

Visceral Leishmaniasis: temporal and spatial distribution in Fortaleza, Ceará State, Brazil, 2007-2017*

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Abstract

Objective: To analyze the temporal trend and describe the spatial distribution of Visceral Leishmaniasis (VL) in Fortaleza from 2007 to 2017. **Methods:** This was an ecological study using segmented temporal regression and thematic mapping. **Results:** Between 2007-2017, 1,660 new cases and 97 deaths were confirmed. The overall incidence rate showed a rising trend (Annual Percent Change - APC=8.7% – 95%CI -3.3;34.1), while the mortality rate (APC=-25.9 – 95%CI -48.5;-10.6) and lethality (APC=-33.0 – 95%CI -53.7;-17.6) showed a falling trend. From 2010-2015 the incidence rate fell (APC=-15.8 – 95%CI -25.1;-4.0), but mortality (APC=18.7 – 95%CI 9.4;50.6) and lethality (APC=40.1 – 95%CI 22.5;72.0) had an upward trend. In 2015-2017, incidence (APC=-24.6 – 95%CI -36.2;-10.3), and mortality (APC=-44.6 – 95%CI -58.8;-17.6) fell, while lethality remained stable (APC=-13.5 – 95%CI -38.7;3.8). High incidence neighborhoods were clustered in the western region of the city, however, mortality and lethality did not present defined spatial patterns. **Conclusion:** VL is endemic in Fortaleza, although there was a reduction in the last three years studied.

Keywords: Visceral Leishmaniasis; Temporal Distribution; Spatial Distribution; Epidemiology; Public Health.

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Introduction

Due to its morbidity and mortality, visceral leishmaniasis (VL) is considered by the World Health Organization (WHO) one of the five neglected diseases whose elimination is a priority.¹ With annual incidence estimated between 50,000 and 90,000 new cases, VL is endemic in around 83 countries or territories. However, in 2018 over 95% of new cases reported to the WHO occurred in just ten countries: Brazil, China, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan and Sudan.¹

In the Americas, VL continues to be a challenge for national and regional surveillance and control programs, given its high incidence and far-reaching geographic distribution.

In the Americas, VL continues to be a challenge for national and regional surveillance and control programs, given its high incidence and far-reaching geographic distribution. The Leishmaniasis Plan of Action for the Americas was approved in 2017. Its objective is to reduce leishmaniasis morbidity and mortality by strengthening infection diagnosis, treatment, rehabilitation, prevention, surveillance and control by 2022.²

Leishmaniasis can progress to severe forms and have high lethality when not adequately treated. In Brazil, all suspected and/or confirmed VL cases are obligatorily notified to the health authorities: the specific Notifiable Health Condition Information System (SINAN) VL form should be filled in completely, and epidemiological investigation should be carried out within 48 hours following case notification.³

Brazil reports 96% of cases occurring in the Americas.² Between 2007 and 2017, VL incidence varied between 1.7 and 2.0 cases per 100,000 inhab., while lethality increased from 5.9% to 8.8%. The highest lethality percentages occurred in 2015 and 2016 (9.0%).⁴

VL has territorial distribution of autochthonous cases in 25% of the 5,570 Brazilian municipalities and is present in 21 of the 27 Federative Units (77.8%).⁶ In

2018, the states of Maranhão (N=653), Pará (N=503), Minas Gerais (N=324) and Ceará (N=308) recorded the highest numbers of confirmed cases in Brazil.⁴

Up until the 1990s, the Northeast region accounted for 90% of cases notified in Brazil. In Ceará, VL has been described since the 1930s but it was only with effect from 1986 that it began to be notified continuously. Between January 2008 and August 2018, 6,347 cases were confirmed in the state of Ceará, with an average of 578 cases per annum and an average incidence rate of 6.7 cases per 100,000 inhab.; 12 VL deaths were notified in 2018, corresponding to 6.4% lethality.⁵

VL has been expanding in medium and large-sized urban areas in Brazil, including Fortaleza, challenging the capital city of Ceará state to prioritize its VL control and surveillance activities.³ Geographic distribution analysis has been used in epidemiological studies, which have identified spatial patterns of morbidity and/or mortality and associated socioeconomic and environmental factors, producing information that contributes to VL prevention and control.⁶

The objective of this study was to analyze the temporal trend and describe the spatial distribution of visceral leishmaniasis incidence, mortality and lethality rates in the municipality of Fortaleza, Ceará state, between 2007 and 2017.

