Stability analysis and optimal control intervention strategies of a malaria mathematical model

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Abstract. Nowadays, cases of death due to malaria have been substantially reduced. However, the incidence of malaria has been concentrated mainly in specific sectors both urban and rural. This suggests that the dynamics of transmission is changing, which generates a new public health alert. In this work we study the malaria disease applied to the municipality of Tumaco (Colombia) through a mathematical model with the objective of contribute to the understanding of the transmission dynamics and development of control intervention strategies. To this end, we formulate a system of ordinary differential equations that describe the malaria disease transmission dynamics for humans and mosquitoes population. We performed the stability analysis, analysis of bifurcations and sensitivity analysis of parameters to the mathematical model, which allowed us to define the following control strategies: indoor fumigation, bed nets, intermittent prophylactic treatment in pregnancy and antimalarial treatment. For these variables we formulated and analyze an optimal control problem in which control strategies are incorporated by treatment (antimalarial and prophylactic in pregnancy) and the combination of the four control variables. The results of the cost-effectiveness analysis suggest that in urban areas it is enough to consider control strategies for treatment, while in rural areas the simultaneous implementation of the four control variables is the most cost-effective strategy.

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1 Introduction

Malaria is a vector borne disease produced by four species of Plasmodium parasites and transmitted by the bite of female *Anopheles* mosquitoes (at least 50 species). This disease is endemic in tropical and subtropical regions, with a high mortality rate in some regions of Africa, Asia and the Americas [51]. In Colombia, this disease is

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presented in 22 of its 33 departments becoming a public health problem of great importance with approximately between 18 and 24 millions of susceptible to contracting this disease. [18].

Although malaria has been typically considered as a problem of the rural and poor zones, this disease is presented in urban zones. However, the economic development and the environmental changes during the twentieth century have reduced the incidence of malaria in urban contexts [58]. In addition, improved housing, drainage of Anopheles breeding sites, expanded personal protection, effective diagnosis and treatment, among other disease controls have contributed to the recent global decline in malaria incidence [58].

Like other epidemiological settings, urban malaria transmission is influenced, in most cases, by population movements from rural to urban areas. This rural population influx into urban areas facilitates the introduction of malaria from places where the disease has high prevalence [14]. Furthermore, these underserved populations generally practice subsistence farming and inhabit poor housing with limited access to health services; such social dynamics favors mosquito breeding in areas considered administratively urban [14].

Despite the fact that malaria prevalence is decreasing in Colombia with a 75% reduction in the number of cases since 2000 [50], Sistema Nacional de Vigilancia en Salud Pública (SIVIGILA) reported an accelerated increase in urban malaria cases from 5.9% in 2011 to 30% in 2015 [50]. Although this increase may be explained by population displacement on account of violence, there is still the possibility of autochthonous urban transmission.The growing number of reports on urban cases of malaria generates concerns that promote the rethinking of the corresponding control strategies, the above motivated us to analyze several cost-effective control strategies to eradicate malaria in rural and urban areas of Tumaco.

The municipality of Tumaco is located on the Pacific Coast of the Nariño state (Colombia), and is part of the alluvial plain, which is characterized by low lands and sludgy valleys. This area is partially covered with jungle and crossed by numerous rivers that mostly flow into the sea. The weather conditions in Tumaco make it an ideal location for the transmission of malaria. Morbidity and mortality due to malaria in Tumaco are very high. In high transmission areas of Tumaco, such as, rural areas, the disease is treated with antimalarial drugs, and through vector controls such as fumigations, elimination of hatcheries or use of repellents [53]. However, these strategies have failed to control the problem due to existence of urban malaria cases. The negative impact on technical aspects, such as improper use of residual action spraying, generates high operating costs in health for urban zones with high population density [25]. For this reason, it is important to identify the most important factors favouring the transmission of the disease to establish strategies for its control.

Since the pioneering work of Ronald Ross [52], a lot of mathematical modelling studies have been carried out to understand the transmission and spread of malaria considering the population of vectors and humans divided in epidemiological classes (see for instance [13, 28, 44, 40]). Furthermore, models have been used to study the factors influencing the appearance of resistance to malaria drugs ([32, 43]). Other authors used population dynamics models that capture the epidemiological effects of spatially heterogeneous environments [4, 8, 48, 3, 15, 37, 7, 8, 6]. Among the control models for vector borne disease are the ones that propose biological control

[42, 29, 41, 1], chemical and biological control [32], preventive control [5, 9], preventive control and treatment[16, 46], vaccination and treatment [30]. Recently Romero-leiton and others [19, 20, 23, 21, 22] propose mathematical models which consider vertical and vector transmission of the disease, and additionally propose control strategies deduced from sensitivity analysis of parameters.

In this work we presented a mathematical model for the transmission dynamics of malaria considering horizontal transmission of infection (contact between a human and a mosquito) as well as vertical transmission (from a pregnant woman to her fetus) as in [21]. Using data obtained from SIVIGILA we asses the efficiency of different controls such as insecticide spray, bed nets, drug treatment, and prophylaxis treatment during pregnancy.

The paper is organized as follows: the mathematical model is formulated in Section 2, qualitative analysis is done in Section 3, transcritical bifurcations analysis in Section 4, sensitivity analysis and numerical simulations in Section 5. The optimal control problem is analyzed in Section 6, numerical results in Section 7, cost-effectiveness analysis of control strategies in Section 8, and discussion in Section 9.

2 Mathematical Model

The system of ordinary differential equations proposed below describe the dynamics of malaria transmission between human and mosquito populations. The assumptions assumed to formulate the model are: the total human population at time t is denoted by $N_h(t)$, and it is divided into susceptible, exposed, infected, and recovered where $S_h(t)$, $E_h(t)$, $I_h(t)$, and $R_h(t)$ represent each class at time t, respectively. The above implies $N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t)$. We assumed that all epidemiological classes above are subject to a per capita mortality rate μ_h.

The vector population N_v is recruited at a constant rate Λ_v, and has a per capita natural death rate μ_v. Since the mosquito does not recover from infection, we only consider susceptible and infected, where S_v, and I_v denote susceptible and infected mosquito populations at time t, respectively, and $N_v(t) = S_v(t) + I_v(t)$.

The transmission rate from a mosquito to a human depends on the average number of bites per day of a female mosquito ϵ. Also, it depends on the probability that an infectious bite gives rise to a new case denoted by β_{hv}. Thus, the infection rate from mosquito to human is given by $\beta_h \frac{I_v}{N_h}$ where $\beta_h = \beta_{hv}\epsilon$. Analogously the infection rate from human to mosquito is $\beta_v \frac{I_h}{N_h}$, where $\beta_v = \beta_{vh}\epsilon$ is the transmission rate from human to mosquito with β_{vh} representing the infection probability of a mosquito due to the contact with an infected human. In addition, we assumed that a proportion $0 \leq p_h \leq 1$ of the birth from infected human (mother) is infected via vertical transmission and pass directly to the infection compartment.

Susceptible human population is recruited at a rate Λ_h, and they get infected at a rate $\beta_h \frac{I_v}{N_h}$ becoming in exposed human, which are infected but not infectious. The exposed human pass to the infectious class at a per capita rate α_h where $1/\alpha_h$ is the latency period. The infected human population increases due to the entrance of the exposed human at a rate $\alpha_h E_H$ and due to infected newborns at a rate $\lambda_h I_h$, with $\lambda_h = p_h/2$. They recover at a per capita rate δ_h, where $1/\delta_h$ is the infectious period, and dye by the disease at a per capita disease mortality rate $\rho_h < \mu_h$. The recovered

human population increases due to the entrance of the infected human at a rate $\delta_h I_h$ and diminish its population due to the loss of immunity and pass to the susceptible class at a per capita rate ω_h.

Analogously, susceptible mosquito population increases is recruited at a constant rate Λ_v, get infected at a rate $\beta_v \frac{I_h}{N_h}$, and pass to the class of infectious mosquitoes. Both populations are subject to a mortality rate μ_v. According to the assumptions above, we get the following system of non linear ODE:

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h + \omega_h R_h - \beta_h \frac{I_v}{N_h} S_h - \mu_h S_h \\
\frac{dE_h}{dt} &= \beta_h \frac{I_v}{N_h} S_h - (\alpha_h + \mu_h) E_h \\
\frac{dI_h}{dt} &= \lambda_h I_h + \alpha_h E_h - (\delta_h + \rho_h + \mu_h) I_h \\
\frac{dR_h}{dt} &= \delta_h I_h - (\omega_h + \mu_h) R_h \\
\frac{dS_v}{dt} &= \Lambda_v - \beta_v \frac{I_h}{N_h} S_v - \mu_v S_v \\
\frac{dI_v}{dt} &= \beta_v \frac{I_h}{N_h} S_v - \mu_v I_v.
\end{aligned} \tag{2.1}$$

Adding the equations for S_v and I_v, we obtain that the mosquito population N_v satisfies

$$\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v,$$

which implies that $0 \leq N_v(t) \leq \bar{N}_v$ for all $t \geq 0$, where

$$\bar{N}_v = \frac{\Lambda_v}{\mu_v}. \tag{2.2}$$

Note that $N_v(t) \to \bar{N}_v$ when $t \to \infty$ which implies $S_v(t) \to \bar{N}_v - I_v$. Therefore, to study the asymptotic behaviour of system (2.1) is enough to analyze the following system in the variables $(S_h, E_h, I_h, R_h, I_v)$ gyven by:

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h + \omega_h R_h - \beta_h \frac{I_v}{N_h} S_h - \mu_h S_h \\
\frac{dE_h}{dt} &= \beta_h \frac{I_v}{N_h} S_h - (\alpha_h + \mu_h) E_h \\
\frac{dI_h}{dt} &= \alpha_h E_h - (\delta_h + \mu_h - \mu_h \tau_h) I_h \\
\frac{dR_h}{dt} &= \delta_h I_h - (\omega_h + \mu_h) R_h \\
\frac{dI_v}{dt} &= \beta_v \frac{I_h}{N_h} (\bar{N}_v - I_v) - \mu_v I_v,
\end{aligned} \tag{2.3}$$

where

$$\tau_h = \frac{\lambda_h - \rho_h}{\mu_h}. \tag{2.4}$$

Table 1: Parameters of model (2.1).

Parameter	**Interpretation**	**Dimention**
Λ_h	Recruitment rate of humans	humans $\times$ day $^{-1}$
μ_h	Human mortality rate	day $^{-1}$
μ_v	Mosquito mortality rate	day $^{-1}$
ω_h	Per capita loss of immunity	day $^{-1}$
β_{hv}	Infection probability of human by mosquito	adimentional
β_{vh}	Infection probability of mosquito by human	adimentional
ϵ	Biting effective rate	day $^{-1}$
$1/\alpha_h$	Exposed period	day
ρ_h	Per capita mortality rate due to infection	day $^{-1}$
$1/\delta_h$	infection period	day
Λ_v	Recruitment rate of mosquitos	mosq $\times$ day $^{-1}$
λ_h	Percentage of vertical transmission	adimentional

When the parameter $\tau_h > 0$ can be interpreted as the average life of the babies infected through vertical transmission that survive the disease.

The set of biological interest is given by

$$\Omega = \{(S_h, E_h, I_h, R_h, I_v) \in R_+^5 : 0 \leq S_h + E_h + I_h + R_h \leq \bar{M}_h,\ 0 \leq I_v \leq \bar{N}_v\}, \tag{2.5}$$

where $\bar{N}_v$ is defined in (2.2) and $\bar{M}_h$ is given by

$$\bar{M}_h = \min\left(\bar{N}_h, \frac{\Lambda_h}{\mu_h(1-\tau_h)}\right), \tag{2.6}$$

being $\bar{N}_h = \Lambda_h/\mu_h$. Observe that the vector field defined by the right side of (2.3) is continuously differentiable in the set Ω, in consequence the Theorem of Picard (see [35]) guarantees the existence and uniqueness of the solutions of (2.3). The following lemma ensures that the set Ω has biological sense, that is, all solutions starting in it remain there for all $t \geq 0$.

