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Incidence of Latent Tuberculosis Infection in a study of household contacts treated in a General Hospital of the City of Buenos Aires

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Introduction: The study of household contacts of patients with tuberculosis (TB) is an essential strategy for the early diagnosis of latent tuberculosis infection (LTBI) and for the establishment of the corresponding treatment for the purpose of reducing TB prevalence in the population.
Objective: To know the incidence of LTBI in household contacts and the degree of compliance with control studies and chemoprophylaxis (ChP).
Materials and Methods: We carried out a retrospective analysis of > 15-year-old household contacts of patients with TB treated in the Hospital General de Agudos Parmenio Piñero between January 2016 and February 2018. Chest x-ray and tuberculin skin test (PPD, Purified Protein Derivative) were requested, considering ≥ 10 mm as a positive cut-off point. The tuberculin skin test was repeated after 3 months in subjects with negative results. ≥ 5 mm was also considered as PPD+ when analyzing the data. The cases in which patients followed > 80% of the indicated regime were considered as compliant with ChP: 3 months of isoniazid in primary ChP and 6 months in secondary ChP.
Results: 4 (1.2%) of the 344 admitted contacts were diagnosed with TB through chest x-rays with pathological images. These 4 contacts with TB were excluded from the study. Within the remaining 340 subjects, with a mean age of 35 ± 16 years, there were 154 (45%) males, 180 (52%) Argentinians and 144 (43%) Bolivians. Of the 193 (57%) subjects who complied with the performance of the basal PPD test, 38 (20%) showed PPD ≥ 10 mm and 89 (46%) ≥ 5 mm. Women were more compliant than men with PPD testing: 122 out of 186 (55%) vs. 71 out of 154 (45%); p = 0.005. There was no significant difference as regards age and nationality. Only 33 (21%) patients complied with the performance of the second PPD test, without any conversions for the 10 mm cut-off point, and with 3 conversions considering ≥ 5 mm as PPD+. Primary ChP was indicated to 55 patients, and secondary ChP to 38 patients. The compliance rate was 75% and 39%, respectively, without a significant association with age, gender or nationality. No adverse event associated with isoniazid was reported.
Conclusion: We found 20% LTBI within the population under study considering ≥ 10 mm as PPD+; 46% was found with ≥ 5 mm PPD. There was a low level of compliance with the performance of the PPD test (though it was higher in women) and of secondary ChP.

Key words: Latent tuberculosis, Tuberculosis, Tuberculin Tests, Primary Health Care

Introduction

LTBI is defined as a state of persistent immune response to prior acquired *Mycobacterium tuberculosis* antigens, without clinical manifestations of active TB. It is calculated that one fourth of the world's population is infected with *M. tuberculosis*. We assume that people with documented LTBI have 5 to 10% risk of TB reactivation throughout their lives; in most cases, it will be manifested within the first 5 years after getting infected. The risk of contracting the disease after the infection depends on many factors, the most important being the immune state of the host[1].

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The tuberculin test (PPD) has been used throughout the world for more than a century to help in the diagnosis of TB, both latent and active. A positive PPD result is associated with a higher risk of current or future active TB. PPD has proven its efficacy in detecting TB, and it is a very low cost test. However, it does have limitations: it has to be properly administered by means of the Mantoux method (intradermal injection) and requires a second visit for its reading[2].

The presence of an induration of ≥ 10 mm in the application site 48 hours after the PPD injection suggests that the patient is at risk of developing tuberculosis in the future, even though many countries with a higher incidence rate use the cut-off point of ≥ 5 mm for early detection of LTBI.

The purposes of this study were to evaluate the percentage of LTBI cases within household contacts treated in a general hospital and the degree of therapeutic compliance following indication of ChP.

Materials and Methods

We carried out a retrospective analysis of > 15-year-old household contacts of TB patients treated in the Hospital General de Agudos Parmenio Piñero between January 2016 and February 2018. We included in this work all subjects living in the same household as a patient with documented TB, and excluded those with history of TB, of < 15 years, and those who were referred to other health centers for follow-up.

The household contact study included gathering of personal data such as presence of risk factors (for example, HIV or another immunological disease, use of immunosuppressive treatment), of TB-related symptoms and history of tuberculous disease, and data related to the tuberculous patient living in the same household (relationship with the patient, TB localization, baciliferous nature, etc.) Most index cases were in our hospital under follow-up.

