Spatiotemporal analysis of visceral leishmaniasis in the state of Bahia, Brazil, 2007 - 2017: Socioeconomic and environmental aspects

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Background. Visceral leishmaniasis (VL) is a neglected zoonosis caused by the parasite *Leishmania infantum*, present throughout the world. In Bahia, a state in the north-eastern region of Brazil, there is a high prevalence.
Objectives. To evaluate the role of socioeconomic and environmental factors in the epidemiology of VL though spatiotemporal analysis.
Methods. Epidemiological data for Bahia were extracted from the System for Notification of Diseases of the Ministry of Health (SINAN), data on prolonged droughts were obtained through the Civil Bureau of the Government of the State of Bahia, and socioeconomic indicators were obtained through the Socioeconomic Performance Index (IPESE) and DATASUS, the Brazilian public unified health system department responsible for providing health data. Relative risk for VL was calculated for age classes, clinical manifestations, comorbidities and deaths, while spatial analysis relied on kernel density analyses to determine spatial patterns. Correlations between socioeconomic indices and epidemiological markers were explored.
Results. From 2007 to 2017, 3 847 new VL cases and 227 deaths were reported in Bahia. The mean incidence was 1.73 per 100 000 population. Cases and deaths were concentrated in the central-northern region of the state, a relatively poor area with a dry/semi-arid climate. Cases were more frequent in urban areas (54.1%), in males (60.7%) and in children aged <10 years (48.2%). Municipalities that declared a state of emergency due to prolonged drought (SECO dataset) and IPESE were positively correlated (p=0.0001 and p=0.013, respectively) with VL cases reported in all age groups. Deaths from VL were significantly correlated with the Gini index (p=0.043).
Conclusion. Our results paint a picture of socioeconomic and climatic vulnerability as determinants of VL epidemiology. Addressing socioeconomic inequalities and enhancing models to predict prolonged drought are actions that should be included in the prevention and control of VL, given that vulnerable populations will be the most affected by the frequency and intensity of extreme climatic events.

Keywords. *Leishmania infantum*, climate, prolonged drought, children

South Afr J Pub Health 2025;8(2):e3324. https://doi.org/10.7196/SHS.2025.v8i2.3324

Visceral leishmaniasis (VL) was considered a rural disease in Brazil. However, its occurrence in urban areas has increased significantly during the past few decades, particularly in the north-eastern region, an area with large vulnerable populations. In the scenario of unplanned urbanisation, rural exodus and environmental transformation, the vector *Lutzomyia longipalpis* has found favourable conditions to spread, and introduce the parasite *Leishmania infantum*.[1,2]

In Bahia, the largest state in the north-eastern region, VL has spread since the 1980s, reaching the coast and the periphery of large cities, previously considered to be ecologically unsuitable for the vector.[3,4] Rural exodus, increased by prolonged drought events, crescent pauperisation of urban populations and increased concentrations of wealth, resulted in rural gentrification in several regions, and contributed to the expansion of endemic areas and emergence of VL foci.[5]

Records of urban cases of VL, especially in regions that had no history of cases, represent an increased risk for the elderly[6] and for children.[7,8] Since the 1970s, most endemic areas have presented cases, particularly in children aged <10 years (80%), with most of these in children aged <5 years (60%).[9-12]

The present study describes the spatiotemporal epidemiology of VL in Bahia between 2007 and 2017 and evaluates potential socioeconomic and environmental determinants of its occurrence and of deaths, with emphasis on the age group 0 - 9 years.

Methods

Study area and data sources

The study covered the entire state of Bahia (564 732.45 km^2), which is divided into 417 municipalities and has an estimated population of 14 016 906, 72% of whom live in urban areas.[13]

We analysed VL cases and deaths in the 417 municipalities of the state between 2007 and 2017, obtained through the System for Notification of Diseases of the Ministry of Health (SINAN). In Brazil, notification of VL is compulsory in the entire national territory (ordinance GM/MS no. 3.418, 31 August 2022). Data were triaged to remove faulty data and duplicates, and the following inclusion criteria were used: new cases, confirmed by immunological and clinical-epidemiological diagnosis, with identification of the municipality of residence. Demographic variables evaluated were sex, self-declared ethnicity and age. We evaluated the Human Development Index (HDI) and urbanisation rate (UR).[14] Data on the municipalities that declared a state of emergency due to prolonged drought during the period studied were provided by the Civil Bureau of the Government of the State of Bahia; this dataset was called SECO. We also included the Socioeconomic Performance Index (IPESE), a synthetic indicator created by dimensions of Health, Education, Economy and Finances, elaborated for valuation of public policy on use of public resources, as declared in Technical Note IPESE 2014, obtained through the Superintendency of Social and Economic Studies of Bahia, and the Gini index (GINI), an instrument that measures inequalities in the distribution of wealth in a specific population, obtained through DATASUS, the Brazilian public unified health system department responsible for providing health data. Data refer to each of the 417 municipalities of the state.

