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Latent and active tuberculosis infections in migrants and travellers: A retrospective analysis from the Spanish +REDIVI collaborative network

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ABSTRACT

Background: Tuberculosis (TB) is the leading cause of infectious disease mortality worldwide. We analysed active and latent TB infections (LTBI) from the Spanish Network for the Study of Imported Infectious Diseases by Travellers and Immigrants (+REDIVI).

Methods: Observational, retrospective, multicentre study of TB and LTBI registered in the +REDIVI network from October 2009 to December 2016.

Results: Of 1008 cases of LTBI, 884 (87.7%) were immigrants; 93 (4.5%), immigrants visiting friends and relatives (VFR); 2 (0.9%), VFR-travellers; and 29 (1.1%), travellers. Absolute (N = 157 vs. N = 75) and relative (12.5% vs. 5.9%) frequency decreased over the study period (p = 0.003). Median time to diagnosis was 24.6 months (females 50.3 vs males 11.9; p < 0.001).

Of 448 TB cases, 405 (90.4%) were in immigrants; 30 (6.7%), VFR-immigrants; 6 (1.3%), VFR-travellers; and 7 (1.6%), travellers. Median time to diagnosis was 62.5 months (females 86.6 vs males 70.1; p = 0.0075).

There were 8 multidrug resistant TB cases and 1 extensively drug resistant case of TB, all in immigrants.

Conclusion: TB was frequently diagnosed more than 5 years after arrival in Spain. Screening programmes for TB and LTBI in immigrants should be considered beyond this time point. Women showed a higher diagnostic delay for both latent and active TB.

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Conflicts of interest

The authors declare having no potential conflicts of interest.

1. Introduction

Tuberculosis (TB) is the first infectious disease reason of mortality. It caused 1.5 million deaths worldwide in 2014. Recent efforts to control this disease have paid off, with an annual decrease in incidence of about 1.5% since 2000 and a reduction in mortality of 47% since 1990. This progress has encouraged global strategies to become more ambitious, from 'Stop TB' to 'End TB' [1].

The relevance of TB among foreigners in high-income countries is increasing and it is a new challenge for disease control [2]. In Spain, the proportion of reported cases of TB in foreign nationals is among the lowest of all high-income countries [3].

The European Centre for Disease Prevention and Control considers Spain as a low incidence of TB country, as its rate is less than 20 cases per 100,000 population per year. In 2015, 5007 new diagnoses were declared(incidence of 10.6 cases per 100,000 population). Of these, 30% were in people born outside of Spain, mostly from Morocco, Romania and Pakistan [4]. Proportion of cases in foreigners varies considerably by region, with Catalonia and Madrid having the highest proportion of cases among non-spanish citizens (37% and 20%, respectively).

The prevalence of multidrug-resistant TB (MDR-TB) in Spain is currently low, only 4.7% of the total cases diagnosed are MDR-TB [4]. However, there is risk of importing MDR-TB and extensively drug-resistant TB (XDR-TB) from countries with a high prevalence [5], with some authors proposing a non-national origin of TB infections as a risk for tuberculostatic resistance [6].

In January 2017, according to municipal registries, there were 4,549,858 foreigners living in Spain, which represents 9.8% of the population, compared to 1.8% in 1999. The absolute increase was nearly 4 million foreign-born nationals who were residing in Spain [7], with this subgroup having about 10 times the risk of developing TB after arrival compared to the local population [8]. Taking into account the actual inequalities in access to healthcare services and often precarious living conditions present in these populations, there is a risk of perpetuating a niche of TB transmission [9]. These particular challenges, shared by other countries with substantial immigrant populations, have prompted calls to develop specific strategies at a global level. The World Health Organization (WHO) has adapted their End TB strategy to respond to the needs of immigrant populations [10].

In addition to the risk of importing TB associated with immigration, travellers are also at risk of infection while they are as they can import latent and active cases of TB. In 2012, Spanish residents made 12.2 million tourism-related trips abroad [11]. While most of these were to destinations in the European Union, 10% (1.22 million trips) were to the Americas and 6.5% to Morocco [11], both high TB prevalence regions.

