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# Seroprevalence of immunoglobulin G and E among out-patients with malaria in Ikorodu LGA, Lagos, Nigeria

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## Abstract

**Background**. Global response to malaria has stalled, despite increased malaria control efforts worldwide. Antibodies are among the immune factors that play a role in mediating protection in malaria, although the mechanism remain unclear. The study evaluated profile of total immunoglobulin G (IgG) and E (IgE) among malaria cases. **Methods**: A hospital based cross-sectional survey of individuals that presented with malaria symptoms and assessed diagnostic care at selected health facilities in Ikorodu Local Government Area (LGA) of Lagos State, Nigeria. Demographic information was recorded using structured questionnaire. Malaria diagnosis was done by microscopy, ELISA was used to evaluate plasma IgG and IgE profiles among malaria positive and control group. Data was analyzed using SPSS version 23. **Results**: LgE plasma level (34760.63±2954.5 pg/ml, p=0.005) was significantly higher in malaria positive cases compared with negative control group (19912.12± 6762.6pg/ml, p<0.01). In contrast, no significant difference between IgG levels in malaria positive (4936.53±211.4 pg/ml) and negative cases (4861.64 498.8pg/ml; p =0.297). Age and IgG profile correlated (r = 0.192; p = 0.010); and negative correlation between IgE profile and age although not significant (r= -0.008; p= 0.911). LgE correlated negatively with parasite density, although not significant (r = -0.019; p =0.833). IgG levels correlated with PCV (r =-0.27; p = 0.001), while IgE did not correlate. **Conclusion**: This study demonstrated increased IgE in uncomplicated malaria cases, and suggests that malaria could be a key differential diagnosis in acutely febrile patients with abnormally elevated IgE levels in malaria endemic area.

**Key word:** malaria, immunoglobulin G, immunoglobulin E, immune response.

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## Introduction

Malaria has continued to be a public health challenge in countries and territories in the tropics and subtropics, despite global efforts in stepping-up investment in research and innovation by the development of new disease-cutting tools, such as insecticide-treated nets, rapid diagnostic tests and more effective malaria medicines. In Nigeria, malaria transmission is stable and accounts for 27% of the global estimate of total malaria cases (highest in the world); and 23% of the global estimate of total malaria deaths (highest in the world) (1). Malaria varies widely in epidemiology and clinical manifestation. Factors such as pattern of exposure to malaria infection, changes in parasite virulence, therapeutic efficacy, local drug resistance patterns, host immune responses and diverse genetic polymorphisms could influence outcome of the disease (2, 3).

Naturally acquired immunity against malaria develops slowly and requires repeated parasite exposure to be maintained (4). It is specific to specie and stage of the infecting Plasmodium species, and wanes rapidly in the absence of an active infection (5,6).

Immunoglobulins, also known as antibodies, are glycoprotein molecules produced by the lymphocytes, in response to the presence of an antigen, they recognize and latch onto antigens in order to remove them from the body. Antibody-dependent mechanisms play important role in protection against malaria. In endemic areas, specific antibodies develop against the merozoites, sporozoites and circumsporozoite protein (CSP) (7). These antibodies are capable of blocking infection of the host cell by sporozoites (pre-erythrocytic) and merozoites (erythrocytic stages) in several ways; either by opsonizing the parasite for phagocytosis, or blocking invasion into host cell (8); by binding to antigens found on merozoite surface or organelles (rhoptries, micronemes and dense granules); by complement-

mediated damage to merozoites; by sterically interfering with the recognition of RBC ligands and other molecules involved in the invasion process; by intra-erythrocytic growth inhibition; by opsonization of infected erythrocytes (9,10,11,12).

Immunoglobulin G (IgG) antibodies have been shown to be a very important component of humoral immunity in the fight against Plasmodium infections as they have been associated with protections against infection (13) and is also a transmission-reducing immunoglobulin (14).

