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Análise espaço-temporal e fatores de risco ambientais associados à Leishmaniose Tegumentar

Spatio-temporal analysis and environment risk factors associated with Cutaneous Leishmaniasis

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Dedicatória

A todos os cientistas, profissionais e cidadãos engajados que trabalham
pela preservação da natureza e
no combate às doenças infecciosas.

Epígrafe

"No começo pensei que estivesse lutando para salvar seringueiras, depois pensei que estava lutando para salvar a Floresta Amazônica. Agora, percebo que estou lutando pela humanidade".

Chico Mendes

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Índice

Resumo

A leishmaniose cutânea (LC) é causada pelo parasita *Leishmania* e é uma das doenças tropicais transmitidas por vetores mais negligenciadas do mundo. O Brasil é o país com maior incidência da doença na América Latina e um dos 10 países do mundo com maior número de casos. No Brasil, a leishmaniose cutânea é uma doença essencialmente zoonótica, e tem como vetor espécies de mosquito palha (Plebotominae) e como reservatório, diversas espécies de mamíferos. A distribuição espaço-temporal da doença no país ainda é pouco conhecida e depende de fatores ambientais que favorecem o desenvolvimento e a coexistência das espécies de parasitas, reservatórios e vetores. Desta forma, o objetivo principal deste estudo foi analisar a dinâmica espaço-temporal dos casos de Leishmaniose Cutânea no Brasil, buscando a relação com fatores ambientais. Foram utilizados dados de casos confirmados de leishmaniose cutânea em nível de município entre os anos de 2001 e 2017. No primeiro artigo, foram aplicados métodos de análise de tendência de Mann-Kendall, varredura espaço-temporal de Kuldorff e análise de hotspots emergentes para identificar os aglomerados e a dinâmica espaço-temporal da doença. Observou-se que a incidência da LC tem diminuido ao longo do tempo, mas que em alguns municípios o número de casos tem aumentado. O principal aglomerado da doença foi encontrado na região Amazônica, e a análise de hotspot mostrou que a dinâmica espaço-temporal da doença nessa região é bastante heterogênea. Também foram encontrados 20 aglomerados secundários da doença, sendo a maioria deles localizados na região sudeste e um no estado da Bahia. No segundo artigo, foi aplicada uma modelagem bayesiana espaço-temporal para avaliar como as mudanças no uso do solo afetam a incidência da LC dentro da região Amazônica. Os resultados mostraram que o aumento do risco de leishmaniose cutânea na região está associado ao desmatamento, e por uma interação positiva entre a cobertura florestal e a pecuária. As paisagens com desmatamento contínuo para a criação de gado extensivo são normalmente encontradas em municípios da fronteira amazônica, onde também encontramos diversos hotspots da doença. Espera-se que os resultados desse estudo possam guiar estudos ecológicos, epidemiológicos e ações de vigilância e controle nos principais focos da doença no país. Além disso, os resultados desse trabalho também ajudam a esclarecer melhor como mudanças ambientais afetam a transmissão da leishmaniose cutânea, os quais podem ser utilizados para guiar ações de planejamento territorial, especialmente na Floresta Amazônica.

Abstract

Cutaneous Leishmaniasis (CL) is a vector-borne disease caused by a parasite of the genus *Leishmania*. It is considered one of the most neglected tropical diseases. Brazil has the highest incidence of CL in America and is one of the ten countries in the world with the highest number of cases. In Brazil, cutaneous leishmaniasis is mainly a zoonotic disease. Vectors are species of Phlebotomies sandflies and reservoirs are several species of mammals. The spatiotemporal distribution of disease cases in Brazil is not well understood and is dependent on environmental factors that are suitable for the development and coexistence of species of parasites, vectors and reservoirs. The main objective of this study is to analyze the spatiotemporal dynamics of Cutaneous Leishmaniasis cases in Brazil and their environmental relationship. Data from CL cases at the municipality level from 2001 to 2017 were used. The first paper employed the Mann-Kendall trend test, Kuldorff scan method, and emerging hotspot analysis to identify the spatiotemporal dynamics and clusters of the disease. Although the incidence of CL has been decreasing over time, there are still a few municipalities with an increased trend. The main cluster of the disease was found in the Amazon region, and the hotspot analysis showed that the spatiotemporal dynamics of the disease in this region is highly heterogeneous. The analysis also identified 20 secondary clusters, primarily located in the southeast region and the state of Bahia. In the second chapter, a spatio-temporal Bayesian model was applied to evaluate how land-use changes have affected CL incidence in the Amazon region. The results showed that the increased risk of Cutaneous Leishmaniasis in the region was associated with deforestation and a positive interaction between forest cover and livestock. Landscapes with ongoing deforestation for extensive cattle ranching are typically found in municipalities within the Amazon Frontier, where we also have several hotspots of the disease.These results can inform future ecological and epidemiological studies, as well as surveillance and control actions in the main focus of the disease in Brazil. Additionally, our findings provide valuable insights into how environmental changes affect the transmission risk of cutaneous leishmaniasis, which can be used to guide land-use planning policies, particularly in the Amazon forest.

Introdução Geral

Cutaneous Leishmaniasis is a vector-borne disease caused by a parasite of the genus *Leishmania* (Order Kinetoplatida), which includes 22 pathogenic species for humans. It is endemic in 89 countries, mainly in tropical, arid, and mediterranean regions, with an estimated number of cases ranging from 0.7 to 1.2 million per year (Alvar et al., 2012; PAHO, 2024).The disease has three main clinical presentations: (1) localized cutaneous leishmaniasis, characterized by one or more ulcerated skin lesions; (2) diffuse cutaneous leishmaniasis, characterized by nodular lesions disseminated throughout the body; and (3) mucocutaneous leishmaniasis, characterized by necrosis of the nasopharyngeal mucosa (Reithinger et al., 2017). Although this disease does not have high mortality rates, the treatment is lengthy and costly (Desjeux, 2004). Patients may also develop sequels, such as permanent scars or facial disfigurement, which can lead to social stigmatization and depressive disorders (Bailey et al., 2019).

Brazil is one of the countries with the highest number of cases of CL in the world, and alongside Afghanistan, Algeria, Colombia, Iran, Syria, Ethiopia, Northern Sudan, Costa Rica, and Peru, account together for 70–75% of the global incidence of the disease (Alvar et al., 2012). A previous study conducted in the Americas showed that CL cases in Brazil have been decreasing over time. However, there are still regions with high incidence rates of the disease, mainly located in the northern states of Brazil, such as Amazonas, Pará, and Mato Grosso, as well as in the northeastern of Brazil, in the Bahia state (Maia-Elkhoury, et al. 2016).

Identifying territorial units of major epidemiological significance is essential for providing guidelines for public health policies, such as prevention, surveillance, and control measures (Brasil, 2017). However, prior to this thesis (chapter 1), the spatial distribution and temporal changes of the disease at a small scale level were not fully understood, except for some local studies conducted in specific states, such as Acre (Melchior et al., 2017), Amazonas (Teles et al., 2019), Paraná (Melo et a.l 2017) and Minas Gerais (Cardoso et al., 2019).

In Brazil, CL is a zoonotic disease transmitted to humans by an infected female phlebotomine sandfly (Psychodidae, Phlebotominae) (Ready et al., 2013). Several mammalian species have been found infected with the parasite. However, for a species to be considered a reservoir it must be capable of sustaining the infection in its organism and have the potential to transmit the parasite to the vector (Ashford, 1996; Haydon et al. 2002; Roque & Jansen 2014ab). The role of different species of neotropical mammals in the transmission of *Leishmania* is not yet fully known, because epidemiological investigations that include ecological and experimental studies in the region are still scarce. However, in Brazil, the potential reservoirs of the disease are wild mammalian species, such as sloths, anteaters (Order Pilosa), armadillos (Order Cingulata), monkeys (Order Primates), and also synanthropic species, such as Didelphis spp. (Order Didelphimorphia), and some rodents, such as *Rattus rattus,* and species of the genus *Proechimys* and *Thrichomys* (Order Rodentia) (Roque & Jansen, 2014a,b).

The spatial distribution of cutaneous leishmaniasis depends on favorable environmental conditions for the coexistence and interaction of parasites, vectors, and reservoirs (Desjeux 2001). In Brazil, most of the species of vectors and reservoirs of CL are usually dependent on forested

habitats. However, the modification of habitats by anthropogenic land use changes has led some of these species to occupy disturbed environments, such as fragmented forests and rural and urban landscapes (Ramos et al., 2014; Filho et al., 2015; Guimarães et al. 2022). For instance, out of the 22 sandfly species responsible for transmitting *Leishmania* to humans and animals in Brazil, 17 (77%) have already been found in anthropogenic environments (Aguiar & Vieira, 2008). In these environments, sandflies may have access to new resources such as artificial shelters and the blood of domestic animals (Guimarães et al., 2022; Costa et al., 2021). In addition, populations of some mammal species, such as opossums and rodents, can benefit from the expansion of crops and the accumulation of domestic waste (Guerra et al., 2015; Mendoza et al., 2020).

The adaptation of vectors and reservoirs to anthropogenic habitats may be altering the dynamics of CL transmission in Brazil (Brasil, 2017). Previously, the disease was mainly limited to the sylvatic zoonotic cycle. Humans typically get infected when they entered protected forests for occupational and recreational activities, such as fishing, hunting, military training, or ecotourism. However, disease transmission dynamics have been changing and expanding geographically over time, particularly in rural and peri-urban regions (Guerra et al., 1998, 2019; Membrive et al., 2012; Rangel et al., 2014; Brazil, 2017). Understanding how different environmental changes have affected the risk of disease transmission is essential to guide policies for developing healthier landscapes (Loh et al., 2015).

Spatiotemporal analyses are powerful tools for exploring and understanding the geographic distribution and impact of environmental changes on the incidence of various infectious diseases (Waller & Gotway, 2004). For example, disease cluster detection methods have been extensively used to identify areas with unusually high disease incidence, temporal trends, and priority areas for surveillance and control measures (Waller & Gotway, 2004; Melchior et al., 2017; Cardoso et al., 2019; Freitas et al., 2019). Statistical methods where the disease dynamics are modeled in function of environmental and socio-economic variables while controlling for spatial-temporal random effects have also been essential to understanding the impact of environment changes on the risk of several diseases (Bangliardo et al., 2013; Hagan et al., 2016; Moraga et al., 2019; Forbes et al., 2021).

Many spatial analyses of diseases utilize health outcome data collected and summarized by governmental agencies, often national health departments, and then released for public use (Waller & Gotway, 2004). Brazil has an important database called SINAN (Notifiable Diseases Information System), which is mainly filled by the notification and investigation data of several diseases cases that are included in the national list of compulsory notifiable diseases in Brazil (Brasil, 2007), including cutaneous leishmaniasis. SINAN is a primary tool for disease surveillance and control in Brazil. It contains essential demographic information for estimating disease risk, including age, sex, municipality of residence, probable municipality of infection, and date of symptom onset. The data is available for download in aggregated format on the website (http://portalsinan.saude.gov.br/sinan-net) or can be requested in individualized and anonymized format through the Ministry of Health. This data source has been used in several research studies worldwide, providing valuable insight into the epidemiology and ecological aspects

of various infectious diseases, such as dengue, chikungunya and Zika (Freitas et al., 2019) malaria (Lorenz et al., 2015), and leishmaniasis (Valero et al. 2021)

This study investigates the spatio-temporal dynamics of cutaneous leishmaniasis cases in Brazil and how environmental changes have affected these dynamics. To achieve this, we applied different spatio-temporal statistical approaches and used data from cutaneous leishmaniasis notifications from municipalities in Brazil over 18 years. The thesis is divided into two chapters in the format of articles. The first chapter applies cluster analyses to identify priority areas for surveillance and to describe the spatial and temporal distribution pattern of cutaneous leishmaniasis in Brazil. The second chapter uses a structured spatiotemporal Bayesian model to assess how different land cover classes and land-use changes affected the incidence of CL in the main cluster of the disease, while adjusting for well-known risk factors such as population, climate, and socioeconomic disadvantage.

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Chapter 1

Spatial-temporal pattern of cutaneous leishmaniasis in Brazil

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Abstract

Background: Cutaneous leishmaniasis (CL) is a vector-borne disease classified by the World Health Organization as one of the most neglected tropical diseases. Brazil has the highest incidence of CL in America and is one of the ten countries in the world with the highest number of cases. Understanding the spatiotemporal dynamics of CL is essential to provide guidelines for public health policies in Brazil. . In the present study we used a spatial and temporal statistical approach to evaluate the dynamics of CL in Brazil..

Methods: We used data of cutaneous leishmaniasis cases provided by the Ministry of Health of Brazil from 2001 to 2017. We calculated incidence rates and used the Mann-Kendall trend test to evaluate the temporal trend of CL in each municipality.. In addition, we used Kuldorff scan method to identify spatiotemporal clusters and emerging hotspots test to evaluate hotspot areas and their temporal trends.

Results: We found a general decrease in the number of CL cases in Brazil (from 15.3 to 8.4 cases per 100,000 habitants) , although 3.2% of municipalities still have an increasing tendency of CL incidence and 72.5% showed no tendency at all. The scan analysis identified a primary cluster in northern and central regions and 21 secondary clusters located mainly in south and southeast regions. The emerging hotspots analysis detected a high spatial and temporal variability of hotspots inside the main cluster area, diminishing hotspots in eastern Amazon and permanent, emerging, and new hotspots in the states of Amapá and parts of Pará, Roraima, Acre and Mato Grosso. The central coast the state of Bahia is one of the most critical areas due to the detection of a cluster of the highest rank in a secondary cluster, and because it is the only area identified as an intensifying hotspot.

Conclusions: Using a combination of statistical methods we were able to detect areas of higher incidence of CL and understand how it changed over time. We suggest that these areas, especially those identified as permanent, new, emerging and intensifying hotspots, should be targeted for future research, surveillance, and implementation of vector control measures.

Keywords: Cutaneous leishmaniasis, Spatiotemporal cluster, Emerging hotspot, Temporal trend, Brazil

Background

Cutaneous leishmaniasis (CL) is a vector-borne disease infecting from 0.7 to 1.2 million people per year [1] and it is classified as one of the most neglected tropical diseases [2]. CL is caused by an obligate parasite of the genus *Leishmania* and is transmitted to humans by the bite of infected female sandflies [3]. It has three primary clinical forms: (1) localized cutaneous, which is characterized by one or multiple ulcerated skin lesions; (2) diffuse, in which the patients present nodular lesions disseminated all over the body; and (3) mucocutaneous, which is characterized by necrosis of the nasopharyngeal mucous tissue [4]. CL is treatable and has a low mortality rate, but it can generate social stigma and depressive disorder due to permanent scars and facial disfigurement [5].

CL occurs in at least 83 countries, mainly in the tropical, arid, and Mediterranean regions [6]. Recently, the World Health Organization classified this disease as a public health problem in the Americas and estimated that between 187 200 and 307 800 cases occur every year [7,8]. Most of CL cases in the Americas occur in Brazil, with an annual mean of newly infected people of 28 166 from 2001 to 2005 and 21 632 from 2006 to 2011 [7]. Brazil is also one of the countries with the highest

number of cases of CL in the world, and alongside Afghanistan, Algeria, Colombia, Iran, Syria, Ethiopia, Northern Sudan, Costa Rica, and Peru account together for 70–75% of the global incidence of the disease [1].

A number of epidemiologic studies report that spatio-temporal distribution of CL is an important factor to be considered when planning mitigation measures to control this disease in seriously affected countries. For example, it has been shown that despite the higher incidence of CL in Costa Rica, Colombia and Syria the majority of the cases are aggregated in spatio-temporal clusters restricted to a few regions scattered throughout these countries [9,10, 11]. The only long-term study assessing spatial and temporal distribution of CL cases in Brazil analyzed temporal variation for the entire country and spatial distribution of cases aggregated by Brazilian states [7]. A few studies in Brazil assessed spatial and temporal variability of CL incidence in a higher resolution (i.e. for each municipality), and all of them were restricted to individual Brazilian states, namely: Paraná [12], Minas Gerais [13], Acre [14] and Amazonas [15].

