

Hierarchical, Domain Type-Specific Acquisition of Antibodies to *Plasmodium falciparum* Erythrocyte Membrane Protein 1 in Tanzanian Children

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ABSTRACT

Plasmodium falciparum erythrocyte membrane protein 1 (PfEMP1) is a variant antigen expressed on the surface of malaria-infected erythrocytes. PfEMP1 attaches to the vascular lining and allows infected erythrocytes to avoid filtration through the spleen. Each parasite genome encodes about 60 different PfEMP1 variants, each PfEMP1 comprises several domains in its extracellular region, and the PfEMP1 repertoire in different parasites contains domain types that are serologically cross-reactive. In this longitudinal study, we followed 672 children living in an area of high malaria transmission during the first years of life and compared the acquisitions of antibodies to 32 Duffy-binding ligand-like (DBL) domains representing different types. For each child, we determined whether an antibody response to each domain was acquired before, after, or at the same time as responses to each of the other domains. We next used this information to calculate population-level odds ratios to measure the odds that antibodies to a given domain were acquired before antibodies to other domains. Odds ratios for 269 of the 496 possible domain combinations were statistically significant. Thus, the sequence in which individuals acquire antibodies to different PfEMP1 domains is ordered, and children in areas of endemicity first acquire antibodies to particular PfEMP1 domains encoded by the so-called group A and B/A *var* genes. The results imply that anti-PfEMP1 antibodies effectively structure PfEMP1 expression and play a major role in limiting parasite multiplication in the blood.