



Published in final edited form as:

BJOG. 2014 January ; 121(1): 22–33. doi:10.1111/1471-0528.12396.

Frequency of the Congenital Transmission of *Trypanosoma cruzi*: A Systematic Review and Meta-Analysis

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Abstract

Background—Chagas disease is caused by the parasite *Trypanosoma cruzi* and endemic in much of Latin America. With increased globalization and immigration, it is a risk in any country due in part to congenital transmission. The frequency of congenital transmission is unclear.

Objective—To assess the frequency of congenital transmission of *T. cruzi*.

Search Strategy—PubMed, Journals@Ovid Full Text, EMBASE, CINAHL, Fuente Academica and BIREME databases were searched using seven search terms related to Chagas disease or *Trypanosoma cruzi* and congenital transmission.

Selection Criteria—The inclusion criteria were the following: Dutch, English, French, Portuguese or Spanish language; case report, case series or observational study; original data on

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Disclosure of Interests

There are no conflicts of interest to disclose.

Contribution to Authorship

EJH conceived the original idea for the article, analyzed the data and wrote the article. XX contributed to the writing of the article and provided methodological expertise. YC and SSE contributed to the writing of the article and the interpretation of the findings. PB participated in data collection, decision-making, and the writing of the article.

Details of Ethics Approval

The procedures of this study received ethics approval from the Tulane University Biomedical Institutional Review Board on January 10, 2013 (Reference Number: 12-412895E).

congenital *T. cruzi* infection in humans; congenital infection rate reported or it could be derived. This systematic review included 13 case reports/series and 51 observational studies.

Data Collection and Analysis—Two investigators independently collected data on study characteristics, diagnosis and congenital infection rate. The principal summary measure – the congenital transmission rate – is defined as the number of congenitally infected infants divided by the number of infants born to infected mothers. A random effects model was utilized.

Main Results—The pooled congenital transmission rate was 4.7% (95% confidence interval: 3.9–5.6%). Endemic countries had a higher rate of congenital transmission compared to non-endemic (5.0% vs. 2.7%).

Conclusions—Congenital transmission of Chagas disease is a global problem. Overall risk of congenital infection in infants born to infected mothers is about 5%. The congenital mode of transmission requires targeted screening to prevent future cases of Chagas disease.

Keywords

Trypanosoma cruzi; congenital infection; Chagas disease; systematic review; meta-analysis

Introduction

Chagas disease, or American trypanosomiasis, is caused by the protozoan parasite *Trypanosoma cruzi*. It is a major cause of morbidity and mortality in the Americas and an estimated 9 million persons are currently infected.^{1,2} *T. cruzi* is primarily transmitted by the Triatomine insect vector (also called the kissing bug), blood transfusion, organ transplant, congenital infection and oral transmission from food contaminated with insect feces.³ Reductions in vector-borne transmission risk in many countries due to large-scale vector control⁴ have focused attention on other modes of transmission such as congenital transmission. This mode of transmission is of concern worldwide, due to the migration of people from Chagas endemic countries of Latin America.⁵

The majority of pregnant women with Chagas is chronically infected and asymptomatic but may be at increased risk of preterm birth, low-birth weight and stillbirth.⁶ Infected newborns can develop a symptomatic infection (congenital Chagas disease) after birth characterized by hepato-splenomegaly, meningoencephalitis, myocarditis, anasarca or anemia; however, the majority of infants present with asymptomatic congenital *T. cruzi* infection, making it highly unlikely they will be diagnosed unless the presence of the infection is specifically sought. As many as 30% of infected infants will progress to the life-threatening cardiac or digestive chronic stages of the disease.^{6,7} Additionally, female infants may perpetuate the multigenerational, vertical transmission of Chagas disease.⁶

Congenital *T. cruzi* transmission cannot be prevented by treating a mother during pregnancy since the teratogenic risks of anti-parasitic treatment (benznidazole and nifurtimox) are not well known and the risk of adverse reactions is high in adults.⁸ However, infected newborns diagnosed and treated during the first year of life have nearly a 100% chance of parasitological cure and low risk of adverse events.^{8–12} Thus, active screening of pregnant women from endemic areas and early screening of infants is particularly important in improving health outcomes of infants.

The rate of transmission from infected mother to infant remains to be summarized quantitatively. In the Southern Cone countries of Latin America (the endemic region), the reported rates of congenital *T. cruzi* transmission vary from 1% to 12%.¹³ In contrast, very little is known about congenital transmission rates in Mexico, Central America⁶ and in non-

endemic countries. A theoretical study estimated that about 40,000 pregnant women and 2,000 newborns could be infected by *T. cruzi* in Canada, Mexico and the United States.¹⁴

Understanding the frequency of congenital *T. cruzi* transmission is important for the continued implementation of screening for pregnant women and early treatment programs for infected newborns. The objectives of this study are to calculate a pooled congenital transmission rate and to describe the rate of transmission by the endemicity of the region and the method of diagnosis of congenital infection. This study systematically reviews the literature for original observational studies and case reports that describe the frequency of congenital *T. cruzi* transmission.

Methods

Eligibility Criteria

The study population consisted of pregnant or recently pregnant women who are infected with *T. cruzi* and their infants. The objective is to assess how often the outcome - congenital transmission of the parasite to their infants – is occurring. Studies included in this systematic review and meta-analysis have different methods of diagnosing congenitally transmitted *T. cruzi* infection in infants. Definitive diagnosis can be made using one or a combination of the following two techniques: (i) parasitological examination of umbilical cord blood or venous blood of the infant at any time after birth and (ii) detecting *T. cruzi*-specific antibodies using serological tests on an infant's blood sample >8 months of age (when maternal antibodies have disappeared).⁸ Other methods of diagnosis sometimes employed or combined with the methods above are polymerase chain reaction (PCR) of the umbilical cord or infant blood sample, hemoculture and xenodiagnosis.

