

## Article

# Malaria Risk Drivers in the Brazilian Amazon: Land Use: Land Cover Interactions and Biological Diversity

William Gonzalez Daza <sup>1,\*</sup>, Renata L. Muylaert <sup>2</sup>, Thadeu Sobral-Souza <sup>3</sup> & Victor Lemes Landeiro <sup>4</sup>

<sup>1</sup> Programa do Pós-Graduação em Ecologia e Conservação da Biodiversidade, Departamento de Biociências, Av. Fernando Corrêa da Costa, 2367, CEP 78060-900, Cuiabá, Mato Grosso, Brazil

<sup>2</sup> Molecular Epidemiology and Public Health Laboratory, School of Veterinary Science, Massey University, New Zealand.

<sup>3</sup> Departamento de Botânica e Ecologia, Instituto de Biociências, Universidade Federal de Mato Grosso (UFMT), Brazil.

<sup>4</sup> Laboratório de Ecologia e Conservação de Ecossistemas Aquáticos, Centro da biodiversidade, Universidade Federal de Mato Grosso (UFMT), Brazil.

\* Correspondence: wgonzalez@unal.edu.co; Tel.: +57 3134274633.

**Abstract:** Malaria is a prevalent disease in several tropical and subtropical regions, including Brazil, where remains a significant public health concern. Despite control efforts, reintroduction of endemics in areas without cases for decades poses a challenge. To assess factors influencing malaria risk, regional outbreak cluster analysis and a spatio-temporal models were developed for the Brazilian Amazon, incorporating climate, land use/cover interactions, endemic bird, and amphibian richness. Results showed that amphibian, bird richness and endemism correlated with a reduction in malaria risk. Presence of forest had a positive effect on risk, but it depended on its juxtaposition with anthropic land uses. Biodiversity and landscape composition, rather than forest formation presence alone, modulated malaria risk in the period. Areas with low endemic species diversity and high human activity, predominantly anthropogenic landscapes posed high malaria risk. This study underscores the importance of considering the broader ecological context in malaria control efforts.

**Keywords:** Malaria; Amazon biome; INLA; Land use/cover interactions; Bird and amphibian richness-endemics; Landscape composition; Biological diversity; Spatio-temporal modeling

## 1. Introduction

Malaria is a tropical and subtropical endemic disease that affects several countries worldwide. In South America, malaria cases were reduced by 58% between 2000-2020, from 1.5 to 0.65 million cases [1]. Yet, malaria remains an important public health problem, far from elimination in several regions. Venezuela, Brazil and Colombia make up 77% of all cases in South America and 68% of those cases were due to *Plasmodium vivax* parasite. Although in Brazil the malaria control efforts have been significant, public health issues still concern, in addition to the increasing reintroduction of endemics in areas without cases for decades [2].

Even though *Anopheles darlingi* is the predominant malaria vector in the Amazonian countries [3], there are 61 *Anopheles* species in Brazil belonging to the subgenus *Anopheles*, *Kerteszia* and *Nyssorhynchus*, some of those species inhabits other biomes such as the “Atlantic Forest” and the “Pantanal” wetlands. The highest vector species richness is located in the Amazon biome, being *Nyssorhynchus* and *Anopheles* the most diversified subgenera [4]. That way, in Brazil the transmission remains highly clustered in the Amazon basin, with 99.5% of the total cases [5, 6]. Most of the vector species are restricted to forest areas being very rare in urban zones [7].

Deforestation is a critical driver associated with increased malaria cases in Amazon [8–11]. The relationship between deforestation and malaria incidence is driven by multiple processes. For instance, an interface between primary forest and human settlements [12, 13], the rapid process of

adaptation of vectors to new modified environments [14–17], food chain shifts, and also low abundance of vector predators [18, 19].

Deforestation is caused by increasing urban infrastructure, crops, agriculture, livestock, mining and other human-induced activities that represent a rise in the contact between human and natural land cover types, where the infected vectors inhabit. Thus, spatial modeling of land use and cover is considered an important tool to understand how malaria increases or decreases due to the distribution of people and changes in vector habitat quality [8, 20–25]. The importance of using landscape-based approaches including landscape configuration in eco-epidemiological models is remarkable, going beyond including the quantity for each category and also its interactions [23, 26, 27].

In addition to understanding the roles of deforestation, understanding the role of biodiversity in malaria prevalence might be fruitful, in terms of the role of predators, competitive species and non-competitive hosts, that is, hosts incapable of being infected by the *Plasmodium*. The effects of human-induced changes on disease prevalence have already been studied for hantavirus [28, 29], Lyme disease [30] and schistosomiasis [31]. Consequently, in diverse ecosystems, the transmission of diseases is disrupted due to a dilution of infectious agents across different species. In other words, if there are more species in an ecosystem, there are more opportunities for a pathogen to infect a non-host species, which reduces the concentration of the pathogen in the environment and, consequently, its transmission to the host species. Overall, the dilution effect highlights the importance of preserving biodiversity as a means of reducing the incidence of infectious diseases [32, 33].

