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A mathematical model for malaria treating both sensitive and resistant strains in a multigroup population

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Abstract

The emergence of drug-resistant malaria parasites in recent years has become a significant public health problem. Drawing from our ealier models [2], which deal with a single population group, a multigroup model is hereby introduced. Human population is assumed fixed in all considerations while that of vectors varry. All the models are nonlinear ordinary differential equations models. The models describe accurately, the current trend in malaria infection in a malaria endemic region. Our focus in analysing the models is on the possibility of establishing some positive asymptotic equilibria. It is shown that (under suitable conditions) the equilibrium points are (globally) asymptotically stable. As a function of some interplay between the various parameters, the equilibrium can lead to endemic infection with sensitive infection only, resistant infection only, or both, or to elimination of both infections. The biological significance of these equilibrium points, namely, their usefulness to practical health officials, also emerges as a byproduct.

Keywords
Asymptotically stable, Equilibrium points, Feasible points, Gametocytes, Resistant parasites, Sensitive parasites, Superinfection.

1.0 Introduction

Malaria is a mosquito-borne infection caused by protozoa of the genus plasmodium. Four species of the parasite, namely: P. falciparum, P. vivax, P. ovale, and P. malariae infect humans. Malaria remains the most important of the tropical diseases, being widespread throughout the tropics, but also occurring in many temperate regions.

The parasites are transmitted by the bite of infected female mosquitoes of the genus Anopheles. Mosquitoes become infected by feeding on the blood of infected people, and the parasites then undergo another phase of reproduction in the infected mosquito. Clinical symptoms such as fever, pains, and sweats may develop a few days after an infected mosquito bite.

In many parts of Africa, where malaria has long been highly endemic, people are infected so frequently that they develop a degree of acquired immunity, and may become asymptomatic carriers of the infection [8]. Treatment and control have become more difficult in recent years with the spread of drug resistant strains of malaria parasites [6, 8, 17]. Drugs such

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as chloroquine, nivaquine, quinine, and fansidar are used for treatment. More recent and more powerful drugs include mefloquine, and halofantrine.

It is estimated that 267 million people are presently infected, with 107 million clinical cases annually; the number of countries affected is put at 103 [17].

The biology of the four species of plasmodium is generally similar and consists of two discrete phases-sexual and asexual . The parasite migrates to the liver where it remains latent for several days while replicating. The latent period is followed by penetration of red blood cells and asexual replication within them. Asexual parasites in the blood, after surviving some developmental period, give rise to sexual stages called gametocytes. Gametocytes can remain in the blood for more than two years [8].

The emergence of drug-resistant strains of malaria parasite has become a significant health problem. Recent pronouncements by the World Health Organisation indicate the availability of strains that are resistant to virtually all known drugs.

Among the four species of plasmodium, P. falciparum causes the most serious illness and it is the most widespread in the tropics. This paper therefore focuses on the dynamics of P. falciparum malaria, although the analysis is similar for all forms of malaria infections.

2.0 Preliminaries

An early fundamental model in the art of mathematical modelling of malaria, due to Ross-Macdonald describes the basic features of the interaction between infected humans (y) and infected mosquito vectors (q). The model is defined as follows:

$$\dot{y} = \alpha q(1-y) - ry,$$
$$\dot{q} = \beta y(1-q) - pq$$

where $\alpha = b\beta\frac{M}{N}, \beta, r, \mu$ are some constants defined as follows (see for e.g. [4]):

N is the size of the human population;
M is the size of the female mosquito population;
$\frac{M}{N}$ is the number of female mosquitoes per human host;
β is the rate of biting on man by a single mosquito (number of bites per unit time);
b is the proportion of infected bites on man that produce an infection;
r is the per capita rate of recovery for humans ($\frac{1}{r}$ is the average duration of infection in the human host);
μ is the per capita mortality rate for mosquitoes ($\frac{1}{\mu}$ is the average lifetime of a mosquito).

In this simple model, the total population of both humans and vectors is assumed fixed, so that the dynamical variables (y and q) are the proportion infected in each population. The first equation describes changes in the proportion of humans infected. New infections are acquired at a rate that depends on the following factors:

(i) the number of mosquito bites per person per unit time ($\beta\frac{M}{N}$)
(ii) the probability that the biting mosquito is infected (q)
(iii) the probability that a bitten human is uninfected ($1-y$)
(iv) the probability that an uninfected person thus bitten will actually become infected (b).