All published research was considered regardless of publication type (e.g. abstract, poster, and article). We included prospective and retrospective observational study designs, as well as case reports. There were no restrictions on time period or limits placed on language at the time of the search, which was completed on October 24, 2012.

Information Sources & Search Strategy

The databases PubMed, Journals@Ovid Full Text, EMBASE, CINAHL (EBSCO), Fuente Academica (EBSCO) and BIREME were chosen for the literature search so as to include as many Latin American studies as possible. The search terms used were “Trypanosoma cruzi OR Chagas AND transmission AND pregnancy,” “congenital AND Trypanosoma cruzi infection,” “congenital AND Chagas infection,” “vertical transmission AND Trypanosoma cruzi,” “vertical transmission AND Chagas,” “maternal fetal transmission AND Trypanosoma cruzi,” and “maternal fetal transmission AND Chagas.”

Refworks was used to merge retrieved citations and eliminate duplicates. Authors were contacted if the full-text article could not be acquired by library services or when there were questions about the study's methods.

Study Selection Criteria

The following inclusion/exclusion criteria were used to select the studies: (i) study is in Dutch, English, French, Portuguese, Spanish; (ii) study is a case report, case series, or observational study (i.e., case-control, cross-sectional, cohort); (iii) study presents original data on congenital *T. cruzi* infection in humans; (iv) the congenital infection rate was reported or it could be derived from data presented. Review articles and articles that employed only placental histopathology as a method of diagnosis were excluded because the

placental defenses are able to contend parasitic infection before it occurs in the neonate. The presence of parasites in the placenta does not confirm a congenital infection.⁶

All database search results were considered for inclusion. First, duplicate records were removed. Abstracts were reviewed to determine study eligibility, based upon the above inclusion criteria. Finally, the full-text of the studies was compiled for final review. In an effort to exclude articles with overlapping cohorts, all of the articles' study populations, time periods, and sample sizes were reviewed, given our knowledge of the co-authors and affiliations. When articles with duplicate data were discovered, the article with the greatest sample size was chosen for inclusion.

Data Collection Process & Data Items

A data abstraction form was created *a priori* and information relevant to the study research question was extracted independently by two investigators. Where there were data discrepancies, the investigators met for discussion until a consensus was made. The following data was collected: author, publication year, and country, sample size, study design (case report, case series, or comparative), study setting (hospital, multi-hospital, population, multi-national, etc.), characteristics of the study (country, endemic/non-endemic), method of diagnosis of congenital infection (e.g. parasitology, serology, PCR), timing of diagnosis (e.g. birth, 8 months, 1 year of age), origin of the diagnostic blood sample (e.g. umbilical cord, heel prick, venous blood), and the congenital infection rate (or the data required to calculate it).

Comparative studies were distinguished as prospective or retrospective observational studies. Non-endemic countries are defined as those where vector transmission to man either does not occur or remains limited, as in the United States, Canada and European countries.

Bias Assessment

Study quality was assessed through stratification of studies during subgroup analysis. A Begg's funnel plot of the natural logarithm of the rates versus their standard errors was used to assess for publication bias. An Egger's regression test was also conducted.

Data Analysis

The principal summary measure is the congenital transmission rate, which is defined as the number of congenitally infected infants divided by the number of infants born to infected mothers. Where the transmission rate was not reported, the investigators calculated one from the information reported. Case reports and case series were not included in the calculation of a summary statistic. If the number of events and sample size could not be calculated, the study could not be included in the meta-analysis.

The pooled congenital transmission rates and 95% confidence intervals (CI) were first calculated using a fixed effects model. The heterogeneity between studies was assessed with the Dersimonian and Laird's Q test and I² statistic.¹⁵ A random effects model was used based on the results.

Two subgroup analyses were planned *a priori* considering the diagnostic method and endemicity. In the first subgroup analysis, the studies were stratified into three groups based on the diagnostic method that was used when diagnosing the congenital infection: (i) parasitology at any time and/or serology after 8 months of age (the reference standards), (ii) PCR and (iii) mixed or other methods. Any studies that performed the serological tests before 8 months of age (without parasitology) were classified in the "mixed or other methods" category due the possible presence of maternal antibodies and thus false positive

tests.¹⁶ If the study reported multiple congenital transmission rates by different methods of diagnosis, we averaged the method-specific rates for inclusion in the pooled analysis and used the separated results in the appropriate subgroup analysis. For the second subgroup analysis, the studies were compared by the endemicity of the country or region in which the study was completed. This is important because individuals in non-endemic countries will have no exposure/re-exposure to vector transmission, the primary mode of transmission, thus decreasing the mother's parasite load. A sensitivity analysis assessed the effect of excluding studies that reported zero outcomes (congenital infections).

All statistical analyses were performed within Microsoft Excel using a previously constructed spreadsheet for generating a descriptive summary statistic and forest plots.¹⁷ We have adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist for reporting.^{18,19}

Results

Of the 256 abstracts retained after duplicates were removed, 96 were excluded because the abstracts indicated the research was not a qualifying study design (case report, case series, or comparative study) or was not completed in humans. One hundred sixty full-text articles were assessed for eligibility. Ninety-five articles did not qualify for inclusion for the following reasons: unoriginal data, not about congenital transmission of Chagas, or an inability to calculate a rate from the data presented. Thirteen studies were case-reports or case series. One study could not be included in the meta-analysis because the number of events and sample size were not reported and could not be calculated. The systematic review and meta-analysis included 64 and 51 articles, respectively (Figure 1).

Eleven case reports and two case series for a total of 14 congenital infections out of 18 births are described in Table 1. Six of the reports are from non-endemic countries.²⁰⁻²⁵ One case report summarized diagnosis in two of three triamniotic, dichorionic infants sharing a placenta, which lends support to the placental mode of transmission.²⁶ Most of the diagnoses were made at birth or within one month of age (n=8); however, timing of diagnosis ranged from prenatal²⁷ to 7 years of age.²⁸ The method of diagnosis was mixed in all but one case, where only serology was used.²⁹ Nine case reports included direct microscopy in combination with serology, PCR, culture, xenodiagnosis, and/or symptomatology.

