Rev Soc Bras Med Trop 49(4):456-464, July-August, 2016
doi:10.1590/0037-8682-0220-2016

Major Article

Prevalence and factors associated with latent tuberculosis infection in an indigenous population in the Brazilian Amazon

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Abstract

Introduction: Recent studies have shown a high incidence and prevalence of latent tuberculosis infection (LTBI) in indigenous populations around the World. We aimed to estimate the prevalence and annual risk of infection (ARI) as well as to identify factors associated with LTBI in an indigenous population from the Brazilian Amazon. **Methods**: We conducted a cross-sectional study in 2011. We performed tuberculin skin tests (TSTs), smears and cultures of sputum samples, and chest radiographs for individuals who reported cough for two or more weeks. Associations between LTBI (TST ≥5mm) and socio-demographic, clinical, and epidemiological characteristics were investigated using Poisson regression with robust variance. Prevalence ratio (PR) was used as the measure of association. **Results**: We examined 263 individuals. The prevalence of LTBI was 40.3%, and the ARI was 2.4%. Age ≥15 years [PR=5.5; 95% confidence interval (CI): 3.5-8.6], contact with tuberculosis (TB) patients (PR=3.8; 95% CI: 1.2–11.9), previous TB history (PR=1.4; 95% CI: 1.2-1.7), and presence of Bacillus Calmette-Guérin (BCG) scar (PR=1.9, 95% CI: 1.2-2.9) were associated with LTBI. **Conclusions**: Although some adults may have been infected years prior, the high prevalence of infection and its strong association with age ≥15 years, history of TB, and recent contact with TB patients suggest that the TB transmission risk is high in the study area.

Keywords: Epidemiology. Health services indigenous. *Mycobacterium tuberculosis*. Public health surveillance. South American Indians.

INTRODUCTION

In recent decades, the National Tuberculosis Control Program of Brazil has employed various interventions to control tuberculosis (TB), including detection of new cases, free distribution of drugs for early treatment of patients, chemoprophylaxis for infected persons, and widespread Bacille Calmette-Guérin (BCG) vaccine distribution. However, the disease remains an important public health problem in Brazil, particularly among populations considered vulnerable, such as homeless persons, prisoners, health professionals, and indigenous populations[1] [2].

Recent studies have shown that the incidence of TB among indigenous populations in various parts of the world is higher than that reported for non- indigenous populations in the same countries[3] [4] [5] [6]. In Brazil, the situation is even more critical, due to higher incidence rates, elevated concentrations of cases along international borders (with a significant proportion of cases involving children and adolescents), drug resistance, prevalence of latent infection with *Mycobacterium tuberculosis* (MTB) exceeding 40%, and reported patterns of recent and ongoing transmission in the investigated villages[7] [8] [9] [10] [11] [12] [13].

Studies conducted over the last decade in the State of Rondônia also illustrate the gravity of the situation in our study area[7] [8] [14] [15] [16]. The occurrence of TB in indigenous territories (IT) was recently documented in a study of the geographic distribution of TB cases reported in the Information System for Notifiable Diseases [*Sistema de Informação de Agravos de Notificação* (SINAN)][17]. The authors of that study showed that in many of Wari's indigenous territories, the incidence rates were surprisingly high, exceeding 240/100,000 inhabitants from 1997 to 2006.

According to Basta and Camacho[18], incidence rate is not the best indicator of the dynamic transmission trends of TB,

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Received 7 June 2016
Accepted 8 August 2016

particularly in small populations like indigenous populations. Young and Mirdad[19] found that using incidence rate to assess the levels of transmission of MTB might be limited by the fact that most individuals who are infected with MTB do not develop the disease, and those who become ill might have been infected for months or years. Therefore, the incidence rate depends on the case report system, which in many places might not reflect the true disease burden due to operational difficulties. Additionally, confirmation of TB diagnosis requires isolation of the bacillus, and this procedure is less accessible in some regions of Brazil, especially in areas with indigenous people[9] [11] [12] [14] [20]. Considering these limitations, some authors[19] [21] [22] have argued that the most appropriate indicator of TB transmission in a particular location is the prevalence of MTB-specific infection.

This study aimed to screen for active TB, to estimate the prevalence and annual risk of infection (ARI) of MTB, and to identify factors associated with latent tuberculosis infection (LTBI) among indigenous Wari' (Pakaanóva) populations from Rondônia (Brazilian Amazon region) in order to provide additional relevant data necessary to reassess control activities targeting indigenous peoples.

METHODS

Study population and area. The State of Rondônia is located in Northern Brazil and is part of the Amazon river basin. According to the latest national census (2010), 1,562,409 inhabitants live in Rondônia, of whom 13,076 (0.8%) declared themselves as indigenous, representing approximately 30 different ethnic groups that live in 20 indigenous territories (**Figure 1**).

