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Major Article

Systematic neonatal screening for congenital Chagas disease in Northeast Brazil: prevalence of *Trypanosoma cruzi* infection in the Southern region of Sergipe

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Abstract

Introduction: Chagas disease is caused by the flagellate protozoan *Trypanosoma cruzi*, being one of the leading causes of morbidity and mortality in the Americas with an estimated six to seven million infected people worldwide. In Brazil, the improvement in vector control and blood donor screening has evidenced the important epidemiological role of congenital transmission of Chagas disease. **Methods:** A serological survey for Chagas disease was performed in 3,952 newborns in the southern region of Sergipe using paper filter disks of dried blood samples. The newborns were screened using the Sergipe State Neonatal Screening Program between July 2015 and July 2016, and 3,749 and 750 blood samples were obtained for the IgG enzyme-linked immunosorbent assay and indirect immunofluorescence assay, respectively. In addition, mothers of the children who presented initial reagent serology were examined. **Results:** Among 3,749 blood samples, samples of two children were positive for the enzyme-linked immunosorbent assay; however, their confirmation test results were negative, suggesting passive transfer of the mother's antibody. One puerpera was identified with Chagas disease, with a prevalence of 0.02%. **Conclusions:** Congenital Chagas disease was not observed in newborns in the Southern region of Sergipe. However, Chagas disease was observed in women of reproductive age. Therefore, effective measurements for monitoring and systematic evaluation should be conducted. The Neonatal Screening Program proved to be an effective public health strategy for the prevention and control of Chagas disease.

Keywords: Chagas disease. Epidemiology. Neonatal screening. *Trypanosoma cruzi.*

INTRODUCTION

At present, Chagas disease (CD) is considered an endemic disease in 21 Latin American countries[1]; however, its prevalence is a growing concern in countries with non-endemic diseases due to the increase in human migration, especially from endemic areas[2]. This has caused a great economic impact in such areas due to recurring hospitalizations and early deaths[3].

Despite the considerable reduction in transmission through vectors and blood transfusions, CD remains a public health problem with high morbidity and mortality[4]. Therefore, the widespread implementation of control measures for other forms of infection, such as congenital transmission, is necessary, and can be defined as a global problem because of its presence in endemic and non-endemic areas[5]. Little attention has been paid to this transmission and although measures have been taken to reduce the number of cases, the genetic response in the placental environment against the infection is not well understood[6]. The congenital transmission is important, especially because it does not limit cases to endemic areas but can also affect non-endemic areas due to the increase in migration, which has become the main transmission route for the disease[7]. The transplacental route is the main vertical transmission route for CD, which can occur at any phase of the disease (acute, undetermined, or chronic) and at any stage of gestation, with the risk being high in the last trimester[8]. In addition, transmission can occur within the birth canal, from contact between the fetal mucous membranes and mother's blood contaminated with *Trypanosoma cruzi*[3].

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The vertical transmission route should be investigated in all newborns whose mothers have positive serology for CD[9].

Approximately 40,000 pregnant women and 2,000 newborns were infected with *T. cruzi* in Canada, Mexico, and United States[10], while the estimated the number of infected pregnant women was 1,400 in Spain, and 43-93 newborns were infected in the same period[11]. A screening test revealed that the general risk of CD via congenital infection is 5%[12,13], especially in Argentina, Bolivia, and Paraguay. However, in Brazil, this rate decreases to approximately 1% for reasons that are still not completely understood[14]. According to a systematic review, the prevalence of CD in pregnant women varies from 0.1% to 8.5%, and the congenital transmission rate is 0-5.2%. The congenital transmission rates are lower than in endemic countries, i.e., 0.75-17% in Argentina, 3.4-11% in Bolivia, 0.49-19% in Chile, 1.44-10% in Paraguay, and 0.13-1.57% in Uruguay, and in non-endemic countries, i.e., 0-28.6% in Spain and 25% in Switzerland[7].

The high rates of recovery in congenital cases, as well as the increase in quality of life and prognosis of patients[14], justify the application of routine screening procedures for CD among pregnant women and newborns in risk areas. However, these measures are neglected in most endemic areas and non-endemic countries that receive Latin American emigrants. In Brazil, only some states conduct prenatal screening for CD, namely Mato Grosso do Sul and Goiás[7]. The 2004 Pan American Health Organization and the 2010 World Health Organization guidelines affirmed the need to implement public health measures for the control, early diagnosis, and elimination of CD congenital transmission worldwide[15,16].

