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MATHEMATICAL MODELING AND ANALYSIS OF THE EFFECT OF OPTIMAL CONTROL OF SUSTAINABLE MALARIA INTERVENTIONS USING WOLBACHIA AND ECO-FRIENDLY STRATEGIES IN ENDEMIC REGIONS FOR POLICY DESIGN

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Abstract. In this study, a mathematical model, MSEIRS-LSEI, was formulated and analysed to assess the impact of environmentally responsible malaria control strategies in Burundi. Human and mosquito populations were divided into several epidemiological compartments to better understand transmission dynamics. Using the next-generation matrix method, the basic reproduction number ($\mathscr{R}_0$) was calculated, revealing a value of 2.046 in the absence of control measures, confirming the endemic nature of the disease in the region. Pontryagin's maximum principle is applied to characterize optimal control strategies, including medical treatments, larval control, and the introduction of mosquitoes infected with the Wolbachia bacterium. Stability analyses show that the epidemic can be locally eradicated if $\mathscr{R}_0$ is less than 1. Numerical simulations based on real-world data demonstrate that these interventions can significantly reduce, or even eliminate, infected human and vector populations. The study recommends the large-scale deployment of these measures and the future integration of vaccination to provide long-term protection for vulnerable populations.

Keywords: MSEIRS-LSEI epidemic model; Wolbachia bacteria; basic reproduction number; stability analysis; sensitivity; optimal control; Burundi.

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1. INTRODUCTION

Malaria, a potentially fatal parasitic disease transmitted by the bite of infected female mosquitoes of the genus Anopheles, remains one of the most critical public health challenges worldwide, particularly in tropical and subtropical regions [2, 17].

According to the World Health Organization (WHO), the sub-Saharan region bears by far the heaviest burden, accounting for more than 90 % of global cases [32, 4] and deaths, disproportionately affecting vulnerable populations such as pregnant women and children under five years of age [31]. The deadliest and most widespread pathogen on the African continent is Plasmodium falciparum [18, 24, 2, 35]. Against this general backdrop, the Republic of Burundi is among the hardest-hit nations in sub-Saharan Africa, with malaria being the leading cause of morbidity and mortality in the country, accounting for nearly 48% of all recorded deaths there [47, 10, 14, 31].

Although traditional vector control interventions such as the large-scale distribution of insecticide-treated bed nets (ITNs) and indoor residual spraying (IRS) campaigns have historically led to significant reductions in transmission, their sustainability and long-term effectiveness are now seriously compromised.

On the one hand, public health programs are facing the rapid emergence of genetic resistance in mosquitoes to chemical pyrethroids, as well as behavioral adaptations by the vectors, which now bite earlier in the evening or outdoors, thereby circumventing protection strategies that rely exclusively on indoor measures [28, 36].

On the other hand, the intensive and prolonged use of these broad-spectrum chemical insecticides has disastrous ecological consequences that raise profound environmental concerns [32, 1, 43, 48, 34].

The chemicals applied are not selective and affect a variety of essential non-target organisms, including bees and other pollinators, aquatic invertebrates, and vertebrates such as birds and amphibians [32, 1, 43].

Furthermore, the leaching and runoff of these residual chemicals into water bodies cause long-term contamination of aquatic resources, affecting fish populations and leading to indirect and hidden toxic effects on human and animal health [20, 43]. These major disruptions to local food chains and global ecological balances lead to a concerning erosion of biodiversity and degrade essential ecosystem processes such as nutrient cycling and natural biological control [11].

Faced with this dual reality of an epidemiological impasse and environmental degradation caused by conventional methods, the exploration of innovative, sustainable, and eco-responsible alternative strategies has become a major public health and ecological emergency for public policy design.

The fundamental novelty of this contribution lies in the formulation of an extended mathematical model that, for the very first time, simultaneously and synergistically combines environmentally friendly strategies (Eco-Friendly Strategies) such as the ecological and non-toxic management of larval breeding sites and the optimization of medical treatments with biological control using the Wolbachia bacterium.

This endosymbiotic bacterium, transmitted from mother to offspring, operates from within the vector by reducing the mosquito's lifespan and blocking the development of the Plasmodium parasite. At the same time, the cytoplasmic incompatibility (CI) mechanism induces genetic sterility, allowing it to supplant wild populations in a self-sustaining manner without releasing any harmful chemicals into the ecosystem.

The central objective of this article is to mathematically model and rigorously analyze the impact of this novel coupling between Wolbachia and Eco-Friendly Strategies to design optimal, sustainable control policies in endemic regions. To this end, an extensive, predictive, deterministic compartmental model, designated MSEIRS-LSEI, has been developed. Unlike traditional approaches that focus solely on adult mosquitoes, this model incorporates the essential early stages of the vector's life cycle (larvae and pupae) and segments the mosquito population by sex to accurately reflect the fact that only females participate in transmission [46, 38, 37], while also capturing the impact of human migration flows and temperature variations on the dynamics of spread.

By specifically contextualizing numerical simulations and the estimation of biological parameters using real epidemiological data from Burundi, this research applies Pontryagin's maximum principle to characterize optimal control trajectories capable of minimizing both the human disease burden and the associated socioeconomic costs.

Through a formal analysis of equilibrium stability and an analytical sensitivity study of the basic reproduction number $\mathscr{R}_0$, this work identifies the most effective levers for action. The ultimate goal of this computational study is to provide a robust, environmentally responsible, and scientifically grounded predictive tool to guide the allocation of health resources, inform

the design of sustainable public health policies, and support public decision-making aimed at the long-term elimination of malaria.

The paper is organized as follows: First, we present our mathematical model in Section 2. In Section 3, we give some basic properties such as equilibrium points and the basic reproduction number. The local and global stability of the equilibria are treated in Section 4. In Section 5, we do the basic reproduction number sensitivity analysis. In Section 6, using Burundian malaria data, we estimate different parameters of Model 1. In Section 7, we study the possibility of controlling the disease by using Pontryagin's Maximum Principle and give some numerical simulations. Finally, we conclude our study and give some recommendations in Section 8

2. MATHEMATICAL MODEL FORMULATION

In this study, we improve an existing malaria transmission dynamics model [6], using a Susceptible–Exposed–Infectious–Recovered (SEIR) framework for humans and a vector-based model for mosquitoes.

The human population is divided into six compartments: Immigrant Humans (M), Susceptible humans (S_h), Exposed (latent) humans (Eh), Infectious humans (I_h), and Recovered humans (R_h), with the total population denoted as $N_h(t) = M + S_h(t) + E_h(t) + I_h(t) + R_h(t)$. The mosquito population is split by sex, focusing on females in four compartments: Susceptible female mosquitoes (Sfv), Exposed female mosquitoes (Em), Infectious female mosquitoes (I_v), and Susceptible male mosquitoes (S_m), expressed as $N_m(t) = L(t) + S_m(t) + S_f(t) + E_v(t) + I_v(t)$. Transitions among these compartments are regulated by biological and epidemiological processes, including infection, recovery, and migration, as illustrated in the accompanying flow chart.

In this study, our model is as follows:

The transmission dynamics of malaria, incorporating a border/migrant screening compartment M and a multi-stage vector population, are governed by the following system of non-linear ordinary differential equations:

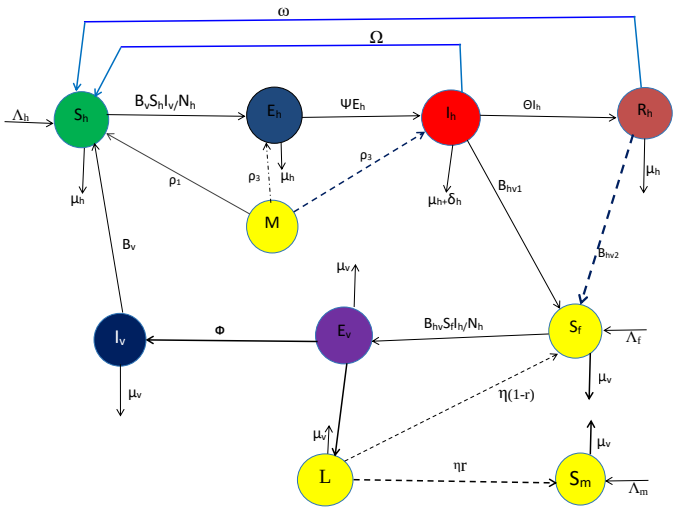


FIGURE 1. Structural diagram of the MSEIRS-LSEI compartmental model describing the dynamics of malaria transmission between human hosts and mosquito vectors, including screening of migrants and the vector's life cycle.

2.0.1. *Human Host Population Dynamics.*

$$
(1)\qquad \begin{cases} \dfrac{dS_h}{dt} &= \Lambda_h + \rho_1 M + \omega_h R_h + \Omega_h E_h - \mu_h S_h - \dfrac{\beta_{vh} I_v S_h}{N_h} \\ \dfrac{dM}{dt} &= \Lambda_M - (\rho_1 + \rho_2 + \rho_3) M \\ \dfrac{dE_h}{dt} &= \dfrac{\beta_{vh} I_v S_h}{N_h} + \rho_2 M - (\mu_h + \psi_h + \Omega_h) E_h \\ \dfrac{dI_h}{dt} &= \psi_h E_h - (\theta + \mu_h + \delta_h) I_h + \rho_3 M + \sigma R_h \\ \dfrac{dR_h}{dt} &= \theta I_h - (\omega_h + \mu_h + \sigma) R_h \end{cases}
$$

where $N_h(t) = S_h(t) + M(t) + E_h(t) + I_h(t) + R_h(t)$ denotes the total human population at time t.

2.0.2. *Mosquito Vector Population Dynamics.*

$$
\begin{cases}
\dfrac{dL}{dt} &= \alpha A - \gamma L - \mu_0 L\left(1 + \dfrac{L}{K + \kappa R_h}\right) - \mu_L L \\
\dfrac{dS_m}{dt} &= r\eta L - \mu_v S_m \\
\dfrac{dS_f}{dt} &= \eta(1-r)L + \Lambda_f - \mu_v S_f - \left(\dfrac{\beta_{hv1} I_h + \beta_{hv2} R_h}{N_h}\right) S_f \\
\dfrac{dE_v}{dt} &= \left(\dfrac{\beta_{hv1} I_h + \beta_{hv2} R_h}{N_h}\right) S_f - (\mu_v + \Phi) E_v \\
\dfrac{dI_v}{dt} &= \Phi E_v - \mu_v I_v
\end{cases} \tag{2}
$$

Initial conditions are:

$M = 0 \quad , S_{h0} > 0, \quad , I_{h0} \geq 0, E_{h0} \geq 0, \qquad R_{h0} \geq 0, \quad S_{m0} > 0, S_{f0} > 0,$

$with \quad L, S_{m0} + S_{f0} > 0 \quad E_{V0} \geq 0, \quad I_{v0} \geq 0,$ with $I_{h0} + I_{v0} > 0, L > 0.$

Where:

The total population for human is:$N_h = S_h + E_h + I_h + R_h$ and the total population for mosquitoes is $N_v = L + S_m + S_f + E_v + I_v$.

