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ORIGINAL ARTICLE

Tuberculosis in Brazil: one country, multiple realities

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ABSTRACT

Objective: To identify the determinants of tuberculosis-related variables in the various regions of Brazil and evaluate trends in those variables over the ten-year period preceding the end of the timeframe defined for the United Nations Millennium Development Goals (MDGs). **Methods:** This was an ecological analytical study in which we utilized eight national public databases to investigate the 716,971 new tuberculosis cases reported between 2006 and 2015. **Results:** Over the study period, there were slight reductions in the prevalence, incidence, and mortality associated with tuberculosis. Brazil did not reach the MDG for tuberculosis-related mortality. Among the performance indicators of tuberculosis control, there were improvements only in those related to treatment and treatment abandonment. In terms of the magnitude of tuberculosis, substantial regional differences were observed. The tuberculosis incidence rate was highest in the northern region, as were the annual mean temperature and relative air humidity. That region also had the second lowest human development index, primary health care (PHC) coverage, and number of hospitalizations for tuberculosis. The northeastern region had the highest PHC coverage, number of hospitalizations for primary care-sensitive conditions, and tuberculosis-related mortality rate. The southern region showed the smallest reductions in epidemiological indicators, together with the greatest increases in the frequency of treatment abandonment and retreatment. The central-west region showed the lowest overall magnitude of tuberculosis and better monitoring indicators. **Conclusions:** The situation related to tuberculosis differs among the five regions of Brazil. Those differences can make it difficult to control the disease in the country and could explain the fact that Brazil failed to reach the MDG for tuberculosis-related mortality. Tuberculosis control measures should be adapted to account for regional differences.

Keywords: Tuberculosis/epidemiology; Tuberculosis, pulmonary/epidemiology; Health status indicators; Social determinants of health; Healthcare disparities.

INTRODUCTION

In 1993, the World Health Organization (WHO) recognized tuberculosis as a global epidemic.[1,2] Despite notable progress, tuberculosis is still a public health problem that continues to be one of the most lethal transmissible diseases worldwide.[3] Brazil ranks 20th in the world in terms of the incidence of tuberculosis.[2] The WHO reported that Brazil is among the 22 countries where the burden of tuberculosis is high, and, therefore, there is a focus on reducing the incidence of tuberculosis in the country.[4] On the basis of those data, combating tuberculosis became one of the eight United Nations Millennium Development Goals (MDGs), the target being a 50% reduction in the incidence, prevalence, and mortality rates associated with the disease by 2015 (in relation to the rates reported for 1990).

Brazil covers approximately 50% of South America and is subdivided into five administrative/geographic regions (northern, northeastern, southeastern, southern and central-west regions). These five regions present different climatic patterns, socioeconomic features, political dynamics, and administrative structures.[5] Although the organization of health care services also differs substantially among the regions, the majority (71%) of the population depends on public health care services provided by the Brazilian Unified Health Care System. The primary health care (PHC) system is often the first point of contact for people who interact with the health care system.[6]

The care provided to patients suspected of having tuberculosis, to those with a confirmed diagnosis of tuberculosis, and to the contacts of tuberculosis patients

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influences the burden of the disease and the levels of its control, as well as the morbidity and mortality associated with the disease.[7] Therefore, the rates of treatment abandonment and retreatment, as well as other major indicators, are evaluated as a part of strategies to control tuberculosis, such strategies including sputum smear microscopy (for diagnosis and during treatment until confirmation of a clinical and bacteriological cure), directly observed therapy (DOT), and immediate sputum smear microscopy/culture in all cases of retreatment.

The decrease in the incidence of tuberculosis has been slow[3] and varies considerably among countries due to differences in the Human Development Index (HDI), sociocultural aspects, political structure, organization of health care services, and the implementation of national tuberculosis control programs (NTCPs).[8] Nevertheless, a multifactorial approach is important for strengthening the strategies to tackle the tuberculosis epidemic. Although epidemiological studies have assessed and reported results related to the dynamics of tuberculosis at the country level,[9] to date, there have been no studies using a multifactorial approach to address this issue over the long term.

The aim of this study was to add to the body of evidence in the literature on tuberculosis by collecting previously unpublished information from various national databases in Brazil. We combined many variables from different contexts into a single study to provide an expanded view of the many determinants of the tuberculosis burden in Brazil. In addition, we assessed the epidemiological trends over the ten-year period leading up to the deadline proposed by the WHO to achieve the MDGs, and we attempted to determine whether Brazil had met the proposed targets.

METHODS

This ecological study linked eight public domain databases to analyze the new tuberculosis cases registered in the Brazilian Case Registry Database between 2006 and 2015.[10] The data were collected from the databases of the Brazilian National Ministry of Health (NMH) *Departamento de Informática do Sistema Único de Saúde* (DATASUS, Information Technology Department of the Brazilian Unified Health Care System),[10] the Brazilian Institute of Geography and Statistics,[11] and the Brazilian National Meteorological Institute.[12]

The DATASUS databases used were those of the Brazilian Tuberculosis Case Registry Database,[10] the Support Room for Strategic Management,[1] the List of Health Indicators and Goals,[13] the National Immunization Program,[14] the National Registry of Health Care Facilities,[15] and the Hospital Information Service.[16] All variables, including detailed descriptions and the formulas used for calculations, together with relevant observations and sources of information, are displayed in Table 1. Analyses were performed in Microsoft Excel as well as with plots. There was no need for research ethics committee approval, because research using public domain information is not evaluated in the Brazilian National Research Ethics Committee system.

RESULTS

During the ten-year study period, 716,971 cases of tuberculosis were reported in Brazil (entries being classified as new cases, cases of recurrence, cases of retreatment after treatment abandonment, unclassified cases, transferred cases, or cases reported post-mortem). If only those classified as new cases are considered, the mean annual number of cases was 85,721. Table 2 shows various aspects of the tuberculosis epidemic in relation to the organization of health, social, economic, and environmental services in the five regions of the country. Figures 1 to 4, which analyze the trends of the epidemic, also clearly show that differences in dynamics among the regions have influenced those trends.

