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Pediatric tuberculosis in the metropolitan area of Rio de Janeiro

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ABSTRACT

Aim: To evaluate the clinical characteristics, diagnostic approach, and treatment outcomes of tuberculosis (TB) in children living in a high-burden metropolitan area.
Methods: This was a retrospective study, based on a medical chart review, involving children under 15 years old treated for TB between 2007 and 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 outcomes were evaluated.
Results: A total of 544 children were enrolled; 71% were treated in PHU, 36% were under 5 years old, and 72% had pulmonary TB (PTB). The 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%), microbiologically confirmed TB (77% vs 60%), and HIV positivity (18.5% vs 4.0%) were significantly more frequent in RC. Treatment in RC (odds ratio (OR) 3.08, 95% confidence interval (CI) 1.74–5.44) and PTB (OR 2.47, 95% CI 1.34–4.56) were independently associated with a microbiological diagnosis of TB. The treatment success rate was 85%. In the logistic regression analysis, HIV-infected children had a 2.5-fold higher risk of an unfavorable outcome (OR 2.53, 95% CI 1.0–6.38; $p = 0.05$).
Conclusions: Opportunities for TB prevention and early TB treatment are missed due to suboptimal close contact screening. Microbiological diagnosis of TB and drug susceptibility testing in children should be made available through more sensitive and accessible tests.

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What this study adds?

- Opportunities for tuberculosis (TB) prevention are probably missed among children with TB due to suboptimal screening of close contacts of patients with pulmonary TB.
- Microbiological 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.

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 (World Health Organization WHO, 2019). In 2019, 73 864 cases of TB were reported in Brazil and 4490 men, women, and children died of TB (Brasil, 2020). 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 are frequently undetected (Dodd et al., 2017). 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 (Newton et al., 2008; Marais et al., 2004). Pediatric studies on TB are scarce in Latin America, and usually based on small-size cohorts.

In this study, clinical and epidemiological characteristics, diagnostic approaches, and treatment outcomes were evaluated in 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 years of age (250 cases) in 2019 (Brasil (2020)).

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

Patients and methods

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, was performed 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 participating center reviewed the medical charts of TB patients using a standardized collection form. Final data management and review was performed by the study-coordinating center.

Data on socio-demographic characteristics, bacille Calmette–Guérin (BCG) vaccination status (Fundação Ataulpho de Paiva, 2019), clinical findings, HIV status, TB clinical form, radiological findings, tuberculin skin test (TST), history of contact with a pulmonary TB (PTB) case, previous screening for latent TB infection (LTBI) and treatment, diagnostic tests for TB, Brazilian clinical scoring system for TB diagnosis (Brasil, 2011), and TB treatment outcome were collected.

PTB was defined as the presence of any parenchymal, pleural, intrathoracic, or mediastinal lymphadenopathy findings on a chest radiograph, as described by the attending physician in the medical chart. The chest radiograph description was classified according to Gie (Gie, 2003). The TST consisted of 2 tuberculin units (TU) of purified protein derivative (PPD) RT 23 (Statens Serum Institut, Copenhagen, Denmark) applied by Mantoux method and read after 48–72 h. 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 3 mm on the right arm, or by checking the vaccination card (Brasil, 2011).

Sputum smear microscopy was available at all study sites. For the primary health units, *Mycobacterium tuberculosis* (MTB) culture and drug sensitivity testing were available at the central reference laboratory (Laboratório Central Noel Nutels — LACEN-RJ) to where the samples were sent; these tests were also available in all university reference centers included in the study. From 2015, Xpert MTB/RIF became available at all sites participating in the study for the analysis of sputum samples, mainly for children over 10 years of age.

TB treatment regimens recommended by the National TB Program (NTP) in Brazil include rifampicin and isoniazid for at least 6 months, with pyrazinamide during the intensive phase (first 2 months). The use of ethambutol in the intensive phase has been recommended for children over 10 years of age in the NTP guidelines since 2011. Treatment with rifampicin and isoniazid may be extended in extrapulmonary forms (as in cases of TB meningoencephalitis) or a poor treatment response. Treatment regimens for drug-resistant TB are made available by the NTP according to the drug resistance profile (Brasil, 2011).