Data analysis

Annual incidence and mortality indices for VL were calculated as the number of new cases (incidence) or the number of deaths (mortality) divided by the total state population, adjusted per 100 000 inhabitants. To evaluate the number of VL cases throughout the period, we created nine age groups. Additionally, cases were stratified into two main groups: 0 - 9 years and >9 years. Chi-squared tests were employed to compare the frequencies between age groups and years. Two-sample proportion tests were used to compare the lethality rates between groups.

We evaluated the frequency of clinical manifestations and co-infections during the study period. Relative risk was calculated between the two main age classes, for clinical manifestations, comorbidities and deaths due to VL. Cases with incomplete data were excluded. Statistical analyses were performed on GraphPad Prism v.5.0 (GraphPad Software Inc., USA), Stata 12 (StataCorp, USA) and JMP 14.3 (SAS Institute, USA). Chi-squared or Fisher's exact tests were used to compare qualitative variables described as percentages, and 95% confidence intervals (CIs) were calculated.

Spatial analyses were based on the municipal net cartographic base for Bahia at the 1:250 000 scale, using Lat/Long projection, and SIRGAS 2000 as the reference geodesic system.[15] Kernel density analysis was applied to evaluate the spatial concentration of the frequencies of VL incidence and deaths, with emphasis on the 0 - 9-year age group. All analyses were performed in QGIS 2.18 (QGIS). Municipality polygons were categorised by interquartile intervals of the variables, and maps were plotted to represent the data. To evaluate the concentration of accumulated VL incidence and mortality per municipality, a kernel density based on the polygon centroids was used to create a continuous response surface, in order to determine hotspots.[16]

To evaluate socioeconomic profile indicators, Spearman correlations were performed to test the correlations of HDI, UR, GINI, SECO and IPESE with VL incidence in the two main age groups (0 - 9 years and >9 years) and the number of deaths per municipality. For this analysis, only municipalities that had at least one case of VL during the study period were considered. HDI, UR and GINI data for each municipality were obtained from the 2010 census.[14] SECO and IPESE were measured annually, so for SECO, we summed the number of notifications for the period, and for IPESE, we calculated the mean for the period for each municipality during the period of study. The numbers of VL cases and deaths correspond to the total of the 11 years (2007 - 2017) per municipality.

Results

Between 2007 and 2017, 4 371 new suspected cases of VL were reported in SINAN. After data triage, 88.0% (n=3 847) were considered new confirmed cases of VL and included in the study. Of these, 227 resulted in death.

Notification of new cases varied from year to year with high points such as 2014, when 14.3% (n=552) of all cases during the study period occurred (Fig. 1A). Deaths from VL had a similar trend, with 15% (n=34) of all deaths in the series occurring during 2014 (Fig. 1A). There were more cases (60.0%) and deaths (55.9%) among males (Fig. 1B). Pardo (mixed ancestry) was the ethnic group with the highest case frequency (70.1%), followed by black (16.2%) and white (12.4%) (Fig. 1C). The coefficient of incidence for VL ranged from 1.57 in 2008 to 3.94 in 2014 (Fig. 1D). The coefficient of mortality ranged from 0.09 in 2008 and 2009 to 0.24 in 2014 (Fig. 1D).

The median (interquartile range) age for VL occurrence in the state of Bahia was 11 (29) years. Fig. 1E presents the variation in the number of VL cases stratified into nine age groups. Children aged 0 - 9 years represented 48.2% of cases (n=1 855), and within this group, children aged ≤5 years accounted for 78.8% of cases (n=1 461). The age group 0 - 9 years accounted for a significantly higher number of cases than any of the other groups (χ^2 p<0.0001) (Fig. 1E). Fig. 1F presents VL cases stratified into two groups, 0 - 9 years and >9 years. Although the two groups have similar distributions, the number of patients aged >9 years is statistically higher (n=1 992; χ^2 p<0.0001). The proportion of cases in children

