MATHEMATICAL MODELS OF DENGUE DISEASE WITH VACCINATION IN THAILAND: STABILITY ANALYSES AND OPTIMAL CONTROL

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Abstract

Dengue fever 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 individuals having documented past dengue infection history are vaccinated and before the initial infection. Our mathematical model is the Susceptible-Infected-Recovered (SIR) and Susceptible-Exposed-Infected-Recovered (SEIR) 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 and globally asymptotically stable. The conditions for locally and globally asymptotically stability are established. The numerical solutions of the control systems and conclusions are presented.

Keywords: Dengue fever, mathematical model, optimal control, vaccination

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Mr. Anusit Chamnan

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Chapter 1
Introduction

1.1 Research Motivation

Dengue is a mosquito-borne viral infection, found in tropical and sub-tropical climates worldwide, mostly in urban and semi-urban areas. The dengue viruses are transmitted by two species of *Aedes* mosquitoes, the *Aedes aegypti*, and the *Aedes albopictus*. The virus responsible for causing dengue is called dengue virus (DENV). There are four DENV serotypes are labeled as DEN-1, DEN-2, DEN-3, and DEN-4, meaning that it is possible to be infected four times [1]. In 2012, dengue ranks as the most important mosquito-borne viral disease in the world. Outbreaks exert a huge burden on populations, health systems, and economies in most tropical countries of the world. The emergence and spread of all four dengue viruses (serotypes) from Asia to the Americas, Africa, and the Eastern Mediterranean regions represent a global pandemic threat. Although the full global burden of the disease is still uncertain, the patterns are alarming for both human health and the economy [2].

Thailand has reported outbreaks of dengue fever for more than 60 years. At present, dengue fever has spread throughout the country, every province, and district. The distribution of the disease is constantly changing depending on the area. Disease surveillance data from the Ministry of Public Health in 2020 found 71,292 cases from 77 provinces, representing a morbidity rate of 107.34 per 100,000 population, 51 deaths, representing a mortality rate of 0.08 per 100,000 population, male-female ratio 1: 0.90, age groups found. The top three are 15-24 years (25.87%), 10-14 years (21.24 %), and 25-34 years (14.09%), respectively. The top five provinces with the highest morbidity rates per 100,000 population are Mae Hong Son (566.59 per 100,000 population), Rayong (325.86 per 100,000 population), Nakhon Ratchasima (234.36 per 100,000 population), Chaiyaphum (219.18 per 100,000 population) Chainat (215.99 per 100,000 population) is shown as Figure 1.1.

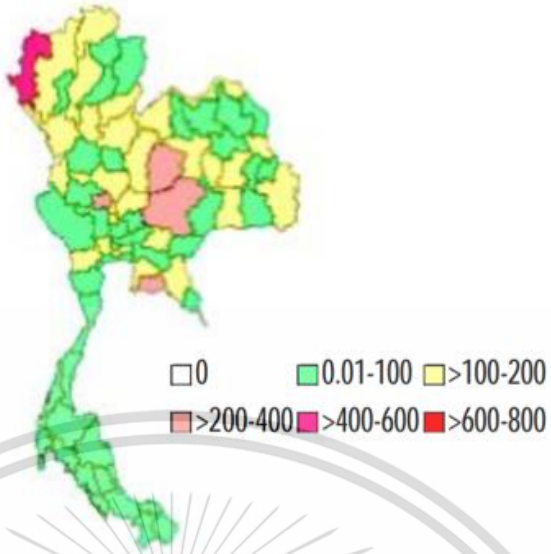


Figure 1.1 Dengue fever rate in Thailand in 2020 per 100,000 population [3].

The regions with the highest morbidity rates were Northeastern region 127.53 per 100,000 population, Northern region 122.05 per 100,000 population, Central region 98.46/100,000 population, Southern region 62.97/100,000 population, respectively is shown as Figure 1.2.

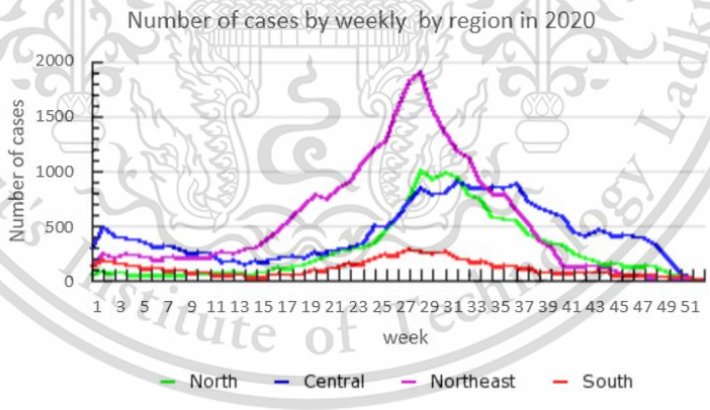


Figure 1.2 Number of cases by weekly by region in 2020 [3].

The effects of vaccination on a model in which the human population is divided into children and adults were studied by Singh et al. [4] and Tasman et al. [5]. They also thought there were two kinds of dengue infections: primary and secondary. People who had a secondary infection were thought to be more vulnerable. Adults were split into three groups in this research, resulting in a human population of three age groups: under 9 years, 9 to 45 years, and 45 to 65 years [6,7]. Chanprasopchai, et al. [8] studied dengue fever and

the effect of vaccination analyze the behavior condition for Routh-Hurwitz criteria of model. Khan and Fatmawati [9] described changes in dengue infection from basic reproductive values which defines a model with hospitalization and presents the changes in detail. The results suggest that spraying insecticides on mosquitoes can significantly reduce dengue infection. Pongsumpun et al. [10] studied a mathematical model of the dengue model with a vertical transmission control mechanism based on the dengue model. The two policy control models were insecticide and vaccinations which simulated the parameters affecting this model control.

This thesis focuses on the dynamic spread of the dengue virus. This is an important factor that determines the spread of vector-borne disease. Vaccines are effective in preventing dengue fever, reduce the rate of hospitalization, and reduce the severity of the disease and serious complications including death. Analyze the report data of the Bureau of Epidemiology, Ministry of Public Health between 2003 and 2020. A mathematical model was developed to analyze and design appropriate optimal controls for dengue transmission with vaccination to reduce the spread of dengue disease.

1.2 Objectives of the study

The mathematical model is developed to analyze dengue fever transmission with vaccination. The used mathematical analysis is the standard dynamical modeling method in order to investigate the dynamical behaviors. The objectives of the study are:

1) To study the dynamical of dengue transmission by using a mathematical model.
2) To formulate a mathematical model of dengue transmission with vaccination for analyzing the epidemic of dengue disease.
3) To develop a mathematical model of dengue transmission with and without optimal control.
4) To develop and design a mathematical model of dengue transmission influenced by vaccination for observing the epidemic of dengue disease as follows:
    1. A simple mathematical model for low-infected endemic areas.
    2. The mathematical model for the outbreak area focuses on regions to reduce the severity of the second infection and is controlled by vaccination.
    3. The mathematical model for outbreak areas focused on provinces with high outbreaks and at risk of re-infection more than 2 serotypes to reduce the severity of re-infection and control it through vaccination.

1.3 Scopes of the study

The scopes of study are as follows:

1) The data used is from the reported cases and annual reports from the Bureau of Epidemiology, Ministry of Public Health during 2003 – 2020 in order to analyze and study the behaviors of dengue fever.
2) The mathematical model is developed based on the data to analyze the dynamical transmission of dengue disease transmission with vaccination, assuming constant population of each class.
3) The mathematical model is developed to analyze the dynamical transmission of dengue fever with and without optimal control, assuming constant population of each class.
4) The standard dynamical modeling method is applied in order to investigate and analyze the dynamical behaviors of the dengue fever mathematical model.
5) The Pontryagin Minimum Principle (PMP) theory is used to solve problems in optimal control.

1.4 Process of the study

The process of the study is as follows:

1) Study the data from the report of Bureau of Epidemiology, Ministry of Public Health, Thailand during 2003-2020.
2) Study the definition and theoretical background and review the described pieces of literature.
3) Formulate the mathematical models.
4) Analyze the mathematical models.
5) Develop the mathematical models.
6) Compare and discuss the results.

1.5 Benefits of the study

This study will be beneficial to related parties as follows:

1) The mathematical model will explain the behaviors in order to understand in detail the dengue dynamical transmission.
2) This study will support a better understanding of dengue transmission with and without optimal control.
3) This study will help to better understand the spread of dengue with the effectiveness of vaccination.

4) This study will be used as a guideline to reduce the spread of dengue disease by using the appropriate controls of the mathematical model.

Chapter 2
Literature Reviews

This chapter will describe the background of dengue disease in order to understand the types of dengue disease, dengue virus, caused of disease, symptoms, and the efficacy of vaccination. The analyze of the dynamical transmission of dengue disease will explain the dengue infectious disease with vaccination. The theoretical background and literature reviews are used in this study which discusses the previous modeling related to the purpose of this study.

2.1 Background of dengue disease

Dengue disease is an infectious disease caused by the dengue virus (DEN or DENV) classified as arbovirus which is a type of virus a single-stranded RNA belonging to the family Flaviviridae and genus Flavivirus. It consists of four serotypes, namely DEN-1, DEN-2, DEN-3, and DEN-4, and can cause disease in humans. The mosquito *Aedes aegypti* and *Aedes albopictus* are important disease carriers. The infection has an incubation period of 4-10 days after being bitten by an *Aedes* mosquito. The body temperature is a high fever between 38 °C and 40 °C [1,2,11-15].

2.1.1 Undifferentiated fever (UF)

Undifferentiated fever is often seen in infants or young children and adults who have been infected with the dengue virus, especially for the first time (i.e. primary dengue infection). There will be simply a fever for 2-3 days, and it may be a simple fever that is indistinguishable from other viral infections. There may also be a rash-like maculopapular rash with symptoms that are comparable to other viral infections that cannot be recognized based on clinical symptoms [1,2,11-15].

