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Environmental and socioeconomic risk factors for visceral and cutaneous leishmaniasis in São Paulo, Brazil

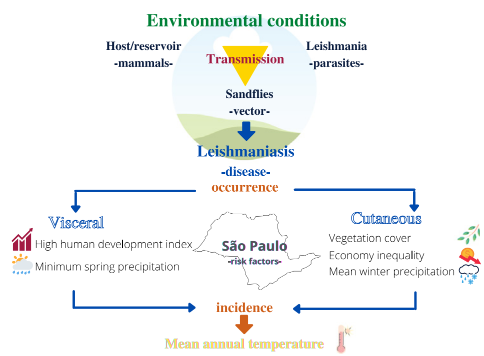
Nerida Nadia H. Valero [a,*], Paula Prist [c], María Uriarte [b]

[a] Departamento de Ecologia, Instituto de Biociências, 321 Rua do Matão, Travessa 14, Cidade Universitária, Universidade de São Paulo, São Paulo, SP CEP 05508090, Brazil
[b] Department of Ecology, Evolution & Environmental Biology, Columbia University, 1200 Amsterdam Ave., New York, NY 10027, United States
[c] EcoHealth Alliance, 520 Eighth Avenue, Ste. 1200, New York, NY 10018, United States of America

HIGHLIGHTS

- Environmental and socioeconomic risk factors for visceral (VL) and cutaneous (CL) leishmaniasis were analyzed.
- Vegetation, socioeconomic factors and climate affect the occurrence and incidence of VL and CL.
- CL occurrence is driven by vegetation cover and economic inequality while VL occurrence by human development.
- Temperature increases both CL and VL incidence.
- Influence of climate change may increase the risk of leishmaniasis in tropical areas.

GRAPHICAL ABSTRACT



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ABSTRACT

Leishmaniasis is a vector-borne disease caused by the protozoan *Leishmania* spp. mainly affecting individuals of low socioeconomic status. In tropical regions the transmission risk to humans depends not only on environmental factors, such as vegetation cover and climate, but also on the socioeconomic characteristics of human populations. However, the relative contribution of these factors to disease risk and incidence is not well understood. Yet this information is critical for the development of epidemiological surveillance schemes and control practices. Leishmaniasis cases have increased in São Paulo state, Brazil over recent years but the underlying risk factors for transmission remain understudied. Here, we use generalized linear mixed models to quantify the association between occurrence and incidence (number of cases) of cutaneous (CL) and visceral (VL) leishmaniasis from 1998 to 2015, and landscape (native vegetation cover), climate (seasonal and interannual variation in precipitation and temperature) and socioeconomic factors (population, number of cattle heads, Human Development Index - HDI, Gini inequality index and income per capita) across the 645 municipalities of São Paulo state, Brazil. For CL, probability of occurrence was greater in municipalities with high native vegetation cover and economic inequality and in years with greater average winter precipitation. For VL, probability of occurrence was greater in years with high minimum spring precipitation and maximum annual temperatures, and in municipalities with larger HDI values and a greater number of cattle heads. The number of VL cases increased during years with high mean fall precipitation and, for both CL and VL the number of cases was greater in years of high annual mean temperature. Understanding how these risk factors influence spatial and temporal variation in the risk and incidence of leishmaniasis can contribute to the development of effective public health policies and interventions.

* Corresponding author.
E-mail address: neridanadia@gmail.com (N.N.H. Valero).

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1. Introduction

Over the past few decades tropical landscapes have been drastically transformed, and over half of the potential forest areas have been converted to agriculture, cattle pastures, and urban development (DeFries and Rosenzweig, 2010; DeFries et al., 2010). Since landscape characteristics influence the biology of disease vectors and their reservoirs (Rodríguez-Morales, 2013), these transformations can alter the distribution and incidence of vector-borne diseases (Reisen, 2010). Loss and fragmentation of natural habitats, for example, may concentrate animal populations in small areas, leading to disease outbreaks or spillovers to adjacent habitats (Brearley et al., 2012). At the same time, the expansion of human settlements near disease reservoirs natural habitats (e.g., forests) can increase frequency of contact between humans and pathogens and consequently disease incidence (de Coster et al., 2014). Since the effects of landscape modification are likely to depend on the ecology of the disease, predicting and managing disease risk for human populations will require a clearer understanding of the relationship between environmental conditions and disease risk (Myers et al., 2014).

One neglected tropical disease affected by environmental characteristics is leishmaniasis. This disease is caused by protozoans of the *Leishmania* genus. In the Americas, female phlebotomine sand flies, mainly of the *Lutzomyia* genus, transmit the parasites to mammalian reservoirs (World Health Organization, 2010). There are two main clinical forms: visceral leishmaniasis (VL) is lethal without treatment, while cutaneous leishmaniasis (CL) causes skin and mucosal ulcerative lesions but does not cause mortality (Dantas-Torres et al., 2012). In the world, the estimated annual number of cases ranges from 0.2 to 0.4 million cases of VL and 0.7 to 1.2 million cases of CL, and is responsible for more than 30,000 deaths each year (World Health Organization Control Team et al., 2012; Ruiz-Postigo et al., 2020).

Human landscape modifications in tropical regions have resulted in increased contact between humans and *Leishmania* vectors (de Santana Martins, 2015). The development and expansion of human populations have led to the proliferation of the disease in settlements close to forests, where conditions are suitable for the development of phlebotomine sand flies (Casanova et al., 2013). Rural-urban migration and expansion of human settlements in peri-urban areas have also increased contact between vectors and both humans and domestic animals. The interconnection between human settlements contributes to the life cycle and dispersion of leishmaniasis vector (Thomaz-Soccol et al., 2018). As a result, sand flies have adapted the transmission cycle to urban environments where rather than depend on reservoirs restricted to areas with dense vegetation, they rely on domestic animals (Vianna et al., 2016).

The transmission cycle of CL leishmaniasis in Neotropical regions, is still maintained in areas with dense vegetation (i.e., forest or vegetation surrounding rural and peri-urban areas) because the vector species of the *Leishmania* responsible for the cutaneous form and their reservoirs are more restricted to natural environments and depend on vegetation (Kariyawasam et al., 2015). For VL, *Leishmania infantum,* the main parasite is transmitted by a synanthropic vector, *Lutzomyia longipalpis* and has the domestic dog (*Canis familiaris*) as the main reservoir, consequently affecting urban and peri-urban human populations (Pace, 2014).

Climate is also an important determinant of the distribution of vectors and pathogens. Temperature, precipitation and relative humidity affect the reproduction, development, behavior and population dynamics of vector-borne diseases such as leishmaniasis (Carvalho et al., 2016). How climate conditions influence leishmaniasis occurrence depend on each vector species, which responds to different climate variables. In general, sand flies need warm temperatures and sustained precipitation to maintain favorable humid conditions (Desjeux, 2001). Too much precipitation can kill them while drought prevents larval development (Ready, 2013). Neotropical sand flies are generally present year around. Their abundance, however, depend on climate seasonality, especially in regions with defined wet-dry and hot-cold seasons because sand flies exhibit diapause in the first instars (i.e., larvae and pupae) to survive until climate conditions for emergence are favorable (Pinheiro et al., 2016). However, suitable temperature and precipitation conditions vary for each sand fly species and according to its geographical distribution. Understanding the effects of climate factors on the epidemiology of leishmaniasis is needed to predict disease risk under a changing climate (World Health Organization, 2010).

Socioeconomic conditions also influence leishmaniasis risk (Alvar et al., 2006). Poverty is usually associated not only with decreased access to health services but also with housing and working conditions that facilitate transmission (Houweling et al., 2016). Populations located in rural and peri-urban areas in tropical regions often settle near vegetation areas, where the transmission cycle of leishmaniasis can be completed. In these areas, housing is constructed of low-quality materials, like straw, mud, or bamboo, which can shelter sandflies and favor leishmaniasis transmission (Argaw et al., 2013). Lack of sewage and garbage collection services, leading to accumulation of waste can also attract potential reservoirs (e.g., domestic mammals) and provide the humidity necessary for vector breeding sites (Machado-Coelho et al., 1999). Agriculture and livestock husbandry can increase risk in rural regions because these activities expose human to sand flies bites and the presence of cattle attract sand flies looking for blood meal (Chaves, 2011).

In this study we analyze the environmental and socioeconomic factors associated with the incidence of leishmaniasis between 1998 and 2015 in the state of São Paulo, Brazil. Brazil has the largest number of leishmaniasis cases in the Americas, with an estimated annual incidence of 4200 to 6300 cases of visceral and 72,800 to 119,600 cases of cutaneous leishmaniasis (World Health Organization Control Team et al., 2012; Graepp-Fontoura et al., 2020). Although São Paulo accounts ~1% of cases (Da Saúde, 2012), understanding the dynamics of leishmaniasis in the state is important because marked climate seasonality coupled with the loss of natural vegetation, agricultural expansion, and urbanization portend changes that are likely to occur in other developing tropical regions within and outside Brazil (Klink and Machado, 2005). We examine the influence of landscape, socioeconomic, and climate factors on probability of occurrence and number of cases of cutaneous and visceral leishmaniasis. We hypothesize that:

a. The occurrence and number of cases of CL, but not of VL, will be higher in municipalities with high vegetation cover, since the vectors and reservoirs of CL are dependent of natural vegetation.

b. The occurrence and number of cases of both clinical forms will increase in municipalities with (a) low socioeconomic conditions and with large at-risk populations or (b)warm temperatures and high precipitation.

2. Material and methods

2.1. Study area

São Paulo state is located in the southeast region of Brazil, has an area of ~248,210 km^2, a population of ~45,5 million (21.8% of Brazil's population) (IBGE https://cidades.ibge.gov.br/brasil/sp/panorama, Access date: 30 April 2018), and is divided into 645 municipalities. The state accounts for 33.5% of national GDP and 22% of the country's population (http://www.imp.seade.gov.br, Access date: 20 March 2019). At present, only 19.28% of the state is covered with remnants of native vegetation (BSDF, 2020), which include two biomes, the Cerrado and the Atlantic forest. The Cerrado originally covered 34% of the state, but only 11% of its area remains (MMA, 2015) while the Atlantic forest covered ~65%, and is now reduced to 23.9% of the state and is highly fragmented (Fundação SOS Mata Atlântica/INPE, 2019). Sugar cane, Eucalyptus plantations and cattle pastures are the dominant agricultural land uses, accounting for ~39% of the state's area (Farinaci and Batistella, 2012).

2.2. Data

2.2.1. Disease incidence

We obtained the number of CL and VL cases reported, according to the place of infection, between 1998 and 2015 for the 645 municipalities from the Center for Epidemiological Surveillance of the State of São Paulo (http://www.saude.sp.gov.br, Access date: 22 March 2017). Leishmaniasis is a disease that requires mandatory notification in Brazil and is reported and confirmed by laboratory analysis in each hospital.

