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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, namely: the use of treated bednets, the use of condoms, a medical treatment of infected persons, and the use of indoor residual spray (IRS). 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 symptomatic infected humans and indoor residual spray is the most cost effective strategy.

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 [6,7] 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 conjunctivitis which normally last for 2–7 days [7–9]. The epidemic capacity of the Zika virus was revealed in an outbreak in Micronesia in 2007 and affected approximately 5000 people [10]. Zika has been detected in serum, saliva, urine, and semen [11–13]. It has also been detected in urine and semen even after it disappears from blood [14]. It has also been observed that the Zika virus can be transmitted through sexual contact. It was reported infected that an infected male had infected a female by having vaginal sexual intercourse, even before the onset of symptoms [15]. After the confirmation of the first case of sexually transmitted Zika virus in Dallas County by the CDC on February 2, 2016 [16], 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 [17], and Europe's first case of a sexually transmitted Zika virus was diagnosed in France in February 2016 [18]. 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 [6,8,19]. 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. In Section 5 we propose an optimal control problem for the minimization of the number of asymptomatic infected humans, symptomatic

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Table 1
State variables descriptions of the zika virus model.

Symbol	Description of variable
S_H	Number of susceptible humans at time t
A_H	Number of asymptomatic infected humans at time t
I_H	Number of symptomatic infected 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

infected humans and total mosquito population while taking note the cost of control interventions. Finally, in Section 6 the 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 Fig. 1. An overview of the notation of the model is given in Tables 1–3.

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 $(S_H(t), A_H(t), I_H(t), R_H(t))$ 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 $S_H(t)$, asymptomatic infected human population $A_H(t)$, symptomatic infected 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 (c.f. Fig. 1):

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

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

$$\frac{dI_H}{dt} = \alpha_H A_H - (\phi + \tau u_3) I_H - \mu_H I_H - \delta_H I_H \tag{1c}$$

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

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

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

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

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

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

The number of susceptible humans, $S_H(t)$ 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 number of susceptible humans reduces by

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

as a result of a contact with an infectious mosquitoes and a sexual contact with symptomatic and asymptomatic infected humans and a natural death at a rate μ_H. We emphasize that also asymptomatic infected humans carry the Zika virus but do not show symptoms yet are able to distribute the virus through sexual contacts. The asymptomatic infected humans increases by force of infection and reduces due to a transition of individuals from the class of asymptomatic infected to the symptomatic infected class at a rate of α_H and a natural death at a rate of μ_H. The symptomatic infected humans 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 symptomatic 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 symptomatic 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 symptomatic infected human, where β_2 is the transmission probability per contact by an symptomatic 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 force of infection for mosquitoes and reduces by progression 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 progression 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 symptomatic infected individuals is less than asymptomatic infected individuals ($\kappa < c$). This is so because on becoming symptomatic,the infected persons may choose to use preventive measures and change their behavior.

3. Mathematical analysis of the Zika virus model

We analyze the theoretical properties of our model (1), c.f. [20].

3.1. Positivity of solution and invariant region

A general property of the system (1) with non-negative initial conditions is to maintain non-negative solutions, which is the content of the following theorem.

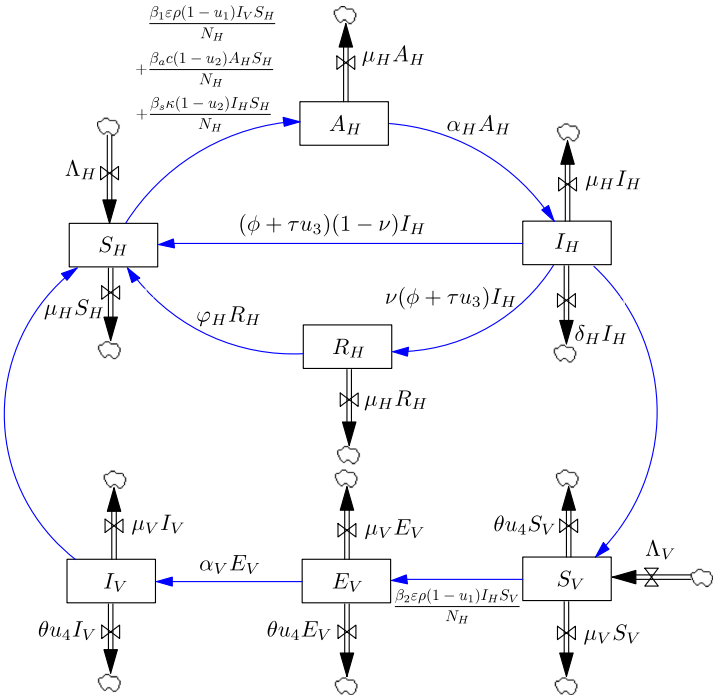

Fig. 1. A schematic view on the Zika virus transmission model. The upper half shows the *S-A-I-R* cycle of the humans, the lower half shows the *S-E-I* dynamics of the mosquitoes.

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 contact rate of asymptomatic infected
κ	Relative human–human contact rate of symptomatic infected
β_a	Probability of disease transmission per contact by asymptomatic infected through sexual activity
β_s	Probability of disease transmission per contact by symptomatic infected 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
θ	Rate constant due to use of indoor residual spray
τ	Rate constant due to treatment effort

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

A proof of this theorem follows the approach of [21], and will be omitted here.

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

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

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 Eqs. (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 $N_H \leq \frac{\Lambda_H}{\mu_H}$ (in the definition of Ω_H) and Eq. (1h) it follows

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

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

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

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

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

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 $N_V := \frac{\Lambda_V}{(\mu_V+\theta u_4)}$, hence Ω is an attracting set. □

3.2. Zika virus free equilibrium

In order to study the behavior 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, $A_H^* = I_H^* = R_H^* = E_V^* = I_V^* = 0$, and the Zika virus model has a disease free equilibrium point given at

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

3.3. Basic reproduction number

In this section, we assume a constant controls and 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

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

$$V = \begin{bmatrix} K_1 & 0 & 0 & 0 \\ -\alpha_H & K_2 & 0 & 0 \\ 0 & 0 & K3 & 0 \\ 0 & 0 & -\alpha_V & K_4 \end{bmatrix},$$

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

$$R_0 = \frac{A_1}{2K_1K_2} + \sqrt{\frac{A_1^2\Lambda_H K_3 K_4^2 + 4K_1K_2\alpha_H\alpha_V(\beta_1\varepsilon\rho(1-u_1))^2\Lambda_V\mu_H}{4\Lambda_H K_1^2K_2^2K_3K_4^2}}.$$

with

$$A_1 = (\alpha_H\beta_s\kappa + \beta_a c K_1)(1-u_2) \quad (3)$$

$$K_1 = (\alpha_H + \mu_H) \quad (4)$$

$$K_2 = (\psi + \sigma u_3 + \mu_H + \delta_H) \quad (5)$$

$$K_3 = (\alpha_V + \mu_V + \theta u_4) \quad (6)$$

$$K_4 = (\mu_V + \theta u_4) \quad (7)$$

We seek for an optimal combination of control strategies that would lead to $R_0 < 1$, which would guarantee that no new Zika infection takes place, as was shown in [20]. Typical cost-effective interventions used in other mosquito related diseases and their endemic areas include insecticides-treated nets (ITNs) and indoor residual spray (IRS). Moreover, since Zika also spreads from one human to another by sexual contact, the use of condoms is on our intervention list. Finally, informing the public and trying to change their behavior is in our catalogue of measures. By a cost-effective combination of these four, we seek to arrive at $R_0 < 1$.

