to treatment for uncomplicated malaria with amodiaquine-sulfadoxine-pyrimethamine (AQ+SP) were associated with surrogates of immunity, including age and proximity to a mosquito breeding site. To further assess associations between immunity and treatment response we studied humoral antimalarial responses in children in Kampala aged 1-10 years who received AQ+SP for treatment of uncomplicated malaria. We measured IgG responses to the following 8 *P. falciparum* antigens via ELISA in 207 pairs of serum samples collected on the day of therapy (Day 0) and 14 days after treatment (Day 14): circumsporozoite protein (CSP), liver stage antigen 1 (LSA1), apical membrane antigen 1 (AMA1), merozoite surface proteins 1, 2, and 3 (MSP 1, 2, 3), and the R0 and R2 domains of glutamine rich protein (GLURP). Results were standardized against pooled immune serum from adults living in Kampala. Our primary outcome was the genotype-adjusted risk of recrudescence within 63 days. Associations were estimated using generalized estimating equations. Age-adjusted IgG responses to AMA1 on Day 0 and Day 14 were significantly higher in those living closer to the breeding site ($p<0.02$). Overall risk of treatment failure was 12%. After adjusting for age and parasite polymorphisms associated with treatment failure, the risk of failing therapy was significantly lower in those with higher AMA1 responses on Day 0 (OR=0.79 / doubling of titer, p=0.01). IgG responses for the other antigens were not significantly associated with treatment response, however there was a trend for protection with higher Day 0 responses to MSP 2 (OR 0.79, p=0.06) and 3 (OR 0.81, p=0.09). Our findings demonstrate that antibody responses to AMA1 are associated with blood-stage immunity as measured by host clearance of parasites in the setting of partially effective therapy.

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EVALUATION OF *PLASMODIUM FALCIPARUM* MULTI-ANTIGEN ANTIBODY DYNAMICS IN INDIVIDUALS EXPERIENCING SUCCESSIVE ANNUAL INFECTIONS LIVING IN THE HYPOENDEMIC PERUVIAN AMAZON

Eva H. Clark[1], Onome Akpogheneta[2], Alexander Kayatani[3], Jean Hernandez[4], Diane W. Taylor[3], OraLee H. Branch[2]

[1]University of Alabama at Birmingham, Gurley, AL, United States, [2]New York University, New York, NY, United States, [3]University of Hawaii, Honolulu, HI, United States, [4]Universidad Nacional de la Amazonia Peruana, Iquitos, Peru

Years of exposure to *P. falciparum* are necessary for the development of immunity in high transmission areas, suggesting that protective humoral responses are disabled by parasite hyperexposure. However, in low transmission areas, such as the Peruvian Amazon, malaria-exposed individuals produce immune responses leading to clinical protection after only a few infections. To investigate the antigens responsible for these effective immune responses, this study used antigen-conjugated beads in a LUMINEX system to compare the pre-, during, and post-infection antibody responses to 8 antigens, including AMA1, CSP, EBA175, LSA1, MSP1, MSP2, MSP3, and MSP6. 34 adults and 21 children with samples from 2-3 successive infections spaced by ~1 year were evaluated. We found that adults maintained AMA1, EBA175, MSP1 and MSP3 responses for >300 days post-infection, while in children responses to only MSP1 and MSP3 lasted for >300 days. Although differences in the magnitude/longevity of responses among 1st, 2nd, and 3rd detected infections are recognizable, in adults there were no significant differences for any antigen. However, antibody levels to EBA175 and MSP-3 were significantly higher among children at the 3rd detected infection than at the 1st, suggesting that these responses are boosted earlier at each subsequent infection. After correlating each antigen response to the others, some antigen pairs were associated with more parasite exposure (AMA1&EBA175, AMA1&MSP3 and EBA175&MSP2), and some were associated with less exposure (EBA175&MSP1 and AMA1&MSP1). When comparing responses in asymptomatic versus symptomatic adults, responses to MSP1, MSP2, MSP3, and MSP6 were found to be significantly higher in asymptomatics than in symptomatics at the 2nd detected infection but not at the 1st. In summary, although MSP1 produced the largest post-infection responses even at the 1st detected infection, other blood-stage antigens, particularly MSP3 (to which even children elicited long-lived responses), were found to be important players in the anti-malarial immune response despite low transmission exposure.

