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# EPIDEMIOLOGICAL DESCRIPTIVE STUDY OF DRUG-RESISTANT TUBERCULOSIS IN PARANÁ, BRAZIL

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### **ABSTRACT**

**Objective:** to describe the sociodemographic and clinical-epidemiological profile of individuals affected by DR-TB and its geographic distribution in Paraná between 2019 and 2023. **Method:** an epidemiological descriptive study was conducted using data from the Information System on Special Treatments for Tuberculosis (SITE-TB). This analysis focused on DR-TB cases reported in Paraná, Brazil, between 2019 and 2023. Data were collected from SITE-TB and analyzed for sociodemographic and clinical variables. Descriptive and inferential statistical analyses, including chi-square and Fisher's exact tests, were performed to explore associations between variables and treatment outcomes. Geographic data were analyzed to identify incidence rates across municipalities. **Results:** the study identified 419 DR-TB cases in Paraná, with a predominance of males (75.2%), primarily white individuals (51.3%), and an average age of 38.3 years. Most cases were new (85.7%) and pulmonary (95.3%). Primary resistance (75.9%) and monoresistance (71.1%) were common. The cure rate was 41.2%, and treatment outcomes were associated with resistance type and history of previous treatments. A visually heterogeneous pattern of case occurrence was observed. **Conclusions:** these results suggest that targeted public health measures and tailored treatment protocols could improve DR-TB management in the state of Paraná.

Keywords: Tuberculosis. Tuberculosis, multidrug-resistant. Epidemiologic studies.

## INTRODUCTION

Tuberculosis (TB) has been eliminated as a public health problem in developed countries. However, it persists among the poor populations and developing countries<sup>(1)</sup>. According to reports from the World Health Organization (WHO), in 2021, more than 10 million people had been diagnosed with the disease, resulting in over 1.5 million deaths globally<sup>(2)</sup>. In response, efforts are underway to reduce the number of deaths, the incidence rate, and to eliminate catastrophic costs to TB-affected households by 2035<sup>(3)</sup>.

The elimination of TB is included in the globally committed agenda and is addressed in the third Sustainable Development Goal (SDG) of the United Nations (UN)<sup>(4)</sup>. The End TB Strategy, proposed by the WHO, sets ambitious targets for the elimination of TB as a public

health problem. This strategy guides countries worldwide to develop and implement their action plans to combat disease. It underscores the importance of patient-centered care, timely diagnosis, and effective treatment as essential components to reduce TB incidence and mortality.

In line with this, Brazil's "National Plan for Ending Tuberculosis as a Public Health Problem" (*Plano Nacional pelo Fim da Tuberculose como Problema de Saúde Pública*) aims to decrease the TB incidence rate by 90% and reduce the number of deaths from the disease by 95% until 2035, compared to 2015 data<sup>(4)</sup>. The plan outlines specific strategies to enhance the effectiveness of TB control measures and ensure equitable access to healthcare services across all regions of the country.

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From this standpoint, drug-resistant tuberculosis (DR-TB) constitutes an additional impediment to the elimination of TB<sup>(5)</sup>. A meta-analysis estimated that the combined global prevalence of DR-TB is 11.6% (95% confidence interval, CI95%: 9.1–14.5)<sup>6</sup>. In Brazil, as per data from the Ministry of Health, there were around 7,900 new cases of DR-TB reported nationwide between 2015 and 2022, with the highest number of notifications occurring in the final year of the historical series<sup>(7)</sup>.

This may represent an additional challenge in disease control within the country, as the difficulties related with the cost and complexity of diagnosing and treating DR-TB, since individuals not adequately treated can exacerbate the transmission of drug-resistant strains of *Mycobacterium tuberculosis*<sup>(8)</sup>. While the global success rate for TB treatment is 86%<sup>(9)</sup>, DR-TB cure rates was 63%<sup>(10)</sup>; in Brazil, in 2020, 53.2% of DR-TB cases were cured<sup>7</sup>. This underscores the significance of the issue within the country.

Furthermore, due consideration must be given to the deleterious effects of the coronavirus disease 2019 (COVID-19) pandemic on the diagnosis, management, and surveillance of the people affected by TB and DR-TB<sup>(11)</sup>. Between 2019 and 2021, Paraná, a southern state of Brazil, recorded treatment default as the second most frequent outcome among cases of DR-TB and predominance of acquired resistance (over 75% of cases), differing from the national average which was 48.5%<sup>(11,12)</sup>.