Brazil did not reach the MDG related to tuberculosis mortality. Substantial differences were observed among the regions, and regional differences should be taken into account when tuberculosis control measures are being planned. Over the study period, there was a slight reduction in the prevalence of tuberculosis in Brazil as a whole (from 46.1% in 2006 to 39.9% in 2015), the reduction being largest (from 48.1% to 37.4%) in the northeastern region and smallest (from 37.5% to 36.4%) in the southern region. The incidence of tuberculosis also decreased slightly in Brazil as a whole (from 38.6 cases/100,000 population in 2006 to 33.1 cases/100,000 population in 2015), the decrease being largest (from 45.8 to 38.8 cases/100,000 population) in the northern region and smallest (from 23.9 to 21.3 cases/100,000 population) in the central-west region. In addition, there was a slight reduction in the tuberculosis-related mortality rate in Brazil as a whole (from 2.5 deaths/100,000 population in 2006 to 2.2 deaths/100,000 population in 2015), the reduction being largest (from 3.1 to 2.6 deaths/100,000 population) in the northeastern region and smallest (from 1.5 to 1.4 deaths/100,000 population) in the central-west region (Figure 1).

In 2006, 2007, and 2008 (prior to the inclusion of ethambutol in the tuberculosis treatment regimen in Brazil), the nationwide tuberculosis-related mortality rates (deaths per 100,000 population) were 2.58, 2.57, and 2.57, respectively (mean, 2.573 ± 0.004). The nationwide tuberculosis-related mortality rate was 2.5 in 2009 (the first year of ethambutol use), after which there were slight reductions. In 2010, 2011, 2012, and 2013, the nationwide tuberculosis-related mortality rate (annual change) was 2.44 (−0.06%), 2.37 (−0.07%), 2.27 (−0.10%), and 2.29 (+0.02%), respectively. That rate was lowest in 2014 and 2015 (2.20 for both), corresponding to a reduction of 0.3% in relation to the 2009 rate (2.345). As illustrated in

Table 1. Description of variables and sources of information related to tuberculosis in Brazil.

Variable	Numerator	Denominator	Unit	Source
Magnitude of tuberculosis (2006-2015)				
TB prevalence	Current number of TB cases	Resident population in the same location and year	Cases/100,000 population	[1,11]
PTB prevalence	Current number of cases of PTB	Resident population in the same location and year	Cases/100,000 population	[10,11]
TB incidence	Total new cases of TB (all forms) in a given period, location, and year	Resident population in the same location and year	Cases/100,000 population	[1]
Smear-positive PTB incidence	Total new cases of smear-positive PTB in a given location and year	Resident population in the same location and year	Cases/100,000 population	[1]
TB-related mortality	Number of deaths due to TB in a given location and year	Resident population in the same location and year	Deaths/100,000 population	[1] for 2006-2014 [32] for 2015
Indicators of TB control (2006-2015)				
First SSM positive	Total number of first SSMs that were positive in a given location and year	Number of cases of PTB or PTB+EPTB in the same location and year	%	[11]
SSM in the 2nd month	Number of SSMs performed by the end of the 2nd month of treatment in a given location and year	Number of first SSMs that were positive in the same location and year	%	[11]
SSM in the 6th month	Number of SSMs performed by the end of the 6th month of treatment in a given location and year	Number of first SSMs that were positive in the same location and year	%	[11]
Patients in DOT	Number of TB cases in which DOT was used in a given location and year	Number of TB cases in the same location and year	%	[11]
Retreatment after relapse or treatment abandonment	Number of cases of relapse or treatment abandonment reported in a given location and year	Number of TB cases reported in the same location and year	%	[11]
Sputum culture in patients previously treated for TB	Number of previously treated cases of TB (relapse or readmission after treatment abandonment) submitted to sputum culture in a given location and year	Number of previously treated cases of TB in the same location and year	%	[11]
Treatment abandonment	Number of cases closed due to treatment abandonment in a given location and year	Number of cases closed in the same location and year	%	[11]
Health care indicators (2008-2015)				
BCG vaccine coverage	Number of BCG vaccinations in children < 1 year of age in a given location and year	Resident population < 1 year of age in the same location and year	%	[14]
Density of physicians	Number of physicians registered with the CNES in a given location and year	Resident population in the same location and year	Physicians/10,000 population	[15,11]
Density of nurses	Number of nurses registered with the CNES in a given location and year	Resident population in the same location and year	Nurses/10,000 population	[15,11]
Density of pharmacists	Number of pharmacists registered with the CNES in a given location and year	Resident population in the same location and year	Pharmacists/10,000 population	[15,11]
PHC coverage	Number of people seen by PHC teams × 3,000 in a given location and year	Resident population in the same location and year	%	[13]

Continued ▸

Variable	Numerator	Denominator	Unit	Source
Hospitalization for PCSCs	Number of hospitalizations for PCSCs in a given location and year	Total clinical hospitalizations in the same location and year	%	(13)
Socioeconomic indicators (2006-2015)				
Hospitalizations for TB	Total hospitalizations for TB in a given location and year	Number of TB cases in the same location and year	Hospitalizations/100 TB cases	(10,16)
Length of hospital stay	Days spent in the hospital for TB in a given location and year	Number of hospitalizations for TB in the same location and year	Mean number of days	(16)
Cost of hospitalization for TB	Amount spent on hospitalizations for TB in a given location and year	Number of days of hospitalization for TB in the same location and year	US$/day	(16)
In-hospital mortality	Number of deaths due to TB in a given location and year	Number of hospital admissions for TB in the same location and year	100	(16)
Summary (2008-2015)				
TB incidence rate	Total new cases of TB (all forms) in a given period, location, and year	Resident population in the same location and year	Cases/100,000 population	(1)
TB mortality rate	Number of deaths due to TB in a given location and year	Resident population in the same location and year	Cases/100,000 population	(1,41)
Density of physicians	Number of physicians registered with the CNES in a given location and year	Resident population in the same location and year	Physicians/10,000 population	(15,10)
Density of nurses	Number of nurses registered with the CNES in a given location and year	Resident population in the same location and year	Nurses/10,000 population	(15,10)
Density of pharmacists	Number of pharmacists registered with the CNES in a given location and year	Resident population in the same location and year	Pharmacists/10,000 population	(15,10)
PHC coverage	Number of people seen by PHC teams × 3,000 in a given location and year	Resident population in the same location and year	%	(13)
Hospitalizations for TB	Number of hospitalizations for treatment of TB in a given location and year	Number of TB cases in the same location and year	Admissions/100 TB cases	(10,15)
Cost of hospitalization for TB	Amount spent on hospitalizations for TB in a given location and year	Number of days of hospitalization for TB in the same location and year	US$/day	(11)
Demographic density	Population of the region	Area of the region in km^2	Population/km^2	(11)
HDI	Geometric mean of the income, education, and longevity indices		-	-
Temperature	-	-	°C	(12)
Relative humidity	Actual vapor pressure	Saturation vapor pressure at the ambient temperature	%	(12)
Latitude	Distance from the Equator		Degree	-

TB: tuberculosis; PTB: pulmonary tuberculosis; SSM: sputum smear microscopy; EPTB: extrapulmonary tuberculosis; DOT: directly observed treatment; PHC: primary health care; PCSCs: primary care-sensitive conditions; CNES: *Cadastro Nacional de Estabelecimentos de Saúde* ([Brazilian] National Registry of Health Care Facilities); PHC: primary health care; HDI: Human Development Index.

