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Modeling the mechanisms of naturally acquired immunity to malaria

Infection with *Plasmodium falciparum* can cause severe malaria in adults and children if they lack malaria-specific immunity. In residents of malaria endemic areas, naturally acquired immunity is first characterized by resistance to the clinical manifestations of malaria and eventually resistance to infection. Anti-malarial immunity may act at different stages of the parasite life cycle; liver-stage immunity would block the initiation of new infections and blood-stage immunity could block erythrocyte invasion and/or destroy infected RBC reducing Parasite Multiplication Rate i.e. the number on newly infected RBC (in which parasites survived until the next reinfection cycle) per one previously infected RBC.

In order to understand the impact of stage-specific immunity, we analyzed a treatment-time-to-reinfection study from Western Kenya, where 197 adults and children were treated with artemether/lumefantrin to clear blood-stage parasites. Individuals who had no detectable blood-stage parasites 2 weeks post-treatment were deemed cured and thus any parasitemia during the subsequent 10 week follow-up was considered a new infection. Children were further categorized into three age groups (0-4 yr, 5-9 yr and 10-14 yr). As previously observed, there was a progressive delay in mean time to reinfection associated with age and adults had lower parasite densities and fewer observed 'peaks' of parasites once infected compared to children.

To understand what forms of immunity could reproduce the observed reinfection curves for each age group we used a modeling approach. We first derived the reinfection functions assuming liver-stage (infection blocking) immunity only or blood-stage (growth slowing) immunity only and fitted them to experimental reinfection proportions. We found that the reinfection curves could be reproduced by the model with blood-stage immunity where each age group had a distribution in the parasite multiplication rate, with a decrease in the mean of this distribution with age.

To gain further insight into acquisition of immunity we developed a stochastic model of malaria infection and blood stage immunity, incorporating both a strain specific as well as a cross reactive or 'general' immunity to all strains. It was able to capture the observed reinfection rates, and remarkably also the observed levels of parasitemia. The model suggests the importance of rapidly-induced, strain-specific immunity in clearing individual infections, and slowly acquired general immunity in bringing down the average Parasite Multiplication Rate with age and magnitude of peaks of parasitemia.

Understanding the dynamics of naturally acquired immunity provides insights for malaria vaccine development as well as a tool for immuno-surveillance in areas experiencing changes in malaria epidemiology due to malaria control interventions.