

Reemergence of Pediatric Tuberculosis and associated aspects: Metropolitan Region of Chile, 2005 to 2018

Reemergencia de la Tuberculosis Pediátrica y aspectos asociados: Región Metropolitana de Chile, 2005 a 2018

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What do we know about the subject matter of this study?

Due to clinical and epidemiological heterogeneity, it is often difficult to diagnose TB in the pediatric population, which poses an additional challenge to the prevention and treatment of the disease in this age group.

What does this study contribute to what is already known?

The results of this study indicate a serious epidemiological reemergence of TB. This should alert clinicians to consider TB as a possible diagnosis when evaluating a pediatric patient with respiratory symptoms.

Abstract

Objective: To describe the socio-epidemiological characteristics of Pediatric Tuberculosis (TB) cases, and aspects associated with its incidence, from 2005 to 2018, in North, Central, and South Metropolitan Health Services of Chile. **Patients and Method:** Descriptive study with an ecological time series. We studied the incidence of annual global TB and according to age, sex, location of tuberculosis, bacteriological confirmation, human immunodeficiency virus (HIV) co-infection, country of origin, and effectiveness of anti-tuberculosis therapy. In addition, a correlation analysis was made between the incidence rate and the proportion of foreign cases. **Results:** Between 2005 and 2018, 160 cases of TB were reported in children under 15, with a median age of 8 years, and 55% male. 56.2% corresponded to Pulmonary TB, of which 65.6% were bacteriologically confirmed. The incidence rate in-

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creased from 0.5 cases x 100,000 inhabitants in 2010, to 4.9 cases x 100,000 inhabitants in 2018. This last year concentrated 20.6% of the cases that occurred in 14 years of observation. The proportion of cases in foreign minors is still lower compared with the cases in Chilean children. A 91.3% success rate, 6.5% of cases transferred to other Services, and 2 deaths were also observed. **Conclusion:** The results of this study show a serious epidemiological reemergence of TB. We recommend that control and eradication policies consider strategies focused on pediatric patients, aiming at actively screening for new cases and more efficient contact tracing.

Introduction

It is estimated that there would be one million cases of pediatric Tuberculosis (TB) worldwide, accounting for approximately 15% of the global incidence and that, during 2018, 233,000 children died due to a TB-associated cause^{1,2,3}.

Clinically, active TB in children mostly presents as disseminated or extrapulmonary and initially may have only mild symptoms such as fever⁴. Indeed, TB can present the signs and symptoms of many common childhood diseases, such as pneumonia, making diagnosis difficult, however, the main obstacle to the accurate diagnosis of active TB is that the infection presents low bacilli in the expectorated sputum, which is another of the particularities of the child with TB^{2,5}.

Due to this clinical and epidemiological heterogeneity, it is often difficult to diagnose TB in the pediatric population, which poses an additional challenge to the prevention and treatment of the disease in this age group^{1,6}.

In countries with low disease prevalence, childhood TB occurs as occasional cases, as was the case in Chile in recent decades. However, after decades of successful results of the Tuberculosis Control and Elimination Program (PROCET), the country has experienced a significant epidemiological reemergence, reaching 14.9:100,000 in 2018, which is one of the highest rates in the last 14 years (7.8). This occurs simultaneously with an increase in new cases of childhood TB, which reached 76 in such year. This was a 90% increase over the previous year^{7,8,9}.

Recognizing and detecting TB cases in the pediatric population is extremely important for the efforts to end TB, since, on the one hand, a new case of pediatric TB can be an indicator of recent transmission in the community, and on the other hand, an untreated case of latent tuberculosis infection in children represents a source for the emergence of future active and contagious cases^{1,10}.

To address this problem, the World Health Organization (WHO) developed a guideline with a series of recommendations to reduce to zero TB deaths in chil-

dren and adolescents, among which is the incentive to conduct more studies on this subject^{11,12}.

In Chile, preliminary reports show that the Central Metropolitan Health Servicesⁱ (CMHS), the Northern ones (NMHS), and the South ones (SMHS) have high rates of TB. These areas also have a high percentage of foreign residents, with 68% of migrants in the Metropolitan Region (MR), which represents 9.8% of the total population seen at these three Health Services¹³. This is an important precedent to consider since the scientific literature suggests a certain association between high TB rates and a high concentration of immigrants^{14,15}.

