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Full Length Research Paper

Analysis of malaria transmission intensity by using serological markers in an endemic setting Bouaké, Côte d'Ivoire

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Abstract

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To eradicate malaria, it is essential to understand its transmission dynamics and to evaluate control strategies. Serological markers are valuable tools for assessing transmission in low-endemicity areas, but there is no consensus on which are the most effective. This study examined IgG antibodies to *Plasmodium falciparum* antigens (Glurp, CSP, LSA1, LSA3, AMA1, SALSA, and total schizont extract) in Bouaké to assess the impact of interventions and identify high-risk areas. The surveys involved 634 participants aged between 2 and 79 years, divided between the dry season (310) and the rainy season (324). ELISA tests were used to measure IgG levels against these antigens. The results showed that antibody levels increased with age and were significantly higher during the rainy season. Seroprevalence was higher in areas south of Bouaké. Surprisingly, people using mosquito nets had high antibody levels, suggesting persistent exposure to the parasite. High antibodies to specific antigens were correlated with a higher risk of infection. These results underline the potential of serological markers for tracking malaria transmission, offering a precise and adaptive method for guiding interventions. By targeting high-risk areas, this approach could improve malaria control strategies and accelerate progress toward eradication, optimizing the impact of interventions in endemic regions.

Keywords: Antigen panel, Bouaké, *Plasmodium falciparum*, ELISA serology, Transmission dynamics.

INTRODUCTION

Malaria poses a significant health challenge, affecting approximately 40% of the world's population, primarily in disadvantaged countries. Worldwide, this scourge has caused more than 249 million infections, with more than 608 thousand deaths in 2022 (WHO, 2023). Africa is by far the region most affected by malaria globally, accounting for almost all malaria cases (94%) and deaths (95%) related to the condition (WHO, 2023). In Côte d'Ivoire, malaria remains endemic, with 81% of the population residing in areas with an incidence rate of 173.43 cases per 1,000 people, thus constituting a socio-economic burden (NMCP, 2023). This endemicity is particularly evident in Bouaké, Côte d'Ivoire's second-largest city, where environmental factors contribute to ongoing transmission (Kanga et al., 2019). These factors contribute to mosquito proliferation and ongoing malaria transmission in several areas of the

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city (Akono et al., 2015; Adou et al., 2019). This endemicity varies considerably and is characterized by a very high heterogeneity of transmission according to and within the neighborhoods (Bousema et al., 2010; Bejon et al., 2011), reflecting the concept of transmission "hot spots", areas with significantly higher transmission rates. Several strategies have been introduced to combat malaria, some of which have helped to reduce the scourge in several African countries (WHO, 2022). These include: the use of long-lasting insecticide-treated mosquito nets; indoor insecticide spraying; rapid diagnostic tests (RDTs) and Artemisinin-based dual therapy. However, areas of low transmission and areas where transmission has been significantly reduced pose considerable challenges for monitoring and evaluation.

Currently, the assessment of transmission is based on parasitological data and the entomological inoculation rate (Yadouleton et al., 2018; Traoré et al., 2019). However, these large-scale methods are difficult to maintain, as they are costly, time-consuming to implement, and lack accuracy due to local variations in transmission (Robert et al., 2006; Niass et al., 2017). They also require large amounts of human resources when transmission is low, such as during the dry season or after a vector control campaign (Lengeler, 2004; Traoré et al., 2019). According to the recommendations of the World Health Organization (WHO), many initiatives are currently underway. The challenges of parasitological and entomological methods (low sensitivity, high costs, limited timeframe) justify the integration of alternative indicators such as serological markers. By overcoming the limitations of traditional approaches, serological markers enable more sensitive and comprehensive surveillance tailored to the needs of specific contexts, thereby strengthening efforts to combat and eliminate malaria. These aim to develop new indicators and methods for assessing transmission, especially at the individual level. Antibody-antigen interactions have been proposed as alternative indicators of intensity and variations in malaria transmission patterns (Mbengue et al., 2010; Niass et al., 2017; Tayipto et al., 2022). Thus, different *Plasmodium* antigens are needed to characterize the infection in-depth and provide a better understanding of the immune profile of infected individuals, given that circulating parasites may be genetically distinct in different malaria-endemic areas and that host genetic factors may influence the immune response to vaccine antigens (John et al., 2005). In addition, this multi-antigenic approach aims to better characterize malaria infection, guide efforts in the fight against this scourge, and the detection of new tools for the rapid diagnosis and prevention of malaria. Immunoglobulin G (IgG) responses directed against several vaccine candidate antigens, including pre-erythrocyte antigens such as Circumsporozoite protein (CSP) (John et al., 2005), hepatic stage antigen 1 and 3 (LSA1, LSA3) (Lu et al., 2020), as well as blood stage antigens such as glutamate-rich protein (Glurp) (Baptista et al., 2022) and apical membrane antigen1 (AMA1). Indeed, these antibodies are associated with protection against infection (Perraut et al., 2005) and immunity that reduces disease transmission. This study aims to assess the potential of these peptide markers to enhance the understanding of malaria transmission dynamics, ultimately guiding more effective intervention strategies.

