Human visceral leishmaniasis: epidemiological, temporal and spacial aspects in Northeast Brazil, 2003-2017

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ABSTRACT

Visceral leishmaniasis is a highly lethal zoonosis transmitted by a sandfly. It is caused by a *Leishmania* protozoan parasite and dogs are the main reservoir. Ceara State is endemic to visceral leishmaniasis and it is considered a high risk transmission area. Temporal and spatial epidemiological studies have been used as tools to analyze the distribution and frequency of human visceral leishmaniasis (HVL). This study aimed to characterize HVL in its epidemiological andtemporal aspects in Ceara State, from 2003 to 2017, as this is a neglected disease and a public health problem. This is an ecological study carried out with HVL confirmed cases in Ceara, using three blocks of years (2003 to 2007, 2008 to 2012 and 2013 to 2017). The disease presented an endemic behavior, affecting mainly male residents in the urban area, especially children under five and young adults between 30 and 49 years old. HVL is recorded in all the municipalities, for more than 10 years, with a growing trend and territorial expansion to the Central and Eastern regions of the State. The results of this study indicated the increase in the incidence and lethality, as well as the expansion of leishmaniasis in Ceara State.

KEYWORDS: Visceral leishmaniasis. Epidemiology. Spatial trend. Temporal trend.

INTRODUCTION

Human visceral leishmaniasis (HVL) is a chronic, highly lethal infectious disease caused by *Leishmania* (*Leishmania*) *infantum chagasi* and transmitted by the *Lutzomya longipalpis* sandfly[1]. Endemic in 97 countries, HVL has a higher incidence in developing countries, mainly in tropical and subtropical areas. India, Bangladesh, Nepal, Ethiopia, Sudan, South Sudan and Brazil reported almost 90% of the world cases and these countries have nearly 200 million people at risk, annually[2].

Present in all regions of Brazil, HVL has adapted to urban and peri-urban areas, directly impacting the endemicity and effectiveness of control actions[3]. The epidemiological profile of HVL in Brazil has been changing due to an increasing and disorganized urbanization, accentuated by a disordered land occupation and precarious living conditions[4,5]. Environmental factors play an important role in the dynamics of HVL transmission and they can explain, at least partially, its geographical expansion[6].

Brazil registered 16.08 cases of HVL per 100,000 inhabitants in 2015, the second greatest number in the world and the first in the Americas[2]. Children under five are more vulnerable to this disease with a rate of 12.67 cases per 100,000 inhabitants recorded in 2017[7]. Ceara State is considered an important epidemiological and

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entomological area for HVL, with environmental conditions favoring the maintenance of the vector. The number of HVL cases has been increased in Ceara, as well as the number of municipalities with new cases notified. These findings are directly related to the fast demographic transition associated to the increasing urbanization of the municipalities and the vector adaptation to the intradomicile environment[8,9].

Temporal trend analyzes are widely used strategies for the surveillance and control actions focusing on vector-borne diseases such as dengue, yellow fever, malaria and leishmaniasis[10]. Another important surveillance tool is the Geographic Information System (GIS), used to analyze spatial patterns of diseases distribution, identifying risk areas, associated factors and indicating priority areas for the development of control actions[11].

The spatial distribution and temporal trend of HVL in Ceara State are important for the planning and management of prevention and control actions. The objective of this study was to characterize the epidemiological, temporal and spatial aspects of HVL in Ceara State, from 2003 to 2017.

METHODS

Ceara State is located in the Northeastern region of Brazil, with a population of almost nine million inhabitants and an area of approximately 149,000 km², divided into 184 municipalities. It has borders to the North with the Atlantic Ocean, to the South with the Pernambuco State, to the East with the states of Rio Grande do Norte and Paraiba, and to the West with Piaui State. Ceara presents 93% of its territory in a tropical hot climate, and it is a predominantly semi-arid region[12]. It is divided into five macro-regions of

health: Metropolitan region of Fortaleza, Northwest region (Sobral), South region (Cariri), Central region (Sertao) and Eastern region (Litoral Leste) (Figure 1)[13].

