



The Role of Human Mobility, Deforestation, and Extreme Weather Events on Malaria in Brazil

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“The Role of Human Mobility, Deforestation, and Extreme Weather Events on Malaria in Brazil”

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The Role of Human Mobility, Deforestation, and Extreme Weather Events on Malaria in Brazil

A dissertation presented
by
Nicholas Joseph Arisco
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in the Department of Global Health and Population

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The Role of Human Mobility, Deforestation, and Extreme Weather Events on Malaria in Brazil

Abstract

Malaria control efforts in Brazil have historically been variable in their success, with the most recent era being no exception. Between 2000 and 2015, the Brazilian National Malaria Prevention and Control Program (NMCP) reduced malaria incidence in the Amazon region by more than 75%, spurring the launch of a plan for the elimination of *Plasmodium falciparum*. Reductions in cases continued, with 2016 marking the lowest recorded year for malaria case counts in Brazil in 35 years. Though the NMCP continued its efforts toward malaria elimination, case counts began increasing between 2016 and 2018. Various challenges to malaria elimination in Brazil have been outlined, of which human mobility and major environmental changes have been outlined as particular challenges to ongoing malaria transmission and policies targeted at elimination. This dissertation will provide the Brazilian NMCP with key information to stratify malaria interventions more accurately toward the end goal of elimination in line with the goals of the World Health Organization Global Technical Strategy for Malaria 2016-2030.

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Chapter I

Introduction

Malaria, a parasitic disease transmitted by *Anopheles* mosquitoes, is a major public health challenge, particularly in developing countries. However, recent efforts to control and eliminate the disease have achieved notable progress. A range of effective interventions exist to mitigate the health burden of malaria, as it is both preventable and curable. Though success rates vary in different regions, an expansion of these interventions from the beginning of the 21st century until 2015 reduced the global malaria burden by 37%¹. In some countries, such as the Democratic Republic of Congo, malaria-associated mortality decreased by 42% between 2000 and 2015, but still resulted in 194,000 deaths annually. Other malaria endemic countries like Brazil achieved a 76% reduction in malaria transmission over the same period, with just 42 deaths in 2015².

The World Health Organization (WHO) recognized a turning point in the global fight against malaria in 2015, which was motivated partly by the Sustainable Development Goals. Recognizing the fragility of progress made toward malaria eradication led to a new era of prioritizing interventions for rapid malaria elimination. The WHO Global Technical Strategy for Malaria 2016 to 2030¹ (WHO-GTS) set the goal of malaria elimination in at least 35 countries by 2030, which would be achieved through a three-pillared structure: (1) universal coverage of malaria diagnostics, treatment, and prevention, (2) acceleration of country's efforts toward elimination, and (3) strengthening and leveraging malaria surveillance as a core intervention. Since launching this framework, progress toward those goals has been variable. In part due to the SARS-CoV-2 pandemic and a lapse in intervention distribution, malaria cases have increased globally from 230

million in 2015 to 247 million in 2021, and deaths increased by ~42,000 in the same period². Yet, while some countries have regressed, others provide hope; Algeria, Kyrgyzstan, Uzbekistan, Argentina, Paraguay, Sri Lanka, and China were certified malaria-free during the same period.

Malaria Control and Elimination in Brazil

The Americas present opportunities for reducing the global malaria burden and achieving the WHO's 2030 target for elimination. Brazil, which is the largest malaria endemic country in the region and responsible for 27% of malaria cases across the Americas in 2021, offers such an opportunity. The history of malaria control in Brazil is marked by both successes and failures. Initial control efforts began in the early 1900s, but large-scale efforts to eliminate the disease started in the 1940s with the pilot of dichloro-diphenyltrichloroethane (DDT) spraying in Pará³. Following successful results, DDT was rolled out nationwide alongside the distribution of chloroquine (CQ) in both cooking salt and as treatment (a strategy later proved to be a failure as it promoted CQ resistance). From the 1940s to 1970, malaria cases in Brazil decreased significantly from 6-8 million to 28,557, with three-quarters of the cases in the Amazon Basin, which contained just 4% of the nation's population in 1970⁴⁻⁶. However, progress towards malaria elimination in Brazil was not sustained.

In the early 1970s, malaria transmission in Brazil remained focal to the Amazon Basin and northeastern Brazil⁷. However, a shift in the political landscape towards a military dictatorship with national security and Amazonian integration as top priority brought about a dramatic change in the Amazon's demographic and ecological landscape⁸. Starting in 1975, the Brazilian National Institute for Colonization and Agrarian Reform (INCRA) incentivized migration from the malaria-free south and southeast into the Amazon for economic opportunities through agricultural

settlements, logging, and mining. This was facilitated by major roadway construction projects that provided access to previously remote regions, and INCRA provided cleared land for settlers to use for agriculture⁹. However, rapid population growth in the Amazon outpaced the development of health and sanitation infrastructure. Additionally, the natural systems of the region were largely undisturbed prior to this project, with only 0.6% of the forest having been cleared by 1975¹⁰. The migration of immunologically naïve individuals to endemic regions, coupled with widespread forest clearing that created conditions favorable to malaria vectors, resulted in malaria cases rising to 169,871 by 1980¹¹.

The changing ecological, demographic, and epidemiological landscape in the Brazilian Amazon led to the establishment of a new understanding of how malaria is transmitted along the Amazon Frontier. ‘Frontier malaria’, characterized by marked spatial and temporal dynamics, set the biological and epidemiological basis for malaria transmission in Brazil¹²⁻¹⁴. Frontier malaria has both spatial and temporal characteristics. Spatially, it operates at three levels: micro/individual (through poor housing quality, intense vector exposure, and heightened vector density due to ecosystem modification), community (through high human mobility rates, disenfranchisement of at-risk individuals, and weak healthcare institutions), and state/national levels (through sporadic, unplanned development for agricultural purposes)¹⁵. Temporally, frontier malaria is characterized by a rapid rise in malaria cases at the opening of a settlement area spurred by increased vector habitat and human-vector contact, followed by more organized land clearance and urban development which amount in a reduction and stabilization of transmission. Because of these dynamics, between 1980 and 1989, malaria increased about 4-fold to just under 600,000 cases. In response, malaria control along the Amazon Frontier was centralized in 1989 by the Ministry of Health with the establishment of the Amazon Basin Malaria Control Programme (PCMAM) and

subsequently the Intensification Plan of Malaria Control Activities in the Legal Amazon (PIACM) in 2000^{16,17}. PCMAM had marked but short-lived success, but the increase in cases seen by 1999 were brought under control by PIACM, which ushered in a new era of Brazilian malaria control and, ultimately, elimination.

Brazilian Era of Elimination & Challenges

In Brazil's modern era of malaria control, two factors have been key to success: first, the establishment of the National Malaria Prevention and Control Program (NMPCP) in 2003, which utilizes a decentralized health system and customized interventions, including bed net campaigns and expansion of a network of ~3,500 malaria outposts for on-site diagnosis and treatment; and second, the concurrent creation of the Malaria Epidemiological Surveillance Information System, which collects case data from diagnostic centers and centralizes it in a near real-time online database¹⁸. A sustained decline in malaria cases followed, culminating in a low of 151,018 in 2016, with 99% of those occurring in the Amazon Basin. This progress led to Brazil being recognized as Malaria Champions of the Americas by the Pan-American Health Organization (PAHO) in 2015, and was concurrent with the WHO-GTS's renewed commitment to elimination¹⁹. At that point, Brazil shifted its goals from malaria control to elimination and establish the Plan for Elimination of Malaria in Brazil which initially aimed to eliminate *Plasmodium falciparum* by 2030, and was updated in 2022 with four goals: (1) reduce malaria cases to <68,000 by 2025, (ii) eliminate transmission of *Plasmodium falciparum* by 2030, (iii) achieve malaria-free status by 2035, and (iv) prevent malaria reintroduction from 2035 onward²⁰.

Despite progress over the last 20 years, eliminating malaria in Brazil faces major and persistent challenges of environmental change and human mobility¹⁷. The transmission dynamics of frontier

malaria are widespread, growing, and evolving. The pro-nationalist, anti-conservationist political environment of the Bolsonaro administration emboldened land speculators to remove forest cover and engage in illegal artisanal across the Amazon, including conservation units and indigenous territories where deforestation is illegal²¹. Humanitarian crises, partly characterized by increased malaria transmission, have developed in the Amazon²². Deforestation in the Brazilian Amazon has rapidly increased since 2016 and often coincides with migration for economic opportunity and the creation of habitat for the primary malaria vector, *Nyssorhynchus (Anopheles) darlingi*²³. Mobility in the Amazon, however, is not unique to the frontier of deforestation. Recent political crises in neighboring Venezuela fueled an influx of malaria-infected individuals to Brazil through the northern state of Roraima and was partially responsible for an increase in malaria cases between 2016 and 2018²⁴. Cross-border movements for economic opportunity like gold mining occur between Venezuela, Guyana, and Brazil, placing certain sub-populations at high risk. Such mobility has been linked with disease reintroduction in regions that have achieved elimination^{25,26}, the spread of drug-resistant parasites within and between countries²⁷⁻³⁰, and has strained relationships between neighboring countries with differing control strategies³¹⁻³³. Complicating matters is the fact that these complex dynamics are unfolding amidst the biggest environmental challenge we face - global climate change. Malaria transmission is greatly influenced by weather conditions^{34,35}. Although predictions on how malaria will respond to climate change vary, changes in extreme weather patterns and weather distribution will add an unpredictable dimension to the battle against malaria elimination in Brazil.

Dissertation Goals and Overview

Fortunately, Brazil's historic fight against malaria transmission in the Amazon has given rise to a key tool and tenant of the WHO-GTS which can help overcome these challenges: strong

surveillance through systematic data collection into the Malaria Epidemiological Surveillance Information System (SIVEP). SIVEP contains a highly detailed database of malaria infections that has the capacity to determine parasite species composition, demographic risk factors of cases, and even mobility of malaria infected individuals³⁶. Despite the interconnectedness of deforestation, human mobility, climate, and malaria transmission in the Brazilian Amazon, the relationships between those factors have not been studied in a manner useful for intervention stratification in Brazil. Determining the relationship between anticipated barriers to malaria elimination and malaria transmission is crucial in informing intervention stratification for the Brazilian Amazon. This understanding can help identify the most effective interventions for each transmission scenario and barrier, ensuring targeted efforts towards malaria elimination. In this dissertation, we leverage publicly available data to rigorously illuminate the relationships between human mobility (Paper I, Chapter II), deforestation (Paper II, Chapter III), climate (Paper III, Chapter IV), and malaria transmission in the Brazilian Amazon in the era of elimination.

Chapter II has three objectives: (1) define and quantify the major types of movement of malaria infections in Brazil (between municipalities within the same state, between municipalities in different states); (2) determine sources and sinks of malaria infections in Brazil between 2003 and 2020 and their temporal stability; and (3) analyze spatiotemporal clusters of sources, sinks, and high movement regions. We do this by using daily, individual-level data from SIVEP. We use network analysis and SatScan clustering to determine movement of malaria cases in Brazil between 2003 and 2020, and time series decomposition to understand seasonality. We characterize municipalities into four types based on their degree and strength in the mobility network. We further use state-stratified multinomial logistic models to determine risk factors for types of imported cases. We find that between-state movement of cases has become proportionally more

important than within-state movement, that source clusters persisted longer than sink clusters, and movement into sinks was seasonal while movement out of sources was not. We further determine areas of high mobility, rather than solely source or sink designations. We find that men, miners, and people of working age had a high risk of being an imported case, and that risk factors varied by state. These results are useful in stratifying source- and sink-specific interventions and active surveillance along common travel routes to areas with low transmission that are candidates for sub-national elimination.

Chapter III has three objectives: (1) determine the sub-annual relationship between ecological change in the Brazilian Amazon and malaria transmission from 2003-2021, controlling for human mobility on a whole-Amazon level, (2) determine that same relationship on a state-specific level, and (3) analyze specific subgroups experiencing the most significant changes in malaria transmission related to deforestation. To achieve objectives (1) and (2), we use a Bayesian spatiotemporal hierarchical logistic modelling approach using the Integrated Nested Laplace Approximation on monthly, municipality level data spanning 2003 and 2021 for the whole-Amazon and stratified those models by state. To achieve objective (3), we couple detailed data on land transitions from MapBiomass³⁷ with SIVEP data and assess trajectories over time and space. We find that both mobility and 1-month lagged deforestation increase malaria transmission on a whole-Amazon level, and that the magnitude and direction of these associations vary by state. We also find that natural land transitioned to mining collocates spatially and temporally with highly concentrated and large increases in malaria cases in miners and indigenous populations. These results solidify the link between deforestation and malaria transmission on a time scale applicable to frontier malaria and demonstrate the possibility of using real-time deforestation alerts as a tool to augment existing malaria surveillance efforts.

Chapter IV has three objectives: (1) deduce causal linkages between lagged temperature, precipitation, diurnal variation, and odds of being infected with malaria from 2003 to 2020 across the whole-Amazon and by state, (2) analyze the effects of coincident and lagged fluctuations in the Oceanic Niño Index on malaria cases across the whole-Amazon and by state, and (3) to determine the effects of coincident and lagged El Niño/La Niña events on monthly weather patterns in each state in the Brazilian Amazon. To achieve objective (1), we fit distributed lag non-linear conditional logistic case-crossover models to a case-crossover dataset of 43,814,769 person-days for the whole-Amazon and stratified by state. We achieve objective (2) by fitting distributed lag non-linear Quasi-Poisson regression at whole-Amazon and state-stratified levels to assess the effect of continuous Oceanic Niño Index Region 3.4 values on monthly, municipality-level malaria cases for the whole Amazon and for each state. Finally, we achieve objective (3) by fitting state- and month-stratified multilevel models to determine the effect of coincident and 6-month lagged El Niño and La Niña events on mean monthly temperature and total monthly precipitation. Across the Amazon, temperature, precipitation, and diurnal variation below and above the median affect malaria transmission, with the effects varying based on the state's climate type and geographical position. Similar results were found regarding the effects of Oceanic Niño Index on malaria, with El Niño events at 0- and 6-month lags associated with hotter temperatures throughout the year, and La Niña events associated with cooler temperatures from January to August. These findings have major implications for proactive malaria control based on weather forecasting and are the most comprehensive results on the impact of weather and extreme events as a barrier to malaria elimination.

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Chapter II

Sources and sinks of malaria in Brazilian municipalities, 2003-2020

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Abstract

Human mobility has challenged malaria elimination efforts but remains difficult to quantify. Brazil, however, collects information which allows monitoring of mobility locally and internationally. Despite history of intense migration in the Brazilian Amazon region, current knowledge of malaria case mobility is limited. We leveraged network analysis and SatScan clustering to quantify and characterize movement of malaria cases in Brazil between 2003 and 2020. We classified municipalities into four types based on their degree and strength in the mobility network. We found that between-state movement of cases has become proportionally more important than within-state movement, that source clusters persisted longer than sink clusters, and movement into sinks was seasonal while movement out of sources was not. We further determined areas of high mobility, rather than solely source or sink designations. Our results have implications for intervention stratification across the Brazilian Amazon in line with the country's goals of *P. falciparum* elimination by 2035.

Introduction

Human mobility within and between countries has historically challenged malaria elimination efforts^{1,2}. Mobile-infected individuals can introduce parasites into regions where parasite prevalence, and thus local immunity, is very low, resulting in outbreaks of malaria^{1,3}. Tracking mobile populations can be challenging and migratory movements may happen unexpectedly (e.g., civil strife, natural disaster) making it difficult to forecast, surveil, and allocate resources for control⁴⁻⁶. Understanding patterns of malaria importation can improve surveillance and facilitate the planning and implementation of elimination programs⁷⁻⁹. Yet, malaria-endemic countries aiming at elimination have limited capacity to track international and within-country malaria importation¹⁰.

Here we comprehensively analyze the patterns of malaria importation in Brazil, identifying municipalities (N=5,570) that are sources and sinks of malaria, considering 18 years of monthly data (from 2003, when the National Malaria Control Program, NMCP, was launched, through the end of 2020). We chose Brazil for three reasons. First, Brazil routinely collects information that allows for systematic monitoring of importation both locally and internationally¹⁰. Nevertheless, it has not been thoroughly analyzed to inform surveillance and elimination efforts. The few studies that have analyzed mobility are restricted to small areas, short periods, or are outdated¹¹⁻¹⁶.

Second, about 99.5% of cases in Brazil are reported in the Amazon region. Malaria transmission in the Amazon, defined as frontier malaria¹⁷⁻¹⁹, operates at three levels: micro/individual (through poor housing quality, intense vector exposure, and heightened vector density due to ecosystem modification), community (through high human mobility rates, disenfranchisement of at-risk individuals, and weak healthcare institutions), and state/national levels (through sporadic, unplanned development for agricultural purposes)¹⁷. The Amazon is marked by intense mobility due to economic activity, exploitation of resources, and interconnectedness of locations²⁰⁻²². In addition, the Brazilian Amazon shares a border with seven countries in South America, and thus cross-border malaria is an issue of concern. While our previous work has shown that 85% of imported malaria cases in Brazil happen within the country^{10,23}, we lack knowledge regarding the spatial and temporal characteristics of in-country importation.

Third, Brazil launched a new elimination plan in 2022 that aims to achieve zero malaria in four phases: (i) reduce malaria cases to less than 68 thousand by 2025, (ii) eliminate *Plasmodium falciparum* malaria and deaths due to malaria by 2030, (iii) achieve zero malaria cases and deaths by 2035, and (iv) prevent the reintroduction of malaria from 2035 onwards²⁴. Yet, the systematic

guidance for stratification and planning of interventions for malaria elimination accounting for malaria importation is hampered by limited knowledge of the dynamics of importation.

Methods

National Malaria Control Program (NMCP)

Malaria control efforts in Brazil varied over time. Between 2003 and 2020, interventions and fluctuations in case counts were divided into four periods: 2003-2008 (capturing the spike in 2005), 2009-2014 (stable/declining trend), 2015-2018 (capturing the rebound in 2017), and 2019-2020 (leveling out/decline and beginning of SARS-CoV-2 pandemic).

Between 2000 and 2003, following a peak of 630,985 cases in 1999, Brazil launched the Intensification Plan of Malaria Control Activities in the Legal Amazon (PIACM) with the goal of reducing malaria cases and mortality by half in 2001 and 2002, respectively²⁵. This plan was largely successful and spurred an increase in funding and intensity of commitment, and in 2003 it was replaced by the National Malaria Prevention and Control Program (NMCP), which expanded its goals to include building local capacity and establishing a national surveillance program known as the Malaria Epidemiological Surveillance Information System (SIVEP)²⁶.

Control efforts contributed to reducing malaria incidence in the Amazon by more than 75% between 2000 and 2015, spurring the launch of a plan for the elimination of *Plasmodium falciparum* in November of 2015²⁷. Other interventions were also rolled out, perhaps most notably in 2010 when the Global Fund supported a project aimed at strengthening local public health capacity in the Amazon by ensuring early diagnosis, timely treatment, distribution of bed nets, and improving municipal and state-level management²⁸. Reductions in cases continued, with 2016

marking the lowest recorded year for malaria case counts in Brazil in 35 years. Though the NMCP continued its efforts toward malaria elimination, case counts began increasing in 2017. In 2019 and 2020, cases plateaued and began to decline again, trending toward 2016 levels. Lastly, in 2022, a new elimination plan was launched with the goal to achieve zero malaria cases and deaths by 2035²⁴.

Data

De-identified data on reported malaria cases in Brazil were obtained from SIVEP for the years 2003 to 2020. SIVEP includes cases reported through both passive and active detection (about 75% of cases are passively detected). All reported cases are confirmed through either a rapid diagnostic test (RDT) or blood smear microscopy. SIVEP contains variables that allow identifying imported cases. These include the country/state/municipality of notification, most likely country/state/municipality of infection, and country/state/municipality of residence (Brazil has 26 states and one federal district, and is divided into 5,570 municipalities, 756 of those in the Brazilian Amazon). The location of infection in SIVEP is determined through standardized epidemiological investigation at the time of diagnosis by laboratory professionals¹⁰.

In this analysis, following criteria used by the NMCP, we defined movement types based on infection and notification areas. A locally acquired case is one in which the notification municipality is the same as the infection municipality, regardless of residence. An imported case is one in which the notification municipality is different from the infection municipality, regardless of residence. We further detailed movements as between- or within-state and calculated the distance between municipalities of infection and notification considering the Euclidean distance between centroids of municipalities using ArcGIS Pro 10.6.1 (ESRI; Redlands, CA).

Additional SIVEP variables used in the analysis are: locality type of infection (urban, artisanal mining – called *garimpo*, settlement, indigenous, rural), date of symptom onset, date of infection, age, sex, parasite species, malaria testing format (active/passive), and type of occupation.

While some malaria cases may be missed due to inadequate access to health facilities, this is expected to be minimal among individuals that are symptomatic because: (i) health care is free and universal; (ii) malaria drugs are only available through the government (they are not sold in drugstores), and one must visit a health facility or laboratory to access them, and (iii) active case detection is conducted by community agents in isolated areas with difficult access.

Network analysis and typology of sources and sinks of malaria

Different methods have been used to estimate movement patterns of malaria-infected individuals. Most commonly, movement has been measured using travel recall data from surveys and, more recently, mobile-phone call record data—both of which are then combined with malaria prevalence data at some spatial scale⁴. Malaria infection rates are then inferred using mathematical models, which are coupled with human movement data to provide mobility patterns of infected individuals. Despite limitations, these methods have proven useful, especially in countries that do not systematically collect data and/or lack a health information system²⁹.

In the case of Brazil, importation can be assessed through SIVEP. This avoids memory loss related to travel recall data and mitigates the fact that cellphone coverage is limited in the Amazon region. We thus leveraged the available data and employed network analysis³⁰ to create mobility networks. Organizing data as a directional network allows for direct measurement of flows of malaria cases and connectivity of geographical locations and has proven effective in informing the stratification of malaria control efforts³¹. These measurements are useful to characterize mobility in the context

of malaria transmission and to generate mobility variables that can be incorporated into explanatory and multivariable modeling frameworks³².

Here, information on the place of notification and infection was used to build mobility networks of infected individuals across time. In each network, municipalities were designated as nodes, and a directional tie was defined as an individual becoming infected in one node and traveling to another node for notification. The strength of ties was denoted as the number of individuals traveling along the defined route in each period. We assessed both the degree of each node (the number of locations each municipality either sends cases to, defined as out-degree or receives cases from, defined as in-degree), and the strength of each node (the number of cases each municipality sends - out-strength, or receives - in-strength) at monthly intervals between 2003 and 2020. Mobility networks were created for both within- and between-state movements.

We further used a Pearson correlation coefficient to determine if node in-strength and out-strength were correlated with the population size of that node. All analyses were conducted in R v3.5.1 using the “network” package³³.

We classified nodes by both their mean in- and out-degree and mean in- and out-strength over the study period, with high and low designations based on the 97.5th percentile: (Type A) high strength, high degree; (B) low strength, high degree; (C) high strength, low degree; (D) low strength, low degree. These categories were detailed for between- and within-state movements. Sources in Type A were designated super-spreaders, while sinks in that category were designated super-receivers. The stability of sources and sinks is assessed across time by calculating the coefficient of variation (CV) of the cases leaving/entering the municipality each month, such that municipalities with higher CVs have more stable monthly cases exported or imported.

Lastly, we captured total movement in and out of an area in each period by extending the demographic concept of the gross migration rate to malaria cases in each municipality, in other words, we calculated the gross case migration rate (GCMR) = (imported malaria cases + exported malaria cases)/(Mid-year population)*1,000.

Multinomial models

We determined risk factors for between- and within-state movements at the individual level (n=5,242,957) by using multinomial logistic regression models. Each case was classified as between- or within-state movement, or locally acquired. Predictors include age category, sex, occupation, parasite species, testing format, locality type of infection, month, and time to care (difference between symptom onset and diagnosis).

Space-time clusters

Space-time clusters of sources, sinks, and high movement areas were determined by using the Kulldorf spatial scan statistic³⁴ based on a Poisson model, and further detailed by within- and between-state movements. A circular spatial scan window, a maximum spatial cluster size of 5% of the population, and a temporal cluster range allowance of 2-6 months were used so that clusters of all relevant sizes could be detected. For the clustering of GCMR values, a normal model was used to accurately reflect the continuous distribution of values. The statistical significance of clusters was tested via likelihood ratio tests, with P-values based on 9,999 Monte Carlo replications, and any cluster with P<0.05 was considered statistically significant. Cluster analyses were run on SaTScan v9.6³⁴.

We performed all demographic analyses in Microsoft Excel v.16.44, and data cleaning and processing in R v.4.0.0 (R core team, 2020). We created data visualizations in R, ArcMap v.10.8 (ESRI; Redlands, CA), and Microsoft PowerPoint.

Results

Malaria transmission from 2003 to 2020

A total of 5,538,943 malaria cases were reported between January 2003 and December 2020. After a peak of 606,069 cases in 2005, a declining trend in cases was observed, except for a small rebound in 2010 and a larger one in 2017-2018 (**Figure 1.1A**). We calculated the Annual Parasite Index (API) as the number of confirmed malaria cases in the municipality of infection divided by the population of the municipality multiplied by 1,000. We followed the NMCP criteria to categorize the API: no malaria: $API=0$, very low: $0 > API < 1$; low: $1 \geq API < 10$; medium: $10 \geq API < 50$; and high: $API \geq 50$. On average, the API declined by almost 15% between 2003 and 2020, with five of the ten municipalities with the largest increases in that period located in Amazonas state (**Figure 1.1B**). Almost a quarter of the municipalities that had high API in 2003 were in that category in 2020, while 97% that had no malaria in 2003 did not have cases reported in 2020 (**Figure 1.1C**). Most municipalities with low API in both years are located at the edge of the Amazon region, bordering other states in Brazil (**Figure 1.1D**), while municipalities with high API in both years were more centrally located in the Amazon, and this was consistent across the study period (**Appendix A Figure A.1**).

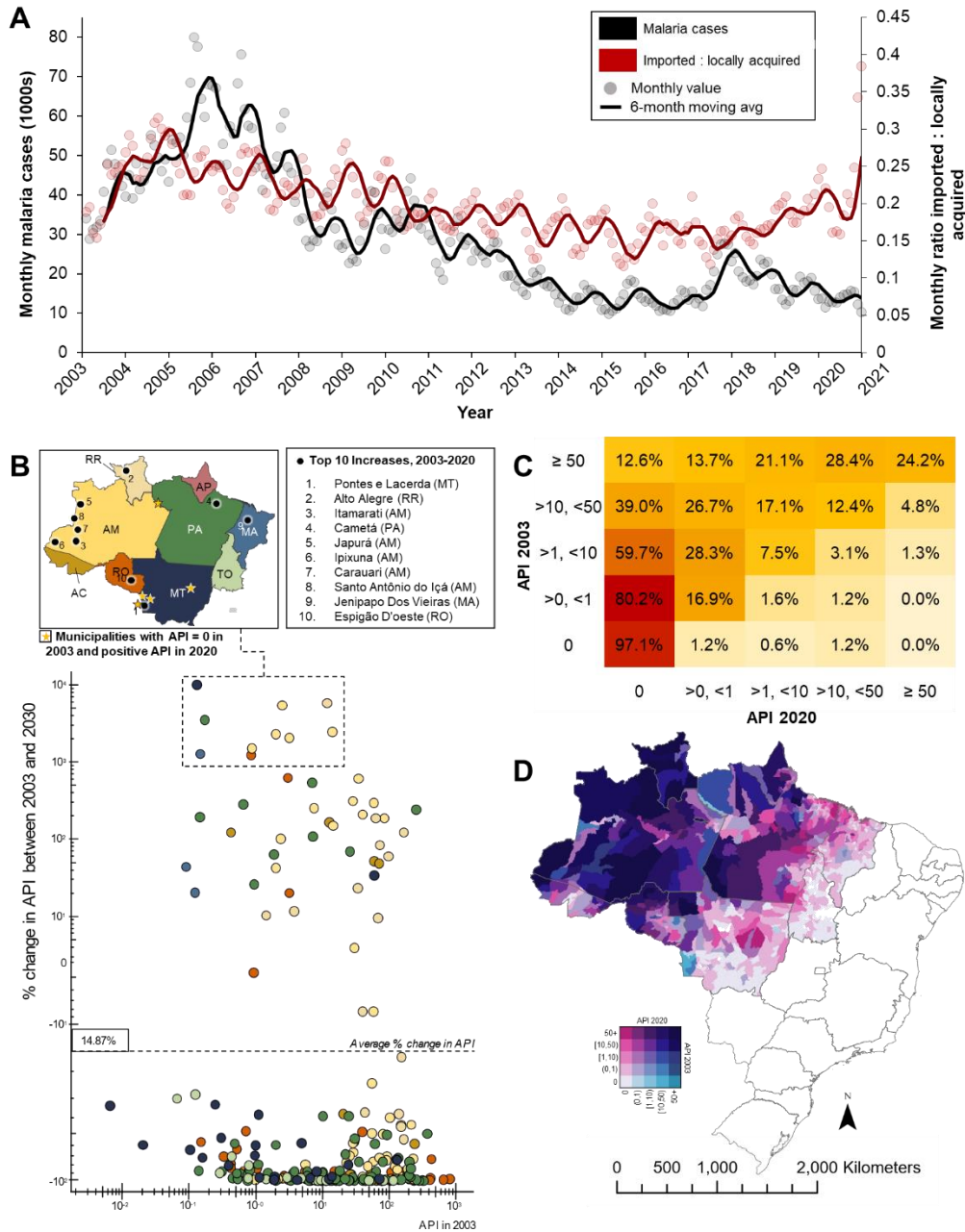


Figure 1.1 Trends in annual parasite index (API) and imported malaria cases in the Brazilian Amazon from 2003 to 2020. (A) Monthly and 6-month moving average of total malaria cases (black) and the ratio of imported : locally acquired malaria cases (red). **(B)** Percent change in API from 2003 to 2020 compared to 2003 values for all municipalities, benchmarked against average change. Top 10 municipalities with the largest changes are shown on the map. Point colors correspond to their respective states on the map. State acronyms: AC=Acre, AP=Amapá, AM=Amazonas, PA=Pará, RO=Rondônia, RR=Roraima, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso. **(C)** Proportion of municipalities in categories of API in 2020 compared to 2003. API values binned based on benchmarks from SIVEP. **(D)** Bivariate map of API in 2003 and 2020, by municipality. **(Methods).**

Patterns of imported malaria

Each reported malaria case has information on the places of notification, infection, and residence. Following the criteria used by the NMCP in Brazil and terminology proposed by the World Health Organization³⁵, we considered a case locally acquired as one in which the place of notification is the same as that of infection, and an imported case as one in which the place of notification is different from that of infection, regardless of residence. Those definitions were applied at two different spatial scales: states (N=27) and municipalities (N=5,570). Annually, on average, 16% (min: 12.0%, max: 21.2%) of malaria cases reported by municipalities were imported, and the mean distance between the place of infection and notification for cases imported between states (333 km) was more than double the mean distance of imported cases within states (149 km). Importation mainly occurred within the same state (ranging from 74.4% in 2019 to 86.1% in 2005 and 2010) (**Appendix A Table A.1**).

We used time series decomposition (**Methods**) to assess whether the seasonal component of locally acquired and imported cases had distinct patterns. Seasonal patterns were largely similar, except for imported cases between states. Maranhão, with lower API and at the edge of the Amazon region, had the most distinct seasonal pattern between locally acquired and imported cases (**Appendix A Figure A.2**).

The spatial pattern of imported malaria reveals that some municipalities in the Amazon receive many imported cases but are also the source of infection of cases exported to other locations. In contrast, municipalities at the edge of the Amazon region, mainly those in the states of Maranhão, Tocantins, and Mato Grosso, receive imported cases, but rarely are the source of infection for cases notified in other municipalities (**Figure 1.2**). To further investigate that pattern, we considered a

ratio relating imported and locally acquired cases (RILA). The ratio shows that there is a core area in the Amazon where, despite the high volume of cases imported and exported to other areas, the bulk of reported cases are locally acquired, while in other municipalities case counts are mainly imported (**Figure 1.3**). During the study period, municipalities with low RILA typically reported the largest API (**Figure 3 and Appendix A Figure A.3B**). In 2020, for example, the average API in municipalities that had more locally acquired cases than imported ones was 46.82 cases per 1,000 population, and those that had more imported cases was 4.54 cases per 1,000 population.

Municipal network of importation

To identify monthly routes of malaria importation between municipalities we used network analysis considering municipalities as nodes connected by directional ties linking the origin of the case (municipality of infection) to the place of reporting of the case (municipality of notification) (**Methods**). Those routes were further classified as within or between states. Considering within-state, the most common route over the entire study period was from the municipality of Porto Velho to Buritis in Rondônia (11.9% of all within-state monthly routes between 2003 and 2020). This route was also the most common importation route (almost 2% of all importation routes over the study period). As for between-state routes, the most frequent route was from Canutama, in Amazonas, to Porto Velho, in Rondônia (Distance between municipalities: 249.88km; 2.2% of all between-states monthly routes, and 1.9% of all importation routes between 2003 and 2020). While the top ten within-state routes in frequency accounted for 96.3% of all within-state monthly routes over the study period, the top ten between-states routes represented only 8.6% of all between-states routes (**Appendix A Table A.2**).

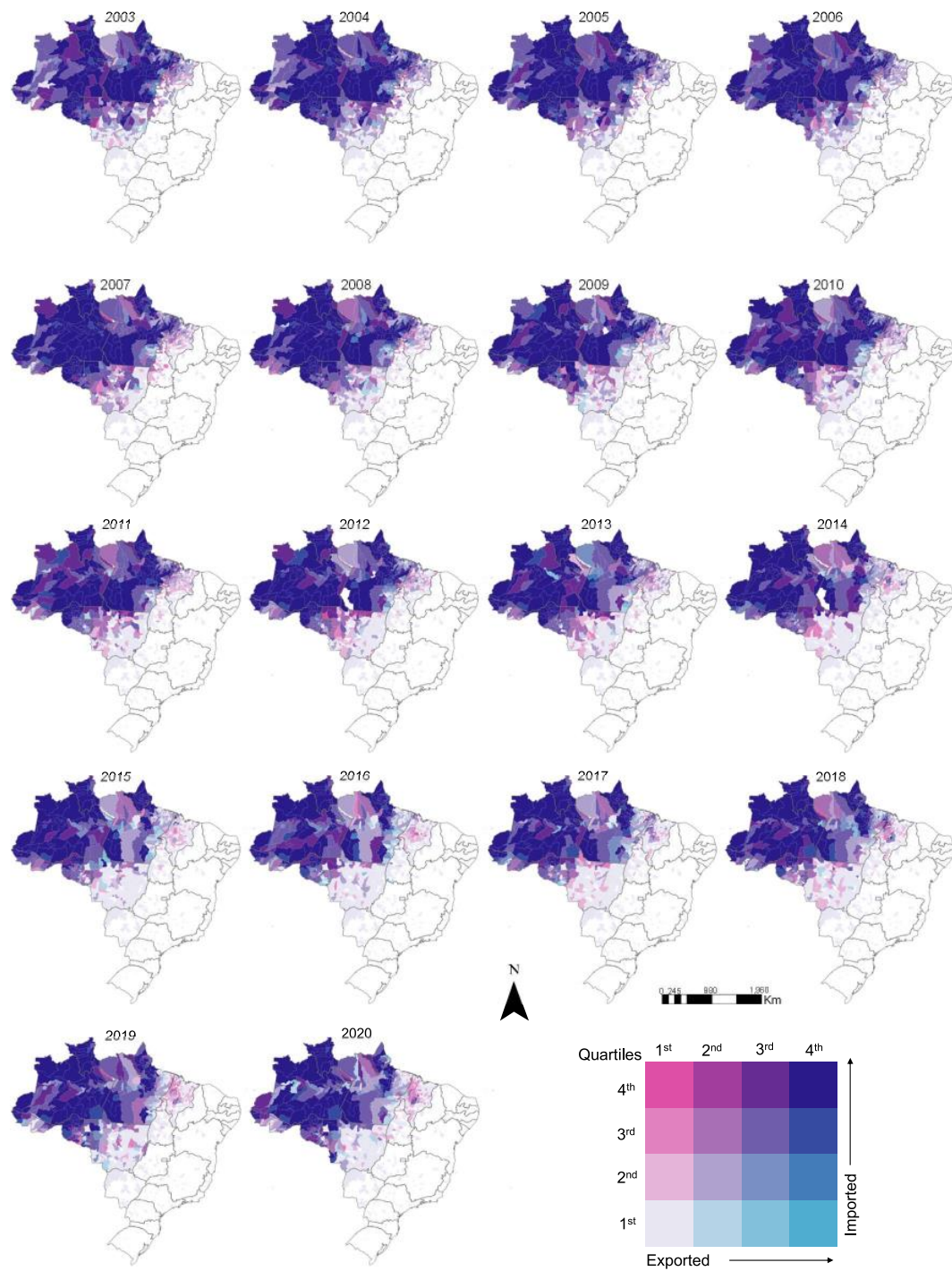


Figure 1.2. Bivariate maps of annual number of malaria cases imported to and exported from each municipality in Brazil, 2003 to 2020. Bivariate distribution based on quartiles.

