Original Article

Mortality due to Chagas disease in Brazil from 1979 to 2009: trends and regional differences

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Abstract

Introduction: Studies on mortality due to parasitic diseases such as Chagas disease are useful to understand the epidemiology and to plan and guide control measures for these diseases. We analyzed mortality trends due to Chagas disease in Brazil and regions, between 1979 and 2009.
Methodology: Mortality data (underlying cause of death) were obtained from the nationwide Mortality Information System (*SIM*) of the Ministry of Health. We calculated crude mortality rates and rates standardized by age, as well as proportional mortality.
Results: In total, 27,560,043 deaths occurred in the study period. In 172,066 deaths, Chagas disease was mentioned as the underlying cause (proportional mortality: 0.62%). The mean crude and age-standardized mortality rates were 3.61 and 5.19 deaths/100,000 inhabitants/year, respectively. During the observation period, Chagas mortality declined significantly at the national level (R^2=97%, p<0.001), with different patterns between regions. There was a significant reduction in mortality in the Central-West (R^2=90%, p<0.001), Southeast (R^2=98%, p<0.001) and South (R^2=94%, p< 0.001), but in the North (R^2=34%, p=0.001) and Northeast (R^2=65%, p<0.001) regions mortality increased.
Conclusions: Despite the overall decline in mortality due to Chagas disease in Brazil, it remains an important public health problem. After successful control of the primary vector *Triatoma infestans*, intervention measures must focus on improved access to health care and secondary prevention. The North and Northeast regions, where vectors other than *T. infestans* have a primary role, need special attention.

Key words: Chagas disease; mortality; temporal trends; neglected Tropical diseases; Brazil

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Introduction

A century after its discovery, Chagas disease remains a neglected tropical disease in Latin America [1,2]. In addition, due to increased international migration, the disease is becoming an emerging disease, mainly in North America and Europe [3-5]. Approximately 15 million people are infected in Latin America [1,5,6], causing 14,000 deaths annually [4,7].

In Brazil, with significant reduction of vector and transfusional transmission, the number of new cases has been drastically reduced in recent years [8]. Recent studies estimate around two to three million infected people in Brazil, as compared to seven million in the 1960s [1,9,10]. There are six thousand fatal cases per year, representing about 43% of the total number of deaths from Chagas disease in Latin America [11,12].

Given the chronic nature of Chagas disease and increased life expectancy in Brazil, it can be assumed that, in the next decades, mortality figures due to the disease will remain at a high level. Here we present data on mortality caused by Chagas disease in Brazil and its geographical regions from 1979 to 2009.

Methodology

Study design and data sources

We conducted a nationwide study using mortality data from the Mortality Information System of the Ministry of Health of Brazil (*SIM - Sistema de Informação de Mortalidade;* SIM/MS/DATASUS), freely accessible at http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10uf.def. We included all deaths that occurred in Brazil between 1979 and 2009, the period available in the database. *SIM* data are based on death certificates

Table 1. Crude and standardized mortality rates (per 100,000 inhabitants) and proportional mortality due to Chagas disease in Brazil and regions, 1979-2009

Region	Deaths (n)	Crude mortality rate	Standardized mortality rate	Proportional mortality (%)
North	1,530	0.45	0.81	0.12
Northeast	23,051	1.67	2.35	0.34
Southeast	98,199	4.84	6.48	0.72
South	10,916	1.55	2.09	0.25
Central-West	38,310	12.26	23.33	2.54
Brazil	172,066	3.61	5.19	0.62

(*declaração de óbito – DO*), consisting of a standardized form with demographic and clinical information (causes of death), completed by physicians.

Chagas disease was identified according to the Ninth and Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD), with the following codes: 086 for the period 1979-1995 (ICD-9) and B57 for 1996-2009 (ICD-10) [13,14].

Population data were obtained from the Brazilian Institute of Geography and Statistics (IBGE; http://www.ibge.gov.br), based on data from the National Population Censuses (1980, 1991 and 2000), the Population Count (1996), and population estimates for intercensus years.