A temporal and spatial analysis ecological study was carried out with confirmed cases of HVL in Ceara State, from January of 2003 to December of 2017. Secondary data from the new cases of HVL from the Department of Informatics of the National Health System - DATASUS and demographic data from IBGE (Brazilian Institute of Geography and Statistics) were used. Ignored, blank, abandoned and transferred cases were excluded. The incidence of HVL cases was calculated by sex, age and area of residence, dividing the number of new cases by the population at risk and multiplying by 100,000. The lethality coefficient was obtained by dividing the number of deaths by the total confirmed cases, multiplied by 100. The incidence was standardized by age group, with the 2010 population census of Ceara as the standard. To reduce the random error and to provide a greater stability of data, incidence coefficients were calculated considering three blocks of years (2003-2007, 2008-2012, and 2013-2017) and according to the classification period for transmission of HVL adopted by the Ministry of Health[14].

The temporal trend of the incidence and lethality coefficients were analyzed by the segmented log-linear regression model using the Joinpoint Regression Program version 4.0.4 (US National Cancer Institute, Bethesda, MD, USA), and the annual percent change (APC) was estimated by a segmented linear regression expressed in graphs, with the identification of inflection points in the trend of the measured values. Each inflection point reflects changes in the trend of HVL indicators. For the choice of the models,
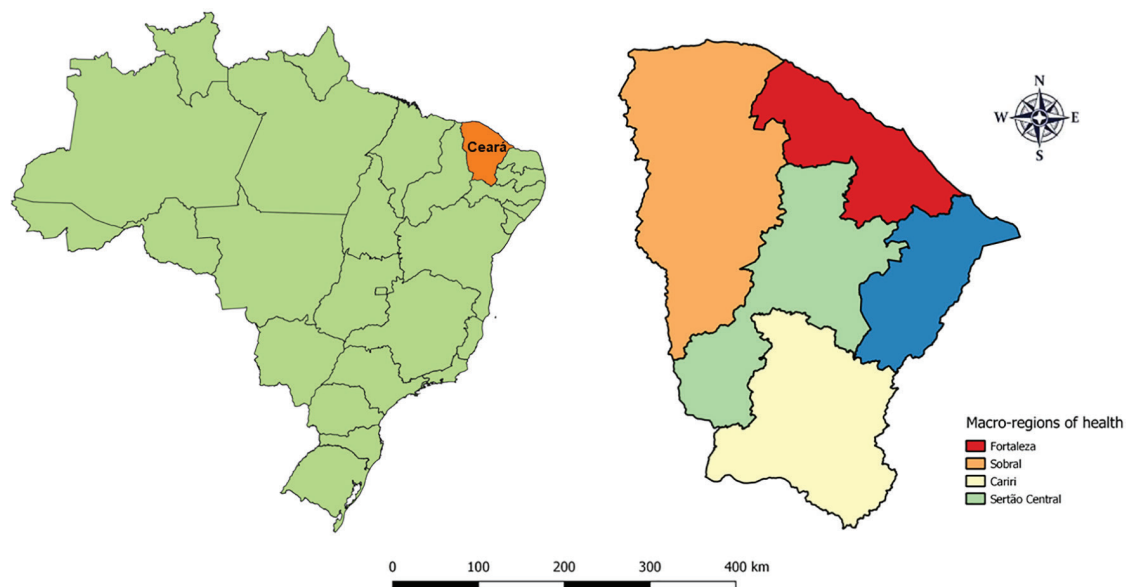

Figure 1 - Political division of Brazil and the health macro-regions of Ceara State, 2018.

the points of trend change were considered, representing a level of statistical significance higher than 95%. The statistical significance was tested by the Poisson model, using the Monte Carlo permutation test, defined the best segment for each regression model.