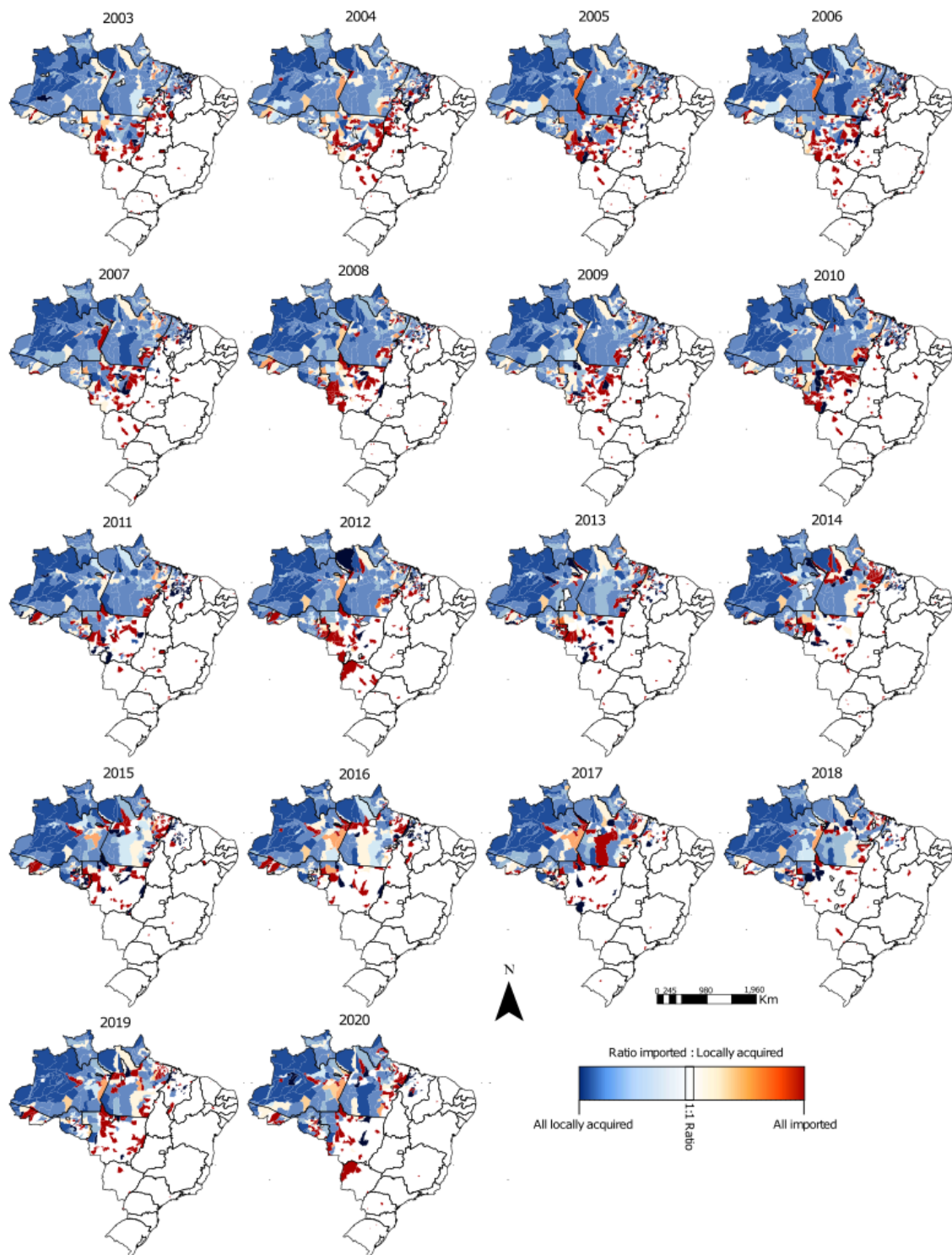


Figure 1.3. Maps of the annual ratio of imported to locally acquired cases in each municipality in Brazil, 2003 to 2020. Municipalities outlined in black with white fill signify a 1:1 ratio.

There was a statistically significant correlation between population size and the number of malaria cases exported from a given municipality (Pearson correlation = 0.064, $P < 0.001$), though this relationship was not significant for the number imported into a municipality. We used a multinomial regression model to identify characteristics of malaria cases that were associated with between- and within-state importation, compared to local transmission (**Appendix A Table A.3**). Individual characteristics that increased the odds of being imported both within- and between-states were if the individual was a male, older than 15 years, working in forestry or artisanal mining, being infected with either *P. falciparum* or having a mixed infection (compared to being infected with *P. vivax*), being detected by means of passive testing, and having >48 hours from symptom onset to time to care.

Municipal sources and sinks of malaria

Using the network of importation, a municipality was considered to be a source of malaria if the number of exported cases was higher than those imported, and a sink if the number of imported cases was higher than those exported. Over the study period, monthly importation of malaria cases was more frequent among municipalities in the same state, while importation between states was more common among municipalities sharing a border (**Figure 1.4A**).

We also considered the strength of the node (number of cases imported in that route, if a sink, or number of cases exported, if a source) and the degree of the node (number of municipalities a source exports cases to, out-degree, and a sink receives cases from, in-degree) to create a typology of municipal sources and sinks of malaria. We classified source and sink nodes by both their mean degree and mean strength over the study period, with high and low designations based on 97.5th percentile thresholds (**Figure 1.4B, Methods**).

Municipality degree and strength varied spatiotemporally, though municipalities with the highest degree and strength on average across the study period were in the state of Pará. Eleven municipalities across the Amazon region were classified as super-spreaders, while fourteen were classified as super-recievers (**Figure 4B-C, Appendix A Table A.4**). Over time, the most consistently within-state super-spreader municipalities were Cruzeiro do Sul (Acre), Manaus (Amazonas), and Itaituba (Pará), while the most consistently between-state super-spreader municipalities were Afuá (Pará), Lábrea (Amazonas), and Cruzeiro do Sul (Acre). Concerning annual trends in super-receiver municipalities, those most frequently designated as within-state super-receivers were Boa Vista (Roraima), Macapá (Amapá), and Santana (Amapá), while those most frequently designated as between-state super-receivers were Macapá (Amapá), Porto Velho (Rondônia), and Rio Branco (Acre). The state that had the highest average between-state out-degree over the study period was Amapá, while the state with the highest between-state in-degree period was Rondônia. Between-state importation of malaria was overwhelmingly represented by routes between Amazonas, Rondônia, and Acre (41.37% of all between movements), while within-state importation was more evenly distributed across malaria-endemic states in Brazil. Porto Velho (Rondônia), and Cruzeiro do Sul (Acre) were most commonly both super-spreaders and super-receivers.

We assessed the stability of sources and sinks across time by calculating the coefficient of variation (CV) of the cases leaving (source) or entering (sink) municipalities each month over the study period (**Methods**). Sources of malaria cases were more stable than sink municipalities between 2003 and 2020 (**Appendix A Figure A.4**).

Intense mobility municipalities

Since many municipalities receive and send malaria cases at high numbers (**Figure 1.2**), and some are both super-spreaders and super-receivers (**Figure 1.4C**), we calculated a gross case migration rate (GCMR) that combines cases imported and exported (**Methods**) and thus quantifies the volume of infected individuals moving in and out of a municipality each month. We observed a positive correlation between GCMR and API (**Appendix A Figure A.5, Appendix A Table A.5**). The top 20 municipalities in GCMR between 2003 and 2020 had an average API of 207.78 cases per 1,000 population, and are mainly in the states of Acre, Amazonas, Pará, Rondônia, and Roraima. The bottom 20 municipalities had an average API of 0.0107 cases per 1,000 population, and are located in Maranhão, Mato Grosso, and Tocantins, at the edge of the Amazon region (**Appendix A Table A.6**).

Spatiotemporal Clustering

To assess whether municipalities identified as sources, sinks, and intense mobility clustered in space and time we used the spatiotemporal scan statistic³⁴ (**Methods**). In total, 372 statistically significant ($P < 0.05$) clusters of source municipalities were detected (91 between-state, 281 within-state), while 384 clusters of sink municipalities were detected (133 between-state, 251 within-state). Source clusters, on average, persisted for 9.99 months, while sink clusters were more transient on average, lasting 5.32 months. The years with the highest number of sink clusters were 2004 for within-state importation, and 2007 for between-state. Broadly, a core group of municipalities persisted as clusters of sources of malaria importation, especially until 2016 (**Figure 1.5A and Appendix A Table A.7**). Regarding intense mobility municipalities, clusters were less frequent over time with 74 clusters of within-state GCMR, 52 between-state, and 71 for all movements (**Figure 1.5B and Appendix A Table A.8**). Clusters had similar duration, an average

of 5.45 months (SD: 0.49) for within-state GCMR, 5.99 months (SD: 0.51) for between-state, and 5.41 months (SD: 0.75) for all movements.

On average, municipalities that tested significantly for clusters had higher API compared to the mean API of all municipalities (**Appendix A Figure A.3A**). Similarly, the API of municipalities was negatively associated with the RILA and this relationship varied by state (**Appendix A Figure A.3B**).

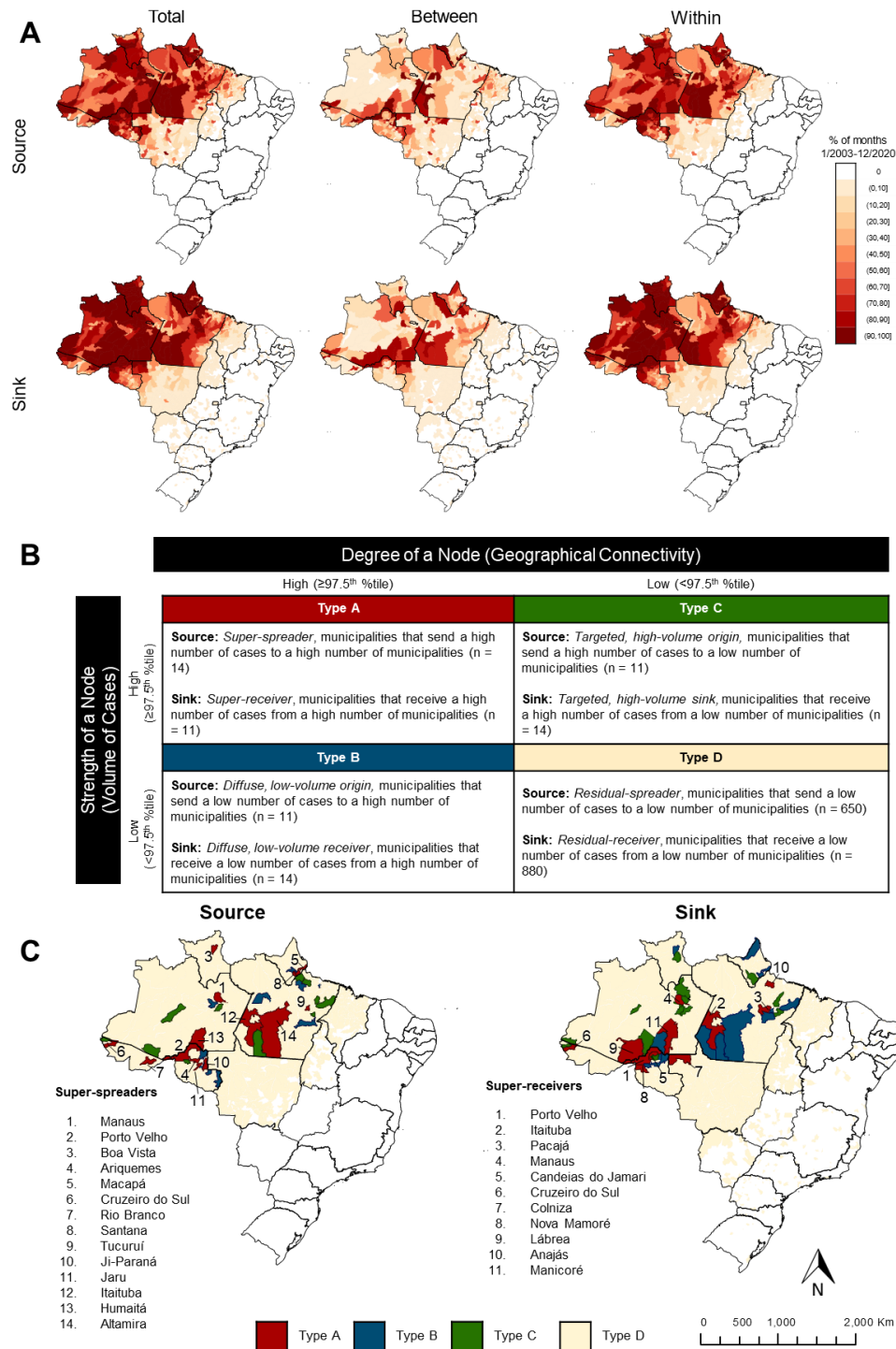


Figure 1.4. Typology of malaria source and sink municipalities. (A) Percentage of months between 2003 and 2020 that each municipality was a source or sink for all movements, between-state movements, and within-state movements. (B) Proposed classification of municipalities considering the malaria case importation pattern. (C) Map of municipality types by source and sink. Super-spreaders and super-recievers are labelled (**Methods**).

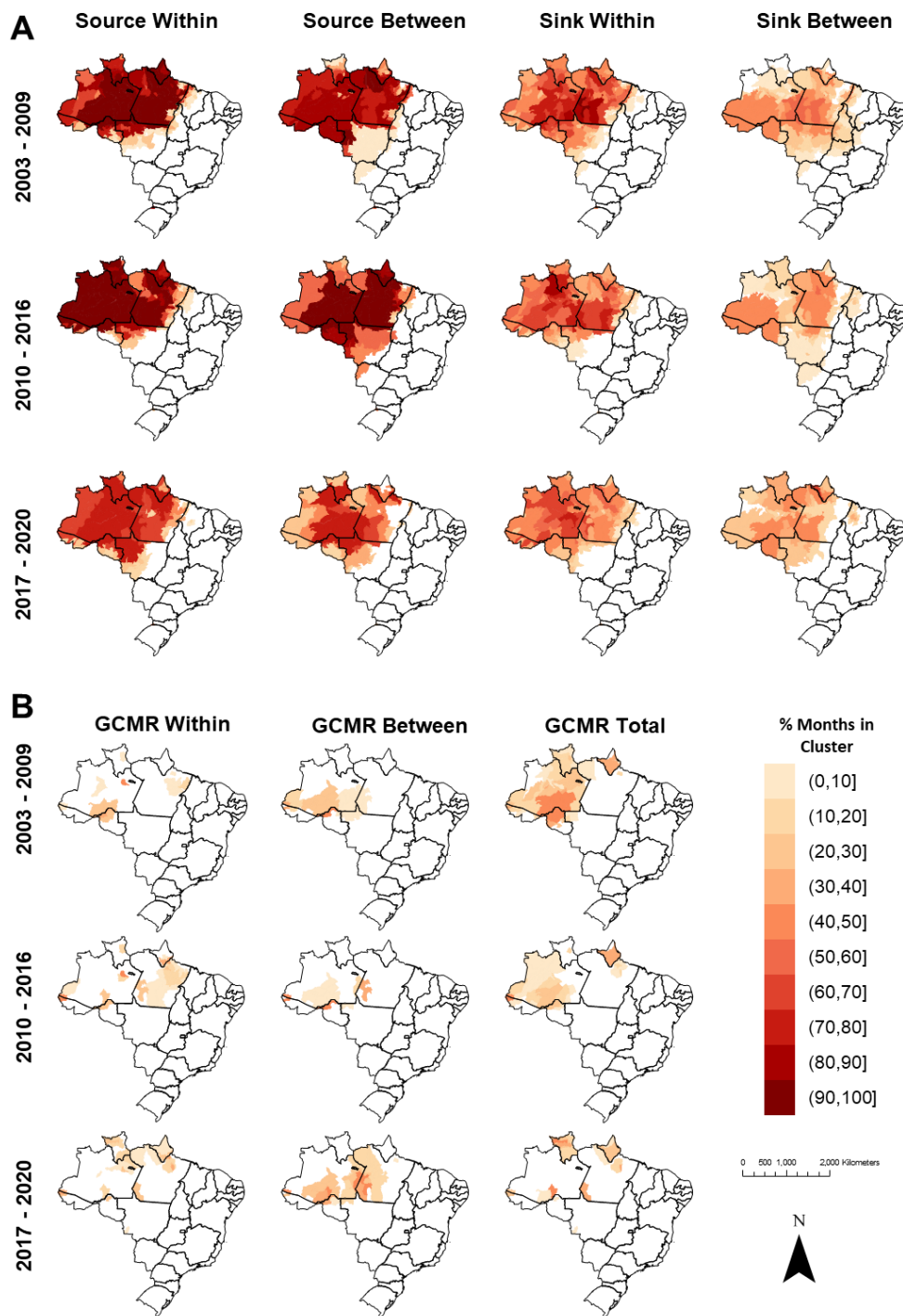


Figure 1.5. Results of SatScan spatiotemporal clustering analysis by time period and movement type. Color scale represents the percent of months each municipality was in a statistically significant cluster. **(A)** Clustering of monthly sink and source values within and between states. **(B)** Clustering of monthly GCMR within states, between states, and total movement.

Discussion

Our results quantify the movement of malaria cases between- and within-states in the Brazilian Amazon, demonstrate key demographic risk factors for imported malaria cases, and highlight geographical regions where intense mobility has been consistently high. We show that most importation occurred within states and that few within-state routes accounted for most movement of malaria infected individuals. We also show that a core group of municipalities in the center of the Brazilian Amazon persisted as clusters of sources of malaria, while municipalities in the eastern edge of the Amazon receive imported cases but rarely are sources. The metrics and analytical framework we developed for mobility, drawn directly from Brazil's routinely collected data, demonstrate a clear path for leveraging patterns of mobility in Brazil's plan for malaria elimination. We determined three main characteristics of mobility in the Brazilian Amazon that may make it more achievable to confront: (1) mobility is seasonal, and certain risk groups dominate imported cases, (2) municipalities characterized by high mobility are temporally consistent, and (3) importation may be maintaining residual malaria transmission in municipalities with low API that could be targets for sub-national elimination.

Seasonality of mobility is often driven by economic opportunity (i.e., mining, deforestation, agriculture)^{23,36-38}. These jobs often begin with clearcutting forest, which creates suitable habitat for *Ny. darlingi*, following the early patterns of frontier malaria¹⁸. Not only does this ecological change increase malaria risk in individuals moving to the area for economic opportunity, but can also increase local risk among residents of the area affected³⁷. Being either a *garimpeiro* or working in forestry increases an individual's odds of being mobile, as they constantly seek for opportunities. Despite mobile cases travelling between municipalities with high API where *garimpo* is happening, like Itaituba in Pará³⁹, they are far more likely to be detected via passive

than active surveillance. This presents an opportunity for the Brazilian NMCP to increase the efficacy of active surveillance in high risk areas, particularly by stratifying surveillance efforts along commonly travelled routes in areas with frequent real-time mining/forestry alerts from the Brazilian National Institute for Space Research's Deforestation Detection in Real Time (INPE-DETER) program⁴⁰.

The spatiotemporal patterns of movement revealed in this study augment capabilities of the Brazilian NMCP to employ intervention stratification in line with the WHO Global Technical Strategy for Malaria³⁵. For example, municipalities in temporally consistent source clusters along the Amazon frontier may benefit from interventions such as larval source management depending on local context^{41,42}, behavioral interventions^{43,44}, active case finding⁴⁵⁻⁴⁷, and improved access to care. On the receiving side, the most temporally consistent sink municipalities were Boa Vista (Roraima), Macapá (Amapá), Santana (Amapá), Porto Velho (Rondônia), and Rio Branco (Acre). In this study, clusters of sources remained stable across time, but migration into sink clusters was less stable. These less-transient clusters may serve as targets for more prolonged and sustainable interventions to reduce transmission. Furthermore, the foci of mobility have changed over time: between 2003 and 2008, mobility of cases was most common in the state of Rondônia, but shifted to Pará starting in 2009. Over the study period, between-state mobility increased proportionally to within-state mobility, peaking during the 2020 period but declining coincident with the beginning of the SARS-CoV-2 pandemic. Between-state mobility in the Brazilian Amazon is complex, as some individuals may travel shorter distances for care between states rather than within their state of infection. From a policy standpoint, state borders may be better seen as fluid boundaries, and mobility clusters may serve as more effective geographic stratification targets.

While some municipalities are uniquely sources or sinks, other municipalities are both. These major movement hubs of malaria cases challenge control and elimination strategies. For instance, Porto Velho is a hub for both in- and out-migration of malaria infected individuals and was the largest, most consistent top-origin and top-receiver municipality^{13,48}. Porto Velho receives an extremely high volume of cases from many municipalities (primarily in Amazonas), while sending a high volume of cases to many municipalities in Acre and Amazonas. Infrastructure projects and tourism have been shown to drive mobility in and out of the municipality at high rates¹³. In riverside localities of Porto Velho, epidemics of malaria have broken out in migratory subpopulations seeking economic opportunity, but with little prior malaria exposure⁴⁸. Construction of hydropower dams along the Maderia River between 2007 and 2010 spurred an increase in the need for temporary laborers and thus influx into the municipality⁴⁹. Migration brought about by this spike in economic opportunity was facilitated by vast travel networks such as BR-364 which connect rural areas to urban centers^{50,51}.

High movement municipalities like Porto Velho with large and dynamic populations may be effective targets for strengthening active surveillance, as transmission intensity is, on average, higher in these regions and many asymptomatic cases may go unnoticed. Asymptomatic infections and parasite drug resistance are key hurdles for elimination²⁵, and major movement hubs may be effective targets for scaling up sentinel site genetic and molecular techniques for diagnosis and parasite genotyping to track these threats^{52,53}. Most municipalities in the Brazilian Amazon are characterized by low-volume movements to few municipalities. These municipalities complicate stratification, as the movements occurring in them are transient and smaller scale, making patterns harder to predict. As Brazil progresses toward elimination, municipalities with lower transmission intensity will be challenged by imported cases fueling the burden of local transmission, especially

along the southwest edge of the Amazon in the states of Mato Grosso, Maranhão, and Tocantins. These municipalities remain receptive to malaria case transmission despite low transmission intensity, and mobility across the Brazilian Amazon makes these municipalities highly vulnerable to re-establishment of endemic transmission. As long as malaria risk stratification in Brazil does not consider mobile populations, elimination will meet intense challenges.

The main strengths of the analysis are two-fold. First, this study illuminates areas with low/no transmission that are at high risk of malaria reintroduction from importation. While Brazil moves toward malaria-free status, sub-national elimination and the maintenance of transmission-free zones is crucial. Our results demonstrate the capabilities of using real-time data to track potential case reintroductions in a simple, effective manner. Second, we demonstrate the power of surveillance data in tracking mobility of malaria infected individuals in fine detail at a country-wide level in a manner applicable to malaria control programs. Rather than relying on complex models for transmission and mobility, these metrics are derived directly from real-time data and the methods used here can be reproduced by government organizations in Brazil to understand the track the ever-changing distribution of malaria risk throughout the country.

This study has some limitations. First, data on the most likely location of infection are based on travel recall and onset of symptoms, which may be subject to recall bias. However, inaccuracies in individual recall are expected to be minimum (given the short time reference) and random. Given the large amount of data analyzed here, we maintain confidence in mobility estimates representing true dynamics. Second, asymptomatic malaria infections are not captured by SIVEP, since individuals do not get sick and thus do not seek care. This is true for any malaria surveillance system. Therefore, the volume of mobility is likely to be higher than our results show.

Conclusion

Human mobility in the Brazilian Amazon is widespread, complex, and challenges malaria elimination²⁵. Vast travel networks characterize the region, and understanding the temporal and spatial dynamics of human mobility is vital for effective stratification of control measures and eventual elimination²². Here, we demonstrate the importance of going beyond the identification of sources and sinks of malaria cases to areas characterized by high total mobility. However, this study only captures symptomatic individuals and those discovered through primarily passive surveillance. A silent reservoir of infectious, asymptomatic cases further challenges the goal of elimination, and obscures the true malaria burden in the Brazilian Amazon. Characterized by ecological complexity and massive geographical scale, traditional techniques for controlling transmission such as vector control are not feasible in all regions of the Brazilian Amazon. As such, the clusters of municipalities illuminated in this study may serve as focal sites for the stratification of control efforts based on receptivity and vulnerability in line with the goals of the WHO Global Technical Strategy for Elimination 2016-2030.

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Chapter III

Ecological Change Alters Malaria Risk in the Brazilian Amazon

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Abstract

Ecological changes in the Brazilian Amazon are deeply tied to human mobility and health. Mining, agriculture, logging, and other activities can alter highly diverse ecological and demographic contexts and promote exposure to vector-borne diseases like malaria. In the Amazon region, intervention stratification is informed by sociodemographic and geographical risk factors, as well as sub-annual malaria seasonality, but the importance of stratifying based on risk factors related to ecological change remains in question. The objective of this study is to fill the knowledge gap on the sub-annual relationship between ecological change in the Brazilian Amazon and malaria transmission, controlling for human mobility. Using data at the highest spatiotemporal scale available, we estimated the effects of deforestation on malaria cases via a stratified Bayesian spatiotemporal hierarchical logistic modelling approach using the Integrated Nested Laplace Approximation between the years 2003 and 2021. We stratify these models by state. We found that a 1% increase in 6-month lagged deforestation increased malaria cases in a given month and municipality by a 6.3% (95% Credible Interval [CrI]: 6.2,6.4%), and that mobility of an infected individual into a municipality increased local cases by 0.17% (95% CrI: 0.12,0.22%). We found that when stratifying by state, the coefficients for deforestation and mobility were highly variable, with some years demonstrating protective effects while in others harmful effects. Our results provide definitive, detailed evidence that on average, deforestation increases malaria transmission, but that the relationship is not spatiotemporally uniform. These results have major implications for stratifying malaria control interventions based on ecological dynamics to assist Brazil in its goal of successfully eliminating malaria.

Introduction

Ecological changes in the Brazilian Amazon are deeply tied to human mobility and health¹⁻⁵. Historically marked by economic booms and busts often associated with the exploitation of local resources, the most dramatic ecological changes in the Amazon started with regional integration plans set by the military government in the late 1970s-early 1980s⁶. Mining, agriculture, cattle ranching, logging, and other activities alter local ecology, providing suitable conditions for the primary malaria vector in Brazil, *Nyssorhynchus* (formerly *Anopheles*) *darlingi*⁷⁻⁹, and thus increase malaria risk^{10,11}. Mobility of malaria-vulnerable populations to the Amazon seeking economic opportunities¹², as well as mobility of malaria-infected individuals within the Amazon, alters local patterns of transmission and threatens elimination efforts. This relationship between environment and malaria transmission is reflected in the concept of frontier malaria, a biological, ecological, and sociodemographic phenomenon that operates across various spatial and temporal scales. It is characterized by a rapid rise in malaria cases at the opening of a settlement area spurred by forest clearing, increased vector density, and more frequent human-vector contact that can occur at time scales shorter than one year. Also, it has a marked temporal component with high transmission following ecological changes, which progressively declines over time^{11,13,14}.

From 1970-2004, deforestation and malaria cases surged in the Amazon¹⁵. To stall and reverse these trends, the Brazilian government enacted disjoint, but temporally coincident policies across environmental and public health sectors. From a health perspective, malaria control programs were implemented during the 1990s and 2000s¹⁶⁻¹⁸, producing a steady decline in cases from 2005 to 2016 when a 37-year low of about 143 thousand cases was recorded. From an environmental perspective, Brazil tightened regulations on forest clearing in 2006, causing the most significant and sustained decline in deforestation rates in history¹⁹. However, both trends have reversed in

recent years. Deforestation started to show an increasing trend in 2016, which escalated to very high levels starting in 2019, and in 2021 the highest annual deforestation rate since 2006 was recorded¹⁹. The recent increase was fueled by changes in legislation introduced by former President Bolsonaro. Those changes contributed to the expansion of illegal mining (mainly artisanal mining, called *garimpo*) in protected lands, particularly indigenous. This culminated in a humanitarian crisis among the Yanomami, who are suffering from severe malnutrition and malaria, among other problems²⁰. Regarding malaria, transmission increased to about 231 thousand cases in 2017 but declined by about 70 thousand cases between 2017 and 2021. However, the current decline in cases hides a large increase in the percentage of malaria cases originating in indigenous and *garimpo* areas in the same period, 62% and 257%, respectively.

Given the connection between ecological change and malaria transmission in the Brazilian Amazon, several studies attempted to quantify the effect of deforestation on malaria. Those studies differed in the methodological approach, data source, spatial and temporal scale of both malaria and deforestation data, metric for deforestation, assumption on the lagged effect of deforestation, and the way in which the concept of frontier malaria was introduced in the analysis^{11,14}. Not surprisingly, conflicting results were found. A 2017 literature review on the topic showed that 32% and 26% of studies found a negative or null/ambiguous association, respectively, between deforestation and malaria transmission, while just 11% found a positive association²¹. The relationship between deforestation and malaria has been analyzed using annual data, for periods of one to thirteen years²²⁻²⁴, but the frontier malaria and entomological literature shows that *Ny. darlingi* ecology responds to deforestation at sub-annual time scales²⁵. Some studies considered a linear, positive relationship (at varying magnitudes) between forest clearing and malaria^{22,24}, while others found evidence for a quadratic relationship²⁶. The effect of deforestation on malaria

transmission was found to be not spatially homogenous but it could vary by active/passive frontier²² and the degree of previous degradation²³. One study suggested that forest fragmentation/high forest-edge density was the key driver of malaria transmission across the Amazon, while others found no relationship between forest cover and malaria transmission²¹.

Shedding light on the effect of deforestation on malaria is critical given the new elimination plan launched by Brazil in 2022. The plan aims to achieve zero malaria cases in four phases: (i) reduce cases to <68,000 by 2025, (ii) eliminate *Plasmodium falciparum* cases and deaths by 2030, (iii) achieve zero cases and deaths by 2035, and (iv) prevent the reintroduction of malaria from 2035²⁷. In this study, we leverage the longest time series (2003-2021) of data with the finest spatial (municipality) and temporal (monthly) resolution available to characterize and quantify the effect of deforestation on malaria in the Brazilian Amazon, controlling for other environmental and social variables, and for the mobility of malaria-infected individuals.

Materials and Methods

Study Area

Brazil is the third largest country in the Americas with an area of 8,510,345 km². It is comprised of 26 states and one federal district, which are further divided into 5,570 municipalities. The Brazilian Amazon extends over nine states and 756 municipalities and accounts for 99.9% of malaria cases reported in the country. Malaria diagnosis and treatment in Brazil are provided by the government free of charge through a vast network of laboratories and health centers.

Data sources

We obtained malaria case data from the Malaria Epidemiological Surveillance Information System (SIVEP), which is facilitated by the Ministry of Health and stores all malaria test results. SIVEP data are of high quality, and low response variables are not those of interest to our study²⁸. All cases are confirmed using either blood smear microscopy (about 96% of cases) or a rapid diagnostic test (RDT). We use individual and daily data on reported positive and negative malaria tests from 2003 to 2021 detailed by municipality. In addition, we considered the importation status. In Brazil, a locally acquired case is defined as a case in which the notification municipality is the same as the infection municipality, regardless of residence location, while an imported case is defined as a case in which the notification municipality is different from the infection municipality, regardless of residence location. SIVEP contains data that enable assessing importation status²⁹. Lastly, we extracted data on the type of locality where the case originated. Localities are sub-municipal areas utilized by the NMCP – no digital shapefiles of localities are available hampering any spatial analysis at that scale. Localities are categorized as (i) indigenous – occur in indigenous lands, (ii) rural, (iii) urban, (iv) *garimpo* – occur in areas where artisanal mining activities are present, and (v) settlement – occur in areas with an established agricultural settlement.

Deforestation data for each municipality was assembled using two monitoring systems from the Brazilian National Institute for Space Research (INPE). PRODES (Measurement of Deforestation by Remote Sensing) provides annual data for deforestation since 1988³⁰. DETER (Deforestation Detection in Real Time) is a remote-sensing-based alert system for forest degradation with daily resolution extending from 2016 to 2021³¹. To estimate municipal deforestation rate by month, we partitioned PRODES data considering the monthly distribution of alerts' area captured by DETER. Specifically, we calculated the total area with a deforestation alert by municipality and month for the years 2016 to 2021. Then, we converted this to a percentage based on the total area of alerts in

that year and municipality. Since the annual distribution for each year was similar, we took the average of all annual distribution and applied that to all years in the dataset. We also looked at the annual rate of deforestation compared to the year prior. We calculated this variable for each municipality by subtracting the previous year's total deforestation from the current year, and then we divided that value by the current year's total deforestation to get the annual rate of change.

Daily precipitation and temperature data were extracted from ERA5, the fifth global reanalysis product from the European Center for Medium-Range Weather Forecasts³². As a reanalysis dataset, ERA5 combines meteorological observations with complex atmospheric modeling to create a global grid of data. ERA5 is available at an hourly temporal resolution and a 30km spatial resolution. We accessed ERA5 data using Google Earth Engine, a geospatial computation platform where daily ERA5 data are available. Because many municipalities are larger than the 30km grid cell of the ERA5 product, we aggregated meteorological variables into a single daily value by taking the average value of observations of precipitation and temperature across a municipality, weighted by the distribution of the population³³. For population data, we used the WorldPop dataset³⁴. We then aggregated weather variables to the monthly level to fit the timescale of this analysis.

We also assembled several variables for each municipality. From the Brazilian Institute of Geography and Statistics (IBGE) we extracted the total population by year and the area of the municipality. The area covered by conservation units was calculated using a shapefile provided by INPE. From the Brazilian Annual Land Use and Land Cover Mapping Project (MapBiomass, a network that has produced annual land cover and land use mapping since 1985)³⁵, we obtained the road network by type (paved, non-paved) in kilometers, and land cover/use data for the years 2003-2021. With the land cover/use data we calculated transitions from natural formation (forest

formation, savanna formation, grassland, salt flat, beach and dune, rivers, lakes, and oceans, and mangroves) into mining (industrial and artisanal).

Seasonality and Lag Periods

To determine seasonality, temporal, and temporal lag patterns between deforestation and malaria transmission, we applied a multiplicative decomposition and correlogram to the monthly malaria cases to determine seasonality of malaria cases and deforestation (**Appendix B Figure B.1A-C**). We determined lag times between malaria cases and deforestation using a cross-correlation function. We determined the lag with the highest correlation coefficient was 1-month, which was included in models and corroborated with entomological and frontier malaria literature in the Amazon region^{11,36-39}.

Spatiotemporal Modelling

We used a Bayesian hierarchical logistic model with spatial, temporal, and spatiotemporal covariance structures to quantify the effect of deforestation on the risk of malaria^{40,41}, controlling for selected variables (**Appendix B Table B.1**). Controls were selected based on scientific knowledge of their association with malaria transmission in the Amazon region^{11,16,42-44}. The outcome variable was monthly malaria cases y in each municipality j , state p , month t , and year k , (y_{jptk}), assumed to follow a zero-inflated Poisson distribution. The model had the form:

$$\begin{aligned} \log(y_{jptk}) = & \beta_0 + \beta_1(\text{Deforestation Rate}_{jt}) + \beta_2(\text{Annual deforestation change}_{jk}) \\ & + \beta_3(\text{Ratio imported: local}_{jt}) + \beta_4(\text{Year}) + \beta_5 X_{jt} + \beta_6 X_{jk} + \beta_7 X_j \\ & + f(\text{Temperature}) + f(\text{Precipitation}) + f(\text{ONI}) + f(\text{Month}) + q_j + v_p \\ & + u_j + \varepsilon_{jptk} \\ & q_j \sim N(0, \sigma_q^2), v_p \sim N(0, \sigma_v^2), u_j \sim N(0, \sigma_u^2), \varepsilon_{jptk} \sim N(0, \sigma_\varepsilon^2), \end{aligned}$$

where β_0 is the intercept, $\beta_1(Deforestation\ Rate_{jt})$ is the coefficient for 1-month lagged percent of forest loss in the municipality of infection j and month t , $\beta_2(Annual\ deforestation\ change_{jk})$ is the coefficient for the percentage change in the forest lost between years k and $k-1$ in municipality j , $\beta_3(Ratio\ imported: local_{jt})$ is the coefficient for the ratio of imported cases to locally acquired cases in the municipality of infection j and month t , $\beta_4(Year)$ is a vector of coefficients for year fixed effects, $\beta_5 X_{jt}$ is a vector of coefficients for covariates observed in municipality j and month t (percentage of cases occurring in *garimpo*, indigenous, settlement, and rural locality types), $\beta_6 X_{jk}$ is a vector of coefficients for covariates observed in municipality j and year k (kilometers of paved and non-paved roads, and total population); and $\beta_7 X_j$ is a vector of coefficients for covariates observed in municipality j (area of the municipality, percentage of the municipality covered by conservation units in 2021). Monthly maximum temperature, $f(Temperature)$, and monthly total precipitation, $f(Precipitation)$, were modelled using a smoothing function where the spline term follows a second-order random walk process which has been demonstrated as appropriate in the literature for modelling small curvatures⁴⁵. The Oceanic Niño index, $f(ONI)$, was modelled as a first-order autoregressive process. Month of year, $f(Month)$, was modelled as a first-order autoregressive process⁴⁶ to account for time-related dependencies in malaria transmission. The term q_j is the municipality-level random effects component, v_p is the state-level random effects component, u_j is the spatial autocorrelation structure between municipalities (modelled as Besag-York-Mollié), and ε_{tjk} represents the municipality-month of year interaction term accounting for residual variation. We mapped the posterior mean random effects to assess for correlation across space⁴⁷ (**Appendix B Figure B.2**).

