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Differential findings regarding molecular epidemiology of tuberculosis between two consecutive periods in the context of steady increase of immigration

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Abstract

The demographic characteristics of the population of Madrid, with a steady increase in immigrants, from 4.7% in 1998 to 17.4% in 2007, provide an opportunity to study in depth the transmission of TB. Our aim was to compare two 3-year longitudinal molecular studies of TB to define transmission patterns and predictors of clustering. Two prospective population-based molecular and epidemiological studies (2002–2004 and 2005–2007) of TB patients were conducted in nine urban districts in Madrid using the same methodology. During the period 2002–2007, 2248 cases of TB were reported, and the incidence decreased from 23.5 per 100 000 in 2002 to 20.8 in 2007 ($p < 0.001$). A total of 1269 isolates were molecularly characterized and included in the study. The comparison between the two periods showed that the percentage of foreign-born patients among TB cases increased from 36.2% to 45.7% ($p < 0.001$). Furthermore, the percentage of clustered cases decreased (36.6% vs. 30.6%; p 0.028), and this decline was associated with a decrease of clustered cases among men and people under 35 years. We also observed a decrease in cases belonging to clusters containing ≥6 people (14.2% vs. 8.2%; $p < 0.001$), and in cases belonging to mixed clusters containing Spanish-born and foreign-born patients (18.5% vs. 11.1%, $p < 0.001$). Our molecular epidemiology study provides clues to interpret the decrease in the incidence of TB in a context of steady increase of immigration. In our region, the decrease in the incidence of TB can be explained predominantly as a result of a decline in recent transmission.

Keywords: immigration, molecular epidemiology, recent transmission, Tuberculosis
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Introduction

Molecular epidemiology studies over the past two decades have improved our understanding of tuberculosis (TB) epidemiology and biology. The use of molecular methods, coupled with classical epidemiological approaches, has afforded greater resolution and accuracy in describing both the local and global epidemiology of TB [1]. Taking into account the local epidemiology of TB, many authors have illustrated the usefulness of molecular techniques in the evaluation of transmission between autochthonous and immigrant populations [2–8], in the determination of spread among human immunodeficiency virus (HIV)-infected people [9–11] and in the monitoring of transmission of drug-resistant strains [12–14].

A previous study conducted in Madrid during 2002–2004, when the percentage of immigrants censused was 12.2%, showed that TB transmission was higher in Spanish-born cases and it was associated mainly with homelessness. This study also showed that foreign-born patients were much less likely to be clustered, suggesting a higher percentage of infection before arriving in Spain, and that TB transmission between Spanish- and foreign-born populations, caused mainly by autochthonous strains, was taking place [8].

The demographic characteristics of the population of Madrid, with a sustained increase in the percentage of immigrants, from 4.7% in 1998 to 17.4% in 2007, and the new epidemiological scenario associated with a great decrease in the proportion of TB cases coinfected with HIV [15], provide an excellent opportunity to study in depth the epidemiology and transmission patterns of TB. The comparison between two periods when important demographic changes were taking place can be very useful to understand the factors that contribute to the incidence of TB and to define new strategies to reinforce the TB control programme. The aim of the present study was to compare two 3-year longitudinal molecular studies of TB in Madrid to define transmission patterns and predictors associated with being in a cluster. We particularly focused on determining whether or not the increase in cases of tuberculosis among immigrants in recent years was modifying recent transmission patterns in Madrid in a scenario with a sustained sharp increase in immigration.

Methods

Design and study population

Two prospective population-based molecular and epidemiological studies of patients diagnosed with TB were conducted in nine urban districts in the south of Madrid (Spain) during 2002–2004 and 2005–2007 using the same methodology. These districts had an official population of 1 459 232 in the first period (12.2% foreign born) and 1 548 761 in the second (15.0% foreign born).

For all patients, information was collected using a standardized protocol. Additional information on HIV status was obtained by cross-matching the Regional Registry of Tuberculosis with the AIDS Regional Registry. All variables were measured in categories, except for age, which was measured as a continuous variable.

Microbiology

Primary isolation and culture of mycobacterial isolates were performed in the two hospitals involved in the study. Susceptibility testing with isoniazid, rifampin, streptomycin and ethambutol was performed using a mycobacterial growth indicator tube streptomycin-isoniazid-rifampin-ethambutol system (Becton Dickinson, Sparks, MD, USA). DNA fingerprinting with the insertion sequence IS*6110* was performed as described previously [16]. Computer-assisted analysis of IS*6110* fingerprints was carried out using Bionumerics 4.0 software (Applied Maths, Kortrijk, Belgium). Supplementary spoligotyping [17] was performed on all isolates that had ≤5 copies of IS*6110* and shared identical restriction fragment length polymorphism (RFLP) patterns. Patients were included in clusters if their RFLP patterns contained (i) ≥6 IS*6110* bands in an identical pattern or (ii) ≤5 identical IS*6110* bands and identical spoligotyping pattern.

Epidemiological investigation

Patients were interviewed and the contact tracing was carried out by the primary healthcare physicians. They sent the questionnaires to the Regional Registry of TB in Madrid, where this information was analysed by two epidemiologists from our research group. For clustered patients, medical records were reviewed and general practitioners were questioned in order to obtain supplementary information about previous exposure to other cases of TB. An epidemiological link was defined as sharing a residence, place of employment, social activity or family relationship with a case patient. The index case of a cluster was defined as the earliest case to demonstrate symptoms. When such data were not available, the index case was considered the patient who commenced treatment earliest.

Statistical analysis

The time-related changes in the incidence of TB were estimated by Poisson regression. In order to identify risk factors for clustering, univariate analysis was performed using the *t*-test for continuous variables and the χ^2 or the Fisher exact test for categorical variables. Factors that were significantly associated with clustering were analysed by multiple logistic regression, using a stepwise approach to identify factors that were independent predictors of clustering.

Results

During the period 2002–2007, 2248 cases of TB were reported. In the first period (2002–2004) there were 1155 cases (1090 in the general population and 65 cases diagnosed in prison) and during the second (2005–2007) 1093 cases (1059 in the general population and 34 cases in prison). The cases bacteriologically confirmed as culture positive by period were 887 and 871 (76.8% vs. 79.7%; p 0.11).

In 2002–2007 the incidence of TB decreased 6% (from 23.5 per 100 000 in 2002 to 20.8 in 2007; p for trend <0.001). This global decrease was associated with a decrease of 9% among foreign-born men (p for trend <0.001), of 7% among Spanish-born women (p for trend = 0.004) and of 6% among Spanish-born men (p for trend = 0.003). The inci-