ORIGINAL ARTICLE

EPIDEMIOLOGICAL ASPECTS OF VISCERAL LEISHMANIASIS IN RIO GRANDE DO NORTE, BRAZIL

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ABSTRACT

Visceral Leishmaniasis (VL) is a parasitic disease caused by *Leishmania* protozoa and transmitted by the bite of sand fly insects. This study aimed to describe the epidemiological aspects of VL in Rio Grande do Norte (RN), using variables inserted in the Information System for Notifiable Diseases, for the period from 2013 to 2019. The chi-square test of independence was used with p<0.05 considered statistically significant. 635 cases of VL were reported in RN, with stability of new cases in the analyzed period. 60% of cases were autochthonous, 84 (50.2%) municipalities in RN had autochthonous cases, with 70 (18.2%) cases in Natal and 58 (15.1%) in Mossoró. The most affected age group was 20-59 year old (57.3%) followed by 0-9 year old (23.8%), 10-19 year old (10.4%) and 60 year old or older (8.5%). There was a positive association between the 0-9 and 10-19 ranges with females and 20-59 with males (p=0.0001). Among the 532 individuals, 54.5% had a low level of education, and these, as well as the illiterate, associated with males (p=0.001). 85.3% of 612 cases were in black/brown group and 77.1% of 632 in urban/periurban residents. 27.6% of 500 were co-infected with HIV, 77.5% in males and 89.8% in adults. 70.7% progressed to cure and 6.8% died from VL. The study shows that the control measures adopted within the scope of the National Program for the Control of Leishmaniasis should be reassessed since there has been no decrease in cases, even though it has had stability over the years in Natal and a tendency to growth in Mossoró, the most affected areas.

KEY WORDS: Visceral leishmaniasis; *Leishmania*; epidemiology.

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INTRODUCTION

Visceral Leishmaniasis (VL) is considered by the World Health Organization (WHO) as one of the most dangerous tropical diseases, whose importance in the context of public health in Brazil has increased significantly in recent years, mainly due to the expansion of urbanization and modification of the habitats of the species involved in the transmission cycle (WHO, 2022; Castro et al., 2016).

VL, popularly known as kala-azar, is an anthropozoonosis caused by protozoa of the genus *Leishmania*, from the Trypanosomatidae family. Among the *Leishmania* species, the most prevalent in the Americas is *Leishmania infantum*. The transmission of leishmaniasis occurs through the bite of female sandflies, which acquire the parasite during the blood meal from infected animals, such as humans or other mammals, wild or domestic, that act as reservoirs (BRASIL, 2019; Batista et al., 2021).

The parasitosis is endemic in 98 countries, including Brazil, whose areas of occurrence progressively increase over the years, affecting mainly poor populations. Although there are specific diagnostic and treatment methods, a large part of the population does not have access to these procedures, which contributes to high mortality rates in these groups. In endemic countries, VL remains neglected by the private sector of the economy. Therefore, despite scarce resources and inadequate infrastructure, it has been up to the public sector to invest in the development of new drugs and more efficient diagnostic methods (Silva & Winck, 2018).

The parasite may be found in the promastigote form when it is in the vector, and in the amastigote form in the vertebrate host, targeting the reticulo-endothelial system in various tissues, infiltrating predominantly in the spleen, bone marrow, liver and lymph nodes. The immune response against the parasite may result in individuals resistant or susceptible to infection. Immune responses involving type 1 helper T cells (Th1) (T-helper 1 lymphocyte) contribute to the control of the infection, since it favors the destruction of the parasite inside the macrophage. The profile of susceptibility to infection involves a Th2-type response that favors parasite multiplication, due to the inhibition of nitric oxide production and reactive oxygen species. In this case, there is proliferation of B lymphocytes and production of the cytokines Interleukin (IL) 4, IL5, IL6, IL10, promoting plasmacytosis and hypergammaglobulinemia which leads to the formation of immune complexes, causing an inefficient humoral response and consequent survival of the parasite. Clinical manifestations include fever, hepatosplenomegaly, with massive splenomegaly, weight loss, cough, diarrhea, pain, and abdominal distension. In the later stage of the disease, patients may develop edema and ascites (Victor, 2021; Van Griensven & Diro, 2019).

Different methods can be used for the diagnosis of VL, and many advances have occurred throughout recent years. However, despite the large number of tests available for identification, none has 100% sensitivity and specificity. Thus, the investigation is routinely carried out based on epidemiological parameters, as well as immunological and parasitological ones, which consists of detecting anti-*leishmania* antibodies and looking for amastigotes of the parasite, respectively (Faria & Andrade, 2012; Brasil, 2019).