Weakly-informative priors for both regression parameters and hyperparameters were assumed. Estimation of posterior marginal distributions was carried out using the integrated nested Laplace approximations (INLA) after setting prior distribution to model parameters (the intercept, coefficients, spatial and temporal effects, and residual effects)⁴⁸. INLA is more computationally efficient than Markov chain Monte Carlo (MCMC) algorithms and provides manageable compute times when using large, complex datasets. INLA has demonstrated the ability to provide posterior estimates comparable in accuracy to traditional MCMC.

To address potential state idiosyncrasies, we run the same model stratified by each state in the legal Brazilian Amazon. All variables in the stratified models were the same as the state model, except for state-level random effects u_j . All models except for the model specific to the state of Acre had the same coefficients, which did not include a coefficient for cases in *garimpo* localities. All statistical analyses were conducted in R version 4.1.3⁴⁹. All mapping was done in ArcGIS Pro and ArcMap 10.8.2⁵⁰.

Sensitivity Analyses

Model robustness checks were performed to assess different choices for penalties of the semi-parametric trends used, specifically a time trend for sequential year-months and splines for temperature/precipitation. Furthermore, we tested different model specifications based on the removal of municipality-level random effects, the inclusion of state-level fixed effects, and the removal of year-level fixed effects (**Appendix B Table B.2**). We also assessed the relationship between 6-month and 12-month deforestation on malaria transmission. Model specifications were assessed using the deviance information criterion (DIC) which provides information on the goodness-of-fit for the model while penalizing for model complexity (**Appendix B Table B.3**).

Results

We used land cover/use data produced by MapBiomass³⁵ and malaria data provided by the Ministry of Health in Brazil (Materials and Methods). Between 2003 and 2021, 5,560,921 cases of malaria were reported, and 207,287 km² of forest cover were removed in the Brazilian Amazon (4.13% of the total Brazilian Amazon area). Considering mean monthly values by municipality over the study period, high deforestation and malaria cases co-occur along the southern border of the Amazon (**Figure 2.1A**), an area known as the arc of deforestation in Brazil⁵¹. The NMCP in Brazil classifies reported malaria cases into categories based on the locality where the case originated. A locality is a small area within a municipality, and among the categories are indigenous and *garimpo* (or areas where artisanal mining is practiced). Malaria cases in indigenous localities broadly follow the arc of deforestation (**Figure 2.1B**), and cases in *garimpo* localities overlap areas with high deforestation in Roraima, southeastern Amazonas, and southern Pará (**Figure 2.1C**). Although by law indigenous lands and conservation units officially demarcated by the government should be preserved (**Figure 2.1D**), illegal deforestation and *garimpo* occur in those areas. In northeastern Mato Grosso, northern Rondônia, and throughout Amazonas and Acre, the peak of deforestation occurred in 2021, and the more recent peak years often collocated with both conservation and indigenous protected areas (**Figure 2.1E**). Furthermore, *garimpo* has expanded in southwestern Pará between 2003 and 2021, overlapping the Mundurukú indigenous land and conservation units (**Figure 2.1F and G**). Similar increases have occurred in northwestern Roraima and northern Mato Grosso, overlapping the Yanomami and Kayapó indigenous lands, respectively.

In 2003, 574.9Ha of natural land (without anthropogenic modification, Materials and Methods) had been transitioned to mining. By 2021, this value increased 5,920.08% to 34,613.65Ha (**Figure 2.2A**). Pará consistency experienced the highest annual amount of natural land transitioned to

mining (72.9% of the total area transitioned over the study period). In 2021, Roraima experienced an increase in natural land transitioned to mining of 439.9Ha, representing a 105.6% increase from 2020. Beginning in 2012, Indigenous lands experienced an exponential increase in cumulative amount of land used for *garimpo* (**Figure 2.2B**). Four protected areas made up most of the mined indigenous lands: Kayapó (in Pará and Mato Grosso states), Mundurukú (in southwestern Pará and eastern Amazonas), Yanomami (in northern Roraima and northern Amazonas), and Tenharim do Igarapé Preto (in southern Amazonas). As a result, despite an overall decline in total annual malaria cases across the Amazon of 59.7% from 2003 to 2021, the proportion of annual cases in *garimpo* and indigenous localities increased 288.2% and 1,052.5%, respectively (**Figure 2.2C-D**). Cases in *garimpo* localities increased dramatically between 2018 and 2021, especially in Pará, Roraima, and Mato Grosso, while cases in indigenous localities have been increasing steadily since 2003 but most significantly between 2017 and 2021 in Amazonas and Roraima. In 2021, 15 municipalities concentrated 97.4% of all malaria cases in *garimpo* localities and 15 (with some overlap) accounted for 82.4% of cases in indigenous localities (**Figure 2.2E-F** and **Appendix B Table B.4-B.5**).

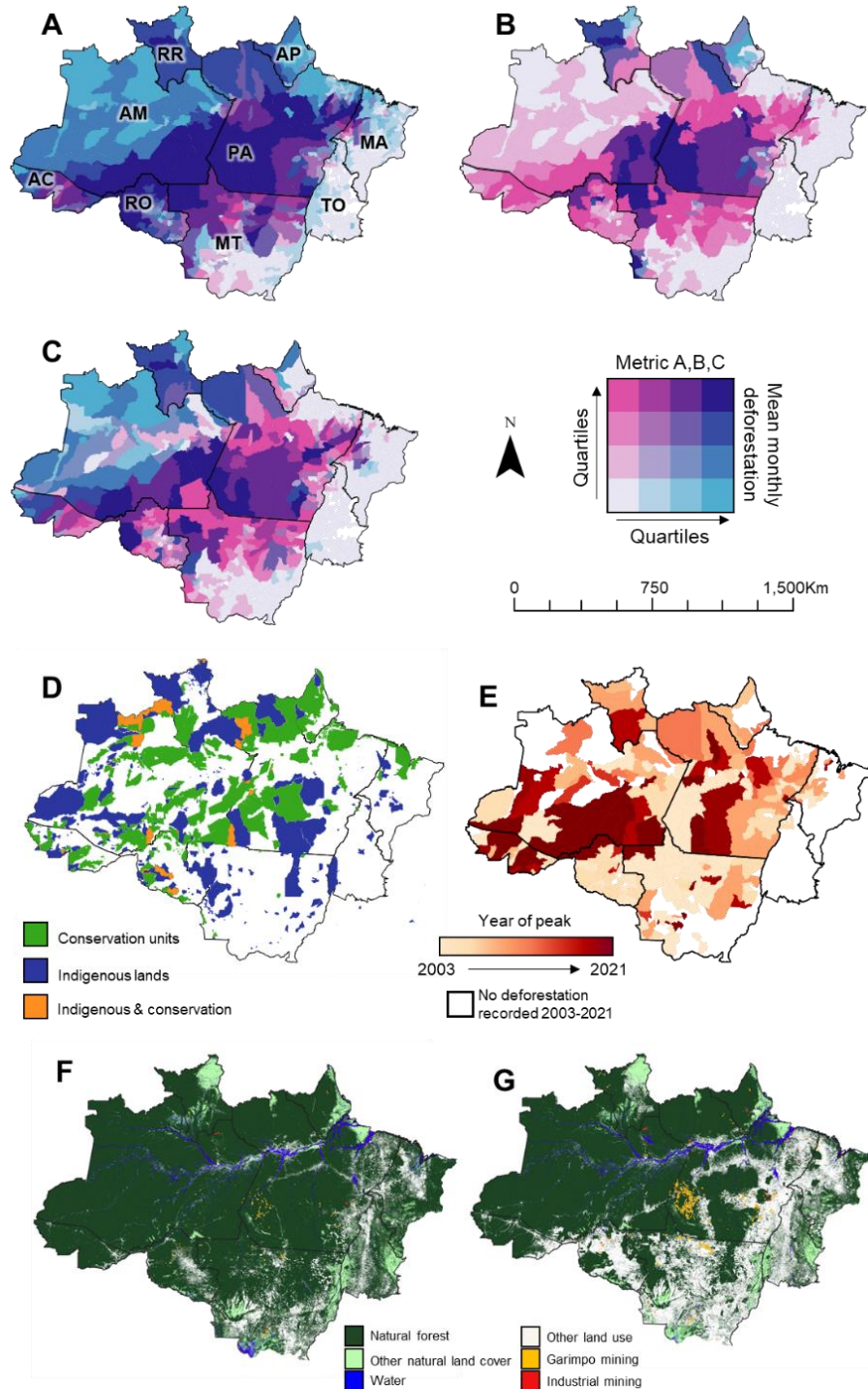


Figure 2.1. Malaria and ecological changes in the Brazilian Amazon, 2003-2021. Bivariate maps of mean monthly deforestation and (A) mean monthly malaria cases, (B) mean monthly malaria cases originated in indigenous localities, (C) mean monthly malaria cases originated in garimpo localities, and (D) Officially demarcated conservation units and indigenous lands. (E) Year when peak of deforestation was observed in each municipality. Maps with land cover and land use in (F) 1985 and (G) 2021. All maps show state boundaries. State acronyms: RO: Rondônia, AC: Acre, AM: Amazonas, RR: Roraima, PA: Pará, AP: Amapá, TO: Tocantins, MA: Maranhão, and MT: Mato Grosso.

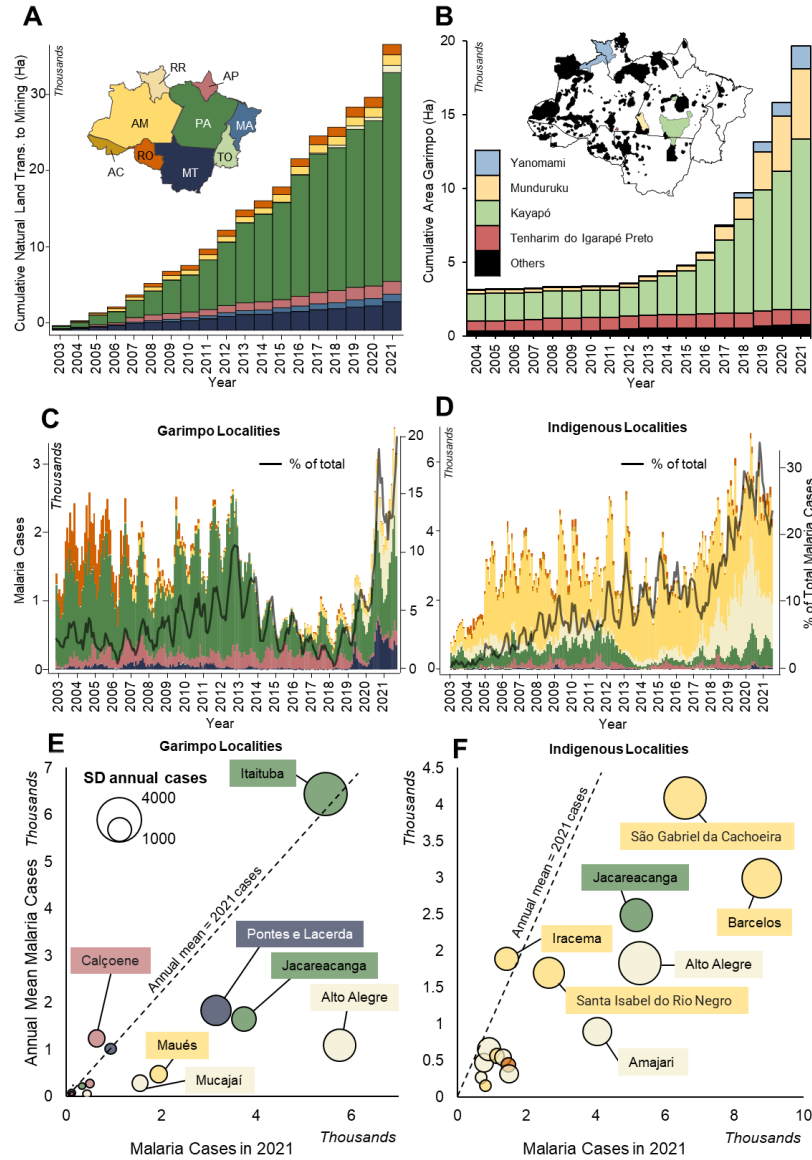


Figure 2.2. Malaria in indigenous and *garimpo* localities, 2003-2021. **(A)** Annual hectares of natural land transitioned to mining by state (colors in the map correspond to those in the bars). **(B)** Annual hectares of indigenous land consumed by *garimpo*. Four indigenous lands with most area destroyed by *garimpo* are highlighted. Monthly number of malaria cases originating in **(C)** *garimpo* and **(D)** indigenous localities, and percentage (line) of those cases among all monthly cases reported. Panels **(E)** and **(F)** compare the total annual cases originating in *garimpo* and indigenous localities from municipalities in 2021 with the mean annual number of cases originating in those same localities across the entire time series, 2003-2021. Specifically, we show the top 10 municipalities for malaria cases in 2021 originating in **(E)** *garimpo* and **(F)** indigenous localities against the mean annual cases in those municipalities from 2003 to 2021. Top 15 municipalities in malaria cases in 2021 originating in **(E)** *garimpo* and **(F)** indigenous localities against top 15 municipalities in terms of mean annual cases in those localities from 2003 to 2021. In graphs **(C)** to **(F)**, colors correspond to state colors shown in **(A)**. State acronyms: RO: Rondônia, AC: Acre, AM: Amazonas, RR: Roraima, PA: Pará, AP: Amapá, TO: Tocantins, MA: Maranhão, and MT: Mato Grosso.

We calculated the mean annual malaria cases originating in *garimpo* (**Figure 2.2E**) and indigenous (**Figure 2.2F**) localities in each municipality in the Legal Amazon. We compared those values against the annual number of cases originating in those locality types in 2021 (**Figure 2.2E-F** show the top 15 municipalities in 2021 for each locality type). Four of the top five municipalities for indigenous cases in 2021 overlapped the Yanomami territory: Barcelos, São Gabriel da Cachoeira, Alto Alegre, and Amajari. Of those, Alto Alegre also had the highest number of cases in *garimpo* localities in 2021 (22.46% of all *garimpo* cases), while Barcelos had the highest number of cases in indigenous localities (16.79% of all indigenous cases). In 2021, the Yanomami territory overlapped eight of the top 15 indigenous case municipalities. The Kayapó and Yanomami territories were most represented in the top 15 municipalities for *garimpo* cases. Itaituba in Pará had the highest average annual malaria cases in *garimpo* areas between 2003 and 2021 (Mean: 6,441.63, SD: 3714.56), and the second highest *garimpo* cases in 2021. This municipality shares land with about 50% of the Mundurukú indigenous territory and overlaps the Kayapó region. Also, in Pará, Jacareacanga had the third highest *garimpo* cases and fourth highest indigenous cases in 2021, and this municipality shares land with the Mundurukú, Kayabi, Kayapó, and Sai Cinza indigenous groups. The Kayapó region is situated between Itaituba and Jacareacanga to the west and Novo Progresso to the east, all of which are in the top 15 municipalities with highest average annual cases in *garimpo* areas.

Focusing on deforestation and malaria cases over time, we found significant correlations between monthly values, except for Roraima state. Annually, however, the correlation was significant for the entire Amazon (0.618, $P < 0.001$) and only four states (**Appendix B Table B.6**). We created scatterplots showing the annual trajectories of deforestation and malaria cases from 1990 to 2021 (**Figure 2.3A**). Roraima and Amazonas were the only states in which deforestation and malaria

cases were higher in 2021 than in 1990. The path to lower deforestation and malaria cases was rather complex, not concurrent, and varied by state (**Figure 2.3A and B**). Overall, the steepest decline in deforestation occurred under President Lula da Silva (2003 to 2011). That trend reversed beginning with President Rousseff in 2011 and intensified under Presidents Temer and Bolsonaro from 2017 onwards (**Figure 2.3C**). This annual relationship between malaria and deforestation hides the complexity of frontier malaria observed at fine spatial and temporal scales. Therefore, we assembled monthly data by municipality on deforestation and malaria cases (municipality of infection) for the period January 2003 to December 2021 (**Methods**). Currently, this is the most detailed and longest time series available to assess the effect of deforestation on malaria controlling for importation of cases, social, and environmental factors.

We expect the effect of deforestation on malaria to be lagged in time. A cross-correlation analysis suggested that overall and, in each state, deforestation is most strongly associated with malaria with a 1-month lag (**Appendix B Fig B.1A-C**). We used a Bayesian spatiotemporal hierarchical logistic regression model to assess the relationship between 1-month lagged deforestation rate and malaria (**Methods, Appendix B Table B.7**). The goal of this paper was to elucidate the effects of environmental changes and related variables on subsequent changes in malaria cases, and as such we will discuss only those covariates. On average, a 1% increase in the monthly deforestation rate is followed by a 6.3% (95% Credible Interval [CrI]: 6.2,6.4%) increase in malaria cases in the following month. Since human mobility can change the local reservoir of parasites, we included the ratio of imported to locally acquired cases as a covariate. The mobility of an infected individual into a municipality was associated with a 0.17% (95% CrI: 0.12,0.22%) increase in malaria cases. Those results remained largely unchanged for different model formulations (**Appendix B Table**

B.8). The percentage of cases in indigenous (RR: 6.0, 95% CrI: 5.9,6.2%) and *garimpo* (RR: 10.7, 95% CrI: 10.6,10.9%) localities in a municipality were also associated with higher malaria cases.

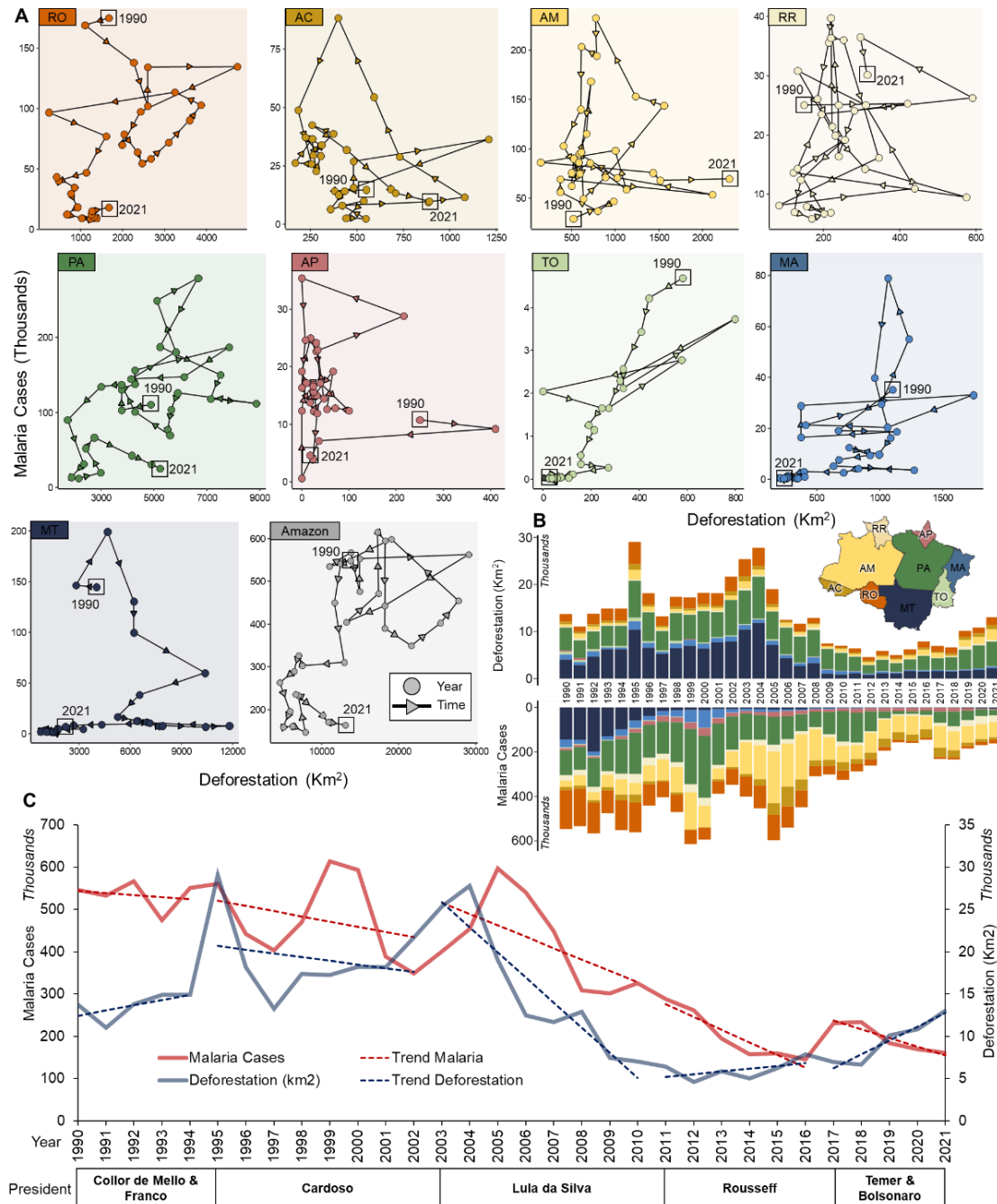


Figure 2.3. Deforestation and Malaria. A. Relationship between annual deforestation (Km²) and malaria cases (thousands) by state and whole Amazon and joint trajectory of annual deforestation and malaria cases for each. Colors correspond to state colors shown in the map in panel B. B. Annual deforestation rate and malaria cases color-coded by state. State acronyms: RO: Rondônia, AC: Acre, AM: Amazonas,

Figure 3 (Continued). RR: Roraima, PA: Pará, AP: Amapá, TO: Tocantins, MA: Maranhão, and MT: Mato Grosso. C. Annual malaria cases and deforestation rate for the whole Amazon, with best fit lines specific to each political administration listed in the table underneath.

We ran the same model stratified by state. All states except Tocantins had a sample size that allowed for model convergence (**Figure 2.4 and Appendix B Table B.9**). The effect of a 1% increase in monthly deforestation on malaria varied by state: 7.4% in Rondônia (95% CrI: 7.0,7.7%), 22% in Acre (95% CrI: 21.4,22.9%), 2.9% in Amazonas (95% CrI: 2.7,3.0%), 5.2% in Pará (95% CrI: 4.9,5.4%), 9.8% in Mato Grosso (95% CrI: 8.8,10.8%), -4.2% in Roraima (95% CrI: -4.8,-3.6%), and -0.9% in Amapá (95% CrI: -1.4,-0.4%). In all states except for Amazonas, Acre (which recorded no *garimpo* cases) and Amapá, the percent of cases in *garimpo* localities increased the number of monthly, municipality-level malaria cases. In all states except Acre, Pará, and Amazonas, the percent of cases in indigenous localities was associated with higher malaria cases.

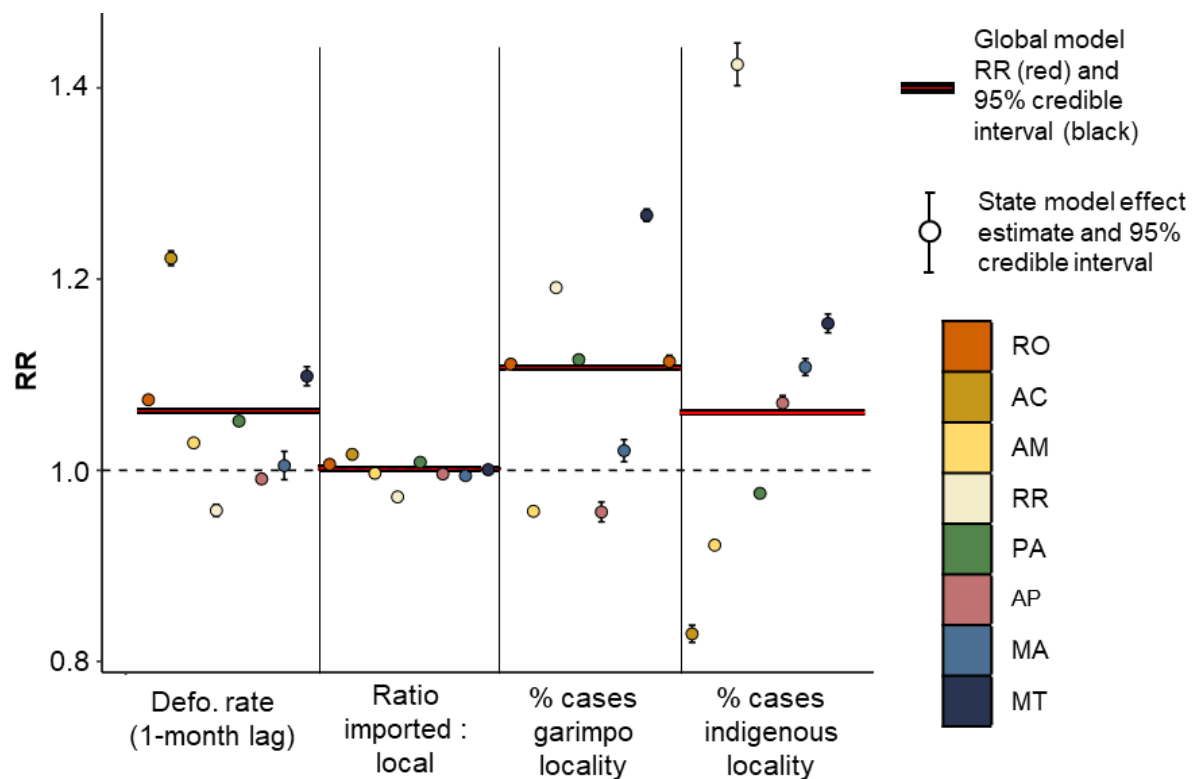


Figure 2.4. Effect of deforestation on malaria. Results from (A) global and (B) state-stratified Bayesian spatiotemporal models (Materials and Methods). In all models the outcome is monthly malaria cases by municipality of infection. RR = Relative Risk, median of the posterior distribution. LCI = lower 95% credible confidence interval. UCI = upper 95% credible confidence interval.

Discussion

We leveraged the longest and most spatiotemporally detailed data available to quantify the relationship between deforestation rate and malaria cases in the Brazilian Amazon, controlling for factors expected to be concurrent and interdependent challenges to malaria elimination in Brazil. Across the entire region, deforestation rate is associated with higher malaria transmission in the proximal month. This relationship held, in varying magnitude, in most states across the Brazilian Amazon, but reversed in some cases. We showed that mining has expanded between 2003 mostly in the state of Pará, and that four indigenous territories are most acutely affected. Finally, despite malaria decreasing across Brazil, we found that *garimpo* and indigenous cases are dramatically increasing, are highly focal, and represent nearly half of all malaria cases. Considering the Brazilian Amazon boasts highly diverse ecological, socio-demographic, economic, and epidemiological contexts, the underlying drivers of deforestation and subsequent malaria transmission must be carefully considered if this information is to be useful in Brazil's goal of malaria elimination.

In 2022, Brazil reinforced its commitment to *P. falciparum* elimination by 2030 and all malaria by 2035²⁷, yet this effort is expected to meet significant challenges⁵². Two highly interdependent dynamics, environmental changes and human mobility, have been cited as key factors that must be understood if elimination is to be successfully achieved⁵². Our previous work detailed patterns of mobility, sources and sinks of malaria infected individuals across the Amazon, and that risk factors such as *garimpo* and forestry increase the likelihood that an individual is mobile (Arisco

et al., forthcoming). Here, we extend this knowledge, and show that the ecological changes associated with those mobility-related activities, controlling for the effect of mobility itself, can be a driving force in augmenting malaria transmission. This study illuminates three crucial points that can aid in Brazil's goals of achieving malaria elimination.

First, among malaria endemic countries, Brazil is in a uniquely privileged position to enact data-driven intervention stratification policies for deforestation and malaria. Forest degradation alerts are collected through Brazil's Deforestation Detection in Real Time (DETER) system³¹, while the Malaria Epidemiological Surveillance Information System (SIVEP) collects near real-time, country-wide data on malaria cases and has the capability of tracking mobile cases²⁹. DETER categorizes alerts into underlying drivers of ecological degradation, such as selective cutting, clearcutting, mining, and fires, while SIVEP collects socioeconomic and demographic risk factors known to influence risk of malaria infection, like occupation, age, and sex. Prior to this study, investigations between deforestation and malaria transmission were done at an annual time step with coarse spatial stratification, and to-date intervention stratification in Brazil does not consider ecological context²⁷. In the era of elimination in the Brazilian Amazon, however, where transmission of *P. falciparum* is highly focal and often occurs in populations rapidly moving for deforestation-associated economic opportunity, annual associations are less useful¹⁴. According to the frontier malaria hypothesis, *P. falciparum* tends to be the dominant parasite when forested land is cleared¹⁴. Hotspots for this parasite species exist predominantly in western Amazonas, Acre (Juruá Valley), and Rondônia, and monthly deforestation was positively associated with malaria in all three states, but most strongly in Acre. In the Juruá Valley, an area referred to as Brazil's most endured malaria hotspot⁵³, the relationship between malaria, deforestation, and mobility is unique. In contrast to malaria dominating rural areas elsewhere in the Amazon, peri-urban and

urban malaria infections are more common here due to mobility and infections associated with seasonal farming⁵²⁻⁵⁴. The biggest source of malaria infections in the Juruá Valley is Guajará in Amazonas, and the most common route of travel from there is to Cruzeiro do Sol in Acre (Arisco et al., forthcoming). In this study, we demonstrate that Guajará's peak deforestation occurred in 2021, while deforestation in other parts of the Juruá Valley peaked in early years signifying an expansion of ecological change. As connectivity from extended urbanization increases between urban centers and newly deforested land in this region, malaria elimination efforts may meet even higher transmission in this region. Surveillance as an intervention is a core pillar of the WHO Global Technical Strategy for Malaria 2016-2030⁵⁵. With the goal of *P. falciparum* elimination on a more immediate horizon, leveraging real-time surveillance data on deforestation warnings from DETER to track the opening of settlements/agricultural land in the Juruá Valley and beyond, and tracking mobility, occupation, and parasite species of infected individuals to/from those regions with SIVEP data, may prove useful in allocating interventions tailored to these complex local contexts.

Second, despite malaria transmission decreasing across the Amazon as a whole, it is increasing dramatically in specific population sub-groups, namely *garimpo* workers and indigenous people, and collocates with ecological change from illegal mining. This distribution of cases has not historically been present. In the early 2000s, deforestation was on the rise despite legislation enacted to curb its growth, and this increase was fueled predominantly by illegal logging and land-grabbing⁵⁶. President Lula da Silva administration, which began in 2003, was integral in developing and enforcing policy instruments to tamp down on illegal deforestation in the Amazonian Arc of Deforestation⁵⁷. One action of particular importance was the designation of 500,000km² of conservation units and 100,000km² of indigenous protected territory between 2003

and 2010, which carried with them strict laws on land-tenure, use, and resource extraction. These policies were successful in reducing deforestation to a 20-year low over the course of the administration. Yet, the Temer, and more significantly Bolsonaro, administrations launched an attack on formerly protected indigenous peoples and conserved environment of the Amazon^{58,59}. As a result, illegal land-grabbing and *garimpo* expanded uncontrolled, including in indigenous territories and conservation units⁵⁹. Conterminously, a dramatic increase in malaria cases has happened among both *garimpo* and indigenous populations, such that in 2021 nearly half of all malaria cases in the Amazon occur in these two groups. These cases are almost all concentrated in 24 municipalities that most commonly share land with the Yanomami, Mundurukú, and Kayapó indigenous territories, which from an elimination perspective makes tackling transmission more feasible. Recently, the newly re-elected Lula da Silva administration issued a health emergency for the Yanomami people, citing *garimpo* activity as a primary cause of an increase in malaria, sexually transmitted infections, and mercury poisoning²⁰. Interestingly, deforestation in Roraima was negatively associated with malaria transmission, and Roraima overlaps a large portion of the Yanomami territory. In comparison to other regions in the Amazon, deforestation in Roraima is relatively low and malaria transmission is high. On the one hand, this may be an example of small-scale deforestation due to mining being particularly harmful for malaria transmission. On the other hand, Roraima is the site of rapid cross-border movement between neighboring countries and states for mining and other reasons⁶⁰, which may be augmenting local transmission in Roraima despite ecological change occurring elsewhere. Despite this, reducing the malaria burden in *garimpo* settings is challenging; knowledge of disease transmission among miners is limited, sites are remote, housing conditions are poor, and populations are highly mobile⁶¹. Here, we demonstrate that deforestation can lead to large increases in malaria transmission in the following month, so as

forest transitions to mining, malaria transmission will likely increase. The spatially concentrated nature of these malaria hotspots, however, does increase the viability of interventions such as Malakit⁶², which provides mobile populations with the ability to diagnose and treat themselves without accessing a malaria outpost. Interventions like Malakit may be useful when coupled with strong active surveillance in lowering the parasite load among mobile populations, but reinvigorated political will and enforcement of conservation and indigenous territory laws will be crucial in curbing spillover of malaria into nearby, at-risk communities.

Finally, understanding sub-annual effects of deforestation on malaria provides insight into how malaria vectors respond to ecological change in the Brazilian Amazon. The results of our analysis corroborate the dynamics of Frontier Malaria, such that the initial opening of settlements is associated with an increase in malaria transmission¹¹. Vector habitat proliferation, higher host density, and frequent human-vector contact combine to create this increase. Various studies have shown that areas with higher amounts of deforestation are associated with higher *Ny. darlingi* density^{7,25}, and our results show that when an area is deforested, on average malaria cases in the subsequent month are higher. Under favorable climatic conditions, *Nyssorhynchus* can complete a life cycle in 10-14 days. Thus, it is likely that if the vector is already present in the area being deforested, it will proliferate easily within the one-month period after deforestation occurs provided precipitation creates adequate habitat. Our models control for climate related variables, and those variables (temperature and precipitation) are vital components to vector development. Vector control strategies in the Brazilian Amazon, specifically in new settlement and mining communities, pose significant challenges. Indoor residual spraying is ineffective when houses are highly porous, insecticide treated net coverage and uptake is extremely low, and larviciding has been viewed as impracticable from a logistical standpoint⁵². Though logistically challenging,

garimpo areas may offer an opportunity for targeted interventions. Though the active *garimpo* frontier is ever moving, this form of mining leaves behind a trail of abandoned mines rife with larval habitat which may cause sustained high levels of malaria transmission in nearby, stationary communities^{63,64}. These abandoned mines also have been linked to legacy mercury exposure in surrounding populations⁶⁵. As *garimpo* mining is curbed from new policy directions, those habitats that support on-going transmission will still exist, and create opportunity for targeted campaigns to reduce malaria cases in nearby communities.

The study has many strengths. Foremost, the spatiotemporal scale of the dataset we use has not previously been considered and allows for a deeper understanding of the ecological and epidemiological mechanisms underpinning the relationship between deforestation and malaria in consideration of known dynamics like frontier malaria. Second, unlike other studies, we control for other key factors expected to challenge malaria elimination in Brazil to isolate the unique effect of deforestation without confounding influences. To date, no study has controlled for the dynamics of human mobility in the Brazilian Amazon when assessing the relationship between deforestation and malaria transmission.

This study has some limitations. First, monthly deforestation values were calculated from alert data, rather than derived directly from satellite imagery. Yet, these data represent the best proxy for sub-annual intensity of deforestation activity available. Second, we conduct our analysis at the municipality level. Municipalities across the Brazilian Amazon range dramatically in size, so in larger municipalities deforestation may not be exactly collocated to areas experiencing the highest burden of transmission. However, finer spatial scales are not available. Third, our primary exposure, monthly deforestation rate, does not account for the subsequent land tenure category to which forested land is transitioned. Deforestation for large agribusiness may differently influence

malaria dynamics by bringing fewer people into contact with deforested area than smaller scale clearing for mining or settlement. However, if this were to be the case, it would result in biasing coefficients on deforestation toward the null, thus underestimating its effect on malaria transmission.