Local empirical Bayesian rate and Moran indices, considering a significance level above 95% (p <0.05), were plotted using the TerraView software, version 4.2.2 (Image Processing Division [DPI], National Institute for Space Research [INPE], Brazil). Results were expressed on maps elaborated by the Quantum-Gis software, version 2.14.8 (Open Source Geospatial Foundation [OSGeo], United States).

The use of the local empirical Bayesian rate aims to smooth the indicators in the space, between the municipalities. This model identifies the posterior distribution, from the application of Bayes' theorem, involving sample data (likelihood function), and from an observed data set (a priori distribution)[15]. Bayesian rates were calculated considering the population at risk and the number of cases for each period analyzed, multiplied by 100,000. To estimate the spatial variability in data analyses, a matrix of spatial proximity was defined, considering the contiguity as a construction strategy[16].

Prior to calculating the local Moran index, the spatial dependence was identified through the global indicator. The calculation of the local Moran index is a suitable method for analyzing the area type distribution that allows the uniqueness analysis between neighbors, with a scatter plot in which the indicator is present on the "X" and "Y" axes, and the Moran index is organized in four quadrants: Q1 (positive values, positive indices); Q2 (negative indicators, negative indices) indicative of positive spatial association, that is, an area in which neighbors have similar values; Q3 (positive values, negative indices) and Q4 (positive values, positive indices), indicative of negative spatial association, *i.e.,* an area compatible with different values[15].

The study was carried out in accordance with the principles of the Resolution 466/2012 of the National Health Council of Brazil[17].

RESULTS

From 2003 to 2017, 6,181 cases of HVL were confirmed in Ceara State, presenting 45 municipalities identified as a moderate transmission area in the period from 2013 to 2017. The mean incidence in this period was 10.4 confirmed cases per 100,000 inhabitants, with a mean of 399 deaths and mean lethality of 6.4%. There were higher incidence in males (6.8 cases per 100,000 male population), children under the age of five (19.5) and urban residents (4.9).

The standardized incidence had an increasing behavior throughout the period, with a peak in the year 2015 (6.6 cases per 100,000 inhabitants) and lower incidences in 2008 (2.6/100,000) and 2012 (3.1/100,000). In the years 2016 and 2017, there was a decrease in the incidence, to 4.8 and 4.5 cases per 100,000 inhabitants, respectively. On the other hand, HVL lethality in the first half of the series (2003 to 2010) showed a decreasing behavior, with an average of 5.9%, and an increment (7.4%) in the second half (Figure 2).

In the segmented trend analysis, HVL had an increasing incidence from 2003 to 2006, with an APC of 31.2% (95% CI: -18.8 to 111.9, p=0.20); from 2006 to 2017, the percentage of annual growth was 2.9% (95% CI: -1.7 to
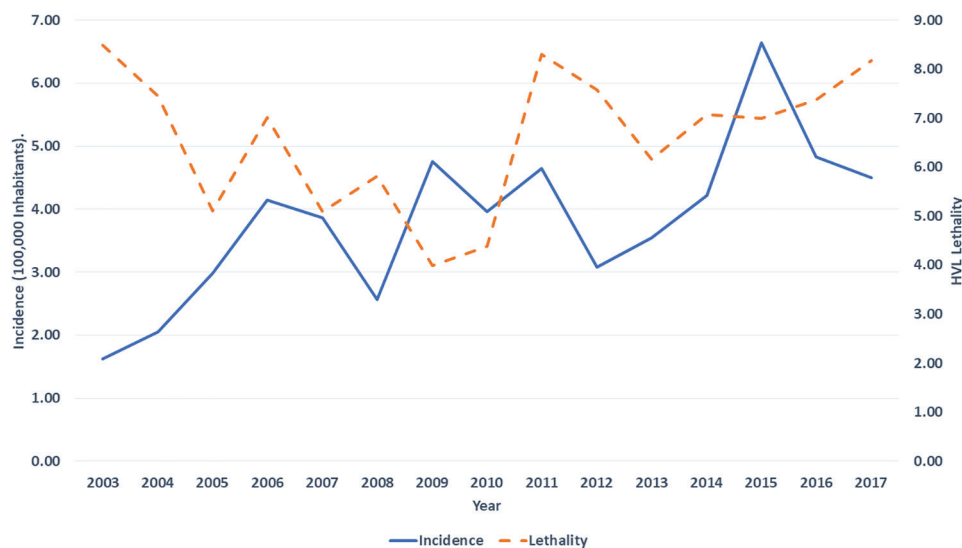

