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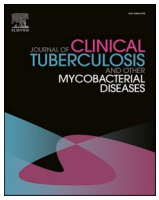

Treatment of drug-resistant tuberculosis in children and young adolescents in Brazil

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ABSTRACT

Introduction: Drug-resistant tuberculosis (DR-TB) is a global threat and a challenge for public health authorities worldwide. In children, the diagnosis is even more challenging and DR-TB is poorly described in the literature, as are its treatment outcomes. In this study, we aimed to describe the treatment of drug-resistant TB in children and young adolescents in Brazil.

Methods: A descriptive epidemiological study of treatment for DR-TB in children under 15 years of age in Brazil between 2013 and 2020. The primary data source was the Information System for Special Tuberculosis Treatments (SITE-TB). Categorical variables were analyzed using relative frequencies (%) and continuous variables by measures of central tendency to characterize the profile of the cases, namely: sociodemographic, clinical characteristics, procedures, tests performed and treatment success. In order to verify the distribution of cases, a spatial analysis was carried out based on the municipality where the cases resided.

Results: Between 2013 and 2020, 19,757 tuberculosis (TB) cases occurred in children aged <15 years in Brazil, and 46 cases of treatment for DR-TB were reported during the same period (annual average of 6 cases). Of these, 73.9% were aged 10–14, 65.2% were male, 4.3% were HIV+ and 43.3% were underweight (BMI<18.5) at the start of treatment. 17.4% had previous contact with TB, 69.6% had primary resistance, 47.8% multidrug resistance. The median duration of treatment was 15 months. DOT and standardized treatment regimen were performed in 52.2% of cases. Bacilloscopy was performed for 97.8% (57.8% positive); culture for 89.1% (75.6% positive), rapid molecular test for 73.9% with proven resistance to rifampicin in 55.8%. Susceptibility testing revealed resistance mainly to isoniazid (87.8%) and rifampicin (60.6%). 73.9% of cases were successfully treated and one death was reported. Cases were treated in 26 Brazilian municipalities, with the majority in Rio de Janeiro (15) and São Paulo (4).

Conclusion: DR-TB treatment was recorded in <1% of general TB cases in children and young adolescents, suggesting underreporting of drug-resistant cases in the country. Despite the low number of registered cases, the data reflect the situation of DR-TB in this population and describe important aspects of the problem, as the child needs comprehensive, individualized care, with support from different professionals. We recommend a strengthening of the country's referral services for the care of children with DR-TB so that surveillance and health care services can work together to identify and follow up cases.

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1. Introduction

Drug-resistant tuberculosis (DR-TB) is currently a global health threat, as its treatment is more difficult and requires drugs that cause more adverse effects – issues that represent a greater challenge for patients, professionals and health services [1]. The problem is associated with increased morbidity and mortality, sequelae, cost and complexity [2].

Worldwide studies estimate that between 3 and 13% of children diagnosed with tuberculosis (TB) may develop DR-TB [3,4,5], but many cases may not be identified due to the difficulty of diagnosing the disease in this age group, as bacteriological identification is not always possible [6].

In children, TB drug resistance is often confirmed or presumed through an epidemiological link, usually with ill adults, and treatment should be based on drug susceptibility findings. Due to the cases specificity, and the increased risk of toxicity, treatment decisions should be made by specialists in qualified health centers [7].

In recent years, DR-TB treatment has advanced with the use of more effective and less toxic oral drugs, contributing to increased adherence and success. In children, the possibility of shorter and safer treatments is also observed, with the inclusion of oral regimens and new drugs [8], however, due to the scarcity of data on treatment in this group, many of the recommendations are still based on the adults treatment [9].

With the advancement of diagnostic technologies and the strengthening of health surveillance in recent years, an increasing number of children are being diagnosed and treated for TB. There has also been an increase in funding for research into childhood TB, but the number of diagnoses and treatments for DR-TB in this group remains low [10].

