A mathematical model for malaria transmission relating global warming and local socioeconomic conditions*

Modelo matemático para transmissão de malária relacionada a aquecimento global e condições socioeconômicas

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Keywords
Malaria, transmission.# Mathematical models.# Greenhouse effect.# Socioeconomic factors. Communicable disease control. Risk. – Sensitivity analysis.

Abstract

Objective
Sensitivity analysis was applied to a mathematical model describing malaria transmission relating global warming and local socioeconomic conditions.
Methods
A previous compartment model was proposed to describe the overall transmission of malaria. This model was built up on several parameters and the prevalence of malaria in a community was characterized by the values assigned to them. To assess the control efforts, the model parameters can vary on broad intervals.
Results
By performing the sensitivity analysis on equilibrium points, which represent the level of malaria infection in a community, the different possible scenarios are obtained when the parameters are changed.
Conclusions
Depending on malaria risk, the efforts to control its transmission can be guided by a subset of parameters used in the mathematical model.

Descritores
Malária, transmissão.# Modelos matemáticos.# Efeito estufa.# Fatores socioeconômicos. Controle de doenças transmissíveis. Risco. – Análise de sensitividade.

Resumo

Objetivo
Aplicar a análise da sensitividade ao controle de transmissão de malária a um modelo, considerando o aquecimento global e as condições socioeconômicas locais.
Métodos
O modelo para a transmissão de malária proposto foi obtido em função de vários parâmetros. A prevalência de malária, em uma comunidade, foi caracterizada pelos valores desses parâmetros. Para estudar os efeitos dos mecanismos de controle, os valores dos parâmetros do modelo são variados em grandes intervalos.
Resultados
A análise da sensitividade do ponto de equilíbrio, que representa o nível de infecção de malária em uma comunidade, oferece os possíveis cenários resultantes da variação dos parâmetros do modelo.

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*Supported by Fapesp (Process n. 98/2827-8).
The publication of this article was subsidied by Fapesp (Process n. 01/01661-3).
Submitted on 30/6/2000. Reviewed on 16/2/2001. Approved on 26/2/2001.

Conclusões

Dependendo-se do nível de risco de malária, as melhores formas de mecanismos de controle da transmissão de malária são dadas por um subconjunto de parâmetros do modelo.

INTRODUCTION

A mathematical model was developed elsewhere[8] taking into account some biological features related to malaria disease, such as partial acquired immunity, immunologic memory and duration of sporogony. From the model equilibrium points were determined and the stability of these points was analyzed. Moreover, the *basic reproduction ratio* related to malaria transmission was obtained. This valuable epidemiological parameter is associated with control or eradication efforts.

In a subsequent study[9] the previously developed model was used to assess the effects of global warming and local socioeconomic conditions on malaria transmission. These effects were assessed analyzing the equilibrium points calculated at different but fixed values of the parameters of the model. Regarding malaria transmission, it was observed that the effects of global warming posed a major challenge in the next years,[3] and the effects of variation in local socioeconomic conditions are much stronger than the effects of the increasing global temperatures.[2]

The epidemiological analysis was restricted to few cases taking into account a combination of the values assigned to the parameters of the model. This because the model was structured with plenty of parameters. There is another way to study this issue instead of combining a great number of parameters, whose values can vary largely. Thus, the sensitivity analysis of the model is carried out with greatly variable parameters. This analysis also provides scenarios of possible outcomes under feasible strategies of intervention.[5-7]

METHODS

In this section, the focus in on the model sensitivity analysis regarding the variation in the parameters of the model. In order to achieve the magnitude of impact of each parameter on the state (dynamic) variables the model and the sensitivity analysis are presented.

Initially, it is taken from Yang[8] the system of differential equations which describes the overall malaria transmission. For humans, the seven compartments are: susceptible (x_1), incubating, *i.e.*, infected but non-infectious (x_2), infectious (x_3), immune (x_4), partially immune (x_5), non-immune but with immunologic memory (x_6) and incubating after reinfection (x_7). The fractions of the host population are described by the following system of differential equations,

$$\begin{cases} \frac{d}{dt}x_1(t) = F_1(z,\Omega) = \mu + (\theta+\alpha)x_2(t) + \pi_3 x_6(t) - [hy_3(t)+\mu]x_1(t) \\ \frac{d}{dt}x_2(t) = F_2(z,\Omega) = hy_3(t)x_1(t) - (\theta+\gamma_1+\mu+\alpha)x_2(t) \\ \frac{d}{dt}x_3(t) = F_3(z,\Omega) = \gamma_1 x_2(t) - (\gamma+\mu)x_3(t) \\ \frac{d}{dt}x_4(t) = F_4(z,\Omega) = \gamma x_3(t) + hy_3(t)x_5(t) + \gamma_1 x_7(t) - (\pi_1+\mu)x_4(t) \\ \frac{d}{dt}x_5(t) = F_5(z,\Omega) = \pi_1 x_4(t) - [hy_3(t)+\pi_2+\mu]x_5(t) \\ \frac{d}{dt}x_6(t) = F_6(z,\Omega) = \pi_2 x_5(t) + \theta x_7(t) - [hy_3(t)+\pi_3+\mu]x_6(t) \\ \frac{d}{dt}x_7(t) = F_7(z,\Omega) = hy_3(t)x_6(t) - (\theta+\gamma_1+\mu)x_7(t) \ , \end{cases} \quad (1)$$

