

Prevalence and evolution of *Mycobacterium tuberculosis* infection in tuberculosis case contacts

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ABSTRACT

Introduction: The tuberculin test is a diagnostic method for detecting latent tuberculosis (TB) infection, especially among disease contact cases. The objective of this study was to analyze the prevalence and evolution of *Mycobacterium tuberculosis* infection among TB contact cases. **Methods:** A retrospective cohort study was performed in a reference center for TB. The study population consisted of 2,425 patients who underwent a tuberculin test from 2003 to 2010 and whose results indicated contact with individuals with TB. The data were collected from the registry book of the tuberculin tests, patient files and the Information System Records of Notification Grievance. To verify the evolution of TB, case records through September 2014 were consulted. Data were analyzed using the Statistical Package for the Social Sciences (SPSS). In all hypothesis tests, a significance level of 0.05 was used. **Results:** From the studied sample, 435 (17.9%) contacts did not return for reading. Among the 1,990 contacts that completed the test, the prevalence of latent TB infection was 35.4%. Of these positive cases, 50.6% were referred to treatment; the dropout rate was 42.5%. Among all of the contacts, the TB prevalence was 1.8%, from which 13.2% abandoned treatment. **Conclusions:** The collected data indicate the need for more effective public policies to improve TB control, including administering tests that do not require a return visit for reading, enhancing contact tracing and encouraging actions that reinforce full treatment adherence.

Keywords: Tuberculosis. Latent tuberculous infection. Communicating search. Tuberculin test.

INTRODUCTION

Tuberculosis (TB), an ancient infectious disease, has established an important means of sustaining the disease transmission chain through its case contacts. Despite being a preventable and curable infectious disease, TB remains a serious public health problem⁽¹⁾⁽²⁾.

The World Health Organization (WHO) estimated that in 2013, there were 9 million new TB cases and 1.5 million deaths due to TB⁽³⁾.

Tuberculosis, a disease caused by *Mycobacterium tuberculosis* (*Mtb*), can affect a number of organs and/or systems. However, the pulmonary form of TB is the most relevant to public health because it is responsible for sustaining

the disease transmission chain, especially the bacillary disease⁽¹⁾. Thus, all people living with an individual with TB must be subject to clinical and epidemiological research and must undergo a tuberculin skin test (TST).

The TST requires an intradermal injection of an *Mtb* purified protein derivative (PPD) to measure the cellular immune response to these antigens⁽¹⁾. This test is an auxiliary diagnostic method to detect the infection in asymptomatic people and should be performed 2-12 weeks after a suspected exposure (immunological window)⁽⁴⁾⁽⁵⁾. Reactor individuals (i.e., those with positive TST results) should be evaluated, and their latent tuberculosis infection (LTBI) must be subjected to treatment to prevent progression to full TB.

The TST can be interpreted as suggestive of TB infection when the test produces induration (localized swelling) ≥ 5 mm in diameter in children who were not vaccinated with *Bacillus Calmette-Guérin* (BCG), or in children who were vaccinated more than two years ago, or in anyone with an immunosuppressive condition. In children vaccinated under two years ago, a TST is considered suggestive of infection when it produces induration ≥ 10 mm in diameter. In adults and adolescents, in addition to epidemiological data, the induration size and the illness risk should be assessed⁽¹⁾.

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The WHO estimates that one-third of the world's population is infected with *Mtb*. However, that does not mean that they are sick, but rather that they have a latent TB infection⁽⁶⁾. Approximately 5% of people cannot stop the multiplication of the bacilli, and they become ill as a result of a primary infection. Another 5%, despite blocking the infection at this early stage, become sick later because of bacilli reactivation or as a result of exposure to a new source of infection⁽¹⁾.

The LTBI corresponds to the period between the penetration of the *Mtb* in the body and the appearance of TB disease. This evolution does not always occur, especially when remedial measures are adopted⁽⁷⁾. The LTBI diagnosis is made upon the basis of a positive TST result, which is associated with the existence of TB disease⁽⁸⁾.

