

Modelling the immune response to malaria with ecological concepts: short-term behaviour against long-term equilibrium

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SUMMARY

A model for the human immune response to the malaria parasite *Plasmodium falciparum* is used to analyse the dynamics of an infection within an individual patient. Previous models either looked at competition between two parasite genotypes or at one parasite clone and the immune response to it. This model describes the course of an infection caused by the blood stages of two parasite genotypes differing in reproductive rate and in the immune response they elicit. The interactions between the genotypes can be interpreted as exploitative competition for red blood cells. Interactions between omnipotent immune cells and parasites resemble a predator–prey relation. In analysing these kinds of models, classical theoretical ecology usually deals with long-term behaviours, i.e. looks for equilibria and conditions for coexistence. However, especially in endemic regions with ongoing transmission, an equilibrium state of infections is unlikely. When reinfections with another parasite genotype were considered, the short-term dynamics of the infection changed dramatically, depending on which genotype was first, when the second one appeared, and what kind of immune response was elicited. If the slow development of immunity to malaria really is due to its genotype specificity, the effects of superinfections will be of great importance.

1. INTRODUCTION

The general mechanisms leading to immunity against malaria and many other parasitic diseases are still poorly understood (e.g. for malaria, see Day & Marsh (1989)). The complexity of the malaria system, where several cell types of the host immune system and different parasite stages are involved, strongly suggests the use of mathematical modelling to gain new insights. The present model aims to increase our limited understanding of the initial dynamics of a malaria infection within an individual patient. To this end it refers to knowledge from theoretical ecology as well as from parasite immunology (see Anderson 1991). Of particular interest here is the relative importance of short-term and long-term behaviour for a single human host and his parasites.

The present approach extends a model formulated by Anderson *et al.* (1989) which describes the immunological responses directed against the asexual forms of the malaria parasite *Plasmodium falciparum*. Their model gives insights into the relative merits of humoral against cell-mediated responses in controlling the parasite within a single human host. For their purposes they assumed a genetically homogeneous parasite population. However, blood samples taken from malaria patients frequently contain mixtures of enzyme types or serotypes, which means polymorphism in parasites either defined by electrophoretic variants of enzymes or serologically different antigens (see, for example, Thaithong *et al.* 1984). This suggests that

these mixtures consist of genetically distinct clones of the same species. Conway *et al.* (1991) detected a mean of two *P. falciparum* clones in the blood of patients in The Gambia. In general, between 30% and 83% of *P. falciparum* infections consists of more than one clone (Day *et al.* 1992). These multiple infections are either the result of a single mosquito inoculation containing different genotypes or of sequential inoculations by different mosquitoes (superinfections). Infections caused by several parasite genotypes should lead to competition between them via different reproductive rates and different abilities to invade erythrocytes. The immune system reveals additional differences between parasite genotypes with respect to protection against immunological attacks, for example in the abilities to vary antigen or suppress parts of the immune system (Mendis *et al.* 1991).

This pattern of competition in the presence of an immune response can be modelled by using ecological concepts such as exploitative and predator-mediated competition. The model presented here uses both to analyse an infection with two parasite genotypes. It takes into account genotype-specific as well as non-specific immune reactions, and the consequences of superinfections can be analysed. In exploring such models, classical theoretical ecology usually deals with long-term behaviours, i.e. looks for equilibria and conditions that allow coexistence (May 1976; Yodzis 1989). However, when the malaria system as a whole is considered, where survival in a given human host and in the whole host population are equally

Table 1. *List of parameters*

(Where explicit values are given they are chosen as in Anderson *et al.* (1989); the death rate of mature gametocytes stems from Miller (1985).)

x	density of uninfected red blood cells (erythrocytes)
y	density of erythrocytes infected with erythrocytic meronts (asexual)
g	density of erythrocytes carrying gametocytes (sexual)
s	density of merozoites (invasive form)
I	density of immune cells
A	constant recruitment of erythrocytes from the bone marrow ($A = 1$)
μ_x	natural death rate of erythrocytes [$\mu_x = 1/120$ (1/days)]
β	rate of infection of erythrocytes by merozoites
r	merozoites released per dying infected erythrocyte ($r = 16$)
μ_y	death rate of infected erythrocytes [$\mu_y = 1/2$ (1/days)]
α_s	death rate of merozoites [$\alpha_s = 1/20$ (1/min)]
α_g	death rate of gametocytes [$\alpha_g = 1/16$ (1/days)]
c	rate of differentiation of asexual parasites into gametocytes
γ	proliferation rate of immune cells in response to infected erythrocytes
λ	proliferation rate of immune cells in response to gametocytes
σ	proliferation rate of immune cells in response to merozoites
k	elimination rate of infected erythrocytes through the immune cells
l	elimination rate of gametocytes through the immune cells
h	elimination rate of merozoites through the immune cells
μ_I	death rate of immune cells [$\mu_I = 1/20$ (1/days)]
ϵ	background replication of immune cells

important, the question of the relevant timescale for within-host dynamics arises: which part of an individual infection is crucial for the survival and transmission of the parasite as well as the state of health of the patient, e.g. for his degree of anaemia? What does the model tell us about the course of an untreated malaria infection and the consequences of super-infections?