Figure 1, there were also reductions in the incidence and prevalence of tuberculosis in the years after the inclusion of ethambutol. However, there were no significant changes between 2010 and 2014 in terms of the proportion of tuberculosis patients who abandoned treatment, although that proportion was lower in 2015 (Figure 2).

Table 2 shows the sociodemographic, climatic, and health care characteristics of the five regions of Brazil. The northern region of the country has the highest mean annual temperature (28°C) and highest mean annual relative humidity (81.5%), as well as having the second lowest mean HDI (0.701), lowest mean PHC coverage (59.5%), and lowest mean annual

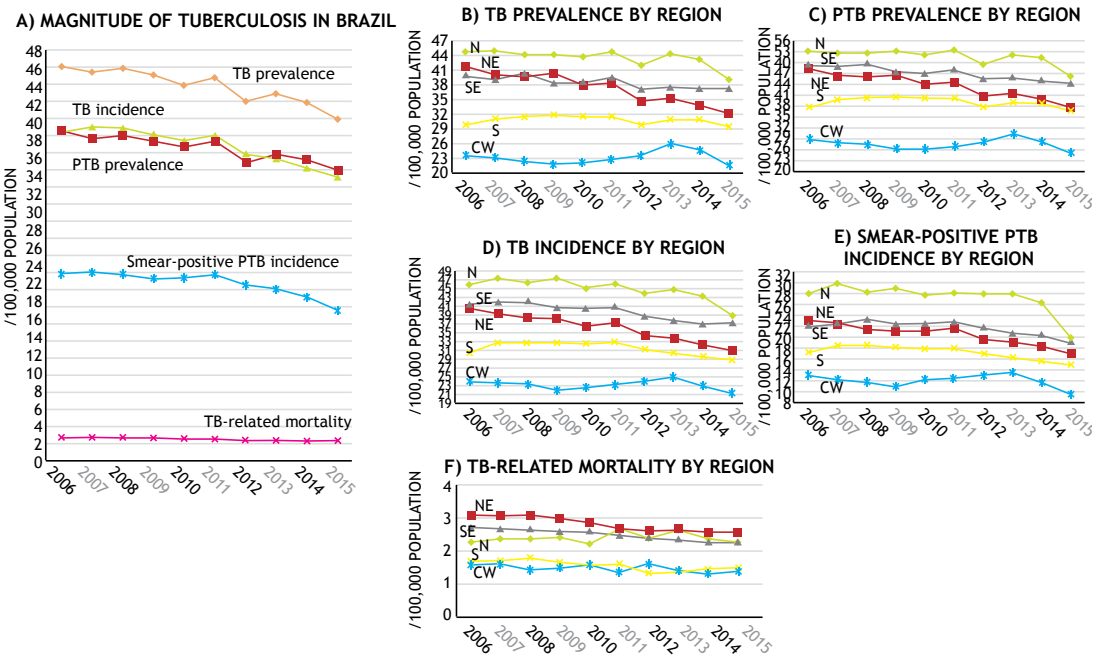

Figure 1. Magnitude of tuberculosis in Brazil as a whole and by region, 2006-2015. TB: tuberculosis; PTB: pulmonary tuberculosis; N: northern; NE: northeastern; SE: southeastern; S: southern; and CW: central-west.

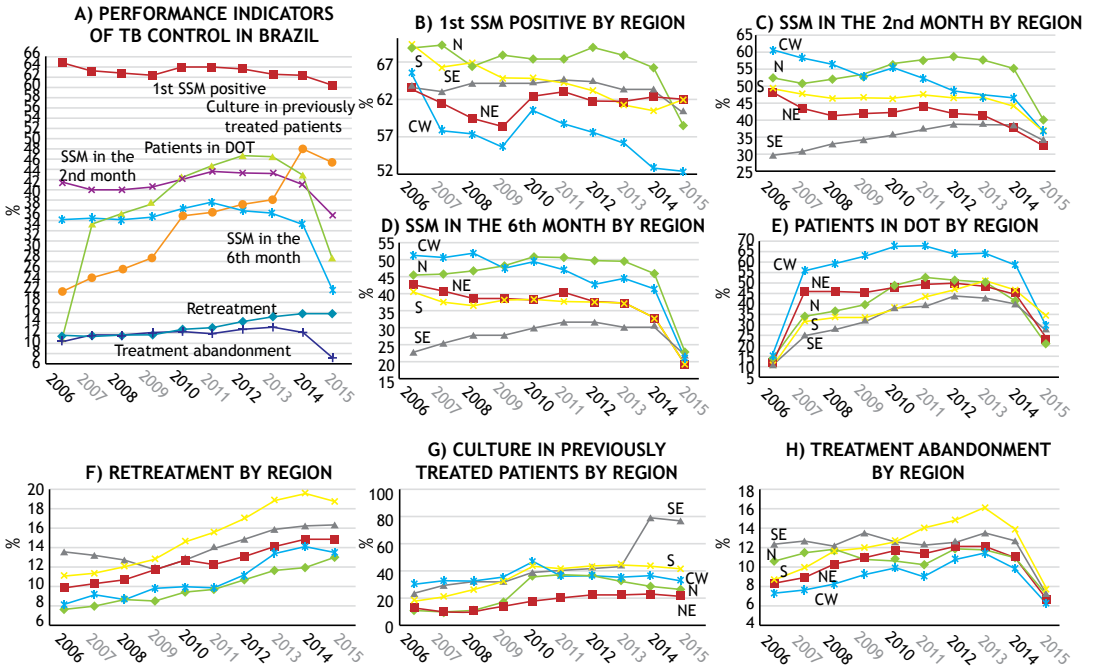

Figure 2. Performance indicators of tuberculosis control in Brazil as a whole and by region, 2006-2015. TB: tuberculosis; SSM: sputum-smear microscopy; DOT: directly observed therapy; PTB: pulmonary tuberculosis; N: northern; NE: northeastern; SE: southeastern; S: southern; and CW: central-west. [a]Among cases of PTB. [b]Among cases in which the 1st SSM was positive. [c]Among all cases of TB.

