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Original Article

Clinical, epidemiological and climatic factors related to the occurrence of cutaneous leishmaniasis in an endemic area in northeastern Brazil

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Abstract

Cutaneous leishmaniasis (CL) is a neglected tropical disease with a wide distribution in the Americas. Brazil is an endemic country and present cases in all states. This study aimed to describe the occurrence, the underlying clinical and epidemiological factors, and the correlation of climatic variables with the frequency of reported CL cases in the municipality of Caxias, state of Maranhão, Brazil. This is a retrospective and descriptive epidemiological study based on data extracted from the Brazilian Information System of Diseases Notification, from 2007 to 2017. Maximum and minimum temperature, precipitation, and relative air humidity data were provided by the Brazilian National Institute of Meteorology. A total of 201 reported autochthonous CL cases were analyzed. The predominance of cases was observed in males (70.1%). The age range between 31 and 60 years old was the most affected, with 96 cases (47.9%). Of the total number of registered cases, 38.8% of the affected individuals were engaged in agriculture-related activities. The georeferenced distribution revealed the heterogeneity of disease occurrence, with cases concentrated in the Western and Southern regions of the municipality. An association was detected between relative air humidity (monthly mean) and the number of CL cases per month ($p = 0.04$). CL continues to be a concerning public health issue in Caxias. In this context, there is a pressing need to strengthen measures of prevention and control of the disease through the network of health services of the municipality, considering local and regional particularities.

Keywords: cutaneous leishmaniasis, neglected disease, epidemiology, tropical weather.

Fatores clínicos, epidemiológicos e climáticos relacionados à ocorrência de leishmaniose cutânea em área endêmica no nordeste do Brasil

Resumo

A leishmaniose cutânea (CL) é uma doença tropical negligenciada, com ampla distribuição nas Américas. O Brasil é um país endêmico e apresenta casos em todos os estados. Este estudo teve como objetivo descrever a ocorrência, os fatores clínicos e epidemiológicos subjacentes e a correlação de variáveis climáticas com a frequência de casos de CL notificados no município de Caxias, estado do Maranhão, Brasil. Este é um estudo epidemiológico retrospectivo e descritivo, com base em dados extraídos da Notificação do Sistema Brasileiro de Informação de Doenças, de 2007 a 2017. Dados máximos e mínimos de temperatura, precipitação e umidade relativa do ar foram fornecidos pelo Instituto Nacional de Meteorologia. Foram analisados 201 casos de CL autóctones relatados. A predominância de casos foi observada no sexo masculino (70,1%). A faixa etária entre 31 e 60 anos foi a mais afetada, com 96 casos (47,9%). Do número total de casos registrados, 38,8% dos indivíduos afetados estavam envolvidos em atividades relacionadas à agricultura. A distribuição georreferenciada revelou a heterogeneidade da ocorrência da doença, com casos concentrados

nas regiões oeste e sul do município. Foi detectada associação entre a umidade relativa do ar (média mensal) e o número de casos de CL por mês (p = 0,04). O CL continua sendo uma questão preocupante de saúde pública em Caxias. Nesse contexto, há uma necessidade premente de fortalecer medidas de prevenção e controle da doença por meio da rede de serviços de saúde do município, considerando as particularidades locais e regionais.

Palavras-chave: leishmaniose cutânea, doença negligenciada, epidemiologia, clima tropical.

1. Introduction

Cutaneous leishmaniasis (CL) is a non-contagious infectious disease caused by different species of protozoa from the genus *Leishmania* (Goto and Lindoso, 2012). The transmission to vertebrate hosts occurs through the bite of infected female phlebotomines (Diptera: Psychodidae) from different genera of the subfamily Phlebotominae (Reithinger et al., 2007; Bailey et al., 2017). In Brazil, *Leishmania* (*Viannia*) *braziliensis* (Vianna, 1911), *Leishmania* (*Viannia*) *guyanensis* (Floch, 1954), and *Leishmania* (*Leishmania*) *amazonensis* (Lainson and Shaw, 1972) are the most relevant species in medical and public health contexts (Padilha et al., 2010; Akhoundi et al., 2016). Clinically, CL is classified as localized cutaneous, disseminated cutaneous, diffuse cutaneous, and mucosal (Silveira et al., 2004). The cutaneous form is more frequent and generally presents itself as a single painless ulcerated lesion of raised edges, with granular bottom (Guerra et al., 2015). The disease is a tropical pathology that requires the attention of health services since diagnosis and treatment are difficult, which may allow lesions to evolve disfiguring and disabling forms, thus impairing the patient's quality of life and impacting their social life (Bennis et al., 2017).

