



# Primary and acquired multidrug-resistant tuberculosis: Predictive factors for unfavorable treatment outcomes in Rio de Janeiro, 2000–2016

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## ABSTRACT

**Objective.** To identify clinical and demographic factors associated with unfavorable treatment outcomes in patients with primary and acquired multidrug-resistant tuberculosis (MDR-TB) in Rio de Janeiro State.

**Methods.** Retrospective cohort study using data on 2 269 MDR-TB cases in 2000–2016. Factors associated with unsuccessful, loss to follow-up, and death outcomes in patients with primary and acquired resistance were investigated with bivariate and multivariate regression.

**Results.** Primary resistance was 14.7% among MDR-TB cases. The unfavorable outcomes proportion was 30.3% in the primary resistance group and 46.7% in the acquired resistance group. There were significant differences in demographic and clinical characteristics between the two groups. Proportionally, the group with primary resistance had more cases among women (46.4% vs. 33.5% in the acquired resistance group), Caucasians (47.3% and 34%), and those with  $\geq 8$  years of schooling (37.7% and 27.4%). Extensively drug-resistant TB patients had 2.2-fold higher odds of unsuccessful outcome than MDR-TB patients, and comorbidities had 2-fold higher odds in the primary resistance group. Extensively drug-resistant TB had 5.43-fold higher odds in the acquired MDR-TB group. Bilateral disease and  $< 8$  years of schooling were associated with unsuccessful outcome in both groups. Being an inmate had 8-fold higher odds of loss to follow-up in the primary resistance group. Culture conversion by the sixth month was a protective factor for all outcomes.

**Conclusions.** Primary resistance cases of MDR-TB constitute a different transmission reservoir, which is related to other chronic diseases associated with higher acquisition of TB. The poor results observed in Rio de Janeiro State can contribute to increasing the transmission of primary MDR-TB, thus favoring drug resistance.

## Keywords

Tuberculosis; epidemiological monitoring; drug resistance; treatment outcome; Brazil.

The resistance of *Mycobacterium tuberculosis* (MTB) to drugs is a major threat and one of the challenges for disease elimination, given that it requires treatment with second-line regimen drugs, which are more expensive, more toxic, and less effective than the first-line regimen. Multidrug-resistant tuberculosis (MDR-TB) is defined as TB with resistance to at least rifampicin and isoniazid. In turn, extensively drug-resistant TB (XDR-TB) is defined as MDR-TB plus resistance to at least one quinolone and one of the three injectable drugs used in the treatment of TB (capreomycin, kanamycin, and amikacin) (1).

Although the main hypothesis for the increase in resistance cases had to do with treatment failures, some studies have shown that person-to-person transmission of MDR-TB is becoming more and more common, therefore resulting in a higher prevalence of primary MDR-TB (2).

The status of primary MDR-TB in Brazil is still poorly understood. The II National Survey on Resistance to Anti-TB Drugs, conducted in 2007–2008, indicated a primary and acquired resistance rate to isoniazid of 6.0% and 15.3%, respectively. For rifampicin, these rates were 1.5% and 8.0%, respectively.

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MDR-TB rates, primary and acquired, were, respectively, 1.4% and 7.5% (3). There is, however, no study showing risk factors associated with unfavorable treatment outcomes for patients with primary MDR-TB.

That said, this study aims to identify the clinical and demographic factors associated with unfavorable treatment outcomes, specifically unsuccessful treatment, loss to follow-up (LTFU), and death of patients with primary and acquired MDR-TB in Rio de Janeiro State (RJ), Brazil's third most populous state (8.2% of the country's population).

## MATERIALS AND METHODS

### Research design and setting

This retrospective cohort study used secondary data from the Special Tuberculosis Treatment Information System (SITETB) in RJ. In terms of incidence, Brazil ranks 12th worldwide in TB cases and 15th in TB-HIV coinfection, and is one of the 30 countries that the World Health Organization (WHO) considers priority for TB control (1). In 2017, Brazil reported 1 041 cases of TB drug resistance, of which 713 (68.5%) were MDR-TB (4). RJ is in southeast Brazil and has a population of approximately 17 million people. Its Human Development Index score is 0.761, ranking fourth among Brazilian states (5). The average annual TB incidence rate in RJ was 63.3 and the mortality rate was 4.2 per 100 000 population in 2018 (4).

### Tuberculosis surveillance system

Brazil has had a disease notification system since 1975, whose quality has been improving since then. In 1993, the Notifiable Diseases Information System (SINAN) was created. The latter allows the notification, investigation, and monitoring of TB cases (6). In 2000, Brazil initiated epidemiological surveillance of MDR-TB, which, in turn, culminated in the implementation of an electronic information system, the SITETB (7). SITETB is used for the compulsory notification and follow-up of TB cases requiring special treatments for patients unable to use the standard TB regimen (2RHZE/4RH) (8). The records are made by health professionals and validated by professionals certified by the National Tuberculosis Program of the Ministry of Health (NTP-MoH). Demographic and clinical data, drug susceptibility testing (DST) results, adverse events, treatment regimens, and outcomes for each patient are registered (9). Whenever treatment with a special regimen is necessary, the case must be coded by SINAN as a regimen change, failure, or drug-resistant TB, and needs to be notified in SITETB.