number of hospitalizations for tuberculosis (11.3). The northeastern region had the highest mean PHC coverage (75.2%), highest mean annual number of hospitalizations for tuberculosis (17.0), and highest mean tuberculosis-related mortality rate (2.9 deaths/100,000 population). The mean population density was highest (89.4 inhabitants/km^2) in the southeastern region. We found that the reductions in

Table 2. Demographic, socioeconomic, climatic, and health care characteristics of Brazil and its regions in relation to tuberculosis.[a]

Characteristics	Brazil as a whole	Region				
		Northern	Northeastern	Southeastern	Southern	Central-west
TB incidence (cases/100,000 population)	36.8 (33.2-39.0)	44.9 (38.9-47.5)	36.2 (31.0-40.7)	39.8 (37.1-42.1)	31.4 (28.8-32.9)	23.1 (21.3-24.9)
TB-related mortality (deaths/100,000 population)	2.4 (2.2-2.6)	2.4 (2.2-2.7)	2.9 (2.6-3.1)	2.5 (2.3-2.7)	1.6 (1.3-1.8)	1.5 (1.3-1.6)
Hospitalization for TB[b] (admissions/100 TB cases)	14.0 (12.8-15.4)	11.3 (10.1-12.6)	17.0 (13.9-20.2)	12.4 (10.9-13.6)	15.1 (13.3-17.5)	15.7 (13.9-17.8)
Cost/day of hospitalization for TB[b] (US$)	38.4 (26.0-49.3)	28.6 (16.0-40.6)	40.2 (28.0-48.9)	36.9 (25.6-49.6)	42.1 (27.4-52.7)	34.5 (19.6-42.0)
PHC coverage (%)	67.5 (64.8-73.0)	59.5 (56.1-68.2)	75.2 (72.7-80.3)	62.8 (59.7-68.2)	72.4 (69.1-78.4)	65.4 (62.5-68.7)
Density of health care workers[b]						
Physicians (staff/10,000 population)	15.3 (13.7-17.1)	8.0 (7.2-9.4)	10.0 (8.9-11.4)	19.8 (17.8-21.8)	16.5 (14.6-18.9)	15.7 (14.0-17.4)
Nurses (staff/10,000 population)	7.4 (5.3-9.8)	5.6 (4.2-7.5)	6.6 (4.8-8.6)	8.2 (5.8-11.0)	7.7 (5.6-10.5)	6.9 (4.8-9.2)
Pharmacists (staff/10,000 population)	1.5 (1.0-1.8)	1.3 (0.9-1.6)	1.2 (0.7-1.5)	1.4 (1.2-1.7)	2.1 (1.3-2.7)	1.7 (1.0-2.2)
Demographic density (inhabitants/km^2)	23.0 (22.0-24.0)	4.2 (3.9-4.5)	35.2 (33.8-36.4)	89.4 (85.8-92.7)	48.9 (47.0-50.7)	9.0 (8.3-9.6)
HDI[c]	0.744 (0.705-0.761)	0.701 (0.684-0.718)	0.685 (0.660-0.703)	0.773 (0.754-0.786)	0.779 (0.756-0.795)	0.769 (0.753-0.780)
Temperature (°C)	25.9 (14.3-34.2)	28.0 (21.7-33.6)	27.0 (19.8-34.2)	24.0 (16.4-29.7)	21.3 (14.3-24.9)	26.9 (20.1-31.0)
Relative air humidity (%)	74.5 (63.0-84.8)	81.5 (77.2-84.7)	72.6 (63.0-78.7)	73.5 (68.6-78.0)	79.0 (77.1-80.7)	69.7% (65.0-76.1)
Latitude, range of extremes	5,2188 ↔ −33,5861	5,2188 ↔ −13,3218	1,2015 ↔ −18,1367	14,3747 ↔ −25,0318	−22,5937 ↔ −33,5861	−7,7107 ↔ −23,8424

TB: tuberculosis; PHC: primary health care; and HDI: Human Development Index. [a]Values expressed as mean (range), except where otherwise indicated, and variables refer to the 2006-2015 period, except where otherwise indicated. [b]For the 2010-2015 period. [c]For the 2008-2015 period.

the indicators of incidence were smallest in the southern region. In that region, the reduction in tuberculosis incidence was 5.46 cases/100,000 population, whereas it was 23.86 cases/100,000 population (the highest value) in the northeastern region, and the reduction in the incidence of smear-positive pulmonary tuberculosis was 10.97 cases/100,000 population, whereas it was 28.60 cases/100,000 population (also the highest value) in the northeastern region. The southern region also showed the smallest decrease in the frequency of treatment abandonment/retreatment (from 8.7% to 7.8%), as shown in Figure 2. The incidence and mortality rates were lowest (23.1 cases/100,000 population and 1.5 deaths/100,000 population, respectively) in the central-west region.

In Brazil as a whole, the mean rates of DOT use and treatment abandonment were 36.7% and 11.4%, respectively, and similar rates were observed in all regions. In most years, the frequency of retreatment was highest in the southern region. Between 2006 and 2009, there was a temporary trend toward a decrease in the frequency of retreatment in the southeastern region, although there was no such trend in any of the other regions. All regions showed trends toward an increase in the proportion of patients in whom sputum culture was performed, that increase being greatest (mean, 214.2%) in the southeastern region, especially in 2014 and 2015 (Figure 2).

One of the main methods of preventing tuberculosis, coordinated by PHC, is immunization with the BCG vaccine, which showed a slight trend toward a decrease in the country but remained at values near 100.0%. The data collected showed a trend toward an improvement in the indicators related to health care workers (except pharmacists), PHC coverage, and hospitalization for primary care-sensitive conditions (PCSCs). Over the study period, PHC coverage, physician density, and nurse density increased by 12.7%, 24.8%, and 84.9%, respectively, while the number of hospitalizations decreased by 14.5% and pharmacist density decreased by 21.4% (Figure 3).