1. MATERIALS AND METHODS

1.1 Study site and population

This cross-sectional investigation was conducted in Bouaké, Côte d'Ivoire, which had a population of 832,371 in 2021 (INS, 2021). Bouaké features flat terrain covered by wooded savannah and is traversed by the Kan River, situated in a humid tropical climate with distinct dry (November to April) and rainy (June to October) seasons (Adou et al., 2019). Participants were included in the cohort after obtaining informed consent from themselves or their parents/legal guardians, provided they resided permanently in the city, regardless of age, sex, or parasitic status. Persons who refused informed consent or had serious acute or chronic illnesses were excluded from the study.

1.2 Data collection and samples

Data were collected during two cross-sectional surveys: one in the dry season (January and February 2023) and another in the rainy season (August and September 2023). Approximately two (2) ml of whole blood was collected from each participant, under sterile conditions, by venipuncture tubes containing or not an anticoagulant (EDTA). After centrifugation, sera were collected–and stored at –20°C for further immunological analysis.

1.3 Panel of Antigens used

A crude extract of schizonts and six asexual stage antigens of *Plasmodium falciparum,* provided by collaborators, were evaluated during the study. These are the following antigens: Glurp (Glutamate Rich Protein), Salsa (Liver stage Antigen), AMA1 (Apical Membrane Antigen 1), CSP (Circumsporozoite protein), $LSA1_{41}$ (Liver stage Antigen 1), LSA3(Liver stage Antigen 1). The description of these antigens was previously published (Koffi et al., 2017). Schizonts extract (SCHZ) from *Plasmodium falciparum* was obtained from a culture of strain 07/03 (Niass et al., 2017).

1.4 Parasitological Examination

Blood thick and thin smears were performed on all participants to determine parasite density and Plasmodium

species. Parasite density was determined by counting the number of parasites per 200 leukocytes and considering a count of 8000 leukocytes per 1µl of blood. The slide was declared negative after examination of 100 microscopic fields without any parasites detected.

1.5 Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assays were performed on sera to measure the level of immunoglobulin G against six recombinant antigens and a crude schizonts extract 07/03. The ELISA protocol used for the determination of IgG has been described previously (Perraut et al., 2005). Plate wells (Maxisorp, Nunc, Roskilde, Denmark) were sensitized by different antigens. Indeed, 100 µL dilute antigens were deposited in each well. The plates were then incubated at 4°C for a whole night. After four washes with a 1X PBS solution containing 0.1% Tween 20 detergent, a blockage was achieved using 150µL of saturation buffer (5% skimmed milk diluted in PBS+ Tween 20) for 2 hours at room temperature. One hundred microliters (100µL) of the sera tested and negative control sera from individuals in Bordeaux not exposed to *Plasmodium* (individuals who had never traveled to a malaria-endemic country and were considered to have encountered no malaria antigens) were diluted to a 1:50 scale. A serum pool (samples with high responses to all antigens included in the study were pooled) was used as a positive control. One hundred microliters of the conjugate (peroxidase-coupled IgG, SIGMA-ALDRICH) diluted to 1:5,000 in the dilution buffer (PBS-0.1%Tween20-0.5% Skim Milk) was added to the wells, followed by incubation for 1 h at room temperature and washed as previously described. Subsequently, the substrate dihydrochloride O-phenylenediamine (OPD, Sigma, United Kingdom) was diluted in citrate buffer and then added to H_2O_2 (Perhydrol), a quantity of 100 µL of the resulting solution was added to each well, and incubation was carried out for 15 minutes away from light. The reaction was then stopped by adding 100 µL of sulfuric acid (H2SO4), and the absorbance (optical density [OD]) was measured at 450 nm with the Micro Plate Read spectrometer. All samples were analyzed in duplicate, and the individual results were expressed as the ΔOD value: ΔOD = ODx - ODn, where ODx represents the average of the individual DO value in the two wells with the antigen and ODn the individual DO value in a white well containing no antigen. The IgG positivity threshold (PT) was calculated using the following formula: PT = mean (ΔODneg) + 3SD. Therefore, exposed individuals were then classified as responders to each antigen if the ΔOD was above the positivity threshold.

1.6 Data analysis

Due to the non-normal distribution of immunological data, non-parametric tests were employed for statistical analyses. The Wilcoxon signed-rank test was applied to compare antibody levels between two independent groups, while the Kruskal-Wallis test examined differences between more than two groups. The Chi-square test performed a comparison of means, and the Spearman correlation coefficient determined the association between two continuous variables. Differences were considered statistically significant when $p<0.05$. All analyses were conducted using R software (version 4.3.1).