For the LTBI diagnosis, there is no gold standard. Test diagnosis, existing tests, the TST and interferon gamma release assays (IGRAs) are indirect approaches that provide immunological evidence regarding the host's sensitization to TB antigens. IGRAs have greater specificity because the antigens for these tests are not contained in the BCG vaccine and in most other mycobacteria, thus excluding the possibility of false positives. Both the TST and IGRAs have reduced sensitivity in immunocompromised patients, and they have low predictive value for the actual progression to active TB^{(9) (10) (11)}. IGRAs tests are not yet available in the public health services in Brazil.

The investigation of TB contacts is recommended as a priority based on their risk of having or developing active TB. The contacts of primary concern include anyone with suggestive symptoms of TB, regardless of their age; children under five years old; people with immunocompromised conditions, especially people living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS); and index-case contacts with multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB)⁽¹²⁾. However, contact investigations are still being neglected by medical professionals and health services in terms of both the search for respiratory symptoms and the implementation and completion of the TST. Many individuals who are subjected to the application of PPD do not return for the reading of its result, interrupting the investigative procedure. The IGRAs tests minimize this issue, as there is no need to return for its completion. Nevertheless, the high cost of these tests prevents their implementation in public health services.

Another problem is the constant unavailability of PPD, which led the Brazilian Ministry of Health to limit the use of the TST among contacts and to treat LTBI in some cases without performing the test⁽¹³⁾.

Considering these factors, this study aimed to analyze the prevalence and evolution of *Mtb* infection among TB case contacts.

METHODS

This retrospective cohort study included data that were collected from the registry book of tuberculin tests performed in the Reference Centre for TB and AIDS, Dr. Bruno Piancastelli Filho, located in Londrina, State of Paraná, Brazil.

The study population consisted of 2,425 individuals who were contained in the registry book of TSTs performed from January 2003 to December 2010 and whose results indicated contact with a TB case. The cases with TST indurations of ≥ 5 mm were considered reactors, as recommended by the Ministry of Health⁽¹⁾.

Data were collected from medical records of individuals with readings from TSTs with indurations ≥ 5 mm. To verify TB evolution, the Information System Records of Notification Grievance [*Sistema de Informação de Agravos de Notificação* (SINAN)] of all individuals who underwent the TST up to September 2014, regardless of the outcome, were consulted. The SINAN was used as a research instrument consisting of demographic variables (gender, age) and laboratory and treatment data (chest radiography, TST, sputum smear, culture, pharmacological therapy, LTBI case evolution and TB closure situation).

Data were tabulated in a spreadsheet in the software Statistical Package for Social Sciences (SPSS, version 20.0, IBM, Chicago, Illinois, USA) and then analyzed and presented in tables and graphs. The categorical variables were presented through absolute and relative frequencies and the continuous ones according to the measures of central tendency (mean) and dispersion (standard deviation). The chi-square test was used to evaluate the association of the dependent variables (LTBI or TB) with the independent variables (gender, age). In all hypothesis tests, when the p -value < 0.05 , the null hypothesis was rejected.

Ethical considerations

This study was approved by the Research Ethics Committee of the State University of Londrina, with CAAE number 4674.0.000.268.-0.

RESULTS

In the period 2003-2010, 2,425 TSTs were performed for TB case contacts, from which 435 (17.9%) did not return for reading.

Among the 1,990 contacts who completed the TST, 704 (35.4%) were reactors. **Table 1** presents the TST results according to gender and age group.

The TST positivity rates were 37.6% among men and 33.5% among women (**Table 1**), with no statistically significant difference in this variable ($p = 0.055$).

Among the 2,425 contacts, the age of TST completion varied from a few days up to 99 years, with an age average of 29.81 years (SD 20.06) [standard deviation (SD) 20.06].

The age group that underwent the most TSTs was the 0- to 15-year-olds (610), noting positivity in 201 (33%) cases. Of the other age groups, the percentage of reactors ranged from 31.6% (26-35 years old) to 39.1% (36-45 years old). There was no statistical association for this variable (**Table 1**).

Among the 704 contacts who reacted positively to the TST, there were LTBI treatment prescriptions made for 356 (50.6%) cases, with a dropout rate of 43%. Of these cases, 55.1% finished the treatment, and 2% were transferred.

TABLE 1 - Prevalence of latent tuberculosis infection among case contacts, according to gender and age group. Londrina, State of Paraná, Brazil, 2014.