In Brazil, there are approximately 600 indigenous territories, which are demarcated Indian reserves set up by the federal government (http://www.funai.gov.br/index.php/indios-no-brasil/terras-indigenas, accessed 16 may 2016). The majority of these territories are located in the Amazon and in remote areas, distant from urban centers. In general, there are natural resources (food and clean water) in these territories, but the population faces some difficulties when attempting to reach municipalities to access the health facilities.

The Wari' (Pakaanova) are a Txapakura-speaking indigenous society located in the municipalities of Guajará-Mirim and Nova Mamoré within Rondônia in the southwest Brazilian Amazonia (approximately 10-11° S, 65-66° W). At the time of fieldwork, there were 2,721 Wari' people who lived in a total of seven indigenous territories (*Igarapé Lage, Igarapé Ribeirão, Pacaás Novas, Rio Guaporé, Sagarana, Rio Negro, and Rio Negro Ocaia*) at the margins of the Mamoré and Pakaanova rivers and in lands covered by interfluvial tropical rainforest on the border with Bolivia. Different sub-groups of Wari' who maintain the same cultural habits and have strong family ties live in each indigenous territory (https://pib.socioambiental.org/pt/povo/wari, accessed 16 May 2016).

Traditionally, subsistence was based on hunting and agriculture, especially of maize. Nowadays, timber and Brazil nuts have become central to the Wari' economy. As with other indigenous groups who live in Rondônia, the Wari' society was strongly affected by massive migration of settlers to Amazonia in the 1960-1970s[7] [8]. Permanent contact between the Wari' and Brazilian national society took place in 1956 and was followed by several epidemics of infectious diseases, including malaria, flu, measles, and TB. Ever since, TB has become an important cause of morbidity and mortality in this population.

We selected one of the Wari´ territories (Igarapé Ribeirão), where TB incidence is six times higher than that reported in the non-indigenous populations and higher than that in other indigenous territories in Rondônia during the last decade[17].

Study design. A cross-sectional epidemiological study was conducted from January 31st to February 14th, 2011, in Igarapé Ribeirão (S 10º 17' 50.1"; W 65° 08' 18.4"), located in the municipality of Nova Mamoré.

In this indigenous territory, our team visited all houses of the heads of household who agreed to be interviewed. They were asked about cough lasting for two or more weeks, weight loss, night sweats, weakness, and other symptoms related to active TB occurring among household members during the time of fieldwork.

Active tuberculosis screening. Physical examinations were performed by three of the authors (JL, DPGR, and PCB), who were accompanied by an indigenous health agent who helped explain the research plan and acted as interpreter when needed, diminishing cultural and linguistic barriers between the researchers and the Wari' (Pakaanova).

The criteria for suspicion of TB were cough lasting for two or more weeks, fever and/or weight loss, and/or weakness[1] [22]. Adults and children under 10 years who were suspected of being infected with underwent sputum examinations. Whenever possible, two sputum samples were collected from the subjects who reported cough for two or more weeks: one at the time of the interview and another the next morning, before breakfast (**Figure 2**). In accordance with standard techniques, the samples were fixed and stained with Ziehl Neelsen stain for sputum smear microscopy and inoculated into Ogawa-Kudoh medium. These procedures were performed at the study site, after which the samples were sent to the National Institute of Amazon Research [*Instituto Nacional de Pesquisas da Amazônia* (INPA)] laboratory and incubated at 98.6°F for 60 days.

Chest radiographs were performed using the posterior-anterior view with portable X-ray equipment adapted to the difficult conditions of the village. Individuals were selected based on the presence of any symptoms suggestive of active TB, previous history of TB, or contact with sick infectious individuals. Abnormalities identified on the posterior-anterior images were further investigated using lateral views. Standardized reports were issued by an experienced pulmonologist in accordance with the recommendations proposed by Den Boon et al[23].

Latent tuberculosis screening. To estimate the prevalence of latent TB infection (LTBI) and the annual risk of TB infection, we administered tuberculin skin tests (TSTs) to all residents regardless of immunization history. We excluded pregnant women, children younger than 2 years, and those with medical conditions that could impair cellular immune response, such as cancer, acquired immunodeficiency syndrome (AIDS), and

