

Article

Optimal Control of Dengue Transmission with Vaccination

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Abstract: Dengue disease is caused by four serotypes of the dengue virus: DEN-1, DEN-2, DEN-3, and DEN-4. The chimeric yellow fever dengue tetravalent dengue vaccine (CYD-TDV) is a vaccine currently used in Thailand. This research investigates what the optimal control is when only individuals having documented past dengue infection history are vaccinated. This is the present practice in Thailand and is the latest recommendation of the WHO. The model used is the Susceptible-Infected-Recovered (SIR) model in series configuration for the human population and the Susceptible-Infected (SI) model for the vector population. Both dynamical models for the two populations were recast as optimal control problems with two optimal control parameters. The analysis showed that the equilibrium states were locally asymptotically stable. The numerical solution of the control systems and conclusions are presented.

Keywords: dengue disease; optimal control; vaccination



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1. Introduction

The dengue epidemic first occurred in the Philippines in 1954. It reached Thailand in 1958. The disease is caused by an infection by any one of the four serotypes of dengue virus, which are labeled as DEN-1, DEN-2, DEN-3, and DEN-4. The dengue viruses are transmitted by two species of the *Aedes* mosquitoes, the *Aedes aegypti* and the *Aedes albopictus*. All four serotypes have a common antigen, resulting in cross-reaction and cross-protection of the four serotypes. The cross protection is not permanent. A person infected by one of the serotypes will have permanent immunity to that serotype, but only partial immunity to the other three. Some of the immunity will last for a short period, approximately 6–12 months. Those people might be re-infected if they happen to meet a different serotype of dengue virus. This second infection is different from the initial infection and is labeled as a secondary dengue infection [1–4] since the symptoms and outcomes of the primary and secondary dengue infections can be quite different. In some individuals (infants or young children), infection by the dengue virus may lead to undifferentiated fever (uf). The individuals are said to have the viral syndrome of dengue fever, which can only be detected through laboratory tests. In older children and adults, infection by the dengue viruses leads to what is usually labeled as dengue fever (DF). People with DF exhibit symptoms such a mild fever, headaches, pain around the eyes, muscular pain, and pain in the bones. If an individual experiences the clinical symptoms of high fever accompanied by bleeding, enlarged liver, and severe shock, he is said to have dengue hemorrhagic fever (DHF). During the fever, there will also be a low platelet count and plasma leakage. If large amounts of plasma leak out, the patient will have a shock condition called dengue shock syndrome (DSS) [5–7]. The last two (DHF and DSS) are the symptoms that the individuals in the secondary dengue infection group experience. These symptoms can be viewed as an allergic reaction.

Since millions of people can be infected by the dengue virus, there is an economic cost to these people becoming sick, and vaccines have been developed. Chimeric yellow fever dengue tetravalent dengue vaccine (CYD-TDV) is one of these vaccines. It was first registered as a dengue vaccine in Mexico. It is now registered in 13 countries around the world, including Thailand, which had a role in its development. This dengue vaccine is the first and only vaccine in the world at the moment to cover all four strains of the dengue virus and is called Dengvaxia[®], which is developed by Sanofi Pasteur to help protect against the dengue disease. The vaccine has an overall effectiveness of 56.5%, which is 74% more effective in older children, 12–14 years old, and 75% effective for DEN-3 and DEN-4 [8,9]. It is reported that the efficacy of the vaccine is higher in children who have previously been infected with dengue fever. The dengue vaccine reduces the severity of the disease by 88.5% and hospitalization by 67.2% [10–12]. In December 2017, the WHO [13] issued a new recommendation that states that the WHO recommends vaccination (with Dengvaxia) only in individuals with a documented past dengue infection. This should be taken into consideration in any models used.

Esteva and Vargas [4,14] were among the first to study the transmission of dengue disease. They developed a mathematical model in which there were compartmental models for both the human and mosquito populations. The human population was described by a Susceptible-Infected-Recovered (SIR) model while the mosquito population was described by an SI (no recovered) model. Pongsumpun et al. [15–17] have also studied the transmission of dengue virus. Most of Pongsumpun's work has been centered on the situation in Thailand since the dengue fever is of major concern to Thailand. She has included an exposed class (E) to the model, making the Susceptible-Infected-Exposed-Recovered (SEIR) model, to describe the dynamics of the human population. In Ref. [16], the author used the SIR model to simulate the possible outcomes of vertical transmission of the virus among mosquitoes. She and her coworkers [17] included vertical transmission in a SEIR model. Syafruddin and Noorani [18] studied the mathematical model for dengue transmission and applied it to the situations in Indonesia and Malaysia. Yaacob [19] studied the mathematical model of the dengue disease in people who have no immunity.

Singh et al. [20] and Tasman et al. [21] considered the effects of vaccination on a model in which the human population is divided into children and adults. They also considered that there were two types of infections, primary and secondary dengue infection. It was assumed that individuals experiencing a secondary infection were at a higher risk. In these studies, the adults were further divided in two groups, so the human population consisted to three groups: less than 9 years, between 9 and 45 years, and between 45 and 65 years [22,23]. Using a similar model to study the transmission of another disease, melioidosis, Tavaen and Viriyapong [24] studied the local and global stability analyses and optimal control for this disease. There are many studies about the effects of the dengue vaccination on the spread of the dengue disease. [25–28]. They have introduced various models to simulate the dynamic of the programs when there is complete vaccination, random mass vaccination, imperfect random mass vaccination, and random mass vaccination with waning immunity levels. They have used optimal control strategies to simulate the results of the programs.

The number of cases and deaths by month and the number of cases and deaths each year in Thailand from 2003–2020 data from the Bureau of Epidemiology at the Ministry of Health is shown in Figure 1. It can be seen in the figure that the dengue fever is prevalent in the rainy season from June to September. The incidence is the highest in July. The number of cases, which fluctuated month to month, tended to increase yearly from 2003 to 2020. The same is true for the number of deaths. When the number of cases is high, there will be more deaths. The percentage of deaths is very small. Using the sources that gave these results, we were interested in the outcome of a vaccination program in which only individuals with a documented past dengue infection (i.e., an individual who would have a secondary dengue infection if bitten by a mosquito infected with a different serotype of the virus) are vaccinated. We used the double Susceptible-Infected-Recovered

(SIR) model for the human population and the Susceptible-Infected (SI) model for the vector population. The analysis of the stability of the model was carried out by using dynamic analysis. The Routh–Hurwitz criteria were applied to analyze the system model for stability. The reproductive number was calculated. The optimal control theory was applied in the transmission model in order to minimize the number of infected humans with primary and secondary infections. Numerical simulation was performed. Results and conclusion are presented in this paper.

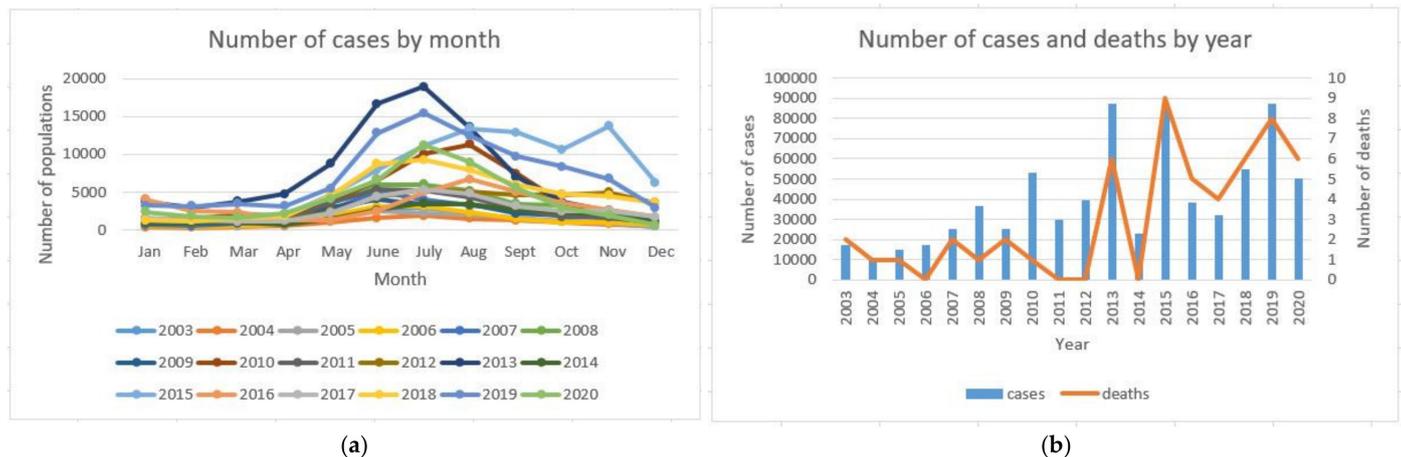


Figure 1. The number of cases by month and the number of cases and deaths each year from 2003–2020 [29]: (a) the number of cases by month; (b) the number of cases and deaths by year.

2. Materials and Methods

2.1. Mathematical Model

The basic mathematical model was the SEIR model presented in ref. [15]. The equations in that model describe the dynamics of the spread of dengue fever when there is only one serotype of the virus present. In this work, the basic SEIR model of [15] was extended to include secondary infection of a different serotype, whereby the members of the recovered population become the susceptible members in the second SIR, effectively providing a framework for describing a vaccination program in which only people who have been infected are considered. In Thailand, the medical status of each Thai citizen is kept at the District Office in each province in the country. It is easy to determine from the past medical histories anyone who was infected with the dengue virus. Dengue fever is one of the five diseases that must be reported to the Thai Ministry of Health. The susceptible human population in the second SIR model used here are the not sick humans who have been infected by the serotype A virus, since they will be the only ones given the vaccine. A person who has no prior history of any dengue infection is not considered to be a candidate for the vaccination. The vector population was divided into two compartments: susceptible and infected (SI). The infected mosquito was the subset of infected mosquitoes transmitting virus B. The human population was subdivided into six population groups. It should be remembered that all of the recovered individuals have the antibodies to a particular serotype of the dengue virus at the end of primary infection. Susceptible people of this kind are not born into this group; they emerge after several months of being infected by a serotype virus. The vector population was classified into two subclasses. The variables are defined in Table 1.

Table 1. The definition of the variables used in the differential system of Equations (1)–(10).

Variables	Definition
$\overline{S_{HP}}$	The number of humans susceptible to primary infection
$\overline{I_{HP}}$	The number of humans with a primary infection
$\overline{R_{HP}}$	The number of humans who have recovered from a primary infection
$\overline{S_{HS}}$	The number of humans susceptible to secondary infection
$\overline{I_{HS}}$	The number of humans with a secondary infection
$\overline{R_{HS}}$	The number of humans who have recovered from a secondary infection
$\overline{S_V}$	The number of susceptible vectors
$\overline{I_V}$	The number of infected vectors

The dynamic transmission of dengue disease with the vaccination model is shown in Figure 2.

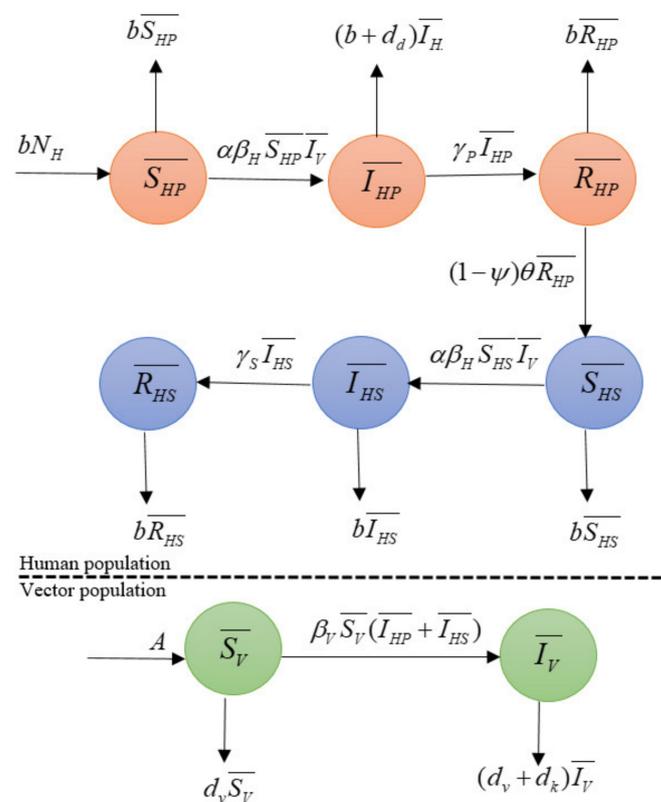


Figure 2. Diagram of the transmission model of dengue disease with the vaccination model of human and vector populations.

The dynamics of human and vector populations and the system of differential equations are given by:

$$\frac{d\overline{S_{HP}}}{dt} = bN_H - \alpha\beta_H\overline{S_{HP}}\overline{I_V} - b\overline{S_{HP}} \tag{1}$$

$$\frac{d\overline{I_{HP}}}{dt} = \alpha\beta_H\overline{S_{HP}}\overline{I_V} - \gamma_P\overline{I_{HP}} - (b + d_a)\overline{I_{HP}} \tag{2}$$

$$\frac{d\overline{R_{HP}}}{dt} = \gamma_P\overline{I_{HP}} - (1 - \psi)\theta\overline{R_{HP}} - b\overline{R_{HP}} \tag{3}$$

$$\frac{d\overline{S_{HS}}}{dt} = (1 - \psi)\theta\overline{R_{HP}} - \alpha\beta_H\overline{S_{HS}}\overline{I_V} - b\overline{S_{HS}} \tag{4}$$

$$\frac{d\overline{I_{HS}}}{dt} = \alpha\beta_H\overline{S_{HS}}\overline{I_V} - \gamma_S\overline{I_{HS}} - b\overline{I_{HS}} \tag{5}$$

$$\frac{d\overline{R_{HS}}}{dt} = \gamma_S \overline{I_{HS}} - b \overline{R_{HS}} \tag{6}$$

$$\frac{d\overline{S_V}}{dt} = A - \beta_V \overline{S_V} (\overline{I_{HP}} + \overline{I_{HS}}) - d_V \overline{S_V} \tag{7}$$

$$\frac{d\overline{I_V}}{dt} = \beta_V \overline{S_V} (\overline{I_{HP}} + \overline{I_{HS}}) - (d_V + d_k) \overline{I_V} \tag{8}$$

with the conditions:

$$\overline{S_{HP}} + \overline{I_{HP}} + \overline{R_{HP}} + \overline{S_{HS}} + \overline{I_{HS}} + \overline{R_{HS}} = N_H \tag{9}$$

$$\overline{S_V} + \overline{I_V} = N_V \tag{10}$$

where the parameters of Equations (1)–(10) are defined in Table 2.

Table 2. The definition of the parameters of the differential system of Equations (1)–(10).

