

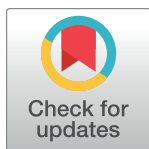
RESEARCH ARTICLE

Estimating the current burden of Chagas disease in Mexico: A systematic review and meta-analysis of epidemiological surveys from 2006 to 2017

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Abstract

Background

In Mexico, estimates of Chagas disease prevalence and burden vary widely. Updating surveillance data is therefore an important priority to ensure that Chagas disease does not remain a barrier to the development of Mexico's most vulnerable populations.

Methodology/Principal findings

The aim of this systematic review and meta-analysis was to analyze the literature on epidemiological surveys to estimate Chagas disease prevalence and burden in Mexico, during the period 2006 to 2017. A total of 2,764 articles were screened and 36 were retained for the final analysis. Epidemiological surveys have been performed in most of Mexico, but with variable study scale and geographic coverage. Based on studies reporting confirmed cases (i.e. using at least 2 serological tests), and taking into account the differences in sample sizes, the national estimated seroprevalence of *Trypanosoma cruzi* infection was 3.38% [95%CI 2.59–4.16], suggesting that there are 4.06 million cases in Mexico. Studies focused on pregnant women, which may transmit the parasite to their newborn during pregnancy, reported an estimated seroprevalence of 2.21% [95%CI 1.46–2.96], suggesting that there are 50,675 births from *T. cruzi* infected pregnant women per year, and 3,193 cases of congenitally infected newborns per year. Children under 18 years had an estimated seropositivity rate of 1.51% [95%CI 0.77–2.25], which indicate ongoing transmission. Cases of *T. cruzi* infection in blood donors have also been reported in most states, with a national estimated seroprevalence of 0.55% [95%CI 0.43–0.66].

collection and analysis, decision to publish, or preparation of the manuscript.

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Conclusions/Significance

Our analysis suggests a disease burden for *T. cruzi* infection higher than previously recognized, highlighting the urgency of establishing Chagas disease surveillance and control as a key national public health priority in Mexico, to ensure that it does not remain a major barrier to the economic and social development of the country's most vulnerable populations.

Author summary

In Mexico, estimates of Chagas disease prevalence and burden vary widely due to the ecology and epidemiology of this disease resulting of many geographical, ecological, biological, and social interactions. Better data are thus urgently needed to help develop appropriate public health programs for disease control and patient care. In this study we performed a meta-analysis from published data on *T. cruzi* infection seroprevalence in Mexico between 2006 and 2017. This systematic review shows a national estimated seroprevalence of *T. cruzi* infection of 3.38% [95%CI 2.59–4.16], with over 4.06 million cases in Mexico, which is higher than previously recognized. The presence of *T. cruzi* infection in specific subpopulations such as pregnant women, children and blood donors also informs on specific risks of infection and calls for the implementation of well-established control interventions. This work confirms the place of Mexico as the country with the largest number of cases, highlighting the urgency of establishing Chagas disease control as a key national public health priority.

Introduction

Chagas disease or American trypanosomiasis is an infection caused by the protozoan parasite *Trypanosoma cruzi*, which is mainly transmitted to humans and other mammals through the contaminated feces of hematophagous bugs called triatomines (family Reduviidae). However, it can also be spread via non-vectorial routes, such as blood transfusion, congenital transmission, organ transplantation, ingestion of food and beverages contaminated with *T. cruzi*, or laboratory accidents [1]. Over the years, infection with *T. cruzi* can cause heart failure or sudden death associated with progressive heart damage [2]. Some patients may also suffer from digestive, neurological or multiple alterations. This disease, classified by the World Health Organization (WHO) within the group of Neglected Tropical Diseases, is a major public health problem in Latin America where it is estimated that 6 to 7 million people are currently infected [1]. Due to human migrations, Chagas disease is emerging in other regions (Europe and United States principally) [3]. Estimates suggest that 80,000 to 120,000 *T. cruzi*-infected immigrants live in Europe, and 300,000 live in the United States [4], and the disease is a growing concern in these regions [5]. The global economic burden of Chagas disease is more than US \$7.2 billion per year, exceeding the costs of other diseases of health impact such as certain cancer (US\$6.7 billion for uterine cancer, US\$4.7 billion for cervical cancer, and US\$5.3 billion for oral cancer) or rotavirus infections (US\$2 billion) [6,7].

In Mexico, estimates of Chagas disease prevalence and burden vary widely, which has complicated the establishment of a strong National Chagas Disease Program for vector control as well as for patient detection and care in the country. For the past several years, the Ministry of Health only reports a few hundred cases per year [8], suggesting that the disease has an

anecdotal burden in terms of public health. On the other hand, other estimates suggest that there are about 1.1 million individuals infected with *T. cruzi* in Mexico, and 29.5 million at risk of infection [9,10]. Higher estimates of up to 6 million cases have also been proposed [11]. The annual cost for medical care for patients in the outpatient setting in this country is estimated between US\$4,463 and US\$9,601, and annual costs for patients admitted via an emergency care unit is between US\$6,700 and US\$11,838 [12].

There are also important regional differences in prevalence levels or number of cases reported in Mexico. For example, between 1928 and 2004 the states with the highest number of human cases reported were Chiapas, Guerrero, Jalisco, Morelos, Nayarit, Oaxaca and Queretaro. Conversely, few cases were reported in the states of Chihuahua, Coahuila, Guanajuato and Estado de Mexico [11]. It is not clear if such differences in prevalence are reflecting true differences in eco-epidemiological conditions, as Mexico is home to an extensive diversity of triatomine species, habitats, and socioeconomic conditions, or if there are bias in disease surveillance among regions [11].

Such wide discrepancies are important to reconcile to ensure that Chagas disease does not remain a major barrier to the development of Mexico's most vulnerable populations. Updating and improving surveillance data for Chagas disease in Mexico is therefore an important public health priority. In this context, the aim of this systematic review and meta-analysis was to estimate Chagas disease prevalence and burden in Mexico. We focused our study on the period from 2006 to 2017, to define current disease status rather than historical/cumulative burden, but our results are nonetheless compared with past reviews [11,13,14] to shed light on possible temporal trends on the status of Chagas disease in the country.

Methods

The current study was conducted in accordance with the PRISMA statement [15] (Supporting information). Potential data sources were identified and selected in different bibliographic databases. The ISI Web of Science (v5.13.1) was chosen because it incorporates many relevant databases including the SciELO Citation Index from 1997 onwards (provides access to leading journals from Latin America, Portugal, Spain and South Africa) and the Web of Science's Core Collection from 1980 onwards (<https://webofknowledge.com/>). A part of the literature was selected from the LILACS database (lilacs.bvsalud.org/en/), which is the most important index of scientific and technical literature of Latin America and the Caribbean. Finally, the BibTri database (<https://bibtri.cepave.edu.ar/>) was also used because it integrates scientific literature specifically related to Chagas disease.

We restricted our search to the period from January 2006 to December 2017, to obtain information on the current status of Chagas disease in Mexico rather than on its historical/cumulative status, which has been summarized in previous reviews [11,13,14]. Selection was made using the search terms 'Chagas disease in Mexico/Enfermedad de Chagas en México' and with the equivalent keywords obtained via Medical Subject Headings (MeSH) website (<https://meshb.nlm.nih.gov/search>), i. e. American Trypanosomiasis, Chagas' Disease, *Trypanosoma cruzi* Infection, Trypanosomiasis in South American.