In the Americas, Brazil is one of the most affected countries, and disease cases are verified with different epidemiological patterns across all federated units, which hinders its control (Alvar et al., 2012; Basano and Camargo, 2004). In the Amazon region, for example, up to 70% of the population is at risk of infection (Guerra et al., 2015; Brasil, 2017).

According to the Ministry of Health, 235,301 cases of CL were reported in the country from 2007 to 2017, with 72,395 cases recorded in the Northeast region, of which 30.4% occurred in the state of Maranhão (Brasil, 2018). Maranhão is located among three biomes with great climatic and ecosystem diversity and pronounced occurrence of deforestation and river siltation (Celentano et al., 2018). It is also one of the states with the highest indicators of poverty in the country, which is observed both at urban and rural areas (Sobel et al., 2010; Tronco and Ramos, 2017). Such factors associated with the increasing rates of migration and ecotourism in the region are critically important in the epidemiology of this neglected disease (Gonçalves Neto et al., 2013).

Despite these conditions related to dissemination, little is known about the occurrence of CL in the Eastern area of Maranhão, which is one of the most populous regions of the state. In this context, this study aimed to describe the clinical, epidemiological, and climatic profile, as well as the spatial dynamics of CL in Caxias, state of Maranhão (Brazil), with the purpose of contributing to the establishment of strategies for the prevention and control of the disease.

2. Material and Methods

This is a retrospective and descriptive study performed in the municipality of Caxias (04°51'32" S and 43°21' 22" W), located in the Eastern part of the state of Maranhão, in Northeast Brazil (Figure 1). Although the state of Maranhão includes the Amazon and Caatinga biomes, Caxias is in an area of Cerrado. The municipality extends for 5,150.667 Km^2 and has a population of 155,129 inhabitants (118,534 in the urban/peri-urban area and 36,595 in the rural area). The mean annual growth rate of the population is 1.12% (IBGE, 2010).

The CL data were collected from the records of the Brazilian Information System of Diseases Notification (*Sistema de Informação de Agravos de Notificação* - SINAN) between May and June 2018 and included all autochthonous cases reported and confirmed in the period between January 2007 and December 2017. Duplicate records and cases with incomplete or unregistered addresses were excluded.

The analysis included the following sociodemographic variables: gender, age, race/ethnicity, educational level, area of residence, and occupation; and the clinical variables: presence of lesion (cutaneous, mucosal) and case evolution.

The following epidemiological indicators of CL were calculated according to the Ministry of Health guidelines: incidence rate of cases in the municipality per 100,000 inhabitants and density of cases (Brasil, 2018). The population data for the municipality were obtained from the Brazilian National Census of 2010.

Statistical analyses were performed in the software BioEstat 5.3 (Belém, Pará, Brazil) and EpiInfo version 7 (Atlanta, Georgia, United States of America) using chi-square tests of independence (X^2) to verify differences in the proportions of the studied variables. One-way ANOVA (F) was used to detect differences between the mean of reported cases per year. In addition, the chi-square test of independence (X^2) was used to verify differences in the proportion of the variables age, race, schooling, area of residence, occupation, clinical form of CL, results of the Montenegro blood test, and disease outcome according to gender (male and female) and variables of residence and occupation, to evaluate the relationship between the disease and activities related to agriculture.

