Research note

Characterization of drug-resistant tuberculosis in Brazil, 2014*

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Abstract

Objective: to describe drug-resistant tuberculosis (DR-TB) notifications in Brazil. **Methods**: this is a descriptive study of clinical and epidemiological characteristics of DR-TB notifications in 2014 on SITETB and TBWeb, these being information systems on which cases involving special treatment regimens are registered. **Results:** there were 1,574 cases, 94.8% of which had the pulmonary form, 27.6% involved primary resistance, and 50.9% were multidrug-resistant; 70.6% of cases were male, 87.0% were between 20 and 59 years old, 60.9% were of Afro-Brazilian, and 68.0% had less than 8 years of schooling; as for comorbidities, 13.1% of patients had AIDS, 11.3% had diabetes, 25.8% made harmful use of alcohol, 21.0% were illegal drugs users, and 22.2% were tobacco users. **Conclusion:** the majority of DR-TB notifications were related to men, young people, Afro-Brazilian and people with low levels of education; there was a high percentage of primary resistance, as well as multidrug-resistance and comorbidities, with emphasis on substance use.

Keywords: Tuberculosis, Multidrug-Resistant; Communicable Diseases; Public Health; Epidemiology, Descriptive.

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Introduction

Tuberculosis (TB) is one of the ten leading causes of death worldwide, affecting mainly low and middle income countries.[1] Inadequate, intermittent or interrupted treatments may select resistant strains, which are transmissible.[2] Resistance to just one drug is classified as mono-resistance, while resistance to more than one drug is classified as poly-resistance. Multidrug-resistance (MDR-TB) is a form of poly--resistance characterized by resistance to, at least, isoniazid and rifampicin.[2] Drug-resistant tuberculosis (DR-TB) is an increasingly frequent phenomenon[1] and has the potential to make inefficacious the available therapeutic regimens.[1]

> *Resistance to just one drug is classified as mono-resistance, while resistance to more than one drug is classified as poly-resistance. Multidrug-resistance (MDR-TB) is a form of poly-resistance characterized by resistance to, at least, isoniazid and rifampicin.*

It is estimated that globally in 2017 rifampicin-resistant TB or MDR-TB occurred in 3.5% of new cases (primary resistance) and in 18.0% of previously treated cases (acquired resistance).[1] According to the same estimates, 7.1% of new cases and 7.9% of previously treated cases had mono-resistance to isoniazid.[1]

In the case of Brazil, the World Health Organization (WHO) estimated an incidence rate of 1.2 MDR-TB or rifampicin-resistant TB cases per 100,000 inhabitants in 2017.[1] These patterns were related to 1.5% new TB cases and 8.0% previously treated cases.[1] In 1997 in Brazil, 10.6% of pulmonary TB cases with a positive bacilloscopy result had some level of drug resistance, 2.2% of which were MDR-TB.[3] In 2006, 1.4% of new TB cases and 7.5% of previously treated cases were MDR-TB.[4]

When describing the epidemiological profile of DR-TB, recent Brazilian studies have used local data[5-9] rather than national data.

The objective of this study was to describe notifications of DR-TB in Brazil.

Methods

This was a descriptive study of DR-TB notifications in 2014. We used data from the São Paulo Tuberculosis Patient Control System (TBWeb), for the Brazilian state of São Paulo, and data from the Tuberculosis Special Treatment Information System (SITETB) for the other Brazilian Federative Units. SITETB is used countrywide to monitor special TB treatments. TBWeb is exclusively used by the state of São Paulo for all TB cases there. We used both systems, because part of the monodrug-resistant cases in the state of São Paulo were only recorded on TBWeb.

The study population was comprised of DR-TB cases diagnosed in 2014, notified on the TBWeb for the state of São Paulo and on the SITETB for the rest of Brazil.

The variables analyzed were:

a) Federative Unit of residence;

b) sex (female; male);

c) ethnicity/skin color (white; black; brown/mixed race; indigenous; unknown), for analysis purposes, the black and brown/mixed race categories were grouped together into the Afro-Brazilian (*negro*, in Portuguese) category;10

d) age group (in years: up to 19; 20 to 59; 60 or more);

e) education level (in years no schooling: illiterate; 1 to 3; 4 to 7, 8 to 11; 12 or more; unknown);

f) presence or absence of alcoholism, diabetes mellitus, AIDS, illegal drugs and tobacco use;

g) TB clinical form (pulmonary, extra-pulmonary, pulmonary and extra-pulmonary);

h) resistance type (acquired; primary); and

i) drug-resistance pattern (MDR; non MDR poly-resistance; mono-resistance to isoniazid; mono-resistance to rifampicin; mono-resistance to streptomycin; mono-resistance to ethionamide; mono-resistance to ethambutol; mono-resistance to pyrazinamide; unknown; not classified).

