Visceral leishmaniasis in Piauí, Brazil, 2007-2019: an ecological time series analysis and spatial distribution of epidemiological and operational indicators

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ABSTRACT

Objective: To analyze epidemiological and operational indicators, the temporal trend and spatial distribution of visceral leishmaniasis (VL), as well as VL-HIV co-infection in the state of Piauí, Brazil, from 2007 to 2019. **Methods:** This was an ecological time series study. Prais-Winsten regression was used to analyze the trend of VL incidence, case fatality ratio and operational indicators. **Results:** Mean VL incidence in the state was 6.03/100,000 inhabitants, with a rising trend in the 40-59 age group [annual percent change (APC) = 3.88; 95%CI 0.49;7.40] and in the regions located in the south of the state: Tabuleiros do Alto Parnaíba (APC = 14.19; 95%CI 3.91;25.50) and Chapada das Mangabeiras (APC = 12.15; 95%CI 6.69;24.96). Mean case fatality ratio was 6.02% and it remained stable. The mean rate of progression to cure was 52.58%, with a falling trend (APC = -5.67; 95%CI -8.05; -3.23). **Conclusion:** There was rising trend in VL incidence and a falling trend in its cure rate.

Keywords: Leishmaniasis, Visceral; Epidemiology; Indicators of Morbidity and Mortality; Disease Notification; Health Information Systems; Time Series Studies.

INTRODUCTION

Visceral leishmaniasis (VL) is a communicable disease with worldwide distribution, typically associated with poor living conditions. According to World Health Organization data, 83 countries or territorial areas are currently considered endemic, or have reported cases of VL; more than 95% of new VL cases globally are concentrated in just ten countries, including Brazil.[1] It is estimated that 50,000 to 90,000 new cases of this disease occur each year, although only 25% to 45% of them are reported.[2]

Historically known as a rural endemic, VL has led to epidemics in several large Brazilian cities in recent decades, making the disease a serious public health problem.[3] There is evidence of the relationship between VL and the country's increasing deforestation and urbanization process, along with human interference in wildlife habitats, leading to the rapid spread of the disease in cities.[4] Certain problems such as low income, lack of medical care and the population having little knowledge about the disease, consequences of the lack of public policies or inefficiency thereof, contribute to the persistence of endemic situations.[5] Another relevant issue is the high frequency of VL and human immunodeficiency virus (HIV) coinfection, due to the high prevalence of the latter when associated with the increase in VL cases, this being a reason for concern among health professionals, including those who work in epidemiological surveillance, given the severity of the cases and the rapid clinical progression of HIV-positive individuals to manifestation of acquired immunodeficiency syndrome (AIDS).[6]

VL is caused by parasites of the *Leishmania donovani* complex, including the species that causes the disease in Brazil, namely *Leishmania infantum*. The mosquito species *Lutzomyia longipalpis* and *Lutzomyia cruzi*, both belonging to the sand fly subfamily, are the two main vectors of VL and transmit the

Study contributions	
Main results	Visceral Leishmaniose (VL) predominated in males and children, was associated with social vulnerability and was a significantly underreported disease. Moreover, it had a strong endemic trend in most of the state of Piauí.
Implications for services	This study offers health services a broad panorama of the VL profile in Piauí, both in relation to the population most affected by the disease and also the locations where the government needs to be more incisive in promoting health actions.
Perspectives	Greater efforts are expected from the government to change the epidemiological scenario of VL in Piauí. Actions to combat the disease should be adopted, focusing on the main vulnerabilities presented in this study.

disease to humans during infected female sand fly blood meals.[7]

Brazil concentrated 97% of VL cases in the Americas in 2019, portraying the seriousness of the problem for the country with regard to its surveillance and control. In the Brazilian territory, during the period from 2007 to 2017, the VL incidence coefficient ranged from 1.7 to 2.0 cases per 100,000 inhabitants, while its case fatality ratio increased from 5.9% to 8.8%: the highest case fatality ratio occurred in 2015 and 2016, and the number of VL deaths corresponded to 9% of total deaths in the 2007-2016 ten-year period.[8]

The Plan of Action to Control Leishmaniasis in the Americas was approved in 2017. It aims to reduce morbidity and mortality by strengthening the diagnosis, treatment, rehabilitation, prevention, surveillance and control of infection by the year 2022.[8]

VL is expanding in Brazil. Its occurrence is highest in the Northeast region of the country, where 56.7% of diagnosed cases were recorded in 2019, with the state of Piauí accounting for 9.6% of Brazil's VL case notifications.[9] The VL incidence rate in Piauí was 5.9/100,000 inhab. in 2018, this being three times higher than the national average of 1.85/100,000 inhab. in the same year.[10]

The objective of this study was to analyze epidemiological and operational indicators, the temporal trend and spatial distribution of visceral leishmaniasis (VL), as well as VL-HIV co-infection in the state of Piauí, in the period from 2007 to 2019.

METHODS

Study design and period

This was an ecological time series study using records of new confirmed cases of VL in people resident in Piauí, notified on the Notifiable Health Conditions Information System (SINAN) between 2007 and 2019. Its unit of analysis was the state of Piauí, divided into 11 health regions, each one aggregating municipalities surrounding an urban center with regional health service referral facilities.