VL is a disease whose notification is mandatory and treatment is offered by the Unified Health System. Intravenous pentavalent antimonials are the most indicated drugs for treatment, despite adverse side effects. The limited therapeutic options available, as well as the absence of a human vaccine to prevent infection highlight the lack of investment in research and development in the field of leishmaniasis. To control canine visceral leishmaniasis cases, the ministry of health (MS) recommends treatment with miltefosine (milteforan®) and, as a prophylactic measure, the use of collars with repellents such as deltamethrin or the combination of imidacloprid and flumethrin, which repel mosquitos (Lindoso, 2018; Brasil, 2019).

In urban areas dogs are the main source of infection. Canine enzooty has preceded the occurrence of human cases and the infection in dogs has been more prevalent than in humans. In the capital from Rio Grande do Norte, Natal, there has been an increase in the number of cases and deaths from VL in recent decades, probably as a result of the large migratory flow that generated a disorderly population growth, associated with social problems and various environmental impacts. With the urbanization of the disease, in the period from 2007 to 2015, 199 autochthonous cases were registered in residents of the capital, with an average of 22 cases per year (Leite & Araújo, 2013; Vieira & Figueiredo, 2021).

Considering the importance and the need to know the epidemiology of VL cases in the most affected areas, the objective of this research was to analyze some clinical-epidemiological variables of this parasitosis in Rio Grande do Norte, observing the spatial distribution and calculating indicators of morbidity and mortality, seeking to collaborate with the planning of control strategies in the State.

MATERIAL AND METHODS

Study design

An epidemiological, descriptive and documentary study that analyzed VL cases confirmed by laboratory or clinical-epidemiological criteria, reported in the Department of Informatics of the Unified Health System (DATASUS) of the Brazilian Ministry of Health, where the information from the SINAN (Information System for Notifiable Diseases) is available are included.

SINAN is a publicly accessible database. Epidemiological data were collected from cases that occurred in the State of Rio Grande do Norte between the period of 2013 to 2019.

Study coverage area

The State of Rio Grande do Norte (RN) is located in the Northeast region of Brazil. It has 167 municipalities, with Natal being the State capital. It has a territorial area of 52,809 km^2 with an estimated population of 3,506,853 inhabitants for the year 2019, with a population density of 59.99 inhabitants/km^2 and an HDI of 0.684 in 2010. Only three of its municipalities have a population equal to or greater than one hundred thousand inhabitants: Natal, Mossoró and Parnamirim. In relation to health, it presented in 2009, 1,932 establishments adhered to the Unified Health System (IBGE, 2020).

Data analysis

Different search filters were applied to retrieve the following variables: year, municipality of notification, area of residence, autochthonous cases in the municipality of residence, sex, age, education level, race, acquired immunodeficiency virus (HIV) co-infection and clinical evolution.

Epidemiological data were collected from confirmed cases of VL, from individuals residing in the State of Rio Grande do Norte, from both genders (male and female), age (categorized into age groups), areas of residence (rural and urban), declared race (black, brown, white, indigenous and yellow) and education level, between the years of 2013 to 2019. Although some epidemiological variables isolated from the case were not reported in SINAN, the case was not discarded, that is, all cases registered were included in the study.

Simple percentages were calculated and the Prevalence Coefficient: (number of disease cases x $10n$/local population in the same period) as an indicator of morbidity. For mortality indicator, the lethality rate was calculated (number of deaths x 100/total number of cases) (OPAS, 2018).

To assess the association between the variables, the chi-square test of independence with analysis of adjusted residuals was used, with values with $p < 0.05$ being considered statistically significant. Microsoft Office Excel 2007 software was used to obtain graphs and tables, SPSS Statistic v.13.0 for analysis and QGIS to build maps.

Ethical guidelines

As this is a documentary study in which public domain data from the official website of the Brazilian Ministry of Health DATASUS were analyzed without identifying the subjects, there is no legal provision for submitting the research to the Research Ethics Committee in accordance with Resolution 466⁄2012 of the National Health Council (CNS, 2012).