Elevated levels of IgE are found in allergic infections and atopic diseases (8) and, also, among people living in malaria-endemic regions (15). However, its role in host defense, parasitic infection and immune surveillance suggests many other potential functions (16). IgE has been shown to play a role in both pathogenesis and protection against malaria disease (17) by activation of nitric oxide (NO) and tumor necrosis factor (TNF) production in monocytes through cross linkage of the CD23 (the low affinity IgE receptors) on their surface leading to parasite death (18).

To explore the possibility of identifying markers of disease protective immunity, this study assessed the seroprevalence of immunoglobulins (IgG and IgE) levels among uncomplicated malaria cases living in endemic areas of Lagos, Nigeria and their association with different clinical indices e.g., parasite density, packed cell volume (PCV), etc. This study also provides data for trend profiling of total IgG and IgE from uncomplicated malaria cases from stored patients' plasma obtained between January 2013 and February 2014 from selected health facilities in Ikorodu LGA, Lagos State, South-West, Nigeria. Knowledge of dynamics underlying malaria immunity is vital in understanding host-parasite relationship and identifying the most effective infection monitoring strategies and parameters that might lead to advances in control / elimination tools.

## Materials and Methods

### Study area

The study was conducted in four (4) health facilities situated in Ikorodu LGA of Lagos State. Ikorodu is one of the twenty LGAs found in Lagos state, south-west political zone of Nigeria. It is the largest LGA in Lagos State with a total area of 345 square kilometers, located to the north-east of Lagos city, within longitudes 6°31'*N* and 6°41'*N* and latitude 3°26'*E* and 3°42'*E*. Ikorodu is bounded to the south by the Lagos Lagoon, to the north by Ogun State, and to the east by Agbowa-Ikosi, a town in Epe LGA of Lagos State. Ikorodu LGA hosts five Local Council Development Areas (LCDA). They are Imota, Igbogbo/Bayeku, Ikorodu west, Ijede, and Ikorodu North LCDAs. The estimated population of Ikorodu LGA is put at 689,045 based on 2006 census with the area hosting members of diverse ethnic affiliations. The area witnesses two distinct seasons; dry and rainy seasons with average humidity level and temperature of 72 percent and 26°C respectively. The study health facilities were: Ijede General Hospital (longitude E3°35'48.5772": latitude N6°33'51.7068"), Imota Primary Health Centre (longitude E3°40'23.6244": latitude N6°39'39.6288"), Bayioku Primary Health Centre (longitude E3°32'34.6884": latitude N6°32'47.9004") and Agura Primary Health Centre (longitude E3°37'38.3916": latitude N6°34'47.2872").

**Study design and population**: A comparative cross-sectional case management study on self-presenting individuals with history of fever (axillary temperature 37.5°C) within 7 days prior to assessment of malaria at the study sites between January 2013 to February 2014.

The inclusion criteria were out-patients that gave written consent at the participating clinic, queried for malaria infection with the presentation of at least one of the following: an axillary temperature ≥ 37.5°C, headache, or a history of fever within the past 7 days, and have not commenced any treatments for malaria. Exclusion criteria were patients with pathological conditions outside malaria such as protozoan or helminthes infection, typhoid fever and HIV/AIDS, congenital manifestations such as sickle cell disease, physiological manifestations such as pregnancy and history of allergy.

Control participants were apparently healthy male and female individuals that were negative for malaria by microscopy and have not had recent malaria episode/ treatment or evidence of congenital or any recent pathological or physiological manifestations.

A minimum sample size of 174 was determined for the study using online sample size estimator: (http://osse.bii.a-star.edu.sg/calculation1.php) at 5% significance level, 14.7% malaria prevalence (19), and the ratio of control to cases was 1:5.

### Sample collection, preparation and storage

Venous blood samples (3 ml) were collected into EDTA vacutainer, mixed gently and labeled. This was used to prepare; thick / thin blood smears for malaria diagnosis, total white blood cell (WBC) count and PCV, and then spun at 1500 RPM for 5 minutes. The plasma was aliquoted into appropriately labeled cryo-vials, and then stored in the freezer at -20°C until required for the determination of immunoglobulin classes (IgG and IgE) using enzyme linked immunosorbent assay (ELISA). Pre-tested questionnaires were used to obtain demographic data, information on current symptoms and previous malaria episodes, as well as history of antimalarial medicines use.