Study site

In 2020 Piauí had an estimated population of 3,281,480 inhabitants, population density of 12.4 inhab. per km² and a human development index of 0.646, ranking 24th among the 27 Brazilian states, below the national average of 0.765.

Data source

The SINAN data on notification of confirmed VL cases were obtained between September and October 2020, while the data on the resident population in September 2020 came from projections made by the Brazilian Institute of Geography and Statistics. Both databases are available on the website of the Brazilian National Health System Information Technology Department (DATASUS) and can be accessed using the TabNet tool.[11]

A 'new VL case" is defined as confirmation of VL, either by laboratory or clinical-epidemiological criteria, reported for the first time in an individual, or by exacerbation of symptoms after 12 months of clinical cure, provided there is no evidence of immunodeficiency.[12] We selected new confirmed leishmaniasis cases notified between 2007 and 2019. The indicators were calculated according to definitions provided in the Indicator Booklet, prepared by the Ministry of Health Technical Group on Leishmaniasis.[13]

Epidemiological indicators

The VL incidence rate was calculated by dividing the number of new VL cases by the resident population during the study period, multiplied by 100,000 inhabitants. The case fatality ratio was calculated by dividing the number of VL deaths by the total number of new VL cases of visceral leishmaniasis multiplied by 100. Percentage laboratory confirmation was calculated by dividing the number of laboratory-confirmed VL cases by the total number of new VL cases multiplied by 100.

Variables

The following sociodemographic variables were analyzed: 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; no information); schooling (illiterate/elementary education; high school education; higher education); zone of residence (urban; rural/periurban; no information); and health region in the state (Carnaubais; Chapada das Mangabeiras; Cocais; Entre Rios; Planície Litorânea; Serra da Capivara; Tabuleiros do Alto Parnaíba; Vale do Canindé; Vale do Rio Guaribas; Vale do Sambito; Vale dos Rios Piauí e Itaueiras).

The following clinical variables were analyzed: VL-HIV coinfection (yes; no; no information); confirmation criterion (laboratory; clinical-epidemiological); diagnosis via parasitology (positive; negative; not performed); diagnosis via indirect immunofluorescence (positive; negative; not performed); and clinical progression (cure; death from VL; transfer; death from other cause; dropout; no information).

Operational indicators

The proportion of VL cases coinfected with HIV was obtained by dividing the total number of new VL cases in HIV coinfected individuals by the total number of new VL cases multiplied by 100. Progression to clinical cure was calculated by dividing the total number of new VL cases that progressed to clinical cure by the total number of new VL cases multiplied by 100. The proportion of VL cases with unknown progression was calculated according to the quotient between the total number of VL cases (new and recurrent) with unknown progression and the total number of VL cases (new and relapsed) with unknown progression multiplied by 100.

Case characterization was presented in terms of absolute and relative frequencies, with association according to sex being verified by the Mantel-Haenszel chi-square test. The Prais-Winsten linear regression model was applied for the trend analysis, calculating annual percent change (APC) and its 95% confidence intervals (95%CI) using Stata version 14 (StataCorp LP, College Station, USA). The trend of the indicators we analyzed was interpreted as rising (p-value<0.05 and positive regression coefficient), falling (p-value<0.05 and negative regression coefficient), and stable (p-value>0.05); in all cases, statistical significance was attested by a p-value<0.05. The indicators were disaggregated by health region and presented in the form of maps, prepared using the Tabwin application.

Ethical considerations

As this was a study that used public domain secondary data in which cases were not identified, there was no need to submit it for approval by a Research Ethics Committee.

RESULTS

A total of 2,521 new confirmed visceral leishmaniasis cases were notified in Piauí between 2007 and 2019. The year with the highest number of cases in the time series analyzed was 2007, accounting for 237 registered VL cases, while the lowest number of occurrences (145 registered cases) was in 2019. The average number of cases recorded per year was 193.9, with an increase or decrease in notifications from one year to another, with greater positive variation observed in the 2013-2014 two-year period (+66 cases), and greater negative variation in the 2007-2008 two year period (-47 cases).

Among children under 9 years of age, most cases were female (62.4%), while in the 20-59 year age group there was a greater proportion of male cases (50.9%) (p<0.001). There was a predominance of people of black/brown race/skin color (91.7%), people who were illiterate or had elementary education (80.1%) and those living in urban areas (67.9%). With regard to clinical aspects, laboratory-confirmed VL cases prevailed (87.4%), and the percentage of positive parasitology tests was higher among males (56.2%). Regarding diagnosis by indirect immunofluorescence test, a higher proportion of positive results was found in females (27.0%), compared to males (21.5%). Moreover, attention is drawn to the percentage of indirect immunofluorescence tests that were not performed, both in the case of males (67.8%) (p=0.002) and females (62.1%) (p=0.002). The proportion of cases of VL-HIV co-infection was 12.4% (p<0.001) in males, this being higher than that found

in females (6.1%). Finally, the proportion of individuals with a record of progression to clinical cure was 52.4% in both sexes. However, there was a considerable percentage of records with no information about this variable (35.9%) (Table 1).