To ascertain the relationship between CL cases reported monthly in the period of 2007 to 2017 and climatic variables

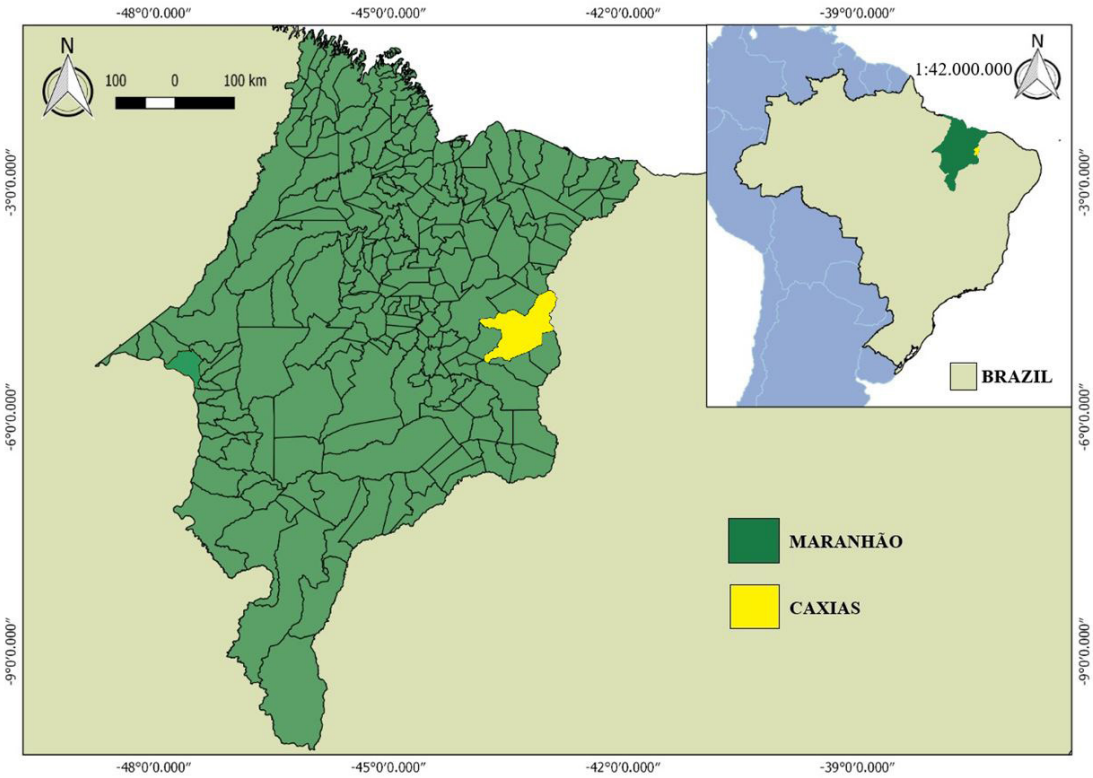

Figure 1. Map of the municipality of Caxias, Maranhão.

(minimum and maximum monthly mean temperature, monthly cumulative rainfall index, and monthly mean relative humidity), the Spearman correlation (r_s) non-parametric test was used, given the non-normality of the compiled data. In all tests, p-values below 0.05 were considered statistically significant. The Terraview 4.2.0 software (*Instituto Nacional de Pesquisas Espaciais*, São Paulo, Brazil) was used to produce the thematic map.

The present study was approved by the Research Ethics Committee of the *Centro de Estudos Superiores de Caxias*, *Universidade Estadual do Maranhão*, under the CAAE 88944518.3.0000.5554 and report nº 2,677,512, issued on May 26, 2018. As per the ethical principles of the Resolution 466/2012 of the Brazilian National Health Council, no signed consent forms were required, as only secondary and official publicly available data were used, without participants' identification.

3. Results

From 2007 to 2017, 201 cases of CL were reported in Caxias, with a mean of 18 cases per year. The highest and lowest numbers of cases were registered in 2015 (29 cases; 14.4%) and 2017 (6 cases; 3.0%), respectively. In 2015, there were 18.6 cases per 100,000 inhabitants, with a density of 5.4 cases per Km^2. No significant difference was observed between the mean number of cases recorded over the years (F = 0.83; p = 0.60) (Table 1).