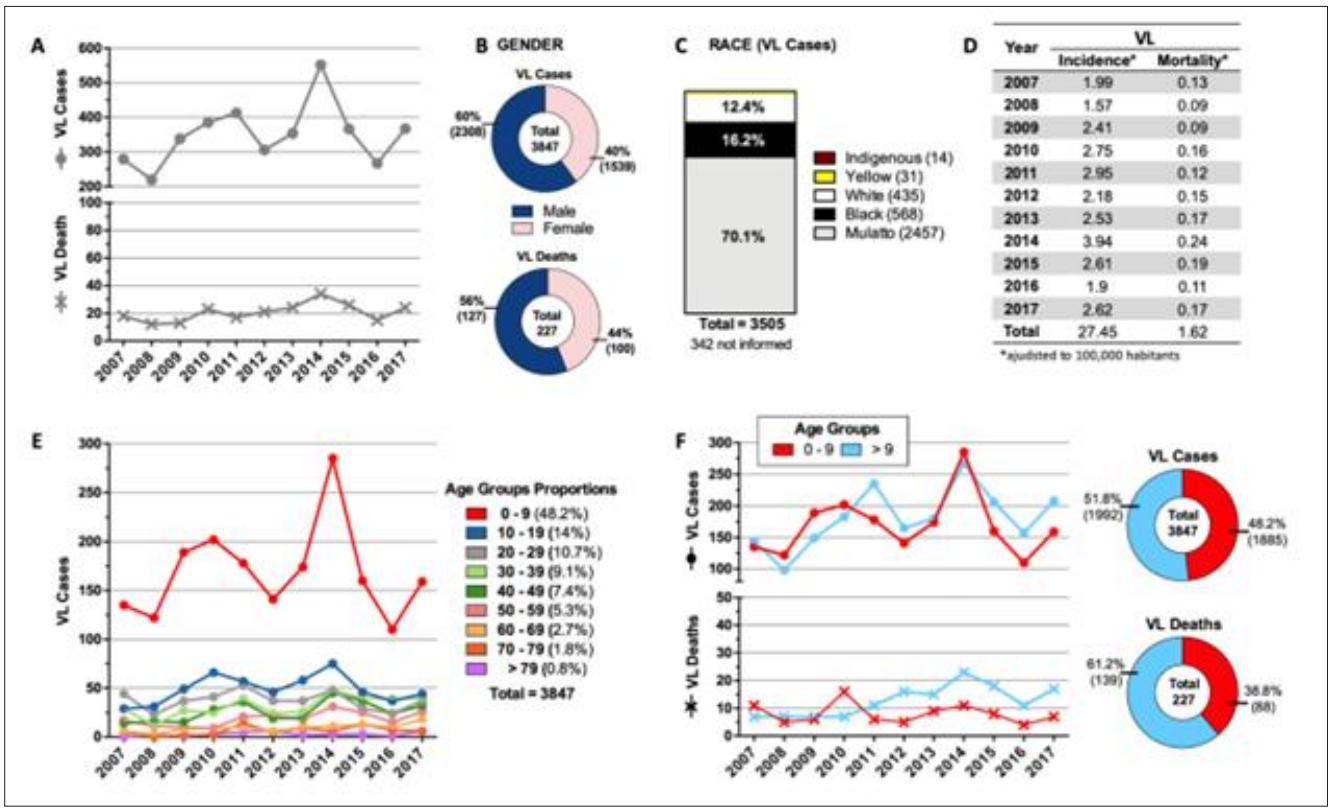


Fig. 1. General view of cases of VL in the state of Bahia, Brazil, 2007 - 2017. (A) Number of cases and deaths per year. (B) Cases and deaths stratified by sex. (C) Cases stratified by ethnic group. (D) Incidence and mortality per year, adjusted per 100 000 population. (E) Cases stratified by age groups. (F) Cases and deaths stratified by two age groups (0 - 9 and >9 years). (VL = visceral leishmaniasis.)

aged <9 years ranged from 41.2% (*n*=110/267) in 2016 to 55.9% (*n*=189/338) in 2009, with a peak (in absolute numbers) in 2014 (*n*=285/552), representing over half of the VL cases duirng the years 2008, 2009, 2010 and 2014 (Fig. 1F).

During the study period, there were cases throughout most of Bahia, in 311 municipalities. However, there was a concentration in municipalities of the health macro-regions of Center-North and Center-East, with 13 municipalities in particular: Juazeiro, Guanambi, Irecê, Canarana, Jequié, Feira de Santana, Salvador, Salinas da Margarida, Andaraí, São Gabriel, Camaçari, Cafarnaum and América Dourada (Fig. 2). Spatial distribution of VL cases and deaths follows the occurrence of cases, concentrated in the health macro-regions of Center-North and Center-East (Fig. 2).

The annual occurrence of VL cases in Bahia in children 0 - 9 years of age, although widely distributed through the state, was also concentrated in the health macro-regions of Center-North and Center-East (Fig. 3). Cases in the age group 0 - 9 years were more frequent in the (peri)-urban zone (56.3%) compared with the rural areas (43.3%) of municipalities, reinforcing the tendency for the disease to be associated with increased urbanisation in Bahia. The spatial distribution of VL cases and deaths in children aged 0 - 9 years showed hotspots in the health macro-regions of Center-North, West and Center-East (Fig. 3).

During the study period, 90.6% (*n*=3 484) of the total number of patients recovered, 5.9% (*n*=227) died, and 3.5% (*n*=136) died of causes not related to VL (Fig. 4A). Of all patients who died of VL, 61.2% were aged >9 years (Fig. 4B). These patients had a 1.53 times higher relative risk of death than the age group 0 - 9 years (95% CI 1.18 - 1.98; $p<0.05$). VL lethality during the study period was 5.9%, the figure of 7.0% for patients aged >9 years being statistically higher ($p<0.01$) than that for younger patients (4.9%). There was no statistically significant difference in deaths between males and females in VL cases as a whole, but among children aged 0 - 9 years, females had a 54% higher risk (95% CI 1.02 - 2.33; $p<0.01$).

