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Factors associated with hospitalizations due to severe malaria in the non-endemic Brazilian region: a case–control study in the extra-Amazon Region from 2011 to 2019

Anderson Coutinho da Silva[1,2], Elisabeth Carmem Duarte[1], Paola Barbosa Marchesini[2], Giselle Maria Rachid Viana[3], Walter Massa Ramalho[1†] and Klauss K. S. Garcia[1*†]

Abstract

Background Malaria is infectious disease with low occurrence in Brazil extra-Amazon Region. Despite this, higher lethality is observed in this region compared to the country's endemic area. Therefore, this study aimed to analyse factors associated with malaria hospitalizations (severe malaria) in the extra-Amazon Region, in order to prevent deaths.

Methods A case–control design was used, utilizing data from the Brazilian Notifiable Diseases Information System (Sinan) and hospitalization records from the Unified Health System (SIH/SUS) from 2011 to 2019. Cases comprised hospitalized malaria patients, while controls included reported malaria notifications without hospitalization. Probabilistic record linkage techniques were employed, and associations were analysed using multiple logistic regression with a 0.05 significance level.

Results The main risk factors identified were: Black or mixed-race ethnicity (OR = 1.22; 95% CI 1.04–1.43), low education (elementary school OR = 2.21; 95% CI 1.78–2.75 or high school OR = 1.72; 95% CI 1.39–2.13), infection outside the extra-Amazon Region (Amazon Region OR = 1.50; 95% CI 1.15–1.96 or abroad OR = 1.72; 95% CI 1.28–2.32), high parasite count (501 to 10,000/mm^3 OR = 1.51; 95% CI 1.27–1.80, 10,001 to 100,000/mm^3 OR = 1.77; 95% CI 2.87–1.96 or higher than 100,000/mm^3 OR = 3.15; 95% CI 2.20–4.50) and delayed treatment (after 3–7 days symptoms onset OR = 1.74; 95% CI 1.36–2.24 or 8 days or more OR = 2.08; 95% CI 1.62–2.66). Active case detection was a protective factor (OR = 0.65; 95% CI 0.54–0.78).

Conclusions Delayed treatment remains a key factor in the occurrence of severe malaria, leading to high parasitaemia and revealing inequalities in access to healthcare based on socioeconomic differences. Travel to the Amazon Region or other countries also poses a challenge, requiring strengthened traveller health strategies and increased surveillance awareness to promptly suspect and identify cases.

Keywords Malaria, Severe malaria, Hospitalizations, Hospital admissions, Extra-Amazon Region, Epidemiological surveillance, Epidemiology

†Walter Massa Ramalho and Klauss K. S. Garcia have contributed equally to this work.

*Correspondence:
Klauss K. S. Garcia
kleydmann25@gmail.com
Full list of author information is available at the end of the article

Background

Malaria is an infectious disease responsible for high morbidity and mortality worldwide, particularly in tropical and subtropical regions [1]. In 2023, according to the World Health Organization (WHO), 263 million new notifications of malaria were reported across 83 countries. Additionally, more than 597,000 deaths were recorded [2].

In 2023, Brazil reported 140,265 new malaria infections [3], 99% of them occurred in the Amazon Region. Conversely, the 1% notified in the extra-Amazon Region are predominantly imported from the Amazon Region or other endemic countries [4, 5]. *Plasmodium vivax* infections are major in the country, accounting for approximately 83% of all notifications [6], and in the extra-Amazon Region imported notifications are major (~ 79%), with an approximate 32% occurrence of *Plasmodium falciparum* infections [5, 7].

Low transmission in the extra-Amazon Region poses challenges for disease surveillance, reducing sensitivity and causing both citizens and healthcare professionals to overlook malaria as a potential diagnosis [8]. In Brazil, malaria diagnosis and treatment are free and provided by the National Health System (SUS). The diagnosis is primarily conducted through microscopic examination of blood, using thin or thick smear techniques (thick drop) or a Rapid Diagnostic Test. In facilities with enhanced diagnostic capacity, the disease can be diagnosed with high sensitivity using Polymerase Chain Reaction (PCR), although the use of this technique is limited due to its cost and complexity [9].

In 2022, according to data from the Ministry of Health, 2114 malaria hospitalizations were recorded in Brazil, representing approximately 1.6% of the malaria notifications reported that year. Of these hospitalizations, about 10.5% (223) occurred in the extra-Amazon Region [10]. Most severe malaria are caused by *P. falciparum*, although severe infections with *P. vivax* have also been reported. Severe malaria often necessitates hospitalization and can lead to death [11].

Severe malaria has been associated in previous studies with factors such as young (< 5 years) or advanced age (> 65 years), comorbidities, travel history and pregnancy. Notably, in low-transmission areas, the lack of immunity to the parasite and treatment delays, including misdiagnosis during the initial medical consultations, play a significant role in exacerbating disease outcomes [12–14]. In regions with limited malaria transmission, travellers are at increased risk due to potential exposure to different malaria strains, often resulting in more severe forms of the disease upon return. Additionally, the presence of comorbidities can also increase the likelihood of complications [12–14].

Malaria notifications in Brazil are reported through two distinct systems. In the Brazilian Amazon Region (endemic area), the Malaria Epidemiological Surveillance Information System (Sivep-Malaria) is used, while in the extra-Amazon Region (non-endemic area), notifications are reported through the Notifiable Diseases Information System (Sinan). These systems operate independently and lack interoperability, meaning that data recorded in one system is not necessarily available in the other. This separation exists due to historical differences in the malaria surveillance model in Brazil [15]. Meanwhile, malaria hospitalizations are recorded in the Hospital Information System of the Unified Health System (SIH/SUS), which exclusively encompasses SUS-funded hospitalizations and has an estimated national coverage of 70 to 80%. SIH/SUS does not present interoperability with Sinan nor with Sivep-Malaria, making hospitalizations surveillance and investigations more challenging [13].