Lemma 1. *The disease-free equilibrium E_0 of the Zika virus model is locally asymptotically stable whenever $R_0 < 1$ and unstable when $R_0 > 1$.*

4. Economic assessment of the Zika virus model

In this section, in line with what is obtain in [24], we economically assess the intervention strategies through the use of optimal control and a cost effectiveness analysis. This is to enable us make informed decision as to the most cost effective strategy among the interventions under consideration. The cost objective function [25] that we aim to minimize in the variables (u_1, u_2, u_3, u_4) is given by

$$C_f(T) = \int_0^T [(m_1u_1(t) + m_2u_2(t))(S_H(t) + A_H(t)) + m_3\tau u_3(t)I_H(t) + m_4\theta u_4(t)N_V(t)]e^{-\eta t}dt, \quad (8)$$

subject to the differential equations of model (1a)–(1g). Here m_1 is the per unit cost of treated bednets, m_2 is the per unit cost of condoms, m_3 is the cost of treatment of symptomatic infected humans and m_4 is the per unit area cost of indoor residual spray. η is a discount rate [25], typically between 3% and 5%. u_1, u_2, represent the fraction of susceptible individuals and asymptomatic infected individuals who make use of ITNs and condoms as a means of minimizing or eliminating mosquito to human contacts and human to human contact through sex. The control u_3 represents the control effort on treatment of symptomatic infectious individuals. The control u_4, the use of IRS, affects the whole mosquito population by increasing its mortality rate.

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

$$\begin{aligned} H_{C_f} &= [(m_1u_1(t) + m_2u_2(t))(S_H(t) + A_H(t)) \\ &\quad + m_3\tau u_3(t)I_H(t) + m_4\theta u_4(t)N_V(t)]e^{-\eta t} \\ &\quad + \lambda_{S_H}\frac{dS_H}{dt} + \lambda_{A_H}\frac{dA_H}{dt} + \lambda_{I_H}\frac{dI_H}{dt} + \lambda_{R_H}\frac{dR_H}{dt} \\ &\quad + \lambda_{S_V}\frac{dS_V}{dt} + \lambda_{E_V}\frac{dE_V}{dt} + \lambda_{I_V}\frac{dI_V}{dt}. \end{aligned} \quad (9)$$

We now substitute Eq. (1) into Eq. (9) to get the corresponding Hamiltonian and applying Pontryagin's maximum principle [24] we obtain

$$\begin{aligned} -\frac{d\lambda_{S_H}}{dt} &= -m_1u_1e^{-\eta t} - m_2u_2e^{-\eta t} \\ &\quad + (\lambda_{S_H} - \lambda_{A_H})\left[\frac{\beta_1\varepsilon\rho(1-u_1)I_V}{N_H} + \frac{\beta_a c(1-u_2)A_H}{N_H} \right. \\ &\quad \left. + \frac{\beta_s\kappa(1-u_2)I_H}{N_H}\right] + \mu_H\lambda_{S_H}, \\ -\frac{d\lambda_{A_H}}{dt} &= -m_1u_1e^{-\eta t} - m_2u_2e^{-\eta t} + (\lambda_{S_H} - \lambda_{A_H})\frac{\beta_a c(1-u_2)S_H}{N_H} \\ &\quad + (\lambda_{A_H} - \lambda_{I_H})\alpha_H + \mu_H\lambda_{A_H}, \\ -\frac{d\lambda_{I_H}}{dt} &= -m_3\tau u_3e^{-\eta t} + (\lambda_{S_H} - \lambda_{A_H})\frac{\beta_s\kappa(1-u_2)S_H}{N_H} \\ &\quad + (\lambda_{S_V} - \lambda_{E_V})\frac{\beta_2\varepsilon\rho(1-u_1)S_V}{N_V} \\ &\quad - (\phi + \tau u_3)\nu\lambda_{R_H} - (\phi + \tau u_3)(1-\nu)\lambda_{S_H} \\ &\quad + (\phi + \tau u_3 + \mu_H + \delta_H)\lambda_{I_H}, \end{aligned}$$

$$
\begin{aligned}
-\frac{d\lambda_{R_H}}{dt} &= (\lambda_{R_H}-\lambda_{S_H})\varphi_H+\mu_H\lambda_{R_H},\\
-\frac{d\lambda_{S_V}}{dt} &= -m_4\theta u_4e^{-\eta t}+(\lambda_{S_V}-\lambda_{E_V})\frac{\beta_2\varepsilon\rho(1-u_1)I_H}{N_H}\\
&\quad+(\mu_V+\theta u_4)\lambda_{S_V},\\
-\frac{d\lambda_{E_V}}{dt} &= -m_4\theta u_4e^{-\eta t}+(\lambda_{E_V}-\lambda_{I_V})\alpha_V+(\mu_V+\theta u_4)\lambda_{E_V},\\
-\frac{d\lambda_{I_V}}{dt} &= -m_4\theta u_4e^{-\eta t}+(\lambda_{S_V}-\lambda_{E_V})\frac{\beta_2\varepsilon\rho(1-u_1)S_H}{N_H}\\
&\quad+(\mu_V+\theta u_4)\lambda_{I_V},
\end{aligned}
$$

and

$$
\begin{aligned}
\frac{d\lambda_{S_H}}{dt} &= \frac{\partial H_{C_f}}{\partial S_H},\\
\frac{d\lambda_{A_H}}{dt} &= \frac{\partial H_{C_f}}{\partial A_H},\\
\frac{d\lambda_{I_H}}{dt} &= \frac{\partial H_{C_f}}{\partial I_H},\\
\frac{d\lambda_{R_H}}{dt} &= \frac{\partial H_{C_f}}{\partial R_H},\\
\frac{d\lambda_{S_V}}{dt} &= \frac{\partial H_{C_f}}{\partial S_V},\\
\frac{d\lambda_{E_V}}{dt} &= \frac{\partial H_{C_f}}{\partial E_H},\\
\frac{d\lambda_{I_V}}{dt} &= \frac{\partial H_{C_f}}{\partial I_H}.
\end{aligned}
$$

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

$$
\frac{\partial H_{C_f}}{\partial u_1} = m_1e^{-\eta t}(S_H+A_H)+\left[(\lambda_{S_H}-\lambda_{A_H})\frac{\beta_1\varepsilon\rho I_VS_H}{N_H}+(\lambda_{S_V}-\lambda_{E_V})\frac{\beta_1\varepsilon\rho I_HS_V}{N_H}\right], \tag{10}
$$

where

$m_1e^{-\eta t}(S_H+A_H)$

is the marginal cost of using treated bednets, and

$(\lambda_{S_H}-\lambda_{A_H})\frac{\beta_1\varepsilon\rho I_VS_H}{N_H}+(\lambda_{S_V}-\lambda_{E_V})\frac{\beta_1\varepsilon\rho I_HS_V}{N_H}$

