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A TARGET FOR INTERVENTION IN *PLASMODIUM FALCIPARUM* INFECTIONS

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Abstract

We present a set of simple mathematical models to investigate interactions between malaria parasites and the human immune system and the differentiation of parasites from asexual, pathogenic into sexual, transmissible blood stages. Each model represents a different combination of empirically based hypotheses, and salient behaviors of each fit criteria developed from clinical data. In all models, however, higher gametocyte conversion rates result in lower peak asexual-form densities. Therefore, to the extent that asexual-form densities are associated with disease symptoms, interventions that stimulate gametocytogenesis should produce unexpected clinical benefits.

In many infectious diseases the severity of clinical symptoms appears to vary directly with pathogen density. Though *Plasmodium falciparum* infections exhibit remarkably wide variation across individuals, populations and particular symptoms, in general terms worse prognoses are associated with higher asexual parasitemias.^{1–12} Most antimalarial drugs aim to kill asexual blood-stage parasites precisely because pathogenesis is associated solely with merogony.

No disease symptoms are associated with gametocytes, the sexual, transmissible forms that may develop from asexual blood-stage parasites, and it is widely accepted that the few host immune responses provoked by gametocytes act only against the life-cycle stages that may subsequently develop within a vector mosquito.^{13–15}, but see ¹⁶ The factors that trigger and regulate the production of gametocytes remain largely mysterious.^{17, 18} The once-common view that conversion is related to some element(s) of host immunity has faded considerably following the demonstration of gametocytogenesis in long-term culture;¹⁹ emphasis has shifted toward genetic or more direct environmental mechanisms.^{20–21}, but see ²² As with the relationship between asexual-form density and clinical severity, higher gametocyte densities are generally but loosely associated with greater infectivities to mosquitoes.^{13, 23–25}

At the human population level, Schuffner's²⁶ study of malaria in epidemic and endemic regions of Sumatra showed that in both regions *P. falciparum* gametocyte prevalence roughly tracks asexual-form prevalence, remaining high and relatively constant across age groups during an epidemic but decreasing with age at an endemic site. In Sri Lanka, an area of epidemic *P. falciparum* malaria, gametocyte prevalence decreases with age, while infectivity measures show no clear trends.²⁷ Githeko and others²⁸ supported Muirhead-Thomson's²⁹ conclusions that in endemic regions of Africa gametocyte prevalence decreases with age and older gametocyte carriers are typically less infectious; however, Githeko and others added the crucial

observation that the ratio of circulating sexual-to-asexual-form densities increases with host age. In a *P. falciparum* endemic region of India, gametocyte densities are lower but conversion rates are higher among adults.³⁰

Epidemiologic surveys invariably report much lower prevalence and densities of *P. falciparum* gametocytes than asexual forms. Because in endemic regions the lowest prevalence and densities of each form typically occur among adults, as does the lowest frequency of clinical attacks, it is widely accepted that the lower gametocyte levels represent indirect consequences of an inhibitory, nonsterilizing anti-disease immunity acquired against asexual blood forms.^{31, 32} That is, even if complicated by superinfection,³³ successful immune attacks on asexual populations should restrain the population growth of their sexual progeny. Whatever primary forces modulate gametocyte production, strong causal connections must exist between the dynamics of immune response, asexual parasitemia, and gametocytemia. This paper uses simple mathematical models to explore one set of such connections, and suggests that understanding the dynamics of *P. falciparum* gametocyte production might lead to unexpected avenues for clinical intervention.

METHODS

The relevant models, their assumptions and their general behaviors are described in detail elsewhere.³⁴ Briefly, each model consists of three nonlinear ordinary differential equations

$$\begin{aligned}dM/dt &= aM - cIM + f_1(M, I), \\dG/dt &= f_1(M, I) - pG, \text{ and} \\dI/dt &= f_2(M, I, L) - cIM - qI,\end{aligned}$$

in which the dynamic variables *M*, *G*, and *I* denote per microliter densities of asexual forms, gametocytes, and immune effectors, respectively; the parameter *L* denotes a time lag used in one form of function *f*₂. The parameters *a*, *c*, *p*, and *q* represent the asexual form replication rate, the capture/removal rate, and the decay rates for gametocytes and immune effectors, respectively. Specific forms of the functions *f*₁ and *f*₂ represent common hypotheses in the malaria literature.

