Factors Associated With Malaria in Indigenous Children Between 2007 - 2018, Amazonas State, Brazil

Mateus Ferreira de Aguiar  
Universidade Federal do Amazonas

Bruna Martins Meireles  
Universidade Federal do Amazonas

Wuelton Marcelo Monteiro  
Fundação de Medicina Tropical do Amazonas: Fundacao de Medicina Tropical Doutor Heitor Vieira Dourado

Maria Jacirema Ferreira Goncalves (jaciremagoncalves@gmail.com)  
Federal University of Amazonas: Universidade Federal do Amazonas  https://orcid.org/0000-0002-8460-8501

Research

Keywords: Malaria, Indigenous health, Associated factors

DOI: https://doi.org/10.21203/rs.3.rs-584349/v1

License: ☑ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: malaria is a serious problem in the Amazonas state, especially in areas near forests. Indigenous populations living in these areas are very vulnerable to malaria infection. In addition, the disease severely affects children because their immune system is less well developed, and thus causes more severe symptoms. Therefore, the intersection between these two groups, indigenous people and children, is characterized by an important public health problem. The objective is to identify the factors associated with malaria in indigenous children in the Amazonas state, Brazil, from 2007 to 2018.

Methods: This is an epidemiological, quantitative and cross-sectional study involving children under 15 years, and using data from health system notifications between 2007 and 2018, with the Amazonas state, Brazil, as a place of residence and probable infection setting. The variables are clinical-epidemiological, laboratorial and case follow-up, which were analyzed then stratified as to whether the case involved indigenous children or those of other races and entries for which no race data was given. The estimation of Odds Ratio with a confidence interval was obtained by multivariate logistic regression.

Results: the factors associated with malaria in indigenous children were attributed to being of the female sex, age from 0 to 4 years, passive case surveillance, high load of parasitemia or lack of data regarding the level of parasitemia, parasitic forms containing *Plasmodium falciparum* were more frequent, as well as timeliness of treatment, which corresponds to the time between the onset of symptoms and the start of treatment being less than 48 hours.

Conclusion: the factors associated with malaria in indigenous children highlight the difference in race, suggest more severity of the disease and more malarial infections in this population, and, as a result, malaria has a great impact on the health of the indigenous children.

Background

Malaria is an infectious disease caused by the protozoa of the genus *Plasmodium* and transmitted to humans by females of the mosquito of the genus *Anopheles*. Two species of parasites are important in public health in Brazil: *Plasmodium vivax*, which causes more comprehensive symptoms and *Plasmodium falciparum*, which has a greater potential for malaria-related deaths\(^1\).

In Brazil, malaria is most severe in the part of the country that belongs to the Amazon region, which concentrates almost all of the cases registered in the country. In addition, the transmission of the disease has a close relationship with forest areas or edges of these areas, since these regions are the natural habitat of the vector. In this sense, indigenous populations present greater vulnerability than the general population, either by their habitat or by their cultural way of live. In 2017, the Legal Amazon concentrated 99% of malaria cases in the country, with 42% of cases registered in the state of Amazonas\(^2\). Between 2017 and 2018, there was a 28% increase in malaria cases among indigenous people in Brazil\(^3\).
Although the disease affects all age groups, when it affects children it gains greater proportions, given the potential of the disease to cause damage, as well as its difficult assessment, since most clinical symptoms are non-specific and most cases occur in places where there are no routine tests available\(^4\). As such, children under 5 years of age are particularly susceptible to infection, disease and death. More than two thirds of malaria-related deaths occur in this age group\(^5\).

Malaria does not endanger the health of the subject only in the active phase of the disease. Malaria sequelae interfere with the quality of life and productivity of the population and, in children, it can jeopardize development and learning\(^6\). Other factors increase the degree of symptoms in this pediatric age group, such as iron deficiency, malnutrition and intestinal parasitoses\(^7, 8\).

Studies point to the severity and poor care with indigenous children and adolescents, who were the main victims of the malaria outbreak that hit the Upper Negro River in 2018, which affected 60\% of this population group\(^9\), and generated a higher level of incidence when compared to non-indigenous people. Thus, children can be the most harmed, since this illness has the potential to impair health by affecting vital organs such as the liver\(^10\). Therefore, the analysis proposed here has the potential to elucidate and discuss this real problem. Thus, the present study sought to identify the factors associated with malaria in indigenous children in the Amazonas state, between 2007 and 2018.

**Methods**

**Type of study:**

This is a cross-sectional, epidemiological study that uses secondary data from the Information System for Epidemiological Surveillance of Malaria (SIVEP-Malaria). Data was retrieved regarding children under 15 years with malaria, for the period from 2007 to 2018, and when the state of Amazonas was given as place of residence and probable infection setting.

This age group was selected because the data available is stratified by age group and not by specific ages. Thus, it is not possible to select children over the age of 14, without entering the category of 20 years of age. Notwithstanding, much of the literature analyzes children under 15 years of age as a group and, as such, this makes it possible to compare data in the analysis with data from other sources.