2.2.2. Landscape data

We calculated total native vegetation cover area by aggregating forest and Cerrado using data from the forest inventory maps of 2000 and 2010 obtained from the Forest Institute of the State of São Paulo (http://www.iflorestal.sp.gov.br, Access date: 23 March 2017). These maps were generated at a 1:50.000 scale, with a minimum mapped area of 2.5 ha, a resolution that allows the identification of small native vegetation areas but not differentiate between the types of vegetation (i.e., primary, secondary forest, etc.). Every native vegetation fragment larger than 2.5 ha was identified, mapped and the calculation of total amount of native vegetation of each municipality. We used the 2000 map to analyze data cases from 1998 to 2006 and the 2010 map for cases between 2007 and 2015 (Supplementary material 1), extracting total native vegetation cover for each municipality.

2.2.3. Socioeconomic data

Since there are specific populations groups that are at risk for leishmaniasis, we considered not only total population but also rural population size and the number of agricultural workers in each population and because both populations are exposed to vegetated areas and also have low socioeconomic status. Municipality-level data for rural and urban population sizes were obtained from the State System of Data Analysis (SEADE http://www.imp.seade.gov.br, Access date: 24 March 2017). The number of agricultural workers was available for 1996 and 2006 and was obtained from Brazilian Institute of Geography and Statistics (IBGE http://www.ibge.gov.br, Access date: 24 March 2017). We used the numbers of agricultural workers from 1999 to analyze disease data from 1998 to 2001 and data from 2006 for disease data from 2002 until 2015. The number of cattle heads per year in each municipality was obtained from the Institute of Agricultural Economics (http://www.iea.agricultura.sp.gov.br, Access date: 24 March 2017).

We included three socioeconomic indicators of human wellbeing. Income per capita is a metric of economic wellbeing; the Gini coefficient captures income inequality and the Human Development Index (HDI) is a composite of three elements: standard of living, life expectancy, and literacy level. Municipality scale average income per capita data were obtained from SEADE while data for the Gini index and HDI were obtained from IBGE. We used HDI information available for 2000 to analyze disease data from 1998 to 2006, and data from 2010 for disease data from 2007 to 2015. We used Gini information available for 2003 and average income per capita data for 2010 to analyze the entire period.

2.2.4. Climate

Climate in the state of São Paulo varies by region. The north and northeast are seasonal, with a wet and warm summer and a dry and cold winter (average temperatures >20°; rainfall >1.200 mm/year) (De Freitas, 2011). In contrast, rainfall in the south and coastal zones is distributed more regularly throughout the year (average temperatures >20°; rainfall ~2.000 mm/year), without a defined dry season (De Freitas, 2011; Peel et al., 2007).

Monthly temperature and precipitation data were obtained from the International Research Institute for Climate and Society of Columbia University (http://iridl.ldeo.columbia.edu, Access date: April 6 2017). Temperature data were derived from the global monthly land surface air temperature data set (ts) at 0.5 °C of National Centers for Environmental Prediction (NOAA NCEP) (Fan and van den Dool, 2008) and for precipitation from Climate Hazards Group Infrared Precipitation with Stations (CHIRPS) with a spatial resolution of 0.05° (Funk et al., 2014). These data were extracted for each month of each year analyzed (1998 to 2015) for each municipality. Because the state presents marked rainfall and temperature seasonality that can influence the abundance of leishmaniasis vectors and therefore, disease incidence, we calculated mean, minimum and maximum temperature and precipitation for each year and each season (spring, summer, Fall and winter). Because each vector responds to different climate variables, we also evaluated the predictive value of several annual or seasonal precipitation and temperature conditions on disease incidence. Details of range of annual and seasonal climate values and maps are provided in Supplementary material 2.

2.3. Statistical analysis

Leishmaniasis cases vary across years in our study period (1998-2015) and across municipalities (Supplementary material 3). To assess the influence of the aforementioned landscape, climate, and socioeconomic variables (Table 1) on CL and VL occurrence and incidence, we fitted generalized linear mixed models. For probability of occurrence, we assumed binomial errors and used a logistic regression model. The distribution of the number of cases was markedly overdispersed, so we used a negative binomial distribution. This two-part approach allowed us to separately examine the factors influencing the probability of occurrence of leishmaniasis from those related to the number of cases. All the models included socio-economic, landscape and climate factors as fixed covariates (Table 1) with year and municipality as random effects. The random effects account for any variability among municipalities and years that are not captured by the fixed covariates. All continuous predictor variables were centered and standardized to facilitate model convergence (Gelman and Hill, 2007). To avoid collinearity, we verified that the Pearson's correlation coefficient among all the variables in the models was $r < 0.4$ and the VIF (variance inflation factor) of the model was <5.

Model selection was performed using Akaike information criterion (AIC) to select the best model within those one with the lowest AIC for both occurrence and number of cases. We used results of the final models to calculate odds-ratios (OR) occurrence and incidence rate ratio (IRR) for number of cases. Model residuals (all four models) from CL and VL cases and CL and VL occurrence were tested for spatial autocorrelation by calculating Moran's *I* from “spdep” R package (Bivand and Wong, 2018). For this analysis, we used the spatial contiguity matrix based on the Queen's case neighborhood relation and treated each year, from 1998 to 2015, separately. This test is commonly used and accepted as a fair evaluation of spatial autocorrelation and dependence especially in disease studies (Fortin et al., 2016; Tsai, 2012). Only the visceral leishmaniasis occurrence model showed spatial autocorrelation, with an aggregated pattern of dispersion so for these data, we fitted a generalized lineal mixed model with spatial autocorrelation using the “spamm” package (Rousset and Ferdy, 2014). All analyses were conducted in R statistical software packages ‘lme4’ for logistic regression (Bates et al., 2014) and ‘glmmADMB’ for the negative binomial model (Skaug et al., 2018). OR and IRR values were calculated using ‘sjPlot’ (Lüdecke, 2020).

3. Results

3.1. Spatiotemporal distribution of visceral and cutaneous leishmaniasis

Between 1998 and 2015, São Paulo had a total of 5583 cases (cumulative incidence of 15.54 per 100,000 inhab.) of cutaneous leishmaniasis and 2574 cases (cumulative incidence 7.08 per 100,000 inhab.) of visceral leishmaniasis. The municipalities of Itariri, Iporanga, Pedro Toledo,

Table 1
Predictor variables. Variables considered in the mix models and their influence on the disease.

Type	Predictor variable	Influence on the disease	Source
Landscape	Total area of native vegetation	Vegetation surrounding an area increases the incidence of leishmaniasis.	http://www.iflorestal.sp.gov.br
Socioeconomic	Total population	Population at risk	http://www.imp.seade.gov.br
	Agricultural workers/ rural population/urban	At risk population group exposed to disease	http://www.ibge.gov.br
	Human Development Index (HDI)	Low HDI, high GINI, low income are predictors of poverty that are associated with disease vulnerability	http://www.ibge.gov.br
	Inequality index (GINI)		http://www.ibge.gov.br
	Income per capita		http://www.imp.seade.gov.br
	Heads of cattle	Cattle could serve as blood-meal source for sand flies	http://www.iea.agricultura.sp.gov.br
Climate	Mean, maximum and minimum temperature and precipitation by year and season at municipality scale	Seasonality of precipitation and temperature influence larval development of sand fly vectors	http://iridl.ldeo.columbia.edu

Eldorado, Ribeira and Ubatuba had the greatest cumulative incidence of CL (range from 16.93 to 31.02 cases per 1000 inhab.) and the municipalities of Ouro Verde, Dracena, Flórida Paulista, Panorama and Nova Guataporanga for VL (range from 3.34 to 4.05 cases per 1000 inhab). Cutaneous leishmaniasis cases were distributed throughout the state but were more common in the southeast part while cases of visceral leishmaniasis were aggregated in the northwest region of the state (Supplementary material 3).

Temporal variation in the number of cases was greater for CL than for VL. The total annual number of CL cases over the study period ranged from a low of 66 cases in 1998 to a maximum of 925 in 2003, peaking between 2002 and 2004, and leveling off to an average number of 260 cases between 2005 and 2015 (Fig. 1A). For VL, the minimum number of cases occurred in 2000 with only 16 cases recorded and then increased steadily reaching a maximum of 294 cases in 2008 and then leveling off to an average number of 169 cases per year and increasing again in 2012 with 206 cases (Fig. 1B).

3.2. Predictors of cutaneous leishmaniasis

3.2.1. Occurrence model

Landscape, climate, and socioeconomic factors influenced the probability of CL occurrence in the state. Native vegetation cover (OR = 1.35, 95% CI = 1.2–1.52), Gini index (OR = 1.92, 95% CI = 1.68-2.19) and average winter precipitation had positive effects on the CL occurrence (OR = 1.23, 95% CI = 1.09–1.39), while maximum spring temperature had a negative association (OR = 0.68, 95% CI = 0.62 -0.74). This means that municipalities with a high amount of native vegetation and high winter precipitations and low spring temperatures are at greater risk for CL occurrence (from 62 to 90%) during the study period (Fig. 2.1 and Table 2, Supplementary material 4, S5 and S6).

3.2.2. Number of cases

Municipalities with higher average annual temperatures (IRR = 1.37, 95% CI = 1.26-1.50) and a larger number of agriculture workers (IRR = 0.85, 95% CI = 0.77-0.93) had a greater number of CL cases. Municipalities with high Fall precipitation (IRR = 0.86, 95% CI = 0.80-0.93) and with a high per capita income (IRR = 0.36, 95% CI = 0.32-0.40) had a lower number of cases during the study period. The Southeast of the state had the higher probability of CL incidence (Fig. 2.2 and Table 2, Supplementary material 4, S5 and S6).

3.3. Predictors of visceral leishmaniasis

3.3.1. Occurrence model

Probability of VL occurrence during the study period was higher in municipalities with a large number of cattle (OR = 1.85, 95% CI = 1.26-2.71) and a high human development index (HDI) (OR = 2.64, 95% CI = 1.55-4.49). VL occurrence was also higher in municipalities

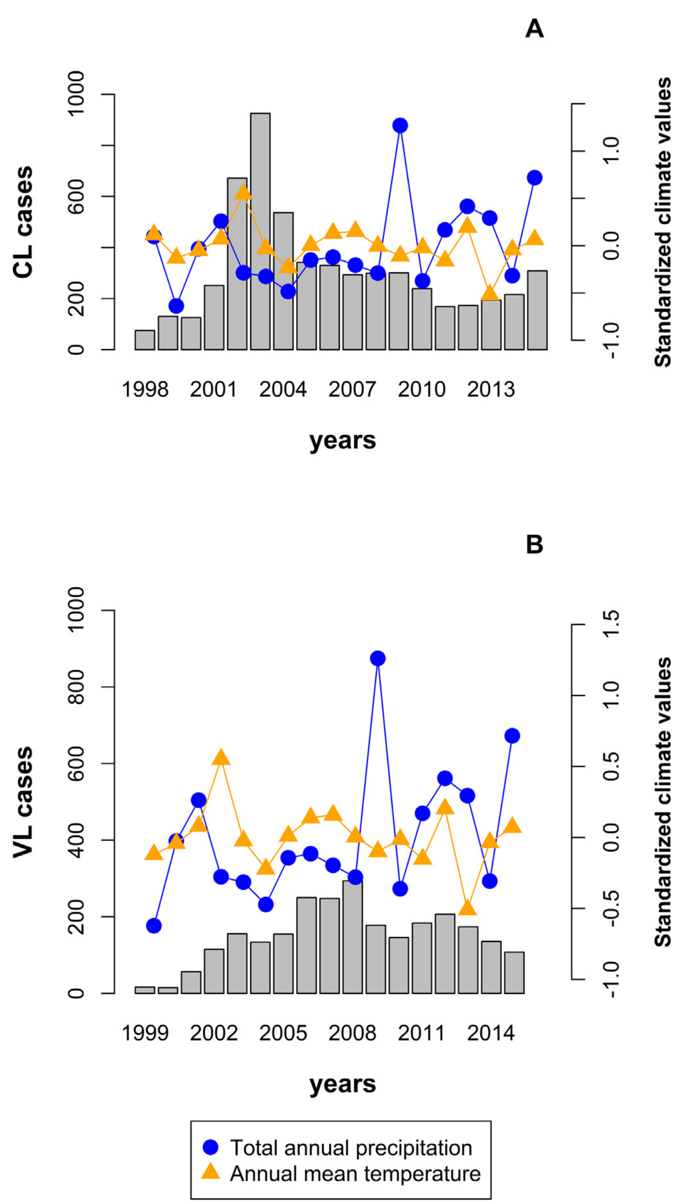

Fig. 1. Leishmaniasis cases and inter-annual mean temperature and total precipitation variability in the state of São Paulo (1998–2015). Grey bars show number of cases of CL (A) and VL (B). Precipitation and temperature were standardized by centering each variable on its mean and divided by its standard deviation.