Lemma 2.1. *The set Ω defined in (2.5) is positively invariant for the solutions of the system (2.3).*

Proof. Since $\lambda_h < \mu_h$, it is clear that $\tau_h < 1$. Adding the first four equations of system (2.3) we obtain that $N_h(t)$ satisfies

$$\frac{dN_h(t)}{dt} = \Lambda_h - \mu_h N_h(t) + \mu_h \tau_h I_h(t). \tag{2.7}$$

If $\tau_h \leq 0$ then we verify that

$$N_h(t) \leq \limsup N_h(t) \leq \frac{\Lambda_h}{\mu_h},$$

while if $0 < \tau_h < 1$ it follows that

$$N_h(t) \leq \limsup N_h(t) \leq \frac{\Lambda_h}{\mu_h(1-\tau_h)}.$$

Therefore

$$N_h(t) \leq \bar{M}_h = min\left(\frac{\Lambda_h}{\mu_h}, \frac{\Lambda_h}{\mu_h(1-\tau_h)}\right). \tag{2.8}$$

On the other hand, since $I_h \leq N_h$ and $I_v \leq N_v$, from the fifth equation of (2.3) we obtain

$$\frac{dI_v}{dt} \leq \beta_v \bar{N}_v - (\beta_v + \mu_v) I_v. \tag{2.9}$$

From (2.9) we obtain the following inequality

$$I_v(t) \leq \limsup I_v(t) \leq \frac{\beta_v \bar{N}_v}{\beta_v + \mu_v} \leq \bar{N}_v.$$

Finally, it can be easily verified that the vector field defined by the right side of (2.3) on $\partial\Omega$ points to the interior of Ω. □

3 Qualitative analysis of equilibrium solutions

3.1 Disease-free equilibrium and the Basic Reproductive Number

The *Disease-Free Equilibrium* of system (2.3) (DFE) denoted by

$$E_0 = (\bar{N}_h, 0, 0, 0, 0)$$

represents the state where the population is free of the infection. The *Basic Reproductive Number*, denoted by R_0, is the average number of secondary infective generated by a single infective during the curse of the infection in a whole susceptible population. It is a threshold that let us determine when an outbreak can occur, or a disease remains endemic. Driesche *et al.* [49] defined R_0 as the spectral ratio of the *Next Generation Operator* associated to the disease-free equilibrium. For a system of ordinary differential equations, the Next Generation Operator is given by the the matrix FV^{-1}, where F and V are the derivatives of the infection vector, f, and the transition vector, v, evaluated at E_0. For model (2.3) f and v are given by

$$f = \begin{pmatrix} \beta_h \dfrac{I_v}{N_h} S_h \\ 0 \\ \beta_v \dfrac{I_h}{N_h}(\bar{N}_v - I_v) \end{pmatrix} \quad \text{and} \quad v = \begin{pmatrix} -(\alpha_h + \mu_h) E_h \\ \alpha_h E_h - (\delta_h + (1-\tau_h)\mu_h) I_h \\ -\mu_v I_v \end{pmatrix},$$

respectively. Differentiating f and v with respect to (E_h, I_h, I_v), and evaluating at E_0 we obtain

$$F = \begin{pmatrix} 0 & 0 & \beta_h \\ 0 & 0 & 0 \\ 0 & \beta_v \dfrac{\bar{N}_v}{\bar{N}_h} & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \alpha_h + \mu_h & 0 & 0 \\ -\alpha_h & \delta_h + (1-\tau_h)\mu_h & 0 \\ 0 & 0 & \mu_v \end{pmatrix}.$$

Therefore, the next generator operator of model (2.3) is given by

$$FV^{-1} = \begin{pmatrix} 0 & 0 & \frac{\beta_h}{\mu_V} \\ 0 & 0 & 0 \\ \frac{\alpha_h\beta_v}{(\alpha_h+\mu_h)(\delta_h+(1-\tau_h)\mu_h)}\frac{\bar{N}_v}{\bar{N}_h} & \frac{\beta_v}{\delta_h+(1-\tau_h)\mu_h}\frac{\bar{N}_v}{\bar{N}_h} & 0 \end{pmatrix}. \tag{3.1}$$

Simple calculations show that the eigenvalues of FV^{-1} are $\xi_1 = 0$, and the solutions of the quadratic equation

$$\xi^2 - \beta_h\beta_v\frac{\bar{N}_v}{\bar{N}_h}\frac{\alpha_h}{(\alpha_h+\mu_h)(\delta_h+(1-\tau_h)\mu_h)}\frac{1}{\mu_v} = 0.$$

Therefore, the basic reproduction number is given by

$$R_0 = \sqrt{\frac{\alpha_h\beta_h\beta_v m}{(\alpha_h+\mu_h)(\delta_h+\mu_h(1-\tau_h))\mu_v}}. \tag{3.2}$$

where $m = \dfrac{\bar{N}_v}{\bar{N}_h}$. By definition, the basic reproductive number R_0 is the expected number of new cases that an infected human would produce during their period of infection in susceptible population to the disease. In this case, from (3.2) we observed that R_0 is product between the new infected mosquitoes produced by an infected human and the new infected humans produced by an infected mosquito. The local stability of E_0 is resumed in the following proposition.

Proposition 3.1. *The equilibrium E_0 of model (2.3) is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.*

Proof. The eigenvalues of Jacobian matrix evaluated in E_0, $J(E_0)$, are μ_h, $-(\omega_h+\mu_h)$ and the roots of the cubic polynomial

$$a_0\xi^3 + a_1\xi^2 + a_2\xi + a_3 = 0, \tag{3.3}$$

where

$$\begin{aligned} a_0 &= 1 \\ a_1 &= (\alpha_h+\mu_h) + [\delta_h + (1-\tau_h)\mu_h] + \mu_v \\ a_2 &= (\alpha_h+\mu_H+\mu_v)[\delta_h+(1-\tau_h)\mu_h] + (\alpha_h+\mu_h)\mu_v \\ a_3 &= (\alpha_h+\mu_h)[\delta_h+(1-\tau_h)\mu_h]\mu_v(1+R_0)(1-R_0). \end{aligned}$$

Since $\tau_h < 1$ $a_i, i = 1, 2$ are positive, and a_3 is positive if and only if $R_0 < 1$. Also, it is easy to show that for $R_0 < 1$, $a_1a_2 > a_3$. Therefore, by the Routh-Hurwitz criterium, it follows that the roots of equation (3.3) have negative real part. □

The previous result suggests that in case of an epidemiological outbreak, if the new infected individuals (humans and mosquitoes) do not have the capacity to produce new infected ones, then the progression of the disease will be controlled. Now, the endemic equilibria are obtained making the derivatives equal to zero, and solving the resulting algebraic system. From the equation (2.7) at equilibrium we obtain

$$N_h = \bar{N}_h + \tau_h I_h,$$

From the third and fourth equations of system (2.3) we obtain

$$\begin{aligned} E_h &= \frac{\delta_h + \mu_h(1-\tau_h)}{\alpha_h} I_h \\ R_h &= \frac{\delta_h}{\omega_h + \mu_h} I_h. \end{aligned} \tag{3.4}$$

Adding the two first equations of (2.3), and solving for S_h we get

$$S_h = \frac{\Lambda_h + \omega_h R_h - (\alpha_h + \mu_h) E_h}{\mu_h}.$$

Substituting R_h, E_h, and after some manipulations we obtain

$$S_h = \frac{\Lambda_h}{\mu_h} - \frac{(\alpha_h + \mu_h)(\delta_h + \mu_h(1-\tau_h))}{\alpha_h \mu_h}(1-\theta_h) I_h, \tag{3.5}$$

where

$$\theta_h = \frac{\omega_h}{(\omega_h + \mu_h)} \frac{\alpha_h}{(\alpha_h + \mu_h)} \frac{\delta_h}{\delta_h + \mu_h(1-\tau_h)} \leq 1. \tag{3.6}$$

Replacing N_h in the fifth equation of system (2.3), and solving for I_v we obtain

$$I_v = \frac{\Lambda_v}{\mu_v} \left(\frac{\beta_v I_h}{\mu_v \frac{\Lambda_h}{\mu_h} + (\beta_v + \mu_v \tau_h) I_h} \right).$$

Replacing E_h and S_h given by (3.4) and (3.5) in the second equation of (2.3) we get

$$\begin{aligned} \frac{\beta_h I_v}{N_h} \left(\frac{\Lambda_h}{\mu_h} - \frac{(\alpha_h + \mu_h)(\delta_h + \mu_h(1-\tau_h))}{\alpha_h \mu_h}(1-\theta_h) I_h \right) &= \\ - \frac{(\alpha_h + \mu_h)(\rho_h + \delta_h + \mu_h - p_h)}{\alpha_h} I_h, & \end{aligned}$$

which is equivalent to

$$\beta_h I_v \left(\frac{\Lambda_h}{\mu_h} \frac{\alpha_h}{(\alpha_h + \mu_h)(\delta_h + \mu_h(1-\tau_h))} - \frac{1}{\mu_h}(1-\theta_h) I_h \right) = I_h N_h.$$

Replacing I_v and N_h in the equation above and simplifying we obtain

$$\begin{aligned} \beta_h \bar{N}_v \mu_v \gamma_v \left[\frac{\Lambda_h \alpha_h}{\mu_h(\alpha_h + \mu_h)(\delta + \mu_h(1-\tau_h)} - \frac{(1-\theta_h)}{\mu_h} I_h \right] &= \\ \mu_v(\bar{N}_h + \tau_h I_h) \times \left(\bar{N}_h + (\gamma_v + \tau_h) I_h \right), & \end{aligned} \tag{3.7}$$

where

$$\gamma_v = \frac{\beta_v}{\mu_v}. \tag{3.8}$$

After some manipulations we obtain that (3.7) is a quadratic equation in the variable I_h given by

$$aI_h^2 + bI_h + c = 0, \tag{3.9}$$

where

$$\begin{aligned} a &= \tau_h(\gamma_v + \tau_h) \\ b &= A(R_0^2 - L) \\ c &= \bar{N}_h^2(1 - R_0^2) \end{aligned} \tag{3.10}$$

with

$$\begin{aligned} A &= \bar{N}_h \frac{(\alpha_h + \mu_h)[\delta + \mu_h(1-\tau_h)](1-\theta_h)}{\alpha_h \mu_h^2} > 0, \\ L &= -\bar{N}_h \frac{(\gamma_v + 2\tau_h)}{A} \end{aligned} \tag{3.11}$$

We observe that the quantity of endemic equilibrium solutions of (2.3) depends on the number of positive solutions of the quadratic equation (3.9). On the other hand the coefficients a, b and c of (3.9) are nor defined sign, and they also depend on the parameters τ_h, γ_v, A, R_0 and L. Consequently, the results of existence of endemic equilibria will be presented in terms of the parameters previously mentioned. In this sense, for

$$\tau_h^* = -\frac{1}{2}\left(\frac{A}{\bar{N}_h} + \gamma_v\right), \tag{3.12}$$

we have the following result.

