Science of the Total Environment 953 (2024) 176064

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Bayesian spatio-temporal modeling to assess the effect of land-use changes on the incidence of Cutaneous Leishmaniasis in the Brazilian Amazon

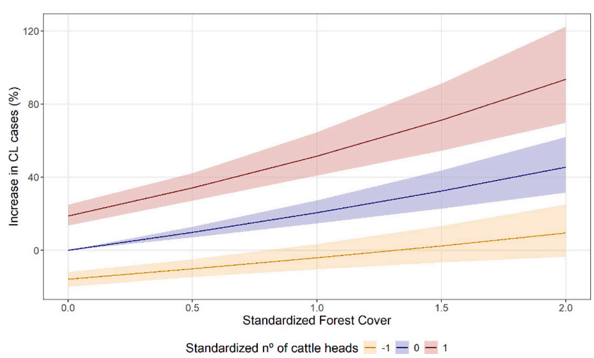
T.P. Portella [a,*], V. Sudbrack [b], R.M. Coutinho [c], P.I. Prado [a], R.A. Kraenkel [d]

[a] *Department of Ecology, Institute of Bioscience, 321 Rua do Matão, Travessa 14, Cidade Universitária, University of São Paulo, São Paulo, SP CEP 05508090, Brazil*
[b] *Department of Ecology and Evolution, University of Lausanne, 1015 Lausanne, Switzerland*
[c] *Federal University of ABC (UFABC), Center for Mathematics, Computation and Cognition, Avenida dos Estados, 5001, Bairro Bangu, Santo André, SP CEP 09210-580, Brazil*
[d] *São Paulo State University (UNESP), Institute for Theoretical Physics (IFT), R. Dr. Bento Teobaldo Ferraz, 271, Bloco II, Barra-Funda, São Paulo, SP CEP 01140-070, Brazil*

HIGHLIGHTS

- Bayesian approach to examine the effect of land-use changes on disease risk
- A high relative risk of Cutaneous Leishmaniasis (CL) occurred in the Amazon Frontier.
- Deforestation, cattle ranching, and forest cover affected CL incidence.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Manuel Esteban Lucas-Borja

Keywords:
Disease risk
Land use change
Spatio-temporal
Bayesian modeling

ABSTRACT

Cutaneous Leishmaniasis (CL) is a vector-borne disease caused by a protozoan of the genus *Leishmania* and is considered one of the most important neglected tropical diseases. The Brazilian Amazon Forest harbors one of the highest diversity of *Leishmania* parasites and vectors and is one of the main focuses of the disease in the Americas. Previous studies showed that some types of anthropogenic disturbances have affected the abundance and distribution of CL vectors and hosts; however, few studies have thoroughly investigated the influence of different classes of land cover and land-use changes on the disease transmission risk. Here, we quantify the effect of land use and land-cover changes on the incidence of CL in all municipalities within the Brazilian Amazon Forest, from 2001 to 2017. We used a structured spatiotemporal Bayesian model to assess the effect of forest cover, agriculture, livestock, extractivism, and- deforestation on CL incidence, accounting for confounding variables such as population, climate, socioeconomic, and spatiotemporal random effects. We found that the increased risk of CL was associated with deforestation, especially modulated by a positive interaction between forest cover and livestock. Landscapes with ongoing deforestation for extensive cattle ranching are typically found in municipalities within the Amazon Frontier, where a high relative risk for CL was also identified. These findings provide

* Corresponding author.
E-mail address: portellatp@gmail.com (T.P. Portella).

https://doi.org/10.1016/j.scitotenv.2024.176064
Received 8 January 2024; Received in revised form 16 August 2024; Accepted 4 September 2024
Available online 7 September 2024

valuable insights into developing effective public health policies and land-use planning to ensure healthier landscapes for people.

1. Introduction

Anthropogenic land-use changes are the major drivers for the emergence of zoonotic diseases, especially for diseases transmitted by vectors and direct animal contact (Loh et al., 2015). The Amazon forest is considered a region of high concern for the emergence of zoonotic diseases, due to its high diversity of vector-borne pathogens and extensive land-use changes (Lorenz et al., 2021). An estimated 116,000 km^2 of forests have been lost in Amazon between 2008 and 2022 (INPE, 2022), driven mainly by agriculture, cattle ranching, logging, mining, and infrastructure buildings (Garrett et al., 2021). The effect of these land-use changes on the disease transmission risk in the Amazon has been widely studied for malaria, where studies have found a positive association between both deforestation and fragmentation on the disease incidence (Hahn et al., 2014; Santos and Almeida, 2018; Chaves et al., 2018). However, for many other vector-borne pathogens, the effect of land-use changes on the transmission risk has still been understudied.

Cutaneous Leishmaniasis (CL) occurs in 89 countries, infecting from 0,7 to 1,2 million people per year, and it is classified as one of the most important neglected tropical diseases (Alvar et al., 2012; PAHO, 2017). Brazil is among the ten countries that together account for 70–75 % of the global incidence of the disease (Alvar et al., 2012). It is also the country with the highest number of cases in America (Maia-Elkhoury et al., 2016), registering 379,571 cases from 2001 to 2017, with the vast majority of these cases occurring in the Amazon region (Portella and Kraenkel, 2021).