**Study population and data source:**

All malaria cases involving patients under 15 years of age and reported to SIVEP-Malaria in the period between 2007 to 2018 are included in the study population. Sampling criteria were not considered, and all records were included.

It is important to note that since these are secondary data, obtained without the identification of the subjects, there is only the episode of malaria as a record, and not the patient itself. In view of this, there may be people with more than one episode of malaria in the period, and thus are counted in the study;
however, where the register states “cure check slide”, these are excluded, since they are reported, but already have a previous entry in the database as a new case.

**Organization of data:**

The SIVEP-Malaria data were made available by the Amazonas Health Surveillance Foundation (FVS-AM), obtained in Excel spreadsheet format and analyzed using Stata® software, version 13.0. These data were reviewed in order to separate the indigenous populations, the other races and the entries for which no race information was given and then filtered again to identify the cases for which the Amazonas state was given as place of residence and probable place of infection.

For the definition of “indigenous”, the criterion of another study on indigenous people in the Amazonas state was adopted due to the high number of entries with data missing in the section “Race”, which represented 51.4% of the notifications in the study period\(^{11}\). The section for race has only been included in the notification form since 2013, and is not mandatory to fill in this information. To deal with this problem, a person was considered indigenous if already had the information on race; in the other cases, we sought to identify whether the place of probable infection was given as “tribal village”, and thus the indigenous race was assigned. It was determined that if the place of infection was a tribal village, it could be assumed that the child would be an indigenous person, since there would be very few cases of non-indigenous children living in a tribal village.

**Study variables:**

The variables used were grouped into the following dimensions:

- clinical-epidemiological and laboratorial findings as follows: sex (male or female); age group (0 to 4, 5 to 9, 10 to 14); type of surveillance slide (active or passive case surveillance), parasitemia level by plus system scale (\(<+/2\) (at less than half a cross), \(+/2\) (half a cross), \(+\) (one cross), \(++\) (two crosses), \(+++\) (three crosses), and \(++++\) (four crosses)); test results (1 - *P. falciparum* (*P. falciparum*, *P. falciparum* and gametocytes of *P. falciparum*, and/or gametocytes of *P. falciparum*); 2 - *P. vivax*; 3 - Mixed (*P. vivax* and gametocytes of *P. falciparum* malaria, and/or *P. falciparum* + *P. vivax*), and others, including *P. malariae* and *P. ovale*);
- monitoring of malaria cases: time between first symptoms and diagnosis (days); time between first symptoms and treatment (days); and treatment opportunity (relationship between date of diagnosis and date of start of treatment), which was considered early when it occurred less than 48 hours.

**Data analysis:**

For descriptive phase, the data were analyzed according to frequency and distribution, and presented the percentages for the categorical variables.

In the analytical phase, we performed a bivariate analysis using the Pearson Chi-square test, which had indigenous race, other races and the missing data on race information (missing data) as a comparison factor. We chose to display the missing data in order to present an overview of the situation, and test in
the multivariate analysis whether the lack of data would alter the association of malaria in indigenous children.

We calculated standardized residuals of the Chi-square test among the categorical variables, which allowed us to identify the characteristic patterns in each category of a variable according to the excess or lack of occurrence of the combination of each category of the other variable. This allowed us to draw conclusions about the significance of the associations, especially in a category. The residuals of the Chi-square test with positive values greater than 1.96 corresponded to the level of significance 5%, and respective confidence of 95%.

For multivariate analysis, logistic regression was used and adjusted in stepwise forward. In the modeling process, the < 0.10 criterion of significance of the P-value was used for inclusion in the model, from the bivariate analysis. Variables with statistical significance, with P value < 0.05, were maintained in the final model, which results were reported using Odds Ratio (OR), together with their confidence intervals (95% CI). The model fit was evaluated using the Hosmer & Lemeshow test.

**Ethical Aspects**

Since the data used had already been registered on the SIVEP-Malaria system, and race classification was completed at the time of notification of the case, there is no need for consent since the authors did not contact the subjects and the database was made available without the identification of the subjects. The project was approved by the Research Ethics Committee (REC) at the Federal University of Amazonas, under Protocol Number 2.302.738.

**Results**

The results are presented in tables containing the characterization of the subjects (Table 1), clinical and laboratorial aspects (Table 2), case monitoring (Table 3) and factors associated with malaria in indigenous children (Table 4). A total of 1,031,756 cases of malaria were registered on the SIVEP-Malaria system, whose place of probable infection and residence was the state of Amazonas, Brazil. Cases with registration errors in age and gender fields, as well as in the cure check slide were excluded. Thus, after this step, 938,714 cases remained for the period from 2007 to 2018. Children under 15 years account for 370,603 of these cases, of which 51.4% were missing data (without information on race). In the cases of children under 15 years of age with race identification, 23.4% are indigenous and 25.1% are classified as other races, which includes blacks, yellow, browns and whites, as in Brazilian pattern it is used skin color to define race groups.