where μ and α are the natural and differential mortality rates of human host, respectively; θ is the natural resistance rate against malaria; γ_1^{-1} and γ^{-1} are the average periods, respectively, to start the production of gametocytes and to build up an effective immune response; π_1, π_2 and π_3 are the rates at which protective immunity, partial immunity and immunologic memory are lost, respectively; and h is the inoculation rate. The quantity $y_3(t)$ is the fraction of infectious mosquitoes. The functions $F_i(z,\Omega)$, for i=1 to 7, z and Ω are defined below.

The mosquito population is divided into three compartments, y_1, y_2 and y_3, the fraction of susceptible, incubating, and infectious mosquitoes, respectively. The mosquito population is described by the following system of differential equations

$$\begin{cases} \frac{d}{dt}y_1(t) = F_8(z,\Omega) = (\mu'+\alpha')[y_2(t)+y_3(t)] - fx_3(t)y_1(t) \\ \frac{d}{dt}y_2(t) = F_9(z,\Omega) = fx_3(t)y_1(t) - [\rho(T)+\mu'+\alpha']y_2(t) \\ \frac{d}{dt}y_3(t) = F_{10}(z,\Omega) = \rho(T)y_2(t) - (\mu'+\alpha')y_3(t) \ , \end{cases} \quad (2)$$

where μ' and α' are, respectively, the natural and induced mortality rates of the mosquitoes, $\rho^{-1}(T)$ is the duration of sporogony in the mosquito, and f is the transmission rate. The temperature, designed by symbol T, was limited and was dependent only to the parameter ρ. The functions $F_i(z,\Omega)$, for i=8 to 10, z and Ω are defined below.

Regarding the first equation of the system (2), which

is slightly different from the equation in Yang's model,[8] it was obtained by applying the relation

$$\mu_e(T) = \rho_1(T)\left(\frac{\phi}{\mu'+\alpha'} - 1\right).$$

The parameters ϕ and $\mu_e(T)$ are, respectively, the rates of oviposition and of eggs becoming non-viable, and $\rho_l^{-1}(T)$ is the duration of the cycle from the egg to the mature adult. The overall model is unchanged. Therefore, μ' and α' should also depend on the temperature.

Defining the functions $F_i(z,\Omega)$, z and Ω. The functions $F_i(z,\Omega)$, for $i=1,2,\ldots,10$, are the elements of the vector $\boldsymbol{F}(z,\Omega)$, which are the state equations of the model. The state variables space z and parameters space Ω are given, respectively, by the vectors

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

and

$$\Omega = [\theta, \gamma_1, \gamma, \mu, \alpha, \rho, \mu', \alpha', \pi_1, \pi_2, \pi_3]^{Tr}.$$

The superscript *Tr* stands for the transposition of the matrix.

Depending on the value of the *basic reproduction ratio* R_0, which is given by

$$R_0 = \frac{\gamma_1}{\theta+\gamma_1+\mu+\alpha} \times \frac{f}{\gamma+\mu} \times \frac{\rho}{\rho+\mu'+\alpha'} \times \frac{h}{\mu'+\alpha'}, \quad (3)$$

the trivial or non-trivial equilibrium point is the atractor.[8] If $R_0 \leq 1$, then the trivial equilibrium point is stable, otherwise the non-trivial equilibrium is stable.

The trivial equilibrium point, which represents a disease-free community, is given by

$$\begin{cases} y_1 = 1 \\ y_i = 0; \end{cases} \qquad for\ i = 2\ and\ 3, \qquad (4)$$

for the vector population, and

$$\begin{cases} x_1 = 1 \\ x_i = 0; \end{cases} \qquad for\ i = 2, 3, \ldots, 7, \qquad (5)$$

for the host population.

