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Short Communication

Risk mapping of visceral leishmaniasis in Brazil

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Abstract

Introduction: Brazil experiences a large number of visceral leishmaniasis (VL) cases. Our objective was to examine both spatial patterns of dispersion and space-time trends for this disease. **Methods:** We used all autochthonous confirmed cases of VL in Brazil from 2001 to 2017. **Results:** Throughout Brazil, 53,715 human cases of VL were recorded. The Northeast, Southeast, and Midwest regions of Brazil were the most affected areas and presented a higher risk of transmission. Regarding spatiotemporal variation, significant differences were observed each year, with a peak in 2005. **Conclusions:** The dynamics of VL showed a clear non-random pattern of spread in Brazil.

Keywords: Mann-Kendall. Surface. Epidemiology. Spatiotemporal. Cluster.

Visceral leishmaniasis (VL) is an infectious disease found worldwide, typically associated with poor living conditions. Brazil encounters a large number of human VL cases, which are gradually spreading across all states[1]. Despite being historically known as a rural endemic disease, VL has reached epidemic proportions in many large Brazilian cities in the past decades[2]. This currently presents a serious public health challenge. The primary etiological agent of VL in the Americas is the protozoan *Leishmania infantum,* whose main urban reservoir is the domestic dog, which plays a key role in the transmission to humans[3]. In Brazil, this parasite is mainly transmitted through the bites of infected phlebotomine sandflies, in particular, the species *Lutzomyia longipalpis*[4].

Geographic data is used to describe and visualize spatial distributions of disease and reveal spatial patterns of association. Several studies have demonstrated that spatial analysis and geoprocessing techniques are useful tools for describing the epidemiology of infectious diseases like VL[2]. Spatial statistics, such as spatial autocorrelation analysis, cluster analysis, and spatiotemporal analysis, are commonly used to describe spatial patterns of diseases and of disease incidence in a particular area. Recent advances in the use of spatial statistics in Geographic Information Systems (GIS) has led to a greater interest in their use for detecting disease trends in public health surveillance. This is often used to investigate and display spatial patterns of infectious diseases[5]. Spatiotemporal patterns can enhance understanding of the underlying dynamics in the spread of disease. The detection of spatial, temporal, and space-time clustering is useful for identifying higher risk areas and when disease surveillance and control are best targeted.

In this study, spatial statistical analyses and geoprocessing tools were used to investigate the spatiotemporal diffusion patterns of VL cases in Brazil and detect trends. For the analyses, data relating to all confirmed, notifiable cases of VL in Brazil from 2001 to 2017 were obtained from the Brazil's National Notifiable Diseases Information System. This data is distributed by DATASUS, the information technology department of the Brazilian Unified Health System of the Brazilian Ministry of Health[6]. Using this information, coefficients of incidence were calculated, reflecting the intensity of morbidity in a given population. After this procedure, we consulted a digital municipal network run by the Brazilian Institute of Geography and Statistics (IBGE)[7]. This step also identified changes in the Brazilian municipality network. This step was necessary to account for municipalities that had been dismembered and were not included in the cartographic database provided by IBGE. Thus, it was necessary to adjust the VL incidence data table by

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analyzing the municipal dismemberments. This allowed us to manage this possible error, since municipalities created after 2011 were not represented in the cartographic base.

Spatial autocorrelation analyses were performed using the GeoDa 0.9 software. Global Moran's I statistics were used to discern spatial autocorrelation and detect the spatial distribution pattern of LV throughout the country. The Local Indicator of Spatial Association (LISA) was used to identify municipalities that had the most significant spatial associations of LV. Moran's I is similar to the Pearson correlation coefficient with values ranging from -1 to +1, although these limits can be exceeded depending on the connectivity matrix. I is zero when there is no spatial autocorrelation, negative when there is negative autocorrelation, and positive when there is clustering. The statistical significance of this index was calculated from the randomness permutation of the value for other areas, until obtaining a pseudo distribution (p) for which the parameters of significance can be computed. These parameters were calculated from 999 random permutations of Moran's I values from the correlation of VL incidence.

