Revista da Sociedade Brasileira de Medicina Tropical 47(6):763-769, Nov-Dec, 2014
http://dx.doi.org/10.1590/0037-8682-0274-2014

Major Article

The changing distribution of malaria in the Brazilian Amazon, 2003-2004 and 2008-2009

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ABSTRACT

Introduction: More than half of the malaria cases reported in the Americas are from the Brazilian Amazon region. While malaria is considered endemic in this region, its geographical distribution is extremely heterogeneous. Therefore, it is important to investigate the distribution of malaria and to determine regions whereby action might be necessary. **Methods:** Changes in malaria indicators in all municipalities of the Brazilian Amazon between 2003-2004 and 2008-2009 were studied. The malaria indicators included the absolute number of malaria cases and deaths, the bi-annual parasite incidence (BPI), BPI ratios and differences, a Lorenz curve and Gini coefficients. **Results:** During the study period, mortality from malaria remained low (0.02% deaths/case), the percent of municipalities that became malaria-free increased from 15.6% to 31.7%, and the Gini coefficient increased from 82% to 87%. In 2003, 10% of the municipalities with the highest BPI accumulated 67% of all malaria cases, compared with 2009, when 10% of the municipalities (with the highest BPI) had 80% of the malaria cases. **Conclusions:** This study described an overall decrease in malaria transmission in the Brazilian Amazon region. As expected, an increased heterogeneity of malaria indicators was found, which reinforces the notion that a single strategy may not bring about uniformly good outcomes. The geographic clustering of municipalities identified as problem areas might help to define better intervention methods.

Keywords: Malaria. Risk ratio. Gini coefficient. Lorenz curve. Brazilian Amazon.

INTRODUCTION

Malaria is considered a treatable disease that results in preventable deaths through the effective actions of health services[1,2]. In spite of this, malaria continues to be a worldwide public health problem, with 243 million cases and a million deaths each year, especially in Africa[1]. In 2007, the Americas reported 797,000 cases, with 57% of the cases originating from Brazil[3]. Of the 458,000 slide-confirmed malaria cases, almost all (99.8%) originated from the Amazon region of the country, which contains 13% of its population.

The distribution of malaria in Brazil might reflect a variety of environmental, host, or vector conditions[4]. Additionally, the distribution of malaria might reflect socio-economic and health resource inequities that are strongly associated with infectious disease risks, including malaria morbidity and mortality[4,5]. Therefore, it is important to describe the changing distribution of malaria because it may help to identify locations where action might be necessary. Malaria disparities and concentrations may be measured using a variety of indicators, which may be compared (absolute or relative) in different geographical areas and over time[6-8].

Although it is known that an uneven distribution of malaria occurs within the Brazilian Amazon region[9], few studies have described this issue in detail, and no investigation has been devoted to observe the time trend of the distribution and concentration of malaria in recent years and in a relevant, control-measure context in Brazil. Therefore, the objective of the present study was to measure the distribution of the indicators and concentration indexes of malaria among all municipalities (over 800) in the Brazilian Amazon over time.

METHODS

This study was designed as a mixed ecologic study analyzing malaria indicators over time and across geographical municipality groups. Malaria data were obtained from the Information System of Malaria [*Sistema de Informação da Vigilância Epidemiológica*-Malária (SIVEP-Malária)], which is maintained by the National Program for Malaria Control

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Received 6 November 2014
Accepted 8 December 2014

of the Ministry of Health (Secretary of Health Surveillance).To decrease year-to-year random variability, malaria cases for the years 2003 and 2004 (first interval/bi-annual) and for the years 2008 and 2009 (second interval/bi-annual) were combined.

Population data, which was made available through the Department of Information of SUS [*Departamento de Informática do Sistema Único de Saúde* (DATASUS)], were obtained from the Brazilian Institute of Geography and Statistics [*Instituto Brasileiro de Geografia e Estatística* (IBGE)]. DATASUS provided the estimated populations during the first and second intervals[10].

