Incidence of Latent Tuberculosis Infection in a Study of School Contacts Comparing Two Cut-off Points of the Tuberculin Test

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Abstract

Introduction: The risk of tuberculosis infection is associated with close and prolonged contact. Daily contact, poorly ventilated classrooms or delay in diagnosing the index case in a school setting could contribute to contagion.

Objective: To know the incidence of latent tuberculosis infection (LTBI) in school contacts comparing two cut-off points of the tuberculin test (PPD, Purified Protein Derivative): $\geq$ 10mm and $\geq$ 5mm. To determine the degree of compliance with the performance of control and chemoprophylaxis (ChP) studies.

Materials and Methods: We carried out a retrospective analysis of bacillary TB school contacts in teenagers between 12 and 19 years old of the Programmatic Area of the Hospital Parmenio Piñero between February 2016 and December 2017. The evaluation included chest x-ray, lab tests and PPD. We analyzed 2 cut-off points of the PPD: $\geq$ 10mm and $\geq$ 5mm, and repeated the test after 3 months in cases with negative results. Primary ChP with isoniazid was indicated for all the contacts, and secondary ChP for those with basal PPD+ or conversion at the third month. We considered ChP compliance in cases where patients followed > 80% of the indicated regime.

Results: 331 (89%) of 373 students to be evaluated participated in the study. TB was diagnosed in 4 students (1.2%) through chest x-ray, and they were excluded. Within the remaining 327, the mean age was 15 ± 1.6 years, and 132 (40%) were male. The basal PPD was $\geq$ 10mm in 20 cases (6.1%), being more frequent in the group of 16-19 years versus the 12-15 years: 10.7% vs. 3.1%; p = 0.004. There wasn't any significant difference regarding sex. 135 contacts (45%) did the second PPD, and 3 conversions were found (2.2%). Primary ChP was indicated for everyone, and secondary ChP for 23 contacts, with 75% and 26% compliance respectively, and without any significant association with age or sex. 4 adverse events were reported (1.2%): polineuritis (n=2), skin allergy and food intolerance. 63 contacts (19.3%) were positive PPD, with PPD $\geq$ 5mm, being more frequent in males: 26.5% vs. 14.4%, p = 0.006; and in 16-19 vs. 12-15 years: 28.2% vs. 13.2%; p < 0.001. With the second PPD we observed 3 conversions (2.2%).

Conclusion: We found 6.1% of LTBI considering a PPD+ $\geq$ 10mm and 19.3% with PPD $\geq$ 5mm. Compliance with the second PPD and the secondary ChP scheme was low.

Key words: Latent tuberculosis; Tuberculin Test; School contacts; Tuberculosis; teenager

Introduction

Tuberculosis is still a pending debt for health systems in many countries that weren't able to prevent children and teenagers from dying as a consequence of this disease. The World Health Organization

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estimates there are 9 million ill people and 1.5 million deaths for tuberculosis in the world every year; this makes it one of the most lethal infectious diseases.[1]

The essential element for the control of tuberculosis (TB) is diagnosing the disease during the first stages and the adequate treatment of patients. However, in order to eliminate it, it is necessary to identify and treat infected individuals before the infection progresses to the disease and the individuals turn into sources of contagion.

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to prior acquired *Mycobacterium tuberculosis* antigens, without clinical manifestations of active TB. It is assumed that individuals with proven LTBI have 5 to 10% risk of reactivation TB throughout their life; in most cases it will be manifested during the first 5 years after getting infected. The risk of contracting the disease after the infection depends on several factors, the most important being the immune state of the host[2].

The diagnostic method that has been used throughout the world for more than a century for TB, both latent and active, is the tuberculin test (PPD). A positive result is associated with a higher risk of current or future active TB. It is an effective, low-cost test but has certain limitations: it requires a correct administration by the Mantoux method (intradermal injection) and needs a second visit for reading the test.[3] The presence of an induration in the application area $\geq$ 10mm, 48 hours after the PPD injection suggests the patient is at risk of developing tuberculosis in the future, even though several countries with a higher incidence rate use a cut-off point of $\geq$ 5mm for early detection of LTBI.

The purposes of this study were to determine the percentage of LTBI cases among school contacts evaluated in a general hospital of the city of Buenos Aires (CABA) and the degree of therapeutic compliance following indication of chemoprophylaxis (ChP).

