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Short Communication

Congenital Chagas disease: alert of research negligence

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Abstract

Introduction: Chagas disease (CD), a neglected endemic disease in Latin America, has acquired new epidemiological characteristics with an increase in the importance of alternative transmission routes such as congenital transmission. We evaluated the scientific research on this subject. **Methods:** We searched the Scielo, BVS, and PubMed databases from 2006 to 2017. **Results:** We identified a small number of published articles, mostly in journals with an impact factor less than 3.0. Studies on human congenital transmission of CD were carried out in only seven different countries. **Conclusions:** Our data highlight the lack of research on congenital CD.

Keywords: Congenital Chagas disease. Publications. Negligence.

Chagas disease (CD), or American trypanosomiasis, is an endemic disease in Latin America classified as a neglected tropical disease by the World Health Organization (WHO). Approximately seven million people are infected with *Trypanosoma cruzi* worldwide, with the main concentration in Brazil, Mexico, and Argentina[1]. Globalization and the intense flow of people through countries, especially Latino immigrants, contribute to the spread of infection to non-endemic areas[2,3]. In the acute phase of the disease, patients may present several clinical manifestations, among them fever, hepatomegaly, splenomegaly, swelling at the inoculation site (chagoma of inoculation), and edema of the eyelid (Romana sign)[2]. Most infected patients, however, are asymptomatic. In approximately one-third of patients, the disease evolves into a symptomatic chronic phase, with clinical manifestations related specifically to the cardiovascular and digestive system[4].

Infected hematophagous Hemiptera of the subfamily Triatominae can transmit the protozoa *T. cruzi* naturally to man and other animals. Alternative transmission routes are blood transfusion, organ transplantation, and sexual, oral, and congenital routes. Since classical forms of CD transmission such as vector and blood transfusion are being controlled, other less frequent forms of transmission such as congenital transmission have been showing increasing epidemiological importance.

Mother-to-child *T. cruzi* transmission may result in premature births, low-weight newborns, and stillbirths[5]. Since its description by Carlos Chagas in 1911[6], several authors have reported the importance of CD congenital transmission, not only experimentally, but mainly in man[4]. Currently, the congenital transmission rate varies greatly depending on the location, being approximately 1% in Brazil and reaching 12% in other Latin American countries[7]. It is estimated that, in endemic regions, approximately two million women of childbearing age have the chronic form of the disease, with an estimated incidence of 15,000 cases per year in Latin America[8].

Data on congenital transmission of CD are heterogeneous, being influenced by the form of control and diagnostic and screening programs, which reinforces the need to intensify the studies and research of patients suspected to have the disease. Despite generating more work and costs, these actions would have the benefit of decreasing the number of infected children and if the child is treated up to 1 year of age, the chance of a cure is higher[8,9]. In this respect, the quality of the tests used for diagnosis is of great importance and may be fundamental to guarantee the early detection of congenital CD transmission. Unfortunately, from a political point of view, CD is considered a Latin American problem and has not attracted the attention of major world research centers.

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In this context, the objective of this work was to evaluate the scientific research on this subject by identifying the number of published articles, the impact factors of the journals in which the articles were published, and the countries where the research was carried out.

A systematic review on congenital transmission of CD was carried out using the Virtual Health Library (BVS), the Scientific Electronic Library Online (Scielo), and Public Medline (PubMed), on February 23, March 3, and February 13 in 2017 and on January 24 in 2018. The study period was from 2006 to 2017 and the descriptors used were "Chagas disease," "congenital transmission," "*Trypanosoma cruzi*," and "pregnancy."

We established the following inclusion criteria: (1) studies involving congenital transmission of CD, (2) studies conducted in humans, and (3) articles written in English. The following types of study were excluded: case reports, review studies, dissertations and theses, studies without epidemiological and diagnostic aspects, and studies performed in animals or in vitro. Within the established study period, 97 articles were found in PubMed, 91 in the BVS database, excluding those in duplicate, result in 100 articles, and no articles on Scielo. After a thorough analysis of the found articles, 32 were eligible for the study proposal, as shown in **Figure 1**.