Conclusion

Brazil faces significant challenges on the road to malaria elimination. As malaria cases decrease overall, unique subgroups are experiencing substantial increases in malaria transmission driven, in part, by ecological change. The modern Amazon frontier, which has extended into previously protected lands, poses unique challenges and opportunities for the new Brazilian government. Here, we demonstrate a clear positive association between deforestation and malaria transmission at short time scales. Leveraging the rich surveillance data collected on both malaria cases and ecological change, Brazil may be able to incorporate new means of intervention stratification into its elimination plan to achieve its intended goal of zero transmission by 2035.

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Chapter IV

Influence of weather and extreme climatic events on malaria transmission in the Brazilian

Amazon

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Abstract

Acute ecological changes in the Amazon, like deforestation and land-use change, are occurring in the context of long-term global climate change. Moreover, recent legislation executed by the Bolsonaro government in Brazil is resulting in record-high deforestation rates, which will affect the climate cycle in the Amazon. Understanding the potential effects of climatic variation on malaria transmission is paramount to better prepare for future changes. This paper aims to clarify these relationships and offer results as to how weather, controlling for human mobility and deforestation, has historically affected malaria incidence in the Brazilian Amazon at a causal level. To deduce causal linkages between temperature, precipitation, diurnal variation, and odds of being infected with malaria, we fit a distributed lag non-linear case-crossover model to individual malaria cases for the whole Amazon and stratified by state. We also use distributed lag non-linear multilevel models to understand the effects of El Niño/La Niña conditions on malaria cases and monthly weather patterns. We found that two-week lagged temperature, rainfall, and diurnal variation above the median increased odds of infection, and that the effect of weather on malaria transmission varied by state. We demonstrated that same month La Niña and extreme El Niño conditions increased malaria risk across the whole Amazon, and that at six-month time lags for those relationships the associations reversed. El Niño had an immediate drying effect in northeastern states, increased precipitation in southern states, and La Niña led to drier conditions across the Amazon. This is the first comprehensive study on the impact of weather on malaria in the Brazilian Amazon, and these results hold major implications for proactive malaria control based on weather forecasting. These results are the first step in understanding how weather may inhibit plans for malaria elimination in Brazil.

Introduction

The Amazon Rainforest is a critical natural carbon sink and regulator of regional and global climates¹. Yet, anti-conservation political forces in the region pose challenges to the future effectiveness of this ecosystem in buffering against climate change^{2,3}. Most of the Amazon is in Brazil, so deforestation policies there carry a particularly high impact. In 2019 the Bolsonaro administration set a political agenda that loosened restrictions on deforestation in the Amazon^{4,5}. Those changes resulted in record-high deforestation rates, which affect the climate cycle in the Amazon through reductions in evapotranspiration leading to less precipitation and warmer, drier microclimates^{4,6-8}, as well as human health, economic production, population movement, and biodiversity⁹⁻¹¹. One key health consequence of climatic variation and environmental change is a change in malaria transmission¹².

The development and survival of the primary malaria vector, *Nyssorhynchus (Anopheles) darlingi*, is highly influenced by temperature and precipitation¹³⁻¹⁵. *Ny. darlingi* requires warm temperatures to develop from egg to adult, and warmer temperatures can lead to increased mosquito activity, biting rates, and malaria transmission. Conversely, cooler temperatures can slow down mosquito development and reduce the rate of malaria transmission^{16,17}. *Ny. darlingi* breeds in partially shaded stagnant pools and along the edges of streams. High levels of rainfall can create more breeding sites along river floodplains and in recently deforested areas thus increasing the number of vectors¹⁸. However, excessive rainfall can also flush away mosquito breeding sites, reducing malaria transmission. Short-term, daily variability in weather, particularly high diurnal variation, can affect the vector's fitness, abundance, and competence around human settlements^{13,14}, while long-term changes in climate are expected to slightly expand the habitable zone for *Ny. darlingi* by 2070¹⁵.

The climate system in the Amazon is becoming more extreme¹⁹. Since the 1950s, the region experienced 20 atypical climatological years, some from El Niño or La Niña (ENSO) events²⁰⁻²⁴. Most severely, an El Niño event manifested extreme drought between 2015 and 2016 causing the hottest, driest period in the Amazon in a century^{25,26}. The effects of ENSO events in the Amazon can vary based on geography²⁷. The Southern Amazon is more directly influenced by atmospheric circulation patterns in the Pacific Ocean, while the North is more indirectly affected by the strength of the Atlantic Intertropical Convergence Zone^{28,29}. The rainy season of December-February tends to be drier in the North and Northeast from El Niño and reverses for La Niña. March-May, which begins the dry season, becomes wetter from El Niño events, particularly in Northern Roraima, Amazonas, and Amapá, and is associated with drying in central and southern states, while La Niña does the opposite. However, the impact of ENSO events on weather can vary widely based on atmospheric conditions, ocean temperatures, and land-surface conditions^{20,24,27}.

Malaria transmission in the Amazon is characterized by an interplay of social, economic, political, environmental, and behavioral factors, operating at multiple spatial and temporal scales³⁰⁻³³. Despite this complexity, Brazil has significantly reduced malaria transmission and in 2015 set the goal of eliminating *P. Falciparum*. However, the road to elimination has and will encounter challenges³⁴. Cases increased by 50% between 2016 and 2018 but since then have been declining. In 2022 Brazil launched a new elimination plan with the goal to achieve zero malaria by 2035. Climate change has been cited as one of the most important challenges Brazil faces as it works toward zero transmission³⁵. Climate change is anticipated to increase the frequency and intensity of ENSO events, and ultimately the extreme weather patterns associated with those events³⁶. Yet at present, there is no comprehensive evidence on the impact of weather patterns and ENSO events on malaria transmission in the Brazilian Amazon³⁷, and thus no early warning system is in place

to help mitigate the consequences of weather anomalies. Here, we estimate the effects of lagged weather (temperature, rainfall, diurnal variation) and ENSO events on malaria transmission on whole-Amazon and state-stratified levels. We also estimate the effects of ENSO events on lagged and coincident state-specific monthly weather patterning. To deduce causal linkages between the exposures and outcome of interest, we fit case-crossover models to individual malaria cases from the years 2003-2020.

Methods

Data Sources

We used individual, daily data on reported malaria cases from 2003 to 2020 detailed by municipality from Brazil's Malaria Epidemiological Surveillance Information System (SIVEP) for this analysis. SIVEP contains variables that enable assessing importation status, which we assigned to each case³⁸. We define a locally acquired case as one which has the same notification and infection municipality, regardless of residence location, and we define an imported case as one with different notification and infection municipalities, regardless of residence location.

We extracted daily precipitation and temperature data from ERA5, the fifth global reanalysis product from the European Center for Medium-Range Weather Forecasts, via Google Earth Engine³⁹. This dataset combines meteorological observations and atmospheric modeling to create a global grid of data. Municipalities in Brazil vary greatly in size, with some larger than the 30km grid cell of the ERA5 product. To ensure that the exposure for each municipality was most valid, we aggregated meteorological variables into a single daily value by taking the average value of observations of precipitation and temperature across a municipality, weighted by the distribution of the population⁴⁰. Population distribution data were extracted from the WorldPop dataset⁴¹. The

variables used from ERA5 were mean 2m air temperature, maximum 2m air temperature, minimum 2m air temperature, and total precipitation.

Other variables used in the analysis were the extent of conservation land in each municipality (extracted from the Brazilian National Institute for Space Research, INPE) and Oceanic Niño Index (ONI) data. ONI data were downloaded from the National Oceanic and Atmospheric Administration from 2003-2020^{42,43}. This metric is a rolling 3-month average of the difference from average sea-surface temperature (1980-2010) in the waters of the east-central tropical Pacific Ocean, known as Niño 3.4. Index values +0.5 indicate El Niño conditions, while values -0.5 indicate La Niña conditions. The final month in the 3-month rolling average was merged into case data and considered as that month's exposure.

Case-Crossover Models

We created a case-crossover dataset for all malaria cases with a municipality of infection in Brazil between 2003 and 2020. The case-crossover approach is a variant of case-control studies where each person serves as their own control, during a time period when they did not get sick^{44,45}. The subject's exposure at the time of infection is compared to exposure on the control days when the event did not occur. By design, the case-crossover approach controls for any confounding variables for the relationship between exposure and outcome that do not change between infection and control days, and thus it is not necessary to include covariates for location, demographic factors, or any variable that changes from month-to-month. We defined a case day as seven days prior to the date of symptom onset. The incubation period for *Plasmodium vivax* (81.9% of all reported infections during the study period) is 12-17 days, while the incubation period for *Plasmodium falciparum* (13.92% of all reported infections during the study period) is 9-14 days. A total of

5,538,943 (13.1% of all cases) cases did not have a date of symptom onset listed, so for each of these observations, we randomly assigned a value from the distribution of the difference in days between the notification date and symptom onset date. For each case day, we identified five matched control days within the same month and municipality of infection (n=43,814,769 person-days). Control days were chosen bidirectionally outside of a ± 4 -day buffer around the case day to account for immediate serial correlation in weather conditions and potential differences in parasite incubation time. We also selected control days to be at least two days from any other control day to minimize day-to-day correlation in weather conditions. We matched by month and, by design, individual which controls for confounding variables that do not change within a month and from place-to-place.

Whole-Amazon and state-stratified distributed lag non-linear conditional logistic regression models were fit to the case-crossover dataset to predict the effect of lagged weekly mean air temperature (average temperature in °C over one, two, and three-weeks in a municipality), weekly total precipitation (accumulated rainfall in meters over one, two, and three-weeks in a municipality), and weekly mean diurnal variation temperature (average difference between daily maximum and minimum temperature in °C over one, two, and three-weeks in a municipality) on the odds an individual was infected with malaria^{46,47}. The model took the form:

$$\text{Logit}(\text{Pr } Y = 1) = b_0 + b_1 \text{Temp}_{it-1 \text{ to } t-3} + b_2 \text{Rain}_{it-1 \text{ to } t-3} + b_3 \text{Diurnal}_{it-1 \text{ to } t-3} + b_4 \text{Week}_i + b_5 \text{ExPrec}_{it} + b_6 \text{MaxDailyTemp}_{it}$$

where, Temp_{it} is the mean temperature in municipality i and week t -lag, Rain_{it} is the rainfall in municipality i and week t -lag, Diurnal_{it} is the diurnal variation in municipality i and week t -lag, week is the week of the year for each case or control day, ExPrec_{it} is an indicator for days with >5cm of rainfall, and MaxDailyTemp_{it} is the daily temperature for each case or control day. The

modeling strategy for weather variables was based on knowledge of how different life stages of malaria vectors respond to weather⁴⁸⁻⁵¹, corroborated by cross-correlation analysis between the time series of weather variables and malaria cases (**Appendix C Figures C.1-C.4**). Weekly weather variables were calculated over one, two, and three-week cumulative time periods. For example, three-week lagged mean temperature is defined as the average temperature over the three-week period prior to infection.

For rainfall, lags of 1-to-3-week cumulative total precipitation were included. Since episodes of heavy rainfall can wash away larvae, extreme rain (defined as > 5cm per day) was treated as a separate variable. Higher temperatures after rainfall speed larval development, but very hot days reduce mosquito activity, so mean temperature was included in two ways: lags coincident with rainfall (1-to-3-week cumulative mean temperature), and maximum temperature on the day of analysis. Furthermore, diurnal variation affects larval and adult mosquito development and fitness¹³, so we also include the weekly mean diurnal variation at 1-to-3-week cumulative lags. Finally, all models controlled for the week of the year that the infection occurred. Since modeling consecutive lags involves putting multiple correlated variables into the regression simultaneously, we fit polynomial distributed lag non-linear models for these exposures^{52,53}. These models constrain the shape of the magnitude of the association with lag in time to follow a polynomial⁵⁴. All three exposures were modeled as natural splines with 4 degrees of freedom (df). We calculated sandwich confidence interval estimates for all models. All statistical analyses were conducted in R version 4.1.3. Models were fit as Poisson regressions in the ‘*gnm*’ and ‘*dlnm*’ packages, and sandwich confidence intervals were calculated for each model with the package ‘*sandwich*’. Model results were predicted against exposure values at varying lags with the ‘*dlnm*’ package.

Oceanic Niño Index and Malaria Models

We used generalized distributed lag non-linear Quasi-Poisson regression at whole Amazon and state-stratified levels to determine the effect of coincident and lagged ONI on monthly, municipality-level malaria cases. The model outcome was monthly, municipality-level malaria cases. All models included ONI lagged at 0-, 3-, and 6-months as natural splines with 3df, as well as fixed and non-linear control variables including the area of the municipality (fixed), municipality population (fixed, annual), conservation area extent in the municipality (fixed), the ratio of imported to local cases in the municipality (fixed, monthly), municipality 1-month lagged deforestation rate (natural spline, 3df), municipality maximum monthly temperature (natural spline, 5df), municipality total monthly precipitation (natural spline, 5df), and a non-linear function for time (4df per year). The whole Amazon model included a fixed effect value for the state, while the state-specific models included fixed effect values for the municipality. Two states, Tocantins and Maranhão, did not have a sample size of cases high enough to be modeled alone so they were modeled together with the same specifications as the whole Amazon model. Models were fit in the ‘gnm’ and ‘dlnm’ packages in R. Model results were predicted against exposure values at varying lags with the ‘dlnm’ package.

Oceanic Niño Index and Weather Models

We used linear multilevel models stratified by months in dry and rainy seasons and by state to understand the effect of El Niño and La Niña events on mean monthly temperature and total monthly precipitation. We designated the rainy season to be the six consecutive months with the most rainfall, and the dry season to be the remaining months, and these varied from state to state. The unit of analysis was at the monthly, municipality level, with the primary outcome being either mean monthly temperature or total monthly precipitation. For each of the two outcomes, 2 models (one for each season) were fit for the whole Amazon and each of the 9 states in the dataset. The

primary predictor in these models was an indicator of the month being an El Niño or La Niña month, defined as being within a period where three consecutive months had an ONI < -0.5 (La Niña) or ONI $> +0.5$ (El Niño)⁵⁵. Notably, the month of April never fit the El Niño definition, while June never fit the La Niña definition. Each model included a random slope for each municipality. Precipitation models included the monthly mean temperature in the municipality, while temperature models included the monthly total precipitation in the municipality. All models were fit using the ‘lme4’ package in R.

Results

A total of 5,407,056 malaria cases were recorded between 2003 and 2020 (**Figure 3.1A**). By 2020, malaria cases were generally concentrated in the states of Acre, Rondônia, Amazonas, Pará, Amapá, and Roraima, though pockets of residual infections remained in western Mato Grosso and central Maranhão (**Figure 3.1B**). On average across the Amazon, the mean daily temperature was 26.46°C (minimum of 8.65°C and maximum of 34.15°C), while daily precipitation ranged from 0cm to 33cm. The year with the lowest annual mean temperature was 2020 (26.08°C), the highest was 2016 (27.02°C), and the largest daily diurnal variation seen was 22.17°C occurring on September 9, 2018, in Mato Grosso. The wettest year was 2009 and the driest was 2020. In general, rainy seasons coincided with cooler temperatures, while dry seasons coincided with warmer ones (**Figure 3.1C, Appendix C Figure C.1-C.3**). Temperature and precipitation in the Amazon both exhibited seasonality which varied by state (**Figure 3.1D**): Rondônia, Acre, and Mato Grosso had similar rainy and dry seasons, while Roraima had a delayed rainy season spanning April-August. Amazonas was the rainiest state, on average, while Tocantins was the hottest state. Over the study period, there were six El Niño events (two of which were extreme with ONI > 1) and eight La Niña events (three of which were extreme with ONI < -1). The most significant deviation of ONI

across the time series occurred between 2014 and 2016, which caused the largest drought experienced by the Amazon in 18 years.

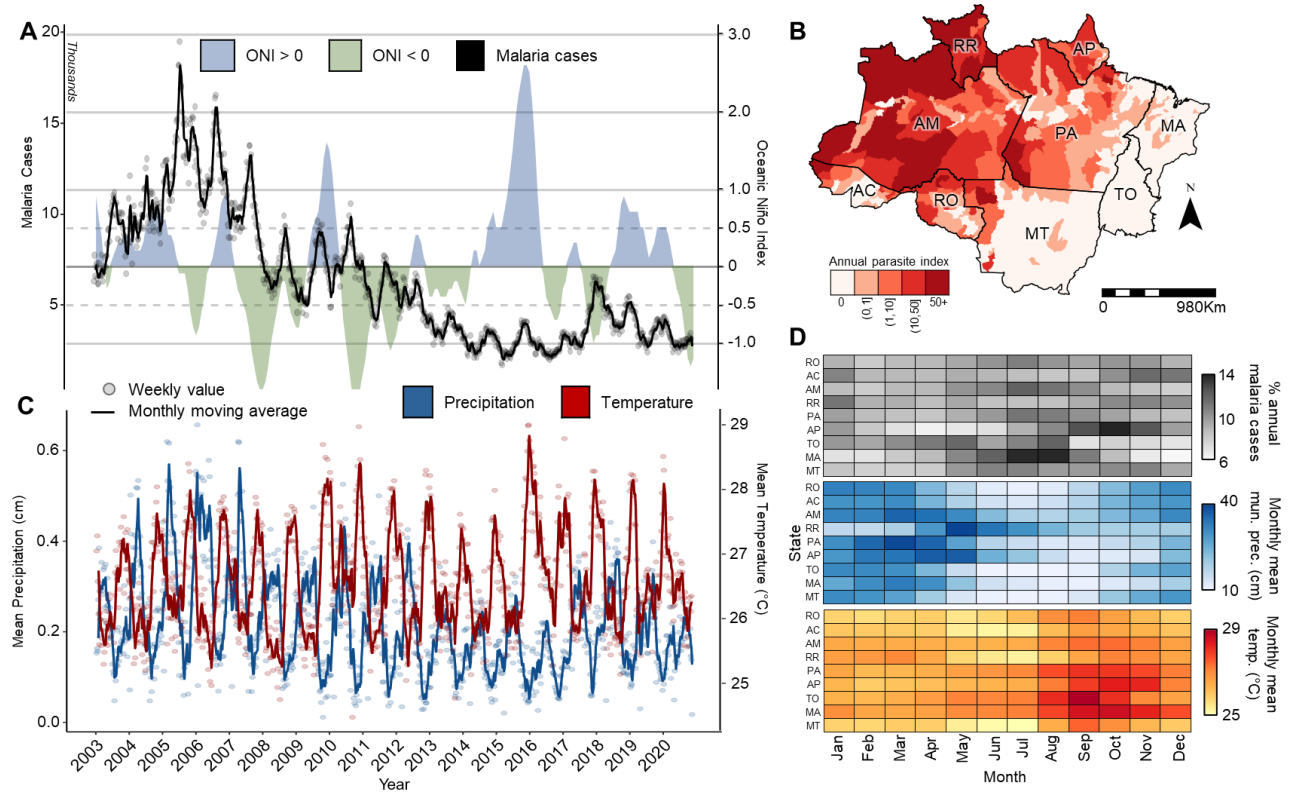


Figure 3.1. Malaria cases, weather patterns, and ONI across space and time. **A.** Weekly malaria cases with monthly moving average and ONI across the study period. **B.** Annual parasite index in 2020. State acronyms: AC=Acre, AP=Amapá, AM=Amazonas, PA=Pará, RO=Rondônia, RR=Roraima, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso. **C.** Weekly municipal average precipitation and temperature, and monthly moving averages. **D.** Monthly, state-specific percentage of cases occurring each month of the year, average total precipitation, and mean temperature over the study period.

We fit a whole-Amazon, distributed lag non-linear conditional logistic regression model to a case-crossover dataset of 43,814,769 person-days to determine the effect of 1-to-3-week lagged mean air temperature, total precipitation, and mean diurnal variation on odds an individual was infected with malaria (**Figure 3.2A, Appendix C Table C.1-C.4, Methods**). All odds ratios are relative to the median (temperature: 26.38°C, precipitation: 0.39cm, diurnal variation: 7.96°C). Across the Amazon, weather conditions that increased odds of malaria infection were one-week lagged temperature below the median, two-week lagged temperature above the median, one-week lagged precipitation above 0cm, two-week lagged temperature above 28cm, one- and two-week lagged diurnal variation beyond the median, and three-week diurnal variation below the median. Weather conditions that decreased the odds of malaria infection were two-week lagged temperature below the median, two- and three-week lagged temperature above the median, and three-week lagged diurnal variation above the median. Those relationships were not all linear. The odds of infection exponentially increased with cooler temperatures at a one-week lag and more intense precipitation at a one-week lag.

Next, we fit state-stratified case-crossover models using the same exposure as the whole Amazon model, which showed unique relationships by state (**Figure 3.2B, Appendix C Table C.5-C.10, Methods**). Some notable common trends arose. In general, states with similar monthly distributions of temperature exhibited similar relationships with the odds of malaria infection. The monthly temperature distribution in Rondônia, Acre, Roraima, and Mato Grosso were most similar and showed consistent malaria transmission throughout the year (**Figure 3.1D**). Those states demonstrated consistent patterns in the following associations: one-week lagged temperature below the median increased odds of malaria infection and above the median decreased odds, two-week lagged temperature had the reverse effect, one-week lagged diurnal variation beyond the

median increased odds of infection, and three-week lagged diurnal variation had the reverse effect. One state with a markedly different effect of temperature and diurnal variation was Pará. Here, one-week lagged temperatures were the least influential on the odds of malaria infection. However, at lags of two weeks, the relationship became U-shaped, such that temperatures $<25.5^{\circ}\text{C}$ and $>28^{\circ}\text{C}$ increased the odds of malaria infection, and this relationship reversed at three-week lags. Diurnal variation in this state had effects opposite to most other states: one- and three-week lagged values below the median increased the odds of infection, while two-week lagged values decreased the odds. The effect of precipitation, however, was more complex. In general, one-week lagged precipitation beyond 10-15cm decreased the odds of malaria infection in Rondônia, Amazonas, Roraima, and Mato Grosso, which all had minimal month-to-month variability in malaria transmission and had similar wet seasons, except for Roraima. At two-week lags, precipitation below the median decreased odds of infection in Amazonas, Mato Grosso, and Roraima but had no effect in Rondônia, while two-week lagged precipitation above the median increased odds of infection in Roraima, Acre, Pará and Amazonas. Pará and Amapá, which had very similar monthly rainfall distributions, demonstrated that precipitation beyond 30cm increased the odds of infection.

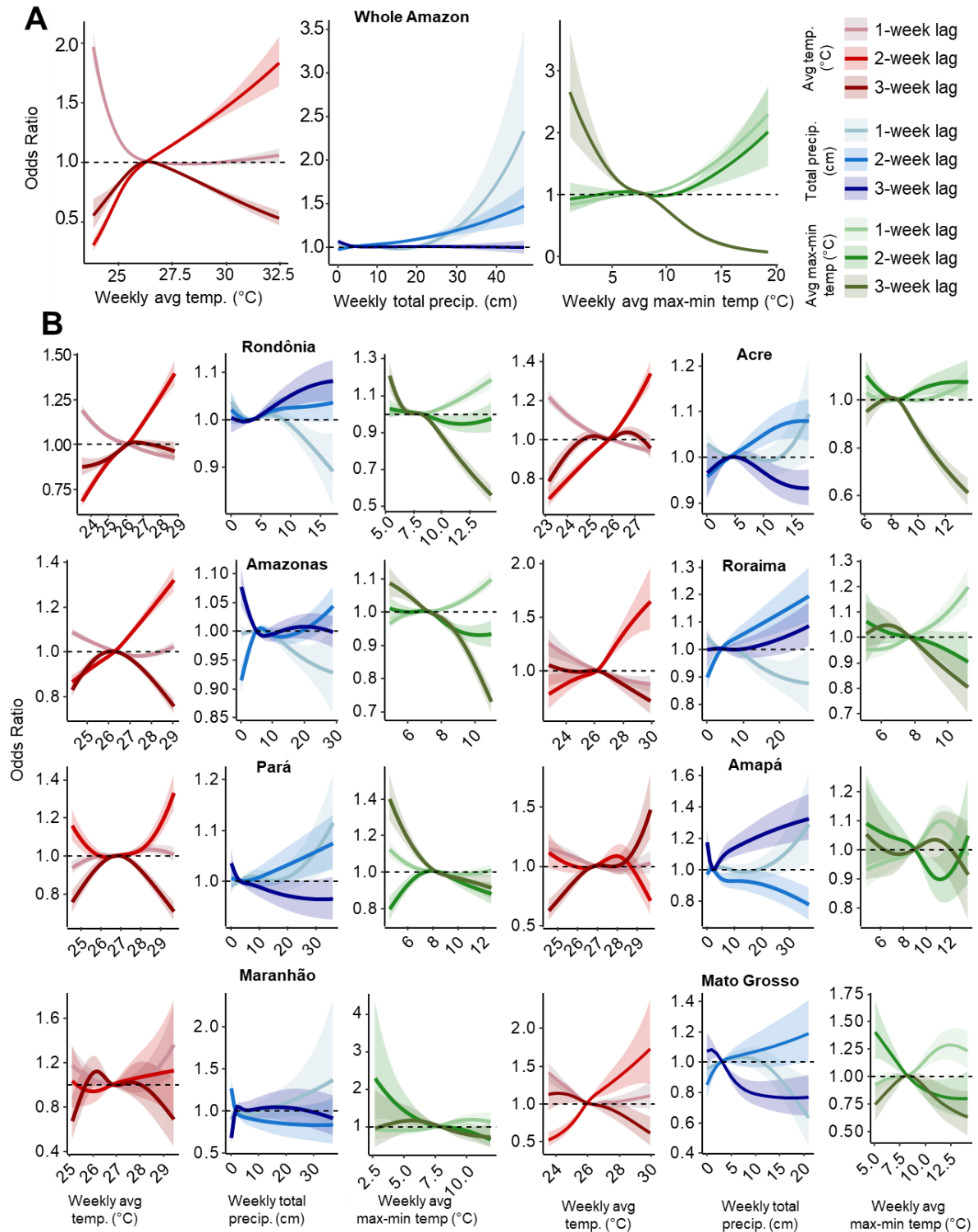


Figure 3.2. Case crossover model results for weather and malaria infection. Lines show the estimated odds of malaria infection, and shaded areas indicate 95% confidence intervals (Methods). **A.** Whole Amazon model results. **B.** State-stratified model results. Coefficients for models at points reflective of temperature and precipitation distributions provided in Appendix C Tables 1-10.

To determine the effect of El Niño and La Niña events on malaria transmission beyond the effects of fluctuations in precipitation and temperature, we fit distributed lag non-linear Quasi-Poisson regression at whole Amazon and state-stratified levels to assess the effect of continuous Oceanic Niño Index Region 3.4 (ONI) values on monthly, municipality-level malaria cases for the whole Amazon and for each state in the dataset (**Figure 3.3, Appendix C Table C.11-C.14B, Methods**). We specifically looked at ONI values in the same month and at three- and six-month lags. ONI values ≤ -0.5 are associated with La Niña conditions, and ONI values ≥ 0.5 are associated with El Niño conditions. Across the whole Brazilian Amazon, coincident ONI values < -0.5 and > 0 were associated with fewer malaria cases in that month, and ONI values of between -0.25 and 0 were associated with more monthly cases. At a 6-month lag, this relationship reversed; ONI values between 0 and 1.5 , and ONI values < -0.5 , were associated with higher monthly malaria cases. These relationships varied by state, with some common trends.

In general, larger states tended to have wider confidence intervals likely owing to the diversity in climate across large spatial scales (**Figure 3.3**). Though the weather in the Amazon is typically influenced by ENSO events on a north-south gradient, grouping states based on where malaria transmission is most geographically concentrated helps elucidate clearer patterns in coefficients. Higher malaria cases in the northernmost states of Roraima and Amapá were associated with same-month ONI values beyond both ENSO event thresholds. At a six-month lag, La Niña ONI values were associated with fewer cases in those two states, and El Niño ONI values were associated with fewer cases in just Amapá. In Acre, where extremely high transmission is focal to the small region of the Juruá Valley, the relationship between ONI and malaria matches that in Amapá across the lag space. Amazonas, which neighbors Roraima to the southwest and Acre to the east, is the largest state in Brazil and has the highest malaria burden. The burden of malaria in this state is diffuse,

but pockets of particularly high, concentrated transmission exist in the northern (bordering Venezuela/Colombia/Roraima) and southwest (bordering Peru/Acre) regions. El Niño ONI values had no effect on malaria cases in Amazonas, while ONI values below the La Niña threshold followed the whole-Amazon model yet were opposite to the relationship seen in Acre and Roraima. The second largest state in Brazil, Pará, has a malaria burden that is highly concentrated in the southwestern municipalities of Itaituba, Jacareacanga, and others in the vicinity. This portion of Pará borders Mato Grosso to the southwest (a large state with low malaria transmission concentrated in the northeast) and is geographically near Rondônia to the east (a small state with high transmission in the north). We find that the relationship between malaria transmission and ONI is similar in these three states across the lag space, but most apparently in Rondônia and Pará. In all three states, same-month La Niña ONI values are associated with higher malaria cases, and at three- and six-month lags that relationship reverses in all three states but is not statistically significant in Mato Grosso (perhaps owing to few malaria cases). In Rondônia and Pará the effect of El Niño ONI values in the same month was associated with higher malaria cases, while at a six-month lag this reversed.

Finally, we fit state- and precipitation season-stratified multilevel models to determine the effect of coincident El Niño and La Niña events on mean monthly temperature and total monthly precipitation (**Figure 3.4, Appendix C Table C.15, Methods**). Concerning temperature, El Niño events associated with warming in both seasons, while La Niña events were associated with cooler rainy seasons and warmer dry seasons, and bordering states showed similar trends. Roraima and Amapá were the exceptions to those patterns. Precipitation was more complex. Most states experienced wetter dry seasons from both El Niño and La Niña events, except the northern states of Roraima (drier with both exposures), Acre, and Mato Grosso (drier in El Niño). La Niña events

were largely associated with drier rainy seasons except for in Rondônia and Tocantins, while El Niño events were associated with drier rainy seasons in Roraima and Amapá but wetter rainy seasons everywhere else.

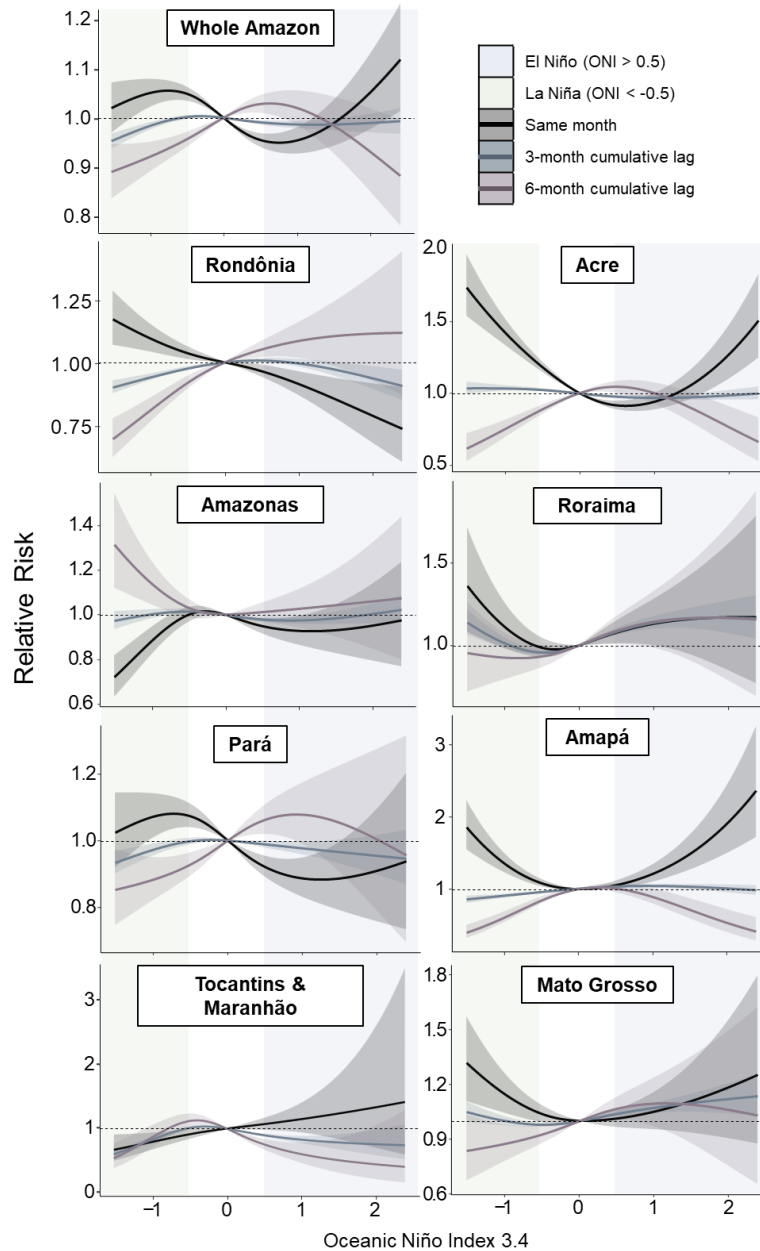


Figure 3.3. Distributed lag non-linear model results for ONI and malaria cases. Lines show the estimated relative risk, and shaded areas indicate 95% confidence intervals (Methods). Coefficients for models predicted at common ONI values are provided in Appendix C Tables 12-14.

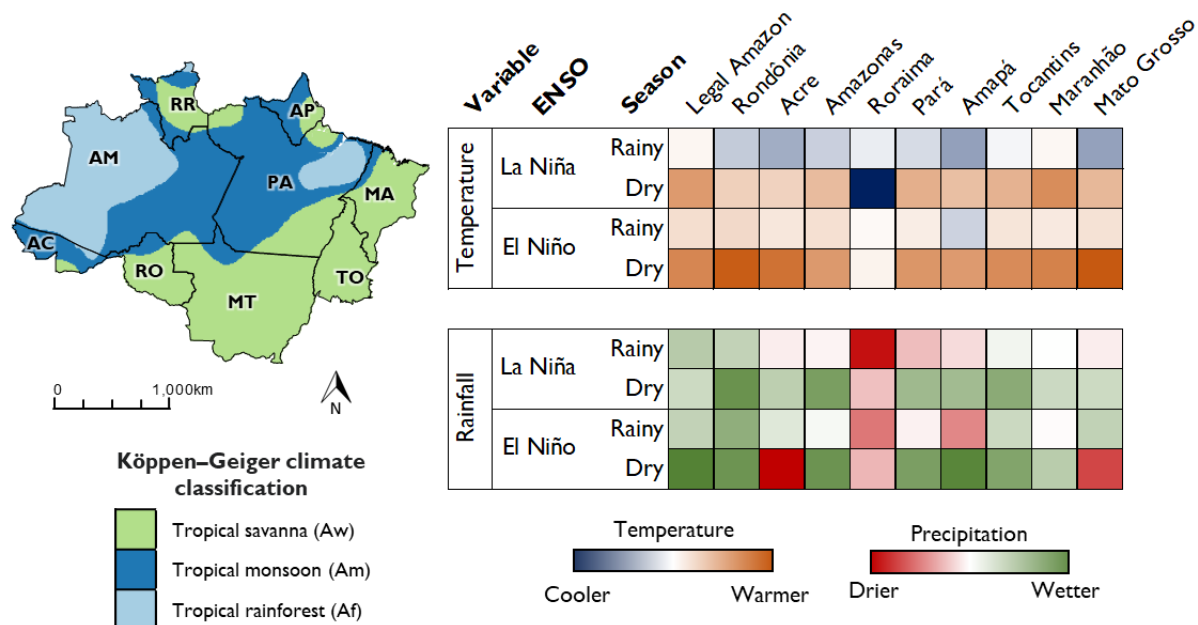


Figure 3.4. ONI and weather model results. Map in the center shows the distribution of Köppen-Geiger climate classifications. State acronyms: AC=Acre, AP=Amapá, AM=Amazonas, PA=Pará, RO=Rondônia, RR=Roraima, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso. Heatmaps for precipitation (left) and temperature (right) show coefficient strength for each month and state (Methods). Coefficient values and statistical significance can be found in Appendix C Table 15.