AbsoluteTB infection risk in travellers is generally considered low. Its rates ranges from of 0.85–1.4 cases per 1000 person-months [12,13]. However, these rates depend on the prevalence of TB in the destination country, the duration of the trip and the activities performed during the stay (and are clearly higher in healthcare workers) [14]. Moreover, there have been reports of imported cases of XDR-TB in travellers [15]. The increasing mobility and improvement in transportation has also created certain concerns, especially with air travels, which may give rise to transmission even during the flight [16]. Indeed, in recognition of this risk, WHO has established specific recommendations for preventing and controlling TB during flights [17].

In Spain, to date there has been no precise evaluation of the relevance of TB in immigrants and travellers at a national level. Data in travellers are almost non-existing, while those for latent TB infections (LTBI) in adult immigrants are limited to certain national reference centres, with a high proportion of immigrants from sub-Saharan Africa [18–20], or to certain population groups such as prisoners [21] or immigrants living with HIV [22], with LTBI prevalence of 17%–49% and TB prevalence of around 6%.

The Spanish National Centre of Epidemiology does not have data on LTBI. The data for active TB are incomplete (as country of origin is only registered in 68% of imported cases, and the living time in Spain in only 35.8%), these makes analysing the information difficult. Our aim was to describe cases of LTBI and TB diagnosed in immigrants and travellers, as registered in the Spanish Network for the Study of Imported Infectious Diseases by Travellers and Immigrants (+REDIVI),

comparing the sociodemographic and clinico-microbiological characteristics between populations.

2. Material and methods

2.1. Design and study population

Observational, retrospective, multicentre study nested in the +REDIVI network [23]. This network had five affiliated centres in 2009, with others joining in later years; nowadays, there were 25 centres from eight Spanish regions. Collaborating centres have specialised units in tropical medicine, medicine for immigrants and travellers, and/or general units on infectious diseases. We analysed patients included from October 2009 to December 2016. Inclusion criteria were: LTBI patients (diagnosed by purified protein derivative (PPD) skin test, quantiFERON test, or positive T-SPOT, without active disease) and TB patients(with microbiological detection of *Mycobacterium tuberculosis*). The definition of the disease as 'imported' depended on the protocol of each centre.

Network members share an anonymised online database. New cases of imported diseases are registered in it. The network was launched in 2009, and the coordinating centre (Ramón y Cajal Hospital) is responsible for managing the database, ensuring quality, and monitoring adherence to a predefined protocol. Database does not contain personal information that could identify patients – only centres had access to personal and clinical data for the cases they manage. A unique identifier is generated for each. Thus, data cannot be directly linked to each patient. Clinicians considered exposure during travel, incubation periods and symptoms in order to evaluate the origin of the disease. A single patient can thus generate more than one case identifier if they have made various trips and have been diagnosed with an imported case following each one.

Variables included on data collection form were demographic characteristics, epidemiological and clinical issues, and a brief description of the disease. Demographic data include: date of birth, sex, country of birth, and country of residence in the past five years.

Clinical and epidemiological data included type) of immunosuppression, the type and duration of travel, date of arrival to Spain, date of return, country of destination (for travellers) or origin (for immigrants), level of risk associated with the travel, performance (or not) of pre-travel consultation, of malaria prophylaxis, and prescription and adherence to anti-malarials. The + REDIVI network classifies patients as: immigrant (person living in Spain but born elsewhere), immigrant visiting friends and relatives (VFR-immigrant: immigrant who returns to country of origin to visit friends and family), traveller visiting friends and relatives (VFR-traveller: first generation of immigrants travelling to their parents' country to visit friends and family), and travellers (conventional international tourists and ex-patriates). Disease-related variables were: date of consultation, reason for visit (based on predefined symptoms and syndromes), and final diagnosis. Cases were classified according to 519 diagnositic codes for 22 possible syndromes. Time to diagnosis was calculated as time elapsed between date of arrival to Spain and the date of consultation when the disease was diagnosed.

2.2. Statistical analysis

Qualitative variables were expressed as absolute and relative frequencies. Quantitative data were expressed as medians and interquartile ranges (IQRs). We calculated 95% confidence intervals (CIs). We used Pearson's correlation coefficient to assess temporal associations, and the Chi-squared test and Fisher's exact test (when necessary) to compare categorical variables. Continuous variables were compared using the Student's *t*-test (when data were normally distributed) or the Wilcoxon test (when they were not). We used R software version 3.4.1 [24].