Parameters	Definition
α	The biting rate of the vector population
ψ	The vaccine efficiency
θ	The recurrent infection rate
N_H	The total number of humans in the study population
N_V	The total number of vectors in the study population
β_H	The transmission rate of dengue virus from vector to human
β_V	The transmission rate of dengue virus from human to vector
b	The birth and natural mortality rate of the human population
d_V	The natural mortality rate of the vector population
d_d	The mortality rate from infection of the human population
d_k	The mortality rate from infection of the vector population
γ_P	The recovery rate of those with a primary infection
γ_S	The recovery rate of those with a secondary infection

The rate of change of both the total population of humans and vectors is zero and given by:

$$\frac{d\overline{S_{HP}}}{dt} + \frac{d\overline{I_{HP}}}{dt} + \frac{d\overline{R_{HP}}}{dt} + \frac{d\overline{S_{HS}}}{dt} + \frac{d\overline{I_{HS}}}{dt} + \frac{d\overline{R_{HS}}}{dt} = 0 \tag{11}$$

$$\frac{d\overline{S_V}}{dt} + \frac{d\overline{I_V}}{dt} = 0 \tag{12}$$

with conditions, we get:

$$d_d \overline{I_{HP}} = 0 \tag{13}$$

$$d_k \overline{I_V} + d_V N_V = A \tag{14}$$

Normalizing the equations by introducing the following normalized variables:

$$S_{HP} = \frac{\overline{S_{HP}}}{N_H}, I_{HP} = \frac{\overline{I_{HP}}}{N_H}, R_{HP} = \frac{\overline{R_{HP}}}{N_H}, S_{HS} = \frac{\overline{S_{HS}}}{N_H}, I_{HS} = \frac{\overline{I_{HS}}}{N_H}, R_{HS} = \frac{\overline{R_{HS}}}{N_H} \tag{15}$$

$$S_V = \frac{\overline{S_V}}{N_V}, I_V = \frac{\overline{I_V}}{N_V} \tag{16}$$

with the additional condition:

$$S_{HP} + I_{HP} + R_{HP} + S_{HS} + I_{HS} + R_{HS} = 1 \tag{17}$$

$$S_V + I_V = 1 \tag{18}$$

The mathematical model of Equations (1)–(8) is now reduced to the following equation:

$$\frac{dS_{HP}}{dt} = b - \alpha\beta_H S_{HP} I_V N_V - bS_{HP} \tag{19}$$

$$\frac{dI_{HP}}{dt} = \alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - (b + d_d) I_{HP} \tag{20}$$

$$\frac{dR_{HP}}{dt} = \gamma_P I_{HP} - (1 - \psi)\theta R_{HP} - bR_{HP} \tag{21}$$

$$\frac{dS_{HS}}{dt} = (1 - \psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - bS_{HS} \tag{22}$$

$$\frac{dI_{HS}}{dt} = \alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - bI_{HS} \tag{23}$$

$$\frac{dI_V}{dt} = \beta_V(1 - I_V)(I_{HP} + I_{HS})N_H - (d_V + d_k)I_V \tag{24}$$

2.2. The Equilibrium Points

Definition 1 ([17]). *The point $\tilde{X} \in \mathbb{R}^n$ is an equilibrium point for the differential equation $\frac{dX}{dt} = f(t, X)$ if $f(t, \tilde{X}) = 0$ for all t .*

Since epidemiological models are inherently dynamical systems, the knowledge of the equilibrium points is vital for determining the behavior of long-term dynamics. Towards this goal, the most important parameter for determining whether an outbreak will occur or not is the basic reproductive number R_0 . The equilibrium points are obtained by setting the right-hand side of Equations (19)–(24) to zero. This system model now admits two equilibrium points, namely the disease-free point and an endemic equilibrium point. The disease-free equilibrium point E_1 is:

$$E_1 = (1, 0, 0, 0, 0) \tag{25}$$

The endemic equilibrium point $E_2 = (S_{HP}^*, I_{HP}^*, R_{HP}^*, S_{HS}^*, I_{HS}^*, I_V^*)$ is:

$$\begin{aligned} S_{HP}^* &= \frac{\tau_1(b(2\theta(\psi-1)\gamma_P) - \tau_2) - \tau_7 + \sqrt{\tau_3(\tau_4 + \tau_5) + \tau_7^2}}{\tau_6} \\ I_{HP}^* &= \frac{b\tau_1\tau_2 + \tau_7 - \sqrt{\tau_3(\tau_4 + \tau_5) + \tau_7^2}}{\tau_6} \\ R_{HP}^* &= \frac{b\tau_1\tau_2 + \tau_7 + \sqrt{\tau_3(\tau_4 + \tau_5) + \tau_7^2}}{\tau_6} \\ S_{HS}^* &= \frac{\tau_7 + (\tau_3 - \tau_{25} + \tau_{26})\sqrt{\tau_3(\tau_4 + \tau_5) + \tau_7^2} + \tau_{22}}{\tau_{18}\tau_{19}\tau_{20}\tau_{21}} \\ I_{HS}^* &= \frac{\tau_7 + (\tau_3 - \tau_{25} + \tau_{26})\sqrt{\tau_3(\tau_4 + \tau_5) + \tau_7^2} - \tau_{22}}{\tau_{18}\tau_{19}\tau_{20}\tau_{21}} \\ I_V^* &= \frac{\sqrt{\tau_3(\tau_4 + \tau_5) + \tau_7^2} - \tau_{22} - \tau_7}{\tau_{27} + \tau_{28}} \end{aligned} \tag{26}$$

where:

$$\begin{aligned}
 \tau_1 &= b\alpha N_H N_V \beta_H \beta_V, \quad \tau_2 = (b + \theta - \theta\psi)(b + \gamma_S), \quad \tau_3 = b^2 \alpha^2 N_H N_V^2 \beta_H^2 \beta_V, \\
 \tau_4 &= 4\theta(\psi - 1)(d_V + d_k)(b + \alpha N_V \beta_H)(b + d_d + \gamma_P)\gamma_P \tau_2, \\
 \tau_5 &= N_H \beta_V b \tau_2, \quad \tau_6 = 2\alpha\theta(\psi - 1)N_H N_V \beta_H (b + \alpha N_V \beta_H)\beta_V \gamma_P (b + d_d + \gamma_P), \\
 \tau_7 &= \alpha N_V \beta_H (\theta(\psi - 1)\gamma_P) + \tau_2, \quad \tau_8 = 2(b + d_d + \gamma_P)\tau_2, \\
 \tau_9 &= 2b^2 \alpha\theta(\psi - 1)(d_V + d_k)N_V \beta_H \gamma_P, \\
 \tau_{10} &= 2b\alpha^2 \theta^2 (\psi - 1)^2 (d_V + d_k)N_V^2 \beta_H^2 \gamma_P (d_d + \gamma_P)\gamma_S, \\
 \tau_{11} &= \theta - \theta\psi + d_d + \alpha N_V \beta_H + \gamma_P + \gamma_S, \\
 \tau_{12} &= \theta(\psi - 1)(\gamma_P + d_d) - \alpha N_V \beta_H - \gamma_S, \\
 \tau_{13} &= (\theta(\psi - 1) - \gamma_P - \gamma_S)(\alpha N_V \beta_H + 1), \\
 \tau_{14} &= \alpha\theta(\psi - 1)N_V \beta_H (d_d + \gamma_P), \quad \tau_{15} = d_d(\theta(\psi - 1) - \alpha N_V \beta_H), \\
 \tau_{16} &= (2b\alpha N_V \beta_H (\theta - \theta\psi)\gamma_P + (b + \theta - \theta\psi)(b + \gamma_S))^2, \\
 \tau_{17} &= b^2 \left(2\theta^2 (\psi - 1)^2 \gamma_P^2 - 2\theta(\psi - 1)\gamma_P \tau_2 + \tau_2^2 \right), \\
 \tau_{18} &= 4b^2 \alpha^2 \theta(\psi - 1)(b + \theta - \theta\psi)N_H N_V^2 \beta_H^2 (b + \alpha N_V \beta_H)^2, \quad \tau_{19} = \beta_V \gamma_P (b + d_d + \gamma_P), \\
 \tau_{20} &= \tau_2 (d_k (b + d_d + \gamma_P) - d_V (b + d_d + \gamma_P) + 1), \quad \tau_{21} = b N_H \beta_V (\theta - \theta\psi)\gamma_P, \\
 \tau_{22} &= b\alpha N_V \beta_H \tau_8 (d_V + d_k) + N_H \beta_V b \tau_7, \\
 \tau_{23} &= \tau_9 (b^3 + b^2 \tau_{11} - b \tau_{12} - \tau_{14} \tau_{15}) - \tau_{10} + \tau_{13} + \tau_1 \tau_{16} \tau_{17}, \\
 \tau_{24} &= b^2 (\theta\psi - \alpha N_V \beta_H + \gamma_S) + b\alpha\theta N_V \beta_H (\psi - 1), \\
 \tau_{25} &= \theta(\psi + 1)(2b\theta\gamma_S + \alpha N_V \beta_H \gamma_P + b\gamma_S), \\
 \tau_{26} &= N_V \beta_H \gamma_S (\alpha\theta\psi - b\alpha - \alpha\theta) + b^2 (1 + b), \\
 \tau_{27} &= 2\alpha^2 N_V^2 \beta_H^2 (d_V + d_k)\tau_8, \quad \tau_{28} = b N_H \beta_V (\theta - \theta\psi)\gamma_P + \tau_2
 \end{aligned}$$

2.3. The Basic Reproductive Number

Definition 2 ([24]). Basic reproductive number (R_0) is defined as the average number of secondary infections when a single infective enters an entirely susceptible population.

The basic reproductive number (R_0) is obtained using the next-generation matrix method [30–32]. We selected I_{HP} , I_{HS} , and I_V to be the classes to construct the F and V matrices, which are important to this method. For our system, the matrices F and V contain new infection terms and transition terms. We evaluated the Jacobian matrices F and V at the disease-free equilibrium point $E_1 = (1, 0, 0, 0, 0)$, where F is non-negative and V is non-singular. The F (gains) and V (losses) matrices are:

$$F = \begin{bmatrix} \frac{\partial f_1}{\partial I_{HP}}(E_1) & \frac{\partial f_1}{\partial I_{HS}}(E_1) & \frac{\partial f_1}{\partial I_V}(E_1) \\ \frac{\partial f_2}{\partial I_{HP}}(E_1) & \frac{\partial f_2}{\partial I_{HS}}(E_1) & \frac{\partial f_2}{\partial I_V}(E_1) \\ \frac{\partial f_3}{\partial I_{HP}}(E_1) & \frac{\partial f_3}{\partial I_{HS}}(E_1) & \frac{\partial f_3}{\partial I_V}(E_1) \end{bmatrix}, \quad V = \begin{bmatrix} \frac{\partial v_1}{\partial I_{HP}}(E_1) & \frac{\partial v_1}{\partial I_{HS}}(E_1) & \frac{\partial v_1}{\partial I_V}(E_1) \\ \frac{\partial v_2}{\partial I_{HP}}(E_1) & \frac{\partial v_2}{\partial I_{HS}}(E_1) & \frac{\partial v_2}{\partial I_V}(E_1) \\ \frac{\partial v_3}{\partial I_{HP}}(E_1) & \frac{\partial v_3}{\partial I_{HS}}(E_1) & \frac{\partial v_3}{\partial I_V}(E_1) \end{bmatrix}$$

where:

$$f = \begin{bmatrix} f_1 \\ f_2 \\ f_3 \end{bmatrix} = \begin{bmatrix} \alpha\beta_H S_{HP} I_V N_V \\ \alpha\beta_H S_{HS} I_V N_V \\ \beta_V (I_{HP} + I_{HS}) N_H \end{bmatrix}, \quad v = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix} = \begin{bmatrix} (\gamma_P + b + d_d) I_{HP} \\ (\gamma_S + b) I_{HS} \\ (d_V + d_k) I_V \end{bmatrix}$$

The required matrices are:

$$F = \begin{bmatrix} 0 & 0 & \alpha\beta_H N_V \\ 0 & 0 & 0 \\ \beta_V N_H & \beta_V N_H & 0 \end{bmatrix}, \quad V = \begin{bmatrix} \gamma_P + b + d_d & 0 & 0 \\ 0 & \gamma_S + b & 0 \\ 0 & 0 & d_V + d_k \end{bmatrix}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{\gamma_P + b + d_d} & 0 & 0 \\ 0 & \frac{1}{\gamma_S + b} & 0 \\ 0 & 0 & \frac{1}{d_V + d_k} \end{bmatrix}$$

Since $R = FV^{-1}$, we have:

$$R = \begin{bmatrix} 0 & 0 & \frac{\alpha N_V \beta_H}{d_V + d_k} \\ 0 & 0 & 0 \\ \frac{N_H \beta_V}{b + d_d + \gamma_P} & \frac{N_H \beta_V}{b + \gamma_S} & 0 \end{bmatrix}$$

R_0 is the dominant eigenvalue of the matrix R ; then, the value of the basic reproductive number is given by:

$$R_0 = \sqrt{\frac{\alpha N_H N_V \beta_H \beta_V}{d_k(b + d_d) + d_V(b + d_d) + \gamma_P(d_V + d_k)}} \tag{27}$$

2.4. Local Stability of Equilibrium Points

Definition 3 ([14]). The equilibrium point E_0 of the system $\dot{X} = f(X)$ is locally asymptotically stable if the matrix $J = \frac{\partial f}{\partial X}(E_0)$ has all its eigenvalues with negative real parts. The equilibrium point E_0 is not stable if at least one of the eigenvalues of the matrix J has a positive real part.

The local stability of each equilibrium point states of this model is determined from the Jacobian matrix at that equilibrium point of the system of Equations (19)–(24). The Jacobian matrix is:

$$J_{E_i} = \begin{bmatrix} -\alpha\beta_H I_V N_V - b & 0 & 0 & 0 & 0 & -\alpha\beta_H S_{HP} N_V \\ \alpha\beta_H I_V N_V & -\gamma_P - d_d - b & 0 & 0 & 0 & \alpha\beta_H S_{HP} N_V \\ 0 & \gamma_P & -(1 - \psi)\theta - b & 0 & 0 & 0 \\ 0 & 0 & (1 - \psi)\theta & -\alpha\beta_H I_V N_V - b & 0 & -\alpha\beta_H S_{HS} N_H \\ 0 & 0 & 0 & \alpha\beta_H I_V N_V & -\gamma_S - b & \alpha\beta_H S_{HS} N_H \\ 0 & \beta_V N_H(1 - I_V) & 0 & 0 & \beta_V N_H(1 - I_V) & -\beta_V N_H(I_{HP} + I_{HS}) - (d_V + d_k) \end{bmatrix} \tag{28}$$

Theorem 1. At the equilibrium point E_1 , the disease-free state is locally asymptotically stable when $R_0 < 1$.

Proof. See the proof of Theorem A1 in Appendix A. □

Theorem 2. The equilibrium point E_2 is locally asymptotically stable when $R_0 > 1$.

Proof. See the proof of Theorem A2 in Appendix A. □

3. Numerical Simulation

In this section, the numerical analysis of the transmission of dengue disease with the vaccination will only consider individuals who have a documented history of past dengue infection or have died from the infection. The parameter values within this model are listed in Table 3. Note that though most of the parameters are taken from the literature, some of the values need to be assumed for the purpose of this investigation. The use of N_H and N_V values of 10,000 for both cases reflects a small rural town, for example, one like

Mae Hong Son, with a lower socio-economic status, which is very useful for investigating the efficiency of the vaccination program. Note that we also assume a constant vector population, which is appropriate for this case since the town is small, and far away from larger cities such as Bangkok. The value of d_d will be assumed to be $1/180$ for both the disease-free and endemic equilibrium cases. This value is close to the reported values of 500 deaths per population of 100,000 [33]. The value of d_k is assumed to be the same as the reported natural mortality rate. The model is then simulated with the use of the Runge–Kutta differential equation solver in MATLAB. The numerical results are shown in Figures 3–6.

