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CHAGAS (M NOLAN, SECTION EDITOR)

# Systematic Review of the Epidemiology of Chagas Disease in the Americas: a Call for Standardized Reporting of Chagas Disease Prevalence

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## Abstract

**Purpose of Review** Estimates of Chagas disease (CD) seroprevalence in the Americas vary greatly. We lack an accurate representation of the state of the disease in this region for various reasons including intranational variability in prevalence and a lack of standardized diagnostic approaches. The goal of this review is to generate an estimate of CD burden in the Americas, by performing a systematic review of recent prevalence papers published after major vector control initiatives.

**Recent Findings** Community-based CD screening programs that focus on a third- to fourth-level administrative division basis are more representative of the prevalence of CD in a particular region of a country.

**Summary** We evaluate *T. cruzi* seroprevalence at a subnational level in the Americas with information published from 2004 to 2018 and discuss the context behind the heavy variation in CD prevalence. We also suggest a solution for standardization of data reporting for future publications.

**Keywords** Chagas disease · *Trypanosoma cruzi* · Systematic review · Latin America · Seroprevalence · Epidemiology

## Introduction

Chagas disease (CD) is a neglected tropical disease caused by infection with the protozoan parasite *Trypanosoma cruzi*. Despite its status as a neglected disease, CD affects an estimated 6 to 8 million people predominantly in the Americas, causing approximately 12,000 deaths each year [1] and is emerging as a public health concern across the world [2•].

Though typically acquired through stercorarian transmission by triatomine insect vector species endemic to the American continent, CD may also be transmitted vertically from an infected mother to her child during pregnancy, via blood or organ donation from an infected individual, or by ingestion of contaminated food or drink [3, 4]. Despite substantial vector control initiatives in the 1990s and early 2000s, CD has become of worldwide concern as its geographic range expands in an increasingly globalized world [5].

### Clinical Presentation

The usual course of this infection is often overlooked by both the patient and caregivers [6]. After a 1 to 2-week incubation period post-infection, patients move into the acute phase of the infection. The acute phase is typically asymptomatic, though may present with non-specific flu-like symptoms [7]. Rarely, CD may debut with myocarditis or meningoencephalitis, in instances of oral CD transmission. This lack of acute, recognizable symptoms leads to many patients not seeking care at onset of infection. The acute phase may last 4 to 8 weeks, after which patients shift to the chronic phase of the disease. Chronic CD patients may remain asymptomatic for life and

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are classified as indeterminate patients [8]. However, 20–30% of CD patients progress to symptomatic disease, including cardiomyopathy, gastrointestinal tract mega-syndromes, or both [4, 8, 9]. In more rare instances, chronic CD patients may display endocrine and neurological symptoms [10, 11]. Immunocompromised patients who may otherwise not present symptoms can experience reactivation of the disease symptoms with a similar presentation to the acute infection and may develop myocarditis or meningoencephalitis as well [12, 13]. Generally, however, CD is colloquially referred to as a "silent killer," which alludes to the way in which patients may remain asymptomatic just until they present with serious illness or sudden death. Furthermore, it is estimated that less than 1% of affected individuals are properly diagnosed and treated as CD is concentrated within poor, underserved populations [6, 13].

## Diagnosis

There is no single, standardized commercial test capable of diagnosing CD. The Pan-American and World Health Organization (PAHO/WHO) suggest that diagnosis in patients suspected of having chronic CD depend upon two serological tests, each based on the detection of different antibodies against two different *T. cruzi* antigens; should the first two test results be discrepant, a third diagnostic test is necessary [14]. Serological tests include enzyme-linked immunosorbent assays (ELISAs), direct or indirect fluorescence assays, direct or indirect hemagglutination assays, and immunoblots based on various antigens excreted by the parasite. Other common methods in use include polymerase chain reaction (PCR) and PCR-based methodologies and microscopic examination of buffy coat samples and rarely used methods include culturing of blood samples and xenodiagnosis. In seroepidemiological surveys to detect chronic Chagas disease, PAHO strongly recommends an ELISA or an immunochromatographic assay as a screening test. That such a wide variety of diagnostic methods available allows for case definition of CD to vary across different studies [15]. Antigens used in serological techniques are often proprietary combinations of recombinant antigens, compounding the variable performance of available diagnostic tests [16]. Moreover, regional variations in the sensitivity of available serological tests, particularly with TcI, further convolute *T. cruzi* diagnosis [17••, 18].