2.1.2 Dengue fever (DF)

Dengue fever (DF) is more common in teenagers and adults. It is usually an acute febrile sickness with severe headache, myalgias, arthralgias, rashes, leucopenia, and thrombocytopenia. Although DF appears to be harmless, it can be a debilitating illness that causes severe headaches, muscle and joint pains, and bone pains (break-bone fever), especially in adults. Unusual hemorrhages, such as gastrointestinal bleeding, hypermenorrhea, and major epistaxis, might happen on occasion. Dengue fever epidemics are rare among locals in dengue endemic locations [1,2,11-15].

2.1.3 Dengue hemorrhagic fever (DHF)

Dengue hemorrhagic fever (DHF) is a 2-7 day acute illness that is more common in children under the age of 15 in hyperendemic areas and is linked to repeated dengue infections. Abnormal bleeding, an enlarged liver, and soreness when pressed, abdominal pain or vomiting are all clinical symptoms. DHF is becoming more common in adults, and it is defined by an immediate start of high fever, as well as signs and symptoms that are comparable to DF in the early febrile phase. Petechiae, easy bruising, a positive tourniquet test (TT), and/or gastrointestinal hemorrhage are all common hemorrhagic diatheses. DHF is particularly common in children who have contracted dengue fever as a result of a secondary infection. Dengue shock syndrome (DSS) arises when plasma leakage becomes highly acute, and symptoms include a weak pulse, a decrease in blood pressure, cold hands/feet, and restlessness [1,2,11-15].

2.1.4 Expanded dengue syndrome (EDS)

Expanded dengue syndrome (EDS) or Unusual dengue symptoms there have been reported of additional cases of unusual symptoms, which are still a minority, about 3-5 percent of all dengue infected cases. The symptoms found are encephalopathy/encephalitis, hepatic failure, dual infection, renal failure, and DHF patients with underlying conditions e.g. thalassemia, liver, kidney, heart, diabetes, hypertension disease [1,2,11-15]. The diagram of the dengue virus infection is shown in Figure 2.1.

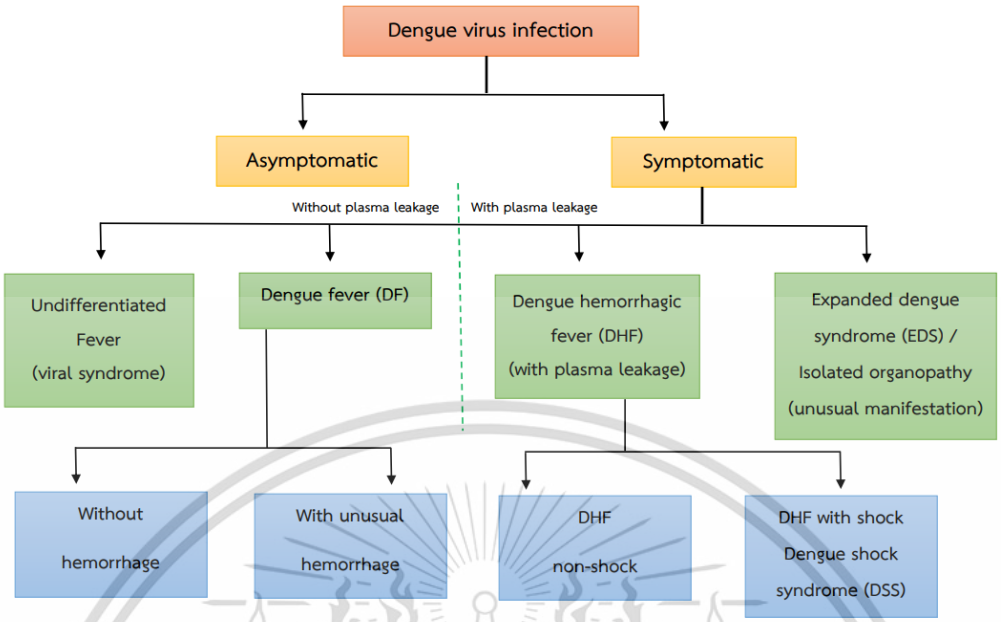


Figure 2.1 Diagram of the dengue virus infection [12].

2.2 Vector of dengue

The two most important common dengue vectors are *Aedes aegypti* and *Aedes albopictus*. All mosquito species go through four distinct stages during their life cycle shown in Figure 2.2. The life cycle of mosquitoes has four stages: egg, larva, pupa, and adult [16-18].

Eggs: Mosquito eggs are very small, only about 1 millimeter. But still can be seen with the naked eye. *Aedes* mosquito eggs cling to the walls of water storage containers, such as water bowls, by clinging to the edges slightly above the water level. The incubation period is about 2 days, it will come out as larvae.

Larva: First when the larva hatches from the egg. It is very small as stage 1 larvae, then the larvae will eat, grow and molt, change to stage 2 larvae, which have grown in size but have the same shape. The larvae will feed and continue to grow into larvae stages 3 and 4. Each change of stage is always molted, when larvae stage 4 matures, the final molt turns into pupae stage. The larval stage lasts about 6 days.

Pupa: The distinctive shape is the large head. Usually floating at the surface of the water, the pupa stops feeding and is the last stage of life in the water. The pupa stage takes about 2 days for the larvae to mature before molting into adult mosquitoes. In a tropical country such as Thailand, it only takes about 10 days, depending on the mosquito species.

Adult: Mosquitoes eventually emerge from the chrysalis after two days to a week in the chrysalis stage. The life cycle usually lasts two weeks. But it can range from 4 days to as

long as a month. An adult mosquito emerges to the surface and flies away, ready to begin its life cycle.

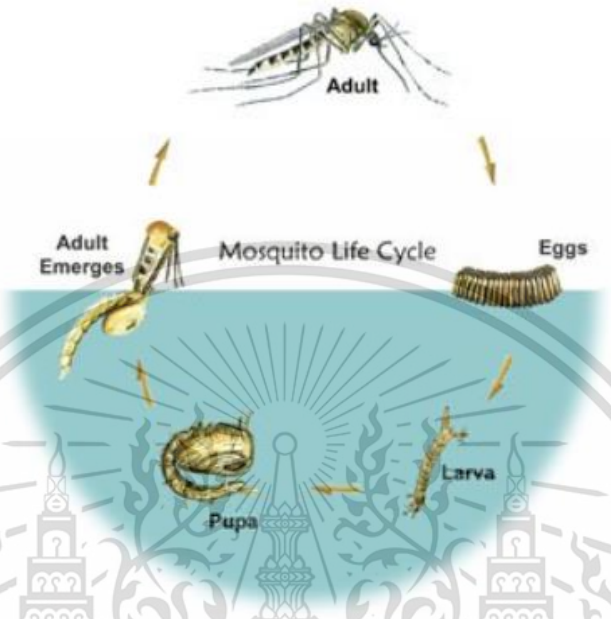


Figure 2.2 Mosquito life cycle [16].

2.2.1 *Aedes aegypti*

The virus that causes dengue fever can be transmitted by the *Aedes aegypti* mosquito. The female mosquito lays her eggs near the house in containers with water and plants. It bites both humans and animals. This species may live in tropical and subtropical areas all year.

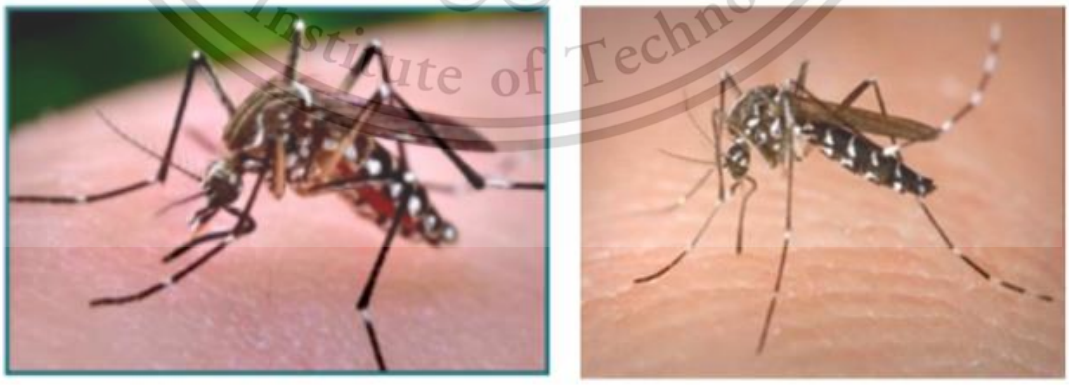


Figure 2.3 *Aedes aegypti* mosquito [17].

General information: *Aedes aegypti* mosquito likes to live in the house or around the house breeding sites include water-filled containers such as water blisters, cement tanks for water, concrete pits in bathrooms, cabinet legs, old tires, cans, vases, rain gutters, coconut shells, and leaf sheaths. *Aedes aegypti* eggs can remain dry for years to wait for the optimum humidity and temperature then the eggs then hatch into larvae. The incubation period for the eggs is about 2.5 – 3.5 days. *Aedes* larvae take about 7-10 days to grow when they enter the adult stage. *Aedes* mosquitoes can mate at about 24 hours of age. Female mosquitoes mate only once but can lay eggs several times. Male *Aedes aegypti* can mate dozens of times in an hour. *Aedes* mosquitoes like to feed on human blood and make a living in the daytime. But it can bite people at night as well. The resting place for *Aedes* mosquitoes after blood sucking includes dark areas in the bathroom, hanging things in the house such as clothes, mosquito nets, curtains, etc. *Aedes aegypti* mosquitoes do not like smelly water. The difference between *Aedes aegypti* and *Aedes albopictus* mosquito is that there are two pairs of white scales on the back of the chest while the *Aedes aegypti* has a single line [16-18].

2.2.2 *Aedes albopictus*

The *Aedes albopictus* mosquito, also called the Asian tiger mosquito, is a mosquito that can transmit the virus that causes dengue fever, native to Asia. Living habits are similar to domesticated mosquitoes but are often found in rural areas, orchards, rubber plantations, parks, and breeding water sources are often natural water sources such as hollow trees, bamboo tubes, etc. However, *Aedes albopictus* mosquitoes can breed in man-made sources such as clay jars, plant pots, etc. The *Aedes albopictus* mosquitoes fly farther than the *Aedes aegypti* mosquitoes and are carriers of dengue fever. This species can survive year-round in tropical and subtropical climates [16-18].

Figure 2.4 *Aedes albopictus* mosquito [18].