The differential equations for total humans and mosquitoes are respectively:

$\frac{dN_h}{dt} = \Lambda_h + (\rho_1 + \rho_2 + \rho_3)M + \Omega_h E_h + \gamma I_h - \mu_h N_h - \delta_h I_h$

$\frac{dN_v}{dt} = \Lambda_m + \Lambda_f + b(S_{fv}, S_{mv}) + b(E_v, S_{mv}) + b(I_v, S_{mv}) - \mu_v(T)N_v - \mu_v S_f$

TABLE 1. Baseline Parameter Values for the Mosquito Vector Population Model

Parameter	**Description**	**Baseline Value**	**Source / Reference**
α	Mosquito oviposition (egg-laying) rate	20.0	[12]
A	Maximum oviposition limit	$[40 - 300.0]$	[42]
γ_L	Larval maturation rate to adult	0.1	[44]
μ_0	Baseline natural mortality rate of larvae	0.01	[33]
K	Environmental carrying capacity for larvae	5000.0	[12]
κ	Density-dependent larval mortality coefficient	0.1	Calibrated
χ	Intraspecific larval competition factor	10.0	[40, 15]
μ_L	Global larval stage mortality rate	0.05	[44]
r	Sex ratio at emergence (proportion of females)	0.5	Biological standard
η_1	Cytoplasmic incompatibility (CI) failure rate	0.1	[49]
μ_v	Natural mortality rate of adult vectors	0.15	[21]
Λ_m	Release rate of Wolbachia-infected males	5.0	[3]
Λ_f	Release rate of Wolbachia-infected females	10.0	[3]
Φ	Vertical transmission efficiency of Wolbachia	0.1	[49]
β_{hv1}	Transmission probability (Infected human $\rightarrow$ vector)	0.35	[12]
β_{hv2}	Transmission probability (Recovered human $\rightarrow$ vector)	0.15	Estimated
η	Effectiveness of the public awareness campaign (u_7)	0.85	[13]

3. MODEL ANALYSIS

The qualitative analysis of the model (1, 2) gives insights on features to understand the characteristics of the spread of malaria.

Let $F = (F_1, F_2, F_3, F_4, F_5, F_6, F_7, F_8, F_9, F_{10})$ be the right-hand side of the system of differential equations (1, 2). It is evident that $F \in C^{\infty}(\mathbb{R}^{10}, \mathbb{R}^{10})$, then the system admits a unique maximal solution in $[0,T)$, where $T > 0$, for any associated Cauchy problem. Hereafter, the existence of a positively invariant set W is regarded. This means that any solution of the system with initial condition in W remains there for all $t \in [0, T)$.

3.1. Positivity and Invariant Region. As the model uses humans and mosquitoes, all state variables must be positive for all time t.

The positivity of the solution is proven using the following Proposition [7].

Proposition 1. *Consider the system of differential equations in* $\mathbb{R}^n$,

$$y = F(t, y),$$

$y(t) = (y_1(t), y_2(t), ..., y_n(t)), F(t,y) = (F_1(t,y), F_2(t,y), ..., F_n(t,y))$, *where* $F(t,y)$ *is defined for all* $t \geq 0, y \in \mathbb{R}$.

Assume that F *has the property that solutions of the initial value problems* $y(t_0) = y_0$ *are unique for* $y_0 \in [0, +\infty)^n, t_0 \geq 0$. *Furthermore, assume that, for all* $j = 1, ..., n, t \geq 0$, *we have* $F_j(t,y) \geq 0$ *whenever* $y \in [0, +\infty)^n, y_j = 0, t \geq 0$. *Then* $y(t) \in [0, +\infty)^n$ *for all* $t \geq t_0 \geq 0$ *for which it is defined, whenever* $y(t_0) \in [0, +\infty)^n$.

Theorem 1. *The trajectories of the system (1,2) starting in the positive octant* ${\mathbb{R}_+}^{10}$ *positive. Furthermore, the region* $W = \left\{ (M, S_h, E_h, I_h, R_h, L, S_m, S_f, E_v I_v) \in {\mathbb{R}_+}^{10} | \quad M > 0, S_h > 0, S_m > 0, S_m, S_f > 0, (E_h, I_h, R_h, E_v, I_v) \geq 0, N_h(t) \leq \frac{\Lambda_h}{\mu_h}, N_v(t) \leq \frac{(\Lambda_f + \Lambda_m)}{\mu_v} \right\}$ *is positively invariant.*

Proof: See the Appendix A.

From the proof of Theorem 1, we deduce the global existence of solutions [23].

3.2. Equilibrium points and Basic Reproductive Number $\mathscr{R}_0$. The DFE (E_0) is a point at which $E_h = E_v = R_h = I_h = I_v = 0$, it is given by:

$$E_0 = (M^0, S_h^0, E_h^0, I_h^0, R_h^0, L^0, S_m^0, S_f^0, E_V^0, I_v^0)$$

$$= \left(\frac{\Lambda_M}{\rho_1+\rho_2+\rho_3}, \frac{\Lambda_h}{\mu_h}, 0, 0, 0, 0, \frac{\Lambda_m}{\mu_v}, \frac{\Lambda_f}{\mu_v}, 0, 0 \right)$$

The $\mathscr{R}_0$ of the model (1,2) is determined utilizing the next generation method as expressed in [8].

For our model, we have:

Let $Y = \Big[(M, S_h, E_h, I_h, R_h, L, S_f, S_m, E_h, I_h)\Big]$, we can writte the system (1, 2) as follows: $\dot{Y} = F(Y) - V(Y)$

We get that the Jacobian matrices of $F(Y)$ and $V(Y)$ at E_0 are respectively:

$$\mathscr{F} = \begin{bmatrix} 0 & 0 & 0 & 0 & \beta_{vh} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_{hv1}\dfrac{\mu_h\Lambda_f}{\mu_v\Lambda_h} & \beta_{hv2}\dfrac{\mu_h\Lambda_f}{\mu_v\Lambda_h} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

and

$$\mathscr{V} = \begin{bmatrix} -(\mu_h+\psi_h) & 0 & 0 & 0 & 0 \\ \psi_h & -(\theta+\mu_h+\delta_h) & 0 & 0 & 0 \\ 0 & \theta & -(\omega+\mu_h) & 0 & 0 \\ 0 & 0 & 0 & B_1 & 0 \\ 0 & 0 & 0 & \theta & -\mu_v(T) \end{bmatrix}$$

where $B_1 = -(\mu_v(T) - \theta(T))$.

Since the next-generation matrix G is given by: $G = FVN-1$, $\mathscr{R}_0$ is the largest eigenvalue of G given by:

Therefore:

$$R_0 = \sqrt{a\,c_1} = \sqrt{\frac{\Lambda_h\beta_{vh}\,\theta}{\mu_v(\mu_v+\theta)} \cdot \frac{\mu_h\Lambda_f}{\mu_v}\,\psi_h(\mu_h+\psi_h)(\delta_h+\mu_h+\theta)\left(\beta_{hv1} + \frac{\beta_{hv2}\,\theta}{\mu_h+\omega}\right)}$$

Factorized form:

$$R_0 = \sqrt{\underbrace{\frac{\beta_{vh}\,\theta}{\mu_v(\mu_v+\theta)}}_{\text{Vector} \to \text{Human}} \cdot \underbrace{\frac{\mu_h\Lambda_f}{\mu_v\Lambda_h}\,\psi_h(\mu_h+\psi_h)(\delta_h+\mu_h+\theta)\left(\beta_{hv1} + \frac{\beta_{hv2}\,\theta}{\mu_h+\omega}\right)}_{\text{Human} \to \text{Vector}}}$$

The endemic equilibrium point (E_1): is a point where there is the persistence of the infection ($E_h \neq 0, I_h \neq 0 R_h \neq 0$, $E_h \neq 0, I_v \neq 0$), it is given by

$$E_1 = (M^*, {S_h}^*, {E_h}^*, {I_h}^*, {R_h}^*, L^* {S_m}^*, {S_f}^*, {I_v}^*),$$

where:

$$M^* = 0, \quad E_h^* = \frac{B}{\psi_h} I_h^*, \quad R_h^* = \frac{\theta}{C} I_h^*,$$
$$E_v^* = \frac{S_f^*}{N_h^*} \frac{\beta_{hv1} I_h^* + \beta_{hv2} R_h^*}{\mu_v + \theta}, \quad I_v^* = \frac{\theta}{\mu_v} E_v^*$$
$$S_m^* = \frac{\Lambda_m + \eta_2 L^*}{\mu_v}, \quad L^* = \frac{b(\cdot)}{\mu_v + \eta_1 + \eta_2}$$
$$S_f^* = \frac{\eta_1 L^* + \Lambda_f}{\mu_v + \frac{1}{N_h^*}[\beta_{hv1} I_h^* + \beta_{hv2} R_h^*]}, \quad S_h^* = \frac{\Lambda_h + (\omega_h \frac{\theta}{C} + \Omega_h \frac{B}{\psi_h} + \gamma) I_h^*}{\mu_h + \frac{\beta_{vh}}{N_h^*} I_v^*}$$

4. Stability Analysis of the Equilibrium Points

4.1. Local and global Stability of Disease-Free Equilibrium Point. Local stability: Studying this stability allows us to determine whether local spread of the disease is inevitable or not in a fully susceptible population.

We show below that the disease will be eliminated locally if $R_0 < 1$.

Thm 1. *: if $\mathscr{R}_0 < 1$, then, the Disease Free-Equilibrium E_0 is locally asymptotically stable and unstable if $R_0 > 1$.*

Proof: The evaluation of the Jacobian of the system (1, 2) at E_0 gives:

To reduce the dimension of the system and simplify the calculations, we exploit the properties of the total population of vectors N_v that satisfy the following relation:

$$\dot{N_v} = \Lambda_m + \Lambda_f - \mu_v N_h \tag{3}$$

Which has a unique equilibrium $N_v = \frac{\Lambda_m + \Lambda_f}{\mu_v}$ that is trivially globally asymptotically stable (GAS).

Therefore, using Vidyasagar Theorem [45], which implies that the stability properties of system (1, 2) are analogous to those of the following system:

$$\frac{dN_h}{dt} = \Lambda_h + (\rho_1 + \rho_2 + \rho_3) M + \Omega_h E_h + \gamma I_h - \mu_h N_h - \delta_h I_h$$
$$\frac{dE_h}{dt} = \frac{\beta_{vh} I_v S_h}{N_h} + \rho_2 M - (\mu_h + \psi_h) E_h$$

$$
\begin{aligned}
\frac{dI_h}{dt} &= \psi_h E_h - \theta I_h + \rho_3 M - \mu_h I_h - \delta_h I_h \\
\frac{dR_h}{dt} &= \theta I_h - (\omega + \mu_h) R_h \\
\frac{dE_v}{dt} &= -\mu_v(T) E_v + (\frac{\beta_{hv1}(T) I_h}{N_h} + \frac{\beta_{hv2}(T) R_h}{N_h}) S_f - \theta(T) E_v \\
\frac{dI_v}{dt} &= \theta(T) E_v - \mu_v(T) I_v
\end{aligned} \tag{4}
$$

From cordinates $(H, E_h, I_h, R_h, E_v, I_v)$, we have a DFE given by$E_0$=$(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, 0, 0)$.

The Jacobian matrix at the above DFE is as follows:

$$
J = \begin{bmatrix}
-\mu_h & \Omega_h & \gamma - \delta_h & 0 & 0 & 0 \\
0 & -(\mu_h + \psi_h) & 0 & 0 & 0 & \beta_{vh} \\
0 & \psi & -(\theta + \mu_h + \delta_h) & 0 & 0 & 0 \\
0 & 0 & \theta & -(\omega + \mu_h) & 0 & 0 \\
0 & 0 & \frac{\dot{N_v} \beta_{hv1}(T)}{N_h} & \frac{\dot{N_v} \beta_{hv2}(T)}{N_h} & -(\mu_v(T) + \theta(T)) & 0 \\
0 & 0 & 0 & 0 & \theta(T) & -\mu_v(T)
\end{bmatrix}.
$$

The Metzler matrix is given by:

$$
J_1 = \begin{bmatrix}
-(\mu_h + \psi_h) & 0 & 0 & 0 & \beta_{vh} \\
\psi & -(\theta + \mu_h + \delta_h) & 0 & 0 & 0 \\
0 & \theta & -(\omega + \mu_h) & 0 & 0 \\
0 & \frac{\dot{N_v} \beta_{hv1}(T)}{N_h} & \frac{\dot{N_v} \beta_{hv2}(T)}{N_h} & -(\mu_v(T) + \theta(T)) & 0 \\
0 & 0 & 0 & \theta(T) & -\mu_v(T)
\end{bmatrix}.
$$

with the usual demographic equilibrium values $N_v = \frac{\Lambda_m + \Lambda_f}{\mu_v}$ and $N_h = \frac{\Lambda_h}{\mu_h}$

Using the properties of the Metzler matrix [39, 16], the eigenvalues of J are: $-\mu_h$ plus the eigenvalues of J_1, so J is stable if and only if it is invertible with $J_1^{-1} < 0$.