For all these articles, titles and abstracts were screened for any indication that the study contained data related to the seroprevalence of *T. cruzi* infection in human populations from Mexico. Typically, this excluded studies of, for example, therapeutic options for patients with chronic Chagas disease, molecular studies of lab strains of the parasite, or experimental model developments (Fig 1). In the second step of the process, full text copies were obtained and articles containing quantitative data on *T. cruzi* infection seroprevalence were retained. Extreme

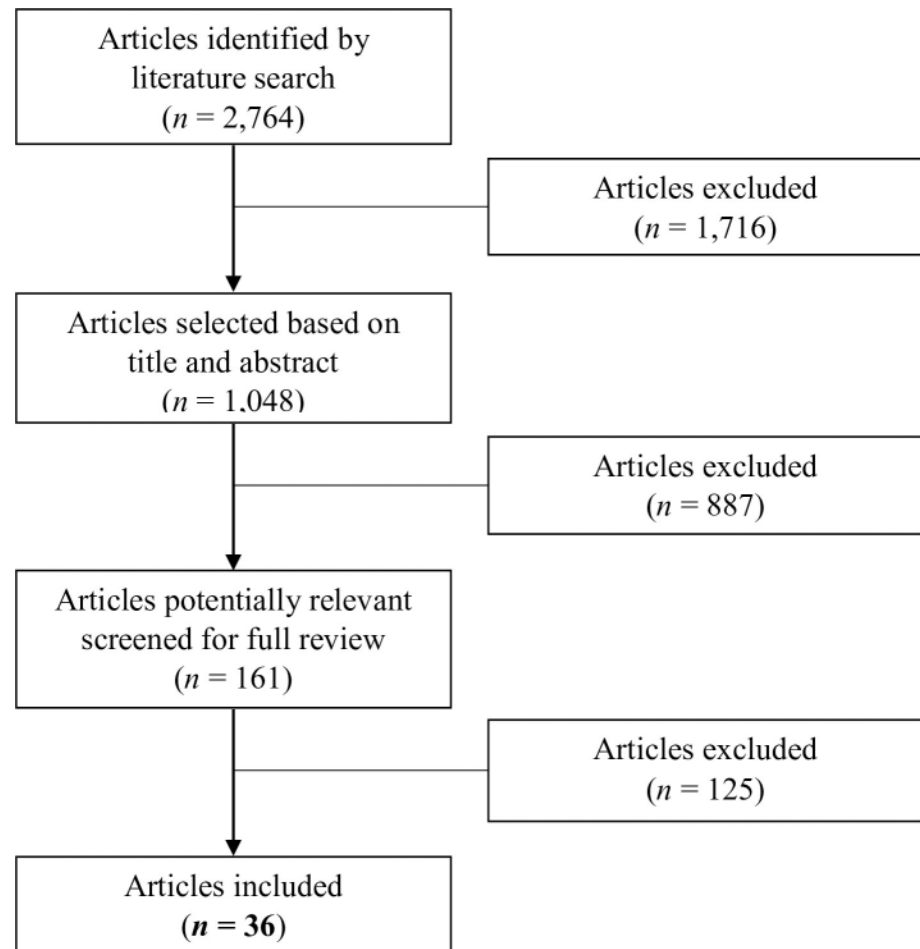


Fig 1. Process flow chart for the identification, screening, eligibility, and inclusion of studies.

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care was taken in cross-validating whether the information contained in each study was unique and not duplicated elsewhere.

The ultimate step was to extract the relevant information contained in the selected articles which included 1) publication data (bibliographic information), 2) sampling dates, 3) sampling strategy (archive, random, volunteers, etc. . .), 4) geographic area covered by the study, 5) studied population (blood donors, patients, pregnant women, newborns, children, random populations), 6) laboratory techniques used (ELISA tests; IHA, PCR. . .) and the number of laboratory techniques used to validate the cases detected, 7) total sample size, number of human cases. Studied populations were then divided into subgroups to allow for analysis of the seroprevalence of *T. cruzi* infection at different levels, including the general population (population sampled in different geographic locations), pregnant women, children (under 18 years old), and blood donors (number of patients).

We calculated two general estimated prevalences 1) the first considering all studies, irrespective of the inclusion of confirmatory diagnostic, and 2) the second including only the studies in which at least 2 serological tests were used (as recommended by the WHO for an accurate identification of cases, see [results](#) part). We further calculated 95% confidence intervals (95%CI) based on the reported data and sample sizes [16,17]. We assessed the extent of publication bias in the selected studies through a funnel plot. Next, we performed a meta-

analysis to calculate the effect size estimate, and the weighted effect size (% weight), based on a random-effects model [18]. For each estimated prevalence, a test for heterogeneity among studies (Q) and the variability of the effect size due to variation between observations (I^2) was calculated, and forest plots were elaborated. The estimated prevalence obtained in each population were then compared to the data reported by the Ministry of Health and with other reviews [8].

Results

A total of 2,764 articles were screened and 36 were retained for the final analysis (see Fig 1). All the articles included in this study corresponded to serological surveys in different populations and settings, including general or specific populations such as pregnant women or blood donors, published between 2006 and 2017 (Table 1). Research on Chagas disease seroprevalence has been performed in most of the Mexican Republic (Fig 2). The states with more studies were Veracruz, Yucatan, and Queretaro. The extent of publication bias in the selected studies (with a total of 79 observations, each of the 36 studies may have several observations of different states, populations. . .) was assessed through a funnel plot (Fig 3), and the symmetric distribution of data points indicated a lack of publication bias or systematic heterogeneity of the dataset.

We first considered the studies in the general population (population sampled in different geographic locations) and in pregnant women (which can be considered as highly representative of the general population as well [55]) to obtain a national estimate. When considering all studies, irrespective of the inclusion of confirmatory diagnostic (i.e. based on a single serological test, 28 studies), the total number of human cases reported in the literature during the period 2006–2017 was 884 with a national estimated prevalence (calculated according to the sample size between studies) of 3.28% [95%CI 2.52–4.03] (Fig 4). The seroprevalence of infection varied between 0.21% and 9.13% depending on the state. Only two studies (in Jalisco and Colima) were based on a single test and when considering only the studies in which at least 2 serological tests had been performed (26 studies), hence cases had been confirmed as currently recommended by the WHO for an accurate identification of cases, the national estimated seroprevalence was 3.38% [95%CI 2.59–4.16], with seroprevalences varying between 0.21% and 12.01% depending on the state (Fig 5). The highest seroprevalence levels were reported in the states of Jalisco, San Luis Potosi, Chiapas, Estado de Mexico, Queretaro, and Oaxaca. Based on a national population of nearly 120 million (National census of 2015), this seroprevalence level would correspond to 4.06 million cases in the country [95%CI 2.45–4.50 million]. On the other hand, the number of cases of *T. cruzi* infection reported by the national program of epidemiologic surveillance of the Ministry of Health during 2006–2017 period reached 8,687 ([8] and Table 2), with a regular increase in the number of cases detected with time.

A few of these studies (7 studies) focused on pregnant women, which may transmit the parasite to their newborn during pregnancy [56]. While these studies only covered 7 states (Fig 6), a total of 212 *T. cruzi*-infected pregnant women were detected, for a global estimated seroprevalence of *T. cruzi* infection of 2.21% [95%CI 1.46–2.96] in this specific population. The highest seroprevalence levels in pregnant women were reported in the states of Jalisco, Oaxaca, and Estado de Mexico. Based on current birth rate in Mexico (2,293,000 births in 2016), this would correspond to 50,675 births from *T. cruzi* infected pregnant women per year. With a congenital transmission rate of 6.3% [22], there may be 3,193 cases of congenitally infected newborns per year in the country.