In Brazil, since 2013, all people with an indication for DR-TB treatment must be registered in the Information System for Special Tuberculosis Treatments (SITE-TB), which complements the National Information System for Notifiable Diseases (SINAN), where TB cases are registered. The system provides a greater amount of data that demonstrates the magnitude of cases and the assistance provided to people with DR-TB and all cases notified to the system are assessed and validated by a team of medical experts [11].

DR-TB has a substantial long-term impact on the psychosocial, neurological and respiratory health of children and adolescents, and so far the number of investigations focused on this age group is limited [8]. This is a priority research topic and is still considered a knowledge gap [7,9], reinforcing the importance of the present study.

Information on DR-TB cases in children in Brazil is even more scarce, which does not allow us to know the real situation of the problem, so this study aims to describe the treatment of the disease in children under 15 years of age in the country, highlighting exposures, characteristics of the resistance in this group and relevant aspects for successful treatment.

2. Method

2.1. Study design

Descriptive epidemiological study; case series type.

2.2. Study population and data collection sources

Children under 15 years of age who had treatment for DR-TB and were reported in the SITE-TB between January 1, 2013 to December 31, 2020 were considered as the study population.

To make some comparisons, we also considered public data of general TB cases in individuals under 15 years of age reported in SINAN in Brazil during the same period, made publicly available by DataSUS, Ministry of Health (MoH) of Brazil [12].

For the current epidemiological surveillance of DR-TB in Brazil, confirmed TB cases with the following diagnosis are considered: case with resistance to any anti-TB drug confirmed by susceptibility testing or rapid molecular test for rifampicin resistance (Xpert MTB/RIF) [13].

The mentioned resistance patterns are as follows: multidrug-resistant TB (MDR-TB), which is defined as resistance to at least rifampicin and isoniazid; monoresistance, caused by an isolate that shows resistance to a single first-line anti-TB drug; polyresistance, caused by an isolate that is resistant to more than one anti-TB drug (but not resistant to both isoniazid and rifampicin simultaneously); and extensively drug-resistant TB (XDR-TB), which is resistant to rifampicin (and may also be resistant to isoniazid) and at least one fluoroquinolone and at least one other "Group A" drug [14,15].

The types of resistance considered were primary resistance, which is present before the start of therapy and due to the transmission of a drug-resistant strain of *Mycobacterium tuberculosis*, and acquired or secondary resistance, which is the emergence of resistance after receiving antituberculosis therapy [16].

For the purposes of this study, individuals under 15 years of age were considered children and young adolescents, based on the age groups referenced by international organizations, including the World Health Organization (WHO) and United Nations (UN) indicators [17,18].

2.3. Place of study

The present study was conducted in Brazil, which consists of 26 Federative Units (UF) and the Federal District, and 5,570 municipalities. The country is the largest in South America and the fifth in the world in terms of area. With continental proportions, it extends over an area of 8,514,876.599 km^2 and according to population estimates, the country, in 2021, had 213.317 million inhabitants, of which 44.039 million were under 15 years of age [19]. It has an infant mortality rate of 11.20 deaths/1,000 live births, a fertility rate of 1.76 children/woman, a Human Development Index (HDI) of 0.76 and Gini Index of 0.54 [20].

2.4. Analysis plan

Categorical and continuous variables were analyzed, grouped according to sociodemographic and clinical characteristics, and the procedures and tests performed for the diagnosis. The variables are: age group, sex, race, HIV test, site of infection, contact with TB, system input type, clinical form, previous treatments, type and pattern of resistance, treatment outcomes, year of diagnosis, municipality of residence, with calculations of absolute and relative frequency measures. For continuous variables, measures of central tendency and dispersion were calculated.

Calculations were also performed from created variables, such as BMI (Body Mass Index) based on weight and height, duration of treatment (date of beginning and end of treatment), and number of procedures and exams performed (based on data recorded for bacilloscopies, cultures, Xpert MTB/RIF, susceptibility test and chest X-ray).