To assess the spatiotemporal trend of the incidence of VL, we used the Mann-Kendall test[8,9]. This test is a robust, sequential, and non-parametric method used to analyze a data series. An advantage of this method is that it is minimally influenced by abrupt changes or an inhomogeneous series. However, this method requires that the data be separate and random; thus, the Mann-Kendall Contextual (CMK) test was performed. This was because geographically, neighboring regions tend to have similar characteristics. The Mann-Kendall test, however, was performed individually on each pixel, not considering the behavior of neighboring pixels. The CMK method is non-parametric and consists of regionalization of the series. It is necessary to consider the magnitude of autocorrelation on signifying testing. To perform this procedure, we applied a mask of the average of pixels with the dimension "3x3" after the variable "S" of the Mann-Kendall test is calculated.

The statistical variable, S, for a series of n data of the Mann-Kendall test is calculated from the sum of the signals (sgn) of the difference, in pairs, of all values of the series (xi) in time (t) with respect to the values in the t + 1 (xj). This is expressed in equations (1) and (2).

$$S = \sum_{i=1}^{n-1} \sum_{j=i+1}^{n} \mathrm{sgn}(x_j - x_i) \qquad (1)$$

$$\mathrm{sgn}(x_j - x_i) = \begin{cases} +1; \text{se } x_j > x_i \\ 0; \text{se } x_j = x_i \\ -1; \text{se } x_j < x_i \end{cases} \qquad (2)$$

The data were compiled and analyzed using the Idrisi Selva 17.02 GIS. The Earth Trends Modeler module was used to analyze trends in the spatially distributed historical series. The final result was a map showing the spatial trend analysis, which allows us to observe changes in disease behavior and determine which regions have experienced significant changes in incidence over time.

During the study period, 53,715 cases of VL were recorded throughout Brazil. Incidence rates varied widely among Brazilian States (**Table 1**). Moran analyzes revealed high-risk clusters, especially in the Northeast, Southeast and Midwest regions (**Figure 1**), and a low-risk cluster in the South region. Regarding spatiotemporal variation, significant differences were observed each year. The results suggest that the high-risk groupings fluctuate considerably, peaking in 2005.

Mann-Kendall analyses showed how the incidence rate changed in each area over time (**Figure 2A** and **Figure 2B**). Both positive and negative trends were observed. These dynamics indicate a clear non-random pattern of spread in specific regions of the country.

When comparing the data in **Table 1** with the maps, it is clear that the incidence rates become diluted when analyzing VL on a large regional scale (i.e. states). VL is a focal disease and local epidemiology may differ widely. For example, the overall incidence of VL in the São Paulo is low, but there is a hotspot in the western region (Araçatuba). Some authors have associated this hotspot with the presence of the Marechal Rondon Highway, which served as an important route for migrants into São Paulo, connecting endemic and non-endemic regions[2]. However, there is no evidence that the entrance of LV was due to migration rather than transportation alone. Besides, the order in which the parasite is transported is not known (e.g., from vectors which then infect hosts or from infected vectors which transmit to local susceptible hosts). We also have identified other important clusters, mainly in the states of Mato Grosso do Sul, Minas Gerais, Tocantins and Roraima. Studies have shown that these VL foci are usually related to areas of expansion, where rural-urban interfaces are occupied by low-income populations and lack adequate infrastructure[10]. Cerbino-Neto et al.[11] studied a Brazilian city and found that the neighborhoods at the rural-urban interface have undergone rapid increases in population density with heavy vegetation cover, and that disordered land occupation have suffered the highest VL incidence rates.

Since 2001, the Northeast States of Maranhão, Piauí and Ceará have been high-risk areas for LV. The urbanization of VL started in the 1980s and first occurred in Northeast cities[10]. Then, VL began to occur endemically and epidemically in large Brazilian cities and has since extended to cities in other regions of the country[11]. Currently VL is endemic in at least 19 Brazilian states[6], and varies in different spatiotemporal scenarios, with alternating periods of many or few municipalities with outbreaks in the Northeast region. Hypotheses to explain this cyclical pattern have considered herd immunity and fluctuations in sandfly population density[10]; however, a definitive explanation is lacking[12].

