# Epidemiological characterization and spatial distribution of visceral leishmaniasis cases in Três Lagoas - MS, Brazil in the period of 2007-2021

Caracterização epidemiológica e distribuição espacial dos casos de leishmaniose visceral em Três Lagoas – MS, Brasil, no período de 2007 a 2021

Caracterización epidemiológica y distribución espacial de casos de leishmaniasis visceral en Três Lagoas – MS, Brasil, de 2007 a 2021

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**Abstract**
This retrospective observational cross-sectional study aimed to analyze the distribution of visceral leishmaniasis (VL) cases in Três Lagoas registered between January 2007 and August 2021, through data processed by the Epidemiological Surveillance Service based on the notification of the National System of Diseases and Notifications. In this period, 231 cases were confirmed, being 137 male (59.3%) and 94 female (40.7%). Was observed a higher prevalence of cases between ages 0-4 years (30.8%), 20-39 (22.5%) and 40-59 (19.9%). Also was observed a higher percentage of infected Caucasian individuals (45.4%) and individuals with low education: elementary school II (22.1%). The most prevalent clinical manifestations were fever (85.3%), splenomegaly (76.6%), weakness (67.1%), weight loss (65.8%) and hepatomegaly (62.8%). It was found that 80.1% of patients received pharmacological treatment, mainly using pentavalent antimonials (56.7%), and that 26 patients (11.3%) died during the period due to complications caused by VL. The spatial analysis showed a homogeneous distribution of VL cases in the city's urban perimeter without predominant regions. Finally, it was observed that the incidence and mortality by VL has been decreasing in recent years, however maintaining high rates of lethality and transmissibility, placing the municipality in the third with the highest transmission rate in the state. In view of these aspects, we conclude that VL is still a serious public health problem in the city and that despite the slight drop in incidence and mortality rates, it still presents values higher than the national average and high dissemination of the disease in the urban area.
**Keywords:** Visceral leishmaniasis; Três Lagoas; Calazar; Neglected diseases.

**Resumo**
Este estudo transversal observacional retrospectivo teve como objetivo analisar a distribuição dos casos de leishmaniose visceral (LV) em Três Lagoas registrados entre janeiro de 2007 e agosto de 2021, por meio de dados processados pelo Serviço de Vigilância Epidemiológica com base na notificação do Sistema Nacional de Agravos e Notificações. Nesse período, foram confirmados 231 casos, sendo 137 homens (59,3%) e 94 mulheres (40,7%). Observou-se maior

prevalência de casos entre as idades de 0-4 anos (30,8%), 20-39 (22,5%) e 40-59 (19,9%). Também foi observado maior percentual de infectados da raça branca (45,4%) e de baixa escolaridade: ensino fundamental II (22,1%). As manifestações clínicas mais prevalentes foram: febre (85,3%), esplenomegalia (76,6%), fraqueza (67,1%), emagrecimento (65,8%) e hepatomegalia (62,8%). Verificou-se que 80,1% dos pacientes receberam tratamento farmacológico, principalmente com antimoniais pentavalentes (56,7%), e que 26 pacientes (11,3%) morreram no período devido a complicações decorrentes da LV. A análise espacial mostrou uma distribuição homogênea dos casos de LV no perímetro urbano da cidade sem regiões predominantes. Por fim, observou-se que a incidência e mortalidade por LV vem diminuindo nos últimos anos, porém mantendo elevados índices de letalidade e transmissibilidade, posicionando o município no terceiro lugar com maior taxa de transmissão do estado. Diante desses aspectos, concluímos que a LV ainda é um grave problema de saúde pública no município e que apesar da ligeira queda nas taxas de incidência e mortalidade, ainda apresenta valores superiores à média nacional e alta disseminação da doença na área urbana.

**Palavras-chave:** Leishmaniose visceral; Três Lagoas; Calazar; Doenças negligenciadas.

**Resumen**
Este estudio observacional transversal retrospectivo tuvo como objetivo analizar la distribución de casos de leishmaniasis visceral (LV) en Três Lagoas registrados entre enero de 2007 y agosto de 2021, a través de datos procesados por el Servicio de Vigilancia Epidemiológica con base en la notificación del Sistema Nacional de Enfermedades y Notificaciones. En este período se confirmaron 231 casos, siendo 137 hombres (59,3%) y 94 mujeres (40,7%). Se observó una mayor prevalencia de casos entre las edades de 0-4 años (30,8%), 20-39 (22,5%) y 40-59 (19,9%). También se observó un mayor porcentaje de individuos caucásicos infectados (45,4%) y de personas con bajo nivel educativo: escuela primaria II (22,1%). Las manifestaciones clínicas más prevalentes fueron fiebre (85,3%), esplenomegalia (76,6%), debilidad (67,1%), pérdida de peso (65,8%) y hepatomegalia (62,8%). Se encontró que el 80,1% de los pacientes recibieron tratamiento farmacológico, principalmente con antimoniales pentavalentes (56,7%), y que 26 pacientes (11,3%) fallecieron durante el período por complicaciones provocadas por LV. El análisis espacial mostró una distribución homogénea de casos de LV en el perímetro urbano de la ciudad sin regiones predominantes. Finalmente, se observó que la incidencia y mortalidad por LV ha venido disminuyendo en los últimos años, sin embargo, manteniendo altas tasas de letalidad y transmisibilidad, colocando al municipio en el tercero lugar con mayor tasa de transmisión del estado. Teniendo en cuenta estos aspectos, se concluye que la LV sigue siendo un grave problema de salud pública en la ciudad y que, a pesar de la leve caída de las tasas de incidencia y mortalidad, aún presenta valores superiores a la media nacional y alta diseminación de la enfermedad en la zona urbana.

**Palabras clave:** Leishmaniasis visceral; Três Lagos; Calazar; Enfermedades desatendidas.

## 1. Introduction

Visceral Leishmaniasis (VL) is a vector disease that affects humans and other animals, with chronic evolution and systemic involvement that can lead to death. This disease is considered by the World Health Organization as one of the five neglected diseases, that encouraging its extinction. Although there are asymptomatic forms of the disease, when patient develops little or no specific symptoms, VL can chronically evolve with high mortality rates when untreated, mainly affecting organs such as the spleen, liver, hemocytopoietic tissue, lungs and kidneys (Souza et al., 2018).

The symptoms may appear abrupt or gradual, like the hepatosplenomegaly, prolonged and irregular fever, anemia with leukopenia, lymphadenopathy, edema, weight loss and cachexia. The time to diagnosis is closely related to the threat of transmission, as the host is at risk of acting as a reservoir. In order to control and treat patients affected by VL in Brazil, all suspected cases need to be notified through a specific form to the Notifiable Diseases Information System (SINAN), it will be responsible for the epidemiological investigation of the case (Brazil, 2019; Carvalho et al., 2018; Brazil 2016).

