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Spatiotemporal Distribution of Cutaneous Leishmaniasis in Relation to Climate Factors, Pará, Brazil, 2007-2019

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Abstract

Spatiotemporal Distribution of Cutaneous Leishmaniasis in Relation to Climate Factors, Pará, Brazil, 2007-2019

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Background Cutaneous leishmaniasis (CL) is an endemic vector-borne disease of Brazil, which is home to ~40% of CL cases in the Americas. Well-known environmental factors associated with incidence include deforestation, precipitation, and temperature, but CL dynamics are highly variable and little data are available for many states. This study evaluates the role of environmental factors on CL incidence in the state of Pará (PA), identifying high-risk and likely regional clusters of disease incidence.

Methods A spatiotemporal ecological study utilizing publicly sourced confirmed cases of CL by reporting municipality was conducted from 2007 through 2019. Cumulative and annual incidence rates were mapped to evaluate spatial heterogeneity. Multivariate negative binomial regression models were generated for the overall period and annually to investigate the associations between factors including minimum temperature, maximum temperature, total precipitation, urbanicity of residence, and Multivariate El Nino Southern Oscillation Index (MEI). Local indicator of spatial autocorrelation (LISA) and Kulldorff spatial scan statistics were conducted to evaluate clustering.

Results Over the study period, 46,163 cases of CL were reported from PA (population 7,588,078). Cumulative incidence was 608 cases per 100,000 people, with average annual incidence of 47 cases per 100,000 people. In the overall model, which explained 57% of variance, monthly minimum temperature, monthly maximum temperature, and monthly total precipitation were significantly, inversely associated with CL incidence in Pará. Urbanicity and

month displayed significant, direct association with CL incidence. Seasonally lagged MEI and year did not achieve significance in the overall model. There was a spatially heterogenous distribution of high-high and low-low risk municipalities across the state, and stable and significant clusters of highest-risk municipalities were found in the northwestern and southwestern regions of the state.

Discussion This study provides insight into the distribution of CL across Pará, showing a likely role of environmental factors including minimum and maximum monthly temperature and total monthly precipitation on disease incidence and clustering in the state. These results suggest possible factors of influence leading to high incidence years and tactics for managing prevention and control efforts of CL in Pará, Brazil.

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LITERATURE REVIEW

Leishmaniasis, a tropical infectious disease, is caused by many species of *Leishmania* protozoa and spread by infected phlebotomine female sandflies (1, 2). Leishmaniasis is broadly distributed across the globe in 98 countries but is concentrated in Africa, Asia, and much of the Americas (3, 2, 4).

Leishmaniasis disease presentation is classified into three categories: cutaneous (CL), visceral (VL), or mucocutaneous (MCL) (5, 1). The disease presentation typically depends on the infecting *Leishmania* species, which is strongly influenced by region (1, 2, 6). CL is the most prevalent form of disease worldwide. CL disease presentation is extremely diverse and dependent upon complex interactions amongst parasite, host, and vector factors, but is most often characterized by a non-healing ulcer at the site of an infecting sandfly bite (1). Most cases of CL remain mild and may be self-healing, which renders a comprehensive accounting of incidence challenging (6). Infections from so-called 'New World' *Leishmania* species are more likely than 'Old World' infections to progress beyond self-healing ulcers (6). In these cases, CL ulcerations may become chronic or, in severe cases, progress to nasopharyngeal destruction, facial disfigurement, or life-threatening systemic infection (6). Acute CL may disseminate locally, a rare clinical presentation that is increasing in frequency in New World infections (1). This manifestation ranges in severity, of which the rarest and most severe is disseminated CL (DCL), which presents as nonulcerating lesions in areas like the face and extensor limb surfaces, may cause deep tissue destruction, and persists indefinitely (1, 6). Some cases of CL can become more severe upon co-infection by strains that cause both CL and MCL (7, 6). Certain sandfly species, particularly members of the *L. Vianna* subgenus in *L. braziliensis* complex are strongly associated with more severe and protracted infections with the possibility of developing MCL

(1). Even mild cases of CL can result in life-long scars or serious disability, sometimes becoming a source of stigma (8). Because patients are often unaware of their bites, a combination of clinical features, epidemiological history, and laboratory diagnosis is most often employed to diagnose CL (6, 2). Prevention of CL relies entirely upon bite prevention, as there are no prophylactic medications or vaccinations currently developed (1, 2). Furthermore, there is no single treatment course following infection, as treatment depends on both infecting species and clinical presentation (2, 9).

CL is the most prevalent form of leishmaniasis worldwide, with over 350 million people considered at-risk and an annual estimated incidence of 2-2.5 million cases globally (5, 2, 6, 8). CL was characterized as a severely neglected and Category I emerging and uncontrolled disease by the WHO as of 2009 (2, 6, 3, 8). Control of CL is made especially challenging due to the multiple infectious pathways: it may be acquired from approximately 20 *Leishmania* species, which interact with multiple arthropod vectors and animal reservoir populations (10, 9, 3). Furthermore, CL vector species often dwell in tropical rainforest biomes, where vector-control interventions such as insecticide usage are both logistically challenging and of dubious conservational merit (11). Finally, the global and local distribution of vector species is dependent on a complex interplay of factors both climatic and anthropogenic and thus prone to change (11).

Nonetheless, the vast majority - over 90% - of CL cases are concentrated in just 7 countries: Afghanistan, Algeria, Iran, Peru, Saudi Arabia, Syria, and Brazil (6). In 2018, 16,167 of 261,608 CL cases reported by the WHO were located in Brazil (8). Only Afghanistan and Pakistan reported higher case numbers in that year (8). Within the Americas region, Brazil accounted for 35% of CL cases reported in 2018 (8*).* Incidence in Brazil has decreased since the turn of the century, with approximately 20,000 cases reported to PAHO in 2017 as compared to approximately 27,000 in 2000 (8, 12). This decline is not perfectly consistent, however; cases increased 38% between 2016 and 2017 (8, 12). Within Brazil, CL is well-established and endemic: every state reports cases (13). Transmission is associated with more than one vector species in each state, with the Amazon region in particular home to over 400 phlebotomine sand fly species, and many may be competent to carry and transmit *Leishmania* (13, 14, 15, 16, 17). To date, seven *Leishmania* species have been indicated as primary causes of CL (1). These *Leishmania* species have distinct geographical distributions and are carried by a host of sandfly species; vector species of sand fly appear to differ by *Leishmania* species (18). Similarly, reservoir populations are many and varied, including species from seven mammal orders (19).

Brazilian CL transmission is distributed unevenly across the population. The majority (68.7%) of cases occur in men, and most cases affect individuals between the ages of 20 and 50 years old (12). As a neglected disease, CL infection is thought to occur mostly among low-income populations (10). A recent study using spatiotemporal statistical scan analysis of incidence across Brazil found the northern and central regions of the country to be a primary cluster for CL infection, with most infections occurring within the Brazilian Legal Amazon (BLA) and a large persistent hotspot located in the northeastern state of Pará (PA) (20, 7).

Pará has been characterized as highly endemic for *Leishmania braziliensis braziliensis* since the 1970s, when species of the genus *Psychodopygus* were reported as the most common phlebotomine fly in the area (21). It is consistently identified as a high-transmission state in modern reports, as well (5, 22, 20). New causative and vector species implicated in the spread of CL have been continuously characterized in Pará through to the present day (14-17). CL transmission in PA is currently thought to be caused by four main *Leishmania* species: *L.* (*Viannia*) *braziliensis, L.* (*Leishmania*) *amazonensis, L.* (*V.*) *lainsoni*, and *L.* (*V.*) *lindenbergi* (23, 24). Of these, the most commonly isolated *Leishmania* species has been *Leishmania (Viannia) lindenbergi* (43.7%) (24). Scientific understanding of PA reservoir and host species remains incomplete: host species for *Leishmania* are potential reservoirs, but because CL dynamics are highly temporally and regionally variable, cumbersome local ecological and parasitological analyses tare necessary to reservoir species identification (19). One literature review identified more than 70 documented host species and 14 potential reservoir species spanning seven mammalian orders in Brazil alone, with putative reservoirs identified as such only when the species had been documented to retain infection or transmit the *Leishmania* parasite to vectors (19).

As with any vector-borne disease, sociodemographic, anthropogenic, and climate factors all play a role in modifying CL transmission cycles. Poverty is frequently cited as a risk factor for infection, and this may act along multiple axes (10). For one, household characteristics associated with low-income status, including non-durable wall construction, the absence of gas stoves, and lack of clean water and sanitation carry an increased risk of CL infection in Brazil (25, 22). Malnutrition also increases host susceptibility to CL infection (4). The high proportion of CL cases among males may be driven by profession, as the sandfly vector species of CL dwell in forests and may be encountered at elevated rates by agricultural or forestry workers (9, 26, 27). Indeed, these historically male-dominated occupations have been found to be significant determinants favoring CL infection (10,27). Other activities occurring in rainforested areas, including fishing, hunting, and firewood collection, are also associated with increased risk of CL infection (10, 26).

Anthropogenic factors including deforestation and urbanization with increased peri-urban expansion are also associated with CL transmission, although directionality varies. This lack of consensus is likely due to the vast number of *Leishmania* vector species and an ensuing variable response to habitat alteration (18). CL transmission risk, unlike VL, appears to remain peripheral to the forest and does not expand directly into urban areas, but peri-urban development may have diverse effects (25). There is no question that the expansion of the wild-urban interface in the modern era has increased human exposure to environments in which *Leishmaniasis* vector species are firmly established. Studies like a Mesoamerica-wide model of CL incidence and distribution found that fragmentation of forests by either agricultural expansion or urbanization, measured via edge metrics, did not rank within the 10 most influential predictors of CL incidence at all, although this may have resulted from the obscuration of fine-grained, highly localized, and variable effects across a broad study area (28). In the state of Rondônia, it has been suggested that increasing urbanization leads to decreased exposure to sandflies, reducing CL transmission (22, 29). On the other hand, a study in the municipality of Caxias, within the state Maranhão, found peri-urban expansion in the region to be associated with increased CL incidence (27). There are few studies investigating statewide CL incidence in PA, but a study centered in the PA municipality of Cametá found deforestation to be a strongly significant, directly associated driver of CL incidence (23).