Theorem 3.2. *Assume $\tau_h \leq \tau_h^*$ $(1 \leq L)$, the system (2.3) has the following behaviour:*

1. *If $R_0 > 1$ there exist one endemic equilibrium .*
2. *If $R_0 \leq 1$, there exist unique $R_0^* \in (0,1)$ such that*
   - *If $0 < R_0 < R_0^*$ there are not endemic equilibria.*
   - *If $R_0 = R_0^*$ there is one endemic equilibrium.*
   - *If $R_0 > R_0^*$ there are two endemic equilibria.*

See A for proof of the Theorem 3.2. The previous result suggests the possible existence of a backward bifurcation when $\tau_h \leq \tau_h^*$ or equivalently $L \geq 1$. Now, we are going to present the case when $\tau_h > \tau_h^*$ $(1 > L)$, which have two possibilities i) $\tau_h < -\gamma_v$ or $\tau_h \geq 0$ and ii) $-\gamma_v < \tau_h < 0$.

Theorem 3.3. *Assume $\tau_h > \tau_h^*$ $(1 > L)$, the system (2.3) has the folowing behaviour:*

1. *If $\tau_h \leq -\gamma_v$ or $\tau_h \geq 0$ we have following two posibilities*

(a) If $R_0 \leq 1$ there are not endemic equilibria.

(b) If $R_0 > 1$ there is a unique endemic equilibrium.

2. If $-\gamma_v < \tau_h < 0$ then

(a) If $R_0 \leq 1$ there is a unique endemic equilibrium.

(b) If $R_0 > 1$ there are two endemic equilibria.

See Appendix A for proof of the Theorem 3.3.

4 Transcritical bifurcations analysis

When forward bifurcation occurs, the condition $R_0 < 1$ is a necessary and sufficient condition for disease eradication, whereas it is no longer sufficient when a backward bifurcation occurs. In fact, the backward bifurcation scenario involves both the existence of a subcritical transcritical bifurcation at $R_0 = 1$ and a saddle-node bifurcation at $R_0 = R_0^* < 1$. The backward bifurcation scenario may be qualitatively described as follows. In the neighborhood of $R_0 = 1$, in the region $R_0^* < R_0 < 1$, a stable disease-free equilibrium coexists with two endemic equilibria: a smaller equilibrium (with a smaller number of infective individuals) which is unstable and a larger one (with a larger number of infective individuals) which is stable. These two endemic equilibria disappear by saddle-node bifurcation when the basic reproductive number R_0 is decreased below the critical value $R_0^* < 1$. For $R_0 > 1$, there are only two equilibria: the disease free-equilibrium, which is unstable, and the larger endemic equilibrium, which is stable.

As a consequence, in the backward bifurcation scenario, if R_0 is nearly below unity, then the disease control depends strongly on the initial sizes of the various sub-populations of the model. On the contrary, reducing R_0 below the saddle-node bifurcation value R_0^*, may result in disease eradication, which guarantees the global stability of the disease free equilibrium. Hence, the sub-threshold R_0^* have a crucial importance in terms of disease control.

In the following we use the results based on center manifold theory described in [2], which prescribes the role of the coefficients $\tilde{a}$ and $\tilde{b}$ of the normal form representing the dynamics system on the central manifold. In this sense, they decide the direction of the transcritical bifurcation. More precisely, if $\tilde{a} < 0$ and $\tilde{b} > 0$, then the bifurcation is forward; if $\tilde{a} > 0$ and $\tilde{b} > 0$ then the bifurcation is backward.

We apply above theory to show that the system (2.3) may exhibit a transcritical bifurcation on following parameter

$$\beta_h \doteq \beta^* = \frac{(\mu_h + \alpha_h)[\delta_h + \mu_h(1 - \tau_h)]\mu_v}{\alpha_h \beta_v m}. \tag{4.1}$$

Observe that the eigenvalues of the Jacobian matrix $J(E_0, \beta^*)$ are given by $\xi_1 = 0$, $\xi_2 = -\mu_h$ and $\xi_3 = -(\mu_h + \omega_h)$ and solutions of following quadratic equation

$$\xi^2 + (\tilde{A} - \tilde{B} + \mu_v)\xi + (\tilde{A}\mu_v - \tilde{A}\tilde{B} - \tilde{B}\mu_v) = 0, \tag{4.2}$$

where

$$\begin{aligned}\tilde{A} &= \alpha_h + \mu_h \\ \tilde{B} &= \mu_h(\tau_h - 1) - \delta_h,\end{aligned}$$

whose solutions are given by

$$\xi_{1,2} = \frac{-(\tilde{A} - \tilde{B} + \mu_v) \pm \sqrt{(\tilde{A} - \tilde{B} + \mu_v)^2 - 4[\tilde{A}\mu_v - \tilde{B}(\tilde{A} + \mu_v)]}}{2}.$$

From above inequality we can see that if discriminant is negative then real part of roots is $-(\tilde{A} - \tilde{B} - \mu_V)/2$, which is less than zero due to $-\tilde{B} > 0$. On the other hand, if discriminant is positive it satisfies

$$\begin{aligned}(\tilde{A} - \tilde{B} + \mu_v)^2 &> (\tilde{A} - \tilde{B} + \mu_v)^2 - 4[\tilde{A}\mu_v - \tilde{B}(\tilde{A} + \mu_v)] \\ (\tilde{A} - \tilde{B} + \mu_v) &> \sqrt{(\tilde{A} - \tilde{B} + \mu_v)^2 - 4[\tilde{A}\mu_V - \tilde{B}(\tilde{A} + \mu_v)]} \\ 0 &> -(\tilde{A} - \tilde{B} + \mu_v) + \sqrt{(\tilde{A} - \tilde{B} + \mu_v)^2 - 4[\tilde{A}\mu_v - \tilde{B}(\tilde{A} + \mu_v)]},\end{aligned}$$

which implies that $\xi_1 < 0$ and $\xi_2 < 0$. Then, in both cases the roots of equation (4.2) have negative real part. Thus $\xi_1 = 0$ is a simple eigenvalue and the other eigenvalues have negative real part. In consequence, when $\beta_h = \beta^*$ (or equivalently when $R_0 = 1$), the disease-free equilibrium E_0 is a non hyperbolic equilibrium.

Now, we denote by $W = (w_1, w_2, w_3, w_4, w_5)$ a right eigenvector associated with $\xi_1 = 0$, which satisfies $J(E_0, \beta^*)W = 0W = \mathbf{0}$. It follows:

$$\begin{aligned}0 &= \frac{\beta_v m(\mu_h + \omega_h)}{\delta_h} w_4 - \mu_v w_5 \\ 0 &= \delta_h w_3 - (\omega_h + \mu_h) w_4 \\ 0 &= \alpha_h w_2 + [\mu_h(\tau_h - 1) - \delta_h] w_3 \\ 0 &= -\mu_h w_1 + \omega_h w_4 - \beta^* w_5.\end{aligned}$$

Replacing β^* defined in (4.1) in above system and using the inequality

$$2\tau_h^* + \gamma_v = -\frac{(\alpha_h + \mu_h)[\mu_h(1 - \tau_h) + \delta_h](1 - \theta)}{\alpha_h \mu_h} < 0,$$

we obtain that

$$W = \frac{m}{\gamma_v} w_5 \left[2\tau_h^* + \gamma_v, -\frac{\mu_h(2\tau_h^* + \gamma_v)}{(\alpha_h + \mu_h)(1 - \theta)}, 1, \frac{\delta_h}{\omega_h + \mu_h}, \frac{\gamma_v}{m}\right]^T. \tag{4.3}$$

On the other hand, the left eigenvector $V = (v_1, v_2, v_3, v_4, v_5)^T$ of the matrix $J(E_0, \beta^*)$ associated to eigenvalue $\xi_1 = 0$ is given by

$$V = -\frac{(1 - \theta)\mu_v}{2\tau_h^* + \gamma_v} v_5 \left[0, 1, \frac{\alpha_h + \mu_h}{\alpha_h}, 0, -\frac{2\tau_h^* + \gamma_v}{(1 - \theta)\mu_v}\right]^T. \tag{4.4}$$

The values of v_5 and w_5 such that $V \cdot W = 1$, are given by

$$\begin{aligned} w_5 &= \frac{1}{\frac{\mu_h}{\alpha_h+\mu_h} + \frac{(\alpha_h+\mu_h)(\theta-1)}{\alpha_h(2\tau_h^*+\gamma_v)} + \frac{\gamma_v}{m\mu_v}} > 0 \\ v_5 &= \frac{\gamma_v}{m\mu_v} > 0. \end{aligned} \tag{4.5}$$

In this case, the coefficient $\tilde{a}$ and $\tilde{b}$ given on Theorem 4.1 of [2] are given by

$$\begin{aligned} \tilde{a} &= \frac{1}{2}\sum_{k,i,j=1}^{5} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0, \beta^*) \\ \tilde{b} &= \sum_{k,i=1}^{5} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(E_0, \beta^*), \end{aligned}$$

which are explicitly computed. Taking into account f_i, $i = 1, ..., 5$ as the functions of the right hand of system (2.3), $x_1 = S_h$, $x_2 = E_h$, $x_3 = I_h$, $x_4 = R_h$, $x_5 = I_v$ and the coefficients w_p, v_q with $p, q = 1, ..., 5$, are the components of eigenvectors W and V defined on (4.3) and (4.4). After some calculations we have:

$$\begin{aligned} \frac{\partial^2 f_1}{\partial x_5 \partial x_2} = \frac{\partial^2 f_1}{\partial x_5 \partial x_3} = \frac{\partial^2 f_1}{\partial x_5 \partial x_4} &= \frac{\beta_h}{\bar{N}_h} \\ \frac{\partial^2 f_2}{\partial x_5 \partial x_2} = \frac{\partial^2 f_2}{\partial x_5 \partial x_3} = \frac{\partial^2 f_2}{\partial x_5 \partial x_4} &= -\frac{\beta_h}{\bar{N}_h} \\ \frac{\partial^2 f_5}{\partial x_3 \partial x_1} = \frac{\partial^2 f_5}{\partial x_3 \partial x_2} = \frac{\partial^2 f_5}{\partial x_4 \partial x_3} &= -\beta_v \bar{N}_v \left(\frac{1}{\bar{N}_h}\right)^2 = -\frac{\beta_v m}{\bar{N}_h} \\ \frac{\partial^2 f_5}{\partial x_5 \partial x_3} &= -\frac{\beta_v}{\bar{N}_h} \\ \frac{\partial^2 f_5}{\partial x_3^2} &= -2\beta_v \frac{\Lambda_v}{\mu_v}\left(\frac{\mu_h}{\Lambda_h}\right)^2 = -2\frac{\beta_v m}{\bar{N}_h}. \end{aligned}$$

In the above expressions we did not consider zero derivatives and cross partial derivatives. Moreover, second partial derivatives with respect to bifurcation parameter β^* in E_0 are always zero except

$$\frac{\partial^2 f_1}{\partial x_5 \partial \beta^*} = -1 \quad \text{and} \quad \frac{\partial^2 f_2}{\partial x_5 \partial \beta^*} = 1.$$

Therefore,

$$\tilde{b} = v_2 w_5 \frac{\partial^2 f_2}{\partial x_5 \partial \beta^*} = -\frac{(1-\theta)\gamma_v}{m(2\tau_h^* + \gamma_v)} w_5 > 0,$$

and

$$\begin{aligned} \tilde{a} &= w_5 v_2 \frac{\partial^2 f_2}{\partial x_5 \partial x_2}(w_2 + w_3 + w_4) + v_5 w_3 \frac{\partial^2 f_5}{\partial x_3 \partial x_1}(w_1 + w_2 + w_4) + \\ &\quad v_5 w_3 \Big[w_5 \frac{\partial^2 f_5}{\partial x_5 \partial x_3} + \frac{w_3}{2}\frac{\partial^2 f_5}{\partial x_3^2} \Big]. \end{aligned} \tag{4.6}$$

Table 2: Estimated values of $\tilde{a}$ given on (4.6) with values of parameters given on Table 3.