This study aims to describe hospitalizations in the extra-Amazon Region and analyse the factors associated with malaria hospitalizations in this region.

Methods

Study design

Considering that malaria in the extra-Amazon Region of Brazil has a lethality rate approximately 72 times higher than in the country's endemic region, understanding the factors associated with severe malaria in this scenario can contribute to enhancing public policies focused on reducing its incidence and, consequently, preventing deaths in the region. This aligns with the goals of the elimination plan, which aims for zero malaria-related deaths by 2030. To contribute to this objective, a case–control study was conducted to analyse factors associated with malaria hospitalizations in the extra-Amazon Region of Brazil (states of Alagoas, Bahia, Ceará, Distrito Federal, Espírito Santo, Goiás, Mato Grosso do Sul, Minas Gerais, Paraíba, Paraná, Pernambuco, Piauí, Rio de Janeiro, Rio Grande do Norte, Rio Grande do Sul, Santa Catarina, São Paulo, and Sergipe) from 2011 to 2019. The study utilized secondary data from two information systems: Sinan and SIH/SUS, covering the years 2011 to 2019.

Access to information from secondary databases of official information systems allowed the use of all available data from the Sinan and SIH/SUS databases, thus, no sampling techniques were used. As these are secondary data, the treatment was performed after collection. To ensure quality control, Sinan variables were used to retrieve a large portion of unspecified malaria diagnoses and other information from SIH/SUS [16]. Additionally, duplicate records were removed. The blank data were accounted as 'not available' information.

The record linkage process

To identify cases and controls, record linkage techniques were employed, specifically probabilistic linkage [17, 18]. Only new infections (Sinan) and malaria hospitalizations (SIH/SUS) recorded in the extra-Amazon states were included. Hospitalizations or infections that occurred in the Amazon Region were not included in this analysis.

The following variables were used for the data linkage process: patient's first name, last name, mother's first name, mother's last name, and date of birth, available in both systems (Sinan and SIH/SUS). The probabilistic record linkage process was performed using R and RStudio statistical analysis software [19] and the parameters for linkage were developed by the research team, as detailed by Garcia et al. [20].

A manual review of the linked records was performed by the involved researchers, and the data were subsequently anonymized. Duplicated records were reviewed, retaining only records where the malaria occurred closest to the hospitalization date to ensure epidemiological data corresponded to the patient's hospitalization. Follow-up exams (Cure Verification Slides—Lâminas de Verificação de Cura—LVC), recommended by the Brazilian Ministry of Health for detecting potential relapses [21], were considered duplicates and excluded from the process.

Definition of cases and controls

Hospitalizations were included as 'cases' if the primary or secondary diagnosis was malaria (ICD-10 B50 to B54). It is emphasized that the criteria for malaria hospitalization are defined by the healthcare professional at the time of patient care, making it impossible to establish a single criterion for all hospitalizations. Linked records were only considered as true linked-pairs when the interval between the onset of malaria symptoms and hospitalization ranged from 53 days before the hospitalization or 4 days after it, based on the study of Llanos-Chea et al. [12]. This time frame ensures that the temporal relationship between the last episode of malaria and hospitalization is met, allowing for more accurate measurement of associated factors.

The 'Controls' were defined as confirmed malaria new infections reported in the extra-Amazon Region (Sinan) that did not evolve to hospitalizations (therefore, did not have a linked-pair in the record linkage process). The detailed flowchart for the Record linkage process can be seen in Fig. 1.

Statistical analysis

To describe hospitalizations, the variables of interest were: Date of hospitalization, Sex, Race/Color, Age group, Parasitic species, Hospitalization region, Hospital ownership and Residence region. The variables of interest in the case–control study were obtained from Sinan (available for both cases and controls) and include: Date of notification, Sex, Race/Color, Age Group, Parasitic Species, Region of Residence, Pregnancy Status, Education Level, Place of Infection, Activities in the Last 15 Days, Parasite Density, Date of Treatment, and Type of Detection. Note that the information is obtained directly through patient investigation form in the case of Sinan and, in the case of SIH/SUS, from the hospital admission authorization form, obtained through patient investigation or their companion. Educational level was categorized according to the highest level of formal education completed by the participant at the time of the investigation as it follows: illiterate, for 0 years of study, elementary school for up to 9 years of study, high school to up to 12 years of school and higher education to more than 12 years of school. For young children who had not yet started school, the category 'Ignored' was assigned. For those attending school, the corresponding education level was recorded based on the Brazilian educational system classification.

The type of detection options are: 'Active detection', which is the systematic search and identification of cases through surveillance activities, such as screening asymptomatic individuals or targeted investigations in risk areas—the health services seek the patient; and 'Passive detection', when individuals seek medical attention for symptoms, relying on healthcare services for diagnosis and reporting—the patient seeks the health services. The criterion for the type of detection is determined by the healthcare professional and recorded in the investigation form. For woman of non-reproductive age and men, 'Not applicable' was applied.

Quantitative analyses of variables included descriptive and analytical statistics. Descriptive analyses were performed according to time, person, and place characteristics. Quantitative maps were constructed using data distribution by quartiles, while volume maps (circles) utilized natural breaks. Flow maps were created, with the municipality of residence as the origin and the municipality of hospitalization as the destination, representing flows/transits.