Twenty-one of the 51 observational studies were conducted in non-endemic countries, with the majority (86%) from Spain. All but five of the studies used a prospective study design. Five studies of the 51 studies provided more than one estimate of congenital transmission by different methods of diagnosis. Twenty-two studies (43%) diagnosed congenital *T. cruzi* infection according to the reference standard: direct microscopy at any age and/or serology at >8 months of age. PCR only was used by nine of the studies to assess the rate of congenital infection. The remainder (n=27) made the diagnosis with other or mixed methods, including one or a combination of direct microscopy, serology, PCR, hemoculture, and xenodiagnoses. Sample sizes varied greatly from 1^{30,31} to 4377 infants,³² while the number of diagnosed congenital cases ranged from 0 (n=13 studies) to 267 infants.³² After excluding the studies without congenital infections, the congenital transmission rates ranged from 0.75%³³ to 28.6%.³⁴ Characteristics of the observational studies included in the meta-analysis are presented in Table 2.

Meta-analysis

Fifty-one studies were selected for inclusion in the meta-analysis. A fixed effects method of analysis did not fit the data well, therefore, a random effects model was used with a continuity correction of 0.5 added to each study with zero events ($Q=45.5$, $P<0.01$, $I^2=0$, $df=50$). We estimated a pooled congenital *T. cruzi* transmission risk of 0.047 (95% CI: 0.039–0.056) or 4.7% (95% CI: 3.9–5.6%) (Figure 2).

Subgroup & Sensitivity Analyses

The method of diagnosis subgroup analysis resulted in pooled, random effects estimates of 4.6% (95% CI: 3.4–5.7%) for the reference standard, 6.0% (95% CI: 4.3–7.7%) for PCR, and 4.5% (95% CI: 3.4–5.5%) for mixed/other methods of diagnosis. Countries or regions that are disease endemic with the potential for vector transmission were almost two times as likely to have congenital transmission (5.0% vs. 2.7%). Removing the studies that reported no cases of congenital transmission slightly increased the pooled estimate of congenital infection risk compared to leaving the study in and adding a continuity correction (4.8% vs. 4.7%). The results of the subgroup and sensitivity analyses and their accompanying heterogeneity statistics can be found in Table 3.

Bias Assessment

The 51 estimates of *T. cruzi* congenital transmission were used to generate a Begg's funnel plot to assess for publication bias. This visual plot (Figure 3) shows a symmetrical distribution of points (natural log transformed rates plotted against the standard error of the rates). The plot and non-significant Egger's regression test ($p=0.20$) indicate a lack of publication bias.

Discussion

Main Findings

This systematic review included 13 case reports or case series and 51 observational studies. We found a pooled rate of congenital transmission of 0.047. This means that in a population of *T. cruzi* infected mothers, 5% of the infants may be congenitally infected. This finding is consistent with the widely accepted 1–12% range of congenital transmission rates that is frequently reported in the literature.¹³ When studies with zero cases of congenital transmission were excluded, the rate increased to 4.8% (95% CI: 4.0–5.7%) of infants. Subgroup analysis by method of diagnosis found the greatest rate of transmission among studies that used PCR, followed by direct microscopy and/or serology, and finally, mixed or other techniques (6.0% vs. 4.6% vs. 4.5%, respectively). Studies conducted in endemic countries or regions compared to non-endemic were more likely to find a higher rate of congenital transmission (5.0% vs. 2.7%).

Interpretation

Our subgroup analysis estimate for studies that used direct parasitology and/or serology after 8 months for diagnosis represents a conservative estimate of the rate of congenital transmission of *T. cruzi* (4.6% (95% CI: 3.4–5.7%)). Direct parasitological methods are highly specific and definitively confirm congenital infection, but they can have a lower sensitivity due to low parasitemia or an inexperienced technician.^{6,35} Additionally, loss to follow-up results in fewer additional blood samples for microscopy detection and confirmatory serology. Bern and colleagues estimated that one-half of all congenital infections are missed.³⁵

The pooled congenital transmission rate for studies utilizing PCR for diagnosis was higher than that of the subgroup that used direct microscopy and/or serology (6.0% vs. 4.6%). This finding is supported by recent literature suggesting that PCR is more sensitive and detects congenital infections earlier than conventional techniques.^{10,36,37} However, PCR has not yet been validated for clinical diagnosis of congenital infection.⁸ Positive PCR results on infant blood indicate fetal exposure to *T. cruzi*, however, trace amounts of parasite DNA, derived from lysed parasites, may also trigger a positive test result. Additionally, it has been suggested that some infected fetuses may be able to “self-cure” their infection.⁶ Therefore, a positive PCR result at birth can hardly be interpreted as indicative of an active infection. Indeed, a positive PCR result can indicate an active infection, but this is not obligatory, especially when only traces are detected. Direct examination and/or late serology after 8 months of age are needed to confirm congenital infection.⁸

Infected mothers can be either in the acute phase (a recent infection displaying mild or no symptoms), characterized by easily detectable parasitemia, or the chronic phase where relatively few parasites can be found in the blood. Although most studies did not report the mothers’ phase of infection, most mothers in our included studies were likely in the chronic phase since the acute phase only lasts a few months. Interestingly, the case series by Moretti and colleagues reports three cases of acute maternal infection with one case of congenital transmission occurring from a mother infected earlier in pregnancy.³⁸ Other studies report that mothers of infected infants had higher parasite loads than seropositive mothers of uninfected infants.^{35,39,40}

On a similar note, during pregnancy, the maternal immune system becomes temporarily depressed in order to prevent fetus rejection and continue the pregnancy.⁴¹ Mothers who transmit *T. cruzi* have lower specific T-cell-mediated immune responses and produce less interferon gamma (IFN- γ). This immune modulation could favor higher parasitemias in the mothers and the subsequent congenital transmission.³⁹ A strongly depressed immune system may be responsible for the 100% congenital transmission rate observed among infants born to HIV positive mothers (3 of 3) in our included study by Scapellato and colleagues.⁴²

Reduction of parasitemia and prevention of future congenital transmission may be feasible through the etiological treatment of infected young women prior to pregnancy.⁴³ In this study by Sosa-Estani and colleagues, which diagnosed congenital infection using the reference standard, no cases of congenital infection were found in 32 infants born to 16 women previously treated with benznidazole.