### Malaria parasite detection (by Microscopy Method)

The thick and thin blood smears were prepared on the same slide, using 12 µl of blood and 2 µl of blood respectively, slides were stained with 3% Giemsa solution for about 45 minutes following the standard guideline (20).

The stained smears were examined under oil immersion (x100) objective by two microscopist using light microscope and parasite counts recorded per number of

WBCs observed using proper counting algorithms. In case of 20% variance in counts between primary and secondary microscopists, the counts closest to that of a third reader were retained. A slide was declared negative only after observing no parasite in 100 microscopic high-power fields, while parasite density was estimated by;

$$\frac{\text{Number of Malaria parasites} \times \text{Absolute WBC count of patient}}{\text{WBC count}} = \text{parasites}/\mu l$$

### Determination of Packed cell volume and Total White Blood Cell count

PCV estimation was performed using the micro method, and WBC counts were manually determined using the Neubauer Counting Chamber (Haemocytometer) (New Improved Neubauer)(20).

### Determination of immunoglobulin classes (IgG and IgE)

Preserved frozen plasma samples were thawed, IgE and IgG estimation was done using ELISA$^{PRO}$ Kits purchased from MABTECH AB Sweden for the quantification of human IgE and IgG in biological fluids.

The ELISA was performed on the principle; ELISA strip plates pre-coated with a capture monoclonal antibody (mAb), to which samples were added was used for IgE and IgG estimation, then captured IgE and IgG were detected by adding a biotinylated mAb followed by streptavidin-horseradish peroxidase (SA-HRP). Addition of enzyme substrate Tetramethylbenzidine (TMB) substrate will result in a colored product with intensity directly proportional to the concentration of IgE and IgG in the samples. The IgE and IgG concentration were determined by comparison to a serial dilution of standard analyzed in parallel. The procedural kit instructions as stipulated by the manufacturers were followed.

ELISA reader (Techan, China) was used to measure the absorbance of the analytes at 450 nm. The mean absorbance value of the blank was subtracted from the standard, the assay background control and the sample values prior to creating the standard curve and determining the IgG and IgE concentrations in the samples. ELISA software which utilizes a 4-parameter curve fitting program (Master Plex 2010 v. 2.0.0.77) was used for the data analysis. The IgG and IgE concentrations were then determined from the values of the standard curve.

### Ethical Consideration

The study protocol was approved by Research Grants and Experimentation Ethics Committee, College of Medicine, University of Lagos, Nigeria (CM/COM/08/VOL. XXIV).

The participants gave written consent to participate and for their blood samples to be used for further malaria testing, after a clear explanation of the study was given to them, with the proviso of willingness to participate or withdraw at any point of the study without affecting the standard care they should receive in the health facilities. All samples had only study identification numbers that could not be linked with personal details of the participants.

### Statistical Analysis

The data from the study were analyzed using SPSS version 23 statistical software. Test for associations and difference were carried out by chi-square analysis, student t-test and analysis of variance where appropriate. Test of statistical significance was set at P value less than 0.05 at 95% confidence interval.

## Results

### Demographic information of the participants at the health facilities

Thick and thin blood smears from a total of 1,675 individuals; 681 (40.7%) males and 994 (59.3%) females, age ranged from 2 years–80 years, the mean age was 19.5 years (SD± 16.1) (Table 1), that consented to the study wer screened

