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Optimal Control of Intervention Strategies and Cost Effectiveness Analysis for a Zika Virus Model

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Abstract

This paper presents an optimal control strategy and a cost effectiveness analysis for the Zika virus disease. A mathematical model for the transmission of the Zika virus is considered with four preventive measures as control: the use of treated bednets, the use of condoms, a medical treatment of infected persons, and the use of indoor residual spray. We obtain the reproduction number R_0 for the disease and carry out a stability analysis. We observe that the disease's free equilibrium state is stable when $R_0 < 1$ but unstable when $R_0 > 1$, which leads to a spread of the disease. We examine the implementation of various combinations of the possible control strategies in order to determine the most cost-effective one. Based on the computational results, we conclude that a strategy that consists of treated bednets, treatment of infected individuals and indoor residual spray is the most cost effective one.

Mathematical Subject Classification (2010): 92B05, 93A30, 93C15.

Key Words: Vector-Borne Disease, Zika Virus, Optimal Control, Cost Effectiveness Analysis, Reproduction Number.

1 Introduction

Zika is a viral infection that is usually spread by the bite of an infected mosquito. It can sometimes be spread by having sex with an infected human. The Zika virus is a flavivirus and is related to other arboviruses such as the yellow fever virus, the Japanese Encephalitis Virus, the Dengue Virus and the West Nile Virus [1]. In 1947, the Zika virus was originally isolated from a febrile sentinel rhesus monkey and from a pool of Aedes Africanus mosquitoes in the Zika forest in Uganda during a yellow fever study [2]. The Zika virus was first detected in humans five years later in 1952 using neutralizing antibody testing in sera from East Africa [2, 4], and it was first isolated in a human in Uganda [5]. It has been estimated that about 80% of infected persons with the Zika virus are asymptomatic [6, 8] and it is known that those with clinical manifestations present Dengue-like symptoms that include arthralgia, particularly swelling, mild fever, lymphadonopathy, skin rash, headaches, retro or bital pain and conjunctivitics which normally last for 2-7 days [6, 10, 9]. The epidemic capacity of the Zika virus was revealed in an outbreak in Micronesia in 2007 and affected approximately 5000 people [11]. Zika has been detected in serum, saliva, urine, and semen [14, 15, 16]. It has also been detected in urine and semen even after it disappears from blood [1]. It has also been observed that the Zika virus can be transmitted through sexual contact. It was reported by the CDC on February 2, 2016 [18] that an infected male had infected a female by having vaginal sexual transmitted Zika virus of the current outbreak in Dallas County. Six more confirmed and probable cases of a sexual transmission of the Zika virus in the US were reported by the CDC on February 26, 2016 [19], and Europe's first case of a sexually transmitted Zika virus was diagnosed in France in Febuary 2016 [20]. Education about the Zika virus' mode of transmission and ways of preventing transmission are essential in order to halt mosquito growth and thus Zika spread among a community or population, at regional, national, and global levels. Control measures available are limited and include the use of insect repellents to protect humans against mosquito bites and sex protection while engage in sexual activities [7]. In this paper, we present optimal control strategies and cost effectiveness analysis to better understand ways to control the transmission of the Zika virus with respect to cost/benefit to the population.

The paper is organized as follows. In Section 2 we present a mathematical model for the Zika virus transmission with four control functions. In Section 3 we carry out our mathematical analysis of this Zika virus model. In Section 4 we economically assess the control strategies involved in the optimal control problem.

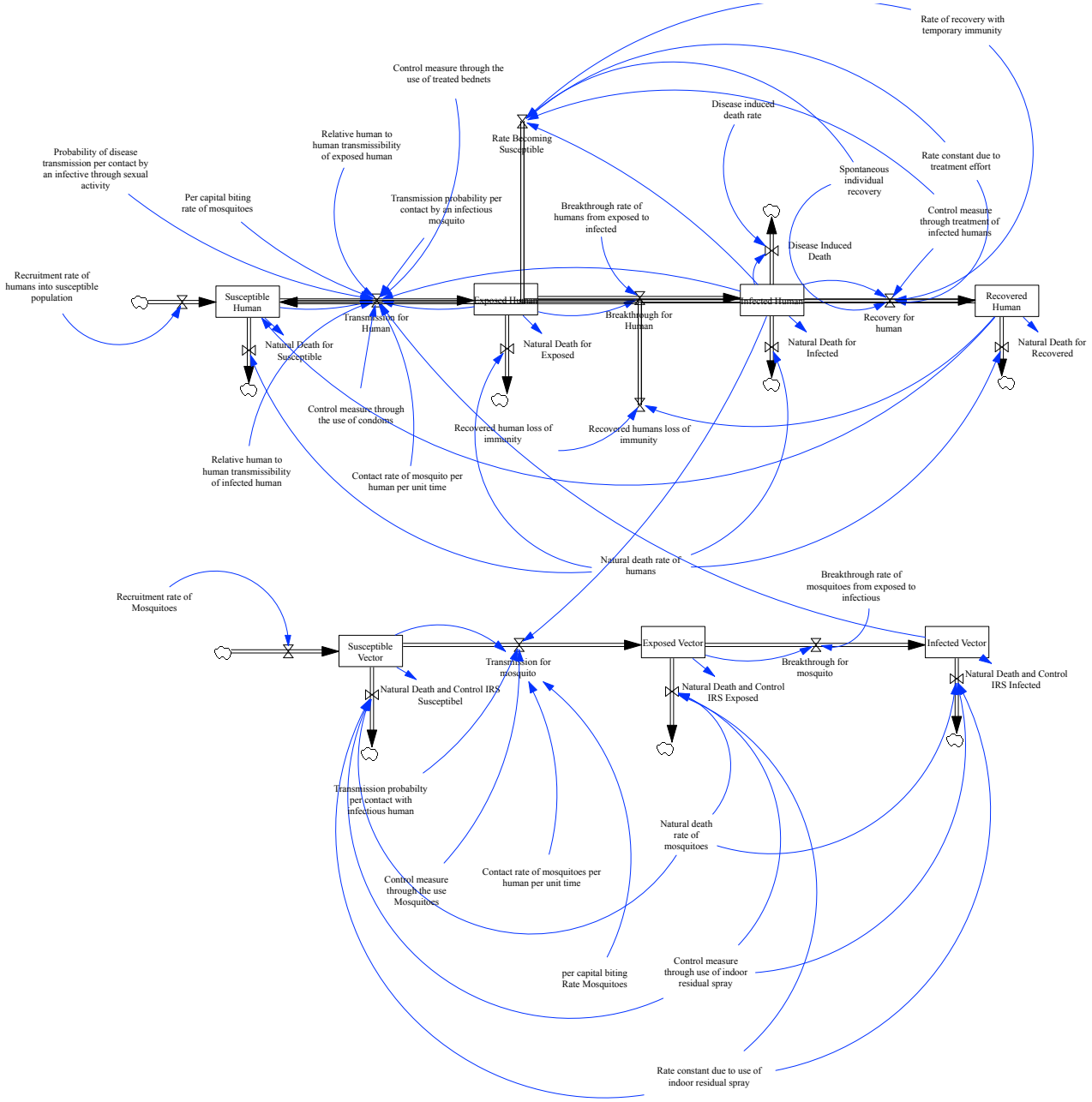


Figure 1: The Zika virus transmission model.

In Section 5 we propose an optimal control problem for the minimization of the number of exposed humans, infectious humans and total mosquito population while taking note the cost of control interventions. Finally, in Section 6 some numerical results are analyzed and interpreted from an epidemiological point of view and cost effectiveness analysis was implemented for the various strategies considered in this work.

2 Derivation of the Model

A deterministic Zika virus transmission dynamics model with intervention strategies is propose to investigate the optimal control strategy against the Zika virus. A schematic overview of the full model is shown in Figure 1. An overview of the notation of the model is given in Tables 1-3.

Table 1: State Variables Descriptions of the Zika Virus Model

Symbol	Description of Variable
S_H	Number of susceptible humans at time t
E_H	Number of exposed (yet to start symptoms) humans at time t
I_H	Number of infected (with symptoms) humans at time t
R_H	Number of recovered humans at time t
S_V	Number of susceptible mosquitoes at time t
E_V	Number of exposed mosquitoes at time t
I_V	Number of infectious mosquitoes at time t
N_H	Total number of human at time t
N_V	Total number of mosquitoes at time t

Table 2: Control Variables and Descriptions of the Zika Virus Model

Symbol	Description of Control
$u_1(t)$	Control measure through the use of treated bednets
$u_2(t)$	Control measure through the use of condoms
$u_3(t)$	Control measure through treatment of infected humans
$u_4(t)$	Control measure through use of indoor residual spray
θ	Rate constant due to use of indoor residual spray
τ	Rate constant due to treatment effort

Table 3: Parameters Descriptions of the Zika Virus Model

Symbol	Description of Parameter
Λ_H	Recruitment rate of humans into susceptible population
μ_H	Natural death rate of humans
φ_H	Recovered humans loss of immunity
ϕ	Spontaneous individual recovery
ν	Rate of recovery with temporary immunity
α_H	Breakthrough rate of humans from exposed to infected
δ_H	Disease induced death rate
c	Relative human-human transmissibility of exposed human
κ	Relative human-human transmissibility of infected human
β	Probability of disease transmission per contact by an infective through sexual activity
β_1	Probability of disease transmission per contact by an infectious mosquito
β_2	Probability of disease transmission per contact by an infected human
ε	Per capital biting rate of mosquitoes
ρ	Contact rate of mosquito per human per unit time
Λ_V	Recruitment rate of mosquitoes
μ_V	Natural death of mosquitoes
α_V	Breakthrough rate of mosquitoes from exposed to infectious

The total population for human hosts at time t is denoted by $N_H(t)$. The total population of vectors (mosquitoes) is $N_V(t)$. They are sub-divided into $(S_H(t), E_H(t), I_H(t), R_H(t))$ and $(S_V(t), E_V(t), I_V(t))$, respectively, with the following meaning: The human host population consist of a susceptible human population $S_H(t)$, exposed (yet to start symptoms) human population $E_H(t)$, infected (with symptoms) human population $I_H(t)$ and recovered human population $R_H(t)$. The vector population consist of susceptible mosquitoes $S_V(t)$, exposed mosquitoes $E_V(t)$ and infected mosquitoes $I_V(t)$. In the Zika virus model, we incorporate four time dependent control measures, namely, the use of treated bednets $u_1(t)$, the use of condoms $u_2(t)$, the treatment $u_3(t)$ and the use of indoor residual spray $u_4(t)$.