Method

A descriptive cross-sectional study and an exploratory ecological study were performed on new confirmed and autochthonous VL cases in the municipality of Fortaleza between 2007 and 2017.

Fortaleza, the capital city of Ceará state, covers a total area of 314,930km², has 2,452,185 inhab. and is Brazil's fifth most populous city.⁷ The municipality is comprised only of urban areas (i.e. it has no rural areas) and its administration is divided into six Regional Executive Secretariats, comprised of 119 neighborhoods.⁷

The study used secondary data taken from the SINAN system. For the purposes of the descriptive analysis (frequency distribution and thematic maps), these data were grouped together into three periods: 2007-2010, 2011-2013 and 2014-2017. The population data were retrieved from the local city government Daily Health Conditions Monitoring System (SIMDA).

The sociodemographic variables studied were: sex (male; female); age group (in years: 0-4; 5-9; 10-19; 20-39; 40-59; 60 or over); race/skin color (white; black; yellow; brown; indigenous); and schooling (illiterate; elementary education; middle school education; high school education; higher education).

Clinical manifestations of VL described in case records were studied, such as fever, weakness, weight loss, cough and/or diarrhea, splenomegaly and hepatomegaly; as well as presence of human immunodeficiency virus coinfection (VL-HIV). Disease progression was also verified: cure; treatment dropout; death from VL; death from other causes; transfer.

The incidence rates were calculated by dividing the number of new cases by the population at risk, multiplied by 100,000 inhab. The mortality rates were calculated by dividing the number of deaths by the population at risk, multiplied by 100,000 inhab. Lethality was calculated by dividing the number of deaths by the number of new cases and multiplying by 100.

Spatial distribution was described through thematic mapping of the incidence rates (cases per 100,000 inhab., categorized into intervals: 0.0; 0.1-5.0; 5.1-10.0; 10.1-15.0; greater than 15); mortality rates (cases per 100,000 inhab.: 0.0; 0.1-1.0; 1.1-2.0; 2.1-4.0; greater than 4.0) and lethality (in percentages: 0.0; 0.1-10.0; 10.1-20.0; 20.1-50.0; greater than 50.0).

The indicators were calculated in a stratified manner, by neighborhoods, and for the city as a whole. All the rates were standardized by age group.

The temporal trend of the calculated indicators was analyzed using the Joinpoint Regression program (US National Cancer Institute, Bethesda, MD, USA). This program estimates the annual percent change (APC) of a segmented linear regression and identifies inflection points. APC represents the positive average percent change when there is an increase, or the negative average percent change when the indicator decreases over a given period. A 95% significance level ($p < 0.05$), Poisson distribution⁸ and a maximum of three joinpoints were established. The segmented linear regression model with two inflection points was chosen, because it was the model that provided the best explanation of the behavior of the indicators over time.

The analyses were performed with the aid of the Stata computer program, version 11.2 (Stata Corp LP,

College Station, TX, USA). The ArcGIS 9.2 computer program was used to build the maps.

Results

A total of 1660 new VL cases and 97 VL deaths were confirmed in the municipality of Fortaleza between 2007 and 2017. The disease was found to be predominant among males (69.4%), people of brown race/skin color (82.1% in 2007-2010, 86.2% in 2011-2013 and 91.8% in 2014-2017), those with schooling up to elementary education in the first period – 14.7% in 2007-2010 –, and with up to middle school education in the other periods – 7.7% in 2011-2013 and 8.7% in 2014-2017. The 0-4 year age group concentrated the highest proportion of new VL cases (30.8%) in the period 2007-2010; with effect from the following year, 2011, frequency was greater among the 20-39 age group – 32.9% in 2011-2013 and 33.2% in 2014-2017 (Table 1).