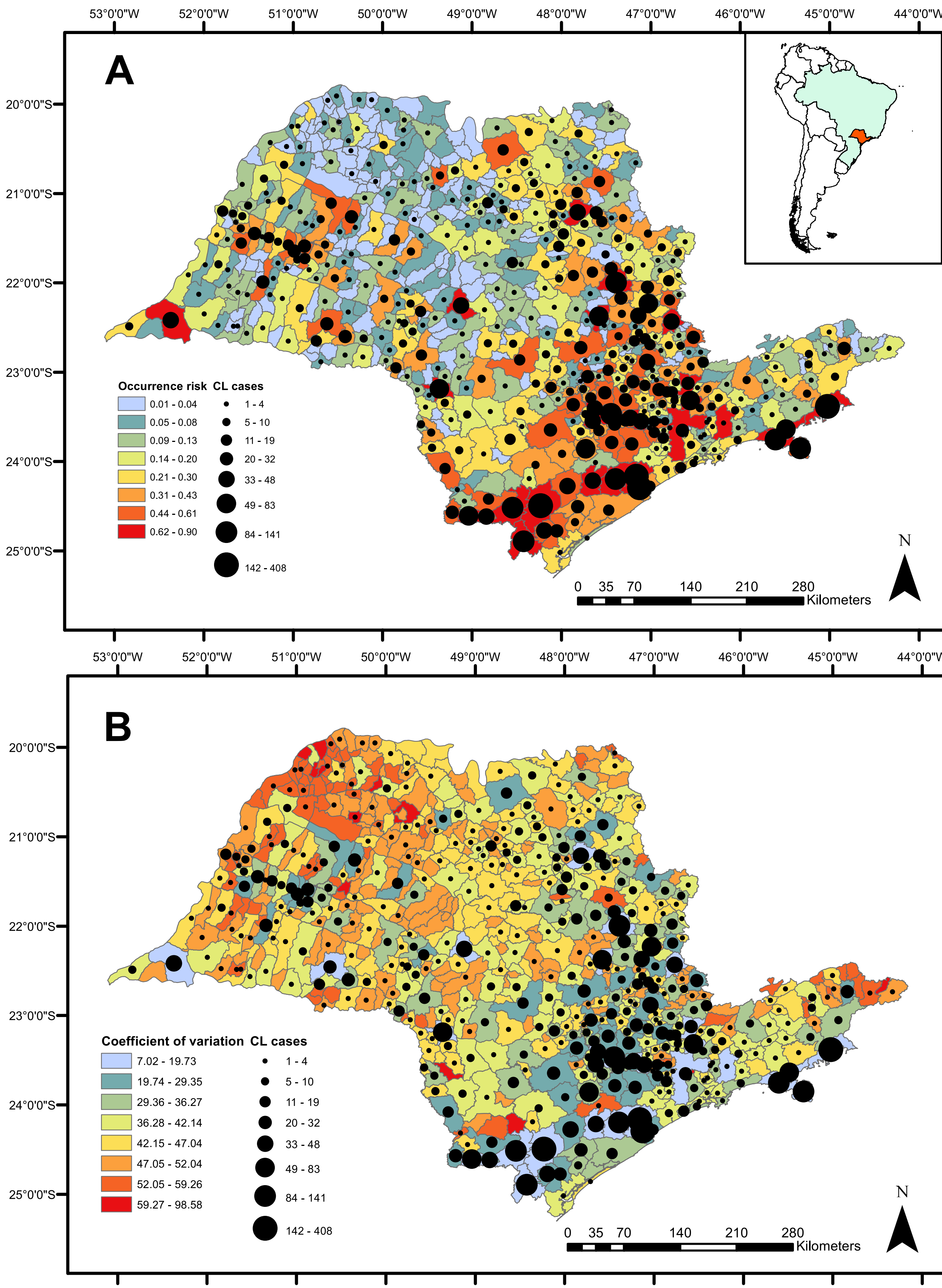

Fig. 2.1. Risk Map of probability occurrence of cutaneous leishmaniasis (0-1) (A) and coefficient of variation (B) across municipalities. Black dots depict number of reported cases between 1998 and 2015.

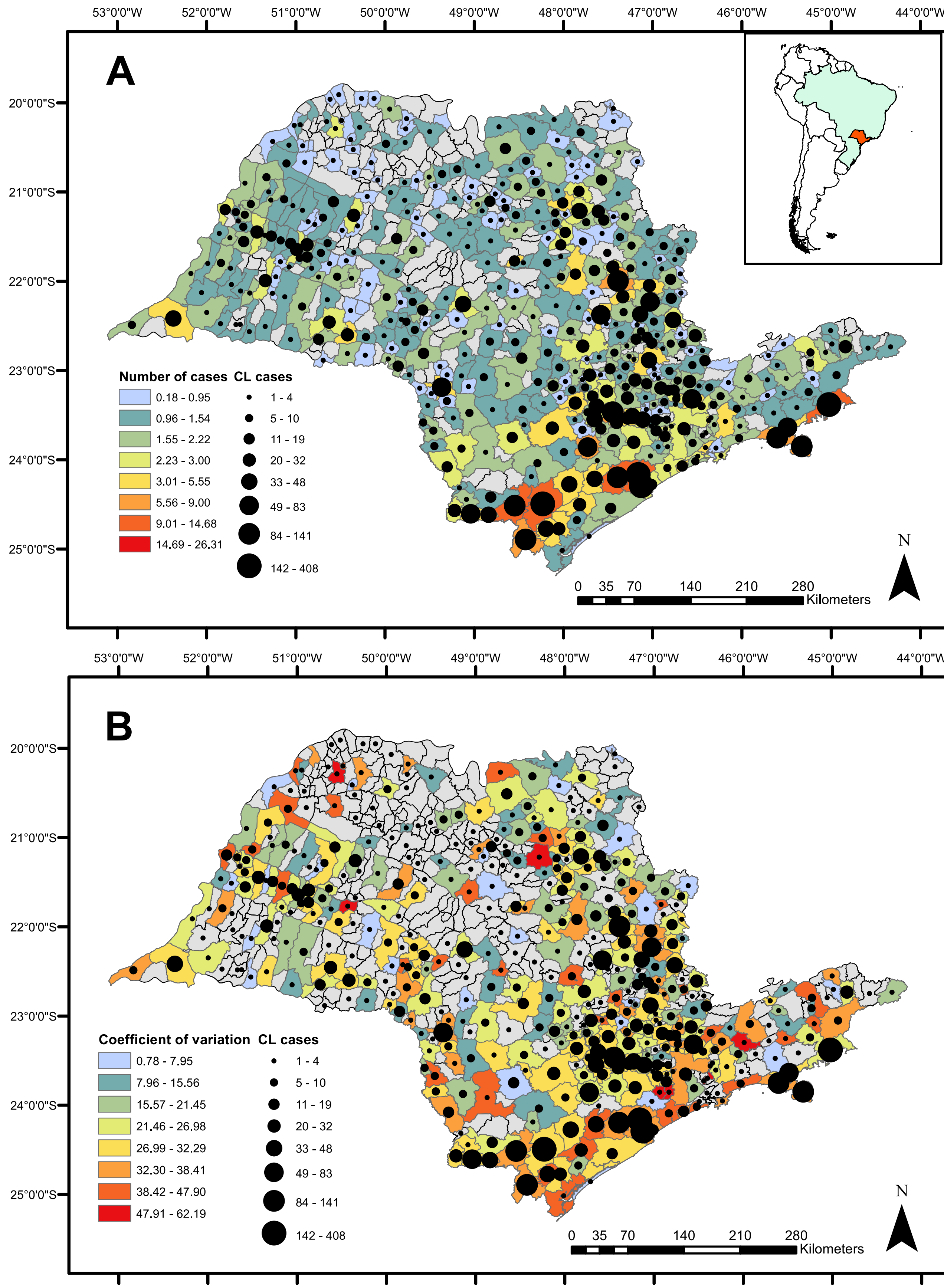

Fig. 2.2. Risk map of probability of number of cutaneous leishmaniasis cases (A) and coefficient of variation (B) across municipalities. Black dots depict number of reported cases between 1998 and 2015.

with high maximum annual temperatures (OR = 1.74, 95% CI = 1.03-2.94) and high minimum spring precipitation (OR = 1.67, 95% CI = 1.10-2.53). High minimum winter precipitation (OR = 0.46, 95% CI = 0.32-0.68) decrease the probability of VL occurrence (Fig. 3.1 and Table 3, Supplementary material 4, S5 and S6).

3.3.2. Number of cases

Municipalities with average Fall precipitation (IRR = 1.20, 95% CI = 1.07-1.36) and mean annual temperature (IRR = 1.17, 95% CI = 1.06–1.31) led to a greater number of VL cases during the study period. Municipalities with more native vegetation cover (IRR = 0.70, 95% CI = 0.62-0.79) and high Gini index values (IRR = 0.74, 95% CI = 0.66-0.83) had a low number of cases, the northwest of the state had the higher probability of VL incidence (Fig. 3.2 and Table 3, Supplementary material 4, S5 and S6).

4. Discussion

Both clinical forms, cutaneous and visceral leishmaniasis have similar transmission cycles, but our results demonstrate that they differ in their eco-epidemiology, corroborating other studies (de Marchi et al., 2019; Karagiannis-Voules et al., 2013). Our results showed that areas at high risk of VL in the state of São Paulo are at low risk for CL and vice versa, suggesting that there is no transmission of the two forms in the same locations. In São Paulo, spatio-temporal patterns in disease incidence reflect landscape, socioeconomic and climatic characteristics. CL occurrence can be predicted by vegetation cover, higher inequality economy, and greater average winter precipitation while VL occurrence by higher human development index, presence of cattle, and higher maximum annual temperature and minimum spring precipitation. Our results also demonstrate that the number of VL cases is lower in forest areas. Finally, years and municipalities with high mean annual temperature had a greater number of cases of both CL and VL, suggesting that temperature had a strong impact on the incidence of leishmaniasis in São Paulo state.

