Assessing naturally acquired immune response and malaria treatment outcomes in Lagos, Nigeria [version 1; referees: awaiting peer review]

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Abstract

Background: There are emerging reports of poor efficacy of artemisinin-based combination treatment (ACT). However, mutations on the Kelch-13 gene marking delayed parasite clearance have no clinically defined relationship with ACT resistance across Africa. With increasing malaria control efforts, declining acquired immunity could be responsible for varying drug response profiles that may be dependent on levels of exposure to infections. To examine antibody responses against malaria and the influence on the efficacy of artemether-lumefantrine (AL), plasma samples were collected, prior to treatment, from individuals presenting with uncomplicated malaria.

Methods: Participants were stratified into two groups: early (within 24 hours, N = 20) and late (between 48 – 72 hours, N = 30) parasite clearance after treatment, as determined by var gene acidic terminal sequence (varATS) polymerase chain reaction. Magnetic bead-based luminex assay was used to profile antibody responses specific to a panel of 21 Plasmodium falciparum sporozoite, merozoite and An. gambiae salivary antigens.

Results: Median fluorescence intensity (MFI) of the antibodies was highest against glutamate-rich protein (GLURP-R0) and lowest against merozoite surface protein (MSP2) antigen. Analysis showed a positive correlation between expression of immunity and age of individuals (P = 0.023). However, there was no association between parasite density and antibody responses, except a significant positive relationship with reticulocyte binding protein-like homologue 5 (Rh5), P = 0.047; Plasmodium exported protein (Hyp2), P = 0.037 and merozoite surface protein 11 (H103), P = 0.038. Though higher levels of antibodies against erythrocyte binding antigens (EBA 140 and 175), MSP1.19, GLURP, circumsporozoite protein (CSP) and Rh4.2 were observed in individuals who recorded early parasite clearance, there was no significant difference in antibody responses in the early and late parasitological response groups.

Conclusions: Characterization of additional markers in larger populations is required to reveal potential immunological correlates of drug efficacy.
Keywords
Delayed parasite clearance, acquired immunity, antibody response, artemether-lumefantrine, varATS, luminex assay, P. falciparum antigens, immune markers

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Introduction
Malaria caused by *Plasmodium falciparum* is a major cause of morbidity and mortality globally. There were approximately 216 million cases of malaria in 2016, an increase of about five million cases over 2015 ([WHO, 2017](https://www.who.int)). Effective scale-up of interventions involving intermittent preventive treatment of pregnant women (IPTp), reduction in human–vector contact, as well as early treatment of malaria cases with artemisinin-based combination treatment (ACT) is required. Artemisinin-based treatment of mild malaria is particularly fundamental to current malaria control efforts. Nevertheless, following a similar trend with the molecular epidemiology of resistance to previous antimalarial drugs ([Wellems & Plowe, 2001](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3301719/)), there have been emerging cases of potential resistance to ACTs in South-East Asia ([Ariey et al., 2014](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3921889/); [Teklemariam et al., 2017](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5279134/)).

Antimalarial drug efficacy is assessed by observing how long a patient takes to clear parasites from their blood following adequate treatment ([WHO, 2009](https://www.who.int)). However, inter-individual variability in parasite clearance and varying in vivo responsiveness to antimalarials could be influenced by factors beyond parasite susceptibility and drug action ([White, 2017](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4768008/)). A major factor could be the contribution of immunity to parasite clearance in highly endemic settings ([Atalde et al., 2017](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5599113/)). This implies that early signs of low-grade infections with drug-resistant parasite variants could remain unnoticed among individuals with high levels of immunity and faster parasite clearance. Also, a false interpretation of drug failure may arise among individuals with lower immunity and slower parasite clearance.

A recent efficacy study of ACT treatment of uncomplicated malaria in Nigeria observed a wide range of drug responses, involving persistence of infections in patients under fifteen years but treatment success among older individuals ([Oyebola et al., submitted report](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6385875/)). This observation possibly indicates the role of acquired immunity in complementing antimalarial drug action in parasite clearance as older individuals living in a high malaria transmission area are believed to have a more developed acquired immunity which can be a major influence on treatment outcomes ([Atalde et al., 2017](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5599113/); [Koffi et al., 2015](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4400664/)). It is essential to carry out population-specific immuno-epidemiological surveillance for antibody predictors of ACT potency in Nigeria. In this study, we tested the hypothesis that variation in parasite responsiveness to artemether-lumefantrine (AL) treatment in Nigeria is a consequence of varying human antibody responses. We profiled antibodies specific to 21 recombinant *P. falciparum* sporozoite and blood-stage antigens as well as *Anopheles gambiae* salivary protein and correlated the expression of the antibodies with efficiency of AL treatment.

