Prevalence and risk factors associated with latent tuberculosis infection in a Latin American region

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Tuberculosis (TB) represents a health problem in Colombia, its control is focused on the search for contacts and treatment of TB cases overestimating the role of latent tuberculosis infection (LTBI) as a reservoir of *M. tuberculosis*. The burden of LTBI in Colombia is unknown. With aimed of estimating the prevalence of LTBI, and knowing the associated risk factors. A cross-sectional study was conducted in four health care centers in Cali. The study population included individuals between 14-70 years who answered a survey evaluating their medical history, sociodemographic and lifestyles factors. The LTBI status was based on tuberculin skin test (TST) positivity using two thresholds: ≥10 mm (TST-10) and ≥15 mm (TST-15). The magnitude of associations was evaluated by logistic regression and a generalized linear model. 589 individuals were included with a TST positivity rate of 25.3% (TST-10) and 13.2% (TST-15). Logistic regression showed that age in a range of 40-69 years, male gender, employment status, and low alcohol consumption were risk factors for TST positivity, while living in the zone (north and suburb) together with secondary studies were protective factors. The generalized linear model showed that the previous predictors including a low body mass index had an effect on TST reaction size. The LTBI prevalence found in the population was moderate, it reflecting the continuous transmission of *M. tuberculosis*. Social factors seem to play a decisive role in the risk of LTBI. Being working men, over 40 years-old with lower level of education, low alcohol consumption and overweight a risk group to prioritized the prophylactic treatment as a strategy for the TB control in the city

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Abstract

Tuberculosis (TB) represents a health problem in Colombia, its control is focused on the search for contacts and treatment of TB cases overestimating the role of latent tuberculosis infection (LTBI) as a reservoir of *M. tuberculosis*. The burden of LTBI in Colombia is unknown. With aimed of estimating the prevalence of LTBI, and knowing the associated risk factors. A cross-sectional study was conducted in four health care centers in Cali. The study population included individuals between 14-70 years who answered a survey evaluating their medical history, sociodemographic and lifestyles factors. The LTBI status was based on tuberculin skin test (TST) positivity using two thresholds: ≥10 mm (TST-10) and ≥15 mm (TST-15). The magnitude of associations was evaluated by logistic regression and a generalized linear model. 589 individuals were included with a TST positivity rate of 25.3% (TST-10) and 13.2% (TST-15). Logistic regression showed that age in a range of 40-69 years, male gender, employment status, and low alcohol consumption were risk factors for TST positivity, while living in the zone (north and suburb) together with secondary studies were protective factors. The generalized linear model showed that the previous predictors including a low body mass index had an effect on TST reaction size. The LTBI prevalence found in the population was moderate, it reflecting the continuous transmission of *M. tuberculosis*. Social factors seem to play a decisive role in the risk of LTBI. Being working men, over 40 years-old with lower level of education, low alcohol consumption and overweight a risk group to prioritized the prophylactic treatment as a strategy for the TB control in the city.

Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. In the last 200 years TB has killed more than a billion people, being the main cause of death due a single infectious agent (*Yap et al., 2018*). Antibiotic resistance, lack or poor vaccination campaigns, globalization and poverty have complicated the control of this disease (*Dheda et al., 2014; Kargi et al., 2017*). In 2017, World Health Organization (WHO) reported 10 million of new TB cases and 1.3 million of TB deaths globally. Eighty percent of TB cases and 70% of deaths occurred in middle-income and low-income and countries (*WHO, 2018b*). Coevolution with humans has allowed this microorganism to develop mechanisms to persist within the host for decades (*Huynh, Joshi & Brown, 2011*). It is estimated that a quarter of the world's population (~1.7 billion or 23% of people) have latent tuberculosis infection (LTBI) (*Houben & Dodd, 2016*), a state of continuous stimulation of the immune system by *M. tuberculosis* without evidence of clinical symptoms of active disease (*Sharma, Mohanan & Sharma, 2012; Yap et al., 2018*). It is thought that 5-10% of these individuals will progress to active TB within the first two years, the risk increases in those patients with suppression of cellular immunity by HIV infection, use of glucocorticoids, blood or organ transplantation, treatment with tumor necrosis factor α inhibitors, malnutrition and diabetes (*Basera, Ncayiyana & Engel, 2017; Chen et al., 2015; Huynh, Joshi & Brown, 2011; Yap et al., 2018*).

The WHO regions South-East Asia, Western Pacific and Africa have a LTBI prevalence above 20%, while Eastern Mediterranean, Europe and The Americas have a LTBI prevalence lower than 17%. The Americas region has the lowest prevalence of LTBI with 11% approximately 108,000 million infected people (*Houben & Dodd, 2016*). However, in the Americas, TB persists as a major public health problem, about 282,000 new TB cases are reported every year and around 18,000 people die from this cause (*WHO, 2018b*). Countries showing the highest morbidity and mortality are Brazil, Peru, Mexico, Haiti and Colombia, representing 68% of the TB cases in the region (*PAHO, 2018*).

Colombia is the third most populated country in Latin America with a population of 49 million inhabitants. Despite the country's efforts to control TB, its incidence has increased in the last decade increasing from 19 cases per 100,000 inhabitants in 2007 to 33 cases per 100,000 in 2017 (*WHO, 2018a*). Local incidence rates highly differ between regions. Cali, is one of the cities with the highest incidence of tuberculosis with (41 cases per 100,000 inhabitants) (*Lesmes Duque & Reina, 2016*) which is higher than the national average (26.5 cases per 100,000 inhabitants) (*Sivigila, 2017*), and with an annual risk of tuberculosis infection (ARTI) of 1.3% (*De la Pava, Salguero & Alzate, 2002*), higher than the 0.1% risk reported for the world population (*Hassan & Diab, 2014*). Two contributing factors for this particular setting are: a) community transmission continues due to the delay in diagnosing cases of active TB, and b) reactivation of LTBI in vulnerable populations (household TB contacts, prisoners, health care workers, immunocompromised patients, children under 5 years-old and the elderly).