Climate factors influencing CL incidence and distribution are many and varied. One recent study of South and Meso-America found that climate variables drove ~80% of the variation in recent past CL case distribution, and that temperature and precipitation seasonality variables alone could explain more than 40% of said variance (28). This suggests a very strong climatic influence on incidence. Temperature, precipitation, and humidity are commonly considered environmental factors (25, 23, 30, 22, 3). Increased CL transmission has been strongly associated with the rainy season in Brazil, possibly indicative of an association between

CL and precipitation level or air humidity (23). Differing tolerances of vector species prevent the identification of a single precipitation range that is favorable to CL transmission: high precipitation has been directly associated with CL incidence in some studies and inversely associated in others (25, 30, but 22, 3). In fact, one study found that CL incidence was highest in areas with narrow seasonal ranges of both temperature and precipitation (28). Vegetation measures are also commonly employed in investigations of the effect of climate on CL, as warm, forested areas are thought to encourage the presence of both reservoir and vector species by providing protection and shelter (5, 31, 25). Indeed, higher measures of the Normalized Difference Vegetation Index (NDVI) and Enhanced Vegetation Index (EVI) have consistently been positively associated with CL (22, 32, 25). CL transmission has also been found to cycle with seasonal El Niño events: a study in Costa Rica found that models using just temperature and MEI could predict CL incidence dynamics with ~75% accuracy, suggesting a powerful connection (30). Previous studies of CL in the northern city of Manaus, Amazonas have found that El Niño Southern Oscillation (ENSO) and downstream meteorologic measures such as precipitation, humidity, and temperature are strong drivers of CL incidence in the study areas (33, 34). One study found El Niño conditions preceding expanded incidence by approximately 4-6 months and La Niña presaging contracted incidence by the same time period (34). Another found the opposite effect, with La Niña driving increased rainfall in the late year to be followed by an increase in CL cases (33). Despite this apparent lack of consensus, it appears highly likely that ENSO effects do have some impact on CL case incidence in Brazil.

Given this close interplay of climate factors and CL, it is no surprise that modern research into the potential effects of climate change in Brazil have shown potentially large impacts on disease dynamics (33, 23, 28, 35, 25). This is due to predicted alteration to 'landscape epidemiologies' that will alter vector-borne disease transmission cycles alongside climate and meteorologic conditions (28, 35, 36, 25). Potential effects will be transmitted along multiple axes, including direct effects on factors like temperature and rainfall, which may influence vector competence and parasite life cycles; indirectly, by effects on vector population viabilities; and indirectly, via socioeconomic status (SES) changes that will alter human interaction patterns with vector species (28). As with other investigations of the drivers of CL incidence, highly localized dynamics and the complexity conferred by multiple vector and reservoir populations appears to complicate studies of the effect of climate change on CL. A study investigating likely climate change impacts on South and Meso-American CL found that increases in temperature and precipitation seasonality – measured as 100-fold the standard deviation of monthly temperature values and the coefficient of variation of monthly precipitation values, respectively -- would contract the geographic range incidence by 35-50% (28). One ecological niche modeling investigation in Southern Brazil found likely expansion in *L. whitmani* populations with a concurrent rise in CL across multiple scenarios of global climate change conditions, while a later study instead found potential habitat expansion for *L. intermedia* in northeastern Brazil and a southerly habitat shift for *L. neivai* (37 but 38). Results such as these highlight the immense complexity involved in forecasting alterations in CL incidence. In summary, CL can be understood to be highly climatologically responsive disease of concern in Pará, with little available data to predict how climate change will affect its incidence or distribution. Taking together the hefty burden of 'New World' CL incidence within Brazil, the persistent hotspot of Brazilian CL incidence within Pará, and the highly variable behavior of the disease over relatively small spatial scales, furthering an understanding of the relationships between climate variables and CL in PA proves meritorious. This study aims to provide insight mechanisms of influence on CL incidence in a region accounting for many cases of the disease. Deeper understandings of factors influencing CL incidence in PA can inform CL management policies within the region in the near future, and may additionally yield useful information in understanding possible trajectories of CL incidence and spatial distribution under the effects of global climate change.

MANUSCRIPT

ABSTRACT

Title: Spatiotemporal Distribution of Cutaneous Leishmaniasis in Relation to Climate Factors, Pará, Brazil, 2007-2019

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Background Cutaneous leishmaniasis (CL) is an endemic vector-borne disease of Brazil, which is home to ~40% of CL cases in the Americas. Well-known environmental factors associated with incidence include deforestation, precipitation, and temperature, but CL dynamics are highly variable and little data are available for many states. This study evaluates the role of environmental factors on CL incidence in the state of Pará (PA), identifying high-risk and likely regional clusters of disease incidence.

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Results Over the study period, 46,163 cases of CL were reported from PA (population 7,588,078). Cumulative incidence was 608 cases per 100,000 people, with average annual

incidence of 47 cases per 100,000 people. In the overall model, which explained 57% of variance, monthly minimum temperature, monthly maximum temperature, monthly total precipitation, urbanicity, and month displayed significant association with CL incidence in Pará. Seasonally lagged MEI and year did not achieve significance in the overall model. There was a spatially heterogenous distribution of high-high and low-low risk municipalities across the state, and stable and significant clusters of highest-risk municipalities were found in the northwestern and southwestern regions of the state.

Discussion This study provides insight into the distribution of CL across Pará, showing a likely role of environmental factors including minimum and maximum monthly temperature and total monthly precipitation on disease incidence and clustering in the state. These results suggest possible factors of influence leading to high incidence years and tactics for managing prevention and control efforts of CL in Pará, Brazil.

INTRODUCTION

Cutaneous leishmaniasis (CL) is the most prevalent disease presentation of the leishmania parasites worldwide, with over 350 million people considered at-risk and an annual estimated incidence of 2-2.5 million cases globally (5, 2, 8). Many areas in the western hemisphere are highly endemic with nearly 40% of CL cases arising in the Americas occur in the nation of Brazil (8). CL is characterized as a severely neglected and Category I emerging and uncontrolled disease by the WHO as of 2009, therefore, improving the understanding of the epidemiology of the disease is crucial to mitigation (8).

Pará, a state in Northern Brazil, is home to one of the highest state incidence rates of cutaneous leishmaniasis infection in the nation, with an average number of cases approximately 3,500 per year. However, there have been very few studies on the specific dynamics of CL infection within Pará relative to its more populous neighbors, despite the highly variable infectious pathway of CL and the Amazonian climates of Pará (14-17, 25). Pará is known to be home to several species of phlebotomine flies that act as vectors for CL, and the Amazon region in particular is home to over 400 phlebotomine sand fly species, many of which may be competent to carry and transmit *Leishmania* (13, 14-17). Additionally, CL is a disease of the forest verge, and Pará is experiencing deforestation at a rapid pace. This opens the possibility of a near-future rapid expansion of CL within the state of Pará, as the disease vectors shift and diversify or as humans encounter vectors at an increasing rate (25).

Climate factors also play a powerful role in CL disease transmission, with one recent study finding climate factors capable of explaining 80% of CL incidence variability alone, with 40% of the explanatory power encompassed by just temperature and precipitation data (28).

Variations in temperature and precipitation are thought to be primarily driven by the rainy season and El Niño Southern Oscillation (ENSO) perturbations, both of which are powerful explanatory factors on their own and may be subject to further alterations because of climate change in the near future (23). Other climatologic factors, including wind speed variation and land use modification are thought to play a role in CL transmission and incidence rates but are largely understudied (10, 25).

To date, no studies have investigated the associations between environmental factors and cutaneous leishmaniasis incidence in Pará at the municipality level of distribution. It is therefore uncertain what factors drive CL in Pará, how these factors may change over the spatial region, and how they have altered over time. This study aims to describe the incidence of CL on a municipality level in Pará, to determine which, if any, environmental factors impact CL incidence in Pará, and to evaluate potential high-risk areas and cluster areas across Pará over the time period 2007-2019.

This investigation is of especial interest in the context of global climate change. CL has been variably predicted to contract or expand in northeastern Brazil under differing climate change scenarios forecasting more drastic seasonal meteorologic variability, possibly downstream of strong influence by hyperlocal weather patterns (28, 38). For this reason, it is crucial to understand and contextualize historical climate data with CL incidence: a better understanding of risk factors for increased CL incidence and the location of high-risk regions could provide information towards understanding a likely future of CL in Pará as meteorologic trends and climate types alter. This study could also inform short-term decision-making processes related to vector control in the aim of future outbreak mitigation and prevention.

METHODS

Ethical considerations

No identifiable information was received as case data was aggregated by municipality and taken from a publicly available data source.

Study setting and population

This study was conducted in Para, a partially coastal state in northern Brazil. Pará is traversed by the lower Amazon River. It is the most heavily populated state in the North Region but only contains ~4% of the Brazilian population. Pará is the second-largest state in Brazil by area. Its capital is the port city of Belem, which lies in the northeast of the state with an estimated population of 1,500,000 people. Pará possesses a primarily tropical monsoon climate type, with some areas of tropical rainforest and a small region of tropical savannah. Broad swaths of Pará are categorized as part of the Amazon rainforest, and Pará is home to the largest biodiversity in the world.

Data collection

Cutaneous leishmaniasis is passively surveilled with healthcare providers reporting cases to the state health notifiable disease system. Total numbers of CL cases by reporting municipality were obtained from the Information System of Diseases Notification (Sistema de Informação de Agravos de Notificação—SINAN) data portal (39). Case numbers were obtained for reporting municipality, as well as sex and age distribution of cases by municipality. Data were collected for January 2007, the earliest date of availability, until December 2019. Data January 2020 and later was excluded, as CL incidence reporting was likely disrupted by the advent of the COVID-19 pandemic.

Social demographic data at the municipality level, including population and percent urban population, were obtained through the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatıstica, IBGE) (40).

Climate data were obtained via the WorldClim database for 2000-2019 (41). Climate variables of interest included minimum monthly temperature, maximum monthly temperature, and total monthly rainfall. The minimum temperature of each year's coldest month, maximum temperature of the year's warmest month, and total annual precipitation were calculated in R from these datasets. Multivariate El Nino Southern Oscillation Index data was obtained through the Physical Sciences Laboratory of the National Oceanic and Atmospheric Administration (NOAA) for 1979-2023 and subsequently cropped to the years of interest (42). This data was used to calculate average annual MEI data.

Statistical analysis

All analyses were conducted using R and R Studio (43). Case data was aggregated by municipality, and then reviewed by age, sex, urbanicity, and year of diagnosis, for the years 2007-2019. A multivariate negative binomial regression model was generated, accounting for overdispersion and seasonal MEI lag, to examine associations between environmental variables of interest and the outcome (incidence of CL) at the municipality level. Collinearity was assessed and corrected by removal of variables with demonstrated collinearity, as indicated by a VIF value over 10. Backwards elimination was conducted to reach final models. Individual years were also used to create models. Overall cumulative models used minimum monthly temperature, maximum monthly temperature, total monthly precipitation, percent of the population considered urban, percent of the population identified male, average annual MEI values, and seasonally lagged monthly MEI data as predictors. Annual models took minimum monthly temperatures, maximum monthly temperature, total monthly precipitation, a seasonally lagged MEI value, urbanicity, and percentage population male into as predictors. Variance inflation factor (VIF) was assessed for each covariate; none were collinear and therefore all kept. Model fit was assessed using Nagelkerke R-squared values.

Spatial analysis

Spatial analysis was conducted using aggregated cases at the municipality level. Baseline information, including annual incidence of cutaneous leishmaniasis per 100,000 people by municipality was obtained, and cumulative incidence mapping per 100,000 people was carried out at the municipality level. A Besag-York-Mollie model was fit to the data and significantly high risk areas were identified using Bayesian exceedance probabilities at a 5% alpha level. Maps were produced in R Studio using WGS84 projection.

