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Tuberculosis in the immigrant population in Italy: state-of-the-art review

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SUMMARY

Although the incidence of tuberculosis (TB) has been decreasing in the European Union/European Economic Area (EU/EEA) in recent decades, specific subgroups of the population, such as immigrants, remain at high risk of the disease. Immigration from areas of high incidence is thought to have fuelled the resurgence of TB in areas of low incidence. Indeed, while immigrants have a high risk of acquiring TB prior to migration, after migration they are exposed to additional risk factors for acquiring or reactivating TB infection, such as poverty, stressful living conditions, social inequalities, overcrowded housing, malnutrition, substance abuse and limited access to health care. In Italy as well, TB has increasingly become a disease for specific population subgroups such as immigrants and in urban settings often driven by reactivation of imported latent TB infection (LTBI). In this paper we present an analysis of the national scientific literature from recent years in order to estimate the burden of TB in foreign-born populations, to establish the burden of TB in migrants by gender, age group and country of origin as well as other relevant subgroups, and evaluate the clinical manifestations of latent or active tuberculosis and treatment response.

Keywords: tuberculosis, immigrants, review.

INTRODUCTION

Tuberculosis currently represents a major global health problem and is one of the main causes of mortality and morbidity among the infectious diseases. After a long time of oblivion, in 1994 the situation led the World Health Organization (WHO) to declare: "TB represents an health emergency worldwide" [1-3]. In 2014, globally, there were an estimated 9.6 million new TB cases: 8.6 million among adults (deaths: 1,360,000) and 1.0 million among children (deaths: 140,000). An estimated 1.2 million (12%) of the 9.6 million people were HIV-positive (deaths: 400,000) [1]. 58% of the 9.6 million new TB cases were in the South-East Asia and Western Pacific regions. In Africa there are 28% of the world's cases, but the incidence is the highest: 281cases for 100,000 inhabitants, against a global average of 133. India, Indonesia and China had the largest number of cases: 23%, 12% and 10% of the global total, respectively [4].

In last decades, the global migration flows have been a significant phenomenon, and in 2015 about 65 million immigrants, mostly coming from high-incidence TB regions, live in industrialized countries. Because of malnutrition and poor hygienic conditions, these populations are especially exposed to TB reactivation or to a new infection [5,

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6]. TB incidence in high-income countries showed an important disparity: while local-born cases have remained static or decreased, foreign-born cases increased. From 2000 to 2013, local-born TB cases in Europe decreased by ~51.3%, whilst foreign-born case notifications increased marginally (~2.3%) [7-12]. Consequently, foreign-born individuals, in 2013, made up over half of all TB cases (median 52.0 %) [7, 13] with incidence rates 8.7-18.4 times that in the local-born population [8, 11, 12, 14-16].

The current epidemiological situation of TB in Italy is characterized by low incidence in the general population, and the cases are mostly concentrated in some risk groups. From 2004 to 2014, about 4300 cases/year of TB have been notified; 52% of them occurred in foreign subjects with a steady increase, parallel with the increased number of immigrants in Italy, in the rate of cases reported among "non-Italian citizens" (from 44% in 2005 to 66% in 2014) [17, 18]. The presence of immigrants from highly endemic areas is considered by many authors the most important co-factor, together with HIV infection, of the recent TB renewal reported in Italy [19-23]. In this setting immigrants can develop TB following three main mechanisms:

α) TB can already be present at their arrival in the host country;

β) TB can be the consequence of the reactivation of latent tuberculosis infection (LTBI) acquired in the country of origin;

γ) primary active TB can follow a new infection acquired in the host country or during a return travel to the country of origin [24-27]. About 40% of notified cases in subjects of foreign nationality fall ill with TB during the first two years of the arrival in our country, in fact the greatest risk for active TB is within the first few years of arrival [22-23,28-30].

This paper specifically aims to estimate the burden of TB in foreign-born populations, to establish the burden of TB in migrants by gender, age group and other relevant subgroups, and evaluate the prevalence of LTBI subjects, the clinical manifestations of active tuberculosis and prophylaxis and/or treatment response. We will pursue these objectives by taking into account that we were observing a dynamic process composed by several consecutive migration waves changing over the years.