Table 1 shows the distribution of reported cases of malaria in children by sex and age group, according to the categories of indigenous people, other races and missing data (without race information). Standardized residuals show an excess of occurrences in female indigenous children and the male gender was statistically significant for other races. With regard to the indigenous age group, there is a higher frequency of malaria in children under five years of age, whose proportion decreases as the age
group increases in contrast to what occurs in other races and in cases of missing data for race information (Table 1).

| Variable             | Indigenous* | Other races | Missing data | P-value |
|----------------------|-------------|-------------|--------------|---------|
| **Age group (years)**|             |             |              |         |
| Less than 1 year of age | 4538 (SR) | 3151 (SR) | 7255 (SR) | < 0.01 |
|                      | 5.23        | 3.38        | 3.81        |         |
|                      | (20.42)     | (-11.67)    | (-7.17)     |         |
| 1 to 4               | 29989 (SR) | 23422 (SR) | 55275 (SR) | 29.00   |
|                      | 34.53       | 25.15       | 29.00       |         |
|                      | (38.51)     | (-32.50)    | (-4.42)     |         |
| 5 to 9               | 29850 (SR) | 31517 (SR) | 65859 (SR) | 34.56   |
|                      | 34.37       | 33.81       | 34.56       |         |
|                      | (0.31)      | (-3.78)     | (3.02)      |         |
| 10 to 14             | 22464 (SR) | 35101 (SR) | 62182 (SR) | 32.63   |
|                      | 25.87       | 37.66       | 32.63       |         |
|                      | (-46.40)    | (40.39)     | (4.25)      |         |
| **Sex**              |             |             |              |         |
| Female               | 41610 (SR) | 41969 (SR) | 87942 (SR) | 46.15   |
|                      | 47.92       | 45.04       | 46.15       | < 0.01  |
|                      | (11.03)     | (-8.82)     | (-1.69)     |         |
| Male                 | 45231 (SR) | 51221 (SR) | 102629 (SR)| 53.85   |
|                      | 52.08       | 54.96       | 53.85       |         |
|                      | (-11.03)    | (8.82)      | (1.69)      |         |

Source: Information System for Epidemiological Surveillance of Malaria (SIVEP-Malaria), data obtained in December, 2019.

Notes:

SR = Standardized Residual

The percentage is shown in the column;

In bold are the residuals of the Chi-square with a positive value greater than 1.96, which corresponds to the level of significance for excess occurrences.

*Indigenous is the combination of the individual with race declared as indigenous or having the tribal village as the place of infection.
Table 2 presents the clinical and laboratorial data of the reported cases of malaria in children, according to the categories of indigenous people, other races and missing data (without race information). As for the type of detection of the malaria cases, it is observed that passive case surveillance prevails among indigenous people, and active case surveillance predominates among other races. The highest parasitic load was identified among indigenous people, which was concentrated between 3 or 4 crosses, although in this regard a large number of data records were identified that were not filled in, i.e., without information regarding the parasitic load when this same information was compared with that of other races. On the other hand, in children of other races, the lower parasitic load (up to 1 cross) was significant, and cases lacking information on race had statistical significance for parasitemia of 2 crosses and 3 or 4 crosses. The disease caused by some form of *P. falciparum* parasite or its combination with *P. vivax* (mixed form) was significant for indigenous children, unlike subjects of other races, whose statistical significance appears for *P. vivax*. In cases where the race field was not filled in, these presented statistical significance in forms exclusively for *P. falciparum* (Table 2).
Table 2
Clinical-laboratorial aspects of malaria in children in indigenous people, other races and missing data, Amazonas state, Brazil, 2007–2018.

| Variable                                      | Indigenous* | Other races | Missing data | P-value         |
|-----------------------------------------------|-------------|-------------|--------------|-----------------|
| **Type of surveillance slide**                |             |             |              | (Pearson Chi-  |
|                                               | N = 86841   | N = 93191   | N = 190571   | square test)    |
|                                               | % (SR)      | % (SR)      | % (SR)       | (< 0.01)        |
| Active case surveillance                      | 40693       | 58777       | 122426       | (-89.42)        |
|                                               | 46.86       | 63.07       | 64.24        | (23.01)         |
|                                               | (-55.81)    | (-55.81)    |              |                 |
| Passive case surveillance                     | 46148       | 34414       | 68145        | (89.42)         |
|                                               | 53.14       | 36.93       | 35.76        | (-23.01)        |
|                                               | (23.01)     | (23.01)     |              |                 |
| **Parasitemia level by plus system scale**   |             |             |              |                 |
| Up to 1 + (up to 10 parasites per 100 thick   | 55272       | 62798       | 171372       | (< 0.01)        |
| film fields)                                  | 63.65       | 67.39       | 71.23        | (-6.77)         |
|                                               | (-12.05)    | (-12.05)    |              |                 |
| ++ (11 to 100 parasites per 100 thick film    | 27001       | 27809       | 63017        | (17.13)         |
| fields)                                       | 31.09       | 29.84       | 26.19        | (-14.79)        |
|                                               | (-5.06)     | (20.49)     |              |                 |
| +++ or more (>100 parasites per one thick film| 2725        | 1953        | 6181         | (11.63)         |
| field)                                        | 3.14        | 2.10        | 2.57         | (-17.45)        |
|                                               | (4.15)      | (-17.45)    |              |                 |
| Number of crosses (+) not filled in           | 1843        | 631         | 1            | (60.13)         |
|                                               | 2.12        | 0.68        | 0.01         | (-51.31)        |
| **Test result**                               |             |             |              |                 |
| *Plasmodium falciparum* (F, F + FG, FG)       |             |             |              |                 |
|                                               | 10891       | 7209        | 23630        | (13.65)         |
|                                               | 12.54       | 7.73        | 12.40        | (-39.34)        |
|                                               | (22.57)     | (-22.57)    |              |                 |
| *Plasmodium vivax*                            |             |             |              |                 |
|                                               | 74959       | 85634       | 165486       | (< 0.01)        |
|                                               | 86.32       | 91.89       | 86.83        | (-17.28)        |
|                                               | (42.37)     | (-22.13)    |              |                 |
| Variable                                      | Indigenous* | Other races | Missing data | P-value |
|----------------------------------------------|-------------|-------------|--------------|---------|
| Mixed (F + V, V + FG)                        | 984         | 345         | 1454         | 0.76    |
|                                              | **14.90**   | **(-15.56)**| **(0.87)**   |         |
| Others (including *P. malariae* and *P. ovale*) | 7           | 3           | 1            | 0.01    |
|                                              | **(3.14)**  | **(0.16)**  | **(-2.81)**  |         |

