Mortality of Chagas’ disease in Brazil: spatial patterns and definition of high-risk areas

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Abstract

OBJECTIVE To describe patterns of spatial distribution of mortality associated with Chagas’ disease in Brazil.

METHODS Nationwide study of all deaths in Brazil from 1999 to 2007, where Chagas’ disease was recorded as a cause of death. Data were obtained from the national Mortality Information System of the Ministry of Health. We calculated the mean mortality rate for each municipality of residence in three-year intervals and the entire period. Empirical Bayes smoothing was used to minimise random variation in mortality rates because of the population size in the municipalities. To evaluate the existence of spatial autocorrelation, global and local Moran’s I indices were used.

RESULTS The nationwide mean mortality rate associated with Chagas’ disease was 3.37/100 000 inhabitants/year, with a maximum of 138.06/100 000 in one municipality. Independently from the statistical approach, spatial analysis identified a large cluster of high risk for mortality by Chagas’ disease, involving nine states in the Central region of Brazil.

CONCLUSION This study defined geographical priority areas for the management of Chagas’ disease and consequently reducing disease-associated mortality in Brazil. Different spatial-analytical approaches can be integrated to provide data for planning, monitoring and evaluating specific intervention measures.

KEYWORDS Chagas’ disease, spatial analysis, ecological studies, epidemiology, mortality, multiple causes of death, Brazil

Introduction

Chagas’ disease remains a neglected tropical disease and a public health problem with social significance and economic implications in most Latin American countries (Moncayo & Silveira 2009; Coura & Vinhas 2010). Recent estimates indicate that 10–15 million people are chronically infected in Latin America, and about 60–100 million are at risk of becoming infected (WHO 2002, 2010; Dias 2007; Coura & Dias 2009). In Brazil, there are 2–3 million individuals in the chronic phase, 1/3 of them suffering from the cardiac and digestive form, which causes high morbidity and mortality (Akhavan 2000; WHO 2002; Almeida et al. 2011). In Latin America, about 14 000 people die annually from Chagas’ disease (Schmunis 2007). Brazil accounts for approximately 43%, with 6000 annual deaths (Martins-Melo et al. 2012). The chronic form of the disease causes 97% of Chagas deaths in Brazil, especially the chronic cardiac form (85%), followed by the chronic digestive form (9%) (Martins-Melo 2011; Martins-Melo et al. 2012).

The increasing globalisation of Chagas’ disease owing to migration of infected people has led to a greater awareness worldwide (Coura & Vinhas 2010; Schmunis & Yadón 2010), especially in the United States and Europe, where migration of infected individuals from endemic countries has become an emerging public health problem (Schmunis & Yadón 2010).

Studies on the occurrence of infectious diseases according to their spatial distribution have become important for public health, especially for planning and performance of disease control measures (Nascimento et al. 2007). In fact, Geographic Information Systems (GIS) have contributed to the effectiveness of interventions through the analysis of spatial data on health (Khan et al. 2010). The use of GIS for monitoring vector-borne diseases such as Chagas’ disease can identify patterns of spatial distribution of incidence or mortality in defined
geographic regions. We describe patterns of spatial distribution and areas of high risk for mortality related to Chagas’ disease in Brazil.

Materials and methods

Study area

The study was conducted in Brazil, the largest country in South America and the fifth of the world in size (8.5 million/km²). Brazil’s population is approximately 190 million, with a density of 22.40 inhabitants/km² in 2011. The Brazilian economy is the largest in Latin America and the sixth largest in the world by Gross Domestic Product (GDP). However, the distribution of income is extremely unequal, with tremendous differences between regions and rural/urban areas (for details see United Nations Development Programme - UNDP Brazil; http://www.pnud.org.br). The country is divided politically and administratively into 27 federal units (26 States and one Federal District) and 5565 municipalities (Figure 1). The Federation is further grouped into five major regions (North, Northeast, Southeast, South and Central-West) with different geographic, socio-economic and cultural characteristics. The municipalities are a territorial area with legal autonomy, being the smallest autonomous units of the Federation.

