Spatial distribution of cutaneous leishmaniasis in the state of Paraná, Brazil

Helen Aline Melo1*, Diogo Francisco Rossoni2*, Ueslei Teodoro1*

1 Postgraduate Program in Health Sciences, Universidade Estadual de Maringá, Maringá, PR, Brazil,
2 Department of Statistics, Universidade Estadual de Maringá, Maringá, Paraná, Brazil

* These authors contributed equally to this work.
* helen_alinemelo@hotmail.com

Abstract

The geographic distribution of cutaneous leishmaniasis (CL) makes it a disease of major clinical importance in Brazil, where it is endemic in the state of Paraná. The objective of this study was to analyze the spatial distribution of CL in Paraná between 2001 and 2015, based on data from the Sistema de Informação de Agravos de Notificação (Information System for Notifiable Diseases) regarding autochthonous CL cases. Spatial autocorrelation was performed using Moran’s Global Index and the Local Indicator of Spatial Association (LISA).

The construction of maps was based on categories of association (high-high, low-low, high-low, and low-high). A total of 4,557 autochthonous cases of CL were registered in the state of Paraná, with an annual average of 303.8 (± 135.2) and a detection coefficient of 2.91. No correlation was found between global indices and their respective significance in 2001 (I = -0.456, p = 0.676), but evidence of spatial autocorrelation was found in other years (p < 0.05). In the construction and analysis of the cluster maps, areas with a high-high positive association were found in the Ivaí-Pirapó, Tibagi, Cinzas-Laranjinha, and Ribeira areas.

The state of Paraná should keep a constant surveillance over CL due to the prominent presence of socioeconomic and environmental factors such as the favorable circumstances for the vectors present in peri-urban and agriculture areas.

Introduction

Leishmaniasis is a globally distributed disease. Approximately 350 million people are currently at risk of contracting at least one of its variants [1]. Brazil had an annual average of 26,965 registered cases of cutaneous leishmaniasis (CL) from 1993 to 2012, with an average detection coefficient of 15.7 cases for every 100,000 inhabitants [2]. Throughout this period, an increasing trend was observed, with higher coefficients in 1994 and 1995, 22.83 and 22.94 cases for every 100,000 inhabitants, respectively [2]. When analyzing the evolution of CL in Brazil, one noticeable factor is its geographical expansion. At the beginning of the 1980s, autochthonous cases were registered in 19 states. By 2003, every state in the country had registered cases of CL [2]. Since the early 1900s, human cases of CL have been registered in northern, western, and southeastern regions of the state of Paraná. In the northern region of Paraná, the disease reached epidemic proportions between the 1930s and 1950s when the area was experiencing...
significant immigration [3]. The incidence dropped drastically during the 1950s as a direct result of public campaigns for the eradication of malaria and the use of insecticides [3]. However, since the 1980s, the incidence of CL has returned to endemic proportions in the state of Paraná [2,4].

In Brazil, *Leishmania (Viannia) braziliensis*, *L. (Leishmania) amazonensis*, and *L. (V.) guyanensis* have been the most frequent causes of CL in humans [2]. In Paraná, CL is directly linked to wild transmission cycles of the parasite in natural foci that persist in forest preserve areas and traditional agricultural production zones [5–7]. Cutaneous leishmaniasis persists in the state despite the replacement of natural vegetation with corn, cotton, and pasture plantings, affecting individuals of all age groups and both genders [5–7]. Anthropogenic actions that affected the environment and increased urbanization and socioeconomic pressure may have contributed to an increase in endemic areas and outbreaks in urban areas [5]. In areas that have been modified by human activity, CL has been found in environmental preservation areas with small patches of forest, such as the cities of Maringá [5,8] and Cianorte [5].

