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INFLUENCE TO MOSQUITOES BITES ON ANTIBODY REPONSES SPECIFIC TO MALARIA ANTIGENS

Ghislain K. Aka[1], André B. Sagna[2], François D. Traore[2], Danielle D. Zoh[1], Bertin N. Tchiekoi[1], Norbert K. Lingue[1], Issa Coulibaly[1], Serge Assi[1], Akré M. Adja[1], Franck Remoue[2], Joseph A. Djaman[3], Anne Poinsignon[2]

[1]Institut Pierre Richet, Bouaké, Côte D'Ivoire, [2]Institut de Recherche pour le Développement, Montpellier, France, [3]Institut Pasteur de Côte d'Ivoire, Abidjan, Côte D'Ivoire

In malaria endemic areas, populations are frequently exposed to salivary components of blood-sucking mosquitoes that could modulate the immune response of the human host by their immunomodulatory properties. Consequences on pathogen-specific immune responses are not well known. Thus, we studied the influence of exposure to the main mosquitoes on the development of antibody (Ab) responses specific to *Plasmodium* antigens acquired during natural infection according to 1/ individual level of exposure to *Anopheles* bites and 2/ the presence of other mosquitoes (*Aedes* and *Culex*). A study was carried out in Bouaké (Côte d'Ivoire) where entomological data and blood samples from children (0-14 years) were collected. We evaluated the Ab responses (IgG, IgG1, IgG3) to 2 blood-stage antigens of *P. falciparum* (AMA-1, MSP-1) by ELISA. The individual level of child exposure to *Anopheles* bites was evaluated by quantifying specific IgG responses to the *Anopheles* gSG6-P1 salivary peptide. Immunological profiles of the anti-*Plasmodium* Ab responses in children were different according to the *Plasmodium* antigens. The comparison of immunological profiles according to the individual exposure level to *Anopheles* bites showed that anti-*Plasmodium* Ab responses were higher in children with low exposure level compared to those highly exposed to *Anopheles* bites. High and low exposed children to *Anopheles* but highly exposed to *Culex* bites have a low level of anti-*Plasmodium* immune responses. These findings suggest that anti-*Plasmodium* immune responses are modulated with the level of exposure to *Anopheles* bites but also to other hematophagous mosquito species. The immunosuppressive effect of the saliva of the mosquitoes has been highlighted. The immunomodulatory properties of mosquitoes' saliva on anti-plasmodial immune responses should be taken into account in epidemiological studies and especially in vaccine trials.

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NATURALLY ACQUIRED ANTIBODIES TO *PLASMODIUM FALCIPARUM* AND THEIR ASSOCIATION WITH REDUCED MALARIA RISK: DISCERNING BETWEEN EXPOSURE AND PROTECTION

Aida Valmaseda[1], Eusebio Macete[2], Augusto Nhabomba[2], Caterina Guinovart[1], Pedro Aide[2], Azucena Bardají[1], Quique Bassat[3], Tacilta Nhampossa[2], Aina Casellas[1], Llorenç Quintó[1], Sergi Sanz[1], Alfons Jiménez[1], Chetan Chitnis[4], Virander Chauhan[5], Carlota Dobaño[1], Ruth Aguilar[1], John Aponte[1], James Beeson[6], Christine Langer[6], Clara Menéndez[7], Pedro L Alonso[7], Deepak Gaur[8], Alfredo Mayor[7]

[1]ISGlobal, Barcelona Center Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain, [2]Centro de Investigação em Saude de Manhiça (CISM), Manhiça, Mozambique, [3]ISGlobal, Barcelona Center Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain; Centro de Investigação em Saude de Manhiça (CISM), Manhiça, Mozambique; and Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain, [4]Department of Parasites and Insect Vectors, Malaria Parasite Biology and Vaccines Unit, Institut Pasteur, Paris, France, [5]Malaria Group, International Centre for Genetic Engineering and Biotechnology (ICGEB), New Delhi, India, [6]Macfarlane Burnet Institute for Medical Research and Public Health, Melbourne, Australia, [7]ISGlobal, Barcelona Center Int. Health Res. (CRESIB), Hospital Clínic - Universitat de Barcelona, Barcelona, Spain and Centro de Investigação em Saude de Manhiça (CISM), Manhiça, Mozambique, [8]Laboratory of Malaria and Vaccine Research, School of Biotechnology, Jawaharlal Nehru University, New Delhi, India