Study population and design

We performed a nationwide ecological study by spatial analysis using deaths related to Chagas’ disease aggregated by municipality of residence. We included all deaths in Brazil from 1999 to 2007, where Chagas’ disease was recorded as a cause of death. In this study, ‘cause of death’ was defined as the notification of Chagas’ disease in any line or part of the death certificate, regardless of being classified as an underlying, primary, secondary or contributing cause of death (so-called multiple causes of death) (Santo 2009).

We obtained data from all 5565 Brazilian municipalities through the Mortality Information System (Sistema Nacional de Mortalidade - SIM) of the Brazilian Ministry of Health. SIM data are publicly available and were obtained from the website of the Department of Informatics of the Unified Health System (DATASUS; http://tabnet.datasus.gov.br/tabdata/sim/dados/cid10_indice.htm). SIM contains information from death certificates, filled out by medical professionals. Chagas’ disease as a cause of death corresponds to the clinical forms included in the category

Figure 1  The country of Brazil divided into 26 states and one Federal District (DF), situated in South America.
B57, according to the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (WHO 2007).

The process of obtaining data about deaths initially involved individual data sets for each Federation Unit and year. Consequently, a total of 243 data sets with about 9 million entries were downloaded and processed (one data set for each of the 27 federal states and each of the 9 years, from 1999 to 2007). First, we checked data sets for completeness in relation to the total number of deaths. Field codes from different data sets were standardised and variables not considered in the analysis eliminated. Then, we identified all death certificates in which Chagas’ disease was recorded in any line of the certificate as cause of death (both underlying and associated causes). We created new variables for causes of death, as in many cases more than one cause was noted in a line.

The population data for the period were obtained from the Brazilian Institute of Geography and Statistics (IBGE), based on a national population census from 2000 and official estimates for the years between censuses (1999 and 2001–2007) (available at http://www.ibge.gov.br).

Statistical analysis

Spatial analysis methods and GIS techniques were used to evaluate the geographic distribution of mortality rates related to Chagas’ disease. We applied the strategy of analysis areas data (polygons). We adopted the municipality of residence as the unit of analysis, to obtain greater accuracy of the differences within and between regions and to reveal the priority areas for interventions.

Two strategies were applied as a basis for the construction of spatial distribution maps of deaths related to Chagas’ disease. First, mortality rates were estimated as three-year means (1999–2001, 2002–2004 and 2005–2007), and for the total period. Mortality rates were calculated as follows: the mean number of deaths related to Chagas’ disease for each period of the triennium or the total period as the numerator; and the population in the middle year of each period (2000, 2003, 2005) as the denominator, by 100 000. Then, to reduce random variability and to provide greater stability of mortality rates mainly in small municipalities, we re-estimated mortality rates by Empirical Bayes Smoothing, to minimise this variation. This method, when estimating the risk of a small area, uses information from neighbouring areas that form the region under study, reducing random fluctuation of the rates. We used the weighted average between the measured values and the overall average rates, in which the weight average is inversely proportional to the population of the region (Assunção et al. 1998).

After descriptive spatial analysis by drawing mortality maps, we assessed the presence of spatial dependence using Global Moran’s I index on the smoothed rates, to identify areas with clusters of similar risks for the outcome of interest, that is, mortality caused by Chagas’ disease. This method of global spatial autocorrelation measures the correlation of a variable with itself in space. Values close to zero indicate an absence of spatial correlation; positive values indicate positive spatial autocorrelation, that is, the existence of similarity between neighbouring municipalities; and negative values show negative spatial autocorrelation (Cliff & Ord 1981).

Then, we assessed local autocorrelation [Local Index of Spatial Association (LISA)] by Local Moran’s index (Anselin 1995). The Local Moran’s Index determines the dependence of local data in relation to neighbours and identifies patterns of spatial association to characterise the occurrence of clusters of polygons (municipalities) (Anselin 1995).