## Genetic Diversity

*T. cruzi* has significant intraspecies genetic diversity, which has historically been accounted for using various nomenclatures generated by different typing methods. Currently, the parasite is separated into seven discrete typing units (DTUs): the human infective TcI through TcVI, and Tcbat, a lineage typically affecting certain *Chiroptera* (bat) species. This nomenclature was adopted based on the findings of multi-locus enzyme electrophoresis and multi-locus sequence typing [19]. These seven DTUs differ in geographic range, ecological niche, host, associated clinical outcomes, and tissue tropism [17••, 20, 21]. These differences result in the prevalence, clinical symptoms, and disease severity varying by region [22]. Chagasic cardiomyopathy may be caused by infection with TcI, II, V, and VI; whereas gastrointestinal mega-syndromes seem to be limited to TcII, V, and VI, and oral outbreaks of acute CD to TcIV [23••]. TcIII, though found humans in the indeterminate form, is mostly seen in wild animal populations [22, 24]. It is likely that sensitivities and specificities of serological diagnostic tests vary when detecting different DTUs, due to differing parasite antigens and consequently different adaptive immune responses. This further impedes standardized diagnosis of CD and necessitates the use of many different diagnostic tests [25]. Furthermore, infections with multiple DTUs may be associated with certain clinical outcomes [26, 27].

## Emerging Concern of CD in the Americas

Though traditionally described as endemic to Latin America, CD should be studied within the context of all of North, Central, and South America. While other continents are beyond the scope of this review, it is important to mention that Chagas disease has been reported in Europe and Asia [28, 29]. In addition to at least 6 million CD cases concentrated in Latin America, it is currently estimated that there are over 300,000 people with CD in the USA [30], and over 5500 people with CD in Canada [31]. Over 41% and 5% of all immigrants to the USA and Canada, respectively, came from Chagas-endemic Latin American countries in 2016; this totals over 18 million people who may be at risk of CD in North American countries typically excluded from CD surveys [32–35]. Furthermore, autochthonous CD transmission has been reported in the USA, and the presence of triatomine insect vectors that harbor the parasite has been documented in Texas to as far north as Pennsylvania [1, 36, 37].

## Current State of CD Research and Purpose of Review

Due to the nature of the disease, estimating the burden of CD is a complex challenge. Current estimates are often conflicting, ranging from as low as 5 million to as high as 18 million affected individuals worldwide [38, 39]. Estimates of annual deaths caused by CD range from 12,000 to 40,000 [40]. The use of different diagnostic tools does not allow for standardized surveying of CD. As patterns of migration, climate, and disease transmission change over time, the prevalence of CD varies by region. Vector control initiatives of the 1990s and early 2000s have been successful in reducing *T. cruzi* transmission in many regions of the Americas. However, in the

specific regions where CD is still highly endemic, more targeted interventions tailored to the relevant transmission routes present in the region are needed [5]. It is crucial to these programs that accurate estimates of CD prevalence are made available at a subnational level. Standardized screening is not currently in practice even in cardiac clinics in endemic countries. The lack of a clear picture of the state of CD burden frustrates efforts to control the disease. We aim to address the knowledge gap by systematically reviewing papers reporting on community and hospital-based Chagas seroprevalence studies that follow the diagnostic algorithm recommended by the WHO. We discuss possible contributing factors to the variability in reported CD estimates. With this systematic review, we hope to generate a more detailed, nuanced picture of Chagas prevalence in the Americas and to provide recommendation for future publications regarding this matter.

## Methods

### Literature Search and Study Selection

A systematic review was conducted in compliance with preferred reporting items for systematic reviews and meta-analyses (PRISMA), in order to identify regional studies reporting *T. cruzi* infection and Chagas disease prevalence in the Americas. The following electronic databases were searched: PubMed (US National Library of Medicine, NIH), Embase (Elsevier), Web of Science (Clarivate Analytics), Cochrane Library (Cochrane), LILACS (BIREME, WHO, PAHO), SciELO (Scientific Electronic Library Online), Scopus (Elsevier), and GIDEON (Global Infectious Diseases and Epidemiology Network Informatics). The specific search strings used for each database are provided in the Supplemental Data section. Studies were included if they (1) were primary studies reporting seroprevalence of *T. cruzi* infection and CD in humans, (2) recruited participants from a community setting, (3) were published between 2004 to August 2018, and (4) were performed in North, Central, or South America, with an exception of island nations. We included studies published in Spanish, Portuguese, and English. Studies were excluded if they (1) showed an obvious selection bias, in which selected participants were not representative of the population intended to be analyzed; (2) recruited only hospitalized participants other than perinatal studies; (3) ranked 0 or 1 in the quality of evidence assessment scores (see *Data extraction*); (4) did not have a full text available; or (5) did not otherwise fit the inclusion criteria. Island nations were excluded as they are not known to have autochthonous CD transmission [41]. Studies showing obvious selection bias are defined as those that only surveyed a particular subset of a population that are more likely to have CD or *T. cruzi* infection, such as studies screening only cardiac disease patients. Case definition for *T. cruzi* infection follows WHO guidelines of diagnosis of at least two positive serological tests based on different methods, with a third confirmatory test in instances of discrepant results.