Using these notations, we then obtain the following system of differential equations from the flow diagram in Figure 1:

$$\frac{dS_H}{dt} = \Lambda_H + (\phi + \tau u_3)(1-\nu)I_H + \varphi R_H - \frac{\beta_1 \varepsilon \rho (1-u_1) I_V S_H}{N_H} - \frac{\beta c (1-u_2) E_H S_H}{N_H} - \frac{\beta \kappa (1-u_2) I_H S_H}{N_H} - \mu_H S_H, \tag{1a}$$

$$\frac{dE_H}{dt} = \frac{\beta_1 \varepsilon \rho (1-u_1) I_V S_H}{N_H} + \frac{\beta c (1-u_2) E_H S_H}{N_H} + \frac{\beta \kappa (1-u_2) I_H S_H}{N_H} - \alpha_H E_H - \mu_H E_H, \tag{1b}$$

$$\frac{dI_H}{dt} = \alpha E_H - (\phi + \tau u_3)(1-\nu) I_H - (\phi + \tau u_3)\nu I_H - \mu_H I_H - \delta_H I_H, \tag{1c}$$

$$\frac{dR_H}{dt} = (\phi + \tau u_3)\nu I_H - \varphi_H R_H - \mu_H R_H, \tag{1d}$$

$$\frac{dS_V}{dt} = \Lambda_V - \frac{\beta_2 \varepsilon \rho (1-u_1) I_H S_V}{N_H} - \mu_V S_V - \theta u_4 S_V, \tag{1e}$$

$$\frac{dE_V}{dt} = \frac{\beta_2 \varepsilon \rho (1-u_1) I_H S_V}{N_H} - \alpha_V E_V - \mu_V E_V - \theta u_4 E_V, \tag{1f}$$

$$\frac{dI_V}{dt} = \alpha_V E_V - \mu_V I_V - \theta u_4 I_V, \tag{1g}$$

$$\frac{dN_H}{dt} = \Lambda_H - \delta_H I_H - \mu_H N_H, \tag{1h}$$

$$\frac{dN_V}{dt} = \Lambda_V - (\mu_V + \theta u_4) N_V \tag{1i}$$

The susceptible human population $S_H(t)$ increases due to a recruitment at a rate Λ_H, a loss of immunity from the recovered class at a rate φ_H and recovered humans without immunity at a rate $(1-\nu)$. The susceptible human population reduces by

$$\frac{\beta_1 \varepsilon \rho (1-u_1) I_V S_H}{N_H} + \frac{\beta c (1-u_2) E_H S_H}{N_H} + \frac{\beta \kappa (1-u_2) I_H S_H}{N_H}$$

as a result of a contact with an infectious mosquitoes and a sexual contact with exposed and infected humans and a natural death at a rate μ_H. The exposed human population increases by

$$\frac{\beta_1 \varepsilon \rho (1-u_1) I_V S_H}{N_H} + \frac{\beta c (1-u_2) E_H S_H}{N_H} + \frac{\beta \kappa (1-u_2) I_H S_H}{N_H}$$

and reduces due to a transition of individuals from the class of exposed to the infected class at a rate of α_H and a natural death at a rate of μ_H. The infected human may recover with temporary immunity at a rate ν and progress to recovered class while the remaining proportion recovers without immunity and become susceptible at a rate $(1-\nu)$. The infected human recover as a result of treatment at a rate $\tau u_3(t)$, where $u_3(t) \in [0,1]$ is the control measure on treatment and ϕ is the proportion of humans who recovered spontaneously (i.e., the body recovers naturally without treatments). The infected human population reduces by natural death and disease induced death at rates μ_H and δ_H respectively. The recovered human population reduces by natural death at a rate μ_H and loss of immunity at a rate φ_H. The susceptible mosquito population increases due to recruitment at a rate Λ_V, reduces by

$$\frac{\beta_2 \varepsilon \rho (1-u_1) I_H S_V}{N_H}$$

upon contact with infected human, where β_2 is the transmission probability per contact by an infected human, natural death at a rate μ_V and death due to use of indoor residual spray $\theta u_4(t)$, where $\theta > 0$ is the rate constant when indoor residual spray is used and $u_4(t) \in [0,1]$ is the control measure by use of indoor residual spray. The exposed mosquito population increases by

$$\frac{\beta_2 \varepsilon \rho (1-u_1) I_H S_V}{N_H}$$

and reduces by breakthrough into infectious class at the rate α_V, natural death at a rate μ_V and control measure by indoor residual spray at a rate $\theta u_4(t)$. The infectious mosquito population increases due to breakthrough from exposed class at a rate α_V and reduces due to natural death at a rate μ_V and control measure by indoor residual spray at a rate $\theta u_4(t)$. we assumed that the rate of contact of susceptible with infected (with symptoms) individuals is less than exposed (yet to start symptoms) individuals ($\kappa < c$). This is so because on becoming symptomatic, the infected persons may choose to use preventive measures and change their behaviour.

3 Mathematical Analysis of the Zika Virus Model

We analyze the properties of our model (1).

3.1 Positivity of Solution

In this section, we will analyse the general properties of the system (1) with non-negative initial conditions since the model describe human host and mosquitoes population. It is important to prove that all variables describing the dynamics of the population will be non-negative, since negative values have are not meaningful in the real-world. Our goal here is to establish that all solutions of the system (1) with non-negative initial conditions will be non-negative for all $t > 0$.

Theorem 1. *Let $S_H(0), E_H(0), I_H(0), R_H(0), S_V(0), E_V(0), I_V(0)$ be non-negative, then the solutions ($S_H(t)$, $E_H(t)$, $I_H(t)$, $R_H(t)$, $S_V(t)$, $E_V(t)$, $I_V(t)$) of the system (1) are non-negative for all $t > 0$.*

Proof. Let $t^* := \sup\{t > 0 : S_H(t) > 0, E_H(t) > 0, I_H(t) > 0, R_H(t) > 0, S_V(t) > 0, E_V(t) > 0, I_V(t) > 0\}$, then $t^* > 0$. Then from equation (1a) we have that

$$\begin{aligned}\frac{dS_H}{dt} &= \Lambda_H + (\phi + \tau u_3)(1-\nu)I_H + \varphi_H R_H \\ &\quad - \frac{\beta_1 \varepsilon \rho (1-u_1) I_V S_H}{N_H} - \frac{\beta c (1-u_2) E_H S_H}{N_H} - \frac{\beta \kappa (1-u_2) I_H S_H}{N_H} - \mu_H S_H \\ &\geq \Lambda_H - \left\{ \frac{\beta_1 \varepsilon \rho (1-u_1) I_V}{N_H} + \frac{\beta c (1-u_2) E_H}{N_H} + \frac{\beta \kappa (1-u_2) I_H}{N_H} + \mu_H \right\} S_H,\end{aligned}$$

which can be re-written as

$$\frac{d}{dt}\left[S_H(t) e^{\int_0^t \{\lambda_1(1-u_1)+\lambda_2(1-u_2)+\lambda_3(1-u_2)\}(s)ds + \mu_H t} \right] \geq \Lambda_H e^{\int_0^t \{\lambda_1(1-u_1)+\lambda_2(1-u_2)+\lambda_3(1-u_2)\}(s)ds + \mu_H t},$$

where we set as abbreviations $\lambda_1 := \frac{\beta_1 \varepsilon \rho I_V}{N_H}, \lambda_2 := \frac{\beta c E_H}{N_H}, \lambda_3 := \frac{\beta \kappa I_H}{N_H}$. Integrating both sides from $t = 0$ to $t = t^*$ and re-arranging we get

$$\begin{aligned}S_H(t^*) &\geq S_H(0)\left\{ e^{-\int_0^{t^*} \{\lambda_1(1-u_1)+\lambda_2(1-u_2)+\lambda_3(1-u_2)\}(s)ds + \mu_H t^*} \right\} \\ &\quad + \left\{ e^{-\int_0^{t^*} \{\lambda_1(1-u_1)+\lambda_2(1-u_2)+\lambda_3(1-u_2)\}(s)ds + \mu_H t^*} \right\} \\ &\quad \times \left\{ \int_0^{t^*} \Lambda_H e^{\int_0^u \{\lambda_1(1-u_1)+\lambda_2(1-u_2)+\lambda_3(1-u_2)\}(x)dx + \mu_H u}\, du \right\} > 0.\end{aligned}$$

Thus, $S_H(t^*)$ being greater or equal than the sum of positive terms, it is also positive. By same argument, it is proved that $E_H > 0, I_H > 0, R_H > 0, S_V > 0, E_V > 0, I_V > 0$ for all $t > 0$. □

3.2 Invariant Region

Theorem 2. *Let $(S_H, E_H, I_H, R_H, S_V, E_V, I_V)$ be the solution of the system (1) with initial conditions and the biological feasible region $\Omega := \Omega_H \times \Omega_V$ with*

$$\Omega_H := \left\{ (S_H, E_H, I_H, R_H) \in \mathbb{R}^4_+ \mid N_H \leq \frac{\Lambda_H}{\mu_H} \right\}$$

and

$$\Omega_V := \left\{ (S_V, E_V, I_V) \in \mathbb{R}^3_+ \mid N_V \leq \frac{\Lambda_V}{(\mu_V + \theta u_4)} \right\}.$$

Then, Ω is positively invariant and attracting with respect to the flow described by system (1).