Understanding spatial patterns with the use of human risk geoprocessing techniques is important for the proper guidance of prevention, surveillance, and control measures [9–11], based on the assumption that spatially related data samples within close proximity to each other possess similar behavior. The use of geoprocessing techniques and statistical spatial analysis enables the creation of maps that detail the risk of occurrence of CL. Based on these analyses, associations between cases of CL and different degrees of anthropogenic activity can be determined in areas where there is notification of the disease, with the goal of identifying possible patterns between such areas [10]. The aim of the present study was to use statistical spatial analysis in the state of Paraná to evaluate the dynamics of CL occurrence from 2001 to 2015 in an attempt to support planning control measures that can effectively mitigate the impact of the disease on the population.

**Materials and methods**

**Study area**

The state of Paraná is in southern Brazil (22˚30’58” and 28˚43’00” S; 48˚05’37” and 54˚37’08” W). It has an area of 199,307.945 km² and an estimated population of 11,163,018, with a demographic density of 52.40 inhabitants per square kilometer in 2015 [12–13]. Paraná has 399 municipalities that are distributed into 10 macro regions (i.e., geopolitical subdivisions that encompass several municipalities with economic and social similarities) and 39 micro regions (i.e., a group of neighboring municipalities) [12–13].

Paraná has three distinct climatic groups, according to the Köppen climate classification system: (1) Humid Subtropical Climate–Mesothermal (Cfa), with an average high temperature of 22˚C that can reach 40˚C in the north, west, and Ribeira river valley and an average low temperature of 18˚C (this is the most widespread type of climate in the state, (2) Temperature Oceanic Climate–Mesothermal (Cfb), with an average temperature of 18–22˚C, and (3) Tropical Rainforest Climate–Megathermal (Af), which is restricted to the coastal strip and has an average temperature above 18˚C [14].

**Data collection**

To analyze the spatial distribution of autochthonous cases of CL in the state of Paraná, we used data from the Sistema de Informação de Agravos de Notificação (SINAN; Information System for Notifiable Diseases) from January 2001 to December 2015. To calculate the detection coefficient (autochthonous cases per 100,000 inhabitants), we used the estimated annual population and the territorial area of each municipality, based on the Instituto Brasileiro de Geografia
e Estatística (Brazilian Institute for Geography and Statistics) [12–13]. We gathered information on gender, age, clinical form of CL, and proportion of CL patients that achieved clinical cure. In the present study, we focused on municipalities with detection coefficients >10.0 because the highest risk for CL transmission in these areas.

Statistical analysis
The spatial analysis was conducted in three stages. In the first stage, a test was performed to detect spatial autocorrelation and verify global spatial dependency against the incidence of autochthonous cases of CL [15]. In the second stage, the Local Indicator of Spatial Association (LISA) was employed to analyze local spatial association, which produces a specific value for each municipality and allows the identification of clusters of municipalities with local similarities in terms of the incidence of CL [15]. In the third stage, maps were constructed by category, with two possible classes of direct association (high-high and low-low) and two possible classes of negative association (high-low and low-high) [15].

To detect spatial autocorrelation, Moran’s Global Index (Moran’s I) was used, defined as:

\[ I_i = \frac{(y_i - \bar{y})}{\sqrt{\sum_{j=1}^{n} (y_j - \bar{y})^2 / n}} \]

where \(y_i, y_j\) are the samples collected at points \(i\) and \(j\), respectively, \(\bar{y}\) is the mean value, \(w_{ij}\) is the spatial neighboring component, and \(n\) is the size of the sample.

For LISA, Moran’s Local Index was used, defined as:

\[ I_i(d) = \frac{(x_i - \bar{x})}{s^2} \sum_{j=1}^{n} w_{ij}(d)(x_j - \bar{x}) \]

where \(x_i\) is the sample collected at point \(i\), \(\bar{x}\) is the mean value, \(w_{ij}\) is the spatial neighboring component, and \(s^2\) is the variance.