The non-trivial equilibrium point, which represents malaria at an endemic level in a community, is given by

$$\begin{cases} y_1(x_3) = \dfrac{\mu'+\alpha'}{fx_3+\mu'+\alpha'} \\ y_2(x_3) = \dfrac{fx_3(\mu'+\alpha')}{[\rho+\mu'+\alpha'](fx_3+\mu'+\alpha')} \\ y_3(x_3) = \dfrac{x_3}{c_1x_3+c_2}, \end{cases} \qquad (6)$$

for the vector population and host population, there are

$$\begin{cases} x_1(x_3) = b_2x_3 + b_3 \\ x_2(x_3) = b_1x_3 \\ x_4(x_3) = \dfrac{[hx_3+(\pi_2+\mu)(c_1x_3+c_2)][h(\gamma_1+\mu)x_3+(\theta+\gamma_1+\mu)(\pi_3+\mu)(c_1x_3+c_2)]}{\pi_1\pi_2(\theta+\gamma_1+\mu)(c_1x_3+c_2)^2} \times (b_4x_3+b_5) \\ x_5(x_3) = \dfrac{h(\gamma_1+\mu)x_3+(\theta+\gamma_1+\mu)(\pi_3+\mu)(c_1x_3+c_2)}{\pi_2(\theta+\gamma_1+\mu)(c_1x_3+c_2)}(b_4x_3+b_5) \\ x_6(x_3) = b_4x_3 + b_5 \\ x_7(x_3) = \dfrac{h(b_4x_3+b_5)x_3}{(\theta+\gamma_1+\mu)(c_1x_3+c_2)}, \end{cases} \qquad (7)$$

plus a third degree polynomial to determine x_3, which is given by

$$A(x_3)^3 + B(x_3)^2 + Cx_3 + D = 0. \quad (8)$$

The auxiliary variables b_1, b_2, b_3, b_4, b_5, c_1 and c_2, and the coefficients of the polynomial A, B, C and D can be found in Yang's study.[8]

The sensitivity analysis provides the range of variation of the model's variables, such as state variables and *basic reproduction ratio*, when the values of the parameters of the model are changed. The state variables in the equilibrium, which are given by the equations (4) and (5), when trivial, and by the equations (6), (7) and (8), when non-trivial, and the *basic reproduction ratio*, which is given by the equation (3), are dependent on the parameters of the model. Since the parameters of the model are not accurate, it is expected that the variables of the model be influence by the inaccuracy of those values. On the other hand, if it is possible to change few parameters with an appropriate intervention, it is interesting to know what parameters should be changed in order to get the better results. Both issues can be addressed applying the sensitivity analysis.

First, the sensitivity analysis for the *basic reproduction ratio* can be performed using equation (3). Note that the *basic reproduction ratio* does not depend on all parameters defined in Ω, for this reason the subset Ω' of Ω is defined, given by

$$\Omega' = [\theta, \gamma, \gamma, \mu, \alpha, \rho, \mu', \alpha']^{Tr},$$

which contains the contributing parameters for the *basic reproduction ratio*. Note that the immunity decline rates do not appear in this subset of parameters space.

The variation in R_0, due to the inaccuracy in the values of the parameters given in Ω', can be measured by

$$\sigma^2_{R_0} = \sum_{j=1}^{8} h_j^2 \sigma^2_{\Omega_j} , \qquad (9)$$

where $(\sigma\Theta)^2$, with $\Theta=\Omega_j'$ and j=1 to 8, are the variances given by the matrix $\boldsymbol{V}_\Omega$, considered diagonal, and h_j, with j=1 to 8, are the elements of the vector $\boldsymbol{H}'$ given by

$$\mathbf{H}' = \frac{\partial R_0(\Omega')}{\partial \Omega'} .$$

Observe that $(h_j)^2(\sigma\Theta)^2$ is the contribution of the j-th parameter to the variance of R_0.

Second, the sensitivity analysis of the state variables at equilibrium can be run by considering the state equations $\boldsymbol{F(z,\Omega)}$ of the model instead of the equations (4) through (8), which provide the trivial and non-trivial equilibrium points. Using the absolute sensitivity function[1] for the covariance matrix $\boldsymbol{V}_z$ of the state variables z,

$$\mathbf{V}_z = \mathbf{H}\mathbf{V}_\Omega \mathbf{H}^{Tr} ,$$

where $\boldsymbol{V}_\Omega$ is the covariance matrix for the 11 parameters of Ω stated above and $\boldsymbol{H}$ is the sensitivity matrix given by

$$\mathbf{H} = \mathbf{J}^{*-1}\mathbf{P} ,$$

with its elements denoted by h_{ij}, with i=1 to 10 and j=1 to 11. Note that the matrix $\boldsymbol{P}$ is given by

$$\mathrm{P} = \left.\frac{\partial \mathrm{F}(z,\Omega)}{\partial \Omega}\right|_{z^k,\Omega} , \quad k = 1 \text{ or } 2 ,$$

where the index 1 refers to the trivial and 2 to the non-trivial equilibrium points, and

$$\mathrm{J}^* = \left.\frac{\partial \mathrm{F}(z,\Omega)}{\partial z}\right|_{z^k,\Omega} , \quad k = 1 \text{ or } 2 ,$$

is the Jacobian matrix. Both matrices should be evaluated at the equilibrium points z^1 and z^2. Observe that $F_i(z,\Omega)$, where i=1 to 10, corresponds to the second member of the system of equations (1) and (2).