Descriptive analyzes were performed using Epi Info 7 and Excel software. In addition, a spatial analysis was performed based on the municipality of residence making use of geographic data from the digital grid of Brazilian municipalities; the software used was ArcGIS® 10.8.

2.5. Ethical considerations

The data used in this study were non-nominal and were provided by the Brazilian MoH. The study works with secondary data and is part of a doctoral project approved by the Research Ethics Committee of the School of Nursing of Ribeirão Preto, University of São Paulo, Brazil.

3. Results

From 2013 to 2020, 19,757 cases of TB in children under 15 years of age were reported in Brazil and in the same period, SITE-TB received 46 cases of treatment for DR-TB, which will be described below.

The year with the highest number of DR-TB cases in children was

2020, with 11 cases, followed by 2018 and 2019, with 10 and 7, respectively. The annual average number of cases during this period was 6.

In terms of sociodemographic characteristics, most of them were between 10 and 14 years old (73.9%) and male (65.2%). Brown or mixed race represented the majority of cases (41.3%), followed by white race (32.7%). Two children were diagnosed HIV+ (5.0%) among 40 tested (Table 1).

As for nutritional status, the BMI could be assessed in 30 children at the start of treatment, and 13 (43.3%) of these were classified as underweight (BMI <18.5), with a median of 18.7, ranging from 10.5 to 28.5 (Table 1).

Only 8 children (17.4%) were reported to have had known contact with another TB case, and the site of probable infection was intradomiciliary for 43.5% of the cases, highlighting the fact that information was missing in several records (47.9%). The pulmonary clinical form was the most common (67.4%) and 89.2% of the cases entered into the system as new cases of DR-TB. 58.7% of the cases had records of previous TB treatments. Most children had primary-type resistance (69.6%) and the multidrug-resistance pattern was the most identified (47.8%), Table 2.

Directly observed treatment (DOT) was registered for 52.2% of the cases. The duration of treatment, measured between the beginning and the end, occurred in up to 462 days, which is, 15 months, for 50% of cases, ranging from 0 days for one death, to 641 days (21 months) for the longest treatment.

The main initial treatment regimen for DR-TB was standardized treatment, occurring in 24 (52.2%) of cases. Different standardized regimens were used, with the following drug combinations being recorded most frequently: Capreomycin, Ethambutol, Pyrazinamide, Levofloxacin and Terizidone for 10 MDR-TB cases and Rifampicin, Pyrazinamide, Ethambutol and Streptomycin for 3 monoresistance cases. Another 22 (47.8%) treatments were individualized, in other words, they were personalised treatments for each case.

Table 1
Socio demographic and health characteristics of treatment for DR-TB in children and young adolescents in Brazil (2013–2020).

Variables	No	%
Age range (years)		
0–4	7	15.2
5–9	5	10.9
10–14	34	73.9
Sex		
Male	30	65.2
Female	16	34.8
Race*		
Brown or mixed race**	19	41.3
White	15	32.7
Black	7	15.2
Asian	2	4.3
Indigenous	1	2.2
Unknown	2	4.3
HIV test		
Positive	2	4.3
Negative	38	82.6
Unrealized	6	13.1
Total	**46**	**100**
Variable	Median	Range
BMI***	18.7	10.5–28.5

* Based on official Brazilian census categories **category named Pardo in portuguese ***information from 30 records.
Source: SITE TB/MoH Brazil.

Table 2
Clinical characteristics of treatment for DR-TB in children and young adolescents in Brazil (2013–2020).

