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Brazilian cities profile, the occurence of tuberculosis and its drug-resistant form

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Abstract *Tuberculosis is closely related to living conditions. This study classifies Brazilian municipalities according to the occurrence of tuberculosis (TB) and drug-resistant TB (DR-TB) cases and describes them with regard to the population's health conditions, tuberculosis control indicators, demographic and socioeconomic profile. In 2014, 327 municipalities reported DR-TB cases. Integrated regions of development or metropolitan regions accounted for 80.1% of national DR-TB cases. Municipalities with DR-TB cases had worse TB outcome indicators, but higher culture test percentages, and more inhabitants and better socioeconomic indicators. The 3,644 municipalities with TB cases, but without DR-TB cases, had the worst socioeconomic indicators among the three groups. The 1,594 municipalities without TB cases had the lowest rates of unemployment and AIDS detection and greater coverage of primary healthcare. The different profiles found in the study can sustain improved national interventions for TB and drug-resistant TB control in Brazil.*

Key words *Drug-resistant tuberculosis, Socioeconomic factors, Cities, Health equity, Public health*

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Introduction

Currently, tuberculosis (TB) is a serious public health problem of global relevance[1]. Despite all accumulated knowledge about the disease, TB is still very much alive and is the most important infectious disease of our times[1,2]. In the world, some 10.4 million people affected by TB were estimated for 2015[1]. In the same year, Brazil recorded 63,189 new TB cases, an incidence rate of 30.9/100 thousand inhabitants[3].

Reducing disease incidence requires early case detection and appropriate treatment until cure. In this context, the proportion of drug-resistant TB cases (DR-TB) reduces the share of successful treatments, making them lengthier, costlier and more toxic[1,2]. It is estimated that, in 2015, 3.9% of new TB cases and 21% of previously treated cases, respectively, had MDR-TB or rifampicin-resistant TB worldwide. In Brazil, 1.5% of new cases and 8% of retreatments, respectively, had MDR-TB or rifampicin-resistant TB[1].

The distribution of TB cases is not homogeneous in the population; it is related to several individual and social factors such as alcohol abuse, HIV coinfection, low schooling, marital status, low income, housing conditions and malnutrition, as well as context-related factors, such as *per capita* Gross Domestic Product (GDP), human development index (HDI) and access to public services and goods[4-6].

From the understanding of social determination of TB and the additional challenge of DR-TB to disease control in a heterogeneous country with a continental dimension such as Brazil, this study classifies the Brazilian municipalities by DR-TB cases, sensitive TB cases or lack of TB cases in 2014, and describes them with regard to their demographic and socioeconomic characteristics and health conditions of the population and specifically of TB control, in order to support national TB actions.

Methods

This is an ecological study about the socioeconomic characteristics of Brazilian municipalities according to evidence of TB and DR-TB cases in 2014. It included all existing Brazilian municipalities in 2014 based on information from the 2010 Demographic Census, that is, 5,565 municipalities out of 5,570 existing in 2014.

To classify the municipalities by occurrence of DR-TB cases, we used data from the TB Special Treatment Information System (SITETB)[7] and the São Paulo State TB Patient Control System (TBWeb)[8]. TB cases under special treatment regimens, including DR-TB treatment, are recorded and monitored in those systems, where patients characteristics, disease, monitoring and case outcomes are available. We used TBWeb data for the State of São Paulo and data from SITETB for the rest of Brazil. Since the State of São Paulo, unlike other Brazilian Federated Units, records its mono-resistant cases only in its own system, namely, TBWeb, we merged the two databases. Regarding SITETB cases, the onset date of treatment was used as a diagnostic date proxy. As for cases among inmates from the State of São Paulo, we used the municipality of residence as the municipality of notification, since TBWeb system only registers *inmate* as municipality of residence.

The classification of other TB cases were retrieved from data of the Brazilian National Information System for Notifiable Diseases (SINAN)[9], where compulsorily notified and confirmed cases are registered and where characteristics of patients, disease, monitoring and outcomes are also available.

Regarding cases' municipality of residence characteristics, with regard to those related to healthcare, we obtained information from the Information Technology Department of the Unified Health System (SUS) for 2014[10]. TB control indicators were calculated from SINAN's data, also for 2014. Finally, as for demographic and socioeconomic variables, we used the 2010 Demographic Census information[11] and the 2012 Atlas of Human Development[12].