Most infected children are asymptomatic, and treatment provides a high rate of cure[14]. Therefore, there is a need for strategies for early diagnosis and treatment. The neonatal screening test conducted in Brazil, also known as *the little foot test*, is considered a good strategy to identify vertical transmission because there are specialized laboratories, multidisciplinary teams providing complementary assistance, and automated information systems in the public health network in all states[17,18]. Sergipe has the *Serviço de Referência em Triagem Neonatal*, the University Hospital of the *Universidade Federal de Sergipe*, that besides conducting health examinations, has a multidisciplinary team for the assessment of children with alterations in their test results.

Sergipe has conditions that are favorable for the multiplication of the vectors of *T. cruzi*, such as poor housing conditions, low investment in sanitary and epidemiological surveillance, and deactivation of or pause in programs to control the disease in some municipalities, which has resulted in a loss of the effectiveness of the Chagas Disease Control Program. In addition, Sergipe is the epicenter for the dispersion of two species that are difficult to control: *Triatoma brasiliensis and Triatoma pseudomaculata*. Most of the triatomine species are found in the Southern region of Brazil, which probably contributes to the increased incidence of CD in this region[19]. Considering the epidemiological importance of CD in Sergipe, specifically in the southern region, and the scarcity of data on this subject, the present study was delineated to estimate the prevalence of CD among newborns and mothers whose children had reactive serology. The study was conducted based on the evaluation of serology tests for CD using blood samples from newborns in the southern region of the Sergipe, collected through the Sergipe Neonatal Screening Program [*Programa de Triagem Neonatal de Sergipe* (PTN/SE)].

METHODS

We conducted a cross-sectional descriptive study that was structured as a serological survey based on the evaluation of serology tests for CD among newborns from the southern region of Sergipe state; the tests were performed by the Sergipe State Neonatal Screening Program from July 2015 to July 2016.

The study was conducted at the University Hospital of the Federal University of Sergipe, Aracaju, Sergipe, Brazil. It is a general reference hospital in screening neonatal and also in the treatment of Chagas disease. The hospital conducts teaching procedures, research, and provides assistance to people in Sergipe, as well as those in neighboring states[20].

Population and sample

The study involved newborns in the Southern region of Sergipe. Sergipe is located in the Northeast of Brazil, with an area of 21,910.3km and demographic density of 89.9 hab/km. It has a population of 2,068,031 people, of which 1,062,982 are women. The Southern region of Sergipe comprises various municipalities: Arauá, Boquim, Cristinápolis, Estância, Indiaroba, Itabaianinha, Pedrinhas, Salgado, Umbaúba, Santa Luzia do Itanhy, and Tomar do Geru (**Figure 1**). The region occupies a total area of 313,099km². The estimated population is 241,292 people distributed between urban (14.3%) and rural areas (12.4%). The territory presents a demographic density of 77.06 hab/km² and a human development index that varies from 0.545 and 0.672 between cities[21].

A total of 4,287 newborns were born in these municipalities from July 2015 to July 2016. Among these, 3,952 children were selected as the study subjects after screening conducted by the Sergipe State Neonatal Screening Program at the University Hospital of the Federal University of Sergipe.

Inclusion and exclusion criteria

All children who underwent the foot test at basic health units and/or maternity units and whose mothers participated in the study after providing signed informed consent were included in the study. Children whose blood samples were insufficient or contaminated were excluded from the study.

Sample collection technique

Samples were collected at the state's basic health units and/or maternity units and sent to the laboratory by mail after being dried at room temperature.

The enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence (IFI) tests conducted using dry blood for *T. cruzi* infection detection was based on the immunoglobulin G (IgG) *anti-T. cruzi* research. A correlation between the mother and fetal IgG is observed from gestational

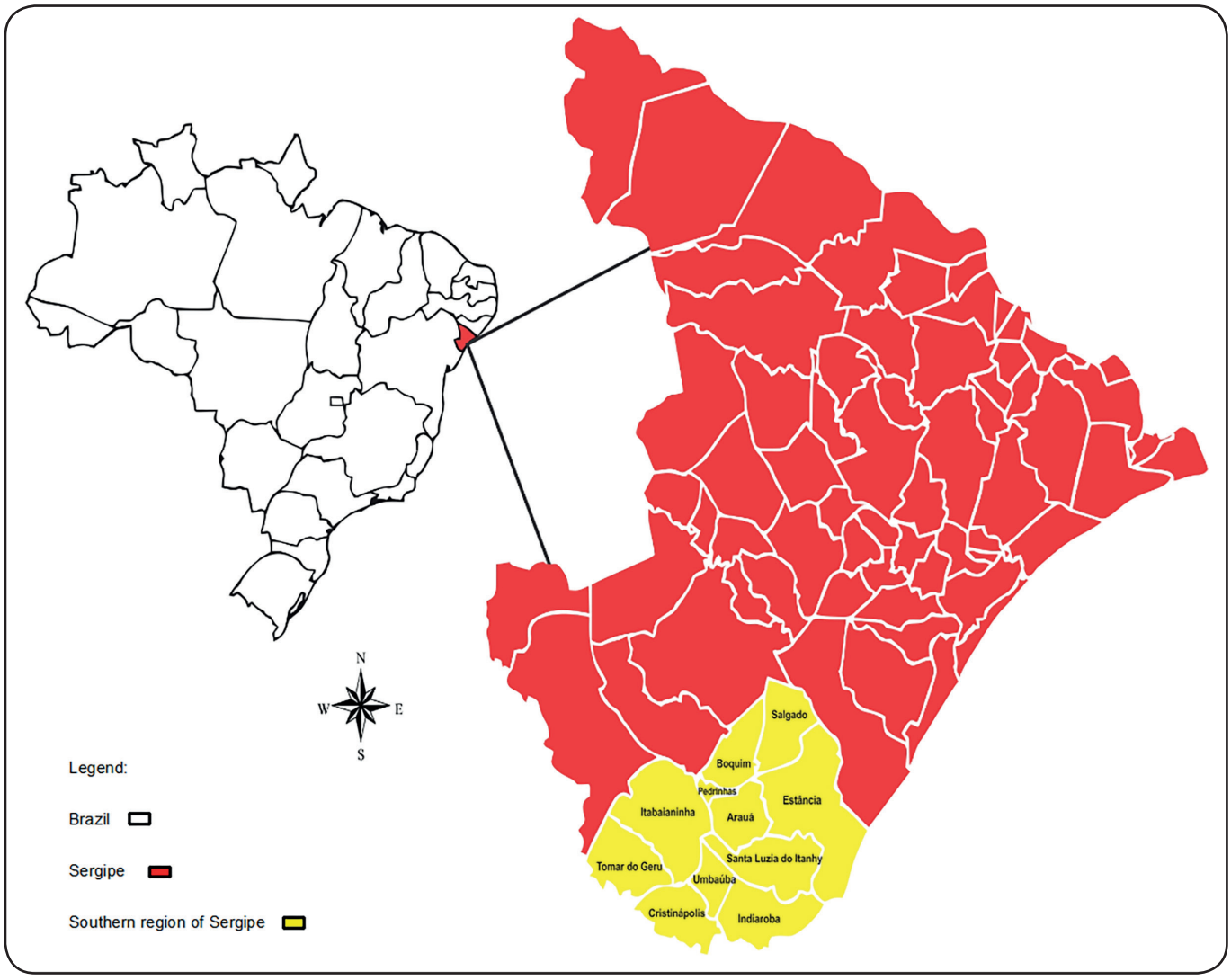

FIGURE 1: Geographic Location of the South Area of Sergipe.

week 33. However, the newborns positive for *T. cruzi* infection were considered to be positive possibly because of maternal infection[22].

Serology screening in blood samples using paper filters

A survey of the children who had the little foot test performed was conducted using the laboratory databases to identify and locate samples.

The samples were first submitted to the *anti-T. cruzi* ELISA IgG (Chagatest ELISA recombinant v.4.0-Wiener) test in the Sergipe Central Laboratory of Public Health (LACEN-SE). All samples with positive ELISA test results and 20% negative samples randomly identified in each municipality were submitted to the IFI test (IFI - Chagas-BIO Manguinhos Disease) at the Laboratory of the University Hospital of the Federal University of Sergipe. In addition, besides internal control for validation of laboratorial technique, an external control of the CD patient was conducted.

