The Burden of Chagas Disease

Estimates and Challenges

Jeffrey D. Stanaway*, Gregory Roth*,†

Seattle, WA, USA

ABSTRACT

Chagas disease, caused by infection with the protozoa *Trypanosoma cruzi* is transmitted most often by Triatominae insect vectors, but also through blood transfusion, organ transplant, and congenital transmission. Between 5 and 18 million people are currently infected and the infection is estimated to cause more than 10,000 deaths annually. The disease has 3 phases: acute, indeterminate, and chronic. The acute phase immediately follows infection. It is typically asymptomatic but produces fever and malaise in up to 5% of people. The indeterminate phase is asymptomatic. More than one-half of those infected will remain in this phase for life and never experience long-term sequelae. After a decade or more, 20% to 30% of people will experience chronic cardiovascular Chagas disease with sequelae including heart failure, arrhythmias, and thromboembolism. Another 15% to 20% will experience chronic digestive sequela including megaesophagus and megacolon. A complete accounting of the burden of Chagas disease requires estimating the prevalence of the infection, the prevalence of each of its sequelae among those with the infection, and the number of deaths attributable to the infection. Attempts to estimate Chagas disease prevalence are complicated by several challenges imposed by the disease's extreme spatial heterogeneity, quickly evolving temporal trends, the decades-long lag between infection and symptomatic disease, biased prevalence data, incomplete recognition of Chagas-attributable deaths, limited data on sequela, and a near total absence of data outside of endemic countries. Even though researchers have found methodological approaches to dealing with these challenges, there is a need for better data.

Chagas disease, also known as American trypanosomiasis, is caused by infection with the protozoa, *Trypanosoma cruzi*. The infection is most commonly transmitted by Triatominae insect vectors, with members of the *Triatoma* genus being the most important transmitters, followed by members of the genera *Rhodnius* and *Panstrongylus*. Transmission to humans occurs not directly through the blood meal, but through infected feces that are deposited during the blood meal, most commonly when the bitten person rubs the infective feces into the bite wound while scratching the area. In addition to vector-borne transmission, *T. cruzi* may be transmitted through blood transfusion and organ transplantation [1]. Finally, congenital transmission occurs in approximately 5% of births to infected mothers [2].

Acute infection is typically asymptomatic, with approximately 5% of cases experiencing symptoms including malaise and fever that may last 4 to 8 weeks. Cases may experience a characteristic unilateral edema of the eyelids, called the Romaña sign, when the triatomine bite occurs near the eye. Death during the acute phase is rare, with <1 death occurring per 2,500 infections [1,3]. After this acute phase, people enter the indeterminate phase that is characterized by chronic asymptomatic infection. At least 50% of infected people will remain in the indeterminate phase for life and experience no long-term sequela. Those who go on to develop long-term sequela will typically remain in the indeterminate phase for at least 10 to 20 years. Of those infected, 20% to 30% will experience cardiac damage from the infection and, with that, develop cardiovascular sequela including heart failure, arrhythmias, and thromboembolism. Most deaths attributable to Chagas disease result from these cardiovascular sequela. Finally, 15% to 20% of cases experience digestive sequela including megaesophagus and megacolon [3,4].

The geographic distribution of Chagas disease is driven largely by the distribution of vector species, and vector-borne transmission is limited to the Americas, between 40°N and 45°S latitude, and below 1,500 m elevation [3]. Prevalence varies considerably within this area and the Pan American Health Organization's (PAHO) country-level seroprevalence estimates for 2005 range from <1 per 10,000 (0.01%) in Panama to nearly 7% in Bolivia (Fig. 1) [5]. Globally, estimates of the number of infected people range from 5 million to 18 million, with most recent research citing estimates between 8 million and 12 million [1,3,6,7]. Estimates of the number of annual deaths are less variable, ranging from 10,600 to 12,500 [8,9]. Results from the Global Burden of Disease Study suggest that, in 2010, Chagas disease was responsible for 550,000 (274,000 to 1,069,000) disability-adjusted life years (DALY), a measure that captures both premature mortality and nonfatal health loss (Fig. 2) [10].

