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Sensitivity, Optimal Control, and Cost-Effectiveness Analysis of Intervention Strategies of Filariasis

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ABSTRACT

In this work, sensitivity, optimal control, and cost-effectiveness of several intervention strategies of filariasis are discussed. We study the intervention strategies that are related to bed-net use, insecticide, and the combination of bed-net use and insecticide. We use Pontryagin's maximum principle to characterize the optimal controls. The Average Cost-Effectiveness Ratio (ACER) and Infection Averted Ratio (IAR) are used to identify the most cost-effective strategy. We also determine the basic reproduction number and investigate the sensitivity of the basic reproduction number on the parameters that are related to bed-net use and insecticide. Based on the ACER values, the most cost-effective strategy to control filariasis is insecticide intervention. On the other hand, the IAR values indicates that bed-net use intervention is the most cost-effective strategy. Furthermore, it is also the most effective strategy to eliminate filariasis. The sensitivity analysis results show that the control parameter related to bed net use and treatment have a central role in reducing the basic reproduction number and filariasis spread.

Keywords:
Optimal Control; Sensitivity Analysis; Cost-Effectiveness Analysis; Filariasis

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1. Introduction

Mosquito-borne diseases such as malaria, dengue fever, chikungunya, and zika cause more than one million deaths every year. Unlike some of the mosquito -borne diseases previously mentioned, filariasis is a mosquito-borne disease which can cause permanent disability [1]. Filariasis is a chronic infectious disease caused by filarial worms and transmitted to humans by infected mosquitoes [2]. More than 120 million people are affected by filarial worm infection in 83 tropical and subtropical countries in several regions, i.e., Southeast Asia, Africa, the Mediterranean, the Western Pacific, and the Americas are endemic areas [3]. In Indonesia, filariasis is an endemic disease in several provinces, e.g., West Sulawesi [4].

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The implementation of the filariasis elimination program is carried out by several methods, namely providing mass drug therapy, preventing and limiting disability, controlling vectors, and developing research related to filariasis. Another intervention usually applied in managing the spread of filariasis is to reduce contact between humans and mosquitoes [3].

In recent years, the spread of filariasis has been studied using mathematical models [5–9]. Supriatna *et al.* [5] developed a mathematical model related to the spread of filariasis to evaluate the long-term impact of treatment of patients with filariasis in West Java, Indonesia. The outcomes of this research are the provision of additional care, controlling the number of contact between humans and mosquitoes, and controlling the mosquito population can reduce the cases of filariasis. Bhunu *et al.* [6] developed a mathematical model of filariasis that considers humans that are still in the incubation period. They found that treatment for elephantiasis patients can reduce the number of filariasis cases. However, filariasis cannot be eliminated if the treatment is only given to humans who have shown clinical symptoms, such as leg swelling (elephantiasis). They suggest that humans who are still in the incubation period should be treated so that the disease can be eradicated. The filariasis model developed to assess the impact of quarantine is discussed in [7]. The result of this study is that treatment for humans who are suffering from filariasis is more effective in reducing filariasis cases when compared to quarantine interventions.

To study the impact of reducing the possibility of the contact between human and mosquito which can disturb transmission process from mosquitoes to humans and from humans to mosquitoes, we considered bed-net use intervention. The treatment that can reduce the filarial parasite in the blood of treated humans was also considered in our model because we wanted to study the impact of reducing the rate of infection from humans to mosquitoes. Furthermore, to investigate the impact of controlling mosquito populations, we also pay attention to the use of insecticides. Hence, in contrast to the previously mentioned studies, we develop a filariasis model with the use of bed-net, treatment, and the use of insecticides. We perform sensitivity analysis to investigate normalized forward sensitivity index [10] of several parameters. Pontryagin's maximum principle is used to solve the optimal control problem. The cost-effectiveness of several intervention strategies of filariasis are also studied by using similar methods used in [11–14].