In this analysis, studies of infants born in endemic countries were more likely to find congenital transmission in their population. This may be partly due to vector transmission in infants during the first few months after birth that are incorrectly attributed to congenital transmission. Further analysis of the studies that used only direct microscopy in the first few days of life (n=6) was not possible since all of the studies were in endemic regions (i.e. no comparison rate could be calculated for non-endemic regions). However, more probable is that continued exposure to infected vectors in endemic regions contributes to increases in maternal parasitemia, which results in an increased risk of congenital transmission.^{38,39,44–46} In the absence of vectors and infected blood transfusions, the propagation of *T. cruzi* infection is dependent upon transgenerational vertical transmission. Burgos and colleagues described a case of triplets where two of the infants who shared a placenta were born congenitally infected.²⁶ Familial clustering has also been described elsewhere.^{6,9,47–50}

The included studies from non-endemic countries had a wider range of rates (0–28.6%) compared to the endemic regions (0–17%), which may be the result of a combination of

smaller sample sizes and random chance, but may also be related to the country of origin of the immigrants in these non-endemic countries. Further research in this area is necessary. Additionally, there is a paucity of studies on the congenital transmission of *T. cruzi* in Central America in the literature. This meta-analysis only identified two studies from Mexico, both of which were very small. Therefore, the pooled transmission rate may not describe the situation in Central America and Mexico, or other regions under-represented in the literature.

Strengths and Limitations

The strengths of this systematic review include searching databases that are primarily devoted to Latin American research and performing strict sub-group analyses by the method of diagnosis. Also, there was no indication of publication bias which supports our thorough search strategy. The limitations are that we did not always have explicit method and timing of diagnosis information, which meant that some studies which may have used the reference standard were included in the mixed/other subgroup analysis. Similarly, we did not stratify the studies that used PCR by the age at which the test was done which may have resulted in some heterogeneity. Often, the age at which the blood sample was taken for PCR analysis was not stated.

A quality assessment of the selected studies was not completed due to lack of variation in key indicators of quality. For instance, all the studies were observational; there were no randomized trials and since the meta-analysis utilized rates, not ratios, there are no unexposed groups to assess. Additionally, the outcome assessment for all studies was objectively assessed even though the methods of diagnosis may have been different.

Another important limitation is the possibility of duplication of data. However, the included studies' methods were thoroughly reviewed for overlapping study populations and articles were excluded as necessary. Even with studies from different time periods, it is possible that the same women may be included in more than one study during different pregnancies, as may be the case with the two studies by de Rissio and colleagues.^{32,51} Lastly, vector transmission cannot be ruled out as a source of infant infection in many of our included studies from endemic regions. This is a problem intrinsic to all studies diagnosing congenital *T. cruzi* infection, except those diagnosing infection with direct parasitological methods at birth.

Conclusion

Congenital transmission of Chagas disease is a global problem. The subgroup and sensitivity analyses provide confidence that congenital infection is occurring in about 5% of infants born to infected mothers. Countries or regions that are disease endemic with the potential for vector transmission to man may be more likely to have congenital transmission. While continued vector control activities and surveillance of blood and tissue banks is beneficial, the congenital mode of transmission requires targeted screening in order to prevent future cases of Chagas disease.

Acknowledgments

We acknowledge and thank Dr. Tanika Kelly for her advice and expertise regarding meta-analysis methods.

Funding

The project described was supported by Grant Number R01AI083563 from the National Institute of Allergy And Infectious Diseases and by Award Number T32HD057780 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development. The content is solely the responsibility of the authors and does not

necessarily represent the official views of the National Institute of Allergy And Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health & Human Development or the National Institutes of Health. There was also support from the Maternal & Child Health Epidemiology Doctoral Training Program by Award Number T03MC07649 from the Health Resources and Services Administration/Maternal Child Health Bureau.

