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Dynamic regulation of single- and mixed-species malaria infection: Insights to specific and non-specific mechanisms of control

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Abstract

Our increasing appreciation of the high prevalence of mixed-species *Plasmodium* infection in malaria-endemic regions has resulted in controversy regarding the likely mechanism(s) of regulation for mixed parasite burden within an individual human host. In the present study, we examined dynamic models of *Plasmodium* spp. regulation by fever and by non-specific (NS) and species-specific (SS) immunity (including the influence of their variable time-delays, duration, and efficacy) in order to assess the likely role of these factors in regulating detectable parasitemia and clinical disease. Our models suggest that in order to observe the irregular waves of fever and parasitemia that are often found in multiply infected subjects, there must be a differential SS immune effect (beyond the regulatory effects of the species-transcendent density-dependent factors previously posited to control mixed-species parasitemia), and time-dependent variation in immunity to the dominant species. By implementation of individual SS immune controls of non-permanent duration, the resulting multi-dimensional model can be viewed as multiple single-species oscillators coupled via a NS species-transcendent controller. This extended model exhibits the essential patterns of long-term mixed infections. Although this 'circuit-immunity' model gives only a qualitative estimate of the complex web of participating agents and reaction pathways, it provides a starting point for future studies of the specific and NS within-host mechanisms that regulate mixed-species malaria infection.

Keywords: Model; Theoretical; Nonlinear dynamics; Plasmodium infections; Malaria; Immunity; Non-specific; Immunity; Specific

1. Introduction

Malaria remains one of the most prevalent and lethal human infectious diseases worldwide (White, 2003). Increasingly sensitive DNA-based testing methods now indicate that a significant minority or even a majority of persons residing in malaria-endemic areas are concurrently infected with two or more *Plasmodium* species (Mehlotra et al., 2000; Purnomo et al., 1999; Snounou et al., 1993; Zhou et al., 1998). In different malaria-endemic regions, infected individuals exhibit varying patterns of detectable *Plasmodium* spp. parasitemia, and, depending on study methodology, conflicting conclusions have been drawn regarding the routine prevalence and clinical significance of mixed-species malaria (Genton et al., 1995; Luxemburger et al., 1996; Molineaux et al., 1980; Postigo et al., 1998); for reviews, cf. McKenzie and Bossert (1997) and Richie (1988)). In particular, controversy persists over the relative importance of non-specific (NS) vs. heterologous immune mechanisms of cross-species interaction, and their contribution to varying levels of infection and disease within the multiply infected individual host (Bruce and Day, 2004; Mason and McKenzie, 1999; Snounou, 2004; Zimmerman et al., 2004).

In the pre-antibiotic era (1930–1940), both single- and combined-species malaria fever therapies were given to groups of patients with chronic bacterial infections in an attempt to ameliorate their diseases (Boyd and Kitchen, 1937, 1938). Data from these studies, as well as studies of naturally infected study volunteers (Jeffery, 1966), have illustrated a large range of clinical and parasitological outcomes (from orderly to seemingly chaotic patterns of

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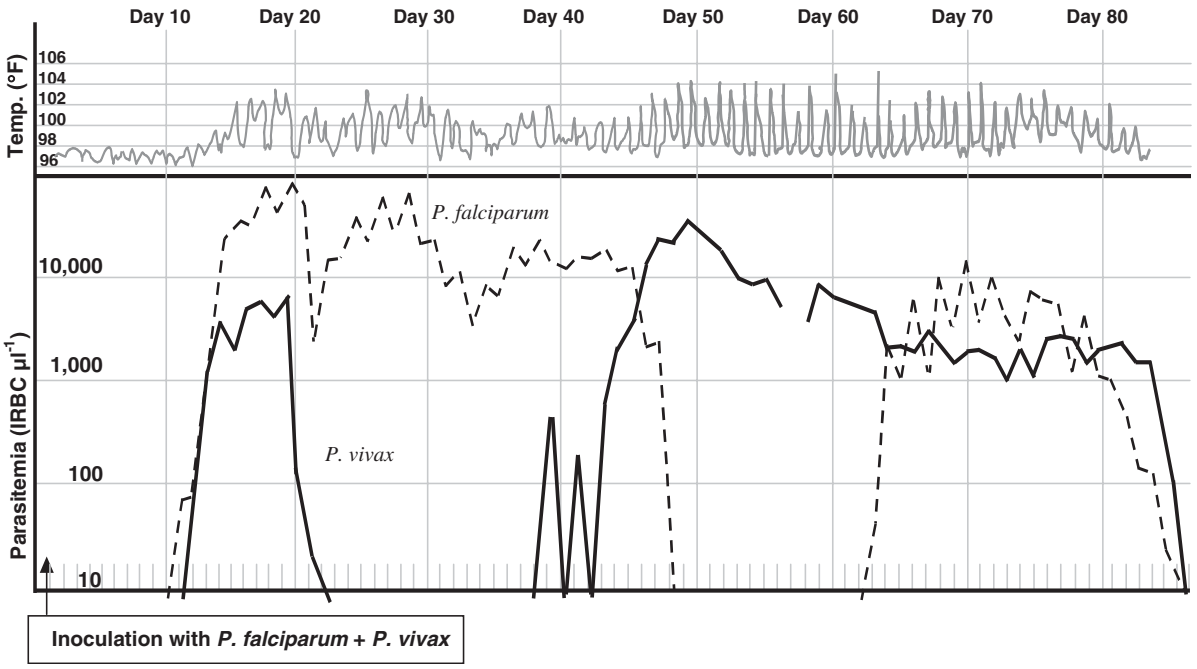