Several factors may have contributed to this scenario of high VL incidence, including the dispersion of the *Lutzomyia longipalpis* vector in conjunction with an average temperature increase in Brazil. Previous studies have shown a strong association between temperature and the distribution of VL vectors and infected dogs within endemic areas in Brazil[13]. Temperature regulates many biological parameters in sandflies[14].

TABLE 1: Incidence rates for LV per Brazilian states and regions from 2001 to 2017. The highlighted states showed a high incidence. *incidence rate per 100,000 inhabitants.

Brazilian Regions	States	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
North	Acre (AC)	0.00	0.00	0.00	0.16	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Amapá (AP)	0.00	0.00	0.00	0.00	0.00	0.00	0.17	0.00	0.00	0.00	0.00	0.14	0.00	0.00	0.00	0.13	0.00
	Amazonas (AM)	0.00	0.07	0.00	0.00	0.00	0.00	0.03	0.03	0.00	0.00	0.06	0.00	0.03	0.03	0.00	0.00	0.00
	Pará (PA)	**0.84**	**1.22**	**2.24**	**4.42**	**5.28**	**5.53**	**4.98**	**5.34**	**3.94**	**3.73**	**4.54**	**3.41**	**3.26**	**2.91**	**3.42**	**4.21**	**5.99**
	Rondônia (RO)	0.07	0.00	0.00	0.00	0.07	0.00	0.21	0.00	0.07	0.00	0.13	0.00	0.12	0.06	0.00	0.00	0.00
	Roraima (RR)	**1.19**	**1.15**	**2.80**	**4.19**	**2.81**	**0.99**	**0.25**	**0.48**	**1.19**	**3.33**	**2.61**	**2.13**	**4.10**	**2.82**	**3.16**	**7.00**	**6.70**
	Tocantins (TO)	**12.41**	**18.06**	**20.97**	**12.20**	**13.56**	**17.79**	**32.24**	**34.67**	**34.05**	**25.59**	**35.48**	**24.05**	**18.94**	**11.49**	**12.80**	**13.96**	**16.51**
Northeast	**Piauí (PI)**	**0.38**	**4.63**	**12.36**	**12.02**	**10.97**	**7.66**	**8.07**	**8.36**	**5.26**	**4.95**	**6.71**	**6.06**	**6.43**	**8.67**	**7.37**	**5.54**	**8.08**
	Maranhão (MA)	**6.11**	**9.00**	**13.21**	**10.23**	**9.03**	**7.91**	**6.59**	**9.13**	**6.85**	**6.66**	**7.22**	**5.02**	**10.29**	**8.22**	**8.53**	**10.22**	**11.80**
	Alagoas (AL)	1.34	4.14	1.82	1.68	1.63	1.51	0.99	0.83	0.99	1.09	1.15	0.95	0.76	1.18	1.32	0.75	1.37