2. Methods

The study is conducted by doing the following steps:

1. Formulating a mathematical model of filariasis that considers the use of bed-nets and insecticides.
2. Identifying the equilibrium points of the model and the conditions for its existence.
3. Determining the basic reproduction number using the next-generation matrix.
4. Performing sensitivity analysis.
5. Determining the solution of the optimal control problem using Pontryagin's maximum principle.
6. Conducting cost-effectiveness analysis by calculating and comparing average cost-effectiveness ratio (ACER) and infection averted ratio (IAR) for each intervention scheme. According to [15], we can calculate ACER and IAR by using the following formulas, respectively.

$$\text{ACER} = \frac{\text{Cost produced by the intervention}}{\text{Number of Infection Averted}} \tag{1}$$

$$\text{IAR} = \frac{\text{Number of infection averted}}{\text{Number of recovered}} \tag{2}$$

3. Results and Discussion

3.1. Model Formulation

In this section, we describe the process of model formulation. Figure 1 shows the flow diagram of compartmens. Human population is divided into four compartments, i.e., susceptible human(S_h), latent human (E_h), infectious human (I_h), and treated human (T_h). On the other hand, we divide the mosquito population into two disjoint compartments, i.e., susceptible mosquito (S_m) and infectious mosquito (I_m).

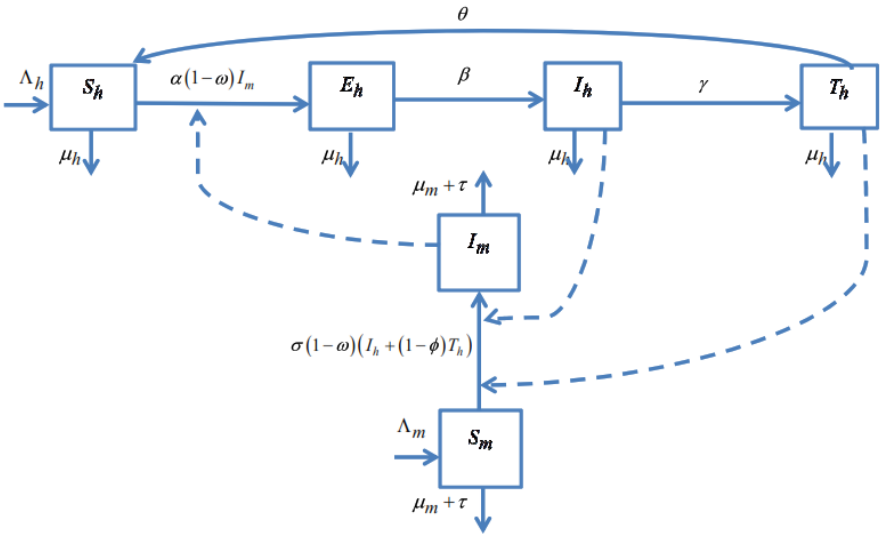

Figure 1. Flow Diagram of Compartments

The total number of susceptible humans increases with constant recruitment which is denoted by Λ_h. Here, we assume that treated humans who recover from filariasis do not get immunity. Hence, as a result of treated humans who recover from filariasis at rate θ, the total number of susceptible humans increases by θT_h. The total number of susceptible humans decreases by $\alpha\,(1-\omega)\,S_h I_m$ as a consequence of new infection that occurs after adequate contact between susceptible humans and infectious mosquitoes. Here, α is the transmission rate from infectious mosquitoes to susceptible humans and ω is the proportion of humans who use bed-net at night. Because of the natural death of susceptible humans, the total number of susceptible humans decreases by $\mu_h S_h$. Here, μ_h is the natural death rate of human. Therefore, we get the following ordinary differential equation that describe the dynamics of susceptible humans.

$$\frac{dS_h}{dt} = \Lambda_h - \alpha\,(1-\omega)\,S_h I_m + \theta T_h - \mu_h S_h.$$

Latent humans are humans who are infected but have not been able to transmit the disease to mosquitoes. The total number of latent humans increases by new infection,

that is $\alpha(1-\omega)S_hI_m$. After the latent period β^{-1} ends, the latent human becomes an infectious human. Hence, the total number of latent humans decreases by βE_h. Moreover, due to the natural death of latent humans, the total number of latent humans also decreases by $\mu_h E_h$. Thus, we have

$$\frac{dE_h}{dt} = \alpha(1-\omega)S_hI_m - \beta E_h - \mu_h E_h.$$

The total number of infectious humans increases by new infectious humans, that is βE_h. Because of the natural death of humans, the total number of infectious humans decreases by $\mu_h I_h$. Here, we assume that the average waiting time of infectious humans to get treatment is γ^{-1}. Hence, the total number of infectious humans decreases by γI_h. Consequently, we get

$$\frac{dI_h}{dt} = \beta E_h - \gamma I_h - \mu_h I_h.$$

The total number of treated humans increases by γI_h and decreases by the natural death of treated human $\mu_h T_h$. The following ordinary differential equation represents the dynamics of treated humans.