Infections are lost by infected people returning to the uninfected class, at a characteristic recovery rate r. Similarly, the second equation describes changes in the proportion of mosquitoes infected. Population changes are determined by the following factors:

(i) the number of bites per mosquito per unit time (β)
(ii) the probability that the biting mosquito is uninfected ($1-q$)
(i) the probability that the bitten human is infected (y).

The loss term (μq) arises from the death of infected mosquitoes. The loss terms for the infected humans and infected vectors both involve death and recovery. For human hosts the recovery rate is typically faster than the death rate, whereas for vectors the opposite is the case. The origin is a local asymptotic equilibrium for this model if $\mu r > \alpha\beta$. Thus infection dies out if the product of the death rates (μ and r) for the two populations is large in the sense that $\mu r > \alpha\beta$. Thus the above formulation is a sensible approximation.

However, this model is highly simplified. The model simply assumes that an infected individual either recovers to join the susceptible group $N(1 - y)$ or dies. It fails to distinguish between the various infected categories of human and vector hosts. Thus it cannot describe accurately the recent trend in malaria infection.

This basic model has been studied, modified and generalized in different directions by various authors (see for e.g., [4, 5, 6, 11]). Aron and May [4] extended this model by introducing another population group z – the latent infected humans (infected but not yet infectious). They conjectured that if the incubation interval in the mosquito has duration r the second equation in the basic model could be replaced by the two dynamical systems:

$$\dot{z} = \alpha y(1-q-z) - q\dot{y}(1-\dot{q}-\dot{z})e^{-\mu r} - \mu z, ,$$
$$\dot{q} = \alpha\dot{y}(1-\dot{q}-\dot{z})e^{-\mu r} - \mu q$$

where the circumflex denotes evaluation at time r in the past: $\dot{y} = y(t-r)$; etc. Here, the two categories of mosquito (uninfected and infected-and-infectious) are now replaced by three categories: a proportion, $1 - q - z$, that are uninfected; a proportion q that are infected and infectious; and a third, new proportion z that are latent (infected but not yet infectious).

Bailey [5] considered two interacting populations–human hosts and mosquito vectors with each group consisting of three subgroups, viz susceptibles, infectives, and isolated (recovered and immune). These are designated by x, y, and z respectively for the human populations and x', y', and z' respectively for the vector populations. It follows that the number of new infections occurring in the human population in time interval δt is $\beta xy'\delta t$, where β is the infection rate. Since the converse arrangement is required to hold for vectors, namely that susceptible vectors are infected by human infectives, the number of new infections occurring in susceptible vectors in time interval $\eth t$ is therefore given by $\beta' x'y\eth t$. If in addition the overall removal rates for the two populations are assumed to be γ and γ', respectively, then the numbers of removals occurring in time δt are $\gamma y\delta t$ and $\gamma' y'\delta t$ for humans and vectors, respectively. The system of differential equations for the dynamic process involved is given as

$$\square = -\beta xy', \square' = -\beta' x'y' + \gamma' y',$$
$$\dot{y} = \beta xy' - \gamma y', \dot{y}' = \beta' x'y - \gamma' y',$$
$$\dot{z} = \gamma y,$$

where β, β', γ, γ' are some constants. Due to its relatively short life-cycle, isolation by immunity is negligible in the mosquito vectors, and hence the only isolation process is by death which is assumed to occur equally in all groups. Hence $\dot{z}' \equiv 0$ (see [6], pp. 61–68).

This model, like the first, also describes the basic interaction between the infected human host population and the mosquito vector population but with an additional group in each population.

Throughout this part, we shall adopt the following notations where applicable.

- N denotes the total human population;
- x denotes susceptibles (the number of people that are uninfected);
- y denotes infectives (the number of people that are severely infected);
- v denotes infected vectors (the population of vectors that can transmit the disease).

where y and Y occur simultaneously, we designate y as the number of individuals infected with parasites that are sensitive to drugs and Y as the number of individuals that are infected with the resistant parasites with or without the sensitive parasites. v and V denote respectively the populations of vectors harbouring sensitive and resistant parasites.