In Paraná, the state plan for TB elimination as a public health issue sets additional goals to enhance the diagnosis of DR-TB<sup>(13)</sup>. One of the crucial targets is achieving 90% of diagnoses through rapid molecular testing for TB (RMT-TB), aimed not only at expediting identification but also at early detection of rifampicin resistance. This is essential to ensure prompt initiation of effective treatment and, consequently, to pursue disease cure more efficiently, contributing to the achievement of targets<sup>(13)</sup>.

In these plans, mitigating barriers to care for individuals with DR-TB within the healthcare system is one of the priority strategies<sup>(4)</sup>. Therefore, there is a need to understand the demographic and health characteristics of people affected by DR-TB, considering the strong

relationship between the disease and poverty. Thus, this research aimed to describe the sociodemographic and clinical-epidemiological profile of individuals affected by DR-TB and its geographic distribution in Paraná between 2019 and 2023.

### **METHODS**

This is an epidemiological descriptive study of DR-TB in the state of Paraná between 2019 and 2023. Data were assessed in the Information System on Special Treatments for Tuberculosis (Sistema de Informações de Tratamentos Especiais da Tuberculose – SITE-TB), an online system of surveillance and treatment follow-up used nationwide. In Brazil, patients can only assess DR-TB treatment trough the public health system, and treatment is only distributed by SITE-TB<sup>(8,14)</sup>.

The recommendations of the Reporting of Studies Conducted using Observational Routinely-collected Data (RECORD) were followed<sup>(15)</sup>. For this population-based study, cases of DR-TB that were registered as residents in Paraná at the notification and treatment in this same state were considered, excluding those marked with a "change of diagnosis" at the end of treatment. After exploring the database, the following variables of interest were delimited and conveniently categorized for subsequent analyses:

- a) gender (male; female);
- b) race/color (white; mixed; black; Asian; ignored/missing);
- c) schooling in years (none; 1–3; 4–7; 8–11; 12 or more; ignored/missing);
- d) age in years (continuous numerical variable)/age group in years (0–19; 20–59; 60 or more);
- e) human immunodeficiency virus (HIV) serology (positive; negative; not performed);
- f) special populations (healthcare professionals; immigrants; incarcerated population; homeless population);
- g) type of entry (new case; re-entry after abandonment; treatment failure; relapse; treatment regimen change; resistance pattern change);
- h) clinical form (pulmonary; extrapulmonary; pulmonary and

extrapulmonary);

- i) directly observed treatment (yes; no; ignored/missing);
- j) number of previous treatments (zero; one; two; three; four; five);
- k) type of resistance (primary; acquired; ignored/missing);
- l) initial resistance pattern (monoresistance; multidrug resistance; polyresistance; rifampicin resistance);
- m) current resistance pattern (monoresistance; multidrug resistance; polyresistance; rifampicin resistance; ignored/missing);
- n) outcomes (cure; abandonment; primary abandonment; treatment failure; under treatment; treatment regimen change; resistance pattern change; death; death from other causes; transferred to another unit; treatment completion).

Records of DR-TB cases in information systems that did not report a variable or filled the option "ignored" were categorized "ignored/missing" and included only in the descriptive analysis - which was conducted by calculating absolute and relative frequencies, as well as mean, median, and standard deviation, if applicable. To perform the geographical distribution of the incidence of these cases, the variable "city of residence at the time of notification" was used as a reference.

For the calculation of the incidence rate of DR-TB cases, the total number of cases by municipality from 2019 to 2023 was considered as the numerator. As the denominator, the number of inhabitants from the 2022 census was used for all years within the period; the result of this division was multiplied by 100,000. The data from the 2022 census were obtained through the *Instituto Brasileiro de Geografia e Estatística* (IBGE) portal. The cases were georeferenced by municipality using Jenks natural breaks classification.

Furthermore, we categorized the variable "closure status" (outcomes) into two groups: treatment success (cure and treatment completion) and treatment unsuccess (primary abandonment, abandonment, TB-related death and treatment failure). We excluded cases with other outcomes, assuming that they do not fully explain the outcome of the case. To establish the presence of an association, the chi-square test of

independence or Fisher's exact test were performed, as deemed appropriate.

Cases with unfilled independent variables were also excluded from this analysis, and if cases accounted for more than 20% of the total, the independent variable was removed. In instances where a statistically significant association between variables was identified (p-value < 0.05), the magnitude and direction of interdependence between them were elucidated through the analysis of adjusted residuals. Values exceeding +1.96 or falling below -1.96, respectively, indicated a positive or negative association.

