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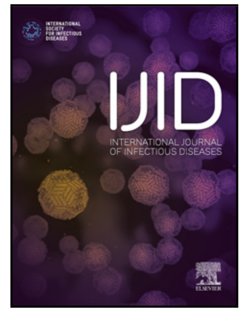

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Determinants of losses in the latent tuberculosis cascade of care in Brazil: a retrospective cohort study

Running Head: Losses in the LTBI cascade in Brazil.

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Highlights

- Cascade of LTBI care was evaluated in 1,264 potential contacts of TB patients
- Major losses occur at initial stages of the LTBI cascade of care
- Older patients are at higher risk of not completing the LTBI cascade of care
- All TB contacts who developed active TB were ≤14years-old

Abstract

Background: The present study evaluated factors associated with losses in the latent tuberculosis infection (LTBI) cascade of care in contacts of tuberculosis (TB) patients, in a referral center from a highly endemic region in Brazil.

Methods: Contacts of 1,672 TB patients were retrospectively studied between 2009 and 2014. Data on TB screening by clinical investigation, radiographic examination and tuberculin skin test (TST) were extracted from medical records. Losses in the cascade of care and TB incidence within 2-year follow-up were calculated.

Results: From a total of 1,180 TB contacts initially identified, only 495 were examined (58% loss), and 20 were diagnosed with active TB at this stage. Furthermore, 435 persons returned for TST result interpretation and 351 (~81%) were TST positive. Among those with positive TST, 249 (73%) were treated with isoniazid for 6 months whereas 51 abandoned therapy early. Three individuals who did not receive LTBI treatment, one with incomplete treatment and another who completed treatment developed active TB**.** A logistic regression analysis revealed that increases in age were associated with losses in the LTBI cascade independent of other clinical and epidemiological characteristics.

Conclusions: Major losses occur at initial stages and older patients are at higher risk of not completing the LTBI cascade of care.

Keywords: tuberculosis, latent TB infection, LTBI cascade, treatment for latent TB.

Introduction

The majority of new cases of Tuberculosis (TB) occur in 30 countries with high disease burden such as Brazil, India, China, and South Africa (WHO, 2019). Furthermore, approximately 1.5 million deaths attributable to TB globally were reported in 2018 (WHO, 2019). Factors that may underlie the slow improvement of TB control include inaccurate diagnosis and loss to follow up of patients or household contacts undergoing anti-TB treatment (Zelner et al., 2018). In Brazil, despite significant investment from the government, the reported reduction in TB incidence (-1.34% per year) is considered insufficient to meet targets established by the World Health Organization (WHO) to reduce the incidence of TB by 90% by 2035 and eliminate TB (less than 1 incident case per 1,000,000 per year) by 2050 (Houben and Dodd, 2016). To achieve the WHO goals, it is critical to develop and implement effective health care policies that improve screening of TB and adherence to treatment of individuals diagnosed with latent TB infection (LTBI) (WHO, 2019).

LTBI is defined by the presence of a specific immune response against *Mycobacterium tuberculosis* (Mtb) in individuals who do not exhibit clinical and radiographic signs of active disease and who had negative microbiologic screening for TB (acid-fast bacilli [AFB] in sputum and Mtb cultures) (Parrish and Carroll, 2011). Approximately one fourth of the world's population is thought to be infected with Mtb, with most individuals developing active disease within the first two years after initial infection (Mendonca et al., 2016). It is imperative to target LTBI treatment in individuals at higher risk of developing active TB, including people with HIV and contacts of patients with pulmonary TB (Secretaria de Vigilância em Saúde, 2011).

Recent studies in Brazil and other high burden countries have described struggles in diagnosis and treatment of LTBI, highlighting the urgent need for new strategies to effectively treat this population (Martinez et al., 2017, Mendonca et al., 2015, Salame et al., 2017). The present study aimed to determine factors associated with losses in the LTBI cascade of care of TB contacts, who were followed up at a reference center for treatment of TB in the city of Salvador, Northeast of Brazil. A secondary aim was to compare the TB incidence between individuals who completed treatment for LTBI and those who did not.

