# An Epidemiological Approach to Study Congenital Chagas' Disease

## *Método Epidemiológico na Investigação da Infecção Congênita pelo Trypanosoma cruzi*

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*Transplacental transmission of Trypanosoma cruzi has been the focus of much attention in highly endemic areas in South America. Frequency of congenital transmission and factors associated with risk of it are still not well understood. Parasite strains may account for part of the geographical variation observed. Methodological differences between the studies do not permit a combined interpretation of results. This paper examines the epidemiological data available from Brazil, Bolivia, and Argentina and discusses possible epidemiological study design to investigate risk factors for transmission.*

***Key words:*** *Chagas' Disease; Congenital Transmission; Trypanosoma cruzi Infection; Case-control Studies; Epidemiology*

## INTRODUCTION

Substantial progress has been achieved in the reduction of *Trypanosoma cruzi* transmission in many endemic countries through the implementation of entomological surveillance and screening of blood donors. Transplacental transmission has been the focus of much attention in highly endemic areas where a large proportion of childbearing-aged women are seropositive for antibodies to *T. cruzi* (Bittencourt, 1992; Azogue, 1993; Andrade et al., 1995).

A crude estimate based on the seroprevalence for *T. cruzi* reported by WHO (Moncayo, 1992) and on an 1% risk of congenital infection indicates that around 8,000 children a year are congenitally infected in Latin America (Dias, 1992), 40% of whom are from Brazil.

Several factors are indicated as probably associated with the maintenance of different levels of infection rates among the populations according to: (a) genetic characteristics, (b) vectors and parasite strains, and (c) cultural differences such as: housing, nutrition, and family size (Anderson & May, 1991). Regional differences in the rate of transplacental transmission of *T. cruzi* and in the severity of the congenital Chagas' disease have been reported (Bittencourt, 1984; WHO, 1991). Methodological aspects of the studies considering the study hypothesis, case definition and sample size may also account for the large difference reported.

Although there is evidence that parasite strain plays an important role in the frequency of congenital transmission (Andrade, 1982; Delgado & Santos-Buch, 1978) it does not appear to be the only factor involved in explaining individual and regional risk diversity (Bittencourt, 1992).

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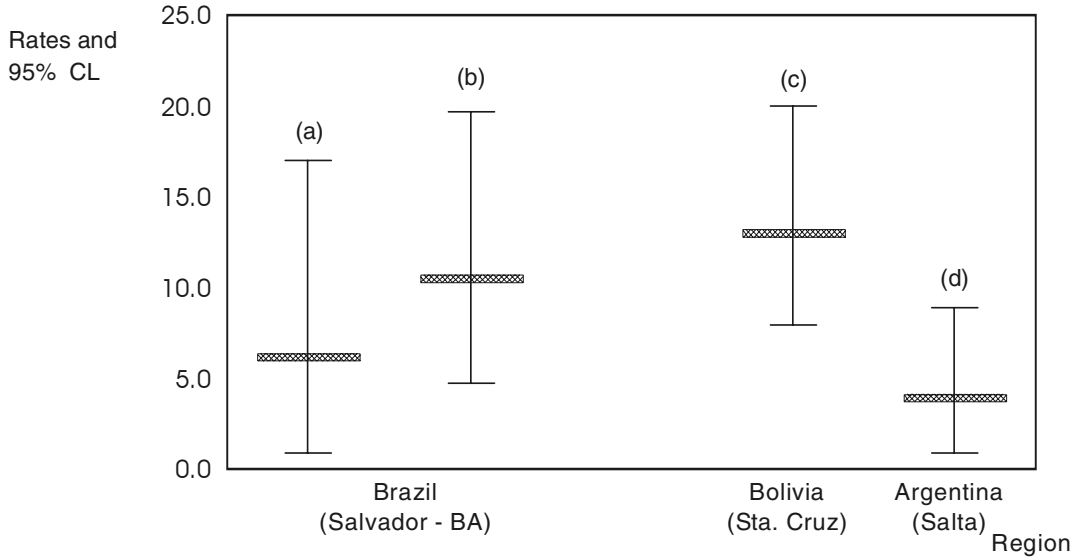
This paper examines the epidemiological data available for Chagas' disease congenital transmission and discusses possible epidemiological study designs to investigate risk factors for transmission. A literature review is included presenting the results of studies in which sufficient information about the selection of participants, diagnostic methods and serological tests are available. Results from studies in three endemic regions are considered: Salvador (Brazil), Santa Cruz de la Sierra (Bolivia) and Salta (Argentina).