1.7 Ethics statement

Ethical approval for this study was obtained from the ethical approval committee by the guidelines of the Ivorian National Reference Center for Malaria Chemoresistance created by interministerial decree n° 393/08/2006. Authorization to conduct the study was obtained from the general management of health centers. Similarly, authorization was obtained via a signed consent form for each participant before sample collection. Participation was voluntary, and there was no penalty for refusing to participate in the study. Participants were also allowed to ask questions before the study began.

2. RESULTS

2.2 Epidemiological characteristics of the study population

The demographic characteristics of the participants are summarized in Table I. The study recruited 310 participants during the dry season (January- February 2023) and 324 participants during the rainy season (August-September 2023) from the city of Bouaké. The sex distribution was similar, resulting in a male-to-female ratio of 0.87. Participants' ages ranged from 2 to 79 years, with a mean age of 31.87 years. Participants were divided into three age groups, with those over 15 years of age being the most represented at both time points in sample collection (**Table I**). Due to ongoing malaria control efforts, the possession and reported use of mosquito nets was lower at 48.11%, with no significant difference observed between the two seasons ($p=0.393$). However, the parasite prevalence by microscopy was 16.67% during the rainy season. No parasitized individuals were observed during the dry season in our study. The results show that the proportion of individuals who reported sleeping under a net was not significantly different between seasons ($p=0.393$).

2.3 Seroprevalence and response of IgG antibody level in the population

Figure 1 shows the seroprevalence of Plasmodium falciparum antigens in the various localities of Bouaké. In the overall cohort, seroprevalence rates for the antigens were as follows: Glurp (83.28%), Salsa (56.78%), CSP (56.47%), LSA1 (67.98%), LSA3 (24.13%), SCHZ (63.09%), and AMA1 (49.68%). No significant differences in seropositivity were observed between women and men

Table I: Demographic characteristics of study participants according to the seasons.

Variable	Dry season (%)	Rainy season (%)	Total (N=634)	p-value
Sex				
Men	144 (22,71%)	151 (23,82%)	295	0,435
Women	166 (26,18%)	173 (27,29%)	339	
Age range				
0-5	51 (08,04%)	71 (11,20%)	122	
5-15	97 (15,30%)	80 (12,62%)	177	0,083
≥15	162 (25,55%)	173 (27,29%)	335	
Use of mosquito nets (MILDA)				
Yes	155 (23,66%)	150 (23,66%)	305 (48,11)	0,393
Not	155 (23,66%)	174 (27,44%)	329 (51,89)	
Number of malaria episodes				
0	145 (22,87%)	94 (14,83%)	239	
≥1; 3<	151 (23,81%)	124 (19,56%)	275	
≥3	14 (02,21%)	106 (16,72%)	120	
Microscopic examination				
Positivity	--	54 (16,67)	54 (8,52)	
Parasite density	--	4873,49	2490,55	

for any of the antigens tested (p>0.1). Seropositivity was higher in the southern regions of Bouaké for all antigens tested, except for LSA3, which had lower seropositivity (15.38%) but was significantly higher in the northwest (30.43%) compared to the south and northeast (p<0.0006187) (Figure 1). Subsequently, we analyzed and compared the prevalence of antibodies according to age between the two seasons. Participants were classified into three age groups: 0-5 years, 5-15 years, and 15 years and over. Individuals aged 15 years and older exhibited significantly higher seroprevalence for Glurp, CSP, LSA1, and SCHZ antigens, regardless of the season. People living in endemic transmission zones are exposed to numerous bites from infected Anopheles mosquitoes as they age. This repeated exposure leads to prolonged and frequent stimulation of the immune system. However, the seroprevalence of the LSA3 antigen was higher in the 0-5 age group (*p=0.032*) during the rainy season and responses to Salsa and AMA1 antigens showed no difference between age groups. The data are summarised in Table II.

As shown in Figure 2, Antigen-specific antibody levels were significantly higher during the rainy season compared to the dry season for all antigens, except for the pre-erythrocytic Salsa antigen. During the rainy season, increased rainfall favours the formation of breeding sites for Anopheles mosquitoes, which amplifies their population and intensifies transmission (Figure 2).

Figure 3 shows the distribution of total IgG antibody responses by age group. To assess the impact of age on specific IgG acquisition, three age groups were defined: less than 5 years of age, between 5 and 15 years of age, and more than 15 years of age. Total IgG antibody responses directed against the different antigens Glurp, Salsa, CSP, LSA1, and SCHZ increased significantly with age except for AMA1 and LSA3 where no significant difference was observed (Figure 3). Adults and children aged 5 to 15 years had higher levels of specific IgG than children younger than 5 years of age.