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 (10) we have the following bounds:

$$
\begin{aligned}
u_1(t)=0 \text{ if } m_1e^{-\eta t}(S_H+A_H) &> (\lambda_{A_H}-\lambda_{S_H})\frac{\beta_1\varepsilon\rho I_VS_H}{N_H}\\
&\quad+(\lambda_{E_V}-\lambda_{S_V})\frac{\beta_1\varepsilon\rho I_HS_V}{N_H},\\
u_1(t)\in(0,1) \text{ if } m_1e^{-\eta t}(S_H+A_H) &= (\lambda_{A_H}-\lambda_{S_H})\frac{\beta_1\varepsilon\rho I_VS_H}{N_H}\\
&\quad+(\lambda_{E_V}-\lambda_{S_V})\frac{\beta_1\varepsilon\rho I_HS_V}{N_H},\\
u_1(t)=1 \text{ if } m_1e^{-\eta t}(S_H+A_H) &< (\lambda_{A_H}-\lambda_{S_H})\frac{\beta_1\varepsilon\rho I_VS_H}{N_H}\\
&\quad+(\lambda_{E_V}-\lambda_{S_V})\frac{\beta_1\varepsilon\rho I_HS_V}{N_H}.
\end{aligned}
$$

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 asymptomatic infected 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

$$
\frac{\partial H_{C_f}}{\partial u_2} = m_2e^{-\eta t}(S_H+A_H)+\left[(\lambda_{S_H}-\lambda_{A_H})\frac{\beta_acI_HS_H}{N_H}+(\lambda_{S_H}-\lambda_{A_H})\frac{\beta_s\kappa I_HS_H}{N_H}\right], \tag{11}
$$

where

$m_2e^{-\eta t}(S_H+A_H)$

is the marginal cost of acquiring condoms and

$(\lambda_{S_H}-\lambda_{A_H})\frac{\beta_acI_HS_H}{N_H}+(\lambda_{A_H}-\lambda_{S_H})\frac{\beta_s\kappa I_HS_H}{N_H}$

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 (11) we have the following bounds:

$$
\begin{aligned}
u_2(t)=0 \text{ if } m_2e^{-\eta t}(S_H+A_H) &> (\lambda_{A_H}-\lambda_{S_H})\frac{\beta cI_HS_H}{N_H}\\
&\quad+(\lambda_{A_H}-\lambda_{S_H})\frac{\beta\kappa I_HS_H}{N_H},\\
u_2(t)\in(0,1) \text{ if } m_2e^{-\eta t}(S_H+A_H) &= (\lambda_{A_H}-\lambda_{S_H})\frac{\beta cI_HS_H}{N_H}\\
&\quad+(\lambda_{A_H}-\lambda_{S_H})\frac{\beta\kappa I_HS_H}{N_H},\\
u_2(t)=1 \text{ if } m_2e^{-\eta t}(S_H+A_H) &< (\lambda_{A_H}-\lambda_{S_H})\frac{\beta cI_HS_H}{N_H}\\
&\quad+(\lambda_{A_H}-\lambda_{S_H})\frac{\beta\kappa I_HS_H}{N_H}.
\end{aligned}
$$

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 asymptomatic infected 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

$$
\frac{\partial H_{C_f}}{\partial u_3} = m_3e^{-\eta t}\tau I_H-\tau\left[\lambda_{I_H}+\nu(\lambda_{S_H}-\lambda_{R_H})-\lambda_{S_H}\right]I_H, \tag{12}
$$

where

$m_3e^{-\eta t}\tau I_H$

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 (12) we have the following bounds:

$$
u_3(t)=0 \text{ if } m_3e^{-\eta t}\tau I_H > \tau\left[\lambda_{I_H}+\nu(\lambda_{S_H}-\lambda_{R_H})-\lambda_{S_H}\right]I_H,
$$

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$u_3(t) \in (0, 1)$ if $m_3 e^{-\eta t}\tau I_H = \tau\left[\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H}\right] I_H$,

$u_3(t) = 1$ if $m_3 e^{-\eta t}\tau I_H < \tau\left[\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H}\right] I_H$.

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

$$\frac{\partial H_{C_f}}{\partial u_4} = m_4\theta e^{-\eta t} N_V - \theta(S_V\lambda_{S_V} + E_V\lambda_{E_V} + I_V\lambda_{I_V}), \tag{13}$$

where

$m_4 e^{-\eta t}\theta N_V$

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 (13) we obtain bounds on the optimal policy as

$u_4(t) = 0$ if $m_4\theta e^{-\eta t} N_V > \theta(S_V\lambda_{S_V} + E_V\lambda_{E_V} + I_V\lambda_{I_V})$,

$u_4(t) \in (0, 1)$ if $m_4\theta e^{-\eta t} N_V = \theta(S_V\lambda_{S_V} + E_V\lambda_{E_V} + I_V\lambda_{I_V})$,

$u_4(t) = 1$ if $m_4\theta e^{-\eta t} N_V < \theta(S_V\lambda_{S_V} + E_V\lambda_{E_V} + I_V\lambda_{I_V})$.

If the marginal benefit for the spray of insecticides against mosquitoes is less than the marginal cost of this spray, then the spray of insecticides is not reasonable. If the marginal cost of spray of insecticides is less than the marginal benefits, then it is optimal to spray insecticides against the mosquitoes.

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

$$J(u_1, u_2, u_3, u_4) = \int_0^{T_f} \left[A_1 A_H + A_2 I_H + A_3 N_V + \frac{1}{2}(C_1 u_1^2 + C_2 u_2^2 + C_3 u_3^2 + C_4 u_4^2)\right] e^{-\eta t} dt, \tag{14}$$

subject to the equations of the model (1) and additionally the total cost at time T, given by

$$C_f(T) = \int_0^T [(m_1 u_1 + m_2 u_2)(S_H + A_H) + m_3\tau u_3 I_H + m_4\theta u_4 N_V] dt, \tag{15}$$

where A_1 and A_2 represent the weight constants of the asymptomatic and symptomatic infected human population, respectively, and A_3 represents the weight constant of the total mosquito 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 [25–28]. Our goal with the given objective function is to minimize the number of symptomatic infected humans, asymptomatic infected humans 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

$$(u_1^*, u_2^*, u_3^*, u_4^*) = min\{J(u_1, u_2, u_3, u_4), (u_1, u_2, u_3, u_4) \in U\}, \tag{16}$$

