Assessing The Effects of Global Warming Up in Malaria Transmission by Mathematical Model

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Abstract

Based on a compartmental model describing the overall transmission of malaria, we assess the effects of the different levels of acquired immunity and temperature-dependent vector related parameter on the state variables and on the basic reproduction ratio by the sensitivity analysis.

keywords: malaria - host-vector interaction - mathematical model - sensitivity

1 INTRODUCTION

Malaria is caused by a protozoan parasite of the genus *Plasmodium*, and transmitted by the bite of female *Anopheles* mosquitoes. Four *Plasmodium* species cause human malaria: *P. falciparum* is the commonest, being associated with a potentially fatal disease, while *P. vivax*, *P. malariae* and *P. ovale* cause clinically significant but non-fatal infections.

Human infection begins when sporozoites are injected by *Anopheles* mosquitoes and move rapidly into the liver. Most bites inject less than 20 sporozoe...
zoites, and few inject more than 100 sporozoites [14]. The first asexual multiplication occurs within liver cells, resulting in the production of 10-40 thousand merozoites per sporozoite. The merozoites are released into the bloodstream and invade red blood cells, where they multiply asexually to produce 8-32 new merozoites. These either repeat the multiplication cycle within red blood cells or develop into the sexual transmission stages called gametocytes. The factors which induce gametocyte production after some asexual cycles are unknown, but it has been suggested that merozoites convert into gametocytes when micro-environmental conditions become unfavorable for parasite multiplication [17].

Male and female gametocytes are taken up by mosquitoes, and fertilization takes place in the mosquito gut. After a further phase of asexual multiplication (sporogony), thousands of sporozoites are produced and migrate to the salivary glands. In highly endemic areas in Kenya, infected An. gambiæ s.l. may harbour up to 117,500 (median 914) sporozoites in their salivary glands [1]. Mosquito survival does not seem to be affected by infection with human Plasmodium species [5] [10] [22], but discordant results have been reported in other vector-parasite systems [12].

Even among people exposed to continuous and intense malaria transmission, as in rural African communities, antimalarial immunity develops rather slowly. Most infants contract their primary malaria attack during the first year of life, while toddlers and juveniles have already developed some tolerance against severe disease. Full sterile immunity against asexual blood stages is rarely seen, and gametocytes seem to be little affected by human immune responses. Unless booster inoculations are received, the efficacy of this partial acquired immunity decreases with time. The poor immunogenicity and the antigenic diversity of malarial antigens have been suggested as causes of the delayed development and short duration of protective immunity [18].

There has recently been a growing interest on the possible effects of global warming on the epidemiology of malaria and other vector-borne diseases [20] [23]. Due to the ‘greenhouse effect’, the global annual average temperature at the surface of the earth is expected to increase between 1.0 to 3.5 °C by the year 2100. The impact of global warming is currently considered by the World Health Organization as one of the largest public health challenges for the next century [20]. The effect of global warming on malaria transmission, for instance, has been examined in terms of increased vectorial capacity [11]
However, the impact of temperature changes may be disproportionately higher in populations with low levels of antimalarial immunity, such as children and adults originated from malaria-free regions [15]. Another aspect of malaria risk is related to the local conditions and developments. The change in malaria transmission can be associated with socio-economic (e.g., prevailing health services and the sanitation improvements) conditions. In most malaria endemic areas the effect of a temperature increase on the disease transmission seems limited, however changes of socio-economic conditions are far more important than a temperature change [11].

In this paper, we present a mathematical model to describe the overall P. falciparum malaria transmission in quantitative terms, considering different levels of acquired immunity among human hosts and vector related parameters dependent on temperature. Mathematical models of malaria transmission, which have recently been reviewed and discussed elsewhere [3] [8] [9] [24], were extensively used to guide the partially effective worldwide eradication efforts between 1955 and 1970 [16] [19]. Based on the model, we analyze the epidemiological impact of temperature changes and socio-economical conditions on malaria incidence by the sensitivity analysis [28] [29].

2 MODEL

In this section we describe briefly the malaria transmission model proposed by Yang [30]. For humans, they used seven compartments which represent the fractions of individuals at a given time $t$ who are susceptible ($x_1$), incubating ($x_2$), infectious ($x_3$), immune ($x_4$), partially immune ($x_5$), non-immune but with immunologic memory ($x_6$) and incubating after re-infection ($x_7$). Incubating hosts are those with asexual blood-stage infection but without infectious gametocytes, while infectious hosts are those with circulating mature gametocytes. Immune hosts are fully protected against new infections, while partially immune hosts still have protective antibodies and other immune effectors but at low levels; if inoculated with sporozoites, however, effective immune responses will be elicited before asexual parasitemia develops. Non-immune hosts with immunologic memory are susceptible to new inoculations, but asexual blood-stage parasitemia is cleared before infectious gametocytes are produced. Therefore, a very simple model of acquired immunity were taken into account by disregarding the age at first infection or the period of
time elapsed to build up an immune response [25] [26]. On the other hand, the mosquito population was divided into three compartments $y_1(t), y_2(t)$ and $y_3(t)$, which are the fractions, respectively, of susceptible, incubating (infected but non-infectious), and infectious mosquitoes at time $t$.

The fractions of the host population, considered constant, were described by the following system of differential equations

$$
\begin{align*}
\dot{x}_1(t) &= \mu + (\theta + \alpha) x_2(t) + \pi_3 x_6(t) - [h y_3(t) + \mu] x_1(t) \\
\dot{x}_2(t) &= h y_3(t) x_1(t) - (\theta + \gamma_1 + \mu + \alpha) x_2(t) \\
\dot{x}_3(t) &= \gamma_1 x_2(t) - (\gamma + \mu) x_3(t) \\
\dot{x}_4(t) &= \gamma x_3(t) + h y_3(t) x_5(t) + \gamma_1 x_7(t) - (\pi_1 + \mu) x_4(t) \\
\dot{x}_5(t) &= \pi_1 x_4(t) - [h y_3(t) + \pi_2 + \mu] x_5(t) \\
\dot{x}_6(t) &= \pi_2 x_5(t) + \theta x_7(t) - [h y_3(t) + \pi_3 + \mu] x_6(t) \\
\dot{x}_7(t) &= h y_3(t) x_6(t) - (\theta + \gamma_1 + \mu) x_7(t),
\end{align*}
$$

where $y_3(t)$ is the fraction of infectious mosquitoes, $\mu$ and $\alpha$ are, respectively, the natural and differential (disease-induced) mortality rates of human host, $\theta$ is the natural resistance rate against malaria, $\gamma_1^{-1}$ and $\gamma^{-1}$ are the average periods, respectively, to initiate the production of gametocytes and to build up an effective immune response, $\pi_1$, $\pi_2$ and $\pi_3$ are, respectively, rates at which protective immunity, partial immunity and immunologic memory are lost, and $h$ is the inoculation rate.