Some studies also focused on or included data on children under 18 years (6 studies), which may indicate more recent transmission. These covered only 4 states (Fig 7), with a global estimated seroprevalence of *T. cruzi* infection of 1.51% [95%CI 0.77–2.25].

Table 1. Characteristics of included studies.

Reference	Year	Population	State	Category Person	Num test validity*	Sample size	Num of cases*
Balan et al. [19]	2011	General population	Campeche	Adults/Children	2	2,800	3
Becerril-Flores et al. [20]	2007	General population	Hidalgo	Adults/Children	2	175	6
Becerril-Flores et al. [20]	2007	General population	Querétaro	Adults/Children	2	39	2
Benière et al. [21]	2007	General population	Jalisco	Adults	1	242	6
Buekens et al. [22]	2018	Pregnant woman	Yucatan	Adults	3	12,160	32
Campos-Valdez et al. [23]	2016	Pregnant woman	Chiapas	Adults	2	1,125	23
Cenalmor-Aparicio [24]	2013	General population	Chiapas	Adults	2	129	25
Dhiman et al. [25]	2009	General population	Chiapas	Adults	2	1,481	121
Escamilla-Guerrero et al. [26]	2012	Blood donor	Mexico City	Adults	2	37,333	64
Estrada-Franco et al. [27]	2006	General population	Mexico State	Children	2	356	22
Galavíz-Silva et al. [28]	2009	Blood donor	Coahuila	Adults	2	65	2
Galavíz-Silva et al. [28]	2009	Blood donor	Nuevo León	Adults	2	809	21
Galavíz-Silva et al. [28]	2009	Blood donor	Tamaulipas	Adults	2	126	5
Gamboa-León et al. [29]	2014	General population	Yucatan	Adults	2	390	9
Gamboa-León et al. [29]	2014	General population	Yucatan	Children	2	685	3
Gamboa-León et al. [30]	2011	Pregnant woman	Guanajuato	Adults	2	488	2
Gamboa-León et al. [30]	2011	Pregnant woman	Yucatan	Adults	2	500	3
García-Montalvo [31]	2011	Blood donor	Yucatan	Adults	2	86,343	607
Guzman-Gómez et al. [32]	2015	General population	Veracruz	Adults/Children	2	184	62
Hernández-Romano et al. [33]	2015	Blood donor	Veracruz	Adults	2	87,232	438
Jiménez-Cardoso et al. [34]	2012	Pregnant woman	Jalisco	Adults	3	558	67
Jiménez-Cardoso et al. [34]	2012	Pregnant woman	Mexico City	Adults	3	97	4
Jiménez-Cardoso et al. [34]	2012	Pregnant woman	Oaxaca	Adults	3	794	35
Jiménez-Coello et al. [35]	2010	General population	Yucatan	Adults	3	60	4
Jiménez-Coello et al. [35]	2010	General population	Yucatan	Children	3	15	2
Juarez-Tobias et al. [36]	2009	General population	Hidalgo	Adults/Children	2	51	1
Juarez-Tobias et al. [36]	2009	General population	San Luis Potosi	Adults/Children	2	933	62
Juarez-Tobias et al. [36]	2009	General population	Veracruz	Adults/Children	2	15	2
Kirchhoff et al. [37]	2006	Blood donor	Jalisco	Adults	3	5,183	41
Kirchhoff et al. [37]	2006	Blood donor	Nayarit	Adults	3	2,113	14
López-Céspedes et al. [38]	2012	General population	Querétaro	Adults	2	258	28
Martínez-Tovar et al. [39]	2014	Blood donor	Mexico State	Adults	2	1,615	5
Molina-Garza et al. [40]	2014	General population	Nuevo León	Adults	2	2,688	52
Monteon et al. [41]	2013	General population	Campeche	Adults	2	128	3
Montes-Rincón et al. [42]	2016	Pregnant woman	Guanajuato	Adults	2	520	20
Newton-Sánchez et al. [43]	2017	General population	Colima	Adults/Children	1	925	22
Novelo-Garza et al. [44]	2010	Blood donor	Aguascalientes	Adults	2	7,187	1
Novelo-Garza et al. [44]	2010	Blood donor	Baja California	Adults	2	6,932	16
Novelo-Garza et al. [44]	2010	Blood donor	Baja California sur	Adults	2	375	0
Novelo-Garza et al. [44]	2010	Blood donor	Campeche	Adults	2	1,530	20
Novelo-Garza et al. [44]	2010	Blood donor	Chiapas	Adults	2	3,873	12
Novelo-Garza et al. [44]	2010	Blood donor	Chihuahua	Adults	2	6,012	26
Novelo-Garza et al. [44]	2010	Blood donor	Coahuila	Adults	2	4,611	10
Novelo-Garza et al. [44]	2010	Blood donor	Colima	Adults	2	636	5
Novelo-Garza et al. [44]	2010	Blood donor	Durango	Adults	2	1,151	4
Novelo-Garza et al. [44]	2010	Blood donor	Guanajuato	Adults	2	6,286	8
Novelo-Garza et al. [44]	2010	Blood donor	Guerrero	Adults	2	4,480	20

(Continued)

Table 1. (Continued)

Reference	Year	Population	State	Category Person	Num test validity*	Sample size	Num of cases*
Novelo-Garza et al. [44]	2010	Blood donor	Hidalgo	Adults	2	4,117	30
Novelo-Garza et al. [44]	2010	Blood donor	Jalisco	Adults	2	7,150	14
Novelo-Garza et al. [44]	2010	Blood donor	Mexico City	Adults	2	5,055	15
Novelo-Garza et al. [44]	2010	Blood donor	Mexico State	Adults	2	54,514	140
Novelo-Garza et al. [44]	2010	Blood donor	Morelos	Adults	2	3,403	26
Novelo-Garza et al. [44]	2010	Blood donor	Nayarit	Adults	2	3,194	50
Novelo-Garza et al. [44]	2010	Blood donor	Nuevo León	Adults	2	36,441	79
Novelo-Garza et al. [44]	2010	Blood donor	Oaxaca	Adults	2	1,554	4
Novelo-Garza et al. [44]	2010	Blood donor	Puebla	Adults	2	7,988	11
Novelo-Garza et al. [44]	2010	Blood donor	Querétaro	Adults	2	3,870	22
Novelo-Garza et al. [44]	2010	Blood donor	Quintana Roo	Adults	2	2,768	55
Novelo-Garza et al. [44]	2010	Blood donor	San Luis Potosi	Adults	2	1,532	4
Novelo-Garza et al. [44]	2010	Blood donor	Sinaloa	Adults	2	1,946	0
Novelo-Garza et al. [44]	2010	Blood donor	Sonora	Adults	2	8,947	12
Novelo-Garza et al. [44]	2010	Blood donor	Tabasco	Adults	2	1,893	34
Novelo-Garza et al. [44]	2010	Blood donor	Tamaulipas	Adults	2	8,263	53
Novelo-Garza et al. [44]	2010	Blood donor	Tlaxcala	Adults	2	532	3
Novelo-Garza et al. [44]	2010	Blood donor	Veracruz	Adults	2	19,599	185
Novelo-Garza et al. [44]	2010	Blood donor	Yucatan	Adults	2	13,045	76
Novelo-Garza et al. [44]	2010	Blood donor	Zacatecas	Adults	2	1,190	0
Olivera-Mar et al. [45]	2006	Pregnant woman	Chiapas	Adults	2	60	3
Olivera-Mar et al. [45]	2006	Pregnant woman	Veracruz	Adults	2	85	3
Portugal-García et al. [46]	2011	General population	Morelos	Adults/Children	2	233	3
Ramos-Ligonio et al. [47]	2006	Blood donor	Veracruz	Adults	3	420	2
Ramos-Ligonio et al. [47]	2010	General population	Veracruz	Adults	2	654	110
Ruiz et al. [48]	2011	Pregnant woman	Veracruz	Adults	2	4,851	20
Salazar et al. [49]	2007	General population	Veracruz	Children	3	150	5
Salazar-Schettino et al. [50]	2009	General population	Querétaro	Children	2	826	11
Salazar-Schettino et al. [51]	2016	General population	NA	Children	2	3,327	37
Sánchez-Guillén et al. [52]	2006	Blood donor	Puebla	Adults	2	2,140	166
Villagrán et al. [53]	2009	General population	Querétaro	Adults/Children	2	1,029	68
Villagrán-Herrera et al. [54]	2014	General population	Querétaro	Adults/Children	2	3	3