The variables analyzed were: TB incidence rate (per 100,000 inhabitants), retreatments among total TB cases (%), culture tests among retreated TB cases (%), culture tests among new TB cases (%), laboratory-confirmed pulmonary cases (%), HIV testing in TB cases (%), TB-HIV coinfection among new cases (%), new TB cases by outcome (cure, loss to follow-up, failure, transference and unknown outcome) (%), directly observed treatment (DOT) (%), population covered by primary healthcare (%), AIDS detection rate (per 100,000 inhabitants), *per capita* average household income (R$), municipal HDI (MHDI), GINI index, population living in extreme poverty (%), population density (people/km^2), life expectancy at birth (years), urban population (%), number of inhabitants, infant mortality (per 1,000 live births), *per capita* GDP (R$), unemployment among the population aged 16 and over (%), population sharing room

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with two or more people (%), illiteracy among the population aged 15 years and over (%), metropolitan region or integrated region of development (RIDE) (the country has 36 metropolitan regions and 3 RIDEs that, in 2014, concentrated 53% of the population)[13].

The municipalities were described by the median and quartiles of the analyzed variables. A comparison was made between the TB indicators of the municipalities a) with reported DR-TB cases and b) without reported DR-TB cases (but with TB cases) through the Mann-Whitney test; additionally, municipalities' demographic and socioeconomic factors a) with reported DR-TB cases, b) without DR-TB cases (but with TB cases) and c) without TB cases were compared through the Kruskal-Wallis test, followed by the Dunn method in the variables in which the hypothesis of equity was rejected. We chose non-parametric tests since the variables did not show a normal distribution[14] evaluated through the Skewness and Kurtosis test. Statistical significance was set at p-value<0.05 for all analyses.

The analyses were performed with Stata/MP 12.0 software, and the map was made in TabWin (DATASUS) version 3.6b.

The project was analyzed and approved by the Human Research Ethics Committee of the Faculty of Health Sciences of the University of Brasilia. The databases analyzed were requested from the Ministry of Health and the State Health Secretariat of São Paulo in accordance with Law on Access to Information (Law Nº 12.527/2011) and the Decree of the Government of the State of São Paulo.

Results

In 2014, of the 5,565 Brazilian municipalities, 3,971 registered a total of 69,150 new TB cases and 13,300 retreatments cases. As for DR-TB, 1,574 cases were distributed across 327 municipalities of residence. There were 3,644 municipalities with TB cases, but without DR-TB cases. The remaining 1,594 municipalities did not report any TB cases (Figure 1).

Compared to the 3,644 municipalities with TB cases, but without DR-TB cases, the municipalities with DR-TB cases had statistically higher ($p = 0.00$): TB incidence rate, percentage of smear test performance (new and retreated cases), percentage of retreatments and TB-HIV coinfection. On the other hand, they had statistically lower ($p = 0.00$): percentage of laboratory-confirmed cases and proportion of DOT. Regarding treatment outcomes, the municipalities with DR-TB cases had a lower percentage of cured cases ($p < 0.01$), and a higher share of loss to follow-up ($p = 0.00$) and transference or unknown outcomes ($p = 0.00$) (Table 1).

The municipalities that registered DR-TB cases had a significantly higher AIDS detection rate than other municipalities with TB cases and those without TB cases (Table 2).

Regarding demographic and socioeconomic indicators, in relation to the other two groups, the municipalities with DR-TB cases had statistically higher ($p < 0.01$): *per capita* average household income, MHDI, *per capita* GDP, life expectancy at birth; and a lower ($p < 0.01$): percentage of illiteracy, infant mortality and percentage of the population living in extreme poverty. On the other hand, they had statistically higher ($p < 0.01$): GINI index, unemployment rate, as well as percentage of the population in the urban area and demographic density (Table 2). The percentage of the population covered by primary healthcare and the percentage of the population that shared a room with two or more persons were significantly lower ($p < 0.01$).

The municipalities with TB, but without DR-TB cases had significantly ($p < 0.01$): the lowest *per capita* household income of the three groups, as well as the lowest MHDI, life expectancy at birth, and *per capita* GDP. This group also had the highest percentage of the population living in extreme poverty and illiteracy (Table 2).