The following bibliometric indicators were evaluated: number of papers published, names of journals and their respective impact factors, year of publication, countries where

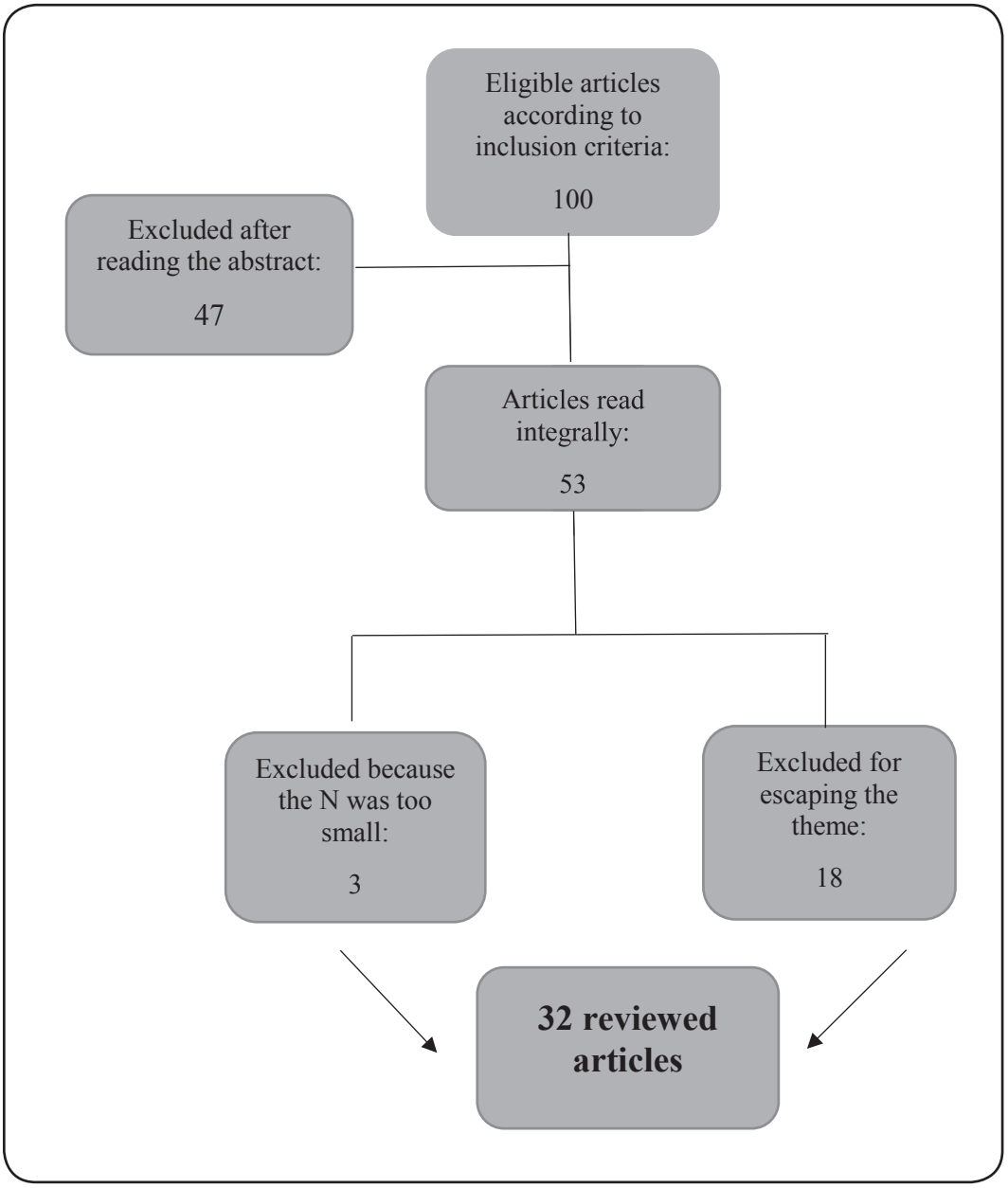

FIGURE 1: Flowchart of bibliographic review articles.

surveys were conducted, sample size, congenital transmission incidence, and diagnosis methods.