Table 3. The parameters used in the numerical simulation.

Parameters	Disease-Free	Endemic	References
α	1/7	1/7	[1,9], [15–17], [29,33]
ψ	1/2	1/2	[1,9], [15–17], [29,33]
θ	$1/(30 \times 6)$	$1/(30 \times 6)$	[1–4]
N_H	10.000	10.000	assumed
N_V	10.000	10.000	assumed
β_H	0.0000080	0.0050	assumed
β_V	0.0000065	0.0030	assumed
b	$1/(365 \times 70)$	$1/(365 \times 70)$	[1,9], [15–17], [29,33]
d_V	1/14	1/14	[1,9], [15–17], [29,33]
d_d	1/180	1/180	assumed
d_k	1/14	1/14	assumed
γ_P	1/10	1/10	[1,9], [15–17], [29,33]
γ_S	1/14	1/14	[1,9], [15–17], [29,33]

For the case of larger cities such as Chiang Mai or Khon Kaen, etc., we assume that:

Case 1: the number humans $N_H = 500,000$ and the number of vectors $N_V = 100,000$, while for

Case 2: the number of humans $N_H = 500,000$ and the number of vectors $N_V = 100,000e^{(-1/14)t}$ to investigate their implications.

Note that Case 2 simulates the situation where the size of the vector population is not constant but is rather a function of time. The exponential power of $-1/14$ is also used to reflect the natural death rate of the vector population. It can be seen from Figures 7 and 8 that there is a small change in trajectory from Case 1 to Case 2, which is to be expected since the total vector population slowly decays.

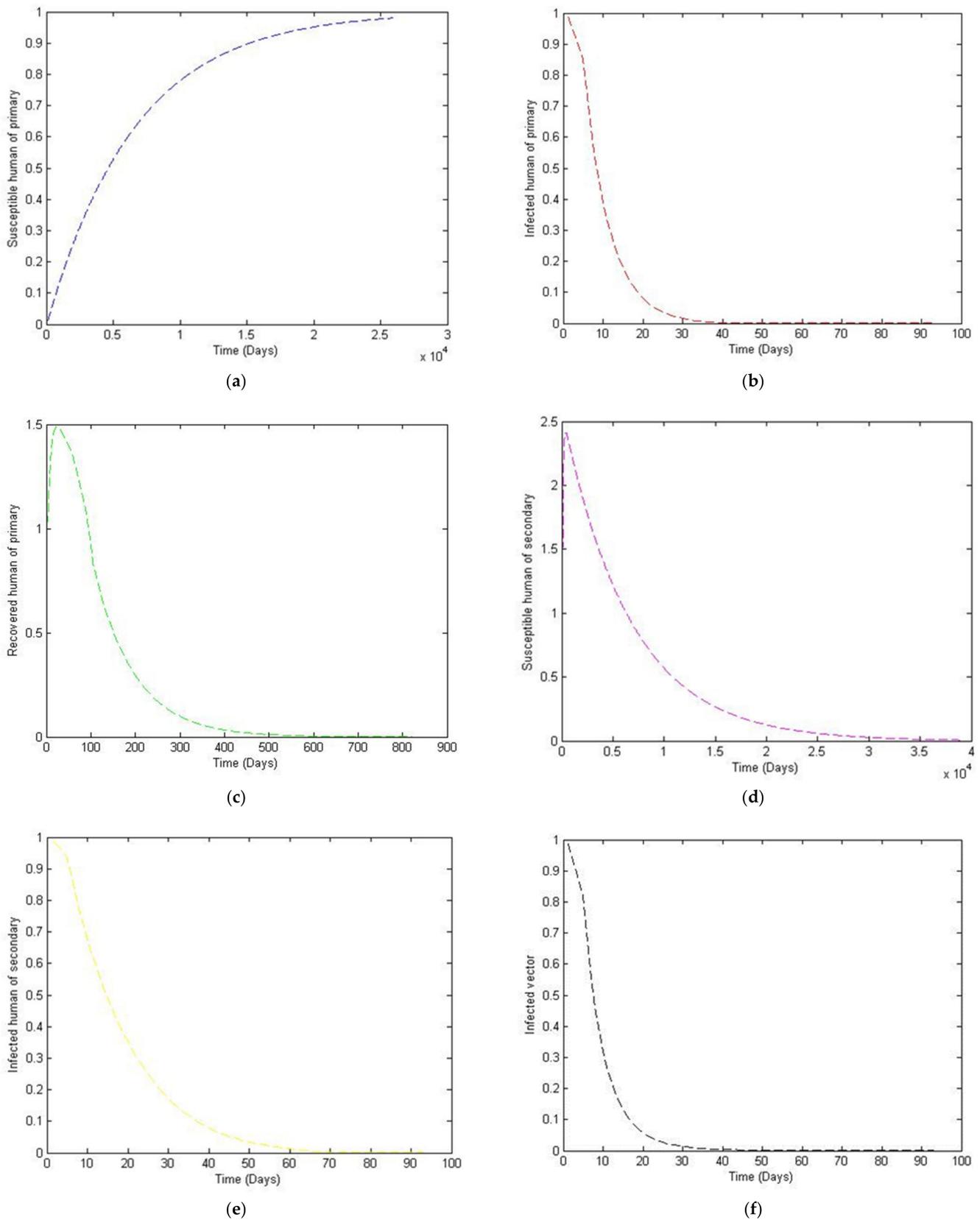


Figure 3. The trajectory of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V toward the disease-free equilibrium point for $R_0 < 1$ with parameter values according to Table 1. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

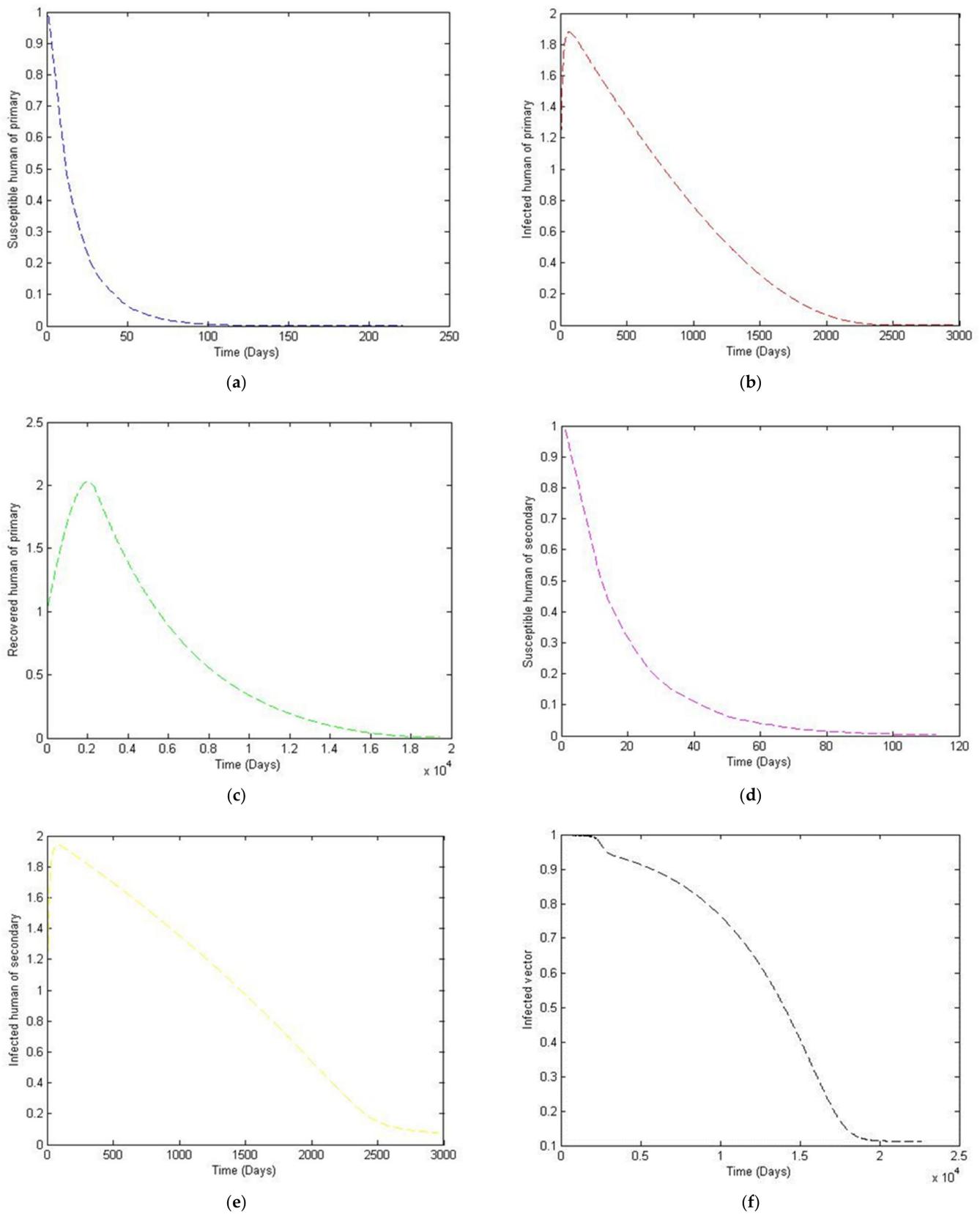


Figure 4. The trajectory of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V toward the endemic equilibrium point, for $R_0 > 1$ with parameter values according to Table 3. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

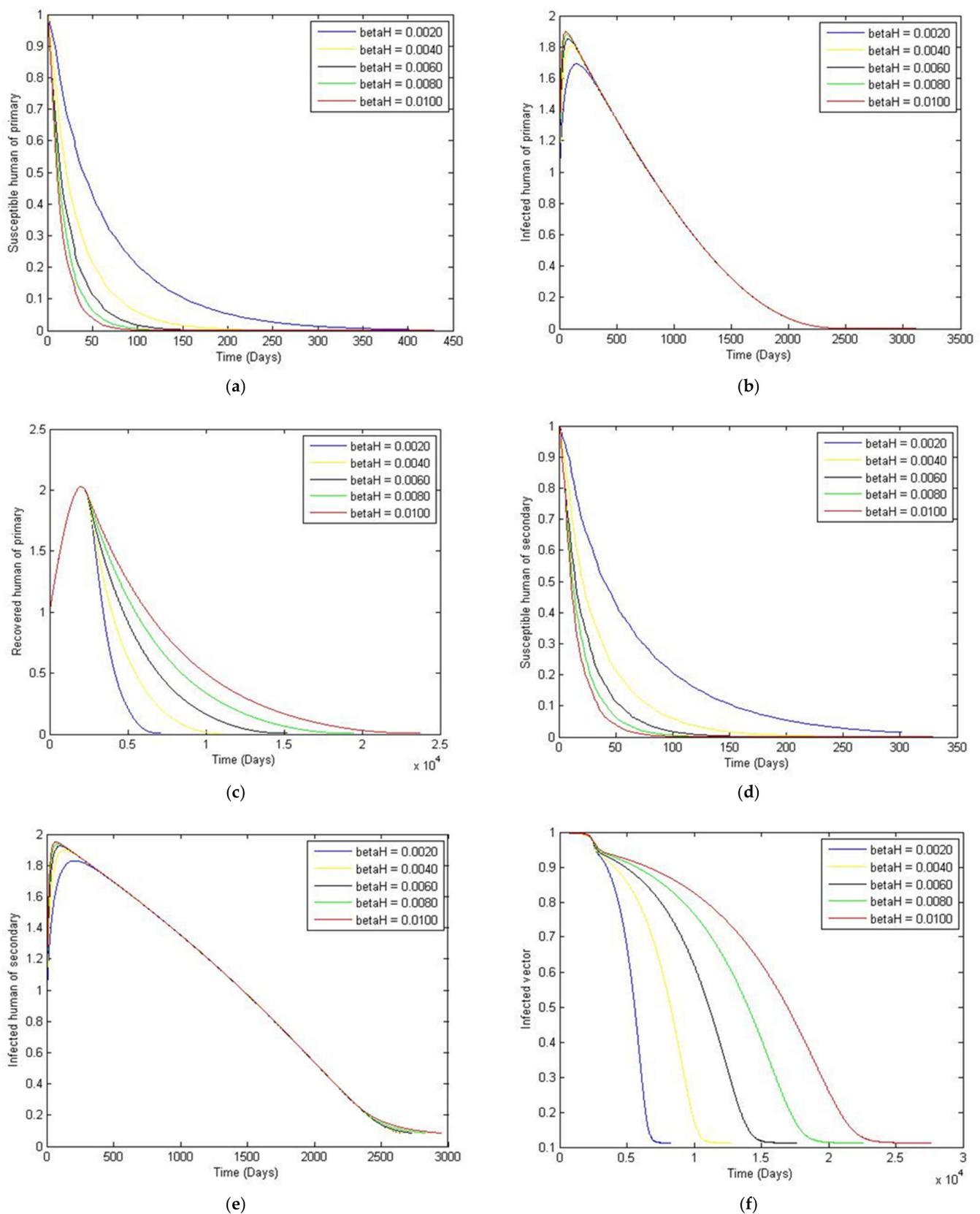


Figure 5. The trajectory of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V toward the endemic equilibrium point for $R_0 > 1$ with a comparison of the transmission rate of the dengue virus from vector to human, $\beta_H = 0.0020, 0.0040, 0.0060, 0.0080, 0.0100$, and parameter values according to Table 3. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