The following model with the corresponding stability analysis were presented in [2].

$$\square = cxq + c(1 - u)xQ - cuyQ - ry, \quad (2.1)$$

$$\square = cuxQ + cuyQ - RY, \quad (2.2)$$

$$\dot{q} = v - \delta q, \quad (2.3)$$

$$\dot{Q} = V - \Delta Q. \quad (2.4)$$

$$\square = -cx(y + Y) + ry + RY, \quad (2.5)$$

where c is the unit contact rate between susceptibles and infected mosquitoes with which new cases occur, ð and Δ are the death or removal rates of sensitive and resistant type mosquitoes respectively. The contribution cuy$Q$ is a case of superinfection. Such a phenomenon has been known to occur in reality (see for e.g. [4, 6]). If an infected individual is re-exposed before recovery, another brood of parasites may result; this is referred to superinfection. In this model it is assumed that the population of infected vectors grow by some influx.

Eliminating x from (2.1) and (2.2) (using $x + y + Y = N$) we get:

$$\square = -ry + cNq + cN(1 - u)Q - cyq - cYq - cyQ - c(1 - u)YQ \quad (2.6)$$

$$\square = -RY + cuNQ - cuYQ, \quad (2.7)$$

$$\dot{q} = v - \delta q \quad (2.8)$$

$$\dot{Q} = V - \Delta Q \quad (2.9)$$

A more appropriate reality is to assume that the sensitive vectors grow by factors proportional to both itself and the resistant type. In this case, equations (2.8) and (2.9) are replaced by

$$\dot{q} = \alpha_1 y + \alpha_2 Y - \delta q, \quad (2.10)$$

$$\dot{Q} = \gamma Y - \Delta Q \quad (2.11)$$

The system (2.6), (2.7), (2.10), and (2.11) has four equilibrium points in which the origin is one. By considering the linearized system near the origin, it is easy to see that the origin is locally asymptotically stable if

$$N \prec \min\left\{\frac{r\delta}{\alpha_1 c}, \frac{R\Delta}{cu\gamma}\right\}$$

and unstable if

$$N \succ \min\left\{\frac{r\delta}{\alpha_1 c}, \frac{R\Delta}{cu\gamma}\right\}$$

The other equilibrium points are $P_1(y_1,Y_1,q_1,Q_1) = \left(\frac{Nc\alpha_1 - r\delta}{c\alpha_1}, 0\frac{Nc\alpha_1 r\delta}{c\delta}, 0\right)$, $P_2(y_2,Y_2,q_2,Q_2) =$

$\left(y_2, \frac{cu\gamma N - r\Delta}{cu\gamma}, q_2, \frac{cu\gamma N - R\Delta}{cu\Delta}\right)$, $P_3(y_3,Y_3,q_3,Q_3) = \left(y_3, \frac{cu\gamma N - R\Delta}{cu\gamma}, q_3, \frac{cu\gamma N - R\Delta}{cu\Delta}\right)$ and each of (y_2, q_2), (y_3, q_3) satisfies some quadratic equation of the form

$$EX^2 + FX + G = 0, \quad (2.12)$$

where E, F and G are some functions of the parameters.

2.1 Proposition PS [16]

Consider the system $\square_1 = f(x_1, x_2)$

$\square_2 = g(x_2)$

with $f(.,.)$ and g(.) continuous throughout a compact subset E of R^2. Define $P(E)$ as the projection of E onto the x_2 axis. Assume

(1) E is positively invariant for the system, and

(2) $x_2 = \hat{x}_2$ is an equilibrium point that is globally asymptotically stable on a subset A of $P(E)$.

Then every trajectory starting in $A' = \{(x_1, x_2): x_2 \in A\}$ tends asymptotically to a point of the form ($\hat{x}_1$, $\hat{x}_2$), where $\hat{x}_1$ is an equilibrium of $\hat{x}_1 = f(x_1, \hat{x}_2)$.

Proof (see [16]

The author [2] extended Proposition PS to R4 and consequently proved that the system (2.6)–(2.9) has a unique positive globally asymptotic equilibrium point.