After analyzing all the inclusive and exclusive criteria of the articles, the selected publications were organized and arranged in chronological order, as shown in **Table 1**, from the most recent (2017) to the oldest (2007). Despite the search for articles from 2006, no article fit within the inclusion criteria in the first year. The 32 selected articles were distributed in 12 different journals with impact factors varying between 1.631 and 8.736. The journals with the most published articles *Acta Tropica* and *The American Journal of Tropical Medicine and Hygiene*, with six articles in each journal. There were few articles between the years 2006 and 2009, but more in the years 2012 and 2015 (five and seven articles, respectively).

Another aspect evaluated was the distribution of the research by country (**Table 1**). Studies on congenital transmission of CD were carried out in only seven different countries, with predominance in Argentina (10 studies), Bolivia (eight studies), and Spain (five studies). Of interest, a single study was conducted in Brazil. In relation to the research time span, short-term and long-term studies were identified, the largest being a retrospective 20-year study (**Table 1**). Of the 30 studies, only one did not report the coverage period.

As noted in **Table 2**, there was a large variation in the sample size among the articles, ranging from 19 to 4355 children. The incidence of CD congenital transmission also differed among the studies, independently of the study area endemicity. In the nine studies conducted in non-endemic areas (four in Buenos Aires and five in Spain), the congenital transmission rate ranged from 2.6% in Spain to 23% in Buenos Aires. In these areas, 55.5% of studies had a transmission rate ≥5%. Of interest, the majority of these mothers came from endemic areas of Latin America (**Table 2**). The congenital transmission rate in the endemic areas varied from 1.98% to 20% in studies carried out, respectively, in Brazil and in Mexico.

The articles we analyzed demonstrated a gamut of methodologies used for the diagnosis of congenital transmission of CD. Indeed, 90% (27/30) of the articles used more than one methodology: parasitological, serological, or molecular, according to WHO recommendations.

For the present study, we conducted a literature review to identify articles published in the last 10 years on CD congenital transmission, using predetermined inclusion and exclusion criteria. At the end of the analysis, 32 articles were selected for content evaluation. Most articles (21/32) were published in the last 5 years; but in 2016, only one article was selected within the pre-established criteria. In this respect, it should be

TABLE 1: Bibliometric indicators of the reviewed articles on congenital Chagas disease.

