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CAN MALARIA PARASITE PATHOGENESIS BE PREVENTED BY TREATMENT WITH TUMOR NECROSIS FACTOR-ALPHA?

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Abstract. We consider a model incorporating the influence of innate and adaptive immune responses on malaria pathogenesis. By calculating the model reproduction number for a special representation of cytokine interaction, we have shown that the cytokine tumour necrosis factor-α can be administered to inhibit malaria infection. We have also found that if the cytokine F^* and a generic drug of efficacy ϵ are administered as dual therapy then clearance of the parasite can be achieved even for a generic drug of low efficacy. Our study is recommending administration of dual therapy as a strategy to prevent parasites from developing resistance to malaria treatment drugs.

1. **Introduction.** Malaria is one of the major public health hazards in the developing world in terms of infection, morbidity and mortality. There are at least 300 million acute cases of malaria each year globally, resulting in more than a million deaths. About 90% of these fatalities occur in Africa [25], mostly in young children below the age of 5. Plasmodium falciparum, a parasite spread by the female anopheles mosquito, is the most common cause of malaria and is responsible for almost all deaths associated with this disease. The parasites invade the red blood cells and multiply within them and burst the cells. Bursting cells release between 8-32 parasites [19] which, within a few minutes, can invade new red blood cells to continue the cycle. Severe loss of red blood cells can result in anaemia and sometimes death. Despite more than three decades of intense research, and a number of clinical trials, there is currently no vaccine that reliably protects against blood stage malaria infection when red blood cells are being systematically destroyed. Research so far has focused on the adaptive immune response to the malaria infection rather than innate immune response [9]. The response against malaria infection is generated by the immune cells. These cells produce a variety of cytokines: pro-inflammatory cytokines such as Interferon gamma (I_γ) and Tumor Necrosis Factor-alpha TNF_α (F) as well as auto-inhibitor cytokine Interleukin-10 ($IL-10$ or I_{10}). Studies in both mice and humans [9], have shown that pro-inflammatory cytokines, I_γ and F are essential mediators of protective immunity to erythrocyte malaria [10, 27]. Resistance to rodent malaria has been found to depend on signals mediated by I_γ. More

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importantly, the difference between lethal and non-lethal infections is known to depend on the host's ability to mount an early I_γ or F response [10, 27, 29, 16]. The cytokines I_γ and F are known [17, 26] to up-regulate the production of nitrogen oxide, which is involved in parasite killing. Moreover, in humans, I_γ production is correlated with resistance to infection with Plasmodium falciparum and it offers protection against clinical attacks of malaria [8]. Another study [see, [9] and the references therein] has concluded that the cytokine F influences the trafficking across endothelium by up-regulating the expression of various cells involved in the immune response and plays a role in both the immunity and the pathology of malaria. Mideo et el [21] considered the problem of infected red blood cell integrity during the asexual reproduction cycle and concluded that the parasite has evolved a strategy to avoid premature immune host lysing. This strategy is responsible for the geometric growth in the parasite population, and leads to fever, anemia and sometimes death [19]. A study by Marijani [22] has quantified this strategy in terms of the number of parasites in an infected red blood cell at the time of its natural death and the corresponding reproduction number. Other studies by Paul et el ([19, 23, 24]), describing human malaria pathogenesis, have concluded that the severity of the disease is linked to parasite preference for infecting certain ages of susceptible red blood cells. The age preference strategy has been shown to have a significant effect on infection dynamics and also helps explain the differences in clinical observations between parasite species [19]. Because the cytokines are produced by several immune cells and the production processes are complex and not well understood from a mathematical modeling point of view and because we want to keep the number of parameters as few as possible, we ignore the details of cytokine production and only consider their effect as described in [27] and [8].

In this paper, we develop a mathematical model of in-host malaria based on the biological processes described in [27, 8, 21]. The model includes susceptible red blood cells (RBCs), infected red blood cells (IRBCs), intracellular and extracellular parasites, and cytokines secreted by the immune cells. For clarity, we first present, in section 2 a model of interactions of RBCs/parasites without explicit interference by the immune system. Next, in section 3, we extend the model to include explicitly the immune response. This response involves the dendritic cells, macrophages and $T-$cells, and a family of cytokines they secrete. Since, however, the parameters involved in this interaction network are mostly unknown, we simplify the model of the immune response by restricting all the pro-inflammatory cytokines by just one, namely, $TNF-\alpha$ (F) and all the anti-inflammatory cytokines by $IL-10$ (I_{10}). Furthermore, we only use stationary values for F and I_{10}. We shall include in the model two drugs. The first drug consists of injection of $T-$cells, which is represented by an increase in the value of $TNF-\alpha$. The second drug decreases the efficacy of the extracellular parasites, P_e, by a factor $1-\epsilon$ $(0<\epsilon<1)$ where ϵ is the potency of the drug.

2. **Formulation of the simple model.** For the simple mathematical model, we introduce the following variables:

R	=	Density of red blood cells	$cell/ml$
R_i	=	Density of infected red blood cells	$cell/ml$
P_i	=	Density of intracellular parasites	$cell/ml$
P_e	=	Density of extracellular parasites	$cell/ml$

The model consists of four ordinary differential equations. The various terms in each equation are based on the experimental literature in [9, 27, 2, 3, 6, 15] etc, and their description is given in Table 1. We shall use the model to analyze the dynamics of malaria pathogenesis in the absence of generic drug treatment and host adaptive immune response to demonstrate a relationship between host and parasite parameters that define a criterion for the successful invasion and persistence of the parasite.

2.1. **Red blood cells (RBCs).** The dynamics of the uninfected red blood cell population being depleted by the malaria parasites are modeled as in [1, 22, 13, 15] by the following equation:

$$\dot{R} = S_r - \mu_r R - k_1 R P_e. \tag{1}$$

The first term represents constant natural replenishment for the red blood cell population, the second term represents natural death of these cells at a constant rate μ_r, and the third term accounts for infection of red blood cells by extracellular parasites. The infected red blood cells incubate the parasites which multiply in them. These cells can die naturally or burst once the parasite population exceeds the cell's carrying capacity [19].