Methods

Clinical study design

The present study was a retrospective cohort of contacts of microbiologically confirmed pulmonary TB patients (positive sputum cultures using solid media), who were followed at the outpatient clinic of the Instituto Brasileiro para Investigação da Tuberculose (IBIT) between 2009 and 2014, with data being extracted during first quarter of 2018. IBIT is a reference center for the investigation and treatment of LTBI and active TB. At IBIT, TB screening is performed in contacts of every patient diagnosed with pulmonary TB. This referral center uses the WHO definition of TB contact, which is "a person living in the same household or who is in frequent contact (> 20 hours per week) with the source case". As part of the routine investigation, all contacts identified during the TB case investigation are invited for a screening visit. During the first visit, the contacts are evaluated by nurse practitioners who perform tuberculin skin testing (TST), chest radiographic examination and bacteriological evaluation of sputum in those with cough in accordance with the Brazilian guidelines (Secretaria de Vigilância em Saúde, 2011). Patients with respiratory symptoms or with abnormal chest radiograph (e.g. infiltration or enlarged nodes) and/or blood laboratory results are then referred to consultation with pulmonologists at IBIT who further excludes TB by microbiological and clinical examination. Of note, for the present study, a positive TST was defined as ≥5mm induration (Secretaria de Vigilância em Saúde, 2011). All health care workers in this facility are routinely trained to identify contacts based on Brazilian guideline definitions from 2000 to 2016 (Secretaria de Vigilância em Saúde, 2011). During the study period, 1,672 patients with active TB were identified and contacts search was performed by the health care workers from IBIT.

For this study, the data were manually extracted from the electronic medical record system used at IBIT (MV System Software, Brazil). Inclusion criteria was the following: to be a close contact of a pulmonary TB patient with documentation of at least one medical appointment at IBIT. The criterium used for diagnosis of LTBI was TST induration ≥ 5mm in the absence of clinical and radiographic signs of the disease. Exclusion criteria included individuals with active TB and/or who had previous TB treatment.

Among the TB contacts who were diagnosed with LTBI, treatment was initiated depending on physician and patient decision to treat. The LTBI treatment was performed with isoniazid, at a dose of 5mg/kg, a maximum of 300mg and at least 180 doses. Individuals undergoing LTBI treatment received pills to be taken at home every 30 days during monthly visits at IBIT and received orientation from the nursing practitioners until the end of treatment. During those visits, the number of doses taken were documented. The main outcomes evaluated were incidence of active TB and treatment abandonment rate, which were extracted from the medical records. Moreover, additional data were extracted from Brazil's Information System for Notifiable Diseases (SINAN) dataset (Ministério da Saúde, 2019) to identify individuals with LTBI who developed active TB in the following two years. The SINAN Notification Information System is filled with notification and investigation of cases of diseases that are included in the national list of compulsory notifiable conditions, that includes TB. Patients need to be registered in the notification system in order to have access to treatment for LTBI through the Brazilian public health system. This registration instrument is sent to the services responsible for the information and / or epidemiological surveillance of the municipal secretariats, which upload the contact in an electronic platform that is accessible to registered health services. The completion of the form and the sending to the epidemiology department are activities exclusively carried out by the health care units, specifically the TB control program.

Data analysis

Categorical variables were presented as absolute values or relative frequencies and compared using the Fisher's exact test (between 2 groups) or Pearson's chi-square test (more than 2 groups), when appropriate. Quantitative variables were expressed as median and interquartile range and compared using the Mann-Whitney *U* test (between 2 groups) or the Kruskal Wallis test. An error type $\alpha = 0.05$ was adopted for all statistical analyzes. A binary multivariable logistic regression analysis was performed using clinical and epidemiological variables with univariate p-value ≤ 0.2, to test independent associations with losses in the LTBI cascade of care . Data analysis was performed using Statistical Package for Social Sciences (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk).

Ethics approval and consent to participate

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the Maternity Research Ethics Committee Climério de Oliveira (protocol number: 65225917.1.0000.5543, approval number: 1.960.723). The anonymity of the study subjects was preserved, and all data accessed by the research team were de-identified. The data were extracted from electronic forms stored in the data repository from IBIT. Due to the retrospective nature of the study, the Ethics Committee exempted collection of informed consent forms.

