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## **Malaria transmission model for different levels of acquired immunity and temperature-dependent parameters (vector)**

Modelo de transmissão de malária em diferentes níveis de imunidade e de parâmetros temperatura-dependentes (vetor)

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### Keywords

Malaria transmission<sup>#</sup>. Epidemiologic models<sup>#</sup>. *Anopheles*, parasitology. *Plasmodium*, physiology<sup>#</sup>. Host parasitic relations. Insect vectors.

### Descritores

Malária, transmissão<sup>#</sup>. Modelos epidemiológicos<sup>#</sup>. *Anopheles*, parasitologia<sup>#</sup>. *Plasmodium*, fisiologia<sup>#</sup>. Relações hospedeiro-parasita. Insetos vetores.

### Abstract

#### Objective

Describe the overall transmission of malaria through a compartmental model, considering the human host and mosquito vector.

#### Methods

A mathematical model was developed based on the following parameters: human host immunity, assuming the existence of acquired immunity and immunological memory, which boosts the protective response upon reinfection; mosquito vector, taking into account that the average period of development from egg to adult mosquito and the extrinsic incubation period of parasites (transformation of infected but non-infectious mosquitoes into infectious mosquitoes) are dependent on the ambient temperature.

#### Results

The steady state equilibrium values obtained with the model allowed the calculation of the basic reproduction ratio in terms of the model's parameters.

#### Conclusions

The model allowed the calculation of the basic reproduction ratio, one of the most important epidemiological variables.

### Resumo

#### Objetivo

Propõe-se um modelo compartimental para descrever a transmissão de malária, levando em consideração duas populações envolvidas: o hospedeiro humano e o vetor mosquito.

#### Métodos

Desenvolveu-se um modelo matemático baseado nas seguintes características: em relação ao hospedeiro humano, assumiu-se a existência de imunidade adquirida e de memória imunológica que, em uma reinfeção, leva ao reforço da resposta imune; em relação ao vetor mosquito, levou-se em consideração que o período médio de desenvolvimento desde ovo até mosquito adulto e o período de incubação extrínseco de parasitas (transformação de mosquitos infectados mas não-infecciosos em mosquitos infecciosos) são dependentes de temperatura ambiente.

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### Resultados

Foram obtidos os valores do equilíbrio no estado estacionário do modelo proposto. Da análise da estabilidade dos pontos de equilíbrio, foi determinada a razão de reprodutibilidade basal.

### Conclusões

Foi obtida uma variável epidemiológica importante, a razão de reprodutibilidade basal, que foi analisada em função dos parâmetros do modelo.

## INTRODUCTION

Malaria is a leading cause of morbidity and mortality in developing countries. About 2,300 million people live in tropical and subtropical areas where malaria transmission occurs. Of these, 300 to 500 million are infected, and 1.5 to 2.7 million die each year, including about 1 million children under age of 5.<sup>26</sup> Traditional methods of malaria eradication and control rely on the use of long lasting insecticides against the mosquito vector and drugs for prevention and disease treatment. Despite major research efforts, effective vaccines are not currently available. The efficacy of control measures has decreased over the past decades because mosquitoes and parasites are becoming more resistant to the commonly used insecticides and anti-malarial drugs.<sup>9</sup> As a result, malaria kills more people today than three decades ago. The main areas affected in the world are Africa (more than 90% of the cases), Southeast Asia, India and South America.<sup>26</sup>

Mathematical models of malaria transmission have recently been reviewed and discussed elsewhere<sup>7,11,23</sup> and were extensively used to guide the worldwide eradication efforts between 1955 and 1970,<sup>16,20</sup> which were partially effective. Though they can provide adequate approximations to some biological and epidemiological features of malaria, most of them so far have not been able to describe quantitatively the overall malaria transmission dynamics.

This is a further effort to describe the *P. falciparum* malaria transmission in quantitative terms. To create a model based on reasonable biological findings, the following paragraphs describe their biological and epidemiological features.