In this context, it is relevant to know the epidemiological evolution of pediatric TB in recent years. The objective of this work is to describe the socio-epidemiological characteristics of pediatric TB cases, and aspects associated with its incidence, between 2005 and 2018, in the Northern, Central, and South Metropolitan Health Services of Chile.

Patients and Method

Descriptive ecological time-series study. We analyzed the cases of pediatric tuberculosis registered by PROCET in the CMHS, NMHS, and SMHS of Chile, between 2005 and 2018. All cases registered in children under 15 years of age were included.

For CMHS and SMHS, all records were available from January 2005 to December 2018, while for NMHS, only records from 2012 onwards were available.

The diagnosed cases were reviewed and the following data were collected from the TB case mandatory notification form: sex, age, location of tuberculosis (pulmonary and extrapulmonary), bacteriological

i The "Health Services" in Chile are functionally decentralized state agencies responsible for the articulation, management, and development of the corresponding health care network, for the execution of integrated actions for the promotion, protection, and recovery of health, as well as the rehabilitation and palliative care of sick population.

confirmation (smear, culture, polymerase chain reaction (PCR), and other methods), co-infection with HIV, commune of residence, country of origin, and effectiveness of anti-tuberculosis therapy.

With the information collected, we calculated incidence rates, using as a denominator the population aged under 15 years registered in the municipalities covered by the NMHS, CMHS, and SMHS, according to the population projections provided by the National Institute of Statistics of Chile (INE).

For the variable effectiveness of anti-tuberculosis therapy, 4 attributes were defined according to the WHO criteria as follow: “overall success” of the treatment if the patient completes the therapy; “abandonment or loss to follow-up” if the patient does not attend therapy for more than 30 days; “failure”, when the smear test remains positive until the fourth month of treatment, or if after becoming negative it reappears positive during the therapy; and “death”, if it occurs during the treatment, regardless of the cause.

Data analysis was performed using the STATA 13.0 statistical software and Microsoft Excel 2016 software. The median and interquartile range were used to characterize the age of the subjects. Using the Shapiro-Wilk normality test, the variables pediatric TB incidence rate and proportion of foreign cases were analyzed determining that the incidence rate is a nonparametric numerical variable. Therefore, Spearman's coefficient was used for the correlation analysis between incidence rate and foreign cases. A p-value <0.05 was considered statistically significant.

This study was authorized by PROCET of all participating Health Services and approved by the CMHS Scientific Ethical Committee.

Results

During the period under study, 160 cases of TB were recorded in children under 15 years of age. Males accounted for 55.0% of the cases. Although the median age was 8 years for males and females (Interquartile range = 12 - 2), this variable shows a bimodal behavior: 45.1% of the cases were distributed between children aged 1 and 2 years (38 cases) and children aged 14 years (34 cases) (figure 1). In both age groups, the most frequent presentation was pulmonary TB.

Of the total cases, 56.2% were pulmonary TB, but only 65.6% of them had bacteriological confirmation by culture, smear, PCR, or other methods. Among the total cases of extra-pulmonary TB (70/160), the most frequent method of confirmation was a biopsy and the most frequent forms were lymph node (24/160) and pleural (18/160).

Of the total cases, 4 children with TB/HIV co-infection were recorded in 2006, 2008, 2012, and 2018, respectively. Regarding the history of TB, most were new cases, with only 2 cases reported as relapse.

Of the 160 cases recorded in the entire period, 33 were reported during 2018. Likewise, the TB incidence rate for the study population, increased from 0.9 to 4.9:100,000 inhabitants, between 2005 and 2018, respectively. It is important to note that at the beginning of the period, the trend was downward, reaching a minimum of 0.5:100,000 in 2010, and then there was a clear annual increase (figure 2).

Between 2012 and 2018, 107 cases occurred, of which 43.9% (47/107) corresponded to the SMHS, 30.9% (33/107) to the CMHS, and 25.2% (27/107) belonging to the NMHS. Table 1 shows the socio-demo-