$$\frac{dT_h}{dt} = \gamma I_h - \theta T_h - \mu_h T_h.$$

The total number of susceptible mosquitoes increases by constant recruitment, that is Λ_m. After sufficient contact with infectious humans and treated humans, susceptible mosquitoes get infected. Hence, the total number of susceptible mosquitoes decreases by $\sigma(1-\omega)(I_h+(1-\phi)T_h)S_m$. ϕ is the parameter that measures the effectiveness of treatment in reducing the transmission from treated humans to mosquitoes. If $\phi = 1$, then treated humans can not transmit the disease. If $\phi = 0$, then the treated humans can transmit the disease similar to infectious humans who do not get treatment. If $\phi \in (0,1)$, then the treatment successfully reduces the transmission from treated humans to susceptible mosquitoes. Here, we assume that the natural death rate of mosquitoes is $\mu_m$and the insecticide-related death rate of mosquitoes is τ. So, the total number of susceptible mosquitoes decreases by $\mu_m S_m + \tau S_m$. As a result, we have

$$\frac{dS_m}{dt} = \Lambda_m - \sigma(1-\omega)(I_h+(1-\phi)T_h)S_m - \mu_m S_m - \tau S_m.$$

The total number of infectious mosquitoes increases by new infection, that is $\sigma(1-\omega)(I_h+(1-\phi)T_h)S_m$. Similar to susceptible mosquitoes, the total number of infectious mosquitoes decreases by $\mu_m I_m + \tau I_m$. Accordingly, we get

$$\frac{dI_m}{dt} = \sigma(1-\omega)(I_h+(1-\phi)T_h)S_m - \mu_m I_m - \tau I_m.$$

Based on the model formulation process above, we have the following system.

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h - \alpha(1-\omega)S_hI_m + \theta T_h - \mu_h S_h,\\
\frac{dE_h}{dt} &= \alpha(1-\omega)S_hI_m - \beta E_h - \mu_h E_h,\\
\frac{dI_h}{dt} &= \beta E_h - \gamma I_h - \mu_h I_h,
\end{aligned} \tag{3}$$

$$\begin{aligned}
\frac{dT_h}{dt} &= \gamma I_h - \theta T_h - \mu_h T_h, \\
\frac{dS_m}{dt} &= \Lambda_m - \sigma(1-\omega)\left(I_h + (1-\phi)T_h\right)S_m - \mu_m S_m - \tau S_m, \\
\frac{dI_m}{dt} &= \sigma(1-\omega)\left(I_h + (1-\phi)T_h\right)S_m - \mu_m I_m - \tau I_m.
\end{aligned}$$

3.2. Reproduction Number

The reproduction number is determined by using NGM (Next Generation Matrix) method that is presented in [16]. Firstly, we determine the disease free equilibrium point. After simple calculation process, we obtain the disease-free equilibrium point $P_0 = \left(S_h^0, E_h^0, I_h^0, T_h^0, S_m^0, T_m^0\right) = \left(\frac{\Lambda_h}{\mu_h}, 0, 0, 0, \frac{\Lambda_m}{\mu_m+\tau}\right)$. Following the method given in [16], we determine F and V. Here, E_h, I_h, T_h, I_m are considered to be infected compartments. Therefore, we get

$$\begin{aligned}
F &= \begin{pmatrix}
0 & 0 & 0 & \alpha(1-\omega)\frac{\Lambda_h}{\mu_h} \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & \sigma(1-\omega)\frac{\Lambda_m}{\mu_m+\tau} & \sigma(1-\omega)(1-\phi)\frac{\Lambda_m}{\mu_m+\tau} & 0
\end{pmatrix}, \\
V &= \begin{pmatrix}
\beta+\mu_h & 0 & 0 & 0 \\
-\beta & \gamma+\mu_h & 0 & 0 \\
0 & -\gamma & \theta+\mu_h & 0 \\
0 & 0 & 0 & \mu_m+\tau
\end{pmatrix}.
\end{aligned}$$