2.4 Total IgG levels against antigens by malaria status

IgG levels were compared between uninfected and *Plasmodium falciparum-infected* participants. The IgG level was not significantly different between infected and uninfected individuals for all antigens during the rainy season. However, a significant difference was observed between uninfected individuals during the rainy and dry seasons for all antigens (*p<0.0001*) except for *Salsa* antigen where there was no difference (*p=0.57*) (Figure 4).

2.5 Association between immunoglobulin G responses and transmission intensity

To assess whether high antibody levels were related to the presence of the parasite, participants were classified

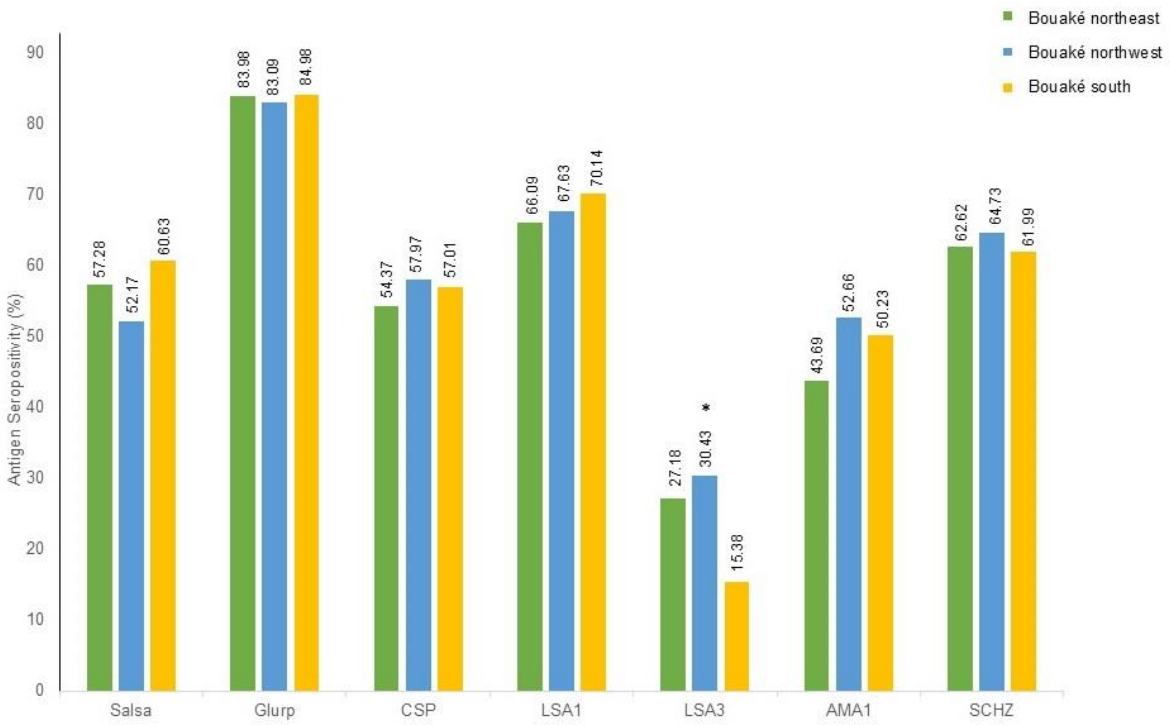

Figure 1: Seroprevalence of *P. falciparum antigens* according to three localities in Bouaké.

Table II: Age-related seroprevalence during the seasons.

Dry season							
Age	Glurp	Salsa	CSP	LSA1	LSA3	SCHZ	AMA1
0-5	52,83	54,71	7,55	24,53	1,88	11,32	39,62
5-15	76,84	58,95	28,42	56,84	5,26	27,37	45,26
≥15	91,35	58,64	51,23	69,75	6,79	43,21	53,7
p-value	**4.244E-09**	0.8622	**9.75E-09**	**4.986e-08**	0.3935	**3.916E-05**	0.148
Rainy season							
Age	Glurp	Salsa	CSP	LSA1	LSA3	SCHZ	AMA1
0-5	73,23	50,7	35,21	69,01	53,52	77,46	53,52
5-15	82,5	48,75	42,5	70	45	92,5	48,75
≥15	93,06	60,69	56,07	84,39	35,83	97,68	50,28
p-value	**0.0001434**	0.1335	**0.006314**	**0.006047**	**0.03236**	**8.596E-07**	0.8359

according to the presence or absence of parasites. Antibody levels were used as a predictor variable in a multivariate logistic regression analysis, adjusted for age, net use, and number of malaria episodes. Overall, higher levels of antibodies against CSP (Odds Ratio (OR)=1.659, 95% confidence interval (CI) =1.154 to 2.384), LSA1 (OR=2.042, CI=1.434 to 2.909), LSA3 (OR=2.627, CI=1.436 to 4.807), SCHZ (OR=2.042, CI=1.787 to 4.444) and AMA1 (OR=2.042, CI=1.250 to 3.947) were associated with an increased likelihood of carrying the *Plasmodium falciparum* parasite. However, there was no association observed for *Glurp* and *Salsa* (Table III).