The mosquitoes population was described by the following system of equations

$$
\begin{align*}
\dot{y}_1(t) &= (\mu' + \alpha') [y_2(t) + y_3(t)] - f x_3(t) y_1(t) \\
\dot{y}_2(t) &= f x_3(t) y_1(t) - [\rho(T) + \mu' + \alpha'] y_2(t) \\
\dot{y}_3(t) &= \rho(T) y_2(t) - (\mu' + \alpha') y_3(t),
\end{align*}
$$

where $\mu'$ and $\alpha'$ are, respectively, the natural and induced (for instance, by insecticides) mortality rates of mosquitoes, $\rho^{-1}(T)$ is the duration of sporogony (development from the gametocyte to the infective sporozoite) in the
mosquito, which depends on the temperature $T$, and $f$ is the transmission rate. Note that the first equation is slightly different of that presented in Yang [30]. The reason is that here we are assuming, explicitly, that the mosquitoes population size is maintained constant on time, which resulted in the temperature dependency only on the parameter $\rho$ (Hereafter we will drop out the symbol $T$).

In Appendix A we present the equilibrium points of systems (1) and (2). Detailed calculations can be found in [30]. In the next section we present the model's sensitivity to its parameters.

3 SENSITIVITY ANALYSIS

The sensitivity analysis gives the range of the variation of the model's variables, such as the state variables and the basic reproduction ratio, when the parameters are varied. The state variables in the equilibrium, which are the trivial, given by equations (14) and (15), and non-trivial, given by equations (16) and (17), and the basic reproduction ratio, given by (19) but rewritten as

$$R_0 = \frac{fh\gamma_1\rho}{(\theta + \gamma_1 + \mu + \alpha)(\gamma + \mu)(\mu' + \alpha')(\rho + \mu' + \alpha')}$$

(3)

are dependent on the parameters of the model. Since the model's parameters are not accurate, then how the inaccuracy of these values can influence the model's variables is treated by the sensitivity analysis.

Let us define the parameter space $\omega$ as

$$\omega = [\theta, \gamma_1, \gamma, \mu, \alpha, \rho, \mu', \alpha', \pi_1, \pi_2, \pi_3]^T$$

(4)

plus $f$ and $h$. Also, we define the state variable $z$ as

$$z = [x_1, x_2, x_3, x_4, x_5, x_6, x_7, y_1, y_2, y_3]^T$$

(5)

where the superscript $T$ stands for the transposition of the matrix. Note that the unreliable estimation of the values in the parameter space results in inaccuracy in the values of the state variable.

The sensitivity analysis is done as follows. Using the absolute sensitivity function [4] we have, for the covariance matrix for the state variables $z$,

$$V_z = H\omega H^T$$

(6)
where $V_\omega$ is the covariance matrix for the 11 parameters of $\omega$ stated in (4) and $H$ is the sensitivity matrix given by

$$H = J^{-1} P,$$

(7)

with its elements denoted by $h_{ij}$. Note that $P$ is given by

$$P = \left. \frac{\partial F[z, \omega]}{\partial \omega} \right|_{z^*, \omega}, \quad k = 1 \text{ or } 2,$$

(8)

where the index 1 refers to the trivial and 2 to the non-trivial equilibrium point, and $J^*$, given by

$$J^* = \left. \frac{\partial F[z, \omega]}{\partial z} \right|_{z^*, \omega}, \quad k = 1 \text{ or } 2,$$

(9)

is the Jacobian matrix evaluated at the equilibrium values $z^1$ and $z^2$. Observe that $F_i[z, \omega]$, where $i = 1 \text{ to } 10$, corresponds to the second member of systems (1) and (2).

If we consider $V_\omega$ diagonal, with its diagonal elements given by $\sigma_{\omega_j}^2$, where $j = 1 \text{ to } 11$, then the variances related to the state variables (the diagonal elements of $V_\omega$) are given by

$$\sigma_{z_i}^2 = \sum_{j=1}^{11} h_{ij}^2 \sigma_{\omega_j}^2; \quad \text{with } i = 1, 2, \ldots, 10.$$

(10)

This expression also gives the contribution of each parameter ($h_{ij}^2 \sigma_{\omega_j}^2$) to the dynamic variables sensitivity.

However, the basic reproduction ratio, given by (3), does not depend on all parameters defined in (4). Let us define a subset $\omega'$ of parameters space $\omega$ as

$$\omega' = [\theta, \gamma_1, \gamma_2, \mu, \alpha, \rho, \mu', \alpha']^T.$$

(11)

Then, the variation in $R_0$, due to the inaccuracy in the parameters, is given by

$$\sigma_{R_0}^2 = \sum_{j=1}^{8} \left( h_{ij} \right)^2 \left( \sigma_{\omega_j} \right)^2,$$

(12)
where \((\sigma_{\omega_j})^2\), with \(j = 1\) to \(8\), are the variances given by \(V_{\omega_j}\), and \(h'_j\), with \(j = 1\) to \(8\), are the elements of the vector

\[
\mathbf{H}' = \frac{\partial R_0(\omega')}{\partial \omega'}.
\] (13)

Observe that \((h'_j)^2(\sigma_{\omega_j})^2\) is the contribution of the \(j\)-th parameter to the variance of \(R_0\).

4 NUMERICAL RESULTS

In this section we assess the effects of different levels of acquired immunity among human hosts and the influence of temperature on the parameter related to vectors by the sensitivity analysis.

Table I shows the range and the mean value of the parameters. The values of the parameters are given in terms of the period of time.

