

## Malaria at international borders: challenges for elimination on the remote Brazil-Peru border

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### ABSTRACT

Understanding local epidemiology is essential to reduce the burden of malaria in complex contexts, such as Brazilian municipalities that share borders with endemic countries. A descriptive study of malaria in the period 2003 to 2020 was conducted using data from the Malaria Epidemiological Surveillance Information System related to a remote municipality with an extensive border with Peru to understand the disease transmission, focusing on the obstacles to its elimination. The transmission increases at the end of the rainy season. During the period of 18 years, 53,575 malaria cases were reported (Mean of API 224.7 cases/1,000), of which 11% were imported from Peru. Thirteen outbreaks of malaria were observed during the studied period, the last one in 2018. The highest burden of cases was caused by *P. vivax* (73.2%), but *P. falciparum* was also prevalent at the beginning of the study period (50% in 2006). Several changes in the epidemiological risk were observed: (1) the proportion of international imported cases of malaria changed from 30.7% in 2003 to 3.5% in 2020 ( $p < 0.05$ ); (2) indigenous people affected increased from 24.3% in 2003 to 89.5% in 2020 ( $p < 0.0001$ ); (3) infected children and adolescents < 15 years old increased from 50.2% in 2003 to 67.4% in 2020 ( $p < 0.01$ ); (4) the proportion of men decreased from 56.7% in 2003 to 50.4% in 2020 ( $p < 0.01$ ); (5) the likelihood of *P. falciparum* malaria has significantly declined ( $p < 0.01$ ). The number of cases and the incidence of malaria in 2019 and 2020 were the lowest in the period of 18 years. The burden of malaria in indigenous areas and its determinants, seasonality, geographical access and the long international border are obstacles for the elimination of malaria that must be overcome.

**KEYWORDS:** Malaria. Epidemiology. Public health surveillance. Indigenous population. Border areas.

### INTRODUCTION

Currently, the world is committed to the elimination of malaria. Aiming at “a world free of malaria”, one of the global technical strategies (GTS) for 2030 is to reduce malaria mortality and case incidence rates by at least 90% when compared to 2015<sup>1</sup>. Transforming malaria surveillance into a core intervention is one of the pillars of GTS. Reliable information and analyses are essential for planning actions and for identifying populations and areas at higher risk for malaria<sup>2</sup>. In Brazil, 144,888 cases of malaria were reported in 2020. From 2000 to 2015, Brazil showed a significant reduction in the number of malaria cases (76%), reaching one of the millennium goals<sup>3</sup>. However, when compared to 2016, there was a 61% increase in the number of cases in 2017<sup>4</sup>.

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The disease has a heterogeneous distribution and its control is focused on certain locations where most of the cases are concentrated and there is a high unstable transmission. As malaria results from specific ecological, sanitary, political and cultural conditions in each place<sup>5</sup>, it is necessary to know the local epidemiology in which the disease is present to establish adequate measures to fight against it. Different determinants are pointed out for malaria endemicity and they are related to the difficulty of disease elimination; the main determinants are: gold mining malaria<sup>6-10</sup>, malaria in indigenous area<sup>11,12</sup>, urban malaria<sup>13-15</sup>, border malaria<sup>4-16</sup> and malaria in conflict zones<sup>17</sup>, each one with different degrees of endemicity. Atalaia do Norte, one of the largest municipalities in Amazonas State, Brazil, is an area historically affected by malaria, with a high incidence of the disease, although it has been poorly studied until now. This study analyzed the epidemiology of malaria in this municipality during the last 18 years (2003-2020) to understand the disease transmission, focusing on the surveillance of malaria as a core intervention to achieve elimination.

## MATERIALS AND METHODS

### Study area

The municipality of Atalaia do Norte (Latitude: 4° 22' 20" South, Longitude: 70° 11' 33" West) is located in the Southwest part of Amazonas State, Brazil, in the Alto Rio Solimoes region, at a distance of 1,138 km in a straight line from the State's capital Manaus, and it is accessible only by river. The municipality has an area of 76,355 km<sup>2</sup>, an estimated population of 19,438 habitants (mean of 0.25 inhabitants per km<sup>2</sup>) and an extensive international border with Peru in the North and West<sup>18</sup>. There are 147 locations scattered over four extensive river basins: Itacoai, Itui, Curuca and Jaquirana, in an inhospitable and difficult-to-access region.

