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Epidemiological trends of Tubercolosis in Italy, 1990-2004

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Abstract

Background: During the last two decades, tuberculosis (TB) has once again emerged as a significant public health problem in Western Countries. The aim of this study is to describe the epidemiology of TB in Italy in the last fifteen years. All routine information sources available (annual notifications, mortality and hospital discharges) were used, and attempts to investigate gender and geographical differences were made.

Methods: Age-standardized annual notification, mortality and hospital discharge rates were calculated. Time trends of annual notifications, mortality and hospital discharges for TB were modelled through Poisson regression, and whenever necessary, negative binomial regression.

Results: The analysis of the temporal trend of TB using the three indicators shows an increase until the middle of 1990s and a following decrease. TB is more frequent in men than in women, with a decremental North to South gradient. There are important geographical and gender differences of the TB decline in Italy, since the decrease of TB frequency is more pronounced in men than in women and it is less evident in the central and, to a lesser extent, the southern parts of the country.

Discussion: Italian guidelines for TB control, which are largely consistent with the international recommendations for low-incidence countries, need to be fully implemented throughout the entire country in order to reach the ultimate goal of disease eradication. Given the high number of TB cases among foreign-born persons, a strong public health commitment on TB control for immigrants, which includes screening, prophylaxis and treatment, is urgently needed.

Keywords: tuberculosis, epidemiology, italy

Introduction

According to WHO tuberculosis (TB) is the most widespread infectious disease in the world: about 9 millions of people are infected every year, and approximately 2 millions die [1, 2]. While the disease is still very common in non-industrialized countries, the incidence of TB has constantly decreased in all industrialized countries during the last century, because of the enhancement of socio-economic, hygienic and therapeutic conditions. Nevertheless, an inversion of this secular decreasing trend of TB since 1985 and during the '90s was noted in most of these countries [3–5].The diffusion of HIV, the immigration from countries with high incidence of TB and the appearance of new marginalized people were identified as the leading causes of this change of the epidemiological trend. Consequently, all industrialized countries have intensified their efforts against TB and a new reduction has been recently observed [6].

The epidemiological trend of the incidence of TB in Italy is similar to the other developed countries. From 1955 to 1995 the crude annual total incidence of TB decreased from 25.26 to 9.12 cases per 100,000 inhabitants. The constant decrease in the incidence of TB in Italy stopped during the '80s and '90s, with the incidence peaking in 1996 [7, 8]; during these years the incidence of pulmonary TB did not decrease and the incidence of extra-pulmonary TB increased largely. TB now has a low incidence among the Italian population, with a crude incidence rate in 2004 of about 7 cases per 100,000 [9].This value of incidence places Italy within the limit of 10 cases per 100,000 inhabitants suggested by WHO to identify countries with a low prevalence of TB.

The aim of this study is to describe the epidemiology of TB in Italy in the last fifteen years, using Poisson and negative binomial regression to analyze temporal trends. All routine information sources available (annual notifications, mortality and hospital discharges) were used, and attempts to investigate gender and geographical differences were made.

Methods

Three different kinds of data available from routine information sources were evaluated to

describe the epidemiology of TB in Italy. Notifications of new TB cases stratified by age, gender and geographical region are available from the Italian Ministry of Health [10] for the period 1993-2004. Mortality (from 1990 to 2002) and hospital discharges for TB (from 1999 to 2003), subdivided by age, gender and geographical region, are available from the Italian National Institute for Statistics (ISTAT) and the Italian Ministry of Health, respectively. Both of which are also accessible from the Health For All (HFA) database, available on the ISTAT web site [11].

Age-standardized annual Notification Rates (NR) of TB, stratified by gender and geographical region, were calculated using the age distribution from the 1991 Italian census population data as the standard population. Age-standardized annual Mortality Rate (MR) and Hospital Discharge Rate (HDR) (direct method, 1991 census Italian population as standard), stratified by gender and geographical region, were obtained directly from the HFA database.