Results

A total of 1,264 TB contacts were initially identified for screening. Of these, 84 (6.6%) could not be confirmed as TB contacts, resulting in 1,180 individuals. In addition, 685 (58.1%) did not present for consultation and therefore were not followed up. Thus, only 495 (41.9%) confirmed contacts could be examined yielding a loss of 58.1% in the LTBI cascade of care (Figure 1). During the screening visit, clinical examination, radiographic evaluation with chest x-rays and microbiological investigation with sputum smears and cultures were performed. This initial screen identified active TB in 20 individuals (4% of the contacts examined).

TST was performed in the remaining 475 individuals without active TB (Figure 1). Of those, 40 individuals did not return for TST interpretation and were not followed up (Table 1 and Figure 1). Search in the SINAN online system revealed that 1 individual who were lost to follow up developed active TB and was evaluated at another health care facility (Figure 1). Persons who did not return were on average older, more frequently referred smoking and had more frequently abnormal chest radiographs than those who returned for TST interpretation (Table 1). On the converse, individuals who returned for TST reading (n=435; Table 1) were more frequently household contacts (P=0.03) and presented with the BCG vaccine scar (P=0.004). Other characteristics were not different between individuals who returned for TST interpretation vs. those who were lost to follow up at this stage (Table 1). Of note, the group of individuals who had TST results registered in the medical records were mostly children. Approximately 74% (n=351) of the TB contacts evaluated were screened positive for LTBI. The individuals who were TST positive in our cohort were similar to those who tested negative with regard to several characteristics including age, sex, household contact status, BCG vaccination scar and radiographic examination (Supplementary Table 1).

Treatment of LTBI was prescribed in 300 (85.5%) individuals, with treatment abandonment being reported in 51 (17%) (Figure 1). The frequency of adverse events was 2%; only one patient required treatment discontinuation because of elevated serum levels of transaminases. LTBI individuals were subsequently separated into groups according to LTBI treatment completion.

Patients who completed full course of isoniazid were included in the group of complete treatment for LTBI (n=249), whereas individuals who were lost to follow up during treatment (n=51) and those who were not treated (n=51) were included in the group of incomplete treatment (Supplementary Table 2).

Individuals who did not receive any treatment were more commonly older, female, had history of smoking (e.g. an individual who reported smoking habit at least once in his/her life) and had more often comorbidities such as hypertension and type-2 diabetes (Supplementary Table 2). Study participants who received complete or incomplete treatment were more frequently household contacts of TB patients than those who were not treated (Supplementary Table 2). Nonspecific abnormal findings in chest radiographs (e.g. infiltrations and/or enlarged nodes) were more common in those who did not receive therapy (Supplementary Table 2).

A total of 5 individuals developed active TB during follow up, of which 3 did not have treatment for LTBI prescribed (representing 5.9% of this group), whereas 1 abandoned treatment and 1 completed isoniazid therapy ($p=0.003$, Supplementary Table 2). Whilst 145 children under 5 years-old were recruited, only 95 (65.5%) received treatment for LTBI. The LTBI individuals who developed active TB were all children ≤ 14 years old.

Given the results presented above, we tried to depict in more details the characteristics of the study population that were associated with losses in the LTBI cascade of care. The majority of our population was under 18 years old (n=387; Supplementary Table 3 and Figure 2A). The adults were mostly female (n=38, 79.2%, $p=0.001$), with a high frequency of hypertension, smoking and abnormal chest radiographs ($p=<0.01$). Approximately 98 % of the children and adolescents had BCG vaccination (Supplementary Table 3 and Figure 2B). Moreover, children and adolescents received more frequently full LTBI treatment (n=239; $p=<0.01$, Supplementary Table 3 and Figure

2B). Moreover, we compared the groups of study participants who were losses at any stage in the LTBI cascade of care with those who fully completed the cascade steps. Individuals who were losses in the cascade were on average older and more frequently female, smokers, and more commonly exhibited abnormal chest radiographs than those who completed the cascade (Table 2). On the converse, the individuals who completed the cascade were more frequently household contacts, had proportionally more TST results recorded and more commonly BCG vaccinated (Table 2). Finally, we performed a multivariable binary logistic regression analysis to identify the characteristics that were independently associated with losses in the LTBI cascade of care. Among the variables that were statistically different between the study groups in univariate analysis, only age remained significantly associated with losses (Figure 3). Indeed, increases of 1 year of age resulted in augmented odds of lost in the LTBI cascade of care (Figure 3).