2.3 Vaccination of dengue fever

Dengvaxia® is a live recombinant tetravalent dengue vaccine or chimeric yellow fever dengue virus tetravalent dengue vaccine (CYD-TDV) developed by Sanofi Pasteur covers 4 serotypes of dengue. The Dengue vaccination program requires a total of 3 injections, 6 months apart are 0, 6, and 12 months [19]. The World Health Organization (WHO) recommends it as a safe vaccine for children and adults aged 9 to 45. However, according to published research reports from the phase 3 study in general, the vaccine's efficacy is not perfect, independent of pre-injection serostatus because most pre-injection blood tests are not available. The vaccine efficacy of the dengue vaccine was moderate 56.5%, meaning it could prevent more than half the number of dengue infections. The dengue vaccine reduces the severity of the disease by 88.5% and hospitalization by 67.2% [19-22]. In December 2017, the WHO [23] 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. Dengvaxia has the potential to lower the burden of dengue disease in areas where the disease is prevalent moderate to high [24]. A cautionary note should be mentioned, there is an increased risk of hospitalization of the vaccinated individual among groups without prior infections. Mass vaccination with the CYD-TDV vaccine should not be done in countries that do not have a history of dengue infections by most of the strains of the DENV. This is why the vaccination programs involving this vaccine have been stopped in countries such as Thailand, where there is a prior history of infections by multiple strains of the DENV's [20-24].

2.4 Dengue fever and vaccine in Thailand

Thailand has long reported outbreaks of dengue fever. The outbreak has spread throughout the country, with cases found in every province and region. Report from the department of disease control the ministry of public health in 2020 found 71292 cases and 51 deaths. The dengue vaccine used in Thailand is Dengvaxia and WHO is recommended for use in children and adults aged 9-45 years as a safe vaccine. Map from the centers for disease control and prevention (CDC) in 2020 shown dengue around the world we can see that Thailand has frequent or continuous risk means that either frequent outbreaks occur or transmission is ongoing are shown in Figures 2.5-2.6 [25,26].

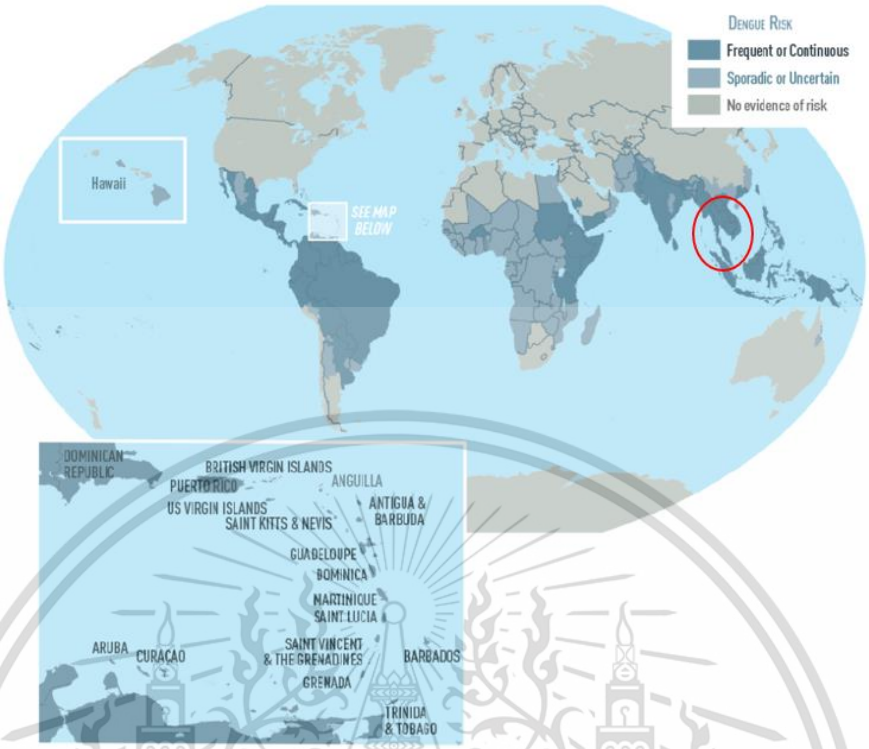


Figure 2.5 Map dengue risk around the world [25].

Figure 2.6 Map dengue risk in Asia and Oceania [26].

2.5 Theorem and definition background

The following are the theoretical concepts that this thesis has defined and applied to research:

Definition 2.1 (Equilibrium point [27,28]) 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.

From van den Driessche and Watmough [27] the vector-host model described by equation:

$$\left.\begin{aligned} \frac{d\bar{S}}{dt} &= b - b\bar{S} + r\bar{I} - \beta_1 \bar{S}\bar{V} \\ \frac{d\bar{I}}{dt} &= \beta_1 \bar{S}\bar{V} - (b+r)\bar{I} \\ \frac{d\bar{M}}{dt} &= c - c\bar{M} - \beta_2 c\bar{M}\bar{I} \\ \frac{d\bar{V}}{dt} &= \beta_2 \bar{M}\bar{I} - \mathrm{c}\bar{V} \end{aligned}\right\}. \tag{2.1}$$

With the conditions $N_h = \bar{S} + \bar{I}$, and $N_v = \bar{M} + \bar{V}$. From Equation (2.1), normalizing the system equation by introducing the following normalized variables:

$$S = \frac{\bar{S}}{N_h},\ I = \frac{\bar{I}}{N_h},\ M = \frac{\bar{M}}{N_v},\ V = \frac{\bar{V}}{N_v}. \tag{2.2}$$

The mathematical model of Equation (2.1) is now normalized to the following equation:

$$\left.\begin{aligned} \frac{dS}{dt} &= \frac{b}{N_h} - bS + rI - \beta_1 SVN_h \\ \frac{dI}{dt} &= \beta_1 SVN_h - (b+r)I \\ \frac{dM}{dt} &= \frac{c}{N_v} - cM - \beta_2 cMIN_v \\ \frac{dV}{dt} &= \beta_2 cMIN_v - \mathrm{c}V \end{aligned}\right\}. \tag{2.3}$$

The equilibrium points are obtained by setting the right-hang side of Equation (2.3) to zero. This system model now admits two equilibrium points, namely the disease-free equilibrium and the endemic equilibrium point.

The disease-free equilibrium point E_1 is:

$$E_1 = (1, 0, 1, 0).$$

The endemic equilibrium point E_2 is:

$$E_2 = \left(\frac{(b+r)(c+\beta_2)}{(b+r+\beta_1)\beta_2}, \frac{\beta_1\beta_2 - (b+r)c}{(b+r+\beta_1)\beta_2}, \frac{c(b+r+\beta_1)}{\beta_1(c+\beta_2)}, \frac{\beta_1\beta_2 - (b+r)c}{\beta_1(c+\beta_2)} \right).$$

Definition 2.2 (The basic reproductive number [27]) the basic reproductive number (R_0) is defined as the average number of secondary infections when a single infective enters an entirely susceptible population (we compute R_0 by next-generation matrix method).

Definition 2.3 (Next generation matrix [27]) Let X be vector of infected classes, such as carrier, infectious, exposed, etc. Let Y be vector of uninfected classes, such as recovered and susceptible. Then

$$\frac{dX}{dt} = \tilde{F}(X,Y) - \tilde{V}(X,Y).$$

$\tilde{F}(X,Y)$: Vector of new infection rates (flows from Y to X).

$\tilde{V}(X,Y)$: Vector of all other rates (not new infection).

These rates include flows from X to Y (for instance, recovery rates), flows within X and flows leaving from the system (for instance, death rates). For each compartment in-flow in $\tilde{V}$ is negative and out-flow in $\tilde{V}$ is positive. The vector-valued function $\tilde{F}(X,Y)$ and $\tilde{V}(X,Y)$ of X and Y given by:

$$F = \left(\frac{\partial \tilde{F}}{\partial X}\right), \quad V = \left(\frac{\partial \tilde{V}}{\partial X}\right),$$

at the disease-free equilibrium point and then, FV^{-1} is called the next generation matrix. The spectral radius (ρ) of FV^{-1} is equal to the basic reproductive number (R_0). The spectral radius of FV^{-1} is equal to the dominant eigenvalue of FV^{-1} that is the maximum eigenvalue of FV^{-1}. Therefore, R_0 equal to the maximum eigenvalue of FV^{-1}.

From van den Driessche and Watmough [27] the dynamics system of the multistrain model equation is described:

$$\left.\begin{aligned}
\frac{d\overline{S}}{dt} &= b + \gamma_1\overline{I_1} + \gamma_2\overline{I_2} - b\overline{S} - \beta_1\overline{S}\,\overline{I_1} - \beta_2\overline{S}\,\overline{I_2} \\
\frac{d\overline{I_1}}{dt} &= \beta_1\overline{S}\,\overline{I_1} + v\overline{I_1}\,\overline{I_2} - \gamma_1\overline{I_1} - b\overline{I_1} \\
\frac{d\overline{I_2}}{dt} &= \beta_2\overline{S}\,\overline{I_2} - v\overline{I_1}\,\overline{I_2} - \gamma_2\overline{I_2} - b\overline{I_2} \\
N &= \overline{S} + \overline{I_1} + \overline{I_2}
\end{aligned}\right\}. \qquad (2.4)$$

From Equation (2.4), normalizing the system equation by introducing the following normalized variables:

$$S=\frac{\overline{S}}{N},\ I_1=\frac{\overline{I_1}}{N},\ I_2=\frac{\overline{I_2}}{N}. \tag{2.5}$$

We also have $S=1-I_1-I_2$. The mathematical model of Equation (2.4) is now reduced to the following equation:

$$\left.\begin{aligned}\frac{dI_1}{dt}&=\beta_1 SI_1N+vI_1I_2N-\gamma_1 I_1-bI_1\\ \frac{dI_2}{dt}&=\beta_2 SI_2N-vI_1I_2N-\gamma_2 I_2-bI_2\end{aligned}\right\}. \tag{2.6}$$

We have

$$X=\begin{bmatrix}I_1\\ I_2\end{bmatrix},\ Y=[S],\ \tilde{F}=\begin{bmatrix}\beta_1 SI_1N\\ \beta_2 SI_2N\end{bmatrix},\ \tilde{V}=\begin{bmatrix}-vI_1I_2N+\gamma_1 I_1+bI_1\\ vI_1\mathrm{I}_2N+\gamma_2 I_2+bI_2\end{bmatrix}.$$