The analysis included demographic indicators (locations and populations of the municipalities), malaria indicators and the measures of changes and concentrations regarding these indicators. The malaria indicators for each municipality included the malaria case numbers and the bi-annual parasite incidence (BPI), which was calculated based on the accumulated number of malaria cases over two years (during the first or second interval) divided by the population during the last year of each biennium, and then multiplied by a thousand. The BPI ratios and differences between the periods were then calculated. The Gini coefficients were determined, and a Lorenz curve was plotted according to methods detailed by other authors[6,7]. Although they are more frequently used to quantify the disparity of a population's income, Gini coefficients have been used to evaluate the degree of heterogeneity of health parameters. In this study, Gini coefficients were used to examine the geographical concentration of malaria cases and utilized a null hypothesis stating that the distribution would be perfectly uniform. The Lorenz curve graphically showed the joint distribution of the accumulated percentage of malaria cases by geographic unit (municipality) *versus* the accumulated percentage of the populations for each of the municipalities, spanning from higher to lower malaria rates among the municipalities. The Gini coefficient corresponds to the area between the observed Lorenz curve and the hypothetical line of absolute homogeneity. In this way, the Gini coefficient will have a zero value if the malaria incidence rates are equal for all units (number of cases proportional to the population) and will have a value of 1 (100%) if all malaria cases occur within a single unit (complete inequality), which indicates maximum heterogeneity.

The data analysis compared the selected, available demographic, epidemiologic and malaria indicators over the study time interval. This study used a comprehensive data set from all of the Brazilian Amazon municipalities (n=805 or 807) for the years 2003 to 2009 and only used public and anonymous data.

RESULTS

For the first study interval (years 2003/2004), the combined population of the 805 Brazilian Amazon municipalities (all of the municipalities of the northern region, and States of Maranhão and Mato Grosso) was 22,310,068; 75.3% of these municipalities had populations less than 25,000 inhabitants, and only 3% had populations of more than 100,000 inhabitants **(Table 1)**. In the second period (years 2008/2009, n=807), as expected, the total population of the region increased by 9.4%, to 24,405,955, and the number of municipalities with less than 25,000 inhabitants decreased to 72.4%.

In spite of the population increase, an important reduction in the malaria case numbers, from about a million (2003/2004) to 730,000 (2008/2009), was observed over the study period (**Table 1**). Additionally, during the study period, the BPI per 1,000 inhabitants for each biennium decreased in the entire region from 45.2 to 29.9 (**Table 1**). Over this same period, the proportion of municipalities considered to be at high transmission risk (BPI greater than 100) dropped from 12.2% to 9.2%.

As expected, this overall reduction in malaria incidences was accompanied by a higher malaria concentration, as measured by the relative risks (RRs) and attributable risks (ARs) of the BPI values for the different quartiles (across all municipalities ranked by BPI values). During the first interval, the fourth quartile compared with the second quartile had a RR of 184.5, and the corresponding RR for the second interval was 863.2, which represented an increase in the polarization among the municipalities. The AR for these same two quartiles was reduced from 150.2 to 97.9 malaria cases per 1,000 inhabitants over the study period **(Table 2)**. However, when calculated as the percent of the second quartiles, the %AR rose from 18.4% to 86.2% (fourth quartile to second).

For both intervals, a Lorenz curve **(Figure 1)** showed great heterogeneity for the malaria cases within the entire region, with an increase of this already extreme polarization over the study period (Gini coefficients from 82% to 87% **-** the area representing the distortion from the diagonal line). For example, the 10% of the population of the municipalities that had the greatest BPIs comprised 67% and 80% of the reported malaria cases for the first (2003/2004) and second intervals (2008/2009), respectively. Additionally, 90% of the cases were concentrated in 21% and 17% of the municipality populations with the highest BPIs for the first and second intervals, respectively.

