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PRIMAQUINE AND TAFENOQUINE IN THE *PLASMODIUM CYNOMOLGI* CAUSAL PROPHYLACTIC MALARIA MODEL

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The relapsing malaria model consisting of *Plasmodium cynomolgi bastianellii* (B strain) in the rhesus is a valuable tool for identifying causal prophylactic drug candidates against *P. vivax* in humans. Historically, the 8-aminoquinolines (8-AQs) primaquine and tafenoquine have been protective at oral doses administered on days -1, 0 and 1 against sporozoites inoculated on day 0, presumably due to drug action against pre-erythrocytic stages. However, recent data suggest that the historically effective dosing regimens are not protective in the modern model. At historically effective doses of the two 8-AQs on days -1, 0, and 1, development of parasitemia was delayed slightly when compared with the untreated animals, but was not prevented. Delay in parasitemia averaged 5 days for the primaquine group (1.78 mg/kg/day) and 3 days for the tafenoquine group (0.316 mg/kg/day) when compared to the controls (vehicle only). Increasing the dose of tafenoquine to 6.0 mg/kg/day has provided complete protection to date, study day 53. While increasing the length of primaquine dosing from 3 to 10 days also provided protection to one monkey in the group, the other developed parasitemia on day 49. In this model, the primary attack is observed in untreated monkeys between days 8-10, the monkeys are treated with chloroquine for 7-10 days, and relapse occurs approximately 10 days after the last chloroquine dose. In the case of drugs with long elimination half-lives, such as tafenoquine, a lengthy delay in development of parasitemia may be attributed to drug still in the system. For primaquine, with a 2 hr elimination half-life in monkeys, other possibilities must be considered; the most likely being hypnozoite latency period. Comparison of 8-AQs to atovaquone-proguanil, an antimalarial with no antihypnozoite activity, will be presented, as will details of the analysis of plasma drug concentration-time data to determine dosing-exposure profiles and plasma drug levels associated with protection.

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SPATIAL AND TEMPORAL PATTERN OF ANTI-MALARIA ANTIBODY RESPONSES AS EVALUATION OF HUMAN EXPOSURE IN THE WESTERN KENYAN HIGHLANDS

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Assessment of exposure to malaria at different altitudes and transmission intensities will inform the implementation and evaluation of malaria control programs. Recently anti malaria antibodies to merozoite surface protein 1 (MSP-1) have been described as the best immunological marker for estimating malaria exposure as a proxy for transmission intensity across various altitudes. The purpose of this study was to determine if the spatial and temporal patterns of antibody (Ab) responses are consistent with varying transmission intensities in the highlands of western Kenya. We measured total IgG levels to *Plasmodium falciparum* MSP-119 in an age stratified cohort (1= ≤1, 2=2-3, 3= 4-14, 4=15-45) of 900 participants from uphill and valley bottom residents at highland site during a low transmission and high malaria transmission season. Total IgG levels to salivary gland peptide gSG6 -P1 were also measured to determine whether micro-heterogeneity exposure to *Anopheles* bites correlates with MSP-1 IgG titers. Significantly higher proportions of sero-positives and total IgG titers were observed in valley bottom residents and in high transmission season. Age stratified cohort revealed intriguing differences; higher titers in 1 yr olds, a decrease in 2-3yr olds with a non significant increase in 4-14 yr old before rising to significantly higher levels in the 15-45yr olds. No significant differences between age groups 1, 2, and 3 across all parameters compared except for seasonal variation, however significant differences were observed between each younger age group and group4. In conclusion, this data confirms a highly heterogeneous malaria exposure at this highland site possibly due to clustered vector densities around major breeding sites near valley bottoms. Whether the high level of Ab in infants is as a result of exposure or exclusively due to maternal antibodies is yet to be elucidated.

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INFLUENCE OF EXPOSURE TO *ANOPHELES* BITES ON THE DEVELOPMENT OF ACQUIRED ANTIBODY RESPONSE TO *PLASMODIUM FALCIPARUM* IN CHILDREN

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Numerous ecological and epidemiological factors could modulate the anti-malaria immunity. Among these factors, the exposure to *Anopheles* bites, especially by active components of *Anopheles* saliva, could play a key role on the development of human immune response to *Plasmodium falciparum*. We investigated here the influence of exposure to *Anopheles* bites on the acquired antibody (Ab) response specific to *P. falciparum* whole schizont extract (WSE) and to CSP vaccine candidate, in children (1-9 years) living in malaria area. A multi-disciplinary and longitudinal study was conducted in two Senegalese villages where intensity of exposure to *Anopheles* bites was clearly different: Mboula, presenting low exposure (BHN =3) versus Gankette, with high exposure (BHN = 120). IgG, IgG1, IgG3 response directed to WSE and CSP antigen were determined before (June), at the peak (September) and after (December) the period of malaria exposure. In Mboula, the peak of exposure was followed by increase of anti-WSE IgG levels whereas low and constant specific IgG response was observed in Gankette. Interestingly, anti-WSE and anti-CSP IgG1 levels were higher in Mboula, whereas specific IgG3 response predominated in Gankette. Specific IgG1 response appeared therefore observed mainly in area presenting low exposure to *Anopheles* bites, whereas IgG3 isotype predominate in high exposure area. In addition, Ab response to WSE and CSP antigens decreased progressively with the season of exposure to *Anopheles* bites and this decrease appeared dependent to IgG1/IgG3 balance and to the level of exposure. Altogether, these results show that the development of anti-malaria Ab response was profoundly different according to areas where the level of *Anopheles* bites exposure was dissimilar. This influence of exposure to bites appeared to differently regulate the balance between specific IgG1 and IgG3 isotype levels, known to be associated with anti-malaria protective immune response. One hypothesis is that the influence of *Anopheles* saliva could be involved in the observed anti-malaria immune regulation.