	Rural areas	Urbans areas
Value of τ_h	0.098	-70.40
Value of τ_h^*	-3.71	-37.75
Value of γ_v	6.23	3.71
Value of R_0	8.04	0.56
Relation	$\tau_h > \tau_h^*$ and $\tau_h > 0$	$\tau_h < \tau_h^*$ and $\tau_h < \gamma_v$
Value of $\tilde{a}$	-1.6 $\times 10^{-11}$	4.10 $\times 10^{-14}$

Due to the analytical complexity in determining the sign of $\tilde{a}$ we verify numerically using with values of parameters given on Table 3, which will be explain in Section 5.

In Table 2 we observe for the values of the parameters corresponding to rural areas that $\tilde{a} < 0$ and hypothesis of the first item of the Theorem 3.3 are satisfied, which implies the occurrence of a forward bifurcation, the above combined with the first item of Theorem 3.3 suggests that the forward bifurcation occurs when $\tau_h > \tau_h^*$ and ($\tau_h \leq -\gamma_v$ or $\tau_h \geq 0$). Analogously, from values of parameters in urban area the condition $\tilde{a} > 0$ and hypothesis of Theorem 3.2 are satisfied, which implies that a backward bifurcation occurs. Newly, this results combined with the Theorem 3.2 suggests that the backward bifurcation occurs when $\tau_h \leq \tau_h^*$. Finally, when $\tau_h > \tau_h^*$ and $-\gamma_v < \tau_h < 0$ seems to exist a kind of pitch fork bifurcation. On the other hand, using Lyapunov's Theorem we have the following result:

Theorem 4.1. *If $\tau_h \leq 0$ and $R_0^2 < \ell$, then the free disease equilibrium E_0 is global asymptotically stable in Ω, where*

$$\ell = 1 + \frac{\beta_h \beta_v \alpha_h m \tau_h}{\mu_v(\alpha_h + \mu_h)[\mu_h(1-\tau) + \delta_h]}. \tag{4.7}$$

Proof. In the Proposition 3.1 we verify that E_0 is local and asymptotically stable Ω when $R_0 < 1$. Let

$$R_1 = \frac{\beta_h \beta_v \alpha_h m}{\mu_v(\alpha_h + \mu_h)[\mu_h(1-\tau_h) + \delta_h]}. \tag{4.8}$$

Simple calculations verify that

$$R_1 = R_0^2 + 1 - \ell.$$

Suppose that $R_0^2 < \ell$, which is equivalent to $R_1 < 1$, and let ($S_h(t)$, $E_h(t)$, $I_h(t)$, $R_h(t)$, $I_v(t)$) a positive solution of system (2.3). Then, by invariance this solution satisfies $N_v(t) \leq \bar{N}_v$, and due to $I_h(t) < N_h(t)$ and $\tau_h \leq 0$ we have

$$\dot{N}_h(t) = \Lambda_h - \mu_h N_h + \mu_h \tau_h I_h > \Lambda_h + \mu_h(1-\tau_h)N_h, \tag{4.9}$$

from (4.9) we obtain $N_h(t) > \frac{\bar{N}_h}{(1-\tau_h)}$. Now, We proof the existence a Lyapunov function for the translated system

$$\dot{x} = F(x + E_0) - F(E_0) = f(x),$$

where $y = 0$ as a trivial equilibrium solution of the system $\dot{y} = F(y)$. Let us consider following function

$$V^*(S_h, E_h, I_h, R_h, I_v) = I_v + \frac{\mu_v}{\beta_h} E_h + \frac{\mu_v(\alpha_h + \mu_h)}{\alpha_h \beta_h} I_h,$$

and let

$$V(\tilde{S}_h, \tilde{E}_h, \tilde{I}_h, \tilde{R}_h, \tilde{I}_v) \doteq V^* \left(S_h - \bar{N}_h, E_h, I_h, R_h, I_v\right). \tag{4.10}$$

The function V satisfies that $V(E_0) = V^*(\mathbf{0}) = 0$ and $V > 0$ $\forall (\tilde{S}_h, \tilde{E}_h, \tilde{I}_h, \tilde{R}_h, \tilde{I}_v) \neq E_0 \in \Omega$; that is, V is positive defined. Define by f_i, $i = 1, ..., 5$ right hand of system (2.3), then the orbital derivative of V along the trajectories of (2.3) is given by

$$\begin{aligned}
\dot{V} &= \frac{\partial V^*}{\partial (S_h - \bar{N}_h)} f_1 + ... + \frac{\partial V^*}{\partial I_v} f_5 = \dot{I}_v + \frac{\mu_v}{\beta_h} \dot{E}_h + \frac{\mu_v(\alpha_h + \mu_h)}{\alpha_h \beta_h} \dot{I}_h \\
&= \left[\frac{\beta_v}{N_h} S_v - \frac{\mu_v(\alpha_h + \mu_h)[\mu_h(1 - \tau_h) + \delta_h]}{\alpha_h \beta_h} \right] I_h - \left[\frac{N_h - S_h}{N_h} \right] I_v \\
&\leq \left[\frac{\beta_v \bar{N}_v}{\frac{\bar{N}_h}{(1-\tau_h)}} - \frac{\mu_v(\alpha_h + \mu_H)[\mu_h(1 - \tau_h) + \delta_h]}{\alpha_h \beta_h} \right] I_h \\
&= \left[\beta_v m(1 - \tau_h) - \frac{\mu_v(\alpha_h + \mu_h)[\mu_h(1 - \tau_h) + \delta_h]}{\alpha_h \beta_h} \right] I_h \\
&= \left[\frac{\mu_v(\alpha_h + \mu_h)[\mu_h(1 - \tau_h) + \delta_h](1 - \tau_h)}{\beta_h \alpha_h} \right] (R_1 - 1) I_h.
\end{aligned}$$

The first factor of the last expression above is no negative and by hypothesis $R_1 < 1$, then $\dot{V} < 0$. Thus, E_0 is a global attractor. □

From above theorem we have the following corollary:

Corollary 4.2. *When $\tau_h = 0$ and $R_0 < 1$, E_0 is global and asymptotically stable.*

5 Sensitivity analysis and numerical simulations

In this section we make sensitivity analysis of parameters using data from Tumaco in the period between the early 2000 and late 2001 where there was an accelerated growth in the incidence of malaria in Tumaco which increased the risk of malaria spreading. In order to establish control measures, at the end of 2001 a census was carried out in Tumaco. Table 3 shows parameter values estimated using census data reported by SIVIGILA [47] in addition to the rankings of parameter values that were obtained from [44]. Also, in the Table 3 we presented two sets of values for parameters: parameters for high transmission areas, which corresponds to rural areas of Tumaco, and low transmission areas, which correspond to urban areas of Tumaco. For rural areas $R_0 = 7.5$ and for urban areas $R_0 = 0.56$.

The numerical simulations of Figures 1 and 2 were made with data of rural and urban areas given in Table 3, respectively, and the Tables 4 and 5 show the endemic equilibrium in each case.

Table 3: Values of parameter of model (2.3) with days as time unity.

Parameters	High transmission areas	Low transmission areas	Rank	Reference
α_h	0.10	0.10	0.007-0.20	[45, 21]
μ_v	0.0039	0.0025	0.0010-0.12	[45, 57, 21]
μ_h	0.00102	0.00125	0.000001-0.002	[45, 21]
ρ_h	0.0090	0.009	0-0.00041	[45, 57, 21]
δ_h	0.0029	0.0029	0.0014-0.017	[45, 57, 21]
β_{HV}	0.70	0.40	0.010-0.80	[45, 21]
β_{VH}	0.20	0.32	0.072-0.69	[45, 21]
ϵ	0.45	0.29	0.25-0.87	[45, 21]
λ_h	0.0002	0.0091	0.00012-0.012	[45, 57, 21]
Λ_v	180	160	100-1000	[45, 21]
Λ_h	100	90	10 - 200	[45, 21]
ω_h	0.01	0.01	0.000055-0.02	[45, 21]

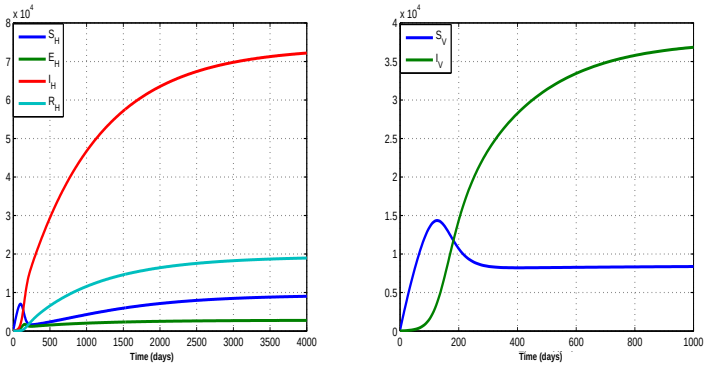

Figure 1: Numerical simulations of model (2.1) with data of rural areas and initial conditions (100, 50, 10, 3, 100, 20). Here $R_0 = 7.5$, $\tau_h = 0.088$, $\tau_h^* = -3.71$ and $\gamma_v = 6.23$. Solutions of system tends to endemic equilibrium (9026, 2774, 72190, 18960, 8595, 37558)

Table 4: Endemic equilibrium of model (2.1) with rural areas data.

$S_H = 9026$	$S_V = 8595$
$E_H = 2774$	$I_V = 37558$
$I_H = 72190$	
$R_H = 18960$	

Table 5: Endemic equilibrium of model (2.1) with urban areas data.

$S_H = 4387$	$S_V = 21252$
$E_H = 1180$	$I_V = 47747$
$I_H = 9985$	
$R_H = 2863$	

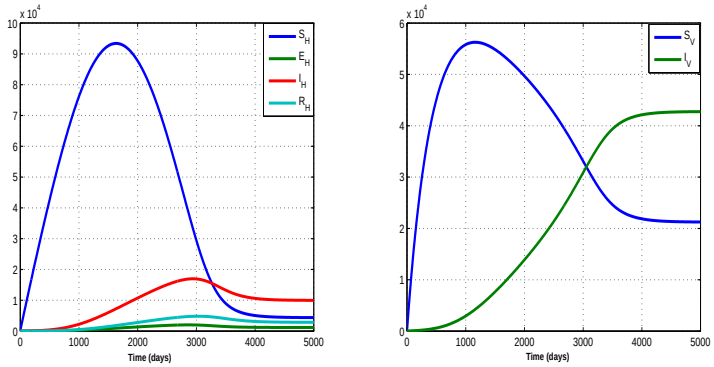

Figure 2: Numerical simulations of model (2.1) with data of urban areas and initial conditions (100, 50, 10, 3, 100, 20). Here $R_0 = 0.56$, $\tau_h = -70.40$, $\tau_h^* = -37.75$ and $\gamma_v = 3.71$. Solutions of system tends to endemic equilibrium (4387, 1180, 9985, 2863, 21252, 47747)

In order to determine the best way to reduce mortality and morbidity due to malaria in human population, it is necessary to know the relative importance of the parameters in the outcome of the disease, which is directly related to the threshold R_0 [44]. Sensitivity indices allow us to measure the relative change in a variable when a parameter is changing. The *normalized forward sensitivity index* of a variable with respect to a parameter is the ratio of the relative change [44].