Malaria is a disease resulting from the infection of a protozoan parasite of the genus *Plasmodium*, and transmitted through the bite of female *Anopheles* mosquitoes. Four *Plasmodium* species cause human malaria: *P. falciparum* is the most common and can cause a potentially fatal disease, while *P. vivax*, *P. malariae* and *P. ovale* cause clinically significant but non-fatal diseases. Humans are infected when sporozoites are injected by *Anopheles* mosquitoes and lodge themselves, within less than 30 minutes, in the liver. Most

bites inject less than 20 sporozoites, and few inject more than 100 sporozoites.<sup>15</sup> About half of the infectious bites will result in blood-stage infections in African children.<sup>10</sup> The first asexual multiplication (exoerythrocytic schizogony) occurs within liver cells, resulting in the production of 10-40 thousand merozoites per sporozoite. The merozoites are released into the bloodstream 5-9 days after inoculation and invade red blood cells, where they multiply asexually (erythrocytic schizogony) to produce 8-32 new merozoites. These either repeat the multiplication cycle within red blood cells every 48 or 72 hours or develop into the sexual transmission stages called gametocytes. Mature gametocytes of *P. falciparum* first appear in the bloodstream about 10 days later. The factors that 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 to parasite multiplication.<sup>18</sup> Intra-species competition in multiple-clone infections is an example of such a situation.<sup>25</sup> Circulating gametocytes remain infectious for about three weeks.<sup>24</sup>

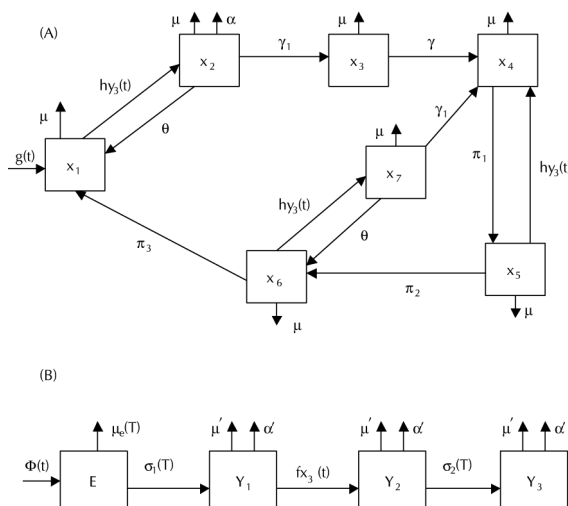
Mosquitoes suck back male and female gametocytes, and fertilization takes place in the mosquito gut. After a phase of asexual multiplication (sporogony) **when thousands of sporozoites are produced, they migrate to the salivary glands.** The incubation period within the mosquito may last 8-22 days. **Sporozoites remain viable for 30-40 days within the salivary glands with survival limited only by the mosquito death.**<sup>5</sup> In highly endemic areas in Kenya, infected *An. gambiae* s.l. may harbour up to 117,500 sporozoites (median 914) in their salivary glands.<sup>4</sup> The proportion of naturally sporozoite-infected mosquitoes (also called sporozoite rate) found is quite variable for different endemic areas. For instance, on average 12% of all *An. gambiae* s.l. found in western Kenya are infected, and percentage may raise to 25% at some time points<sup>3</sup>. In contrast, only 0.01% of the local *Anopheles* vectors were found to be infected in an area of low and unstable malaria transmission in western Venezuela.<sup>22</sup> **Mosquito survival does not seem to be affected by infection with human *Plasmodium* species.**<sup>8,12,21</sup> But discordant results have been reported in other vector-parasite systems.<sup>13</sup>

Even among people exposed to continuous and intense malaria transmission, as in rural African communities, antimalarial immunity develops rather slowly. Therefore, immunity should be described as a continuum of different levels of protection rather than a yes/no response. Most infants get infected in their first year of life, while older children and teenagers have some tolerance against severe disease, known as anti-toxic immunity. In addition, most African adolescents and adults are asymptomatic, although they maintain low parasitemia throughout the transmission season. 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.<sup>19</sup>

Based on the above biological findings, a mathematical model was developed to describe the overall transmission of malaria. Based on this model, a subsequent paper<sup>31</sup> analyzes the epidemiological impact of temperature changes and social and economic conditions on malaria incidence in communities with different levels of acquired immunity.

## METHODS

A malaria transmission model was developed based on the extensively discussed biological aspects. The model considers human hosts and vector mosquitoes distributed over a series of compartments. The two diagrams presented in Figure show the flow between the several compartments.



**Figure** - The schematic diagrams of the overall malarial transmission: human host (A) and mosquito vector (B).

The following descriptions and equations are related to Figure. The input rates  $g(t)$  and  $\Phi(t)$  are further described in the Appendix.