In this study, World Health Organization (WHO) definitions of TB treatment outcomes were used (World Health Organization WHO, 2013); outcomes were successively grouped as favorable (TB cure or treatment completed) or unfavorable (treatment failed, death, or lost to follow-up).

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

Statistical analysis

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

Ethical issues

This study was conducted in accordance with the Declaration of Helsinki and Resolution 466/12 of the Brazilian National Health Council of the Ministry of Health principles and was approved by the Research Ethics Committee of Oswaldo Cruz Institute — Fiocruz (coordinating center) on April 19, 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, or treatment outcome were missing, resulting in a final sample of 544 children with TB (92% of the eligible cases). Most children were treated in PHU (71%). Fifty-one percent were female. The median age of the children was 84 months (interquartile range (IQR) 36–144 months) and 36% were under 5 years of age. The majority (97%) had received the BCG vaccination.

Among the 222 children with previous TB contact, information on LTBI was available for 78 (35%), and only 17% (13/78) had been treated for LTBI (Table 1).

Clinical presentation and diagnostic approach

PTB was the most frequent form (72%), and almost all children (98%) underwent chest radiography. Among the 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 the HIV-infected children, information on the time of HIV diagnosis was available for 27 (87%): HIV infection had been diagnosed before TB in 22 children and at the time of TB diagnostic investigation in five. None of the 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 bacillus (AFB) 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). No statistically significant difference in age between children with and without a confirmed TB diagnosis was found ($p = 0.85$). MTB drug susceptibility testing was performed on 19% of culture-positive samples (17/90), with a single child with multidrug-resistant TB (MDR-TB) 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 years, only six children used 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 a microbiological diagnosis in the logistic regression analyses (Table 3).

Socio-demographic and clinical characteristics of children with TB treated in PHU and RC

We observed significant differences in age groups, sex, TB forms, confirmed TB cases, and HIV infection between patients treated in PHU and those treated in RC (Table 4). EPTB (56% vs 32%), microbiologically confirmed TB (77% vs 60%), and HIV positivity (18.5% vs 4.0%) were significantly more frequent in RC.

TB treatment outcomes

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

Children treated in PHU had a significantly higher rate of treatment success (88% vs 76% in RC). However, when the factors associated with a favorable outcome were analyzed, excluding 28 (5%) patients transferred out, no significant difference in outcomes between the sites was observed (Table 5). In logistic regression, HIV infection was the only variable independently associated with the treatment outcome when controlled by age and sex: HIV-infected children had a 2.5-fold higher risk of unfavorable outcome than HIV-uninfected patients (OR 2.53, 95% CI 1.0–6.38; $p = 0.05$.

Table 1
Socio-demographic characteristics and data on TB prevention among children with TB treated in primary health units and reference centers in the metropolitan area of Rio de Janeiro, Brazil ($N = 544$).

Characteristic	Frequency (%)
Sex	
Female	276 (50.7)
Male	268 (49.3)
Median age in months (IQR)	84 (36–144)
Age group (months)	
0–12	55 (10.1)
13–59	140 (25.7)
60–120	169 (31.1)
121–179	180 (33.1)
BCG status ($n = 232$)	
Unvaccinated	6 (2.6)
Vaccinated	226 (97.4)
Previous contact with a pulmonary TB patient ($n = 323$)	
No	101 (31.3)
Yes	222 (68.7)
Relationship with the TB case ($n = 222$)	
Parent	126 (56.7)
Grandparent	28 (12.6)
Sibling	13 (5.9)
Aunt/uncle	26 (11.7)
Cousin	6 (2.7)
Neighbor	4 (1.8)
Other	19 (8.6)
LTBI treatment among those with previous contact with a TB patient ($n = 78$)	
No	65 (83.3)
Yes	13 (16.7)

BCG, bacille Calmette–Guérin; IQR, interquartile range; LTBI, latent tuberculosis infection; TB, tuberculosis.

Discussion

Here we present the results of a cohort of pediatric TB patients that appears to be 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 fourth one by mortality rate (4.6 deaths/100 000 inhabitants) (Brasil, 2020).