Time trends of annual notifications, mortality and hospital discharges for TB were modelled through Poisson regression, and whenever necessary, negative binomial regression [12-15]. The negative binomial regression is used to estimate count models when the Poisson estimation is inappropriate due to over-dispersion. While in a Poisson distribution the mean and the variance are equal, binomial negative regression should be applied when the variance is greater than the mean. This over-dispersion was tested by the Poisson goodness-of-fit test, and considered significant at 0.05 level. From the Poisson and the binomial negative regression we derived an incidence rate ratio for the annual notification rate, for the mortality rate and for the hospital discharge rate during the periods 1993-2004, 1990-2002 and 1999-2003, respectively. The incidence rate ratio estimates the average relative change in rate per year. For example, an incidence rate ratio of 1.00 indicates no change (a flat regression line), whereas a ratio of 0.80 indicates a 20% average decrease (indicated with a negative percentage) and a ratio of 1.20 indicates a 20% average increase from one year to the next.

We calculated incidence rate ratios for the entire periods available as well as for the periods before and after 1996, year in which the maximum TB incidence during the study period was noted. Finally, for TB annual notifications and mortality we calculated an average yearly incidence rate before and after 1996; in this case an incidence rate ratio of 1.00 indicates no change before and after 1996, an incidence rate ratio of 0.80 indicates a 20% decrease of incidence after 1996 compared to the period until 1996, and an incidence rate ratio of 1.20 indicates a 20% increased incidence.

All statistical calculations were performed using Stata version 8.0 (College Station, TX, Stata Corporation, 2003).

Results

The age-standardized annual Notification Rate (NR) for TB in 2004 in Italy was 8.70 per 100,000 inhabitants among males, almost twice the rate of women (5.45 per 100,000). There is a quite clear North to South gradient, since the NR is higher in the northern and central part of the country. Both in males and females the NR shows an increasing trend from 1993 up to 1996, the year in which the highest frequency of notifications was noticed, and a decreasing trend after 1996. The percentage decrease of NR from 1993 up to 2004 is 19.02% among men and 5.82% among women. This decreasing trend is not the same for all geographical regions of the country: while it is clearly visible in the North and the Islands, it is less evident in the Centre and in the South (Table 1).

Mortality data confirms that TB is more frequent in men than in women, with an age-standardized Mortality Rate (MR) in 2002 of 0.90 per 100,000

Table 1. Age-standardized TB annual Notification Rate (NR) x 100,000 inhabitants, 1993-2004, Italy.

Areas	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Males												
North	15.94	16.32	10.62	14.80	12.96	11.47	10.66	12.18	11.77	9.92	11.51	11.13
Center	9.90	10.73	9.79	11.74	11.96	12.21	11.33	11.23	11.70	11.02	11.29	11.32
South	6.35	6.69	7.04	9.71	9.49	9.51	9.26	9.01	8.29	8.16	8.07	7.43
Islands	6.36	8.88	6.43	8.39	11.07	5.38	5.00	4.57	5.03	5.17	5.15	4.06
Italy	10.74	11.41	8.63	11.90	11.30	9.93	9.41	9.95	9.48	8.63	9.27	8.70
Females												
North	8.82	9.54	6.16	9.46	8.79	7.69	6.75	8.16	7.81	6.87	7.92	7.16
Center	5.23	5.87	4.81	7.27	7.43	6.73	6.45	6.75	6.69	6.99	7.27	7.92
South	1.30	1.50	2.14	3.13	3.33	3.73	3.14	2.80	2.65	2.84	2.70	2.01
Islands	3.52	5.75	3.65	4.25	5.86	2.85	2.56	2.36	2.37	2.79	2.63	2.17
Italy	5.79	6.57	4.71	7.00	6.94	6.06	5.37	5.95	5.74	5.46	5.90	5.45

Table 2. Age-standardized TB annual Mortality Rate (MR) per 100,000 inhabitants, 1990-2002, Italy.