RESULTS

In the study period (2013-2019), 635 cases of Visceral Leishmaniasis were reported in Rio Grande do Norte, where stability was observed in relation to the number of cases per year (Figure 1). Cases were reported in 39 (23.5%) of the 167 municipalities in Rio Grande do Norte, with 65.2% of notifications in the capital Natal and 24.4% in the city of Mossoró (Figure 2). As for the origin of the infection, from the 635 cases, 60% were autochthonous, 4.1% were allochthonous and 35.9% were undetermined. It is noted that 84 (50.2%) municipalities in RN had autochthonous cases, with 70 (18.2%) cases in Natal and 58 (15.1%) in Mossoró.
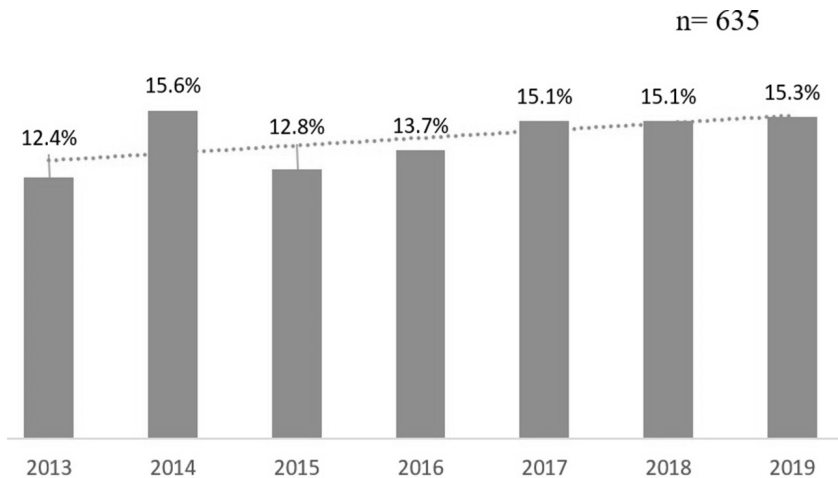

Figure 1. Visceral Leishmaniasis cases reported in Rio Grande do Norte State, between the years of 2013 and 2019.
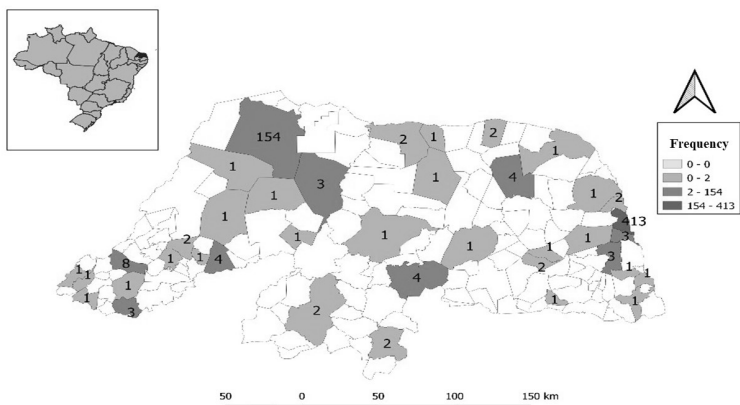Source: Survey Data, 2020.

Figure 2. Spatial distribution of Visceral Leishmaniasis cases (n=635) by municipality of notification in Rio Grande do Norte State, between the period from 2013 and 2019
Source: Survey Data, 2020.

Among the 632 cases whose area of residence was registered, 77.1% were in urban/peri urban areas.

From the 635 cases, 70.1% were male. The most affected age group was 20-59 years old (57.3%) followed by 0-9 years old (23.8%), 10-19 (10.4%) and 60 years old or older (8.5 %). Analyzing the distribution of age group by sex, a positive association was observed between the groups 0-9 and 10-19 years old with females and 20-59 years old with males (p=0.0001). There is no association with sex in the age group of 60 years old or older (Table 1).

532 people had their education level registered. From these, 54.5% had low education level, 11.1% had medium/high education level and 10.1% were illiterate. Analyzing the distribution of education level by gender, it was found that low education level and illiterate are associated with males and the variable does not apply with females (p=0.001). However, it is worth noting that in 103 cases the educational level was ignored.

In the total of 635 notifications, 612 had their race registered, with black/brown individuals being the most affected (85.3%), followed by white (14.2%), indigenous (0.2%) and yellow (0. 3%). Analyzing the two most prevalent race categories by sex, it is noted that in both, black/brown individuals were the most infected, with 86.5% in males and 83.8% in females, however, without statistical association. (p=0.383). In 23 cases the information on race was ignored.

Table 1. Visceral Leishmaniasis cases by age group, sex and education, in Rio Grande do Norte State, between the period from 2013 and 2019.