According to the American Cutaneous Leishmaniasis Surveillance Program in Brazil [16], identifying territorial units of major epidemiological significance is essential to provide guidelines for public health policies as prevention, surveillance, and control measures. In order to contribute to this effort in this study we analyzed a dataset ranging from 2001 to 2017 to investigate for the first time the spatial and temporal dynamics of CL at the municipality level in Brazil. Using exploratory maps, built with Geographic Information System (GIS), and spatial and temporal statistical methods, we determined in which areas in Brazil CL incidence is higher and whether it increased, stabilized or decreased over time. In addition to an up-to-date discussion on

spatiotemporal aspects of CL, we also suggest which areas in Brazil might be important for future research, monitoring and control measures.

Methods

Study area

Brazil has 5570 municipalities distributed in 26 states which are grouped in five macroregions: north, northeast, midwest, southeast and south. These macroregions were established in the 1970s by IBGE (*Instituto Brasileiro de Geografia e Estatística*) to facilitate the survey and dissemination of statistical data in Brazil to add a perspective to the understanding of national territory organization and to help the federal government, as well as states and municipalities, in the implementation and management of public policies and investments. In addition, Brazil has also an area called Legal Amazon, which was created by the government in the 1950s to prompt the development of socio-economic policies in this region. Currently, Brazilian Legal Amazon (BLA) area covers all states from North region (Amazonas, Acre, Rondônia, Roraima, Amapá, Tocantins and Pará), the state of Mato Grosso (Midwest) and part of Maranhão (Northeast). It covers 720 municipalities, with an approximate area of 5 217 423 km², corresponding to 61% of the Brazilian territory [17].

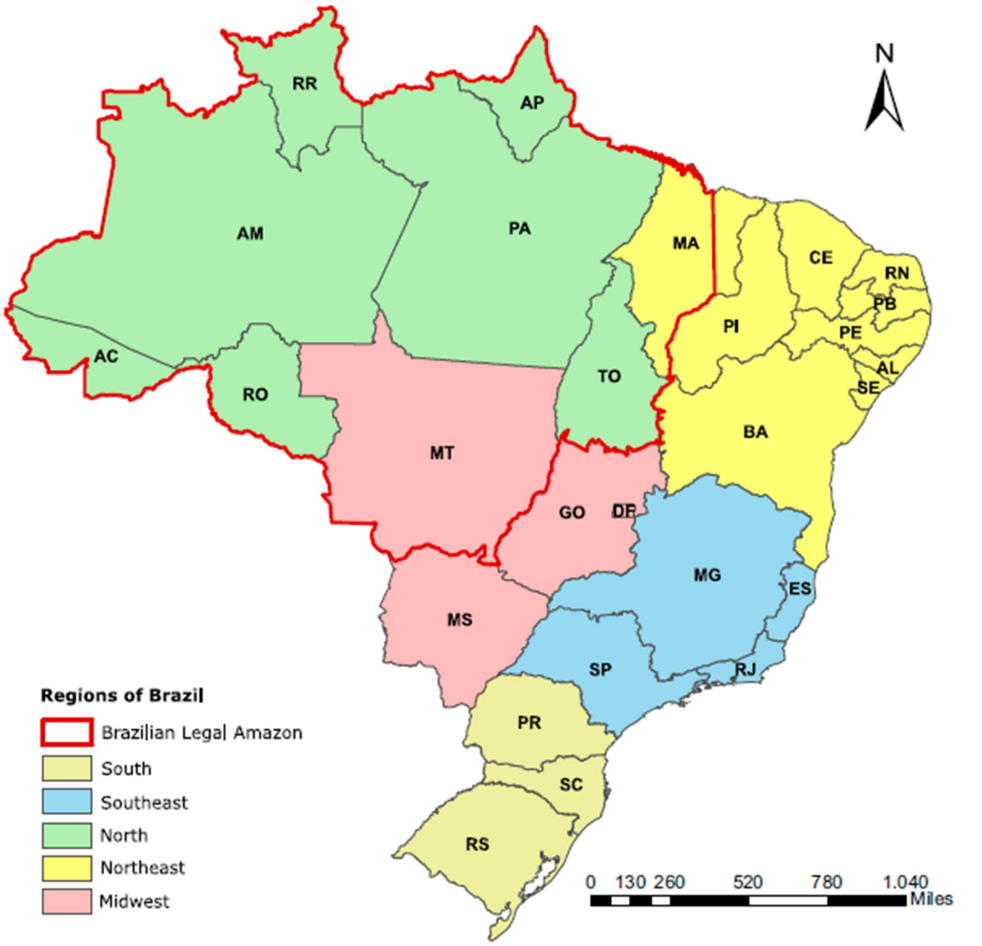

Fig 1: Map of Brazil and its territorial divisions.

Data collection

A data set on individual-level, anonymized, cases of CL comprising a period ranging from 2001 to 2017 was provided by the Information System of Notifiable Disease (SINAN – *Sistema de Informação e Notificação de Agravos*) of the Ministry of Health of Brazil. Confirmed CL cases were grouped by year and municipality, and CL annual incidence was calculated with the estimated annual population data extracted from Brazilian Institute for Geography and Statistics (IBGE – *Instituto Brasileiro de Geografia e Estatística*).

Created in 1990, SINAN is the official nationwide platform for epidemiological surveillance of all compulsory notifiable diseases, which

are defined by the National Compulsory Notification List of diseases. It is responsible for notification, investigation and, in the case of communicable diseases, follow-up and the outcome of patient's treatment. Notification is usually made by health professionals in the most peripheral administrative level (i.e. health care units) through standardized individual notification record by disease or condition type. All compulsory notifiable disease should be notified by the public, private and philanthropic health services. If the notifying health facility does not have computerized system, the physical records should be sent periodically to the municipal, regional or state office to be further digitalized and submitted to the national database [18].

Cutaneous leishmaniasis has been included by a specific federal statement on the national list of compulsory notifiable diseases since 2001 [19]. Only confirmed CL cases are notified, and they are diagnosed through clinical-epidemiological or laboratory criteria, mainly through direct parasitological examination, Montenegro Intradermal Test (MIT) or histopathological examination [20]. The dataset of confirmed CL cases is publicly available and can be accessed on the SINAN webpage (http://www2.datasus.gov.br/DATASUS/index.php?area=0203).

Temporal trend analysis

First, we explored temporal trends of incidence for all country and for all municipalities affected by the disease. We used the LOESS curve fitting (locally weighted scatterplot smoothing) [21] to assess the tendency line of annual CL incidence in Brazil. To adjust the curve we used a combination of parameters to minimized an excessive weight in the smoothing and avoid over-adjustment. We found a better curve adjustment with an alpha value of 0.6. Since Brazil has thousands of

municipalities, it is not feasible to visualize the time trend curves for each municipality individually. Therefore, we used the Mann Kendall Trend Test [22,23] to evaluate if there was a significant temporal trend on the time series of each municipality, we categorized the municipalities according to their time trend and we plotted the obtained results on a map. The Mann-Kendall trend test is a non-parametric test for identifying trends in time series data and it works comparing the relative magnitudes of sample data rather than the data values themselves [24]. We used the statistical software R 3.6.3 (Lucent Technologies, Jasmine Mountain, USA)to perform the LOESS curve fitting and ARCGIS 10.4 (ESRI, Red-lands, CA, USA) to perform Mann Kendall Trend test.

Spatial-temporal analysis

Scan statistic method

The spatial-temporal scanning method proposed by Kulldorffs [25] was used to find spatiotemporal clusters of CL by detecting an excess of cases in a given region and period of time. This method makes the assumption that the disease cases are generated by a non-homogenous Poisson process and, under the null hypothesis, the expected cases for each municipality are proportional to their population size. This method was implemented through a two-dimensional cylindrical window: an ellipse base, representing the potential cluster's geographic areas and the height representing the period of study (number of years). The radius of the cylinder window varied in both spatial size and temporal length until it reached a previously defined maximum area of 15% of the population size and 90% of the study period.

Within each cylinder, the actual and expected number of disease cases, along with a Poisson generalized likelihood ratio (GLR) is

calculated. The *P*-value for detected cluster was assessed using Monte Carlos simulation, where the maximum likelihood from the actual data was compared to the maximum likelihood from each 999 random simulated data sets generated under the null hypothesis. The cylinder with the maximum likelihood and with more than its expected number of cases was designated the most likely cluster. The other–cylinders for which the likelihood value was statistically significant were defined as secondary clusters, and were ranked according to their likelihood ratio test statistics [25,26]. Scan statistics analysis were performed using SatScan software v9.6 (Boston, MA, USA) and the results were visualized using ArcGIS 10.4 (ESRI, Redlands, CA, USA).

Emerging hotspot analysis

Before running the temporal hotspot analysis we transformed our data into a 3D cube format with bins fixed in space (x, y) and time (z). The space value (x, y) was assigned as the coordinates of each municipality and the time value (z) was the incidence of CL in each municipality per year of study. Thereafter, to evaluate spatiotemporal hotspots of Cutaneous Leishmaniasis incidence in each municipality we applied the Emerging Hot Spot Analysis tool (ArcGIS 10.4,) using a combination of Getis ord Gi* statistic and Mann Kendall Trend test.

The Getis ord Gi* statistic [27] was used to identify areas of aggregation of higher incidence of CL in Brazil. This method works by summing the incidence value of one municipality and its neighbors comparing proportionally to the sum of incidence of all municipalities. When the local sum is much different than the expected, and that difference is too large to be the result of random chance, a statistically significant *Z* score is the result. The Getis-Ord Gi* statistic generates *Z*

scores (standard deviations) and *P* values (statistical probabilities) for each bin. A *Z* score above 1.96 means that there is a statically significant hot spot at a significant level of P <0.05 and the larger a bin's *Z*-score the more intense the hotspot is. Due to the cube structure of the data, neighboring bins exist both in time and in space. The emerging hotspot package used an adapted formula of kernel density search radius to define the neighborhood size in space [28] and temporal neighbors were defined using one prior time-step interval.

The Mann-Kendall statistic [22,23] was used to evaluate a statistically significant temporal trend across the time series of *Z*-scores resulting from Getis-Ord Gi statistic. In this test, the bin value of the first time period is compared to the bin value for the second. If the first is smaller than the second, the result is a +1, if it is larger the result is -1, and if the two values are tied, the result is zero, indicating no trend in the values over time. Each pair of time steps was compared over the 17-year series, generating the Mann-Kendall statistics with associated trend *Z*-score and P-value for each bin. Based on the variance for the values in the bin time series, the number of ties, and the number of time periods, the observed sum is compared to the expected sum (zero) to determine if the difference is statistically significant or not. A small *P*-value indicates the trend is statistically significant, and the sign associated with the *Z*-score determines if the series has a monotonic increase (positive *Z*-score) or decrease trend (negative *Z*-score). The hotspot and trend results from the Getis Ord Gi* and Mann-Kendall statistic were used to categorize each municipality [29] (see Table 1 for definition of the hotspots categories).

Table 1 – Category name and definition of statistically significant hotspots representing different temporal states (ESRI ArcGIS Pro [30]).

Hot spot category name	Definition
Intensifying	A location that has been a statistically significant hot spot for more than 90% of temporal series, including the final time step (2017). In addition, the intensity of clustering of high counts in each time step is increasing.
Persistent	A location that has been a statistically significant hot spot for more than 90% of the temporal series, with no discernible trend indicating an increase or decrease in the intensity of clustering over time.
Historical	The most recent time period is not hot, but at least ninety percent of the time-step intervals have been statistically significant hot spots.
Consecutive	A location with a single uninterrupted run of statistically significant hot spot bins in the final time-step intervals. The location has never been a statistically significant hot spot prior to the final hot spot run and less than ninety percent of all bins are statistically significant hot spots.
Sporadic	A location that is an on-again then off-again hot spot. Less than 90% of time series have been statistically significant hot spot.
New	A location that is a statistically significant hot spot only on the last time steps of the time series.
Diminishing	A location that has been a statistically significant hot spot for more than 90% of the time series. In addition, the intensity of clustering of high incidence in each time step is decreasing, or the most recent year is not hot.

Results

CL cases distribution and temporal trends

During 2001–2017 period, a total of 379 571 cases of CL were registered in 73.8% of municipalities in Brazil with an average incidence of 11.86 cases per 100 000 inhabitants. The number of municipalities

with confirmed CL cases was highest in 2002 (n = 2156) and lowest in 2016 (n = 1635). The CL incidence reported per year in Brazil showed that there is a tendency for reduction in number of cases. This curve also followed the fluctuation of the number of municipalities with CL-positive cases, with maximum value in the year 2003 and the minimum value in 2016 (Figure 2).

Despite the wide distribution of cases approximately 80% of them occurred in only 10% of municipalities which were located mainly in Brazilian Legal Amazon (BLA), especially in the states namely Maranhão (MA), Mato Grosso (MT), Pará (PA) and Rondônia (RO), and outside of BLA in the state of Bahia (BA) (Figure 3A). The temporal trend analysis for each municipality showed that 24.2% of them had a decrease in CL incidence, 3.2% had an increase, whereas 72.5% showed no tendency at all (Figure 3B).

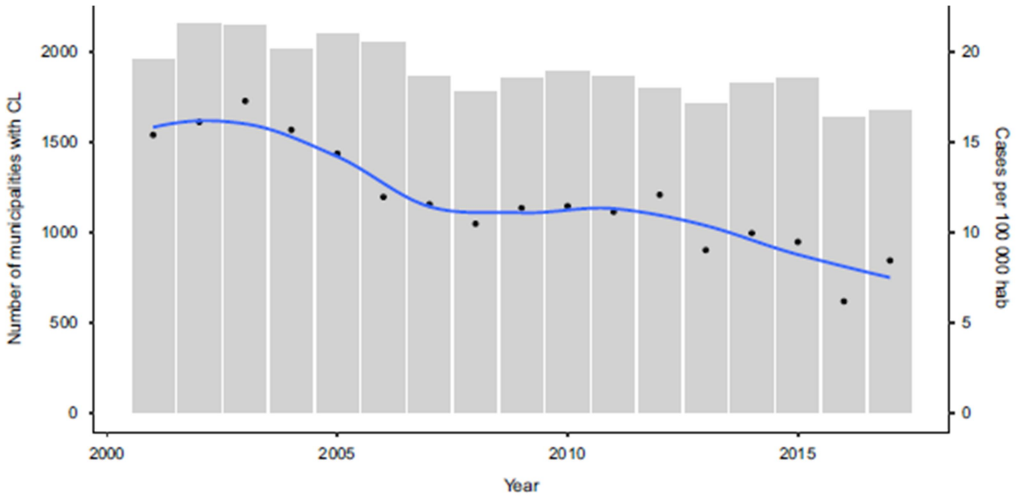

Fig. 2 Number of municipalities with cutaneous leishmaniasis records and cutaneous leishmaniasis incidence rates per 100 000 habitants reported in Brazil during 2001–2017 period. The plotted points correspond to incidence rates and the lines consist in short term trends (fitted with locally estimated scatterplot smoothing LOESS).

