

VISCERAL LEISHMANIASIS IN BRAZIL BETWEEN 2007 AND 2021

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Abstract: Introduction: Leishmaniasis is a parasitic disease responsible for affecting about 100 endemic countries. Furthermore, it is a disease associated with poverty and the World Health Organization (W.H.O.) characterizes it as a highly neglected tropical disease. Its most common presentation is visceral leishmaniasis (VL). In Latin America, Brazil concentrates more than 99% of cases. **Goal:** To understand the territorial epidemiological distribution of cases of visceral leishmaniasis in Brazil, as well as the most affected populations. **Methodology:** This is a descriptive observational study, whose data were collected by the DataSUS platform. The collection started from the Hospital Information System (SIH), through hospital morbidity data by place of residence between January 2007 and December 2021. **Results and Discussion:** The Northeast is the most affected Region, accumulating more than half of the cases in the country. Only three states in Brazil (Maranhão, Minas Gerais and Ceará) account for almost 40% of cases of the disease. Among the 10 states with the highest number of cases, seven are in the North and Northeast regions, the poorest regions of the country, corroborating the fact that it is an associated disease and poverty. Furthermore, if the public without racial information is disregarded, 83.36% of those affected are black and brown. **Conclusion:** VL remains a neglected disease, affecting the most vulnerable population in the country and with a series of challenges: few therapeutic options, suboptimal diagnoses and little access to information about the disease in the community.

INTRODUCTION

Leishmaniasis is a parasitic disease responsible for affecting about 0.7 to 1 million new cases annually in almost 100 endemic countries. In addition, it is a disease

associated with poverty and the World Health Organization (W.H.O.) characterizes it as a highly neglected tropical disease, which urgently needs public policies and the development of new treatments.¹

The infection caused in the population occurs through the bite of female sandflies infected by the etiological agents of the genus *Leishmania*, which today have at least 20 different species.² Each species is responsible for causing different clinical manifestations, including varying mortality rates. The two main forms of clinical presentation are: visceral leishmaniasis and cutaneous leishmaniasis.¹ Visceral leishmaniasis (VL) is caused by *Leishmania donovani* in Asia and Africa and by *Leishmania infantum* in the Mediterranean Basin, Middle East, Central Asia, South America and Central America.³ This is the most severe systemic form of the disease and is usually fatal if left untreated.⁴ Cutaneous leishmaniasis is usually limited to an ulcer that heals spontaneously within 18 months, but can also cause scarring and disfigurement, and stigmatization for cosmetic results.¹

In 2015, only seven countries (Kenya, South Sudan, India, Brazil, Ethiopia, Somalia and Sudan) reported more than 90% of the world's cases of visceral leishmaniasis.³ In Latin America, Brazil registers more than 99% of the continent's estimated 3,500 annual cases.¹ Thus, this work seeks to understand how the territorial epidemiological distribution of cases of visceral Leishmaniasis occurs in Brazil, as well as the most affected populations.

METHODOLOGY

This is a descriptive observational study, whose objective is to understand the epidemiological distribution of visceral leishmaniasis in Brazil. Data were collected by the DataSUS platform, through

information collected by the Notifiable Diseases Information System (SINAN). The collection started from the Hospital Information System (SIH), through hospital morbidity data by place of residence between January 2007 and December 2021. The information was characterized by regions of Brazil according to hospitalizations by year of attendance. The indicators used were: gender, age, color/race, Deaths and mortality rates. The study was carried out in line with the principles of Resolution 466/2012 of the National Health Council of Brazil.

RESULTS AND DISCUSSION

Visceral leishmaniasis, also known as kala-azar, is a protozoan infection caused essentially by *Leishmania donovani* and *Leishmania infantum* (a synonym of *Leishmania chagasi* in South America).⁴⁻⁶ The parasite exists in 2 distinct forms: a promastigote form found in the vector and an amastigote form, which develops intracellularly in the susceptible mammalian host. Infection occurs after inoculation of promastigotes into the skin following the bite of an infected sand fly. Promastigotes are taken up by macrophages, where they develop into amastigotes and multiply within phagolysosomes. Later, the parasites can spread and infect cells of the reticuloendothelial system in various tissues, predominantly infiltrating the spleen, bone marrow, liver, and lymph nodes.⁵⁻⁷ In Brazil, Visceral *Leishmania* is its most frequent presentation Table 1.0.