To analyse factors associated with hospitalizations, the Odds Ratio (OR) with a 95% confidence interval (CI) and a significant level of 5% ($p < 0.05$) was used. Chi-square tests were conducted alongside OR calculations, followed by multiple logistic regression analysis to evaluate hospitalization outcomes. The final model was constructed by including all variables and subsequently removing non-significant variables one by one (backwards method). Statistical analyses were performed using RStudio and Jamovi (2.3.28). QGIS 3.16 was used for geographical

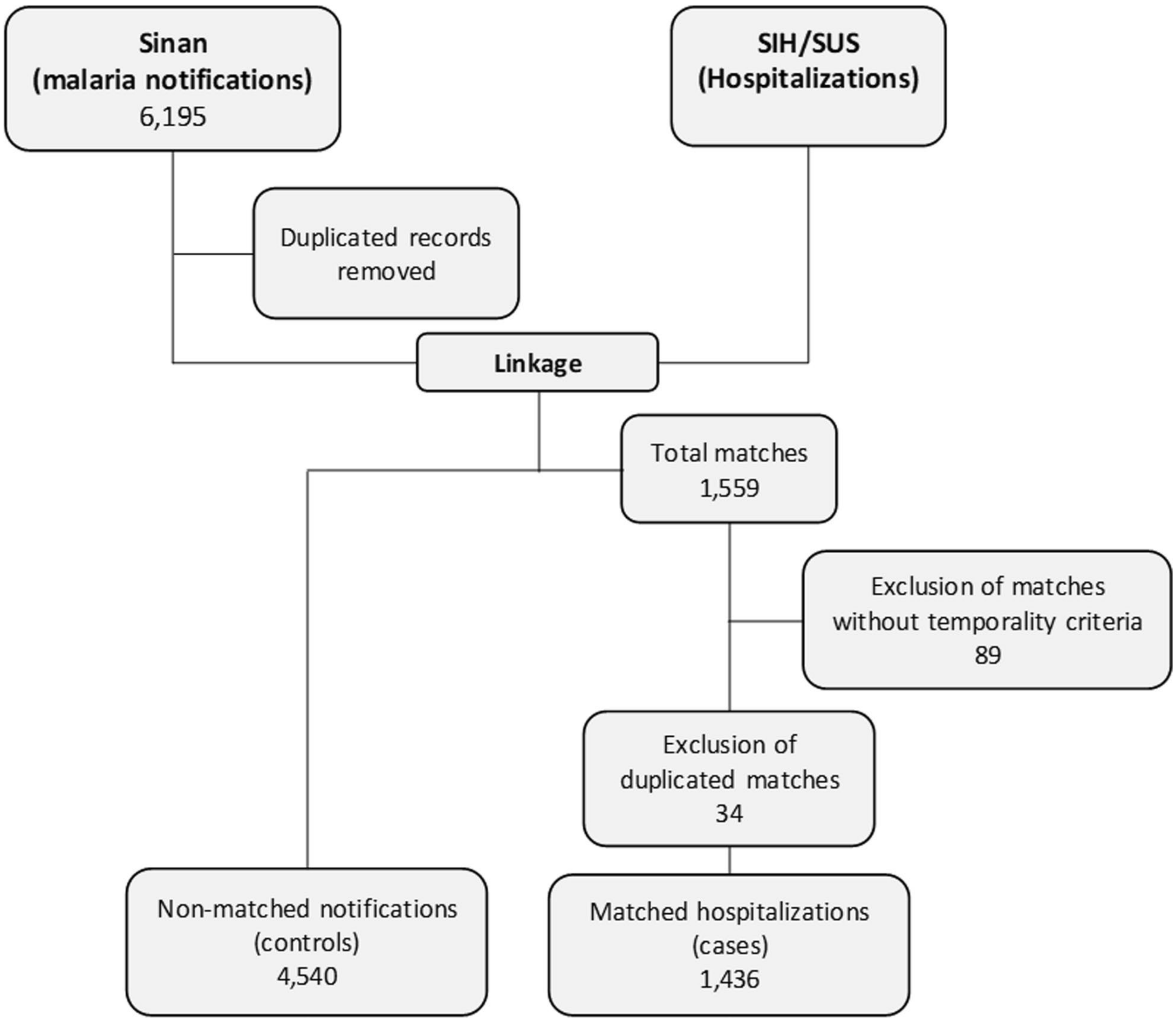

Fig. 1 Flowchart of the record linkage and selection of cases and controls in the study. Source: Author's elaboration

data plots. The design and analyses were based on the analytical strategy from the study previously published by Garcia and colleagues [22].

Results

Epidemiological scenario

From 2011 to 2019, 6195 malaria new infections were recorded in the extra-Amazon Region. Among the states, São Paulo reported the highest number of notifications (23.1%), followed by Rio de Janeiro (11.4%), Minas Gerais (9.8%), Espírito Santo (9.0%), and Goiás (8.0%), with São Paulo consistently leading every year. At the municipal level, notifications were widely distributed, although there was a noticeable concentration in major capitals, including São Paulo (10.6%), Rio de Janeiro (9.8%), Goiânia (5.3%), Brasília (3.9%), and Belo Horizonte (3.7%).

The predominant profile of notifications was male (78.2%), Black or mixed-race (47.0%), and aged between 20 and 39 years (47.9%). Most individuals resided in the extra-Amazon Region (87.8%), and the majority reported probable infection in the Amazon Region (47.4%). Travel/transport-related activities were the most reported exposure (35.9%), and the most prevalent species was *P. vivax* (63.0%), with parasitaemia (parasite density) typically up to 500 parasites per mm3 (43.7%). Most notifications (38.3%) indicated a delay of 3 to 7 days from symptom onset to treatment initiation.

From 2011 to 2019, 2137 hospitalizations were recorded in the extra-Amazon Region. Most hospitalizations were reported in São Paulo (30.2%), followed by Piauí (9.9%) and Goiás (8.0%). São Paulo led in hospitalizations every year. However, when considering hospitalization rates, Piauí ranked first, with 0.74 hospitalizations per 100,000 inhabitants, followed by Goiás (0.29) and the Federal District (0.22). The average hospitalization rate for the extra-Amazon Region was 0.14 hospitalizations per 100,000 inhabitants.