For the descriptive and inferential analyses, the SPSS® software was used; and for geoprocessing, GeoDa® was employed. Regarding ethical aspects, it was approved by the Ethics Committee of the State University of Maringá, under opinion nº 6233844. In accordance with Resolutions nº 466/2012 and nº 674/2022, a favorable opinion was obtained from the Ethics Committee, with the ethical appreciation presentation certificate (CAAE) n. 63981922.6.0000.0104.

## **RESULTS**

There were 6,748 cases of DR-TB registered in Brazil, between 219 and 2023, and 422 in the state of Paraná. From those, three were not TB, resulting in 419 cases as the basis for the descriptive and spatial analysis. Subsequently, for inferential analysis, 133 cases were excluded due to treatment outcome, the final 286 cases with an outcome of interest were considered. Of these, 49 notifications were disregarded because they had uncompleted independent variables, leaving 237 cases.

Regarding the 419 cases initially included, there was a higher frequency of men (75.2%), of white race/color (51.3%), with 4 to 7 years of study (32.5%) and average age of 38.3 years. The majority did not have HIV coinfection (75.4%) and did not belong to special populations. There was a predominance of new cases (85.7%) and clinical pulmonary form (95.3%). Less than half of the patients performed directly observed treatment (46.3%) and had previous TB treatment (43.8%) (Table 1).

In relation to the resistance profile, the

majority was identified with the primary type of resistance (75.9%) and with the monoresistance pattern in the initial (71.1%) and current (70.6%) treatment. Concerning to the outcome, only 41.2% of cases were cured, however, 22.7%

were still undergoing treatment at the time of collecting these data. Moreover, it is noteworthy the large amount of missing data that was visualized, reaching 23.6% in the directly observed treatment variable (Table 1).

**Table 1.** Sociodemographic and clinical-epidemiological characteristics of drug-resistant tuberculosis cases in Paraná, Brazil, 2019–2023