Definition 5.1. The normalized forward sensitivity index of variable u, that depends differentially on a parameter p, is defined by

$$\Gamma_p^u \doteq \frac{\partial u}{\partial p}\frac{p}{u}. \tag{5.1}$$

From (5.1) we derive an analytical expression for the sensitivity index of R_0 with respect to each parameter. The values obtained are described in Table 6.

Table 6: Sensitive index to R_0 with respect to parameters.

Parameter	Index in rural areas	Index in urban areas
α_h	0.005	0.000069
μ_v	-1	-1
μ_h	0.3745	0.1220
ρ_h	-1.1780	- 0.3805
δ_h	-0.6118	-0.1398
β_{hv}	0.50	0.50
β_{vh}	0.50	0.50
ϵ	1	1
λ_h	1.0091	0.0077
Λ_v	0.50	0.50
Λ_h	-0.50	-0.50

Observe that in urban areas, R_0 is most sensitive to death or emigration mosquitoes rate μ_v and bite rate ϵ; obviously, a higher contact and bite rate generates many more cases of infected individuals, which makes these parameters directly proportional to R_0. On the other hand, in rural areas R_0 has most of sensitivity to infection death rate ρ_h and vertical transmission rate λ_h. In both cases, others parameters with high sensitivity are the transmission probabilities rates β_{hv} and β_{vh}; birth rates Λ_h and Λ_v; recovery rate δ_h and the mortality or emigration rate of humans μ_h. Given that $\Gamma_\epsilon = +1.0$, increasing (or decreasing) ϵ 10% implies that R_0 increases (or decreases) in 10%; similarly, as $\Gamma_{\Lambda_h} = -0.50$, then increasing (or decreasing) Λ_h in 10% implies that R_0 increases (or decreases) in 5%. An analogous reasoning can be made for others sensitivity indexes.

The information provided by sensitivity indices to R_0 allow us to propose control strategies that affect the parameters of greater sensitivity in both rural and urban areas of Tumaco.

6 The optimal control problem

In this section, we use results obtained in the previous section to formulate an optimal control problem in which the state equations were obtained from (2.1). We define the following control variables: u_1 is the control variable associated with bed nets (BN), u_2 is the control variable associated with antimalarial treatment (AT), u_3 is the control variable associated with intermittent prophylactic treatment in pregnancy (IPTp), and u_4 is the control variable associated with indoor residual spraying (IRS). We incorporated the following hypothesis in the system (2.1): susceptible humans become exposed by contact with infected mosquitoes at a rate $(1-u_1)\beta_{hv}\epsilon\frac{I_v}{N_h}S_h$, where $u_1 \in [0,1]$ ($u_1 = 0$ represents no efficacy of the control, while $u_1 = 1$ indicates that the use of the control is completely effective). On the other hand, we assume that infected humans recover at a rate $\delta_h + \xi_2 u_2$, where δ_h is spontaneous recovery rate, and $\xi_2 \in [0,1]$ represents the effectiveness of the treatment. The rate at which newborns are infected is given by $(1-u_3)\lambda_h$, where λ_h is the vertical transmission rate, $\mu_3 \in [0,1]$ ($u_3 = 0$ is assumed if treatment during pregnancy is not effective, and $u_3 = 1$ if the treatment is completely effective, that is, there is no vertical transmission). Finally, we assume that the mosquitoes population are decreasing because of the use of insecticides, given by the term $\xi_4 u_4$, where $\xi_4 \in [0,1]$ represents the insecticide. In this sense, we have that the control variable $u_1(t)$ provides information about the amount of bed nets that must be supplied, $u_2(t)$ and $u_3(t)$ the amount of medication that should be provided, while $u_4(t)$ gives information about the amount of insecticide that should be applied to the population at time t.

With the propose to minimize the number of infected humans and mosquitoes we define the following performance index or cost function:

$$J(x_0, v) = \int_{t_0}^{t_1} f_0(t, x, v)dt, \tag{6.1}$$

where

$$\begin{aligned} v(t) &= (u_1(t), u_2(t), u_3(t), u_4(t)) \\ f_0(t,x,v) &= f_1(t,x) + h(t,v). \end{aligned} \tag{6.2}$$

In the previous expressions x_0 is a initial condition, x is the solution of system (2.1) evaluated in v, and additionally

$$f_1(t,x) = c_1 E_H + c_2 I_H + c_3 I_V, \tag{6.3}$$

where c_1, c_2 and c_3 represent social costs, which depend of number of infection cases due to malaria and number of bites by mosquitoes. On the other hand, the function $h(t,v)$ define the absolute costs associated to control strategies, such that implementation, ordering, distribution, merchandizing, among others. More generally,

$$h(t,v) = \frac{1}{\kappa}\sum_{i=1}^{4} d_i u_i(t)^{\kappa},$$

where $\kappa = 1/2, 1, 2, ..., n$, and d_i is the relative weight to the cost associated with the implementation of the control variable u_i. For the purposes of this document, we will assume that $\kappa = 2$ to refer to the non-linearity of the absolute costs. With the above considerations, the following control problem is formulated:

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h + \omega_h R_h - [1-u_1(t)]\beta_{hv}\epsilon\frac{I_v}{N_h}S_h - \mu_h S_h \\
\frac{dE_h}{dt} &= [1-u_1(t)]\beta_{hv}\epsilon\frac{I_v}{N_h}S_h - (\alpha_h+\mu_h)E_h \\
\frac{dI_h}{dt} &= [1-u_3(t)]\lambda_h I_h + \alpha_h E_h - [\delta_h + \xi_2 u_2(t) + \rho_h + \mu_h]I_h \\
\frac{dR_h}{dt} &= [\delta_h + \xi_2 u_2(t)]I_h - (\omega_h+\mu_h)R_h \\
\frac{dS_v}{dt} &= \Lambda_v - [1-u_1(t)]\beta_{vh}\epsilon\frac{I_h}{N_h}S_v - [\xi_4 u_4(t) + \mu_v]S_v \\
\frac{dI_v}{dt} &= [1-u_1(t)]\beta_{vh}\epsilon\frac{I_h}{N_h}S_v - [\xi_4 u_4(t) + \mu_v]I_v,
\end{aligned} \tag{6.4}$$

with the performance index or cost function

$$\begin{aligned}
J(x_0,u_1,u_2,u_3,u_4) &= \int_0^T [c_1 E_H + c_2 I_H + c_3 I_V + \\
&\quad \frac{1}{2}\left(d_1 u_1(t)^2 + d_2 u_2(t)^2 + d_3 u_3(t)^2 + d_4 u_4(t)^2\right)]dt,
\end{aligned} \tag{6.5}$$

and the boundary conditions:

$$\begin{aligned}
x(0) &= (\bar{S}_h, \bar{E}_h, \bar{I}_h, \bar{R}_h, \bar{S}_v, \bar{I}_v) = x_0 \\
x(T) &= (S_{h_f}, E_{h_f}, I_{h_f}, R_{h_f}, S_{v_f}, I_{v_f}) = x_1.
\end{aligned} \tag{6.6}$$

For the control problem we assume that the initial time is zero, $t_0 = 0$, the final time $t_1 = T$ is a fixed implementation time of the control strategies, and the final state x_1 is variable and the initial state x_0 is given by endemic equilibrium of (2.1). Additionally, we assume that the coordinates of vector v defined in the first equation of (6.2) are controls that belong to the following set

$$\mathcal{U} = \{u(t) : u(t) \quad \text{is Lebesgue measurable and} \quad 0 \le u(t) \le 1, t \in [0,T]\},$$

called *the set of admissible controls*. The following result guarantees the existence of an optimal initial condition x^* and an optimal control u^* of the control problem with state equation (6.4):

Theorem 6.1. *Consider the control problem with state equations (6.4). There exist a unique pair* $(x_0^*, v^*) \in \mathcal{F}$ *such that*

$$J(x_0^*, v^*) = \min\{J(x_0, v) : v = (u_1, u_2, u_3, u_4) \quad u_i \in \mathcal{U}\}, \tag{6.7}$$

where $J(x_0, v)$ *is the performance index defined in (6.5), where* $\mathcal{U}$ *is the* admisibles set controls.

The proof of the Theorem 6.1 is derived from the classic existence theorem presented in [54].

Proof. We use the following notation $x = (S_H, E_H, I_H, R_H, S_V, I_V)$. Let $U = [0,1]^4$ the set where v assume its values (controls set), and $f(t, x, v)$ the right side of (6.4), that is

(6.8)
$$f(t,x,v) = \begin{pmatrix} \Lambda_h + \omega_h R_h - (1-u_1)\beta_h \frac{I_v}{N_h} S_h - \mu_h S_h \\ (1-u_1)\beta_h \frac{I_v}{N_h} S_h - (\alpha_h + \mu_h) E_h \\ (1-u_3)\lambda_h I_h + \alpha_h E_h - (\delta_h + \xi_2 u_2 + \rho_h + \mu_h) I_h \\ (\delta_h + \xi_2 u_2) I_h - (\omega_h + \mu_h) R_h \\ \Lambda_v - (1-u_1)\beta_v \frac{I_h}{N_h} S_v - (\xi_4 u_4 + \mu_v) S_v \\ (1-u_1)\beta_v \frac{I_h}{N_h} S_v - (\xi_4 u_4 + \mu_v) I_v \end{pmatrix} = \begin{pmatrix} h_1 \\ h_2 \\ h_3 \\ h_4 \\ h_5 \\ h_6 \end{pmatrix}.$$

Following a similar process used in Section 5.1 of [22] we verify that f defined on 6.8 is of class C^1, and there exists a constant $C > 0$ such that

1. (a) $|f(t,0,0)| \leq C$
   (b) $|f_x(t,x,v)| \leq C(1+|v|)$
   (c) $|f_v(t,x,v)| \leq C$.
2. The set of feasible pairs $\mathcal{F}$ is non-empty.
3. The control set U is convex.
4. $f(t,x,v) = \alpha(t,x) + \beta(t,x)v$.
5. The integrand of the performance index $f_0(t,x,v)$ defined in (6.5) is convex for $v \in U$.
6. $f_0(t,x,v) \geq c_1|v|^b - c_2$ with $c_1 > 0$ and $b > 1$.

