# Patologia das Doenças 2

Yvanna Carla de Souza Salgado
(Organizadora)

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(Organizadora)

# Patologia das Doenças 2

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# APRESENTAÇÃO

As obras “Aspectos das Doenças Tropicais II e III” abordam uma série de livros de publicação da Atena Editora. Em seu volume II e III, apresentam em seus capítulos, aspectos gerais e epidemiológicos das doenças tropicais analisados em algumas regiões brasileiras.

As doenças tropicais são assim designadas por se tratarem de um conjunto de doenças infecciosas que ocorrem nas regiões tropicais e subtropicais. Em uma ação que objetiva a avaliação dos indicadores globais e o combate e controle dessas doenças, a Organização Mundial da Saúde lançou uma classificação de “doenças tropicais negligenciadas” para agrupar as doenças tropicais endêmicas, causadas por agentes infecciosos ou parasitas principalmente entre a população mais carente e, cuja prevenção e controle são dificultados pela escassez de investimentos.

Essas doenças afetam especialmente as populações pobres da África, Ásia e América Latina. Juntas, causando aproximadamente entre 500 mil a um milhão de óbitos anualmente, segundo dados da Organização Mundial da Saúde. Nos últimos anos ocorreu o ressurgimento da Dengue e a emergente ameaça da Chikungunya e Zika, doenças transmitidas por mosquitos vetores, em diferentes países da América. Inúmeros fatores estão associados ao ressurgimento dessas doenças como crescimento populacional urbano desordenado, mudanças climáticas, aspectos socioeconômicos, modificação dos ecossistemas pela ação antropológica, entre outros.

Neste volume II, dedicado às Doenças Tropicais, reunimos um compilado de artigos com estudos dirigidos sobre Dengue, Chikungunya, Zica e Malária em regiões brasileiras, com o intuito de ampliar o conhecimento dos dados epidemiológicos, contribuindo assim para a formulação de políticas públicas de apoio dirigidas às diferentes características regionais deste país continental.

A obra é fruto do esforço e dedicação das pesquisas dos autores e colaboradores de cada capítulo e da Atena Editora em elaborar este projeto de disseminação de conhecimento e da pesquisa brasileira. Espero que este livro possa permitir uma visão geral e regional das doenças tropicais e inspirar os leitores a contribuírem com pesquisas para a promoção de saúde e bem estar social.

Yvanna Carla de Souza Salgado

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## THE USE OF LLINS REDUCES MALARIA INCIDENCE IN THE AMAZON REGION

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**ABSTRACT:** Malaria remains as the parasitic disease with the greatest impact worldwide. In Brazil, in the last years, almost all cases of disease have been recorded in the Amazon region. The fight against the vectors through insecticide treated nets is the main combat strategy. This study aimed to determine the protective effect of these devices on the malaria incidence in one municipality of Amazon. Was conducted with information the Brazilian Ministry of Health and with the analysis of 10,050 slides of thick blood smears that were prepared and examined in loco. The Shapiro-Wilk test was used to determine the normality of the data and the Mann-Whitney test was used for all comparisons of the analyzed variables. The significance level was set at $p \leq 0.01$. The results revealed a significant reduction in malaria cases in all analyzed variables, including the species of the involved parasite, the level and type of infection, and the gender and age of the diagnosed individual ($p < 0.01$). These findings confirmed that these devices are an important tool for controlling the disease, as they represented a new variable inserted in the context of combating the disease in the studied population. Therefore, the use of insecticide-treated nets is recommended as a preventive measure to control malaria, and guidance to the population regarding the correct way to use this device is required to avoid problems such as the loss of naturally acquired immunity, reduction in the protective effect of the device and the development of resistance to the insecticide.

**KEYWORDS:** Malaria; Vector; Amazon; Nets; Insecticide

## INTRODUCTION

Malaria is the parasitic disease with the greatest *impact worldwide*. According to World Health Organization (WHO) estimates, approximately 198 million new cases were recorded in 2013, resulting in 584 thousand deaths (WHO, 2014).

The disease resulting from this infection has a classical *clinical* presentation consisting of episodes of chills followed by high fever, malaise, nausea, headache, and joint pain. Malaria is caused by several species of protozoa of the genus *Plasmodium*, with *P. falciparum* being the most prevalent species (NADJM & BEHRENS, 2012) which is usually transmitted *via the bite* of an infected female mosquito of the *genus Anopheles*.