Among the three groups, the municipalities without TB cases had significantly lower ($p < 0.01$): unemployment rate, GINI index, AIDS detection rate, percentage of the population sharing rooms with two or more persons and population density. These municipalities also had the highest proportion of the population covered by primary healthcare ($p<0.01$), and infant mortality ($p < 0.01$) (Table 2).

Discussion

In 2014, all the federative units and the Federal District had TB cases, totaling 3,971 municipalities. DR-TB was found in dwellers of 327 municipalities, of which 146 were RIDEs or metropolitan regions, concentrating 80.1% of the country's DR-TB cases. The number of DR-TB cases in state capitals may be related to higher demographic density and socioeconomic conditions[15]. However, this may indicate the existence

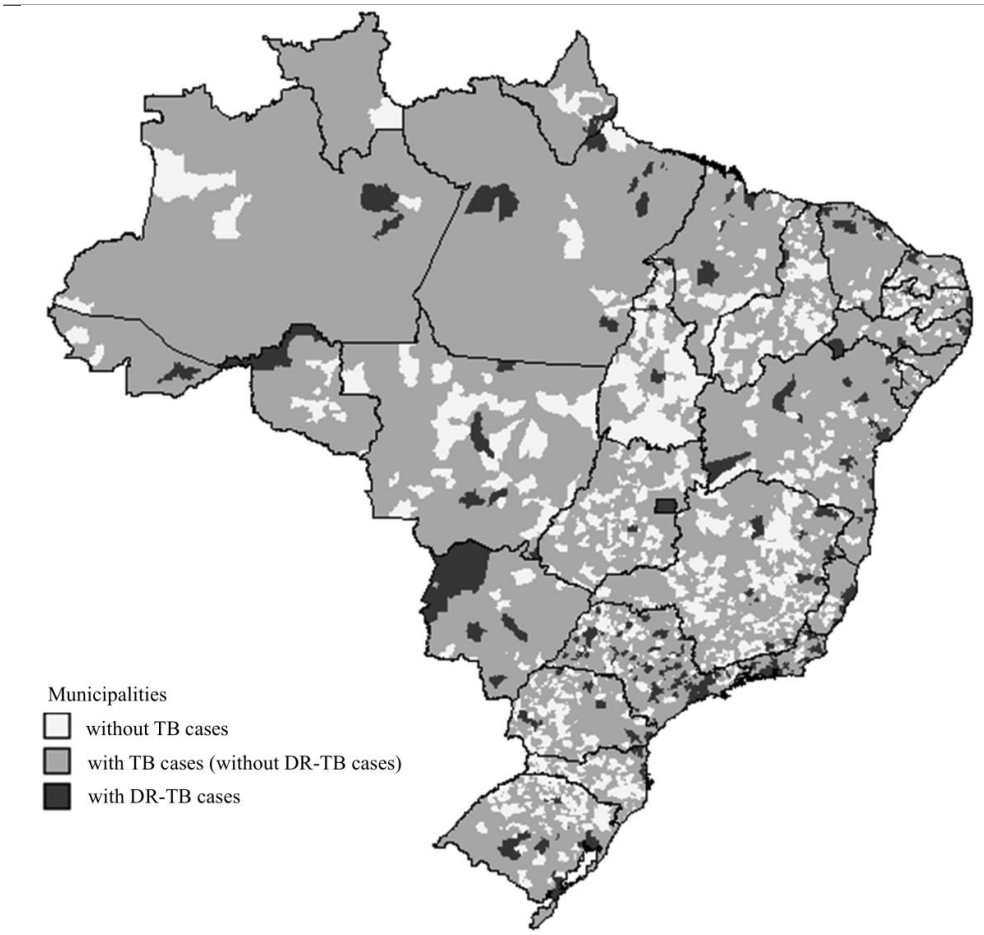

Figure 1. Brazilian municipalities according to the occurrence of TB and DR-TB cases, Brazil, 2014.

of more sophisticated and diagnostic structure available in certain localities, resulting in easier access to mycobacterial culture and drug susceptibility tests[15].

Municipalities with more than 100,000 inhabitants prevailed among those with DR-TB cases, a phenomenon also evidenced by the demographic and socioeconomic characteristics of municipalities with DR-TB cases, which had a larger population and a higher *per capita* average household income, *per capita* GDP and MHDI. Better social indicators in municipalities with DR-TB cases compared to those without cases could show a pattern of distribution of DR-TB cases different from TB cases as a whole[2,6], but intra-municipal social disparities should also be considered. On the other hand, better social indicators could also indicate a Brazilian municipal profile that is able to perform a drug-resistance diagnosis.