Gender           Male         315 (75.2)           Female         104 (24.8)           Race/color         ****           White         215 (51.3)           Mixed         157 (37.5)           Black         35 (8.4)           Assian         3 (0.7)           Ignored/missing         9 (2.1)           Schooling (in years)         ****           None         13 (3.1)           1-3         54 (12.9)           4-7         136 (32.5)           8-11         124 (29.5)           12 or more         23 (5.5)           Ignored/missing         69 (16.5)           Age (in years) – mean; median; standard deviation         ***           -89         38.3; 36.0; 14.8           HIV serology         ***           Positive         47 (11.2)           Negative         316 (75.4)           Not performed         56 (13.4)           Healthcare worker – n (%)         ***           Yes         5 (1.2)           No         340 (81.1)           Ignored/missing         74 (17.7)           Inmigrant         ***           Yes         6 (1.4)           No         <	Variable	n (%)
Female         104 (24.8)           Race/color         215 (51.3)           Mixed         157 (37.5)           Black         35 (8.4)           Asian         3 (0.7)           Ignored/missing         9 (2.1)           Schooling (in years)         1.3 (3.1)           1-3         54 (12.9)           4-7         136 (32.5)           8-11         124 (29.5)           12 or more         23 (5.5)           Ignored/missing         69 (16.5)           Age (in years) - mean; median; standard deviation         8.3 (3.6.0; 14.8           HIV serology         8.1 (75.4)           Positive         47 (11.2)           Negative         316 (75.4)           Not performed         56 (13.4)           Healthcare worker - n (%)         4 (17.7)           Yes         5 (1.2)           No         340 (81.1)           Ignored/missing         74 (17.7)           Inmigrant         Yes           Yes         68 (16.2)           No         277 (66.1)           Ignored/missing         74 (17.7)           Incarcerated population         277 (66.1)           Yes         28 (6.7)           No<	Gender	
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Schooling (in years)       Schooling (in years)         None       13 (3.1)         1-3       54 (12.9)         4-7       136 (32.5)         8-11       124 (29.5)         Ignored/missing       69 (16.5)         Age (in years) – mean; median; standard deviation       69 (16.5)         0-89       38.3; 36.0; 14.8         HIV serology       70         Positive       47 (11.2)         Nogative       316 (75.4)         Not performed       56 (13.4)         Healthcare worker – n (%)       5 (1.2)         No       340 (81.1)         Ignored/missing       74 (17.7)         Immigrant       74 (17.7)         Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       74 (17.7)         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       28 (6.7)         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       70 (2.2)         Nee-entry after		
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12 or more       23 (5.5)         Ignored/missing       69 (16.5)         Age (in years) – mean; median; standard deviation       38.3; 36.0; 14.8         HIV serology       47 (11.2)         Positive       316 (75.4)         Not performed       56 (13.4)         Healthcare worker – n (%)       5 (1.2)         Yes       5 (1.2)         No       340 (81.1)         Ignored/missing       74 (17.7)         Immigrant       74 (17.7)         Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       277 (66.1)         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       28 (6.7)         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       70 (18.1)         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3) <td></td> <td></td>		
Ignored/missing       69 (16.5)         Age (in years) – mean; median; standard deviation       38.3; 36.0; 14.8         0–89       38.3; 36.0; 14.8         HIV serology       Feather Standard (75.4)         Positive       47 (11.2)         Not performed       56 (13.4)         Healthcare worker – n (%)       ***         Yes       5 (1.2)         No       340 (81.1)         Ignored/missing       74 (17.7)         Immigrant       ***         Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       ***         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       ***         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       ***         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)		
Age (in years) – mean; median; standard deviation       38.3; 36.0; 14.8         HIV serology       47 (11.2)         Positive       47 (11.2)         Negative       316 (75.4)         Not performed       56 (13.4)         Healthcare worker – n (%)       Yes         Yes       5 (1.2)         No       340 (81.1)         Ignored/missing       74 (17.7)         Immigrant       Yes         Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       New case         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		
0−89	Ignored/missing	69 (16.5)
HIV serology Positive		
Positive	0–89	38.3; 36.0; 14.8
Negative       316 (75.4)         Not performed       56 (13.4)         Healthcare worker – n (%)       ***         Yes       5 (1.2)         No       340 (81.1)         Ignored/missing       74 (17.7)         Immigrant       ***         Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       ***         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       ***         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       ***         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)	HIV serology	
Negative       316 (75.4)         Not performed       56 (13.4)         Healthcare worker – n (%)       ***         Yes       5 (1.2)         No       340 (81.1)         Ignored/missing       74 (17.7)         Immigrant       ***         Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       ***         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       ***         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       ***         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)	Positive	47 (11.2)
Not performed       56 (13.4)         Healthcare worker – n (%)       Yes         Yes       5 (1.2)         No       340 (81.1)         Ignored/missing       74 (17.7)         Immigrant       74 (17.7)         Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       277 (66.1)         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       28 (6.7)         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       59 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)	Negative	· · · · · · · · · · · · · · · · · · ·
Healthcare worker – n (%) Yes		
Yes       5 (1.2)         No       340 (81.1)         Ignored/missing       74 (17.7)         Immigrant       74 (17.7)         Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       277 (66.1)         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       28 (6.7)         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       76 (18.1)         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		
No       340 (81.1)         Ignored/missing       74 (17.7)         Immigrant       74 (17.7)         Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       277 (66.1)         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       4 (17.7)         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		5 (1.2)
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Immigrant       Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       74 (17.7)         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       79         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       70         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		
Yes       6 (1.4)         No       339 (80.9)         Ignored/missing       74 (17.7)         Incarcerated population       78 (16.1)         Yes       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       28 (6.7)         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		74 (17.7)
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Ignored/missing       74 (17.7)         Incarcerated population       68 (16.2)         No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       28 (6.7)         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       78 (18.1)         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		
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No       277 (66.1)         Ignored/missing       74 (17.7)         Homeless population       28 (6.7)         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       78 (18.1)         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		(0 (1( 2)
Ignored/missing       74 (17.7)         Homeless population       28 (6.7)         Yes       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       59 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		· · · · · · · · · · · · · · · · · · ·
Homeless population       28 (6.7)         No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		
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No       315 (75.2)         Ignored/missing       76 (18.1)         Type of entry         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)	• •	
Ignored/missing       76 (18.1)         Type of entry       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)		28 (6.7)
Ignored/missing       76 (18.1)         Type of entry       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)	No	315 (75.2)
Type of entry         New case       359 (85.7)         Re-entry after abandonment       25 (6.0)         Treatment failure       10 (2.4)         Relapse       8 (1.9)         Regimen change       14 (3.3)         Resistance pattern change       3 (0.7)	Ignored/missing	76 (18.1)
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Re-entry after abandonment  Treatment failure  Relapse  Regimen change  Resistance pattern change  25 (6.0)  10 (2.4)  8 (1.9)  14 (3.3)  Resistance pattern change  3 (0.7)		359 (85.7)
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Resistance pattern change 3 (0.7)		
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Variable	n (%)
Pulmonary	399 (95.3)
Extrapulmonary	11 (2.6)
Pulmonary/extrapulmonary	9 (2.1)
Directly observed treatment	
Yes	194 (46.3)
No	126 (30.1)
Ignored/missing	99 (23.6)
Number of previous treatments	· · · (== · · · )
Zero	183 (43.8)
One	171 (40.8)
Two	42 (10.0)
Three	13 (3.1)
Four	9 (2.1)
Five	1 (0.2)
Type of resistance	
Primary	318 (75.9)
Acquired	99 (23.6)
Ignored/missing	2 (0.5)
Initial resistance pattern	
Monoresistance	298 (71.1)
Multi-resistance	16 (3.8)
Polyresistance	12 (2.9)
Rifampicin resistance	93 (22.2)
Current resistance pattern	
Monoresistance	296 (70.6)
Multi-resistance	83 (19.8)
Polyresistance	12 (2.9)
Rifampicin resistance	26 (6.2)
Ignored/missing	2 (0.5)
Outcomes	
Cure	174 (41.2)
Abandonment	53 (12.6)
Primary abandonment	1 (0.2)
Treatment failure	7 (1.7)
Under treatment	95 (22.7)
Regimen change	16 (3.8)
Resistance pattern change	2 (0.5)
Death	12 (2.9)
Death from other causes	15 (3.9)
Transferred to another unit	5 (1.2)
Treatment completed	39 (9.3)