### Study sample

In June 2019, the SITETB database contained information from a cohort of patients notified with MDR-TB in RJ from January 2000 to December 2016. Patients with the following attributes were excluded from the sample: those non-resident in RJ, undergoing treatment, with unknown outcomes, with a change in the diagnosis, or those with DST records not indicating resistance to, at least, rifampicin and isoniazid. Cases were divided into two groups according to the type of resistance: primary or acquired. According to NTP-MoH (8), the definitions are: *Primary resistance* is a new case of TB including (a) a

patient never treated for TB; (b) a patient in treatment with a basic regimen, evolving to failure and subsequent diagnosis of drug-resistant TB; and (c) a patient in treatment with a basic regimen, who underwent culture and a drug sensitivity test at the beginning of treatment, with subsequent diagnosis of drug-resistant TB. *Acquired resistance* occurs if the patient reports previous TB treatments, except for the situations described in (b) and (c).

SITETB and SINAN do not have an interface. A manual linkage using Microsoft Excel was performed to check the consistency of the information about cases of primary resistance registered in SITETB. All cases with primary resistance were compared using patient name, their mother's name, and date of birth. If the patients had been previously notified and had not met criteria (b) and (c), the former were reclassified as acquired resistance.

### Treatment outcomes

For the statistical analysis performed below, three treatment outcomes were operationalized as binary dependent variables: (i) unsuccessful; (ii) LTFU; and (iii) death. Treatment outcomes were classified according to the WHO definitions (10): *Cured*: the patient should have at least three negative cultures after the 12th month of treatment. *Treatment completed*: the patient completed the time stipulated for the treatment, with favorable clinical and radiological evolution, but without the follow-up cultures. *LTFU*: a patient whose treatment was discontinued for two consecutive months or more. *Death*: a patient who died for any reason during the treatment. *Failure*: two or more positive cultures out of the three recommended after the 12th month of treatment, or three consecutive positive cultures after the 12th month of treatment, at least 30 days apart. Failure may also be considered according to medical evaluation, and the decision to change treatment early due to clinical and radiological worsening. *Unsuccessful*: the sum of patients who had the outcome classified as death, LTFU, or failure.

### Independent variables

The following independent variables were included on the right-hand side of the regression equations: sex, age under 40 years, less than eight years of schooling, race/skin color, HIV infection, diabetes, comorbidities (viral hepatitis, renal insufficiency, neoplasia, silicosis, transplant, mental disorder, prolonged use of corticosteroids, use of TNF-alpha inhibitors, seizure, and undefined others), illicit drug use, alcohol abuse, smoking, unemployment, inmate, drug resistance category (MDR-TB or XDR-TB), treatment regimen (standardized or individualized), the extent of disease (presence of chest cavity and/or bilateral disease), and six-month culture conversion. This last variable assigns the value 1 to patients who had at least two negative cultures until the sixth month after the start of treatment, value 0 otherwise. Only variables that had a maximum of 10% of missing values were selected.

### Statistical analysis

According to the nature of each variable, number (frequency) and mean (standard deviation) were used to describe

the characteristics of the patients with primary and acquired MDR-TB. The demographic and clinical characteristics were analyzed with descriptive statistics. Pearson's chi-squared test was employed for the comparison of categorical variables.

To verify the factors related to each outcome, a bivariate logistic regression was run. The crude odds ratio (OR) with 95% confidence intervals (95% CI) was calculated. Subsequently, the variables with  $\leq 0.20$  significance were included in the multivariate logistic model. A backward method was performed using Hosmer-Lemeshow goodness of fit test for calibration and determining the adjusted odds ratio (ORa). Variables associated with outcomes with  $\leq 0.10$  significance in the adjusted model were reported. Statistical analyses were performed using Stata software package version 13.1.

## Ethical considerations

The study protocol was approved by the Research Ethics Committee of the Federal University of Rio de Janeiro (CAAE 10126919.2.0000.5257), which waived the need for written informed consent from participants as the study was based on secondary data and involved no more than minimal risk. Only one investigator (MB) had access to both identified and de-identified codes and prepared the anonymous database that was analyzed.

## RESULTS

### Descriptive analysis

Between 2000 and 2016, 2 477 cases of MDR-TB were reported in SITETB RJ. In total 208 cases were excluded: 8 non-residents in RJ, 11 undergoing treatment, 3 unknown outcome, 11 diagnosis change, and 175 DST records not indicating resistance to, at least, rifampicin and isoniazid. Among the 2 269 cases analyzed, 347 were recorded as cases of primary MDR-TB. Among these, 132 patients were reported in SINAN, and 13 were reclassified as acquired resistance. Of the total 2 269 cases included in the sample, 334 (14.7%) were primary resistance. The overall mean age was 39 years ( $\pm 13.3$ ), 1 466 (64.5%) were male, and 1 281 (57.9%) were living in Rio de Janeiro city, the capital of RJ.

Proportionally, the primary resistance group included more patients with the following characteristics than the acquired resistance group: women (46.4% and 33.5%, respectively); aged up to 24 years (22.2% and 14%); Caucasian (47.3% and 34%); with eight or more years of schooling (37.7% and 27.4%); with diabetes (13.2% and 9.0%); and with comorbidities (14.3% and 11.6%) (Table 1).

In addition, unemployment was more frequent in the acquired resistance group than in the primary resistance group (17.1% and 12.6%, respectively); as were alcohol abuse (12.3% and 9.3%); illicit drug use (8.5% and 4.5%); and bilateral disease (77.3% and 62.8%).

The proportion of unsuccessful outcome was 30.3% in the primary resistance group and 46.7% in the acquired resistance group. LTFU was the most frequent unfavorable outcome in both groups at 12.3% among patients with primary resistance and 20.3% among those with acquired resistance; followed by death, with 10.8% in the primary resistance group and 16.1% in the acquired resistance group.

