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The Risk of Malaria Infection for Travelers Visiting the Brazilian Amazonian Region: a mathematical modelling approach

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EM, MAMS conceived the study. EM conducted all mathematical modelling analyses with valuable inputs by CS. MAMS, ESB, GZL, LSC, EAGF conducted all field collections. MAMS identified field specimens. EM, MAMS, JEC, GZL wrote the manuscript with valuable contributions from ESB, LSC and EAGF. All authors contributed to the final draft of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest/Disclosure

The authors have declared no conflicts of interest.

Data statement

Malaria data is available in Table_A1_Malaria.

Field collection data employed in the study is available under request from corresponding author. The raw data will be publicly available on a data repository when the project is concluded in 2020.

Abstract

Background: Human mobility between malaria endemic and malaria-free areas can hinder control and elimination efforts in the Amazon basin, maintaining *Plasmodium* circulation and introduction to new areas.

Methods: The analysis begins by estimating the incidence of malaria in areas of interest. Then, the risk of infection as a function of the duration of stay after t_0 was calculated as the number of infected travelers over the number of arrived travelers. Differential equations were employed to estimate the risk of nonimmune travelers acquiring malaria in Amazonian municipalities. Risk was calculated as a result of the force of the infection in terms of local dynamics per time of arrival and duration of visit.

Results: Maximum risk occurred at the peak or at the end of the rainy season and it was nonlinearly (exponentially) correlated with the fraction of infected mosquitoes. Relationship between the risk of malaria and duration of visit was linear and positively correlated. Relationship between the risk of malaria and the time of arrival in the municipality was dependent on local effects of seasonality.

Conclusions: The risk of nonimmune travelers acquiring malaria is not negligible and can maintain regional circulation of parasites, propagating introductions in areas where malaria has been eliminated.

Keywords

Malaria risk; Mathematical modeling; Rural settlements; Amazon; Brazil

1. Background

Malaria is a frequently imported, life-threatening tropical disease in international travelers from malaria-free to malaria-endemic regions [1–4]. Globalization has increased the number of international travelers who travel for tourism, business, or visits with friends and families from industrialized countries to geographical destinations that have a high risk of malaria, increasing the risk of exposure to malaria-causing parasites [3]. Although national and international control efforts have led to declining malaria transmission in the majority of endemic countries [5, 6], those who visit endemic areas, especially in sub-Saharan Africa and Oceania, remain at high risk of acquiring *Plasmodium* infection [3]. For Swedish travelers, the relative risk of acquiring malaria was >250 in sub-Saharan endemic countries of Africa, followed by India and southern Africa (RR = 50), with a lower level in Southeast Asia, South America and Arab countries (RR < 10) [1].

Imported *Plasmodium* infection can threaten the success of malaria control programs in endemic countries [7, 8]. In China, residual transmission across Chinese international borders and imported malaria from African endemic countries represent major challenges to elimination [8, 9]. In Swaziland, Africa, malaria is in the elimination phase; however, 25- to 44-year-old males who travel to Mozambique and spend on average 28 nights represent the primary risk for malaria reemergence and risk to elimination [10]. On Bioko Island, imported malaria is responsible for the prevalence of the disease in much of the capital

Malabo and its surroundings [11]. Similarly, although there is a decline in malaria incidence throughout Nepal, imported malaria linked to population mobility from India challenges the success of the control effort that is primarily focused on decreasing the disease burden in indigenous populations [12].

The Brazilian Amazon is the destination of more than 650 thousand tourists annually. The majority are from malaria-free areas; therefore, tourists are highly susceptible to acquiring *Plasmodium* infection [13]. In addition, local and regional tourism and migration contribute to *Plasmodium* propagation to both new areas in the process of human occupation and other locations where the disease has been controlled or eliminated [14–16]. Malaria emergence was associated with ecological and socioeconomic factors and intensive human movement from both endemic and nonendemic areas to a new rural Amazonian settlement in Rondônia state [14]. Recently, the Venezuelan economic and humanitarian crisis has been held responsible for dispersing malaria and other vector-borne diseases to areas along the Brazilian, Colombian and Guyana borders [17]. Imported malaria threatens the success of control programs because of commercial activities and illegal mining along the international borders of Suriname, the Guyanas and other Amazonian countries in South America [18–21].

The most severe form of malaria is associated with *Plasmodium falciparum* [6]. There are only a few antimalarial drugs available for the treatment of *P. falciparum* infection. To complicate this scenario, the efficacy of current antimalarial drugs used either in prevention or treatment is decreasing worldwide because of the emergence of multidrug resistance. In 2014, resistance to artemisinin combination therapies (ACTs) was reported in more than 60 countries worldwide [6, 5, 22, 23]. In the Greater Mekong Subregion, partial resistance to ACTs has been reported for *P. falciparum*, and chloroquine resistance is an increasing problem for the treatment of *Plasmodium vivax* malaria [24–26]. The origin of drug resistance has been associated with a convergence of factors such as socioeconomic status of a population, human movement, and environmental disturbance in the gem-mining industry in Pailai at the Thailand-Cambodia border. In addition, poor living conditions, social disorganization, a continuous flow of non-immune migrants from neighboring countries and antimalarial drug marketing are involved in the genesis of the chloroquine-resistance network [27].

Malaria transmission is a dynamic process determined by multiple moving factors, including those associated with human parasite reservoirs and mosquito vectors that facilitate *Plasmodium* propagation from a human reservoir [28]. In the Brazilian Amazon, Sallum et al. [29] showed that vector competence of the exophilic population of the primary vector *Nyssorhynchus darlingi* was low in rural municipalities of Cruzeiro do Sul, Mâncio Lima, Lábrea, Machadinho D'Oeste and São Gabriel da Cachoeira. However, *Plasmodium* dispersion in the human population was enhanced by the high human-biting rate and the relatively high susceptibility of *Ny. darlingi* to *P. vivax* infection. The highest estimated value of the basic reproduction number (R_0) for *P. vivax* was identified in a rural settlement in Machadinho D'Oeste ($R_0 = 58.7$), and the second highest ($R_0 = 55.5$) was found in São Gabriel da Cachoeira. These values indicate that one single human infected with *P. vivax* in that specific location, at the time of data collection, was able to produce approximately 60

secondary new cases of malaria taken into consideration the local mosquito population. This value was within the range of the estimated R_0 for *P. falciparum* malaria in endemic areas of sub-Saharan Africa.

Considering the high potential of malaria transmission in the studied areas and the high number of susceptible visitors (approximately half million) to Amazonia yearly, the risk of non-immune host acquiring *Plasmodium* infection was estimated using reported malaria cases in 10 municipalities of the Amazon Region, including the 26 rural communities where entomological data were obtained as described by Sallum et al. [29]. The mathematical model used was an extension of the one presented by Massad et al. [13].

2. Materials and Methods

2.1 Study sites

Malaria incidence data from the municipalities of Cruzeiro do Sul, Mâncio Lima, and Rodrigues Alves in Acre state; Guajará, Humaitá, Itacoatiara, Lábrea, Presidente Figueiredo, and São Gabriel da Cachoeira in Amazonas state; and Machadinho D'Oeste in Rondônia state, in Amazonian Brazil, were employed in the mathematical model analysis (Fig. 1). These municipalities are characterized by a wet season, a dry season and wet-dry transition months. The mean annual regional rainfall is higher than 2,000 mm, and the mean temperature is ~26 °C. The mean annual relative humidity is ~59% but varies substantially with rainfall and surface water. The rural and periurban communities were selected as representatives of moderate or high malaria transmission areas.