The mean time between first symptoms experienced by the patient and official notification of the case was 42.3 days, with a median of 18 days. Of the cases, 63.5% (*n*=2 443) were notified up to a month after the first symptoms, 32.5% (*n*=1 251) after 1 - 6 months, 2.8% (*n*=109) after 6 months to a year, and 1.1% (*n*=44) after over a year. It is possible that variations in the average time between diagnosis and treatment are due to inconsistencies in filling out the information in the official notification form.

In 75.2% of cases (*n*=2 981), the date when treatment was started was provided. In this group, the mean time between symptoms and starting treatment was 46.5 days, with a median of 23 days. Of these patients, 57.9% (*n*=1 675) were treated within a month of first experiencing symptoms, 37.7% (*n*=1 091) from 1 to 6 months, 2.9% (*n*=83) from 6 months to a year, and 1.5% (*n*=42) after over a year.

Of all notified cases, 89.5% (*n*=3 444) had fever, 75.5% (*n*=2 905) weakness, 70.2% (*n*=2 701) weight loss, 69% (*n*=2 653) pallor, 66.4% (*n*=2 554) splenomegaly, 54.8% (*n*=2 109)

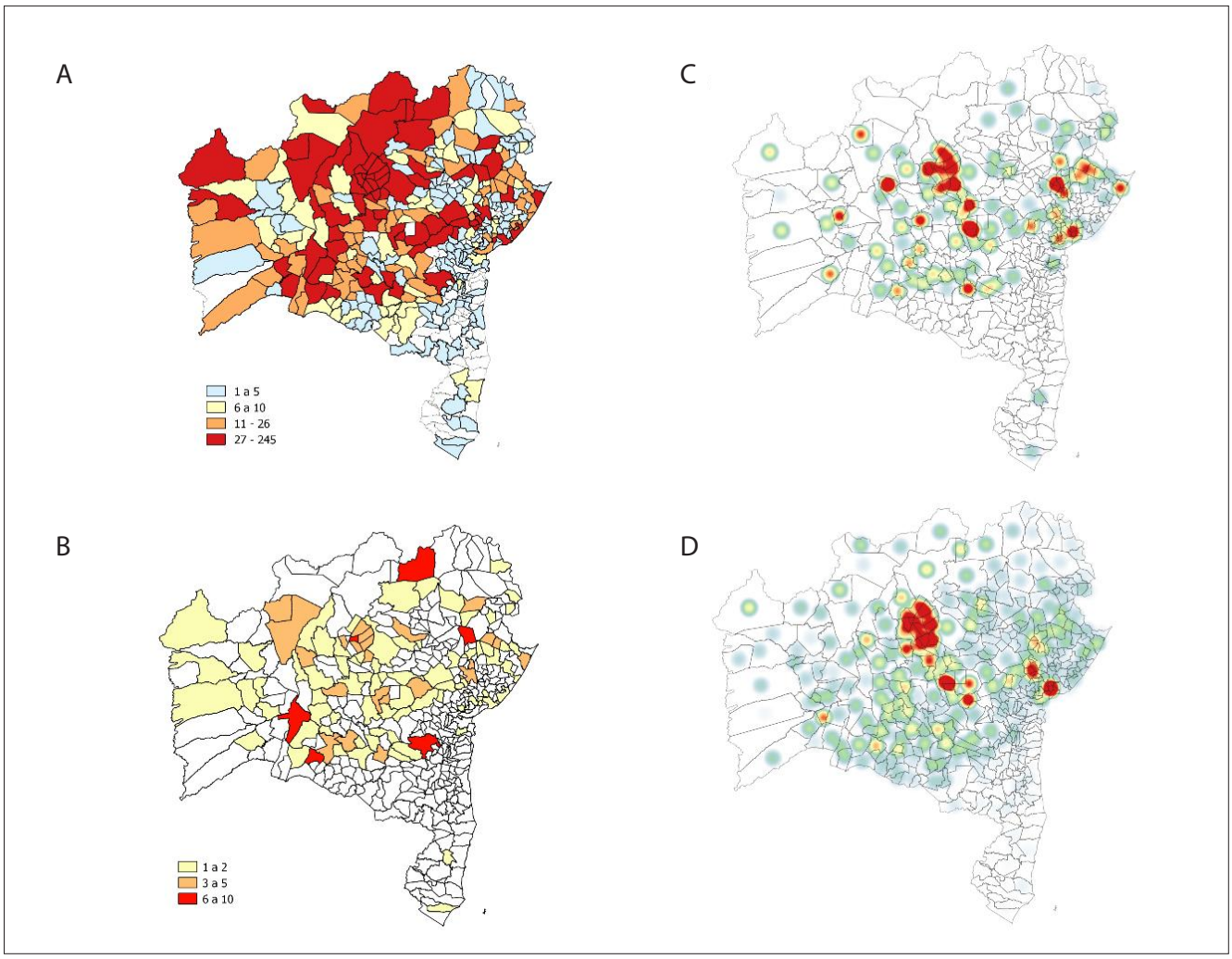


Fig. 2. Distribution of VL cases (A), deaths (B), cumulative incidence (C) and mortality concentration (D) in the state of Bahia, Brazil, 2007 - 2017. (VL = visceral leishmaniasis; *Kernel concentration analysis using polygon centroids and accumulated incidence and mortality for VL per municipality.)*