The infected red blood cell population is assumed to evolve according to the equation

$$\dot{R}_i = k_1 R P_e - k_2 R_i \left(\frac{{P_i}^2}{{P_i}^2 + (N R_i)^2} \right) - \mu_{ri} R_i. \tag{2}$$

The first term in equation (2) represents a gain for this population due to infection of susceptible red blood cells, the second term represents bursting of infected red blood cells as the number of parasites within them reaches 32 [19]. The study by Gravenor M. B. et al. [12] suggests that the parasite population is controlled by density-dependent mechanisms. Accordingly, we have assumed a variable bursting rate for infected red blood cells that is dependent on the densities of the infected red blood cells and the intracellular parasites. The last term represents natural death of these cells at a constant rate μ_{ri}.

2.2. **Parasites.** During the malaria blood stage, the parasites infect the susceptible red blood cells and multiply asexually in these cells [19, 21, 23, 24]. For an infected red blood cell, one of two scenarios can happen (i) either the infected red blood cell will burst once the number of parasites within it reaches 32 [19], or (ii) the infected red blood cell will die naturally before the number of parasites within it reaches 32. The growth of this population is described by

$$\begin{aligned} \dot{P}_i = k_{pi} P_i \left(1 - \frac{{P_i}^2}{{P_i}^2 + (N R_i)^2} \right) &+ k_1 n^* R P_e \\ &- k_2 N R_i \left(\frac{{P_i}^2}{{P_i}^2 + (N R_i)^2} \right) - n_1 \mu_{ri} P_i. \end{aligned} \tag{3}$$

The first term represents the logistic growth of intracellular parasites, the second term is a gain for the population of intracellular parasites as more susceptible red blood cells are infected by extracellular parasites with multiplication rate n^* per cycle, the third term accounts for loss of intracellular parasites due to bursting [19] of infected red blood cells at a variable bursting rate [11, 12]. The fourth term accounts for loss of intracellular parasites due to natural death of infected red

blood cells. Each IRBC that dies naturally releases on average n_1 parasites. The parasites released into the blood stream can immediately invade more red blood cells to continue the infection cycle [19, 21].

The dynamics of the extracellular parasite population is given by the following equation:

$$\dot{P}_e = k_2 N R_i \left(\frac{{P_i}^2}{{P_i}^2 + (NR_i)^2} \right) + n_1 \mu_{ri} P_i - k_1 n^* R P_e - \mu_{pe} P_e. \tag{4}$$

The first three terms in this equation have been explained in equations (1)-(2). The fourth term represents natural death rate of extracellular parasites at a constant rate μ_{pe}.

3. Mathematical analysis for the model.

Lemma 3.1. *Consider a system of differential inequalities*

$$\frac{dx_i}{dt} \geq A_i x_i + \sum_{j=1}^{n} B_{ij} x_j + \epsilon \quad (i = 1, \cdots\cdots n) \tag{5}$$

where

$$B_{ij} \geq 0, \ \ \epsilon \geq 0. \quad \textit{If } x_i(0) \geq \epsilon \textit{ for } i = 1, \cdots\cdots, n,$$

then $x_i(t) \geq 0$ *for all* $t > 0$ *and* $1 \leq i \leq n$.

Proof. Without loss of generality we may assume that $\epsilon > 0$, since the case $\epsilon = 0$ follows by approximating the system with a sequence $\epsilon = \epsilon_k, \ \ \epsilon_k \downarrow 0$.

Suppose the assertion $x_i(0) \geq \epsilon > 0$ for $1 \leq i \leq n$, is not true. Then there exists a smallest number $t_0 > 0$, such that

$$x_i(t) > 0 \quad \text{for } 1 \leq i \leq n, \ \ 0 \leq t < t_0$$

$$x_i(t_0) = 0 \quad \text{for at least one } i, \text{ say } i = i_0.$$

Then x_{i_0} is a decreasing function and

$$\frac{dx_{i_0}}{dt}(t_0) \leq 0.$$

From the differential inequality (5) for $x_{i_0}(t)$ we get

$$\frac{dx_{i_0}}{dt}(t_0) \geq \sum_{j=1}^{n} B_{ij} x_j(t_0) + \epsilon \geq \epsilon > 0$$

which is a contradiction. □

For the state variables in our model, we always take

$$R(0) \geq 0, \ \ R_i(0) \geq 0, \ \ P_i(0) \geq 0, \ \ P_e(0) \geq 0.$$

Then from lemma 3.1 we conclude that

$$R(t) \geq 0, \ \ R_i(t) \geq 0, \ \ P_i(t) \geq 0, \ \ P_e(t) \geq 0, \quad \text{for all } t \geq 0.$$

The parasite free equilibrium point of the system (1)-(4) is given by

$$x_{00} = (R^*, R_i^*, P_i^*, P_e^*) = \left(\frac{S_r}{\mu_r}, 0, 0, 0 \right).$$

We use the technique by van Driesche and Watmough [32] to find the model reproduction number as outlined below. Consider the infected states arranged in the order $(R_i,\ P_i,\ P_e)$:

$$\dot{R}_i = k_1 R P_e - k_2 R_i \left(\frac{P_i^2}{P_i^2 + (NR_i)^2}\right) - \mu_{ri} R_i, \tag{6}$$

$$\dot{P}_i = k_{pi} P_i \left(1 - \frac{{P_i}^2}{{P_i}^2 + (NR_i)^2}\right) + k_1 n^* R P_e - k_2 N R_i \left(\frac{{P_i}^2}{{P_i}^2 + (NR_i)^2}\right) - n_1 \mu_{ri} P_i, \tag{7}$$

$$\dot{P}_e = k_2 N R_i \left(\frac{{P_i}^2}{{P_i}^2 + (NR_i)^2}\right) + n_1 \mu_{ri} P_i - k_1 n^* R P_e - \mu_{pe} P_e. \tag{8}$$