2.2 Mosquito collections

Females of the Anophelinae subfamily were collected from 62 houses in the selected communities in the municipalities listed in Fig. 1, from January 2015 to November 2017. Human landing collections (HLCs) were outdoors in the peridomestic environment within ~5–10 m of each house. Localities were at least 2.5 km apart and were positioned in the center of a 1 km radius circle to avoid sampling more than one house within the same 3.14 km^2 area. Although there was active malaria transmission and reported cases in all communities, house selection was based on forest cover percentage as described in Sallum et al. [29].

Human landing collections were conducted for one night at each of the 62 houses, from 18:00–0:00 h. The number of collectors ranged from one to three individuals, depending on their availability during the field collections. Every hour, female mosquitoes were euthanized with ethyl acetate ($C_4H_8O_2$) vapors in the field and stored in silica gel separated by date, location, house, and hour of collection. Specimens were morphologically identified to species, labeled, and stored individually with silica gel at room temperature for subsequent analysis.

2.3 Mosquito processing and *Plasmodium* identification

All *Ny. darlingi* DNA samples were tested for *Plasmodium* spp. infection following the procedures in Bickersmith et al. [30].

2.4 Malaria epidemiological data

Data on the number of malaria cases by epidemiological week and annual parasite incidence (API) of *P. vivax* and *P. falciparum* were requested from the Ministry of Health, Sistemas de Informações de Vigilância Epidemiológica (SIVEP) Malaria [31], through the Electronic System of the Citizen Information Service (Sistema Eletrônico do Serviço de Informações ao Cidadão - e-SIC) (https://esic.cgu.gov.br/sistema/site/index.aspx), protocols # 25820001316201742, # 25820003892201813, # 25820004426201847, and # 25820004717201835.

Malaria incidence data were collected for the 10 municipalities in Acre, Amazonas and Rondônia states. In the moderate to high malaria endemicity communities, most infections were locally acquired. As a proxy of the susceptible fraction of the affected population (see below), we employed the mean annual malaria parasite index (annual parasite incidence, API) of the municipalities in the month previous to the mosquito collections (Table A.1).

3. Calculations

3.1 Fitting the incidence to a continuous function

The analysis began by considering malaria incidence in the localities studied. The data were obtained from SIVEP Malaria [31] through the Citizen Information Service, Ministry of Health of Brazil (https://esic.cgu.gov.br/sistema/site/index.aspx). We calculated the incidence of malaria at the time of data collection, denoted $Incidence(t)$, which is the number of new malaria cases per unit time. This value is equal to the product of the force of infection, λ (incidence-density rate or *per capita* incidence), times the number of susceptible humans, $S_H(t)$. This value is also the product of the ratio of mosquitoes-to-humans, $N_M(t)/N_H(t)$, times the mosquito biting rate, a; times the vector competence, b (see below); times the prevalence of *Plasmodium* infection in the mosquitoes, $I_M(t)/N_M(t)$; and times the number of susceptible humans, $S_H(t)$, or:

$$Incidence(t) = \lambda(t)S_H(t) = \frac{N_M(t)}{N_H}ab\frac{I_M}{N_M(t)}S_H(t) \quad (1)$$

The incidence data from the 10 municipalities studied were then fitted to the continuous function:

$$Incidence\,(t) = c_1 exp\left[-\left(\frac{t-c_2}{c_3}\right)^2\right] + c_4 \quad (2)$$

Where c_i, ($i = 1, \ldots, 4$) are the fitting parameters.

3.2 Calculating the risk of malaria

The risk of acquiring malaria is commonly defined as the frequency of infections, the number of new infections over the number of individuals at risk, for a given period. The simplest way to calculate the risk is to follow a cohort of non-immune visitors, such as $S_{t_0}(t)$, that arrive together at time $t = t_0$ and calculate the total number of infected travelers as

a function of the duration of stay after t_0, I_{t_0}. Then, the risk of infection as a function of the duration of stay after t_0 was calculated as the number of infected travelers over the number of arrived travelers, that is:

$$\pi_{t_0}(t) = \frac{\int_{t_0}^{t} I_{t_0}(s)ds}{S_{t_0}(t_0)} \tag{3}$$

Remark 1: In this simple cohort model, some of the travelers' state variables and parameters depend on the time of arrival t_0 (that defines the cohort) and are indexed by it to maintain accountability.

Some assumptions are necessary and are as follows:

- **a.** The local population is assumed to be large enough in comparison to the number of visitors. Therefore, travelers are subject to the same force of infection as locals, but they do not contribute to the local force of infection.
- **b.** Spatial homogeneity is assumed; that is, the mosquitoes are uniformly distributed over the region.
- **c.** The model is compartmented. In such a model, the state variables are actual densities. To simplify their expression, the densities are multiplied by a small unitary area so that they become numbers.

Visitors, once in the Amazon region, may leave the region, become infected, recover, or die (either from the infection or from natural causes), in any order, even simultaneously. Table 1 shows the state variables and parameters used in the models.

The number of new infections among travelers as a function of time is:

$$I_{t_0}(t) = \lambda(t)S_{t_0}(t) \tag{4}$$

Next, we calculated the number of susceptible individuals as a function of time. Given the assumptions above, and specifically condition (d), that number is given by the following differential equation:

$$\frac{ds_{t_0}(t)}{dt} = -\left[\lambda(t) + \sigma_{t_0}(s) + \mu\right]S_{t_0}(t) \tag{5}$$

The solution of equation (5) is straightforward:

$$S_{t_0}(t) = S_{t_0}(t_0)exp\left\{-\int_{t_0}^{t}\left[\lambda(s) + \sigma_{t_0}(s) + \mu\right]ds\right\} \tag{6}$$

From equations (4) and (6), the following is obtained:

$$I_{t_0}(t) = \lambda(t) S_{t_0}(t_0) exp\left\{ - \int_{t_0}^{t} \left[\lambda(s) + \sigma_{t_0}(s) + \mu \right] ds \right\} \quad (7)$$

Finally, the risk of malaria in travelers is given by:

$$\pi_{t_0}(t) = \frac{\int_{t_0}^{t} I_{t_0}(s) ds}{s_{t_0}(t_0)} = \int_{t_0}^{t} \lambda(s) exp\left\{ - \int_{t_0}^{s} \left[\lambda(s') + \sigma_{t_0}(s') + \mu \right] ds' \right\} ds \quad (8)$$

Equation (8) can be calculated analytically or numerically depending on the form of $\lambda(t)$ and $\sigma_{t_0}(t)$, and it provides an upper bound to the risk of infection.

Remark 2: In the particular case in which all parameters are constant, the risk can be calculated analytically in a simple way as follows:

$$\pi_{t_0}(t) = \frac{\lambda}{\lambda + \sigma + \mu} \{ 1 - exp[-(\lambda + \sigma + \mu)t - t_0] \} \quad (9)$$

Finally, equation (8) is a function of two variables: the duration of the visit ($t - t_0$) and the time of arrival t_0. Varying both variables, it is possible to build a three-dimensional surface of risk.

4. Results

The parameters obtained from the fitting equation (1) for the locations studied, grouped in accordance with the municipalities, are presented in Table 2. Figure 2 shows the results of the fitting procedures for Lábrea, Amazonas state, which was included here to illustrate the results. The results of the fitting model for the remaining 9 municipalities are shown in Appendix A.

The calculated risks of acquiring malaria in Lábrea are presented in Table 3, which was included to illustrate the results. Figure 3 shows the risks of acquiring malaria calculated for Lábrea that were included to illustrate the results of the mathematical modeling analyses.