It is straightforward to prove that the spectral radius of FV^{-1} is

$$\rho\left(FV^{-1}\right) = \sqrt{\frac{\alpha(1-\omega)\Lambda_h}{(\mu_m+\tau)\mu_h}v_1},$$

where

$$v_1 = \frac{\sigma(1-\omega)\beta\Lambda_m}{(\beta+\mu_h)(\gamma+\mu_h)(\mu_m+\tau)} + \frac{\sigma(1-\omega)(1-\phi)\beta\gamma\Lambda_m}{(\beta+\mu_h)(\gamma+\mu_h)(\theta+\mu_h)(\mu_m+\tau)}.$$

Therefore, the reproduction number is given as follows

$$R_0 = \sqrt{\frac{\alpha(1-\omega)^2\Lambda_h\sigma\beta\Lambda_m(\theta+\mu_h+(1-\phi)\gamma)}{(\mu_m+\tau)^2(\beta+\mu_h)(\gamma+\mu_h)(\theta+\mu_h)\mu_h}}.$$

Based on Theorem 2 in [16], we obtain the following Theorem.

Theorem 1. *The disease free equilibrium point P_0 is stable if $R_0 < 1$. On the other hand, P_0 is unstable if $R_0 > 1$.*

3.3. Sensitivity Analysis

In this section, we perform sensitivity analysis to identify the effect of several parameters, e.g., Λ_m, τ, ω, ϕ, on the basic reproduction number. We determine the normalized forward sensitivity index that is described in [10]. The sensitivity index of

each parameter is given as

$$\begin{aligned}
\Upsilon_{\Lambda_m}^{R_0} &= \frac{\partial R_0}{\partial \Lambda_m} \times \frac{\Lambda_m}{R_0} = \frac{1}{2} > 0,\\
\Upsilon_{\tau}^{R_0} &= \frac{\partial R_0}{\partial \tau} \times \frac{\tau}{R_0} = \frac{-\tau}{\tau + \mu_v} < 0,\\
\Upsilon_{\phi}^{R_0} &= \frac{\partial R_0}{\partial \phi} \times \frac{\phi}{R_0} = \frac{-\phi\gamma}{\theta + \mu_h + \gamma\,(1-\phi)} < 0,\\
\Upsilon_{\omega}^{R_0} &= \frac{\partial R_0}{\partial \omega} \times \frac{\omega}{R_0} = \frac{-\omega}{1-\omega} < 0.
\end{aligned}$$

$\Upsilon_{\Lambda_m}^{R_0} = 0.5$ shows that 1% increase in Λ_m causes 0.5% increase in R_0. Hence, we can reduce the basic reproduction number by reducing the recruitment rate of mosquitoes. $\Upsilon_{\tau}^{R_0} = \frac{-\tau}{\tau+\mu_v}$means that 1% increase in τ will produce $\frac{\tau}{\tau+\mu_v}$ decrease in R_0. Therefore, the basic reproduction number decreases as τ increases. However, the magnitude of the decrease in R_0 depends on the baseline value of τ and μ_v. To determine the sensitivity index of the parameters, we use the parameter values presented in Table 1 as the baseline of parameter values.

Table 1. Parameter Values

Parameter	Values	Unit	Source
Λ_h	$\frac{500\times1.98}{365\times100}$	human $\times$ day^{-1}	Estimated
Λ_m	6	mosquitoes $\times$ day^{-1}	[7]
μ_h	$\frac{1}{65\times365}$	day^{-1}	[17]
μ_m	$\frac{1}{13}$	day^{-1}	[18], [19]
α	0.01×0.01	mosquito^{-1} $\times$ day^{-1}	[7]
σ	1.52×0.01	human$^{-1}\times$day^{-1}	[8]
β	$\frac{1}{6\times4\times7}$	day^{-1}	[20]
γ	$\frac{1}{7}$	day^{-1}	[4]
θ	$\frac{1}{6\times7}$	day^{-1}	[3]
τ	0.001	day^{-1}	Assumed
ω	20%		Assumed
ϕ	20%		[21], [22]