Proof. Adding the expression in the right hand sides of the equations (1a)-(1g) in system (1) gives system (1h)-(1i). The number of infected humans is bounded by the total population, i.e., $0 \leq I_H \leq N_H$. From $N_H \geq \frac{\Lambda_H}{\mu_H}$ (in the definition of Ω_H) and equation (1h) it follows

$$\frac{dN_H}{dt} \leq \Lambda_H - \mu_H N_H \leq 0.$$

Similarly, from $N_V \geq \frac{\Lambda_V}{(\mu_V + \theta u_4)}$ (in the definition of Ω_V) and equation (1i) it follows

$$\frac{dN_V}{dt} \leq \Lambda_V - (\mu_V + \theta u_4) N_V \leq 0.$$

By a standard comparison theorem [22], it follows that

$$0 \leq N_H(t) \leq N_H(0) e^{-\mu_H t} + \frac{\Lambda_H}{\mu_H}(1 - e^{-\mu_H t})$$

and

$$0 \leq N_V(t) \leq N_V(0)e^{-(\mu_V+\theta u_4)t} + \frac{\Lambda_V}{(\mu_V+\theta u_4)}(1-e^{-(\mu_V+\theta u_4)t}).$$

Hence, the set Ω is positively invariant. Thus for $t \to \infty$ we have that $0 \leq N_H \leq \frac{\Lambda_H}{\mu_H}$ and $0 \leq N_V \leq \frac{\Lambda_V}{(\mu_V+\theta u_4)}$, hence Ω is an attracting set. □

3.3 Zika Virus Free Equilibrium

In order to study the behaviour of the Zika virus model at its equilibrium, we set the right hand side of all the equations in system (1) to zero. Thus at this disease free state, $E_H^* = I_H^* = R_H^* = E_V^* = I_V^* = 0$, and the Zika virus model has a disease free equilibrium point given at

$$E_0 = (S_H^*, E_H^*, I_H^*, R_H^*, S_V^*, E_V^*, I_V^*) = \left(\frac{\Lambda_H}{\mu_H}, 0, 0, 0, \frac{\Lambda_V}{(\mu_V+\theta u_4)}, 0, 0\right). \tag{2}$$

3.4 Basic Reproduction Number

The matrices F and V (defined and derived as in [23]) for the new infection terms and remaining transfer terms at disease free equilibrium respectively are given by

$$F = \begin{bmatrix} \beta c(1-u_2) & \beta\kappa(1-u_2) & 0 & \beta_1\varepsilon\rho(1-u_1) \\ 0 & 0 & 0 & 0 \\ 0 & \frac{\beta_2\varepsilon\rho(1-u_1)\Lambda_V\mu_H}{\Lambda_H(\mu_V+\theta u_4)} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} (\alpha_H+\mu_H) & 0 & 0 & 0 \\ -\alpha_H & (\phi+\tau u_3+\mu_H+\delta_H) & 0 & 0 \\ 0 & 0 & (\alpha_V+\mu_V+\theta u_4) & 0 \\ 0 & 0 & -\alpha_V & (\mu_V+\theta u_4) \end{bmatrix},$$

respectively. Thus, the basic reproduction number (also defined as in [23]) is given by

$$R_0 = \sqrt{\frac{\varepsilon^2\rho^2\beta_1\beta_2\alpha_H\alpha_V\Lambda_V(1-u_1)^2\mu_H + (\alpha_H+\mu_H-\beta c(1-u_2))(\mu_V+\theta u_4)\beta\kappa\alpha_H(1-u_2)}{\Lambda_H(\alpha_H+\mu_H-\beta c(1-u_2))(\phi+\tau u_3+\mu_H+\delta_H)(\alpha_V+\mu_V+\theta u_4)(\mu_V+\theta u_4)^2}}.$$

3.5 Stability Analysis for the Zika Virus Free Equilibrium

At the disease free equilibrium point, the Jacobian of the subsystem (1a)-(1g) is

$$J_0 = \begin{bmatrix} -\mu_H & -\beta c(1-u_2) & Q_6 & \varphi_H & 0 & 0 & -\beta_1\varepsilon\rho(1-u_1) \\ 0 & -Q_1 & \beta\kappa(1-u_2) & 0 & 0 & 0 & \beta_1\varepsilon\rho(1-u_1) \\ 0 & \alpha_H & -Q_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & (\phi+\tau u_3)\nu & -Q_5 & 0 & 0 & 0 \\ 0 & 0 & -\frac{\beta\varepsilon\rho(1-u_1)\Lambda_V\mu_H}{(\mu_V+\theta\mu_4)} & 0 & -Q_4 & 0 & 0 \\ 0 & 0 & \frac{\beta\varepsilon\rho(1-u_1)\Lambda_V\mu_H}{(\mu_V+\theta\mu_4)} & 0 & 0 & -Q_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\alpha_V & -Q_4 \end{bmatrix}$$

where as abbreviations we set

$$\begin{aligned} Q_1 &:= (\alpha_H+\mu_H-\beta c(1-u_2)), \\ Q_2 &:= (\phi+\tau u_3+\mu_H+\delta_H), \\ Q_3 &:= (\varphi_H+\mu_H), \\ Q_4 &:= (\mu_V+\theta u_4), \\ Q_5 &:= (\mu_V+\alpha_V+\theta\mu_4), \\ Q_6 &:= ((\phi+\tau u_3)(1-\nu)-\beta\kappa(1-u_2)). \end{aligned}$$

There are seven Eigenvalues for the Zika virus model, three of the Eigenvalues are $-\mu_H, -(\mu_V+\theta u_4)$ and $-(\varphi_H+\mu_H)$. The other four Eigenvalues are the solution of the 4th order polynomial

$$f(\lambda) = \lambda^4 + k_1\lambda^3 + k_2\lambda^2 + k_3\lambda + k_4, \tag{3}$$

where as abbreviations we set

$$\begin{aligned} k_1 &:= Q_1 + Q_2 + Q_3 + Q_4, \\ k_2 &:= (Q_3(Q_1 + Q_2) + Q_4(Q_1 + Q_2 + Q_3) + Q_1Q_2 - \beta\kappa\alpha_H(1 - u_2)), \\ k_3 &:= (Q_3Q_4(Q_1 + Q_2) + (Q_3 + Q_3)(Q_1Q_2 - \beta\kappa\alpha_H(1 - u_2))), \\ k_4 &:= Q_1Q_2Q_3Q_4(1 - R_0). \end{aligned}$$

The coefficient k_1 is always positive, but k_2, k_3, and k_4 maybe not: We can see that if $R_0 < 1$, then $k_4 > 0$, and $Q_1Q_2 > \beta\kappa\alpha_H(1 - u_2)$, $k_2 > 0$ and $k_3 > 0$. Thus $k_i > 0$ for all $i = 1, 2, 3, 4$, and this implies that there are no positive real solution for the polynomial. Applying the Routh-Hurwitz criterion [24] to the polynomial equation (3), we have that all determinants of the Hurwitz matrices are positive. Thus, if $R_0 < 1$, the disease free equilibrium is locally asymptotically stable.

If $R_0 > 1$, then $k_4 < 0$, we have that $f(0) < 0$ and $\lim_{\lambda\to\infty} f(\lambda) = \infty$. Thun there exist a $\lambda^* > 0$ with $f(\lambda^*) = 0$. This implies the instability of the disease free equilibrium.

Note that if $R_0 = 1$, the disease will also die out.

4 Economic Assessment of the Zika Virus Model

In this section, in line with what is obtain in [25], we economically assess the intervention strategies through the use of optimal control and a cost effectiveness analysis. This is to enable use make informed decision as to the most cost effective strategy among the interventions under consideration. The cost objective function [26] that we aim to minimize in the variables (u_1, u_2, u_3, u_4) is given by

$$C_f = \int_0^T [((m_1u_1(t) + m_2u_2(t))(S_H(t) + E_H(t)) + m_3\tau u_3(t)I_H(t) + m_4\theta u_4(t)N_V(t)]e^{-\eta t}dt, \tag{4}$$

subject to the differential equations of model (1a-1g) (1). Here m_1 is the cost of treated bednets, m_2 is the cost of condoms, m_3 is the cost of treatment and m_4 is the cost of indoor residual spray. η is a discount rate [26], typically between 3% and 5%.

When denoting by λ_{S_H} , λ_{E_H} , λ_{I_H}, λ_{R_H} , λ_{S_V} , λ_{E_V}, and λ_{I_V} the shadow prices associated with their respective classes, the Hamiltonian equation for the cost function is give as

$$\begin{aligned} H_{C_f} &= [((m_1u_1(t) + m_2u_2(t))(S_H(t) + E_H(t)) + m_3\tau u_3(t)I_H(t) + m_4\theta u_4(t)N_V(t)]e^{-\eta t} \\ &\quad +\lambda_{S_H}\tfrac{dS_H}{dt} + \lambda_{E_H}\tfrac{dE_H}{dt} + \lambda_{I_H}\tfrac{dI_H}{dt} + \lambda_{R_H}\tfrac{dR_H}{dt} + \lambda_{S_V}\tfrac{dS_V}{dt} + \lambda_{E_V}\tfrac{dE_V}{dt} + \lambda_{I_V}\tfrac{dI_V}{dt}. \end{aligned} \tag{5}$$

We now substitute equation (1) into equation (5) to get the corresponding Hamiltonian and applying Pontryagin's maximum principle [25] we obtain

$$\begin{aligned} -\frac{\partial\lambda_{S_H}}{\partial t} &= -m_1u_1e^{-\eta t} - m_2u_2e^{-\eta t} \\ &\quad +(\lambda_{S_H} - \lambda_{E_H})\left[\frac{\beta_1\varepsilon\rho(1 - u_1)I_V}{N_H} + \frac{\beta c(1 - u_2)E_H}{N_H} + \frac{\beta\kappa(1 - u_2)I_H}{N_H}\right] + \mu_H\lambda_{S_H}, \\ -\frac{\partial\lambda_{E_H}}{\partial t} &= -m_1u_1e^{-\eta t} - m_2u_2e^{-\eta t} + (\lambda_{S_H} - \lambda_{E_H})\frac{\beta c(1 - u_2)S_H}{N_H} + (\lambda_{E_H} - \lambda_{I_H})\alpha_H + \mu_H\lambda_{E_H}, \\ -\frac{\partial\lambda_{E_H}}{\partial t} &= -m_3\tau u_3e^{-\eta t} + (\lambda_{S_H} - \lambda_{E_H})\frac{\beta\kappa(1 - u_2)S_H}{N_H} + (\lambda_{S_V} - \lambda_{E_V})\frac{\beta_2\varepsilon\rho(1 - u_1)S_V}{N_V} \\ &\quad +(\phi + \tau u_3)\nu\lambda_{R_H} - (\phi + \tau u_3)(1 - \nu)\lambda_{S_H} + (\phi + \tau u_3 + \mu_H + \delta_H)\lambda_{I_H}, \\ -\frac{\partial\lambda_{R_H}}{\partial t} &= (\lambda_{R_H} - \lambda_{S_H})\varphi_H + \mu_H\lambda_{R_H}, \\ -\frac{\partial\lambda_{S_V}}{\partial t} &= -m_4\theta u_4e^{-\eta t} + (\lambda_{S_V} - \lambda_{E_V})\frac{\beta_2\varepsilon\rho(1 - u_1)I_H}{N_H} + (\mu_V + \theta u_4)\lambda_{S_V}, \\ -\frac{\partial\lambda_{E_V}}{\partial t} &= -m_4\theta u_4e^{-\eta t} + (\lambda_{E_V} - \lambda_{I_V})\alpha_V + (\mu_V + \theta u_4)\lambda_{E_V}, \\ -\frac{\partial\lambda_{I_V}}{\partial t} &= -m_4\theta u_4e^{-\eta t} + (\lambda_{S_V} - \lambda_{E_V})\frac{\beta_2\varepsilon\rho(1 - u_1)S_H}{N_H} + (\mu_V + \theta u_4)\lambda_{I_V}, \end{aligned}$$

and

$$\begin{aligned}
\frac{dS_H}{dt} &= \frac{\partial H_{C_f}}{\partial S_H}, \\
\frac{dE_H}{dt} &= \frac{\partial H_{C_f}}{\partial E_H}, \\
\frac{dI_H}{dt} &= \frac{\partial H_{C_f}}{\partial I_H}, \\
\frac{dR_H}{dt} &= \frac{\partial H_{C_f}}{\partial R_H}, \\
\frac{dS_V}{dt} &= \frac{\partial H_{C_f}}{\partial S_V}, \\
\frac{dE_H}{dt} &= \frac{\partial H_{C_f}}{\partial E_H}, \\
\frac{dI_H}{dt} &= \frac{\partial H_{C_f}}{\partial I_H}.
\end{aligned}$$