hepatomegaly, 44% (*n*=1 692) cough and/or diarrhoea, 29.7% (*n*=1 144) jaundice, 28.1% (*n*=1 081) oedema, and 11.6% (*n*=445) haemorrhage. Also, 19.9% of patients with VL (*n*=764) had an (unspecified) co-infection diagnosed at the time of admission, and 1.7% (*n*=65) were HIV positive.

The frequency of clinical manifestations, stratified into the two age classes, is presented in Fig. 4C. Fever, pallor, splenomegaly, hepatomegaly, and cough and/or diarrhoea were statistically more frequent in children aged 0 - 9 years, while weakness, weight loss and jaundice were statistically more frequent in patients aged >9 years. Fig. 4D presents an analysis of the association between patient age and clinical signs. Hepatomegaly was 1.27 times more frequent in patients aged 0 - 9 years than in those aged >9 years (95% CI 1.20 - 1.34; $p<0.0001$), while jaundice was 2.17 times more frequent in patients aged >9 years compared with those aged 0 - 9 years (95% CI 1.79 - 2.63; $p<0.0001$). No difference was found with regard to frequency of co-infections. However, patients aged >9 years had a 5.3 times higher relative risk of HIV co-infection than the younger age group (95% CI 2.71 - 10.33; $p<0.0001$). In this population, risk of death from VL was 53% higher in patients aged >9 years (95% CI 1.18 - 1.98; $p<0.0012$).

The number of VL cases, total and stratified between 0 - 9 and >9 years, was significantly correlated with SECO and IPESE, while the number of deaths was also correlated with GINI (Table 1).

Of total deaths from VL, most were in males (55.9%; *n*=127). However, between 0 - 9 years, females were in the majority (59.1%; *n*=52).

Discussion

The epidemiology of VL in Brazil is characterised by the effects of socioeconomic inequality, lack of knowledge, and difficulty in identifying the signs and symptoms of the disease owing to low levels of formal education. An underfunded health infrastructure results in delayed diagnosis and increased mortality,[8] and affects the occurrence in children, particularly between 0 and 5 years of age.[5,17,18]

The tendency for the spatial distribution of VL to increase in the state of Bahia, and the annual variations in incidence, are particularly associated with periods of prolonged drought,