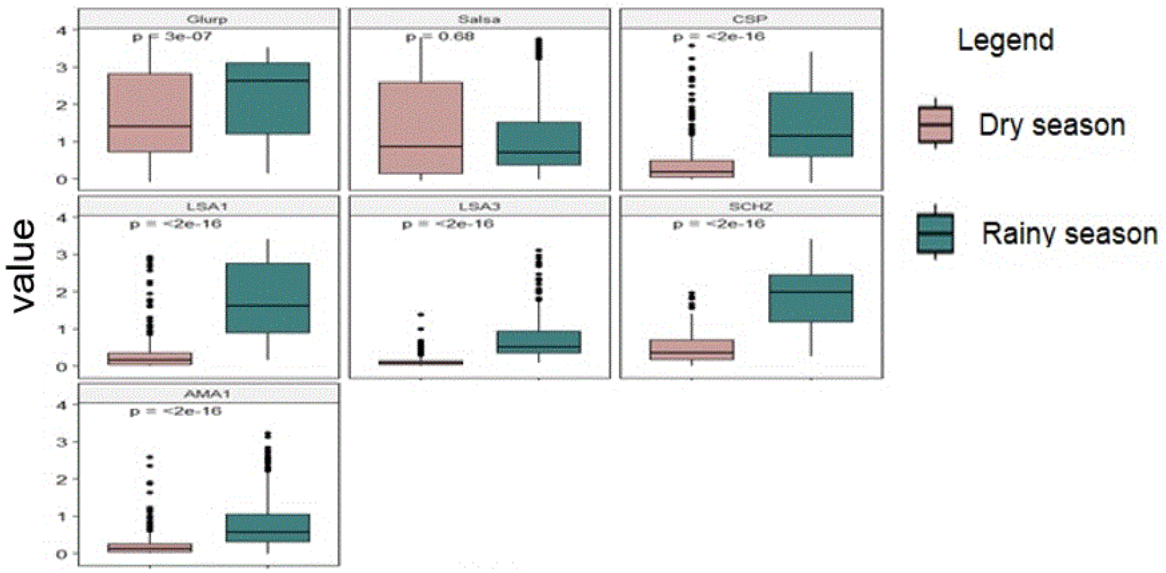

Figure 2: Level of immunoglobulin G (IgG) against the different parasite antigens according to the seasons.

2.6 Impact of net use and previous malaria episodes on IgG levels

Specific IgG levels against Glurp, Salsa, LSA1, AMA1, and SCHZ were significantly higher in mosquito net users compared to non-users. However, no differences were observed in the CSP and LSA3 antigens. Furthermore, Specific IgG levels against Glurp, Salsa, LSA1, and AMA1 exhibited a decreasing trend with an increasing number of previous malaria episodes, except for CSP and SCHZ, where the levels increase (Table IV).

3. DISCUSSION

Monitoring changes in transmission intensity and identifying persistent malaria areas using accurate tools are crucial in malaria control programs. This allows the effectiveness of the program to be measured and interventions to be adjusted accordingly. Serology targeted at the specific antigen of *Plasmodium* has been suggested as a potential approach to the challenges of surveillance of malaria transmission (Corran et al., 2007; kusi et al., 2014). This method could enhance the monitoring and assessment of malaria transmission dynamics alongside other epidemiological tools (Assefa et al., 2019). In this work, the IgG antibody profile directed against several *Plasmodium falciparum* was compared during two separate transmission seasons in the central region of Côte d'Ivoire.

The study of the interaction between the host's immune system and the parasites showed that in our study, 95.90% of participants responded to at least one of the seven antigens tested, and the antigens were positively correlated with each other, suggesting that these antigens at the asexual stage are well recognized by the immune system. Indeed, six antigens (Glurp, CSP, LSA1, LSA3, Total Schizonts Extract, and AMA1) exhibited greater responses during the rainy season compared to the dry season, with no significant variation observed across health districts. Seasonal variations in malaria transmission were observed, indicating differing transmission dynamics (Traoré et al., 2019). The observed variations in antibody levels against some of the antigens measured between the two seasons reflect differences in the mode of transmission of malaria. This highlights the use of serology as a tool for monitoring malaria transmission (corran et al., 2007; Mbengue et al., 2010; kusi et al., 2014). However, the specific IgG level for Salsa is higher in times of low transmission than in times of high transmission, suggesting that it may not be as appropriate for monitoring high transmission. Although we were unable to measure the entomological inoculation rate during sampling, which is a limitation, the level of antibodies observed suggests differences in disease transmission from one season to the next.

