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## ORIGINAL ARTICLE

# Tuberculosis among young contacts of patients with multidrug-resistant pulmonary tuberculosis in a reference hospital

Q2 Evelyn F. Rubin <sup>a</sup>, Sheila C. Lucena <sup>b</sup>, Marcela Bhering <sup>c,\*</sup>, Lorrayne Gonçalves <sup>d</sup>, Fabiana Falcão <sup>d</sup>, Margareth Dalcomi <sup>c</sup>, Giovanni B. Migliori <sup>e</sup>, Laura Saderi <sup>f</sup>, Giovanni Sotgiu <sup>f</sup>, Afrânio Kritski <sup>a</sup>, Anna C.C. Carvalho <sup>d</sup>

Q3 <sup>a</sup> Universidade Federal do Rio de Janeiro (UFRJ), Faculdade de Medicina, Programa Acadêmico de Tuberculose, Rio de Janeiro, Rio de Janeiro, Brazil

<sup>b</sup> Secretaria Municipal de Saúde do Rio de Janeiro, Hospital Municipal Raphael de Paula Souza, Rio de Janeiro, Rio de Janeiro, Brazil

<sup>c</sup> Fundação Oswaldo Cruz, Escola Nacional de Saúde Pública, Centro de Referência Professor Hélio Fraga, Rio de Janeiro, Rio de Janeiro, Brazil

<sup>d</sup> Laboratory of Innovations in Therapies, Education and Bioproducts (LITEB), Oswaldo Cruz Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Rio de Janeiro, Brazil

<sup>e</sup> Maugeri Clinical Institutes IRCCS, Clinical Epidemiology Service for Respiratory Diseases, Maugeri, Italy

<sup>f</sup> University of Sassari, Department of Medical, Surgical and Experimental Sciences, Clinical Epidemiology and Medical Statistics Unit, Sassari, Italy

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### KEYWORDS

Tuberculosis;  
Multidrug-resistant tuberculosis;  
Contact tracing;  
Children;  
Adolescent

### Abstract

**Objectives:** Young contacts of pulmonary tuberculosis (TB) patients face a higher risk of TB. Still, few studies have evaluated this risk among contacts of patients with pulmonary multidrug-resistant tuberculosis (MDR-TB). This study aimed to describe the incidence rate and the prevalence of TB infection (TBI) and TB disease (TBD) in young contacts of patients with MDR-TB.

**Methods:** The authors retrospectively evaluated contacts of patients with pulmonary TB aged 0 to 19 for TBI and TBD in Rio de Janeiro between 2006 and 2016. Based on the drug susceptibility pattern and/or therapeutic regimen of the index case, contacts were classified into MDR-TB and non-MDR-TB contacts. A tuberculin skin test  $\geq 5$  mm was considered positive. Preventive therapy with isoniazid was offered to eligible contacts. Bivariate and multivariate logistic regressions estimated factors associated with TBI.

**Results:** 439 contacts were screened; 129 were MDR-TB and 310 were non-MDR-TB contacts. TBI prevalence was 68.2% in MDR-TB vs. 61.9% in non-MDR contacts ( $p = 0.23$ ). Tuberculin conversion was higher among MDR-TB contacts (45.5% vs 17.1%;  $p = 0.04$ ). TBD incidence rate was 47.7 in non-MDR and 179.6 per 100,000 person-months in MDR-TB contacts ( $p = 0.65$ ), for a total TBD

\* Corresponding author.

E-mail: marbhering@gmail.com (M. Bhering).

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prevalence of 2.5%. The overall TPT completion rate was 67.2%; 71.5% in non MDR-TB and 59% in MDR-TB contacts ( $p = 0.04$ ).

**Conclusion:** The authors identified a high prevalence of TBI among contacts of pulmonary MDR and non-MDR-TB patients, with a higher tuberculin conversion rate in MDR-TB ones, highlighting the urgency of effective TPT regimens for young contacts of patients with pulmonary MDR-TB.