The resistance pattern was based on the resistance record of each drug, regardless of the diagnosis method applied. Cases classified as DR-TB on the information systems, but with no resistance record, were included in the analysis as "unknown" resistance pattern.

We described cases by means of absolute and relative frequencies. Data were analyzed using STATA version 12.0.

The study project was approved by the University of Brasília Health Sciences Faculty Human Research Ethics Committee: Report No. 1,431,237. The databases we analyzed were requested from the Ministry of Health and from the São Paulo State Health Department, in accordance with Law No. 12,527/201111 and São Paulo State Government Decree No. 58,052/2012.[12]

Results

In 2014, 1,574 DR-TB cases were reported in Brazil, most of them in the Southeast region (53.0%), in particular the states of São Paulo and Rio de Janeiro (Table 1). All state capital cities reported at least one case, except for Boa Vista, the capital of the only state with no reported cases: Roraima.

Table 1 – Distribution of drug-resistant tuberculosis cases per Federative Unit (FU), Brazil, 2014

Region and FU	Cases N (%)
North	
Rondônia	6 (0.4)
Acre	3 (0.2)
Amazonas	55 (3.5)
Pará	50 (3.2)
Roraima	–
Amapá	2 (0.1)
Tocantins	2 (0.1)
Northeast	
Maranhão	23 (1.5)
Piauí	3 (0.2)
Ceará	95 (6.0)
Rio Grande do Norte	11 (0.7)
Paraíba	16 (1.0)
Pernambuco	71 (4.5)
Alagoas	9 (0.6)
Sergipe	10 (0.6)
Bahia	114 (7.2)
Southeast	
Minas Gerais	38 (2.4)
Espírito Santo	9 (0.6)
Rio de Janeiro	333 (21.2)
São Paulo	454 (28.8)
South	
Paraná	45 (2.9)
Santa Catarina	42 (2.7)
Rio Grande do Sul	137 (8.7)
Midwest	
Mato Grosso do Sul	17 (1.1)
Mato Grosso	7 (0.4)
Goiás	9 (0.6)
Federal District	1 (0.1)
Unknown	12 (0.8)
Brazil	**1,574 (100.0)**

Table 2 – Type and resistance pattern of drug-resistant tuberculosis cases in Brazil, 2014

Variables	Frequency N (%)
Resistance type	
Primary	434 (27.6)
Acquired	1,102 (70.0)
Unknown	38 (2.4)
Drug resistance pattern	
Multidrug-resistant (MDR)	801 (50.9)
Non MDR poly-resistance	149 (9.5)
Mono-resistance to isoniazid	342 (21.7)
Mono-resistance to rifampicin	141 (9.0)
Mono-resistance to streptomycin	71 (4.5)
Mono-resistance to ethionamide	–
Mono-resistance to ethambutol	5 (0.3)
Mono-resistance to pyrazinamide	3 (0.2)
Unknown	44 (2.8)
Not classified	18 (1.1)

Of the total number of cases, 27.6% (434) had primary resistance (Table 2). Among the 801 MDR-TB cases, 159 (20.5%) had primary resistance and 615 (79.5%) had acquired resistance. Among the 774 pulmonary or pulmonary plus extra-pulmonary MDR-TB cases, 159 were new cases and 615 were previously treated ones.

Regarding personal characteristics, 70.6% (1,111) were male, 87.0% (1,370) were 20 to 59 years old, 60.9% (959) were Afro-Brazilian and 68.0% (1,070) had less than eight years of schooling (Table 3).

In relation to clinical characteristics, most of the cases were exclusively pulmonary, 94.8% (1,492), 13.1% (206) had AIDS and 11.3% (178) had diabetes. The use of illicit drugs, harmful use of alcohol and tobacco were reported, respectively, by 21.0% (330), 25.8% (406) and 22.2% (350) of cases (Table 3). Of the total cases, 56.5% (890) had some of the comorbidities studied, and the use of substances (alcohol, tobacco and /or illegal drugs) was reported in 42.0% (661) of cases.

All analyzed variables had more than 90% completeness.