To identify critical or transition areas, we used the Moran Scatterplot Map, based on Local Moran’s Index, to compare the value of each the municipality studied with neighbouring municipalities and to display spatial dependence and spatial patterns. The quadrants generated in this technique are interpreted as follows: Q1 (positive values, positive means) and Q2 (negative values, negative means), indicating points of positive spatial association or similar to neighbours, that is, representing municipalities with high and low mortality rates also surrounded by municipalities with high and low coefficients, respectively; Q3 (positive values, negative means) and Q4 (negative values, negative means), indicating points of negative spatial association, that is, municipalities with low and high mortality rates surrounded by municipalities with high and low rates, respectively. The first two categories represent areas of agreement and the last two transition areas (Anselin 1995).

For the spatial representation of the Moran Scatterplot Map, Moran Maps were used, considering only statistically significant values ($P < 0.05$). High risk for mortality caused by Chagas’ disease areas was considered when formed by municipalities covered by class Q1 of the Moran Map.

The neighbourhood matrix was used to estimate the spatial variability of data, which considers only the border municipalities (neighbours of first order) for analysis. The size of the radius used in the analysis of spatial autocorrelation was defined by the correlation between the highest z-score of the Global Moran Index and the distance band. After running the tool from 350 to 800 km, we identified a radius of 640 km to present the best z-score (ESRI 2010).
Digital maps were obtained from the cartographic basis of IBGE, in shape file (.shp) format, compatible with ArcGIS software version 9.3 (Environmental Systems Research Institute – ESRI, Redlands, CA) and TerraView software version 4.1 (Instituto Nacional de Pesquisas Espaciais – INPE). These software packages were used for processing, analysis and presentation of cartographic data and to calculate the indicators of global and local spatial autocorrelation as well as for the construction of thematic maps.

Ethics
This study is based on secondary data, and all presented information is public domain. No variables allowed the identification of individuals.

Results
Spatial distribution of Chagas’ mortality
Between 1999 and 2007, there were 53 930 deaths in which Chagas’ disease was mentioned on any part of the death certificate. 55% (3050/5565) of municipalities reported at least one death related to Chagas’ disease in this period. The mean mortality in Brazil was 3.37 per 100 000 inhabitants/year, ranging from 0.0 to 138.06 deaths per 100 000 inhabitants.

Figure 2 presents spatial distribution of mean mortality rates in three different periods. The Bayesian method generated more stable corrected rates, as shown in Figure 3. In general, both Figures show a clear concentration of municipalities with high mortality in the central region of Brazil, including the Federal District, major parts of Goiás state and the so-called Triângulo Mineiro region of north-western of Minas Gerais and northern of São Paulo states. Some areas of Mato Grosso do Sul, Bahia and Tocantins state were also affected. In addition, there were some small high-mortality areas in the bordering area of Paraná and São Paulo states, in southern Piauí and in north-central regions of Bahia state. The mortality patterns in these regions did not change considerably over time.

Table 1 details demographic data and death rates of the 24 municipalities with 50 or more deaths caused by Chagas’ disease per 100 000 inhabitants. Most of these municipalities are located in the states Minas Gerais (15) and Goiás (7). The municipality of Abadia dos Dourados (MG) had the highest mortality related to Chagas disease with a relative risk of 46 as compared to the country’s average (Table 1). The 24 municipalities are responsible for 3.0% of deaths related to Chagas’ disease as multiple causes of death, but only account for 0.14% of the Brazilian population.

Spatial clusters of high risk for mortality caused by Chagas’ disease
Spatial autocorrelation, as expressed by Global Moran’s I index, is depicted in Table 2. For all periods, values for mortality rates because of Chagas’ disease were highly significant, evidencing spatial autocorrelation between municipalities with similar patterns in Brazil.