### Abstract Screening and Selection of Full Texts

Abstracts were screened according to the previously mentioned criteria using the systematic review software Covidence [42]. Each abstract was reviewed by two separate team members, and in instances where the first two did not agree, a third team member resolved the conflicts. The remaining texts were assessed for eligibility by two team members along with a third tie-breaker. Studies were excluded for the following reasons: (1) they were published before the year 2004; (2) they were not from the Americas; (3) they showed obvious selection bias; (4) they were not a primary study; (5) they were duplicate references or multiple papers reporting on the same cohort; (6) no full text was available; or (7) they otherwise did not fit the inclusion criteria. Data was extracted from the remaining full texts, and some studies were further excluded from the analysis. Reasons for exclusion at this point were if they were found not to have followed the WHO guidelines for Chagas disease diagnosis; if they were found to be duplicate papers reporting on the same cohort; if they did not provide sufficient information; did not have a full text available; or did not otherwise fit the inclusion criteria. The remaining studies were included in the analysis.

### Data Extraction

Data extraction was performed using the online cloud-collaboration software Airtable. Airtable is a database-spreadsheet hybrid software. The list of full texts to extract data from was uploaded to a database and linked to an associated database of data extraction forms. These forms could be filled out online by team members. Each study was reviewed by at least one team member; if reviewers were unsure about data extraction, the study was flagged and reviewed by a second team member. Data on the following factors was collected: location of study (country, state, and city); setting of study (urban, sub-urban, or rural); setting of participant recruitment (community-based, hospital-based, or blood donors); diagnostic methodology used as well as reported prevalence; and participant demographic data. The data extraction tool may be found in the Supplemental Material.

The Joanna Briggs Institute Prevalence Critical Appraisal Tool was adapted for use in evaluating the quality of evidence of each paper [43•]. The tool poses ten questions (Supplemental Material) on the quality of evidence in a prevalence paper. For each criterion met, the paper received 1 point, with the highest possible score being a 10. Papers that received average quality assessments of less than 2 in this

manner were excluded on the basis of poor quality of evidence.

### Statistical Analyses

All descriptive statistics were performed using the Stata 14 statistical package [44].

## Results

### Study Selection

As shown in our PRISMA flow diagram, Fig. 1, the search strings used returned a total of 13,909 abstracts. Five thousand eight hundred ninety-seven duplicate abstracts were removed. From the remaining 8012 abstracts, 344 more duplicates were identified and deleted, leaving 7668 abstracts. Six thousand seven hundred forty of these abstracts were determined to be irrelevant to the systematic review. The remaining 928 texts were assessed for eligibility by two team members along with a third team member as the tie-breaker. Six hundred eighteen texts were excluded, and data was extracted from the remaining 310 texts. After further exclusion, 190 texts were ultimately included in the data analysis. Studies were published in English (66.84%), Spanish (7.37%), and Portuguese (25.79%). The distribution of article types was 8 conference abstracts (4.21%), 176 indexed journal articles (92.63%), 5 non-indexed journal articles (2.63%), and 1 preliminary report (0.53%).

### Results Summary

The reported prevalence per country did not have a clear trend when considering year of publication (Supplemental material). Data from 18 different countries was included. An overall sum of 36,634,829 people/blood units were considered among the 190 studies included (Fig. 1). Community-based screening studies accounted for the majority (117 or 56.25%), while blood-bank screening studies accounted for 40 (21.05%) studies. Hospital-based screening studies accounted for 30 (15.79%); of these, 24 studies focused on perinatal screening.

The general prevalence of CD in the Americas was 0.29%. The highest seroprevalence was found in Bolivia (22.8%), Guatemala (3.9%), and Peru (3.8%) (Table 1). Among the 21 endemic countries for CD, 4 countries known to have cases of *T. cruzi* infections (Nicaragua, Uruguay, Surinam, Belize) did not appear in the final selection of studies.

### Diagnostic Methodology

Study size ranged from 63 to 29,000,000 participants, with a median of 1100 participants. We only included studies that followed the WHO-recommended diagnostic algorithm for *T. cruzi* detection [11]. Overall, 189, 103, and 26 studies used at least 2, 3, and 4 diagnosis tests, respectively. Seventy-one studies used a combination of ELISA, hemagglutination (indirect or direct), immunofluorescence (indirect or direct), and/or immunoblot, and over 95% of studies used at least 1 ELISA.

### Setting of Study and Participant Recruitment

Ninety-seven (51.05%) of the total 190 studies included study sites in rural regions; 76 of these studies were exclusively in rural regions, while the other 21 also included sub-urban and urban study sites in addition to rural (Fig. 2). The majority of studies (120 or 63.2%) screened recruited participants from a community setting; of these community-based studies, 68.3% ($n = 84$) took place in rural regions (Supplementary data). Mean prevalence is higher in rural settings as compared to urban and sub-urban settings in most countries (Fig. 2).

**Subnational Prevalence Estimates** Considering secondary-level administrative divisions (i.e., state, district, province), Argentina's mean prevalence ranged from 0.02 to 67% (M = 16.76%, SD = 15.9), Bolivia 1.54 to 64.5% (M = 34.6%, SD = 18.6), Brazil 0.0 to 38.1% (M = 4.89%, SD = 9.48), Colombia .11 to 33.5% (M = 5.94%, SD = 8.8), Mexico 0.36 to 20% (M = 4.68, SD = 5.8), Panama 1.0 to 5.88% (M = 3.56%, SD = 13.33), Peru .057 to 14.9% (M = 5.05, SD = 5.09), USA .007 to 1.3% (M = .30 SD = .43), and Venezuela 0.74 to 20.9% (M = 6.97, SD = 6.75) (Table 1).

