Determinants of losses in the tuberculosis infection cascade of care among children and adolescent contacts of pulmonary tuberculosis cases: A Brazilian multi-centre longitudinal study

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Summary

Background Approximately 10% of the global tuberculosis (TB) burden is in children. Identification, diagnosis, and early treatment of *Mycobacterium tuberculosis* infection (TBI) is critical to prevent progression to TB in children. The risk of TB, including severe disease, is highest in children <5 years old. We evaluated the cascade of TBI care among child and adolescent TB contacts to identify factors associated with losses in the cascade.

Methods Close contacts ≦ 18 years old of pulmonary TB patients enrolled between 2015 and 2019 in a multi-centre Brazilian cohort were followed for up to 24 months and classified according to age groups: <5 years, 5–9 years, 10–14 years and 15–18 years. Data on clinical investigation, radiographic examination, IGRA testing at baseline and 6 months, initiation and completion of TB preventive treatment (TPT) were collected. Multivariable regression analyses identified factors associated with TBI and losses in the cascade of care in children and adolescents.

Findings Among 1795 TB contacts initially identified, 530 (29·5%) were ≤18 years old. Losses for all steps in the cascade were especially high in children <5 years old (88%) because at this age all contacts are recommended to initiate TPT. As a proportion of all children, completion of TPT was low (between 10% and 13%) in all age-groups. Furthermore, multivariable regression revealed that younger age of contacts and TB index cases who were female, had pulmonary cavities, and persistent cough were independently associated with losses in the cascade of care among persons ≤18 years old.

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Interpretation Losses in the TBI cascade were the highest among children <5 years, which was the group at highest risk for TB among the four age groups. The findings highlight the need to improve screening, initiation, and completion of TPT of young children who are close contacts of people with TB in Brazil.

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Keywords: Latent tuberculosis; Contact; Pediatric; TBI cascade; Children

Research in context

Evidence before this study

Due to the high risk of tuberculosis (TB) disease, the rapid progression to TB, and the challenge of diagnosis, the WHO recommends contact tracing for children exposed to TB. Early identification of M. tuberculosis infection, ruling out active TB, and timely preventive therapy are interventions that can prevent progression to TB disease. Our group showed how the "cascade of care" can identify losses in each phase of care of contacts of TB index cases. Although there are cascade of care studies about the general TB population, we did not find in the literature the use of "cascade of care" in child and adolescent contacts of TB index cases.

Added value of this study

Previous studies have identified factors that are utilized in tracing adult contacts of TB cases, but information on paediatric contacts is very limited. We explored each stage of the "cascade of care" in children ≤ 18 years of age, and also in these age categories: <5 years, 5–9 years, 10–14 years and 15–18 years. Additionally, we showed the losses by type in each stage of the cascade of care in child and adolescent contacts. Our results showed a significantly higher loss in the care cascade among children <5 years of age; most did not initiate TB preventive treatment when recommended.

Implications of all the available evidence

By identifying losses at each stage of the cascade of care among child and adolescent contacts, this information can guide decision-making strategies to improve TB control in children.

Introduction

Tuberculosis (TB) is a major public health problem. Approximately one-quarter of the world population is infected with *Mycobacterium tuberculosis* (Mtb), representing up to 2 billion people, and there are approximately 10 million new cases and 1·3 million of deaths yearly.[1,2] TB is now the second leading cause of death due to an infectious disease, behind coronavirus (COVID-19) and above HIV/AIDS.[2] Brazil is among the 30 countries identified by the World Health Organization (WHO) as having a high TB burden[2]; these countries account for 82% of TB cases worldwide.[2] There is a major global effort against TB, such as the WHO END-TB strategy,[3] which aims to reduce TB cases and associated deaths by 90% and 95%, respectively, by 2035. For this to be achieved, there must be early diagnosis and initiation of treatment for people with active TB, and treatment of TB infection (TBI) to prevent progression to TB disease.[4–6]

There is a high risk of progression to TB among children with Mtb infection, particularly those <5 years old, and those who were close contacts of TB cases.[7,8] Globally, only 29% of children <5 years of age and 1.6% of children >5 years old who were close contacts of active TB cases received TPT in the period 2018–2020.[2] Despite the strategies implemented by the National TB Control Program in Brazil, TB rates have changed little in recent years.[9] Among the Ministry of Health's most recent recommendations has been the provision of TPT to all TB contacts with a positive interferon-gamma release assay (IGRA) or tuberculin skin test (TST), as well as to all close contacts ≤5 years of age or persons living with HIV (PLWH), regardless of the screening test result.[9] TPT in people with TBI at high risk of active TB is a critical component of TB elimination worldwide; it can reduce TB risk by 60–90%.[10] Identification of contacts with TBI is a priority of TB control programs worldwide, especially in vulnerable populations such as children and adolescents.[11]

The cascade of care among contacts of persons with active TB involves multiple steps, from the identification of persons at risk of TBI, evaluations to rule out active TB, initiating TPT in persons with TBI, and completing a course of TPT.[12] The analysis of this cascade helps identify gaps in health care delivery that could be improved. Identification of timepoints at which loss to follow-up occurs, as well as the reasons for such losses, are key for TB prevention, and interrupting Mtb transmission.

Our group has previously reported the cascade of care among close TB contacts in Brazil (without categorization or exclusion by age),[12,13] but that investigation did not delineate the cascade in children. The current literature does not provide detailed evaluation of factors associated with losses to care in the cascade of TBI care in children. The present study was conducted to fill this important knowledge gap, and help inform decision-making strategies to improve TB control.

Methods

Ethics statement

All regulatory documents were approved by the Research Ethics Committee of all participating sites. (CAAE: 25102414.3.2009.5543). Written informed consent was obtained from each participant or their legally responsible guardians, at the time of study enrolment. The anonymity of study subjects was preserved; all research data were de-identified. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

Overall study design

We conducted a longitudinal study within a Brazilian cohort of culture-confirmed pulmonary TB cases and their close contacts; all participants were enrolled in the Regional Prospective Observational Research in Tuberculosis (RePORT)-Brazil cohort between August 2015 and July 2019,[14] and followed for 24 months. Details of the cohort of contacts of patients diagnosed with pulmonary TB in the RePORT-Brazil consortium have been published previously.[12,14] Contacts were defined as individuals exposed to a culture-positive pulmonary TB case for at least 4 h in one week in the 6 months prior to TB diagnosis, since a previous study[15] showed that this definition increased the rate of diagnosis of recent active pulmonary TB cases and for the detection of TB infection among contacts of active pulmonary TB cases in a Brazilian cohort.

For this study, paediatric close TB contacts were classified into four age groups, as follows: <5 years, 5–9 years, 10–14 years, 15–18 years, consistent with a previously published systematic review,[8] furthermore, we performed the TBI cascade of care in each age group. The paediatric close contacts cohort is a convenience sampling.