All of the statistical analyses were performed with software R environment confidence interval of 95% [16] and with package “spdep” [17–18]. This package provides a collection of functions to create spatial weights matrix objects from polygon contiguities, from point patterns by distance and tessellations, for summarizing these objects, and for permitting their use in spatial data analysis, including regional aggregation by minimum spanning tree.

Results
From 2001 to 2015, 4,557 cases of CL were diagnosed in the state of Paraná, with an average annual case rate of 303.8 (±135.2), a detection coefficient of 2.91, and a density of 0.023 cases per km². The year with the highest number of cases was 2003 (609 cases) with a detection coefficient of 6.35 (Fig 1). Males between 20 and 59 years of age were most affected, with a predominance of the cutaneous clinical form and evolution of the majority of the treated cases to clinical cure (77.77%) (Table 1).

The occurrence of CL cases was verified in 268 municipalities (61.17%); of these, eight municipalities (2.99%) had a detection coefficient ≥ 71.0, 35 municipalities (13.06%) had a detection coefficient between 10.0 and 71.0, 95 municipalities (35.45%) had a detection coefficient between 2.5 and 10.0, and 130 municipalities (48.51%) had a detection coefficient <2.5.

Among the 268 municipalities in the state with registered cases of CL, the following were especially notable: 341 in Londrina (7.48%), 331 in Cianorte (7.26%), 279 in Cerro Azul
(6.12%), 232 in Jussara (5.09%), 184 in Terra Boa (4.04%), 177 in Bandeirantes (3.88%), 158 in Adrianópolis (3.47%), 134 in Umurama (2.84%), 111 in Japurá (2.44%), and 86 in Maringá (1.89%). Altogether, these municipalities comprised 44.61% of all cases of CL in the study period. The municipalities with the highest detection coefficients were Jussara (237.47), Adriano pólis (165.03), Cerro Azul (108.29), Ivatuba (108.11), and Japurá (89.35) (Table 2).

Table 1. Demographic and clinical characteristics of cutaneous leishmaniasis cases in the state of Paraná, Brazil, from 2001 to 2015 by the chi-squared test.

| Characteristic            | n   | %    | p-value   |
|---------------------------|-----|------|-----------|
| Gender                    |     |      | <0.001    |
| Male                      | 3,137 | 68.84|           |
| Female                    | 1,420 | 31.16|           |
| Age Group (years)         |     |      | <0.001    |
| >1                        | 33  | 0.72 |           |
| 1–4                       | 76  | 1.67 |           |
| 5–9                       | 184 | 4.04 |           |
| 10–14                     | 228 | 5.00 |           |
| 15–19                     | 281 | 6.17 |           |
| 20–39                     | 1,490 | 32.70|           |
| 40–59                     | 1,435 | 31.49|           |
| 60–64                     | 278 | 6.10 |           |
| 65–69                     | 228 | 5.00 |           |
| 70–79                     | 246 | 5.40 |           |
| ≥80                       | 78  | 1.71 |           |
| Clinical form             |     |      | <0.001    |
| Cutaneous                 | 4,145 | 90.96|           |
| Mucocutaneous             | 410 | 9.00 |           |
| Not informed              | 2   | 0.04 |           |
| Case outcome              |     |      | <0.001    |
| Clinical cure             | 3,544 | 77.77|           |
| Abandonment of treatment  | 107 | 2.35 |           |
| Death related to CL        | 7   | 0.15 |           |
| Death of other cause       | 62  | 1.36 |           |
| Transfer                   | 44  | 0.97 |           |
| Change diagnosis           | 44  | 0.97 |           |
| Not informed              | 749 | 16.44|           |

Fig 1. Distribution of cutaneous leishmaniasis cases in the state of Paraná, Brazil, from 2001 to 2015.