At the disease free equilibrium point $(S,I_1,I_2)=(1,0,0)$ we get:

$$F=\begin{bmatrix}\frac{\partial(\beta_1 SI_1N)}{\partial I_1} & \frac{\partial(\beta_1 SI_1N)}{\partial I_2}\\ \frac{\partial(\beta_2 SI_2N)}{\partial I_1} & \frac{\partial(\beta_2 SI_2N)}{\partial I_2}\end{bmatrix}=\begin{bmatrix}\beta_1N & 0\\ 0 & \beta_2N\end{bmatrix},$$

$$V=\begin{bmatrix}\frac{\partial(-vI_1I_2N+\gamma_1 I_1+bI_1)}{\partial I_1} & \frac{\partial(-vI_1I_2N+\gamma_1 I_1+bI_1)}{\partial I_2}\\ \frac{\partial(vI_1\mathrm{I}_2N+\gamma_2 I_2+bI_2)}{\partial I_1} & \frac{\partial(vI_1\mathrm{I}_2N+\gamma_2 I_2+bI_2)}{\partial I_2}\end{bmatrix}=\begin{bmatrix}b+r_1 & 0\\ 0 & b+r_2\end{bmatrix},$$

and

$$V^{-1}=\begin{bmatrix}\frac{1}{b+r_1} & 0\\ 0 & \frac{1}{b+r_2}\end{bmatrix}.$$

Then

$$FV^{-1}=\begin{bmatrix}\beta_1N & 0\\ 0 & \beta_2N\end{bmatrix}\begin{bmatrix}\frac{1_1}{b+r_1} & 0\\ 0 & \frac{1}{b+r_2}\end{bmatrix}=\begin{bmatrix}\frac{\beta_1N}{b+r_1} & 0\\ 0 & \frac{\beta_2N}{b+r_2}\end{bmatrix}.$$

Therefore

$$R_0=\max\left\{\frac{\beta_1N}{b+r_1},\frac{\beta_2N}{b+r_2}\right\}.$$

Theorem 2.1 (Stability [28]) The equilibrium points E_i of the system $\frac{dX}{dt} = f(t, X)$ is locally asymptotically stable if the Jacobian matrix $J = \frac{\partial}{\partial x}(E_i)$ has all its eigenvalue with negative real parts. The equilibrium point E_0 is unstable if at least one of the eigenvalues of the matrix J has a positive real part. From Equation (2.6) the Jacobian matrix is defined as:

$$J_{E_i} = \begin{bmatrix} \beta_1 SN + vI_2N - r_1 - b & vI_1N \\ -vI_2N & \beta_2 SN - vI_1N - r_2 - b \end{bmatrix}. \quad (2.7)$$

Assumed that λ_1 and λ_2 be eigenvalues of the Jacobian matrix J_{E_i}.

For real eigenvalues, the behavior of the solution can be classified into one of the three possible categories.

Case 1: If both eigenvalues are positive $\lambda_1 > 0, \lambda_2 > 0$, then we have an unstable node.

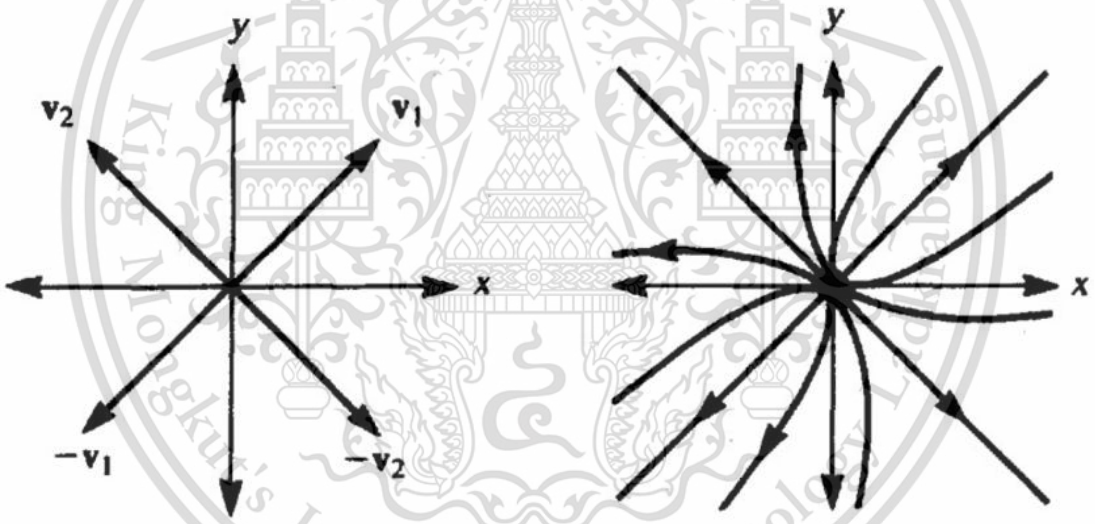


Figure 2.7 Sketches of the eigenvalues and solution curve of both positive are unstable node [28].

Case 2: If eigenvalues are of opposite sign $\lambda_1 > 0, \lambda_2 < 0$ or $\lambda_1 < 0, \lambda_2 > 0$, then we have a saddle point.

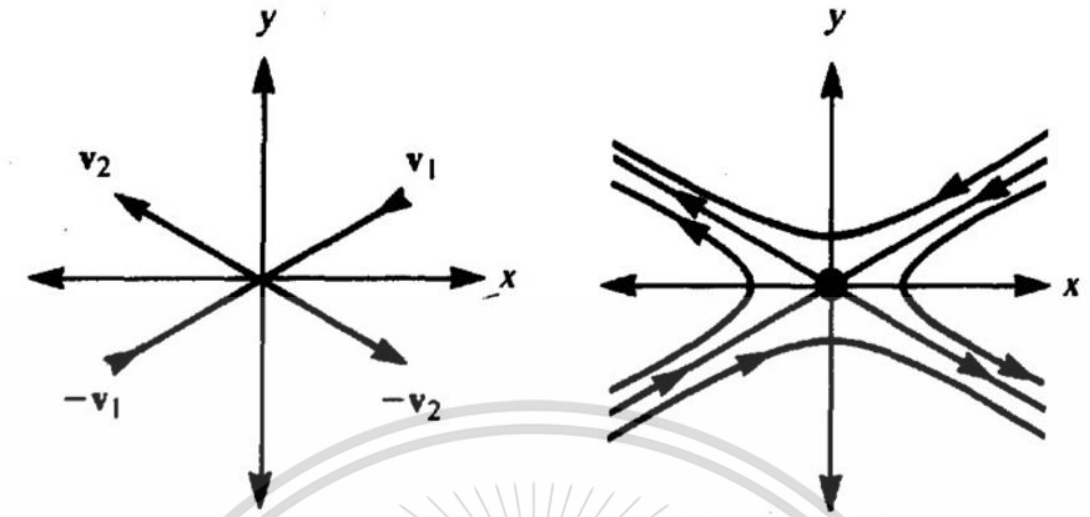


Figure 2.8 Sketches of the eigenvalues and solution curve of opposite signs are saddle point [28].

Case 3: If both eigenvalues are negative $\lambda_1 < 0, \lambda_2 < 0$, then we have a stable node.

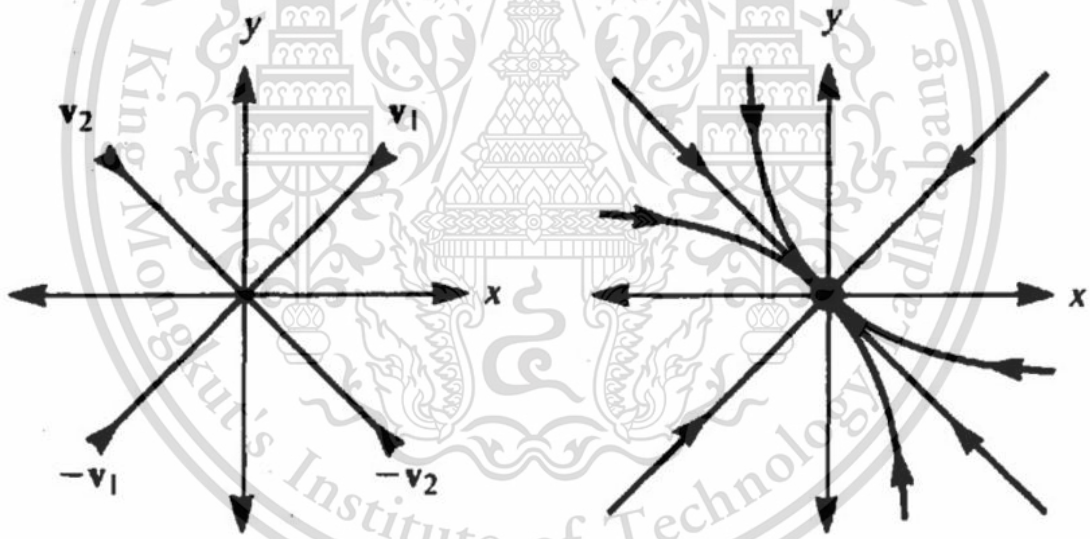


Figure 2.9 Sketches of the eigenvalues and solution curve of both negative are stable node [28].

For complex eigenvalues $\lambda = a \pm bi$, we make a distinction between the following scenarios. The solution's behavior can be classified into one of three groups.

Case 1: If eigenvalues have a positive real part $a > 0$, then we have a unstable spiral.

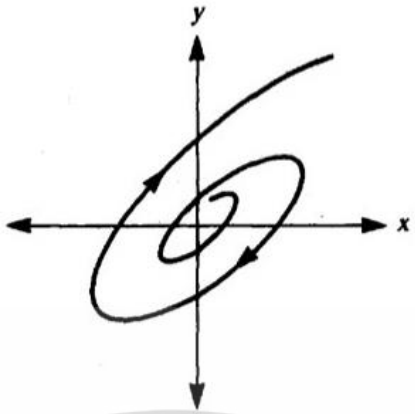


Figure 2.10 Solution curve when eigenvalues are complex with positive are a unstable spiral [28].