All the patients underwent a chest x-ray. For the diagnosis of tuberculous infection, we performed the Mantoux test with 2 PPD-RT23 tuberculine units (TUs). The application of the PPD was performed by trained personnel of the hospital's vaccination service. It was measured after 48 hours. An induration of 10 mm or more was considered positive; and the application of the PPD was repeated after 3 months in negative cases. "Conversion" was defined as a second PPD injection of ≥ 10 mm, with an increase of > 5 mm with regard to the basal test.

Primary chemoprophylaxis with isoniazid was indicated for 3 months to patients younger than 35 years old. Isoniazid was indicated for 6 months to patients with positive PPD or PPD converters. Treatment was considered as completed when there was > 80% compliance with the prescribed therapeutic regimen.

We also analyzed the incidence of LTBI considering a PPD cut-off point of ≥ 5 mm, without applying any therapeutic regimen in these cases (except for immunosuppressed or HIV patients). For this cut-off point, we considered a > 5 mm increase in the second PPD as a conversion.

Monthly follow-up visits were established, as well as lab control after one month and then according to clinical criterion. Patients did not show signs or symptoms indicative of treatment suspension.

All the collected data were included in a database created for that purpose and analyzed through descriptive statistics tools and Chi-square test.

Results

344 contacts were admitted and TB was diagnosed in 4 (1.2%) cases that showed a chest x-ray with pathological images. The 4 contacts with TB were excluded from the study. Within the remaining 340 subjects (154 males, 45%) with a mean age of 35 ± 16 years, there were 180 (52.6%) Argentinians, 144 (42.7%) Bolivians and the rest (n = 16; 4.7%) included Peruvians, Paraguayans and Colombians. The contacts under evaluation were 127 index cases (2.7 contacts/case), most of them with pulmonary TB (n = 108; 85%), baciliferous (n = 83; 65%) and with cavitary lesions in imaging studies (n = 70; 55%). Regarding the previous description, we find that most of the contacts under evaluation had been exposed to pulmonary TB (n = 292; 86%), baciliferous TB (n = 227; 67%) and cavitary TB (n = 195; 57%).

193 (57%) out of the 340 contacts under evaluation complied with the performance of the basal PPD test, and 38 (20%) had a PPD of ≥ 10 mm. Women were more compliant than men with PPD testing: 122 out of 186 (55%) vs. 71 out of 154 (45%); p = 0.005. There was no significant difference as regards age and nationality (**Table 1**). Only 33 out of 155 (21%) patients performed the second PPD, and there weren't any conversions (**Figure 1**).

TABLE 1. Compliance with the performance of the PPD test according to gender, age, and nationality

	Comply with PPD test	Do not comply with PPD test	p Value
Gender			
Men	71 (21%)	83 (24%)	0.005
Women	122 (36%)	64 (19%)	
Nationality			
Argentinians	109 (32%)	71 (21%)	0.17
Foreigners	85 (25%)	75 (22%)	
Age			
<35 years old	109 (32%)	84 (25%)	0.80
≥ 35 years old	85 (25%)	62 (18%)	