The contributions to new infections come from three sources namely, infection of susceptible red blood cells (first term in equation (6)), increase in the population of intracellular parasites due to infection of red blood cells (second term in equation (7)) and newly produced extracellular parasites due to bursting and natural death of infected red blood cells (first and second terms of equation (8)). The matrix for new infections is given by:

$$\mathcal{F} = \begin{pmatrix} k_1 R P_e \\ k_1 n^* R P_e \\ k_2 N R_i \left(\frac{{P_i}^2}{{P_i}^2 + (NR_i)^2}\right) + n_1 \mu_{ri} P_i \end{pmatrix}.$$

The Jacobian matrix $\mathcal{DF}|(x_{00})$ at the parasite free equilibrium is given by;

$$F = \mathcal{DF}|(x_{00}) = \begin{pmatrix} 0 & 0 & \frac{k_1 S_r}{\mu_r} \\ 0 & 0 & \frac{k_1 n^* S_r}{\mu_r} \\ 0 & n_1 \mu_{ri} & 0 \end{pmatrix}.$$

The other dynamical changes in the model are given by:

$$\mathcal{V} = \begin{pmatrix} k_2 R_i \left(\frac{{P_i}^2}{{P_i}^2 + (NR_i)^2}\right) + \mu_{ri} R_i \\ -k_{pi} P_i \left(1 - \frac{{P_i}^2}{{P_i}^2 + (NR_i)^2}\right) + k_2 N R_i \left(\frac{{P_i}^2}{{P_i}^2 + (NR_i)^2}\right) + n_1 \mu_{ri} P_i \\ k_1 n^* R P_e + \mu_{pe} P_e \end{pmatrix}.$$

The Jacobian matrix of $\mathcal{V}$, calculated at the parasite free equilibrium, is given by:

$$V = \mathcal{DF}|(x_{00}) = \begin{pmatrix} \mu_{ri} & 0 & 0 \\ 0 & -k_{pi} + n_1 \mu_{ri} & 0 \\ 0 & 0 & \frac{k_1 n^* S_r}{\mu_r} + \mu_{pe} \end{pmatrix}.$$

The largest absolute eigenvalue of the product

$$FV^{-1} = \begin{pmatrix} 0 & 0 & \frac{k_1 S_r}{\mu_r \left(\mu_{pe} + \frac{k_1 n^* S_r}{\mu_r}\right)} \\ 0 & 0 & \frac{k_1 n^* S_r}{\mu_r \left(\mu_{pe} + \frac{k_1 n^* S_r}{\mu_r}\right)} \\ 0 & \frac{n_1 \mu_{ri}}{n_1 \mu_{ri} - k_{pi}} & 0 \end{pmatrix}.$$

is called the basic reproduction number [32] and is given by;

$$R_{00} = \sqrt{\left(\frac{n_1 \mu_{ri}}{(n_1 \mu_{ri} - k_{pi})}\right)\left(\frac{k_1 n^* S_r}{(\mu_{pe} \mu_r + k_1 n^* S_r)}\right)}. \tag{9}$$

The positivity of the number R_{00} requires that $n_1\mu_{ri} > k_{pi}$. From the general theory of [32] we know that the parasite-free equilibrium is asymptotically stable for $R_{00} < 1$. This result can also be verified directly through a local stability analysis. In the next section, we maintain the malaria pathogenesis dynamics presented above but include the role of innate and adaptive immune responses and treatment to demonstrate their potential role in immunopathology.

4. **Model incorporating treatment and the immune response.** The equations (1)-(4) are used as a first step towards formulating a model which includes treatment with a drug of constant efficacy ϵ and the adaptive immune response. Malaria has long been associated with the following cytokines: Tumour necrosis factor-α (F), Interferon-γ (I_γ), and the anti-inflammatory cytokine (I_{10}). Exactly how these cytokines interact with the immune cells in humans is not biologically clear [4]. Hence, in this study, we ignore cytokine production dynamics and consider the levels of the cytokines F^*, I_γ^* and the anti-inflammatory cytokine I_{10}^* to be at their optimal levels [4]. We have also replaced the red cell infection parameter k_1 in the equations (1)-(4) by a cytokine moderated infection parameter $\hat{k}_1 = k_1\left(\frac{c_\gamma}{I_\gamma^*+c_\gamma}\right)$ [4]. The model is now given by equations (10)-(13).

4.1. **Red-cell dynamics.** The dynamics of the uninfected red blood cell population is given by:

$$\dot{R} = S_r + k_r\left(\frac{F^*}{F^*+k_F I_{10}^*+c_F}\right) - \hat{k}_1 R P_e\,(1-\epsilon)\left(\frac{c_R}{F^*+c_R}\right)\mu_r R. \quad (10)$$

The first term is as defined in equation (1), the second term represents up-regulation of the healthy red blood cells [27, 4] in response to the cytokine F^* inhibited by the cytokine I_{10} [7]. The red blood cells are infected by parasites as in the third term of equation (1), but this process is now resisted by the cytokines I_γ^* and F^* [27]. The infected red blood cell population evolves according to the following equation:

$$\begin{aligned}\dot{R}_i &= \hat{k}_1 R P_e\,(1-\epsilon)\left(\frac{c_R}{F^*+c_R}\right) - k_2 R_i\left(\frac{P_i^2}{P_i^2+(NR_i)^2}\right)\\ &- k^* N R_i\left(\frac{F^*}{F^*+k_F I_{10}^*+c_F}\right) - \kappa R_i r_e - \mu_{ri} R_i. \quad (11)\end{aligned}$$

In equation (11), the first term is a gain for this population resulting from the infection of healthy red blood cells, where the parameter ϵ represents the constant drug efficacy, $0 \le \epsilon \le 1$. The third term represents apoptosis induced by the cytokine F [31]. Terms 2, 4 and 5 are as explained in equation (2).