In the Brazilian Amazon, CL is a zoonotic disease caused by a protozoan of the genus *Leishmania* (Kinetoplastida: Trypanosomatidae) and is transmitted to mammalian hosts by the bite of infected Phlebotominae sandflies (Diptera: Psychodidae) (Ready, 2013). When humans are infected, they develop skin ulcers that can evolve into the mucocutaneous form, which can cause permanent tissue scars and partial or total destruction of the mucosal tissues of the nose, throat, and mouth (Reithinger et al., 2007). CL is a life-burden disease and its skin sequels can also cause further psychological disorders such as depression (Bailey et al., 2019).

The eco-epidemiology of CL in the Brazilian Amazon is a complex process that depends on the species of vectors, parasites, and hosts involved (Rangel et al., 2018). At least seven species of *Leishmania* parasites responsible for CL have been identified in the region: one species of subgenus *Leishmania* and six of subgenus *Viannia*. These parasites can be transmitted to a mammalian host by about nine species of primary vectors belonging to the genera *Nyssomyia*, *Bichromomyia*, *Lutzomyia*, *Migonemyia*, and *Psychodopygus* (Rangel et al., 2018). The role of mammalian species as reservoirs is not fully understood due to the lack of eco-epidemiological studies in the region. However, Roque and Jansen's (2014) identified several mammal species that are potential reservoirs for the disease. These include native species of sloths, anteaters (Order Pilosa), armadillos (Order Cingulata), monkeys (Order Primates), Opossuns (*Didelphis* spp., Order Didelphimorphia, synanthropic), and the exotic species *Rattus rattus* (Order Rodentia).

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

Although there is evidence suggesting that changes in land use affect the distribution of CL vectors and hosts, only a few studies have thoroughly examined the relationship between land-use changes and the risk of CL in the Brazilian Amazon. Codeço et al. (2021) recently explored the correlation between the number of CL cases and agrarian economic dynamics in the region. Other studies have used machine learning techniques to predict the occurrence of CL in Brazil (Purse et al., 2017) and the Amazon basin (Chavy et al., 2019). Karagiannis-Voules et al. (2013) applied a Bayesian geostatistical approach to evaluate the influence of different environmental and socioeconomic factors on the number of CL cases in Brazil. However, most of these studies were exploratory or predictive and did not take into account the spatial correlation of the data, which may bias the estimation of the influence of environmental variables on the incidence or occurrence of the disease (Waller and Gotway, 2004). Although Karagiannis-Voules et al. (2013) was the only inferential study to account for spatial autocorrelation in the data, it assumed a single relationship between risk factors and CL incidence in all geographic regions of Brazil. As a result, this approach limits the identification of risk factors specific to different ecological zones, such as the Amazon forest (Karagiannis-Voules et al., 2013; Loh et al., 2015). Furthermore, their model is purely spatial and does not consider the temporal variation of CL incidence and land use variables, which are highly heterogeneous in space and time and change rapidly in the Amazon region (Garrett et al., 2021; Portella and Kraenkel, 2021).-.

In this study, we used an inferential statistical approach to assess how different land cover and land-use changes affect the incidence of CL in the Brazilian Amazon, controlling for well-known risk factors such as population, climate, and socioeconomic vulnerability. Because CL incidence and land-use are heterogeneous in time and space in the Amazon (Garrett et al., 2021; Portella and Kraenkel, 2021), we extracted these data for each year and municipality over 17 years and quantified their influence on CL incidence using the spatiotemporal Bayesian approach. We also tested different combinations of random effects to account for any spatiotemporal unexplained variation in the incidence pattern. With this rigorous statistical analysis using a large temporal dataset, we provide the most comprehensive approach to understanding how land-use changes in the Brazilian Amazon have affected the risk of CL in humans. We also identified landscape characteristics that need to be prioritized in CL epidemiologic surveillance and control strategies.

2. Material and methods

2.1. Study area

The Brazilian Amazon has an area of approximately 4.2 million km^2 (49 % of Brazilian territory), which encompasses 503 municipalities located in the states of Acre (AC), Amapá (AP), Amazonas (AM), Pará (PA), Rondônia (RO), Roraima (RR), and part of Maranhão (MA), Tocantins (TO), and Mato Grosso (MT) (Fig. 1). It has a population of ~22 million people, which is ~10 % of the Brazilian population (IBGE, http://www.ibge.gov.br, Access date: 15 February 2022). At present, 78,32 % of the region is covered by native vegetation, which comprises mainly dense and tropical rainforests, and 14,96 % is covered by agriculture, which consists mainly of cattle pasture and soybean crops (Mapbiomas, 2020).

2.2. Data collection

2.2.1. Disease cases and population

The database of CL cases reported in the 503 municipalities from 2001 to 2017 was provided by the Brazilian Ministry of Health. The notification of CL cases has been mandatory in Brazil since 2001, and all the CL records from public and private healthcare facilities are stored in a national database called SINAN (Sistema de Informação de Agravos de Notificação). The data provided were at the individual level and anonymized and all new CL cases confirmed by laboratory or clinical-epidemiological criteria were filtered and aggregated by year and municipality of infection.

The population data per year and municipality were extracted from IBGE (http://www.ibge.gov.br, Access date: 15 February 2022). Since men are most affected by CL in both rural and peri-urban environments in Amazon (Benício et al., 2015; Guerra et al., 2015), we also considered the proportion of the male population in each municipality in the model. The population data stratified by sex were available only from 2000 and 2010 on the IBGE dataset. We used the male population of 2000 to analyze disease data from 2000 to 2007 and data from 2010 to analyze disease data from 2008 to 2017.