Discussion

We comprehensively analyzed the effects of both weather and ENSO fluctuations on malaria transmission in the Brazilian Amazon and demonstrated how ENSO events impact weather in Amazonian states. Across the entire region, we showed that three-week lagged temperatures above and below the median were protective against malaria infections, while one-week lagged temperatures below and two-week lagged temperatures above the median increased the odds of infection. We also showed that malaria infection risk increased with increasing one- and two-week lagged total precipitation and diurnal variation, while three-week diurnal variation had the opposite effect. Though these relationships varied markedly by state, two-week lagged temperatures, one-week lagged diurnal variation, and two-week lagged precipitation beyond the median most

frequently increased infection risk. For extreme events, we demonstrated that same month La Niña and extreme El Niño conditions increased malaria risk across the whole Amazon, and that La Niña events in the same month commonly increased malaria risk. In general, six-month exposure to ENSO events had reverse effects to same-month exposure. Finally, we showed that El Niño events most frequently led to warmer, wetter rainy and dry seasons, while La Niña events led to cooler, drier rainy seasons, and warmer, wetter dry seasons. Our results have major implications for clarifying the short- and long-term role of weather on the ecological determinants of malaria transmission in Brazil and may help prepare for the future impacts of a changing climate on malaria transmission as the country moves toward elimination.

Weather in the Brazilian Amazon can influence malaria transmission by altering vector ecology and human behavior, and both factors further depend on seasonal weather patterns, hydrology, and land-use change. For vector ecology and seasonal patterns, *Ny. darlingi* is sensitive to temperature and precipitation fluctuations across Brazil. Vector abundance in some regions is positively correlated with rainfall, with populations peaking during the rainy months of the year, while in other areas vector density peaks toward the transition between rainy and dry seasons¹⁷. A study conducted in Rondônia explains this dynamic by distinguishing two types of transmission in the Amazon: riverine and dry land malaria^{56,57}. In dryland areas, breeding sites more commonly originate after the rainy season when floods at the margin of rivers retreat to their original size. That retreat leaves behind large stable water collections which result in high vector density and malaria transmission at the beginning of the dry season. On the other hand, in riverine areas, whole forested areas can be flooded during the rainy season due to dense tributary networks, creating low water flow breeding habitats highly favorable to *Ny. darlingi* and causing malaria to peak in the rainy season. The Amazon flood plain is large, complex, and dynamic, and both transmission

scenarios are present throughout⁵⁸⁻⁶⁰. Yet, the relationship between weather and malaria transmission is highly dependent on local ecology and land-use⁶¹. Frontier malaria provides a key example; cleared forest collects rainfall and creates larval habitat more readily than fully forested areas, and a warmer microclimate associated with deforestation can increase adult vector fitness and speed both larval and adult development time⁶².

Our findings may show that the effects of El Niño and La Niña may in part be related to common modes of transmission in an area. For example in Amazonas, La Niña events are associated with a drier rainy season and fewer malaria cases in the same month, but a wetter dry season and more malaria at six-month lags. These relationships lend to riverine malaria being common in Amazonas, because drying during the rainy season may reduce *Ny. darlingi* habitat while prolonged precipitation throughout the dry season may sustain vector breeding. On the other hand, in states like Roraima where intense transmission on the northern border lies outside the Amazon flood plain, La Niña, and El Niño tend to lead to drier conditions regardless of season, and at three-month lags associated with more malaria perhaps owing to dry land transmission dynamics. As climate change makes seasonal dynamics associated with ENSO fluctuations more severe, understanding these spatial and temporal patterns can improve state and municipal malaria program capacity to plan for shifts in transmission intensity.

Though seasonal trends offer insight into intervention planning and future challenges, immediate influences of weather variability are crucial for proper intervention stratification in the meantime. Here, we show that higher rainfall, temperature, and diurnal variation in the two weeks leading up to infection create conditions more favorable for malaria transmission, while higher diurnal variation and temperatures above and below the median reduce transmission at three-week time lags. There are several explanations for this related to host behavior, vector ecology, and

Plasmodium biology. From a host perspective, high precipitation leading to flooding may disrupt one's ability to travel for occupation and may increase the frequency of peridomicile biting from an increased time near home^{56,63,64}. From a vector perspective, different time lags relate to different parts of the mosquito lifecycle. One- and two-week lagged temperature is most likely to have immediate effects on adult mosquito behavior. Some studies have shown that the optimal temperature for transmission in the immediate temporal vicinity ranged from 25-26°C and decreased dramatically with higher temperatures, and our results demonstrate an elevated risk for infection at temperatures below 26°C in the same week^{65,66}. *Plasmodium* develops most effectively at 25°C and development in the mosquito takes one to two weeks. Our results corroborate this relationship: three-week lagged temperatures above and below the median reduce the odds of malaria infection. Fluctuations in daily temperature also influence *Anopheles* life history traits; a study of *Anopheles stephensi* showed that higher diurnal variation at mean temperatures of 18°C reduced vector survival in the first 21 days of life, but at mean temperatures of 24°C increased survival¹³. Here, we do not assess an interaction between temperature and diurnal variation but do find that at three-week lags exposure to less diurnal variation results in higher odds of being infected, while more diurnal variation does the opposite. The variability of these relationships in each state may lend to different average temperature and precipitation patterns, which we reinforce by showing that geographically close regions have similar exposure-response curves.

This study has several strengths. It is the first, most comprehensive country-wide analysis of the effects of weather patterns and extreme events on malaria transmission in the Brazilian Amazon. We analyze both coincident and lagged variables to shed light on the time-varying nature of these complex exposure-response relationships, which carry important implications for malaria control. We leverage case-crossover analysis, which controls for non-time varying and time-varying

confounders outside the exposure-response window naturally, improving the causal inference of model estimates. Finally, we analyze continuous variations in the Oceanic Niño Index as it relates to malaria transmission, rather than solely El Niño and La Niña cutoffs, which provides a more granular understanding of how lesser or more extreme deviations in sea surface temperature can influence the risk of disease.

This study also has some limitations. First, the state-level model stratification is coarse, and transmission, especially in large states, varies spatially. The estimates from these models may more truly reflect the relationship between exposure and outcome where malaria transmission is most strong. Second, SIVEP does not capture asymptomatic infections, which is true for all routinely collected administrative records. There are likely more infections occurring than are accounted for in the outcome variable of our models, which may cause model coefficients to be underestimated.

Conclusion

The relationship between weather, extreme events, and malaria transmission is complex and spatiotemporally variable, but is also modified by deforestation, human mobility, and a changing climate. Here, we lay the foundation for the relationship between climatological variables, ENSO fluctuations, and malaria transmission in Brazil at the whole Amazon and state-specific levels. Our results suggest that climate change could have significant impacts on the risk of malaria transmission in the Brazilian Amazon, and that these impacts are likely to vary spatially. Those impacts are likely to influence the behavior of humans, vectors, and parasites. As the natural history of the Amazon region continues to change with the weather becoming more extreme, responding to fluctuations in weather will be integral in achieving the country's goal of malaria elimination by 2035.

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Chapter V

Conclusion

This dissertation comprehensively examines three interconnected, ubiquitous, and ongoing challenges that Brazil faces on the path to malaria elimination by 2035. Our findings fill significant gaps on how dynamical anthropogenic and natural processes in the Brazilian Amazon will individually and collectively influence malaria transmission and provide key insight into how Brazil may adequately respond to those changes at fine spatial and temporal scales. The malaria scenario in the Brazilian Amazon has been subject to storied successes matched by historic regressions, which have been largely at the will of political shifts that changed the transmission landscape^{1,2}. This dissertation serves as a strong foothold from which Brazil can launch a more targeted, sustainable approach to malaria elimination to avoid the pitfalls of years past. With a strong commitment to elimination as a policy of state and considering the key risks for regression presented in this dissertation, Brazil's new era of malaria elimination may be the final chapter in its historical fight against malaria.

An Opportunity for a Planetary Health Approach

The malaria transmission scenario in the Brazilian Amazon is a Planetary Health problem. The field of Planetary Health is predicated on the interaction between changing natural systems, human population dynamics, and the ultimate health and environmental consequences that arise from those interactions^{3,4}. Yet, the discipline aims to go deeper than associations between ecological drivers and health effects; Planetary Health also considers the underlying anthropogenic drivers, proximate causes of health effects, and mediating factors that either enhance or inhibit those relationships⁴. The results of this dissertation clarify the stepwise relationship between key

ecological drivers (deforestation, climate), proximate causes (exposure to malaria vectors), mediating factors (human behavior, mobility, sociodemographic factors), and the ultimate outcome of malaria transmission.

In the case of Brazil, the underlying, historical drivers of malaria transmission are clear. From a country perspective, political structures in the last 50 years have promoted a shifting demographic makeup (population booms) and heightened resource demand across the Amazon, which come at the expense of natural systems^{2,5}. The promise of economic opportunity and improved quality of life through agriculture, mining, forestry, and other activities resulted in a booming Amazon Frontier, characterized by a wide network of transportation routes, rapid land-use change, extended urbanization⁶, degradation of natural carbon sinks, and ultimately changes in the biogeochemical system in the Amazon Basin. From a global perspective, coincident acceleration in resource consumption has occurred, leading to heightened greenhouse gas emissions and ultimately a more extreme climate.

Until the work presented in this dissertation, the relationship between proximal ecological changes, malaria exposure, mediating factors, and ultimately disease transmission was unclear^{7,8}. We show that heightened resource demand has led to accelerations in forest clearing, and on a whole-Amazon level forest clearing increases malaria transmission, with certain population subgroups like *garimpo* workers and indigenous groups acutely at risk. Yet, this ecological driver of malaria transmission is predicated on human behavior and mobility; while certain populations may be mobile but live in harmony with forests and use them sustainably (i.e., indigenous groups), *garimpo* workers exhibit high mobility along the frontier of deforestation in the Amazon. Furthermore, deforestation, mobility, and malaria risk in the Amazon intimately connect to climatological conditions, which can promote or inhibit vector proliferation, pathways for

migration, and human behavior. Changes in infectious disease exposure, however, do not translate directly to changes in disease burden; elimination policies related to surveillance, treatment, and behavioral interventions have the capability of reducing and halting transmission if informed by comprehensive knowledge of the system of malaria in Brazil.

Co-benefits of Conservation, Indigenous Rights, and Malaria Elimination

The Brazilian Amazon is at a turning point. After tumultuous years under President Jair Bolsonaro, the progressive administration of President Luis Inácio Lula da Silva, which historically championed forest conservation, indigenous rights, and public health, has been reinstated at a crucial time. The Amazon is being deforested at remarkably fast rates, humanitarian crises have arisen in indigenous groups⁹, mining activity has created legacy health challenges across the Amazon^{10,11}, weather patterns are becoming more extreme and unpredictable, and encroachment on both conservation units and indigenous territories poses serious threats to cultural and biological diversity¹². At a time when nearly one-third of malaria cases are concentrated in indigenous territories and a quarter are in *garimpo* areas, many overlap conservation units, policies that aim to curb malaria elimination through ensuring the sanctity of protected areas may be uniquely powerful. Furthermore, by creating cross-sectoral policies, Brazil may be able to more efficiently achieve the benchmarks set out in the Sustainable Development Goals by the intended target of 2030¹³.

The political structures in Brazil exist to create such policies. The National Indigenous Peoples Foundation (FUNAI) and the Brazilian Institute of the Environment and Renewable Natural Resources (IBAMA) exist to protect the rights of indigenous groups and forested areas. During the Bolsonaro administration, these organizations were headed by agribusiness magnates and

military officials, but the Lula da Silva administration aims to restore those seats of power to Indigenous leaders and environmentalists¹⁴. The humanitarian crisis among the Yanomami in Northern Roraima and Amazonas, which was exacerbated in part by abandonment from IBAMA and FUNAI during the Bolsonaro administration^{9,15}, has provided insight into the capabilities of cross-sectoral response since the start of the Lula da Silva administration. Numerous organizations have come together to confront the crisis among the Yanomami, including heightened health surveillance and provision of medical care, strict enforcement of conservation and indigenous policies through seizure of mining equipment and property associated with harmful activity, and other tactics¹⁶. Though evidence of declining malaria rates has yet to come about, the power of a multisectoral response should not be underestimated, especially given the clear interconnectedness between ecological drivers, population disenfranchisement, and health burdens in Brazil.

Concluding Remarks

From the turn of the century until 2016, Brazil achieved monumental reductions in malaria transmission. The fragility of those gains was realized in the 2017 and 2018, as transmission increased when confronted by a government with an anti-public health agenda, humanitarian crises in neighboring countries and at home, the SARS-CoV-2 pandemic, extreme climatic events, and an ever-changing Amazon Frontier. Despite these barriers, Brazil has since regained its progress and in 2022 committed to malaria elimination by 2035, highlighting the country's resiliency and optimism for a healthier future. Over the next 13 years, many of the challenges Brazil has faced on the road to malaria elimination will persist. However, through cross-sectoral collaboration, strong disease surveillance as a core intervention, and integration of ecological, climatological, and demographic risk factors known to influence transmission in intervention stratification, key barriers to malaria elimination in Brazil may be surpassed.

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Appendix A

Chapter II supplementary materials

Table A.1. Summary of total and imported cases (only between/within-states in Brazil), broken down by within- and between-state movements.

Year	Total			Within-State			Between-State		
	Cases	Imported Cases	% of total	Cases	% of imported	Average Distance Travelled (Km)	Cases	% of imported	Average Distance Travelled (Km)
2003	408762	70344	17.21%	60126	10218	85.47%	10218	14.53%	309.05
2004	464899	96182	20.69%	82150	14032	85.41%	14032	14.59%	315.79
2005	606069	116183	19.17%	99888	16295	85.97%	16295	14.03%	304.33
2006	549380	103232	18.79%	86258	16974	83.56%	16974	16.44%	263.04
2007	457470	78875	17.24%	65982	12893	83.65%	12893	16.35%	309.01
2008	314917	54341	17.26%	43812	10529	80.62%	10529	19.38%	309.32
2009	308400	53498	17.35%	45102	8396	84.31%	8396	15.69%	297.99
2010	333474	53081	15.92%	45675	7406	86.05%	7406	13.95%	367.61
2011	294126	45775	15.56%	39008	6767	85.22%	6767	14.78%	400.98
2012	275760	41436	15.03%	34232	7204	82.61%	7204	17.39%	374.57
2013	204988	26856	13.10%	21304	5552	79.33%	5552	20.67%	374.77
2014	163313	22238	13.62%	18352	3886	82.53%	3886	17.47%	342.68
2015	165203	19698	11.92%	16270	3428	82.60%	3428	17.40%	336.23
2016	151018	20646	13.67%	16406	4240	79.46%	4240	20.54%	305.58
2017	237456	30759	12.95%	24362	6397	79.20%	6397	20.80%	284.97
2018	242589	33413	13.77%	26321	7092	78.77%	7092	21.23%	307.45
2019	189393	30033	15.86%	22319	7714	74.31%	7714	25.69%	373.61
2020	171726	28991	16.88%	21511	7480	74.20%	7480	25.80%	417.07

Table A.2. Top 10 most common importation routes across all categories, within states, and between states by number and percentage of all routes in that category. State acronyms: AC=Acre, AP=Amapá, AM=Amazonas, PA=Pará, RO=Rondônia, RR=Roraima, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

All routes of importation			
Porto Velho→Buritis	RO	21358	1.98%
Canutama→Porto Velho	AM→RO	19970	1.85%
Cantá→Boa Vista	RR	19200	1.78%
Careiro→Manaus	AM	18741	1.73%
Pacajá→Tucuruí	PA	18229	1.69%
Iranduba→Manaus	AM	17892	1.66%
Candeias do Jamari→Porto Velho	RO	17664	1.63%
Moju→Tailândia	PA	16349	1.51%
Rodrigues Alves→Cruzeiro do Sul	AC	14981	1.39%
Rio Preto da Eva→Manaus	AM	14978	1.39%
Routes of within-state importation			
Porto Velho→Buritis	RO	21358	11.94%
Cantá→Boa Vista	RR	19200	10.73%
Careiro→Manaus	AM	18741	10.48%
Pacajá→Tucuruí	PA	18229	10.19%
Iranduba→Manaus	AM	17892	10.00%
Candeias do Jamari→Porto Velho	RO	17664	9.88%
Moju→Tailândia	PA	16349	9.14%
Rodrigues Alves→Cruzeiro do Sul	AC	14981	8.38%
Rio Preto da Eva→Manaus	AM	14978	8.37%
Nova Mamoré→Buritis	RO	12910	7.22%
Routes of between-state importation			
Canutama→Porto Velho	AM→RO	19970	2.21%
Guajará→Cruzeiro do Sul	AM→AC	14063	1.56%
Lábrea→Porto Velho	AM→RO	9896	1.10%
Almeirim→Laranjal do Jari	PA→AP	6935	0.77%
Maués→Itaituba	AM→PA	5618	0.62%
Colniza→Machadinho D'Oeste	MT→RO	5552	0.62%
Itaituba→Maués	AM→PA	4746	0.53%
Porto Velho→Rio Branco	RO→AC	4325	0.48%
Humaitá→Porto Velho	AM→RO	3356	0.37%
Rondolândia→Ji-Paraná	MT→RO	3247	0.36%

Table A.3. Multinomial logistic regression results (reference group is locally acquired cases)

	Between- state	<i>p</i> -value	Within- state	<i>p</i> -value
Intercept	0.018	<0.001	0.028	<0.001
Age (ref: <5 years)				
5-15 years	0.910	<0.001	0.931	<0.001
16-24 years	1.584	<0.001	1.341	<0.001
25-40 years	1.891	<0.001	1.483	<0.001
41-64 years	2.079	<0.001	1.515	<0.001
65+ years	1.463	<0.001	1.380	<0.001
Sex (ref: Female)				
Male	1.323	<0.001	1.131	<0.001
Occupation (Binary)				
Artisanal mining (<i>Garimpo</i>)	5.839	<0.001	2.123	<0.001
Forestry	2.633	<0.001	1.204	<0.001
Agriculture	0.835	<0.001	1.073	<0.001
Domestic	0.829	<0.001	0.839	<0.001
Hunter/Fisher	0.955	0.027	1.102	<0.001
Special area of infection				
Indigenous	0.207	<0.001	0.824	<0.001
Rural	0.406	<0.001	1.892	<0.001
Artisanal mining (<i>Garimpo</i>)	0.268	<0.001	1.291	<0.001
Settlement	0.254	<0.001	1.906	<0.001
Parasite species (ref: <i>P. vivax</i>)				
<i>P. falciparum</i>	1.230	<0.001	1.081	<0.001
Mixed/other	1.555	<0.001	1.239	<0.001
Testing format (ref: Active)				
Passive testing	2.492	<0.001	2.841	<0.001
Month of year (ref: January)				
February	0.961	0.004	0.946	<0.001
March	0.858	<0.001	0.849	<0.001
April	0.800	<0.001	0.812	<0.001
May	0.820	<0.001	0.805	<0.001
June	0.837	<0.001	0.839	<0.001
July	0.863	<0.001	0.933	<0.001
August	0.926	<0.001	0.962	<0.001
September	0.902	<0.001	0.939	<0.001
October	1.007	0.600	0.931	<0.001
November	1.006	0.626	0.908	<0.001
December	1.084	<0.001	0.973	<0.001
Time to care (ref: <24hrs)				
>48hrs	1.323	<0.001	1.595	<0.001
24-48hrs	0.902	<0.001	0.979	<0.001

Table A.4. Top 10 municipalities by node designation (Methods).

Sink			
Type A	Type B	Type C	Type D
Porto Velho	Ariquemes	Itapuã do Oeste	Alta Floresta D'Oeste
Nova Mamoré	Machadinho D'Oeste	Rodrigues Alves	Cabixi
Candeias do Jamari	Buritis	Alvarães	Cacoal
Cruzeiro do Sul	Cujubim	Autazes	Cerejeiras
Lábrea	Humaitá	Canutama	Colorado do Oeste
Manaus	Boa Vista	Careiro	Corumbiara
Manicoré	Altamira	Guajará	Costa Marques
Anajás	Itupiranga	Irlanduba	Espigão D'Oeste
Itaituba	Novo Progresso	Presidente Figueiredo	Guajará-Mirim
Pacajá	Novo Repartimento	Rio Preto da Eva	Jaru
Colniza	Paragominas	Cantá	Ji-Paraná
Source			
Type A	Type B	Type C	Type D
Ariquemes	Cacoal	Buritis	Alta Floresta D'Oeste
Jaru	Machadinho D'Oeste	Mâncio Lima	Cabixi
Ji-Paraná	Ouro Preto do Oeste	Boca do Acre	Cerejeiras
Porto Velho	Vilhena	Careiro	Colorado do Oeste
Cruzeiro do Sul	Manacapuru	Tefé	Corumbiara
Rio Branco	Ananindeua	Afuá	Costa Marques
Humaitá	Belém	Anajás	Espigão D'Oeste
Manaus	Breves	Jacundá	Guajará-Mirim
Boa Vista	Marabá	Novo Progresso	Nova Brasilândia D'Oeste
Altamira	Santarém	Paragominas	Pimenta Bueno
Itaituba	Porto Grande	Tailândia	Presidente Médici

Table A.5. Annual Pearson correlation between GCMR (Methods) and annual parasite index. LCI = Lower bound of 95% confidence interval. UCI = Upper bound of 95% confidence interval.

Correlation GCMR x API				
Year	Pearson Correlation	LCI	UCI	P-value
2003	0.820	0.692	0.794	<0.001
2004	0.876	0.762	0.843	<0.001
2005	0.878	0.676	0.857	<0.001
2006	0.849	0.749	0.892	<0.001
2007	0.795	0.747	0.860	<0.001
2008	0.788	0.806	0.894	<0.001
2009	0.796	0.773	0.827	<0.001
2010	0.809	0.826	0.869	<0.001
2011	0.768	0.766	0.783	<0.001
2012	0.729	0.821	0.834	<0.001
2013	0.715	0.716	0.758	<0.001
2014	0.778	0.781	0.814	<0.001
2015	0.801	0.746	0.767	<0.001
2016	0.810	0.805	0.821	<0.001
2017	0.751	0.740	0.781	<0.001
2018	0.777	0.798	0.833	<0.001
2019	0.770	0.736	0.883	<0.001
2020	0.898	0.797	0.911	<0.001
All Years	0.813	0.807	0.819	<0.001

Table A.6. Top and Bottom 20 municipalities with respect to GCMR (Methods) and mean annual parasite index.

Bottom 20				Top 20		
Rank	Municipality	Mean annual GCMR	Mean API	Municipality	Mean annual GCMR	Mean API
1	Poxoréu	0.0154	0.0063	Rodrigues Alves	220.83	466.29
2	Chapada da Natividade	0.0145	0.0000	Itapuã do Oeste	217.36	268.83
3	Dom Aquino	0.0136	0.0068	Cantá	180.64	241.33
4	Itiquira	0.0129	0.0000	Candeias do Jamari	152.14	254.96
5	Sucupira do Riachão	0.0123	0.0000	Nova Mamoré	126.28	130.84
6	Natividade	0.0114	0.0000	Ferreira Gomes	123.95	80.23
7	Figueirópolis	0.0114	0.0000	Pedra Branca do Amapari	120.72	168.22
8	Loreto	0.0107	0.0000	Ibituruna	110.95	156.32
9	Sucupira do Norte	0.0106	0.0639	Porto Grande	109.66	136.44
10	Araioses	0.0104	0.0174	Pacajá	105.60	136.45
11	Duque Bacelar	0.0103	0.0687	Rio Crespo	104.20	127.58
12	Sambaíba	0.0101	0.0111	Mâncio Lima	102.85	488.84
13	Fortaleza dos Nogueiras	0.0090	0.0000	Careiro	102.38	163.20
14	Alvorada	0.0070	0.0000	Mazagão	98.92	157.90
15	Barão de Grajaú	0.0064	0.0000	Serra do Navio	94.58	151.87
16	Água Doce do Maranhão	0.0057	0.0114	Iracema	91.54	117.28
17	São João Bautista	0.0054	0.0217	Campo Novo de Rondônia	89.75	107.03
18	Várzea Grande	0.0052	0.0012	Anajás	89.15	474.73
19	Guiratinga	0.0050	0.0040	Cujubim	85.61	211.03
20	Coelho Neto	0.0025	0.0026	Rio Preto da Eva	82.01	116.15

Table A.7. Results from SatScan analysis of within- and between-state sources and sinks of malaria infected individuals. Only clusters with $P < 0.05$ were included in the table.

Year	Source			Sink		
	# of Clusters	Average radius of Clusters (Km)	Average Cluster Duration (Months)	# of Clusters	Average radius of Clusters (Km)	Average Cluster Duration (Months)
<i>Within-State</i>						
2003	26	59.41	8.38	19	257.11	4.74
2004	27	78.45	7.85	25	160.04	5.16
2005	21	98.03	7.67	16	171.49	5.31
2006	18	117.44	11.00	15	154.59	5.40
2007	19	98.48	10.63	17	126.00	5.00
2008	18	73.91	9.94	19	248.93	4.74
2009	18	131.20	9.78	16	253.80	5.19
2010	17	97.69	10.12	18	217.43	5.44
2011	22	96.21	7.55	17	168.45	4.65
2012	15	67.81	10.87	15	226.48	5.47
2013	13	135.01	9.23	9	238.87	4.78
2014	12	127.22	10.42	15	491.21	4.47
2015	14	125.32	10.00	15	319.23	5.00
2016	13	114.27	12.00	9	268.97	6.00
2017	11	187.00	10.55	9	315.95	5.78
2018	11	167.68	10.18	11	279.74	5.91
2019	5	413.56	5.60	6	317.27	5.50
2020	6	226.49	5.17	5	422.77	4.78
<i>Between-State</i>						
2003	6	254.15	5.00	8	123.47	5.75
2004	7	166.67	5.57	12	89.87	5.50
2005	8	198.02	12.00	11	132.45	5.82
2006	9	145.45	11.33	11	142.22	5.18
2007	5	313.66	12.00	13	83.75	4.54
2008	5	300.58	12.00	6	101.99	4.83
2009	5	349.35	10.00	7	119.32	5.86
2010	5	250.01	12.00	9	112.82	5.44
2011	4	295.93	12.00	8	130.80	5.63
2012	6	170.18	9.00	6	114.47	5.83
2013	3	603.31	12.00	6	247.20	5.83
2014	3	665.27	12.00	4	121.52	6.00
2015	3	646.97	9.33	5	148.51	4.40
2016	4	343.17	12.00	6	199.51	4.83
2017	7	191.55	11.00	6	213.53	5.17
2018	5	126.97	10.00	5	178.12	5.80
2019	4	298.68	6.00	7	171.73	5.00
2020	5	173.97	5.40	6	203.22	5.83

Table A.8. Results from clustering analysis of gross migration rate of infected individuals, using the Scan Statistics. Only clusters with $P < 0.05$ were included.

Year	Within-State GCMR			Between-State GCMR			Total GCMR		
	# of Clusters	Average radius of Clusters (Km)	Average Cluster Duration (Months)	# of Clusters	Average radius of Clusters (Km)	Average Cluster Duration (Months)	# of Clusters	Average radius of Clusters (Km)	Average Cluster Duration (Months)
2003	2	80.67	6	1	193.83	6	2	188.10	6
2004	2	80.67	6	1	0	6	2	371.23	6
2005	1	0	6	2	103.60	4.5	3	197.78	5
2006	3	64.07	6	2	6.68	6	3	168.74	5.6
2007	3	0	5.6	2	6.68	5.5	6	137.36	5.8
2008	3	24.51	6	3	128.89	6	7	118.21	5.4
2009	6	35.85	5.6	3	106.38	6	5	50.33	5.6
2010	7	44.80	6	4	3.34	6	5	26.92	6
2011	6	49.85	5.8	1	0	6	4	78.16	5.5
2012	6	36.79	5.3	3	4.45	6	4	40.87	4.7
2013	5	22.12	5.8	3	4.45	6	3	210.76	5.6
2014	3	20.33	6	3	4.45	6	3	131.08	5.6
2015	3	20.33	6	4	3.34	6	2	76.97	6
2016	3	20.33	6	3	70.37	5.6	2	74.01	6
2017	4	25.91	6	4	51.80	6	6	38.20	6
2018	5	21.78	6	4	51.80	6	5	66.73	6
2019	12	38.94	4.27	9	36.75	5.11	9	21.63	4.44
2020	11	8.04	4.18	4	49.78	5.75	7	0	4.85

Figure A.1. Municipality-level annual parasite index ([cases / population] * 1000) by municipality of infection.

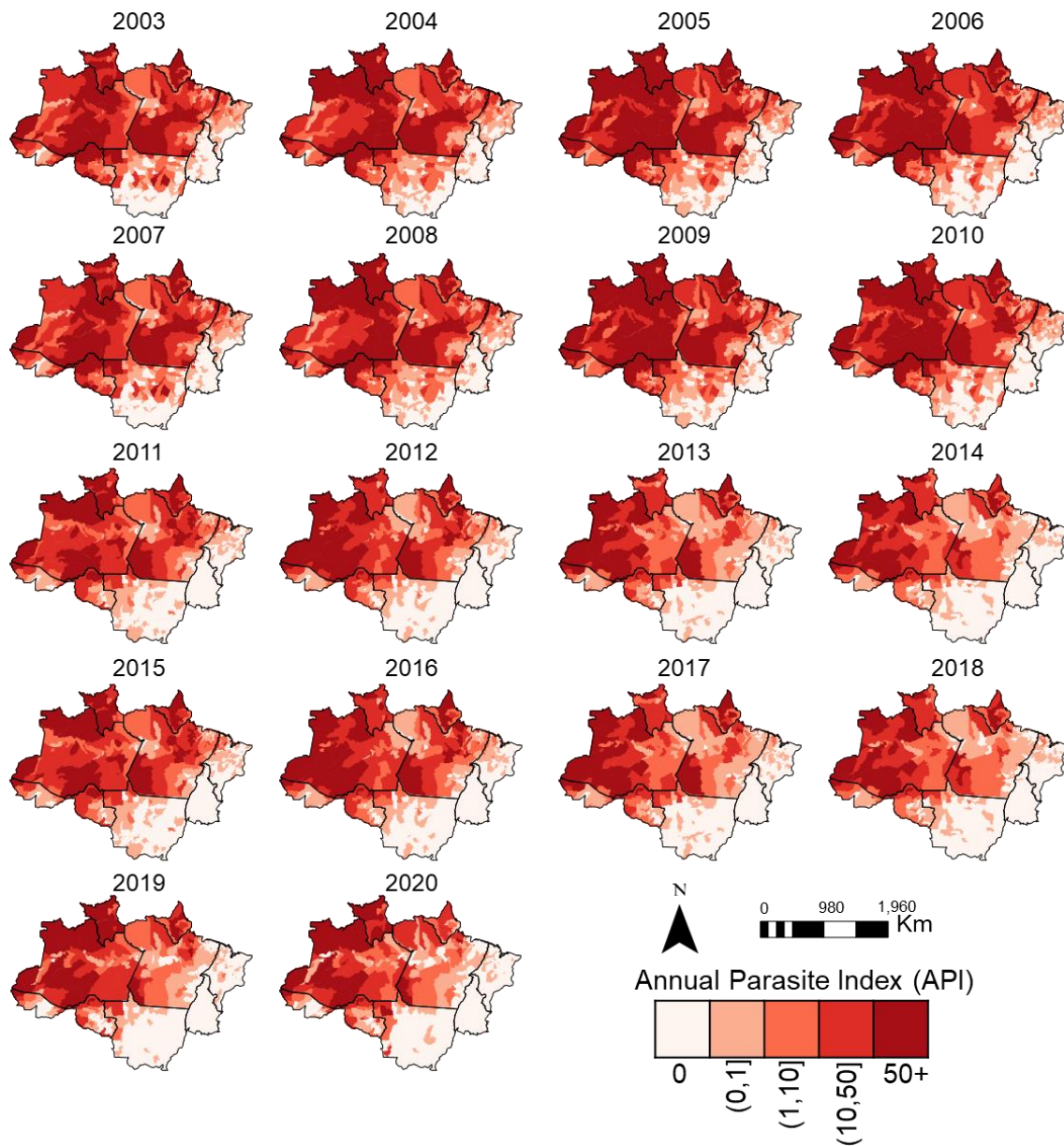


Figure A.2. Seasonal component to malaria cases by importation type, state, and year.

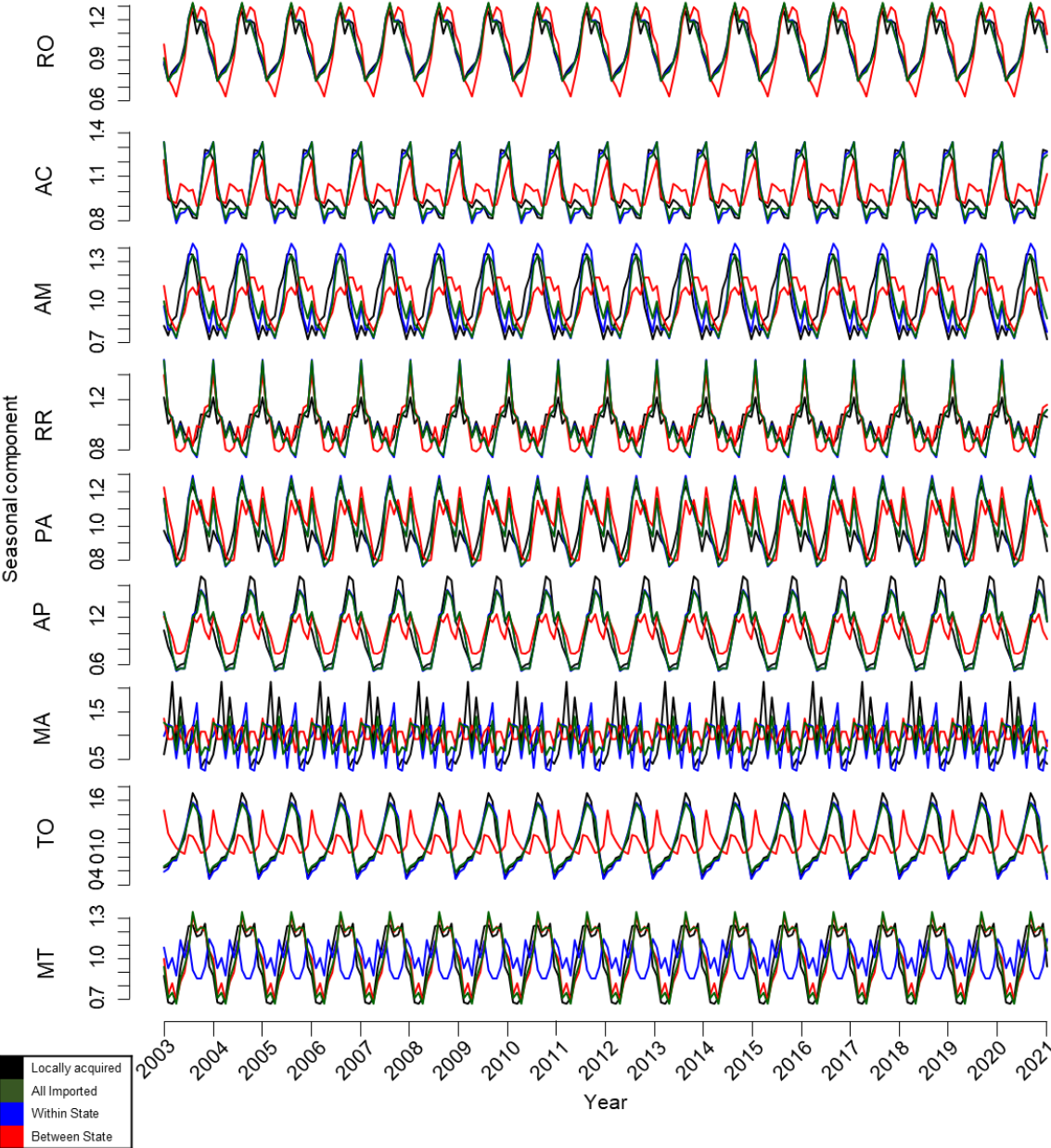


Figure A.3. A. Boxplots of annual parasite index ([cases / population] * 1000) in significant clusters, by cluster type and year group. Box plot horizontal lines: 25th, 50th, and 75th percentile, bars beyond boxes signify 95th percentile bounds. **B.** Regression lines and R^2 coefficients between the RILA and municipality level API, by state and year group.