Source: Information System for Epidemiological Surveillance of Malaria (SIVEP-Malaria), data obtained in December, 2019.

Notes:

SR = Standardized Residual

The percentage is shown in the column;

In bold are the residuals of the Chi-square with a positive value greater than 1.96, which corresponds to the level of significance for excess occurrences;

Test result: F = *Plasmodium falciparum*; FG = *Plasmodium falciparum* gametocytes; V = *Plasmodium vivax*;

*Indigenous is the combination of the individual with race declared as indigenous or having the tribal village as the place of infection.

Regarding the number of days between the date of onset of symptoms and the date of diagnosis, the statistical significance for zero days and more than 7 days is noted in the indigenous population. The other races showed statistical significance for 1, 2, 3 and more than 7 days. The data missing information on race were significant for 1 to 7 days, indicating that there is no distinction for early diagnosis in this category. With regard to the time between diagnosis and the start of treatment, the result is similar to the days between the first symptoms and treatment, with the exception of cases in which there is no data on race information, the significance of which was 3 days or more (Table 3).
Table 3
Timeliness of diagnosis and treatment of malaria, in indigenous people, other races and missing data, Amazonas state, Brazil, 2007–2018

| Variable                                      | Indigenous* | Other races | Missing data | P-value          |
|-----------------------------------------------|-------------|-------------|--------------|------------------|
| Days between the first symptoms and the diagnosis | N = 86841 (SR) | N= 93191 (SR) | N = 190571 (SR) | (Pearson Chi-square test) |
| 0                                             | 22542 25.96 | 15185 16.30 | 35882 18.83  | (< 0.01)         |
|                                               | (51.46)  (-31.45) | (-16.23) | | |
| 1                                             | 17927 20.65 | 22175 23.80 | 44739 23.48 |                  |
|                                               | (-18.02)  (7.60) | (8.69) | | |
| 2                                             | 14118 16.26 | 18816 20.19 | 36376 19.09 |                  |
|                                               | (-21.11)  (13.48) | (6.20) | | |
| 3                                             | 9117 10.50 | 12346 13.25 | 25079 13.16 |                  |
|                                               | (-20.93)  (7.35) | (11.37) | | |
| 4 to 7                                        | 10403 11.98 | 13163 14.13 | 28154 14.77 |                  |
|                                               | (-19.21)  (1.73) | (14.78) | | |
| >7                                            | 12724 14.65 | 11493 12.33 | 20325 10.67 |                  |
|                                               | (27.27)  (3.41) | (-26.07) | | |
| Days between diagnosis and treatment           | N = 86841 | N = 93191 | N = 190571 |                  |
| 0                                             | 18899 21.77 | 13717 14.72 | 28814 15.12 | (< 0.01)         |
|                                               | (46.98)  (-17.60) | (-24.53) | | |
| 1                                             | 17784 20.48 | 21761 23.35 | 42185 22.14 |                  |
|                                               | (-12.79)  (11.06) | (1.24) | | |
| 2                                             | 14686 16.91 | 18920 20.31 | 35553 18.66 |                  |
|                                               | (-15.12)  (14.88) | (-0.10) | | |
| 3                                             | 9777 11.26 | 12657 13.58 | 25212 13.23 |                  |
|                                               | (-16.07)  (7.66) | (6.98) | | |
| 4 to 7                                        | 11874 13.67 | 14011 15.04 | 29901 15.69 |                  |
The result of the multivariate logistic regression analysis, which estimates the factors associated with malaria in indigenous children and other races, with the respective values of crude OR and adjusted OR, is presented in Table 4. For this analysis, data without race information were excluded, since the focus is cases involving those of indigenous race. In Tables 1 to 3, it was observed that the cases of missing data can be excluded, and cause no loss in the identification of the associated factors, since these present similarity in statistical significance with other races, and do not present divergence of the factors associated with malaria in indigenous children shown in Tables 1, 2 and 3.