2.2.2. Land-use data

We selected five land cover and land use changes based on their extent in the Amazon biome and their expected impact on CL disease transmission. Table 1 provides information on the selected variables, their expected impact on vector and host populations, and their influence on human-vector interactions.

Data on forest cover and deforestation were obtained from the MapBioma 5.1. database for the years 2001 to 2017 (Projeto Mapbiomas, 2020). We calculated the percentage (%) of natural forest area, and the total amount of area (ha) deforested between year t-1 and t for each year and municipality. Data on permanent agriculture area (ha), amount of non-timber forest product (NTFP) material collected (ton), and the number of heads of cattle per municipality and year (2001–2017) were obtained from the IBGE Automatic Recovery System (SIDRA) database (IBGE, http://www.ibge.gov.br, Access date: 15 February 2022).

2.2.3. Climate and socioeconomic covariates

The incidence of CL can be influenced by climatic conditions, as temperature and precipitation affect the distribution and abundance of *Leishmania* vectors (Peterson and Shaw, 2003; Chaves et al., 2014) as well as the parasite's development (Hlavacova et al., 2013). So we also added in our model temperature and precipitation data as confounding variables. Rainfall data were obtained from the University of California Santa Barbara from Climate Hazard Group Infrared Precipitation Stations (CHIRPS) with a spatial resolution of 0.05°, and surface temperature data was extracted from National Centers for Environmental Prediction (NOAA NCEP) with a spatial resolution of 0.5°. We calculated total annual rainfall (mm) from monthly data, and annual mean temperature (°C) from 7-day average data for each municipality and year (2001–2017).

CL transmission risk is associated with poor socioeconomic conditions (Alvar et al., 2006), so we used data from the Basic Human Needs (BHN) dimension of the Social Progress Index (SPI) calculated in 2014 by Imazon (https://imazon.org.br) as a model covariate. This dimension provides information about the capacity of a municipality to meet basic human necessities such as health care, sanitation, and adequate housing. It is measured using several variables provided by IBGE, PNUD, and the