### Participants

Most screened individuals were between 18 and 65 years old (59.4%), and the next largest demographic was children (< 18 years, 40.0%). In addition, 48.7% of the studies ($n = 74$, excluding pregnant women) presented information about sex, with 57.6% (1,122,102) men. Prevalence tended to be higher in older age groups, particularly in upper middle-income countries (Supplementary data).

## Discussion

The current burden of Chagas disease as reported in peer-reviewed journals and conference abstracts does not accurately reflect the complete picture in terms of epidemiology. This is evidenced by the fact that 4 of 21 endemic countries that are considered endemic for Chagas disease did not appear in the final selected papers. Furthermore, there are considerable hindrances that make the estimation of the burden even more complex.

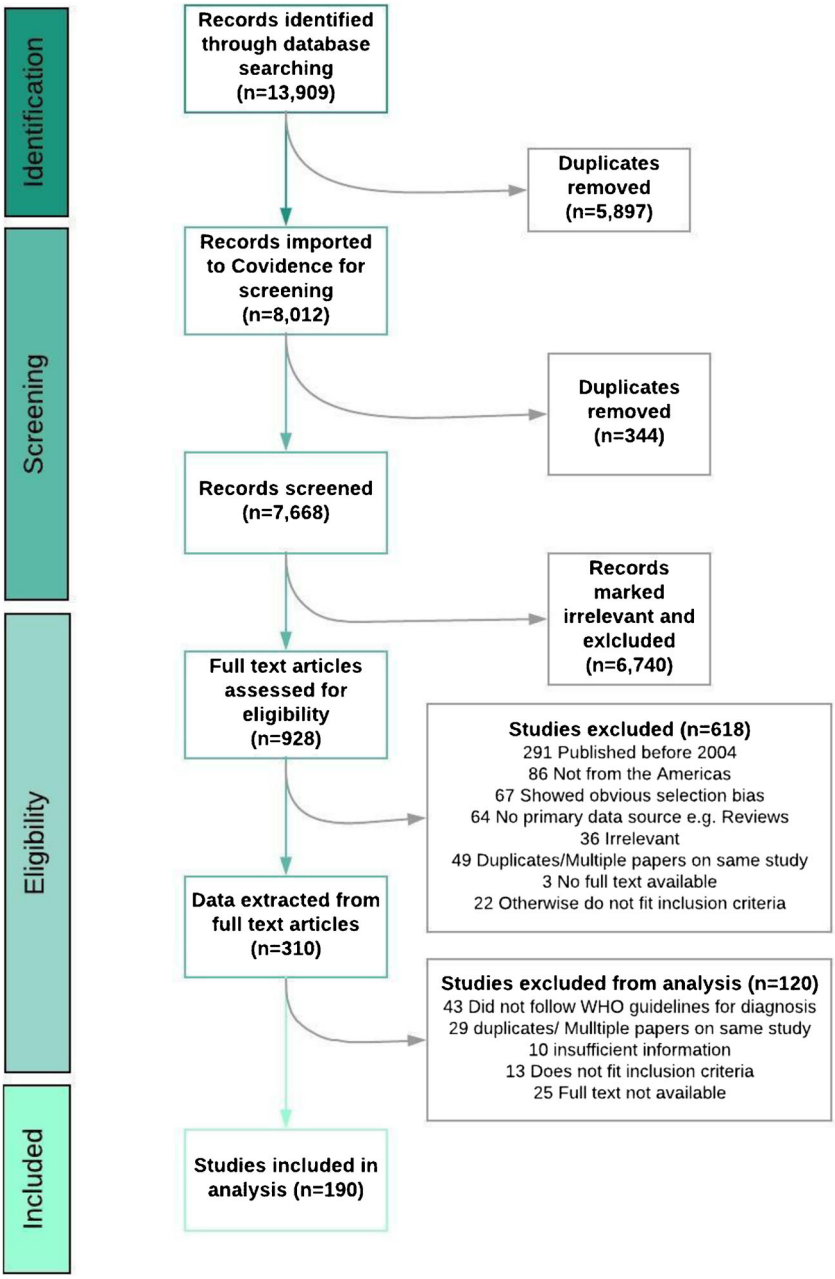


**Fig. 1** PRISMA data: study selection

In order to appropriately carry out disease control measures, the true state of CD burden must be assessed so that time and resources may be spent wisely. Resources for Chagas disease are limited, and conducting studies without an appropriately sensitive and specific diagnostic approach can convey misleading results. This may confuse stakeholders and discourage interest in mitigation strategies. It is important to highlight that most of the studies excluded during the full-text article assessment were left out because the case definition did not follow the WHO guidelines. Previous to this step, the search had included information on 58,594,577 individuals. While it is true that the complexity behind the diagnosis of Chagas disease is challenging and varies by region, DTUs, and many other factors, there is a lack of a reliable and gold standards for diagnosis. Furthermore, while several efforts to estimate the burden of Chagas disease have been made, more congruence is urgently needed across research groups and health authorities.