Consider the Jacobian matrix,

$$J_1 = \begin{bmatrix} -(\mu_h+\psi_h) & 0 & 0 & 0 & \beta_{vh} \\ \psi_h & -(\theta+\mu_h+\delta_h) & 0 & 0 & 0 \\ 0 & \theta & -(\omega+\mu_h) & 0 & 0 \\ 0 & \dfrac{N_v^*\,\beta_{hv1}(T)}{N_h^*} & \dfrac{N_v^*\,\beta_{hv2}(T)}{N_h^*} & -(\mu_v+\theta) & 0 \\ 0 & 0 & 0 & \theta & -\mu_v \end{bmatrix},$$

$$N_v^* = \frac{\Lambda_f}{\mu_v}, \qquad N_h^* = \frac{\Lambda_h}{\mu_h},$$

so that

$$\frac{N_v^*}{N_h^*} = \frac{\mu_h(\Lambda_f+\Lambda_m)}{\mu_v\Lambda_h}.$$

Calculate the determinant by expanding along the first row. We introduce the short-hands.

$$S_1 := -(\mu_h+\psi_h), \quad S_2 := -(\theta+\mu_h+\delta_h), \quad S_3 := -(\omega+\mu_h),$$

$$S_4 := -(\mu_v+\theta), \quad S_5 := -\mu_v, \qquad\qquad r := \frac{N_v^*}{N_h^*},$$

one finds (after straightforward expansion and substitution)

$$\det(J_1) = S_1\,S_2\,S_3\,S_4\,S_5 \;+\; \beta_{vh}\,\psi_h\,\theta\,\frac{N_v^*}{N_h^*}\Big(\theta\,\beta_{hv2}(T)+(\omega+\mu_h)\,\beta_{hv1}(T)\Big).$$

Using the Identity

$$\theta\,\beta_{hv2}(T)+(\omega+\mu_h)\beta_{hv1}(T) = (\omega+\mu_h)\Big(\beta_{hv1}(T)+\frac{\beta_{hv2}(T)\,\theta}{\omega+\mu_h}\Big),$$

and substituting $S_1=-(\mu_h+\psi_h)$, $S_2=-(\theta+\mu_h+\delta_h)$, $S_3=-(\omega+\mu_h)$, $S_4=-(\mu_v+\theta)$, $S_5=-\mu_v$, we may factor the determinant as

$$\det(J_1) = -(\mu_h+\psi_h)(\theta+\mu_h+\delta_h)(\omega+\mu_h)(\mu_v+\theta)\mu_v$$
$$\Bigg[1-\underbrace{\frac{\beta_{vh}\,\theta}{\mu_v(\mu_v+\theta)}\cdot\frac{\mu_h\Lambda_f}{\mu_v\Lambda_h}\,\psi_h(\mu_h+\psi_h)(\delta_h+\mu_h+\theta)\Big(\beta_{hv1}(T)+\frac{\beta_{hv2}(T)\,\theta}{\mu_h+\omega}\Big)}_{R_0^2}\Bigg].$$

Recognizing the bracketed expression as $1-R_0^2$ with

$$R_0^2 \;=\; \frac{\beta_{vh}\,\theta}{\mu_v(\mu_v+\theta)}\cdot\frac{\mu_h\Lambda_f}{\mu_v\Lambda_h}\,\psi_h(\mu_h+\psi_h)(\delta_h+\mu_h+\theta)\Big(\beta_{hv1}(T)+\frac{\beta_{hv2}(T)\,\theta}{\mu_h+\omega}\Big), \tag{5}$$

We arrive at the compact product form;

$$\boxed{\det(J_1) = -(\mu_h+\psi_h)(\theta+\mu_h+\delta_h)(\omega+\mu_h)(\mu_v+\theta)\mu_v\big(1-R_0^2\big).}$$

Take: P=

$$\boxed{\det(J_1) = -(\mu_h + \psi_h)(\theta + \mu_h + \delta_h)(\omega + \mu_h)(\mu_v + \theta)\mu_v.}$$

$$\boxed{\det(J_1) = P\big(1 - R_0^2\big).}$$

If $R_0^2 < 1$, then J_1 is invertible and $J_1^{-1} < 0$, which implies that the DFE is locally asymptotically stable.

If $R_0^2 > 1$, then $J_1^{-1} > 0$ and therefore J_1 is not a Hurwitz matrix, and consequently DFE is unstable.(Details in the Appendix).

Global stability of the DFE E_0

Considering infected individuals $I(t) = (E_h, I_h(t), R_h(t), E_v(t), I_v(t))^T$, we seek a condition under which:

$$I(t) \xrightarrow[t\to\infty]{} 0 \qquad \forall \left(M^0, S_h^0, E_h^0, I_h^0, R_h^0, L^0, S_m^0, S_f^0, E_v^0, I_v^0\right) \in \Omega.$$

Using epidemiological bounds, we have the following:

$$S_h \le S_h^0, \quad S_f \le S_f^0, \quad S_m \le S_m^0, \quad R_h \le R_h^0 \tag{6}$$

Also, it is noted that $M(t) \to 0$ with $\frac{dM}{dt} = -\rho_1 M - \rho_2 M - \rho_3 M$ and thus the M-terms are transient sources that vanish as $t \to \infty$

Lyapnov Function. Let us consider the linear positive definite function given by:

$$V\left(E_h, I_h, R_h, E_v, I_v\right) = E_h + aI_h + dR_h + bE_v + cI_v$$

where a,b,c,d are positive constants.

The differentiation along trajectories is given by:

$$\frac{dV}{dt} = \frac{dE_h}{dt} + a\frac{I_h}{dt} + d\frac{dR_h}{dt} + b\frac{dE_v}{dt} + c\frac{dI_v}{dt}$$

$$\frac{dV}{dt} = \frac{\beta_{vh} I_v S_h}{N_h} + \rho_2 M - (\mu_h + \psi_h)E_h$$

$$+a[\psi_h E_h - \theta I_h + \rho_3 M - \mu_h I_h - \delta_h I_h - \gamma I_h] + d[I_h - (\omega + \mu_h)R_h]$$

$$+b[-\mu_v(T)E_v + (\tfrac{\beta_{hv1}(T)I_h}{N_h} + \tfrac{\beta_{hv2}(T)R_h}{N_h})S_f - \theta(T)E_v] + c[\theta(T)E_v - \mu_v(T)I_v]$$

From the DFE, we have that:

$$S_h^0 = \frac{\Lambda_h}{\mu_h}, \quad S_m^0 = \frac{\Lambda_m}{\mu_v}, \quad S_f^0 = \frac{\Lambda_f}{\mu_v}$$

Also, let:

$$B_{vh} = \beta_{vh}, B_{hv1} = \frac{\beta_{hv1}\mu_h\Lambda_f}{\mu_v\Lambda_h}, B_{hv2} = \frac{\beta_{hv2}\mu_h\Lambda_f}{\mu_v\Lambda_h}$$

(6) $$A = \mu_h + \psi_h, \quad B = \theta I_h + \mu_h + \delta_h + \gamma, \quad C = \omega + \mu_h, \quad D = \theta + \mu_v, \quad E = \mu_v$$

$$R_0^2 \;=\; \frac{B_{hv2}\,\theta, \psi_h (B_{hv1} C + B_{hv2}\theta)}{ABCD}$$

Applying (6) and keeping M terms as a grouped source $(\rho_2 + a\rho_3)M$, we get the following:

$$\frac{dV}{dt} \leq \Big[-(\mu_h + \psi_h) + a\psi_h \Big] E_h + \Big[-a(\theta + \mu_h + \delta_h + \gamma) + d\theta + bB_{hv1} \Big] I_h$$
$$+ \Big[-d(\omega + \mu_h) + + bB_{hv2} \Big] R_h + \Big] I_h + \Big[-d(\omega + \mu_v) + C\omega \Big] E_v + \Big[B_{vh} - C\mu_v \Big] I_v$$
$$+ \Big[\rho_2 + a\rho_3 \Big] M$$
$$\frac{dV}{dt} \leq \alpha E_h + \alpha I_h + \alpha R_h + \alpha E_v + \alpha I_v$$

The Positive $a, \quad b, \quad c, \quad d$ are given by:

(6) $$a = \frac{\mu_h + \psi_h}{\psi_h}, \quad b = \frac{B_{vh}}{\mu_v}, \quad c = \frac{B_{vh}\theta}{\mu_v(\mu_v + \theta)}, \quad d = \frac{bB_{hv2}}{\omega + \mu_h}$$

Taking (4.1) in (4.1), we have:

$$\alpha E_h = 0, \quad \alpha R_h = 0, \quad \alpha E_v = 0, \quad \alpha I_v = 0$$

Therefore,

$$\frac{dV}{dt} \leq \alpha I_h + \Big[\rho_2 + a\rho_3 \Big] M$$

The replacement of (4.1) in (4.1) gives the following results:

$$\alpha_{I_h} = -\frac{\mu_h + \psi_h}{\psi_h} \Big(\mu_h + \delta_h + \gamma + \theta \Big) + \frac{bB_{vh}\theta}{\mu_h + \omega} + bB_{hv1}$$
$$\alpha_{I_h} = -\frac{AB}{\psi_h} \Big[1 - B_{vh}\psi_h \theta \frac{(B_{hv1} C + B_{hv2}\theta)}{ABCD} \Big]$$
$$\alpha_{I_h} = -\frac{AB}{\psi_h} \Big[1 - R_0^2 \Big]$$

Hence,

If $R_0 \leq 1$, then $\alpha_{I_h} \leq 0$

$R_0 = 1$ then $\alpha_{I_h} = 0$

$R_0 \geq 1$ then $\alpha_{I_h} \geq 0$

As $(\rho_2 + a\rho_3)M$ is the only source remaining and as $M(t) = M(0)e^{-(\rho_2 + a\rho_3)t} t \to 0$ when $t \to \infty$.

The source term $(\rho_2 + a\rho_3)M(t)$ decays exponentially to zero.

Therefore, for all sufficiently large t, the source is arbitrarily small. Equivalently, we can write: $\frac{dV}{dt} \leq -\frac{AB}{\psi_h}\left[1 - R_0^2\right] + \varepsilon(t)$ where $\varepsilon(t) \to 0$ as $t \to \infty$.

When $R_0 < 1$, the coefficient of I_h is negative. Therefore, $\frac{dV}{dt} \leq 0$ all large enough t, and $\frac{dV}{dt} < 0$ except where $I_h(0) = 0$. The largest invariant set iside $\{X : \frac{dV}{dt} = 0\}$ is the DFE.

By LaSalle's invariance principle [19], the infection vector $X(t) \to 0$ as $t \to \infty$, The combination of this with the decay of the non-infected compartment, we can conclude, is that the full system converges to the DFE.

So, if $R_0 < 0$, the derivative eventually becomes nonnegative and only zero in the DFE; therefore, the DFE is globally asymptotically stable.