The overall parasite prevalence in our study was 8.52%, with a significant observed difference between the different residential areas (Bouaké South: 4.97%; Bouaké North-West: 13.59%; Bouaké North-East: 7.24% (p=0.011)). This difference between the different areas of Bouaké can be justified by local variations in the semi-urban environment (presence of lowlands in certain neighborhoods, agricultural practices, and the diversity of habitat types). In the present study, children under 15 years of age had a parasitic prevalence of 12.04%. This result is consistent with epidemiological data that show that children are often

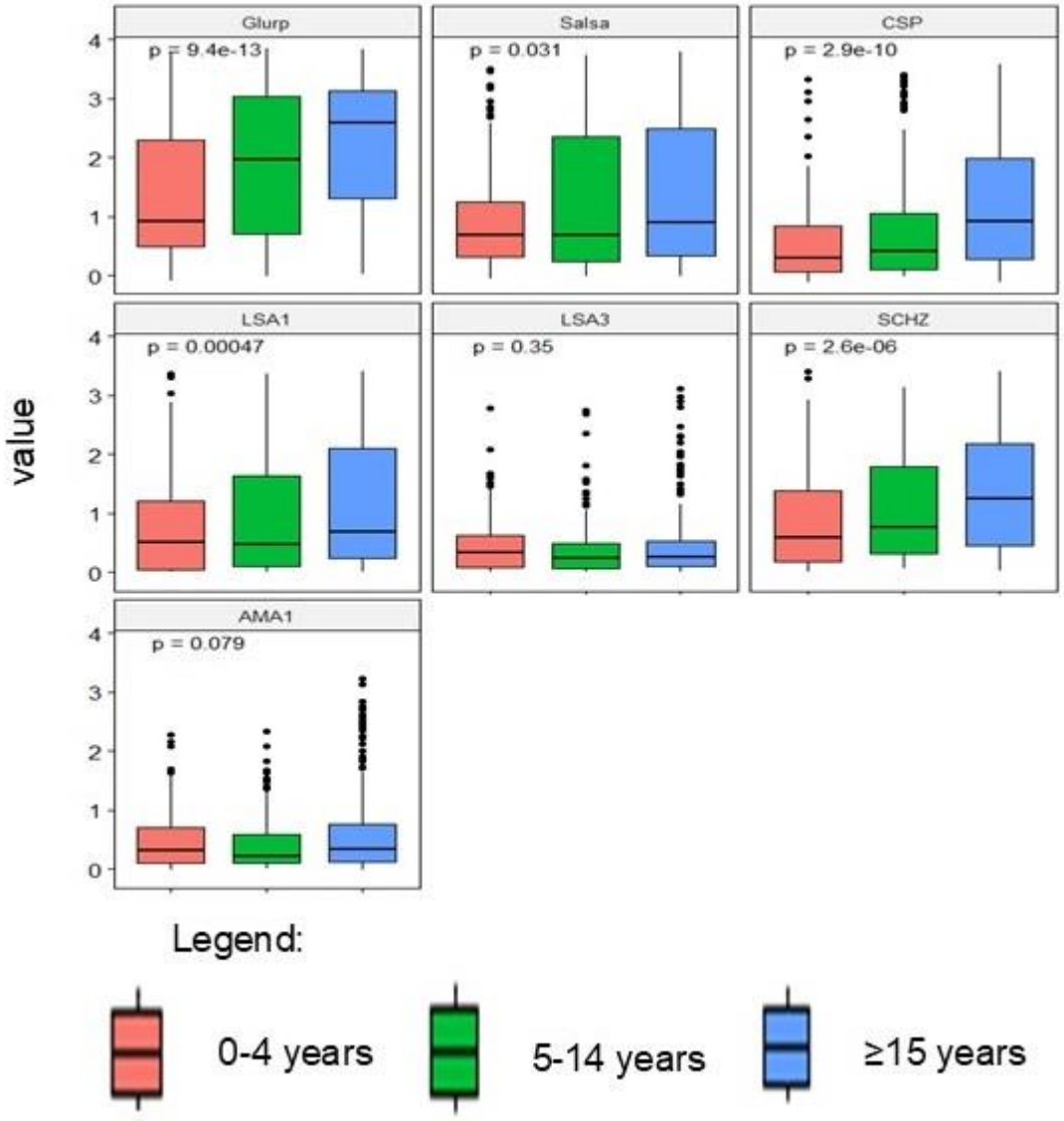

Figure 3: Distribution of total IgG antibody responses by age classification.

the most affected by malaria because of their still-developing immunity (Ranjha et al., 2023).