Methods

**Study design and sample collection**
This observational study of a 28-day follow-up was conducted in Ijede and Agbowa General Hospitals (GH) in Ikorodu, a peri-urban settlement in Lagos, South-West Nigeria, from August – November, 2016 following the revised WHO drug efficacy protocol ([WHO, 2009](https://www.who.int)). Briefly, individuals (1–70 years) presenting at the hospital with symptoms of uncomplicated malaria were screened for *Plasmodium falciparum*, first by rapid diagnostic test (RDT), followed by microscopy (Olympus BX53M, UK). The recruitment criteria included fever in the preceding two days, no history of antimalarial intake in the previous four weeks and *P. falciparum* parasitaemia >2000/μl of blood on presentation ([WHO, 2009](https://www.who.int)). Infants under one year of age were excluded from each dataset to avoid any influence of maternally derived antibodies ([Drakeley et al., 2005](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1170688/)). Confirmed cases of uncomplicated malaria were treated with appropriate doses of AL (Coartem, Novartis, Switzerland) according to national policy on malaria treatment ([FMoH, 2005](https://www.fmoh.gov.ng/)). Based on an expected maximum treatment failure rate of 5% in a related population ([Ojurongbe et al., 2013](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3724789/)) and the desired confidence level (95%) and precision (5%), a minimum of 73 patients were required ([WHO, 2009](https://www.who.int)). An additional 20% was added as provision for patients lost to follow up. Participants and/or their parents/guardians were instructed on how and when to take the evening dose. Following consent, participants were followed up on days 1, 3, 7, 14, 21 and 28 post-treatment. Before the first treatment was administered, whole blood samples were collected from which plasma was extracted and stored at -20°C for serological assays. Plasma samples were collected prior to treatment and participants were stratified into two groups: individuals with parasite clearance within 24 hours (early group, N=20) and the others with clearance between 48–72 hours (late group, N=30).

**Ethical approval and consent to participate**
Individuals were requested to provide a written informed consent or assent (by parents/guardians of children below 15 years) before progressing on any study-related procedure. Ethical approval for the study was obtained from the Nigerian Institute of Medical Research Ethics Committee (IRB/17/019) and the Management Board of the health facilities.

**varATS qPCR assessment of parasite clearance**
*Plasmodium falciparum* DNA was extracted from pre- and post-treatment dried blood spots using the QiaAmp DNA mini-kit (Qiagen, Germany). The *var* gene acidic terminal sequence (*varATS*) quantitative PCR was used to detect multi-copy genomic sequences of infections ([Hofmann et al., 2015](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4320042/)). Briefly, genomic DNA of the parasite was amplified in 20μl reaction containing 1x Taqman mastermix (Life Technologies, United Kingdom) and run in CFX96 Touch™ real-time PCR detection system (Bio-Rad, United Kingdom). The primer/probe sequences and the cycling conditions are described in **Table 1**. The starting quantity (SQ) values of the parasite samples were estimated against laboratory grown *P. falciparum* 3D7 standard control (with medonic read of 3.74 x 10⁷ erythrocytes/μl and thin film parasitaemia of 1197 parasites/μl of blood). The serial dilution procedure is described in **Dataset 1**: Datasheet 1 ([Oyebola et al., 2018](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6385875/)).

