Infectious Diseases

The burden of Tuberculosis in a province of a low incidence country: epidemiological differences between Italy-born, regular foreigner and irregular foreigner TB cases

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Keywords

Tuberculosis • Surveillance • Epidemiology • Migration status • End TB strategy

Summary

Introduction. *Tuberculosis (TB) represent a serious public health issue even in most developed countries, where TB cases are mostly concentrated in some risk groups, like immigrants from high-incidence TB countries. Aim of the study was to describe the occurrence of TB in Siracusa Local Health Authority (Italy) and to explore its determinants in three different populations: Italy-born, regular foreigner and irregular foreigner.*
Methods. *Cases were classified per patient origin and legal ground: Italy-born (IB); regular foreigners (REF); irregular foreigners (IRF). All the notifications were evaluated and uploaded to the Notification System of Infectious Diseases (PREMAL) by the Epidemiology Unit of the Prevention Department of Siracusa LHA.*
Results. *During the study period, 183 TB cases were detected: 72 (39.3%) were Italy-born, 26 (14.2%) were regular foreigners and 85 (46.5%) were irregular foreigners. Overall, foreign-born cases (regularly and irregularly residents) accounted for 60.7% of all cases. We demonstrated significative differences in epidemiological, demographic and clinical features among the three different groups.*
Furthermore, we registered a decrease in TB notifications of 59.5% among Italy-born patients, 46.0% among regular foreigners and 95.5% among irregular foreigners, who, however, remain the population group with the highest incidence of tuberculosis in Siracusa LHA.
Conclusions. *TB control in migrants is considered key to achieving TB elimination in low TB incidence countries, in accordance with the World Health Organization (WHO)'s End TB Strategy, that set ambitious targets for 2020–2035, including 90% reduction in TB incidence and 95% reduction in TB deaths by 2035, compared with 2015.*

Introduction

Tuberculosis (TB) is one of the oldest diseases known to affect humans and still represent one of major cause of death worldwide [1]. TB, caused by the bacillus *Mycobacterium tuberculosis*, is primarily a pulmonary disease. However, *M. tuberculosis* also infects lymph nodes, the pleura, bone, the central nervous system and other organs. These clinical presentations constitute extra-pulmonary TB. While 10% of those infected develop active disease, the majority of individuals mount an effective immune response leading to successful containment of *Mycobacterium tuberculosis* growth; a condition known as latent TB infection (LTBI) [2].
Despite the UN's resolution of ending tuberculosis infection by 2035, it remains a major public health challenge. Tuberculosis used to be the leading cause of death in infectious diseases and became the second after COVID-19 during the pandemic [1], including among persons living with human immunodeficiency virus (HIV) infection [3].
More than 10 million people continue to fall ill with TB every year. About a quarter of the global population is estimated to have been infected with TB. The reported global number of people newly diagnosed with TB was 7.5 million in 2022. This is the highest number since WHO began global TB monitoring in 1995. Globally in 2022, TB caused an estimated 1.30 million deaths [1].
Geographically, most TB cases in 2022 were in the WHO regions of South-East Asia (46%), Africa (23%) and the Western Pacific (18%), with smaller shares in the Eastern Mediterranean (8.1%), the Americas (3.1%) and Europe (2.2%) [1].
TB epidemiology is strongly influenced by social and economic development and health-related risk factors such as undernourishment, diabetes, HIV infection, alcohol use disorders and smoking. Strictly sense, TB can be considered a social disease [4].
A World Health Organization (WHO) initiative, The End Tuberculosis Strategy, set ambitious targets for 2020–2035, including 20% reduction in TB incidence and 35% reduction in the absolute number of TB deaths by 2020