<table>
<thead>
<tr>
<th>parameter</th>
<th>range</th>
<th>mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\theta^{-1}(d))</td>
<td>1 - 4 [7]</td>
<td>2.5</td>
</tr>
<tr>
<td>(\gamma^{-1}(d))</td>
<td>15 - 19 [6]</td>
<td>17</td>
</tr>
<tr>
<td>(\gamma^{-1}(d))</td>
<td>50 - 150 [24]</td>
<td>100</td>
</tr>
<tr>
<td>(\pi^{-1}(d))</td>
<td>40 - 60 [24]</td>
<td>50</td>
</tr>
<tr>
<td>(\pi^{-1}(y))</td>
<td>0.2 - 5 [2]</td>
<td>2.6</td>
</tr>
<tr>
<td>(\pi^{-1}(y))</td>
<td>1 - 20 [2]</td>
<td>10.5</td>
</tr>
<tr>
<td>(\mu^{-1}(y))</td>
<td>50 - 55 [2]</td>
<td>52.5</td>
</tr>
<tr>
<td>(\alpha^{-1}(y))</td>
<td>2450 - 2964</td>
<td>2707</td>
</tr>
<tr>
<td>(\mu'^{-1}(d))</td>
<td>10 - 14 [6]</td>
<td>12</td>
</tr>
<tr>
<td>(\alpha'^{-1}(d))</td>
<td>98 - 191.8</td>
<td>144.9</td>
</tr>
<tr>
<td>(\rho^{-1}(d))</td>
<td>8 (31°C) - 22 (20°C) [13] [16]</td>
<td>15</td>
</tr>
</tbody>
</table>

Table I. The values found in the literature for the parameters of the model.

The symbols \(d\) and \(y\) stand, respectively, for days and years.

The above table was obtained from the literature for the parameters \(\theta, \gamma_1, \gamma, \pi_1, \pi_2, \pi_3, \mu, \mu'\) and \(\rho\). In relation to differential (\(\alpha\)) and induced (\(\alpha'\)) mortality rates, we assumed decreasing of, respectively, around 2 and 6 % in the expected life-span.
The above periods must be converted to rates. For this purpose, we use the relation

\[ p \pm \sigma_p \cong r \pm \sigma_r , \]

where \( p \) and \( r \) stand, respectively, for the periods and the corresponding rates, \( \sigma_{p,r} \) for the standard deviations and the identities

\[
\begin{align*}
  r &= \frac{1}{p} \\
  \sigma_r &= \frac{\sigma_p}{p^2} .
\end{align*}
\]

Note that \( p \) is the arithmetic mean between the maximum and the minimum values, which is given in the third column of Table I, and \( \sigma_p \) is the half range between the maximum and the minimum values related to \( p \). The transformations are presented in Table II.

<table>
<thead>
<tr>
<th>parameter ( \theta ) (( d^{-1} ))</th>
<th>mean</th>
<th>standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \gamma_1 ) (( d^{-1} ))</td>
<td>0.4</td>
<td>0.24</td>
</tr>
<tr>
<td>( \gamma ) (( d^{-1} ))</td>
<td>0.01</td>
<td>0.005</td>
</tr>
<tr>
<td>( \pi_1 ) (( d^{-1} ))</td>
<td>0.02</td>
<td>0.004</td>
</tr>
<tr>
<td>( \pi_2 ) (( y^{-1} ))</td>
<td>0.38</td>
<td>0.35</td>
</tr>
<tr>
<td>( \pi_3 ) (( y^{-1} ))</td>
<td>0.095</td>
<td>0.086</td>
</tr>
<tr>
<td>( \mu ) (( y^{-1} ))</td>
<td>0.019</td>
<td>0.0009</td>
</tr>
<tr>
<td>( \alpha ) (( y^{-1} ))</td>
<td>0.0004</td>
<td>0.00004</td>
</tr>
<tr>
<td>( \mu' ) (( d^{-1} ))</td>
<td>0.083</td>
<td>0.014</td>
</tr>
<tr>
<td>( \alpha' ) (( d^{-1} ))</td>
<td>0.007</td>
<td>0.002</td>
</tr>
<tr>
<td>( \rho ) (( d^{-1} ))</td>
<td>0.067</td>
<td>0.031</td>
</tr>
</tbody>
</table>

Table II. The corresponding rates of the parameters given in Table I. The symbols \( d^{-1} \) and \( y^{-1} \) stand, respectively, for \( \text{days}^{-1} \) and \( \text{years}^{-1} \).

All the following results are based on the values shown in Table II. By the fact that the sensitivity is fundamentally a local analysis, all discussions presented below are valid only on the above range of values of the parameters.

We perform the sensitivity analysis of the basic reproduction ratio and the equilibrium values with respect to the parameters of the model. Firstly, in Table III we summarize the equilibrium values calculated with the mean
values of the parameters, which are shown in the second column of Table II. We considered three rates (given in $days^{-1}$): $h = 0.18$ and $f = 0.12$, $h = 0.70$ and $f = 0.19$ and $h = 2.0$ and $f = 0.26$.

\[
\begin{array}{ccc}
P_1 & P_2 & P_3 \\
0.776 & 0.129 & 0.033 \\
0.0009 & 0.002 & 0.0015 \\
0.0052 & 0.0125 & 0.009 \\
0.0046 & 0.165 & 0.423 \\
0.0565 & 0.378 & 0.39 \\
0.156 & 0.308 & 0.14 \\
0.0002 & 0.005 & 0.006 \\
0.993 & 0.974 & 0.976 \\
0.004 & 0.015 & 0.014 \\
0.003 & 0.011 & 0.010 \\
\end{array}
\]

\[R_0 \quad 1.30 \quad 8.0 \quad 31.23\]

Table III. The equilibrium values of human and mosquito populations and the basic reproduction ratio $R_0$, for $h = 0.18$ and $f = 0.12$ ($P_1$), for $h = 0.70$ and $f = 0.19$ ($P_2$) and for $h = 2.0$ and $f = 0.26$ ($P_3$).

The rates are given in $days^{-1}$.

Table III are focusing three regions: disease at a low endemic level (Amazon), disease at an intermediate endemic level (South East Asia) and disease at a high endemic level (Africa). The disease-free community, but potentially under risk (South East of Brazil) was not taken into account because the Jacobian, given by equation (9) evaluated at the trivial equilibrium point, has one zero column.

The sensitivity analysis of the basic reproduction ratio with respect to the parameters given in (11) can be done by the equation (12). This equation takes into account the contributions of each parameter to the variance of the basic reproduction ratio. In Table IV we show the sensitivity analysis of the basic reproduction ratio, for $h = 0.18$ and $f = 0.12$ ($P_1$), $h = 0.70$ and
\[ f = 0.19 \ (P_2) \] and \[ h = 2.0 \] and \[ f = 0.26 \ (P_3) \] (given in \( \text{days}^{-1} \)).