(a) *Falciparum malaria*

Human malaria is caused by four species of the genus *Plasmodium* (Protozoa). *P. falciparum* causes the most serious illness and is responsible for 90% or more of world-wide malaria morbidity and mortality. Its complex life cycle comprises several stages, and alternates between a human host and a female mosquito vector (*Anopheles*). After being transmitted by a biting mosquito, the infectious sporozoites enter liver parenchyma cells within minutes. Following one generation of asexual multiplication (one week), which is not accompanied by illness, each sporozoite releases about 30000 merozoites into the blood stream. Within a few minutes they invade red blood cells (erythrocytes), thereby initiating the erythrocytic cycle. This cycle is a repeated sequence of replication within

erythrocytes, release of 8–32 merozoites per infected cell, and rapid penetration of new erythrocytes. The cell rupture is highly synchronized, occurs every 48 h (for an explanation see Kwiatkowski & Nowak (1991)), and is accompanied by fever. The asexually proliferating stages within erythrocytes are called erythrocytic meronts. Some of them differentiate into the sexual forms (gametocytes). Infectious gametocytes are responsible for transmission back to a mosquito. In the mosquito, maturation into extracellular gametes followed by sexual reproduction and asexual multiplication (sporozoites) concludes the life cycle. Usually a mosquito gut contains one to three oocytes, each of which gives rise to about 1000 sporozoites.

(b) *The human immune response*

In higher organisms, parasitic diseases usually stimulate more than one host defence mechanism. Which response dominates, humoral (antibodies) or cell-mediated (macrophages, T- and B-cells), specific or non-specific, depends on the parasite. Generally cell-mediated responses are more effective against intracellular parasites. In malaria, such responses combat the intracellular parasite stages in liver and blood. These non-antibody mechanisms, in which immunoregulatory molecules (cytokines) are thought to be important, can affect the growth of the parasite within erythrocytes (Mendis *et al.* 1990). Antibodies directed against merozoites can partly prevent the reinvasion of erythrocytes.

Although more details about the immune response against malaria are known, ‘no clear picture of the mechanisms of naturally acquired immunity has emerged yet’ (Day & Marsh 1991). However, it seems that within a *Plasmodium* species several serotypes or genotypes differ in resistance, depending on a variety of ‘immune response genes’ (Roitt *et al.* 1989). Thus, in addition to slow development and dependence on reinfections, the major characteristics of immunity to malaria are species-, genotype- and stage specificity.

2. THE MODEL

The model studies the dynamics of the different host and parasite cell types in the bloodstream during the main part of the *P. falciparum* life cycle in its human host. At a given time t we denote the densities of uninfected erythrocytes by $x(t)$, of erythrocytic meronts (here called infected erythrocytes) by $y(t)$, of gametocytes by $g(t)$, and of merozoites by $s(t)$ (complete list of parameters in table 1). Erythrocytes are assumed to be produced by the bone marrow at a constant rate A , to die naturally at the fixed rate μ_x , and to be infected by contact with merozoites at the rate β . Multiple infections of single erythrocytes are considered negligible. Thaithong *et al.* (1984), for example, found only about 5% of erythrocytes with two or more parasites. Infected erythrocytes die rapidly at the rate μ_y , thereby releasing r merozoites per cell. Merozoites die at rate α_s . A proportion c of the infected erythrocytes develop into gametocytes; thus a linear relation between the two densities is assumed. Gametocytes die at rate α_g .