METHODS

We performed an analysis of the more recent national scientific literature and retrieved data provided by infectious disease and migration experts of our group. The literature search was conducted by consulting Medline, and The Cochrane Library, for works published over the last 15 years up to June 2016. Articles considered in our study had to be descriptive and/or analytic observational studies, experimental studies, narrative reviews, systematic reviews and meta-analyses; they had to be published in English, and include data obtained only/mainly from Italy. Additional data were taken into account even with unpublished studies concerning the Apulia region.

Latent tuberculosis infection

Latent tuberculosis infection (LTBI) represents a state of equilibrium in which the host is able to control the infection but not completely eradicate the bacteria; this is related to a persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active disease. About one-third of the world's population is estimated to have LTBI; these individuals are the largest reservoir for potential transmission. The greatest danger for patients with LTBI is the risk of reactivation cases (active TB after remote infection) and the subsequent silent spread to close contacts; the lifetime risk of reactivation is estimated to be 5-10%, with the majority developing TB disease within the first five years after initial infection [31]. The diagnosis of LTBI is initially done by two immunologic tests (tuberculin skin test, TST or interferon-γ release assay, IGRA) in patients without clinical signs or symptoms of disease and a normal chest radiograph. The tuberculin skin test (TST), based on purified protein derivative (PPD), is inexpensive and easy to perform for identification of *M. tuberculosis* (MT)-infected subjects, but the reading after 72 hours is subjective and requires a second visit, presenting a problem due to the high mobility of this population. Certain alternative assays, based on the detection of interferon-γ (IFN-γ) produced by effector T-cells in vitro [32-35]. TST has been carried out, as a mass screening of the immigrant population, when the cost-benefit ratio allowed it. The majority of active TB infections in low prevalence regions is attributed to LTBI reac-

tivation (47-87%). However, the risk is considerably higher in presence of predisposing factors. In fact, impaired immunity, as in the case of HIV infection, increases the risk to 10% per year [36]. Immigrants, especially the irregular ones, represent a cohort of subjects particularly fragile in many cases. In fact they have the combined risk of coming from countries with high incidence of TB and being vulnerable because of their relegated social position in countries of destination, which can result in immune-depression; this may facilitate the transition from LTBI to active TB [37]. Recent evidences suggest that the distribution of LTBI and TB among immigrants is uneven: LTBI prevalence among recent immigrants seem to increase as a function of TB prevalence in the country of origin [38, 39].

In this stage of infection, the guidelines - strongly recommended from the WHO, for a public health approach to the management of LTBI in high risk individuals, as immigrants from high TB burden countries - suggest it would be highly appropriate to carry out a specific TB prophylaxis, because the reactivation of TB can be averted by preventive treatment [40]. Despite this recommendation to treat LTBI, many challenges remain, including convincing asymptomatic subjects to accept treatment, regimen non-adherence or default, concerns about adverse side effects, and the inability to enforce treatment for a non-communicable infection that may remain latent lifelong [41]. The prophylaxis can be administered in two ways: directly observed therapy (DOT) or self-administered therapy (SAT). The DOT is the standard method for treating active TB, but adherence to treatment and completion rates for LTBI remain low, particularly for medically and socially vulnerable patient populations and for newly arrived immigrants [42, 43].

Studies of LTBI on the immigrant population resident in Italy are few, probably because it is difficult to make scientifically reliable screening, given the poor adherence of the tested subjects. The results of these studies were sometimes discordant on the basis of the considered time frame and the features (ethnicity, gender, age, etc.) of the immigrant tested; they showed a prevalence of positivity to the TST variable between 30-50% among the people examined [31, 37, 44].

In 2003-2008 (906 subjects), 2009 (452 subjects) and 2015 (82 subjects), we conducted three studies on different types of immigrants (by age, sex, ethnicity, time of permanence in Italy, etc.) [37]. The prevalence of TST positivity, confirmed by the IGRA test, was respectively: 26.5%, 27.6%, and 29.6%; despite the small growth trend over time, it is not significantly very different. The ethnic prevalence reflected the migration flows: in the first study subjects were mostly Eastern European (typically Balkan), in the second study they were mainly from Sub-Saharan Africa, and mainly from Asia in the third study (Pakistanis and Syrians). Overall, subjects who have joined an anti-TB prophylactic treatment were initially less than 50%, and only 27% completed the course of therapy. Adherence to treatment did not differ between the various ethnic groups, while men were more adherent than women. Prophylactic treatment of shorter duration (isoniazid + rifampicin) had a greater adherence than those more prolonged (only isoniazid) about 60% vs. 28%.