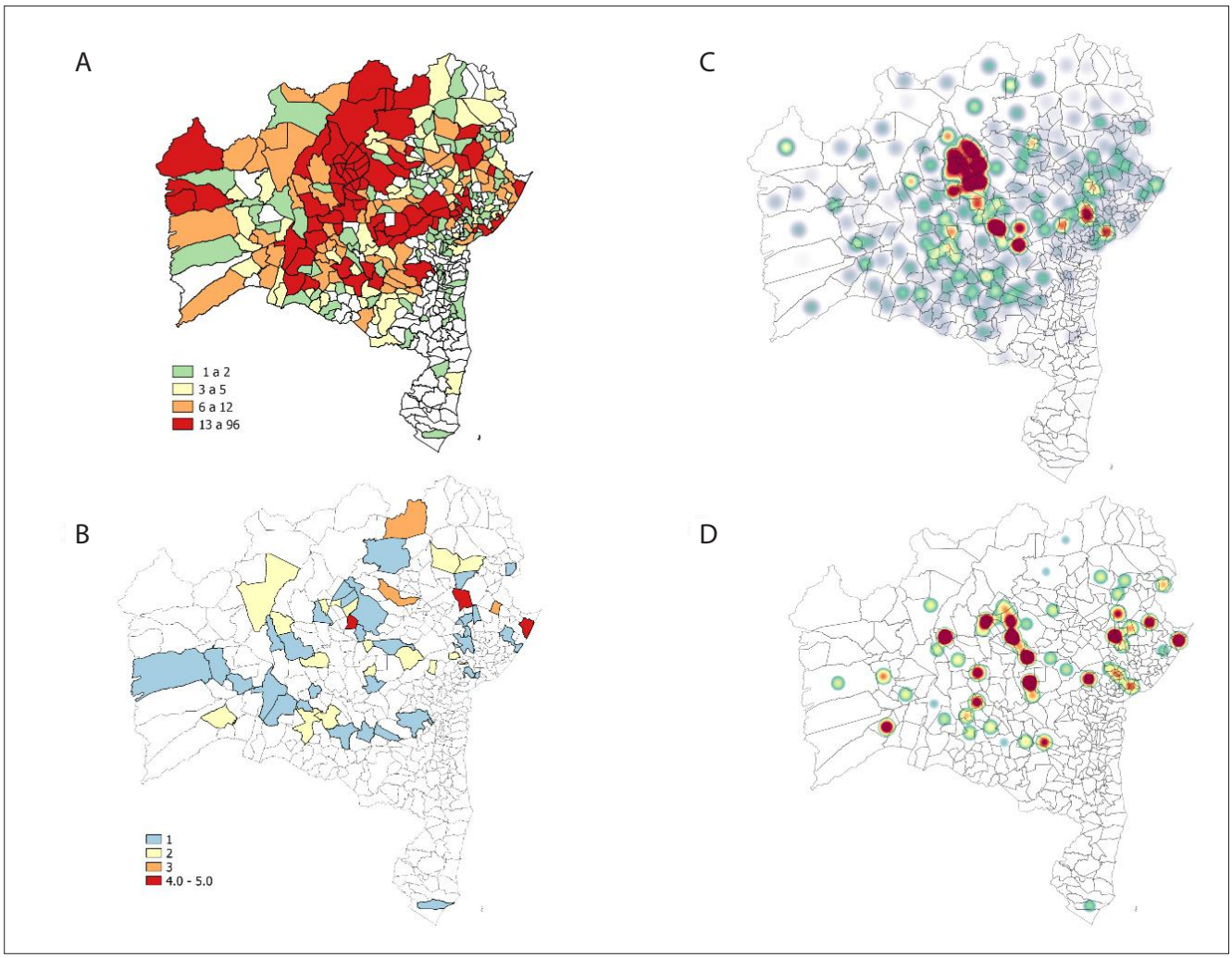


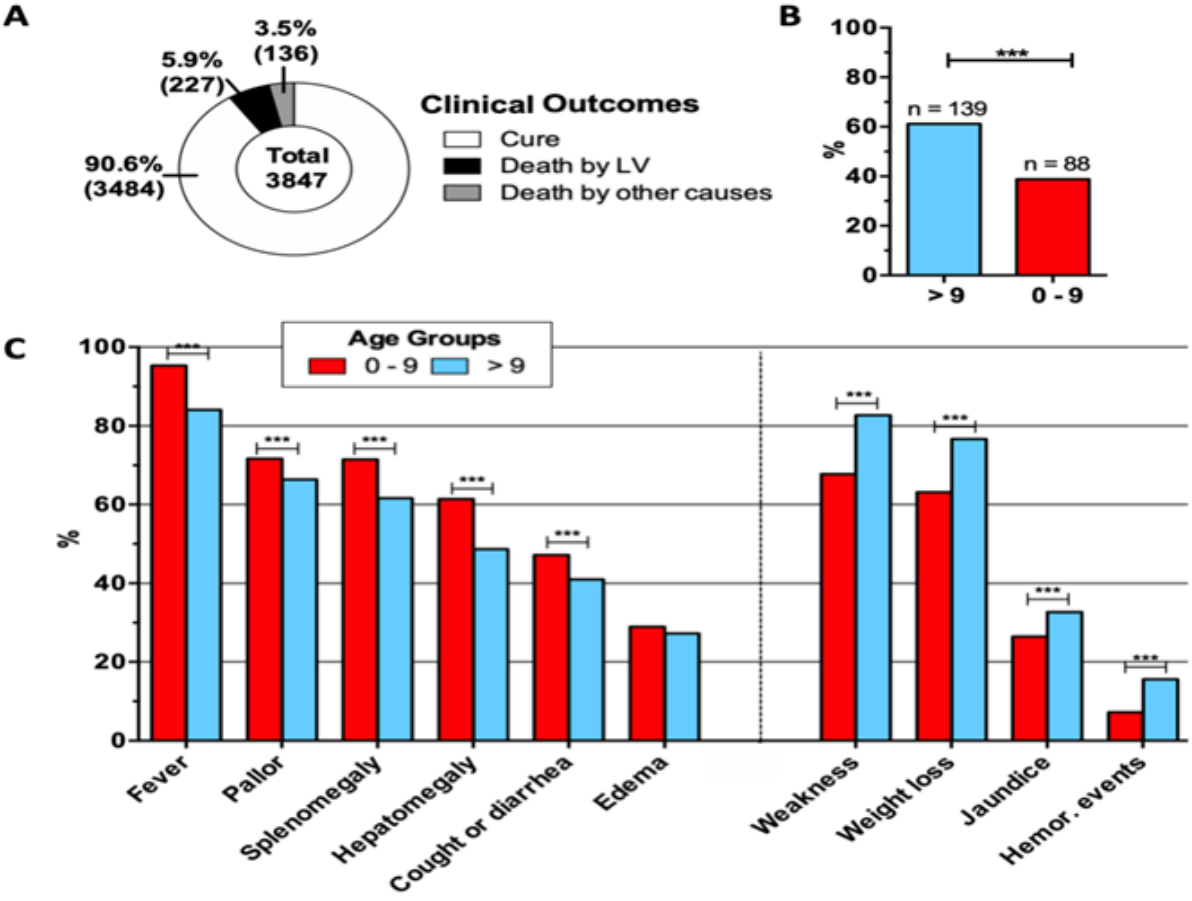
Fig. 3. Distribution of VL cases (A), deaths (B), cumulative incidence (C) and mortality concentration (D) among children aged 0 - 9 years in the state of Bahia, Brazil, 2007 - 2017. (VL = visceral leishmaniasis; *Kernel concentration analysis using polygon centroids and accumulated incidence and mortality for VL per municipality.)*