Visceral Leishmaniasis	Sex				p value
	Male		Female		
Age group	n	%	n	%	
0-9 years old	70	15.7	81	42.6 [+]	
10-19 years old	39	8.8	27	14.2 [+]	
20-59 years old	295	66.3[+]	69	36.3	0.0001
60 years old or +	41	9.2	13	6.8	
Total	445	100	190	100	
Education	n	%	n	%	
Illiterate	47	12.8 [+]	7	4.2	
Low education level*	218	59.4 [+]	72	43.6	
Medium/high education level **	42	11.4	17	10.3	0.001
Not applicable	60	16.4	69	41.9 [+]	
Total	367	100	165	100	

[+] Positive association – independence chi-square. *Low education level: Incomplete elementary degree, incomplete elementary degree, complete high school degree. **Medium/high education level: Completed secondary education, incomplete higher education and complete higher education
Source: Survey Data, 2020.

From the 500 cases of VL registered, 27.6% were co-infected with HIV. Table 2 shows that 77.5% of the cases occurred in males, with no statistical association between the variables (p=0.127). 89.8% of the cases were in adults, however, there are records among the elderly and adolescents. In 135 cases, information on the presence or absence of HIV co-infection was ignored.

Table 2. Cases of Visceral Leishmaniasis Coinfection with HIV by sex, in Rio Grande do Norte State, between the years of 2013 and 2019.

Visceral Leishmaniasis	Co-infection with HIV				
	Yes		No		p value
Sex	n	%	n	%	
Male	107	77.5	256	70.7	0.127
Female	31	22.5	106	29.3	
Total	138	100	362	100	
Age group					
0-9 years old	-	-	83	23.0	
10-19 years old	3	2.2	45	12.4	
20-59 years old	124	89.8	202	55.8	-
60 years old or +	11	8.0	32	8.8	
Total	138	100	362	100	

Source: Survey Data, 2020.

Regarding the outcome of the cases, 70.7% were cured and 6.8% of the individuals died from VL (Table 3).

Deaths from VL occurred more frequently in males with a total of 74.4% of cases and the age group most affected was the one with 20-59 years old with 69.8% followed by 0-9 years old (14.0%), 60 years old or older (11.6%) and 10-19 years old (4.6%).

Regarding the distribution of VL cases during pregnancy, from 635, only 0.3% were in pregnant women, 86.9% did not apply and 1.7% were ignored.

The average prevalence coefficient in the period in the State was 2.58 for every 100,000 inhabitants (Figure 3).

The lethality percentage was 6.7%. The highest level was found in 2016 (11.5%), followed by 2015 (8.6%), 2019 (7.2%), 2017 and 2018, both with 6.2%, 2014 (5%) and 2013 (2.5%).

Table 3. Evolution of cases affected by Visceral Leishmaniasis in Rio Grande do Norte State, between the years of 2014 and 2019.

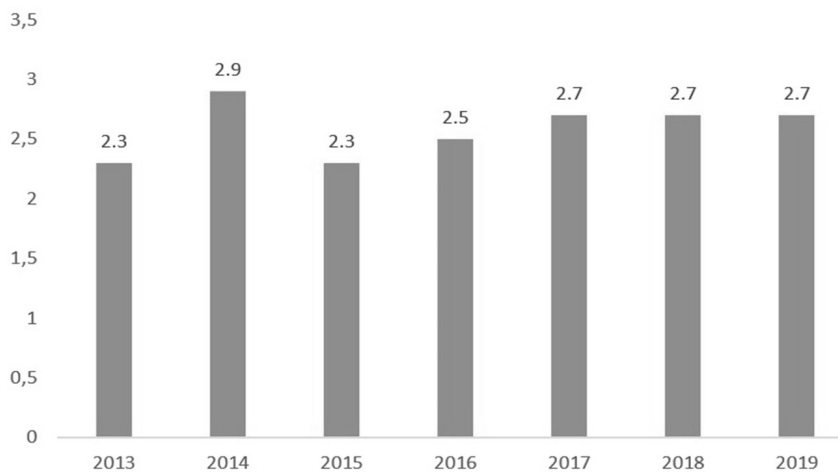| Evolution of VL cases	n	%
Cure	449	70.7
Death by LV	43	6.8
Withdraw	6	0.9
Death from another cause	29	4.6
Transfer	38	6.0
Ignored	70	11.0
Total	635	100

Source: Survey Data, 2020.

Figure 3. Prevalence coefficient per 100,000 inhabitants of Visceral Leishmaniasis in Rio Grande do Norte State, between 2013 and 2019.
Source: Survey Data, 2020.