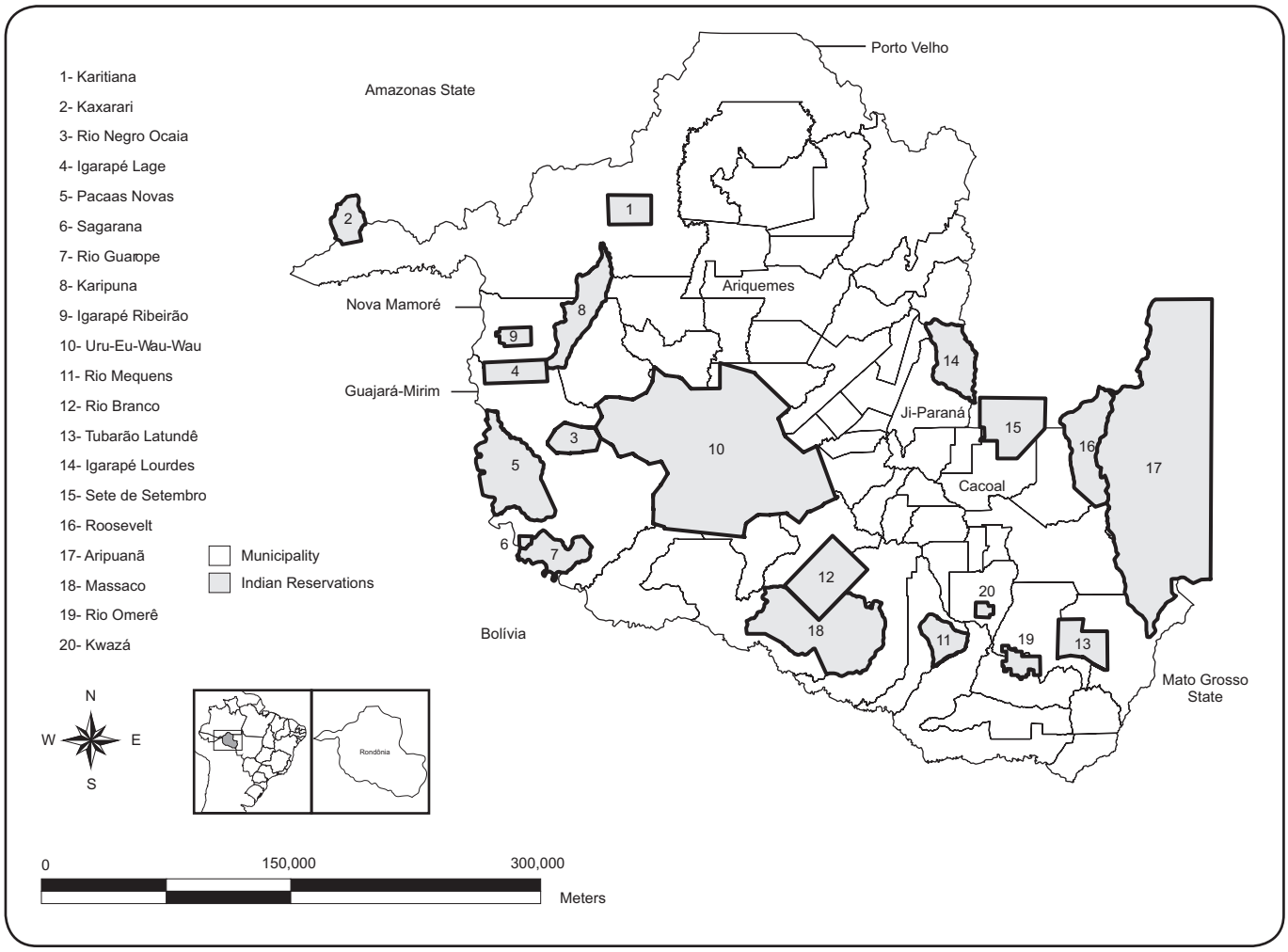

FIGURE 1. Map of the State of Rondônia, including municipalities and Indian Reservations (indigenous territories).

renal failure (**Figure 2**). These medical conditions were determined during the questionnaire interview. TSTs involved intradermal injection of 0.1mL [2 tuberculin units (TU)] of tuberculin Purified Protein Derivative (PPD) RT23 (Statens Serum Institute, Copenhagen, Denmark) in the middle third of the left forearm, according to the guidelines proposed by Arnadottir et al.[21] The evaluation of the TST reactions was performed within 72 hours after inoculation by three different readers who were trained to use a standardized method.

According to current guidelines of the Brazilian Ministry of Health for HIV-infected, immunodeficient, and other vulnerable groups, individuals who had TST reactions greater than or equal to 5mm were considered to have LTBI[1]. In order to assess the reliability and agreement between TST readers, we computed the intra-class correlation coefficient, which was greater than 0.90 for all three readers.

Individuals younger than 15 years who had TST reactions ≥ 5mm, without any signs and symptoms of TB or previous treatment for TB, were referred for treatment of LTBI (chemoprophylaxis)[1].