## CONGENITAL TRANSMISSION OF *T. CRUZI*

Most of the information available on congenital transmission has been gathered from descriptive and case reports. In Brazil, Bittencourt et al. (1985) reported an incidence of 1.6% and 10.5% among stillbirths and live births, with birth weight over and below 2,000 g, respectively. In Santa Cruz de La Sierra, Bolivia, seropositivity for *T. cruzi* antibodies in the female population is about 54%. It was estimated that 9.5% of pregnant women have transmitted infection to their newborns (Azogue, 1993). In Argentina, congenital transmission ranges from 0.7% to 10.4% (Bittencourt et al., 1991).

Figure 1 presents 95% confidence limits (95% CL) estimated from infection rates reported in different studies in Latin America: (a) are results from Bittencourt & Barbosa (1972) on 300 miscarriages in Salvador, 48 from Chagasic women — the incidence rate of congenital transmission was estimated at 6.2% (95% CL 1.0%-17.0%); (b) Bittencourt et al. (1972) reported a 10.% (4.7%-19.7%) incidence of congenital transmission in 500 premature births, most of them stillbirths; (c) in Santa Cruz, Bolivia, Azogue et al. (1985) reported a seroprevalence of 51% for pregnant women in an endemic area, 13% (8.0%-20%) of the newborns presented *T. cruzi* by direct examination of placenta or cord blood. Transmission was more common in newborns with weight below 2.500g; (d) In Argentina, Zaidenberg & Segovia (1993) described 16% seropositivity among 968 pregnant women and 4% (1.0%-9.0%) of congenital infection.

**FIGURE 1.** Congenital *T. cruzi* Transmission. Rates and 95% Confidence Limits




Selection of cases: (a) Miscarriages N=48; (b) Prematures N=93; (c) Prematures N=161; (d) Live births N=149

These results suggest a large variation in the risk of *T. cruzi* congenital transmission ranging from 1.0% (Salvador and Salta) to 20.0% (Santa Cruz and Salvador). However, the 95% confidence limits of the estimates reported overlap, indicating that this difference may not be statistically significant. The large confidence intervals observed may be explained by the small sample size of most of the studies.

Meta-analysis has been used to combine results of observational studies or clinical trials increasing the power of the analysis and reducing the variability in the estimates (Spector & Thompsom, 1991). In the particular case of *T. cruzi* congenital transmission this approach will not be of much help due to the differences in the populations studied and in the case definitions adopted. Some studies included all products of pregnancy while others only live births.

There is some controversy regarding how to report the estimates of congenital transmission. Prevalence rates instead of incidence are usually reported in neonatal epidemiology as it is not possible to detect all products of conception. Congenital transmission has to be confirmed by the identification of *T. cruzi* in the newborn. Information on spontaneous and induced abortion and stillbirths are specially difficult to obtain in developing countries (Barreto et al., 1992). For this reason, some reports limit the estimates of congenital transmission to live births, not including stillbirths and miscarriages, therefore underestimating the rate of transmission. Also, eventually, both seropositive and seronegative mothers are included in the denominator of the rates, underestimating again the risk of *T. cruzi* congenital transmission.

There are few analytical studies designed to assess possible risk factors associated to Chagas' disease congenital transmission. Castilho & Silva (1976), in a matched case-control study in São Paulo, found no association between maternal seropositivity and underweight children. In an endemic area in Bahia, seropositive mothers aged 15-24 years were at higher risk of fetal losses than older seropositive mothers (Mota et al., 1985). In a follow-up study in Bolivia, all 35 underweight children born to seropositive mothers with parasites detected in the placenta but negative in the cord blood presented parasitaemia after 30 days. No case of parasitaemia was observed in a comparison group of children born to seropositive mothers with negative placentae (Azogue & Darras 1991). Considering 22.5% (8/35) of children lost to follow-up, the positive predictive value of an infected placenta for congenital transmission ranged from 77.2% (considering all children lost to follow-up as having no parasitaemia) to 100% (considering all children lost to follow-up as having parasitaemia).