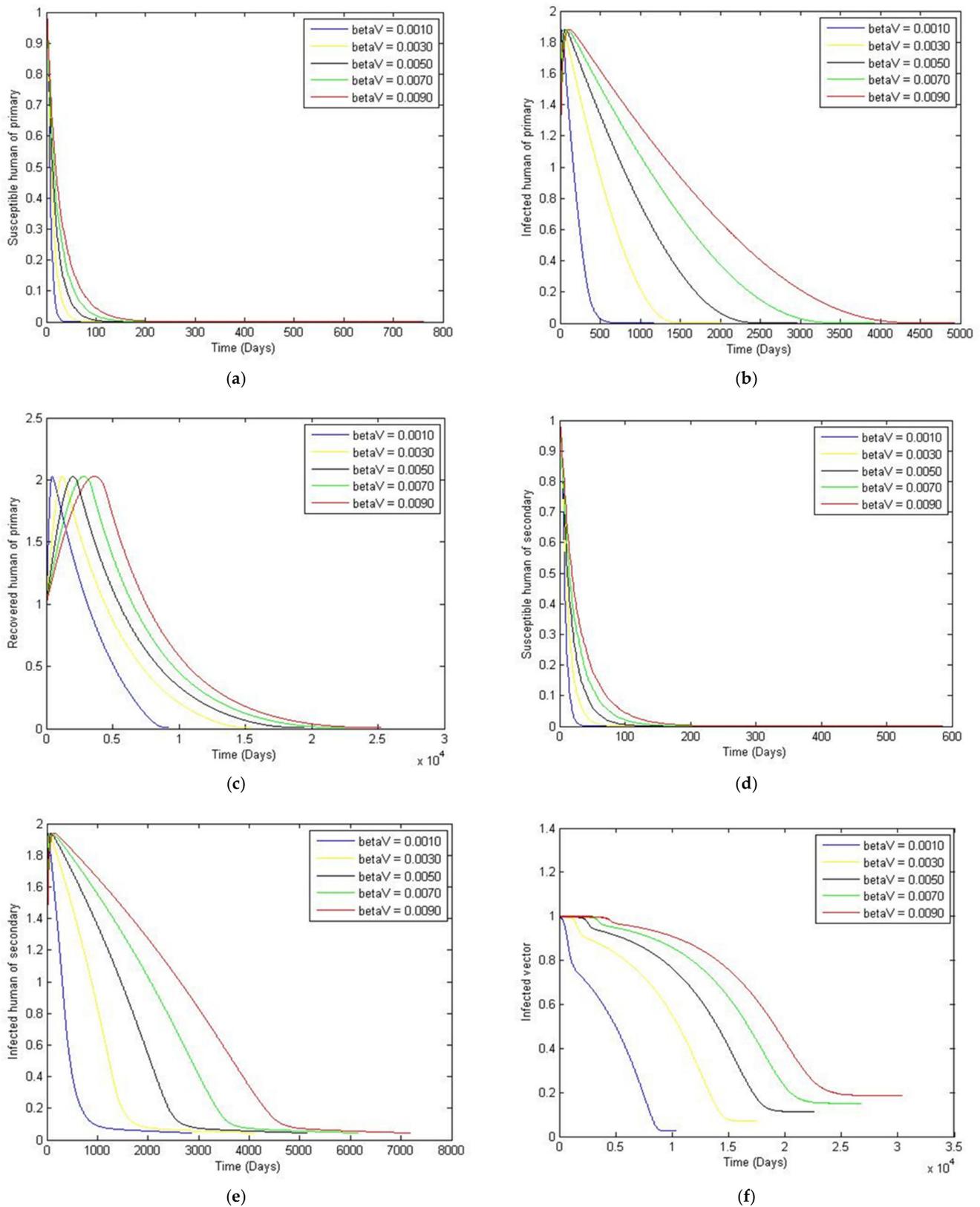


Figure 6. The trajectory of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V toward the endemic equilibrium point for $R_0 > 1$ with a comparison of the transmission rate of the dengue virus from human to vector, $\beta_V = 0.0010, 0.0030, 0.0050, 0.0070, 0.0090$, and parameter values according to Table 3. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

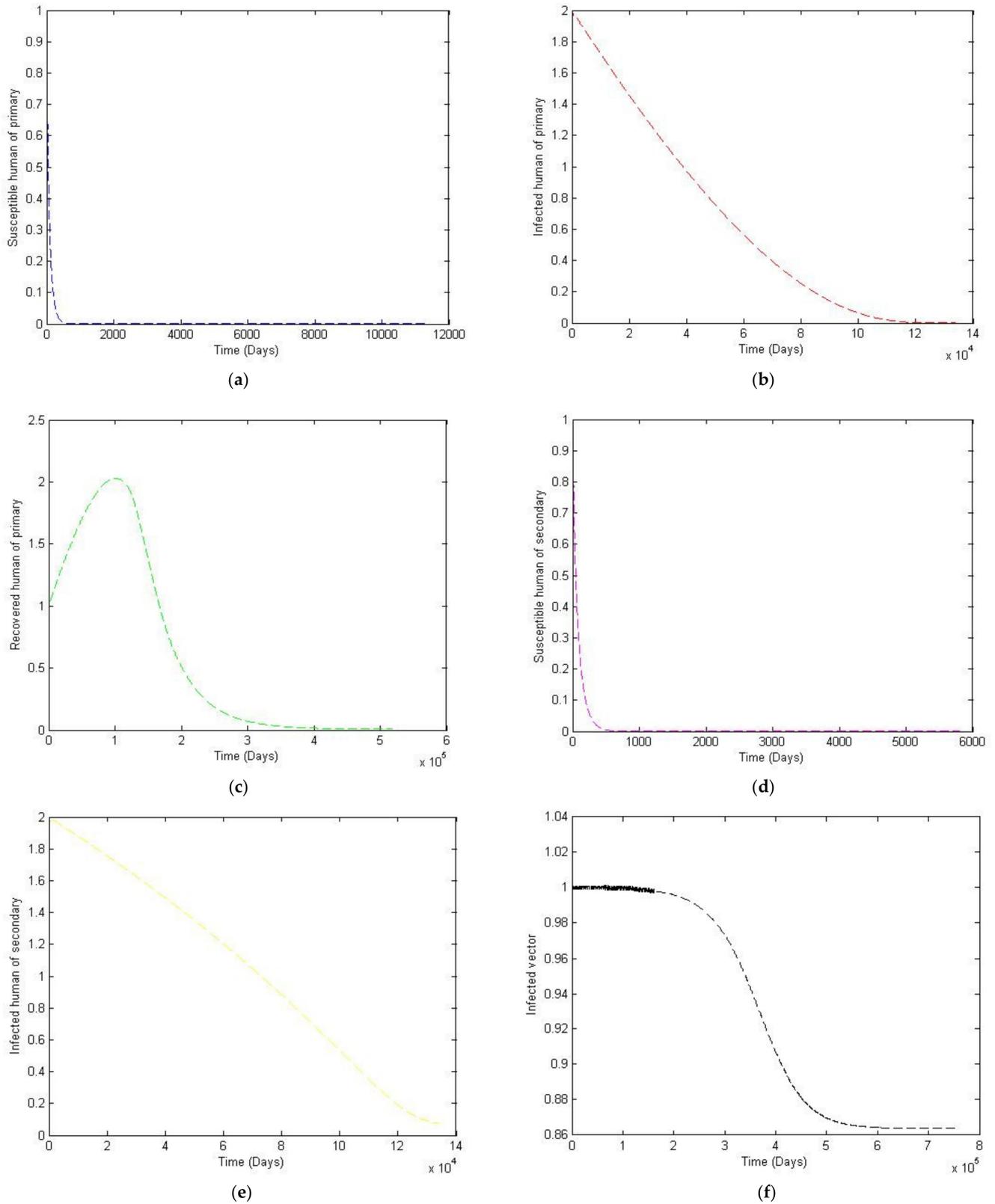


Figure 7. The trajectory of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V toward the endemic equilibrium point for $R_0 > 1$ with parameter values according to Table 3; changes $N_H = 500,000$, and $N_V = 100,000$. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

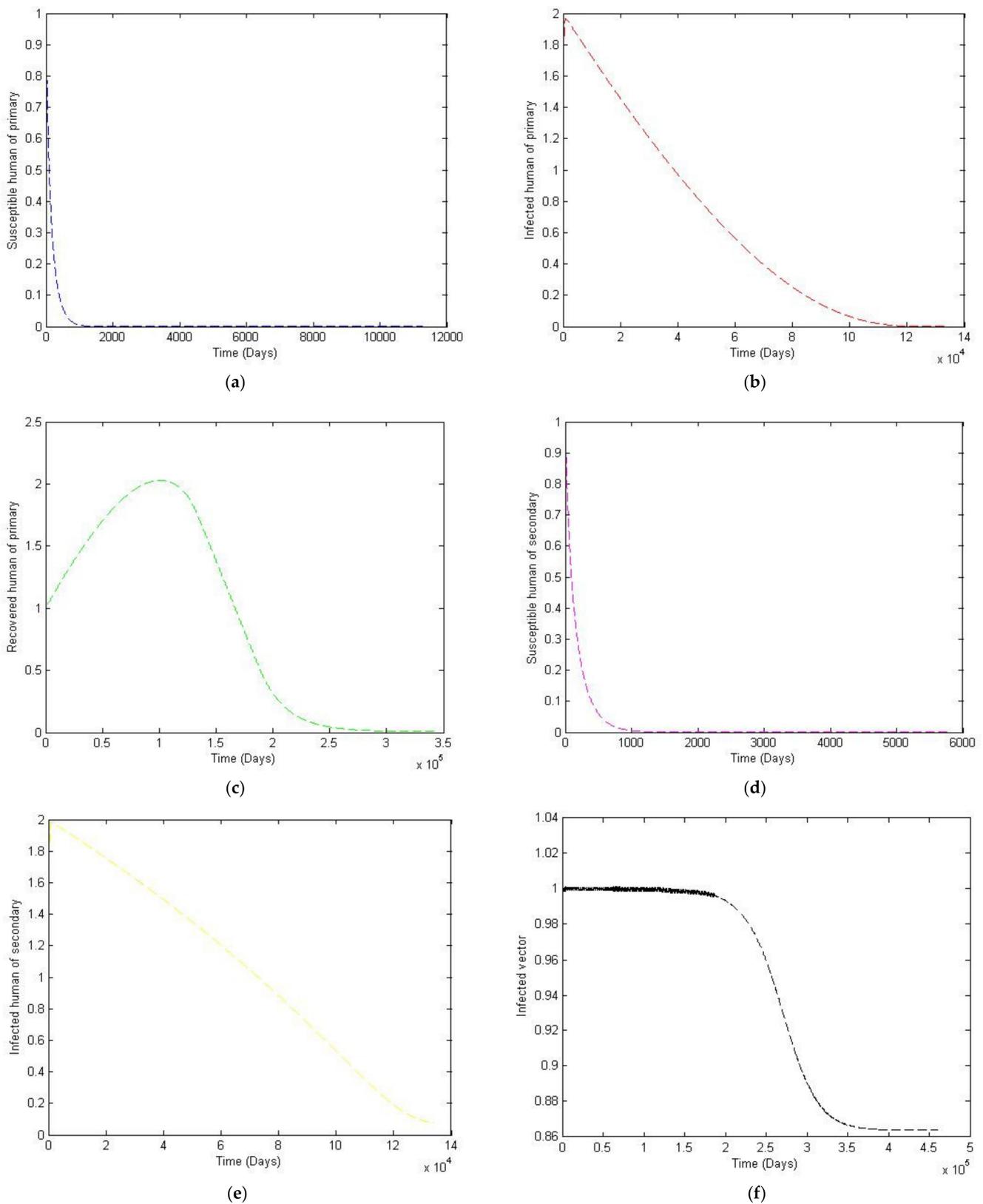


Figure 8. The trajectory of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V toward the endemic equilibrium point for $R_0 > 1$ with parameter values according to Table 3; changes $N_H = 500,000$, and $N_V = 100,000e^{(-1/14)t}$. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

Sensitivity Analysis of Parameters

The index tells us which parameters have a high impact on the basic reproductive number, R_0 , and should be targeted by intervention strategies. In addition, the sensitivity index allows us to measure relative changes in variables as parameters change. The normalized forward sensitivity index of a variable related to a parameter is the ratio of the relative change in the variable to the relative change in the parameter [34].

Definition 4 (Chitnis, Hyman, and Cushing [34]). *The normalized forward sensitivity index of R_0 , which depends differentiably on a parameter p , is defined by:*

$$\frac{R_0}{p} = \frac{\partial R_0}{\partial p} \times \frac{p}{R_0} \tag{29}$$

Given an expression for R_0 in Equation (27), the sensitivity index of Equation (29) can now be used to evaluate the index of each parameter. Note that the sensitivity index could be a function of some parameters, or a number, signifying its independence of any parameter. Table 4 shows the sensitivity index of R_0 to all the parameters of Table 3.

Table 4. Sensitivity indices $\frac{R_0}{p}$ evaluated at the baseline parameter values of Table 1.

Parameters	Sensitivity
α	0.5
N_H	0.5
N_V	0.5
β_H	0.5
β_V	0.5
b	-0.0001141
d_V	-0.1666667
d_d	-0.20825858
d_k	-0.3333333
γ_P	-0.2916001

Figure 9 plots a comparison of the R_0 values against the changes in d_d and γ_P . It can be seen that as the d_d and γ_P values change, the increment of R_0 in d_d is more pronounced than that of γ_P . This is reflected in the $\frac{R_0}{p}$ index, where $\frac{R_0}{d_d}$ is significantly larger than $\frac{R_0}{\gamma_P}$. Note that a similar definition to Equation (29) with regards to the sensitivity of I_V^* with respect to the parameters could also be given. However, due to the algebraic complexities of I_V^* in Equation (26), a numerical plot is instead given. It is apparent in Figure 10 that as β_V changes, the endemic equilibrium I_V^* also changes somewhat linearly.

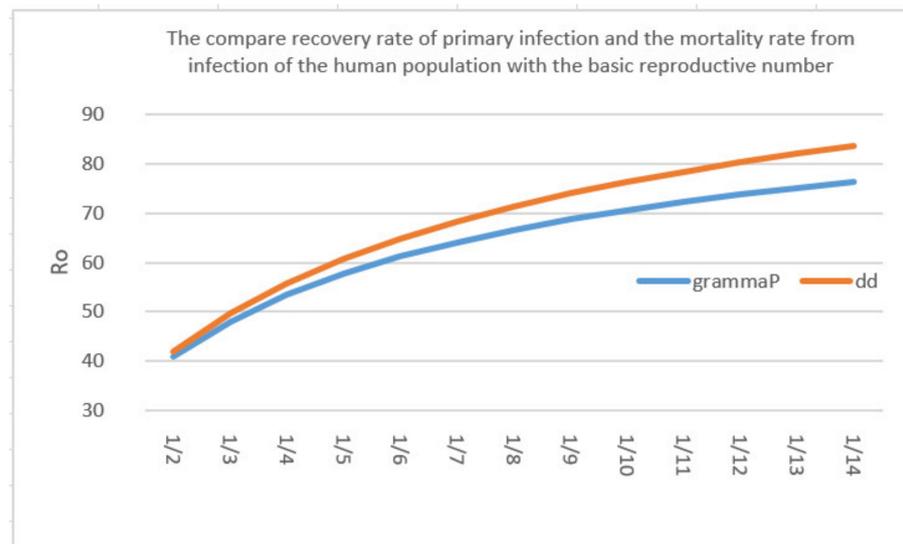


Figure 9. A comparison of parameters between d_d and γ_P with R_0 .

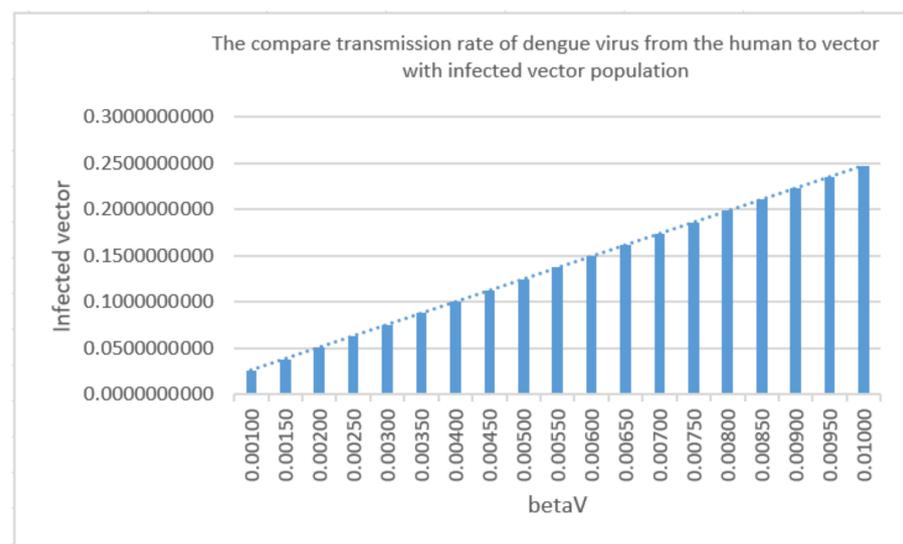


Figure 10. A comparison of parameters between β_V with I_V^* .