Several predators can significantly control populations of disease-carrying mosquitoes, both aquatic and terrestrial ecosystems. The aquatic predators of mosquitoes are made up of different taxa, such as tadpoles, but few species identified as effective predators [19], fish [34], being a very effective predator such as *Poecilia reticulata*, *Gambusia affinis*, and the most important group, macroinvertebrates such as Belostomatidae, Notonectidae and Odonata [18, 35, 36]. The most common and effective terrestrial predators are Arachnida, mammals such as insectivorous bats [37], and birds like the flycatcher [38]. Although the majority of groups that regulate mosquito populations have been briefly discussed, it is worth noting the intricacy of a pristine ecosystem. Any ecosystem disruption can lead to an ecological imbalance resulting in a decline of the ecosystem's ability to control disease-carrying mosquito populations.

Three main factors determine the distribution and biological cycle of malaria: (1) anthropological factors such as migrations, economic activities (hunting, fishing, agriculture), race, age, gender; (2) Environmental factors such as temperature, relative humidity, altitude, precipitation and (3) ecological factors such as vegetation types, biological interactions, nutrient availability, among others. Previous studies evaluated the biological factors [39], the land use - land cover (here after LULC) influence [8, 20–23, 23–25, 40], and malaria spatial patterns [41]. However, the combined impact of land use, biodiversity and environmental factors on a macro ecological scale (biome) in Brazil has not been studied yet.

Here we examined the dynamics of malaria and the impact of LULC, local biodiversity and other environmental factors as drivers of malaria risk at Amazon. Specifically, we aimed to understand: i) how the land use types can increase or decrease the malaria risk, ii) how the combination, or interaction, of different land use types can affect malaria risk, iii) whether biodiversity would dilute malaria in more rich regions, and iv) how climatic variables correlates with malaria. We expected that Amazonian municipalities with high levels of anthropogenic land use (high habitat modification) and with low biological richness had higher Malaria prevalence. This information will contribute to the understanding of the spatio-temporal dynamics of malaria across Amazonia, in addition to improving regional and municipal prevention plans.

## 2. Materials and Methods

### 2.1. Dataset

This study was developed with data for the Brazilian municipalities within the Amazon boundaries, whereas municipality polygons were our sampling units (See Figure S1). The Amazon boundaries used here is a map provided by the Instituto Brasileiro de Geografia e Estatística [42].

## 2.2. Malaria Cases and Population Data

Human annual Malaria cases (infection location) for each municipality from 2007 to 2018 were provided by Brazil's Epidemiological Surveillance Information System for malaria [43]. Due to the low amount of *P. ovale* and *P. malariae* (mostly African and Asian distribution) cases, the models were restricted to *P. vivax* and *P. falciparum*. The mixed-infection cases were added to both *falciparum* and *vivax* cases. The cases were downloaded without stratification by age, sex or race. The Annual Parasite Index (API) was calculated as Annual cases/Population\*1000. The total population size was downloaded directly from Instituto Brasileiro de Geografia e Estatística [44].

## 2.3. Land use – land cover (LULC)

LULC rasters with 100 m cell-size resolution were downloaded from “Projeto MapBiomass” collection 5.0 to reconstruct landscape structure annual information for 2007-2018, based on Landsat images [45]. Data was extracted through Google Earth Engine, with 13 LULC classes: forest plantation, mining, sugar cane, wetland, temporary crops, grassland, other non-forest formation, savanna, river, lake and ocean, urban infrastructure, pasture and forest formation. We obtained the area of each LULC classification for each municipality in hectares from 2007 to 2018 using zonal statistics in QGIS 3.8.2 (2018). Then, the LULC areas were divided by the municipality area in order to calculate the proportion of each LULC class for each municipality. Finally, in order to characterize the municipalities and their land use change dynamics throughout the years analyzed, the % change of the most important uses in terms of anthropic activities and natural habitats were plotted on maps.

## 2.4. Environmental variables

The precipitation seasonality has a high influence in terms of malaria outbreaks [24, 46, 47]. We assigned to each municipality a climatic zone to establish which are the four rainiest months, the four driest months, the four warmest months and finally the four coldest months. We used two climatic variables from the historical monthly weather data from Worldclim from the year 2007 to 2018 with spatial resolution of 2.5 minutes (pixel area ~21 km<sup>2</sup>) the average maximum temperature (°C) and monthly precipitation (mm) [48]. Each climatic zone formed by a 250,000 km<sup>2</sup> grid = 500 km \* 500 km (see figure S2A). We used the municipality centroid to determine its climatic zone (figure S2B). After defining the dry and rainy seasons (each season composed of four months), we calculated the total rainfall and average of temperature values. Thus we obtained the next four climatic variables: (1) Total rainfall in the dry season, (2) Total rainfall in the rainy season, (3) Maximum temperature in the dry season and (4) Maximum temperature in the rainy season. The seasons observed were confirmed using the rainfall trends in the Amazon from the past eight decades [49]. Finally, the last environmental variable measured was the mean municipality altitude extracted from EarthEnv with 1 km<sup>2</sup> cell-size resolution [50].

## 2.5. Biological Diversity variables

We used data from birds, mammals, amphibian species richness and endemism as biological diversity proxy. We used them due to high quality data availability for these three groups commonly used in macro ecological studies [51–53]. These data were extracted from the Patterns of Vertebrate Diversity and Protection in Brazil database [54]. Those variables were fixed for all the years studied due to the absence of yearly information and represented on maps the zonal average by municipality to make comparisons with the other variables analyzed and its possible impact on malaria risk.