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HAPLOTYPES OF FC GAMMA (FCΓ) RECEPTOR (FCΓRIIA AND FCΓRIIIB) PREDICT SUSCEPTIBILITY TO HIGH-DENSITY PARASITEMIA AND FUNCTIONAL CHANGES IN CIRCULATING IFN-Γ LEVELS IN CHILDREN WITH *PLASMODIUM FALCIPARUM* MALARIA IN WESTERN KENYA

Collins O. Ouma[1], Gregory C. Davenport[2], Samuel Kiplagat[1], Stephen Garcia[2], Prakasha Kempaiah[2], Ateefa Chaudhary[2], Tom Were[1], Samuel B. Anyona[1], Evans Raballah[1], James B. Hittner[3], John M. Vulule[4], John M. Ong'echa[1], Douglas Perkins[2]

[1]University of New Mexico/KEMRI, Kisumu, Kenya, [2]University of New Mexico, Albuquerque, NM, United States, [3]College of Charleston, Charleston, SC, United States, [4]KEMRI, Kisumu, Kenya

The development of protective immunity against *Plasmodium falciparum* is partially mediated through binding of malaria-specific IgG to Fc gamma (γ) receptors. Human FcγRIIA-H/R-131 and FcγRIIIB-NA1/NA2 exhibit polymorphic variability associated with differential binding to IgG subtypes and malaria disease outcomes. The role of FcγRIIA-H/R131 and FcγRIIIB-NA1/NA2 haplotypes in conditioning susceptibility to high-density parasitemia (HDP; ≥10,000 parasites/μL), a clinical manifestation of severe malaria in *P. falciparum* holoendemic areas, however, is largely undefined. As such, the role of FcγRIIA-H131R/FcγRIIIB-NA1/NA2 haplotypes was investigated in children (n=528) presenting with acute malaria at a rural hospital in western Kenya. Since variations in the FcγR may alter interferon gamma (IFN-γ) levels, a mediator of both innate and adaptive immune responses, additional functional analyses were carried out in the context of the FcγR haplotypes. Results reveal that circulating IFN-γ was negatively correlated with parasitemia levels ($r=-1.740$, $P=0.005$). Children with HDP also had lower circulating IFN-γ levels than the non-HDP group ($P<0.001$). Multivariate logistic regression analyses controlling for covariates revealed that carriage of the FcγRIIA-131R/FcγRIIIB-NA1 haplotype was associated with protection against HDP (OR; 0.48, 95%CI, 0.31-0.76; $P=0.002$), while carriage of FcγRIIA-131H/FcγRIIIB-NA1 haplotype increased susceptibility to HDP (OR; 1.49, 95%CI, 1.04-2.14; $P=0.031$) relative to individuals without these haplotypes. Carriers of the FcγRIIA-131H/FcγRIIIB-NA1 (131H/NA1) haplotype had significantly lower IFN-γ levels relative to non-carriers ($P=0.046$), while FcγRIIA-131R/FcγRIIIB-NA1 (131R/NA1) haplotype had elevated IFN-γ levels relative to non-carriers ($P=0.067$). These results demonstrate that variations at the FcγR gene are associated with functional changes in IFN-γ production, and susceptibility to HDP in children with *falciparum* malaria.