All variables tested in the bivariate analysis presented statistical significance for inclusion in the multivariate analysis. In the final model, we highlight the factors associated with malaria in indigenous children which presented the greatest magnitude: female sex (OR = 1.12; 95% CI 1.10–1.14); age group of younger than one year (OR = 2.2; 95% CI 2.09–2.31), with a reduction of the OR as age increases, maintaining statistical significance; passive case surveillance (OR = 1.81; 95% CI 1.77–1.84); high load of parasitemia (OR = 1.54; 95% CI 1.44–1.63) and the lack of filling in of the parasitic load field (OR = 3.07; 95% CI 2.79–3.39); mixed parasitic infections (F + V, V + FG) (OR = 2.74; 95% CI 2.42–3.11); timeliness of treatment, i.e., start of treatment within 48 hours from the date of the first symptoms (OR = 2.05; 05% CI 1.98–2.12) (Table 4).
Table 4
Crude and adjusted Odds Ratio of malaria-associated factors in indigenous children, Amazonas state, Brazil, 2007–2018.

| Variables                      | %    | Crude OR | CI 95%      | Adjusted OR | CI 95%      |
|-------------------------------|------|----------|-------------|-------------|-------------|
| **Sex**                       |      |          |             |             |             |
| Male                          | 52.08| 1        | 1           | 1.12        | 1.10–1.14   |
| Female                        | 47.92| 1.12     | 1.10–1.14   | 1.12        | 1.10–1.14   |
| **Age group (years)**         |      |          |             |             |             |
| Less than 1 year              | 5.23 | 2.25     | 2.14–2.36   | 2.20        | 2.09–2.31   |
| 1 to 4                        | 34.37| 2.00     | 1.95–2.04   | 1.95        | 1.90–2.20   |
| 5 to 9                        | 25.87| 1.48     | 1.44–1.51   | 1.43        | 1.40–1.46   |
| 10 to 14                      | 25.87| 1        | 1           | 1           |             |
| **Type of surveillance slide**|      |          |             |             |             |
| Active case surveillance      | 46.86| 1        | 1           | 1           |             |
| Passive case surveillance     | 53.14| 1.94     | 1.9–1.97    | 1.81        | 1.77–1.84   |
| **Parasitemia level by plus system scale** |      |          |             |             |             |
| Up to 1 + (up to 10 parasites per 100 thick film fields) | 63.65 | 1  | 1           | 1           |
| ++ (11 to 100 parasites per 100 thick film fields) | 31.09 | 1.10 | 1.08–1.12 | 1.17        | 1.14–1.19   |

Source: Information System for Epidemiological Surveillance of Malaria (SIVEP-Malaria), data obtained in December, 2019.

Notes:

OR: Odds Ratio;

CI 95%: 95% confidence interval.

Significance level < 0.10 for crude analysis; significance level < 0.05 for adjusted analysis.

Timeliness of treatment: time from the onset of symptoms to the start of treatment.

Test result: F = *Plasmodium falciparum*, FG = *Plasmodium falciparum* gametocytes; V = *Plasmodium vivax*. 
| Variables                                                                 | %   | Crude OR | CI 95%       | Adjusted OR | CI 95%       |
|--------------------------------------------------------------------------|-----|----------|--------------|-------------|--------------|
| +++ or more (>100 parasites per one thick film field)                    | 3.14| 1.58     | 1.49–1.68    | 1.54        | 1.44–1.63    |
| Number of crosses (+) not filled in                                      | 2.12| 3.31     | 3.02–3.63    | 3.07        | 2.79–3.39    |
| Test result                                                              |     |          |              |             |              |
| **Plasmodium vivax**                                                     | 12.54| 1      |              | 1            |              |
| **P. falciparum (F, F + FG, FG)**                                        | 86.32| 1.72    | 1.67–1.78    | 1.71        | 1.65–1.76    |
| **Mixed (F + V, V + FG)**                                                | 1.13| 3.26     | 2.88–3.68    | 2.74        | 2.42–3.11    |
| **Timeliness of treatment (hours)**                                      |     |          |              |             |              |
| > 48h                                                                    | 1   | 1        |              | 1            |              |
| ≤ 48h                                                                    | 2.31| 2.23–2.38| 2.05        | 1.98–2.12    |

Source: Information System for Epidemiological Surveillance of Malaria (SIVEP-Malaria), data obtained in December, 2019.

Notes:

OR: Odds Ratio;

CI 95%: 95% confidence interval.

Significance level < 0.10 for crude analysis; significance level < 0.05 for adjusted analysis.

Timeliness of treatment: time from the onset of symptoms to the start of treatment.

Test result: F = *Plasmodium falciparum*, FG = *Plasmodium falciparum* gametocytes; V = *Plasmodium vivax*.

**Discussion**

The factors associated with malaria in children refer to the need for proper care of this population group. The differences observed between indigenous people and other races indicate that the disease differentially affects this ethnic group.