Areas	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002
Males													
North	1.80	1.80	1.60	1.70	1.50	1.90	1.80	1.40	1.50	1.30	1.10	1.00	1.10
Center	1.60	1.20	1.40	1.30	1.60	1.30	1.40	1.50	1.20	1.20	1.10	1.00	1.00
South	1.40	1.50	1.30	1.10	1.30	1.50	1.40	1.20	1.10	1.00	0.80	0.70	0.70
Islands	1.30	1.40	1.30	1.10	1.30	1.60	1.20	1.50	1.20	0.90	0.80	1.00	0.40
Italy	1.60	1.60	1.40	1.50	1.40	1.70	1.50	1.40	1.30	1.20	1.00	0.90	0.90
Females													
North	0.60	0.70	0.50	0.60	0.50	0.70	0.50	0.70	0.60	0.50	0.50	0.40	0.40
Center	0.40	0.70	0.40	0.50	0.60	0.70	0.70	0.60	0.40	0.50	0.40	0.40	0.40
South	0.50	0.40	0.60	0.30	0.40	0.40	0.50	0.30	0.40	0.50	0.30	0.30	0.30
Islands	0.50	0.40	0.40	0.60	0.50	0.40	0.50	0.50	0.50	0.50	0.40	0.30	0.10
Italy	0.50	0.60	0.50	0.50	0.50	0.60	0.60	0.60	0.50	0.50	0.40	0.40	0.40

and 0.40 per 100,000, respectively. Mortality is higher in the North and in the Centre than in the South and the Islands. Taking into account the entire period from 1990 up to 2002, the MR in all regions of the country tends to be quite stable in the first half of the '90s, and then declines until 2002 (Table 2).

The analysis of the age-standardized Hospital Discharges Rate (HDR) during the period 1999-2003 further confirms the higher occurrence of TB in males than in females, the decremental North to South gradient, as well as the decreasing trend of TB frequency in Italy. The percentage decrease of the HDR from 1999 to 2003 is of 37.14% in men and 32.14% in women and it is less marked in the Centre compared to other geographical areas of the country (Table 3).

Table 3. Age-standardized TB annual Hospital Discharges Rate (HDR) per 100,000 inhabitants, 1999-2004, Italy.

Areas	1999	2000	2001	2002	2003
Males					
North	31.30	27.70	24.50	20.30	17.40
Center	24.10	23.20	20.60	18.50	18.90
South	24.50	22.40	19.60	19.20	17.30
Islands	29.50	22.20	23.20	20.40	17.10
Italy	28.00	24.90	22.40	19.60	17.60
Females					
North	20.30	16.90	17.80	15.10	13.00
Center	13.00	14.60	12.50	12.40	11.50
South	13.50	11.60	11.00	10.10	8.70
Islands	16.70	11.60	14.10	14.90	11.00
Italy	16.80	14.60	14.70	13.30	11.40

The decline of TB during the entire study period was confirmed by the calculation of the incidence rate ratio for the NR and the MR through Poisson or negative binomial regression (Table 4). The NR shows a statistically significant decreasing trend

Table 4. TB Incidence Rate Ratios calculated on the basis of Notification Rate (NRR, Annual Notification Rate Ratio), Mortality Rate (MRR, Mortality Rate Ratio) and Hospital Discharges Rate (HDRR, Hospital Discharges Rate Ratio), Italy.

	NRR (95% CI) [period]	MRR (95% CI) [period]	HDRR (95% CI) [period]
Males	0.981 (0.969-0.993)[a]	0.970 (0.956-0.983)[a]	
	[1993-2004]	[1990-2002]	---
	1.021 (0.943-1.105)[a]	1.010 (0.991-1.030)[b]	
	[1993-1996]	[1990-1996]	---
	0.972 (0.960-0.984)[a]	0.926 (0.901-0.951)[b]	0.895 (0.888-0.902)[b]
	[1997-2004]	[1997-2002]	[1999-2003]
	0.907 (0.821-1.003)[a]	0.805 (0.731-0.897)[a]	
	[1997-2004 vs 1993-1996]	[1997-2002 vs 1990-1996]	---
Females	0.992 (0.975-1.010)[a]	0.992 (0.974-1.011)[a]	
	[1993-2004]	[1990-2002]	---
	1.034 (0.912-1.173)[a]	1.031 (1.004-1.059)[b]	
	[1993-1996]	[1990-1996]	---
	0.976 (0.959-0.992)[a]	0.919 (0.888-0.951)[b]	0.916 (0.896-0.937)[a]
	[1997-2004]	[1997-2002]	[1999-2003]
	0.986 (0.865-1.125)[a]	0.966 (0.841-1.110)[a]	
	[1997-2004 vs 1993-1996]	[1997-2002 vs 1990-1996]	---