	Bahia (BA)	0.90	1.35	2.57	3.30	3.72	2.69	1.63	1.34	2.31	2.68	2.70	2.02	1.94	3.00	2.28	1.31	1.71
	Ceará (CE)	**0.20**	**0.25**	**2.50**	**2.97**	**3.77**	**6.68**	**6.28**	**6.20**	**7.71**	**6.06**	**6.79**	**4.31**	**4.86**	**5.94**	**5.18**	**3.55**	**3.94**
	Paraíba(PB)	1.61	0.17	0.68	0.56	0.64	0.94	0.63	0.75	0.40	0.61	0.79	0.55	0.72	1.29	0.98	0.76	0.99
	Pernambuco (PE)	0.10	0.77	0.71	0.86	0.74	0.71	0.73	0.87	0.78	0.65	0.64	0.50	0.52	1.19	1.33	0.86	1.07
	Rio Grande do Norte (RN)	1.99	0.46	1.28	1.66	1.30	1.74	1.96	2.35	2.68	2.24	3.19	2.60	1.99	2.50	1.51	1.30	1.92
	Sergipe (SE)	2.04	1.25	0.75	1.60	1.88	1.85	3.30	1.70	2.03	3.87	2.87	2.42	2.14	2.88	2.94	2.30	3.02
Southeast	Espírito Santo (ES)	0.06	0.03	0.03	0.06	0.12	0.03	0.00	0.06	0.14	0.09	0.20	0.00	0.05	0.03	0.20	0.28	0.62
	Minas Gerais (MG)	**0.46**	**1.65**	**1.80**	**3.01**	**2.28**	**2.09**	**2.08**	**2.45**	**2.45**	**2.54**	**2.19**	**1.68**	**1.52**	**1.73**	**2.16**	**2.53**	**3.75**
	Rio de Janeiro (RJ)	0.00	0.01	0.00	0.01	0.01	0.05	0.01	0.00	0.01	0.00	0.01	0.02	0.04	0.01	0.03	0.02	0.02
	São Paulo (SP)	0.04	0.25	0.40	0.33	0.36	0.60	0.59	0.64	0.44	0.42	0.44	0.50	0.40	0.33	0.29	0.25	0.30
South	Paraná (PR)	0.01	0.01	0.01	0.02	0.01	0.02	0.04	0.00	0.00	0.01	0.00	0.02	0.00	0.01	0.04	0.06	0.04
	Rio Grande do Sul (RS)	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.07	0.02	0.02	0.01	0.02	0.04	0.01	0.02	0.08
	Santa Catarina (SC)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.06
Midwest	Goiás (GO)	0.04	0.27	0.45	0.33	0.34	0.51	0.37	0.45	0.51	0.60	0.41	0.36	0.44	0.63	0.50	0.42	0.62
	Mato Grosso (MT)	0.16	0.31	0.38	0.74	0.84	0.79	1.11	2.08	2.29	1.86	1.73	1.22	1.10	0.51	0.91	0.53	0.68
	Mato Grosso do Sul (MS)	**2.37**	**8.64**	**9.03**	**10.73**	**10.70**	**10.33**	**10.03**	**10.42**	**8.02**	**8.95**	**10.63**	**12.15**	**9.27**	**5.74**	**4.12**	**4.38**	**5.25**
	Distrito Federal (DF)	0.00	0.00	0.00	0.04	0.09	0.21	0.12	0.23	0.23	0.12	0.31	0.26	0.11	0.04	0.10	0.20	0.03