The three forms (A, B, and C) of the parasitologic function *f*₁ represent the rate of gametocyte conversion as A) a constant proportion of the asexual forms *M*, such that *f*₁ = *g*_A*M*; B) proportional to the rate of contact between the immune effectors *I* and the asexual forms *M*, such that *f*₁ = *g*_B*IM*; and C) proportional to the rate of contact among the asexual forms *M*, such that *f*₁ = *g*_C*M*².

The three forms (1, 2, and 3) of the immunologic function *f*₂ represent the rate of immune-response reaction as A) a constant proportion of the asexual forms *M*, such that *f*₂ = *s*₁*M*; B) proportional to the rate of contact between the immune effectors *I* and the asexual forms *M*, such that *f*₁ = *s*₂*IM*; and C) a constant proportion of the asexual forms *M* present at the point in time (*t* - *L*), i.e. the point *L* time units previous, such that *f*₂ = *s*₃*M*(*t* - *L*).

For each of the resulting nine systems of equations we obtained numerical approximations to solutions, in most cases setting parameter values *a* = 1.39, *p* = 0.28, and *q* = 0.01 and initial conditions *M*₀ = 0.01 or 0.1, *G*₀ = 0, and *I*₀ = 0.00001. These values are consistent with the relevant empirical literature, as described in detail elsewhere.³⁴ We did not consider solutions in which values of *M* exceeded 1,000,000, roughly a 20% parasitemia.

For comparisons to empirical data we used criteria essentially identical to those of Kitchen and Putnam,³⁵ focusing on the magnitude and timing of peak asexual-form parasitemia and gametocytemia. To the five patient's charts included in their paper we added nine other such

charts,^{36–38} partial charts constructed from other studies,³⁹ and information from two recent reviews of gametocyte biology.^{13, 17} Almost all of this data is clinic-based, with corresponding biases,³⁴ but we found no alternative sources of comparably detailed information.

RESULTS

Since for each of the nine models at least some small region of parameter space fits the bounds of our *P. falciparum* criteria, it appears that none can be excluded solely on the basis of the data we considered. Several additional criteria that might be used to assess models and focus further empirical research are examined elsewhere.³⁴

For models that include an immunologic function of form 1 or form 3, peak M values decrease as any of the parameters c, g, or s increase. That is, as one would expect, any improvement in the sensitivity or capture efficiency of the immune response with respect to the asexual forms will decrease peak asexual-form abundance. More interestingly, increasing the coefficient of conversion to the sexual form has the same effect. For models that include an immunologic function of form 2, (A2, B2, C2), our results are more complex: as c increases, peak M values increase monotonically if s is very small (typically < 0.03) but exhibit a concave response to c with higher s values. Thus, increasing the capture efficiency of the immune response does not always decrease the peak asexual-form abundance; in fact for very low sensitivities it always increases it. As the parameters g or s increase, peak M values decrease monotonically; in model A2 this response of M to increasing g is consistent but considerably subdued in regions with small s values. Figure 1 illustrates the generalized decrease in peak asexual-form abundance with increasing values of the parameter g and indicates that the sensitivity of this response might be used to discriminate among models.

DISCUSSION

Transformations from asexual to sexual form represent an inherent constraint in *Plasmodium* biology, an unavoidable and irreversible exchange of one growth rate and growth mode for another. Scattered in vitro studies have identified various biochemical modulators of gametocytogenesis such as steroid hormones,⁴⁰ phorbol diesters,⁴¹ cyclic AMP,⁴² hypoxanthine,⁴³ and a nucleic-acid synthesis inhibitor.⁴⁴ These agents are of uncertain physiologic relevance to malaria, and as yet few clinical reports juxtapose gametocyte production, asexual parasitemia, and disease symptoms. Nonetheless, our results argue that focused research along these lines might yield unanticipated benefits: if severity is in any manner causally associated with peak asexual-form density or with the rate at which that peak is attained, interventions that boost gametocytogenesis should improve prognosis. The prospect of deploying a vaccine, a drug, or any agent with the specific aim of increasing gametocyte production is too remote and too intimidating to contemplate in general populations, but there may be clinical settings in which such applications would be more restricted, protected, and urgent.