Fever was the most frequent clinical manifestation, with 96.1% in 2007-2010, 93.3% in 2011-2013 and 92.6% in 2014-2017, followed by splenomegaly, with 79.5% in 2007-2010, 72.7% in 2011-2013 and 61.6% in 2014-2017; an exception occurred in the third period, when weight loss came in second place: 67.9%. VL-HIV coinfection was proportionally more absent than present: it was not found in 75.1% of cases in the period 2007-2010, 65.4% in 2011-2013 and 61.3% in 2014-2017. Progression of cases achieving cure was most frequent in all periods: 82.5% in 2007-2010, 78.7% in 2011-2013 and 78.2% in 2014-2017. On the other hand, lethality grew over the three periods, from 4.0% in 2007-2010 to 5.6% in 2011-2013 and to 10.3% in 2014-2017 (Table 1).

In the first period, from 2007 to 2010, 17 neighborhoods had incidence above 15 cases per 100,000 inhab., located mainly in the western region of Fortaleza. A group of neighborhoods located in the southeast region of the city also stood out with incidence of between 10.1 and 15 cases per 100,000 inhab.; in this second region, a total of 17 neighborhoods fell into this incidence rate. In the same period, the mortality rate was found to be scattered all over Fortaleza, with the exception of the city's northeast region. A similar pattern was found in relation to lethality, although one neighborhood in the southeast of the city stood out with 100% lethality (1 death) (Figure 1).

Table 1 – Sociodemographic and clinical characteristics and progression of visceral leishmaniasis cases (N=1660) in Fortaleza, Ceará, 2007-2017

Characteristics	2007 a 2010 (N=828)		2011 a 2013 (N=465)		2014 a 2017 (N=367)	
	N	(%)	N	(%)	N	(%)
Sex^a						
Female	284	34.3	133	28.6	90	24.5
Male	543	65.6	332	71.4	277	75.5
Age group (in years)^a						
0-4	255	30.8	87	18.7	48	13.1
5-9	41	4.9	24	5.2	14	3.8
10-19	85	10.3	41	8.8	27	7.4
20-39	212	25.6	153	32.9	122	33.2
40-59	181	21.9	115	24.7	119	32.4
≥60	53	6.4	45	9.7	36	9.8
Race/skin color						
White	50	6.0	13	2.8	12	3.3
Black	5	0.6	4	0.9	2	0.5
Yellow	3	0.4	4	0.9	0	0.0
Brown	680	82.1	401	86.2	337	91.8
Indigenous	2	0.2	0	0.0	0	0.0
Unknown	88	10.6	43	9.2	16	4.4
Schooling^a						
Illiterate	6	0.7	4	0.9	5	1.4
Elementary education	122	14.7	28	6.0	17	4.6
Middle school	70	8.5	36	7.7	32	8.7
High school	112	13.5	28	6.0	30	8.2
Higher education	15	1.8	7	1.5	2	0.5
Clinical manifestation						
Fever	796	96.1	434	93.3	340	92.6
Weakness	603	72.8	324	69.7	222	60.5
Weight loss	602	72.7	333	71.6	249	67.9
Cough and/or diarrhea	404	48.8	225	48.4	161	43.9
Splenomegaly	658	79.5	338	72.7	226	61.6
Hepatomegaly	610	73.7	305	65.6	203	55.3
VL-HIV Coinfection^b						
Yes	70	8.5	61	13.1	83	22.6
No	622	75.1	304	65.4	225	61.3
Unknown	136	16.4	100	21.5	59	16.1

To be continue

Continuation

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Characteristics	2007 a 2010 (N=828)		2011 a 2013 (N=465)		2014 a 2017 (N=367)	
	N	(%)	N	(%)	N	(%)
Progression						
Cure	683	82.5	366	78.7	287	78.2
Treatment dropout	8	1.0	6	1.3	3	0.8
Death from visceral leishmaniasis	33	4.0	26	5.6	38	10.3
Death from other causes	19	2.3	25	5.4	8	2.2
Transfer	12	1.4	11	2.3	16	4.4
Unknown/blank	73	8.8	31	6.7	15	4.1

a) The difference in the number of observations is due to excluded unknown e blank records.

b) VL-HIV coinfection: visceral leishmaniasis and Human Immunodeficiency Virus (HIV) coinfection.