*Num test validity (number of laboratory techniques used), Num of cases (number of human cases detected). $I^2 = 99.54\%$; $Q = 1,948$.

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Several additional studies also evaluated *T. cruzi* infection in blood donors (9 studies), and seropositive human cases were detected in every state of the Mexican Republic, except for Baja California Sur, Sinaloa, and Zacatecas (Fig 8). The total number of blood donor cases reported was 2,300 corresponding to a national estimated seroprevalence of 0.55% [95% CI 0.43–0.66]. The highest seroprevalence was observed in the states of Quintana Roo, Tabasco, Puebla, Campeche and Nayarit.

Finally, we also examined the type of serological test performed in these studies. The most widely used tests were indirect hemagglutination, followed by Chagatest ELISA from Wiener lab, and immunofluorescence assays (Table 3), which represented 67.8% of all tests used. Several other commercial ELISA tests were also used (24.7% of tests), and in-house tests including ELISA, and western blot represented 3.7% of the tests used.

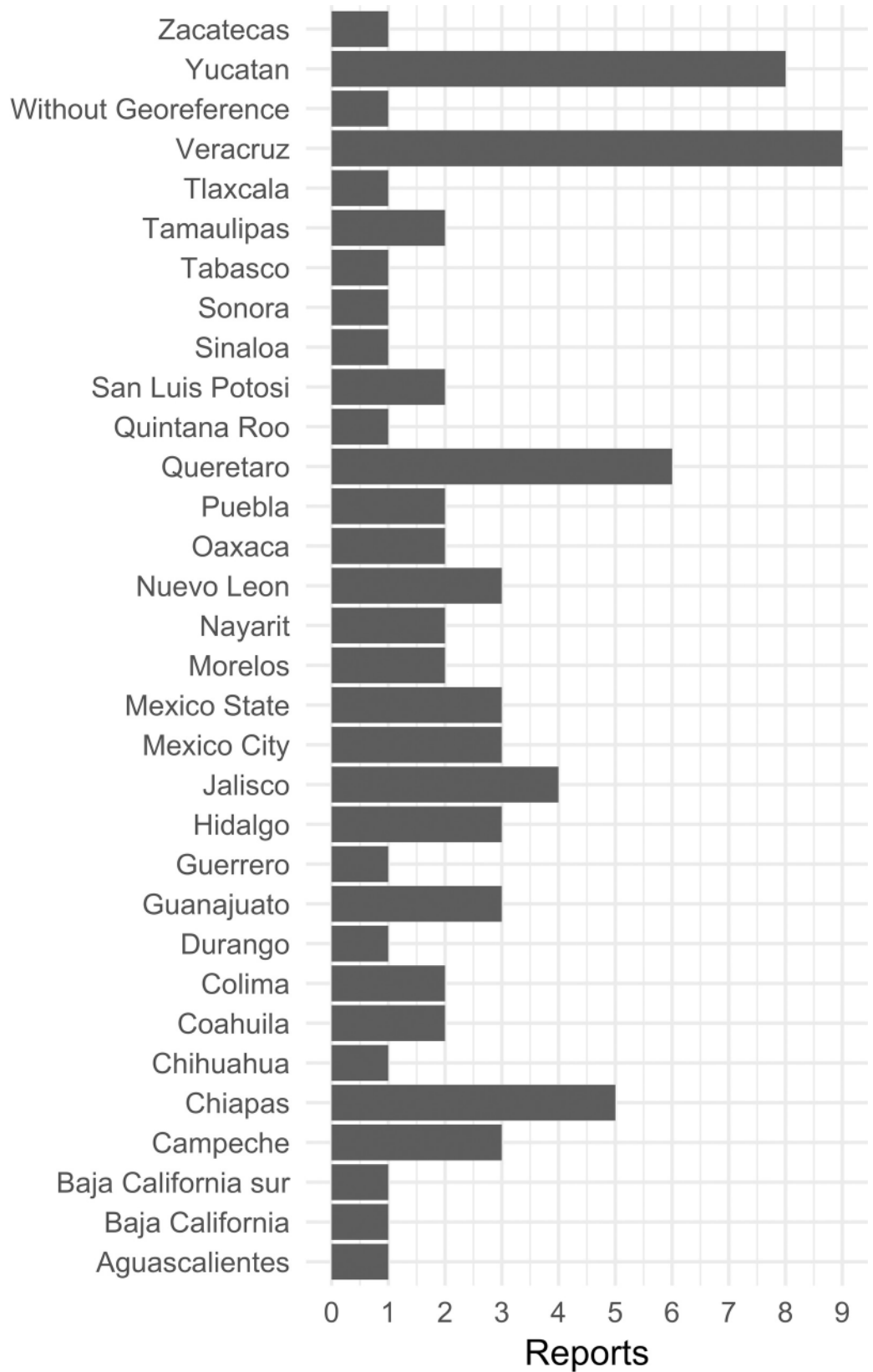


Fig 2. Number of publications which report human cases of *T. cruzi* seropositivity from states of Mexico, 2006–2017. Each publication can cover several states.

