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An antigenic diversification threshold for falciparum malaria transmission at high endemicity

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In malaria and several other important infectious diseases, high prevalence occurs concomitantly with incomplete immunity. This apparent paradox poses major challenges to malaria elimination in highly endemic regions, where asymptomatic \textit{Plasmodium falciparum} infections are present across all age classes creating a large reservoir that maintains transmission. This reservoir is in turn enabled by extreme antigenic diversity of the parasite and turnover of new variants. We present here the concept of a threshold in local pathogen diversification that defines a sharp transition in transmission intensity below which new antigen-encoding genes generated by either recombination or migration cannot establish. Transmission still occurs below this threshold, but diversity of these genes can neither accumulate nor recover from interventions that further reduce it. An analytical expectation for this threshold is derived and compared to numerical results from a stochastic individual-based model of malaria transmission that incorporates the major antigen-encoding multigene family known as \textit{var}. This threshold corresponds to an "innovation" number we call $R_{\text{div}}$; it is different from, and complementary to, the one defined by the classic basic reproductive number of infectious diseases, $R_0$, which does not readily apply under large and dynamic strain diversity. This new threshold concept can be exploited for effective malaria control and applied more broadly to other pathogens with large multilocus antigenic diversity.

1. What is your pathogen? Multiple options possible (e.g. if working on coinfections)
   
   \textbf{Protozoan} : Plasmodium falciparum

2. On a scale of 1-5 is your work mostly eco/epidemiological or evolutionary? 3

3. On a scale of 1-5 is your work mostly theoretical or experimental/empirical?
   
   1 (100% theoretical or experimental)