It is still possible to observe worldwide incidence ranging from 50 to 90 thousand cases annually, being endemic in more than 80 countries, among which the following stand out: Brazil, China, India, Iraq, Ethiopia, Kenya, Nepal, Sudan, South Sudan and Somalia, responsible for about 95% of cases worldwide (WHO, 2020; Bezerra et al., 2018). Brazil is the country that most reports cases in America, and approximately 96% of cases, mainly due to social, economic and environmental characteristics favorable to the proliferation and spread of mosquito vectors (PAHO 2018; Araújo et al., 2013; Lara-Silva et al., 2015).

The prevalence of VL in Brazil ranged from 1.2 to 1.98 cases per 100,000 inhabitants, in the last decade (2010 to 2019). In 2019 was registered the highest fatality rate (9%) in the last 10 years. In the same year were confirmed autochthonous cases of VL in 24 Brazilian states (88.9%), distributed in all 5 regions of the country. The Northeast region was responsible for the largest number of case records in the country, with 49.1% of cases, followed by the North region (19.98%) and the Southeast region (12.77%) (Brazil, 2019; Brazil, 2021). In 2019 the Midwest region was responsible for 5.1% of VL cases in the country. The state of Mato Grosso do Sul (MS) was responsible for 75.3% of cases in this region, placing the state in eighth position in number of cases, and fifth in overall incidence, with 3.5 cases per 100,000 inhabitants (Brazil, 2019; Brazil, 2021). Therefore, it was observed that VL has been expanding in some urban areas of the state, including Três Lagoas, with a transmission rate of 13.4 in the period 2014 to 2019, only behind Campo Grande (85.8%) and Corumbá (13.6%). In addition, the municipality ranks second in number of deaths from VL, only behind of Campo Grande, which has encouraged prioritizing disease control and surveillance activities (SES – MS, 2020).

The action plan for leishmaniasis on the American continent was created and approved in 2017. It has purposed the reduction of the morbidity and mortality of the LV, as well as to assist in the diagnosis and treatment strategies, aiming the control of the disease until the year 2022.

Epidemiological analyzes using geographic distribution techniques as well as analysis of spatial patterns of morbidity and/or mortality; socioeconomic and environmental factors can provide important information to contribute with the prevention and control of the VL. Thus, this study aimed to analyze, to characterize epidemiologically and describe the spatial distribution of cases of visceral leishmaniasis in Três Lagoas, state of MS, from 2007 to 2021.

## 2. Methodology

A retrospective, observational cross-sectional study of confirmed and autochthonous VL cases in the city of Três Lagoas, from 2007 to August 2021, was carried out. Data were collected from SINAN and from the department of epidemiological surveillance, being grouped and tabulated in the Excel software.

Analysis the data were grouped into three periods: 2007-2011, 2012-2016 and 2017-2021. The following demographic variables were analyzed: gender (male and female); age group (in years: 0-4; 5-9; 10-19; 20-39; 40-59; ≥60); ethnicity (Caucasian, afro-descendant, asian, mulatto, indigenous); education (illiterate, elementary school I, elementary school II, high school, higher education); treatment (Pentavalent antimony, amphotericin B, pentamidine, liposomal amphotericin B, other or untreated) and disease evolution (Cure, abandonment, death from VL, death from other causes and ignored or untreated). In addition, the frequency of clinical manifestations of VL recorded in each case, such as fever, weakness, weight loss, splenomegaly, hepatomegaly, edema, hemorrhagic phenomena, jaundice, cough, were also studied. The cases that progressed to death were characterized separately according to the variables used in the study.

Spatial distribution was performed through the making of thematic maps, separated by neighborhoods (district zoning model 2015 containing 36 neighborhoods) showing the number of total cases in each neighborhood. Similarly, thematic maps were constructed showing the number of deaths per neighborhood, and another map showing the lethality by neighborhood, the latter being categorized into intervals (<10% lethality; 11-20% lethality; 21 -30% lethality and 31-40% lethality) for the total period analyzed. All the maps were made with the program ArcGIS 10.8 (Esri – USA).

The incidence of each year was calculated by dividing the total number of cases in the year by the population at risk, multiplied by 100,000 inhabitants. To calculate the mortality rate, the number of deaths in one year was divided by the number of people at risk, multiplied by 100,000 inhabitants. Finally, to determine the lethality, the number of deaths in the year was

divided by the number of cases in the same period, multiplied by 100. Subsequently, averages of these incidences were performed covering the grouped periods.

Statistical analyzes were performed using the SAS-University Edition software, by index case year and subsequently with a pre-established period of 5 years (2007-2011; 2012-2016; 2017-2021) and total period (2007-2021). The statistic significant values were determined by $p < 0.005$.

## 3. Results

From January 2007 to August 2021, 1192 suspected cases of VL were reported, with 231 confirmed cases (19.4%) and 26 deaths (11.3%). There was a predominance of cases in males (59.3%) during the epoch analyzed. A higher percentage in man was observed in the period 2007-2011 (61%) and a lower percentage, from 2012 to 2016 (54.3%), however, were not observed statistically significant differences. Analyzing the age groups, there was a greater predominance between 0-4 years old (30.8%), followed by 20-39 years old (22.5%) in the analysis of the total period, separately, it was observed that the 20-39 age group had a higher proportion of new cases during the period 2017-2021 (34.1%) (Table 1).

The analysis of the predominance in different ethnicities showed a higher percentage of cases in Caucasians (45.4%), followed by mulatto individuals (39%), when analyzed throughout the period. However, there is a predominance of mulatto individuals between 2012-2016 (58.7%) and 2017-2021 (50%). There was also a predominance of cases in individuals with complete elementary school II, either when analyzing the entire period (22.1%) or when analyzing each group among 2007 to 2011 (19.9%), 2012 to 2016 (19, 6%) and 2017 to 2021 (31.8%). The number of cases with data ignored or not applied (46.7%) is highlighted, mainly due to cases in the age group of 0-4 years old (not applied) and the lack of filling in the data (ignored). Still, was verified a lower prevalence of cases in illiterate individuals (0.9%) and people with higher education (3%), without statistical significance (Table 1).

About the most prevalent clinical manifestations: fever was present in 85.3% of patients throughout the period, 80.9% in 2007-2011, 93.5% from 2012 to 2016 and 90.9% between 2017 and 2021. Splenomegaly was the second most frequent clinical manifestation (76.6%) in the entire period analyzed, maintaining this position in each of the periods: 2007-2011 (77.3%), 2012-2016 (71.7%) and 2017-2021 (79.5%). The others manifestations such as weakness (67.1%), weight loss (65.8%) and hepatomegaly (62.8%) were also frequently observed in all periods. Interestingly, the cough was observed in more than 50% of patients throughout the period, ranging from 45.5% in 2017-2021 to 52.2% in 2012-2016. Among the clinical manifestations with less predominance, we had hemorrhagic phenomena (6.1%), jaundice (18.2%) and edema (24.2%) (Table 1).