Notably, at the end of the 1980s, access to malaria preventive and *control measures* was expanded with the installation of long-lasting insecticide-treated nets (LLINs) impregnated with insecticides such as deltamethrin, which belongs to the *pyrethroid group* of insecticides (SANTOS *et al*, 2007). The results were satisfactory (CARNEVALE *et al*, 1992) and the use of these nets was expanded by distribution in endemic areas around the world.

At the end of 2011, the Brazilian Ministry of Health provided financial *support* for the purchase and distribution of LLINs to certain municipalities located in the *Legal Amazon*, which is an area that records almost all of the total registered *malaria cases* in the country. Several municipalities adjacent to the *Trans-Amazonian highway* received this assistance, including the municipality of Pacajá in the state of Pará (PA), which received 16,850 LLINs.

Accordingly, following the WHO guidance, a distribution of mosquito nets impregnated with deltamethrin was initiated in January 2012 as a *preventive* measure for the disease. However, two years after the *installation* of these *mosquito nets*, neither scientific evidence nor an epidemiological analysis are available to determine the efficacy of this device for *preventing and controlling* malaria in the municipality of Pacajá-PA.

Considering the lack of evidence on the efficacy of this device in Pacajá-PA, this study aimed to determine the *protective effect of LLINs* with respect to the incidence of malaria in the municipality of Pacajá and the epidemiological profile of this infection before and after the *installation* of these nets.

## MATERIALS AND METHODS

This study was conducted in 2012 and 2013 in the municipality of Pacajá, which is located in the s*outhwestern* mesoregion of Pará State, Brazil, adjacent to the *Trans-Amazonian Highway* (BR 230). This municipality has a population of about 40.000 inhabitants.

The investigation was a descriptive cross-sectional study with the first phase consisting of an epidemiological survey using data obtained from the database of the *Epidemiological Surveillance* System *for Malaria* (*Sistema de Informação da Vigilância Epidemiológica - Malária* SIVEP-MALARIA) of the Brazilian Ministry of Health between 2010 and 2011 (before the *installation* of LLINs). The second phase of the study was conducted between 2012 and 2013 (after the distribution and *installation* of LLINs) and consisted of 10,050 slides for malaria diagnosis and *Plasmodium* species identification, which were prepared and examined *in loco*, according to the method described by Walker (BRASIL, 2013). The mean malaria prevalence was calculated from the data obtained in these two phases, and epidemiological characteristics of the disease in the population studied were compared.

The thick smear technique was used to *diagnose malaria* and to identify the *Plasmodium* species. For preparing the thick smears, drops of peripheral blood were collected from the participants' fingertips, placed on glass slides, and smeared (square-shaped, two smears per slide). After drying, the slides were immersed in methylene blue for two seconds for *dehemoglobinization* and then stained with *2% Giemsa/phosphate buffer solution* for 10 minutes. Subsequently, the slides were washed with phosphate buffer, dried, and viewed under an optical microscope with an immersion objective, according to the method described by Walker.

This study was submitted to and approved by the *Human Research Ethics Committee* of the Institute of Health Sciences, Federal University of Pará (Universidade Federal do Pará), under number 351.836, and it is in agreement with the guidelines and standards recommended by Resolution Nº. 466 (from December 12, 2012) of the *National Health Council*.

The BioEstat 5 software was used for the statistical analysis. The Shapiro-Wilk test was used to determine the normality of the data. The Mann-Whitney test was used for independent samples in all comparisons of the variables analyzed between 2010-2011 and 2012-1013 because the data were not normally distributed. Thus, the data are expressed as medians and interquartile ranges. The percent difference was calculated using the following equation: $\Delta\% = \{Group\ 1 - Group\ 2\}$. Statistical *significance* was set at $p \leq 0.01$ with an error ($\alpha$) of 1%.

## RESULTS

### Reduction in the Incidence of Malaria

In total, 16,500 LLINs were installed in the studied population between January and March 2012, and the incidence of malaria cases significantly decreased ($p < 0.0001$) two years after their installation compared with two years before their installation (Table 1), even considering the reduced number of tests performed over the study period ($p < 0.01$).

| Variables | Examined Slides | Positive slides | <1/2 | 1/2+ | + | ++ | +++ | ++++ |
|---|---|---|---|---|---|---|---|---|
| **Period** | **Md (IR)** | **Md (IR)** | **Md (IR)** | **Md (IR)** | **Md (IR)** | **Md (IR)** | **Md (IR)** | **Md (IR)** |
| **2010-2011** | 1.010 (325.5) | 275.5 (101.7) | 63 (38) | 21 (15.5) | 25 (15.5) | 158.5 (68.7) | 15 (8.5) | 7 (0.1) |
| **2012-2013** | 457 (222) | 60 (48) | 13 (8.7) | 4 (2) | 7 (4.5) | 31 (26) | 2 (1.2) | 0 (0) |
| **p-*value*** | **< 0.0001** | **< 0.0001** | **< 0.0001** | **< 0.0001** | **< 0.0001** | **< 0.0001** | **< 0.0001** | **0.01** |
| **Md= Median; IR= Interquartile Range.** | | | | | | | | |