Figure 2 - Temporal distribution of HVL incidence and lethality coefficients in Ceara State, 2003-2017.

7.8, p=0.20). Lethality declined from 2003 to 2007, with an annual percent variation of -10.6% (95% CI: -25.3 to 7.0, p=0.20), increasing in the period from 2007 to 2017, with an APC of 4.4% (95% CI: -0.5 to 9.5, p = 0.10) (Table 1). These analyzes were not significant.

Fortaleza health region showed a significant and constant growth in the period between 2003 and 2010 (APC = 1.3, 95% CI: 0.2 to 2.3, p=0.024), with a peak of 910.2 cases per 100,000 inhabitants in 2009. From 2010, a statistically significant reduction was observed (APC = -1.2, 95% CI: -2.3 to -0.2, p=0.026). In the Sobral region, there was a tendency to increase with statistical significance, presenting inflection in 2009 (APC = 8.7, 95% CI: 0.1 to 18.1, p=0.047), with a significant fall between 2009 to 2017 (APC = -6.0, 95% CI: -10.5 to -1.3, p=0.018). In the regions of Cariri, Sertao and Litoral Leste, there were no inflections in the period 2003 to 2017. The Cariri and Sertao regions showed a decrease in the incidence coefficients, but with no statistical significance (APC = -0.6 and -2, 2, respectively); only in the Litoral Leste region there was a significant increase in HVL incidence coefficients (APC = 5.2, 95% CI: 2.2 to 8.3, p = 0.002) (Table 2).
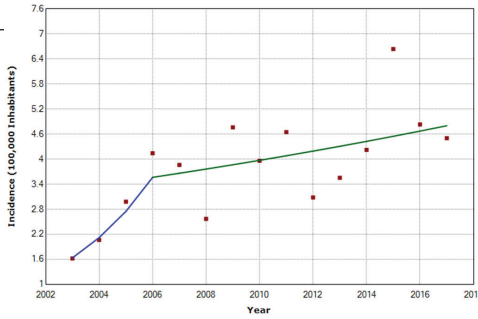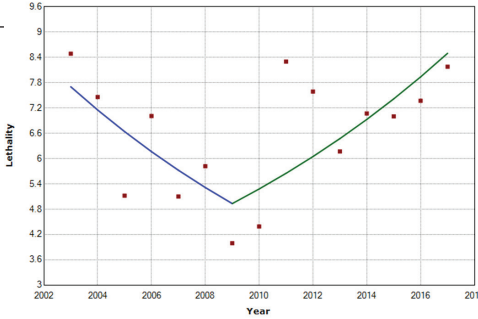
The HVL had the highest incidence coefficient value in the Sobral health region in the first period, with an average of 14.4 cases per 100,000 inhabitants, followed by Cariri (12.6), Sertao (7.9), Fortaleza (7.4) and Litoral Leste (2.0), with expansion in the period, mainly in the Sobral and Sertao Central regions, and a slight reduction in the Cariri region.

In the last period of the study, the analysis showed a greater territorial advance in the Sobral region, with cases in 37 of the 47 municipalities (78.7%), with an incidence above 30 cases per 100,000 inhabitants and a reduction in the Litoral Leste region. In the Cariri region, the number of municipalities with an incidence of HVL above 30 cases per 100,000 inhabitants expanded to all 24 municipalities (Figure 3).