Discussion

Understanding losses in the cascade of care for LTBI and clinical outcomes of TB contacts is key for TB control and elimination strategies. Identification of the determinants that lead to losses may expand detection of LTBI cases in high TB-burden settings and reduce incident cases (Alsdurf et al., 2016, Morrison et al., 2008). In this study, we found an incidence of active TB in contacts of 2.2/100,000 inhabitants (95% CI:1.5/100,000 – 3.2/100,000), highlighting the importance of systematic screening in of such population. Herein, we found significant losses in the LTBI cascade in a cohort of TB contacts from a primary care center that is a reference for TB care in the state of Bahia, Brazil. While increasing age was a factor independently associated with losses, all incident TB cases occurred in younger individuals (all ≤ 14years old). These findings highlight that the LTBI care cascade is ineffective even in a center renowned for high quality of TB care. Additional studies that evaluate losses in the LTBI cascade of care in other centers from high-burden cities in Brazil are warranted to determine the extent of this problem.

Our results identified that losses in the LTBI care cascade occurred primarily during the initial screening, implementation and completion of treatment for LTBI. These results are similar to those reported by other studies in Brazil (Salame et al., 2017), Uganda (Armstrong-Hough et al., 2017) and Vietnam (Fox et al., 2013). Moreover, a systematic review performed in middle to low-income countries from the Americas, European, African and Asian continents also confirmed this critical breakdown in LTBI screening and treatment (Morrison et al., 2008). Notably, in our study, 4 of the 5 individuals who developed active TB were initially seen by the health care service but failed to be adequately followed up.

While our study may appear to have a low number of screened TB contacts (41.9% of all the potential contacts identified), it is higher than the reported average for the State of Bahia (31.6%) (Secretaria de Vigilância em Saúde, 2017). Of note, a recent study carried out in São José do Rio Preto, São Paulo (Southeast Brazil) found that active case detection is not systematically performed despite the existence of a program specifically dedicated to providing assistance to TB contacts (Wysocki et al., 2016). Another study reported that only 43% of the contacts were screened with TST, very similar to our findings (Salame et al., 2017).

Most of the study subjects in our cohort were children and adolescents. Interestingly, only 88 (47%) of the 189 countries reporting TB cases described data on the number of contacts under 5 years of age who started treatment for LTBI (WHO, 2019). The present study recruited 145 children under the age of 5 years old (30.5% of the entire study population), although successfully implemented LTBI treatment was observed in only 94 individuals (65%). It is possible that the inability to effectively treat LTBI has led to the fact that all the TB incident cases occurred in persons ≤14 years old. In Brazil, one of the difficulties that may impair treatment of LTBI in children is a lack of trained clinical staff in primary and secondary health units (Mendonca et al., 2015). This is unlikely to explain the screening and treatment implementation within the cohort at IBIT, given the high percentage of patients who initiated and completed LTBI treatment. A study in Malawi identified that LTBI treatment in children was hampered by a lack of materials to perform TST and equipment to perform diagnostic x-ray examination, although shortage of trained personnel to interpret TST results and high workload of health care professionals appeared to be the most important barriers (Hector et al., 2017). These observations strongly support the idea that optimization of TB screening and implementation of treatment for LTBI in children is crucial, particularly in those who are household contacts of those with active TB.

Although the primary approach to diagnose LTBI traditionally consists of TST, interferon gamma release assays (IGRA) have emerged as an alternative to address the high rate of failure to return for TST interpretation (Albanese et al., 2015, Salame et al., 2017), which compromises LTBI diagnosis. In contrast, our study found that only 40 individuals (8% of those tested with TST) failed to return for interpretation. These differences made us hypothesize that there may be specific actions taken by healthcare providers to increase return for TST interpretation, including explanation of the importance of TB screening particularly in non-household contacts.

