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Burden of Chagas disease in Brazil, 1990–2016: findings from the Global Burden of Disease Study 2016

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ABSTRACT

Chagas disease continues to be an important cause of morbidity, mortality and disability in several Latin American countries, including Brazil. Using findings from the Global Burden of Disease Study 2016 (GBD, 2016), we present years of life lost, years lived with disability, and disability-adjusted life years due to Chagas disease in Brazil, by sex, age group, and Brazilian states, from 1990 to 2016. Results are reported in absolute numbers and age-standardized rates (per 100,000 population) with 95% uncertainty intervals. In 2016, 141,640 disability-adjusted life years (95% uncertainty intervals: 129,065–155,941) due to Chagas disease were estimated in Brazil, with a relative reduction of 36.7% compared with 1990 (223,879 disability-adjusted life years (95% uncertainty intervals: 209,372–238,591)). Age-standardized disability-adjusted life year rates declined at the national level (−69.7%) and in all Brazilian states between 1990 and 2016, but with different regional patterns. The decrease in the disability-adjusted life year rates was driven primarily by a consistent reduction in the years of life lost rates, the main component of total disability-adjusted life years for Chagas disease. The highest fatal and non-fatal burden due to Chagas disease was observed among males, the elderly, and in those Brazilian states encompassing important endemic areas for vector transmission in the past. Despite the consistent reduction in its burden during the period, Chagas disease is still an important and neglected cause of health lost due to premature mortality and disability in Brazil. Efforts should be made to maintain the political interest and sustainability of surveillance and control actions for Chagas disease, prevent the risk of re-emergence of vector transmission in endemic areas, and provide health care to chronically infected individuals, including early diagnosis and treatment interventions.

1. Introduction

Chagas disease (or American trypanosomiasis) is a parasitic disease caused by the protozoan parasite *Trypanosoma cruzi* (World Health Organization, 2015, 2018). *Trypanosoma cruzi* is transmitted to humans primarily by infected faeces of blood-sucking triatomine bugs which occur only in the Americas (World Health Organization (WHO), 2018. Chagas disease (American trypanosomiasis) – Fact sheet. (http://www.who.int/en/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis; accessed February 15, 2018)). Other important transmission routes include blood transfusion, organ transplantation, mother-to-child transmission and oral transmission (World Health Organization, 2015, 2018 (http://www.who.int/en/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis; accessed February 15, 2018)).

Chagas disease is considered a neglected tropical disease and remains a public health problem with social significance and economic implications in most Latin American countries, where transmission is typically vector-borne (World Health Organization, 2015, 2018 (http://www.who.int/en/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis; accessed February 15, 2018)). Chagas disease has become a global emerging public

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health problem due to migration of infected individuals from Latin American endemic countries to non-endemic areas, particularly the United States, Canada, many European countries and some Western Pacific countries (Requena-Méndez et al., 2015; World Health Organization, 2015, 2018 (http://www.who.int/en/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis; accessed February 15, 2018)). The principal transmission routes in these countries are blood transfusion, organ transplantation and vertical transmission (Requena-Méndez et al., 2015). Approximately 6–8 million people worldwide, mostly in Latin American countries, are estimated to be infected with *T. cruzi* (World Health Organization, 2018 (http://www.who.int/en/news-room/fact-sheets/detail/chagas-disease-(american-trypanosomiasis; accessed February 15, 2018) ; Pan American Health Organization (PAHO), 2018. (http://www.paho.org/hq/index.php?option=com_topics&view=article&id=10&Itemid=40743&lang=en; accessed February 20, 2018)), and more than 70 million people are at risk of infection (World Health Organization, 2015). An estimated 7100–10,000 people die annually from clinical manifestations of Chagas disease (GBD 2016 Causes of Death Collaborators, 2017; Pan American Health Organization (PAHO), 2018. Chagas disease. (http://www.paho.org/hq/index.php?option=com_topics&view=article&id=10&Itemid=40743&lang=en; accessed February 20, 2018)), and approximately 219,000–251,000 disability-adjusted life years (DALYs) are lost due to the disease worldwide (GBD 2016 DALYs and HALE Collaborators, 2017).

In Brazil, one of the most important Chagas disease endemic countries, the number of new cases of Chagas disease has been reduced dramatically in recent years, mainly due to the reduction in intradomiciliary vector-borne transmission (typically by the kissing bug *Triatoma infestans*, the principal vector in the country), and control of transmission via blood transfusion (Martins-Melo et al., 2014; Dias et al., 2016). Currently, there is no accurate estimation of the Chagas disease prevalence in the country, owing to a lack of updated national or regional serological surveys of *T. cruzi* infection in the general population and few population-based systematic studies conducted in endemic areas (Silveira et al., 2011; Martins-Melo et al., 2014). Estimates indicate that approximately 1.2–4.6 million people are infected with *T. cruzi* in Brazil (Martins-Melo et al., 2014; World Health Organization, 2015), causing approximately 6000 deaths annually, most of them due to cardiac forms of the disease (Martins-Melo et al., 2012a, 2012c).

Despite being an important cause of early mortality and disability and producing a significant economic burden in endemic countries (Martins-Melo et al., 2012a; Lee et al., 2013; Cucunubá et al., 2016), no previous systematic studies have assessed the fatal and non-fatal burden of Chagas disease in Brazil. Understanding the trends and levels of Chagas disease burden in endemic areas is crucial in assessment of the success of surveillance and control programs and identification of enduring challenges (Martins-Melo et al., 2014, 2018; Herricks et al., 2017; GBD Tuberculosis Collaborators, 2018). Using findings from the Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (GBD 2016), we present estimates of the burden of Chagas disease in Brazil, by sex, age group, and all 27 Brazilian states, from 1990 to 2016.

2. Material and methods

2.1. Study overview

In this study, we used the GBD 2016 results to analyse the burden of Chagas disease in Brazil from 1990 to 2016. The GBD study is a systematic, scientific effort to quantify the comparative magnitude of health loss due to diseases, injuries, and risk factors by sex, age group, and location over time (GBD 2016 DALYs and HALE Collaborators, 2017). The GBD study uses as the main population health metric the DALYs or years of healthy life lost due to premature death and disability, a measure of health loss due to both fatal and non-fatal disease burden (GBD 2016 DALYs and HALE Collaborators, 2017). DALYs are estimated by summing the years lived with any short-term or long-term disability (YLDs) and years of life lost (YLLs) due to premature mortality from a given cause (GBD 2016 DALYs and HALE Collaborators, 2017; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017). One DALY is equivalent to one healthy year of life lost due to a specific disease or injury (GBD 2016 DALYs and HALE Collaborators, 2017).

GBD 2016 estimated the burden of 333 diseases and injuries and 84 risk factors for 195 countries and territories, some of which were estimated at the subnational level, including Brazil (GBD 2016 DALYs and HALE Collaborators, 2017; GBD 2016 Risk Factors Collaborators, 2017). For each cycle of the GBD study, the entire time series is re-estimated to incorporate new data and methods. Thus, the GBD 2016 results supersede all previous GBD results (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). The conceptual and analytical framework for GBD 2016, with details of data processing and the analytical approach, has been published elsewhere (GBD 2016 DALYs and HALE Collaborators, 2017; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; GBD 2016 Risk Factors Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017). Here, we summarize the key points of the GBD 2016 methods used for analysis of the burden of Chagas disease in Brazil.

2.2. GBD cause definition of Chagas disease

The GBD cause list is organised hierarchically into four levels that are mutually exclusive and collectively exhaustive (GBD 2016 DALYs and HALE Collaborators, 2017; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017). Chagas disease is a level 3 cause, which is included in the level 2 group of "Neglected tropical diseases and malaria" belonging to the level 1 group "Communicable, maternal, neonatal, and nutritional diseases" (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017). The case definition of Chagas disease used for GBD 2016 was based on the International Classification of Diseases (ICD)-9 codes 086.0–086.2 and 425.6, and ICD-10 codes B57-B57.5 and K93.1 (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017).