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SPATIAL DISTRIBUTION, HABITAT CHARACTERIZATION AND DYNAMICS OF *ANOPHELES GAMBIAE* MOLECULAR FORMS LARVAL BIOTOPES ALONG AN URBANIZATION GRADIENT IN THE CITY OF YAOUNDÉ, CAMEROON

Billy F. Tene[1], Christophe N. Antonio[2], Colince Kamdem[2], Philippe Bousses[3], Didier Fontenille[3], Nora J. Besansky[4], Carlo Costantini[1]

[1]IRD-UR016/OCEAC, Yaoundé, Cameroon, [2]LRP-OCEAC, Yaoundé, Cameroon, [3]IRD-UR016, Montpellier, France, [4]University of Notre Dame, Notre Dame, IN, United States

Increasing urbanization in Africa is drawing the attention of public health managers on urban malaria, and it raises the question of whether malaria vectors have the potential to adapt to the environmental stressors normally encountered in the most densely populated cities. In the forest domain of southern Cameroon, the molecular forms M and S of *Anopheles gambiae* segregate along urbanization gradients, suggesting that a

process of adaptation by the M form to the urban environment is under way (Kamdem et al., submitted). This process is presumably driven by the ability of M larvae to develop successfully in polluted urban habitats. To characterize the larval biotopes of M and S and their dynamics, we conducted a longitudinal survey of *An. gambiae* larval habitats to assess their distribution and relationship with human activities in the capital Yaoundé and peri-urban neighborhoods. A total of 2,449 potential mosquito breeding sites were examined, of which about 20% contained *An. gambiae* larvae. Anopheline larval habitats were more abundant in urban compared to rural or suburban areas. Seasonal fluctuations in breeding sites availability were more pronounced in the rural than urban habitat. Draining streams and swamps were associated with no or very low larval densities. Human activities such as vegetable market gardening, housing in swampy areas, and construction sites were associated with breeding sites of *An. gambiae*. Unexpectedly, *An. gambiae* larvae were collected from urban breeding sites highly polluted with organic matter. PCR identification revealed that only the M molecular form of *An. gambiae* was present in the most urbanized settings, whereas the S form was by far the most abundant in the rural sites, the suburban ones being transitional between these extremes. These findings provide evidence that the malaria vector *An. gambiae* s.s. is adapting to urban waste waters, and clearly partition the distribution of the molecular forms M and S between urban and rural areas.

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SPATIAL-TEMPORAL DISTRIBUTION OF IMMATURE AND ADULT MALARIA VECTORS IN FOUR ECOLOGICAL SETTINGS IN COASTAL KENYA

Francis M. Mutuku[1], Charles H. King[2], Peter L. Mungai[1], Eric M. Muchiri[1], Edward D. Walker[3], Uriel Kitron[4]

[1]Division of Vector-Borne and Tropical Neglected Diseases, Msambweni, Kenya, [2]Center for Global Health and Diseases, Case Western Reserve University, Cleveland, OH, United States, [3]Department of Microbiology and Molecular Genetics, Michigan State University, East Lansing, MI, United States, [4]4Department of Environmental Studies, Emory University, Atlanta, GA, United States

The on-going malaria control activities in Kenya through use of Insecticide treated nets (ITN) and Indoor residual spraying (IRS) necessitate up-to-date information on malaria vectors. An ecological study of the spatial-temporal distribution of immature and adult malaria vectors was conducted in eight villages (two in each of four ecological settings) in the south coast of Kenya. Longitudinal larval surveys were conducted monthly in selected larval habitats from May 2009 to March 2010 using standard dipper. Additionally, adult malaria vectors were concurrently collected using pythremum spray collection (PSC) and clay pots in 10 houses from March 2009 to March 2010. A total of 285 Anopheline larvae were sampled during the 10 months of larval sampling. The number and quality of larval habitats sampled in each ecological setting fluctuated with rainfall. *Anopheles* larvae were found most frequently in larval habitats located in the estuarine habitats, accounting for 81% of the total larvae sampled. The majority of the larvae were *An. gambiae* s.l (88%), with *An. funestus* comprising the rest (12%). Mean density of *Anopheles* larvae was 3 times higher in the estuarine habitats compared to the other three ecological settings combined. Abundance and density of *Anopheles* larvae was highly associated with depth, pH and conductivity of aquatic habitats. Correspondingly, 69% (962/1386) of the adult mosquitoes were *An. gambiae* s.l with *An. funestus* comprising the remaining 31% (424/1386). An average of 7 *An. gambiae* s.l and 2 *An. fune*stus mosquitoes were collected each month in the estuarine environment compared to <1 mosquito of each species in the other ecological settings. Overall, densities of adult malaria vectors were low throughout the study period, and were highly dependent on rainfall throughout the 12 months. Both abundance and composition of malaria vectors was dependent on the ecological setting and modulated by rainfall. While these findings are not surprising, only limited data was available for the south coast of Kenya. The findings of study will be useful for the planning and implementation of control strategies for malaria vectors.