From 2006 to 2015, there was a trend toward an increase in the number of hospitalizations for tuberculosis treatment, although the in-hospital tuberculosis-related mortality rates remained stable. The mean length of hospital stay was 23.3 days, and there was a noticeable reduction in hospitalization costs from 2011 onward (Figure 4). The mean frequency of hospitalization for tuberculosis treatment was lowest in the northern region, as was the mean length of hospital stay and the mean total hospitalization cost. Of the patients with active tuberculosis, 14.0% were admitted to the hospital for treatment, generating a mean cost of US$38.40 per day (Figure 4).

DISCUSSION

To our knowledge, there have been no previous studies including all of the variables evaluated in the present study, stratifying the findings by region, and

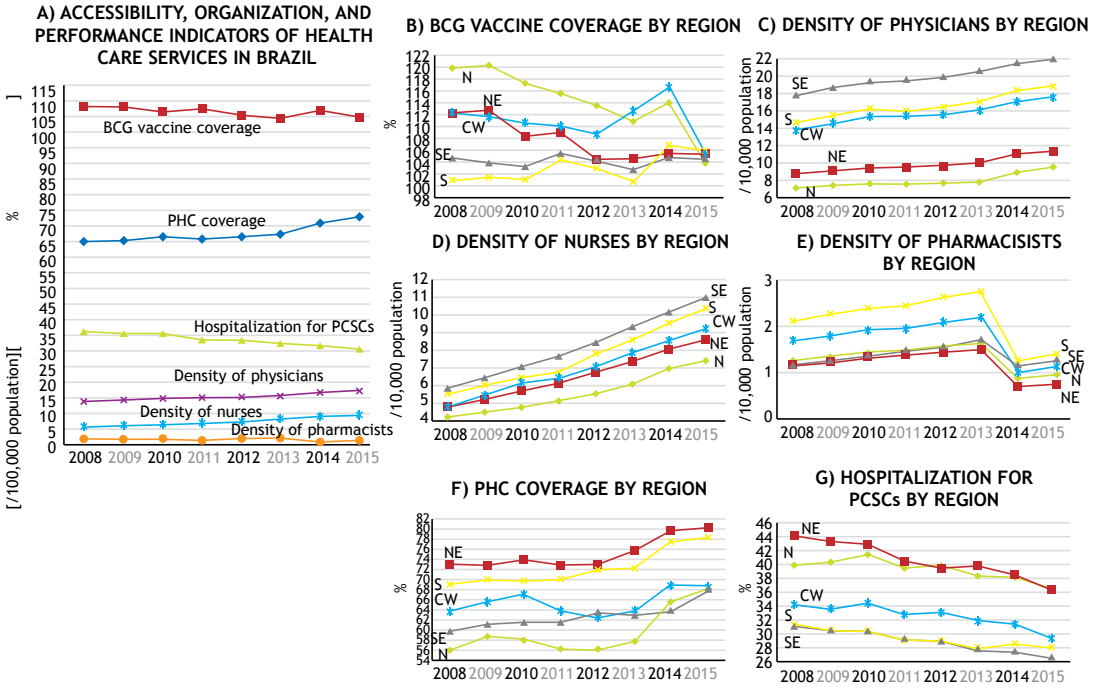

Figure 3. Accessibility, organization, and performance indicators of health care services in Brazil as a whole and by region, 2006-2015. PHC: primary health care; PCSCs: primary care-sensitive conditions; N: northern; NE: northeastern; SE: southeastern; S: southern; and CW: central-west.

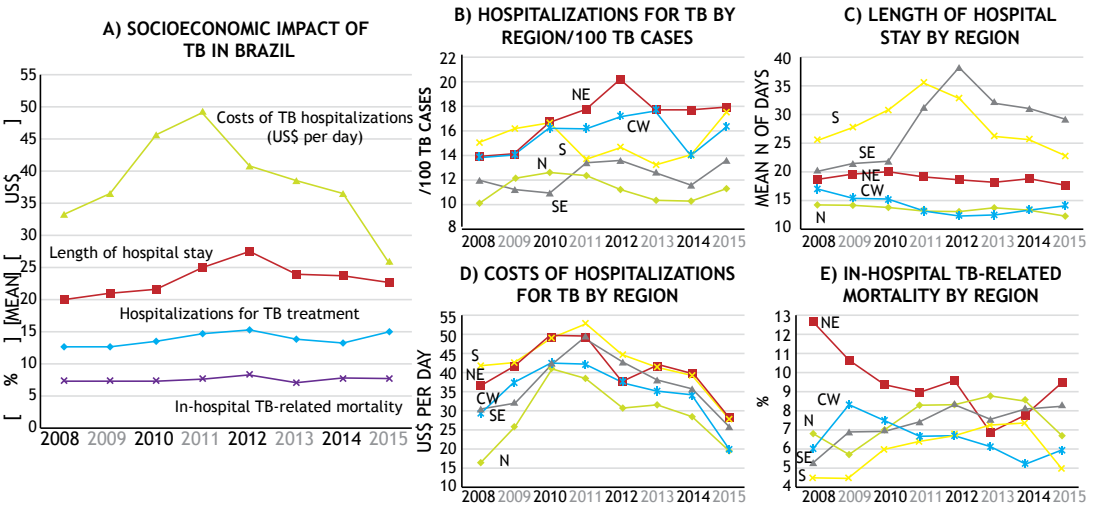

Figure 4. Socioeconomic impact of tuberculosis in Brazil as a whole and by region, 2006-2015. TB: tuberculosis; PHC: primary health care; PCSCs: primary care-sensitive conditions; N: northern; NE: northeastern; SE: southeastern; S: southern; and CW: central-west.

analyzing the long-term trends in Brazil. Although the WHO reported that all MDGs related to tuberculosis have been achieved,[4] our findings show that Brazil has failed to reach the mortality rate goal. The only region in the country that achieved the goal of reducing the tuberculosis-related mortality rate by 50.0% in relation to the 1990 rate, as proposed in the MDGs, was the southeastern region, where it was reduced from 4.6 to 2.3 deaths/100,000 population.