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

The Hamiltonian H from the objective function (14) subject to (1) and cost function (15) is

$$\begin{aligned}
H = {} & [A_1 A_H + A_2 I_H + A_3 N_V \\
& + \frac{1}{2}(C_1 u_1^2 + C_2 u_2^2 + C_3 u_3^2 + C_4 u_4^2)]e^{-\eta t} && (17a)\\
& + \lambda_{S_H}\left[\Lambda_H + (\phi + \tau u_3)(1-\nu) I_H + \varphi_H R_H \right. \\
& \left. - \frac{\beta_1\varepsilon\rho(1-u_1) I_V S_H}{N_H} \right. \\
& \left. - \frac{\beta_a c(1-u_2) A_H S_H}{N_H} - \frac{\beta_s\kappa(1-u_2) I_H S_H}{N_H} - \mu_H S_H\right] && (17b)\\
& + \lambda_{A_H}\left[\frac{\beta_1\varepsilon\rho(1-u_1) I_V S_H}{N_H} + \frac{\beta_a c(1-u_2) A_H S_H}{N_H} \right. \\
& \left. + \frac{\beta_a c(1-u_2) I_H S_H}{N_H} - \alpha_H A_H - \mu_H A_H\right] && (17c)\\
& + \lambda_{I_H}[\alpha_H A_H - (\phi + \tau u_3) I_H - \mu_H I_H - \delta_H I_H] && (17d)\\
& + \lambda_{R_H}[(\phi + \tau u_3)\nu I_H - \varphi_H R_H - \mu_H R_H] && (17e)\\
& + \lambda_{S_V}\left[\Lambda_V - \frac{\beta_2\varepsilon\rho(1-u_1) I_H S_V}{N_H} - (\mu_V + \theta u_4) S_V\right] && (17f)\\
& + \lambda_{E_V}\left[\frac{\beta_2\varepsilon\rho(1-u_1) I_H S_V}{N_H} - \alpha_V E_V - (\mu_V + \theta u_4) E_V\right] && (17g)\\
& + \lambda_{I_V}[\alpha_V I_V - (\mu_V + \theta u_4) I_V] && (17h)\\
& + \lambda_{C_f}[((m_1 u_1 + m_2 u_2)(S_H + A_H)) + m_3\tau u_3 I_H \\
& + m_4\theta u_4 N_V], && (17i)
\end{aligned}$$

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

$$\begin{aligned}
\frac{d\lambda_{S_H}}{dt} = {} & (\lambda_{S_H} - \lambda_{A_H}) \\
& \times \left[\frac{\beta_1\varepsilon\rho(1-u_1) I_V}{N_V} + \frac{\beta_a c(1-u_2) A_H}{N_H} + \frac{\beta_s\kappa(1-u_2) I_H}{N_H}\right] \\
& + \mu_H\lambda_{S_H} - (m_1 u_1 + m_2 u_2)\lambda_{C_f} && (18a)\\
\frac{d\lambda_{A_H}}{dt} = {} & (\lambda_{S_H} - \lambda_{A_H})\frac{\beta_a c(1-u_2) S_H}{N_H} + \mu_H\lambda_{A_H} \\
& + (\lambda_{A_H} - \lambda_{I_H}) - (m_1 u_1 + m_2 u_2)\lambda_{C_f} - A_1 && (18b)\\
\frac{d\lambda_{I_H}}{dt} = {} & (\lambda_{S_H} - \lambda_{A_H})\frac{\beta_s\kappa(1-u_2) S_H}{N_H} \\
& + (\lambda_{S_H} - \lambda_{A_H})\frac{\beta_2\varepsilon\rho(1-u_1) S_V}{N_V} \\
& + (\phi + \tau u_3)\nu\lambda_{R_H} - (\phi + \tau u_3)(1-\nu)\lambda_{S_H} \\
& + (\phi + \mu_H + \tau u_3 + \delta_H)\lambda_{I_H} - m_3\tau u_3\lambda_{C_f} - A_2 && (18c)\\
\frac{d\lambda_{R_H}}{dt} = {} & (\lambda_{R_H} - \lambda_{S_H})\varphi_H + \mu_H\lambda_{R_H} && (18d)\\
\frac{d\lambda_{S_V}}{dt} = {} & (\lambda_{S_V} - \lambda_{E_V})\frac{\beta_2\varepsilon\rho(1-u_1) I_H}{N_V} \\
& + (\mu_V + \theta u_4)\lambda_{S_V} - m_4\theta u_4\lambda_{C_f} - A_3 && (18e)\\
\frac{d\lambda_{E_V}}{dt} = {} & (\lambda_{E_V} - \lambda_{I_V})\alpha_V + (\mu_V + \theta u_4)\lambda_{E_V} - m_4\theta u_4\lambda_{C_f} - A_3 && (18f)
\end{aligned}$$

$$\frac{d\lambda_{I_V}}{dt} = (\lambda_{S_V} - \lambda_{E_V})\frac{\beta_1\varepsilon\rho(1-u_1)S_H}{N_V} + (\mu_V + \theta u_4)\lambda_{I_V} - m_4\theta u_4\lambda_{C_f} - A_3 \tag{18g}$$

$$\frac{d\lambda_{C_f}}{dt} = 0 \tag{18h}$$

By applying Pontryagin's maximum principle [24] and an existence result for an optimal control (see [29]), 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 (see the equation in Box I).*
where λ_{S_H}, λ_{A_H}, λ_{I_H}, λ_{R_H}, λ_{S_V}, λ_{E_V}, and λ_{I_V} are the adjoint variables satisfying (18) and the following transversality conditions:

$$\lambda_{S_H}(T_f) = \lambda_{A_H}(T_f) = \lambda_{I_H}(T_f) = \lambda_{R_H}(T_f) = \lambda_{S_V}(T_f) = \lambda_{E_V}(T_f) = \lambda_{I_V}(T_f) = \lambda_{C_f}(T) = 0. \tag{20}$$

Proof. From [29], 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:

$$0 = \frac{\partial H}{\partial u_1} = u_1^c C_1 e^{-\eta t} + \left[(\lambda_{S_H} - \lambda_{A_H})\frac{\beta_1\varepsilon\rho I_V^* S_H^*}{N_H} + (\lambda_{S_V} - \lambda_{E_V})\frac{\beta_2\varepsilon\rho I_H^* S_V^*}{N_H} + m_1\lambda_{C_f}(S_H^* + A_H^*)\right] \tag{21a}$$

$$0 = \frac{\partial H}{\partial u_2} = u_2^c C_2 e^{-\eta t} + \left[(\lambda_{S_H} - \lambda_{A_H})\frac{\beta_a c E_H^* S_H^*}{N_H} + (\lambda_{S_H} - \lambda_{A_H})\frac{\beta_s\kappa I_H^* S_H^*}{N_H} + m_2\lambda_{C_f}(S_H^* + A_H^*)\right] \tag{21b}$$

$$0 = \frac{\partial H}{\partial u_3} = u_3^c C_3 e^{-\eta t}\left[\tau(\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H})I_H^* + m_3\lambda_{C_f} I_H^*\right] \tag{21c}$$

$$0 = \frac{\partial H}{\partial u_4} = u_4^c C_4 e^{-\eta t} - \left[\theta(S_V^*\lambda_{S_V} + E_V^*\lambda_{E_H} + I_V^*\lambda_{I_H}) + m_4\lambda_{C_f}(S_V^* + E_V^* + I_V^*)\right] \tag{21d}$$