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## 1 Introduction

2 The presence of *Mycobacterium tuberculosis* (MTB) strains  
3 resistant to the most effective anti-tuberculosis (TB) drugs  
4 poses a significant threat to the elimination of TB.<sup>1,2</sup> Globally,  
5 it is estimated that 400,000 people were diagnosed  
6 with rifampicin-resistant TB (RR-TB) or with multidrug-resistant  
7 TB (MDR-TB, i.e., resistant to at least rifampicin and  
8 isoniazid).<sup>2</sup> In Brazil, between 2015 and 2023, 17,200 new  
9 cases of drug-resistant (DR-TB) were reported; of these,  
10 1060 were diagnosed in 2023, representing an increase of  
11 6% compared to those diagnosed in 2018.<sup>3</sup>

12 Nearly a quarter of the world's population is estimated to  
13 be infected with MTB.<sup>4</sup> Children under 5 years old are at a  
14 significantly higher risk of developing TB disease (TBD) after  
15 TB infection (TBI), with a cumulative incidence approaching  
16 20% within 2 years of exposure, and are more likely to present  
17 with severe forms of TB disease.<sup>5</sup>

18 The detection of TBI and its preventive treatment (TPT)  
19 with isoniazid and/or rifamycins among close contacts of  
20 patients with drug-susceptible pulmonary TB represents a  
21 public health priority.<sup>2,6</sup> However, when the present study  
22 was carried out, no TPT regimen had been widely validated  
23 for contacts of patients with MDR-TB. In 2024, the World  
24 Health Organization (WHO) included 6 months of daily levofloxacin  
25 as a TPT option for people exposed to MDR/RR-TB in  
26 the WHO guidelines for TPT<sup>7</sup> (replacing the previously proposed  
27 conditional recommendation)<sup>8</sup> based on the results of  
28 two clinical trials (VQUIN MDR and The TB-CHAMP) that were  
29 recently published.<sup>9,10</sup> However, the final results of these  
30 studies, although they have demonstrated a lower percentage  
31 of TBD in the levofloxacin-treated group than in the placebo  
32 group, the difference found was not statistically significant.

33 In Brazil, few studies have assessed the prevalence of TBI  
34 and TBD in contacts of patients with MDR-TB, with a small  
35 proportion of children and adolescents evaluated.<sup>11,12</sup> The  
36 present study aims to assess the prevalence of TBI and TBD  
37 in children and adolescents contacts of patients with drug-  
38 susceptible and drug-resistant pulmonary TB, as well as the  
39 incidence of TBD among contacts exposed to isoniazid preventive  
40 therapy.

## 41 Material and methods

### 42 Data and sample

43 This retrospective cohort study included contacts aged 0 to  
44 19 years old who were screened for TBD and TBI at the pediatric  
45 pneumology outpatient clinic of the Municipal Hospital

Raphael de Paula Souza, a reference center for screening of  
46 young contacts of patients with MDR/XDR-TB in Rio de  
47 Janeiro. The state of Rio de Janeiro stands out with the  
48 third-highest TB incidence and the second-highest TB mor-  
49 tality rate in Brazil, recorded, respectively, at 70.7 in 2023  
50 and 4.7 per 100,000 inhabitants in 2022. Additionally, Rio de  
51 Janeiro accounts for 15% of all notified DR-TB patients in  
52 the country.<sup>3</sup>

53 Eligible contacts underwent their first assessment from  
54 January 2006 to December 2016, and the last follow-up visit  
55 occurred before January 2019. Children and adolescents who  
56 lived in the same household or had close contact with a  
57 patient with pulmonary TB (henceforth named "index case")  
58 and underwent at least one tuberculin skin test (TST) were  
59 eligible for the study. Information regarding index cases (clinical  
60 and radiological data, microbiological testing, including  
61 sputum smear microscopy, culture, and rapid molecular testing,  
62 and drug susceptibility testing—DST - results) was  
63 retrieved from contact referral forms and the Tuberculosis  
64 Special Treatment Notification System (SITE-TB).<sup>6</sup>

65 Contacts whose index cases did not have clinical/laboratory  
66 information available to define if they had MDR or non-  
67 MDR pulmonary TB, contacts without TST results, and those  
68 whose contact with the index case occurred >2 years before  
69 the first visit were excluded. All children and adolescents  
70 recruited in the study were evaluated and followed by the  
71 same medical professional (SCL), responsible for the pediatric  
72 TB outpatient clinic at Raphael de Paula e Souza Hospital.  
73 EFR and SCL jointly reviewed all the medical records.  
74

### Operational definitions of key terms

75 Index case: patient with pulmonary TB from whom the con-  
76 tact assessment was carried out. Contacts were classified  
77 according to the pattern of drug resistance to anti-TB drugs  
78 or treatment regimens prescribed for the index case as MDR-  
79 TB and non-MDR-TB contacts. The diagnosis of TB in the  
80 index case was based on a positive rapid molecular test  
81 (Xpert MTB/RIF; Cepheid, Sunnyvale, CA, USA) and/or spon-  
82 taneous, induced, or bronchoalveolar lavage sputum culture  
83 of MTB.<sup>6</sup>

