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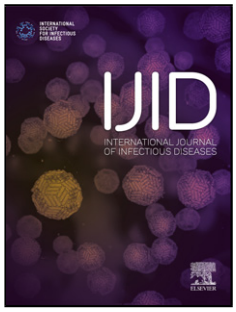

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Pediatric tuberculosis in the metropolitan area of Rio de Janeiro

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Highlights

- Tuberculosis in childhood was until recently considered a neglected disease and many cases are not identified.
- TB screening of children who are close contacts of pulmonary TB cases is recommended by national and international guidelines.
- TB diagnosis in children is hampered by clinical characteristics of TB in this age group and the lack of sensitive and accessible diagnostic methods.
- This is the largest cohort of TB in childhood ever published in Brazil, to our knowledge.
- Rio de Janeiro is the state with the second highest TB incidence rate in Brazil and the highest mortality rate in the country.

What this study adds?

- Opportunities for TB prevention are probably missed among children with TB due to sub-optimal screening of close contacts of patients with PTB.
- Microbiologic diagnosis of TB in children is limited in primary health units in the metropolitan area of Rio de Janeiro, being higher in reference centers.
- Infrequent use of TB drug resistance tests prevents the identification of resistant forms of TB in children.

ABSTRACT

Purpose: to evaluate clinical characteristics, diagnostic approach and treatment outcome of tuberculosis (TB) in children living in a high burden metropolitan area.

Methods: a retrospective study, based on medical chart review, involving children under 15 years old treated for TB from 2007 to 2016, in four primary health units (PHU) and three reference centers (RC) in five cities of Rio de Janeiro metropolitan area. Factors associated with TB treatment setting, microbiological diagnosis and treatment outcome were evaluated.

Results: 544 children were enrolled; 71% were treated at PHU, 36% were under 5 years old and 72% had pulmonary TB (PTB). HIV prevalence was 10% (31/322). Fifty-three percent had at least one microbiological test for TB, 68% of them (196/287) had TB confirmed. Among 222 children with previous TB contact, information on LTBI was available for 78 (35%), and only 17% (13/78) were treated. Extrapulmonary TB (56% vs. 32%), microbiological confirmed TB (77% vs. 60%) and HIV positivity (18.5% vs. 4.0%) were significantly more frequent in RC. Treatment at RC (OR=3.08; 95% CI 1.74-5.44) and PTB (OR=2.47; 95% CI 1.34-4.56) were independently associated with microbiological diagnosis of TB. Treatment success rate was 85%. In the logistic regression, HIV-infected children had a 2.5-fold higher risk of unfavorable outcome (OR= 2.53; 95% CI: 1.0-6.38; p= 0.05).

Conclusion: opportunities of TB prevention and early TB treatment are missed due to suboptimal close contact screening. Microbiological diagnosis of TB and susceptibility drug testing in children should be made available through more sensitive and accessible tests.

Keywords: tuberculosis, latent tuberculosis infection, pediatric tuberculosis, Mycobacterium tuberculosis

INTRODUCTION

Tuberculosis (TB) remains one of the main causes of morbidity and mortality worldwide. Despite advances in TB control in the last decade, Brazil is still among the 30 countries with the highest TB and TB-HIV co-infection burden [1]. In 2019, 73.864 TB cases were reported in Brazil and 4.490 men, women and children died of TB [2]. Globally, 10% of cases (around 1 million), with 239,000 deaths, were estimated to occur in children in 2015, but the situation may be even worse, since pediatric TB deaths is frequently undetected [3]. Children, particularly those under 5 years of age, present a higher risk of rapidly progressing from TB infection to disease and more often develop extrapulmonary and disseminated forms [4,5]. Pediatric studies on TB are scarce in Latin America, and usually based on small size cohorts.

In the present study, we evaluate clinical and epidemiological characteristics, diagnostic approach and treatment outcome of a large cohort of children treated for TB in primary health units (PHU) and reference centers (RC) for TB in the metropolitan area of Rio de Janeiro, the second state in Brazil by number of TB cases in children under 10 (250 cases) in 2019 [2].

A better understanding of these aspects may improve the clinical presumption of TB in children, guiding to correct identification of risk factors and improving the diagnostic approach.

PATIENTS AND METHODS

We performed a retrospective study of children under 15 years of age treated for TB in four PHU and three RC (university hospitals) in five cities of the metropolitan area of Rio de Janeiro, from January 2007 to December 2016, as part of a large collaborative project. All participating units are public institutions of the Brazilian Unified Health System (*Sistema Único de Saúde* - SUS).