The association between malaria in children and the female sex is an enigma, because one would not expect a sex difference, nor a different association of other races and that which is already known in adults, whose predominance is the male sex\(^{14}\). No other studies were identified that found an association between malaria and female sex in indigenous children.
The fact of finding a stronger association of malaria in the lower age group is an indicator of the severity of the problem in this population. It is known that children under one year of age have an immature immune system, which makes them more vulnerable to infectious agents. Because malaria is affecting children so early, there is a risk that the sequelae of the disease will also affect this population more strongly, in addition to the risk of the multiple malarial diseases accumulated throughout life, since the first experiences occur at an early age. From the clinical and child development point of view, malaria has a combination of biological determinants, such as immunity, as well cultural ones in the form of housing, coexistence in society, as well as the socio-political aspect, in relation to access to health services. These elements must contribute to malaria in indigenous areas presenting differentiated epidemiological behavior.

Malaria is widely distributed in other races among children aged 10 to 14 years, and may be related to intra-and peridomicile transmission, if we take into account housing conditions and the proximity of forest areas, vector density and basic sanitation. In addition, the responsibility of helping parents with household income often results in a situation where the child is exposed to proximity to the vector, and can thus contribute to infection.

Indigenous people have a specific health policy, so primary care in the National Health Service (SUS) should adapt its actions aimed at these peoples by considering their organizational models in order to favor health promotion and malaria prevention. Some characteristics, such as the high mobility of indigenous people, the difficulty of access to their regions by health teams and the persistent incursion of gold miners hinder malaria control actions in these regions contributes to the change in the epidemiological profile of the disease.

Passive case surveillance is prevalent for cases of infection in indigenous children under 5 years of age. This results from the care that mothers take in taking their children to health care facilities as soon as the first symptoms appear. Differently, in other races, the prevalence of active case surveillance demonstrates the efficiency of investments and efforts established to ensure the increase in the network of malaria laboratories throughout the Amazonas state, with an increase of 72% in 10 years. However, even with the incentive for the development of rapid tests in Brazil, especially in regions away from large centers, in indigenous regions only passive case surveillance occurs in most cases. Moreover, the indigenous areas of Brazil have a health care system marked by a lack of professionals and consequent difficulties in the access of their populations to these services.

One of the most used techniques for laboratory diagnosis of malaria is the thick blood smear that seeks the specific confirmation of the disease. This technique is important because it allows the visualization of parasites, species identification and stages of development and quantification, which is essential data for clinical evaluation. The thick blood smear is a sensitive method capable of detecting 0.001% parasitemia. However, the method becomes less sensitive when the individual is infected with more than one species of plasmodium, 29% of infections diagnosed by thick blood smear as being that of
Plasmodium vivax, when analyzed by PCR, were identified as mixed infections\(^2\). On the SIVEP-Malaria system, parasitemias were quantified by plus system scale, presented in crosses to facilitate presentation and explanation. In this format, indigenous people have greater parasitic load than other races, which demonstrates that, because they live in places more vulnerable to mosquito breeding sites, they can be more parasitized due to the abundance of bites, or their immune system is not as competent in containing the multiplication of parasites after infection\(^2\).

As for the Plasmodium species present, \(P.\) vivax was evidenced as an infectious agent prevalent in other races, similar to another study\(^2\). This trend can be explained by factors such as its wide geographical distribution, since \(P.\) vivax establishes itself under higher temperature conditions\(^2\), and is characterized by more comprehensive and sometimes insidious symptoms such as fever, headache and chills. It is worrying that the cases of \(P.\) falciparum and mixed malaria (\(P.\) f. and \(P.\) v.) are predominant in indigenous people, since it represents more severity in these cases. On the other hand, as the symptoms are more exacerbated, this may contribute to the rapid search for diagnosis, since passive case surveillance was significant among indigenous people. In addition, indigenous people under 15 years of age have diverse forms of infection, with the prevalence of \(P.\) falciparum plus \(P.\) vivax and \(P.\) vivax plus \(P.\) falciparum gametocytes, even if the greater occurrence of cases in the Amazonas state is caused by \(P.\) vivax, thus demonstrating an extremely worrying situation, for presenting resistance to usual drugs and barrier prophylaxis such as the mosquito net, in the case of \(P.\) vivax\(^1\).

The timeliness of treatment of malaria among indigenous people in less than 48 hours meets the recommendations of the Brazilian Ministry of Health, and is an important factor for the control of the disease, since the earlier the treatment, the lower the possibility of spread, by reducing the source of infection. It is also an indicator of the level of care provided, because in the context studied, indigenous children had both diagnosis and treatment earlier when compared to the other races. It may be that those responsible take care of the children promptly, as soon as the first symptoms appear, and seek the health service where the diagnosis and treatment are performed. It is also possible that it is related to organization of the health service in indigenous areas, in which access is facilitated and usually the person who does the thick blood smear examination is a professional living in the area or even an indigenous professional, which generates proximity and ease of access\(^2\).