Atalaia do Norte is located in the Amazon rainforest, with the rainy season between November and March, decreasing in April and May and the dry season from June to October, when the rivers decrease in volume and reach the lowest levels. Approximately 80% of the population is indigenous. Part of the Vale do Javari Indigenous Land is located in this municipality, one of the largest indigenous lands in the world, inhabited by the Marubo, Matses (Mayuruna), Kanamari, Matis, Kulina-Pano and Korubo ethnic groups. Peruvian and Colombian immigrants also live in the municipality's headquarters. Vale do Javari is the territory with the highest concentration of isolated (and not contacted) indigenous people in the world. Access to rural locations is by small boats and occasionally by air with small landing strips in some

villages and flights conducted by the military in small aircraft that provide services to the State, at a very high cost. There are no commercial planes in this area. Laboratory diagnosis and treatment are supported by the Brazilian Ministry of Health. The local health service is responsible for malaria outside indigenous areas while malaria in indigenous areas is managed by professionals from the Special Indigenous Unit of the Vale do Javari Sanitary District (DSEI-VJ) organized in seven base poles with health structures. All cases must be reported to the Epidemiological Surveillance Information System (SIVEP-Malaria), a robust Ministry of Health database filled in by local health workers.

### Epidemiological design

A descriptive study of the information contained in SIVEP-Malaria was carried out from 2003 to 2020 for the municipality. All positive cases by the probable location of infection were filtered for variables such as origin (imported vs autochthonous), spatial (municipality, urban area, rural area, indigenous area and settlements), temporal (month and year), demographic (sex and age group) and parasitological (*Plasmodium* species).

An endemic curve was constructed and analyzed using the number of cases for each month in the period studied. The time series were observed to separate different periods for the analysis. As the data series met the normality criteria, the endemic curve was elaborated in two stages: a) the mean and standard deviations of the cases from each month were calculated for the all the period (2003-2020). The upper limit was calculated by adding two standard deviations to the mean. The lower limit was calculated by subtracting two standard deviations and the mean of cases. Months that exceeded the upper limit of the average were excluded from the initial analysis; b) the means and standard deviations were recalculated for each month, after excluding the epidemic months, to build the expected endemic curve for the municipality. Graphs were made with the expected and the observed number of cases. Months were considered epidemic when they exceeded the expected upper limit. Such classification was an adaptation for the study to demonstrate the frequency variation in the time series. For the analysis of the duration of epidemics, the classification described by Braz *et al.*<sup>19</sup> was used: short (one to four epidemic months in a year); medium (five to eight epidemic months in a year) and long (nine to 12 epidemic months in a year).

### Statistical analysis

All data were analyzed using the Epi Info 7 software (Centers for Disease Control and Prevention, Atlanta,

USA). Absolute and frequency analyzes of variables were performed. The  $\chi^2$  test was used to analyze the proportions of sex, age group, origin of cases and *Plasmodium* species. To quantify the strength of the association between variables, Odds ratios (OR) were used. Mean and standard deviation (SD) were calculated for quantitative data. The Student's t-test was used to compare means (specially time variables). A p value <0.05 was considered significant, with 95% confidence intervals (CI95%) for all hypothesis tests.

### Ethical considerations

The research was submitted and approved by the Institute Oswaldo Cruz (IOC) Research Ethics Committee (CAAE 74999617.7.0000.5248) and by the National Research Ethics Commission (CONEP,) opinion issued N° 2,666,109 of May 2018.

### RESULTS

From 2003 to 2020 a total of 53,610 (annual mean  $\pm$  SD:

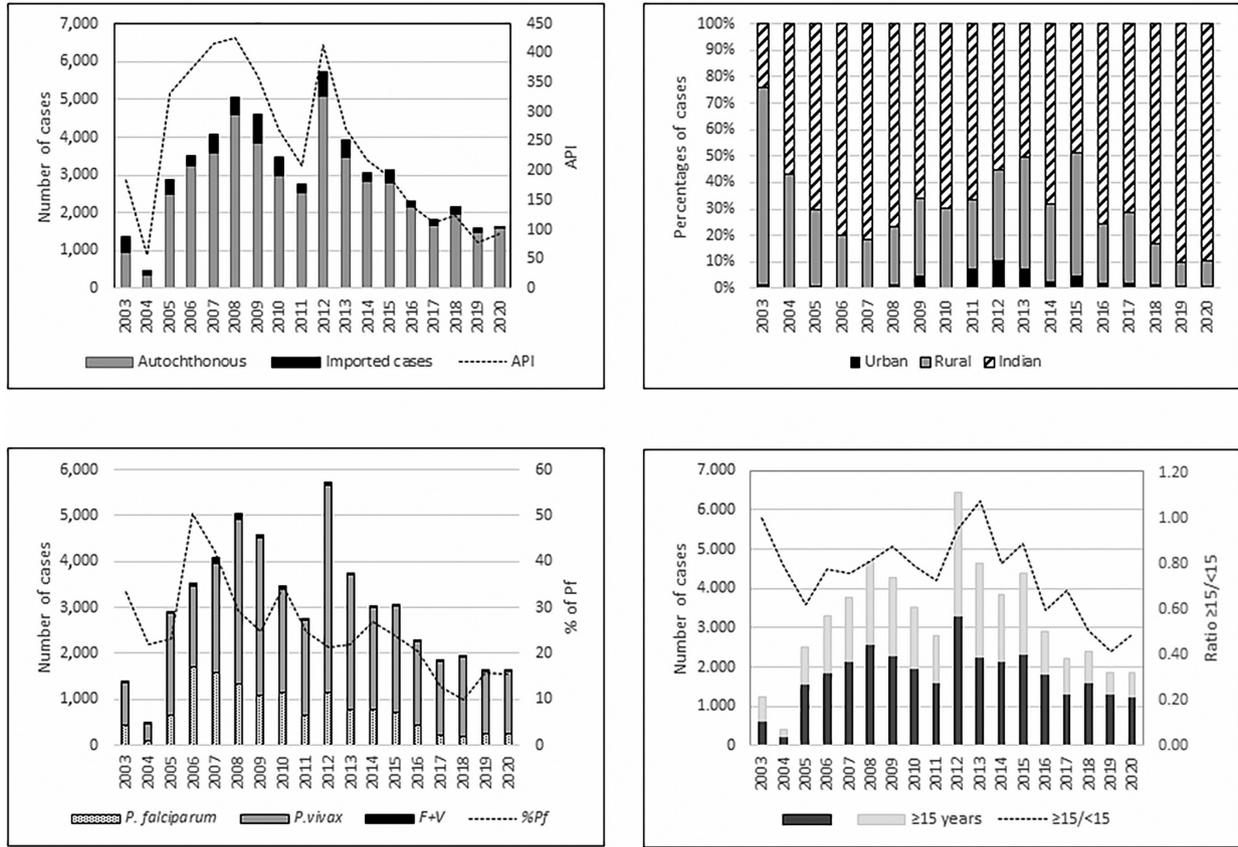
2,976  $\pm$  1,377, 95% CI: 2,292-3,662) cases of malaria were reported in the municipality of Atalaia do Norte (Table 1). Between 2005 and 2008 there was an increase in the number of cases, followed by a reduction from 2009 to 2011 and a new peak in 2012. However, from 2013 to 2020 the municipality has been showing a decrease in the number of cases. The average API (annual parasitic incidence) was 224.7 cases per 1,000 inhabitants (range 37.6-373.8 cases per 1,000/inhabitants). The API in 2019 was 78.2, the lowest in the last 15 years. Despite the decrease in API, the municipality remained classified as having a high epidemiological risk throughout the period of analysis (Figure 1A).

Of the total reported cases, 47,691 (89.0%) were autochthonous and 5,919 (11.0%) were imported from other municipalities or countries. Of the imported cases, 93.5% were from other States and/or countries. During the period, there was a great fluctuation in the ratio autochthonous: international imported malaria cases. The likelihood of an autochthonous case was 12 times higher in 2020 than in 2003 (OR= 12.3, 95% CI: 9.2-16.3,  $p \leq 0.01$ ). Most imported cases from other countries came from Peru.