Physicians and/or medical students at each participant center reviewed medical charts of TB patients using a standardized collection form. Final data management and review was performed by the study-coordinating center.

Data on sociodemographic characteristics, BCG vaccination status [6], clinical findings, HIV status, TB clinical form, radiological findings, tuberculin skin test (TST), history of contact with pulmonary TB (PTB) case, previous screening for latent TB infection (LTBI) and treatment, diagnostic tests for TB, Brazilian clinical scoring system for TB diagnosis [7], and TB treatment outcome were collected.

Pulmonary TB was defined as the presence of any parenchymal, pleural, intrathoracic or mediastinal lymphadenopathy findings on chest radiograph as described by the attending physician in the medical chart. The chest radiograph description was classified according to Gie [8]. Tuberculin skin testing (TST) consisted of 2 tuberculin units of purified protein derivative (PPD) RT 23 (Statens Serum Institut, Copenhagen, Denmark) applied by the Mantoux method and read after 48-72 hours. The result was considered positive for a skin induration $\geq$ 5 mm. BCG status was confirmed by the presence of a deltoid scar greater than 3mm in the right arm or by checking the vaccination card [7].

Sputum smear microscopy was available in all study sites. MTB culture and drug sensitivity tests were available for the primary units in the central reference laboratory (*Laboratório Central Noel Nutels* – LACEN-RJ) to where the samples were sent and in all university reference centers included in the study. From 2015, X-pert MTB/RIF became available in all sites participating in the study for analysis of sputum samples mainly for children over 10.

TB treatment regimens recommended by the National TB Program (NTP) in Brazil include rifampicin and isoniazid for at least six months with pyrazinamide during the intensive phase (first two months). The use of ethambutol in the intensive phase is recommended for children over 10 years of age in NTP guidelines since 2011. Treatment with rifampicin and isoniazid may be extended in extrapulmonary forms (as in cases of TB meningoencephalitis) or poor treatment response. Treatment regimens for drug resistant TB are made available by NTP according to the drug resistance profile [7].

We used TB treatment outcome definitions from World Health Organization (WHO) [9] and successively grouped them as favorable outcome (TB cure or treatment completed) or unfavorable outcome (treatment failed, death or lost to follow-up).

The database was checked to avoid duplication of cases eventually transferred from PHU to RC. In these cases, the health care setting assigned to the child was the one where the child performed most of the TB treatment.

Statistical analysis

The association of categorical variables with setting of TB treatment (PHU or RC), microbiological diagnosis and TB treatment outcome (favorable or unfavorable) was assessed using the chi-square or Fischer's exact test, when indicated. Non-parametric median test was used to compare continuous variables and the Mann Whitney test to compare age distribution between children with or without microbiologically confirmed TB. The level of significance chosen was 5% (two-tailed p values). Odds Ratio (OR) were calculated and the respective 95% confidence intervals (CI) presented. Multivariate analysis models using logistic regression, by backward stepwise, were constructed to evaluate the variables independently associated with microbiological diagnosis (all the children included) and TB treatment outcome (children transferred out were excluded from the analysis), starting with all variables that resulted statistically significant in the univariate analysis ($p \leq 0.05$) or with a trend toward significant association, plus sex and age. We used the IBM SPSS Statistics program, version 23, for statistical analyses.

Ethical issues

This study was carried out in accordance with Declaration of Helsinki and Resolution 466/12 of the Brazilian National Health Council of the Ministry of Health principles and approved by the Research Ethics Committee of Oswaldo Cruz Institute - Fiocruz (coordinating center) on April 19th, 2017.

RESULTS

Study population

A total of 592 children started anti-TB treatment during the study period. Among them, 48 (8%) were excluded because data on sex, age, TB site and treatment outcome were missing, corresponding to a final sample of 544 children with TB; 92% of the eligible cases. Most children were treated at PHU (71%). Females were 51%, the median age was 84 months (IQR 36-144), 36% were under 5 years of age, and 97% were BCG-vaccinated.

Among 222 children with previous TB contact, information on LTBI was available for 78 (35%), and only 17% (13/78) were treated for LBTI (Table1).

Table 1. Sociodemographic characteristics and data on tuberculosis (TB) prevention among children with TB treated at primary health units (PHU) and reference centers (RC) in the metropolitan area of Rio de Janeiro, Brazil (N = 544).