In addition to climatic and socioeconomic diversity, we observed substantial differences among the regions of Brazil, in terms of the magnitude of tuberculosis and general indicators of PHC performance, as well as in terms of the cost of tuberculosis, tuberculosis control, and specific indicators, such as the number of hospitalizations for tuberculosis. In 2015, Brazil was classified as having a high level of human development overall, ranking 79th in the worldwide ranking of countries by HDI,[17] although that level

was classified as low in the northern and northeastern regions. The HDI was highest for the southern and central-west regions, where the incidence of and mortality associated with tuberculosis were lowest. One study, analyzing data from 165 countries for the 2005-2011 period, identified a significant association between the HDI and tuberculosis-related morbidity.[18] Another study, using data from the 22 countries with the highest tuberculosis burden, detected a significant inverse correlation between HDI and the incidence of tuberculosis, showing that a one-point increase in the former cause the latter to decrease by 11.0% (95% CI: 2.03-19.06).[19]

Demographic heterogeneity may be another factor influencing the incidence of and mortality associated with tuberculosis in Brazil, where the population density is high in some regions and low in others. Tuberculosis transmission is associated with crowding, such as that seen in metropolitan areas in Brazil,[20] the region with the second highest tuberculosis incidence rate being the southeastern region, which is the most populous region of the country. A study conducted in 36 Turkish provinces (evaluating a collective total of 43,560,619 inhabitants) demonstrated a positive correlation between population density and the incidence of tuberculosis, the former being found to be an independent predictor of the latter.[8]

In the present study, we showed that the rates of treatment abandonment in Brazil have decreased since 2012. However, we also found that the annual retreatment rate in the country has increased, especially since 2009, reaching 15.9% in 2015, higher than the 12.0% reported for Morocco,[21] although the tuberculosis burden is higher in Brazil. In the southern region of Brazil, we observed a considerable increase in the treatment abandonment rate and a higher retreatment rate. A local study conducted in the state of Rio Grande do Sul (the fifth most populous state in the country) revealed major flaws in the Rio Grande do Sul State Tuberculosis Control Program.[22]

Although the use of DOT has increased in Brazil, by 2012 it was still below the 100.0% goal the WHO expected to be achieved worldwide by 2010.[23] In China, only 13.9% of the population was covered by the DOT strategy in 2012.[24] In Ethiopia, coverage was better, 70.0% of the population being covered by DOT in 2011.[25] The challenges for improving DOT coverage include financial and logistical barriers to health care access,[26] as well as the lengthy commitment required of human resources,[26,27] the need for a mixed public-private approach, and the need for professional awareness of the importance of DOT in all patients with tuberculosis (not only those who are smear-positive).[28]

The Brazilian NTCP recommends that tuberculosis control measures, including diagnosis and treatment monitoring, be decentralized.[29] However, expanding actions to address tuberculosis at PHC clinics and to decentralize control measures continues to be a challenge in Brazil,[30] where heterogeneous levels of organization, due to different regional administrative conditions, impede the decentralization process.[31] Therefore, the NTCP operates in different formats in many areas of the five regions and difficulties in achieving timely case management have been reported.[32]

Most of the Brazilian population depends on public health care services,[6] and the PHC system is the gateway to those services. Therefore, the level of PHC coverage of the population represents an important marker of access to health care services in the country. In 2015, the PHC coverage in Brazil was 73.0%, corresponding to an increase of 12.7% compared with that of 2006.

Among the five regions examined, the PHC coverage was lowest in the northern region, which also had the lowest concentrations of physicians and nurses, potentially delaying the diagnosis and evaluation of contacts of tuberculosis cases, thus favoring the maintenance of the transmission chain and probably accounting for our finding that the incidence rates were highest in that region. In addition, the combination of higher numbers of patients with smear-positive pulmonary tuberculosis, high treatment abandonment rates, and high retreatment rates also affects the rate of possible transmissions, which could explain the higher incidence and mortality rates in the region. Furthermore, other infectious diseases are endemic to the northern region, and the experience of clinicians with those other diseases could favor the local diagnosis of tuberculosis, which could have increased the tuberculosis incidence rate in the region.

Strategies aimed only at increasing PHC coverage and health professional awareness do not always produce actions consistent with the needs of the population, and the recommendations outlined in tuberculosis guidelines must therefore be followed.[33] We posit that higher PHC coverage does not necessarily lead to greater positive health impacts, given the regional differences in hospitalizations for PCSCs. Regions with extremely different PHC coverage exhibit similarly high rates of hospitalization for PCSCs. The northeastern region has good PHC coverage but presented the lowest expansion of the DOT strategy, a high number of hospitalizations for PCSCs, and higher rates of hospital admissions for and mortality due to tuberculosis. In view of these findings, the problem of tuberculosis in the northeastern region appears to be unique, not only in terms of the specific tuberculosis control measures required but also in terms of the quality and general effectiveness of health care services. A previous study demonstrated that the public health care system in the northeastern region is inefficient because of the low density of health care professionals and the low number of individuals who graduate with a health-related degree.[34]

Failure to diagnose and treat tuberculosis accurately and in a timely manner maintains the chain of transmission, thus increasing the number of hospitalizations, health expenditures, and even mortality

rates. In addition, tuberculosis affects the active work force and can therefore have a negative socioeconomic impact.[26,35] The rates of hospitalization for tuberculosis are 33.3% in China and 66.5% in Spain, substantially higher than the rate in Brazil, and hospitalizations account for a significant portion of the total costs associated with the disease.[36,37] In Brazil, hospital admissions for tuberculosis are avoided, being limited to special situations and patients with complications of the disease.[29] In contrast, hospitalization is a routine measure during the intensive phase of tuberculosis treatment in some countries in Eastern Europe and Central Asia.

The longer hospital stays observed in the southern and southeastern regions of Brazil could be explained by the lack of financial resources for infrastructure, the imbalance between the density of health care service providers and that of the population, and the migration of inhabitants from other regions.[34] The high population density can reduce the number of available beds, delaying the initiation of appropriate treatment in patients who require hospitalization, thus increasing the length of the hospital stay, hospitalization costs, and the risk of death. However, studies investigating hospitalization for other causes have also shown that hospitalization costs are higher in the southern region than in the northern region, likely because of the lower technological complexity of the hospitals in the latter.[38]

One influential factor in the estimates of the epidemiological aspects of tuberculosis is the pharmacological treatment used. In 1979, the basic treatment regimen recommended for new cases in Brazil was rifampin, isoniazid, and pyrazinamide for two months, followed by rifampin and isoniazid for four months. The inclusion of ethambutol was recommended for patients undergoing retreatment and for those with meningoencephalitis, the second phase of treatment being extended to seven months in the latter. Patients in whom those treatments failed were treated with a regimen of streptomycin, pyrazinamide, ethambutol, and ethionamide for three months, followed by ethambutol and ethionamide for nine months. In the 1980s and 1990s, there were occasional changes in the treatment employed in cases of treatment-resistant tuberculosis. Ethambutol was not added to the basic treatment regimen to be used in the treatment induction phase (for patients ≥ 10 years of age) until 2009, the same year in which the use of fixed-dose combination tablets was introduced.[39]

The results of the present study show that there have been slight reductions in the rates of incidence, prevalence, and mortality associated with tuberculosis in Brazil. Those reductions might be related, in part, to the introduction of ethambutol and of the fixed-dose combination tablets, which could have increased patient adherence to treatment by reducing the risk of forgetfulness.[40]

The Brazilian NMH should encourage tuberculosis researchers to assess factors related to the degree of decentralization and the causes of noncompliance with NTCP recommendations, as well as differences in the reasons for and frequency of hospitalizations for tuberculosis, together with the mean length of hospital stays, hospitalization costs, and in-hospital mortality, in order to obtain a better understanding of the regional differences in the country. We recommend a partnership between the NMH and universities or research groups investigating tuberculosis, in order to increase the validity of the studies. We anticipate that such studies will identify specific measures to improve tuberculosis control in Brazil.