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**Dataset 1**

**Dilution procedure**

<table>
<thead>
<tr>
<th>Dilution factor</th>
<th>Concentration (copies/μl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10³</td>
</tr>
<tr>
<td>2</td>
<td>10²</td>
</tr>
<tr>
<td>4</td>
<td>10¹</td>
</tr>
<tr>
<td>8</td>
<td>10⁰</td>
</tr>
</tbody>
</table>

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Multiplex magnetic bead-based immunoassay (MAGPIX™)

Twenty-one Bovine Serum Albumin (BSA)-conjugated antigens specific to *P. falciparum* and *Anopheles gambiae* salivary peptide gSG6 antigen (Ag) were included. The peptides used in our study were sourced and designed at the London School of Hygiene and Tropical Medicine (LSHTM) following procedures described by Ambrosino et al. (2010). An N-terminal cysteine residue was added to allow a unidirectional coupling to BSA by the manufacturer (Gen-Script HK Inc., Hong Kong, China). A summary of antigens and peptides used is given in Table 2. Luminex assay was performed in a dimly lit room. After counting Ag-coated bead, an equal number of beads for each fluorescent bead region was mixed and distributed in a 96-well white polystyrene round-bottom microtitre plate (Fisher Scientific, USA) to reach a final concentration of 1500 beads/region/Ag in each well. The supernatant was removed and 100μL plasma at the appropriate dilution were added in duplicate wells. Plasma dilutions were done in PBS 1x supplemented with 0.05 % Tween 20 and 1% of BSA (PTB buffer). Plates were incubated at room temperature for 45 minutes under constant shaking (350 rpm).

Data analysis

All statistical analyses were conducted in Graphpad Prism 7.04. Analysis of luminex data was accomplished by quantifying median fluorescence intensity (MFI). For data normalization, the raw intensity values for antigens were divided by the median intensity of naïve controls and log 2 transformed to generate median-normalized–fold-over-control (FOC) values. Antigens were considered sero-reactive if the MFI of an individual sample was greater than a cut-off defined as the average plus 2 S.D of the reactivity of corresponding *P. falciparum* antigens in UK control plasma. Individual plasma samples were considered seropositive for a particular antigen if the corresponding log_2(FOC) ≥ 1. Association between antibody levels and parasite density was assessed using Spearman’s correlation coefficient. Analysis of variance (ANOVA) was used to determine the relationship between age categories and overall immune response. To study the association between parasitaemia and levels of antibody responses, Spearman’s correlation (r_s) was used. The relationship between antibody levels and treatment response (measured as parasite clearance within 24 hours i.e., early clearance, and clearance between 48–72 hours i.e., late clearance) was assessed using Spearman’s correlation. Bonferroni correction was used to counteract the effect of multiple testing.

Results

Baseline information on the study participants

In this study, 561 individuals were screened, resulting in 150 of them testing positive for falciparum malaria. Eighty-nine patients met the inclusion criteria, were enrolled and followed up. Participants were categorized into three age groups: 1–5 years; 6–14 years and ≥15 years old. Nearly two-thirds of enrollees were female. While about half of them were in the ≥15 years category (Table 3). Based on the detection of parasite DNA in peripheral blood by varATS qPCR assay (Dataset 1: Datasheets 2 and 3 (Oyebola et al., 2018)), two main parasite clearance profiles were described: individuals with parasite
clearance within 24 hours (early group, N=20) and the others with clearance between 48–72 hours (late group, N =30).

**Prevalence of antibody response and parasite density**
The prevalence of positive antibody response against the 21 antigens was high. Sero-positivity and sero-reactivity of antibodies against the 21 antigens are detailed in Dataset 1: Datasheet 4 (Oyebola et al., 2018). As shown in Figure 1, antibody response (stated as median fluorescence intensity) was highest against GLURP (R0) and lowest against MSP2 antigen. When antibody responses and parasite load were compared, no significant correlation was observed between parasitaemia (log-transformed parasite density) observed at recruitment and antibody responses against all antigens except a significant positive correlation to Rh5 ($P = 0.047$, $r_s = 0.32$); Hyp2 ($P = 0.037$, $r_s = 0.34$) and H103 ($P = 0.038$, $r_s = 0.34$) (Dataset 1: Datasheet 5 (Oyebola et al., 2018)).

**Association between antibody responses and age of participants**
Results of analysis of variance (ANOVA) between antibody responses against the different targets and the age of participants are described in Figure 2. The ANOVA results of antibody responses and the age groups of individuals (1–5; 6–14 and ≥15 years) showed an increase in antibody responses with age, $P = 0.0023$ (Figure 2). However, there was no significant

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**Table 2. Features of antigens tested by Luminex Assay.**