3. Results

12,044 episodes of imported disease were registered during the study period. Of them 7246 (60.2%) were in immigrants and 4798 (39.8%) in travellers. The median number of episodes per year was 1476 (IQR 1275 to 1546). Fig. 1 presents the geographic distribution of patients attended by region of birth.

3.1. Latent tuberculosis infection

1008 patients were considered to have LTBI(8.4% of the total cases diagnosed in the +REDIVI network). LTBI rate was higher in immigrants (12.2% n = 884),while it was lower in: VFR-immigrants in 4.5% (n = 93), travellers 1.1% (n = 29), and VFR-travellers 0.9% (n = 2). Most cases (n = 671, 66.7%) were men, and the median age

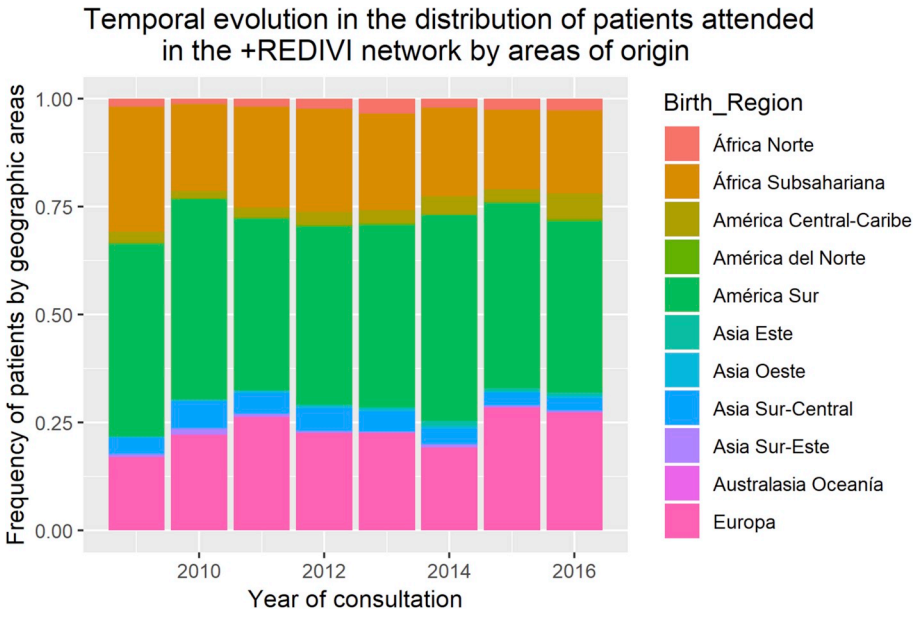

Fig. 1. Timeline distribution of patients attended in the +REDIVI network according to areas of origin.

was 30 years (IQR 22.7 to 37.2). Number of cases decreased from 157 in 2009 (12.3% of infections registered that year) to 75 (5.9%) in 2016 (Pearson's correlation coefficient = −0.88; p = 0.003). This trend remained significant when stratifying by type of case, except in VFR-travellers (Fig. 2). A linear regression showed a significant association with the number of patients born in sub-Saharan Africa attended per year (p = 0.02).

We performed a subgroup analysis by sex in immigrant patients. Men were younger than women (mean 28.5 years vs 34.7 years; p < 0.001), had a shorter time to diagnosis (median 40.3 months vs 59.5 months; p < 0.001), and had lower prevalence of HIV (1.2% vs 3.4%, p = 0.03).

In travellers, median duration of travel was 96 days (IQR 30 to 331.8). There were six cases in children, all VFR-travellers.

Table 1 summarises data on cases of LTBI. Fig. 3 shows the countries of origin in immigrants with LTBI.

3.2. Tuberculosis

There were 448 cases of TB, (3.7% of the episodes registered in the +REDIVI network). 58.7% were in males. Median age was 33.3 years (IQR 26.4 to 40.4). Overall 405 (90.4%) cases were in immigrants; 30 (6.7%), in VFR-immigrant; 6 (1.3%), in VFR-travellers; and 7 (1.6%), in travellers. The annual ammount of cases was stable over 50 during the study period. This figure supposes from 2.7% to 5.0% of the total infections detected by + REDIVI each year. There was no significant temporal trend (Pearson's correlation coefficient = 0.33; p = 0.44) in the overall analysis or in the stratified analysis by type of patient (Fig. 2). Table 2 shows the characteristics of TB cases. Fig. 4 shows countries of origin in immigrants with TB. Analyzing by sex in immigrants, there was no difference in mean age (34.5 years vs 34.7 years; p = 0.85), distribution of countries of origin (p = 0.42), syndromes at presentation (p = 0.2), or HIV prevalence of(9.8% vs 6.3%, p = 0.34).