<table>
<thead>
<tr>
<th>rank</th>
<th>( R_0 \ (P_1) )</th>
<th>( R_0 \ (P_2) )</th>
<th>( R_0 \ (P_3) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \theta \ (0.46) )</td>
<td>( \theta \ (17.4) )</td>
<td>( \theta \ (266.7) )</td>
</tr>
<tr>
<td>2</td>
<td>( \gamma \ (0.42) )</td>
<td>( \gamma \ (15.8) )</td>
<td>( \gamma \ (241.2) )</td>
</tr>
<tr>
<td>3</td>
<td>( \rho \ (0.12) )</td>
<td>( \rho \ (4.95) )</td>
<td>( \rho \ (70.2) )</td>
</tr>
<tr>
<td>4</td>
<td>( \mu' \ (0.10) )</td>
<td>( \mu' \ (3.75) )</td>
<td>( \mu' \ (57.3) )</td>
</tr>
<tr>
<td>5</td>
<td>( \gamma_1 \ (0.02) )</td>
<td>( \gamma_1 \ (0.67) )</td>
<td>( \gamma_1 \ (10.3) )</td>
</tr>
<tr>
<td>6</td>
<td>( \alpha' \ (0.003) )</td>
<td>( \alpha' \ (0.10) )</td>
<td>( \alpha' \ (1.48) )</td>
</tr>
<tr>
<td>7</td>
<td>( \mu \ (10^{-7}) )</td>
<td>( \mu \ (10^{-6}) )</td>
<td>( \mu \ (10^{-4}) )</td>
</tr>
<tr>
<td>8</td>
<td>( \alpha \ (10^{-13}) )</td>
<td>( \alpha \ (10^{-12}) )</td>
<td>( \alpha \ (10^{-11}) )</td>
</tr>
</tbody>
</table>

\[ \sigma^2_{R_0} = 1.12 \quad 42.3 \quad 647.2 \]

Table IV. The sensitivity analysis of the basic reproduction ratio \( R_0 \), for \( h = 0.18 \) and \( f = 0.12 \ (P_1) \), for \( h = 0.70 \) and \( f = 0.19 \ (P_2) \) and for \( h = 2.0 \) and \( f = 0.26 \ (P_3) \). The rates are given in \( \text{days}^{-1} \).

The standard deviation (the square root of the variance) of \( R_0 \) for the three equilibrium points are: \( \sigma_{R_0} = 1.06 \ (P_1) \), \( \sigma_{R_0} = 6.51 \ (P_2) \) and \( \sigma_{R_0} = 25.44 \ (P_3) \).

Table IV shows that 98.2% of variation in \( R_0 \) is due to three parameters which are related to the state variables \( x_3 \) and \( y_3 \), plus the mortality rate of the vector population \( \mu' \). Note that the two most sensitive (together contribute with 78.6%) human related parameters \( \theta \) and \( \gamma^{-1} \) are, respectively, the natural resistance rate and period of time to build up the effective immunity; and the third and fourth most sensitive (together contribute with 19.6%) are vector related parameters \( \rho^{-1} \), which is the duration of sporogony, and \( \mu' \). The vital dynamics parameters \( \mu \) and \( \alpha \) related to human population are practically insensitive. Also, the sensitivity of the input rate \( \gamma_1 \) to the infectious individuals \( x_3 \) is negligible. Observe that this parameter shows a narrow range (one fourth) of variation in comparison with the three most sensitive parameters.

Based on the sensitivity analysis of \( R_0 \) with respect to the eight parameters, we can draw following results. To reduce the risk of malaria infection looking naively only to the decreasing in \( R_0 \), the most effective mechanisms
are those related to prevent the increasing in the fractions of infectious individuals $x_3$ and mosquitoes $y_3$. Observe that there are two mechanisms to decrease the number of infectious individuals: by increasing the natural resistance rate (by drug treatment) or by decreasing the period of time to build up the immunity (by vaccination). In relation to vector population, the controlling effects must increase the duration of sporogony (by avoiding the global warm up by pollution) and/or increase the mortality rate (by applying insecticide).

The sensitivity of $R_0$ shows that the eradication condition can be achieved only in the situation of malaria at a very low risk. Next, we analyze the variation of equilibrium points (the state variables) with the variation in the parameters.

The sensitivity analysis of the equilibrium points with respect to the parameters given in (4) can be done by the equation (10). This equation takes into account the contributions of each parameter to the variance of the equilibrium points. The matrix Jacobian given by equation (9) evaluated at the equilibrium points can be inverted by the Gauss-Jordan method [21]. The following results are based on Table III for three malaria endemic regions.

Firstly, malaria at a very low endemic level area is considered. Table V shows the sensitivity analysis of the state variables for $h = 0.18$ and $f = 0.12$ (given in days$^{-1}$).

<table>
<thead>
<tr>
<th>rank</th>
<th>$x_1 (10^{-3})$</th>
<th>$x_2 (10^{-8})$</th>
<th>$x_3 (10^{-6})$</th>
<th>$x_4 (10^{-6})$</th>
<th>$x_5 (10^{-4})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\theta$ (26.9)</td>
<td>$\theta$ (38.5)</td>
<td>$\rho$ (23.6)</td>
<td>$\rho$ (34.0)</td>
<td>$\theta$ (22.8)</td>
</tr>
<tr>
<td>2</td>
<td>$\rho$ (24.2)</td>
<td>$\rho$ (36.9)</td>
<td>$\gamma$ (20.0)</td>
<td>$\gamma$ (20.0)</td>
<td>$\pi_2$ (19.9)</td>
</tr>
<tr>
<td>3</td>
<td>$\gamma$ (7.65)</td>
<td>$\gamma$ (10.4)</td>
<td>$\theta$ (13.2)</td>
<td>$\gamma$ (7.39)</td>
<td>$\rho$ (15.1)</td>
</tr>
<tr>
<td>4</td>
<td>$\pi_3$ (5.62)</td>
<td>$\mu'$ (4.71)</td>
<td>$\pi_3$ (1.26)</td>
<td>$\mu'$ (4.71)</td>
<td>$\gamma$ (6.09)</td>
</tr>
<tr>
<td>5</td>
<td>$\mu'$ (4.82)</td>
<td>$\pi_3$ (3.09)</td>
<td>$\mu'$ (0.75)</td>
<td>$\pi_1$ (0.83)</td>
<td>$\mu'$ (3.01)</td>
</tr>
<tr>
<td>6</td>
<td>$\gamma_1$ (1.03)</td>
<td>$\pi_2$ (0.42)</td>
<td>$\gamma_1$ (0.51)</td>
<td>$\gamma_1$ (0.77)</td>
<td>$\gamma_1$ (0.88)</td>
</tr>
<tr>
<td>7</td>
<td>$\pi_2$ (0.64)</td>
<td>$\alpha'$ (0.12)</td>
<td>$\pi_2$ (0.14)</td>
<td>$\pi_2$ (0.70)</td>
<td>$\pi_3$ (0.38)</td>
</tr>
<tr>
<td>8</td>
<td>$\alpha'$ (0.12)</td>
<td>$\gamma_1$ (0.03)</td>
<td>$\alpha'$ (0.02)</td>
<td>$\pi_3$ (0.47)</td>
<td>$\alpha'$ (0.08)</td>
</tr>
<tr>
<td>9</td>
<td>$\mu$ (10^{-3})</td>
<td>$\mu$ (10^{-3})</td>
<td>$\mu$ (10^{-4})</td>
<td>$\alpha'$ (0.12)</td>
<td>$\pi_1$ (10^{-4})</td>
</tr>
<tr>
<td>10</td>
<td>$\pi_1$ (10^{-4})</td>
<td>$\pi_1$ (10^{-4})</td>
<td>$\pi_1$ (10^{-5})</td>
<td>$\mu$ (10^{-5})</td>
<td>$\mu$ (10^{-5})</td>
</tr>
<tr>
<td>11</td>
<td>$\alpha$ (10^{-12})</td>
<td>$\alpha$ (10^{-11})</td>
<td>$\alpha$ (10^{-12})</td>
<td>$\alpha$ (10^{-12})</td>
<td>$\alpha$ (10^{-12})</td>
</tr>
</tbody>
</table>