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Description</th>
<th>Gene identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh2030</td>
<td>Rho1try protein 2</td>
<td>PF3D7_0905400</td>
</tr>
<tr>
<td>Etramp5.Ag1</td>
<td>Early transcribed membrane antigen1</td>
<td>PF3D7_0532100</td>
</tr>
<tr>
<td>SBP1</td>
<td>Skeleton-binding protein</td>
<td>PF3D7_0501300</td>
</tr>
<tr>
<td>EBA175</td>
<td>Erythrocyte binding antigen-175</td>
<td>PF3D7_0731500</td>
</tr>
<tr>
<td>EBA140</td>
<td>Erythrocyte binding antigen-140</td>
<td>PF3D7_1301600</td>
</tr>
<tr>
<td>GST</td>
<td>Glutathione S-transferase</td>
<td>PF3D7_1419300</td>
</tr>
<tr>
<td>Rh5</td>
<td>Reticulocyte binding protein-like homologue 5</td>
<td>PF3D7_0424100</td>
</tr>
<tr>
<td>HSP40</td>
<td>Heat shock protein 40-subfamily A</td>
<td>PF3D7_1437900</td>
</tr>
<tr>
<td>MSP1.19</td>
<td>Merozoite surface protein 1.19</td>
<td>PF3D7_0903000</td>
</tr>
<tr>
<td>gsG6</td>
<td>An. gambiae salivary protein</td>
<td>gi</td>
</tr>
<tr>
<td>CSP</td>
<td>Circumsporozoite protein</td>
<td>PF3D7_0304600</td>
</tr>
<tr>
<td>MSP2.CH150</td>
<td>Merozoite surface protein 2</td>
<td>PF3D7_0206800</td>
</tr>
<tr>
<td>RH4.2</td>
<td>Reticulocyte binding protein-like homologue 4</td>
<td>PF3D7_0424200</td>
</tr>
<tr>
<td>MSP2</td>
<td>Merozoite surface protein 2</td>
<td>PF3D7_0206800</td>
</tr>
<tr>
<td>Hyp2</td>
<td>Plasmodium exported protein (hyp2)</td>
<td>PF3D7_1002000</td>
</tr>
<tr>
<td>SEA</td>
<td>Schizont egress antigen</td>
<td>PF3D7_1021800</td>
</tr>
<tr>
<td>AMA1</td>
<td>Apical membrane antigen</td>
<td>PF3D7_1133400</td>
</tr>
<tr>
<td>H103</td>
<td>Merozoite surface protein 11</td>
<td>PF3D7_1036000</td>
</tr>
<tr>
<td>GLURP (R0)</td>
<td>Glutamate-rich protein</td>
<td>PF3D7_1035300</td>
</tr>
<tr>
<td>GexP</td>
<td>Plasmodium exported protein</td>
<td>PF3D7_0402400</td>
</tr>
<tr>
<td>Enramp4.Ag2</td>
<td>Early transcribed membrane antigen2</td>
<td>PF3D7_0423700</td>
</tr>
</tbody>
</table>

---

**Table 3. Demographic profile of participants.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number screened n (%)</th>
<th>Number positive for <em>P. falciparum</em> n (%)</th>
<th>Number enrolled n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>157 (27.99)</td>
<td>19 (12.67)</td>
<td>18 (27.69)</td>
</tr>
<tr>
<td>Female</td>
<td>404 (72.01)</td>
<td>131 (87.37)</td>
<td>47 (72.31)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 5 yrs</td>
<td>138 (24.60)</td>
<td>22 (14.67)</td>
<td>13 (20.0)</td>
</tr>
<tr>
<td>6–14 yrs</td>
<td>80 (14.26)</td>
<td>12 (8.0)</td>
<td>21 (32.31)</td>
</tr>
<tr>
<td>≥15 yrs</td>
<td>343 (61.14)</td>
<td>116 (77.33)</td>
<td>31 (47.69)</td>
</tr>
</tbody>
</table>

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*– Plasmodium falciparum*
difference ($P = 0.2$) between antibody levels against Etramp5.Ag, MSP1.19, SBP1, GST and age even though antibody titres were lowest among individuals in 1–5 years age group but increased with age. In addition, anti-Rh5 and anti-gSG6 titres reduced with age although the statistical relationship ($P = 0.426$) was insignificant (Dataset 1: Datasheet 6 (Oyebola et al., 2018)).