The map in **Figure 2** highlights the Brazilian Amazon region and shows the following: I) the municipal borders (in gray) and the state borders (in black); II) deaths by place of occurrence during the second interval (2008/2009), which are represented by circles; III) the municipalities stratified by BPI in the first interval (2003/2004): BPI≥50 per 1,000 inhabitants (yellow, orange, and red scales) or BPI<50 per 1,000 inhabitants (blue scale); and IV) the RRs of the BPIs (BPI of the second interval (2008/2009) divided by the BPI of the first interval), according to the strata defined above. The BPIs were based on autochthonous cases (acquired within the municipality). For example, in the worst situation, the municipalities in the darkest red had higher BPI levels during the first interval (2003/2004), which then rose (RR>1.2) during the study period (2008/2009). In the best situation, the municipalities in light blue initially had lower BPI levels (2003/2004), which then decreased (RR<0.8) during the study period (2008/2009). A special comment is needed for areas mapped in the white. These municipalities initially had no malaria cases (n=128), and their RRs were impossible to calculate for any value in the second interval. Therefore, all of

TABLE 1 - The municipality distribution by population and malaria indicators (number of incident cases and bi-annual parasite incidence). Amazon region: Brazil, 2003-2004 and 2008-2009.

Period	Indicators 2003-2004 (n=805 municipalities)	2008-2009 (n=807 municipalities)
Population (inhabitants)		
Total	22,310,068 inhabitants	24,405,955 inhabitants
Limits (min and max)	994 to 1,527,314 inhabitants per municipality	1,114 to 1,709,010 inhabitants per municipality
Median	12,600 inhabitants per municipality	14,309 inhabitants per municipality
0-25,000 inhabitants	606 (75.3%) municipalities	584 (72.4%) municipalities
>100,000 inhabitants	24 (3.0%) municipalities	31 (3.8%) municipalities
Incident cases		
Total (new cases)	1,008,035 cases	730,264 cases
Limits (min and max)	0 to 148,439 cases per municipality	0 to 54,770 cases per municipality
Median	22 cases per municipality	4 cases per municipality
Zero malaria cases	126 (15.6%) municipalities	256 (31.7%) municipalities
<100 malaria cases	519 (64.5%) municipalities	589 (73.0%) municipalities
>2,000 malaria cases	93 (11.5%) municipalities	78 (9.7%) municipalities
Bi-annual parasite incidence*		
BPI (region)	45.2 cases/1,000 inhabitants	29.9 cases/1,000 inhabitants
Limits (min e max)	0 to 1,963.6 cases/1,000 inhabitants per municipality	0 to 1,826.5 cases/1,000 inhabitants per municipality
Median	1.5 cases/1,000 inhabitants per municipality	0.27 cases/1,000 inhabitants per municipality
<10 cases/1,000 inhabitants	557 (69.2%) municipalities	624 (77.3%) municipalities
>100 cases/1,000 inhabitants	98 (12.2%) municipalities	74 (9.2%) municipalities

***BPI:** accumulated number of malaria cases over two years/population.

TABLE 2 - Malaria concentration indicators among the municipalities, clustered by bi-annual parasite incidence quartiles. Amazon Region: Brazil, 2003-2004 and 2008-2009.

Indicators	Period 2003-2004 (n=805 municipalities) Strata[a]				2008-2009 (n=807 municipalities) Strata[a]			
	1	2	3	4	1	2	3	4
BPI[b]/1,000 inhabitants	0.067	0.818	6.440	150.986	0.00	0.114	2.026	98.025
RR[c]	--	ref.	7.87	184.51	--	ref.	17.84	863.24
AR[c]/1,000 inhabitants	--	ref.	5.62	150.17	--	ref.	1.91	97.91
%AR[c]	--	ref.	687.0%	18,351.1%	--	ref.	1,683.9%	86,224.5%
Gini coefficient			82.2%				86.9%	

[a]Strata were defined by BPI quartiles, which included strata 1, municipalities(25%) with lower BPIs (202 municipalities in 2003-2004 and 256 municipalities in 2008-2009), and strata 4, municipalities (25%) with higher BPIs (201 municipalities in 2003-2004 and 202 municipalities in 2008-2009) [b]**BPI:** Bi-annual parasite incidence rates (cases accumulated over two years per 1,000 inhabitants); [c]**RR**: The BPI ratio for each period; **AR**: The BPI difference for each period; stratum 2 was considered as a reference (ref.) to estimate the RR and AR because stratum 1presented BPIs that were equal to zero(2008_2009), which prevented ratio calculations.