Our search found a CD prevalence of 0.29% in the Americas. According to the WHO [41], the overall prevalence of individuals infected with *T. cruzi* in Latin America was 4.3% in 1980–1985, 1.4% in 2005, and 1.1% in 2010. Considering the variability we found in prevalence at a state level, it is evident that we do not have enough information to have an informed estimate, particularly at a country or regional level. Furthermore, as has been previously discussed, the

**Table 1** Mean prevalence by country and comparison to WHO estimate

| Country | State/Region | Mean | SE | [95% Conf. Interval] | | Overall screened | Confirmed positive | Prevalence | WHO prevalence estimate | DTUs reported in region [17, 20] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Argentina** | Country-wide | 9.9002 | 5.796538 | -6.193569 | 25.99397 | | | | | TcV, TcVI, |
| | Buenos Aires | 2.7575 | 0.7756973 | .2888851 | 5.226115 | | | | | TcII, TcI |
| | Chaco | 29.81429 | 7.11973 | 12.39293 | 47.23564 | | | | | |
| | Chaco, chaqueña region | 27.8 | | | | | | | | TcV, TcVI [45] |
| | Cordoba | 6.25 | | | | | | | | TcV, TcVI [45] |
| | Corrientes | 6.26 | | | | | | | | |
| | Las Lomitas | 17.5 | | | | | | | | |
| | Salta | 9.73 | | | | | | | | |
| | Salta and Chaco | 0.89 | | | | | | | | |
| | San Luis | 21.18 | | | | | | | | |
| | San Luis and Corrientes | 11.7 | | | | | | | | |
| | San Martin | 26.1 | 0 | 26.1 | 26.1 | | | | | |
| | Santa Fé | 1.7 | | | | | | | | |
| | Santa Fe, La Capital | 29.2 | | | | | | | | |
| | **Total** | **14.3415707** | | | | **227623** | **5575** | **2.44922525** | 3.64 | |
| **Bolivia** | Country-wide | 23.31 | | | | | | | | TcV |
| | Chaco | 51 | 3.818246 | 40.39885 | 61.60115 | | | | | |
| | Cochabamba | 32 | 12.1 | -121.7451 | 185.7451 | | | | | |
| | Loja | 1.54 | | | | | | | | |
| | Santa Cruz | 25.225 | 10.46497 | -8.079209 | 58.52921 | | | | | |
| | Tarija | 37.45 | 3.55 | -7.657027 | 82.55703 | | | | | |
| | **Total** | **28.4208333** | | | | **353239** | **80444** | **22.7732498** | 6.1 | |
| **Brazil** | Country-wide | 9.74125 | 9.287523 | -19.81579 | 39.29829 | | | | | |
| | Amazonas | 10.6 | 7.311179 | -20.85746 | 42.05746 | | | | | |
| | Bahia | 14.3 | 10.8 | -122.927 | 151.527 | | | | | |
| | Ceará | 2.358 | 0.6373884 | .588326 | 4.127674 | | | | | |
| | Mato Grosso | 0.35 | 0.25 | -2.826551 | 3.526551 | | | | | |
| | Minas Gerais | 5.875 | 4.104335 | -3.588724 | 15.3405 | | | | | TcII |
| | Pernambuco Pernambuco, Minas Gerais, Sao | 0.17 | | | | | | | | |
| | Paulo | 0.001 | | | | | | | | |
| | Piauí | 9.8 | | | | | | | | |
| | Rio Grande | 0.4 | | | | | | | | |
| | Rio Grande do Norte | 5.9 | | | | | | | | |
| | Rio Grande do Sul | 0.365 | 0.065 | -.4609033 | 1.190903 | | | | | |
| | Rondonia | 1.2 | | | | | | | | |
| | Sao Paulo | 2.47 | 1.119553 | -.6383788 | 5.578379 | | | | | |
| | Sergipe | 0.2 | 0.2 | -2.341241 | 2.741241 | | | | | |
| | **Total** | **4.24868333** | | | | **2217662** | **5722** | **0.25801948** | 0.03 | |
| **Canada** | Country-wide | 0.824 | 0.276 | -2.682913 | 4.330913 | **13128** | **14** | **0.10664229** | No data | |
| | Ontario | 0.55 | 0.45 | -5.167792 | 6.267792 | | | | | |
| **Chile** | Country-wide | 0.824 | 0.276 | -2.682913 | 4.330913 | | | | | TcI, TcII, TcV |
| | Coquimbo | 3.4 | | | | | | | | |
| | **Total** | **2.112** | | | | **22671** | **320** | **1.41149486** | 0.7 | |
| **Colombia** | Country-wide | 9.75 | 7.05 | -79.82874 | 99.32874 | | | | | TcI, TcII, TcIII, TcV [46] |