4.1. Spatio-temporal variation of visceral and cutaneous leishmaniasis incidence across the state of São Paulo

Urban development increased the incidence of CL and VL in São Paulo state in the last decades (Klink and Machado, 2005). However, differences in the drivers of interannual variability in the number of cases reflect variation in the spatial distribution of the disease and in the transmission cycles of the two forms. Cutaneous leishmaniasis has been historically present in native forest areas of the state; however, human activities have altered its epidemiology. CL incidence first increased in the 1920 with the construction of the railroad system and was later associated with forest clearing for highway construction (Filho, 1981). Over the study period, CL incidence reflects patterns of human development in rural and peri-urban environments close to vegetation. CL cases are reported in 70% of the municipalities of the state of São Paulo but the greatest numbers of cases are observed in municipalities with high vegetation cover in the SE part of the state. The municipality of Itariri has the highest cumulative incidence of CL followed by Iporanga, Pedro Toledo, Eldorado, Ribeira and Ubatuba as were observed in other studies (Forattini et al., 1976; Lopes et al., 2009). Vegetation cover in these municipalities ranges between 90 and 45% and CL incidence in recent years has been high in densely populated peri-urban areas with surrounding vegetation (Temponi et al., 2018).

On the other hand, VL incidence is highly aggregated in the NW part of the state. The disease in this region is associated with the recent introduction of the vector *Lutzomyia longipalpis* to urban areas, which was first recorded in Araçatuba and Birigui in 1997 and was followed by an increase in canine and human reported cases of VL. Vegetation cover ranged between 1.4 and 3.8% in the five municipalities with highest cumulative incidence of VL. These municipalities were classified by other studies as intense to moderate transmission areas (Cardim et al., 2016; de Paula, 2016) and are located in the west of the state, close to Mato Grosso do Sul state, where studies suggest that the expansion of the disease started after the construction of the Bolivia-Brazil pipeline (Antonialli et al., 2007; Pasquali et al., 2019; Sevá et al., 2017) and the Marechal – Rondon highway (Cardim et al., 2013; Oliveira, 2016) to the northwest and east west of the state (Rancan et al., 2020) and also from the western region of São Paulo to Paraná state (Naufal Spir et al., 2017). However, to be able to determine what factors are leading to this spread, it will be necessary to perform studies with high resolution location data.

The incidence of leishmaniasis can also be affected by climate conditions since the sand flies depends on climate factors (Dias et al., 2007). We observed that the number of CL cases peaked between 2002 and 2004, and for VL, between 2008 and 2012. Mean annual temperature were particularly high in 2002, 2006, 2007 and 2012, and total annual precipitation peaked in 2009 and 2011–2013 (Fig. 1). These anomalous climate conditions are probably related to episodes of El Niño and La Niña Southern Oscillation. El Niño leads to warmer condition which decreases the amount of rainfall and moisture supply while the opposite conditions are present during La Niña (Miralles et al., 2013).

The results also reflect climate differences among municipalities in the state (Supplementary material 2). Municipalities with high CL incidence in the southeast of the state have high total annual precipitation (range from 1264 to 2671 mm/month) relative to the rest of the state but areas in the northwest with high VL incidence have warmer temperatures range from 22 to 25 °C. This variability among municipalities

Table 2
Mean and standard deviation SE for parameters of the best model for cutaneous leishmaniasis. OR odds-ratio and IRR incidence rate ratio; CI Confidence Interval with p-value.

Model	Predictor	Estimate	SE	OR	95% CI	p-value
Binomial[e]	GINI	0.65079	0.06720	1.92	1.68–2.19	<0.001
	Vegetation cover	0.30205	0.06083	1.35	1.20–1.52	<0.001
	Total population[c]	0.07395	0.05708	1.08	0.96–1.20	0.195
	Maximum spring temperature	−0.38600	0.04555	0.68	0.62–0.74	<0.001
	Mean winter precipitation	0.20789	0.06296	1.23	1.09–1.39	0.001
Model	**Predictor**	**Estimate**	**SE**	**IRR**	**95% CI**	**p-value**
Negative binomial[b,d,e]	Agricultural workers[a]	−0.1649	0.0476	0.85	0.77–0.93	0.001
	Income per capita	−1.0214	0.0553	0.36	0.32–0.40	<0.001
	Mean annual temperature	0.3181	0.0435	1.37	1.26–1.50	<0.001
	Mean fall precipitation	−0.1491	0.0405	0.86	0.80–0.93	<0.001

[a] The number of agricultural workers in the municipality was included at population at risk because they work close to vegetation and places them at risk for the disease.
[b] Size of population was included in negative binomial model as an offset.
[c] No at risk population group significant, we remained with the size of the population although it was not significant because they are the population exposed to leishmaniasis.
[d] Landscape variables were not significant in CL Negative Binomial model.
[e] AIC values for both models binomial of 8417.1 and Negative binomial of 7916.9.

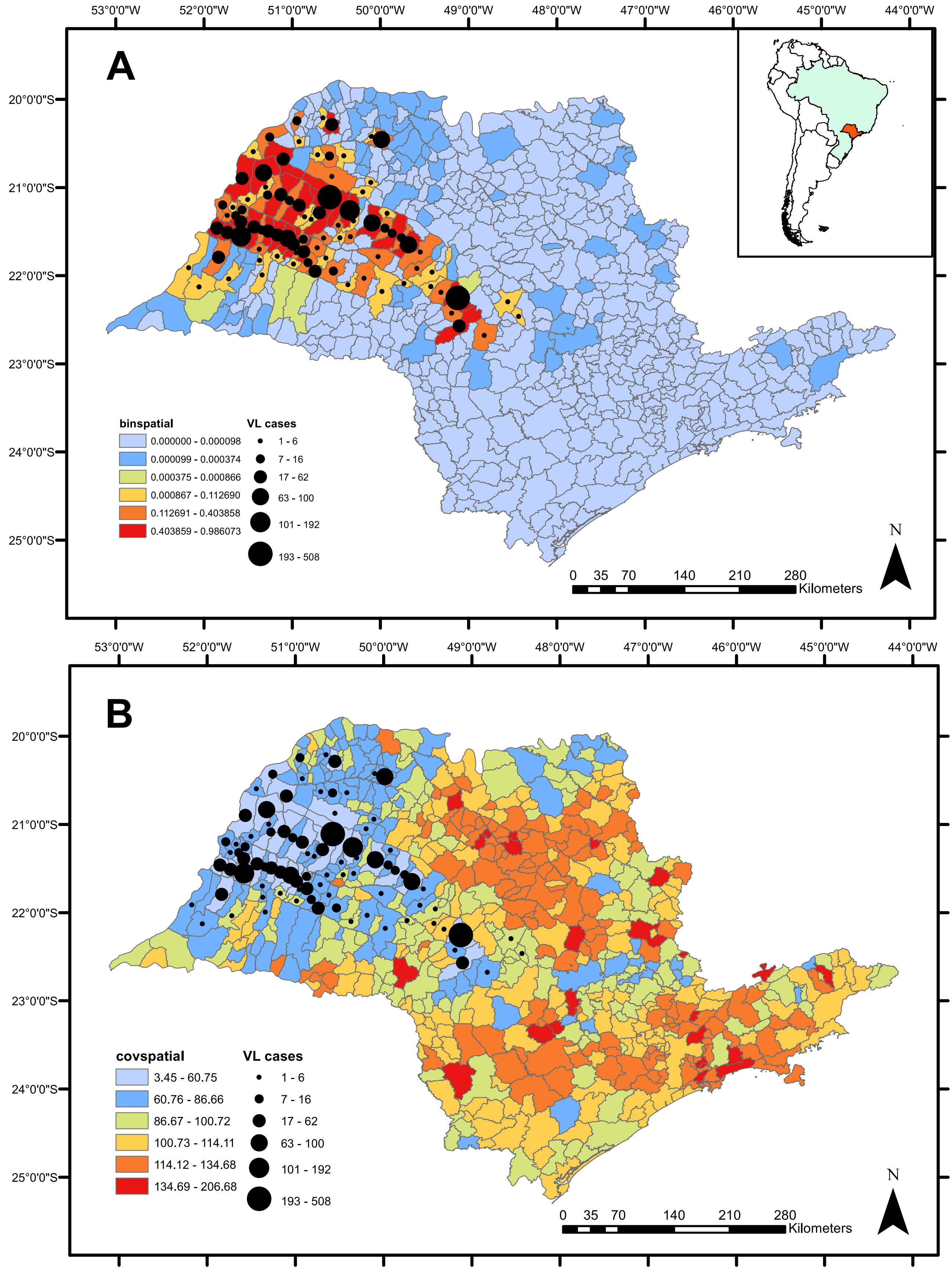

Fig. 3.1. Risk map of probability occurrence of visceral leishmaniasis (0-1) (A) and coefficient of variation (B) across municipalities. Black dots depict number of reported cases between 1999 and 2015.