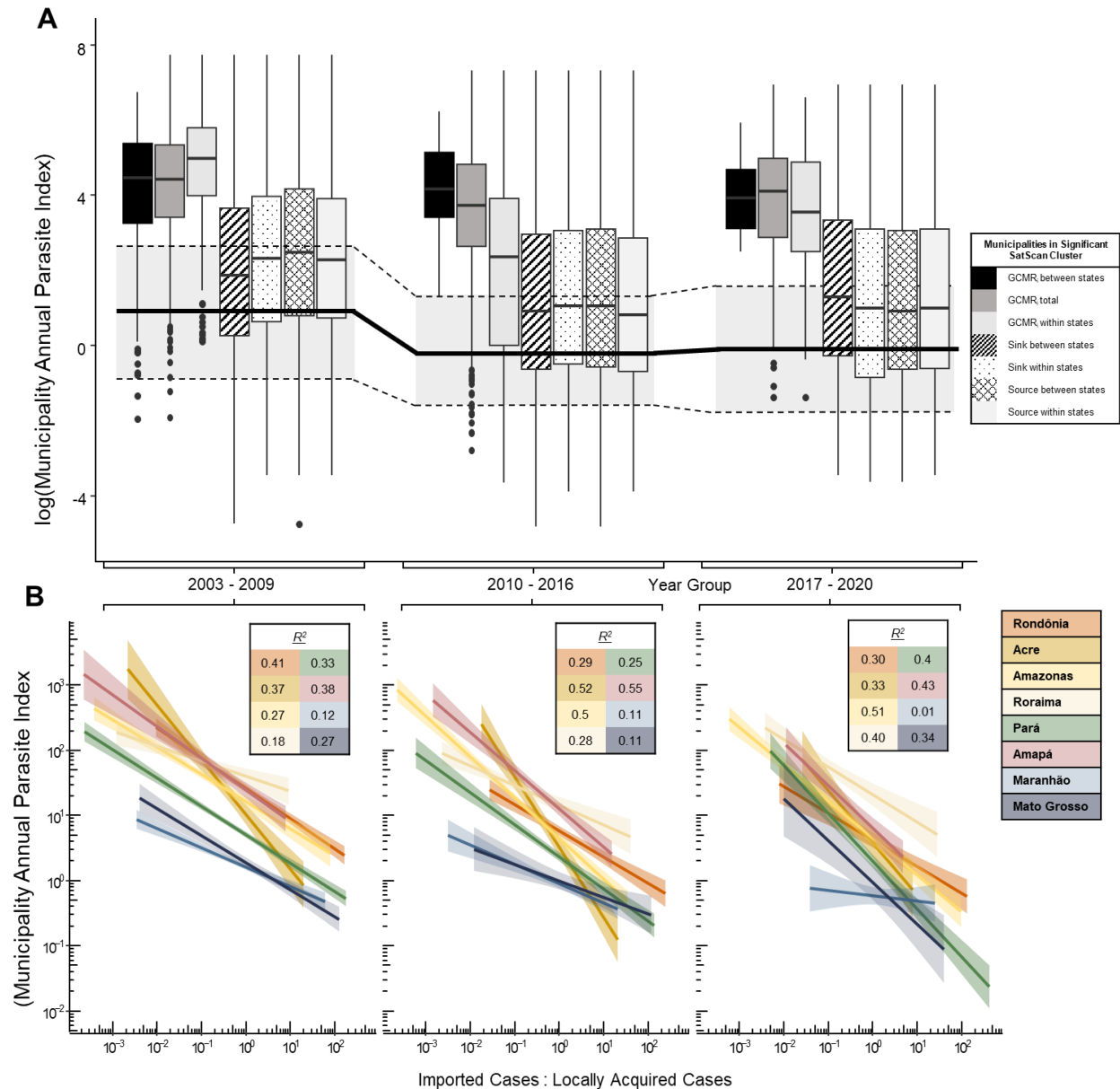


Figure A.4. Boxplot of coefficient of variation for each mobility flow in each municipality and month.

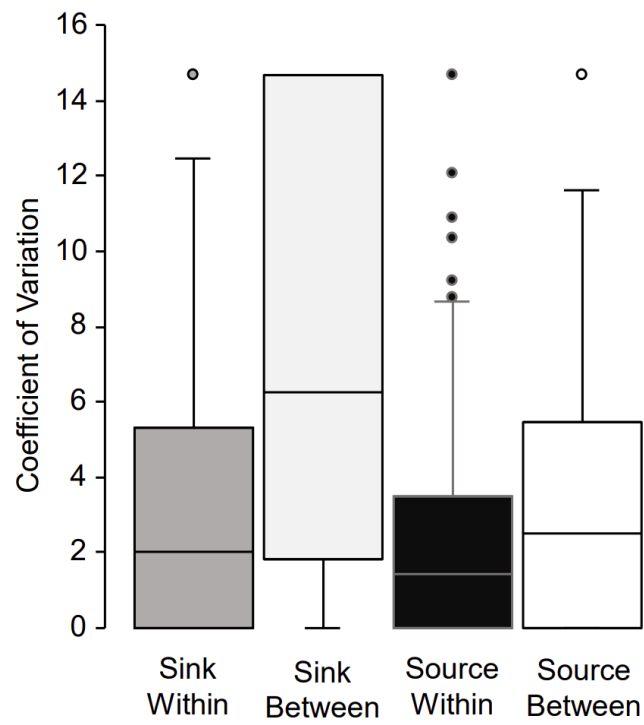
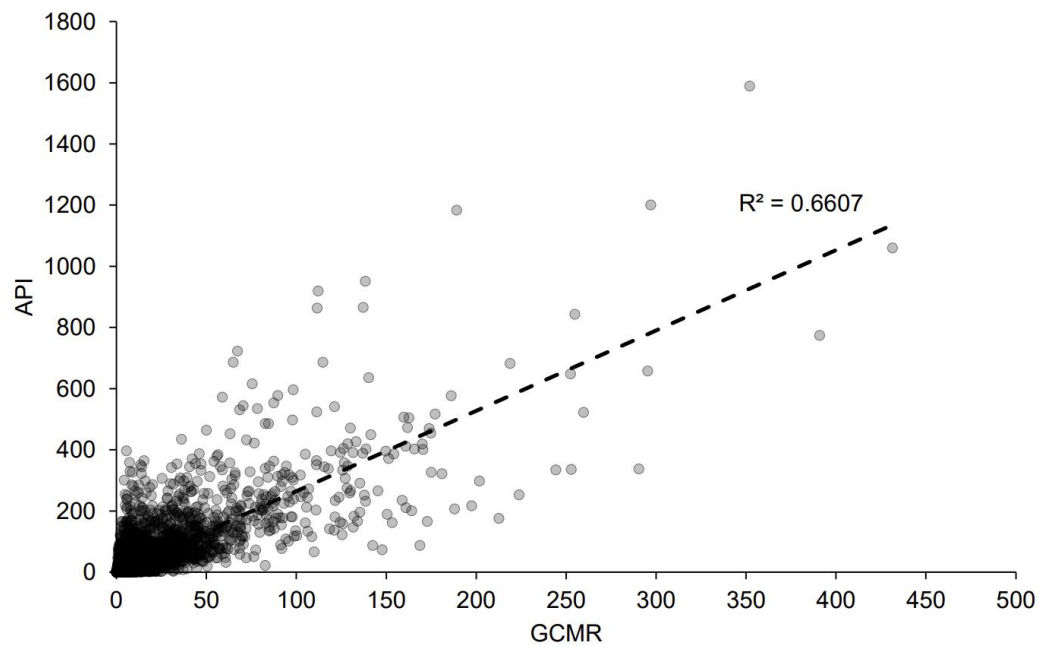


Figure A.5. Correlation between GCMR (Methods) and annual parasite index.



Appendix B

Chapter III supplementary materials

Table B.1. Details of variables included in the model.

Variable	Format	Temporal Scale	Spatial Scale	Definition	Specification	Source
1-Month Lagged Deforestation Rate	Continuous	Monthly	Municipality	Percent of total municipality area deforested in a given month	Linear	INPE
Ratio Imported : Local Cases	Continuous	Monthly	Municipality	Ratio of cases that are imported into a municipality compared to cases that are locally acquired in that municipality	Linear	SIVEP
Area of Municipality	Continuous	Fixed	Municipality	Area in Km2 of municipality	Linear	IBGE
% Municipality in Conservation Land	Continuous	Fixed	Municipality	Percent of total municipality area that is in conservation units in 2021	Linear	IBGE
% cases in garimpo localities	Continuous	Monthly	Municipality	Percent of total municipality cases that occur in garimpo localities within the municipality	Linear	SIVEP
% cases in indigenous localities	Continuous	Monthly	Municipality	Percent of total municipality cases that occur in indigenous localities within the municipality	Linear	SIVEP
% cases in settlement localities	Continuous	Monthly	Municipality	Percent of total municipality cases that occur in settlement localities within the municipality	Linear	SIVEP
% cases in rural localities	Continuous	Monthly	Municipality	Percent of total municipality cases that occur in rural localities within the municipality	Linear	SIVEP
Population	Continuous	Yearly	Municipality	Number of people living in municipality at mid-year	Linear	IBGE
Km non-paved roads	Continuous	Fixed	Municipality	Kilometers of unpaved roads (gravel and dirt) in the municipality as of 2021	Linear	MapBiomias
Km paved roads	Continuous	Fixed	Municipality	Kilometers of paved roads in the municipality as of 2021	Linear	MapBiomias
Maximum temperature	Continuous	Monthly	Municipality	Average maximum temperature in each month of the analysis in Celsius	1st order autoregressive	ERA5
Total precipitation	Continuous	Monthly	Municipality	Total monthly accumulated precipitation in each month of the analysis in meters	1st order autoregressive	ERA5
Oceanic Niño Index	Continuous	Monthly	Whole Amazon	Rolling 3-month average temperature anomaly in surface waters for Zone 3.4	1st order autoregressive	NOAA

Table B.2. Bayesian spatiotemporal model sensitivity analysis model specifications.

Model Designation									
Parameters	M1	M2	M3	M4	M5	M6	M7	M8	M9
Fixed Effects									
Deforestation rate (1-month lag)	X	X	X	X	X	X	X	X	X
Ratio imported : local cases		X	X	X	X	X	X	X	X
Area of municipality			X	X	X	X	X	X	X
Population			X	X	X	X	X	X	X
% municipality in conservation land				X	X	X	X	X	X
% cases in garimpo localities				X	X	X	X	X	X
% cases in indigenous localities				X	X	X	X	X	X
% cases in settlement localities				X	X	X	X	X	X
% cases in rural localities				X	X	X	X	X	X
Km non-paved roads					X	X	X	X	X
Km paved roads					X	X	X	X	X
Year (Fixed)	X	X	X	X	X		X	X	
State (Fixed)							X		
Random Effects									
State	X	X	X	X	X	X		X	X
Municipality	X	X	X	X	X	X	X	X	X
Non-linear terms									
Year (1st order autoregressive)						X			
Month (1st order autoregressive)	X	X	X	X	X		X	X	X
Year-month (1st order autoregressive)									
Monthly maximum temperature (2nd order random walk)	X	X	X	X	X	X	X		X
Monthly total precipitation (2nd order random walk)	X	X	X	X	X	X	X		X
Monthly maximum temperature (Natural spline 3df)								X	
Monthly maximum temperature (Natural spline 3df)								X	
Oceanic Nino Index (1st order autoregressive)	X	X	X	X	X	X	X	X	X
Spatial Effects									
Municipality (Besag-York-Mollie)	X	X	X	X	X	X	X	X	X
Interaction terms									
Spatial municipality term * month	X	X	X	X	X	X	X	X	
Spatial municipality term * year-month									X
Convergence?	Y	Y	Y	Y	Y	Y	Y	FAILED	Y

Table B.3. Deviance information criterion (DIC) and marginal likelihood from model sensitivity analysis. Model specifications in Appendix B Table 1.

Model	DIC	Marginal Likelihood
M1	-252698.6	-2036866
M2	-253611.8	-2036851
M3	-53183.6	-1972140
M4	-67327.89	-1958359
M5	-67314.2	-1958352
M6	-67279.21	-1958297
M7	-67357.61	-1958366
M8	NA	NA
M9	-262857.9	-1080730

Table B.4. Top 15 municipalities with the most cases in each locality type, garimpo and indigenous, with overlapping indigenous territories.

Municipality of infection	State	Locality type	Year	Cases	% total	Overlapping Indigenous Land
Alto Alegre	Roraima	Garimpo	2021	5756	22.46%	Yanomami
Itaituba	Pará	Garimpo	2021	5459	21.31%	Mundurukú, Kayapó
Jacareacanga	Pará	Garimpo	2021	3736	14.58%	Mundurukú, Kayabi, Sai Cinza, Kayapó
Pontes e Lacerda	Mato Grosso	Garimpo	2021	3144	12.27%	Chikitano
Maués	Amazonas	Garimpo	2021	1939	7.57%	Andira-Marau
Mucajá	Roraima	Garimpo	2021	1549	6.05%	Yanomami
Aripuanã	Mato Grosso	Garimpo	2021	929	3.63%	Aripuanã, Arara do Rio Branco
Calçoene	Amapá	Garimpo	2021	635	2.48%	None
Pedra Branca do Amapari	Amapá	Garimpo	2021	487	1.90%	Waiãpi
Almeirim	Roraima	Garimpo	2021	434	1.69%	Yanomami
Colíza	Pará	Garimpo	2021	327	1.28%	Parque do Tumucumaque, Rio Paru D'Esse
Japurá	Mato Grosso	Garimpo	2021	135	0.53%	Piripkura, Kawahiva do Rio Pardo, Arara do Rio Branco
Olapoque	Amazonas	Garimpo	2021	109	0.43%	Alto e Médio Rio Negro
Atamanira	Amapá	Garimpo	2021	106	0.41%	Laçá
			Total	106	97.02%	Kayapó
Municipality of infection	State	Locality type	Year	Cases	% total	Overlapping Indigenous Land
Barcelos	Amazonas	Indigenous	2021	8792	16.79%	Yanomami, Jurubaxi-ia
São Gabriel da Cachoeira	Amazonas	Indigenous	2021	6581	12.57%	Yanomami, Alto e Médio Rio Negro
Alto Alegre	Roraima	Indigenous	2021	5274	10.07%	Yanomami
Jacareacanga	Pará	Indigenous	2021	5169	9.87%	Mundurukú, Kayabi, Sai Cinza, Kayapó
Anajari	Roraima	Indigenous	2021	4042	7.72%	Yanomami
Santa Isabel do Rio Negro	Amazonas	Indigenous	2021	2643	5.05%	Yanomami, Uteuxi, Jurubaxi-ia, Médio Rio Negro
Itacema	Roraima	Indigenous	2021	1494	2.85%	Yanomami
Guajará-Mirim	Rondônia	Indigenous	2021	1471	2.81%	Rio Negro Ocaia, Rio Guaporé, Pacaas Novas, Uru-Eu-Wau-Wau
Atalaia do Norte	Amazonas	Indigenous	2021	1422	2.72%	Vale do Javari
Caracará	Roraima	Indigenous	2021	1316	2.51%	Yanomami
Tapauá	Amazonas	Indigenous	2021	1146	2.19%	Paumari do Lago Paricá, Apuriná do Igarapé São João, Deni, Banawá, Hi Merimã
Pacaraima	Roraima	Indigenous	2021	913	1.74%	São Marcos
Mucajá	Roraima	Indigenous	2021	818	1.56%	Yanomami
Uiramutã	Roraima	Indigenous	2021	777	1.48%	Raposa Serra do Sol
Japurá	Amazonas	Indigenous	2021	694	1.33%	Alto e Médio Rio Negro
			Total	777	81.26%	

Table B.5. Top 15 municipalities with the most cases in each locality type, rural, settlement project, and urban.

Municipality of infection	State	Locality type	Year	Cases	Percent of total
Porto Velho	Rondônia	Rural	2021	6395	10.92%
Manaus	Amazonas	Rural	2021	4493	7.67%
Cruzeiro do Sul	Acre	Rural	2021	3615	6.17%
Tefé	Amazonas	Rural	2021	2272	3.88%
Canutama	Amazonas	Rural	2021	2112	3.61%
Coari	Amazonas	Rural	2021	2027	3.46%
Guajará	Amazonas	Rural	2021	2006	3.42%
Anajás	Pará	Rural	2021	1989	3.40%
São Gabriel da Cachoeira	Amazonas	Rural	2021	1764	3.01%
Rodrigues Alves	Acre	Rural	2021	1704	2.91%
Carauari	Amazonas	Rural	2021	1515	2.59%
Candeias do Jamari	Rondônia	Rural	2021	1316	2.25%
Tapauá	Amazonas	Rural	2021	1271	2.17%
Humaitá	Amazonas	Rural	2021	1092	1.86%
Porto Grande	Amapá	Rural	2021	1074	1.83%

Municipality of infection	State	Locality type	Year	Cases	Percent of total
Candeias do Jamari	Rondônia	Settlement project	2021	927	10.07%
Tefé	Amazonas	Settlement project	2021	859	9.33%
Manicoré	Amazonas	Settlement project	2021	850	9.23%
Porto Velho	Rondônia	Settlement project	2021	790	8.58%
São Gabriel da Cachoeira	Amazonas	Settlement project	2021	605	6.57%
Lábrea	Amazonas	Settlement project	2021	520	5.65%
Cruzeiro do Sul	Acre	Settlement project	2021	500	5.43%
Caroebe	Roraima	Settlement project	2021	359	3.90%
Manaus	Amazonas	Settlement project	2021	300	3.26%
Iracema	Roraima	Settlement project	2021	236	2.56%
Humaitá	Amazonas	Settlement project	2021	231	2.51%
Maués	Amazonas	Settlement project	2021	223	2.42%
Apuí	Amazonas	Settlement project	2021	221	2.40%
Alto Alegre	Roraima	Settlement project	2021	200	2.17%
Jutaí	Amazonas	Settlement project	2021	188	2.04%

Municipality of infection	State	Locality type	Year	Cases	Percent of total
Barcelos	Amazonas	Urban	2021	2851	20.77%
São Gabriel da Cachoeira	Amazonas	Urban	2021	2046	14.90%
Porto Velho	Rondônia	Urban	2021	1916	13.96%
Cruzeiro do Sul	Acre	Urban	2021	942	6.86%
Tapauá	Amazonas	Urban	2021	554	4.04%
Carauari	Amazonas	Urban	2021	458	3.34%
Candeias do Jamari	Rondônia	Urban	2021	457	3.33%
Mâncio Lima	Acre	Urban	2021	378	2.75%
Tefé	Amazonas	Urban	2021	337	2.46%
Manaus	Amazonas	Urban	2021	286	2.08%
Ipixuna	Amazonas	Urban	2021	207	1.51%
São João da Baliza	Roraima	Urban	2021	205	1.49%
Boa Vista	Roraima	Urban	2021	203	1.48%
Jacareacanga	Pará	Urban	2021	183	1.33%
Japurá	Amazonas	Urban	2021	175	1.27%

Table B.6. Pearson correlation of annual and monthly deforestation with malaria cases, by state and for the whole Amazon.

Annual Df x Cases				Monthly Df x Cases		
State	Correlation	P-value		State	Correlation	P-value
RO	0.500*	0.004		RO	0.408*	<0.001
AC	-0.255	0.159		AC	-0.252*	<0.001
AM	-0.070	0.702		AM	0.196*	0.003
RR	0.113	0.539		RR	0.102	0.125
PA	0.514*	0.003		PA	0.348*	<0.001
AP	-0.094	0.608		AP	0.396*	<0.001
TO	0.874*	<0.001		TO	0.462*	<0.001
MA	0.587*	<0.001		MA	0.690*	<0.001
MT	0.159	0.384		MT	0.463*	<0.001
Whole Amazon	0.618*	<0.001		Whole Amazon	0.458*	<0.001

Table B.7. Results from whole-Amazon Bayesian spatiotemporal model. LCI = lower bound of 95% credible interval, UCI = upper bound of 95% credible interval, RR = median of posterior.

Global Model - Outcome: Monthly Cases by Infection Municipality			
Variable	LCI	RR	UCI
Intercept	1.321277237	2.918628084	7.905275654
Deforestation rate (1-month lag)	1.061879428	1.063074858	1.064271642
Ratio imported : local cases	1.001162577	1.00168991	1.002217522
Area of municipality	1.181606028	1.378472895	1.609415403
% municipality in conservation land	1.200564036	1.351061409	1.521225118
% cases in garimpo localities	1.106082484	1.107561102	1.109041697
% cases in indigenous localities	1.058750254	1.060434914	1.062122253
% cases in settlement localities	1.050053587	1.051675044	1.053299004
% cases in rural localities	1.020520631	1.023341594	1.02617035
Population	0.698316064	0.699864033	0.701415432
Km non-paved roads	0.952403543	1.113357378	1.302246421
Km paved roads	1.189459971	1.39359839	1.634046855

Table B.8. Coefficient for 1-month lagged deforestation rate by model specification described in Table 1. LCI = lower bound of 95% credible interval, UCI = upper bound of 95% credible interval, RR = median of posterior.

Deforestation Rate (1-month lag)			
Model Formulation (Key in Table S6)	LCI	RR	UCI
M1	1.052114	1.053306	1.054499
M2	1.052094	1.053286	1.054479
M3	1.062589	1.063788	1.064988
M4	1.061878	1.063073	1.06427
M5	1.061879	1.063075	1.064272
M6	1.061888	1.063084	1.064281
M7	1.061879	1.063075	1.064272
M8	NA	NA	NA
M9	1.055995	1.05728	1.058566

Table B.9. Results from state-specific Bayesian spatiotemporal model. LCI = lower bound of 95% credible interval, UCI = upper bound of 95% credible interval, RR = median of posterior.

Variable	RO			AC			AM			RR		
	LCI	RR	UCI	LCI	RR	UCI	LCI	RR	UCI	LCI	RR	UCI
Intercept	12.502	14.799	17.421	1.986	3.036	4.679	26.447	39.662	58.553	25.938	42.976	71.302
% deforestation 1m lag	1.071	1.074	1.077	1.214	1.222	1.230	1.027	1.029	1.030	0.952	0.958	0.964
Mun. area	0.902	1.480	2.438	0.248	0.719	1.656	1.309	1.897	2.752	0.583	1.323	3.006
% mun in conservation unit	0.844	1.228	1.797	0.508	1.042	2.095	0.856	1.212	1.708	0.512	1.170	2.677
mun population	1.284	1.293	1.301	0.198	0.208	0.218	0.560	0.563	0.565	0.704	0.722	0.741
imported : local cases	1.003	1.006	1.009	1.012	1.017	1.021	0.995	0.997	0.998	0.969	0.972	0.975
% cases in garimpo locality	1.107	1.111	1.115	NA	NA	NA	0.955	0.957	0.960	1.187	1.191	1.195
% cases in settlement locality	1.130	1.138	1.146	0.918	0.929	0.939	0.928	0.931	0.934	1.027	1.040	1.053
% cases in rural locality	0.925	0.935	0.945	0.886	0.898	0.909	0.712	0.716	0.719	1.053	1.065	1.078
% cases in indigenous locality	1.107	1.114	1.120	0.820	0.829	0.838	0.918	0.922	0.925	1.402	1.425	1.447
km2 unpaved roads	0.835	1.113	1.492	1.363	3.218	6.121	0.610	0.962	1.512	0.720	1.229	2.099
km2 paved roads	0.552	0.844	1.291	1.689	4.149	12.709	2.414	3.489	5.030	0.641	1.118	1.949

Variable	PA			AP			MA			MT		
	LCI	RR	UCI	LCI	RR	UCI	LCI	RR	UCI	LCI	RR	UCI
Intercept	3.211	5.698	9.953	6.119	17.775	52.828	0.242	0.591	1.464	0.402	0.647	1.036
% deforestation 1m lag	1.049	1.052	1.054	0.986	0.991	0.996	0.990	1.005	1.020	1.089	1.098	1.108
Mun. area	0.834	1.622	3.159	0.458	1.445	4.555	0.927	1.224	1.614	2.108	3.434	5.681
% mun in conservation unit	1.047	1.806	3.086	0.416	1.445	5.015	0.909	1.233	1.680	0.805	1.126	1.574
mun population	0.115	0.119	0.123	1.404	1.439	1.475	1.285	1.530	1.833	0.609	0.661	0.716
imported : local cases	1.007	1.008	1.009	0.993	0.996	0.999	0.992	0.994	0.997	0.999	1.001	1.002
% cases in garimpo locality	1.111	1.116	1.120	0.946	0.956	0.967	1.009	1.020	1.032	1.260	1.267	1.273
% cases in settlement locality	1.171	1.174	1.177	0.980	0.987	0.994	1.094	1.103	1.113	1.050	1.057	1.064
% cases in rural locality	1.287	1.295	1.303	0.982	0.994	1.007	1.226	1.245	1.264	1.118	1.129	1.140
% cases in indigenous locality	0.972	0.976	0.979	1.063	1.070	1.078	1.099	1.108	1.117	1.144	1.154	1.163
km2 unpaved roads	0.715	1.266	2.246	0.705	1.914	5.197	0.914	1.195	1.565	0.374	0.589	0.923
km2 paved roads	0.685	1.289	2.418	0.459	1.236	3.331	0.832	1.017	1.243	0.632	0.946	1.420

Figure B.1. Partial cross-correlation between deforestation and malaria cases at lags of 1-24 months.

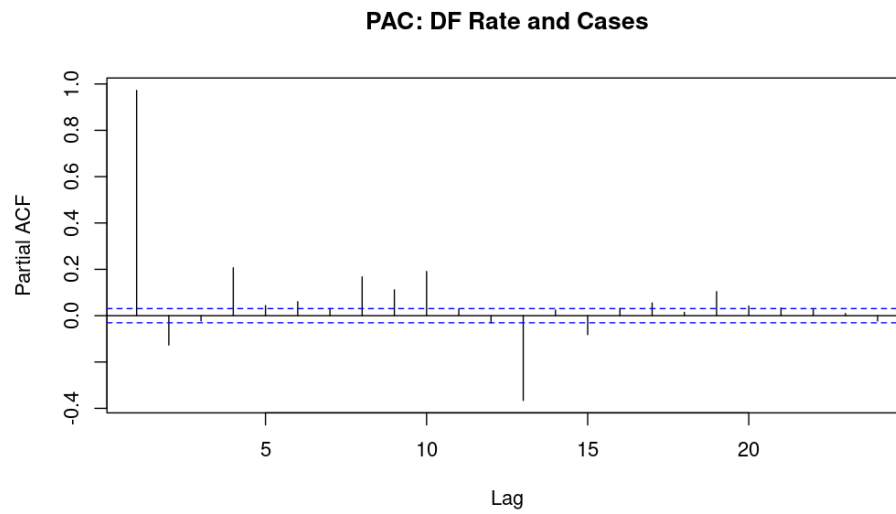


Figure B.2. Partial cross-correlation between deforestation and malaria cases at lags of 1-24 months, by state. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima, PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

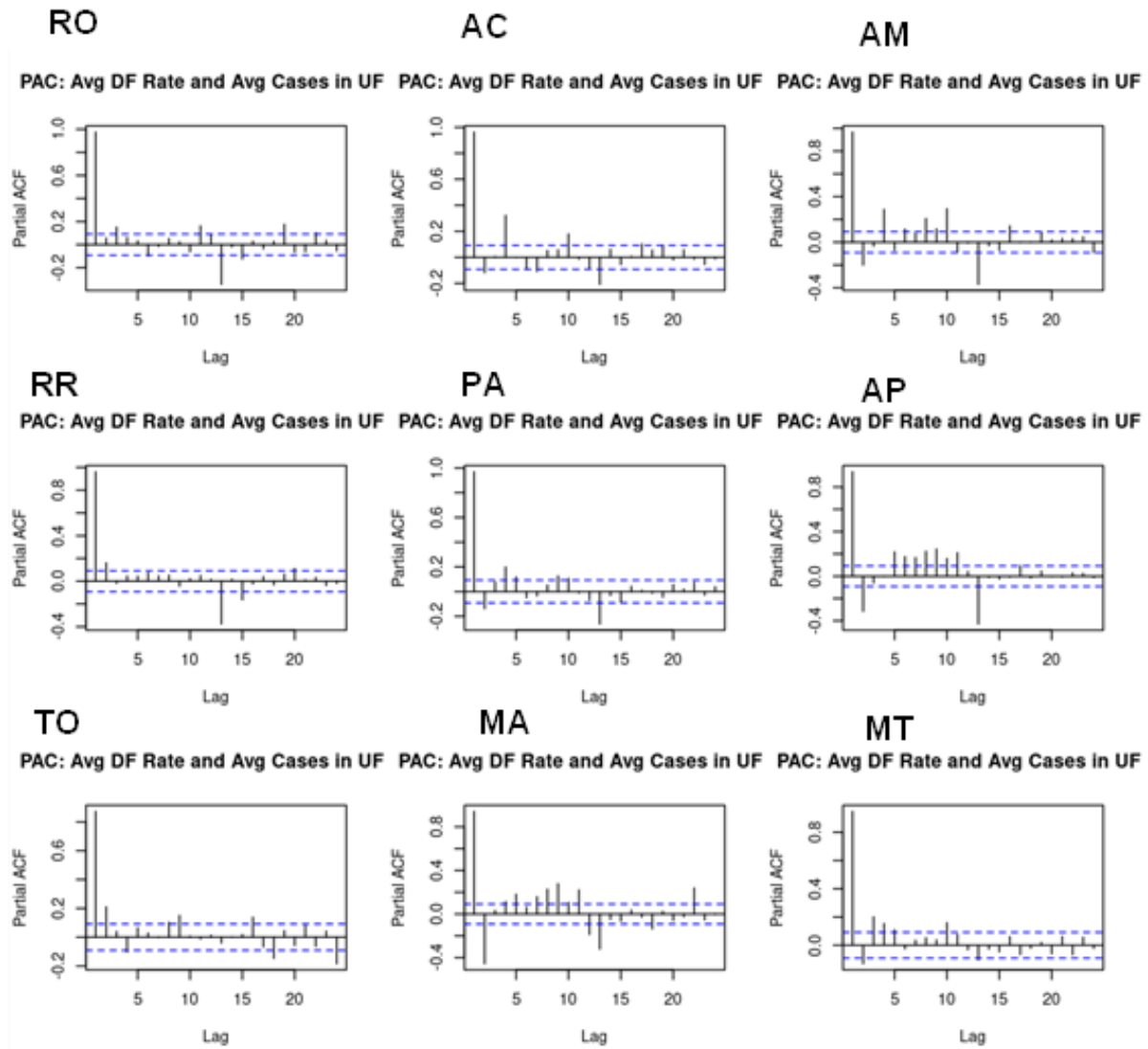


Figure B.3. Seasonal component to time series decomposition for each state. Deforestation: Red. Malaria cases: Black. State code: 11 = Rondônia, 12 = Acre, 13 = Amazonas, 14 = Roraima, 15 = Pará, 16 = Amapá, 17 = Tocantins, 21 = Maranhão, and 51 = Mato Grosso.

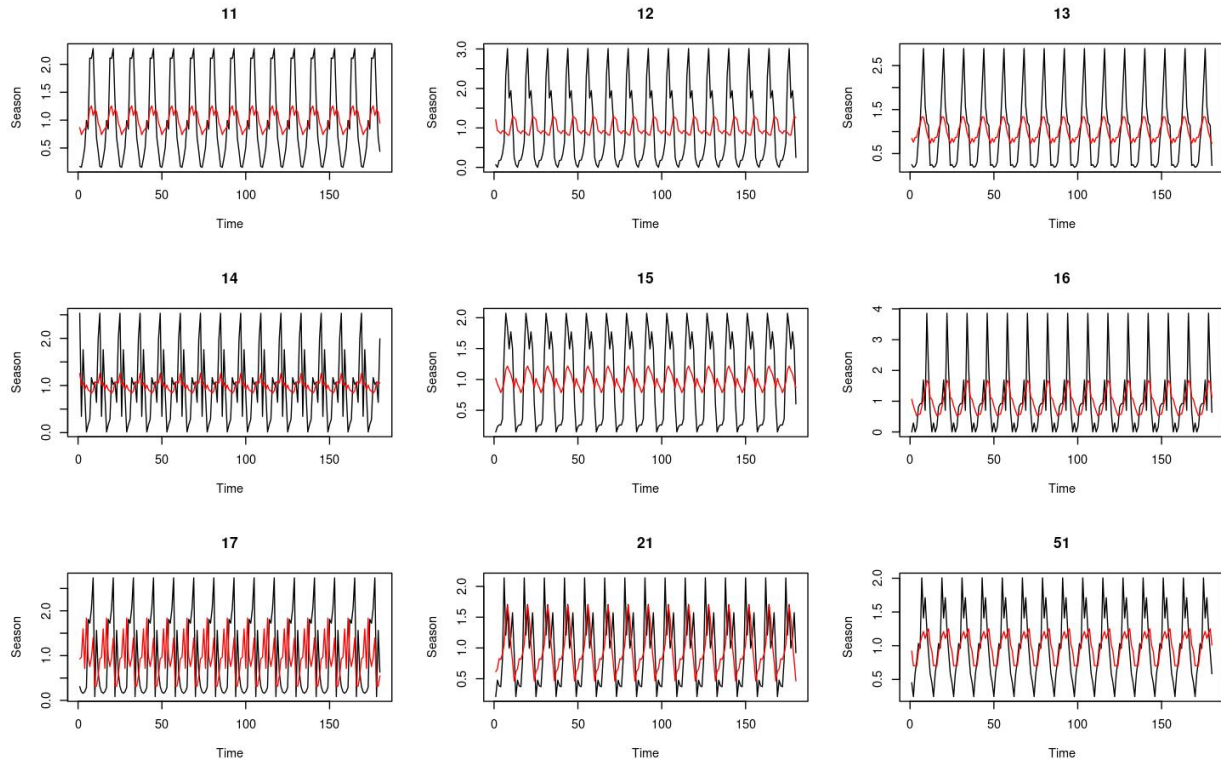
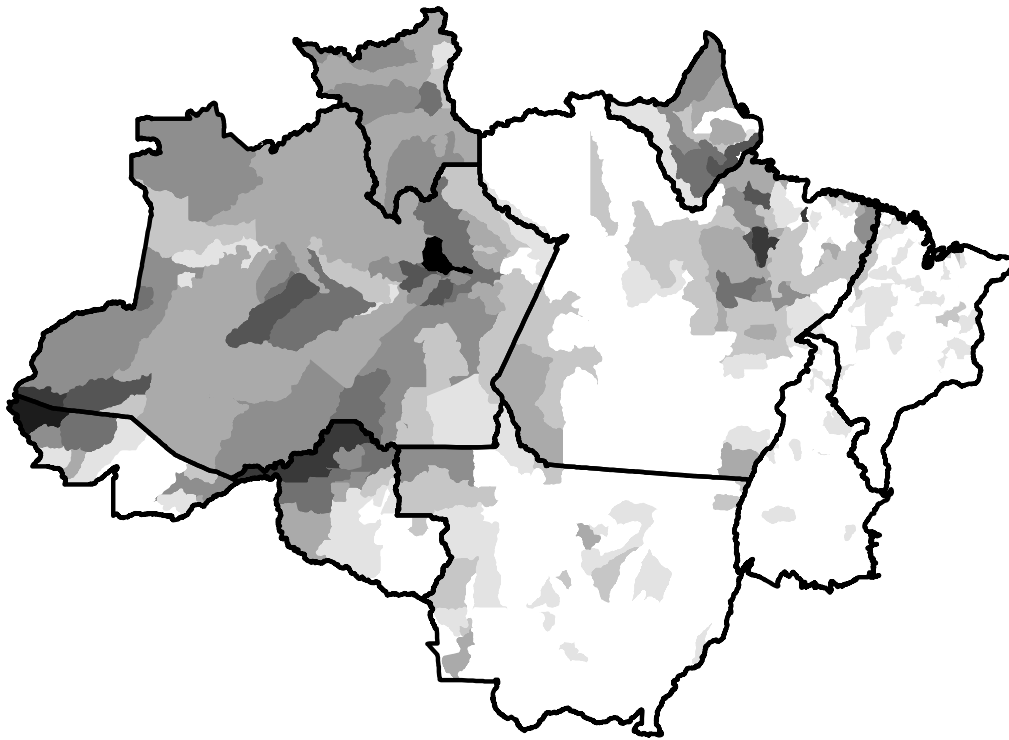


Figure B.4. Spatial residuals from 1-month lagged global Bayesian spatiotemporal model.



Appendix C

Chapter IV supplementary materials

Table C.1. Coefficients for whole-Amazon case crossover model, averaged over lags. All exposures.

Weekly total precipitation (m)	RR	LCI	UCI	Weekly mean diurnal variation (°C)	RR	LCI	UCI
0.00	1.033	1.020	1.046	1.18	1.461	1.306	1.635
0.05	1.001	0.999	1.003	2.18	1.360	1.251	1.478
0.10	1.006	0.996	1.015	3.18	1.269	1.199	1.342
0.15	0.996	0.984	1.008	4.18	1.189	1.149	1.229
0.20	1.005	0.989	1.021	5.18	1.121	1.101	1.140
0.25	1.035	1.011	1.059	6.18	1.066	1.056	1.076
0.30	1.086	1.047	1.126	7.18	1.024	1.020	1.028
0.35	1.160	1.097	1.226	8.18	0.976	0.974	0.978
0.40	1.259	1.162	1.364	9.18	0.911	0.905	0.918
0.45	1.388	1.244	1.549	10.18	0.849	0.839	0.858
				11.18	0.791	0.780	0.803
				12.18	0.738	0.725	0.751
Weekly mean temperature (°C)	RR	LCI	UCI				
23.85	0.758	0.745	0.770	13.18	0.689	0.673	0.704
24.85	0.863	0.855	0.871	14.18	0.643	0.624	0.662
25.85	0.962	0.958	0.965	15.18	0.600	0.578	0.623
26.85	1.025	1.021	1.028	16.18	0.560	0.534	0.588
27.85	1.045	1.036	1.055	17.18	0.523	0.493	0.555
28.85	1.049	1.034	1.064	18.18	0.489	0.455	0.525
29.85	1.040	1.016	1.064	19.18	0.456	0.420	0.496
30.85	1.022	0.984	1.061				
31.85	1.000	0.947	1.056				

Table C.2. Coefficients for whole-Amazon case crossover model using the exposure of mean temperature, specific to each lag.