For humans, the seven compartments 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 reinfection ( $x_7$ ). 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 some 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.

The mosquito population is divided into three compartments  $Y_1$ ,  $Y_2$  and  $Y_3$ : number of susceptible, incubating (infected but non-infectious), and infectious mosquitoes at time  $t$ , respectively.

The interaction between human hosts and the mosquito vector can be described by a system of equations from which it is possible to draw the following assumptions. This model, in which the effects of aging on the possible encounter between humans and mosquitoes are ignored, is based on the simplified assumption of homogeneously mixed populations of humans and mosquitoes.<sup>4</sup> A very simple model of acquired immunity was assumed, that is, the age at first infection or the period of time elapsed to build up the immune response<sup>27,28,30</sup> are not considered.

The fractions of the host population are described by the following system of differential equations

$$\begin{cases} \dot{x}_1(t) = \mu + (\theta + \alpha)x_2(t) + \pi_3x_6(t) - [hy_3(t) + \mu]x_1(t) \\ \dot{x}_2(t) = hy_3(t)x_1(t) - (\theta + \gamma_1 + \mu + \alpha)x_2(t) \\ \dot{x}_3(t) = \gamma_1x_2(t) - (\gamma + \mu)x_3(t) \\ \dot{x}_4(t) = \gamma x_3(t) + hy_3(t)x_5(t) + \gamma_1x_7(t) - (\pi_1 + \mu)x_4(t) \\ \dot{x}_5(t) = \pi_1x_4(t) - [hy_3(t) + \pi_2 + \mu]x_5(t) \\ \dot{x}_6(t) = \pi_2x_5(t) + \theta x_7(t) - [hy_3(t) + \pi_3 + \mu]x_6(t) \\ \dot{x}_7(t) = hy_3(t)x_6(t) - (\theta + \gamma_1 + \mu)x_7(t) \end{cases} \quad (1)$$

where  $y_3(t)$  will be defined below;  $\mu$  and  $\alpha$  are the natural and differential (disease-induced) mortality rates for the human host, respectively;  $\theta$  is the natural

resistance rate against malaria; and  $\gamma_1^{-1}$  and  $\gamma^{-1}$  are the average periods to initiate the production of gametocytes and build up an effective immune response respectively. The rates at which protective immunity, partial immunity, and immunologic memory wane are represented by  $\pi_1$ ,  $\pi_2$  and  $\pi_3$  respectively. Finally,  $h$  is the inoculation rate. Note that the derivative regarding the time of the state variables was represented by a point, for instance,

$$x_i(t) \equiv \frac{d}{dt} x_i(t).$$

Observe that the sum of the system of equations (1) obeys

$$\sum_{i=1}^7 \dot{x}_i(t) = \mu - \mu \sum_{i=1}^7 x_i(t) = 0,$$

which is due to the relation  $x_1(t) + x_2(t) + x_3(t) + x_4(t) + x_5(t) + x_6(t) + x_7(t) = 1$ .

The mosquito population is described by the following system of equations

$$\begin{cases} \dot{Y}_1(t) = \phi \frac{\sigma_1(T)}{\sigma_1(T) + \mu_e(T)} [Y_1(t) + Y_2(t) + Y_3(t)] - [fx_3(t) + \mu' + \alpha'] Y_1(t) \\ \dot{Y}_2(t) = fx_3(t) Y_1(t) - [\sigma_2(T) + \mu' + \alpha'] Y_2(t) \\ \dot{Y}_3(t) = \sigma_2(T) Y_2(t) - (\mu' + \alpha') Y_3(t) \end{cases} \quad (2)$$

where  $\mu'$  and  $\alpha'$  are the natural and induced (for example, by insecticides) mortality rates of mosquitoes, respectively, and  $\phi$  is the rate of oviposition. The parameters dependent on the temperature  $T$  are the rate of eggs becoming non-viable,  $\mu_e(T)$ , the cycle duration, from the egg to the mature adult, and the duration of sporogony (development from the gametocyte to the infective sporozoite) in the mosquito, represented by  $\sigma_1^{-1}(T)$  and  $\sigma_2^{-1}(T)$ , respectively. Finally,  $f$  is the transmission rate. Note that the ratio  $\sigma_1(T)/[\sigma_1(T) + \mu_e(T)]$  is the probability of egg transformation during the period of time  $\sigma_1^{-1}(T)$  into an adult mosquito. Also, the disease-induced mortality among infected mosquitoes was neglected. The mosquito population can be set as fractions according to

$$y_i(t) = \frac{Y_i(t)}{Y_1(t) + Y_2(t) + Y_3(t)}; \quad \text{for } i = 1, 2 \text{ and } 3. \quad (3)$$

Therefore,  $y_3(t)$  is the fraction of infectious mosquitoes. The general model from which this simplified (and approximated) model version was drawn can be found in the Appendix.