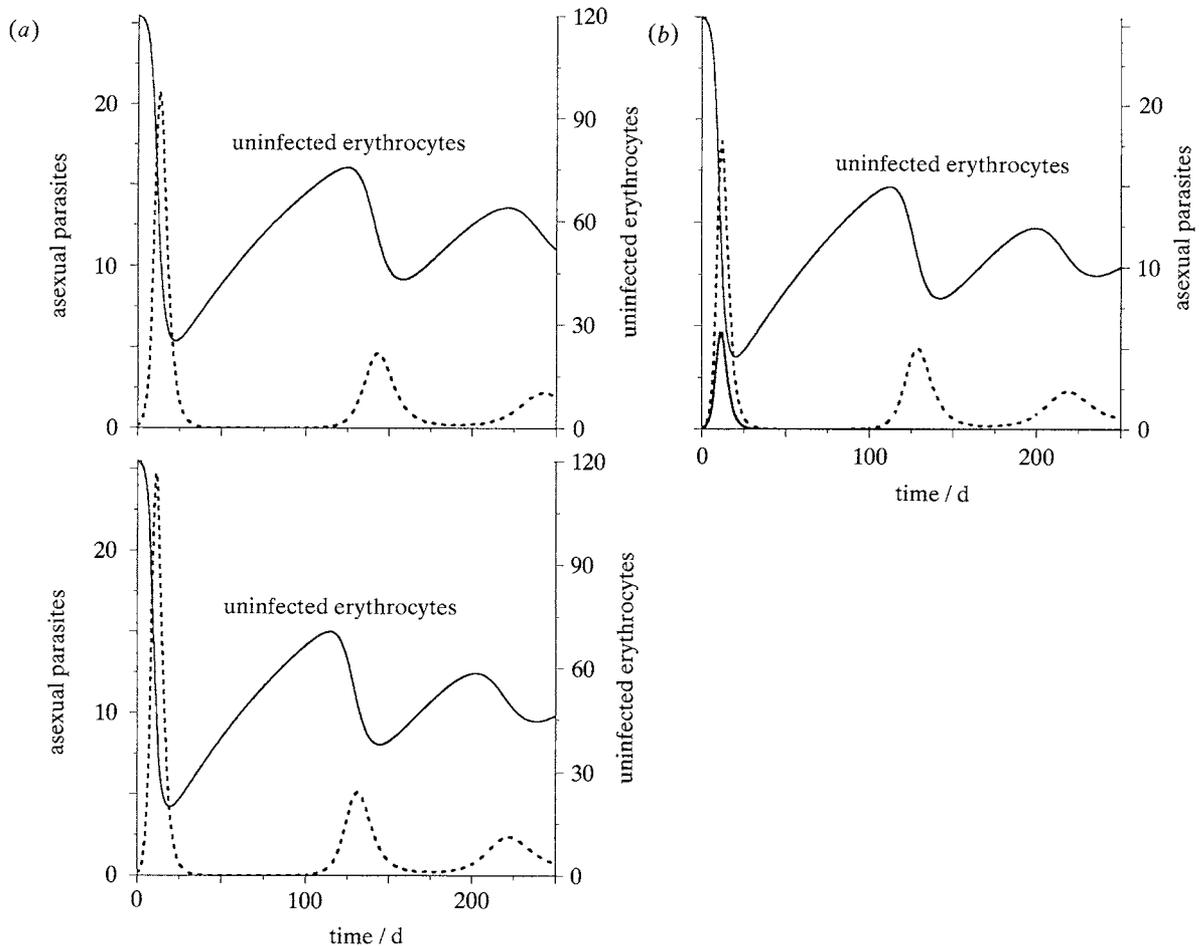


Figure 1. The influence of competition in the absence of any immune response. (a) The timecourse of an infection with either asexual parasite (broken line) genotypes 1 (above) or 2 (below) is shown and the respective influence on the level of uninfected erythrocytes. (b) The outcome of competition for the two genotypes. Whereas genotype 1 (thick line) is eliminated completely after its first peak parasitaemia (concentration of asexual parasites in the blood), genotype 2 (broken line) reaches a low equilibrium density ($y_2^* = 1.21$, $g_2^* = 0.36$, $s_2^* = 0.12$ and $x^* = 50.05$). The specific parameters for the two genotypes are set to $\beta_1 = 0.09$, $c_1 = 0.018$ and $\beta_2 = 0.1$, $c_2 = 0.02$ (compare with Anderson *et al.* 1989).

(a) Competition between two parasite genotypes

Competition is assumed to imply differences in the rate of infection of erythrocytes (β) and the rate of differentiation into gametocytes (c). As indicated in table 1, some of the parameters are thought to be fixed for both genotypes ($\mu_y, \alpha_g, \alpha_s, r$).