4. The Optimal Control Problem

In this section, the solution of the optimal control problem is discussed. The Pontryagin Minimum Principle (PMP) theory is used to solve this problem. Equations (19)–(24) will be recast as a control problem. The purpose of this is to recast the problem as one of minimizing the number of infected humans to achieve an optimal outcome. Since, the system consists of two dynamics, one for the humans and the other for the vectors, two control parameters will be needed, u_1 for the human population and u_2 for the vector population. u_1 is the vaccination rate and u_2 is the rate at which the breeding of the *Aegypti* mosquitoes is annihilated. This model can be written as the system of the equation as follows:

$$\frac{dS_{HP}}{dt} = b - \alpha\beta_H S_{HP} I_V N_V - bS_{HP} \tag{30}$$

$$\frac{dI_{HP}}{dt} = \alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - (b + d_d) I_{HP} \tag{31}$$

$$\frac{dR_{HP}}{dt} = \gamma_P I_{HP} - (1 - \psi)\theta R_{HP} - bR_{HP} \tag{32}$$

$$\frac{dS_{HS}}{dt} = (1 - \psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - bS_{HS} - u_1(t)I_{HS} \tag{33}$$

$$\frac{dI_{HS}}{dt} = \alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - bI_{HS} \tag{34}$$

$$\frac{dR_{HS}}{dt} = \gamma_S I_{HS} - bR_{HS} \tag{35}$$

$$\frac{dS_V}{dt} = \frac{A}{N_V} - \beta_V S_V (I_{HP} + I_{HS}) N_H - d_V S_V - u_2(t)S_V \tag{36}$$

$$\frac{dI_V}{dt} = \beta_V S_V (I_{HP} + I_{HS}) N_H - (d_V + d_k) I_V - u_2(t)\beta_V S_V (I_{HP} + I_{HS}) N_H \tag{37}$$

In terms of the normalized compartments, the differential equations become:

$$\frac{dS_{HP}}{dt} = b - \alpha\beta_H S_{HP} I_V N_V - bS_{HP} \tag{38}$$

$$\frac{dI_{HP}}{dt} = \alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - (b + d_d) I_{HP} \tag{39}$$

$$\frac{dR_{HP}}{dt} = \gamma_P I_{HP} - (1 - \psi)\theta R_{HP} - bR_{HP} \tag{40}$$

$$\frac{dS_{HS}}{dt} = (1 - \psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - bS_{HS} - u_1(t)I_{HS} \tag{41}$$

$$\frac{dI_{HS}}{dt} = \alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - bI_{HS} \tag{42}$$

$$\frac{dI_V}{dt} = \beta_V S_V (I_{HP} + I_{HS}) N_H - (d_V + d_k) I_V - u_2(t)\beta_V S_V (I_{HP} + I_{HS}) N_H \tag{43}$$

All parameters retain same definitions as before. The optimal control problems of Equations (38)–(43), require a definition of the objective function given as:

$$J(u_1, u_2) = \min \int_0^T \left[X_1 I_{HP} + X_2 I_{HS} + \frac{1}{2} (X_3 u_1^2(t) + X_4 u_2^2(t)) \right] dt \tag{44}$$

with initial condition $S_{HP} \geq 0, I_{HP} \geq 0, R_{HP} \geq 0, S_{HS} \geq 0, I_{HS} \geq 0, R_{HS} \geq 0, S_V \geq 0,$ and $I_V \geq 0$. The constants $X_1, X_2, X_3,$ and X_4 are weight constants and the terms $X_3 u_1^2(t)$ and $X_4 u_2^2(t)$ represent the costs associated with the control variables u_1 and u_2 , respectively. We can assign an optimal solution of this model optimal control problem by using the Lagrangian and the Hamiltonian of the problems. The Lagrangian of the optimal control problem is given by:

$$L(I_H, I_V, u_1, u_2) = X_1 I_{HP} + X_2 I_{HS} + \frac{1}{2} (X_3 u_1^2(t) + X_4 u_2^2(t)) \tag{45}$$

Theorem 3. We consider the objective function J given by Equation (44) with $(u_1, u_2) \in U$ subjecting to the control system of Equations (38)–(43) with initial condition. There exists $u^*(t) = \{u_1^*(t), u_2^*(t)\} \in U$ such that $J(u_1^*, u_2^*) = \min\{J(u_1, u_2) | (u_1, u_2) \in U\}$.

Proof. See the proof of Theorem A3 in Appendix A. □

Theorem 4. There exists the adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5,$ and λ_6 under the control that satisfies the following:

$$\begin{aligned}
 \frac{d\lambda_1}{dt} &= \lambda_1(t)(\alpha\beta_H I_V N_V + b) - \lambda_2(t)(\alpha\beta_H I_V N_V), \\
 \frac{d\lambda_2}{dt} &= -X_1 + \lambda_2(t)(\gamma_P + d_d + b) - \lambda_3(t)\gamma_P - \lambda_6(t)(\beta_V N_H(1 - I_V - u_2^*(t) + I_V u_2^*(t))), \\
 \frac{d\lambda_3}{dt} &= \lambda_3(t)((1 - \psi)\theta + b) - \lambda_4(t)((1 - \psi)\theta), \\
 \frac{d\lambda_4}{dt} &= \lambda_4(t)(\alpha\beta_H I_V N_V + b) - \lambda_5(t)(\alpha\beta_H I_V N_V), \\
 \frac{d\lambda_5}{dt} &= -X_2 + \lambda_4(t)(u_1^*(t)) + \lambda_5(t)(\gamma_S + b) - \lambda_6(t)(\beta_V N_H(1 - I_V - u_2^*(t) + I_V u_2^*(t))), \\
 \frac{d\lambda_6}{dt} &= \lambda_1(t)(\alpha\beta_H S_{HP} N_V) - \lambda_2(t)(\alpha\beta_H S_{HP} N_V) + \lambda_4(t)(\alpha\beta_H S_{HS} N_V) \\
 &\quad - \lambda_5(t)(\alpha\beta_H S_{HS} N_V) + \lambda_6(t)(\beta_V N_H(1 - u_2^*(t))(I_{HP} + I_{HS}) + (d_V + d_k)).
 \end{aligned}
 \tag{46}$$

with the boundary conditions:

$$\lambda_1(t) = \lambda_2(t) = \lambda_3(t) = \lambda_4(t) = \lambda_5(t) = \lambda_6(t) = 0
 \tag{47}$$

In addition, the optimal control variables are given by:

$$u_1^*(t) = \max\left(\min\left(\frac{\lambda_4 I_{HS}^*}{X_3}, u_1^{\max}\right), 0\right)
 \tag{48}$$

$$u_2^*(t) = \max\left(\min\left(\frac{\lambda_6(1 - I_V^*)\beta_V(I_{HP}^* + I_{HS}^*)N_H}{X_4}, u_2^{\max}\right), 0\right)
 \tag{49}$$

Proof. See the proof of Theorem A4 in Appendix A. □

The simulation results for the optimal states are presented in Figures 11–15 and the optimal controls are shown in Figure 14 using parameter values according to Table 1.

Figures 11–15 show the simulation results of the system of Equations (38)–(43) with and without controls of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} , and I_V . The plot of Figure 11 is obtained by setting the weight X_1 to be equal to X_2 . Figure 12 presents the case in which the weight X_1 less than X_2 . Figure 13 presents the case where X_1 is at least 10 times greater than X_2 . Figure 14 presents the case in which the weight X_1 is greater than X_2 . Figure 15 presents the case where X_1 is at least 10 times greater than X_2 . Note that the main goal of the control is to minimize the number of infected humans with primary infection I_{HP} , as well as the secondary infection I_{HS} . The main emphasis, however, is on the secondary infectious individuals. For each of these scenarios, a comparison is also made with the case where no control is applied. If $X_1 = X_2$, the convergence time to equilibrium is significantly faster than if X_1 is less than X_2 , X_1 is much less than X_2 , X_1 is greater than X_2 , and X_1 much greater than X_2 . Moreover, as the weight of X_1 increases, the steady state of infected individuals of the secondary population I_{HS}^* gradually decreases to zero. The trajectory of the infected vectors gradually deviates from the no-control case. No significant change seems to occur to the trajectories as the weight X_2 is increased, except for the infected vectors, which appear to approach zero for a large weight of 100. With no control measures, it will take longer for equilibrium to be reached.

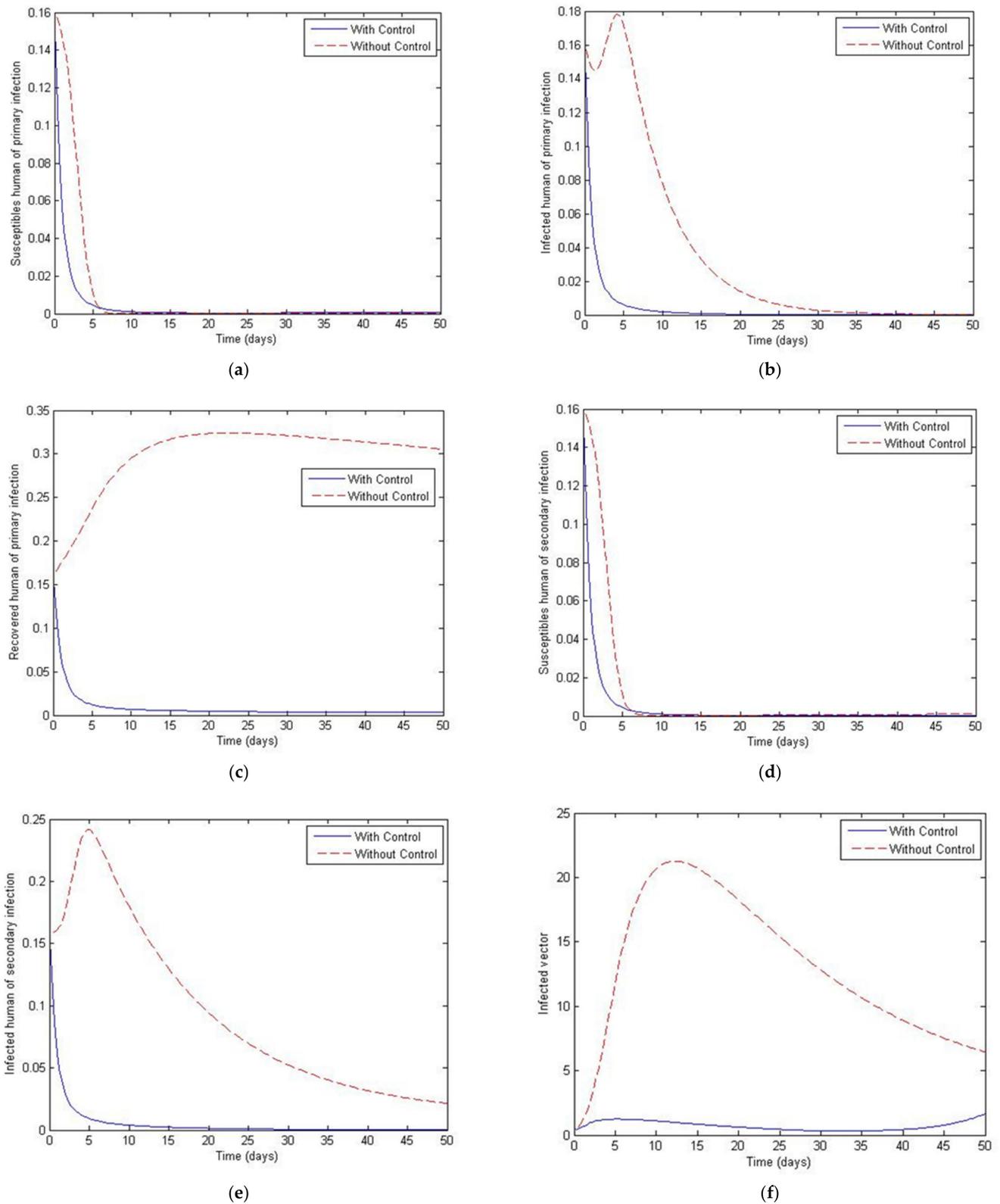


Figure 11. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V for $X_1 = 100$, $X_2 = 100$. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

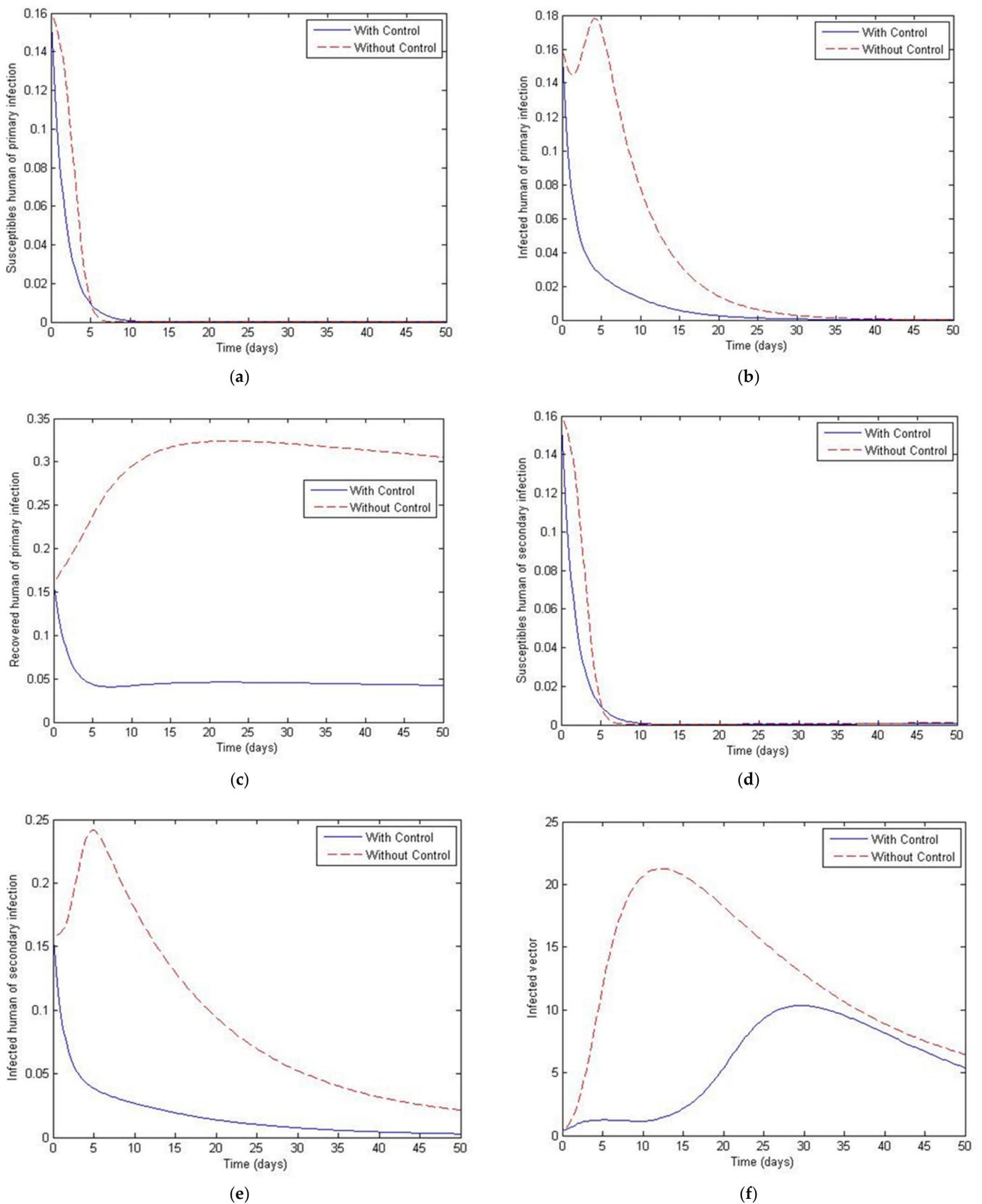


Figure 12. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V with $X_1 = 50$, $X_2 = 100$. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