Antibody levels and treatment response
The relationship between immune response and the efficiency of treatment was analyzed by stratifying clearance of parasitaemia between early (within 24 hours) and later (48–72 hours) delay measured by varATS qPCR. As shown in Figure 3, we observed a different range of antibody values to the 21 antigens studied. More titre values were obtained against EBA 175,
EBA 140, MSP1.19, CSP, Rh4.2 and GLURP among individuals with early parasite clearance than in the late parasite clearance group. However, there was no statistical difference in antibody responses in both groups (P > 0.05).

**Discussion**

Antimalarial treatment efficacy has been associated with drug pharmacokinetics, pharmacodynamics and parasite genetics (Ariey *et al.*, 2014; Barnes *et al.*, 2009). However, little has been reported on the influence of acquired immunity on treatment outcome. In this study, we examined the association between antibody profiles of malaria antigens with parasite clearance following artemether-lumefantrine treatment in Lagos, Nigeria. Antibody response to *P. falciparum* antigens develops gradually in malaria endemic areas, low in children under five years of age and progressively increasing to reach the highest level in adults (Stanisic *et al.*, 2009). That was largely the case in this study as there was a positive relationship between age and response to antigens except GST and SBP1 levels which had no clear association with the age of participants. Interestingly, *P. falciparum* GST antigen has been linked with the development of artemisinin resistance (Lisewski *et al.*, 2018). SBP1 is a trans-membrane protein, located in parasite-induced membranous structures within the Maurer’s clefts that are thought to function as a sorting compartment between the parasite and the infected red blood cells (Kats *et al.*, 2015). SBP1 plays a key role in parasite virulence by influencing adherence to endothelial receptors to avoid splenic clearance (Mundwiler-Pachlatko & Beck, 2013). Anti-SBP1 immunity thus prevents endothelial adherence and severe manifestation of infections which should be influenced by exposure and age of the human host. However, why there was no clear relationship between acquired immunity against SBP1 and GST antigens and the age of individuals in this study may be a subject for future investigations.

Furthermore, we observed a reduction in the expression levels of anti-Rh5 antibodies with increasing age in line with a recent observation in another endemic population (Valmaseda *et al.*, 2017). This finding has a crucial implication on the design of Rh5 targeted antimalarial vaccines as effectiveness may differ between individuals of different age groups. A plausible explanation for this outcome is that Rh5 is highly conserved, essential for parasite survival and frequently exposed to the immune system thus may be undergoing strong selective pressure that favours parasites expressing less Rh5 (Volz *et al.*, 2016; Weaver *et al.*, 2016). In essence, as the host grows older, less Rh5 antigen is expressed which may eventually cause a reduction in the production of anti-Rh5 immunity. Rather than increase with age, a progressive age-dependent decrease of antibody response to gSG6 was reported in this study. *An. gambiae* salivary gland protein (gSG6) is a serological marker of exposure to malaria vectors (Rizzo *et al.*, 2011). Previous reports have interpreted decline of anti-gSG6 antibody with age as natural desensitization to gSG6 proteins following prolonged exposure to infection (Remoue *et al.*, 2006; Rizzo *et al.*, 2011). However, additional studies will be important to explain the mechanism behind natural desensitization of antibodies to the gSG6 antigen.

Our findings compare with reports showing high expression levels of Rh5 antibody with high parasite densities (Gomez-Escobar *et al.*, 2010) although we did not observe any evidence of increasing antibody levels with parasite load except for a positive association of Rh5, Hyp2 and H103 with parasitaemia. In addition, there was no significant difference in the antibody responses to treatment in the study population. Although there were higher antibody values recorded against EBA 175, EBA 140, MSP1.19, CSP, Rh4.2 and GLURP among individuals with early response to treatment, there was no sufficient
Conclusions
This study reveals that expression levels of antibody against a panel of malaria antigens are largely modulated by age but no consistent association between antibody response to Rh5, Hyp2 and H103 and parasite density was observed. Our findings also suggest modest correlation of high antibody levels against the panel of 21 parasite antigens with treatment efficacy in the population. Characterization of additional markers in larger populations is required to identify immune markers of treatment efficacy.

Data availability
The data underlying this study is available from FigShare: Dataset 1. Assessing naturally acquired immune response and malaria treatment outcomes in Lagos, Nigeria. https://doi.org/10.6084/m9.figshare.6024119 (Oyebola et al., 2018) under a CC BY 4.0 licence.

Competing interests
No competing interests were disclosed.

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