## CASE-CONTROL DESIGN TO STUDY RISK FACTOR FOR CONGENITAL TRANSMISSION

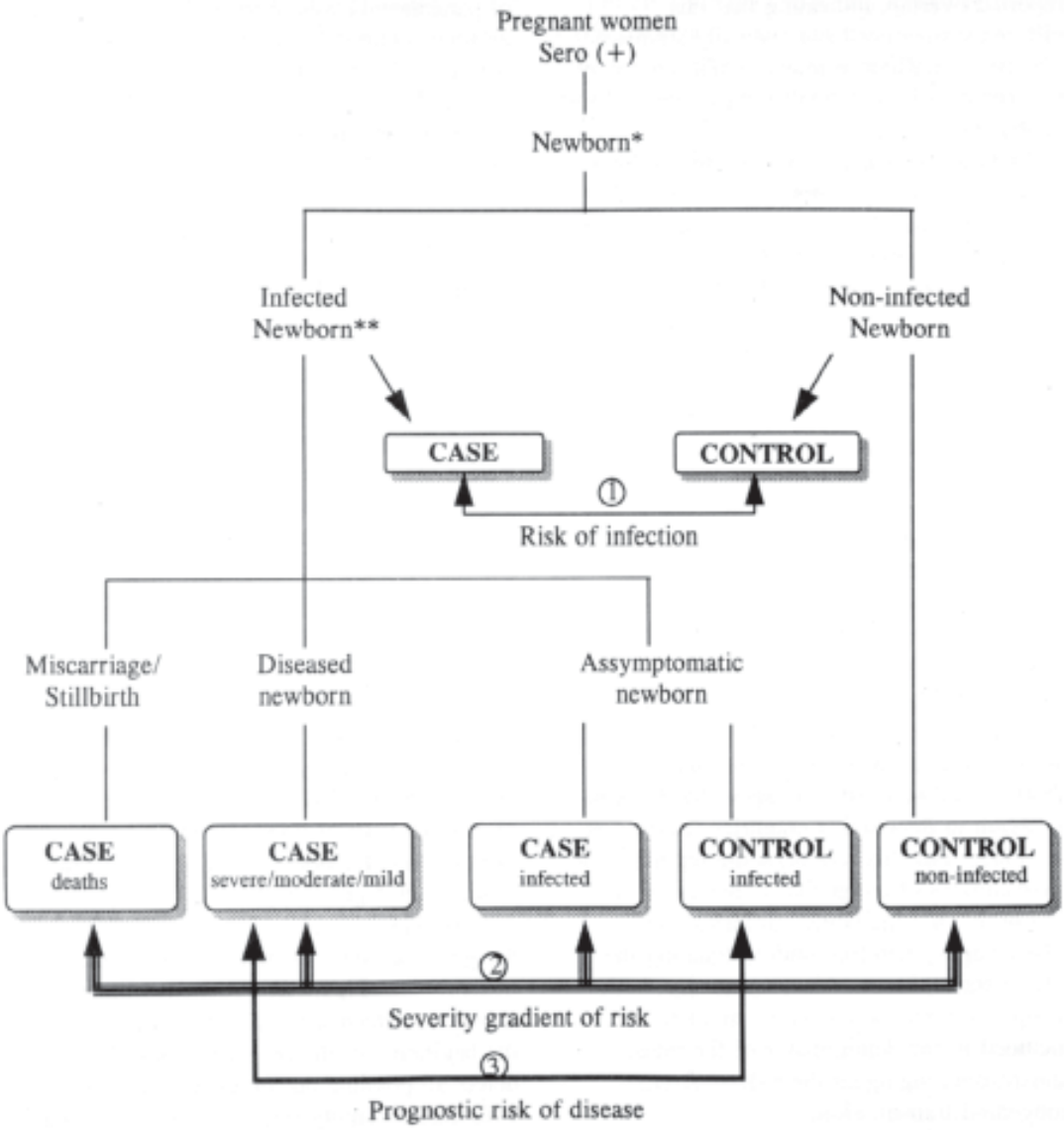
Case-control studies have been used to explore etiological associations in epidemiology. Furthermore, the identification of infected newborns as "cases" allows prompt medical attention since treatment is effective at an early stage of infection (Zaidenberg & Segovia 1993). The case-control methodology is useful for rare events and may be applied to establish the frequency of *T. cruzi* vertical transmission and to examine risk factors for congenital infection in different degrees of disease severity.

Different approaches may be used to design a case-control study for congenital transmission (Figure 2). Pregnant women should be screened for *T. cruzi* antibodies at the beginning of the pregnancy in order to detect all possible outcomes. Endemic areas with high fecundity rates should be selected. A selection bias of participants may be avoided by working in areas with high coverage for prenatal care.