Close contacts with i) a positive IGRA result, or ii) <5 years old or iii) with HIV infection (ii) and iii) regardless of IGRA result), were recommended to receive TPT,[2,16] according to Brazilian guidelines. The TPT administered was isoniazid 5 to 10 mg/kg daily (300 mg maximum), for 6–9 months.[9]

TBI cascade: definitions of each stage and losses

We evaluated the cascade of care regarding the diagnosis and treatment of TBI among contacts of TB cases, as previously reported by our group[12] and others.[17–19] Our focus was on the losses at each stage of care. For this study we considered four stages: i) TB contacts who were clinically examined and evaluated with chest X-ray, IGRA and HIV serologic testing, ii) received a recommendation for TPT, iii) started the recommended TPT and iv) completed TPT (defined as: >6 months of isoniazid or 4 months of rifampicin). Contacts who did not undergo the second IGRA (which was obtained at month 6 if negative at baseline), did not initiate the recommended TPT, or did not complete the TPT that was initiated, were defined as losses in the TBI cascade.

Statistical analysis

Gaussian distribution was assessed by the Kolmogorov-Smirnov test. Continuous data were presented as medians and interquartile ranges (IQR) and categorical variables were expressed as proportions. To compare differences between outcome groups (losses vs no losses in the TBI cascade among ≤ 18-year-old contacts and according to the age group stratified) we used the Mann-Whitney *U* (between 2 groups) or Kruskal-Wallis test (between >2 groups) for continuous variables and the Fisher's exact test (2 × 2 comparisons) and Pearson's chi-square test ($\chi 2$) (other types of comparisons) for categorical variables. In addition, we compared the characteristics of TB cases according to contact status in the TBI cascade. Considering that a TB case can have more than one contact, we used the Chi-square test and the Mann Whitney *U* test for survey data.[20] A multivariable mixed-effects logistic regression model,[21] with a random effect per "TB case" variable (due to the possible correlation between the outcome in the TBI cascade of the contacts of the same TB case) was performed to assess the associations between clinical characteristics of TB cases and contacts, with losses in the cascade of care. Parameters with *p*-values ≤0.2 in univariate analyses were included in multivariable models. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 25.0 (IBM statistics), Graphpad Prism 8.0 (GraphPad Software, San Diego, CA), Stata 15 (StataCorp), and R 3.1.0 (R Foundation, Austria).

Role of the funding source

The funders had no role in study design, data collection and interpretation, or the decision to submit the work for publication.

Results

Clinical Characteristics of study participants

Our cohort was focused among 1795 TB contacts initially identified, of 592 patients with culture-positive pulmonary TB. There were 530 (29.5%) TB contacts

≤18 years who were investigated for TBI at RePORT-Brazil clinical sites. The characteristics of these patients are presented in Supplementary Table 1 stratified according to age group: <5 years (n=100), 5–9 years (n=142), 10–14 years (n=173) and 15–18 years (n=115). The groups differed in terms of self-reported race/ethnicity (p<0.001), BCG scarring (p<0.001), HIV infection (p=0.02), smoking (p<0.001), alcohol consumption (p<0.001), illicit drug use (p<0.001), income (p=0.04), body mass index (BMI) (p<0.001) and TB symptoms such as cough (p=0.02), fever (p=0.01), weight loss (p=0.05) and chest pain (p=0.03). Of note, the group of contacts <5 years old had a lower frequency of BCG scarring and a higher frequency of HIV infection, as well as a higher proportion with cough or fever, than the other groups. Only those older than 10 years reported consumption of alcohol, tobacco, or illicit drugs (Supplementary Table 1).

TBI cascade of care in contacts of TB cases ≤18 years old

We next concatenated all contacts ≤ 18-years-old in a single analysis group and stratified according to the occurrence of loss at any stage of the TBI cascade of care. Losses occurred mainly in younger individuals (median: 7.9 years; IQR:3.7–13.8, p<0.001), and in those living with HIV (3.1%, p=0.02) (Table 1). Furthermore, TB index cases of the contacts who were losses were frequently living with equal or less than a minimum wage (40%, p=0.02), and presented more commonly with cavitary lung lesions (47%, p=0.01) and persistent cough (34.7%, p=0.02) (Table 1) than the index cases of participants who completed the cascade.

A previous study from our group of the entire TB contact cohort of RePORT-Brazil, which included the adult population, noted that there were substantial losses in the TBI cascade at all the steps.[12] Here, we restricted the analyses to persons aged < 18 years. First, the 530 patients ≤18 years of age were included, and we observed that 291 contacts (54.9%) were recommended to receive TPT. Of the 530, 139 (26.2%) initiated treatment and only 65 (12.3%) completed it (Figure 1A). When we evaluated the cascade according to the recommendation to receive TPT, 139/291 (47.8%) initiated TPT, and 65/139 (46.8%) completed it (Figure 1B).

To describe the factors independently associated with the overall losses in the TBI cascade of care, we performed logistic regression analyses of clinical and sociodemographic factors stratified by age group. We found that younger age was significantly associated with loss in the TBI cascade (per 1 year increase; aOR:0.89; 95%CI:0.85–0.92; p=0.004) (Figure 1B). Moreover, when characteristics of the TB index cases were compared, we found that female sex (aOR:1.73; 95%CI:1.20–2.51; p=0.004), cavitary lung lesions (aOR:2.00; 95%CI:1.36–2.96; p=0.003), and persistent cough (aOR:1.44; 95%CI:1.33–3.14; p=0.04) were all independent risk factors for losses in the TBI cascade (Figure 1C).

Characteristics of participants according to losses in the TBI cascade of care stratified by age group

No statistically significant difference was observed in any age group when characteristics of the contacts who were lost at any stage of the TBI cascade of care were compared to those who successfully completed the cascade (Table 2). Regarding the characteristics of the TB index cases, we observed that the TB index cases of contacts <5 years who were losses in the cascade were less likely to report use of illicit drugs (p=0.03), as well as a lower frequency of nocturnal sweating at baseline (p=0.03) and persistent nocturnal sweating (p=0.02) compared to the index cases of contacts who completed the cascade.

In addition, we found that in the group of contacts <5 years, the median time (per week) from detection of the TB index case to detection of contacts was greater in contacts who lost the TBI cascade. In contrast, in the group of contacts 5–9 years, the median time (per week) was higher in the group that completed the TBI cascade (p=0.04). Notably, there was no difference between contact screening time in the 10–14 year old and 15–18 year old groups (Supplementary Figure 1A).

In the group of contacts aged 5–9 years, the TB index cases of those who were more often female (p=0.04), were less commonly living with HIV (p=0.03) and presented more frequently with persistent cough (p=0.04) than those contacts who completed the cascade. TB index cases of contacts 10–14 years old who were lost in the TBI cascade exhibited a higher proportion of positive AFB smear results (p=0.04) and cavitary lung lesions detected by chest x-ray (p=0.04) than the index cases of contacts who completed the TBI cascade (Table 2). Additionally, TB index cases of contacts aged 15–18 years who discontinued the TBI cascade reported smoking (p=0.05), illicit drug use (p=0.04), and HIV coinfection (p<0.001) at a lower frequency than the TB cases of contacts who completed all the steps of the cascade (Table 2). Interestingly, TB cases directly linked to contacts who were lost in the cascade more commonly reported passive smoking (p=0.01), a higher proportion of positive AFB smears (p=0.02), increased frequency of pulmonary cavities (p=0.04) and persistent cough (p=0.04) than TB index cases of contacts who completed the TBI cascade of care (Table 2).