Data analysis

We present the crude mortality rate and proportional mortality due to Chagas Disease by region of residence and year of occurrence of death. Mortality rates were calculated by dividing the number of deaths in each calendar year by the population, and presented per 100,000. Proportional mortality was calculated by dividing the number of deaths from Chagas disease by the total number of deaths, multiplied by 100. To avoid differences in age profile of the regions analyzed, which may influence the observed trends, mortality rates were standardized by age using the direct method, considering the Brazilian population of the year 2010 as standard.

Trend analysis of indicators was performed by simple linear regression and correlation. To avoid autocorrelation between the terms of the regression equation, we used the artifice to centralize the variable year, transforming it into calendar year less 1994 (observation year - 1994), as this was the midpoint of the series.

Calculation of indicators and preparation of tables and figures was performed using Microsoft Excel spreadsheets (Microsoft Corporation; Redmond, Washington, USA). We used SPSS for Windows version 15.0 (Statistical Package for the Social Sciences; IBM, SPSS Corporation, Chicago, USA) for linear regression and scatterplots.

Ethics

This study was solely based on publicly available secondary anonymous data, with no possibility of identification of individuals; thus approval by an ethical review board was not necessary.

Results

In total, there were 27,560,043 deaths between 1979 and 2009 in Brazil. Chagas disease was mentioned as the underlying cause of death in 172,066 (0.62%) cases. The mean mortality rate in the period was 3.61/100 000 inhabitants/year. Most (57.1%) deaths occurred in the Southeast region (98,199), followed by the Central-West 22.3% (38,310), Northeast 13.4% (23,051), South 6.4% (10,916) and North regions 0.9% (1,530). Crude and standardized mortality rates and proportional mortality in Brazil and regions over the observation period are depicted in Table 1. The highest mortality was observed in the Central-West region. Standardized data showed a considerable increase of mortality, as compared to crude data.

Trends of crude mortality rates, standardized mortality rates, and proportional mortality in Brazil and regions are presented in Figures 1-3. There was a significant decrease of both mortality rates (crude: R^2 = 97%; standardized: R^2 = 98%) and proportional mortality (R^2 = 97%) in the country (all $p < 0.001$; Table 2). Mortality in the Central-West peaked at 21.73 (crude rate) and 43.53 (standardized rate) in the

Figure 1. Crude mortality rate due to Chagas disease in Brazil and regions, 1979-2009

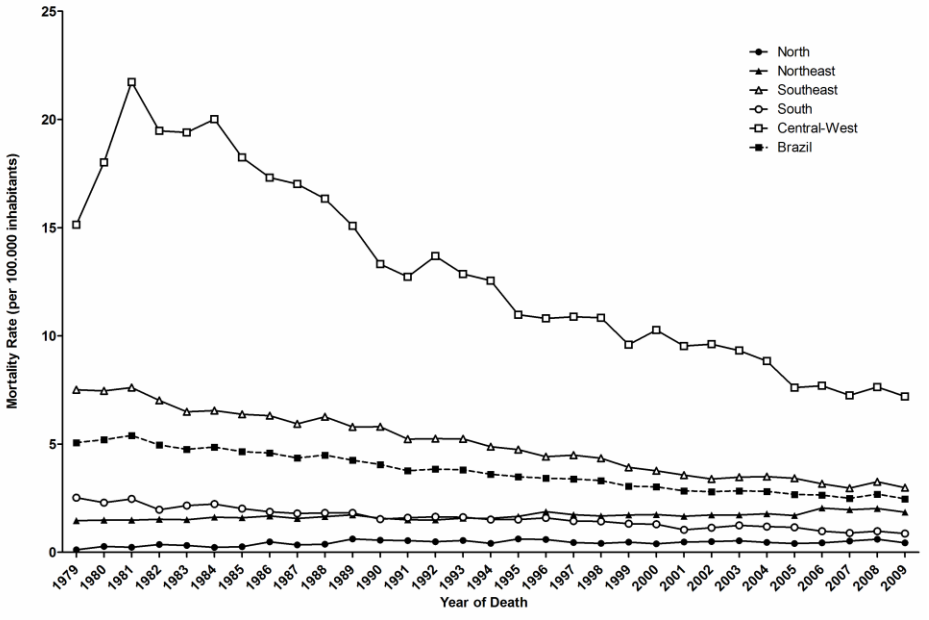


Figure 2. Standardized mortality rate due to Chagas disease in Brazil and regions, 1979-2009