## Factors associated with treatment outcomes in bivariate models

Table 2 shows the bivariate analyses of the factors associated with unsuccessful, LTFU, and death as outcomes for the group with primary resistance. In this group, the unsuccessful outcome was more likely in patients characterized by XDR-TB, illicit drug use, bilateral disease, less than eight years of schooling, unemployment, and comorbidities. LTFU was associated with being an inmate, illicit drug use, less than eight years of schooling, smoking, and cavitory disease.

The factors associated with the acquired resistance group are displayed in Table 3. Unsuccessful outcome was more likely in patients who were under 40 years old, with less than eight years of schooling, Afro-Brazilian, HIV-positive, illicit drug users, unemployed, with XDR-TB, and bilateral and cavitory disease. LTFU was associated with the following attributes: male, under 40 years old, less than eight years of schooling, Afro-Brazilian, HIV-positive, illicit drug use, alcohol abuse, smoking, unemployment, cavitory disease, and being an inmate. Having comorbidities and diabetes were protective factors for unsuccessful outcome and LTFU. Death was associated with the factors less than eight years of schooling, HIV-positive, comorbidities, bilateral disease, and XDR-TB. Culture conversion by the sixth month of treatment was a protective factor for all outcomes in both groups.

## Factors associated with treatment outcomes in the multivariate models

Regarding unsuccessful outcome in the primary resistance group (Table 4), XDR-TB (ORa 12.2; 95% CI 2.24–66.41) had a 12.2-fold higher odds than MDR-TB, while bilateral disease (ORa 1.92; 95% CI 1.06–3.47) and the presence of comorbidities (ORa 2.06; 95% CI 0.94–4.49) had nearly 2-fold higher odds. Having less than eight years of schooling was found to be associated with unsuccessful outcome (ORa 2.05; 95% CI 1.13–3.72) and LTFU (ORa 2.30; 95% CI 0.99–5.34).

As for the outcome LTFU in the primary resistance group, illicit drug users (ORa 3.38; 95% CI 0.94–12.11) and smokers (ORa 2.91; 95% CI 0.99–8.52) had approximately 3-fold higher odds. Being an inmate (ORa 8.00; 95% CI 1.33–47.79) was found to have 8-fold higher odds. Regarding death, unemployment (ORa 2.87; 95% CI 1.17–7.04) was associated with 2.8-fold higher odds.

Regarding unsuccessful outcome in the acquired resistance group (Table 5), XDR-TB (ORa 5.43; 95% CI 3.11–9.47) had 5.4-fold higher odds than MDR-TB. Being under 40 years old, being Afro-Brazilian, and illicit drug use were found to be associated with unsuccessful and LTFU outcomes. HIV-positive and bilateral disease were found to be associated with unsuccessful and death outcomes. Having less than eight years of schooling was associated with all outcomes.

Unemployment was found to be associated only with the unsuccessful outcome (ORa 1.34; 95% CI 0.98–1.81); and smoking (ORa 1.58; 95% CI 1.02–2.45) only with LTFU. Comorbidity was associated with death (ORa 1.88; 95% CI 1.22–2.88) and was a protective factor for LTFU (ORa 0.36; 95% CI 0.21–0.62). In both groups, culture conversion by the sixth month was a protective factor for all outcomes, especially for unsuccessful and death outcomes.

**TABLE 1. Demographic and clinical characteristics of 1 935 cases with acquired and 334 cases with primary MDR/XDR-TB notified in Rio de Janeiro State, 2000–2016**

Characteristics	Primary resistance (%) N = 334	Acquired resistance (%) N = 1 935	p-value *
<b>Sex</b>			
Female	155 (46.4)	648 (33.5)	<0.001
Male	179 (53.6)	1 287 (66.5)	
<b>Age range</b>			
0–11	2 (0.6)	2 (0.1)	<0.001
12–17	13 (3.9)	30 (1.5)	
18–24	59 (17.7)	239 (12.4)	
25–44	134 (40.1)	992 (51.3)	
45–64	111 (33.2)	604 (31.2)	
≥65	15 (4.5)	68 (3.5)	
<b>Ethnic group</b>			
Caucasian	158 (47.3)	658 (34.0)	<0.001
Afro-Brazilian	170 (50.9)	1 202 (62.1)	
Unknown	6 (1.8)	74 (3.8)	
<b>Years of schooling</b>			
None	13 (3.9)	100 (5.2)	<0.001
1–3	60 (17.9)	370 (19.1)	
4–7	109 (32.7)	770 (39.8)	
8–11	84 (25.1)	407 (21.0)	
≥12	42 (12.6)	124 (6.4)	
Unknown	26 (7.8)	164 (8.5)	
<b>Residence (n = 2 211)</b>			
Capital	207 (65.5)	1 287 (66.5)	0.003
Other municipalities	109 (34.5)	648 (33.5)	
<b>Site of disease</b>			
Extrapulmonary	2 (0.6)	18 (0.9)	0.010
Pulmonary	321 (96.1)	1 897 (98.0)	
Both	11 (3.3)	20 (1.1)	
<b>HIV status (n = 2 103)</b>			
Negative	288 (92.0)	1 648 (92.1)	0.974
Positive	25 (8.0)	142 (7.9)	
<b>Other factors</b>			
Diabetes	44 (13.2)	175 (9.0)	0.018
Alcohol abuse	31 (9.3)	238 (12.3)	0.937
Illicit drug use	15 (4.5)	164 (8.5)	0.013
Smoking	30 (9.0)	158 (8.2)	0.617
Inmate	6 (1.8)	30 (1.6)	0.740
Unemployed	42 (12.6)	331 (17.1)	0.039
Comorbidities**	48 (14.3)	224 (11.6)	0.146
<b>Chest radiography (n = 2 247)</b>			
Cavitation	259 (78.3)	1 560 (81.4)	0.175
Bilateral	208 (62.8)	1 485 (77.3)	<0.001
<b>Categories of drug resistance</b>			
MDR-TB	324 (97.0)	1 805 (93.3)	0.008
XDR-TB	10 (3.0)	130 (6.7)	
<b>Outcomes</b>			
Cured	129 (38.6)	493 (25.5)	<0.001