Variables and study instruments. Data on age, sex, education, occupation of the household members, family income (in multiples of the national minimum wage), and number of people per house were collected during home visits. Household contact with patients with active TB in the previous two years was also evaluated. Reports of previous history of TB treatment and BCG vaccination were confirmed by consulting the Information System for Notifiable Diseases database and vaccination cards, respectively.

Data collection instruments for this research were developed from the research group's experience[11] and after consultation and adaptation from (i) The First National Health and Nutrition Survey of Indigenous peoples in Brazil[24] and (ii) The Questionnaire for Evaluation of Primary Health Care Performance in TB Control in Brazil[25].

Statistical analysis. The following formula was used to estimate the Annual Risk Infection (ARI): $ARI = 1 - (1 - p)^{1/b}$, where p corresponds to the prevalence of infection (TST reactions ≥5mm) obtained from the tuberculin survey and b corresponds to the mean age of individuals who underwent TST[26].

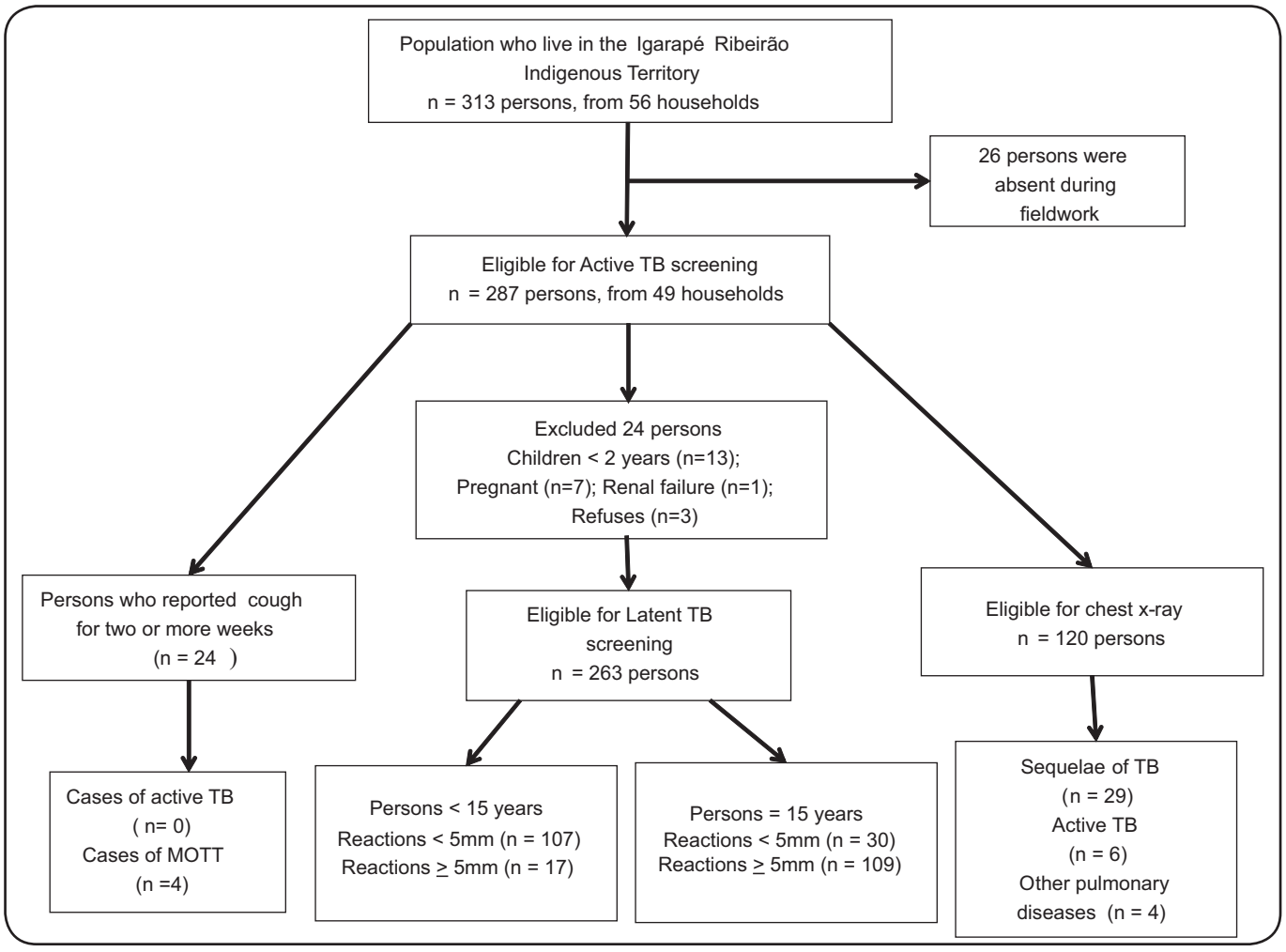

FIGURE 2. Flowchart of the screening stages for participants in Igarapé Ribeirão, Rondônia, Brazilian Amazon in 2011. **TB**: tuberculosis; **MOTT:** *Nontuberculous Mycobacteria*.

