 and RR 4.3, 95% CI 1.6-11.4, p=0.004, respectively).

DISCUSSION

In Pavia province, located in Lombardy, Northern Italy, the epidemiology of tuberculosis changed over the study period, with a progressive increment in the number of cases in immigrant patients and a decrement among Italian-born patients, as documented elsewhere (La tubercolosi in Italia Rapporto, 2008). Tuberculosis in Italy is increasingly associated with specific population subgroups: immigrants from countries with a high endemic infection (aged 25-34) and elderly Italian natives and the homeless (Odone *et al.*, 2011). The trend of a reduction of the tuberculosis incidence among Italians has been constant in recent years, despite the resurgence of tuberculosis cases among immigrants.

These data support the observation that TB in a foreign-born population does not have a significant influence on tuberculosis in the native population in the European Union (Sandgren *et al.*, 2013). A possible explanation is the rapid tuberculosis diagnosis among immigrants, that assures a reduced exposure time among Italians. Immigrants are perceived as "at risk" for tuberculosis by physicians and health care workers in general and consequently this allows a rapid tuberculosis diagnosis. In a recent paper published by Italian authors, the median health care delay in tuberculosis diagnosis was significantly higher for Italian compared with foreign-born patients (60 vs 18 days) (Gagliotti *et al.*, 2006). Moreover, data on

clustering of the *M. tuberculosis* strain, that represents the degree of tuberculosis transmission, show that the percentage of clustered isolates among immigrants in Lombardy is about 50% and is positively associated with a low level of integration in the system (corresponding to low income, lack of high school diploma, alcohol dependence) (Franzetti *et al.*, 2010).

Data on resistance to anti-tuberculosis drug are comparable to those reported in the Piedmont region (La Tubercolosi in Piemonte Rapporto, 2014), in particular no difference in resistance to drugs was observed between Italians and immigrants.

Tuberculosis is associated with numerous comorbidities, above all among Italians, the main ones being HIV infection, diabetes and COPD. Each of these comorbidities is a challenge in the setting of tuberculosis infection. HIV is frequently associated with EPTB, a lower cure rate and increased mortality. Various aspects of therapy, such as drug interactions, overlapping toxicity and the risk of immune reconstitution inflammatory syndrome hamper the treatment of tuberculosis HIV-infected persons (Yang *et al.*, 2014).

Diabetes mellitus triples the risk of developing active tuberculosis following infection compared to patients without diabetes and is an increasingly recognized comorbidity that can both accelerate tuberculosis and complicate tuberculosis treatment (Alkabab, *et al.*, 2015). In addition, COPD increases by 3-fold the relative risk of developing active tuberculosis, and a significant association between a history of tuberculosis and COPD in adults has been observed (O'Toole *et al.*, 2015). The correlation of comorbidities and older age in Italians accounts for the increased mortality associated with tuberculosis observed among Italians.

EPTB prevalence was stable during the study period, whereas in other European or American study groups an increment in the EPTB form was observed. The genetic background of our population, mainly Caucasians, that

are not associated with an increased EPTB risk (Sandgren *et al.*, 2013; Peto *et al.*, 2009; te Beek *et al.*, 2006; Fiske *et al.*, 2010, Forssbohm *et al.*, 2008) might account for this. An increased risk of EPTB was observed only among patients from Africa, as reported elsewhere (Fiske *et al.*, 2010). Moreover, HIV infection was associated with an increased risk of EPTB, as a direct correlation exists between tuberculosis and HIV-induced immunodepression (Naing *et al.*, 2013). Both factors remained independently associated with the EPTB risk.

This study has a number of limitations. First, the use of administrative discharge data and the lack of clinical details and the relatively broad classification of comorbidities may not be entirely accurate, as they may have been misclassified.

Secondly, there are no data available concerning immigrants' length of stay in Italy at time of tuberculosis diagnosis.

In conclusion, this study underscores the high risk of tuberculosis among immigrants in Pavia province, while a decreasing trend among Italian-born subjects was consistently observed in the same time period. Italian-born patients show a higher mortality risk associated with tuberculosis, due to older age and co-morbidities.

Source of funding

None

Competing interests

The authors have no competing interests to declare.

Authors' contributions

ES, LP, LS and LM designed the study and drafted the manuscript. EF, MV, LP, LM, ES were involved in the management of data. PM and AM were in charge of laboratory diagnosis and notification of tuberculosis, LS and ES performed the statistical analysis. All authors reviewed the manuscript and approved the final version.

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