TBI cascade of care in contacts of TB cases by age group

We next examined the losses at each stage of the TBI care cascade according age group of the contacts (Figure 2). All (100%) children <5 years of age were

Characteristics	Losses in the TBI cascade (*n*=259)	No losses in the TBI cascade (*n*=271)	*p*-value
Characteristics of the TB Contacts			
Age — median (IQR)	7.9 (3.7—13.8)	11.8 (8.5—14.5)	**<0.001**
Sex — no. (%)	126 (48.6)	141 (52.0)	0.487
Race/Ethnicity — no. (%)			0.765
White	47 (18.2)	48 (17.7)	
Black	46 (17.8)	47 (17.3)	
Asian	1 (0.4)	0 (0.0)	
Pardo	163 (63.2)	174 (64.2)	
Indigenous	1 (0.4)	2 (0.7)	
BCG scar — no. (%)	245 (94.6)	258 (95.2)	0.844
HIV-infection— no. (%)	8 (3.1)	1 (0.4)	**0.018**
Smoking — no. (%)	7 (2.7)	10 (3.7)	0.625
Passive smoking — no. (%)	84 (32.8)	77 (28.4)	0.298
Alcohol consumption — no. (%)	22 (8.5)	23 (8.5)	1
Illicit drug use — no. (%)	6 (2.3)	5 (1.8)	0.768
Income — no. (%)			0.269
More than a minimum wage	80 (32.1)	93 (35.8)	
Equal or less than a minimum wage	99 (39.8)	104 (40.0)	
Without income	70 (28.1)	63 (24.2)	
BMI (kg/m^2)-median (IQR)	17.5 (15.6—21.1)	18.4 (15.7—21.4)	0.137
Symptoms of TB— no. (%)			
Cough	20 (10.3)	14 (5.7)	0.104
Fever	5 (2.6)	1 (0.4)	0.092
Weight Loss	3 (1.5)	7 (2.9)	0.523
Fatigue	3 (1.5)	8 (3.3)	0.360
Night sweats	1 (0.5)	2 (0.8)	0.054
Chest paint	4 (2.1)	2 (0.8)	0.413
Immunotherapy— no. (%)	3 (1.2)	0 (0.0)	NA
Other comorbidities— no. (%)	60 (23.2)	53 (19.6)	0.340
Time per week ($V1_{TB}$-$V1_C$) — median (IQR)	5.7 (2—11)	5.4 (3—8)	0.263
Characteristics of the TB cases			
Age — median (IQR)	35 (24—43)	36· (26—42)	0.496
Male — no. (%)	82 (60.7)	79 (64.8)	**0.040**
Race/Ethnicity — no. (%)			0.844
White	15 (11.1)	17 (14.0)	
Black	33 (24.4)	23 (19.0)	
Asian	1 (0.7)	1 (0.8)	
Pardo	85 (63.0)	78 (64.5)	
Indigenous	1 (0.7)	2 (1.7)	
BMI (kg/m^2)-median (IQR)	20.1 (18.1—23.5)	20.4 (18.4—22.5)	0.978
Income — no. (%)			**0.019**
More than a minimum wage	44 (33.3)	41 (34.5)	
Equal or less than a minimum wage	53 (40.2)	43 (36.1)	
Without income	35 (26.5)	35 (29.4)	
Smoking — no. (%)	75 (55.6)	61 (50.0)	0.384
Passive smoking — no. (%)	51 (38.1)	40 (33.3)	0.512
Alcohol consumption — no. (%)	112 (83.0)	99 (81.1)	0.115
Illicit drug use — no. (%)	55 (40.7)	46 (37.7)	0.701
HIV infection — no. (%)	32 (23.7)	32 (26.2)	0.667
Dysglycemia status — no. (%)			0.072
Diabetes	37 (27.4)	43 (35.2)	
Prediabetes	53 (39.3)	50 (41.0)	
Normoglycemia	45 (33.3)	29 (23.8)	

Table 1 *(Continued)*

Characteristics	Losses in the TBI cascade (*n*=259)	No losses in the TBI cascade (*n*=271)	*p*-value
Positive AFB — no. (%)	111 (82.2)	98 (80.3)	0.750
Cavities on chest X-ray— no. (%)	63 (47.0)	48 (39.7)	**0.003**
DST — no. (%)			0.117
Sensitive	237 (91.5)	225 (84.9)	
Rifampicin-Isoniazid resistance	5 (1.9)	7 (2.6)	
Rifampicin resistance	0 (0.0)	0 (0.0)	
Isoniazid resistance	17 (6.6)	33 (12.5)	
Symptoms of TB— no. (%)			
Cough	124 (91.9)	114 (93.4)	0.812
Fever	110 (81.5)	98 (80.3)	0.874
Weight Loss	118 (88.7)	111 (91.0)	0.680
Fatigue	115 (85.2)	98 (80.3)	0.324
Night sweats	93 (69.4)	88 (72.1)	0.681
Chest paint	94 (69.6)	85 (69.7)	1.000
Persistence of symptoms— no. (%)			
Cough	43 (34.7)	30 (26.3)	**0.024**
Fever	1 (100)	3 (100)	NA
Weight Loss	9 (6.7)	9 (7.4)	1.000
Fatigue	23 (20.0)	26 (23.6)	0.523
Night sweats	74 (54.8)	71 (58.2)	0.616
Chest paint	10 (8.7)	14 (12.7)	0.390
Other comorbidities— no. (%)	40 (25)	34 (21.1)	0.107