The higher incidence of TB cases in urban centers is described in literature as due to the higher population density and often very poor living conditions[2,6]. This is consistent with what was found in this study, in which municipalities without TB cases had better social indicators than municipalities with TB cases but without DR-TB cases.

Regarding TB control indicators, municipalities with DR-TB cases had the lowest percentage of cure, the highest percentage of loss to follow-up and transference or unknown outcome. These indicators may show a better quality of follow-up for people with TB in the group of municipalities without DR-TB cases. Municipalities without DR-TB cases had the highest coverage of primary healthcare and percentage of DOT execution, which would corroborate the hypothesis of better follow-up[16]. DOT is a fundamental strategy for the prevention of resistant

Table 1. Indicators of tuberculosis control in Brazilian municipalities according to the occurrence of DR-TB cases, Brazil, 2014.

Variables	Median (Q1-Q3*)		p
	Municipalities with DR-TB cases	Municipalities without DR-TB cases, with TB cases	
TB incidence rate (/100,000)	34.17 (22.3 – 53.5)	19.71 (11.9 – 31)	0.00
Culture test among new cases (%)	20.29 (7.1 – 50.3)	0 (0 – 33.3)	0.00
Laboratory-confirmed pulmonary cases (%)	91.82 (85.7 – 98.4)	100 (80.3 - 100)	0.00
HIV testing in new TB cases (%)	85.71 (66.7 – 95.7)	80 (46.7 - 100)	0.62
TB-HIV coinfection among new cases (%)	7.14 (2.4 – 12.5)	0 (0 – 3.8)	0.00
Cure among new TB cases (%)	73.27 (61.8 - 85)	77.78 (50 - 100)	< 0.01
Loss to follow-up among new TB cases (%)	6.53 (0 - 12)	0 (0 - 0)	0.00
Death among new TB cases (%)	0 (0-2,9)	1 (0-0)	0.00
Transference and unknown outcome among new TB cases (%)	6.01 (0 – 15.7)	0 (0 - 20)	0.00
Failure among new TB cases (%)	0 (0 - 0)	0 (0 - 0)	0.00
Retreatment among total TB cases (%)	15.43 (9.8 - 20)	0 (0 – 14.3)	0.00
Culture tests among retreated TB cases (%)	50 (14.6 – 77.8)	0 (0 – 66.7)	0.00
Directly observed treatment (%)	49.05 (20 - 75)	60 (14.3 - 100)	0.00

*Quartiles.

strains selection by promoting the adequate drug intake[2,17]. The low quality of follow-up is being associated with MDR-TB[18] at the individual level. Still, we must consider the complex social dynamics of large cities. Its specificities, such as the over-representation of vulnerable population groups and unequal access to healthcare services may generate greater difficulties in follow-up and adherence to treatment in these settings[19].

The proportion of laboratory-confirmed cases was statistically higher in municipalities without DR-TB cases. On the other hand, culture testing was higher among new and retreated cases. Culture is a laboratory test that provides material for the diagnosis of DR-TB, which may indicate higher access and, therefore, a higher DR-TB diagnostic capacity in these municipalities. According to WHO estimates, Brazil detected only 45% of its MDR-TB cases in 2014[20]. Thus, it is assumed that increasing the supply of culture and drug susceptibility testing for TB cases could increase the number of diagnosed cases[15,21]. Thus, to prevent resistant strains from becoming the dominant TB circulating type, it would be necessary to improve the laboratory capacity, together with the massive increase of DR-TB diagnosis and treatment[22,23].

Municipalities with DR-TB cases had a significantly higher percentage of retreatment cases. Retreatment is pointed out in the literature as the largest predictor of DR-TB[2] and is associated with DR-TB cases within Brazil[24-26] and abroad[18,27-31]. This result may indicate a lower capacity to manage TB cases in municipalities with drug-resistant cases, either due to their health network characteristics or to their complex social dynamics.

The proportion of TB-HIV coinfection and the AIDS detection rate were also higher in municipalities with DR-TB, both indicators are re-

Table 2. Demographic and socioeconomic characteristics of municipalities according to the occurrence of TB cases and DR-TB cases, Brazil, 2014.