The mean VL incidence rate in the study period was 6.03/100,000 inhab., ranging from 7.57 in 2007 to 4.43 in 2019. A rising trend in this indicator was observed in the Chapada das Mangabeiras region (APC = 12.15; 95%CI 6.69;24.96) and the Tabuleiros do Alto Parnaíba region (APC = 14.19; 95%CI 3.91;25.50), located in southern Piauí. A falling trend was only found in the Planície Litorânea region (APC = -8.77; 95%CI -14.45;-2.71). The mean case fatality ratio was 6.02%, ranging from 6.33% in 2007 to 4.14% in 2019, so that the trend was found to be stable (Table 2; Figure 1).

Table 1 – Sociodemographic and clinical characteristics of new visceral leishmaniasis cases (n=2,521), Piauí, 2007-2019

Variables	Total		Male		Female		p-value[a]
	n	%	n	%	n	%	
Age group (in years)							<0.001
0-9	1,077	42.7	557	33.0	520	62.4	
10-19	212	8.4	143	8.5	69	8.3	
20-39	646	25.6	529	31.3	117	14.0	
40-59	415	16.5	331	19.6	84	10.1	
≥60	171	6.8	128	7.6	43	5.2	
Race/skin color							0.150
Black/brown	2,311	91.7	1,562	92.5	749	89.9	
White	115	4.6	67	4.0	48	5.8	
Yellow	18	0.7	10	0.6	8	1.0	
Indigenous	7	0.2	6	0.4	1	0.1	
No information	70	2.8	43	2.5	27	3.2	
Schooling[b]							0.678
Illiterate/elementary education	1,065	80.1	825	79.8	240	81.1	
High school education	246	18.5	200	19.3	46	15.5	
Higher education	19	1.4	9	0.9	10	3.4	
Zone of residence							0.438
Urban	1,713	67.9	1,149	68.1	564	67.7	
Rural/periurban	726	28.8	492	29.1	234	28.1	
No information	82	3.3	47	2.8	35	4.2	
Confirmation criterion							0.603
Laboratory	2,203	87.4	1471	87.1	732	87.9	
Clinical-epidemiological	318	12.6	217	12.9	101	12.1	

Continuation

Table 1 – Sociodemographic and clinical characteristics of new visceral leishmaniasis cases (n=2,521), Piauí, 2007-2019

Variables	Total		Male		Female		p-value[a]
	n	%	n	%	n	%	
Diagnostic parasitology							0.002
Positive	1,374	54.5	949	56.2	425	51.0	
Negative	464	18.4	315	18.7	149	17.9	
Not performed	683	27.1	424	25.1	259	31.1	
Diagnosis using indirect immunofluorescence							0.002
Positive	588	23.3	363	21.5	225	27.0	
Negative	271	10.7	180	10.7	91	10.9	
Not performed	1,662	65.9	1,145	67.8	517	62.1	
VL[c]-HIV[d] coinfection							<0.001
Yes	261	10.4	210	12.5	51	6.1	
No	1,906	75.6	1,265	74.9	641	77.0	
No information	354	14.0	213	12.6	141	16.9	
Clinical progression							0.071
Cure	1,321	52.4	873	51.7	448	53.8	
Death from VL[c]	153	6.1	95	5.6	58	7.0	
Transfer	110	4.4	68	4.0	42	5.0	
Death from other cause	23	0.9	17	1.0	6	0.7	
Dropout	9	0.3	8	0.5	1	0.1	
No information	905	35.9	627	37.2	278	33.4	

a) Mantel-Haenszel chi-square test; b) Records filled in with 'not applicable' (n=990) or 'no information' (n=201) were excluded; c) VL: Visceral leishmaniasis; d) HIV: Human immunodeficiency virus.

Table 2 – Visceral leishmaniasis incidence rate trend (per 100,000 inhabitants), case fatality ratio trend (%) and operational indicator trend (%), Piauí, 2007-2019

Variables	Annual percent change (%)	95%CI[a]		p-value	Trend
		LL	UL		
Epidemiological indicators					
Overall incidence rate	-1.16	-4.47	2.27	0.468	Stable
Incidence rate per health region					
Carnaubais	3.52	-5.81	13.77	0.437	Stable
Chapada das Mangabeiras	12.15	6.69	24.96	0.040	Rising
Cocais	-2.47	-6.76	2.01	0.246	Stable
Entre Rios	-1.99	-5.61	1.76	0.263	Stable

Continuation

Table 2 – Visceral leishmaniasis incidence rate trend (per 100,000 inhabitants), case fatality ratio trend (%) and operational indicator trend (%), Piauí, 2007-2019