Lag	Temperature (°C)	RR	LCI	UCI
1 week	23.85	1.146	1.134	1.157
1 week	24.85	1.069	1.062	1.076
1 week	25.85	1.017	1.014	1.019
1 week	26.85	0.986	0.983	0.988
1 week	27.85	0.973	0.966	0.980
1 week	28.85	0.975	0.964	0.987
1 week	29.85	0.990	0.971	1.010
1 week	30.85	1.014	0.982	1.047
1 week	31.85	1.043	0.996	1.093
2 week	23.85	0.777	0.761	0.794
2 week	24.85	0.880	0.869	0.891
2 week	25.85	0.963	0.959	0.967
2 week	26.85	1.059	1.054	1.065
2 week	27.85	1.189	1.173	1.204
2 week	28.85	1.318	1.289	1.348
2 week	29.85	1.448	1.391	1.507
2 week	30.85	1.580	1.481	1.686
2 week	31.85	1.718	1.565	1.887
3 week	23.85	0.851	0.830	0.872
3 week	24.85	0.918	0.906	0.930
3 week	25.85	0.982	0.977	0.987
3 week	26.85	0.982	0.977	0.987
3 week	27.85	0.904	0.892	0.916
3 week	28.85	0.816	0.797	0.835
3 week	29.85	0.725	0.696	0.756
3 week	30.85	0.638	0.596	0.682
3 week	31.85	0.558	0.506	0.614

Table C.3. Coefficients for whole-Amazon case crossover model using the exposure of total precipitation, specific to each lag.

Lag	Precipitation (m)	RR	LCI	UCI
1 week	0	1.016	1.008	1.025
1 week	0.05	1.000	0.999	1.002
1 week	0.1	0.991	0.985	0.997
1 week	0.15	0.969	0.959	0.978
1 week	0.2	0.963	0.949	0.977
1 week	0.25	0.973	0.951	0.996
1 week	0.3	1.000	0.964	1.039
1 week	0.35	1.044	0.985	1.107
1 week	0.4	1.105	1.015	1.203
1 week	0.45	1.186	1.055	1.332
2 week	0	0.961	0.949	0.974
2 week	0.05	1.005	1.003	1.007
2 week	0.1	1.020	1.011	1.028
2 week	0.15	1.032	1.020	1.043
2 week	0.2	1.047	1.032	1.062
2 week	0.25	1.066	1.048	1.084
2 week	0.3	1.088	1.066	1.110
2 week	0.35	1.113	1.085	1.142
2 week	0.4	1.142	1.104	1.181
2 week	0.45	1.174	1.124	1.227
3 week	0	1.057	1.042	1.073
3 week	0.05	0.996	0.994	0.998
3 week	0.1	0.995	0.986	1.003
3 week	0.15	0.996	0.985	1.007
3 week	0.2	0.997	0.983	1.010
3 week	0.25	0.997	0.982	1.013
3 week	0.3	0.998	0.980	1.015
3 week	0.35	0.998	0.978	1.017
3 week	0.4	0.997	0.976	1.020
3 week	0.45	0.997	0.972	1.022

Table C.4. Coefficients for whole-Amazon case crossover model using the exposure of diurnal variation, specific to each lag.

Lag	Diurnal variation (°C)	RR	LCI	UCI
1 week	1.175	0.903	0.848	0.961
1 week	3.175	0.944	0.915	0.974
1 week	5.175	0.979	0.969	0.989
1 week	7.175	0.997	0.995	1.000
1 week	9.175	1.015	1.009	1.020
1 week	11.175	1.057	1.045	1.068
1 week	13.175	1.122	1.103	1.141
1 week	15.175	1.208	1.175	1.242
1 week	17.175	1.314	1.259	1.372
1 week	19.175	1.436	1.351	1.526
2 week	1.175	0.966	0.851	1.097
2 week	3.175	1.000	0.938	1.066
2 week	5.175	1.020	0.999	1.041
2 week	7.175	1.010	1.006	1.015
2 week	9.175	0.968	0.958	0.977
2 week	11.175	0.956	0.937	0.976
2 week	13.175	0.984	0.952	1.017
2 week	15.175	1.043	0.986	1.104
2 week	17.175	1.129	1.033	1.233
2 week	19.175	1.234	1.090	1.397
3 week	1.175	1.677	1.437	1.956
3 week	3.175	1.345	1.244	1.453
3 week	5.175	1.123	1.096	1.151
3 week	7.175	1.017	1.011	1.022
3 week	9.175	0.928	0.918	0.938
3 week	11.175	0.783	0.766	0.800
3 week	13.175	0.624	0.603	0.646
3 week	15.175	0.476	0.449	0.504
3 week	17.175	0.353	0.323	0.386
3 week	19.175	0.258	0.227	0.292

Table C.5. Coefficients for state-stratified case crossover model using the exposure of mean temperature, averaged over lags. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima, PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

Temperature (°C)	RR	LCI	UCI	Temperature (°C)	RR	LCI	UCI
RO				PA			
23.470	0.703	0.672	0.735	24.533	0.818	0.781	0.856
24.470	0.802	0.785	0.820	25.533	0.916	0.895	0.936
25.470	0.920	0.911	0.930	26.533	0.988	0.982	0.994
26.470	1.039	1.032	1.045	27.533	0.991	0.982	1.000
27.470	1.124	1.102	1.146	28.533	0.961	0.939	0.983
28.470	1.206	1.170	1.244	29.533	0.945	0.911	0.979
AC				AP			
23.145	0.659	0.622	0.697	24.555	0.786	0.719	0.859
24.145	0.850	0.826	0.873	25.555	0.900	0.856	0.947
25.145	0.969	0.954	0.984	26.555	0.981	0.969	0.993
26.145	1.045	1.037	1.053	27.555	1.034	1.007	1.062
27.145	1.177	1.147	1.208	28.555	1.063	1.000	1.131
AM				29.555	1.066	0.962	1.180
24.268	0.778	0.757	0.799	MA			
25.268	0.929	0.918	0.941	25.105	0.813	0.669	0.987
26.268	1.000	1.000	1.000	26.105	1.087	1.010	1.170
27.268	1.027	1.015	1.038	27.105	1.011	0.979	1.045
28.268	1.029	1.010	1.049	28.105	1.097	0.971	1.239
RR				29.105	1.071	0.877	1.307
22.761	1.030	0.911	1.165	MT			
23.761	1.011	0.936	1.092	23.480	0.792	0.688	0.913
24.761	0.998	0.953	1.044	24.480	0.869	0.797	0.947
25.761	0.994	0.982	1.005	25.480	0.954	0.927	0.982
26.761	1.029	1.008	1.050	26.480	1.068	1.036	1.101
27.761	1.063	1.014	1.115	27.480	1.166	1.075	1.265
28.761	1.058	0.986	1.134	28.480	1.193	1.063	1.340
29.761	1.021	0.923	1.130	29.480	1.161	0.991	1.360

Table C.6. Coefficients for state-stratified case crossover model using the exposure of total precipitation, averaged over lags. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima, PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

Precipitation (meters)	RR	LCI	UCI	Precipitation (meters)	RR	LCI	UCI
RO				PA			
0	1.063	1.032	1.094	0	1.031	1.007	1.056
0.05	1.023	1.014	1.032	0.05	1.002	0.993	1.011
0.1	1.064	1.035	1.093	0.1	1.001	0.981	1.021
0.15	1.022	0.966	1.081	0.15	0.997	0.974	1.021
AC				0.2	1.009	0.979	1.039
0	0.950	0.900	1.002	0.25	1.036	0.998	1.077
0.05	1.008	1.000	1.016	0.3	1.080	1.025	1.137
0.1	1.006	0.969	1.043	0.35	1.139	1.059	1.226
0.15	1.031	0.971	1.094	AP			
AM				0	1.139	1.077	1.205
0	0.979	0.952	1.006	0.05	1.014	0.974	1.055
0.05	1.000	0.999	1.001	0.1	1.040	0.984	1.099
0.1	0.980	0.965	0.996	0.15	1.068	1.000	1.140
0.15	0.966	0.946	0.986	0.2	1.106	1.023	1.196
0.2	0.959	0.932	0.988	0.25	1.154	1.046	1.274
0.25	0.960	0.915	1.007	0.3	1.213	1.063	1.385
RR				0.35	1.283	1.071	1.538
0	0.931	0.880	0.985	MA			
0.05	1.014	1.004	1.024	0	0.750	0.653	0.862
0.1	1.032	0.994	1.072	0.05	0.877	0.800	0.962
0.15	1.032	0.982	1.085	0.1	0.879	0.777	0.993
0.2	1.053	0.988	1.122	0.15	0.914	0.786	1.062
0.25	1.095	0.996	1.204	0.2	0.945	0.787	1.134
				0.25	0.971	0.770	1.225
				0.3	0.993	0.726	1.358
				0.35	1.010	0.657	1.552
				MT			
				0	0.857	0.772	0.951
				0.05	0.940	0.901	0.982
				0.1	0.850	0.771	0.938
				0.15	0.756	0.646	0.884
				0.2	0.603	0.447	0.813

Table C.7. Coefficients for state-stratified case crossover model using the exposure of diurnal variation, averaged over lags. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima, PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

Diurnal variation (°C)	RR	LCI	UCI	Diurnal variation (°C)	RR	LCI	UCI
RO				PA			
5.348	1.232	1.174	1.293	4.521	1.252	1.176	1.333
6.348	1.072	1.048	1.097	5.521	1.176	1.134	1.220
7.348	1.013	1.002	1.023	6.521	1.107	1.083	1.131
8.348	0.985	0.980	0.989	7.521	1.044	1.034	1.054
9.348	0.916	0.901	0.931	8.521	0.983	0.980	0.987
10.348	0.840	0.818	0.864	9.521	0.926	0.912	0.941
11.348	0.778	0.750	0.807	10.521	0.879	0.857	0.902
12.348	0.726	0.694	0.758	11.521	0.841	0.813	0.870
13.348	0.682	0.648	0.719	12.521	0.810	0.773	0.848
14.348	0.646	0.607	0.687	AP			
AC				4.746	1.066	0.957	1.187
6.090	1.075	1.011	1.142	5.746	1.021	0.944	1.104
7.090	1.025	1.002	1.049	6.746	0.993	0.936	1.053
8.090	1.007	1.000	1.013	7.746	0.986	0.952	1.021
9.090	0.960	0.951	0.970	8.746	0.997	0.991	1.003
10.090	0.888	0.867	0.909	9.746	1.010	0.989	1.033
11.090	0.826	0.799	0.854	10.746	1.013	0.963	1.066
12.090	0.773	0.739	0.808	11.746	0.996	0.927	1.070
13.090	0.726	0.683	0.772	12.746	0.964	0.877	1.059
AM				MA			
4.897	1.055	1.024	1.087	2.635	1.930	1.196	3.115
5.897	1.043	1.028	1.057	3.635	1.690	1.205	2.371
6.897	1.014	1.010	1.018	4.635	1.477	1.164	1.874
7.897	0.966	0.960	0.973	5.635	1.288	1.091	1.520
8.897	0.903	0.889	0.917	6.635	1.121	1.031	1.218
9.897	0.830	0.812	0.849	7.635	1.003	1.000	1.006
10.897	0.753	0.729	0.776	8.635	0.947	0.885	1.012
RR				9.635	0.851	0.751	0.965
5.082	1.019	0.937	1.108	10.635	0.706	0.592	0.842
6.082	1.018	0.974	1.064	11.635	0.547	0.425	0.705
7.082	1.012	0.993	1.031	MT			
8.082	0.982	0.971	0.994	5.131	0.941	0.788	1.124
9.082	0.933	0.897	0.970	6.131	1.025	0.929	1.130
10.082	0.895	0.844	0.949	7.131	1.051	0.992	1.114
11.082	0.866	0.794	0.945	8.131	1.009	1.002	1.016
				9.131	0.943	0.908	0.979
				10.131	0.873	0.804	0.948
				11.131	0.803	0.710	0.908
				12.131	0.733	0.628	0.856
				13.131	0.667	0.554	0.802
				14.131	0.604	0.482	0.755

Table C.8. Coefficients for state-stratified case crossover model using the exposure of mean temperature, specific to each lag. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima, PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

Lag	Temperature (°C)	RR	LCI	UCI	Lag	Temperature (°C)	RR	LCI	UCI
RO					PA				
1 week	23.480	1.190	1.165	1.215	1 week	24.543	0.937	0.904	0.971
1 week	24.480	1.080	1.064	1.096	1 week	25.543	0.990	0.971	1.009
1 week	25.480	1.019	1.012	1.026	1 week	26.543	1.000	0.995	1.005
1 week	26.480	0.985	0.981	0.990	1 week	27.543	1.016	1.007	1.025
1 week	27.480	0.950	0.937	0.963	1 week	28.543	1.033	1.011	1.055
1 week	28.480	0.929	0.909	0.949	1 week	29.543	1.011	0.977	1.047
2 week	23.480	0.679	0.647	0.712	2 week	24.543	1.155	1.076	1.239
2 week	24.480	0.832	0.809	0.855	2 week	25.543	1.020	0.984	1.057
2 week	25.480	0.950	0.938	0.962	2 week	26.543	0.992	0.983	1.002
2 week	26.480	1.046	1.038	1.053	2 week	27.543	1.009	0.993	1.026
2 week	27.480	1.189	1.162	1.217	2 week	28.543	1.087	1.045	1.130
2 week	28.480	1.342	1.288	1.398	2 week	29.543	1.293	1.210	1.383
3 week	23.480	0.871	0.819	0.925	3 week	24.543	0.756	0.702	0.815
3 week	24.480	0.893	0.866	0.921	3 week	25.543	0.907	0.875	0.940
3 week	25.480	0.952	0.938	0.965	3 week	26.543	0.996	0.986	1.006
3 week	26.480	1.008	1.000	1.017	3 week	27.543	0.966	0.951	0.982
3 week	27.480	0.995	0.970	1.020	3 week	28.543	0.856	0.824	0.889
3 week	28.480	0.968	0.925	1.013	3 week	29.543	0.722	0.677	0.771
AC					AP				
1 week	23.155	1.212	1.181	1.244	1 week	24.565	1.143	1.065	1.226
1 week	24.155	1.103	1.083	1.124	1 week	25.565	1.091	1.045	1.139
1 week	25.155	1.031	1.022	1.040	1 week	26.565	1.020	1.009	1.032
1 week	26.155	0.988	0.983	0.993	1 week	27.565	0.975	0.950	1.001
1 week	27.155	0.954	0.937	0.971	1 week	28.565	0.979	0.923	1.038
2 week	23.155	0.693	0.653	0.735	1 week	29.565	1.020	0.932	1.117
2 week	24.155	0.812	0.785	0.840	2 week	24.565	1.115	0.974	1.275
2 week	25.155	0.925	0.909	0.942	2 week	25.565	1.015	0.938	1.098
2 week	26.155	1.042	1.033	1.050	2 week	26.565	0.985	0.965	1.006
2 week	27.155	1.218	1.182	1.254	2 week	27.565	1.065	1.014	1.118
3 week	23.155	0.784	0.727	0.846	2 week	28.565	1.017	0.909	1.138
3 week	24.155	0.949	0.913	0.985	2 week	29.565	0.728	0.608	0.870
3 week	25.155	1.016	0.996	1.036	3 week	24.565	0.617	0.536	0.711
3 week	26.155	1.015	1.006	1.025	3 week	25.565	0.813	0.751	0.880
3 week	27.155	1.014	0.979	1.049	3 week	26.565	0.976	0.956	0.996
AM					3 week	27.565	0.996	0.952	1.042
1 week	24.278	1.087	1.070	1.104	3 week	28.565	1.068	0.961	1.188
1 week	25.278	1.038	1.028	1.047	3 week	29.565	1.436	1.205	1.710
1 week	26.278	1.000	1.000	1.000	MA				
1 week	27.278	0.979	0.971	0.987	1 week	25.115	1.171	1.019	1.345
1 week	28.278	0.992	0.978	1.006	1 week	26.115	1.035	0.974	1.099
2 week	24.278	0.864	0.837	0.893	1 week	27.115	0.990	0.962	1.019
2 week	25.278	0.933	0.918	0.949	1 week	28.115	1.042	0.935	1.161
2 week	26.278	1.001	1.000	1.001	1 week	29.115	1.254	1.040	1.511
2 week	27.278	1.107	1.090	1.124	2 week	25.115	1.029	0.789	1.343
2 week	28.278	1.224	1.191	1.258	2 week	26.115	0.942	0.847	1.047
3 week	24.278	0.828	0.797	0.860	2 week	27.115	1.024	0.971	1.080
3 week	25.278	0.960	0.943	0.977	2 week	28.115	1.071	0.875	1.312
3 week	26.278	1.000	1.000	1.000	2 week	29.115	1.112	0.770	1.607
3 week	27.278	0.947	0.932	0.962	3 week	25.115	0.675	0.506	0.900
3 week	28.278	0.848	0.824	0.873	3 week	26.115	1.116	1.001	1.243
RR					3 week	27.115	0.997	0.946	1.052
1 week	22.771	1.252	1.127	1.391	3 week	28.115	0.983	0.803	1.203
1 week	23.771	1.162	1.091	1.238	3 week	29.115	0.768	0.532	1.107
1 week	24.771	1.085	1.045	1.125	MT				
1 week	25.771	1.020	1.011	1.030	1 week	23.490	1.403	1.278	1.540
1 week	26.771	0.964	0.948	0.981	1 week	24.490	1.228	1.155	1.305
1 week	27.771	0.921	0.884	0.958	1 week	25.490	1.057	1.037	1.079
1 week	28.771	0.891	0.840	0.944	1 week	26.490	0.983	0.960	1.007
1 week	29.771	0.870	0.798	0.949	1 week	27.490	1.003	0.941	1.069
2 week	22.771	0.781	0.635	0.959	1 week	28.490	1.034	0.943	1.132
2 week	23.771	0.862	0.762	0.976	1 week	29.490	1.072	0.938	1.226
2 week	24.771	0.929	0.867	0.997	2 week	23.490	0.509	0.422	0.613
2 week	25.771	0.973	0.956	0.991	2 week	24.490	0.631	0.563	0.707
2 week	26.771	1.104	1.070	1.139	2 week	25.490	0.863	0.831	0.897
2 week	27.771	1.305	1.211	1.405	2 week	26.490	1.114	1.064	1.166
2 week	28.771	1.481	1.324	1.656	2 week	27.490	1.270	1.128	1.430
2 week	29.771	1.629	1.377	1.928	2 week	28.490	1.440	1.213	1.709
3 week	22.771	1.054	0.857	1.298	2 week	29.490	1.627	1.256	2.109
3 week	23.771	1.009	0.889	1.144	3 week	23.490	1.110	0.899	1.372
3 week	24.771	0.990	0.921	1.064	3 week	24.490	1.122	0.990	1.271
3 week	25.771	1.001	0.983	1.019	3 week	25.490	1.045	1.003	1.089
3 week	26.771	0.966	0.936	0.998	3 week	26.490	0.975	0.931	1.021
3 week	27.771	0.885	0.821	0.954	3 week	27.490	0.916	0.810	1.034
3 week	28.771	0.802	0.716	0.898	3 week	28.490	0.802	0.671	0.958
3 week	29.771	0.720	0.608	0.853	3 week	29.490	0.665	0.514	0.860

Table C.9. Coefficients for state-stratified case crossover model using the exposure of total precipitation, specific to each lag. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima, PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

Lag	Precipitation (m)	RR	LCI	UCI	Lag	Precipitation (m)	RR	LCI	UCI	Lag	Precipitation (m)	RR	LCI	UCI
RO					PA					MA				
1 week	0	1.037	1.014	1.061	1 week	0	0.992	0.975	1.008	1 week	0	0.886	0.824	0.953
1 week	0.05	1.006	1.000	1.012	1 week	0.05	1.007	1.000	1.013	1 week	0.05	0.953	0.893	1.017
1 week	0.1	0.988	0.968	1.008	1 week	0.1	1.007	0.991	1.022	1 week	0.1	0.978	0.881	1.086
1 week	0.15	0.921	0.875	0.970	1 week	0.15	1.001	0.981	1.022	1 week	0.15	1.029	0.897	1.182
2 week	0	1.021	0.988	1.054	1 week	0.2	1.008	0.981	1.035	1 week	0.2	1.088	0.919	1.289
2 week	0.05	1.007	0.999	1.016	1 week	0.25	1.027	0.991	1.064	1 week	0.25	1.156	0.926	1.444
2 week	0.1	1.025	0.998	1.052	1 week	0.3	1.059	1.006	1.115	1 week	0.3	1.234	0.899	1.693
2 week	0.15	1.031	0.994	1.069	1 week	0.35	1.103	1.023	1.190	1 week	0.35	1.321	0.839	2.081
3 week	0	1.004	0.971	1.037	2 week	0	1.005	0.981	1.030	2 week	0	1.263	1.125	1.419
3 week	0.05	1.009	1.001	1.017	2 week	0.05	1.000	0.991	1.008	2 week	0.05	0.915	0.842	0.994
3 week	0.1	1.050	1.024	1.077	2 week	0.1	1.007	0.986	1.028	2 week	0.1	0.879	0.773	1.001
3 week	0.15	1.076	1.038	1.115	2 week	0.15	1.019	0.991	1.047	2 week	0.15	0.855	0.720	1.015
AC					2 week	0.2	1.031	0.998	1.066	2 week	0.2	0.838	0.682	1.029
1 week	0	1.028	1.003	1.054	2 week	0.25	1.044	1.005	1.085	2 week	0.25	0.827	0.655	1.044
1 week	0.05	0.999	0.995	1.003	2 week	0.3	1.058	1.013	1.104	2 week	0.3	0.822	0.633	1.068
1 week	0.1	0.992	0.970	1.015	2 week	0.35	1.071	1.021	1.124	2 week	0.35	0.822	0.609	1.109
1 week	0.15	1.024	0.971	1.080	3 week	0	1.035	1.008	1.062	3 week	0	0.670	0.576	0.778
2 week	0	0.957	0.915	1.001	3 week	0.05	0.995	0.987	1.004	3 week	0.05	1.006	0.923	1.096
2 week	0.05	1.008	1.002	1.014	3 week	0.1	0.988	0.969	1.007	3 week	0.1	1.021	0.906	1.151
2 week	0.1	1.049	1.023	1.075	3 week	0.15	0.978	0.954	1.002	3 week	0.15	1.038	0.892	1.209
2 week	0.15	1.077	1.039	1.115	3 week	0.2	0.971	0.942	1.001	3 week	0.2	1.036	0.863	1.244
3 week	0	0.965	0.908	1.026	3 week	0.25	0.966	0.933	1.001	3 week	0.25	1.016	0.824	1.252
3 week	0.05	1.001	0.993	1.008	3 week	0.3	0.964	0.927	1.003	3 week	0.3	0.979	0.777	1.234
3 week	0.1	0.967	0.937	0.997	3 week	0.35	0.964	0.924	1.006	3 week	0.35	0.930	0.723	1.196
3 week	0.15	0.935	0.900	0.972	AP					MT				
AM					1 week	0	1.003	0.967	1.041	1 week	0	0.951	0.879	1.030
1 week	0	0.995	0.982	1.009	1 week	0.05	1.009	0.983	1.035	1 week	0.05	1.018	0.987	1.049
1 week	0.05	1.000	1.000	1.001	1 week	0.1	0.988	0.948	1.029	1 week	0.1	1.016	0.946	1.092
1 week	0.1	0.994	0.985	1.002	1 week	0.15	0.982	0.931	1.037	1 week	0.15	0.892	0.787	1.011
1 week	0.15	0.971	0.956	0.986	1 week	0.2	1.004	0.938	1.075	1 week	0.2	0.676	0.505	0.905
1 week	0.2	0.951	0.927	0.975	1 week	0.25	1.053	0.960	1.154	2 week	0	0.843	0.762	0.933
1 week	0.25	0.936	0.892	0.982	1 week	0.3	1.129	0.988	1.291	2 week	0.05	1.023	0.981	1.066
2 week	0	0.914	0.892	0.937	1 week	0.35	1.237	1.020	1.499	2 week	0.1	1.062	0.959	1.177
2 week	0.05	1.002	1.001	1.003	2 week	0	0.967	0.914	1.023	2 week	0.15	1.108	0.964	1.274
2 week	0.1	0.992	0.980	1.004	2 week	0.05	0.940	0.906	0.976	2 week	0.2	1.167	0.989	1.377
2 week	0.15	0.991	0.975	1.008	2 week	0.1	0.925	0.873	0.981	3 week	0	1.068	0.959	1.190
2 week	0.2	1.002	0.982	1.023	2 week	0.15	0.920	0.855	0.990	3 week	0.05	0.904	0.868	0.941
2 week	0.25	1.021	0.996	1.048	2 week	0.2	0.902	0.827	0.984	3 week	0.1	0.788	0.713	0.871
3 week	0	1.076	1.043	1.110	2 week	0.25	0.873	0.792	0.962	3 week	0.15	0.764	0.664	0.880
3 week	0.05	0.998	0.997	0.999	2 week	0.3	0.835	0.749	0.931	3 week	0.2	0.764	0.644	0.905
3 week	0.1	0.994	0.981	1.008	2 week	0.35	0.790	0.698	0.895					
3 week	0.15	1.003	0.985	1.021	3 week	0	1.174	1.099	1.253					
3 week	0.2	1.007	0.985	1.029	3 week	0.05	1.069	1.030	1.109					
3 week	0.25	1.004	0.979	1.029	3 week	0.1	1.138	1.077	1.203					
RR					3 week	0.15	1.182	1.103	1.266					
1 week	0	1.042	1.009	1.077	3 week	0.2	1.221	1.125	1.325					
1 week	0.05	0.999	0.992	1.006	3 week	0.25	1.256	1.145	1.377					
1 week	0.1	0.980	0.953	1.007	3 week	0.3	1.286	1.164	1.422					
1 week	0.15	0.932	0.892	0.973	3 week	0.35	1.313	1.179	1.462					
1 week	0.2	0.899	0.846	0.954										
1 week	0.25	0.880	0.799	0.968										
2 week	0	0.897	0.853	0.943										
2 week	0.05	1.016	1.008	1.025										
2 week	0.1	1.055	1.019	1.092										
2 week	0.15	1.092	1.039	1.148										
2 week	0.2	1.130	1.060	1.204										
2 week	0.25	1.169	1.084	1.261										
3 week	0	0.996	0.936	1.060										
3 week	0.05	0.999	0.990	1.008										
3 week	0.1	0.999	0.965	1.034										
3 week	0.15	1.015	0.969	1.062										
3 week	0.2	1.037	0.979	1.098										
3 week	0.25	1.065	0.996	1.139										

Table C.10. Coefficients for state-stratified case crossover model using the exposure of diurnal variation, specific to each lag. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima, PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

Lag	Diurnal variation (°C)	RR	LCI	UCI	Lag	Diurnal variation (°C)	RR	LCI	UCI	Lag	Diurnal variation (°C)	RR	LCI	UCI
RO					RR					MA				
1 week	5.348	0.997	0.973	1.021	1 week	5.082	0.952	0.904	1.002	1 week	2.635	0.903	0.652	1.251
1 week	6.348	1.011	0.997	1.026	1 week	6.082	0.953	0.926	0.981	1 week	3.635	0.885	0.701	1.118
1 week	7.348	1.006	1.000	1.013	1 week	7.082	0.978	0.966	0.990	1 week	4.635	0.879	0.744	1.039
1 week	8.348	1.000	0.997	1.003	1 week	8.082	1.013	1.005	1.021	1 week	5.635	0.891	0.793	1.001
1 week	9.348	1.015	1.003	1.026	1 week	9.082	1.048	1.020	1.077	1 week	6.635	0.927	0.874	0.983
1 week	10.348	1.040	1.019	1.061	1 week	10.082	1.107	1.062	1.153	1 week	7.635	0.996	0.994	0.998
1 week	11.348	1.070	1.042	1.098	1 week	11.082	1.188	1.119	1.260	1 week	8.635	1.096	1.041	1.153
1 week	12.348	1.103	1.069	1.137	2 week	5.082	1.060	0.957	1.175	1 week	9.635	1.164	1.058	1.282
1 week	13.348	1.140	1.100	1.181	2 week	6.082	1.025	0.971	1.082	1 week	10.635	1.173	1.029	1.338
1 week	14.348	1.180	1.131	1.231	2 week	7.082	1.005	0.984	1.027	1 week	11.635	1.133	0.945	1.358
2 week	5.348	1.025	0.975	1.078	2 week	8.082	0.995	0.980	1.009	2 week	2.635	2.284	1.197	4.357
2 week	6.348	1.013	0.986	1.040	2 week	9.082	0.974	0.928	1.022	2 week	3.635	1.837	1.163	2.904
2 week	7.348	1.006	0.994	1.018	2 week	10.082	0.943	0.874	1.017	2 week	4.635	1.503	1.090	2.073
2 week	8.348	0.994	0.989	1.000	2 week	11.082	0.905	0.804	1.019	2 week	5.635	1.261	1.010	1.575
2 week	9.348	0.972	0.952	0.993	3 week	5.082	1.010	0.896	1.138	2 week	6.635	1.095	0.980	1.223
2 week	10.348	0.953	0.919	0.989	3 week	6.082	1.042	0.981	1.108	2 week	7.635	1.002	0.998	1.006
2 week	11.348	0.945	0.901	0.991	3 week	7.082	1.029	1.005	1.054	2 week	8.635	0.971	0.883	1.068
2 week	12.348	0.946	0.893	1.001	3 week	8.082	0.975	0.959	0.991	2 week	9.635	0.913	0.763	1.091
2 week	13.348	0.955	0.893	1.022	3 week	9.082	0.914	0.866	0.965	2 week	10.635	0.808	0.629	1.039
2 week	14.348	0.972	0.895	1.055	3 week	10.082	0.858	0.788	0.933	2 week	11.635	0.682	0.476	0.978
3 week	5.348	1.205	1.130	1.285	3 week	11.082	0.806	0.708	0.918	3 week	2.635	0.935	0.449	1.950
3 week	6.348	1.047	1.015	1.080	PA					3 week	3.635	1.039	0.619	1.744
3 week	7.348	1.001	0.987	1.014	1 week	4.521	1.123	1.079	1.169	3 week	4.635	1.117	0.778	1.605
3 week	8.348	0.990	0.984	0.997	1 week	5.521	1.062	1.036	1.089	3 week	5.635	1.146	0.892	1.471
3 week	9.348	0.928	0.907	0.950	1 week	6.521	1.022	1.005	1.039	3 week	6.635	1.104	0.974	1.251
3 week	10.348	0.847	0.815	0.882	1 week	7.521	1.005	0.997	1.012	3 week	7.635	1.005	1.001	1.010
3 week	11.348	0.769	0.730	0.810	1 week	8.521	0.998	0.995	1.000	3 week	8.635	0.889	0.802	0.987
3 week	12.348	0.696	0.654	0.740	1 week	9.521	0.989	0.977	1.001	3 week	9.635	0.801	0.659	0.974
3 week	13.348	0.627	0.583	0.674	1 week	10.521	0.987	0.967	1.006	3 week	10.635	0.744	0.564	0.981
3 week	14.348	0.563	0.517	0.614	1 week	11.521	0.992	0.968	1.018	3 week	11.635	0.708	0.475	1.056
AC					1 week	12.521	1.004	0.972	1.038	MT				
1 week	6.090	1.030	1.004	1.058	2 week	4.521	0.791	0.730	0.857	1 week	5.131	0.913	0.829	1.007
1 week	7.090	0.999	0.985	1.013	2 week	5.521	0.888	0.846	0.933	1 week	6.131	0.961	0.902	1.025
1 week	8.090	0.997	0.993	1.001	2 week	6.521	0.963	0.934	0.993	1 week	7.131	0.986	0.947	1.027
1 week	9.090	0.999	0.993	1.005	2 week	7.521	1.000	0.987	1.014	1 week	8.131	0.996	0.991	1.000
1 week	10.090	0.998	0.982	1.014	2 week	8.521	0.995	0.990	0.999	1 week	9.131	1.054	1.027	1.083
1 week	11.090	1.009	0.986	1.032	2 week	9.521	0.964	0.942	0.986	1 week	10.131	1.152	1.085	1.223
1 week	12.090	1.030	1.002	1.060	2 week	10.521	0.933	0.899	0.968	1 week	11.131	1.237	1.133	1.351
1 week	13.090	1.061	1.025	1.100	2 week	11.521	0.906	0.863	0.951	1 week	12.131	1.275	1.147	1.418
2 week	6.090	1.100	1.039	1.165	2 week	12.521	0.882	0.826	0.941	1 week	13.131	1.268	1.122	1.432
2 week	7.090	1.037	1.011	1.063	3 week	4.521	1.409	1.284	1.546	1 week	14.131	1.222	1.058	1.411
2 week	8.090	1.002	0.995	1.009	3 week	5.521	1.247	1.181	1.316	2 week	5.131	1.400	1.156	1.695
2 week	9.090	1.014	1.002	1.025	3 week	6.521	1.125	1.089	1.162	2 week	6.131	1.271	1.126	1.433
2 week	10.090	1.042	1.014	1.071	3 week	7.521	1.039	1.024	1.054	2 week	7.131	1.140	1.059	1.228
2 week	11.090	1.061	1.020	1.104	3 week	8.521	0.991	0.986	0.996	2 week	8.131	1.015	1.006	1.024
2 week	12.090	1.071	1.017	1.128	3 week	9.521	0.972	0.949	0.996	2 week	9.131	0.923	0.879	0.970
2 week	13.090	1.073	1.001	1.150	3 week	10.521	0.955	0.918	0.994	2 week	10.131	0.863	0.774	0.962
3 week	6.090	0.948	0.878	1.023	3 week	11.521	0.936	0.888	0.986	2 week	11.131	0.824	0.703	0.966
3 week	7.090	0.990	0.961	1.020	3 week	12.521	0.915	0.852	0.982	2 week	12.131	0.801	0.660	0.973
3 week	8.090	1.008	0.999	1.016	AP					2 week	13.131	0.792	0.631	0.994
3 week	9.090	0.948	0.936	0.961	1 week	4.746	0.930	0.864	1.001	2 week	14.131	0.792	0.601	1.043
3 week	10.090	0.854	0.827	0.881	1 week	5.746	0.945	0.895	0.999	3 week	5.131	0.736	0.579	0.936
3 week	11.090	0.772	0.737	0.807	1 week	6.746	0.959	0.920	1.000	3 week	6.131	0.839	0.731	0.962
3 week	12.090	0.700	0.659	0.744	1 week	7.746	0.971	0.947	0.995	3 week	7.131	0.935	0.863	1.013
3 week	13.090	0.638	0.588	0.691	1 week	8.746	0.992	0.988	0.996	3 week	8.131	0.998	0.988	1.008
AM					1 week	9.746	1.043	1.025	1.061	3 week	9.131	0.969	0.918	1.023
1 week	4.897	0.963	0.947	0.979	1 week	10.746	1.090	1.047	1.135	3 week	10.131	0.879	0.780	0.990
1 week	5.897	0.992	0.983	1.001	1 week	11.746	1.086	1.028	1.147	3 week	11.131	0.787	0.659	0.940
1 week	6.897	1.000	0.997	1.002	1 week	12.746	1.035	0.966	1.109	3 week	12.131	0.717	0.575	0.895
1 week	7.897	1.005	1.001	1.010	2 week	4.746	1.089	0.942	1.260	3 week	13.131	0.664	0.510	0.865
1 week	8.897	1.024	1.013	1.035	2 week	5.746	1.065	0.958	1.185	3 week	14.131	0.624	0.453	0.859
1 week	9.897	1.054	1.038	1.070	2 week	6.746	1.046	0.967	1.133					
1 week	10.897	1.094	1.071	1.117	2 week	7.746	1.033	0.986	1.083					
2 week	4.897	1.009	0.975	1.044	2 week	8.746	1.010	1.002	1.018					
2 week	5.897	0.998	0.982	1.015	2 week	9.746	0.950	0.919	0.982					
2 week	6.897	1.002	0.998	1.006	2 week	10.746	0.900	0.834	0.971					
2 week	7.897	0.976	0.968	0.984	2 week	11.746	0.908	0.818	1.008					
2 week	8.897	0.944	0.926	0.962	2 week	12.746	0.969	0.846	1.110					
2 week	9.897	0.930	0.904	0.957	3 week	4.746	1.052	0.894	1.238					
2 week	10.897	0.932	0.893	0.971	3 week	5.746	1.014	0.901	1.140					
3 week	4.897	1.086	1.042	1.132	3 week	6.746	0.989	0.907	1.078					
3 week	5.897	1.053	1.034	1.074	3 week	7.746	0.983	0.934	1.034					
3 week	6.897	1.012	1.007	1.017	3 week	8.746	0.995	0.987	1.004					
3 week	7.897	0.984	0.975	0.994	3 week	9.746	1.020	0.986	1.055					
3 week	8.897	0.935	0.914	0.955	3 week	10.746	1.033	0.955	1.117					
3 week	9.897	0.847	0.820	0.876	3 week	11.746	1.011	0.906	1.128					
3 week	10.897	0.739	0.705	0.774	3 week	12.746	0.961	0.830	1.112					

Table C.11. Coefficients for whole-Amazon Oceanic Niño Index and malaria model, averaged over lags.