2.3. Study location and time period

Brazil, officially called the Federal Republic of Brazil, is the largest country in South America (with a total territory of 8.5 million km^2) and had an estimated population of 207.7 million inhabitants in 2017 (Brazilian Institute of Geography and Statistics – IBGE in Portuguese; https://www.ibge.gov.br/apps/populacao/projecao/). The country is divided politically and administratively into 27 federative units (26 states and the Federal District) and 5570 municipalities, grouped into five geographic macro-regions (South, Southeast, Central-West, North and Northeast). In this study, we present estimates of Chagas disease burden at a national level and for all federative units (26 states and the Federal District), herein simply named as states.

GBD 2016 estimated the cause-specific burden for all diseases and injuries for the years 1990–2016. Here we focused on burden

estimates for 2016, with reference to changes in the Chagas disease burden from 1990. GBD 2016 results by location and year can be explored further in dynamic data visualizations at https://gbd2016.healthdata.org/gbd-compare and https://gbd2016.healthdata.org/gbd-search.

2.4. Data sources and modelling strategy

The GBD 2016 data sources and modelling process for mortality and morbidity estimates for all causes and for specific analysis of Chagas disease burden have been detailed elsewhere (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; GBD 2016 Risk Factors Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017). For Brazil, the main mortality data source used in GBD 2016 for the estimation of Chagas disease deaths was the Brazilian Mortality Information System (Sistema de Informações sobre Mortalidade – SIM in Portuguese) database, adjusted by other national and international sources (França et al., 2017; GBD Brazil Collaborators, 2018). Vital registration data were adjusted and corrected for mortality completeness and for garbage coding (assignment of causes of death that could not or should not be classified as the underlying cause of death, including ill-defined codes and the use of intermediate causes), with redistribution of these for defined causes based on the GBD algorithms (Naghavi et al., 2010; Marinho et al., 2016; GBD 2016 Causes of Death Collaborators, 2017). GBD 2016 used the Cause of Death Ensemble modelling (CODEm) to estimate the Chagas disease by location, age group, sex, and year (GBD 2016 Causes of Death Collaborators, 2017). The CODEm approach applies mixed effects or spatiotemporal Gaussian process regression models to mortality rates or cause fractions with varying combinations of predictive covariates. Predictive validity testing determined the optimal ensemble of models (GBD 2016 Causes of Death Collaborators, 2017). The ensemble with the highest out-of sample predictive validity was selected from differently weighted combinations of individual models (GBD 2016 Causes of Death Collaborators, 2017; GBD 2016 Brazil Collaborators, 2018). A Detailed description of the CODEm framework has been published elsewhere (GBD 2016 Causes of Death Collaborators, 2017).

GBD 2016 used available data from population-representative studies of Chagas disease seroprevalence to produce consistent non-fatal estimates for Chagas disease (Marinho et al., 2016; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). GBD 2016 used the DisMod-MR 2.1, a Bayesian meta-regression tool, to estimate the non-fatal outcomes due to Chagas disease by sex, age, location and year. This tool adjusts for variations in study methods between data sources and imposes consistency between data for different parameters such as incidence and prevalence (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). GBD 2016 included a set of five sequelae as part of the direct Chagas disease burden estimation: symptomatic acute infection, megaviscera, heart failure, atrial fibrillation, and chronic asymptomatic infection. Each non-fatal sequela was estimated separately (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). GBD 2016 estimated the prevalence of Chagas disease and its sequelae incorporating seroprevalence data and cause-specific mortality rates (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Detailed non-fatal modelling methods for Chagas disease and other specific causes are described in detail elsewhere (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). GBD 2016 data sources and publications used to estimate the Chagas disease morbidity and mortality are presented in Supplementary Table S1 and are available at http://ghdx.healthdata.org/gbd-2016/data-input-sources?locations=135&components=5&causes=346.

2.5. DALY estimation

In this study, we used DALYs and the component YLLs and YLDs to assess the burden of Chagas disease in Brazil. Detailed DALY estimation methods were described in the GBD publications (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; GBD 2016 Risk Factors Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017). YLLs were estimated by multiplying the number of deaths due to Chagas disease in each age group by the normative standard life expectancy at the age of death (GBD 2016 Causes of Death Collaborators, 2017). The GBD standard life expectancy is based on the lowest death rates for each age group observed in countries with a population greater than 5 million. In GBD 2016, the standard life expectancy at birth was 86.6 years (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). YLDs were estimated by multiplying the prevalence of each sequela related to Chagas disease by its disability weights for each location, sex, age group, and year, and then aggregating the estimates for all sequelae to the cause level (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Disability weights quantify the relative severity of the sequelae on a scale from 0 (perfect health) to 1 (equivalent to death) (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). Disability weights were derived from population-based surveys and an open web-based survey (Salomon et al., 2015; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). The sequelae due to Chagas disease and their associated disability weights are shown in Supplementary Table S2. Finally, DALYs due to Chagas disease were computed as the sum of YLLs and YLDs (GBD 2016 DALYs and HALE Collaborators, 2017).

Results are presented in absolute numbers and age-standardized rates (per 100,000 population) of DALYs, YLLs and YLDs due to Chagas disease by sex, age group, year and location Age-standardized rates were calculated using the GBD 2016 world population standard (GBD 2016 DALYs and HALE Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017). The estimates are reported with their 95% uncertainty intervals (UIs), which are based on 1000 runs of the models for each quantity of interest, with the mean considered as the point estimate and the 2.5th and 97.5th percentiles considered as the 95% UIs (GBD 2016 DALYs and HALE Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017).

We report positive and negative percentage changes to show increasing and decreasing variations between 1990 and 2016, respectively, in addition to annualized rates of change (ARC) for the entire period.

2.6. Ethics statement

This research has been conducted as part of the GBD study, coordinated by the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, USA. This study was based on data which are publicly available, and ethics approval was not applicable.

3. Results

3.1. Overall burden

In 2016, Chagas disease caused an estimated 141,640 DALYs (95% UI: 129,065–155,941) in Brazil, with a relative reduction of 36.7% compared with 1990 (223,879 DALYs (95% UI: 209,372–238,591)) (Table 1). Similarly, age-standardized DALY rates

Table 1
Number of disability-adjusted life-years and age-standardized disability-adjusted life-year rates (per 100,000 population) due to Chagas disease in Brazil and individual states in 1990 and 2016, with the absolute percentage change and annualized rate of change for 1990–2016.