$\sigma_{x_1}^2$ | 71.0 | 94.7 | 59.5 | 69.0 | 68.3 |
Table V (a)

<table>
<thead>
<tr>
<th>rank</th>
<th>$x_6 (10^{-3})$</th>
<th>$x_7 (10^{-9})$</th>
<th>$y_1 (10^{-2})$</th>
<th>$y_2 (10^{-7})$</th>
<th>$y_3 (10^{-7})$</th>
</tr>
</thead>
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<td>1</td>
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<td>$\gamma (14.6)$</td>
<td>$\rho (37.8)$</td>
<td>$\rho (85.1)$</td>
</tr>
<tr>
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<td>$\rho (8.71)$</td>
<td>$\theta (81.6)$</td>
<td>$\theta (9.59)$</td>
<td>$\gamma (35.2)$</td>
<td>$\gamma (19.2)$</td>
</tr>
<tr>
<td>3</td>
<td>$\pi_3 (6.90)$</td>
<td>$\gamma (22.0)$</td>
<td>$\mu' (3.26)$</td>
<td>$\theta (23.2)$</td>
<td>$\theta (12.6)$</td>
</tr>
<tr>
<td>4</td>
<td>$\gamma (3.04)$</td>
<td>$\mu' (11.8)$</td>
<td>$\pi_3 (0.92)$</td>
<td>$\mu' (11.8)$</td>
<td>$\mu' (4.24)$</td>
</tr>
<tr>
<td>5</td>
<td>$\mu' (1.21)$</td>
<td>$\pi_3 (5.48)$</td>
<td>$\rho (0.39)$</td>
<td>$\pi_3 (2.22)$</td>
<td>$\pi_3 (1.21)$</td>
</tr>
<tr>
<td>6</td>
<td>$\gamma_1 (0.44)$</td>
<td>$\gamma_1 (1.22)$</td>
<td>$\gamma_1 (0.37)$</td>
<td>$\gamma_1 (0.89)$</td>
<td>$\gamma_1 (0.48)$</td>
</tr>
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<td>$\pi_2 (0.88)$</td>
<td>$\pi_2 (0.10)$</td>
<td>$\alpha' (0.30)$</td>
<td>$\pi_2 (0.14)$</td>
</tr>
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<td>$\alpha' (0.03)$</td>
<td>$\alpha' (0.30)$</td>
<td>$\alpha' (0.08)$</td>
<td>$\pi_2 (0.25)$</td>
<td>$\alpha' (0.11)$</td>
</tr>
<tr>
<td>9</td>
<td>$\mu (10^{-3})$</td>
<td>$\mu (10^{-3})$</td>
<td>$\mu (10^{-4})$</td>
<td>$\mu (10^{-4})$</td>
<td>$\mu (10^{-4})$</td>
</tr>
<tr>
<td>10</td>
<td>$\pi_1 (10^{-4})$</td>
<td>$\pi_1 (10^{-4})$</td>
<td>$\pi_1 (10^{-5})$</td>
<td>$\pi_1 (10^{-5})$</td>
<td>$\pi_1 (10^{-5})$</td>
</tr>
<tr>
<td>11</td>
<td>$\alpha (10^{-12})$</td>
<td>$\alpha (10^{-12})$</td>
<td>$\alpha (10^{-12})$</td>
<td>$\alpha (10^{-12})$</td>
<td>$\alpha (10^{-12})$</td>
</tr>
</tbody>
</table>

$\sigma^2_{z_1}$ 32.2 215.6 29.3 111.6 123.1

Table V (b)

Table V. The sensitivity analysis for the equilibrium point $P_1$. The exponent between parenthesis in the first row is the multiplying factor of the column.

The standard deviation of the state variables are: $\sigma_{x_1} = 0.27$, $\sigma_{x_2} = 0.001$, $\sigma_{x_3} = 0.0077$, $\sigma_{x_4} = 0.008$, $\sigma_{x_5} = 0.08$, $\sigma_{x_6} = 0.18$, $\sigma_{x_7} = 0.0004$, $\sigma_{y_1} = 0.54$, $\sigma_{y_2} = 0.0033$ and $\sigma_{y_3} = 0.0035$.

When a community is at a very low risk of malaria, we observe that the parameters $\rho$, $\theta$ and $\gamma$ are, generally, the most sensitive parameters for all state variables. The number of times that the previous three parameters appear leading the ranking in relation to the state variables are, respectively, 5, 4 and 1. At fourth and fifth ranking appear $\mu'$ and $\pi_3$. In general, these five parameters contribute practically with all the variations in the state variables. On the other hand, $\mu$, $\pi_1$ and $\alpha$ are the least sensitive parameters. Other loss of immunity parameters, $\pi_2$ and $\pi_3$, are also few sensitive. In this situation, the susceptible individuals can reach unity value, that is, the population can be free of the disease.