The authors report no relationships that could be construed as a conflict of interest.
This research was funded by the Bill and Melinda Gates Foundation (grant number OPP 1070441).
From the *Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA; and the †Division of Cardiology, University of Washington, Seattle, WA, USA. Correspondence: J. D. Stanaway (stanaway@uw.edu).

GLOBAL HEART

VOL. 10, NO. 3, 2015
ISSN 2211-8160/$36.00.
http://dx.doi.org/10.1016/j.gheart.2015.06.001

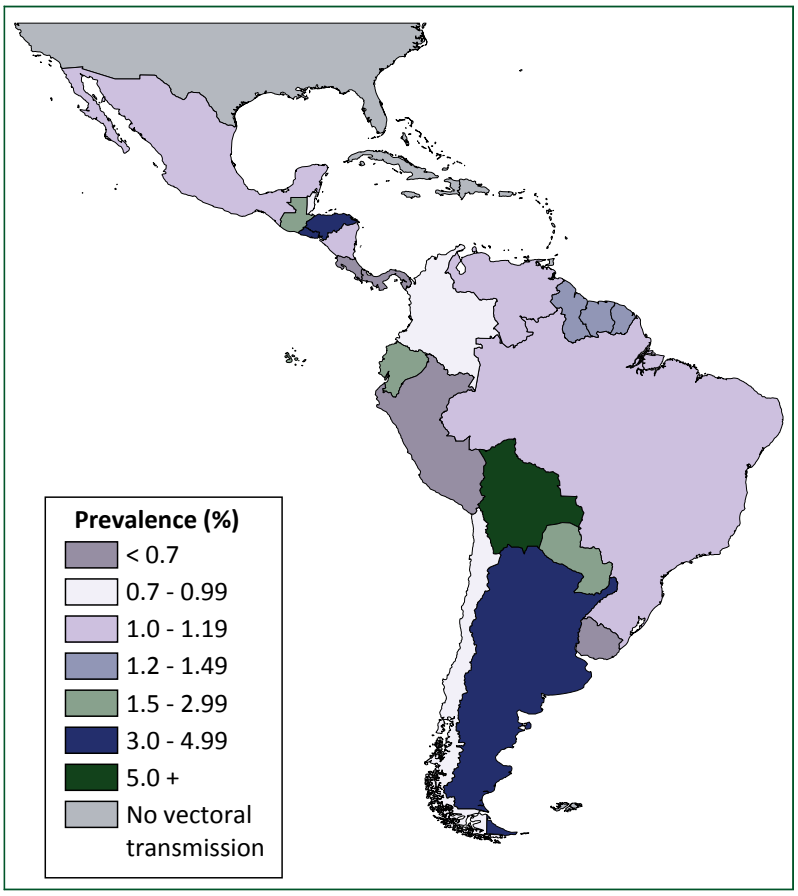

FIGURE 1. Chagas disease seroprevalence estimates for 2005 by country. Map prepared based on data from OPS/WHO/NTD/ID [5].

Control and elimination efforts have reduced incidence and shrunk the geographic limits of transmission in many parts of Latin America. Country-level ministries of health, PAHO, and the World Health Organization have coordinated 4 large-scale control initiatives for Chagas disease: the Southern Cone Initiative (launched in 1991); the Andean Initiative (launched in 1997); the Central American and Mexico Initiative (launched in 1998); and the Amazon Initiative (launched in 2004). These efforts have included education, housing improvements, insecticide spraying, and more rigorous screening of blood donors. The efforts have reduced the area and intensity of endemic vector-borne transmission throughout the region and greatly reduced transmission through blood transfusion. Globally, between 1990 and 2006, the annual number of Chagas-attributable deaths is estimated to have declined from 45,000 to 12,500; the number of new cases annually has declined from 700,000 to 41,200; and the population at risk has declined from 100 million to 28 million [9]. The Southern Cone region has experienced some of the most notable successes, and PAHO has, somewhat controversially, certified that transmission by *Triatoma infestans* was interrupted in Uruguay (in 1997), Chile (1999), and Brazil (2006) [11,12]. And while control efforts have reduced incidence in endemic countries, increased migration has expanded the geographic distribution of prevalent infections. Chagas disease is now seen among Latin American immigrant populations in North America, Europe, Australia, and Japan [6]. It is estimated that 4.2% of Chagas-related DALY and 21.7% Chagas-related health care costs now occur outside of Latin America [7].