**Table 1**

*Demographic characteristics of participants that were screened for malaria at the health facilities in Ikorodu LGA, Lagos State, Nigeria*

| Description | Positive No (%) | Negative No (%) | $\chi^2$ | P-value |
|---|---|---|---|---|
| Sex of respondents | | | | |
| Male | 132 (45.5) | 549(39.6) | 3.434 | 0.064 |
| Female | 158(54.5) | 836(60.4) | | |
| Total | 290(100.0) | 1385(100.0) | | |
| Age of respondents | | | | |
| <=5 years | 61(21.0) | 337(24.3) | 51.09 | 0 |
| 6 – 10 years | 100(34.5) | 226(16.3) | | |
| >10 years | 129(44.5) | 822(59.4) | | |
| Total | 290(100.0) | 1385(100.0) | | |
| Fever | | | | |
| Yes | 282(97.2) | 1177(85.0) | 32.08 | 0 |
| No | 8(2.8) | 208(15.0) | | |
| Total | 290(100.0) | 1385(100.0) | | |
| Chill | | | | |
| Yes | 226(77.9) | 883(63.8) | 21.54 | 0 |
| No | 64(22.1) | 502(36.2) | | |
| Total | 290(100.0) | 1385(100.0) | | |
| Body Pains | | | | |
| Yes | 180(62.3) | 920(66.4) | 1.821 | 0.177 |
| No | 109(37.7) | 465(33.6) | | |
| Total | 289(100.0) | 1385(100.0) | | |
| Headache | | | | |
| Yes | 255(87.9) | 1066(77.0) | 17.29 | 0 |
| No | 35(12.1) | 319(23.0) | | |
| Total | 290(100.0) | 1385(100.0) | | |

**X2: Chi squared**. Significant at p<0.005

**Table 2**

*Demographic characteristics of participants used for the profile of IgG and IgE study (n=179)*

| Description | Malaria positive (Test) (n=125) | Healthy Control (HC) (n=29) | Febrile Control (FC) (n=25) | P-Value |
|---|---|---|---|---|
| | No (%) | No (%) | No (%) | |
| Sex | | | | |
| Male | 56 (44.8) | 14 (48.3) | 11 (44.0) | P = 0.936 |
| Female | 69 (55.2) | 15 (51.7) | 14 (56.0) | |
| Age (years) | | | | |
| Mean ±SD | 16.4±13.1 | 29.0±7.5 | 19.3±10.9 | P<0.001 |
| ≤ 5 | 17 (13.6) | 0 | 3 (12.0) | P<0.001 |
| 6 - 10 | 42 (33.6) | 0 | 1 (4.0) | |
| > 10 | 66 (52.8) | 29 (100) | 21 (84.0) | |
| Temperature (°C) | | | | |
| Mean ± SD | 37.2±1.4 | 36.3±0.6 | 37.0±1.3 | P = 0.001 |
| < 37.5 | 74 (59.2) | 29 (100) | 20(80.0) | |
| ≥ 37.5 | 51 (40.8) | 0 | 5 (20.0) | P<0.001 |
| Packed Cell Volume | | | | |
| Mean ±SD | 34.5±4.6 | 37.1±4.6 | 34.8±7.1 | P = 0.042 |
| | | | | r= 0.911 |
| Malaria Geometric Mean Parasite Density (GMPD) (parasites/µL) | 11,183 | | | |
| Range | 63 – 202,010 | | | |
| Malaria Diagnosis | | | | |
| *P falciparum* | 282 (97%) | | | |
| *P malarie* | 3 (1.04%) | | | |
| *P ovalae* | 3 (1.04%) | | | |
| *P falciparum + P malariae* | 2 (0.7%) | | | |

*Significant at p<0.005*

for malaria infection to enable selection of participants for enrollment in the IgG and IgE profile study. The health facility-based prevalence of malaria at Ikorodu LGA was 20.9%. The *Plasmodium specie* found in the infected individuals were mostly single specie infection of *Plasmodium falciparum* alone 282 (97%), *Plasmodium malariae* 3 (1.04%) and *Plasmodium ovalae* 3 (1.04%), others are mixed infection of *P falciparum* and *P malariae* 2 (0.7%).