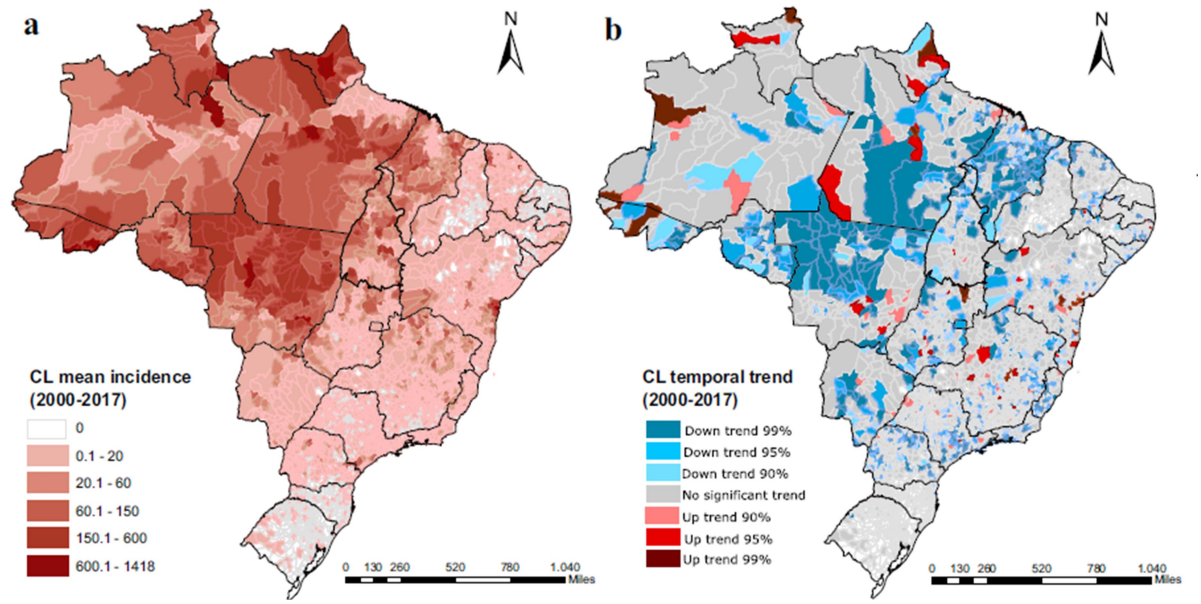

Fig. 3 Spatial distribution of cutaneous leishmaniasis incidence mean rate per 100 000 inhabitants (A) and temporal trend of CL incidence stratified at the municipality level (B) during 2001–2017 period

Spatial-temporal clusters and hotspots

The most likely cluster detected has a relative risk of 12 ($P <$ 0.001) for 2001–2015 period and covers the whole BLA (Figure 4). In the secondary clusters the first cluster in the rank was located in the central coast of Bahia (BA) and has a relative risk of 39.2 ($P < 0.001$) for 2003–2017 period. The scan statistics also identified 20 more secondary clusters located in 90 municipalities scattered throughout mainly in the states of Minas Gerais (MG), São Paulo (SP), and Paraná (PR), with a relative risk ranging from 1.7 (from 2001 to 2004 and $P < 0.05$) to 22.7 (2001 to 2009 and $P < 0.001$) (Table 2).

The emerging hotspot analysis identified significant areas of agglomeration of high incidence of CL in space and time (Figure 5). These hotspots were located inside the most likely cluster area, excluding

the central part of the Amazonas State (AM), east of Pará (PA), and most of Maranhão (MA) (Figure 5). Another hotspot detected in the analysis was located in the central coast of Bahia, overlapping the area covered by the first in the rank of secondary clusters, as showed in Figure 4.

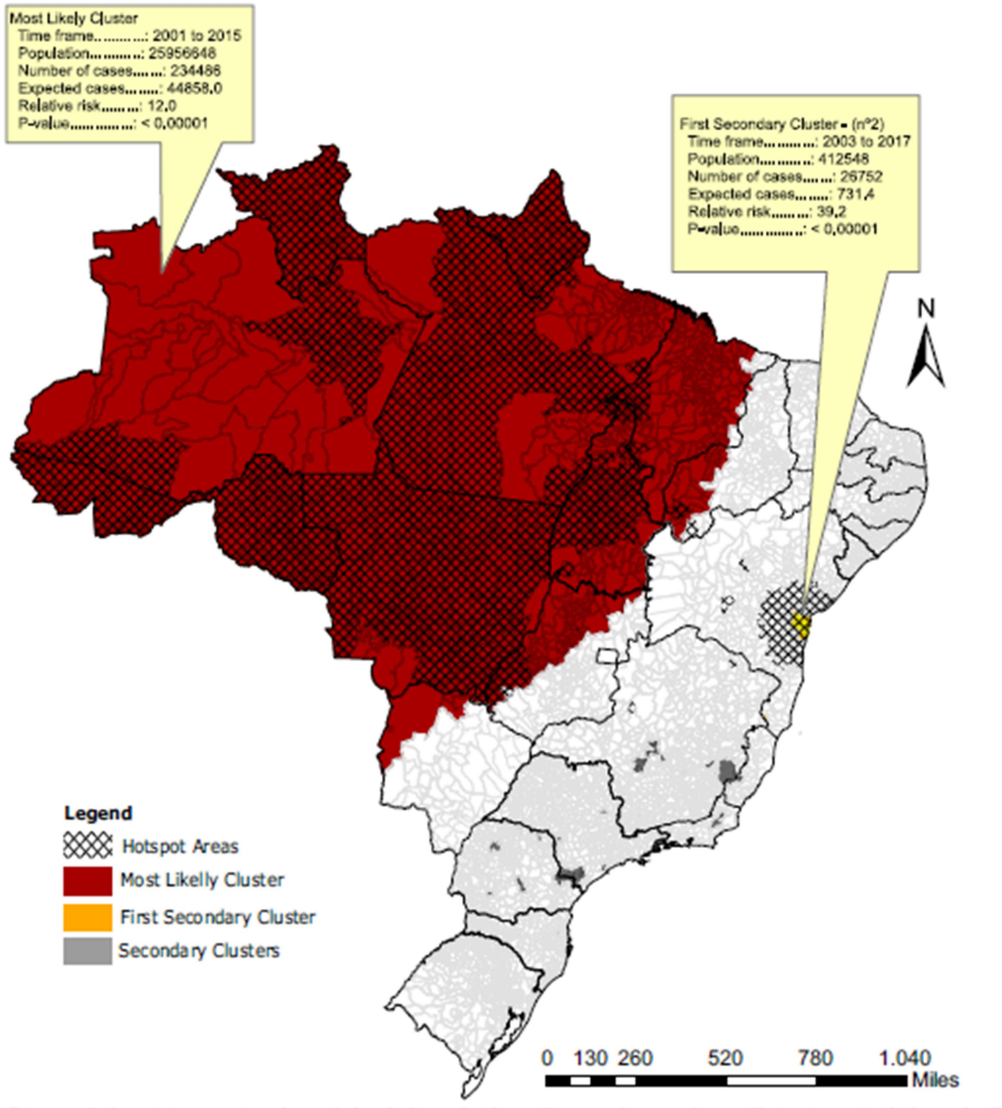

Fig. 4 Cutaneous leishmaniasis space–time clusters (colored) obtained with spatial–temporal scan analysis, and hotspot areas (grid) obtained with emerging hotspot analysis (period of time ranging 2001–2017)

Table 2- Cutaneous leishmaniasis secondary clusters detected in Brazil between 2001–2017 using the space-time scan statistic.

Nº	Center	State	Nº Cities	Observed Cases	Expected Cases	Relative Risk	Year	P-Value
2	Nilo Peçanha	BA	20	26752	731.42	39.27	2003-2017	<0.001
3	Jussara	PR	9	1553	229.79	6.78	2001-2015	<0.001
4	Itariri	SP	2	592	26.08	22.73	2001-2009	<0.001
5	Conceição de Ipanema	MG	33	2828	933.26	3.05	2003-2017	<0.001
6	Itaoca	SP	10	916	142.87	6.42	2002-2016	<0.001
7	Cerro Azul	PR	1	324	30.35	10.68	2002-2016	<0.001
8	Paraty	RJ	2	418	74.98	5.58	2001-2006	<0.001
9	Rio Bonito do Iguaçu	PR	1	76	4.35	17.48	2004-2005	<0.001
10	Prudentópolis	PR	1	97	10.81	8.98	2002-2003	<0.001
11	Bandeirantes	PR	4	252	77.89	3.24	2001-2013	<0.001
12	Sarutaiá	SP	3	75	10.74	6.99	2002-2003	<0.001
13	Florestópolis	PR	2	57	6.38	8.94	2001-2002	<0.001
14	Blumenau	SC	1	107	34.79	3.08	2006	<0.001
15	Trajano de Moraes	RJ	4	72	15.65	4.60	2005-2006	<0.001
16	Rio Acima	MG	1	58	12.98	4.47	2006-2017	<0.001
17	Luz	MG	9	87	25.26	3.45	2014-2015	<0.001
18	Conceição do Pará	MG	3	53	14.65	3.62	2002-2005	<0.001
19	Pirassununga	SP	1	96	39.69	2.42	2001-2005	<0.001
20	Careaçu	MG	1	17	1.37	12.39	2001-2002	<0.001
21	Mangaratiba	RJ	2	130	73.10	1.78	2001-2004	<0.05

BA: Bahia; CE: MG: Minas Gerais; PR: Paraná; RJ: Rio de Janeiro; SC: Santa Catarina; SP: São Paulo.

A general decreasing trend in CL incidence was also found in the hotspot temporal analysis, whereas most of the hotspots identified were classified as historical or reducing hotspot. Most of the reducing hotspots were located in western BLA, although the temporal hotspot analysis also showed an intensifying hotspot placed in the coast of Bahia, in addition to persistent and recent hotspots located mainly in Amapá (AP), most of

Roraima (RO), east of Acre (AC), west of Pará and south of Mato Grosso do Sul (MS) (Figure 5).

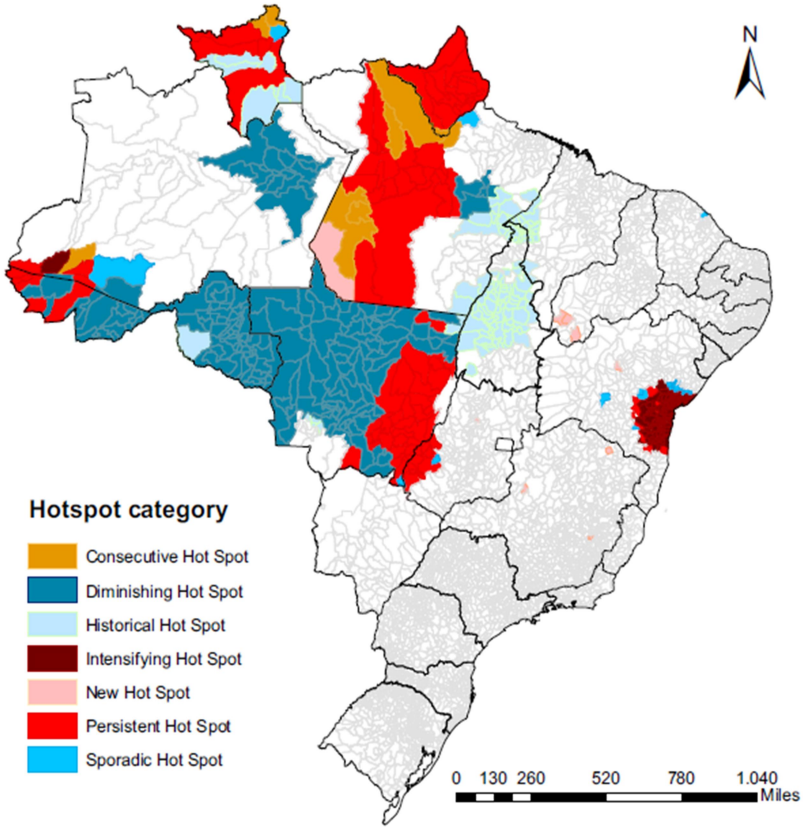

Fig. 5 Cutaneous leishmaniasis hotspots using gets Ord Gi analysis and categorized according to their temporal trend using Mann Kendall Trend test (period of time ranging 2001–2017)

Discussion

To our knowledge, the present study describes for the first time spatial and temporal patterns of cutaneous leishmaniasis cases at municipality level for entirely Brazil. Despite Brazil being one of the countries with the highest incidence of CL in the world, most of the cases recorded from 2001 to 2017 were concentrated to specific regions. In addition, although we have found a general reduction of cases in Brazil,

our results also showed that some municipalities had a stationary or an increasing tendency of CL incidence.

The spatiotemporal statistical scan showed that all municipalities in Brazilian Legal Amazon are included in the CL primary cluster. This is in agreement with a previous study that found that the states of Amapá, Roraima, Amazonas, Pará and Acre had the highest incidence of CL between 2001 and 2011 [7]. However, differently from this study, [7] evaluated the distribution of CL cases aggregated by Brazilian states and could not detect high incidence of CL in relatively small geographic areas in south, southeast and northeast of Brazil. Previous studies that accessed CL distribution in municipalities of Paraná [12] and Minas Gerais [13] also detected similar cluster areas as detected in this study, even using different methodologies. The only exception was the Jequitinhonha region and northern Minas Gerais, which were not included in any cluster in the present study, probably due to differences in the data sets composition. Therefore, the detection of similar regions with high incidence of CL in previous studies corroborates our results and highlights the relevance of the detected cluster areas to the surveillance and control of CL Leishmaniasis in Brazil.

Based on the emerging hotspot analysis, we found a high spatial and temporal heterogeneity of hotspots inside the primary cluster. This method did not find a large agglomeration of CL cases in the central part of Amazonas and eastern Pará, but it did find a predominance of reducing hotspot in western BLA and permanent and emerging hotspots in northern and eastern BLA. These results corroborate previous studies that showed a high spatial and temporal variability of CL cases in some states in northern Brazil. In accordance to our study, Teles et al. [15] found a smaller incidence of the disease in the interior of Amazonas and a high number of cases neighboring the State capital (Manaus), where we found

a reducing hotspot. Additionally, similarly to this study Teles et al. [15] also found a higher number of CL cases in municipalities located in the southern border of Amazonas with Acre. Analyzing a period of time ranging from 2007 to 2013, Melchior et al. [14] found only one high-risk cluster of CL in southern part of Acre, but similarly to our study they also found that this region had a diminishing temporal trend of CL incidence.

Although a high incidence of CL has been historically found in the central coast of Bahia [31], this is the first time that this region has been identified as a cluster and an intensifying hotspot. It worth emphasizing that due to the risk of an increased trend of CL incidence and the risk of expansion of CL to neighboring regions, as previously reported for Rio de Janeiro state [32], the central cost of Bahia should be targeted as a high priority region for future surveillance and control measures of cutaneous leishmaniasis.

The clusters and hotspots found in this study may suggest that CL tend to be spatially and temporally distributed in Brazil and that environmental factors might play a role in modulating this distribution [33]. Previous studies have shown that the incidence of American cutaneous leishmaniasis is positively associated with the amount of forest cover, high diversity of possible reservoir mammal species and favorable climatic conditions for the development of sand-flies vectors, such as warm and hot weather and low annual seasonality of temperature and precipitation [34,35,36]. These environmental variables are typical of the Legal Amazon region in which we detected the most likely cluster of CL. Other studies have also shown positive association of CL cases and human environmental changes such as deforestation [37], settlements near forested areas [32, 38] and development of agriculture crops [39,40]. These activities are predominant at the border of the Legal Amazon in a location called “Arc of Deforestation” [41], where we found most of the

CL hotspots. Future studies should focus on understanding how these anthropogenic variables are affecting spatiotemporal dynamics of the disease in this area.

The presence of permanent and intensifying areas included in hotspots suggests that the strategies adopted for the control of CL in these regions might have not been efficient in reducing the number of cases. In Brazil, prevention strategies have mainly focused on diagnosis and treatment of the human disease, reducing morbidity, deformities and deaths, rather than on the control of vectors [42]. According to World Health Organization [43] an effective strategy for reducing human leishmaniasis is to control sand fly vectors and implementing health education in local communities, giving them important knowledge about individual protection measures and environmental modifications that can reduce the presence and frequency of vectors and hosts in the peridomicile and intradomicile areas [44]. Such an approach requires the proper knowledge of local epidemiology, which vector and host species are involved, their habitats, vector flight range, and seasonality [43]. However, the transmission patterns of CL are highly variable in Brazil, and little is known about the ecology of vector and mammalian reservoir species involved in the transmission cycle in many regions of the country [45,46]. Therefore, the CL hotspot areas identified in this study should be considered as priorities in public health campaigns and should be used to guide future baseline studies about eco-epidemiology of CL transmission. This study has two key limitations: First, is the use of secondary data, that can have different sources of errors including typing errors and the occurrence of underreporting cases due to the low coverage of public health agencies in remote areas of the country. However, the SINAN have seen considerable improvements in the last decades, including the mandatory notification of CL on both public and private service since

2001. Furthermore, CL diagnoses and treatment is free for all Brazilian citizens in the unified public health system (SUS), and thus the records of most of the CL cases in Brazil must have been included in SINAM [40]. Second, the analysis at the municipality level could not have revealed the actual site of disease focus. For more accurate analysis, future studies should examine the spatial distribution of CL at a finer scale (eg. zip code), however this data are poorly available in SINAN.