https://doi.org/10.1371/journal.pone.0185401.g001
The results of the global indices and their respective significance revealed no correlation in 2001 (I = -0.456, p = 0.676). In subsequent years, statistical evidence of a spatial correlation (Table 3) allowed the construction of LISA cluster maps (Fig 2). Fig 2 shows a high-high cluster area in municipalities in the Lower Ivaí Basin in each year from 2002 to 2015. High-high clusters were also observed in other basins, such as those of the Pirapó, Tibagi, and Ivaí Rivers. These were smaller in 2010 and 2014 and not evident in 2002. In the Ribeira River basin, a high-high association was found during the study years, except in 2002, 2005, 2010, 2011, 2012, and 2014. In 2010, Curitiba was a high-high cluster area, with a direct association for the occurrence of CL. In 2003, the highest number of municipalities with a direct association was found in the Ivaí River Basin and Pirapó River Basin. In the municipalities of the Lower Iguaçu River Basin, a positive association was found only in 2005 (Fig 2).

Discussion

The spatial distribution of CL in all Brazilian states shows the importance of this disease in the country [2]. The spatial distribution of CL demonstrates the significance of this disease throughout Brazil, with an increase in the number of cases in the 1980s and 1990s [2]. In Paraná, the disease has been registered in areas of ancient colonization, contrary to the expectation that the increase in human activities in the environment would result in the elimination of natural foci of CL [2]. The majority of infected individuals in Paraná during the study period were male and located in municipalities where the main economic activity is agriculture [6,7]. The most

Table 2. Number and detection coefficient of cases of cutaneous leishmaniasis in municipalities with a detection coefficient >10.0 in the state of Paraná, Brazil, from 2001 to 2015.

| Municipality         | No. of cases | Detection coefficient* | Municipality         | No. of cases | Detection coefficient* |
|----------------------|--------------|------------------------|----------------------|--------------|------------------------|
| Abatíá               | 22           | 19.13                  | Japurá               | 111          | 89.35                  |
| Adrianópolis         | 158          | 165.03                 | Jussara              | 232          | 237.47                 |
| Araruna              | 23           | 11.44                  | Lobato               | 10           | 15.29                  |
| Ariranha do Ivaí     | 9            | 23.58                  | Munhoz de Melo       | 6            | 11.21                  |
| Bandeirantes         | 177          | 35.85                  | Nova Tebas           | 11           | 10.58                  |
| Cambira              | 13           | 12.17                  | Pinhalão             | 25           | 26.49                  |
| Cândido de Abreu     | 54           | 20.88                  | Porto Rico           | 5            | 13.68                  |
| Carlópolis           | 82           | 39.69                  | Prudentópolis        | 81           | 11.21                  |
| Cerro Azul           | 279          | 108.29                 | Rio Bom              | 13           | 26.22                  |
| Cianorte             | 331          | 32.89                  | Rio Bonito do Iguaçu | 75           | 32.67                  |
| Colorado             | 50           | 15.00                  | Sabaudia             | 11           | 12.57                  |
| Conselheiro Mairinck | 9            | 16.66                  | Santa Amélia         | 9            | 14.84                  |
| Corumbataí do Sul    | 12           | 19.53                  | São Carlos do Ivaí   | 12           | 12.65                  |
| Cruzeiro do Sul      | 8            | 11.56                  | São Jerônimo da Serra| 67           | 39.26                  |
| Doutor Camargo       | 74           | 85.12                  | São Jorge do Ivaí    | 72           | 80.54                  |
| Doutor Ulysses       | 37           | 40.48                  | São Jorge do Patrocínio| 39          | 45.26                  |
| Enéas Marques        | 12           | 13.24                  | São Tomé             | 49           | 61.74                  |
| Engenheiro Beltrão   | 71           | 33.81                  | Terra Boa            | 184          | 79.61                  |
| Grande Rios          | 14           | 13.01                  | Tomazina             | 47           | 35.25                  |
| Icaraíma             | 38           | 28.01                  | Tuneiras do Oeste    | 66           | 52.08                  |
| Itambaracá           | 32           | 32.68                  | Uniflor              | 7            | 19.47                  |
| Itatuba              | 48           | 108.11                 | **Total**            | 2,685        | 38.69                  |