and 90% reduction in TB incidence and 95% reduction in TB deaths by 2035, compared with 2015 [5-6].
The current TB epidemiological situation in Italy, as in many other industrialized countries, is characterized by an incidence lower than 10 cases/100,000 inhabitants in the general population, a threshold within which the WHO defines Italy as "low endemic country" [7]. In countries with low TB incidence, the cases are mostly concentrated in some risk groups, like immigrants from high-incidence TB countries. In Italy, 2,480 cases of TB have been notified in 2021, with a notification rate of 4 per 100,000. A foreign origin was detected in more than half of all TB cases (57.9%) [8].
Immigrants arriving from high-incidence TB countries may pose a threat to TB control in low incidence host countries. In Italy, a significant positive correlation between TB notification rates and immigration numbers was observed [9]. Besides the immediate morbidity and mortality from any resurgence of TB, there would also be the increased economic cost of treatment of cases, tracing and preventive treatment of contacts, as well as concern over the potential emergence of drug-resistant forms of TB, that are emerging as a greater threat and causing higher mortality rates [9]. TB in migrants from TB-endemic countries can be the result of different processes: arrival in the host country with prevalent active TB, entering the host country with latent tuberculosis infection (LTBI) that reactivates after arrival, new infection in the host country, or infection when travelling back and forth from the host country to the country of origin [10, 11]. TB control in migrants is therefore considered key to achieving TB elimination in accordance with the World Health Organization's End TB Strategy [5, 6].
Aim of the current study was to describe the occurrence of TB in Siracusa Local Health Authority (LHA), Italy, over a ten-year period (2014-2023) and to explore its determinants in three different populations, concerning demographic and epidemiological data, clinical features and risk factors for TB infection and transmission.

Methods

We conducted a ten-year retrospective analysis of all TB notifications in Siracusa LHA, from 1st January 2014 to 31st December 2023. According to ISTAT data, censed foreign born people account for 3.9% of the population (384,866 province population). The presence of regular foreigners in the province of Siracusa is lower than at national level, where migrants represent 8.6% of the resident population [12]. Any official data are available for irregular foreigners. According to an estimation by ISMU Foundation (Initiatives and Studies on Multi-ethnicity), an independent and highly qualified research centre, the estimated number of irregular foreigners is about a mean of 8.1% of regular immigrants through the years 2014-2023 (last available data for the year 2021) [13].
Cases were classified per patient origin and legal ground: Italy-born (IB); regular foreigners (REF); irregular foreigners (IRF) (*i.e.,* foreigners without residence permit, as migrants landed on our coasts).
By law, TB notification is mandatory in Italy, according to Ministerial Decree 15 December 1990 "Information system of infectious and diffusive diseases" (and subsequent amendment in Ministerial Decree 29 July 1998) [14 15]. All the notifications regarding the considered period were evaluated and uploaded to the Notification System of Infectious Diseases (PREMAL) by the Epidemiology Unit of the Prevention Department of Siracusa LHA.
A TB case was defined as all forms of active TB, including pulmonary and extrapulmonary TB. For the distribution between pulmonary and extrapulmonary TB, cases with both pulmonary and extrapulmonary TB were categorized as pulmonary TB. Diagnosis was either microbiologically confirmed or based on clinical and/or paraclinical findings suggestive of TB, prompting TB treatment. Information on how TB cases were detected was not available. There was no systematic TB screening among migrants during the study period.
Cases notified more than one time within 12 months were included using first notification, unless they had an outcome report of treatment completion or TB cure within the same 12-month period.
Number of TB cases and TB incidence (/100,000 population per year) were investigated for the considered period both for the total population and for the three principal population subgroups.
Calculation of TB incidence in the not Italy-born population was made with two different methods and using different data sources: first considering as denominators the data on immigrants regularly registered (subjects who own a regular residence permit) [16] and secondly considering the estimated prevalence of not regularly registered immigrant presence, by an independent research centre [17].
Study variables were analysed differentiating between the three principal subgroups. Comparison between groups were made using the calculation of odds ratio (OR) and its 95% confidential intervals (95% CI). Continuous variables (*i.e.,* age at notification) were compared using the student t-test for unpaired data. Statistical analysis was performed using Stata.