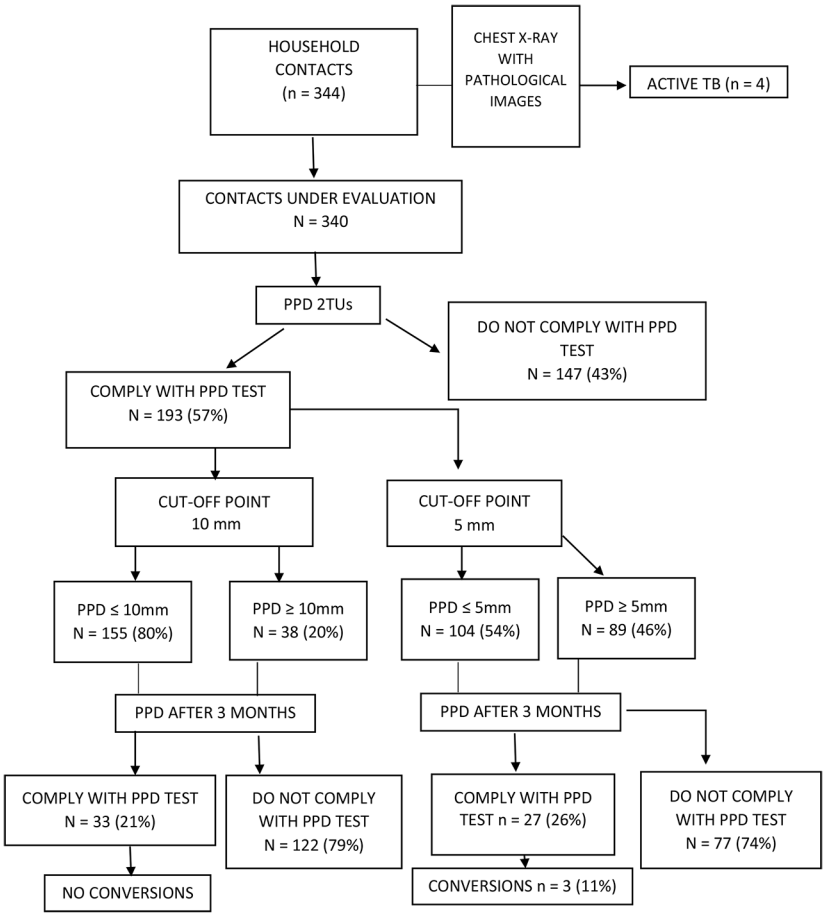

Figure 1. Compliance with the performance of the PPD test and results obtained considering 10 and 5 mm as cut-off points to diagnose latent tuberculosis infection

No significant differences were found in the proportion of PPD+ contacts when grouping them together according to age, gender, and nationality (**Table 2**). No index case characteristics were found, either (positive smear test, presence of cavitations) (**Table 3**).

TABLE 2. Comparison of results obtained with the PPD test within the different groups under evaluation

	PPD < 10 mm	PPD ≥ 10 mm	p Value	PPD < 5 mm	PPD ≥ 5 mm	p Value
Gender						
Men	52	18	0.11	40	30	0.50
Women	103	20		64	59	
Age						
< 35 years old	86	23	0.57	59	50	0.93
≥ 35 years old	69	15		45	39	
Nationality						
Argentinians	89	20	0.86	58	50	0.95
Bolivians	62	13		46	39	

TABLE 3. Comparison of the results obtained with the PPD test among the contacts, according to the characteristics of the index case

	PPD < 10 mm	PPD ≥ 10 mm	p Value	PPD < 5 mm	PPD ≥ 5 mm	p Value
Smear test						
Positive	108	20	0.44	71	61	0.41
Negative	47	18		33	28	
Pulmonary lesions						
Cavitary	92	20	0.45	61	51	0.36
Non-cavitary	63	13		43	38	

When considering ≥ 5 mm as a cut-off point for LTBI, we found that the percentage of PPD+ contacts increased to 46%, and there were 3 tuberculine test variations: basal PPD = 0 (in all of the cases) and second PPD of 7, 7 and 9 mm (**Figure 1**).

If we take into account only household contacts of patients with baciliferous TB, we find 260 cases, 153 (59%) of which complied with the performance of the PPD test. 33 (22%) had cut-off points of ≥ 10 mm. There isn't a significant difference when comparing them with the total number of cases evaluated in this study, including index cases with extrapulmonary TB. Within this sub-group, the amount of contacts with LTBI increases to 50% if we consider ≥ 5 mm PPD as the cut-off point.

Primary chemoprophylaxis was indicated to 55 patients, and secondary chemoprophylaxis to 38. The indicated treatment was completed by 41 (75%) and 15 (39%) patients, respectively. No significant relationship is found between compliance and age, gender, and nationality. The results obtained from therapeutic compliance with primary and secondary chemoprophylaxis are shown in **Tables 4** and **5**, respectively.

No adverse event associated with isoniazid was reported.

TABLE 4. Comparison of therapeutic compliance with primary ChP according to gender and nationality

Groups	Total	Comply with pChp	Do not comply with pChp	p Value
Gender				
Men	17	9	8	0.920
Women	22	12	10	
Nationality				
Argentinians	27	20	7	0.383
Foreigners	30	19	11	

pChp: primary chemoprophylaxis

TABLE 5. Comparison of therapeutic compliance with secondary ChP according to gender, age, and nationalit

	Total	Comply with sChp	Do not comply with sChp	p Value
Gender				
Men	14	8	6	0.304
Women	18	7	11	
Age				
< 35 years old	21	8	13	0.91
≥ 35 years old	15	6	9	
Nationality				
Argentinians	20	8	12	0.942
Foreigners	17	7	10	

sChp: secondary chemoprophylaxis

Discussion

In this study we show the incidence of LTBI in household contacts treated in a general hospital of the city of Buenos Aires. It was carried out within a population with limited financial resources and a TB incidence of approximately 100 cases every 100,000 inhabitants.