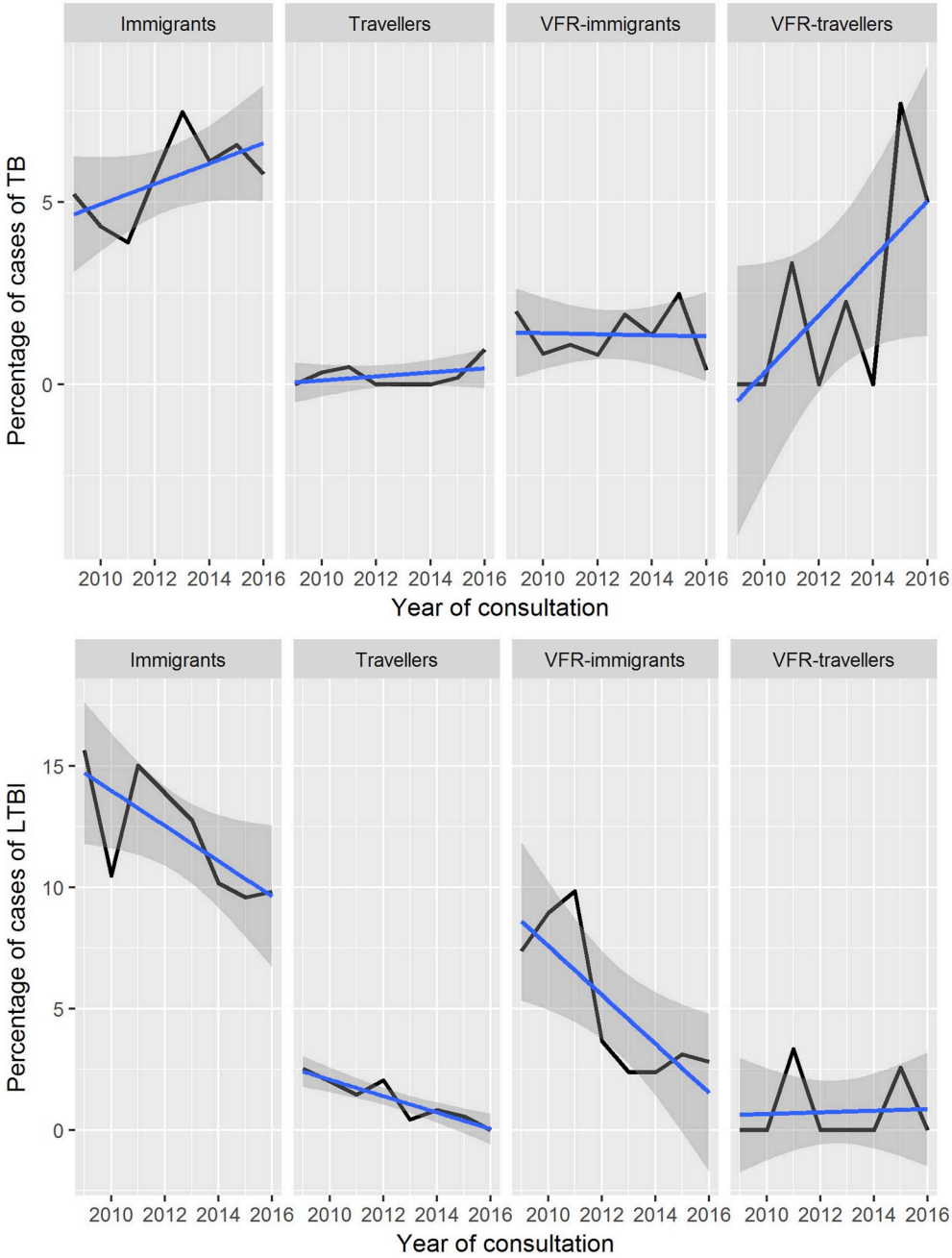

Fig. 2. Temporal evolution of cases of latent tuberculosis infection (LTBI) and tuberculosis (TB) in the +REDIVI network, disaggregated by type of case.