**Table 1** - Malaria cases between 2003 and 2020 distributed by the area of origin.

Year	Autochthonous cases						Imported cases				
	Urban		Rural		Indian		Total autochthonous		Imported		Total
	n	% <sup>a</sup>	n	% <sup>a</sup>	n	% <sup>a</sup>	n	% <sup>b</sup>	n	% <sup>b</sup>	n
2003	14	1.5	698	74.2	229	24.3	941	69.3	417	30.7	1,358
2004	0	0.0	161	43.4	210	56.6	371	78.3	103	21.7	474
2005	25	1.0	711	28.6	1,751	70.4	2,487	86.3	395	13.7	2,882
2006	2	0.1	652	20.1	2,586	79.8	3,240	91.8	289	8.2	3,529
2007	5	0.1	652	18.2	2,924	81.7	3,581	87.8	496	12.2	4,077
2008	50	1.1	1,010	22.0	3,523	76.9	4,583	90.7	471	9.3	5,054
2009	183	4.7	1,122	29.0	2,559	66.2	3,864	84.1	731	15.9	4,595
2010	10	0.3	892	30.0	2,067	69.6	2,969	85.5	505	14.5	3,474
2011	179	7.0	677	26.6	1,693	66.4	2,549	92.2	217	7.8	2,766
2012	522	10.3	1,758	34.6	2,800	55.1	5,080	88.8	638	11.2	5,718
2013	254	7.3	1,466	42.2	1,750	50.4	3,470	88.4	457	11.6	3,927
2014	69	2.4	829	29.3	1,929	68.2	2,827	92.1	242	7.9	3,069
2015	126	4.5	1,309	46.8	1,364	48.7	2,799	89.3	336	10.7	3,135
2016	38	1.8	486	22.5	1,634	75.7	2,158	94.1	136	5.9	2,294
2017	34	2.0	450	26.7	1,201	71.3	1,685	92.4	138	7.6	1,823
2018	24	1.2	306	15.5	1,647	83.3	1,977	91.1	193	8.9	2,170
2019	15	1.0	134	9.0	1,348	90.0	1,497	93.9	98	6.1	1,595
2020	14	0.9	156	9.7	1,443	89.5	1,613	96.6	57	3.4	1,670
Total	1,564	3.3	13,469	28.2	32,658	68.5	47,691	89.0	5,919	11.0	53,610

<sup>a</sup>The denominator is the total autochthonous cases per year; <sup>b</sup>The denominator is the total cases per year.



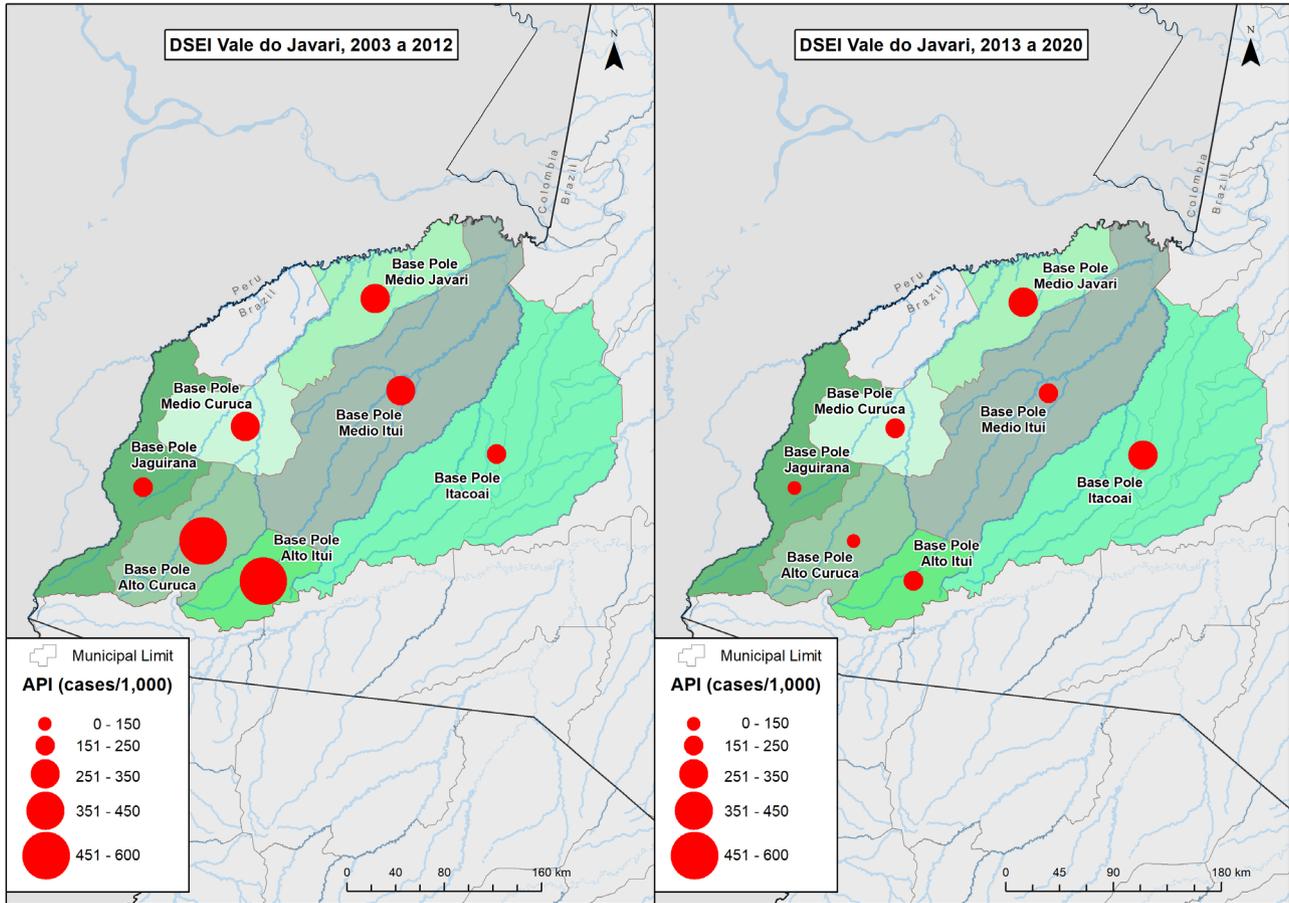
**Figure 1** - Malaria epidemiology in the municipality of Atalaia do Norte between 2003-2020. A) Number of autochthonous and imported malaria cases and API in the municipality of Atalaia do Norte; B) Distribution of cases in urban, indigenous and rural areas during the study period; C) Distribution of cases according to *Plasmodium* species and the percentage of *P. falciparum*; D) Cases of malaria according to the age group and the ratio  $\geq 15$ :  $< 15$  years old.