Reference	Article	Journal/impact factor	Country	Research time span
Murcia et al., 2017	Treatment of Infected Women of Childbearing Age Prevents Congenital *Trypanosoma cruzi* Infection by Eliminating the Parasitemia Detected by PCR	*The Journal of Infectious Diseases*/6.723	Spain	2013-2015
Buekens et al., 2017	Congenital Transmission of *Trypanosoma cruzi* in Argentina, Honduras, and Mexico: An Observational Prospective Study	*The American Journal of Tropical Medicine and Hygiene*/2.456	Mexico, Honduras, and Argentina	2011-2014
Montes-Rincón et al., 2016	*Trypanosoma cruzi* seroprevalence in pregnant women and screening by PCR and microhaematocrit in newborns from Guanajuato, Mexico	*Journal Acta Tropica*/2.380	Mexico	2014-2015
Vargas et al., 2015	Seroprevalence of *Trypanosoma cruzi* Infection in Schoolchildren and in Pregnant Women from an Amazonian Region in Orellana Province, Ecuador	*The American Journal of Tropical Medicine and Hygiene*/2.456	Ecuador	2012
Kaplinski et al., 2015	Sustained Domestic Vector Exposure Is Associated with Increased Chagas Cardiomyopathy Risk but Decreased Parasitemia and Congenital Transmission Risk Among Young Women in Bolivia	*Clinical Infectious Diseases*/8.736	Bolivia	2010-2013
Volta et al., 2015	Diagnosis of congenital *Trypanosoma cruzi* infection: A serologic test using Shed Acute Phase Antigen (SAPA) in mother-child binomial samples	*Journal Acta Tropica*/2.380	Argentina (Buenos Aires)	2008-2011
Luquetti et al., 2015	Congenital transmission of *Trypanosoma cruzi* in central Brazil. A study of 1,211 individuals born to infected mothers	*Memórias do Instituto Oswaldo Cruz*/1.789	Brazil	1994-2014
Rendell et al., 2015	*Trypanosoma cruzi*-Infected Pregnant Women without Vector Exposure Have Higher Parasitemia Levels: Implications for Congenital Transmission Risk	*PLOS One*/4.411	Bolivia	2010-2011
Moscatelli et al., 2015	Urban Chagas disease in children and women in primary care centres in Buenos Aires, Argentina	*Memórias do Instituto Oswaldo Cruz*/1.789	Argentina (Buenos Aires)	2005-2007
Soriano-Arandes et al., 2014	Controlling congenital and paediatric Chagas disease through a community health approach with active surveillance and promotion of paediatric awareness	*BMC Public Health*/2.209	Spain	2011

Continue...

TABLE 1: Continuation.