84 MDR-TB contact: contacts of patients with pulmonary TB  
85 caused by MTB strains resistant to at least rifampicin and iso-  
86 niazid, including patients with extensively drug-resistant TB  
87 (XDR-TB; i.e., MDR-TB plus resistance to a second-line  
88 injectable drug and a fluoroquinolone) and pre-extensively  
89 drug-resistant TB (pre-XDR, i.e. MDR-TB patients with resis-  
90 tance to one of the second-line injectable drugs and/or any  
91 fluoroquinolone), according to the definitions of XDR-TB at  
92 the time of the study.<sup>6</sup>  
93

94 Non-MDR-TB contact: contacts of patients with pulmonary TB whose DST showed susceptibility to all first-line drugs, resistance profile different from MDR-TB, or, in the absence of DST, when the index case has had a clinical and radiological response to the standard first-line TB treatment.

100 Positive TST: an induration  $\geq 5$  mm 48–72 h after TST using 2IU of PPD-RT23 (Statens Serum Institut, Copenhagen/Denmark), applied by the Mantoux method.<sup>13</sup>

103 Tuberculin conversion: defined as an increase of at least 10 mm in skin induration in a second TST performed at week 8 after the first negative TST.<sup>13</sup>

106 Tuberculosis preventive therapy (TPT): 6 months of isoniazid treatment was offered to all asymptomatic contacts with positive TST, normal physical examination, and negative findings on the chest radiograph. Contacts considered at high risk of TB progression by the attending physician received isoniazid regardless of TST result.<sup>13</sup>

112 Tuberculosis infection (TBI): contacts without clinical symptoms or laboratory results compatible with TBD, who had a TST result equal to or greater than 5 mm and a normal chest radiography.<sup>13</sup>

116 Tuberculosis disease (TBD): the presence of clinical and radiographic findings suggestive of active TB disease, as well as a positive TST result, as described in the clinical scoring system of the Brazilian Ministry of Health.<sup>6</sup> For children and adolescents without microbiological confirmation, the score obtained in the MS scoring system was used to define TB cases, as follows: 40 points (very likely diagnosis); 30–35 points (possible diagnosis); and  $<25$  points (diagnosis is unlikely). For cases in which it was possible to collect a biological sample, the presence of acid-fast bacilli on direct examination, positive Xpert MTB/RIF result and/or positive MTB culture were considered confirmed TBD cases.

128 Co-prevalent tuberculosis disease: contacts diagnosed with TBD up to 8 wk from the index case's first medical visit.

130 Incident tuberculosis disease: contacts diagnosed with TBD after 8 wk from the first medical visit.

132 Follow-up group: contacts of patients with pulmonary MDR-TB without TBD at the first evaluation who attended at least two medical visits with an interval of more than one week between them.

## 136 Statistical analysis

137 Qualitative variables were summarized as absolute and relative frequencies and compared using the chi-square or Fisher's exact test. Quantitative variables were described as medians (interquartile ranges) due to their non-parametric distribution, evaluated by the Shapiro-Wilk test, and compared using the Mann-Whitney test.

143 The overall prevalence of TBI was calculated using TST-positive results at baseline and after 8 wk as the numerator.

145 TBD incidence rates (per 100,000 person-months) were calculated in the MDR-TB and non-MDR-TB groups and overall, with incident TB patients as the numerator and the total number of person-month contacts as the denominator, as well as for groups according to completion or non-completion-of-preventive therapy. Incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were calculated in both cases.

Bivariate logistic regressions were performed to assess the association between TBI and independent variables. Variables with significance levels  $\leq 0.20$  in univariate analysis were included in multivariate logistic regression models. A  $p$ -value  $<0.05$  was adopted to define a statistically significant difference. STATA version 16 software (StatsCorp, Texas, USA) was used for all calculations.

## Ethical approval statement

The study protocol was approved by the Research Ethics Committee of Instituto Oswaldo Cruz (CAAE 3007 1420 0 0000 5248), Fiocruz, and successively by the Municipal Health Secretary of Rio de Janeiro, which granted permission for the use of the identified data for the study and waived the need for written informed consent from participants as the study was based on secondary data and involved no more than minimal risk. All patients had an identification number, and to protect patient's confidentiality, only two investigators (EFR and SCL) had access to both identified and de-identified codes; she prepared the anonymous database that was used in the study.