DISCUSSION

In the period analyzed in this study, notifications of Visceral Leishmaniasis cases in Rio Grande do Norte State show a stability of cases, with a slight increase in the last five years. The urbanization of VL is evident, since many cases occurred in residents of urban/peri-urban areas and in centers such as the capital Natal and the city of Mossoró, the second largest one in the State, with autochthonous cases of the parasitosis. This finding can be explained by several factors, among them: environmental transformations caused by deforestation and habitat destruction, anthropic actions, urban expansions and human migrations, socioeconomic level, quality of health services, animal husbandry, failures in urban planning and entomological surveillance measures and control of canine visceral leishmaniasis (OPAS, 2017; Almeida et al., 2020). The geographic expansion is related to the large concentration of cases in the Brazilian Northeast, since the first endemic regions occurred in rural areas close to river environments, where agricultural activities were carried out. However, as time went by and the migration process took place, VL began to be registered in medium and large cities, undergoing an urbanization process and mainly affecting people of greater social vulnerability and in precarious housing conditions (Lima et al., 2020).

The fact that at least half of the municipalities in the State of Rio Grande do Norte have autochthonous cases and that there is stability with a tendency to increase notifications, may be the result of difficulties in implementing measures to control the disease. Factors such as: scarcity of staff, lack of investments in public health, priorities to combat other endemic diseases to the detriment of VL and the little involvement of municipal managers, can make the control of the parasite unfeasible. It is also noteworthy that the population may refuse to visit health agents in homes for chemical control and the canine reservoir, with resistance on the part of animal tutors, as well as the community, to the practice of euthanasia. Therefore, it is necessary to reassess the control measures both in terms of combating the vector and the canine host. In addition, the State's commitment should be expanded with the guarantee of human, material and financial resources for the continuity of proposed activities, including investment in training health teams, in technologies for mapping the most vulnerable areas and in communicative action that improves the dialogue with the social groups affected by the grievance (Zuben & Donalísio, 2016; Costa et al., 2018).

The adult population was the most infected, being associated with males, while children and adolescents were associated with females. The presence of infected children may be related to immunological immaturity, where diseases are more frequent at this stage of life, and may be related to malnutrition, considered a risk factor in developing countries such as Brazil (Sousa et al., 2018).

Regarding the predominance of female adolescents, sociocultural and behavioral factors may contribute to the infection. In vulnerable social environments, it is common for female adolescents to be forced to spend a large part of their time in the intradomestic environment and annexes performing domestic activities, such as cleaning the animal shelters, where the vector is found. The domiciliation of sand fly species and the preference for dark environments inside houses and concentration in shelters for farm animals such as chickens and pigs, shows that the risk in these areas is greater for those who stay in them longer. Regarding the association of males with the age group from 20 to 59 years old, it may be linked mainly to the work activities performed by these individuals (BRASIL, 2016; Lima et al., 2019).

The results showed that the highest occurrences in males are illiterate and with low education level. These individuals, due to restricted job opportunities, engage in manual work, which leads them to be more exposed to the vector, such as: agriculture, civil construction in recently deforested areas, animal husbandry and mining, making them more exposed to the bite of the insect vector of leishmaniasis. Also, education, in addition to qualifying for the search for better jobs, is also an important tool for health promotion, as it is responsible for training individuals about disease prevention and the search for health services (Castro et al., 2016; Costa et al., 2018; Rios Júnior et al., 2020).

The results showed that the race most infected were black/brown. This may be related to the fact that more than half of the population of Rio Grande do Norte self-declare as brown (IBGE, 2011). In this context, as there are no studies that determine the risk by race/ethnicity, but by social conditions, can be more concentrated among people in social vulnerability, being in conditions of poverty and inadequate housing conditions (Martins et al., 2018).

The results show that 27,6% of those infected with *Leishmania* were also HIV positive, occurring in both male and female in a higher percentage in adults, but also found in adolescents and elderly ones. VL is characterized by an opportunistic infection in immunocompromised patients induced post-transplants, post-anticancer chemotherapy, chronic corticosteroid users and among other immunosuppressive diseases. All presentation forms of infection by *Leishmania* spp. have already been described in people infected with HIV. The classic VL triad is also the most common manifestation of the disease in co-infection: hepatosplenomegaly, fever and pancytopenia, observed in 75% of cases (Moura et al., 2020; Alemayehu et al., 2016). The growth of the geographic areas of VL and HIV/AIDS cases has been marked by the urbanization of the first and the ruralization of the second. The epidemiological result of this simultaneous expansion resides mainly in the fact that people with HIV/AIDS living in VL endemic areas are at greater risk of manifesting it and that LV-HIV co-infection accelerates the clinical course of HIV infection. Therefore, visceral leishmaniasis is considered an opportunistic infection among patients with HIV who live or have lived in areas considered endemic for this parasitosis (Costa et al., 2021; Pereira et al., 2020).

