**Symptomatic malaria is associated with enhanced protection from reinfection with homologous *Plasmodium falciparum* circumsporozoite protein epitopes**

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Sequence diversity in parasite antigens is one of the major hurdles in designing efficacious vaccines against *Plasmodium falciparum.* The first WHO-recommended vaccine against malaria, RTS,S/AS01, targets the *P. falciparum* parasite circumsporozoite protein (CSP). Although efficacious against parasites with genetically similar CSP, significant antigenic variation results in the vaccine being less effective against heterologous CSP types. In this study, we show that most of the diversity of C-terminal CSP sequence haplotypes in infected people in Kenya can be defined by 8 amino acid positions present in the CD4+ and CD8+ T-cell epitopes. We found that the hazard of reinfection with parasites containing homologous CD4+ and CD8+ T-cell epitope types was significantly lower among those with symptomatic exposure to parasites -

CD4+ T-cell (aHR 0.63, 95% CI: 0.45 - 0.89) and CD8+ T-cell epitope types (aHR 0.71, 95% CI: 0.52 - 0.97). This decreased hazard after symptomatic exposure was not observed for reinfections with random epitope types. Together, this shows that the sequence diversity of CSP can be drastically reduced to a manageable number of types, which can potentially serve as a guide for design of the next generation of vaccines targeting CSP that are able to overcome antigenic variation and broaden protection.