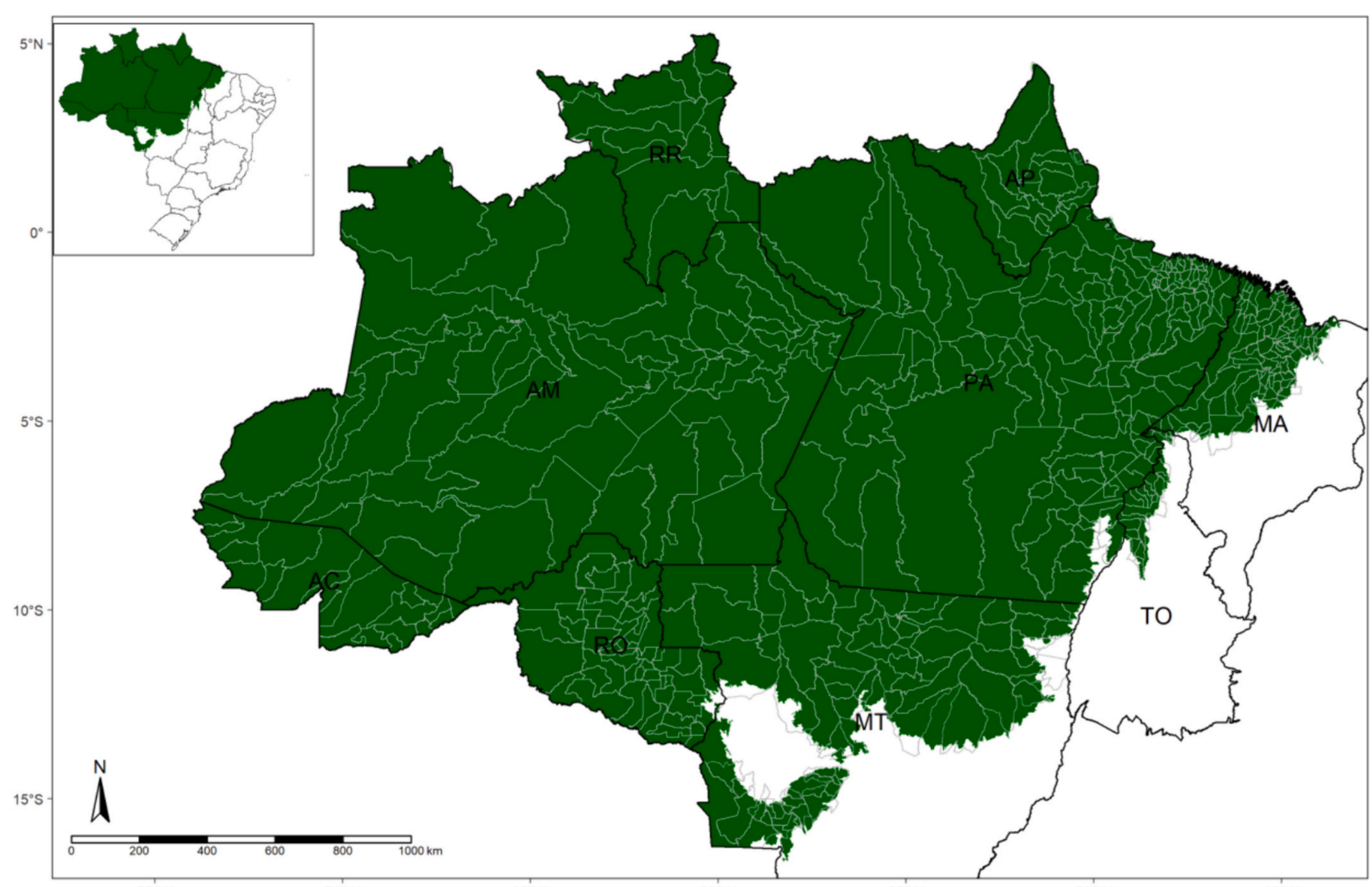


Fig. 1. Delimitation of the Brazilian Amazon Forest (green area) with its nine states (black line) and 503 municipalities (gray lines).States names: Acre (AC), Amapá (AP), Amazonas (AM), Pará (PA), Rondônia (RO), Roraima (RR), and part of Maranhão (MA), Tocantins (TO), and Mato Grosso (MT).

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

Land use variable	Expected effect	Influence on the disease	Source	Temporal resolution	Spatial resolution
Forest cover	+	It is the main habitat of vectors and mammal hosts.	Aguiar and Vieira, 2018; Roque and Jansen, 2014	Yearly (2001–2017)	30 m
Permanent crops	+	It can serve as a habitat and food source for hosts and vectors and influence their abundance.	Alexander et al., 2001, 2009; Mendoza et al., 2020	Yearly (2001–2017)	Municipality (n = 497)
Deforestation	+	It can increase interaction between vectors and humans.	Nogueira-Neto et al. (1998)	Yearly (2001–2017)	30 m
Extrativism (NTFP)	+	It can increase the exposure of humans to vectors.	Guerra et al. (2019)	Yearly (2001–2017)	Municipality (n = 497)
Heads of cattle	+	It could serve as a blood-meal source for sandflies which can affect their distribution and abundance.	Bern et al. (2010)	Yearly (2001–2017)	Municipality (n = 497)

Brazilian Ministry of Health for 2010 and 2012. Its values range from 0 (worst) to 100 (best) (Santos et al., 2018).

2.3. Data preprocessing

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

We also checked the correlation between the fixed-effect variables by performing a Pearson's rank correlation index with the corrplot package in R (Wei and Simko, 2021). Next, we tested multicollinearity between variables by computing the variance-inflation factors (VIF), which represents the amount of variability of a covariate that is explained by other covariates (Craney and Surles, 2002). VIF was assessed using the 'vif' function of the HH package in R (Heiberger and Holland, 2015). The area of Permanent Crop, number of cattle heads, and amount of non-timber forest product were log-transformed before analysis. To make model comparable, all explanatory variables were standardized by subtracting the mean from each value and dividing by the standard deviation.

2.4. Statistical analysis

We fitted a spatio-temporal Bayesian model containing the five land-use, two climatic, and one socioeconomic explainable variables as fixed effect: proportion of forest cover, area of permanent crops (ha), number of cattle heads, amount of non-timber forest product (ton) and total amount of area deforest in year t-1 and t (ha); mean temperature (°C), total precipitation (mm) and basic humans needs (BHN). We also added the interaction between forest and livestock and between forest and permanent agriculture as fixed effects. We hypothesized that the presence of livestock and permanent crops around forested areas could increase the influence of forest cover on CL transmission risk. The underlying assumption is that the populations of some vectors and host species that depend on forested habitats may be positively affected by the food and shelter resources provided by crops and livestock around forested areas. The response variable was the number of CL cases controlled by the total population as an offset term. All variables were modeled for each year and municipality.

Random effects were included in the model to account for any unexplained excess variation in the data, which may be associated with unknown or unmeasured covariates. It was assumed that this extra variation in the data might be linked to some characteristic of each municipality and year of study (unstructured spatial and temporal random effects), which were modeled as independent and identically distributed random effects (iid). We also assumed that this extra heterogeneity variation might be linked to a characteristic correlated in space and time (structured spatial and temporal random effects). The spatially structured random effect was modeled using a conditional autoregressive structure (CAR), which assumes that the disease pattern in one municipality is similar to the adjacent municipalities. The temporally structured random effect was modeled using a random walk of first order (rw1), which assumes that the incidence in a year is more similar to the years close in time than the years further apart. Further details regarding the model structure can be found in the supplementary material (SM-1).

We tested the model with all covariates using a negative binomial distribution with different combinations of the random effects described previously and compared them using the deviance information criterion (DIC). The model with the smallest DIC was the best supported by the data and was selected as the final model (Spiegelhalter et al., 2002).

We evaluated the performance of the final model by calculating the RMSE and R^2 between the predicted and observed CL relative risk. The observed risk was calculated by the standardized incidence ratio, which is defined as the ratio of the observed to the expected cases (Moraga, 2019). The expected number of cases represents the total number of cases that a municipality would expect if the population of this municipality behaved the way the population of the standard (Brazilian Amazon region) behaves. We also get the probability integral transform (PIT) histogram to evaluate the model goodness fit. According to Gneiting et al. (2007), a uniform PIT distribution means the predictive distribution is coherent with the data, suggesting a well-fitted model.