Significant statistical association was identified between treatment outcome and four independent variables: number of previous treatments, type of resistance, and initial and current resistance pattern. We observed that three previous TB treatments, primary

resistance, and the initial and current pattern of monoresistance were positively associated with treatment success; conversely, acquired resistance and the initial and current pattern of rifampicin resistance were positively associated with treatment unsuccess (Table 2).

**Table 2.** Sociodemographic and clinical-epidemiological characteristics of drug-resistant tuberculosis cases, according to treatment outcome, in Paraná, Brazil, 2019–2023

Variable	Treatment outcome Success – n (%)	Unsuccess – n (%)	p-value
Gender			

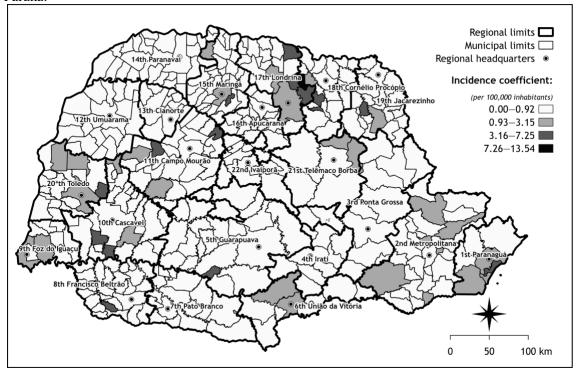
	Treatment outcome	Treatment outcome	
Variable	Success – n (%)	Unsuccess – n (%)	p-value
Male	134 (73.6)	48 (26.4)	0.892*
Female	41 (74.5)	14 (25.5)	0.692
Race/color			
Mixed	58 (65.9)	30 (34.1)	
Black	14 (77.8)	4 (22.2)	0.201†
Asian	2 (100.0)	0 (0.0)	$0.201^{\dagger}$
White	101 (57.8)	28 (45.2)	
Schooling (in years)			
1–3	33 (71.7)	13 (28.3)	
4–7	66 (70.1)	29 (24.9)	0.100‡
8–11	61 (76.3)	19 (23.7)	$0.199^{\dagger}$
12 or more	15 (93.7)	1 (6.3)	
Age group (in years)	- ( )	( /	
0–19	13 (68.4)	6 (31.6)	
20–59	147 (75.4)	48 (24.6)	$0.441^{\dagger}$
60 or more	15 (65.2)	8 (34.8)	J <u>.</u>
HIV serology	10 (00.2)	o (5)	
Positive	11 (61.1)	7 (38.9)	
Not performed	23 (76.7)	7 (23.3)	$0.439^{\dagger}$
Negative Negative	141 (74.6)	48 (25.4)	0.437
Type of entry	141 (74.0)	48 (23.4)	
Re-entry after abandonment	3 (37.5)	5 (62.5)	
Treatment failure	4 (57.1)	3 (42.9)	
Relapse	2 (66.7)	1 (33.3)	$0.090^\dagger$
Regimen change	5 (71.4)	2 (28.6)	0.090
New case	161 (75.9)	51 (24.1)	
Clinical form	101 (73.9)	31 (24.1)	
	2 (50.0)	2 (50 0)	
Extrapulmonary	2 (50.0)	2 (50.0)	$0.294^{\dagger}$
Pulmonary/extrapulmonary	4 (100.0)	0 (0.0)	0.294
Pulmonary	169 (73.8)	60 (26.2)	
Directly observed treatment	71 (71 0)	20 (20 0)	
No	71 (71.0)	29 (29.0)	$0.455^{\dagger}$
Yes	104 (75.9)	33 (24.1)	
Number of previous treatments	00 (74.1)	20 (25 0)	
Zero	80 (74.1)	28 (25.9)	
One	77 (80.2)	19 (19.8)	0.001*
Two	13 (61.9)	8 (38.1)	$0.031^{\dagger}$
Three	3 (37.5)+	5 (62.5)	
Four	2 (50.0)	2 (50.0)	
Type of resistance			
Primary	$149 (76.8)^+$	45 (23.2)	0.035*
Acquired	26 (60.5)-	$17(39.5)^+$	0.033
Initial resistance pattern			
Monoresistance	$147 (79.0)^+$	39 (21.0)-	
Multi-resistance	4 (57.1)	3 (48.9)	$0.003^{\dagger}$
Polyresistance	5 (71.4)	2 (28.6)	0.003
Rifampicin resistance	19 (51.4)	18 (48.6) <sup>+</sup>	
Current resistance pattern			
Monoresistance	$149 (79.3)^{+}$	39 (20.7)	
Multi-resistance	18 (54.5)	15 (45.5)+	0.001*
Polyresistance	5 (71.4)	2 (28.6)	$0.001^{\dagger}$
Rifampicin resistance	3 (33.3)	6 (66.7) <sup>+</sup>	