4.1 An Economic Assessment of Treated Bednets

Differentiating the Hamiltonian H_{C_f} with respect to the use of treated bednets u_1 we obtain

$$\frac{\partial H_{C_f}}{\partial u_1} = m_1 e^{-\eta t}(S_H + E_H) + \left[(\lambda_{E_H} - \lambda_{S_H})\frac{\beta_1 \varepsilon \rho I_V S_H}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_1 \varepsilon \rho I_H S_V}{N_H}\right], \tag{6}$$

where

$$m_1 e^{-\eta t}(S_H + E_H)$$

is the marginal cost of using treated bednets, and

$$(\lambda_{E_H} - \lambda_{S_H})\frac{\beta_1 \varepsilon \rho I_V S_H}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_1 \varepsilon \rho I_H S_V}{N_H}$$

is the marginal benefit from the use of treated bednets. The optimal policy is attained when the marginal cost of using treated bednets is equal to marginal benefit as a result of the use of treated bednets. From (6) we have the following bounds:

$$u_1(t) \in \begin{cases} \{0\}, \text{ if} & m_1 e^{-\eta t}(S_H + E_H) > (\lambda_{E_H} - \lambda_{S_H})\frac{\beta_1 \varepsilon \rho I_V S_H}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_1 \varepsilon \rho I_H S_V}{N_H}, \\ (0,1), \text{ if} & m_1 e^{-\eta t}(S_H + E_H) = (\lambda_{E_H} - \lambda_{S_H})\frac{\beta_1 \varepsilon \rho I_V S_H}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_1 \varepsilon \rho I_H S_V}{N_H}, \\ \{1\}, \text{ if} & m_1 e^{-\eta t}(S_H + E_H) < (\lambda_{E_H} - \lambda_{S_H})\frac{\beta_1 \varepsilon \rho I_V S_H}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_1 \varepsilon \rho I_H S_V}{N_H}. \end{cases}$$

The implication of this is that a Zika virus prevention by the use of treated bednets will attain its optimum when the marginal benefit is greater than the marginal cost for the use of treated bednets. Therefore, all susceptible and exposed humans are encouraged to use treated bednets in the quest to combat the scourge. The effective use of treated bednets will increase the number of susceptible humans and uninfected mosquitoes since the treated bednets serve as a barrier between human and mosquitoes.

4.2 An Economic Assessment of Condoms

Differentiating H_{C_f} with respect to the use of condoms u_2 we obtain

$$\frac{\partial H_{C_f}}{\partial u_2} = m_2 e^{-\eta t}(S_H + E_H) + \left[(\lambda_{E_H} - \lambda_{S_H})\frac{\beta c I_H S_H}{N_H} + (\lambda_{E_H} - \lambda_{S_H})\frac{\beta \kappa I_H S_H}{N_H}\right], \tag{7}$$

where

$$m_2 e^{-\eta t}(S_H + E_H)$$

is the marginal cost of acquiring condoms and

$$(\lambda_{E_H} - \lambda_{S_H})\frac{\beta c I_H S_H}{N_H} + (\lambda_{E_H} - \lambda_{S_H})\frac{\beta \kappa I_H S_H}{N_H}$$

is the marginal benefit. The optimal policy is attained when the marginal cost for using condoms is equal to marginal benefit from the use of condoms. From (7) we have the following bounds:

$$u_2(t) \in \begin{cases} \{0\}, \text{ if} & m_2 e^{-\eta t}(S_H + E_H) > (\lambda_{E_H} - \lambda_{S_H})\frac{\beta c I_H S_H}{N_H} + (\lambda_{E_H} - \lambda_{S_H})\frac{\beta \kappa I_H S_H}{N_H}, \\ (0,1), \text{ if} & m_2 e^{-\eta t}(S_H + E_H) = (\lambda_{E_H} - \lambda_{S_H})\frac{\beta c I_H S_H}{N_H} + (\lambda_{E_H} - \lambda_{S_H})\frac{\beta \kappa I_H S_H}{N_H}, \\ \{1\}, \text{ if} & m_2 e^{-\eta t}(S_H + E_H) < (\lambda_{E_H} - \lambda_{S_H})\frac{\beta c I_H S_H}{N_H} + (\lambda_{E_H} - \lambda_{S_H})\frac{\beta \kappa I_H S_H}{N_H}. \end{cases}$$

The implication of this is that a Zika virus prevention by the use of condoms will attain optimality when the marginal benefit is greater than the marginal cost using the condoms. Therefore, all susceptible and exposed humans are encouraged to use condoms in the quest to combat the scourge. The effective use of condoms will increase the number of susceptible humans.

4.3 An Economic Assessment of Treatment

Differentiating H_{C_f} with respect to the treatment u_3 we obtain

$$\frac{\partial H_{C_f}}{\partial u_3} = m_3 e^{-\eta t}\tau I_H + \tau\left[\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H}\right] I_H, \tag{8}$$

where

$$m_3 e^{-\eta t}\tau I_H$$

is the marginal cost of treatment and

$$\tau\left[\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - (\lambda_{S_H}\right] I_H$$

is the marginal benefit. The optimal policy is attained when the marginal cost of a treatment is equal to marginal benefit from a treatment. From (8) we have the following bounds:

$$u_3(t) \in \begin{cases} \{0\}, \text{ if} & m_3 e^{-\eta t}\tau I_H > \tau\left[\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H}\right] I_H, \\ (0,1), \text{ if} & m_3 e^{-\eta t}\tau I_H = \tau\left[\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H}\right] I_H, \\ \{1\}, \text{ if} & m_3 e^{-\eta t}\tau I_H < \tau\left[\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H}\right] I_H. \end{cases}$$

If the marginal benefit of a treatment is higher than the marginal cost for being treated then all infected humans will pursue full treatment. If not, then only few infected human will pursue treatment.

4.4 Economic Assessment of Indoor Residual Spray

Differentiating H_{C_f} with respect to the use of indoor residual spray u_4 we obtain

$$\frac{\partial H_{C_f}}{\partial u_4} = m_4\theta e^{-\eta t} N_V + \theta(S_V\lambda_{S_V} + E_V\lambda_{E_V} + I_V\lambda_{I_V}), \tag{9}$$

where $m_4\theta e^{-\eta t}N_V$ is the marginal cost of acquiring indoor residual spray and $\theta(S_V\lambda_{S_V} + E_V\lambda_{E_V} + I_V\lambda_{I_V})$ is the marginal benefit. The optimal policy is attained when the marginal cost for using an indoor residual spray is equal to the marginal benefit as a result of the use of indoor residual spray.

From (9) we obtain bounds on the optimal policy as

$$u_4(t) \in \begin{cases} \{0\}, \text{ if} & m_4\theta e^{-\eta t}N_V > \theta(S_V\lambda_{S_V} + E_V\lambda_{E_V} + I_V\lambda_{I_V}), \\ (0,1), \text{ if} & m_4\theta e^{-\eta t}N_V = \theta(S_V\lambda_{S_V} + E_V\lambda_{E_V} + I_V\lambda_{I_V}), \\ \{1\}, \text{ if} & m_4\theta e^{-\eta t}N_V < \theta(S_V\lambda_{S_V} + E_V\lambda_{E_V} + I_V\lambda_{I_V}). \end{cases}$$

If the marginal benefit of the use of indoor residual spray is higher than the marginal cost of the use of indoor residual spray then all susceptible individuals will seek protection through the use of indoor residual spray, because that is the optimal strategy then.

5 Analysis of Optimal Control of the Zika Virus Model

To investigate the optimal efforts needed to control the Zika virus, we consider the objective functional

$$J(u_1,u_2,u_3,u_4) = \int_0^{T_f}\left[A_1E_H + A_2I_H + A_3N_V + \frac{1}{2}(C_1u_1^2 + C_2u_2^2 + C_3u_3^2 + C_4u_4^2)\right]e^{-\eta t}dt, \tag{10}$$

subject to equations of the model (1) and the total cost function give by

$$C_f = \int_0^{T}[((m_1u_1 + m_2u_2)(S_H + E_H) + m_3\tau u_3 I_H + m_4\theta u_4 N_V]dt, \tag{11}$$

where A_1,A_2 represents the weight constants of the exposed, infected human population and A_3 represents the weight constant of the mosquitoes total population. C_1, C_2, C_3 and C_4 are weight constants for use of treated

bednets, condoms, treatment and indoor residual spray. Keeping in line with what is in other literature on cost of control of epidemics, we assume that there is no linear relationship between the coverage of these interventions and their corresponding costs, hence we choose a quadratic cost on the controls [27, 28, 29, 26]. Our goal with the given objective function is to minimize the number of infected humans, exposed human and total mosquito population, while minimizing the cost of control $u_1(t)$, $u_2(t)$, $u_3(t)$ and $u_4(t)$. We seek an optimal control u_1^*, u_2^*, u_3^* and u_4^* such that

$$(u_1^*(t), u_2^*(t), u_3^*(t), u_4^*(t)) = min\{J(u_1, u_2, u_3, u_4), (u_1, u_2, u_3, u_4) \in U\}, \tag{12}$$

where U is the set of measurable functions defined from $[0, T_f]$ onto $[0, 1]$. We use Pontryangin's Maximum Principle to solve the optimal control problem and the derivation of necessary conditions.