The system of equation (1) and (2) can be studied dynamically and in the steady state. The dynamic simulation of the system of equation produces trajec-

tories for each state variable (representing each compartment) along time, until they reach asymptotic (equilibrium) values when certain initial values are given. The steady state analysis of the system of equation creates a situation where the state variables do not change with time because it is considered that they have reached the asymptotic equilibrium. Epidemiological assertions can drawn based on the scenarios provided in both dynamic and steady state analyses, which are the subject of a subsequent work.<sup>31</sup> Here there is a demonstration on how to calculate the equilibrium points and analyze their stability.

### The equilibrium points

The steady state equilibrium points are reached when the differential equations do not change with time. This situation is attained when the derivative of the state variables assumes the zero value, that is, for instance,

$$x_1(t) = 0.$$

By calculating the zeros (roots) of a non-linear set of algebraic equations, given by the coupled system of equation (1) and (2), two equilibrium points were obtained. These two sets of solutions are valid if the rate at which eggs become non-viable obeys the relation

$$\mu_e(T) = \sigma_1(T) \left( \frac{\phi}{\mu' + \alpha'} - 1 \right) \quad (4)$$

Observe that there must be  $\phi > \mu' + \alpha'$  for the equilibrium points to be biologically reasonable, that is, they are such that  $\mu_e(T)$  is being positively defined.

The two equilibrium points are showed below. All the intermediate calculations were omitted and only the final results are presented. The state variables expressed without the time represent the values assumed in the steady state equilibrium.

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

$$\begin{cases} y_1 = 1 \\ y_i = 0; \end{cases} \quad \text{for } i = 2 \text{ and } 3, \quad (5)$$

for vector population, and

$$\begin{cases} x_1 = 1 \\ x_i = 0; \end{cases} \quad \text{for } i = 2, 3, \dots, \text{ and } 7 \quad (6)$$

for host population.

The second is malaria at **endemic levels (non-trivial)** equilibrium point, which is given as a function of  $x_3$ . For the vector population

$$\begin{cases} y_1(x_3) = \frac{\mu' + \alpha'}{fx_3 + \mu' + \alpha'} \\ y_2(x_3) = \frac{fx_3(\mu' + \alpha')}{[\sigma_2(T) + \mu' + \alpha'](fx_3 + \mu' + \alpha')} \\ y_3(x_3) = \frac{x_3}{c_1x_3 + c_2}, \end{cases} \quad (7)$$

where

$$\begin{cases} c_1 = \frac{\sigma_2(T) + \mu' + \alpha'}{\sigma_2(T)} \\ c_2 = \frac{\mu' + \alpha'}{f} c_1. \end{cases}$$

For the host population

$$\begin{cases} x_1(x_3) = b_2x_3 + b_3 \\ x_2(x_3) = \frac{b_1x_3}{[hx_3 + (\pi_2 + \mu)(c_1x_3 + c_2)][h(\gamma_1 + \mu)x_3 + (\theta + \gamma_1 + \mu)(\pi_3 + \mu)(c_1x_3 + c_2)]} \\ x_4(x_3) = \frac{\pi_1\pi_2(\theta + \gamma_1 + \mu)(c_1x_3 + c_2)^2}{\times(b_2x_3 + b_3)} \\ x_5(x_3) = \frac{h(\gamma_1 + \mu)x_3 + (\theta + \gamma_1 + \mu)(\pi_3 + \mu)(c_1x_3 + c_2)}{\pi_2(\theta + \gamma_1 + \mu)(c_1x_3 + c_2)}(b_1x_3 + b_3) \\ x_6(x_3) = \frac{b_4x_3 + b_5}{h(b_2x_3 + b_3)} \\ x_7(x_3) = \frac{h(b_2x_3 + b_3)x_3}{(\theta + \gamma_1 + \mu)(c_1x_3 + c_2)}, \end{cases} \quad (8)$$