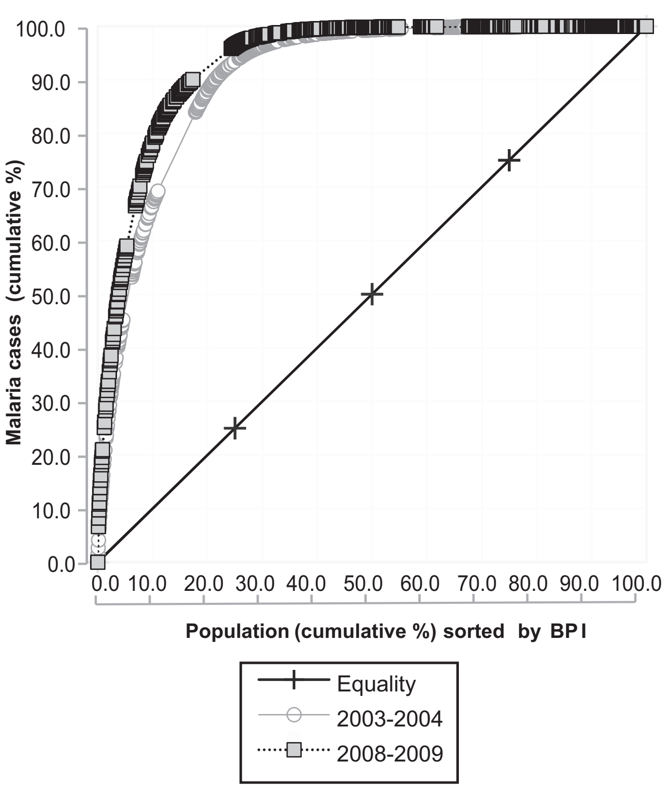

FIGURE 1 - Lorenz curve – Malaria case distributions (cumulative %) by population (cumulative %) among municipalities, which were sorted by bi-annual parasite incidence. Amazon Region: Brazil, 2003-2004 and 2008-2009. [Gini coefficients: 0.822 (2003-2004) and 0.869 (2008-2009). **BPI:** bi-annual parasite incidence.]

these areas remained white, even though 19 of them reported malaria during the second interval, and none of these areas achieved high BPI levels. Another special group of interest was the 147 municipalities that initially (2003/2004) had malaria but then became malaria-free during the study period (they are included within the light blue- or yellow-colored municipalities).

The geographic distribution of the RR values mapped in **Figure 2** shows a general trend of increasing malaria transmission in northwest Brazil(red and dark blue) for the States of Amazonas and Acre and for the Northern region of Pará (quadrants A1-3, B1-3 and C1-2). At the same time, we observed a trend of reduced malaria (light blue or yellow) in the central-western portion of the country for the States of Mato Grosso (C3-4 and D3-4), Tocantins (D3 and E3), and Maranhão (E2-3) and for the Southeast region State of Pará (C3 and D2-3).

Mortality from malaria remained low and included 203 deaths during the first interval (2003/2004) and 152 deaths during the second interval (2008/2009); a 0.02% case fatality rate was calculated for both intervals **(Table 3)**. Considering the location where the malaria deaths occurred during the second interval **(Figure 2)**, it is important to note that many of these deaths occurred outside of the transmission areas (the beige areas) or within the recently diminishing transmission areas (light blue and yellow areas).

DISCUSSION

This study identifies indicators that quantify the reduction and concentration of malaria cases in the Brazilian Amazon. Briefly, between the biennium years of 2003/2004 and 2008/2009, low mortality rates (0.02%) continued, and the number of municipalities reporting no malaria cases among residents increased from 15.6% to 31.7%. Moreover, the RR and %ARs increased between the higher and lower transmission areas over this period. In the first and second bienniums of the study period, the top 10% of the population originated from the municipalities with the highest malaria incidences had 67% (2003/2004) and 80% (2008/2009) of the malaria cases, respectively. Consequently, there was also a corresponding increase in the Gini coefficient from 82% to 87% during the study period, which supported the observation of an increase in the malaria case concentrations.