Only in <30% of subjects with LTBI, follow-up was possible; 4 patients in the first study and 5 in the second study presented within three years a form of active TB; none of them had done the prophylaxis. In the third study, we started a prophylactic treatment in 18 subjects (isoniazid plus rifampicin for 3 months): 13 (72.2%) completed the cycle. Follow-up is ongoing, and we currently do not signal any active case of TB.

Although most of them came from countries where the rate of BCG vaccination is still high, only a minority of them, no more than 30%, remembered that they had been vaccinated against. Our data show a lower prevalence than those observed in other centres [31, 37, 44]. However, this can be a normal epidemiology pattern related both to the type and the period of immigration. Furthermore, the presence of immunosuppression could also influence TST positivity, then our results may be an expression that some causes of immunodeficiency other than HIV infection, such as malnutrition and fatigue, for the most recently arrived subjects, cannot be excluded, due to the very difficult migratory journey.

Active tuberculosis

The prevalence and incidence of active tuberculosis in immigrant populations has been the subject of many analyses; these studies were very heterogeneous, for the selection of patients, ethnicity, gender, age. Furthermore some of the studies

showed local characteristics, while others had a broader evaluating the clinical and epidemiological aspect nationwide. However, they give us a fairly accurate overall idea about the active tuberculosis disease in immigrants.

In a retrospective study, Odone observed 5377 TB cases notified in Emilia-Romagna from 1996 to 2006; 1964 of them (36.5%) were not Italy-born. Morocco was the most represented country among foreign TB cases (28.3%, n=398 cases). Immigrants TB cases showed an increase of 213% during the study period (from 93 in 1996 to 291 in 2006). For what concerns TB localization, 62.4% had pulmonary TB and 31.2% extra pulmonary TB. Six percent had disseminated TB forms. Common extra pulmonary sites included the peripheral lymph nodes, the genitourinary tract and the pleura, which were affected in 10.6%, 5% and 4.5% of all tuberculosis cases reported, respectively. Less frequent incidents were gastro-intestinal (1.7%), vertebral (1.4%), osseous non-vertebral (1.2%) and meningeal (0.5%) localization. The likelihood of disseminated TB was significantly higher among immigrants [45].

In the same geographical area, Lombardi studied 255 TB strains that were isolated between 2008 and 2011; 168 of these (65.9%) were from foreign-born patients. The annual proportion of foreign-born cases out of the total TB isolation increased from 60.8% in 2008 to 67.5% in 2011. Asians represented the largest proportion of foreign-born cases (66, 39.3%), followed by Eastern Europeans (49, 29.2%), Africans (45, 26.8%) and South Americans (8, 4.7%). Among Asian populations, most patients were Pakistani (48.5%); Romanian immigrants accounted for 69.3% of Eastern-European TB cases, whereas Morocco accounted for 33% of Africans. Concerning TB localization, 168 patients (65.9%) had pulmonary TB and 87 (34.1%) extra-pulmonary TB. Common extra-pulmonary sites included peripheral lymph nodes (35.6%), pleura (18.4%), osseous (9.2%), urinary tract (8%) and meningeal (4.6%) localization [46].

Mammina have searched on the Surveillance of TB in Sicily from 2010 to 2013. In this period, 456 of the 876 notified TB cases (52.05%) were foreign-born subjects. The rate of the annual distribution of TB cases in immigrants increased (2010 *vs* 2013, from 36.4% to 54.4%), and in the last two years under consideration exceeds that in the native population. Among all the TB cases reported over the period 2010-2013, without any distinction between Italians and immigrants, pulmonary location was diagnosed in 82.5% of them [47].

Baussano investigated the rates of and risk factors for TB infection, transmission and disease in a cohort of 27,358 socially marginalized immigrants who were systematically screened (1991-2010) in Piedmont. Active TB prevalence was 2.7% and annual infection incidence was 1.7% (1.4%-2.1%); its prevalence and incidence of infection increased as a function of the estimated TB incidence in the immigrants' countries of origin. The estimated TB incidence during the study period, was relatively stable (~20 cases/100,000 persons). The estimated prevalence of active TB cases (2.7%), was considerably higher than the estimated incidence rates among the general population in the respective different countries of origin. This finding, according to the authors, "*might reflect demographic and socioeconomic differences between socially marginalized immigrants and the general population in the countries of origin, such as age distribution and the poor social and living conditions of socially marginalized immigrants*" [48].