The disease, in most individuals, has progressed to cure. The reported deaths occurred more frequently in males and in adults, although it was also observed in children, adolescents and the elderly. Deaths can occur due to late diagnosis, associations with comorbidities, co-infections, immunological immaturity, malnutrition and other risk factors. The prolonged duration of clinical manifestations and late patients´ treatment have been identified as a risk factor for disease lethality. In addition to considering the lack of access to health services, adult men may also ignore the warning signs, due to the feelings of fear, shame, and behavioral causes such as impatience, carelessness, life priorities, and even with issues related to the form of organization of health services, generating a late diagnosis. Having a diagnosis at an advanced stage of the disease makes death almost always an inevitable consequence, even when the patient is in treatment (Rios Júnior et al., 2020; Cunha et al., 2020).

Children are quite susceptible to VL and deaths may occur due to cellular immunological immaturity, with malnutrition as a risk factor. In older adults, the evolution to death occurs as a result of immunosenescence, as it may also be related to the lack of knowledge of health professionals who consider it predominantly a childhood condition, not considering on many occasions this clinical suspicion in the older adults (Sousa et al., 2018; Lima et al., 2018).

The variation in the prevalence of VL is enormous among Brazilian cities and States. This variation may be related to several factors including geographic region, population studied and the sensitivity and specificity of diagnostic tests (Sales et al., 2017). The mean prevalence coefficient in Rio Grande do Norte State for the period studied (2013-2019) was 2.58 per 100,000 inhabitants. The northeast of Brazil in the period (2012-2021) had the highest number of VL cases and VL/HIV coinfections compared to other regions of the country. Although the largest notifications are in Natal and Mossoró the 2 largest cities of the State, according to the Brazilian Ministry of Health (2022a), the cities of Pau dos Ferros and Patu are in the highest risk stratifications for VL in the years 2018-2020. The Brazilian Ministry of Health (2022b) showed that the average incidence coefficient per 100,000 inhabitants in Rio Grande do Norte for the period studied (2013-2019) is 1.6, which is below when compared to the general average of the North and Northeast States region. This coefficient is below the States of Maranhão, Piauí, Ceará, Sergipe and Bahia and above the average of the States in the Southeast and Midwest regions (BRASIL, 2022b).

Within the limitations of the research, it is possible to point out the difficulty in knowing the municipality of infection, since many registration forms present this data as indeterminate. In this way, the distribution of cases was based on the municipality of notification, which is not always the municipality where the infection occurred. Regarding the quality of the SINAN record, failures were observed in filling out the notification forms, verifying the lack of some socioeconomic variables, which prevents a more in-depth study of the epidemiological characteristics in different locations.

In the State of Rio Grande do Norte, between the years of 2013 and 2019, 635 cases of VL were reported with stability of cases over the period. Half of the municipalities had autochthonous cases, most of which notifications occurred in residents of urban/peri urban areas and in the two largest cities in the State, Natal and Mossoró.

In the epidemiological profile of the infected, males prevailed, aged between 20 and 59 years old, brown/black, with low education. A statistically significant higher occurrence was observed in female children and adolescents and in male adults. Higher prevalence was also observed in illiterate and low-educated male individuals. The presence of individuals co-infected with the HIV virus was reported, with adult males being the most affected. However, the presence of infection was also observed in co-infected adolescents and older adults. Regarding the evolution of cases, most individuals were cured, although deaths from VL have also been recorded.

The study shows that the control measures adopted within the scope of the National Leishmaniasis Control Program in the municipal spheres must be reassessed, since there has been no reduction in the number of cases, but a stability over the years, with a tendency to growth, in the city of Mossoró.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest to disclose.

REFERENCES

1. Alemayehu M, Wubshet M, Mesfin N. Magnitude of visceral leishmaniasis and poor treatment outcome among HIV patients: meta-analysis and systematic review. *HIV AIDS (Auckl) 23*: 75-80, 2016.

2. Almeida CP, Cavalcante FRA, Moreno JO, Florêncio CMGD, Cavalcante KKS, Alencar CH. Leishmaniose visceral: distribuição temporal e espacial em Fortaleza, Ceará, 2007-2017. *Epidemiol Serv Saúde 5:* 1-9, 2020.