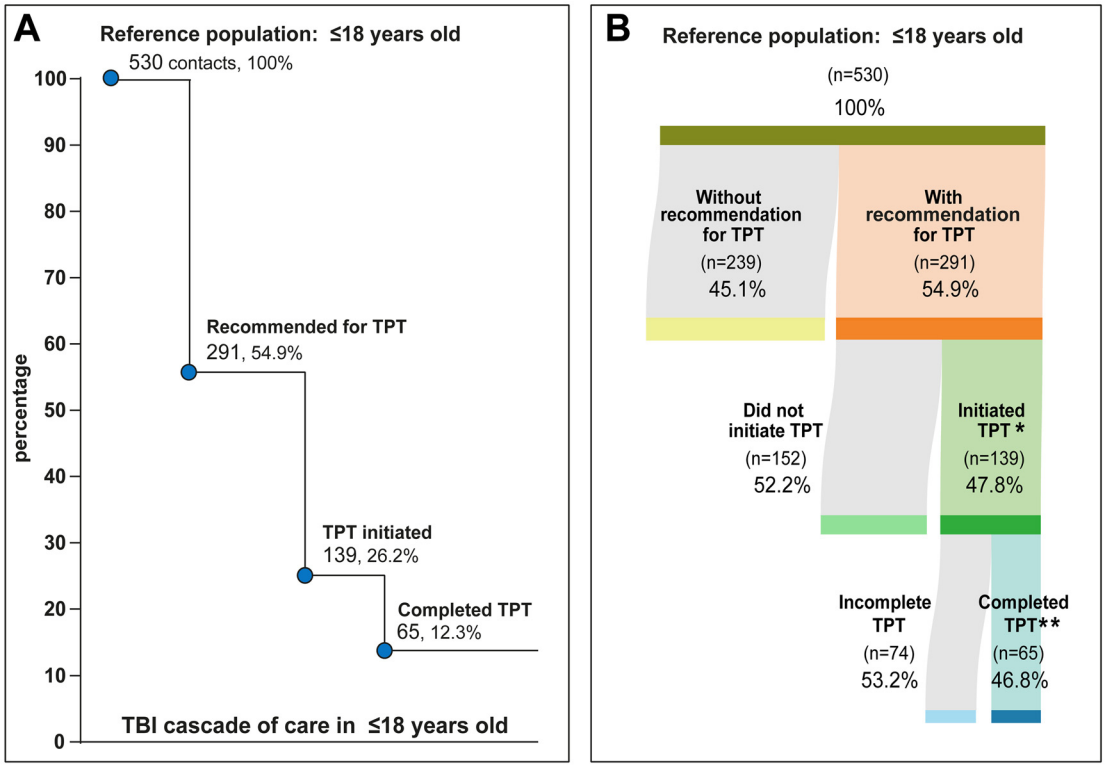
***Table 1*: Characteristics of contacts ≤ 18 years old according to losses and no losses in the TBI cascade of care.**
Note: Data represent no. (%), except for age and BMI, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Mann-Whitney *U* test and categorical variables were compared using the Fisher's exact test (2 × 2 comparisons) and Pearson's chi-square test ($\chi 2$) (other comparisons).
Contacts who did not perform the 2nd IGRA were excluded.
Definition of income: monthly money received in the household, categorized in wage on this study. One Brazilian minimum wage was $266/month (The World Bank), the average value in the period (2015–2019).
Definition of alcohol consumption: Past or current any consumption of alcohol. *Definition of passive smoking:* Living with someone who smokes. *Definition of illicit drug use:* Past or current illicit drug use (marijuana, cocaine, heroin, or crack).
Definition of persistence of symptoms: Patients who in the initial evaluation interview (month 0) reported indicated symptom and in the evaluation of visit 2 (month 2) still reported having such symptom.
Definition of Pardo ethnicity: mixture of European, black and Amerindian.
Other comorbidities: include cancer, kidney disease, chronic obstructive pulmonary disease, emphysema, allergies, and asthma. In contacts, this information was self-reported for contacts or their parents or legal caregivers.
For contact characteristics, all information for children <5 was collected from their parents or legal guardians. The information of the contacts between 5 to 18 years of age was collected from themselves accompanied by their parents or legal caregivers.
Time (VI_{TB}-VI_C): time (in weeks) difference between the visit 1 of the TB case and the visit 1 of the contact.
P-values marked with bold indicate statistical significance.
Abbreviations: TB: tuberculosis, BMI: Body Mass Index, AFB: acid-fast bacilli, DST: Drug-susceptibility testing, BCG: Bacille Calmette-Guérin, IGRA: Interferon-Gamma Release Assays, NA: Not applicable.

recommended to initiate TPT; however, only 21% initiated TPT. This was the stage at which the greatest loss occurred (79%); notably it was also the stage of greatest loss for all four age groups. In addition, in the <5-year-old group, only 12% completed TPT (Figure 2A).

The age groups of 5–9 years and 15–18 years had similar percentages of contacts in whom TPT was recommended (47.2% and 45.2%, respectively). The group aged 10–14 years had a lower proportion of contacts who were recommended to receive TPT (41.6%). At the stage when TPT initiation was recommended, children 5–9 years and 10–14 years old had similar proportions: 26.1% and 27.2%, respectively. In those 15–18 years old, 45.2% were recommended to receive TPT, and 22.6% initiated it. (Figure 2A, 2B, 2C and 2D).

Evaluation of the last stage of the care cascade found that the lowest proportion of contacts who completed TPT was 10–14 years old (9.8%), followed by those <5 years old (12%), 15–18 years old (13%) and 5–9 years old (13.4%) (Figure 2A, 2B, 2C and 2D).

Furthermore, we evaluated within each age group the cascade according to the TPT recommendation. In <5 years old completed TPT when recommended 12 (57.1%), 19 (51.3%) in 5–9 years old, 17 (36.2%) in 10–14 years old group and 15 (57.7%) in 15–18 years old (Figure 3A,3B, 3C and 2D).



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	Parameters	Model	Adjusted Odds ratio (95%CI)	p-value
Charact. of contacts	Age (years)	unadjusted	0.89 (0.86-0.93)	**<0.001**
		adjusted	0.89 (0.85-0.92)	**0.004**
Characteristics of TB index	Sex (female)	unadjusted	1.03 (1.09-1.57)	**0.003**
		adjusted	1.73 (1.20-2.51)	**0.040**
	Cavities on chest X-ray	unadjusted	1.47 (1.04-2.08)	**0.035**
		adjusted	2.00 (1.36-2.93)	**0.003**
	Persistent cough	unadjusted	1.89 (0.93-3.86)	**0.024**
		adjusted	1.44 (1.33-3.14)	**0.040**

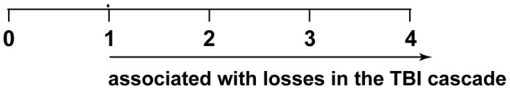

Figure 1. Cascade in TBI care in contacts of TB cases and factors associated to losses in the TBI cascade in contacts ≤18 years old. (A) Losses and drop-outs at each stage of the TBI cascade of care in ≤18 years old, percentages were calculated among the number of contacts initially identified. Percentages were calculated among the number of contacts initially identified. **(B)** Sankey diagram display the number of contacts who initiated treatment and those who completed treatment according to the category of TPT recommendation. **(C)** Generalized estimating equations analysis to evaluate association between epidemiological and clinical characteristics and losses in the TBI cascade of care in ≤18 years old. The study population was stratified according to complete TPT in the TBI cascade (variables included in the adjusted model: age (years), sex (female), cavities on chest X-ray exhibited univariate *p*-values≤0.2 (See Table 1 for details). Significant *p*-values are shown in bold-type font.

* This group also includes 8 contacts in the group ≤18 years old who initiated TPT without recommendation of the RePORT-Brazil medical staff.

**This group includes the 2 contacts (≤18 years) who initiated TPT without the recommendation of the RePORT-Brazil medical staff.

Abbreviations: TB: tuberculosis, TPT: Tuberculosis preventive treatment.