**Table 1** (continued)

| Country | State/Region | Mean | SE | [95% Conf. Interval] | | Overall screened | Confirmed positive | Prevalence | WHO prevalence estimate | DTUs reported in region [17, 20] |
|---|---|---|---|---|---|---|---|---|---|---|
| | Antioquia | 1 | | | | | | | | |
| | Bogota | 0.11 | | | | | | | | |
| | Bolivar | 0.975 | 0.725 | -8.236998 | 10.187 | | | | | |
| | Boyacá | 2.435 | 0.3977751 | 1.169102 | 3.700898 | | | | | |
| | Casnare | 10.34333 | 3.358851 | -4.108635 | 24.7953 | | | | | |
| | Guaira | 33.5 | | | | | | | | |
| | Huila | 0.15 | | | | | | | | |
| | Santander | 3.2 | | | | | | | | |
| | Sure | 0.82 | | | | | | | | |
| | **Total** | **6.228333** | | | | **418800** | **1489** | **0.35553964** | 0.96 | |
| **Costa Rica** | Country-wide | 0.335 | 0.265 | -3.032144 | 3.702144 | **305256** | **496** | **0.16248657** | **0.17** | |
| **Ecuador** | Country-wide | 2.9 | 2.8 | -32.67737 | 38.47737 | | | | | TcV |
| | Guayas | 0.5 | | | | | | | | |
| | Orellana | 3.6 | | | | | | | | |
| | | **Total** | **2.33333333** | | | **11116** | **267** | **2.40194315** | 1.38 | |
| **El Salvador** | Country-wide | 1.7 | | | | | | | | |
| | Sonosate and Ahuachapán | 3.8 | | | | | | | | |
| | Sonosate | 3.6 | | | | | | | | |
| | **Total** | **3.03333333** | | | | **95282** | **1695** | **1.77892991** | 1.3 | TcI |
| **Guatemala** | | 3.9 | | | | **228** | **9** | **3.94736842** | 1.23 | |
| **Guyana** | | 0.35 | | | | **2000** | **7** | **0.35** | 0.84 | |
| **Honduras** | | 1.001 | | | | **25563** | **256** | **1.0014474** | 0.92 | TcI [47] |
| **Mexico** | Country-wide | 2.3004 | 1.286759 | -1.272216 | 5.873016 | | | | | TcI, TcIV [47] |
| | Chiapas | 2.04 | | | | | | | | |
| | Guanajuato | 12 | 8 | -89.64964 | 113.6496 | | | | | |
| | Jalisco and Nayarit | 0.7 | | | | | | | | |
| | Mexico City | 0.367 | 0.003 | .3288814 | .4051186 | | | | | |
| | Morelos | 20 | | | | | | | | |
| | Nuevo Leon | 2.8 | | | | | | | | |
| | Puebla | 2.795 | 1.555 | -16.96315 | 22.55315 | | | | | |
| | Queretaro | 8.13 | | | | | | | | |
| | San Luis Potosi | 6.5 | | | | | | | | |
| | State of Mexico | 9.1 | | | | | | | | |
| | Veracruz | 3.866 | 3.234411 | -5.114165 | 12.84617 | | | | | |
| | Veracruz y Chiapas | 4.1 | | | | | | | | TcI |
| | Yucatan | 3.55 | 1.25 | -12.33276 | 19.43276 | **395172** | **2421** | **0.61264462** | 0.78 | TcI, TcIV |
| | **Total** | **5.58917143** | | | | | | | | |
| **Panama** | Country-wide | | | | | | | | | |
| | Chepo/Chiman | 5.88 | | | | | | | | |
| | Chilibre | 1.9 | | | | | | | | |
| | La Chorrera | 2.9 | | | | | | | | |
| | Total | 3.56 | | | | **3532** | **77** | **2.18006795** | 0.52 | |
| **Paraguay** | Oriental Region, several departments | 0.24 | | | | **12776** | **31** | **0.24264245** | 0.44 | TcII, TcIII, TcV, TcVI |
| **Peru** | Country-wide | 4.7 | | | | | | | | TcV [48] |
| | Arequipa | 5.9625 | 2.012993 | -.4437412 | 12.36874 | | | | | |