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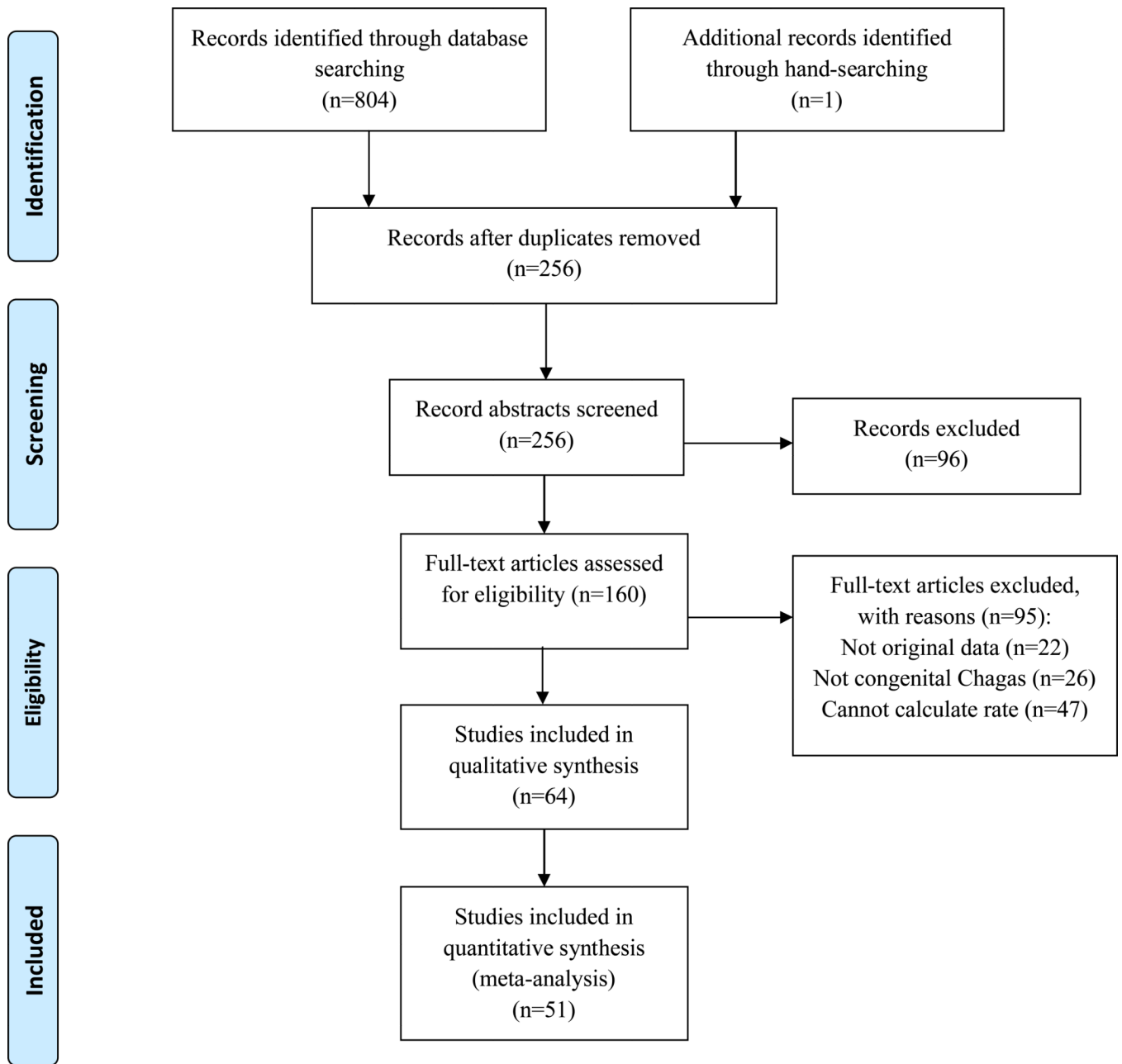


Figure 1.
PRISMA flow diagram of study selection process.

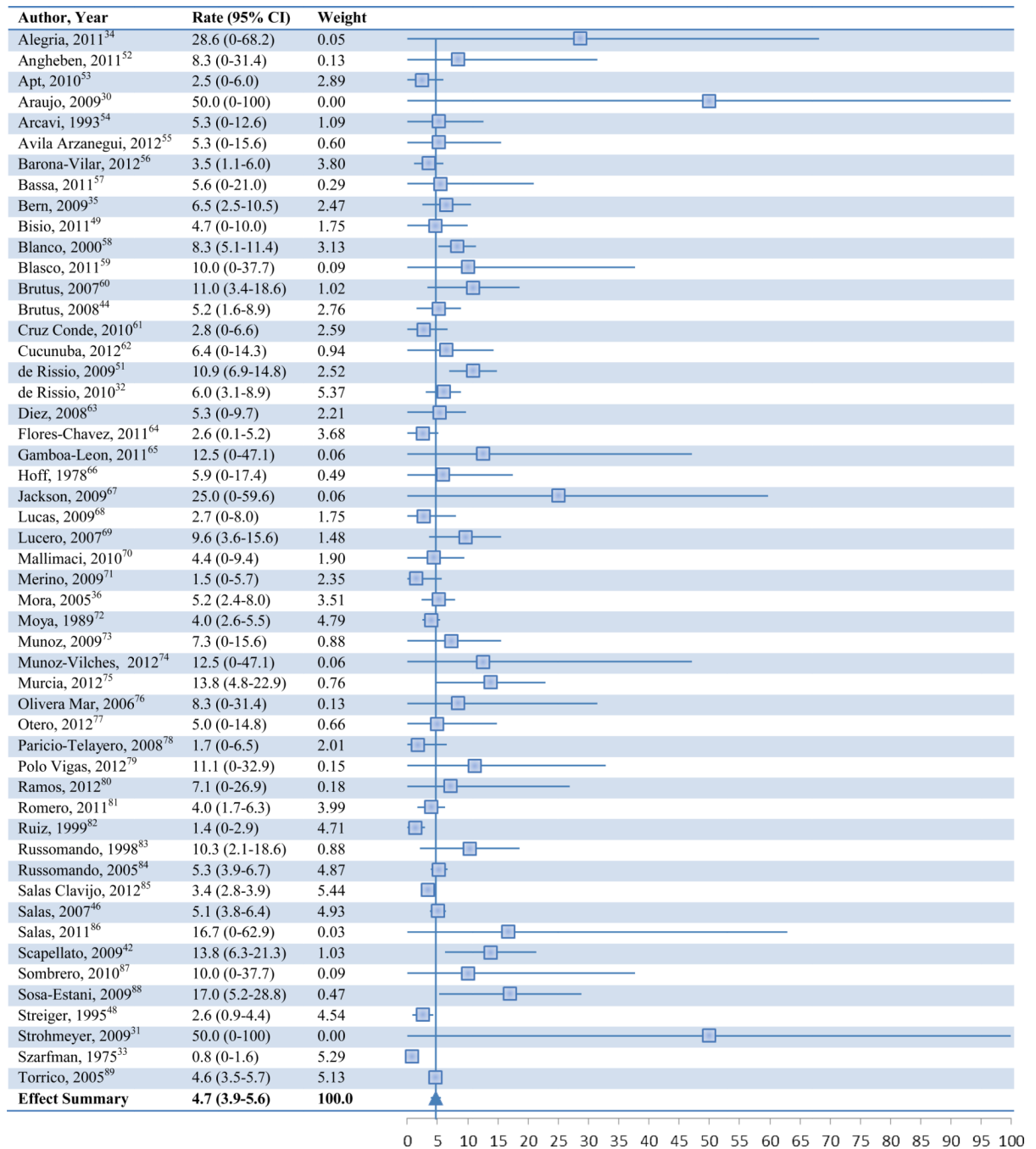


Figure 2. Forest plot of congenital *T. cruzi* transmission rates of the included studies and effect summary. A random effects model was used with a continuity correction of 0.5 added to each study with zero events ($Q=45.5$, $P<0.01$, $I^2=0$, $df=50$). The effect summary includes 51 estimates of congenital transmission, for a total of 819 cases of congenital transmission from 16,537 infants of infected mothers.