It is well known that the Brazilian Amazon region has environmental settings that are prone to malaria transmission, especially human factors that include demographic and socio-economic conditions. *An. darling* is the principal vector of malaria in both Latin America as well as Brazil and is found in

TABLE 3 - Malaria mortality indicators. Amazon Region: Brazil, 2003-2004 and 2008-2009.

Indicator	2003-2004 (n=805 municipalities)	2008-2009 (n=807 municipalities)
Total malaria deaths	203 deaths	152 deaths
Overall malaria fatality rate	0.02 deaths per 100 cases	0.02 deaths per 100 cases
Limits (min and max)	0 - 21 deaths per municipality	0 - 11 deaths per municipality
Zero malaria deaths	691 (85.8%) municipalities	716 (88.7%) municipalities
≥ 3 malaria deaths	14 (1.7%) municipalities	10 (1.2%) municipalities

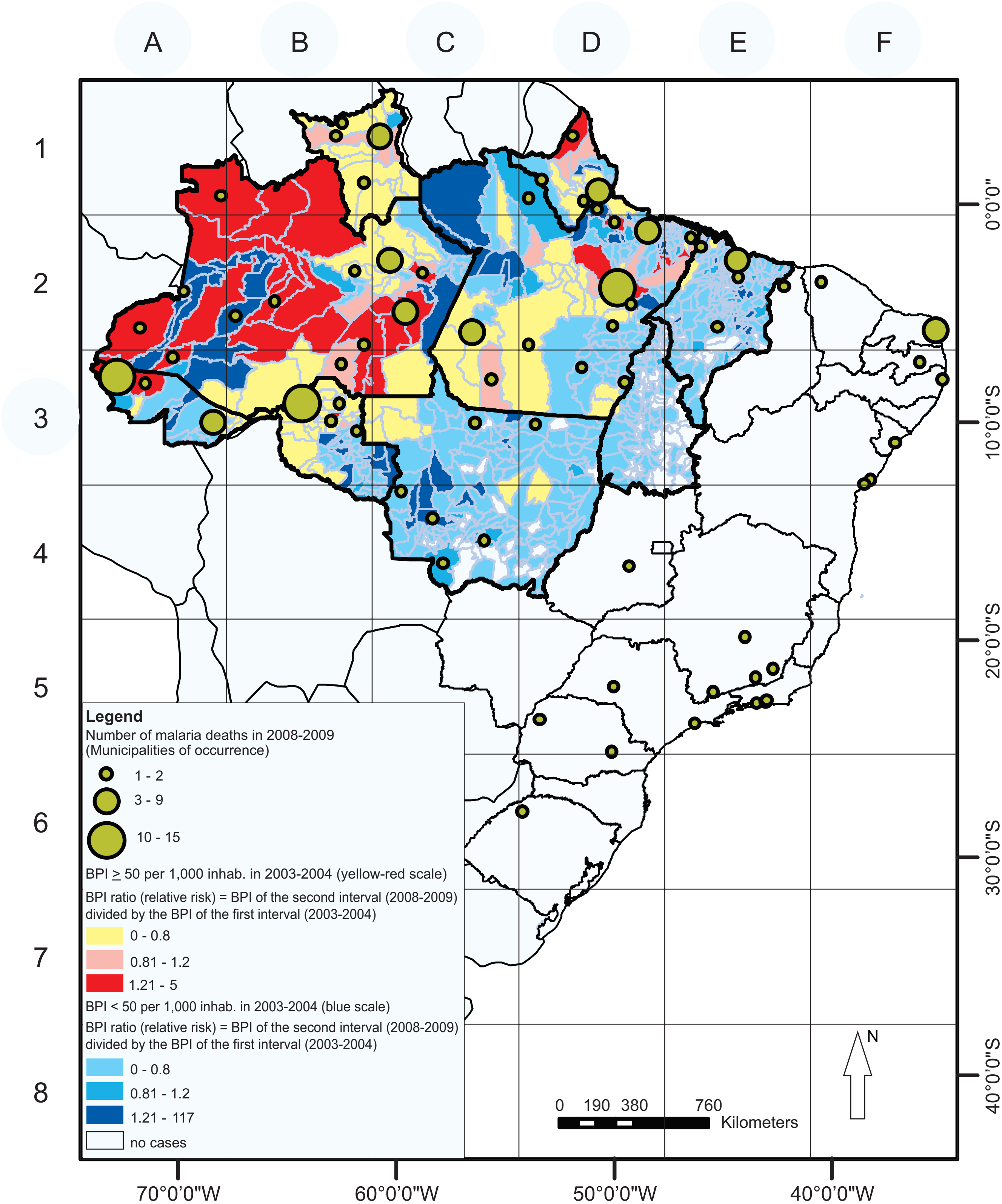

FIGURE 2 - Geographic distribution of the bi-annual parasite incidence (BPI) rate, by population stratum, in the Amazon region and malaria deaths in all of the Brazilian municipalities. Brazil, 2003-2004 and 2008-2009.

approximately 80% of the country. However, 99.8% of the malaria cases originate from the Brazilian Amazon region, which contains only 14% (n=775) of the municipalities and 13% (24 million) of the country's population[10,11]. Environmental factors, such as warm temperatures, high rainfall, high humidity, low altitude and extensive surface-water collections promote high vector populations that are stable throughout the year without significant seasonal variation. Consequently, along with the introduction of the parasite, many types of human activities will result in significant transmission unless extreme control measures are implemented[11].

Several important human activities and behaviors favor man-vector contact, such as the settling of new forested areas, the type of land that is used for economic gain, precarious/temporary living conditions, and mobility and migration throughout the region. Man's development of the Amazon, which intensified in the 1960s, was a rapid and somewhat disorderly process that included inadequate infrastructure and services for numerous human settlements. Of all of the adverse effects resulting from the modern occupation of the Brazilian Amazon, perhaps the most notable was deforestation and