3.0 Multigroup models

Now, we consider a case of a heterogeneous interacting population groups: *Ni*, $i = 1, 2, ..., k$; $N = \sum_{i=1}^{k} N_i$. This consideration becomes necessary in view of the fact that resistivity of parasites to a particular antimalaria drug is a function of geographical distribution. We denote by y_i and Y_i respectively sensitive and resistant infecteds associated with group N_i; the corresponding vectors are denoted by q_i and Q_i respectively. Vectors from group j infect susceptibles of group i at a rate of c_{ij}. The probability that a susceptible in group i is infected by a resistant vector from group j is denoted by u_j; the complementary probability is $1 - u_j$. The model for this spatial heterogeneity is then described by the following system of differential equations: $\square_i = \sum_{i=1}^{k} [\, c_{ij}N_iq_j + c_{ij}N_i(1 - u_j)Q_j - c_{ij}q_j(y_i + Y_i) - c_{ij}y_iQ_j - c_{ij}(1 - u_j)Y_iQ_j] - r_iy_i$

(3.1)

$$\square_i = \sum_{i=1}^{k} [\, u_jc_{ij}Q_j(N_i - Y_i)] - R_iY_i, \tag{3.2}$$

$$\dot{q}_i = \nu_i - \delta_iq_i, \tag{3.3}$$

$$\dot{Q}_i = V_i - \Delta_iQ_i. \tag{3.4}$$

If vectors grow by factors proportional to the number of infecteds then equations (3.3) and (3.4) are replaced by

$$\dot{q}_i = \alpha_{1i}y_i + \alpha_{2i}Y_i - \delta_iq_i, \tag{3.5}$$

$$\dot{Q}_i = \gamma_i Y_i - \Delta_iQ_i, \tag{3.6}$$

$c_{ij} \geq 0$, $0 < u_i \leq 1$, $r_i > 0$, $R_i > 0$, α_{1i}, $\alpha_{2i} > 0$, $\delta_i > 0$, $\Delta_i > 0$,$\gamma_i > 0$ and $0 \leq y_i + Y_i \leq N_i$.

Let $X = (y_1, ..., y_k, Y_1, ..., Y_k, q_1, ..., q_k, Q_1, ..., Q_k)^T$. Then X is a $4k$-dimensional vector whose first, second, third, and fourth k components are respectively those of $y_i (i = 1, ..., k)$, $Yi (i = 1, ..., k)$, $q_i (i = 1, ..., k)$, and $Q_i (i = 1, ..., k)$.

For the stability analysis of the system (3.1)–(3.4) we shall generalize Proposition PS so that $(x_1, x_2) \in R^{4k}$ and $x_2 \in R^{3k}$. As can be seen from the system, both vector groups are each disconnected from the system as a whole.

Clearly $q_i \to \frac{u_i}{\delta_i}, Q_i \to \frac{V_i}{\Delta_i}$ as $t \to \infty$. By application of Proposition PS with $x_2 \in R^{2k}$ to the equations (3.2) and (3.4) we deduce, $\dot{Y} \to \frac{N_i \sum_{j=1}^{k} u_j c_{ij} \frac{V_j}{\Delta_j}}{\sum_{j=1}^{k} u_j c_{ij} \frac{V_j}{\Delta_j} + R_i}$. Hence equation (3.1) has the form

$$\dot{y}_i = \dot{y}_i = -\left(r_i + \sum_{j=1}^{k} [c_{ij}q_j + c_{ij}Q_j] \right) y_i + (N_i - Y_i) \sum_{j=1}^{k} c_{ij} \left[q_j + (1 - u_j) Q_j \right]$$

or

$$\dot{y}_i = -A_i(t)y_i + B_i(t)$$

where $A_i(t) \to A_i = r_i + \sum_{j=1}^{k}\left[c_{ij}\frac{v_j}{\delta_j} + c_{ij}\frac{V_j}{\Delta_j}\right] \succ 0$

as $t \to \infty$ and $B_i(t) \to B_i = (N_i - Y_i)\sum_{j=1}^{k} c_{ij}\left[\frac{v_j}{\delta_j} + (1-u_j)\frac{V_j}{\Delta_j}\right] \succ 0$

as $t \to \infty$ The rest of the proof follows by mimicking the idea used by the author in a previous paper [2].