and the unknown  $x_3$  can be calculated from the third degree algebraic equation

$$A(x_3)^3 + B(x_3)^2 + Cx_3 + D = 0. \quad (9)$$

**The auxiliary parameters** of the above equations are

$$\begin{cases} b_1 = \frac{\gamma_1 + \mu}{\gamma_1} \\ b_2 = \frac{\theta + \gamma_1 + \mu + \alpha}{h} b_1 c_1 \\ b_3 = \frac{\theta + \gamma_1 + \mu + \alpha}{h} b_1 c_2 \\ b_4 = \frac{\gamma_1 + \mu}{\pi_3} b_1 + \frac{\mu}{\pi_3} b_2 \\ b_5 = \frac{\mu}{\pi_3} (R_0^{-1} - 1), \end{cases}$$

where  **$R_0$  is the basic reproduction ratio** defined by

$$R_0 = \frac{fh}{r}, \quad (10)$$

which is the inverse of the parameter  $b_3$  with  $r$  being given by

$$r = \frac{(\theta + \gamma_1 + \mu + \alpha)(\gamma + \mu)(\mu' + \alpha')[\sigma_2(T) + \mu' + \alpha']}{\gamma_1\sigma_2(T)}.$$

Finally, the coefficients of the third degree algebraic equation are

$$A = \mu(\gamma_1 + \mu)b_1h^2 + \mu[\pi_1(\pi_2 + \gamma_1 + \mu) + (\theta + \gamma_1 + \mu)(\pi_3 + \mu) + (\gamma_1 + \mu)(\pi_2 + \mu)]c_1b_1h + \mu(\theta + \gamma_1 + \mu)[\pi_1\pi_2(1 + b_1 + b_2 + b_4) + (\pi_3 + \mu)(\pi_1 + \pi_2 + \mu)b_4]c_1^2,$$

which is always positive,

$$B = \{\mu(\gamma_1 + \mu)h^2 + \mu[\pi_1(\pi_2 + \gamma_1 + \mu) + (\theta + \gamma_1 + \mu)(\pi_3 + \mu) + (\gamma_1 + \mu)(\pi_2 + \mu)]c_1h + (\theta + \gamma_1 + \mu)\pi_1 + \mu(\pi_2 + \mu)(\pi_3 + \mu)c_1^2\} \frac{\mu}{\pi_3} (R_0^{-1} - 1) + \mu[\pi_1(\pi_2 + \gamma_1 + \mu) + (\theta + \gamma_1 + \mu)(\pi_3 + \mu) + (\gamma_1 + \mu)(\pi_2 + \mu)]c_2b_1h + 2\mu(\theta + \gamma_1 + \mu)[\pi_1\pi_2(1 + b_1 + b_2 + b_4) + (\pi_3 + \mu)(\pi_1 + \pi_2 + \mu)b_4]c_1c_2,$$

$$C = \{\mu[\pi_1(\pi_2 + \gamma_1 + \mu) + (\theta + \gamma_1 + \mu)(\pi_3 + \mu) + (\gamma_1 + \mu)(\pi_2 + \mu)]h + 2(\theta + \gamma_1 + \mu)(\pi_1 + \mu)(\pi_2 + \mu)(\pi_3 + \mu)c_1\} \frac{\mu}{\pi_3} c_2 (R_0^{-1} - 1) + \mu(\theta + \gamma_1 + \mu)[\pi_1\pi_2(1 + b_1 + b_2 + b_4) + (\pi_3 + \mu)(\pi_1 + \pi_2 + \mu)b_4]c_2^2$$

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  $R_0$  is not dependent on the immunity loss rates.**<sup>29</sup>

The equation systems (1) and (2) present only the above two equilibrium points. Regarding equation (9), this one has only one positive and real root. After a **massive calculation, it is possible to show that the values of  $R_0$ , at which the above coefficients  $B$ ,  $C$  and  $D$  assume null values,** obey

$$R_B > R_C > R_D \equiv 1,$$

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 given by equation (9), it is possible to obtain: no positively defined root if  $R_0 < 1$  (there is no change in the polynomial coefficients); a null solution if  $R_0 = 1$ , and only one positive solution if  $R_0 > 1$  (the coefficients signal changes only once). Therefore, the trivial equilibrium point is reached if  $R_0 \leq 1$  and the unique non-trivial equilibrium point if  $R_0 > 1$ .