Data analyses were performed to associate TST results with the following independent variables: sex, age, income, education level of the head of household, number of persons per family, history of TB, contact with TB patients, presence of a BCG scar, and chest radiograph findings.

Prevalence ratio (PR) adjusted for covariates in a Poisson regression model with robust variance was used as the measure of association. After univariate analysis, variables that were statistically significant ($p<0.20$) were included in the multivariate model using the stepwise forward method. Variables that met the statistical significance threshold of 0.05 or were considered scientifically relevant were retained in the final model.

The analyses were performed with the statistical software R, version 2.13.1 and Statistical Package for Social Science, version 9.0 (IBM, Chicago, USA).

Ethical considerations. This study was performed in accordance with the Declaration of Helsinki. According to the Resolution of the Brazilian National Health Council, which regulates studies involving indigenous populations, the written informed consent was read and explained to volunteers and leaders of the community before beginning fieldwork. Due to the high illiteracy rate, oral consent was often obtained with the health agents as witnesses.

All data were collected and analyzed anonymously, and written informed consents were stored in boxes in the office of the research coordinator. The study protocol was approved by the National Commission for Ethics in Research of the National Health Council and the Research Ethics Committee of the National School of Public Health (#327/2008 and #176/07).

RESULTS

All indigenous individuals present in the village of Igarapé Ribeirão at the time of the team visit were evaluated, totaling 263 subjects in 49 households (approximately 85% of the total resident population). Twenty-six losses due to absence and 3 refusals were reported. In addition, 21 persons were excluded from latent TB screening, including 7 pregnant women, 13 children under two years of age, and one person with chronic renal failure who was undergoing hemodialysis

(**Figure 2**). There were no cases of diabetes, cancer, or human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in the study population.

The mean age was 22.2 years (standard deviation=18.5 years). There was a predominance of men (53.7%) and young people (58.5% were younger than 19 years) in this population. Residents who were absent during fieldwork had similar age and sex distributions (mean age of 19.8 years and 54% men). In most households, the main provider had no schooling, performed informal work, and earned less than one minimum wage equivalent monthly (**Table 1**). Houses were small and poorly constructed, often with many residents (data not shown). The use of firewood for cooking was a common practice among families.

During the home visits, 49 (18.6%) individuals had a history of TB treatment, and five (1.9%) subjects reported contact with patients infected with TB in the last two years. One 54-year-old woman was in treatment for TB, resulting in a prevalence of active disease of 380.2/100,000 inhabitants. In addition, 24 (9.1%) persons reported respiratory symptoms, and 34 sputum samples were collected for laboratory analysis. All cultures were negative for MTB. Atypical species of the genus *Mycobacterium* [(Nontuberculous Mycobacteria (MOTT)] were isolated from four subjects, but clinical investigation did not detect active tuberculosis or non-tuberculous mycobacterial disease (**Figure 2**). BCG scars were apparent in 95.0% of the subjects.

In total, 120 chest radiographs were performed. Of these, 39 demonstrated some abnormality. Twenty-nine (24.1%) were consistent with pulmonary sequelae due to TB, six (5%) were suggestive of active TB, and four showed other pulmonary pathologies. The main radiological findings were calcified nodules (n=17, 43.6%), fibrotic beams (n=11, 28.2%), and infiltration/consolidation (n=11, 28.2%). Notwithstanding, the association with TST response was not statistically significant (**Table 2**).

A total of 263 TSTs were performed, with reactions ranging from 0 to 29mm (median=4mm, standard deviation=7.6mm). Reactions greater than 10mm were more prevalent in adults over 20 years old. Of the 103 individuals without TST reactions (0mm), 71 (68.9%) were children under 10 years of age (**Figure 3**). The prevalence of MTB infection was 40.3%, and the annual risk of infection was 2.4% in the study population.

TABLE 1

Education level and occupation of the head of household and monthly household income in the previous 12 months in Igarapé Ribeirão, Rondônia, Brazilian Amazon in 2011.

	Number	Percentage
Education level of the head of household		
no schooling	20	40.8
primary education (1st to 4th grade) - incomplete	4	8.2
primary education (1st to 4tth grade) - complete	11	22.4
second phase of primary education (5th to 8th grade) -incomplete	9	18.4
second phase of primary education (5th to 8th grade) -complete	1	2.0
high school - incomplete	2	4.1
high school - complete	1	2.0
no information	1	2.0
Total	**49**	**100.0**
Occupation of the head of household		
indigenous health agent	1	2.0
leader/Cacique	2	4.1
informal work*	42	85.7
farming/fishing/poultry/livestock	1	2.0
unemployed	1	2.0
housewife	1	2.0
other	1	2.0
Total	**49**	**100.0**
Monthly household income		
no fixed income (casual work)	4	8.2
less than one MW equivalent**	18	36.7
1 to 3 MW	21	42.9
4 to 9 MW	1	2.0
unsure	5	10.2
Total	**49**	**100.0**

MW: minimum wage. *Working on farms and/or manual labor for daily payment. **Approximately US$250.00.