4.2. **Parasite-dynamics.** The dynamics of the intracellular parasites is given by

$$\begin{aligned}\dot{P}_i &= k_{pi} P_i\left(1-\frac{P_i^2}{P_i^2+(NR_i)^2}\right) + \hat{k}_1 n^* R P_e\,(1-\epsilon)\left(\frac{c_R}{F^*+c_R}\right)\\ &- k_2 N R_i\left(\frac{P_i^2}{P_i^2+(NR_i)^2}\right) - n_1\mu_{ri} P_i. \quad (12)\end{aligned}$$

The terms in this equation are as explained in equation (3) but the gain, term 2, is inhibited by the cytokines I_γ and F [27]. The extracellular parasites evolve according to

$$\begin{aligned}\dot{P}_e &= k_2 N R_i \left(\frac{P_i^2}{P_i^2 + (NR_i)^2}\right) + n_1 \mu_{ri} P_i - k_{tp} N r_e P_e \\ &- \hat{k}_1 n^* R P_e (1-\epsilon) \left(\frac{c_R}{F^* + c_R}\right) - \mu_{Pe} P_e. \end{aligned} \tag{13}$$

The terms in this equation are as explained in equation (4) but the infection term (term 4), is inhibited by the cytokines I_γ and F [27].

5. **The reproduction number for the model.** To measure the influence of the adaptive immune response, we calculate the reproduction number for the model (10)-(13) as a function of the cytokines and compare it with the reproduction number of the previous model (1)-(4). The reproduction number for the model (10)-(13) is calculated in a similar manner as before and is given by:

$$R_{01} = \sqrt{\left(\frac{n_1 \mu_{ri}}{(n_1 \mu_{ri} - k_{pi})}\right)\left(\frac{R^* \hat{k}_1 n^* (1-\epsilon)\left(\frac{c_R}{F^*+c_R}\right)}{\mu_{pe} + N k_{tp} r_e + \hat{k}_1 n^* (1-\epsilon) R^* \left(\frac{c_R}{F^*+c_R}\right)}\right)}.$$

Taking $\epsilon = 0$, $F^* = 0$, $I_\gamma^* = 0$, and $I_{10}^* = 0$, the reproduction number R_{01} reduces to the reproduction number R_{00}. Increasing the amount of both F^* and I_γ^* or increasing the amount of either F^* or I_γ^*, decreases the reproduction number R_{01}, suggesting that boosting the amount of either cytokine can lower the susceptibility of the host. Biologically, however, there is a limit to the amount of either F^* or I_γ^* the body can produce. Moreover, the cytokine I_γ is only produced when a pathogen is detected. Hence, in the absence of the pathogen the cytokine I_γ^* can only be administered externally. The question is whether the cytokines F^* and I_γ^* can be administered externally to boost the host immune system and lower the susceptibility of the host to malaria infection. Once infected with the malaria parasite, pathogenesis may take different forms as was illustrated by Marijani [22]. According to [22], it is possible for the model (10)-(13) to have a unique endemic equilibrium point or to posses multiple endemic equilibrium points, with a possibility of backward bifurcation.

6. **Parameter values.**

7. **Simulation.** We begin by investigating the level of uncertainty and sensitivity in the model parameters using Latin Hypercube Techniques [14]. The partial rank correlation coefficients, plotted in Figure 1, show the impact of the various parameters on the reproduction number R_{01}. We can see that the reproduction number is highly positively correlated to k_{pi}, the rate of growth of intracellular parasites, and highly negatively correlated to μ_{ri}, the natural death rate of infected red blood cells and the parameter n_1, another intracellular parasite related parameter. The range of the parameter n_1 is given in [19]. The parameter μ_{ri} is also known [19, 13]. The parameter k_{pi} has not been estimated clinically or experimentally. Using the parameter values in [Table 1], we have found by an iterative procedure that $n_1 = 16$ is the threshold value for which $R_{01} = 1$ (figure 2). Using this value of n_1 and the parameter values in Table 1, we have estimated the value of the growth rate of parasites to be $k_{pi} = 0.08745$. One can use the parameters in Table 1 to study the

TABLE 1. List of parameters used in this model

Name	Discription	Value used	Source
S_r	Constant source of red blood cells $(cell/mil.day)$	2.5×10^9	[19, 13]
μ_r	Natural death rate of RBCs (day^-1)	0.01	[19, 13]
k_1	Infection rate $(ml/cell.day)$	2×10^{-9}	[15]
k_2	Bursting rate of IRBC $(ml/cell.day)$	$(0.05,\ 0.4)$	[11, 2]
N	Number of parasites that fills RBCs	32	[19]
μ_{ri}	Death rate of infected RBCs (day^-1)	$[0.01,\ 0.022]$	[19, 13]
k_{pi}	Rate of growth of intracellular parasites (day^-1)	0.08745	Estimated [22]
$k_1 n^*$	Threshold	10^{-8}	Estimated [22]
n_1	Average number of intracellular parasites released (day^-1)	$[8,\ 32]$	[19]
μ_{pe}	Natural death rate of extracellular parasites (day^-1)	0.0208	[19, 13]
k_r	Recruitment rate (day^-1)	2×10^5	[2]
k_F	Scalar	1.1	[11, 2]
c_F	Saturation constant for F^*	$50pg/ml$	[7]
c_R	Recruitment constant for RBC	$169pg/ml$	[2]
k^*	Parasite growth inhibition rate by F^*	0.024	[2]
k	Effector cell killing rate	2×10^{-9}	[22, 13, 15]
r_e	Maximum number of effector cells $\frac{1}{ml}$ blood	[4000,15000]	[19, 2]
k_{tp}	Parasite removal rate by effector cells	0.01	Estimated [22]

following questions: (a) Can we demonstrate the effect of administering doses of the cytokine F on the immune response to blood- stage malaria infection? (b) What is the least efficacy value of the malaria treatment drug, measured by the parameter ϵ in equations (10)-(13), that can bring the parasite load under control? (c) When dual therapy is used involving a generic drug of efficacy ϵ and a cytokine F^* based drug, what is the least amount ϵ^* and the least amount of F^* required to clear the malaria infection? These questions will be considered in our simulation.