All the contacts underwent a chest x-ray to discard active TB, and 57% returned to consultation with the PPD result: LTBI could be observed in 20% of the patients, when considering a PPD of ≥ 10 mm, and 46% with a PPD of ≥ 5 mm. No significant differences were found according to age, gender and nationality, or to the baciliferous condition or the presence of pulmonary cavitations in the index case. There was a very low level of compliance (21%) among patients with a negative basal PPD who had been asked to repeat the procedure after 3 months.

Countries with a high incidence of TB, such as Mexico, Brazil and Ecuador use the ≥ 5 mm cut-off point as PPD+, with the purpose of trying to reduce the annual TB rate[4, 6]. Some countries are experiencing an important reduction in TB cases, whereas in others, the number of TB patients is decreasing very slowly. Brazil and China, for example, are two of the countries that showed large and sustained reduction in TB cases for the last 20 years[7]. China, has particularly made spectacular progress in the control of tuberculosis: the country's incidence rate recorded in 2017 experienced a 14.3% decrease in comparison with 2012 and an annual decrease of almost 3%, which is more than the global average,

placing great emphasis both on prevention and treatment[8]. It is worth mentioning that this cut-off point is also used in European countries and in the United States, which have a low incidence of TB[9, 10].

One of the limitations of LTBI control studies is the lack of a reference method to determine the accuracy of the tests that are being used at present (PPD, quantiferon). The decision to use a higher cut-off point (10 mm) makes the tuberculine test more specific, but when the 5 mm cut-off point is used, the test becomes more sensitive and thus more useful if we want to quickly reduce the prevalence of LTBI within the population. If we take into account this cut-off point suggested at the Argentine Consensus of Tuberculosis, the proportion of contacts identified as LTBI in the population of the study has doubled[11].

We didn't find any relationship between the PPD+ and the baciliferous or cavitary index cases, as one would expect. Probably, we would need more patients to prove that relationship. On the other hand, given the fact that the population under study has high TB prevalence, the evaluated contacts could also have other sources of exposure.

The probability that contacts with diagnosed LTBI would develop the disease is estimated to be 5-10%, with predominance of cases among extreme aged individuals, people with immune dysfunction or immigrants from countries with high TB incidence, all of which determine the importance of the therapeutic approach (secondary ChP)[3]. 39% compliance was obtained in the evaluated population, not differing from the data reported in published studies: 30-60%, being the rate closer to 30% than to 60% in most cases[12-15].

As a consequence, shorter regimes are being considered, as for example, a recently published open trial performed in nine countries reveals that the 4-month regimen of rifampicin for the prevention of tuberculosis was associated with a higher rate of treatment completion and a better safety profile[6]. Another study evaluating directly observed once-weekly chemoprophylaxis with rifapentine + isoniazid for 3 months showed the same efficacy than daily self-administered isoniazid for 9 months[16].

This study hasn't been designed to evaluate causes associated with a low level of ChP compliance. The factors described in other studies include lack of information regarding the disease, the absence of symptoms and long treatments that require periodic controls. We observed that women were more compliant than men with the performance of the PPD test; this may be associated with factors such as stronger interest in personal and family care or having more time to go to health facilities with limited opening hours.

The purpose of primary ChP is to avoid tuberculous infection in healthy people exposed to a contagious source. It is worth mentioning that 75% of contacts with indication of primary ChP complied with the indicated regime. This could be related to the fact that the duration of primary QhP is shorter than that of secondary ChP (3 vs. 6 months). Secondary QhP had only 39% compliance.

Conclusion

We conclude that, within the evaluated population of an area with an annual TB incidence of 100/100,000 inhabitants, we found 20% LTBI when considering ≥ 10 mm as PPD+ and 46% with ≥ 5 mm PPD. 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 PPD was low (though it was higher in women). Secondary ChP compliance was poor, too. If we optimize the control of the contacts and improve chemoprophylaxis compliance guidelines, the TB incidence rate in our population could be progressively reduced.

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