5. Local and Global Stability of the Endemic Equilibrium Point

Thm 2. *If $R_0 > 1$, the EE of the dynamical system (1, 2) is locally asymptotically stable.*

Proof. :The evaluation of the Jacobian of the system(4)at the endemic equilibrium point (E_1)gives: □

At the endemic equilibrium (EE), the infection Jacobian is

$$J_I = \begin{bmatrix} -d_1 & 0 & 0 & 0 & c_1 \\ \psi_h & -d_2 & 0 & 0 & 0 \\ 0 & \theta & -d_3 & 0 & 0 \\ 0 & c_2 & c_3 & -d_4 & 0 \\ 0 & 0 & 0 & \theta & -d_5 \end{bmatrix},$$

where we use the shorthand

$$d_1 = \mu_h + \psi_h, \quad d_2 = \mu_h + \delta_h + \gamma + \theta, \quad d_3 = \mu_h + \omega_h,$$

$$d_4 = \mu_v + \theta, \quad d_5 = \mu_v, \quad c_1 = \frac{\beta_{vh} S_h^*}{N_h^*},$$

$$c_2 = \frac{\beta_{hv1} S_f^*}{N_h^*}, \quad c_3 = \frac{\beta_{hv2} S_f^*}{N_h^*}.$$

The characteristics equation $Q(\lambda) = \det(J_I - \lambda I)$ can be written in the polynomial form as follow:

$$Q(\lambda) = (d_1+\lambda)(d_2+\lambda)(d_3+\lambda)(d_4+\lambda)(d_5+\lambda) \\ - c_1\psi_h\left[(d_2+\lambda)(d_3+\lambda)(d_4+\lambda) - \theta c_2(d_3+\lambda) - \theta c_3(d_2+\lambda)\right].$$

This gives:

$$\det(M_2) = \psi_h\left[(d_2+\lambda)(d_3+\lambda)(d_4+\lambda) - \theta c_2(d_3+\lambda) - \theta c_3(d_2+\lambda)\right].$$

Thus, the characteristic polynomial of the infection block is

$$Q(\lambda) = (d_1+\lambda)(d_2+\lambda)(d_3+\lambda)(d_4+\lambda)(d_5+\lambda) \\ - c_1\psi_h\left[(d_2+\lambda)(d_3+\lambda)(d_4+\lambda) - \theta c_2(d_3+\lambda) - \theta c_3(d_2+\lambda)\right].$$

Using Hurwitz Matrix and Determinants,by applying the standard construction rule.

$$H_{ij} = a_{2j-i}, \qquad a_0 = 1,\ a_k = 0 \text{ for } k<0 \text{ or } k>5.$$

This yields the Hurwitz matrix.

$$H = \begin{pmatrix} a_1 & a_3 & a_5 & 0 & 0 \\ 1 & a_2 & a_4 & 0 & 0 \\ 0 & a_1 & a_3 & a_5 & 0 \\ 0 & 1 & a_2 & a_4 & 0 \\ 0 & 0 & a_1 & a_3 & a_5 \end{pmatrix}.$$

The Hurwitz determinants are the leading principal minors of this matrix.

Δ_1

The top-left 1×1 block: $\Delta_1 = \det([a_1]) = a_1$.

Δ_2

The top left 2×2 block: $\Delta_2 = \begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix} = a_1a_2 - a_3$.

Δ_3

The top-left 3×3 block: $\Delta_3 = \begin{vmatrix} a_1 & a_3 & a_5 \\ 1 & a_2 & a_4 \\ 0 & a_1 & a_3 \end{vmatrix}$.

The expansion gives the following.

$$\Delta_3 = a_1(a_2a_3 - a_1a_4) - a_3(a_3) + a_5(a_1) = -a_1^2a_4 + a_1a_2a_3 + a_1a_5 - a_3^2.$$

Δ_4

The top-left 4×4 block: $H_4 = \begin{pmatrix} a_1 & a_3 & a_5 & 0 \\ 1 & a_2 & a_4 & 0 \\ 0 & a_1 & a_3 & a_5 \\ 0 & 1 & a_2 & a_4 \end{pmatrix}$.

Using Schur's complement [27], one obtains the compact closed form:

$$\Delta_4 = -a_1^2 a_4^2 - a_1 a_2^2 a_5 + a_1 a_2 a_3 a_4 + 2a_1 a_4 a_5 + a_2 a_3 a_5 - a_3^2 a_4 - a_5^2.$$

The full 5×5 determinant satisfies

$$\Delta_5 = a_5 \Delta_4.$$

For all roots of

$$Q(\lambda) = \lambda^5 + a_1\lambda^4 + a_2\lambda^3 + a_3\lambda^2 + a_4\lambda + a_5$$

To have a negative real part, the necessary and sufficient conditions are

$$\Delta_1 > 0, \quad \Delta_2 > 0, \quad \Delta_3 > 0, \quad \Delta_4 > 0, \quad a_5 > 0.$$

(Since $\Delta_5 = a_5\Delta_4$, positivity of a_5 and Δ_4 guarantees $\Delta_5 > 0$.)

At $\lambda = 0$, the infection-block determinant is:

$$Q(0) \;=\; d_1 d_2 d_3 d_4 d_5 \;-\; c_1\psi_h\Big(d_2 d_3 d_4 - \theta c_2 d_3 - \theta c_3 d_2\Big),$$

where

$$d_1 = \mu_h + \psi_h, \quad d_2 = \mu_h + \delta_h + \gamma + \theta, \quad d_3 = \mu_h + \omega_h,$$

$$d_4 = \mu_v + \theta, \quad d_5 = \mu_v, \quad \psi = \psi_h,$$

and

$$c_1 = \frac{\beta_{vh} S_h^*}{N_h^*}, \qquad c_2 = \frac{\beta_{hv1} S_f^*}{N_h^*}, \qquad c_3 = \frac{\beta_{hv2} S_f^*}{N_h^*}.$$

$$\frac{Q(0)}{d_1 d_2 d_3 d_4 d_5} = 1 \;-\; \frac{c_1\psi\big(d_2 d_3 d_4 - \theta c_2 d_3 - \theta c_3 d_2\big)}{d_1 d_2 d_3 d_4 d_5}.$$

This motivates the definition

$$\boxed{R_0^2 \;:=\; \frac{c_1\psi\big(d_2 d_3 d_4 - \theta c_2 d_3 - \theta c_3 d_2\big)}{d_1 d_2 d_3 d_4 d_5}}.$$

Hence

$$Q(0) = d_1 d_2 d_3 d_4 d_5\,(1 - R_0^2).$$

Step 2: Substituting DFE values. At the DFE,

$$S_h^0 = \frac{\Lambda_h}{\mu_h}, \qquad S_f^0 = \frac{\Lambda_f}{\mu_v}, \qquad N_h^0 = S_h^0 = \frac{\Lambda_h}{\mu_h}.$$

Therefore

$$c_1 = \beta_{vh}, \qquad c_2 = \beta_{hv1}\frac{\mu_h\Lambda_f}{\mu_v\Lambda_h}, \qquad c_3 = \beta_{hv2}\frac{\mu_h\Lambda_f}{\mu_v\Lambda_h}.$$

Introduce the shorthand

$$K := \frac{\mu_h\Lambda_f}{\mu_v\Lambda_h},$$

so that $c_2 = \beta_{hv1}K$ and $c_3 = \beta_{hv2}K$.

Step 3: R_0^2 in parameter form. Substituting, we obtain

$$R_0^2 \;=\; \frac{\beta_{vh}\,\psi}{d_1d_2d_3d_4d_5}\Big(d_2d_3d_4 - \theta K(\beta_{hv1}d_3 + \beta_{hv2}d_2)\Big).$$

Writing the d_i in terms of the original model parameters:

$$d_1 = \mu_h + \psi_h, \quad d_2 = \mu_h + \delta_h + \gamma + \theta, \quad d_3 = \mu_h + \omega_h, \quad d_4 = \mu_v + \theta, \quad d_5 = \mu_v,$$

We recover the explicit formula for R_0^2 given in the main text.

Thus,

$$Q(0) > 0 \iff R_0^2 < 1 \quad \text{(DFE locally stable)},$$

$$Q(0) = 0 \iff R_0^2 = 1 \quad \text{(bifurcation point)},$$

$$Q(0) < 0 \iff R_0^2 > 1 \quad \text{(DFE unstable, endemic equilibrium emerges)}.$$

Global Stability of the EE.

Thm 3. *Assume all parameters are positive and $R_0 > 1$, so that a unique endemic equilibrium*

$$X^* = (M^*, S_h^*, E_h^*, I_h^*, R_h^*, S_f^*, E_v^*, I_v^*, S_m^*, L^*)$$

with strictly positive components exists. Assume further that the larval birth function $b(\cdot,\cdot)$ is smooth, nonnegative, and yields a unique positive larval equilibrium L^*.

Then the Lyapunov function:

$$V(X) \;=\; \sum_{x\in S} x^*\left(\frac{x}{x^*} - 1 - \ln\frac{x}{x^*}\right),$$

satisfies

$$\dot{V} \;\le\; -W(X) + Ce^{-\lambda t},$$

for some constant $C > 0$ and $\lambda > 0$, with a continuous function $W \geq 0$ such that

$$W(X) = 0 \quad \Longleftrightarrow \quad X = X^*.$$

Hence the endemic equilibrium X^* is globally asymptotically stable in the feasible region (the positive cone).

The proof follows the standard relative-entropy (Volterra) template used in many host–vector models [26].

All parameters are positive.

There exists a unique endemic equilibrium (EE)

$$X^* = \left(S_h^*, M^*, E_h^*, I_h^*, R_h^*, L^*, S_m^*, S_f^*, E_v^*, I_v^*\right),$$

with

$$E_h^*, I_h^*, R_h^*, S_h^*, S_f^*, E_v^*, I_v^*, L^*, S_m^* > 0.$$

We already know $M^* = 0$ from $\dot{M} = -(\rho_1 + \rho_2 + \rho_3)M$.

Existence requires $R_0 > 1$.

The larval birth function $b(\cdot,\cdot)$ is such that the total mosquito subsystem is well-posed and L, S_m, S_f remain bounded for $t \geq 0$ and have positive equilibria.

Define the convex function

$$\phi(u) = u - 1 - \ln u, \quad u > 0.$$

Note that $\phi(u) \geq 0$ with equality iff $u = 1$.

Lyapunov function. Consider the classical relative-entropy (Kullback–Leibler) type Lyapunov function [29]

$$V(X) = \sum_{x \in S} x^* \, \phi\left(\frac{x}{x^*}\right),$$

where the sum is over the state variables with positive equilibrium value

$$S = \{S_h, E_h, I_h, R_h, S_f, E_v, I_v, S_m, L\}.$$

(We exclude M since $M^* = 0$.) Written out:

$$V = S_h^*\left(\tfrac{S_h}{S_h^*} - 1 - \ln \tfrac{S_h}{S_h^*}\right) + E_h^*\left(\tfrac{E_h}{E_h^*} - 1 - \ln \tfrac{E_h}{E_h^*}\right) + I_h^*\left(\tfrac{I_h}{I_h^*} - 1 - \ln \tfrac{I_h}{I_h^*}\right)$$

$$+R_h^*\left(\frac{R_h}{R_h^*}-1-\ln\frac{R_h}{R_h^*}\right)+S_f^*\left(\frac{S_f}{S_f^*}-1-\ln\frac{S_f}{S_f^*}\right)+E_v^*\left(\frac{E_v}{E_v^*}-1-\ln\frac{E_v}{E_v^*}\right)$$
$$+I_v^*\left(\frac{I_v}{I_v^*}-1-\ln\frac{I_v}{I_v^*}\right)+S_m^*\left(\frac{S_m}{S_m^*}-1-\ln\frac{S_m}{S_m^*}\right)+L^*\left(\frac{L}{L^*}-1-\ln\frac{L}{L^*}\right).$$

Properties: $V \geq 0$ for all positive states and $V = 0$ iff $x = x^*$ for every $x \in S$.

