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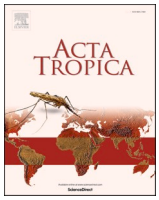

Drastic reduction in the notification of acute cases of Chagas disease in the Northeast region of Brazil. Epidemiological evaluation in the period 2001–2021

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ABSTRACT

Chagas disease (CD), caused by the protozoan *Trypanosoma cruzi* (*T. cruzi*), is a neglected disease endemic to some Latin American countries, including Brazil. Soon after infection, individuals develop an acute phase, which in most cases is asymptomatic and may go undetected. However, when CD is detected early, notification in the Notifiable Diseases Information System (SINAN), is mandatory. This study aimed to evaluate the information registered in the SINAN database and to determine the epidemiological profile of acute CD in Northeast Brazil, an endemic region, from 2001 to 2021. According to this survey, 1,444 cases of acute CD were reported in the Northeastern region of Brazil during this period. During the first six years, referred to as period 1, 90.24% of the notifications were registered, while the number of notifications significantly decreased in the subsequent years, referred to as period 2. Most individuals diagnosed with acute CD were Afro-Brazilian adults. All known routes of infection by the parasite were reported. Vector-borne transmission was predominant during period 1 (73.29%) and oral transmission during period 2 (58.87%). All nine states in Northeast Brazil reported cases in both periods. A higher incidence of disease was reported in Rio Grande do Norte (RN) during period 1, and in Maranhão (MA) during period 2. Our results show that CD remains a significant public health challenge.

1. Introduction

The etiological agent of Chagas disease (CD) is the hemoflagellate parasite, *Trypanosoma cruzi* (*T. cruzi*) (Chagas, 1909). According to the World Health Organization (WHO), approximately 6 to 7 million people worldwide are infected with T. cruzi, which is endemic to Latin America. For many years, the main route of infection was considered to be vector-borne by triatomine bugs (Monteiro et al., 2018). Some years ago, the oral route of infection with *T. cruzi*, caused by eating or drinking food contaminated with triatomine or its feces, gained importance in Brazil (Alberto Toso et al., 2011). An increase in the number of acute CD cases caused by oral infection has made this mode of infection more frequent than vector-borne infections in some regions of Brazil (Barbosa et al., 2015). Other traditional modes of transmission include transfusion and transplacental infection (Cevallos and Hernández, 2014; Lidani et al., 2019; Wendel and Gonzaga, 1993).

CD is divided into two phases: an initial acute phase and a late chronic phase. Parasitemia is detectable in the bloodstream during the acute phase of the disease. This phase can be asymptomatic or accompanied by nonspecific symptoms, such as a transient febrile illness (Chagas, 1916). The mortality rate during the acute phase is extremely low (Martins-Melo et al., 2012).

A few months after the infection, individuals progress to the chronic phase of the disease, which can persist throughout life. Most people develop an asymptomatic chronic phase of CD, however, 10–15% of the infected individuals develop the digestive form of the disease,

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characterized by complications in the gastrointestinal tract (Köberle, 1968). Approximately 30% develop the cardiac form of the disease, which is considered as the most severe form of CD, characterized by cardiac complications that could lead to sudden death (Chagas and Villela, 1922).

In Brazil, the Northeastern region has one of the highest rates of CD (Santos et al., 2020). Although in most of infected people CD is identified during the chronic phase, however, notification of acute cases when applicable is mandatory. On occurrence of the disease, the characteristics of the affected patient, infection, and disease need to be described in a notification form. These notifications are registered in the Notifiable Diseases Information System (SINAN) database which is available online. Here, we have outlined the epidemiological features of acute CD observed over the last 21 years in Northeast Brazil, a significant endemic region.