Variables	Annual percent change (%)	95%CI[a]		p-value	Trend
		LL	UL		
Planície Litorânea	-8.77	-14.45	-2.71	0.009	Falling
Serra da Capivara	-1.90	-12.15	9.54	0.709	Stable
Tabuleiros do Alto Parnaíba	14.19	3.91	25.50	0.010	Rising
Vale do Canindé	2.15	-11.21	17.53	0.745	Stable
Vale do Rio Guaribas	-1.85	-6.83	3.40	0.448	Stable
Vale do Sambito	-2.56	-21.26	20.59	0.794	Stable
Vale dos Rios Piauí e Itaueiras	-4.14	-11.50	3.82	0.268	Stable
Casa fatality ratio (%)	-2.62	-6.72	1.66	0.202	Stable
Operational indicators (%)					
Laboratory confirmation	0.58	0.29	0.87	0.001	Rising
HIV[b,c] testing	0.66	-0.20	1.53	0.120	Stable
Parasitology	-1.48	-2.94	0.00	0.050	Stable
Immune testing	-10.69	-18.59	-2.03	0.021	Falling
VL[d]-HIV[b,c] coinfection	1.90	-2.34	6.33	0.347	Stable
Progression to clinical cure	-5.67	-8.05	-3.23	<0.001	Falling
Progression unknown	7.02	2.18	12.09	0.008	Rising

a) 95%CI; 95% confidence interval (LL = lower limit; UL = upper limit); b) Data with effect from 2008; c) HIV: Human immunodeficiency virus; d) VL: Visceral leishmaniasis.

Regarding the VL operational indicators, there was an increase in the percentage of cases with laboratory confirmation (APC = 0.58; 95%CI 0.29;0.87) and in the percentage of cases with unknown information about clinical progression (APC = 7.02; 95%CI 2.18;12.09). There was a downward trend in the percentage of cases with immune testing (APC = -10.69; 95%CI -18.59;-2.03) and in progression to clinical cure (APC = -5.67; 95%CI -8.05;-3.23) (Table 2; Figure 2).