The use of two complementary approaches employed in this study allowed us to describe more precisely the spatial and temporal patterns of CL in Brazil. However, similar to all spatial clustering approaches, the statistical methods used in this study have limitations in accuracy and sensitivity. The scan is one of the most frequently employed methods of spatial and temporal cluster analysis and has the advantage of being adjusted for heterogeneous population and to look for clusters without specifying their specific localities overcoming the pre-selection bias [47]. However, this method has the disadvantage of not identify accurately the right format of very irregular clusters, and thus often report large clusters that contain several low-risk areas inside it [48,49]. Therefore, we believe that this happened in our primary cluster due to the presence of some municipalities with low incidence rates. According to Han et al. [49], this issue could be improved by choosing ellipse radius values lower than 50%. However, due to the low population in northern Brazil (approximately 12.13% of Brazilian population) the analysis continued detecting a big and a few informative clusters, even when we reduce the radius length. In this sense, the gets Ord Gi analysis improved our study describing greater spatial and temporal heterogeneity in this area.

Conclusions

In this study the spatial-temporal dynamics of CL in Brazil has been analyzed for at the municipality level and with a wider temporal range than previous works. The scan method showed that the main cluster is located in the Brazilian Legal Amazon and that most of the secondary clusters are located in the southern and southeastern regions of Brazil. The emerging hotspot analysis identified a higher spatiotemporal variability of hotspot inside the BLA. Using this method, it was also possible to detect diminishing hotspots in the east and persistent, emergent, and new hotspots, mainly in municipalities of the states of Pará, Rondônia, and Roraima, Acre and south of Mato Grosso. Furthermore, we showed that the central coast of Bahia was one of the most critical regions for CL due to the presence of a cluster with the highest rank in a secondary cluster and an intensifying hotspot. Despite a general decrease trend of CL cases in Brazil found in this study, the identification of areas of persistent, emergent, new, and intensifying hotspots suggest that the control measures in these regions are not effective in controlling the disease. The results reported herein may assist and guide future research about CL eco-epidemiology and the implementation of disease control measures in Brazil.

Abreviations

BLA:Brazilian legal amazon; CL: Cutaneous leishmaniasis; IBGE: Brazilian Institute for Geography and Statistics (Instituto Brasileiro de Geografia e Estatística); LOESS: Locally estimated scatterplot smoothing; SINAN:Information System of Notifiable Disease; AC: Acre; AL; Alagoas; AP: Amapá; AM: Amazonas; BA: Bahia; CE: Ceará; DF: Distrito Federal; ES: Espírito Santo; GO: Goiás; MA: Maranhão; MT: Mato Grosso; MS: Mato Grosso do Sul; MG: Minas Gerais; PA: Pará;

PB: Paraíba; PR: Paraná; PE: Pernambuco; PI: Piauí; RR: Roraima; RP: Rondônia; RJ: Rio de Janeiro; RN: Rio Grande do Norte; RS: Rio Grande do Sul; SC: Santa Catarina; SP: São Paulo; SE: Sergipe; TO: Tocantins.

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Authors' contributions

TPP and RAK designed research; TPP performed research and analyzed data; TPP wrote the main draft of the manuscript, RAK wrote, revised and edited the manuscript.

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Data availability

All data used are publicly available. (http://www2.datasus.gov.br/DATASUS/index.php?area=0203)

Ethics approval and consent to participate

Ethics approval was not necessary because this study analysed only publicly available data, not including identifiable information.

Conflict of interest:

We declare no competing interests

Consent for publication

Not applicable.

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Chapter 2

Deforestation for cattle ranching increases the risk of cutaneous leishmaniasis in the Brazilian Amazon

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Abstract

Cutaneous Leishmaniasis is a vector-borne disease caused by a protozoan of the genus *Leishmania* and is considered one of the most important neglected tropical diseases. The Brazilian Amazon Forest harbors one of the highest diversity of *Leishmania* parasites and vectors and is one of the main focuses of the disease in the Americas. Previous studies showed that anthropogenic disturbances are an important predictor for the occurrence of the disease in the region, however, little is known about the effect of different types of land cover and land-use changes on the disease transmission risk. Here we quantify the effect of land use and land-cover changes on the incidence of Cutaneous Leishmaniasis in all municipalities within the Brazilian Amazon Forest, from 2001-2017. We used a structured spatiotemporal Bayesian model to assess the effect of forest cover, agriculture, livestock, extractivism, and deforestation on CL incidence, accounting for confounding variables such as population, climate, socioeconomic, and spatiotemporal random effects. We found that the increased risk of Cutaneous Leishmaniasis was associated with deforestation, especially modulated by a positive interaction between forest cover and livestock. Landscapes with ongoing deforestation for extensive cattle ranching are typically found in municipalities within the Amazon Frontier, where a high relative risk for Cutaneous Leishmaniasis was also identified. These findings provide valuable insights into developing effective public health policies and land-use planning to ensure healthier landscapes for people.

Keywords: Disease risk, Zoonosis, land use change, Spatio-temporal, Bayesian modeling

1. Introduction

Anthropogenic land-use changes are the major drivers for the emergence of zoonotic diseases, especially for diseases transmitted by vectors and direct animal contact (Loh et al., 2015). The Amazon forest is considered a region of high concern for the emergence of zoonotic diseases, due to its high diversity of vector-borne pathogens and extensive land-use changes (Lorenz et al., 2021). An estimated 116,000 km² of forests have been lost in Amazon between 2008 and 2022 (INPE, 2022), driven mainly by agriculture, cattle ranching, logging, mining, and infrastructure buildings (Garret et al., 2021). The effect of these land-use changes on the disease transmission risk in the Amazon has been widely studied for malaria, where studies have found a positive association between both deforestation and fragmentation on the disease incidence (Hahn et al., 2014; Santos & Almeida 2018; Chaves et al., 2018). However, for many other vector-borne pathogens, the effect of land-use changes on the transmission risk has still been understudied.

Cutaneous Leishmaniasis (CL) ranks among one of the most important neglected tropical diseases (PAHO, 2017); and the majority of CL cases occur in Brazil, mainly in the Amazon region (Alavar et al., 2012; Portella & Kraenkel, 2021). Cutaneous leishmaniasis is caused by a protozoan of the genus *Leishmania* (Kinetoplastida: Trypanosomatidae) and is transmitted to mammals by the bite of infected Phlebotominae sandflies (Diptera: Psychodidae) (Ready et al., 2013). When humans are infected, they develop skin ulcers that can evolve into the mucocutaneous form, which can cause permanent tissue scars and partial or total destruction of the mucosal tissues of the nose, throat, and mouth (Reithinger et al. 2007). CL is a life-burden disease and its skin sequels can also cause further psychological disorders such as depression (Bailey et al., 2019).

Landscape transformation in the Amazon has affected the distribution and population dynamics of *Leishmania* vectors and hosts. In the Brazilian Amazon, most sandflies are found mainly in forested areas where these insects have suitable moisture conditions, rich organic matter, and available shelter for development (Aguiar & Vieira, 2018). However, the modification of habitats by anthropogenic land-use changes has led some of these species to occupy disturbed environments such as fragmented forests, and rural and urban landscapes (Ramos et al., 2014; Filho et al., 2015; Guimarães et al. 2022). In addition, the land use conversion caused by the expansion of agriculture has offered a great abundance of food for the Leishmania reservoirs, such as rodents, which can reach higher abundance in those regions (Mendoza et al., 2020).

Despite the evidence on the influence of land-use changes on the distribution of CL vectors and hosts, the effect of land-use changes on the incidence of CL in humans in the Brazilian Amazon is still not completely understood. Most of the studies that investigated environmental effects on the incidence of CL in tropical regions suggested that climate variables are the most important predictor of CL risk (Karagiannis-Voules et al. 2013; Purse et al., 2017). However, these studies analyzed CL transmission risk over a wider geographical range and they considered that different ecological geographic zones have the same risk factor, which may not be appropriate to identify specific disease risks at a local level (Loh et al., 2015).

In that sense, a recent study focusing only on the Amazon forest found that anthropogenic factors rather than climate have the greatest impact on the risk of CL transmission (Chavy et al. 2019). In this study, the authors used an ecological niche modeling approach to assess the influence of the human footprint index (HFI) on the occurrence of CL over a specific period. Land cover and land-use changes are the main

drivers of changes in HFI in the Amazon. Considering these factors in risk modeling is fundamental to understanding how CL risk responds to human occupation and land use in a complex and dynamic environment such as the Brazilian Amazon Rainforest.

In this study, we used a spatiotemporal Bayesian approach to explore how different land cover classes and land-use changes affected the incidence of CL in the municipalities Brazilian Amazon while adjusting for well-known risk factors such as population, climate, and socioeconomic disadvantage. With this study, we provide an important understanding of how anthropogenic pressures in the Amazon affect the CL transmission risk in humans and identify landscape characteristics that must be prioritized in epidemiological surveillance and control strategies.

2. Material and Methods

2.1 Study Area

The Brazilian Amazon has an area of approximately 4.2 million km² (49% of Brazilian territory), which encompasses 503 municipalities located in the states of Acre (AC), Amapá (AP), Amazonas (AM), Pará (PA), Rondônia (RO), Roraima (RR), and part of Maranhão (MA), Tocantins (TO), and Mato Grosso (MT) (IBGE, 2021) (Figure 1). It has a population of ~ 22 million people, which is ~ 10% of the Brazilian population (IBGE, 2021). At present, 78,32 % of the region is covered by native vegetation, which comprises mainly dense and tropical rainforests, and 14,96% is covered by agriculture, which consists mainly of cattle pasture and soybean crops (Mapbiomas, 2020).

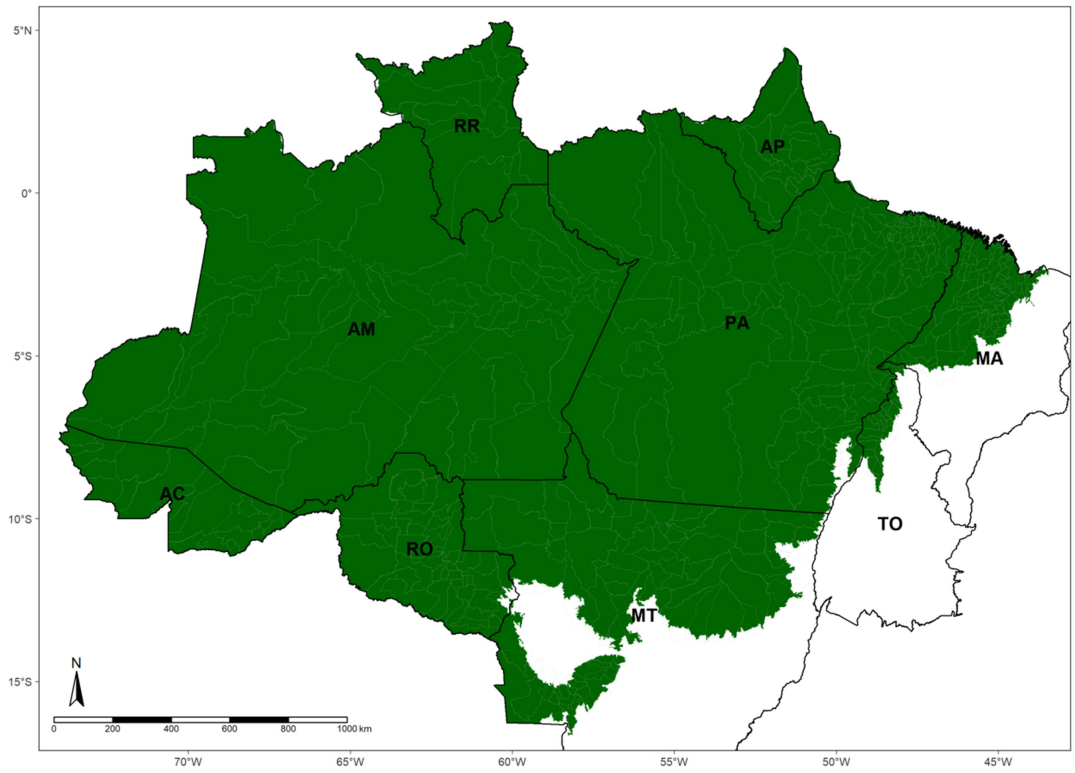

Figure 1- States and municipalities of the Brazilian Amazon Forest (green area). States names: Acre (AC), Amapá (AP), Amazonas (AM), Pará (PA), Rondônia (RO), Roraima (RR), and part of Maranhão (MA), Tocantins (TO), and Mato Grosso (MT).

2.2. Data Collection

2.2.1. Disease Cases and Population

The database of CL cases reported in the 503 municipalities from 2011 to 2017 was provided by the Brazilian Ministry of Health. The notification of CL cases has been mandatory in Brazil since 2001, and all the CL records from public and private healthcare facilities are stored in a national database called SINAN (Sistema de Informação de Agravos de Notificação). The data provided were at the individual level and

anonymized and all new CL cases confirmed by laboratory or clinical-epidemiological criteria were filtered and aggregated by year and municipality of infection.

The population data per year and municipality were extracted from IBGE (2021). Since men are most affected by CL in both rural and peri-urban environments in Amazon (Benício et al., 2015; Guerra et al., 2015), we also considered the proportion of the male population in each municipality in the model. The population data stratified by sex were available only from 2000 and 2010 on the IBGE dataset, so we used the male population of 2000 to analyze disease data from 2000 to 2007 and data from 2010 to analyze disease data from 2009 to 2017.

2.2.3. Land-use Data

We selected five land cover and land use changes based on their extension on the Amazon biome and their expected influence on the population of vectors and hosts and their interaction with humans (Table 1). Because most species of vectors and hosts are mainly forest-dependent (Aguiar & Vieira, 2018; Roque & Jansen 2014), we also tested the interaction effect of forest on livestock and permanent agriculture.

Data on forest cover and deforestation were obtained from the MapBioma 5.1. database for the years 2001 to 2017 (Projeto Mapbiomas, 2020). We calculated the percentage of natural forest area and the total amount (ha) of yearly forest loss for each year and municipality. Data on permanent agriculture area (ha), amount of non-timber forest product (NTFP) material collected (ton), and the number of heads of cattle per municipality and year were obtained from the IBGE Automatic Recovery System (SIDRA) database (IBGE, 2021).

Table 1: Predictor land-use variables considered in the spatial-temporal model and their expected influence on the disease.

Land use variable	**Expected effect**	**Influence on the disease**	**Source**
Forest cover	+	It is the main habitat of vectors and mammal hosts.	Aguiar & Vieira, 2018; Roque & Jansen 2014
Permanent crops	+	It can serve as a habitat and food source for hosts and vectors and influence their abundance.	Alexander et al. 2001, 2009; Mendoza et al., 2020
Deforestation	+	It can increase interaction between vectors and humans.	Nogueira-Neto et al (1998)
Extrativism (NTFP)	+	It can increase the exposure of humans to vectors.	Guerra et al. (2019)
Heads of cattle	+	It could serve as a blood-meal source for sandflies which can affect their distribution and abundance.	Bern et al, (2010)

2.2.4. Climate and Socioeconomic covariates

Rainfall data were obtained from the University of California Santa Barbara from Climate Hazard Group Infrared Precipitation Stations (CHIRPS) with a spatial resolution of 0.05º, and surface temperature data was extracted from National Centers for Environmental Prediction

(NOAA NCEP) with a spatial resolution of 0.5º. We calculated total annual rainfall (mm) from monthly data, and annual mean temperature (ºC) from 7-day average data for each municipality and year (2001-2017).

CL transmission risk is associated with poor socioeconomic conditions (Alvar et al., 2006), so we used data from the Basic Human Needs dimension of the Social Progress Index (SPI) as a model covariate. This dimension provides information about the capacity of a municipality to meet basic human necessities such as health care, sanitation, and adequate housing. It is measured using several variables provided by IBGE, PNUD, and the Brazilian Ministry of Health for 2010 and 2012. Its values range from 0 (worst) to 100 (best) (Santos et al., 2018).