The maximum risk of a susceptible person acquiring malaria calculated according to equation (8) for the 10 municipalities studied is presented in Table 4. For the purpose of comparison, the maximum risk of malaria was normalized for the municipalities studied. The results are shown in Figure 4.

4.1 Correlation between risk of infection and prevalence of infection in mosquitoes

Figure 5 shows the prevalence of infection of *Plasmodium*, both *P. vivax* and *P. falciparum*, in all anopheline mosquitoes collected in the localities studied for each municipality.

Figure 6 shows the correlation between the fraction of infected mosquitoes and the maximum risk of malaria infection of visitors remaining in each city for four weeks for the 10 municipalities studied. Mâncio Lima was an outlier and was excluded from the

association between both variables above. However, Mâncio Lima is included in the figure to illustrate the difference between Mâncio Lima and the remaining municipalities.

The maximum risk is nonlinearly (exponentially) correlated with the fraction of infected mosquitoes. This can be understood by considering equation (8), which correlated the risk of infection with the force of infection $\lambda(t)$. The force of infection for vector-borne diseases such as malaria is given by the product of the ratio of mosquitoes to humans, $N_M(t)/N_H(t)$, times the mosquito biting rate, a, times the vector competence, b and times the prevalence of *Plasmodium* infection in the mosquitoes, $I_M(t)/N_M(t)$. Equation (8) can now be rewritten in terms of the components of the force of infection, as:

$$\pi_{t_0}(t) = ab\frac{N_M}{N_H}\int_{t_0}^{t}\frac{I_M(s)}{N_M(s)}exp\left\{-ab\frac{N_M}{N_H}\int_{t_0}^{s}\left[\frac{I_M(s)}{N_M(s)}ds'\right]ds' + \int_{t_0}^{t}\left[+\sigma_{t_0}(s')+\mu\right]ds'\right\}ds \quad (10)$$

Therefore, a nonlinear relationship should be expected between the risk, $\pi_{t_0}(t)$, and the fraction of infected mosquitoes, $\frac{I_M(s)}{N_M(s)}$.

5. Discussion

The risk of non-immune travelers acquiring *Plasmodium* infection varies according to the time of arrival and the duration of the visit in 10 municipalities of the Amazon region with active transmission. On one hand, the relationship between the risk of acquiring malaria and the duration of the visit is linear and positively correlated. Longer visits (e.g., up to 4 weeks) always increase this risk, independent of the municipality. On the other hand, the relationship between the risk of malaria and the time of arrival in the municipality is more complex and dependent on local effects of seasonality. The maximum risk occurred (1) in the middle of the rainy season in Mâncio Lima (13%; March), São Gabriel da Cachoeira (5%; May), Cruzeiro do Sul (4%; March), Presidente Figueiredo (3%; March), and Machadinho D-Oeste (1%; February); (2) at the end of the rainy season in Guajará (7%; May), Humaitá (7%; May), and Itacoatiara (8%; July); and (3) in the middle of the dry season in Lábrea (1%; July) and Rodrigues Alves (6%; July).

The maximum risk of *Plasmodium* infection can explain malaria prevalence in some localities studied and in their surroundings. The dependence of local communities on the economic activities and town health centers promotes mobility and migration between rural-urban and urban-rural areas, in the westernmost municipalities of Cruzeiro do Sul, Mâncio Lima, Rodrigues Alves-AC, and Guajará-AM [32], thus exacerbating the persistence of high malaria incidence [33]. In Mâncio Lima, the maximum risk of malaria was nonlinearly correlated with the fraction of infected mosquitoes, likely due to the time of the field collections, which were conducted in the low transmission season for this locality, when mosquito frequency was low. This contradictory scenario of low human exposure to anopheline female bites and high malaria risk can be understood when considering human behavior, such as the host tolerance threshold to mosquito bites. In an entomological

scenario of low mosquito frequency, human defensive behavior against mosquito bites decreases, sometimes resulting in successful *Plasmodium*-infective bites [34]. In addition, a low biting rate can be compensated by an increased number of blood meals per gonotrophic cycle, boosting the transmission potential of the local mosquito population as proposed by Tedrow et al. [35]. In Presidente Figueiredo-AM, the human biting rate was high, but the fraction of anopheline-infected mosquitoes was low. In a scenario of high exposure to mosquitoes, human threshold tolerance can be easily reached, decreasing the success of *Plasmodium* transmission [34]. Transmission intensity is determined by *Plasmodium* infection acquired from a local or an imported source and human *Plasmodium* infection duration. Poor access to antimalarial treatment or a high prevalence of both subpatent and asymptomatic infections increase *Plasmodium* infection duration in an infectious host, and thus the local transmission potential [28]. A high percentage of undetected asymptomatic and subpatent *P. vivax* infections (61.9%) were recorded in the Remansinho, Lábrea-AM [36]. The prevalence of undetected infection in Mâncio Lima is unknown, but it could be high enough to explain the force of infection detected in this study.

Socioeconomic and political instabilities is not uncommon in malaria endemic countries and together can cause either discontinuity or interruption of control programs, thus leading to increase and intensification of transmission. In malaria-endemic areas of South America, the recent humanitarian crisis in Venezuela caused an unprecedent Venezuelan exodus to neighboring endemic countries, which have been facing decrease in malaria incidence for almost a decade. Cross border mobilization of *Plasmodium*-infected hosts increased imported malaria into Brazil, Colombia, Ecuador, Guiana, further fueling the risks of *Plasmodium* infections in endemic and nonendemic areas of the neighboring countries [17, 37–41]. The impact of *P. falciparum*, *P. vivax* and mixed *Plasmodium*-infected hosts may have contributed to dispersion of infection and reintroduction of *P. falciparum* into areas where this parasite was eliminated, such as Sao Gabriel da Cachoeira-AM [29], and other localities studied.

In Brazil, malaria transmission has been controlled in areas outside the Amazon, however, these areas maintain a low annual malaria incidence, with imported and local infections, but the latter linked to *Nyssorhynchus* and *Kerteszia* vector species. Within the country-level transmission network, the Amazon basin is the major spreader of *P. vivax* parasites to areas outside the Amazon [42]. Mathematical models proposed herein to calculate the risk of acquiring malaria by a susceptible person visiting the Amazon region can be employed to indicate the risk of exporting parasites both within and outside the Amazon region. The potential of local, regional, and country level *Plasmodium* parasite dispersion should not be ignored when targeting malaria elimination. Furthermore, knowledge of the potential for Amazonian regional dispersion is important for tailoring policies for economic development, poverty reduction and malaria control.

The Amazonian biome offers multiple opportunities for international tourism. A key destination for gastronomic tourism is in the Peruvian region of Iquitos, Loreto. The cultural heritage and biological diversity of this region create an environment for an exquisite and tremendously varied gastronomy [43]. This region is one of the hotspots of malaria incidence in South America, ranked in the top 5 in South America in 2018 [6]. Some of the

greatest numbers of species of certain groups of fauna and flora on the planet are found in Brazil's Amazonian forest [44]. Thus, this region is a highly desirable destination for ecological tourism in Brazil. Most foreign tourists are from malaria-free areas. The origins of foreign tourists visiting Amazonia are Europe (65%), North America (19%) and other areas (Japan, Australia and Latin America; 16%) [45]. The predominant motivation of these non-immune travelers is contact with nature, and most stay on average 3 to 5 nights during the July – August or December – January seasons [45]. Of the possible visit lengths, one week is associated with the lowest risk of acquiring malaria, whereas the tourism seasons may be associated with a higher risk depending on the locality visited.