Most of the cases were reported among males (141 cases; 70.1%). The most affected age group was between 31 and 60 years old, with 96 (47.9%) cases. Regarding race, 139 (69.2%) cases were reported among mixed race people. Among all those affected by CL, 117 (63.0%) had primary education, 114 (57.5%) lived in the urban area, 70 (38.8%) worked in agriculture and cattle raising, 197 (98.0%) presented the cutaneous form, 59 (90.7%) had a positive intradermal reaction test result, and 196 (97.5%) were healed after treatment. The highest proportion of men with CL (58 cases; 32.4%) were involved in occupations related to the agricultural sector ($X^2 = 8.35$; p = 0.03) (Table 2).

The great majority of the individuals living in the urban area did not present CL associated with work (96; 50.2%) ($X^2 = 54.1$; $p < 0.000001$). Moreover, the majority of those who had occupations unrelated to agriculture did not present the disease associated with these activities (106; 59.8%) ($X^2 = 152.9$; $p < 0.000001$) (Table 3).

Regarding the spatial distribution of disease in the municipality between 2007 and 2017, a higher concentration of cases was observed in the urban and peri-urban areas (Western and Southern regions of the municipality), with a predominance of cases in the Second District. A low concentration of cases was observed in the Northern and Eastern regions of the urban area of Caxias (Figure 2).

Regarding the climatic variables, a weak positive correlation was observed between the relative air

Table 1. Number, percentage of cases, detection rate per 100,000 inhabitants, and density of cutaneous leishmaniasis cases reported between 2007 and 2017, in the municipality of Caxias, state of Maranhão, Brazil.

Variable	Years											Total	Test
	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017		
Number of cases	24	14	14	28	22	22	9	23	29	10	6	201	F = 0.83
Percentage (%)	11.9	7.0	7.0	13.9	10.9	10.9	4.5	11.5	14.4	5.0	3.0	100.0	$p = 0.60$
Incidence rate per 100,000 inhabitants	15.4	9	9	18	14.2	14.2	5.8	14.8	18.6	6.4	3.8	-	
Density of cases per Km^2	4.6	2.7	2.7	5.4	4.3	4.3	1.7	4.5	5.6	1.9	1.2	-	

Km^2 = square kilometers; F = result of Analysis of Variance (one-way ANOVA); p = value of p.

Table 2. Demographic and clinical characteristics analyzed according to gender (male and female) in patients with cutaneous leishmaniasis between 2007 and 2017 in the municipality of Caxias, state of Maranhão, Brazil.

Variable	Sex		Total	Test
	Male N (%)	Female N (%)		
Age (N = 201)				
0-30 years old	34 (16.9)	21 (10.4)	55 (27.3)	$X^2 = 2.52$
31-60 years old	70 (35.0)	26 (12.9)	96 (47.9)	$p = 0.28$
61 years old or more	37 (18.4)	13 (6.4)	50 (24.8)	
Total	141 (70.1)	60 (29.9)	201 (100.0)	
Race (N = 201)				
White	20 (9.9)	9 (4.4)	29 (14.4)	$X^2 = 0.59$
Black	25 (12.4)	8 (3.9)	33 (16.4)	$p = 0.74$
Mixed-race	96 (48.1)	43 (21.3)	139 (69.2)	
Total	141 (70.1)	60 (29.9)	201 (100.0)	
Scholarity (N = 186)				
Without schooling	36 (19.3)	10 (5.3)	46 (24.7)	$X^2 = 3.33$
Elementary and Middle school (complete / incomplete)	77 (41.8)	40 (21.5)	117 (63.0)	$p = 0.34$
High School (complete / incomplete)	13 (6.9)	4 (2.1)	17 (9.1)	
Higher Education (complete / incomplete)	5 (2.6)	1 (0.5)	6 (3.2)	
Total	131 (70.4)	55 (29.6)	186 (100.0)	
Residence (N = 198)				
Urban	85 (43.1)	29 (14.6)	114 (57.5)	$X^2 = 2.44$
Rural	54 (27.2)	30 (15.1)	84 (42.5)	$p = 0.11$
Total	139 (70.2)	59 (29.8)	198 (100.0)	
Occupation (N = 181)				
Agricultural worker	58 (32.4)	12 (6.6)	70 (38.8)	$X^2 = 8.35$
Retired/pensioner	25 (13.8)	11 (6.0)	36 (19.8)	$p = 0.03$
Student	16 (8.8)	11 (6.0)	27 (14.9)	
Others	30 (16.5)	18 (9.9)	48 (26.5)	
Total	129 (71.2)	52 (28.8)	181 (100.0)	
Clinical form (N = 201)				
Cutaneous	138 (68.9)	59 (29.3)	197 (98.0)	$X^2 = 0.04$
Mucosal	3 (1.4)	1 (0.4)	4 (2.0)	$p = 0.83$
Total	141 (70.1)	60 (29.9)	201 (100.0)	