## Results

### Sociodemographic and clinical characteristics of contacts

Out of 529 contacts evaluated during the study period, 14 (2.6%) were excluded due to a lack of data on the index case. Among the remaining 515 contacts, 69 (13.4%) TST was not performed, and 7 (1.6%) did not return for TST reading, resulting in their exclusion from the study. 439 contacts were included, corresponding to 215 index cases (138 patients with non-MDR-TB and 77 patients with MDR-TB). The HIV serology result was known in 130/215 (60.4%) of index cases, with 25.4% (33/130) resulting positive.

Among contacts, 310 (70.6%) were contacts of patients with non-MDR-TB, and 129 (29.4%) were contacts of patients with MDR-TB. In both groups, most index cases were parents (53.5%). Index cases with MDR-TB had a higher frequency of sputum smear positivity, cavitations, and bilateral disease on chest radiography. DST resistance results for at least one drug were available for 34.3% (151/439) of contacts. Among MDR-TB contacts, the most common resistance pattern was MDR-TB (77.5%), and for non-MDR-TB contacts, the most common was polyresistance (72.2%) (Table 1).

### Tuberculosis infection

Figure 1 presents the TBI evaluation flow among contacts. TST positivity at the first assessment was 59.5% (261/439). Among the 178 contacts with an initial negative TST, 93 (52.2%) underwent a second TST after 8 wk. Early tuberculin conversion was observed in 19 out of 93 individuals (20.4%). The final prevalence of TBI was 63.8% (280/439).

Tuberculin conversion was significantly higher in MDR-TB contacts (45.5% vs. 17.1%;  $p = 0.04$ ). However, the percentage of initially negative TST contacts who returned for a second TST was lower among MDR-TB than non-MDR-TB contacts (24% vs. 62%, respectively). Considering the combined TST

**Table 1** Sociodemographic and clinical characteristics of 439 children and adolescent contacts by drug resistance pattern of index cases (non-MDR-TB and MDR-TB).

	Contacts -total <i>n</i> = 439 (%)	Non-MDR-TB <i>n</i> = 310 (%)	MDR -TB <i>n</i> = 129 (%)	<i>p</i> -value <sup>a</sup>
<i>Contacts characteristics</i>				
Sex				0.06
Female	225 (51.2)	150 (48.4)	75 (58.1)	
Male	214 (48.8)	160 (51.6)	54 (41.9)	
Age; years (Median [IQR] <sup>b</sup> )	7 [3–10]	7 [3–10]	6 [3–10]	0.49
Age range				0.95
0–4	158 (36.0)	110 (35.5)	48 (37.2)	
5–9	148 (33.7)	107 (34.5)	41 (31.8)	
14-Oct	115 (26.2)	80 (25.8)	35 (27.1)	
15–19	18 (4.1)	13 (4.2)	5 (3.9)	
BCG scar ( <i>n</i> = 436)				
Absent	9/436 (2.1)	7/308 (2.3)	2/128 (1.6)	0.63
Present	427/436 (97.9)	301/308 (97.7)	126/128 (98.4)	
Previous TB treatment	1/439 (0.2)	1 (0.3)	0 (0.0)	1
Previous TPT	7/439 (1.6)	1 (0.3)	6 (4.7)	0.003
Symptom at the 1st consultation				
Cough	50/420 (11.9)	41/297 (13.8)	9/123 (7.3)	0.06
Fever	14/420 (3.3)	10/297 (3.4)	4/123 (3.3)	0.95
Weight loss	5/420 (1.2)	5/297 (1.7)	0/123 (0.0)	0.33
Lymphadenopathy	5/420 (1.2)	3/297 (1.0)	2/123 (1.6)	0.63
Comorbidities <sup>a</sup>	40/434 (9.2)	30/308 (9.7)	10/126 (7.9)	0.72
HIV status				
Negative	44/45 (97.8)	34/35 (97.1)	10/10 (100.0)	1
Positive	1/45 (2.2)	1/35 (2.9)	0/10 (0.0)	
<i>Index case characteristics</i>				
Relationship with the contact				0.02
Parent	235/439 (53.5)	158/310 (51.0)	77/129 (59.7)	
Siblings	28/439 (6.4)	25/310 (8.1)	3/129 (2.3)	
Grandparents	66/439 (15.0)	42/310 (13.6)	24/129 (18.6)	
Others	110/439 (25.1)	85/310 (27.4)	25/129 (19.4)	
Same household	358/381 (94.6)	234/256 (91.4)	124/125 (99.2)	0.002
Slept with child	54/336 (16.1)	34/238 (14.3)	20/98 (20.4)	0.17
Smear positivity	370/398 (93.0)	243/269 (90.3)	127/129 (98.5)	0.003
Pulmonary cavitation	140/163 (85.9)	27/42 (64.3)	113/121 (93.4)	<0.0001
Pulmonary form				0.01
Unilateral	39/161 (24.2)	16/40 (40.0)	23/121 (19.0)	
Bilateral	122/161 (60.0)	24/40 (60.0)	98/121 (81.0)	
Type of drug resistance				
Primary resistance	21/144 (14.6)	4/22 (18.2)	17/122 (13.9)	
Acquired resistance	123/144 (85.4)	18/22 (81.8)	105/122 (86.1)	0.53
Pattern of drug-resistance (DST) <sup>c</sup>				<0.0001
Mono <sup>d</sup>	5/151 (3.3)	5/22 (22.7)	0/129 (0.0)	
Poly <sup>e</sup>	16/151 (10.6)	16/22 (72.7)	0/129 (0.0)	
MDR	117/151 (77.5)	0/22 (0.0)	117/129 (90.7)	
XDR	12/151 (8.0)	0/22 (0.0)	12/129 (9.3)	
RR	1/151 (0.7)	1/22 (4.6)	0/129 (0.0)	
HIV positivity	30/152 (19.7)	17/47 (36.2)	13/105 (12.4)	0.002