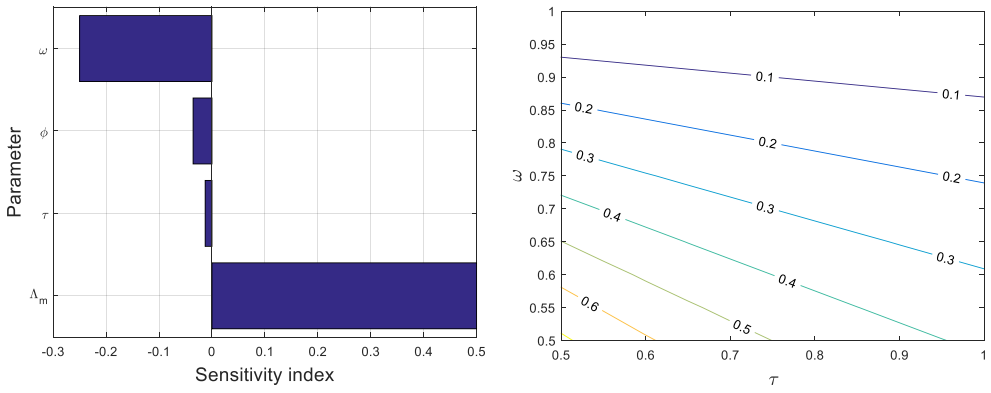

Figure 2. Sensitivity of R_0(a) and relationship between τ, ω, and R_0(b)

After substituting the parameter values, we obtain $\Upsilon_{\Lambda_m}^{R_0} = 0.500$, $\Upsilon_{\tau}^{R_0} = 0.013$, $\Upsilon_{\phi}^{R_0} = -0.036$, and $\Upsilon_{\omega}^{R_0} = 0.250$. These results show that we must control the growth of

mosquito population. Moreover, the use of bed-net and treatment which can reduce the filarial worm in the blood of treated humans have a central role in filariasis control. relationship between τ, ω, and R_0 can be seen in Figure 2.

3.4. Optimal Control Problem

For the optimal control model, we set $\omega = u_1$ and $\tau = u_2$. Therefore, the optimal control model is given as follows

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h - \alpha\left(1-u_1\right) S_h I_m + \theta T_h - \mu_h S_h,\\
\frac{dE_h}{dt} &= \alpha\left(1-u_1\right) S_h I_m - \beta E_h - \mu_h E_h,\\
\frac{dI_h}{dt} &= \beta E_h - \gamma I_h - \mu_h I_h,\\
\frac{dT_h}{dt} &= \gamma I_h - \theta T_h - \mu_h T_h,\\
\frac{dS_m}{dt} &= \Lambda_m - \sigma\left(1-u_1\right)\left(I_h + (1-\phi)\, T_h\right) S_m - \mu_m S_m - u_2 S_m,\\
\frac{dI_m}{dt} &= \sigma\left(1-u_1\right)\left(I_h + (1-\phi)\, T_h\right) S_m - \mu_m I_m - u_2 I_m.
\end{aligned} \tag{4}$$

Our purposes are to determine the control strategy that minimizes the number of infectious humans and latent humans as well as the costs of interventions. Hence, we intend to examine the control strategy that minimizes the following objective function

$$\mathrm{O}\left(u_1, u_2\right) = \int_0^T \left(D_1 E_h + D_2 I_h + D_3 {u_1}^2 + D_4 {u_2}^2\right) dt, \tag{5}$$

subject to system (4). D_1 and D_2 are the relative cost weight for E_h and I_h, respectively. $D_3$and D_4 are the relative cost weight associated with bed-net use and insecticide, respectively. The final time is T. We will determine u_1^+, u_2^+, such that

$$\mathrm{O}\left(u_1^+, u_2^+\right) = \min_U \left(u_1, u_2\right),$$

where

$$U = \left\{u_1 : [0,T] \to [0, u_1^{\max}], u_2 : [0,T] \to [0, u_2^{\max}], \textit{are Lebesgue measurable}\right\}.$$

We solve the optimal control problem by applying Pontryagin's maximum principle. Based on the objective function (5) and the optimal control model (4), we establish the Hamiltonian function H as follows

$$\begin{aligned}
\mathrm{H} \quad &= D_1 E_h + D_2 I_h + D_3 {u_1}^2 + D_4 {u_2}^2\\
&+ w_1\left[\Lambda_h - \alpha\left(1-u_1\right) S_h I_m + \theta T_h - \mu_h S_h\right]\\
&+ w_2\left[\alpha\left(1-u_1\right) S_h I_m - \beta E_h - \mu_h E_h\right]\\
&+ w_3\left[\beta E_h - \gamma I_h - \mu_h I_h\right]\\
&+ w_4\left[\gamma I_h - \theta T_h - \mu_h T_h\right]\\
&+ w_5\left[\Lambda_m - \sigma\left(1-u_1\right)\left(I_h + (1-\phi)\, T_h\right) S_m - \mu_m S_m - u_2 S_m\right]\\
&+ w_6\left[\sigma\left(1-u_1\right)\left(I_h + (1-\phi)\, T_h\right) S_m - \mu_m I_m - u_2 I_m\right].
\end{aligned} \tag{6}$$