2. Methods

2.1. Study area

The present study was conducted using data from the Northeast Brazil, a region with an area of 1558,000 km^2 and housing an estimate of 54,658,515 inhabitants (Census 2022). The region is comprised of nine states: Alagoas (AL), Bahia (BA), Ceará (CE), Maranhão (MA), Paraíba (PB), Pernambuco (PE), Piauí (PI), Rio Grande do Norte (RN) and Sergipe (SE) (Fig. 4).

2.2. Data collection and study design

This study was based on secondary data available on the Notifiable Diseases Information System (SINAN) website. The collection and analysis of data were performed from August to December 2023. All confirmed cases of acute CD reported in the Northeastern region of Brazil between 2001 and 2021 were analyzed. The details of the form of notification for acute CD are presented in supplementary material 1 (S1). Using the information mentioned in these forms, the profile of acute CD we investigated by evaluating the number of infections that occurred each year, the characteristics of the infected people, the route of infection, and the incidence of the disease inside the nine states of Northeast Brazil.

2.3. Data analysis

In order to infer if there are difference in the number of reported cases within categories such as gender, race, age range, confirmation criteria and routes of infection, we performed Chi-squared tests under the null hypothesis that the number of cases should be equally distributed between categories. Since all data was analyzed considering two time periods (see details in results bellow), we performed a Chi-squared test for each variable at each period. Unreported categories were excluded from all tests. Results were considered statistically significant when p value was ≤ 0.05. All tests were performed using R language (version 4.3.1).

2.4. Ethics

Data collected from the SINAN used in this study are available in the public domain, however, they do not allow individuals to be identified. The guidelines of the Resolution of the National Health Council no. 510/2016 excluded the need to seek approval from any Research Ethics Committee (CEP) for a study using data from the public domain that does not provide the identification of individuals.

3. Results

3.1. Number of notifications of acute Chagas disease

From 2001 to 2021, a total of 1444 cases of acute CD were reported in the Northeast region of Brazil. The evaluated years were divided into two periods: period 1 (2001–2006) with a high number of notifications, totaling 1303 reports, and period 2 (2007–2021) during which notifications significantly decreased to 141 (Fig. 1A). Notably, 90.24% of notifications (1303) occurred within the first six years of period 1, with a dramatic reduction to 9.76% (141) in the following years (Fig. 1B). With respect to the incidence rate, during the period 1, the annual rate of notified acute CD ranged from 0.073 to 0.782 cases per 100,000 inhabitants and during the period 2, it ranged from 0.002 to 0.06 cases per 100,000 inhabitants (Fig. 1C).

3.2. Characteristics of the population reported with acute Chagas disease

During period 1, a higher number of females were notified to have acute CD (55.64% *versus* 44.28%, $\chi^2 = 16.8, p \leq 0.001$), however, during period 2 both sexes were infected in similar proportions (53.19% *versus* 46.81%, $\chi^2 = 0.57$, $p = 0.45$) (Table 1). During both periods, the infections occurred mainly among adults who declared themselves as Afro-Brazilian (Afro-Brazilian, $\chi^2 = 804.7, p \leq 0.001$ for period 1 and $\chi^2 = 194.5$, $p \leq 0.001$ for period 2). In period 1, the age range of most infected individuals varied from 40 to 59 years, and in the period 2, the age range decreased to 20 to 39 years. The age range shown statistically significant difference during period 1 ($\chi^2 = 3357.8$, $p \leq 0.001$) and during period 2 ($\chi^2 = 206.4$, $p \leq 0.001$) (Table 1). Confirmation of infection was carried out using laboratory methods including parasitological and immunological methods. A few suspected cases were confirmed by analyzing whether the individuals reside in or visited an endemic area to the disease (epidemiological link), or by considering the individuals' symptoms (clinical criteria) (Table 1).