By Time derivative for a single variable x with weight x^* we have:

$$\frac{d}{dt}\left[x^*\,\phi\left(\frac{x}{x^*}\right)\right]=\left(1-\frac{x^*}{x}\right)\dot{x}.$$

Therefore,

$$\dot{V}=\sum_{x\in S}\left(1-\frac{x^*}{x}\right)\dot{x}. \tag{6}$$

By introducing the forces of infection:

$$\lambda_h := \frac{\beta_{vh}I_v}{N_h}, \qquad \lambda_v := \frac{\beta_{hv1}I_h+\beta_{hv2}R_h}{N_h}.$$

Substitute the host and vector dynamics into (5). After grouping by flows one obtains

$$\begin{aligned}
\dot{V} = {} & \left(1-\tfrac{S_h^*}{S_h}\right)\left[\Lambda_h+\rho_1 M+\omega_h R_h+\Omega_h E_h+\gamma I_h-\mu_h S_h-\lambda_h S_h\right] \\
& +\left(1-\tfrac{E_h^*}{E_h}\right)\left[\lambda_h S_h+\rho_2 M-(\mu_h+\psi_h)E_h\right] \\
& +\left(1-\tfrac{I_h^*}{I_h}\right)\left[\psi_h E_h+\rho_3 M-(\mu_h+\delta_h+\gamma+\theta)I_h\right] \\
& +\left(1-\tfrac{R_h^*}{R_h}\right)\left[\theta I_h-(\omega_h+\mu_h)R_h\right] \\
& +\left(1-\tfrac{S_f^*}{S_f}\right)\left[\eta_1 L+\Lambda_f-\mu_v S_f-\lambda_v S_f\right] \\
& +\left(1-\tfrac{E_v^*}{E_v}\right)\left[\lambda_v S_f-(\mu_v+\theta)E_v\right] \\
& +\left(1-\tfrac{I_v^*}{I_v}\right)\left[\theta E_v-\mu_v I_v\right] \\
& +\left(1-\tfrac{L^*}{L}\right)G(L,S_m,S_f,E_v,I_v) \\
& +\left(1-\tfrac{S_m^*}{S_m}\right)\left[\Lambda_m+\eta_2 L-\mu_v S_m\right].
\end{aligned}$$

At the endemic equilibrium (E_1^*), each RHS vanishes.

$$0=\Lambda_h+\omega_h R_h^*+\Omega_h E_h^*+\gamma I_h^*-\mu_h S_h^*-\lambda_h^* S_h^*,$$

$$0=\lambda_h^* S_h^*-(\mu_h+\psi_h)E_h^*, \qquad 0=\psi_h E_h^*-(\mu_h+\delta_h+\gamma+\theta)I_h^*,$$

and so on for the other equations.

Subtracting these equilibrium-weighted balances from (5) produces telescoping cancellations.

The host infection chain gives:

$$S_h \ \to^{\lambda_h} \ E_h \ \to^{\psi_h} \ I_h \ \to^{\theta} \ R_h$$

contributes terms that combine into

$$\lambda_h S_h^* \left(\frac{S_h}{S_h^*} - \frac{E_h}{E_h^*} - \ln \frac{S_h/E_h}{S_h^*/E_h^*} \right),$$

which is non-positive by the convexity of ϕ.

Analogous identities are retained for the vector chain $S_f \to^{\lambda_v} E_v \to^{\theta} I_v$.

After grouping all flows, every term in $\dot{V}$ is nonpositive.

Hence,

$$\dot{V} \leq 0, \quad \text{with equality iff } E_1 = E_1^*.$$

According to the LaSalle invariance principle [30], the endemic equilibrium E_1^* is **globally asymptotically stable** under the stated assumptions.

6. Analytical Sensitivity Analysis of $\mathscr{R}_0$.

To formally assess the impact of each parameter on the epidemic threshold, the elasticity-normalised sensitivity index is used. This index measures the relative change in a variable with respect to a parameter.

If $\mathscr{R}_0$ is differentiable with respect to a given parameter p, the normalised elasticity sensitivity index, denoted by:

$\Upsilon_p^{\mathscr{R}_0}$, is calculated analytically using the following formula:

$$\Upsilon_p^{\mathscr{R}_0} = \frac{\partial \mathscr{R}_0}{\partial p} \times \frac{p}{\mathscr{R}_0}$$

The interpretation of the normalised sensitivity index depends on both its sign and its absolute numerical value. Qualitatively, the sign of the index indicates the direction of the change: a positive index ($\Upsilon_p^{\mathscr{R}_0} > 0$) means that an increase in the parameter p leads to a rise in $\mathscr{R}_0$, reflecting a pro-epidemic effect that exacerbates the transmission of the disease, whilst a negative index ($\Upsilon_p^{\mathscr{R}_0} < 0$) shows that an increase in p reduces the value of $\mathscr{R}_0$, which corresponds to a protective effect that limits the spread. Quantitatively, the numerical value measures the intensity of this impact as a direct proportion; for example, an elasticity value of $+0.5$ indicates

that a precise increase of 1% in the parameter under study leads to a 0.5% rise in $\mathscr{R}_0$, thereby enabling the model parameters to be rigorously classified according to their ability to influence the control or spread of the epidemic.

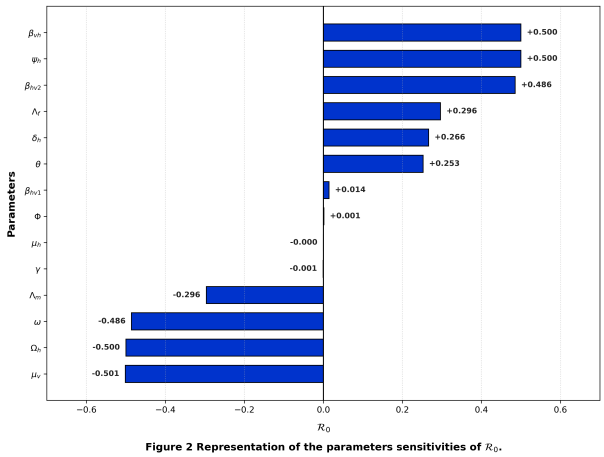


FIGURE 2. A Tornado diagram showing the normalised sensitivity index of the model parameters relative to the basic reproduction number $\mathscr{R}_0$. It classifies the parameters according to their ability to amplify (positive values) or reduce (negative values) the spread of the epidemic

6.1. Biological Interpretation of the Established Indicators. Ranked by absolute magnitude in the tornado diagram, the factors affecting epidemic dynamics reveal both accelerators and inhibitors of transmission. Critical positive drivers include the probability of transmission from mosquitoes to humans ($\beta_{vh} = +0.5000$), which shows a 1% increase in transmission probability boosts $\mathscr{R}_0$ by 0.5%, emphasizing the importance of physical barriers like mosquito nets. The progression rate of exposed humans ($\psi_h = +0.4999$) and the transmission from subclinical individuals ($\beta_{hv2} = +0.4856$) also enhance the spread of infection, underscoring the role of asymptomatic carriers in sustaining transmission. Additionally, the recruitment of female mosquitoes ($\Lambda_f = +0.2963$), human mortality ($\delta_h = +0.2664$), and recovery rate ($\theta = +0.2528$) contribute positively to epidemic dynamics. Conversely, parameters with a negative impact ($\Upsilon < -0.25$) present potent intervention levers. The natural mortality of mosquitoes influenced by temperature ($\mu_v = -0.5014$) emerges as the most sensitive factor, indicating that a mere 1% rise in mortality can reduce $\mathscr{R}_0$ by 0.5014%. Moreover, human immune dynamics, particularly the temporary immunity rate ($\Omega_h = -0.4999$) and immunity loss

rate ($\omega = -0.4856$), are crucial in preventing reinfection. The recruitment of male mosquitoes ($\Lambda_m = -0.2963$) negatively impacts reproduction, reflecting sexual competition and limiting the production of viable female larvae.

Lastly, a subset of parameters appears to have a negligible short-term impact on epidemic thresholds. For example, transmission by clinically infected humans ($\beta_{hv1} = +0.0144$) and factors like mosquito transmission ($\Phi = +0.0014$), human births ($\gamma = -0.0007$), and natural mortality in humans ($\mu_h = -0.0001$) are unlikely to significantly influence $\mathscr{R}_0$

7. Parameter Estimation and Optimal Control Formulation

As is well known, malaria is a global problem, with each country having its own malaria data; for our study, we focused on Burundi, but the analysis can be generalized to other countries.

7.1. Initial conditions. In our simulation, we considered the base year 2021, where the total human population (N_h) was 13000000 [25], and the number of infected humans was 498481 [10].

Assuming that N_m= 67000000 and $I_v = 1800$, we used $S_h(0) = 13000000 - 498481 = 12501519, R_h(0) = 0, S_v(0) = 1698200, S_f, S_m$.

Using parameters of Table 1, without the strategic deployment of the optimal health intervention$u_1 = u_2 = u_3 = u_4 = u_5 = u_6 = u_7 = u_8 = 0$); under these baseline conditions, $\mathscr{R}_0$ = 2.43.

As $\mathscr{R}_0 > 1$, the number of new cases will keep increasing in the population over time t.

Therefore, there is a need for effective strategies to control the spread of malaria in Burundi and minimize or eradicate malaria infection.

8. Optimal Control Problem Formulation.

When discussing malaria prevention, factors that favor malaria transmission are considered, such as human population density, mosquito population, environmental factors, and transmission rate between humans and mosquitoes. If any one of the factors promoting malaria is controlled, malaria infection cases will be significantly reduced.

Moreover, as we probably cannot control the human population, control methods are applied to reduce the vector population, minimize transmission of infection between mosquitoes and humans, and treat infected humans.

We considered preventive measures and treatment of infectious individuals, where $u_2(t)$ represents all preventive measures and $u_1(t)$ represents the effort on treatment of infectious individuals with effective use of drugs, including medical tests and hospitalization.

With preventive measures and effort on treatment of infectious individuals, the system (1, 2) becomes:

$$\begin{aligned}
\frac{dSh}{dt} &= \Lambda_h + \rho_1 M_v + (\omega_h Rh_v + u_3 Rh_v) + \Omega_h Eh_v - \mu_h Sh_v - \lambda_{h,\text{bites}} - u_8 Sh_v \\
\frac{dM}{dt} &= \Lambda_M - (\rho_1 + \rho_2 + \rho_3 + u_8) M_v \\
\frac{dEh}{dt} &= \lambda_{h,\text{bites}} + \rho_2 M_v - (\mu_h + \psi_h) Eh_v - \Omega_h Eh_v \\
\frac{dIh}{dt} &= \psi_h Eh_v - (\theta + u_2) Ih_v + \rho_3 M_v - \mu_h Ih_v - \delta_h Ih_v + \sigma Rh_v \\
\frac{dRh}{dt} &= (\theta + u_2) Ih_v - (\omega_h + \mu_h + u_3) Rh_v - \sigma Rh_v
\end{aligned}$$

$$\begin{aligned}
\frac{dL}{dt} &= (1-u_6)(1-\eta u_7)\alpha A - \gamma_L L_v - \text{density_dep} - (\mu_L + u_5) L_v \\
\frac{dSm}{dt} &= r\eta_1 L_v - \mu_v Sm_v - \Lambda_m (1-\eta u_7)(1-u_6) \\
\frac{dSf}{dt} &= \eta_1 (1-r) L_v + \Lambda_f (1-u_4)(1-\eta u_7) - (\mu_v + u_4) S_f - \lambda_{v,\text{bites}} \\
\frac{dEv}{dt} &= \lambda_{v,\text{bites}} - (\mu_v + \Phi + u_4 + u_1) E_v \\
\frac{dIv}{dt} &= \Phi Ev_v - (\mu_v + \Phi + u_4 + u_1) I_v
\end{aligned}$$

The control set $\mathscr{U}$ is a Lebesgue measurable defined as:

$$\mathscr{U} = \Big\{ (u_1(t), u_2(t), (u_3(t)(u_4(t)(u_w(t)) | 0 \le u_1 \le u_{1max}, 0 \le u_2 \le u_{2max}, 0 \le u_3 \le u_{3max}, 0 \le u_4 \le u_{4max}, 0 \le u_w \le u_{wmax} \Big\}$$ from $[0,T] \subset [0,1]$ and it serves as the boundary conditions of the problem.