A main criterion to identify vaccine candidates against malaria is the proof that acquired immunity against them is associated with protection from disease. We aimed to study the protective role of IgG/IgM antibody responses against 23 pre-erythrocytic and erythrocytic antigens from *Plasmodium falciparum*, including members of the EBA and PfRh families, and novel antigens merely or not previously studied in malaria-exposed populations (AARP, CyRPA, P41). We measured antibody levels by Luminex® in plasma from Mozambican children (n=261) who were monitored from birth until 3 years of age for clinical malaria. Aiming for a better approach to find correlates of protection against clinical malaria and overcome heterogeneity in malaria exposure that can confound our results, we compared classical cox regression models to models estimated after excluding children unexposed during the follow-up, defined by clinical and serological data. Also, to measure the antibody direct effect on the malaria episode, we limited the follow-up time to the time the specific IgG drop to 25% of their levels at first contact, that ranged from 78 days (PTRAMP) to 550 days (P41). Either excluding the non-exposed individuals or limiting the follow-up time in the analyses was useful to avoid antibodies' associations with higher risk of clinical malaria (which are exposure markers). Protective associations were found for IgG (and IgG breadth) at 24 months old (and not at younger ages), although the antibody levels were not necessarily higher than at younger ages. Together, these findings show the importance of age in the acquisition of protective immunity and of either excluding non-exposed population or limiting the follow-up time according to antibody decay when studying correlates of protection.

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THE IMPACT OF CONCURRENT EXPOSURE TO *PLASMODIUM FALCIPARUM* ON THE DEVELOPMENT OF NATURALLY ACQUIRED IMMUNITY TO MALARIA IN YOUNG MALAWIAN CHILDREN

Priyanka Barua[1], Upeksha P. Chandrasiri[1], James G. Beeson[2], Kathryn G. Dewey[3], Kenneth Maleta[4], Per Ashorn[5], Stephen J. Rogerson[1]

[1]The Department of Medicine (RMH), Peter Doherty Institute for Infection and Immunity, The University of Melbourne, Melbourne, Australia, [2]Burnet Institute for Medical Research and Public Health, Melbourne, Australia, [3]University of California, Davis, CA, United States, [4]University of Malawi, Malawi, Malawi, [5]University of Tampere and Tampere University Hospital, Tampere, Finland

Antibodies targeting the blood-stage of malaria and variant antigens expressed on the surface of infected erythrocytes are important indicators of naturally-acquired immunity against malaria. To identify their role in development of immunity in infancy, the levels of antibodies against merozoite surface proteins (MSP1 19kD, MSP2), erythrocyte binding antigen 175 (EBA175), reticulocyte binding protein homologue 2A (PfRh2), schizont extract and variant surface antigens for parasite lines E8B, R29, 3D7 overexpressing *Var* A were measured in plasma from 18 month old Malawian infants in a randomised controlled trial of nutrient supplements. Children were actively followed from birth and had malaria testing for febrile episodes. Of 601 children, 144 experienced malaria episodes before 18 months. Antibody prevalence was higher in children who had experienced episodes of clinical malaria, or who were parasitaemic at the time of sample collection than children with no malaria history. Children who had experienced clinical malaria were significantly more commonly seropositive for MSP1, MSP2, schizont extract and E8B parasite-line. Antibody prevalence did not differ between children having single and multiple episodes. Antibody levels also differed with history of malaria episodes or parasitaemia. Children who were parasitaemic at sample collection had significantly higher levels of antibodies for all the antigens except PfRh2. Children with malaria episodes had higher antibody levels