which intensify migration of vulnerable populations from rural endemic zones to urban areas, together with their domestic animals.[3,4,19-22] This trend contributes to geographical expansion into new areas,[23,24] and Dantas-Torres and Brandão-Filho[25] highlight that, in these conditions and in the presence of susceptible reservoirs, the disease could easily assume an epidemic cycle in the new environments.

During the study period, several municipalities declared a state of climate emergency due to prolonged drought, especially in the semi-arid and arid areas in the central and northern parts of the state, where the majority of VL cases occurred. The predominance of VL cases in urban areas indicates this zoonosis's current tendency to urbanisation,[2,26] as also observed by Botelho and Natal[27] and Silva *et al*.[28] in Campo Grande, state of Mato Grosso do Sul, and Palmas, state of Tocantins, where 99% and 97.2% of cases, respectively, occurred in urban zones.

The patterns observed with regard to the more common clinical signs, independent of age group, are similar to what was described by Brazuna *et al*.,[29] who observed fever (95.3%), splenomegaly (83.6%), hepatomegaly (75.8%), weakness (74.1%), weight loss (72.2%) and dry cough/diarrhoea (50.6%). Similar symptoms were reported by Queiroz *et al*.,[8] Pastorino *et al*.[30] and Pedrosa and Rocha.[31] Mourão *et al*.[32] observed that, apart from being commonly reported signs of the disease, jaundice, renal damage and oedema were observed in the later phase of the disease. Symptoms most commonly associated with age 0 - 9 years in Bahia (fever, pallor, splenomegaly, weakness, weight loss, hepatomegaly, cough and diarrhoea) are similar to those observed among children in Pernambuco by Queiroz *et al*.,[8] who reported fever, increased abdominal volume, pallor, anorexia and cough as the most frequent symptoms, as well as an association with malnutrition.[33,34]

According to Franke *et al*.[21] in their study of human cases of VL in Bahia between 1985 and 1999, the time between the first symptoms and diagnosis of the disease was about 3 months. This is concerning, as the means observed for some years and age groups in our study indicate that even after 20 years there has been little advance in early detection of human VL in the



D

Age Groups	Clinical Manifestations	Relative Risk (95% CI)	*p*-value
0 – 9 years old	Fever	1.12 (1.09 – 1.15)	< 0.0001
	Pallor	1.07 (1.03 – 1.12)	0.0007
	Splenomegaly	1.16 (1.11 – 1.21)	< 0.0001
	Hepatomegaly	1.27 (1.20 – 1.34)	< 0.0001
	Cough or diarrhea	1.14 (1.07 – 1.23)	0.0002
	Edema	0.98 (0.86 – 1.10)	0.7078
> 9 years old	Weakness	1,21 (1.16 – 1.25)	< 0.0001
	Weight loss	1.21 (1.16 – 1.25)	< 0.0001
	Jaundice	2.17 (1.79 – 2.63)	< 0.0001
	Hemorrhagic events	1.25 (1.13 – 1.38)	< 0.0001

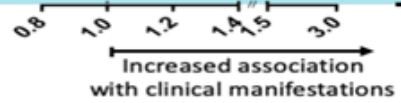


*Fig. 4. Descriptive analyses of VL cases and deaths. (A) Clinical evolution of cases. (B) Deaths in the age groups 0 - 9 years and >9 years. (C) Clinical signs observed in the age groups 0 - 9 years and >9 years. (D) Clinical manifestations and RR for VL aggravation and death. (VL = visceral leishmaniasis; RR = relative risk; CI = confidence interval; *** = statistical significance; the markers in the RR column in D = value and 95% CI.)*

Table 1. Correlation analysis between socioeconomic indices and occurrence of VL cases in the total population, >9 years and 0 - 9 years, and deaths from VL in the state of Bahia, Brazil, 2007 - 2017