<sup>\*</sup>positive association; "negative association; \*chi-square test of independence; †Fisher's exact test.

Based on the spatial distribution, a visually heterogeneous pattern of case occurrence was observed among the 399 municipalities. It was identified that 355 cities had an incidence rate between 0.00–0.92 cases per 100,000 inhabitants; 28 municipalities had between 0.93–

3.15 cases per 100,000 inhabitants; 15 municipalities had between 3.16–7.25 cases per 100,000 inhabitants; and Jataizinho had the highest incidence rate (7.26–13.54 cases per 100,000 inhabitants), as depicted in Figure 1.

**Figure 1.** Spatial distribution of the incidence of drug-resistant tuberculosis in the 399 municipalities of Paraná.



## **DISCUSSION**

The profile of DR-TB cases in Paraná exhibits common characteristics with those identified in both national and international studies. The findings align regarding the predominance of new cases among males<sup>(16)</sup>, with an average age of 38 years<sup>(16-18)</sup>, presenting the pulmonary clinical form<sup>(19)</sup>, along with approximately 13% of cases demonstrating coinfection with HIV<sup>(19)</sup>. Notably, this profile mirrors findings from a study involving individuals affected by non-resistant tuberculosis in the state of Paraná<sup>(20)</sup>.

Nevertheless, disparities between our study and the one conducted using national data are evident. The national research identified a predominance of cases among black individuals (60.9%) and those with less than eight years of education (68.0%)<sup>(19)</sup>. Additionally, it was found

that in Brazil, acquired drug resistance (70.0%) and multidrug-resistant patterns (50.9%) were predominant, contrasting with the situation in Paraná, where primary drug resistance (75.9%) and monoresistant patterns prevailed.

We observed that more than 25% of individuals afflicted by DR-TB in the state of Paraná belonged to a special population group, with the incarcerated population being the most affected, representing 16.2% of the total notifications. The "State Plan for Ending Tuberculosis as a Public Health Problem, 2022–2030" (*Plano Estadual pelo Fim da Tuberculose como Problema de Saúde Pública, 2022–2030*) underscores the importance of prioritizing the diagnosis and treatment of TB in special populations<sup>(13)</sup>.

In this context, a study conducted in Espírito Santo, Brazil, investigated the occurrence of TB in 34 prison units. The research revealed that the

rate of diagnosed cases reached 17.3 cases per thousand individuals, with a low percentage of cure (72.6%)<sup>(21)</sup>. We should mention that, in these cases, directly observed treatment significantly reduced the likelihood of treatment failure (odds ratio, OR: 0.29; 95%CI: 0.01–0.76), including the progression to DR-TB, a strategy deemed highly efficacious<sup>(21)</sup>.

However, despite directly observed treatment being a primary recommendation for treatment adherence, including for special populations<sup>(4)</sup>, it was found that fewer than 50% of cases with DR-TB received this form of follow-up. As an alternative solution, a study in Norway highlighted that supervised treatment can also be administered via video calls, a proposal that has shown to increase adherence, reduce the duration of home visits by healthcare providers, and garner better acceptance among patients<sup>(22)</sup>.