LTBI seems to be a reservoir from which active tuberculosis will emerge (*Abubakar et al., 2018*), representing a challenge for the aims of the End TB Strategy (90% reduction in the TB incidence by 2035) (*Houben & Dodd, 2016*). However, to detect LTBI in humans is difficult. Historically the LTBI detection has been made by assessing the T-cell response against *M.*

tuberculosis using the tuberculin skin test (TST) or the interferon-gamma release assays (IGRA). These tests are useful to identify people who could benefit with prophylaxis and leading the control of TB incidence and transmission (*Abubakar et al., 2018*). Nevertheless, both TST and IGRA has limitations in sensitivity and specificity, and there is a lack of a gold standard (*Stout et al., 2018*).

There are limited data on the epidemiology and risk of LTBI in the general population, mainly from developing countries. In our region, there is only one published study that describes the TST reactivity in the source population (*del Corral et al., 2009*). The aim of this study was to estimate the prevalence of latent tuberculosis infection and identify the risk factors associated with a positive result in the TST. This may allow to determine the potential size of the current reservoir of infection, and to provide information to implement control measures.

Material & Methods

Study design

This cross-sectional study was conducted from September 27, 2016 to December 1, 2017 in Cali, Colombia. Cali is the third most important city in the country with a population of 2,394,925 inhabitants and TB incidence of 41 cases per 100,000 inhabitants (*Lesmes Duque & Reina, 2016*). Individuals were recruited from 4 hospitals, three of them were primary health care facilities and a secondary-care hospital. The hospitals were located in 3 different areas (north, suburb and center).

Participants and data collection

1079 volunteers with ages ranging from 14 to 70 years-old completed a standardized questionnaire including demographic, socioeconomic and clinical data and behavioral habits. Considering an estimated of 42.7% LTBI (*del Corral et al., 2009*) with a 95% confidence level, 4% precision and 10% non-response rate, the sample size calculated was 647 individuals. Exclusion criteria for this study were history of chronic diseases (hypertension, diabetes and cancer), previous TB disease or chronic respiratory symptoms, heart disease, advanced liver disease, and immunosuppressive conditions (HIV/AIDS infection, transplant and lupus), pregnancy and lactation. 629 (58.3%) subjects were subjected to TST. 589 individuals were included for further study (**Fig. 1**). All individuals provided written informed consent. This study was approved by the ethics committee of the Universidad del Valle-CIREH (#008-015).

Overcrowding was defined considering households that live in homes with more than three to less than five people per room. The Bacillus Calmette-Guérin (BCG) vaccine status was evaluated by visual inspection (vaccination scar). Social level was defined as a composite index developed by analysis based on characteristics of the dwelling, source of drinking water, type of toilet facilities and features of the neighborhood. Social level index was categorized into tertiles of (1) extremely-low, (2) low and (3) medium for being a population with low resources. History of smoking was defined as tobacco use in the last 6 months. Alcohol consumption was stratified into 4 levels: high (consumption between 350-750 mL, ≥ 4 times/week), moderate (consumption between 250-750 mL, 2-3 times/week), low (consumption between 50-100 mL, once/week) and nothing. Physical activity was defined as Yes (exercise always or ≥ 3 times/week), No (never exercise or <2 times/week). The body-mass index (BMI) was classified as underweight (<18.5

Kg/m^2), normal weight (≥18.5 to 24.9 Kg/m^2), overweight (≥25 to 30 Kg/m^2) and obesity (≥30 Kg/m^2) according to the classification proposed by WHO (*OMS, 2003*).

Tuberculin skin test

Five units of tuberculin purified protein derivate (PPD) of *M. tuberculosis* Mammalian® (BB-NCIPD Ltd., Sofia, Bulgaria) in 0.1 mL was injected in the dorsal surface of the forearm. The induration was measured 48-72 hours after injection (*Rieder et al., 2011*).

Determination of latent infection by *M. tuberculosis*

Two different thresholds were considered for a positive TST result. An induration of 10 mm or more (TST-10) and a BCG-dependent induration that for the vaccinated participants was positive at 15 mm or large (TST-15) according to the current CDC guidelines (*ATS, 2000*). Given that vaccination actions in Colombia have their beginnings in the 60s, and the BCG regular application was intensified from the 70s as part of public health strategies against preventable diseases defined by the PAHO/WHO (*MinSalud*). For the primary analysis, if the BCG status was unknown, it was assumed that the individuals had been vaccinated (consistent with international recommendations) (*Abubakar et al., 2018*). All the participants with a positive TST result had a standard antero-posterior and lateral chest radiograph (CXRs). LTBI was defined as a positive TST result in the absence of TB respiratory symptoms and normal radiological findings. Active TB was suspected if the individuals had radiological abnormalities, chronic cough (more than 3 weeks), weight loss, night sweats, and fever. All cases with suspected TB were excluded and addressed to the tuberculosis program for TB treatment.

Statistical analysis

Kolmogorov-Smirnov's test revealed that quantitative data did not follow a normal distribution, so non-parametric statistics were used. Continuous data were compared using the Mann-Whitney U test or Kruskal-Wallis test. The Dunn's test was used to analyze variables with more than two categories, the significance values were adjusted by Bonferroni correction. To analyze the association between LTBI and the independent variables a Pearson's Chi-square test or Fisher's exact test with odds ratio (OR) and 95% confidence intervals were used.
Multivariate logistic regression and generalized linear regression models were used to determine the associations between the independent variables and TST positivity or TST induration, respectively.

In the logistic regression model, the Backward: Wald method was used, controlling each factor. The selection of predictors within the model was performed using the likelihood criteria (input $p \leq 0.05$, output $p \geq 0.10$). In the generalized linear model, a custom model with a normal distribution and an identity link function was used. The model was constructed using the main effects method, and parameter estimates to select the best model were calculated using the maximum likelihood method accompanied by a robust covariance estimator. The β coefficients reported were standardized. For all models, bootstrap analysis was performed with 5000 samples to compare the effect measures obtained in the original model with the bootstrapped model. The analyzes were performed using the statistical package SPSS 24.0 (SPSS Inc., Chicago, IL, United States).