If the covariance matrix $\boldsymbol{V}_\Omega$ is considered a diagonal matrix, with its diagonal elements given by $(\sigma\Theta)^2$, with $\Theta=\Omega_j$, where j=1 to 11, then the variance related to the state variables (the diagonal elements of $\boldsymbol{V}_z$) are given by

$$\sigma^2_{z_i} = \sum_{j=1}^{11} h_{ij}^2 \sigma^2_{\Omega_j} \; ; \; with \; i = 1, 2, \ldots, 10 . \qquad (10)$$

This expression provides the contribution of each parameter, given by $(h_{ij})^2(\sigma\Theta)^2$, with $\Theta=\Omega_j$, to the variance of the dynamic variables.

To obtain useful epidemiological information, the actual values for the parameters of the model should be known. Since their values can vary largely, Table 1 shows the range and the mean value that the average periods can assume and the corresponding rates and the standard deviations.

As can be noted, the above table was obtained from the literature for the parameters θ, γ_1, γ, π_1, π_2, π_3, μ, μ' and $\rho(T)$. Concerning the differential (α) and induced (α') mortality rates, it is assumed a decrease of about 2% and 6%, respectively, in the expected life span.

Table 1 presents the parameters of the model in terms of average periods (as the arithmetic mean between the maximum and the minimum values) and their inverses, which are the rates. Let's call, in general, the average periods as p and the rates as r. The standard deviations related to the parameter p, designed by σ_p, were calculated as the half between the maximum and the minimum values that one parameter can assume.

Table 1 - The values found in the literature for the model's parameters. The symbols d and y stand, respectively, for days and years.

Parameter	Range (in period)	Average period	Rate	Standard deviation
θ (d)	1–4	2.5	0.4	0.24
γ_1 (d)	15–19	17	0.059	0.007
γ (d)	50–150	100	0.01	0.005
π_1 (d)	40–60	50	0.02	0.004
π_2 (y)	0.2–5	2.6	0.38	0.35
π_3 (y)	1–20	10.5	0.095	0.086
μ' (y)	50–55	52.5	0.019	0.0009
α (y)	2450–2964	2707	0.0004	0.00004
μ' (d)	10–14	12	0.083	0.014
α' (d)	98–191.8	144.9	0.007	0.002
ρ(T) (d)	10(31°C)–26(20°C)	18	0.067	0.031

Rev Saúde Pública 2001;35(3):224-31
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The average periods and their standard deviations should be transformed according to

$$\begin{cases} r = \dfrac{1}{p} \\ \sigma_r = \dfrac{\sigma_p}{p^2} \end{cases},$$

since the model includes rates.

The focus is on the sensitivity analysis of a mathematical model for malaria transmission, considering temperature change and local socioeconomic conditions. For this reason, temperature-independent parameters θ, γ_1, γ, π_1, π_2 and π_3 are considered here as being associated roughly and indirectly to the general local socioeconomic conditions. And, evidently, temperature-dependent parameters ρ, μ' and α' are considered here as being associated to temperature changes.[9] Also, three representative risk areas for malaria are considered by assigning particular values for the inoculation h and transmission f rates.

In the next section, based on the above values for the parameters of the model, the sensitivity analysis was performed to assess control efforts to malaria transmission. It is noteworthy, however, that the sensitivity is fundamentally a local analysis, therefore the discussion below is valid only for the above range of the values for the parameters of the model and transmission rates.

RESULTS

In this section control efforts to malaria transmission are assessed considering a mathematical model developed with different levels of acquired immunity among human hosts and the impact of temperature on the parameters associated with vectors. Sensitivity analysis is used to this assessment, taking into account the values for the parameters of the model presented in Table 1 and three representative transmission 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. The three couple of transmission rates focus three representative regions of malaria transmission: a low endemic area (for example, the Amazon), an intermediate endemic area (South East Asia) and a high endemic area (Africa).

Table 2 summarizes the equilibrium values calculated with the mean values of the parameters showed in the fourth column of Table 1, taking into account three transmission rates ($days^{-1}$): h=0.18 and f=0.12 (Region I), h=0.70 and f=0.19 (Region II), and h=2.0 and f=0.26 (Region III).

Table 2 - The equilibrium values (in fractions) for human and mosquito populations for Regions I, II and III calculated with values given in Table 1.