The Hamiltonian H from the objective function (10) subject to (1) and cost function (11) is

$$\begin{aligned}
H &= [A_1E_H + A_2I_H + A_3N_V + \frac{1}{2}(C_1u_1^2 + C_2u_2^2 + C_3u_3^2 + C_4u_4^2)]e^{-\eta t} && \text{(13a)}\\
&+\lambda_{S_H}\left[\Lambda_H + (\phi + \tau u_3)(1-\nu)I_H + \varphi_H R_H - \frac{\beta_1\varepsilon\rho(1-u_1)I_V S_H}{N_H}\right.\\
&\qquad \left. - \frac{\beta c(1-u_2)E_H S_H}{N_H} - \frac{\beta c(1-u_2)I_H S_H}{N_H} - \mu_H S_H\right] && \text{(13b)}\\
&+\lambda_{E_H}\left[\frac{\beta_1\varepsilon\rho(1-u_1)I_V S_H}{N_H} + \frac{\beta c(1-u_2)E_H S_H}{N_H}\right.\\
&\qquad \left. + \frac{\beta c(1-u_2)I_H S_H}{N_H} - \alpha_H E_H - \mu_H E_H\right] && \text{(13c)}\\
&+\lambda_{I_H}[\alpha_H E_H - (\phi + \tau u_3)(1-\nu)I_H - (\phi + \tau u_3)\nu I_H - \mu_H I_H - \delta_H I_H] && \text{(13d)}\\
&+\lambda_{R_H}[(\phi + \tau u_3)\nu I_H - \varphi_H R_H - \mu_H R_H] && \text{(13e)}\\
&+\lambda_{S_V}\left[\Lambda_V - \frac{\beta_2\varepsilon\rho(1-u_1)I_H S_V}{N_H} - (\mu_V + \theta u_4)S_V\right] && \text{(13f)}\\
&+\lambda_{E_V}\left[\frac{\beta_2\varepsilon\rho(1-u_1)I_H S_V}{N_H} - \alpha_V E_V - (\mu_V + \theta u_4)E_V\right] && \text{(13g)}\\
&+\lambda_{I_V}[\alpha_V I_V - (\mu_V + \theta u_4)I_V] && \text{(13h)}\\
&+\lambda_{C_f}[((m_1u_1 + m_2u_2)(S_H + E_H)) + m_3\tau u_3 I_H + m_4\theta u_4 N_V], && \text{(13i)}
\end{aligned}$$

where λ_{S_H}, λ_{E_H}, λ_{I_H}, λ_{R_H}, λ_{S_V}, λ_{E_V}, and λ_{I_V} are the co-state variables given by the system

$$\begin{aligned}
\frac{\partial\lambda_{S_H}}{\partial t} &= (\lambda_{S_H} - \lambda_{E_H})\left[\frac{\beta_1\varepsilon\rho(1-u_1)I_V}{N_V} + \frac{\beta c(1-u_2)E_H}{N_H} + \frac{\beta\kappa(1-u_2)I_H}{N_H}\right]\\
&\quad +\mu_H\lambda_{S_H} - (m_1u_1 + m_2u_2)\lambda_{C_f} && \text{(14a)}\\
\frac{\partial\lambda_{E_H}}{\partial t} &= (\lambda_{S_H} - \lambda_{E_H})\frac{\beta c(1-u_2)S_H}{N_H} + \mu_H\lambda_{E_H}\\
&\quad +(\lambda_{E_H} - \lambda_{I_H}) - (m_1u_1 + m_2u_2)\lambda_{C_f} - A_1 && \text{(14b)}\\
\frac{\partial\lambda_{I_H}}{\partial t} &= (\lambda_{S_H} - \lambda_{E_H})\frac{\beta\kappa(1-u_2)S_H}{N_H} + (\lambda_{S_H} - \lambda_{E_H})\frac{\beta_2\varepsilon\rho(1-u_1)S_V}{N_V} +\\
&\quad (\phi + \tau u_3)\nu\lambda_{R_H} - (\phi + \tau u_3)(1-\nu)\lambda_{S_H} + (\phi + \mu_H + \tau u_3 + \delta_H)\lambda_{I_H}\\
&\quad -m_3\tau u_3\lambda_{C_f} - A_2 && \text{(14c)}\\
\frac{\partial\lambda_{R_H}}{\partial t} &= (\lambda_{R_H} - \lambda_{S_H})\varphi_H + \mu_H\lambda_{R_H} && \text{(14d)}\\
\frac{\partial\lambda_{S_V}}{\partial t} &= (\lambda_{S_V} - \lambda_{E_V})\frac{\beta_2\varepsilon\rho(1-u_1)I_H}{N_V} + (\mu_V + \theta u_4)\lambda_{S_V} - m_4\theta u_4\lambda_{C_f} - A_3 && \text{(14e)}\\
\frac{\partial\lambda_{E_V}}{\partial t} &= (\lambda_{E_V} - \lambda_{I_V})\alpha_V + (\mu_V + \theta u_4)\lambda_{E_V} - m_4\theta u_4\lambda_{C_f} - A_3 && \text{(14f)}\\
\frac{\partial\lambda_{I_V}}{\partial t} &= (\lambda_{S_V} - \lambda_{E_V})\frac{\beta_1\varepsilon\rho(1-u_1)S_H}{N_V} + (\mu_V + \theta u_4)\lambda_{I_V} - m_4\theta u_4\lambda_{C_f} - A_3 && \text{(14g)}\\
\frac{\partial\lambda_{C_f}}{\partial t} &= 0 && \text{(14h)}
\end{aligned}$$

By applying Pontryagin's maximum principle [25] and an existence result for an optimal control (see [30]), we obtain

Theorem 3. *An optimal control $(u_1^*, u_2^*, u_3^*, u_4^*)$ that minimizes $J(u_1, u_2, u_3, u_4)$ is given by*

$$u_1^* = \max\left\{0, \min\left(1, \frac{\left[(\lambda_{E_H} - \lambda_{S_H})\frac{\beta_1 \varepsilon \rho I_V^* S_H^*}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_2 \varepsilon \rho I_H^* S_V^*}{N_H} + m_1 \lambda_{C_f}(S_H^* + E_H^*)\right]}{C_1} e^{-\eta t}\right)\right\}, \tag{15a}$$

$$u_2^* = \max\left\{0, \min\left(1, \frac{\left[(\lambda_{E_H} - \lambda_{S_H})\frac{\beta c E_H^* S_H^*}{N_H} + (\lambda_{E_H} - \lambda_{S_H})\frac{\beta \kappa E_H^* S_H^*}{N_H} + m_2 \lambda_{C_f}(S_H^* + E_H^*)\right]}{C_2} e^{-\eta t}\right)\right\}, \tag{15b}$$

$$u_3^* = \max\left\{0, \min\left(1, \frac{\left[\tau(\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H})I_H^* + m_3 \lambda_{C_f} I_H^*\right]}{C_3} e^{-\eta t}\right)\right\}, \tag{15c}$$

$$u_4^* = \max\left\{0, \min\left(1, \frac{\left[\theta(S_V^* \lambda_{S_V} + E_V^* \lambda_{E_H} + I_V^* \lambda_{I_H}) + m_4 \lambda_{C_f}(S_V^* + E_V^* + I_V^*)\right]}{C_4} e^{-\eta t}\right)\right\}, \tag{15d}$$

where λ_{S_H}, λ_{E_H}, λ_{I_H}, λ_{R_H}, λ_{S_V}, λ_{E_V}, and λ_{I_V} are the adjoint variables satisfying (14) and the following transversality conditions:

$$\lambda_{S_H}(T_f) = \lambda_{E_H}(T_f) = \lambda_{I_H}(T_f) = \lambda_{R_H}(T_f) = \lambda_{S_V}(T_f) = \lambda_{E_V}(T_f) = \lambda_{I_V}(T_f) = \lambda_{C_f}(T) = 0. \tag{16}$$

Proof. From [30], the existence of an optimal control is a consequence of the convexity of the integrand of J with respect to u_1, u_2, u_3, and u_4, a priori boundedness of the state variables, and the Lipschitz property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by differentiating the Hamiltonian function, evaluated at the optimal control. Then the adjoint system can be written as:

$$0 = \frac{\partial H}{\partial u_1} = u_1^* C_1 e^{-\eta t} + \left[(\lambda_{E_H} - \lambda_{S_H})\frac{\beta_1 \varepsilon \rho I_V^* S_H^*}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_2 \varepsilon \rho I_H^* S_V^*}{N_H} + m_1 \lambda_{C_f}(S_H^* + E_H^*)\right], \tag{17a}$$

$$0 = \frac{\partial H}{\partial u_2} = u_2^* C_2 e^{-\eta t} + \left[(\lambda_{E_H} - \lambda_{S_H})\frac{\beta c E_H^* S_H^*}{N_H} + (\lambda_{E_H} - \lambda_{S_H})\frac{\beta \kappa I_H^* S_H^*}{N_H} + m_2 \lambda_{C_f}(S_H^* + E_H^*)\right], \tag{17b}$$

$$0 = \frac{\partial H}{\partial u_3} = u_3^* C_3 e^{-\eta t} + \left[\tau(\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H})I_H^* + m_3 \lambda_{C_f} I_H^*\right], \tag{17c}$$

$$0 = \frac{\partial H}{\partial u_4} = u_4^* C_4 e^{-\eta t} + \left[\theta(S_V^* \lambda_{S_V} + E_V^* \lambda_{E_H} + I_V^* \lambda_{I_H}) + m_4 \lambda_{C_f}(S_V^* + E_V^* + I_V^*)\right]. \tag{17d}$$

From (17), we obtain

$$\begin{aligned}
u_1^* &= \frac{\left[(\lambda_{E_H} - \lambda_{S_H})\frac{\beta_1 \varepsilon \rho I_V^* S_H^*}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_2 \varepsilon \rho I_H^* S_V^*}{N_H} + m_1 \lambda_{C_f}(S_H^* + E_H^*)\right]}{C_1}, \\
u_2^* &= \frac{\left[(\lambda_{E_H} - \lambda_{S_H})\frac{\beta c E_H^* S_H^*}{N_H} + (\lambda_{E_H} - \lambda_{S_H})\frac{\beta \kappa I_H^* S_H^*}{N_H} + m_2 \lambda_{C_f}(S_H^* + E_H^*)\right]}{C_2}, \\
u_3^* &= \frac{\left[\tau(\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H})I_H^* + m_3 \lambda_{C_f} I_H^*\right]}{C_3}, \\
u_4^* &= \frac{\theta(S_V^* \lambda_{S_V} + E_V^* \lambda_{E_H} + I_V^* \lambda_{I_H}) + m_4 \lambda_{C_f}(S_V^* + E_V^* + I_V^*)}{C_4}.
\end{aligned}$$

Thus, by standard control arguments involving the bounds on the controls, we conclude that

$$\begin{aligned}
u_1^* &= \begin{cases} 0, & \text{if } u_1^* \le 0, \\ u_1^*, & \text{if } 0 < u_1^* < 1, \\ 1, & \text{if } u_1^* \ge 1, \end{cases} \\
u_2^* &= \begin{cases} 0, & \text{if } u_2^* \le 0, \\ u_2^*, & \text{if } 0 < u_2^* < 1, \\ 1, & \text{if } u_2^* \ge 1, \end{cases} \\
u_3^* &= \begin{cases} 0, & \text{if } u_3^* \le 0, \\ u_3^*, & \text{if } 0 < u_3^* < 1, \\ 1, & \text{if } u_3^* \ge 1, \end{cases} \\
u_4^* &= \begin{cases} 0, & \text{if } u_4^* \le 0, \\ u_4^*, & \text{if } 0 < u_4^* < 1, \\ 1, & \text{if } u_4^* \ge 1. \end{cases}
\end{aligned}$$