## 2.6. Model building

After the variable transformation (common logarithm), we analyzed variable distribution in order to determine if they have a good representation across the study region. Skewed variables were eliminated from the analysis after a graphical method confirmation through the histograms and normality plots (see figure S3). We also performed a Spearman correlation analysis ( $p < 0.05$  of significance) (See figure S4), finding the most correlated variables ( $> 0.8$  of correlation) and eliminating them from the analysis based on the most appropriate biological criteria. The final selected variables are shown in table 1.

**Table 1.** Covariate description (values per municipality) including environmental, LULC classifications and diversity after the correlation analysis and the selection based on the data distribution (see figures S3 and S4). Each of these variables are described for the Amazon biome. Number of total and endemic mammal species were eliminated from the analysis due to high correlation with birds. \*For the details of the species maps methodology for each taxonomic group see [54].

Variable	Variable type	Description
Altitude	Climatic	Municipality mean altitude, M.A.M.S.L. (static variable).
Precipitation wet season	Climatic	Total mean precipitation in the wet season (mm).
Precipitation dry season	Climatic	Total mean precipitation in the dry season (mm).
Temperature wet season	Climatic	Mean maximum temperature (°C) in the wet season.
Temperature dry season	Climatic	Mean maximum temperature (°C) in the dry season.
Forest Formation	Land use land cover	Dense rainforest, evergreen seasonal forest, open rainforest, semi deciduous seasonal forest, deciduous seasonal forest, wooded savanna, alluvial open rainforest (floodplain forests and Igapó forests) (% of municipality).
Grassland	Land use land cover	Regions within the Amazonia/Cerrado/Orinoco ecotone with predominance of herbaceous strata (% of municipality).
Pasture	Land use land cover	Area of pasture, predominantly planted, linked to agricultural activity. Areas of natural pasture are predominantly classified as Grassland which may or may not be grazed (% of municipality).
Temporary crops	Land use land cover	Areas occupied with agricultural crops of short or medium duration, generally with a vegetative cycle of less than one year, which after harvest require new planting to produce (% of municipality).
Urban Infrastructure	Land use land cover	Urbanized areas with a predominance of non-vegetated surfaces, including trails, roads and buildings (% of municipality).
River, lakes and ocean	Land use land cover	As the name denotes, rivers, reservoirs, dams, ocean in the East coast zone in the Amazon region, lakes and other water bodies (% of municipality).
Endemic amphibians*	Diversity	Mean endemic amphibians species number (static variable).
Endemic birds*	Diversity	Mean endemic bird number species (static variable).
Bird richness*	Diversity	Mean bird number of species (static variable).

We initially used cluster analysis to identify the spatial pattern of malaria (random, aggregate or uniform) and then, we utilized integrated nested Laplace approximation (INLA) analysis to validate the risk factors (LULC, environmental variables and local diversity) driving malaria risk. Cluster analysis is a technique used to identify groups or observations in a dataset based on the similarity of their attributes. In disease spatial analysis, cluster analysis can be used to identify spatial areas with a high prevalence or incidence of a particular disease. INLA is a Bayesian method used for fitting models to spatial data. It is particularly useful for spatial analysis because it can handle complex spatial structures, including spatial correlation, time dependence, and can provide accurate estimates of uncertainty. In disease spatial analysis, INLA can be used to model the spatial distribution of a disease, taking into account the underlying spatial structure of the data and any potential confounding variable [55]. Using both cluster analysis and INLA together can provide a more comprehensive analysis of disease spatial patterns.

The cluster analysis models were developed using a retrospective spatiotemporal model under permutation probability using a maximal cluster size of 50% of the total annual municipality population using SaTScan™. The null hypothesis of no clustering was rejected when the simulated p-value was lower than or equal to 0.05. For the INLA analysis we used two models for *P. vivax* and two for *P. falciparum*, covariates models (see table 1) and interactions models with the landscape configuration (the land use combinations present in a defined area).

To address the issue of highly uneven population distribution across the Amazonian municipalities the malaria cases were standardized by utilizing the function 'expected' (expected cases) before incorporating them into the INLA models [56]. Accordingly, we performed two models for each parasite, the first one with the covariates described in table 1 and the second one with the LULC interactions, that is the relationship between multiple land use land cover types and their combined effect on malaria risk. Once we determined the influence of each combination of LULC on malaria risk through the INLA models, we created a 10 x 10 km mesh with each cell representing a specific geographic area. Using this mesh, we constructed a zonal histogram to identify the LULC combinations present in each cell for each year. Finally, we created annual color-coded maps showing the associated malaria risk values for each LULC combination across the study area.

All the models were performed with non-informative priors. We included an 'independent and identically distributed (iid) random effects often used to account for overdispersion [57] and a Besag-York-Mollier spatial term where the observations and data in contiguous municipalities may be spatially correlated compared to areas that are further apart [56, 58].

The model choice was based on the fit and adequacy, the cross-validation check via conditional predictive ordinate (CPO) values, the log likelihood, the dispersion, and the correlation between the mean fitted values and the observed cases. All analysis were performed using the R language (R Core Team, 2022). The correlation analysis was performed using the R package Vegan [61]; the expected values were calculated with the SpatialEpi R package, the neighborhood matrix with the spdep R package, for the spatiotemporal models, we used the R package INLA 21.11.22 [55, 62] and the coefficient plots were created using coefINLA R package [63], for the maps, zonal statistics and zonal histograms we used QGIS 3.8.2 (2018).