State variable	Region I	Region II	Region III
x_1	0.776	0.129	0.033
x_2	0.0009	0.002	0.0015
x_3	0.0052	0.0125	0.009
x_4	0.0046	0.165	0.423
x_5	0.0565	0.378	0.39
x_6	0.156	0.308	0.14
x_7	0.0002	0.005	0.006
y_1	0.993	0.974	0.976
y_2	0.004	0.015	0.014
y_3	0.003	0.011	0.010

The corresponding *basic reproduction ratio* are: R_0=1.3 (Region I), R_0=8.0 (Region II), and R_0=31.23 (Region III). Note that the fractions of infectious humans (x_3) and mosquitoes (y_3), together with the fraction of incubating humans (x_2), are reduced in Region III in comparison with Region II. Therefore, a high level of malaria transmission prevents in some extent the serious malaria disease because the fractions x_2 and x_3 are decreased by increasing the fractions of immune (x_4) and partially immune (x_5) individuals.

The sensitivity analysis was run for the *basic reproduction ratio* and the equilibrium values in relation to the variation in the values of the parameters of the model.

First, the variation in the *basic reproduction ratio* was analyzed when parameters can vary. The sensitivity analysis of the *basic reproduction ratio* regarding the parameters given in the space of parameters Ω' can be performed with equation (9). This equation takes into account the contributions of each parameter to the variance of the *basic reproduction ratio*. In Table 3 the sensitivity analysis of R_0 for the Regions I, II and III is showed.

Table 3 - The sensitivity analysis of the basic reproduction ratio for the Regions I, II and III considering the values given in Table 1.

Rank (parameter)	Region I	Region II	Region III
1 (θ)	0.46	17.4	266.7
2 (γ)	0.42	15.8	241.2
3 (ρ)	0.12	4.95	70.2
4 (μ')	0.10	3.75	57.3
5 (γ_1)	0.02	0.67	10.3
6 (α')	0.003	0.10	1.48
7 (μ)	10^{-7}	10^{-6}	10^{-4}
8 (α)	10^{-13}	10^{-12}	10^{-11}
Sum of variance	1.12	42.3	647.2

The standard deviation (the square root of the variance) of R_0 for the Regions I, II and III are1.06, 6.51 and 25.44, respectively. Restricted to the variations range for the parameters of the model given in Table 1, the sensitivity of R_0 shows that eradication can be achieved only in the scenario of very low malaria risk (Region I), because the value of R_0 can be reduced below unity.

Table 3 shows that 98.2% of the 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 μ'. Note that the two most sensitive (together they contribute to 78.6%) human-related parameters θ and γ are the natural resistance rate and period of time to build up the effective immunity, respectively; and the third and fourth most sensitive (together they contribute to 19.6 %) are vector-related parameters ρ, which is the duration of sporogony, and μ'. The vital dynamics parameters α and μ related to human population are practically insensitive, and the sensitivity of the input rate γ_1 to the infectious individuals x_3 and additional mortality rate of latent and infectious mosquitoes α' are negligible.

Based on the sensitivity analysis of R_0 regarding the eight parameters, the following results can be drawn. To reduce the risk of malaria infection, simplistically considering only decreasing in R_0, the most effective efforts are those related to the prevention of the increase 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: increasing the natural resistance rate (drug treatment) or decreasing the period of time to build up immunity (vaccination). Regarding the vector population, control efforts should increase the duration of sporogony (avoiding global warming due to pollution effects) and/or increase the mortality rate (insecticide use). Nevertheless, control efforts directed to human population are not only much more efficient but realistic than those ones directed to vectors.

Second, the variation in the equilibrium points (state variables) is analyzed with the variation in the values of the parameters of the model. The sensitivity analysis of the equilibrium points in relation to the space of parameters Ω can be carried out with equation (10). This equation takes into account the contributions of each parameter to the variance of coordinates of the equilibrium point. The Jacobian matrix $\boldsymbol{J}$ evaluated at the equilibrium point can be inverted by the Gauss-Jordan method.[4]

First, a very low endemic area of malaria (Region I) is considered. Table 4 shows the sensitivity analysis of the state variables for h=0.18 and f=0.12 ($days^{-1}$).

Standard deviations for the state variables $x_1, x_2, x_3, x_4, x_5, x_6, x_7, y_1, y_2$ and y_3 are 0.27, 0.001, 0.0077, 0.008, 0.08, 0.18, 0.0004, 0.54, 0.0033, and 0.0035, respectively.

When a community lives in an area of very low risk of malaria, the parameters ρ, θ and γ in general are the most sensitive ones for all state variables. The times these three parameters appear leading the ranking in relation to the state variables are 5, 4 and 1, respectively. At fourth and fifth ranking comes μ' and π_3. In general, these five parameters nearly contribute with all the variations in the state variables. On the other hand, μ, π_1 and α are the least sensitive parameters. Other parameters for immunity decline π_2 and π_3 are also less sensitive. In this scenario, susceptible individuals can reach unity value, that is, the population can be disease-free.