Reference	Article	Journal/impact factor	Country	Research time span
Fabbro et al., 2014	Trypanocide treatment of women infected with *Trypanosoma cruzi* and its effect on preventing congenital Chagas	*PLOS Neglected Tropical Disease*/4.446	Argentina	2012-2013
Velázquez et al., 2014	Predictive role of polymerase chain reaction in the early diagnosis of congenital *Trypanosoma cruzi* infection	*Journal Acta Tropica*/2.380	Argentina (Buenos Aires)	2004-2009
Bua et al., 2013	How to improve the early diagnosis of *Trypanosoma cruzi* infection: relationship between validated conventional diagnosis and quantitative DNA amplification in congenitally infected children	*PLOS Neglected Tropical Disease*/4.446	Argentina	2008-2011
Murcia et al., 2013	Risk factors and primary prevention of congenital Chagas disease in a nonendemic country	*Clinical Infectious Diseases*/8.736	Spain	2007-2011
Apt et al., 2013	Congenital infection by *Trypanosoma cruzi* in an endemic area of Chile: a multidisciplinary study	*Transactions of the Royal Society of Tropical Medicine and Hygiene*/1.631	Chile	2006-2009
Duffy et al., 2013	Analytical Performance of a Multiplex Real-Time PCR Assay Using TaqMan Probes for Quantification of *Trypanosoma cruzi* Satellite DNA in Blood Samples	*PLOS Neglected Tropical Disease*/4.446	Argentina	2011-2012
Ortiz et al., 2012	Presence of *Trypanosoma cruzi* in pregnant women and typing of lineages in congenital cases	*Journal Acta Tropica*/2.380	Chile	2006-2010
Otero et al., 2012	Congenital transmission of *Trypanosoma cruzi* in non-endemic areas: evaluation of a screening program in a tertiary care hospital in Barcelona, Spain	*The American Journal of Tropical Medicine and Hygiene*/2.456	Spain	2008-2010
Clavijo et al., 2012	Prevalence of Chagas disease in pregnant women and incidence of congenital transmission in Santa Cruz de la Sierra, Bolivia	*Journal Acta Tropica*/2.380	Bolivia	2006-2008
Barona-Vilar et al., 2012	Prevalence of *Trypanosoma cruzi* infection in pregnant Latin American women and congenital transmission rate in a non-endemic area: the experience of the Valencian Health Programme (Spain)	*Epidemiology and Infection*/2.515	Spain	2009-2010
Cardoso et al., 2012	Maternal fetal transmission of *Trypanosoma cruzi*: a problem of public health little studied in Mexico	*Experimental Parasitology*/1.623	Mexico	2006-2008
Bisio et al., 2011	Urbanization of congenital transmission of *Trypanosoma cruzi*: Prospective polymerase chain reaction study in pregnancy	*Transactions of the Royal Society of Tropical Medicine and Hygiene*/1.631	Argentina (Buenos Aires)	2002-2007
Flores-Chavez et al., 2011	Surveillance of Chagas disease in pregnant women in Madrid, Spain, from 2008 to 2010	*Eurosurveillance*/5.98	Spain	2008-2010
Romero et al., 2011	Door-to-door screening as a strategy for the detection of congenital Chagas disease in rural Bolivia	*TM & IH. Tropical Medicine and International Health*/2.519	Bolivia	2004-2007
Brutus et al., 2010	Detectable *Trypanosoma cruzi* Parasitemia during Pregnancy and Delivery as a Risk Factor for Congenital Chagas Disease	*The American Journal of Tropical Medicine and Hygiene*/2.453	Bolivia	2004-2005
Rissio et al., 2010	Congenital *Trypanosoma cruzi* Infection. Efficacy of Its Monitoring in an Urban Reference Health Center in a Non-Endemic Area of Argentina	*The American Journal of Tropical Medicine and Hygiene*/2.453	Argentina	1994-2004
Mallimaci et al., 2010	Early diagnosis of congenital *Trypanosoma cruzi* infection, using shed acute phase antigen, in Ushuaia, Tierra del Fuego, Argentina	*The American Journal of Tropical Medicine and Hygiene*/2.453	Argentina	2001-2002
Apt et al., 2010	Vertical transmission of *Trypanosoma cruzi* in the Province of Choapa, IV Region, Chile. Preliminary Report (2005-2008)	*Biological Research*/1.328	Chile	2006-2008
Bern et al., 2009	Congenital *Trypanosoma cruzi* Transmission in Santa Cruz, Bolivia	*Clinical Infectious Diseases*/8.736	Bolivia	2006-2007
Diez et al., 2008	The Value of Molecular Studies for the Diagnosis of Congenital Chagas Disease in Northeastern Argentina	*The American Journal of Tropical Medicine and Hygiene*/2.453	Argentina	ND
Brutus et al., 2008	Congenital Chagas disease: Diagnostic and clinical aspects in an area without vectorial transmission, Bermejo, Bolivia	*Journal Acta Tropica*/2.380	Bolivia	2002-2004
Salas et al., 2007	Risk factors and consequences of congenital Chagas disease in Yacuiba, south Bolivia	*TM & IH. Tropical medicine and International Health*/2.519	Bolivia	2003-2005

ND: not determined.

TABLE 2: Epidemiological aspects of congenital Chagas disease in selected articles.