Moran spatial index corroborated the findings of clusters of municipalities in the descriptive maps (Figures 2 and 3). During the progress of Chagas’ disease mortality in the period, we identified a large cluster of municipalities with high risk for mortality (Q1 – High/High) in central Brazil. This cluster covered almost all municipalities of Goiás and Minas Gerais, the Federal District and some municipalities of São Paulo, Mato Grosso, Mato Grosso do Sul, Tocantins, Piauí and Bahia state (Figure 4). Beside this major cluster, we identified four smaller high-risk areas (Figure 4). Clusters of municipalities with low mortality rates (Q2 – Low/Low) were located in the South, in the Northeast and in the North regions (Figure 4).

In the observation period, the main cluster was surrounded by small clusters of municipalities with lower values (Q4 – Low/High). There were also some municipalities with high values (Q3 – High/Low) near clusters of low values (Q2) – transition areas, with reduced mortality rates. The cluster in southeast Piauí State increased the number of municipalities with high mortality rates in the period 2005–2007 (Figure 4).

Discussion
This is the first systematic spatial analysis of Chagas’ disease, using mortality data. We identified spatial clusters of municipalities with high mortality rates related to Chagas’ disease in Brazil, in particular an extended risk area encompassing nine states. Different spatial-analytical approaches confirmed the geographic extension of this cluster. We defined priority areas for intervention, appropriate management of patients with chronic infection and the consequent reduction in cases or deaths, considering epidemiological and operational conditions in the Brazilian municipalities affected.

The spatial distribution of mortality associated with Chagas’ disease was heterogeneous with the presence of deaths in all Brazilian states. The inequality of the risk of dying of Chagas’ disease among geographical areas was identified by the presence of groups with high mortality.
rates in the states of Minas Gerais, Goiás, Distrito Federal, São Paulo, Paraná, Mato Grosso, Mato Grosso do Sul, Tocantins, Bahia and Piauí. This geographical feature was also observed in intra-regional variations between the states that had the highest mortality rates for the period. The state of Goiás, for example, had the highest mortality rates, but enormous variations between municipalities. Municipalities with higher risk were usually surrounded by others with higher rates and/or intermediaries. On the other hand, within groups of municipalities with high rates, some presented lower rates than the national average. This reveals that the spatial distribution of mortality associated with Chagas’ disease is, similar to other vector-borne diseases, heterogeneous and focal, even in geographically close areas (Cecere et al. 2004; Vazquez-Prokopec et al. 2005; Kitron et al. 2006; Atanaka-Santos et al. 2007; Guimaraes et al. 2008; Mischler 2011; Parise et al. 2011; Rollemberg et al. 2011).

Differences between municipalities may also have been caused by underreporting because of problems in the local health system, such as lack of access to specialised services in these municipalities leading to migration of patients to the major urban centres (Martins-Melo et al. 2012), owing to an inability of health professionals to properly diagnose Chagas’ disease, and inefficiency of the epidemiological surveillance services.

Figure 2 Spatial distribution of mean mortality rates related to Chagas’ disease (per 100 000 inhabitants) based on multiple causes of death by municipality, Brazil, 1999–2007.
Our data show that spatial patterns of coefficients between municipalities did not occur randomly. The global Moran index showed autocorrelation of mortality associated with Chagas’ disease, and local Moran index identified clusters of municipalities with high mortality rates and defined priority areas for surveillance and control of Chagas’ disease in Brazil. In fact, Chagas’ disease as a focal disease depends not only on the presence of vector, but also on certain other conditions, such as access to health services and poor living conditions (Silveira et al. 2011).

Local Moran statistic identified critical or high priority areas formed by the municipalities covered by the class Q1 Moran Map. The local spatial autocorrelation analysis performed revealed a pattern of extreme concentration of municipalities with high rates of mortality associated with Chagas’ disease in the central areas of Brazil.

In Brazil, Penna et al. (2009) have recently identified disease clusters for prioritisation of control measures in high-risk areas, defining areas with highest detection rates of leprosy by using spatial scan statistics. Consequently, the National Leprosy Control Program targeted these areas as priority regions and is financing research projects focussing on these areas (Alencar et al. 2012). A similar approach is proposed to be performed by the National Chagas’ Disease Control Program.