TB, tuberculosis; MDR-TB, multidrug-resistant tuberculosis; TPT, tuberculosis preventive treatment.

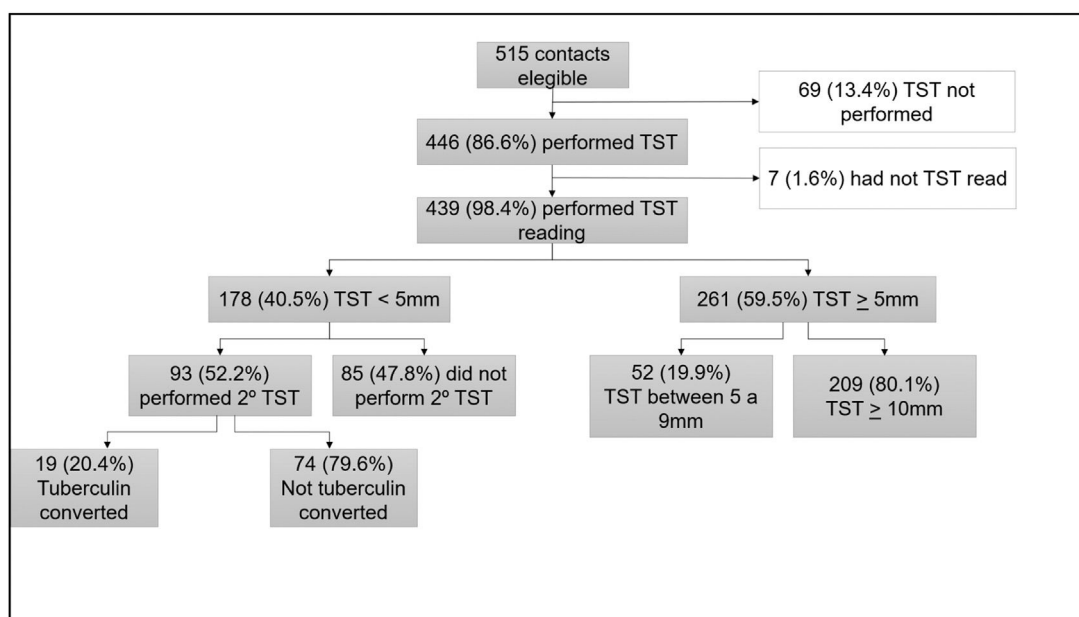
<sup>a</sup> Comparison between non-MDR and MDR contacts.

<sup>b</sup> Median [IQR 25–75]; \*26 different comorbidities were recorded; asthma was the most common (35 %; 14/40).

<sup>c</sup> Information on the number of index cases that underwent DST or the results of DST for drug-sensitive patients was not available. In these cases, the contact classification in MDR or non-MDR-TB was based on information on the treatment regimen adopted by the index case and the respective therapeutic response collected.

<sup>d</sup> Mono = resistance to one drug only (5 resistant to Isoniazid).