### Selection of Cases and Controls

Cases and controls should be selected from among the products of conception of seropositive mothers. **Cases** may be defined as all types of pregnancy outcomes in which

**FIGURE 2.** Case-Control Design: Risk Factors for Congenital *T. cruzi* Transmission




* Live birth, miscarriage, Stillbirth
** Presence of *T. cruzi* in histopathologic of placenta and in cord blood of newborn

*T. cruzi* is detected, and controls as those outcomes which are parasitologically negative. High specificity in the definition of a case in the case-control methodology is required to assure the validity of the study. Conversely to what is normally desired in clinical practice, sensitivity in the diagnosis is not so important (Brenner & Savitz, 1990, Hulley et al., 1988). The same principle must be applied to case definition of transplacental transmission. Specificity may be increased by selecting as cases only those children with *T. cruzi* in the microhematocrit and on histological examination of placenta. This strategy tends to produce real estimates of the relative risk. Serological tests are not recommended for research purposes due to the low sensitivity and specificity of IgM antibodies for detecting congenital infection (Bittencourt, 1976). Although xenodiagnosis is highly sensitivite in the acute phase of infection, the results are only available after 30 days and it is very difficult to perform (Minter-Goedbloed et al., 1978).

Selection of cases and controls depends on the study objectives. Three possibilities are indicated in Figure 2. To assess risk factors for congenital infection, cases would be selected from among infected newborns and controls from non-infected ones. By stratifying cases according to severity such as fetal losses, stillbirth, diseased children and asymptomatic infection compared to non-infected children, it would be possible to estimate risk factors for severity of infection and disease. Asymptomatic infected newborn are suitable controls to study prognostic factors in comparison with clinically diseased children. The selection of controls in a case-control study is very prone to bias. The restriction of cases to live births may induce equivocal results by studying only surviving babies.

## Assessment of Exposure Variables

Exposures relative to the mother, newborn, and environment and housing conditions may be assessed. Mothers' age, obstetric history, knowledge of serological results, comorbidity, history of transfusion, use of vitamin and food supplemention during pregnancy, compliance with prenatal services, migration, length of residence in rural areas and socioeconomic conditions are the most common characteristics to be explored. Sex, anthropometric measures and clinical manifestations of the children should be recorded. Housing characteristics include family size and presence of triatomines. Serological evaluation of the siblings would be desirable. Risk factors for other pathologies should be evaluated as potential confounders.

Parasite density may influence the risk of *T. cruzi* congenital transmission. Quantitative approaches to estimate human intensity of infection should be developed to help to identify risk of transmission.

Sample size has been one of the major limitations to most epidemiological studies. The statistical power of a study to assess epidemiological etiological association depends on the number of participants. To define a proper sample size one should take into account the study design, the feasibility of the project in terms of time and resources, expected number of cases to be detected during the study period and the frequencies of the main exposure variables. For a case-control study, 150 cases and 300 controls would have an 85% power to detect statistical associations with relative risks over 1.8, for frequencies of exposures over 15% among controls, adopting a 5% level of significance. Considering a highly endemic area with 50% seroprevalence among pregnant women and 4% for congenital transmission, this would require the screening of around 9,500 eligible participants in order to select the desirable number of cases. Very few localities would meet the epidemiological conditions for such a study.

Further studies are required to assess risk factors associated with congenital transmission. There is a need to develop preventive strategies, to identify groups at higher risk and to confirm regional differences. An adequate site of the study and proper study design should be proposed to achieve unequivocal results.

## RESUMO

ANDRADE, A. L. S. S. ; ZICKER, F. & MARTELLI, C. M. T. **Método Epidemiológico na Investigação da Infecção Congênita pelo *Trypanosoma cruzi***. Cad. Saúde Públ., Rio de Janeiro, 10 (suplemento 2): 345-351, 1994.

A transmissão transplacentária do *Trypanosoma cruzi* vem despontando como tema de interesse em anos recentes, especialmente em áreas endêmicas da América do Sul. A freqüência da infecção e os possíveis fatores associados à transmissão congênita ainda não estão bem esclarecidos. Diferenças regionais em relação às taxas de transmissão têm sido explicadas por variações nas cepas de parasitas. Os aspectos metodológicos inerentes à formulação das hipóteses e os respectivos delineamentos dos diferentes estudos não permitem uma combinação de resultados para auxiliar a interpretação das diferenças observadas. Neste artigo explora-se as evidências epidemiológicas relativas às variações nas taxas de infecção congênita do Brasil, Bolívia e Argentina e propõe-se um modelo para investigação de fatores de risco para transmissão.


**Palavras-Chave**: Doença de Chagas; Transmissão Congênita; Infecção por *Trypanosoma cruzi*; Estudos de Casos e Controles; Epidemiologia

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