A subset of 125 smear positive plasma samples, 25 malaria negative febrile cases and 29 malaria negative healthy controls that met the inclusion criteria were assayed for IgE and IgG by ELISA. The age of the participants whose IgG and IgE profile were evaluated ranged from 2 years – 80 years, the mean age was 16.4 ±13.1 years (Table 2). The study participant's age distribution showed that malaria prevalence was highest among the age group 10 years and above and this was statistically significant (p<0.001) (Table 2). The sex distribution of 125 *P. falciparum* infected participants were; males 56 (44.8%) and females 69 (55.2%) and the clinical severity of malaria was uniformly spread over both sexes (Table 2).

Out of the 125 malaria positive patients with history of fever only 51 (40.8%) of them had a temperature of 37.5°C and above at presentation during the study. The mean PCV of the malaria cases in this study was 34.5 ±4.6%, this was lower in malaria positive cases than malaria negative cases and the difference was statistically significant (P = 0.042) (Table 2). The level of parasitaemia ranged from 63 – 202,010 parasites/µl and geometric mean parasite density of 11,183 parasites /µl. (Table 2).

The plasma level of IgE were significantly increased in uncomplicated malaria cases (p= 0.001), IgE profile correlated with parasite density (Table 3) while IgG plasma profile neither differed between the groups nor correlated with parasite density (p= 0.842) (Table 3).

Immunoglobulin levels of *P falciparum* malaria infected cases were compared in different sex, there were no significant variation in the mean immunoglobulin levels of the infected male and female participants (P>0.05) as shown in Table 4.

There was however a negative correlation between

age and IgG profile (r =-0.185; p=0.039); negative correlation between IgE profile and age although not significant (r =-0.008; p = 0.911), there was no correlation between age and IgE. There was correlation between IgG levels and PCV (r =-0.27; p = 0.001). IgE did not show any correlation with PCV.

**Table 3**
*Profile of immunoglobulin E (IgE) and IgG among malaria positive and negative individuals*

| Immunoglobin | Malaria Positive (n= 125) (pg/ml) | Malaria Negative (n= 54) (pg/ml) | P-value |
|---|---|---|---|
| IgG | | | |
| Mean ± SEM | 4936.5±211.4 | 4861.0±299.6 | 0.842 |
| IgE | | | |
| Mean ± SEM | 34760.6±2954.5 | 19912.1±3907.6 | 0.005 |

**Table 4**
*Immunoglobulin Levels in Malaria infected males and Females*

| Immunoglo bulin Levels | Malaria Positive Males participants (pg/ml) | Malaria Positive Females participants (pg/ml) | P- value |
|---|---|---|---|
| IgG | 4898.79±2226.16 | 4967.16± 2486.071 | 0.873 |
| IgE | 34086.59±33962.52 | 35307.68±32497.930 | 0.838 |

## Discussion

In this study, malaria prevalence was significantly higher among study participants aged 10 years and above, showing a shift in the usual trend of children aged less than five years being more predisposed to malaria, this is in agreement with other findings (21,22), intensified malaria control intervention focused on this group of children (less than 5 years) could attribute to the change in trajectory of the disease.

The malaria positive cases had history of fever, chills and headache, the relationship of which is significant, suggesting that parasitaemia is usually accompanied by fever, chills and headache. The study (23) had a similar report, although it has been shown that clinical presentations of malaria are highly variable and overlaps with that of a number of other common illnesses, including pneumonia, which are associated with significant morbidity and mortality (24, 25, 26). This re-emphasizes the policy on malaria diagnosis (testing) before treatment. The National malaria policy on prompt parasitological confirmation by microscopy or RDTs required in all patients suspected of malaria before treatment is still widely advocated in sub-Saharan Africa, especially in young children (27, 28, 29).

Individuals living in areas where the endemicity of malaria is high, have significantly elevated levels of both total IgE and specific antimalarial IgE antibodies in blood. Our study showed significantly elevated plasma IgE level among malaria positive cases and IgE level correlated with parasite density, similar observations were seen in reports from South-South zone of Nigeria (30), South Sudan (31) and Thailand (32), they reported higher IgE values in malaria patients which increased almost exponentially with severity of the disease, and indicates that IgE could play a role in the pathogenesis of malaria infection as the blood concentrations are significantly higher in patients with cerebral or other forms of severe disease than in those with uncomplicated malaria (15).