3.3. Reported routes of infection with Trypanosoma cruzi

Using the SINAN database, the routes of infection with *T. cruzi* in were found to be vector-borne, oral, transfusion, transplacental, and accidental transmissions (Table 2). During period 1 the most frequent route of infection was found to be vector-borne transmission ($\chi^2 = 1866.6, p \leq 0.001$) and during period 2 oral transmission ($\chi^2 = 106.3, p \leq 0.001$) (Fig. 2 and Table 2). During period 1, vector-borne transmission occurred in 73.29% of the cases and no oral transmission was reported. However, during period 2, vector-borne transmission occurred in only 14.18% of the cases while 58.87% were found to be oral infections (Fig. 3 and Table 2).

3.4. Notification of acute Chagas disease in the Northeast states in Brazil

During period 1, all nine of Northeastern states in Brazil reported cases of acute CD, and most cases were reported in the most populated state of Bahia (BA) (Fig. 4A and C). During period 2, eight states reported cases of acute CD, most of which were reported in the Maranhão (MA) state (Fig. 4B and D). The incidence rate of notifications revels that during the period 1, the state of Rio Grande do Norte (RN), showed a higher incidence of CD notification, reaching 7.53 notifications per 100,000 inhabitants (Fig. 5A). However, during the period 2, a higher incidence rate of CD notifications was observed in Maranhão (MA) that presented 0.78 notifications per 100,000 inhabitants (Fig. 5B). During both periods, some cases of infections were reported in Northeast Brazil, however, they occurred outside this region. Moreover, during period 2, the number of infections occurring outside the Northeast Brazil significantly increased compared to the observed in period 1 (Fig. 4C and D).

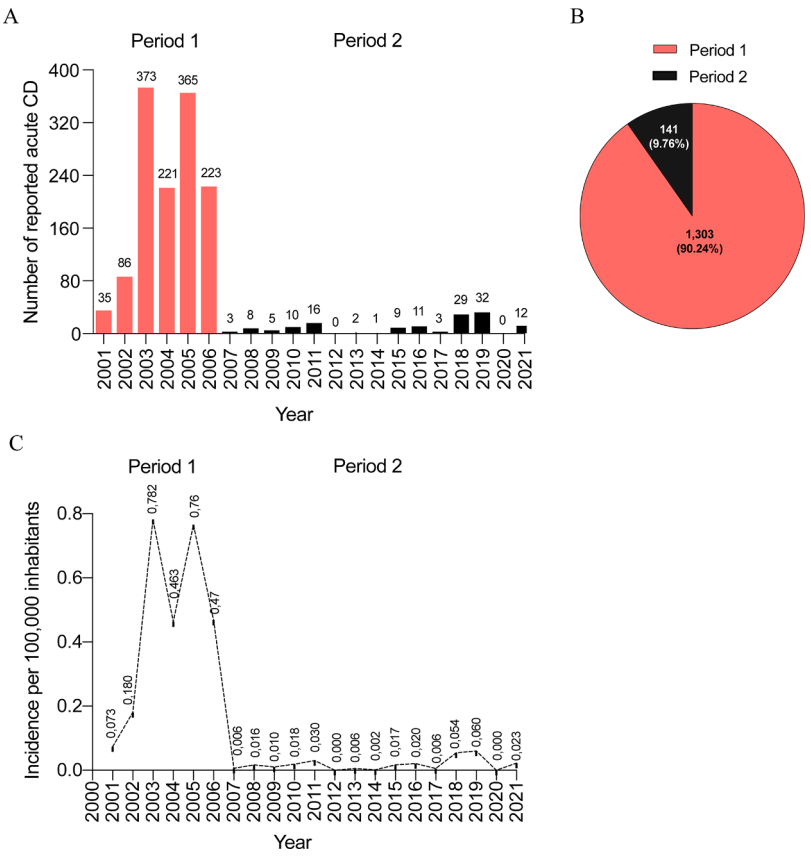

Fig. 1. Number and incidence of acute Chagas disease in the Northeast region of Brazil. a. Number of notifications of acute CD in Northeast Brazil registered in the SINAN database from 2001 to 2021. Period 1 refers to the period from 2001 to 2006 and period 2 refers to the period from 2007 to 2021. b. Percentage of notifications occurring in the periods 1 and 2. c. Incidence of acute CD per 100,000 inhabitants registered in Northeast Brazil from 2001 to 2021.