Eventually we arrive at $y_i \to \frac{B_i}{A_i}$ as $t \to \infty$ which is the required result. Hence the system (3.1)–(3.4) has a unique positive globally asymptotic equilibrium.

The analysis of the system (3.1), (3.2), (3.5), and (3.8), we begin with the following definitions: is more complex than that of the corresponding ungrouped system (2.6), (2.7), (2.10), and (2.11). We begin with the following definitions. For vectors $\boldsymbol{a}$ and $\boldsymbol{b}$, where $\boldsymbol{a} = (a_1, ..., a_k)^T$, $\boldsymbol{b} = (b_1, ..., b_k)^T$, let $a \otimes b$ be the vector whose components are the products of the corresponding components of its arguments, i.e. $\boldsymbol{a} \otimes \boldsymbol{b} = (a_1b_1, ..., a_kb_k)^T$. It is easy to see that the operation is symmetric, bilinear, associative and commutative. If diag(**d**) for a vector **d** means the diagonal matrix (of appropriate dimension) whose ith diagonal entry is d_i and **1** means the vector with all components equal to 1, then $a \otimes \boldsymbol{b}$ = diag($\boldsymbol{a}$)$\boldsymbol{b}$ and $\boldsymbol{a}.\boldsymbol{b} = (\boldsymbol{a} \otimes \boldsymbol{b}).\mathbf{1}$ (where . means dot product). If $\boldsymbol{B}$ is a matrix, $\boldsymbol{a} \otimes \boldsymbol{B}$ is a matrix with $(\boldsymbol{a} \otimes \boldsymbol{B})_{ij} = a_iB_{ij}$. Let $\boldsymbol{y} = (y_1, ..., y_k)^T$, $\boldsymbol{Y} = (Y_1, ..., Y_k)^T$, $\boldsymbol{q} = (q_1, ..., q_k)^T$, $\boldsymbol{Q} = (Q_1, ...,Q_k)^T$. With these definitions, the vector form of system (3.1), (3.2), (3.5), and (3.6) is:

$\square = -\boldsymbol{r} \otimes \boldsymbol{y} + (\boldsymbol{N} \otimes \boldsymbol{C})\boldsymbol{q} + (\boldsymbol{N} \otimes \boldsymbol{C})((\mathbf{1} - \boldsymbol{u}) \otimes \boldsymbol{Q}) - ((\boldsymbol{y} + \boldsymbol{Y}) \otimes \boldsymbol{C})\boldsymbol{q}$

$-(\boldsymbol{y} \otimes \boldsymbol{C})\boldsymbol{Q} - (\boldsymbol{Y} \otimes \boldsymbol{C})((\mathbf{1} - \boldsymbol{u}) \otimes \boldsymbol{Q}),$ (3.7)

$\square = -\boldsymbol{R} \otimes \boldsymbol{Y} + (\boldsymbol{N} \otimes \boldsymbol{C})(\boldsymbol{u} \otimes \boldsymbol{Q}) - (\boldsymbol{Y} \otimes \boldsymbol{C})(\boldsymbol{u} \otimes \boldsymbol{Q})$ (3.8)

$\dot{q} = \alpha_1 \otimes \boldsymbol{y} + \alpha_2 \otimes \boldsymbol{Y} - \delta \otimes \boldsymbol{q},$ (3.9)

$\dot{Q} = \gamma \otimes \boldsymbol{Y} - \Delta \otimes \boldsymbol{Q},$ (3.10)

Consider the system $\dot{y}_i = \left(\sum_{j=1}^{n} w_{ij}y_j(N_i - y_i)\right) - g_iy_i$ (3.11)

where w_{ij} , N_i, g_i are constants and $w_{ij} > 0$, $N_i > 0$, $g_i > 0$, $y_i \geq 0$. Let y be the vector whose components are y_i, $i = 1, ... ,n$; A the matrix of linear terms, and $Q(y)$ the vector of quadratic terms in (3.5). Then the vector form of the system is, $\square = Ay - T(y)$ (3.12)

Lajmanovich and Yorke (see [10]) proved that solutions to system (3.6) are globally asymptotically stable with limiting value determined by the stability modulus $s(A)$ of the matrix A. This is defined as the maximum real part of the eigenvalues of A, i.e., $s(A) = \max\{\mathrm{Re}\,\lambda : \lambda$ an eigenvalue of $A\}$. Precisely, the following theorem was proved by Lajmanovich and Yorke.