Case 2: If eigenvalues are pure imaginary $a = 0$, then we have a neutral center.

Figure 2.11 Solution curve when eigenvalues are complex with zero are a neutral center [28].

Case 3: If eigenvalues have a negative real part $a < 0$, then we have a stable spiral.

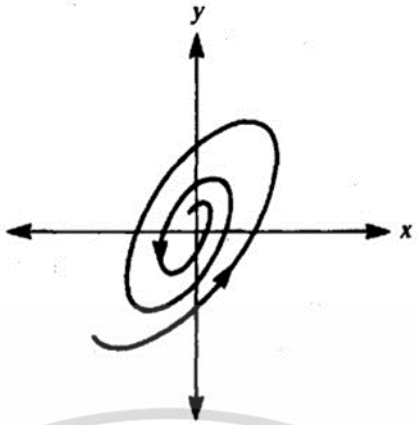


Figure 2.12 Solution curve when eigenvalues are complex with negative are a stable spiral [28].

Theorem 2.2 *(*Routh-Hurwitz *[28])* Considering the general equation and vector notation are given*:*

$$\left.\begin{aligned}\frac{dX_i}{dt} &= w_i\left(X_1, X_2, X_3, ..., X_n\right)\\ \frac{dX}{dt} &= W\left(X\right)\end{aligned}\right\}. \tag{2.8}$$

Where $X=(X_1, X_2, X_3, ..., X_n)$, and $W=(W_1, W_2, W_3, ..., W_n)$. The equilibrium point can be setting the right-hand side of the equation above to zero yields*:*

$$W\left(X\right)=0.$$

Then we get equilibrium points $\overline{X}=(X_1, X_2, X_3, ..., X_n)$, and satisfying $W\left(\overline{X}\right)=0$. The obtained Jacobian matrix of $W(X)$ is*:*

$$\left.\begin{aligned}J &= \frac{\partial W}{\partial X}\left(\overline{X}\right)\\ J &= \begin{bmatrix}\frac{\partial w_1}{\partial X_1} & \frac{\partial w_2}{\partial X_2} & \cdots & \frac{\partial w_n}{\partial X_n}\\ \vdots & \vdots & \ddots & \vdots\\ \frac{\partial w_n}{\partial X_1} & \frac{\partial w_2}{\partial X_2} & \cdots & \frac{\partial w_n}{\partial X_n}\end{bmatrix}_{\overline{X}}\end{aligned}\right\}. \tag{2.9}$$

Where J is matrix dimension $n\times n$, I is $n\times n$ identity matrix, and eigenvalues λ of this now satisfy*:*

$$\det\left(J-\lambda I\right)=0. \tag{2.10}$$

The characteristic equation is polynomial of degree n:

$$\lambda^n + \Delta_1\lambda^{n-1} + \Delta_2\lambda^{n-2} + \Delta_3\lambda^{n-3} + \ldots + \Delta_n = 0. \qquad (2.11)$$

The coefficients of characteristic polynomial of Equation *(2. 11)*, defined n matrices as follows*:*

$$H_1 = [\Delta_1],$$

$$H_2 = \begin{bmatrix} \Delta_1 & 1 \\ \Delta_3 & \Delta_2 \end{bmatrix},$$

$$H_3 = \begin{bmatrix} \Delta_1 & 1 & 0 \\ \Delta_3 & \Delta_2 & \Delta_1 \\ \Delta_5 & \Delta_4 & \Delta_3 \end{bmatrix}, \cdots,$$

$$H_i = \begin{bmatrix} \Delta_1 & 1 & 0 & 0 & \cdots & 0 \\ \Delta_3 & \Delta_2 & \Delta_1 & 1 & \cdots & 0 \\ \Delta_5 & \Delta_4 & \Delta_3 & \Delta_2 & \cdots & 0 \\ \Delta_{2i-1} & \Delta_{2i-2} & \Delta_{2i-3} & \Delta_{2i-4} & \cdots & \Delta_i \end{bmatrix}, \ldots,$$

$$H_n = \begin{bmatrix} \Delta_1 & 1 & 0 & 0 & \cdots & 0 \\ \Delta_3 & \Delta_2 & \Delta_1 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & \Delta_n \end{bmatrix},$$

where the (r,m) term in the matrix H_i is

Δ_{2r-m} for $0 < 2r - m < n,$

1 for $2r = m,$

0 for $2r < m,$ or $2r > n + m.$

Then all eigenvalues have negative real parts. The equilibrium point $\bar{X}$ is stable if and only if the determinants of all Hurwitz matrices are positive*:*

$$\det H_i > 0 \qquad (i = 1, 2, 3, \ldots, \mathrm{n}).$$

Routh-Hurwitz Criteria for example $n = 1, 2, 3, 4$

$n = 1$: $\Delta_1 > 0.$

$n = 2$: $\Delta_1 > 0,\ \Delta_2 > 0.$

$n = 3$: $\Delta_1 > 0,\ \Delta_3 > 0,\ \Delta_1\Delta_2 - \Delta_3 > 0.$

$n = 4$: $\Delta_1 > 0,\ \Delta_3 > 0,\ \Delta_4 > 0,\ \Delta_1\Delta_2\Delta_3 - \Delta_1^2\Delta_4 - \Delta_3^2 > 0.$

Theorem 2.3 (Lyapunov [28]) Let $x = 0$ be an equilibrium point $\dot{x} = f(x)$ and $f(x): \phi \subset \mathbb{R}^n.$ Let $V(x): \phi \to \mathbb{R}$ be a continuously differentiable function such that:

$i)\ V(0) = 0,$

$ii) V(x) > 0$ in ϕ, except at $x = 0,$

$iii)\dot{V}(0)=0,$

$iv)\dot{V}(x)<0$ in ϕ, except at $x=0.$

If $\dot{V}(x)<0$ in $\phi-\{0\}$, then $x=0$ is globally asymptotically stable.

Theorem 2.4 (LaSalle's [28]) Let $f:D\subset R^n$ be a compact invariant set with respect to $\dot{x}=f(x)$. Let $V(x)$ be a continuously differentiable function defined over R^n such that $\dot{V}(x)\leq 0$ in D.

Let P be a set of all points in D where $\dot{V}(x)=0$ and E be the largest invariant set in P. Then every solution stating in D approaches E as $t\to\infty$. Moreover, if the set P contains only one point $x=0$, then $x=0$ this point is asymptotically stable in D.

Definition 2.5 (Optimal control [29]) Our basic optimal control problem consists of finding a piecewise continuous control $u(t)$ and associated state variable $x(t)$ to minimize the given objective functional,

$$\max_u \int_{t_0}^{t_1} f(t,x(t),u(t))dt.$$

Subject to

$$\begin{aligned} x'(t)&=g(t,x(t),u(t)),\\ x(t_0)&=x_0 \text{ and } x(t_1) \text{ free.} \end{aligned} \tag{2.12}$$

Such a maximizing control is called an optimal control. By the term $x(t_1)$, free refers to the fact that the value of $x(t_1)$ is unrestricted. In all three arguments, f and g will always be continuously differentiable functions for our purposes. As a result, the associated states will always be piecewise differentiable, because the control will always be piecewise continuous.

Definition 2.6 (Hamiltonian [29]) If $u^*(t)$ and $x^*(t)$ are optimal for problem Equation (2.12), then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that

$$H(t,x^*(t),u(t),\lambda(t))\leq H(t,x^*(t),u^*(t),\lambda(t)),$$

for all control $u(t)$, where the Hamiltonian H is

$$H=f(t,x(t),u(t))+\lambda(t)g(t,x(t),u(t)),$$

and

$$\frac{d\lambda}{dt}=-\frac{\partial H(t,x^*(t),u^*(t),\lambda(t))}{\partial x},$$

$$\lambda(t_1) = 0.$$

We have already shown with this adjoint and Hamiltonian, $H_u = 0$ at $u^*(t)$. Namely, the Hamiltonian has a critical point, in the u variable, at $u^*(t)$.

Theorem 2.7 [29] Suppose that $f(t,x,u)$ and $g(t,x,u)$ are both continuously differentiable functions in their three arguments and concave in u. Suppose u^* is an optimal control for problem Equation (2.12), with associated state x^*, and λ a piecewise differentiable function with $\lambda(t) \geq 0$ for all t. Suppose for all $t_0 \leq t \leq t_1$

$$H_u\left(t, x^*(t), u^*(t), \lambda(t)\right) = 0.$$

Then for all controls u and each $t_0 \leq t \leq t_1$, we have

$$H\left(t, x^*(t), u(t), \lambda(t)\right) \leq H\left(t, x^*(t), u^*(t), \lambda(t)\right).$$

2.6 Mathematical modeling studies

This section reviews the work of other researchers related to the objectives of this thesis. Some of the related works are as follows,

In 2015, Phaijoo and Gurung [30] studied the SIR model of dengue disease transmission with a fraction of susceptible host and infected host population aware. This model supposed that the populations do not interact with the mosquitoes. The diagram of a mathematical model of dengue fever with and without awareness is shown in Figure 2.13.

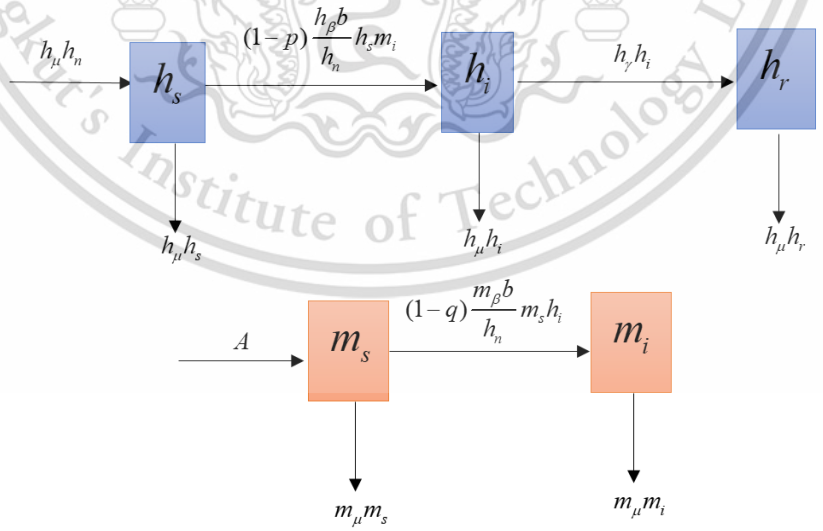


Figure 2.13 The diagram of a mathematical model of dengue fever with and without awareness [30].