Table 1
Characteristic of the population reported with acute Chagas disease in Northeast Brazil from 2001 to 2021[a].

		Period 1			Period 2		
		Number	%	*Chi*	Number	%	*Chi*
Gender	Male	577	44.28	χ^2=16.8	66	46.81	χ^2=16.8
	Female	725	55.64	$p \leq 0.001$	75	53.19	$p = 0.45$
	Unreported	1	0.08		0	0.00	
Race	White	322	24.71	χ^2=804	33	23.40	χ^2=194
	Afro-Brazilian[b]	766	58.79	$p \leq 0.001$	103	73.05	$p \leq 0.001$
	Yellow	22	1.69		3	2,13	
	Indigenous	15	1.15		1	0.71	
	Unreported	178	13.66		1	0.71	
Age range (years)	<1	7	0.54	χ^2=3357	2	1.42	χ^2=206
	1 to 4	5	0.38	$p \leq 0.001$	4	2.84	$p \leq 0.001$
	5 to 7	11	0.84		10	7.09	
	8 to 14	18	1.38		6	4.26	
	15 to 19	28	2.15		11	7.80	
	20 to 39	391	30.01		52	36.88	
	40 to 59	619	47.51		37	26.24	
	60 to 64	75	5.76		3	2.13	
	65 to 69	65	4.99		6	4.26	
	70 to 79	56	4.30		7	4.96	
	80 or more	26	2.00		3	2.13	
	Unreported	2	0.15		0	0.00	
Confirmation criteria	Laboratory	1130	86.72	χ^2=1771	127	90.07	χ^2=115
	Epidemiological link	52	3.99	$p \leq 0.001$	0	0.00	$p \leq 0.001$
	Clinical	88	6.75		4	2.84	
	Unreported	33	2.53		10	7.09	

[a] Period 1. 2001–2006, $N = 1303$; Period 2. 2007–2021, $N = 141$.
[b] Afro-Brazilian = (black + brown);.

Table 2
Routes of infection with *Trypanosoma cruzi* reported in SINAN database from 2001 to 2021[a].

	Notifications	
Route of infection	Period 1	Period 2
Vector-borne	955 (73.29%)	20 (14.18%)
Oral	0 (0.00%)	83 (58.87%)
Transfusion	7 (0.54%)	0 (0.00%)
Congenital	4 (0.31%)	0 (0.00%)
Accidental	0 (0.00%)	1 (0.71%)
Unreported	337 (25.86%)	37 (26.24%)
Chi-Square test	χ^2=1866	χ^2=106
	$p \leq 0.001$	$p \leq 0.001$

[a] Period 1. 2001–2006, $N = 1303$; Period 2. 2007–2021, $N = 141$.