We also plotted the Relative Risk (RR) of CL in each municipality estimated by the model. Relative risk is the disease risk in each municipality compared to the average risk in all municipalities. Thus, a value above one means a higher than average risk, while a value below one means a lower than average risk. The estimated mean RR and coefficient of variation among years were summarized for each municipality. We also calculate the coefficient of variation (CV) for the estimated RR in each year and municipality, which is the ratio between the standard error and the mean of the posterior distribution of the estimated RR, multiplied by 100.

The relative risk (RR) for each land-use explanatory variable was calculated using the model's Bayesian estimates for the standardized coefficients, which express the change in risk relative to the average for the Brazilian Amazon for increase of one standard deviation in each explanatory variable. Since our model used a negative binomial distribution with a log link function, this change in RR of each covariate was calculated by exponentiating the coefficient values estimated by the model.

The models were fitted using the Integrated Nested Laplace Approximation (INLA) method through the R-INLA package (Rue et al., 2009). INLA is a computationally alternative approach to MCMC (Markov Chain Monte Carlo), and it has been used successfully in a great variety of applications, including spatial-temporal disease modeling (Blangiardo et al., 2013; Moraga, 2019). The maps and graphics were produced using ggplot2 (Wickham, 2016) and tmap (Tennekes, 2018) packages on R R 4.1.1 (R Core Team, 2021). The codes developed for data analysis and visualization are available in a public repository (https://github.com/portellatp/leish_amazon).

3. Results

3.1. Description of CL cases and covariates

Between 2001 and 2017, the 503 municipalities of the Brazilian Amazon had a total of 204,605 CL cases recorded, with an average incidence of 6.5 per 100,000 inhabitants. The highest cumulative incidence of CL is concentrated in the southern Amazon Frontier, followed by the north of the states of Amazonas and Amapá, and the center of Pará State. In general, the incidence of CL on Amazon decreased over the years, with the largest number of CL cases occurring in 2003 (17,683) and the lowest in 2016 (6691) (Fig. S2, SM-2).

Table 2 shows the mean, standard deviation, and range values of land use, climate, and socio-economic covariates for the municipalities of the Brazilian Amazon Forest between 2001 and 2017. The municipalities with the highest percentage of forest cover are located in the central-western of the Amazon. The largest number of cattle heads and deforestation rates are concentrated in municipalities of the Amazon forest frontier and the southeast of Pará state. Areas of permanent agriculture were located mainly in the municipalities of the central Pará, Rondônia, and northern Mato Grosso states, and NTFP in central Amazonas and Maranhão (Fig. S3 SM-2). Between 2001 and 2017, there was an increase in the total number of cattle heads and a decrease in the amount of forest cover, deforestation, NTFP, and areas of permanent agriculture over the Amazon (Fig. S4, SM2).

3.2. Statistical modeling

The results of model selection with different combinations of random effects are presented in Table 3. The model with the lowest value of DIC was Model 7, which included unstructured (iid) and structured (rw1) temporal random effects, unstructured (iid) and structured (CAR) spatially random effects, and the interaction between spatially unstructured (iid) and temporally structured (rw1) random effects, as described in the methodology section.

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

Table 4 presents the results of the final model, including the estimated regression coefficients, Standard deviation, and 95 % Bayesian Credible Intervals. The results of the model indicate that the influence of forest cover on the incidence of CL is dependent on the amount of cattle heads. Fig. 2 illustrates this relationship. For example, the estimated increase in the number of CL cases is 21 % for a one-standard-deviation increase in forest cover, assuming no change in the number of cattle heads. However, an equivalent amount of forest cover with a one-standard-deviation increase in livestock resulted in a 52 % increase in the number of CL cases, and with a one-standard-deviation decrease in livestock resulted in a 4 % decrease in the number of CL cases (Fig. 2). Our model also demonstrated that a one-standard-deviation increase in forest loss resulted in a mean increase of 6 % in the number of CL cases. Our model did not identify any substantial relationship between CL number of cases and the other land-use variables.

Regarding the socioeconomic and climate covariates, we found a positive association between CL number of cases and the proportion of the male population and a negative association between CL number of cases and total rainfall, mean temperature, and human basic needs index (Table 4).

The coefficient values of random effects are shown in Table 4. These random effects represent the residual spatiotemporal heterogeneity of CL risk that was not explained by the fixed effects. The remaining non-explainable variation in CL risk was captured mainly by the spatially structured and spatial-time interaction random effect.

Table 2
Descriptive statistics of land use, climate, and socio-economic variables used for the Bayesian spatio-temporal model. The variables were analyzed at the municipality level in the Brazilian Amazon from 2001 to 2017.

Variable	Mean (± SD)	Range
Forest cover (%)	58.1 (26.4)	2.9–99.7
Deforestation (ha)	3800.7 (6656.1)	3.7–138,200.4
Permanent Agriculture (ha)	1299.4 (3273.4)	0.0–43,568.0
Extrativism (ton)	1271.4 (10,265.4)	0.0–506,888.0
Cattle heads (n°)	109,384.1 (166,012.7)	0.0–2,282,445.0
Mean temperature (°C)	27.2 (1.2)	22.4–34.3
Total precipitation (mm)	2122.6 (480.5)	815.8–4209.5
Population (n°)	37,991.3 (118,537.9)	1109.0–2,130,264.0
SPI – basic human needs	57.7 (6.9)	31.24–83.72
Male population (%)	52 (1.5)	46.7–60.3

Table 3
Model selection results for random effects. All tested models included all land-use and cofounder explainable variables. CAR: conditional autoregressive; rw1: random walk of first order, iid municipality: spatial unstructured component; iid year: temporal unstructured component. DIC: deviance information criterion.