*Cases per 100,000 inhabitants.

https://doi.org/10.1371/journal.pone.0185401.t002
affected age group was 20–59 years, probably related to the agriculture work or recreational activities like fishing near riparian forests of rivers and streams where the enzootic cycle of *Leishmania* remains [5]. This was also observed in the municipality of Teodoro Sampaio in the state of São Paulo, Brazil [19], and in the country of Iran [20], which have features that are distinctive from Paraná, signifying that men may engage in behaviors that can lead to a higher risk of CL. Previous studies reported that the proportion of infected individuals is similar between agricultural and domestic workers [6,7]. The majority of urban residents acquired CL in Paraná during the study period in the rural area suggesting that pendulum migration is an important risk factor for CL in mesoregions north central, western center and northwest. In the state of Paraná [6]. The considerable number of women and children with CL that have been identified in studies in Paraná, including the present study, corroborate this assessment [6,7]. The number of female cases (31.15%), although less than males, is notable. Such cases appear to be more related to activities that are connected with agricultural work and the construction of residences and domestic animal shelters that are in close proximity to modified native forest where the environment is fresher and more pleasant [7].

Although cases of CL were registered in 268 municipalities, the municipalities with the highest detection coefficients were concentrated in the Ivaí-Pirapó CL hub, which is part of the Paraná-Paranapanema CL production circuit [7]. Examples of this are Jussara and Cianorte, which have large areas of moderately or highly altered residual forest and also secondary forests [5–7]. In the Alto Ribeira hub within the Ribeira circuit [7], the municipalities of Adria­polis and Cerro Azul had elevated CL detection coefficients.

Londrina is part of the Ivaí-Pirapó hub. Although the municipality of Londrina had a detection coefficient <10 because of its larger population, it was responsible for the highest number of cases of CL between 2001 and 2015. A cluster of municipalities with high detection coefficients was identified in the Cinzas-Laranjinha area (Parana-Paranapanema circuit), one example of which is the municipality of Bandeirantes. Cases of CL were also registered in the municipalities of Cândido de Abreu and Prudentópolis in the Tibagi area (Paraná-Paranapanema circuit). A notable occurrence of cases was observed in the municipalities of the Lower Iguazu area (Paraná-Paranapanema circuit), such as Rio Bonito do Iguacu and Enéas Marques.

| Year | Detection coefficient | Global Moran Index | p   |
|------|-----------------------|--------------------|-----|
| 2001 | 0.60                  | -0.456             | 0.676 |
| 2002 | 1.57                  | 3.028              | <0.01 |
| 2003 | 6.35                  | 7.344              | <0.01 |
| 2004 | 3.49                  | 9.276              | <0.01 |
| 2005 | 2.64                  | 2.689              | <0.01 |
| 2006 | 2.67                  | 4.856              | <0.01 |
| 2007 | 3.17                  | 11.120             | <0.01 |
| 2008 | 4.03                  | 11.145             | <0.01 |
| 2009 | 2.97                  | 11.084             | <0.01 |
| 2010 | 1.86                  | 9.227              | <0.01 |
| 2011 | 2.39                  | 8.305              | <0.01 |
| 2012 | 2.90                  | 9.272              | <0.01 |
| 2013 | 1.87                  | 6.473              | <0.01 |
| 2014 | 3.02                  | 11.946             | <0.01 |
| 2015 | 4.04                  | 8.376              | <0.01 |

https://doi.org/10.1371/journal.pone.0185401.t003
Areas of high anthropogenic impact that is related to agriculture, especially corn, soybeans, sugar cane, and pasture, focus cases of CL in Paraná state [5].