To evaluate spatial heterogeneity at the municipality level, both spatial and aspatial goodness of fit testing was conducted. Spatial autocorrelation was tested using Moran I statistics, including the Global Moran I for Poisson distributions. Candidate clusters of CL incidence by municipality were visualized using a Local Moran's I Local Indicators of Spatial Association

(LISA) evaluation under the constant risk Poisson assumption. Finally, Kulldorff's Scan Statistics were used to visualize the most likely clusters of CL cases within Pará.

RESULTS

Study area and population

A total of 46,163 cases were identified through the Sistema de Informação de Agravos de Notificação (SINAN) database in Pará from January 2007 – December 2019. Pará is comprised of 143 municipalities (Figure 1). Of those, 140 reported at least one visceral leishmaniasis case during the study period (Figure 2a). Baseline visual evaluation with no adjustment, for population or otherwise, shows high case counts in the western half of the state and uneven case distribution. Of these cases reported to SINAN, 664 lacked demographic information. Of those with reported demography, the overwhelming majority of cases were male (80.5%) and mixed-race (71.8%), and most were 20-39 years of age (49.3%) (Table 1). The lowest incidence year was 2016, with only 1,737 cases reported. Over the study time, case reporting rates were relatively constant. The highest number of cases were reported in 2014 and 2015 (each 4,526), each of which accounts for 9.8% of the cases reported during the study period. This is 2.6 times higher than 2016, which immediately followed.

The total population of Pará was 7,588,078 in 2010, resulting in a cumulative incidence of 608 cases per 100,000 persons during the study period. The average annual cutaneous leishmaniasis incidence for the state was 47 cases per 100,000 persons. Santarem in the central northern region of Pará, with a population of 294,774, reported the highest cumulative case count (2,156 cases), while a close neighbor, Medicilandia, reported the highest average annual incidence (7,161 cases per 100,000 persons) during the study period.

Environmental conditions varied across the state and by year, with minimum temperatures ranging from 20.0 to 24.1C during the study period, maximum temperatures ranging from 31.3 to 36.1C, annual precipitation ranging from 1352 to 3248mm, and average monthly MEI ranging from -4.6 to 3.1 (Table S1).

Multivariate analysis

In the overall, multi-year, model, minimum temperature, maximum temperature, precipitation, urbanicity, and month of reporting were all significantly associated with incidence at an alpha level of 5% (Table 2). The associations of seasonally lagged MEI and year did not attain significance. Of significant covariates, urbanicity index and month were positively associated, while average monthly precipitation, monthly maximum temperature, and monthly minimum temperature were negatively associated. Urbanicity and minimum temperature both had particularly large-magnitude estimates (β). Average precipitation had the smallest estimate value. Model predictive power was good, with a pseudo-R-squared value of 0.57, meaning that approximately 57% of the spatiotemporal distribution of CL incidence in Pará could be explained by the model (Table 2).

Annual models were very consistent overall and had similar pseudo-R-squared values to the overall model (Table S2). MEI value attained significance in many of the annual models, unlike the overall model. Minimum monthly temperature, maximum monthly temperature, monthly precipitation, and urbanicity were all significantly associated with CL incidence in annual models. The associations of minimum monthly temperature, maximum monthly temperature, and monthly precipitation were mostly negative, while urbanicity was consistently positively associated. The directionality of lagged MEI association was variable.

Akaike Information Criterion (AIC) scores were lower for all fitted models than their null counterparts, as were deviances, indicating that incorporating the utilized covariates into modeling improved explanatory power of the spatiotemporal variability of CL relative to a purely spatial fitting.

Spatial analyses

To investigate patterns of CL across reporting municipalities, one choropleth each was made depicting prevalence (Figure 2a), cumulative incidence (Figure 2b), and annual incidence (Figure S1). Prevalence mapping demonstrates that the highest number of cases over the study period appears in a Y-shape across the state's municipalities, with relatively low counts in the coastal north and border municipalities (Figure 2a). Calculations of cumulative incidence show that this pattern of occurrence is strengthened after accounting for population sizes in differing municipalities: low-incidence municipalities cluster in the coastal north, where the state capitol of Belem lies, while some sparsely populated municipalities in the west have high incidence rates (Figure 2b). The uneven patterning of both prevalence and cumulative incidence maps suggest CL may be spatially heterogenous, i.e., irregularly distributed across Pará. Cumulative incidence mapping utilizes maximal available data but may be skewed by contributions from high-incidence or epidemic years. Therefore, annual incidence maps of the three highest- and lowest-incidence years in Pará were made; the close consistency of these six maps with the pattern of incidence in cumulative maps suggests that CL distribution is, in fact, consistent regardless of the severity of CL in a given year (Figure S1). Spatial and aspatial smoothing tactics were used to account for possible noise in the incidence rate data due to low CL counts (Figures S2, S3). Of spatial empirical Bayes tactics used, smoothing under a Queen's contiguity neighbor framework, pictured, was marginally most impactful on root mean-squared error (RMSE) (Figure S1). Overall, neither smoothing approach altered CL incidence maps, suggesting the cumulative distribution of cases across Pará is not strongly influenced by noisy municipalities. Statistical exploration via chi-square testing for overdispersion under a Poisson probability model indicated significant spatial heterogeneity under the null (Statistic = 93,788, p-value = 0.002).

A Besag-York-Mollie model was therefore used to account for both spatially structured and spatially independent processes contributing to the observed heterogeneity of CL incidence. The $\tau 2$ parameter had a mean value of 2.75, while $\sigma 2$ had mean 0.27, suggesting that more of the total variability in state-wide CL incidence is due to spatially structured processes than aspatial processes. Exceedance probability mapping of the model results indicated that broad swaths of the western half of the state, excepting the central western edge, are areas of significantly high risk for CL infection (Figure 3d). Interestingly, these central western edge regions are situated in the only regions of Pará that are described as having tropical monsoon climates, rather than the predominating tropical rainforest climate of the state. The high-risk municipalities consistently remain classified as such year after year, even when comparing epidemic years like 2014 and 2015 with the study period's year of lowest incidence, 2016 (Figure 3abc).

A test of Global Moran's I after Empirical Bayes smoothing, used to check for spatial autocorrelation of CL across the study period, found very high likelihood of clustering while accounting for both sparse data and possible outliers (Statistic = 0.455, p-value = 0.002). Exploratory mapping towards identification of local clusters of high-risk municipalities was undertaken via Local Moran's I testing under a constant risk assumption. This revealed clusters of high risk municipalities in the northwestern extreme of the state, in the Amazon Basin mesoregion, as well as in the southwestern corner and extending into the central-eastern region (Figure 4a). Low risk municipalities clustered together largely near Belem, in the northeast, and in the southeastern extreme of the state. There were a small number of discordant municipalities, largely appearing in between clusters and therefore likely artifactual. Clustering was not identically dispersed across the state in the highest- and lowest-incidence years of 2014/2015 and 2016, but the expansive high-risk cluster remained in both years, as did the low-risk cluster in the northeast (Figure 5). This suggests that, while there is some mutability in the exact composition of high- and low-risk clustering in Para year-by-year, some regions of the state can reliably be considered hot spots. Kuldorff's spatial scan statistics at $\alpha = 2$ generated a most likely cluster encompassing the western half of the state, even when clusters sizes were restricted to a maximum incorporation of 25% of Para's population (Figure 4b). The most likely cluster encompasses western municipalities clustered as high-risk under the earlier Local Moran's I testing, while the largest secondary cluster appears to be composed of eastern high-risk municipalities.

DISCUSSION

Overall, our study findings demonstrate persistent CL transmission across the study period, and heterogenous distribution across the state of Pará. Across the study period, the PA municipality with the highest total case count of CL was the central northern municipality of Santarém, population 294,774. A close neighbor, Medicilândia, reported the highest average annual incidence (7,161 cases per 100,000 persons) during the study period. The western region of the state exhibited a consistently high incidence rate, as is also indicated by the available data on cumulative incidence and prevalence through the study period. High risk regions were distributed in very similar manners in both high-incidence (epidemic) and low-incidence years, for example 2015 as compared to 2016. This suggests that these municipalities may be good candidates for intensive control and prevention programs in any given year. The stability of high-risk region placement suggests that interventions designed to control vector and reservoir abundance have high potential. These high-incidence municipalities all share a tropical rainforest climate and have few large urban areas. Notably, the most highly rainforest-covered region of Pará does not appear to lie within this high-risk cluster, possibly due to the density of forest and its relative inhospitableness.

Environmental conditions all varied by year, as expected, with precipitation having a particularly broad IQR. In the overall model, average maximum temperature, average minimum temperature, and average monthly precipitation were significantly and inversely associated with monthly incidence. Urbanicity was significantly positively associated, while seasonally lagged MEI and year showed no significant association. In this first study to evaluate the municipality level CL incidence in Pará, our results were consistent with previous studies of CL in Brazil with a disease profile that was highly variable and highly responsive to climate (27, 32, 10). In these other Brazil studies, CL incidence was associated with a few climate factors (MEI and temperature) in some studies, or almost entirely with anthropogenic factors (30, 44, 34 but 10). A study of CL predictors across Meso- and South America found that temperature and precipitation variables were the strongest predictors of CL distribution, with seasonality also ranking as one of the more significant predictors (28). A Costa Rica study fitting linear models of CL incidence to climate predictors found much higher predictivity up to 12 months ahead when models incorporate climate variables, although this study did not interrogate directionality of association (30). Interestingly, the Costa Rican study found a 3-year cycle of CL incidence associated with MEI and temperature; the shorter time increments used in our study may explain the non-significance of MEI in the overall model (30). A study in Bahía, Brazil, found that dry conditions lead to spikes in CL incidence 3 months later with improved model performance when MEI and maximum noontime temperature were included (44). In Manaus, a study using wavelet analysis found that during La Niña events, CL incidence spikes following increased late-fall rainfall, suggesting a relationship of climatic variables mediated by MEI values (33). In our overall model, the extremely low p-values of significant parameters and high (0.57) pseudo-R-squared value of the model also support these variables' roles as drivers of CL incidence in Pará. This robust pseudo-R-squared value indicates that approximately 57% of CL incidence variability is captured by the model, which echoes previous findings that models using only abiotic predictors to model CL distribution can account for a vast majority of variance in disease incidence (28). Potential remains for increasing explanatory power by incorporating more parameters, including landscape predictors that are more fine-scaled than simple urbanicity measures, such as irrigated land area or measures of canopy density, as used elsewhere (28). The lack of significance associated with inter-annual comparisons demonstrates that CL incidence did not significantly change across the study period, suggesting no broad temporal trends in CL incidence in Pará during the study period. This is consistent with work in Maranhao suggesting alteration in fine- but not coarse-grained spatial incidence of CL in Brazil (45).