	Latent tuberculosis infection				P value
	no (TST 0-4mm)		yes (TST ≥ 5mm)		
	n	%	n	%	
Gender (n = 1990)					
male	567	62.4	342	37.6	0.055
female	719	66.5	352	33.5	
Age group (n = 1,957)*					
0-15	409	67.0	201	33.0	0.259
16-25	206	63.0	121	37.0	
26-35	195	68.4	90	31.6	
36-45	162	60.9	104	39.1	
46-55	130	61.9	80	38.1	
≥ 56	162	62.5	97	37.5	

TST: tuberculin skin test. *Unknown age in 33 cases.

The prevalence of TB among all contacts was 1.8% (44). **Figure 1** shows the period in which the disease diagnosis occurred in relation to the implementation of the TST, excluding two cases (one that did the TST after initiation of treatment and one after a previous treatment).

It was noted that 22 (52.4%) patients had the notification and initiation dates of treatment during the same period as when they underwent the TST, that is, at the time of the initial investigation. Among the others, 14 (33.4%) developed TB between 1-24 months afterward and six (7.2%) developed TB between 25-96 months after undergoing the TST (**Figure 1**).

Table 2 shows the results of the tests performed on the contacts that had TB.

Among the contacts that developed TB, 25 (78.2%) had positive sputum smear results. Among the seven who had cultures performed, the presence of the bacillus was identified in six. The chest radiography results showed 40 suggestive TB cases. Anti-HIV tests were not performed in 17 (38.6%) patients with TB, and two patients were HIV-positive.

Figure 2 shows the closure situation of the TB cases among the contacts, indicating a 72.7% cure rate.

DISCUSSION

Considering that the individuals who performed the TST in the reference center had some reason to investigate *Mtb* infection and that a portion of those individuals did not return for the test reading, there was the need to determine the prevalence and evolution of LTBI and TB among these disease case contacts. The literature contains few studies regarding TST administration

TABLE 2 - Distribution of contacts (n = 44) who developed active tuberculosis according to performed tests. Londrina, State of Paraná, Brazil, 2014.

Performed tests	Number	Percentage
Sputum smear microscopy (n = 32)		
1 positive sample	14	43.8
2 positive samples	10	31.3
3 positive samples	1	3.1
1 negative sample	5	15.6
2 negative samples	2	6.2
Sputum culture (n = 7)		
positive	6	85.7
negative	1	14.3
Chest X-ray (n = 44)		
suspicious	40	90.9
normal	4	9.1
Tuberculin test (n = 44)		
0 to 4mm	11	25.0
≥ 5mm	20	45.5
test not completed	13	29.5
HIV test (n = 27)		
positive	02	7.4
negative	25	92.6

HIV: human immunodeficiency virus.