An intermediate endemic malaria area (Region II) is considered. Table 5 shows the sensitivity analysis of the state variables for h=0.70 and f=0.19 ($days^{-1}$).

The standard deviations for the state variables $x_1, x_2, x_3, x_4, x_5, x_6, x_7, y_1, y_2$ and y_3 are 0.08, 0.001, 0.0074, 0.102, 0.14, 0.16, 0.004, 0.43, 0.011 and 0.007, respectively.

When a community lives in an area of intermediate risk of malaria, the parameters π_2, γ and π_3 in general are the most sensitive ones for all state variables. The times these three parameters appear leading the ranking in relation to the state variables are 4, 3 and 2, respectively. In one occasion μ' reveals to be the most sensitive parameter. At fourth and fifth ranking comes θ and ρ. In general, these five parameters nearly contribute with all the variations in the state variables. On the other hand, μ, α, μ'

Table 4 - The sensitivity analysis of the equilibrium point for the Region I considering the values given in Table 1. The ranking of the contribution of the parameters is based on the x_1; if the ranking changes, this is set between parenthesis. The exponent between parenthesis in the first row is the multiplying factor of the entire column.

Rank (Par.)	x_1 (10^{-3})	x_2 (10^{-8})	x_3 (10^{-6})	x_4 (10^{-6})	x_5 (10^{-4})	x_6 (10^{-3})	x_7 (10^{-9})	y_1 (10^{-2})	y_2 (10^{-7})	y_3 (10^{-7})
1 (θ)	26.9	38.5	23.6 (ρ)	34.0 (ρ)	22.8	11.5	92.3 (ρ)	14.6 (γ)	37.8 (ρ)	85.1 (ρ)
2 (ρ)	24.2	36.9	20.0 (γ)	20.0 (θ)	19.9 (π_2)	8.71	81.6 (θ)	9.59 (θ)	35.2 (γ)	19.2 (γ)
3 (γ)	7.65	10.4	13.2 (θ)	7.39	15.1 (ρ)	6.90 (π_3)	22.0	3.26 (μ')	23.2 (θ)	12.6 (θ)
4 (π_2)	5.62	4.71 (μ')	1.26	4.71 (μ')	6.09 (γ)	3.04 (γ)	11.8 (μ')	0.92	11.8 (μ')	4.24 (μ')
5 (μ')	4.82	3.69 (π_3)	0.75	0.83 (π_2)	3.01	1.21	5.48 (π_2)	0.39 (ρ)	2.22 (π_3)	1.21 (π_2)
6 (γ_1)	1.03	0.42 (π_2)	0.51	0.77	0.88	0.44	1.22	0.37	0.89	0.48
7 (π_3)	0.64	0.12 (α')	0.14	0.70	0.38 (π_3)	0.39	0.88	0.10	0.30 (α')	0.14
8 (α')	0.12	0.03 (γ_1)	0.02	0.47 (π_3)	0.08	0.03	0.30	0.08	0.25 (π_2)	0.11
9 (μ)	10^{-3}	10^{-3}	10^{-4}	0.12 (α')	10^{-4} (π_1)	10^{-3}	10^{-3}	10^{-4}	10^{-4}	10^{-4}
10 (π_1)	10^{-4}	10^{-4}	10^{-5}	10^{-5} (μ)	10^{-5} (μ)	10^{-4}	10^{-4}	10^{-5}	10^{-5}	10^{-5}
11 (α)	10^{-12}	10^{-11}	10^{-12}	10^{-12}	10^{-12}	10^{-12}	10^{-12}	10^{-12}	10^{-12}	10^{-13}
Sum of var.	71.0	94.7	59.5	69.0	68.3	32.2	215.6	29.3	111.6	123.1

Table 5 - The sensitivity analysis of the equilibrium point for the Region II considering the values given in Table 1. The ranking of the contribution of the parameters is based on the x_1; if the ranking changes, this is set between parenthesis. The exponent between parenthesis in the first row is the multiplying factor of the entire column.