We consider the objective functional for this problem, which is given by:

Variables: x(t) = $(M, S_h, E_h, I_h, R_h, L, S_m, S_f, E_v, I_v, \ldots)$

$$\min_{(u_1,\ldots,u_8)\in U} J(u_1,\ldots,u_8) = \int_0^{t_f} \Big[A_1 E_h(t) + A_2 I_h(t) + A_3 I_v(t) + \frac{1}{2}(K_1 u_1^2 + K_2 u_2^2 + K_3 u_3^2 + K_4 u_4^2$$

$$+K_5u_5^2+K_6u_6^2+K_7u_7^2+K_8u_8^2)\Big]dt$$

We incorporate the controls as follows:

The controls $u_{1max},u_{1max},u_{1max},u_{2max},u_{3max},u_{4max},u_{5max},u_{6max},u_{7max},u_{8max}$ and u_{7max} depend on the relative amount of resources for each control action to be executed. The cost weights $K_1,K_2,K_3,K_4,K_5,K_6,K_7,K_8$ and K_7 depend on the importance of the control measures in reducing disease transmission and on the cost per unit of each control measure implemented. The terms $K_1u_1^2,K_2u_1^2,K_3u_1^2,K_4u_1^2,K_5u_1^2,K_6u_1^2$ and $K_7u_2^2$ represent the costs associated with prevention and treatment, respectively.

Where:

• $E_h(t)$, $I_h(t)$,$R_h(t)$ of Γ represents infectious human at the end of treatment and preventive measures application, the integral term represents the harmful effect of treatment and preventive measures.

• K_1 is the cost weight for vaccinating susceptible individuals.

• K_2 is the cost weights of screening of immigrants entering the country.

• $K_3$is the cost weights of control of susceptible mosquitoes and larvae using Environmental management.

• K_4 is the cost weight of reducing the spread of the infection(Reduce contact).

• K_5 is the cost weights of Introduction of Wolbachia (rearing and release of infected mosquitoes)

• K_6 is the cost weights of Treatment

• K_7 is the cost weights of Second-line treatment and chemoprevention.

• K_8 is the cost weights of Second-line treatment and chemoprevention.

8.1. Characterization of the Optimal control.

Thm 4. [9]*: If* $\Gamma(u_1^*,u_2^*,u_3^*,u_4^*,u_5^*,u_6^*,,u_7^*)$ *is an optimal control for the states* S_h^*,M^*, $E_h^*I_h^*,R_h^*,L^*,S_m^*,S_f^*,E_v^*$, *and* I_v^* *of the system* ***(1, 2)*** *that minimizes* $\Gamma(u_1,u_2)$ *over* $\mathscr{U}$*, then there exists adjoint variables* $\lambda_M^*,\lambda_{S_h}^*,\lambda_{E_h}^*,\lambda_{I_h}^*,\lambda_{R_h}^*$, $\lambda_L^*,\lambda_{S_f}^*,\lambda_{S_m}^*,\lambda_{E_v}^*$ *and* $\lambda_{I_v}^*$ *satisfying the following equations:*

For S_h,

$$\frac{\partial H}{\partial S_h} = \lambda_h \left(-\omega_h - \frac{\beta_{vh} I_v}{N_h} \right) + \lambda_{E_h} \frac{\beta_{vh} I_v}{N_h}$$

$$\lambda'_{S_h} = \mu_h \lambda_{S_h} + \frac{\beta_{vea} I_v}{N_h} (\lambda_{S_h} - \lambda_{E_h})$$

Using the same method, we get:

$\lambda'_M = -\rho_1 \lambda_{S_h} + (\rho_1 + \rho_2 + \rho_3)\lambda_M - \rho_2 \lambda_{E_h} - \rho_3 \lambda_{I_h}$;
$\lambda'_{E_h} = -A_1 - \lambda_{S_h} \Omega_h + (\omega_h + \psi_h)\lambda_{E_h} - \psi_h \lambda_{I_h}$;
$\lambda'_{I_h} = -A_2 - \lambda_{S_h} \psi + (\theta + \mu_h + \delta_h + \psi)\lambda_{R_h} - \frac{\beta_{hv1} S_f}{N_h} \lambda_{S_f} + \frac{\beta_{hv1} S_f}{N_h} \lambda_{E_v}$;
$\lambda'_{R_h} = -A_3 - \lambda_{S_h} \omega_e + (\omega_e + \mu_h)\lambda_{R_h} - \frac{\beta_{hv2} S_f}{N_h} \lambda_{S_f} + \frac{\beta_{hv2} S_f}{N_h} \lambda_{E_v}$;
$\lambda'_L = (\mu_v + \eta_1 + \eta_2)\lambda_L - \eta_2 \lambda_{S_m} - \eta_1 \lambda_{S_f}$;
$\lambda'_{S_m} = \mu_v \lambda_{S_m}$;
$\lambda'_{S_f} = \mu_v \lambda_{S_f} + \left(\frac{\beta_{hv1} I_h}{N_h} + \frac{\beta_{hv2} R_h}{N_h} \right) (\lambda_{S_f} - \lambda_{E_v})$;
$\lambda'_{E_v} = (\mu_v + \theta)\lambda_{E_v} - \theta \lambda_{I_v}$;
$\lambda'_{I_v} = \mu_v \lambda_{I_v} + \frac{\beta_{vea} S_h}{N_h} (\lambda_{S_h} - \lambda_{E_h})$ Where the above Adjoint Equations are given by:

$$\frac{d\lambda_i}{dt} = -\frac{\partial \mathscr{H}(x)}{\partial x_i}$$

Conditions of transversality are:

$$\lambda_i(T) = 0 \quad \text{for all } i$$

Therefore:

$$\lambda_M(T) = \lambda_{S_h}(T) = \lambda_{E_h}(T) = \lambda_{I_h}(T) = \lambda_{R_h}(T) = \lambda_L(T) = \lambda_{S_m}(T) = \lambda_{s_f}(T) = \lambda_{E_v}(T) = \lambda_{I_v}(T) = 0$$

The Hamiltonian $\mathscr{H}(x)$ is given by:

$$\mathscr{H}(x) = L(x,u) + \sum_{i=1}^{10} \lambda_i b_i(x,u)[41]$$

Therefore, considering (1, 2)

$$\begin{aligned}
\mathscr{H} = {} & A_1 E_h + A_2 I_h + A_3 I_v + \frac{1}{2} \left(K_1 u_1^2 + K_2 u_2^2 + K_3 u_3^2 + K_4 u_4^2 + K_5 u_5^2 + K_6 u_6^2 + K_7 u_7^2 + K_8 u_8^2 \right) \\
& + \lambda_{S_h} \left[\Lambda_h + \rho_1 M + (\omega_h R_h + u_3) + \Omega_h E_h - \mu_h S_h - \frac{\beta_{vh} I_v S_h (1-u_1)(1-\eta u_7)}{N_h} - u_8 S_h \right] \\
& + \lambda_M \left[\Lambda_M - (\rho_1 + \rho_2 + \rho_3 + u_8) M \right] \\
& + \lambda_{E_h} \left[\frac{\beta_{vh} I_v S_h (1-u_1)(1-\eta u_7)}{N_h} + \rho_2 M - (\mu_h + \psi_h + \Omega_h) E_h \right]
\end{aligned}$$

$$+\lambda_{I_h}\left[\psi_h E_h-(\theta+u_2)I_h+\rho_3 M-(\mu_h+\delta_h)I_h+\sigma R_h\right]$$

$$+\lambda_{R_h}\left[(\theta+u_2)I_h-(\omega_h+\mu_h+u_3+\sigma)R_h\right]$$

$$+\lambda_L\left[(1-u_6)(1-\eta u_7)\alpha S_m(S_f+e)N_f\left(1-\frac{L}{K}\right)-\gamma L-\mu_0 L\left(1+\frac{L}{K+\kappa\chi}\right)-(\mu_L+u_5)L\right]$$

$$+\lambda_{S_m}\left[r\eta_1 L-\mu_v S_m-\Lambda_m(1-\eta u_7)(1-u_6)\right]$$

$$+\lambda_{S_f}\left[\eta_1(1-r)L+\Lambda_f(1-u_4)(1-\eta u_7)-(\mu_v+u_4)S_f-\frac{(1-u_1)(1-\eta u_7)(\beta_{hv1}I_h+\beta_{hv2}R_h)}{N_h}S_f\right]$$

$$+\lambda_{E_v}\left[\frac{(1-u_1)(1-\eta u_7)(\beta_{hv1}I_h+\beta_{hv2}R_h)}{N_h}S_f-(\mu_v+\Phi+u_4+u_1)E_v\right]$$

$$+\lambda_{I_v}\left[\Phi E_v-(\mu_v+\Phi+u_4+u_1)I_v\right]$$

Optimal controls are given by: $\frac{\partial H}{\partial u_i}=0$ The application of Pontryagin's Maximum Principal [22] with optimal control existence as described by Fleming et al. [5] gives:

$$u_1=\frac{(\lambda_{E_h}-\lambda_{S_h})\beta_{vh}I_v S_h(1-\eta u_7)+(\lambda_{E_v}-\lambda_{S_f})\Lambda_{hv}S_f+(\lambda_{E_v}E_v+\lambda_{I_v}I_v)N_h}{K_1 N_h}$$

$$u_2=\frac{(\lambda_{I_h}-\lambda_{R_h})I_h}{K_2}$$

$$u_3=\frac{(\lambda_{R_h}-\lambda_{S_h})R_h-\lambda_{S_h}}{K_3}$$

$$u_4=\frac{\lambda_{S_f}\Lambda_f(1-\eta u_7)+\lambda_{S_f}S_f+\lambda_{E_v}E_v+\lambda_{I_v}I_v}{K_4}$$

$$u_5=\frac{\lambda_L L}{K_5}$$

$$u_6=\frac{\lambda_L(1-\eta u_7)\alpha S_m(S_f+\varepsilon)N_f\left(1-\frac{L}{K}\right)-\lambda_{S_m}\Lambda_m(1-\eta u_7)}{K_6}$$

$$u_7=\frac{\eta\cdot\Psi_{Wolb}}{K_7}$$

$$u_8=\frac{\lambda_{S_h}S_h+\lambda_M M}{K_8}$$

Solving the above equations and using the bounds which are $0\leq u_1\leq u_{1\max}$ and $0\leq u_2\leq u_{2\max}$, we obtain the optimal control $\Gamma(u_1^*,u_2^*,u_3^*,u_4^*,u_5^*,u_6^*)$ that minimizes

$\Gamma(u_1,u_2,u_3,u_4,u_5,u_6)$:

$$u_1^* = \max\left(0,\min\left(u_{max},\frac{(\lambda_{E_h}-\lambda_{S_h})\beta_{vh}I_vS_h(1-\eta u_7)+(\lambda_{E_v}-\lambda_{S_f})\Lambda_{hv}S_f+(\lambda_{E_v}E_v+\lambda_{I_v}I_v)N_h}{K_1N_h}\right)\right)$$

$$u_2^* = \max\left(0,\min\left(u_{max},\frac{(\lambda_{I_h}-\lambda_{R_h})I_h}{K_2}\right)\right)$$

$$u_3^* = \max\left(0,\min\left(u_{max},\frac{(\lambda_{R_h}-\lambda_{S_h})R_h-\lambda_{S_h}}{K_3}\right)\right)$$

$$u_4^* = \max\left(0,\min\left(u_{max},\frac{\lambda_{S_f}\Lambda_f(1-\eta u_7)+\lambda_{S_f}S_f+\lambda_{E_v}E_v+\lambda_{I_v}I_v}{K_4}\right)\right)$$

$$u_5^* = \max\left(0,\min\left(u_{max},\frac{\lambda_L L}{K_5}\right)\right)$$

$$u_6^* = \max\left(0,\min\left(u_{max},\frac{\lambda_L(1-\eta u_7)\alpha S_m(S_f+\varepsilon)N_f\left(1-\frac{L}{K}\right)-\lambda_{S_m}\Lambda_m(1-\eta u_7)}{K_6}\right)\right)$$

$$u_7^* = \max\left(0,\min\left(u_{max},\frac{\eta\cdot\Psi_{Wolb}}{K_7}\right)\right)$$