[a] Data obtained by Binomial Negative Regression (see text)
[b] Data obtained by Poisson Regression (see text)

in men, with a yearly average relative decrease of -1.90% (95% CI: -3.10%, -0.70%), whereas in women the yearly decrease is lower (-0.80%) and not statistically significant (95% CI: -2.50%, +1.00%). It is interesting to note that in both sexes there is a statistically significant decrease in the North and the Islands, while no reductions are observed for the Centre and the South (data not shown). The analysis of the MR shows a similar pattern, since there is a statistically significant decreasing trend of mortality in men (-3.00%, 95% CI: -4.40%, -1.70%), but not in women (-0.80%; 95% CI: -2.60%, +1.10%); in this case, however, there are not clear differences among the geographical areas of the country (data not shown).

As previously reported, descriptive statistics show that both the NR and the MR for TB increased in the first half of the '90s with a peak in the years 1995-1996, with a following decrease in the second part of the study period. Therefore, it seems very appropriate to calculate incidence rate ratios separately for the periods before and after 1996 (Table 4). In the first half of the '90s there are no significant changes of the NR and the MR in men, whereas in women there is a statistically significant yearly increase only for mortality in the period 1990-1996 (+3.10%; 95% CI: +0.40%, +5.90%). By contrast, the NR and the MR show a statistically significant decrease in both sexes in the second part of the study period. In the period 1999-2003 there is also a statistically significant reduction of the HDR, with an average yearly decrease of -10.50% in men (95% CI: -11.20%, -9.80%) and of -8.40% in women (95% CI: -10.40%, -6.30%) (Table 4). However, it should be pointed out that the decline of TB during the second part of the study period is not homogeneously distributed throughout the country: considering both the NR and MR in both sexes, in the Centre the only statistically significant reduction is observed for the NR in men, while in the South the reduction of the MR in women does not reach the statistical significance (data not shown).

In order to perform a more direct comparison between the two study periods, we calculated average yearly incidence rates before and after 1996 for both annual notifications and mortality: the incidence rate ratio in this case is the incidence rate in the second period of study divided by the incidence rate in the first period (Table 4). The incidence rate ratios are always less than one in both sexes, indicating a reduction both for the NR and the MR. However, this reduction is statistically significant only for the MR in men, where an overall decrease of -19.50% is observed between the periods 1997-2002 and 1990-1996 (95% CI: -26.90%, -10.30%). The decline of both NR and MR between the two study periods is more pronounced in the North and, to a lesser extent, in the Islands, compared to the central and southern part of the country (data not shown).

Discussion

Using surveillance and survey data to update estimates of incidence, WHO has recently calculated that in 2004 there were 8.9 million new cases of TB (140 per 100,000 population) worldwide. More than 80% of these new cases occurred in the African, South-East Asia and Western Pacific regions [1]. The lowest incidences of TB are in the United States, Canada and Western Europe, where, after transient increases during the mid-1980s and early 1990s [3-5, 16, 17], case rates are stable or declining [1, 18, 19]. The increased immigration from countries where TB is prevalent, the interaction between TB and HIV infection, and the decay in the health care infrastructure that supports TB control programs were felt to be the principal reasons of the resurgence of TB. The following decrease was due mainly to the renewed funding for TB control, the improved case finding and surveillance, and the wider use of directly observed therapy [6]. If renewed efforts succeed in again forcing TB rates downward, it is now imperative, from a public health point of view, to carry out detailed analyses of epidemiological trends both at national and international level and to maintain a level of control that is long and intensive enough to reach the final goal of eliminating the disease.

The epidemiology of TB in Italy has been described in this study using three different types of data from routine information sources: TB notifications, mortality and hospital discharges. Each of these data sources has its own limitations [8]. Under-notifications of TB cases are a recognized problem in Italy [20-22] as well as in other countries [23], and, therefore, the TB notification rate is always lower than the actual TB incidence rate. However, the fraction of under-reported cases is sometimes partially offset by overdiagnosis and by double reporting of individual cases. In addition, TB mortality is under-reported, since TB is not always indicated as the leading cause of death [8]. Hospital discharges for TB take into account repeated hospital admissions of the same patients and this explains, together with the under-notification of TB cases, why the HDRs are always higher than the NRs [8]. However the epidemiological trends of NRs, MRs and HDRs for TB in this study appear to be quite consistent, and we believe that, taken together, the three indicators are able to adequately describe the epidemiology of the disease in Italy.