7.1. **Numerical simulation.** Figure 2 describes the evolution of extracellular parasites for various values of the parameter n_1 $(8 \leq n_1 \leq 32)$ and the corresponding reproduction numbers. The figure shows that the replication of extracellular parasites in the host is fastest for $n_1 = 8$. At this level of replication, each parasite released from an infected red blood cell generates on average 1.6679 secondary infections. The replication of extracellular parasites decreases as n_1 increases and likewise the reproduction number decreases as n_1 increases. This replication strategy can be described as the immune escape strategy by the parasites (see also [22]), a strategy that avoids easy detection of infected red blood cells as the parasites escape from naturally dying infected red blood cells. Figures 3 and 4 show the evolution of red blood and infected red blood cell populations for $n_1 = 24$ for various values of externally administered amounts of the cytokine F^*. It is clear that these

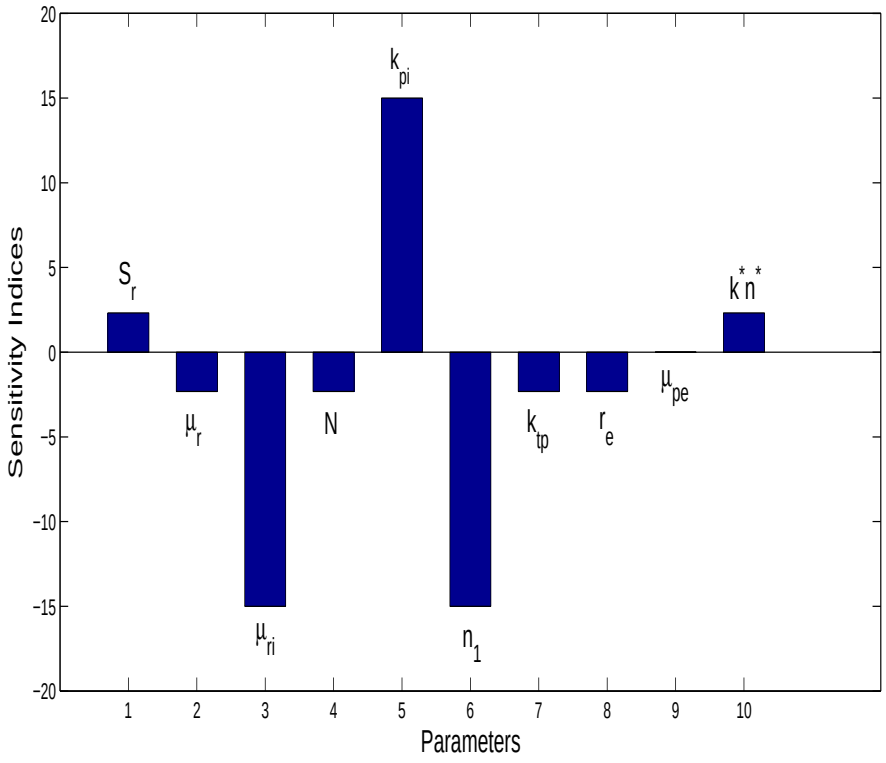

FIGURE 1. A diagram showing the sensitivity of the reproduction number to various model parameters.

two figures describe a scenario in which the infection does not establish itself. The susceptible red cell population (Figure 3) declines to a steady state level which is 80% of the infection free case. The infected red cell population (Figure 4) increases initially, reaching a peak, and then declines to zero. The severity of the infection is reduced with increasing amounts of the administered cytokine F^*. The extracellular parasite population increases to a peak but is eventually cleared (Figure 5). The peak of the infection is greatest for $F^* = 0$ and decreases with increasing amounts of the administered cytokine F^*. Figures 6, and 7 show the evolution of the susceptible red blood and the infected red blood cell populations for $n_1 = 12$ for various values of the cytokine F^*. These figures describe a scenario in which the infection establishes itself. Figure 6 shows that more susceptible red blood cells escape the infection as the amount the cytokine F^* administered increases. This is supported by Figures 7 and 8 which show smaller populations of infected red blood cells and extracellular parasites as F^* increases. Figure 9 describes two scenarios, namely a host who is not on malaria treatment and a host who is on malaria treatment starting on day 2 after infection. The figure shows that the populations of infected red blood cells, intracellular parasites and extracellular parasites clear from the host who is treated with a drug efficacy of at least $\epsilon^* = 0.7$. For such a patient, the drop in the red blood cell count is significantly smaller. A comparison of Figures 6, 7

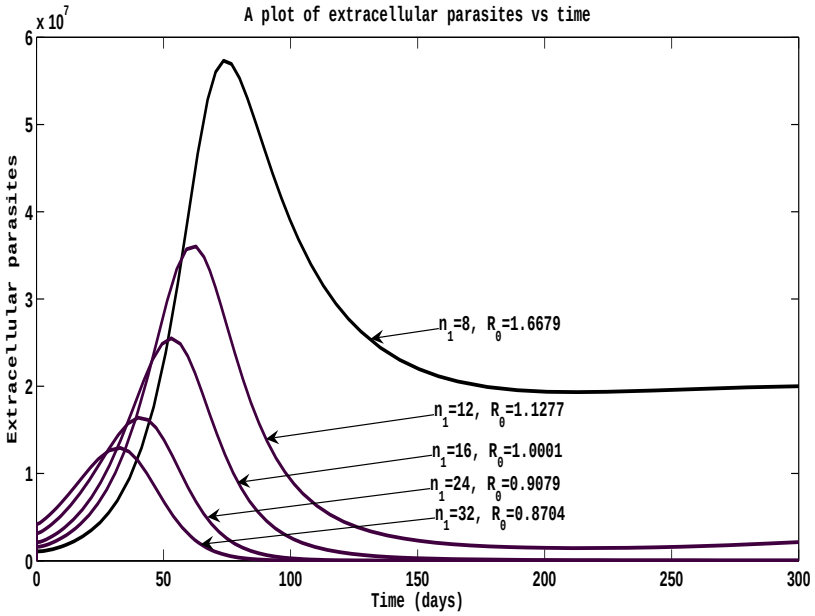

FIGURE 2. Population level plots for extracellular parasites for various values of n_1.