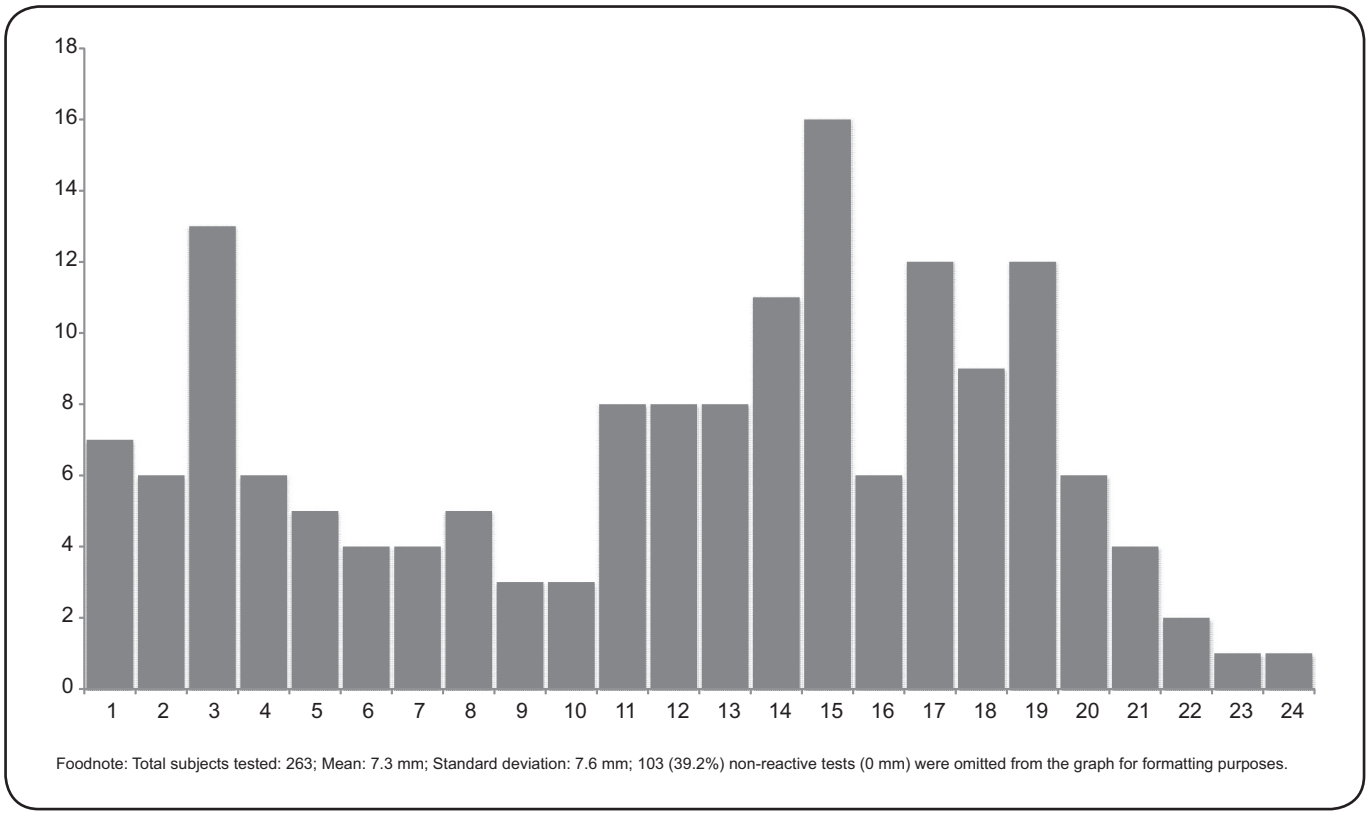

FIGURE 3. Distribution of tuberculin test reaction size (mm) in Igarapé Ribeirão, Rondônia, Brazilian Amazon in 2011. There were 263 total subjects tested. The mean (standard deviation) is 7.3 (7.6)mm. One hundred and three (39.2%) non-reactive tests (0mm) were omitted from the graph for formatting purposes.

Using Poisson regression, univariate analysis showed that the following variables were associated with TST responses ≥ 5mm: age, education level of head of household, number of persons per household, previous history of TB, and contact with a patient infected with TB in the previous 2 years. However, in the final model, only age, contact with a patient infected with, previous history of TB, and BCG scar remained associated with TST responses ≥ 5mm (**Table 2**).