Although the retrospective nature of this 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. The WHO recommends that contacts under 5 years old be treated for LTBI once active TB is excluded (World Health Organization WHO, 2018). The NTP in Brazil recommends that children under 10 years old who are household contacts of PTB cases be evaluated, and that if they test TST-positive and active TB is excluded, they should be treated for LTBI. However, in practice, contact investigation is suboptimal. In

Table 2
Clinical and radiographic characteristics of children with 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)
Other	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 smear microscopy, culture, or Xpert MTB/RIF ($n = 287$)	
Negative	91 (31.7)
Positive	196 (68.3)
Median age in months (IQR) according to microbiological diagnosis status ($n = 287$)[a]	
Confirmed	119 (49–156)
Not confirmed	120 (60–156)
TB diagnosis based on scoring system ($n = 122$)[b]	
Very likely (≥40)	96 (78.7)
Possible (30–39)	24 (19.7)
Unlikely (<29)	2 (1.6)
Findings on chest radiography ($n = 373$)	
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 radiological 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)
SLfxEtoTrdEZ (MDR-TB case)	1 (0.2)

AFB, acid-fast bacilli; E, ethambutol; Eto, ethionamide; H, isoniazid; IQR, interquartile range; Lfx, levofloxacin; MDR-TB, multidrug-resistant tuberculosis; MTB, *Mycobacterium tuberculosis*; O, ofloxacin; R, rifampicin; S, streptomycin; TB, tuberculosis; Trd, terizidone; Z, pyrazinamide.

[a] $p = 0.85$, Mann–Whitney test.

[b] National Tuberculosis Program guideline. Ministry of Health, 2011.

2019, the proportion of contacts evaluated in Brazil was 55%, being 37% in the city of Rio de Janeiro (Brasil, 2020). LTBI management among contacts is one of the global targets included in the End TB Strategy, as well as in the NTP in Brazil (WHO, 2015; Brasil, 2017).

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 this sample and mainly affected children under 5 years old, as described in the literature (Marais et al., 2004; Cruz and Starke, 2010).

The prevalence of HIV infection was 10% amongst children with TB in this cohort. However, more than 40% of patients had not been tested for HIV even though testing has been recommended by the Brazilian NTP since 2011 (Brasil, 2011). In this study, the prevalence of TB–HIV co-infection was higher in RC (18.5% vs 4% in PHU). RC have better diagnostic and management resources, therefore more complex, difficult-to-manage TB cases are usually referred to RC, such as cases with EPTB and HIV co-infection. In the retrospective study by Matos et al. (2012), 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 were found to be HIV-infected. Dos Santos Dias et al. (2015), analyzing data from the Brazilian TB notification system between 2007 and 2011, reported a national HIV seroprevalence of 12% among TB patients under 15 years old, similar to that found in the present study. Early identification of HIV infection in children with TB allows the treatment of both diseases to be tailored, considering the possibility of antiretroviral and anti-TB drug interactions, higher incidence of adverse drug events, and the risk of immune reconstitution syndrome (Kay et al., 2018; Venturini et al., 2014). 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 TB preventive treatment (World Health Organization WHO, 2018). However, it is possible that the information had not been recorded in the medical chart for 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 a TB diagnosis in children remains a challenge to overcome. The paucibacillary TB in children and the difficulties in obtaining an appropriate respiratory sample (especially from the youngest) limit microbiological confirmation in children (Perez-Velez and Marais, 2012; Cuevas et al., 2012). 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 (Du Preez et al., 2018; Moon et al., 2019). The high yield of microbiological diagnosis of TB in this sample may have been a consequence of more severe forms of TB in these children and/or the 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 had undergone a diagnostic test had TB confirmed by AFB smear, MTB culture, or Xpert 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 six children, and three 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 (World Health Organization WHO, 2019).

In this scenario, scoring systems for the diagnosis of PTB in children represent a widely used resource in Brazil. Since 2002, the

Table 3
Univariate and multivariate analysis to assess the association between socio-demographic characteristics and clinical variables with microbiological diagnosis (AFB, culture, Xpert MTB/RIF) of 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	–	–
Male sex	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	–	–

AFB, acid-fast bacilli; CI, confidence interval; OR, odds ratio; TB, tuberculosis.