### 3. Results

#### 3.1. Malaria cases

In total, 2,827,546 cases were reported, whereas *P. vivax* cases were the most abundant (85.2% of cases), followed by *P. falciparum* (13.7% of cases) and mixed forms (0.9% of cases). In general, from 2007-2018 there was a decreasing trend for *P. vivax* and *P. falciparum* cases, both peaking in 2007. The northern zone in the Amazon region concentrated the largest quantity of cases (Figures S5 and S6), for both *P. vivax* and *P. falciparum*. In 2007 the Amazonas state (AM) registered the highest number of cases (total cases), with 203,164 cases that represented 38.3% of all the cases from 2007-2018.

There were areas with absence or rare cases, where the relative risk maps, however, showed positive risk. Another region that presents high API and relative risk is the northern areas in the Amapá state, a state composed mainly by forest cover, grassland and a big river cover due to the mouth of the Amazon river. Over the years, the API relative risk in the northwest Amazon region has consistently increased. This area is mostly characterized by grasslands and pastures that may or may not be grazed, and forms the ecotone between the savannahs of the Orinocense plains and the Amazon biome. Additionally, this region has experienced significant natural habitat modification in the past two decades (see S8). Regarding *P. falciparum*, the pattern remains quite similar, albeit with fewer risk values and smaller clusters. The Amazon's northwestern and northeastern regions also exhibited elevated API values and positive risk values (see figure S6).

#### 3.2. Spatial clusters

According to our analysis, we have identified three distinct clusters for both *P. vivax* and *P. falciparum*, each with varying levels of risk, geographic coverage, time windows, and location (See table 2). The clusters associated with *P. vivax* had larger expected and observed cases, indicating a higher incidence of this strain of the disease in the affected areas. Additionally, our findings revealed that cluster number 2 for falciparum malaria had a consistent location within regions that have experienced significant natural cover transformation over the past two decades, specifically in the Para state (North east Amazon zone).



**Table 2.** Results of the cluster analysis for *P. vivax* and *P. falciparum*. The clusters shown here were significant ( $p<0.00001$ ) and the risk value was calculated by measuring the ratio between observed cases and expected cases. Its geographical extension and location can be observed in figure S7.

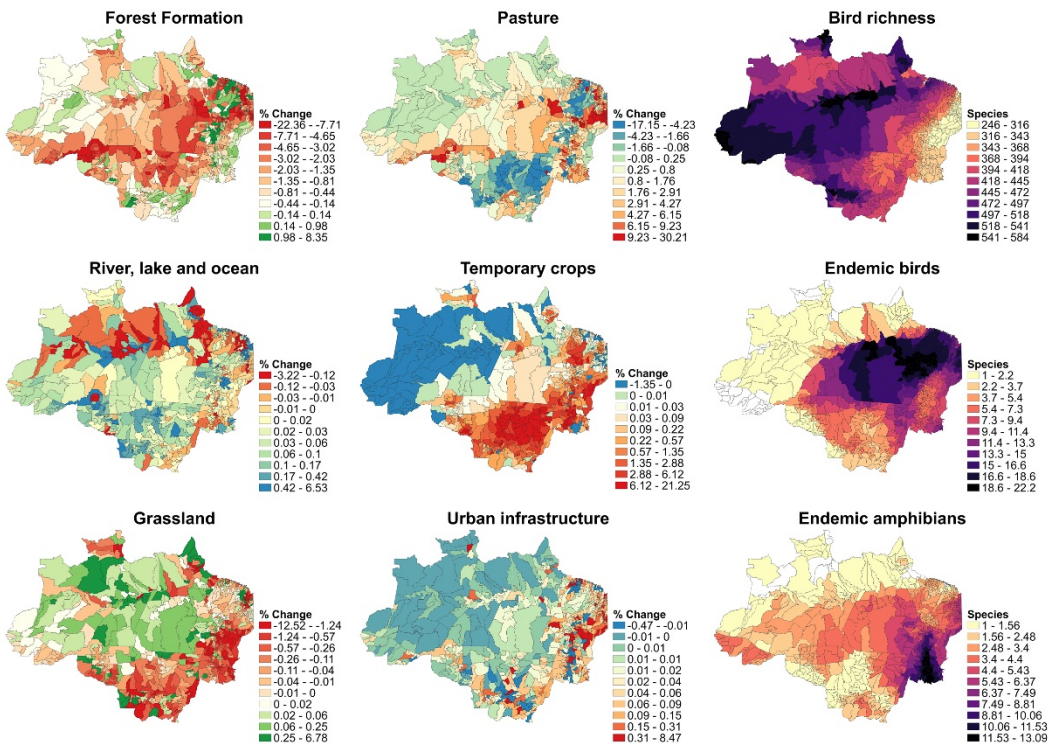
<i>P. vivax</i>				<i>P. falciparum</i>			
Cluster Time	Observed cases	Expected cases	Risk	Cluster Time	Observed cases	Expected cases	Risk
(1) 2013-2017	353,973	231,923.58	1.53	(1) 2013-2018	83,331	47,915.42	1.74
(2) 2010-2011	163,179	86,675.19	1.88	(2) 2009-2012	65,919	38,388.91	1.72
(3) 2007-2008	136,239	81,743.78	1.67	(3) 2007-2008	21,794	9,446.12	2.31