Models	Random effect	DIC
Model 1	No random effect	63,827
Model 2	CAR	54,107
Model 3	CAR + iid municipality	54,091
Model 4	CAR + iid municipality + iid year	53,586
Model 5	CAR + iid municipality + iid year + rw1	53,582
Model 6	CAR + iid municipality + iid year + rw1 + iid.municipality: iid.time	53,389
Model 7	CAR + iid municipality + iid year + rw1 + iid.area:rw1	51,750

Table 4
Spatio-temporal Bayesian model results for land-use, climate and socioeconomic explainable variables and random effects. SD: Standard deviation of the regression coefficient.

Variable	Regression Coefficient	
	Mean (±SD)	Credible Interval (95 %)
Fixed effects		
Land-use		
Forest cover (%)	0.19 (±0.03)	(0.14, 0.24)
Deforestation (ha)	0.06 (±0.01)	(0.03, 0.09)
Permanent crop (ha)	0.03 (±0.02)	(−0.01, 0.06)
Non-timber forest product (ton)	0 (±0.02)	(−0.03, 0.03)
Number of cattle heads	0.17 (±0.02)	(0.12, 0.22)
Forest and cattle interaction	0.06 (±0.02)	(0.01, 0.1)
Forest and permanent crop interaction	−0.02 (±0.02)	(−0.05, 0.02)
Climate		
Mean temperature (°C)	−0.1 (±0.02)	(−0.15, −0.06)
Total precipitation (mm)	−0.08 (±0.01)	(−0.11, −0.05)
Socioeconomic		
Basic human needs	−0.07 (±0.03)	(−0.12, −0.02)
Male population (%)	0.19 (±0.02)	(0.15, 0.23)
Random effects		
Spatial heterogeneity (IID, spatially unstructured)	0.0003 (±0.0001)	
Spatial heterogeneity (CAR, spatially structured)	0.15 (±0.03)	
Temporal heterogeneity (IID, temporally unstructured)	0.02 (±0.0)	
Temporal heterogeneity (RW1, temporally structured)	0.002 (±0.003)	

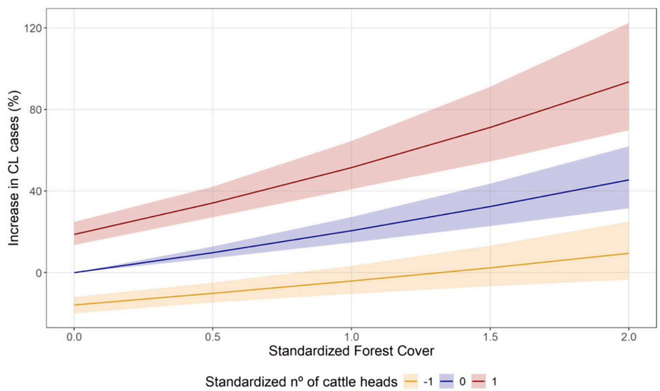


Fig. 2. Plot showing the effect of the amount of forest cover on CL number of cases when there is a higher amount of cattle heads (line in red), a lower amount of cattle heads (line in yellow), and no change in the mean amount of cattle heads (line in blue). The number of cattle heads and the amount and forest cover are standardized. SD: standard deviation change on the number of cattle heads.

3.3. *Map of relative risk*

The map of average CL Relative Risk for the entire study period and their 95 % credible interval width are shown in Fig. 3. The annual map of CL's relative risk is found in Fig. S1 in the Supplementary material (SM-2). As expected, the intensity of Relative Risk (RR) follows the spatial patterns of the cumulative relative incidence. In general, the municipalities with the highest RR are located in the Amazon frontier region, where we also found high amounts of forest cover, deforestation rates, and cattle heads (Fig. S3 SM-2). We also found high RR of CL in the municipalities located in the northern part of the Brazilian Amazon, especially in the north of the states of Amazonas, Pará, and in the entire state of Roraima.

4. Discussion

To the best of our knowledge, this study represents the most comprehensive investigation of the impact of land-use changes on CL cases in the Brazilian Amazon Forest. It offers novel insights into the dynamics of the disease in the region. Previous studies have identified forest cover as a significant risk factor for CL transmission in several Neotropical regions (Karagiannis-Voules et al., 2013; Valero et al., 2021; Valero and Uriarte, 2020). However, in the Brazilian Amazon Forest, the observed incidence of the disease in many municipalities where the forest is well preserved is low. We provide an explanation for this pattern, namely, the occupation by cattle herds of areas with forest remnants. In our statistical model, the influence of forest cover on CL incidence in the Brazilian Amazon forest is dependent on the presence and amount of livestock. This means that in some areas where the forest cover is high but the number of cattle heads is relatively low, the influence of forest cover on CL risk is drastically diminished, and in some cases, could even be negative. In addition, many authors have stated, based on empirical observation, that deforestation is an essential risk factor for CL transmission risk (Neto et al., 1998; Ready, 2008; Guerra et al., 2015). However, to the best of our knowledge, our study was the first to statistically assess and quantify the influence of deforestation on the increased number of CL cases in the Brazilian Amazon Forest. Other studies have not found this association (Rodrigues et al., 2019; Santos et al., 2024), probably because they used purely spatial models and used the cumulative sum of the deforested area over several years as a covariate. Conversely, using a spatial-temporal model approach with a 17-year temporal series of forest loss enables us to develop a more robust assessment of the impact of recent deforestation activity on the number of CL cases each year.