A recent study demonstrated that contacts of pulmonary TB patients not receiving antitubercular treatment are at increased risk of withdrawing from the isoniazid treatment of LTBI (OR: 7.30; 95% CI: 1.00-53.3) in the city of Rio de Janeiro, Brazil (Mendonca et al., 2016). Sociodemographic factors should be considered as they may also impact LTBI treatment adherence. Currently supported treatment of LTBI in Brazil is the 6 months isoniazid regimen, while an alternative three-month approach with once weekly directly observed isoniazid-rifapentine is highly efficient (Sterling et al., 2011). Shorter treatment duration could increase adherence, offering an alternative to that implemented by the Brazilian government. Furthermore, a report indicates that 6-month treatment of LTBI with isoniazid may be inferior (International Union Against Tuberculosis

Committee on Prophylaxis, 1982) and is contraindicated by the American Thoracic Society (ATS) / Centers of Disease Control and Prevention (CDC) for children.

Whilst our study has several strengths including a well characterized cohort with thorough follow up data and including a younger population, there are limitations that warrant discussion. There are limitations similar to other retrospective studies based on analysis of secondary data, such as loss to follow up information. Regardless, the results presented here illuminate a serious situation in the follow up of a population with high risk of developing active TB disease, even in a TB treatment referral center with a high cure rate of active TB cases.

Conclusions

This study demonstrates significant losses in the LTBI cascade in an important TB referral center from large city in Brazil. Most of the losses occurred in the first step of the cascade which was the initial screening. Older age was the most important factor associated with the losses, although incident active TB cases preferably occurred in children and adolescents.

Contributions: Conceived and designed the study: NCNA, CMSC, EMN, BBA. Performed the experiments: MBA, JMC-A, MSR, PSS-M, GMM, IMBM, ICPES, LLA, CMA, LAS. Analyzed the data: NCNA, MBA, JMC-A, EMN, BBA. Wrote the paper: NCNA, MBA, KMC-A, BBA

Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Potential conflicts of interest: The authors declare that they have no conflicts of interest.

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Figure Legends

Figure 1. Study flowchart
The flow chart depicts the retrospective cohort investigation performed at IBIT. Grey dashed lines represent exclusions from the study. Red squares indicate TB occurrence. TST, tuberculin skin test. Tx, treatment. See Methods for details in study design.