Observe that

$$f_v(t,x,v) = \begin{pmatrix} \beta_h \frac{I_v}{N_h} S_h & 0 & 0 & 0 \\ -\beta_h \frac{I_v}{N_h} S_h & 0 & 0 & 0 \\ 0 & -\xi_2 I_h & -\lambda_h I_h & 0 \\ 0 & \xi_2 I_h & 0 & 0 \\ \beta_v \frac{I_h}{N_h} S_v & 0 & 0 & -\xi_4 S_v \\ -\beta_v \frac{I_h}{N_h} S_v & 0 & 0 & -\xi_4 I_v \end{pmatrix}.$$

The norm of f_v satisfies

$$\begin{aligned}
|f_v(t,x,v)| &= \sqrt{2\beta_h^2 I_v^2\left(\frac{S_h}{N_h}\right)^2 + 2\beta_v^2 S_v^2\left(\frac{S_h}{N_h}\right)^2 + 2\xi_2^2 I_h^2 + \lambda_h^2 I_h^2 + \xi_4^2 S_v^2 + \xi_4^2 I_v^2} \\
&\leq \sqrt{(2\beta_h^2 + \xi_4^2) I_v^2 + (2\beta_v^2 + \xi_4^2) S_v^2 + (2\xi_2^2 + \lambda_h^2) I_h^2} \\
&\leq \sqrt{2(\beta_h^2 + \xi_4^2 + \beta_v^2)\frac{\Lambda_v^2}{\mu_v^2} + (2\xi_2^2 + \lambda_h^2)\frac{\Lambda_h^2}{\mu_h^2}} \\
&\leq \sqrt{\max\left\{\frac{2(\beta_h^2 + \beta_v^2 + \xi_4^2)}{\mu_v^2}, \frac{2\xi_2^2 + \lambda_h^2}{\mu_h^2}\right\}(\Lambda_h^2 + \Lambda_v^2)}.
\end{aligned}$$

In consequence, taking $C = \sqrt{\max\left\{\frac{2(\beta_h^2+\beta_v^2+\xi_4^2)}{\mu_v^2}, \frac{2\xi_2^2+\lambda_h^2}{\mu_h^2}\right\}(\Lambda_h^2 + \Lambda_v^2)}$ we prove the literal 1 (c). Following a similar procedure we verify 1 (a) and 1 (b). On the other hand, since f is of class C^1 then the Picard's Existence and Uniqueness Theorem guarantees the existence of a unique solution of the initial value problem $x' = f(t,x,0)$, $x(0) = x_0$ which implies that $\mathcal{F}$ is not empty, wich proves literal (2). The literals (3), (4) and (5) are immediate from the definition of convexity. Finally, the performance index f_0 defined in (6.5) satisfies

$$f_0(t,x,v) \geq \frac{1}{2}\min\{d_1,d_2,d_3,d_4\}(u_1^2 + u_2^2 + u_3^2 + u_4^2).$$

taking $b = 2$, $c_2 = 0$ and $c_1 = 1/2\min\{d_1,d_2,d_3,d_4\}$ we verifies the literal (6). The properties $(1)-(6)$ complete the proof. □

Now, we use Pontryagin principle for bounded controls to calculate optimal control of the control problem defined by (6.4), (6.5) and (6.6). To this end, we observe that the Hamiltonian is given by

$$\begin{aligned}
H(t,x(t),v(t),z(t)) &= f_0(t,x,v) + z(t)\cdot f(x,t,u) \\
&= c_1E_h + c_2I_h + c_3I_v + \frac{d_1u_1^2}{2} + \frac{d_2u_2^2}{2} + \frac{d_3u_3^2}{2} + \frac{d_4u_4^2}{2} + \\
&\quad z_1\left[\Lambda_h + \omega_h R_h - (1-u_1)\beta_h\frac{I_v}{N_h}S_h - \mu_h S_h\right] + \\
&\quad z_2\left[(1-u_1)\beta_h\frac{I_v}{N_h}S_h - (\alpha_h + \mu_h)E_h\right] + \\
&\quad z_3\left[(1-u_3)\lambda_h I_h + \alpha_h E_h - (\delta_h + \xi_2 u_2 + \rho_h + \mu_h)I_h\right] + \\
&\quad z_4\left[(\delta + \xi_2 u_2)I_h - (\omega_h + \mu_h)R_h\right] + \\
&\quad z_5\left[\Lambda_v - (1-u_1)\beta_v\frac{I_h}{N_h}S_v - (\xi_4 u_4 + \mu_v)S_v\right] + \\
&\quad z_6\left[(1-u_1)\beta_v\frac{I_h}{N_h}S_v - (\xi_4 u_4 + \mu_v)I_v\right], \qquad (6.9)
\end{aligned}$$

where z_i, $i = 1,2,...,6$ are the *adjoint variables* which determine the adjoint system. The adjoint system and state equations (6.4) define the optimal system. In the following theorem is presented the existence of the optimal control:

Theorem 6.2. *For the pair $(x_0^*, v^*) \in \mathcal{F}$ there exist a corresponding optimal solution $x^*(t)$ that minimize $J(x_0, v)$ in $[0, T]$. Moreover, there exits an adjoint function*

$$z(t) = (z_1(t), z_2(t), z_3(t), z_4(t), z_5(t), z_6(t))$$

such that

(6.10)
$$\begin{cases} \dot{z_1} = & \mu_h z_1 + \frac{u_1-1}{N_h^2}\Big[\beta_h I_v(E_h + I_h + R_h)(z_2 - z_1) + \beta_v I_h S_v(z_5 - z_6)\Big] \\ \dot{z_2} = & -c_1 - \alpha_h z_3 + (\alpha_h + \mu_h)z_2 + \frac{u_1-1}{N_h^2}\Big[\beta_h I_v S_h(z_1 - z_2) + \beta_v I_h S_v(z_5 - z_6)\Big] \\ \dot{z_3} = & -c_2 - \big[(1-u_3)\lambda_h - (\delta_h + \rho_h + \mu_h + \xi_2 u_2)\big]z_3 - (\delta_h + \xi_2 u_2)z_4 + \\ & \frac{u_1-1}{N_h^2}\Big[\beta_h I_v S_h(z_1 - z_2) + \beta_v S_v(S_h + E_h + R_h)(z_6 - z_5)\Big] \\ \dot{z_4} = & -\omega z_1 + (\omega_h + \mu_h)z_4 + \frac{u_1-1}{N_h^2}\Big[\beta_h I_v S_h(z_1 - z_2) + \beta_v I_h S_v(z_5 - z_6)\Big] \\ \dot{z_5} = & (\xi_4 u_4 + \mu_v)z_5 + \frac{u_1-1}{N_h}\beta_v I_h(z_6 - z_5) \\ \dot{z_6} = & -c_3 + (\xi_4 u_4 + \mu_v)z_6 + \frac{u_1-1}{N_h}\beta_h S_h(z_2 - z_1), \end{cases}$$

with transversality condition $z_i(t) = 0$ for $i = 1, 2, ..., 6$ which satisfies

(6.11)
$$\begin{cases} u_1^* = & \min\left\{\max\left\{0, \frac{\beta_h I_v S_h(z_2 - z_1) + \beta_v I_h S_v(z_6 - z_5)}{d_1 N_h}\right\}, 1\right\} \\ u_2^* = & \min\left\{\max\left\{0, \frac{\xi_2 I_h}{d_2}(z_3 - z_4)\right\}, 1\right\} \\ u_3^* = & \min\left\{\max\left\{0, \frac{\lambda_h I_h}{d_3} z_3\right\}, 1\right\} \\ u_4^* = & \min\left\{\max\left\{0, \frac{\xi_4(z_5 S_v + z_6 I_v)}{d_4}\right\}, 1\right\}. \end{cases}$$

Proof. The Principle of Pontryagin guarantees the existence of adjoint variables z_i, $i = 1, 2, ..., 6$ that satisfy

(6.12)
$$\begin{aligned} \dot{z_i} = \frac{dz_i}{dt} &= -\frac{\partial H}{\partial x_i} \\ z_i(T) &= 0, \quad i = 1, 2, ..., 6 \\ H(x(t), v^*(t), z(t), t) &= \max_{v \in U} H(x(t), v(t), z(t), t). \end{aligned}$$

The adjoint system (6.12) is rewritten as

$$\begin{aligned}
\dot{z_1} &= -\frac{\partial H}{\partial S_h}, \quad z_1(T) = 0 & \dot{z_4} &= -\frac{\partial H}{\partial R_h}, \quad z_4(T) = 0 \\
\dot{z_2} &= -\frac{\partial H}{\partial E_h}, \quad z_2(T) = 0 & \dot{z_5} &= -\frac{\partial H}{\partial S_v}, \quad z_5(T) = 0 \\
\dot{z_3} &= -\frac{\partial H}{\partial I_h}, \quad z_3(T) = 0 & \dot{z_6} &= -\frac{\partial H}{\partial I_v}, \quad z_6(T) = 0.
\end{aligned}$$

Replacing the derivatives of H with respect to S_h, E_h, I_h, R_h, S_v and I_v, in the above equations we obtain the system (6.10). The optimality conditions for the Hamiltonian are given by

$$\frac{\partial H}{\partial u_1^*} = \frac{\partial H}{\partial u_2^*} = \frac{\partial H}{\partial u_3^*} = \frac{\partial H}{\partial u_4^*} = 0,$$

or equivalently

$$\begin{aligned}
\frac{\partial H}{\partial u_1^*} &= \beta_h \frac{I_v}{N_h} S_h(z_1 - z_2) + \beta_h \frac{I_h}{N_h} S_v(z_5 - z_6) + d_1 u_1^* = 0 \\
\frac{\partial H}{\partial u_2^*} &= \xi_2 I_h(z_4 - z_3) + d_2 u_2^* = 0 \\
\frac{\partial H}{\partial u_3^*} &= d_3 u_3^* - z_3 \lambda_h I_h = 0 \\
\frac{\partial H}{\partial u_4^*} &= d_4 u_4^* - \xi_4(z_5 S_v + z_6 I_v) = 0.
\end{aligned}$$

From above equations we obtain

$$\begin{aligned}
u_1^* &= \frac{\beta_h \frac{I_v}{N_h} S_h(z_2 - z_1) + \beta_v \frac{I_h}{N_h} S_v(z_6 - z_5)}{d_1} \\
&= \frac{\beta_h I_v S_h(z_2 - z_1) + \beta_v I_h S_v(z_6 - z_5)}{d_1 N_h} \\
u_2^* &= \frac{\xi_2 I_h}{d_2}(z_3 - z_4) \\
u_3^* &= \frac{\lambda_h I_h}{d_3} z_3 \\
u_4^* &= \frac{\xi_4(z_5 S_v + z_6 I_v)}{d_4}.
\end{aligned}$$

In consequence, u_1^* satisfies

$$u_1^* = \begin{cases} 1 & if \quad \frac{\beta_h I_v S_h/N_h(z_2 - z_1) + \beta_v I_h S_v/N_h(z_6 - z_5)}{d_1} > 0 \\ \frac{\beta_h I_v S_h(z_2 - z_1) + \beta_v I_h S_v(z_6 - z_5)}{d_1 N_h} & if \quad 0 \leq \frac{\beta_h I_v S_h/N_h(z_2 - z_1) + \beta_v I_h S_v/N_h(z_6 - z_5)}{d_1} \leq 1 \\ 0 & if \quad \frac{\beta_h I_v S_h/N_h(z_2 - z_1) + \beta_v I_h S_v/N_h(z_6 - z_5)}{d_1} < 0, \end{cases}$$

o equivalently

$$u_1^* = \min\left\{\max\left\{0, \frac{\beta_h I_v S_h(z_2 - z_1) + \beta_v I_h S_v(z_6 - z_5)}{d_1 N_h}\right\}, 1\right\}. \tag{6.13}$$

Using similar reasoning for u_2^*, u_3^* and u_4^* we obtain the characterization (6.11) which completes the proof. □

7 Numerical results

In this section numerical simulations of the control problem are performed in order to observe the effects of control and prevention strategies. For simulations we use the forward-backward sweep method developed by Lenhart and Workman [54]. The implementation time of control strategies was approximately 4 months. The control strategies considered are the following:

1. Strategy I: Combination of antimalarial treatment and intermittent prophylactic treatment in pregnancy.

2. Strategy II: Combination of the four controls.

Table 7 presents the values of the relative weights associated with the control problem.

Table 7: The values of the parameters associated with the control problem.

	Parameter	Value	Reference
Relative weights	d_1	0.01	[46]
	d_2	0.01	[46]
	d_3	0.01	[46]
	d_4	0.01	[46]
Social Costs	c_1	0.00001	Assumed
	c_2	0.001	Assumed
	c_3	0.001	Assumed
Effectivenes treatment	ξ_2	0.6	[34]
	ξ_4	0.6	[34]

7.1 Numerical simulations for strategy I

In this strategy controls u_2 and u_3 represent antimalarial treatment and prophylactic treatment in pregnancy, respectively. Figures 3 and 4 show the behavior of the solutions in rural and urban areas, respectively, which decreased in presence of control, while the same populations grew in the absence of control. The maximum cost reached in the rural area was 24.1, and in urban area was 4.75.