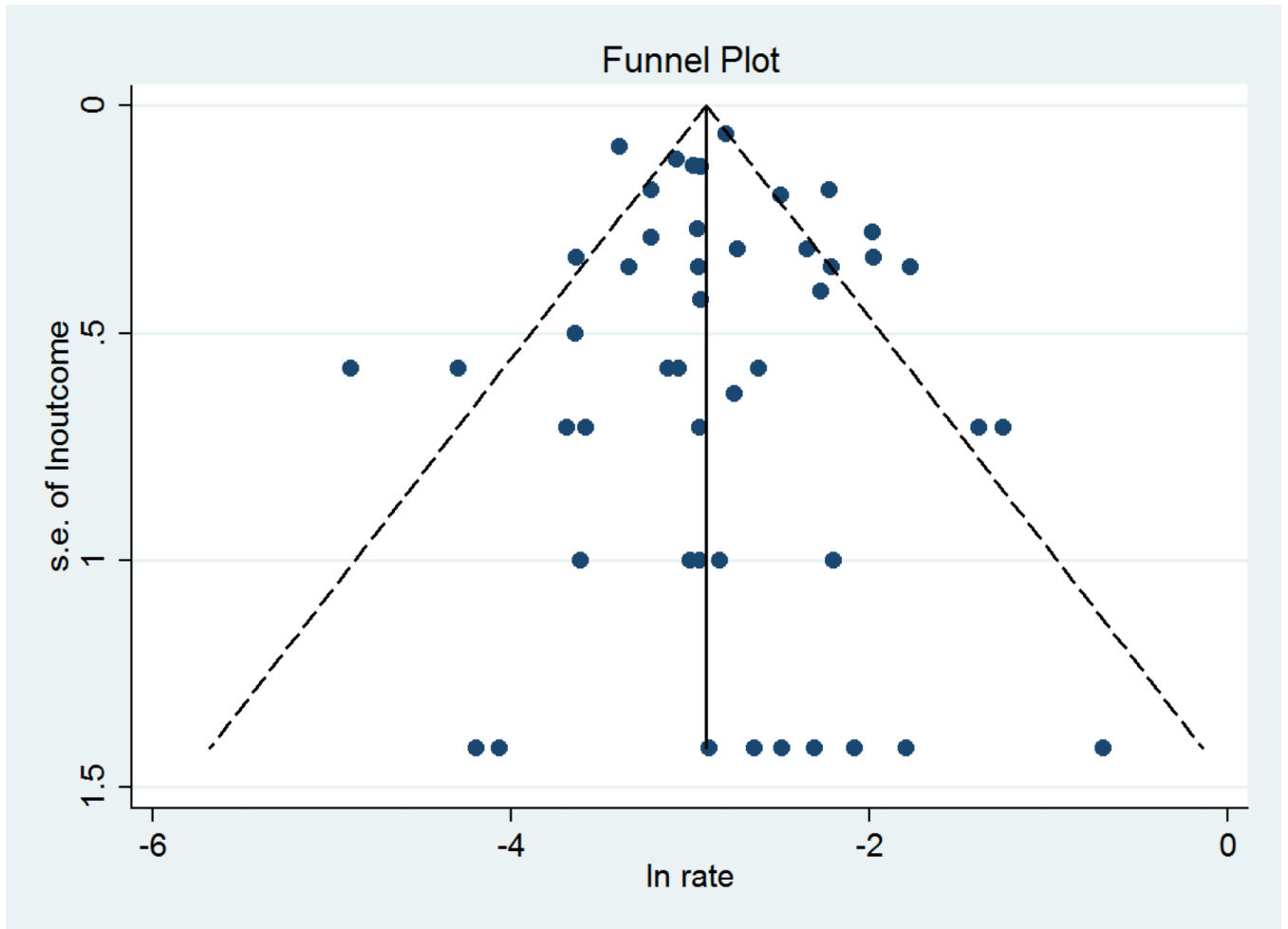


Figure 3. Funnel plot, using data from 51 studies of the rate of *T. cruzi* congenital transmission plotted against the standard error of the rate.

Table 1
 Characteristics of selected case reports and case series that describe congenital *T. cruzi* infection

Author, Publication Year	Country	Sample Size	Study Design	Study Setting	Method of diagnosis of congenital infection	Timing of diagnosis
Burgos, 2009 ²⁶	Argentina	2 of 3 triplets	Case report	Hospital	microhematocrit, serology (IHA, ELISA), PCR	16 days (MH), 30 days (MH), 7 months (S)
Da-Costa-Pinto, 2001 ²⁸	Brazil	1/1	Case report	Hospital	symptoms, serology, xenodiagnosis	7 years
Fiss, 2010 ²⁹	Brazil	1/1	Case report	Hospital	serology	1.5 years
Gilson, 1995 ²¹	United States	0/1	Case report	Hospital	parasitology	birth
Guarro, 2007 ²²	Spain	1/1	Case report	Hospital	parasitology, culture	birth
Jackson, 2009 ²³	Switzerland	2/2	Case series	Hospital	parasitology, PCR	birth
Mansilla, 1999 ³⁰	Argentina	1/1	Case report	Hospital	symptoms, parasitology	2 weeks
Moretti, 2005 ³⁸	Argentina	1/3	Case series	NA	microhematocrit, serology (ELISA, IIF, IHA)	birth
Munoz, 2007 ²⁴	Spain	1/1	Case report	Hospital	ELISA × 2, PCR	2 years
Okumura, 2004 ²⁷	Brazil	1/1	Case report	Hospital	parasitology	pregnancy, autopsy
Pavia, 2009 ⁹¹	Colombia	1/1	Case report	Hospital	hemoculture, PCR	2 and 4 months
Riera, 2006 ²⁵	Spain	1/1	Case report	Hospital	microhematocrit, culture, PCR	birth
Voelker, 2012 ⁹²	United States	1/1	Case report	Hospital	parasitology, serology, PCR	2 weeks