The results of this study show clearly that the incidence of TB in Italy is low, that the disease is more frequent in males than in females, and that there is an evident decremental North to South gradient. Italy should be considered as a low TB incidence country, since the NR is lower than 10 cases per 100,000 and declining [24]. The Italian TB NR is similar to those reported for most western European countries [18] and slightly higher than the NR in the United States [19]. An overall male/female ratio higher than one is a phenomenon that occurs worldwide [1, 18, 19], since smoking, alcohol consumption, poor living conditions and occupational exposure to risk factor for TB are usually more frequent in males [25]. There are some important geographical differences, since the disease is more frequent in northern and central parts of the country than in the South and the Islands. These differences cannot be ascribed to a larger under-notification in the South and the Islands, since the North to South gradient concerns the notifications as well as mortality and hospital discharges. The higher concentrations of subjects at risk, such as AIDS patients and immigrants, in the North and the Centre is the most likely explanation of the geographical gradient [7], since it is well known that both AIDS incidence and immigration are higher in these part of the country [26, 27].

Several studies have shown the effects of the distribution of HIV infection and of immigration from countries at high prevalence of TB on TB incidence in Italy [22, 28-31]. The proportion of TB cases in Italy occurring in foreign-born persons increased during the study period, starting from 8.1% in 1992 [7] the rate continued to rise to 10.7% in 1995 [7], to 22.0% in 1999 [9] and finally to 39.4% in 2004 [9, 18]. According to most recent WHO estimates, the HIV prevalence in adult incidence cases is 13% [1]. The interactions between immigration from developing countries, the distribution of HIV/AIDS in the population and the ageing of the indigenous population are the most likely explanations of the major finding of our study, that is the geographical and gender differences of the TB decline in Italy.

The decrease of TB frequency in Italy is more pronounced in men than in women and it is less evident in the central and, to a lesser extent, the southern parts of the country. The case of the Lazio Region, located in the centre of Italy, is emblematic from this point of view. The NR has not appreciably declined during the study period as in other Italian regions, and an increase has occurred during the last two years. While TB cases among persons born in Italy have decreased progressively during the study period, there is clear increase of TB cases among foreign-born persons, and, in 2003, for the first time the TB cases among foreigners were more than those occurring in the indigenous population [32]. This highlights the necessity to implement specific measures targeted at high-risk groups to effectively control TB in Italy.

It is important to note that the WHO framework for TB control [1] is designed primarily for countries with a high incidence of tuberculosis. Therefore, it is not sufficiently comprehensive for low incidence countries in Europe, as it fails to take into account the technical sophistication and the resources at the disposal of these countries, which allows for a much more aggressive approach to the disease. Recently, a WHO working group, the International Union against Tuberculosis and Lung Disease (IUATLD) and the Royal Netherlands Tuberculosis Association (KNCV) developed a new framework for low incidence countries, that includes: i) a general approach to TB which ensures rapid detection and treatment of all cases and prevention of unnecessary deaths; ii) an overall control strategy aimed at reducing the incidence of TB infection (risk-group management and prevention of transmission of infection in institutional settings); and iii) a TB elimination strategy aimed at reducing the prevalence of TB infection (outbreak management and provision of preventive therapy for specified groups and individuals) [33].

The analysis of the epidemiological trend of TB in Italy during the last fifteen years, carried out in this study using three different kinds of data obtained from routine information sources, clearly shows that we cannot relax our efforts against TB. The Italian guidelines for TB control [34] are largely consistent with the international recommendations for low-incidence countries, but they need to be fully implemented throughout the entire country, particularly those concerning immigrants. Some recent experiences from Italy have shown that specific TB programs for immigrants may be feasible and cost-effective [35, 36]. A strong public health commitment on TB control among immigrants, which includes screening, prophylaxis and treatment, is urgently needed.

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