	Cases of VL							
	0 - 9 years		>9 years		Total		Deaths from VL	
Indices	r	*p*-value	r	*p*-value	r	*p*-value	r	*p*-value
HDI	0.063	0.279	0.016	0.789	0.045	0.436	0.050	0.388
UR	0.048	0.408	–0.048	0.404	–0.018	0.758	0.006	0.917
GINI	0.100	0.082	0.010	0.866	0.036	0.535	0.117	0.043*
SECO	0.285	<0.0001*	0.286	<0.0001*	0.313	<0.0001*	0.140	0.013*
IPESE	0.163	0.0004*	0.202	0.0004*	0.192	0.0007*	0.176	0.002*

VL = visceral leishmaniasis; r = Spearman's statistic; IPESE = Socioeconomic Performance Index; HDI = Human Development Index; UR = urbanisation rate; GINI = Gini index, SECO = state of emergency due to drought.
*Statistically significant ($p<0.05$).

state, which is reflected in the lethality of the disease. The average time between first symptoms and diagnosis/beginning of treatment in children aged 0 - 9 years in the present study (53 days) is similar to that observed in Pernambuco[8] (43 days from first symptoms to hospital admission). Oliveira *et al.*[35] and Leite and Araújo[36] found even more worrying situations in Campo Grande (78.2 days), and Mossoró, state of Rio Grande do Norte (78.6 days). In Madrid, Spain, Prieto Tato *et al.*[37] observed shorter times between first symptoms and diagnosis/treatment in children aged <15 years (20.2 days), which reflect higher standards of living and a more robust public health system. According to Barbosa and Costa,[9] Abdelmoula *et al.*[38] and Alvarenga *et al.*,[39] more than 56 days between first symptoms and a medical consultation is associated with poor prognosis. Reducing the lethality of VL in Brazil requires investing in medical personnel trained for clinical diagnosis, provision of adequate laboratory support for case confirmation, and active surveillance in endemic areas.

Araujo *et al.*[40] suggest that infectious complications, haemorrhages and severe anaemia are the main causes of death from VL, associated with age and malnutrition. According to Sampaio *et al.*,[41] bleeding, jaundice, dyspnoea and bacterial co-infections are potential independent predictors of risk of death in children aged <15 years. Bouts of vomiting and co-infection with HIV,[42] especially in children aged <5 years, are also associated with a substantial risk of death from VL.[43,44] De raújo *et al.*[45] and Driemeier *et al.*[46] reported that identification of clinical and laboratory features associated with the infection facilitates early diagnosis, reducing the risk of death in high-risk patients.

In the present study, children aged 0 - 9 years and people aged >70 were the age groups most affected, similar to observations reported by Guerra *et al.*[47] in the state of Roraima, Brazil, with 52.4% of cases in children aged <10, and Araujo *et al.*,[40] with 63.8% of cases in children aged 0 - 9 years. Donato *et al.*[48] highlighted the vulnerability of children aged <1 year and people aged >50, potentially associated with either immune immaturity or immunocompromise[49-51] and aggravated by comorbidities. The relatively high prevalence of VL in children and the elderly suggests that the transmission cycle is associated with environments in and around the home, where people in these age groups spend most of their time.

The relationship between VL cases and deaths and social vulnerability, as observed in our study, supports what has been widely observed in other studies, as higher concentrations of cases occur in areas characterised by social inequality, poor housing, lack of sanitation and low formal education,[52] and high population density as a result of disorganised growth of the urban periphery of medium-sized and large cities.[53-58]

Conclusion

Our results indicate that a situation of harsh socioeconomic and climatic vulnerability influences the epidemiology of VL. In the light of current evidence on climate change, it is urgently necessary to overcome socioeconomic inequalities, foster research on vaccines and treatments, and implement effective measures to prevent and control the disease.

The Sixth Assessment Report of the Intergovernmental Panel on Climate Change (IPCC)[59] emphasises the predicted increases in the frequency and intensity of extreme climatic events, exacerbating the impacts of socioeconomic and environmental inequalities on VL epidemiology.

Declaration. None.

Acknowledgements. We thank the Directorship for Epidemiological Surveillance of the Secretariat for Health of the state of Bahia (Divep/SESAB), the co-ordination of vector-borne diseases. the regional health nuclei of the mid-east and mid-north, especially the local surveillance and entomology teams, and the secretariats for health of the municipalities of Carfanaum, América Dourada, Jacobina, Itaberaba, Nova Redenção Wagner and Acari.

Author contributions. LBdC: methodology data collection, data analysis, writing; RL: conceptualisation, spatial analysis, validation, writing; MS: methodology, data analysis, writing; CGZ: data collection, data analysis, writing; ESS: methodology, data analysis, writing; EMN: data collection, data analysis, writing; CRF: conceptualisation, data analysis, validation, writing.

Funding. None.

Data availability statement. The data generated and analysed during the present study are available from the corresponding author upon reasonable request.

Conflicts of interest. None.

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Received 27 March 2025. Accepted 4 September 2025.