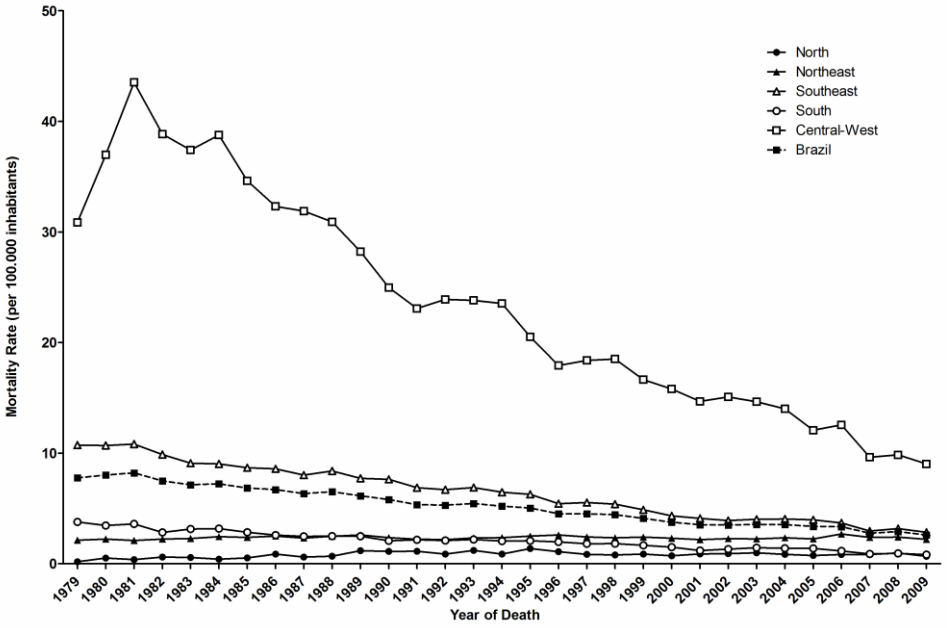
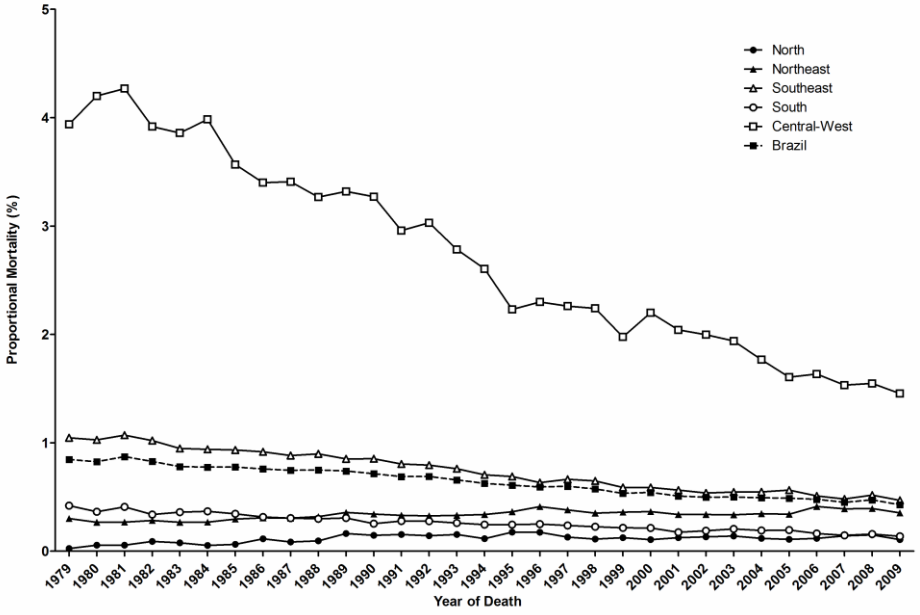