Rank (Par.)	$x_1(10^{-4})$	$x_2(10^{-8})$	$x_3(10^{-6})$	$x_4(10^{-4})$	$x_5(10^{-3})$	$x_6(10^{-3})$	$x_7(10^{-6})$	$y_1(10^{-2})$	$y_2(10^{-6})$	$y_3(10^{-6})$
1 (γ)	31.5	60.2 (π_3)	26.6	44.2	12.3 (π_2)	10.5 (π_3)	13.9 (π_2)	11.1 (μ')	35.5 (π_2)	19.4 (π_2)
2 (θ)	19.8	21.5 (π_2)	20.6 (π_3)	34.3 (π_3)	4.30	9.97 (π_3)	1.66	3.31 (π_3)	26.8 (γ)	14.7 (γ)
3 (ρ)	9.68	7.09 (γ_1)	7.36 (π_2)	9.68	1.31 (γ)	2.75 (γ)	0.86 (γ)	2.97 (θ)	20.8 (π_3)	11.4 (π_3)
4 (π_3)	5.76	3.34 (γ)	0.23 (ρ)	7.95	1.02 (π_3)	0.97 (ρ)	0.24 (ρ)	0.35 (γ)	15.1 (ρ)	4.89 (θ)
5 (μ')	1.93	1.48 (ρ)	0.10 (θ)	7.52 (π_1)	0.97 (ρ)	0.46 (θ)	0.10 (γ_1)	0.29 (α')	12.1	3.78 (ρ)
6 (γ_1)	1.07	0.31 (θ)	0.07 (π_1)	0.04	0.21	0.12 (π_1)	0.05 (μ')	0.27 (π_2)	8.95 (θ)	0.10
7 (π_3)	0.48	0.21 (π_1)	0.02 (μ)	0.03 (μ)	0.19 (μ')	0.05 (μ')	0.03 (π_1)	0.05 (γ_1)	0.31 (α')	0.01 (μ)
8 (π_1)	0.08	0.07 (μ')	0.01 (γ_1)	10^{-3} (θ)	0.17	0.03 (γ_1)	0.02 (π_1)	0.05	0.19 (γ_1)	10^{-4}
9 (α')	0.05	0.06 (μ)	10^{-13} (α)	10^{-13} (α)	10^{-3}	0.01 (μ)	10^{-3}	10^{-4} (μ)	0.02 (μ)	10^{-14} (α)
10 (μ)	10^{-4}	10^{-3} (α')	0 (μ')	0 (μ')	10^{-4}	10^{-3} (α')	10^{-4}	10^{-14} (α)	10^{-4} (π_1)	0 (μ')
11 (α)	10^{-11}	10^{-13}	0 (α')	0 (α')	10^{-13}	10^{-14}	10^{-14}	0 (ρ)	10^{-14}	0 (α')
Sum of var.	70.3	94.2	55.0	103.7	20.5	24.9	16.9	18.4	119.8	54.2

and α' are the least sensitive parameters. In one occasion ρ reveals to as the least sensitive parameter.

Finally, a very high endemic malaria area (Region III) is considered. Table 6 shows the sensitivity analysis of the state variables for h=2.0 and f=0.26 ($days^{-1}$).

The standard deviations for the state variables x_1, x_2, x_3, x_4, x_5, x_6, x_7, y_1, y_2 and y_3 are 0.05, 0.001, 0.006, 0.15, 0.11, 0.22, 0.005, 0.86, 0.0053 and 0.008, respectively.

When a community lives in an area of very high risk of malaria, the parameters ρ, π_2 and π_3 in general are the most sensitive parameters for all state variables. The times these three parameters appear leading the ranking in relation to the state variables are, 5, 2 and 1, respectively. In one occasion μ' and γ appear as the most sensitive parameters. At fourth and fifth ranking appear θ and γ. In general, these five parameters contribute nearly with all the variations in the state variables. On the other hand, μ, μ' and α' are the least sensitive parameters. In one occasion ρ appears as the least sensitive parameter.

From Tables 4, 5 and 6 it can be noted that loss of immunity parameters (π_1, π_2 and π_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 only parameter temperature-dependent (ρ) contributes to the variation of the state variables when inoculation and transmission rates are increased from low to moderate values, and then to very high values. In general the parameter θ and γ are the greatest contributors to the variation in the state variables to all values of inoculation and transmission rates.

Regarding the state variables, in general, the fraction of non-immune but with immunologic memory x_6 is, in absolute values, the most influenced by the parameters variation. However, as it is 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 that, when there is a low risk of malaria the most sensitive parameters are those related to the acquisition of the parasites (θ, γ and ρ), while in intermediate and high risk areas of malaria, the immunity decline parameters (π_1, π_2 and π_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 rise with the increase in the inoculation and transmission rates. The

Table 6 - The sensitivity analysis of the equilibrium point for the Region III considering the values given in Table 1. The ranking of the contribution of the parameters is based on the x_1; if the ranking changes, this is set between parenthesis. The exponent between parenthesis in the first row is the multiplying factor of the entire column.