On the other hand, seasonality was associated with CL incidence in PA with higher incidence in the wet season late in the year, as has also been found in Costa Rica, the Brazilian state Manaus, and the PA municipality of Caméta (30, 33, 23). When controlling for all other covariates, monthly minimum temperature and monthly maximum temperature were negatively associated with CL, suggesting that incidence may occur within an 'optimal band': if either minimum or maximum temperatures increase too much, transmission decreases. This may be due to effects on survival or behavior of the vector and reservoir species in response to meteorologic conditions. Finally, precipitation was negatively associated with CL incidence in the overall model when controlling for all other covariates. This suggests that higher precipitaition may impact vector populations, possibly by shifting environmental conditions outside of a similar 'optimal band' of rainfall. This reinforces the results of a bevy of studies carried out in other regions. These include: a boosted regression tree (BRT) study across Meso- and South America which found high sensitivity of CL distribution to ENSO, temperature, and precipitation factors, a comparison of time-series models in Bahía that found increased CL 3-5 months after decreased precipitation and strong incidence seasonality, a Costa Rica study finding excellent predictivity of models incorporating temperature and MEI, and a Manaus study finding strong responsivity to late-fall rain increases under La Niña conditions (28, 44, 30, 33). A study among forest fragments near Belém, PA, found that that *L. antenusi* sandflies were the most frequently captured putative vector species, and that they decreased in abundance following periods of rainfall (34), providing possible insight into the mechanism underpinning our model findings, as it reflects conditions within PA itself.

Urbanicity was used in this study as a proxy measure for the disturbance of the natural environment by human factors. Our findings of a strong, direct relationship echo previous work carried out in French Guiana, which used ecological niche modelling to investigate the relative contribution of environmental factors like those used in our study and human factors like population density, human poverty indices, and human footprint (31). Compellingly, this study found that areas of high CL risk overlapped with zones experiencing the highest anthropogenic pressure; this suggests that the role of environmental factors may be overshadowed by human drivers in urban and peri-urban environments (31). This effect was most visible on a fine scale in an ecological niche modelling study, but may partially explain the strong effect of urbanicity found in our models (31). Within Brazil, a high-resolution integrated nested Laplace approximation-based study found an association between not only humid, warm climates but also socioeconomic factors including poverty and CL incidence (22). Areas with the lowest socioeconomic status were the most highly affected, while areas with highest access to clean water and sanitation were affected the least (22). In this study, urbanicity may be partially confounded by more precise metrics of poverty and living standard; nonetheless, high prevalence of poor living conditions and poverty within urban regions of PA are likely contributors to this outcome.

The annual models broadly followed the results of the overall model. Average maximum and minimum temperatures, average monthly precipitation, and urbanicity achieved significance in all years. In annual models but not the overall model, lagged MEI values achieved significance in most years, suggesting that El Niño effects are impactful of CL incidence when examined on a finer temporal scale. Minimum monthly temperature and maximum monthly temperature were both inversely associated with CL incidence. Precipitation was similarly negatively correlated across annual models. This reinforces the finding from the overall model that rainfall has a dampening effect on CL incidence. There was little difference in the annual models when comparing one high-incidence year and low-incidence year models; both tracked the overall trend of the annual models closely. McFadden's pseudo-R-squared values for all annual incidence models were similarly predictive to the overall model, with values around 57%.

This study has several limitations. The most significant of these hinges on the passive nature of CL surveillance in Brazil. Many CL infections are likely unreported, as initial bites are subtle and may never develop into severe cases. Dependence upon healthcare reporting consistently leads to under-reporting, especially in areas with poor access to healthcare. This affect may be stronger in more sparsely populated or poorer regions of the study area. These factors contribute to a likely higher true burden of disease than that captured by this study. Model power could be strengthened with the incorporation of additional covariates, such as normalized difference vegetation index (NDVI) values and measures of anthropogenic habitat changes. As some prior fine-scale studies have found strong effects of both climate and sociological factors, the incorporation of further sociodemographic information such as tree coverage, human footprint measures, and social vulnerability index could provide a more thorough picture of likely impactful factors (22, 31). Seroprevalence studies and the incorporation of factors such as distance traveled to health care and municipality-level income data would improve future studies. Misclassification bias is also likely in this study, as it is impossible to ascertain from reporting data where a patient was bitten: rather, only the reporting locale is available. Incorporating travel history from patients would alleviate some of this misclassification bias, especially around Belem.

This is the first known study to examine the association between climactic factors and CL incidence in PA as a monthly time-series regression. Overall, it is clear from the results that environmental factors do play a significant role in influencing the incidence of CL in the PA. Cases cluster strongly in the west, recapitulating coarser scale research by Portella and Kraenkel (20). Further research incorporating other variables, as well as more candidate climatic drivers of CL incidence, including NDVI and ground-level wind speed, would expand the study by strengthening the explanatory power of the models. Such expanded studies would greatly aid in the prediction of likely high-incidence years and regions, enabling heightened monitoring and increased vigilance of healthcare providers in areas which may be high-risk for CL outbreaks in a given year. Despite its limitations, this study contributes to our understanding of CL incidence within the state of Para and is helpful in elucidating fine-grained trends.

CONCLUSIONS

SUMMARY

This study aimed to: describe the incidence and prevalence of cutaneous leishmaniasis in the Brazilian state of Pará from the years 2007 until 2019, explore the spatiality of these factors and elucidate possible clustered municipalities that were high-risk for CL infection and evaluate likely candidate climatic and sociologic variables (like urbanicity, temperature, precipitation, and MEI), for strength of association and explanatory power when applied to CL incidence and distribution in Pará. A review of all spatial parameters affirmed a likely cluster located in the western half of the state of Pará, with extensions into both the northerly and southerly extreme of the state. Models confirmed that climatic factors as well as urbanicity were significantly associated with incidence across the state. In future studies, explanatory power could be raised from ~60% by incorporating more covariates to reflect the effect of anthropogenic change and other likely significant factors.

PUBLIC HEALTH IMPLICATIONS

The results of this study offer an enhanced understanding of the disease, cutaneous leishmaniasis, and its responsivity to climate and environment. Analyses demonstrated a trend towards higher CL incidence as MEI tends towards El Niño-like effects, which is a hallmark weather pattern of global climate change. This can enable public health officers in areas that are likely to be affected by this change to intervene early and mitigate effects, whether by carrying out vector control or increasing public awareness of CL in areas where CL is likely to spread or increase in incidence. Furthermore, spatial analyses revealed areas of highest disease burden as well as areas of highest risk for disease. These pieces of information are useful to health officers wishing to allocate resources more efficiently, towards municipalities that are the most affected or are most at-risk, and to forecast likely years of high CL incidence. Municipalities in discordant High-Low clusters can examine their own policies in contrast to their neighbors' and navigate towards more effective prevention and mitigation policy based on differences. Areas with high risk, especially those with high risk in low-incidence years, can use this knowledge to maintain baseline vector control policies at a reasonable level. This study highlights the utility of a more active surveillance or detection system for CL in Brazil, as counts were likely low and more accurate data could drive much more powerful experimentation.

FUTURE DIRECTIONS

Further research describing the nature, composition, and life cycle of the vector populations, as they may change across Pará municipalities, would provide great insight into what factors may remain un-accounted for. There are considerably many other climatic factors, including wind speed, NDVI, mean diurnal range, water vapor, and land usage purpose, that may act to influence cutaneous leishmaniasis. Social factors of access to healthcare, marginality, and daily occupation should also be considered, as these influence the likelihood of cases being detected by the Brazilian Ministry of Health, or the odds of encountering a vector species of CL. It is also pertinent that some municipalities have proportionally more citizens employed in jobs that take them to the forest verge, such as lumber-industry jobs, where they are much more likely to contact CL than citizens who live in Belem and work in dockyards, for instance.

The results of this study are useful to public health officials who would like to forecast about CL incidence, be it quantitatively or spatially, by drawing inference from areas of high likelihood and significant drivers of CL incidence as identified by this paper. Future studies should be implemented to strengthen models and account for further likely factors of import in the causal chain of CL infection.

REFERENCES

1. Bailey MS, Lockwood DNJ. Cutaneous leishmaniasis. *Clinics in Dermatology*. 2007/03/01/ 2007;25(2):203-211. doi:https://doi.org/10.1016/j.clindermatol.2006.05.008
2. De Vries HJC, Reedijk SH, Schallig HDFH. Cutaneous Leishmaniasis: Recent Developments in Diagnosis and Management. *American Journal of Clinical Dermatology*. 2015;16(2):99-109. doi:10.1007/s40257-015-0114-z
3. Pigott DM, Bhatt S, Golding N, et al. Global distribution maps of the leishmaniases. *eLife*. 2014/06/27 2014;3:e02851. doi:10.7554/eLife.02851
4. Reithinger R, Dujardin J-C, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *The Lancet Infectious Diseases*. 2007;7(9):581-596. doi:10.1016/S1473-3099(07)70209-8
5. Alvar J, Vélez ID, Bern C, et al. Leishmaniasis Worldwide and Global Estimates of Its Incidence. *PLoS ONE*. 2012;7(5):e35671. doi:10.1371/journal.pone.0035671
6. Hepburn NC. Cutaneous leishmaniasis: current and future management. *Expert Review of Anti-infective Therapy*. 2003/12/01 2003;1(4):563-570. doi:10.1586/14787210.1.4.563
7. Rodrigues MGDA, Sousa JDDB, Dias ÁLB, Monteiro WM, Sampaio VDS. The role of deforestation on American cutaneous leishmaniasis incidence: spatial-temporal distribution, environmental and socioeconomic factors associated in the Brazilian Amazon. *Tropical Medicine & International Health*. 2019;24(3):348-355. doi:10.1111/tmi.13196
8. Organization WH. Leishmaniasis. https://apps.who.int/neglected_diseases/ntddata/leishmaniasis/leishmaniasis.html
9. Kaye P, Scott P. Leishmaniasis: complexity at the host–pathogen interface. *Nature Reviews Microbiology*. 2011/08/01 2011;9(8):604-615. doi:10.1038/nrmicro2608
10. Buzanovsky LP, Sanchez-Vazquez MJ, Maia-Elkhoury ANS, Werneck GL. Major environmental and socioeconomic determinants of cutaneous leishmaniasis in Brazil - a systematic literature review. *Revista da Sociedade Brasileira de Medicina Tropical*. 2020;53doi:10.1590/0037-8682-0291-2019
11. Lainson R, Shaw JJ. Epidemiology and ecology of leishmaniasis in Latin-America. *Nature*. 1978/06/01 1978;273(5664):595-600. doi:10.1038/273595a0
12. Organization P-AH, World Health Organization ROftA. *Leishmaniasis: Epidemiological Report of the Americas*. Vol. 7. 2019.
13. Rangel EF, Lainson R. Proven and putative vectors of American cutaneous leishmaniasis in Brazil: aspects of their biology and vectorial competence. *Memórias do Instituto Oswaldo Cruz*. 2009;104(7):937-954. doi:10.1590/s0074-02762009000700001
14. Silveira FT, Ishikawa EAY, De Souza AAA, Lainson R. An outbreak of cutaneous leishmaniasis among soldiers in Belém, Pará State, Brazil, caused by<i>Leishmania (Viannia) lindenbergi</i>n. sp. *Parasite*. 2002;9(1):43-50. doi:10.1051/parasite/200209143
15. Silveira FT, Lainson R, Shaw JJ, Braga RR, Ishikawa EE, Souza AA. [Cutaneous leishmaniasis in Amazonia: isolation of Leishmania (Viannia) lainsoni from the rodent Agouti paca (Rodentia: Dasyproctidae), in the state of Pará, Brazil]. *Revista do Instituto de Medicina Tropical de Sao Paulo*. 1991 Jan-Feb 1991;33(1):18-22. doi:10.1590/s0036-46651991000100004
16. Silveira FT, Shaw JJ, Braga RR, Ishikawa EA. Dermal Leishmaniasis in the Amazon Region of Brazil: A New Parasite from the State of Para. *Memórias do Instituto Oswaldo Cruz*. 1987;82(2):3.