In the present study, the municipalities where the risk of acquiring malaria was estimated represent ecological and social attractions for national and international visitors. Modern spiritual movements based on the use of ayahuasca, a mixture of Amazonian plant that includes *Banisteriopsis caapi*, *Psychotria viridis*, *Diplopterys cabrerana*, have emerged in Brazil [46]. The ayahuasca shamanic ceremonial claim to be able to cure mental and physical illness and allow communication with the spirit world [47]. These healing retreats are an important economic activity receiving caravans of people from everywhere in the Cruzeiro do Sul municipality, where the maximum risk of acquiring malaria for a four-week visit is 4% in March.

The municipalities of Humaitá and Presidente Figueiredo are ecological tourist attractions in Brazil. The forest commodities exploitation is the emblematic economic activity of communities inhabiting the settlement project Santa Maria Auxiliadora in Humaitá [48]. This area is one of the localities in which mosquito fauna was sampled in the current study. During field work, the potential of this settlement as a tourist paradise became clear (Fig. 7A). The municipality of Presidente Figueiredo, Amazonas state, emerged as a location for ecological tourism due to its abundance of fresh waters, jungle, natural resources, caves and waterfalls (e.g., Uherek and Gouveia [49]), such as the Urubuí River falls (Fig. 7B). The ecotourism occurs all year around, but it intensifies in the dry season, and in the weekends. As a result, a larger number of tourists visit the river beaches of Humaitá (Fig. 7A) or the waterfalls of Presidente Figueiredo (Fig. 7B) during three to four months in the dry season (June – September). The associated risk of acquiring malaria for a non-immune traveler staying one week in Presidente Figueiredo or Humaitá in July is 0.1 – 0.5% or 1 – 5 cases in 1,000 visitors. Finally, a word of advice for travelers planning to visit one of the regions analysed in this paper: discuss with your doctor the risk of acquiring malaria and cost-benefit of malaria chemoprophylaxis [50].

6. Conclusions

Mathematical modeling calculations demonstrated that the risk of a susceptible person acquiring *Plasmodium* infection is not negligible in the Brazilian Amazon basin. The risk is heterogeneous and varies depending on the length of stay, time of arrival to a locality, entomological potential, and force of infection of local vector population. The model adopted in the study quantified components of transmission dynamics, and the analytical approach adopted can provide import information for planning malaria interventions. Our

results highlight the need for further investigations focusing on risk of malaria transmission outdoors with involvement of *Ny. darlingi* and other anophelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Risk of a susceptible tourist acquiring malaria is not negligible in the Brazilian Amazon.
- Maximum risk is nonlinearly correlated with the fraction of infected mosquitoes, but it is correlated with the force of infection.
- Human migration within the Amazon basin maintains *Plasmodium* propagation in the region.
- Human movement back and forth Amazon facilitate *Plasmodium* dispersion to areas with potential for parasite reemergence.
- Malaria transmission can peak either in the dry or rainy season, depends on the region.

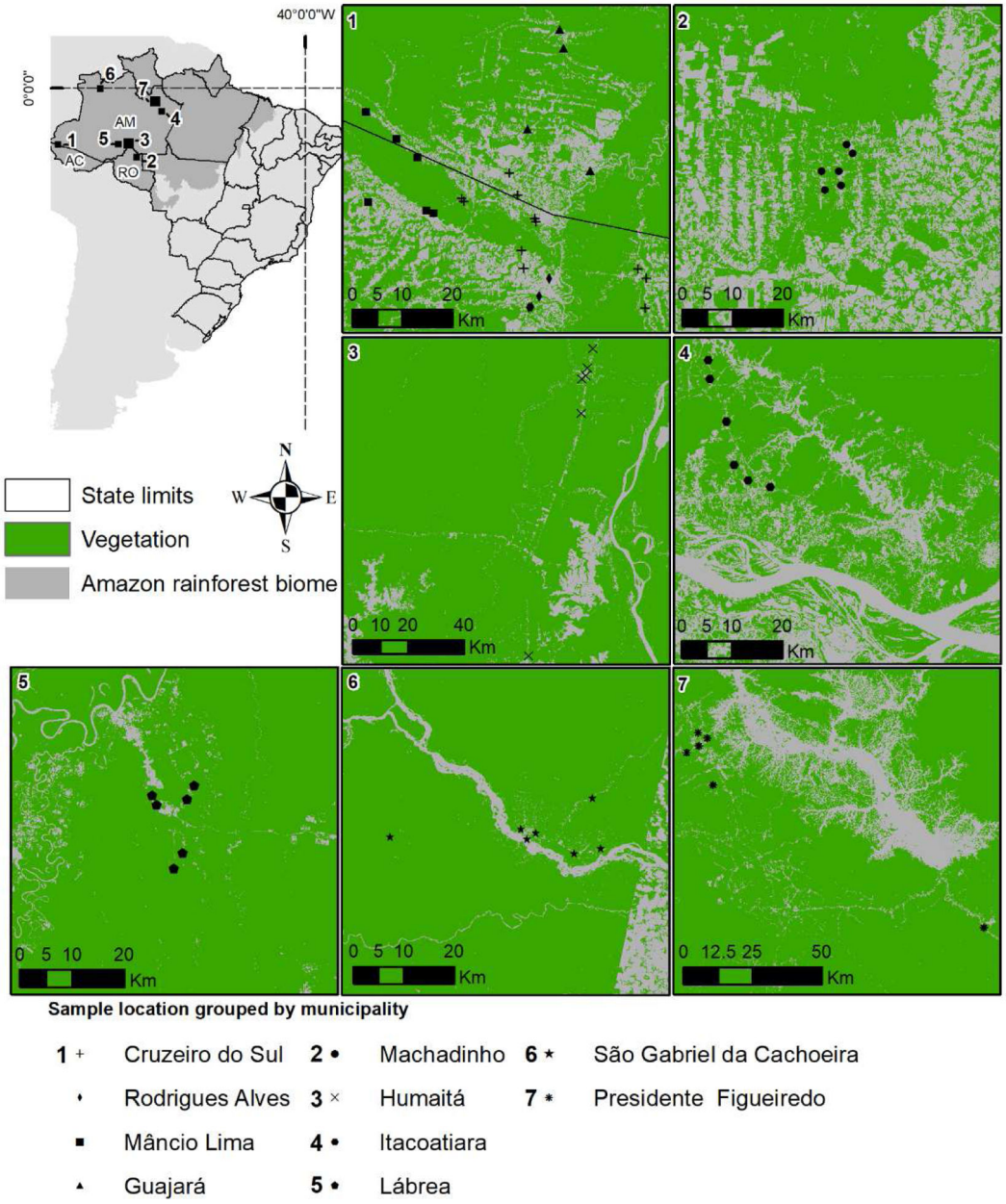

Figure 1.

Specimen collection sites in ten municipalities in the states of Acre, Amazonas and Rondônia, Brazil. Locations are represented by black dots. Numbers 1–7 represent the municipalities as follows: 1 - Cruzeiro do Sul, Mâncio Lima, Rodrigues Alves, AC and Guajará, AM; 2 - Machadinho D'Oeste, RO; 3 – Humaitá; 4 -Itacoatiara; 5 - Lábrea; 6 - São Gabriel da Cachoeira; 7 - Presidente Figueiredo, AM. AM = Amazonas state; AC = Acre state; RO = Rondônia state.