Most hospitalizations occurred in male patients (77.0%), Black or mixed-race individuals (45.6%), and those aged 20 to 39 years (45.1%). The most reported parasitic species was unspecified malaria (46.0%). Hospitalizations primarily took place in the Southeast region (45.2%), within the public healthcare system (71.8%), and among residents of the extra-Amazon Region (94.2%). The description of hospitalization profiles for the period analysed is detailed in Table 1.

Most hospitalizations occurred in state capitals, totalling 52.7% of all hospitalizations. Exceptions are Wenceslau Guimarães in Bahia state and Domingos Martins in the state of Espírito Santo (Fig. 2a). According to SIH/SUS data, 91.6% (1958) of hospitalizations in the extra-Amazon Region occurred in the patient's state of residence. At the municipal level, 58.2% (893) of hospitalizations took place in the patient's municipality of residence. Among hospitalizations that did not occur in the municipality of residence, 56.1% (501) were recorded in state capitals. Although some hospitalization originated from the Amazon Region, these were less frequent. A significant flow of hospitalizations to capitals within the extra-Amazon Region was noted (Fig. 2b and Table 2).

Table 1 Description of hospitalizations for malaria reported in the SIH/SUS in states in the extra-Amazon Region, Brazil, 2011 to 2019. Source: SIH/SUS

	Hospitalizations (N = 2137)	%
Year		
2011	333	15.60
2012	277	13.00
2013	281	13.10
2014	210	9.80
2015	184	8.60
2016	175	8.20
2017	179	8.40
2018	264	12.40
2019	234	10.90
Sex		
Female	491	23.00
Male	1646	77.00
Race/Color		
Black or mixed race	974	45.60
White	722	33.80
Asian	33	1.50
Indigenous	1	0.00
Unknown	407	19.00
Age group		
Less than 1 year	29	1.40
1 to 9 years	92	4.30
10 to 19 years	136	6.40
20 to 39 years	965	45.20
40 to 59 years	737	34.50
60 years or older	178	8.30
Parasitic species		
P. vivax	518	24.20
P. falciparum	497	23.30
P. malariae	123	5.80
P. ovale	14	0.70
Monkey malaria (*Plasmodium* species from monkeys)	2	0.10
Unspecified malaria (ICD10-B54)	983	46.00
Region of hospitalization		
Central-West	282	13.20
Northeast	582	27.20
Southeast	966	45.20
South	307	14.40
Hospital ownership		
Public Service	1534	71.80
Private Service	601	28.10
Unknown	2	0.10
Region of residence		
Amazon Region	123	5.80
Extra-Amazon Region	2014	94.20

The 'Unknown' category for Race/Color was not specified in the hospital admission authorization form. Data on 'Unknown' Hospital Ownership could not be identified

Case and control profile and analysis of associated factors

From the probabilistic record linkage results, 1,436 cases and 4,540 controls were identified. In the final multiple analysis model, the following factors were significantly associated with hospitalization: Black or mixed-race ethnicity (OR = 1.22; 95% CI 1.04–1.43); education level up to elementary (OR = 2.21; 95% CI 1.78–2.75) or high school (OR = 1.72; 95% CI 1.39–2.13); blood smear conducted through active case detection (OR = 0.65; 95% CI 0.54–0.78); infection in the Amazon Region (OR = 1.50; 95% CI 1.15–1.96) or other countries (OR = 1.72; 95% CI 1.28–2.32); diagnosis with *P. falciparum* or mixed malaria (OR = 1.38; 95% CI 1.13–1.68); parasite density levels 501 to 10,000/mm^3 (OR = 1.51; 95% CI 1.27–1.80), 10,001 to 100,000/mm^3 (OR = 1.77; 95% CI 2.87–1.96) or higher than 100,000/mm^3 (OR = 3.15; 95% CI 2.20–4.50); and symptom onset intervals of 3–7 days (OR = 1.74; 95% CI 1.36–2.24) or 8 days or more (OR = 2.08; 95% CI 1.62–2.66). The results of the univariate, full and adjusted logistic regression analyses are presented in Table 3.

Discussion

This study provides a significant contribution to understanding the factors associated with severe malaria hospitalizations in a non-endemic region, expanding the knowledge of the disease's dynamics in areas with epidemiological patterns distinct from those observed in the Amazon Region. By addressing sociodemographic vulnerabilities, such as ethnicity, education level, and the origin of cases, the study identified critical gaps in the malaria surveillance and response system in the extra-Amazon Region. These findings hold practical and policy implications not only for Brazil but also for other countries facing similar challenges. On a global scale, the results offer an applicable model for malaria-free countries vulnerable to imported cases, supporting the development of adaptable strategies for surveillance, risk mitigation, and rapid outbreak response, ultimately contributing to the reduction of severe cases.

Approximately half of the malaria cases reported in Piauí from 2002 to 2013 were autochthonous. While imported cases occur are registered at the end of the rainy season, particularly in municipalities bordering Maranhão [23]. This trend was observed in hospitalizations originating from municipalities near the Maranhão border and from Maranhão itself. Regarding the high number of hospitalizations in Wenceslau Guimarães, Bahia, it was the result of an outbreak in 2018, which led to 50 confirmed cases, mainly within a settlement area [24].

It is important to understand that hospitalization is determined by medical criteria, not solely by clinical condition. Patients who are difficult to treat and more likely to relapse are hospitalized more frequently, as are children. In some cases, such as outbreaks like the one in Piauí, to prevent relapses and severe malaria cases, most patients are hospitalized until treatment is completed. Thus, not only the severity but also medical caution may be factors that lead to hospitalization in the extra-Amazon Region.