**Table 1** (continued)

| Country | State/Region | Mean | SE | [95% Conf. Interval] | | Overall screened | Confirmed positive | Prevalence | WHO prevalence estimate | DTUs reported in region [17, 20] |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cajamarca | 14.9 | | | | | | | | |
| | Ica | 0.96 | | | | | | | | |
| | Loreto | 0.962 | | | | | | | | |
| | Tacna | 0.057 | | | | | | | | |
| | **Total** | **4.59025** | | | | **9578** | **368** | **3.84213823** | **0.44** | |
| **United States** | Country-wide | 0.1383333 | 0.1323384 | -.4310727 | .7077394 | | | | | |
| | California | 0.785 | 0.455 | -4.996323 | 6.566323 | | | | | |
| | California and Arizona | 0.04 | | | | | | | | |
| | New York | 0.0075 | 0.0005 | .0011469 | .0138531 | | | | | |
| | North Carolina | 0.032 | | | | | | | | |
| | Texas | 0.4326 | 0.2223955 | -.1848689 | 1.050069 | | | | | |
| | **Total** | | | | | **32389016** | **1493** | **0.00460959** | No data | |
| **Venezuela** | Country-wide | 4.933333 | 4.933333 | -9.814022 | 19.68069 | | | | | TcI, TcIV [49] |
| | Aragua | 1 | | | | | | | | TcIV [49] |
| | Carabobo | 13.25 | 7.65 | -83.95247 | 110.4525 | | | | | TcI [49] |
| | Lara | 6.52 | 2.159738 | -.3532491 | 13.39325 | | | | | TcI, TcIV [49] |
| | Monagas | 2.8 | | | | | | | | TcI [49] |
| | Sucre | 3.12 | | | | | | | | TcI, TcIV [49] |
| | Vargas | 20.2 | | | | | | | | TcI [49] |
| | **Total** | 7.40333329 | | | | 64763 | 1456 | 2.24819727 | 0.71 | |
| **TOTAL** | | | | | | 36567405 | 102140 | 0.27931979 | | |

prevalence of CD and risk of acquiring the infection at a regional level varies greatly with time. Our search showed considerable variability per secondary-level administrative divisions on each country. When studying the epidemiology of CD, the most accurate estimations come at a higher-level administrative division. Having a more accurate estimate of the prevalence would allow for the optimization of initiatives, resources, and prevention measures for CD.

The gap between data generated for governmental disease survey purposes and that of community-based research is such that current community-based research does not properly depict the entire epidemiological picture. An example of this is that Mexico, the two states that account for 70.1% of deaths attributed to Chagas disease according to government data (Oaxaca and Guerrero), did not show up in our final search [50].

## Vector Distribution and Prevalence

Vector control has been one of the most effective methods for preventing *T. cruzi* transmission in endemic areas. The Southern Cone Initiative, a vector control program to prevent and control CD, began in 1991 and targeted Argentina, Brazil, Bolivia, Brazil, Chile, Paraguay, and Uruguay. Similar programs were also created in the Americas, including the Initiative of the Andean Countries, targeting Bolivia, Colombia, Ecuador, Peru, and Venezuela in 1997; the Initiative of Central America and Mexico, targeting Belize, Costa Rica, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, and Panama in 1998; and the Initiative of the Amazon Countries, focusing on Bolivia, Brazil, Colombia, Ecuador, Guyana, French Guyana, Peru, Suriname, and Venezuela in 2004 [35]. We found Bolivia and Peru to be among the countries with the highest CD prevalence, which is possibly a reflection of both being some of the last to adopt the aforementioned vector control initiatives. Although these international efforts for controlling the disease have enabled important advances, the challenge goes beyond the establishing national estimates of prevalence or risk of infection, to identifying specific areas with high infection rate for prioritized preventive actions. In this context, the knowledge and monitoring CD prevalence at the secondary-level administrative division level is crucial to drive effective control strategies. Furthermore, considering risk factors for particular means of transmission is important to tailor interventions such as improved housing, vector control, and prenatal screening to the appropriate setting.

## Setting of Study

Reported prevalence of CD differed between studies that took place in rural regions and studies that took place in urban settings. This is notable in studies from Argentina, Colombia, and Peru (Table 1). However, studies included participants from highly endemic states and often did not make the distinction between rural, sub-urban, and urban setting in the analysis.

## Setting of Participant Recruitment

While blood-banks provide a valuable estimate of disease burden in the donor population, who are generally healthy and young, the inclusion requirements of those screened resulted in a selection bias. Prevalence in community studies therefore tends to be higher than those based on data from blood banks. Furthermore, most of the community-based studies were conducted in areas known to house the insect vector and to be endemic for CD.

