

Prevalence of latent tuberculosis infection and incidence of tuberculin conversion among school contacts older than 5 years in the City of Buenos Aires

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ABSTRACT

Introduction. Tuberculosis continues to be a common problem in settings of socioeconomic vulnerability. Our primary objective was to establish the prevalence of latent infection and tuberculin conversion among school contacts of tuberculosis cases.

Population and methods. In a programmatic area in the south of the City of Buenos Aires, the prevalence of latent infection and tuberculin conversion was assessed in 691 children and adolescents using the tuberculin skin test. The association between loss to follow-up by the health care team and the demographic, school, and baseline care characteristics was studied, and the level of adherence when isoniazid chemoprophylaxis was indicated was described.

Results. According to established definitions, the prevalence of latent infection was between 3.4% (95% confidence interval [CI]: 2.3–5.2) and 11.6% (95% CI: 9.3–14.4) in the 610 contacts with at least one skin test. The incidence of tuberculin conversion was between 0.3% and 6.8% in the 294 assessed participants. Age older than 18 years, a higher prevalence of unmet basic needs in the school district, attending the afternoon school shift, negative sputum smear results in the index case, and absence of baseline skin test were associated with contact lost to follow-up.

Conclusions. The incidence of tuberculin conversion among school contacts was low. Adherence to isoniazid treatment remains limited. Factors associated with loss of contact tracing were identified, which may guide strategies necessary to improve this process.

Keywords: latent tuberculosis; contact tracing; school health services; epidemiology; treatment adherence.

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INTRODUCTION

Worldwide, tuberculosis is the second leading infectious cause of death in the general population. The overall incidence of tuberculosis was estimated at 1.2 million new cases in 2019 among children and adolescents, with approximately 230 000 deaths.¹ In Argentina, 720 tuberculosis deaths were reported in 2018; and the City of Buenos Aires (CABA) had the third highest tuberculosis reporting rate nationwide.²

Although households were historically considered the main setting of tuberculosis transmission among children, it has recently been suggested that, in regions with a high incidence of tuberculosis, up to 50% of cases in adolescents may occur through transmission in the school setting.^{3,4} Currently, in Argentina, all classmates are considered close contacts, and the active case-finding strategy for the identification of a schoolchild with tuberculosis involves the complete assessment of all classmates.⁵

In a previous study conducted in Argentina on tuberculosis infection among school contacts, the prevalence was 6.1% and the incidence of tuberculin conversion was 2.2%. Some limitations of that study were that they did not include primary school contacts and did not assess the

determinants of loss to follow-up.⁶

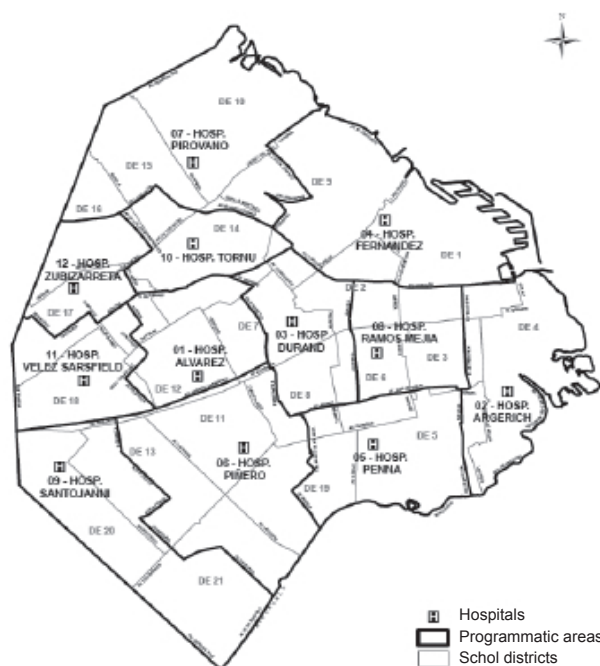
The objectives of this study were to describe the prevalence of latent tuberculosis infection and the incidence of tuberculin conversion among school contacts, and to identify determinants of loss to follow-up in these contacts.