N = number of cases; X^2 = Chi-square; p = value of p.

Table 2. Continued...

Variable	Sex		Total	Test
	Male N (%)	Female N (%)		
Montenegro's intradermal reaction (N = 65)				
Positive	44 (67.9)	15 (23.0)	59 (90.7)	$X^2 = 0.22$
Negative	5 (7.6)	1 (1.5)	6 (9.3)	$p = 0.63$
Total	49 (75.3)	16 (24.7)	65 (100.0)	
Evolution (N = 201)				
Cure	138 (68.9)	58 (28.8)	196 (97.5)	$X^2 = 0.25$
Death by other causes	3 (1.4)	2 (0.9)	5 (2.5)	$p = 0.61$
Total	141 (70.1)	60 (29.9)	201 (100.0)	

N = number of cases; X^2 = Chi-square; p = value of p.

Table 3. Demographic characteristics of notified cases of cutaneous leishmaniasis according to the variable disease related to work, between 2007 and 2017, in the municipality of Caxias, state of Maranhão, Brazil.

Variable	CL related to work		Total N (%)	Test
	Yes N (%)	No N (%)		
Zone				
Urban	13 (6.7)	96 (50.2)	109 (56.7)	$X^2 = 54.1$
Rural	52 (27.0)	31 (16.1)	83 (43.3)	$p < 0.000001$
Total	65 (33.8)	127 (66.2)	192 (100.0)	
Ocupation				
Agricultural worker	65 (36.9)	5 (2.8)	70 (39.5)	$X^2 = 152.9$
Onother situation	1 (0.5)	106 (59.8)	107 (60.5)	$p < 0.000001$
Total	66 (37.2)	111 (62.8)	177 (100.0)	

CL = Cutaneous leishmaniasis; N = number of cases; X^2 = Chi-square; p = value of p.

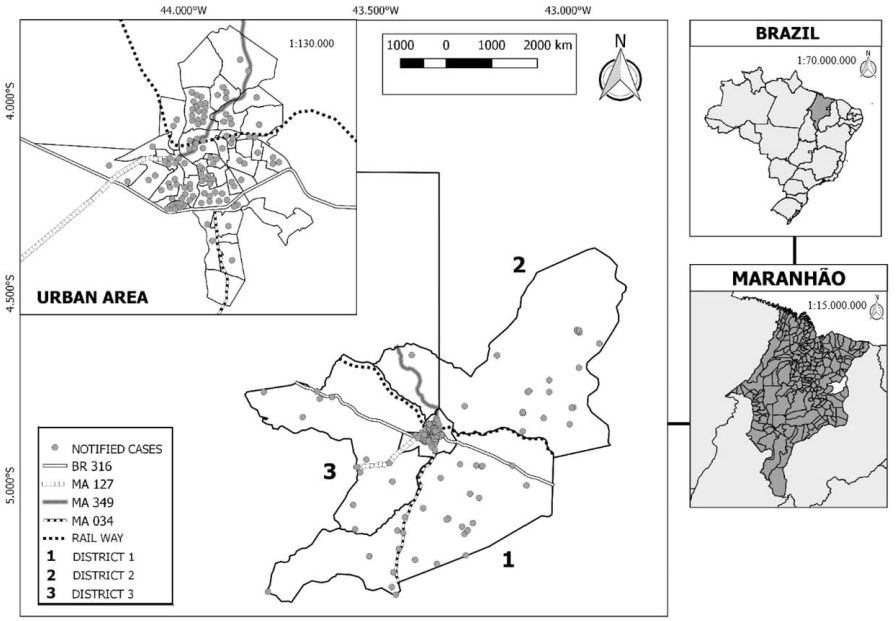

Figure 2. Representation of the spatial distribution of reported cases of CL between 2007 and 2017 in the municipality of Caxias, state of Maranhão, Brazil.