Variables	Median (Q1-Q3*)			p
	Municipalities with DR-TB cases	Municipalities without DR-TB cases, with TB cases	Municipalities without TB cases	
AIDS detection rate	6.99 (3.5 – 11.4)	0 (0 –6.2)	0 (0 – 0)	< 0.01
Infant mortality (per 1,000 live births)	12.2 (9.7 – 14.8)	14.2 (9.9 – 20)	19.96 (13.2 – 29.4)	< 0.01
Life expectancy at birth (years)	74.82 (73.2 – 76.1)	73.11 (70.8 – 75)	73.81 (71.7 – 75.2)	< 0.01
Population covered by basic healthcare (%)	77.64 (59.3 – 98.3)	100 (87.3 - 100)	100 (100 - 100)	< 0.01
Population sharing room with two or more people (%)	27.16 (19.7 – 35.1)	24.98 (17.2 – 34.3)	17.61 (11.6 – 26.8)	< 0.01
Per capita average household income (R$)	656.07 (442 – 861.7)	424.8 (262.9 – 623.8)	471.42 (289.5 – 623.8)	< 0.01
Number of inhabitants	112,032 (30,830- 274,838)	15,379 (8,165- 28,791.5)	4,850 (3,202- 7,774)	< 0.01
Population living in extreme poverty (%)	2.15 (0.1 - 7)	8.44 (1.9 – 21.1)	5.39 (1.8 - 17)	< 0.01
Unemployment in the population aged 16 or over (%)	7.6 (5.9 – 10.1)	6.18 (4.3- 8.4)	4.52 (2.5 – 6.8)	< 0.01
Illiteracy among the population aged 15 years and over	6.56 (4.1 – 12)	14.41 (8.4- 25.5)	12.78 (8.6- 22)	< 0.01
Per capita GDP (R$)	15,107.63 (9,506 – 25,396)	8,743.45 (4,898 – 14,580)	9,481.21 (5,592 – 14,915)	< 0,01
MHDI	0.73 (0.7 – 0.8)	0.66 (0.6 – 0.7)	0.67 (0.6 – 0.7)	< 0.01
GINI index	0.52 (0.5 – 0.6)	0.51 (0.5- 0.6)	0.48 (0.4 – 0.5)	< 0.01
Population density (people / km2)	164.91 (57 – 633.7)	26.01 (12.1- 57.2)	17.32 (8.4 – 29.1)	< 0.01
Urban population (%)	93.93 (79.9 – 98.6)	66.91 (48.7 – 83.1)	56.19 (40.3 – 72.2)	< 0.01

*Quartiles.

ferred in the literature to be associated with DR-TB at the individual[25,32,33] and collective levels[34,35].

The use of several sources of information with different reference dates such as health information systems, the 2010 Demographic Census and the 2012 Atlas of Human Development is a limitation of this study. The use of secondary data is a possible limitation since they may have collection and registration uniformity problems in information systems, as well as problems in the diagnosis. Nonetheless, the study was built on population data with national coverage in a continental country, allowing the distribution of TB forms in the Country and the profile of municipalities in order to sustain public policies and guide future studies about the determination of the context on the incidence of TB and its resistant form.

In conclusion, the study showed the distribution of the forms of the disease across the country and found significant differences between the groups of municipalities without TB cases, with sensitive TB cases and with DR-TB cases in relation to the health conditions of the pop-

ulation, TB control indicators, demographic and socioeconomic profile. Insofar as they consider drug-resistance, the results of this study address a growing problem in Brazil[36] and a priority issue for addressing TB[37]. Thus, inputs contribute to improve national municipalities' stratification according to their characteristics, as adopted in the recent "National plan to end TB as a public health problem"[38]. Consequently, case search, drug-resistance investigation and patient-centered follow-up are priority actions to be improved according to the municipal profile. The activities required to enhance these actions will depend on the diagnosis of each territory and will encompass the qualification of professionals, their working processes and the support network. In short, the results of this study can support programmatic decisions for disease control, especially with regard to targeting and prioritizing actions and strategic areas.

Collaborations

MG Jacobs and VL Pinto Júnior contributed significantly to the work, approved the content, and agreed to subsequent revisions as well as final revision of the manuscript.

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ERRATUM

p. 2379

where it reads:
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