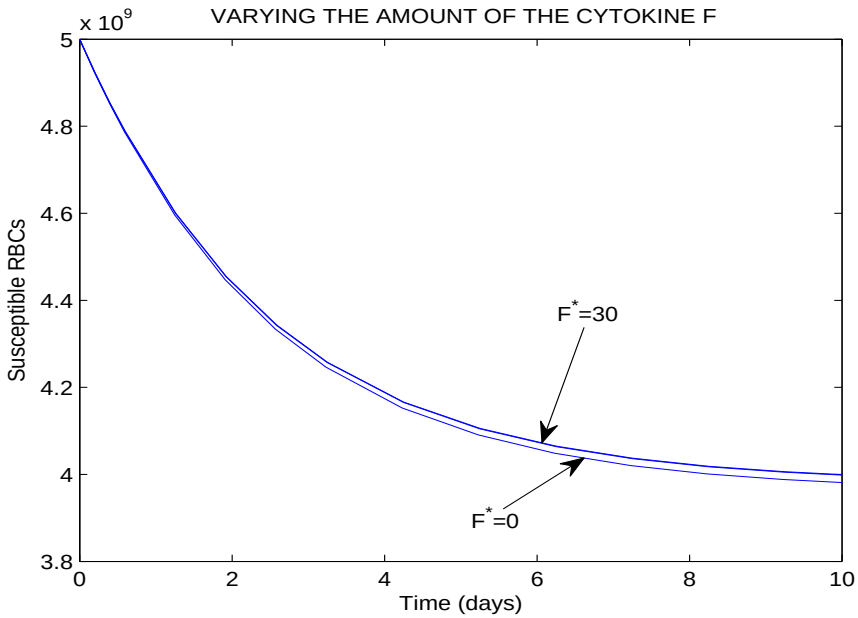

FIGURE 3. Population level plots for susceptible red blood cells for various values of F^* and $n_1 = 24$.

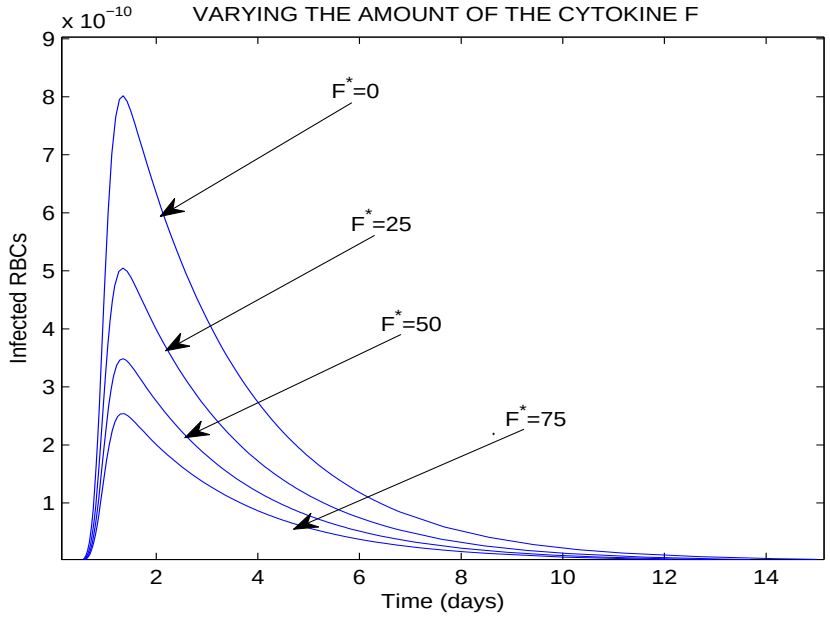

FIGURE 4. Population level plots for infected red blood cells for various values of F^* and $n_1 = 24$.

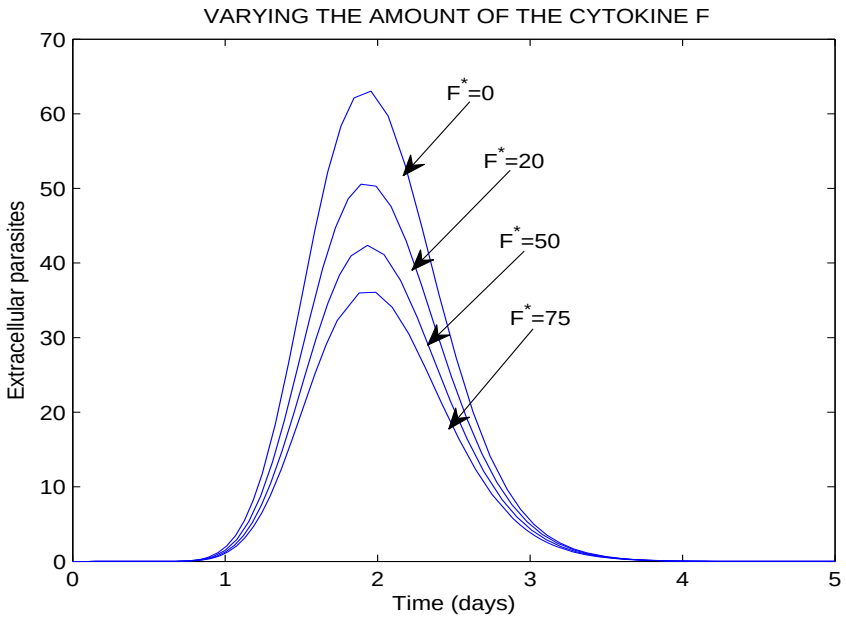

FIGURE 5. Population level plots for extracellular parasites for various values of F^* and $n_1 = 24$.