Malaria at an intermediate endemic level area is considered. Table VI shows the sensitivity analysis of the state variables for $h = 0.70$ and $f = 0.19$. 69
(given in $\text{days}^{-1}$).

$$
\begin{array}{cccccc}
\text{rank} & x_1 (10^{-4}) & x_2 (10^{-8}) & x_3 (10^{-6}) & x_4 (10^{-4}) & x_5 (10^{-3}) \\
1 & \gamma (31.5) & \pi_3 (60.2) & \gamma (26.6) & \gamma (44.2) & \pi_2 (12.3) \\
2 & \theta (19.8) & \pi_2 (21.5) & \pi_3 (20.6) & \pi_3 (34.3) & \theta (4.30) \\
3 & \rho (9.68) & \gamma_1 (7.09) & \pi_2 (7.36) & \rho (9.68) & \gamma (1.31) \\
4 & \pi_2 (5.76) & \gamma (3.34) & \rho (0.23) & \pi_2 (7.95) & \pi_3 (1.02) \\
5 & \mu' (1.93) & \rho (1.48) & \theta (0.10) & \pi_1 (7.52) & \rho (0.97) \\
6 & \gamma_1 (1.07) & \theta (0.31) & \pi_1 (0.07) & \gamma_1 (0.04) & \gamma_1 (0.21) \\
7 & \pi_3 (0.48) & \pi_1 (0.21) & \mu (0.02) & \mu (0.03) & \mu' (0.19) \\
8 & \pi_1 (0.08) & \mu' (0.07) & \gamma_1 (0.01) & \theta (10^{-3}) & \pi_1 (0.17) \\
9 & \alpha' (0.05) & \mu (0.06) & \alpha (10^{-13}) & \alpha (10^{-13}) & \alpha' (10^{-3}) \\
10 & \mu (10^{-4}) & \alpha' (10^{-3}) & \mu' (0) & \mu' (0) & \mu (10^{-4}) \\
11 & \alpha (10^{-11}) & \alpha (10^{-13}) & \alpha' (0) & \alpha' (0) & \alpha (10^{-12}) \\
\end{array}
$$

$\sigma^2_{z_i}$: 70.3 94.2 55.0 103.7 20.5

Table VI (a)

$$
\begin{array}{cccccc}
\text{rank} & x_6 (10^{-3}) & x_7 (10^{-6}) & y_1 (10^{-2}) & y_2 (10^{-6}) & y_3 (10^{-6}) \\
1 & \pi_3 (10.5) & \pi_2 (13.9) & \mu' (11.1) & \pi_2 (35.5) & \pi_2 (19.4) \\
2 & \pi_2 (9.97) & \theta (1.66) & \pi_2 (3.31) & \gamma (26.8) & \gamma (14.7) \\
3 & \gamma (2.75) & \gamma (0.86) & \theta (2.97) & \pi_2 (20.8) & \pi_3 (11.4) \\
4 & \rho (0.97) & \rho (0.24) & \gamma (0.35) & \rho (15.1) & \theta (4.89) \\
5 & \theta (0.46) & \gamma_1 (0.10) & \alpha' (0.29) & \mu' (12.1) & \rho (3.78) \\
6 & \pi_1 (0.12) & \mu' (0.05) & \pi_3 (0.27) & \theta (8.95) & \gamma_1 (0.10) \\
7 & \mu' (0.05) & \pi_1 (0.03) & \gamma_1 (0.05) & \alpha' (0.31) & \mu (0.01) \\
8 & \gamma_1 (0.03) & \pi_3 (0.02) & \pi_1 (0.05) & \gamma_1 (0.19) & \pi_1 (10^{-4}) \\
9 & \mu (0.01) & \alpha' (10^{-3}) & \mu (10^{-4}) & \mu (0.02) & \alpha (10^{-16}) \\
10 & \alpha' (10^{-3}) & \mu (10^{-4}) & \alpha (10^{-14}) & \pi_1 (10^{-4}) & \mu' (0) \\
11 & \alpha (10^{-14}) & \alpha (10^{-14}) & \rho (0) & \alpha (10^{-14}) & \alpha' (0) \\
\end{array}
$$

$\sigma^2_{z_i}$: 24.9 16.9 18.4 119.8 54.2

Table VI (b)

Table VI. The sensitivity analysis for the equilibrium point $P_3$. The exponent between parenthesis in the first row is the multiplying factor of the column.
The standard deviation of the state variables are: $\sigma_{x_1} = 0.08$, $\sigma_{x_2} = 0.001$, $\sigma_{x_3} = 0.0074$, $\sigma_{x_4} = 0.102$, $\sigma_{x_5} = 0.14$, $\sigma_{x_6} = 0.16$, $\sigma_{x_7} = 0.004$, $\sigma_{y_1} = 0.43$, $\sigma_{y_2} = 0.011$ and $\sigma_{y_3} = 0.007$.

When a community is at an intermediate risk of malaria, we observe that the parameters $\pi_2$, $\gamma$ and $\pi_3$ are, generally, the most sensitive parameters for all state variables. The number of times that the previous three parameters appear leading the ranking in relation to the state variables are, respectively, 4, 3 and 2. In one time $\mu'$ appears as the most sensitive parameter. At fourth and fifth ranking appear $\theta$ and $\rho$. In general, these five parameters contribute practically with all the variations in the state variables. On the other hand, $\mu$, $\alpha$, $\mu'$ and $\alpha'$ are the least sensitive parameters. In one time $\rho$ appears as the least sensitive parameter.

Finally, malaria at a very high endemic level area is considered. Table VII shows the sensitivity analysis of the state variables for $h = 2.0$ and $f = 0.26$ (given in $\text{days}^{-1}$).