Materials and Methods

We carried out a retrospective analysis of bacillary TB school contacts of the Programmatic Area of the Hospital General de Agudos Parmenio Piñero between February 2016 and December 2017 in teenagers between 12 and 19 years old. Once the index case is notified to the staff of the School Health Program, the school contacts are called with the different services for conducting the studies and doing the tests with the specialists.

6 educational institutions were referred for the control of contacts that belonged to the classes with index cases. We excluded cases with chest x-ray compatible with active TB, history of TB, current TB diagnosis and those who did not complete the requested basal studies. We collected data from every contact with regard to comorbidities, presence of risk factors or symptoms associated with TB and history of tuberculosis disease.

All the patients underwent chest x-ray, hemogram and hepatogram. For the diagnosis of tuberculosis infection, we performed the Mantoux test with 2 tuberculin units (TUs) of PPD-RT23, at the hospital's vaccination unit, and the same operators measured the induration after 48 hours. An induration of 10mm or more was considered positive; and the application was repeated after 3 months in negative cases. "Conversion" was defined as a second PPD injection of $\geq$ 10mm with an increase of > 5mm compared to the basal test. Primary chemoprophylaxis with isoniazid (300 mg/day) was indicated for 3 months to all students with PPD < 10mm, with the possibility of being prolonged for 6 months if conversion was observed. Isoniazid was indicated for 6 months in patients with positive basal PPD. The treatment was considered as completed when there was > 80% compliance with the prescribed therapeutic regimen.

Also, an analysis was carried out with a PPD cut-off point of $\geq$ 5mm, considering a > 5mm increase in the second PPD as conversion. No therapeutic regimen was applied in this regard.

Monthly visits were arranged for follow-up, and lab controls were established according to the clinical criterion in each case.

The school health area of the hospital stayed in contact with the institutions included in the study during at least 2 years for monitoring possible new TB cases.

All the collected data were included in a database created for that purpose and analyzed through descriptive statistics tools. The Chi-Square Test was used for group comparison.

Results

We identified 373 students to be evaluated, and 331 (89%) completed the studies. TB was diagnosed in 4 (1.2%) cases through a chest x-ray, and those students were excluded from the study. Within the remaining 327, the mean age was 15 ± 1.6 years and 132 (40%) were male.

The basal PPD was ≥ 10mm in 20 cases (6.1%), being more frequent in the group of 16-19 years versus the 12-15 years: 14 out of 131 (10.7%) vs. 6 out of 196 (3.1%); p = 0.004. There was no significant difference as regards the sex (**Table 1**). Only 135 patients (45%) underwent the second PPD, and 3 conversions were found (2.2%).

TABLE 1. Comparison of PPD results obtained in the different groups under evaluation

Students	Total	PPD < 10 mm	PPD ≥ 10mm	χ^2 p = < 0.05	PPD < 5 mm	PPD ≥ 5mm	χ^2 p = < 0.05
Sex							
Males	132	120 (91%)	12 (9%)	0.64	97 (73%)	35 (27%)	0.006
Females	195	187 (96%)	8 (4%)		167 (86%)	28 (14%)	
Age							
12-15 years	196	190 (97%)	6 (3%)	0.004	170 (87%)	26 (13%)	0.0007
16-19 years	131	117 (89%)	14 (11%)		94 (72%)	37 (28%)	

TABLE 2. Therapeutic compliance of primary ChP according to age and sex

Students	Total	Complies with p ChP	Does not comply with p ChP	p < 0.05
Sex				
Males	119	70 (59%)	49 (41%)	0.73
Females	183	104 (57%)	79 (43%)	
Age				
12-15 years	186	112 (60%)	74 (40%)	0.24
16-19 years	116	62 (53%)	54 (47%)	

Primary ChP was indicated for every student in contact with a case of bacillary TB (n= 327), and secondary ChP was administered to 23 students, excluding two for history of convulsions, one for increased transaminases in the basal hepatogram and another one with history of recent ChP. The compliance rate was 58% and 26%, respectively (Figure 1), without a significant association with age and sex (Table 2).

4 adverse events were reported (1.2%): polineuritis (n = 2), skin allergy and food intolerance, which required treatment interruption.