Subtype of leishmaniasis	Number of cases in Brazil between 2007-2021
Visceral	32.984
Cutaneous	6.489
Cutaneous-mucosa	2.338
Not specified	8.178

Table 1.0 - Number of patients hospitalized for leishmaniasis in Brazil between 2007-2021.

Source: Ministry of Health - SUS Hospital Information System (SIH/SUS). 2022. ⁸

Brazil has different hospitalization rates according to the different regions of the country Table 2.0. Between 2007 and 2021, the Region with the highest incidence of hospitalizations per residence was the Northeast with 17,374 patients, representing 52.67% of total cases, followed by the Southeast, North, Midwest and South regions. The Brazilian state with the highest incidence of cases was Maranhão with 4,693 patients (14.23%), followed by Minas Gerais with 4,456 (13.51%) and Ceará with 3,947 (11.97%). These three states alone were responsible for 39.7% of the country's cases. The state of Minas Gerais, despite being the second with the number of cases, has a population greater than the sum of the states of Maranhão and Ceará. Thus, proportionally, Minas Gerais would have a much lower ratio of cases/inhabitant. Furthermore, among the 10 states with the highest number of cases, seven are in the North and Northeast regions, the poorest regions of the country, corroborating the fact that it is a disease associated with poverty and, therefore, neglected.

Within the Northeast region, the region most affected by VL, the states that had the most cases of the disease were Maranhão, Ceará, Bahia, Piauí, Pernambuco, Rio

Grande do Norte, Sergipe, Alagoas and Paraíba, respectively. The Southeast region represented 19.3% of the cases, having the second state with the highest incidence in the country. The highest rates in the Region were in the states of Minas Gerais (68% of cases in the Southeast), São Paulo, Espírito Santo and Rio de Janeiro.

The third most affected Region was the North, accounting for 18.7% of cases. The states with the highest rates of hospitalizations were Tocantins, Pará, Roraima, Amazonas, Rondônia, Amapá and Acre, respectively. The Midwest region generated 8.7% of the country's cases and the highest rates were registered in Mato Grosso do Sul (59% of the Region's cases), Goiás, Mato Grosso and the Federal District, respectively. The South region of Brazil was the least affected by VL in the country, since it is the furthest from the tropical zone, representing less than 0.3% of cases since 2007.

The most affected age group is between 1 and 4 years old, accounting for 30.86% of cases Table 3.0. The age group from 1 day to 9 years old accounts for about 49.8% of all VL cases. Adolescents aged 10 to 19 years represent 9.9% of cases. Regarding the adult audience, 27.87% are between 20 and 49 years old and 13.43% are over 50 years old. Regarding the distribution by gender in the country, the rate of affected persons is approximately 2:1 male/female, Table 4.0.

The Brazilian population is predominantly made up of brown and black people. In the case of VL, 52.5% of those affected are brown and only 8.8% are white. Among the data reported by SINAN, 33.6% of those hospitalized did not have information about color/race. Disregarding the public without racial information, 83.36% of those affected are black and brown Table 5.0.