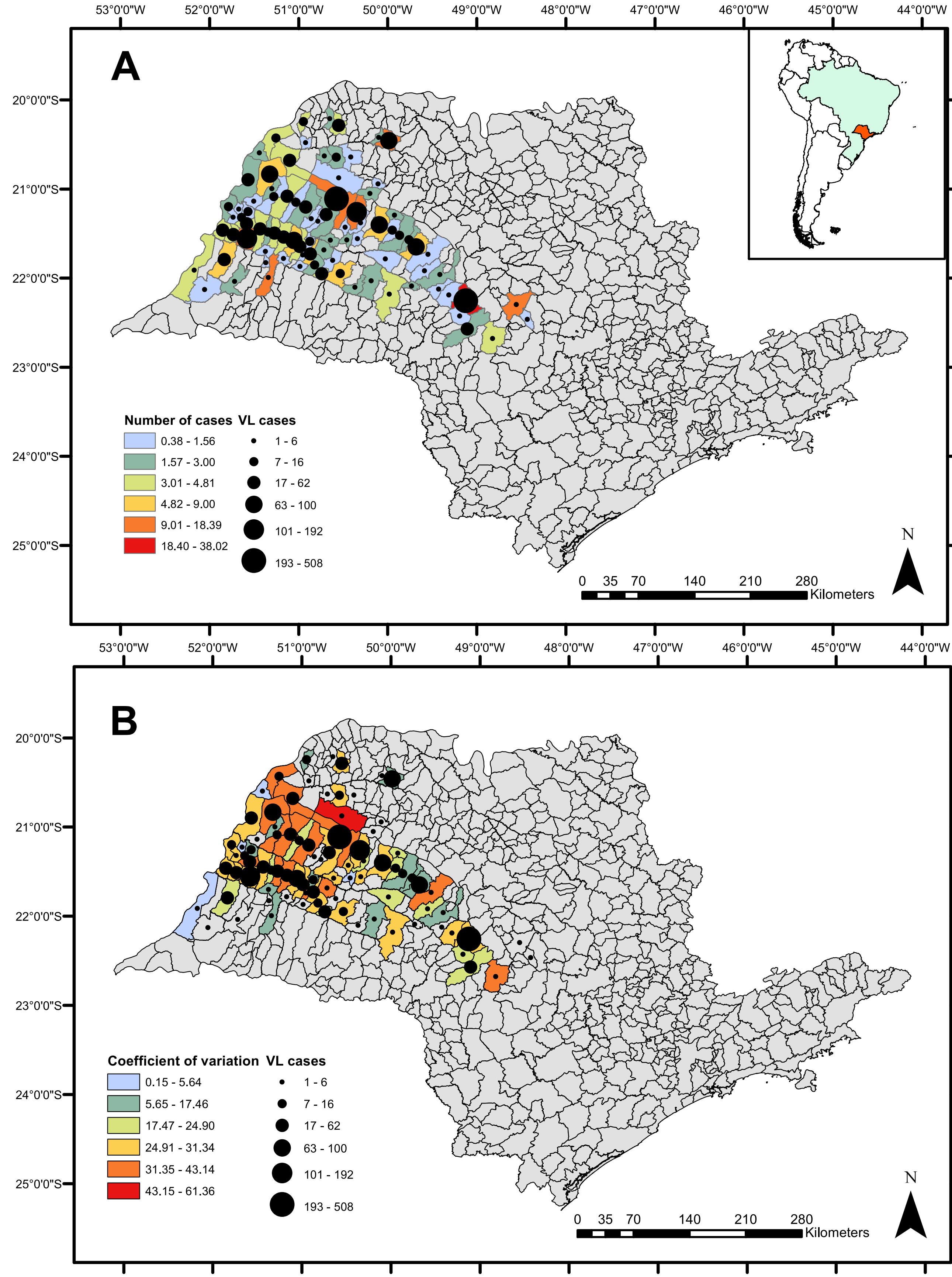

Fig. 3.2. Risk map of probability of number of visceral leishmaniasis cases (A) and coefficient of variation (B) across municipalities. Black dots depict number of reported cases between 1999 and 2015.

Table 3
Mean and Standard deviation SE for parameters of the best model for visceral leishmaniasis. OR odds-ratio and IRR incidence rate ratio; CI Confidence Interval with p-value.

Model	Predictor	Estimate	SE	OR	95% CI	P-value
Binomial[c,d] Spatial analysis	Total population[b]	−0.1271	4.8459	0.88	6.6-05 -1.17 + 04	0.979
	HDI	0.9710	0.2704	2.64	1.55–4.49	<0.001
	Cattle	0.6155	0.1946	1.85	1.26–2.71	<0.001
	Maximum annual temperature	0.5567	0.2667	1.74	1.03–2.94	0.018
	Minimum winter precipitation	−0.7663	0.1977	0.46	0.32–0.68	<0.001
	Minimum spring precipitation	0.5127	0.2120	1.67	1.10–2.53	0.008
Model	**Predictor**	**Estimate**	**SE**	**IRR**	**95% CI**	**P-value**
Negative binomial[a,d]	GINI	−0.2954	0.0576	0.74	0.66–0.83	<0.001
	Vegetation cover	−0.3549	0.0593	0.70	0.62–0.79	<0.001
	Mean annual temperature	0.1609	0.0543	1.17	1.06–1.31	0.003
	Mean fall precipitation	0.1848	0.0610	1.20	1.07–1.36	0.002

[a] Size of population was included in negative binomial model as an offset.
[b] No at risk population group significant, we remained with the size of the population although it was not significant because they are the population exposed to leishmaniasis.
[c] Landscape variables were not significant in VL Binomial model.
[d] AIC values for both models binomial of 1708.3 and Negative binomial of 2120.2.

together with vegetation cover and socioeconomic conditions could also contribute to variability in the incidence across the years.

4.2. Effects of socioeconomic and environmental factors on disease incidence

4.2.1. Influence of landscape cover

Our results show that the municipalities with high amount of native vegetation cover had greater CL occurrence, probably because both CL vectors and mammal reservoirs involved in the CL cycle are forest-dependent (Fernández, 2012). Additionally, the abundance of the sand fly species involved in CL transmission (e.g., *Lutzomyia intermedia, L. neivai*) is positively associated with the presence of dense vegetation (i.e. *Lutzomyia whitmani*) (Quintana et al., 2012), likely because immature sand fly instars are dependent on the presence of leaf litter and trees (Shimabukuro et al., 2010; Souza et al., 2014). The number of CL cases, however, was not influenced by vegetation cover, probably because intermediate vectors, such as *Lutzomyia whitmani,* which was formerly found in forest environments, is now associated with peri-urban transmission of CL. This vector can survive in areas with low vegetation cover (Dos Santos et al., 2009).

Native vegetation cover was not a significant predictor of VL occurrence in our analyses, confirming results from a simulation study (Karagiannis-Voules et al., 2013), but other regional studies have found significant positive associations between VL and native vegetation cover (Almeida and Werneck, 2014). A lower number of cases were observed in areas with high native vegetation cover. This finding may reflect the fact that some synanthropic vectors such as L. *longipalpis* prefer areas with low vegetation cover (e.g., urban areas) (Casaril et al., 2014; de Araújo et al., 2013).

4.2.2. Influence of socioeconomic factors

Our results show that the probability of CL occurrence is greater in municipalities with high economic inequality while the number of cases decreases in municipalities with higher per capita income, corroborating our predictions. This finding is consistent with the observation that low socioeconomic status in peri-urban settlements lead to higher exposure to CL vectors (Rodríguez-Morales et al., 2010).

The number of CL cases was lower in municipalities with fewer agricultural workers, suggesting that CL transmission risk affects areas distant from agricultural activities (Filho, 1981). The census of 2000 confirmed extensive migration of agricultural workers to urban areas with more than 50% of population living in rural areas holding nonagricultural jobs (Caiado and dos Santos, 2003). For VL, the probability of occurrence cases increased with higher HDI. This social metric can characterize municipalities with extensive urban areas, where the transmission cycle of VL is present (Salomón et al., 2015). The number of VL cases also decreased in areas with high inequality index values which are common in urban municipalities. Although other studies relate VL cases with low income in urban environments (Almeida and Werneck, 2014), municipalities of the NW of the state where most VL cases occur, have high agro-livestock industrial development and high HDI values. HDI values in these municipalities, however, high HDI values could mask the presence of populations with low socioeconomic conditions which are vulnerable to leishmaniasis (Bern et al., 2000). In addition, the presence of cattle close to human settlements can promote the presence of sand flies, which construct their breeding sites in cattle sheds (Afonso et al., 2012; Bern et al., 2010; Queiroz et al., 2012).

4.2.3. Influence of climate factors

São Paulo exhibits marked climate seasonality in most of the state with a hot rainy and a cool dry season. This climate variability across the state and during years affects the occurrence of both clinical forms. This may happen because vector proliferation, which is extremely linked to climate conditions, increase disease incidence (Fonseca et al., 2021). However, temperature and precipitation conditions favorable to sand flies vary for each species(Ebi and Hess, 2017). In general, adverse climate conditions delay the emergence of new adults and foster larval diapause, extending average developmental times from eggs to adults from 40 days to 3–9 months (Nieto et al., 2006) (Fig. 4).

In the state of São Paulo, high mean winter precipitation influences the occurrence of CL. This may be explained because CL vectors (i.e., *Lutzomyia whitmani*) achieve higher abundances in south western and east states of Brazil during the dry season (de Souza et al., 2004; Nascimento et al., 2013) and in periods of moderate precipitation (Barata et al., 2011; Colla-Jacques et al., 2010). Above average precipitation for this season may lead to an increase in the abundance of these vectors, since this may be a limiting factor for the survival of the species. In our results, high maximum spring temperatures (September, October and November) were not favorable for CL occurrence, probably because high temperatures affect Neotropical sand flies species involved in CL transmission, which do not tolerate temperatures over 25 °C (Barata et al., 2011).

For CL cases, associated with annual mean temperatures, warmer temperatures are favorable for the development of both sand flies and parasites within the vector (Hlavacova et al., 2013), increasing disease risk. São Paulo had a CL peak of cases during 2002 and 2004, and at this time total precipitation was also low due to warm ENSO conditions (Kayano and Andreoli, 2006). Other studies also found associations between CL cases and climate anomalies - ENSO and La Niña (cold rainy ENSO conditions) (Acosta Cardona, 2015; Cabaniel et al., 2005; Cardoso et al., 2019). Therefore, higher temperatures and low

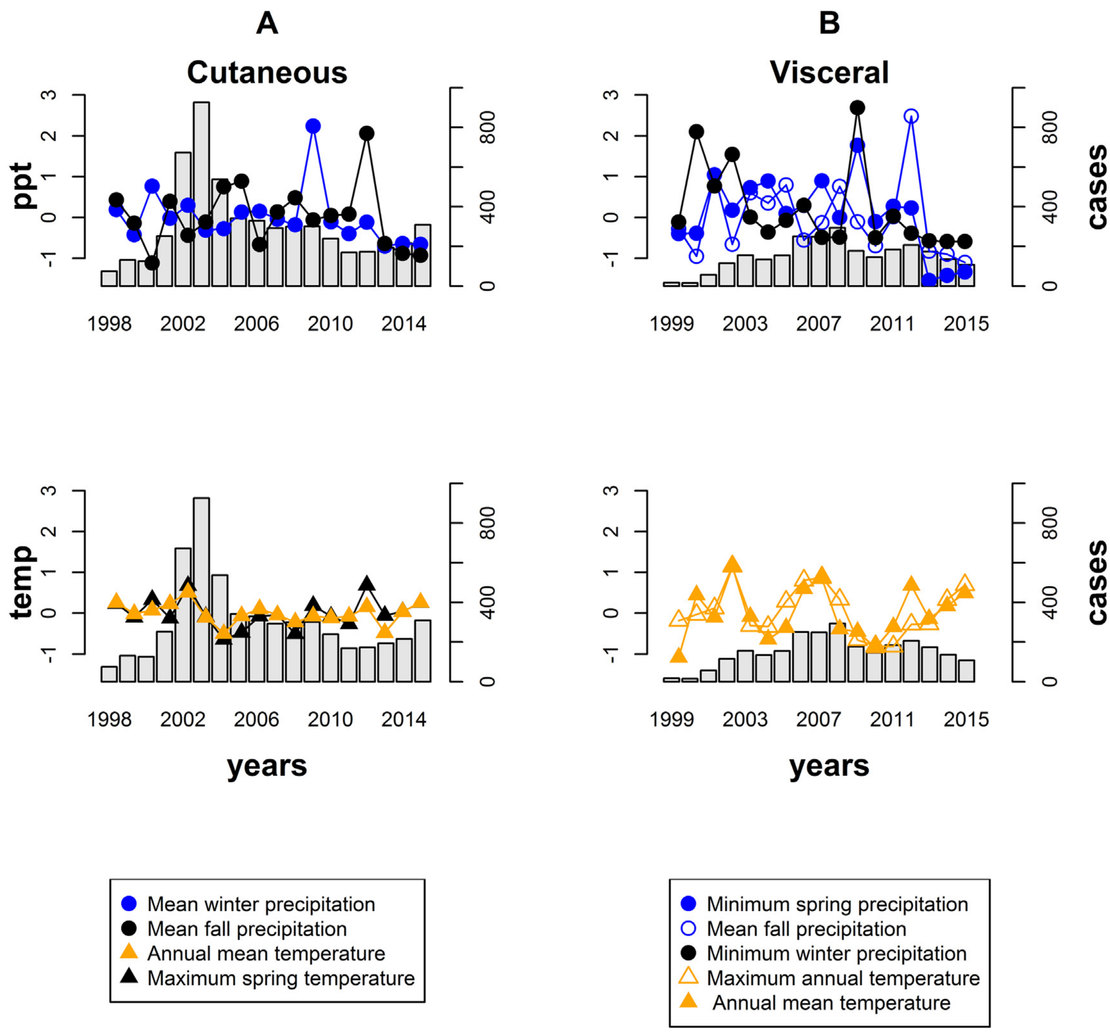

Fig. 4. Climate predictor variables for cutaneous (A) and visceral (B) leishmaniasis for 1998-2015. Climate data were standardized by centering each variable on its mean and divided by its standard deviation. Among variables with positive effect on disease risk, precipitation variables are in blue and temperature variables are in orange. Climate variables with negative influence are in black. Grey bars show the number of cases of CL and VL.

precipitation appear to be leading to a boost in CL cases in São Paulo, probably because the main suspected vectors for this region - L. *whitmanii* and *L. intermedia* - prefer warm conditions with moderate precipitation and relative humidity, typical of the dry season of São Paulo (Barata et al., 2011; Peterson and Shaw, 2003). In addition, years of high mean Fall precipitation were associated with a decrease in the number of CL cases. This may happen because periods of high precipitation in this time of the year could increase soil water moisture and reduce the survival of first instars by drowning, consequently reducing the abundance of sand flies during the dry season (winter), and contributing to the decrease of CL cases (Colla-Jacques et al., 2010; Karagiannis-Voules et al., 2013).