Figure 3 shows the spatial distribution of the VL epidemiological and operational indicators according to the state of Piauí's health regions. The regions with the highest mean VL incidence rates were Entre Rios, where the capital Teresina is located (7.33/100,000 inhab.), Chapada das Mangabeiras (7.11/100,000 inhab.) and Serra da Capivara (6.84/100,000 inhab.) in the south, and Cocais (6.51/100,000 inhab.) in the northern region of the state. The highest proportion of laboratory confirmed cases corresponded to the Planície Litorânea region (93.2%), while only two regions had laboratory confirmation lower than 80%: Serra da Capivara and Vale do Canindé. The highest mean case fatality ratios were found in the Vale dos Rios Piauí e Itaueiras region (8.0%) and the Entre Rios region (7.7%), with the lowest ratio corresponding to the Serra da Capivara region (2.3%). A higher proportion of progression to cure was found in the northern region of the state, mainly in the Planície Litorânea region (66.7%) and the Entre Rios region (61.6%). Piauí's health region with the lowest cure rate was Tabuleiros do Alto Parnaíba (6.3%).
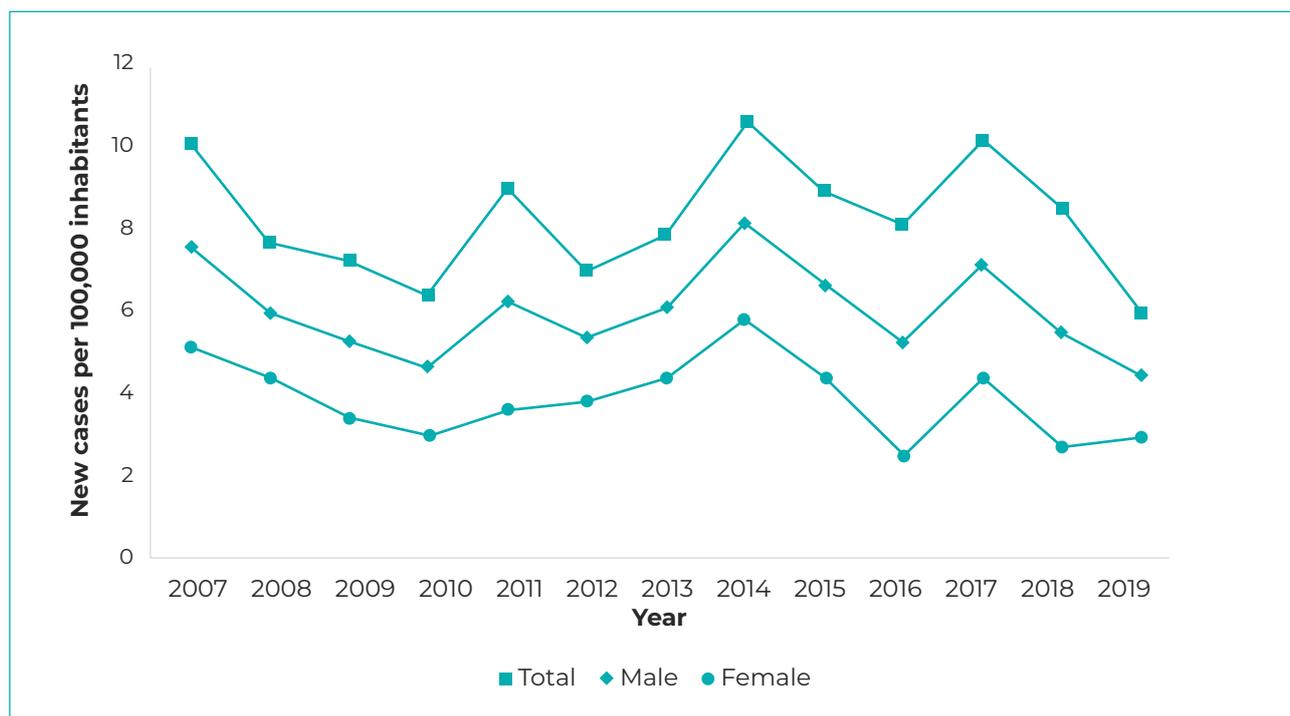
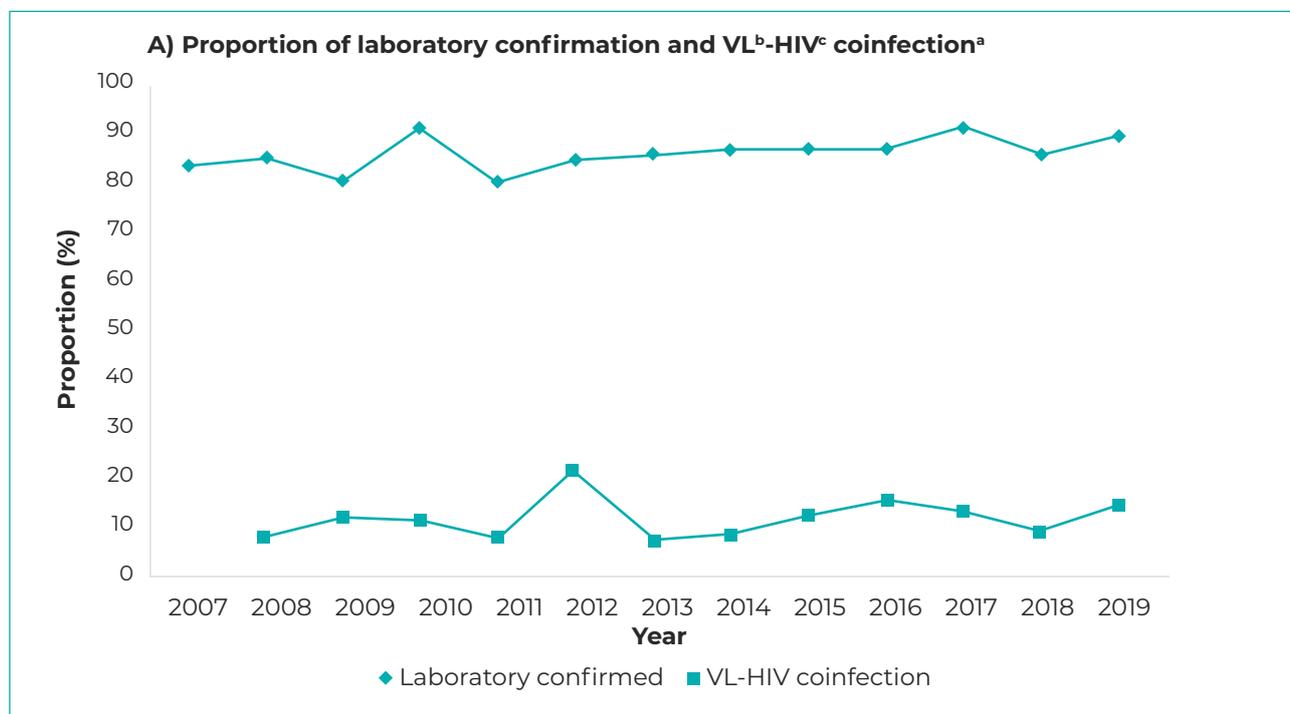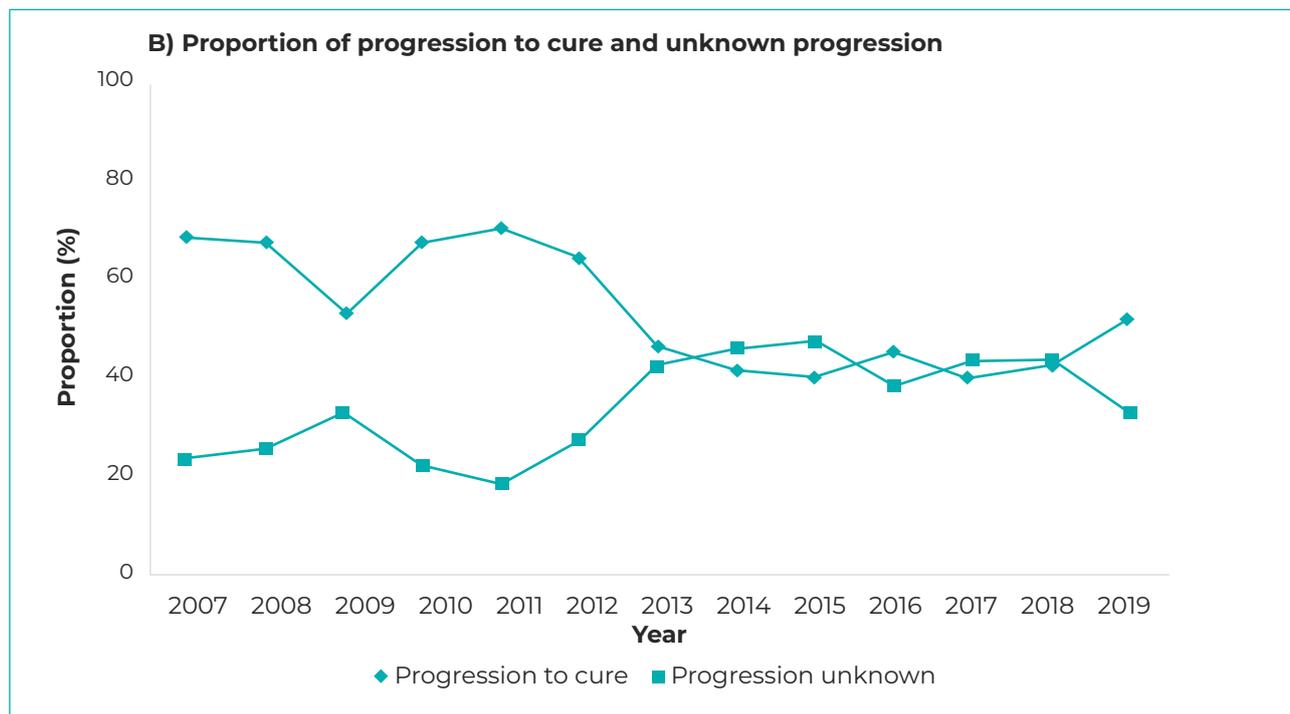**Figure 1 – Visceral leishmaniasis incidence rate progression, total and by sex, Piauí, 2007-2019**