2.3. Data Preprocessing

Before the analysis, we checked the summary statistics and missing values for all covariates. We excluded six municipalities from the analysis that did not have complete demographic or land-use data. Most of these municipalities were created after 2010 and were not included in the Brazilian demographic census.

We also checked the correlation between the fixed-effect variables by performing a Pearson's rank correlation index with the corrplot package in R (Wei & Sinko 2021). Next, we tested multicollinearity between variables by computing the variance-inflation factors (VIF), which represents the amount of variability of a covariate that is explained by other covariates (Craney et al., 2002). VIF was assessed using the vif function of the HH package in R (Heiberger et al., 2015). Before the analysis, all the fixed-effect variables were standardized by subtracting the mean from each value and dividing by the standard deviation.

2.4. Statistical Analysis

To quantify the effect of landscape and their climate and socioeconomic covariates on the incidence of Cutaneous Leishmaniasis we fitted a hierarchical spatiotemporal Bayesian model. We assumed that the observed counts of Cutaneous Leishmaniasis cases (O_{it})for the ith municipality in the year t followed a Negative Binomial distribution with mean $\lambda\lambda_{it}$ and scale parameter $\Phi\Phi$:

$O_{it} \sim NegBin\ (\lambda\lambda_{it}\ \Phi\Phi)$

And

$Log(\lambda\lambda_{it}) = log(E_{it}) + log(\Theta_{it})$

Where E_{it} (the expected number of cases in $_i$ postal area and year ($_t$) is an offset to control for population size. The mean log relative risk (RR), log($\lambda\lambda_{it}$) for each predictor was modeled as:

$log(\lambda\lambda_{it}) = \alpha_0 + (Rain_{it})\ \beta_1 + (Temp_{it})\ \beta_2 + (BHN_{it})\ \beta_3 + (\%For_{it})\ \beta_4 + (log(Agri_{it})\ \beta_5 + (log(Ext_{it}))\ \beta_6 + (log(Defor_{it}))\ \beta_7 + (log(Cattle_{it}))\ \beta_8 + (log(Cattle_{it}))^* (\%For_{it})\ \beta_9 + (log(Agri_{it}))^* (\%For_{it})\ \beta_{10} + \mu_i + \nu_i + \gamma_t + \rho_t + \psi_{it}$

where:

1. α_0 is an overall intercept term

2. β_1 through β_3 are coefficients for fixed effects of time-varying climate and socioeconomic covariates in each municipality: β_1 is the coefficient for total rainfall (Rainit); β_2 is the coefficient for mean temperature (Tempit); β_3 is the coefficient for Basic Human Needs Index (BHNit).
3. β_4 through β_8 are coefficients for fixed effects of time-varying land use covariates in each municipality: β_4 is the coefficient for the percentage of forest habitat (%Forit); β_5 is the coefficient log Permanent Agriculture area (log(Agriit); β_6 is the coefficient for log extractivist ton (log(Extit))); β_7 is the coefficient for the log of forest area loss (log(Extit))), β_8 is the coefficient for the number of cattle heads (log(Cattleit))
4. β_9 is the coefficient for the interaction term between the forest and the number of cattle heads, and β_{10} is the coefficient for the interaction term between the forest and the amount of Permanent Agriculture;
5. μi is a spatially structured random effect with mean zero and variance σu modeled using a Besag ICAR model (Besag, 1974) to account for spatial autocorrelation, and νi is a spatially unstructured random effect with mean zero and variance σv. The two spatial components were modeled together using Besag-York-Mollie (BYM) model (Besag et al. 1991)
6. γt is a temporally structured random effect, modeled with a first-ordered random walk (rw1) model, and ρt is a temporal unstructured random effect.
7. ψit is a space-time interaction effect, incorporated in the model to account for any residual spatiotemporal variation that was not captured by the spatial or temporal main effects, and was assumed to be temporally structured (rw1) and spatially unstructured (IID).

All priors were assigned as uninformative distributions (log-Gamma with parameters 1 and 0.00005). We also tested different options of random effects and compared them using the deviance information

criterion (DIC) (Spiegelhalter et al., 2002). We have found that the model with all random effects described previously produced lower DIC values, and we, therefore, used this as the preferred model. Full details on model selection for spatial and temporal effects are found in Table S1 of the Supplementary material.

We evaluated the performance of the final model by calculating the RMSE and R^2 between the predicted and observed LC relative risk. We also get the probability integral transform (PIT) histogram to evaluate the model goodness fit. According to Gneiting et al. (2007), a uniform PIT distribution means the predictive distribution is coherent with the data, suggesting a well-fitted model.

Finally, we used model results to map CL Relative Risk (RR) for The Brazilian Amazon. Relative risk is the disease risk in each municipality compared to the average risk in all municipalities. Thus, a value above one means a higher than average risk, while a value below one means a lower than average risk. The mean RR and coefficient of variation of model results among years were summarized for each municipality. The annual map of CL's relative risk is found in Figure S1 in the Supplementary material.

The models were fitted using the Integrated Nested Laplace Approximation (INLA) method through the R-INLA package (Rue et al., 2009). INLA is a computationally alternative approach to MCMC (Markov Chain Monte Carlo), and it has been used successfully in a great variety of applications, including spatial-temporal disease modeling (Bangliardo et al., 2013; Moraga, 2019). All the data processing, visualization, and analysis were made using R package 4.1.1 (R Core Team, 2021), and the codes are available in a public repository .

3. Results

3.1. Description of CL cases and covariates

Between 2001-2017, the 503 municipalities of the Brazilian Amazon had a total of 204,605 CL cases recorded, with an average incidence of 6.5 per 100 000 inhabitants. The highest cumulative incidence of CL is concentrated in the southern Amazon Frontier, followed by the north of the states of Amazonas and Amapá, and the center of Pará State. In general, the incidence of CL on Amazon decreased over the years, with the largest number of CL cases occurring in 2003 (17,683) and the lowest in 2016 (6,691) (Fig. S2, Supplementary material)

Table 2 shows the mean, standard deviation, and range values of land use, climate, and socio-economic covariates for the municipalities of the Brazilian Amazon Forest between 2001 and 2017. The municipalities with the highest percentage of forest cover are located in the central-western of the Amazon. The largest number of cattle heads and deforestation rates are concentrated in municipalities of the Amazon forest frontier and the southeast of Pará state. Areas of permanent agriculture were located mainly in the municipalities of the central Pará, Rondônia, and northern Mato Grosso states, and NTFP in central Amazonas and Maranhão (Fig. S3 Supplementary material). Between 2001 and 2017, there was an increase in the total number of cattle heads and a decrease in the amount of forest cover, deforestation, NTFP, and areas of permanent agriculture over the Amazon (Fig. S4 Supplementary material)

Table 02 – Descriptive statistics of land use, climate, and socio-economic covariates (2001-2017) at the level of municipality in the Brazilian Amazon

Variable	**Mean (± SD)**	**Range**
Forest cover (%)	58.1 (26.4)	2.9 - 99.7
Deforestation (ha)	3800.7 (6656.1)	3.7 - 138200.4
Permanent Agriculture (ha)	1299.4 (3273.4)	0.0 - 43568.0
Extrativism (ton)	1271.4 (10265.4)	0.0 - 506888.0
Cattle heads (nº)	109384.1 (166012.7)	0.0 - 2282445.0
Mean temperature (ºC)	27.2 (1.2)	22.4 - 34.3
Total precipitation (mm)	2122.6 (480.5)	815.8 - 4209.5
Population (nº)	37991.3 (118537.9)	1109.0 - 2130264.0
SPI – basic human needs	57.7 (6.9)	31.24 – 83.72
Male population (%)	52 (1.5)	46.7-60.3

3.2. Statistical modeling

Overall, our model fitted well the data (R^2= 0.87, RMSE=1.14). The predicted SIR value is very close to the observed one, and PIT had an overall uniform distribution (Fig. S5 - Supplementary material). All variables included in the model had a correlation < 0.45 and the Variance Inflation Factor (VIF) of all variables was lower than 2.3, which indicates no strong collinearity among the fixed-effects variables (Table S2 and Fig.S6 - Supplementary material)

Our model found that municipalities with higher forest cover (RR 1.21, Credible interval: 1.15-1.27), cattle herds (RR 1.19, CI 1.13-1.25), and deforestation rates (RR 1.05, CI 1.01-1.10) had a higher number of

CL cases. We also found a positive interaction effect between forest cover and livestock (RR 1.05, CI 1.01-1.10), indicating that CL incidence was even higher in the municipalities that had the higher values of these two factors together. No significant relationship was found between permanent agriculture, NTFP, or the interaction between permanent agriculture and forest cover on the CL incidence (see Figure 2 and Table S3 in the Supplementary Material).

Regarding the socioeconomic and climate covariates, we found that municipalities with higher proportion of males (RR 1.21, CI 1.16-1.26) had a greater incidence of CL, while municipalities with higher total rainfall (RR 0.92, CI 0.89-0.95), mean temperature (RR 0.90, CI 0.86-0.94), and human basic needs index (RR 0.94, CI 0.89-0.98) had lower incidence of CL (Figure 2, Table S3 of Supplementary material).

The coefficient values of random effects are shown in Table S3 of Supplementary material. These random effects represent the residual spatiotemporal heterogeneity of CL risk that was not explained by the fixed effects. The remained non-explainable variation in CL risk was captured mainly by the spatially structured and spatial-time interaction random effect.

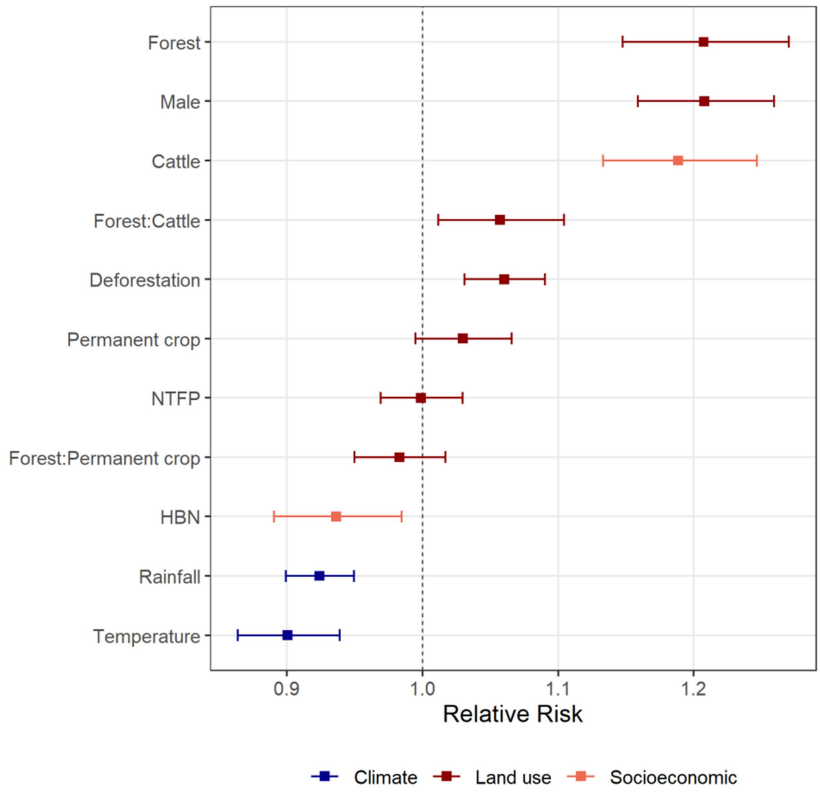

Figure 2- Relative Risk with credible interval (95%) for standardized coefficients for the effects of land use, climate, and socioeconomic covariates of municipalities on the relative risk of CL cases estimated by the spatiotemporal model.

3.3. Map of Relative Risk

The map of average CL Relative Risk for the entire study period and their 95% credible interval width are shown in Figure 3. As expected, the intensity of Relative Risk (RR) follows the spatial patterns of the cumulative relative incidence. In general, the municipalities with the highest RR are located in the Amazon frontier region, where we also found high amounts of forest cover, deforestation rates, and cattle herds (Figure 3 Supplementary material). We also found high RR of CL in the

municipalities located in the northern part of the Brazilian Amazon, especially in the north of the states of Amazonas, Pará, and in the entire state of Roraima.

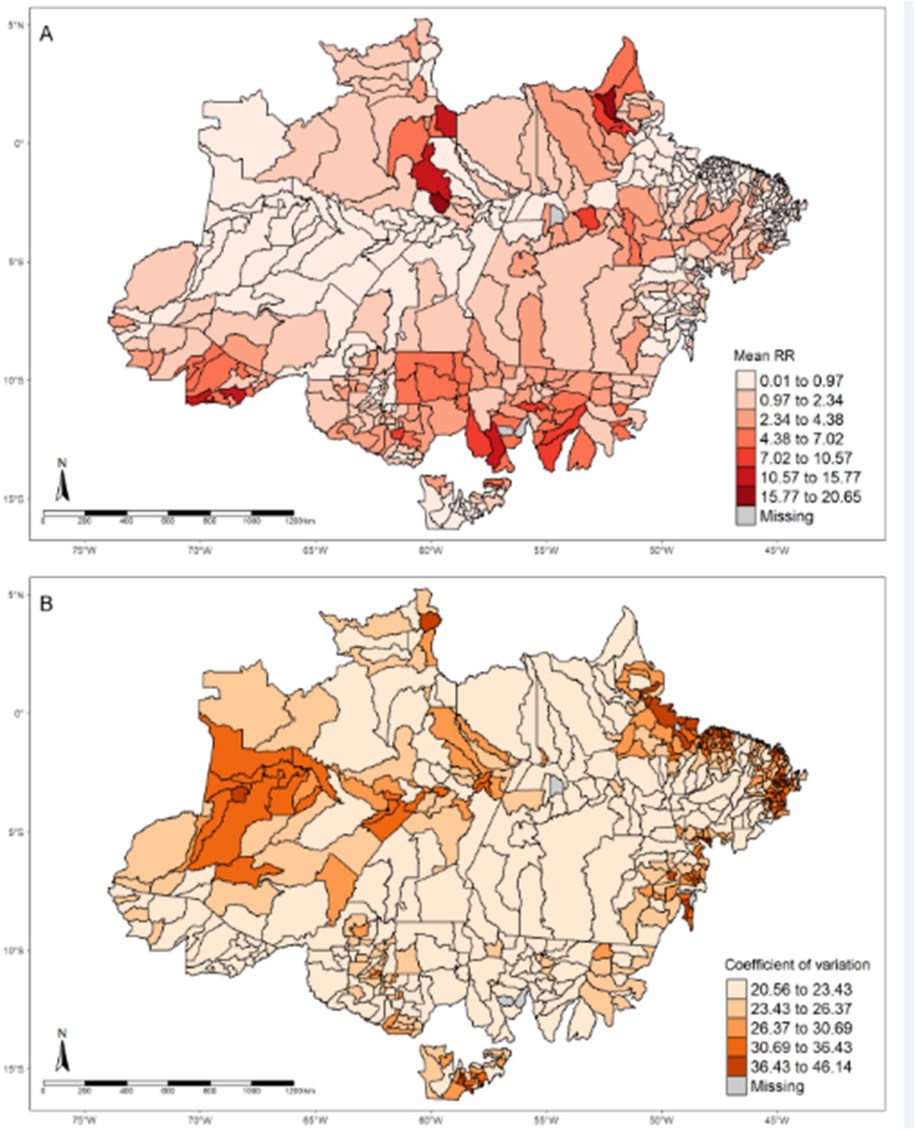

Figure 3- Mean estimated Relative Risk (RR) (A) and 95% credible interval width (B) across the Brazilian Amazon Forest.