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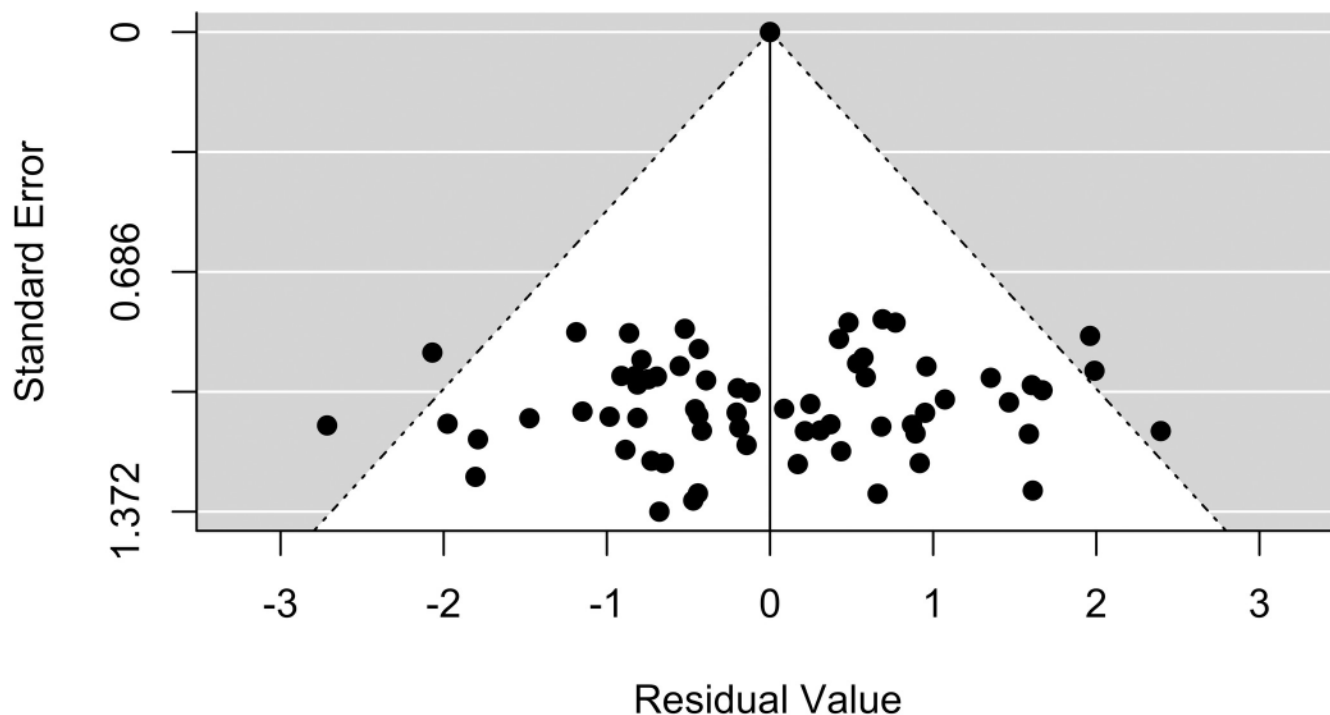


Fig 3. Funnel plot for the examination of study bias. The plot is based on 79 observations from 36 publications which report human cases of *T. cruzi* seropositivity from states of Mexico, 2006–2017.

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Discussion

Chagas disease remains one of the most relevant parasitic disease in the Americas, but its epidemiology in Mexico is still poorly understood. Better data are thus urgently needed to help develop appropriate public health programs for disease control and patient care. In this study we analyzed published data on *T. cruzi* seroprevalence of infection in Mexico between 2006 and 2017. A total of 36 studies were identified, covering most of the country with the notable exception of the state of Michoacán. To take into account the sample size heterogeneity among studies, we analyzed the data based on meta-analysis techniques using a random-effects model. Due to discrepancies in previous studies often attributed to diagnostic methods and uncertainties about the confirmation of cases [57], current recommendations of health agencies request a minimum of 2 serological techniques for accurate diagnostic [10]. Based on this criterion, we found a national estimated seroprevalence of *T. cruzi* infection of 3.38%, corresponding to 4.06 million cases in the country. Only a few studies were discarded for lack of confirmatory testing, indicating that most of recent studies followed current guidelines for the accurate diagnostic of cases. This seroprevalence level can thus be considered rather conservative, but it is much higher than previous estimates. For example, the Pan American Health Organization (PAHO) estimated that 1,100,000 individuals were infected with *T. cruzi* in Mexico in 2006, and 29,500,000 were at risk of infection [58], and a national prevalence of 0.65% (with 733,333 cases) was established in 2010 by the Mexican Ministry of Health [59]. The most recent estimates from the WHO based on 2010 data reports 876,458 cases [10], corresponding to a national prevalence of 0.78%. Our analysis of data from the last decade thus suggests that the magnitude of *T. cruzi* infection in Mexico may have been underestimated in these previous reports. Based on ours data, annual cost for medical care in the outpatient setting was estimated between US\$18 and US\$39 billion, and annual costs in emergency care unit

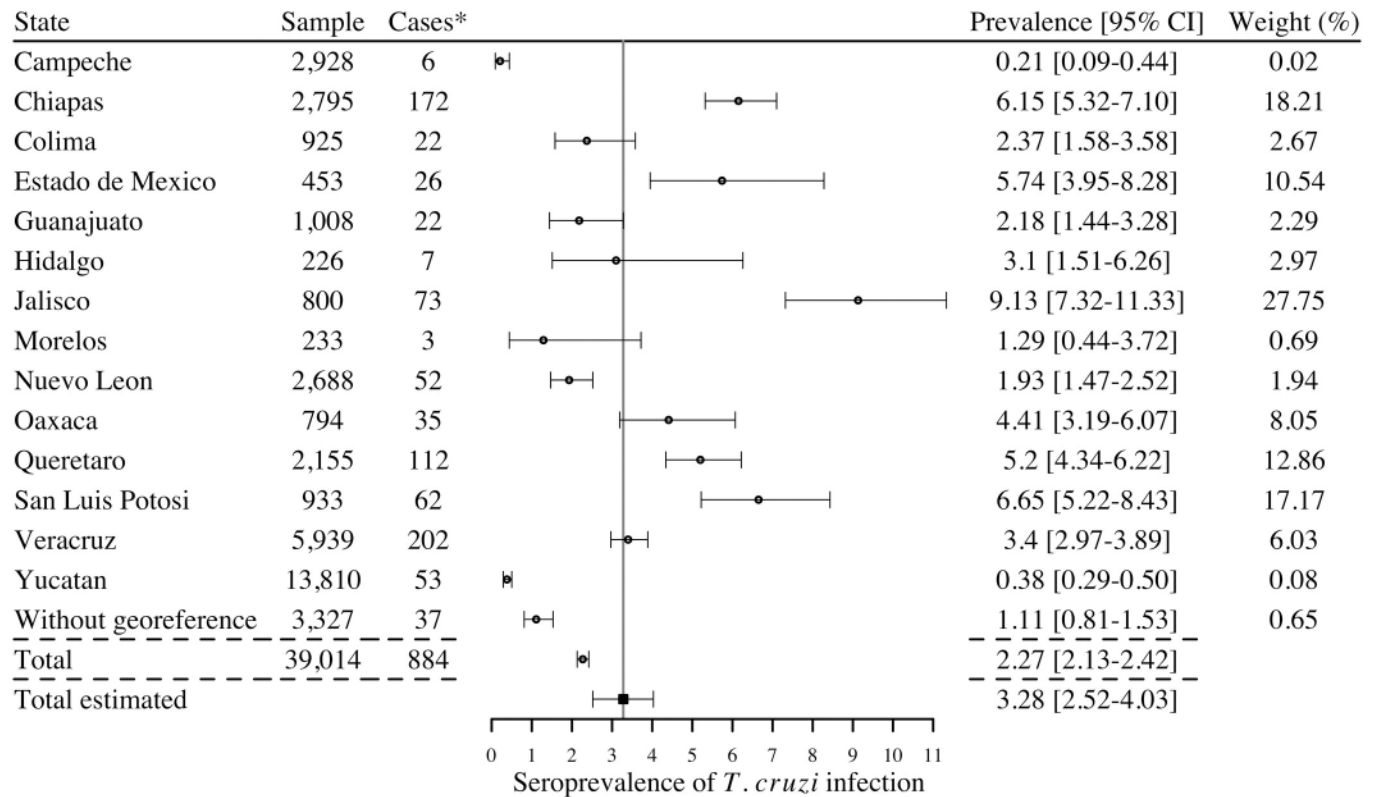


Fig 4. Cases of *Trypanosoma cruzi* infection detected in serological surveys of general populations and pregnant women during 2006–2017 (28 studies). *Cases are reported using 1 or more serological tests to determine the infection. $I^2 = 98.56\%$; $Q = 625$.