7.2 Numerical simulations for strategy II

In this strategy, the controls u_1, u_2, u_3 and u_4 represent bed nets, antimalarial treatment, prophylactic treatment in pregnancy and indoor fumigation, respectively, they are used to minimize the performance index J. Figures 5 and 6 show the behavior of infected population in rural and urban areas, respectively. The maximum cost reached in rural areas was 17.25, and in urban areas was 8.1.

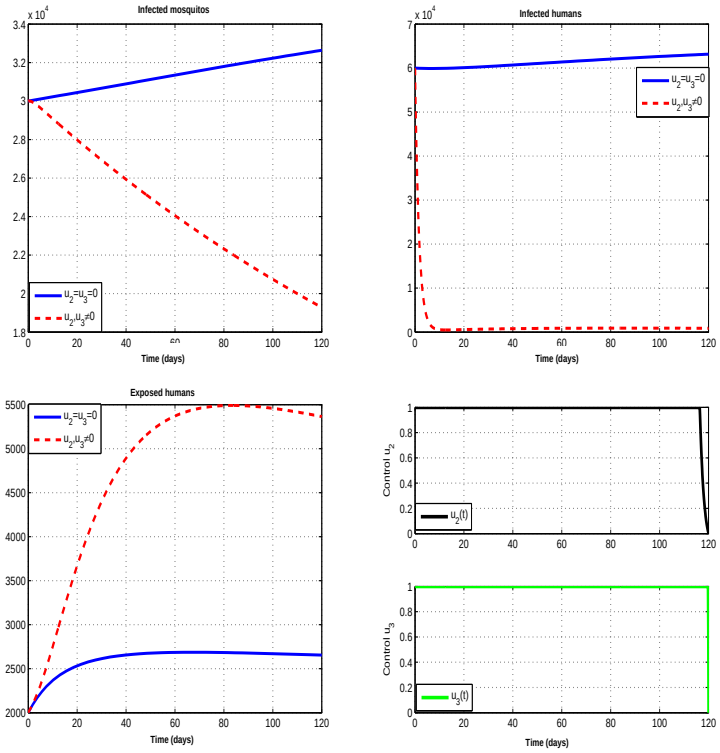

Figure 3: Strategy I in rural areas. The maximum cost reached is 24.1

8 Cost-effectivness analysis of control strategies

In this section, a cost-effectiveness analysis is carried out with the purpose to determine the best cost-effective strategy for the control of malaria disease. To this end, we use the incremental cost-effectiveness rate (ICER), which is defined as the ratio between cost variation and effect variation, that is

$$ICER = \frac{\Delta\, Cost}{\Delta\, Effect}. \tag{8.1}$$

In order to quantify the cost-effectiveness of the control strategies we follow a process similar to the one performed in [29]. We consider the index of infections avoided (IAR), which is defined as the quotient of the number of infections avoided (IE) and the number of successful recoveries (RE), that is,

$$IAR = \frac{IE}{RE}. \tag{8.2}$$

In the above equation, the numerator is the difference between the total number of infectious individuals obtained of simulation without controls and the total number of infectious individuals obtained of simulation with controls. Also the ICER values of each control strategy are calculated by mean of the equation (8.1). The maximum

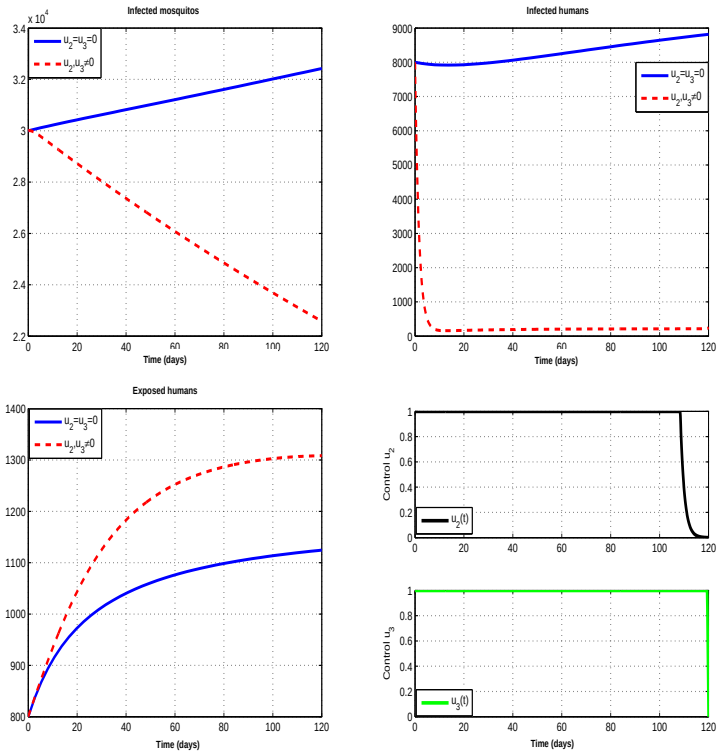

Figure 4: Strategy I in urban areas. The maximum cost reached is 4.75

IAR value for each of the control strategies in high and low transmission areas is presented in Tables 8 and 9.

Table 8: IAR in rural areas.

	Strategy I	Strategy II
IE	72000	72190
RE	22000	21000
IAR	3.3	3.4

Table 9: IAR in urban areas.

	Strategy I	Strategy II
IE	9900	9985
RE	2200	2500
IAR	4.5	4

From Tables 8 and 9 we can see that the most cost-effective strategy in terms of IAR and total cost of the intervention, is strategy II for rural area and strategy I for urban area. However, for more clarity, ICERs of each strategy in each zone are

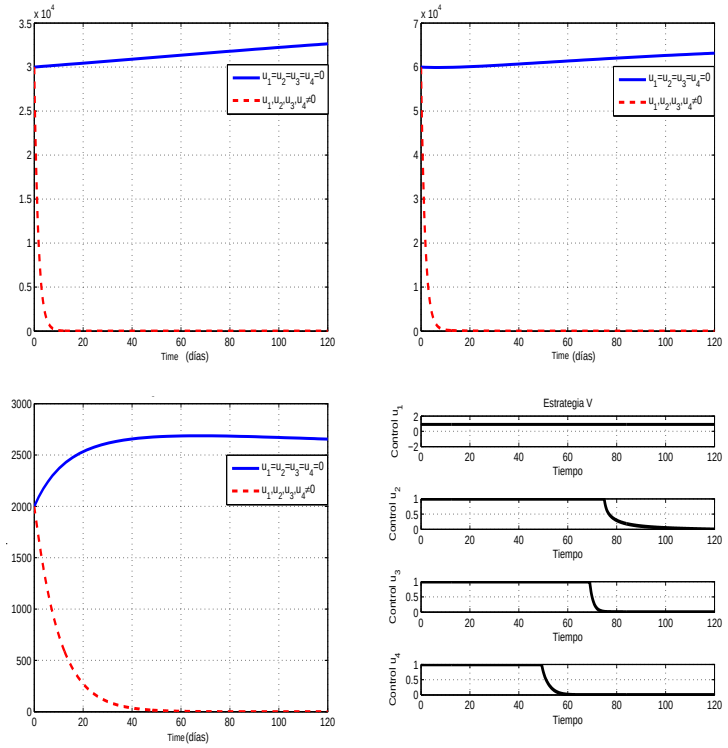

Figure 5: Strategy II in rural areas. The maximum cost reached is 17.25

examined. In Tables 10 and 11 we classify the control strategies implemented for the model (6.4) in increasing order of effectiveness in rural and urban areas, respectively.

Table 10: ICER in rural areas. Comparison betwen strategies I and II.

Strategy	Total evited infections	Total cost	ICER
Estrategia I	72000	24.1	0.00033
Estrategia II	72190	17.25	-0.036

ICER in Table 10 was computing as follow:

$$\begin{aligned} ICER(I) &= \frac{24.1}{72000} = 0.00033 \\ ICER(II) &= \frac{17.25 - 24.1}{72190 - 72000} = -0.036. \end{aligned}$$

We obtain ICERs of Table 11 as following:

$$\begin{aligned} ICER(I) &= \frac{4.75}{9900} = 0.00047 \\ ICER(II) &= \frac{8.1 - 4.75}{9985 - 9900} = 0.039 \end{aligned}$$

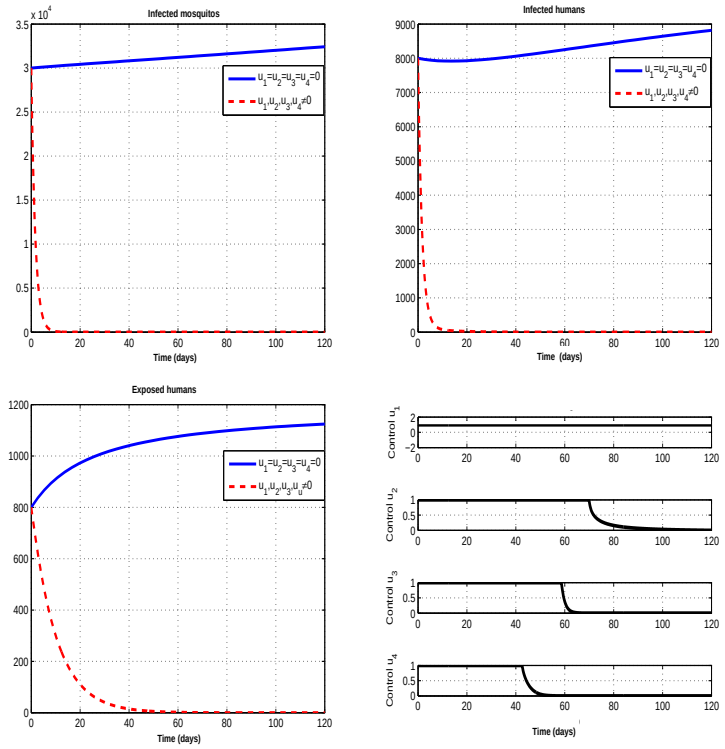

Figure 6: Strategy II in urban areas. The maximum cost reached is 8.1

Table 11: ICER in urban areas. Comparison betwen strategies I and II.

Strategy	Total evited infections	Total cost	ICER
Estrategia I	9900	4.75	-0.18
Estrategia II	9985	8.1	0.039

For rural area the comparison between strategies I and II showed the existence of a cost saving of strategy II with respect strategy I. Since the ICER of strategy II is lower than the ICER of strategy I, then strategy I is more expensive and less effective than strategy II. Therefore, strategy I is excluded from the set of strategies for rural areas. Using analogous reasoning, strategy II is excluded for urban areas. These results partially coincide with those shown in Tables 8 and 9, in which strategy II has the highest IAR value in rural areas and strategy I has the highest IAR in urban areas.

9 Conclusions

Since in Colombia the indicators of life quality in rural areas are lagging behind, the control of malaria in these places require great efforts. There are worrying levels in

health indicators, which show high fertility rates, high infant and maternal mortality, low life expectancy, high levels of malnutrition, low levels of schooling, higher rates of illiteracy and low levels of coverage of basic water sanitation services, drinking water, sewerage and energy. In addition, in these areas predominant ethnic groups with a culture that implies different customs and ways of relating to society, with predilection of ancestral medicine which is a challenge for the health care of these communities [36].