The most frequently used treatment was Pentavalent Antimonial (56.7%), followed by Amphotericin B (13%) and Liposomal Amphotericin (9.5%), however, in the period 2017-2021, Liposomal Amphotericin was the second drug most used (27.3%). The percentage of the cases that were not treated or ignored was of 19.9%, in the SINAN form. It is noteworthy that in the period 2007-2011 and 2012-2016, the percentage of untreated or ignored was 27% and 15.2% respectively and that in the period 2017-2021; this percentage suffered a drop, with only 2.3%. The evolution of cases by cure was the most frequent in all periods analyzed: 2007-2011 (79.5%), 2012-2016 (84.8%), 2017-2021 (77.2%) and total (80, 1%). Furthermore, there is an increase in deaths from VL over the analyzed periods: 2007-2011 (8.5%), 2012-2016 (15.2%) and 2017-2021 (15.9%). It is also noteworthy that 5.2% of all individuals with VL do not have a documented outcome or evolution of the disease (Table 1).

**Table 1**. Epidemiological and clinical characteristics of visceral leishmaniasis cases in Três Lagoas, MS.

| Characteristics | 2007 – 2012 (N=141) | | 2012 – 2016 (N=46) | | 2017 – 2021 (N= 44 ) | | Total (N=231) | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| **Gender** | | | | | | | | |
| Male | 86 | 61 | 25 | 54.3 | 26 | 59.1 | 137 | 59.3 |
| Female | 55 | 39 | 21 | 45.7 | 18 | 40.9 | 94 | 40.7 |
| **Age Group (Years)** | | | | | | | | |
| 0-4 | 45 | 31.9 | 14 | 30.4 | 12 | 27.3 | 71 | 30.8 |
| 5-9 | 14 | 9.9 | 3 | 6.5 | 2 | 4.5 | 19 | 8.2 |
| 10-19 | 13 | 9.2 | 4 | 8.7 | 4 | 9.1 | 21 | 9.1 |
| 20-39 | 30 | 21.3 | 7 | 15.2 | 15 | 34.1 | 52 | 22.5 |
| 40-59 | 29 | 20.6 | 12 | 26.1 | 5 | 11.4 | 46 | 19.9 |
| >60 | 9 | 6.4 | 5 | 10.9 | 6 | 13.6 | 20 | 8.6 |
| Ignored | 1 | 0.7 | 1 | 2.2 | 0 | 0 | 2 | 0.9 |
| **Ethnicity** | | | | | | | | |
| Caucasian | 76 | 54 | 12 | 26.1 | 17 | 38.7 | 105 | 45.4 |
| Afro-descendant | 14 | 9.9 | 6 | 13.0 | 3 | 6.8 | 23 | 10 |
| Asian | 1 | 0.7 | 0 | 0 | 0 | 0 | 1 | 0.4 |
| Mulatto | 41 | 29 | 27 | 58.7 | 22 | 50 | 90 | 39 |
| Ignored | 9 | 6.4 | 1 | 2.2 | 2 | 4.5 | 12 | 5.2 |
| **Education** | | | | | | | | |
| Illiterate | 2 | 1.4 | 0 | 0 | 0 | 0 | 2 | 0.9 |
| Elementary School I | 25 | 17.7 | 8 | 17.4 | 7 | 15.9 | 40 | 17.3 |
| Elementary School II | 28 | 19.9 | 9 | 19.6 | 14 | 31.8 | 51 | 22.1 |
| High School | 11 | 7.8 | 8 | 17.4 | 4 | 9.1 | 23 | 10 |
| University education | 4 | 2.8 | 0 | 0 | 3 | 6.8 | 7 | 3,0 |
| Ignored/Not Applicable | 71 | 50.4 | 21 | 45.6 | 16 | 36.4 | 108 | 46.7 |
| **Clinical manifestation** | | | | | | | | |
| Fever | 114 | 80.9 | 43 | 93.5 | 40 | 90.9 | 197 | 85.3 |
| Weakness | 90 | 63.8 | 32 | 69.6 | 33 | 75 | 155 | 67.1 |
| Weight loss | 96 | 68 | 26 | 56.5 | 30 | 68.2 | 152 | 65.8 |
| Splenomegaly | 109 | 77.3 | 33 | 71.7 | 35 | 79.5 | 177 | 76.6 |
| Hepatomegaly | 83 | 58.9 | 27 | 58.7 | 35 | 79.5 | 145 | 62.8 |
| Edema | 28 | 19.9 | 14 | 30.4 | 14 | 31.8 | 56 | 24.2 |
| Hemorrhagic phenomena | 12 | 8.5 | 1 | 2.2 | 1 | 2.3 | 14 | 6.1 |
| Jaundice | 30 | 21.3 | 8 | 17.4 | 4 | 9.1 | 42 | 18.2 |
| Cough | 73 | 51.8 | 24 | 52.2 | 20 | 45.5 | 117 | 50.6 |
| **Treatment** | | | | | | | | |
| Pentavalent antimony | 82 | 58.2 | 27 | 58.7 | 22 | 50 | 131 | 56.7 |
| Amphotericin B | 16 | 11.3 | 5 | 10.9 | 9 | 20.4 | 30 | 13 |
| Liposomal amphotericin B | 3 | 2.1 | 7 | 15.2 | 12 | 27.3 | 22 | 9.5 |
| Others | 2 | 1.4 | 0 | 0 | 0 | 0 | 2 | 0.9 |
| Ignored or Untreated | 38 | 27 | 7 | 15.2 | 1 | 2.3 | 46 | 19.9 |
| *Disease Evolution* | | | | | | | | |
| Cure | 112 | 79.5 | 39 | 84.8 | 34 | 77.2 | 185 | 80.1 |
| Abandonment | 1 | 0.7 | 0 | 0 | 0 | 0 | 1 | 0.4 |
| Death by LV | 12 | 8.5 | 7 | 15.2 | 7 | 15.9 | 26 | 11.3 |
| Death from others causes | 3 | 2.1 | 0 | 0 | 1 | 2.3 | 4 | 1.7 |
| Transfer | 2 | 1.4 | 0 | 0 | 1 | 2.3 | 3 | 1.3 |
| Ignored | 11 | 7.8 | 0 | 0 | 1 | 2.3 | 12 | 5.2 |

Source: Authors (2021).