Results

Socio-demographic and behavioral characteristics

A total of 589 participants were included in this study for a response rate of 54.6% (**Fig. 1**). As seen in **Table 1**, age was classified into 6 groups from 19 to 70 years-old. 55.2% individuals were in the range of 40-59 years and the average age was 43.8 ± 13.2 years. Women constituted 80% of the total population. The distribution of the individuals within the three social levels was homogeneous (~ 30%). 5.4% of participants lived in overcrowded. More than half of the individuals had completed high school studies, were unemployed, and lived in the northern zone. In relation to the lifestyle of this population, the majority were overweight or obese, did not perform regular physical activity, do not have a history of smoking or current cigarette consumption, and do not consume alcohol. Only 9% of the individuals had no visible BCG scar.

Prevalence of latent tuberculosis infection

The overall prevalence of latent tuberculosis using a threshold ≥ 10 mm (TST-10) was 25.3% (149/589), and with a threshold ≥ 15 mm (TST-15) was 13.2% (78/589). There was a gradual increase in the LTBI prevalence with age, reaching the highest prevalence in the 60-69 years category. The LTBI prevalence was higher in male (33.9%) for TST-10, and (17.8%) for TST-15 (**Table 1**). As shown in **Figure 2**, for both thresholds TST-10 and TST-15, the LTBI rate increased in male and female along with age growing, but the LTBI prevalence in male was significantly higher than in female for the 40-49 years category [OR: 3.72, 95% CI 1.38-10.03] TST-10 (**Table 2**) and [OR: 5.07, 95% CI 1.69-15.1] TST-15 (**Table S1**).

The LTBI prevalence determined by TST-10 and TST-15 was higher in individuals of social level 3 (medium), with primary education level, employees, residents of the central area, smokers, low dose alcohol users, who perform regular physical activity, and overweight and obese individuals. In contrast, no differences were observed in the LTBI prevalence with respect to overcrowding within households, and the BCG status (**Table 1**).

Demographic, socio-economic, behavioral factors and their association with TST induration

The average induration between individuals TST+ and TST- using the threshold ≥10 mm (16 mm vs 2.9 mm) or ≥15 mm (19.7 mm vs 4.2 mm) in both cases was significant (p= 0.000), and it was located above the cut-off point established for each case. The TST induration independent of threshold showed association with multiple variables including age, educational status, employment situation, residence zone, alcohol consumption and BMI (**Table 1**).

The average induration in individuals under 29 years-old showed significant differences compared to individuals over 30 years-old. Individuals with a level of primary education had a higher average in the TST induration compared to individuals with higher education (p<0.05). It was also observed that individuals residing in the center of city presented a higher average in TST induration compared to individuals residing in the northern zone (p= 0.000), and suburb (p=

0.040). Individuals with low alcohol consumption had a greater induration in TST compared to individuals with moderate consumption (*p*= 0.006). Regarding BMI, it was initially observed that individuals with underweight compared to overweight and obese individuals had a lower TST induration (*p*<0.05). However, with the adjustment of the significance values no statistical differences were observed.

The generalized linear model showed that age from 30 years old, residing in the northern or suburb zone, having higher education (secondary and post-secondary), and a lower BMI have a joint effect on the TST induration. The coefficient of determination found was 0.141 (14.1%). The bootstrapping results confirmed the estimates obtained with the generalized linear regression model. **Table 3** shows the standardized β coefficients and likelihood values.

Demographic, socio-economic, behavioral factors and their association with TST positivity (≥ 10 mm)

As shown in **Table 4**, when 14-19 years category was taken as reference group, it was found that after 30 years, the risk of LTBI increased significantly with ORs from 4.31 to 7.78. In this cross-sectional study, male presented a 0.70-fold higher risk of LTBI compared to female [OR= 1.70, 95% CI 1.10-2.64]. The education distribution showed that a higher education level decreases the risk of LTBI when compared with a primary or lower level [OR= 0.59, 95% CI 0.39-0.86 for secondary]. Being an employee significantly increased the LTBI risk [OR= 1.89, 95% CI 1.30-2.75]. When the risk of LTBI by zones was evaluated with reference to the high prevalence center zone (50%), It was observed that lived in the north or suburb zone decreased the LTBI risk [OR= 0.29, 95% CI 0.17-0.48] and [OR= 0.27, 95% CI 0.15-0.49], respectively. While low alcohol consumption significantly increased the risk of latent tuberculosis [OR = 2.28, 95% CI 1.13-4.59]. No association was observed between BCG scar and TST positivity.

In the multivariate logistic regression analysis (**Table 5**), it was found that the age from 30 years-old with ORs from 4.29 to 8.30, belong to the male gender [OR = 1.71, IC 95 1.04-2.84], be active at work [OR = 1.56, 95% CI 1.02-2.38] and low alcohol consumption [OR = 2.40, 95% CI 1.13-5.11] are risk factors for latent tuberculosis, while living in the north or suburb zone of the city reduced LTBI risk [OR = 0.32, 95% CI 0.18-0.55] and [OR = 0.28, 95% CI 0.15-0.52], respectively.
The model presented 12.8% sensitivity and 97.3% specificity with a Cox & Snell R-square coefficient of 0.098 (9.8%). The bootstrapping results confirmed the estimates obtained with the initial model, and corroborated the significance of the predictor (age 30-39 years) within the model.

Demographic, socio-economic, behavioral factors and their association with TST positivity (≥ 15 mm)

In the bivariate analysis for the threshold TST-15, only three variables showed an association with the TST positivity (**Table 4**). It was observed that a higher education level (secondary) [OR = 0.52, 95% CI 0.32-0.85] and living in the north [OR = 0.22, 95% CI 0.12-0.41] or suburb zone [OR = 0.19, 95% CI 0.09-0.38] reduced the risk of LTBI. In contrast, low alcohol consumption significantly increased the chance of latent tuberculosis [OR = 2.34, 95% CI 1.05-5.22]. In contrast, low alcohol consumption was a risk factor for LTBI [OR = 2.34, 95% CI 1.05-5.22].