No new cases of active TB were identified in the study population. However, eight children under 15 years old were referred for chemoprophylaxis. In addition, some other diseases were detected, including two cases of chronic obstructive pulmonary disease, one possible case of heart disease, and a lung tumor in one person. Individuals with abnormal radiographic findings, but no bacteriological confirmation, were referred to the local health clinic for follow-up and treatment.

DISCUSSION

As in other studies involving indigenous peoples[24] [27], the study population was predominantly young and poor with limited access to formal education, and the study participants lived in overcrowded and smoky houses, which are considered favorable for TB transmission[1] [6].

Similar high levels of ARI and prevalence of MTB infection had been reported among indigenous groups in the Brazilian Amazon region[17], in the Midwest region among the Xavante[9], in indigenous Wari' (Pakaanóva) populations from *Lage*[15], and in the Suruí people of *Sete de Setembro*[8] in Rondônia.

The ARI estimate in the present study was comparable to that seen for indigenous/native populations from Canada in the 1970´s, where the ARI was approximately 5%[28]. The ARI, which does not depend on the reliability of case reporting[19], indicated high levels of TB transmission in Rondônia's indigenous territories, consistent with the high frequency of reported previous TB treatment.

The associations between rates of TB infection and age, contact with a patient infected with TB in the last 2 years, and history of TB, were all statistically significant and of substantial magnitude, which is consistent with current knowledge about the transmission of TB and similar to previous studies[9] [11] [15] [16]. In contrast to those studies, which used odds ratios, the present study estimated prevalence ratios, which is considered a more accurate measure of association in settings with a prevalence of infection as high as often seen in indigenous populations[29].

On the other hand, in contrast to a case-control study that indicated that socioeconomic variables were associated with active TB in an indigenous population from the Midwest region of Brazil[30], in our study, socioeconomic variables, such as income, educational level, and number of persons per household, did not show a significant association to latent tuberculosis infection.

Consequently, we assumed that the factors associated with latent tuberculosis infection are different from those associated

TABLE 2

Crude and adjusted prevalence ratios for associations between selected variables and TST response ≥ 5mm using a Poisson regression model in Igarapé Ribeirão, Rondônia, Brazilian Amazon in 2011.

Variables	Number	Crude PR	95% CI	Adjusted PR	95% CI
Sex					
female	122	1.00		1.00	
male	141	1.19	(0.92-1.54)	1.14	(0.94-1.37)
Age (years)					
< 15	124	1.00		1.00	
≥ 15	139	5.72	(3.65-8.97)	5.49	(3.48-8.63)
Monthly household income					
≥1 MW: equivalent*	111	1.00			
<1 MW: equivalent	122	0.92	(0.71-1.21)	--	--
Education level of the head of household					
1 to 4 years	97	1.00			
no schooling	186	0.69	(0.54-0.89)	--	--
Number of household residents					
1 to 4	55	1.00			
5 to 9	202	0.68	(0.53-0.88)	--	--
>10	26	0.53	(0.29-0.95)	--	--
History of TB					
no	212	1.00		1.00	
yes	47	2.18	(1.79-2.65)	1.43	(1.19-1.71)
Contact with a patient infected with TB in the past 2 years					
no	254	1.00		1.00	
yes	5	1.67	(1.06-2.63)	3.80	(1.21-11.88)
BCG vaccination scar					
no	15	1.00		1.00	
yes	242	0.62	(0.44-0.87)	1.35	(0.89-2.03)
indeterminate	6	1.14	(0.71-1.82)	1.85	(1.18-2.88)
Chest radiograph report					
normal	81	1.00			
healed lesion/scar	29	0.85	(0.67-1.08)	--	--
active Lesion	6	0.98	(0.68-1.42)	--	--
other pathology	4	0.59	(0.22-1.57)	--	--

TST: tuberculin skin test**; PR:** prevalence ratio; **95% CI**: 95% confidence interval; **MW:** minimum wage; **TB**: tuberculosis; **BCG:** bacille Calmette-Guerin. *Approximately US$250.00

with active TB, not only because the study population seems to be homogeneous with regard to the variables related to socioeconomic level, but also because *Mycobacterium tuberculosis* seems to be spreading over indigenous territories in Brazilian Amazon, regardless of socioeconomic status.