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is between US\$27 and US\$48 billion [12]. In addition, recent studies pointing out a low sensitivity of commercial serological tests for *T. cruzi* diagnostic [22,32,60], some of which are widely used in Mexico (Table 3) also raise concerns that the seroprevalence of *T. cruzi* infection may even be higher than currently detected. Improvements in serological tests are thus urgently needed for a more reliable disease surveillance [61]. Our analysis nonetheless places Mexico as the country with the largest number of cases of *T. cruzi* infection as previously estimated [10], and highlights the urgency of establishing national priorities for the control of parasite transmission and patient care as well as improved epidemiologic surveillance.

Our results also point out to some regional differences in *T. cruzi* infection seroprevalence among states. The ecology and epidemiology of Chagas disease are the result of many geographical, ecological, biological, and social interactions [62], which may explain some of these differences. High seroprevalence levels have been previously reported for several states including Jalisco, Chiapas, Queretaro, Oaxaca, Veracruz, and Morelos [11], suggesting a well-established endemicity in these states. States with seroprevalence levels higher than previously reported also emerged through our study, in spite of limited sample sizes. These include San Luis Potosi, Estado de Mexico, Hidalgo and Guanajuato.

T. cruzi infection is also present at a significant estimated seroprevalence in pregnant women in Mexico. Despite the limited information available for this specific population, we could estimate that there are 50,675 births from *T. cruzi* infected pregnant women per year, corresponding to 3,193 cases of congenitally infected newborns per year in the country. This prevalence is again higher than previous estimates [63], strengthening the urgency of addressing congenital Chagas disease in the country. Because infected newborns can be effectively

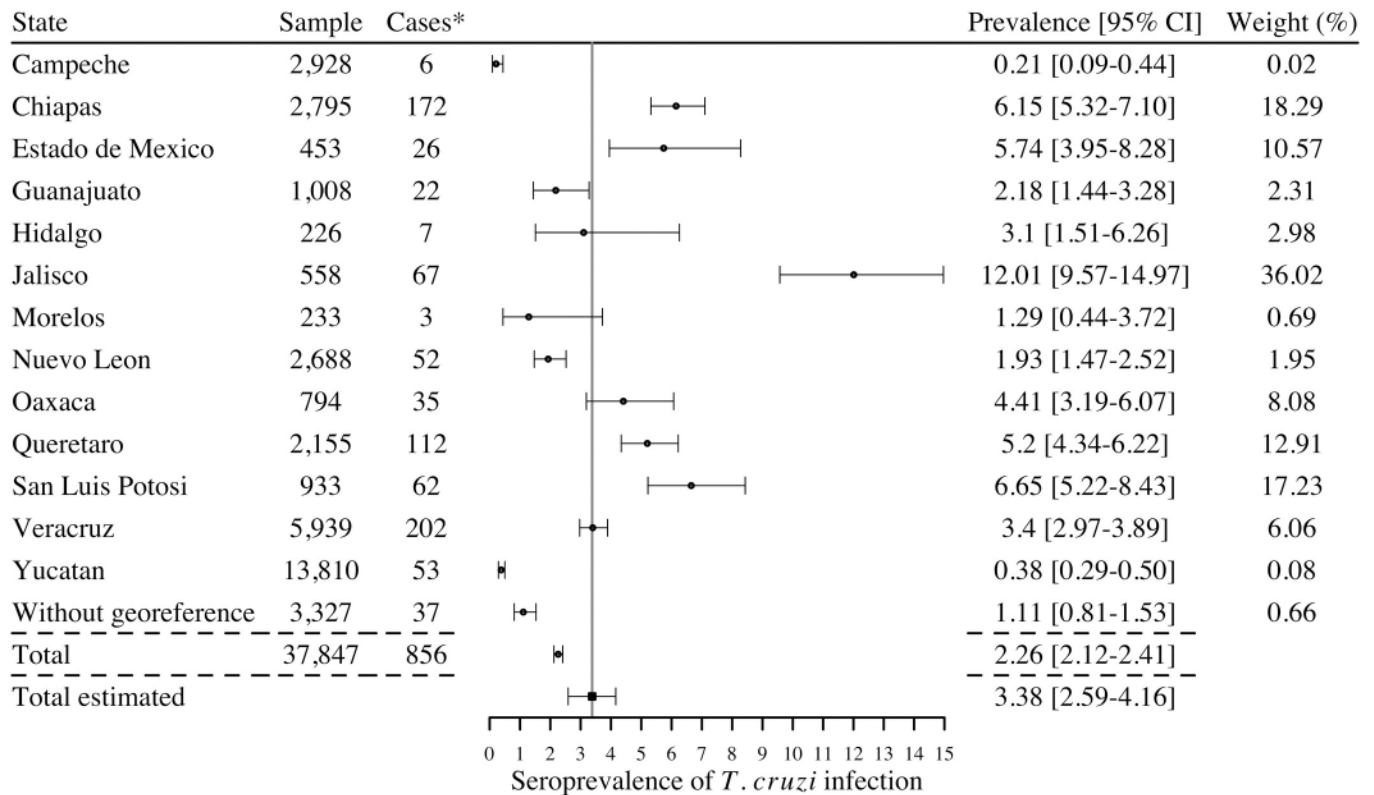


Fig 5. Confirmed cases of *Trypanosoma cruzi* seropositivity detected in serological surveys of general populations and pregnant women during 2006–2017 (26 studies). *Cases are reported using 2 or more serological tests to determine the infection. $I^2 = 98.52\%$; $Q = 610$.

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treated, the lack of specific screening programs to identify them is a missed opportunity for the control of the disease. Indeed, a recent health economic study in the US evidenced the large benefits of maternal screening for *T. cruzi* infection, as lifetime societal savings due to screening and treatment was estimated at \$634 million saved for every birth year cohort [64].

Table 2. Number of new cases of Chagas disease per years, reported by the Ministry of Health, in all the states of Mexico [8].

Years	Sample
2006	400
2007	392
2008	679
2009	613
2010	528
2011	801
2012	830
2013	762
2014	735
2015	1,095
2016	994
2017	856
Total	8,687