4. Discussion

This study examined the impact of land use and land cover changes on Cutaneous Leishmaniasis incidence in the municipalities of the Brazilian Amazon Forest. Our research identified a positive

association between forest cover, livestock, deforestation, and an increased risk of CL incidence. Our relative risk map corroborates with the incidence map, which shows the highest relative risk of CL in municipalities of the Amazon Frontier, where there is a combination of high amounts of forest cover, cattle ranching, and deforestation rates (Calentano & Verissimo, 2007; Rodrigues et al., 2009). Previous research has also found increased risk factors for Malaria transmission in municipalities with these landscape characteristics (Castro et al., 2006; Santos & Almeida 2018), and we now demonstrate that these regions also display significant risk factors for CL transmission in humans.

The increased incidence of CL in municipalities with a combination of high forest cover and livestock might be related to an increased sandfly abundance and a higher likelihood of human-vector contact in these regions. Although most sandfly species are dependent on forest habitat, several studies have reported high densities of CL vectors in vegetation near rural settlements, particularly in association with animal shelters (Ramos et al., 2014; Guimarães et al., 2022; Costa et al., 2021; Pereira Junior et al., 2019). These studies indicate that animal shelters may provide sandflies with abundant food and places to rest and lay eggs. Sandflies are also typically attracted to peri- and intradomiciliary areas of rural properties near forested areas to seek blood from humans and domestic animals (Rosário et al., 2017; Chagas et al., 2018; Neitzke-Abreu et al., 2020), which may increase contact rates between humans and sandflies, and hence the transmission risk of CL in these areas.

In addition, other studies showed that deforestation and pasture matrix in the Amazon forest prompted a reduction in the diversity of small mammals and an increase in the density of important reservoirs of *Leishmania*, such as *Didelphis marsupialis* and *Proechimis* species

(Palmerin et al., 2020; Roque & Jansen, 2014). According to the hypothesis of the dilution effect, areas with low biodiversity and a high density of competent reservoirs tend to show an increase in the risk of disease transmission due to the amplification of infected hosts and a higher chance of encounters between vectors and infected reservoirs (Keesing et al., 2006). The impact of biodiversity loss on the risk of infectious disease transmission has been extensively studied for some vector-borne diseases, such as malária, Lyme disease and West Nile virus (Ostfeld and Keesing, 2012; Laporta et al. 2013). Therefore, similar mechanisms may also play a role in the transmission of CL as demonstrated in a recent study by Kocher et al. (2023) in French Guiana. In this study, they found a higher prevalence of Leishmania parasites on sandflies in disturbed environments with fewer mammal species and a greater abundance of Leishmania reservoirs.

We did not find an association between NTFP and permanent crops with CL incidence. In contrast to our study, Guerra et al. (2019) found higher incidence rates of CL in municipalities that contained the highest amounts of latex and nuts production in the state of Acre in Brazil. This study, however, did an exploratory and descriptive analysis and did not use statistical modeling that accounts for spatial autocorrelation and confounder effects. The association between permanent crop and CL cases was also previously found elsewhere (Purse et al., 2017; Gutierrez et al., 2018). However, differently from our study, other researchers investigated the effect of specific types of permanent crops, such as coffee (Ocampo et al., 2012; Lana et al. 2021), cocoa (Figueroa et al., 2014), and banana (Membrive et al., 2012), on the risk of CL transmission. Different crop types may have distinct effects on Leishmania vectors and host species, as Alexander et al. (2001) demonstrated in two systems of coffee cultivation in Colombia. Because

we found a marginal effect between permanent crop and CL incidence, we suggest that future studies investigate the effects of different types of cultivation on the CL transmission risk.

Our risk map showed that municipalities within the Amazonian frontier have a higher relative risk for CL. This result is consistent with our findings that forest cover, livestock, deforestation, and the proportion of the male population have a positive effect on CL risk, while the socioeconomic conditions have a negative effect, as the combination of these landscape and socioeconomic characteristics is typically found in the Amazonian frontier region (Guerra et al., 2015; Guerra et al., 2019; Calentano & Verissimo, 2007; Rodrigues et al., 2009). It is also in accordance with the findings of Codeço (2021), who observed a positive association between areas of farmer and cattle production with a higher prevalence of Cutaneous leishmaniasis. Therefore, to reduce the transmission of CL we recommend the implementation of prevention and control strategies in municipalities with these characteristics. These actions should include recommendations for residents and workers in the region such as the use of insect repellents, and personal protective equipment, and implementation of environmental management strategies such as improving housing conditions and building homes distantly located from forested areas and animal shelters (PAHO, 2017).

Our model also identified some residual risk components that were attributed to the spatial random effect. This result means that there must be other characteristics affecting the risk of CL transmission in these municipalities that were not captured by the fixed effects in our model (Figure S7 Supplementary material). We hypothesize that the expansion of urban areas close to the forest and the presence of newly arrived immigrants with low immunity to CL may also play an important role in the risk of CL transmission in these municipalities. Unfortunately, to our

knowledge the data required to test this hypothesis was unavailable. We recommend that further studies investigate additional environmental and social factors that may impact the risk of CL transmission in these areas.

Although we have made the most geographically comprehensive assessment of the effects of land use change on CL incidence based on statistical modeling, this study has a few drawbacks. First, we used data from the surveillance system that may have issues, such as typing errors and incomplete information. Moreover, we analyzed environmental and disease data aggregated at the municipal level, which do not capture the fine-scale determinants of disease transmission risk. Additionally, socioeconomic variables for Amazonian municipalities were not available for all years of the study period. However, we incorporated structured and non-structured temporary random effects in our model, which captures any other temporal variability that may not have been explained by the fixed effects. Hence, to our knowledge, our results are based on the best data available.

5. Conclusion

In summary, this study used rigorous spatiotemporal statistical analysis to identify land use factors associated with an increase in cutaneous leishmaniasis incidence in the Brazilian Amazon Forest. Additionally, we also showed that deforestation and the interaction between forest cover and cattle ranching are landscape risk factors for cutaneous leishmaniasis transmission in this region. Based on our results and current literature we believe that these environmental changes, commonly found in municipalities of the Amazon Frontier, are probably creating suitable conditions for the proliferation of vectors and reservoirs, as well as an increase in human-vector contact rates. Therefore, to control

CL in the Brazilian Amazon forest, we recommend reducing this settlement model and replacing it with a more sustainable and healthier landscape for the environment and people. We also recommend targeting the high-risk areas identified in our study for surveillance and control measures.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Tatiana P. Portella: Conceptualization, Investigation, Data curation, Methodology , Software , Visualization, Resources, Formal analysis, Writing – original draft. Vitor Sudbrack: Resources, Software, Data Curation, Writing – review & editing. Renato Coutinho: Methodology, Validation, Writing – review & editing, Paulo I Prado: Methodology, Supervision, Validation, Writing – review & editing. Roberto A. Kraenkel: Project administration, Supervision, Writing – review & editing.

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General Discussion and Conclusion

Cutaneous Leishmaniasis is a neglected tropical disease that affects from 0.7 to 1.2 million of people per year in at least 89 countries. Brazil is among the top ten countries with the highest number of CL cases worldwide (Alvar et al. 2012; PAHO, 2024), but how the disease is distributed and the environmental factors that have been modulating it are not well understood. This thesis presents a detailed analysis of the spatial-temporal disease distribution over a long period of time and in a finer spatial scale in Brazil.

In the first chapter, we used different methods to investigate the spatiotemporal pattern of the disease in Brazil. Our goal was to identify priority areas for surveillance and to develop hypotheses about the environmental factors that may have been influencing these spatial and temporal patterns.

We found that the disease was registered in 73,8% of the municipalities, with most cases (80%) concentrated in only 10%, located mainly in the northern states of Brazil and the southeastern region of Bahia. This result supports the findings of Maia-Elkhoury (2016) who found that the highest incidence of the disease was in the states of north and northeast of Brazil. Our results also indicate a reduction in CL cases in Brazil over time, but a small percentage of municipalities (3.2%) showed an increasing trend. These municipalities were located mainly in the Amazonas, Pará, Acre, Amapá, Roraima, Mato Grosso, Tocantins, Minas Gerais, São Paulo, and Bahia states.

The cluster analysis revealed that the most likely cluster of the disease occurred in the northern region, covering the entire legal

Amazon. Additionally, significant clusters of the disease were found in Bahia, São Paulo, Minas Gerais, and Paraná states during different periods. The hotspot analysis revealed a high spatial and temporal heterogeneity within the main cluster of the disease incidence. Hotspots were detected on the border of the Legal Amazon, spanning across Acre, Rondonia, and Mato Grosso states, the central region of Pará, a few areas of Amazon state, and the northern part of Legal Amazon, including Amapá and Roraima state. While many of these hotspots have decreased over time, some of them have persisted or emerged more recently (consecutive, new, or emerging hotspots).

The geographic and temporal pattern of the hotspots found in the main cluster of CL indicates that the disease dynamics are highly heterogeneous within the Amazon region. This finding is consistent with previous studies conducted in Acre (Melchior et al. 2017) and Amazon states (Teles et al., 2010). As the hotspots were mainly found in regions with high pressure of land occupation and exploitation, we hypothesized that land-use changes played a significant role in modulating disease dynamics in those municipalities. This assumption was supported by Chavy et al (2019), who found that the human footprint was the most important environmental variable to explain CL occurrence in the Brazilian Amazon.

In line with this hypothesis, the second chapter focuses on understanding how land use changes have affected disease incidence within the primary cluster. Because disease risk factors can vary across ecological regions (Loh et al., 2015), we restricted our analysis to the Amazon biome and excluded municipalities with more than 50% of their territory in the Cerrado.

We used a structured spatiotemporal Bayesian model to assess how different land cover classes affected the incidence of CL, while adjusting for well-known risk factors such as population, climate, and socioeconomic disadvantage. We found that the increased risk of Cutaneous Leishmaniasis was associated with deforestation, especially modulated by a positive interaction between forest cover and livestock.

These land-use characteristics are typically found in municipalities on the Amazon frontier. These areas often have a high percentage of forest cover, which is cleared for livestock farming. Over time, the amount of forest cover is reduced, cattle ranching is abandoned, and deforestation decreases (Rodrigues et al., 2009; Codeço et al. 2021). Based on our findings, there is a negative relationship between the age of settlement and the incidence of cutaneous leishmaniasis. This may explain the decreasing hotspots observed in areas with older occupation of the Amazon Frontier and persistent, new, consecutive, and emerged hotspots in municipalities with more recent occupation.

Our results showed that other environmental and socioeconomic determinants also influenced the disease incidence in the region. Mean temperature and total precipitation had a negative effect, while the proportion of males and the socioeconomic index had a positive effect. Additionally, the spatial random effect captured an important residual risk component, indicating the possible existence of other variables that affect the incidence pattern in the region that were not included in our model. It is possible that the expansion of urban areas close to the forest and the presence of newly arrived immigrants with low immunity to CL may also play an important role in the risk of CL transmission in these municipalities, as suggested in other studies elsewhere (Ashford, 2000; Pigott et al., 2014).

This study did not investigate the environmental factors that affected all clusters of the disease. We believed that it is important to investigate the cluster of the central coast of Bahia in future studies, as the hotspot analysis found an intensifying hotspot in this area. According to a recent study by Sevá et al. (2023), the incidence of CL in Bahia is related to the proximity of rural and peri-urban areas adjacent to forests. Additionally, the *Nyssomyia whitmani*, which is the one of the main vector of CL in Bahia, has increased its range of climatic suitability (Peterson & Shaw, 2003; Da Costa et al., 2008) and has been favored by anthropogenic disturbances (Fernandéz et al., 2020). It would be worthwhile to explore the influence of environment and climate changes on the eco-epidemiology of the disease in this region.

We hope our results contribute to the understanding of the spatiotemporal dynamics of CL cases in Brazil and the effects of environmental changes on their incidence. In this study, we identified areas of higher cluster and hotspots of the disease, which can guide priority areas for surveillance, control measures, and future eco-epidemiological studies. Additionally, our results highlight how anthropogenic pressures have affected the disease incidence in the region of higher CL transmission risk. These findings could guide land-use planning policies, especially in the Amazon Forest, to provide healthier landscapes for humans and the environment.

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Supplementary Material – Chapter 1

S1. Clusters Detected from Spatial-temporal Scan analysis

1.Location IDs included.: 130353, 130356, 130260, 130320, 130185, 130115, 130250, 130255,
130083, 130110, 130030, 130190, 130400, 130008, 130310, 130200, 130440, 130395, 130063, 130430, 130010, 130080, 130068, 130290, 130130, 140023, 140050, 140047, 140060, 130050, 130040, 130330, 150300, 130300, 130340, 150797, 130120, 150390, 130270, 140020, 150530, 140028, 150510, 140030, 150360, 140017, 150375, 130410, 150805, 130420, 140010, 150285, 130002, 150100, 150145, 130014, 140005, 130426, 130360, 150040, 150680, 140015, 150475, 150619, 130280, 140002, 140040, 150480, 130160, 150565, 130220, 130170, 130090, 150815, 150600, 140045, 140070, 130230, 130210, 150503, 130240, 150445, 130380, 130100, 150050, 510325, 150172, 110013, 160027, 160080, 110080, 110094, 110020, 150590, 130423, 110110, 150060, 510080, 510337, 130370, 150835, 110175, 510615, 510140, 110026, 130006, 510895, 110040, 510629, 150310, 110002, 510517, 160005, 110160, 160015, 110180, 150780, 110011, 510025, 110060, 110140, 510757, 150085, 160040, 510279, 110015, 130350, 110100, 110045, 160053, 110012, 130390, 160060, 110155, 160030, 150580, 510285, 110143, 150730, 110070, 510626, 110120, 160023, 150450, 130195, 110025, 110130, 110170, 510515, 510410, 510621, 510880, 110004, 110009, 150180, 150548, 510510, 110034, 110090, 510560, 510642, 160025, 160021, 110018, 510805, 510627, 160070, 510794, 150030, 150110, 110028, 510680, 110050, 110147, 510320, 110033, 110014, 130070, 160055, 110148, 110029, 110032, 150808, 510619, 160050, 160010, 110001, 150543, 150070, 160020, 130406, 150520, 510455, 150250, 110150, 150280, 110010, 110037, 110145, 130060, 150506, 510190, 150120, 120001, 130020, 150810, 150770, 150210, 150460, 110092, 150178, 510558, 110149, 150400, 120080, 150034, 110030, 510454, 510305, 150490, 510790, 130140, 120038, 150553, 150276, 510452, 150640, 110007, 510724, 150125, 510787, 510830, 150330, 150309, 150215, 110006, 150795, 120013, 150200, 150370, 120040, 120050, 510774, 150010, 150380, 150570, 150277, 110005, 120045, 110008, 510800, 150470, 150840, 150616, 510850, 150497, 510792, 510890, 130150, 510735, 150420, 150130, 150295, 150775, 120017, 110003, 120034, 110146, 510370, 150140, 150630, 150790, 510330, 150613, 150080, 150304, 150442, 150750, 510268, 510525, 150260, 150150, 150157, 150635, 150715, 510263, 150020, 510730, 150650, 150800, 150700, 150820, 510624, 510860, 170740, 211153, 150563, 150013, 150190, 171630, 120030, 150710, 510335, 150275, 120070, 150670, 150340, 150240, 150746, 150796, 150175, 510677, 510269, 150290, 170380, 172030, 170215, 150720, 150740, 150745, 150618, 150549, 172210, 211285, 170230, 150658, 120060, 150440, 150293, 170390, 171886, 150270, 150320, 170389, 170220, 510618, 510622, 150095, 170600, 150405, 170190, 150660, 150410, 171395,