ESTIMATING CHAGAS BURDEN: APPROACHES AND CHALLENGES

At its most basic level, estimating the burden of Chagas disease requires estimating the prevalence of the infection and the number of deaths attributable to it. A complete accounting of Chagas disease burden, however, requires estimating the frequency of symptomatic sequela of the disease, including the incidence of symptomatic acute infection and the prevalence of chronic cardiovascular and digestive sequelae. Attempts to estimate the prevalence of Chagas disease are complicated by several challenges imposed by the disease's extreme spatial heterogeneity, quickly evolving temporal trends, the decades-long lag between infection and symptomatic disease, biased prevalence data, incomplete recognition of Chagas-attributable deaths, limited data on sequela, and a near total absence of data outside of endemic countries.

Challenges in estimating prevalence

The risk of Chagas disease varies tremendously not only between countries, but also within them. Thus, community-based seroprevalence studies rarely (if ever) offer a representative view of the burden of Chagas disease for a country as a whole. Moreover, because studies tend to be preferentially conducted in communities in which Chagas disease is known to be endemic or hyperendemic, prevalence estimates from community-based studies almost universally represent a biased sample. If taken directly, results from these studies would yield dramatic overestimates of national Chagas disease prevalence. Similarly, blood donations make a convenient study sample and a number of Chagas disease seroprevalence surveys have been conducted among blood donors. The bias here tends to be the opposite of that seen in community-based studies with seroprevalence among blood donors being systematically lower than national averages. Moreover, a review of published data reveals that these biases are profound. Whereas PAHO estimated the national prevalence of Chagas disease in Brazil to be 1.02% in 2005 [5], a survey of Brazilian blood donors in that same year found a prevalence of only 0.15% [13], and a community based study in Porto Letícia, São Paulo, reported a prevalence of 5.6% [14]. Studies have typically used some means of statistical correction to account for these known biases. In some cases, investigators have conducted meta-analyses of community-based studies to develop estimates of prevalence among those living in endemic areas and then adjusted these estimates downward based on the

proportion of each country's population living in endemic areas [15]; others have taken a similar approach using separate estimates to account for systematic differences between rural and urban areas [5].

Control initiatives have produced dramatic declines in the incidence of Chagas disease in many countries (e.g., Brazil, Chile, and Uruguay). Conversely, other countries have seen little or no success in controlling Chagas disease and have experienced stable prevalence (e.g., Bolivia). Producing current prevalence estimates, therefore, demands recent data. And capturing these complex trends requires serial data sources that are not available for all countries. Efforts to deal with inadequate data across time include extrapolations from older data based on expert knowledge of each country's control initiatives [5] and drawing information from neighboring countries and from trends in Chagas disease mortality to inform prevalence trends [15].

Though arguably less important than the aforementioned challenges to estimating prevalence in endemic countries, limited data exist from which to estimate Chagas disease prevalence in migrant populations outside of Latin America. Given the relatively small numbers of infections outside of endemic countries, the problem is sometimes circumvented by producing estimates only for endemic countries [5,15]. Others have attempted to make estimates using data on the numbers of immigrants from endemic country and the prevalence of Chagas disease in their home countries [6,16–18].

Challenges in estimating mortality

Estimates of Chagas-attributable mortality are typically derived from vital registration records. Most Chagas disease endemic countries have relatively complete vital registration records for the past several decades [8]. The challenges of Chagas-attributable mortality estimation, therefore, are not those seen with prevalence estimation: the mortality data may be assumed to nationally representative with complete time-series available for most endemic countries. Instead, the primary challenge here is that Chagas-attributable deaths are often not recognized as such and may be misclassified as being attributable to another cause. It is likely that Chagas-attributable deaths are most commonly attributed to non-Chagas disease cardiovascular causes. Moreover, the frequency with which this misclassification occurs appears to vary greatly by country. If we assume that age-specific Chagas-attributable mortality rates are similar across endemic countries, then we would expect the ratio of deaths to prevalent cases to also be similar across endemic countries, varying only with differences in the age-structure of the population and of cases. Results from the Global Burden of Disease Study, however, suggest that there is wide variability in this ratio—far beyond what can be explained by differences in mortality rates, age distributions of Chagas disease infection, or small errors in underlying prevalence estimates. The results here suggest that Chagas-attributable deaths are most often detected in Brazil, Chile, and Venezuela, where mortality to prevalence ratios are high, and are frequently misclassified in Bolivia, Honduras, and Mexico, where mortality to prevalence ratios are roughly an order of magnitude lower [15,19].

