Evolution of the Frontier Malaria in the Brazilian Amazon: a Retrospective Observational Study from a Local-level Perspective

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Topic: Health, Morbidity & Wellbeing

Introduction. We investigate how frontier malaria in the Brazilian Amazon has spatially and temporally evolved in the period 2007-2023. This is a novel contribution for three reasons. First, studies at aggregate levels such as municipalities hide internal heterogeneities and lead to ecological fallacies since malaria and human population may be spatially clustered at a small number of localities with specific land uses [1]. We use a bottom-up perspective: departing from locality-level information (the lowest disaggregated level available in the Brazilian Malaria Surveillance System – SIVEP-Malaria), we identify spatial configurations of frontier malaria that scale up into a regional pattern over time. Second, since the majority of malaria information and are not spatially identified at SIVEP-Malaria, we developed a method that identified virtually all localities. Third, we unveil the space-time evolution of the frontier malaria in terms of patterns of malaria incidence by types of parasites and autochthons (at the same locality of residence) versus imported infection (at a different locality, including from another country), types of land use in the localities (economic activities and residential categories such as urban, rural, indigenous, *garimpo*), and socioeconomic and demographic characteristics of infected people. The space-time evolution of evolution allows to identify the consolidation of distinct (and heterogeneous) frontier malaria regions over time and over distinct governmental periods.

Theoretical focus. Local malaria transmission in Brazil is virtually all concentrated in the Amazon, with 99%-100% cases [2]. Despite efforts from the Brazilian government to eliminate malaria [3] and other successful initiatives in neighbor Amazonian countries [4, 5], the difficulties to control and eliminate malaria stem from the complex intersection of biological, ecological, political, demographic, social and economic factors determining malaria transmission in the Amazon, in which has been referred in the literature as *frontier malaria* [5-11]. It is related with distinct land uses and economic activities such as peasant and commercial agriculture and cattle ranching, logging, *garimpo* (mechanized, usually illegal mining), industrial mining, extractive activities, expansion of urban activities and large-scale "development" projects such as road building, dams and hydroelectrical powerplants. Frontier expansion has been facilitated by the opening of road networks that have been historically associated with high malaria incidence [12, 13], flight connections to remote *garimpo* areas and looseness of environmental legislation [1, 2, 14], and with poverty and inequality [15] and violence [16, 17].

The definition above suggests that there is not a single Amazon frontier, but several frontiers according the land use, economic and population patterns of territorial occupation and their evolution over time. In this regard, qualifying a *frontier malaria* involves analyzing the evolution and outcome, over time and space, of interaction between patterns of human settlement and human mobility [1, 14, 18, 19], environmental change, land use strategies and deforestation [19-22] and changes in the ecology of vectors that favors malaria transmission [21]. Previous research has validated associations between malaria risk and roads, dam construction, industrial mining, regions where agricultural settlements potentialize risk through work activity and labor flow [11], as well as higher malaria risk related to occupational-related sociodemographic characteristics [8, 23]. Malaria transmission has been closely associated with changes in policies and environmental enforcement [1], and recent upward trend since the Bolsonaro government has been mostly concentrated in indigenous and mining areas [24]. Previous studies also show that the incidence of *P. falciparum* is more likely when malaria is imported from neighbor countries such as Venezuela [25] and Peru and Colombia [26].

While several studies have discussed frontier malaria at aggregate levels such as municipalities [11, 27], it is implicit in its the definition above that the dynamics of malaria transmission may depend upon both local-level mechanisms and the characteristics of the context [8, 10, 28]. Human mobility or immobility is an example of the importance of understanding how malaria incidence at local levels and how it can scale up to a municipal or regional pattern of malaria risk [1, 14, 19]. This has been observed in areas combining the

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interaction between *garimpos*, rural and urban areas [1, 14, 20], indigenous areas and *garimpos* [1, 14, 24, 25], or rural and urban areas [18]. At consolidated frontiers, higher articulation with urban areas favors land uses intensive in the use of natural capital, such as forests and water, as is the case of the expansion of *garimpos* within the Yanomami Indigenous Territory [1, 14, 24]. Furthermore, each frontier malaria may imply high selectivity in terms of occupational profile (such as among *garimpo* workers), demographic characteristics (such as predominantly young males in *garimpos*), ethnicity (such as indigenous populations with strong interactions with outsiders, mainly *garimpo* workers) [1, 14, 24] and areas of initial colonist settlements [8, 10, 29], especially those with precarious housing conditions, lack of bed nets and access to health care and prevention [30, 31]. For example, malaria among indigenous groups in the Brazilian Amazon has been associated with higher severity compared to other race/ethnic groups due to high parasitemia, health burdens due to cases of P. falciparum and high prevalence among children [32].