<table>
<thead>
<tr>
<th>rank</th>
<th>$x_1 (10^{-4})$</th>
<th>$x_2 (10^{-8})$</th>
<th>$x_3 (10^{-6})$</th>
<th>$x_4 (10^{-3})$</th>
<th>$x_5 (10^{-4})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\rho$ (21.8)</td>
<td>$\pi_3$ (24.6)</td>
<td>$\gamma$ (18.2)</td>
<td>$\rho$ (15.5)</td>
<td>$\pi_2$ (49.2)</td>
</tr>
<tr>
<td>2</td>
<td>$\theta$ (4.63)</td>
<td>$\rho$ (23.6)</td>
<td>$\pi_3$ (8.42)</td>
<td>$\pi_1$ (4.65)</td>
<td>$\rho$ (38.7)</td>
</tr>
<tr>
<td>3</td>
<td>$\pi_3$ (1.22)</td>
<td>$\pi_2$ (18.8)</td>
<td>$\pi_2$ (6.45)</td>
<td>$\pi_2$ (2.11)</td>
<td>$\pi_1$ (16.0)</td>
</tr>
<tr>
<td>4</td>
<td>$\pi_2$ (0.77)</td>
<td>$\mu'$ (4.71)</td>
<td>$\rho$ (3.78)</td>
<td>$\theta$ (1.33)</td>
<td>$\theta$ (13.3)</td>
</tr>
<tr>
<td>5</td>
<td>$\mu'$ (0.48)</td>
<td>$\gamma_1$ (4.54)</td>
<td>$\theta$ (1.46)</td>
<td>$\gamma_1$ (0.06)</td>
<td>$\mu'$ (1.93)</td>
</tr>
<tr>
<td>6</td>
<td>$\pi_1$ (0.19)</td>
<td>$\theta$ (4.23)</td>
<td>$\pi_1$ (0.32)</td>
<td>$\gamma$ (10^{-3})</td>
<td>$\gamma_1$ (0.57)</td>
</tr>
<tr>
<td>7</td>
<td>$\gamma_1$ (0.18)</td>
<td>$\pi_1$ (0.93)</td>
<td>$\mu'$ (0.19)</td>
<td>$\pi_3$ (10^{-3})</td>
<td>$\alpha'$ (0.05)</td>
</tr>
<tr>
<td>8</td>
<td>$\alpha'$ (0.02)</td>
<td>$\mu$ (0.15)</td>
<td>$\gamma_1$ (0.06)</td>
<td>$\mu$ (10^{-4})</td>
<td>$\gamma$ (0.03)</td>
</tr>
<tr>
<td>9</td>
<td>$\mu$ (0.01)</td>
<td>$\alpha'$ (0.12)</td>
<td>$\mu$ (0.05)</td>
<td>$\alpha$ (10^{-14})</td>
<td>$\pi_3$ (0.01)</td>
</tr>
<tr>
<td>10</td>
<td>$\gamma$ (10^{-4})</td>
<td>$\gamma$ (10^{-3})</td>
<td>$\alpha'$ (10^{-3})</td>
<td>$\mu'$ (0)</td>
<td>$\mu$ (10^{-3})</td>
</tr>
<tr>
<td>11</td>
<td>$\alpha$ (10^{-13})</td>
<td>$\alpha$ (10^{-14})</td>
<td>$\alpha$ (10^{-15})</td>
<td>$\alpha'$ (0)</td>
<td>$\alpha$ (10^{-13})</td>
</tr>
</tbody>
</table>

$\sigma^2_{z_i}$ 29.3 81.8 39.0 23.6 119.8

Table VII (a)
Table VII. The sensitivity analysis for the equilibrium point $P_3$. The exponent between parenthesis in the first row is the multiplying factor of the column.

The standard deviation of the state variables are: $\sigma_{z_1} = 0.05$, $\sigma_{z_2} = 0.001$, $\sigma_{z_3} = 0.006$, $\sigma_{z_4} = 0.15$, $\sigma_{z_5} = 0.11$, $\sigma_{z_6} = 0.22$, $\sigma_{z_7} = 0.005$, $\sigma_{y_1} = 0.86$, $\sigma_{y_2} = 0.0053$ and $\sigma_{y_3} = 0.008$.

When a community is at a very high risk of malaria, we observe that the parameters $\rho$, $\pi_2$ and $\pi_3$ are, generally, the most sensitive parameters for all state variables. The number of times that the previous three parameters appear leading the ranking in relation to the state variables are, respectively, 5, 2 and 1. In one time $\mu'$ and $\gamma$ appear as the most sensitive parameters. At fourth and fifth ranking appear $\theta$ and $\gamma$. In general, these five parameters contribute practically with all the variations in the state variables. On the other hand, $\mu$, $\mu'$ and $\alpha'$ are the least sensitive parameters. In one time $\rho$ appears as the least sensitive parameter.

From Tables V, VI and VII we note that the immunity loss parameters ($\pi_1$, $\pi_2$ and $\pi_3$) increase their contribution to the variation in the state variables in proportion to the increasing in the inoculation ($h$) and transmission ($f$) rates. On the other hand the unique parameter dependent on the temperature ($\rho$) contributes to the variation of the state variables, when
the inoculation and transmission rates increase, from moderate to relatively small, and thereafter to very high. In general the parameter \( \theta \) and \( \gamma \) are the most contributors to the variation in the state variables to all values of inoculation and transmission rates.

With respect to the state variables, in general, the fraction of non-immune but with immunological memory \( x_6 \) is, in absolute values, the most influenced by the variation in the parameters. However, as expected, when a community is at a very low risk of malaria, the most affected by the variation in the parameters is the fraction of the susceptible individuals \( x_1 \). For this reason, when malaria is at a low risk the most sensitive parameters are those related to the acquisition of the parasites (\( \theta, \gamma \) and \( \sigma \)), while in the intermediate and high at risk of malaria, the loss of immunity parameters (\( \pi_1, \pi_2 \) and \( \pi_3 \)) increase their contribution to the variation of the state variables.

Observe that the fraction of effectively immune \( x_4 \) and partially immune \( x_5 \) individuals increase with the increasing in the inoculation and transmission rates. The fraction of individuals with immunological memory also follows quite the same pattern. This result corroborates with the observation that most African adolescents and adults are usually free of clinical symptoms of malaria, although they maintain low parasitemia throughout the transmission season. Therefore, the efficacy of partial immunity that decreases with the time can be related to the booster inoculations [18].

Finally, we observe that the parameters that are the most sensitive and contribute practically to all variation in the basic reproduction ratio are also contributing, in general, to the great variations in the state variables.

5 FINAL COMMENTS

From a model which takes into account the different level of acquired immunity among humans and vector related parameter dependent on the temperature, we performed the sensitivity analysis of the basic reproduction ratio and the equilibrium points with respect to the model's parameters. In order to do this, we considered three possible malaria endemic regions.

If a well organized health system is acting in a community, then drug treatment and vaccination (when available) can be administrated regularly and promptly. We observed that the parameters \( \theta \) and \( \gamma \), which can be related to the socio-economic conditions, are, in general, the most contrib-
utors to the variation in both basic reproduction ratio and the equilibrium points. The parameter dependent on the temperature $\rho$ contributed to the variation with relatively high values, but less prominent at an intermediate malaria risk. These results, in some fashion, corroborate with the statement that the changes of socio-economic conditions are far more important than a temperature change [11].

Finally, it seems to be more realistic that, in a specified region, the socio-economic conditions (deterioration or improvement) can be managed by humans rather than the temperature variation (pollution in the environment). Therefore, in malaria at-risk region, a good health system and, also, a well organized and oriented management of the surrounding environs can avoid the out-break of malaria transmission in areas relatively secure.