<sup>e</sup> Poly = resistance to two or more drugs except to both rifampicin and isoniazid (1 Rifampicin+Ethambutol; 7 Isoniazid+Streptomycin; 2 Rifampicin+Streptomycin; 2 Isoniazid+Pyrazinamide+Ethambutol; 3 Isoniazid +Ethambutol; 1 Isoniazid +Ethambutol+Amikacin+Ofloxacin).



**Figure 1** Flowchart of tuberculin skin test (TST) results among children and adolescents contacts of patients with non-MDR-TB and MDR-TB.

207 results, TBI prevalence was slightly higher in contacts of  
 208 MDR-TB patients, but the difference between groups was  
 209 not statistically significant (68.2% vs. 61.9%,  $p=0.23$ )  
 210 (Table 2).

### 211 Tuberculosis disease

212 At the initial assessment, 1.6% (7/439) of contacts were  
 213 diagnosed with TBD and were classified as co-prevalent  
 214 cases. 411 contacts (TST-positive and TST-negative) were  
 215 followed for a median of 30 wk (IRQ 20 to 45), and 4 additional  
 216 contacts (0.97%) developed TB, representing incident  
 217 cases. Combined, these accounted for 2.5% of the cohort  
 218 diagnosed with TBD, with 2.26% (7/310) in the non-MDR-TB  
 219 group and 3.1% (4/129) in the MDR-TB group. The incidence  
 220 rate of TBD among contacts of patients with MDR-TB was  
 221 179.6 per 100,000 person-months vs. 47.7 per 100,000 person-  
 222 months for contacts of patients with non-MDR-TB, for an  
 223 incidence rate ratio (IRR) of 3.76 (IRR 3.76; 95% CI:

0.30–197.2), but this difference was not statistically significant  
 224 ( $p=0.27$ ).  
 225

226 Microbiological confirmation of TBD was available for only  
 227 2 (18.2%) of 11 contacts. Ten of 11 contacts (91%) had pul-  
 228 monary TB. The median age was 7.0 years, and three chil-  
 229 dren were <5 years old. Among 8 children tested, all were  
 230 HIV seronegative. DST was available in only 1 contact of a  
 231 patient with MDR-TB, who presented a different DST pattern  
 232 and had secondary resistance to anti-TB drugs.

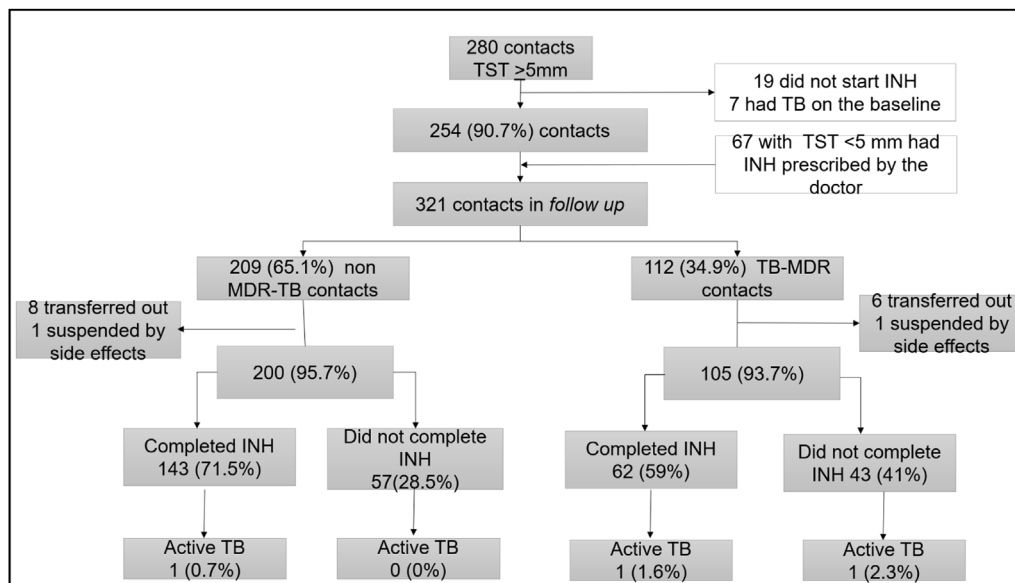
233 Among 11 contacts with TBD, 5 had previously started  
 234 TPT with isoniazid; 2 were already on TPT at the baseline  
 235 visit and 3 had started TPT after the first visit but were lost  
 236 to the follow-up during TPT, returning to medical care after  
 237 insurgence of TB symptoms. DST results were available only  
 238 for one contact of a patient with non-MDR-TB who developed  
 239 TBD by a fully sensitive MTB strain during follow-up. Treat-  
 240 ment was successful for seven children, one was lost to fol-  
 241 low-up, and three were transferred out (Table S1 and S2 in  
 242 the Supplementary Material).  
 243

**Table 2** Tuberculin skin test (TST) response of children and adolescents who are a close contact of non-MDR-TB and MDR-TB patients.