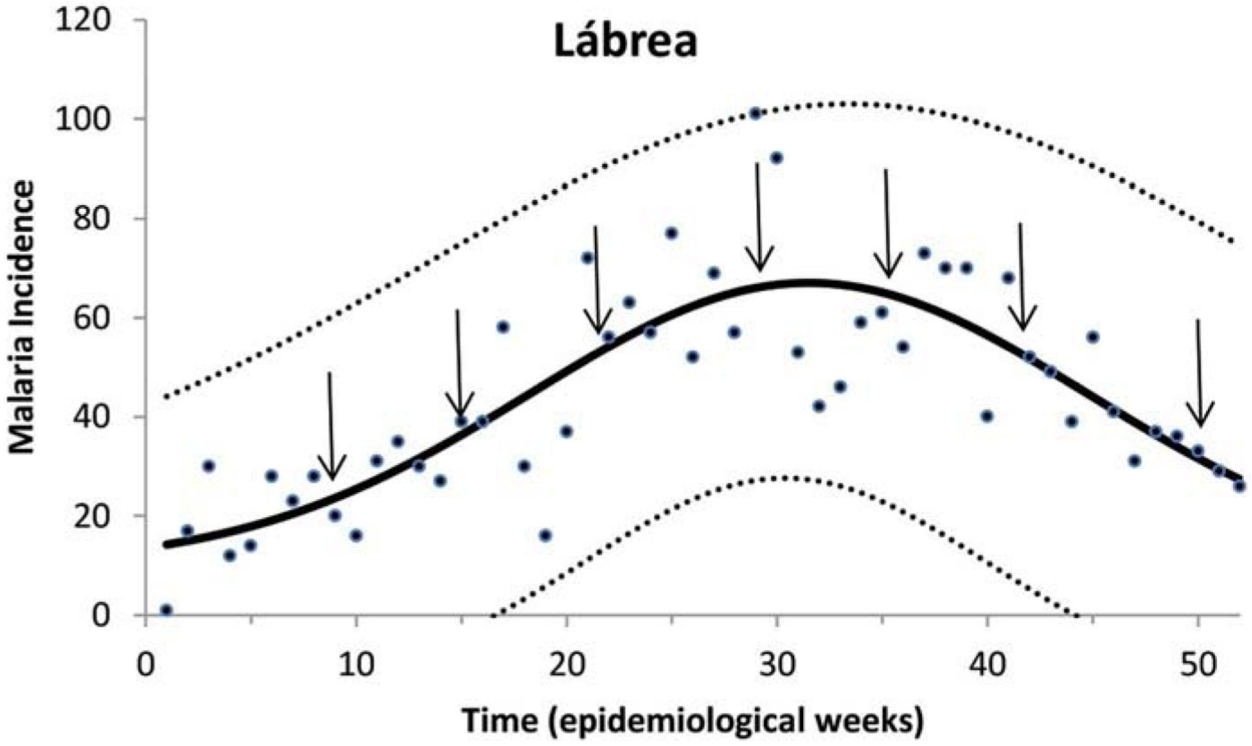

Figure 2.

Results of the fitting modeling of the incidence of malaria for Lábrea, Amazonas state, according to equation (1). Blue dots are actual data. The continuous line represents the mean incidence, and the dotted lines represent the 95% confidence interval. The arrows show the time travelers arrive at the town

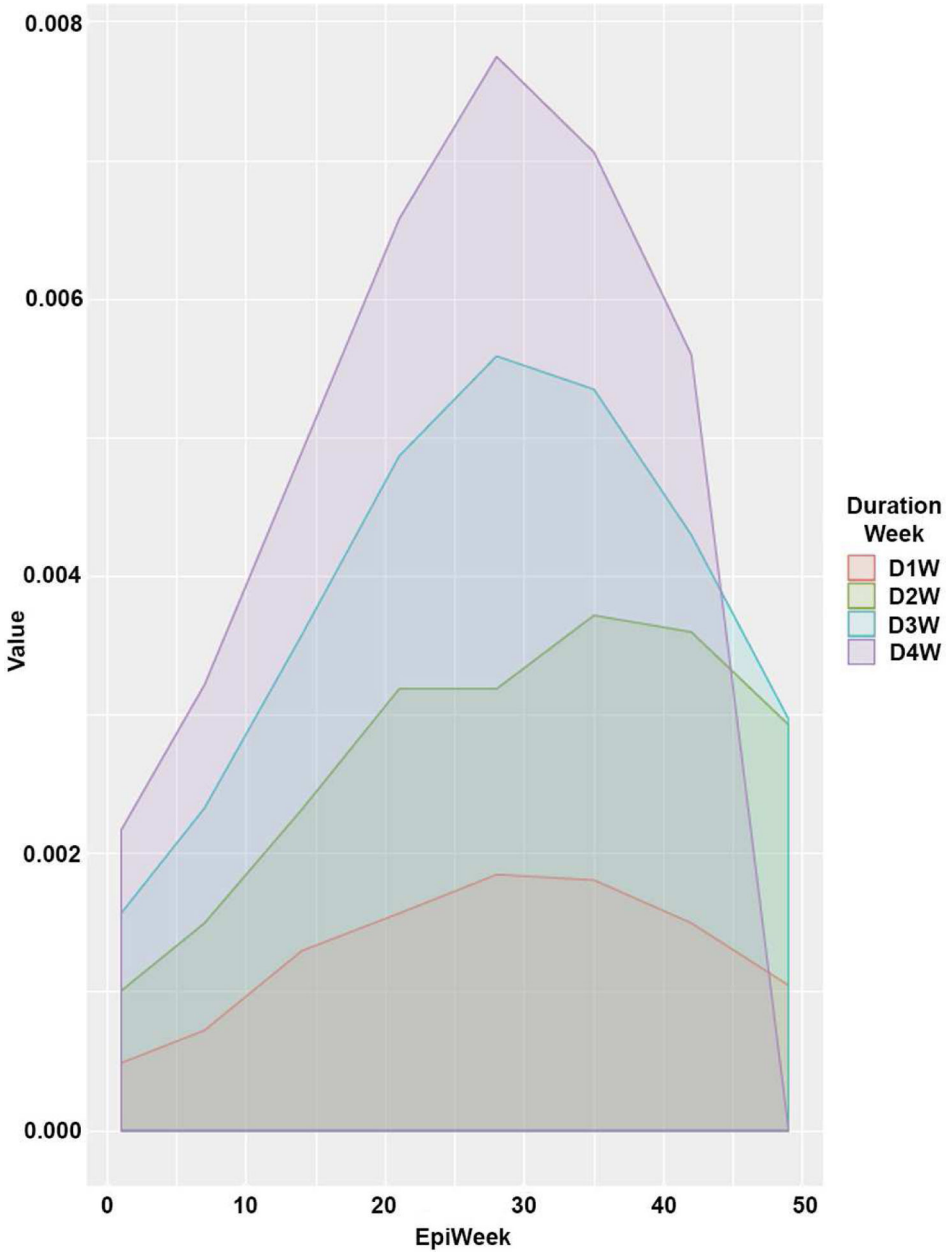

Figure 3.
Results of the risks of malaria calculated for the municipality of Lábrea, Amazonas state, Brazil.