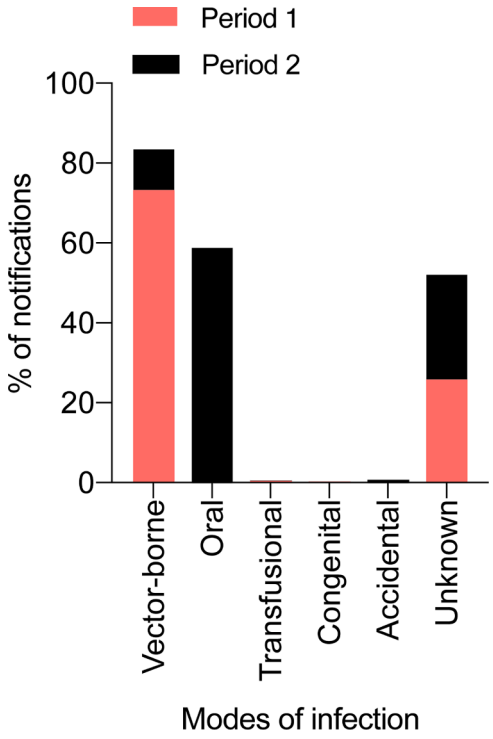

Fig. 2. Registered routes of infection with *Trypanosoma cruzi*. Percent of notifications of acute CD in Northeast Brazil from 2001 to 2021 registered in the SINAN database, involving the vector-borne, oral, transfusion, congenital, accidental, or unknown mode of infection. The period 1 refers to the period from 2001 to 2006, and the period 2 refers to the period from 2007 to 2021.

4. Discussion

We show a drastic decrease in the notifications of acute CD over the last 21 years in Northeast Brazil. Between 2001 and 2006, there was a notably high number of reported cases. Similar trends during this period were reported in both the North and Northeast Brazil, as well as in other endemic countries (Santos et al., 2020; Sasagawa et al., 2014). Consistent with our findings, several studies have also reported a decline in cases of acute CD in Brazil from 2006 onward (Dias et al., 2016; Santos et al., 2020). This reduction may be attributed to the implementation of programs aimed at controlling *T. cruzi* infection (Dias et al., 2002). These initiatives in Brazil and other Latin America countries strategically focus on the elimination of the vector insect (Ramsey and Schofield, 2003; Silveira and Vinhaes, 1999). However, it is important to note that a limitation of our study is the potential underreporting of cases in the SINAN, which may be due to the asymptomatic presentation of acute CD or their presentation with nonspecific symptoms.

Characteristics of patients with acute CD changed over time. In the period 1, the disease affected more women than men. During period 2, both sexes were equally affected by the disease. Through literature, it is shown that acute or chronic CD can affect more females than males in Northeast Brazil (De Medeiros et al., 2022; Santos et al., 2020) and in other regions of the country (De Albuquerque et al., 2020). The physical characteristics more frequently reported among infected people in Northeastern Brazil were Afro-Brazilian adults, similar to the findings of other studies (Santana et al., 2022; Santos et al., 2020).

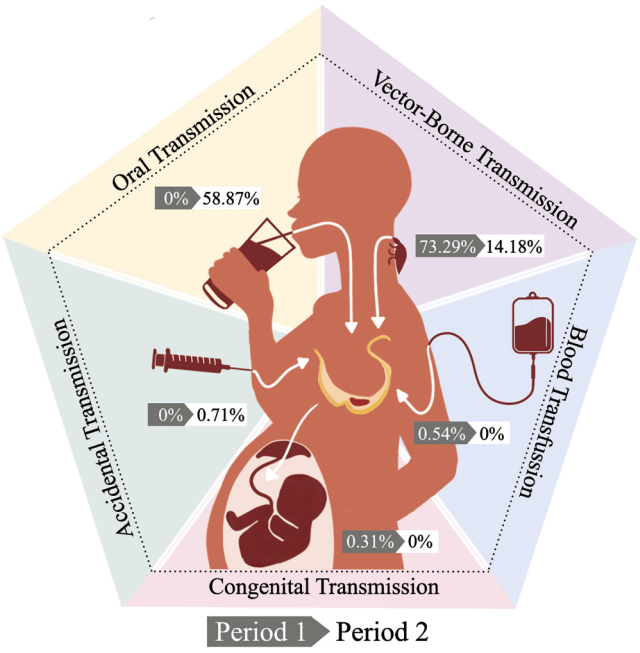

Fig. 3. Routes of infection with *Trypanosoma cruzi* notified in the Northeast Brazil from 2001 to 2006 (Period 1) and from 2007 to 2021 (Period 2).