Methods

Data processing and management. Municipality health systems collect several information on malaria cases and upload them into the Brazilian Malaria Surveillance System (SIVEP-Malaria). While existing since 2003, public data is available since 2007. Besides notifications of malaria cases, it includes information on types of parasites and clinical tests and treatments, socioeconomic and demographic information about patients, where notification was done (e.g., health posts), locality of residence and likely infection and its type (e.g., urban, rural, *garimpo* etc).

A locality (*localidade*) is spatially represented as a point. It can be urban neighborhoods, indigenous hamlets, *garimpos*, rural settlements, fishing and infrastructure sites among others. Since many localities lack coordinates in the SIVEP database, imputation was used following four steps. First, gathering spatial databases with coordinates or spatial features (points, lines, and polygons), including the National Address Register for Statistical Purposes (CNEFE-IBGE), Indigenous Villages and hamlets from the Brazilian Indigenous Foundation (FUNAI), watercourses from the National Water Agency (ANA), and geospatial data from the National Institute of Colonization and Agrarian Reform (INCRA). Second, standardizing locality names at SIVEP-malaria (i.e., lowercase letters, no accents, no prepositions, etc.). Third, applying textual similarity methods from the RapidFuzz library [33]. Finally, we added the identified localities in the previous step to the existing localities that had coordinates identified in the SIVEP dataset.

SIVEP-Malaria classifies 44 distinct types of localities and aggregate them in 5 groups: urban (including some typically urban infrastructures such as airports, road and rail stations), *garimpos*, indigenous (hamlets and protected indigenous lands), rural (hamlets, villages, typically rural infrastructure and productive sites such as dams and hydroelectric powerplants, rural community ports, roads and sawmills), and rural settlements (which, for the purpose of this article, we aggregated to the category "rural").

Modelling strategy. We used three steps to identify and characterize the frontier malaria in the Amazon over time (space-time frontier malaria evolution). It will involve three steps. First, descriptive statistics show how the spatial identification of localities in the SIVEP-Malaria database increased spatial identification (coverage) of malaria cases.

Second, we identify if changes in malaria cases and their levels across land uses are statistically significant over time. A discrete-time multinomial model measures the odds of malaria cases in individuals living in a locality *i* with a specific land use *L* at time *t* (*t* = 2007, …, 2023):

$$\log\left(\frac{\pi_{it}^{L}}{\pi_{it}^{r}}\right) = \alpha^{L} + \beta_{t}^{L} X_{\mathrm{it}}^{L} \qquad (2)$$

where $\log\left(\frac{\pi_{it}^{L}}{\pi_{it}^{r}}\right)$ represents the log-odds of a malaria case in locality of type L (L= 1 representing rural localities, L = 2 indigenous, L = 3 *garimpo*) between t=2007, …2023 rather than a positive malaria case at *r*, the reference category (r = L = 0 urban). The coefficient α^{L} , estimates the intercept, X_{it}^{L} is a matrix of time-varying covariates representing malaria cases at each year, *t*, for a locality *i* with land use *L,* and β_{t}^{L} is a matrix of vectors of the average effects of X_{it}^{L}on the log-odds of a malaria case. We obtained Maximum Likelihood (ML) estimates for the categorical dependent variable data and estimated robust standard errors given the clustered nature of the data [34, 35], with localities clustered within years. The effects of a percent change in the covariates on the odds of out-migration are estimated using the odds ratio, e^{β}:

$$\%\,\mathrm{OR} = 100 \times \left(e^{\beta^{L}} - 1\right) \qquad (3)$$

Finally, spatial analysis involved two procedures. First, we identified clusters of localities over time with different levels of concentration of malaria cases and NMMs. Indicators were annualized to enable comparisons between periods of different lengths. Cartographic representation involved the non-parametric Kernel Density Estimation (KDE), which estimates the probability density function of a random variable.