APPENDIX

A EQUILIBRIUM POINTS

The determination of the equilibrium points and the analysis of their stability were given in [30]. Here we transport the two equilibrium points.

The first is malaria disease-free equilibrium point, given by

\[
\begin{align*}
y_1 & = 1 \\
y_i & = 0 \quad \text{for } j = 2 \text{ and } 3
\end{align*}
\]

for vector population given as fractions, and

\[
\begin{align*}
x_1 & = 1 \\
x_i & = 0 \quad \text{for } j = 2, \ldots, \text{ and } 7
\end{align*}
\]

for host population.

The second is malaria at an endemic level equilibrium point, given by

\[
\begin{align*}
y_1(x_3) & = \frac{\mu'+\alpha'}{f_{x_3}+\mu'+\alpha'} \\
y_2(x_3) & = \frac{f_{x_3}(\mu'+\alpha')}{(\mu+\mu'+\alpha')(f_{x_3}+\mu'+\alpha')} \\
y_3(x_3) & = \frac{x_3}{c_1 x_3 + c_5}
\end{align*}
\]
where

\[
\begin{align*}
  c_1 &= \frac{\nu + \mu' + \alpha'}{\rho} \\
  c_2 &= \frac{\nu' + \alpha'}{f} c_1
\end{align*}
\]

for the vector population. For the host population, we have

\[
\begin{align*}
x_1(x_3) &= b_2 x_3 + b_3 \\
x_2(x_3) &= b_1 x_3 \\
x_4(x_3) &= \frac{b_4 x_3 + b_5}{\pi_2 (\theta + \gamma_1 + \mu)(c_1 x_3 + c_2)} (b_4 x_3 + b_5) \\
x_5(x_3) &= \frac{b_4 x_3 + b_5}{\pi_2 (\theta + \gamma_1 + \mu)(c_1 x_3 + c_2)} (b_4 x_3 + b_5) \\
x_6(x_3) &= b_4 x_3 + b_5 \\
x_7(x_3) &= \frac{b_4 x_3 + b_5}{(\theta + \gamma_1 + \mu)(c_1 x_3 + c_2)} (b_4 x_3 + b_5)
\end{align*}
\]

plus

\[
A (x_3)^3 + B (x_3)^2 + C x_3 + D = 0 .
\]

The auxiliary parameters of the above equations are

\[
\begin{align*}
  b_1 &= \frac{\nu + \mu}{\gamma_1} \\
  b_2 &= \frac{\theta + \gamma_1 + \mu + \alpha}{h} b_1 c_1 \\
  b_3 &= \frac{\theta + \gamma_1 + \mu + \alpha}{h} b_1 c_2 \\
  b_4 &= \frac{\gamma_1 + \mu}{\pi_2} b_1 + \frac{\mu}{\pi_3} b_2 \\
  b_5 &= \frac{\mu}{\pi_3} (R_0^{-1} - 1)
\end{align*}
\]

where \(R_0 = t_3^{-1}\) is the basic reproduction ratio defined by

\[
R_0 = \frac{fh}{r} ,
\]

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with \( r \) being given by
\[
r = \frac{(\theta + \gamma_1 + \mu + \alpha) (\gamma + \mu) (\mu' + \alpha') (\rho + \mu' + \alpha')}{\gamma \rho},
\]
and the coefficients of the third degree algebraic equation are
\[
A = \mu (\gamma_1 + \mu) b_4 h + \mu [\pi_1 (\pi_2 + \gamma_1 + \mu) + (\theta + \gamma_1 + \mu) (\pi_3 + \mu) + (\gamma + \mu) (\pi_2 + \mu) c_1 b_4 h
+ (\theta + \gamma_1 + \mu) [\pi_1 \pi_2 (1 + b_1 + b_2 + b_4) + (\pi_3 + \mu) (\pi_1 + \pi_2 + \mu) b_4] c_1^2],
\]
which is always positive,
\[
B = \mu (\gamma_1 + \mu) h^2 + \mu [\pi_1 (\pi_2 + \gamma_1 + \mu) + (\theta + \gamma_1 + \mu) (\pi_3 + \mu) + (\gamma + \mu) (\pi_2 + \mu)] c_1 h
+ (\theta + \gamma_1 + \mu) (\pi_1 + \mu) (\pi_2 + \mu) (\pi_3 + \mu) c_1^2 \frac{\mu}{\pi_2} (R_0^{-1} - 1)
+ (\theta + \gamma_1 + \mu) [\pi_1 \pi_2 (1 + b_1 + b_2 + b_4) + (\pi_3 + \mu) (\pi_1 + \pi_2 + \mu) b_4] c_1 c_2,
\]
\[
C = \mu [\pi_1 (\pi_2 + \gamma_1 + \mu) + (\theta + \gamma_1 + \mu) (\pi_3 + \mu) + (\gamma + \mu) (\pi_2 + \mu)] h
+ 2 (\theta + \gamma_1 + \mu) (\pi_1 + \mu) (\pi_3 + \mu) c_1 \frac{\mu}{\pi_3} c_2 (R_0^{-1} - 1)
+ (\theta + \gamma_1 + \mu) [\pi_1 \pi_2 (1 + b_1 + b_2 + b_4) + (\pi_3 + \mu) (\pi_1 + \pi_2 + \mu) b_4] c_2^2.
\]
and
\[
D = (\theta + \gamma_1 + \mu) (\pi_1 + \mu) (\pi_2 + \mu) (\pi_3 + \mu) \frac{\mu}{\pi_3} c_2^2 (R_0^{-1} - 1).
\]
Observe that \( R_0 \) does not depend on the immunity loss rates [27].

The system of equations (1) and (2) presents only the above two equilibrium points. After a massive calculation, it is possible to show that the value of \( R_0 \), at which the coefficients take null values, obeys
\[
R_B > R_C > R_D = 1,
\]
where, for instance, \( R_B \) means the value of \( R_0 \) that satisfies \( B = 0 \), and so on. By applying the Descartes signal rule to the polynomial (18), we do not have any positively defined root if \( R_0 < 1 \) (there is no change in the signal of the coefficients of the polynomial), a null solution if \( R_0 = 1 \) and only one positive solution, if \( R_0 > 1 \) (the signal of the coefficients changes only one time). Therefore, we have the trivial equilibrium point if \( R_0 \leq 1 \) and the unique non-trivial equilibrium point if \( R_0 > 1 \).
References