3.3. LULC change

During 2007-2018 there was a notable land use change (figure 1). The forest formation in the northern area of Mato Grosso, as well as in nearly all of Acre, Rondonia, and Amazonas states, showed a significant decline. Porto Velho – RO had one of the highest negative trends in all of the Amazon region. In 40 municipalities there was a reduction of approximately 10% to 22% of forest cover in the period. Grassland had a cover reduction as well but differently from forest formation, the higher percentage change was in the south west and south east parts of the Amazon region (Mato Grosso, Tocantins and Maranhão states). Temporary crops had a notable increase within the agriculturally expansive states (Mato Grosso, Maranhão, and Pará). We want to remark that those changes are more accented in smaller municipalities, due to the fact those are maps that have been represented in proportion (land use area / municipality total area \* 100).

3.4. Diversity variables

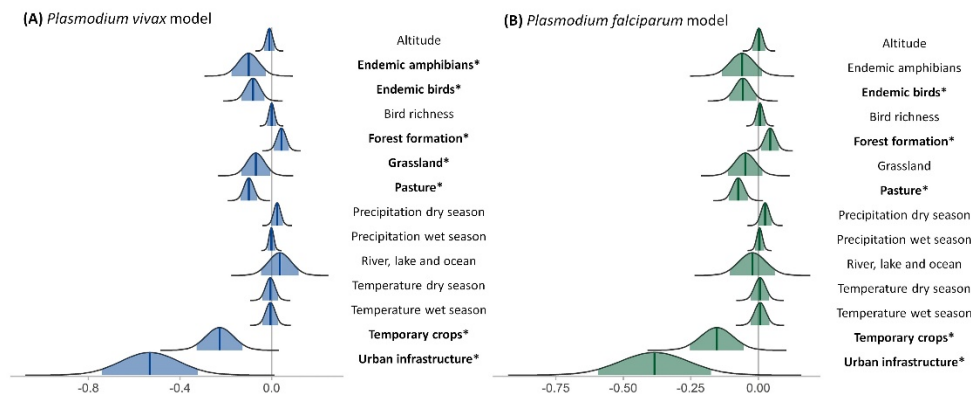
The Acre, western Amazonas and the north of Roraima States contained the greatest bird richness values. In the Mato Grosso state, the southern region also shows a high number of bird species due to high influence of the Pantanal wetlands. Para and eastern Maranhão states showed high mean endemic bird species number, the other states showed smaller numbers of endemic species even in the absence of information for Acre and some municipalities of Amazonas, Roraima and Amapá. Finally, the Tocantins state exhibited the highest number of endemic amphibians (figure 1).



**Figure 1.** The left and center column shows LULC percentage change (%) between the 2007-2018 at the municipality level, the negative values represent a decrease and positive values represent an increase in land use - land cover area of each covariate. The right column shows the average species richness maps at municipality level.

3.5. Covariate significance

After identifying over dispersion in both *P. vivax* and *P. falciparum* cases, we opted to employ the zero-inflated negative binomial error distribution for the covariates model and the negative binomial family for the interactions models. For *P. vivax* covariate model, the cpo values ranged from 0 to 0.99 with a mean of 0.43, for the *P. falciparum* covariate model, the cpo values ranged from 0 to 0.99 with a mean of 0.62. The table S9, S10 and the figure 2 shows the average and range values for each covariate. There was a difference in the effects of each covariate for *P. vivax* and *P. falciparum* risk. Forest formation had a positive effect on the relative risk for both *Plasmodium* species. Endemic amphibians, endemic birds, grassland, pasture, temporary crops and urban infrastructure had a negative effect on the relative risk of *P. vivax*. For *P. falciparum*, endemic birds, pasture, temporary crops, and urban infrastructure had a negative effect on the relative risk.