The formalization of these assumptions leads to seven coupled autonomous ordinary differential equations for the changes in $x(t)$, $y_i(t)$, $g_i(t)$ and $s_i(t)$ with respect to time:

for uninfected erythrocytes,

$$dx/dt = A - \mu_x x - \sum_{i=1}^2 \beta_i s_i x; \quad (1)$$

for infected erythrocytes,

$$dy_i/dt = \beta_i x s_i - \mu_y y_i - c_i y_i, \quad (2), (3)$$

for gametocytes,

$$dg_i/dt = c_i y_i - \alpha_g g_i; \quad (4), (5)$$

and the merozoites,

$$ds_i/dt = \mu_y r y_i - \alpha_s s_i - \beta_i x s_i; \quad (6), (7)$$

where the subscript i denotes the genotype ($i = 1, 2$).

Although the parasite life cycle is synchronous, I used a continuous time model because infected cells are continuously present in the blood and the immune response as a whole is not synchronized.

(b) Incorporating the immune system

The model assumes that the immune system can be represented by a single omnipotent cell type, the 'immune cell'. These immune cells are assigned all the abilities of antibodies, T-cells, B-cells and macrophages. Thus, whereas genotype specificity becomes one of the main features of the immune response, details concerning mechanisms are ignored. As a consequence, the different immunorelevant structures of a parasite genotype are treated as fixed for all its life stages (but see Mendis *et al.* 1991). The density of immune cells is denoted by $I(t)$, their natural death rate by μ_I . They are thought to be stimulated to proliferation by each parasite stage separately, that is, to reproduce by fission at rates proportional to their own density times the respective densities of merozoites, infected erythrocytes and gametocytes ($\sigma I s + \gamma I y + \lambda I g$, see equations (14), (15) and table 1). The immune

response is assumed to result in inactivation or death of merozoites, infected erythrocytes, and gametocytes at a net rate proportional to the density of immune cells (hsI , κyI , lgI , respectively, equations (8)–(13) and table 1). Genotype-specific inactivation of parasites together with genotype-specific stimulation of the immune cells is referred to here as a ‘simple’ immune response whereas the case including a non-specific component is termed cross immunity.

These assumptions lead to an additional equation of Lotka-Volterra type for the immune cells and a modification of equations (2)–(7) to include the specific and non-specific inactivation of each parasite stage:

for infected erythrocytes,

$$dy_i/dt = \beta_i xs_i - \mu_y y_i - c_i y_i - \left(\sum_{j=1}^2 k_{ij} I_j \right) y_i; \quad (8), (9)$$

for gametocytes,

$$dg_i/dt = c_i y_i - \alpha_g g_i - \left(\sum_{j=1}^2 l_{ij} I_j \right) g_i; \quad (10), (11)$$

for merozoites,

$$ds_i/dt = \mu_y ry_i - \alpha_s s_i - \beta_i xs_i - \left(\sum_{j=1}^2 h_{ij} I_j \right) s_i; \quad (12), (13)$$

and for immune cells,

$$dI_i/dt = I_i(\sigma_i s_i + \gamma_i y_i + \lambda_i g_i - \mu_i) + \epsilon/2; \quad (14), (15)$$

where k_{ii} , l_{ii} , h_{ii} ($i = 1, 2$) represent genotype-specific, and k_{ij} , l_{ij} , h_{ij} ($i \neq j$) non-specific, elimination or inactivation of the different parasite stages, respectively. Immune cell stimulation is thought to be specific only ($\sigma_i s_i + \gamma_i y_i + \lambda_i g_i$, see equations (14) and (15)). The term ϵ denotes the very low background replication of immune cells independent of any external stimulation through parasites.

3. RESULTS OF ANALYSIS AND SIMULATIONS

(a) *The basic model and competition*

Two situations without an immune response were used to establish a reference point: an infection with only one parasite genotype (basic model, see Appendix), and the case of two competing genotypes. When only one genotype was present, the densities of uninfected erythrocytes and the three parasite stages eventually reached equilibrium values (equations (A 1)–(A 4), see Appendix). If two parasite genotypes were competing for erythrocytes, no coexistence was possible (figure 1*b*). Nevertheless, by growing until the erythrocyte level fell below a critical value (x_c , see Appendix), both clones could build up a first peak of parasitaemia simultaneously. These first peaks were lower than that achieved by one genotype only (figure 1*a*). The reduction was more pronounced for the genotype with the lower values for the infection rate of erythrocytes and for the rate of differentiation into gametocytes (figure 1). The parasite genotype that had the lower erythrocyte threshold was the one that prevailed in the long run. Although the other genotype was eliminated after its first peak, the superior one reached its equilibrium of the basic model.