Variables	No	%
Place of likely contagion		
Intradomiciliary	20	43.5
Social/community	2	4.3
Other	2	4.3
Unknown	22	47.9
TB case contact		
Yes	8	17.4
No	38	82.6
Clinical form of TB		
Pulmonary	31	67.4
Extrapulmonary	8	17.4
Both	7	15.2
Type of extrapulmonary TB (n=15)		
Ganglionary	7	46.7
Pleural	4	26.7
Miliary	1	6.7
Meningoencephalic	1	6.7
Osseous	1	6.7
Other	1	6.7
Number of previous TB treatments		
None	19	41.3
1	19	41.3
2	6	13.1
3	2	4.3
System input type		
New Case	41	89.2
Failure	2	4.3
Relapse	2	4.3
Change of the resistance pattern	1	2.2
Resistance type		
Primary	32	69.6
Secondary or acquired	12	26.1
Unknown	2	4.3
Initial resistance pattern		
Multiresistance (MDR-TB)	22	47.8
Resistant to rifampicin	10	21.7
Monoresistance	9	19.6
Polyresistance	3	6.5
Extensive drug-resistance (XDR-TB)	1	2.2
Unknown	1	2.2
Total	**46**	**100**

Source: SITE TB/MoH Brazil.

Adverse drug reactions were reported in 3 (6.5%) cases, and included nausea, vomiting, joint pain, insomnia and severe peripheral neuropathy.

For diagnostic and treatment control tests, bacilloscopy was performed in 45 (97.8%) of the cases, with some having the test performed up to 20 times, and 26 (57.8%) cases had a positive result on the first examination. Culture was performed for 41 (89.1%) cases, with a positive result for 31 (75.6%). The cases had up to 20 diagnostic and follow-up cultures, but none of them were positive after the 5th test. For the Xpert MTB/RIF, the performance of at least one test was recorded in 34 (73.9%) cases, with rifampicin resistance detected in 55.8% of them in the first test (Table 3).

Chest X-ray was performed in 41 (89.1%) cases, being the unilateral non-cavitary presentation the most identified in the first exam, for 16 (39.0%) cases, followed by the bilateral cavitary presentation, for 9 cases (21.9%). It was also noted that 50% of cases had at least 8 follow-

Table 3
Procedures and tests performed during treatment for DR-TB in children and young adolescents in Brazil (2013–2020).

Procedure/Test	Cases that underwent at least one procedure/test	Median number of procedure/test performed	Range
Bacilloscopy	45 (97.8%)	3	0–20
Culture	41 (89.1%)	2	0–20
Xpert MTB/RIF	34 (73.9%)	2	0–20
Chest X-ray	41 (89.1%)	2	0–10
Follow-up medical appointment	46 (100.0%)	8	1–21

Source: SITE TB/MoH Brazil.

up medical appointments during treatment (Table 3).

The line probe assay (LPA), a test that was not implemented nationwide at the time of the study, was performed in 6 (13.0%) cases and detected rifampicin (R) rpoB, isoniazid (H) inhA and isoniazid (H) KatG mutations.

In the susceptibility test, of the 32 children tested, resistance to isoniazid was detected in 29 (90.6%) and to rifampicin in 20 (62.5%). A smaller number of children were tested for susceptibility to other drugs, with emphasis on pyrazinamide, where resistance was detected in 5 (62.5%) of the 8 tests performed, and streptomycin, in 10 (33.3%) of the 30 (Fig. 1).

Regarding the treatment outcomes, we observed that most of them were successful: cure (n=21; 45.7%) or complete treatment (n=13; 28.2%). There was one death (1) and some changes in regimen (4) or resistance pattern (2). We also highlight 5 cases that were still in treatment at the time of data collection.

The spatial analysis of the cases showed that 12 brazilian federated units (FU) registered treatment of DR-TB. The FUs with the most cases being Rio de Janeiro (43.5%), followed by São Paulo (15.2%) and Paraná (8.7%). Cases were distributed among 26 Brazilian municipalities, with 15 cases in Rio de Janeiro and 4 in São Paulo (Fig. 2).

4. Discussion

The study aimed to describe the DR-TB treatment in Brazilian children. 46 cases were identified, 69.6% had primary resistance, 47.8% MDR-TB pattern. Resistance was detected mainly to isoniazid and rifampicin, and 73.9% of the children were successfully treated. As for the monitoring system, SITE-TB, it has shown advances in the follow-up of cases and is an important source of information for surveillance and research in the country [11].