Empirical data that bear on the question are few and puzzling. In his pioneering study of naturally acquired clinical malaria cases in Caucasians, Thomson³⁷ noted positive relationships among patient age (and previous exposure), leukocyte proliferation, levels of gametocyte production, and mildness of symptoms. He used the ratio of sexual to asexual-form peaks to measure “gametocyte producing power” and found to be this 10-fold higher in mild cases. Kitchen and Putnam³⁵ reported appreciably higher ratios of sexual to asexual forms in patient groups that cleared infections without treatment than in those that required drug intervention. Sinton and others⁴⁵ observed that mild cases, with scanty asexual forms, were the more likely gametocyte producers among British patients, but in acute cases among Indian patients, those with the most numerous asexual forms were the most likely to produce

gametocytes. Jeffery's⁴⁶ analysis of a *P. falciparum* strain that had lost its gametocyte-producing capacity noted that the strain had apparently retained its previous levels of asexual parasitemia and clinical response.

Koella and Antia⁴⁷ recently developed a model that resembles our model A1: it also describes a pathogen in which replicating stages interact with simple immune agents and terminally differentiate into transmission stages. Their objectives and results, unlike ours, encompass host mortality (by setting a lethal pathogen density) and transmission success (as proportional to transmission-stage density). We support their conclusion that an optimizing pathogen should delay production of its transmission stages, in the circumstances described, until just before its replicating stages kill its host or are cleared by its host's immune system; this appears to follow directly from conjoining an arithmetic growth of transmission stages and a geometric growth of replicating stages.³⁴ On the basis of work in progress we also agree that intermediate levels of investment in transmission stages may maximize pathogen transmission (albeit not necessarily pathogen numbers) and that optimal investment may depend on the specifics of interactions between pathogens and host immune mechanisms.

A natural *P. falciparum* infection may be a genetically diverse mixture of parasites, which may differ in gametocyte production, drug resistance, immunogenic profile, and other traits.^{20, 48–50} This diversity may also be of clinical importance. For instance, the fraction of infections that are symptomatic or drug-resistant may derive from the frequencies of recombination among parasite clones, mediated by local characteristics of transmission.^{51, 52}, but see ^{53, 54} Although it appears that parasite diversity could not affect the key result presented here, it is important to note that in their current form the underlying models do not encompass any aspect of mixed malaria infections. Given that gametocytes are the currency of *Plasmodium* evolution, it seems likely that their production is a fulcrum of intraspecific and interspecific interactions.^{55, 56}

Our models do not address any aspect of the parasite's erythrocytic environment.^{57–60} Most critically, our caricature of the human immune response is merely that. Our models could be extended by incorporating key features of other models with respect to mixed-genotype infections, erythrocytic environments, more precise immune characteristics, and other factors.^{61–67} However, it seems unlikely that these shortcomings substantially bias our conclusion: our conclusion follows from the observation that an asexual form that becomes a gametocyte does not become multiple asexual forms. Such diversions may have corresponding clinical benefits, which might be amplified by targeted intervention. We hope that further empirical studies will provide insights into this intriguing possibility.

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Figure 1.

Curves illustrating the result that for all parameter sets in all models increasing values of the parameter g lead to decreases in peak asexual-form densities. The two panels represent models with **A**, the three different forms of the immunologic function f_2 , with parameter settings $c = 0.01$ and $s = 1.4$ for A1 and A3, $s = 0.07$ for model A2, and **B**, the three different forms of the parasitologic function f_1 , with parameter settings $c = 0.001$ and $s = 1.4$. For model A3 the time lag $L = 0.7$. Horizontal axes represent values of g and vertical axes represent the base 10 logarithm of per microliter peak M abundance. With increasing values of g , peak M values in these examples show decreases of **A**, 67% for model A3, 17% for A1, and 7% for A2, and

B, 59% for model B1, 54% for C1, and < 1% for A1. Note that the simplest, doubly-linear model, A1, is common to both panels and shows relatively flat responses in each.