# Impact of Immigration on Pulmonary Tuberculosis in Spanish Children

A Three-Decade Review

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**Background:** Tuberculosis causes significant morbidity and mortality worldwide. In the last years, international travel and immigration have led to important changes in the epidemiology of this disease. Drug resistance has emerged as an important threat to tuberculosis control. Data regarding the impact of immigration and the incidence of drug-resistant strains in children are lacking.

**Methods:** Retrospective review of patients diagnosed with pulmonary tuberculosis at La Paz Children's Hospital in a 30-year period. Data were collected with regard to the clinical, radiologic, microbiologic, and demographic characteristics of patients, and data from the 3 decades of the study were compared using  $\chi^2$  test and Fisher exact test.

**Results:** A total of 507 cases of tuberculosis were identified, 414 of which had pulmonary involvement. During the study, there was a significant decrease in tuberculous meningitis: 10.4% in 1978–1987, 5.6% in 1988–1997, and 2.9% in 1998–2007 (P < 0.05). The most frequent reason for a consultation was case contact investigation. The adult source case was identified in 64% of patients. We observed an increase in extrafamilial contacts (8% in 1978–1987 and 18% in 1998–2007, P < 0.01), including 4 cases of immigrant caretakers. Tuberculosis in immigrant children has increased with time: 2% in the period 1978–1987, 6% in 1988–1997, and 46% in 1998–2007 (P < 0.001). The primary resistance rate to isoniazid in our population was 6.5%.

**Conclusions:** Tuberculosis in our area continues to be a major health problem, especially among foreign-born children. As drug-resistant strains are increasing, initial therapy with 4 drugs is recommended in our population.

Key Words: tuberculosis, immigration, drug-resistance

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Tuberculosis continues to be one of the most widespread infections in the world. In 2007, the World Health Organization (WHO) estimated 431,518 new cases and 63,765 deaths in Europe.<sup>1</sup> The enormous increase in international travel and immigration from high tuberculosis-burden countries in the last decades has led to higher rates of imported tuberculosis, especially in major cities.<sup>2,3</sup> At present, one-third of the cases of tuberculosis in the European Union are found in foreign-born individuals.<sup>4</sup>

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Spain has one of the highest incidence of tuberculosis among Western Europe countries, with an estimated rate of 30 new tuberculosis cases per 100,000 population and year.<sup>1</sup> Immigration had little impact on tuberculosis until recent years, but lately an increase in the cases among immigrants has been reported, with rates greater than 100 new cases per 100,000 population.<sup>5–7</sup> Most immigrants come from countries that have high resistance rates to first-line antitubercular drugs.<sup>1</sup>

Drug resistance is one of the main causes for the low success rates in tuberculosis treatment and represents a serious threat to global efforts to control tuberculosis.<sup>8,9</sup> It makes therapy longer, more expensive, less effective, and poorly tolerated.<sup>2,10</sup> Multidrug-resistant tuberculosis has been reported in all regions of the world.<sup>11,12</sup> Approximately, 1.6% of new tuberculosis cases worldwide are multidrug resistant<sup>13</sup> and 0.1% of new tuberculosis cases in Spain,<sup>1</sup> where drug-resistance is much more common in foreign-born patients.<sup>14–16</sup>

In industrialized countries, children make up less than 5% of cases of tuberculosis,<sup>17</sup> and in most of the world there is a paucity of data concerning drug resistance rates and the effects of immigration on pediatric tuberculosis.<sup>3,18–20</sup> None of the studies in Spain regarding drug-resistance rates or the impact of immigration on tuberculosis has focused on children.<sup>5,6,14–16</sup>

The objectives of our study were as follows: (1) to compare the frequency, clinical and radiologic manifestations, and source of infection of pulmonary tuberculosis in children treated in our hospital during the 3 decades from 1978 to 2007; (2) to evaluate the influence of immigration from endemic countries on childhood tuberculosis; and (3) to describe the epidemiologic features of patients infected by drug-resistant strains. Data from the first 2 decades have already been published,<sup>21</sup> but the effect of immigration and the appearance of drug-resistant strains were not previously addressed.

# PATIENTS AND METHODS

Patients aged 15 years or less diagnosed with pulmonary tuberculosis during a 30-year period, from January 1978 to December 2007, at La Paz Children's Hospital (Madrid, Spain) were retrospectively reviewed. Our hospital is a tertiary center in the northern area of Madrid, but children from other areas of Madrid and the rest of the country can be referred to our unit. We classified sites of tuberculous disease as pulmonary (affecting lung, pleura, or intrathoracic lymph nodes) and extrapulmonary. The number of patients diagnosed with extrapulmonary tuberculosis during the study period was recorded.