Characteristic	**Frequency (%)**
Sex Female Male	 276 (50.7) 268 (49.3)
Median age in months (IQR)*	84 (36-144)
Age group (months) 0 – 12 13 – 59 60 – 120 121 – 179	 55 (10.1) 140 (25.7) 169 (31.1) 180 (33.1)
BCG status (n=232) Unvaccinated Vaccinated	 6 (2.6) 226 (97.4)
Previous contact with a pulmonary TB patient (n=323) No Yes	 101 (31.3) 222 (68.7)

Relationship with the TB case (n=222)	
Parents	126 (56.7)
Grandparents	28 (12.6)
Siblings	13 (5.9)
Uncles	26 (11.7)
Cousins	6 (2.7)
Neighbors	4 (1.8)
Others	19 (8.6)
LTBI treatment among those with previous contact with a TB patient (n=78)**	
No	65 (83.3)
Yes	13 (16.7)

** IQR= interquartile range; ** LTBI= latent tuberculosis infection*

Clinical presentation and diagnostic approach

PTB was the most frequent form (72%) and almost all children (98%) underwent chest radiography. Among extrapulmonary TB (EPTB) forms, peripheral lymphadenopathy and pleural TB were the more prevalent (67%). TB meningoencephalitis was diagnosed in 29 children (14%); 62% of them (18 cases) were under 5 years of age. HIV prevalence was 10% (31/322). Among HIV-infected children, information on time of HIV diagnosis was available for 27 (87%): in 22 HIV-infection was diagnosed before TB and in 5 at the time of TB diagnostic investigation. None of HIV-infected children had previous treatment for LTBI registered in the medical chart.

Fifty-three percent of children (287/544) had at least one microbiological test for MTB done (acid-fast bacilli smear, MTB culture or Xpert MTB/RIF). Forty one percent (80/195) of children under 5 years old underwent at least one microbiological test; this percentage was 59% among those over 5 years old (207/349). We did not find a statistically significant difference in age of children with or without a confirmed TB diagnosis (p=0.85). MTB drug susceptibility test was performed on 19% of culture-positive samples (17/90), with a single multidrug-resistant tuberculosis (MDR-TB) child detected. Considering the

children undergoing at least one microbiological/molecular test, 68% (196/287) of TB cases were bacteriologically confirmed. Ninety-three percent of children were treated with a regimen containing rifampicin, isoniazid and pyrazinamide. Although ethambutol use has been recommended in NTP guidelines since 2011 for children older than 10, only 6 children used the ethambutol during the intensive phase. The child with MDR-TB was treated with a six-drug regimen containing three second-line drugs (levofloxacin, ethionamide and terizidone) (Table 2).

Being treated at a RC and presenting PTB (isolated or combined with EPTB forms) were independently associated with microbiological diagnosis in logistic regression analyses (Table 3).

Table 2: Clinical and radiographic characteristics of children with tuberculosis (TB) disease (N=544).

Characteristic	**Frequency (%)**
TB form	
Pulmonary	333 (61.2)
Extrapulmonary	153 (28.1)
Pulmonary + extrapulmonary	58 (10.7)
Extrapulmonary TB sites (n= 211)	
Peripheral lymphadenopathy	85 (40.3)
Pleural	57 (27.0)
Meningoencephalitis	29 (13.7)
Osteoarticular	22 (10.4)
Ocular	4 (1.9)
Cutaneous	2 (0.95)
Abdominal	2 (0.95)
Others	10 (4.7)
HIV test result (n=322)	
Negative	291 (90.4)
Positive	31 (9.6)
Tuberculin skin test response (n=397)	
Negative	81 (20.4)
Positive	316 (79.6)
AFB* result (n=265)	
Negative	96 (36.2)

Positive	169 (63.8)
Culture for MTB (n=127)**	
Negative	37 (29.1)
Positive	90 (70.9)
Xpert MTB/RIF findings (n=6)	
Undetectable	3 (50.0)
Detectable and sensitive to rifampicin	3 (50.0)
MTB drug resistance profile (n= 17)	
Sensitive	14 (85)
Resistant to streptomycin	2 (10)
MDR-TB	1 (5)
Microbiological diagnosis by baciloscopy, culture or X-pert MTB/RIF (n=287)	
Negative	91 (31.7)
Positive	196 (68.3)
Median age in months (IQR) # according to microbiological diagnosis status (n=287)# #	
Confirmed	119 (49 – 156)
Not confirmed	120 (60 – 156)
TB diagnosis based on scoring system (n= 122) * **	
Very likely (≥ 40)	96 (78.7)
Possible (30 to 39)	24 (19.7)
Unlikely (< 29)	2 (1.6)
Findings on chest radiography (n= 374)	
Normal	36 (9.7)
Unilateral pulmonary involvement, non cavitary	119 (31.9)
Cavitary lesions	52 (13.9)
Hilar/mediastinal adenopathy	48 (12.9)
Bilateral pulmonary involvement, non cavitary	43 (11.5)
Pleural effusion	39 (10.5)
Miliary pattern	6 (1.6)
Other radiologic findings	30 (8.0)
Treatment regimen (n=528)	
2HRZ/4HR	498 (94.3)
2HRZE/4HR	6 (1.1)
2HRZ/7HR	20 (3.8)
2HZES/10HE	2 (0.4)
3SEO/9EO	1 (0.2)
SLfxEtoTrdEP (MDR-TB case)	1 (0.2)