In the multivariate analysis (**Table 6**), in agreement with the regression model obtained for TST-10, it was observed that belonging to the male gender [OR = 1.76, CI 95 0.98-3.17] and low alcohol consumption [OR = 2.33, 95% CI 0.98-5.56] increased the risk of LTBI, but showed no significance. While living in the north [OR = 0.25, 95% CI 0.14-0.47] or suburb zone [OR = 0.19, 95% CI 0.09-0.39] and had a secondary education level [OR = 0.49 95% CI 0.29-0.83] were associated with a significant reduction in LTBI risk. The model presented 5.1% sensitivity and 99.0% specificity with a Cox & Snell R-square coefficient of 0.069 (6.9%). The bootstrapping results corroborated the findings of the logistics model.

Discussion

The risk factors associated with the acquisition of LTBI in the general population are rarely reported, and such studies are scarce (*Chen et al., 2015; Martinez et al., 2013; Ncayiyana et al., 2016; Yap et al., 2018*). This is the first study that evaluates the prevalence of latent tuberculosis, and the associated factors in the general population in Colombia, using two thresholds to classify TST positivity. A cut-off point ≥10 mm was used as the main criterion to define the positivity to *M. tuberculosis* infection following CDC guidelines (*WHO, 2018c*), and LTBI prevalence of 25.3% lower compared to the reported prevalence was found in previous studies conducted in patients of a trauma unit (38%) (*Alzate et al., 1993*), and health care workers of the city (36.8%) (*Barbosa et al., 2015*). Compared to population-based studies, the LTBI prevalence observed in this study was lower than that reported in the source population of Medellín-Colombia (42.7%) (*del Corral et al., 2009*), and in urban informal settlements of Lima-Peru (52%) (*Martinez et al., 2013*) and Johannesburg-South Africa (34.3%) (*Ncayiyana et al., 2016*), but higher than the estimated prevalence for the Americas region (11%) (*Houben & Dodd, 2016*), and that of other countries with a high TB incidence such as China where a 20% prevalence in adults of a rural area (170), and Singapore where a prevalence of 12.7% was found for urban area residents (*Yap et al., 2018*) using IGRA. These observations suggest that the LTBI prevalence in urban settlements is high and variable. The differences found with respect to other studies can be partially explained by the type of population, this study included participants without chronic diseases underlying that may predispose to the infection, and most belonged to a social level 2 (low) and 3 (medium).

Considering a possible effect of BCG vaccination on the TST specificity, a higher threshold was used (≥15 mm) showing a prevalence of 13.2% that coincides with the LTBI prevalence found by Yap *et al* (*Yap et al., 2018*) in Singapore. The use of a threshold as TST-15 in some studies has shown a higher likelihood of detecting *M. tuberculosis* infection (*Wang et al., 2002*), and is a predictor of progression to TB comparable to IGRAs (*Abubakar et al., 2018*). In the present study, it is thought that the effect of vaccination was minimal because in Colombia this vaccine is administered in a single dose at birth and as it has been demonstrated its effect on the outcome of TST decreases after 15 years (*Wang et al., 2002*), and 82% of the participants were over 30 years-old. No association was found between the absence of BCG scar and TST positivity, this observation is in line with reported in other studies conducted in South Africa, a high TB burden setting where BCG is given at birth, and the TST is performed more than 10 years later (*Farhat et al., 2006; Mahomed et al., 2011*).

Using a TST-10 threshold, it was found that age, male gender, be employed, and low alcohol consumption increase the risk of LTBI, while living in the north or suburb zone decreases it. A large number of TB cases reported in Cali are located in the central zone included communes 9 and 11, an area that is characterized by harbor vulnerable population in conditions of overcrowding, malnutrition, and drug use, for which to living in zones distant from this point reduces the LTBI risk. On the other hand, our data indicate that after 30 years, the risk of LTBI increases significantly compared with the age group of 14-19 years. Agreeing with other studies where they report a high LTBI prevalence with advanced age (*Belo & Naidoo, 2017; Chen et al., 2015; Gao et al., 2015; Lee et al., 2014; Yap et al., 2018*). It is unknown whether the increase in age is the risk factor to acquire LTBI (*Lee et al., 2014*) or likely the increase in age from 30-39 years reflects a cumulative exposure to people with TB within the community allowing to develop a detectable immune response against *M. tuberculosis* infection (*Belo & Naidoo, 2017; do Prado et al., 2017; Gao et al., 2015*).

It was found that the LTBI prevalence in men was significantly higher compared to women especially between 40-49 years. A finding that coincides with the evidence by Chen *et al* (*Chen et al., 2015*) in rural population of China, and with community-based studies in South Africa (*Ncayiyana et al., 2016*) and Peru (*Martinez et al., 2013*), showing epidemiological differences based on sex for the LTBI prevalence. This is consistent with the ratio (2:1) between men and women observed in TB epidemiological studies (*Rhines, 2013*). Two possible explanations are proposed: 1) a large proportion of women remain at home, and are less likely to be exposed compared to men who have more active social responsibilities (*Gao et al., 2015; Kizza et al., 2015*), 2) there is a differential susceptibility to *M. tuberculosis* infection or predisposition to delayed-type hypersensitivity responsiveness dependent on gender (*Verhagen et al., 2012*). Being employed was associated with an increased LTBI risk. One possible explanation is that the transmission of *M. tuberculosis* is occurring in public transport, which is overcrowded and with little ventilation, the possibility of acquiring *M. tuberculosis* infection between people who often use this type of transport to travel long distances to their work and are repeatedly exposed (*Oni et al., 2012*).