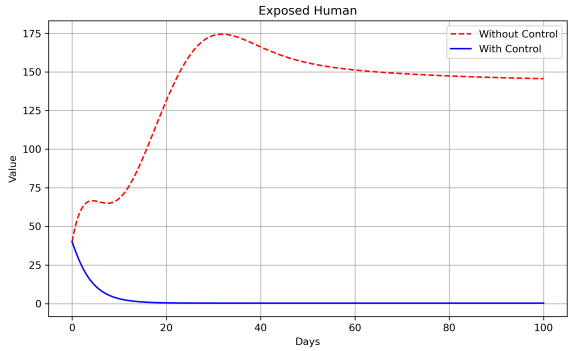
$$u_8^* = \max\left(0,\min\left(u_{max},\frac{\lambda_{S_h}S_h+\lambda_M M}{K_8}\right)\right)$$

9. SIMULATIONS OF THE MODEL AND NUMERICAL RESULTS.

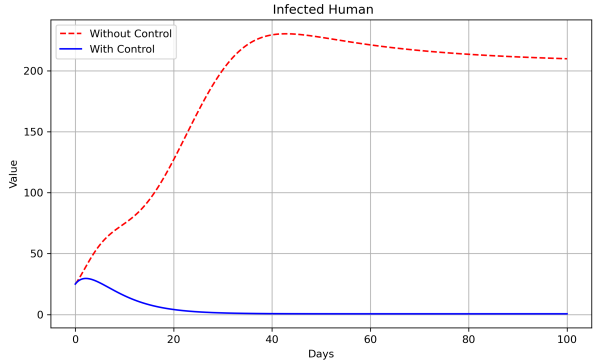
The simulations consist of investigating the results of the use of different combinations of control strategies to analyze the evolution of the disease, and this was done using MATLAB with time given in days.

We estimated the parameters of the MATLAB model (1, 2) using data from the Department of National Health Information System of Burundi. Unavailable data were estimated by referring to published literature on malaria in other countries where malaria is endemic compared to Burundi.

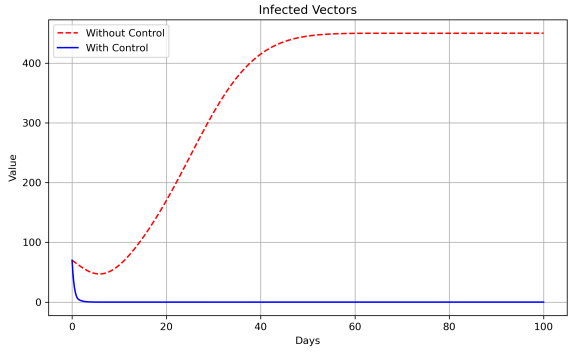
The numerical simulation gives the following figures:



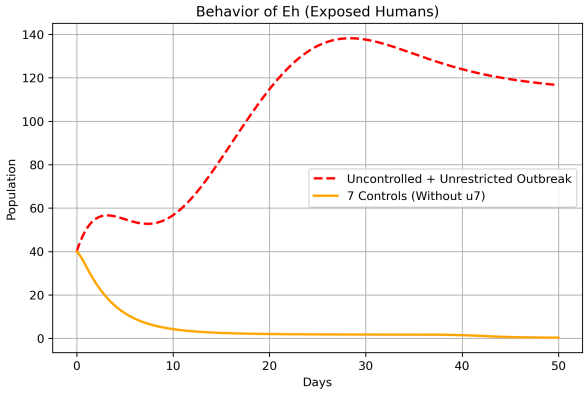
(A) Time series of the exposed human population (E_h)



(B) Time series of the infected human population (I_h)

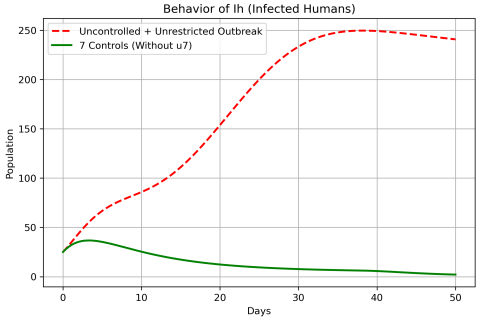


(C) Time series of the infected vector (mosquito) population (I_v)

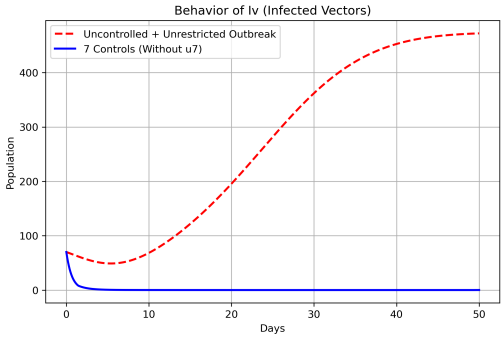


(D) Short-term behaviour (50 days) of exposed humans (E_h) under the effect of 7 combined control measures without public awareness campaigns (u_7)

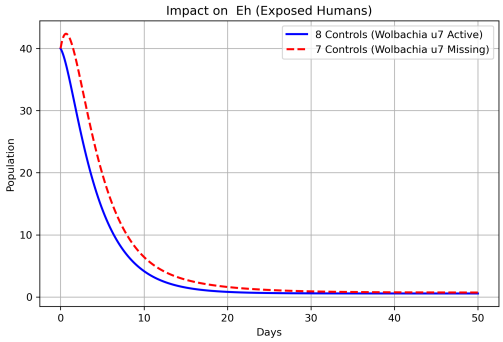
FIGURE 3. Numerical simulations of the model's dynamics over 100 days, comparing the behaviour of key compartments with and without the application of global control strategies



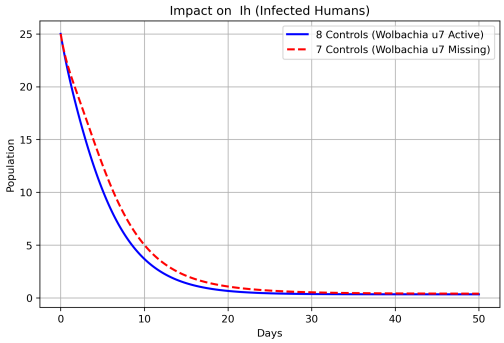
(A) Changes in the infected human population (I_h) during an uncontrolled epidemic, compared with the application of 7 control measures without u_7



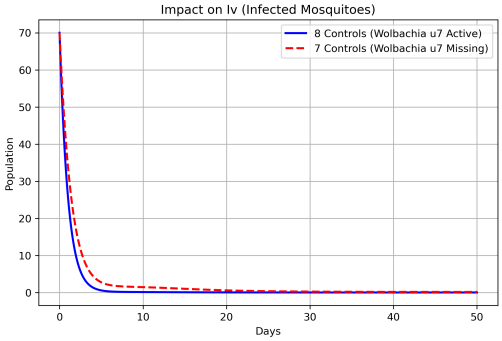
(B) Changes in the population of infected vectors (I_v) under the same partial control scenarios



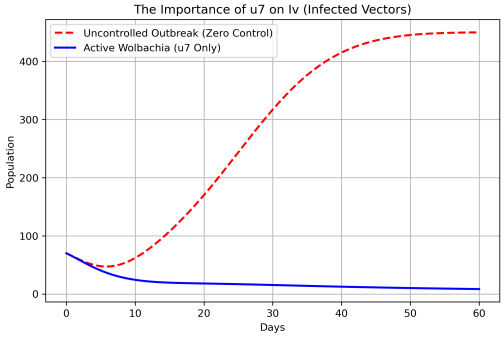
(C) Direct comparison of the exposed human population (E_h) when campaign u_7 is active (8 controls) versus when it is absent (7 controls)



(D) Direct comparison of the infected human population (I_h) under the same conditions for the activation of u_7

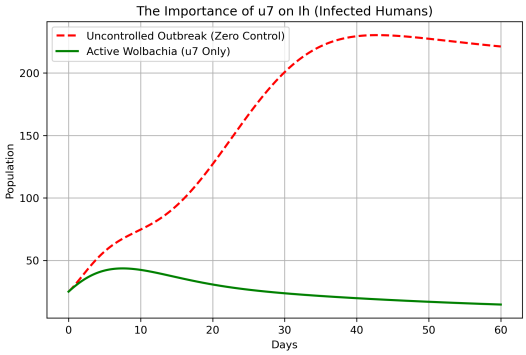


(A) Comparison of the population of infected mosquitoes (I_v), highlighting the increase in efficiency brought about by u_7

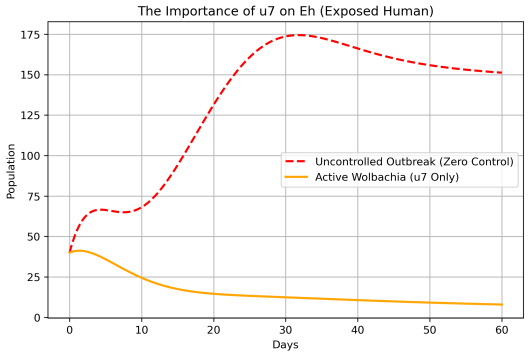


(B) Assessment of the exclusive impact of campaign u_7 on the population of infected vectors (I_v) compared with a complete lack of control

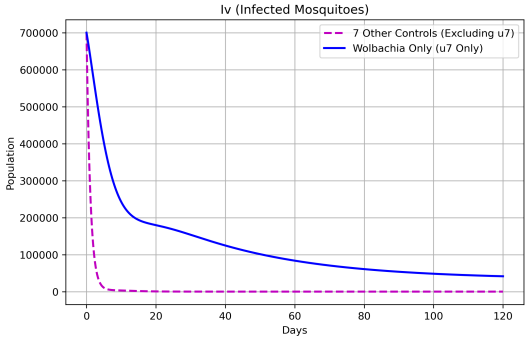
FIGURE 4. Analysis of the impact of control strategies over 50 days, highlighting the effect of enabling or disabling parameter u_7 (effectiveness of the awareness campaign linked to the release of Wolbachia)



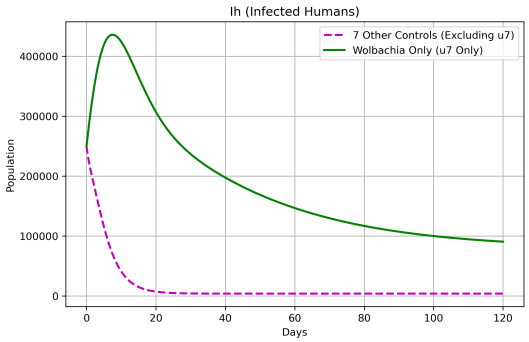
(A) Short-term impact of the isolated application of campaign u_7 on the infected human population (I_h)



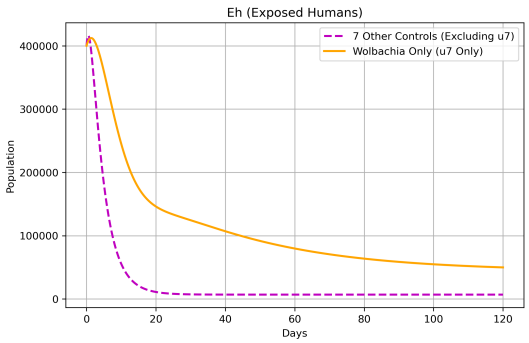
(B) Short-term impact of the isolated application of campaign u_7 on the exposed human population (E_h)