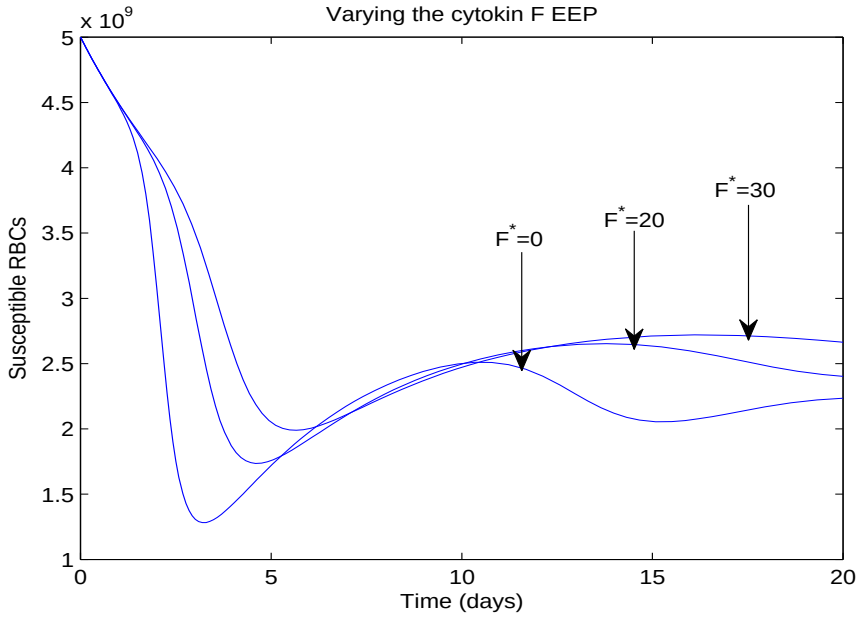

FIGURE 6. Population level plots for susceptible red blood cells for various values of F^* and $n_1 = 12$.

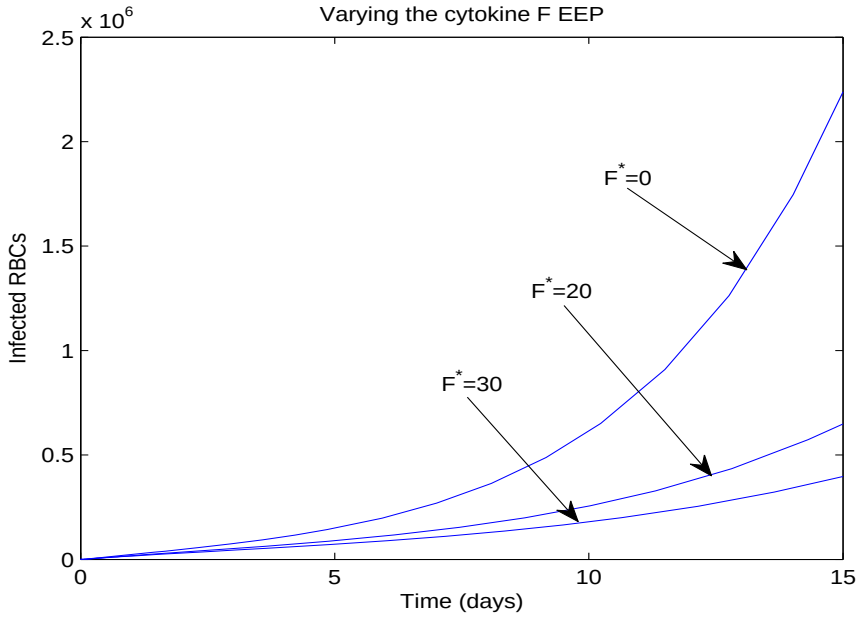

FIGURE 7. Population level plots for infected susceptible red blood cells for various values of F^* and $n_1 = 12$

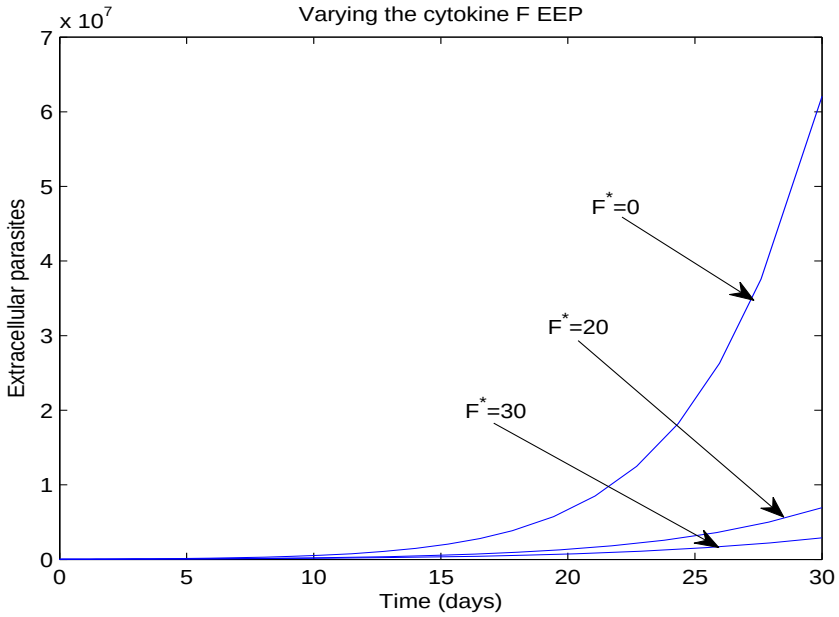

FIGURE 8. Population level plots for extracellular parasites for various values of F^* and $n_1 = 12$.

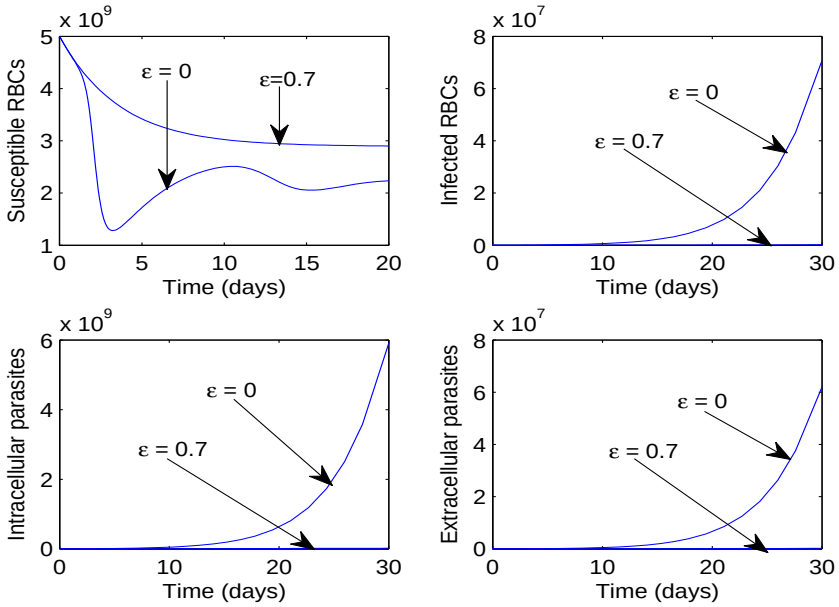

FIGURE 9. Plots showing the effect of treatment for $n_1 = 12$.