Characteristics of the TB Contacts	<5 years old (*n*=100)			5−9 years old (*n*=142)			10−14 years old (*n*=173)			15−18 years old (*n*=115)		
	Losses in the TBI cascade (*n*=88)	No losses in the TBI cascade (*n*=12)	*p*-value	Losses in the TBI cascade	No losses in the TBI cascade	*p*-value	Losses in the TBI cascade	No losses in the TBI cascade	*p*-value	Losses in the TBI cascade	No losses in the LBI cascade	*p*-value
Age − median (IQR)	3 (1−4)	3 (1−4)	0.328	7 (6-8)	8 (7−9)	0.870	13 (11−4)	13 (7−14)	0.850	17 (16−18)	17 (16−18)	0.390
Sex − no. (%)	44 (50.0)	5 (41.7)	0.760	26 (47.3)	50 (57.5)	0.300	36 (52.9)	54 (51.4)	0.877	20 (41.7)	32 (47.8)	0.572
Race/Ethnicity − no. (%)			0.347			0.648			0.807			0.583
White	24 (27.3)	1 (8.3)		8 (14.8)	19 (21.8)		9 (13.2)	18 (17.1)		6 (12.5)	10 (14.9)	
Black	6 (6.8)	2 (16.7)		8 (14.8)	8 (9.2)		16 (23.5)	22 (21.0)		16 (33.3)	15 (22.4)	
Asian	1 (1.1)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Pardo	57 (64.8)	9 (75.0)		38 (70.4)	60 (69.0)		43 (63.2)	63 (60.0)		25 (52.1)	42 (62.7)	
Indigenous	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	2 (1.9)		1 (2.1)	0 (0.0)	
BCG scar − no. (%)	80 (90.9)	12 (100.0)	0.591	52 (94.5)	83 (95.4)	1	66 (97.1)	99 (94.3)	0.483	47 (97.9)	64 (95.5)	0.639
HIV-infection− no. (%)	5 (5.7)	0 (0.0)	1	2 (3.6)	1 (1.1)	0.560	1 (1.5)	0 (0.0)	0.393	0 (0.0)	0 (0.0)	NA
Smoking − no. (%)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	1 (1.0)	1	6 (12.5)	9 (13.4)	1
Passive smoking − no. (%)	29 (33.3)	5 (41.7)	0.747	18 (33.3)	19 (21.8)	0.168	15 (22.4)	34 (32.4)	0.170	22 (45.8)	19 (28.4)	0.075
Alcohol consumption − no. (%)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	3 (4.4)	2 (1.9)	0.383	16 (33.3)	21 (31.3)	0.842
Illicit drug use − no. (%)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	6 (12.5)	5 (7.5)	0.522
Income − no. (%)			0.067			0.951			0.601			0.253
More than a minimum wage	26 (30.6)	2 (16.7)		22 (40.7)	33 (37.9)		22 (33.8)	37 (37.8)		10 (22.2)	21 (33.3)	
Equal or less than a minimum wage	33 (38.8)	3 (25.0)		21 (38.9)	38 (43.7)		28 (43.1)	41 (41.8)		17 (37.8)	22 (34.9)	
Without income	26 (30.6)	7 (58.3)		11 (20.4)	16 (18.4)		15 (23.1)	20 (20.4)		18 (40.0)	20 (31.7)	
BMI (kg/m2)-median (IQR)	16.1 (14.8−18.1)	17.2 (14.8−18.3)	0.277	16.3 (15.3−18.6)	15.5 (14.7−18.1)	0.920	18.5 (16.3−22.2)	18.9 (16.8−22.1)	0.644	20.5 (19.6−23.6)	21 (19.1−24.3)	0.078
Symptoms of TB− no. (%)												
Cough	11 (15.9)	1 (12.5)	1	3 (8.6)	7 (8.8)	1	2 (3.8)	4 (4.1)	NA	4 (10.5)	2 (3.4)	0.206
Fever	4 (5.8)	0 (0.0)	1	1 (2.9)	1 (1.3)	1	0 (0.0)	0 (0.0)	1	0 (0.0)	0 (0.0)	NA
Weight Loss	0 (0.0)	1 (12.5)	NA	0 (0.0)	2 (2.5)	1	0 (0.0)	1 (1.0)	1	3 (7.9)	3 (5.1)	0.676
Fatigue	0 (0.0)	0 (0.0)	NA	0 (0.0)	1 (1.3)	1	0 (0.0)	7 (7.1)	NA	3 (7.9)	0 (0.0)	0.057
Night sweats	0 (0.0)	0 (0.0)	1	0 (0.0)	1 (1.3)	1	0 (0.0)	0 (0.0)	NA	1 (2.6)	1 (1.7)	1
Chest paint	1 (1.4)	0 (0.0)	NA	0 (0.0)	1 (1.3)	1	0 (0.0)	0 (0.0)	NA	3 (7.9)	1 (1.7)	0.296
Other comorbidities− no. (%)	16 (18.2)	5 (41.7)	0.122	16 (29.1)	16 (18.4)	0.153	17 (25.0)	23 (21.9)	0.713	11 (22.9)	9 (13.4)	0.217
Characteristics of the TB cases												
Age − median (IQR)	30 (24−41)	29 (26−32)	0.674	35 (24−42)	34 (26−40)	0.801	36.5 (27−42)	37 (25−44)	0.881	32 (20−44)	38 (27−42)	0.213
Male − no. (%)	38 (59.4)	7 (63.6)	1	23 (51.1)	44 (67.7)	**0.044**	30 (51.7)	51 (60.0)	0.391	22 (56.4)	40 (71.4)	0.188
Race/Ethnicity − no. (%)			0.913			0.268			0.198			0.621
White	7 (11.1)	1 (9.1)		6 (13.6)	6 (9.4)		8 (13.8)	12 (14.3)		6 (15.4)	6 (10.7)	
Black	14 (22.2)	3 (27.3)		7 (15.9)	6 (9.4)		14 (24.1)	10 (11.9)		11 (28.2)	16 (28.6)	
Asian	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		1 (1.7)	0 (0.0)		0 (0.0)	1 (1.8)	
Pardo	42 (66.7)	7 (63.6)		30 (68.2)	52 (81.3)		35 (60.3)	61 (72.6)		21 (53.8)	31 (55.4)	
Indigenous	0 (0.0)	0 (0.0)		1 (2.3)	0 (0.0)		0 (0.0)	1 (1.2)		1 (2.6)	2 (3.6)	
BMI (kg/m2)-median (IQR)	20 (18.1−23)	19.3 (14.8−21.4)	0.258	19.9 (18.3−22)	20.3 (18.1−22)	0.069	20.7 (18.4−24.4)	20.8 (18.7−22.7)	0.415	19.9 (18.3−22.8)	21.7 (19.5−23)	0.163
Income − no. (%)			0.607			0.860			0·179			0.281
More than a minimum wage	22 (34.9)	3 (30.0)		15 (34.1)	25 (39.1)		21 (38.2)	26 (31.7)		9 (23.1)	25 (46.3)	
Equal or less than a minimum wage	20 (31.7)	5 (50.0)		17 (38.6)	15 (23.4)		23 (41.8)	31 (37.8)		20 (51.3)	16 (29.6)	
Without income	21 (33.3)	2 (20.0)		12 (27.3)	24 (37.5)		11 (20.0)	25 (30.5)		10 (25.6)	13 (24.1)	
Smoking − no. (%)	34 (53.1)	7 (63.6)	0.745	26 (57.8)	34 (52.3)	0.697	32 (55.2)	40 (47.1)	0.396	15 (38.5)	33 (58.9)	**0.048**
Passive smoking − no. (%)	20 (31.7)	6 (54.5)	0.148	19 (42·2)	17 (26.6)	0.101	19 (32.8)	29 (34.5)	0.859	20 (51.3)	14 (25.0)	**0.010**
Alcohol consumption − no. (%)	52 (81.3)	9 (81.8)	1	35 (77.8)	59 (90.8)	0.097	49 (84.5)	68 (80.0)	0.659	32 (82.1)	47 (83.9)	1
Illicit drug use − no. (%)	28 (43.8)	9 (81.8)	**0.025**	20 (44.4)	29 (44.6)	1	19 (32.8)	34 (40.0)	0.481	8 (20.5)	21 (37.5)	**0.040**
HIV infection − no. (%)	22 (34.4)	3 (27.3)	0.742	10 (22.2)	29 (44.6)	**0.025**	11 (19.0)	24 (28.2)	0.238	3 (7.7)	21 (37.5)	**<0.001**
Dysglycemia status − no. (%)			0.812			0.470			0.896			0.430
Diabetes	18 (28.1)	4 (36.4)		17 (37.8)	22 (33.8)		21 (36.2)	22 (25.9)		7 (17.9)	16 (28.6)	
Prediabetes	24 (37.5)	3 (27.3)		10 (22.2)	27 (41.5)		17 (29.3)	41 (48.2)		18 (46.2)	21 (37.5)	
Normoglycemia	22 (34.4)	4 (36.4)		18 (40.0)	16 (24.6)		20 (34.5)	22 (25.9)		14 (35.9)	19 (33.9)	