Region/State	Number of DALYs (95% UI)			Age-standardized DALY rates (per 100,000) (95% UI)			ARC 1990–2016 (%)
	1990	2016	% Change 1990–2016	1990	2016	% Change 1990–2016	
Brazil	223878.6 (209371.8–238590.7)	141640.3 (129065.0–155941.4)	−36.7	233.18 (219.34–247.29)	70.69 (64.49–77.81)	−69.7	−4.6
North							
Acre	84.2 (72.4–98.0)	101.0 (81.3–124.5)	20.0	38.98 (33.74–45.14)	18.07 (14.78–22.13)	−53.6	−3.0
Amapá	36.4 (30.1–44.6)	79.0 (61.499.6	116.9	27.07 (22.66–32.59)	15.35 (12.21–19.15)	−43.3	−2.2
Amazonas	222.3 (178.7–277.2)	360.3 (266.5–477.2)	62.0	22.90 (18.62–28.16)	12.91 (9.80–16.91)	−43.6	−2.2
Rondônia	898.5 (787.3–1020.3)	722.9 (619.2–837.6)	−19.5	173.75 (154.00–194.26)	50.57 (43.59–57.98)	−70.9	−4.8
Roraima	38.5 (32.5–45.0)	60.1 (47.6–75.3)	56.1	42.57 (36.41–49.58)	17.40 (13.99–21.53)	−59.1	−3.4
Pará	959.4 (821.3–1135.0)	1166.6 (936.8–1425.1)	21.6	37.62 (32.61–44.03)	18.71 (15.17–22.64)	−50.3	−2.7
Tocantins	1,088.6 (948.0–1260.5)	1428.7 (1231.2–1636.4)	31.2	235.96 (206.16–271.22)	117.48 (101.71–134.35)	−50.2	−2.7
Northeast							
Alagoas	3041.4 (2700.6–3430.4)	2647.5 (2,303.8–3014.9)	−13.0	210.41 (187.22–236.02)	93.60 (81.94–106.31)	−55.5	−3.1
Bahia	20396.7 (18343.8–22653.6)	18735.3 (16387.0–21601.5)	−8.1	283.79 (256.14–314.02)	133.85 (117.15–154.12)	−52.8	−2.9
Ceará	1659.5 (1394.9–2019.4)	2169.1 (1848.7–2575.7)	30.7	42.51 (35.99–51.31)	26.69 (22.80–31.51)	−37.2	−1.8
Maranhão	743.6 (604.4–916.7)	832.4 (661.5–1,054.8)	11.9	28.15 (23.00–34.49)	15.53 (12.52–19.62)	−44.8	−2.3
Paraíba	1338.8 (1175.9–1536.9)	1313.1 (1128.6–1523.2)	−1.9	66.21 (58.00–75.96)	34.99 (30.15–40.54)	−47.2	−2.5
Pernambuco	5550.1 (4934.4–6266.3)	3898.6 (3353.1–4546.9)	−29.8	121.63 (108.50–136.36)	45.55 (39.28–52.89)	−62.5	−3.8
Piauí	1733.2 (1514.4–1986.8)	2024.5 (1758.6–2326.7)	16.8	122.62 (107.38–139.79)	71.62 (62.52–82.14)	−41.6	−2.1
Rio Grande do Norte	562.3 (477.3–669.9)	674.5 (556.5–820.3)	20.0	37.48 (31.99–44.26)	20.72 (17.20–25.28)	−44.7	−2.3
Sergipe	498.6 (433.0–572.1)	534.9 (453.3–636.1)	7.3	58.10 (50.63–66.31)	27.58 (23.55–32.54)	−52.5	−2.9
Southeast							
Espírito Santo	507.0 (427.9–601.8)	571.2 (439.6–733.4)	12.7	31.56 (26.89–37.19)	14.29 (11.03–18.33)	−54.7	−3.1
Minas Gerais	66445.1 (60263.8–73009.9)	32072.5 (28205.5–36191.8)	−51.7	645.82 (590.78–705.02)	145.90 (128.76–164.24)	−77.4	−5.7
Rio de Janeiro	3276.4 (2,819.1–3827.4)	2865.2 (2236.4–3645.5)	−12.5	32.94 (28.43–38.21)	15.25 (11.92–19.45)	−53.7	−3.0
São Paulo	53765.9 (49204.8–58994.9)	32023.1 (27567.8–37056.8)	−40.4	234.71 (215.50–256.60)	67.55 (58.44–78.03)	−71.2	−4.8
South							
Paraná	11743.8 (10645.0–13009.2)	6558.6 (5677.0–7563.7)	−44.2	217.89 (198.76–239.58)	56.54 (49.19–65.24)	−74.0	−5.2
Rio Grande do Sul	2412.5 (2057.8–2829.0)	2174.9 (1719.3–2741.0)	−9.8	36.33 (31.22–42.58)	16.39 (12.94–20.75)	−54.9	−3.1
Santa Catarina	667.6 (548.2–825.7)	900.7 (675.2–1203.3)	34.9	24.47 (20.31–29.81)	12.76 (9.53–16.96)	−47.9	−2.5
Central-West							
Distrito Federal	7552.2 (6813.6–8351.0)	5494.6 (4758.5–6319.3)	−27.2	891.93 (811.96–976.08)	208.64 (181.04–239.62)	−76.6	−5.6
Goiás	35442.2 (32471.2–38475.9)	19081.7 (17009.4–21502.0)	−46.2	1614.43 (1485.32–1747.50)	327.05 (292.81–368.12)	−79.7	−6.1
Mato Grosso	1351.1 (1197.7–1510.0)	1700.0 (1469.0–1958.5)	25.8	133.49 (119.06–148.48)	58.72 (50.90–67.42)	−56.0	−3.2
Mato Grosso do Sul	1862.5 (1669.1–2063.2)	1449.2 (1248.1–1658.9)	−22.2	176.72 (158.97–195.19)	57.78 (49.95–66.14)	−67.3	−4.3

95% UI, 95% uncertainty interval.

Table 2
Number of years of life lost and age-standardized years of life lost rates (per 100,000 population) due to Chagas disease in Brazil and individual states in 1990 and 2016, with the absolute percentage change and annualized rate of change for 1990–2016.

Region/State	Number of YLLs (95% UI)			Age-standardized YLL rates (per 100,000 population) (95% UI)			ARC 1990–2016 (%)
	1990	2016	% Change 1990–2016	1990	2016	% Change 1990–2016	
Brazil	205014.7 (192399.6–216881.0)	116521.8 (108044.3–125832.5)	−43.2	213.56 (201.34–225.13)	58.42 (54.19–63.04)	−72.6	−5.0
North							
Acre	58.2 (51.6–65.2)	52.6 (44.6–61.5)	−9.7	27.06 (24.13–30.30)	9.78 (8.39–11.34)	−63.9	−3.9
Amapá	20.9 (18.5–23.6)	34.0 (28.7–39.4)	62.1	16.18 (14.38–18.18)	7.01 (5.99–8.06)	−56.6	−3.2
Amazonas	112.1 (99.5–126.5)	112.5 (95.6–132.7)	0.3	11.89 (10.63–13.33)	4.30 (3.67–5.02)	−63.9	−3.9
Rondônia	796.8 (693.8–914.3)	560.4 (482.4–649.2)	−29.7	154.25 (136.14–173.00)	39.71 (34.30–45.75)	−74.2	−5.2
Roraima	26.9 (23.4–30.6)	28.6 (24.3–33.6)	6.2	30.13 (26.46–34.05)	8.69 (7.48–10.12)	−71.1	−4.8
Pará	658.2 (586.2–738.9)	624.5 (523.2–737.6)	−5.1	26.08 (23.38–29.16)	10.25 (8.66–12.00)	−60.7	−3.6
Tocantins	982.4 (843.8–1149.2)	1244.8 (1069.5–1434.0)	26.7	213.94 (185.52–248.43)	103.26 (88.97–118.72)	−51.7	−2.8
Northeast							
Alagoas	2762.9 (2432.3–3127.8)	2313.5 (1990.2–2666.3)	−16.3	190.94 (168.79–215.38)	81.97 (70.87–94.19)	−57.1	−3.3
Bahia	18705.8 (16763.6–20769.4)	16589.1 (14322.7–19161.0)	−11.3	259.92 (234.07–287.44)	119.04 (103.05–137.08)	−54.2	−3.0
Ceará	1194.9 (1013.5–1463.0)	1451.1 (1252.1–1669.2)	21.4	30.68 (26.15–37.67)	18.00 (15.59–20.54)	−41.3	−2.1
Maranhão	429.0 (369.4–503.8)	377.3 (324.6–432.2)	−12.1	16.52 (14.17–19.32)	7.25 (6.28–8.26)	−56.1	−3.2
Paraíba	1047.8 (938.3–1181.7)	961.5 (839.2–1083.5)	−8.2	52.04 (46.44–58.90)	25.72 (22.47–28.97)	−50.6	−2.7
Pernambuco	4791.7 (4248.8–5397.7)	3026.0 (2602.2–3479.1)	−36.8	105.08 (93.72–117.76)	35.55 (30.60–40.81)	−66.2	−4.2
Piauí	1491.3 (1297.4–1703.7)	1704.4 (1481.7–1962.8)	14.3	105.78 (92.72–120.06)	60.61 (52.92–69.65)	−42.7	−2.1
Rio Grande do Norte	385.7 (337.9–440.7)	392.7 (333.9–463.6)	1.8	25.90 (22.76–29.50)	12.12 (10.36–14.26)	−53.2	−2.9
Sergipe	387.8 (341.3–442.2)	364.2 (309.7–422.5)	−6.1	45.57 (40.31–51.52)	18.92 (16.27–21.79)	−58.5	−3.4
Southeast							
Espírito Santo	325.3 (290.6–364.2)	221.4 (191.1–256.6)	−31.9	20.31 (18.23–22.56)	5.50 (4.75–6.35)	−72.9	−5.0
Minas Gerais	62899.9 (56577.7–68941.7)	28072.9 (24739.5–32020.5)	−55.4	612.10 (558.10–669.10)	127.94 (113.06–145.49)	−79.1	−6.0
Rio de Janeiro	2194.3 (1957.9–2440.7)	1219.1 (1060.3–1391.1)	−44.4	21.76 (19.62–24.07)	6.37 (5.55–7.24)	−70.7	−4.7
São Paulo	49008.0 (44645.5–53911.1)	25936.6 (22557.6–29757.9)	−47.1	213.33 (195.83–233.30)	54.79 (47.80–62.77)	−74.3	−5.2
South							
Paraná	10597.0 (9600.6–11737.5)	5166.1 (4492.3–5930.3)	−51.2	196.76 (179.07–216.57)	44.63 (39.06–51.15)	−77.3	−5.7
Rio Grande do Sul	1618.2 (1455.3–1798.6)	1018.0 (875.3–1176.7)	−37.1	24.49 (22.11–27.05)	7.50 (6.47–8.66)	−69.4	−4.6
Santa Catarina	359.1 (320.1–399.5)	265.5 (228.2–310.2)	−26.1	13.58 (12.15–15.04)	3.74 (3.23–4.35)	−72.5	−5.0
Central-West							
Distrito Federal	7152.2 (6418.0–7949.8)	4865.1 (4187.5–5652.8)	−32.0	849.89 (772.67–933.56)	186.55 (161.20–215.97)	−78.1	−5.8
Goiás	34195.1 (31319.2–37311.5)	17385.3 (15382.4–19639.9)	−49.2	1562.82 (1436.62–1692.25)	300.64 (267.92–339.19)	−80.8	−6.3
Mato Grosso	1,160.8 (1033.3–1287.4)	1367.1 (1165.8–1590.7)	17.8	115.27 (103.53–127.79)	47.46 (40.86–54.98)	−58.8	−3.4
Mato Grosso do Sul	1652.1 (1479.3–1836.6)	1167.8 (999.2–1334.5)	−29.3	156.88 (140.89–173.46)	46.67 (40.10–53.18)	−70.2	−4.7