In the spatial statistical analysis, the global Moran indices in the three periods from 2003 to 2007 (I=0.28; p=0.001); 2008 to 2012 (I=0.32; p=0.001) and from 2013 to 2017 (I=0.31; p=0.001) showed that the municipalities were spatially dependent, with the presence of self correlation throughout the State. Local spatial association (LISA) indicators showed clusters in the three periods in the Sobral, Cariri and Litoral Leste regions, while in the Fortaleza and Sertao Central regions, no clusters were identified in any of the periods, due to the absence of a significant spatial self correlation. Clusters were identified considering the similarity between municipalities and categorized into high incidence clusters located in the Northern and Southern areas. Low incidence clusters placed in the East and West areas, high incidence municipalities neighboring low

Table 1 - Joinpoint regression analysis of the incidence and lethality coefficients by HVL in Ceara State, 2003-2017.

Indicator	APC* 1	IC 95%**	p value	APC* 2	IC 95%**	p value	Graphics
		2003 to 2006			2006 to 2017		
Incidence	31.2	-18.8 a 111.9	0.2	2.9	-1.7 a 7.8	0.2	
		2003 to 2007			2007 to 2017		
Lethality	-10.6	-25.3 a 7.0	0.2	4.4	-0.5 a 9.5	0.1	

*APC: *Average Percentual Change*. **IC 95%: Confidence interval of 95%.

Table 2 - Joinpoint regression analysis of the HVL incidence coefficients per year and by health regions in Ceara State, 2003-2017.

Health regions	APC* 1	CI 95%**	p value	APC 2	CI 95%	p value	Graphics
	2003 to 2010			2010 to 2017			
Fortaleza	1.3	0.2 to 2.3	0.024	-1.2	-2.3 to -0.2	0.026	
	2003 to 2009			2009 to 2017			
Sobral	8.7	0.1 to 18.1	0.047	-6.0	-10.5 to -1.3	0.018	
	2003 to 2017						
Cariri	-0.6	-4.4 to 3.4	0.763	-	-	-	
	2003 to 2017						
Sertao	-2.2	-7.0 a 2.9	0.364	-	-	-	
	2003 to 2017						
East Coast	5.2	2.2 a 8.3	0.002	-	-	-	

* APC: *Annual Percent Change*. ** CI 95%: Confidence interval of 95%.

2003 - 2007   2008 - 2012   2013 - 2017

Cases per 100,000
- 0.00 - 0.00
- 0.01 - 5.00
- 5.01 - 10.00
- 10.01 - 30.00
- 30.00 - 70.00
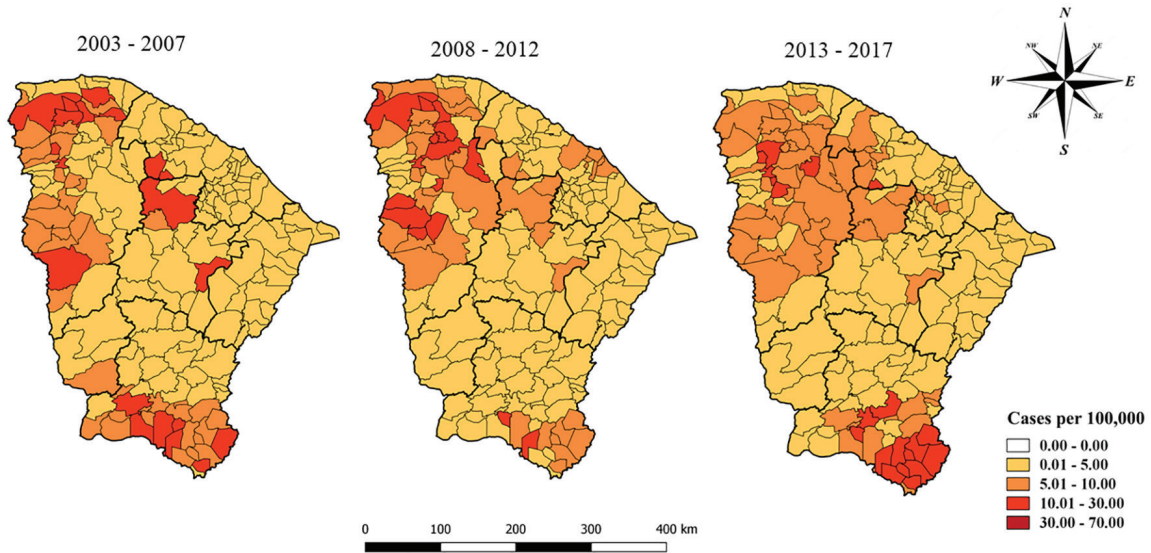
Figure 3 - Local Bayesian inference of the standardized incidence of HVL in Ceara State, 2003-2017.