Table 1
Characteristics of patients with imported LTBI.

	Immigrants N = 884	VFR-immigrants N = 93	VFR-travellers N = 2	Travellers N = 29	P value
Median (IQR) age, in years	29.1 (22.2–35.8)	37.4 (30.9–46.3)	5.3 y 5.4 años	33.7 (30.4–38.7)	**<0.001**
Male sex (%)	69.2	49.5	50	42.4	**<0.001**
Percentage of total patients with LTBI in 5 most frequent countries of origin (in immigrants) or destination (in travellers) in each category	Bolivia 19.6% Cameroon 11.2% Senegal 8.3% E. Guinea 5.9% Guinea 5.7%	Bolivia 24.7% E. Guinea 12.9% Nigeria 7.5% Morocco 7.5% Senegal 6.5%	E. Guinea 50% Pakistan 50%	Bolivia 10.3% India 10.3% Tanzania 6.9% E. Guinea 6.9% Vietnam 3.4%	**<0.001**
Median (IQR) time from arrival in Spain to diagnosis, in months	24.47 (4.4–66.8)	107.5 (54.6–163.5)	0.6 and 0.8	1.56 (0.4–7.1)	**<0.001**
Most frequent syndrome of presentation	Health check-up	Health check-up	Health check-up	Health check-up	1
Co-infection with HIV	16 (1.8%)	2 (2.1%)	0	0	0.82

E. Guinea: Equatorial Guinea; IQR: interquartile range; LTBI: latent tuberculosis infection; VFR: visiting friends and relatives.

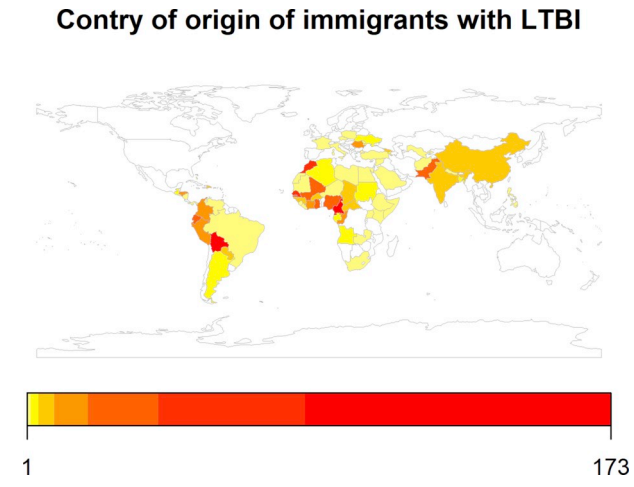

Fig. 3. Absolute number of immigrant patients with LTBI, by country of origin.

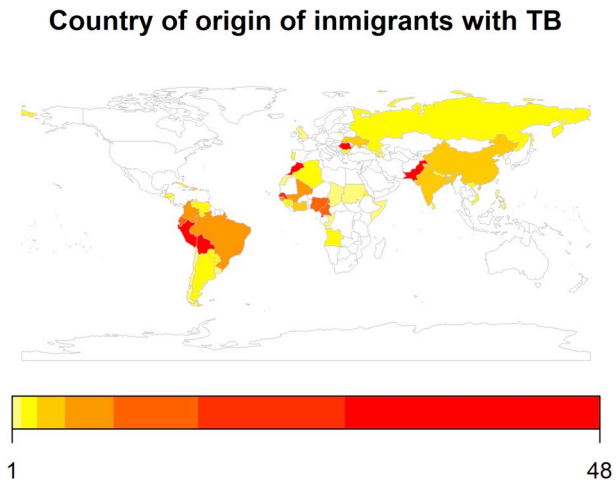

Fig. 4. Absolute number of immigrant patients with tuberculosis, by country of origin.

However, we did observe differences in the median time to diagnosis, which was longer in females than in males (86.6 months vs 70.1 months, p = 0.0075).