3.1 Theorem LY

The solutions to system (24 approach the origin if $s(A) \leq 0$ and approach a unique positive equilibrium $\hat{y}$ if $s(A) > 0$, provided $y_i(0) > 0$ for some $\boldsymbol{i}$. Furthermore in this case $0 < \hat{y}_i(0) < N_i$ for each $I = 1, 2, ... ,n$.

Now, back to system (3.1), (3.2), (3.5), and (3.6). I do not know a complete analytical characterization of this system. However, with much restrictions as below, we arrive at some reasonable results:

If Q_i is fixed at its equilibrium, i.e. $\gamma_iY_i - \Delta_iQ_i = 0$

$\Rightarrow \qquad Q_i = \frac{\gamma_i}{\Delta_i}Y_i = \eta_iY_i$ (3.13)

where $\eta_i = \frac{\gamma_i}{\Delta_i}$. At this point, equation (3.2) becomes identical to equation (3.13). It follows that the resistant infecteds' subsystem is equivalent to the LY system; hence the resistant infecteds' subsystem tends asymptotically to a fixed nonnegative vector, say $\boldsymbol{Y^*}$. From (3.13), this also means that the resistant

vectors' subsystem tends asymptotically to a fixed vector, $\eta \otimes \boldsymbol{Y}^*$, where $\eta_i = \frac{\gamma_i}{\Delta_i}$. From equation (3.2), the matrix of coefficients for the resistant infecteds, which is disconnected from that of the sensitive infecteds, is

$$\boldsymbol{A}_Y = \text{diag}(\boldsymbol{N})\boldsymbol{C}\text{diag}(\boldsymbol{u} \otimes \eta) - \text{diag}(\mathbf{R})$$

and the vector of quadratic terms is $\boldsymbol{T} = (\boldsymbol{Y} \otimes \boldsymbol{C})(\mathbf{u} \otimes \eta \otimes \boldsymbol{Y})$. Thus, from theorem LY, $Y^* = 0$ if $s(\boldsymbol{A}_Y) \leq 0$, and $\boldsymbol{Y}^* \neq 0$ if $s(\boldsymbol{A}_Y) > 0$. Hence, $\boldsymbol{Q}^* = 0$ if $s(\boldsymbol{A}_Y) \leq 0$ and $\boldsymbol{Q}^* \neq 0$ if $s(\boldsymbol{A}_Y) > 0$. Again, note that if $(\boldsymbol{Y}(0),\boldsymbol{Q}(0))^T = (0, 0)^T$, then $\dot{q} = 0 \Rightarrow q_i = \frac{\alpha_i}{\delta_i} y_i = \xi_i y_i$. At this point,

$$\dot{y}_i = \left(\sum_{j=1}^{k} c_{ij} \xi_j y_j (N_i - y_i) \right) - r_i y_i$$

In this case, the sensitive infected humans' subsystem becomes identical to system (3.13) and hence it tends asymptotically to a fixed nonnegative vector y^*. The matrix of coefficients for the linear terms of the sensitive vectors when $\boldsymbol{Y}^T = \mathbf{0}^T$, $\boldsymbol{Q}^T = \mathbf{0}^T$, $\boldsymbol{q}^T = \mathbf{0}^T$ is $A_y = \text{diag}(\boldsymbol{N})C\text{diag}(\xi) - \text{diag}(\boldsymbol{r})$ and the vector of quadratic terms is $\boldsymbol{W}_y = (\mathbf{y} \otimes \mathbf{C})(\xi \otimes \boldsymbol{y})$, y tends asymptotically to 0 if $s(\boldsymbol{A}_y) \leq 0$ and to a fixed nonnegative vector y^*if $s(\boldsymbol{A}_y) > 0$. Hence, both infections die out if both $s(\boldsymbol{A}_y) \leq 0$ and $s(\boldsymbol{A}_Y) \leq 0$. Thus, our subconclusion is as follows:

***Theorem* 3.1**

(*i*) $(y,\boldsymbol{Y},\boldsymbol{q},\boldsymbol{Q})^T = (0,0,0,0)^T$ is asymptotically stable if $s(\boldsymbol{A}_Y) \leq 0$ and $s(\boldsymbol{A}_y) \leq 0$.