Both cases and occurrence were predicted by minimum spring precipitation. This may happen because this variable may influence the abundance of *Lutzomyia longipalpis* (Belo et al., 2014). Spring relative humidity directly affects the survival and development of eggs and later sand fly instars in diapause (Pérez-Cutillas et al., 2015; Salomon, 2021). Since relative humidity is extremely linked and is dependent on the amount of precipitation, we hypothesize that increases in this variable can lead to increases in relative humidity and favor VL vector occurrence and abundance. VL cases were also predicted by winter and fall precipitation and annual temperatures.

An increase in the minimum values of precipitation in the winter season can decrease the number of VL cases, because it can exceed the soil moisture tolerance limits of the vector decreasing its survival rates (Casanova et al., 2013). Temperatures in São Paulo state are in the favorable range for the development of the vector and parasite (Hlavacova et al., 2013).In general, an increase in mean fall and mean winter precipitation together with hotter temperatures seems to have contributed to the increase of VL cases (2006–2008 and 2011–2013) across our study period. However, we need to point out that VL and CL can be diseases with a diagnosis delay, and the date of infection is not always the same as the date of diagnosis and registration in the system. In addition, we are working with yearly scale disease data, which may not show the clear relationships with monthly climate variables.

Our study has several limitations. The large spatial and temporal scale of the analysis (i.e., municipality and year data), precludes a detailed understanding of the short term effects of climate on disease as well as fine-grained mechanisms of dispersal. A focus on the number of cases and the presence/absence of the disease does not allow a mechanistic understanding of some important aspects of the disease life cycle. For example, we are not considering the distribution and abundance of potential vectors. Nevertheless, our results demonstrate that environmental and socio-economic factors are linked with CL and VL occurrence and incidence in tropical areas. Furthermore, epidemiological surveillance in São Paulo is organized at larger scales and our results can contribute to design preventive measures and identify high risk municipalities.

5. Conclusions

One of our main findings is that municipalities with high mean annual temperature have a greater number of both VL and CL cases, an issue of great concern given that climate change is expected to lead to higher temperatures in tropical regions and can exacerbate leishmaniasis risk in these areas. Our results also demonstrate that low socioeconomic conditions of populations living in these areas exacerbate disease occurrence. Currently, public health policies regarding the control of both clinical forms of leishmaniasis are focused on reducing contact between human, domestic animals, and vectors. Our results can inform these policies, through the choice of priority municipalities for action and can also help in development of new policies. For example, CL occurrence is more likely to occur in municipalities with high native vegetation cover. Therefore, preventive measures as adequate protection against sand flies' bites measures (e.g., insect repellent, indoors mosquito nets), should be implemented in these municipalities and for people employed in forest-related activities. For VL, occurrence and number of cases are both related to climatic conditions (e.g., spring precipitation and annual temperatures), suggesting an increase in monitoring activities should be focused in areas and years with anomalies in climate conditions our risk maps can be used to identify priority areas for surveillance activities and to inform future studies.

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CRediT authorship contribution statement

Nerida Nadia H. Valero: Conceptualization, Investigation, Resources, Data curation, Formal analysis, Writing – original draft, Visualization, Funding acquisition. **Paula Prist:** Resources, Formal analysis, Writing – review & editing. **María Uriarte:** Methodology, Project administration, Supervision, Validation, Writing – review &editing.

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.

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References

Acosta Cardona, L.A., 2015. Evaluación de factores ambientales y climáticos como elementos de riesgo asociados con la transmisión del dengue y la leishmaniasis a diferentes escalas temporales y espaciales en Colombia. Universidad Nacional de Colombia.

Afonso, M.M.D.S., Duarte, R., Miranda, J.C., Caranha, L., Rangel, E.F., 2012. Studies on the feeding habits of Lutzomyia (Lutzomyia) longipalpis (Lutz & Neiva, 1912) (Diptera: Psychodidae: Phlebotominae) populations from endemic areas of American Visceral Leishmaniasis in Northeastern Brazil. J. Trop. Med. https://doi.org/10.1155/2012/858657.

Almeida, A.S., Werneck, G.L., 2014. Prediction of high-risk areas for visceral leishmaniasis using socioeconomic indicators and remote sensing data. Int. J. Health Geogr. 13, 7. https://doi.org/10.1186/1476-072X-13-13.

Alvar, J., Yactayo, S., Bern, C., 2006. Leishmaniasis and poverty. Trends Parasitol. 22, 552–557. https://doi.org/10.1016/j.pt.2006.09.004.

Antonialli, S.A.C., Torres, T.G., Filho, A.C.P., Tolezano, J.E., 2007. Spatial analysis of American visceral leishmaniasis in Mato Grosso do Sul State, Central Brazil. J. Infect. 54, 509–514. https://doi.org/10.1016/j.jinf.2006.08.004.

Argaw, D., Mulugeta, A., Herrero, M., Nombela, N., Teklu, T., Tefera, T., Belew, Z., Alvar, J., Bern, C., 2013. Risk factors for visceral Leishmaniasis among residents and migrants in Kafta-Humera, Ethiopia. PLoS Negl. Trop. Dis. 7, 9. https://doi.org/10.1371/journal.pntd.0002543.

Barata, R.A., Paz, G.F., Bastos, M.C., Andrade, R.C.O., De Barros, D.C.M., E Silva, F.O.L., Michalsky, É.M., Pinheiro, A.da C., Dias, E.S., 2011. Phlebotomine sandflies (Diptera: Psychodidae) in Governador Valadares, a transmission area for American tegumentary leishmaniasis in State of Minas Gerais, Brazil. Rev. Soc. Bras. Med. Trop. 44, 136–139.

Bates, D., Mächler, M., Bolker, B.M., Walker, S.C., 2014. Fitting linear mixed-effects models using lme4. J. Stat. Softw. 1–51.

Belo, V.S., Strichiner, C.J., Barbosa, D.S., Nascimento, B.W.L., Horta, M.A.P., da Silva, E.S., Werneck, G.L., 2014. Risk factors for adverse prognosis and death in American visceral leishmaniasis: a meta-analysis. PLoS Negl. Trop. Dis. 8, 1–9. https://doi.org/10.1371/journal.pntd.0002982.

Bern, C., Joshi, A.B., Jha, S.N., Das, M.L., Hightower, A., Thakur, G.D., Bista, M.B., 2000. Factors associated with visceral leishmaniasis in Nepal: bed-net use is strongly protective. Am. J. Trop. Med. Hyg. 63, 184–188.

Bern, C., Courtenay, O., Alvar, J., 2010. Of cattle, sand flies and men: a systematic review of risk factor analyses for South Asian visceral leishmaniasis and implications for elimination. PLoS Negl. Trop. Dis. 4, 1–10. https://doi.org/10.1371/journal.pntd.0000599.

Bivand, R.S., Wong, D.W.S., 2018. Comparing implementations of global and local indicators of spatial association. TEST 27, 716–748. https://doi.org/10.1007/s11749-018-0599-x.

Brearley, G., Rhodes, J., Bradley, A., Baxter, G., Seabrook, L., Lunney, D., Liu, Y., Mcalpine, C., 2012. Wildlife disease prevalence in human-modified landscapes. Biol. Rev. 1–16. https://doi.org/10.1111/brv.12009.

BSDF, 2020. Brazilian Foundation for Sustainable Development [WWW Document]. URL. BSDF (accessed 12.1.20). http://geo.fbds.org.br/.

Cabaniel, S.G., Rada, T.L., Blanco, G.J., Rodríguez-Morales, A., Escalera, A.J., 2005. Impacto de los eventos de El Niño Southern Oscillation (ENSO) sobre la leishmaniosis cutánea en Sucre, Venezuela, a través del uso de información satelital, 1994-2003. Rev. Peru. Med. Exp. Salud Publica 22, 32–37.

Caiado, A.S.C., dos Santos, S.M.M., 2003. Fim da dicotomia rural-urbano? Um olhar sobre os processos socioespaciais. São Paulo Perspect. 17, 115–124. https://doi.org/10.1590/S0102-88392003000300012.

Cardim, M.F.M., Rodas, L.A.C., Dibo, M.R., Guirado, M.M., Oliveira, A.M., Chiaravalloti-Neto, F., 2013. Introduction and expansion of human American visceral leishmaniasis in the state of Sao Paulo, Brazil, 1999–2011. Rev. Saude Publica 47, 1–9. https://doi.org/10.1590/S0034-8910.2013047004454.

Cardim, M.F.M., Guirado, M.M., Dibo, M.R., Neto, F.C., 2016. Visceral leishmaniasis in the state of Sao Paulo, Brazil: spatial and space-time analysis. Rev. Saude Publica 50, 1–11. https://doi.org/10.1590/S1518-8787.2016050005965.

Cardoso, D.T., De Souza, D.C., De Castro, V.N., Geiger, S.M., Barbosa, D.S., 2019. Identification of priority areas for surveillance of cutaneous leishmaniasis using spatial analysis approaches in Southeastern Brazil. BMC Infect. Dis. 19, 318. https://doi.org/10.1186/s12879-019-3940-4.

Carvalho, B.M., Rangel, E.F., Vale, M.M., 2016. Evaluation of the impacts of climate change on disease vectors through ecological niche modelling. Bull. Entomol. Res. 1–12. https://doi.org/10.1017/S0007485316001097.

Casanova, C., Andrighetti, M.T.M., Sampaio, S.M.P., Marcoris, M.L.G., Colla-Jacques, F.E., Prado, Â.P., 2013. Larval breeding sites of Lutzomyia longipalpis (Diptera: Psychodidae) in visceral leishmaniasis endemic urban areas in Southeastern Brazil. PLoS Negl. Trop. Dis. 7, 1–9. https://doi.org/10.1371/journal.pntd.0002443.