Data were collected from medical records regarding the clinical and epidemiologic characteristics of patients diagnosed with pulmonary tuberculosis, as well as results of tuberculin skin test, microbiologic studies and radiologic investigations. We con-

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sidered immigrant children those born abroad or born in Spain of immigrant parents.

The diagnosis of tuberculosis was based on: (1) a positive tuberculin skin test and an abnormal chest radiograph (clinical, epidemiologic, and laboratory data were also considered); or (2) a culture or smear positive for *Mycobacterium tuberculosis*. Tuberculin skin test was considered positive when induration 48 to 72 hours after intradermal administration of 2 tuberculin units/0.1 mL of RT-23 tuberculin (Statens Serum Institute, Copenhagen, Denmark) was  $\geq$ 5 mm in children with clinical or radiologic data suggestive of tuberculosis, in situations of case contact investigation, in immunocompromised or HIV-infected children, and in those with a previously negative tuberculin skin test. In any other case, the test was considered positive when induration was  $\geq$ 10 mm, including BGC vaccinated children.<sup>22</sup>

The definition of tuberculosis drug resistance followed the WHO and International Union against Tuberculosis and Lung Disease Guidelines.<sup>23</sup>

Statistical analysis was performed using SPSS statistical software, version 15.0 (SPSS Inc., Chicago, IL). Comparisons between the 3 decades of the study were made using  $\chi^2$  test and Fisher exact test. *P* < 0.05 were considered statistically significant.

## RESULTS

# Number of Cases

A total of 507 cases of tuberculosis were identified, of which 414 (82%) had pulmonary involvement. The annual distribution of cases is shown in Figure, Supplemental Digital Content 1, http://links.lww.com/INF/A388. The mean annual number of cases of pulmonary tuberculosis was 15 in 1978–1987, 18 in 1988–1997, and 9 in 1998–2007. There was a nonsignificant trend towards a higher rate of pulmonary tuberculosis over time: 77.6% in 1978–1987 (149 of 192), 82.1% in 1988–1997 (175 of 213), and 88.2% in 1998 to 2007 (90 of 102).

#### Age and Sex

Of the cases, 65% occurred in children less than 5 years old, 23% in children from 6 to 10 years, and 12% in children greater than 10 years. No significant differences were found regarding the number of cases per age group in each decade. Mean age was 4.2 years in 1978–1987, 4.8 years in 1988–1997, and 3.5 years in 1998–2007. No differences were observed in the rate of tuberculosis in infants: 14.8% in 1978–1987, 7.4% in 1988–1997, and 13.3% in 1998–2007. In the 3 decades, the male:female ratio was 1:1.

## **Reason for Consultation**

No significant differences were found between the 3 decades. The most frequent reason for consulting was contact investigation of confirmed adult cases (40%), followed by general (27%) and respiratory symptoms (19%) and tuberculin screening (11%).

## **Radiologic Findings**

The most common findings were hilar lymphadenopathy (38%), pulmonary infiltrates (20%), and mixed forms (33%). Five percent had pleural effusion, 2% cavitation, and 2% miliary pattern. No significant differences were found between the 3 decades regarding radiologic manifestations.

## Source of Infection

The adult source case was identified in 64% of the patients: 67.1% in the first decade, 58.3% in the second and 70% in the third (P = NS). The source of infection was a close relative in most cases (33% father, 19% mother, 30% aunts and uncles, 8%

grandparents), with no significant differences between the 3 decades. On the other hand, there was a significant increase of children in whom the adult source case was a more distant relative (cousins, mother's or father's new partner) in the period 1998– 2007 (P < 0.01), together with an increase of cases due to extrafamilial contacts during the same period (8% of the cases in the first 2 decades and 18% in the last decade, P < 0.01). In this last decade, we have identified 7 children in whom the adult source case was their caretaker. Four of these caretakers were immigrants from high tuberculosis-burden countries.