Results

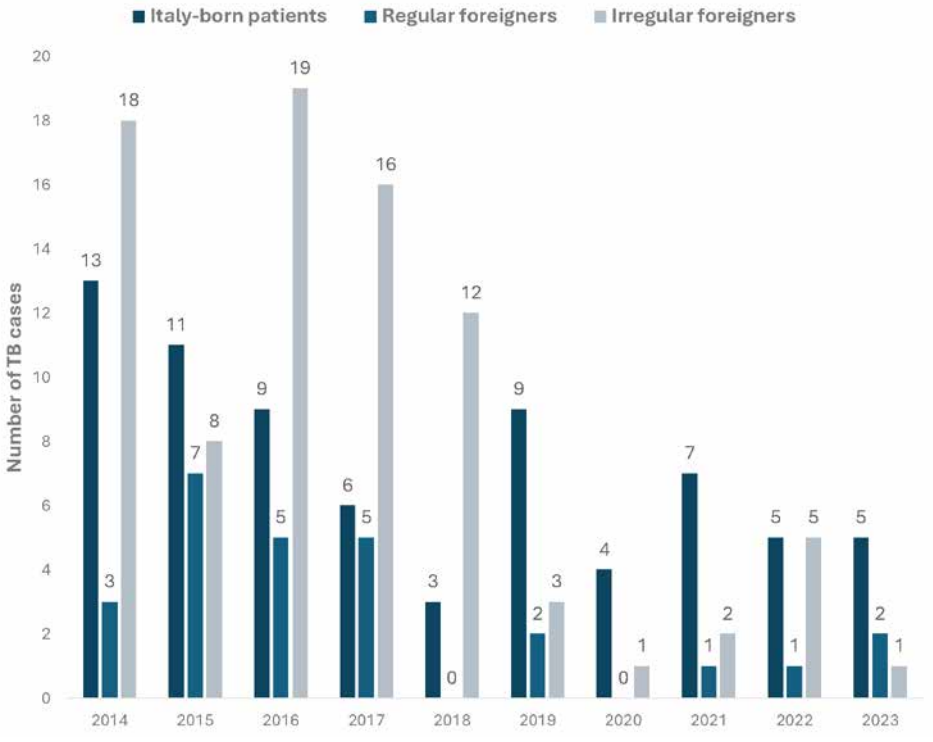
During the ten-year study period, 183 TB cases were detected and included in the study: 136 (74.3%) males and 47 (25.7%) females. Of the total, 72 (39.3%) were Italy-born patients, 26 (14.2%) were regular foreigners and 85 (46.5%) were irregular foreigners. Overall, foreign-born cases (regularly and irregularly residents) accounted for 60.7% of all cases (n = 111), while regularly residents (Italy-born and foreign-born) accounted for 53.5% (72 cases) (Tab. I). Figure 1 shows the distribution of the reported cases in the three groups of patients by year of notification.

Tab. I. Demographic and clinic characteristics of patients.

	TOT		IB		ReF		IrF	
	n	%	n	%	n	%	n	%
N	183		72	39.3%	26	14.2%	85	46.4%
Sex								
Males	136	74,3%	47	65,3%	16	61,5%	73	85,9%
Age								
Mean age (±SD)	38.4 (±22.3)		54.9 (±23.4)		38.8 (± 16.6)		24.4 (± 10.0)	
0-19	46	25,1%	7	9,7%	9	34,6%	36	42,4%
20-39	62	33,9%	12	16,7%	11	42,3%	41	48,2%
40-59	36	19,7%	17	23,6%	3	11,5%	8	9,4%
60-79	26	14,2%	23	31,9%	3	11,5%	0	0,0%
≥ 80	13	7,1%	13	18,1%	0	0,0%	0	0,0%
TB localization[1]								
Pulmonary	75	41,0%	25	34,7%	14	53,8%	36	42,4%
Extra_pulmonary	24	13,1%	5	6,9%	1	3,8%	18	21,2%
Unknown	84	45,9%	42	58,3%	11	42,3%	31	36,5%
TB type[2]								
New cases	63	34,4%	21	29,2%	12	46,2%	30	35,3%
Relapse cases	13	7,1%	8	11,1%	4	15,4%	1	1,2%
Unknown	107	58,5%	43	59,7%	10	38,5%	54	63,5%

[1] Information available for 99 patients. [2] Information available for 76 patients. IB: Italy-born; ReF: regular foreigners; IrF: irregular foreigners.

Fig. 1. Number and distribution of the TB cases in the three study groups reported by year to the Siracusa LHA from 2014 to 2023.



During the study period, TB incidence rate (IR) was 2.4/100,000 inhabitants among regular residents (both Italians and foreigners); specifically, IR in the Italy-born was 1.8/100,000, while in the regular foreigners IR was 17.7/100,000 ($p < 0.00001$). Overall, TB notification rate declined from 3.2/100,000 inhabitants in 2014 to 1.3/100,000 in 2023 in Italy-born group (-59.5%; $p = 0.07$, ns), while in the same period, TB notification rate declined from 24.2/100,000 to 13.1/100,000 in the regular foreigners (-46.0%; $p = 0.22$, ns). Using the estimation by ISMU (as reported in "Methods"), we calculated an IR reduction of 95.5% among irregular foreigners ($p < 0.0001$).