### Autochthonous cases

Among the autochthonous cases recorded in the study period, 1,564 (3.3%) occurred in urban areas (annual mean:  $91 \pm 134.3$  95% CI: 22.1-160.2) and 46,127 (96.7%) in rural areas (annual mean  $2,619 \pm 1,153$ , 95% CI: 2,026-3,212) ( $p < 0.05$ ). Of the rural cases, 32,658 (68.5%) were in indigenous areas (annual mean  $1,836 \pm 877$ , 95% CI: 1,385-2,287) and 13,469 (28.2%) in other rural areas (annual mean  $783 \pm 444.9$ , 95% CI: 554.4-1,012) ( $p < 0.05$ ) (Figure 1B). During the study period, rural areas contributed with more than 95% of the notified cases each year. In indigenous areas, the higher numbers of cases was registered in the years 2008 (3,523 cases), 2007 (2,924 cases) and 2012 (2,800 cases). However, it was observed that in 2003, rural areas exceeded the number of notifications with respect to indigenous areas [698 (74.1%) vs 229 (24.3%)] (Figure 1B). In 2019, there was a 24% decrease in the number of cases compared to 2018, but in 2020 there was an increase of 7% compared to 2019; the greatest prominence occurred in non-indigenous rural areas, which showed a 56.2% reduction in 2019 compared to 2018, but a low increase in 2020 (7.7%).

### Malaria in indigenous areas

Malaria data in indigenous areas showed two different moments. The first period, from 2003 to 2012, when the highest number of cases was recorded ( $n = 20,342$  cases, 68.6% of autochthonous cases), characterizing it as an epidemic period, in which the *base pole* with more cases was Alto Itui (4,662 cases, 22.9%), but the average API for the period showed that the greatest burden of the disease taking place in Alto Curuca (565.2 cases/1,000) and Alto Itui Poles (519.7 cases/1,000). The second period was from 2013 to 2020 when 12,316 cases were recorded, characterizing it as a post-epidemic period, and most of the cases were reported in Itacoai Pole (2,767 cases, 22.5%). Significant differences were found when comparing the cases in indigenous areas and other autochthonous cases during the two periods ( $p < 0.0001$ ). The highest API in this period was 303.6 cases/1,000 inhabitants in the Middle Javari Pole. The mean of cases from the 2003-2012 period was higher ( $2,906 \pm 893$  cases, 95% CI: 2,080-3,732) than the 2013-2020 period ( $1,540 \pm 241$  cases, 95% CI: 1,338-1,741), ( $p < 0.05$ ) (Figure 2). The proportion of



**Figure 2** - Mean of the Annual Parasitic Incidence (API) according to *base poles* from the Special Indigenous Health District of Vale do Javari (DSEI-VJ). Epidemic period: 2003-2012 and post-epidemic period: 2013-2020.

indigenous people affected increased from 24.3% in 2003 to 89.5% in 2020 ( $p < 0.0001$ ) and currently, the greatest burden of malaria occurs in indigenous areas.