The quartic function (known as the quartile kernel) smoothed the data to create a continuous curve, giving more weight to points close to the value of interest. The cell size and bandwidth used were 1 and 100 km, respectively.

We used the SKATER method [36] (Spatial 'K'luster Analysis by Tree Edge Removal, Appendix A) to produce homogeneous clusters/regions. It uses an iterative algorithm to classify contiguous spatial units (cell grids) to maximizes the variance between regions and minimize the variance within each region. The variables included the percentage of infection cases in urban, rural, *garimpo* and indigenous areas, percentage of autochthonous cases and cases identified as *P. falciparum*. A restriction was imposed requiring that each region contain at least 10% of the total population of the Legal Amazon.

Expected results

Descriptive analysis. We will discuss, based on Table 1, how we improved spatial identification of localities, including by type of locality (rural, urban indigenous, *garimpo*). From 162,840 localities in the Brazilian Amazon Region (corresponding to 3,601,061 malaria cases between 2007 and 2023), only 7.1% had localities spatially identified. Our approach increasing identification to 98.4% (corresponding to 99.4% malaria cases in 2007-2023). We will also discuss levels and patterns of the temporal evolution of malaria by type of locality (Figure 1).

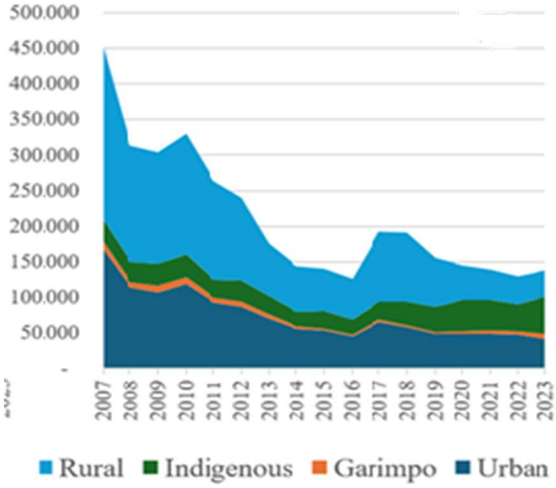

Figure 1 – Malaria cases by types of localities, Brazilian Amazon, 2007-2023. Source: SIVEP-Malaria

Temporal evolution of malaria cases by land use. The next step is to analyze if the evolution of malaria cases and differences across land uses shown in Figure 1 are statistically significant over time. Based on Figure 2, we will discuss how period effects associated with each year between 2007 and 2022 impact the odds of malaria incidence in a *garimpo,* indigenous or rural locality of residence compared to an urban locality and to 2023.

Space-time density of malaria cases. An expected finding from the analysis of Figure 2 is that the incidence of malaria cases across land uses have important differences in levels and patterns over time. As suggested in the literature review, contextual factors related to distinct governmental terms be a hypothetical explanation. Additionally, given the vast territory, the Amazon may contain several frontiers with distinct malaria dynamics. Thus, a spatial analysis allows us to understand the space-time evolution and heterogeneity of the malaria frontier. We will analyze the density of malaria cases for governmental periods and how they are associated with clusters of higher densities of malaria cases (Figure 3).

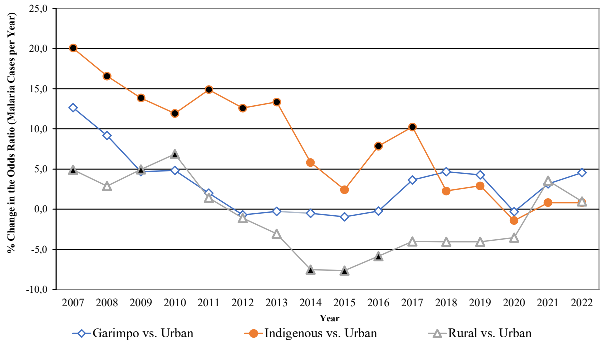

Figure 2 - Estimated coefficients for years (2007-2022, taking 2023 as reference) in the multinomial model of malaria cases by types of localities of residence [1].