Our results show an increase in the risk of TST positivity in light drinkers compared to non-drinkers. Numerous studies *in vivo* and *in vitro* have shown that alcohol intake dependent on the amount consumed is associated with an impaired immune system increasing susceptibility to respiratory infections such as pneumonia and tuberculosis, as well as the reactivation of latent disease (*Happel & Nelson, 2005; Rehm et al., 2009; Silva et al., 2018*). The relationship between low levels of alcohol consumption and TB risk remains unclear. Soh *et al* (*Soh et al., 2017*), in a cohort of middle-aged and elderly Chinese adults, found that low-dose intake of alcohol (monthly to weekly frequency) was associated with a lower risk of TB compared to non-drinkers, but their observation was limited only to non-smokers. In contrast, in current smokers the consumption of alcohol at low levels did not show any protective effect for the development of TB, but the intake of two or more drinks daily acted synergistically with the smoking to increase the TB risk. Narasimhan *et al* (210) in a study of household and community contacts in India, observed that male gender, alcohol consumption and cigarette consumption were risk factors for positivity to PPD in the bivariate analysis, while In the multivariate analysis, these 3 variables did not show an individual but joint effect on the increase in the risk of LTBI [OR = 3.93, 95% CI 1.3-11.9]. Similarly, Narasimhan *et al* (210) in a study of household and community contacts in India, observed that male gender, alcohol consumption and smoking were risk factors for TST positivity. These three variables in the multivariate analyses showed a joint effect on the LTBI risk [OR = 3.93, 95% CI 1.3-11.9].

These studies suggest that alcohol and smoking are strongly correlated. In the present study, a low proportion of individuals was smoking (11.5%), so the influence of this factor on the findings is ruled out. The small number of participants with moderate and high alcohol consumption could difficult the comparisons between the categories, hiding any possible association with TST positivity. Given the low rate of TST positivity, the lack of reactivity due to immunosuppressive effects of alcohol is not ruled out.

When the TST-15 threshold was used, similar results to those observed with TST-10 were found. The male gender and low alcohol consumption increased the LTBI risk. In contrast, residing in the north or suburb zones and having secondary education level decreased risk within the model. The association between a higher level of education and a reduction in the LTBI risk can be explained by an improvement in the quality of life of individuals, and awareness of health risks dependent on lifestyle habits, thus reducing their exposure to recognized TB risk factors such as poverty, overcrowding, smoking, and malnutrition (*Lonnroth et al., 2009*). These findings coincide with the findings reported in other population-based studies in China (*Chen et al., 2015*), Singapore (*Yap et al., 2018*) and South Africa (*Ncayiyana et al., 2016*).
The average induration using both thresholds TST-10 and TST-15 was above the cut-off points, allowing us to rule out any possible effects of BCG vaccination or cross-reactivity with non-tuberculous mycobacteria (*Borroto et al., 2011*). This suggests that the threshold ≥10 mm in the city is a useful tool to confirm *M. tuberculosis* infection in agreement with the recommendation of CDC (*ATS, 2000*), while the threshold ≥ 15 mm can be used as an increased risk indicator for the development of TB in asymptomatic individuals (*Ministry of Health, 2010*). In support of this recommendation, Shero *et al* (*Shero et al., 2014*) in the population of Ethiopia (TB incidence: 164/100.000 inhabitants) using a TST-10 showed that the average TST induration in community controls was 7.9 mm less than the observed in our study, while in household contacts and patients with TB was 13.6 mm and 18.1 mm, respectively.

The TST induration in the generalized linear model was influenced by the increase in age from 40 years, a higher level of education, reside in the north or suburb zone, low alcohol consumption and underweight. Coinciding with the variables previously associated with TST positivity in the logistic models for TST-10 and TST-15, except for the association with the BMI < 18.5 Kg/m^2. The results found show a negative association between an underweight and the TST induration, explaining the low average TST induration evidenced in these individuals compared with normal weight, overweight or obesity individuals. These results contrast with previous studies where it has been observed that a lower BMI is associated with an increase in the TB incidence (*Hanrahan et al., 2010*), and is an important risk factor for the development of TB (*Lonnroth et al., 2010; Patra et al., 2014*). Meanwhile, overweight and obesity are protective factors (*Hanrahan et al., 2010; Kim et al., 2018; Lin et al., 2018*). The relationship between BMI and LTBI risk is not well described (*Chen et al., 2015; Saag et al., 2018*). Several population-based studies in rural areas of China have shown that overweight (*Chen et al., 2015*) (170), and obesity (187) significantly increases the LTBI risk. These studies have also evidenced a non-significant negative association between a lower BMI and LTBI. A behavior similar to that observed our study, where crude ORs of 0.18 for TST-10 and 0.35 for TST-15 were found.

There were some limitations in this study. At first, its cross-sectional nature did not allow establishing temporality or causality between LTBI and the associated factors. Second, the strict exclusion criteria employed prevented the evaluation of effect of known TB risk factors (e.g. close contact with TB patients, diabetes, malnutrition, and HIV status) on TST positivity. So, the aim to get a representative sample of the population may not have been fully achieved. However, a better immune response could provide an interpretable result in the TST. Third, individuals from other zones of the city (East and South) were not included, which implies selection bias, given that people living in the eastern area have a high TB risk. Fourth, since there is no gold standard for the LTBI diagnosis, the estimation of its prevalence could be affected by TST performance. Fifth, there is a possibility of misclassification of drinkers by a self-report bias and the ability to remember. Sixth, as in any observational study, there could be a residual confounding effect of unknown or unmeasured factors in the associations observed. Despite these limitations, this study has an adequate sample size and statistical power, and is the first population-based study of LTBI prevalence and associated risk factors in Colombia, so it provides valuable information in a country with an intermediate TB burden, where BCG is administered at birth.