Figure 3. Proportional mortality due to Chagas disease in Brazil and regions, 1979-2009



year 1981. Similar to the pattern observed at the national level, rates in these regions, along with those in the South, decreased steadily during the study period (Figures 1-3; Table 2). The largest decrease was observed in the Central-West, with a linear annual decrease of 0.45 deaths per 100,000 inhabitants (Table 2). In contrast, the North and Northeast regions showed a slight but statistically significant increasing trend of Chagas disease mortality rates and proportional mortality, with the exception of the standardized mortality rate in the Northeast, which showed stabilization (Table 2).

Discussion

The present study describes the magnitude and trends of mortality due to Chagas disease over a period of 31 years, on a nationwide level. The data show an overall decline of mortality due to Chagas disease, but also demonstrated different regional patterns. Highly endemic areas such as the Central West and Southeast showed a steady decline over the years, whereas in the North and Northeast, where incidence is known to be relatively low, mortality figures have been increasing or maintained at a stable level [15].

The disparities in mortality trends among regions reflect the effectiveness of national control measures and control policies, which focused mainly on vector transmission and blood transfusion. The program directed its efforts to the elimination of transmission by the primary vector, the kissing bug *Triatoma infestans*. This vector is not frequent in the North and Northeast regions [15-17]; thus these regions did not benefit considerably from vector control actions performed in the last decades, as other vectors not affected by the intervention measures, such as *Triatoma brasiliensis* and *Triatoma pseudomaculata*, prevail in those areas [16,18]. In the Northeast region with the exception of Bahia state (an endemic area for *T. infestans* in the past), *T. brasiliensis* and *T. pseudomaculata* are native species with a center of endemism in the northeastern savannah region [16,17]. Interruption of transmission of Chagas disease by *T. infestans* had little effect on vector transmission in most states in the Northeast (Maranhão, Ceará, Rio Grande do Norte, Alagoas and Sergipe states) and other regions (Espírito Santo and Santa Catarina states). It can be assumed that Chagas mortality will remain a public health problem for decades in these regions [18,19], and control actions must be performed to reduce transmission by vectors other than *T. infestans*.

In the Amazon region the majority of new cases of Chagas disease is mainly caused by oral route of transmission, through the consumption of natural products such as the palm products *açaí* juice, *juçara* juice and *bacaba* [1,20,21]. This mode of transmission and emerging public health concerns for safe foods encourage surveillance activities aimed at pasteurizing

Table 2. Linear regression analysis on trends of mortality due to Chagas disease in Brazil and regions, 1979-2009

Indicator	Equation	R^2	p	Trend
Mortality rate				
Brazil				
Crude	Y= 3.73 – 0.099x	0.97	<0.001	Descending
Standardized	Y= 5.19 – 0.185x	0.98	<0.001	Descending
North				
Crude	Y= 0.43 + 0.008x	0.34	0.001	Crescent
Standardized	Y= 0.81 + 0.013x	0.20	0.011	Crescent
Northeast				
Crude	Y= 1.68 + 0.014x	0.65	<0.001	Crescent
Standardized	Y= 2.35 + 0.003x	0.03	0.338	Stabilization
Southeast				
Crude	Y= 5.01 – 0.161x	0.98	<0.001	Descending
Standardized	Y= 6.48 – 0.269x	0.98	<0.001	Descending
South				
Crude	Y= 1.58 – 0.049x	0.94	<0.001	Descending
Standardized	Y= 2.09 – 0.087x	0.95	<0.001	Descending
Central-West				
Crude	Y= 12.94 – 0.450x	0.90	<0.001	Descending
Standardized	Y= 23.33 – 1.061x	0.93	<0.001	Descending
Proportional mortality				
Brazil	Y= 0.64 – 0.015x	0.98	<0.001	Descending
North	Y= 0.11 + 0.002x	0.33	0.001	Crescent
Northeast	Y= 0.33 + 0.004x	0.62	<0.001	Crescent
Southeast	Y= 0.74 – 0.021x	0.97	<0.001	Descending
South	Y= 0.26 – 0.008x	0.95	<0.001	Descending
Central-West	Y= 2.73 – 0.097x	0.97	<0.001	Descending