[1] Observation points highlighted in black are those with statistical significance of $p<0.10$.

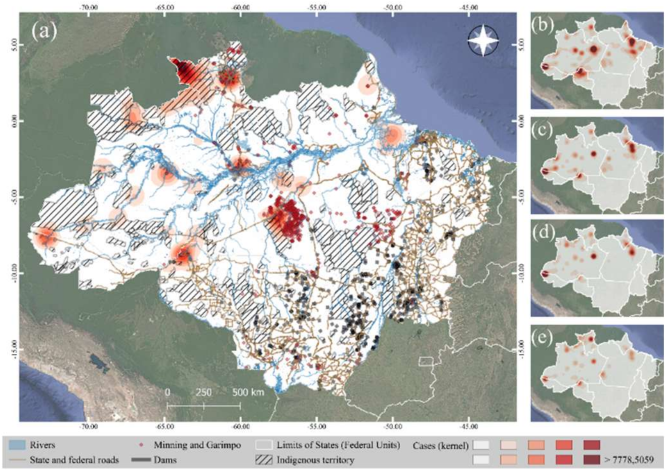

Figure 3 – Density of malaria cases in the Brazilian Legal Amazon – 2007 to 2023. Panels: (a) 2023; (b) 2007-2010; (c) 2011-2014; (d) 2015-2018; (e) 2019-2022. Source:

SIVEP-Malaria, 2023; IBGE, 2023

The heterogeneity of the Malaria Frontier: Space-time Evolution and Clustering. We propose a regionalization of the frontier malaria considering the spatial heterogeneities and temporal contingencies previously discussed (Figure 4). The application of the SKATER method resulted in resulted in five regions: Northwestern (NWFM), Southeastern (SEFM), Southwestern (SWFM), Northern (NOFM), and Northeastern (NEFM). Then, we discuss the main features of these frontier malaria regions testing the statistical significance of differences of means of variables that the literature review suggests as those that have historically defined and characterized the frontier malaria. We will use ANOVA, t and Z tests between each governmental period and the overall period (2007-2023) for each frontier malaria region (Table 1).

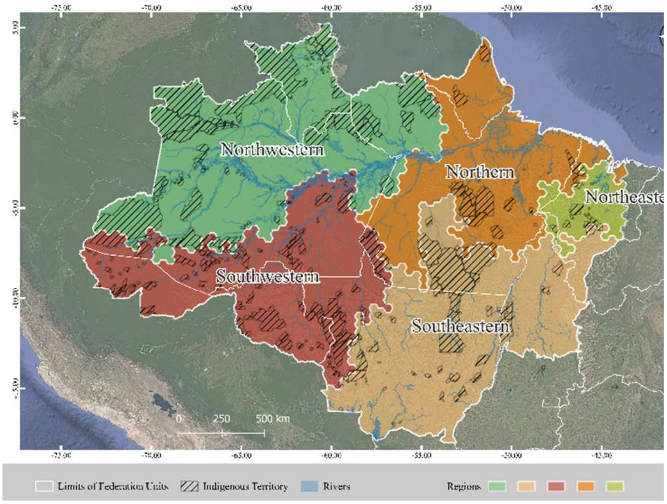

Figure 4 – Frontier malaria regions in the Brazilian Amazon, 2007-2023

Table 1 – Characteristics of frontier malaria regions and difference of means between each governmental periods and the whole period of analysis (2007-2023) for each region. (*Note: tests not included yet*)