17. Silveira FT, Souza AAA, Lainson R, Shaw JJ, Braga RR, Ishikawa EA. Cutaneous Leishmaniasis in the Amazon Region: Natural Infection of the Sandfly Lutzomyia Ubiquitalis by Leishmania in Para State, Brazil. *Memórias do Instituto Oswaldo Cruz*. 1991;86(1):3.
18. Rangel EF, Lainson R, Carvalho BM, Costa SM, Shaw JJ. Sand Fly Vectors of American Cutaneous Leishmaniasis in Brazil. In: Rangel EF, Shaw JJ, eds. *Brazilian Sand Flies : Biology, Taxonomy, Medical Importance and Control*. Springer International Publishing; 2018:341-380.
19. Roque ALR, Jansen AM. Wild and synanthropic reservoirs of Leishmania species in the Americas. *International Journal for Parasitology: Parasites and Wildlife*. 2014/12/01/ 2014;3(3):251-262. doi:https://doi.org/10.1016/j.ijppaw.2014.08.004
20. Portella TP, Kraenkel RO. Spatial-temporal pattern of cutaneous leishmaniasis in Brazil. *Infectious Diseases of Poverty*. 2021;
21. Ward RD, Shaw JJ, Lainson R, Fraiha H. Leishmaniasis in Brazil: VIII. Observations on the phlebotomine fauna of an area highly endemic for cutaneous leishmaniasis, in the Serra dos Carajas, Pará State. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1973/01/01/ 1973;67(2):174-183. doi:https://doi.org/10.1016/0035-9203(73)90142-9
22. Karagiannis-Voules D-A, Scholte RGC, Guimarães LH, Utzinger J, Vounatsou P. Bayesian Geostatistical Modeling of Leishmaniasis Incidence in Brazil. *PLoS Neglected Tropical Diseases*. 2013;7(5):e2213. doi:10.1371/journal.pntd.0002213
23. Da Silva Sousa Júnior A, Gonçalves NV, Do Socorro Carvalho Miranda C, et al. Cutaneous leishmaniasis spatial distribution and epidemiological and environmental risk factors in Cametá, state of Pará, Brazil. *The Brazilian Journal of Infectious Diseases*. 2020;24(4):330-336. doi:10.1016/j.bjid.2020.06.008
24. Gonçalves LP, Santos TVD, Campos MB, et al. Further insights into the eco-epidemiology of American cutaneous leishmaniasis in the Belem metropolitan region, Pará State, Brazil. *Revista da Sociedade Brasileira de Medicina Tropical*. 2020;53doi:10.1590/0037-8682-0255-2020
25. Valero NNH, Uriarte M. Environmental and socioeconomic risk factors associated with visceral and cutaneous leishmaniasis: a systematic review. *Parasitology Research*. 2020/02/01 2020;119(2):365-384. doi:10.1007/s00436-019-06575-5
26. Martins LM, Rebêlo JMM, Santos MCFVd, Costa JML, Silva ARd, Ferreira LA. Ecoepidemiologia da leishmaniose tegumentar no Município de Buriticupu, Amazônia do Maranhão, Brasil, 1996 a 1998. *Cadernos de Saúde Pública*. 2004;20
27. Oliveira RS, Pimentel KBA, Moura ML, et al. Clinical, epidemiological and climatic factors related to the occurrence of cutaneous leishmaniasis in an endemic area in northeastern Brazil. *Brazilian Journal of Biology*. 2021;81(3):557-565. doi:10.1590/1519-6984.224937
28. Purse BV, Masante D, Golding N, et al. How will climate change pathways and mitigation options alter incidence of vector-borne diseases? A framework for leishmaniasis in South and Meso-America. *PLOS ONE*. 2017;12(10):e0183583. doi:10.1371/journal.pone.0183583
29. Shaw JJ, De Faria DL, Basano SA, et al. The aetiological agents of American cutaneous leishmaniasis in the municipality of Monte Negro, Rondônia state, western Amazonia, Brazil. *Annals of Tropical Medicine & Parasitology*. 2007/12/01 2007;101(8):681-688. doi:10.1179/136485907X229103
30. Chaves LF, Pascual M. Climate Cycles and Forecasts of Cutaneous Leishmaniasis, a Nonstationary Vector-Borne Disease. *PLoS Medicine*. 2006;3(8):e295. doi:10.1371/journal.pmed.0030295

31. Chavy A, Ferreira Dales Nava A, Luz SLB, et al. Ecological niche modelling for predicting the risk of cutaneous leishmaniasis in the Neotropical moist forest biome. *PLOS Neglected Tropical Diseases*. 2019;13(8):e0007629. doi:10.1371/journal.pntd.0007629
32. Santos Alfos MMd, Chaves SAdM, Magalhaes MdAFM, et al. Ecoepidemiology of American Visceral Leishmaniasis in Tocantins State, Brazil: Factors Associated with Occurance and Spreading of the Vector. In: Claborn D, ed. *The Epidemiology and Ecology of Leishmaniasis*. Intech; 2017:chap 6.
33. da Silva AS, Andreoli RV, de Souza RAF, et al. Impact of El Niño on the dynamics of American cutaneous leishmaniasis in a municipality in the western Amazon. *Acta Tropica*. 2021/10/01/ 2021;222:106032. doi:https://doi.org/10.1016/j.actatropica.2021.106032
34. Ferreira De Souza RA, Andreoli RV, Toshie Kayano M, Lima Carvalho A. American cutaneous leishmaniasis cases in the metropolitan region of Manaus, Brazil: association with climate variables over time. *Geospatial Health*. 2015;10(1)doi:10.4081/gh.2015.314
35. Ryan L, Silveira FT, Lainson R, Shaw JJ. Leishmanial infections in Lutzomyia longipalpis and Lu. antunesi (Diptera: Psychodidae) on the island of Marajó, Pará State, Brazil. *Transactions of The Royal Society of Tropical Medicine and Hygiene*. 1984;78(4):547-548. doi:10.1016/0035-9203(84)90081-6
36. Ryan SJ, Carlson CJ, Mordecai EA, Johnson LR. Global expansion and redistribution of Aedes-borne virus transmission risk with climate change. *PLOS Neglected Tropical Diseases*. 2019;13(3):e0007213. doi:10.1371/journal.pntd.0007213
37. Peterson AT, Shaw J. Lutzomyia vectors for cutaneous leishmaniasis in Southern Brazil: ecological niche models, predicted geographic distributions, and climate change effects. *International Journal for Parasitology*. 2003/08/01/ 2003;33(9):919-931. doi:https://doi.org/10.1016/S0020-7519(03)00094-8
38. McIntyre S, Rangel EF, Ready PD, Carvalho BM. Species-specific ecological niche modelling predicts different range contractions for Lutzomyia intermedia and a related vector of Leishmania braziliensis following climate change in South America. *Parasites & Vectors*. 2017;10(1)doi:10.1186/s13071-017-2093-9
39. Health Mo. Brazil Information System for Notifiable Diseases. 2024. http://portalsinan.saude.gov.br/
40. Statistics IoGa. IBGE. https://www.ibge.gov.br/en/home-eng.html
41. Fick SE, Hijmans RJ. WorldClim 2: new 1-km spatial resolution climate surfaces for global land areas. *International Journal of Climatology*. 2017;37(12):4302-4315. doi:https://doi.org/10.1002/joc.5086
42. Laboratory NPS. Multivariate ENSO Index Version 2 (MEI.v2). National Oceanographic and Atmospheric Administration. 2024. https://psl.noaa.gov/enso/mei/
43. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing; 2018. https://www.R-project.org/
44. Lewnard JA, Jirmanus L, Júnior NN, et al. Forecasting Temporal Dynamics of Cutaneous Leishmaniasis in Northeast Brazil. *PLoS Neglected Tropical Diseases*. 2014;8(10):e3283. doi:10.1371/journal.pntd.0003283
45. Goncalves Neto VS, Barros Filho AKD, Santos AMD, et al. An analysis of the spatiotemporal distribution of American cutaneous leishmaniasis in counties located along road and railway corridors in the State of Maranhao, Brazil. *Revista da Sociedade Brasileira de Medicina Tropical*. 2013;46(3):322-328. doi:10.1590/0037-8682-0056-2012

TABLES

Table 1. Descriptive characteristics of patients diagnosed with cutaneous leishmaniasis in Pará, Brazil, 2007-2019

Patient Characteristic	**Number of Cases (%) N=45,499**
Age	
< 1 - 19	11,072 (24.3)
20-39	22,434 (49.3)
40-59	9,074 (19.9)
60-79	2,057 (4.5)
80 +	198 (0.43)
Race	
White	6,384 (14.0)
Black	4,186 (9.2)
Asian	612 (1.3)
Mixed	32,655 (71.8)
Indigenous	679 (1.5)
Unknown	983 (2.2)
Sex	
Male	36,618 (80.5)
Female	8,880 (19.5)
Year of Diagnosis	
2007	4,432 (9.7)
2008	3,845 (8.5)
2009	3,532 (7.8)
2010	2,465 (5.4)
2011	3,811 (8.4)
2012	4,280 (9.4)
2013	3,227 (7.1)
2014	4,529 (10.0)
2015	3,803 (8.4)
2016	1,745 (3.8)
2017	3,373 (7.4)
2018	3,206 (7.0)
2019	3,251 (7.1)

Table 2. Overall Multivariate Analysis of Climatologic and Sociologic Risk Factors with Cutaneous Leishmaniasis Incidence in Pará, Brazil, 2007-2019.

Covariate	**Estimate (β)**	**Std. Error**	**p-value**	**Pseudo R2**
Overall Model				**0.570**
Intercept	24.317	7.019	0.001*	
Year	-0.003	0.004	0.337	
Month	0.016	0.005	0.001*	
Average Minimum Temperature, Monthly	-0.413	0.011	<0.001*	
Average Maximum Temperature, Monthly	-0.272	0.013	<0.001*	
Average Precipitation, Monthly	-0.002	0.0001	<0.001*	
Seasonally Lagged MEI Value	0.022	0.014	0.110	
Percent Population Urban	2.018	0.059	<0.001*	

*Statistically significant at 5% significance level (p<0.05)

FIGURES

Figure 1. Map of Pará, Brazil.