#### Microbiology

The percentage of children with a positive culture for *Mycobacterium tuberculosis* was higher during the study period: 25% in 1978–1987, 38% in 1988–1997 and 53% in 1998–2007 (P < 0.05). Gastric aspirate culture was positive in 26% of the cases in the period 1978–1997 and in 51% in 1998–2007 (P < 0.01). Acid-fast smears of gastric aspirates were positive in 5% in 1978–1997 and in 12% in 1998–2007 (P < 0.01). This improvement in microbiologic diagnosis is strongly related to the introduction of automated culture methods in liquid media (BacT/ALERT 3D, bioMérieux) and the use of polymerase chain reaction in the last period of our study.<sup>24</sup>

## **Drug-Resistant Strains**

Drug susceptibility testing of *Mycobacterium tuberculosis* isolates became a routine at our hospital in 1998. Of 48 positive cultures since 1998, 4 were drug-resistant strains representing a primary resistance rate to at least one first-line therapeutic agent of 8.3%. Two children were infected by isoniazid-resistant strains and 2 by multidrug-resistant strains (one was resistant to isoniazid, rifampin, and streptomycin, and the other to all first line drugs and amikacin). There were no extensively-drug resistant cases. Both children with multidrug-resistant tuberculosis were immigrants (one from China and one from Romania) and both children with isoniazid-resistant tuberculosis were Spanish. None of these children had been previously treated for tuberculosis nor had received isoniazid prophylaxis. If we consider only the children from our hospital's area, the primary resistance rate to first-line drugs was 6.5%.

## Immunocompromised Patients

Eight cases involved immunocompromised patients (4 HIVinfected, 3 renal transplantation, and 1 had a primary immunodeficiency). All HIV patients had previously known HIV infection and became later infected by *Mycobacterium tuberculosis*. In the last 10 years, there have been no cases of tuberculosis in HIVinfected children.

#### **Cases Among Immigrants**

During the 30 years of the study, 54 cases (13%) were immigrants, with a higher rate over time: 2% in the period 1978–1987, 6% in 1988–1997, and 46% in 1998–2007 (P < 0.001). In the last year of the study, 75% of the cases occurred in immigrant children. The most frequent places of origin were Africa and South America (each accounting for 35% of the cases in immigrants), followed by East Europe (15%) and Asia (13%) (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/A389).

## **Extrapulmonary Manifestations**

The most common extrapulmonary manifestations in the 3 decades were lymphadenopathy (46 cases) and meningitis (35 cases). There has been a significant decrease in tuberculous meningitis during the study period: 10.4% in 1978–1987, 5.6% in 1988–1997, and 2.9% in 1998–2007 (P < 0.05) (Table 1).

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TABLE 1.	Extrapulmonary	Manifestations of	
Childhood Tuberculosis			

Extrapulmonary Forms	No. Patients (%)		D	
	1978–1987	1988 - 1997	1998-2007	Г
Meningitis	20 (10.4)	12 (5.6)	3 (2.9)	< 0.05
Lymphatic	16 (8.4)	23 (10.8)	7(6.7)	NS
Abdominal	5(2.6)	3(1.4)	2(2)	NS
Skeletal	5(2.6)	3(1.4)	5(4.9)	NS
Other	1(0.5)	4(2)	1(1)	NS
Total	47(24.4)	45 (21.2)	18 (17.6)	NS

## DISCUSSION

The clinical features of the children included in our study were similar to those previously reported, with pulmonary tuberculosis accounting for 82% of all cases. Children less than 5 years had the highest rate, because the risk of progression from infection to disease is higher in younger patients.<sup>25,26</sup> The most frequent reason for consulting was case contact investigation, as most children with tuberculosis remain asymptomatic.<sup>25</sup> Our study confirms that when symptoms appear they are usually general and nonspecific and that the most frequent radiologic manifestation is intrathoracic lymphadenopathy. Bacteriologic diagnosis of tuberculosis is also difficult in children.<sup>27,28</sup> Acid-fast smears of sputum or gastric aspirate samples are positive in less than 20% of children,<sup>26,29-31</sup> and positive gastric aspirate cultures from children with suspected tuberculosis range from 20% to 60%.<sup>20,31-33</sup> These facts emphasize the importance of extensive contact investigation of confirmed adult cases to control tuberculosis.<sup>28</sup> As it has been reported in prior studies, in our patients the source of infection was most commonly an adult family member.9,19,34 However, we have observed an increase of cases due to extrafamilial contact, mainly immigrant caretakers, together with an increase in cases in which the source was a more distant relative. These facts are strongly related to the socioeconomic changes that have taken place in Spain in the last decade, especially the progressive increase in women's employment,35 and also to the specific features of life of the immigrant population.<sup>15</sup> A survey of living conditions of immigrant families in Madrid has showed that most of them live in shared flats, with an average of 6.5 people per flat and 2.3 people per room.<sup>36</sup>