2003 - 2007   2008 - 2012   2013 - 2017

Moran index
- not significant
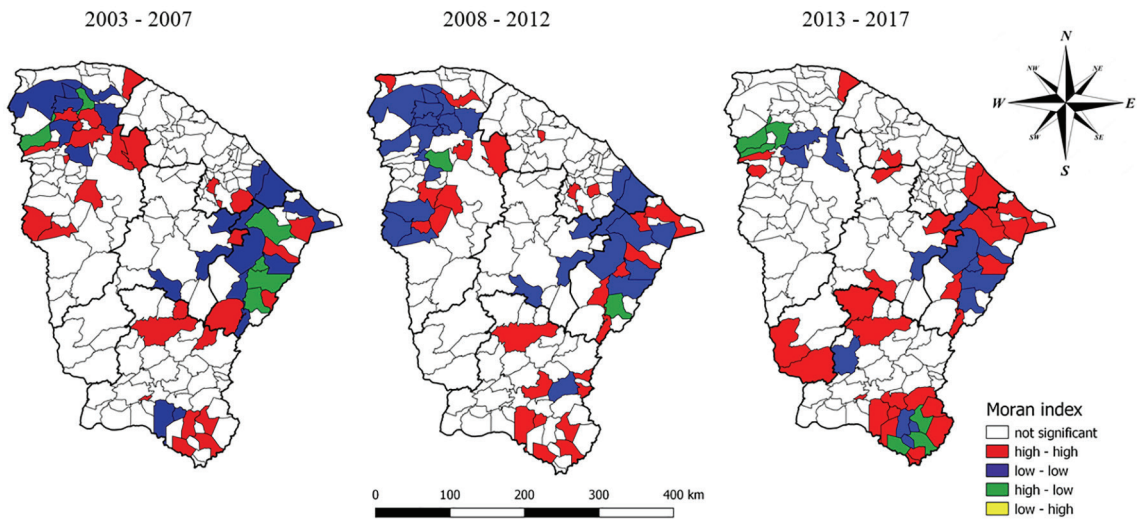- high - high
- low - low
- high - low
- low - high

Figure 4 - Local Moran index of the standardized incidence of HVL in Ceara State, 2003-2017.

incidence municipalities placed in the East area. In this analysis, no clusters formed by low incidence municipalities neighboring high incidence municipalities municipalities of categorization were identified. (Figure 4).

DISCUSSION

The present study evidenced a high number of confirmed cases of human visceral leishmaniasis in Ceara State, mainly in males under the age of five and residents of urban areas. In addition, the indicators point to an increase in the incidence coefficients in the period 2003 to 2006, and lethality from 2007 to 2017, highlighting the health regions of Sobral and Cariri.