(continued)

**TABLE 1. Demographic and clinical characteristics of 1 935 cases with acquired and 334 cases with primary MDR/XDR-TB notified in Rio de Janeiro State, 2000–2016 (continued)**

Characteristics	Primary resistance (%) N = 334	Acquired resistance (%) N = 1 935	p-value *
Treatment completed	104 (31.1)	538 (27.8)	
Died	36 (10.8)	311 (16.1)	
Loss to follow-up	41 (12.3)	392 (20.3)	
Failed	24 (7.2)	201 (10.4)	

OR, odds ratio; 95% CI, 95% confidence interval; TB, tuberculosis; MDR-TB, multidrug-resistant TB; XDR-TB, extensively drug-resistant TB; HIV, human immunodeficiency virus.

\*Comparison between primary and acquired MDR/XDR-TB using Pearson's chi-squared test

\*\*Except diabetes and HIV

Source: Prepared by the authors from the study results.

**TABLE 2. Bivariate analysis: predictors of unsuccessful, lost to follow-up, and death outcomes among 334 primary MDR/XDR-TB notified cases in Rio de Janeiro State, 2000–2016**

Predictors	Unsuccessful	Lost to follow-up	Death
	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value
<b>Sex</b>			
Female	1.0	1.0	1.0
Male	0.88 (0.55–1.41) 0.611	1.12 (0.58–2.16) 0.731	0.66 (0.33–1.32) 0.246
<b>≥40 years</b>			
Yes	1.0	1.0	1.0
No	1.18 (0.72–1.92) 0.508	1.39 (0.68–2.83) 0.360	1.14 (0.56–2.29) 0.707
<b>Years of schooling</b>			
≥8 years	1.0	1.0	1.0
<8 years	1.60 (0.95–2.69) 0.074	2.26 (1.02–4.99) 0.043	1.35 (0.60–3.01) 0.461
<b>Afro-Brazilian</b>			
No	1.0	1.0	1.0
Yes	1.20 (0.75–1.93) 0.439	1.29 (0.66–2.53) 0.445	0.92 (0.45–1.87) 0.822
<b>HIV status (n = 313)</b>			
Negative	1.0	1.0	1.0
Positive	1.56 (0.67–3.62) 0.295	1.37 (0.44–4.24) 0.578	1.70 (0.54–5.29) 0.359
<b>Diabetes</b>			
No	1.0	1.0	1.0
Yes	0.84 (0.41–1.72) 0.646	0.48 (0.14–1.64) 0.246	0.56 (0.16–1.94) 0.369
<b>Comorbidities*</b>			
No	1.0	1.0	1.0
Yes	1.52 (0.80–2.89) 0.197	1.05 (0.41–2.66) 0.912	1.55 (0.63–3.79) 0.330
<b>Illicit drug use</b>			
No	1.0	1.0	1.0
Yes	2.09 (0.73–5.94) 0.165	5.40 (1.81–16.10) 0.002	(-)
<b>Alcohol abuse</b>			
No	1.0	1.0	1.0
Yes	0.78 (0.33–1.82) 0.573	1.42 (0.51–3.94) 0.494	0.54 (0.12–2.38) 0.421

(continued)

**TABLE 2. Bivariate analysis: predictors of unsuccessful, lost to follow-up, and death outcomes among 334 primary MDR/XDR-TB notified cases in Rio de Janeiro State, 2000–2016 (continued)**

Predictors	Unsuccessful	Lost to follow-up	Death
	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value
<b>Smoking</b>			
No	1.0	1.0	1.0
Yes	1.37 (0.62–3.01) 0.423	2.41 (0.96–6.05) 0.060	0.56 (0.12–2.48) 0.452
<b>Unemployed</b>			
No	1.0	1.0	1.0
Yes	1.68 (0.86–3.27) 0.125	1.51 (0.62–3.68) 0.357	2.67 (1.15–6.17) 0.021
<b>Categories of drug resistance</b>			
MDR-TB	1.0	1.0	1.0
XDR-TB	9.93 (2.07–47.66) 0.004	(-)	2.13 (0.43–10.45) 0.351
<b>Six-month culture conversion</b>			
No	1.0	1.0	1.0
Yes	0.19 (0.11–0.34) <0.001	0.35 (0.16–0.74) 0.006	0.09 (0.02–0.31) <0.001
<b>Chest radiography (n = 324)</b>			
No cavitation	1.0	1.0	1.0
Cavitation	1.40 (0.77–2.54) 0.260	2.82 (0.97–8.19) 0.057	0.68 (0.31–1.50) 0.350
Unilateral	1.0	1.0	1.0
Bilateral	1.82 (1.09–3.02) 0.021	1.30 (0.65–2.63) 0.450	1.60 (0.74–3.45) 0.226
<b>Inmate</b>			
No	1.0	1.0	1.0
Yes	2.34 (0.46–11.83) 0.301	7.63 (1.48–39.17) 0.015	(-)
<b>Treatment regimen</b>			
Standardized	1.0	1.0	1.0
Individualized	1.30 (0.78–2.14) 0.301	0.94 (0.46–1.94) 0.884	0.71 (0.32–1.58) 0.411

OR, odds ratio; 95% CI, 95% confidence interval; TB, tuberculosis; MDR-TB, multidrug-resistant TB; XDR-TB, extensively drug-resistant TB; HIV, human immunodeficiency virus.  
\*Except diabetes and HIV  
**Source:** Prepared by the authors from the study results.