On the day prior to the ELISA test, the samples on the 3-mm diameter paper filter disks were placed on plates coated with *T. cruzi*. For the elution step, 200µL of phosphate-buffered saline (PBS) was added to the disks; these were shaken at 100rpm for 60 minutes and maintained at 4°C for 14-16 hours (overnight). The ELISA test protocol was then performed on the paper filter pieces after washing with buffer in accordance with the manufacturer's instructions with the following modification: the incubation time was doubled after the addition of the diluted conjugate.

For the IFI test, the samples were eluted by adding 100µL of PBS to the 3-mm disks; these were shaken at 100rpm for 1 hour and maintained overnight in the refrigerator at 4°C for a maximum of 16 hours. On the testing day, 10µL of the eluate was transferred to antigen-sensitized slides following the IFI manufacturer's protocol the Institute of Immunobiology Technology Bio Manguinhos in Rio de Janeiro City.

Active search for children with positive ELISA and IFI test results of blood samples on paper filters

The collaboration of all health secretaries and coordinators at primary care sites was requested to identify children whose ELISA and IFI results were positive as well as their respective mothers; means of transportation for venous blood collection and evaluation and outpatient follow-up was offered to all participants. At the first contact, all mothers were provided information and explanation about the study; upon agreeing to participate in the study, they signed the informed consent form before proceeding with study.

To confirm CD vertical transmission, a sample of venous blood was collected from children and mothers. The sample was obtained through a peripheral venous puncture and submitted to ELISA and IFI tests in LACEN and at the University Hospital laboratory, respectively. The children and mothers who presented positive serological results for CD were guaranteed follow-up and treatment in the outpatient clinic of infectious diseases at the University Hospital. In addition, the following laboratory and complementary exams were made available: abdominal ultrasonography, electrocardiogram, echocardiogram, and X-ray. General guidelines were followed for participants with negative CD results.

Ethical considerations

This study was approved by the Human Research Ethics Committee of the Federal University of Sergipe and registered under the number CAAE 55348616.7.0000.5546. The study complied with the criteria established in Resolution 466/2012 of the National Health Council.

The confirmatory exams of CD were performed after the acquiring signed informed consent from mothers or tutors.

RESULTS

A total of 3,952 blood samples from newborns from the Southern region of Sergipe were screened by the Sergipe Neonatal Screening Program from July 2015 to July 2016.

Table 1 presents an approximately homogeneous distribution by sex and domicile zone, with a slight predominance for men (47.9%) and urban areas (52.6%).

A total of 203 samples were excluded because they were considered inadequate for analysis due to insufficient material or fungal contamination. In total, 3,749 samples were submitted for ELISA testing, of which two were positive. The positive samples and 20% of negative samples (748 samples) were submitted for IFI testing, resulting in a total of 750 samples. The samples from this test were considered negative as observed in **Figure 2**.

Two newborns from the municipality of Itabaianinha had positive ELISA results; however, they had negative serology for the IFI test (**Figure 2**). The active search for these children and their mothers were conducted for serological confirmation of the disease.

TABLE 1: Demographic distribution of participants. Seroprevalence of congenital Chagas disease in the southern municipalities of Sergipe from July 2015 to July 2016.

Municipalities	Sex						Zone					
	female		male		not informed		urban		rural		not informed	
	n	%	n	%	n	%	n	%	n	%	n	%
Arauá	61	38.6	85	53.8	12	7.6	72	45.6	86	54.4	0	0.0
Boquim	158	47.7	150	45.4	23	6.9	167	50.5	157	47.4	7	2.1
Cristinápolis	141	49.7	129	45.4	14	4.9	197	69.4	71	25.0	16	5.6
Estância	484	45.1	509	47.4	81	7.5	750	69.8	312	29.1	12	1.1
Indiaroba	126	47.9	128	48.7	9	3.4	102	38.8	157	59.7	4	1.5
Itabaianinha	300	46.9	315	49.3	24	3.7	240	37.5	382	59.8	17	2.7
Pedrinhas	65	52.0	56	44.8	4	3.2	96	76.8	27	21.6	2	1.6
Salgado	131	48.3	133	49.1	7	2.6	90	33.2	178	65.7	3	1.1
Santa Luzia do Itanhy	96	44.1	113	51.8	9	4.1	66	30.3	149	68.3	3	1.4
Tomar do Geru	87	44.6	92	47.2	16	8.2	85	43.6	103	52.8	7	3.6
Umbaúba	190	48.2	184	46.7	20	5.1	214	54.3	167	42.4	13	3.3
Total	1,839	46.5	1,894	47.9	219	5.6	2,079	52.6	1,789	45.3	84	2.1