Brazil is considered one of the countries with the highest TB burden in the world. Although it is not yet included in the list of priority countries for DR-TB [1], this remains a relevant and urgent problem. DR-TB is considered a global public health crisis that directly affects disease elimination plans and the STOP TB strategy [21]. There is still limited knowledge about the situation of resistance in children, as even general TB is underreported in this group due to the diagnosis challenges [3,7,8,22].

The number of treatments for DR-TB in children in the country in the period is apparently low, compared with number of cases of general TB reported during the same period and age group. Although the expected data on resistance in children are not available nationally, international studies evaluating the burden of the disease estimate that up to 13% of children with general TB may be resistant [3,4,5], suggesting the existence of underreporting, a challenge for disease control, fact already described in studies that compared data from different Brazilian information systems [23,24].

Additionally, it is important to consider that the COVID-19 pandemic has directly affected the control and reorganization of TB care, potentially leading to increased resistance [25,26]. These trends may be better observed in the coming years since this study analyzed data up to 2020, year with a slight increase in the number of cases.

A large proportion of cases are concentrated in young adolescents, aged 10–14 years, who are more easily diagnosed and have an increased risk of exposure to TB [7,27]. In this group, the disease generally presents more like that of adults, is more often infectious, and is a major source of transmission [28]. In addition, adolescents are vulnerable and prone to challenges in follow-up and treatment adherence, reinforcing the importance of additional counseling for this age group [6].

Low BMI and HIV co-infection were identified in some children, which demonstrates the clinical fragility that can be caused by or cause the disease [4,29,30]. This information may be underestimated, as many records did not have weight and height data, and six children were not tested for HIV, but it demonstrates the importance of follow-up and comprehensive care for cases, since malnutrition in children with DR-TB may be associated with increased mortality and poorer treatment

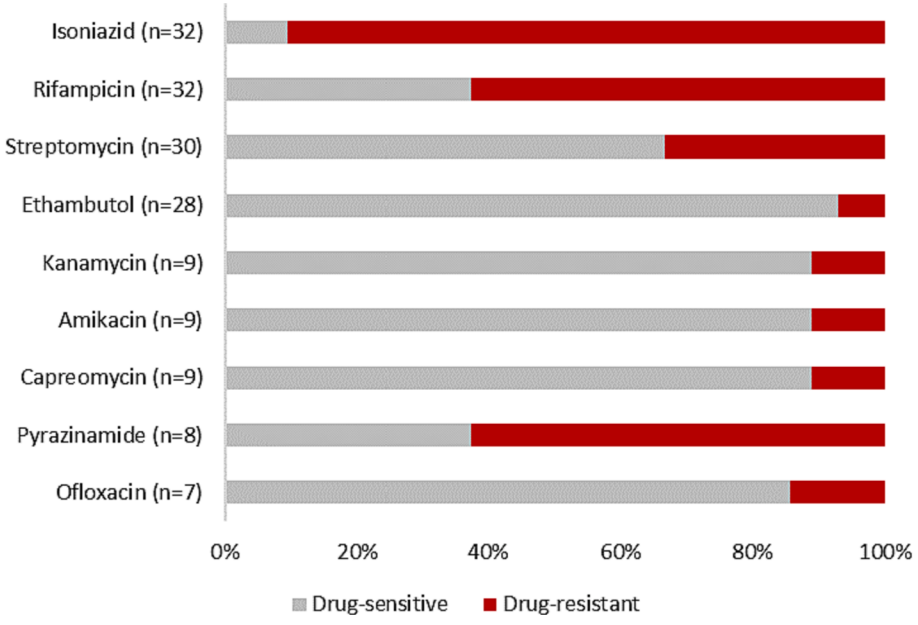

Fig. 1. Result of susceptibility test performed during treatment for DR-TB in children and young adolescents in Brazil (2013–2020). Source: SITE TB/MoH Brazil.