Table 2 *(Continued)*

Characteristics of the TB Contacts	<5 years old (*n*=100)			5–9 years old (*n*=142)			10–14 years old (*n*=173)			15–18 years old (*n*=115)		
	Losses in the TBI cascade (*n*=88)	No losses in the TBI cascade (*n*=12)	*p*-value	Losses in the TBI cascade	No losses in the TBI cascade	*p*-value	Losses in the TBI cascade	No losses in the TBI cascade	*p*-value	Losses in the TBI cascade	No losses in the LBI cascade	*p*-value
Positive AFB – no. (%)	47 (73.4)	9 (81.8)	0.719	32 (71.1)	51 (78.5)	0.500	50 (86.2)	64 (75.3)	**0.040**	36 (92.3)	40 (71.4)	**0.018**
Cavities on chest X-ray– no. (%)	21 (32.8)	5 (45.5)	0.498	18 (40.9)	23 (35.4)	0.687	34 (58.6)	34 (41.0)	**0.042**	26 (66.7)	26 (47.3)	**0.038**
DST – no. (%)			0.364			0.879			0.392			0.108
Sensitive	59 (92.2)	11 (100.0)		41 (91.1)	58 (89.2)		51 (87.9)	69 (83.1)		37 (94.9)	45 (84.9)	
Rifampicin-Isoniazid resistance	1 (1.6)	0 (0.0)		0 (0.0)	1 (1.5)		2 (3.4)	3 (3.6)		1 (2.6)	2 (3.8)	
Rifampicin resistance	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Isoniazid resistance	4 (6.3)	0 (0.0)		4 (8.9)	6 (9.2)		5 (8.6)	11 (13.3)		1 (2.6)	6 (11.3)	
Symptoms of TB– no. (%)												
Cough	58 (90.6)	11 (100.0)	0.583	40 (88.9)	59 (90.8)	0.757	53 (91.4)	82 (96.5)	0.270	39 (100.0)	54 (96.4)	0.511
Fever	49 (76.6)	11 (100.0)	0.107	35 (77.8)	53 (81.5)	0.636	49 (84.5)	67 (78.8)	0.515	33 (84.6)	43 (76.8)	0.438
Weight Loss	57 (90.5)	11 (100.0)	0.583	40 (90.9)	61 (93.8)	0.712	50 (87.7)	79 (92.9)	0.376	34 (87.2)	51 (91.1)	0.736
Fatigue	56 (87.5)	10 (90.9)	1	38 (84.4)	56 (86.2)	0.791	49 (84.5)	66 (77.6)	0.392	31 (79.5)	47 (83.9)	0.597
Night sweats	42 (65.6)	11 (100.0)	**0.027**	27 (60.0)	46 (70.8)	0.305	41 (71.9)	57 (67.1)	0.583	29 (74.4)	41 (73.2)	1
Chest paint	46 (71.9)	10 (90.9)	0.271	33 (73.3)	46 (70.8)	0.832	40 (69.0)	56 (65.9)	0.721	27 (69.2)	40 (71.4)	0.823
Persistence of symptoms– no. (%)												
Cough	14 (24.1)	1 (9.13)	0.434	16 (40.0)	12 (20.3)	**0.042**	22 (41.5)	22 (26.8)	0.092	19 (48.7)	16 (29.6)	**0.043**
Fever	1 (100.0)	0 (0.0)	NA	2 (100.0)	2 (100.0)	NA	3 (100.0)	2 (100.0)	NA	1 (100.0)	2 (100.0)	NA
Weight Loss	4 (6.3)	0 (0.0)	1	4 (8.9)	4 (6.2)	0.714	2 (3.4)	9 (10.6)	0.200	2 (5.1)	3 (5.4)	1
Fatigue	10 (18.5)	1 (11.1)	1	9 (23.7)	16 (27.6)	0.813	13 (24.5)	20 (26.7)	0.840	5 (16.1)	14 (26.9)	0.294
Night sweats	32 (50.0)	10 (90.9)	**0.018**	22 (48.9)	38 (58.5)	0.338	36 (62.1)	42 (49.4)	0.172	22 (56.4)	33 (58.9)	0.835
Chest paint	4 (7.4)	0 (0.0)	1	6 (15.8)	6 (10.3)	0.532	8 (15.1)	12 (16.0)	1	3 (9.7)	7 (13.5)	0.737

***Table 2*: Characteristics of TB contacts and their TB cases according to the age group and losses in the TBI cascade.**

Note: Data represent no. (%), except for age and BMI, which is presented as median and interquartile range (IQR). Continuous variables were compared using the Mann-Whitney *U* test and categorical variables were compared using the Fisher's exact test (2 × 2 comparisons) and Pearson's chi-square test ($\chi 2$) (other comparisons). Age categories: based on the previous study.[8]

Definition of income: monthly money received in the household, categorized in wage on this study. One Brazilian minimum wage was $266/month (The World Bank), the average value in the period (2015–2019). *Definition of alcohol consumption:* Past or current any consumption of alcohol. *Definition of passive smoking:* Living with someone who smokes.

Definition of illicit drug use: Past or current illicit drug use (marijuana, cocaine, heroin, or crack). *Definition of persistence of symptoms*: Patients who in the initial evaluation interview (month 0) reported indicated symptom and in the evaluation of visit 2 (month 2) still reported having such symptom.

Definition of Pardo ethnicity: mixture of European, black and Amerindian. Other comorbidities: include cancer, kidney disease, chronic obstructive pulmonary disease, emphysema, allergies and asthma. This information was self-reported for contacts or their parents or legal caregivers.

For contact characteristics, all information for children <5 was collected from their parents or legal guardians. The information of the contacts between 5 and 18 years of age was collected from themselves accompanied by their parents or legal caregivers.