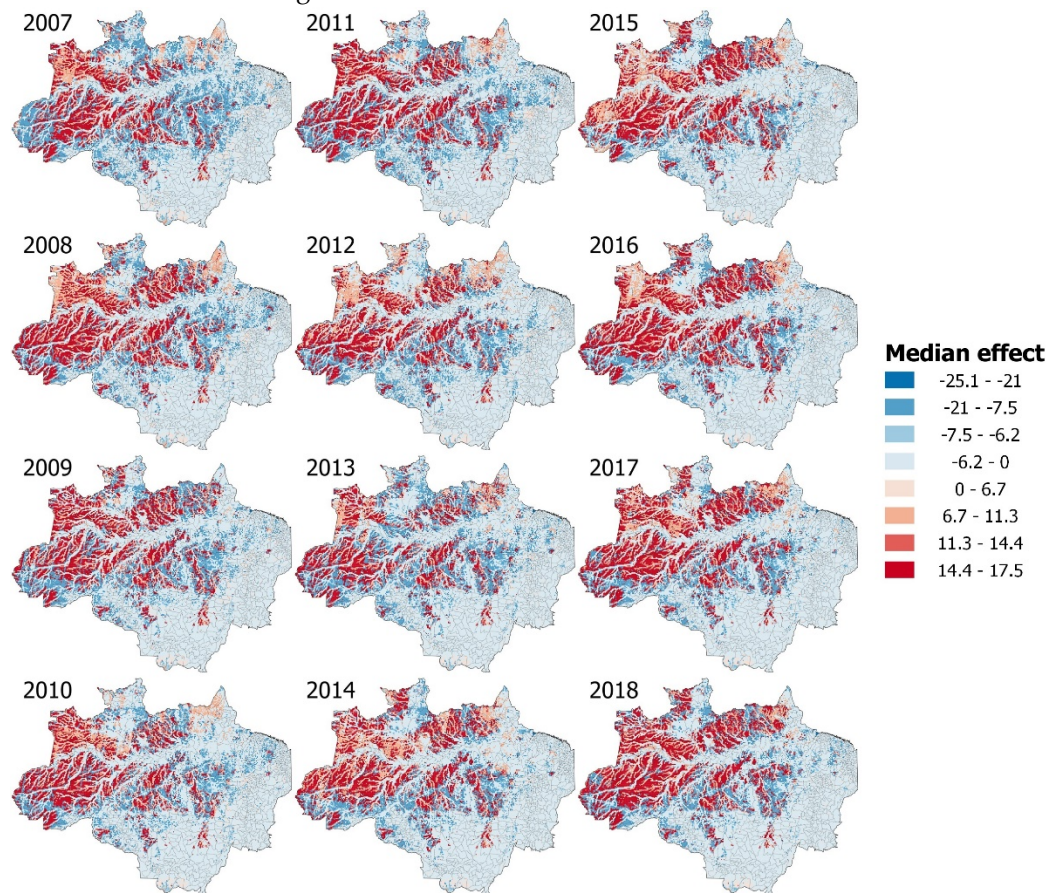


**Figure 2.** Coefficient plots of posterior distributions effect sizes with the median (dark blue and green lines) and 95% credible intervals (light blue and green shades) of each covariate for (A) *Plasmodium vivax* cases in blue and (B) *Plasmodium falciparum* cases in green, the significant effects are represented in bold face and marked with an asterisk.

3.6. Interactions models and effect maps

We found 50 unique landscape configuration combinations from 2007 to 2018 (See the example for the 2018, figure S9). In the INLA interaction models we estimate the mean effect for every possible combination (57 combinations for the six LULC categories used), of which we found four positive and seven negative significant landscape configurations for *P. vivax* model and one positive and one negative significant for *P. falciparum* models (See table S11). For *P. vivax*, the landscape configuration that showed the highest average effect was (1) Grassland \* River Lake and Ocean (2) Pasture \* Grassland \* Temporary crops (3) Forest Formation \* River Lake and Ocean and (4) Pasture \* Forest Formation \* Grassland. The other seven combinations all had a negative effect on estimated risk, with the strongest negative effect being for Forest formation \* Urban infrastructure. In the case of *P. falciparum*, we found only two landscape significant combinations, (Main reason why we did not make maps representing the average effect in each 10 \* 10 square, we would have only 2 colors represented which would not be informative), (1) Grassland \* River Lake and Ocean with positive risk effect and (2) Forest Formation \* Grassland \* River Lake and Ocean with negative mean effect. All of these interaction effects and single land use effects were mapped for each year (see figure 3) for *P. vivax* in order to see in more detail each effect on the spatial interaction pattern in all the

analyzed years. For *P. falciparum* the cpo values ranged from 0 to 0.99 with a mean of 0.51, in the case of *P. vivax* the values ranged from 0 to 0.98 with a mean of 0.31.



**Figure 3.** INLA median effect on the credible intervals in the *P. vivax* risk based on the LULC interaction model (100 km<sup>2</sup> mesh maps). Lower values cells (blue) and the higher values cells (red) are based on the landscape configuration (see supplementary materials) for all years (2007 – 2018).

#### 4. Discussion

Our findings suggest that the risk of malaria is influenced by a complex interaction of ecological and anthropogenic factors that determine a non-random distribution. One notable factor is the richness and endemism of amphibians, mammals, and birds, which appears to reduce the risk of malaria. Additionally, the presence of forest was found to have a positive effect on malaria risk, but this relationship was dependent on the contact with anthropic land uses where humans inhabit. The covers of anthropic activities were found to reduce the malaria risk, possibly due to the vector habitat loss and homogenization of the landscape. However, when these land use covers came into contact with other land uses such as water cover and natural habitats of the vector, the effect was reversed, and the risk of malaria increased.

The detected clusters suggest that malaria cases distribution was far from random, and display the same trend with past investigations showing high malaria rates in the municipalities Mâncio Lima - AC, Rodrigues Alves - AC and Cruzeiro do Sul – AC [41] and the other municipalities that make up each of the clusters, mainly the Amazonas, Northern Acre and the western zone of Para states. Permutational and Bayesian analysis present similarity in the spatial pattern, where the largest clusters contain municipalities with highest risk values due to highly suitable conditions for malaria transmission.