The concept of the **basic reproduction ratio  $R_0$** , given by the equation (10), will be discussed in the section 3. However, this parameter plays mathematically an important role, as showed in the next subsection.



## The stability analysis

The two equilibrium points, the disease-free community and the disease at endemic levels have a strong influence in the behavior of the disease transmission in a community. These two equilibrium points are the final reachable situations, even though there could be infinitely different initial distributions of malaria in a community. Therefore, the conditions whether one of the two equilibrium points will prevail in the community must be known. **The stability analysis, an important mathematical tool, provides the conditions that guarantee the stability of the two equilibrium points.**

The stability of the equilibrium point can be performed by calculating the roots of the eigen-equation (or characteristic polynomial). The eigen-equation, denoted by  $\Lambda(\lambda)$ , is defined by the determinant of a special matrix, that is

$$\Lambda(\lambda) \equiv \det(J^* - \lambda I) \quad (11)$$

where  $J^*$  is the Jacobian (the partial derivatives of the state equations, which are the second members of the equation systems (1) and (2), with respect to the state variables) evaluated at the equilibrium point, and  $I$  is the  $10 \times 10$  identity matrix. In this study situation, the degree of the polynomial  $\Lambda(\lambda)$  is 10 (there are ten differential equations). Therefore, 10 roots (real or complex values) must be determined, that is  $\Lambda(\lambda_i) = 0$  for  $i = 1$  to 10. If all the eigen-values (the roots of the polynomial,  $\lambda_i$ ) have negative real part, then the equilibrium point is stable. In other words, this state equilibrium point is the unique final reachable situation of the disease in the community, regardless the initial distribution of the disease in this community.

The conditions that guarantee the stability of the disease-free community are presented here. The case where the disease is at an endemic levels requires more elaborated techniques. Substituting the trivial equilibrium point, given by equations (5) and (6), into the eigen-equation (11),

$$\Lambda(\lambda) = \Lambda_6(\lambda)\Lambda_4(\lambda) \quad (12)$$

where  $\Lambda_6(\lambda)$  and  $\Lambda_4(\lambda)$  are polynomials of degree 6 and 4, respectively. The polynomial  $\Lambda_6(\lambda)$  has the eigen-values given by

$$\begin{cases} \lambda_1 = -\mu \\ \lambda_2 = -(\theta + \gamma_1 + \mu) \\ \lambda_3 = -(\pi_1 + \mu) \\ \lambda_4 = -(\pi_2 + \mu) \\ \lambda_5 = -(\pi_3 + \mu) \\ \lambda_6 = 0 \end{cases}$$

with the null eigen-value resulting from the equation (4). The roots of this polynomial reveal that the trivial equilibrium point may be stable, since all the eigen-values are negative. The final answer about the stability will be provided by the polynomial  $\Lambda_4(\lambda)$ , which is given by

$$\Lambda_4(\lambda) \equiv \det(J_4^* - \lambda I_{4 \times 4}) \quad ,$$

where  $J_4^*$  is the matrix

$$J_4^* = \begin{bmatrix} -(\theta + \gamma_1 + \mu + \alpha) & 0 & 0 & h \frac{\mu' + \alpha'}{\sigma_1(T)E} \\ \gamma_1 & -(\gamma + \mu) & 0 & 0 \\ 0 & f \frac{\sigma_1(T)E}{\mu' + \alpha'} & -[\sigma_2(T) + \mu' + \alpha'] & 0 \\ 0 & 0 & \sigma_2(T) & -(\mu' + \alpha') \end{bmatrix}$$

Note that the diagonal elements of  $-J_4^*$  are positives and their off-diagonal elements are non-positives. Hence, a mathematical theorem related to matrix states that  $-J_4^*$  is an  $M$ -matrix,<sup>6</sup> and therefore, if the expression

$$(\theta + \gamma_1 + \mu + \alpha)(\gamma + \mu)(\mu' + \alpha')[\sigma_2(T) + \mu' + \alpha'](1 - R_0) \quad (13)$$

is positively defined, then  $\Lambda_4(l)$  has all eigen-values with negative real part. Hence, the trivial equilibrium point is stable<sup>14</sup> if  $R_0 < 1$ . Note that the *basic reproduction ratio*  $R_0$  was already defined by the equation (10).