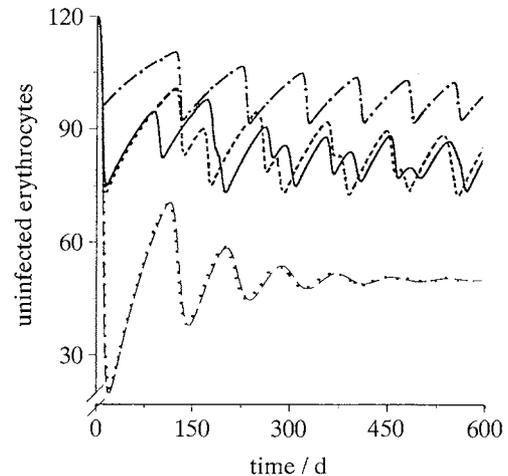


Figure 2. The long-term behaviour of the erythrocyte level. The number of parasite genotypes and the presence or absence of an immune response influences the level of uninfected erythrocytes (defined in arbitrary units). The erythrocyte abundance is of importance for the parasites as a resource and for the patient in terms of the degree of anaemia and therefore for survival in both cases. Without an immune response, the curves for one (lower broken line) and two (dotted line) parasite genotypes are identical (the simulations started with the same initial parasite density in both cases, with two genotypes this means half of the value each). Also shown are the curves for one parasite with immune response (dot-dash line), two parasites with simple immune response (broken line) and two parasites with cross immunity (solid line).

(b) *Including an immune response*

In the presence of an immune response, two cases were considered: a simultaneous and a successive appearance of the two parasite genotypes in the blood stream.

When the two genotypes were assumed to appear at the same time the following results were obtained. First, the level of uninfected erythrocytes was significantly higher when an immune response was taken into account (figure 2). Second, despite this fact, erythrocytes as a common resource of the two genotypes could still be limiting if the background replication and the initial densities of the respective immune cells were low (figure 3). When the resource level fell below a critical value, the parasite population crashed before the immune cells had reached a high enough density to have had substantial effects. In this case the threshold was approximately the same with an immune response as without it, due to the very slow initial growth of the immune cell population ($x_{ei} > x_c$ for $i = 1, 2$; figure 3). Third, the first peak parasitaemia of the parasite genotype that had been superior in competition was greatly reduced. Fourth, coexistence of the two parasite genotypes was possible in some cases in the presence of an immune response while there was none in its absence. However, the genotypes were present simultaneously only during the first peak of their parasitaemia (figure 4) even in situations where they could coexist. Fifth, the immune system not only prevented the elimination of the inferior genotype after its first peak parasitaemia but also allowed for a second

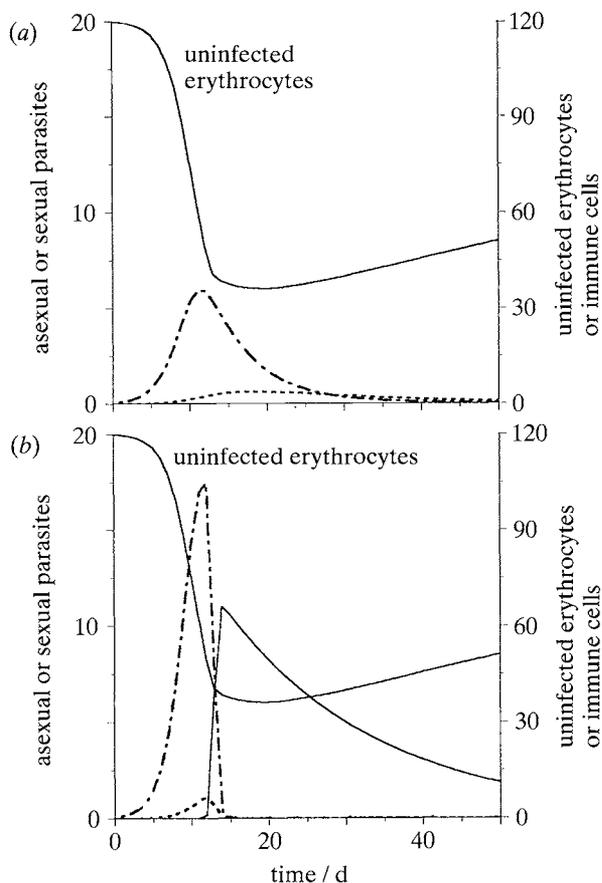


Figure 3. The limiting effect of the resource. The two parasite genotypes are competing in the presence of an immune system with a very low background replication of immune cells ($\epsilon = 10^{-8}$; other parameters as in figure 4). (a) The first peak parasitaemia of genotype 1 is not high enough to stimulate a noticeable immune response ($I_1 < 0.63$). Thus the parasite density crashes because the erythrocyte abundance passes a critical level ($x_c = 55.38$; see Appendix). (b) Although the density of genotype 2 elicits an immune response (immune cells, lower solid line) it breaks down before the immune cells have had substantial effects ($x_c \approx 50.05$). Here the effect of the immune response mainly is to accelerate the elimination of the parasite (compare steepness of peaks in (a) and (b)). Asexual parasites (dot-dash line), sexual parasites (broken line).

peak of this genotype before the better genotype had its second one (compare figures 1b and 4). Those second peaks were equally high. In the case of cross immunity, the difference between the first peaks of the two genotypes was a bit more pronounced (not shown). However, the inferior first genotype could build up a second and third peak while the better one had only had a second peak during the same time period (about 200 d).