Table 1. Comparison of the mean number of malaria cases diagnosed between 2010 and 2011 (before the implementation of malaria prevention measures using LLINs) with cases diagnosed between 2012 and 2013 (immediately after the use of these nets), using plus signs to classify the level of parasitemia.

Source: **Period:** 01/2010 to 12/2011- SIVEP/Malaria/Brazilian Ministry of Health; **Period:** 04/2012 to 12/2013 Slides examined after an active search. Blood slide examination: **< 1/2** (less than 40 parasites counted in 100 examined microscopic fields); **1/2+** (40 to 60 parasites counted in 100 examined microscopic fields); **+** (1 parasite counted in 1 examined microscopic field); **++** (2 to 20 parasites counted in 1 examined microscopic field); **+++** (21 to 200 parasites counted in 1 examined microscopic field); **++++** (more than 200 parasites counted in 1 examined microscopic field).

Table 1 also shows that the reduced incidence of malaria infections was significant at all levels of parasitemia (p < 0.01). The reduction in positive slides was Δ% = -215.5%. The reductions for the cases < ½ and < ½ + were Δ% = - 50% and Δ% = - 17%, respectively. In addition, as presented in Table 1, the cases (+; Δ% = - 18%); (++; Δ% = - 127.5%); (+++; Δ%= - 13%); and (++++; Δ%= - 7%) were also statistically reduced (p < 0.01) between the studied periods.

There were no cases of disease with a parasitemia level of four crosses (++++) recorded after the use of LLINs. Notably, this is the higher and more dangerous level of parasitemia, especially in the disease type known as malignant tertian, which is caused by *P. falciparum*.

Figure 1 shows the results of *positive malaria cases* by gender. The analysis also revealed a significant reduction of cases in the period between 2012 and 2013 for both males (Δ% = -147.5%; p < 0.0001) and females (Δ% = -70.5%; p < 0.0001), compared with the period between 2010 and 2011.

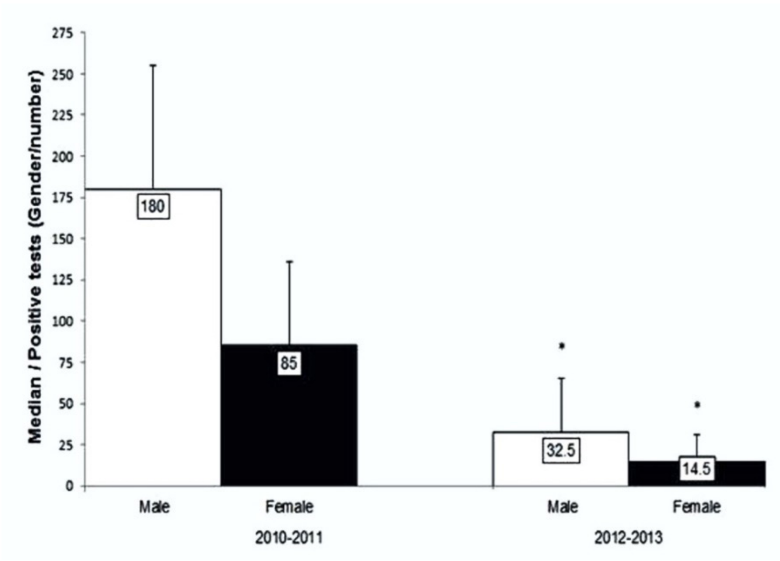


Figure 1. Results of *positive malaria cases* by gender. The analysis also revealed a significant reduction of cases in the period between 2012 and 2013 for both males (Δ% = -147.5%; $p < 0.0001$) and females (Δ% = -70.5%; $p < 0.0001$), compared with the period between 2010 and 2011. The symbol (*) indicates $p < 0.01$.