The systems of differential equations that describe the present model are for the human and vector population are as follows:

$$\left.\begin{aligned}
\frac{dh_s}{dt} &= h_\mu h_n - (1-p)\frac{h_\beta b}{h_n} h_s m_i - h_\mu h_s \\
\frac{dh_i}{dt} &= (1-p)\frac{h_\beta b}{h_n} h_s m_i - h_\mu h_i - h_\gamma h_i \\
\frac{dh_r}{dt} &= h_\gamma h_i - h_\mu h_r \\
\frac{dm_s}{dt} &= A - (1-q)\frac{m_\beta b}{h_n} m_s h_i - m_\mu m_s \\
\frac{dm_i}{dt} &= (1-q)\frac{m_\beta b}{h_n} m_s h_i - m_\mu m_i
\end{aligned}\right\}. \qquad (2.13)$$

The description of state variables and parameters are defined as Table 2.1.

Table 2.1 The definition of the parameters and variables used in Equation (2.13).

Parameters & Variables	Definition
h_s	The number of susceptibles in the host population
h_i	The number of infectives in the host population
h_r	The number of removals in the host population
m_s	The number of susceptibles in the vector population
m_i	The number of infectives in the vector population
h_n	The constant host (human) population size
m_n	The constant vector (mosquito) population size
p	The fraction of susceptible host population aware of dengue transmission
q	The fraction of infected host population aware of dengue transmission
h_μ	The birth/death rate in the host population
m_μ	The death rate in the vector population
h_β	The transmission probability from vector to host
m_β	The transmission probability from host to vector
b	The biting rate
h_γ	The recovery rate in the host population
A	The recruitment rate

The influence of awareness factors on dengue fever transmission dynamics was investigated using a dengue model. The transmission of the disease was studied with and without the existence of disease awareness in the host population. Only a small percentage of the vulnerable host population is meant to be exposed to mosquitos. The community is expected to be aware of disease transmission and to take all reasonable precautions, such as using insect repellent, mosquito nets, and other similar measures, to avoid mosquito bites. Furthermore, because the population is segregated owing to knowledge, a portion of the diseased host population is not expected to spread the disease. Because of increased awareness, the disease is thought to impact fewer humans and mosquitoes. When the host population is unaware of the disease, a significant number of people are seen to be affected. As a result, the current study implies that by raising host population knowledge, a large number of susceptible hosts can be rescued from infection. As a result, raising public awareness about the disease's transmission is critical to halting the spread of dengue fever.

In 2015, Hossain et al. [31] investigated and extensively assessed a mathematical model to determine effective control techniques for the transmission dynamics of a vector-borne disease. The basic reproduction number is shown to be totally responsible for the disease's global dynamics. The model's numerical simulations show that preventative actions taken at the aquatic and adult phases reduce the number of new dengue virus cases. The numerical simulations show that taking preventative measures carefully is more successful than treating diseased people.

In 2018, Chanprasopchai et al. [8] studied the mathematical model of dengue disease for the effect of dengue vaccination to analyze the behaviors of transmission of dengue fever with the Dengvaxia vaccination. Only one strain of the DF virus was considered, and there was no assumption of age structure in human populations. The population is divided into two groups are the human and vector population. The diagram described the transmission of dengue disease with the effect of vaccination is shown in Figure 2.14. The variables and parameters are defined in Table 2.2.

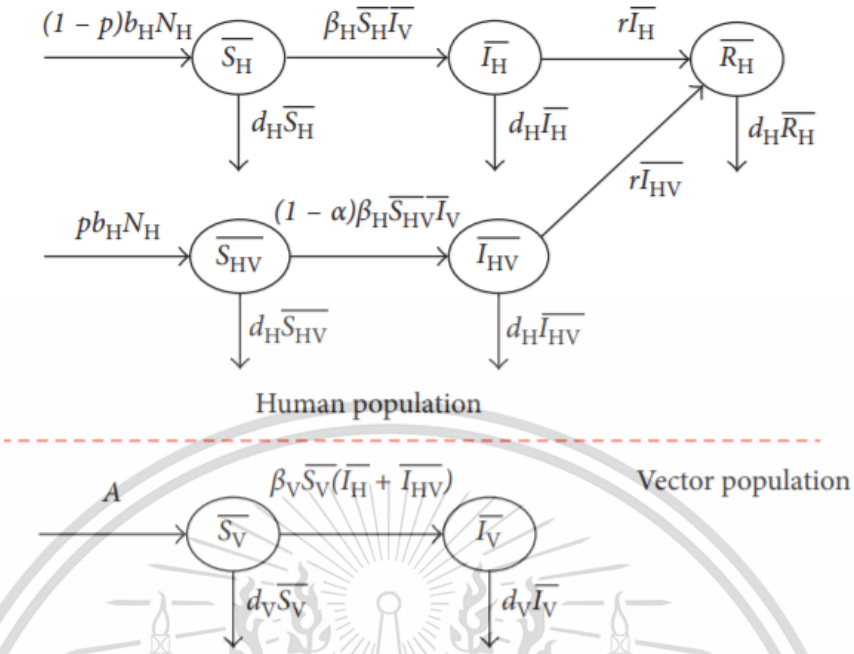


Figure 2.14 Dynamical transmission in the human and mosquitoes with the effect of vaccination incorporated [8].

Table 2.2 The definition of the parameters and variables used in Equation (2.14).

Parameters & Variables	Definition
$\overline{S_H}$	The number of the susceptible human without vaccinated at time t
$\overline{S_{HV}}$	The number of the susceptible human with vaccinated at time t
$\overline{S_V}$	The number of the susceptible vector at time t
$\overline{I_H}$	The number of the infected human without vaccinated at time t
$\overline{I_{HV}}$	The number of the infected human with vaccinated at time t
$\overline{I_V}$	The number of the infected vector at time t
$\overline{R_H}$	The number of the recovered human at time t
p	The fraction of newborns vaccinated
α	The vaccine efficacy
β_V	The transmission rate of dengue virus from human to vector
β_H	The transmission rate of dengue virus from vector to human
A	The constant recruitment rate of vector
N_V	The total number of vector
N_H	The total number of human
b_H	The birth rate of humans

Parameters & Variables	Definition
d_H	The death rate of humans
d_V	The death rate of vectors

The nonlinear system of the differential equation describing the dynamics is given by:

$$\left.\begin{aligned}
\frac{d\overline{S_H}}{dt} &= (1-p)b_H N_H - \beta_H \overline{S_H}\,\overline{I_V} - d_H \overline{S_H} \\
\frac{d\overline{I_H}}{dt} &= \beta_H \overline{S_H}\,\overline{I_V} - (\gamma + d_H)\overline{I_H} \\
\frac{d\overline{R_H}}{dt} &= \gamma\left(\overline{I_H} + \overline{I_{HV}}\right) - d_H \overline{R_H} \\
\frac{d\overline{S_{HV}}}{dt} &= pb_H N_H - (1-\alpha)\beta_H \overline{S_{HV}}\,\overline{I_V} - d_H \overline{S_{HV}} \\
\frac{d\overline{I_{HV}}}{dt} &= (1-\alpha)\beta_H \overline{S_{HV}}\,\overline{I_V} - (\gamma + d_H)\overline{I_{HV}} \\
\frac{d\overline{S_V}}{dt} &= A - \beta_V \overline{S_V}\left(\overline{I_H} + \overline{I_{HV}}\right) - d_V \overline{S_V} \\
\frac{d\overline{I_V}}{dt} &= \beta_V \overline{S_V}\left(\overline{I_H} + \overline{I_{HV}}\right) - d_V \overline{I_V}
\end{aligned}\right\}. \qquad (2.14)$$

The result from the analysis, the simulation numerical find that the influence of dengue vaccination with the infected human without vaccination there is a significant reduction in the total hospitalization time needed to treat the illness. This means that vaccines can help reduce the severity of the disease.

In 2019, Pongsumpun et al. [10] studied the SEIR mathematical model of dengue transmission with vertical transmission and optimal control. This model, considered a control mechanism of two policies, Policy 1 is insecticide administration and vaccination, and Policy 2 is insecticide administration and isolation. The normalized system of differential equations are defined as following:

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \mu_H\left(1-S_H\right)-\frac{b\beta_H}{N_H}S_H I_V N_V \\
\frac{dE_H}{dt} &= \frac{b\beta_H}{N_H}S_H I_V N_V-\left(\varepsilon_H+\mu_H\right)E_H \\
\frac{dI_H}{dt} &= \varepsilon_H E_H-\left(\mu_H+\gamma_H\right)I_H \\
\frac{dE_V}{dt} &= b\beta_V S_V I_H-\left(\varepsilon_V+\mu_V\right)E_V \\
\frac{dI_V}{dt} &= \frac{M}{N_V}+\varepsilon_V E_V-\mu_V I_V
\end{aligned}\right\}. \qquad (2.15)$$

The variables and parameters of Equation (2.15) are defined in Table 2.3.

Table 2.3 The definition of the parameters and variables used in Equation (2.15).

Parameters & Variables	Definition
S_H	The number of susceptible human individual at time t
E_H	The number of exposed human individual at time t
I_H	The number of infected human individual at time t
E_V	The number of exposed vector individual at time t
I_V	The number of infected vector individual at time t
N_H	The total number of human population
N_V	The total number of vector population
μ_H	The death rate of human population
μ_V	The death rate of vector population
β_H	The transmission probability from the vector to human population
β_V	The transmission probability from the human to vector population
b	The biting rate of the human population
ε_H	The intrinsic incubation rate
ε_V	The extrinsic incubation rate
γ_H	The recovery rate of the human population
M	The number of mosquitoes transovarially infected

Two control inputs can be attributed, namely u_1 for the human population and u_2 for the mosquito population.

Policy 1: Insecticide administration and vaccination.