In endemic countries such as Brazil, people are infected with *T. cruzi* in different ways, including vector-borne, oral, transfusion, transplacental, and accidental infections (Lidani et al., 2019; Murcia et al., 2013; Wendel and Gonzaga, 1993). During the period analyzed, all these routes of infection were reported. Oral infection with the parasite gained prominence in Brazil last decade, after some outbreaks caused by the consumption of açaí (Euterpe oleracea) palm fruit (Barbosa et al., 2016; Nóbrega et al., 2009), sugar cane (*Saccharum officinarum*) juice and other foods contaminated with infected vector or their feces, especially in the state of Amazonas, in the Northern region of the country (Barbosa et al., 2015). The obtained data showed that oral infection also gained importance in the Northeast region from 2007 onward, in agreement with other authors, (Monsalve-Lara et al., 2021), while the vector-borne infection drastically decreased during the same period, probably as a result of the programs organized to control infection with *T. cruzi* (Ramsey and Schofield, 2003).

Recent studies have shown that CD is present among the infections transmissible by blood transfusions in Brazil (Pessoni et al., 2019; Santos et al., 2022). Moreover, some authors have demonstrated that blood donors in the states of the Northeast had a percentage positive for CD in the same period analyzed here (Abreu et al., 2021; Melo et al., 2009). We found a low transmission of the disease by transfusion from 2001 to 2006 (period 1), which reduced to zero from 2007 to 2021 (period 2). These data are in accordance with the lower infection rate found in period 2, however, it can also be related to increased screening and discarding of infected blood, as described in other regions of Brazil (Monich et al., 2017).

Some cases of infections occurred outside Northeast Brazil. Our data showed that in period 1, 0.61% of the infections occurred outside Northeast Brazil, and in period 2, it significantly increased to 17.71%. In recent years, increased globalization and facilities for population