In the period 2011-2013, 17 neighborhoods had incidence greater than 15 cases per 100,000 inhab., located mainly in the western region of Fortaleza; 10 of these neighborhoods already had high incidence in the period 2007-2010. Between 2011 and 2013, the mortality and lethality rates were scattered all over Fortaleza, although a group of neighborhoods with higher rates was found in the city's central region, when of them with a mortality rate greater than 5 deaths per 100,000 inhab.

Between 2014 and 2017, only five neighborhoods, located mainly in the southwest of the city, had incidence greater than 15 cases per 100,000 inhab. It is important to emphasize that two of these neighborhoods did not have cases in the two previous periods. A group of neighborhoods located in the north and south-central regions of Fortaleza had incidence varying between 0.1 and 5.0 cases per 100,000 inhab. In the same period, the mortality rates and lethality were concentrated in the western and southern regions of the city, and two neighborhoods there had 100% lethality (1 death in each neighborhood) (Figure 1).

The segmented temporal trend analysis found two inflection points in the indicators analyzed, the first in 2010 and the second in 2015. Three segments were found over the period 2007-2017: the first between 2007 and 2010; the second between 2010 and 2015; and the third between 2015 and 2017.

Between 2007 and 2010, the VL incidence rate increased from 3.5 to 4.8 cases per 100,000 inhab.

From 2011 until 2013 there was a sharp fall, from 4.4 to 2.2 cases per 100,000 inhab., followed by a smoother reduction in the rate, between 2014 and 2017, from 2.3 to 1.1 cases per 100,000 inhab. Analysis by inflection point for the period 2007 to 2010 found a rising trend, although it was not statistically significant (APC=8.7 – 95%CI -3.3;34.1). With effect from 2010, this indicator showed a falling trend up until 2015 (APC=-15.8 – 95%CI -25.1;-4.0). This annual change fell even more in the final three years, from 2015 to 2017, when a statistically significant reduction in VL incidence was found (APC=-24.6 – 95%CI -36.2;-10.3) (Table 2).

Between 2007 and 2010, the VL mortality rate reduced from 0.2 to 0.1 deaths per 100,000 inhab. The rate oscillated between 2011 and 2013. In 2014 and 2015 the rate rose again to 0.2 and 0.3 deaths per 100,000 inhab., respectively. In 2016, the rate dropped sharply to 0.1 deaths per 100,000 inhab. and remained the same in 2017. The mortality rates fell in the first period, from 2007 to 2010 (-25.9 – 95%CI -48.5;-10.6), and in the third period, from 2015 to 2017 (-44.6 – 95%CI -58.8;-17.6). However, in the period from 2010 to 2015, an increase in VL mortality was found (APC=18.7 – 95%CI 9.4;50.6) (Table 2).

Between 2007 and 2010, VL lethality fell from 6.3% to 1.8%. With effect from 2011 up until 2015 there was a sharp increase, from 4.2% to 8.5%, followed by another increase between 2016 and 2017, from 4.9% to 6.7%. The temporal trend of lethality was statistically significant only in the first and second periods.