As shown in Table 2, the distribution of malaria per *Plasmodium* species responsible for infection and diagnosed in the studied periods also exhibited a significant reduction ($p < 0.0001$).

| **Variables** | **F** | **V** | **F+V** | **M** | **O** |
|---|---|---|---|---|---|
| **Period** | Md (IR) | Md (IR) | Md (IR) | Md (IR) | Md (IR) |
| **2010-2011** | 33.5 (16.5) | 244 (102.7) | 2 (1.5) | 0 | 0 |
| **2012-2013** | 6 (3.1) | 47 (37) | 0 (0.1) | 0 | 0 |
| **p-*value*** | **< 0.0001** | **< 0.0001** | **0.002** | - | - |
| **Md = Median; IR = Interquartile Range.** | | | | | |

Table 2. Distribution of malaria cases before and after the implementation of malaria prevention measures using LLINs, according to the *Plasmodium* species

Source: **Period:** 01/2010 to 12/2011- SIVEP/Malaria/Brazilian Ministry of Health; **Period:** 04/2012 to 12/2013; The slides were examined after an active search.

F (*Plasmodium falciparum*); V (*Plasmodium vivax*); F+V (mixed *P. falciparum* and *P. vivax* infection); M (*Plasmodium malariae*) and O (*Plasmodium ovale*)

## Reduction of *P. falciparum* Malaria in All Age Groups

There was also a significant reduction ($p < 0.0001$) in infections caused by *P. falciparum* (Table 3) in all age groups.

| Age Group | Child | Adult | Elderly | Total |
|---|---|---|---|---|
| **Period** | Md (IR) | Md (IR) | Md (IR) | Md (IR) |
| **2010-2011** | 76.8 (27.8) | 127.5 (70.3) | 20.5 (12.4) | 224.8 (90.3) |
| **2012-2013** | 15 (10.5) | 36 (15) | 5 (3.2) | 56 (22.1) |
| **p-*value*** | **< 0.0001** | **< 0.0001** | **< 0.0001** | **< 0.0001** |

Table 3. Cases of ***Plasmodium falciparum*** malaria before and after the implementation of malaria prevention measures using LLINs, according to the patients' age groups.

Md = Median; IR = Interquartile Range.

Source: **Period:** 01/2010 to 12/2011- SIVEP/Malaria/Brazilian Ministry of Health; **Period:** 04/2012 to 12/2013; The slides were examined after an active search.

CHILD (aged 6 months to 14 years); ADULT (aged 15 to 49 years); ELDERLY (50 years and older).

## DISCUSSION

Malaria has been shown to be the main health problem in several populations worldwide. In Brazil, almost all cases of the disease (99.7%) have been recorded in the Amazon region (BRASIL, 2013) .Several measures following the WHO's recommendations have been developed over time to control the *chain* of malaria transmission, including indoor residual spraying, treatment with combinations of drugs, larval control (CARNEVALE *et al*, 1992; URSING *et al*, 2014; WHO, 2014) and (currently) the use of LLINs, with the latter yielding excellent results in several countries (JOSHI *et al*, 2003; KARCH *et al*, 1993; URSING *et al*, 2014; ZHANG & YANG, 1996). According to the report from the United Nations Children's Fund (UNICEF), the use of LLINs saved the lives of 125 thousand people in ten African countries between 2001 and 2007 (UNICEF, 2103).

LLINs impregnated with *deltamethrin* have been used in the Amazon, where malaria is endemic, but the results have been contradictory. Some studies indicate a low protective effect of LLINs (SANTOS *et al*, 1998), while others show a high protective effect of these devices (XAVIER & LIMA, 1986).

In the present study, the median values of malaria infections were compared before and after the *installation* of LLINs for malaria *prevention* in the municipality of Pacajá-PA, Brazilian Amazon region. The results showed a significant decrease in all levels of parasitemia in the disease ($p < 0.01$), including malaria with two crosses (++), which, according to the classification of the Brazilian Ministry of Health, is the most common level of parasitemia of malaria infections observed in Amazonian cities (BRASIL, 2013). The parasitemia level with four crosses (++++), which is particularly severe for the infection caused by *P. falciparum (*NORONHA *et al*, 2000) was already low before the *installation* of LLINs and was no longer observed after their use.

Malaria is a disease with a wide spectrum, ranging from subclinical or asymptomatic cases to toxemic cases, which can progress to a severe condition and even to death if not specifically and *properly treated* in a *timely* manner—also depending on the level of parasitemia and the *Plasmodium* species.

Due to its shorter life-*cycle* in different tissues, the elevated production of merozoites during both tissue and erythrocytic schizogony, and its ability to infect red blood cells of any age, *P. falciparum* can promote *hyperparasitemia,* which is closely related to the severity of infection. Moreover, *P. falciparum* is the only species that clearly alters the microcirculation, contributing to *worsening* the disease. Therefore, the majority of the cases of severe malaria and deaths in several places worldwide are caused by *P. falciparum*, although there are several reports of severe infections caused by *P. vivax (*GOMES, 2009). Therefore, these severe forms of the disease require rapid and appropriate actions for patient care.