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210440, 211080, 210450, 210360, 211070, 210470, 520640, 171270, 521960, 210930, 520215, 522145, 211065, 520810, 171620, 210460, 171800, 520750, 521970, 171865, 521280, 210720, 211270, 520055, 520340, 510719, 521487, 211210, 210670, 210545, 210350, 510040, 510460, 211174, 210420, 521295, 170560, 210180, 210330, 210462, 221120, 170700, 520945, 521925, 510670, 510120, 520470, 500793, 520465, 521370, 211190, 521690, 521470, 521308, 211107, 520980, 172093, 520753, 211040, 210173, 220130, 521720, 210500, 522160, 520725, 220855, 521220, 210800, 171525, 210940, 521385, 220660, 220440, 210230, 521090, 210770, 521890, 210730, 220080, 520235, 211260, 520710, 521100, 522015, 521015, 510030, 220975, 521940, 210030, 210320, 210790, 521486, 522028, 211027, 521200, 521520, 210010, 520500, 520929, 171780, 521120, 520540, 221063, 521860, 210300, 520760, 220600, 220560, 211110, 521020, 521030, 210592, 500640, 522170, 521935, 521460, 521565, 210640, 521810, 210080, 520552, 220170, 170240, 520440, 521870, 521945, 211195, 520320, 520890, 520960, 220290, 172090, 520393, 520090, 220323, 220885, 520570, 220450, 220740, 500320, 220870, 500520, 220300, 210340, 521390, 510060, 220190, 521900, 210660, 520860, 220310, 210390, 210220, 521060, 210170, 520530, 220590, 520490, 521340, 521310, 521160, 170555, 220225, 220620, 171215, 521350, 220530, 500330, 170270, 171515, 210780, 521040, 220930, 522108, 210210

Coordinates.....: (-2.02981,-60.0234)
Semiminor axis.....: 17.35
Semimajor axis.....: 17.35
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2001/1/1 to 2015/12/31
Population.....: 25956648
Number of cases.....: 234486
Expected cases.....: 44858.05
Annual cases / 100000.: 61.2
Observed / expected...: 5.23
Relative risk.....: 12.06
Log likelihood ratio..: 266530.419225
Test statistic.....: 266530.419225
P-value.....: < 0.00000000000000001

2.Location IDs included.: 292260, 293120, 290540, 291730, 291345, 293290, 292467, 293160,
293350, 292575, 291120, 290580, 292275, 291570, 292240, 291820, 291890, 290195, 293210, 292070

Coordinates.....: (-13.604,-39.1091)
Semiminor axis.....: 0.50
Semimajor axis.....: 0.76
Angle (degrees).....: 90.00
Shape.....: 1.50
Time frame.....: 2003/1/1 to 2017/12/31
Population.....: 412548
Number of cases.....: 26752

Expected cases.....: 731.42
Annual cases / 100000.: 428.4
Observed / expected...: 36.58
Relative risk.....: 39.27
Log likelihood ratio..: 71184.659077
Test statistic.....: 69746.436901
P-value.....: < 0.00000000000000001

3.Location IDs included.: 411300, 410550, 412720, 412610, 411240, 411160, 412530, 410730,
410750
Coordinates.....: (-23.6219,-52.4693)
Semiminor axis.....: 0.27
Semimajor axis.....: 0.27
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2001/1/1 to 2015/12/31
Population.....: 132738
Number of cases.....: 1553
Expected cases.....: 229.79
Annual cases / 100000.: 79.2
Observed / expected...: 6.76
Relative risk.....: 6.78
Log likelihood ratio..: 1646.521990
Test statistic.....: 1646.521990
P-value.....: < 0.00000000000000001

4.Location IDs included.: 352330, 353720
Coordinates.....: (-24.2834,-47.1736)
Semiminor axis.....: 0.062
Semimajor axis.....: 0.062
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2001/1/1 to 2009/12/31
Population.....: 25828
Number of cases.....: 592
Expected cases.....: 26.08
Annual cases / 100000.: 265.9
Observed / expected...: 22.70
Relative risk.....: 22.73
Log likelihood ratio..: 1282.919384
Test statistic.....: 1282.919384
P-value.....: < 0.00000000000000001

5.Location IDs included.: 311740, 316360, 311600, 313120, 316805, 313770, 314400, 315890,
312352, 315190, 320245, 314053, 316760, 320265, 315015, 315415, 313055, 320115, 320300, 315935, 315725, 311340, 313940, 313950, 317005, 310220, 316447, 316095, 310205, 315350, 313090, 320010, 317115

Coordinates.....: (-19.9326,-41.6908)
Semiminor axis.....: 0.59
Semimajor axis.....: 0.59
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2003/1/1 to 2017/12/31
Population.....: 527176
Number of cases.....: 2828
Expected cases.....: 933.26
Annual cases / 100000.: 35.5
Observed / expected...: 3.03
Relative risk.....: 3.05
Log likelihood ratio..: 1245.253649
Test statistic.....: 1245.253649
P-value.....: < 0.00000000000000001

6.Location IDs included.: 352215, 410020, 354280, 352120, 350270, 352265, 350535, 350540,
351480, 412863
Coordinates.....: (-24.6393,-48.8413)
Semiminor axis.....: 0.25
Semimajor axis.....: 0.76
Angle (degrees).....: 80.00
Shape.....: 3.00
Time frame.....: 2002/1/1 to 2016/12/31
Population.....: 81355
Number of cases.....: 916
Expected cases.....: 142.87
Annual cases / 100000.: 75.1
Observed / expected...: 6.41
Relative risk.....: 6.42
Log likelihood ratio..: 929.634175
Test statistic.....: 805.086812
P-value.....: < 0.00000000000000001

7.Location IDs included.: 410520
Coordinates.....: (-26.0891,-52.8691)
Semiminor axis.....: 0
Semimajor axis.....: 0
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2002/1/1 to 2016/12/31
Population.....: 17256
Number of cases.....: 324
Expected cases.....: 30.35
Annual cases / 100000.: 125.0
Observed / expected...: 10.68
Relative risk.....: 10.68
Log likelihood ratio..: 473.697847
Test statistic.....: 473.697847

P-value.....: < 0.00000000000000001

8.Location IDs included.: 330380, 355540
Coordinates.....: (-23.2221,-44.7175)
Semiminor axis.....: 0.28
Semimajor axis.....: 0.56
Angle (degrees).....: 30.00
Shape.....: 2.00
Time frame.....: 2001/1/1 to 2006/12/31
Population.....: 115803
Number of cases.....: 418
Expected cases.....: 74.98
Annual cases / 100000.: 65.3
Observed / expected...: 5.57
Relative risk.....: 5.58
Log likelihood ratio..: 375.363460
Test statistic.....: 353.896064
P-value.....: < 0.00000000000000001

9.Location IDs included.: 412215
Coordinates.....: (-25.4874,-52.5292)
Semiminor axis.....: 0
Semimajor axis.....: 0
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2004/1/1 to 2005/12/31
Population.....: 15098
Number of cases.....: 76
Expected cases.....: 4.35
Annual cases / 100000.: 204.8
Observed / expected...: 17.48
Relative risk.....: 17.48
Log likelihood ratio..: 145.799657
Test statistic.....: 145.799657
P-value.....: < 0.00000000000000001

10.Location IDs included.: 412060
Coordinates.....: (-25.2111,-50.9754)
Semiminor axis.....: 0
Semimajor axis.....: 0
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2002/1/1 to 2003/12/31
Population.....: 48906
Number of cases.....: 97
Expected cases.....: 10.81
Annual cases / 100000.: 105.1
Observed / expected...: 8.98
Relative risk.....: 8.98
Log likelihood ratio..: 126.682508

Test statistic.....: 126.682508
P-value.....: < 0.00000000000000001

11.Location IDs included.: 410240, 411100, 412310, 410010
Coordinates.....: (-23.1078,-50.3704)
Semiminor axis.....: 0.14
Semimajor axis.....: 0.21
Angle (degrees).....: 0
Shape.....: 1.50
Time frame.....: 2001/1/1 to 2013/12/31
Population.....: 51099
Number of cases.....: 252
Expected cases.....: 77.89
Annual cases / 100000.: 37.9
Observed / expected...: 3.24
Relative risk.....: 3.24
Log likelihood ratio..: 121.820496
Test statistic.....: 119.359222
P-value.....: < 0.00000000000000001

12.Location IDs included.: 355120, 353880, 410470
Coordinates.....: (-23.2721,-49.4763)
Semiminor axis.....: 0.074
Semimajor axis.....: 0.29
Angle (degrees).....: 60.00
Shape.....: 4.00
Time frame.....: 2002/1/1 to 2003/12/31
Population.....: 46644
Number of cases.....: 75
Expected cases.....: 10.74
Annual cases / 100000.: 81.8
Observed / expected...: 6.98
Relative risk.....: 6.99
Log likelihood ratio..: 81.521507
Test statistic.....: 65.217206
P-value.....: < 0.00000000000000001

13.Location IDs included.: 410800, 410280
Coordinates.....: (-22.8623,-51.3882)
Semiminor axis.....: 0.080
Semimajor axis.....: 0.24
Angle (degrees).....: -60.00
Shape.....: 3.00
Time frame.....: 2001/1/1 to 2002/12/31
Population.....: 26916
Number of cases.....: 57
Expected cases.....: 6.38
Annual cases / 100000.: 104.7
Observed / expected...: 8.94
Relative risk.....: 8.94

Log likelihood ratio..: 74.235028
Test statistic.....: 64.289420
P-value.....: < 0.00000000000000001

14.Location IDs included.: 420240
Coordinates.....: (-26.9155,-49.0709)
Semiminor axis.....: 0
Semimajor axis.....: 0
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2006/1/1 to 2006/12/31
Population.....: 306872
Number of cases.....: 107
Expected cases.....: 34.79
Annual cases / 100000.: 36.0
Observed / expected...: 3.08
Relative risk.....: 3.08
Log likelihood ratio..: 48.017940
Test statistic.....: 48.017940
P-value.....: 0.000000000000089

15.Location IDs included.: 330590, 330460, 330530, 330480
Coordinates.....: (-22.0638,-42.0643)
Semiminor axis.....: 0.15
Semimajor axis.....: 0.58
Angle (degrees).....: 45.00
Shape.....: 4.00
Time frame.....: 2005/1/1 to 2006/12/31
Population.....: 67095
Number of cases.....: 72
Expected cases.....: 15.65
Annual cases / 100000.: 53.9
Observed / expected...: 4.60
Relative risk.....: 4.60
Log likelihood ratio..: 53.534909
Test statistic.....: 42.827927
P-value.....: 0.0000000000083

16.Location IDs included.: 315480
Coordinates.....: (-20.0876,-43.7878)
Semiminor axis.....: 0
Semimajor axis.....: 0
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2006/1/1 to 2017/12/31
Population.....: 8834
Number of cases.....: 58
Expected cases.....: 12.98
Annual cases / 100000.: 52.3
Observed / expected...: 4.47

Relative risk.....: 4.47
Log likelihood ratio..: 41.807699
Test statistic.....: 41.807699
P-value.....: 0.000000000020

17.Location IDs included.: 313880, 310510, 312320, 314050, 312340, 311980, 313030, 316820,
310020
Coordinates.....: (-19.7911,-45.6794)
Semiminor axis.....: 0.23
Semimajor axis.....: 1.13
Angle (degrees).....: 36.00
Shape.....: 5.00
Time frame.....: 2014/1/1 to 2015/12/31
Population.....: 105020
Number of cases.....: 87
Expected cases.....: 25.26
Annual cases / 100000.: 40.3
Observed / expected...: 3.44
Relative risk.....: 3.45
Log likelihood ratio..: 45.863223
Test statistic.....: 34.184428
P-value.....: 0.000000016

18.Location IDs included.: 311760, 315140, 314580
Coordinates.....: (-19.7456,-44.8945)
Semiminor axis.....: 0.091
Semimajor axis.....: 0.091
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2002/1/1 to 2005/12/31
Population.....: 33449
Number of cases.....: 53
Expected cases.....: 14.65
Annual cases / 100000.: 42.4
Observed / expected...: 3.62
Relative risk.....: 3.62
Log likelihood ratio..: 29.797115
Test statistic.....: 29.797115
P-value.....: 0.00000075

19.Location IDs included.: 353930
Coordinates.....: (-21.996,-47.4257)
Semiminor axis.....: 0
Semimajor axis.....: 0
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2001/1/1 to 2005/12/31
Population.....: 70832
Number of cases.....: 96

Expected cases.....: 39.69
Annual cases / 100000.: 28.3
Observed / expected...: 2.42
Relative risk.....: 2.42
Log likelihood ratio..: 28.486883
Test statistic.....: 28.486883
P-value.....: 0.0000023

20.Location IDs included.: 311360
Coordinates.....: (-22.0424,-45.696)
Semiminor axis.....: 0
Semimajor axis.....: 0
Angle (degrees).....: 0
Shape.....: 1.00
Time frame.....: 2001/1/1 to 2002/12/31
Population.....: 6271
Number of cases.....: 17
Expected cases.....: 1.37
Annual cases / 100000.: 145.1
Observed / expected...: 12.39
Relative risk.....: 12.39
Log likelihood ratio..: 27.157414
Test statistic.....: 27.157414
P-value.....: 0.0000075

21.Location IDs included.: 330260, 330010
Coordinates.....: (-22.9594,-44.0409)
Semiminor axis.....: 0.19
Semimajor axis.....: 0.29
Angle (degrees).....: 90.00
Shape.....: 1.50
Time frame.....: 2001/1/1 to 2004/12/31
Population.....: 195255
Number of cases.....: 130
Expected cases.....: 73.10
Annual cases / 100000.: 20.8
Observed / expected...: 1.78
Relative risk.....: 1.78
Log likelihood ratio..: 17.949910
Test statistic.....: 17.587248
P-value.....: 0.033

Supplementary Material – Chapter 2

Table S1- Model selection results for random effect

Models	**Random**	**DIC**	**WAIC**
MODEL1	No random effect	63827	63840
MODEL2	besag	54107	54174
MODEL3	bym	54091	54158
MODEL4	bym+idtime	53586	53657
MODEL5	bym+idtime+rw1	53582	53652
MODEL6	bym+idtime+rw1+id.area:id.time	53389	53494
MODEL7	bym+idtime+rw1+id.area:rw1	51750	51836

Figure S1- Cutaneous Leishmaniasis relative risk per year in the municipalities of the Brazilian Amazon Forest estimated by the model.

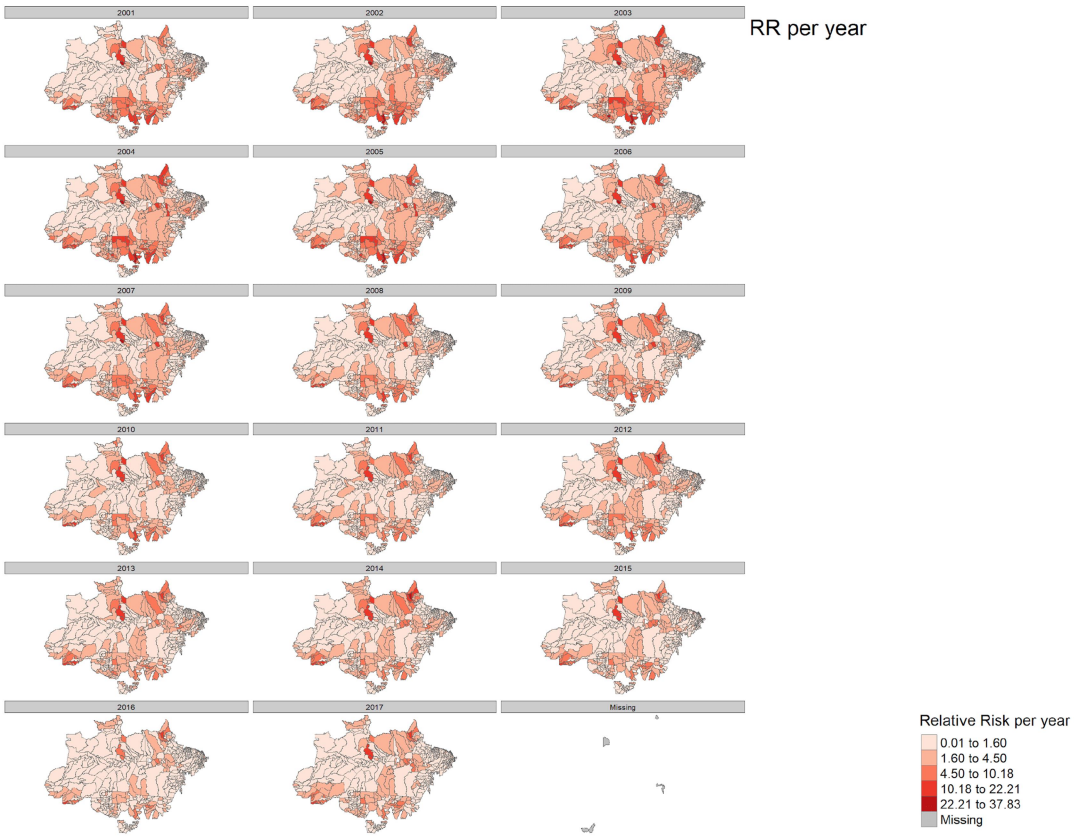

Figure S2- Total number of Cutaneous Leishmaniasis cases per year in the municipalities of Brazilian Amazon.