**DISCUSSION**

The study showed that of the 2 269 MDR-TB cases in the sample, 14.7% were primary resistance MDR-TB. Some studies conducted in different regions of Brazil show a variation in primary resistance MDR-TB of between 0.3% and 8.3% (11–14). However, these studies considered only patients who had no previous treatment record. In this study an expanded definition was adopted. Therefore, it includes cases of patients who start treatment with a basic regimen, progressing to failure and subsequent diagnosis of drug-resistant TB, or who undergo culture and sensitivity testing at the beginning of treatment and following tests for resistant TB. With this same definition, a study conducted in São Paulo with 156 MDR-TB patients found

**TABLE 3. Bivariate analysis: predictors of unsuccessful, lost to follow-up, and death outcomes among 1 935 acquired MDR/XDR-TB notified cases in Rio de Janeiro State, 2000–2016**

Predictors	Unsuccessful	Lost to follow-up	Death
	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value
<b>Sex</b>			
Female	1.0	1.0	1.0
Male	1.09 (0.90–1.32) 0.347	1.27 (0.99–1.61) 0.051	0.96 (0.74–1.25) 0.808
<b>≥40 years</b>			
Yes	1.0	1.0	1.0
No	1.30 (1.08–1.56) 0.005	1.58 (1.26–2.00) <0.001	0.92 (0.72–1.18) 0.558
<b>Years of schooling</b>			
≥8 years	1.0	1.0	1.0
<8 years	1.72 (1.40–2.12) <0.001	1.73 (1.31–2.29) <0.001	1.68 (1.23–2.29) 0.001
<b>Afro-Brazilian</b>			
No	1.0	1.0	1.0
Yes	1.36 (1.12–1.65) 0.001	1.64 (1.28–2.11) <0.001	0.99 (0.76–1.28) 0.968
<b>HIV status (n = 1 790)</b>			
Negative	1.0	1.0	1.0
Positive	1.42 (1.01–2.01) 0.042	1.47 (0.99–2.19) 0.051	1.45 (0.95–2.21) 0.078
<b>Diabetes</b>			
No	1.0	1.0	1.0
Yes	0.72 (0.52–0.99) 0.043	0.39 (0.23–0.66) <0.001	0.77 (0.49–1.22) 0.270
<b>Comorbidities*</b>			
No	1.0	1.0	1.0
Yes	0.82 (0.61–1.08) 0.170	0.41 (0.26–0.65) <0.001	1.54 (1.09–2.18) 0.012
<b>Illicit drug use</b>			
No	1.0	1.0	1.0
Yes	1.87 (1.35–2.60) <0.001	2.89 (2.07–4.05) <0.001	0.79 (0.49–1.26) 0.334
<b>Alcohol abuse</b>			
No	1.0	1.0	1.0
Yes	1.20 (0.92–1.58) 0.174	1.53 (1.12–2.09) 0.007	1.06 (0.73–1.52) 0.742
<b>Smoking</b>			
No	1.0	1.0	1.0
Yes	1.12 (0.81–1.55) 0.486	1.69 (1.18–2.44) 0.004	0.48 (0.27–0.85) 0.012
<b>Unemployed</b>			
No	1.0	1.0	1.0
Yes	1.55 (1.22–1.97) <0.001	1.51 (1.15–1.99) 0.003	0.96 (0.69–1.33) 0.844
<b>Categories of drug resistance</b>			
MDR-TB	1.0	1.0	1.0
XDR-TB	5.57 (3.54–8.76) <0.001	0.65 (0.39–1.08) 0.100	2.51 (1.69–3.73) <0.001
<b>Six-month culture conversion</b>			
No	1.0	1.0	1.0
Yes	0.18 (0.15–0.23) <0.001	0.44 (0.34–0.58) <0.001	0.11 (0.06–0.17) <0.001

(continued)

**TABLE 3. Bivariate analysis: predictors of unsuccessful, lost to follow-up, and death outcomes among 1 935 acquired MDR/XDR-TB notified cases in Rio de Janeiro State, 2000–2016 (continued)**

Predictors	Unsuccessful	Lost to follow-up	Death
	OR (95% CI) p-value	OR (95% CI) p-value	OR (95% CI) p-value
<b>Chest radiography (n = 1 923)</b>			
No cavitation	1.0	1.0	1.0
Cavitation	1.63 (1.28–2.07) <0.001	1.36 (1.00–1.86) 0.047	1.03 (0.75–1.41) 0.842
Unilateral	1.0	1.0	1.0
Bilateral	1.93 (1.54–2.42) <0.001	1.01 (0.77–1.32) 0.926	2.66 (1.83–3.87) <0.001
<b>Inmate</b>			
No	1.0	1.0	1.0
Yes	0.99 (0.48–2.05) 0.995	2.31 (1.09–4.90) 0.028	0.36 (0.08–1.55) 0.175
<b>Treatment regimen</b>			
Standardized	1.0	1.0	1.0
Individualized	1.55 (0.73–0.89) <0.001	1.02 (0.81–1.29) 0.834	0.97 (0.75–1.25) 0.817

OR, odds ratio; 95% CI, 95% confidence interval; TB, tuberculosis; MDR-TB, multidrug-resistant TB; XDR-TB, extensively drug-resistant TB; HIV, human immunodeficiency virus.  
\*Except diabetes and HIV  
**Source:** Prepared by the authors from the study results.