Rank (Par.)	$x_1(10^{-4})$	$x_2(10^{-8})$	$x_3(10^{-6})$	$x_4(10^{-3})$	$x_5(10^{-4})$	$x_6(10^{-3})$	$x_7(10^{-6})$	$y_1(10^{-2})$	$y_2(10^{-6})$	$y_3(10^{-6})$
1 (ρ)	21.8	24.6 (π_3)	18.2 (γ)	15.5	49.2 (π_2)	34.8	21.6 (π_2)	24.8	27.1 (μ')	60.5
2 (θ)	4.63	23.6 (ρ)	8.42 (π_3)	4.65 (π_1)	38.7 (ρ)	9.94 (π_2)	0.95 (ρ)	23.3 (γ)	0.88 (π_1)	3.01 (μ')
3 (π_3)	1.22	18.8 (π_2)	6.45 (π_2)	2.11 (π_2)	16.0 (π_1)	2.60 (θ)	0.85 (θ)	10.8	0.70 (α')	0.48 (π_1)
4 (π_2)	0.77	4.71 (μ')	3.78 (ρ)	1.33 (θ)	13.3 (θ)	0.51 (π_1)	0.35 (π_1)	6.77	0.15	0.08
5 (μ')	0.48	4.54 (γ_1)	1.46 (θ)	0.06 (γ_1)	1.93	0.13 (π_3)	0.30 (γ_1)	4.94	0.01 (θ)	0.07 (α')
6 (π_1)	0.19	4.23 (θ)	0.32	10^{-3} (γ)	0.57 (γ_1)	0.10 (γ_1)	0.27 (π_3)	1.68	10^{-4} (γ_1)	0.01 (θ)
7 (γ_1)	0.18	0.93 (π_1)	0.19 (μ')	10^{-3} (π_3)	0.05 (α')	10^{-3} (γ)	0.11 (μ')	1.67 (θ)	10^{-5} (γ)	10^{-4}
8 (α')	0.02	0.15 (μ)	0.06 (γ_1)	10^{-4} (μ)	0.03 (γ)	10^{-4} (μ)	10^{-3}	0.13	10^{-5} (π_3)	10^{-5} (γ)
9 (μ)	0.01	0.12 (α')	0.05	10^{-14} (α)	0.01 (π_3)	10^{-15} (α)	10^{-3} (γ)	0.07	10^{-6}	10^{-5} (π_3)
10 (γ)	10^{-4}	10^{-3}	10^{-3} (α')	0 (μ')	10^{-3} (μ)	0 (μ')	10^{-4} (μ)	0.06 (γ_1)	10^{-16} (α)	10^{-6} (μ)
11 (α)	10^{-13}	10^{-14}	10^{-15}	0 (α')	10^{-13}	0 (α')	10^{-15}	10^{-14}	0 (ρ)	10^{-17}
Sum of var.	29.3	81.8	39.0	23.6	119.8	48.1	24.4	74.2	28.9	64.2

fraction of individuals with immunologic memory also follows the same pattern. This result corroborates the observation that most African adolescents and adults are usually free of clinical malaria symptoms, although they sustain a low parasitemia throughout the transmission season. This can be noted looking at the fractions of incubating (x_2) and infectious (x_3) individuals: these state variables initially rise with an increase in the inoculation and transmission rates and, then decrease. The efficacy of partial immunity that decreases with time can be associated to the booster inoculations.

The parameters that are the most sensitive and nearly contribute with all variation in the *basic reproduction ratio* are also contributing, in general, to the great variations in the state variables.

DISCUSSION

From a model that takes into account different levels of acquired immunity among humans and vector-related parameters dependent on the temperature, the sensitivity analysis of the *basic reproduction ratio* and the equilibrium points was carried out regarding the parameters of the model. In order to do this, three possible malaria endemic regions were considered.

Control efforts against malaria infection can be directed toward human and mosquito populations. The scenarios presented by the sensitivity analysis show that the most efficient control efforts are those related to humans. Therefore, treatment of diseased individuals and vaccination of susceptible individuals will reduce malaria infection in all variation range of inoculation and transmission rates. However, the increase in the mortality rate of the mosquitoes will be efficient only in areas where there is a relatively high risk of malaria.

If a community has a well-organized health system, then drug treatment and vaccination (when available) can be administrated regularly and promptly. It was observed that the parameters θ and γ, which can be related to socioeconomic conditions, in general are the greatest contributors to the variation in both *basic reproduction ratio* and equilibrium points. The temperature-dependent parameter ρ contributed to the variation with relatively high values, but less prominently in an area of intermediate malaria risk. These results corroborate with the statement that changes in socioeconomic conditions are far more important than temperature changes.[2]

For a certain region, it seems more realistic to manage the socioeconomic conditions (deterioration or improvement) rather than controlling the temperature changes (environmental pollution). Therefore, in areas of malaria risk, a good health system combined with a well-organized and objective managing of the surrounding environment could avoid outbreaks of malaria with relatively safety.

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