The mean incidence in the period classified Ceara as an area of intense transmission to HVL. Even with an increasing incidence, lethality had a decreasing trend until 2010; this may indicate an improvement in diagnosis and appropriate treatment. However, since 2011, lethality has increased again, with an average above the maximum value defined by the Brazilian Ministry of Health. This indicator demonstrates a deficiency in patient care[18]. The Brazilian Visceral Leishmaniasis Surveillance and Control Program has prioritized efforts to reduce lethality, elaborating strategies to avoid about 250 annual deaths, not only because of the relevance of the outcome, but also because of the greater feasibility of achieving it compared to the substantial reduction in the incidence[19].

The age group with the highest occurrence of confirmed cases in Ceara was the children under the age of five. A study carried out in the Pernambuco State reported that 336 (68.5%) cases of HVL were recorded in this age group[20].

The occurrence of cases in children may be related to the relative cellular immune immaturity aggravated by the presence of malnutrition, a condition that is still very common in endemic areas[21].

The register of higher prevalence of the disease among males is not yet fully understood: some studies suggest the existence of a male hormone factor[22], while others claim that a greater male body exposure would favor the high frequency of the disease[23]. The results of the present study were similar to those reported in the Brazilian States of Bahia[24], Maranhao[25], Pernambuco[26], Piaui[27] and Minas Gerais[28]. In the Americas, the highest number of HVL cases was reported in males (66.3%), and the age group most affected was the children under the age of 10 (39.1%). Children under the age of five were the most affected age group in Colombia (83.7%), Honduras (71.4%) and Venezuela (66.7%)[2].

According to IBGE, 85% of the Brazilian population live in urban areas, which creates favorable conditions for the reemergence of visceral leishmaniasis. Environmental and climate changes, reduction of investments in health and education, discontinuity of control actions, adaptation of the vector to man-modified environments, immunosuppressive factors, social and environmental conditions in large urban agglomerations are also important factors[29].

The highest values of HVL incidence coefficients in the health regions of Sobral and Cariri demonstrated that the disease is present mainly in municipalities with a high rate of growth and urbanization, an intense migration of people, favoring a strength of the anthropic action on the environment. The changes in human behavior and in the natural environment of the vector and reservoirs exert great impact on the epidemiological profile of leishmaniasis, making it emergent in some urban areas[30]. The flow of people attracted to the regions of Sobral and Cariri has also allowed the migration of reservoirs from endemic areas, introducing possible infected animals that were not identified by the zoonoses surveillance services. Another important factor is the urban expansion by a real pressure exerted by estate speculation, which caused deforestation and increases the probability of vector interaction with humans and reservoirs (dogs, foxes, marsupials)[4]. It is still common to observe the circulation of animals between urban centers for commercial purposes in veterinary stores, as in the municipalities of Sobral (Sobral region) (3°41'10" S, 40°20'59" W), Juazeiro do Norte (14'14" S, 39°19'20" W), Barbalha (7°18'20" S, 39°18'9" W) and Crato (Cariri region) (39°24'34" W). The epidemiological changes of HVL in Brazil are directly associated to urbanization as a consequence of environmental changes, migration, interaction and dissemination of infected reservoirs to areas without transmission, as well as the adaptation of the *L. longipalpis* vector to the peridomicile environment[31].

The regions of Sobral and Cariri have geographic elevations such as plateaus and valleys, with temperature, vegetation and fauna favoring sand flies reproduction[14,32]. Probably, the decreasing and significant behavior of HVL incidence in the health regions of Fortaleza and Sobral, from 2010 to 2017, was related to the drought period: rainfall indexes were lower than the average of 800 mm from 2009 to 2017, according to the Groundwater Information System (SIAGAS); which may have influenced the decrease of organic matter, soil moisture and, consequently, the reproduction of leishmaniasis vectors[33]. Different rainfall averages were observed in distinct regions of Ceara State, mainly in the Acarau hydrographic region. The precipitation index in 2011 was 1,020 mm, reaching only 170 mm in 2015 in the municipality of Sobral. In the municipality of Acarau, the rainfall index in 2011 was 1,150 mm and in 2015 was 223 mm, and both municipalities are located in the Northern region of Ceara.