Total IgG antibody levels increased with age, indicating a gradual accumulation of IgG against a broader range of parasitic antigens. This accumulation of antiparasitic IgG thus widens the range of antibodies present in older people (Stanisic et al., 2015). These findings are consistent with other previous studies of antigens in people living in areas where malaria is prevalent (Niass et al., 2017; Omondi et al., 2021; Sourabié et al., 2022). In addition, infected individuals had higher antibody levels than the non-parasitized participants in the study population. Infection with Plasmodium typically enhances and sustains parasite-specific antibody responses, potentially increasing levels by approximately 20%. In addition, individuals not parasitized during the rainy season had higher IgG levels than in the dry season, suggesting the presence of persistent sub-microscopic parasites that trigger continuous antibody production. About 20 to 50% of human mosquito infections are due to the presence of sub-microscopic parasites (Okell et al., 2012). Comparable antibody levels between infected and uninfected individuals during the rainy season could be due to intense transmission, indicated by a high parasite load associated with a prevalence of sub-microscopic parasites and genetic diversity often seen in the form of multiple infections (Diouf et al., 2019; Sondo et al., 2020; Kyei-Baafour et al., 2021). This production of antibodies without

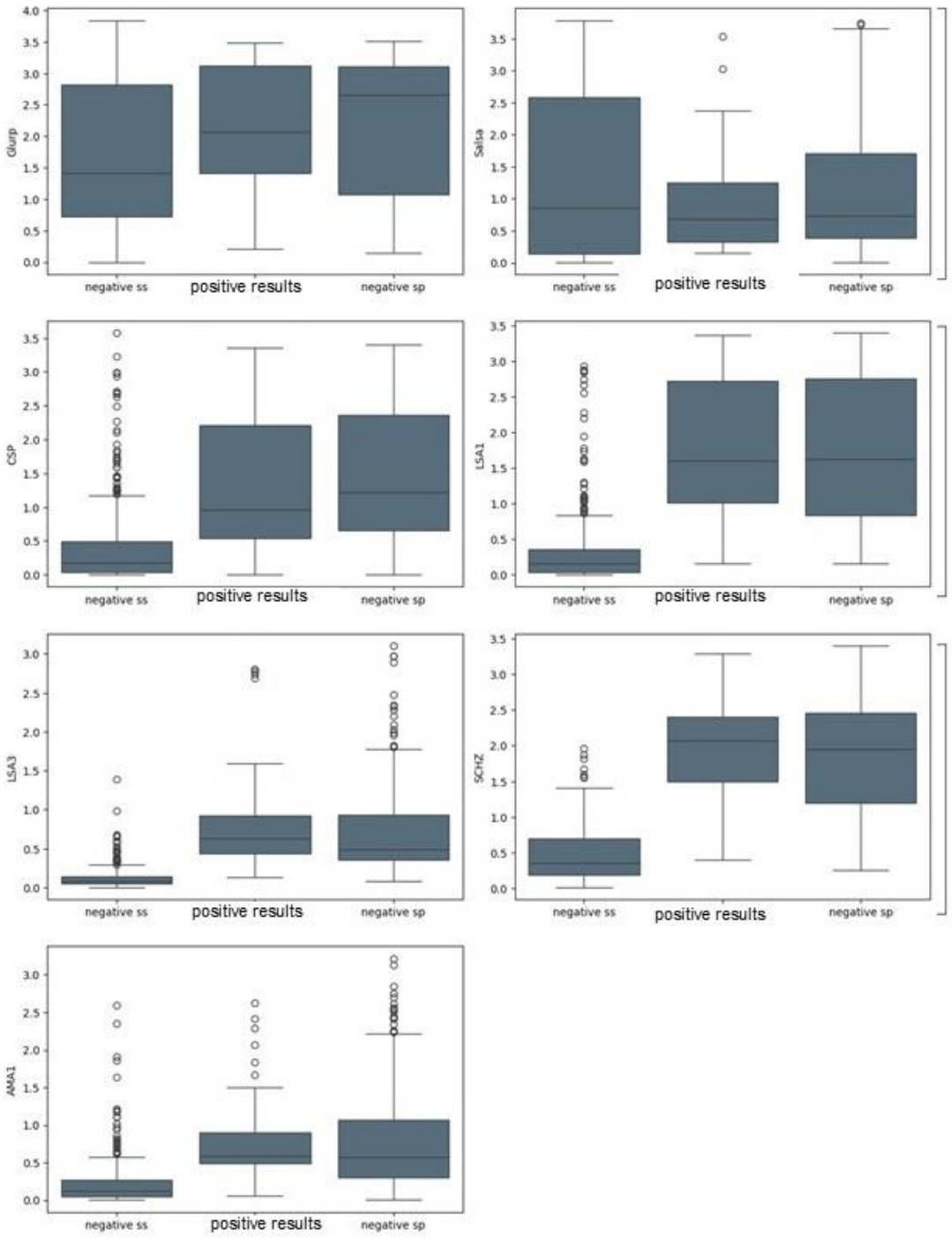

Figure 4: Level of total IgG antibody responses by malaria status.