If the parasite genotypes entered the blood successively with a delay of two or more days, as expected the long-term behaviour of the system remained the same as in a simultaneous start. But the short-term behaviour changed dramatically depending on who was first, when the second genotype appeared, and what kind of immune attack was elicited (figure 5). With cross immunity, the interesting cases were those in which the first genotype was inferior in competition. If, for example, the second (better) genotype came 2 d later,

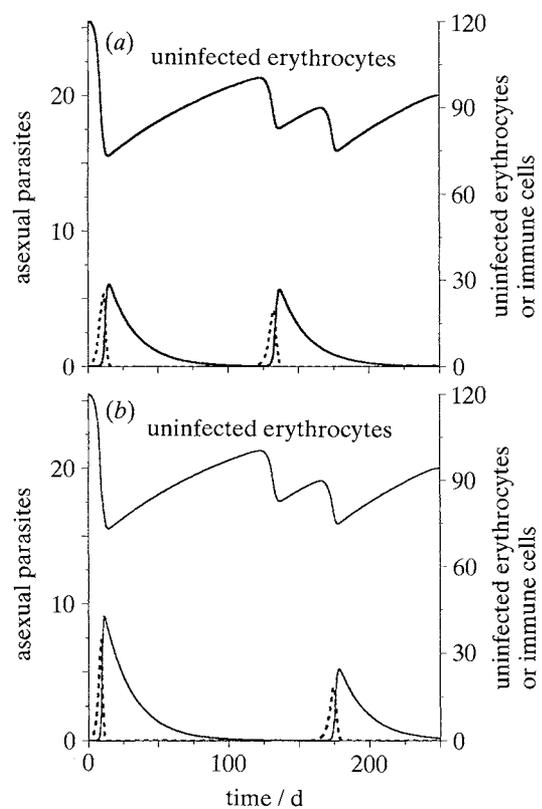


Figure 4. The influence of the immune system. The consequences of competition between two asexual parasite (broken line) genotypes ((a) genotype 1, (b) genotype 2) in the presence of a 'simple' immune response (immune cells, lower solid line) are depicted (no cross immunity). There are specific immune cells for each parasite genotype ($k_{11} = 0.05$, $\gamma_1 = 0.1$, $h_{11} = 0.1$, $\sigma_1 = 1$, $l_{11} = 0.05$, $\lambda_1 = 0.1$, $k_{22} = 0.06$, $\gamma_2 = 0.12$, $h_{22} = 0.12$, $\sigma_2 = 1.2$, $l_{22} = 0.06$, $\lambda_2 = 0.12$; compare with Anderson *et al.* (1989), $k_{ij} = h_{ij} = l_{ij} = 0$ for $i \neq j$ and $i, j = 1, 2$, $\epsilon = 0.01$). The parameter values representing competition are as in figure 1. Comparing the peak parasitaemias shown here with those of figure 1b illustrates the additional influence of the immune system.

then both parasites could develop comparable levels of parasitaemia nearly simultaneously (figure 5a). If the second infection was introduced at the peak parasitaemia of the first genotype, that is 9 d later, then the first density peak of the second (better) genotype was both greatly reduced and shifted to a later point in time than when it was present alone (figure 5b). When the first parasite was superior in competition and cross immunity was included, there was no chance for the second (inferior) one to build up a considerable parasitaemia (not shown).

4. DISCUSSION

The questions posed in the introduction concerned the relevant timescale for analysing the course of an untreated malaria infection and the consequences of superinfections. Here I contrast the natural course of an infection with the behaviour of the model to suggest some answers.