where $w_1, w_2, ..., w_6$ are adjoint variables. Next, we determine the adjoint system. The adjoint system for the optimal control problem is given as follows

$$\begin{aligned}
\frac{dw_1}{dt} &= -\frac{\partial \mathrm{H}}{\partial S_h} = (w_1 - w_2)\,\alpha I_m\,(1-u_1) + w_1\mu_h,\\
\frac{dw_2}{dt} &= -\frac{\partial \mathrm{H}}{\partial E_h} = (w_2 - w_3)\,\beta + w_2\mu_h - D_1,\\
\frac{dw_3}{dt} &= -\frac{\partial \mathrm{H}}{\partial I_h} = (w_3 - w_4)\,\gamma + w_3\mu_h + (w_5{-}_6)\,\sigma\,(1-u_1)\,S_m - D_2,\\
\frac{dw4}{dt} &= -\frac{\partial \mathrm{H}}{\partial T_h} = (w_4 - w_1)\,\theta + w_4\mu_h,\\
\frac{dw_5}{dt} &= -\frac{\partial \mathrm{H}}{\partial S_m} = w_5\,(u_2+\mu_m) + (w_5 - w_6)\,\sigma\,(1-u_1)\,(I_h + (1-\phi)\,T_h),\\
\frac{dw_6}{dt} &= -\frac{\partial \mathrm{H}}{\partial I_m} = (w_1 - w_2)\,\alpha\,(1-u_1)\,S_h + w_6\,(u_2+\mu_m),
\end{aligned}$$

with boundary conditions $w_i(T) = 0$ for $i = 1, ...6$. The derivative of Hwith respect to control parameters u_1 and u_2 are, respectively, given as follows

$$\begin{aligned}
\frac{\partial \mathrm{H}}{u_1} &= 2D_3u_1 + (w_1 - w_2)\,\alpha I_m S_h + (w_5 - w_6)\,\sigma S_m\,(I_h + (1-\phi)\,T_h),\\
\frac{\partial \mathrm{H}}{u_2} &= 2D_4u_2 - w_5S_m - w_6I_m.
\end{aligned}$$

After solving $\frac{\partial \mathrm{H}}{\partial u_1} = \frac{\partial \mathrm{H}}{\partial u_2} = 0$, we get

$$\begin{aligned}
u_1^* &= \frac{(w_2 - w_1)\,\alpha I_m S_h + (w_6 - w_5)\,\sigma S_m\,(I_h + (1-\phi)\,T_h)}{2D_3},\\
u_2^* &= \frac{w_5S_m + w_6I_m}{2D_4}.
\end{aligned} \tag{7}$$

Based on the upper and lower bound of u_1 and u_2, the optimal value u_1^+ and u_2^+ are, respectively, given by

$$\begin{aligned}
u_1^+ &= \min\{\max\{0, u_1^*\}, 1\},\\
u_2^+ &= \min\{\max\{0, u_2^*\}, 1\}.
\end{aligned}$$

3.5. Effectiveness and Cost Effectiveness

For the effectiveness and cost-effectiveness analysis, we adopt the following measures.

1. We regard infectious humans and latent humans as infected humans. Consequently, the total number of infected humans in the course of Tperiod with and without control are, respectively, given by

$$T_{wc} = \int_0^T (E_h^*(t) + I_h^*(t))\,dt, \quad T_{woc} = \int_0^T (E_h(t) + I_h(t))\,dt. \tag{8}$$

   where E_h^* and I_h^* represent the number of latent humans and infectious humans when the control strategy is applied. Consequently, $T_{av} = T_{woc} - T_{wc}$ is the total number of infected humans avoided because of the implementation of control strategy.