95% UI, 95% uncertainty interval.

Table 3
Number of years lived with disability and age-standardized years lived with disability rates (per 100,000 population) due to Chagas disease in Brazil and individual states in 1990 and 2016, with the absolute percentage change and annualized rate of change (ARC) for 1990–2016.

Region/State	Number of YLDs (95% UI)			Age-standardized YLD rates (per 100,000) (95% UI)			ARC 1990–2016 (%)
	1990	2016	% Change 1990–2016	1990	2016	% Change 1990–2016	
Brazil	18863.9 (12289.5–27523.4)	25118.5 (16363.4–36219.3)	33.2	19.62 (12.95–28.09)	12.27 (8.02–17.73)	−37.5	−1.8
North							
Acre	26.0 (16.1–39.0)	48.5 (30.0–72.1)	86.3	11.92 (7.42–17.57)	8.29 (5.27–12.24)	−30.4	−1.4
Amapá	15.5 (9.6–23.5)	45.1 (29.0–66.7)	191.1	10.89 (6.96–15.96)	8.33 (5.34–12.20)	−23.5	−1.0
Amazonas	110.2 (66.9–164.8)	247.8 (155.3–368.7)	124.9	11.00 (6.86–16.27)	8.61 (5.51–12.63)	−21.8	−1.0
Rondônia	101.7 (63.0–149.7)	162.5 (103.7–237.9)	59.8	19.50 (12.36–29.08)	10.86 (7.02–15.95)	−44.3	−2.3
Roraima	11.6 (7.1–17.5)	31.5 (19.8–47.0)	172.4	12.44 (7.82–18.46)	8.71 (5.68–13.04)	−30.0	−1.4
Pará	301.2 (188.2–452.3)	542.1 (340.8–817.6)	80.0	11.54 (7.39–17.17)	8.46 (5.31–12.54)	−26.7	−1.2
Tocantins	106.2 (66.7–158.5)	183.9 (118.3–267.6)	73.2	22.02 (14.00–32.76)	14.22 (9.23–20.81)	−35.4	−1.7
Northeast							
Alagoas	278.5 (178.8–414.5)	334.0 (214.4–484.1)	19.9	19.46 (12.71–28.46)	11.63 (7.54–16.57)	−40.2	−2.0
Bahia	1690.9 (1088.0–2481.9)	2146.2 (1387.2–3109.3)	26.9	23.87 (15.58–34.22)	14.81 (9.66–21.52)	−38.0	−1.8
Ceará	464.5 (292.7–696.6)	718.1 (461.4–1082.1)	54.6	11.83 (7.50–17.45)	8.69 (5.59–13.13)	−26.5	−1.2
Maranhão	314.6 (196.1–476.4)	455.1 (291.8–666.8)	44.7	11.63 (7.24–17.41)	8.28 (5.36–12.23)	−28.8	−1.3
Paraíba	290.9 (182.7–439.5)	351.6 (225.0–523.0)	20.9	14.17 (8.86–21.28)	9.27 (5.92–13.82)	−34.6	−1.6
Pernambuco	758.4 (484.1–1119.0)	872.6 (556.5–1272.9)	15.1	16.56 (10.63–24.67)	10.00 (6.47–14.57)	−39.6	−1.9
Piauí	241.9 (155.1–367.3)	320.1 (200.9–474.3)	32.3	16.84 (10.79–25.43)	11.01 (6.92–16.02)	−34.6	−1.6
Rio Grande do Norte	176.6 (110.0–267.1)	281.8 (176.1–413.5)	59.6	11.58 (7.29–17.24)	8.60 (5.41–12.54)	−25.8	−1.2
Sergipe	110.7 (68.8–165.9)	170.7 (108.4–250.5)	54.1	12.54 (7.84–18.66)	8.66 (5.54–12.84)	−30.9	−1.4
Southeast							
Espírito Santo	181.7 (114.2–272.7)	349.7 (221.7–517.3)	92.5	11.25 (7.13–16.51)	8.79 (5.64–12.96)	−21.9	−1.0
Minas Gerais	3545.2 (2323.4–5090.0)	3999.6 (2652.1–5744.7)	12.8	33.72 (22.25–48.07)	17.96 (11.94–25.71)	−46.7	−2.4
Rio de Janeiro	1082.1 (675.0–1583.5)	1646.1 (1069.1–2410.2)	52.1	11.19 (7.14–16.22)	8.88 (5.80–13.03)	−20.6	−0.9
São Paulo	4757.8 (3112.7–6966.4)	6086.6 (3932.0–8981.9)	27.9	21.38 (14.08–30.65)	12.76 (8.23–18.70)	−40.3	−2.0
South							
Paraná	1146.8 (731.0–1708.3)	1392.5 (885.2–2042.7)	21.4	21.12 (13.78–31.09)	11.91 (7.62–17.42)	−43.6	−2.2
Rio Grande do Sul	794.4 (491.0–1185.3)	1157.0 (743.9–1705.0)	45.6	11.84 (7.37–17.59)	8.89 (5.76–13.11)	−25.0	−1.1
Santa Catarina	308.5 (195.2–461.3)	635.3 (406.6–932.8)	105.9	10.90 (7.03–16.02)	9.02 (5.80–13.28)	−17.2	−0.7
Central-West							
Distrito Federal	400.1 (257.7–574.1)	629.5 (418.1–895.9)	57.4	42.05 (27.06–59.31)	22.10 (14.84–30.98)	−47.4	−2.5
Goiás	1247.1 (810.8–1811.4)	1696.4 (1128.6–2383.8)	36.0	51.61 (33.78–74.12)	26.41 (17.62–37.16)	−48.8	−2.6
Mato Grosso	190.3 (120.1–288.7)	332.9 (216.5–490.3)	74.9	18.23 (11.61–26.95)	11.26 (7.36–16.49)	−38.2	−1.9
Mato Grosso do Sul	210.4 (130.4–312.9)	281.4 (178.9–408.9)	33.7	19.84 (12.59–29.34)	11.11 (7.17–16.09)	−44.0	−2.2

95% UI, 95% uncertainty interval.