These factors are in agreement with our findings as in southern Brazilian areas, where temperature is colder, there is a low-risk cluster of VL transmission. Notably, low temperatures decrease metabolism and the bite rate of these insects and increase the extrinsic incubation period of the parasite, thereby lowering the overall reproduction rate[14]. Thus, climate change, resulting in an increase in temperature, can accelerate the rate of geographical expansion of VL.

These results indicate that the spatial statistics approach may play an important role in the recognition and analysis of spatial structure of LV epidemiology and control in Brazil. These approaches have also been used to investigate spatial clustering of dengue, zika, and sleep disease, among other lesser known arboviruses[15]. The spatial clustering of VL may be related to social factors (e.g., population density, socioeconomic inequality, access to health services) and environmental characteristics[5]. In

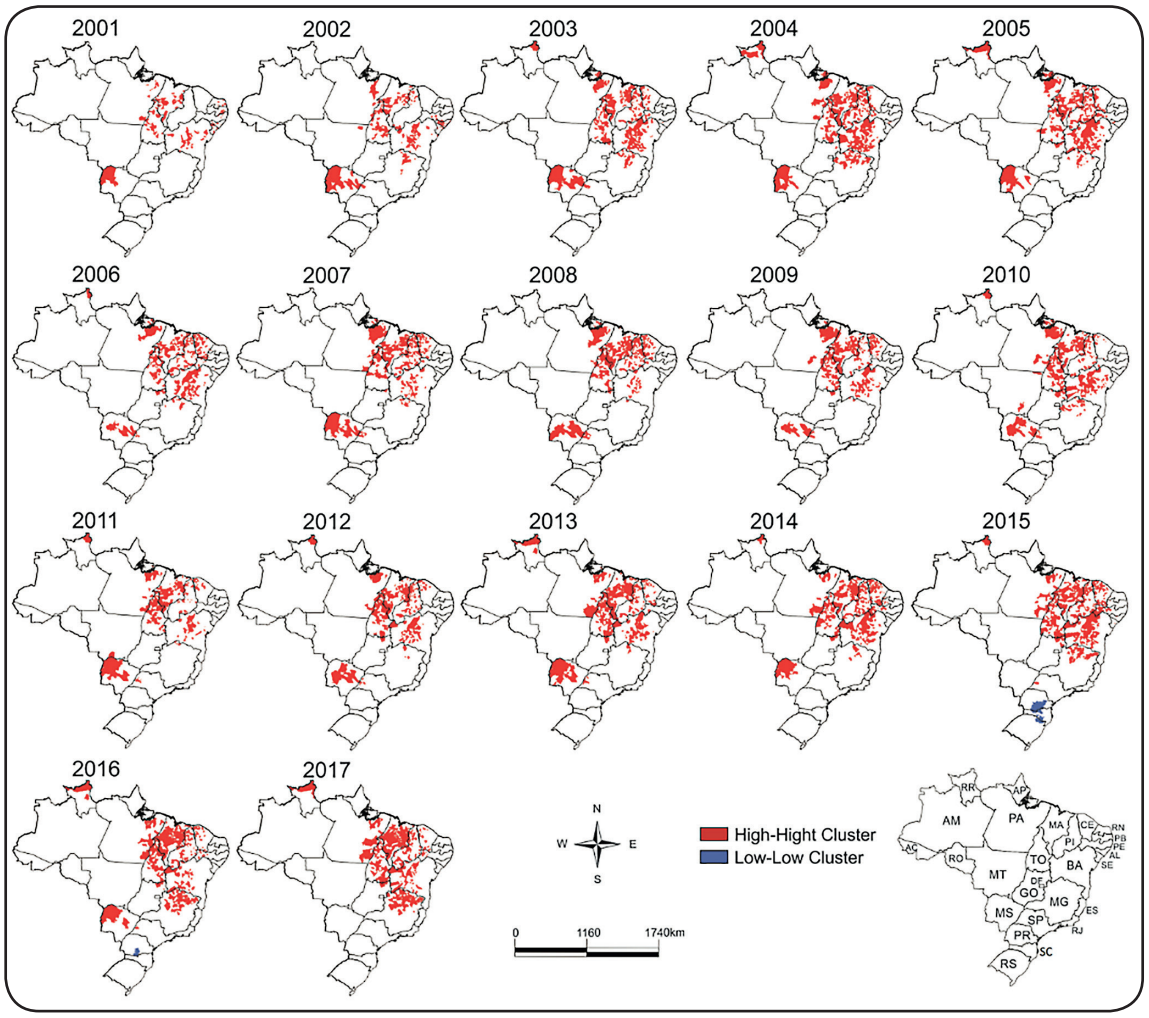

FIGURE 1: Moran I analysis of Visceral Leishmaniasis in Brazil from 2000 to 2017. High-risk clusters are represented in red and low-risk clusters in blue. Acronyms for each State: Acre - AC; Alagoas - AL; Amapá - AP; Amazonas - AM; Bahia - BA; Ceará - CE; Distrito Federal - DF; Espírito Santo - ES; Goiás - GO; Maranhão - MA; Mato Grosso - MT; Mato Grosso do Sul - MS; Minas Gerais - MG; Pará - PA; Paraíba - PB; Paraná - PR; Pernambuco - PE; Piauí - PI; Roraima - RR; Rondônia - RO; Rio de Janeiro - RJ; Rio Grande do Norte - RN; Rio Grande do Sul - RS; Santa Catarina - SC; São Paulo - SP; Sergipe - SE; Tocantins - TO.