Region/Federation Unit	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Total
TOTAL	213	3.063	2.815	2.399	2.469	2.093	2.347	2.502	2.432	2.250	2.774	2.814	2.103	1.445	1.265	32.984
North region	30	730	546	405	553	436	381	315	305	376	435	614	466	334	244	6.170
Rondônia	-	-	-	1	-	1	3	-	-	1	-	2	1	-	1	10
Acre	-	1	-	-	-	1	1	1	1	-	-	-	-	-	-	5
Amazonas	-	5	-	-	-	1	2	-	-	-	1	1	4	-	1	15
Roraima	-	3	5	10	11	5	15	18	22	38	28	14	11	13	16	209
Pará	16	177	187	156	227	165	161	153	157	167	258	372	251	183	91	2.721
Amapá	-	-	1	1	-	3	1	1	-	-	-	-	-	-	-	7
Tocantins	14	544	353	237	315	260	198	142	125	170	148	225	199	138	135	3.203
Northeast region	114	1.231	1.279	1.157	1.191	1.005	1.399	1.675	1.539	1.168	1.430	1.583	1.160	769	674	17.374
Maranhão	34	384	299	221	238	221	524	432	406	337	463	457	295	192	190	4.693
Piauí	19	194	171	158	169	147	186	218	218	167	181	207	139	70	80	2.324
Ceará	19	309	388	311	299	237	297	403	393	282	264	300	184	145	116	3.947
Rio Grande do Norte	6	77	65	66	78	68	59	84	57	46	48	69	61	33	33	850
Paraíba	3	30	29	27	37	19	32	42	31	36	47	44	37	15	13	442
Pernambuco	21	87	58	42	60	57	56	109	110	78	137	135	163	98	104	1.315
Alagoas	1	17	14	23	25	17	20	29	33	28	36	69	46	53	40	451
Sergipe	3	34	43	90	66	55	51	42	58	45	68	83	65	33	17	753
Bahia	8	99	212	219	219	184	174	316	233	149	186	219	170	130	81	2.599
Southeast region	39	730	632	508	457	405	353	341	448	573	757	467	327	225	214	6.476
Minas Gerais	22	421	427	344	331	231	213	227	320	442	608	336	225	152	157	4.456
Espírito Santo	-	2	10	1	2	2	-	1	4	9	13	9	3	4	2	62
Rio de Janeiro	-	2	3	1	-	6	5	5	3	4	7	3	5	8	3	55
São Paulo	17	305	192	162	124	166	135	108	121	118	129	119	94	61	52	1.903
South region	-	9	3	10	4	3	4	6	3	8	9	10	10	6	6	91

Paraná	-	2	-	3	1	1	2	2	1	4	1	4	4	1	3	29
Santa Catarina	-	3	-	5	1	2	-	1	2	2	3	1	2	1	1	24
Rio Grande do Sul	-	4	3	2	2	-	2	3	-	2	5	5	4	4	2	38
Midwest region	30	363	355	319	264	244	210	165	137	125	143	140	140	111	127	2.873
Mato Grosso do Sul	18	251	246	218	160	167	122	100	70	53	68	56	63	46	59	1.697
Mato Grosso	6	43	55	45	44	32	30	12	16	15	9	11	16	14	11	359
Goiás	4	42	31	40	38	27	40	35	39	41	52	61	51	38	42	581
Federal District	2	27	23	16	22	18	18	18	12	16	14	12	10	13	15	236

Table 2.0 Number of patients hospitalized for visceral leishmaniasis according to each Region and Brazilian state between 2007 and 2021.

Source: Ministry of Health - SUS Hospital Information System (SIH/SUS). Dados de janeiro de 2015 até março de 2016 sujeitos a retificação. 2022. ⁸

Region / Age	Less than one year	1 to 4 years	5 to 9 years	10 to 14 years	15 to 19 years	20 to 29 years	30 to 39 years	40 to 49 years	50 to 59 years	60 to 69 years	70 to 79 years	80 years or over	Total
TOTAL	2.848	10.178	3.398	1.693	1.575	3.146	3.014	2.702	2.037	1.358	740	295	32.984
North region	751	2.329	729	332	246	494	436	329	223	171	96	34	6.170
Northeast region	1.525	5.534	1.857	962	883	1.702	1.566	1.299	980	617	293	156	17.374
Southeast region	362	1.601	611	304	276	606	690	714	585	403	247	77	6.476
South region	7	14	3	-	12	7	16	10	7	8	7	-	91
Midwest region	203	700	198	95	158	337	306	350	242	159	97	28	2.873

Table 3.0 - Distribution by age group of the population hospitalized for visceral leishmaniasis in Brazil between the years 2007 and 2021 according to the regions of the country by place of residence.