Figure 2 – Visceral leishmaniasis operational indicator proportion progression and VL-HIV coinfection case proportion progression, Piauí, 2007-2019

Continuation

Figure 2 – Visceral leishmaniasis operational indicator proportion progression and VL-HIV coinfection case proportion progression, Piauí, 2007-2019

a) Data with effect from 2008; b) VL: Visceral leishmaniasis; c) HIV: Human immunodeficiency virus.
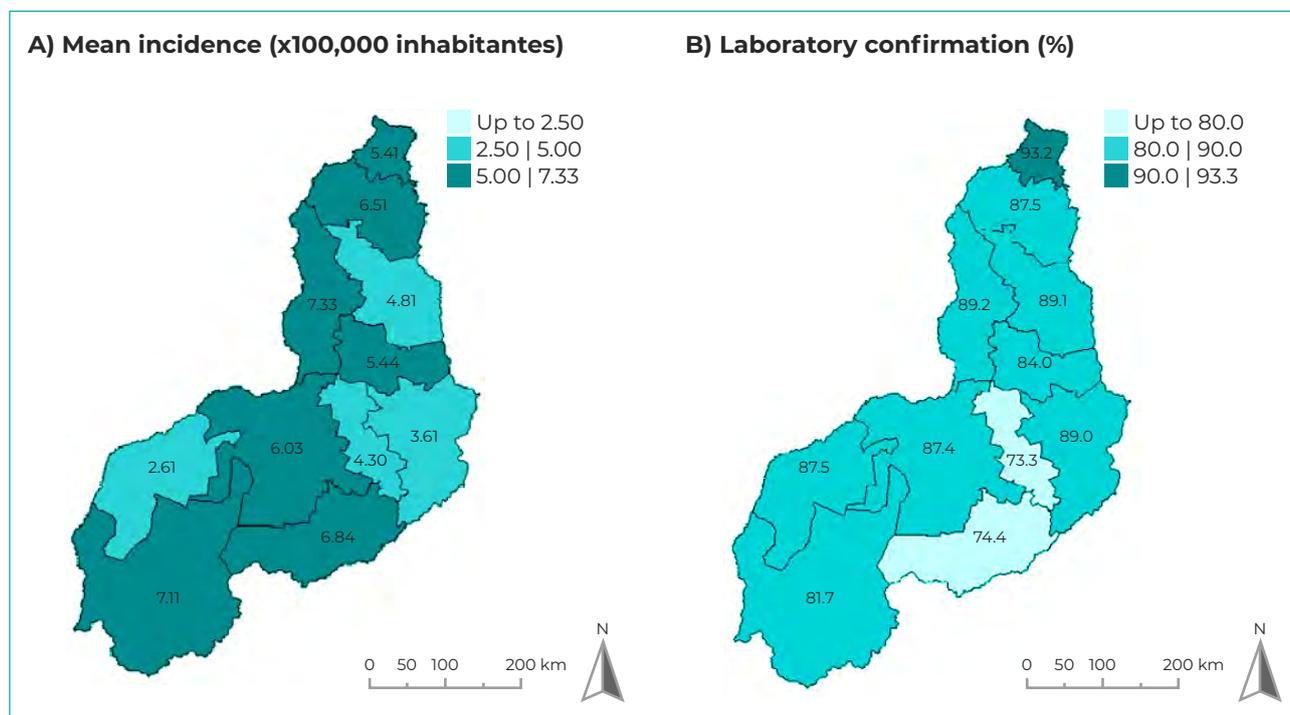