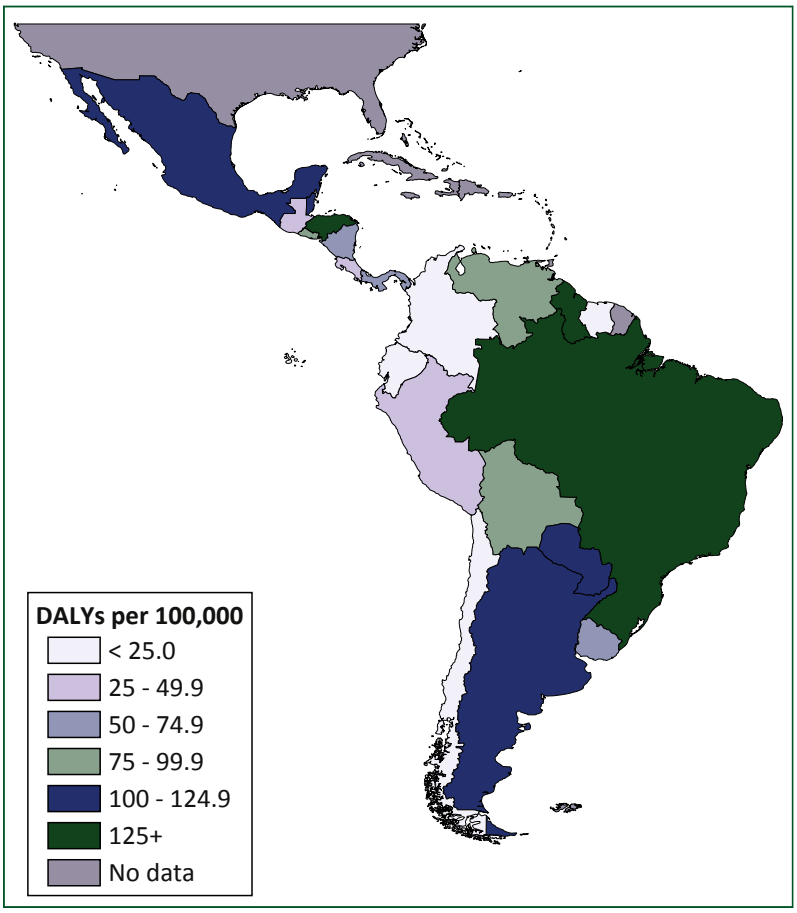

FIGURE 2. Disability-adjusted life years (DALY) attributable to Chagas disease, per 100,000 people, for 2010, by country. Map prepared based on data from Murray et al. [10].

Challenges in estimating prevalence of sequelae

For Chagas disease, the most notable sequelae are symptomatic acute infection, chronic cardiovascular sequelae (e.g., heart failure and atrial fibrillation), and chronic digestive sequela (e.g., megaesophagus and megacolon). Almost no reliable population-level data exist on either the incidence of symptomatic acute infection or the prevalence of chronic sequela. Consequently, the prevalence of sequelae are generally estimated as the product of seroprevalence and the proportion of those infected who experience a given sequela. Estimates of the proportion of cases that experience these sequelae exist; however, these are most often based on some combination of old data and expert opinion. Recent age-specific estimates for the frequency of these outcomes are sparse. Also the frequency of some sequelae may differ in different parts of Latin America. Most

notably, digestive sequelae are thought to be most common south of the Amazon River and much rarer in northern countries [4]. The lack of detailed data on these sequelae present a challenge to developing accurate age-sex-country–specific estimates of the prevalence of each outcome.