P-values marked with bold indicate statistical significance. Abbreviations: TB: tuberculosis, yr.: years, BMI: Body Mass Index, AFB: acid-fast bacilli, Drug-susceptibility testing: DST, BCG: Bacille Calmette-Guérin, NA: Not applicable.

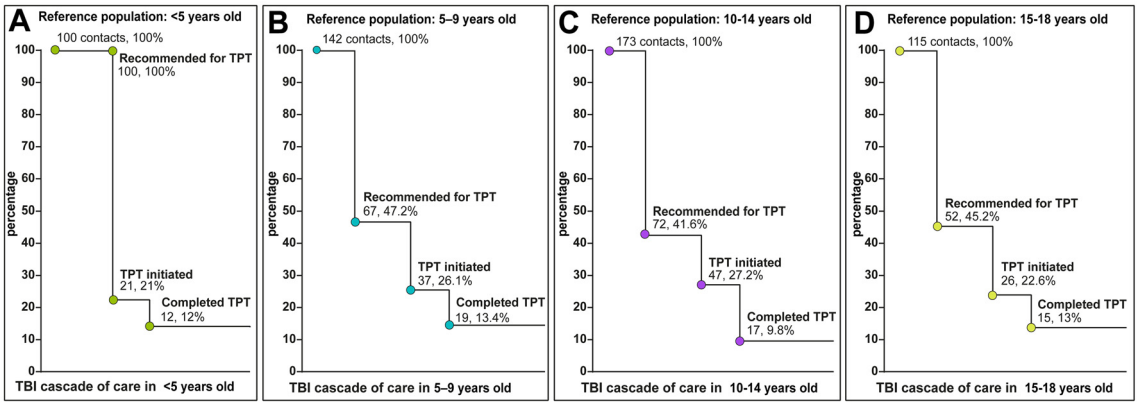

Figure 2. Cascade in TBI care in contacts of TB cases according to the age group. Losses and drop-outs at each stage of the TBI cascade of care in ≤18 years old, percentages were calculated among the number of contacts initially identified in **(A)** <5 years old **(B)** 5–9 years old **(C)** 10–14 years old and **(D)** 15–18 years old. Age categories: based on the previous study.[8] Percentages were calculated among the number of contacts initially identified.

Abbreviations: TB: tuberculosis, TPT: Tuberculosis preventive treatment.

Considering the percentages of losses at each stage of the TBI cascade of care, we evaluated the types of losses in each age group. We found an alarming result, the total loss was significantly higher (88%) in the group of children < 5 years old compared to children 5–9 (39%), 10–14 (39%) and 15–18 years old (44%) ($\chi 2$ p<0.001) (Figure 3E). Furthermore, in the <5-year-old group, 62% did not initiate the recommended TPT, the highest proportion among the four age groups ($\chi 2$ p=0.004) (Figure 3E). Contacts < 5-years-old also more frequently did not perform a second IGRA test (when indicated) (16%) ($\chi 2$ p=0.01). Children 10–14 years of age had a slightly higher proportion of contacts who did not complete the initiated TPT (18%), but it was not statistically significant ($\chi 2$ p=0.58). Due to the number in each age group, we did not perform multivariable analyses for each group.

Discussion

The investigation of close contacts is an important strategy to identify persons with TBI and prevent active TB, which thereby decreases the risk of Mtb transmission. In our cohort of contacts of pulmonary TB index cases, we evaluated losses in the cascade of care among children and adolescents and found a significant loss in the TBI care cascade in children at highest risk of progression to TB—those under 5 years of age (88%). In addition, 62% of these study participants did not initiate TPT, 10% of those who started TPT did not complete the treatment and 16% did not perform the second IGRA test when it was necessary. These findings are of great concern because the greatest focus of screening and tracing of TB contacts should be placed on children during their first 5 years of life, as this is a period of high risk of progression from TBI to active disease. Indeed, the risk of TB incidence among exposed infants and children is very high, reaching 20% within 2 years of exposure.[7,8]

Many previous studies have described the investigation of contacts in children and adults for TBI and TPT,[8,19,22,23] however we have previously demonstrated that the use of the TBI cascade of care can provide a greater depth of understanding of the dynamics of TBI care and follow-up of contacts of TB index cases.[12,13,17] Using the cascade of TBI care in children and adolescents grouped by age and all <18 years, we showed that the greatest loss occurred at the stages of recommendation and initiation of TPT. This finding is consistent with other studies that noted important losses during the first steps of the cascade of care,[24] such as the identification of contacts, initiation of the investigation, and starting TPT.[25] Factors such as lack of knowledge about the risks of TBI in children and adolescents, missed visits, and prolonged treatment, was noted in a recent review of the paediatric TB infection cascade of care.[26] In addition, factors related to health care teams, such as lack of knowledge of protocols and personnel turnover, as well as scarce investments in public health policies, substantially affect the success of TPT.

In Brazil, TPT is recommended for Mtb-infected people, identified through tuberculosis skin test (TST) or IGRA, when they are at risk of developing TB, once active TB is excluded.[6,9] Our study revealed an important gap in the indication of TPT in children and adolescents, and 53.2% of those who initiated TPT did not complete treatment. This proportion was higher than those described in two Brazilian cohorts of children and adolescents:[18] the first reported a dropout rate of TPT of approximately 25%, and the second[19] reported a TPT dropout rate of 27.3%. These differences may be due to the classification of age groups in the studies, and to