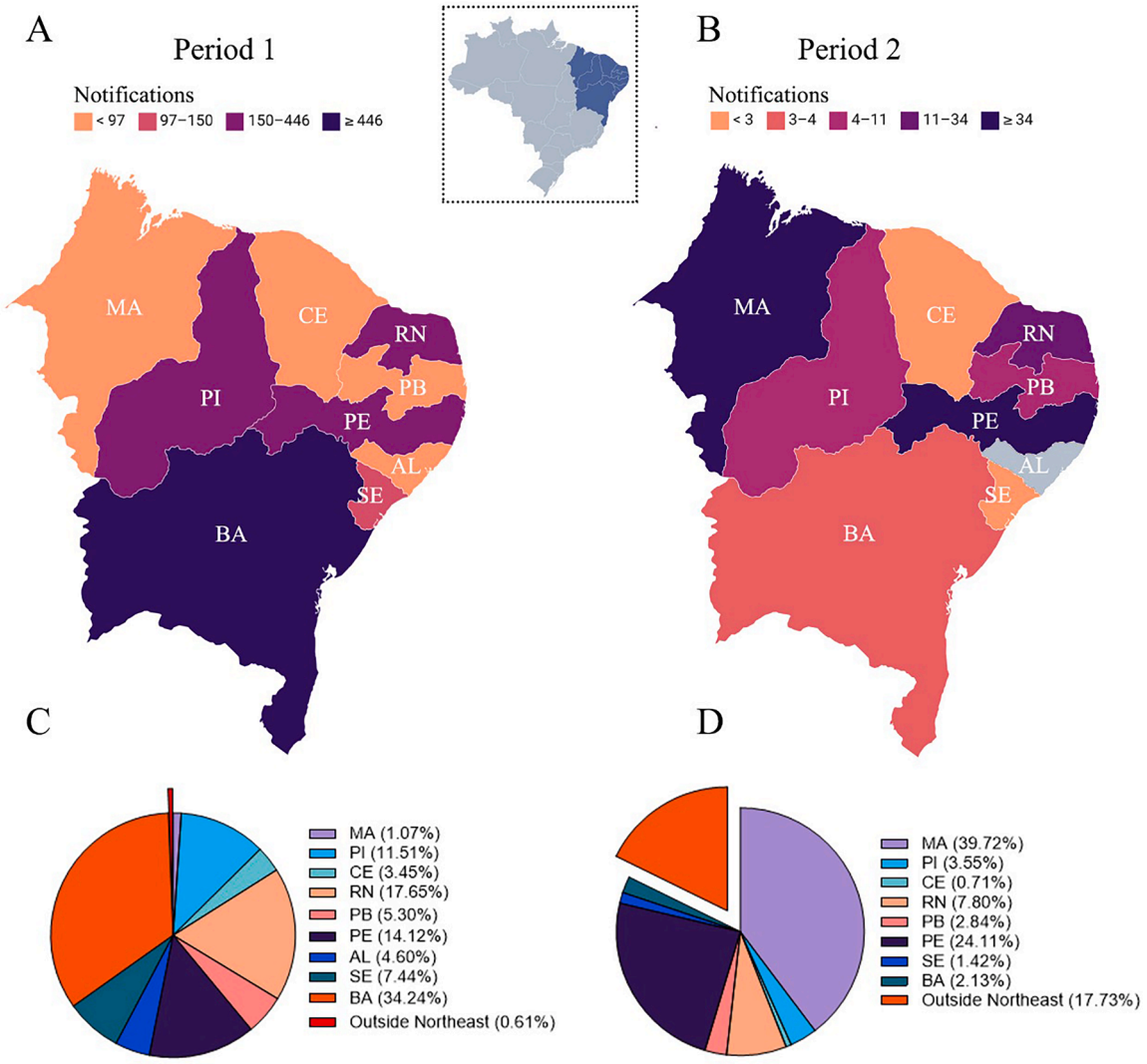

Fig. 4. Notifications of acute Chagas disease registered in each state of Northeast Brazil. a and b. maps of the Northeast region of Brazil indicating the incidence of notifications registered in each state respectively during the periods 1 and 2. c and d. graphical representation of the percentage of notifications in each state of Northeast Brazil, or outside of Northeast. Period 1 refers to the period from 2001 to 2006, and the period 2 refers to the period from 2007 to 2021. MA=Maranhão, PI=Piauí, CE=Ceará, RN=Rio Grande do Norte, PB=Paraíba, PE=Pernambuco, AL=Alagoas, SE=Sergipe, BA=Bahia.

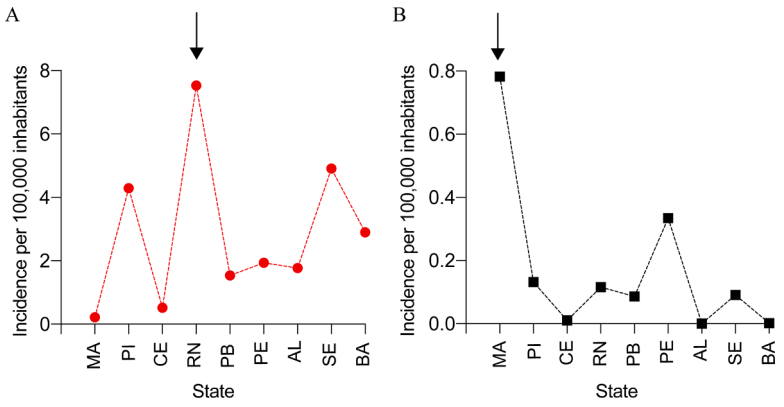

Fig. 5. Incidence of acute Chagas disease in each state of Northeast Brazil. a. Incidence of acute CD, per 100,000 inhabitants registered in the nine states of Northeast Brazil from 2001 to 2006 (Period 1). b. Incidence of acute CD per 100,000 inhabitants registered in the nine states of Northeast Brazil from 2007 to 2021 (Period 2). In a and b, the arrows indicate the highest incidence registered during the respective periods. MA=Maranhão, PI=Piauí, CE=Ceará, RN=Rio Grande do Norte, PB=Paraíba, PE=Pernambuco, AL=Alagoas, SE=Sergipe, BA=Bahia.

migration have contributed to an increased number of people being infected outside their original region. The migration of infected people has made CD a public health problem in non-endemic countries (Da Costa-Demaurex et al., 2019; Di Girolamo et al., 2016; Elkheir et al., 2021).