A meta-analysis encompassing over 430,000 patients indicated that the likelihood of developing DR-TB is 42% higher in individuals coinfected with HIV compared to those without the coinfection<sup>(23)</sup>. The presence of HIV affected 11.2% of the participants in our study; moreover, over 13% were not tested. These findings underscore the importance for public health authorities to prioritize expanding dual testing for individuals with either infection (TB or HIV) and to implement appropriate treatment strategies.

Furthermore, the post-pandemic scenario resulting from COVID-19 has been observed to impede disease control efforts, primarily due to a reduction in new TB diagnoses, screening, and treatment, potentially leading to an upsurge in new cases of DR-TB<sup>(24)</sup>. In our study, although 22.7% of cases are still under treatment, only 41.2% achieved cure as an outcome, with loss to follow-up occurring in over 50 cases. Thus, challenges persist regarding treatment completion.

In Paraná, primary drug resistance is predominant (75.9%). As an explanatory hypothesis, this reflects the possibility of high transmission of resistant strains within the state. Strategies to address this issue should incorporate systemic approaches, including strengthening healthcare systems focused on interrupting transmission and utilizing innovative diagnostic and screening techniques,

as well as developing new drugs with mechanisms of action that reduce treatment duration and enhance adherence<sup>(25)</sup>.

Considering the predominance of monoresistance in Paraná, early identification of this condition is crucial to prevent progression to severe forms of resistance consequently, ensure the highest likelihood of cure. A positive association has been observed between treatment success and monoresistance and primary resistance. In the case of monoresistance, this may be attributed to the utilization of less complex therapeutic regimens, thus increasing the probability of achieving a cure.

A study reinforces our findings by reporting that the likelihood of cure in cases of primary resistance is increased by 6.3 times (95%CI: 2.35–16.79) compared to cases with acquired resistance<sup>(26)</sup>. The literature suggests that the demographic and socioeconomic profile of individuals with primary resistance characterized by females, white individuals, young people, and those with higher levels of education<sup>(27,28)</sup>. This profile constitutes a distinct group from those with acquired resistance and may be less associated with socially vulnerable groups, thereby potentially increasing the likelihood of cure.

The positive effect of previous treatment on successful outcomes in DR-TB contradicts the findings of a study which showed that previous treatment was associated with unfavorable outcomes<sup>(29)</sup>. We hypothesized that prior experience may have increased adherence to medical instructions consequently, and, improved therapeutic outcomes. Also, we that rifampicin resistance observed positively associated with treatment failure, which may be justified by the fact that its resistance is often associated with bacterial strains more difficult to treat<sup>(30,31)</sup>.

In this context, the WHO issued new treatment guidelines for rifampicin-resistant TB, incorporating shorter and fully oral drug regimens. These modifications have direct implications for case outcomes and necessitate further investigation<sup>(32)</sup>. However, it is essential to underscore that all explanatory hypotheses regarding the observed relationships in the research necessitate additional scrutiny through

subsequent scientific investigations to validate or refute the interpretations provided herein.

Regarding the spatial distribution of DR-TB cases, a heterogeneous pattern was evident, with most municipalities predominantly exhibiting an incidence coefficient between 0.00–0.92 cases per 100,000 inhabitants. A study analyzing the geographic distribution of drug-sensitive TB in the macro-regions of Paraná indicated that the higher detection of the disease in specific areas might be attributed to programmatic and socioeconomic factors, a phenomenon that may similarly apply to DR-TB<sup>(32)</sup>.

Coordination between different levels of healthcare is essential to providing comprehensive care, which is an indispensable condition for achieving the objectives and targets set by the state, the country, and the WHO. This ensures a seamless continuum of care, which is crucial for meeting the ambitious goals of TB control. Effective coordination not only facilitates the timely diagnosis and treatment of TB but also enables better management of patient follow-up and adherence to treatment protocols.

As limitations of this study, we mention the use of secondary data, which are inherently susceptible to data entry errors, as well as the substantial level of incompleteness, hindering a comprehensive analysis of the true epidemiological landscape. Furthermore, portion of these data were collected during the COVID-19 pandemic, which may have led to changes in the pattern of diagnosis, treatment, and notification due to the strain on healthcare services, particularly in surveillance capacities.

## **CONCLUSION**

We identified that DR-TB cases were predominantly among males, white individuals, those with 4 to 11 years of education, and with a mean age of 38 years. These cases did not present TB-HIV coinfection and were not part of special populations. Most cases were new, exhibited pulmonary form, primary resistance, and monoresistance. Our findings indicated that previous treatments, as well as the type and pattern of resistance, were associated with success or failure of the treatment. Georeferencing revealed a heterogeneous pattern

of DR-TB incidence among different municipalities.