Variables	Non MDR-TB n (%)	MDR-TB n (%)	OR (95% CI)	<i>p</i> -value
Initial TST response				
< 5 mm	132 (42.6)	46 (35.7)	1	0.20
≥ 5 mm	178 (57.4)	83 (64.3)	1.34 (0.87–2.05)	
Second TST - tuberculin conversion				
Yes	14 (17.1)	5 (45.5)	4.05 (1.08–15.13)	0.04
No	68 (82.9)	6 (54.5)		
TBI prevalence <sup>a</sup>				
TST- positive	192 (61.9)	88 (68.2)	1.32 (0.85–2.04)	0.23
TST- negative	118 (38.1)	41 (38.8)		

MDR-TB, multidrug-resistant tuberculosis; TST, tuberculin skin test.

<sup>a</sup> Combined TST results.



**Figure 2** Flowchart of isoniazid preventive therapy among children and adolescents contacts of non-MDR-TB and MDR-TB patients. INH, isoniazid; TST, tuberculosis skin test. One contact of patient with MDR-TB developed TBD and did not start TPT.

## 243 TB preventive therapy

244 Among the 321 contacts who initiated preventive therapy  
245 with isoniazid, 254 (79.1 %) had TST-positive results, while 67  
246 (20.9 %) were contacted at high risk for TBD, including 35 chil-  
247 dren under 5, who initiated TPT even presenting TST-negative  
248 results. Of these, 209 (65.1 %) were contacts of patients with  
249 non-MDR-TB, and 112 (34.9 %) of MDR-TB (Figure 2).

250 No significant differences were found for the occurrence  
251 of adverse events or time of exposure to isoniazid between  
252 the group of contacts. The overall adherence was 67.2 %  
253 (205/305), but it was significantly higher among non-MDR-  
254 TB: 71.5 % (143/200) vs. 59.0 % (62/105) ( $p = 0.04$ ).

255 Three contacts developed TBD after preventive therapy  
256 initiation with isoniazid; 2 of these contacts were in the  
257 MDR-TB group and both index cases had secondary resis-  
258 tance. The TB incidence rate was not significantly higher  
259 among MDR-TB contacts who did not complete preventive  
260 therapy, but the sample size was too small (Supplementary  
261 material S3). The contact of a patient with RR-TB received  
262 TPT with isoniazid and did not develop TBD during the fol-  
263 low-up period.

264 Regarding the association between TBI and the indepen-  
265 dent variables in the final multivariate model, the risk of TBI  
266 increased with the age of contact (OR 1.13; 95 % CI  
267 1.03–1.25) and decreased when the index case was a grand-  
268 parent (OR 0.33; CI95 % 0.12–0.93) or HIV-positive (OR 0.28;  
269 CI95 % 0.12–0.69). The infectivity of the index case (assessed  
270 by sputum smear positivity and the presence of cavitation on  
271 the chest radiograph), as well as the presence of resistance  
272 to anti-TB drugs, were not associated with TBI among con-  
273 tacts in the final model (Supplementary material S4).

## 274 Discussion

275 In Brazil, the risk of TB infection and disease among young  
276 contacts of patients with pulmonary MDR/XDR-TB is not well

277 known.<sup>6,11,12</sup> In the present study the authors found a high  
278 prevalence of TBI among contacts (59.5 %) at the initial  
279 assessment, which increased to 63.8 % after the second TST.  
280 These findings are similar to those reported in low and mid-  
281 dle-income countries, which showed a spectrum of TB infec-  
282 tion prevalence ranging from 57 % to 72 % amidst both  
283 pediatric and adult contacts of patients with MDR-TB,<sup>14,15</sup>  
284 while contacts of individuals harboring drug-susceptible TB  
285 exhibited rates between 44 % and 83 %.<sup>16,17</sup>