There was no significant variation in the mean plasma IgG level in participants with and without malaria infection, this agrees with studies; on outpatients aged 1- 60 years with malaria symptoms in South-South zone of Nigeria (30). Also, the study (33), showed that the mean IgG level in HIV malaria co-infected patients did not differ significantly when compared with that of HIV patients without malaria.

In contrast, it has been shown that total IgG in uncomplicated malaria cases increased significantly (by five-fold) in comparison with IgG of healthy Thai donors living, in Chantaburi, East Thailand (15). Report (34) on a cohort of children between 6 months and 17 years in Minna, Niger State, North-central zone of Nigeria showed higher IgG profile among positive cases compared to negative, and suggests a strong relationship between production of specific antibodies and P. falciparum transmission, rather than protective immunity, alluding that antibody could serve as a potential marker of both exposure to *P. falciparum* and protection against disease.

The negative correlation between IgG antibody level and parasitaemia observed in this study agrees with other findings (30,35). A study (15), also observed that the concentrations of the IgG antibodies during the early course of infection are higher in patients with uncomplicated malaria than in those with severe disease, and that antibodies are important for protection by reducing parasitaemia and alleviating clinical illness in *P. falciparum* malaria.

This study showed a negative significant correlation between age and IgG profile, which is in agreement with the findings of (36), that showed IgG negatively correlating with the ages of the malaria infected children. In contrast, (34), showed that IgG profile increased with age, but the difference was not statistically significant. There are different schools of thought as to whether the production of IgG as a result of *P. falciparum* infection increases or decreases with age, a statistical difference has been observed in the seropositivity between the youngest ( 12 years) and the other age categories; but did not differ significantly between the middle age (13–40 years) and the older (>40 years) categories (37). The study (38), showed that the seroprevalence of IgG increased with age, higher in older children and adults and that *P. falciparum* infection appears to be a factor of variation of the age-dependent development of anti-malarial IgG responses.

Antibody production, especially IgE induction reflects a switch from Th1 to Th2, due to repeated exposure of the immune system to the parasites and involves a shift from IgM/G- to IgE that increase with age till puberty (39). This

study observed a negative correlation between IgE profile and age although not significant, and is in contrast with some studies that showed increase in levels of IgE antibodies with age, and suggests that IgE may play a role in protection against malaria, as previously suggested (40, 41)

Mean IgG and IgE levels of malaria infected participants were compared in different sex, there were no significant variation in IgG and IgE values of the malaria positive male and female participants when compared with malaria negative of both genders, this agrees with report by (30).

PCV, a test used to screen for anaemia (42), mean PCV of malaria cases was significantly lower than negative control group, and a negative correlation between PCV and IgG level was seen, while IgE did not correlate PCV. The study (43), reported no correlation between severity of anaemia and IgG levels in patients with malaria, although immune haemolysis could occur in malaria patients with high IgG profile, other factors such as marrow suppression or ineffective erythropoiesis play important role in the pathogenesis of post-malaria anaemia. Furthermore, malaria - induced anaemia has been reported as being multifactorial, with haemolysis occurring more frequently in non-immune children, and suggested that IgE may have been indirectly implicated in these effects although their role in the development of anaemia is not well understood (44). The study (45), reported higher levels of IgE in severe malarial anaemia patients in comparison with uncomplicated, cerebral malaria and control groups.

## Conclusion

This study demonstrates considerable increase in the plasma total IgE profile among the individuals with malaria, and also showed no significant difference between IgG and IgE immune responses against malaria parasites among male and female malaria positive cases, but IgG varied with age. This study suggests that malaria may be a key differential diagnosis in acutely febrile patients with abnormally elevated IgE levels in malaria endemic area.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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None.

## Authors' contributions

All the authors have made substantial contributions to the conception of the article, contributed significantly to writing the manuscript, revised it critically for important intellectual content, approved its final version and agreed to its submission.

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