3. Batista FMA, Sousa RA, Aguiar BGA, Ibipaina AB, Albuquerque LPA, Mendonça VJ, Costa CLN. Perfil epidemiológico e tendência temporal da leishmaniose visceral: Piauí, Brasil, 2008 a 2018. *Cad Saúde Pública 37*: 1-9, 2021.

4. BRASIL. Ministério da Saúde. *Guia de vigilância em saúde. 2016.* Available in: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/l/leishmaniose-visceral-1. Access in: 11.abr.2022.

5. BRASIL. Ministério da Saúde. *Leishmaniose visceral: o que é, causas, sintomas, tratamento, diagnóstico e prevenção. 2019.* Available in: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/l/leishmaniose-visceral-1. Access in: 13.abr.2022.

6. BRASIL. Ministério da Saúde. *Estratificação de risco de leishmaniose visceral por município de infecção. Brasil, 2018 a 2020.* 2022a. Available in: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/l/leishmaniose-visceral/arquivos/estratificacaolv18a20.pdf. Access in: 05.feb.2023.

7. BRASIL. Ministério da Saúde. *Coeficiente de incidência de leishmaniose visceral, por 100.000 habitantes. Brasil, Grandes Regiões e Unidades Federadas. 1990 a 2021*. 2022b. Available in: https://www.gov.br/saude/pt-br/assuntos/saude-de-a-a-z/l/leishmaniose-visceral/ arquivos/atualizacao-21-10-2022/lv-coef_incidencia.pdf . Access in: 05.feb.2023.

8. Castro JM, Rodrigues SM, Silva STP, Costa FCL, Rodrigue ACC, Vieira LDF, Cabrera GPB. Conhecimento, percepções de indivíduos em relação à leishmaniose visceral humana como novas ferramentas de controle. *Ensaios Cienc Biol Agrar Saúde 20*: 93-103, 2016.

9. CNS. Conselho Nacional de Saúde (Brasil). *Resolução no 466, de 12 de dezembro de 2012*. 2012. Available in: https://conselho.saude.gov.br/resolucoes/2012/Reso466.pdf. Access in: 14.apr.2022.

10. Costa DNCC, Bermudi PMM, Rodas LAC, Nunes CM, Hiramoto RM, Tolezano JE, Cipriano RS, Cardoso GCD, Codeço CT, Chiaravalloti-Neto F. Leishmaniose visceral em humanos e relação com medidas de controle vetorial e canino. *Rev Saúde Pública 52*: 1-11, 2018.

11. Cunha CR, Filho ASR, Lopes TB, Araújo MHM, Caladrini TSS, Neves MNSS, Fecury AA, Menezes RAO. Tipificação epidemiológica dos casos de leishmaniose visceral humana no Brasil, no período de 2013 a 2017. *Rev Eletron Acervo Saúde 41*: 1-10, 2020.

12. Costa RKE, Holanda EC, Andrade SM, Nascimento MSV, Soares LF, Oliveira EH. Visceral Leishmaniasis and Human Immunodeficiency Virus Coinfection: epidemiological profile of cases reported in São Luís-Maranhão, Brazil. *Res Soc Dev. 10*: 1-10, 2021.

13. Faria AR, Andrade HM. Diagnóstico da leishmaniose visceral canina: grandes avanços tecnológicos e baixa aplicação prática. *Rev Pan-Amaz Saúde 3*: 47-57, 2012.

14. IBGE. Instituto Brasileira de Geografia Estatística. *Censo demográfico 2010 – características da população e do domicílio*. 2011. Available in: https://biblioteca.ibge.gov.br/visualizacao/ periodicos/93/cd_2010_caracteristicas_populacao_domicilios.pdf. Access in: 14.apr.2022.

15. IBGE. Instituto Brasileiro de Geografia e Estatística. *Cidades e estados - Rio Grande do Norte*. 2020. Available in: https://www.ibge.gov.br/cidades-e-estados/rn.html Access in: 18.jun.2022.

16. Leite IA, Araújo LB. Leishmaniose visceral: aspectos epidemiológicos relacionados aos óbitos em Mossoró-RN. *Rev Patol Trop 42*: 301-308, 2013.

17. Lima DA, Novo SPC, Nunes FS, Maciel EMSG. Aspectos epidemiológicos, sociais e ambientais relacionados a transmissão e ao controle da leishmaniose visceral canina na Ilha da Marambaia, Mangaratiba - Rio de Janeiro. *Rev Saúde Meio Ambiente 9:* 64-81, 2019.