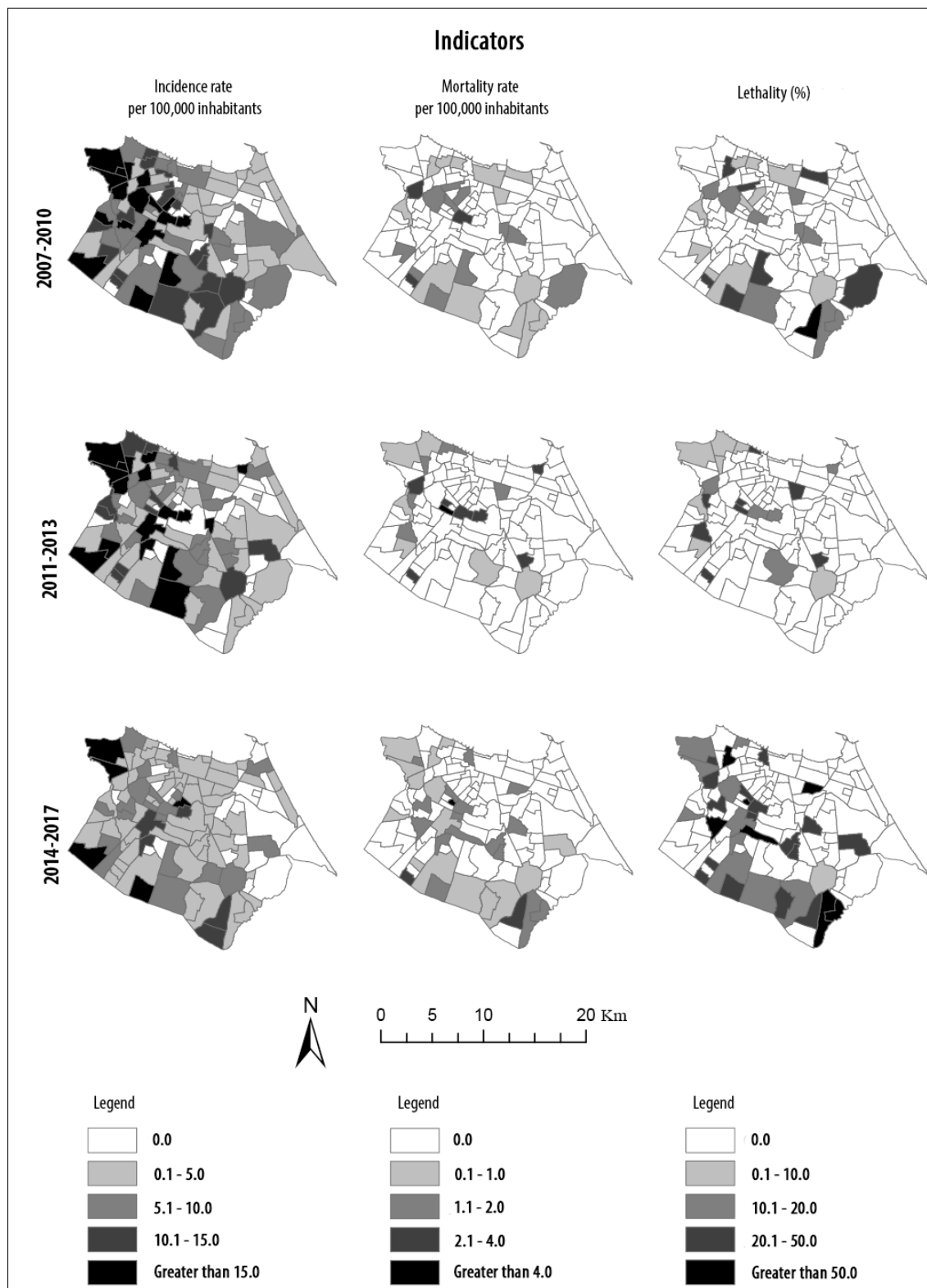


Figure 1 – Visceral leishmaniasis incidence, mortality and lethality rates in neighborhoods of Fortaleza, Ceará, 2007-2010, 2011-2013 and 2014-2017

Table 2 – Analysis of the temporal trend^a of visceral leishmaniasis rates (standardized per 100,000 inhab.) (N=1.660) in Fortaleza, Ceará, 2007-2017

Variables	2007 a 2010		2010 a 2015		2015 a 2017	
	APC ^b	IC95% ^c	APC ^b	IC95% ^c	APC ^b	IC95% ^c
Incidence rate (per 100,000 inhab.)	8.7	-3.3;34.1	-15.8	-25.1;-4.0	-24.6	-36.2;-10.3
Mortality rate (per 100,000 inhab.)	-25.9	-48.5;-10.6	18.7	9.4;50.6	-44.6	-58.8;-17.6
Lethality (%)	-33.0	-53.7;-17.6	40.1	22.5;72.0	-13.5	-38.7;3.8

a) Segmented linear regression.

b) APC: average percent change.

c) 95%CI: 95% confidence interval.