The reduction in the number of cases of *malaria infection* with high levels of parasitemia and the absence of records of these high levels in cases of *P. falciparum* malaria after the use of LLINs in all age groups ($p < 0.0001$) may indicate a protective effect of this device against the species that cause the vast majority of *severe malaria* cases and deaths worldwide. It is also noteworthy that *preventing malaria deaths* is the main goal of the Brazilian *National Malaria Control Program (Plano Nacional de Controle da Malária, PNCM) (*OLIVEIRA-FERREIRA *et al*, 2010).

The present study also revealed a significant decrease in the incidence of infections caused by *P. vivax* and in co-infections (mixed *malaria* infections) by *P. vivax* and *P. falciparum* ($p < 0.0001$). Infections caused by *P. vivax* represent approximately 90% of all malaria cases reported in Brazil (BRASIL, 2013), demonstrating that this species greatly contributes to maintaining the malaria epidemic levels in this region.

The reduced incidence of malaria infections observed in this study is due to several factors, which include the following: *malaria vector control* by insecticide *spraying*, active searches for *Plasmodium*, diagnosis and treatment *in loco*, the population's *awareness* of the mode of transmission and of the *clinical characteristics* of the disease, and especially the use of LLINs because the majority of the bites (and malaria infections) occur indoors and by *endophagic* mosquitoes, such as *Anopheles darlingi*, which is the main vector of malaria in Brazil and exhibits an anthropophilic and *endophagic* behavior (DEANE & DEANE, 1986). The LLINs, which have a useful life of approximately 2 to 3 years (WILLIAMS & PINTO, 2012), protects individuals specifically at this point because some of these bites occur while they are sleeping.

The m*alaria control programs usually aim to reach at least* 80% of *people at risk* of malaria in a given area, with the use of *LLINs (*MALARIA CONSORTIUM, 2009). In the current study, even with only 42% of the surveyed population using *LLINs,* the results obtained were satisfactory. These data indicate that increasing the use of this device may lead to the effective control of the disease in the municipality, which would be positive not only for health but also for the municipality's economy because the high rate of malaria is a potential obstacle against economic development in the area of occurrence (WILLIAMS & PINTO, 2012).

Other studies (GUPTA *et al*, 1999; LANGHORNE-NDUNGU *et al*, 2008) indicate that the naturally acquired immunity to malaria, the development of which usually requires *repeated infections,* is important for preventing further *worsening* of the disease, especially in endemic regions. Therefore, a *full coverage of* LLINs for *all age* groups would have a long-term *negative impact* on the development of natural immunity, especially in children (DOOLAN et al, 2009; SNOW & MARSH, 2002). One must consider, however, that the losses resulting from the development of naturally acquired immunity in children are lower than the losses resulting from the effects of the disease in *malaria-endemic areas* where LLINs are not used.

This study demonstrated a decrease in malaria cases in both genders ($p < 0.0001$), with a predominance in males ($p < 0.0001$). This finding was demonstrated previously by other studies (KATSURAGAWA *et al*, 2009; VAZ & GONÇALVES, 2009) and can be explained by the fact that *males* are more *susceptible to malaria infection* because of greater contact with the mosquito vector due to their economic activities. This hypothesis is reinforced by the fact that the adult age group was more affected by the infection.

## CONCLUSION

This study demonstrated that malaria remains an endemic disease in the municipality of Pacajá-PA. However, the use of LLINs proved to be an effective preventive measure, with a high level of protection against this infection. There was a significant reduction in the incidence of malaria cases when the parameters level of parasitemia, parasite species, gender and age of the vertebrate host, or simply the total number of infections diagnosed were taken into consideration. Although other factors might have influenced this reduced number of malaria infections, the LLIN can be considered a potential disease-control tool because it represents a new variable inserted in the context of combating the disease in the studied population. Regardless of the use of LLINs, adult men are still the most affected because they are *responsible* for their *families' livelihood, which* is still based on plant extraction, hunting, and fishing, and these activities increase the men's exposure to disease vector bites.

Based on the results presented in this study, the expansion of the distribution of LLINs is recommended so that this preventive measure reaches the coverage recommended by other m*alaria control programs* with greater experience in using these devices. In addition, guidance to the population regarding the correct way to use LLINs is required to avoid problems such as a reduced protective effect of the device and the development of resistance to deltamethrin.

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