We found that there was an overlap of high risk for mortality in areas with high rates of seroreactivity for Chagas’ disease, and with high rates of infestation by the previous main vector Triatoma infestans in the past (Camargo et al. 1984, Passos & Silveira 2011, Silveira et al. 1984, 2011). This pattern was observed in the area of the central cluster, the clusters of southeast of Mato
in the study period. This relationship is exemplified by the observed pattern in Rio Grande do Sul in the extreme south of Brazil, where the highest rates of infected T. infestans were found (Passos & Silveira 2011; Silveira 2011; Silveira et al. 2011), whereas mortality related to Chagas’ disease in our study showed low values in this region. Future studies will have to work on regional differences of transmission, morbidity and mortality.

The interpretation of results must take into consideration that there may be some limitations arising from the notification and storage of data on mortality (Drumond & Marcopito 2006). The use of secondary data may show inconsistency in the quantity and quality of the information. Another limitation refers to possible underreporting of deaths (Santo 2009) that may have occurred despite the important progress over the period under study, both in the coverage of the Mortality Information System (SIM) and in the quality of information of causes of death. We included multiple causes of death to reduce this error. The coverage (ratio of deaths reported and estimated) SIM also

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<th>Population*</th>
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<th>Deaths (MC)</th>
<th>Rates (UC)†</th>
<th>RR Rates (MC)†</th>
<th>RR‡</th>
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<td>138.06 40.96</td>
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<td>40</td>
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<td>33.78</td>
<td>99.83 29.62</td>
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<td>17</td>
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<td>1438</td>
<td>1596</td>
<td>64.40</td>
<td>23.08</td>
<td>71.48 21.21</td>
</tr>
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UC, underlying cause; MC, multiple causes.
*Average population.
†Calculated using the population of the year 2003.
‡The relative risk (RR) refers to the national mean.

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<th>Period</th>
<th>Global Moran’s index</th>
<th>P-value</th>
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<tbody>
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<td>1999–2001</td>
<td>0.3222</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2002–2004</td>
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</tr>
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<td>2005–2007</td>
<td>0.2695</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1999–2007</td>
<td>0.3755</td>
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Grosso, north-central and São-Francisco valley of Bahia and the border between São Paulo and Paraná (Passos & Silveira 2011; Silveira et al. 2011). Despite the recent elimination of the most important vector species in Brazil, in these areas many people are still infected, as evidenced by these high-risk areas for Chagas’ mortality. However, these findings may be contradictory and vector presence and prevalence of infection in humans in the past are ineffective in predicting whether or not there were changes in the patterns of mortality indicators in the municipalities Table 2

Global Moran’s index for the mean rates of mortality related to Chagas’ disease and their significance levels (multiple causes of death), Brazil 1999–2007

<table>
<thead>
<tr>
<th>Period</th>
<th>Global Moran’s index</th>
<th>P-value</th>
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<td>1999–2001</td>
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varies between regions in the country, especially in the North and Northeast. Its coverage in 2001 was 82.3% for the country as a whole, ranging from 96.1% in Rio Grande do Sul and 48.8% in Maranhão (Ministry of Health of Brazil 2004). The proportion of deaths from ill-defined causes is also unequally distributed between regions, rural and urban areas, age groups and socio-economic strata (Drumond & Marcopito 2006). However, we believe that this underreporting is at random and not associated with Chagas’ mortality.

We conclude that the use of spatial analysis tools for defining priority areas is a feasible strategy for surveillance and control of Chagas’ disease. Control of vector transmission and recognition of Chagas’ disease as a chronic condition by health authorities is needed. Clinical management of chronic disease, in primary care and reference service, needs to be improved, and adequate access to health services and social care for individuals with chronic Chagas’ disease should be guaranteed. Integrated care of chronic patients and intervention measures to reduce morbidity and mortality should be established, considering geographical areas of risk.

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