The LISA map analysis revealed that only the municipalities of Jussara and Cianorte in the Ivaí-Pirapó area maintained a high-high association from 2002 to 2015. These municipalities play a major role in the production of CL in this area [7]. Previous studies have investigated *Leishmania* infection in dogs and wild animals in these areas [21–25]. The high number of phlebotomine sandflies in areas of altered native forest in the Ivaí-Pirapó area [3,26–28] may partially explain the persistence of the high-high cluster throughout the duration of the study period. Interestingly, the sandfly species *Nyssomyia neivai* (Pinto), *Nyssomyia whitmani* (Antunes & Coutinho), and *Migonemyia migonei* (França) were identified as *Leishmania* vectors [3,29,30], which are widely distributed in the state of Paraná [31]. In 2003, the high-high association covered all CL production areas in Paraná, with the exception of the Lower Iguaçu area.

The spatial analysis of the SINAN data from 2001 to 2015 allowed visualization of the local and global distribution, cluster formation, and spatial instability and identification of outliers.
of CL throughout the state of Parana [32]. Beyond the use of georeferencing instruments, it is important to further investigate the migration of human populations and local conditions that influence the risk for CL in the referenced areas [33].

The public health surveillance should take into account the differences between the transmission patterns of each locality and the identified high-risk cluster in developing actions to mitigate the properties of the zoonosis in the state of Parana. Moreover, the disease affects specific areas, such as Alto Ribeira, Ivaí-Pirapó, Tibagi, and Cinzas-Laranjinha. This suggests that health authorities need to provide information and develop campaigns regarding the importance of early diagnosis and treatment of CL, with the goal of reducing the emergence of new cases and preventing mucocutaneous cases of the disease. Moreover, the control of sandflies is essential to block the spread of the disease.

Conclusion

The state of Paraná should keep a constant surveillance over cutaneous leishmaniasis due to the prominent presence of socioeconomic and environmental factors such as the favorable circumstances for the vectors present in peri-urban and agriculture areas.

Ivaí-Pirapó, Tibagi, Cinzas-Laranjinha, and Ribeira areas form the four-major hot spot CL areas in the state of Paraná.

Acknowledgments

The authors would like to thank the State Health Department of Paraná who provided much of the core data on which this research study is based.

Author Contributions

Conceptualization: Helen Aline Melo, Ueslei Teodoro.

Data curation: Helen Aline Melo, Diogo Francisco Rossoni.

Formal analysis: Helen Aline Melo, Diogo Francisco Rossoni, Ueslei Teodoro.

Investigation: Helen Aline Melo, Ueslei Teodoro.

Methodology: Helen Aline Melo, Diogo Francisco Rossoni, Ueslei Teodoro.

Project administration: Helen Aline Melo.

Supervision: Ueslei Teodoro.

Visualization: Helen Aline Melo.

Writing – original draft: Helen Aline Melo, Ueslei Teodoro.

Writing – review & editing: Helen Aline Melo, Ueslei Teodoro.

References

1. Desjeux P (2004) Leishmaniasis: current situation and new perspectives. Comp Immunol Microbiol Infect Dis 27(5), 305–318. https://doi.org/10.1016/j.cimid.2004.03.004 PMID: 15225981

2. Ministério da Saúde (2016) Guia de vigilância em saúde, (1st. ed. at.). Brasilia: Ministério da Saúde.

3. Luz E, Membrive N, Castro EA, Oreure J, Pratlong F, Dedet JA, et al. (2000) Lutzomyia whitmani (Diptera: Psychodidae) as vector of Leishmania (V.) braziliensis in Parana state, southern Brazil. Ann Trop Med Parasitol 94(6), 623–631. PMID: 11064764

4. Sistema de Informação de Agravos de Notificação (2015) Brasilia: Ministério da Saúde.
5. Lima AP, Minelli L, Teodoro U, Comunelhio E (2002) Distribuição da leishmaniose tegumentar por imagens de sensoreamento remoto orbital, no Estado do Paraná, Brasil. An Bras Dermatol 77(7), 681–692.