Schepisi analysed three TB case finding interventions performed from November 2009 to March 2014 in five different sites in Rome and one site in Milan. Among 6347 migrants enrolled, only 292 (4.6%) completed diagnostic evaluation for tuberculosis; active TB was diagnosed in 11 individuals representing 0.17% of those screened and 3.8% of those who completed diagnostic evaluation. Two were extra pulmonary TB cases, and the others were pulmonary cases. The most frequently reported countries of origin according to different study phases were Afghanistan, Romania, Somalia, Eritrea, Morocco [49].

These different and quite varied studies, however, give some pretty clear indications that may be useful to better understand and fight tuberculosis infection in the immigrant population:

1) The incidence of TB in the immigrant population is very high, accounting in 2014 for 66% of new cases occurring in Italy. The average age is young and active disease has manifested itself, in most cases, within two years after the arrival in our country [22].
2) The ethnicity of immigrants suffering from TB is extremely varied, the spread of infection in our country is linked to various factors (eth-

nic clusters, economic, familiar etc.), but also to "epidemiology of home country", these factors determine the distribution of TB subjects in several parts of Italy. The distribution of the geographical origin of TB cases in Italy, mirrored the distribution of the geographical origin of migrant populations in the country. In Italy, the largest share of foreign born TB cases come from the Middle East (36.6%) and Africa (21.7%), followed by European region (19.7%), South East Asian region (11.5%), American region (5.4%) and Western Pacific region (4.8%) [45]. The majority of TB cases among foreigners were from Romania, Ethiopia, Eritrea, Pakistan and Morocco [46].

3) Extra pulmonary TB disease was more common among immigrants; extra-pulmonary sites included mainly peripheral lymph nodes, but also pleura, bone, urinary tract, gastro-intestinal and meningeal localization [46]. For what concerns the ethnicity, significantly different patterns of TB localization were found among Eastern European patients (81.6% Pulmonary-TB vs 18.4% extra pulmonary-TB) and Africans (48.9% pulmonary-TB vs 51.1% extra pulmonary-TB) [45-47]. These data are not just Italian, but are also present in other European studies. In fact evidence from the UK showed extra-pulmonary TB to be associated with being of foreign origin [50]. In UK in 2010, 54% of foreign-born TB cases had extra-pulmonary TB while this percentage was only 31% in UK-born TB cases [51].

Genotyping analyses

Recent studies on genomics and molecular evolution of *M. tuberculosis*, assessed with the spoligo-typing assay, have demonstrated how the organism has evolved in different lineages [52]. The genotyping is used to trace the evolution of different strains of *M. tuberculosis*, in order to obtain information that relates to the spread of strains, the degree of infectivity and pathogenicity [53]. In fact different strains of *M. tuberculosis* may have different interactions with the host, a different potential for transmission and they may infect different human populations following a typical geographical distribution. Genotyping, furthermore, is very important to distinguish reactivation of remotely acquired LTBI from TB transmission. The presence of more individuals with TB isolates of the same genotype suggest a recent common infection, while the presence of patients with an isolate unique, different from others, suggests that there may be a reactivation of LTBI [54]. There are 62 identified main lineages/sub-lineages [53, 55, 56].

A) East Asian lineage, which includes the spoligotype-defined Beijing family, and is highly prevalent in many countries of East and Southeast Asia and is rapidly spreading in Eastern Europe. This genotype seems to have a tendency to determine extra-pulmonary and it appears to be transmitted more easily and to be more virulent than other strains of *M. tuberculosis* [57, 58].

B) Euro-American lineage, which is the most frequent lineage in Europe and the Americas, has also spread across different regions of Africa and the Middle East, and includes the spoligotype families T, Haarlem, Latin American-Mediterranean (LAM), S and X. In Europe about 25% of the isolates belongs to the family genotypic Haarlem, while in South America about 50% of the strains belongs to the lineage LAM. Within this family, LAM7 is predominant in Asia Minor (Turkey), LAM10 in Cameroon. The genotype T family has been found in all continents and representing 30% of the total. The X lineage, of Anglo-Saxon likely ancestral origin, is represented with discrete significance in the North and South America. The S lineage, highly prevalent in Sicily and Sardinia, would be identical to the South African clade [57, 58].