NA=information not available; IHA=indirect hemagglutination; ELISA=enzyme immunoassay; PCR=polymerase chain reaction; IIF=indirect immunofluorescence; MH=microhematocrit; S=serology

Table 2

Characteristics of included observational studies of congenital *T. cruzi* infection

First Author, Publication Year	Country	Study setting	Sample Size (B+/B of M+)	Method of diagnosis of congenital infection	Timing of diagnosis	Congenital infection rate	Study weight
Alegria, 2011 ³⁴	Spain	hospital	2/7	microhematocrit, PCR, serology	birth	28.6*	0.05
Angheben, 2011 ⁵²	Italy	multi-hospital	0/6	microhematocrit, PCR, serology	birth, 1 month, 8 months	0	0.13
Apt, 2010 ⁵³	Chile	health centers	2/80	parasitology, serology (IIF, ELISA), PCR	birth	2.5	2.89
Araujo, 2009 ³⁰	Brazil	multi-hospital	0/1	serology	6 months	0	0.00
Arcavi, 1993 ⁵⁴	Argentina	hospital	2*/38	microhematocrit, serology (IIF, IHA)	neonatal period	5.3	1.09
Avila Arzanegui, 2012 ⁵⁵	Spain	hospital	1/19	serology, PCR	birth-1 week (PCR/S), 1 months (PCR), 8-9 months (S)	5.3*	0.60
Barona-Vilar, 2012 ⁵⁶	Spain	multi-hospital	8/226	microhematocrit, serology (IIF, ELISA), PCR × 2 samples	birth (MH/PCR/S), 2-3 months (PCR), 7-9 months (PCR/S), 12 months (S)	3.7	3.80
Bassa, 2011 ⁵⁷	Spain	NA	0/9	PCR	NA	0	0.29
Bern, 2009 ³⁵	Bolivia	hospital	10/154	parasitology, serology (IIF, ELISA), PCR	birth, 7 days, 21 days, 30 days, 90 days, 180 days, 270 days	6.5	2.47
Bisio, 2011 ⁴⁹	Argentina	hospital	3/64	microhematocrit, serology (ELISA, Western Blot)	birth-3 days (MH), 8 months (S)	4.7	1.75
Blanco, 2000 ⁵⁸	Argentina	hospital	26/315	microhematocrit, serology (IHA, ELISA, IIF)	birth-30 days (MH), 3 months, 6 months (MH/S)	7.1	3.13
Blasco, 2011 ⁵⁹	Spain	hospital	0/5	microhematocrit, PCR, serology	birth (MH/PCR), 1 month (MH/PCR), 9 months (PCR/S)	0	0.09
Brutus, 2007 ⁶⁰	Bolivia	population – communities	8/73	serology	6-24 months	11.0*	1.02
Brutus, 2008 ⁴⁴	Bolivia	hospital	8/153	parasitology	birth	5.2	2.76
Cruz Conde, 2010 ⁶¹	Spain	hospital	2/72	PCR or microhematocrit, serology (ELISA/IIF)	birth (PCR/MH), > 7 months (S)	2.7	2.59
Cucunuba, 2012 ⁶²	Colombia	multi-hospital	0/34	hemoculture, serology (ELISA, IIF)	birth-1 year	0	0.94
de Rissio, 2009 ⁵¹	Argentina	multi-hospital	29/267	parasitology, serology (IIF, IHA, ELISA)	birth-1 year	12.8	2.52
de Rissio, 2010 ³²	Argentina	multi-hospital	267/4377*	parasitology, serology × 2 (ELISA, IHA, IIF)	1-12 months (P), 6-12 months (S)	10.9	5.37