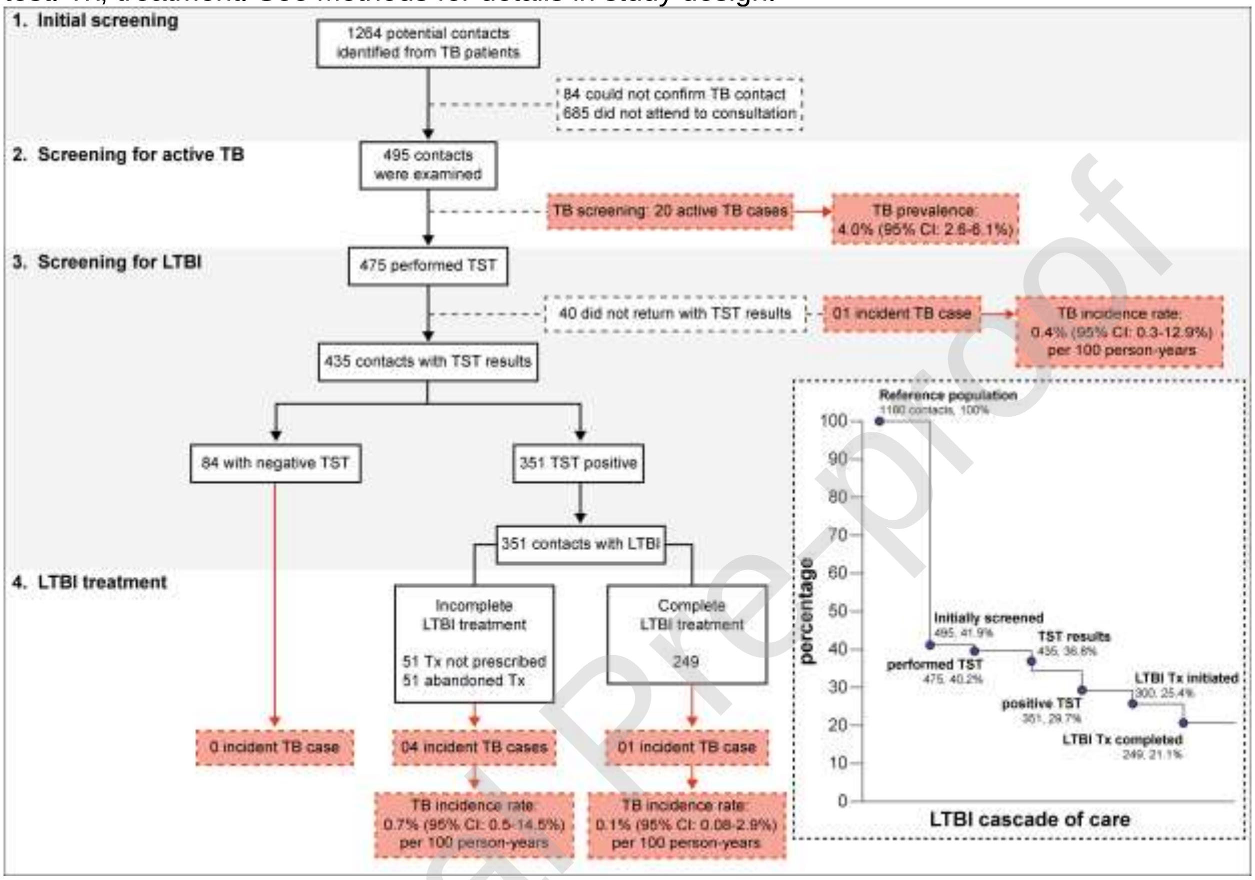

Figure 2. Characteristics of study participants
(A) Density Plot visualizes age distribution of contacts. **(B)** Heatmap based on age distribution of the contacts shows the characteristics of sex, BCG vaccine, TST, LTBI treatment, and incidence TB of the participants.