C) genotype EAI (East African Indian) corresponding to Indo-Oceanic lineage, which has a prevalence across Asia between 24.3 and 33.8%, is represented especially in the South - East Asia. It includes the spoligotype-defined Central Asian (CAS) family; it was divided into CAS1-Dehli, essentially localized in the Middle East, in central and southern Asia, and CAS1-Kilimanjaro. In Europe and Australia, these strains were related only with immigrants from South Asia [53, 57, 58].

D) the West African I and the West African II lineages (from which *Mycobacterium bovis* originated), corresponding to strains traditionally identified as *Mycobacterium africanum* [57].

E) Manu genotype is, finally, a family of new feedback from India [58]

Based on this new knowledge, it is almost natural to make the genotypic study Tb infection in individuals immigrants who suffer from TB, in order to determine whether it is a new infection or the reactivation of a latent form, establish the epidemiological patterns of transmission within the same ethnic group, between different ethnic groups genotypically different or to the native population. This choice also allows to highlight the most virulent and, possibly, resistant strains of mycobacteria.

Garzelli evaluated, during a 4-year period the molecular characteristics of the *M. tuberculosis* isolates (MTBC), in a cohort of 1080 TB patients living in Tuscany, 466 of which were foreign-born patients [59]. The country of birth of immigrants was known for 94.5% patients: 27.9% were from Africa, 23.6% from Asia, 22.3% from Eastern Europe, and 11.6% from Central and South America. MTBC isolates of the Euro-American lineage were highly prevalent and represented 57.9% of all isolates. Within this lineage, the family T represented 36.3% of all isolates, Haarlem 34.4%, LAM 25.6%, S 1.5% and X 2.2%. The distribution of isolates of the T family consisted of patients of Eastern Europe and Africa for the large majority of cases. Eastern Europe, Africa and the Americas were the major geographical areas of birth of Haarlem TB patients. Among the LAM isolates, Africa (particularly the Mediterranean countries) and South America accounted for the origins of most patients. Very few have been the cases due to S strains (four among immigrants). X strains were rarely found as well.

A total of 37 isolates (7.9%) were of EAI family, the Indo-Oceanic phylo-geographical lineage which is prevalent all around the Indian Ocean. Most isolates were from Asian patients.

A relatively high number of isolates (59, 12.7% of the total) belonged to the East Asian lineage, in particular to the Beijing family, and the number of immigrants with this isolate has been increasing during the years of survey. Asia accounted for the origin of most patients (36/59); this was expected, as Asia has been the main source of importation of Beijing strains to European countries; there was also a consistent proportion from eastern Europe and South America (mainly Peru).

Strains of East African-Indian lineage (CAS family), 29 patients (6.2%) were found, mostly in Asian immigrants (21/29) (Pakistan in particular). The frequency of this genotype increased in Tuscany starting from 2003.

Mycobacterium africanum strains (16 isolates) were similarly isolated only from immigrants coming from Africa, but their number showed a steady decrease.

M. bovis strains (6 isolates) accounted for 1.3% of all TB cases presented by immigrants. All the patients were young people (mean age, 28 years); this clearly prevalent strain in the Italian population would seem to indicate recently acquired infection in immigrants.

Mammina observed the distribution of MTBC isolates in 70 foreign-born patients. By spoligotyping they were attributed to 14 different lineages and 33 sub-lineages. The most represented genotypes were: Haarlem 35.7%, T 20.0%, CAS and LAM 8.6%, EAI 5.7%; in 2013 two strains belonging to the Beijing lineage, and three strains belonging to *M. bovis* were also identified [47].

These studies emphasize the great heterogeneity of the lineage/circulating sub-lineage reflecting in a very effective complexity of the epidemiological picture, highlighting the coexistence of indigenous strains and import and showing at the same time a very limited clustering in terms both of the frequency and amplitude of the same cluster. Moreover, there is little evidence that the foreign-born population transmit TB to the local born population [59].