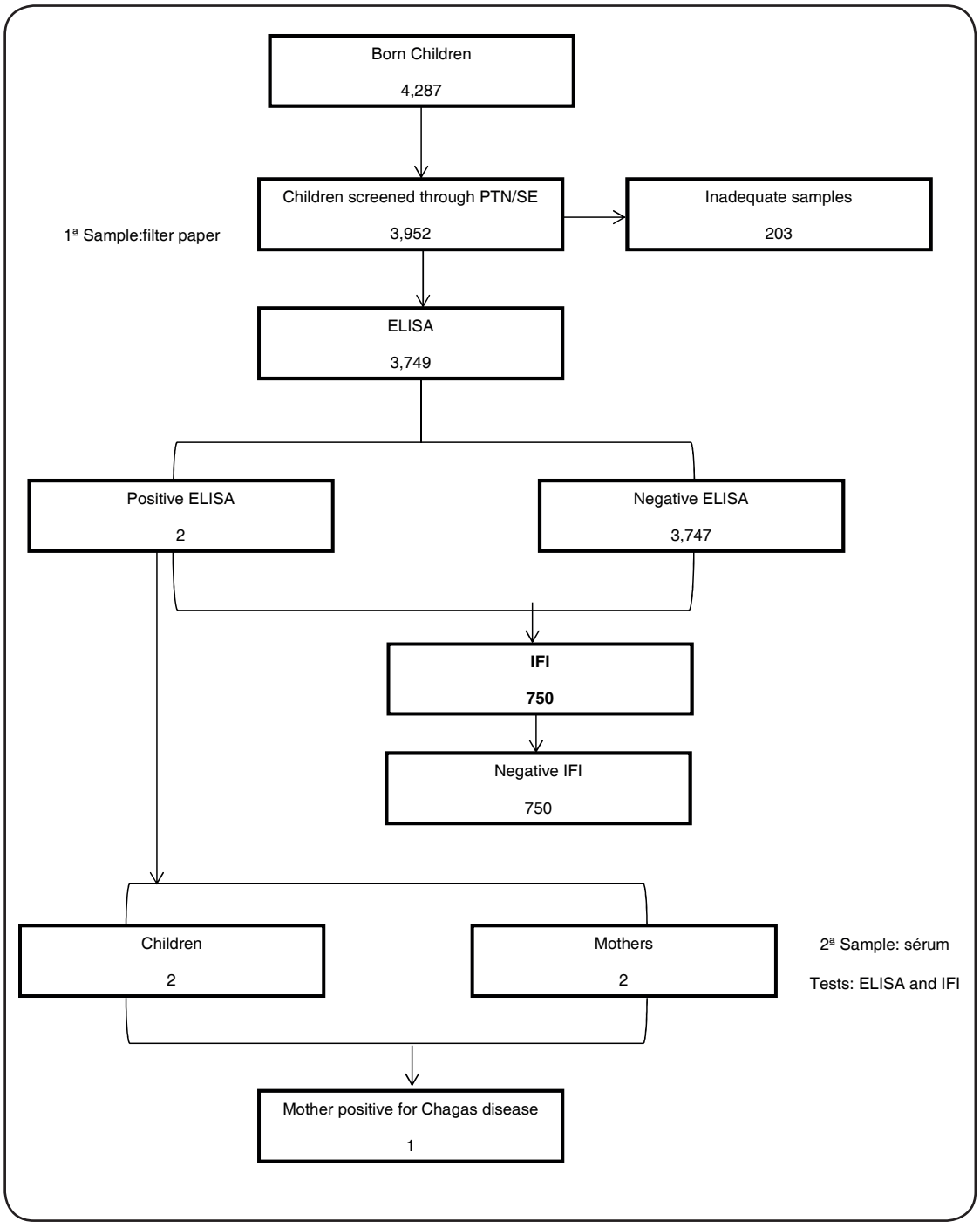

FIGURE 2: Neonatal screening for congenital Chagas disease infection in the Southern Region of Sergipe, Brazil, July 2015 to July 2016. **PTN/SE:** Programa de Triagem Neonatal de Sergipe; **IFI:** indirect Immunofluorescence test; **ELISA:** immunoenzymatic test;