Fig. 1. Typical clinical history of a Boyd and Kitchen (1938) patient shows intermittent cycles of *P. falciparum* and *P. vivax* parasitemia (lower panel), with corresponding periods of intermittent or daily fever (upper panel).

species-specific (SS) parasitemia, see Fig. 1) among individuals with multi-*Plasmodium* species infections (Boyd and Kitchen, 1937, 1938; Bruce et al., 2000; Jeffery, 1966; Molineaux et al., 2002). Antimalarial treatment trials have also contributed to insight regarding mixed-species *Plasmodium* infections, in that undocumented infection with a second untreated species is frequently unmasked following successful treatment of a presenting 'symptomatic' species (for review, see Mayxay et al., 2004).

The impetus to understand the factors that constrain erythrocyte infection by human parasite species is at least three-fold: first, only blood-stage infections are associated with clinical pathogenesis; second, if it were possible to identify the factors responsible for limiting or killing blood-stage parasites, chances for advancing strategies to develop vaccines against all four human *Plasmodium* species parasites would improve; third, if interspecies effects prove to be physiologically significant, a policy of selective elimination of one human malaria species might increase the pathogenesis caused by the remaining species.

Some of the biological mechanisms that are proposed to influence the parasitemia of multiple infection include (a) species competition for location and resources (erythrocytes), (b) innate host immune effector responses, (c) acquired host immune effectors (or more likely a contribution of both), and (d) human genetic factors that limit erythrocyte invasion. Considering these biological mechanisms, it follows that regulation of parasitemia may be species- or strain-specific (SS), or as recently proposed, species-transcending, yielding a net 'density-dependent' limitation on overall *Plasmodium* infection (Bruce and Day, 2003; Bruce et al., 2000; Good et al., 1998; Harpaz et al., 1992).

Our goal in the present paper is to study the observed features of host regulation of blood-stage parasitemia in both single and multiple *Plasmodium* species infections, using dynamic systems approach. Given the complexity of human immunity, which is made of multiple cell-types, cytokines, signaling pathways, antigens etc., we take a reductionist approach based on the immune system's functional processes and the timing of its effects, rather than its actual components. From this standpoint, the immune system can be thought of as self-regulating feedback circuit, which gets input/stimulation from parasite antigens and responds by clearing them with suitable effector mechanisms (see e.g. Herzenberg and Black, 1980).

One of the earliest models along these lines involves four populations—uninfected and parasitized red blood cells (RBCs), free merozoites, and immune effector responses, which are coupled by a system of differential equations that represent the basic processes of growth, stimulation, clearance, and loss (Anderson et al., 1989). More recent models have exploited both discrete (stochastic) and continuous formulations (Recker et al., 2004; Molineaux et al., 2001; Paget-McNicol et al., 2002). Some of these have been limited to *Plasmodium falciparum* (Pf) dynamics and, in particular, this species's immune evasion strategies (e.g. surface antigen variation) in explaining its observed complex patterns of parasitemia.

Our present approach follows extensive earlier work of Mason and coworkers, who developed a model of mixed malaria infection (*P. falciparum*/*P. malariae* (Pf–Pm) and *P. falciparum*/*P. vivax* (Pf–Pv)), regulated by innate (NS)