From (21), we obtain

$$u_1^c = \frac{\left[(\lambda_{A_H} - \lambda_{S_H})\frac{\beta_1\varepsilon\rho I_V^* S_H^*}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_2\varepsilon\rho I_H^* S_V^*}{N_H} - m_1\lambda_{C_f}(S_H^* + A_H^*)\right]}{C_1}$$

$$u_2^c = \frac{\left[(\lambda_{A_H} - \lambda_{S_H})\frac{\beta_a c A_H^* S_H^*}{N_H} + (\lambda_{A_H} - \lambda_{S_H})\frac{\beta_s\kappa I_H^* S_H^*}{N_H} - m_2\lambda_{C_f}(S_H^* + A_H^*)\right]}{C_2}$$

$$u_3^c = \frac{\left[\tau(\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H})I_H^* - m_3\lambda_{C_f} I_H^*\right]}{C_3}$$

$$u_4^c = \frac{\theta(S_V^*\lambda_{S_V} + E_V^*\lambda_{A_H} + I_V^*\lambda_{I_H}) - m_4\lambda_{C_f}(S_V^* + E_V^* + I_V^*)}{C_4}.$$

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

$$u_1^* = \begin{cases} 0, & \text{if } u_1^c \le 0, \\ u_1^c, & \text{if } 0 < u_1^c < 1, \\ 1, & \text{if } u_1^c \ge 1, \end{cases}$$

$$u_2^* = \begin{cases} 0, & \text{if } u_2^c \le 0, \\ u_2^c, & \text{if } 0 < u_2^c < 1, \\ 1, & \text{if } u_2^c \ge 1, \end{cases}$$

$$u_3^* = \begin{cases} 0, & \text{if } u_3^c \le 0, \\ u_3^c, & \text{if } 0 < u_3^c < 1, \\ 1, & \text{if } u_3^c \ge 1, \end{cases}$$

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

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 (18) and (20), with characterization (19). 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 (18) and (20); the state problem has initial values, and the adjoint problem has terminal values. We remark that this restriction is common in control problems, see [25,27,28]. □

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 (20), 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 (19). 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 [28]). We chose the following set as weight factors:

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

These weight values are selected based on the efforts required to provide the strategies under consideration. The factors A_i are higher than the C_j factors, because we want to emphasize in our optimization on the size of the groups that should be as small as possible. Among the three groups A_H (asymptomatic infected humans), I_H (symptomatic infected humans), N_V (vector population, the size of the symptomatic infected humans is considered as the most critical one, hence the highest attention (resulting in $A_2 = 500$) is paid to them. The cost for controlling the spread of the disease is comparatively smaller but still significant, which results in values for C_j for $j = 1, 2, 3, 4$ between 20 and 40. For example, creating awareness and advertising condoms is the cheapest $C_2 = 20$, whereas indoor residual spray is more expensive, hence $C_4 = 40$. These values are of course adjustable and may differ from country to country, region to region.

As initial state variables we set

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

These values represent a small community with around 1000 inhabitants. The Zika outbreak began some time before. Still, most of the inhabitants (three quarter) are susceptible, while one quarter are asymptomatic. There is only a small group of symptomatic infected (about 1%), and also a small group of recovered inhabitants (3%). The mosquito population outnumbered the human population by a factor of 10, but we assume also here that only about 1% of them are actually infected.

Using these sets of values we 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.

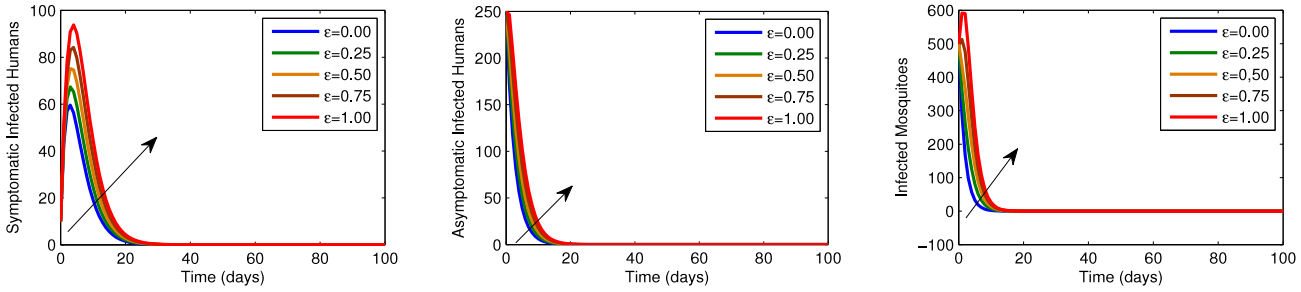
$$u_1^* = \max\left\{0, \min\left(1, \frac{\left[(\lambda_{A_H} - \lambda_{S_H})\frac{\beta_1 \varepsilon \rho I_V^* S_H^*}{N_H} + (\lambda_{E_V} - \lambda_{S_V})\frac{\beta_2 \varepsilon \rho I_H^* S_V^*}{N_H} + m_1 \lambda_{C_f}(S_H^* + A_H^*)\right]}{C_1} e^{\eta t}\right)\right\} \tag{19a}$$

$$u_2^* = \max\left\{0, \min\left(1, \frac{\left[(\lambda_{A_H} - \lambda_{S_H})\frac{\beta_a c A_H^* S_H^*}{N_H} + (\lambda_{A_H} - \lambda_{S_H})\frac{\beta_s \kappa A_H^* S_H^*}{N_H} + m_2 \lambda_{C_f}(S_H^* + A_H^*)\right]}{C_2} e^{\eta t}\right)\right\} \tag{19b}$$

$$u_3^* = \max\left\{0, \min\left(1, \frac{\left[\tau(\lambda_{I_H} + \nu(\lambda_{S_H} - \lambda_{R_H}) - \lambda_{S_H})I_H^* + m_3 \lambda_{C_f} I_H^*\right]}{C_3} e^{\eta t}\right)\right\} \tag{19c}$$

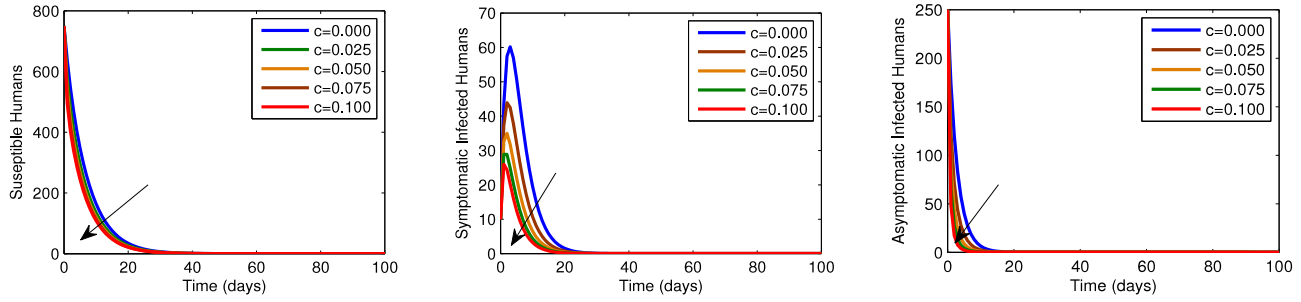
$$u_4^* = \max\left\{0, \min\left(1, \frac{\left[\theta(S_V^* \lambda_{S_V} + E_V^* \lambda_{E_H} + I_V^* \lambda_{I_H}) + m_4 \lambda_{C_f}(S_V^* + E_V^* + I_V^*)\right]}{C_4} e^{\eta t}\right)\right\}, \tag{19d}$$

Box I.