**AFB= acid fast bacilli; **MTB= Mycobacterium tuberculosis; E= ethambutol; Eto= Ethionamide; H= isoniazid; Lfx= Levofloxacin; O= Ofloxacin; R= rifampicin; S= streptomycin; Trd=Terizidone; Z= pyrazinamide. MDR-TB= multidrug-resistant tuberculosis*

**** National Tuberculosis Program guideline. Ministry of Health, 2011.# IQR= interquartile range ## p=0.85, Mann Whitney test.*

Table 3. Uni and multivariate analysis to assess the association between sociodemographics and clinical variables with microbiological diagnosis *(AFB, Culture,* Xpert MTB/RIF*)* of tuberculosis (TB).

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value
Age (months)	1.0 (0.9-1.0)	0.64		
Reference center	2.2 (1.3-3.7)	0.002	3.08 (1.74-5.44)	< 0.001
HIV positivity	0.5 (0.2-1.1)	0.12	-	-
Males	0.7 (0.4-1.1)	0.13	0.60 (0.35-1.03)	0.06
Pulmonary/Combined TB presentation	1.9 (1.1-3.2)	0.04	2.47 (1.34-4.56)	0.004
Cavitary lesion	1.98 (0.95 – 4.13)	0.08	-	-
Expectoration	1.5 (0.7-3.5)	0.43	-	-

OR= odds ratio.

Sociodemographic and clinical characteristics of children with TB treated at PHU and RC

We observed significant difference regarding age groups, sex, TB forms, confirmed TB cases and HIV infection among patients treated in PHU and RC (Table 4). Extrapulmonary TB (56% vs. 32%), microbiological confirmed TB (77% vs. 60%) and HIV positivity (18.5% vs. 4.0%) were significantly more frequent in RC.

Table 4. Univariate analysis of sociodemographic and clinical characteristics of children with tuberculosis (TB) treated at primary health units (PHU) and reference centers (RC)

Variables	PHU n= 384 n (%)	RC n= 160 n (%)	p value
Age group (months) 0 – 12 13 – 60 61 – 120 121 - 179	 35 (9.1) 123 (32.0) 88 (22.9) 138 (35.9)	 20 (12.5) 42 (26.3) 56 (35.0) 42 (26.3)	0.008
Median age (months)(IQR)*	90 (36 - 144)	84 (42 - 130)	0.15
Female	210 (54.7)	66 (41.2)	0.005
TB site Pulmonary Extra-pulmonary Combined	 262 (68.2) 95 (24.7) 27 (7.0)	 71 (44.4) 58 (36.2) 31 (19.4)	< 0.001
HIV test positivity (n=322)	8/198 (4.0)	23/124 (18.5)	< 0.001
Diagnosis by any laboratory method (baciloscopy, culture, Xpert MTB/RIF) (n=287)	89 (60.1)	107 (77.0)	0.04

**IQR= interquartile range; Median test.*

TB treatment outcome

TB treatment success rate was 85%, reaching 89% (460/516) when we excluded children transferred to another health unit. The percentage of children lost to follow-up was 9% and 7 children (1%) died because of TB (including the child with MDR-TB). Among these children, all but one had PTB (1 child had TB meningitis), 3 children were under 5 and 1 patient was HIV-infected.

Children treated at PHU had significantly higher rate of treatment success (88% vs. 76% in RC). However, when we analyzed the factors associated with a favorable outcome, excluding 28 (5%) patients transferred out, no significant difference in outcome between sites was observed. In logistic

regression, HIV infection was the only variable independently associated with treatment outcome. HIV-infected children had a 2.5-fold higher risk of unfavorable outcome than HIV-uninfected patients (OR= 2.53; 95% CI: 1.0-0.638; p= 0.05) (Table 5).