Casaril, A.E., Monaco, N.Z.de N., de Oliveira, E.F., Eguchi, G.U., Filho, A.C.P., Pereira, L.E., Oshiro, E.T., Galati, E.A.B., Mateus, N.L.F., de Oliveira, A.G., 2014. Spatiotemporal analysis of sandfly fauna (Diptera: Psychodidae) in an endemic area of visceral leishmaniasis at Pantanal, central South America. Parasit. Vectors 7, 1–12. https://doi.org/10.1186/1756-3305-7-364.

Chaves, L.F., 2011. Phlebotomine Sand Fly Species Co-occurrence at the Local Scale: Differences Between Agricultural and Forested Areas entre áreas agrícolas y forestales LI, pp. 35–39.

Colla-Jacques, F.E., Casanova, C., do Prado, Â.P., 2010. Study of sand fly fauna in an endemic area of American cutaneous leishmaniasis and canine visceral leishmaniasis in the municipality of Espírito Santo do Pinhal, São Paulo, Brazil. Mem. Inst. Oswaldo Cruz 105, 208–215. https://doi.org/10.1590/S0074-02762010000200017.

Da Saúde, M., 2012. Sala de apoio à gestão estratégica (SAGE). [WWW document]. URL. http://sage.saude.gov.br/ (accessed 9.27.17).

Dantas-Torres, F., Solano-Gallego, L., Baneth, G., Ribeiro, V.M., de Paiva-Cavalcanti, M., Otranto, D., 2012. Canine leishmaniosis in the Old and New Worlds: Unveiled similarities and differences. Trends Parasitol. 28, 531–538. https://doi.org/10.1016/j.pt.2012.08.007.

de Araújo, V.E.M., Pinheiro, L.C., de Mattos Almeida, M.C., de Menezes, F.C., Morais, M.H.F., Reis, I.A., Assunção, R.M., Carneiro, M., 2013. Relative risk of visceral leishmaniasis in Brazil: a spatial analysis in urban area. PLoS Negl. Trop. Dis. 7, 9. https://doi.org/10.1371/journal.pntd.0002540.

de Coster, G., Filho, F.A., dos Santos, R.F., 2014. Human health risks of forest conservation. Proc. Natl. Acad. Sci. U. S. A. 111, E1815. https://doi.org/10.1073/pnas.1401544111.

De Freitas, G.K., 2011. São Paulo Secretariat of environment, Brazili. In: Cook, J., Freeman, S., Levine, E., Hill, M. (Eds.), Shifting Course: Climate Adaption for Water Management Institutions. World Wildlife Fund, Washington, DC, pp. 56–61.

de Marchi, M.N.A., Caldart, E.T., Martins, F.D.C., Freire, R.L., 2019. Spatial analysis of leishmaniasis in Brazil: a systematized review. Rev. Inst. Med. Trop. Sao Paulo 61. https://doi.org/10.1590/S1678-9946201961068.

de Paula, E.M.N., 2016. Distribuição espacial da Leishmaniose visceral no estado de São Paulo, Brasil, no período de 1970 a 2014, pp. 1–67.

de Santana Martins, M., 2015. The Use of Geographic Information Systems and Cological Niche Modeling to Map Transmission Risk for Visceral Leishmaniasis in Bahia, Brazil. Louisiana State University.

de Souza, C.M., Pessanha, J.E., Barata, R.A., Monteiro, É.M., Costa, D.C., Dias, E.S., 2004. Study on phlebotomine sand fly (Diptera: Psychodidae) Fauna in belo horizonte, State of Minas Gerais, Brazil. Mem. Inst. Oswaldo Cruz Rio Janeiro 99, 795–803.

DeFries, R., Rosenzweig, C., 2010. Toward a whole-landscape approach for sustainable land use in the tropics. Proc. Natl. Acad. Sci. U. S. A. 107, 19627–19632. https://doi.org/10.1073/pnas.1011163107.

DeFries, R.S., Rudel, T., Uriarte, M., Hansen, M., 2010. Deforestation driven by urban population growth and agricultural trade in the twenty-first century. Nat. Geosci. 3, 178–181. https://doi.org/10.1038/ngeo756.

Desjeux, P., 2001. The increase in risk factors for leishmaniasis worldwide. Trans. R. Soc. Trop. Med. Hyg. 95, 239–243. https://doi.org/10.1016/S0035-9203(01)90223-8.

Dias, E.S., França-Silva, J.C., Costa, J., Monteiro, É.M., Paula, K.M.De, Macedo, C., Barata Andrade, R., 2007. Flebotomíneos (Diptera : Psychodidae) de um foco de leishmaniose tegumentar no Estado de Minas Gerais Sandflies (Diptera : Psychodidae) in an outbreak of cutaneous leishmaniasis in the State of Minas Gerais. Rev. Soc. Bras. Med. Trop. 40, 49–52.

Dos Santos, D.R., Dos Santos, A.R., Dos Santos, E.S., De Oliveira, O., Poiani, L.P., Da Silva, A.M., 2009. Observações sobre a atividade diurna de Nyssomyia whitmani (Diptera: Psychodidae) na área urbana de Maringá, Paraná, Brasil. Epidemiol. Serv. Saúde 18, 227–236. https://doi.org/10.5123/s1679-49742009000300005.

Ebi, K.L., Hess, J.J., 2017. The past and future in understanding the health risks of and responses to climate variability and change. Int. J. Biometeorol. 1–10. https://doi.org/10.1007/s00484-017-1406-1.

Fan, Y., van den Dool, H., 2008. A global monthly land surface air temperature analysis for 1948–present. J. Geophys. Res. 113, D01103. https://doi.org/10.1029/2007JD008470.

Farinaci, J.S., Batistella, M., 2012. Variação na cobertura vegetal nativa em São Paulo: um panorama do conhecimento atual. Rev. Árvore 36, 695–705.

Fernández, M.S., 2012. Eco-epidemiología de vectores de Leishmania spp. en el noreste de la Argentina (Provincia de Misiones). Universidad de Buenos Aires.

Filho, N.A.de A., 1981. Notas e Comunicações Leíshmaniose Tegumentar Americana e o desmatamento da Amazônia. Acta Amaz 11, 187–189.

Fonseca, E.D.S., Guimarães, R.B., Prestes-Carneiro, L.E., Tolezano, J.E., Rodgers, M.D.S.M., Avery, R.H., Malone, J.B., 2021. Predicted distribution of sand fly (Diptera: Psychodidae) species involved in the transmission of Leishmaniasis in São Paulo state, Brazil, utilizing maximum entropy ecological niche modeling. Pathog. Glob. Health 115, 108–120. https://doi.org/10.1080/20477724.2020.1870031.

Forattini, O.P., Rabello, E.X., Serra, O.P., Cotrim, M.das D., Galati, E.A.B., Barata, J.M.S., 1976. Observações sobre a transmissão da leishmaniose tegumentar no estado de São Paulo, Brasil. Rev. Saude Publica 31–43.

Fortin, M.-J., Dale, M.R.T., Ver Hoef, J.M., 2016. Spatial analysis in ecology. Wiley StatsRef: Statistics Reference Online. John Wiley & Sons, Ltd, pp. 1–13 https://doi.org/10.1002/9781118445112.stat07766.pub2.

Fundação SOS Mata Atlântica/INPE, 2019. Atlas dos Remanescentes Florestais da Mata Atlântica, 2017-2018. São Paulo.

Funk, C.C., Peterson, P.J., Landsfeld, M.F., Pedreros, D.H., Verdin, J.P., Rowland, J.D., Romero, B.E., Husak, G.J., Michaelsen, J.C., Verdin, A.P., 2014. A quasi-global precipitation time series for drought monitoring. U.S. Geol. Surv. Data Ser. 832, 1–12 (doi:1.

Gelman, A., Hill, J., 2007. Data Analysis Using Regression and Multilevel/Hierarchical Models. Cambridge University Press, New York, Cambridge https://doi.org/10.2277/0521867061.

Graepp-Fontoura, I., Soeiro Barbosa, D., Nascimento, L.F.C., Fontoura, V.M., Ferreira, A.G.N., Arrais Sampaio Santos, F.A., Sousa, B.S., Santos, F.S., Santos-Neto, M., Dos Santos, L.H., Abreu-Silva, A.L., 2020. Epidemiological aspects and spatial patterns of human visceral leishmaniasis in Brazil. Parasitology 147, 1665–1677. https://doi.org/10.1017/S0031182020001754.

Hlavacova, J., Votypka, J., Volf, A.P., 2013. The effect of temperature on Leishmania (Kinetoplastida: Trypanosomatidae) development in sand flies. J. Med. Entomol. 50, 955–958. https://doi.org/10.1603/ME13053.

Houweling, T.A.J., Karim-Kos, H.E., Kulik, M.C., Stolk, W.A., Haagsma, J.A., Lenk, E.J., Richardus, J.H., de Vlas, S.J., 2016. Socioeconomic inequalities in neglected tropical diseases: a systematic review. PLoS Negl. Trop. Dis. 1–28. https://doi.org/10.1371/journal.pntd.0004546.

Karagiannis-Voules, D.A., Scholte, R.G.C., Guimarães, L.H., Utzinger, J., Vounatsou, P., 2013. Bayesian geostatistical modeling of leishmaniasis incidence in Brazil. PLoS Negl. Trop. Dis. 7, 13. https://doi.org/10.1371/journal.pntd.0002213.

Kariyawasam, K.K.G.D.U.L., Edirisuriya, C.S., Senerath, U., Hensmen, D., Siriwardana, H.V.Y.D., Karunaweera, N.D., 2015. Characterisation of cutaneous leishmaniasis in Matara district, southern Sri Lanka: evidence for case clustering. Pathog. Glob. Health 109 (7), 336–343. https://doi.org/10.1179/2047773215Y.0000000032.

Kayano, M.T., Andreoli, R.V., 2006. Relationships between rainfall anomalies over northeastern Brazil and the El Niño-Southern Oscillation. J. Geophys. Res. 111, D13101. https://doi.org/10.1029/2005JD006142.

Klink, C.A., Machado, R.B., 2005. Conservation of the Brazilian Cerrado. Conserv. Biol. 19, 707–713. https://doi.org/10.1111/j.1523-1739.2005.00702.x.

Lopes, L.M., Biller, F.L., Pinho, N., de Lima, C., Ribeiro, E.R.B., 2009. Perfil ecoepidemiológico dos casos de LTA nos municípios de Pedro de Toledo, Eldorado e Itariri-SP nos últimos anos. Saúde Colet. 6, 288–290.

Lüdecke, D., 2020. sjPlot: Data Visualization for Statistics in Social Science.

Machado-Coelho, G.L.L., Assunção, R., Mayrink, W., Caiaffa, W.T., 1999. American cutaneous leishmaniasis in Southeast Brazil: space-time clustering. Int. J. Epidemiol. 28, 982–989. https://doi.org/10.1093/ije/28.5.982.