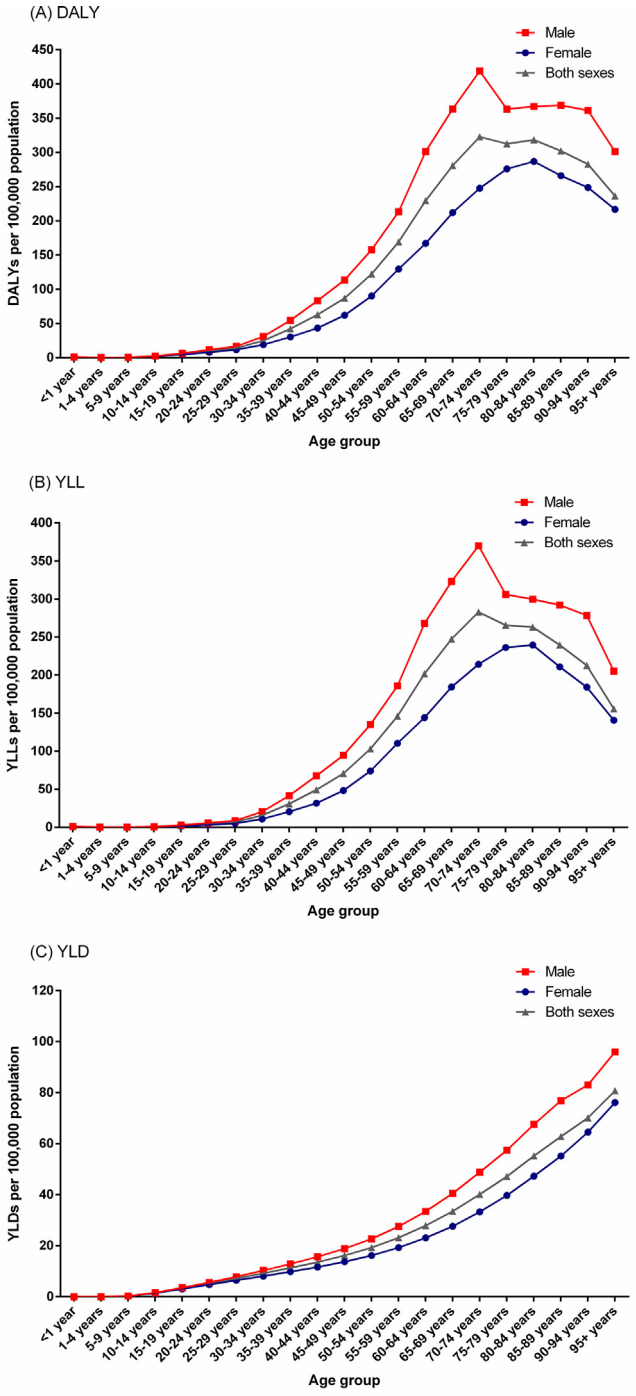

Fig. 1. Age- and sex-specific rates (per 100,000 population) of (A) disability-adjusted life-years, (B) years of life lost, and (C) years lived with disability due to Chagas disease in Brazil, 2016.

declined by 69.7%, from 233.18 DALYs/100,000 (95% UI: 219.34–247.29) in 1990 to 70.69 DALYs/100,000 (95% UI: 64.49–77.81) in 2016, with an ARC of −4.6% (Table 1). YLLs contributed to 91.6% of national DALYs due to Chagas disease in 1990 (205,015 YLLs versus 18,864 YLDs) and 82.6% in 2016 (116,522 YLLs versus 25,119 YLDs). Brazil was responsible for 64.7% of all global DALYs due to Chagas disease in 2016 (218,991 DALYs).

Both the number and age-standardized rates of YLLs decreased at the national level between 1990 and 2016, with an ARC of −5.0% (Table 2). The number of national YLDs increased by 33.2% between 1990 and 2016, while the age-standardized YLD rates declined by 37.5% during the same period, with an ARC of −1.8% (Table 3).

3.2. Age–sex distribution

In 2016, the age-standardized DALY rate was higher in males (89.61 DALYs/100,000 population (95% UI: 80.76–98.39)) than in females (54.51 DALYs/100,000 population (95% UI: 48.54–63.23)), with a male-to-female DALY ratio of 1.6:1. The highest age-specific DALY rates for both sexes combined were observed among the age groups above 60 years (>200 DALYs/100,000 population), with a peak in the age group of 70–74 years (322.98 DALYs/100,000 population (95% UI: 290.60–362.64)) (Fig. 1A). The same age-specific pattern was observed for males, whereas DALY rates peaked in the age group of 80–84 years for females (Fig. 1A).

The highest YLL rates were observed in males (75.20 YLLs/100,000 population (95% UI: 68.82–82.38) versus 44.04 YLLs/100,000 population (95% UI: 39.58–51.98) for females; a male-to-female YLL ratio of 1.7:1) and for people aged 70–74 years for both sexes combined (Fig. 1B). The same age-specific pattern was observed for males, whereas it peaked in the age group of 80–84 years for females (Fig. 1B). The highest YLD rates were observed in males (14.41 YLDs/100,000 population (95% UI: 9.49–20.52) versus 10.48 YLDs/100,000 population (95% UI: 6.81–15.24) for females; a male-to-female YLD ratio of 1.4:1) and among those aged above 70 years for both sexes combined, with a peak in the age group 95 years and older. The same age-specific pattern was observed for both males and females (Fig. 1C).

3.3. Geographical variations in the Chagas disease burden

Table 1 shows the number of DALYs and age-standardized DALY rates due to Chagas disease in Brazil and its states in 1990 and 2016. In 2016, the highest numbers of DALYs due to Chagas disease at the subnational level were observed in the states of Minas Gerais, São Paulo and Goiás, whereas the highest age-standardized DALY rate was observed in the state of Goiás (327.05 DALYs/100,000 population (95% UI: 292.81–368.12)), 4.6 times higher than the national average, followed by the Distrito Federal and Minas Gerais (Table 1; Fig. 2A). Several states with the lowest number of DALYs showed an increase between 1990 and 2016, mainly in the North and Northeast regions, while the states with the highest number of DALYs, such as Minas Gerais and Goiás, presented the highest declines in the same period. However, the age-standardized DALY rates due to Chagas declined in all 27 Brazilian states between 1990 and 2016, with the highest decreases observed in the states of Goiás, Minas Gerais, and Distrito Federal (a relative reduction of 75% or more), while the smallest decreases were observed in the states of Ceará and Piauí (Table 1).

Tables 2 and 3 present the absolute number and age-standardized rates of YLL and YLD due to Chagas disease in Brazil and its states in 1990 and 2016, respectively. The levels and trends of age-standardized rates of YLL and YLDs by Brazilian states were similar to those patterns observed for age-standardized DALY rates, with the highest values in 2016 for Goiás, Distrito Federal and Minas Gerais (Tables 2 and 3; Fig. 2B and C), and declining trend for all states between 1990 and 2016, but with faster declines observed for YLLs than YLDs (Tables 2 and 3). The absolute number of YLDs increased for all Brazilian states during the period (Table 3).