From the 53 Brazilian municipalities located on the border with Peru, Colombia, Venezuela, Suriname, Guyana, and French Guiana, 39 presented high risk values, consistent with the



investigation of [4], that reviewed the spatialization of malaria in Brazil. This reaffirms the importance of carrying out early control and prevention alerts, due to the combination of high migration rates and their remote locations from larger health centers and political administrative centers, it is anticipated that these municipalities will be the most affected areas in the future.

The *P. vivax* and *P. falciparum* spatial patterns were differentiated. Those differences are still not completely understood and might be due multiple reasons. For instance, the Duffy gene is randomly distributed in the population and more frequently found in Afro-descendants from the West African region [64], the difference in the *Plasmodium* species niches [4], the *Plasmodium* species time of gametocyte production and their lifespan [65], or the relapses, a blood-stage infection only for *P. vivax* and *P. ovale*, arising from the activation of hypnozoites after the primary infection [66]. On the other hand, the Brazilian government launched a campaign in 2003 for the prevention and control of malaria (acronym in Portuguese PNCM) where its process and result indicators are specifically the percentage of *P. falciparum* cases, autochthonous cases of *P. falciparum*, parasitic index falciparum annual (IFA), among others meaning this differential control effort [67].

Although climatic variables are very important in malaria transmission at local scales, no detectable effect was found for our lattice dataset at the municipality level for explaining annual risk. At the biome level, the spatial and temporal scale at which the climatic variables were measured can affect the inferred malaria cases-climatic influence [68]. Although micro-scale environmental characteristics are lost when we aggregate data for a year at the municipality level (such as the differences in the land uses temperature), biome-scale models are a fundamental tool due to the fact that epidemiological data are frequently reported at the administrative regions [69]. In addition, the primary socio-ecological processes that lead to the rise and resurgence of zoonotic diseases may take place on a biome-scale level [70–72].

The anthropic land uses like pasture, temporary crops and urban infrastructure had a negative effect on malaria transmission risk. However, in the interaction models, various landscape combinations had a positive effect on malaria transmission where those anthropic land uses were present (e.g. Pasture \* Forest formation \* Grassland in *P. vivax*), thus corroborating that human activities such as cattle ranching, grazing, or mining (not analyzed in this model but with much existing information on the positive influence on malaria infections) by themselves do not represent all the risk, but rather, the contact zones and landscape configuration of the areas where the main vectors inhabit. Several investigations have shown that deforestation, changes in land use, and anthropic activities are related to the malaria transmission in the Amazon, in some cases with positive effect [15, 16, 73], in others negative effect [74], demonstrating that the LULC influence is highly context specific [75].

Although the *Anopheles* species populations per se do not have a perfect correlation with malaria cases, the habitat suitability mediated by the environment is a factor that determines the probability of contact between humans and the pathogen [40]. The prediction and habitat suitability maps of the primary vectors of malaria (*A. darlingi* and *A. nuneztovari*) throughout the Amazon biome [76] show areas of high suitability in common with areas of positive effect on the transmission of the maps made from effect of landscape interactions (e.g. eastern Amazon state), where forest cover or water were always present, optimal places for the oviposition, development and growth of mosquitoes [3]. Although some *Anopheles* species can adapt to modified environments [8, 12, 77], they still need the forest for its life cycle [39]. On the other hand, is important to mention that the malaria cases are influenced not only by the forest cover but the activities on it, like forest clearance [8, 12] and changes in the habitat suitability due to the forest disturbance [77], finally, the areas with more forest cover are the areas with higher deforestation rates [10].

Zoonotic disease transmission is also subject to changes in landscape heterogeneity and configuration due to the changes in contact zones, distribution and availability of vectors, pathogens, and hosts [78]. According to long-term mathematical modeling, malaria population dynamics in developing forest areas show that cases behave as a convex declining curve, the cases increasing until reaching a peak and descending until reaching a lower point close to zero due to the reduction of forest formation and the social incomes related to health facilities [20]. We believe that the effects of

landscape interactions are correlated with the heterogeneity of the habitat, in this sense, in cells with a greater number of land uses (greater diversity of habitats) and with the presence of preserved forest, the contact between the infected vector and human greatly increases and is reduced as landscape homogenization occurs with a predominance of anthropogenic land uses. On the other hand, it is worth mentioning that although the reduction of forest is a factor that could affect the populations of some *Anopheles* species, the appearance of species adapted to modified environments can play a fundamental role in the transmission of homogenized environments, and in addition to the appearance of other diseases of medical importance mediated by anthropophilic vectors such as dengue, zika, chagas, yellow fever, etc [79, 80].

In relation to the influence of diversity on the prevalence of malaria, the intermediate disturbance hypothesis is something that could support ecosystems with a medium anthropic intervention that present high values of species richness [81]. As mentioned earlier, it is worth noting that municipalities with significant variations in their spatial characteristics may also demonstrate elevated levels of both malaria cases and species diversity. In other words, areas with high spatial heterogeneity, such as complex landscapes configurations, may have a higher likelihood of malaria outbreaks. Accordingly, the relationship between malaria cases and species richness (speaking of predator diversity and non-competent hosts) could be correlative but not causal [71]. However, several investigations support the hypothesis of the dilution effect with explanation of the underlying mechanisms that could help to reduce cases. In Central America, the decrease in amphibian populations caused by the pathogenic fungus *Batrachochytrium dendrobatidis* has been found to have a direct correlation with the rise in malaria cases. This aligns with the finding that a higher number of endemic species in an area can have a negative impact on the risk of malaria transmission [82].