Miralles, D.G., van den Berg, M.J., Gash, J.H., Parinussa, R.M., de Jeu, R.A.M., Beck, H.E., Holmes, T.R.H., Jiménez, C., Verhoest, N.E.C., Dorigo, W.A., Teuling, A.J., Johannes Dolman, A., 2013. El Niño–La Niña cycle and recent trends in continental evaporation. Nat. Clim. Chang. 4, 122–126. https://doi.org/10.1038/nclimate2068.

Mma, M.do M.A., 2015. Projeto TerraClass Cerrado 2013, Mapeamento do Uso e Cobertura do Cerrado. Brasília - DF.

Myers, S.S., Gaffikin, L., Golden, C.D., Ostfeld, R.S., Redford, K.H., Ricketts, T.H., Turner, W.R., Osofsky, S.A., 2014. Reply to De Coster et al.: exploring the complexity of ecosystem-human health relationships. Proc. Natl. Acad. Sci. 111, E1816–E1816. https://doi.org/10.1073/pnas.1402671111.

Nascimento, B.W.L., Saraiva, L., Neto, R.G.T., Lamy Serra e Meira, P.C., Sanguinette, C.de C., Tonelli, G.B., Botelho, H.A., Belo, V.S., Da Silva, E.S., Gontijo, C.M.F., Filho, J.D.A., 2013. Study of sand flies (Diptera: Psychodidade) in visceral and cutaneous leishmaniasis areas in central western of Minas Gerais state – Brazil. Acta Trop. 125, 262–268. https://doi.org/10.1016/j.actatropica.2012.11.005.

Naufal Spir, P.R., Prestes-Carneiro, L.E., Fonseca, E.S., Dayse, A., Giuffrida, R., D'Andrea, L.A.Z., 2017. Clinical characteristics and spatial distribution of Visceral leishmaniasis in children in São Paulo state: an emerging focus of Visceral leishmaniasis in Brazil. Pathog. Glob. Health 111, 91–97. https://doi.org/10.1080/20477724.2017.1289666.

Nieto, P., Malone, J.B., Bavia, M.E., 2006. Ecological niche modeling for visceral leishmaniasis in the state of Bahia, Brazil, using genetic algorithm for rule-set prediction and growing degree day-water budget. Geospat. Health 115–126.

Oliveira, A.M., 2016. Estudo da expansão da Leishmaniose Visceral no estado de São Paulo e de fatores intervenientes. Universidade de São Paulo.

Pace, D., 2014. Leishmaniasis. J. Infect. 20, 1–9. https://doi.org/10.1016/j.jinf.2014.07.016.

Pasquali, A.K.S., Baggio, R.A., Boeger, W.A., González-Britez, N., Guedes, D.C., Chaves, E.C., Thomaz-Soccol, V., 2019. Dispersion of Leishmania (Leishmania) infantum in central-southern Brazil: evidence from an integrative approach. PLoS Negl. Trop. Dis. 13, e0007639. https://doi.org/10.1371/journal.pntd.0007639.

Peel, M.C., Finlayson, B.L., McMahon, T.A., 2007. Updated world map of the Köppen-Geiger climate classification. Hydrol. Earth Syst. Sci. 11, 1633–1644. https://doi.org/10.5194/hess-11-1633-2007.

Pérez-Cutillas, P., Goyena, E., Chitimia, L., De la Rúa, P., Bernal, L.J., Fisa, R., Riera, C., Iborra, A., Murcia, L., Segovia, M., Berriatua, E., 2015. Spatial distribution of human asymptomatic Leishmania infantum infection in southeast Spain: a study of environmental, demographic and social risk factors. Acta Trop. 146, 127–134. https://doi.org/10.1016/j.actatropica.2015.03.017.

Peterson, A.T., Shaw, J., 2003. Lutzomyia vectors for cutaneous leishmaniasis in Southern Brazil: ecological niche models, predicted geographic distributions, and climate change effects. Int. J. Parasitol. 33, 919–931. https://doi.org/10.1016/S0020-7519(03)00094-8.

Pinheiro, M.P.G., de Medeiros Silva, M.M., Júnior, J.B.S., da Silva, J.H.T., Alves, M.de L., De Melo Ximenes, M.de F.F., 2016. Sand flies (Diptera, Psychodidae, Phlebotominae), vectors of Leishmania protozoa, at an Atlantic Forest Conservation Unit in the municipality of Nísia Floresta, Rio Grande do Norte state, Brazil. Parasit. Vectors 9, 1–8. https://doi.org/10.1186/s13071-016-1352-5.

Queiroz, M.F.M., Varjão, J.R., de Moraes, S.C., Salcedo, G.E., 2012. Análise da fauna flebotomínica (Diptera: Psychodidae) em Barra do Garças, Estado de Mato Grosso, Brasil, e a influência das variáveis ambientais na densidade vetorial de Lutzomyia longipalpis (Lutz & Neiva, 1912). Rev. Soc. Bras. Med. Trop. 45, 313–317. https://doi.org/10.1590/S0037-86822012000300007.

Quintana, M.G., Fernández, M.S., Salomón, O.D., 2012. Distribution and abundance of phlebotominae, vectors of leishmaniasis, in Argentina: spatial and temporal analysis at different scales. J. Trop. Med. 2012, 1–16. https://doi.org/10.1155/2012/652803.

Rancan, E.A., Chagas, E.F.B., Sperança, M.A., Carvalho, V.C.de L., Martins, L.P.A., Suzuki, R.B., 2020. Spatio-temporal distribution of human American visceral leishmaniasis in the Western region of Sao Paulo State, from 2004 to 2018. Rev. Inst. Med. Trop. Sao Paulo 62, e80. https://doi.org/10.1590/S1678-9946202062080.

Ready, P.D., 2013. Biology of phlebotomine sand flies as vectors of disease agents. Annu. Rev. Entomol. 58, 227–250. https://doi.org/10.1146/annurev-ento-120811-153557.

Reisen, W.K., 2010. Landscape epidemiology of vector-borne diseases. Annu. Rev. Entomol. 55, 461–483. https://doi.org/10.1146/annurev-ento-112408-085419.

Rodríguez-Morales, A.J., 2013. Ecoepidemiología y epidemiología satelital: nuevas herramientas en salud pública y su utilidad en la leishmaniasis tegumentaria americana, pp. 1057–1080 https://doi.org/10.13140/2.1.2131.0244.

Rodríguez-Morales, A.J., Pascual-González, Y., Benítez, J.A., López-Zambrano, M.A., Harter-Griep, R., Vilca-yengle, L.M., Cárdenas, R., 2010. Asociación entre la incidencia de leishmaniosis cutánea y el índice de desarrollo humano y sus componentes en cuatro estados endémicos de Venezuela. Rev. Peru. Med. Exp. Salud Publica 27, 22–30.

Rousset, F., Ferdy, J.B., 2014. Testing environmental and genetic effects in the presence of spatial autocorrelation. Ecography (Cop.) 37, 781–790. https://doi.org/10.1111/ecog.00566.

Ruiz-Postigo, J.A., Grout, L., Jain, S., 2020. Global leishmaniasis surveillance, 2017-2018, and first report on 5 additional indicators. Wkly Epidemiol. Rec. 95 (25), 265–289.

Salomon, O.D., 2021. Lutzomyia longipalpis, gone with the wind and other variables. Neotrop. Entomol. https://doi.org/10.1007/s13744-020-00811-9.

Salomón, O.D., Feliciangeli, M.D., Quintana, M.G., Afonso, M.M.D.S., Rangel, E.F., 2015. Lutzomyia longipalpis urbanisation and control. Mem. Inst. Oswaldo Cruz 110, 831–846. https://doi.org/10.1590/0074-02760150207.

Sevá, A.da P., Mao, L., Galvis-Ovallos, F., Tucker Lima, J.M., Valle, D., 2017. Risk analysis and prediction of visceral leishmaniasis dispersion in São Paulo State, Brazil. PLoS Negl. Trop. Dis. 11, 1–17. https://doi.org/10.1371/journal.pntd.0005353.

Shimabukuro, P.H.F., da Silva, T.R.R., Fonseca, F.O.R., Baton, L.A., Galati, E.A.B., 2010. Geographical distribution of American cutaneous leishmaniasis and its phlebotomine vectors (Diptera: Psychodidae) in the state of São Paulo, Brazil. Parasit. Vectors 3, 12. https://doi.org/10.1186/1756-3305-3-121.

Skaug, H., Fournier, D., Nielsen, A., Magnusson, A., Bolker, B.M., 2018. Generalized Linear Mixed Models Using AD Model Builder.

Souza, T.L., Figueiredo, F.B., Almeida, A.B., Benigno, C.V., Pontes, C.S., Souza, M.B., 2014. Natural breeding sites of phlebotomine sand flies (Diptera: Psychodidae) on Marambaia Island, Rio de Janeiro State, Brazil. Souza TL, Figueiredo FB, Almeida AB, Benigno C V, Pontes CS, Souza MB. 2014. Nat. Breed. sites phlebotomine sand flies (Diptera Psychodidae) Marambaia Island, Rio Janeiro State, Brazil. Acta Trop. 136, 104–107. https://doi.org/10.1016/j.actatropica.2014.04.008 (doi.

Temponi, A.O.D., de Brito, M.G., Ferraz, M.L., Diniz, S.D.A., da Cunha, T.N., Silva, M.X., 2018. Ocorrência de casos de leishmaniose tegumentar americana: uma análise multivariada dos circuitos espaciais de produção, Minas Gerais, Brasil, 2007 a 2011. Cad. Saude Publica 34, 1–15. https://doi.org/10.1590/0102-311x00165716.

Thomaz-Soccol, V., Gonçalves, A.L., Piechnik, C.A., Baggio, R.A., Boeger, W.A., Buchman, T.L., Michaliszyn, M.S., Rodrigues dos Santos, D., Celestino, A., Aquino, J., Leandro, A. de S., Paz, O.L.de S.da, Limont, M., Bisetto, A., Shaw, J.J., Yadon, Z.E., Salomon, O.D., 2018. Hidden danger: unexpected scenario in the vector-parasite dynamics of leishmaniases in the Brazil side of triple border (Argentina, Brazil and Paraguay). PLoS Negl. Trop. Dis., 12 https://doi.org/10.1371/journal.pntd.0006336.

Tsai, P.J., 2012. Application of Moran's test with an empirical Bayesian rate to leading health care problems in Taiwan in a 7-year period (2002–2008). Glob. J. Health Sci. 4, 63–77. https://doi.org/10.5539/gjhs.v4n5p63.

Vianna, E.N., Morais, M.H.F., de Almeida, A.S., Sabroza, P.C., Reis, I.A., Dias, E.S., Carneiro, M., 2016. Abundance of lutzomyia longipalpis in urban households as risk factor of transmission of visceral leishmaniasis. Mem. Inst. Oswaldo Cruz 111, 302–310. https://doi.org/10.1590/0074-02760150366.

World Health Organization, 2010. Control of the leishmaniases. World Health Organ. Tech. Rep. Ser, pp. 1–202 https://doi.org/10.1038/nrmicro1766.

World Health Organization Control TeamAlvar, J., Vélez, I.D., Bern, C., Herrero, M., Desjeux, P., Cano, J., Jannin, J., de Boer, M., 2012. Leishmaniasis worldwide and global estimates of its incidence. PLoS One 7, 1–12. https://doi.org/10.1371/journal.pone.0035671.