The profiles of hospitalizations in the extra-Amazon Region predominantly affected men, Black or mixed-race individuals, and those aged 20 to 39 years. In a study of Brazil's Extra-Amazon Region, Garcia et al. [5] identified a similar profile. According to the authors, this profile is closely linked to socioeconomic factors, such as education, economic activity, and income, which are inherently related to social inequalities. The analyses indicated that patients with lower educational attainment (elementary or high school) were more likely to be hospitalized than those with higher education. A similar profile was found by Forero-Peña et al. [25] in Venezuela, which was closely related to economic activities.

There was also an association between hospitalization risk and Black or mixed-race ethnicity. According to Silva et al. [26], most of the Black population holds less-skilled positions with lower pay, lives in areas with limited infrastructure services, and faces greater restrictions in accessing healthcare. When this population does access healthcare, the quality and effectiveness tend to be lower, contributing to an increased risk of severe malaria cases.

According to Degarege et al. [27] in a meta-analysis conducted, low education levels are usually associated with low income and low-standard housing, which are linked to a higher risk of malaria, heavily influenced by the limited access to diagnosis, treatment, and prevention measures, often due to difficulty in accessing these services because of a lack of economic resources. Education is connected to occupational opportunities and improved life status, further increasing knowledge and access to information that promotes health and health services, leading to better acceptance of prevention practices carried out by the individual as well as those promoted by local health services. At the same time, it promotes higher income and better housing [27]. Moreover, the difficulty in accessing services, whether due to distance and transportation costs or low quality of the services, contributes to delays in treatment.

Proper and timely treatment of malaria significantly reduces hospitalization risk. The low incidence of malaria in the extra-Amazon Region makes its diagnosis challenging for local physicians, as it is not part of their routine practice [28]. For example, in Rio de Janeiro, a healthcare professional in an emergency department is 466 times less likely to identify a malaria case than a dengue case. Moreover, 55% of malaria cases treated at the Evandro Chagas National Institute of Infectious Diseases (a reference centre in Rio de Janeiro) were initially misdiagnosed as dengue during the first consultation [28]. The adjusted regression model showed that patients treated more than 48 h after symptom onset were more likely to be hospitalized, with increasing likelihood for delays of 3–7 days or 8 days or more. Nearly all severe malaria cases are caused by *P. falciparum*, while *P. vivax* and *P. malariae* rarely cause severe complications [29].

Active detection was protective against hospitalization compared to passive detection. This is closely linked to surveillance activities during outbreaks and patient follow-ups during treatment. The notification of autochthonous cases, which represent a risk of reintroduction and a sharp increase in cases in a short time, is an alert for healthcare services. This alert prompts temporary sensitization of local surveillance systems, increasing the detection of undiagnosed patients and follow-up of those identified through an index case. These actions improve timely diagnosis and, consequently, reduce