While the exact contribution of birds to human malaria infections remains unclear, the impact of native bird species on malaria cases may be attributed to a comparable mechanism as observed in the study conducted by [33]. Their findings revealed that an increase in bird diversity resulted in a decrease in the incidence of West Nile virus due to the host competition. Also the non-competent host hypothesis could explain the importance of the bird and mammal's community, the greater the diversity, the bigger the number of non-competitive hosts for various types of pathogens [83]. The bird richness was highly correlated with the mammal richness, so it is possible that mammals also play a fundamental role in malaria control, e.g. the high diversity of warm-blooded hosts decreased malaria cases in the Atlantic Forest in Brazil [84], demonstrating the importance of the availability of several hosts to decrease the probability of infection of humans by being bitten by infected mosquitoes.

On the other hand, and taking the avian malaria transmission system as a model, the richness and structure of the bird community and the characteristics of the landscape are determining factors in explaining the prevalence of *Plasmodium* [85]. However, the conclusions from these studies are scale-dependent, diverse host communities commonly inhibit the spread of parasites on small scales and follow a generally hump-shaped nonlinear relationship [86]. Our methodological approach enabled us to detect the effect of the endemics of birds, mammals, and amphibians and the incidence of malaria in humans. This highlights the importance in identifying and analyzing the complex relationships between different biological factors influencing the spread of this disease. However, understanding the patterns of the composition of the possible hosts (community structure, that is, a step beyond richness) at different temporal events is crucial to predict where and specifically how specific relationships between diversity and disease occur in natural systems [87].

## 5. Conclusions

Malaria is part of complex system that includes several components with specific characteristics, including human and vector population dynamics, imperfect detection, recrudescence, and several other factors. It's patterns occur at multiple scales such as local, regional and biome. The LULC and interaction analysis at biome scale, indicate that forest formations alone are not responsible for driving most of the transmission risk. The biological endemic diversity context in addition to landscape composition modulate overall risk, areas with the presence of humans living close to the forest, mostly at areas with active deforestation predominantly anthropogenic landscapes and smaller values of richness and endemic species, represent the typical pathogenic landscape of the high-risk areas. Thus, in all over the Amazon biome, it is important to plan a long-term sustainable development such as ecotourism, agroforestry, sustainable forestry, sustainable fisheries, renewable energy without abruptly modifying the ecosystem cycles and their components and not take as an excuse the homogenization of the landscape with anthropic activities and deforestation for malaria control. The bird, and amphibian patterns suggest a potential effect in the cases reduction. We recommend future research with time replicates, community composition analysis in order to directly test the dilution effect and thus be able to give another argument in favor of conservation and nature-based solutions.

**Supplementary Materials:** The following supporting information can be downloaded at: [www.mdpi.com/xxx/s1](http://www.mdpi.com/xxx/s1). Figure S1. Study area: The legal Amazon municipalities in gray, all the municipalities of Brazil in white with faded border color. and in black line the American countries.

Figure S2. Climatic zones in the studied area in order to extract the precipitation and temperature data for each season. A. The total mean rainfall for each month for each climatic zone (Y axis: 0-1500 mm of rain, X axis: each month represented by color bars from January to December) showing the differences in the rain and dry seasons for the region. B. Municipalities centroids used to determine the climatic zone (Dashed lines limit), if the centroid fall into the square (500 \* 500 km) the season was determined by the rain pattern of its correspondent climatic zone.

Figure S3. Covariate's histogram plots.

Figure S4. Correlation plot based on the Pearson correlation analysis (significance p value=0.01), the X marked correlations were non-significant.

Figure S5. (GIF *Plasmodium vivax*). *Plasmodium vivax* maps in time sequence, in the left column, the RR (relative risk calculated by the INLA model), in the right column the API (Annual parasite index), for each municipality between the year 2007 to 2018.

Figure S6. (GIF *Plasmodium falciparum*). *Plasmodium falciparum* maps in time sequence, in the left column RR (relative risk calculated by the INLA model), in the right column the API (Annual parasite index) the for each municipality between the year 2007 to 2018.

Figure S7. Detected outbreak clusters in the studied area. The map on the left represents the three clusters for Malaria *vivax* cases, the map on the right represents the three clusters for malaria *falciparum* cases.

Figure S8. Land use and land cover map for the year 2018 in the legal Amazon (100 m pixel resolution).

Figure S9. Land use and land cover configuration for the artificial grid of 10 km \* 10 km for 2018. Each letter and color in the legend represents land use type and their unique combinations per cell. T: Temporary crops, F: Forest formation, G: Grassland, P: Pasture, R: River, lake or ocean and U: Urban infrastructure.

Table S9. Model estimates for the *Plasmodium vivax* risk.

Table S10. Model estimates for the *Plasmodium falciparum* risk.

Table S11. Model estimates for the *Plasmodium falciparum* and *Plasmodium vivax* interactions models. Each letter represents land use type. T: Temporary crops, F: Forest formation, G: Grassland, P: Pasture, R: River, lake or ocean and U: Urban infrastructure.

Table S12. First 40 municipalities with the higher predicted cases for the *Plasmodium vivax* interactions model with its state and IBGE code.

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