The data presented by the SIVEP-Malaria system, like any secondary data, have potential biases, which are out of the researchers’ control, such as the lack of standardization in data collection, which affects the quality of the records, the coverage that can vary in time and space and the lack of information, as in the case of the variable race and parasitemia, both showing a high degree of lack of data. In the first case, it was demonstrated that the classification method used in this work, including the indigenous village as a place of probable infection contributed to the increase in race data completeness; though in the second case, the lack of information about parasitemia was used in the analysis, and the lack of quantitative parasitemia data limited the interpretation of the parasitic burden. For parasitic missing data, a possibility would be both high and low parasitic load, since both make counting difficult and require
greater skill of the microscopist, which may be a fragility in indigenous areas. Although these limitations have not compromised the interpretations of this study, additional analyses are necessary in order to unravel both the epidemiological situation of malaria involving indigenous people and the functioning of the program as a working process in the control of the malaria endemic.

**Conclusion**

The factors associated with malaria in indigenous children in the Amazonas state may be indicative that the disease is facilitated by the way of life of the indigenous people and the organization of health services in that region. Understanding these factors contributes to the formation of strategies to adapt the care to these peoples, who often are in a situation of vulnerability, either due to geographical, economic or biological questions.

The results suggest that actions that are appropriate to the peculiarity of this population need to be developed with a view to reducing the incidence of malaria in children, especially among children under two years of age, so that this race does not suffer greater damage, such as from repeated infections, when acquiring malaria early. Thus, it is up to those responsible to improve actions in order to contain malaria in these peoples, and the results of this research may support more assertive decisions by professionals responsible for reducing infection in these areas.

**Abbreviations**

SIVEP-Malaria: Information System for Epidemiological Surveillance of Malaria; FVS-AM: Amazonas Health Surveillance Foundation; F or *P. falciparum* or *P. f.: Plasmodium falciparum*, FG: *Plasmodium falciparum* gametocytes; V or *P. vivax* or *P.

*n.: Plasmodium vivax, P. malariae. Plasmodium malariae, P. ovale. Plasmodium ovale*, OR: Odds Ratio; 95% CI: 95% confidence interval; SR: Standardized Residual; SUS: National Health Service; PCR: Polymerase Chain Reaction

**Declarations**

**Availability of data and materials**

The data used in this research were collected in indigenous populations, protected by specific laws to these populations in Brazil. That way, we cannot make this data available. According to Brazilian legislation (http://www.planalto.gov.br/ccivil_03/_ato2011-2014/2011/lei/l12527.htm), the authors are responsible for the confidentiality of the analyzed data. Therefore, free access to the data used in our research is allowed on reasonable request. If some researcher need to access the data set, can request to Ethics Committee of the Amazonas Federal University, where the macro project is registered.

Details for contact:
Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Amazonas Federal University (approval under Protocol number 2,302,738).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Amazonas Research Foundation [Fundação de Amparo à Pesquisa do Estado do Amazonas (FAPEAM)]

Authors’ contributions

Conceptualization: WMM, BMM and MJFG; data acquisition: BMM and MJFG; formal analysis and writing original draft: MFA, WMM, BMM and MJFG; reviewing and editing: MFA, WMM, BMM and MJFG. All authors read and approved the final manuscript.

Acknowledgements

In this study, the first author received a scientific initiation scholarship from the National Council for Scientific and technological development (CNPq).

References

1. Carlos BC, Rona LDP, Christophides GK, Souza-Neto JA. A comprehensive analysis of malaria transmission in Brazil. Pathog Glob Health. 2019;113:1-13. doi:10.1080/20477724.2019.1581463

2. Mendes AM, Leite MS, Langdon EJ, Grisotti M. O desafio da atenção primária na saúde indígena no Brasil. Rev Panam Salud Publica. 2018;42:e184. doi: 10.26633/RPSP.2018.184.

3. Ministério da Saúde. Situação epidemiológica da malária. 2018.
   http://portalarquivos2.saude.gov.br/images/pdf/2018/agosto/30/3.%20c%20-%20malaria_CIT_30_agos_2018_cassiopeterka.pdf. Accessed 16 Apr 2019.
4. Schumacher RF, Spinelli E. Malaria in children. Mediterr. J. Hematol. Infect. Dis. 2012; 4:1e2012073. doi: https://doi.org/10.4084/mjhid.2012.073.

5. World Health Organization. Global technical strategy for malaria 2016-2030. Geneva, World Health Organization, 2015.
   https://apps.who.int/iris/bitstream/handle/10665/176712/9789241564991_eng.pdf?ua=1?sequence=1. Accessed 15 Aug 2019.

6. Silva SV, Reyes-Lecca RC, Pinheiro TRA, Lacerda MVG. Malaria is associated with poor school performance in an endemic area of the Brazilian Amazon. Malar J 2009; 8:230. doi:10.1186/1475-2875-8-230.

7. Arruda EF, Araujo FM, Guimaraes MGS, Nogueira R, Ramalho AA, Nunes MS. Associação entre malária e anemia em área urbana de transmissão do Plasmodium: Mâncio Lima, Acre, Brasil. Cad. saúde pública. 2016; 32:9. doi:10.1590/0102-311X00115514

8. Benzecry SG, Alexandre MA, Vítor-Silva S, Salinas JL, de Melo GC, Marinho HA, et al. Micronutrient deficiencies and Plasmodium vivax malaria among children in the Brazilian Amazon. Plos One. 2016; 11(3):e0151019. doi: 10.1371/journal.pone.0151019.