We observed 7 cases in travellers, whose median duration of travel was 30 days (IQR 15.5 to 725). Four (57.1%) of these cases were diagnosed after high risk trips, and only two (28.6%) of the patients had undergone a pre-travel consultation.

There were two cases of TB in children, both in VFR-travellers.

3.3. Multidrug-resistant and extensively drug-resistant tuberculosis

There were 8 cases of MDR-TB in the +REDIVI network during the study period. All occurred in immigrants and 62.5% (n = 5) in women. Median age was 31.5 years (IQR 26.5 to 35.6). Patients were coming from Romania (n = 4), Peru (n = 1), the Ukraine (n = 1), Nepal (n = 1), and the Dominican Republic (n = 1). Median time to diagnosis was 73.9 months (IQR 53.6 to 94.9). Five cases presented as respiratory

Table 2
Characteristics of patients with imported tuberculosis.

	Immigrants N = 405	VFR-immigrants N = 30	VFR-travellers N = 6	Travellers N = 7	P value
Median (IQR) age, in years	33.2 (26–40.1)	37.2 (32.9–40.9)	9.7 (6.1–15.6)	33.2 (29.5–39.2)	**0.007**
Male sex (%)	58	63.3	50	85.7	0.46
Percentage of total patients with TB in 5 most frequent countries of origin (in immigrants) or destination (in travellers) in each category	Romania 11.9% Morocco 11.4% Bolivia 11.1% Peru 9.1% Pakistan 9.1%	Bolivia 23.3% Romania 16.7% Peru 10% Morocco 10% Senegal 6.7%	Morocco 66.6% Peru 16.7% Ecuador 16.7%	India 28.6% Sudan 14.26% Rusia 14.26% UK 14.26% El Salvador 14.26%	**<0.001**
Median (IQR) time from arrival in Spain to diagnosis, in months	62.6 (24.2–225.7)	113.4 (85.4–145.8)	0.9 (0.2–4.4)	1.7 (1.1–2.4)	**<0.001**
Most frequent syndrome of presentation	Respiratory 38% Fever 19.6% Adenopathies 16%	Respiratory 23.3% Fever 20% Abnormal lab tests 16.7%	Fever 50% Respiratory 16.7% Abnormal lab tests 16.7%	Respiratory 57.1% Fever 28.6% Abnormal lab tests 14.3%	0.6
Type of tuberculosis	212 (52.3%)	15 (50%)	2 (33.3%)	6 (85.7%)	0.25
Pulmonary	193 (47.7%)	15 (50%)	4 (66.7%)	1 (14.3%)	
Extrapulmonary					
Co-infection with HIV	31 (7.65%)	4 (13.3%)	0	0	0.55

IQR: interquartile range; VFR: visiting friends and relatives.

syndromes, one due to abnormal laboratory tests, one following a health check-up, and one due to adenopathies. None of the patients had an HIV co-infection.

There was one case of XDR-TB in a 37 year old male Venezuelan immigrant, who presented to the health care centre three days after arriving in Spain with a respiratory syndrome but no HIV co-infection.

4. Discussion

4.1. Latent tuberculosis infection

Most cases of LTBI registered in the network were in asymptomatic immigrants undergoing a check-up. Spanish clinical practice guidelines recommend systematic screening for LTBI in recent (<5 years) immigrants from highly endemic areas (>50 per 100,000 population) [25], which probably explains the time since arrival in Spain we observed in our cohort. Median age in immigrants was 29.1 years (IQR 22.2 to 35.8). Most of them were men. In travellers and VFR, the median age was slightly higher. No clear difference between sexes were found. There were only two cases in VFR-travellers.

The number of imported cases shows a clear downward trend both in absolute and relative terms. This fact could be related to different factors. Changing migratory flows (especially in sub-Saharian migrants) and countries of origin in immigrants received over the study period could partly explain the decreasing number of patients from sub-Saharan Africa whose cases were registered in the network. Another factor could be the progresively global decrease in TB [1]. We cannot rule out lower screening rates in immigrant population as a possible explanation.

Regarding the country of origin, the most frequent was Bolivia. Then we found several sub-Saharan Africa countries. This probably reflects a combination of factors, including the number of immigrants coming from these countries, their prevalence of LTBI, the migratory routes used, and usual practices in tropical medicine units that assess patients for the presence of LTBI during screening for Chagas disease [26–28].