36% of primary resistance cases. Note that only 5% of patients reported not having undergone previous treatment for TB (15). Another study conducted in RJ showed that approximately 30% of XDR-TB cases had no previous treatment for multidrug resistance. This suggests that a high proportion of cases of XDR-TB is due to primary infection in RJ (16). It may also mean that patients with primary resistance can begin basic TB treatment, with the diagnosis delayed by the absence of initial drug resistance detection.

Proportionally, the primary resistance group had more females, Caucasians, younger patients, schooling, diabetes, and other comorbidities than the acquired group. A study conducted in China found that women had a 1.64-fold increased risk of primary MDR-TB (17). In Peru, a study conducted in the urban area of Lima showed that patients with primary resistance were younger and had better schooling. These results highlight that primary MDR-TB cases constitute a different reservoir of transmission, less related to lower socioeconomic groups and more related to other chronic diseases associated with higher TB acquisition (18).

Furthermore, studies in Brazil, India, and South Africa also showed a high incidence rate of MDR-TB among contacts, mainly among children and young people (19–21). The characteristics of cases of the primary resistance group differ from those of the acquired resistance group. Probably, the former is likely to be composed of people who spend more time in contact with infected people, like in the household (15). More recently, epidemiology and genetics studies with MDR-TB patients in China identified 93 clusters, in which 69% of the cases had epidemiological links with people they knew. The most common relationships between cases were social, such as living in the

**TABLE 4. Multivariate analysis: predictors of unsuccessful, lost to follow-up, and death outcomes among 334 primary MDR/XDR-TB notified cases in Rio de Janeiro State, 2000–2016**

Predictors	Unsuccessful	Lost to follow-up	Death
	ORa (95% CI) p-value	ORa (95% CI) p-value	ORa (95% CI) p-value
<b>Years of schooling</b>			
≥8 years	1.0	1.0	
<8 years	2.05 (1.13–3.72) 0.018	2.30 (0.99–5.34) 0.051	
<b>Unemployment</b>			
No			1.0
Yes			2.87 (1.17–7.04) 0.021
<b>Drug use</b>			
No		1.0	
Yes		3.38 (0.94–12.11) 0.061	
<b>Smoking</b>			
No		1.0	
Yes		2.91 (0.99–8.52) 0.051	
<b>Categories of drug resistance</b>			
MDR-TB	1.0		
XDR-TB	12.2 (2.24–66.41) 0.004		
<b>Chest radiography</b>			
Unilateral	1.0		
Bilateral	1.92 (1.06–3.47) 0.030		
<b>Comorbidities*</b>			
No	1.0		
Yes	2.06 (0.94–4.49) 0.068		
<b>Six-month culture conversion</b>			
No	1.0	1.0	1.0
Yes	0.19 (0.10–0.35) <0.001	0.36 (0.16–0.81) 0.015	0.08 (0.25–0.28) <0.001
<b>Inmate</b>			
No		1.0	
Yes		8.00 (1.33–47.79) 0.023	

ORa, adjusted odds ratio; 95% CI, 95% confidence interval; TB, tuberculosis; MDR-TB, multidrug-resistant TB; XDR-TB, extensively drug-resistant TB.  
\*Except diabetes and HIV  
**Source:** Prepared by the authors from the study results.

same residential complex, in the same street, or attending the same public places (22).

Socioeconomic factors are connected to the health-disease process and are significant predictors of the outcome of TB. Regarding treatment outcome, the cases with primary MDR-TB had a higher therapeutic success rate than the cases with acquired resistance (69.7% and 53.3%, respectively). The superior performance of the primary resistance group was also observed in another study that showed 6.3-fold higher odds of cure (15). Higher socioeconomic status is associated with a nearly 3-fold increased risk of primary MDR-TB as compared

**TABLE 5. Multivariate analysis: predictors of unsuccessful, lost to follow-up, and death outcomes among 1 935 acquired MDR/XDR-TB notified cases in Rio de Janeiro State, 2000–2016**

Predictors	Unsuccessful		Lost to follow-up	
	ORa (95% CI) p-value	ORa (95% CI) p-value	ORa (95% CI) p-value	ORa (95% CI) p-value
<b>≥40 years</b>				
Yes	1.0	1.0		
No	1.24 (0.98–1.57) 0.068	1.55 (1.19–2.01) 0.001		
<b>Years of schooling</b>				
≥8 years	1.0	1.0	1.0	
<8 years	1.61 (1.23–2.10) <0.001	1.52 (1.12–2.05) 0.006	1.50 (1.05–2.15) 0.023	
<b>Afro-Brazilian</b>				
No	1.0	1.0		
Yes	1.42 (1.14–1.86) 0.002	1.67 (1.26–2.22) <0.001		
<b>Unemployment</b>				
No	1.0			
Yes	1.34 (0.98–1.81) 0.058			
<b>Illicit drug use</b>				
No	1.0	1.0		
Yes	1.74 (1.11–2.74) <0.001	2.34 (1.56–3.53) <0.001		
<b>Smoking</b>				
No		1.0		
Yes		1.58 (1.02–2.45) <0.001		
<b>HIV status (n = 1 790)</b>				
Negative	1.0		1.0	
Positive	1.57 (1.00–2.48) 0.048		1.61 (0.98–2.65) 0.057	
<b>Categories of drug resistance</b>				
MDR-TB	1.0		1.0	
XDR-TB	5.43 (3.11–9.47) <0.001		2.26 (1.42–3.62) 0.001	
<b>Chest radiography</b>				
Unilateral	1.0		1.0	
Bilateral	2.20 (1.66–2.93) <0.001		2.90 (1.86–4.51) <0.001	
<b>Comorbidities*</b>				
No		1.0	1.0	
Yes		0.36 (0.21–0.62) <0.001	1.88 (1.22–2.88) 0.004	
<b>Six-month culture conversion</b>				
No	1.0	1.0	1.0	
Yes	0.17 (0.13–0.23) <0.001	0.48 (0.36–0.64) <0.001	0.08 (0.04–0.14) <0.001	