### Seasonality and epidemics peaks

The high transmission season starts in April with a peak in June-July and a decrease in August. The low transmission season occurs between September and December. During the study period, 13 epidemic episodes were detected, 12 were classified as short-term epidemics, and one as long-term epidemics (nine months). The 2003-2012 epidemic period registered nine (69.2%) peaks, eight of short duration (mean 49 days) and one of long duration. During the post-epidemic period (2013-2020), there were four (30.8%) peaks, all of them of short duration (mean 45 days). There is no record of outbreaks since October 2015 (Figure 3).

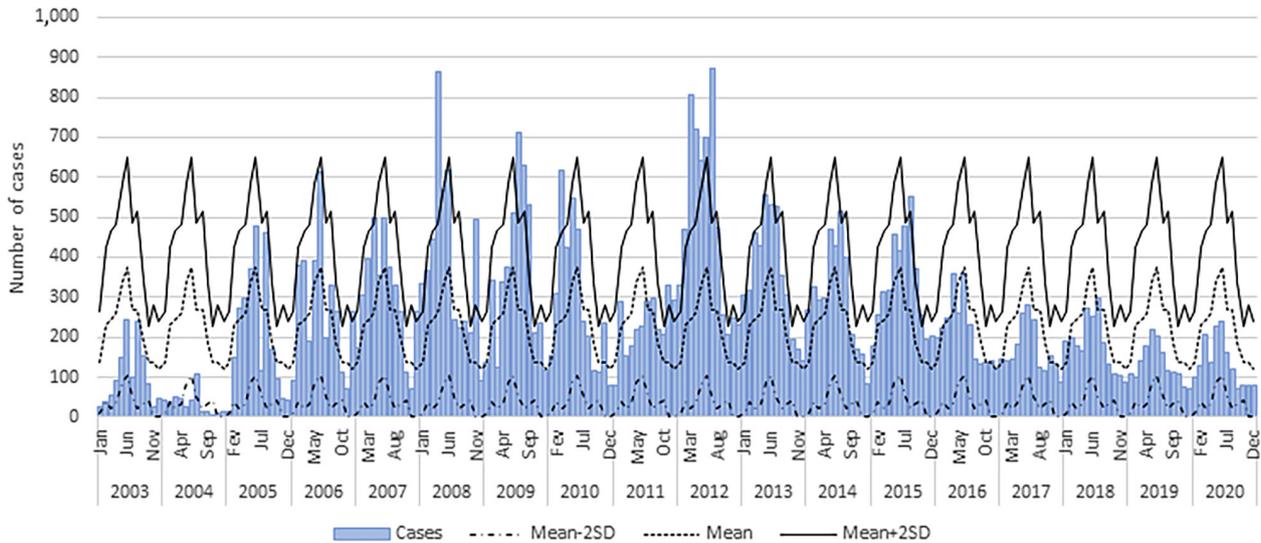
### Analysis by *Plasmodium* species

There were 13,427 cases caused by *P. falciparum* (25.3%, range 10-50.4), 38,836 by *P. vivax* (73.2%, range

and 797 mixed infections by *P. vivax* and *P. falciparum* (1.5%). In 2012, Rapid Diagnostic Tests (RDT) were introduced and a total of 351 cases (0.7%) were reagent for *P. non-falciparum*. As no cases caused by *P. malariae* were diagnosed by the thick blood smear, all RDT-diagnosed cases could be assigned to *P. vivax*. The annual mean of *P. falciparum* cases was  $746 \pm 493$  (95% CI: 501-999) and of *P. vivax* was  $2,158 \pm 990$  (95% CI: 1,665-2,650),  $p < 0.0001$ . In 2006, *P. falciparum* was responsible for 50.4% of the cases and in 2007 for 42.1%. Evaluation of the epidemic period (2003-2012) showed that *P. falciparum* accounted for 29% of the cases and in the post-epidemic period (2013-2020), for 18.7%. Comparing with the epidemic period, the likelihood of *P. falciparum* cases in the post-epidemic period was 0.6 (95% CI: 0.5-0.6,  $p < 0.01$ ) (Figure 1C).

### Age group and sex analysis

During the study period, 56.5% of cases were diagnosed in children under 15 years old (of whom 22.8% were under 5 years old). At the beginning of the period, 50.2% of cases



**Figure 3** - Endemic curve of malaria cases in the municipality of Atalaia do Norte, from 2003 to 2020.

were in children under 15 years old (of whom 20.5% were under 5 years); in 2020, 67.4% of cases were in children under 15 years old (of whom 31.9% were under 5 years). The likelihood of having malaria in a child <15 years old was significantly higher in 2020 in comparison with 2003 (OR: 2.1, 95% CI: 1.8-2.5  $p < 0.01$ ) (Figure 1D). Differences by sex were also assessed: 55% of men were affected by malaria, with a ratio male/female of 1.2:1. In 2003, 56.7% of cases were among men and in 2020, they represented 50.4% of the cases. This difference was statistically significant (OR: 0.8 95% CI: 0.7-0.9,  $p < 0.01$ ), with a current lower burden of cases in males comparing 2003 with 2020.