Table 4. Correlation between the number of cases of cutaneous leishmaniasis reported monthly and the meteorological variables in the municipality of Caxias, state of Maranhão, Brazil, from 2007 to 2017.

Pairs of variables	r_s	*p*
Number of cases and average monthly maximum temperature	-0.10	0.21
Number of cases and minimum monthly average temperature	0.03	0.68
Number of cases and monthly accumulated rainfall index	0.15	0.07
Number of cases and monthly average relative air humidity	0.18	0.04*

r_s = Spearman Correlation. p = value of p; *significant at 5% level.

humidity and the number of CL cases ($r_s = 0.18$; p = 0.04). No association was detected between the number of CL cases and maximum monthly mean temperature, minimum monthly mean temperature, or cumulative monthly rainfall index, during the study period (Table 4).

4. Discussion

CL is a neglected parasitic disease with widespread distribution in the Americas, where Brazil stands out as the head country in disease distribution (Alvar et al., 2012). The municipality of Caxias, east of Maranhão, is an endemic area for this infection, this is the first study that evaluated in a systematic way the occurrence, distribution and climatic factors associated with the CL in an 11-year historical series. Despite the disease control measures, the results show that the municipality maintains unequal patterns of temporal and spatial distribution of cases. The associated factors refer to environmental changes that occurred with the felling of forests and the establishment of populations in peripheral locations in the urban area and the regional climatic factors that allow the reproduction of the vectors.

The distribution of cases by gender showed that males were more affected by the disease. This result is in conformity with data reported by previous studies performed in several municipalities in Brazil, such as Buriticupu in the state of Maranhão (85.7%) (Martins et al., 2004); Jussara in the state of Paraná (82.5%) (Figueira et al., 2014); Teodoro Sampaio in the state of São Paulo (75.6%) (Oliveira et al., 2016); Rio Preto da Eva in the state of Amazonas (68.1%) (Júnior et al., 2009); and Vicência in the state of Pernambuco (59.4%) (Vasconcelos et al., 2017).

The predominance of CL among males is still unclear in the scientific literature. Studies suggest that engagement in agriculture-related activities increases the disease risk in males in some populations, due to the greater exposure to the risk of infection, both at the natural habitat of the vector and in wild and/or peri-domicile environments (Kaye and Scott, 2011).

In pathophysiological terms, some studies reason that sex hormones, such as estradiol and testosterone, may be one of the factors responsible for the greater susceptibility of males to infectious diseases, such as CL. Such hormones act through mechanisms of modulation of the immune response that vary between genders, thus influencing even severe forms of the disease (Guerra-Silveira and Abad-Franch, 2013; Bernin and Lotter, 2014). However, the distribution by gender may vary according to geographic location (Rostami et al., 2013; Guerra, 2019).

Regarding the age group of affected individuals, infection prevailed among individuals from the age range between 31 and 60 years old, which includes individuals in productive age. This age profile was also reported in other studies performed in the country (Figueira et al., 2014; Oliveira et al., 2016). Despite the predominance of the disease in adults, notifications at extreme ages (among children and elderly) suggest that the contact with the vector may occur at home and/or in the peridomiciliary environment (Reis et al., 2013). The presence of light sources and the rearing of domestic animals (chickens, pigs, dogs, cats, etc.) represent potential attractors that can lead to the increase in the population density of phlebotomine sand flies in such environments (Membrive et al., 2012; Mondolfi et al., 2019).

In this study, the predominant level of schooling among infected individuals was primary education. Noteworthy, a significant number of illiterate individuals were also affected. In fact, low schooling is an aggravating factor for infection, since these individuals are mainly rural residents and tend to work in the field, where they usually acquire the infection (Nikouee et al., 2017). Regarding race/ethnicity, the results show a predominance of infection among mixed-race. Similar data were found in other cities in Northeast Brazil, such as Vicência in the state of Pernambuco (83.1%) (Vasconcelos et al., 2017). It is important to highlight that the mixed-race population has a strong prevalence in Maranhão due to the extensive miscegenation present in the state (Martins et al., 2004).