ORa, adjusted odds ratio; 95% CI, 95% confidence interval; TB, tuberculosis; MDR-TB, multidrug-resistant TB; XDR-TB, extensively drug-resistant TB; HIV, human immunodeficiency virus.  
\*Except diabetes and HIV  
**Source:** Prepared by the authors from the study results.

with acquired resistance and, conversely, lower socioeconomic status is associated with increased risk of acquired MDR-TB (18).

In this study, low schooling and unhealthy behavior factors (illicit drug use, smoking) were associated with the

unsuccessful outcome or LTFU in both groups. Low schooling may restrict understanding of the disease, leading to errors in treatment mainly due to the inappropriate use of medicines. Low schooling also makes it difficult to comply with routines and performance tests, contributing to unfavorable results (23). Unemployment, being Afro-Brazilian, illicit drug use, smoking, and being under 40 years old were associated with LTFU among acquired resistance cases. Unemployment was the only factor associated with death among primary MDR-TB cases. Although many studies show that socioeconomic or behavioral factors are a risk for MDR-TB, these factors may also indicate poor access to health services (24).

Among the acquired MDR-TB group, death was associated with less than eight years of schooling, being HIV-positive, bilateral disease, comorbidity, and XDR-TB, as found by other authors (25–28). HIV-positive patients had a 1.6-fold higher rate of mortality than those who were HIV-negative. However, HIV-positive was only associated with the acquired resistance group. One hypothesis is that low adherence to TB treatment and the use of intermittent treatment regimens—factors associated with worse outcomes and which are frequent in this group (28)—also occur in antiretroviral treatment.

Being an inmate was found to be a variable strongly associated with LTFU in the primary resistance group. In 2012, a study conducted in a prison in RJ showed that 83% of MTB strains belonged to one of the 13 identified clusters, suggesting high intrainstitutional transmission (29). In the same year, RJ had around 20 000 inmates distributed across 37 prison units (29). LTFU, in turn, may be related to scarce interaction between prison health care and health care services coordinated by municipal and state authorities. Such interaction decreases the probability that medication is taken. According to Sánchez and Larouzé, people in jail tend to reject impositions beyond those already suffered. Moreover, the coercive strategies often employed to ensure the intake of medication end up having limited effectiveness (30). These results confirm the recent statements issued by NTP-MoH, according to which prisons have favorable conditions for amplifying TB or primary MDR-TB in the general population and are reservoirs of the disease (4).

Moreover, having XDR-TB was more strongly associated with the unsuccessful outcome in the primary MDR-TB group than in the acquired MDR-TB group (ORa 12.2 and 5.43, respectively). This fact may reflect the delay in the diagnosis of drug resistance and an increase in the severity of the cases, as drug sensitivity tests for second-line drugs are only performed in patients known to have MDR-TB (31).

Having comorbidities was a protective factor for LTFU among the acquired resistance group. Perhaps this is because tertiary care provided a better resolution for these patients' comorbidities and, therefore, they adhered to treatment more frequently (16).

Finally, as other studies have shown, culture conversion by six months was a protective factor in both groups, being a good predictor for treatment success (32, 33).

For a long time, the WHO recommendation for the detection of drug resistance targeted patients with a history of TB treatment, not considering patients with primary drug resistance (34). Although the Xpert MTB/RIF molecular test has been available since 2014, only 30% to 40% of TB patients under treatment have been analyzed using the molecular test (4). Although the NTP-MoH recommendation is that culture

achievement and drug sensitivity testing have to be performed for all retreatment cases, in RJ, culture was performed in only 19.8% of patients in 2018 (6). Among the cases with a positive culture, drug sensitivity testing was performed in only 58.6%. Moreover, only 34.2% of the contacts of new cases of pulmonary TB with laboratory confirmation were examined (4). This poor performance can contribute to increasing the transmission of primary MDR-TB, therefore driving the spread of drug resistance, as has already been observed in countries such as China, India, and South Africa (24).

One of the limitations of this study was the impossibility of using drug resistance as an independent variable, due to the low number of DSTs reported for first- and second-line drugs. Another limitation is that until 2015, in the SITETB database, variables related to diabetes, comorbidities, illicit drug use, alcohol abuse, and smoking when classified as “no” can also mean lack of information. There is also no standardization for the classification of alcohol abuse, smoking, and mental health disorders. At any rate, the statistical findings reported here are robust due to the large sample size on which they are based.