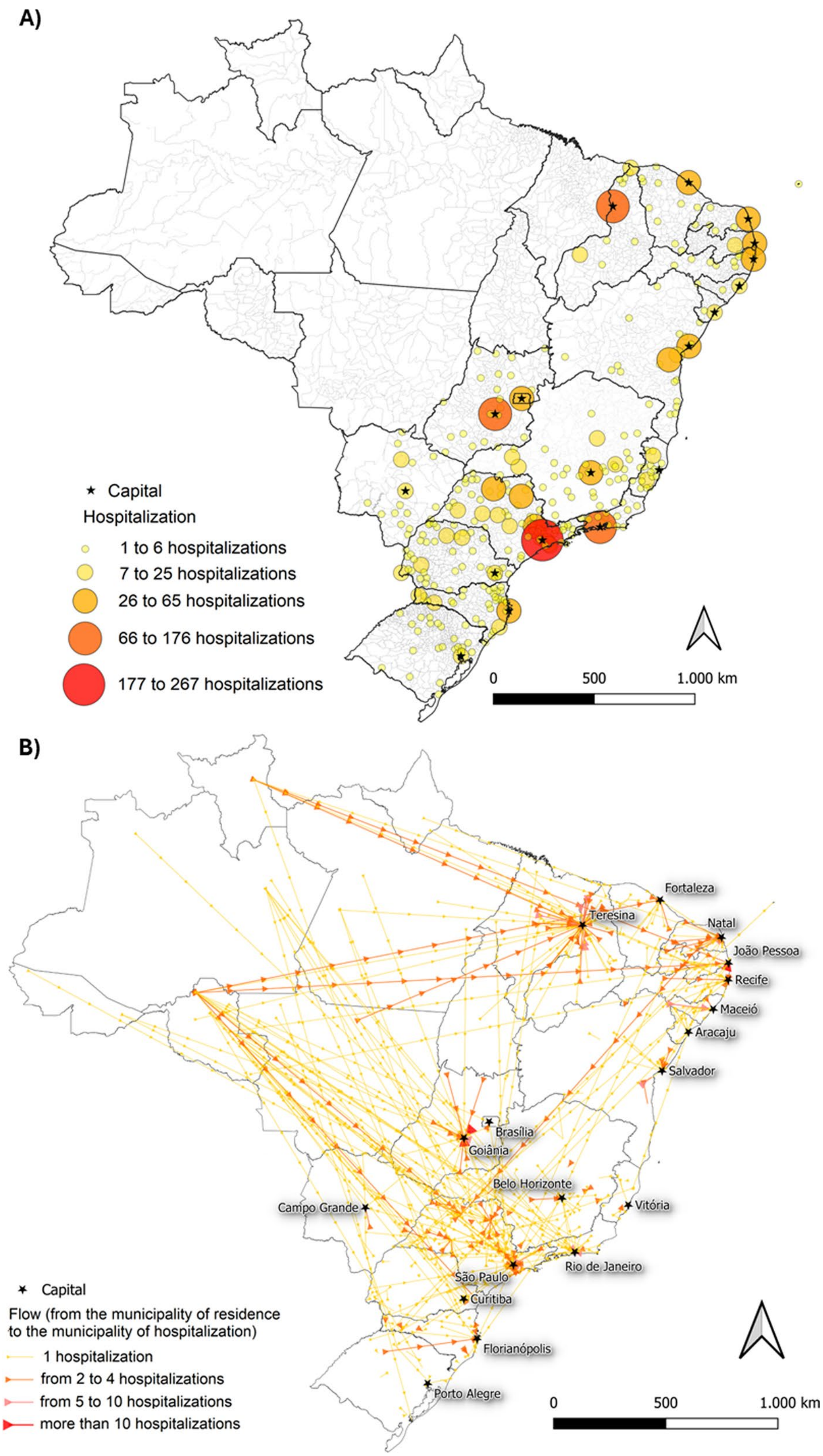

Fig. 2 Malaria hospitalizations in the extra-Amazon Region of Brazil, 2011–2019. **A** Hospitalizations by municipality; **B** hospitalization flows from the municipality of residence in the Extra-Amazon Region (**B**). Source: SIH/SUS

Table 2 Profile of study cases and controls and chi-square, Extra-Amazon Region, Brazil, 2011 to 2019. Source: SIH/SUS and Sinan

	Cases 1436	**% 24.00**	**Controls 4540**	**% 76.00**	**Total 5976**	**% 100.0**	**χ^2**
Sex							0.70
Male	1125	78.30	3531	77.80	4656	77.90	
Female	311	21.70	1009	22.20	1320	22.10	
Pregnant							0.093
No	160	11.14	554	12.20	714	11.95	
Yes	16	1.11	30	0.66	46	0.77	
Not applicable	1.240	86.35	3.856	84.93	5.096	85.27	
Unknown	20	1.39	100	2.20	120	2.01	
Race/Color							< 0.001*
Asian	12	0.80	49	1.10	61	1.00	
White	571	39.80	1956	43.10	2527	42.30	
Indigenous	5	0.30	23	0.50	28	0.50	
Black or mixed race	790	55.00	2020	44.50	2810	47.00	
Unknown	58	4.04	492	10.84	550	9.20	
Education level							< 0.001*
Illiterate	13	0.90	38	0.80	51	0.90	
Elementary school	436	30.40	1026	22.60	1462	24.50	
High school	351	24.40	934	20.60	1285	21.50	
Higher education	203	14.10	886	19.50	1089	18.20	
Unknown	433	30.15	1656	36.48	2.089	34.96	
Age group							0.028*
0 to 9 years	55	3.80	115	2.50	170	2.80	
10 to 19 years	92	6.40	238	5.20	330	5.50	
20 to 39 years	682	47.50	2178	48.00	2860	47.90	
40 to 59 years	493	34.30	1600	35.20	2093	35.00	
60 years or older	114	7.90	409	9.00	523	8.80	
Residence zone							< 0.001*
Rural	146	10.20	603	13.30	749	12.50	
Urban	1,214	84.50	3564	78.50	4778	80.00	
Unknown	76	5.29	373	8.22	449	7.51	
Type of detection							< 0.001*
Active Search	293	20.40	1356	29.90	1649	27.60	
Passive Search	1143	79.60	3184	70.10	4327	72.40	
Place of Infection							< 0.001*
Infection in the Extra-Amazon Region	140	9.70	741	16.30	881	14.70	
Infection in the Amazonian Region	703	49.00	2119	46.70	2822	47.20	
Imported from other countries	593	41.30	1680	37.00	2273	38.00	
Activities in the last 15 days							0.006*
Travel/transport-related activities	546	38.00	1607	35.40	2153	36.00	
Rural activities	137	9.50	523	11.50	660	11.00	
Road and dam construction	43	3.00	190	4.20	233	3.90	
Domestic work	40	2.80	149	3.30	189	3.20	
Gold mining/Mining	161	11.20	407	9.00	568	9.50	
Others	398	27.70	1186	26.10	1584	26.50	
Unknown	111	7.73	478	10.53	589	9.86	
Parasitic Species							< 0.001*
P. vivax	853	59.40	2889	63.60	3742	62.60	
P. falciparum and mixed malaria	574	40.00	1582	34.80	2156	36.10	

Table 2 (continued)

	Cases 1436	% 24.00	Controls 4540	% 76.00	Total 5976	% 100.0	$χ^2$
Others (*P. malariae* and *P. ovale*)	9	0.60	69	1.50	78	1.30	
Parasite density (parasites per mm^3)							< 0.001*
1 to 500	440	30.60	2172	47.80	2612	43.70	
501 to 10,000	599	41.70	1732	38.10	2331	39.00	
10,001 to 100,000	279	19.40	470	10.40	749	12.50	
> 100,000	118	8.20	166	3.70	284	4.80	
Interval between symptom onset and treatment							< 0,001*
Up to 48 h	157	10.90	908	20.00	1065	17.80	
3 to 7 days	612	42.60	1682	37.00	2294	38.40	
8 days or more	645	44.90	1844	40.60	2489	41.60	
Unknown	22	1.53	106	2.33	128	2.14	

Ignored and blank entries were categorized as 'Unknown' and were not included in the chi-square statistics. 'Not applicable' refers to men and women of non-reproductive age

* $p < 0.05$ are considered statistically significant

hospitalization risk [5, 20]. The severity of the disease is intrinsically related to the level of parasitaemia, especially when it comes to malaria caused by *P. falciparum*, which is capable of infecting red blood cells of all ages, while *P. vivax* prefers young red blood cells [30]. Similarly, the level of parasitaemia results in symptoms arising from haematological changes and the immune response, which is usually higher in children without immunity to the disease [31]. Thus, case detection through active case finding is also a protective factor, as it can identify asymptomatic cases or those with few symptoms before they reach high parasitaemia that results in more severe clinical symptoms.