the products and controlling the export of untreated juice and other products to other regions and out of the country [20]. However, mortality due to acute form of the disease, which occurs most commonly after oral infection, does not play a significant role, with nationwide and Amazon region Chagas deaths due to acute disease reported at 2.8% and 11%, respectively [12].

In addition to factors related to the control of vector transmission, the explanation for regional differences of mortality due to Chagas disease may also be related to different rates of migration between high and low endemic regions and unequal recognition of the disease as a public health threat by health professionals of these regions [22]. There are also remarkable regional differences in terms of access to diagnosis and treatment, the quality of care provided, diagnostic capacity, and quality of data [23]. Besides the control of vector and transfusional transmission of Chagas disease, it is assumed that the improved survival of patients resulting from better quality of health care may have contributed to the downward trend in mortality observed in the Central-West, Southeast and South [10]. The improved coverage of serological screening of blood donors substantially reduced the rates of transmission by transfusion in Brazil [24]. In addition, other transmission routes dependent on the enzootic cycle of transmission are also important, such as extra domiciliary vector transmission [8,25,26].

Mother-to-child transmission plays only a minor role in the country, except in the state of Rio Grande do Sul, which has the highest rates of mother-to-child transmission, as indicated by the data collected in a recent survey of seroprevalence in children under five years of age [26]. However, due to the absence of a systematic program of routine serological screening during prenatal care in endemic areas, and the fact that the majority of children with congenital transmission are clinically asymptomatic, it is difficult to estimate the actual prevalence of congenital Chagas disease in Brazil [27].

Chagas disease is emerging as an opportunistic disease, with reactivation of chronic disease in the form of meningoencephalitis and/or myocarditis, whether as an AIDS-defining condition or as an event that is associated with induced immunosuppression such as in transplants [27,29].

Aspects related to the focus of surveillance should be reviewed and must expand beyond acute cases. The increased survival of people with Chagas disease [2,30] will further increase the frequency of association with other chronic and degenerative diseases, with a need for comprehensive care of this population [31,32]. Control measures must go beyond classical actions such as vector control and serological screening of blood donors and should include comprehensive secondary prevention to avoid serious complications as well as social and financial costs [12]. Additionally, the unfavorable figures in the North and Northeast clearly indicate the need for a new approach in epidemiological surveillance of Chagas disease.

It is known that mortality rates related to Chagas disease are strongly influenced by the unequal distribution of deaths and by possible differences in age structures of populations in regions of Brazil. In this study, in addition to the crude mortality rates, we also present age-standardized rates. Regional differences caused by different age distribution can thus be reduced. Standardized rates were remarkably higher than crude rates, but these estimates should only be used for comparative analysis, as the crude rates represent the actual values.

The interpretation of mortality data over a period of more than 30 years on a nationwide context should take into consideration some limitations [32]. In general, secondary data contain inconsistencies regarding quality of data [14,15]. Deaths may be underreported, and this error probably has changed over time and regions [14]. Interpretation of trend data and regional differences should consider these circumstances. In fact, despite progress over the study period in both *SIM* coverage and quality of information on causes of death, coverage varied among states and regions of the country, especially in the North and Northeast [33-36]. Diagnostic criteria of *T. cruzi* infection are standardized throughout the country, which reduces possible random variations of the differences in mortality between regions [37]. Diagnosis of chronic Chagas disease is made after consideration of the patient's history (including epidemiological risk factors) and clinical examination. The chronic phase of Chagas disease is routinely diagnosed by commercial serologic methods, such as enzyme-linked immunoassays (ELISA), indirect immunofluorescence antibody test (IFAT), radioimmunoassay precipitation assay (RIPA), and indirect hemagglutination with whole or semipurified extracts of the epimastigotes of *T. cruzi*. The diagnosis is based on two subsequent tests based on different antigens or techniques to increase accuracy. When results are discordant, a third assay may be used to confirm or refute the diagnosis, or repeat sampling may be required [37].