THE PREVALENCE OF CHAGAS

Andean Latin America

The Andean Latin American region includes Bolivia, Ecuador, and Peru. PAHO estimates that 31.5% of the Bolivian population lives in endemic areas and that Chagas disease seroprevalence in Bolivia is 6.8%, the highest of any country in the world [5]. Community-based studies have found that seroprevalence approaches 50% in some parts of the country [20,21]. In Ecuador, 46.9% of the population lives in endemic areas and PAHO estimates the national seroprevalence to be 1.7% [5]. Studies have reported community-level seroprevalence estimates ranging from 0% to 6% [22]. Peru has the lowest prevalence of Chagas disease in the region: 12.4% of the population lives in endemic areas and the national seroprevalence is estimated to be 0.7% [5]. Still, some parts of the country remain heavily affected and studies have reported communities with seroprevalence approaching 10% [23].

Central Latin America

Approximately 10% of the population of Colombia lives in Chagas disease endemic areas, and the national prevalence is estimated to be nearly 1.0% [5]. A study of pregnant women found that 4% were infected in 1 endemic community, and among women over 30 years of age prevalence was 7.5% [24]. In Mexico, PAHO estimates that 27.6% of population lives in endemic areas and that the national prevalence is approximately 1.0% [5]. Studies have identified communities in which prevalence approaches 20% [25,26]. A serial study of blood donors in Mexico City reported prevalence declining from 1.3% in 1992 to 0.6% in 2003 [27]. Another study of blood donors in Mexico City between 2004 and 2009 found a seroprevalence of less than 0.2% [28]. In Panama, although 30.9% of the population lives in endemic areas, PAHO estimates the prevalence of Chagas disease to be only 0.006% [5]. Still, Chagas disease remains a serious problem in some parts of the country with 1 study finding a prevalence of 5.9% in rural communities in the eastern part of the country [29]. In Venezuela, PAHO estimates that 18.5% of population lives in endemic areas and that the national prevalence is 1.2% [5]. Studies have identified communities in which prevalence approaches 10%. A serial study of blood donors reported prevalence declining from 1.1% in 1990 to <0.8% in 1998 [30].

Southern Latin America

Argentina has the highest prevalence of Chagas disease in Southern Latin America: PAHO estimates the prevalence to be 4.1%, with 18.8% of population living in endemic areas [5]. Community-based studies have consistently found pockets of very high prevalence: several studies have reported communities with prevalence exceeding 25% [31–33] with 1 study finding a prevalence of 53% in a Chaco province community in 2000 [34]. Whereas vector-borne transmission has been interrupted in both Chile and Uruguay, nearly 1% of the population remains infected in both countries [5].

Tropical Latin America

Approximately 12% of Brazil's population lives in Chagas disease endemic areas and the national prevalence is estimated to be roughly 1.0%. Despite its relatively modest prevalence, with its large population PAHO estimates that nearly 2 million people are infected in Brazil, making it the country with the largest absolute number of Chagas disease cases [5]. As such, it has also been the site of much Chagas disease research. A serial study of blood donors at the Uberaba Regional Blood Center reported prevalence declining from 0.4% in 1995 to 0.08% in 2009 [13]. Community-based studies have reported prevalence ranging from 0% to nearly 25% (Fig. 3) [14,35–45].

FREQUENCY OF CARDIOVASCULAR SEQUELA

Electrocardiographic abnormalities are common among Chagas disease cases with a large cohort study of older adults in Bambui, Brazil, finding abnormalities in 87.6% of Chagas disease cases versus 77.7% of non-Chagas disease cases. Most commonly, findings that were significantly more common among those with Chagas disease were minor asymptomatic abnormalities including right bundle branch blocks (23.2% of Chagas vs. 3.3% of non-Chagas