Due to the a priori boundedness of the state system, adjoint system, and the resulting Lipschitz structure of the ODEs, we obtain the uniqueness of the optimal control for small T_f. The uniqueness of the optimal control follows from the uniqueness of the optimality system, which consists of (14) and (16), with characterization (15). There is a restriction on the length of the time interval in order to guarantee the uniqueness of the optimality system. This smallness restriction of the length on the time is due to the opposite time orientations of (14) and (16); the state problem has initial values, and the adjoint problem has terminal values. We remark that this restriction is common in control problems, see [28, 29, 26]. □

6 Numerical Solution and Cost Effectiveness Analysis

In this section, we examine the Zika virus model and study the effects of combined strategies on the transmission dynamics of the disease. The optimal control set is obtained by solving the optimality system, consisting of the state and adjoint systems. An iterative scheme is used for solving the optimality system. We start to solve the state equations with a guess for the controls over the simulated time using the fourth order Runge–Kutta scheme. Because of the transversality conditions (16), the adjoint equations are solved by a backward fourth order Runge–Kutta scheme using the current iterations' solutions of the state equation. Then the controls are updated by using a convex combination of the previous controls and the value from the characterizations (15). This process is repeated and iterations are stopped if the values of the unknowns at the previous iteration are very close to the ones at the present iteration (see [29]). We chose the following set as weight factors:

$$A_1 = 60, A_2 = 500, A_3 = 60, C_1 = 25, C_2 = 20, C_3 = 30, C_4 = 40,$$

and as initial state variables

$$S_H(0) = 750, E_H(0) = 250, I_H(0) = 10, R_H(0) = 20, S_V(0) = 10000, E_V(0) = 500, I_V(0) = 100$$

to illustrate the effect of different optimal control strategies on the transmission of Zika virus in a population. All numerical simulations were carried out using the parameter values shown in Table 4.

Table 4: Parameter values used for the model simulations

Parameter	Range	Value	Source
ε	$0.3 - 1$	0.5	[31]
β_1	$0.1 - 0.75$	0.4	[31]
β_2	$0.3 - 0.75$	0.5	[32]
$\frac{1}{\alpha_H}$	$2 - 7$	5	[33]
$\frac{1}{\alpha_V}$	$8 - 12$	10	[31, 34]
$\frac{1}{\mu_V}$	$4 - 35$	14	[31, 32]
μ_H		$\frac{1}{(360\times 60)}$	[26]
c	$0 - 1$	0.6	[37]
k	$0 - 1$	0.3	[37]
β	$0 - 001 - 0.10$	0.05	[37]
Λ_H		0.000011	[26]
Λ_V		0.071	[36]
δ_H		0.0003	Assumed
η		$\frac{3}{365} - \frac{5}{365}\%$	[26]
ρ		0.1	Assumed
φ_H		0.02	Assumed
ϕ		0.05	Assumed
ν		0.023	Assumed
m_1		$\$2.5 - 5.0$	[26]
m_2		\$0.24	[35]
m_3		\$2.00	[26]
m_4		\$1.50	[26]
θ		0.75	Assumed
τ		0.15	Assumed

We investigate and compare numerical results in the following scenario:

Strategy A: Treated bednets+condoms+treatment.

Strategy B: Treated bednets+indor residual spray+treatment.

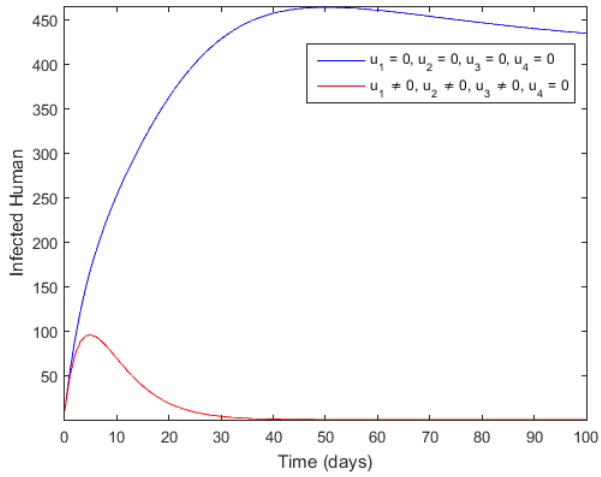
Strategy C: Condoms+indoor residual spray+treatment.

Strategy D: Treated bednets+condoms+indoor residual spray.

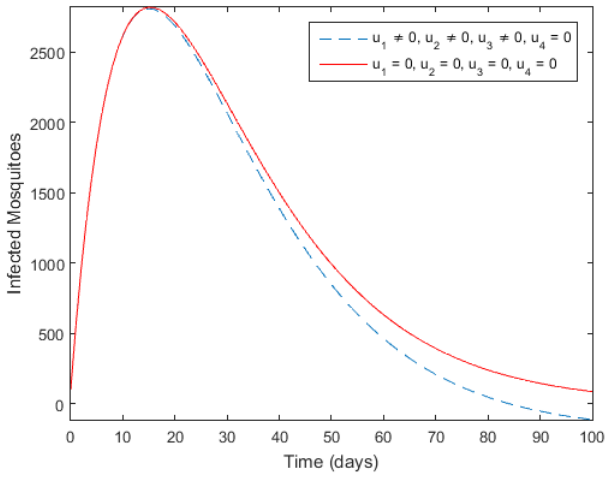
Strategy E: Treated bednets+condoms+indoor residual spray+treatment.

6.1 Strategy A: Treated Bednets, Condoms and Treatment

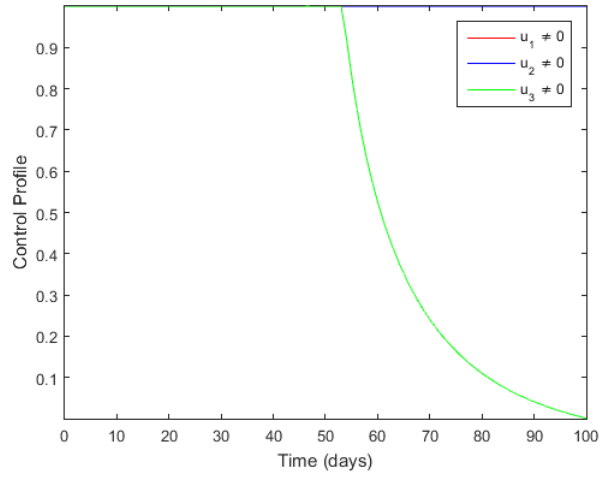
In this strategy, controls u_1, u_2, and u_3 were used to optimize the objective function while we set control u_4 to zero. In Figure 2(a) and Figure 2(b), it is observed that there is a significant drop in the number of infected humans when there is control compared to situation when there is no control. Moreover, a slight change only occurs in the mosquito population. Figure 2(c) and Figure 2(d) represent the control profiles and cost for implementing the strategy. The total cost when the strategy is implemented throughout the simulated time horizon is $\$83,304$. The control profile for u_1 and u_2 are both at their respective upper bound throughout the time horizon, whereas u_3 is at its upper bound for 53 days before dropping to its lower bound.



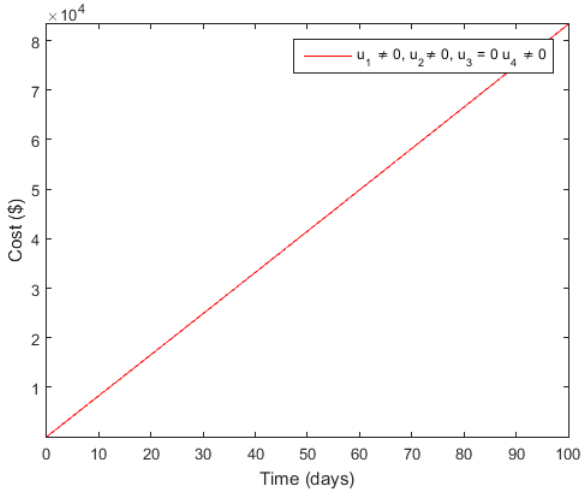
(a) Simulation for infected humans.



(b) Simulation for infected mosquitoes.



(c) Simulation for controls.

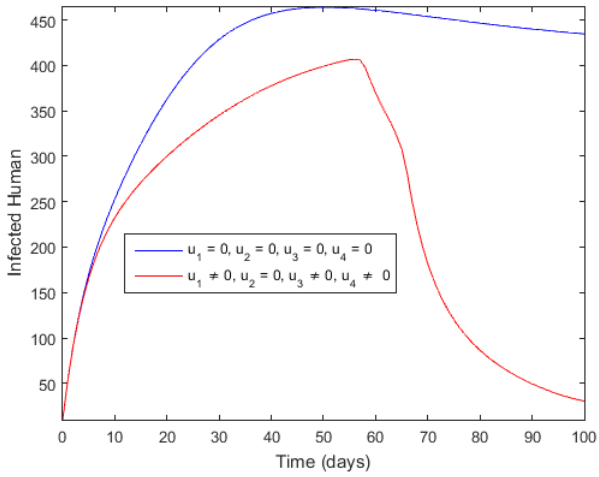


(d) Simulation for cost.

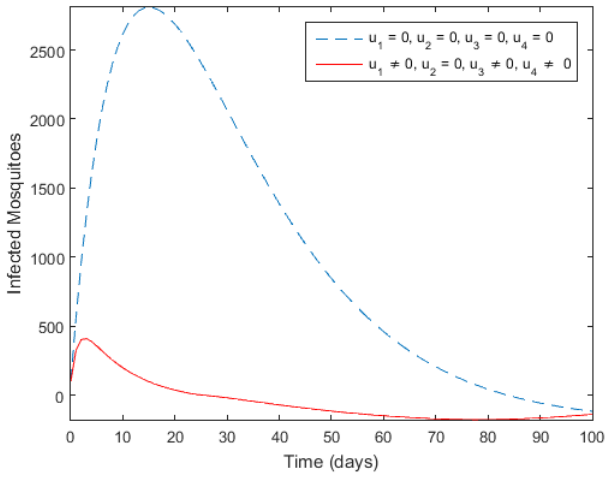
Figure 2: The effects of treated bednets, condoms, and treatment on the transmission of the Zika virus.