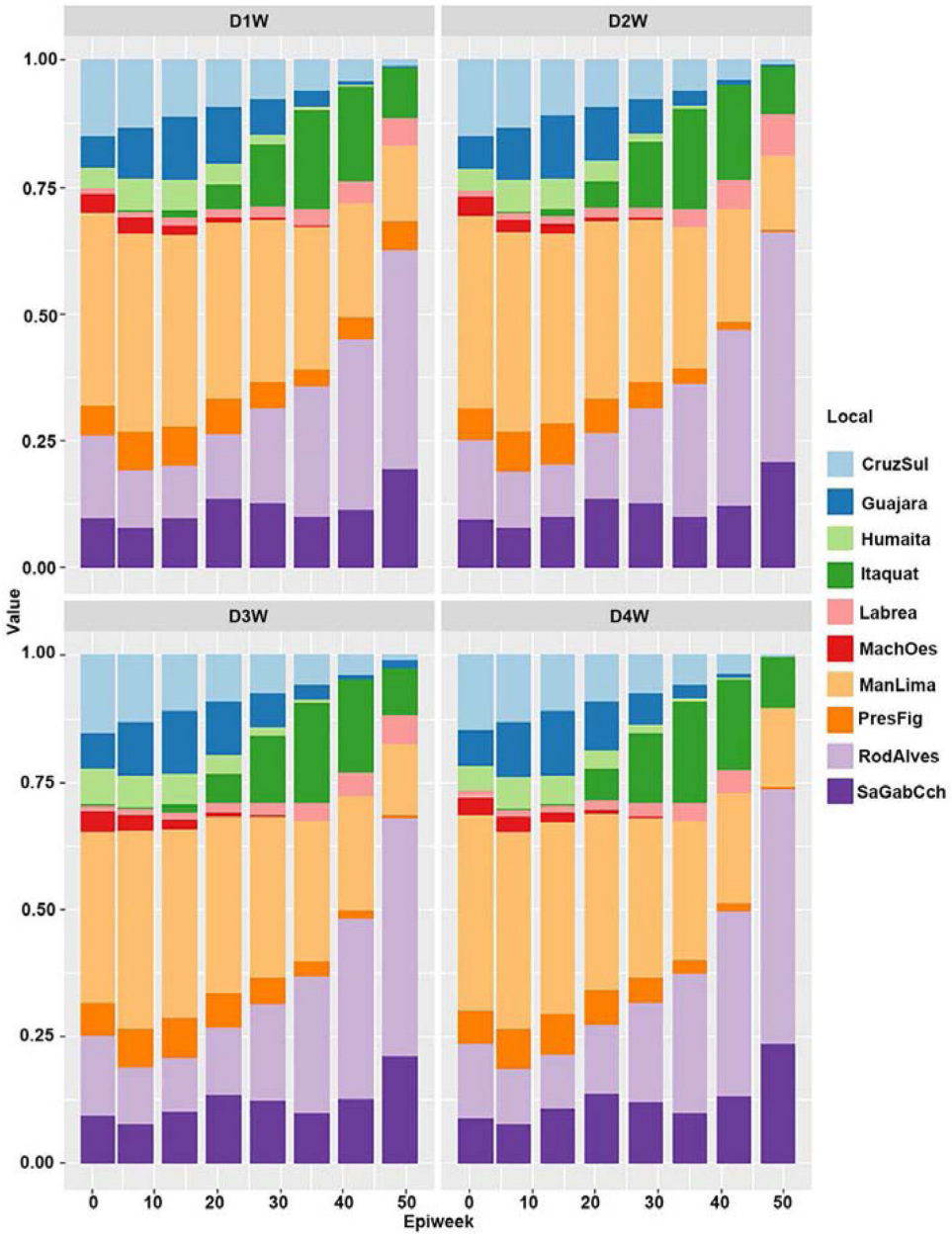

Figure 4.
Maximum risk of malaria calculated according to equation (8) and normalized for comparison purposes for the 10 municipalities studied.

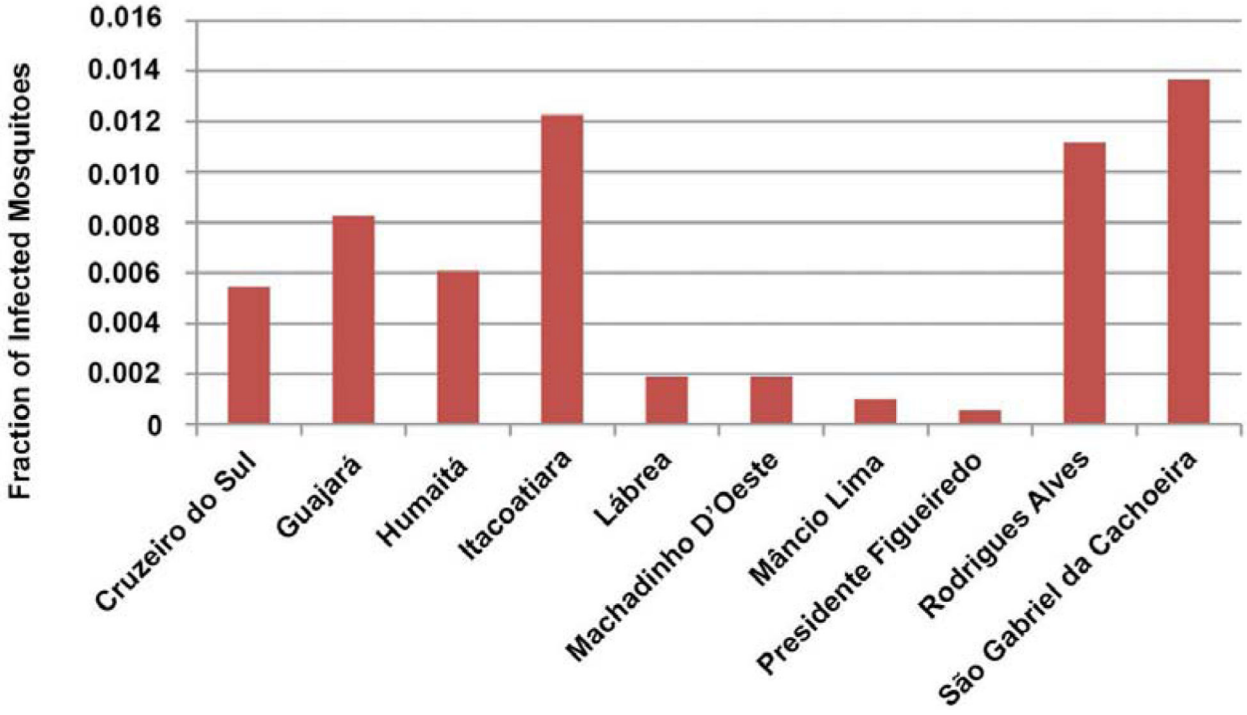

Figure 5.
Proportion of infected Anophelinae mosquitoes with both *P. vivax* and *P. falciparum* for the 10 municipalities studied.

