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Complex Determination of the Gametocyte Conversion Rate

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Malaria transmission is a fascinating field of study at the intersection of evolutionary biology and infectious disease control, with many questions awaiting answers. Do parasites alter their investment into transmission in response to factors in the human host, such as immune response? Do they sense transmission intensity, for example the frequency of *Anopheline* bites, and if so, how do they respond to it? What is the impact of the genetic background of the parasite, human host, and vector? In a recent article we have discussed how population-based studies can inform this research [1]. In their response, Reece and Schneider have misinterpreted key points of our article.

In order to study if and when malaria parasites adjust the gametocyte conversion rate in response to external factors, in vitro parasite culture, animal models, and controlled human infection trials have been used, historic malariatherapy data reviewed, and mathematical modeling applied.

It remains challenging to confirm processes observed in controlled systems in epidemiological field studies. Epidemiological data is inherently noisy, with densities of asexual parasites and gametocytes in many asymptomatic infections around the technical limit of detection. Developing *Plasmodium falciparum* gametocytes sequester in inner organs for 10 days, and sampling in cohorts is usually not sufficiently frequent to compare densities of mature gametocytes to asexual densities at the time of gametocyte conversion, further complicating studies on triggers of gametocyte commitment. Few studies have assessed the conversion rate directly [2]; parameters frequently gathered, such as the proportion of all infections carrying detectable gametocytes, or densities of mature gametocytes, are only indirect measures.

In our recent article we have focused on these difficulties when interpreting data from epidemiological studies [1]. We have shown that in many cases differences in the proportion of gametocyte-positive infections might be explained by different mean asexual parasite densities, for example when children with little acquired immunity and high parasite densities are compared to adults with high levels of acquired immunity and low parasite densities [3]. In other situations, an adjustment to the gametocyte conversion rate seems plausible, but hasn't been proven in field studies, for example in the case of altered gametocyte densities in mixed-species infections [4]. We have made suggestions for further research, such as the use of molecular markers for early gametocytes [5], or field studies to assess whether *P. falciparum* gametocyte densities follow asexual densities with a lag of 10

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days. It is unclear how Reece and Schneider could have interpreted these points as a rejection of a variable gametocyte conversion rate.

For the design of malaria control strategies, it is relevant to identify factors that shape infectivity at the population level [6]. Studies in controlled systems can certainly inform field research to this aim, but it is important to understand the limitations of each approach. Individuals enrolled in controlled human infections were malaria-naïve, while in endemic countries individuals build up immunity gradually over time. Parasite densities in most animal models and in in vitro culture are markedly higher than in asymptomatic infections. If quorum sensing or competition for limited resources were to play a role, these models might not fully represent common natural situations. Data to parameterize mathematical models is scarce.

Reece and Schneider are correct that failure to replicate a result from the lab in a population-based study does not mean the process does not occur. We have never made such claims. But it would be equally wrong not to consider technical limitations when interpreting field studies. Only a careful evaluation of all factors will yield results that will withstand the test of time.

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