TB/HIV co-infection

The global impact of the co-infection TB/HIV is one of the major public health challenges of our time. Worldwide TB is the most common opportunistic infection in HIV-infected persons, and it is one of the leading causes of death in these subjects [60]. People with HIV/AIDS disease and infected with *M. tuberculosis* are at 10 times greater risk of developing TB compared with HIV-uninfected individuals, often with atypical presentation of the disease [61-63]. The presence of TB also complicates HIV infection through a number of mechanisms including increased viral replication and CD4/CD8 cell proliferation [64].

The World Health Organization estimated that 11% of the 10.4 million new cases of tuberculosis that occurred in 2015 were reported in HIV-positive persons (1.2 million cases), with 400,000 deaths from TB. The proportion of HIV-positive

TB cases is highest in Africa (31%) and it is over 50% in some areas of South Africa [4].
Annual data collection rounds of the TB Surveillance Europe 2016 have estimated TB/HIV co-infection in 41 countries of Europe. In these countries, 207.996 of 233.450 notified TB patients had documented HIV test results; a total of 16.708 (8.0%) TB cases were detected with HIV-positive status. This is higher than the 7.8% of co-infection recorded in 2013. The Regional trend is influenced by the sharp increase in TB/HIV co-infection in the countries of Eastern Europe, Russia and Central Asia [17].
Co-infection is especially common among certain marginalized populations, such as homeless people, injecting drug users and immigrants. Foreign-born individuals represented ≥60% of notified TB/HIV co-infected cases in Belgium, Denmark. United Kingdom (>80%), France and the Netherlands while lower percentages (~30%) were reported in Italy and Spain [65].
According to data provided by the AIDS Action Center, the Higher Institute of Health, in Italy, since 1993 there has been a steady increase in cases of TB in patients with AIDS, who have gone from 6.8% in 1993 to 11% in 2010. In this period of 4075 cases of TB/HIV co-infection reported 34.1% are immigrants; just over half of these came from Africa, while the rest were mainly from South America and Eastern Europe. The rate of co-infected immigrants has increased over time going from 10.8% in 1993 to 64.6% in 2010 [66].
Some studies have pointed out, albeit from different perspectives and in different periods, the characteristics of the TB/HIV co-infection among immigrant population living in Italy.
Scotto observed, in a study covering the year 2003, that among 300 immigrants, hospitalised in 35 Italian Infectious Diseases Units with active tuberculosis, 31 (10.3%) presented TB/HIV co-infection. Almost half (48.4%) of the patients came from Africa, 20% were Asiatic, 20.3% came from Eastern Europe and 11.3% from South America. The clinical TB forms, among co-infected patients, were distributed as follows: lung tuberculosis in 21/31 cases (67.8%), lymph node tuberculosis in 4 cases (12.9%), pleural TB in 2 cases (6.4%), and one case (3.2%) each for bone TB, urinary TB, central nervous system (CNS) and muscular TB. Three patients had a multiple localization of TB. When analyzing the country of origin, together with the different TB forms we observed that extra-pulmonary forms were clearly prevalent among immigrants of Asian origin [20].
Camoni studied the characteristics of TB/HIV co-infected immigrants reported to the National AIDS Registry since 1993, the year in which TB was introduced as an AIDS-defining disease, to 2010. In this period, 4867 cases of AIDS were reported; among these, 1390 (28.6%) had TB (any location). The rate of TB/HIV co-infection increased from 10.8% in 1993 to 64.6% in 2010. The majority of immigrants (55.3%) originated from Africa, 29.0% from South America, 7.9% from Eastern Europe and 5.7% from Asia; the remaining originated from other European countries, North America and Oceania. Specifically, the proportion of TB/HIV co-infected immigrants originating from Africa and Eastern Europe increased in the period of survey, while the co-infected immigrants coming from South America, decreased in the same period. The 46.8% of co-infected patients presented pulmonary TB, 48.3% had extra-pulmonary TB and 4.9% had both forms of TB [67].
Ingrosso did a meta-analysis on risk factors for TB and TB/HIV co-infection in immigrant people in Italy. From January 1980 to January 2013, 13 references fulfilled inclusion criteria and took into consideration the relationship between HIV status and TB. Some of them reported that immigrants affected by TB had a higher probability to be HIV positive than Italian TB patients [45, 68-69]. On the contrary, another study reported that HIV infection was less frequent among immigrants compared to Italians [70]. According to other studies the association was weak and not significant [71-73]. In order to dissect the heterogeneity of these results in the association TB/HIV, the data of co-infection were analysed from 1996, when combined antiretroviral therapy for HIV was introduced. It was found that the TB/HIV co-infection was strongly represented in immigrants, in fact HIV positivity was about 3 times higher in TB affected immigrant people than among Italians [74].
From these data it can be assumed that the TB/HIV co-infection is an important health problem for the immigrant population and the number of AIDS and TB cases among foreign-born people increased progressively over time, similarly to the increase in the number of immigrants present in Italy [75,76]. This finding suggests that immigrant people have less access, except in the case