2. Following [13], we use $\bar{E}$ to measure the effectiveness of intervention.

$$\bar{E} = \frac{T_{av}}{T_{woc}} \tag{9}$$

3. Following [11], the Average Cost-Effectiveness Ratio (ACER) and the Infected Averted Ratio (IAR) are given by

$$\begin{aligned} ACER &= \frac{TC}{T_{av}}, \\ IAR &= \frac{T_{av}}{T_r}, \end{aligned} \tag{10}$$

where $TC = \int_0^T \left(D_3 {u_1}^2 + D_4 {u_2}^2\right) dt$ and $T_r = \int_0^T \theta T_h dt$are total cost of intervention and total number of recovered humans during T period, respectively.

3.6. Numerical Simulations

The parameter values used are presented in Table 1 which gives $R_0 = 7.5196$. The initial condition used is $S_h(0) = 100$, $E_h(0) = 10$, $I_h(0) = 5$, $S_m(0) = 200$, $T_h(0) = 30$, and $I_m(0) = 30$. For the numerical study, we set $D_1 = 1, D_2 = 4, D_3 = 1$, and $D_4 = 3$. Here we assume that $u_1^{\max} = 0.8$ and $u_2^{\max} = 0.1$. We investigate the following strategy.

1. Strategy 1: The Effect of Bed-Net Use Intervention only.
In this part, we investigate the effects of the bed-net use intervention only. For the numerical simulations, we set $u_1 \geq 0$ and $u_2 = 0$. Figure 3 shows that strategy 1 can reduce filariasis cases. Without a control strategy, the peak of the number of infected humans almost reaches 25. Without control, the number of infected humans at the end of the period is 6. When strategy 1 is implemented, the number of infected humans at the end of the period decreases to near 0. Moreover, when strategy 1 is applied, the peak of the number of infected humans is about 15 only. Figure 3 shows that the optimal value of u_1 should be always at its upper bound.

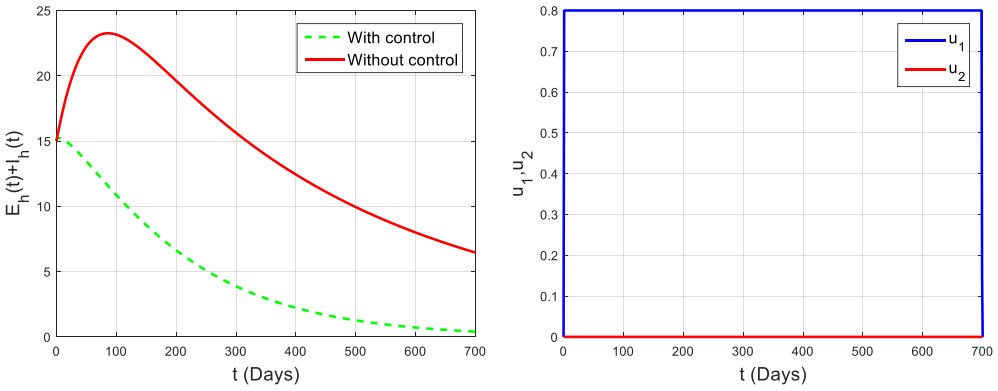

Figure 3. Dynamics of infected human and control profile when strategy 1 is applied

2. Strategy 2: The Effect of Insecticide Intervention only.
Now, we explore the effect of insecticide intervention only. We conduct the numerical simulations with $u_1 = 0$ and $u_2 \geq 0$. Figure 4 shows that filariasis cases can be controlled when strategy 2 is implemented. If strategy 2 is implemented, the number

of infected humans at the end of the period is 2. Figure 4 shows that control u_2 should be always at its upper bound.

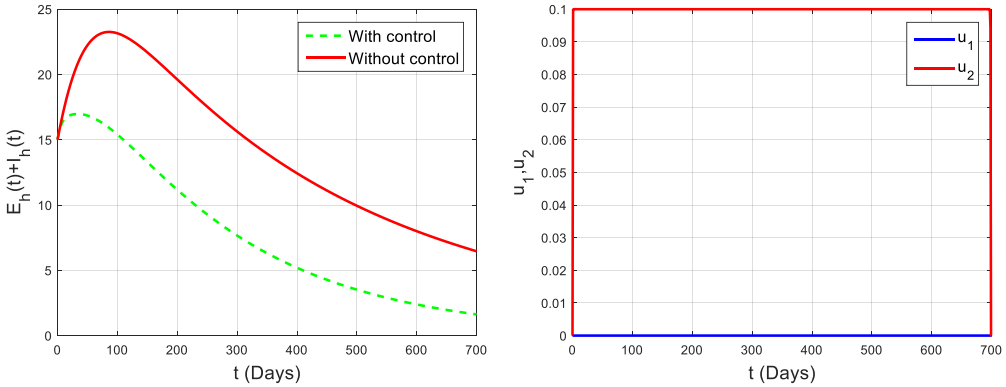

Figure 4. Dynamics of infected human and control profile when strategy 2 is applied