The higher number of CL cases in municipalities with higher forest cover and livestock may be associated with a combination of factors that may include an increased density of sandflies and the proximity of humans to sandfly habitats. Such factors can increase the chances of human-vector contact and, consequently, the risk of disease transmission. Several studies have reported high densities of CL vectors in highly vegetated areas (Kocher et al., 2022) and vegetation near rural settlements, particularly in association with animal shelters (Ramos et al., 2014; Guimarães et al., 2022; Costa et al., 2021; Pereira Júnior et al., 2019). Additionally, sandflies have generalist feeding habits, including the blood of cattle (Pereira Júnior et al., 2019; Costa et al., 2021). The greater livestock biomass in these areas might contribute to an increased density of CL vectors due to the greater availability of food resources. In addition, domestic animal shelters may provide organic material that sandflies use for breeding, further contributing to a higher density of these vectors (Bern et al., 2010; Ramos et al., 2014). It is also possible that sandflies may be attracted to the residences and workplaces of humans who work with cattle and reside near forest, to seek their blood and the blood of domestic animals. This pattern has been extensively documented in several rural regions (Rosário et al., 2017; Chagas et al., 2018; Neitzke-abreu et al., 2020), and could potentially increase the human-vector contact rate and the risk of CL infection in humans.

In addition, deforestation and forest-pasture matrix in the Amazon forest could result in a reduction in the diversity of small mammals and an increase in the density of important reservoirs of *Leishmania*, such as *Didelphis marsupialis* and *Proechimys* spp. (Palmeirim et al., 2020; Roque and Jansen, 2014). Areas with low biodiversity and a high density of competent reservoirs tend to exhibit an increase in the risk of disease transmission due to the amplification of infected hosts and a higher chance of encounters between vectors and infected reservoirs (Keesing et al., 2006). The impact of biodiversity loss on the risk of infectious disease transmission has been extensively studied for some vector-borne diseases, such as malaria, Lyme disease, and West Nile virus (Ostfeld and Keesing, 2012; Laporta et al., 2013). Therefore, similar mechanisms may also play a role in the transmission of CL. A higher prevalence of *Leishmania* parasites on sandflies in disturbed environments with lower mammal species and a greater abundance of *Leishmania* reservoirs have been indeed recorded in French Guiana (Kocher et al., 2022).

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

Previous studies have identified that CL hotspots are located in areas that have undergone extensive land-use transformations (Chavy et al., 2019; Portella and Kraenkel, 2021). However, to develop more target control measures for the disease, it is essential to understand how each type of land-use characteristic affects disease incidence (Loh et al., 2015). Our statistical analysis has revealed that the landscape characteristics that have the greatest impact on the number of CL cases in the