The Brazilian experience mirrors what occurs in other countries. For instance, in Australia, traveller movements occur constantly, with approximately 324 cases reported annually between 2012 and 2022, exhibiting a demographic profile similar to that observed in Brazil's extra-Amazon Region, primarily men aged 20 to 39 years [32]. The main difference lies in the origin of imported cases, which reflect global trends. A high prevalence of *P. falciparum* cases is reported from African countries, whereas Australia has received the highest number of *P. vivax* cases, accounting for up to one-third of imported cases [32]. Nevertheless, imported malaria represents an ongoing threat to malaria-free countries due to the potential for reintroduction of transmission and the occurrence of severe cases requiring intensive care unit hospitalization. This risk is often exacerbated by diagnostic delays caused by a lack of clinical suspicion, which is influenced by determinants similar to those identified in Brazil's extra-Amazon Region [32].

In the extra-Amazon Region, only 19% of malaria cases are treated within 48 h of symptom onset, compared to 60% in the Amazon Region, where malaria is more quickly suspected. Delays in diagnosis and treatment contribute to the higher proportion of severe malaria cases in non-endemic areas. Also, malaria fatality rates in the extra-Amazon Region can be up to 123 times higher than in the Amazon Region [8, 33].

In the context of global changes, climate change can directly or indirectly impact human health and malaria transmission. Long-term predictive models suggest that climate change will significantly affect efforts to eradicate malaria if environmental interventions do not continue, further increasing the population at risk for the disease [24, 34]. Furthermore, climate change may impact the achievement of the goals proposed by Brazil's National Malaria Elimination Plan, which aims to eliminate autochthonous disease transmission by 2035 [35], potentially causing disease outbreaks in both the Extra-Amazon and Amazon Regions, as well as deaths resulting from severe cases.

Limitations

Some limitations of this study are worth noting. First, the use of secondary data sources, including Sinan and the SIH/SUS, inherently limits the analysis due to potential issues with data quality. These datasets may be influenced by reporting errors, inconsistencies, or incomplete records, which could affect the robustness of the findings. Specifically, the lack of information on critical factors such as malaria relapses, reinfections, patient symptomatology, and prior medical history constrains the scope

Table 3 Univariate, full and multiple logistic regression (adjusted) 2011 to 2019

Variable	Crude model			p-value	Full model			p-value	Adjusted model			p-value
	Odds Ratio	95%CI			*Odds Ratio*	95%CI			*Odds Ratio*	95%CI		
Sex												
Male	1.03	0.90	1.19	0.65	1.01	0.81	1.27	0.90				
Female (REF)												
Pregnant												
Yes	1.68	0.91	3.09	0.10	1.31	0.53	3.25	0.56				
No (REF)												
Race/Color												
Asian	0.84	0.44	1.59	0.59	1.72	0.72	4.09	0.22	1.40	0.61	3.20	0.43
White (REF)												
Indigenous	0.75	0.28	1.97	0.55	0.68	0.14	3.34	0.64	0.96	0.25	3.69	0.96
Black or mixed-race	1.34	1.18	1.52	< 0.001*	1.22	1.03	1.45	0.02*	1.22	1.04	1.43	0.02*
Education level												
Illiterate	1.49	0.78	2.85	0.23	2.08	0.98	4.45	0.06	1.77	0.89	3.51	0.10
Elementary school	1.86	1.54	2.24	< 0.001*	2.49	1.95	3.17	< 0.001*	2.21	1.78	2.75	< 0.001*
High school	1.64	1.35	2.00	< 0.001*	1.76	1.40	2.23	< 0.001*	1.72	1.39	2.13	< 0.001*
Higher education (REF)												
Residence zone												
Urban	1.41	1.16	1.71	< 0.001*	1.30	0.97	1.74	0.08				
Rural (REF)												
Type of detection												
Active Search	0.60	0.52	0.70	< 0.001*	0.69	0.57	0.84	< 0.001*	0.65	0.54	0.78	< 0.001*
Passive Search (REF)												
Place of infection												
Extra-Amazon Region (REF)												
Amazonian Region	1.76	1.44	2.14	< 0.001*	1.43	1.06	1.93	0.02*	1.50	1.15	1.96	< 0.01*
Imported from other countries	1.87	1.52	2.29	< 0.001*	1.66	1.18	2.33	< 0.01*	1.72	1.28	2.32	< 0.001*
Activities in the last 15 days												
Rural activities (REF)												
Travel/transport-related activities	1.30	1.05	1.60	0.02*	1.18	0.88	1.59	0.26				
Road and dam construction	0.86	0.59	1.26	0.45	0.73	0.45	1.18	0.20				
Domestic work	1.03	0.69	1.52	0.90	0.88	0.52	1.52	0.66				
Gold mining/Mining	1.51	1.16	1.96	< 0.01*	1.30	0.92	1.83	0.14				
Others	1.28	1.03	1.60	0.03*	1.15	0.85	1.54	0.37				
Parasitic species												
P. vivax (REF)												
P. falciparum and mixed malaria (REF)	1.23	1.09	1.39	< 0.001	1.43	1.15	1.76	<0.001*	1.38	1.13	1.68	0.001*
Others (*P. ovale* and *P. malariae*)	0.44	0.22	0.89	0.02*	0.59	0.24	1.46	0.25	0.52	0.21	1.25	0.14
Age group												
0 to 9 years	1.53	1.10	2.13	0.01*	1.53	0.58	4.05	0.39				
10 to 19 years	1.23	0.96	1.59	0.11	0.97	0.66	1.42	0.86				
20 to 39 years (REF)												
40 to 59 years	0.98	0.86	1.12	0.81	0.92	0.77	1.10	0.37				
60 years or older	0.89	0.71	1.11	0.31	0.97	0.71	1.32	0.85				
Parasite density												
1 to 500 (REF)												
501 to 10,000	1.71	1.49	1.96	< 0.001*	1.50	1.24	1.81	< 0.001*	1.51	1.27	1.80	<0.001*
10,001 to 100,000	2.93	2.45	3.51	<0.001*	2.23	1.72	2.90	<0.001*	2.25	1.77	2.87	< 0.0.001*
> 100,000	3.51	2.71	4.54	< 0.001*	3.06	2.09	4.49	< 0.001*	3.15	2.20	4.50	< 0.001*