(*ii*) $(\boldsymbol{y},\boldsymbol{Y},\boldsymbol{q},\boldsymbol{Q})^T = (\boldsymbol{y}^*,\mathbf{0},\boldsymbol{q}^*,\mathbf{0})$T, (where $\boldsymbol{y}^*,\boldsymbol{q}^*$ are some positive vectors) is asymptotically stable if $s(\boldsymbol{A}_Y) \leq 0$ and $s(\boldsymbol{A}_y) > 0$.

Next, we examine the case, $s(\boldsymbol{A}_Y) > 0$. Let $\boldsymbol{E}_1 = \boldsymbol{Y} - \boldsymbol{Y}^*$, $\boldsymbol{E}_2 = \boldsymbol{Q} - \boldsymbol{Q}^*$. Then the equation for the sensitive (human and vectors) subsystems become

$$\square = -\boldsymbol{r} \otimes \boldsymbol{y} + (\boldsymbol{N} \otimes \boldsymbol{C})\boldsymbol{q} + (\boldsymbol{N} \otimes \boldsymbol{C})((\mathbf{1} - \boldsymbol{u}) \otimes (\boldsymbol{Q}^* + \boldsymbol{E}_2)) - ((\boldsymbol{y} + \boldsymbol{Y}^* + \boldsymbol{E}_1) \otimes \boldsymbol{C})\boldsymbol{q}$$
$$-(\boldsymbol{y} \otimes \boldsymbol{C})(\boldsymbol{Q}^* + \boldsymbol{E}_2) - ((\boldsymbol{Y}^* + \boldsymbol{E}_1) \otimes \boldsymbol{C})((\mathbf{1} - \boldsymbol{u}) \otimes (\boldsymbol{Q}^* + \boldsymbol{E}_2)), \quad (3.14)$$

$$\dot{q} = \alpha_1 \otimes \boldsymbol{y} + \alpha_2 \otimes (\boldsymbol{Y}^* + \boldsymbol{E}_1) - \delta \otimes \boldsymbol{q}. \quad (3.15)$$

At equilibrium, $\square = 0$, $\dot{q} = 0$, $E_1, E_2 \to 0$. From (3.14) and (3.15), this condition leads to a vector quadratic equation in each of $\boldsymbol{y}$ and $\boldsymbol{q}$, whose complete analytical characterization is elusive. However, for special cases such as $\boldsymbol{u} = 1$, $\alpha_2 = 0$, we again obtain asymptotic stability as follows: If $\boldsymbol{u} = \mathbf{1}$, $\alpha_2 = 0$, then at equilibrium $q_i = \frac{\alpha_{1i} y_i}{\delta_i} = w_i y_i$ (say). At this point, we see from equation (3.14) that

$$\square = -\boldsymbol{r} \otimes \boldsymbol{y} + (\boldsymbol{N} \otimes \boldsymbol{C})(\mathrm{w} \otimes \boldsymbol{y}) - ((\boldsymbol{y} + \boldsymbol{Y}^* + \boldsymbol{E}_1) \otimes C)(\boldsymbol{w} \otimes \boldsymbol{y}) - (\boldsymbol{y} \otimes \boldsymbol{C})(\mathrm{Q}^* + \boldsymbol{E}_2).$$

Now, $o(E_1,E_2) \to 0$ as $||E_1||, ||E_2|| \to 0$. Hence

$$\square = ((\boldsymbol{N} - \boldsymbol{y}) \otimes \boldsymbol{C})(\mathrm{w} \otimes \boldsymbol{y}) - (CQ^* + \boldsymbol{r}) \otimes \boldsymbol{y} - (\boldsymbol{Y}^* \otimes \boldsymbol{C})(\mathrm{w} \otimes \boldsymbol{y}) \quad (3.16)$$