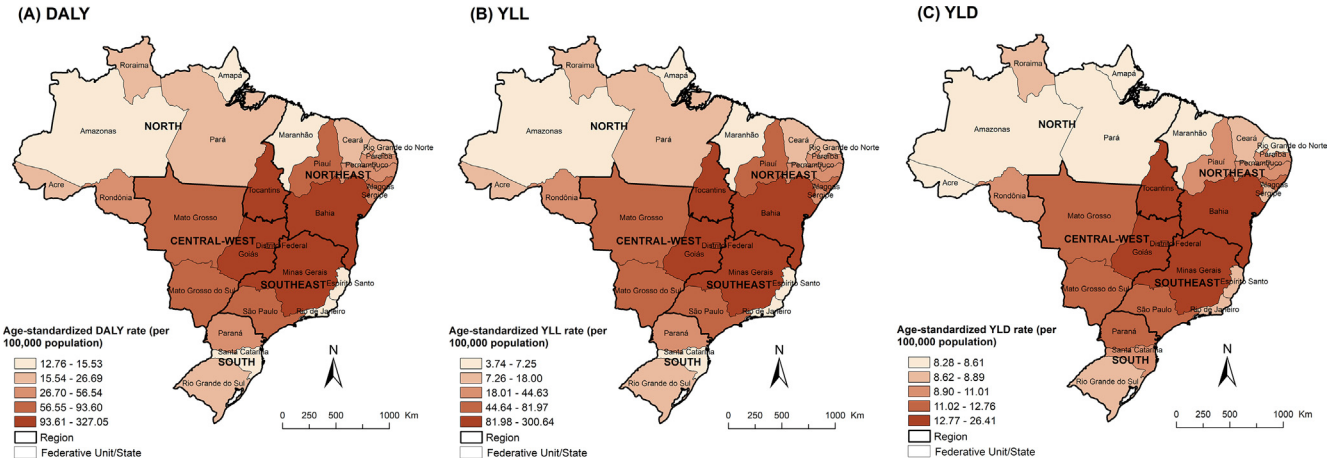

Fig. 2. Age-standardized rates (per 100,000 population) of (A) disability-adjusted life-years, (B) years of life lost, and (C) years lived with disability due to Chagas disease by state in Brazil, 2016. Map produced using ArcGIS version 9.3 (Esri, Redlands, CA, USA). Source of shapefile: Brazilian Institute of Geography and Statistics (IBGE in Portuguese; https://mapas.ibge.gov.br/bases-e-referenciais/bases-cartograficas/malhas-digitais.html).

4. Discussion

To our knowledge, this is the first report to present a comprehensive overview of levels and trends of fatal and non-fatal burden due to Chagas disease in Brazil from 1990 to 2016 based on the GBD results. Our study showed that the age-standardized DALY rates due to Chagas disease has decreased considerably in Brazil and all Brazilian states during the last 27 years, but Chagas disease remains an important cause of health loss due to premature mortality and disability in the country, mainly in the elderly. The decrease in the DALY rates was driven primarily by a consistent decrease in the age-standardized YLL rates, the main component of total DALYs for Chagas disease. The highest fatal and non-fatal burdens due to Chagas disease were observed among males and the elderly, and in the Brazilian states encompassing important endemic areas for the disease in the past (e.g., Goiás and Minas Gerais).

The age-standardized DALY rates due to Chagas disease were higher in males compared with females, driven primarily by a higher difference between the sexes observed in age-standardized YLL rates, the main component of total DALYs. This pattern corroborates the findings of previous large-scale mortality studies carried out in Brazil (Santo, 2009; Martins-Melo et al., 2012a; da Nóbrega et al., 2014). Although the relationship between sex and risk of *T. cruzi* infection is controversial and still a matter of debate, the highest burden of Chagas disease in males, mainly the fatal burden, can be explained by sociocultural, environmental, behavioural, and access to healthcare factors, that favour disease exposure and progression to severe forms (Martins-Melo et al., 2012a, 2016, 2018). In fact, Brazilian males are less likely to search for health services, which can lead to delayed diagnosis and, consequently, result in an advanced and severe phase of Chagas disease, reducing the survival time with the disease (da Nóbrega et al., 2014; Martins-Melo et al., 2016).

The higher Chagas disease burden among the elderly can be explained mainly by the chronic nature of the disease in most cases and the ageing process of patients infected in the past (Lima e Costa et al, 2001; Lima-Costa et al., 2010; Martins-Melo et al., 2012a; 2012c; da Nóbrega et al., 2014). In addition to specific surveillance and control measures, the increased knowledge about the natural history of disease and improvements in access to health care may have contributed in part to the increased life expectancy of Chagas disease patients, leading to the occurrence of most deaths at a more advanced age (Martins-Melo et al., 2012a, 2012c; da Nóbrega et al., 2014). The increased survival and aging of Chagas disease patients may increase the likelihood of simultaneous occurrence of chronic comorbidities such as cardiovascular diseases and neoplasias, increasing the risk of complications, severity and fatality from the disease (Alves et al., 2009; Martins-Melo et al., 2012a, c).

There was a geographic variation in the Chagas disease burden in the Brazilian states during the study period. The highest age-standardized DALY rates were observed in states traditionally considered as important endemic areas for vector transmission in recent decades, located mainly in Central-West, Southeast and Northeast regions (Silveira, 2011a; Silveira et al., 2011; Martins-Melo et al., 2012a–d). In fact, the high burdens in the states of Goiás, Minas Gerais, Bahia, and Tocantins are consistent with areas of high rates of Chagas disease seroprevalence and with high rates of infestation by the main vector *T. infestans* in the past, as shown in serological and entomological surveys performed in 1975–1980 (Silveira et al., 2011) and 1975–1983 (Silveira, 2011a), respectively. The high burden in the Distrito Federal can be explained by intense migration of people from rural endemic areas to urban centres during recent decades (Pereira, 1984; Drumond and Marcopito, 2006; Dias, 2013). In Brazil, it is estimated that 75% of people affected by Chagas disease are now living in urban areas (Dias, 2013). The presence of infected individuals in urban areas increased the demand for medical and social assistance, in addition to increasing the risk of congenital transmission (Dias, 2013).

The consistent decrease in age-standardized DALY rates due to Chagas disease in Brazil from 1990 to 2016 follows the observed pattern of decline in morbidity and mortality indicators in Brazil during recent decades, mainly in the highly endemic areas (Ostermayer et al., 2011; Martins-Melo et al., 2012a, 2012b, 2014; da Nóbrega et al., 2014). The decline in Chagas disease burden might be attributed in part to the impact of the surveillance and control program measures implemented in recent decades (Martins-Melo et al., 2014; Dias et al., 2016). With the implementation of systematic entomological surveillance and screening of blood donors, the control of vectorial and transfusional transmission of Chagas disease were achieved in most endemic areas, drastically reducing the number of new acute cases and deaths in recent years (Silveira, 2011b; Silveira and Dias, 2011; Martins-Melo et al., 2012a; World Health Organization, 2018). In addition, we emphasize that other factors not related to Chagas disease-specific control programs may have played an important role in the decline of its burden in Brazil, such as human migration, increased urbanization, general improvements in socio-economic and sanitary conditions, and access to healthcare services (Dias,

2013; Martins-Melo et al., 2016). Despite the steady decline in DALY rates in Brazil and all states, what stands out is the increase in the absolute number of DALYs in some states located mainly in the North and Northeast regions. This can be explained, at least in part, by the low impact of the elimination of Chagas disease transmission by the main vector – *T. infestans* – on the local transmission dynamics, since this was not the leading transmission route in the North and Northeast regions (Drumond and Marcopito, 2006; Braz et al., 2011; Silveira, 2011a). In addition, with the control of the vector domiciliary transmission by its principal vector, *T. infestans*, other types of transmission routes have become more relevant (Dias et al., 2016). These are directly related to the enzootic cycle of infection, such as extra-domiciliary vector transmission and domiciliary vector transmission without vector colonization, and oral transmission (Coura, 2015; Dias et al., 2016). Oral transmission was the most frequent infection route involved in the acute cases recorded in Brazil in recent years, mostly in the Amazon region (Dias et al., 2016).