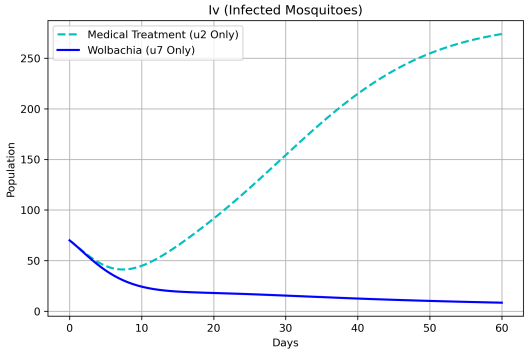
(A) Changes over 120 days in the population of infected mosquitoes (I_v) under the influence of the other control measures versus Wolbachia alone



(B) Changes over 120 days in the infected human population (I_h) under the two scenarios being compared

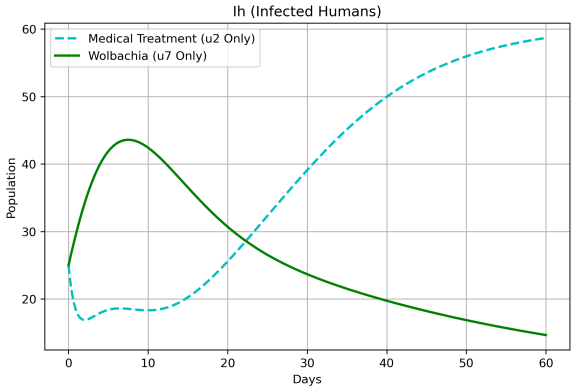


(C) Changes in the exposed human population (E_h) over 120 hours, confirming the downward trend observed in both approaches

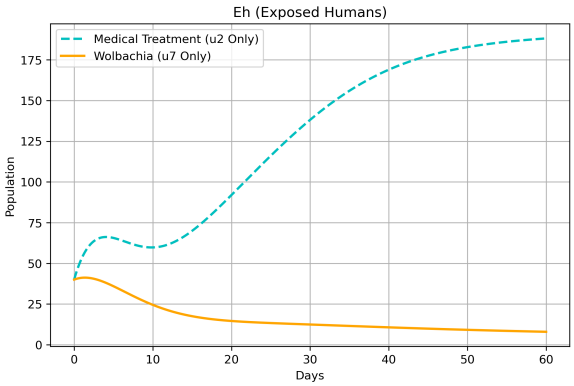


(D) A comparative analysis focusing on infected vectors (I_v) between a single administration of medical treatments (u_2) and a single application of Wolbachia (u_7)

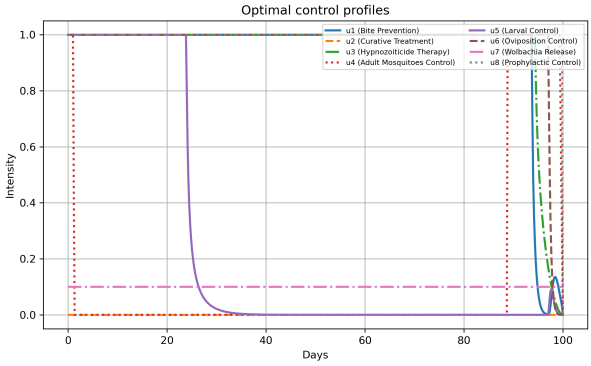
FIGURE 5. A long-term comparative study of the relative effectiveness of the exclusive deployment of the Wolbachia bacterium (u_7 alone) versus a combination of all other traditional control measures, excluding u_7.



(A) Comparison of the long-term effect of medical treatment alone (u_2) versus Wolbachia alone (u_7) on infected humans (I_h)



(B) Comparison of the same intervention policies (u_2 alone vs u_7 alone) on exposed humans (E_h)



(C) Intensity profiles of optimal control trajectories (u_1 to u_8) over 100 days, illustrating the gradual roll-out and phasing out of measures (prevention, treatments, larval control, etc.) to minimise cost and infection

FIGURE 6. Evaluation of the performance of individual medical and biological interventions, supplemented by the intensity-over-time profiles of optimal controls

To assess the effectiveness of the proposed intervention strategies, numerical simulations were carried out using MATLAB, analysing population dynamics over a given time horizon and highlighting the overall impact of control measures compared with an uncontrolled epidemic

scenario. In the absence of any intervention, the exposed (Figure 3a) and infected (Figure 3b) human populations increase rapidly before reaching a stable endemic equilibrium, maintaining a population of approximately 300 infected humans. Similarly, the population of infected vectors (Figure 3c) explodes before stabilising at a critical level of around 40,000 infected mosquitoes, confirming the persistence of malaria in the region.

Conversely, the application of optimal control disrupts this dynamic by causing the number of infected mosquitoes to fall dramatically from the very first days, causing all infected and exposed compartments to converge rapidly towards zero, thereby ensuring a disease-free state. Furthermore, the short-term behaviour over 50 days of the exposed human population under the effect of seven combined control measures, but without the public awareness campaign (u_7), shows a much less pronounced reduction in exposure (Figure 3d).

The crucial role of this awareness campaign (u_7), which is directly linked to the release of Wolbachia bacteria, is examined in greater detail over 50 days to analyse the specific impact of its implementation or omission. By comparing the trends in infected human populations (Figure 4a) and infected vectors (Figure 4b) against an uncontrolled epidemic, a marked improvement is observed as soon as a partial control comprising seven measures—excluding u_7—is implemented. The importance of public awareness becomes even more evident when directly comparing scenarios where campaign u_7 is active (eight control measures) versus when it is absent (seven control measures), both for the exposed human population (Figure 4c) and for the infected human population (Figure 4d), as the absence of u_7 consistently slows the rate at which infections decline. This beneficial effect is even more pronounced in the population of infected mosquitoes (Figure 4a), confirming the significant increase in effectiveness provided by this measure. Furthermore, an assessment of the exclusive impact of the u_7 campaign shows that its implementation alone is sufficient to significantly reduce the population of infected vectors compared with a situation where no control measures are in place (Figure 4b).

To explore this analysis further, a long-term comparative study spanning 120 days was conducted to assess the relative effectiveness of deploying Wolbachia bacteria exclusively (u_7 alone) compared with a combination of all other traditional control measures. In the short term, the standalone implementation of the u_7 campaign leads to a gradual reduction in the number of infected humans (Figure 5a) and exposed humans (Figure 5b). Analysis of the 120-day trajectories of the infected mosquito population (Figure 5a), the infected human population

(Figure 5b), and the exposed human population (Figure 5c) confirms a general downward trend for both approaches, although the combination of the seven other traditional control measures leads to a faster eradication of the disease than the Wolbachia strategy alone. Nevertheless, a comparative analysis focusing on infected vectors between a single administration of medical treatments (u_2) and a single application of Wolbachia (u_7) reveals that the latter is significantly more effective at sustainably reducing the population of infected mosquitoes over time (Figure 5d).

Finally, the long-term performance of individual medical and biological interventions is complemented by an assessment of the temporal intensity profiles of optimal control measures. A comparison of the long-term effect of medical treatment alone (u_2 alone) with that of Wolbachia alone (u_7 alone) shows that medical treatment has a stronger immediate curative impact on infected (Figure 6a) and exposed (Figure 6b) humans in the short term, whilst Wolbachia emerges as a more sustainable ecological lever in the long term. The intensity profiles of the optimal control trajectories developed over 100 days clearly illustrate the distribution and gradual withdrawal of efforts to minimise both the economic cost and the disease burden (Figure 6c). It can thus be seen that control u_2, associated with curative treatment, is immediately set to its upper limit before gradually decreasing to zero around the 50th day of intervention. In contrast, the profile of control u_1 remains strictly constant at its initial value until the 12th day, increases to reach a peak, then decreases around the 21st day; this fluctuating and oscillatory behaviour repeats itself until the 48th day, at which point the control effort drops definitively to zero, confirming the local eradication of the infection.

10. Conclusion

This study allowed the MSEIRS-LSEI extended compartmental model to be formulated and rigorously analyzed to assess the combined impact of traditional medical interventions and innovative ecological strategies against malaria. The calculation of the basic reproduction number, which yielded a value of $\mathscr{R}_0 = 2.046$ under uncontrolled initial conditions, formally confirmed the endemic nature of the disease in Burundi and highlighted the long-term ineffectiveness of isolated intervention methods. Through local and global stability analysis, validated by the next-generation matrix method and Lyapunov functions, it was demonstrated that the epidemic can be permanently eradicated at the local level if the reproduction number is kept below unity.

The sensitivity analysis also highlighted the most critical levers for action, identifying host-vector transmission probabilities and recruitment rates as the main drivers of the amplification or suppression of the infection dynamics.

The application of Pontryagin's maximum principle has allowed us to characterize an optimal control strategy structured around eight interdependent levers, minimizing both the human burden of the disease and the associated socio-economic costs. Numerical simulations carried out over different time horizons have validated the overwhelming superiority of a multi-sectoral and synchronous approach. Whilst a lack of intervention condemns the population to a critical steady state of persistent infections, the immediate deployment of optimal control or the long-term integration of the ecological bacterium Wolbachia succeeds in forcing all infected populations to converge towards a disease-free equilibrium. Furthermore, the amplifying role of the public awareness campaign (u_7) and the targeted effectiveness of larval management emerge as indispensable complements to maximize the sustainability of traditional medical treatments. These results provide a robust, environmentally responsible and scientifically sound predictive tool to guide the design of sustainable health policies and support public decision-making towards the definitive eradication of malaria in endemic regions.

11. Public Health Recommendations

Based on the analytical results and the optimal control trajectories obtained, policy-makers and health authorities should prioritise a multisectoral and integrated approach to bring about a sustainable decline in the malaria epidemic curve. It is strongly recommended that a shift towards biological control be initiated through the large-scale release of mosquitoes infected with the Wolbachia bacterium, an ecological strategy that utilises cytoplasmic sterility to neutralise the reproductive systems of wild vectors without disrupting ecosystems. To ensure the success of such an innovation, the government must increase community awareness campaigns to overcome reluctance and maximize social acceptance of this technology. Clinically, universal access to artemisinin-based combination therapies (ABCTs) must be guaranteed at the first signs of an epidemic resurgence, thereby immediately reducing the parasite reservoir in human hosts. This curative treatment must be combined with rigorous environmental management through the application of non-toxic biological larvicides and the systematic clearance of stagnant water to destroy larval breeding sites near homes.

Finally, in light of the impact of migration flows highlighted by the model, the authorities must put in place strict screening and preventive treatment protocols at the borders to prevent the reintroduction of imported parasitic strains, whilst accelerating the roll-out of routine malaria vaccination to prioritise the protection of children under five and pregnant women.

12. Future Research Directions

Although this work lays the foundations for an integrated and environmentally responsible approach to managing malaria transmission, several avenues for mathematical and biological extension are worth exploring in future research. A key avenue would be to evolve this deterministic model into a stochastic modelling framework to capture the impact of random fluctuations and environmental uncertainties inherent in real-world epidemic dynamics. Furthermore, the integration of spatial structures via partial differential equations or metapopulation models would enable the precise mapping of geographical connectivity and local human movements, thereby providing a tool for the geographical targeting of Wolbachia mosquito releases. From a biological perspective, the introduction of specific compartments dedicated to the genetic resistance of vectors to chemical pyrethroids and the emerging resistance of parasites to artemisinin-based treatments would enhance the robustness of optimal control trajectories. Finally, the incorporation of real-time climate data—in particular seasonal variations in temperature and rainfall, which directly govern the egg-laying cycle and lifespan of Anopheles mosquitoes—would enable the calibration of a highly predictive early-warning system to optimise the timing of public health interventions in endemic regions.

Author Contributions

Venant Niyonkuru: Conceptualization, mathematical formalization, theoretical analysis, computer implementation, numerical simulations, collection and processing of clinical and environmental data, and drafting of the first version of the manuscript (original draft).
Kinyanjui Matthew, Moore Stephen, Mutuku Winifred: Supervision of the research project, methodological validation, critical analysis of the model's structure, and thorough review and editing of the manuscript.

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CONFLICT OF INTERESTS

The author(s) declare that there is no conflict of interests.

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