6.2 Strategy B: Treated Bednets, Indoor Residual Spray and Treatment

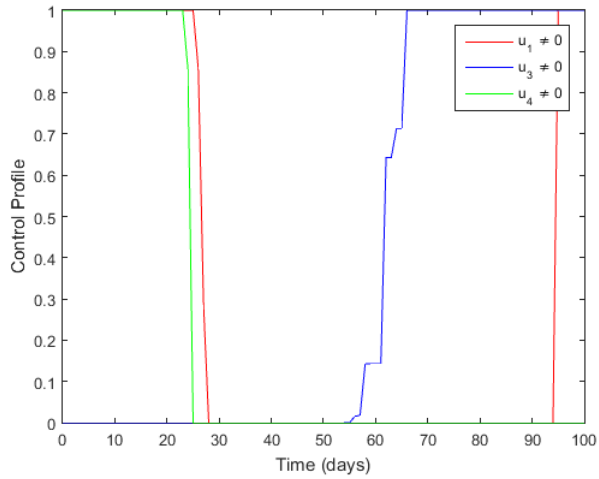
In this strategy, we used controls u_1, u_3, and u_4 to optimize the objective function while we set control u_2 to zero. In Figure 3(a) and Figure 3(b), it is observed that there is a significant drop in both the number of infected humans and the mosquito population when there is control compared to situation when there is no control. Figure 3(c) and Figure 3(d) represent the control profile and cost for implementing strategy B. The total cost when the strategy is implemented throughout the time horizon is $\$36,208$. The control profiles for u_1 and u_4 are both at their respective upper bound for 25 and 23 days, respectively, before dropping to their lower bound. Control function u_3 is at its lower bound for 55 days before jumping to its upper bound.



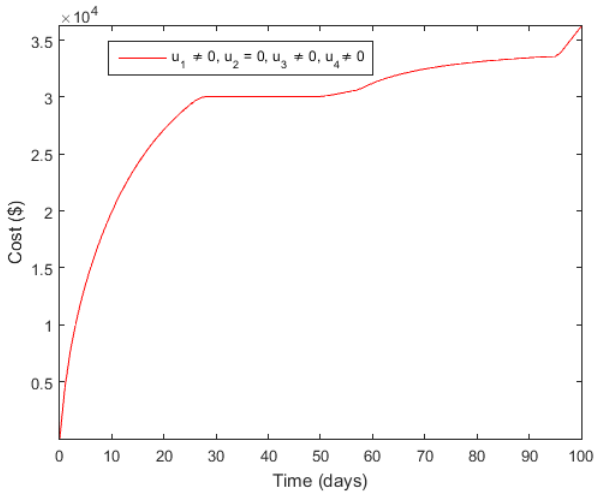
(a) Simulation for infected humans.



(b) Simulation for infected mosquitoes.



(c) Simulation for controls.

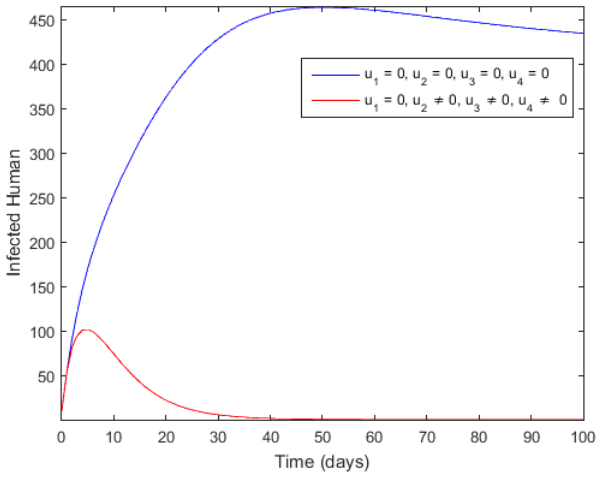


(d) Simulation for cost.

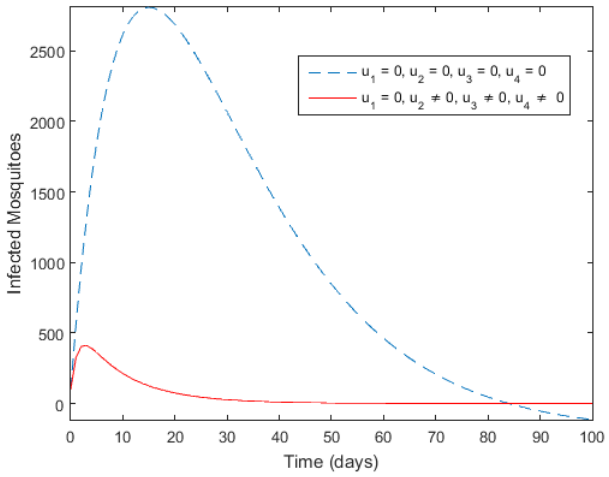
Figure 3: The effects of treated bednets, indoor residual spray, and treatment on transmission of the Zika virus.

6.3 Strategy C: Condoms, Indoor Residual Spray and Treatment

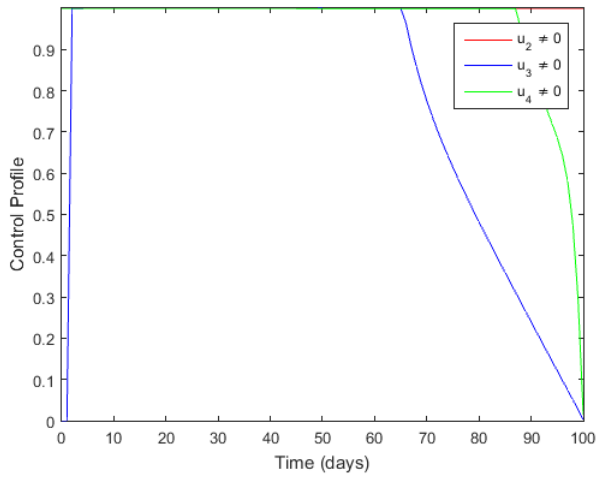
In this strategy, we used controls u_2, u_3, and u_4 to optimize the objective function, while we set control u_1 to zero. In Figure 4(a) and Figure 4(b), it is observed that there is a significant drop in both the number of infected humans and the mosquito population when there is control compared to situation when there is no control. Figure 4(c) and Figure 4(d) represent the control profile and cost for implementing strategy C. The total cost when the strategy is implemented throughout the time horizon is $\$46,261$. The control profile for u_2 is at its upper bound throughout the time horizon, whereas u_2 and u_4 are both at their respective upper bound for 65 and 87 days, respectively, before dropping to their lower bounds.



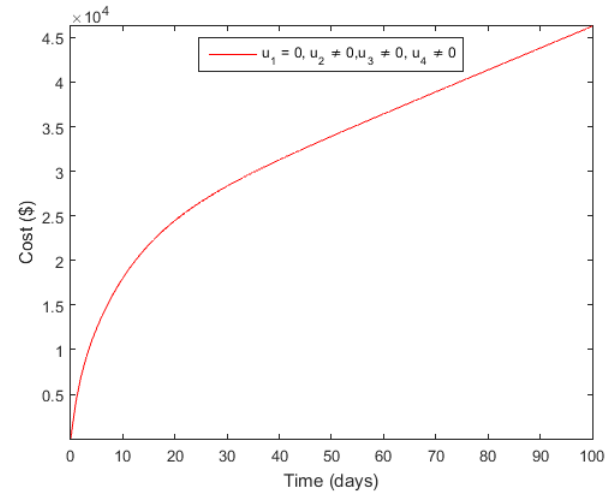
(a) Simulation for infected humans.



(b) Simulation for infected mosquitoes.



(c) Simulation for controls.

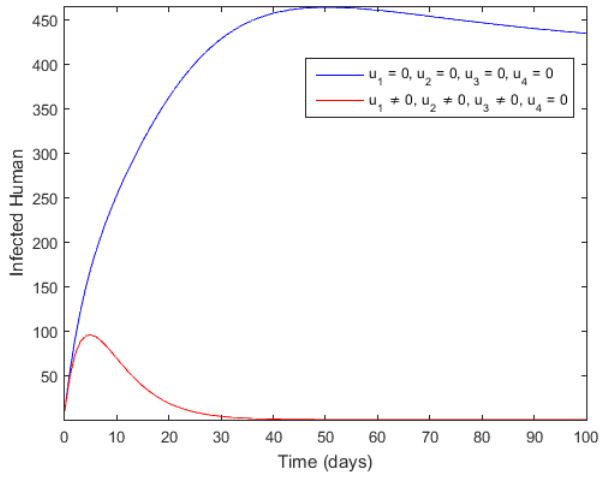


(d) Simulation for cost.

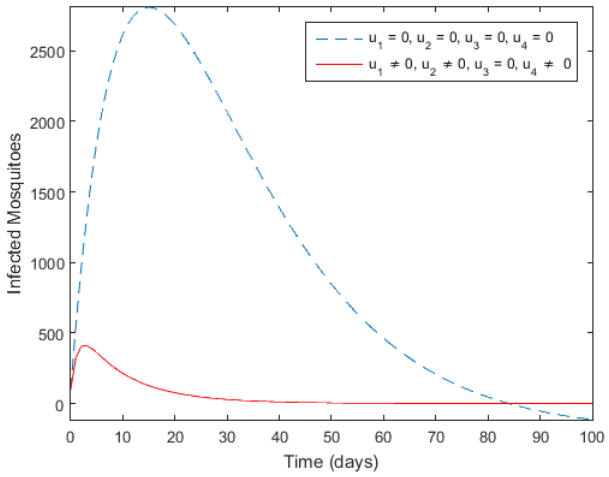
Figure 4: The effects of condoms, indoor residual spray and treatment on transmission of the Zika virus.

6.4 Strategy D: Treated Bednets, Condoms and Indoor Residual Spray

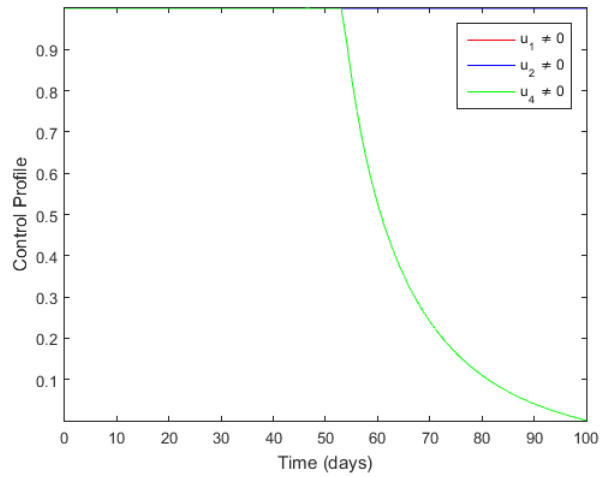
In this strategy, we used controls u_1, u_2 and u_4 to optimize the objective function while we set control u_3 to zero. In Figure 5(a) and Figure 5(b), it is observed that there is a significant drop in both number of infected humans and mosquito population when there is control compared to situation when there is no control. Figure 5(c) and Figure 5(d) represent the control profile and cost for implementing strategy D. The total cost when the strategy is implemented throughout the study period is $\$100,350$. The control profiles for u_1 and u_2 are at their upper bound throughout the time horizon while u_4 is at its upper bound for 53 days before dropping to its lower bound.