Although CL was related to the rural environment, it was verified that most of the patients investigated in this study resided in the urban zone, which corroborates other similar studies (Vasconcelos et al., 2017; Medina-Morales et al., 2017). However, it was also verified that these individuals executed activities in the agricultural sector, which shows that CL is an occupational disease. The incidence of new cases related to agricultural activity has been widely reported in epidemiological studies, reaffirming the high risk of acquiring the disease that the workers face when in contact with a wild environment, in which the exposure to the infected vector most frequently occurs (Martins et al., 2004; Cella et al., 2011).

Several factors influence the occurrence of CL. Climatic factors, such as air temperature, rainfall and humidity influence the oviposition, favoring greater or lesser vector occurrence. However, wind speed, in particular,

may be determinant in the population density once it may completely inhibit sand fly activities, in addition to allowing them to seek domestic environments for shelter, facilitating contact with man (Cotteaux-Lautard et al., 2016; Dokhan et al., 2016). This fact demonstrates the need for continued entomological surveillance actions, considering climatic and meteorological factors as important conditions in the monitoring of CL endemicity (Souza et al., 2015; López et al., 2018).

In a study carried out at the municipality of Caxias from March 2013 to February 2015, 982 female sand flies were captured, the majority of which (n = 769) were collected from the urban area. In total, 51 were infected with *Leishmania* sp., with the highest infection rate (12.7%) being observed in the rural area (Silva et al., 2017). Despite the predominance of infected vectors in the rural environment, their presence in urban areas, both domiciliary and peridomiciliary, may be influencing the dynamics of disease occurrence in the municipality, as the process of demographic expansion approximates the population and domestic animals to the natural foci of the disease (Ramezankhani et al., 2018).

Noteworthy, the significant number of cases in the peri-urban zone of Caxias, near major transportation routes such as the BR-316, the state railroad, and the highway network (MA 127, MA 349, and MA 034) may play a role in the expansion of the disease occurrence, given the high flow of people in this area. As an example, a study conducted between 2000 and 2009 in 61 municipalities in the state of Maranhão located along the three main road and state rail corridors concluded that these could markedly influence the disease dissemination and maintenance (Gonçalves Neto et al., 2013).

The migration in areas with significant disease incidence, the urban/peri-urban expansion process, land settlements, hunting activities, and military training are some of the conditions that may adversely affect the occurrence of CL human cases (Melo et al., 2018). We found that the cutaneous form of leishmaniasis prevailed in the last years in Caxias, representing almost the total number of those infected. CL cases are recorded in the municipality based on the Montenegro Test results. Despite the high CL incidence in the municipality, almost all patients evolved to healing after treatment with pentavalent antimonial.

Regarding the climatic features, a significant correlation was observed between the number of CL cases and the relative air humidity, which may be related to the biology of the disease vector. It is known that phlebotomine sand flies usually live on humid substrates in the soil and successfully proliferate with the increasing humidity due to the rainfall, thus increasing the chances of infection (Alencar, 2007). However, despite the influence of the rain and moisture on the proliferation of phlebotomine sand flies, another study showed that high levels of precipitation may cause the destruction of breeding sites due to soil flooding. Therefore, the vector's reproductive success is higher in the period immediately after the rainfall (Macedo et al., 2008).

The present study has limitations inherent to the quality and coverage of secondary data. Factors such as the lack or incompleteness of information and duplicate records highlight the gaps still present in the notification system (Bezerra et al., 2018). In this context, there is still an urge to improve the quality of notification of the disease in the municipality.

Because it is an endemic area, strengthening of public policies are still required for the implementation of disease control and prevention measures in the most vulnerable areas of Caxias. In addition, the implementation of new studies to identify vectors and possible infected reservoirs will further aid in controlling the disease. In conclusion, based on the epidemiological and climatological characterization of disease occurrence presented in this study, preventive and control methods considering local and regional particularities are proposed for the municipality.

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