Brazil has made remarkable progress in Chagas disease control during recent decades, chiefly due to the interruption of the vectorial transmission by *T. infestans*, the principal intradomiciliary vector in several endemic areas, and universal blood screening for *T. cruzi* infection by blood banks (Silveira, 2011b; Silveira and Dias, 2011; Dias et al., 2016; World Health Organization, 2017). Nevertheless, after vector and transfusion transmission control, there are still key challenges to maintain and expand Chagas disease control in the country such as sustainability of control strategies, risk of re-emergence (due to the residual and natural foci of triatomines, and the domiciliation of new vectors) or emergence in non-endemic areas, and provision of care to acute and chronically infected individuals, including their co-infections and co-morbidities (Bello Corassa et al., 2017; World Health Organization, 2017). Efforts should be made towards Chagas disease prevention, control and care in Brazil to maintain the political interest and continuous surveillance and control actions, development of new drugs and new insecticides, promotion of hygiene practices to prevent oral transmission, better peridomicile management, and increase in pre-natal screening to prevent congenital transmission (Dias et al., 2016; Bello Corassa et al., 2017). In addition, a substantial burden of chronic cases in the adult and older populations still remains in the country, demanding improvement of the implementation, coverage, access and quality of health care for Chagas disease patients, including early diagnosis and treatment interventions (Martins-Melo et al., 2012a; 2014; Dias et al., 2016).

In addition to the GBD 2016 general limitations, which have been described in detail elsewhere (GBD 2016 DALYs and HALE Collaborators, 2017; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; GBD 2016 Risk Factors Collaborators, 2017; GBD 2016 Causes of Death Collaborators, 2017), some specific GBD limitations related to Chagas disease in Brazil should be mentioned, mainly those related to coverage and quality of available epidemiological data (Martins-Melo et al., 2014, 2018; França et al., 2017). For mortality data, although the SIM database has undergone significant improvements and progress in coverage (proportion of deaths reported and estimated) and quality of information on causes of death in recent decades, the mortality coverage and proportion of ill-defined causes presented variations among the Brazilian states, with higher proportions of underreporting of deaths and ill-defined causes of death in some states in the North and Northeast regions (Martins-Melo et al., 2012a, 2016, 2018; Capuani et al., 2017; Corrêa et al., 2017; GBD 2016 Brazil Collaborators, 2018). Furthermore, the underlying cause of death may have been coded as a complication or aggravation associated with Chagas disease (e.g., cardiomyopathy, heart failure) (Santo, 2009; Martins-Melo et al., 2012c). Although the GBD study uses comparable and standardized methods and processes for correction of underreporting of deaths and redistribution of garbage codes, the regional variations can substantially affect mortality estimates, which should be interpreted with caution for some states, especially in the North and Northeast regions (GBD 2016 Causes of Death Collaborators, 2017; França et al., 2017). In addition, due to the time lag between mortality data reporting and the availability of databases, estimates for 2016 are mainly based on data and trends from previous years (Global Burden of Disease Cancer Collaboration, 2017).

For non-fatal disease estimation, large-scale seroprevalence surveys for Chagas disease are scarce or absent in several areas of the country (Martins-Melo et al., 2014. When data are of poor quality or unavailable for a location (subnational unit, country or region), GBD estimates are driven using model covariates and data available from neighbouring locations with a similar health profile (GBD 2015 DALYs and HALE Collaborators, 2016; GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). However, estimates for populations and time periods with sparse or absent data are less precise, which consequently leads to wider uncertainty intervals for a particular location and time period (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017; Global Burden of Disease Cancer Collaboration, 2017), as verified for YLD estimates in several states. Thus, although the levels and trends of Chagas disease burden are consistent with the epidemiological profile of the disease in the country, the burden estimates for Chagas disease presented in this study should be interpreted with caution, mainly in Brazilian states with larger uncertainty intervals. The strength of this study includes the relevance of GBD estimates to demonstrate the importance of Chagas disease as a cause of years of healthy life lost due to premature death and disability in Brazil and its states over a 27 year period, as well as providing an up-to-date comparative assessment of Chagas disease burden with other countries or regions (Brant et al., 2017; GBD 2016 DALYs and HALE Collaborators, 2017).

Based on the GBD 2016 estimates, our study showed a declining trend in Chagas disease burden in Brazil during the 27 year study period. However, the disease persists as an important and neglected cause of loss of years of healthy life due to premature mortality and disability in the country. The highest burden due to Chagas disease was observed for males, the elderly, and in highly endemic states for vector transmission (with the exception of the Distrito Federal) in the past. Despite significant progress in disease control in the country, there is a need to maintain and expand the control and surveillance measures for the main routes of transmission in endemic areas to prevent the risk of disease re-emergence, as well as prevention measures for oral transmission (especially in the Amazon region) and increased pre-natal screening to prevent congenital transmission. Furthermore, the need to ensure adequate coverage, access, and quality of the health care (diagnosis, treatment, management, and follow-up of cases) for Chagas disease patients, seeking to prevent the occurrence of severe forms and deaths from the disease is reinforced.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpara.2018.11.008.

References

Alves, R.M.A., Thomaz, R.P., Almeida, E.A., Wanderley, J.S., Guariento, M.E., 2009. Chagas' disease and ageing: the coexistence of other chronic diseases with Chagas, disease in elderly patients. Rev. Soc. Bras. Med. Trop. 42, 622–628.

Bello Corassa, R., Aceijas, C., Alves, P.A.B., Garelick, H., 2017. Evolution of Chagas' disease in Brazil. Epidemiological perspective and challenges for the future: a critical review. Perspect. Public Health 137, 289–295.

Brant, L.C.C., Nascimento, B.R., Passos, V.M.A., Duncan, B.B., Bensenõr, I.J.M., Malta, D.C., Souza, M.F.M., Ishitani, L.H., França, E., Oliveira, M.S., Mooney, M., Naghavi, M., Roth, G., Ribeiro, A.L.P., 2017. Variations and particularities in cardiovascular disease mortality in Brazil and Brazilian states in 1990 and 2015: estimates from the Global Burden of Disease. Rev. Bras. Epidemiol. 20, 116–128.

Braz, S.C.M., Melo, M.F.A.D., Lorena, V.M.B., Souza, W.V., Gomes, Y.M., 2011. Chagas disease in the State of Pernambuco, Brazil: analysis of admissions and mortality time series. Rev. Soc. Bras. Med. Trop. 44, 318–323.

Capuani, L., Bierrenbach, A.L., Pereira Alencar, A., Mendrone Jr, A., Ferreira, J.E., Custer, B., Ribeiro, A.L.P., Cerdeira Sabino, E., 2017. Mortality among blood donors seropositive and seronegative for Chagas disease (1996–2000) in São Paulo, Brazil: a death certificate linkage study. PLoS Negl. Trop. Dis. 11, e0005542.

Corrêa, R.A., José, B.P.S., Malta, D.C., Passos, V.M.A., França, E.B., Teixeira, R.A., Camargos, P.A.M., 2017. Burden of disease by lower respiratory tract infections in Brazil, 1990 to 2015: estimates of the Global Burden of Disease 2015 study. Rev. Bras. Epidemiol. 20, 171–181.

Coura, J.R., 2015. The main sceneries of Chagas disease transmission. The vectors, blood and oral transmissions-a comprehensive review. Mem. Inst. Oswaldo Cruz 110, 277–282.

Cucunubá, Z.M., Okuwoga, O., Basáñez, M.G., Nouvellet, P., 2016. Increased mortality attributed to Chagas disease: a systematic review and meta-analysis. Parasites Vectors 9, 42.

da Nóbrega, A.A., de Araújo, W.N., Vasconcelos, A.M.N., 2014. Mortality due to Chagas disease in Brazil according to a specific cause. Am. J. Trop. Med. Hyg. 91, 528–533.

Dias, J.C.P., 2013. Human Chagas disease and migration in the context of globalization: some particular aspects. J. Trop. Med. 2013, 789758.