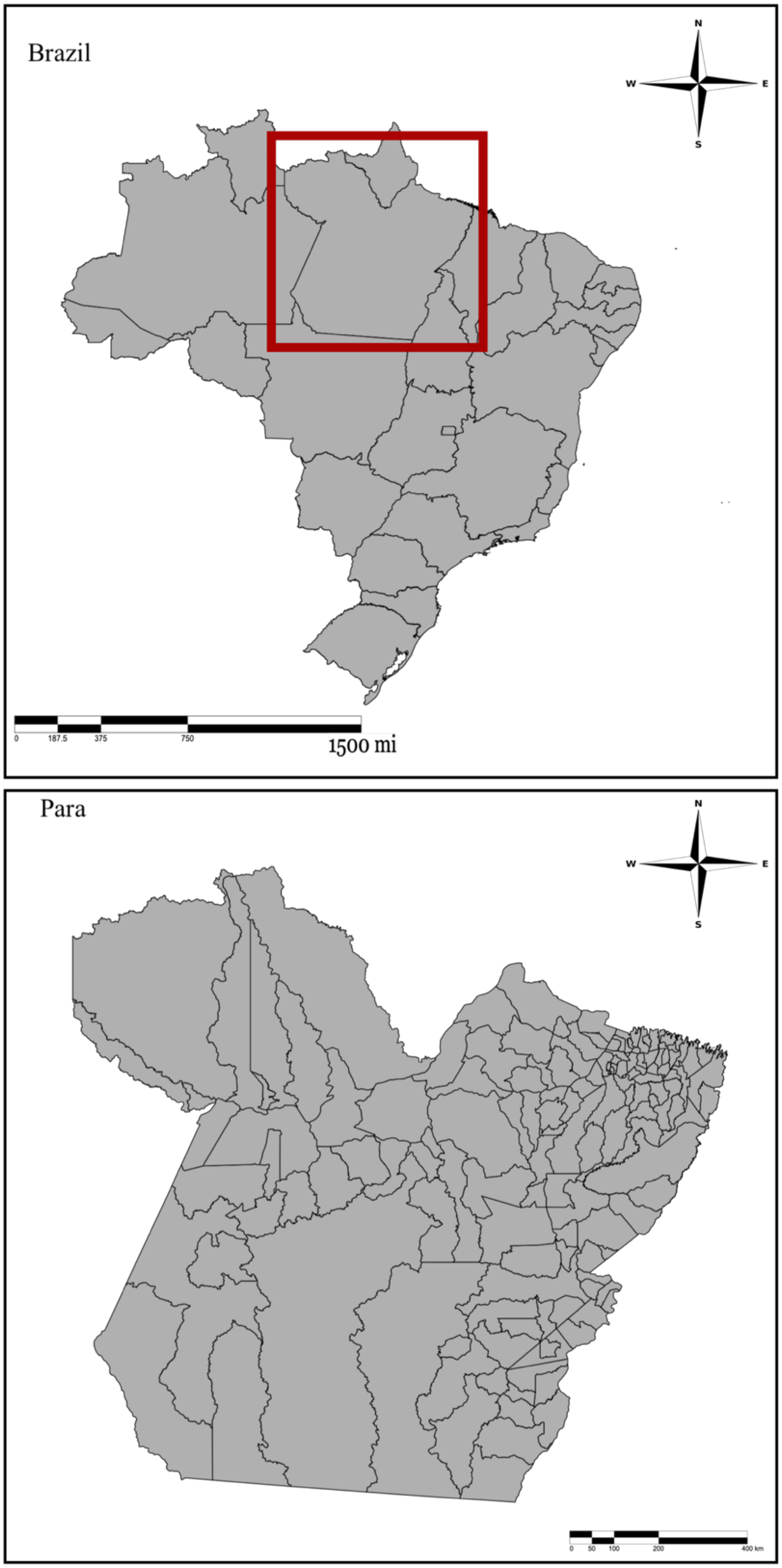
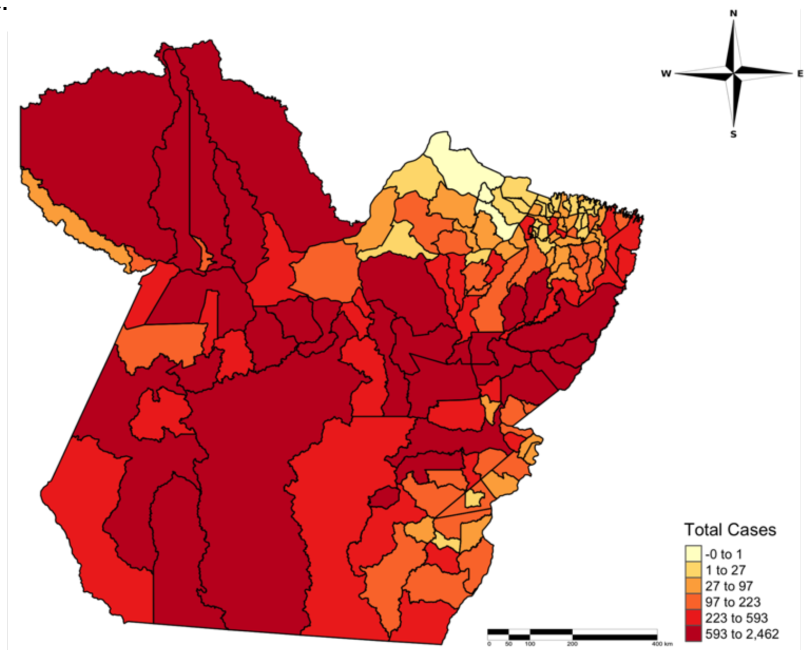


Figure 2. a) Distribution of Cutaneous Leishmaniasis Cases by Reporting Municipality, Pará, Brazil, 2007-2019. b) Cumulative Incidence of Cutaneous Leishmaniasis Cases by Reporting Municipality, Pará, Brazil, 2007-2019.

a.



b.

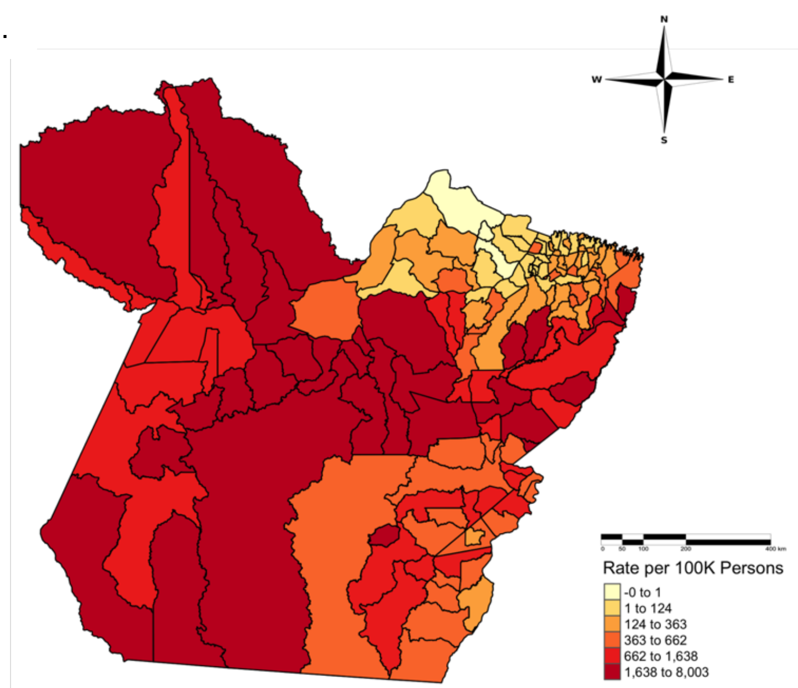


Figure 3. Municipalities Considered Significant High Risk Areas for Cutaneous Leishmaniasis, Pará, Brazil. a) 2014 & b) 2015 are highest-incidence years, c) 2016 is the lowest-incidence year, and d) 2007-2019 synthesizes data from all years.

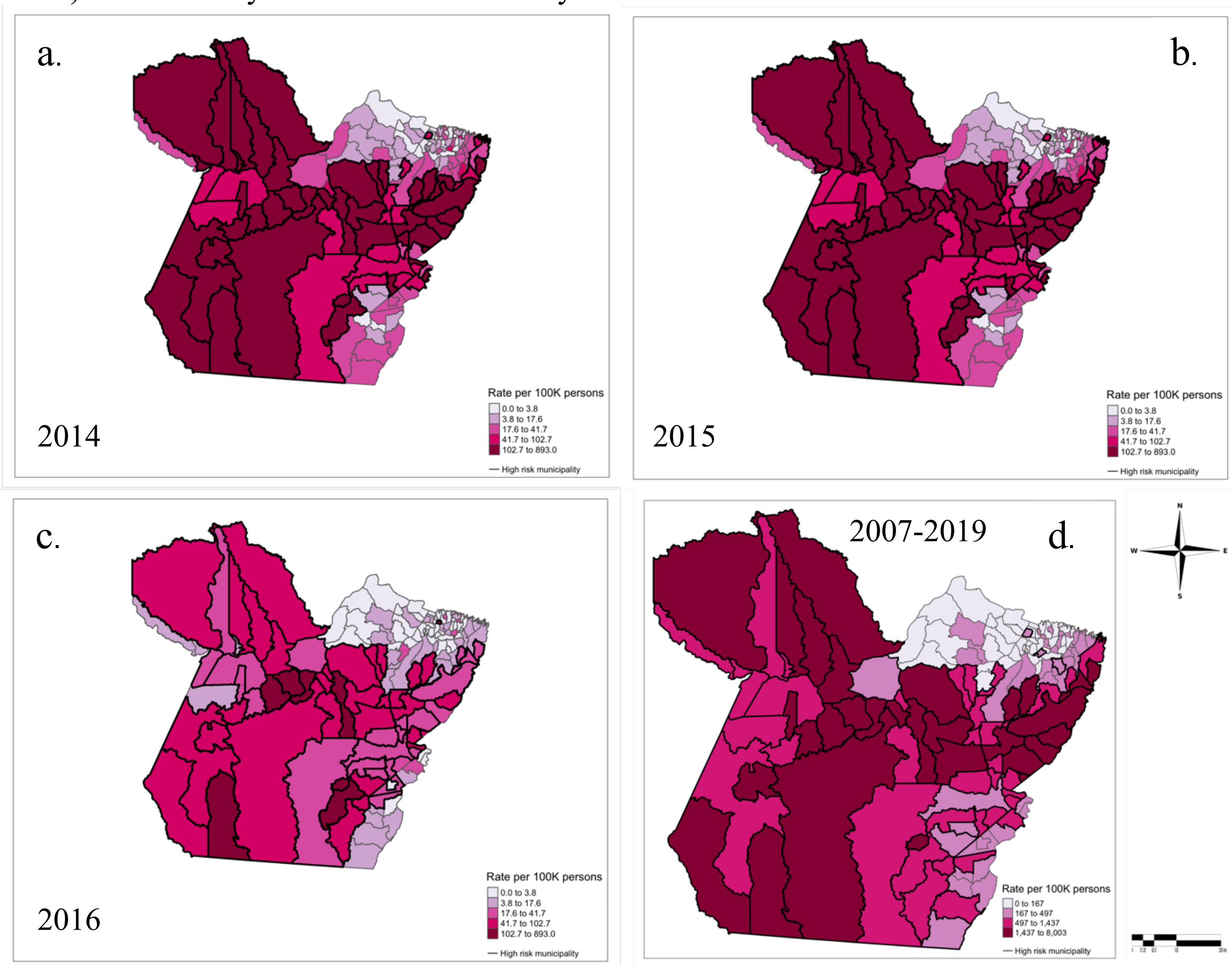


Figure 4. a) Local Spatial Autocorrelation of Cutaneous Leishmaniasis Incidence in Pará, Brazil, 2007-2019. b) Locations of Most Likely Cutaneous Leishmaniasis Clustering in Pará, Brazil, 2007-2019.