In the analysis with cut-off points of ≥ 5mm, 63 students were positive (19.3%), being more frequent in males: 35 of 132 (26.5%) vs. 28 of 195 (14.4%), p = 0.006; and in the group of 16 to 19 years old, compared to the 12 to 15 years old group: 37 of 131 (28.2%) vs. 26 of 196 (13.2%); p < 0.001. With the second PPD we observed 3 conversions (2.2%) (Figure 1).

No new cases of TB were reported to the school health area from the school divisions included in the study during the following 2 years after the inclusion period.
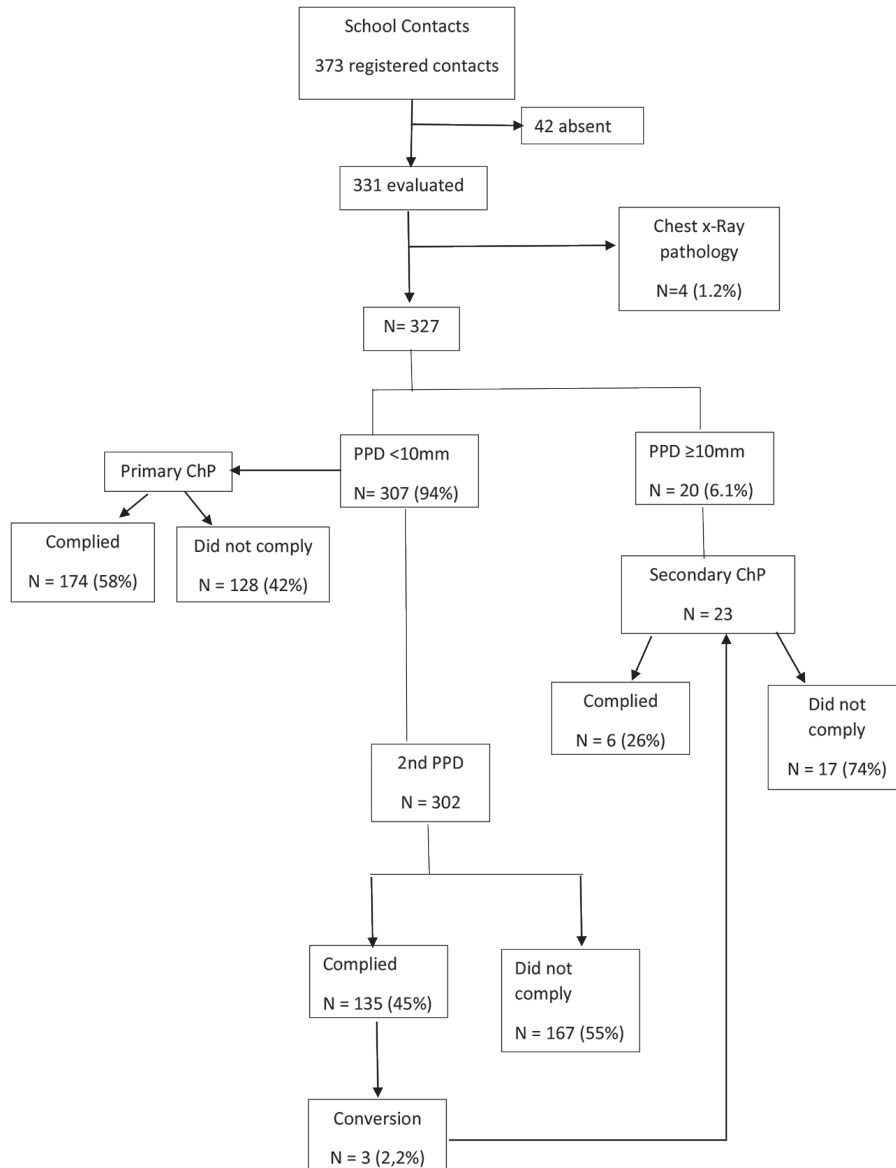
Figure 1. Compliance with the performance of the PPD and chemoprophylaxis (ChP).

Discussion

In this study we show an incidence of LTBI in school contacts of 6.1%, considering PPD+ ≥ 10mm and 19.3% with PPD ≥ 5mm, obtaining conversions with similar percentage (2.2%) in both cut-off points. Our area of assistance is related to a population with limited financial resources and a TB incidence of approximately 100 cases every 100,000 inhabitants during the period under evaluation. The outbreak control carried out in high-prevalence areas is highly profitable and shall be done with every case of TB. There was a high degree of compliance with the control studies, but low adherence to the prescribed treatment.