A high prevalence of intestinal parasitosis is another known condition associated with LTBI[31]. Some authors have reported high levels of intestinal parasitosis in indigenous groups in Brazil[32], including in our study area[33]. Additionally, considering that 95% of individuals had a BCG scar, there was a substantial proportion (59.7%) of the population with TST reactions <5mm, of whom 39.2% had no reaction at all (TST equal 0mm). The majority of non-reactors were children under 10 years and individuals who had been vaccinated with BCG. Zembrzuski et al.[34] observed a 74.4% rate of reactions <5mm despite BCG vaccination coverage (>90%) among the Xavante of Mato Grosso in the Midwest region of Brazil. Similarly, Escobar et al.[15] observed reactions <5mm in 58.4% of the Wari' (Pakaanóva) people, whereas in the Suruí people, Basta et al.[8] found 27.1% with reactions <5mm, including individuals with recent BCG revaccination. Some TST reactions between 5 and 10mm might have been actually related to infection by atypical *Mycobacterium* and BCG rather than *M. tuberculosis*. However, a 10-mm threshold could misclassify true MTB infections, as indicated in the current Brazilian guidelines[1].

The reasons for non-reactivity among indigenous subjects with BCG scars remain uncertain. Longhi et al.[35] suggested that non-reactivity to TST might be associated with deficiencies in cellular immune response and genetic susceptibility. The authors argue that there is a predominance of T-helper 2 (Th2) cellular immune responses in indigenous people. This might favor progression to active TB with the manifestation of more severe forms of the disease, exuberant symptoms, and high bacterial loads. Additionally, many polymorphisms have been described in genes associated with the expression of cytokines involved in immune responses. In the case of native populations, these polymorphisms induce a predominantly Th2 immune response, affecting the course of the infection. The authors emphasized the need for studies that analyze the cellular activity of macrophages and lymphocytes in the immune response to MTB and extend current knowledge of polymorphisms related to illness susceptibility, in order to elucidate the involvement of immunological and genetic factors in this process.

Another possible explanation for the significant proportion of non-reactors to TST is that PPD RT23, which was used in the study, could have been improperly refrigerated, causing denaturation and consequent underestimation of the presence of TST reactions >5mm. Given the storage and handling procedures for tuberculin implemented in anticipation of the high risk in field conditions, we consider it highly unlikely that the sensitivity of the PPD RT23 was affected.

This study has some limitations. Misclassification of MTB infection is inherent to TST, which relies on measurements that are difficult to perform and are the basis for a threshold that cannot account for blurred limits of intermediate values (between 5mm and 10mm). As misclassification in this setting is presumably non-differential and the proportion of intermediate reactions was small, the measures of association may have been weakened by a small margin. The high prevalence of respiratory symptoms (9.1%) compared to the expected level of 1%[1] is another limitation. Additionally, reports obtained in interviews conducted with the aid of interpreters are more susceptible to bias. Communication barriers may have limited the detection of medical conditions, although health workers providing regular health care at the village were able to report severe chronic diseases. However, history of TB treatment was confirmed with data available from the National Information System for Notifiable Diseases.

In conclusions, our results illustrate the TB epidemic among indigenous people in the state of Rondônia. Inequalities, poverty, and socioeconomic disadvantages create a fertile ground for the spread of the disease, while promoting the transmission of MTB in the region. Considering results from recent studies conducted in Rondônia[7] [8] [14] [15] [16] [17] [20], the measures employed to control TB in indigenous territories during the last decade do not seem to have impacted TB transmission. The high risk of disease and transmission reported in Igarapé Ribeirão might be representative of other indigenous territories. Therefore, we conclude that within indigenous territories, there is need to apply more stringent control measures, including increased active searches for respiratory symptoms and use of chemoprophylaxis, which has effectively prevented TB in the indigenous Guarani-Kaiowá people from the Midwest region of Brazil[36], as well as further rigorously supervised treatment.

Besides that, public investments and inter-sectorial policies to mitigate social inequalities in Brazil are expected to impact control of TB and other endemic diseases related to poverty. In conclusion, we believe the analysis conducted in this manuscript can support policy formulation and improve control strategies for those vulnerable groups.

Conflicts of interest

The authors declare that there is no conflict of interest.

Acknowledgments

We acknowledge Dr. Julia Ignez Salem from the National Institute for Amazon Research and Cleoni Alves Mendes Lima for their support in the analysis of laboratory tests. We thank Nilda de Oliveira Barros, coordinator of the state program for tuberculosis control in Rondônia for technical support and Perceverando Ribeiro Machado Neto and Luiz Carlos Corrêa Alves for performing chest radiographs and radiological reports, respectively. We are grateful to the staff members of the Polo Base Guajará-Mirim from *Distrito Sanitário Especial Indígena* (DSEI) Porto Velho, who supported us in all the stages of the research, including the first contacts with the community, logistical support, and transportation through the last stage when researchers returned to the territories with the lab results and followed up with the research subjects.

Financial support

We received support from the Brazilian National Council for Technological Development [*Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq)], process number 402505/2008-5.

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