Reference	Sample size (child)	Incidence of congenital transmission	Endemic area?	Maternal nationality
Murcia et al., 2017	160	10%	No	Bolivia
Buekens et al., 2017	503	0% Honduras, 6.6% Argentina, and 6.3% Mexico	Yes	Honduras, Argentina, Mexico
Montes-Rincón et al., 2016	20	20%	Yes	Mexico
Vargas et al., 2015	1649	ND	Yes	Ecuador
Kaplinski et al., 2015	1000	6.8%	Yes	Bolivia
Volta et al., 2015	91	23%	No	69.23% Argentina; 18.68% Bolivia; 12% Paraguay
Luquetti et al., 2015	1212	1.98%	Yes	Brazil
Rendell et al., 2015	135	11.7%	Yes	Bolivia
Moscatelli et al., 2015	19	Varied	Yes	58.7% Argentina; 17% Bolivia; 12.4% Peru; 10% Paraguay
Soriano-Arandes et al., 2014	42	6.9%	No	90.5% Bolivia
Fabbro et al., 2014	354	15.3%	No	85% Argentina; 10% Bolivia; 4% Paraguay
Velázquez et al., 2014	468	10.47%	No	63.5% Argentina; 26.8% Bolivia; 8.2% Paraguay
Bua et al., 2013	843	11.27%	No	60% Argentina; 35% Bolivia; 5% Paraguay
Murcia et al., 2013	65	13.8%	No	96.6% Bolivia; 3.4% Paraguay
Apt et al., 2013	4280	4.7%	Yes	Chile
Duffy et al., 2013	74	4.05%	Yes	Argentina
Ortiz et al., 2012	100	3%	Yes	Chile
Otero et al., 2012	20	5%	No	34% Equador; 18% Bolivia; 13% Peru
Clavijo et al., 2012	3579	3.4%	Yes	ND
Barona-Vilar et al., 2012	217	14.15%	No	30% Equador; 21.7% Bolivia, 17.8% Colombia; 6.4% Argentina
Cardoso et al., 2012	106	4.7%	Yes	ND
Bisio et al., 2011	83	2.6%	No	37.5% Argentina; 24% Bolivia; 23.1% Paraguay; 1% Peru; 14.4% indeterminate
Flores-Chavez et al., 2011	152	5%	No	44.4% Bolivia
Romero et al., 2011	299	7.48%	Yes	Bolivia
Brutus et al., 2010	147	6.1%	Yes	Bolivia
Rissio et al., 2010	4355	4.4%	Yes	Argentina
Mallimaci et al., 2010	68	2.5%	Yes	Argentina
Apt et al., 2010	80	2.5%	Yes	Chile
Bern et al., 2009	138	6.4%	Yes	Bolivia
Diez et al., 2008	121	9.9%	Yes	Argentina
Brutus et al., 2008	231	5.2%	Yes	Bolivia
Salas et al., 2007	2742	5.1%	Yes	Bolivia

ND: not determined.

emphasized that continuous research is extremely important for an understanding of the biological and clinical aspects of a disease and is dependent on the interest of development agencies and the scientific community. Regarding CD, one of the most widespread diseases in the Americas, significant advances in different areas are still lacking, such as the knowledge of its pathogenesis, the development of new treatments, and the follow-up of congenital transmission cases[10-13]. Such limitations are associated with the fact that CD presents important sociocultural and political-economic aspects that do not attract investments.

Few are the well-qualified journals that currently contribute significantly to the dissemination of scientific research on CD.

Our review identified articles in 12 different journals with impact factors between 1.631 and 8.736, suggesting a lack of interest of the scientific community in the topic. Only 10% of the articles were published in journals with an impact factor greater than 5.0. As trypanosomiasis occurs mainly in one of the poorest parts of the world, it does not have the same repercussion as other more widely distributed protozoa, such as malaria. Therefore, it represents a regional problem, naturally generating greater interest only in Latin America. This, in turn, explains why most of the studies were conducted in Argentina and Bolivia. Nevertheless, there was some interest in the subject in Spain, the only European country with identified articles (five). The increased interest in non-endemic areas may be associated with a greater occurrence of CD congenital transmission in these localities owing to extensive migration, reaching European and Asian countries as well as cities and states without vector transmission[3,14].

Among the endemic localities, Bolivia was the country with the most studies performed as well as the country with the greatest impact on congenital transmission in non-endemic areas, which corroborates the fact that the largest number of immigrants in Europe with CD are Bolivians[3]. Strangely enough, only one study fulfilling the pre-defined criterion was carried out in Brazil. According to the 2nd Brazilian Consensus on CD, although Brazil has advanced in vector and blood bank control, over the years, Brazil has had few published studies on CD, making it difficult to systematize data on this topic[15]. Despite being considered a compulsory notification disease, according to the Brazilian Consensus, Brazil does not provide any specific surveillance of pregnant women or children.