## DISCUSSION

Our results showed that this municipality has a long history of high incidence of malaria with several outbreaks<sup>20-22</sup>. However, few studies have been conducted in this area to understand the epidemiology of the disease. The annual mean API during the period was 206.7 cases/1,000 inhabitants, and despite the significant decrease in recent years, the municipality is still considered of high epidemiological risk. This value is almost 20 times higher than the annual mean API in the Amazon region, in the same period (mean API: 11 cases/1,000 inhabitants)<sup>3</sup>. In 1994, the National Health Foundation reported an important number of deaths in the indigenous population that was initially attributed to hepatitis, but was later demonstrated to be malaria, the main cause of morbidity and mortality in that outbreak<sup>21,23</sup>. Sampaio *et al.*<sup>21</sup> showed that the cases were related to the distance between villages and extractive areas and that the disease was spread, not radiated from a single focus. In 1997, the non-governmental organization

“Doctors Without Borders” (MSF in the French acronym) started a disease control initiative in the Vale do Javari, training Indigenous Health Agents (AIS in Portuguese) and Indigenous Malaria Microscopists (MIM in Portuguese) from Matis, Kanamary, Marubo, Maioruna and Culina ethnic groups. At the end of 1999, the Brazilian government started the implementation of Special Indigenous Health Districts (DSEIs in its Portuguese) with support from the MSF. After structuring the DSEI, the work of MSF was completed leaving the indigenous primary health workers and microscopists well trained<sup>20</sup>.

Brazil was one of the countries that reached the “combat HIV/AIDS, malaria, and other diseases” Millennium Development Goals (MDG), with a decrease of 75% of malaria cases in 2015 (142,583 cases) compared to 2000, when 615,247 cases were reported<sup>24</sup>. In contrast to the reduction of cases in Brazil after the epidemic in 2005 and 2006, malaria burden in the city of Atalaia do Norte continued extremely high, with a peak in 2008 and another one in 2012. These peaks seem to have been caused by the discontinuity of malaria actions. Fewer cases in 2003 and 2004 were likely underreported. After 2013, malaria cases decreased and in 2019 the lowest number of cases in the last 15 years was reported. This success can be attributed to the intensification of the malaria control program in the municipality with expansion of the diagnostic network in rural localities, especially in indigenous areas. An active community participation combined with surveillance, vector control, active case detection and treatment was part of the success. In 2020, the Pan American Health Organization (PAHO) recognized the efforts made and awarded the municipality as “Champions” of Malaria in the Americas<sup>25</sup>. However, it is not yet possible to let the guard

down and programs need to maintain their activities as API and number of cases are still very high. The COVID-19 pandemic is an additional obstacle for achieving the goals, at least in the foreseen time<sup>26</sup>.

The percentage of imported cases reported has decreased from 30.7% in 2003 to 3.5% in 2020 ( $p < 0.05$ ). The greatest malaria burden occurred in rural areas, being the indigenous ones the most impacted, accounting for 61% of the total cases, but the epidemiology has changed: whereas in 2003 only 24% of cases were reported in indigenous areas, in 2020 almost 90% of cases were in these areas. Similar findings in other areas were pointed out by others in a similar context<sup>10,27,28</sup>. In addition to the combined work between the professional teams of indigenous health and the municipality, the assistance of indigenous leaders and communities is essential. The use of RDT for the effective diagnosis and treatment is paramount in areas in which there are not enough health services structures. This work should be strengthened, as well as the improvement of the DSEI structure in the most distant and difficult-to-access locations. More studies are needed to understand the differences of malaria burden in this enormous indigenous area that has a complex epidemiology.

Seasonality in malaria has variations from one year to another. The greatest transmission occurs at the end of the rainy season and the low number of cases is during the dry season. A study carried out in the Loreto region, in the Peruvian Amazon, an area that borders the Javari River Valley, showed the same evidence of continuous transmission with an increase in the number of cases from February to July<sup>29,30</sup>. Control actions must be implemented before the beginning of the highest transmission season. Activities should be carried out simultaneously on both sides of the frontier for a greater probability of success<sup>19,27</sup>.