Conclusions

The LTBI prevalence in our population without associated comorbidities and measured using two thresholds TST (≥10 mm and ≥15 mm) was moderate (25.3% and 13.2%, respectively), reflecting a significant TB burden and the ongoing transmission of *M. tuberculosis* in the community. Several risk factors traditionally associated with TB (age, educational status, gender, employment situation, BMI and alcohol consumption) showed association with the positivity and induration of TST in the three multivariate models. Unexpectedly, a lower BMI (<18.5 kg/m^2) showed a negative and significant association with the TST induration, and the LTBI prevalence in underweight individuals was low. Contrasting with studies that have shown an increase in the TB risk among underweight individuals. Additional studies are required to validate our findings and identify other risk factors associated with LTBI. Given that BCG vaccination does not confer protection against TB in adults, and most people who develop it in Colombia are vaccinated. The community identification of high-risk groups and the prophylactic LTBI treatment to prevent progression to TB could be a cost-effectiveness strategy of great impact in the city of Cali.

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Table 1(on next page)

Prevalence of LTBI using two TST thresholds (≥10 mm and ≥15 mm) according to socio-demographic and behavioral characteristics of the population, and its association with TST measurement (*n*= 589).

Characteristics	*n* (%)	TST-10 %	TST-15 %	TST (millimeters)		
				Mean	SD	*P*
Age (years)						
14-19	31 (5.3)	6.5	6.5	3.42	4.20	
20-29	74 (12.6)	13.5	5.4	4.15	4.76	
30-39	96 (16.3)	22.9	11.5	5.32	5.63	0.000
40-49	145 (24.6)	31.0	13.8	6.95	6.73	
50-59	180 (30.6)	26.7	16.7	6.87	7.01	
60-69	63 (10.7)	34.9	17.5	8.05	7.82	
Gender						
Male	118 (20.0)	33.9	17.8	7.03	6.81	0.267
Female	471 (80.0)	23.1	12.1	6.04	6.49	
Social level						
1	212 (36.0)	22.6	9.4	5.83	5.59	
2	198 (33.6)	23.2	15.2	5.97	6.63	0.251
3	179 (30.4)	30.7	15.6	7.03	7.46	
Overcrowding						
> 3 person/room	32 (5.4)	25.0	15.6	6.06	6.04	0.766
≤ 3 person/room	557 (94.6)	25.3	13.1	6.25	6.60	
Educational status						
Primary or less	215 (36.5)	32.1	18.6	7.58	7.32	0.001
Secondary	321 (54.5)	21.5	10.6	5.52	6.07	
Post-secondary	53 (9.0)	20.8	7.5	5.15	5.25	
Employment situation						
Employee	259 (44.0)	32.0	16.2	7.08	7.21	0.034
Unemployed	330 (56.0)	20.0	10.9	5.58	5.93	
Zone						
North	334 (56.7)	22.2	10.8	5.63	6.13	
Suburb	183 (31.1)	21.3	9.3	5.71	5.37	0.001
Central	72 (12.2)	50	34.7	10.44	9.26	
Physical activity						
No	412 (69.9)	23.1	12.6	5.95	6.27	0.414
Yes	177 (30.1)	30.5	22.2	6.92	7.17	
Ever smoked						
Yes	89 (15.1)	29.2	14.6	6.90	6.95	0.311
No	500 (84.9)	24.6	13.0	6.12	6.50	
Current smoking						
Yes	68 (11.5)	29.4	16.2	7.00	7.37	0.641
No	521 (88.5)	24.8	12.9	6.14	6.45	
Alcohol consumption						
High	6 (1.0)	16.7	0.0	5.33	4.23	
Moderate	35 (5.9)	17.1	8.6	4.46	5.77	
Low	35 (5.9)	42.8	25.7	6.46	8.47	0.012
Nothing	513 (87.1)	24.8	12.9	6.16	6.44	
BMI (kg/m²)						

<18.5	20 (3.4)	5.0	5.0	3.35	3.63	
≥18.5 a 24.9	248 (42.1)	22.6	12.9	5.81	6.57	0.025
≥25 a 30	229 (38.9)	28.4	14.0	6.70	6.53	
≥30	92 (15.6)	29.3	14.1	6.89	6.94	
BCG Scar						
Yes	536 (91.0)	25.4	15.1	6.25	6.52	0.670
No	53 (9.0)	24.5	13.1	6.13	7.03	

BCG, Bacillus Calmette-Guérin; BMI, body mass index; TST, Tuberculin Skin Test; CI, confidence interval; OR, odds ratio; SD, Standard deviation.

Table 2(on next page)

LTBI rate differences among male and female by age groups with a threshold TST-10

Age (years)	Male			Female			OR (95% CI)	*p*
		TST-positive			TST-positive			
	N	*n*	%	N	*n*	%		
14-19	12	0	0	19	2	10.5	------	*0.510
20-29	11	0	0	63	10	15.9	------	0.155
30-39	17	6	35.3	79	16	20.3	2.15 (0.69-6.69)	0.181
40-49	19	11	57.9	126	34	27.0	3.72 (1.38-10.03)	0.007
50-59	44	16	36.4	136	32	23.5	1.86 (0.89-3.86)	0.094
60-69	15	7	46.7	48	15	31.3	1.93 (0.59-6.23)	0.274

*p value was calculated from Fisher's exact test

Table 3(on next page)

Generalized linear model for the predictors of TST induration

Variables	*β	SD β	95% CI	*p*	B β	B SD β	B 95% CI	B *p*
Intercept	9.057	1.603	5.91; 12.2	0.000	9.057	1.638	5.96; 12.3	0.000
Education (Secondary)	-1.414	0.653	-2.70; -0.13	0.030	-1.414	0.675	-2.73; -0.07	0.042
Education (Post-secondary)	-1.890	0.882	-3.62; -0.16	0.032	-1.890	0.915	-3.66; -0.15	0.040
BMI (<18.5 kg/m²)	-2.295	0.779	-3.82; -0.77	0.003	-2.295	0.873	-4.09; -0.63	0.005
Zone (North)	-3.923	1.155	-6.18; -1.66	0.001	-3.923	1.179	-6.34; -1.73	0.002
Zone (Suburb)	-4.154	1.175	-6.46; -1.85	0.000	-4.154	1.201	-6.59; -1.91	0.001
Alcohol consumption (Low)	3.126	1.408	0.37; 5.88	0.026	3.126	1.484	0.42; 6.17	0.044
Age (40-49 years)	2.583	1.003	0.62; 4.55	0.010	2.583	1.045	0.44; 4.57	0.015
Age (50-59 years)	1.734	0.999	-0.22; 3.69	0.082	1.734	1.027	0.09; -0.35	0.097
Age (60-69 years)	3.366	1.271	0.87; 5.86	0.008	3.366	1.300	0.85; 5.99	0.008

* Standardized Coefficients, SD: Standard deviation; B: Bootstrapped for 5000 samples

Table 4(on next page)

Socio-demographic and behavioral characteristics of the population and its association with TST positivity using two thresholds (≥10 mm, *n*=149) and (≥15 mm, *n*=78).