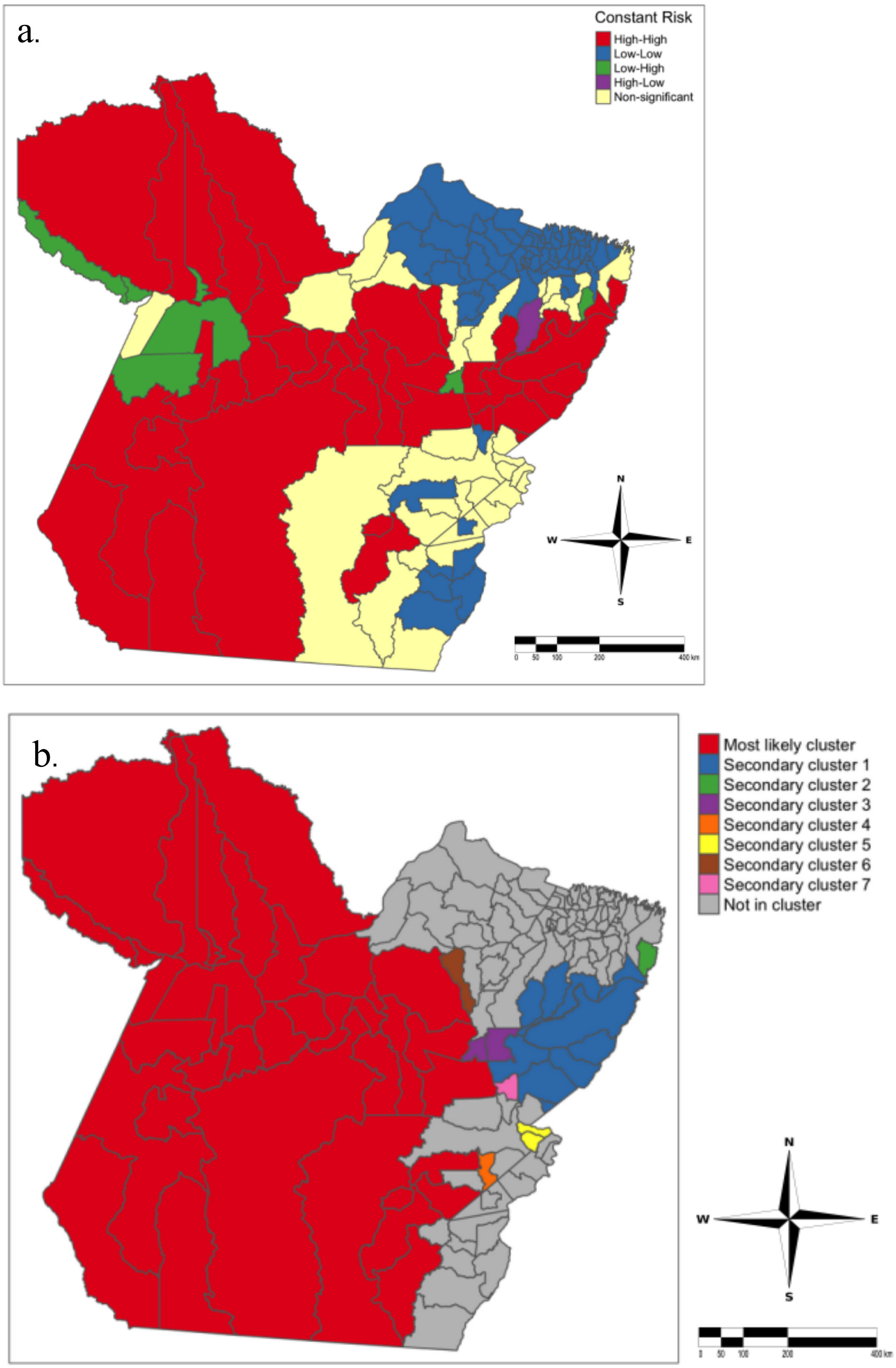
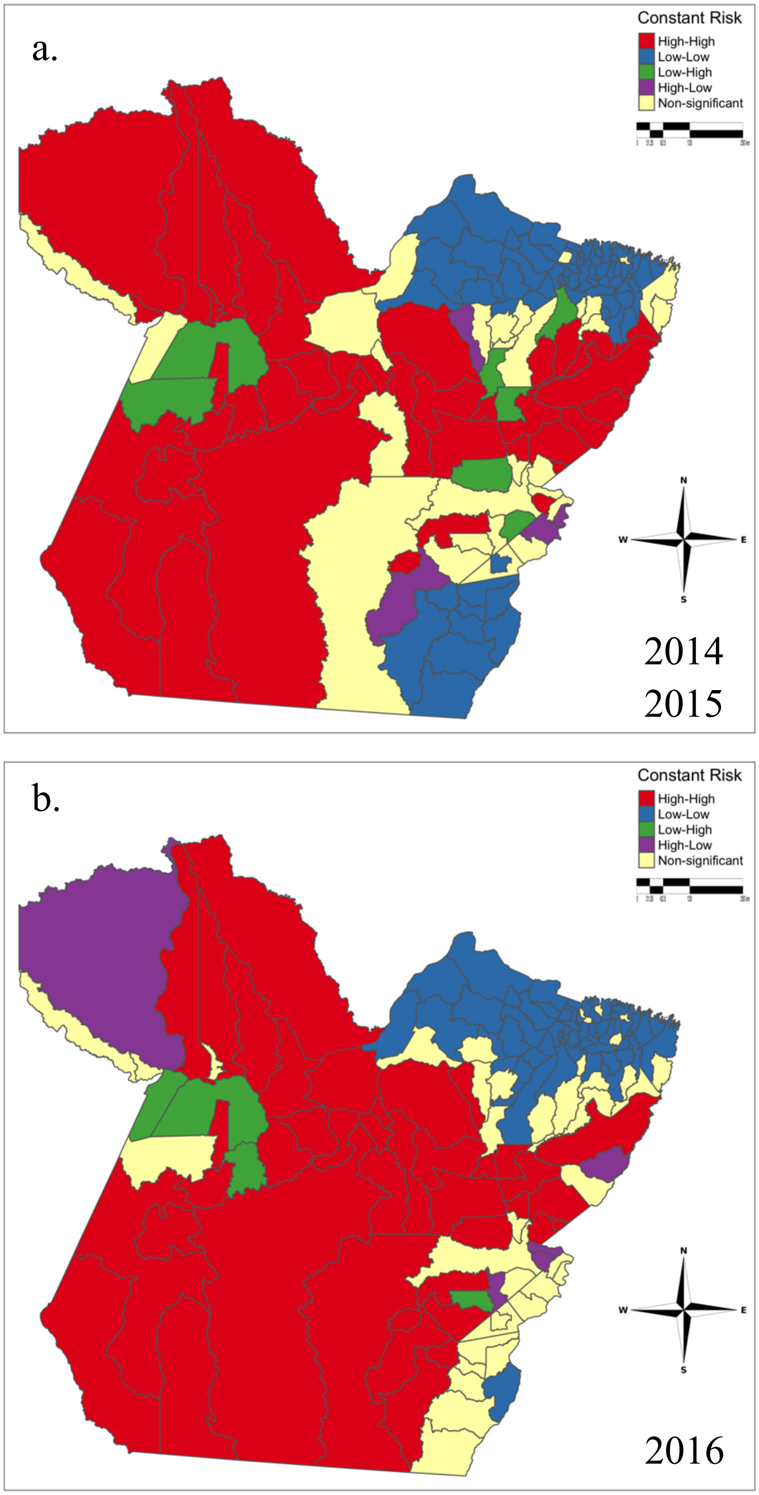


Figure 5. Local Spatial Autocorrelation of Cutaneous Leishmaniasis Incidence in Pará, Brazil, a)/ 2014/2015, highest-incidence years b). 2016, lowest-incidence year.



SUPPLEMENT

Table S1. Descriptive characteristics of environmental factors of interest in Pará, 2007-2019.

Environmental Factor		**Median (IQR)**
Minimum Monthly Temperature (C)		
	2007	22.0 (20.3, 23.7)
	2008	21.5 (19.9, 23.1)
	2009	22.0 (20.7, 23.3)
	2010	22.0 (19.9, 24.1)
	2011	21.9 (20.7, 23.1)
	2012	21.4 (20.0, 22.9)
	2013	22.0 (20.7, 23.2)
	2014	21.3 (20.1, 22.6)
	2015	22.0 (20.8, 23.2)
	2016	22.0 (20.2, 23.8)
	2017	22.0 (21.0, 23.0)
	2018	22.0 (20.7, 23.3)
	2019	21.9 (20.1, 23.8)
Maximum Monthly Temperature (C)		
	2007	33.0 (31.8, 34.2)
	2008	33.1 (31.8, 34.4)
	2009	33.1 (32.1, 34.0)
	2010	33.6 (31.7, 35.5)
	2011	33.0 (31.3, 34.7)
	2012	33.2 (31.9, 34.5)
	2013	32.9 (31.3, 34.5)
	2014	33.0 (31.9, 34.1)
	2015	33.8 (32.4, 35.3)
	2016	33.8 (32.3, 35.2)
	2017	33.8 (31.8, 35.9)
	2018	33.5 (32.4, 34.6)
	2019	33.9 (31.8, 36.1)
Annual Precipitation (mm)		
	2007	2098.9 (1607.4, 2590.5)
	2008	2360.6 (1856.0, 2865.2)
	2009	2461.2 (1831.3, 3091.2)
	2010	2103.6 (1591.2, 2615.9)
	2011	2519.2 (1844.8, 3193.7)
	2012	2186.0 (1582.3, 2789.7)
	2013	2340.5 (1817.7, 2863.3)
	2014	2300.9 (1634.6, 2967.3)
	2015	2004.7 (1352.6, 2656.8)
	2016	2223.9 (1399.4, 3048.5)
	2017	2247.1 (1414.7, 3079.5)
	2018	2273.8 (1875.1, 2672.4)
	2019	2315.4 (1382.6, 3248.1)
Average Monthly Multivariate ENSO Index		
	2007	-0.8 (-1.6, 0.0)
	2008	-1.1 (-1.3, -0.9)
	2009	0.3 (-1.0, 1.6)
	2010	-1.8 (-4.6, 1.0)
	2011	-1.3 (-1.9, -0.8)
	2012	-0.3 (-0.7, 0.1)
	2013	-0.3 (-0.7, 0.1)
	2014	-0.1 (-0.5, 0.4)
	2015	1.7 (0.3, 3.1)
	2016	0.0 (-1.5, 1.6)
	2017	-0.6 (-0.9, -0.2)
	2018	-0.5 (-1.4, 0.5)
	2019	0.3 (0.1, 0.5)

Table S2. Annual Multivariate Analyses of Climatologic and Sociologic Factors with Cutaneous Leishmaniasis Incidence in Pará, Brazil, 2007-2019.