In a study carried out in the city of Ponta Pora, Brazil, three environmental variables (maximum temperature, relative humidity and rainfall) were positively correlated with the abundance of sandflies[34]. In Tocantins State, between 2007 and 2014, a positive correlation was observed between the HVL incidence coefficient and climate/environmental variables, such as temperature, air humidity and precipitation[35]. El Niño episodes were related to the variation in the annual incidence of HVL in Bahia State, suggesting an early warning system based on these episodes to help reducing the health impact of disease in susceptible regions in Brazil[36].

In the rainy season, the phlebotomine population increases as the insects feed on the sap of the vegetation and begin their reproductive cycle. Female phlebotomines may use urban dogs as blood source and the organic extract accumulated in the soil favors oviposition, thus raising the vector population and the risk of HVL transmission. In these conditions, it is possible that there is a high correlation between the HVL incidence and environmentalissues, especially in urban areas. In a study carried out in the city of Sobral, an elevation of the phlebotomine population was observed in the rainy season (January to April), in 2005 and 2006, confirming the relationship between vector density and rainfall[32].

The incidence of HVL in the Sertao region decreased from 2003 to 2017, which may be related to the dry season[13]. In the Cariri region, the incidence was not statistically significant, which can be explained by the fact that it presents environmental conditions different

from other regions of Ceara, such as semi-humid climate, mean precipitation above 1,000 mm probably due to the proximity with the plateau of Araripe, with humidity levels comparable to the Amazon and Atlantic Forest and lower temperature than the rest of Ceara, with a mean temperature of 27 °C[37]. In this way, the vector population tends to remain balanced with entomological fluctuations within the expected[38].

The increasing incidence of HVL in the Litoral Leste region was concentrated in the municipalities of Aracati (4°33'46" S, 37°46'9" W), Jaguaruana (4°49'51" S, 37°46'54" O) and Russas (4°56'21" S, 37°58'43" W). These three municipalities are part of the Jaguaribe river basin, in the Eastern Ceara State. This river has been suffering with construction of irrigation canals, banana plantations, shrimp farming and irregular occupation[39]. PossIt is possible that these factors are associated with the increase and dispersion of HVL cases in this region. Ximenes *et al.*[40], in 2007, identified the influence of anthropic actions on the environment on the elevation of the phlebotominal population, favoring the emergence of HVL cases. In Minas Gerais State, ecological aspects and behavior of sandflies in endemic areas evidenced that the devastation of large wild areas for economic exploitation expanded the disease to peripheral urban centers[41]. In Bihar, India, 80% (750/938) of HVL cases were related to the agricultural activity[42].

The spatial expression of incidence after employing the empirical Bayesian smoothing model pointed to the health regions of Sobral and Cariri with a concentration of municipalities at higher risk of transmission. This situation points to the hypothesis that these regions are the ones that suffered great anthropic actions impacting the environment andfavoring the adaptation of the sandfly in inhabited areas[40].

The formation of clusters in the sSe was in accordance with the incidence areas established by the Baysian model, where in the first two periods (2003 to 2007 and 2008 to 2012) the formation of high incidence clusters in the Sobral and Cariri health regions was detected. In the third period (2013 to 2017), there was a decrease in the clustering of municipalities in the Sobral region, possibly because of the non spatial significance as the incidence progressed in this area. During this last period, it was possible to identify a cluster of high incidence municipalities in the Central Sertao region. The set of low incidence municipalities observed in the Litoral Leste has also been identified as the astest growing region for this indicator. This phenomenon becomes important because it portrays the early phase of HVL transmission, pointing to an opportune moment of intervention for the control of HVL in the region.

This study used secondary data; a lower consistency and completeness of data is possible, as well as poor information regarding the factors that influence the expansion of HVL. The identification of causes for the increased lethality in the last period of the study is not clear.

ACKNOWLEDGMENTS

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