its paradoxical effect on malaria transmission. Initially, deforestation was not only harmful to the ecosystem but also resulted in increases in vector-borne diseases; this detrimental effect was well documented by Achcar et al[12].According to these authors, deforestation was accompanied by a loss of biodiversity and alterations in the ecosystem, which, in the initial phase, led to vector proliferation and a rise in the diseases transmitted by those vectors, one being malaria[12]. Afterwards, the later effect of deforestation appeared. An increase in urbanization and ecological stabilization led to dramatic changes to the physical environment and the extinction of certain niches, which negatively impacted malaria vector populations. This notion of a late *protective effect* of deforestation in certain areas of the Amazon is supported by the epidemiologic data of the present study, which spans the past decade. For example, the number of municipalities reporting no malaria in its residents increased from 15.6% to 31.7% during the 7-year study period, and this may be associated with the late process of Amazon urbanization.

However, other factors may have contributed to these results. Malaria in the Brazilian Amazon is historically known to be associated with manual gold mining, where independent operators extract gold from small surface plots. Duarte and Fontes showed the association between malaria transmission and this type of gold extraction in this region (State of Mato Grosso) between the years of 1985 and 1996, including a decrease of malaria incidences when this practice diminished[13]. Like gold mining, timber extraction and aquaculture are strongly associated with malaria in this region, with malaria rising and falling in this region as these activities fluctuate over the long term. For example, in the case of timber, stricter regulations are now in place that governs the exploration and extraction of this non-renewable resource, which may discourage this activity. Aquaculture activities fluctuate with commercial demands and influence the population at risk for malaria over time. Another factor to consider is the expansion of mono-crop agriculture in certain regions, which results in both a reduction of vector habitats as well as the excessive use of insecticides[14, 15].