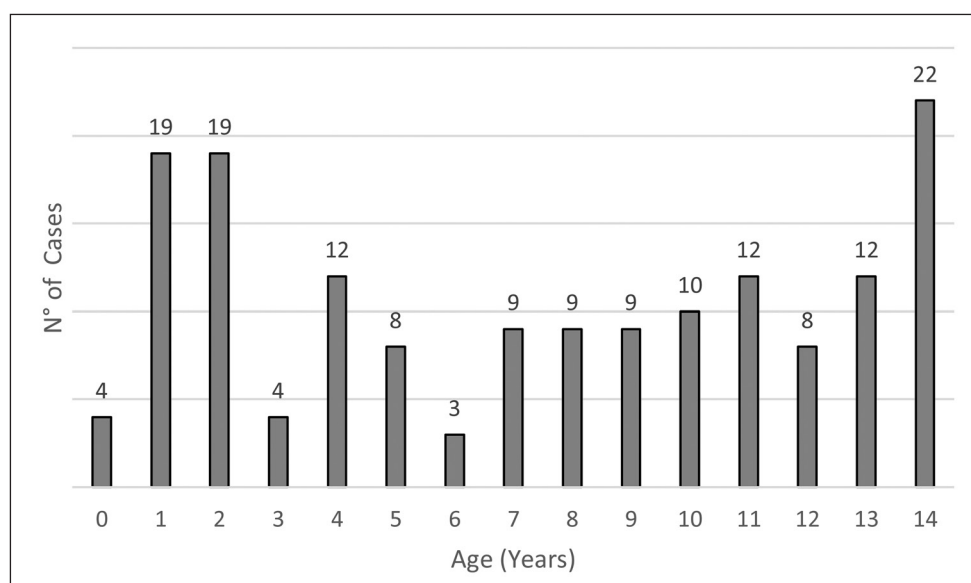


Figure 1. Pediatric TB cases in the Northern, Central, and South Metropolitan Health Services, by age. Chile 2005 - 2018. Source: Authors' own elaboration. TB: tuberculosis.

graphic and clinical characteristics by Health Service for the entire period.

Of the 160 cases observed, 25% were children not born in Chile. The proportion of foreign cases remained present, although irregularly during the 14 years of observation, showing a clear increase in the last year. Between 2005 and 2017, there were on average 8 cases of children born in Chile and 2 cases of foreign children annually, however, in 2018, there were 21 cases of

Chilean children and 12 cases of children coming from abroad. Those 12 children represented 30% of all foreign cases in the period studied. Of the 21 Chilean children, 9 had had contact with foreign relatives with TB.

The Spearman correlation analysis, which evaluated whether there was an association between the incidence rate and the proportion of foreign cases, did not show statistical significance relating to both variables ($p = 0.3936$). Figure 3 shows the distribution of pedia-

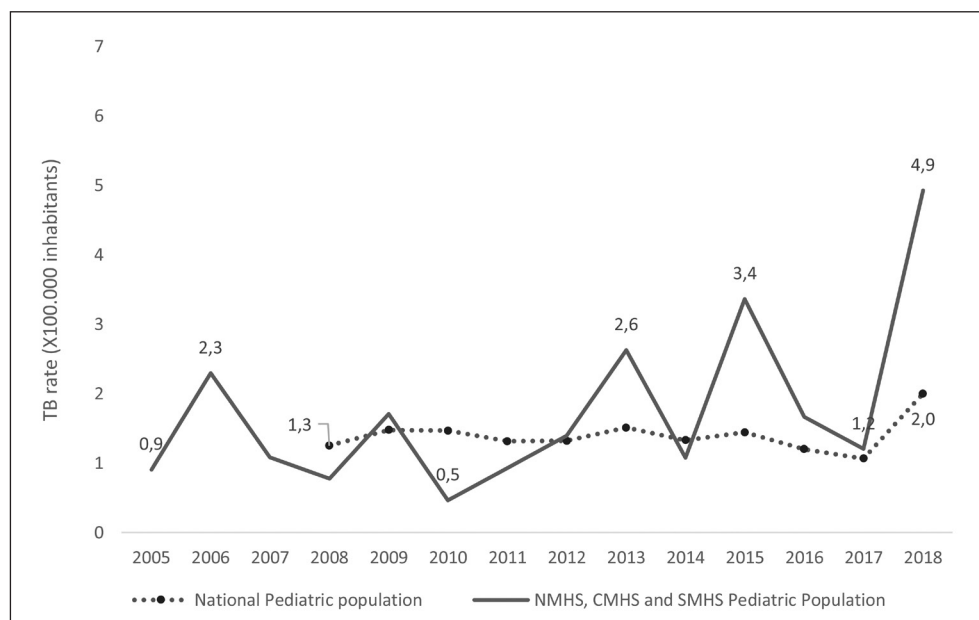


Figure 2. Pediatric TB incidence rate in the Northern, Central, and South Metropolitan Health Services, and National pediatric TB incidence rate, between 2005 and 2018. Source: Authors' own elaboration. TB: tuberculosis

Table 1. Socio-demographic and clinical characteristics of pediatric TB cases, between 2005 and 2018, in the Northern, Central, and South Metropolitan Health Services of Chile.