1

Characteristics	TST-10				TST-15		
	N	*n* (%)	OR (95% CI)	*p*	*n* (%)	OR (95%CI)	*p*
Age (years)							
14-19	31	2 (1.3)	Reference		2 (2.6)	Reference	
20-29	74	10 (6.7)	2.26 (0.46-11.0)	0.300	4 (5.1)	0.83 (0.14-4.77)	1.00
30-39	96	22 (14.8)	4.31 (0.95-19.5)	0.042	11 (14.1)	1.87 (0.39-8.97)	0.424
40-49	145	45 (30.2)	6.52 (1.49-28.5)	0.005	20 (25.6)	2.32 (0.51-10.5)	0.262
50-59	180	48 (30.2)	5.27 (1.21-22.9)	0.014	30 (38.5)	2.90 (0.65-12.8)	0.143
60-69	63	22 (14.8)	7.78 (1.69-35.7)	0.003	11 (14.1)	3.06 (0.63-14.7)	0.146
Gender							
Male	118	40 (26.8)	1.70 (1.10-2.64)	0.016	21 (26.9)	1.57 (0.91-2.72)	0.103
Female	471	109 (73.2)	Reference		57 (73.1)	Reference	
Social level							
1	212	48 (32.2)	0.66 (0.42-1.04)	0.071	20 (25.6)	0.56 (0.30-1.03)	0.062
2	198	46 (30.9)	0.68 (0.43-1.08)	0.101	30 (38.5)	0.96 (0.55-1.68)	0.895
3	179	55 (36.9)	Reference		28 (35.9)	Reference	
Overcrowding							
> 3 person/room	32	8 (5.4)	0.98 (0.43-2.24)	0.968	5 (6.4)	1.23 (0.45-3.29)	0.683
≤ 3 person/room	557	141 (94.6)	Reference		73 (93.6)	Reference	
Educational status							
Post-secondary	53	11 (7.4)	0.55 (0.27-1.14)	0.106	4 (5.1)	0.35 (0.12-1.05)	0.052
Secondary	321	69 (46.3)	0.59 (0.39-0.86)	0.006	34 (43.6)	0.52 (0.32-0.85)	0.008
Primary or less	215	69 (46.3)	Reference		40 (51.3)	Reference	
Employment situation							
Employee	259	83 (55.7)	1.89 (1.30-2.75)	0.001	42 (53.8)	1.58 (0.98-2.55)	0.059
Unemployed	330	66 (44.3)	Reference		36 (46.2)	Reference	
Zone							
North	334	74 (49.7)	0.29 (0.17-0.48)	0.000	36 (46.2)	0.22 (0.12-0.41)	0.000
Suburb	183	39 (26.2)	0.27 (0.15-0.49)	0.000	17 (21.8)	0.19 (0.09-0.38)	0.000
Central	72	36 (24.2)	Reference		25 (32.1)	Reference	
Physical activity							
No	412	95 (63.8)	0.68 (0.46-1.01)	0.057	52 (66.7)	0.83 (0.50-1.39)	0.497
Yes	177	541 (36.2)	Reference		26 (33.3)	Reference	
Ever smoked							
Yes	89	26 (17.4)	1.27 (0.77-2.09)	0.356	13 (16.7)	1.14 (0.60-2.18)	0.680
No	500	123 (82.6)	Reference		65 (83.3)	Reference	
Current smoking							
Yes	68	20 (13.4)	1.27 (0.72-2.21)	0.407	11 (14.1)	1.31 (0.65-2.62)	0.448
No	521	129 (86.6)	Reference		67 (85.9)	Reference	
Alcohol consumption							
High	6	1 (0.7)	0.61 (0.07-5.25)	0.648	0 (0.0)	-----	0.347
Moderate	36	6 (4.0)	0.61 (0.25-1.49)	0.273	3 (3.8)	0.62 (018-2.06)	0.428

Low	35	15 (10.1)	2.28 (1.13-4.59)	0.018	9 (11.5)	2.34 (1.05-5.22)	0.032
No	513	127 (85.2)	Reference		66 (84.6)	Reference	
BMI (kg/m^2)							
<18.5	20	1 (0.7)	0.18 (0.02-1.38)	0.065	1 (1.3)	0.35 (0.04-2.74)	0.301
≥18.5 a 24.9	248	56 (37.6)	Reference		32 (41.0)	Reference	
≥25 a 30	229	65 (43.6)	1.35 (0.89-2.05)	0.146	32 (41.0)	1.09 (0.65-1.86)	0.732
≥30	92	27 (18.1)	1.42 (0.83-2.44)	0.197	13 (16.7)	1.11 (0.55-2.22)	0.767
BCG Scar							
No	53	13 (8.7)	0.96 (0.49-1.84)	0.893	8 (10.3)	1.18(0.53-2.61)	0.677
Yes	536	136 (91.3)	Reference		70 (89.7)	Reference	

Table 5(on next page)

Risk factors associated with TST-10 positivity using a logistic regression

Variables	β	Wald	OR*	95% CI	*p*	B *p*
Intercept	-2.007	6.670			0.010	0.007
Gender (Male)	0.540	4.420	1.71	1.04-2.84	0.036	0.027
Employment situation (Employee)	0.445	4.272	1.56	1.02-2.38	0.039	0.040
Zone (North)	-1.153	16.185	0.32	0.18-0.55	0.000	0.000
Zone (Suburb)	-1.267	16.547	0.28	0.15-0.52	0.000	0.000
Alcohol consumption (Low)	0.874	5.139	2.40	1.13-5.11	0.023	0.032
Age (30-39 years)	1.455	3.414	4.29	0.92-20.0	0.065	0.034
Age (40-49 years)	1.986	6.719	7.28	1.62-32.7	0.010	0.008
Age (50-59 years)	1.514	3.929	4.55	1.02-20.3	0.047	0.025
Age (60-69 years)	2.116	7.160	8.30	1.76-39.1	0.007	0.004

*From a multivariate logistic regression model with age, gender, social level, overcrowding, educational status, employment situation, zone, exercise, ever smoking, current smoking, alcohol consumption, BMI and BCG scar.