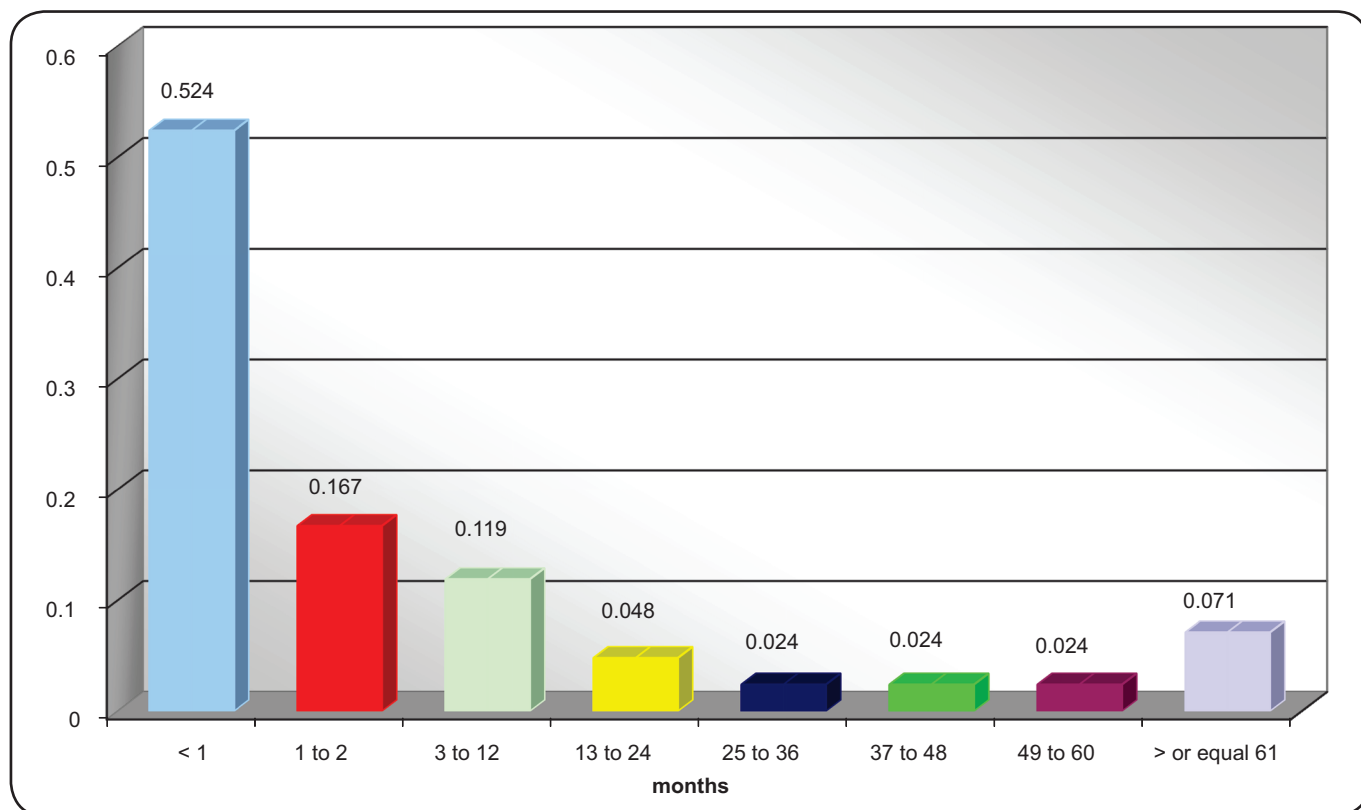


FIGURE 1 - Period between performing the tuberculin test and the development of tuberculosis among contacts (n = 42). Londrina, State of Paraná, Brazil, 2014).