Because vaccination has a limited effect on the exposed and infected populations, it is assumed that u_1 will have no effect on E_H and I_H. As a result of the insecticide administration, it is believed that u_2 will act on both E_V and I_V. The following equations represent the control model for Policy 1:

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \mu_H\left(1-S_H\right)-\frac{b\beta_H}{N_H}S_H I_V N_V - u_1(t)S_H \\
\frac{dE_H}{dt} &= \frac{b\beta_H}{N_H}S_H I_V N_V - \left(\varepsilon_H+\mu_H\right)E_H \\
\frac{dI_H}{dt} &= \varepsilon_H E_H - \left(\mu_H+\gamma_H\right)I_H \\
\frac{dE_V}{dt} &= b\beta_V S_V I_H - \left(\varepsilon_V+\mu_V\right)E_V - u_2(t)E_V \\
\frac{dI_V}{dt} &= \frac{M}{N_V}+\varepsilon_V E_V - \mu_V I_V - u_2(t)E_V - u_2(t)I_V
\end{aligned}\right\}. \qquad (2.16)$$

Policy 2: Insecticide administration and isolation.

The isolation control u_1 anticipates the removal of diseased human persons from the system in this case. However, because isolation has a small impact on vulnerable and exposed populations, it is believed that u_1 will have no impact on S_H and E_H. Because the insecticide administration has comparable effects to Policy 1, it is believed that u_2 will act on both E_V and I_V once more. The following is the control model for Policy 2:

$$\left.\begin{aligned}
\frac{dS_H}{dt} &= \mu_H\left(1-S_H\right)-\frac{b\beta_H}{N_H}S_H I_V N_V \\
\frac{dE_H}{dt} &= \frac{b\beta_H}{N_H}S_H I_V N_V - \left(\varepsilon_H+\mu_H\right)E_H \\
\frac{dI_H}{dt} &= \varepsilon_H E_H - \left(\mu_H+\gamma_H\right)I_H - u_1(t)I_H \\
\frac{dE_V}{dt} &= b\beta_V S_V I_H - \left(\varepsilon_V+\mu_V\right)E_V - u_2(t)E_V \\
\frac{dI_V}{dt} &= \frac{M}{N_V}+\varepsilon_V E_V - \mu_V I_V - u_2(t)E_V - u_2(t)I_V
\end{aligned}\right\}. \qquad (2.17)$$

The optimal control problems of system Equations (2.16) and Equation (2.17), require a definition of the objective function as follows:

$$J\left(u_1,u_2\right)=\min\int_0^T\left(B_0 I_H(t)+\frac{1}{2}B_1u_1^2+\frac{1}{2}B_2u_2^2\right)dt, \qquad (2.18)$$

where $B_0, B_1,$ and B_2 are weight associated with the human infective population, the control variables u_1, and u_2 respectively. Although the administration of Policy 2 resulted in a faster reduction of the infected human population, this came at a higher cost in the initial effort; whereas the necessary vaccination effort of Policy 1 is substantially lower, while producing enhanced all-round epidemic management. The behavior of the control system when the weight functions $B_0, B_1,$ and B_2 were changed was also investigated. Both parameters β_H and β_V control methods are numerically demonstrated to be resistant to changes in transmission probabilities. As a result, in addition to insecticides, immunizations and isolation can also aid in the effective and optimal control of dengue fever.

In 2020, Ullah et al. [32] constructed an epidemic model with a nonlinear saturation incidence rate and saturated treatment function to investigate the transmission dynamics of vector-borne illnesses. The saturated treatment function, as well as this form of incidence rate, describe the effect of delayed therapy. They begin by formulating a mathematical model, after which they give the model's fundamental analysis, which includes the solution's positivity and boundedness. The variables and parameters of Equation (2.19) are defined as Table 2.4.

Table 2.4 The definition of the parameters and variables used in Equation (2.19).

Parameters & Variables	Definition
$S_H(t)$	The number of susceptible human individual at time t
$E_H(t)$	The number of exposed human individual at time t
$I_H(t)$	The number of infected human individual at time t
$R_H(t)$	The number of recovered human individual at time t
$S_V(t)$	The number of susceptible vector individual at time t
$E_V(t)$	The number of exposed vector individual at time t
$I_V(t)$	The number of infected vector individual at time t
Λ_H	The recruitment rate of hosts
Λ_V	The recruitment rate of vectors
β_1	The host constant rate
β_2	The vectors constant rate
ξ_V	The transmission from E_H to I_H class
ξ_H	The transmission from E_V to I_V class

Parameters & Variables	Definition
$N_H(t)$	The total number of human population
$N_V(t)$	The total number of vector population
α_1	The saturation in hosts
α_2	The saturation in vectors
d_H	The natural mortality rate in host population
d_V	The natural mortality rate in vectors
δ_H	The disease-induced death in infected host class
γ	The treatment rate
b	The delay in treatment

The transmission diagram of both host and vector population is depicted in Figure 2.15.

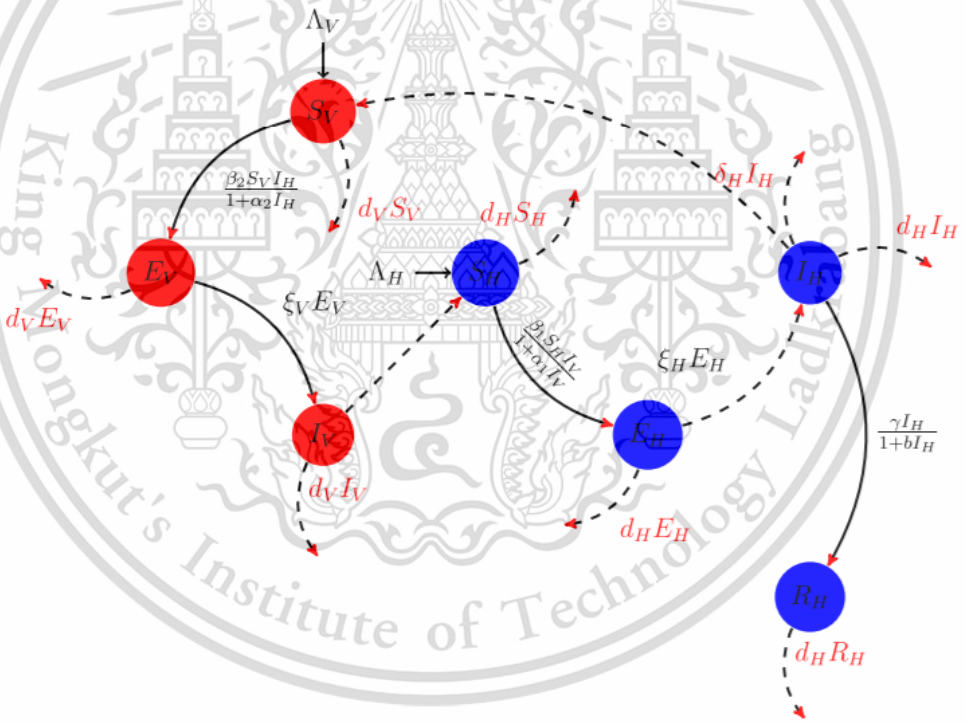


Figure 2.15 Flowchart describing the transmission of the vector-host disease [32].

The following system of differential equations can be used to numerically represent the suggested vector-host epidemic model:

$$\left.\begin{aligned}
\frac{dS_H(t)}{dt} &= \Lambda_H - \frac{\beta_1 S_H I_V}{1+\alpha_1 I_V} - d_H S_H \\
\frac{dE_H(t)}{dt} &= \frac{\beta_1 S_H I_V}{1+\alpha_1 I_V} - \xi_H E_H - d_H E_H \\
\frac{dI_H(t)}{dt} &= \xi_H E_H - d_H I_H - \delta_H I_H - \frac{\gamma I_H}{1+bI_H} \\
\frac{dR_H(t)}{dt} &= \frac{\gamma I_H}{1+bI_H} - d_H R_H \\
\frac{dS_V(t)}{dt} &= \Lambda_V - \frac{\beta_2 S_V I_H}{1+\alpha_2 I_H} - d_V S_V \\
\frac{dE_V(t)}{dt} &= \frac{\beta_2 S_V I_H}{1+\alpha_2 I_H} - \xi_V E_V - d_V E_V \\
\frac{dI_V(t)}{dt} &= \xi_V E_V - d_V I_V
\end{aligned}\right\}. \qquad (2.19)$$

They concentrated their efforts on developing a control problem in order to reduce the spread of infection in a community. In the newly proposed vector-host model, take into account the sensitivity results from the previous section and incorporate three time-dependent control variables to design an optimal control problem Equation (2.20).

$$\left.\begin{aligned}
\frac{dS_H(t)}{dt} &= \Lambda_H - \frac{\beta_1 S_H I_V}{1+\alpha_1 I_V}\left(1-u_1(t)\right) - d_H S_H \\
\frac{dE_H(t)}{dt} &= \frac{\beta_1 S_H I_V}{1+\alpha_1 I_V}\left(1-u_1(t)\right) - \xi_H E_H - d_H E_H \\
\frac{dI_H(t)}{dt} &= \xi_H E_H - d_H I_H - \delta_H I_H - \frac{\gamma u_2(t) I_H}{1+bI_H} \\
\frac{dR_H(t)}{dt} &= \frac{\gamma u_2(t) I_H}{1+bI_H} - d_H R_H \\
\frac{dS_V(t)}{dt} &= \Lambda_V - \frac{\beta_2 S_V I_H}{1+\alpha_2 I_H}\left(1-u_1(t)\right) - d_V S_V - u_3(t) S_V \\
\frac{dE_V(t)}{dt} &= \frac{\beta_2 S_V I_H}{1+\alpha_2 I_H}\left(1-u_1(t)\right) - \xi_V E_V - d_V E_V - u_3(t) E_V \\
\frac{dI_V(t)}{dt} &= \xi_V E_V - d_V I_V - u_3(t) I_V
\end{aligned}\right\}. \qquad (2.20)$$

These time-dependent control methods are denoted by $u_1(t), u_2(t)$, and $u_3(t)$ where $u_1(t)$ indicates bed-net or mosquito repellent preventative control. The second control

function, $u_2(t)$ is used to improve infected human therapy (raise R), while the third control function, $u_3(t)$ is utilized to spray insecticide against vector populations. The corresponding objective function for the purposed model to minimize the infection is given as follows:

$$J(u_1,u_2,u_3)=\int_0^{T_f}\left\{C_1I_H+C_2N_V+\frac{1}{2}\left(L_1u_1^2+L_2u_2^2+L_3u_3^2\right)\right\}dt. \quad (2.21)$$

The constants $C_1, C_2, L_1, L_2,$ and L_3 represent the balancing cost factors and T_f denotes the final time level. They developed four distinct strategies by combining different control factors. The following is a graphical representation of the influence of each strategy on disease dynamics and eradication.