Table 5. Univariate analysis of clinical characteristics associated with treatment outcome of children with tuberculosis (TB) treated at primary health units (PHU) and reference centers (RC).*

Variables	Favourable outcome n=460 n (%)	Unfavourable outcome n=56 n (%)	OR (95% CI)	p value
Site of TB treatment				
PHU	338 (90.6)	35 (9.4)	1	0.11
RC	122 (85.3)	21 (14.7)	1.66 (0.93 – 2.97)	
Age group (months)				
0 – 12	42 (80.8)	10 (19.2)	1	
13 – 60	146 (91.8)	13 (8.2)	0.37 (0.15 – 0.91)	0.03
61 – 120	123 (91.8)	11 (8.2)	0.38 (0.15 – 0.95)	0.04
121 - 179	149 (87.1))	22 (1.9)	0.62 (0.27 – 1.41)	0.25
Sex				
Female	240 (90.6)	25 (9.4)	1	0.32
Male	220 (87.6)	31 (12.4)	1.35 (0.77 – 2.36)	
TB site				
Pulmonary	281 (88.4)	37 (11.6)	1	
Extra-pulmonary.	131 (91.6)	12 (8.4)	0.70 (0.35 – 1.38)	
Combined	48 (87.3)	7 (12.7)	1.11 (0.47 – 2.63)	
HIV test result (n=309)				
Negative	249 (89.2)	30 (10.8)	1	0.07
Positive	23 (76.7)	7 (23.3)	2.53 (1.0 – 6.38)	
TB diagnosis by any microbiological method (n=271)				
No	72 (85.7)	12 (14.3)	1	0.56
Yes	165 (88.2)	22 (11.8)	0.80 (0.38 – 1.70)	

Cavitation on chest-radiograph (n=396) No Yes	 310 (89.9) 48 (94.4)	 35 (10.1) 3 (5.9)	 1 0.55 (0.16 – 1.87)	 0.45

** Children transferred out were excluded from the analysis. OR= odds ratio.*

DISCUSSION

Here we present the results of a cohort of pediatric TB patients that, to our knowledge, is the largest ever published in Brazil. This cohort of children with active TB was diagnosed and treated in PHU and RC in the metropolitan area of Rio de Janeiro, the second city by TB incidence rate in Brazil (93.7 cases/100,000 inhabitants) and the first one by mortality rate (4.3 deaths/100,000 inhabitants) [2].

Notwithstanding the retrospective nature of the study does not allow us to state that the low percentage (17%) of children undergoing LTBI treatment among those with a previous TB contact is a consequence of failures in contact screening, this actually may have occurred. LTBI treatment of children with close contact with PTB patients is a public health priority. WHO recommends that contacts under 5 years old be treated for LTBI once active TB is excluded [10]. NTP in Brazil recommends that children under 10 years old who are household contact of PTB cases be evaluated and, if TST-positive and since active TB is excluded, should be treated for LTBI. However, in practice, contact investigation is performed sub-optimally. In 2019, the proportion of contacts evaluated in Brazil was 55%, being 37% in the city of Rio de Janeiro [2]. LTBI management among

contacts is one of the global target included in the End TB strategy as well as in the NTP in Brazil [11,12].

A large majority of children had PTB; peripheral lymphadenopathy and pleural disease were the most frequent EPTB forms. TB meningoencephalitis (a threatening consequence of hematogenous MTB dissemination) represented 14% of EPTB cases in our sample and mainly affected under-five children, as described in the literature [5,13].

The prevalence of HIV infection was 10% amongst children with TB in our cohort. However, more than 40% of patients were not HIV-tested even though testing is recommended by the Brazilian NTP since 2011 [7]. In our study, the prevalence of TB-HIV co-infection was higher in RC (18.5% vs. 4%). RC have better diagnostic and management resources, therefore more complex, difficult-to-manage TB cases are usually referred to RC, such in cases of EPTB and HIV co-infection. In the retrospective study by Matos et al. (2012) [14], performed at a reference hospital for pediatric HIV patients in Rio de Janeiro, 56% of TB patients were tested for HIV and 17% of them resulted HIV-infected. Dos Santos Dias et al (2015) [15], analyzing data from the Brazilian TB notification system between 2007-2011, reported a national HIV seroprevalence of 12% among TB patients under 15 years old, similar to that we found. Early identification of HIV infection in children with TB allows treatment of both diseases be tailored considering the possibility of antiretroviral and anti-TB drugs interaction, higher incidence of adverse drug events and the risk of immune reconstitution syndrome [16,17]. It should also be noted that there was no record of previous LTBI treatment among HIV-infected children, although these children represent a priority group for the preventive TB treatment [10]. However, it is possible that the information has not

been recorded in the medical chart of TB treatment, as some children with HIV infection identified before TB diagnosis were followed up at another medical service for the care of HIV infection.