6. Monteiro WM, Neitzke HC, Lonardoni MVC, Silveira TGV, Ferreira MEMC, Teodoro U (2008) Distribuição geográfica e características epidemiológicas da leishmaniose tegumentar americana em áreas de colonização antiga do Estado do Paraná, Sul do Brasil. Cad Saúde Pública 24(6), 1291–1303. PMID: 18545755

7. Monteiro WM, Neitzke HC, Silveira TGV, Lonardoni MVC, Teodoro U, Ferreira MEMC (2009) Poles of American tegumentary leishmaniasis production in northern Paraná State, Brazil. Cad Saúde Pública 25(5), 1083–1092. PMID: 1948493

8. Teodoro U, Kühl JB, Rodrigues M, Santos ES, Santos DR, Maróstica LM (1998) Flebotomineos cole-tados em matas remanescentes e abrigos de animais silvestres de zoológico no perímetro urbano de Maringá, Sul do Brasil. Estudo Preliminar. Rev Soc Bras Med Trop 31(6), 517–522. PMID: 9659694

9. Eisen RJ, Eisen L (2008) Spatial modeling of human risk of exposure to vector-borne pathogens based on epidemiological versus arthropod vector data. J Med Entomol 45(2), 181–192. PMID: 18402133

10. Magalhães GB (2012) O uso do geoprocessamento e da estatística nos estudos ecológicos em epide-miologia: o caso da dengue em 2008 na região metropolitana de Fortaleza. Hygeia, 8(15), 63–77.

11. Medrondo RA, Valencia LIO, Fortes BPM, Braga RCC, Ribeiro SV (2003) Análise espacial da soroprevalência da hepatite A em crianças de uma região carente de Duque de Caxias, RJ, Brasil. Rev bras epidemiol 6(4), 328–334.

12. Instituto Brasileiro de Geografia e Estatística (2010) Censo Demográfico 2010. Available at: http://www.ibge.gov.br/estadocenso/perfil.php?sigla=pr [accessed April 2, 2016].

13. Instituto Brasileiro de Geografia e Estatística (2016) Estimativas Populacionais. Available at: http://www.ibge.gov.br/estadocenso/perfil.php?sigla=pr [accessed March 1, 2016].

14. Instituto Agronômico do Paraná (2002) Cartas Climáticas do Paraná. Available at: http://www.iapar.br/modules/contenido/conteudo.php?contenido=677 [accessed March 1, 2016]

15. Anselin L (2013) Spatial econometrics: methods and models. Dordrecht: Springer.

16. R Development Core Team (2014) R: a language and environment for statistical computing, Vienna: R Foundation for Statistical Computing.

17. Bivand R, Piras G (2015). Comparing Implementations of Estimation Methods for Spatial Econometrics. Journal of Statistical Software, 63(18), 1–36

18. Bivand R., Hauke J, Kossowski T. (2013). Computing the Jacobian in Gaussian spatial autoregressive models: An illustrated comparison of available methods. Geographical Analysis, 45(2), 150–179.

19. da Silva Fonseca E, D'Andreazza LAZ, Taniguchi HH, Hiramoto RM, Tolezano JE, Guimarães RB (2014) Spatial epidemiology of American cutaneous leishmaniasis in a municipality of west São Paulo State, Brazil. J Vector Borne Dis 51(4), 271–275. PMID: 25540957

20. Mollaiolo A, Almohammadi A, Shirzadi MR, Malek MR (2015) Geographic information system-based analysis of the spatial and spatio-temporal distribution of zoonotic cutaneous leishmaniasis in Golestan province, north-east of Iran. Zoonoses Public Health 62(1), 18–28. https://doi.org/10.1111/zph.12109 PMID: 24628913

21. Zanzarini PD, Santos DR, Santos AR, Oliveira O, Poiani LP, Lonardoni MVC, et al. (2005) Leishmaniose tegumentar americana canina em municípios do norte do Estado do Paraná, Brasil. Cad Saúde Pública 21(6), 1957–1961. https://doi.org/10.1590/S0102-311X2005000600047