POPULATION AND METHODS

This study was conducted in the School Health division of Hospital General de Agudos Parmenio Piñero, which covers schools located within its programmatic area in the south of the CABA (*Figure 1*). The schools included in this study belonged to districts 7, 8, 9, and 10, where the prevalence of unmet basic needs (UBNs), according to the 2010 census, were 9.8%, 13.8%, 5.3%, and 3.8%, respectively.

The study had a retrospective, analytical, observational cohort design. It included all classmates of cases with pulmonary, pleural, laryngeal, or miliary tuberculosis (reported through the epidemiological surveillance system between 4-1-2019 and 4-30-2020) attending primary or secondary public or private schools aged 6 to 20 years, without a personal history of tuberculosis or a history of positive tuberculin skin test (TST). All classmates shared the classroom

FIGURE 1. Programmatic areas in the Ministry of Health and school districts in 2020



Source: Ministry of Health and Education of the Government of the City of Buenos Aires.

Note: At the time of the study, the programmatic area corresponding to Hospital Cecilia Grierson was not geographically delimited

for at least 4 hours a day.

The baseline standardized assessment of contacts included history-taking and physical examination, baseline TST (TST1), and a chest X-ray evaluated by the physicians of each local team. The invitation to have the TST1 was made in writing through the school. The timing of the final assessment depended on the baseline results; in the absence of initial evidence of latent infection, it was performed between 90 and 120 days after the first one, again with a clinical examination and a control TST (TST2). In the case of asymptomatic contacts with a positive TST1, isoniazid was prescribed and follow-up was prolonged to 6 months. Of the 10 health care providers included, 6 prescribed isoniazid to asymptomatic contacts with a negative TST1 and a normal X-ray but 4 did not; this was related, in part, to the existing heterogeneity in the guidelines and recommendations on this matter.^{5,7-10}

Dependent variables were latent infection, tuberculin conversion, tuberculosis disease (secondary case), X-ray compatible with tuberculosis (according to the physician in charge of registration), and final knowledge of contact's infection status by the health care team.

Conversion was analyzed based on 3 definitions or criteria existing in the bibliography to consider the arc of potential outcomes. Definition 1: TST1 value below 10 mm, TST2 value equal to or greater than 10 mm, and difference between the 2 tests of at least 5 mm.¹¹ Definition 2 (used by the treating teams at the time of the study): TST1 value below 10 mm, TST2 value equal to or greater than 10 mm.⁵ Definition 3: for contacts of bacilliferous cases, TST1 value below 5 mm, TST2 value equal to or greater than 5 mm, difference between the 2 tests of at least 5 mm.¹²

The presence of latent infection was defined in asymptomatic participants with any positive TST. As in the definition of conversion, 2 definitions of positive TST were analyzed: equal to or greater than 10 mm for all contacts (this one was used by the treating teams), or equal to or greater than 10 mm for contacts of non-bacilliferous cases and equal to or greater than 5 mm in settings where the index case was bacilliferous.¹²

Final knowledge of infection status by the health care team was a dichotomous variable, affirmative if the participant had both TSTs (TST1 and TST2)—regardless of results—or if they had a TST1 equal to or greater than 10 mm (in which case, it was regarded as a latent infection case and waiving the need for TST2).

Tuberculosis disease during follow-up was considered present if the participant—initially asymptomatic—received a medical diagnosis of tuberculosis at any time during the follow-up period.

Independent variables were age, school, attending the afternoon school shift, school location in districts 7 or 8 (with higher UBNs than districts 9 or 10), health center in charge, sputum smear result of index case (dichotomous: bacilliferous or not), and duration of isoniazid chemoprophylaxis.

Ethical considerations

This study was approved on August 14th, 2019 by the Human Ethics Committee of the School of Medicine of University of Buenos Aires. Personal data were anonymized and their confidentiality was warranted for analysis.

Statistical analysis

Considering a latent infection prevalence of 6% (2–10%), for an $\alpha = 0.05$, the sample size was estimated at 589 participants.

A univariate analysis (describing proportions with confidence intervals for categorical variables and medians with interquartile range for numerical variables with non-normal distribution), a bivariate analysis (using the χ^2 test or Fisher's test for proportions, and the t test or the Mann-Whitney test for comparison of group numerical variables), and a multivariate analysis using logistic regression (initially considering variables with p values < 0.2 in the model, for final inclusion with a p value < 0.05) were performed, also taking into account the effect of school grouping.