of acute illness; moreover, they may have a poor knowledge of HIV transmission routes and AIDS symptoms; all this can lead to a delay in diagnosis and, therefore, to a greater possibility that will establish the co-infection TB/HIV; in fact the number of late-testers for TB/HIV is very high among immigrants [67].

Drug resistance

Since its introduction, the specific antibiotic therapy has been the best way to combat active tuberculosis; unfortunately, from the very beginning antibiotic therapy has been associated with the emergence of drug-resistant strains of *M. tuberculosis* [77]. Resistance to anti-TB drugs has been highlighted to be greater in immigrants than in native populations of their host countries [78, 79]. The main factors that can determine the occurrence of resistance in immigrant subjects are: the incorrect use of anti-TB drugs, low patient compliance, or poor quality of drugs [80]. The types of drug resistance are essentially: *MDR (multidrug resistant)*: resistance to rifampicin and isoniazid; *XDR (Extensively drug resistant)*: MDR + resistance to fluoroquinolones + to at least one of the injectable II line (amikacin, kanamycin and capreomycin). The emergence of XDR-TB strains is, almost always, a result of mismanagement of MDR cases [81].

The recent European and Italian TB epidemiological picture shows an increasing number of multidrug resistant-TB (MDR-TB), particularly in Eastern European individuals: the majority are from the former Soviet Union (FSU), and in migrants from high MDR-TB burden countries to low endemic areas [82, 83].

In our previous study we observed that out of 300 subjects immigrants with active TB, MDR was demonstrated in 16% of 5.3% of cases presented a XDR [20].

Lombardi studied anti-TB drugs susceptibility in 239 (93.7%) strains of infected patients, by evaluating the distribution of respective resistance patterns in Italian vs. foreign-born TB cases. Mono-resistance to isoniazid (H) in Italian-born cases was documented in 9.2% of cases, resistance to H and any other first line drug (FLD) in 4.6% of cases and MDR-TB in 1.3% of cases. Among immigrants, mono-H resistance was found in 10.1%, poly-H in 12.8% of cases, and MDR-TB in 7.4% of cases. The proportion of MDR-TB was significantly higher among immigrants from Eastern Europe, the resistance trends among foreign-born increased significantly over time [84].

Fattorini collected about 2671 cases in immigrants between 2008 and 2010, and proved that individuals from medium and high risk countries retained their higher risk of developing MDR-TB even after moving to a low endemic country; he then showed a strong evidence of an association between MDR-TB and immigration status. The overall MDR-TB prevalence was 3.8%, but its rate was low in Italians (1.4%), while it was high in immigrants from the FSU, Romania and all other foreign countries (30.3%, 5.9% and 4.1% respectively) [85].

There seems to be an interesting correlation between genotypes of *M. tuberculosis* and drug resistance; in fact the Beijing lineage was found to be the single most dominant genotype among the pre-XDR and XDR isolates [47, 86, 87].

CONCLUSIONS

There is no doubt that the TB constitutes a primary health issue important to the immigrant population, especially if illegal; it is a major public health problem in Italy as well as in other low-incidence countries. The still growing trend of cases, the severity of the disease often accompanied to HIV infection and drug resistance characteristics, assume dramatic connotations.

However we must not forget that tuberculosis is mainly a social disease, inequitably affecting poor people, in fact the poverty-related factors such as poor living conditions and under nutrition increase the likelihood of infection and subsequent progression to active disease [88]. Improved living conditions and availability of specific drugs supply would certainly decrease the incidence of TB. Concordant with increasing interest in the social determinants of health in general, and of tuberculosis in particular, the Sustainable Development Goals and WHO's new End TB Strategy place emphasis on social protection and poverty-alleviation programmes [89].

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