Trypanosoma cruzi infection was confirmed in one of the mothers by serology through blood obtained by venipuncture. However, her children showed negative serology in both tests (**Table 2**).

The prevalence among puerperae was 0.02%. This corresponds to the number of puerpera infected in 3,749 samples of neonates examined, with a 95% confidence interval.

DISCUSSION

In this study, we attempted to estimate the prevalence of CD among newborns and their mothers, who had initial positive serology results through PTN/SE. The results obtained were considered good based on the quality of the kits used and the sensibility of the tests, with additional national questionnaires and the experience of technicians as important factors in the

TABLE 2 - Seropositivity for *Trypa cruzi* antibodies in confirmatory tests of samples from the southern region of Sergipe from July 2015 to July 2016.

Participant	Number	Serological test/venous blood samples			
		ELISA		IFI	
		positive	negative	positive	negative
Newborn	2	-	2	-	2
Mother	2	1	1	1	1
Total	4	1	3	1	3

ELISA: enzyme immunoassay; **IFI:** indirect immunofluorescence.

reduction of hindered results. The active search for mothers whose children had positive outcomes revealed that the rates of maternal death with *T. cruzi* infection was minimal. Considering that from gestational week 33, there is a correspondence between maternal and fetal IgG and that most children in this study at the time of sampling were newborns[18,22], a small number of participants were excluded (5.1%) because of insufficient screening or contamination by mold owing to technical problems during storage. Thus, it is suggested that future studies should include examinations conducted immediately after sampling.

The risk of spontaneous abortion is 1.8 times greater in women with anti-*T. cruzi* antibodies, leading to the hypothesis that higher the number of spontaneous abortions smaller the chance of identifying children infected by *T. cruzi* in serological surveys in areas with controlled or inactive vector transmission[23]. According to data from the state Health Secretary of Sergipe[24], the number of post-abortion curettage in the southern region of Sergipe during the study period was 372. This does not justify the non-identification of children infected with *T. cruzi* during the study period but points to a possibility. Therefore, this fact suggests the need for further investigation on *T. cruzi* infection among women with a history of abortion.

The use of samples collected routinely for neonatal screening on paper filters allowed the evaluation of 87.5% of children born in the study period. Among these, two children demonstrated positive results for the ELISA test: however, these were negative for the IFI test. A study of 23,308 samples collected on paper filter disks demonstrated that the dry blood ELISA test had a high number of false positive results due to its high sensitivity. Immunoenzymatic tests with dry blood can be used with the same specificity as the IFI[22] test and is considered the best procedure to be used in mass seroepidemiological surveys[25].

Venous blood samples were collected from two newborns with initially positive ELISA results and their respective mothers; these new samples demonstrated negative results for ELISA and IFI tests in both newborns. Nevertheless, *T. cruzi* infection was confirmed in one of the mothers. The median age of these newborns was four days at the time of the first blood sample collection using paper filter disks, suggesting passive transmission of maternal antibodies. The age of the children during the second sampling was >9 months, as recommended by the II Brazilian Consensus on Chagas Disease[4]. The results of this study evidenced the existence of CD in one puerpera but with the absence of congenital transmission. This finding suggests the importance of epidemiological surveillance programs for vectors and serological screening of donors in blood banks to control the transplacental transmission of *T. cruzi*[24].