The spatial distribution of VL cases in the period 2007-2011 showed that 26 urban neighborhoods (72.2%) had at least one confirmed VL case with homogeneous distribution within the city, with a slight prevalence in the northeast and east regions of the municipality (Figure 1). During this period, there were still confirmed cases in rural regions of the municipality and the number of cases was similar to those found in the urban environment. In the period 2012-2016, the number of neighborhoods with at least one case of VL decreased to 21 urban neighborhoods (58.3%), observed homogeneous distribution within the municipality (Figure 1). Cases were also identified in rural areas in a quantity similar found in the urban perimeter. In 2017-2021 remained in 21 urban neighborhoods (58.3%) with at least one case of VL and a slight prevalence in the northeast and east regions of the city (Figure 1), without cases of VL in the rural area. Finally, the analysis of the entire period (2007-2021) showed that 27 urban neighborhoods (75%) confirmed at least one case of VL during the period, maintaining a homogeneous distribution within the municipality, but with an area interconnected with neighborhoods with more than 10 cases from the northeast region to the southwest region of the municipality.
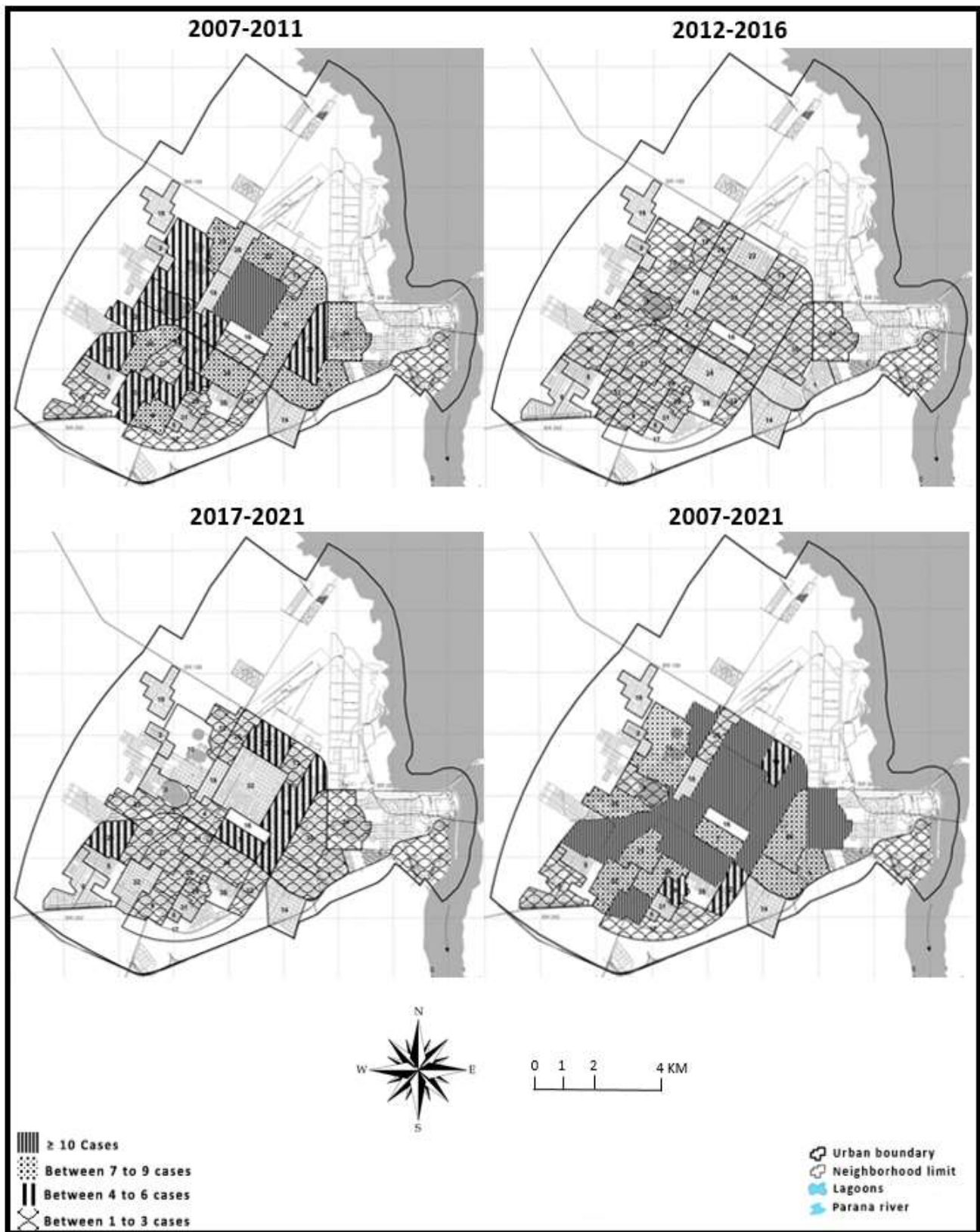
The analysis of deaths from VL showed a predominance in males (53.8%), however in the periods 2012-2016 and 2017-2021, the percentage of deaths in women was higher (57.1%). It was observed that the age group 40-59 years concentrated the highest number of deaths from VL (34.7%), followed by >60 (26.9%) and 0-4 (19.3%) . Still, it was found that 84.6% of these patients who died from VL underwent pharmacological treatment, being the most used: Pentavalent Antimonial (34.6%), Amphotericin B (26.9%) and Liposomal Amphotericin (23.1%) (Table 2). The statistical analysis did not show statistical significance for the differences in the percentage of deaths by sex, age or pharmacological treatment.

The spatial distribution of deaths from VL, in the period 2007-2021, showed that 15 urban neighborhoods (41.7%) had at least one confirmed death from VL with distribution in a central area ranging from the northeast to the southwest of the city. Deaths from VL were also registered in the rural area in quantity similar to those found in the urban region (Figure 2). The spatial distribution of the percentage of lethality by neighborhood, in the period 2007-2021 was analyzed and observed an emphasis on three more peripheral neighborhoods, which presented a lethality percentage ranging from 31 to 40% (Figure 2).

The analysis of the incidence of VL showed, in the period 2007-2011, an average incidence of 30.8 cases per 100,000 inhabitants, with a maximum incidence in 2008 (63.2 cases per 100,000 inhabitants) and a minimum in the year of 2011 (9.6 cases per 100,000 inhabitants). In the subsequent period (2012-2016) there was a decrease in this average incidence (8.2 cases per 100,000 inhabitants), minimum incidence in 2013 (3.7 cases per 100,000 inhabitants) and maximum in 2016 (10.3 cases per 100,000 inhabitants), with statically relevant decrease ($p=0.0003$). In the period (2017-2021) there was a further decrease in the average incidence (6.7 cases per 100,000 inhabitants), a minimum incidence in 2020 (2.4 cases per 100,000 inhabitants) and maximum in the year 2017 (12.7 cases per 100,000 inhabitants). Not observed statistical significance when compared to the previous period (2012-2016), however was observed statistical significance when compared to the 2007-2011 period ($p<0.0001$).

The average mortality rate from VL in the period 2007-2011 was determined at 2.5 cases per 100,000 inhabitants, a maximum mortality rate in 2008 (4.5 cases per 100 thousand inhabitants) and a minimum in 2007 (1.2 cases per 100,000 inhabitants). In the following period (2012-2016), there was a decrease in the average mortality rate (1.3 cases per 100,000 inhabitants), with a minimum mortality in the years 2014, 2015 and 2016 (0.9 cases per 100,000 inhabitants) and maximum in 2012 (1.9 cases per 100,000 inhabitants), but without statistical significance. In the period from 2017 to 2021, there was a decrease in the average mortality rate (1.0 cases per 100,000 inhabitants). The maximum mortality rate was observed in 2019 (2.5 cases per 100,000 inhabitants) and minimum in 2020 (no deaths registered), without statistical significance.