The analysis of the non-trivial equilibrium point cannot be performed analytically, only numerically. However, as discussed above, this point is biologically viable if, and only if,  $R_0 > 1$  because in this case there is only one non-trivial equilibrium point. On the other hand, on this range of  $R_0$ , by the equation (13), the trivial equilibrium point is unstable. Therefore, at  $R_0 = 1$ , there occurs a branching, from a disease-free situation to disease at endemic levels in the community.

In **summary**, the disease-free community is always the final reachable situation if  $R_0 \leq 1$ . If  $R_0 > 1$ , then the disease is established at endemic levels in the community, and its prevalence increases with the increase of  $R_0$ . This parameter will be discussed in the next section.

## DISCUSSION

**An overall malaria transmission model was developed taking into account different levels of acquired immunity among human hosts and temperature-dependent parameters related to vector mosquitoes.** There were not included the information from recent immunological, epidemiological, molecular and theoretical studies

which demonstrated the need to **subdivide the immunity** to malaria into immunity against infection, (mild and severe) disease and, most importantly, transmission. The analysis was restricted to the immunity against (severe) disease and transmission. **Acquiring immunity was treated as something that has a finite duration and requires boosting.** To develop a model disregarding the hyper-infection, a different approach to Aron's propositions<sup>12</sup> was applied

The model was analyzed in its steady state to determine the equilibrium points. The two equilibrium points play an important role depending on the value of the **basic reproduction ratio**. This value, given by equation (10), can be re-written as

$$R_0 = \frac{\gamma_1}{\theta + \gamma_1 + \mu + \alpha} \times \frac{f}{\gamma + \mu} \times \frac{\sigma_2(T)}{\sigma_2(T) + \mu' + \alpha'} \times \frac{h}{\mu' + \alpha'}$$

to be better understood. Note that  $R_0$  is a product of four terms. The **first term** is the probability that an individual will survive (and also recover naturally) during the latent period  $\gamma_1^{-1}$  and will be in the infective state. The **second term** is related to the number of susceptible mosquitoes infected with gametocytes by an infectious individual during his/her entire infective period. The **third term** is the probability that a mosquito will survive during the latent period  $\sigma_2^{-1}(T)$  and be in the infective state. Finally, the **last term** corresponds to the number of susceptible individuals infected with sporozoites by an infectious mosquito during its entire infective period. The gametocytes take-up by mosquitoes and the injection of sporozoites in the human host occur when female *Anopheles* mosquitoes bite humans. Hence,  $R_0$  is proportional to both the inoculation rate  $h$  and the transmission rate  $f$ . For this reason, the entomological parameter given by the ratio between human and mosquito population sizes appears quadratically.<sup>17</sup>

Observe that the **first two terms** of  $R_0$  are related to the **infection of a susceptible mosquito**, while the **last two** are related to the **infection of a susceptible individual**. So there should be a chain reaction to produce a new infection among mosquitoes. First, an infectious mosquito, during its infective period, must inject sporozoites in the susceptible individuals. Then these sporozoites must evolve into gametocytes in the infected human host. Finally, during the infective period of these infectious individuals, gametocytes must be taken up by susceptible mosquitoes. Therefore, the **basic reproduction ratio** measures the number of secondary infections produced by an infectious mosquito in a completely susceptible mosquito population. For

that reason, **areas with higher values of  $R_0$  require more efforts regarding malaria prevention measures.**

Note that the **three types of immunity loss rates do not appear in the basic reproduction ratio** formulae, however, the effects can be measured indirectly on the malaria transmission. **The effect of the three types of human immune responses against malaria delay the recurrence of the individuals**, who already have had contact with parasite, to the susceptible category. The immunity boosting also avoids the flow into the susceptible compartment. Therefore, if a community is at high risk for malaria (high value of  $R_0$ ), then it will show a lower prevalence of individuals with asexual blood-stage infection but without infectious gametocytes. This same community is also relatively free of severe infection due to the boosting of immunity by reinfection.

**The basic reproduction ratio is associated with the control or eradication efforts.** The control or eradication efforts increase with the increasing of the **basic reproduction ratio**. The epidemiological results drawn from this model are presented in a subsequent study.<sup>31</sup>

## APPENDIX

The general model, from which the system of equation (1) and (2) were obtained, can be expressed in terms of delayed equations.