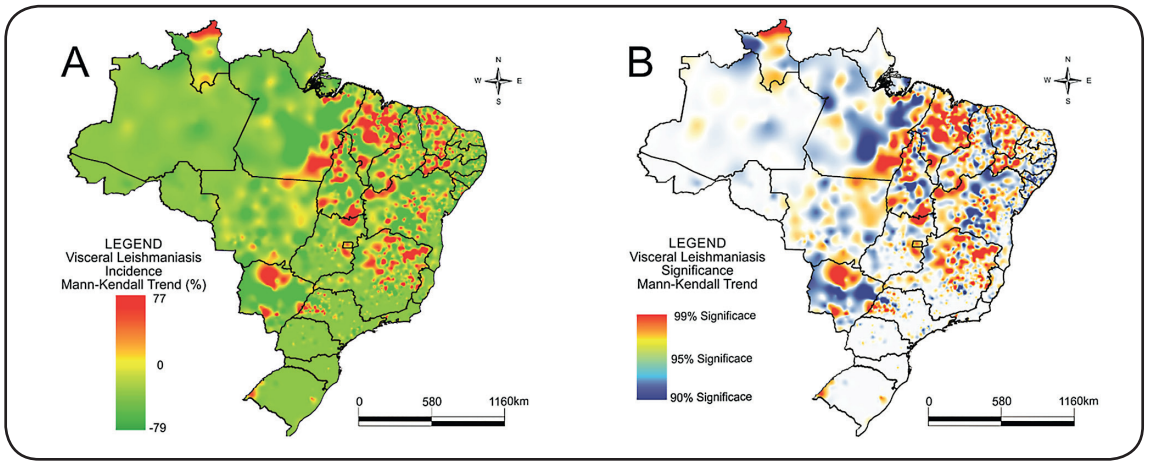

FIGURE 2: Mann-Kendall analysis of VL in Brazil from 2001 to 2017. **(A)** Positive trends (increase in cases) are represented in red whereas negative trends (decrease in cases) are represented in green. **(B)** Significance of the Mann-Kendall test in each area.

Brazil, additional factors that have been positively correlated with VL include houses with mud floors and/or mud walls, the presence of dogs, birds, or horses in the neighborhood[12], and inadequate sanitation infrastructure[13]. These factors likely create favorable conditions for the propagation of sandflies and subsequent VL transmission.

This study is limited by the use of secondary data sources and a lack of consideration of the distribution areas of the vectors, which are crucial for transmission but very difficult to measure. Despite the limitations, the analysis used here was found to be ideal for developing and targeting control measures in specific areas where VL cases have increased over the years. The evolution of VL from a rural to an urban condition requires a new rationale for surveillance and control systems. It will become essential for epidemiological surveillance to be able to perceive the clustering of areas with high rates of VL. Sevá et al.[2] showed that the dispersion of infected humans is affected by the spatial distribution of vectors and infected dogs. Thus, strategies to prevent the spread of the disease in humans and dogs must address all three components of the VL dynamic cycle. Prevention and control measures should not only focus on vector control, but also the avoidance of vector-human contact (e.g., insecticide spraying) and vector-dog contact (e.g., insecticide infused collars and vaccines). Cost-effective analysis suggests that the most efficient strategy should be chosen. Spatiotemporal diffusion patterns and the detection of clusters is useful information to aid epidemiological surveillance activities focused on predicting the spread of VL in specific and critical high-risk areas.

The rapid geographic expansion of VL in Brazil, coupled with fluctuations in the yearly incidence, make it difficult to control the disease and vector. The Northeast, Southeast, and Midwest regions of the country were the most affected areas, presenting a higher risk of transmission. The spatiotemporal analyzes allow clearer visualizations of the epidemiology and present opportunities to improve surveillance. This allows specific actions to be taken in high-risk areas, optimizing resources. The quantification of the degree of VL infection clustering is possible through the use of Geoprocessing tools and spatial statistical analyses, revealing spatiotemporal characteristics of VL in Brazil. Spatiotemporal diffusion patterns and the detection of high-risk clusters may provide useful information to aid epidemiological surveillance in predicting and controlling the spread of VL.

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Conflict of interest

The authors declared that they have no competing interests.

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