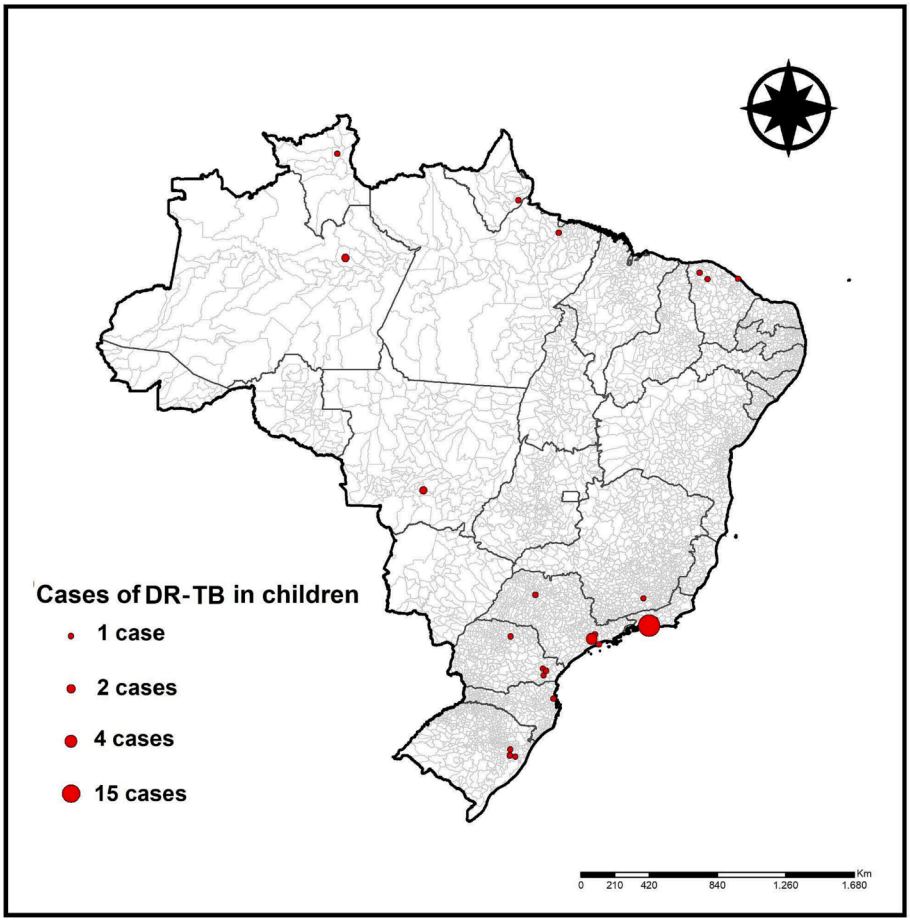

Fig. 2. Spatial distribution of treatment for DR-TB in children and young adolescents according to municipality of residence, Brazil (2013–2020). Source: SITE TB/MoH Brazil.

outcomes, especially in those who are co-infected [31].

DR-TB cases in children usually result from contact with a person with TB among their family [32], acquiring primary DR-TB, which was the type of resistance most frequently identified in the cases; however, the results are inconsistent with the data from the history of previous contact with TB cases, which was only confirmed for 17% of the children. The household was the most commonly reported site of probable infection, and the number of cases without information on this variable suggests a possible failure in the investigation and search of contacts of these children.

Contact tracing is one of the most important strategies for disease control and is even more necessary for DR-TB cases. According to a systematic review [33], 51.4% of contacts of investigated TB cases had latent TB infection, making them potential candidates for treatment, thus demonstrating the great value of this measure in preventing the spread of infection. It is also known that children benefit more from preventive treatment, as they are at greater risk of developing TB disease [34].