4.2. Active tuberculosis

Among cases in immigrants, Romania was the most common country of origin, followed by Latin American countries. This fact contrasts with data coming from the Spanish National Centre of Epidemiology, where Morocco is the leading country, followed by Romania and Bolivia. However, this database has data on the country of origin only for 68% of the patients born outside of Spain [4]. There were approximately 50 cases of TB each year. This number remained stable over the study period, representing about 4% of the total diagnoses made in the +REDIVI network. In the 2018 Spanish National Centre of Epidemiology report, the number of cases in non-Spanish people did go down, although this decrease was lower than that observed in the Spanish population [4]. Median time to diagnosis from the time of arrival was 62.5 months (IQR 25.2 to 225.7), which is longer comparing to current estimates that establish the highest risk for TB in immigrants within the first two years after arrival [3]. In fact, new data are questioning this hypothesis, with results that support a more persistent high risk of TB in immigrants for upwards of 10 years [29]. Our data are consistent with this latter possibility, as many as 25% of the cases of TB were in immigrants who had lived in Spain for 18 years or longer at the time of diagnosis. The fact that immigrants are generally more socioeconomically deprived probably favours reactivation of TB as well as reinfection from contact with bacilliferous patients [30]. Nevertheless, recent studies using molecular genotypification have reported that immigrants are less likely than autoctonous populations to belong to clusters with indications of recent transmission, suggesting that most of these cases are due to reactivations of LTBI [3]. This is in line with the report of migrants health worsening during their stay in the host country [31].

4.3. Multidrug-resistant tuberculosis

There were 8 cases of MDR-TB in immigrants, mostly from Eastern Europe. This result underlines the importance of high-quality healthcare for immigrants, not only for humanitarian reasons (which is reason enough by itself), but also to halt the dissemination of multidrug-resistant strains of TB in Spain and in the European Union. Moreover, substantial advances in treatments available for MDR-TB and multidrug-resistant strains of LTBI make early detection of cases – and their contacts – even more important [32,33]. Maintaining universal acces to healthcare seems more essential than ever [34].

We also observed one case of XDR-TB that was diagnosed three days after arriving in Spain. The patient came from Venezuela, and his infection could have represented a risk for the people on his flight, raising questions about the necessity for even stricter control of airplane passengers.

Cases in children (6 LTBI and 2 TB) were only in VFR-travellers, suggesting that this group may need to receive specific services, such as special pre-travel advice, systematic post-travel screening, or even administration of the Bacillus Calmette-Guérin (BCG) vaccine at birth.

We also observed a pronounced delay in diagnosis among females, in both LTBI and TB. Women have been reported to be an especially vulnerable subgroup [35,36], justifying specific efforts to detect infections more quickly in this population.

4.4. Limitations

Although the +REDIVI network covers a large part of the Spanish national territory, with a total of 25 collaborating centres, the network does not register all cases of TB or LTBI in travellers and immigrants, so we cannot rule out a possible selection bias. Similarly, understanding whether an infection was imported or acquired in the country where the study took place is not straightforward, and the decision to register the case in the network depended on each centre, so inclusion of data was probably not homogeneous. Nor can we estimate the frequency over the total number of immigrants from a particular area, as healthy immigrants are not included. We can only calculate absolute numbers and the relative frequency of cases compared to other diseases. Furthermore, the diagnostic algorithms for LTBI are not uniform across centres, and we can rule out neither false positives (for example, for PPD in patients vaccinated with BCG) nor false negatives (especially in immunodepressed individuals). However, the sample size was very large, with a total of 12,004 episodes of infectious disease in immigrants and travellers, so we consider the data to be fairly representative.

5. Conclusion

There was a high percentage of cases in immigrants who had arrived in the country more than five years previously. Given these results, we propose that screening programmes for LTBI and TB in immigrants should be performed extending the current threshold of five years after arrival to improve detection of late imported cases as well as early cases acquired in our country. A diagnostic delay of both LTBI and TB in female immigrants was noticed, a subgroup that tends to be especially vulnerable.

Among travellers, on the other hand, the relevance of both infections is much lower, though the fact that the only children with detected cases were VFR-travellers suggests that these children are at greater risk than the general population of children. Specific preventive measures could be warranted.

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