Figure 3 – Visceral leishmaniasis mean incidence rate and operational indicator spatial distribution, Piauí, 2007-2019
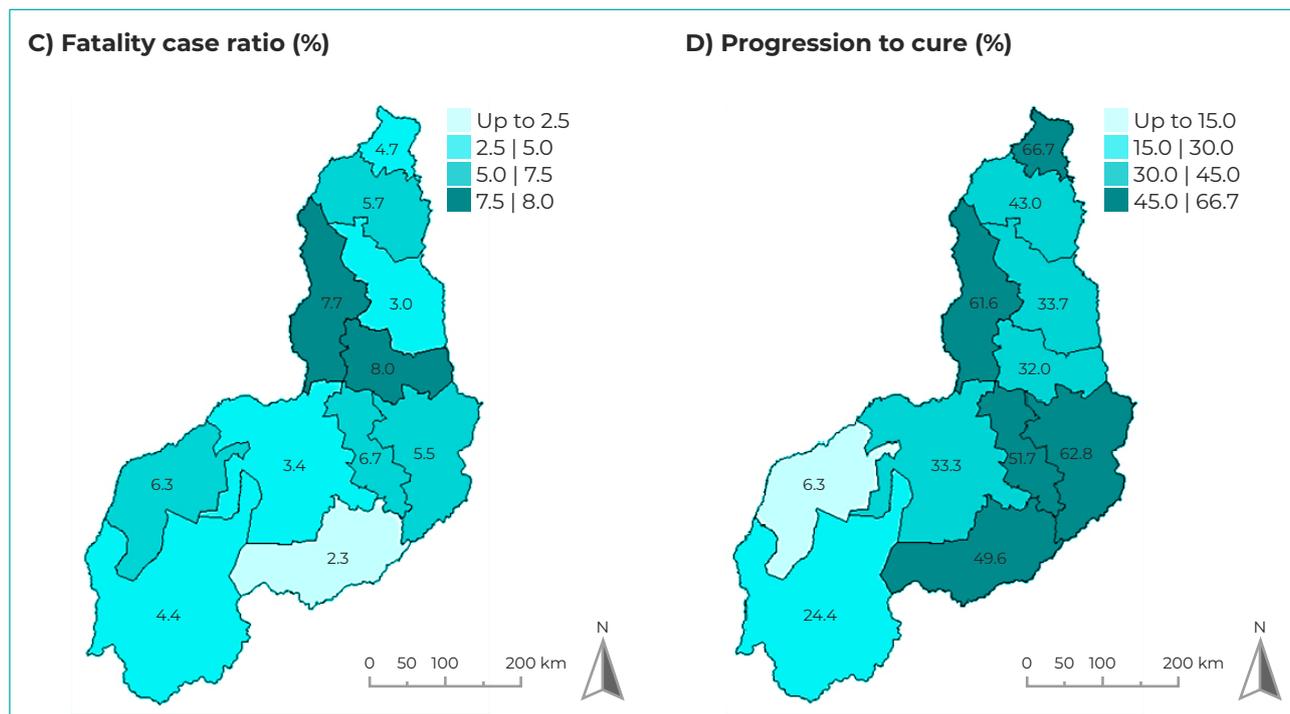
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Continuation

C) Fatality case ratio (%)

Up to 2.5
2.5 | 5.0
5.0 | 7.5
7.5 | 8.0

4.7
5.7
7.7   3.0
8.0
3.4   6.7   5.5
6.3
2.3
4.4

0   50 100   200 km

N

D) Progression to cure (%)

Up to 15.0
15.0 | 30.0
30.0 | 45.0
45.0 | 66.7

66.7
43.0
61.6   33.7
32.0
33.3   51.7   62.8
6.3
49.6
24.4

0   50 100   200 km

N

Figure 3 – Visceral leishmaniasis mean incidence rate and operational indicator spatial distribution, Piauí, 2007-2019

DISCUSSION

The study analyzed the epidemiological context of VL in Piauí over a 13 year period. The state has high occurrence of VL cases, and factors such as socioeconomic inequalities and environmental conditions have contributed to the increase in cases of the disease.[14]

A higher proportion of VL was observed in males and in people aged between 20 and 59 years. These data corroborate results of studies conducted in the city of Teresina,[15] and in the northern region of the state of Minas Gerais,[16] where higher proportions of VL were identified, 67% and 64% respectively, in males and in people in this age group. Regarding higher VL occurrence among males, there is a hypothesis that the disease is related to hormonal factors.[17] However, other authors suggest that occurrence of VL may be associated with occupational risks.[14,16] It should be noted that both sexes can be affected by

VL, and that from the analysis made, one cannot conclude that being of the male sex is a risk factor for infection.