Overall, the median age of all TB patients was 38.4 (±22.3 SD) years, rising from 54.9 (±23.6) years in Italy-born patients to 38.8 ± 16.6 years ($p = 0.0021$)

and 24.4 ± 10.0 years ($p < 0.0001$) in regular foreigners and irregular foreigners, respectively. Among the latter, 93.0% of them was aged between 15 and 44 years old, while this percentage fell to 60.0% ($p < 0.0001$) and 26.4% ($p < 0.0001$) among regular foreigners and Italy-born patients, respectively.

Classification of TB type at the moment of diagnosis was available for 41.5% of patients (Tab. I). Among those 76 patients, a total of 63 (82.9%) were classified as "new cases", 13 (17.1%) as "re-treated cases", either failure or relapses. Regular foreigners were more frequently "new cases" (39.5%; $p = 0.71$, ns), while "relapse cases" status was found more frequently among Italy-born patients (10.5%; $p = 0.70$; ns), although without any statistical significance.

TB localization was available for 54.1% of patients (Tab. I); among them, 75 (75.8%) had pulmonary TB, 24 (24.2%) had extra pulmonary TB. Common extra pulmonary sites included pleura, intestine and peritoneum, which were affected in 4.9%, 3.8% and 3.3% of all TB cases reported, respectively. The likelihood of extra pulmonary TB was more common among irregular foreigners, although without statistical significance.

Regarding the geographical distribution of TB cases origin, Romania was the most represented country among the regular foreigners (44.0%, n = 11 cases), followed by Germany, Morocco and Sud Sudan (8.0%), while Somalia was the most represented country among the irregular foreigners (25.6%, n = 22 cases), followed by Gambia (12.8%, 11 cases), Eritrea and Nigeria (11.6%, 10 cases) (Tab. II). According to WHO Regions [18], a half of all patients (50.5%) came from the African Region, 31.5% from Eastern Mediterranean Region and 17.1% from European Region. Only 1 patient (0.9%) came from South-East Asia Region.

The occupation status was known only for 38.3% of patients, with difference among the three study-groups: 58.3% (n = 42) for Italy-born patients, 28% (n = 7) for regular foreigners and for 24.4% for irregular foreigners (n = 21). 57.1% of them were workers, 21.4% unemployed, 4.3% underage (< 18 y/o), 5.7% housewives, 21.4% retired. Among the workers, there were house cleaners, construction workers, street sellers, caregivers, agricultural day labourers, waiters, and traders.

The TB multidrug-resistant (MDR TB) status was known for only three patients; all of them were from Romania and were regularly resident in Italy.

The risk factors for TB identified in our study were reported for only four patients. They were HIV infection (1 case), HCV infection (1 case), homeless status (1 case) and pregnancy (1 case).

Four patients died from TB during the study period: 2 cases among irregular foreigners, 1 patient among Italy-born patients and 1 case was regular foreigner. Among them, there was 1 case of MDR TB and 2 cases of previously treated patients. The mean age of those four patients was 41,3 years (20 years for irregular foreigners, 43 for regular foreigners and 72 for Italy-born).

Discussion

In this study, we reported the epidemiological updates of TB incidence in Siracusa LHA throughout a 10-year observational study and we analysed the differences among three different study groups: Italy-born, regular foreigner and irregular foreigner patients.

TB still represent a serious public health issue in more developed countries, where has increasingly become a disease for specific population subgroups. Immigrants are an important population group at risk and their presence may affect the epidemiological situation in host TB low-incidence countries [19]. We showed that migrants, both regulars and irregulars, accounted for 60,7% of all TB cases in Siracusa LHA, although they constitute only a small fraction of the entire population. Indeed, during the study period, regular foreigners constituted 3.7% of the population, they accounted for 14.2% of all TB cases and their TB incidence rate was approximately 9.8-fold higher compared to Italy-born patients. Likewise, even if irregular foreigners constituted only 0.7% of the population (according to an estimation [13], they accounted for just under half (46.4%) of all TB cases.

Furthermore, our study demonstrated significative differences in epidemiological, demographic and clinical features among the three different groups. Italy-born patients were older than regular foreigners; 73.6% of Italy-born were > 40 years, while 76.9% of regular foreigners and 90.6% of irregular foreigners were younger than 40 years, respectively. Given the different mean age between the Italian and migrant patients, TB among elderly was mostly detected among the Italy-born group. Also, the proportion of males was different

Tab. II. Geographical origins of not Italy-born TB cases (both regular and irregular foreigners) by World Health Organization (WHO) region.