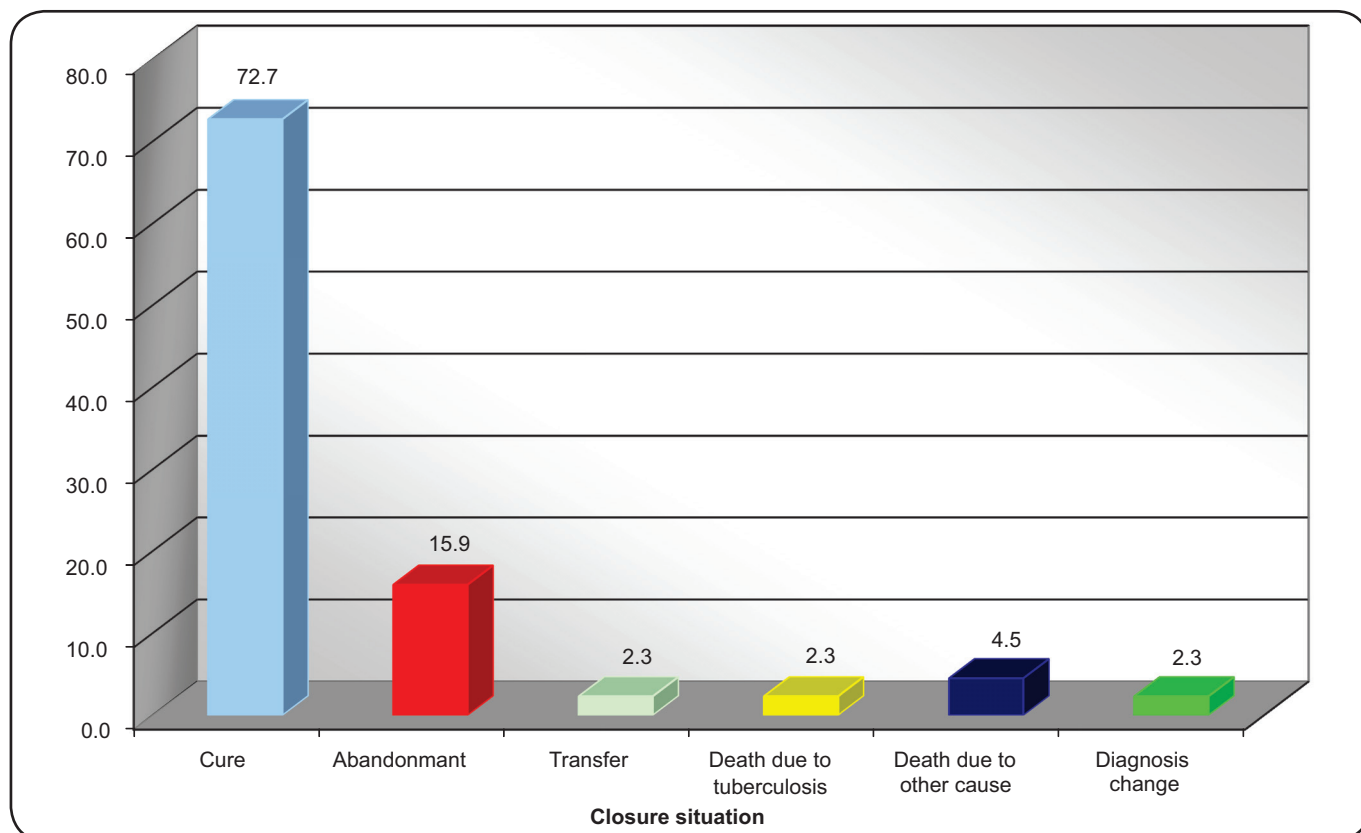


FIGURE 2 - Distribution of active tuberculosis cases among the contacts (n = 44) according to their closure situation. Londrina, State of Paraná, Brazil, 2014.

and case outcomes among contacts, identifying the need for research involving this group, which is of great epidemiological relevance for TB control.

A completed TST that has been performed in full – with its results having been read – allows for the identification of LTBI and the adoption of therapeutic measures to aid in avoiding the progression to active TB. During the study period, 2,425 TSTs were performed in the TB case contacts. It was noted that 17.9% did not complete the test. This shortfall may have reflected the patients' lack of knowledge about the importance of the TST and/or their personal non-adherence to the health professionals' recommendations. The need to return for a test result within 72 hours may be a limiting factor for TST completion. This situation could be partially resolved with the implementation of IGRAs, despite their high cost.

The prevalence of LTBI observed in this study was lower than that observed in systematic reviews conducted in low- (51.4%)⁽¹⁴⁾ and middle-income (51.5%)⁽¹⁵⁾ countries and was higher than that identified in high-income countries (28.1%)⁽¹⁵⁾.

It is believed that in areas with a high prevalence of TB infection, the positivity rate of the TST can range between 25% and 55% in the general population. Where there is a significant incidence of HIV infection, the probability of obtaining false-negative results increases⁽¹⁶⁾. A study conducted in Pakistan showed positive results for the TST in 49.9% of patient household contacts with positive sputum smears⁽¹⁷⁾.

The TST positivity rate was higher among men, with no statistically significant difference ($p = 0.055$). However, this finding assumes epidemiological importance because, as with the active TB cases, the LTBI prevalence should also be higher among men.

The average age among individual reactors to the TST was slightly higher (30.98 years/SD 20.33) than among non-reactors (29.24 years/SD 20.38), with a p value at the limit of statistical significance between the two groups ($p = 0.05$).

The TST positivity rate was similar for all age groups, with no statistically significant difference. However, we emphasize that the youngest age group, from 0-15 years old, had a positivity of 33%. Considering that the children and adolescents studied may have had few contact opportunities with TB outside their home environment and considering the need for close and prolonged contact for transmission to occur, it can be inferred that *Mtb* infection is occurring in this environment. The Brazilian Ministry of Health estimates that in the case of a sick child, the probable source of infection is the adult who lives with them⁽¹⁸⁾. Therefore, the groups at high risk for infection are the contacts of positive pulmonary TB cases and those living in poor socioeconomic conditions⁽⁴⁾.