and 8 shows the same evolutionary characteristics for the infected red blood cell and extracellular parasite populations. This suggests that externally administering the

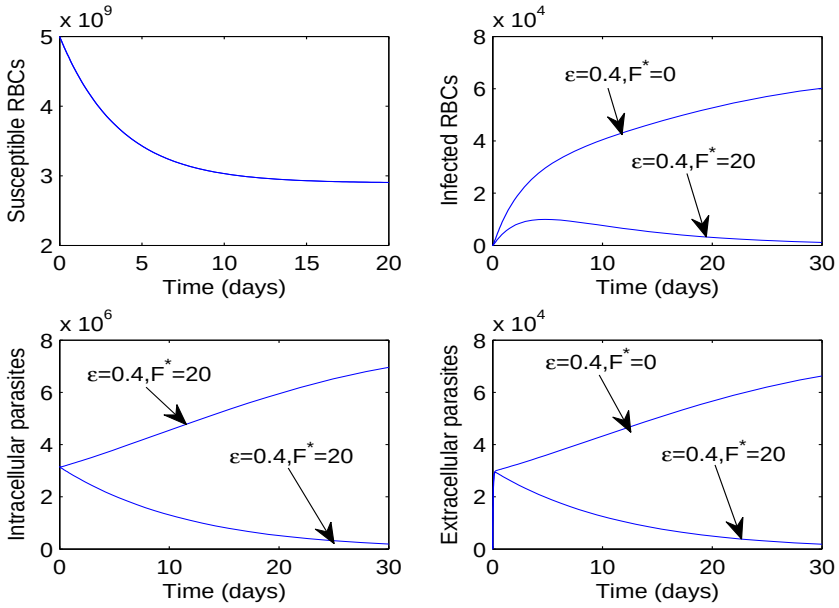

FIGURE 10. Plots showing the advantages of dual therapy for $n_1 = 12$.

cytokine F^* induces similar parasite suppressive characteristics as administering a malaria treatment drug of efficacy ϵ. Figure 9 illustrates the effect of the drug efficacy, ϵ, on the progress of malaria. For $n_1 = 12$ and $F^* = 0$, the disease continues to grow if $\epsilon = 0$, but is cleared if $\epsilon = 0.7$. The malaria parasite is not cleared as long as $\epsilon < 0.7$ (Figures not shown here). On the other hand, if $F^* > 0$ then lower efficacy clears the disease, as illustrated in Figure (10), namely, with $F^* = 20$ and a drug efficacy level of $\epsilon = 0.4$ the malaria infection is cleared.

8. **Discussion and conclusions.** This paper has considered the possibility of administering the cytokine F^* externally as a strategy to hinder pathogenesis of the malaria parasite. We have computed the model reproduction number, R_{01}, as a function of the cytokine F^*, and the parameter n_1 which denotes the number of parasites in a dying infected red blood cell. R_{01} is a decreasing function of the cytokine amount F^*, and is related to the parameter n_1 in a manner that suggests that the malaria parasite has preference for infecting older red blood cells. This latter result has been inferred from the fact that an endemic infection results when there is only few parasites in a naturally dying infected red blood cell (that is $8 \leq n_1 \leq 15$) while when the number of parasites in a naturally dying infected red blood cell is high (that is $16 \leq n_1 \leq 32$), the infection is cleared by the immune system (Figure 2). Figure 4 illustrates the effect of the cytokine F^* on the pathogenesis of the malaria parasite. The larger the amount of F^* the less severe the infection. This conclusion is supported by the population of extracellular parasites which reaches the highest peak for $F^* = 0$ and reaches lower peaks for $F^* > 0$. Figures 6 and 7 show the evolution of susceptible red blood cells and extracellular parasite populations for $n_1 = 12$. Figure 6 shows that the larger F^* is the larger

the population of susceptible red blood cells that is not infected. For $F^* = 30$ almost 20% of the susceptible red blood cells escape the infection compared to the case $F^* = 0$ after twenty days of the infection. Figure 7 shows the advantage of administering the cytokine F^* as the number of infected red blood cell for $F^* = 30$ is only 10% of the case $F^* = 0$, a result supported by Figures 8, 9 which together suggest that the adminstration of the cytokine F^* has the same effect as treating with a generic drug. Figure 9 shows that a generic drug of efficacy $\epsilon = 0.7$ will clear the malaria infection. While the administration the cytokine F^* appears to have the same effect, it is not known how much of this cytokine a host can tolerate. Figure 10 shows two scenarios namely treating with a generic drug of efficacy $\epsilon = 0.4, F^* = 0$, and dual therapy with a generic drug of efficacy $\epsilon = 0.4$ and a cytokine based drug $F^* = 20$. The strategy $\epsilon = 0.4, F^* = 0$ leads to an endemic infection while the strategy $\epsilon = 0.4, F^* = 20$ leads to clearance of the infection even though the efficacy of the generic drug is only $\epsilon = 0.4$. Although dual therapy offers opportunities for clearing the malaria infection with generic drugs of low efficacy, it is advisable to treat with generic drugs of efficacy $\epsilon \geq 0.7$ in order to avoid the parasite developing resistance to either the generic drug or the cytokine. Our study has demonstrated the potential for dual therapy between generic and cytokine based drugs, although the amount of the cytokine F^* that can be tolerated by the body has not been investigated.

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