Dias, J.C.P., Ramos Jr., A.N., Gontijo, E.D., Luquetti, A., Shikanai-Yasuda, M.A., Coura, J. R., Torres, R.M., Melo, J.R.C., Almeida, E.A., Oliveira Jr, W., 2016. 2nd Brazilian consensus on Chagas disease, 2015. Rev. Soc. Bras. Med. Trop. 49, 3–60.

Drumond, J.A.G., Marcopito, L.F., 2006. Internal migration and distribution of Chagas disease mortality, Brazil, 1981–1998. Cad. Saude Publica 22, 2131–2140 (Article in Portuguese).

França, E.B., de Azeredo Passos, V.M., Malta, D.C., Duncan, B.B., Ribeiro, A.L.P., Guimarães, M.D., Abreu, D.M., Vasconcelos, A.M.N., Carneiro, M., Teixeira, R., Camargos, P., Melo, A.P.S., Queiroz, B.L., Schmidt, M.I., Ishitani, L., Ladeira, R.M., Morais-Neto, O.L., Bustamante-Teixeira, M.T., Guerra, M.R., Bensenor, I., Lotufo, P., Mooney, M., Naghavi, M., 2017. Cause-specific mortality for 249 causes in Brazil and states during 1990–2015: a systematic analysis for the global burden of disease study 2015. Popul. Health Metr. 15, 39.

GBD 2015 DALYs and HALE Collaborators, 2016. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388, 1603–1658.

GBD 2016 Risk Factors Collaborators, 2017. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390, 1345–1422.

GBD 2016 DALYs and HALE Collaborators, 2017. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390, 1260–1344.

GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390, 1211–1259.

GBD 2016 Causes of Death Collaborators, 2017. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390, 1151–1210.

GBD Brazil Collaborators, 2018. Burden of disease in Brazil, 1990–2016: a systematic subnational analysis for the Global Burden of Disease Study 2016. Lancet 392, 760–775.

Global Burden of Disease Cancer Collaboration, 2017. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 3, 524–548.

GBD Tuberculosis Collaborators, 2018. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. Lancet Infect. Dis. 18, 261–284.

Herricks, J.R., Hotez, P.J., Wanga, V., Coffeng, L.E., Haagsma, J.A., Basáñez, M.-G., Buckle, G., Budke, C.M., Carabin, H., Fèvre, E.M., Fürst, T., Halasa, Y.A., King, C.H., Murdoch, M.E., Ramaiah, K.D., Shepard, D.S., Stolk, W.A., Undurraga, E.A., Stanaway, J.D., Naghavi, M., Murray, C.J.L., 2017. The global burden of disease study 2013: what does it mean for the NTDs? PLoS Negl. Trop. Dis. 11, e0005424.

Lee, B.Y., Bacon, K.M., Bottazzi, M.E., Hotez, P.J., 2013. Global economic burden of Chagas disease: a computational simulation model. Lancet Infect. Dis. 13, 342–348.

Lima e Costa, M.F., Barreto, S.M., Guerra, H.L., Firmo, J.O., Uchoa, E., Vidigal, P.G., 2001. Ageing with *Trypanosoma cruzi* infection in a community where the transmission has been interrupted: the Bambuí Health and Ageing Study (BHAS). Int. J. Epidemiol. 30, 887–893.

Lima-Costa, M.F., Peixoto, S.V., Ribeiro, A.L.P., 2010. Chagas disease and mortality in old age as an emerging issue: 10 year follow-up of the Bambuí population-based cohort study (Brazil). Int. J. Cardiol. 145, 362–363.

Marinho, F., Passos, V.M.A., França, E.B., 2016. New century, new challenges: changes in the burden of disease profile in Brazil, 1990–2010. Epidemiol. Serv. Saude 25, 713–724 (Article in Portuguese).

Martins-Melo, F.R., Alencar, C.H., Ramos Jr, A.N., Heukelbach, J., 2012a. Epidemiology of mortality related to Chagas' disease in Brazil, 1999–2007. PLoS Negl. Trop. Dis. 6, e1508.

Martins-Melo, F.R., Ramos Jr, A.N., Alencar, C.H., Heukelbach, J., 2012b. Mortality due to Chagas disease in Brazil from 1979 to 2009: trends and regional differences. J. Infect. Dev. Ctries. 6, 817–824.

Martins-Melo, F.R., Ramos Jr., A.N., Alencar, C.H., Heukelbach, J., 2012c. Multiple causes of death related to Chagas' disease in Brazil, 1999 to 2007. Rev. Soc. Bras. Med. Trop. 45, 591–596.

Martins-Melo, F.R., Ramos, A.N., Alencar, C.H., Lange, W., Heukelbach, J., 2012d. Mortality of Chagas' disease in Brazil: spatial patterns and definition of high-risk areas. Trop. Med. Int. Health 17, 1066–1075.

Martins-Melo, F.R., Ramos Jr, A.N., Alencar, C.H., Heukelbach, J., 2014. Prevalence of Chagas disease in Brazil: a systematic review and meta-analysis. Acta Trop. 130, 167–174.

Martins-Melo, F.R., Ramos Jr., A.N., Alencar, C.H., Heukelbach, J., 2016. Mortality from neglected tropical diseases in Brazil, 2000–2011. Bull. World Health Organ. 94, 103–110.

Martins-Melo, F.R., Carneiro, M., Ramos Jr., A.N., Heukelbach, J., Ribeiro, A.L.P., Werneck, G.L., 2018. The burden of Neglected Tropical Diseases in Brazil, 1990–2016: a subnational analysis from the Global Burden of Disease Study 2016. PLoS Negl. Trop Dis. 12, e0006559.

Naghavi, M., Makela, S., Foreman, K., O'Brien, J., Pourmalek, F., Lozano, R., 2010. Algorithms for enhancing public health utility of national causes-of-death data. Popul. Health Metr. 8, 9.

Ostermayer, A.L., Passos, A.D.C., Silveira, A.C., Ferreira, A.W., Macedo, V., Prata, A.R., 2011. The national survey of seroprevalence for evaluation of the control of Chagas disease in Brazil (2001–2008)]. Rev. Soc. Bras. Med. Trop. 44, 108–121 (Article in Portuguese).

Pereira, M.G., 1984. Characteristics of urban mortality from Chagas' disease in Brazil's Federal District. Bull. Pan. Am. Health Organ. 18, 1–9.

Requena-Méndez, A., Aldasoro, E., de Lazzari, E., Sicuri, E., Brown, M., Moore, D.A., Gascon, J., Muñoz, J., 2015. Prevalence of Chagas disease in Latin-American migrants living in Europe: a systematic review and meta-analysis. PLoS Negl. Trop. Dis. 9, e0003540.

Salomon, J.A., Haagsma, J.A., Davis, A., de Noordhout, C.M., Polinder, S., Havelaar, A. H., Cassini, A., Devleesschauwer, B., Kretzschmar, M., Speybroeck, N., Murray, C. J., Vos, T., 2015. Disability weights for the Global Burden of Disease 2013 study. Lancet Glob. Health. 3, e712–e723.

Santo, A.H., 2009. Chagas disease-related mortality trends, state of São Paulo, Brazil, 1985 to 2006: a study using multiple causes of death. Rev. Panam. Salud Publica 26, 299–309 (Article in Portuguese).

Silveira, A.C., 2011a. Entomological survey (1975–1983). Rev. Soc. Bras. Med. Trop. 44, 26–32 (Article in Portuguese).

Silveira, A.C., 2011b. New challenges and the future of control. Rev. Soc. Bras. Med. Trop. 44, 122–124 (Article in Portuguese).

Silveira, A.C., Dias, J.C.P., 2011. The control of vectorial transmission. Rev. Soc. Bras. Med. Trop. 44, 52–63 (Article in Portuguese).

Silveira, A.C., Silva, G.R., Prata, A., 2011. Seroprevalence survey of human Chagas' infection (1975–1980). Rev. Soc. Bras. Med. Trop. 44, 33–39.

World Health Organization (WHO), 2015. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly. Epidemiol. Rec. 90, 33–44.