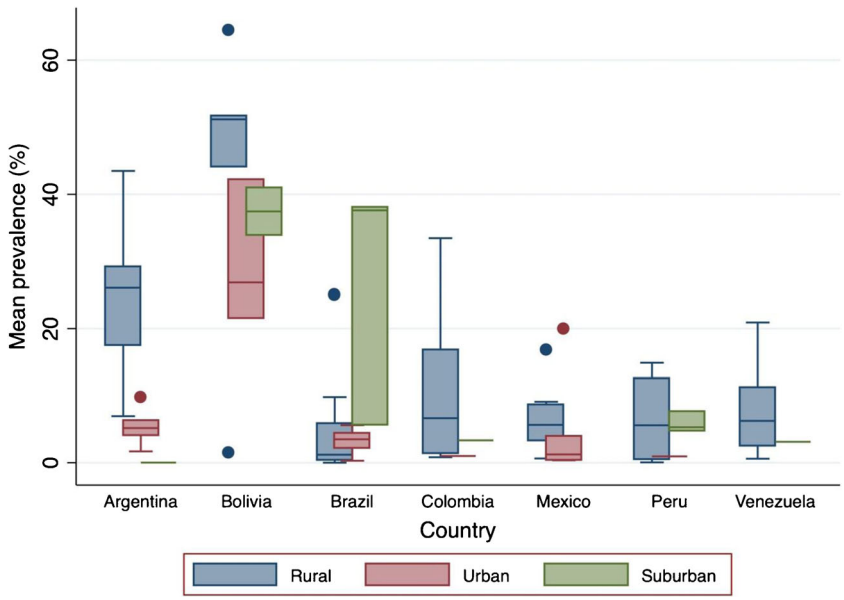


**Fig. 2** Mean prevalence in countries with most studies by setting

### Clinical Manifestation of *T. cruzi* Infection

Clinical features in Chagas disease are variable across geographic spaces. Because we included community studies, studies conducted in pregnant women, and blood banks, clinical manifestations were not often reported. However, high prevalence often did not correspond to places with known clinical manifestation of Chagas disease. For example, Peru has very few reported cases of Chagas cardiomyopathy (17 cases reported countrywide in 2017 [50]), despite relatively high seroprevalence (> 5%) in Arequipa, the Peruvian city most represented in our search. The discrepancies between reported manifestations of CD may be due to multiple reasons, including variances in DTU, reporting, vector control, and host genetics. As has been suggested by Messenger et al., diverse genetic characteristics of the parasite may be a reason for the disproportional clinical affections and prevalence [23••]. Furthermore, mixed infections with more than one DTU are likely more common than previously thought.

### Migration and CD Burden

Some of the studies conducted in areas of low endemicity reported higher prevalences than expected. This is possibly due to the fact that many of these studies screened immigrant populations from countries of high endemicity, such as the Luna et al. (2017) study that screened Bolivian immigrants in Argentina. Similarly, the vast majority of cases reported in the USA are concentrated in immigrant populations from highly endemic countries.

### Limitations

One of the main limitations of this review was the heterogeneity of studies, which made standardizing data collection across all included studies difficult. Another limitation was that many otherwise eligible studies did not follow the recommended WHO guidelines for diagnosis and were excluded from the review. The wide range of diagnostic tests used in surveyed studies, and their differing sensitivity and specificity, may also influence reported CD prevalence rates. When authors did not directly report prevalence of CD, we did not report their data in order to avoid misinterpretation. Finally, other factors such as the presence of undocumented migrants from endemic countries in some areas, as the USA, may underestimate the CD prevalence due to the lower likelihood of these individuals to participate in this type of activity. Despite these limitations, the present review provides, to our knowledge, the first systematic review to focus on Chagas disease prevalence for the whole region of the Americas.

## Reporting Recommendations

As mentioned in "Limitations," the studies included in this systematic review differed greatly in their approaches to screening for *T. cruzi* infection, reporting of results and seroprevalence estimates. In order to facilitate future systematic reviews and data sharing across countries and research groups, we propose the following general set of guidelines to follow when planning to conduct a *T. cruzi* seroprevalence study:

1. Prior to implementation, study designs should be assessed using a tool such as the Joanna Briggs Institute Prevalence Critical Appraisal Tool or the STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) Checklist [43•, 51].
2. Data should be collected and summarized on secondary or tertiary subnational administrative level, such as state, district, or county. Furthermore, we recommend that data on the following variables be gathered: birthplace, current residence, setting of participant recruitment (hospital-based, community-based, or blood-bank), setting of study (rural, sub-urban, or urban), and DTUs present in samples, if typing is being performed. When discussing DTUs, if possible, multiple blood samples from different timepoints should be drawn in order to better assess concomitant infections with multiple DTUs, as infection with multiple DTUs might not be apparent from a single sample.
3. Diagnosis of *T. cruzi* infection should be made using the WHO/PAHO recommendations of two serological tests detecting different antibodies to two different antigens in order to confirm Chagas disease. The specific diagnostic tests used should be noted.
4. For a given specific geographic area, the following statistics should be reported: mean prevalence of *T. cruzi* infection stratified by age, age distribution of all participants, and age distribution of infected participants, including mean age and standard deviation.

## Conclusion

Chagas disease is a complex, multifactorial disease. Current available data on Chagas disease epidemiology leaves a wealth of uncertainty and lacks rigorous methodology and standardization of terms across publications. This systematic review is an evidence that there is much to be done in the standardization of terms in Chagas research. It is of utmost importance that future research follows agreed-upon guidelines for CD diagnosis as established by the WHO and reports prevalence data in a standardized manner. Furthermore, the intranational variability in estimates require that reporting of data is conducted at a subnational level. Better estimation of disease burden will allow for

tailored Public Health interventions, research, and optimization of the limited resources destined towards this neglected disease.

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## Compliance with Ethical Standards

**Conflict of Interest** Mónica Miranda-Schaeubinger, Indira Chakravarti, Kárita Cláudia Freitas Lidani, Zahra Omidian, and Robert H. Gilman declare no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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