Equation (3.16) can be identified with system (??) with the matrix

$$\boldsymbol{B}_y = \text{diag}(\boldsymbol{N} - \boldsymbol{Y}^*)\boldsymbol{C}\text{diag}(\mathrm{w}) - \text{diag}(\boldsymbol{C}\boldsymbol{Q}^* + \boldsymbol{r}), \quad (3.17)$$

as the matrix of coefficients for the linear term and $\boldsymbol{Z}_y = -(\boldsymbol{y} \otimes \boldsymbol{C})(\boldsymbol{w} \otimes \boldsymbol{y})$, as the vector of quadratic terms. Thus, $\boldsymbol{y} \to \mathbf{0}$ and consequently, $\boldsymbol{q} \to \mathbf{0}$ if $s(\boldsymbol{B}) \leq 0$ and $\boldsymbol{y} \to \boldsymbol{y}^* \neq 0$ and consequently $\boldsymbol{q} \to \mathrm{w} \otimes \boldsymbol{y}^*$ if $s(\boldsymbol{B}_y) \geq 0$.

Hence, we adjoin to the subconclusions in theorem 3.1 the following similar results and thus obtain a more general conclusion as regards the stability analysis of the system (3.1), (3.2), (3.5) and (3.6):

***Theorem* 3.2**

(*i*) $(\boldsymbol{y},\boldsymbol{Y},\boldsymbol{q},\boldsymbol{Q})^T = (\mathbf{0},\boldsymbol{Y}^*,\mathbf{0},\boldsymbol{Q}^*)^T$ is asymptotically stable if $s(\boldsymbol{A}_Y) > 0$ and $\boldsymbol{u} = \mathbf{1}$, $\alpha_2 = 0$ leads to $s(\boldsymbol{B}_y) \leq 0$.

(*ii*) $(\boldsymbol{y},\boldsymbol{Y},\boldsymbol{q},\boldsymbol{Q})^T = (\boldsymbol{y}^*,\boldsymbol{Y}^*,\boldsymbol{q}^*,\boldsymbol{Q}^*)^T$ is asymptotically stable if $s(\boldsymbol{A}_Y) > 0$ and $\boldsymbol{u} = \mathbf{1}$, $\alpha_2 = 0$ leads to $s(\boldsymbol{B}) > 0$, where $\boldsymbol{B}_y$ is the matrix in (3.17).

Thus, in case (*i*), sensitive infection dies out and in case (*ii*), an endemic state is reached for both infections.

***Remark* 3.3**

A complete analytical characterization and or solution of the system (3.1), (3.2), (3.5) and (3.6) proves elusive. It is certainly of interest to know the asymptotic limit(s) for all possible u when $s(\boldsymbol{A}_Y) > 0$, and $s(\boldsymbol{B}_y) > 0$.

4.0 Conclusion

This paper focuses on malaria infection in a multigroup population. The first model is typical of a situation in which there is a sudden out break of infection for each of the population groups. In this case, infected vectors arrive at a constant rate from the rest of the groups. This model shows that resistant infectives persist and nearly everybody could be infected with the resistant parasite if the death rate of resistant vectors is small. This is seen from the fact that $Y_i(t) - N_i$ as $\Delta_i \to 0$. Since resistant infectives are less sensitive to the drug, major health efforts should be geared towards destroying the parasites.

The second multigroup model describes more accurately the current trend in malaria infection, especially in Sub-Saharan Africa, for instance, where strains that are resistant to virtually all known drugs have emerged. Since efforts should be directed towards eliminating resistant parasites (and hence resistant infection), conditions leading to the results of theorem 1 should serve as guides to a health management board. Condition (i) of the theorem shows that eventually both strains of the parasites are eliminated. Condition (ii) shows that resistant parasites die off. On the other hands, theorem 3.2 shows that resistant parasites/infection persist in both conditions of the theorem. Condition (ii) shows that an endemic state is reached for both infections. These models differ considerably from the ealier models of malaria infection such as [3, 4, 5, 6, 11] in that each model here addresses acurately the evolution of resistant infection and the results here are more complex than the earlier results of the author [2].

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