In conclusion, a primary resistance of 14.7% among MDR-TB cases was found in RJ in 2000–2016. The cases with primary MDR-TB had a higher therapeutic success rate than the cases

with acquired resistance. Differences between the groups indicate that primary MDR-TB cases constitute a different reservoir of transmission, less related to lower socioeconomic groups and more related to other chronic diseases associated with higher TB acquisition. Moreover, the poor results observed in RJ can contribute to increasing the transmission of primary MDR-TB, therefore driving the spread of drug resistance. Recommendations include (1) improving the use of Xpert MTB/RIF as the first approach to a presumed TB patient, (2) increasing the early diagnosis of drug resistance, and (3) improving TB contact tracing.

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## Tuberculosis multirresistente primaria o adquirida: factores predictivos de resultados desfavorables del tratamiento en Rio de Janeiro entre el 2000 y 2016

### RESUMEN

**Objetivo.** Determinar cuáles son los factores clínicos o demográficos asociados con resultados desfavorables del tratamiento en pacientes con tuberculosis multirresistente (TB-MDR) primaria o adquirida en el estado de Rio de Janeiro.

**Métodos.** Estudio retrospectivo de cohorte con datos de 2 269 casos de TB-MDR entre el 2000 y el 2016. Se analizaron los factores asociados con resultados desfavorables, pacientes perdidos en el seguimiento o muerte en pacientes con resistencia primaria o adquirida mediante modelos de regresión bifactorial y multifactorial.

**Resultados.** En los casos de TB-MDR, la resistencia primaria fue de 14,7%. La proporción de resultados desfavorables fue de 30,3% en el grupo con resistencia primaria y de 46,7% en el grupo con resistencia adquirida. Las diferencias en las características demográficas y clínicas de los dos grupos fueron significativas. Proporcionalmente, el grupo con resistencia primaria tuvo más casos en las mujeres (46,4% frente a 33,5% en el grupo con resistencia adquirida), las personas caucásicas (47,3% frente a 34%) y en aquellas personas con 8 o más años de escolarización (37,7% frente a 27,4%). Los pacientes con tuberculosis extensamente resistente tenían 12,2 veces más probabilidades de tener un resultado desfavorable que los pacientes con TB-MDR. La comorbilidad fue 2 veces mayor en el grupo con resistencia primaria. El grupo con TB-MDR adquirida tenía 5,43 veces más probabilidades de tener tuberculosis extremadamente resistente. En ambos grupos, se asoció la enfermedad bilateral y menos de 8 años de escolarización con resultados desfavorables. En el grupo con resistencia primaria, las probabilidades de perder al paciente en el seguimiento fueron 8 veces mayores en los presidiarios. La conversión del cultivo a los seis meses fue un factor protector en todos los resultados.

**Conclusiones.** Los casos de resistencia primaria de TB-MDR constituyen un reservorio de transmisión diferente, que está relacionado con otras enfermedades crónicas asociadas con una mayor adquisición de tuberculosis. Los resultados insatisfactorios observados en el estado de Rio de Janeiro pueden contribuir a aumentar la transmisión de la TB-MDR primaria, y por lo tanto favorecer la farmacorresistencia.

**Palabras clave** Tuberculosis; monitoreo epidemiológico; resistencia a medicamentos; resultado del tratamiento; Brasil.

## Tuberculose multirresistente primária e adquirida: preditores de desfechos desfavoráveis do tratamento no Rio de Janeiro, 2000–2016

### RESUMO

**Objetivo.** Identificar fatores demográficos e clínicos associados a desfechos desfavoráveis do tratamento em pacientes com tuberculose multirresistente primária e adquirida no Estado do Rio de Janeiro.

**Métodos.** Estudo de coorte retrospectivo baseado em dados de 2.269 casos de tuberculose multirresistente no período 2000–2016. Fatores associados aos desfechos de falha terapêutica, perda de seguimento e óbito em pacientes com resistência primária e adquirida foram analisados em modelos de regressão bivariada e multivariada.

**Resultados.** Observou-se resistência primária em 14,7% dos casos de tuberculose multirresistente. Desfechos desfavoráveis ocorreram em 30,3% no grupo com resistência primária e 46,7% no grupo com resistência adquirida. Verificaram-se diferenças significativas quanto às características demográficas e clínicas entre os dois grupos. Proporcionalmente, o grupo com resistência primária apresentou mais casos em pacientes do sexo feminino (46,4% vs. 33,5% no grupo de resistência adquirida), caucasianos (47,3% vs. 34%) e com escolaridade  $\geq 8$  anos (37,7% vs. 27,4%). A tuberculose extensivamente resistente foi associada a uma chance 12,2 vezes maior de falha terapêutica que a tuberculose multirresistente e a chance de presença de comorbidades foi 2 vezes maior no grupo com resistência primária. A chance de ocorrência de tuberculose extensivamente resistente foi 5,43 maior no grupo com tuberculose multirresistente adquirida. Doença bilateral e escolaridade  $< 8$  anos foram associados à falha terapêutica em ambos os grupos. Estar encarcerado foi associado a uma chance 8 vezes maior de perda de seguimento no grupo com resistência primária. A conversão da cultura após seis meses de tratamento foi um fator de proteção para todos os desfechos.

**Conclusões.** Os casos de tuberculose multirresistente com resistência primária constituem um reservatório de transmissão distinto que está relacionado a outras doenças crônicas associadas a uma taxa maior de tuberculose. Os resultados ruins observados no Estado do Rio de Janeiro podem contribuir para aumentar a transmissão da tuberculose multirresistente primária, favorecendo a resistência aos medicamentos.

**Palavras-chave** Tuberculose; monitoramento epidemiológico; resistência a medicamentos; resultado do tratamento; Brasil.