In the model, the interactions between parasite genotypes and immune cells are modelled in analogy to

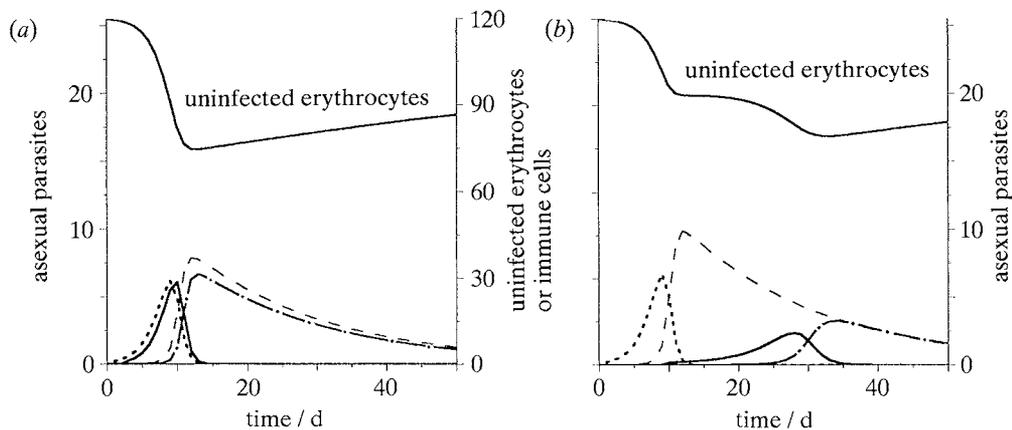


Figure 5. Superinfections. The effects of a time shift between the first (dotted line) and the second (solid line) parasite genotype entering the blood system are shown. The second genotype is superior with respect to competition (compare with figure 1). The immune response is genotype specific and includes cross immunity ($\gamma_i, \sigma_i, \lambda_i$ for $i = 1, 2$ and ϵ as in figure 4, $k_{11} = 0.045$, $h_{11} = 0.09$, $\iota_{11} = 0.045$, $k_{22} = 0.054$, $h_{22} = 0.108$, $\iota_{22} = 0.054$, and additionally $k_{12} = 0.005$, $k_{21} = 0.006$, $h_{12} = 0.01$, $h_{21} = 0.012$, $\iota_{12} = 0.005$, $\iota_{21} = 0.006$). (a) The second parasite enters the human blood system 2 d later. (b) The second parasite comes when the first has reached its peak, that is, 9 d later. Immune cells against parasite 1 (broken line), immune cells against parasite 2 (dot-dash line).

ecological interactions. Erythrocytes play the role of a common resource in exploitative competition between the two genotypes. The immune cells act like predators on the three parasite stages, either with or without overlap in their food niches, depending on whether cross immunity is included or not. Thus from an ecological point of view some of the results are not surprising: that a resource shared by two competitors benefits from the presence of their predators but still can be a limiting factor (figures 2 and 3) and that predators can mediate coexistence of their prey. These results mainly describe the long-term behaviour of malaria–man interactions within one host.

For parasites confined to a single host, the situation described by the model, two things are most important. They must build up high levels of asexual parasitaemia leading to effective gametocytogenesis, and gametocytes must be highly infectious to mosquitoes.

First, to multiply effectively within a given host a parasite must evade the immune system, and in cases of superinfections a specific parasite genotype must be affected by the presence of other genotypes as little as possible. So, how does an untreated primary *P. falciparum* infection look from the point of view of the parasite? If an infection results in recovery and not in death, the human immune system brings the erythrocytic parasite stages under control only after a variable number of erythrocytic cycles. The parasite, therefore, is able to build up a high first peak of parasitaemia. This peak is followed by a sudden decrease in the numbers of circulating parasites to non-clinical levels. Afterwards a low but fluctuating level of parasites is interrupted by occasional outbreaks (Kreier & Baker 1987). Eventually the parasite is eliminated from the blood after a period that usually ranges from a few months to one year. This means that a period of two to four weeks (Molineaux 1988), namely the phase of the first peak parasitaemia, is of great importance for the parasite as well as for the patient. Depending on the initial state of the immune system (figure 3), the patient might suffer from severe anaemia during this

initial phase. In the simulations this anaemia also was the main reason for the crash of the parasite population.

The course of infection described above is essentially what happens to a person who gets infected on a visit to an area with malaria, or who lives in an area with unstable malaria. For people living in an endemic region (stable malaria), the situation is very different because they are regularly exposed to reinfections with the same or other parasite genotypes (Molineaux 1988). Because immunity builds up slowly and is assumed to depend on new infections (boosting), as well as to be serotype- or genotype specific (Day & Marsh 1991), an equilibrium state of infections is unlikely. It is therefore more important to take repeated superinfections into account and to examine the dynamic, short-term behaviour of an infection. When superinfections were looked at from the point of view of the parasite, as was done in the simulations, the conclusion with respect to the timescale was the same. Although, as before, the genotype superior in competition won in the long run, both could build up first peak parasitaemias of comparable heights (figure 5a) or the inferior (first) was even able to suppress the superior (second) one for the first few days (figure 5b). Thus, whereas the long-term behaviour of the infection was unaffected by the length of the time shift between the appearance of two genotypes, it was one of the main factors determining the actual relation between the two first-peak parasitaemias. Here a time difference of 2 d (figure 5a) could be the result of different developmental times in the liver of two simultaneously inoculated parasite genotypes, whereas a difference of 9 d (figure 5b) would probably mean two separate inoculations.