22. Lonardoni MVC, Silveira TGV, Alves WA, Maia-Elkhoury ANS, Membrive UA, Membrive NA, et al. (2006) Leishmaniose tegumentar americana humana e canina no Município de Mariluz, Estado do Paraná, Brasil. Cad Saúde Pública, 22(12), 2713–2716. PMID: 17096049

23. Massunari GK, Voltarelli VEM, Santos DR, Santos AR, Poiani LP, de Oliveira O, et al. (2009) A serological and molecular investigation of American cutaneous leishmaniasis in dogs, three years after an outbreak in the Northwest of Paraná State, Brazil. Cad Saúde Pública, 25(1), 97–104. PMID: 19180291

24. Voltarelli EM, Araaes SMAA, Perles TF, Lonardoni MVC, Teodoro U, Silveira TGV (2009) Serological survey for Leishmania sp. infection in wild animals from the municipality of Maringá, Paraná State, Brazil. J Venon Anim Toxins Incl Trop Dis 15(4), 732–744.

25. Membrive NA, Rodrigues G, Gualda KP, Bernal MVZ, Oliveira DM, Lonardoni MVC, et al. (2012) Environmental and animal characteristics as factors associated with American cutaneous leishmaniasis in rural locations with presence of dogs, Brazil. PLoS One 7(11), e47050.

26. Teodoro U, Silveira TGV, Santos DR, Santos ES, Santos AR, Oliveira O, et al. (2001) Frequência da fauna de flebotomíneos no domicílio e em abrigos de animais domésticos no peridomicílio, nos municípios de Cianorte e Doutor Camargo–Estado do Paraná—Brasil. Rev Pat Trop 30(2), 209–223.
27. Reinhold-Castro KR, de Lima Scodro RB, de Cassia Dias-Sversutti A, Neitzke HC, Rossi RM, Kühl JB, et al. (2008) Evaluation of sandfly control measures. Rev Soc Bras Med Trop 41(3), 269–276. PMID: 18719807

28. Reinhold-Castro KR, Fenelon VC, Rossi RM, Brito JEC, Freitas JS, Teodoro U (2013) Impact of control measures and dynamics of sand flies in southern Brazil. J Vector Ecol 38(1), 63–68. https://doi.org/10.1111/j.1948-7134.2013.12009.x PMID: 23701608

29. Oliveira DM, Reinhold-Castro KR, Bernal MVZ, Legriffon CMO, Lonardoni MVC, Teodoro U, et al. (2011) Natural infection of *Nyssomyia neivai* by *Leishmania (Viannia)* spp. in the state of Paraná, southern Brazil, detected by multiplex polymerase chain reaction. J Vector Borne Dis 11(2), 137–143.

30. Neitzke-Abreu H, Reinhold-Castro KR, Venazzi MS, Scodro RBL, de Cassia Dias A, Silveira TGV, et al. (2014) Detection of *Leishmania (Viannia)* in *Nyssomyia neivai* and *Nyssomyia whitmani* by multiplex polymerase chain reaction, in southern Brazil. Rev Inst Med Trop São Paulo 56(5), 391–395. https://doi.org/10.1590/S0036-46652014000500004 PMID: 25229218

31. Silva AMD, Camargo NJD, Santos DRD, Massafera R, Ferreira AC, Postai C, et al. (2008) Diversidade, distribuição e abundância de flebotomíneos (Diptera: Psychodidae) no Paraná. Neotrop Entomol 37 (2):209–225. PMID: 18506303

32. Câmara G, Monteiro AM, Fucks SD, Carvalho MS, Druck S, Câmara G, et al. (2002) Análise espacial e geoprocessamento. In: Druck S, Carvalho MS, Câmara G, Monteiro AMV (Eds.). Análise espacial de dados geográficos. Brasília: EMBRAPA, p.01–26.

33. Lovelock J (2010) Gaia: alerta final. Rio de Janeiro: Intrínseca.