The prevalence of CD in one parturient in this study (0.02%) was lower than that observed in pregnant women (0.3%) in a study conducted in Pelotas[3], with no confirmation of congenital CD, and in Mato Grosso do Sul (0.1%)[26]. Conversely, a greater CD prevalence was observed in puerperae (1%) from Minas Gerais, where vertical transmission was confirmed in three children[27]. The prevalence of congenital transmission has been <1% in the last decade in Brazil[13]. Despite knowing the complexity and multiplicity of the factors involved, it should be recognized that the vector control measures adopted in the 1990s, initiated by the Southern Cone to control CD, resulted in a considerable decrease in the cases of the disease in the last years[4]. In the current study, the serum-positive puerpera who had an infectious disease was an agricultural worker, aged 41 years, illiterate, and lived in a house of mud for approximately 25 years and had cats and dogs. The woman never received a blood transfusion and was unaware of her serological status; she showed no signs of impairments in the circulatory (normal electrocardiogram and chest X-ray) and digestive systems (normal and radiological evaluation of the esophagus and colon). Her clinical profile revealed that she had the indeterminate chronic form of CG. This condition may last for life or progress to a cardiac, digestive, or associated form. CD progresses silently without clinical symptoms in most people infected with *T. cruzi*. This is understood to be the critical problem of congenital CD because the lack of knowledge about the serology of the woman makes her a potential transmitter[28]. The asymptomatic form of the disease and late diagnosis may aggravate the patients' clinical condition and disease evolution, which may interfere with the prognoses of cases[29].

The puerpera who tested seropositive for anti-*T. cruzi* antibodies has resided in the rural area of Itabaianinha since birth. This municipality is located in the transition region between the Atlantic Forest and caatinga. Therefore, it is subject to ecotone effects that harbor most triatomines species, and probably contribute to infection in the local population[19]. Between

1999 and 2017[30], Itabaianinha presented the highest number of registered CD cases (64), followed by Umbaúba (16); Estância (11); Boquim and Pedrinhas (7); Indiaroba and Cristinápolis (6); Simão Dias (4); Arauá, Canindé de São Francisco, Lagarto, Nossa Senhora do Socorro, Pinhão, and Tomar do Geru (2); and Capela, Carira, Cumbe, Itabaiana, Moita Bonita, Nossa Senhora da Glória, Pedra Mole, Poço Verde, Porto da Folha, Santa Luzia do Itanhy, São Cristóvão, and São Domingos (1). These data demonstrate the lack of investments in the Chagas Disease Control Program in Sergipe. It is noted that the epidemiology of dengue, chikungunhya, and zika viruses in the cities and areas leads to the relocation of agents and resources for its control, negatively affecting the development of the Chagas Disease Control Program. Another point that should be considered is the patient assistance that is marked by a fragile health system organized in a fragmented system dealing with acute conditions, despite the number of chronic diseases in Brazil and the hierarchical structure and by the hierarchical structure and without communication between reference and counter reference[31].

The confirmation of CD in one parturient in the Southern region of Sergipe establishes the evidence of *T. cruzi* infection in women of reproductive ages. The literature reports great variability in CD seroprevalence rates in pregnant women and children, ratifying the importance of studies that demonstrate the current epidemiological situation of this type of infection. The current knowledge on the epidemiology of CD in Brazil, mainly in Sergipe remains limited, due to the underreporting of the cases, non-existence of disease screening programs in pregnant women and newborns at national level or in endemic areas, in addition, as children congenitally infected are asymptomatic. This points to a need to perform new research for the real understanding of the epidemiological situation that will contribute to measures taken among health professionals who provide assistance to pregnant women and newborns.

Considering that most women infected with *T. cruzi* are asymptomatic and unaware of their serological status, the congenital transmission may constitute a public health problem, because this type of transmission contributes to the occurrence of new cases. As long as there are women of reproductive age with CD[28], strategies in public health policies for disease prevention and control should be maintained. The PTN/SE proved to be an excellent strategy because of the existence of a laboratory and outpatient structure (operational ease for sample collection and high sensitivity of ELISA testing) and for the diagnosis and treatment of confirmed cases. Therefore, this strategy could be used together with other public health policy strategies in areas that are endemic to this disease.

In conclusion, congenital CD was not observed in newborns in the southern region of Sergipe. However, CD infection diagnosed in women of reproductive age indicates the need for effective measures for monitoring and systematic evaluation as public health policies for the prevention and control of the disease. The detection of CD through PTN proved to be an efficient strategy, which could be funded by the Single Health System and included in prenatal and screening tests of newborns in areas that are endemic to the disease.

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Conflict of interest

The authors declare that there is no conflict of interest.

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