18. Lima MES, Nascimento CEC, Ericeira AJP, Silva FJLA. Perfil epidemiológico de crianças internadas com leishmaniose visceral em um Hospital Universitário do Maranhão. *Rev Soc Bras Enferm Ped 18*: 15-20, 2018.

19. Lima RSC, Oliveira MR, Albuquerque BA, Conceição, HN, Pereira BM, Ximenes JC, Câmera Perfil clínico, epidemiológico e espacial de leishmaniose visceral em área endêmica do estado do Maranhão, Brasil. *Mundo Saúde 1*: 171-182, 2020.

20. Lindoso JAL. Diversidade clínica e tratamento da leishmaniose visceral. *Rev Inst Adolfo Lutz 77*: 1-8, 2018.

21. Martins CP, Brandão MGSA, Braga MM, Sampaio LBF, Barros LM, Pacheco JSB. Monitoramento epidemiológico com instrumento de apoio à gestão de saúde: análise das notificações de leishmaniose visceral em Sobral, Ceará. *Rev Adm Saúde 18*: 1-13, 2018.

22. Moura YS, Oliveira EH, Neto JAON, Lima LA, Bessa LSS, Barros LMM, Holanda EC, Oliveira MM. Perfil epidemiológico dos casos notificados de coinfecção leishmaniose visceral/ HIV no Piauí, Brasil no período de 2010 a 2019. *Braz J Health Rev 3*: 19595-19607, 2020.

23. OPAS. Organização Pan-Americana da Saúde. *Indicadores de saúde: Elementos Conceituais e Práticos*. 2018. Available in: https://iris.paho.org/bitstream/ handle/10665.2/49057/9789275720059_por.pdf?sequence=5&isAllowed=y. Access in: 18.jun.2022.

24. OPAS. Organização Pan-Americana de Saúde (OPAS). Organização Mundial da Saúde (OMS). *Plan de acción para fortalecer la vigilancia y control de las leishmaniasis en las Américas 2017-2022*. 2017. Available: https://iris.paho.org/bitstream/handle/10665.2/34144/PlanAccionLeish20172022spa.pdf?sequence=1&isAllowed=y. Access in: 13.apr.2022.

25. Pereira JSF, Fonseca ALGP, Pereira KS. Perfil epidemiológico dos casos de coinfecção por HIV e leishmaniose visceral no Tocantins entre os anos de 2016 a 2018. *Facit Bus Technol J 1*: 113-120, 2020

26. Rios Júnior WO, Ferreira JFIS, Souza VC, Costa JLM, Vasconcelos MA, Ellery LL, Filho AHBV, Gomes MMR, Marques VF. Leishmaniose visceral em Sobral, Ceará: análise epidemiológica comparativa de dois quinquênios. *Rev Eletron Acervo Saúde. 12*: 1-10, 2020.

27. Sales DP, Martins NS, Silva MIS. Aspectos epidemiológicos da leishmaniose visceral canina e humana no estado do Maranhão, Brasil (2009-2012). *Rev Bras Ciênc Vet 24:*144-150, 2017.

28. Silva CMHS, Winck CA. Leismaniose visceral canina: revisão de literatura. *Rev Uni Vale Rio Verde 16*: 1-12, 2018.

29. Sousa NA, Linhares CB, Pires FGB, Teixeira TC, Lima JS, Nascimento MLO. Perfil epidemiológico dos casos de leishmaniose visceral em Sobral-CE, 2011 a 2015. *SANARE Rev Pol Públicas 17:* 51-57, 2018.

30. Vieira VPC, Figueiredo NM. Leishmaniose visceral canina: Breve revisão e relatos de casos. *Rev Veterin Zootecnia 28*: 1-12, 2021.

31. Van Griensven J, Diro E. Visceral leishmaniasis: recent advances in diagnostics and treatment regimens. *Infect Dis Clin North Am 33*: 79-99, 2019.

32. Victor VAS. *Imunologia aplicada ao desenvolvimento de novas estratégias de controle para a leishmaniose visceral*. Dissertação: Mestrado em Biociências e Biotecnologia em Saúde. Instituto Aggeu Magalhães: Recife, 2021. 79 p.

33. WHO. World Health Organization. *Leishmaniasis*. 2022. Available in: https://www.who.int/leishmaniasis/burden/en/. Acess in: 15.abr.2022.

34. Zuben APBV, Donalísio MR. Dificuldades na execução das diretrizes do Programa de Vigilância e Controle da Leishmaniose Visceral em grandes municípios brasileiros. *Cad Saúde Pública. 6*: 2-11, 2016.