Data were processed using the Stata 14 statistical software (Statacorp LP® 2015, TX, USA).

RESULTS

Characteristics of participants, schools and health centers

The study included 691 participants who were close school contacts corresponding to 23 index cases of tuberculosis from 19 schools under the coverage of 10 health care providers. In relation to index cases, 74% had a positive sputum smear (17/23) and 17% (5/23) had a negative sputum smear with a positive culture. No culture data were available for 1 index case.

The mean age of the participants was 14.7 years (SD: 3 years); the age range was 8 to 20 years, with a sex distribution of 50% male and 50% female.

The 19 schools corresponded to 4 districts of the City of Buenos Aires (7, 8, 9, and 10), which accounted for 49.1%, 35.8%, 12.6%, and 2.6% of the total number of participants, respectively. In terms of school level, there were 15 secondary schools and 4 primary schools. In addition, 15 were public and 4, private. Finally, 63 participants (9% of the total; 95% CI: 7.2–11.5) from 3 different schools attended the afternoon shift. Each health care provider assessed between 24 (3.5% of the total number) and 133 (19.3% of the total) participants.

Tuberculin skin test

It was observed that 294 participants (42.5% of the total; 95% CI: 38.9–46.3) had both TSTs; 306 participants (44.3%; 95% CI: 40.6–48), only TST1; and 10 (1.4%; 95% CI: 0.8–2.7), only TST2. It is worth noting that no TST was performed in 81 participants (11.7%; 95% CI 9.5–14.3).

In relation to the results of the tests mentioned above, a non-normal asymmetric distribution with a positive trend was observed in both (*Figure 2*).

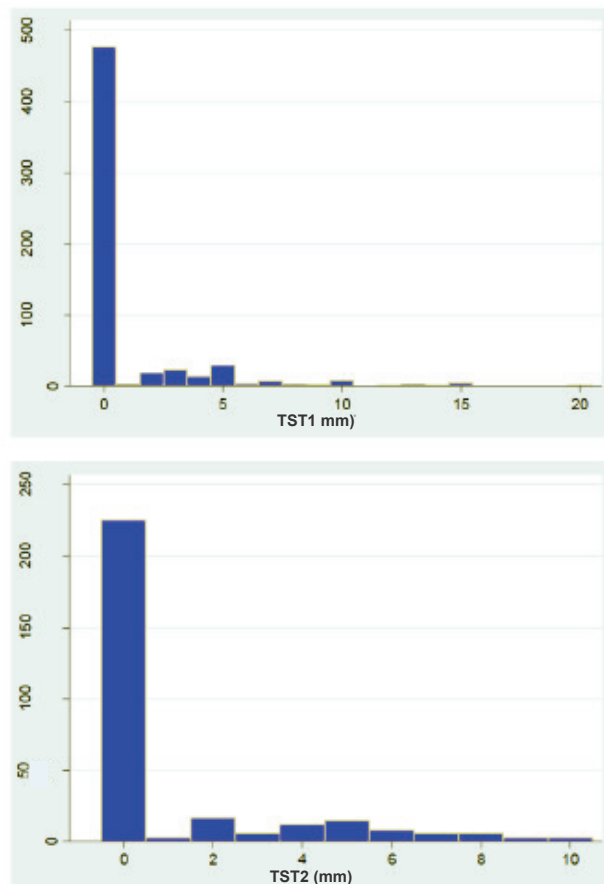
In 294 participants who had both TSTs (TST1 and TST2), the incidence of test conversion was analyzed and the different definitions/cut-off points proposed in the bibliography were analyzed for sensitivity (*Table 1*).

Considering all the participants who had at least 1 positive TST, the overall prevalence of latent *Mycobacterium tuberculosis* infection was obtained. Out of a total of 610 participants who had at least 1 TST, the prevalence ranged from 3.4% to 11.6%, depending on the cut-off point selected to define test positivity (*Table 2*).