B: Bootstrapped for 5000 samples

Table 6(on next page)

Risk factors associated with TST-15 positivity using a logistic regression

Variables	β	Wald	OR*	95% CI	*p*	B *p*
Intercept	-0.421	2.011			0.156	0.168
Gender (Male)	0.564	3.534	1.76	0.98-3.17	0.060	0.085
Education (Secondary)	-0.711	7.066	0.49	0.29-0.83	0.008	0.008
Zone (North)	-1.381	19.241	0.25	0.14-0.47	0.000	0.000
Zone (Suburb)	-1.653	20.31	0.19	0.09-0.39	0.000	0.000
Alcohol consumption (Low)	0.845	3.619	2.33	0.98-5.56	0.057	0.080

*From a multivariate logistic regression model with age, gender, social level, overcrowding, educational status, employment situation, zone, exercise, ever smoking, current smoking, alcohol consumption, BMI and BCG scar.

B: Bootstrapped for 5000 samples

Figure 1

Flow chart for the uptake, assessment and clinical diagnosis of infections in the population.

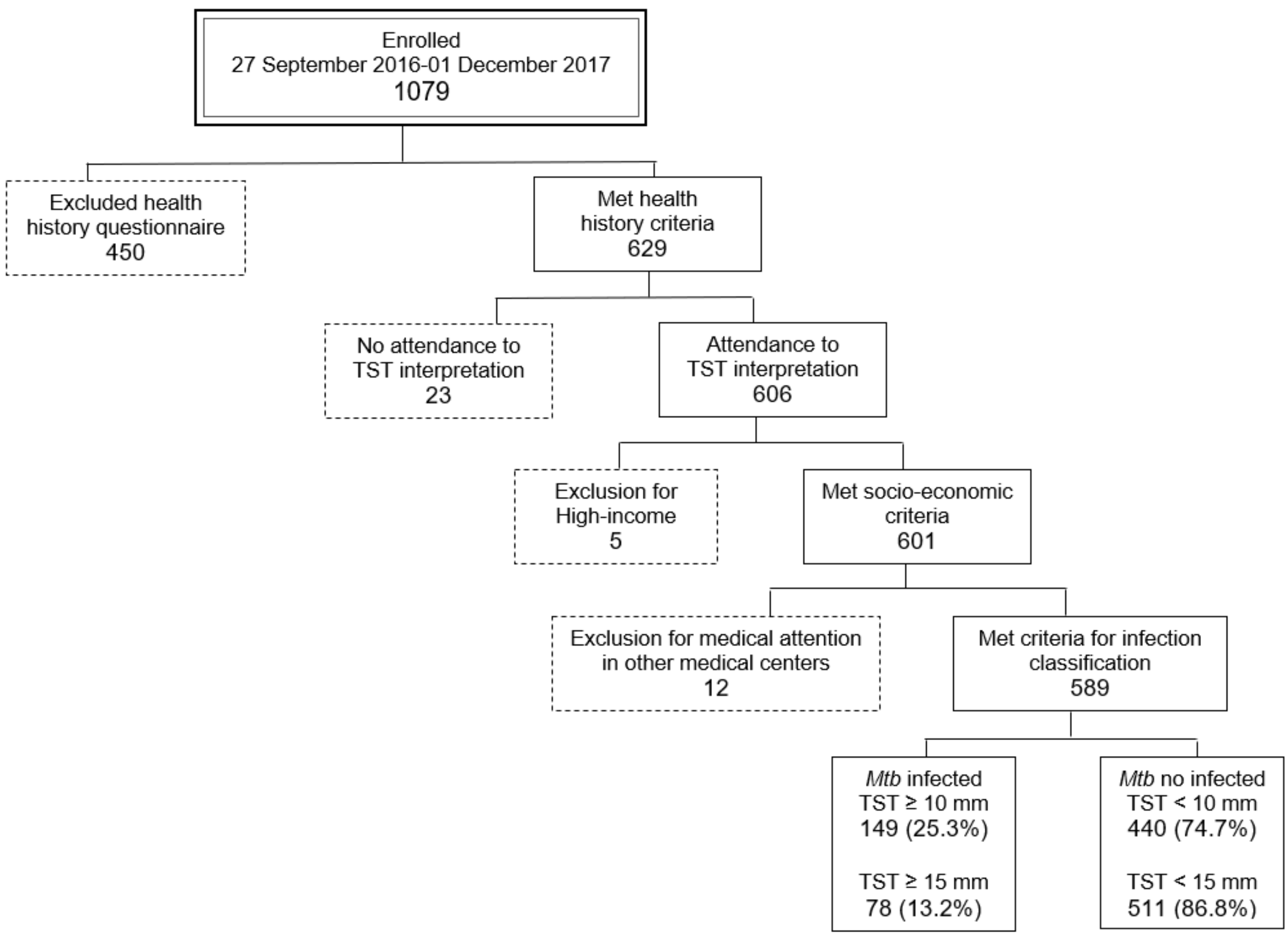

Figure 2

Age-specific trend of LTBI using two thresholds (≥10 mm and ≥15 mm) in the population stratified by sex.