286 A significant proportion of tuberculin conversion (TC) was  
287 observed (20.4 %), as described in a previous study carried  
288 out in the same city<sup>16</sup>, emphasizing the importance of a sec-  
289 ond TST for initially TST-negative contacts. TC was higher  
290 among MDR-TB contacts (45.5 % vs. 17.7 %), plausibly attrib-  
291 utable to prolonged exposure to a symptomatic index  
292 case,<sup>18</sup> but this finding may have been biased by the differ-  
293 ent proportion of contacts who returned for the second TST  
294 between the two groups. However, recently it has been  
295 described that the risk of acquiring TBI and developing TBD  
296 among contacts of patients with RR/MDR-TB may persist for  
297 up to a year despite index case treatment and evaluation of  
298 contacts for TBI and TBD at baseline.<sup>19</sup>

299 While early studies suggested attenuated pathogenicity  
300 of drug-resistant MTB strains,<sup>20,21</sup> later research by Snider  
301 et al. found no differences in transmissibility between drug-  
302 susceptible and resistant strains.<sup>22</sup> Limited prospective stud-  
303 ies indicate that transmissibility depends on specific geno-  
304 mic mutations.<sup>23</sup>

305 Most research on pediatric and adolescent contacts of  
306 patients with drug-resistant TB has been conducted in high  
307 TB-HIV co-infection settings, such as South Africa.<sup>24</sup>

308 In the contacts, HIV infection increases the risk of TB  
309 infection and disease.<sup>5,15</sup> In this study, only 10 % of contacts  
310 were tested for HIV, with one (2.2 %) testing positive.

311 The authors did not find a statistically significant differ-  
312 ence in the risk of TBD between contact groups. Several  
313 studies on the incidence of secondary TBD among household  
314 contacts with MDR-TB had low statistical power or did not

315 include a control group.<sup>11,12,25</sup> The present findings are similar to previous studies that reported TBD rates of 1.2% to 316 7.8% among MDR contacts.<sup>11,22,26</sup>

318 In the present study, TPT initiation with INH was lower among MDR-TB contacts (34.9% vs 65.1%), as well as the 319 adherence to TPT (59.0% vs. 71.5%), and three out of four 320 individuals who developed incident TBD were MDR-TB 321 contacts. Contacts of MDR-TB patients who did not complete 322 TPT had a higher risk of TB, though the small sample size 323 limits the reliability of this finding. Similarly, Kritski et al. 324 reported TBD in 4% of contacts receiving isoniazid-based 325 TPT compared to 9% of untreated contacts.<sup>11</sup> However, their 326 study focused on adult contacts, where prior exposure to 327 isoniazid-sensitive TB may have influenced outcomes. A 328 Peruvian study found that TPT with isoniazid-protected 329 contacts under 20 years of age against pulmonary MDR-TB (HR 330 0.19; 95% CI 0.05–0.66), but not against mono-isoniazid- 331 resistant TB (HR 0.80; 95% CI 0.23–2.80).<sup>25</sup>

333 Despite the lower adherence to TPT among MDR-TB 334 contacts, the authors can consider that TPT completion rates in 335 this study were moderate to high. A meta-analysis has 336 reported completion rates near 90% in research centers,<sup>27</sup> 337 but in routine practice, lower completion rates are found, 338 with less than half of individuals who start TPT completing 339 treatment in some settings.<sup>28,29</sup>

340 Considering the retrospective design of the present study, 341 based on medical records and electronic notification 342 records, the authors faced limitations in the completeness 343 of the information, particularly concerning data from index 344 cases (such as HIV serological status, chest radiograph find- 345 ings or DST results), since these patients were followed up in 346 other medical services. However, the same medical doctor 347 evaluated and followed all contacts and, together with 348 another physician, reviewed all the medical records and 349 filled out the forms, ensuring the application of the same 350 contact evaluation protocol and, therefore, increasing data 351 quality.

352 In conclusion, the authors found a high prevalence of TBI 353 among children and adolescents who were contacts of pul- 354 monary MDR and non-MDR-TB patients, with a higher tuber- 355 culin conversion rate in MDR-TB contacts. However, the 356 prevalence of TBI and TBD did not significantly differ 357 between MDR-TB and non-MDR-TB contact groups.

358 The results reinforce the need for timely assessment of 359 contacts of patients with MDR-TB and the provision of TPT 360 with effective treatment regimens that have yet to be 361 defined and effectively implemented.

## 362 Conflicts of interest

363 The authors declare no conflicts of interest.

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## Supplementary materials

Supplementary material associated with this article can be 379 found in the online version at doi:10.1016/j.jpmed.2025. 380 01.008. 381

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