People of black/brown race/skin color were the most affected by the disease, corroborating data from another study carried out in Teresina, in which the authors attributed this result to (i) the difficulty in defining race/skin color in the Brazilian population and (ii) the fact that the largest local population is low-income and of black or brown race/skin color, and coincidentally the group most affected by the disease.[17]

Most (80%) of the cases occurred in people who were illiterate or had only elementary schooling, thus confirming poverty as one of the determinants of the higher occurrence of VL, since (i) low schooling is a marker of low income and (ii) socioeconomic inequality is high in the state of Piauí. Moreover, the results of the present study confirm the evidence that individuals with low schooling tend to have a

lower level of knowledge about VL prevention measures, thus favoring higher incidence of VL cases.[18]

There was a higher proportion of occurrence of VL in urban areas, which accounted for the greatest growth in cases in relation to other areas. Underreporting in rural areas, as a consequence of lack of resources, infrastructure and availability of diagnostic tests, along with the migratory process, precarious socioeconomic conditions and rising deforestation to build houses, roads and factories, are factors that possibly contributed to the increase of cases in urban regions.[19,20] Shortcomings in surveillance activities, such as active tracing and identification of suspected cases, added to the scarcity of qualified financial and human resources, are important factors for the lack of VL control in urban centers.[20]

Part of the registered cases had VL-HIV coinfection, with higher occurrence among males. Antiretroviral therapy (ART) leads to increased immune response in people living with HIV, reducing opportunistic infections and complications arising from HIV infection. However, low adherence of the HIV-positive population to ART and low demand for care are factors that possibly explain the high frequency of people with this coinfection.[21] It is therefore important to carry out detailed investigation of cases in order to confirm and/or rule out VL-HIV coinfection, including testing people with suspected or confirmed VL for HIV. Equally important is ensuring treatment of both diseases, considering that leishmaniasis favors the worsening of HIV infection in individuals with VL.[10]

According to this study, of Piauí's 11 health regions, Chapada das Mangabeiras and Tabuleiros do Alto Parnaíba are those that have a rising trend, being regions of agrarian expansion located in the southern part of the state. These results are possibly related to the fact that this rural population has greater social

vulnerability and lower levels of knowledge about prevention measures.[14]

A study conducted in one of Piauí's municipalities suggested that expansion of VL in urban-rural transition areas suggests that expansion of peripheral neighborhoods in cities may be a determining factor for the persistence of the disease in urban areas.[22] Furthermore, occupying recently deforested areas means that humans can come into closer contact with the breeding environment of the vector that causes the disease and with wildlife reservoirs bearing the parasite.[23]

The high rates of VL in different regions of the state of Piauí can also be explained by the absence of prevention and control measures in part of the municipalities, contrary to Ministry of Health recommendations, besides the lack of trained human resources at the local level.[16] Sousa et al.[24] emphasized that according to studies conducted in Brazil, the VL control measures implemented thus far have not been capable of eliminating the transmission of the disease nor preventing the occurrence of new endemics.

The Vale dos Rios Piauí e Itaueiras region and the Entre Rios region had the highest VL case fatality ratios. In relation to Brazil as a whole,[20] the highest VL case fatality ratio (9%) in the last ten years was registered in 2019. This data is ratified by a study conducted in Piauí,[14] between 2015 and 2017, which found a case fatality ratio greater than 7%. The case fatality ratio in the Norte de Minas health macro-region,[4] between 2011 and 2015, of around 8%, was equally high. Late diagnosis and the increase in the number of cases in people who have comorbidities are factors that can explain the high case fatality ratio found, with infectious complications and hemorrhages being the main causes of death from VL.[16,25]

We found a reduction in cases that progressed to cure over the years studied, reaching the lowest percentage (33.1%) in 2019. Otherwise, there was an increase in the

frequency of notifications with unknown information about this outcome, which also reached a higher percentage in 2019. These data suggest that this parameter is distorted because of these information losses. Another study conducted in Piauí,[14] between 2015 and 2017, found similar results to this research, having reported a cure rate above 39%. Another study points out that there is a falling trend in progression to cure among children under 1 year old and is significantly low in individuals over 60 years old.[26] Furthermore, the proportional increase in unknown information can contribute to a reduction in the clinical cure rate.

The limitations of this study relate to it being based on data from secondary sources, which are subject to inaccurate information and underreporting, duplicate records and/or errors in filling out the forms.

Based on the results presented, we conclude that VL remains a neglected disease in Piauí, with a worrisome rising incidence trend and a high percentage of cases under treatment with unknown progression, suggesting failures in actions for VL care, surveillance and control in the state.

Studies that have analyzed VL in the state of Piauí are still scarce. In this sense, this analysis contributes to greater knowledge of the epidemiological situation of VL in the state of Piauí, and consequently, to the identification of areas at risk of vector transmission and needing entomological and zoonotic surveillance. Considering the rising trend of VL in some of the state's health regions, further studies are needed in these regions in order to identify the conditioning factors of this health condition and ultimately eliminate transmission of the disease.

AUTHORS' CONTRIBUTION

Chaves AFCP contributed to the study concept and design, data analysis and interpretation, drafting and critical reviewing the intellectual content of the manuscript. Costa IVS, De Sousa Neto FA and Brito MO contributed to data analysis and interpretation, and drafting the preliminary versions. Mascarenhas MDM contributed to the study design, data analysis, drafting and critically reviewing the intellectual content of the manuscript. All authors have approved the final version of the manuscript and are responsible for all aspects thereof, including ensuring its accuracy and integrity.

CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest.

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