The first-line test to confirm diagnosis of acute-phase disease is direct examination of blood, by microscopy of fresh preparations of anticoagulated blood. This diagnosis can be made by observation of the parasite in a blood smear by microscopic examination. Thick and thin blood smears are made and stained for visualization of parasites [20,37].

Until the 1960s, diagnosis of the chronic phase was based on parasitological methodologies (xenodiagnosis, inoculation in experimental animals, blood culture) and serological test complement fixation (specifically, the Machado and Guerreiro reaction, used in Brazil until 1995). Diagnostic methods improved between 1960 and 1975 as blood culture techniques advanced and continue to be employed until the present. Results are comparable to those of xenodiagnosis with the advantage of allowing the isolation of the parasite. Inoculation of experimental animals is no longer used as a diagnostic method due to operational difficulties, as well as its low sensitivity in the chronic phase. Other serological tests that may be implemented include the following: indirect hemagglutination test (IHA); indirect immunofluorescence test (which has high sensitivity and was used to test more than one million samples in Brazil in the national serological survey, and determined very accurately the prevalence of the disease); and ELISA immunoassay test. This second historical period in the evolution of the diagnosis witnessed the development of methods that form the basis of the diagnosis in only 15 years, the period of our study. The combination of serological methods for diagnosis of infection increased the sensitivity and specificity. In the third period, from 1976 to the present, molecular biological methods have improved, although have not yet been considered for implementation in routine diagnostics of health services in the country. These methods are available in reference research centers for Chagas disease.

Despite being a disease associated with poverty and rural populations, the majority of deaths related to

Chagas disease occur in the state capitals [11,12]. This situation, combined with improvements in the quality of the *SIM* database in recent years [35], suggests it is unlikely that changes in coverage and the proportion of deaths from defined causes in *SIM* have affected the total number of deaths from Chagas disease as the underlying cause in the period.

This study used data on mortality due to Chagas disease merely as the underlying cause of death. This factor has caused a considerable loss of information contained in death certificates and underestimated rates [12,14,19,38,39]. The use of multiple causes of death considers all causes and would give a more reliable estimate [40,41]. In fact, we have shown recently with data from 1999 to 2007 that the use of multiple causes of death increased Chagas mortality by 21% [11,12,19,42]. However, the Brazilian SIM mortality data set only included information on multiple causes after the year 1999; thus this information could not be used in the present analysis.

Despite the limitations mentioned, the results of this study show internal consistency as well as consistency with existing knowledge about Chagas disease, and are highly representative, as all deaths from Chagas disease during the period 1979 to 2009 in Brazil were included.

Currently the chronic cases of Chagas disease are not subject to compulsory notification in Brazil. For surveillance purposes, sample surveys are conducted which are both labor- and cost-intensive. To provide more information at low cost, mortality data can be used as an indicator of the epidemiological situation in an area of risk. These data may be more useful than morbidity data, because they often have greater completeness and validity. The present study exemplifies the use of this type of analysis to support the planning and evaluation of activities aimed at the monitoring and control of Chagas disease in Brazil.

We conclude that control of Chagas disease remains a challenge for public health, and probably will remain so for many years. Serious attention and continued surveillance of the main mechanisms of transmission in endemic and emerging regions are needed. New control strategies for oral transmission (in the Amazon region) and secondary vectors such as *T. brasiliensis* and *T. pseudomaculata* (in the Northeast region) must be implemented and assessed systematically. In addition, adequate access to health services and social assistance should be guaranteed for the large number of individuals afflicted with chronic Chagas disease during the last decades.

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