First Author, Publication Year	Country	Study setting	Sample Size (B+/B of M+)	Method of diagnosis of congenital infection	Timing of diagnosis	Congenital infection rate	Study weight
Diez, 2008 ⁶³	Argentina	hospital	2/104	microhematocrit	birth	1.9*	2.21
			9/104	PCR	birth	8.7*	
Flores-Chavez, 2011 ^{64,7}	Spain	multi-hospital	4/152*	serology	NA	2.6	3.68
Gamboja-Leon, 2011 ⁶⁵	Mexico	multi-hospital	0/4	serology (ELISA × 2, Stat-Pak)	10 months	0	0.06
Hoff, 1978 ⁶⁶	Brazil	hospital	1/17	parasitology, culture, serology (IIF)	birth-102 days	5.8	0.49
Jackson, 2009 ⁶⁷	Switzerland	hospital	2/8	parasitology, PCR, serology	birth (P/PCR), 9 months (S)	25.0	0.06
Lucas, 2009 ⁶⁸	Spain	hospital	1/37*	microhematocrit, PCR, serology	birth (MH/PCR), 6 months, 12 months (S)	2.7	1.75
Lucero, 2007 ⁶⁹	Argentina	multi-hospital	8/104	parasitology, serology (IHA, ELISA)	birth	7.7	1.48
			12/104	PCR	birth	11.5	
Mallimaci, 2010 ⁷⁰	Argentina	not stated	3/68	microhematocrit, serology (IHA, ELISA)	birth (MH), > 9 mo (S)	4.4	1.90
Merino, 2009 ⁷¹	Spain	hospital	0/33	PCR	0, 1, 7-9 months	0	2.35
Mora, 2005 ³⁶	Argentina	health centers	8/272	microhematocrit	birth-15 days	2.9	3.51
			18/287	hemoculture	birth-15 days	6.3	
			15/235	PCR	birth-15 days	6.4	
Moya, 1989 ⁷²	Argentina	hospital	29/721	Strout method, xenodiagnosis, hemoculture, serology (IIF, IHA)	birth (P), 1st year of life (P/S)	4.02*	4.79
Munoz, 2009 ⁷³	Spain	multi-hospital	3/41	parasitology, PCR × 2, serology	birth (P/PCR), 1 month (PCR), >8 months (S)	7.3	0.88
Munoz-Vilches, 2012 ⁷⁴	Spain	hospital	0/4	microhematocrit, PCR, serology (ELISA, IIF)	birth-30 days (MH/PCR), 4 months (PCR/S), 8 months (S)	0	0.06
Murcia, 2012 ⁷⁵	Spain	hospital	9/65	PCR, serology (IIF, ELISA × 2)	0-2 month, 6, 9, 12 months (culture/PCR), 12 months (S)	13.8	0.76
Olivera Mar, 2006 ⁷⁶	Mexico	multi-hospital	0/6	hemoculture, PCR	birth	0	0.13
Otero, 2012 ⁷⁷	Spain	hospital	1/20	PCR	21 days	5.0	0.66
Paricio-Telayero, 2008 ⁷⁸	Spain	multi-hospital	0/29	microhematocrit, PCR, immune precipitation	0-1 month (MH/PCR), 7 months (immune precip.)	0	2.01
Polo Vigas, 2012 ⁷⁹	Spain	hospital	1/9	PCR	birth	11.1*	0.15
Ramos, 2012 ⁸⁰	Spain	hospital	0/7	serology (ELISA, IIF), PCR	birth, 1 year	0	0.18

First Author, Publication Year	Country	Study setting	Sample Size (B+/B of M+)	Method of diagnosis of congenital infection	Timing of diagnosis	Congenital infection rate	Study weight
Romero, 2011 ⁸¹	Bolivia	door to door & antenatal care	12/299	microhematocrit	birth	4.0	3.99
Ruiz, 1999 ^{82,7}	Argentina	hospital	3/219	Strout method	birth	1.4	4.71
Russomando, 1998 ⁸³	Paraguay	multi-hospital	6/58	parasitology, PCR, hemoculture, serology (ELISA, IIF)	varies: birth-8 months	10	0.88
Russomando, 2005 ⁸⁴	Paraguay	2 departments (states)	20/1385	parasitology	birth-6 months (1995-7); >=6 months (1998-)	1.44	4.87
			60/815	PCR	birth- 6 months (1995-7); >=6 months (1998-)	7.4	
			89/1248	serology (ELISA, IIF)	birth-6 months (1995-7); >=6 months (1998-)	7.0	
Salas Clavijo, 2012 ⁸⁵	Bolivia	multi-hospital	125/3725	parasitology	birth	3.4	5.44
Salas, 2007 ⁴⁶	Bolivia	hospital	58/1144	parasitology	birth, 1 month	5.1	4.93
Salas, 2011 ⁸⁶	Spain	hospital	0/3	serology (IIF, ELISA) × 2, PCR	NA	0	0.03
Scapellato, 2009 ⁴²	Argentina	hospital	13/94	parasitology × 3, serology × 2 (IHA, ELISA, latex agglutination)	<6 months (P), >6 months (S)	13.8	1.03
Sombrero, 2010 ⁸⁷	Spain	hospital	0/5	parasitology, serology, PCR	birth (P/PCR), 30 days (P/PCR), 9 months (S/PCR)	0	0.09
Sosa-Estani, 2009 ⁸⁸	Argentina	hospital	8/47	microhematocrit, serology	birth-3 months (P), 8 months (S)	17.0	0.47
Streiger, 1995 ⁴⁸	Argentina	hospital	9/341	parasitology, Strout, and/or Xenodiagnosis, serology (HAI, IIF)	Birth, first months of life	2.64	4.54
Strohmeier, 2009 ³¹	Italy	hospital	0/1	parasitology	1 month	0	0.00
Szarfman, 1975 ³³	Argentina	hospital	3/400	parasitology	0-3 days	0.75	5.29
Torrico, 2005 ⁸⁹	Bolivia	hospital	71/1538*	microhematocrit, hemoculture, PCR	birth-1 month	4.6	5.13

NA=information not available;

⁷ retrospective study design;

⁷ no study design reported

* calculated;

(B+/B of M+)=infected infants/all infants of infected mothers; IHA=indirect hemagglutination; ELISA= enzyme linked immunosorbent assay; PCR=polymerase chain reaction; IIF=indirect immunofluorescence; HAI= hemagglutination inhibition; MH=microhematocrit, S=serology; P=parasitology

Table 3

Results of Subgroup and Sensitivity Analyses

Method of Diagnosis	No. of studies	Pooled congenital infection rate (95% CI)	Q statistic (P-value)	I ²	Random effects weight
Direct parasitology and/or serology	22	4.6% (3.4–5.7%)	27.8 (P<0.01)	24.5	84.6
PCR	9	6.0% (4.3–7.7%)	8.4 (P=0.27)	4.9	56.3
Mixed/other	27	4.5% (3.4–5.5%)	22.3 (P=0.06)	0	93.5
Endemicity of Country					
Endemic	30	5.0% (4.0–6.0%)	30.9 (P<0.01)	6.2	128.4
Non-endemic	21	2.7% (1.9–3.5%)	16.7 (P=0.86)	0	56.4
Sensitivity Analysis					
Excluding studies with zero congenital infections	38	4.8% (4.0–5.7%)	39.8 (P<0.01)	7.1	153.4