WHO Region	TOT		IB		ReF		IrF	
Eastern Mediterranean region (WHO-EMRO)	35	19,1%	0	0,0%	3	11,5%	32	37,6%
European region (WHO-EURO)	91	49,7%	72	100,0%	19	73,1%	0	0,0%
South-East Asia region (WHO-SEARO)	1	0,5%	0	0,0%	0	0,0%	1	1,2%
The African region (WHO-AFRO)	56	30,6%	0	0,0%	4	15,4%	52	61,2%

IB: Italy-born; ReF: regular foreigners; IrF: irregular foreigners.

between the three-study groups: males were 65.3% among Italy-born, 61.5% and 85.9% among regular foreigners and irregular foreigners, respectively. The latter were more frequently "new cases" than regular foreigner and Italy-born patients. The "unknown" TB type status was significantly associated with irregular status. Extra pulmonary disease was more common among irregular immigrants. The higher proportion of extrapulmonary TB among irregular migrants (approximately 3-fold higher compared to Italy-born patients) is consistent with previous founding [20-21], and it could be attributed to the large proportion of migrants from Africa countries in our study (approximately one third of all patients and more than 60% of all irregular foreigners) [22]. From a public health perspective, extrapulmonary TB is less important for TB transmission, but extrapulmonary TB is often attributed to reactivation [23], which emphasizes the need to consider latent TB infection (LTBI) screening among migrants. Our data are in accordance with other studies [24-29].

The observed higher TB incidence rate in foreign-born (regular and irregular residents) in our study may had two different dynamics: an increase in the absolute number of foreign-born (regular and irregular residents) TB cases, mainly explained by increased immigration from high TB endemic countries; a decrease TB incidence among native population [30]. According to data, regular and irregular migration increased in Siracusa LHA by 23.4% from 2014 to 2023 [31, 32]. Our results are in accordance with trends at the national level [8].

Migrants are a heterogeneous group, characterised by specific language and cultural identities, with specific health needs. They include undocumented people, asylum seekers, migrants temporarily resettled, or newly resettled during the year.

Among migrants, we observed significative differences in TB risk between regular residents and irregular immigrants, with the former population being more affected. Compared to irregular foreigners, the observed lower TB IR in regular foreigners may be explained by the decreasing risk of TB in the latter group after staying in a low burden country, as well as by the gradual improvement in health care strategies addressing migrants, especially regular ones, from high TB burden countries [33]. However, the legal process for becoming resident (and consequently permanently entitled to health assistance) requires time, a job position and permanent housing, all factors well known to affect the risk of TB reactivation in migrants [33].

There are different drivers of TB in migrants that act along all the migration trajectory: pre-departure (in the country of origin), transit, arrival and early settlement (in the host country), return travel (in the country of origin, again). First, TB burden in the country of origin probably is the most important societal level determinant [34-36]. Secondly, migrants, particularly asylum seekers and refugees, are at high risk of TB due both to the perilous situation they are escaping from, and to the dangerous conditions encountered during migration. Thirdly, risk after arrival is influenced by migrant, social and health policies in the host country [37]. Finally, once resettled, migrants usually travel back to their country of origin without seeking pre-travel advice [34-38].

Overall, provincial TB incidence rate estimation was 4.6/100.000; it was quite lower than other northern and central region [24-27] and in line with the most recent national data (4.2 cases/100.000, from 6.5/100000 in 2017) [8]. For all study-groups, TB notification curve presents a decreasing trend throughout the study period, although with different magnitude between the groups and isolated annual increases. Irregular immigrants presented major fluctuations within the decreasing trend, probably explained by differences and fluctuations in the total number of migrants and their risk profile.

From 2020 a remarkable reduction of TB notifications was observed in every of the three-population groups. Overall, we passed from a mean of 24.3 notifications per year in the pre-pandemic period (years from 2014 to 2019), to a mean of 8.5 notifications per year in the pandemic one (2020-2023). However, the observed reduction was significantly different among the three population groups, with a major magnitude observed in irregular foreigners (from a mean of 12.7 notification per year in the pre-pandemic years, to a mean of 2.5 in the pandemic one; -80.3% notifications per year), followed by regular foreigners (from 3.7 notification/year to 0.8; -78.4% per year) and Italy-born patients (from 8.5 to 5.3; -37.6% per year).