Source: Ministry of Health – SUS (Unified Health System) Hospital Information System (SIH/SUS). 2022. ⁸

Region	Male	Female	Total
TOTAL	20.505	12.479	32.984
North region	3.618	2.552	6.170
Northeast region	10.937	6.437	17.374
Southeast region	4.029	2.447	6.476
South region	62	29	91
Midwest region	1.859	1.014	2.873

Table 4.0 - Distribution by gender of the population hospitalized for visceral leishmaniasis in Brazil between the years 2007 and 2021 according to the regions of the country by place of residence.

Source: Ministry of Health – SUS (Unified Health System) Hospital Information System (SIH/SUS). 2022.⁸

Region	White	Black	Brown	Yellow	Indian	Without information	Total
TOTAL	2.918	933	17.318	444	282	11.089	32.984
North region	230	110	4.063	54	141	1.572	6.170
Northeast region	610	209	8.906	278	94	7.277	17.374
Southeast region	1.531	514	2.967	79	21	1.364	6.476
South region	56	9	17	-	-	9	91
Midwest region	491	91	1.365	33	26	867	2.873

Table 5.0 - Distribution by color/race of the population hospitalized for visceral leishmaniasis in Brazil between the years 2007 and 2021 according to the regions of the country by place of residence.

Source: Ministry of Health – SUS (Unified Health System) Hospital Information System (SIH/SUS). 2022.⁸

RECOGNITION AND TREATMENT

The classic diagnosis of VL is through microscopic observation of the parasite's amastigote stage in tissue specimens or cultures. Sensitivity is tissue dependent: over 90% in spleen, 50-80% in bone marrow and even lower in lymph node aspirates.³ The technique is also important because sensitivity increases with longer reading time and with more microscope fields examined.⁹

Splenic aspirates are considered the gold standard, but the procedure carries a risk of bleeding in 1 out of 1,000 procedures.¹⁰ Several serological tests are available, including direct agglutination test, ELISA, immunofluorescence and western blot. These antibody detection techniques share a high sensitivity for acute visceral disease but are not strictly specific for that stage of disease.¹¹

Traditionally, the treatment of VL has been based on the use of pentavalent antimonials (Sb51), introduced in the 1940s.^{6,12} Since the 1980s, conventional amphotericin B deoxycholate has been increasingly used in high-income countries. Subsequently, different lipid formulations of amphotericin B were developed, mainly liposomal amphotericin B, which combine high efficacy with low toxicity.¹³ Liposomal amphotericin B is the only treatment approved by the US Food and Drug Administration (FDA). Several studies have been conducted in low- and middle-income countries with paromomycin, an inexpensive and effective parenteral drug with an acceptable toxicity profile that can be easily administered on an outpatient basis by intramuscular injection.¹⁴

In Brazil, treatment is performed with Meglumine Antimoniate and/or Amphotericin B, both available in the Unified Health System.¹⁵⁻¹⁶ Antimoniate is the first line of choice, Amphotericin being an expensive drug and recommended only in case of contraindications such as the renal,

hepatic, cardiac failure, during pregnancy and in patients older than 50 years.¹⁵ The average cost per hospitalization for leishmaniasis in Brazil varies according to the different regions of the country Table 6.0.

The South region, despite being the least affected, has the highest average cost. On the other hand, the Northeast region, second with the most cases, is the second cheapest, costing an average of R\$ 488.88 per person. The annual average expenditure on hospitalizations for visceral leishmaniasis in the country is R\$ 1,232,892.89. A fact that could be avoided if efficient public policies were implemented to control the disease in the population.

Visceral leishmaniasis is a disease with a high cure rate if treatment is started in the early stages of the disease. Between 2007-2021, the death rate from the disease was 4.17% Table 7.0. However, the South region, which has the lowest incidence in the country, has the highest mortality rate in the country, 7.69%. This could be explained by the fact that 24.18% of those affected were 50 years of age or older, with the most aggressive treatment for this public. This relationship could also explain the higher average cost for hospitalized patients in the South region, since treatment for those over 50 years old is done with Amphotericin B, a drug of high commercial value.