These results suggest that targeted public health measures and tailored treatment protocols could improve DR-TB management in the state of Paraná, considering the utilization of the most effective diagnostic methods and, particularly, the implementation of actions that support treatment adherence in a manner centered on the individual, biological, and social needs of people with TB. For this, we understand that coordination between different levels of healthcare is essential.

Further research should focus on contributing to these underlying factors demographic and clinical characteristics to enhance DR-TB control efforts. Emphasizing a holistic approach to TB care that integrates advanced diagnostic techniques with patientcentered treatment plans can significantly enhance treatment outcomes. comprehensive approach not only addresses the medical needs of TB patients but also considers their social and economic contexts, thereby improving overall health outcomes and moving closer to the elimination of TB as a public health threat.

## ESTUDO EPIDEMIOLÓGICO DESCRITIVO DA TUBERCULOSE DROGARRESISTENTE NO PARANÁ, BRASIL

### **RESUMO**

Objetivo: descrever o perfil sociodemográfico e clínico-epidemiológico dos indivíduos afetados pela TB-DR e sua distribuição geográfica no Paraná entre 2019 e 2023. **Método:** estudo epidemiológico descritivo realizado com dados do Sistema de Informações sobre Tratamentos Especiais para a Tuberculose (SITE-TB). Esta análise teve como foco os casos de DR-TB relatados no Paraná, Brasil, entre 2019 e 2023. Os dados foram coletados do SITE-TB e analisados quanto às variáveis sociodemográficas e clínicas. Análises estatísticas descritivas e inferenciais, incluindo testes de qui-quadrado e exato de Fisher, foram realizadas para explorar associações entre variáveis e desfechos do tratamento. Os dados geográficos foram analisados para identificar as taxas de incidência entre os municípios. **Resultados:** o estudo identificou 419 casos de TB-DR no Paraná, com predomínio do sexo masculino (75,2%), principalmente indivíduos brancos (51,3%) e idade média de 38,3 anos. A maioria dos casos foi nova (85,7%) e pulmonar (95,3%). Resistência primária (75,9%) e monorresistência (71,1%) foram comuns. A taxa de cura foi de 41,2%, e os resultados do tratamento foram associados ao tipo de resistência e histórico de tratamentos anteriores. Um padrão visualmente heterogêneo de ocorrência dos casos foi observado. **Conclusões:** os resultados sugerem que medidas de saúde pública direcionadas e protocolos de tratamento sob medida poderiam melhorar o manejo da TB-DR no estado do Paraná.

Palavras-chave: Tuberculose. Tuberculose multirresistente. Estudos epidemiológicos.

## ESTUDIO EPIDEMIOLÓGICO DESCRIPTIVO DE LA TUBERCULOSIS FARMACORRESISTENTE EN PARANÁ, BRASIL

#### RESUMEN

Objective: describir el perfil sociodemográfico y clínico-epidemiológico de los individuos afectados por TB-DR y su distribución geográfica en Paraná-Brasil entre 2019 y 2023. Método: estudio epidemiológico descriptivo realizado con datos del Sistema de Información sobre Tratamientos Especiales para la Tuberculosis (SITE-TB). Este análisis se centró en los casos de DR-TB reportados en Paraná, Brasil, entre 2019 y 2023. Los datos fueron recogidos del SITE-TB y analizados en cuanto a las variables sociodemográficas y clínicas. Se realizaron análisis estadísticos descriptivos e inferenciales, incluyendo pruebas de chi-cuadrado y exacta de Fisher, para explorar asociaciones entre variables y desenlaces del tratamiento. Los datos geográficos fueron analizados para identificar las tasas de incidencia entre los municipios. Resultados: el estudio identificó 419 casos de TB-DR en Paraná, con predominio del sexo masculino (75,2%), principalmente individuos blancos (51,3%) y edad media de 38,3 años. La mayoría de los casos fueron nuevos (85,7%) y pulmonares (95,3%). Resistencia primaria (75,9%) y monorresistencia (71,1%) fueron comunes. La tasa de curación fue del 41,2%, y los resultados del tratamiento se asociaron con el tipo de resistencia y el historial de tratamientos anteriores. Se observó un patrón visualmente heterogéneo de ocurrencia de los casos. Conclusiones: los resultados sugieren que medidas de salud pública dirigidas y protocolos de tratamiento a medida podrían mejorar el manejo de la TB-DR en el estado de Paraná-Brasil.

Palavras chave: Tuberculosis. Tuberculosis multirresistente. Estudios epidemiológicos.

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