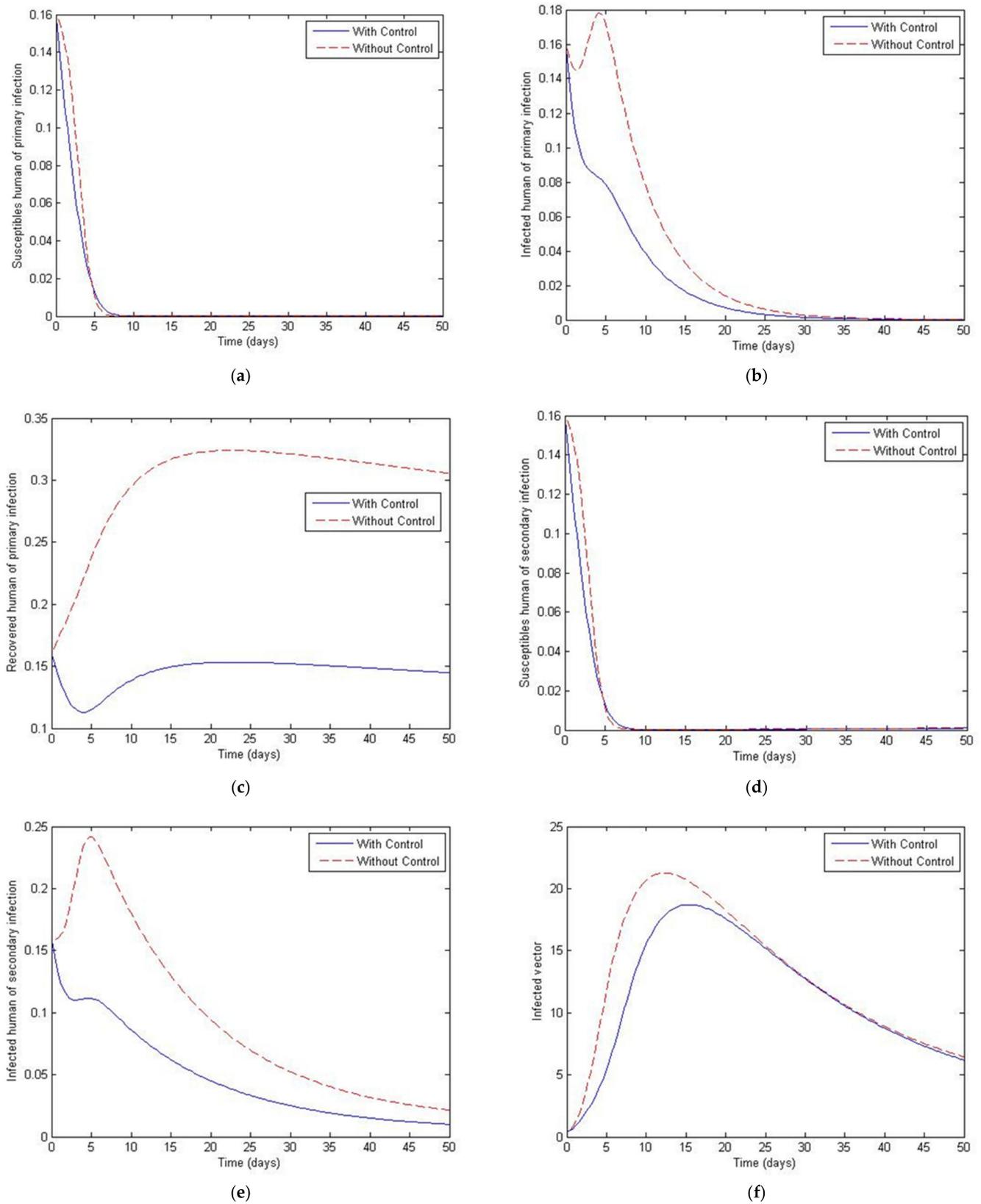


Figure 13. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V when $X_1 = 0.00001$, $X_2 = 100$. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

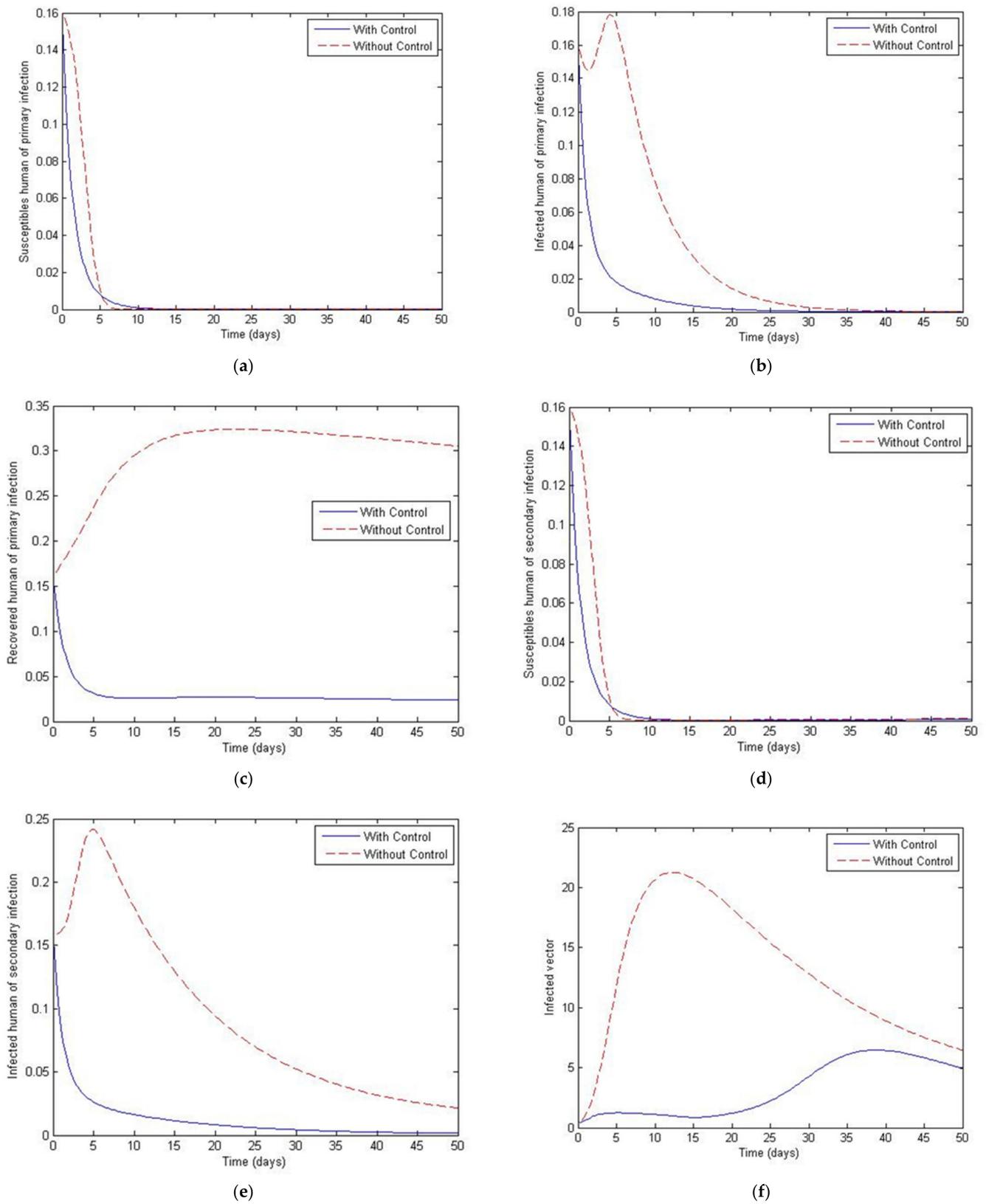


Figure 14. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V when $X_1 = 100$, $X_2 = 50$. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

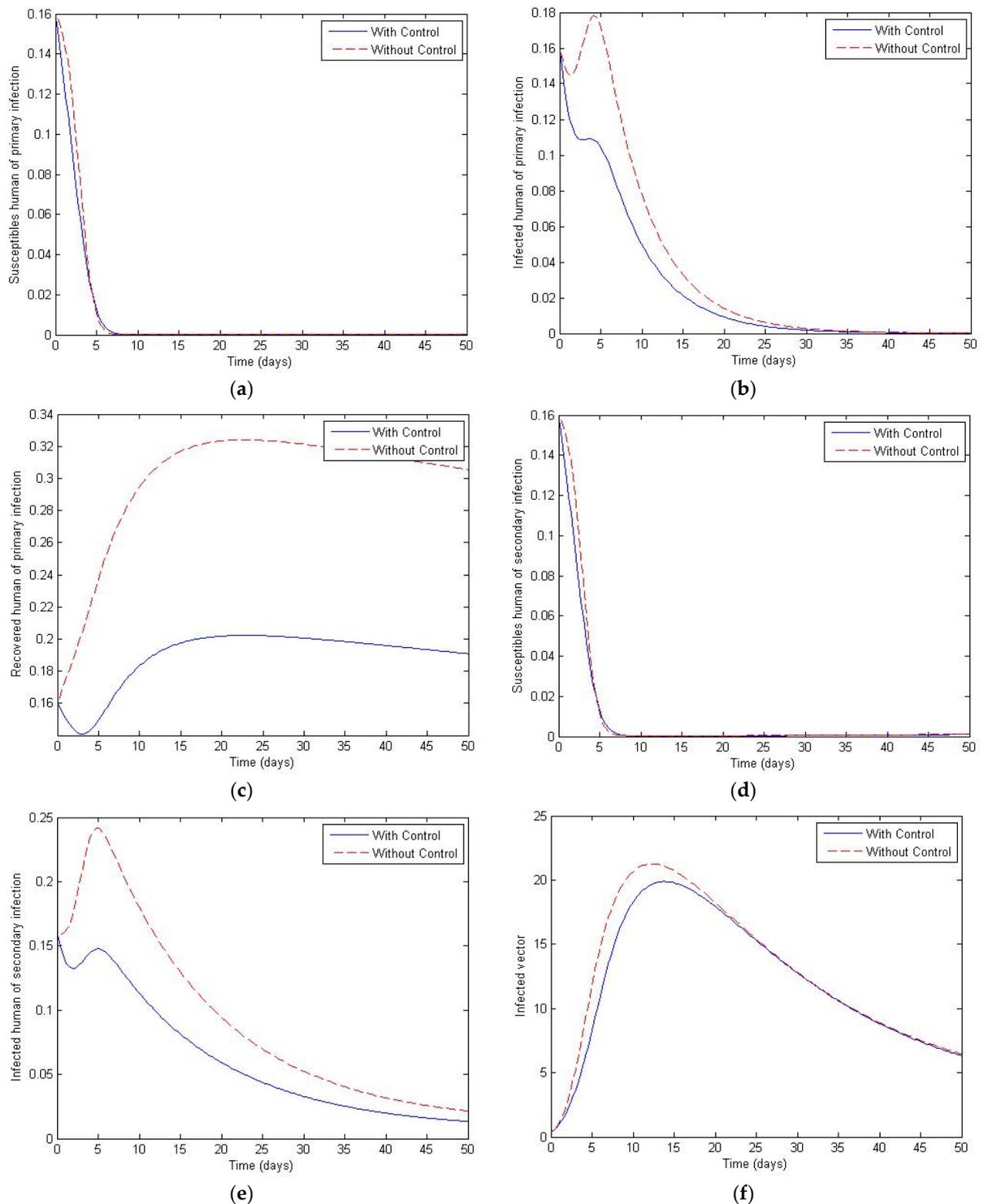


Figure 15. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V when $X_1 = 100$, $X_2 = 0.00001$. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

Figure 16a shows that to maintain the optimal control of the infected population, $u_1(t)$ would have to be at 50%, 70%, and 90% for the first 25 days, after which the control

required will show an exponential decline to zero. Figure 16b shows the values required to maintain optimal control when $u_2(t)$ is used as the controlling factor. The application of 50%, 70%, and 90% of $u_2(t)$ for achieving optimal control should be maintained for the first 47 days, after which the amount of control steadily decreases to zero.

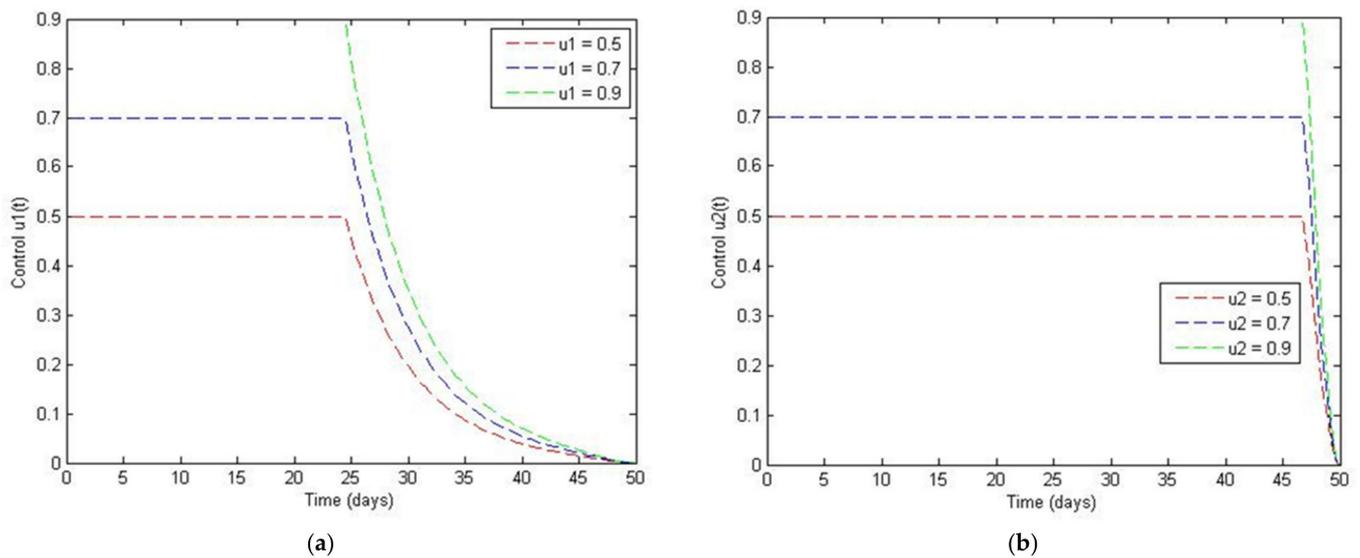


Figure 16. Simulation results of the control: (a) The vaccination rate $u_1(t)$ and (b) the *Aegypti* breeding destroying rate $u_2(t)$ when $X_1 = 100$, $X_2 = 100$.