By comparing 2020 to 2003, there were differences in the risk of having malaria between men and women ( $p < 0.01$ ), but these differences were not observed when the entire period was analyzed. Other studies have consistently shown the changing pattern between men and women over time<sup>10,31</sup>. In the Amazon region, malaria has long been considered an occupational disease associated with mining, extractive activities and other predominantly male occupations<sup>32</sup>. The quarantine due to COVID-19 led to a reduction in the occupational mobility. This may explain, at least partially, the decrease in the percentage of cases among men in 2020, but this fact must be clarified. Changes in the most affected age group were also observed. In 2003, 58% of the individuals affected were less than 15 years old; in 2020, 60.8% of those affected were under 15 years old ( $p < 0.01$ ). Similar changes were observed in other contexts with long histories of malaria and a high epidemiological risk in the

Amazon region<sup>3,10,21</sup>. Taking these findings into account, it is imperative to carry out field studies to establish the presence of asymptomatic infections. Several studies have shown that after many malaria episodes in high epidemiological risk areas, adults may develop clinical immunity and not show (or show few) symptoms, while children, who have not yet developed this type of immunity, are more likely to suffer from symptomatic clinical malaria<sup>33,34</sup>.

Although *P. vivax* has been the most prevalent *Plasmodium* species in the municipality, in the last years, that was not always the case. In the study of Sampaio *et al.*<sup>21</sup>, 68.2% of the detected cases were due to *P. falciparum* and during the first years of our study, *P. falciparum* contributed with 50% of the cases in 2006. After the introduction of artemisinin-based combination treatment schedules (ACTs) in 2007, the percentage of cases due to *P. falciparum* had decreased to 10%. However, in 2019, there was an increase of 31% in cases compared to 2018<sup>3</sup>. One of the goals of the Brazilian National Malaria Control Program is to eliminate cases caused by *P. falciparum*, and to achieve this goal actions against this parasite, that are more susceptible to vector control activities are necessary. The reduction of vector control activities is one of the indicators that shows that the work of health services has been well executed<sup>35</sup>. Worryingly, the COVID-19 pandemic can also be an obstacle to achieving this goal<sup>26,36</sup>.

Vale do Javari Indigenous Land is frequently targeted by illegal gold miners, fishermen, hunters, drug traffickers and religious organizations from Brazil, Colombia and Peru. Invasions into the territory have increased over recent years<sup>37</sup>. Despite the decrease of imported cases from Peru in the last years, the international border of 1,180 km long may be one of the obstacles to malaria control. Both countries are separated by the Javari River that can be easily crossed, and the inhabitants are permanently moving to both sides of the frontier in search of health, goods and services. In the region of Loreto, the bordering area in the Peruvian Amazon, malaria cases have almost tripled in recent years<sup>38</sup> and riverside communities living at the border of Peru have a fragile structure of health services. The study by Braz and Barcellos<sup>22</sup>, carried out in 2016 and 2017, showed that Atalaia do Norte forms a conglomerate with six other municipalities bordering Peru, maintaining a high incidence of the disease. It is worth mentioning that malaria in border areas is difficult to control due to the displacement of people, border conflicts, cultural differences and complicated national public health regulations<sup>39</sup>. Control strategies involve necessarily a coordinated work between both countries. Sharing epidemiological information systematically can be the first step to start a coordinated work<sup>40</sup>.

As we used secondary data of the surveillance program, there are some limitations. Malaria cases are likely to be underreported due to the geographical extension as well as the lack of access to health services. However, in Brazil, malaria is a disease that is diagnosed and treated within the Brazilian National Health System (SUS in Portuguese). Antimalarial drugs are provided after a laboratory diagnostic test. There are no other health services available in this area and apparently, there is no illegal trade for selling antimalarials to the populations. Thus, we believe that the underdiagnosis is not that high. Finally, we believe that strengthening local epidemiological surveillance to understand the situation and taking appropriate and early actions is a fundamental pillar that will lead to the elimination of malaria in areas of complex epidemiology such as the Javari River Valley.

## CONCLUSION

The burden of malaria in indigenous areas and its determinants, seasonality, geographical access and the extensive international border between Brazil and Peru are obstacles for the elimination of malaria that must be overcome to reach the GTS for 2030.

## AUTHORS' CONTRIBUTIONS

MPC and MCSM conceived the study, wrote the protocol and implemented the study; MPC, MCSM, MBM, JG, NBA and RS analyzed and interpreted data; RS did the maps. MPC and MCSM wrote the first draft. All authors read and approved the final manuscript.

## CONFLICT OF INTERESTS

Authors declare that they have no conflicting interests.

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