LTBI treatment was prescribed for 50.6% of the reactors to the TST. However, until 2009, the Brazilian Ministry of Health prescribed LTBI treatment mainly for cases with TST results of $\geq 10\text{mm}$ and, in some situations, when the TST was smaller than this value⁽¹⁸⁾. After this period, the National Tuberculosis Control Program recommended that adult contacts with TST results of $\geq 5\text{mm}$ take the LTBI treatment. In the present study, LTBI treatment evaluation in accordance with the recommendations of each period was not the aim of the research.

The WHO has established guidelines recommending LTBI treatment in children under five years old living with relatives or in close contact with people with TB since they removed the diagnosis of active TB due to proper clinical evaluation⁽¹²⁾.

In this study, 228 children under five completed the TST, with 63 (27.6%) positive cases, from which 57 had test results of 10mm or more. However, only 15 (26.3%) underwent LTBI treatment because, at the time that the TST was performed, there was no recommendation for this procedure from the Brazilian Ministry of Health⁽¹⁸⁾. However, LTBI treatment for this age group became a subsequent priority⁽¹⁾. The dropout rate among the children who underwent treatment for LTBI was 60%. This finding reflected caregiver non-compliance, as they were directly responsible for the administration of the drug.

Considering only the 85 children 0-2 years old who underwent the TST, 20 cases had a result of 10mm or more. The Brazilian Ministry of Health considers this finding suggestive of infection, and it demonstrates the non-interference of the BCG vaccine⁽¹⁾. However, only seven of the children were under LTBI treatment. It was not possible in the other cases to identify the reason the treatment was missed.

The great challenge in the interpretation of the TST is identifying the cutoff point of the result and in which population the LTBI treatment should be recommended, considering that not all individuals develop TB at some point in life⁽¹⁹⁾.

The LTBI treatment was prescribed for 155 (43.5%) men and 201 (56.4%) women. The average age of individuals who had LTBI treatment prescribed to them was 32.5 years old (SD = 18.0), ranging from one to 79 years. This treatment is prescribed only in cases with a high risk of disease because age is one of the risk factors for hepatotoxicity by isoniazid, especially for those people aged 65 and over⁽¹⁸⁾. In this study, the LTBI treatment was prescribed for 18 (36.0%) cases of this age group, among the 50 who presented as reactors to the TST.

LTBI treatment with isoniazid reduces active TB disease risk from 90% to 60%, depending on the length and compliance with the treatment⁽¹⁸⁾.

The dropout rate of LTBI treatment was high among the study patients, with an average of 2.74 (SD = 1.59) months of treatment compliance until abandonment. The dropout rate was lower during the first month (31.4%), reaching 49.7% by the second month.

Among the 148 cases demonstrating non-compliance with the LTBI treatment, 19 (12.8%) reported a side effect. This finding suggests that the presence of side effects would not be the reason for treatment abandonment. One or more side effects have been identified, including digestive (14), joint (8), neurological (6) and cutaneous (6) effects.

The prevalence of TB among all contacts was 1.8%. Studies in countries with high TB incidence have shown that the prevalence can reach 5% or more of the contacts, particularly among family members⁽¹²⁾. In a meta-analysis of TB case contact research, the prevalence of active TB was 3.1% in low- and middle-income countries and 1.4% in high-income countries⁽¹⁵⁾.

The TB incidence found among contacts was 2.7 times higher in men than in women, higher than what occurred in Brazil in 2012, when the incidence rate was 2.1 times higher in men⁽²⁰⁾.

In the 0- to 15-year-old age group, six cases progressed to TB, five in the pulmonary type and one in the ganglionic type. It is noteworthy that none of these cases had undergone LTBI treatment before, reinforcing the need to pay special attention to this age group.

In general, approximately 3.5% to 5.5% of all household contacts and 9.6% of little children are diagnosed with TB at the time of their initial evaluation⁽¹²⁾. TB in children is a neglected problem in health agendas, especially considering that this age group is most impacted by high morbidity and mortality⁽²¹⁾.

In this study, the diagnosis of most TB cases occurred concomitantly or in the second month after the TST completion, confirming the need for greater contact surveillance. In the meta-analysis cited above, those individuals diagnosed with TB during the initial investigation or in the first three months after the index patient diagnosis were not considered contacts⁽¹⁵⁾.