We hypothesized that COVID-19 pandemic played an important role in reducing the observed trend in notifications. Worldwide, the pandemic demonstrated a disproportionate impact on access to essential TB services characterised by pronounced drops in the number of TB cases notified [1, 39], that was likely to reflect two distinct challenges: under-reporting and missed (or delayed) TB diagnosis on a large scale. Decreasing notification could, however, also indicate a real less in TB transmission, due to restrictions and protective measures during the pandemic [39, 40].

Most developed countries, with low TB incidence levels and with the aim to achieve the TB elimination goal, have two major impediments, namely the reactivation of latent TB infection (LTBI) among the elderly population (especially in native population) and among other risk groups, including immigrants from high TB incidence countries [41]. The elderly are considered a large reservoir for *Mycobacterium tuberculosis* infection, especially due to the reactivation of latent infections [42]. Furthermore, aging of the immune system is considered a driver factor for active TB, as well the presence of comorbidities [43].

Due to their vulnerability, it is important to control TB among migrants. Strengthening screening for active TB at arrival can potentially reduce the high TB risk following immigration. However, given the long-term TB risk related to reactivation of TB [28], LTBI screening and treatment could be important tools to reduce subsequent reactivation among the high-risk groups. Furthermore, as many TB cases develop years after arrival, long-term access to preventive health care

should be prioritized so that TB signs can be spotted and diagnostics initiated [44].

The most important strength of our study is taking into consideration the differences among different groups of populations, in terms of the epidemiological, demographic and clinical features. Because tuberculosis is a disease with a strong social connection [4], its understanding demands that the impact of social and economic factors on the individual (including countries of birth, migration status, living conditions), be considered as much as the mechanisms by which *Mycobacterium tuberculosis* cause damage to the human body [45]. In this sense, TB has been considered a marker of social inequities in health [46].

The analysis of data at the local level is another strength of our study. In our view, having in-depth analyses of the local epidemiological situation is extremely useful for putting in place actions targeted to the specific needs of the local context, first and foremost appropriate prevention measures. Leveraging local data sources and integrating them with regional and national data sources will provide more timely and geographically specific analyses to support local insights and specific policy development.

There are some limitations to address. The first is the TB incidence estimation among irregular immigrants, in the absence of any official data regarding the real size of this population, that could lead to a its wrong estimation in this population (see "Methods" section for details).

Another limiting is basing only on notified cases as a unique source of information. Although the surveillance system is considered quite efficient in Italy, it can be hampered by under-reporting and inconsistency.

Another limitation was the lack of some information, such as MDR situation, presence of risk factors (HCV, HBV, HIV, alcohol and drug abuse), type of housing, job description, that were available in a small number of patients. Maintaining data quality and completeness to provide an optimal and efficient report is essential requirement for the establishment of notifiable diseases information system architecture.

Conclusions

This study provides a clear description of the current epidemiology of TB in Siracusa LHA, which will help inform appropriate public health action and health service provision. In this study, we have found an overall decline in TB notifications during the study period, in line with the End TB Strategy milestones. Discontinuation of services due to the COVID-19 pandemic could have contributed to the reduction of notifications in 2020, especially among undocumented immigrants. There is no doubt that the TB constitutes a primary health issue important to the immigrant population, that still represent the group with the highest number of cases. The enhancement of health care strategies directed to immigrants from high TB burden countries should be a priority in the efforts towards global TB elimination.

It is a common misconception that migrants simply 'import' TB from abroad. They "present a tuberculosis picture from the country of origin" and not from the host country where the disease eventually manifests [47]. Indeed, differential pathogen exposure can explain much of the higher incidence of TB among migrants and ethnic minorities, due to both pre-migration residence in high-incidence countries and maintenance of transnational links with the country of birth or ethnic origin. However, positing this as the sole driver fails to address the complex interplay of factors driving the vulnerability of migrant and ethnic groups to infection and progression to active disease. Furthermore, certain migrant and ethnic groups face barriers to accessing treatment including cultural differences in treatment-seeking behaviours, stigmatisation of sufferers, and barriers to healthcare access. TB in ethnic minorities does not occur in isolation but against a backdrop of socioeconomic, political and cultural context that affects their knowledge, attitudes and behaviours. 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 [37-48].

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Conflicts of interest statement

Authors declare no conflict of interest.

Authors' contributions

FC: conceptualization, methodology, statistical analysis, original draft preparation and writing. FC, EDP, CR: acquisition of data. FC, FB EDP, MLC: formal analysis and interpretation of data. FC, FB: writing, review and editing. FC, EDP, MLC: supervision and project administration. All authors have read and agreed to the submitted version of the manuscript.

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