**Figure 1**. Distribution of visceral leishmaniasis cases by neighborhoods of Três Lagoas - MS in the periods: 2007-2011, 2012-2016, 2017-2021 and 2007-2021.
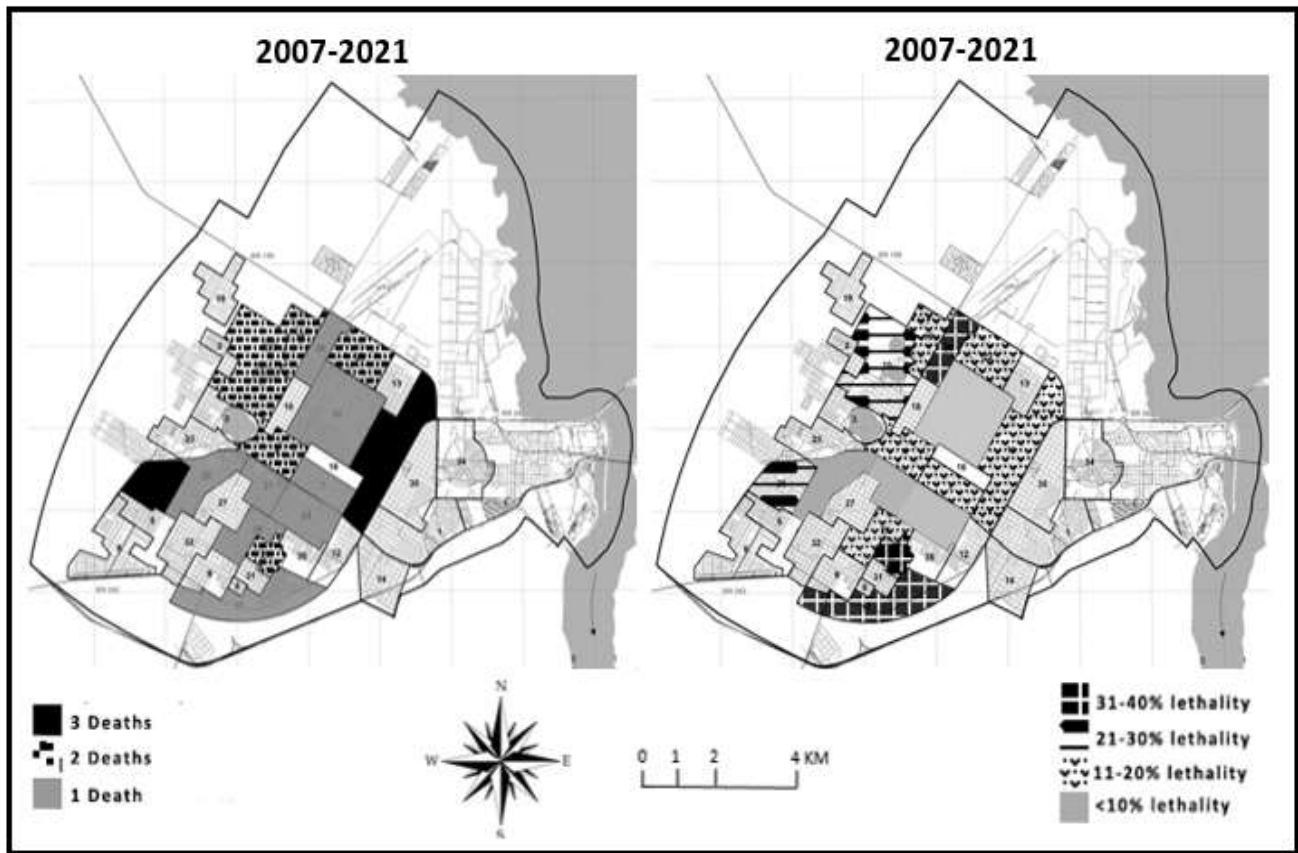


Source: Authors (2021).

**Table 2.** Epidemiological and clinical characteristics of deaths from visceral leishmaniasis in Três Lagoas, MS.

| Characteristics | 2007 – 2011 (N=12) | | 2011 – 2016 (N=7) | | 2017 – 2021 (N= 7 ) | | Total (N=26) | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | N | % |
| **Gender** | | | | | | | | |
| Male | 8 | 66.7 | 3 | 42.9 | 3 | 42.9 | 14 | 53.8 |
| Female | 4 | 33.3 | 4 | 57.1 | 4 | 57.1 | 12 | 46.2 |
| **Age Group (Years)** | | | | | | | | |
| 0-4 | 3 | 25 | 1 | 14.3 | 1 | 14.3 | 5 | 19.3 |
| 5-9 | 0 | 0 | 1 | 14.3 | 0 | 0 | 1 | 3.8 |
| 10-19 | 0 | 0 | 0 | 0 | 1 | 14.3 | 1 | 3.8 |
| 20-39 | 1 | 8.3 | 0 | 0 | 1 | 14.3 | 2 | 7.7 |
| 40-59 | 4 | 33.4 | 3 | 42.8 | 2 | 28.6 | 9 | 34.7 |
| >60 | 3 | 25 | 2 | 28.6 | 2 | 28.6 | 7 | 26.9 |
| Ignored | 1 | 8.3 | 0 | 0 | 0 | 0 | 1 | 3.8 |
| **Treatment** | | | | | | | | |
| Pentavalent antimonial | 6 | 50 | 2 | 28.6 | 1 | 14.3 | 9 | 34.6 |
| Amphotericin B | 3 | 25 | 1 | 14.3 | 3 | 42.8 | 7 | 26.9 |
| Pentamidine | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Liposomal amphotericin B | 1 | 8.3 | 3 | 42.8 | 2 | 28.6 | 6 | 23.1 |
| Others | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ignored or Untreated | 2 | 16.7 | 1 | 14.3 | 1 | 14.3 | 4 | 15.4 |

Source: Authors (2021).

Finally, the average percentage of lethality by VL in the period 2007-2011 was calculated at 11.7% with maximum percentage in 2011 (30%) and minimum in 2007 (3.1%). In the period from 2012 to 2016, there was an increase in the percentage of average lethality (19.6%), with minimum percentage in 2016 (8.3%) and maximum in 2013 (50%), without statistical significance. In the period from 2017 to 2021, there was a further decrease in the percentage of lethality (14.5%), a maximum percentage of lethality in the year 2019 (27.2%) and a minimum in the year 2020, without death records. When comparing the periods of 2012-2016 and 2017-2021, no statistical significance was observed.

**Figure 2**. Distribution of deaths for visceral leishmaniasis and percentage of lethality by neighborhood in Três Lagoas - MS.



Source: Authors (2021).