In this work, we focused on the transmission of the malaria disease in the municipality of Tumaco (Colombia) through mathematical modeling. Since the presence of malaria in Tumaco both in rural and urban areas, is linked to environmental factors (temperature, humidity, rainfall and vegetation), genetic factors (Duffy receptor in erythrocytes and hemoglobinopathies), human and vector behavior (use of measures of personal protection, inadequate consumption of medicines, bite habits), and socioeconomic factors (type of housing, population movements and economic activity), then such factors must be taken into account for the formulation and implementation of adequate control strategies and cost-effective [36]. For above reason, four control variables were included in the mathematical modeling: use of mosquito nets, antimalarial treatment, prophylactic treatment in pregnancy and indoor fumigation. The previous control variables were combined to generate two different control strategies: the first consists of the combination of prophylactic treatment in pregnancy and antimalarial treatment, and the second consists in the application of the four control variables simultaneously. We derived and analyzed the necessary conditions for the existence of optimal controls of disease both in rural and urban areas. The cost-effectiveness of control strategies was also analyzed in order to determine the most effective strategy to eliminate malaria with the lowest cost.

Although our model (2.3) is simple, it predicts possible outcomes of malaria transmission in Tumaco. The qualitative and bifurcation analysis of the model revealed different scenarios in which there is always the infection-free state, while depending on certain conditions there may be one or two endemic equilibria. An interesting fact is that for certain values of the parameters there are two kinds of bi-stability regions. In the first one the disease-free equilibrium and the endemic equilibrium coexist, which means that depending on the initial conditions of the populations, the disease will be cleared out or will be spread. In the second case the introduction of infected individuals (mosquitoes or humans) always will progress to endemic disease, and depending on the initial conditions, the population will approach to a state with low or with high number of infected individuals.

The above results were obtained in terms of the following parameters: i) the basic reproduction number, R_0; the average life of the babies infected through vertical transmission that survive the disease, τ_h; iii) number of new infections generated by a mosquito, γ_v; and iv) threshold parameters τ^* and R_0^* that do not have biological interpretation but are involved in the bifurcation of equilibrium solutions. The qualitative and bifurcation analysis suggest that:

1. for $\tau_h \leq \tau_h^*$ there is a backward bifurcation in which the infection-free equilibrium E_0 bifurcates into two endemic equilibria; E_1 asymptotically stable and E_2 unstable.

2. for $\tau_h > \tau_h^*$ we have the following option:

(a) if $\tau_h \leq -\gamma_v$ or $\tau_h \geq 0$, there is a forward bifurcation in which the infection free equilibrium E_0 bifurcates to the endemic equilibrium E_1.

(b) if $-\gamma_v < \tau_h < 0$, it seems to exist a kind of pitch fork bifurcation in which an unstable endemic equilibrium E_1 bifurcates to into two endemic equilibria; E_1 unstable and E_2 asymptotically stable.

We observe that both in the forward bifurcation and in tree bifurcation the spread of malaria can be controlled if $R_0 < 1$. However, in the backward bifurcation is necessary that $R_0 < R_0^* < 1$. From the sensitivity analysis we observe that in urban areas, R_0 is most sensitive to death or emigration mosquitoes rate μ_v and bite rate ϵ;. In rural area R_0 has most sensitivity to infection death rate ρ_h and vertical transmission rate λ_h. From the 2.1 we formulated the state equation of the optimal control problem and from the information provided by sensitivity indices to R_0 we proposed control strategies based on the following control variables: u_1 is the control variable associated with bed nets (BN), u_2 is the control variable associated with antimalarial treatment (AT), u_3 is the control variable associated with intermittent prophylactic treatment in pregnancy (IPTp), and u_4 is the control variable associated with indoor residual spraying (IRS).

The analysis of IAR and ICER indices suggest that the combination of the four control variables is the most cost-effective strategy to control malaria. The combination of treatment, prevention and prophylaxis is the least expensive strategy because it shortens the time of eradication of the disease, which implies a reduction in the economic resources that must be invested to control it.

On the other hand, the control problem was also solved numerically using data from urban area of Tumaco. Currently, the urban malaria phenomenon in Colombia is considered a serious problem in public health [26], very little is known about its epidemiological characteristics which is necessary to implement adequate control measures. The origin of cases of urban malaria is not fully established, which makes it impossible to know the magnitude of the problem and to identify the zones of the city where the transmission is autochthonous. [26].

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A Existence of endemic equilibria

Proof of Theorem 3.2. Let us start rewriting L as a function of τ_h; that is

$$L(\tau_h) = -\frac{2\bar{N}_h}{A}\tau_h - \frac{2\bar{N}_h\gamma_v}{A}. \tag{A.1}$$

We observe that L satisfies the following properties

1. $L(\tau_h^*) = 1$.
2. $L(\tau_h) > 0$ if and only if $\tau_h < -\dfrac{\gamma_v}{2}$.

Since L is a decreasing linear function that satisfies the property i), then $\tau_h > \tau_h^*$ if and only if $L < 1$. On the other hand, since $A > 0$ then $\tau_h^* < -\gamma_v/2$. In order to determine the existence of positive solutions of equation (3.9) we apply the Descartes rule for a polynomial of order two to the coefficients a, b and c given in Table 12 and Table 13.

Table 12: Signs of the coefficients a, b and c of the quadratic equation (3.9) in terms of τ_h, τ_h^* and R_0 under the condition $\tau_h \leq \tau_h^*$.

	$\tau_h \leq \tau_h^*$ $(L \geq 1)$		
	$0 < R_0 \leq 1$	$1 < R_0 < L$	$R_0 \geq L$
$\tau_h \in (-\infty, -\gamma_v]$	$a \geq 0$, $b < 0$, $c \geq 0$	$a \geq 0$, $b < 0$, $c < 0$	$a \geq 0$, $b \geq 0$, $c < 0$
$\tau_h \in (-\gamma_v, -\gamma_v/2]$	$a < 0$, $b < 0$, $c \geq 0$	$a < 0$, $b < 0$, $c < 0$	$a < 0$, $b \geq 0$, $c < 0$

Table 13: Signs of the coefficients a, b and c of the quadratic equation (3.9) in terms of τ_h, τ_h^* and R_0 under the condition $\tau_h > \tau_h^*$.

	$\tau_h > \tau_h^*$ $(1 > L)$		
	$0 < R_0 < L$	$L \leq R_0 \leq 1$	$R_0 > 1$
$\tau_h \in (-\infty, -\gamma_v]$	$a \geq 0$, $b < 0$, $c > 0$	$a \geq 0$, $b \geq 0$,$c \geq 0$	$a \geq 0$, $b \geq 0$, $c < 0$
$\tau_h \in (-\gamma_v, -\gamma_v/2)$	$a < 0$, $b < 0$, $c > 0$	$a < 0$, $b \geq 0$, $c \geq 0$	$a < 0$, $b \geq 0$, $c < 0$
$\tau_h \in [-\gamma_v/2, 0)$	$a < 0$, $b > 0$, $c > 0$	$a < 0$, $b > 0$, $c \geq 0$	$a < 0$, $b > 0$, $c < 0$
$\tau_h \in [0, \infty)$	$a \geq 0$, $b > 0$, $c > 0$	$a \geq 0$, $b > 0$, $c \geq 0$	$a \geq 0$, $b > 0$, $c < 0$

Assume $\tau_h \leq \min\{\tau_h^*, -\gamma_v\}$ $(1 \leq L)$. Let us only consider the case $\tau_h \leq -\gamma_v$ since the case $-\gamma_v < \tau_h < -\gamma_v/2$ contradicts the assumption. We can see in Table 12 that for $R_0 > 1$ the coefficients a, b, and c only have one change of sign, then, according to Descartes rule, (3.7) has only one positive root I_h^*. When $0 < R_0 < 1$, the coefficients have two changes of sign, therefore there may be two real roots or none depending if the discriminant $\Delta = b^2 - 4ac$ is bigger or less than zero. In order to obtain the conditions on the parameters for positive real roots in this case, we substitute the coefficients a, b, and c in Δ, obtaining

$$\Delta = A^2[R_0^2 - L]^2 - 4\tau_h(\gamma_v + \tau_h)\bar{N}_h^2(1 - R_0^2). \tag{A.2}$$

From definition of L given on (3.11), we can replace A^2 by $N_h^2(\gamma_v + 2\tau_h)^2 \frac{1}{L^2}$, and after some simplifications the expression for Δ can be written as the following four degree polynomial in the variable R_0.

$$\Delta(R_0) = A^2\left(R_0^4 + b_1 R_0^2 + c_1\right), \tag{A.3}$$

with

$$\begin{aligned} b_1 &= 2L\left[\frac{L}{U} - 1\right] \\ c_1 &= \frac{\gamma_v^2}{(\gamma_v + 2\tau_h)^2}L^2 > 0 \\ U &= \frac{\bar{N}_h^2(\gamma_v + 2\tau_h)^2}{2\tau_h(\gamma_v + \tau_h)} > 0. \end{aligned} \tag{A.4}$$

The graph of $\Delta(R_0^2)$ is a parabola that open upside with $\Delta(0) = A^2c_1 > 0$, and $\Delta(1) = A^2(1 + b_1 + c_1) = A^2(1 - L)^2 \geq 0$. On the other hand, the roots of equation (A.3) are obtained by solving the following quadratic equations

$$\begin{aligned} R_0^2 &= -\frac{b_1}{2} + \frac{1}{2}\sqrt{b_1^2 - 4c_1} \\ R_0^2 &= -\frac{b_1}{2} - \frac{1}{2}\sqrt{b_1^2 - 4c_1}. \end{aligned} \tag{A.5}$$

It is easy to check that the expression $b_1^2 - 4c_1 \geq 0$. From inequality

$$\frac{b_1^2}{4} > \frac{b_1^2}{4} - c_1$$

we can verify that right hand of first equation of (A.5) is less than zero, that is, first equation of (A.5) has not real roots while second equation of (A.5) has two real solutions with opposite sign, but due to $R_0 > 0$ we do not consider the negative root. Now, let us see that the positive root R_0^* satisfies $R_0^* < \sqrt{L}$. In fact, from definition of b_1 we have that

$$-\frac{b_1}{2} = -L\left[\frac{L}{U} - 1\right] = L\left[1 - \frac{L}{U}\right] < L$$

therefore

$$-\frac{b_1}{2} - \frac{1}{2}\sqrt{b_1^2 - 4c_1} < L - \frac{1}{2}\sqrt{b_1^2 - 4c_1} < L.$$

Then, the positive root R_0^* of second equation of (A.5) satisfies $0 < R_0^* < L$. Above implies that there exists at least one real root of the polynomial of order four (A.3) on the interval $(0, \sqrt{L})$. Furthermore, since for $R_0 > 1$, $\Delta(R_0) > 0$ then $R_0^* \in (0, 1)$, that is, there exists a unique $R_0^* \in (0, 1)$ such that $\Delta(R_0^*) = 0$. Thus, when $0 < R_0 < R_0^*$, $\Delta(R_0) < 0$ there is not real solutions; when $R_0 = R_0^*$, $\Delta(R_0^*) = 0$ then there is one positive solution; while for $R_0 > R_0^*$, $\Delta(R_0) > 0$ and there are two positive solutions. □

Proof of Theorem 3.3. For case i) from Table 13 we observe that $a \geq 0$ and when $R_0 \leq 1$ it is verify that $c \geq 0$, which implies that cuadratic equation (3.9) has or two real roots of the opposite sign or two negative roots or a couple of complex roots, anyways there are not endemic solutions. When $R_0 > 1$ there is only one change of sign and according to Descartes rule there is only one positive root. Now, in case ii) of Table 13 we can verify that when $R_0 \leq 1$ there is only one change of sign in coefficients, which implies that there exists one positive root. When $R_0 > 1$ there are two change of signs of coefficients, then, according to Descartes rule there are two or one positive root depending of the sign of the discriminant $b^2 - 4ac$. But in this case the discriminant is always positive, which implies there are two positive roots of cuadratic equation (3.9). □

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