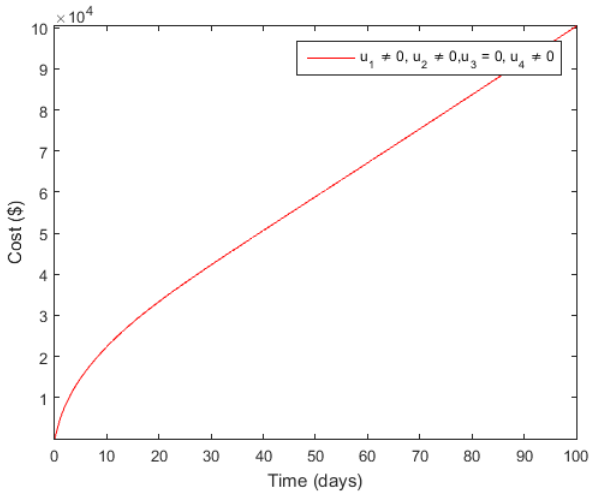
(a) Simulation for infected humans.



(b) Simulation for infected mosquitoes.



(c) Simulation for controls.

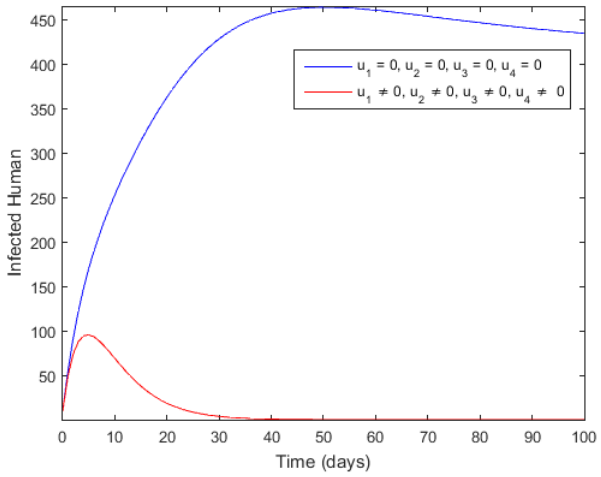


(d) Simulation for cost.

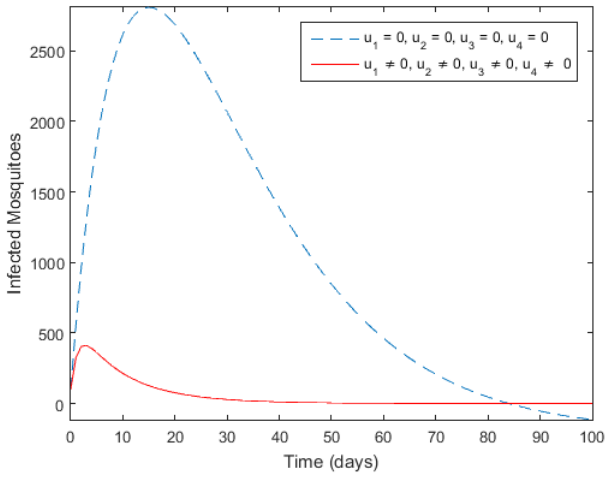
Figure 5: The effects of treated bednets, condoms and indoor residual spray on transmission of the Zika virus.

6.5 Strategy E: Treated Bednets, Condoms, Indoor Residual Spray and Treatment

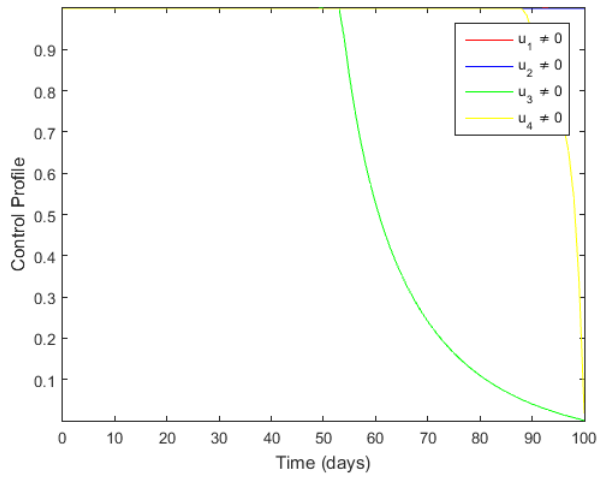
In this strategy, we used all the controls to optimize the objective function. In Figure 6(a) and Figure 6(b), it is observed that there is a significant drop in both number of infected humans and mosquito population when there is control compared to situation when there is no control. Figure 6(c) and Figure 6(d) represent the control profile and cost for implementing strategy E. The total cost when the strategy is implemented throughout the time horizon is $\$104,560$. The control profiles for u_1 and u_2 are at their upper bounds throughout the study period while u_3 and u_4 is at their upper bound for 53 and 88 days, respectively, before dropping to their lower bounds.



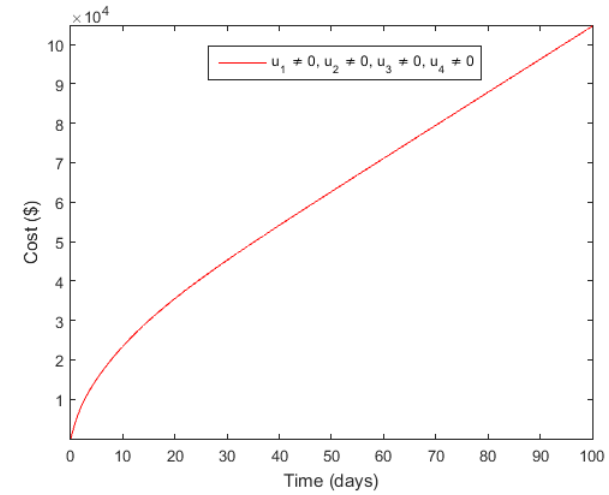
(a) Simulation for infected humans.



(b) Simulation for infected mosquitoes.



(c) Simulation for controls.



(d) Simulation for cost.

Figure 6: The effects of treated bednets, condoms, indoor residual spray and treatment on transmission of Zika virus.

6.6 Cost Effectiveness Analysis

We consider the Incremental Cost-Effectiveness Ratio (ICER) in this study. In ICER, when comparing two competing intervention strategies incrementally, one intervention is compared with the next less-effective alternative. The ICER numerator includes the differences in intervention costs, averted disease costs, costs of prevented cases and averted productivity losses if applicable. While, ICER's denominator is the difference in health outcomes (e.g., the total number of infection averted, the number of susceptibility cases prevented) [26].

From our model simulation results, we present the strategies in order of increasing effectiveness in Table 5.

Table 5: Incremental Cost Effectiveness for the Strategies

Strategy	Total Infection Averted	Cost($)	ICER
B	414.1392	36,208	87.4295
D	432.4993	100,350	3493.5540
C	434.7281	46,261	−24268.2161
A	434.7377	83,304	4026413.0435
E	434.7377	104,560	∞

We obtain the ICER in Table 5 using the formula

$$ICER = \frac{CostOfStrategyP - CostOfStrategyQ}{TotalNumberOfInfectionsAvertedUsingP - TotalNumberOfInfectionsAvertedUsingQ}.$$

Thus,

$$\begin{aligned} ICER(B) &= \frac{36,208}{414.1392} = 87.4295, \\ ICER(D) &= \frac{100,350 - 36,208}{432.4993 - 414.1392} = 3493.5540, \\ ICER(C) &= \frac{46,261 - 100,350}{434.7281 - 432.4993} = -24268.21608, \\ ICER(A) &= \frac{83,304 - 46,261}{434.7373 - 434.7281} = 4026413.0435, \\ ICER(E) &= \frac{104,560 - 83,304}{434.7373 - 434.7373} = \infty. \end{aligned}$$

Comparing strategy B and strategy D, the lower ICER for strategy B suggests that strategy D is strongly dominant over strategy B which means that strategy D is more costly and less effective compared to strategy B. We exclude strategy D and recompute ICER for the remaining strategies, see Table 6.

Table 6: Exclusion of strategy D.

Strategy	Total Infection Averted	Cost($)	ICER
B	414.1392	36,208	87.4295
C	434.7281	46,261	488.2728
A	434.7377	83,304	4026413.0435
E	434.7377	104,560	Inf

Comparing strategy B and strategy C, the lower ICER for strategy B suggests that strategy C is strongly dominant over strategy B which means that strategy C is more costly and less effective compared to strategy B. We exclude strategy C and recompute ICER for the remaining strategies, see Table 7.

Table 7: Exclusion of strategy C.

Strategy	Total Infection Averted	Cost($)	ICER
B	414.1392	36,208	87.4295
A	434.7377	83,304	22286.3801
E	434.7377	104,560	Inf

Comparing strategy B and strategy A, the lower ICER for strategy B suggests that strategy A is strongly dominant over strategy B which means that strategy A is more costly and less effective compared to strategy B. We exclude strategy A and recompute ICER for the remaining strategies, see Table 8.

Table 8: Excluding strategy A.

Strategy	Total Infection Averted	Cost($)	ICER
B	414.1392	36,208	87.4295
E	434.7377	104,560	3318.2999

Based on the computational results above, strategy B is less costly and more effective when compared to strategy E. Thus, we conclude that strategy B which is the combination of treated bednets, indoor residual spray and treatment of infected individuals is the most cost effective of all the strategies for the control of the Zika virus considered in this work.

Conclusion

We derived and analyzed a mathematical model for the transmission of the Zika virus disease taking into consideration four preventive measures as controls, namely, the use of treated bednets, the use of condoms, the treatment of infected patients, and the use of an indoor residual spray. We obtained the reproduction number for the model and carried out a stability analysis. It was observed that the disease free equilibrium state is stable when $R_0 < 1$ but unstable when $R_0 > 1$ which leads to a spread of the disease. We simulated the model equations to study the effects of combined strategies on the transmission of the Zika virus. It was observed that when strategy A is implemented, the total cost is \$83,304 and the number of avoided infections is 434.7377. Similarly, the cost of implementing strategies B, C, D, and E are \$36,208, \$46,261, \$100,350 and \$104,560 and the numbers of avoided infections are 414.1392, 434.7281, 432.4993 and 434.7377, respectively. We examine the implementation of various combinations of the controls in order to determine the most cost-effective strategy among all the control strategies considered. Based on the computational results obtained, we conclude that a strategy based on treated bednets, treatment of infected individuals, and indoor residual spray is the most cost effective of all our examined strategies for a control of the Zika virus.

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Conflict of Interests

The authors declare that there is no conflict of interests.

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