Socio-demographic and clinical characteristics	Tuberculosis cases (n = 160)		
	NMHS*	CMHS	SMHS
Cases: n (%)	27 (100%)	68 (100%)	65 (100%)
Sex: n (%)			
Female	11 (40.7%)	33 (48.5%)	28 (43.1%)
Male	16 (59.3%)	35 (51.5%)	37 (56.9%)
Age (yr): Median (IQR)			
Female	2 (10-2)	7 (11-2)	5 (9-2)
Male	8 (14-3)	9 (13-4)	9 (12-5)
Total	7 (13-2)	8 (12-3)	8 (11-3)
Localizationn: n (%)			
TB Pulmonary	20 (74.1%)	37 (54.4%)	42 (64.6%)
TB Pulmonar BC**	16 (59.3%)	30 (44.1%)	13 (30.9%)
TB Extrapulmonary	7 (25.9%)	31 (45.6%)	23 (35.4%)
Morbidity associated: n (%)			
Coinfection TB/HIV	2 (7.4%)	2 (2.94%)	0 (0.0%)

n = 160 cases, between 2005 and 2018. (IQR) = interquartile range. TB: tuberculosis; MHS: Meropolitan Health Service; C: Central; N: Northern; S South HIV: human immunodeficiency virus. *The data corresponding to the NMHS cover only the period between 2012 and 2018. **TB Pulmonary BC: Pulmonary Tuberculosis bacteriological confirmed. Source: Authors' own elaboration.

tric TB cases in native-born and foreign-born, between 2005 and 2018.

The communes that presented the highest number of TB cases in children under 15 years of age were Santiago, San Bernardo, Recoleta, Maipú, and Estación Central, accounting for 61.7% of all cases in the study population during the study period.

Figure 4 shows the distribution of TB incidence rate in children under 15 years of age by commune, during 2018. Among all communes, Recoleta stands out, which presented an incident rate of 23.4:100,000 inhabitants, while the SMHS has 3 communes with rates close to 10 cases per hundred thousand (San Joaquín, San Bernardo, and Pedro Aguirre Cerda).

Regarding the outcome of treatment, out of the total cases only 92 were considered, excluding those cases with incomplete records, as well as cases that occurred during 2018, many of which had not yet completed their treatment at the start of this research. Of the total cases evaluated, we observed a 91.3% overall success rate. 6.5% of cases were transferred from Service, so they would be categorized as “loss to follow-up”. Treatment failure was not reported in any of the cases. Of the 92 cases, 2 children died. The first, aged 12 years and with history of Down’s Syndrome, died in 2013 due to cardiac complications, and the second one, aged 7 years, died in 2015 with no other history reported. Both belonged to CMHS.

Figure 3. Distribution of pediatric TB cases in native-born and foreign-born, in the Northern, Central, and South Metropolitan Health Services, between 2005 and 2018. Source: Authors’ own elaboration. TB: tuberculosis