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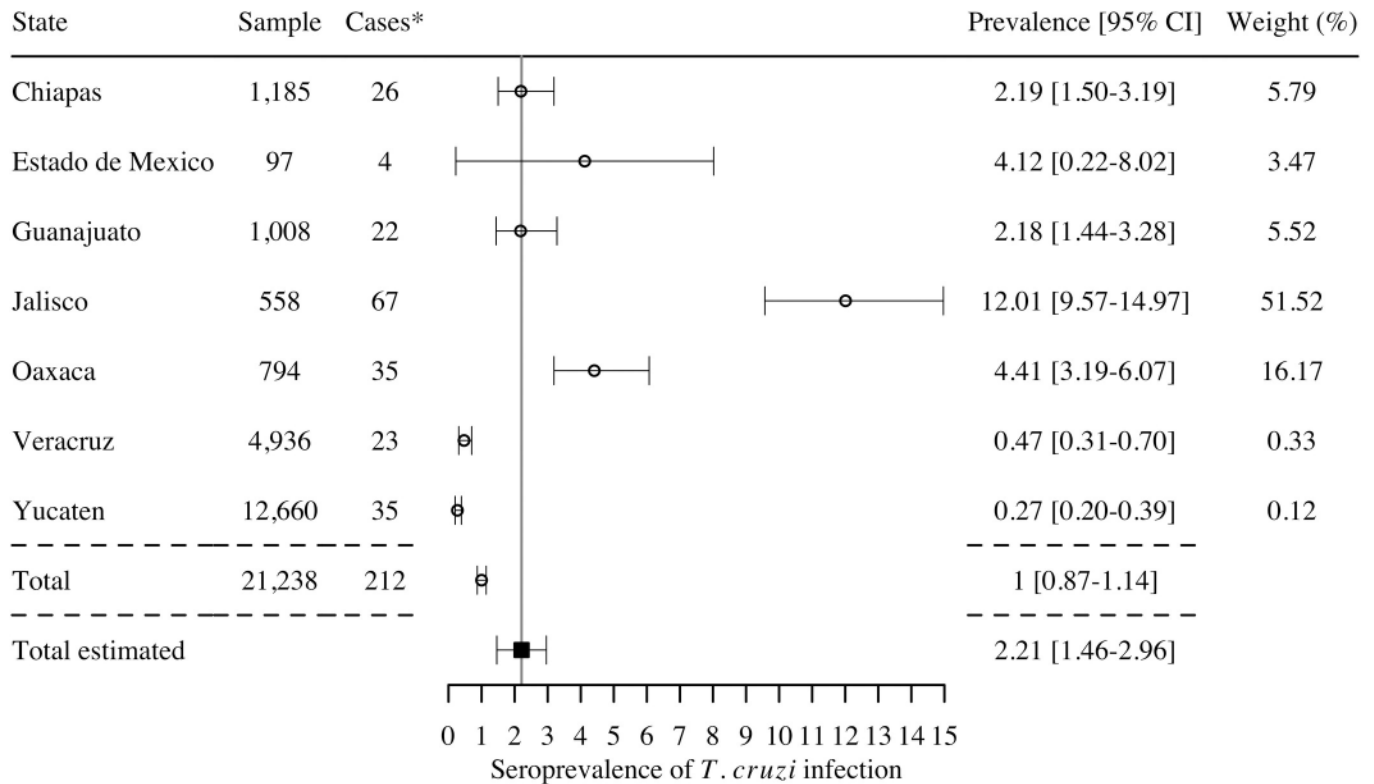


Fig 6. Prevalence of seropositive pregnant women by state, 2006–2017 (7 studies). *Cases are reported using 2 or more serological tests to determine the infection. $I^2 = 93.27\%$; $Q = 134$.

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Very limited information is available on *T. cruzi* infection in children. Nonetheless, we were able to identify a few studies in children up to 18 years, who presented an average prevalence of 1.51%. This may indicate more recent and active transmission compared to data on adult populations, and suggests that the incidence of *T. cruzi* infection has been fairly stable over time. Therefore, effective vector control programs tailored to the extensive diversity of triatomine species present in Mexico [65] are urgently needed to reduce vectorial *T. cruzi* transmission to human populations [66,67].

Blood transfusion has been considered the second most important mode of transmission of Chagas disease in Mexico [68]. In 1998, the screening of almost 65,000 blood donors from 18 government-run transfusion centers showed a 1.5% prevalence of anti-*T. cruzi* antibodies in blood donors [69]. The highest prevalence was detected in the states of Hidalgo, Tlaxcala, Puebla, Chiapas y Yucatan, as expected from previous reports, whereas the northern states of Nuevo Leon and Chihuahua, had the lowest seroprevalence in blood donors. For the period between 1978–2004, Cruz-Reyes *et al.* defined a national prevalence of positive serology in blood banks of 2.03% [11]. In our study, the national estimated prevalence detected in blood donors was lower with 0.55%. These differences can be explained by the increased reliability of serologic screening of blood donors with the passing of legislation making screening mandatory in the year 2000 [13,70]. The addition of a pre-screening questionnaire to exclude high-risk individuals may also have led to a lower prevalence in screened donors. The highest prevalence of 1.99% is detected in the state of Quintana Roo and the lowest in Baja California Sur, Sinaloa and Zacatecas (with a prevalence of 0%).

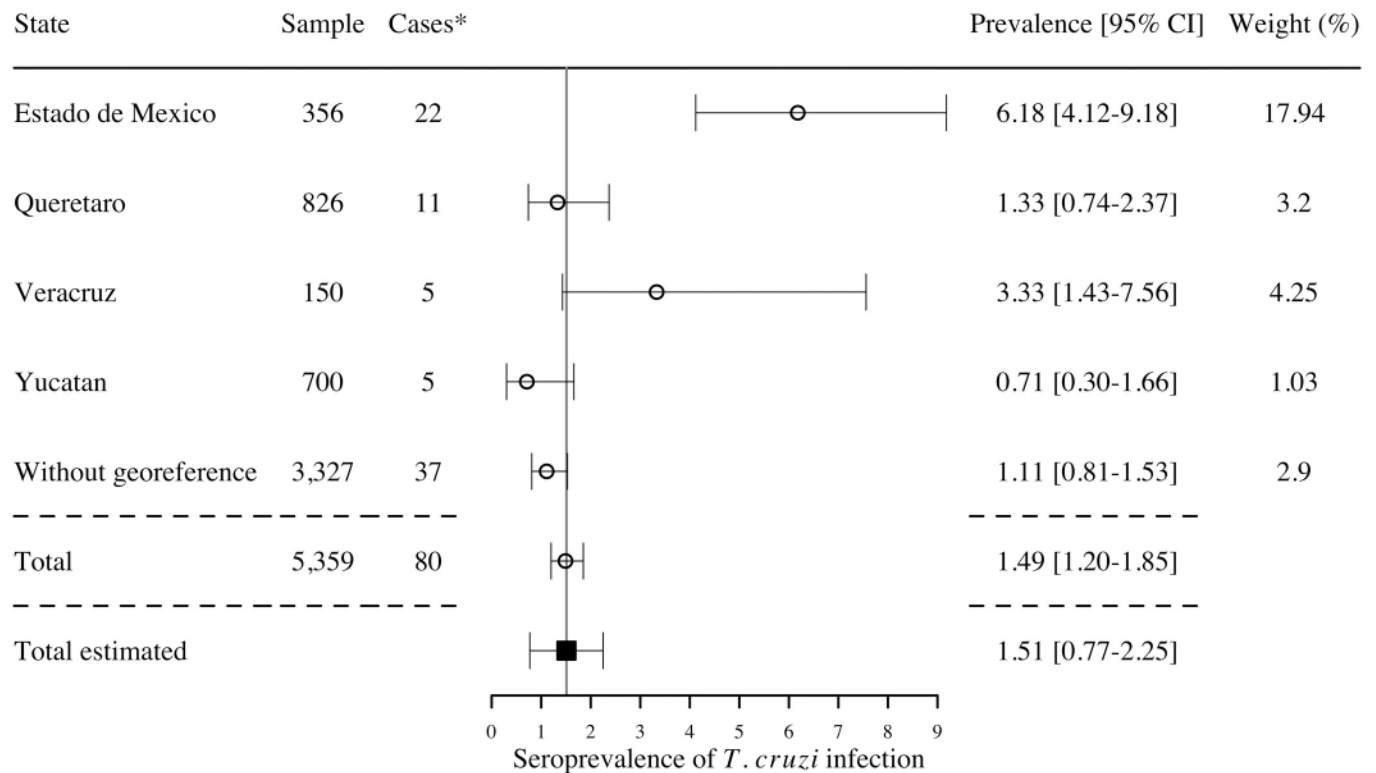


Fig 7. Prevalence of seropositive children under 18 years by state, 2006–2017 (6 studies). *Cases are reported using 2 or more serological tests to determine the infection. $I^2 = 52.18\%$; $Q = 19$.