Covariate	**Estimate (β)**	**Std. Error**	**p-value**	**Pseudo R-Sq**
2007				**0.548**
Intercept	13.012	1.981	<0.001*	
Minimum Temperature	-0.525	0.037	<0.001*	
Maximum Temperature	-0.056	0.048	0.244	
Precipitation	0.000	0.001	0.663	
Seasonally Lagged MEI Value	0.079	0.085	0.353	
Percent Population Urban, 2010	2.411	0.203	<0.001*	
2008				**0.562**
Intercept	16.502	1.728	<0.001*	
Minimum Temperature	-0.426	0.036	<0.001*	
Maximum Temperature	-0.269	0.046	<0.001*	
Precipitation	-0.003	0.001	<0.001*	
Seasonally Lagged MEI Value	-1.117	0.306	<0.001*	
Percent Population Urban, 2010	2.382	0.219	<0.001*	
2009				**0.575**
Intercept	17.499	1.833	<0.001*	
Minimum Temperature	-0.437	0.038	<0.001*	
Maximum Temperature	-0.252	0.048	<0.001*	
Precipitation	-0.002	0.0004	<0.001*	
Seasonally Lagged MEI Value	-0.179	0.088	0.042*	
Percent Population Urban, 2010	1.941	0.202	<0.001*	
2010				**0.598**
Intercept	14.349	1.920	<0.001*	
Minimum Temperature	-0.430	0.039	<0.001*	
Maximum Temperature	-0.155	0.046	<0.001*	
Precipitation	-0.003	0.001	<0.001*	
Seasonally Lagged MEI Value	0.048	0.047	0.307	
Percent Population Urban, 2010	2.040	0.218	<0.001*	
2011				**0.566**
Intercept	15.735	1.969	<0.001*	
Minimum Temperature	-0.346	0.037	<0.001*	
Maximum Temperature	-0.292	0.047	<0.001*	
Precipitation	-0.004	0.001	<0.001*	
Seasonally Lagged MEI Value	-1.161	0.211	<0.001*	
Percent Population Urban, 2010	1.967	0.209	<0.001*	
2012				**0.560**
Intercept	12.634	1.999	<0.001*	
Minimum Temperature	-0.392	0.042	<0.001*	
Maximum Temperature	-0.138	0.051	0.006*	
Precipitation	-0.001	0.0005	0.005*	
Seasonally Lagged MEI Value	-0.680	0.153	<0.001*	
Percent Population Urban, 2010	2.255	0.224	<0.001*	
2013				**0.583**
Intercept	15.507	1.902	<0.001*	
Minimum Temperature	-0.273	0.039	<0.001*	
Maximum Temperature	-0.291	0.047	<0.001*	

Precipitation	-0.003	0.0004	<0.001*	
Seasonally Lagged MEI Value	1.042	0.131	<0.001*	
Percent Population Urban, 2010	2.264	0.203	<0.001*	
2014				**0.550**
Intercept	13.200	1.995	<0.001*	
Minimum Temperature	-0.222	0.044	<0.001*	
Maximum Temperature	-0.260	0.052	<0.001*	
Precipitation	-0.003	0.0005	<0.001*	
Seasonally Lagged MEI Value	-0.360	0.197	0.068	
Percent Population Urban, 2010	2.324	0.208	<0.001*	
2015				**0.551**
Intercept	13.477	1.952	<0.001*	
Minimum Temperature	-0.281	0.043	<0.001*	
Maximum Temperature	-0.215	0.049	<0.001*	
Precipitation	-0.003	0.001	<0.001*	
Seasonally Lagged MEI Value	-0.227	0.097	0.019*	
Percent Population Urban, 2010	2.329	0.207	<0.001*	
2016				**0.624**
Intercept	15.980	1.837	<0.001*	
Minimum Temperature	-0.432	0.040	<0.001*	
Maximum Temperature	-0.226	0.045	<0.001*	
Precipitation	-0.001	0.0005	0.024*	
Seasonally Lagged MEI Value	0.043	0.072	0.550	
Percent Population Urban, 2010	1.972	0.217	<0.001*	
2017				**0.58**
Intercept	19.491	1.713	<0.001*	
Minimum Temperature	-0.420	0.039	<0.001*	
Maximum Temperature	-0.295	0.042	<0.001*	
Precipitation	-0.004	0.0005	<0.001*	
Seasonally Lagged MEI Value	0.924	0.233	<0.001*	
Percent Population Urban, 2010	1.837	0.217	<0.001*	
2018				**0.575**
Intercept	16.271	1.914	<0.001*	
Minimum Temperature	-0.308	0.041	<0.001*	
Maximum Temperature	-0.288	0.046	<0.001*	
Precipitation	-0.001	0.001	0.072	
Seasonally Lagged MEI Value	0.404	0.109	<0.001*	
Percent Population Urban, 2010	1.129	0.213	<0.001*	
2019				**0.573**
Intercept	16.866	1.767	<0.001*	
Minimum Temperature	-0.374	0.037	<0.001*	
Maximum Temperature	-0.258	0.043	<0.001*	
Precipitation	-0.002	0.0005	<0.001*	
Seasonally Lagged MEI Value	-0.086	0.276	0.754	
Percent Population Urban, 2010	1.390	0.213	<0.001*	

*statistically significant at 5% significance level (p<0.05).

Figure S1. Highest and Lowest Annual Cutaneous Leishmaniasis Incidence by Reporting Municipality, in Pará, Brazil, 2007-2019.

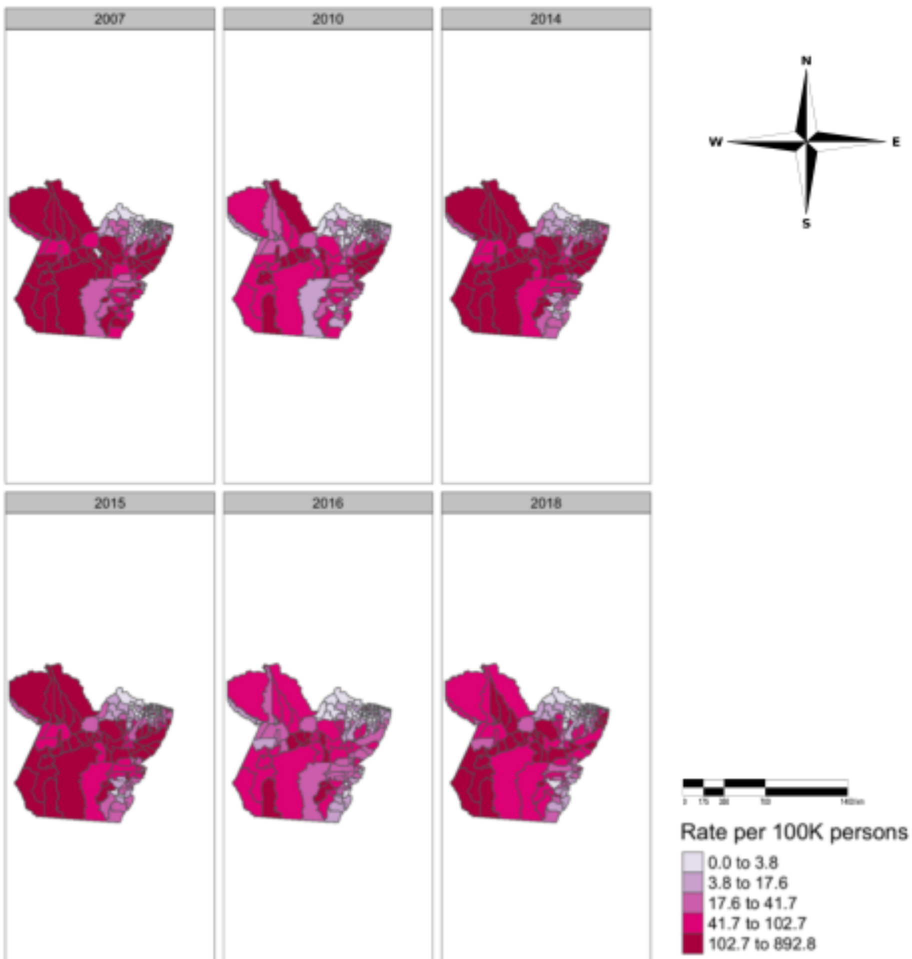


Figure S2. Comparative Raw (Left) and Aspatially Smoothed (Right) Incidence Rates of Cutaneous Leishmaniasis, Pará, Brazil, 2007-2019.

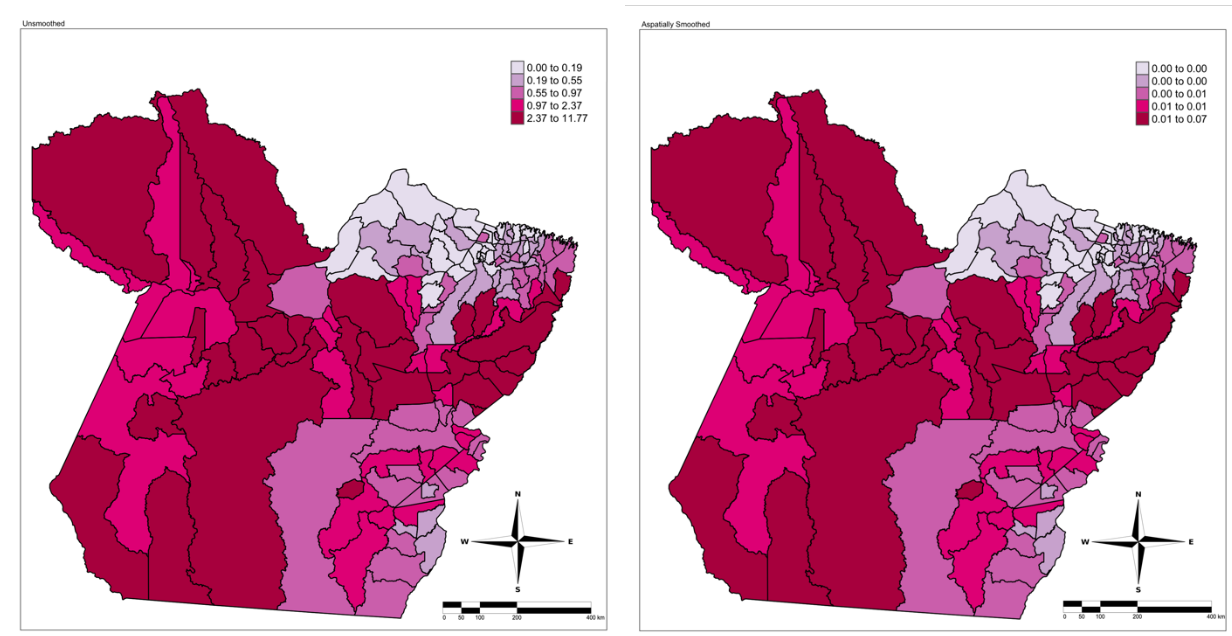


Figure S3. Comparative Raw (Left) and Spatially Smoothed (Right) Incidence Rates of Cutaneous Leishmaniasis, Pará, Brazil, 2007-2019.