From 2007 to 2010, there was a decrease of -33.0 (95%CI -53.7;-17.6); while in the following period from 2010 to 2015, this indicator showed a 40.1 rising trend (95%CI 22.5;72.0). With effect from 2015, VL lethality was found to be stable (APC=-13.5 – 95%CI: -38.7;3.8) (Table 2).

Discussion

The VL indicators remained high and had cyclical behavior, despite the reduction in the incidence and mortality rates and despite the reduction in lethality. Moreover, the disease spread to an even greater number of neighborhoods in Fortaleza. People in the 20-59 age group became more affected, which implies a negative impact for the municipality's economy.

The highest incidence rates were concentrated in the western region of Fortaleza, while the lowest were limited to neighborhoods in the city's eastern region, following a pattern similar to that found for the period 2001-2007, possibly justified by neighborhood infrastructure. Fortaleza is socioeconomically divided. The neighborhoods in the west of the city, characterized as "peripheral", have worse structural conditions, both in terms of housing and sanitation, and these conditions are related to the occurrence of VL, while the neighborhoods in the east of the city are better developed economically and have better housing conditions and urban infrastructure.^{3,9}

A cyclical pattern with a certain amount of stability in the VL incidence rate was also found by a study conducted between 1999 and 2015, in the city of Araçatuba, SP. Its authors suggest that the reduction in cases occurred possibly as a result of control actions having been implemented.¹⁰ Other studies, conducted in the city of Aracaju, SE, between 1999 and 2008, and

in the state of Piauí, between 2007 and 2011, found the same cyclical pattern: a peak in the number of VL cases and incidence approximately every five years, which can be explained by the long-course characteristic of the disease, with signs of infection occurring later.¹¹⁻¹³

Despite variable incidence rates having been identified in the three periods studied, incidence in the majority of Fortaleza's neighborhoods was below 5 cases per 100,000 inhab.; there was also a reduction in the number of neighborhoods with incidence rates greater than 15 cases per 100,000 inhab. This falling trend was also found in the state of Alagoas, in 2013, when VL incidence in humans that year was the lowest in the study period from 2007 to 2013¹⁴.

Similar findings were found by a study conducted in the state of Sergipe, between 2010 and 2015, which identified diffuse scattering of VL cases. Despite the reduction in incidence in 2012, as a possible consequence of the state's surveillance actions, some of Sergipe's municipalities continued to notify new cases, indicating that there were areas where the disease persists and is actively transmitted.¹⁵

Expansion of leishmaniasis in Fortaleza may be directly related to the urbanization of both the disease and the vector, socio-environmental changes and migration of human and canine populations from endemic areas, introducing the parasite to new environments.^{12,16} Almost 70% of VL cases were found to be males. This fact has also been found by other studies, which found percentages between 60 and 75%, pointing to greater male susceptibility to the disease.^{13,17-20} Hormonal factors and factors related to exposure to the vector have been held responsible for increased risk of infection in males.¹¹

People of brown race/skin color were the most affected, differently to what was reported by a study

conducted in the municipality of Bauru, SP, where 49.3% of notified VL cases were among people of white race/skin color.²¹ This difference probably occurred because of the distinct racial characteristics of the populations of the two municipalities.

In Fortaleza the disease more frequently affected individuals with low schooling levels. A similar situation was detected in Pernambuco, between 2003 and 2015, when 12.9% of that state's cases had incomplete elementary education.²² Schooling is a proxy variable to the extent that it can suggest that poor socioeconomic conditions and vulnerabilities are more frequent among individuals affected by the disease. Notwithstanding, poor filling in of this variable on the investigation form hinders interpretation.