So far, there is no registered vaccine that prevents human leishmaniasis. Most people who recover from leishmaniasis are immune to new infections, providing good justification for the focus of research on vaccine development. As patients with untreated visceral leishmaniasis are reservoirs of parasites, the important role of delay in treatment in maintaining transmission, for example, the duration between the onset of symptoms and adequate treatment, has recently been highlighted, since these people

Region	Average value per hospitalization	Number of admissions from 2008-2021	Average admissions per year from 2008-2021	Average annual expenses with hospitalizations
TOTAL	R\$ 526,69	32.771	2340,9	R\$ 1.232.892,89
North region	R\$ 448,01	6.140	438,6	R\$ 196.497,19
Northeast region	R\$ 488,88	17.260	1232,9	R\$ 602.740,15
Southeast region	R\$ 669,6	6.437	459,8	R\$ 307.882,08
South region	R\$ 1.148,88	91	6,5	R\$ 7.467,72
Midwest region	R\$ 582,5	2.843	203,1	R\$ 118.305,75

Table 6.0 Average hospitalization cost of the Brazilian population diagnosed with visceral leishmaniasis between the years 2008 and 2021 according to regions of the country by place of residence.

Source: Ministry of Health – SUS (Unified Health System) Hospital Information System (SIH/SUS). 2022. ⁸

Region	Deaths	Mortality rate
TOTAL	1.377	4,17
North Region	207	3,35
Northeast Region	724	4,17
Southeast Region	273	4,22
South Region	7	7,69
Midwest region	166	5,78

Table 7.0 Mortality indicators population hospitalized for visceral leishmaniasis in Brazil between the years 2007 and 2021 according to regions of the country by place of residence.

Source: Ministry of Health - SUS Hospital Information System (SIH/SUS). 2022. ⁸

are highly infectants. Thus, the early detection and initiation of treatment of cases is one of the main control strategies.¹⁷

Vector control strategies in Asia are based on indoor residual spraying, long-term insecticide nets and environmental management. Although a long-lasting insecticidal net provides some personal protection against sand fly bites, its effectiveness in reducing the incidence of visceral leishmaniasis at a population level is not established. On the other hand, selective residual spraying outdoors in villages can be effective in reducing vector density. Data from an observational study showed that mass distribution of long-lasting insecticidal bed nets in Sudanese villages had a 59% protective effect (95% CI 25–78) against visceral leishmaniasis^{17–20} months after distribution.¹⁸ In Brazil, the effectiveness of the national policy to cull infected dogs is contested.¹⁹ This is even more evident given the fact that there are three canine vaccines registered in Brazil or Europe, conferring some protection under natural conditions.²⁰

The Asian Visceral Leishmaniasis Elimination Initiative and the 2012 London Declaration on Neglected Tropical Diseases have raised global awareness of leishmaniasis and substantially increased funding for control.²¹ Despite this increased interest, some of the classic challenges of a tropical disease neglected remain intact: few therapeutic options, suboptimal diagnoses and little access to information in communities – mainly for cutaneous leishmaniasis, which is not included in the priority classifications.

CONCLUSION

Visceral leishmaniasis is the most common clinical presentation among the subtypes of the disease and affects different regions of the country differently. The Northeast is the most affected region, accumulating more than half of the cases in the country. Only three states in Brazil (Maranhão, Minas Gerais and Ceará) account for almost 40% of cases of the disease. Among the 10 states with the highest number of cases, seven are in the North and Northeast regions, the poorest regions of the country, corroborating the fact that it is an associated disease and poverty. Furthermore, if the public without racial information is disregarded, 83.36% of those affected are black and brown, which already reflects a situation of social and racial inequality implicit in the entire health-disease process, thus being a neglected disease, as already reported. by WHO.

CONFLICT OF INTERESTS

There is not any.

FINANCING

The own researchers.

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