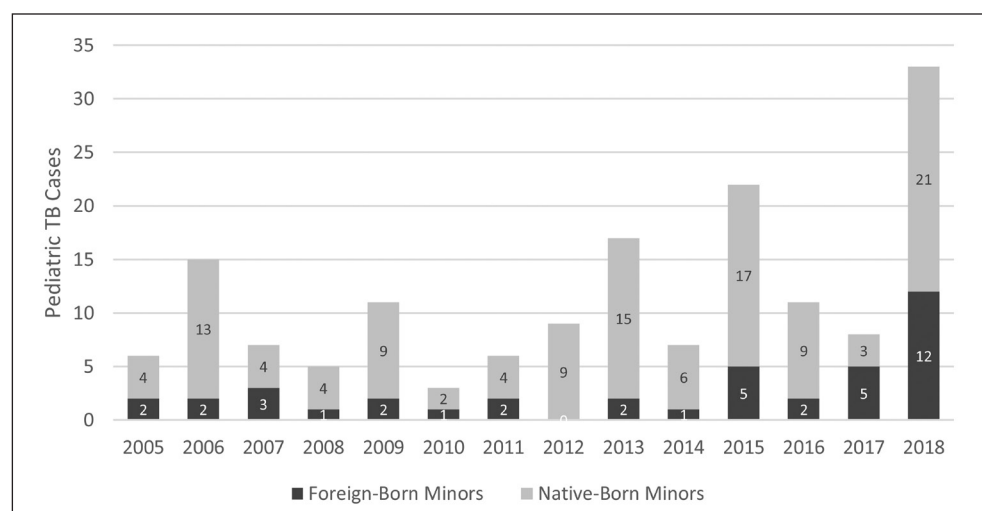
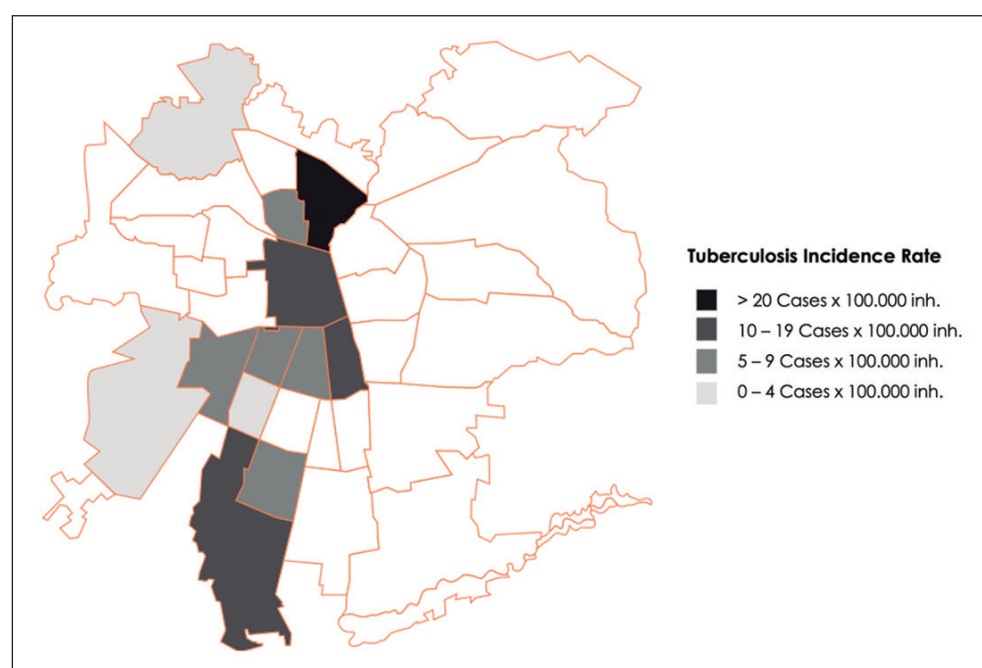


Figure 4. Distribution of Pediatric TB incidence rate in the Northern, Central, and South Metropolitan Health Services, and National pediatric TB incidence rate, 2018



Discussion

The population covered by this study represents 17.8% of the national pediatric population and concentrates 30.6% of all reported cases of pediatric TB in the country during the last 5 years. In addition, the cases registered in these three Services account for 43.4% of the total cases reported during 2018⁹. Therefore, it is possible to affirm that the behavior of cases in the NMHS, CMHS, and SMHS can be a good indicator of what is happening at a national level.

In Chile, the incidence of childhood TB is still a small percentage among total TB cases (2.6%), being below Latin American figures (12%), however, the 2018 incidence of pediatric TB in this study (4.9:100,000 inhabitants), was four times higher than 2017, and is clearly higher than the national rate (figure 2)^{7,8}.

According to age, cases are bimodal, i.e., most cases are concentrated in infants and school-age children, as described by the evidence⁴. Likewise, there is a high percentage of extrapulmonary TB cases compared with the forms of adult TB described in the literature, without significant differences between Services^{3,9}. Children infected with TB/HIV rarely appear during the period.

One of the relevant aspects showed by the results is that the incidence rate of TB in children under 15 years of age, from 2010 to 2018 experienced a worrying increase of cases from 0.5:100,000 inhabitants to 4.9:100,000 inhabitants. This progressive increase reached its maximum in the last year. 20.6% of the cases in the 14 years of observation occurred in 2018, which evidences the epidemiological re-emergence of TB in the region.

Regarding cases in children born outside Chile, it is observed that this characteristic is present in a percentage of the cases reported since the beginning of the period studied; however, this condition does not seem to imply a condition of greater vulnerability than that shared with Chilean children, who are equally exposed to poor living conditions. The correlation analysis performed establishes that the increase in the incidence rate of pediatric TB cannot be attributed to the increase in foreign cases.