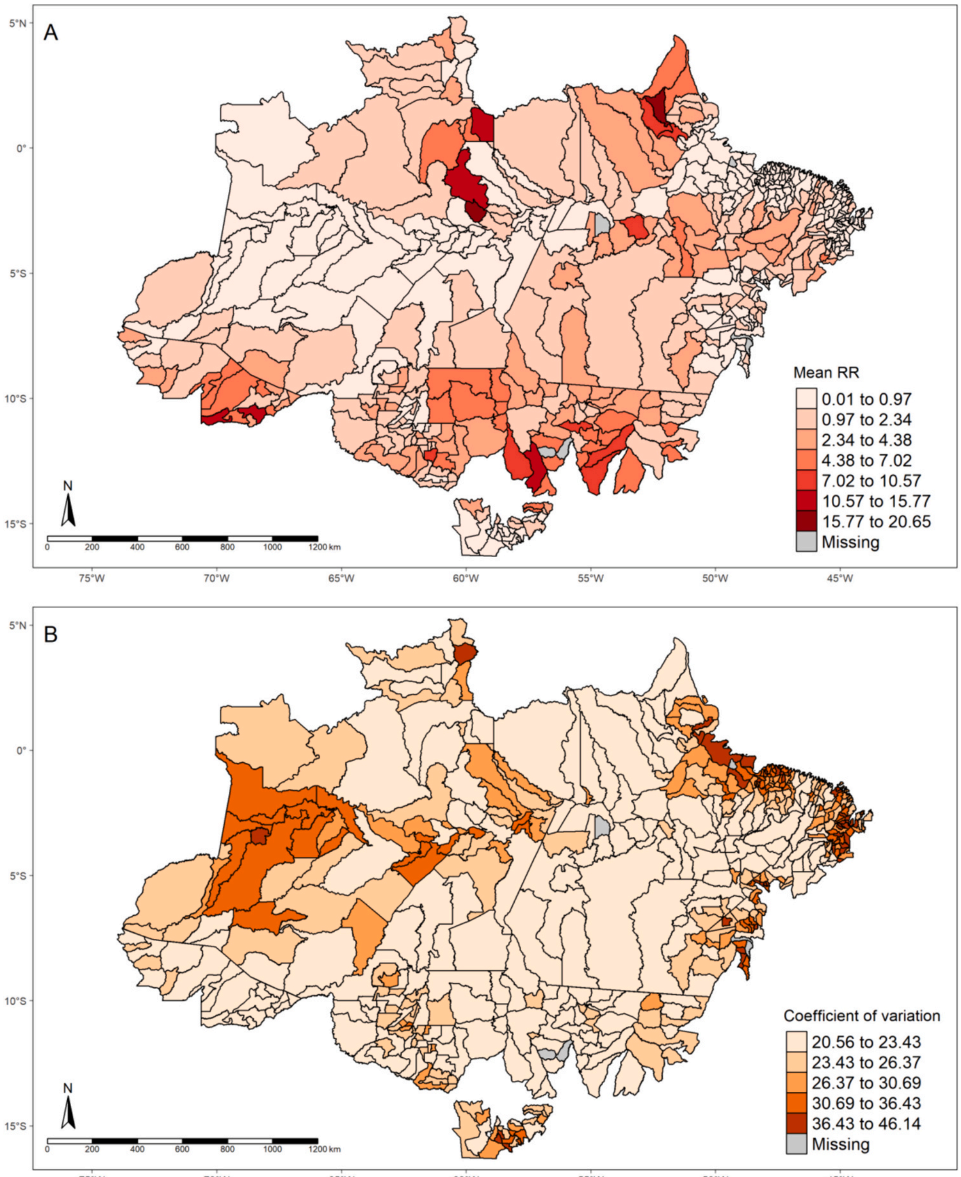


Fig. 3. Map of the mean (A) and coefficient of variation (B) of CL Relative Risk estimated by the spatiotemporal Bayesian model across the Brazilian Amazon Forest from 2011 to 2017.

Brazilian Amazon Forest are a combination of higher forest cover and livestock, and to a lesser extent, recent deforestation activity. This mosaic of landscapes is especially found in municipalities that are in the initial stage of frontier occupation (Guerra et al., 2015; Guerra et al., 2019; Calentano and Veríssimo, 2007; Rodrigues et al., 2009). This process of land occupation, which is mainly driven by livestock farming, has also been demonstrated to have a negative impact on biodiversity (Nunes et al., 2022) and climate (Nepstad et al., 2014). We recommend that policymakers prioritize the investment in more sustainable alternatives of economic development in the Amazon, making its landscape healthier for the environment and humans, and adopting a one-health perspective. As a more short-term measure, we recommend the implementation of prevention and control strategies in municipalities with these characteristics. These actions should include recommendations for residents and workers in the region such as the use of insect repellents, and personal protective equipment, and implementation of environmental management strategies such as improving housing conditions and building homes distantly located from forested areas and animal shelters (PAHO, 2017).

Our model also identified some residual risk components that were attributed to the spatial random effect. This result means that there must be other characteristics affecting the risk of CL transmission in these municipalities that were not captured by the fixed effects in our model (Fig. S7 SM-4). We hypothesize that the expansion of urban areas close to the forest and the presence of newly arrived immigrants with low immunity to CL may also play an important role in the risk of CL transmission in these municipalities. Unfortunately, to our knowledge the data required to test this hypothesis was unavailable. We recommend that further studies investigate additional environmental and social factors that may impact the risk of CL transmission in these areas.

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

5. Conclusion

In summary, this study used rigorous spatiotemporal statistical analysis to identify land use factors associated with an increase in CL incidence in the Brazilian Amazon Forest. Additionally, we also showed that deforestation and the interaction between forest cover and cattle ranching are landscape risk factors for CL transmission in this region. Based on our results and current literature we believe that these environmental changes, commonly found in municipalities of the recent Amazon Frontier, are probably creating suitable conditions for the proliferation of vectors and reservoirs, as well as an increase in human-vector contact rates. Therefore, to control CL in the Brazilian Amazon forest, we recommend focusing the surveillance and control measures on the municipalities where these landscape characteristics are predominant. In addition, we suggested that public policymakers invest in more sustainable alternatives for the economic development of the Brazilian Amazon Forest to make the landscape of its municipalities healthier for the environment and people.

Funding

TPP PhD studies were funded by CAPES (Process: PDSE - 88882.327896/2019-01), VS Master studies were funded by FAPESP (grant number: 2018/23984-0), PIP has been supported by CNPq (grant number: 313055/2020-3), RAK by CNPq (grant number: 315641/2021-5) and FAPESP (contract number: 2021/14335-0).

CRediT authorship contribution statement

T.P. Portella: Writing – original draft, Visualization, Software, Investigation, Formal analysis, Data curation, Conceptualization. **V. Sudbrack:** Writing – review & editing, Software, Resources, Data curation. **R. Coutinho:** Writing – review & editing, Validation, Methodology. **P.I. Prado:** Writing – review & editing, Validation, Supervision, Methodology. **R.A. Kraenkel:** Writing – review & editing, Supervision, Project administration.

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.

Data availability

Data will be made available on request.

Acknowledgements

We would like to acknowledge Dr. Haavard Rue and Dr. Leonardo Bastos for their valuable assistance in the INLA package. We also would like to thank Dr. Tatiane Cristina Moraes de Sousa and the anonymous reviewers for their valuable comments and suggestions, which have improved the final version of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.176064.

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