Among the states of Northeast Brazil, Rio Grande do Norte (RN) showed a higher incidence of acute CD during period 1 (between 2001 and 2006). Notably, no studies have addressed the status of CD in this state during this initial period. In contrast, during period 2, several studies have shown high seropositive rates for CD in Rio Grande do Norte, (Brito et al., 2012). The municipalities in this state presented a high density of *T. cruzi*-infected dogs, which serve as domestic reservoirs of the parasite, within both domestic and peridomestic environments (Araújo-Neto et al., 2019; Freitas et al., 2018). In addition, there is a high density of native vector species infected with *T. cruzi*, particularly the *Triatoma brasiliensis* vector in this state (Barbosa-Silva et al., 2019; Lilioso et al., 2017; Lima-Neiva et al., 2021).

During period 2, a higher incidence of acute CD was noted in Maranhão (MA), where, *T. cruzi* was found in wild mammals and dogs (Costa et al., 2021; Da Costa et al., 2015). However, it has been reported that the mortality rate due to CD in Maranhão is the lowest in Northeast Brazil (Sousa et al., 2020).

Given that no vaccine against CD has yet been approved (Camargo et al., 2022), and that the approved medication is most effective when administered during the acute phase of the disease (Pandey et al., 2021), early identification of infected individuals and prompt notification are crucial for disease control. The data extracted from notifications, which include the occurrence and incidence of the disease, the most common modes of transmission, and the regions of prevalence, along with aspects such as vector distribution and infection rate, are essential for developing effective prevention and control strategies. Therefore, the insights gained by study will enhance our understanding of the disease and aid in the formulation of public health policies aimed at controlling the transmission of *T. cruzi* and CD.

5. Conclusion

Studying the last 21 years of acute CD notifications in Northeast Brazil demonstrated that despite a drastic reduction in the number and incidence of notifications, CD is still present in this region and thus is a public health problem. During the analysis period, infections occurred primarily through vector-borne transmission, followed by the oral route. Therefore, we highlight the importance of not only notifying confirmed cases of acute and chronic CD, but also the accurately filling the form of notification. This will be helpful in planning new public health policies to control and prevent CD.

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Supplementary material

S1- SINAN form of notification http://www.portalsinan.saude.gov.br/images/documentos/Agravos/Chagas/Chagas_v5.pdf.

CRediT authorship contribution statement

Laryssa Bezerra Santos: Writing – original draft, Validation, Methodology, Investigation. **Julyane Corato da Silva:** Writing – review & editing, Investigation. **Maria Gabriela Gomes Abdala:** Writing – review & editing, Investigation. **Marina Taissa Santiago da Silva:** Writing – review & editing, Investigation. **José Jeferson Gomes de Souza:** Writing – review & editing, Investigation. **Ana Rachel Vasconcelos de Lima:** Writing – review & editing, Validation. **Alessandra Abel Borges:** Writing – review & editing, Validation. **Abelardo Silva-Júnior:** Writing – review & editing, Validation. **Ênio José Bassi:** Writing – review & editing, Validation. **Flávia S. Damasceno:** Writing – review & editing, Validation, Methodology. **Marcos Vinicius Carneiro Vital:** Writing – review & editing, Validation, Formal analysis. **Müller Ribeiro-Andrade:** Writing – review & editing, Validation, Methodology, Conceptualization. **Maria Cláudia Silva:** Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that the research was conducted without conflict of interest.

Data availability

Data will be made available on request.

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