The fractions of the human host population are described by the following system of differential equations

$$\begin{cases} \dot{x}_1(t) = g(t) + \theta x_2(t) + \pi_3 x_6(t) - [hy_3(t) + \mu]x_1(t) \\ \dot{x}_2(t) = hy_3(t)x_1(t) - (\theta + \mu + \alpha)x_2(t) - e^{-(\theta + \mu + \alpha)\tau}hy_3(t - \tau)x_1(t - \tau) \\ \dot{x}_3(t) = e^{-(\theta + \mu + \alpha)\tau}hy_3(t - \tau)x_1(t - \tau) - (\gamma + \mu)x_3(t) \\ \dot{x}_4(t) = \gamma x_3(t) + hy_3(t)x_5(t) + e^{-(\theta + \mu)\tau}hy_3(t - \tau)x_6(t - \tau) - (\pi_1 + \mu)x_4(t) \\ \dot{x}_5(t) = \pi_1 x_4(t) - [hy_3(t) + \pi_2 + \mu]x_5(t) \\ \dot{x}_6(t) = \pi_2 x_5(t) + \theta x_7(t) - [hy_3(t) + \pi_3 + \mu]x_6(t) \\ \dot{x}_7(t) = hy_3(t)x_6(t) - (\theta + \mu)x_7(t) - e^{-(\theta + \mu)\tau}hy_3(t - \tau)x_6(t - \tau) \end{cases} \quad (14)$$

where  $\tau$  is the period of time delayed from the infection until the appearance of gametocytes and  $g(t)$  is the human input rate. The exponent function is related to the probability that humans do not leave the classes  $x_2$  and  $x_7$  or die during the time interval  $\tau$ .

The amount of mosquitoes in different classes is described by the following system of equations

$$\begin{cases} \dot{Y}_1(t) = e^{-\mu_e(T)\tau_1}\phi[Y_1(t - \tau_1) + Y_2(t - \tau_1) + Y_3(t - \tau_1)] - [fx_3(t) + \mu' + \alpha']Y_1(t) \\ \dot{Y}_2(t) = fx_3(t)Y_1(t) - (\mu' + \alpha')Y_2(t) - e^{-(\mu' + \alpha')\tau_2}fx_3(t - \tau_2)Y_1(t - \tau_2) \\ \dot{Y}_3(t) = e^{-(\mu' + \alpha')\tau_2}fx_3(t - \tau_2)Y_1(t - \tau_2) - (\mu' + \alpha')Y_3(t) \end{cases} \quad (15)$$



where  $\tau_1'$  and  $\tau_2'$ , temperature-dependent, are the periods of time elapsed since the oviposition until the development into an adult mosquito and since the infection until the production of sporozoites, respectively.

To obtain the approximated model, it was allowed

$$g(t) = \mu + \alpha x_2(t) \quad (16)$$

to have a constant population size, and the following relations

$$\begin{cases} \tau &= \gamma_1^{-1} \\ \tau_1' &= \sigma_1^{-1}(T) \\ \tau_2' &= \sigma_2^{-1}(T) \end{cases}$$

to transform the time-delayed differential equations into ordinary differential equations. The parameters  $\gamma_1^{-1}$  and  $\sigma_2^{-1}(T)$  are the average periods of time spent, respectively, in the compartments  $x_2$  (and also  $x_7$ ).  $Y_2$ , and  $\sigma_1^{-1}(T)$  is the average periods of time spent in the

virtual (in the sense of not considered class) compartment  $E$  (egg class).

Finally, the first equation of the system of equations (2) can be better understood in terms of the virtual egg compartment  $E$ . All the viable eggs, given by the net oviposition  $\phi[Y_1(t) + Y_2(t) + Y_3(t)]$ , must survive during the period  $\sigma_1^{-1}(T)$  and evolve into adult mosquitoes and the probability of that is  $\sigma_1(T)/[\sigma_1(T) + \mu_e(T)]$ . Therefore, the input rate in the susceptible mosquitoes class is given by

which is the first term of the second member of the first equation of the system of equations (2)

$$\Phi(t) = \phi \frac{\sigma_1(T)}{\sigma_1(T) + \mu_e(T)} [Y_1(t) + Y_2(t) + Y_3(t)] ,$$

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