ONI	RR	LCI	UCI
-1.5	0.869	0.829	0.910
-1.25	0.911	0.881	0.943
-1	0.951	0.929	0.973
-0.75	0.984	0.968	0.999
-0.5	1.005	0.993	1.016
-0.25	1.009	1.002	1.016
0	1.000	1.000	1.000
0.25	0.985	0.978	0.992
0.5	0.973	0.960	0.986
0.75	0.965	0.948	0.982
1	0.960	0.939	0.982
1.25	0.959	0.932	0.986
1.5	0.960	0.926	0.995
1.75	0.964	0.921	1.009
2	0.969	0.915	1.026
2.25	0.976	0.910	1.047
2.5	0.983	0.904	1.069

Table C.12. Coefficients for whole-Amazon Oceanic Niño Index and malaria model, specific to each lag.

Lag	ONI	RR	LCI	UCI	Lag	ONI	RR	LCI	UCI	Lag	ONI	RR	LCI	UCI
Same mon	-1.5	1.029	1.021	1.037	3-month	-1.5	1.003	1.001	1.005	6-month	-1.5	0.978	0.969	0.986
Same mon	-1.25	1.049	1.034	1.063	3-month	-1.25	1.001	0.998	1.005	6-month	-1.25	0.957	0.942	0.972
Same mon	-1	1.055	1.034	1.075	3-month	-1	0.995	0.989	1.000	6-month	-1	0.938	0.917	0.960
Same mon	-0.75	1.050	1.022	1.078	3-month	-0.75	0.983	0.976	0.991	6-month	-0.75	0.921	0.892	0.952
Same mon	-0.5	1.037	1.000	1.076	3-month	-0.5	0.970	0.959	0.980	6-month	-0.5	0.906	0.866	0.948
Same mon	-0.25	1.021	0.972	1.072	3-month	-0.25	0.954	0.939	0.969	6-month	-0.25	0.892	0.840	0.947
Same mon	0	1.000	1.000	1.000	3-month	0	1.000	1.000	1.000	6-month	0	1.000	1.000	1.000
Same mon	0.25	0.972	0.965	0.980	3-month	0.25	0.995	0.993	0.997	6-month	0.25	1.018	1.009	1.028
Same mon	0.5	0.955	0.942	0.969	3-month	0.5	0.991	0.987	0.995	6-month	0.5	1.028	1.010	1.046
Same mon	0.75	0.950	0.930	0.970	3-month	0.75	0.988	0.982	0.994	6-month	0.75	1.028	1.002	1.054
Same mon	1	0.955	0.928	0.982	3-month	1	0.987	0.979	0.994	6-month	1	1.019	0.985	1.055
Same mon	1.25	0.968	0.934	1.005	3-month	1.25	0.986	0.977	0.995	6-month	1.25	1.004	0.960	1.051
Same mon	1.5	0.990	0.944	1.038	3-month	1.5	0.987	0.975	0.998	6-month	1.5	0.983	0.927	1.042
Same mon	1.75	1.019	0.960	1.081	3-month	1.75	0.988	0.973	1.003	6-month	1.75	0.958	0.890	1.031
Same mon	2	1.053	0.979	1.133	3-month	2	0.990	0.971	1.009	6-month	2	0.930	0.849	1.018
Same mon	2.25	1.093	1.001	1.193	3-month	2.25	0.992	0.969	1.015	6-month	2.25	0.900	0.807	1.004
Same mon	2.5	1.136	1.024	1.260	3-month	2.5	0.994	0.967	1.023	6-month	2.5	0.870	0.765	0.990

Table C.13. Coefficients for whole-Amazon Oceanic Niño Index and malaria model, specific to each lag. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima, PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

ONI	RO			PA			AM			RR			TO & MA			UCI
	RR	LCI	UCI	ONI	RR	LCI	UCI	ONI	RR	LCI	UCI	ONI	RR	LCI	UCI	
-1.5	0.734	0.675	0.798	-1.5	0.819	0.736	0.911	-1.5	0.926	0.821	1.045	-1.5	0.969	0.866	1.084	
-1.25	0.783	0.738	0.832	-1.25	0.871	0.806	0.942	-1.25	0.971	0.890	1.059	-1.25	1.005	0.927	1.090	
-1	0.834	0.800	0.869	-1	0.922	0.872	0.974	-1	1.010	0.952	1.072	-1	1.035	0.979	1.094	
-0.75	0.883	0.859	0.909	-0.75	0.965	0.927	1.004	-0.75	1.038	0.997	1.080	-0.75	1.054	1.015	1.095	
-0.5	0.929	0.910	0.949	-0.5	0.995	0.965	1.025	-0.5	1.047	1.018	1.077	-0.5	1.057	1.028	1.086	
-0.25	0.969	0.958	0.981	-0.25	1.006	0.989	1.024	-0.25	1.033	1.016	1.050	-0.25	1.037	1.020	1.055	
0	1.000	1.000	1.000	0	1.000	1.000	1.000	0	1.000	1.000	1.000	0	1.000	1.000	1.000	
0.25	1.018	1.005	1.032	0.25	0.984	0.967	1.002	0.25	0.965	0.948	0.982	0.25	0.958	0.941	0.976	
0.5	1.022	0.998	1.046	0.5	0.967	0.936	0.998	0.5	0.941	0.911	0.971	0.5	0.923	0.894	0.953	
0.75	1.011	0.978	1.045	0.75	0.950	0.909	0.993	0.75	0.929	0.891	0.970	0.75	0.896	0.859	0.936	
1	0.988	0.943	1.034	1	0.933	0.879	0.991	1	0.929	0.881	0.980	1	0.877	0.831	0.925	
1.25	0.954	0.896	1.017	1.25	0.917	0.845	0.995	1.25	0.939	0.879	1.003	1.25	0.863	0.806	0.923	
1.5	0.914	0.838	0.997	1.5	0.902	0.807	1.007	1.5	0.957	0.880	1.040	1.5	0.854	0.783	0.930	
1.75	0.869	0.776	0.974	1.75	0.886	0.766	1.026	1.75	0.982	0.884	1.090	1.75	0.848	0.760	0.946	
2	0.821	0.711	0.949	2	0.871	0.723	1.050	2	1.013	0.889	1.154	2	0.845	0.737	0.970	
2.25	0.773	0.647	0.923	2.25	0.857	0.681	1.079	2.25	1.050	0.895	1.230	2.25	0.845	0.714	0.999	
2.5	0.726	0.587	0.898	2.5	0.843	0.639	1.111	2.5	1.090	0.902	1.317	2.5	0.845	0.691	1.033	
ONI	AC			AP			RR			MT						UCI
	RR	LCI	UCI	ONI	RR	LCI	UCI	ONI	RR	LCI	UCI	ONI	RR	LCI	UCI	
-1.5	1.111	0.988	1.249	-1.5	0.192	0.135	0.272	-1.5	1.455	1.193	1.774	-1.5	1.151	0.986	1.345	
-1.25	1.111	1.023	1.208	-1.25	0.332	0.257	0.429	-1.25	1.210	1.050	1.395	-1.25	1.069	0.956	1.195	
-1	1.107	1.048	1.170	-1	0.543	0.454	0.649	-1	1.033	0.938	1.138	-1	1.003	0.931	1.081	
-0.75	1.096	1.057	1.136	-0.75	0.803	0.708	0.911	-0.75	0.922	0.862	0.987	-0.75	0.959	0.912	1.008	
-0.5	1.075	1.047	1.103	-0.5	1.031	0.940	1.131	-0.5	0.877	0.834	0.923	-0.5	0.942	0.909	0.976	
-0.25	1.041	1.025	1.058	-0.25	1.103	1.046	1.164	-0.25	0.905	0.878	0.933	-0.25	0.956	0.936	0.976	
0	1.000	1.000	1.000	0	1.000	1.000	1.000	0	1.000	1.000	1.000	0	1.000	1.000	1.000	
0.25	0.962	0.945	0.978	0.25	0.837	0.795	0.882	0.25	1.134	1.097	1.172	0.25	1.061	1.036	1.085	
0.5	0.934	0.905	0.964	0.5	0.704	0.642	0.772	0.5	1.267	1.194	1.344	0.5	1.123	1.077	1.171	
0.75	0.918	0.881	0.957	0.75	0.609	0.528	0.702	0.75	1.379	1.273	1.493	0.75	1.180	1.114	1.251	
1	0.912	0.868	0.958	1	0.541	0.432	0.676	1	1.467	1.327	1.622	1	1.234	1.142	1.333	
1.25	0.915	0.864	0.969	1.25	0.490	0.348	0.689	1.25	1.530	1.349	1.736	1.25	1.283	1.158	1.421	
1.5	0.924	0.863	0.990	1.5	0.453	0.278	0.738	1.5	1.570	1.338	1.842	1.5	1.328	1.160	1.519	
1.75	0.940	0.865	1.021	1.75	0.424	0.219	0.821	1.75	1.589	1.298	1.945	1.75	1.369	1.151	1.630	
2	0.960	0.869	1.062	2	0.402	0.172	0.942	2	1.591	1.237	2.047	2	1.409	1.132	1.753	
2.25	0.985	0.873	1.111	2.25	0.384	0.134	1.105	2.25	1.582	1.164	2.150	2.25	1.446	1.106	1.890	
2.5	1.012	0.877	1.168	2.5	0.369	0.104	1.312	2.5	1.566	1.087	2.257	2.5	1.483	1.077	2.041	

Table C.14A. Coefficients for state-stratified Oceanic Niño Index and malaria model, specific to each lag. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima.

Lag	ONI	RO			AC			AM			RR		
		RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
Same month	-1.5	1.169	1.068	1.281	1.724	1.528	1.946	0.726	0.640	0.823	1.350	1.076	1.695
Same month	-1.25	1.130	1.055	1.211	1.565	1.429	1.713	0.806	0.733	0.887	1.215	1.025	1.442
Same month	-1	1.094	1.041	1.151	1.422	1.333	1.516	0.886	0.827	0.948	1.107	0.979	1.251
Same month	-0.75	1.063	1.025	1.101	1.294	1.237	1.353	0.955	0.910	1.002	1.029	0.944	1.121
Same month	-0.5	1.036	1.011	1.062	1.181	1.146	1.217	1.002	0.969	1.035	0.984	0.927	1.044
Same month	-0.25	1.016	1.003	1.030	1.082	1.064	1.100	1.016	0.998	1.034	0.976	0.945	1.008
Same month	0	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Same month	0.25	0.984	0.971	0.997	0.943	0.927	0.960	0.972	0.954	0.991	1.039	1.004	1.075
Same month	0.5	0.964	0.940	0.989	0.916	0.886	0.946	0.950	0.916	0.984	1.077	1.010	1.148
Same month	0.75	0.941	0.906	0.976	0.916	0.875	0.960	0.935	0.888	0.985	1.107	1.010	1.213
Same month	1	0.913	0.867	0.962	0.941	0.886	1.000	0.928	0.866	0.995	1.130	1.000	1.278
Same month	1.25	0.883	0.823	0.948	0.990	0.916	1.069	0.927	0.847	1.016	1.147	0.977	1.347
Same month	1.5	0.852	0.775	0.936	1.061	0.963	1.168	0.932	0.829	1.047	1.159	0.944	1.424
Same month	1.75	0.819	0.726	0.924	1.155	1.024	1.301	0.940	0.812	1.089	1.166	0.900	1.511
Same month	2	0.786	0.677	0.914	1.272	1.100	1.471	0.952	0.796	1.139	1.170	0.851	1.608
Same month	2.25	0.754	0.628	0.905	1.414	1.189	1.682	0.967	0.779	1.199	1.171	0.799	1.716
Same month	2.5	0.722	0.582	0.896	1.579	1.289	1.935	0.983	0.763	1.265	1.170	0.746	1.835
3-month	-1.5	0.902	0.877	0.927	1.036	0.996	1.077	0.975	0.936	1.015	1.133	1.061	1.211
3-month	-1.25	0.922	0.904	0.940	1.036	1.007	1.065	0.990	0.962	1.019	1.066	1.016	1.117
3-month	-1	0.941	0.928	0.954	1.035	1.016	1.054	1.003	0.984	1.023	1.011	0.979	1.044
3-month	-0.75	0.959	0.951	0.969	1.031	1.019	1.043	1.012	0.999	1.026	0.973	0.952	0.996
3-month	-0.5	0.976	0.969	0.983	1.024	1.016	1.033	1.015	1.006	1.025	0.957	0.941	0.974
3-month	-0.25	0.990	0.986	0.994	1.014	1.008	1.019	1.011	1.005	1.016	0.967	0.957	0.977
3-month	0	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
3-month	0.25	1.006	1.002	1.010	0.987	0.981	0.993	0.988	0.982	0.994	1.043	1.031	1.054
3-month	0.5	1.007	0.999	1.015	0.977	0.967	0.988	0.980	0.969	0.990	1.082	1.061	1.104
3-month	0.75	1.004	0.993	1.015	0.972	0.959	0.985	0.976	0.962	0.990	1.113	1.084	1.143
3-month	1	0.996	0.981	1.011	0.970	0.954	0.986	0.976	0.959	0.993	1.136	1.099	1.175
3-month	1.25	0.985	0.964	1.006	0.971	0.952	0.990	0.979	0.958	1.001	1.152	1.105	1.202
3-month	1.5	0.971	0.943	0.999	0.974	0.952	0.997	0.985	0.958	1.013	1.162	1.102	1.226
3-month	1.75	0.954	0.919	0.991	0.980	0.953	1.007	0.994	0.960	1.029	1.167	1.091	1.248
3-month	2	0.936	0.892	0.983	0.987	0.954	1.020	1.004	0.962	1.049	1.167	1.074	1.270
3-month	2.25	0.918	0.865	0.974	0.995	0.956	1.036	1.016	0.964	1.071	1.165	1.052	1.291
3-month	2.5	0.899	0.837	0.965	1.004	0.957	1.053	1.029	0.966	1.096	1.161	1.028	1.312
6-month	-1.5	0.696	0.624	0.776	0.622	0.534	0.724	1.309	1.119	1.532	0.951	0.721	1.253
6-month	-1.25	0.752	0.693	0.816	0.686	0.612	0.768	1.216	1.081	1.368	0.934	0.759	1.150
6-month	-1	0.810	0.763	0.859	0.753	0.695	0.815	1.137	1.045	1.236	0.923	0.795	1.073
6-month	-0.75	0.866	0.831	0.903	0.822	0.778	0.867	1.074	1.013	1.138	0.921	0.829	1.023
6-month	-0.5	0.919	0.894	0.945	0.888	0.857	0.921	1.029	0.990	1.070	0.932	0.867	1.001
6-month	-0.25	0.964	0.949	0.979	0.950	0.931	0.969	1.006	0.985	1.027	0.958	0.922	0.997
6-month	0	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
6-month	0.25	1.029	1.012	1.045	1.033	1.012	1.055	1.004	0.982	1.027	1.047	1.005	1.090
6-month	0.5	1.052	1.020	1.085	1.043	1.003	1.086	1.011	0.969	1.055	1.087	1.007	1.174
6-month	0.75	1.071	1.022	1.123	1.031	0.975	1.090	1.018	0.957	1.083	1.119	1.002	1.250
6-month	1	1.086	1.016	1.161	0.999	0.929	1.075	1.026	0.943	1.116	1.142	0.985	1.325
6-month	1.25	1.097	1.002	1.202	0.952	0.868	1.044	1.034	0.925	1.155	1.157	0.953	1.405
6-month	1.5	1.106	0.981	1.246	0.895	0.797	1.004	1.042	0.903	1.202	1.165	0.908	1.496
6-month	1.75	1.111	0.953	1.296	0.831	0.721	0.958	1.051	0.877	1.258	1.168	0.852	1.600
6-month	2	1.115	0.922	1.349	0.765	0.643	0.910	1.059	0.849	1.322	1.165	0.791	1.717
6-month	2.25	1.117	0.888	1.407	0.700	0.569	0.861	1.068	0.819	1.394	1.160	0.727	1.849
6-month	2.5	1.119	0.853	1.468	0.638	0.501	0.813	1.078	0.788	1.473	1.153	0.666	1.996

Table C.14B. Coefficients for state-stratified Oceanic Niño Index and malaria model, specific to each lag. State acronyms: PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

Lag	ONI	PA			AP			MA & TO			MT		
		RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI	RR	LCI	UCI
Same month	-1.5	1.026	0.921	1.143	0.649	0.467	0.903	0.749	0.664	0.846	1.312	1.104	1.559
Same month	-1.25	1.052	0.969	1.143	0.712	0.555	0.915	0.846	0.772	0.927	1.222	1.073	1.393
Same month	-1	1.073	1.009	1.141	0.778	0.649	0.933	0.940	0.879	1.005	1.145	1.042	1.258
Same month	-0.75	1.081	1.033	1.132	0.844	0.742	0.960	1.017	0.970	1.067	1.083	1.013	1.157
Same month	-0.5	1.073	1.039	1.109	0.905	0.828	0.990	1.060	1.025	1.096	1.037	0.991	1.084
Same month	-0.25	1.044	1.025	1.063	0.958	0.912	1.006	1.052	1.033	1.071	1.010	0.986	1.035
Same month	0	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Same month	0.25	0.955	0.937	0.973	1.037	0.987	1.090	0.935	0.918	0.953	1.002	0.978	1.028
Same month	0.5	0.921	0.890	0.953	1.075	0.979	1.181	0.882	0.851	0.914	1.012	0.965	1.062
Same month	0.75	0.899	0.856	0.944	1.116	0.966	1.289	0.845	0.803	0.889	1.028	0.959	1.103
Same month	1	0.887	0.830	0.948	1.159	0.937	1.434	0.821	0.767	0.878	1.050	0.953	1.157
Same month	1.25	0.883	0.808	0.965	1.205	0.888	1.634	0.806	0.738	0.882	1.077	0.945	1.226
Same month	1.5	0.887	0.790	0.996	1.253	0.825	1.902	0.800	0.713	0.898	1.108	0.934	1.314
Same month	1.75	0.896	0.772	1.039	1.304	0.754	2.254	0.801	0.693	0.926	1.144	0.920	1.422
Same month	2	0.910	0.756	1.094	1.357	0.680	2.711	0.806	0.674	0.964	1.184	0.904	1.550
Same month	2.25	0.927	0.741	1.160	1.413	0.606	3.293	0.815	0.657	1.011	1.227	0.886	1.699
Same month	2.5	0.947	0.726	1.235	1.472	0.538	4.027	0.826	0.641	1.066	1.273	0.866	1.869
3-month	-1.5	0.936	0.903	0.969	0.577	0.513	0.648	0.990	0.953	1.027	1.048	0.995	1.104
3-month	-1.25	0.955	0.931	0.980	0.693	0.636	0.754	1.002	0.975	1.029	1.022	0.985	1.061
3-month	-1	0.973	0.955	0.991	0.816	0.769	0.866	1.012	0.993	1.030	1.001	0.976	1.026
3-month	-0.75	0.988	0.975	1.001	0.929	0.891	0.970	1.018	1.005	1.031	0.986	0.970	1.003
3-month	-0.5	0.998	0.988	1.008	1.010	0.980	1.042	1.019	1.009	1.028	0.980	0.969	0.992
3-month	-0.25	1.002	0.996	1.008	1.033	1.015	1.052	1.012	1.007	1.018	0.985	0.978	0.992
3-month	0	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
3-month	0.25	0.995	0.989	1.001	0.942	0.926	0.959	0.986	0.980	0.992	1.020	1.012	1.028
3-month	0.5	0.989	0.978	0.999	0.890	0.863	0.917	0.974	0.963	0.984	1.039	1.025	1.054
3-month	0.75	0.983	0.969	0.998	0.848	0.808	0.889	0.964	0.950	0.978	1.057	1.037	1.078
3-month	1	0.977	0.958	0.997	0.815	0.756	0.878	0.957	0.940	0.974	1.073	1.045	1.101
3-month	1.25	0.972	0.945	0.998	0.788	0.704	0.883	0.952	0.931	0.974	1.087	1.050	1.124
3-month	1.5	0.966	0.931	1.002	0.768	0.652	0.904	0.949	0.922	0.976	1.099	1.051	1.150
3-month	1.75	0.961	0.915	1.009	0.751	0.603	0.936	0.947	0.913	0.982	1.110	1.048	1.177
3-month	2	0.955	0.898	1.016	0.738	0.556	0.980	0.946	0.903	0.990	1.121	1.042	1.206
3-month	2.25	0.950	0.880	1.026	0.727	0.511	1.034	0.945	0.894	1.000	1.131	1.034	1.236
3-month	2.5	0.944	0.861	1.036	0.717	0.470	1.095	0.945	0.884	1.011	1.140	1.025	1.268
6-month	-1.5	0.853	0.748	0.973	0.512	0.344	0.762	1.307	1.130	1.512	0.837	0.678	1.034
6-month	-1.25	0.867	0.785	0.957	0.673	0.500	0.907	1.186	1.062	1.324	0.855	0.730	1.002
6-month	-1	0.883	0.821	0.949	0.855	0.690	1.060	1.089	1.005	1.179	0.875	0.781	0.980
6-month	-0.75	0.903	0.857	0.952	1.024	0.880	1.191	1.018	0.962	1.078	0.898	0.830	0.972
6-month	-0.5	0.929	0.895	0.964	1.127	1.015	1.252	0.979	0.941	1.018	0.926	0.879	0.977
6-month	-0.25	0.962	0.942	0.982	1.115	1.052	1.182	0.974	0.953	0.995	0.961	0.934	0.989
6-month	0	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
6-month	0.25	1.036	1.014	1.059	0.856	0.806	0.910	1.039	1.016	1.063	1.038	1.007	1.069
6-month	0.5	1.062	1.019	1.107	0.736	0.653	0.830	1.075	1.030	1.121	1.067	1.007	1.130
6-month	0.75	1.075	1.011	1.143	0.644	0.531	0.781	1.100	1.035	1.170	1.086	0.996	1.184
6-month	1	1.077	0.989	1.173	0.573	0.427	0.769	1.116	1.027	1.213	1.096	0.971	1.236
6-month	1.25	1.069	0.953	1.199	0.516	0.337	0.790	1.124	1.008	1.254	1.096	0.931	1.291
6-month	1.5	1.053	0.905	1.224	0.471	0.263	0.843	1.124	0.976	1.295	1.090	0.879	1.352
6-month	1.75	1.030	0.850	1.249	0.433	0.202	0.929	1.119	0.936	1.337	1.078	0.819	1.418
6-month	2	1.003	0.790	1.273	0.401	0.154	1.050	1.109	0.890	1.382	1.062	0.755	1.492
6-month	2.25	0.973	0.729	1.298	0.374	0.116	1.208	1.096	0.841	1.428	1.042	0.691	1.572
6-month	2.5	0.942	0.671	1.324	0.350	0.087	1.404	1.082	0.792	1.477	1.022	0.629	1.659

Table C.15. Coefficients for state- and season-stratified Oceanic Niño Index and weather models, specific to each lag. State acronyms: RO=Rondônia, AC=Acre, AM=Amazonas, RR=Roraima, PA: Pará, AP=Amapá, TO=Tocantins, MA=Maranhão, and MT=Mato Grosso.

Wet Season							
State	Event	<i>Precipitation</i>			<i>Temperature</i>		
		Estimate	Std. Error	P-value	Estimate	Std. Error	P-value
RO	El Niño	0.049	0.003	<0.001	0.371	0.017	<0.001
AC	El Niño	0.014	0.003	<0.001	0.241	0.023	<0.001
AM	El Niño	0.004	0.003	<0.001	0.311	0.015	<0.001
RR	El Niño	-0.040	0.016	0.009	0.062	0.110	0.572
PA	El Niño	-0.004	0.002	0.102	0.183	0.012	<0.001
AP	El Niño	-0.036	0.009	<0.001	-0.090	0.032	0.004
TO	El Niño	0.023	0.002	<0.001	0.260	0.014	<0.001
MA	El Niño	-0.001	0.002	0.591	0.216	0.013	<0.001
MT	El Niño	0.028	0.001	<0.001	0.291	0.013	<0.001
RO	La Niña	0.027	0.003	<0.001	-0.106	0.017	<0.001
AC	La Niña	-0.005	0.003	0.069	-0.166	0.023	<0.001
AM	La Niña	-0.003	0.003	0.202	-0.096	0.015	<0.001
RR	La Niña	-0.071	0.011	<0.001	-0.036	0.076	0.636
PA	La Niña	-0.019	0.002	<0.001	-0.072	0.012	<0.001
AP	La Niña	-0.011	0.008	0.2	-0.192	0.030	<0.001
TO	La Niña	0.006	0.002	0.005	-0.019	0.014	0.189
MA	La Niña	0.001	0.002	0.779	0.086	0.013	<0.001
MT	La Niña	-0.005	0.001	<0.001	-0.190	0.012	<0.001
Dry Season							
State	Event	<i>Precipitation</i>			<i>Temperature</i>		
		Estimate	Std. Error	P-value	Estimate	Std. Error	P-value
RO	El Niño	0.065	0.006	<0.001	1.583	0.097	<0.001
AC	El Niño	-0.076	0.008	<0.001	1.381	0.129	<0.001
AM	El Niño	0.066	0.004	<0.001	0.998	0.039	<0.001
RR	El Niño	-0.022	0.004	<0.001	0.126	0.048	0.009
PA	El Niño	0.059	0.002	<0.001	1.027	0.027	<0.001
AP	El Niño	0.074	0.005	<0.001	0.984	0.063	<0.001
TO	El Niño	0.056	0.004	<0.001	1.132	0.082	<0.001
MA	El Niño	0.031	0.001	<0.001	1.222	0.032	<0.001
MT	El Niño	-0.055	0.003	<0.001	1.615	0.078	<0.001
RO	La Niña	0.066	0.004	<0.001	0.462	0.067	<0.001
AC	La Niña	0.030	0.006	<0.001	0.440	0.086	<0.001
AM	La Niña	0.059	0.003	<0.001	0.664	0.035	<0.001
RR	La Niña	-0.019	0.004	<0.001	-0.453	0.046	<0.001
PA	La Niña	0.043	0.002	<0.001	0.787	0.024	<0.001
AP	La Niña	0.042	0.004	<0.001	0.628	0.057	<0.001
TO	La Niña	0.052	0.003	<0.001	0.750	0.056	<0.001
MA	La Niña	0.023	0.001	<0.001	1.114	0.028	<0.001
MT	La Niña	0.023	0.002	<0.001	0.695	0.052	<0.001

Figure C.1. Weekly malaria cases (points) and monthly moving average (line) by state.

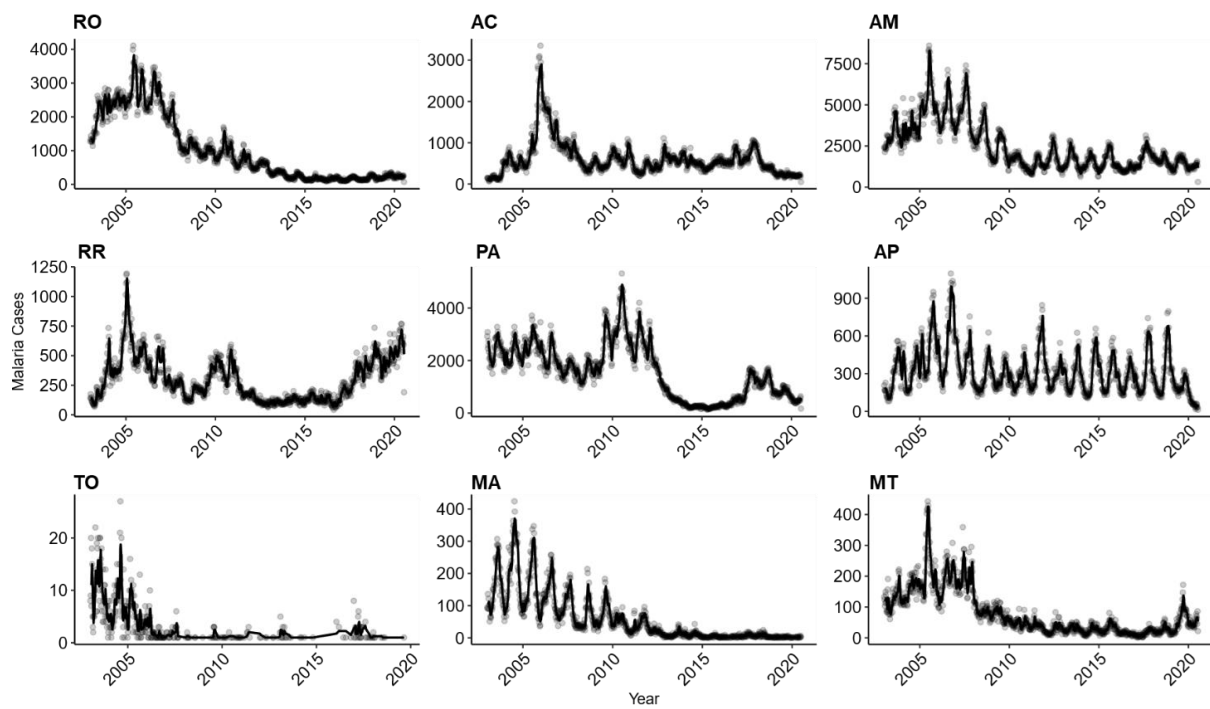


Figure C.2. Weekly mean municipality precipitation (points) and monthly moving average (line) by state.

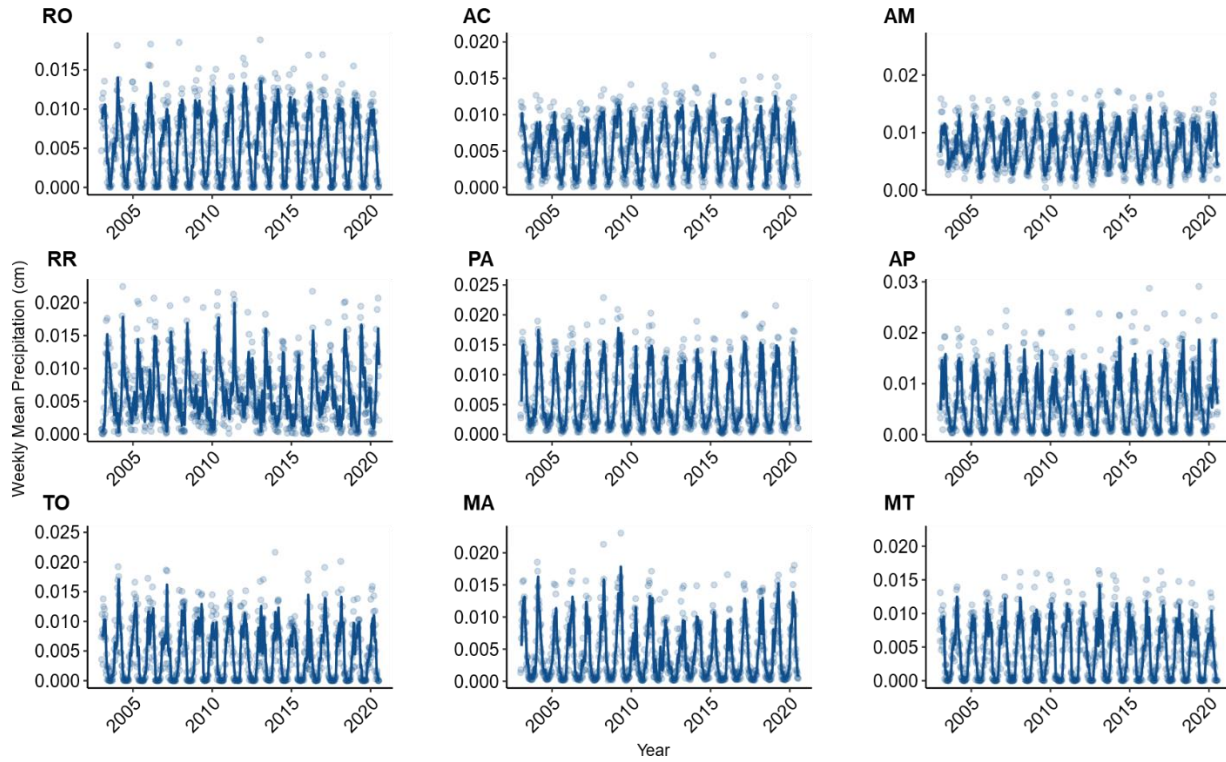


Figure C.3. Weekly mean temperature (points) and monthly moving average (line) by state.

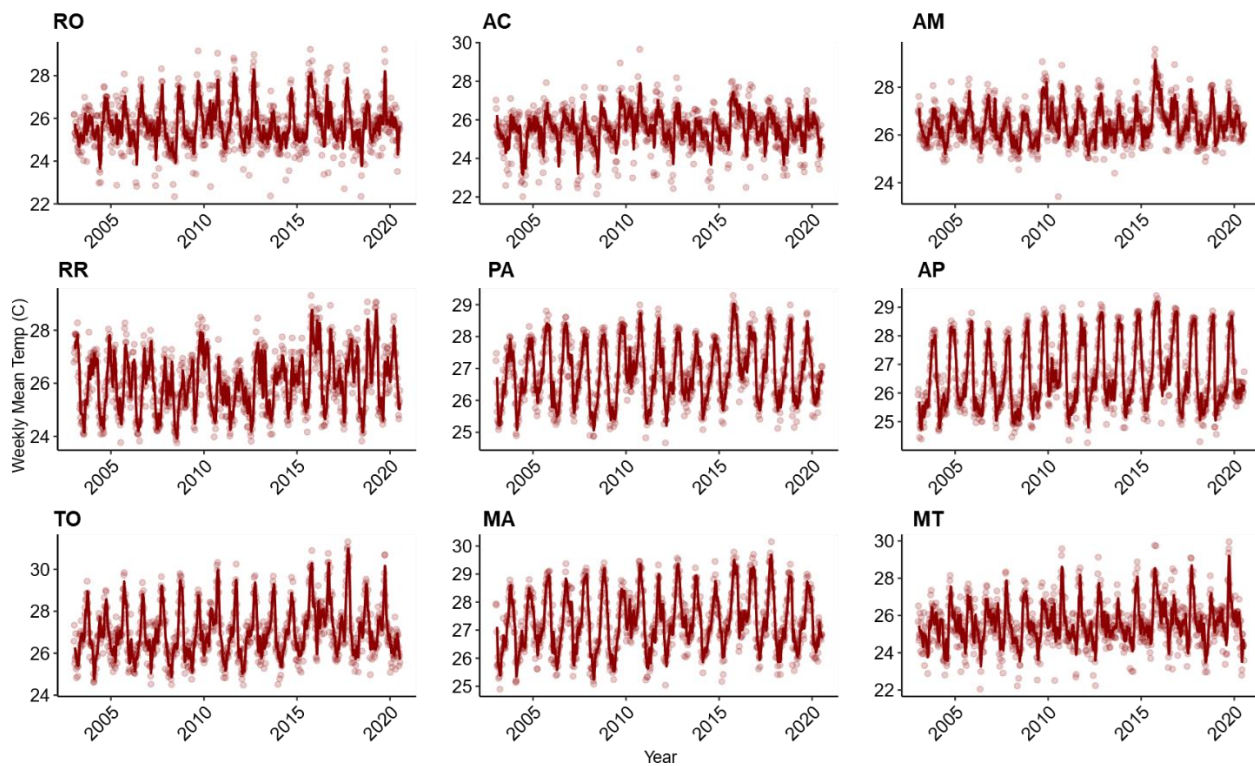


Figure C.4. Partial autocorrelation function for maximum temperature, total precipitation, and cases confirming ideal lags of one-, two-, and three-weeks.