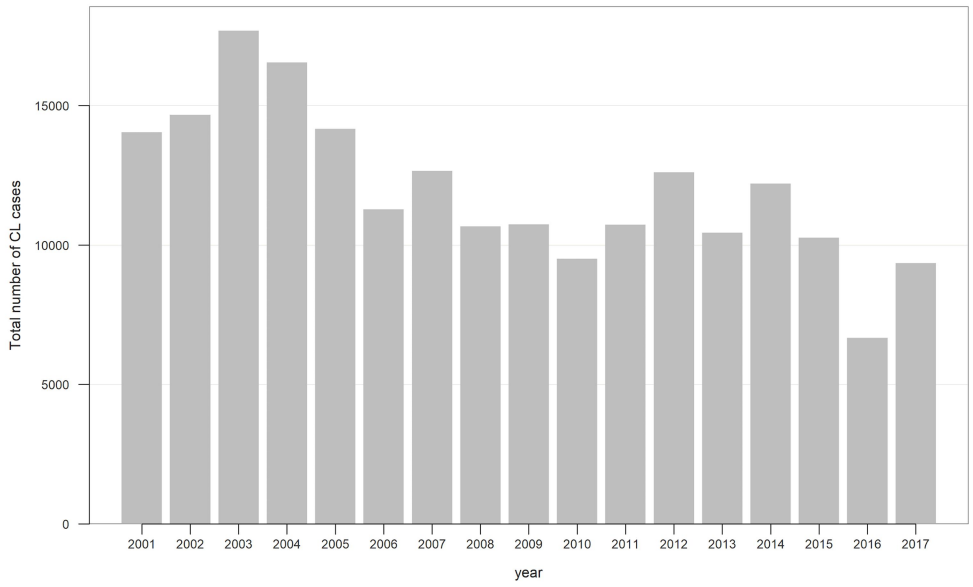

Figure S3- Spatial distribution of land cover and land use covariates in the municipalities of the Brazilian amazon Forest, 2002-2017.

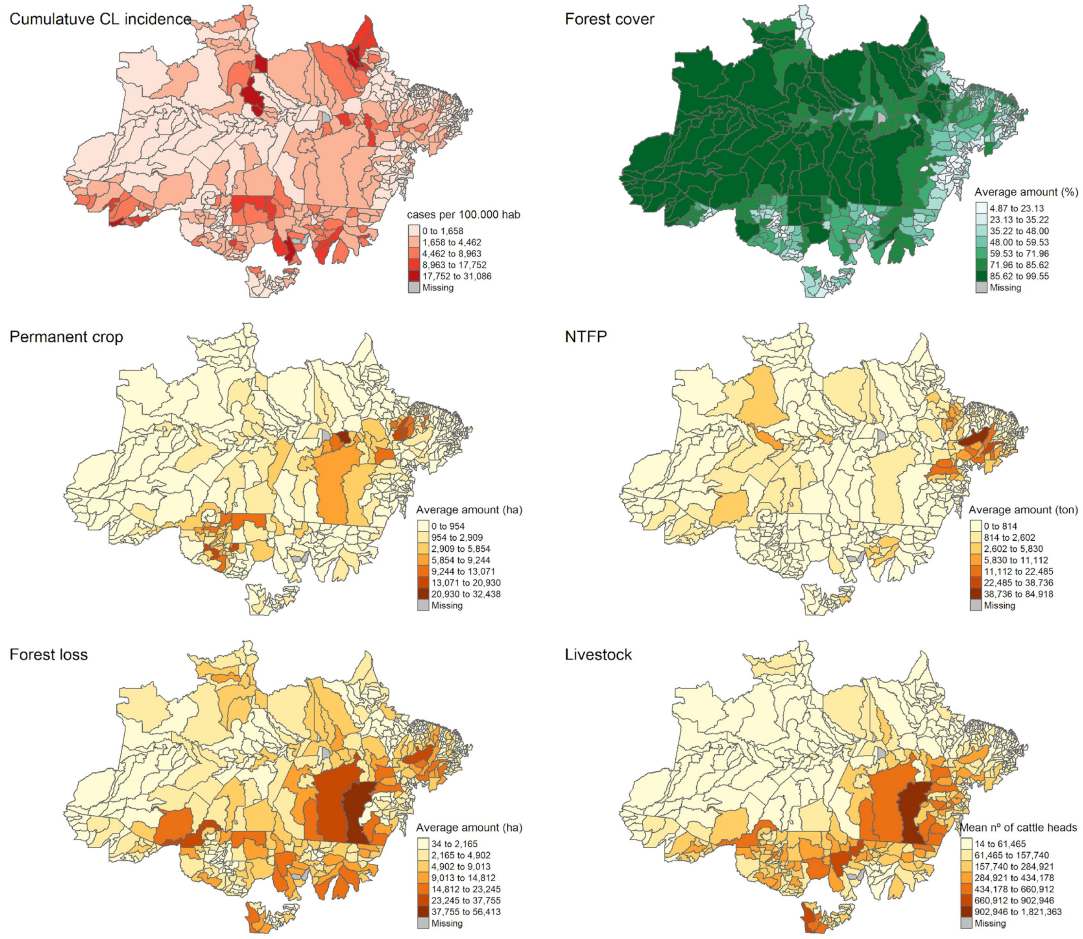

Figure S4- Temporal distribution of covariates in the municipalities of the Brazilian Amazon Forest, 2001-2017

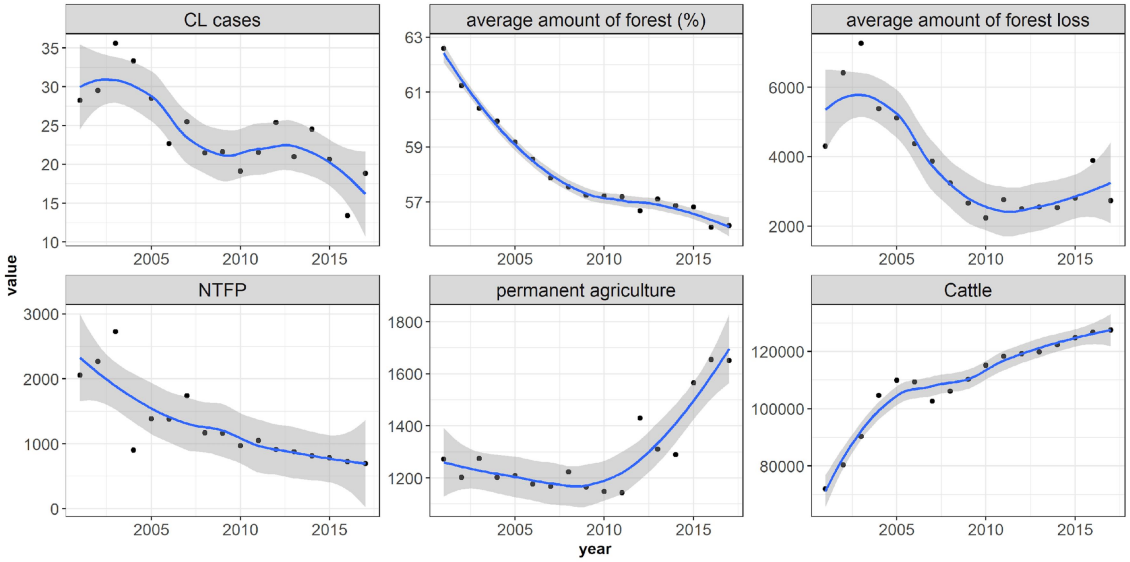

Figure S5 – Scatterplot with the number of observed and predict risk values (above) and distribution of PIT (probability integral transformation) values.

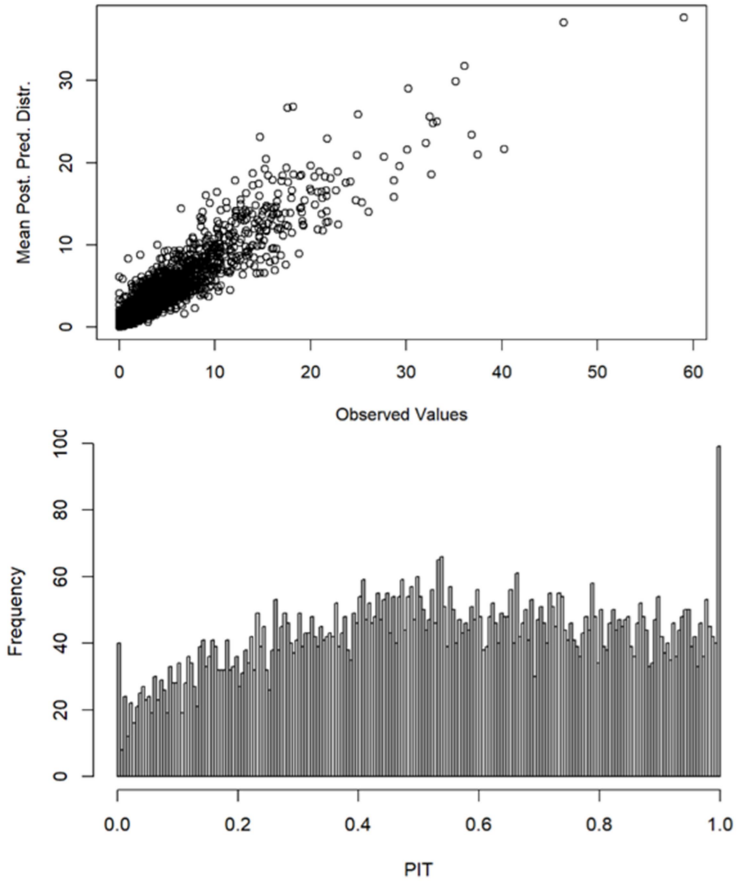

Table S2 – Variation Inflation Factor results

Variable	**VIF**
Temperature	1.19
Precipitation	1.55
Forest	1.67
GINI	1.16
Permanent Crop	1.36
Deforestation	1.71
NTFP	1.15
Cattle	2.29

Figure S6 – Pearson correlation result among the model covariates

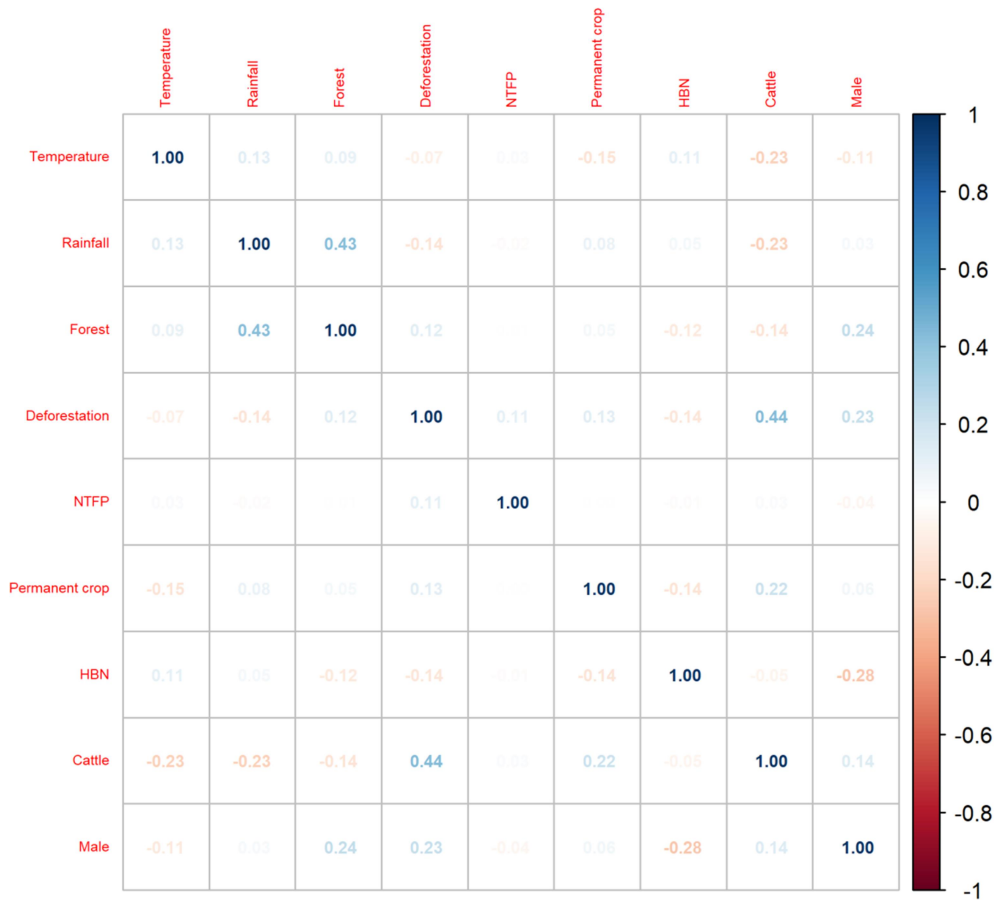

Table S3- Parameters estimates for the covariates and random effects of spatiotemporal model.

Variable	Regression Coefficient		Relative Risk	IC (95%)
	Mean	±SD		
Fixed Effects				
Forest	0,19	0,03	1,21	(1,15-1,27)
Deforestation	0,06	0,01	1,06	(1,03-1,09)
Permanent crop	0,03	0,02	1,03	(0,99-1,07)
NTFP	0	0,02	1	(0,97-1,03)
Cattle	0,17	0,02	1,19	(1,13-1,25)
Forest:Cattle	0,06	0,02	1,06	(1,01-1,1)
Forest:Permanent crop	-0,02	0,02	0,98	(0,95-1,02)
Temperature	-0,1	0,02	0,9	(0,86-0,94)
Rainfall	-0,08	0,01	0,92	(0,9-0,95)
HBN	-0,07	0,03	0,94	(0,89-0,98)
Male	0,19	0,02	1,21	(1,16-1,26)
Random Effects				

Spatial heterogeneity (IID, spatially unstructured)	0.0003	0.0001		
Spatial heterogeneity (CAR, spatially structured)	0.15	0.03		
Temporal heterogeneity (IID, temporally unstructured)	0.02	0.01		
Temporal heterogeneity (RW1,temporally structured)	0.002	0.003		
Space-time interaction term (IID:RW1)	0.12	0.008		

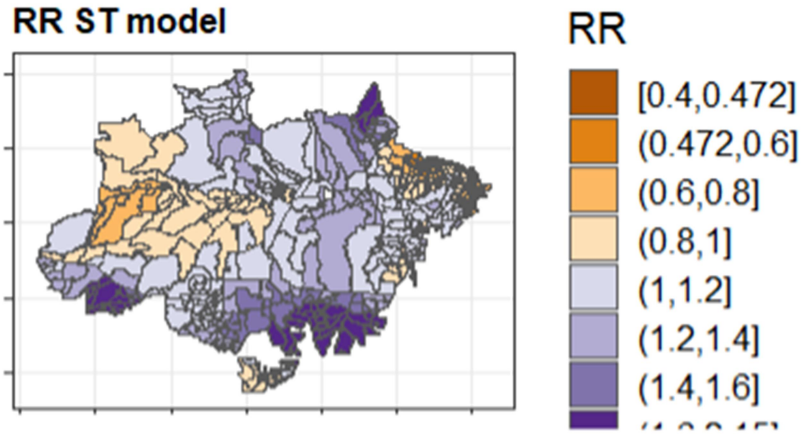

Figure S7 – Posterior mean of the residual spatial relative risk for the Cutaneous Leishmaniasis in the Brazilian Amazon using the Bayesian spatiotemporal model