Despite all being part of the same country, the five regions of Brazil present distinct tuberculosis scenarios. Regional differences may have contributed to difficulties in controlling the disease in the country and to the failure to reach the MDG for tuberculosis-related mortality. Such differences should be taken into consideration in order to adapt tuberculosis control measures to those distinct scenarios. Some variables influencing the dynamics of tuberculosis are intrinsic and difficult to circumvent, whereas others, such as the performance indicators of the activities proposed by the NTCP and implemented at PHC clinics, can and should be modified.

Investigations aimed at explaining operational differences in NTCPs may contribute to improving the tuberculosis situation nationwide, although the need to improve the performance of health care facilities in the clinical management of tuberculosis is already evident. In large countries such as Brazil, where there are contrasting socioeconomic, climatic, and health care conditions, there is also a need for a stratified analysis of similar variables to determine compliance with tuberculosis control measures and action plans.

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AUTHOR CONTRIBUTIONS

AOC: collection/analysis/interpretation of data, drafting of the manuscript, and approval of the final version; ACM: study conception/design, analysis/interpretation of data, drafting/revision of the manuscript, and approval of the final version; LON: data collection, interpretation of climatic data, and approval of the final version; KAR: interpretation of data, drafting of the manuscript, and approval of the final version; PC: analysis/interpretation of data and drafting/revision of the manuscript, and approval of the final version.