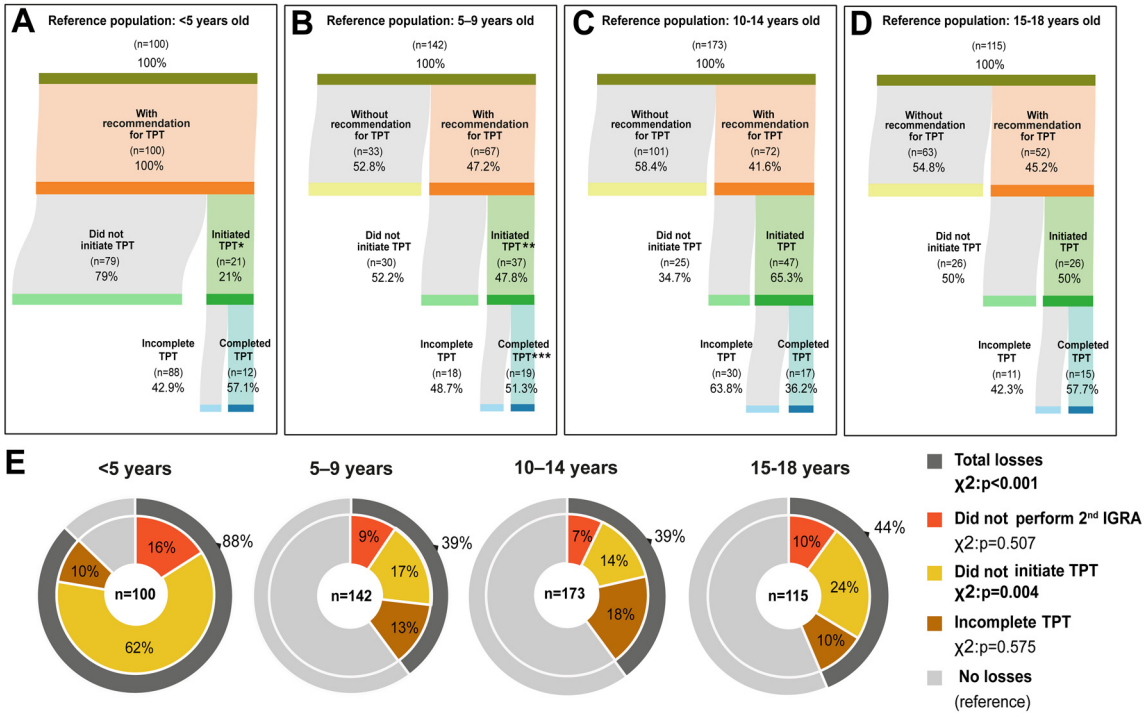

Figure 3. Cascade in TBI care in contacts of TB cases according to TPT recommendation and type of losses in the TBI cascade of care according to the age group. Sankey diagrams display the number of contacts who initiated treatment and those who completed treatment according to the category of TPT recommendation in **(A)** <5 years old **(B)** 5–9 years old **(C)** 10–14 years old and **(D)** 15–18 years old. Age categories: based on the previous study.[8] Percentages were calculated among the number of contacts initially identified. **(E)** Distribution of type of losses in the TBI cascade of care (%) by age groups. The comparisons of IGRA results frequencies (%) between the types of losses were made with the chi-square test (χ^2).

* This group also includes 2 contacts who initiated TPT without recommendation of the RePORT-Brazil medical staff.

**This group includes the 6 contacts who initiated TPT without the recommendation of the RePORT-Brazil medical staff.

*** This group also includes 2 contacts who initiated TPT without recommendation of the RePORT-Brazil medical staff.

Abbreviations: TB: tuberculosis, TPT: Tuberculosis preventive treatment, IGRA: Interferon-Gamma Release Assays.

which population TPT was recommended, since in Brazil the guidelines for recommending TPT varied over the years.[6,9,16] Of note, our findings were consistent with data from migrant populations in high-income countries, highlighted by a recently published meta-analysis demonstrating that only 52% of migrants (adults and children) testing positive for TBI initiated or completed treatment.[27]

TPT with daily isoniazid for 6 to 9 months has been described as cost-effective in children,[28,29] though, recent systematic reviews have identified important factors affecting the initiation and maintenance of TPT, including fear of stigma, knowledge gaps, poor access to tests for the identification of TBI (TST and IGRA,) deficiency in performing chest radiography to identify active TB (before recommending and initiating TPT), the perception of parents or caregivers regarding the risk of TBI, and prolonged treatment regimens.[17,23,26]

Another important result from our study was that the greatest loss in the cascade occurred in children <5 years old; the main component factors a substantial loss in the cascade were not having performed the 2nd IGRA (when negative at baseline) and not having initiated the recommended TPT. This finding is related to what was reported in 2021 by the WHO[2]; there has been slow progress in the detection of paediatric TB in the world, particularly in contacts <5 years old. IGRA testing and initiating and maintaining the TPT require taking children to health centres, which may explain the fear of the caregivers of exposing children to places with increased risk of Mtb infection, with waiting times for care, which are often prolonged due to the poor infrastructure of the health system.[30,31] Additionally, during care of the TB index case, there is often not enough time to correctly explain the importance of ruling out TBI or TPT among contacts.[25,32]

In a previous study, our group showed how the time between the diagnosis of the index TB case and the care of the contact was directly related to completing the care cascade.[12] In the present study, when we assessed the same comparison by age group, we found that among children < 5 years-old there was a statistically significant

association between the delay in screening for TB and loss in the care cascade. This result is relevant because there is evidence that the majority of TB cases among contacts are diagnosed during the first 6 months after the diagnosis of the TB index case.[33–35]

Intriguingly, we identified that contacts <18 years old of TB index cases with characteristics such as being female, having persistent cough, and pulmonary cavitary disease were independent risk factors for losses in the TBI cascade. To our knowledge, there have been no previous studies describing the relationship of these factors with losses in the TBI cascade of care in contacts. Nevertheless, two of these factors are related to increased risk of Mtb transmission to children. Extensive lung disease in the index case, observed on x-ray, has been associated with an increased risk of Mtb infection in contacts,[34] and the duration of cough in the TB index case has also been shown to increase the risk of Mtb transmission to children.[36] We hypothesize that TB index cases who are caregivers of children and present with more severe clinical disease may be less likely to take their children to health care centres to perform TBI screening and to initiate and complete TPT.

This study had several limitations. First, we use a definition of close contacts that made it likely that some people were at low risk of TB infection, yet the definition had the advantage of casting a wide net of people with TB exposure. Paediatricians did not examine all paediatric close contacts enrolled in RePORT-Brazil. In addition, we did not obtain the type and time of exposure of the contacts to the TB index case, which could have affected the number of contacts with a positive IGRA result. We did not assess the parental relationship between the children and the index case, nor whether a TB index case was the primary caregiver of the contacts. In addition, some associations were significant due to the absence of characteristics in some age groups in the study. Furthermore, due to the number of contacts in each age group, it was not possible to perform multivariable analyses in these groups. Finally, we did not collect psychosocial data on the reasons why families did not continue with the follow-up and treatment of children. Despite these limitations, the findings from our multi-centre, prospective cohort study point to a serious situation in the evaluation and treatment of a population at high risk of developing active TB disease, even in high-quality referral centres for TB treatment.

Children and adolescents living in low-income countries face major barriers to completing TBI investigation and treatment. Our findings of losses in the cascade of care of paediatric and adolescent close TB contacts demonstrate the urgent need for enhanced implementation of public health policies already established to optimize screening, diagnosis and treatment of TBI in paediatric TB contacts, particularly those in the first 5 years of life.

Contributors

Conceptualization, T.R.S., M.C.F., M.C.S., V.C.R., and B.B.A.; Data verification and curation, M.B.A., M.A-P., and B.B.A.; Investigation, L.S., M.B.A., M.S.R., M.C.F., B.D., J.R.L.S., A.L.K., S.C., V.C.R., T.R.S., M.C.S., and B.B.A.; Formal analysis, M.B.A., M.A-P., and B.B.A.; Funding acquisition, B.D., J.R.L.S., A.L.K., S.C., V.C.R., T.R.S., M.C.S., M.C.F., and B.B.A.; Methodology, L.S., M.B.A., M.A-P., and B.B.A.; Project administration, M. C.F., T.R.S., and B.B.A.; Resources, M.B.A., T.R.S., and B.B.A.; Software, M.B.A., M.A-P., M.C.F., T.R.S., and B. B.A.; Supervision, T.R.S., and B.B.A.; Writing—original draft, L.S., M.B.A., M.A-P., and B.B.A.; Writing—review and editing, all authors.

Data sharing statement

The data that support the findings of this study will be available upon reasonable request to the corresponding author of the study.

Declaration of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. All other authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lana.2022.100358.

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