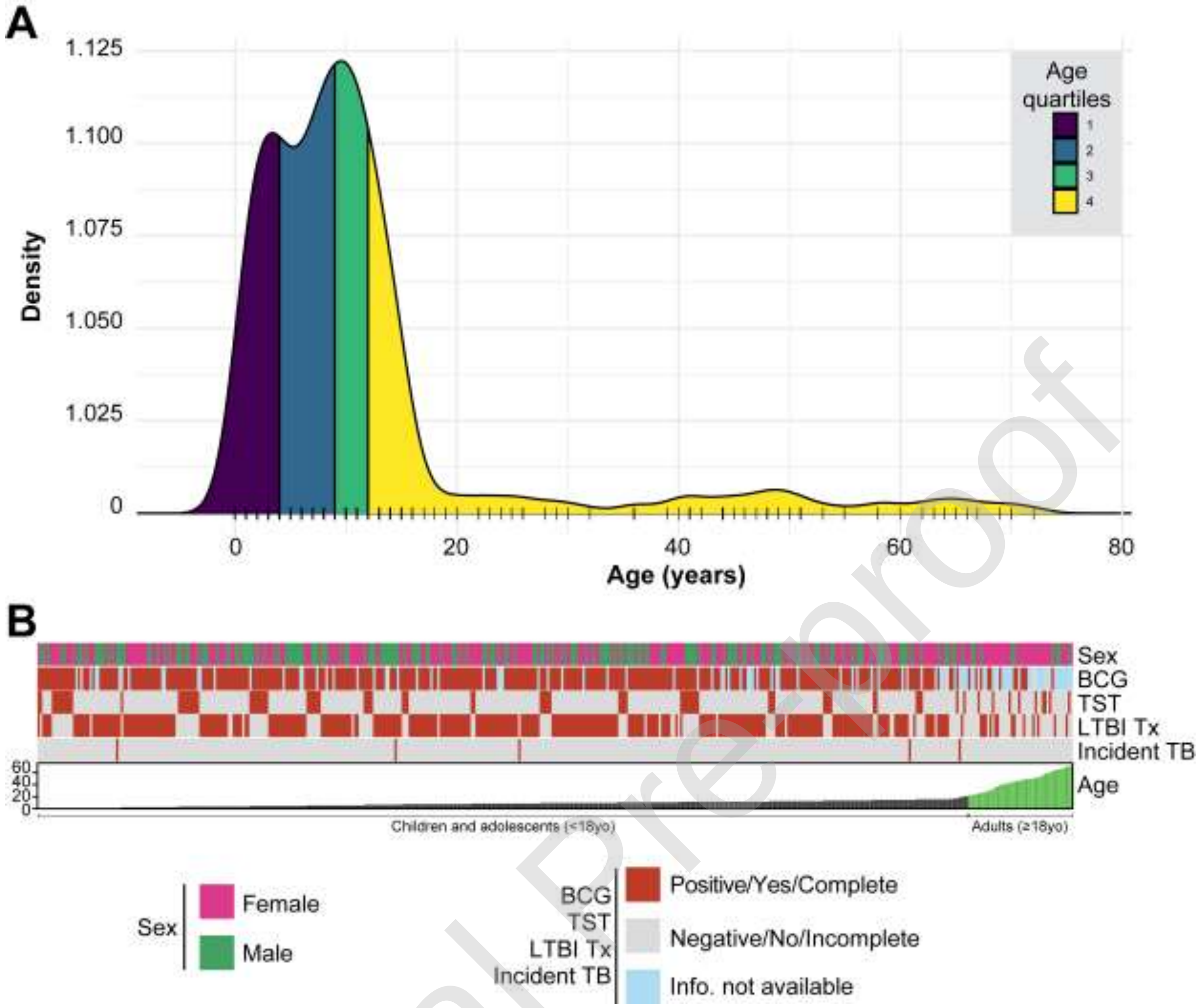

Figure 3. Multivariable logistic regression analysis to evaluate association between epidemiological and clinical characteristics and losses in the LTBI cascade of care
Using the study population stratified according to occurrence of losses in the LTBI cascade (total losses in the LTBI cascade vs. complete LTBI cascade, see Table 2 for detailed univariate comparisons). A binary logistic regression analysis was then employed with each variable individually (unadjusted) and then all variables shown in Table 2 were included in a multivariable model (adjusted). For age, calculations were performed per increase of 1 year.

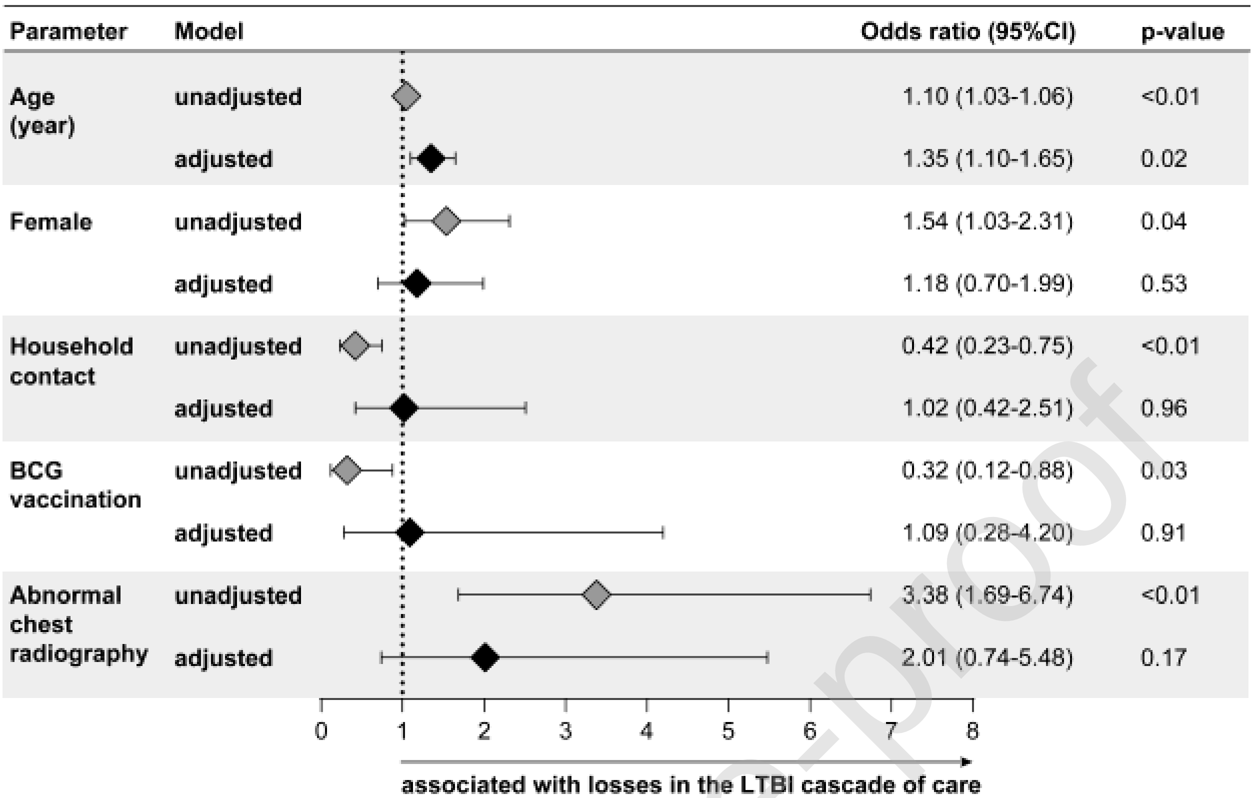
Parameter
Model
Odds ratio (95%CI)
p-value
Age (year)
unadjusted
1.10 (1.03-1.06)
<0.01
adjusted
1.35 (1.10-1.65)
0.02
Female
unadjusted
1.54 (1.03-2.31)
0.04
adjusted
1.18 (0.70-1.99)
0.53
Household contact
unadjusted
0.42 (0.23-0.75)
<0.01
adjusted
1.02 (0.42-2.51)
0.96
BCG vaccination
unadjusted
0.32 (0.12-0.88)
0.03
adjusted
1.09 (0.28-4.20)
0.91
Abnormal chest radiography
unadjusted
3.38 (1.69-6.74)
<0.01
adjusted
2.01 (0.74-5.48)
0.17
0 1 2 3 4 5 6 7 8
associated with losses in the LTBI cascade of care