## 4. Discussion

The datas showed a reduction of VL in the analyzed periods, especially in the incidence and mortality; however, the city of Três Lagoas is ranked as the third municipality with the highest VL transmission rate in the state of Mato Grosso do Sul, subsequently Campo Grande and Corumbá (SES – MS, 2020). In addition, the average incidence found in the period with the lowest number of cases (2017-2021) is considered high equaling those found in the north and northeast regions, where VL has the highest incidence (Araújo, 2017)

It was observed that almost 60% of VL cases in the city occurred in male individuals, maintaining this percentage in all evaluated periods. Studies on the incidence of VL in other cities in the country also point to a greater susceptibility of men to the disease, with a percentage between 58 and 75% of cases (Rodrigues et al., 2020; Souza et al., 2018; Rocha et al., 2018; Lisboa et al., 2016; Araújo, 2016; Ortiz et al., 2015). It is considered that the greater exposure of men to sources of contamination, due to the performance of occupational and behavioral activities as well as hormonal factors are responsible for this higher percentage of infection (Ortiz et al., 2015). Furthermore, studies show that sex hormones can influence the immune response causing greater infectivity, prevalence and clinical severity in men (Araújo Albuquerque et al., 2021).

The classification of VL cases by age groups showed the highest total percentage in children aged 0-4 years (30.8%), followed by 20-39 years (22.5%) and 40-59 years (19.9%). Corroborating these results, an epidemiological study of VL in the city of Bauru - SP found that 32.3% of cases occurred in children under 5 years of age, and another study in Fortaleza -CE from 2009 to 2013 showed that 31.5 % of cases occurred in this same age group (Ortiz et al., 2015; Rodrigues et al., 2017). However, a new study in the city of Fortaleza - CE, showed that from 2014 to 2017, the percentage of cases in this age group decreased

considerably (13.1%), with cases in the 20-39 age group being concentrated. (33.2%) and 40-59 years (32.4%) (Almeida et al., 2020). The greater susceptibility and severity of VL in young children can be explained by the relative immaturity of the immune system, especially the adaptive cellular immune system, which is further aggravated by factors such as malnutrition (Pérez-Cabezas et al., 2019; Gama et al., 2013; Ostyn et al., 2011). The abundant presence of the vector mosquito in urban areas, especially in the surroundings regions, exposes this population to VL (Almeida et al., 2020).

The most predominant ethnicity among VL cases in the city was Caucasian (45.4%), followed by mulatto (39%) when analyzed throughout the study period, but in the 2012-2016 periods and 2017-2021 the highest percentage of cases was in mulatto (58.7% and 50% respectively). Although other studies corroborate a higher prevalence in Caucasian (Ortiz et al., 2015) or in mulatto (Souza et al., 2018; Lisboa 2016; Batista et al., 2013). We hypothesized that this characteristic is due to the ethnic particularity of the population of the municipality.

In the city, VL was more frequent in individuals with low education, elementary II (22.1%) and elementary I (17.3%). This predominance is habitually observed in epidemiological studies of VL in different cities across the country, corroborating the findings of this study (Souza et al., 2018; Lisboa et al., 2016; Ortiz et al., 2015). The relationship of low education and conditions of economic vulnerability in individuals affected by VL is quite frequent, however, there is a high percentage of people classified as ignored or not applied, these being young children (before starting school life) and individuals who information had not collected. Still, there is a low percentage of cases of illiterate individuals (0.9%), and this characteristic is explained as a particularity of the city, which has low illiteracy rates in the population.

The analysis of the most frequent clinical manifestations showed that the main symptoms presented by patients with VL were fever (85.3%), splenomegaly (76.6%), weakness (67.1%), weight loss (65.8%) and hepatomegaly (62.8%). Corroborating these findings, Almeida et al. (2020) observed that fever was present in more than 90% of patients with VL, followed by weight loss (67.9%), splenomegaly (61.6%), weakness (60.5 %) and hepatomegaly (55.3%). Furthermore, studies by Ortiz et al. (2015) and Alvarenga et al., (2010) also showed consubstantial frequency of the symptoms mentioned. Interestingly, cough was observed in over half of patients, similar with that one found by Almeida et al. (2020). This phenomenon is explained by the thoracoabdominal organ compromising, causing greater abdominal volume, responsible for adaptations in respiratory mechanics, which can trigger respiratory symptoms such as dyspnea and cough (Silva et al., 2013; Bispo et al., 2020).

Pharmacological treatment was administered to more than 80% of patients with VL throughout the analyzed period (2007-2021), with pentavalent antimonial treatment being the most used (56.7%) followed by amphotericin B (13%) and amphotericin Liposomal B (9.5%). Treatment with pentavalent antimony still remains the first choice, however, some countries have resistant strains, leading to low drug efficiency in VL treatment (Jha et al., 2013; Chakravarty; Sundar et al., 2010). In addition, due to severe side effects resulting from treatment with pentavalent antimony, drugs such as liposomal amphotericin B, which present less development of side effects and high cure rates (Jha et al., 2013; Sundar; Chakravarty 2012).

Between 2008 and 2017, the mortality rate from VL has been increasing across the country (6.2% to 8.8%) and in the municipality of Três Lagoas, it was no different. Was observed a growing percentage of death in periods (2007-2011: 8.5%; 2012-2016: 15.2%; 2017-2021: 15.9%) which led to an average lethality of 11.7% (2007-2011); 19.6% (2012-2016) and 14.5% (2017-2021), representing rates well above those found in the analysis of the average lethality in the country (Brasil, 2017). VL cure rates in the city were above 80%, similar to that found by Almeida et al. 2020 (78.2%) in a study carried out in Fortaleza - CE and slightly higher than the reported in Latin America in 2016 (70%) and 2017 (71.3%) (PAHO, 2019).

Mortality from VL in the city was higher in men (53.8%), when analyzed throughout the study period (2007-2021), but in the periods 2012-2016 and 2017-2021 the percentage of women was higher, with 57,1% in both periods. Botelho and Natal (2009), analyzing the epidemiological profile of VL in Campo Grande - MS, showed that 75% of deaths occurred in men, which is corroborated by Ortiz and Anversa (2015) who demonstrated that 61.3% of deaths for VL occurred in Bauru – SP were

in men. The large number of infected men, leading to a higher percentage of mortality, could be relation with hormonal factors that can regulate and influence by the immune response, responsible for control of the levels of mast cells, eosinophils, macrophages and dendritic cells (Araújo Albuquerque et al., 2021). Liu et al. (2005 and 2006) demonstrated that testosterone could give rise to the increase of susceptibility to the infection, inducing apoptosis, immunosuppression, attenuation of MAPK signaling and increased the disease. In a study carried out in 2016 in India, it was observed that testosterone could increase the anti-inflammatory microenvironment and favor the persistence of the parasite (Mukhopadhyay et al., 2016).

Deaths from VL were concentrated primarily in the ages 40-59 years (34.7%) and >60 years (26.9%), followed by those under 4 years (19.3%). These data are corroborated by national data on deaths and mortality by age group between 2008 and 2017, which show a higher percentage of deaths in individuals over 50 and under 4 years of age. Studies suggest that the highest percentage of deaths in these extreme ages is mainly due to the immaturity of the immune system in childhood, and the decreased efficiency of the immune system (immunosenescence), compromising, in both, mainly the cellular immune response (Pérez-Cabezas et al., 2019; Gama et al., 2013; Ostyn et al., 2011). It should be noted that 84.6% of the individuals who died had undergone some pharmacological treatment, but despite the efficiency of the drugs, the emergence of resistant strains, the delay in diagnosis/treatment, adverse effects and other comorbidities presented by patients, may be responsible for the mortality of these individuals (Santiago et al., 2021; Jha et al., 2013; Chakravarty; Sundar et al., 2010).