MDR-TB, characterized by resistance to both rifampicin and isoniazid, was the most commonly reported, and the results of susceptibility tests indicated that these two drugs had the highest percentage of resistance among the cases. The fact that almost half of the children already showed resistance to both drugs differs from the data for general cases of DR-TB in Brazil, which show that about 50% of the cases initially present resistance to only rifampicin [35]. One weakness of this classification may reside in fact that other resistances may not be being tested frequently in the country.

It was observed that slightly more than half of the cases were treated using the DOT strategy, a model strongly recommended by the WHO for all TB cases, especially DR-TB, even with new forms of supervision such as video-observed treatment (VOT) [9,36]. The absence of direct treatment monitoring may be related to lower adherence rates, treatment dropout, and difficulty in monitoring drug toxicity or side effects, as well as hindering the timely provision of additional support to patients [7]. Children, in particular, should also be monitored to determine response to therapy and for early detection of adverse events [37].

Treatment regimens for DR-TB in Brazil have changed over the years with the incorporation of new drugs [38]. In this study, standardized regimens accounted for just over half of the treatments. In Brazil, standardized regimens are used for the most frequently identified DR-TB profiles for programmatic purposes to facilitate case management and rational use of drugs.

For cases that are not usual, such as less frequent combinations of resistance, presence of comorbidities, toxicities, and patients with multiple therapeutic schemes, individualized schemes are elaborated [13], which underscores the need to have a qualified referral network for the correct evaluation and follow-up of each case. The patient-centered approach is very important in DR-TB, with attention to patient preferences and social, vulnerability, cultural and environmental aspects of care, in addition to adherence strategies and monitoring of clinical response and treatment safety [9].

Diagnostic data demonstrate the occurrence of follow-up, with most cases undergoing bacilloscopy, culture, Xpert MTB/RIF and chest X-Ray at different times during treatment.

Half of cases had at least 8 follow-up medical appointment and the number of evaluations should take into account the individual aspects of each case and the duration of treatment, which had a median of 15 months. A lower number of follow-ups raises the possibility that they are

not being reported in the system or may indicate other individual problems within the services, such as professionals being overloaded or patients not returning for all consultations. It is strongly recommended to follow children and young adolescents and perform the necessary tests to timely diagnose treatment failure, relapse or resistance to other drugs [9].

Adverse reactions were recorded in a minimal number and treatments were completed at a higher percentage (73.9%) than the global average success rate for the DR-TB treatment, which was only 60% in the world in 2021 [1], possibly indicating that these treatment cases in Brazil received good care and adequate follow-up.

Overall, we can conclude that despite the small number of cases, the data reflect the situation of DR-TB in children and young adolescents in Brazil, and describe important facets of the problem. This was only possible due the existence of a robust information system with follow-up data.

The study advances knowledge and can support the formulation of evidence-based policies to guide the treatment and care of children with DR-TB, aiming for comprehensive care in which cases are timely identified by the health system and referred for treatment [21].

Children and young adolescents with DR-TB need comprehensive, individualized care, with the support of different professionals (doctors, nurses, pharmacists, nutritionists, social workers, psychologists and others). This is also a group that should be encouraged to return to school when they are no longer infected and the family and caregivers should be involved as active members of the health care team [37], which is why it is important that services in Brazil are prepared and trained to deal fully with these cases.

It is important to highlight that the study has limitations due to the use of secondary data, which are susceptible to poor quality records. Additionally, due to the long study period (8 years), some treatment or diagnostic strategies were introduced by the Brazilian health system during this time, making it impossible to evaluate some periods for some variables.

We recommend the strengthening reference services and public health units in the country for the care of children and young adolescents with DR-TB. This will enable surveillance and healthcare services to work together for the timely identification and continuous follow-up of cases to achieve adherence, cure and prevention of deaths and new infections.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that might appear to influence the work reported in this article.Although the cited agencies supported the research, the funders had no role in the study design; in the collection, analysis, and interpretation of the data; and in the decision to submit the article for publication.

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