Table 1. Characteristics of the TB contacts by TST result

Characteristic	TST with result n=435	TST without result* n=40	P-value
Age -median (IQR)	9 (4-12)	24 (8-51.5)	<0.01
Female	243 (55.9)	23 (57.5)	0.87
Smoking	11 (6.5)	9 (40.9)	<0.01
Household contact domiciliary	394 (90.6)	31 (77.5)	0.03
BCG vaccination	332 (96.5)	13 (76.5)	0.004
Abnormal chest radiography	29 (6.8)	7 (26.9)	0.003
Completed the treatment for LTBI	251 (83.1)	1 (50.0)	0.31
Type 2 diabetes mellitus	8 (1.8)	0 (0.0)	1.00
Asthma	64 (14.7)	5 (12.5)	0.82
Hypertension	8 (1.8)	2 (5.0)	0.2
TB symptoms	3 (1.2)	0 (0.0)	1.00
Active TB diagnosis during follow up	5 (1.1)	1 (2.5)	0.41

Data represent no. and %, except for age which is reported as median and interquartile range. *TST without result: performed TST but patients did not return to read the result. TB: Tuberculosis; TST: Tuberculosis skin test. Data were compared using the U Mann Whitney and Fisher's exact test.

Table 2. Characteristics of individuals according to losses in the LTBI cascade of care

Characteristic	Total losses in the LTBI cascade of care (n=142)	Complete LTBI cascade of care* (n=300)	P-value
Age- median (IQR)	13 (6-29)	8 (4-11)	<0.01
Female	90 (63.4)	176 (52.9)	0.043
Smoking	16 (25.8)	4 (3.1)	<0.01
TST performed			<0.01
Yes	102 (71.8)	333 (100)	
No	40 (28.2)	0 (0)	
Contact type			<0.005
Household contact	118 (83.1)	307 (92.2)	
Other close contact	24 (16.9)	26 (7.8)	
BCG vaccination	84 (91.3)	261 (97)	0.035
Abnormal Radiography	19 (15.6)	17 (5.2)	0.001
DM2	5 (3.5)	3 (0.9)	0.06
Ashtma	16 (11.3)	53 (15.9)	0.2
LTBI treatment	53 (37.3)	249 (83)	<0.01

Data represent no. and %, except for age which is reported as median and interquartile range.
LTBI: Latent Tuberculosis Infection; TST: Tuberculosis skin test. *TST negative: 84 patients