Not surprisingly, there is great variation in the prevalence of LTBI in school students (from 3 to 23%)[4-9], which can be associated with different PPD cut-off points, different age ranges and TB prevalence in the population under evaluation.

The Argentine Consensus of Tuberculosis proposes the use of 5mm cut-off point for close contacts of bacillary TB[10]. While the population under study has an exposure of < 6 hours daily (and shouldn't be considered as close contacts), the decision to use a higher cut-off point (10mm) makes the tuberculin test a more specific one, whereas with 5mm it makes it more sensitive and useful if we want to quickly decrease TB prevalence in the population with ChP treatment of recently infected cases (with higher risk of developing the disease and perpetuate the cycle of infection, disease, contagion).

Regardless of the cut-off point used to consider the PPD as positive, we found significant differences with respect to age, being more frequent between 16 and 19 years. With regard to the data for the 5mm cut-off point, there was also higher prevalence in males. This could be associated with the fact that older teenagers may have their source of infection outside their circle of daily activities, beyond the educational institution.

In teenagers, TB may develop following the first infection, or as a reactivation of a previous childhood infection[11-13]; this determines the importance of early detection and therapeutic approach.

The low degree of compliance with the PPD after the third month (less than half of the contacts) could be related to the following aspects: limited resources of the health system for the follow-up of the contacts, associated with the fact of being asymptomatic and requiring time availability from adults in charge[14, 15].

Primary ChP was indicated for all negative PPD students, obtaining a low degree of treatment compliance, and being even lower with secondary ChP. The adolescence is characterized by great biological and psychosocial changes, the risk of substance consumption, as for example tobacco, alcohol and drugs, plus problems with adherence to medical treatments[16]. As a consequence, shorter treatments are being studied. One study evaluated a daily regime of rifampicin and isoniazid for 3 months as treatment for LTBI in children and teenagers, and showed that it is safe, with a higher rate of compliance in comparison with isoniazid for 6 or 9 months[17]. Another research that analyzed chemoprophylaxis directly observed once a week using rifapentine plus isoniazid for 3 months showed the same efficacy in comparison with daily isoniazid self-administered during 9 months[18].

4 adverse events were reported: skin allergy, food intolerance and 2 cases of polyneuritis that required treatment interruption. No hepatotoxicity was found, making it possible to confirm the safety profile of chemoprophylaxis with isoniazid in teenagers.

The school health area of the hospital carried out a subsequent follow-up, during 2 years, to determine the development of the disease, and didn't report any TB case in the school classes included in the study, despite the low degree of therapeutic compliance.

There is huge controversy over the interaction of the BCG vaccine (Bacillus Calmette-Guérin) and the PPD. Various authors published studies concluding that the influence of the vaccine tends to disappear 10 to 15 years after it was administered. In 2013, the authors Piñero et al published a study conducted in a population of 1,074 kids from various geographical areas, most TB endemic. By stratifying the analysis according to different age ranges, it was proven that the effect of the vaccine disappears 3 years after its administration.19 In Argentina, the BCG vaccine is applied to newborns, so we believe it would be convenient to use the ≥ 5mm cut-off point without taking into account the history of vaccination. This could help redirect resources towards treatment and follow-up of cases with proven LTBI only (secondary ChP), thus delaying the beginning of ChP for 3 months in asymptomatic teenagers with normal chest x-ray and negative PPD, until the tuberculine test variation is confirmed. As regards the 5mm cut-off point, it is used in several countries such as Mexico, Brazil, Ecuador, China, some European countries and the United States of America, with the purpose of reducing the annual TB rate[20-26]; and also avoiding the ChP treatment of students without diagnosis of LTBI (through PPD or quantiferon), furthermore taking to account the fact that they belong to groups with risk of reinfection[27, 28].

Conclusion

We conclude that, within the evaluated population of an area with an annual TB incidence of 100/100,000 inhabitants, we found 6.1% LTBI when considering PPD+ ≥ 10mm and 19.3% with PPD ≥ 5mm. A

lower cut-off point allows for the identification of a higher proportion of infected patients. The level of compliance with the performance of the second PPD and secondary ChP was low.

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