Occurrence of tuberculosis disease and radiological studies

The initial clinical assessment included 548 asymptomatic participants (79.3% of the total), 4 with symptoms compatible with

FIGURE 2. Distribution of tuberculin skin tests values (mm) (TST1: n = 600; TST2: n = 304)



tuberculosis and 139 (20% of the total) who had not been recorded. Of the 4 participants with symptoms, 1 was confirmed as a case of tuberculosis, 2 were ruled out, and 1 was lost to follow-up.

No cases of new symptom onset during follow-up were recorded in those with a documented final assessment, which accounted for 297 of the 548 initially asymptomatic participants. No record of final symptom assessment was observed in 251 participants (45.8%).

The initial radiological assessment was recorded in 515 participants (75%; 95% CI: 71–78). Of these, 1 (0.2% of the total radiological assessments) was assumed to be compatible with tuberculosis and corresponded to the case with initial symptoms of tuberculosis.

Household situation

In 467 participants (68% of the total number), the presence of persons with respiratory symptoms was recorded. An affirmative response

TABLE 1. Frequency and incidence of tuberculin skin test conversion, according to different definitions (n = 294)

| | Frequency | Incidence |
|--------------|-----------|-----------|
| Definition 1 | 1 | 0.3% |
| Definition 2 | 2 | 0.7% |
| Definition 3 | 20 | 6.8% |

• Definition 1: TST1 < 10 mm; TST2 ≥ 10 mm. Difference between TST1 and TST2 ≥ 5 mm.

• Definition 2: TST1 < 10 mm; TST2 ≥ 10 mm.

• Definition 3: TST1 < 5 mm and TST2 ≥ 5 mm if index case is bacilliferous; TST1 < 10 mm and TST2 ≥ 10 mm if index case is not bacilliferous.

TABLE 2. Frequency and overall prevalence of *Mycobacterium tuberculosis* infection as per the tuberculin skin test, using different definitions of positivity (n = 610)

| | Frequency | Overall prevalence |
|---------------------|-----------|--------------------------|
| Definitions 1 and 2 | 21 | 3.4% (95% CI: 2.3–5.2) |
| Definition 3 | 71 | 11.6% (95% CI: 9.3–14.4) |

• Definitions 1 and 2: positive TST ≥ 10 mm.

• Definition 3: positive TST ≥ 5 mm if index case is bacilliferous, or ≥ 10 mm if index case is not bacilliferous.

was recorded in only 2 participants; none of them had symptoms and both had a TST1 result of 0 mm.

Adherence to chemoprophylaxis

Compliance with complete chemoprophylaxis with 1 drug (3 months) was observed in 133 participants (28.7%; 95% CI: 24.7–33) of 464 candidates. In addition, 245 participants (52.8%; 95% CI: 48.2–57.3) did not initiate treatment with the prescribed medication (Table 3).

Twenty-one participants met the criteria to receive chemoprophylaxis with 2 drugs according to latent infection treatment guidelines; 19 of them had a TST1 of 10 mm or more, and in the other 2, conversion was documented (according to definition 2). Compliance with complete chemoprophylaxis with 2 drugs (6 months) was observed in 10 participants (47.6%; 95% CI: 26.3–

69.8) of the total of 21 candidates. In addition, 5 participants did not initiate treatment with the prescribed medication.

Final knowledge of infection status

The health care teams recorded final knowledge of participants' infection status in 317 of the 691 contacts (45.9%; 95% CI: 42.2–49.6). Five independent variables were maintained in the final model, excluding participants with missing data on any of these (n = 59) for a total of 632 observations (Table 4).

The intraclass correlation interval was 0.49 (95% CI: 0.29–0.69) for school and close to 0 for health care provider. This means that 49% of the variability in individual outcome was attributable to the clustering of participants among schools and that no contextual effect attributable to the health effector was observed in the model, having taken into account the aforementioned school effect.

TABLE 3. Duration (months) of treatment with isoniazid as primary chemoprophylaxis in candidates to receive it (n = 464)

| Duration of treatment with isoniazid | Participants (n) | Proportion (%) | 95% CI |
|--------------------------------------|------------------|----------------|------------|
| 0 months | 245 | 52.8 | 48.2–57.3* |
| 1 month | 44 | 9.5 | 7.1–12.5 |
| 2 months | 42 | 9 | 6.8–12 |
| 3 months | 133 | 28.7 | 24.7–33 |
| Total | 464 | 100 | - |

CI: confidence interval.