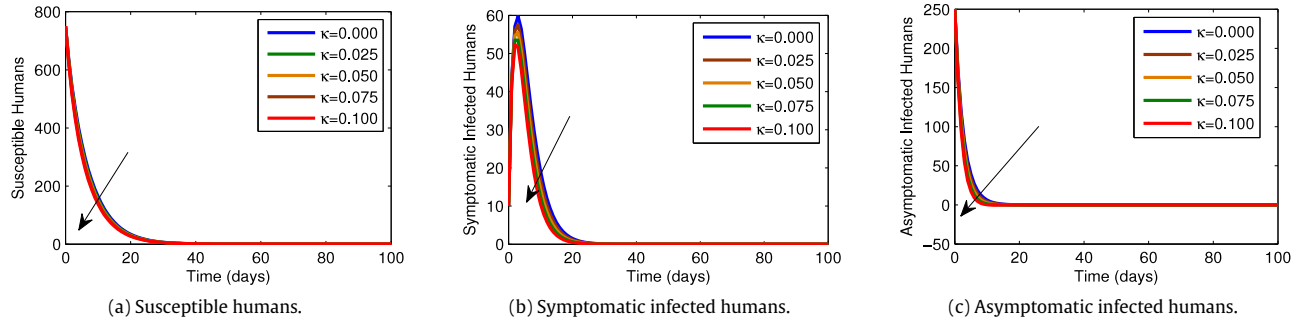
(a) Symptomatic infected humans. (b) Asymptomatic infected humans. (c) Infected mosquitoes.

Fig. 2. Varying the per capital bite rate of the mosquitoes ε between 0.0 and 1.0.



(a) Susceptible humans. (b) Symptomatic infected humans. (c) Asymptomatic infected humans.

Fig. 3. Varying the human–human contact rate of asymptomatic infected c between 0.0 and 0.1.



(a) Susceptible humans. (b) Symptomatic infected humans. (c) Asymptomatic infected humans.

Fig. 4. Varying the human–human contact rate of symptomatic infected κ between 0.0 and 0.1.

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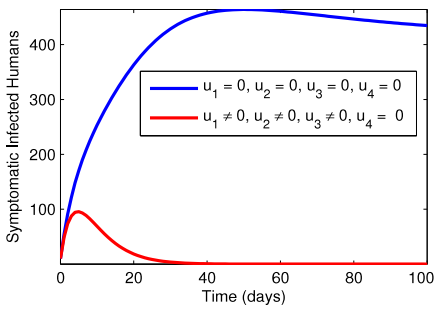
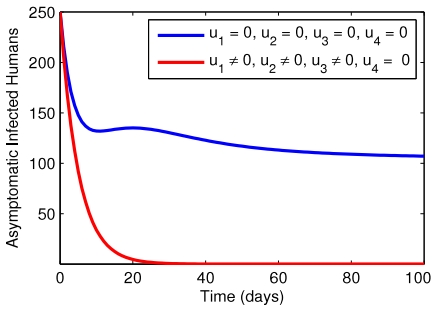
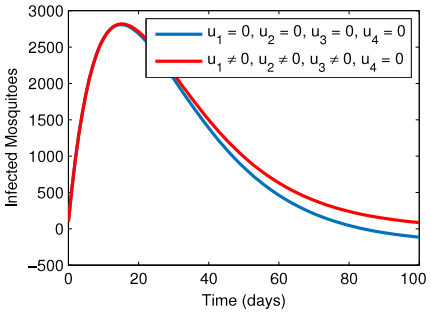


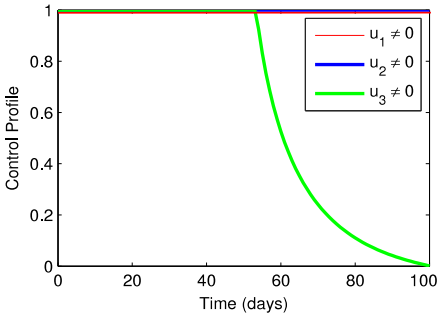
(a) Symptomatic infected humans (red), in comparison to a base run with no control (blue).



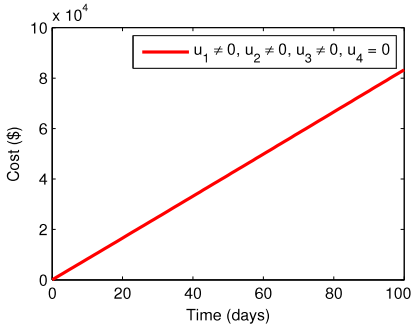
(b) Asymptomatic infected humans (red), in comparison to a base run with no control (blue).



(c) Infected mosquitoes (red), in comparison to a base run with no control (blue).



(d) Dynamic of controls.



(e) Dynamic of cost.

Fig. 5. The effects of the strategy "treated bednets, condoms, and treatment" on the transmission of the Zika virus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Parameter values used for the model simulations.

Parameter	Range	Value	Source
ε	$0.3-1$	0.5	[30]
β_1	0.1–0.75	0.4	[30]
β_2	0.3–0.75	0.5	[31]
$\frac{1}{\alpha_H}$	2–7	5	[32]
$\frac{1}{\alpha_V}$	8–12	10	[30,33]
$\frac{1}{\mu_V}$	4–35	14	[30,31]
μ_H		$\frac{1}{(360\times60)}$	[25]
β_a	0–1	0.6	[34]
β_s	0–1	0.3	[34]
c	0.001–0.10	0.05	[34]
κ	0.001–0.10	0.05	[34]
Λ_H		0.000011	[25]
Λ_V		0.071	[35]
δ_H		0.0003	Assumed
η		$\frac{3}{365}-\frac{5}{365}\%$	[25]
ρ		0.1	Assumed
φ_H		0.02	Assumed
ϕ		0.05	Assumed
ν		0.023	Assumed
m_1		$2.5-5.0	[25]
m_2		$0.24	[36]
m_3		$2.00	[25]
m_4		$1.50	[25]
θ		0.75	Assumed
τ		0.15	Assumed

For some parameters in Table 4 there are singular values given, for others there are intervals, from which we chose a particular singular value each in order to set up or models. This approach raises the question how sensitive the results are to perturbations of these input values. Thus before discussing strategies on dealing with the Zika virus, we take a look into the sensitivity of the results depending on the actual choice of input values. For a "mixed strategy" with $u_1(t) = \cdots = u_4(t) = 0.5$ for all t we varied a single parameter and analyzed the behavior of the variables. As examples for this part of our study, we show the results for three parameters (ε, c, and κ) for three variables each, see Fig. 2, Fig. 3, and Fig. 4, respectively. An arrow in each Figure indicates the general direction of the quantitative behavior. It turns out that the quantity of the result changes, sometimes by a factor of 2 in the number of humans or mosquitoes on a particular day. The qualitative behavior, that is, the shape of the curvature of the solution, is very similar. From this we conclude that small deviations in each of the parameters (for example, by misjudging such parameter from empirical data) leads also to small deviations in the output results, and does not render the results completely useless.