Table 3 (continued)

Variable	Crude model			p-value	Full model			p-value	Adjusted model			p-value
	Odds Ratio	95%CI			*Odds Ratio*	95%CI			*Odds Ratio*	95%CI		
Interval between symptom onset and treatment												
Up to 48 h (2 days) (REF)												
3 to 7 days	2.10	1.74	2.55	<0.001*	1.70	1.30	2.22	<0.001*	1.74	1.36	2.24	<0.001*
8 days or more	2.02	1.67	2.45	<0.001*	2.07	1.59	2.69	<0.001*	2.08	1.62	2.66	<0001*

Ignored and blank entries were categorized as 'Unknown' and were not included in the statistics

REF: Value of reference; Adjusted logistic regression model: Pseudo-R2: 0.0611. AIC: 4027. CI: Confidence Interval

* $p < 0.05$ are considered statistically significant

of the analysis, as these elements can contribute to the understanding of hospitalization risks.

Additionally, the likelihood of underreported malaria cases must be considered. Underreporting of cases—especially undiagnosed or asymptomatic infections—can lead to an underestimation of both 'cases' and 'controls' groups. This is particularly relevant given that active case detection was identified as a protective factor, highlighting the possibility that undiagnosed cases are influencing the associations.

Finally, while probabilistic record linkage techniques were employed to identify malaria cases that evolved into hospitalizations, the completeness of the identifying variables could have influenced the results, as well as underreported cases. These limitations underscore the need for improved data quality, comprehensive case documentation, and enhanced surveillance systems with interoperability.

Conclusion

The study identified as risk factors for malaria hospitalizations people with: Black or mixed-race ethnicity, low education, infected in the Amazon Region or abroad, or infected by *P. falciparum* or mixed infections, and delayed treated. This profile reveals inequalities in access to healthcare and also education and means to prevention, showing that socioeconomic differences also affects severe malaria. Active case detection was found as a protective factor, as it detects cases before it reaches high parasitaemia.

The transmission risk of malaria in the extra-Amazon Region remains closely linked to travel to endemic areas and economic activities, leading to delayed diagnoses, treatment challenges, and increased case severity due to lack of immunity. Raising awareness among surveillance systems and individuals traveling to or returning from endemic areas is critical to improving early diagnosis and preventing severe outcomes.

In areas with sustained transmission in non-endemic regions, proactive local surveillance has proven effective in early diagnosis and treatment, reducing the need for hospitalizations. However, the potential impacts of climate change, such as expanded vector activity, highlight the need for vigilance to prevent outbreaks and reintroduction of autochthonous transmission.

To reduce malaria-related deaths, strengthening health communication strategies, expanding diagnostic networks, and leveraging telehealth for guiding patients and healthcare providers are essential steps. Further research is also necessary to explore associated factors in endemic regions and utilize hospital-based data to enhance surveillance and management in the extra-Amazon Region.

Abbreviations

PCR	Polymerase chain reaction
Sivep-Malaria	Malaria Epidemiological Surveillance Information System
SINAN	Notifiable diseases information system
SIH/SUS	Hospital Information System of the Unified Health System
SUS	National Health System
LVC	Lâminas de Verificação de Cura
ICD	International Classification of Diseases
CI	Confidence interval
LGPD	General Data Protection Law
mm^3	Cubic millimetre
WHO	World Health Organization

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Author contributions

Conceptualization, A.C.S. and K.K.S.G.; methodology, A.C.S. and K.K.S.G.; validation, A.C.S. and K.K.S.G.; formal analysis, A.C.S., E.C.D., G.M.R.V., P.B.M, W.M.R. and K.K.S.G.; investigation, A.C.S. E.C.D., G.M.R.V., P.B.M, W.M.R. and K.K.S.G.; data curation, A.C.S. and K.K.S.G.; writing/original draft preparation, A.C.S.; writing/review and editing, A.C.S., E.C.D., G.M.R.V., P.B.M, W.M.R. and K.K.S.G.; visualization, A.C.S. and K.K.S.G.; supervision, K.K.S.G. and W.M.R.; project administration, A.C.S. and K.K.S.G.; All authors have read and agreed to the published version of the manuscript.

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Data availability
Sensitive information such as names and dates of birth are not available. Other data are available upon reasonable request.

Declarations

Ethics approval and consent to participate
In compliance with the National Health Council Resolution No. 510 of April 7, 2016, the study was submitted to the Research Ethics Committee at the University of Brasília (CEP/UnB). Approval for data handling and linkage is documented in the committee's re-port number 5.008.210. Measures were taken to mitigate the risk of exposing personal data, in accord-ance with the General Data Protection Law (LGPD)—Law No. 13.709 of August 14, 2018.

Consent for publication
Patient consent was waived according to the Brazilian National Health Council resolution number 510/2016 which states that research using secondary data of National Databases do not require patient's consent to be conducted.

Competing interests
The authors declare no competing interests.

Author details
[1]Center of Tropical Medicine, University of Brasilia, Brasília 70904-970, Brazil. [2]Health Secretariat of Health and Environmental Surveillance, Ministry of Health, Brasilia 70719-040, Brazil. [3]Evandro Chagas Institute, Ministry of Health, Belém 66093-020 , Brazil.

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