9. Instituto Sócio Ambiental. Surto de malária afeta rendimento escolar no Alto Rio Negro. 2018. https://www.socioambiental.org/pt-br/noticias-socioambientais/surto-de-malaria-afeta-rendimento-escolar-no-alto-rio-negro. Accessed 25 Jun 2020.

10. Cheaveau J, Marasinghe D, Akakpo S, Deardon R, Naugler C, Chin A. The Impact of Malaria on Liver Enzymes: A Retrospective Cohort Study (2010–2017). Open Forum Infect. Dis. 2019;6:1. doi:10.1093/od/ofz234.

11. Meireles BM, Sampaio SV, Monteiro WM, Gonçalves MJF. Factors associated with malária in indigenous populations: A retrospective study from 2007 to 2016. Plos One. 2020;15:e0240741. doi: https://doi.org/10.1371/journal.pone.0240741.

12. Cornell Statistical Consulting Unit. Using Adjusted Standardized Residuals for Interpreting Contingency Tables. Statnews #95. Created December 2018. Last updated August 2020. https://www.cscu.cornell.edu/news/statnews/95_conttableresid.pdf. Accessed 25 Apr 2021.

13. Paul P, Pennell ML, Lemeshow S. Standardizing the power of the Hosmer–Lemeshow goodness of fit test in large data sets. Statistics in Medicine 2013;32:67-80. doi:10.1002/sim.5525

14. Sheila SV, Siqueira AM, Sampaio VS, Guinovart C, Reyes-Lecca RC, et al. Declining malaria transmission in rural Amazon: changing epidemiology and challenges to achieve elimination. Malar J 2016;15:266. doi:10.1186/s12936-016-1326-2

15. Diniz LMO, Figueiredo BCG. O sistema imunológico do recém-nascido. Rev. Méd. Minas Gerais 2014;24:233-240. doi: http://www.dx.doi.org/10.5935/2238-3182.20140056

16. Braz RM, Duarte EC, Tauil PL. Caracterização das epidemias de malária nos municípios da Amazônia Brasileira em 2010. Cad. Saúde Pública 2013;29:935-944. doi: 10.1590/S0102-311X2013000500011
17. Sousa JR, Santos ACF, Almeida WS, Albarado KVP, Magno LD, et al. Malaria situation in the Lower Amazon Region, Pará State, Brazil, from 2009 to 2013: an epidemiological approach. Rev Panam Salud Publica. 2015;6:39-47. doi: http://dx.doi.org/10.5123/S2176-62232015000400006.

18. Rodrigues EC, Lopes Neto D. Malaria control in an Amazon municipality. Rev Latino-Am Enfermagem. 2011;19:1297-1305. doi:10.1590/S0104-11692011000600004

19. Menezes RAO, Gomes MSM, Mendes AM, Nacher M, Pimenta TS, et al. Enteroparasite and vivax malaria co-infection on the Brazil-French Guiana border: Epidemiological, haematological and immunological aspects. PLoS ONE 2018;13(1): e0189958. doi:10.1371/journal.pone.0189958.

20. Oliveira-Ferreira J, Lacerda MVG, Brasil P, Ladislau JLB, Tauil PL, Daniel-Ribeiro CT. Malaria in Brazil: an overview. Malar J 2010;9:115-120. doi:10.1186/1475-2875-9-115

21. Recht J, Siqueira AM, Monteiro WM, Herrera SM, Herrera S, Lacerda MVG. Malaria in Brazil, Colombia, Peru and Venezuela: current challenges in malaria control and elimination. Malar J. 2017;16:273. doi:10.1186/s12936-017-1925-6.

22. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Imunização e Doenças Transmissíveis. Guia de tratamento da malária no Brasil. Brasília: Ministério da Saúde, 2020. http://bvsms.saude.gov.br/bvs/publicacoes/guia_tratamento_malaria_brasil.pdf. Accessed 15 Dec 2020.

23. Costa MRF, Vieira PPR, Ferreira CO, Lacerda MVG. Diagnóstico molecular da malária em uma unidade de atenção terciária na Amazônia Brasileira. Rev. Soc. Bras. Med. Trop. 2008;41:381-385. doi:10.1590/S0037-86822008000400011

24. Mendes AM, Lima MS, Maciel AGP, Menezes RAO, Eugenio NCC. Malária entre povos indígenas na fronteira Brasil-Guiana Francesa, entre 2007 e 2016: um estudo descritivo. Epidemiol. Serv. Saúde. 2020;29: e2019056. doi:10.5123/S1679-49742020000200012

25. Almeida ACG, Kuehn A, Castro AJM, Sheila VS, Figueiredo EFG, et al. High proportions of asymptomatic and submicroscopic Plasmodium vivax infections in a peri-urban area of low transmission in the Brazilian Amazon. Parasit Vectors. 2018;11:194. doi:10.1186/s13071-018-2787-7