Figures 17 and 18 plot the cases of $N_H = 500,000$ and $N_V = 100,000$, and of $N_H = 500,000$ and $N_V = 100,000e^{(-1/14)t}$, respectively. The later values were chosen to investigate the case where the total vector population is not constant. Both figures show a significant decay of both the primary and secondary infective populations to zero in the controlled population compared to the uncontrolled population, which peaks at around 0.25 before decaying to about zero. Note that there is again a small change across the trajectories from Figure 17 to Figure 18, which is to be expected since the total number of vectors is slowly decayed as a function of time.

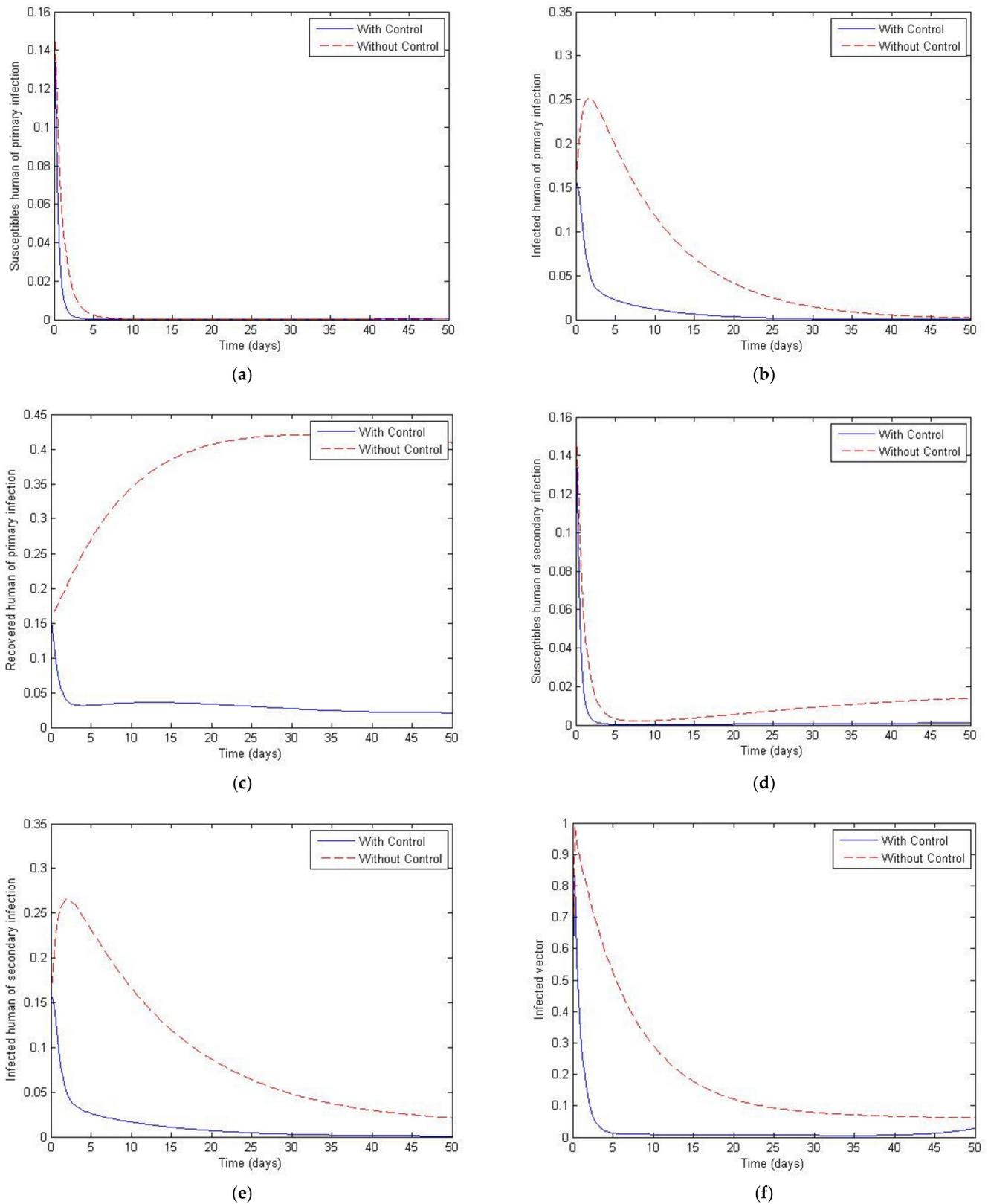


Figure 17. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V with $X_1 = 100$, $X_2 = 100$, $N_H = 500,000$, $N_V = 100,000$. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

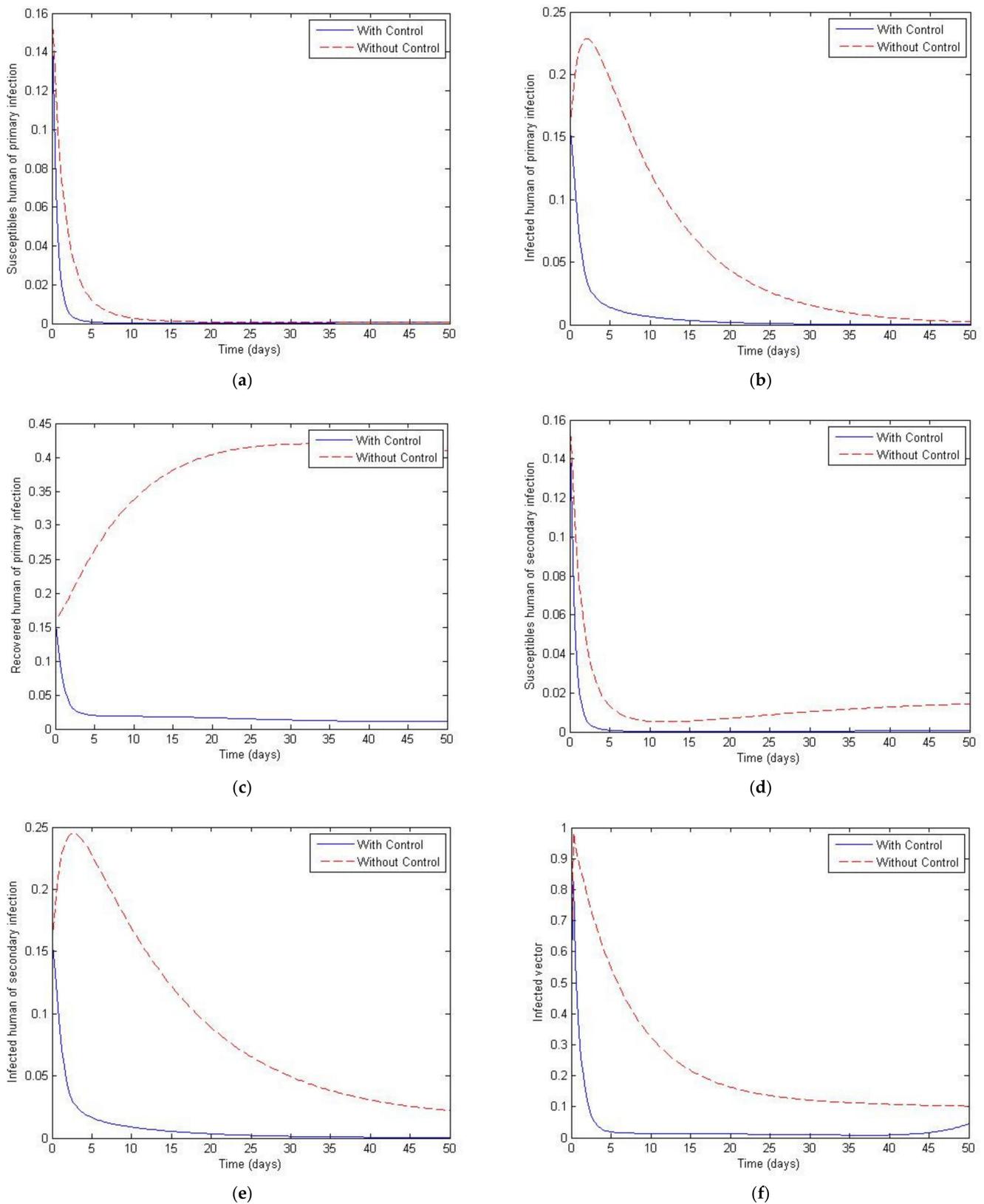


Figure 18. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP} , I_{HP} , R_{HP} , S_{HS} , I_{HS} and I_V with $X_1 = 100$, $X_2 = 100$, $N_H = 500,000$, $N_V = 100,000e^{(-1/14)t}$. (a) Susceptibles of primary infection (b) Infected population with primary infection (c) Recovered human of primary infection (d) Susceptibles of secondary infection (e) Infected human of secondary infection (f) Infected vector.

5. Discussion and Conclusions

In this paper, we analyzed the effects of different vaccination strategies to prevent secondary dengue infection in order to reduce the severity of the disease. The dynamic of the dengue fever transmission model assumes that the human and vector population are constant. The analysis was based on the use of the Routh–Hurwitz criteria to establish local asymptotic stability. The equilibrium points that we found were disease-free convergence to $E_1 = (1, 0, 0, 0, 0, 0)$ and the endemic equilibrium point. The basic reproductive number was defined as R_0 . If R_0 is less than one, then the disease-free state exists and is locally asymptotically stable; it is unstable when R_0 is greater than one. We simulated the numerical solution of the parameters with different values, as shown in Figure 5. We can see that if the transmission rate of dengue virus from vector to human β_H is large, then the convergence to an equilibrium point becomes slower for susceptible humans to primary and secondary infection. The number of humans recovered from primary infection, the number of humans with primary or secondary infection, and the number of infected vectors will converge to an equilibrium point more rapidly. Likewise, in Figure 6, we see that if the transmission rate of the dengue virus from human to vector β_V is large, then there is a slower convergence to an equilibrium point of the susceptible humans. Similarly, humans who recovered from a primary infection, humans infected with a primary or secondary infection, and infected humans will converge to an equilibrium point more quickly, i.e., $E_2(S_{HP} = 0.00003, I_{HP} = 0.00022, R_{HP} = 0.00810, S_{HS} = 0.00002, I_{HS} = 0.00031)$. However, the infected vector will converge to a different equilibrium point. In addition, this will also make the basic reproductive number R_0 greater than one. Changing β_V to a different value affects the convergence time for reaching the equilibrium point, as shown in Figure 8. To investigate whether there is a limitation on the model when there is a non-constant total vector population N_V , two further cases were also considered. The first case had the largest total human population N_H at 500,000, and a large N_V of 100,000. The second case kept N_H the same, whilst the N_V was treated as an exponential function of time. Results showed that although having a non-constant N_V does have some effect on the trajectories, such a change is quite small compared to that of the constant vector population case.

We adopted an optimal control approach using the vaccination rate and a rate for destroying the breeding of the *Aegypti* mosquito in order to minimize the number of humans with primary or secondary infections. To do this, we used the Pontryagin Minimum Principle (PMP) method to solve the optimal control problem with conditions X_1 equal X_2 , X_1 less than X_2 , X_1 much less than X_2 , X_1 greater than X_2 , and X_1 much greater than X_2 . We can see that, if there are no controls, the number of humans with primary or secondary infections increases. This will cause the solution to converge to the equilibrium point over a longer time. With the controls in place, the number of mosquitoes in the infected vector population and the number of people who need to be vaccinated will decrease over time, as shown in Figures 11–18.

Author Contributions: Conceptualization, A.C., P.P. and N.W.; methodology, A.C.; software, N.W.; validation, A.C., P.P., I.-M.T. and N.W.; writing—original draft preparation, A.C. and N.W.; writing—review and editing, A.C., P.P., I.-M.T. and N.W.; supervision, P.P., I.-M.T. and N.W.; project administration, P.P.; funding acquisition, P.P. All authors have read and agreed to the published version of the manuscript.

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Appendix A

Theorem A1. *At the equilibrium point E_1 , the disease-free state is locally asymptotically stable when $R_0 < 1$.*

Proof. The eigenvalues of the Jacobian at the equilibrium point of the disease-free state are obtained by first evaluating the matrix equation at the disease-free state $E_1 = (1, 0, 0, 0, 0, 0)$.

$$\det(J_{E_1} - \lambda I) = 0 \tag{A1}$$

where I is a 6×6 identity matrix. Solving this equation, we obtain the characteristic equation, a six-order polynomial equation. The eigenvalues are the solutions of the equations:

$$\lambda_1 = \lambda_2 = -b, \lambda_3 = -(b + \theta(1 + \psi)), \lambda_4 = -(b + \gamma_S),$$

$$\lambda_5 = -\left(\frac{1}{2}\varepsilon_1 + \sqrt{\varepsilon_1^2 - 4\varepsilon_2 - \varepsilon_3}\right), \text{ and } \lambda_6 = -\left(\frac{1}{2}\varepsilon_1 - \sqrt{\varepsilon_1^2 - 4\varepsilon_2 - \varepsilon_3}\right).$$

where $\varepsilon_1 = (b + d_d + d_k + d_V + \gamma_P)$, $\varepsilon_2 = b(d_k + d_V) + d_d(d_k + d_V)$, and $\varepsilon_3 = \alpha N_H N_V \beta_H \beta_V + \gamma_P(d_k + d_V)$. As we see, all the eigenvalues have a negative real part and the disease-free equilibrium point (E_1) is locally asymptotically stable. \square

Theorem A2. *The equilibrium point E_2 is locally asymptotically stable when $R_0 > 1$.*

Proof. The Jacobian for this case is obtained when the endemic state E_2 defined by Equation (26) is substituted in the Jacobian matrix of Equation (28) $J_{E_2} = (S_{HP}^*, I_{HP}^*, R_{HP}^*, S_{HS}^*, I_{HS}^*, I_V^*)$ where $S_{HP}^*, I_{HP}^*, R_{HP}^*, S_{HS}^*, I_{HS}^*$, and I_V^* are defined by the equation of the endemic equilibrium point (E_2), we set:

$$\det(J_{E_2} - \lambda I) = 0 \tag{A2}$$

For the first eigenvalue we have $\lambda_1 = -(b + \gamma_S) < 0$ and $\lambda_2 = -(b + d_d + \gamma_S) < 0$. The characteristic equation is:

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0 \tag{A3}$$

where:

$$a_1 = 3b + \theta(1 - \psi) + d_k + d_V + 2\alpha N_V \beta_H I_V^* + N_H(I_{HP}^* - I_{HS}^* + \alpha N_V(S_{HP}^* - S_{HS}^*)(I_V^* - 1)\beta_H)\beta_V,$$

$$a_2 = (b + \alpha N_V \beta_H I_V^*)(3b - 2\theta(\psi - 1) + \alpha N_V \beta_H I_V^*) + d_k(3b + \theta - \theta\psi + 2\alpha N_V \beta_H I_V^*)$$

$$+ N_H(\alpha N_V(S_{HP}^* - S_{HS}^*)(I_V^* - 1)(3b + \theta - \theta\psi + 2\alpha N_V \beta_H I_V^*)(\beta_H + I_{HP}^* - I_{HS}^*))\beta_V$$

$$+ d_V(3b + \theta - \theta\psi + 2\alpha N_V \beta_H I_V^*),$$

$$a_3 = b^2(b + \theta - \theta\psi) + 2b\alpha N_V \beta_H I_V^{*2}(b + \theta - \theta\psi) + \alpha^2 N_V^2 \beta_H^2 I_V^{*2}(b + \theta - \theta\psi)$$

$$+ (b + \alpha N_V \beta_H I_V^*)(3b + 2\theta - 2\theta\psi + \alpha N_V \beta_H I_V^*)(d_k + d_V)$$

$$+ b\alpha N_H N_V \beta_H \beta_V S_{HP}^* \begin{pmatrix} 2bI_V^* - 2b - 2b\theta I_V^* + 2\alpha N_V \beta_H - \alpha N_V \beta_H I_V^* + \alpha N_V \psi I_V^* \\ + \alpha\theta N_V + 2\alpha N_V \beta_H I_V^* + \alpha^2 N_V \beta_H I_V^* + \alpha^2 \theta \psi N_V \beta_H I_V^* \end{pmatrix}$$

$$+ b\alpha N_H N_V \beta_H \beta_V S_{HS}^* \begin{pmatrix} 3b + 2b\theta - 2b\psi - 3b^2 - 2bI_V^* + 2b\psi I_V^* + 2\alpha N_V \beta_H I_V^* \\ - \alpha\psi N_V I_V^* - 3\alpha N_V \beta_H I_V^* + \alpha\psi N_V \beta_H I_V^* \end{pmatrix}$$

$$+ b\alpha N_H N_V \beta_H \beta_V T_{HP}^*(6I_V^* + 2\psi + \alpha N_V \beta_H I_V^*) + b\alpha N_H N_V \beta_H \beta_V I_{HS}^* I_V^*(6 + 2\psi - \alpha N_V \beta_H),$$

$$a_4 = (b + \theta - \theta\psi)(b + \alpha N_V \beta_H I_V^*)^2(d_k + d_V) + N_H \beta_V(b + \theta - \theta\psi)(b + \alpha N_V \beta_H I_V^*)^2(I_{HP}^* - I_{HS}^*)$$

$$+ b\alpha N_V(I_V^* - 1)\beta_H((b + \theta - \theta\psi)(S_{HP}^* - S_{HS}^*)(b + \alpha N_V \beta_H I_V^*) + \alpha\theta(\psi - 1)N_V S_{HP}^* I_V^* \beta_H \gamma_P).$$

where $S_{HP}^*, I_{HP}^*, S_{HS}^*, I_{HS}^*$, and I_V^* are defined in Section 2.2 (The Equilibrium Point) and all parameter values are defined in Table 3. Using Routh–Hurwitz criteria [35,36] for

$n = 4$, the endemic equilibrium point is stable if conditions (i) – (iv) below are satisfied. Since symbolic computation may be difficult, to illustrate whether conditions (i) – (iv) are indeed satisfied due to the algebraic numerical complexities, numerical simulations of conditions (i) – (iv) are instead given. It is seen from Figure 1A that conditions (i) – (iv) are indeed satisfied. This means that the polynomial of Equation (A3) is Hurwitz.

$$(i) a_1 > 0(ii) a_3 > 0(iii) a_4 > 0(iv) a_1 a_2 a_3 - a_3^2 - a_1^2 a_4 > 0$$

Hence, the endemic equilibrium point will be locally asymptotically stable. □

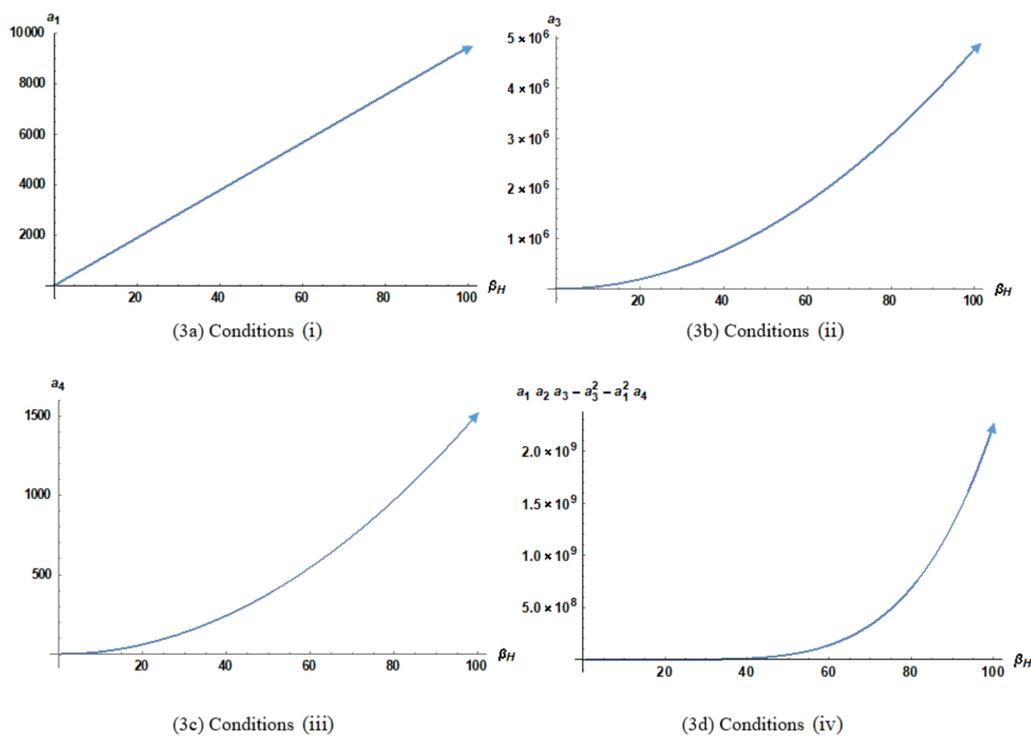


Figure A1. All parameter spaces of endemic equilibrium are satisfied with the Routh–Hurwitz criteria.

Theorem A3. We consider the objective function J given by Equation (44) with $(u_1, u_2) \in U$ subjecting to the control system of Equations (38)–(43) with initial condition. There exists $u^*(t) = \{u_1^*(t), u_2^*(t)\} \in U$ such that $J(u_1^*, u_2^*) = \min\{J(u_1, u_2) | (u_1, u_2) \in U\}$.

Proof. We apply the existence of an optimal control problem from [37,38]. □

The control set U is closed and convex by its definition above and the integrand of the function Equation (38) is also convex in U . It is obvious that these states and the control variable are nonnegative. Since the solution to the systems given by Equations (38)–(43) are bounded, the control function will be convex in U . Let q_1 and q_2 be two positive constants and $\zeta > 1$. If we now set $q_2 = \min(I_{HP}(t), I_{HS}(t))$, $q_1 = \min(X_3, X_4)$, and $\zeta = 2$, the Lagrangian function L can be rewritten as:

$$\begin{aligned} L(I_{HP}, I_{HS}, u_1, u_2) &= X_1 I_{HP} + X_2 I_{HS} + \frac{1}{2} (X_3 u_1^2(t) + X_4 u_2^2(t)) \\ &\geq q_2 (I_{HP} + I_{HS}) + q_1 (|u_1|^2 + |u_2|^2) \\ &= q_2 + q_1 (|u_1|^2 + |u_2|^2) \end{aligned} \tag{A4}$$

The optimal control of this model is obtained by applying Pontryagin’s Minimum Principle [38].

Theorem A4. *There exists the adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ and λ_6 under the control that satisfies the following:*

$$\begin{aligned}
 \frac{d\lambda_1}{dt} &= \lambda_1(t)(\alpha\beta_H I_V N_V + b) - \lambda_2(t)(\alpha\beta_H I_V N_V), \\
 \frac{d\lambda_2}{dt} &= -X_1 + \lambda_2(t)(\gamma_P + d_d + b) - \lambda_3(t)\gamma_P - \lambda_6(t)(\beta_V N_H(1 - I_V - u_2^*(t) + I_V u_2^*(t))), \\
 \frac{d\lambda_3}{dt} &= \lambda_3(t)((1 - \psi)\theta + b) - \lambda_4(t)((1 - \psi)\theta), \\
 \frac{d\lambda_4}{dt} &= \lambda_4(t)(\alpha\beta_H I_V N_V + b) - \lambda_5(t)(\alpha\beta_H I_V N_V), \\
 \frac{d\lambda_5}{dt} &= -X_2 + \lambda_4(t)(u_1^*(t)) + \lambda_5(t)(\gamma_S + b) - \lambda_6(t)(\beta_V N_H(1 - I_V - u_2^*(t) + I_V u_2^*(t))), \\
 \frac{d\lambda_6}{dt} &= \lambda_1(t)(\alpha\beta_H S_{HP} N_V) - \lambda_2(t)(\alpha\beta_H S_{HP} N_V) + \lambda_4(t)(\alpha\beta_H S_{HS} N_V) \\
 &\quad - \lambda_5(t)(\alpha\beta_H S_{HS} N_V) + \lambda_6(t)(\beta_V N_H(1 - u_2^*(t))(I_{HP} + I_{HS}) + (d_V + d_k)).
 \end{aligned}
 \tag{A5}$$

with the boundary conditions:

$$\lambda_1(t) = \lambda_2(t) = \lambda_3(t) = \lambda_4(t) = \lambda_5(t) = \lambda_6(t) = 0
 \tag{A6}$$

In addition, the optimal control variables are given by:

$$u_1^*(t) = \max\left(\min\left(\frac{\lambda_4 I_{HS}^*}{X_3}, u_1^{\max}\right), 0\right)
 \tag{A7}$$

$$u_2^*(t) = \max\left(\min\left(\frac{\lambda_6(1 - I_V^*)\beta_V(I_{HP}^* + I_{HS}^*)N_H}{X_4}, u_2^{\max}\right), 0\right)
 \tag{A8}$$

Proof. The Hamiltonian for the optimal control of this model is defined as given by:

$$H = L(I_{HP}, I_{HS}, u_1, u_2) + \lambda_1 \frac{dS_{HP}}{dt} + \lambda_2 \frac{dI_{HP}}{dt} + \lambda_3 \frac{dR_{HP}}{dt} + \lambda_4 \frac{dS_{HS}}{dt} + \lambda_5 \frac{dI_{HS}}{dt} + \lambda_6 \frac{dI_V}{dt}
 \tag{A9}$$

$$\begin{aligned}
 H &= X_1 I_{HP} + X_2 I_{HS} + \frac{1}{2}(X_3 u_1^*(t) + X_4 u_2^*(t)) \\
 &\quad + \lambda_1 [b - \alpha\beta_H S_{HP} I_V N_V - b S_{HP}] \\
 &\quad + \lambda_2 [\alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - (b + d_d) I_{HP}] \\
 &\quad + \lambda_3 [\gamma_P I_{HP} - (1 - \psi)\theta R_{HP} - b R_{HP}] \\
 &\quad + \lambda_4 [(1 - \psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - b S_{HS} - u_1(t) I_{HS}] \\
 &\quad + \lambda_5 [\alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - b I_{HS}] \\
 &\quad + \lambda_6 [(1 - u_2(t))\beta_V(1 - I_V)(I_{HP} + I_{HS})N_H - (d_V + d_k)I_V]
 \end{aligned}
 \tag{A10}$$

The adjoint associated system is obtained as follows:

$$\begin{aligned}
 \frac{d\lambda_1}{dt} &= \lambda_1(t)(\alpha\beta_H I_V N_V + b) - \lambda_2(t)(\alpha\beta_H I_V N_V), \\
 \frac{d\lambda_2}{dt} &= -X_1 + \lambda_2(t)(\gamma_P + d_d + b) - \lambda_3(t)\gamma_P - \lambda_6(t)(\beta_V N_H(1 - I_V - u_2^*(t) + I_V u_2^*(t))), \\
 \frac{d\lambda_3}{dt} &= \lambda_3(t)((1 - \psi)\theta + b) - \lambda_4(t)((1 - \psi)\theta), \\
 \frac{d\lambda_4}{dt} &= \lambda_4(t)(\alpha\beta_H I_V N_V + b) - \lambda_5(t)(\alpha\beta_H I_V N_V), \\
 \frac{d\lambda_5}{dt} &= -X_2 + \lambda_4(t)(u_1^*(t)) + \lambda_5(t)(\gamma_S + b) - \lambda_6(t)(\beta_V N_H(1 - I_V - u_2^*(t) + I_V u_2^*(t))), \\
 \frac{d\lambda_6}{dt} &= \lambda_1(t)(\alpha\beta_H S_{HP} N_V) - \lambda_2(t)(\alpha\beta_H S_{HP} N_V) + \lambda_4(t)(\alpha\beta_H S_{HS} N_V) \\
 &\quad - \lambda_5(t)(\alpha\beta_H S_{HS} N_V) + \lambda_6(t)(\beta_V N_H(1 - u_2^*(t))(I_{HP} + I_{HS}) + (d_V + d_k)).
 \end{aligned}
 \tag{A11}$$

Using the optimal conditions, we find that:

$$\frac{\partial H}{\partial u_1} = \frac{\partial H}{\partial u_2} = 0 \text{ at } u_1 = u_1^*(t) \text{ and } u_2 = u_2^*(t)
 \tag{A12}$$

Therefore:

$$\begin{aligned} \frac{\partial H}{\partial u_1} &= X_3 u_1 - \lambda_4 I_{HS} = 0 \\ u_1^*(t) &= \frac{\lambda_4 I_{HS}}{X_3} \end{aligned} \quad (A13)$$

$$\begin{aligned} \frac{\partial H}{\partial u_2} &= X_4 u_2 - \lambda_6 (1 - I_V) \beta_V (I_{HP} + I_{HS}) N_H = 0 \\ u_2^*(t) &= \frac{\lambda_6 (1 - I_V) \beta_V (I_{HP} + I_{HS}) N_H}{X_4} \end{aligned} \quad (A14)$$

Using the property of the control set, we can say that:

$$u_1^*(t) = \begin{cases} 0 & \text{if } \frac{\lambda_4 I_{HS}}{X_3} \leq 0, \\ \frac{\lambda_4 I_{HS}}{X_3} & \text{if } \frac{\lambda_4 I_{HS}}{X_3} < u_1^{\max}, \\ u_1^{\max} & \text{if } \frac{\lambda_4 I_{HS}}{X_3} \geq u_1^{\max}. \end{cases} \quad (A15)$$

$$u_2^* = \begin{cases} 0 & \text{if } \frac{\lambda_6 (1 - I_V) \beta_V (I_{HP} + I_{HS}) N_H}{X_4} \leq 0, \\ \frac{\lambda_6 (1 - I_V) \beta_V (I_{HP} + I_{HS}) N_H}{X_4} & \text{if } \frac{\lambda_6 (1 - I_V) \beta_V (I_{HP} + I_{HS}) N_H}{X_4} < u_2^{\max}, \\ u_2^{\max} & \text{if } \frac{\lambda_6 (1 - I_V) \beta_V (I_{HP} + I_{HS}) N_H}{X_4} \geq u_2^{\max} \end{cases} \quad (A16)$$

The simulation results for the optimal states are presented in Figures 11–15 and the optimal controls are shown in Figure 16. □

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