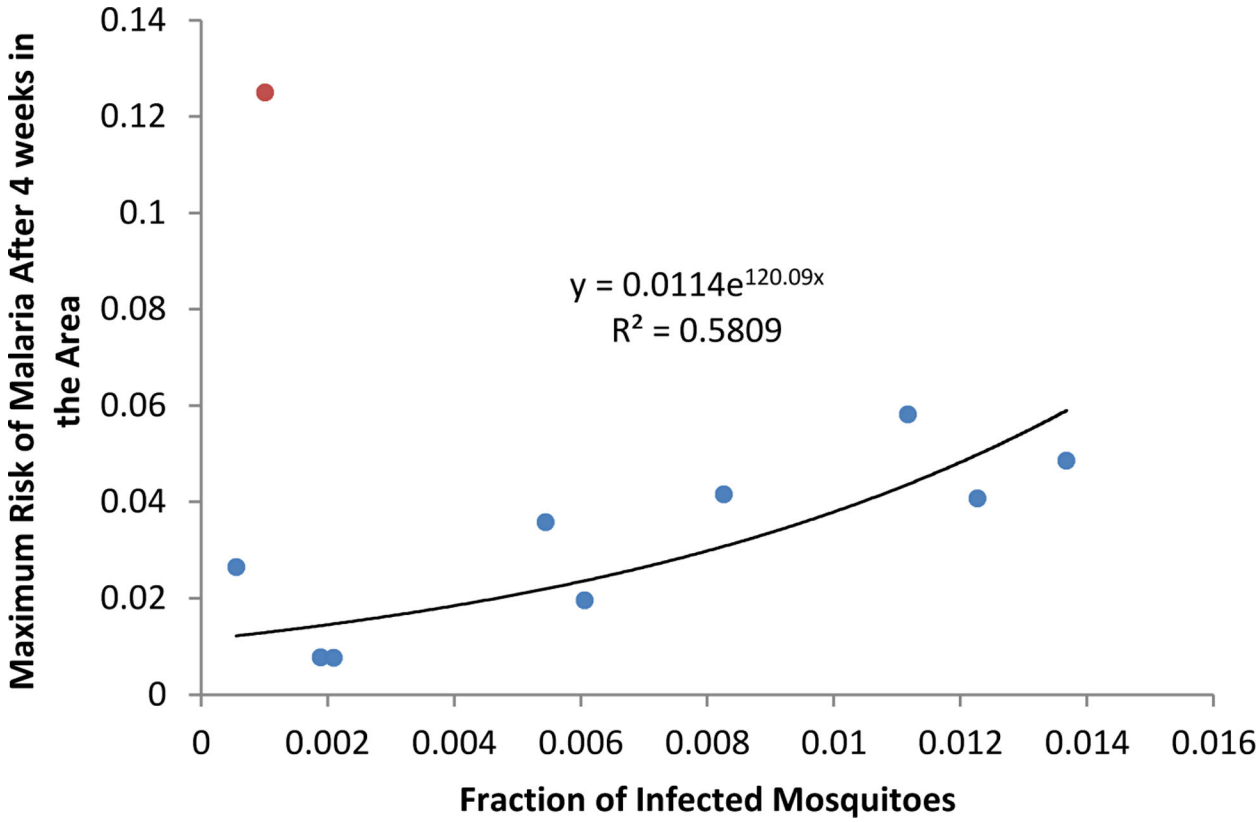

Figure 6.

Correlation between maximum risk of infection and the fraction of infected *Anopheles* mosquitoes with both *P. vivax* and *P. falciparum* for 10 municipalities studied. Mâncio Lima (red dot) was an outlier.

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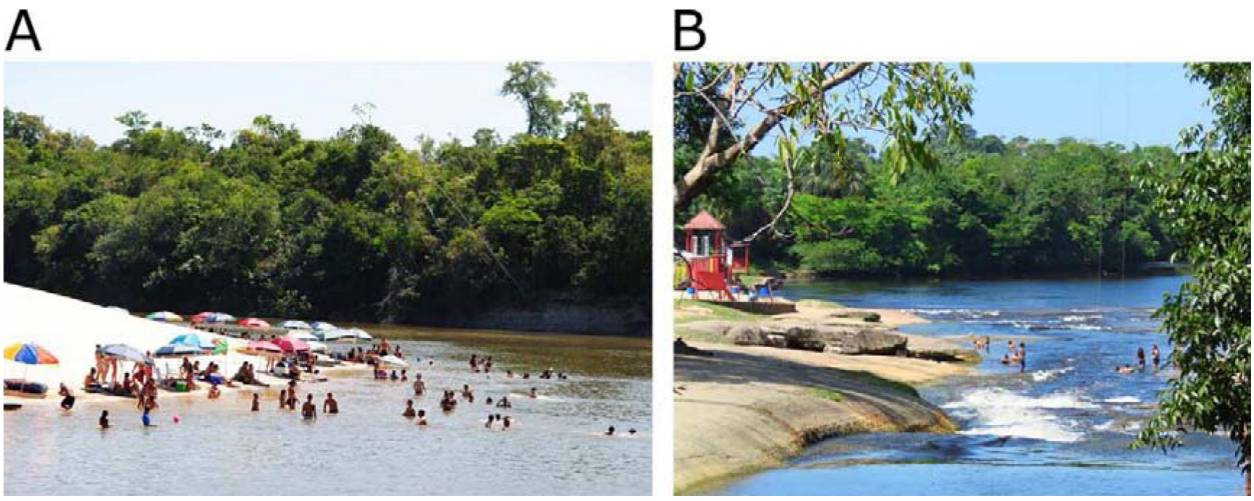

Figure 7.

Paradise hotspots for tourism in th municipalities where the risk of non-immune travelers acquiring *Plasmodium* spp. is not negligible. (A) The shorelines of the Ipixuna River offer an amazing scenario for river beach tourists in Santa Maria Auxiliadora and Humaitá-AM. This image was taken July 17, 2016, by GZL using a Nikon D3000 camera (aperture and depth of field = f/7.1; shutter speed = 1/200 s; ISO speed = ISO-100). (B) Waterfalls of the Urubuí River in the tourist city of Presidente Figueiredo-AM receive hundreds of thousands of tourists every year. This image was taken August 18, 2017, by ESB using a Canon PowerShot SX60 HS camera (aperture and depth of field = f/5; shutter speed = 1/1000 s; ISO speed = ISO-320). The images were not edited or cropped from the originals.

Table 1.

State variables and parameters used in the models.

$S_{t_0}(t)$	Number of susceptible travelers at time t that belong to cohort t_0
$I_{t_0}(t)$	Number of new infections of travelers belonging to the cohort $t_0$during the interval between t and $t + dt$
λ(t)	Force of infection in the Amazon region at time t
σ_{t_0}	Rate at which the travelers belonging to cohort t_0 return home
μ	Natural mortality rate of travelers (assumed constant)

Table 2.

Fitting parameters of fitting equation (1) for the studied locations grouped according to the municipalities.

Municipality	**c_1 (95% C.I.)**	**c_2 (95% C.I.)**	**c_3 (95% C.I.)**	**c_4 (95% C.I.)**	**RMSE***
Lábrea	57.77 (42.37–79.96)	31.50 (30.78–33.41)	349.84 (179.81–786.64)	10.26 (−14.75–23.03)	12.46
Cruzeiro do Sul	596.59 (565.24–637.29)	15.21 (14.13–16.10)	451.54 (362.21–570.97)	−31.35 (−79.85–2.06)	49.43
São Gabriel da Cachoeira	272.96 (232.84–360.63)	23.03 (21.21–30.50)	103.32 (24.17–279.42)	121.40 (67.16–188.25)	53.55
Rodrigues Alves	74.52 (62.81–86.93)	32.09 (30.64–34.15)	225.61 (126.75–385.81)	53.46 (42.96–63.60)	14.97
Presidente Figueiredo	58.35 (48.53–68.07)	17.57 (16.78–18.67)	249.10 (139.95–425.98)	−0,035 (−20,038–29.97)	13.51
MâncioLima	277.65 (230.93–323.91)	18.99 (18.11–20.18)	388.56 (218.31–664.47)	9.42×10^{-4} (−49.81–53.45)	27.94
Guajará	92.61 (77.02–108.04)	17.79 (16.97–18.91)	178.24 (100.14–295.63)	1.28×10^{-4} (−29.98–36.45)	15.69
Humaitá	43.36 (36.07–50.58)	14.65 (13.97–15.57)	151.75 (85.26–251.69)	2.02×10^{-5} (−7.05–8.98)	5.30
Itaquatiara	97.24 (80.89–113.43)	33.39 (31.84–35.48)	149.08 (83.76–247.26)	3.71×10^{-6} (−19.01–20.08)	15.91
Machadinho D'Oeste	16.64 (13.84–19.41)	8.76 (8.35–9.31)	205.132 (115.25–340.22)	$-1{,}54\times10^{-3}$ (−4.01–4.99)	5.18

*Root Mean Square Errors

Table 3.