Some contacts may be considered index cases when symptoms predate the initially notified TB case. However, there is no agreed upon definition of the acceptable time from onset of symptoms to diagnosis. Patients may delay seeking treatment, or the health system can delay investigation of suspected TB. It is important to identify these delays to take actions to improve TB control⁽²²⁾.

A study performed with TB cases identified that 30.1% of household contacts were considered symptomatic. The evaluation of these cases was performed using information collected by the index case and not from the contact's individual clinical assessment⁽²³⁾.

The investigation of contacts is important among people who are newly infected with *Mtb* because there is a higher risk for the development of the active disease within 1-2 years after infection acquisition⁽⁷⁾. In this study, that 81% of contacts with TB developed the disease within the first year following the initial investigation, increasing to 85.7% after a 24-month period. This finding reinforces the importance of maintaining contact surveillance, beyond the scope of the initial clinical and laboratory research.

The LTBI or TB treatments initiated early constitute effective actions toward TB control. A study that assessed the impact of LTBI treatment in an indigenous Brazilian population found that 13% of contacts became sick within 30 days after the diagnosis of the index case, 34.8% between 30 and 180 days and 52.2% after 180 days. These findings highlighted the necessity of this option of TB control when established early⁽²⁴⁾.

A study conducted in six Brazilian cities found a lower proportion of TB diagnoses being performed in primary health care settings, as they take longer to be accomplished. The data improve in the specialized services, where consultations and examinations are offered at the same place⁽²⁵⁾. This fact can be reflected in the TB case controls and contacts and is demonstrated by the non-attendance of the TST reading at the recommended time and the high LTBI treatment and TB dropout rates.

Sputum smear microscopy can detect 60% to 80% of pulmonary TB cases, which is important from an epidemiological⁽¹⁾ point of view. In this study, sputum smear positivity was slightly below that index.

Although the chest X-ray is an important means of TB diagnosis, pulmonary changes are not demonstrated in up to 15% of cases⁽⁷⁾. In this study, pulmonary changes were demonstrated in 90.9% of patients, corresponding to all cases with isolated or associated pulmonary forms of TB.

Not all of the TB cases reacted to the PPD. This finding may indicate cutaneous anergy related to some immunosuppressive condition; alternatively, some cases may have been within an immunological window.

Of all of the TB cases, none had been subjected to treatment with isoniazid, except for one case that had previously treated TB. This finding further strengthens the importance of LTBI treatment in case contacts.

The WHO stressed the importance of voluntary counseling related to the administration of HIV tests on current TB patients⁽²⁶⁾. Infection diagnosis often occurs during the TB treatment course, compounding the medical stress faced by the patient. It is estimated that offered HIV testing coverage reaches 70% in Brazil⁽¹⁾. However, this index was not achieved among the studied contacts who had a positivity prevalence of 15%⁽¹⁾. This result was higher than the one observed in this study (**Figure 2**).

In the TB cases among the study contacts, the evolution to healing was 72.7%; considering only cases with sputum smears or positive cultures, this percentage reached 75%. These case outcome percentages are higher than the index presented in 2012 in Brazil, in which 70.6% of bacilliferous pulmonary TB cases were cured. However, the WHO recommends the healing of at least 85% of bacilliferous pulmonary TB cases⁽²⁰⁾. The dropout rate among the TB cases was 15.9%, decreasing to 10.7% when considering the smear-positive cases, a percentage similar to that presented in the same report (10.5%).

This study examined all of the recorded cases of contacts who underwent the TST and their treatment or the evolution of TB. However, it was not possible to verify if the contact investigation covered all cases, as the data were collected from the TST registry book. It is possible that many contacts may not have sought care, which could imply poor health service coverage. It is necessary to note that the limitations of this study relate primarily to the nature of secondary data use. This limitation could have been minimized by seeking the direct participation of nurses from the study's reference center for research tasks and data collection. The nurses could assist with answering questions, identifying contacts and conducting relevant medical record searches. Their results could support the service management of TB control.

The results of this study show a high prevalence of LTBI among contacts and the need for better control of this infection to break the disease transmission chain. This need for improved control is especially important because the cases that evolved to TB were never subjected to LTBI treatment. Yet, many

individuals do not return for their TST reading, and many abandoned their LTBI and TB treatments. The health team must intensify the search and investigation of contacts recommended for LTBI treatment to improve TB-related indicators.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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