Table 4
Univariate analysis of socio-demographic and clinical characteristics of children with 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)			0.008
0–12	35 (9.1)	20 (12.5)	
13–60	123 (32.0)	42 (26.3)	
61–120	88 (22.9)	56 (35.0)	
121–179	138 (35.9)	42 (26.3)	
Median age (months) (IQR)	90 (36–144)	84 (42–130)	0.15
Female	210 (54.7)	66 (41.2)	0.005
TB site			<0.001
Pulmonary	262 (68.2)	71 (44.4)	
Extrapulmonary	95 (24.7)	58 (36.2)	
Combined	27 (7.0)	31 (19.4)	
HIV test positivity (*n* = 322)	8/198 (4.0)	23/124 (18.5)	<0.001
Diagnosis by any laboratory method (smear microscopy, culture, Xpert MTB/RIF) (*n* = 287)	89 (60.1)	107 (77.0)	0.04

IQR, interquartile range, median test; TB, tuberculosis.

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 (Brasil, 2002). The high accuracy of this scoring system has been described by several authors, both in HIV-infected and not infected children (Sant'Anna et al., 2006; Edwards et al., 2007; Pedrozo et al., 2009; Pearce et al., 2012; David et al., 2017). In the present study, the score result was recorded for only 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.

Table 5
Univariate analysis of clinical characteristics associated with treatment outcomes in children with TB treated in primary health units (PHU) and reference centers (RC)[a].

Variables	Outcome		OR (95% CI)	*p*-Value
	Favorable *n* = 460 *n* (%)	Unfavorable *n* = 56 *n* (%)		
Site of TB treatment				
PHU	338 (90.6)	35 (9.4)	1	
RC	122 (85.3)	21 (14.7)	1.66 (0.93–2.97)	0.11
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	
Male	220 (87.6)	31 (12.4)	1.35 (0.77–2.36)	0.32
TB site				
Pulmonary	281 (88.4)	37 (11.6)	1	
Extrapulmonary	131 (91.6)	12 (8.4)	0.70 (0.35–1.38)	0.30
Combined	48 (87.3)	7 (12.7)	1.11 (0.47–2.63)	0.82
HIV test result (*n* = 309)				
Negative	249 (89.2)	30 (10.8)	1	
Positive	23 (76.7)	7 (23.3)	2.53 (1.0–6.38)	0.07
TB diagnosis by any microbiological method (*n* = 271)				
No	72 (85.7)	12 (14.3)	1	
Yes	165 (88.2)	22 (11.8)	0.80 (0.38–1.70)	0.56
Cavitation on chest-radiograph (*n* = 396)				
No	310 (89.9)	35 (10.1)	1	
Yes	48 (94.4)	3 (5.9)	0.55 (0.16–1.87)	0.45

CI, confidence interval; OR, odds ratio; TB, tuberculosis.
[a] Children transferred out were excluded from the analysis.

We observed a high treatment success rate in the overall sample (85%), lower than that described by European countries (88–100%) (Abubakar et al., 2008; Ziemele et al., 2017; Gafar et al., 2019), but higher than that reported from some African countries (around 77%) (Flick et al., 2016; Wobudeya et al., 2017). The mortality rate in this study (1%) is comparable to the case fatality rate described by Jenkins et al. in countries with low HIV prevalence (0.9%) (Jenkins et al., 2017). In the multivariate analysis, HIV infection was the only variable independently associated with the treatment outcome, with a risk of unfavorable outcome 2.5 times higher among children infected with HIV. Children with TB–HIV co-infection or unknown HIV status have a higher risk of death, adverse drug reactions, and treatment default (Kay et al., 2018; Jenkins et al., 2017; Mirutse et al., 2019). Similar results have been described in Brazil, where TB–HIV co-infected children are more likely to be institutionalized, readmitted after treatment default, and to have unfavorable outcomes (default and death) (Dos Santos Dias et al., 2015).

This study has in-built limitations related to its retrospective design (data quality and completeness), that may have biased some findings (Campbell et al., 2020). However, the study enabled a collaborative network between PHU and RC caring for children with TB to be implemented and a large cohort representative of high TB burden areas in the metropolitan area of Rio de Janeiro to be described. The results underscore the need for more accessible and sensitive diagnostic resources for TB in children, as well as the urgent

need to prioritize the screening of children who are close contacts of PTB cases, 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 the design of prospective, quality observational studies involving children with presumptive TB, with a special focus on new TB diagnostic tests and child-friendly anti-TB drug formulations.

Authors' contributions

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

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Ethical approval

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

Conflict of interest

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

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