Discussion

In Brazil, in 2014, almost one third of reported DR-TB cases had never been treated for TB and more than a half had MDR-TB. Most of them were men, were Afro-Brazialian, of working age, had a low education level and had at least one comorbidity, with emphasis on the use of substances. The relative frequency of primary resistance cases was higher than that described for Brazil in 2010 (between 6.0% and 8.0%),13 which may suggest transmission of resistant strains or improved DR-TB diagnosis. The latter hypothesis considers the expansion of sensitivity test supply, as well as expansion of rapid molecular testing for TB.[14]

MDR-TB predominance among DR-TB was also found in the Brazilian state of Espírito Santo: 47.7% between 2002 and 2012;[9] the poly-resistance, reported by the same study was higher than the percentages we found (namely 14.0% and 9.5%).[9] Regarding forms of mono-resistance, our results show predominance of mono-resistance to isoniazid, followed by mono-resistance to rifampicin. Similar results were found in previous studies.[5,7,9] Notwithstanding, predominant mono-resistance to streptomycin had already been reported in the municipality of São José do Rio Preto, in the state of São Paulo, between 2009 and 2013.[6]

The number of pulmonary MDR-TB cases reported in 2014 accounted for 43.7% of those estimated by WHO for Brazil that year (19.4% of primary cases and 64.7% of acquired cases).[15] The WHO estimates were based on reported cases, on underreporting estimated by specialists and on the most recent

Table 3 – Demographic and clinical characteristics of drug-resistant tuberculosis cases in Brazil, 2014

Variable	Frequency N (%)
Sex	
Female	463 (29.4)
Male	1,111 (70.6)
Age group (in years)	
≤19	83 (5.3)
20-59	1,370 (87.0)
≥60	121 (7.7)
Education level (in years of schooling)	
None	99 (6.3)
1-3	507 (32.2)
4-7	464 (29.5)
8-11	255 (16.2)
≥12	104 (6.6)
Unknown	145 (9.2)
Ethnicity/skin color	
White	546 (34.7)
Afro-Brazilian	959 (60.9)
Asian	6 (0.4)
Indigenous	10 (0.6)
Unknown	53 (3.4)
Clinical form	
Pulmonary	1,492 (94.8)
Extra-pulmonary	30 (1.9)
Pulmonary + extra-pulmonary	52 (3.3)
Comorbidity	
AIDS	206 (13.1)
Diabetes mellitus	178 (11.3)
Illegal drugs use	330 (21.0)
Harmful use of alcohol	406 (25.8)
Tobacco use	350 (22.2)

Brazilian survey on drug resistance.[16] The difference found may arise from an overestimation by WHO, given the known limitations of the method,[16] but it may also indicate a hidden endemic situation in the Brazil.

The predominance of men, Afro-Brasilian, young people, and people with low levels of education was also found in other municipal, state and local studies between 2000 and 2013; with an exception in the municipality of Porto Alegre, in the state of Rio Grande do Sul, between 2006 and 2007, when most DR-TB cases (64.3%) were w hite individuals.[5-9,17-20] This variation is possibly due to regional differences in the ethnic composition of population. The DR-TB case profile is the same as that associated with treatment of drug-sensitive TB cases loss to follow-up.[21-23] This convergence suggests the need to improve monitoring of these groups, to prevent resistant forms of the disease.

One in nine DR-TB cases had AIDS (11.3%), a higher proportion than that found among MDR-TB cases in Espírito Santo State between 2000 and 2004 (9.5%).[18] HIV/AIDS and DR-TB co-infection is more complex due to how each infection is managed.[24] In relation to diabetes, the percentage we found was in-between those found in Porto Alegre and in the states of Espírito Santo and Amazonas between 2000 and 2013 (they ranged from 7.7% to

13.6%).[5,9,20] Diabetes has the potential to interfere with TB treatment, with higher risk of treatment failure, TB recurrence and death.[25]

The relative frequency of substance use is consistent with that found in São José do Rio Preto between 2009 and 2013,[6] as well as among MDR-TB cases at the São Paulo State Referral Center in 2010.[19] In Espírito Santo, among DR-TB cases reported between 2002 and 2012,[9] a higher percentage of tobacco and alcohol users was reported. Exclusively in relation to alcohol, the result of our study is notably higher than the data for the state of Amazonas between 2000 and 2011 (6.2%).[20] In general, the high percentages suggest that TB services need to be capable of providing care focused on DR-TB patients and psycho-social support.[26] These are priorities of the End TB Strategy.[27]

The use of data from two information systems – TBWeb and SITETB – may indicate a limitation of this study, due to potential non-uniformity of data collection and recording. Underreporting of DR-TB cases may be another limitation, although their notification is compulsory in Brazil.[28]

This study outlined the profile of DR-TB cases reported in Brazil in 2014, and found a relative frequency of primary DR-TB cases higher than previous levels[13] and a lower number of pulmonary MDR-TB cases than that estimated by the WHO.[15]

We hope that these results will be able to inform programmatic decisions referring to DR-TB in Brazil, considering its magnitude, territorial distribution and specificities of the most affected groups.

Authors' contributions

Jacobs MG and Pinto Junior VL contributed to the study conception. Jacobs MG analyzed the data and wrote the first version of the manuscript. Both authors revised the manuscript, wrote and approved the final version of the manuscript.

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