Even so, one aspect to consider is that the evidence establishes that children born in a low-incidence country, whose parents were born in countries with a higher rate of TB, are at higher risk of infection with TB^{16,17} which could explain the results of the statistical analysis performed. Indeed, this study shows that of the 33 cases reported in 2018, 21 children were Chilean, but 9 had had contact with foreign relatives with TB.

The epidemiological situation evidenced by the SMHS should be given special attention. The 16 cases reported by this Service during 2018, account for 21.1%

of the cases of that year at the national level, doubling the number of cases that occurred in the CMHS and the NMHS. 7 of these 16 cases were foreign children (6 Haitian children and 1 Peruvian child).

Although the proportion of TB cases in children born abroad seems to be increasing, 56% of the SMHS cases in 2018 were born in Chile and, therefore, it is important to identify factors other than the country of birth. Probably, the causes behind this epidemiological reemergence are those social determinants historically involved in the spread of diseases such as poverty and social vulnerability.

Unlike the other Services studied, in the SMHS, there is not a single commune with a particularly high incidence of TB, but rather an entire area of increasing incidence. Among them, the communes of Pedro Aguirre Cerda, San Bernardo, and San Joaquín stand out, with rates close to 10:100,000 inhabitants. Considering the socioeconomic context shared by the communes in the south of the MR, there may be another indication that the increase in pediatric TB is more pronounced in communes with greater social vulnerability, higher rates of overcrowding, and lower educational and economic levels.

In this regard, it should be noted that 60% of the communes covered by the SMHS have figures above the poverty index of the MR (5.4%) and, based on an indicator that considers the dimensions of income, education, and health, 70% of the communes are defined as "high or medium-high social priority"^{18,19}. Thus, poverty is still a determining factor in the appearance of the disease and its subsequent transmission. Living conditions, precarious housing, overcrowding, comorbidities, drug abuse, and lack of knowledge make people highly vulnerable, whether they are foreigners or Chileans^{14,15}.

Regarding the results of the therapy, there was a high degree of success (91.3%), higher than that observed in the Americas (79%), confirming that children with tuberculosis usually have an excellent clinical outcome if diagnosed on time and adequately treated^{7,20}. However, the evidence warns about the diagnostic difficulties of childhood TB, both in clinical screening and the ability to detect the bacillus in children, as well as the use of drugs that are difficult for children to digest, and the marked tendency towards prevention strategies aimed at adults; all of these factors could result in underdiagnosing the pathology, poor adherence to treatment or a poor outcome^{2,5,21,22}.

Thus, not only is there a clinical duty to identify, diagnose, and treat children for a curable disease, but by ignoring childhood TB, efforts to control the TB epidemic will ultimately fail because, as noted above, children provide the reservoir from which future cases will develop^{23,24}.

In this sense, one of the control measures that Chile has adopted is the mandatory use of the BCG vaccine according to the regulations of the Chilean Ministry of Health, however, given the growing anti-vaccine movement, it is pertinent to reaffirm the efficacy and safety of the vaccine, as it has been shown that its use reduces the risk of miliary and meningeal tuberculosis in children, and its early application, with wide coverage, considerably reduces mortality due to pediatric TB^{25,26}.

On the other hand, in general, current TB control efforts seem to be mainly oriented toward reducing transmission by treating smear-positive adults, while little emphasis is placed on reducing the vulnerability of communities²³. Thus, at a programmatic level, policymakers and public health workers need to design services and allocate resources considering the pediatric population²⁷.

In addition to the above, the adequate and timely management of contacts is crucial for the prevention of TB, and to achieve this, it is essential the transition from a passive model of screening to an active one, considering the characteristics of the vulnerable population.

Conclusions

The results of this study show a serious epidemiological reemergence of TB in the region, moving Chile away from the eradication threshold. The rate of TB in the pediatric population has increased since 2010. Children aged 1 to 2 years and preadolescents accounted for most of the cases, where pulmonary TB is the most frequent presentation. The above allows alerting clinicians about the obligation to consider TB as a possible diagnosis when evaluating a pediatric patient with respiratory symptomatology. Given the reemergence

of pediatric cases, it is recommended that control and eradication policies consider strategies focused on this group, aiming at actively screening new cases and making contact studies more efficient.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author. to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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