In general, the areas with malaria are reducing in size; however, this study showed that clusters (across municipal/state borders) of high, and even rising, transmission still occurred during the study period. In these specific areas, future research should assess environmental and socio-economic risk factors, such as non-urban areas with poor access to malaria diagnoses and treatments as well as areas where standard vector control efforts continue to have little impact, to explain these results. It is noteworthy that Brazil's border areas with other countries show a variety of malaria transmission levels, i.e., they are not all hyper-transmission areas, as is commonly reported for borders with other endemic countries. Additionally, it is important to clarify the role of the human asymptomatic malaria infections as a reservoir capable for maintaining the disease at low transmission rates or promoting the recurrence of malaria transmission or malaria epidemics in the Brazilian Amazon region. A recent study showed that 41.9% (338/807) of the municipalities in the Amazon region underwent a malaria epidemic in 2010[14]. Moreover, another study suggested the existence of a high prevalence of asymptomatic malaria infections in two localities in Rondônia (a Brazilian state)[16]. Furthermore, Alves et al[17] described that individuals with asymptomatic malaria (with parasitemia below the threshold of microscopic detection) infected mosquitoes at a low infection rate (an infection rate of 1.2% and an average of one oocyst per infected mosquito)[17]. These authors discussed the consequences of these findings and considered that most malaria control measures focus on symptomatic patient treatment. Further studies will be necessary to justify active surveillance and treatment for asymptomatic malaria.

As expected, in this study, when the number of malaria cases decreased, the transmission of malaria became more concentrated over time due to both an increased number of municipalities that become malaria-free and the, albeit decreasing, number of municipalities that still continued to have high or even rising rates. Malaria case concentration is not a recent phenomenon, as observed by the distortion of the Lorenz curve (from the hypothetical diagonal line of a homogenous distribution) at the beginning of the period as well as at the end of the study period. Although several environmental factors may also be related to this phenomenon, health services have an important role in providing care to respond to this situation. It is understandable that providing uniform health care and outcomes (including malaria prevention, treatments and diagnoses) across the Brazilian Amazon regions is a difficult task. Therefore, less access to quality health care may occur in the poorer populations that are most susceptible to malaria. The universal application of malaria control interventions in the Brazilian Amazon region might not explicitly address areas with the greatest malaria problems, leading to disparities in malaria control outcomes. This would be especially true if the high-risk groups that are living in isolated communities cannot access the control measures. The present study may help to identify target areas of interest where site visits could identify more specific factors associated with these trends.

It should be reinforced that overall malaria lethality (case fatality rate) is generally very low in Brazil, but still, each malaria death is potentially preventable. Relatively few malaria-related deaths occurred in areas of high transmission, and many of these occurred outside of the Amazon region or in very low transmission areas within the region. Future studies should aim to better understand if there is a delay in the diagnosis and treatment of malaria and, if so, identify the reason(s) for these delays. Lack of disease awareness on the part of either the patient or receiving medical staff in areas of no/decreasing transmission may be important factors that should be addressed.

This study has some limitations that need to be discussed. The indicator of malaria incidence was positive malaria examinations (smears). However, positive smears might not always reflect the true incidence of malaria because an individual might have repeated smears performed for a single malaria episode. Most likely, this *error* in incidence tally would have occurred during both study intervals and would not have significantly affected the trend in malaria indicators over the study period. This study used a secondary data census. In Brazil, malaria is a compulsory, notifiable disease, which means that every malaria case must be reported to a malaria information system called SIVEP-Malaria, which is an information system with adequate accuracy that is based on reports from 3,400 malaria labs (in 2008)[9,10]. The biennium data were used to reduce year-to-year variations because the transmission rates at the municipality level were low. The years 2003/2004 happened to be the first biennium in which the data were felt to be sufficiently reliable for our study purposes. The second biennium (2008/9) provided the most recent data at the time of the study's conception and resulted in a seven-year span for the study period.

In conclusion, malaria transmission is decreasing, and lethality is low in the Brazilian Amazon. As expected, in this epidemiologic context, an increased concentration of malaria cases was observed in the municipalities in the study region, which is useful information to stress the need for continued monitoring of this type of data. At the same time, the geographic clustering of municipalities that are problem areas might warrant site visits for more detailed assessments of the risk factors that favor transmission and might result in better intervention methods. Finally, the notion that a single strategy could bring about uniformly good outcomes is probably not true, and more attention needs to be paid to specific local conditions and foci of intense transmission.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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