Region	*period*	*Malaria cases*	*Number of autochthonous cases*	*Number of imported cases**	*P. falciparum and mixed (%)*	*P. Vivax (%)*	*Infected men (%)*	*Infected women (%)*	*Infected at age 15-39 (%)*	*Infected indigenous (%)*	*Infected black (%)*	*Infected white (%)*	*Race/Color Missing (%)*
Northwestern (NWFM)	2007-2010	427.167	274.356	7.952	15,97%	84,03%	59,56%	40,42%	42,43%	0,00%	0,01%	0,00%	99,99%
	2011-2014	236.537	152.869	12.923	10,69%	89,31%	59,49%	40,51%	43,31%	23,11%	45,09%	4,19%	26,79%
	2015-2018	269.687	181.458	10.698	9,51%	90,49%	59,22%	40,78%	42,55%	40,52%	51,58%	3,34%	4,02%
	2019-2022	290.637	192.120	5.420	17,97%	82,03%	58,62%	41,38%	43,47%	49,99%	46,08%	2,65%	0,98%
	2023	79.595	55.762	1.439	19,82%	80,18%	56,93%	43,07%	41,61%	59,79%	38,24%	1,79%	0,00%
Southeastern (SEFM)	2007-2010	7.160	3.040	161	25,38%	74,62%	70,45%	29,53%	51,33%	0,00%	0,03%	0,01%	99,96%
	2011-2014	4.122	1.598	76	13,22%	86,78%	71,40%	28,60%	50,51%	26,66%	46,75%	19,43%	4,46%
	2015-2018	1.641	941	51	3,66%	96,34%	67,34%	32,66%	49,73%	51,49%	39,31%	8,65%	0,00%
	2019-2022	3.949	853	25	2,89%	97,11%	73,36%	26,64%	55,96%	19,12%	64,70%	15,47%	0,00%
	2023	1.117	407	14	5,28%	94,72%	69,56%	30,44%	55,06%	29,90%	57,39%	12,18%	0,00%
Southwestern (SWFM)	2007-2010	528.079	393.112	981	15,85%	84,15%	61,31%	38,67%	45,90%	0,00%	0,01%	0,00%	99,99%
	2011-2014	298.396	225.879	505	16,35%	83,65%	59,93%	40,06%	45,84%	7,26%	61,14%	8,89%	21,47%
	2015-2018	218.698	168.974	373	16,23%	83,77%	58,71%	41,29%	45,76%	6,31%	85,98%	6,94%	0,15%
	2019-2022	169.115	114.330	614	12,98%	87,02%	62,33%	37,67%	47,60%	16,99%	73,13%	8,98%	0,03%
	2023	33.607	23.317	155	13,81%	86,19%	62,06%	37,94%	46,16%	23,14%	68,05%	8,25%	0,00%
Northern (NOFM)	2007-2010	426.364	283.197	13.553	19,28%	80,72%	63,39%	36,60%	47,55%	0,00%	0,02%	0,00%	99,98%
	2011-2014	279.171	184.849	6.137	17,24%	82,76%	63,20%	36,80%	48,13%	3,90%	70,89%	6,92%	17,05%
	2015-2018	157.532	111.966	1.735	6,13%	93,87%	62,04%	37,96%	47,96%	4,54%	87,59%	7,08%	0,00%
	2019-2022	101.460	60.687	523	9,80%	90,20%	64,60%	35,40%	49,55%	7,30%	83,78%	8,25%	0,00%
	2023	22.948	11.284	176	15,19%	84,81%	68,45%	31,55%	52,39%	6,58%	84,31%	8,72%	0,00%
Northeastern (NEFM)	2007-2010	10.115	3.077	3.702	41,69%	58,31%	74,04%	25,91%	66,41%	0,00%	0,04%	0,00%	99,96%
	2011-2014	4.733	456	3.183	27,83%	72,17%	83,18%	16,82%	74,22%	1,18%	76,74%	13,59%	5,60%
	2015-2018	2.238	263	1.368	14,39%	85,61%	82,08%	17,92%	70,69%	6,34%	80,16%	11,35%	0,04%
	2019-2022	3.076	133	589	13,26%	86,74%	86,96%	13,04%	70,03%	2,89%	83,88%	12,06%	0,00%
	2023	935	8	130	15,51%	84,49%	86,10%	13,90%	71,55%	0,75%	85,88%	12,73%	0,00%
Overall Total		**3.578.079**	**2.444.936**	**72.483**	**15,23%**	**84,77%**	**61,06%**	**38,93%**	**45,66%**	**12,80%**	**38,57%**	**3,70%**	**44,46%**

*Different locality/community likely infection and residence

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