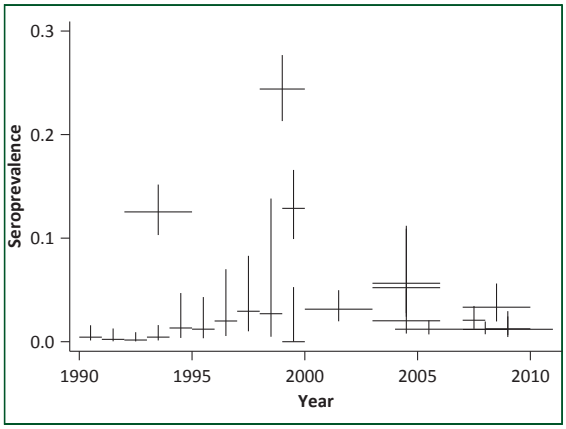

FIGURE 3. Seroprevalence estimates from community-based studies conducted in Brazil from 1990 onward [14,35–45]. The width of each cross represents the period captured in that study, the height of each cross represents the 95% confidence interval of the seroprevalence estimate, with the intersection representing the point estimate.

disease cases). Notably, however, atrial fibrillation was seen in 6.1% of Chagas disease cases, 3.4 (95% confidence interval [CI]: 1.89 to 6.14) times as often as it was seen among those without the infection [46]. Based on research by Salomon et al. [47] for the Global Burden of Disease Study, the disability weight for "cardiac conduction disorders and cardiac dysrhythmias" is 0.145.

Cardiomyopathy is arguably the most common serious sequela of Chagas disease. Older studies of Chagas disease progression have reported cardiomyopathy in >50% of observed cases [48]. However, more recent research suggests that cardiomyopathy is less common, occurring in 20% to 30% of cases. Results from a retrospective cohort study of 499 *T. cruzi* seropositive blood donors found that 24% had "definite Chagas cardiomyopathy." Among Chagas disease patients 60 years of age and older, 30% were found to have cardiomyopathy (Fig. 4) [49]. The corresponding disability weights range from 0.037 for mild heart failure to 0.186 for severe heart failure [47].

Little data exist on the occurrence of nonfatal stroke among community-based Chagas disease cases. The Bambui cohort study of older adults found that 5.2% of the Chagas disease cases had experienced a stroke, compared with 2.9% of those without the infection, suggesting a 78% (95% CI: 6 to 201%) greater risk of stroke among Chagas disease cases [50]. An analysis of data from the same cohort found that the risk of death from stroke was 2.36× as great among Chagas disease cases (95% CI: 1.25 to 4.44) [51]. The corresponding disability weights range from 0.021 for the sequela "stroke: long-term consequences, mild" to 0.567 for "stroke: long-term consequences, severe plus cognition problems" [47].

SUMMARY

The next iteration of the Global Burden of Disease Study is being released and should offer an ever clearer and more up-to-date picture of Chagas disease. Moreover, work in geospatial niche mapping [52] may soon produce risk maps that will help overcome some of the modelling challenges related to the extreme spatial heterogeneity of Chagas disease and allow the Chagas research community to draw on methods that have been used to improve burden estimates for diseases such as malaria. Still, there is a clear need for better data on the occurrence of various Chagas disease sequelae, most notably there is a need for data that allow for a more complete and precise understanding of the age distribution and spatial variability in these outcomes. Finally, there exists a need for Chagas-attributable deaths to be accurately recognized and reported as such. Work in understanding the burden of Chagas disease is ongoing, and improvements in both data and methods are likely to yield increasingly accurate and insightful results.

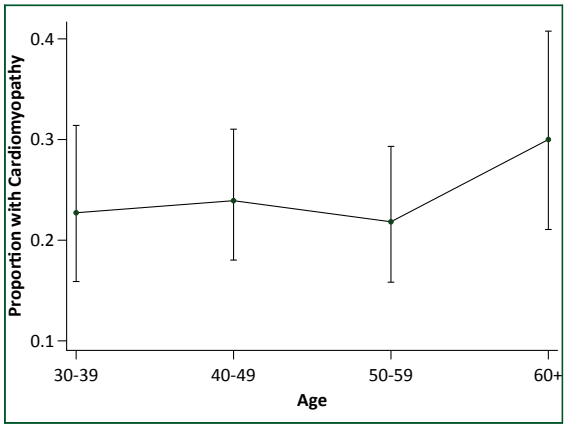

FIGURE 4. Proportion of Chagas disease cases with cardiomyopathy (and 95% confidence intervals) by age. Based on data from a retrospective cohort study of 499 *T. cruzi* seropositive blood donors [49].

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