Microbiological confirmation of TB diagnosis in children remains a challenge to overcome. The paucibacillary TB in children and the difficulties in obtaining an appropriate respiratory sample (especially among the youngest) limit microbiological confirmation in children [20,21]. In our sample, over half (53%) of the children diagnosed with active TB underwent a microbiological or molecular test for TB, but MTB culture was performed in only 23%. However, among children undergoing a microbiological test, 68% had a positive result, a percentage much higher than that described in other low-middle income countries, where TB diagnosis of the vast majority of children is based only on clinical and radiological findings [18,19]. The high yield of microbiological diagnosis of TB in our sample may have been a consequence of more severe forms of TB in our children and/or availability of better diagnostic resources and laboratory support in RC. However, it is noteworthy that the Brazilian Notifiable Diseases Information System (SINAN) in 2019 registered that 67% (748/1110) of PTB cases under 15 years old who undergone diagnostic test had TB confirmed by AFB smear, MTB culture or X-pert MTB/RIF (SINAN/Ministry of Health. May/2020; data not published).

The low proportion of patients undergoing MTB culture explains, at least in part, why only 17 children had drug susceptibility testing. On the other hand, during the study period Xpert MTB/RIF was used in only 6 children, and 3 tested positive and sensitive to rifampicin. Therefore, the single MDR-TB case diagnosed is probably under-estimating the problem of drug resistance as

according to WHO estimates, rifampicin-resistant/MDR-TB cases may represent 1.5% of new cases and up to 8% of previously treated TB cases diagnosed in Brazil [1].

In this scenario, scoring systems for diagnosis of PTB in children represent a widely used resource in Brazil. Since 2002, Brazilian NTP has recommended the scoring system for the diagnosis of intrathoracic TB in children and adolescents with microbiological tests not performed or initially negative [22]. The high accuracy of this scoring system has been described by several authors, both in HIV-infected and not infected children [23–27]. In our study, the score result was recorded only for 22% of children, and the vast majority had a score higher than 30 (TB diagnosis probable or very likely). However, clinical experience makes us suppose that the score parameters were taken into consideration by physicians at the time of TB diagnosis in children, although not registered in the medical records.

We observed a high treatment success rate in the overall sample (85%), lower than that described by European countries (88% - 100%) [28-30], but higher than found in some African countries (around 77%) [31-32]. The mortality rate found in our study (1%) is comparable to the case fatality rate described by Jenkins et al in countries with low HIV prevalence (0.9%) [33]. In multivariate analysis, HIV infection was the only variable independently associated with treatment outcome, with a risk of unfavorable outcome 2.5 times higher among children HIV-infected. Children with TB-HIV co-infection or unknown HIV status have higher risk of death, adverse drug reaction and default to treatment [16,33,34]. Similar results were described in Brazil, where TB-HIV co-infected

children were more likely to be institutionalized, readmitted after treatment default and have unfavorable outcomes (default and death) [15].

Our study has in-built limitations related to its retrospective design (data quality and completeness), that may have biased some findings [35]. However, the study enabled to implement a collaborative network between PHU and RC caring for children with TB and describe a large cohort representative of high TB burden areas in the metropolitan area of Rio de Janeiro. Our results underscore the need and use for more accessible and sensitive diagnostic resources for TB in children, as well as it is urgent to prioritize the screening of children who are close contacts of PTB, mainly if HIV-infected, under an appropriate diagnostic and therapeutic cascade for active and latent TB in Rio de Janeiro. We hope that the data presented here will contribute to design prospective, quality observational studies involving children with presumptive TB, with special focus on new TB diagnostic tests and children-friendly anti-TB drug formulations.

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Author's contribution

ACCC designed the study, the analysis plan and wrote the first draft of the manuscript. PSM, CAAC, TM and CCS coordinated data collection at the study sites. ACCC, PSM, LS and GS did the statistical analyses. All authors interpreted data, critically reviewed and approved the final version of the manuscript.

Declaration of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Ethical approval

The study was approved by the Research Ethics Committee of Oswaldo Cruz Institute - Fiocruz (coordinating center) on April 19th, 2017.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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