In the last decades, there has been an important increase in immigration from South America, Africa, and Eastern Europe in Spain. In 1997, there were 719,647 foreigners registered in Spain, and 10 years after there were almost 4 million. In Madrid, in 2007, foreigners represented 12% of the population. The 3 most frequent countries of origin are Morocco, Romania, and Ecuador.<sup>37</sup> The estimated rate of tuberculosis in these countries is 92 cases per 100,000 inhabitants per year in Morocco and greater than 100 cases per 100,000 inhabitants per year in Romania and Ecuador. Resistance to isoniazid is greater than 4% in the 3 countries.<sup>1,38</sup> Immigrant children born in countries with high rates of tuberculosis are at higher risk of developing disease because they may have been exposed to tuberculosis in their home country, when they return, or when they are exposed to infectious adults within their home.<sup>3</sup> Many of the new tuberculosis cases in immigrants are a result of reactivations of infections acquired abroad,<sup>2</sup> and more than a half of the foreign-born tuberculosis patients develop the disease during the first 2 years after arrival.<sup>7,15,16</sup> Although in the Madrid area the incidence of tuberculosis has decreased in the last decade, cases among immigrants have increased. In 1997, 5.8% of tuberculosis cases occurred in immigrants, whereas in 2007, they

account for almost 46% of all tuberculosis cases.<sup>39</sup> The significant rise in the proportion of cases in immigrant children that we have observed has also been reported in other Spanish cities, other European countries and the United States.<sup>16,26,29,40,41</sup> In 2005, 55% of the total cases of tuberculosis and 25% in children in the United States occurred among the foreign-born.<sup>42</sup> In Madrid, in 2007, 47% of children with tuberculosis were immigrants.<sup>39</sup> Therefore, when caring for immigrant children, including those adopted internationally, it is important to consider their risk for tuberculosis<sup>26,43</sup> and for being infected by drug-resistant strains.

The global burden of drug-resistant tuberculosis in children is unknown,44 but in Madrid patterns of drug-resistance are different between Spanish-born and foreign-born individuals.<sup>39</sup> We found a high rate of primary resistance in our study, but this may not reflect the rate of the general population in Spain, because ours is a referral center and the number of patients with a positive culture in our study is limited. Data from children diagnosed with pulmonary tuberculosis in the Unites States between 1993 and 2001 show an isoniazid resistance rate of 7.3%, to any first-line drug of 15.2% and to at least isoniazid and rifampin (multidrugresistant) of 1.6%.<sup>26</sup> A recent study from Spain, which includes both children and adults, reports a primary resistance rate to any first-line drug of 8.3%, to isoniazid 4.9% and 1.3% multidrugresistant. Drug-resistant tuberculosis was far more common in the immigrant population.<sup>14</sup> Another study from our country yielded similar results, with resistance to first-line drugs in new tuberculosis cases of 6.1% in Spanish patients and 15.8% in immigrants.<sup>16</sup> The emergence of drug resistant strains shows the importance of routine testing of Mycobacterium tuberculosis drug susceptibility. The Spanish Society for Pediatric Infectious Diseases has issued new guidelines for the management of drug-resistant tuberculosis in children. Initial treatment with 4 antitubercular drugs is recommended in all cases, except in those where the index case is susceptible to isoniazid, rifampin, and pyrazinamide. Treatment of drug-resistant tuberculosis in children should be closely monitored to ensure compliance and avoid the dissemination of drug-resistant strains. Directly-observed treatment is recommended in multidrugresistant cases.45

Extrapulmonary tuberculosis is more common in children than adults, occurring in approximately 25% of infants and children less than 4 years of age.<sup>3,19</sup> In our study, we have found that 21% of all tuberculosis cases had extrapulmonary disease. As it has been documented in prior studies, the most common extrapulmonary manifestation is lymphadenitis,<sup>26,29</sup> followed by central nervous system involvement.<sup>19,25</sup> The latter is the most severe form of childhood tuberculosis, with mortality or long-term neurologic sequelae occurring in almost 50% of cases.<sup>46</sup> Our rate of tuberculous meningitis is higher than that reported in other series,<sup>19,25</sup> but has decreased significantly with time. In 2002, we had already reported a nonsignificant trend towards a lower rate of tuberculous meningitis,<sup>21</sup> although vaccination with BCG had been discontinued in our country in 1987. In this study we have confirmed the decrease of tuberculous meningitis, which may be due to improvements not only in socioeconomic conditions but also in case contact investigation.

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