On the other hand, even though CD does not receive the desired attention, it has an important role in the maturing Latin American scientific community, which has been responsible for the main findings of this disease, including its discovery. Thus, we expect CD to continue to be a driving force in Latin American research, helping to solve social problems and contributing to expand the knowledge about this endemic disease.

Conflicts of Interest: The authors declare that there is no conflict of interest.

REFERENCES

1. World Health Organization. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec. 2015;(6):33-44.
2. Bern C. Chagas' Disease. New Engl J Med. 2015; 373(5):456-66.
3. Requena-Méndez A, Aldasoro E, de Lazzari E, Sicuri E, Brown M, Moore DAJ, et al. Prevalence of Chagas Disease in Latin-American Migrants Living in Europe: A Systematic Review and Meta-analysis. PLoS Negl Trop Dis. 2015;9(2):1-15.
4. Westphalen EVNA, Bisugo MC, Araújo M de FL. Aspectos epidemiológicos e históricos do controle da doença de Chagas no Continente Americano. Secretaria de Saúde de São Paulo. 2012;9(105):17-34.
5. Brutus L, Schneider D, Postigo J, Romero M, Santalla J, Chippaux J. Congenital Chagas disease: Diagnostic and clinical aspects in an area without vectorial transmission, Bermejo, Bolivia. Acta Trop. 2008;106(3):195-9.
6. Chagas C. Moléstia de Carlos Chagas ou thyreoidite parasitaria: nova doença humana transmitida pelo barbeiro (*Conorhinus megistus*). Conferência realizada perante a Associação Medico Cirúrgica de Minas Gerais na sessão solene de 30 de julho de 1911. Rio de Janeiro: Manguinhos. 1911; 20 p.
7. Dias JCP, Amato Neto V. Prevention concerning the different alternative routes for transmission of *Trypanosoma cruzi* in Brazil. Rev Soc Bras Med Trop. 2011;44(Suppl 2):68-72.
8. Carlier Y, Sosa-Estani S, Luquetti AO, Buekens P. Congenital Chagas disease: An update. Mem Inst Oswaldo Cruz. 2015;110(3):363-8.
9. Rodriguez JB, Falcone BN, Szajnman SH. Detection and treatment of *Trypanosoma cruzi:* a patent review (2011-2015). Expert Opin Ther Pat . 2016;26(9):993-1015.
10. De Rissio AM, Riarte AR, García MM, Esteva MI, Ruiz AM, Quaglino M. Congenital *Trypanosoma cruzi* infection. Efficacy of its monitoring in an urban reference health center in a non-endemic area of Argentina. Am J Trop Med Hyg. 2010;82(5):838-45.
11. Flores-Chavez M, Merino F, Garcia-Bujalance S, Martin-Rabadan P, Merino P, Garcia-Bermejo I, et al. Surveillance of Chagas disease in pregnant women in Madrid (Spain), 2008-2010. Trop Med Int Heal. 2011;16:368.
12. Salas NA, Cot M, Schneider D, Mendoza B, Santalla JA, Postigo J, et al. Risk factors and consequences of congenital Chagas disease in Yacuiba, south Bolivia. Trop Med Int Heal. 2007;12(12):1498-505.
13. Salas NA, Postigo JR, Schneider D, Santalla JA, Brutus L, Chippaux JP. Prevalence of Chagas disease in pregnant women and incidence of congenital transmission in Santa Cruz de la Sierra, Bolivia. Acta Trop. 2012;124(1):87-91.
14. Angheben A, Anselmi M, Gobbi F, Marocco S, Monteiro G, Buonfrate D, et al. Chagas disease in Italy: Breaking an epidemiological silence. Eurosurveillance. 2011;16(37):1.
15. Dias JCP, Novaes Ramos A, Dias Gontijo E, Luquetti A, Aparecida Shikanai-Yasuda M, Rodrigues Coura J, et al. II Consenso Brasileiro em Doença de Chagas, 2015. Epidemiol e Serviços Saúde. 2016;25(21):1-10.