Unlike what was found by Almeida et al. (2020), who showed a greater prevalence of cases in neighborhoods on the outskirts of Fortaleza –CE and neighborhoods with low socioeconomic status and deficient urban infrastructure, VL cases in the city showed a homogeneous distribution in different urban neighborhoods and rural with 75% of neighborhoods presenting at least one case of VL. This homogeneous distribution of cases can be explained from a study carried out by Oliveira et al. (2010) in Três Lagoas, where the circulation of sandflies was evaluated, showing that 86.8% of the monitored neighborhoods showed circulation of sandfly species., mainly in the intra and peri domiciliary environment (88.4%). The neighborhoods with the highest number of human cases of VL are also those with the highest detection of sandfly species, mainly of the genus *Lutzomyia* spp.

The distribution of the percentage of deaths and lethality by neighborhood was homogeneous, with slightly higher lethality and deaths in more peripheral neighborhoods of the city, corroborating what was observed by Almeida et al. (2020), which showed that peripheral neighborhoods with infrastructure and sanitation problem may be more susceptible to VL cases.

Finally, this study shows the epidemiological situation of VL in Três Lagoas, in last 15-year (2007-2021), and despite oh having used secondary data (SINAN and the municipality's Epidemiological Surveillance Secretariat), which may present some inaccuracy, the study allowed an overview of VL in the city, which can help in decision-making and policies to deal with the disease.

# 5. Conclusion

We conclude that there was a decrease in the incidence and mortality of VL, during the analyzed periods. However, Três Lagoas-MS still presents the incidence and mortality well above the national average. Despite the decrease in these rates over the years, it was found that municipality had high rates of transmission and cases of VL, what kept the city as one of the three municipalities with the highest transmission rate in the Mato Grosso do Sul. It showed an increase in the percentage of lethality, higher averages than those found at the national level. Finally, we conclude that the city has a homogeneous distribution of VL cases in all neighborhoods. With that, suggest that prophylactic measures and health education should be carried out throughout the city in order to reduce the percentage of new cases. All these data corroborate the classification and maintenance of the city as an endemic area for visceral leishmaniasis.

**Acknowledgments**

**References**

Almeida C. P., Cavalcante, R. F. A., Moreno, J. O., Florêncio, C. M. G. D., Cavalcante, K. K. S., & Alencar, C. H. (2020). Leishmaniose visceral: distribuição temporal e espacial em Fortaleza, Ceará, 2007-2017. *Epidemiologia e Serviços de Saúde* 29(5):e2019422.

Alvarenga, D. G., Escalda, P. M. F., Costa, A. S. V., & Monreal, M. T. F. D. (2010). Leishmaniose visceral: estudo retrospectivo de fatores associados à letalidade. *Revista da Sociedade Brasileira de Medicina Tropical* 43(2): 194-1997.

Araújo, A. C., Gonçalves, N. N. V. M., Dantas-Torres, F., Ferreira, F., & Horta, M. C. (2016). Visceral Leishmaniasis in Petrolina, state os Pernambuco, Brazil, 2007-2013. *Revista do Instituto de Medicina Tropical de São Paulo* 58(1):29-33.

Araújo, D. C. (2017). Análise espacial dos casos de Leishmaniose visceral. *Arquivos em Ciência da Saúde* 24(2):71-75.

Araújo, V. E. M., Pinheiro, L. C., Almeida, M. C. M., Menezes, F. C., Morais, M. H. F., Reis, I. A., Assunção, R. M., & Carneiro, M. (2013). Relative risk of visceral leishmaniasis in Brazil: a spatial analysis in urban area. *PLoS Neglected Tropical Diseases*, 7(11): 2540.

Araújo-Albuquerque, L. P., Lezama-Davila, C., Alexander, J., & Satoskar, A. R. (2021). Influence of sex hormones on the immune response to leishmaniasis. *Parasite Immunology* 43(10-11):e12874.

Batista, F. M. A. (2014). Leishmaniose: Perfil epidemiológico dos casos notificados no estado do Piauí entre 2007 e 2011. *Revista Univap* 20(35):44-53.

Bezerra, J. M. T. Burden of leishmaniasis in Brazil and federated units, 1990-2016: Findings from global burden of disease study 2016. *PLoS Neglected Tropical Disease* 12(9): e0006697.

Bispo, A. J. B., Almeida, M. L. D., Almeida, R. P., Bispo-Neto, J., Brito, A. V. O., & França, C. M. (2020) Pulmonary involvement in human visceral leishmaniasis: Clinical and tomographic evaluation. *PLoS ONE* 15(1): e0228176.

Botelho, A. C. A., & Natal, D. (2009). Primeira descrição epidemiológica da leishmaniose visceral em Campo Grande, Estado de Mato Grosso do Sul. Revista da Sociedade Brasileira de Medicina Tropical. 45(5):503-508.

Brasil. (2016). Ministério da Saúde. SINAN – Sistema de Informação de Agravos de Notificação. Portal da Saúde, 2016. Funcionamento. http://portalsinan.saude.gov.br/funcionamentos>.

Brasil. (2017). Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Coordenação Geral de Doenças Transmissíveis. Leishmaniose Visceral. https://portalarquivos2.saude.gov.br/images/pdf/2019/janeiro/28/leishvisceral-17-novo-layout.pdf

Brasil. (2019a). Ministério da Saúde. Boletim Epidemiológico. Secretaria de Vigilância em Saúde. Doenças tropicais negligenciadas. Número especial. https://www.gov.br/saude/pt-br/media/pdf/2021/marco/3/boletim_especial_doencas_negligenciadas.pdf

Brasil. (2019b). Ministério da Saúde. Boletim Epidemiológico. Secretaria de Vigilância em Saúde 2003 a 2019: Da criação da secretaria de vigilância em saúde aos dias atuais. https://portalarquivos2.saude.gov.br/images/pdf/2019/setembro/25/boletim-especial-21ago19-web.pdf

Brasil (2021). Ministério da Saúde. Boletim Epidemiológico. Secretaria de Vigilância em Saúde. Doenças tropicais negligenciadas. Número especial. https://www.gov.br/saude/pt-br/media/pdf/2021/marco/3/boletim_especial_doencas_negligenciadas.pdf

Carvalho, L. S., Rosas, L. M. S., Wanderley, H. R. C., Faria, M. D., & Barberino M. L. (2018). Fichas de notificação da leishmaniose visceral: a tecnologia como aliada. *Revista Interdisciplinar em Saúde,* 7(2):16. https://periodicos.uniarp.edu.br/index.php/ries/article/view/1406

Chakravarty, J., & Sundar, S. (2010). Drug resistance in leishmaniasis. *Journal Global Infection Disease* 2(2):167–176.