TABLE 4. Relative risk of lack of final knowledge of *Mycobacterium tuberculosis* infection status by the health care team based on selected variables (n = 632)

| | Relative risk | 95% CI | p |
|---------------------------------------|---------------|-----------|-------|
| Aged 18 years or older | 1.25 | 0.99–1.58 | 0.06 |
| School in a district with UBNs | 3.35 | 0.83–13.5 | 0.09 |
| Afternoon shift | 1.71 | 1.24–2.35 | 0.001 |
| Index case with positive sputum smear | 0.66 | 0.47–0.92 | 0.015 |
| Recorded TST1 | 0.66 | 0.51–0.85 | 0.001 |

CI: confidence interval; p: statistically significant value.

TST1: baseline tuberculin skin test; UBNs: unmet basic needs.

DISCUSSION

Several findings in this study deserve to be highlighted.

The prevalence of latent infection among school contacts is variable and depends on the setting. We found a prevalence of latent infection of 3.4–11.6%, which was similar to that reported previously,^{6,13–16} although there are also differences with other studies with higher prevalence values, probably due to higher population prevalence in the studied region, an older schoolchildren age, a greater exposure among index cases and contacts and/or a greater diagnostic method sensitivity.

The incidence of tuberculin conversion among school contacts is probably low. Considering the TST cut-off point of 10 mm, the incidence of conversion was less than 1%, which is consistent with a previous local study.⁶ In both studies, contact lost to follow-up represents a specific risk of selection bias; therefore, the actual incidence of tuberculin conversion is probably somewhat higher than what has been documented. Other studies also provide similar evidence^{17–20} and found higher values in boarding school cases.^{21,22}

The incidence of secondary cases of active tuberculosis is higher in closed educational communities and its detection depends on the follow-up period. It is worth noting that,

during the 3-month follow-up period, no incidence of secondary cases of active tuberculosis was observed, regardless of the degree of adherence to isoniazid chemoprophylaxis.

The international experience coincides in the low incidence of secondary cases,^{13–15,23–25} although incidences between 3% and 6% have also been reported.^{16,26–29} Boarding schools and schools where teachers were index cases showed higher values (17–42%).^{22,30}

The loss to follow-up is large if several points of contact are raised. Both in this study and in previous ones, it was observed that the TST2 coverage did not reach 50% of target contacts.^{6,19} Some authors have proposed that simpler courses of action may be considered in resource-limited settings.³¹

There are predictors of contact loss to follow-up. The protective factor of the bacilliferous nature of the index case may have been related to a greater concern on the part of the families and/or a greater intensity of actions on the part of health care providers. This aspect and the role of age have also been observed in previous studies.³² It has been described that many schoolchildren attending the afternoon shift help with family work activities or in the care of younger siblings during the day.³³ Such vulnerable situation may be acting as a barrier to health care access.

Adherence to isoniazid chemoprophylaxis is low. Less than one-third of the contacts who were prescribed chemoprophylaxis with 1 drug completed the 3-month regimen. Adherence to chemoprophylaxis is problematic and accounts for a global challenge in the management of tuberculosis in general³¹ and in the context of school registries in particular.^{6,16,19,29,34,35}

The methodological strengths of this study include its cohort design and the multilevel analysis that allowed us to assess the extent of correlation between some results.

In relation to the limitations of this study, it is worth pointing out the existence of missing data and the absence of potentially interesting individual variables (e.g., participants' socioeconomic level, physical proximity in the classroom, or social connection with the index case). The loss to follow-up made it difficult to accurately estimate both the incidence of tuberculin conversion and the occurrence of secondary cases, although it is noteworthy that no new cases were reported to treating teams from the epidemiological surveillance system or the school authorities during the registration period.

CONCLUSIONS

The prevalence of latent tuberculosis infection among school contacts was within the values previously reported at a local level and the incidence of tuberculin conversion was low. Adherence to isoniazid treatment remains limited. Factors associated with loss to follow-up were identified, which may guide the implementation of strategies necessary to improve this process. ■

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