REFERENCES

1. Brasil. Ministério da Saúde. Sala de Apoio à Gestão Estratégica (SAGE) [homepage on the Internet]. Brasília: SAGE; c2017 [cited 2017 Aug 28]. Situação de saúde e indicadores de morbidade da tuberculose. Available from: http://sage.saude.gov.br/
2. World Health Organization. Global tuberculosis report 2018. Geneva: World Health Organization; 2018.
3. Cazabon D, Alsdurf H, Satyanarayana S, Nathavitharana R, Subbaraman R, Daftary A, et al. Quality of tuberculosis care in high burden countries: the urgent need to address gaps in the care cascade. Int J Infect Dis. 2017;56:111-116. https://doi.org/10.1016/j.ijid.2016.10.016
4. World Health Organization. Global Tuberculosis Report 2015. Geneva: World Health Organization; 2015.
5. Peres P, Ricci P, Rennó LR. A variação da volatilidade eleitoral no Brasil: Um teste das explicações políticas, econômicas e sociais. Lat Am Res Rev. 2011;46(3):46-68. https://doi.org/10.1353/lar.2011.0049
6. Brasil. Presidência da República. Casa Civil [homepage on the Internet]. Brasília: a Presidência; c2015 [cited 2017 Nov 22]. 71% dos brasileiros têm os serviços públicos de saúde como referência. Available from: https://www.gov.br/casacivil/pt-br/assuntos/noticias/2015/junho/71-dos-brasileiros-tem-os-servicos-publicos-de-saude-como-referencia
7. Matteelli A, Rendon A, Tiberi S, Al-Abri S, Voniatis C, Carvalho ACC, et al. Tuberculosis elimination: where are we now?. Eur Respir Rev. 2018;27(148):180035. https://doi.org/10.1183/16000617.0035-2018
8. Taylan M, Demir M, Yılmaz S, Kaya H, Sen HS, Oruc M, et al. Effect of human development index parameters on tuberculosis incidence in Turkish provinces. J Infect Dev Ctries. 2016;10(11):1183-1190. https://doi.org/10.3855/jidc.8101
9. Fernandes FMC, Martins ES, Pedrosa DMAS, Evangelista MDSN. Relationship between climatic factors and air quality with tuberculosis in the Federal District, Brazil, 2003-2012. Braz J Infect Dis. 2017;21(4):369-375. https://doi.org/10.1016/j.bjid.2017.03.017
10. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Informática do SUS (DATASUS) [homepage on the Internet]. Brasília: DATASUS; 2016 [cited 2017 Aug 21]. Sistema de Informação de Agravos de Notificação (SINAN): Tuberculose. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/tubercbr.def
11. Instituto Brasileiro de Geografia e Estatística (IBGE) [homepage on the Internet]. Rio de Janeiro: IBGE; c2017 [cited 2017 Aug 23]. Available from: https://ww2.ibge.gov.br/home/default.php
12. Brasil. Ministério da Agricultura, Pecuária e Abastecimento. Instituto Nacional de Meteorologia (INMET) [homepage on the Internet]. Brasília: INMET; c2017 [cited 2017 Sep 19]. Banco de Dados Meteorológicos. Available from: https://bdmep.inmet.gov.br/
13. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Informática do SUS (DATASUS) [homepage on the Internet]. Brasília: DATASUS; c2016 [cited 2017 Aug 28]. Indicadores Regionais, Estaduais e Nacionais do Rol de Diretrizes, Objetivos, Metas e Indicadores 2015. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?pacto/2015/cnv/coapcirbr.def
14. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Informática do SUS (DATASUS) [homepage on the Internet]. Brasília: DATASUS; c2017 [cited 2009 Jul 20]. Sistema de Informações do Programa Nacional de Imunização. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?pni/cnv/cpniuf.def
15. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Informática do SUS (DATASUS) [homepage on the Internet]. Brasília: DATASUS; c2017 [cited 2017 Aug 23]. Cadastro Nacional de Estabelecimentos de Saúde (CNES). Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?cnes/cnv/prid02br.def
16. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Informática do SUS (DATASUS) [homepage on the Internet]. Brasília: DATASUS; c2016 [cited 2017 Aug 28]. Procedimentos Hospitalares do SUS. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/qiuf.def
17. United Nations Development Programme. Human Development Report 2016. Human Development Report for Everyone. New York City: United Nations Development Programme; 2016. 193p.
18. Castañeda-Hernández DM, Tobón-García D, Rodríguez-Morales AJ. Association between tuberculosis incidence and the Human Development Index in 165 countries of the World [Article in Spanish]. Rev Peru Med Exp Salud Publica. 2013;30(4):560-568. https://doi.org/10.17843/rpmesp.2013.304.233
19. Bozorgmehr K, San Sebastian M. Trade liberalization and tuberculosis incidence: a longitudinal multi-level analysis in 22 high burden countries between 1990 and 2010. Health Policy Plan. 2014;29(3):328-351. https://doi.org/10.1093/heapol/czt020
20. Gonçalves MJ, Leon AC, Penna ML. A multilevel analysis of tuberculosis associated factors. Rev Salud Publica (Bogota). 2009;11(6):918-930. https://doi.org/10.1590/S0124-00642009000600008
21. Dooley KE, Lahlou O, Ghali I, Knudsen J, Elmessaoudi MD, Cherkaoui I, et al. Risk factors for tuberculosis treatment failure, default, or relapse and outcomes of retreatment in Morocco. BMC Public Health. 2011;11:140. https://doi.org/10.1186/1471-2458-11-140
22. Mendes AM, Bastos JL, Bresan D, Leite MS. Epidemiologic situation of tuberculosis in Rio Grande do Sul: an analysis about Sinan's data between 2003 and 2012 focusing on indigenous peoples. Rev Bras Epidemiol. 2016;19(3):658-669. https://doi.org/10.1590/1980-5497201600030015
23. DOTS Expansion Working Group, World Health Organization & Stop TB Partnership. DOTS Expansion Working Group strategic plan, 2006-2015. Geneva: World Health Organization; 2006. 91p.
24. Lei X, Huang K, Liu Q, Jie YF, Tang SL. Are tuberculosis patients adherent to prescribed treatments in China? Results of a prospective cohort study. Infect Dis Poverty. 2016;5:38. https://doi.org/10.1186/s40249-016-0134-9
25. Hamusse SD, Demissie M, Teshome D, Lindtjørn B. Fifteen-year trend in treatment outcomes among patients with pulmonary smear-positive tuberculosis and its determinants in Arsi Zone, Central Ethiopia. Glob Health Action. 2014;7:25382. https://doi.org/10.3402/gha.v7.25382
26. Karumbi J, Garner P. Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev. 2015;2015(5):CD003343. https://doi.org/10.1002/14651858.CD003343.pub4
27. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ. 2007;85(9):660-667. https://doi.org/10.2471/BLT.07.043497
28. Onozaki I, Raviglione M. Stopping tuberculosis in the 21st century: goals and strategies. Respirology. 2010;15(1):32-43. https://doi.org/10.1111/j.1440-1843.2009.01673.x
29. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Coordenação Geral de Desenvolvimento da Epidemiologia em Serviços. Guia de Vigilância em Saúde. Vol 2. Brasília: Ministério da Saúde; 2017.
30. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Brasil livre da tuberculose: Plano Nacional pelo fim da Tuberculose como problema de Saude Publica. Brasília: Ministério da Saúde; 2017. 40p.
31. Spedo SM, Tanaka OY, Pinto NR. The challenge of decentralization of the Unified National Health System in large cities: the case of São Paulo, Brazil [Article in Portuguese]. Cad Saude Publica. 2009;25(8):1781-1790. https://doi.org/10.1590/S0102-311X2009000800014
32. Arakawa T, Magnabosco GT, Andrade RL, Brunello ME, Monroe AA, Ruffino-Netto A, et al. Tuberculosis control program in the municipal context: performance evaluation. Rev Saude Publica. 2017;51(0):23. https://doi.org/10.1590/s1518-8787.2017051006553
33. Satyanarayana S, Subbaraman R, Shete P, Gore G, Das J, Cattamanchi A, et al. Quality of tuberculosis care in India: a systematic review. Int J Tuberc Lung Dis. 2015;19(7):751-763. https://doi.org/10.5588/ijtld.15.0186
34. Gramani MC. Inter-regional performance of the public health system in a high-inequality country. PLoS One. 2014;9(1):e86687. https://doi.org/10.1371/journal.pone.0086687
35. DiStefano MJ, Schmidt H. mHealth for Tuberculosis Treatment Adherence: A Framework to Guide Ethical Planning, Implementation, and Evaluation. Glob Health Sci Pract. 2016;4(2):211-221. https://doi.org/10.9745/GHSP-D-16-00018
36. Ronald LA, FitzGerald JM, Benedetti A, Boivin JF, Schwartzman

K, Bartlett-Esquilant G, et al. Predictors of hospitalization of tuberculosis patients in Montreal, Canada: a retrospective cohort study. BMC Infect Dis. 2016;16(1):679. https://doi.org/10.1186/s12879-016-1997-x

37. Culqui DR, Rodríguez-Valín E, Martínez de Aragón MV. Epidemiología de las hospitalizaciones por tuberculosis en España: análisis del conjunto mínimo básico de datos 1999-2009. Enferm Infecc Microbiol Clin. 2015;33(1):9-15. http://doi.org/10.1016/j.eimc.2013.12.015.
38. Peixoto SV, Giatti L, Afradique ME, Lima-Costa M. Cost of Public Hospitalization Among Elderly in Brazil's Unified Health System [Article in Portuguese]. Epidemiol Serv Saude. 2004;13(4):239-246. https://doi.org/10.5123/S1679-49742004000400006
39. Ballestero JGA, Garcia JM, Bollela VR, Ruffino-Netto A, Dalcolmo MMP, Moncaio ACS, et al. Management of multidrug-resistant tuberculosis: main recommendations of the Brazilian guidelines. J Bras Pneumol. 2020;46(2):e20190290. http://dx.doi.org/10.36416/1806-3756/e20190290
40. Mendes NM, Costa RR, Dias AM, Lopes CB, Souza DM, Silva MR, et al. Perfil de resistência a fármacos antituberculose em um hospital de referência do Estado de Minas Gerais. Rev Med Minas Gerais. 2014;24(Suppl 5):43-46. http://www.dx.doi.org/10.5935/2238-3182.20140072
41. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Protocolo para vigilância do óbito com menção de tuberculose nas causas de morte. Brasília: Ministério da Saúde; 2017. 70p.