3. Strategy 3: The Effect of Bed-Net Use and Insecticide Intervention.
The effect of the combination of bed-net and insecticide intervention is studied in this subsection. We set both $u_1 \geq 0$ and $u_2 \geq 0$. Figure 5 shows that strategy 3 can reduce the number of infected humans. When strategy 3 is applied, the number of infected humans at the end of the period decreases near 0. Figure 5 shows that control $u_1$should be at its upper bound throught 700 days. On the other hand, control $u_2$should be at its upper bound at day 50^{th}.

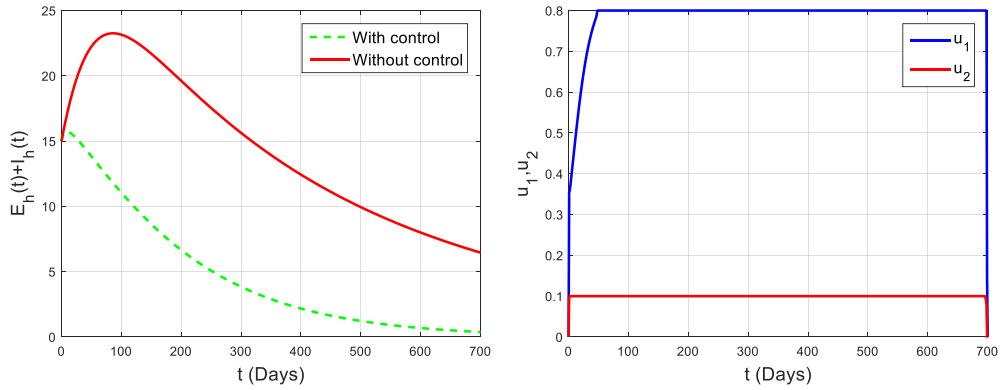

Figure 5. Dynamics of infected human and control profile when strategy 3 is applied

We will find it difficult to determine the most effective strategy in controlling filariasis cases if we only compare the figures and the number of infected humans at the end of the period of each strategy. Here we determine the effectiveness of each strategy using (9). The results obtained are listed in Table 2.

Table 2. Effectiveness of each strategy

Strategy	Effectiveness $\bar{E}$
1	0.67159
2	0.46206
3	0.66878

It is clear that the most effective strategy is strategy 1. Now we investigate the most cost-effective strategy using ACER and IAR. We use formula (10) to determine the ACER and IAR of the strategies. The results are given in Table 3. From the ACER

Table 3. Cost-effectiveness of each strategy

Strategy	T_{av}	TC	Recovered Human	ACER	IAR
1	6829.6166	446.7419	116.0824	0.065412	58.8342
2	4698.7897	20.9367	123.9002	0.0044558	37.924
3	6800.998	455.9003	116.2083	0.067034	58.5242

values presented in Table 3, strategy 2 is the most cost-effective. It is followed by strategy 1. The least cost-effective strategy is strategy 3. Therefore, the average cost for each infected human prevented when strategy 2 is employed is lower than when strategy 1 or strategy 3 is implemented. Based on the IAR values listed in Table 3, the most cost-effective strategy is strategy 1, followed by strategy 3, then strategy 2. Hence, the positive impact of curing one infected human on the number of infected humans prevented when strategy 1 is practiced is higher than when strategy 2 or strategy 3 is implemented.

4. Conclusion

In this work, we discuss sensitivity, optimal control, and cost-effectiveness analysis of intervention strategies of filariasis. We solve the optimal control problem using Pontryagin's maximum principle. Our findings suggest that the most effective strategy is bed-net use intervention. Using ACER approach, we find that the most cost-effective strategy is insecticide intervention. On the other hand, based on the IAR approach, the most cost-effective strategy is bed-net use intervention. Also, the sensitivity analysis results supports that bed-net use and treatment has a central role in reducing the reproduction number and filariasis spread.

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