We investigate and compare numerical results in the following scenario:

Strategy A: Treated bednets+condoms+treatment.
Strategy B: Treated bednets+indoor 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 Figs. 5(a) and 5(b) it is observed that there is a significant drop in the number of symptomatic resp. asymptomatic infected humans when there is control compared to situation when there is no control. Moreover, a slight change only occurs in the mosquito population, see Fig. 5(c). Figs. 5(d) and 5(e) 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.

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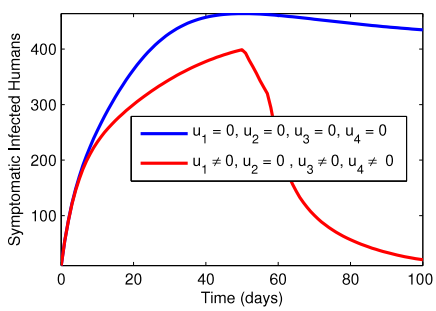
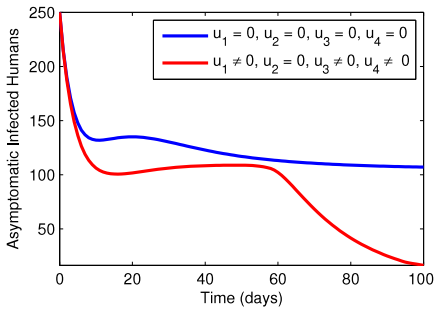
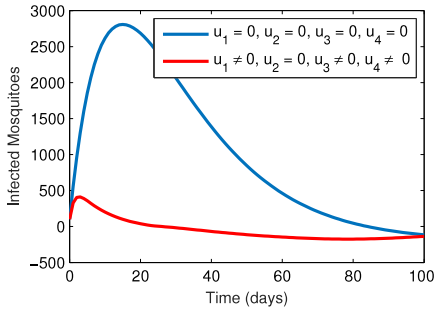


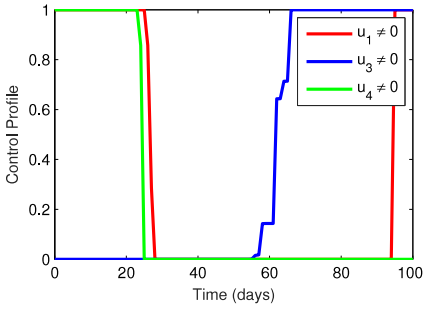
(a) Symptomatic infected humans (red), in comparison to a base run with no control (blue).



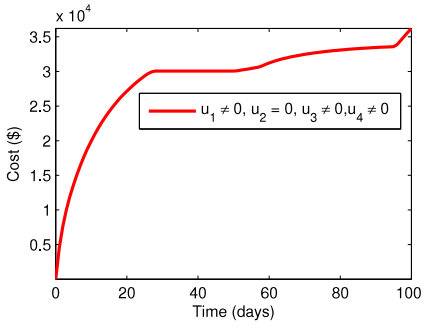
(b) Asymptomatic infected humans (red), in comparison to a base run with no control (blue).



(c) Infected mosquitoes (red), in comparison to a base run with no control (blue).



(d) Dynamic of controls.



(e) Dynamic of cost.

Fig. 6. The effects of the strategy "treated bednets, indoor residual spray, and treatment" on the transmission of the Zika virus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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 Figs. 6(a), 6(b) and 6(c) it is observed that there is a significant drop in both the number of symptomatic and asymptomatic infected humans, and the mosquito population, respectively, when there is control compared to situation when there is no control. Figs. 6(d) and 6(e) 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.

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 Fig. 7(a), Fig. 7(b) and Fig. 7(c), it is observed that there is a significant drop in both the number of symptomatic and asymptomatic infected humans, and the mosquito population, respectively, when there is control compared to situation when there is no control. Figs. 7(d) and 7(e) 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.

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 Fig. 8(a), Fig. 8(b) and Fig. 8(c), it is observed that there is a significant drop in both number of symptomatic and asymptomatic infected humans, and mosquito population, respectively, when there is control compared to situation when there is no control. Figs. 8(d) and 8(e) 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.

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	∞

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 Fig. 9(a), Fig. 9(b) and Fig. 9(c), it is observed that there is a significant drop in both number of symptomatic and asymptomatic infected humans, and mosquito population, respectively, when there is control compared to situation when there is no control. Figs. 9(d) and 9(e) 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.

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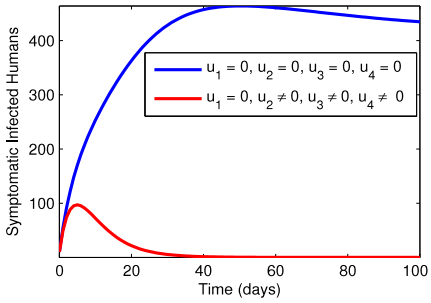
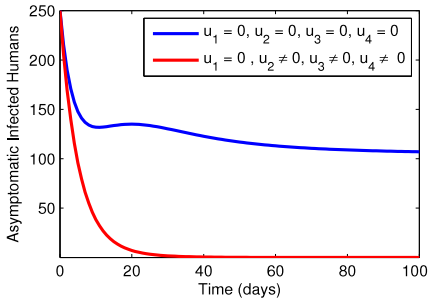
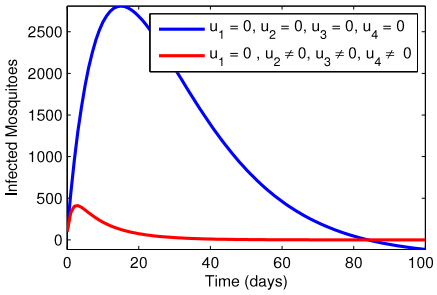


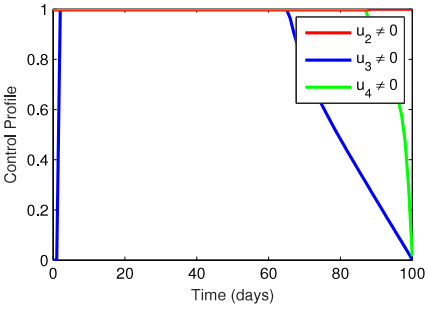
(a) Symptomatic infected humans (red), in comparison to a base run with no control (blue).



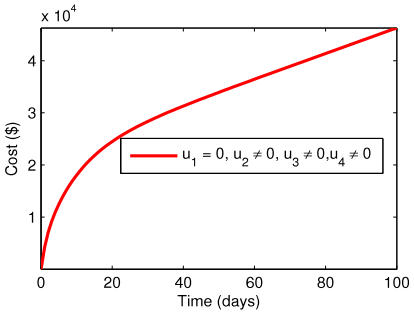
(b) Asymptomatic infected humans (red), in comparison to a base run with no control (blue).