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ENVIRONMENTAL CHANGE AND THE MICROBIAL ECOLOGY OF *ANOPHELES GAMBIAE*

Thomas M. Gilbreath, III[1], Eliningaya Kweka[2], Guiyun Yan[1]

[1]University of California Irvine, Irvine, CA, United States, [2]Kenya Medical Research Institute, Kisumu, Kenya

Recent studies suggest that land use changes, such as deforestation, strongly enhance the productivity of malaria vectors, and thus malaria transmission. This is because deforestation exposes aquatic habitats to sunlight, resulting in increased temperatures. Further, sunlight may induce changes in the microbial communities that mosquito larvae use for nutrition. This study utilized field-based microcosm approaches in combination with water chemistry analyses and pyrosequencing for microbial diversity in order to examine the impacts of environmental change in *An. gambiae* larval habitats and habitat vector productivity. Results of habitat productivity in different land use scenarios have demonstrated a significant effect of land use and canopy cover on larval malaria vector survivorship and habitat productivity. Survivorship in semi-forested and naturally forested areas was reduced 20% and 99%, respectively when compared to areas that had been deforested. Interestingly, when microcosm temperature in the field was controlled, temperature was shown to have the strongest effect on pupation rate while larval survivorship was more affected by algal biomass. Microbial diversity analyses show significant differences in bacterial communities from deforested, semi-forested, and forested habitats. Bacterial communities in the surface microlayers and larval guts from the same habitat also showed significant differences in composition and suggested a selective assimilation of photosynthetic microbes. These preliminary results suggest that *An. gambiae* ss preferentially feeds on photosynthetic microbes in the surface microlayer of their habitats and that the role of microbial community changes induced by light may play a more important role than temperature in some scenarios.

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PROFILING GUT MICROBIOTA IN MOSQUITO *ANOPHELES GAMBIAE* USING PYROSEQUENCING

Ying Wang[1], Thomas M. Gilbreath, III[2], Phanidhar Kukutla[1], Guiyun Yan[2], Jiannong Xu[1]

[1]New Mexico State University, Las Cruces, NM, United States, [2]University of California, Irvine, Irvine, CA, United States

Mosquito *Anopheles gambiae* is a major malaria vector. Vector competence is determined by the tripartite eco-interactions among microbes, malaria and mosquito immunity. Mosquito gut harbors diverse microbial communities. However, little is known about the dynamics of the gut microbiota from larva to adult and its impact on the gut eco-symbiotic interplays. Early studies of the gut bacteria relied on culture-and/or cloning-based low throughput techniques that characterize only a small fraction of the microbiota. Using pyrosequencing approach targeting the V1-3 hypervariable region of the 16S rRNA gene, we gained an unprecedented view of the diversity present in the gut microbiota and were able to detail the dynamics of the gut microbial community from larva to adult and assessed the effect of blood feeding on the gut community. Pyrosequencing yielded 79592 sequences from 14 samples of a lab reared *An. gambiae*. The sequences correspond to 260 genera belonging to 11 phyla with dominances of *Proteobacteria*, *Bacteroidetes, Actinobacteria* and *Firmicutes*. The structure of gut microbiota changes along the life stages. Among the tags obtained from larva, more than half (54.3%) belong to the Family *Enterobacteriaceae* (unable to classify to genus). *Microbacterium* (23.7%) is abundant only in larva. Pupa