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Strengths and limitations

A major strength of our analysis was to consider the sample size heterogeneity among studies and the reliability of serological testing performed, and to ensure it followed WHO recommendations for confirmation of cases using at least a second test. Hence, our estimates of seroprevalence are robust and conservative. On the other hand, there are some limitations. First, some heterogeneity among study designs and particularly sampling strategies and recruitment of subjects may have generated some bias. For example, the difference in the number of studies performed per state can lead to over- or under-estimation of the prevalences. Also, while we did not detect major publication bias, there was an uneven coverage of the different states by research studies, which may be a confounding factor affecting differences in *T. cruzi* infection prevalence among states. This highlights the need for much improved nationwide disease surveillance to clearly identify geographic heterogeneities in *T. cruzi* transmission and Chagas disease epidemiology. Finally, the small number of studies/sample sizes for some of the subgroup analysis also add uncertainties to our estimates of *T. cruzi* estimated seroprevalence in specific subpopulations.

Conclusion

In conclusion, our systematic review and meta-analysis estimates a national seroprevalence of *T. cruzi* infection of 3.38%, with 4.06 million cases in Mexico, which is higher than previously recognized. It places Mexico as the country with the largest number of cases, highlighting the urgency of establishing Chagas disease control as a key national public health priority, to ensure that it does not remain a major barrier to the economic and social development of

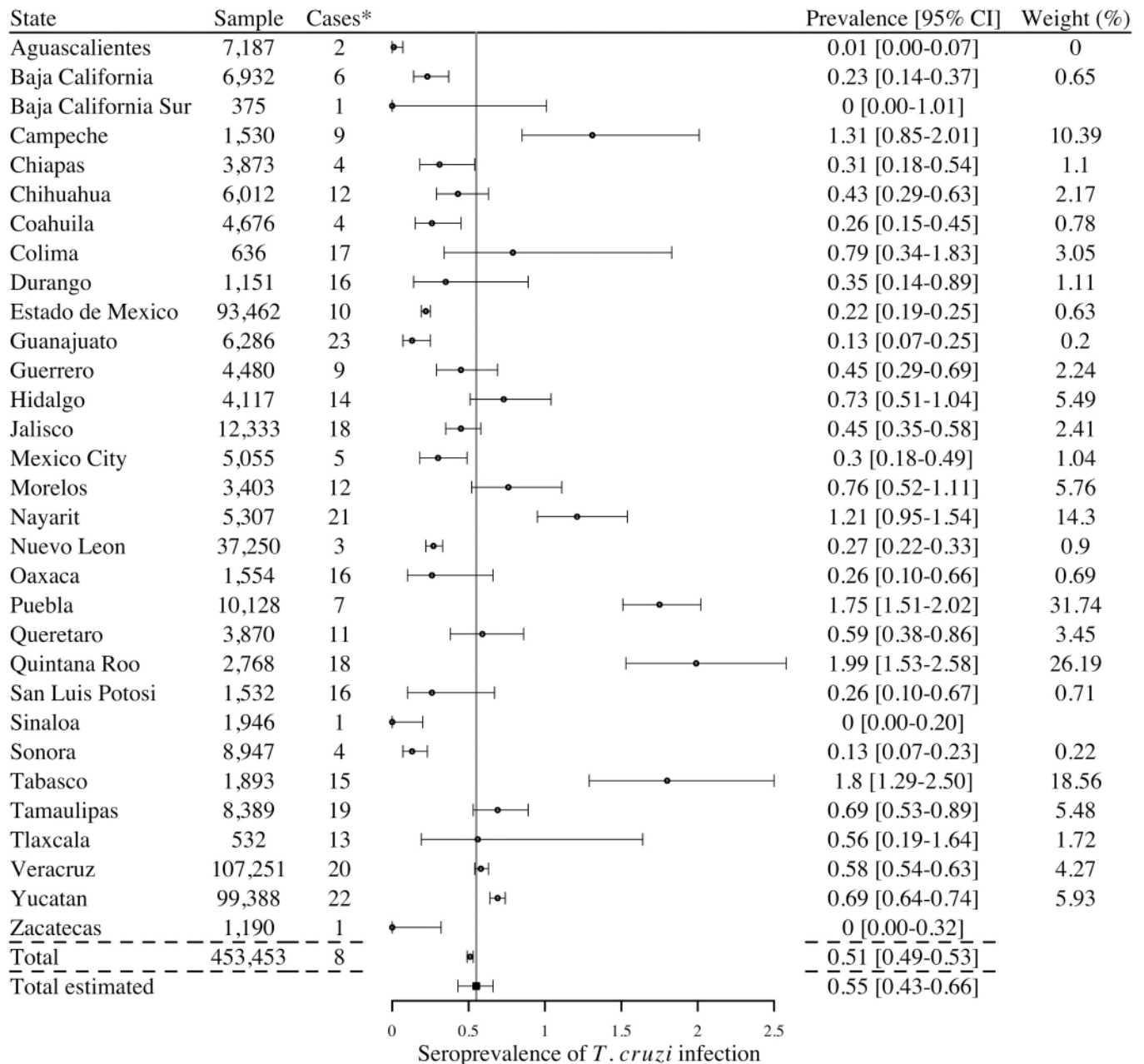


Fig 8. Prevalence of positive serology in blood banks by state, 2006–2017 (9 studies). *Cases are reported using 2 or more serological tests to determine the infection. I² = 99.19%; Q = 1,114.

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Mexico’s most vulnerable populations. It remains essential to strengthen effective surveillance for Chagas disease in all the country to obtain more precise data. The presence of *T. cruzi* infection in specific subpopulations such as pregnant women, children and blood donors also informs on specific risks of infection, and calls for the implementation of well-established control interventions [56,67,71]. Finally, while our estimates are conservative and based on confirmed cases, the lack of sensitivity of current serological tests observed in Mexico suggest that the true magnitude of Chagas disease in the country may still be underestimated, and the

Table 3. Type of diagnostic tests used in epidemiological studies in Mexico.

Type of test	Sample	Cases
IHA, Indirect hemagglutination	391,148	2,005
Chagatest Elisa (v. 3.0, 4.0 or unspecified), Wiener Lab	234,282	1,234
IFA, Immunofluorescence assays	103,396	962
BioElisa Chagas, Biokit/Werfen	89,021	448
Chagas Recombinant Micro-Elisa Kit, Accutrack	88,787	558
Elisa Kit, Bioschile	87,342	672
In-House Elisa with Antigenic Extract	34,832	521
Chagas STAT-PAK rapid test, Chembio	18,208	293
Abbott Chagas' EIA Kit, Abbott Lab Meridian	7,296	55
Chagas Elisa Kit, Meridian Biosci.	7,296	55
RIPA, Radioimmunoprecipitation	7,296	55
WB, Western blot	5,379	216
Enzyme Chagas Kit, Interbiol	214	8
Chagatek Elisa, Lomos-Biomerieux	184	62
Total	1,074,681	7,144

<https://doi.org/10.1371/journal.pntd.0006859.t003>

development of more reliable diagnostic tests will be key for an effective identification of cases as well as improved patient care [61].

Supporting information

S1 Checklist.

(PDF)

S1 Flow Diagram.

(PDF)

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