(c) Infected mosquitoes (red), in comparison to a base run with no control (blue).

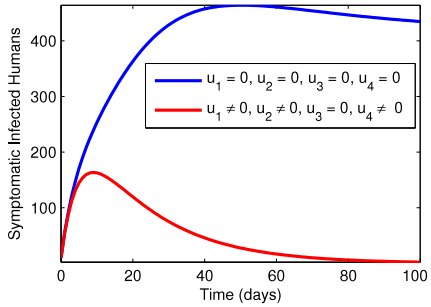


(d) Dynamic of controls.

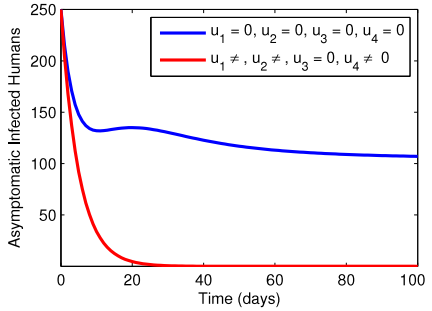


(e) Dynamic of cost.

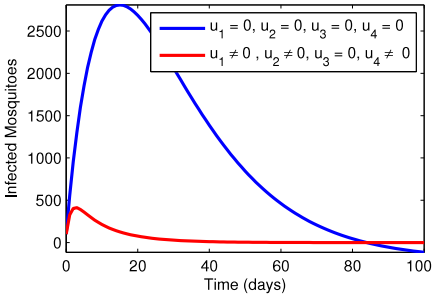
Fig. 7. The effects of the strategy "condoms, indoor residual spray and treatment" on the transmission of the Zika virus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



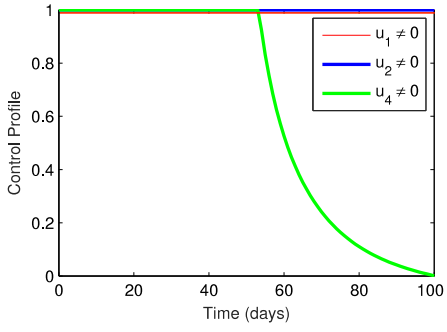
(a) Symptomatic infected humans (red), in comparison to a base run with no control (blue).



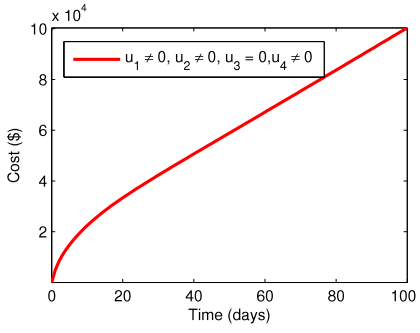
(b) Asymptomatic infected humans (red), in comparison to a base run with no control (blue).



(c) Infected mosquitoes (red), in comparison to a base run with no control (blue).



(d) Dynamic of controls.



(e) Dynamic of cost.

Fig. 8. The effects of the strategy "treated bednets, condoms and indoor residual spray" on the transmission of the Zika virus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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) [25].

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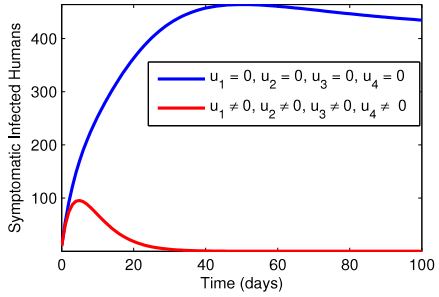
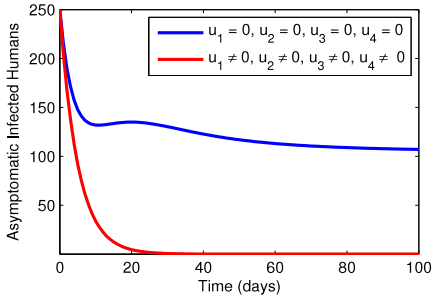
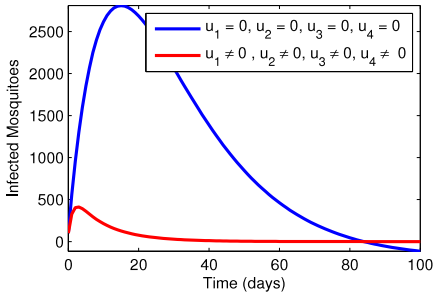


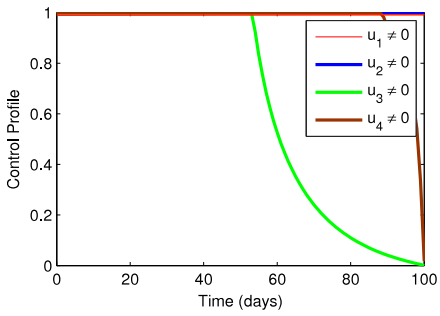
(a) Symptomatic infected humans (red), in comparison to a base run with no control (blue).



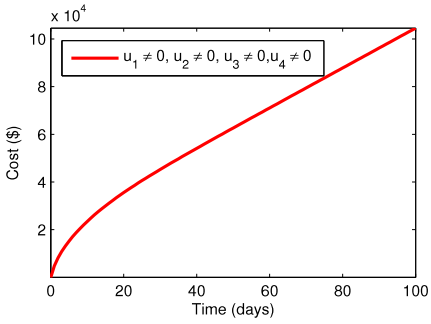
(b) Asymptomatic infected humans (red), in comparison to a base run with no control (blue).



(c) Infected mosquitoes (red), in comparison to a base run with no control (blue).



(d) Dynamic of controls.



(e) Dynamic of cost.

Fig. 9. The effects of the strategy "treated bednets, condoms, indoor residual spray, and treatment" on the transmission of Zika virus. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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	∞

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

We obtain the *ICER* in Table 5 using the formula (see the equation in Box II).

Thus,

$$ICER(B) = \frac{36,208}{414.1392} = 87.4295,$$

$$ICER(D) = \frac{100,350 - 36,208}{432.4993 - 414.1392} = 3493.5540,$$

$$ICER(C) = \frac{46,261 - 100,350}{434.7281 - 432.4993} = -24268.21608,$$

$$ICER(A) = \frac{83,304 - 46,261}{434.7373 - 434.7281} = 4026413.0435,$$

$$ICER(E) = \frac{104,560 - 83,304}{434.7373 - 434.7373} = \infty.$$

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.

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	∞

Table 8
Exclusion of strategy A.

Strategy	Total infection averted	Cost($)	*ICER*
B	414.1392	36,208	87.4295
E	434.7377	104,560	3318.2999

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.

Based on the computed 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 symptomatic infected humans is the most cost effective of all the strategies for the control of the Zika virus considered in this work.

7. 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

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

Box II.

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 interest

The authors declare that there is no conflict of interests.

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