Second, to be highly infectious the parasite must have an optimal rate of transformation into gametocytes most of which can infect mosquitoes. There is evidence that the infectiousness of gametocytes changes over time, that they are most infectious at rather low abundances (Carter & Graves 1988), and that infectivity is lost during the infection crisis as a result of

cytokine activity (Naotunne *et al.* 1991), that is, shortly after the asexual parasites have reached their peak. This means that transmission would be effective mainly at the beginning of a malaria infection.

As argued above, for the state of health of an individual patient (e.g. degree of anaemia), as well as for the local parasite population, in terms of survival and transmission the first peak of parasitaemia is very important. Thus, although it is sensible to study the long-term behaviour of a malaria infection by looking at equilibria and conditions for coexistence of competing parasite genotypes, one has to be careful with respect to the relevant timescale. Neglecting the short-term behaviour leads to underestimating important features of the initial dynamics of an infection such as the influence of superinfections. According to the results of the model, for the patient, superinfections with different parasite genotypes might mean having to deal with more small 'relapses' (figure 5). However, if immunity to malaria really is genotype specific, the exposure of the immune system to different parasite genotypes by superinfections could lead to a faster development of immunity. This leads to further questions: how often can superinfections establish a high enough first peak parasitaemia to keep the specific parasite genotype in the human population? Can they stimulate the immune system of the patient enough to accelerate the development of immunity? The interesting open questions about host-parasite interactions within an individual host are concerned more with short-term dynamics than with long-term equilibria.

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APPENDIX 1 BASIC MODEL WITH ONE PARASITE GENOTYPE AND NO IMMUNE SYSTEM

When the human host is infected by only one parasite genotype, the seven equations (1)–(7) reduce to four. Equation (1) simplifies to

$$dx/dt = A - \mu_x x - \beta s x,$$

and the three other equations are obtained by simply omitting the indices in equations (2)–(7). This system eventually reaches an equilibrium state with the following densities:

$$x^* = \frac{\alpha_s(\mu_y + c)}{\beta[\mu_y(r-1) - c]}, \quad (\text{A } 1)$$

$$y^* = \frac{\mu_x(\bar{x} - x^*)}{(\mu_y + c)}, \quad (\text{A } 2)$$

$$g^* = \frac{\mu_x c(\bar{x} - x^*)}{\alpha_y(\mu_y + c)}, \quad (\text{A } 3)$$

$$s^* = \frac{\mu_x[\mu_y(r-1) - c](\bar{x} - x^*)}{\alpha_s(\mu_y + c)}, \quad (\text{A } 4)$$

where $\bar{x} = A/\mu_x$ denotes the equilibrium density of erythrocytes in the absence of any infection.

The parasite is able to persist within its host if the equilibria y^* and s^* (and therefore g^*) are positive. This leads to the following two persistence conditions for the parasite:

$$[\mu_y(r-1) - c] \beta A > \alpha_s \mu_x (\mu_y + c), \quad (\text{A } 5)$$

$$\mu_y(r-1) > c. \quad (\text{A } 6)$$

These are also the conditions for the stability of the equilibria (A 1)–(A 4) obtained by local stability analysis around the equilibria (see, for example, Yodzis 1989).

For *P. falciparum*, the number of merozoites released per infected erythrocyte (r) lies between 8 and 32, the death rate of infected erythrocytes (μ_y) is 0.5, and the rate of differentiation into gametocytes (c) ranges 'from very low, or non-production, to rates of gametocytogenesis in excess of 50% of parasites developing into gametocytes at peak production' (Carter & Graves 1988). Thus condition (A 6) is always fulfilled, and the persistence of the parasite as well as the stability of the equilibria are solely determined by inequality (A 5).

The critical value x_c for the erythrocyte level, below which the parasite population crashes, is determined by the growth conditions for the asexual parasite stages ($dy/dt > 0$ and $ds/dt > 0$). It coincides with the equilibrium value for the uninfected erythrocytes:

$$x_c = x^*. \quad (\text{A } 7)$$

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