prior protection makes it possible to assess the intensity of transmission in a given region. A high level of antibodies may indicate the presence of the parasite at the time of testing or recent contact of the individual with the parasite. Similar results were obtained by Kyei-Baafoour *et al.,* who, in 2021 in Ghana, found individuals carrying *Plasmodium* had a higher IgG level than uninfected individuals (Kyei-Baafour et al., 2021).

Insecticide-treated mosquito nets are one of the main prevention strategies against malaria, reducing direct exposure to Anopheles mosquito bites, the main vector for transmission of the parasite *Plasmodium* (Eisele et al.,

Table III: Immunoglobulin G (IgG) response related to the presence of the parasite

Antigens	AUC	Odds ratio (OR)	IC	p-value
Glurp	0,77	1.390	0.975 - 1.982	0.068
Salsa	0,77	0.913	0.620 - 1.341	0.642
CSP	0,80	1.659	1.154 - 2.384	0.0062**
LSA1	0,81	2.042	1.434 - 2.909	0.000076***
LSA3	0,84	2.627	1.436 - 4.807	0.0017**
SCHZ	0,85	2.818	1.787 - 4.444	0.000008***
AMA1	0,81	2.222	1.250 - 3.947	0.0065**

IC : Intervalle de Confiance (trust interval), *** : p< 0.001, ** : p < 0.01, * : p< 0.05

Table IV: average IgG according to the use of impregnated mosquito nets and the number of malaria episodes.

Antigens	MILDA IS			Malaria episodes			
	Yes	Not	p-value	0	1-2	≥3	p-value
Glurp	1.762	1.686	**0.019** *	1.826	1.642	1.552	**0.000****
Salsa	1.432	1.270	**0.001****	1.404	1.319	1.155	**0.000****
CSP	0.464	0.411	0.064	0.419	0.448	0.525	**0.019***
LSA1	0.404	0.269	**0.000****	0.354	0.324	0.296	**0.010****
LSA3	0.131	0.118	0.441	0.124	0.125	0.128	0.969
AMA1	0.281	0.179	**0.000****	0.218	0.244	0.184	**0.033***
SCHZ	0.548	0.460	**0.019***	0.506	0.497	0.562	**0.000****

The Wilcoxon test
*** : p< 0.001, ** : p-value < 0.01, * : p< 0.05

2010; WHO, 2023). Our results indicated that IgG levels were higher in users of impregnated nets compared to non-users. This could be attributed to inadequate use of nets by residents or the use of damaged nets. In addition, these differences could also be related to the fact that individuals go to bed late under the nets. Therefore, the protective effect is compromised if exposed to the pests (Traoré et al., 2019). High levels of IgG in net users highlight the persistent obstacles in the fight against malaria. They underline the need for an integrated and adaptive approach combining mosquito nets, vaccination, immunological surveillance, and interventions against resistant vectors. The fight against malaria must remain dynamic and adapt to local realities to maximize the effectiveness of strategies. However, the use of certain antimalarial antibody responses, such as the one directed against the CSP antigen, to monitor the intensity and pattern of transmission in the future, with the introduction of RTS, S/AS01, and R21/Matrix-M vaccines may complicate the use of certain antimalarial antibody responses, such as those directed against the CSP antigen, for monitoring transmission intensity and patterns. Indeed, these vaccines have the CSP antigen as their main component, and the induction of responses by vaccination could mask or attenuate the levels of naturally acquired reactions (Kyei-Baafour et al., 2021). The data collected highlights the value of specific IgG antibodies as markers of malaria transmission. More specifically, a strong correlation was observed between high levels of antibodies to the proteins CSP, LSA3, LSA1, AMA1, and total schizont extract, on the one hand, and the presence of the parasite, on the other, offering a valuable opportunity

to target interventions in high-risk areas. These results argue in favour of integrating seroprevalence into malaria control strategies.

CONCLUSION

The study highlights significant variations in malaria transmission depending on the localities targeted, observed through the levels of antibodies measured. The results indicate that antibodies to total schizont extracts, LSA1, LSA3, and CSP can be used as predictive tools to identify high-risk areas and monitor disease intensity. Integrating serological markers could make it possible to optimize the distribution of resources such as mosquito nets and vaccination campaigns. These markers provide a valuable basis for developing targeted intervention strategies. In addition, the evolution of antibodies could be analyzed after vaccination (RTS, S or R21) to better understand their interaction with natural immunity.

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