People in the 0-4 years age group as the most affected group was also found by a study conducted in the period 2002-2009, in Ceará's reference hospital for communicable diseases: when examining 196 medical records of children age 0-12 years, 33.2% of cases corresponded to children under 2 years old, and 29.0% corresponded to the 2-4 years age group.²³ Greater susceptibility of children may be explained by low immunity, greater exposure to the vector in the area around the household and poor nutritional status, which are common events in endemic regions.²²

While in the first period assessed, 2007-2010, there were more cases and greater vulnerability among children, in the following periods, 2011-2013 and 2014-2017, the 20-39 age group became the most affected by the disease, probably due to the increase in the number of cases of VL-HIV coinfection among individuals of adult age, who are more susceptible to immune system suppression. This characteristic was reported by another epidemiological study conducted in Ceará between 2007 and 2011. Up to 2006, the population of children with VL in the state was greater than that of adults; after that, however, there was a leveling of VL occurrences among both age groups and with effect from 2008 there was an increase in cases among adults.²⁴

The most frequent clinical manifestations in confirmed VL cases in Fortaleza were fever and splenomegaly. These symptoms were also found in Aracaju, SE, between 1999 and 2008.¹¹ This pattern was also found by a study of clinical and epidemiological characteristics of VL cases conducted in the city of Campo Grande, MS,¹⁸ and in the state of

Pernambuco.²⁵ In endemic areas, any clinical picture of febrile hepatosplenomegaly should be investigated as a suspected case of VL. Findings involving lymphadenomegaly, common in India and Sudan, were not described in the cases studied here, nor in other studies conducted in Brazil.²

VL-HIV coinfection was low in Fortaleza, taking into consideration the possibility of leishmaniasis behaving as an opportunistic infection in view of the immunosuppressed condition of these patients.²⁶ This form of coinfection, considered to be a serious Public Health problem, requires characterization, identification and solving of the difficulties involved in the progression of both diseases.²⁷

The proportional increase in the presence of VL-HIV coinfection found over the three periods was also reported in 2017, by Reis et al.: when comparing coinfection incidence between 2001-2006 and 2007-2014, those authors found greater occurrence of death among males, probably because they accounted for a greater proportion of treatment dropout.²⁸

Mortality rates and lethality were also found to be scattered, even though over 70% of neighborhoods had no deaths recorded. It is important to highlight that lethality of between 20.1 and 50.0 per 100 inhab. increased from 5.0% (2007-2010) to 12.6% of Fortaleza's neighborhoods (2014-2017).

In Brazil as a whole, between 2000 and 2011, VL mortality rates and VL lethality showed rising and statistically significant rising trends, even though they fell in some regions. Standing out are Brazil's North and Southeast regions, where rising mortality was recorded, and the Northeast region, where the increase in fatal cases was significant over the entire period.²⁷

A similar finding to that of our study was identified in the city of Belo Horizonte, MG, between 1994 and 2007: the local mortality rate showed an annual rising trend, although lethality remained stable, whereas in Fortaleza a rising trend in the lethality rate was found.²⁹

The main factors contributing to the increase in lethality include late diagnosis and expansion of the epidemic, affecting individuals with comorbidities. Complications resulting from infections and hemorrhages are recognized as the main risk factors for VL mortality.¹¹ Moreover, there is little research on the efficacy of recommended drugs currently used to treat the disease, and greater efforts are needed to

improve care for patients with critical forms of VL in order to avoid deaths.²

This study has limitations related to secondary data taken from the SINAN system, such as some fields being inadequately filled in, as well as missing or incomplete information. However, this did not compromise the information, given the large volume of notifications in Fortaleza.

In conclusion, there was a reduction in visceral leishmaniasis incidence over the three periods studied, despite the disease persists with its endemic and scattered behavior throughout Fortaleza. The highest incidence rates were found in neighborhoods in the western region of the city. With regard to mortality rates and lethality, they were found to be rising, with scattered distribution in the city's diverse urban regions. The data denote the endemic nature

of visceral leishmaniasis in the municipality, pointing to the need for actions enabling the occurrence of the disease in the population to be reduced, mainly among the population living in areas of greater risk.

Authors' contributions

Almeida CP, Florêncio CMGD, Cavalcante KKS, Moreno JO, Cavalcante FRA and Alencar CH were responsible for the concept of the study and for coordinating it, preparing the proposal, reviewing the literature, drafting the article and substantially reviewing it. Almeida CP and Alencar CH were responsible for analyzing and interpreting the data. All the authors have approved the final version and are responsible for all aspects thereof, including the guarantee of its accuracy and integrity.

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