Risks of malaria calculated according to equation (8) for the city of Lábrea, Amazonas state, as a function of the time in epidemiological weeks of arrival in the city and the duration of the visit in weeks.

Duration in weeks of the visit / **Time of arrival in the locality**	**1**	**2**	**3**	**4**
1	9.42×10^{-4} (0–9.42×10^{-4})	1.01×10^{-3}. (0–1.66×10^{-3})	1.57×10^{-3}. (0–2.54×10^{-3})	2.17×10^{-3}. (0–3.46×10^{-3})
7	7.24×10^{-4} (9.36×10^{-5}–1.05×10^{-3})	1.50×10^{-3} (2.37×10^{-4}–2.15×10^{-3})	2.33×10^{-3} (4.34×10^{-4}–3.30×10^{-3})	3.22×10^{-3} (6.86×10^{-4}–4.50×10^{-3})
14	1.13×10^{-3} (4.96×10^{-4}–1.45×10^{-3})	2.32×10^{-3} (1.06×10^{-3}–2.97×10^{-3})	3.58×10^{-3} (1.68×10^{-3}–4.55×10^{-3})	4.90×10^{-3} (2.38×10^{-3}–6.20×10^{-3})
21	1.57×10^{-3} (9.36×10^{-4}–1.89×10^{-3})	3.19×10^{-3} (1.93×10^{-3}–3.84×10^{-3})	4.87×10^{-3} (2.99×10^{-3}–5.84×10^{-3})	6.58×10^{-3} (4.06×10^{-3}–7.88×10^{-3})
28	1.85×10^{-3} (1.22×10^{-3}–2.17×10^{-3})	3.72×10^{-3} (2.45×10^{-3}–4.36×10^{-3})	5.59×10^{-3} (3.70×10^{-3}–6.56×10^{-3})	7.75×10^{-3} (4.90×10^{-3}–8.766×10^{-3})
35	1.81×10^{-3} (1.18×10^{-3}–2.13×10^{-3})	3.36×10^{-3} (2.36×10^{-3}–4.24×10^{-3})	5.35×10^{-3} (3.46×10^{-3}–6.32×10^{-3})	7.06×10^{-3} (4.53×10^{-3}–8.35×10^{-3})
42	1.05×10^{-3} (8.63×10^{-4}–1.82×10^{-3})	2.93×10^{-3} (2.66×10^{-3}–3.58×10^{-3})	4.30×10^{-3} (2.40×10^{-3}–5.27×10^{-3})	5.60×10^{-3} (3.08×10^{-3}–6.90×10^{-3})
49	1.05×10^{-3} (4.17×10^{-4}–1.37×10^{-3})	2.04×10^{-3} (7.73×10^{-4}–2.68×10^{-3})	2.97×10^{-3} (1.07×10^{-3}–3.94×10^{-3})	----

Table 4.

Maximum risk of acquiring malaria by visiting the ten Amazonian municipalities studied. The risk was calculated according to equation (8).

City (week)	Risk for 1- week visit (95% C.I.)	Risk for 2- week visit (95% C.I.)	Risk for 3- week visit (95% C.I.)	Risk for 4- week visit (95% C.I.)
Lábrea (week 28)	1.85×10^{-3} (1.22×10^{-3} – 2.17×10^{-3})	3.72×10^{-3} (2.45×10^{-3} – 4.36×10^{-3})	5.59×10^{-3} (3.70×10^{-3} – 6.56×10^{-3})	7.75×10^{-3} (4.90×10^{-3} – 8.76×10^{-3})
Cruzeiro do Sul (week 14)	8.89×10^{-3} (7.71×10^{-3} – 1.06×10^{-2})	1.76×10^{-2} (1.54×10^{-2} – 2.01×10^{-2})	2.69×10^{-2} (2.29×10^{-2} – 3.05×10^{-2})	3.58×10^{-2} (3.04×10^{-2} – 4.03×10^{-2})
São Gabriel da Cachoeira (week 21)	1.21×10^{-2} (9.27×10^{-3} – 1.42×10^{-2})	2.43×10^{-2} (1.81×10^{-2} – 2.90×10^{-2})	3.65×10^{-2} (2.60×10^{-2} – 4.43×10^{-2})	4.86×10^{-2} (3.27×10^{-2} – 5.99×10^{-2})
Rodrigues Alves (week 28)	1.43×10^{-2} (1.19×10^{-2} – 1.68×10^{-2})	2.88×10^{-2} (2.40×10^{-2} – 3.40×10^{-2})	4.34×10^{-2} (3.62×10^{-2} – 5.13×10^{-2})	5.82×10^{-2} (4.84×10^{-2} – 6.89×10^{-2})
Presidente Figueiredo (week 14)	6.47×10^{-3} (3.08×10^{-3} – 1.10×10^{-2})	1.31×10^{-2} (6.29×10^{-3} – 2.21×10^{-2})	1.97×10^{-2} (9.57×10^{-3} – 3.33×10^{-2})	2.65×10^{-2} (1.28×10^{-2} – 4.46×10^{-2})
MâncioLima (week 14)	3.04×10^{-2} (1.93×10^{-2} – 4.17×10^{-2})	6.15×10^{-2} (3.94×10^{-2} – 8.40×10^{-2})	9.30×10^{-2} (5.99×10^{-2} – 1.27×10^{-1})	1.25×10^{-1} (8.10×10^{-2} – 1.69×10^{-1})
Guajará (week 14)	1.00×10^{-2} (4.89×10^{-3} – 1.59×10^{-2})	2.04×10^{-2} (1.02×10^{-2} – 3.20×10^{-2})	3.09×10^{-2} (1.55×10^{-2} – 4.84×10^{-2})	4.16×10^{-2} (2.09×10^{-2} – 6.50×10^{-2})
Humaitá (week 14)	4.99×10^{-3} (3.32×10^{-3} – 5.55×10^{-2})	9.97×10^{-3} (6.55×10^{-3} – 1.37×10^{-2})	1.49×10^{-2} (9.56×10^{-3} – 2.05×10^{-2})	1.96×10^{-2} (1.24×10^{-2} – 2.73×10^{-2})
Itacoatiara (week 35)	1.08×10^{-2} (5.71×10^{-3} – 1.53×10^{-2})	2.13×10^{-2} (1.07×10^{-2} – 3.06×10^{-2})	3.13×10^{-2} (1.49×10^{-2} – 4.58×10^{-2})	4.07×10^{-2} (1.82×10^{-2} – 6.07×10^{-2})
Machadinho D'Oeste (week 7)	1.90×10^{-3} (1.12×10^{-3} – 2.79×10^{-3})	3.19×10^{-3} (2.25×10^{-3} – 5.06×10^{-3})	5.37×10^{-3} (3.67×10^{-3} – 8.41×10^{-3})	7.62×10^{-3} (4.43×10^{-3} – 1.12×10^{-2})