Ferreira, C. G. X., Oliveira, M. D., Suguimoto, F., Souza, R. F., Machado, A. M., & Machado, A. R. S. R. (2021). Avaliação retrospectiva dos casos confirmados de Leishmaniose Tegumentar Americana em Três Lagoas - MS no período de 2007 a 2019. *Brazilian Journal of Development,* 7(1):13535-13550.

Gama, M. E. A., Gomes, C. M. C., Silveira, F. T., Laurenti, M. D., Gonçalves, E. G., Silva, A. R., & Corbett, C. E. P. (2013). Severe visceral leishmaniasis in children: the relationship between cytokine patterns and clinical features. *Revista da Sociedade Brasileira de Medicina Tropical* 46(6): 741-745.

Jha R. K., Sah, A. K., Shah, D. K., & Sah, P. (2013). Treatment of visceral leishmaniasis: Safety and efficacy. *Journal of Nepal Medical Association* 52(192): 6-45-51.

Lara-Silva, F. O., Michalsky, E. M., Fortes-Dias, C. L., Fiuza, V. O. P., Pessanha, J. E. M, Regina-Silva, S., Avelar, D. M., Silva, M. A., Lima, A. C. V. M. R., Costa, A. J. A., Machado-Coelho, G. L. L., & Dias, E. S. (2015). Epidemiological aspects of vector, parasite, and domestic reservoir in areas of recent transmission and no reported human cases of visceral leishmaniasis in Brazil *Acta Tropica* 148(1):128-136.

Lisboa, A. R., Leite, F. C., Dantas, A. E. F., Oliveira, I. B., Evangelista, T. R., & Souza, J. B. G. (2016). Análise epidemiológica de leishmaniose visceral em Municípios do Sertão Paraibano. *Revista Brasileira de Educação e Saúde* 6(3):05-12.

Liu, L., Wang, L., Zhao, Y., Wang, Y., Wang, W., & Qiao, Z. (2006). Testosterone attenuates p38 MAPK pathway during *Leishmania donovani* infection of macrophages. *Parasitology Research* 99(1):189-193.

Liu, L., Benten, P. M., Wang, L., Hao, X., Li, Q., Zhang, H., Guo, D., Wang, Y., Wunderlich, F., & Qiao, Z. (2005) Modulation of *Leishmania donovani* infection and cell viability by testosterone in bone marrow-derived macrophages: signaling via surface binding sites. *Steroids* 70(1):604- 614.

Mukhopadhyay, D., Mukherjee, S., Glosh, S., & Roy, S. (2016). A male preponderance in patients with Indian post kala-azar dermal leishmaniasis is associated with increased circulating levels of testosterone. *International Journal of Dermatology* 55(5):e250-255.

Oliveira, G. M. G., Figueiró-Filho, E. A., Andrade, G. M. C., Araújo, L. A., Oliveira, M. L. G., & Cunha, R, V. (2010) Flebotomíneos (Diptera: Psychodidae: Phlebotominae) no município de Três Lagos, área de transmissão intensa de leishmaniose visceral, estado de Mato Grosso do Sul. *Revista Pan-Amazônia de Saúde* 1(3):83-94.

Organização Mundial de Saúde – OMS (2020). Leishmaniose. Geneva: Organização Mundial de Saúde. https://www. who.int/en/news-room/fact-sheets/detail/leishmaniasis

Organização Pan-Americana da Saúde OPAS (2019). Organização Mundial da Saúde. Leishmanioses. Informe Epidemiológico das Américas. Informe de Leishmanioses Nº7. https://iris.paho.org/bitstream/handle/10665.2/50505/2019-cde-leish-informe-epi-das-americas.pdf?seq

Organização Pan-Americana da Saúde – OPAS (2018). Organização Mundial da Saúde – OMS. Leishmanioses: informe epidemiológico das Américas. https://www.paho.org/leishmaniasis

Ortiz, R. C.; & Anversa, L. (2015). Epidemiology of visceral leishmaniasis in Bauru, São Paulo, Brazil, 2004-2012: a descriptive study. *Epidemiologia e Serviços Saúde* 24(1):97–104.

Ostyn, B., Gidwani, K., Khanal, B., Picado, A., Chappuis, F., Singh, S. P., Rijal, S., Sundar, S., & Boelaert, M. (2011). Incidence of Symptomatic and Asymptomatic *Leishmania donovani* infections in High-Endemic Foci in India and Nepal: a prospective study. *PLoS Neglected Tropical Disease* 5(1): e1284.

Pérez-Cabezas, B., Cecílio, P., Gaspar, T. B., Gärtner, F., Vasconcellos, R., & Cordeiro-Silva, A. (2019). Understanding resistance vs. susceptibility in visceral leishmaniasis using mouse models of *Leishmania infantum* infection. *Frontiers in Cellular and Infection Microbiology* 9(30).

Pinto, A. L. (2016). Mapa estratificado do Município de Três Lagoas. Universidade Federal de Mato Grosso do Sul. Programa de Pós-Graduação em Geografia. Laboratório de Monitoramento Ambiental. Datum: Sirgas 2000 22S. Prefeitura Municipal de Três Lagoas – MS.

Rocha, M. A. N. (2018). Epidemiological aspects of human and canine visceral leishmaniasis in State of Alagoas, Northeast, Brazil. Brazilian *Journal of Biology* 78(4):609-614.

Rodrigues, A. C. M. (2017) Epidemiologia da leishmaniose visceral no município de Fortaleza, Ceará. *Pesquisa Veterinária Brasileira* 37(10): 1119-1124.

Rodrigues, F. R., Sousa, V. C., & Oliveira, E. H. (2020). Análise do perfil epidemiológico da leishmaniose visceral no estado do Piauí no período de 2009 a 2018. Research, Society and Development 9(11): e489119170.

Santiago, A. S., Pita, S. S. R., & Guimarães, E. T. (2021). Tratamento da leishmaniose, limitações da terapêutica atual e a necessidade de novas alternativas: Uma revisão narrativa. *Research, Society and Development* 10(7):e29510716543.

Secretaria de Estado de Saúde – SES (2020). Governo do Estado de Mato Grosso do Sul. Boletim Epidemiológico. Leishmaniose Visceral. Vigilância em Saúde. Gerência Técnica de Zoonoses. Semana Epidemiológica 32. https://www.vs.saude.ms.gov.br/wp-content/uploads/2020/08/Boletim-Epidemiol%C3%B3gico-Leishmaniose-SE-32.pdf

Silva, A. O. (2013). Adaptações crônicas sobre a função pulmonar em indivíduos infectados pela leishmaniose visceral. *Fisioterapia e Movimento* 26(2):403-411.

Souza, J. M. S., Ramalho, W. M., & Melo, M. A. (2018). Demographic and clinical characterization of human visceral leishmaniasis in the state of Pernambuco, Brazil between 2006 and 2015. Revista da Sociedade Brasileira de Medicina Tropical 51(5):622-630.

Sundar, S., & Chakravarty, J. (2012). Leishmaniasis: an update of current pharmacotherapy. *Expert Opinion on Pharmacotherapy* 14(1):53–63.