Strategy 1: treatment and insecticides spray controls $(u_2\neq 0, u_3\neq 0, u_1=0)$.

Strategy 2: prevention and insecticides spraying controls $(u_1\neq 0, u_3\neq 0, u_2=0)$.

Strategy 3: prevention and treatment controls $(u_1\neq 0, u_2\neq 0, u_3=0)$.

Strategy 4: prevention, treatment and insecticides spraying controls $(u_1\neq 0, u_2\neq 0, u_3\neq 0)$.

The impact of each strategy on the disease dynamics is analyzed graphically and discussed in detail. From the graphical interpretations, it is found that strategies 1, 3, and 4 except strategy 2 are useful and can be used for disease minimization. But, from the simulation of strategy 4, we conclude that the implementation of all control interventions at the same time is the most useful strategy against disease eradication.

In 2021, Khan and Fatmawati [33] investigated the dynamics of dengue fever transmission during hospitalization using a mathematical model. For the year 2018, they assessed the basic reproduction number for infected cases in East Java Province to be $R_0=1.1138$. The parameters of the dengue model were calculated using confirmed notified cases from East Java province, Indonesia, in 2018. They developed a model for dengue fever with hospitalization and described its dynamics in depth. The optimal control problem is numerically solved, with the solutions consisting of a control system for several techniques. The goal of this case study is to reduce the number of dengue-infected hosts and vectors while minimizing the costs of applying the controls u_1 and u_2, namely, prevention u_1 and insecticides u_2 efforts as control variables in the model. The following objective function can be used to express this goal:

$$J(u_1,u_2)=\min\int_0^{t_f}\left(E_V+I_V+E_h+I_h+\frac{c_1}{2}u_1^2+\frac{c_2}{2}u_2^2\right)dt, \quad (2.22)$$

where E_h and E_v are the numbers of exposed hosts and vector, I_h and I_v are the numbers of infected hosts and vector, t_f is the final time, and c_1 and c_2 are positive weights. The optimal control problem is numerically solved, with the solutions consisting of a control system for several techniques. Controls such as preventive and insecticides may play the most important role in disease eradication in the community. The results imply that preventing humans from being bitten by mosquitos and spraying mosquitos with insecticides can greatly reduce dengue fever illness and the spread of the disease in the community.

In this research, we developed a mathematical model of dengue disease from [8,30,31] and applied an optimal control from [10,32,33]. We formulate the transmission models for dengue disease considering vaccinations before the first infection (primary) and after infection (secondary). Initially, we create a mathematical model and dynamics system equation to describe the model. In all mathematical models, found the equilibrium points and the basic reproductive number by the next generation. We study the local stability of equilibrium points by using Routh-Hurwitz, the global stability of equilibrium points by using Lyapunov function. The optimal control, formulate an optimal control problem with control functions, and obtain the optimal control characterization.

Chapter 3

Research methodology

This chapter presents data preparation, data analysis, and the outline of this thesis. Data on dengue fever (DF) and dengue hemorrhagic fever (DHF) each year from 2003 to 2020 by the actual data from the Bureau of Epidemiology, Department of Disease Control, Ministry of public health, Thailand.

3.1 Data preparation

All actual data related to dengue disease are collected and analyzed to get the thesis results. The historical numbers of dengue disease in Thailand during 2003-2020 are shown in Table 3.1-3.3 which is including reported cases, death cases, morbidity rate per 100,000 population, and mortality rate per 100,000 population [3,34,35].

Table 3.1 Number of monthly cases of dengue fever (DF) for each year from 2003-2020 [34].

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
2003	928	816	961	1,202	1,906	2,644	2,956	2,277	1,364	1,106	911	421	17,492
2004	354	302	410	508	1,014	1,602	1,889	1,528	1,298	1,020	760	496	11,181
2005	684	591	500	649	1,800	2,453	2,254	2,119	1,632	1,122	860	406	15,070
2006	572	429	570	745	1,848	3,075	3,183	2,360	1,486	1,073	978	743	17,062
2007	678	506	843	1,078	2,655	5,080	3,965	3,249	2,622	2,022	1,679	1,069	25,446
2008	1,247	1,210	1,450	1,694	3,622	6,023	6,003	5,216	3,438	3,213	2,325	1,204	36,645
2009	1,049	876	1,037	1,349	2,988	4,060	3,473	3,351	2,164	1,898	1,817	1,132	25,194
2010	1,496	1,528	2,020	1,868	3,666	6,631	10,037	11,299	7,463	3,630	2,229	1,282	53,149
2011	1,125	956	973	1,315	3,501	5,337	5,203	4,352	2,741	1,696	1,615	945	29,759
2012	857	938	1,106	1,338	2,412	4,372	5,377	5,080	4,645	4,683	4,938	3,575	39,321
2013	3,781	2,918	3,783	4,723	8,784	16,663	18,947	13,555	6,972	3,653	2,574	1,149	87,502
2014	887	856	1,010	770	1,436	2,637	3,552	3,365	2,697	2,292	2,237	1,431	23,170
2015	1,367	1,160	1,511	1,939	4,645	7,937	11,068	13,461	12,922	10,660	13,731	6,252	86,653
2016	4,057	2,505	2,347	1,307	1,230	2,503	4,991	6,676	5,012	3,498	2,627	1,713	38,466

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
2017	1,598	1,229	1,104	1,174	2,230	4,411	5,368	4,812	3,179	2,484	2,512	1,742	31,843
2018	1,272	1,183	1,544	1,790	4,532	8,765	9,257	7,976	5,936	4,712	4,493	3,616	55,076
2019	3,250	3,127	3,466	3,159	5,491	12,811	15,493	12,469	9,731	8,345	6,785	2,910	87,037

Table 3.2 Number of monthly deaths of dengue fever (DF) for each year from 2003-2020 [34].

	Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec	Total
2003	0	0	0	0	0	0	0	1	1	0	0	0	2
2004	0	0	0	0	1	0	0	0	0	0	0	0	1
2005	0	0	0	0	0	0	1	0	0	0	0	0	1
2006	0	0	0	0	0	0	0	0	0	0	0	0	0
2007	0	0	0	0	0	0	0	2	0	0	0	0	2
2008	0	0	0	0	0	1	0	0	0	0	0	0	1
2009	0	0	0	0	0	0	1	0	0	0	0	1	2
2010	0	0	0	0	0	0	0	0	1	0	0	0	1
2011	0	0	0	0	0	0	0	0	0	0	0	0	0
2012	0	0	0	0	0	0	0	0	0	0	0	0	0
2013	0	1	0	0	4	0	0	1	0	0	0	0	6
2014	0	0	0	0	0	0	0	0	0	0	0	0	0
2015	0	0	0	0	0	1	2	2	0	2	1	1	9
2016	2	0	0	0	0	0	2	0	1	0	0	0	5
2017	0	0	0	0	0	2	1	0	0	0	0	1	4
2018	0	0	0	0	0	1	1	2	1	1	0	0	6
2019	0	0	0	1	1	1	2	2	0	0	0	1	8
2020	0	0	0	0	0	3	1	1	1	0	0	0	6

Table 3.3 Number of Morbidity and Mortality rate per 100,000 by year from 2003-2020 of dengue hemorrhagic fever (DHF) [35].

Year	Cases	Morbidity rate per 100000 pop.	Deaths	CFR (%) pop.	Mortality rate per 100000 pop.	Total number pop.
2003	63,657	101.14	75	0.12	0.12	62,939,819
2004	39,135	62.59	48	0.12	0.08	62,526,710
2005	45,893	73.79	71	0.15	0.11	62,195,878
2006	46,829	74.78	59	0.13	0.09	62,623,416
2007	65,581	104.21	95	0.14	0.15	62,933,515
2008	89,626	141.78	102	0.11	0.16	63,214,022
2009	56,651	89.27	50	0.09	0.08	63,457,439
2010	116,947	183.59	139	0.12	0.22	63,701,703
2011	69,800	109.1	63	0.09	0.1	63,977,185
2012	78,337	122.26	81	0.1	0.13	64,075,986
2013	154,444	241.03	136	0.09	0.21	64,076,033
2014	41,082	63.25	49	0.12	0.08	64,955,313
2015	144,952	222.58	148	0.1	0.23	65,124,716
2016	63,931	97.71	64	0.1	0.1	65,426,907
2017	53,961	81.68	71	0.13	0.11	66,060,027
2018	86,922	131.58	114	0.13	0.17	66,060,027
2019	131,157	197.27	142	0.11	0.21	66,486,458
2020	72,130	108.79	51	0.07	0.08	66,301,242

3.2 Data analysis

All raw data, including dengue fever and dengue hemorrhagic fever, were collected for data analysis. To obtain the results of the thesis such as the number of cases and deaths monthly of dengue fever (DF) and the number of morbidity and mortality rate per 100,000 of dengue hemorrhagic fever (DHF) by year from 2003-2020.

3.3 Research outline

This thesis is organized as follows: Chapter 1 explains the research motivation, objectives of the thesis, scope of this thesis, benefits of the thesis, and outline of the

thesis. Theory and literature review are explained in Chapter 2 which is introduced the background of dengue disease with vaccination. Research methodology is presented in Chapter 3. Chapter 4 presents analyze of SEIR dengue infectious transmission model with vaccination (Paper 1 for the conference). Optimal control of dengue transmission with vaccination (Paper 2) and local and global stability analysis of dengue disease with vaccination and optimal control (Paper 3) are presented in Chapter 5 and 6 respectively. The conclusion and suggestion are summarized in Chapter 7. All research papers for this thesis title, Local and global stability analyses of mathematical models of dengue disease with vaccination in Thailand and their optimal control, are shown in Figure 3.1.

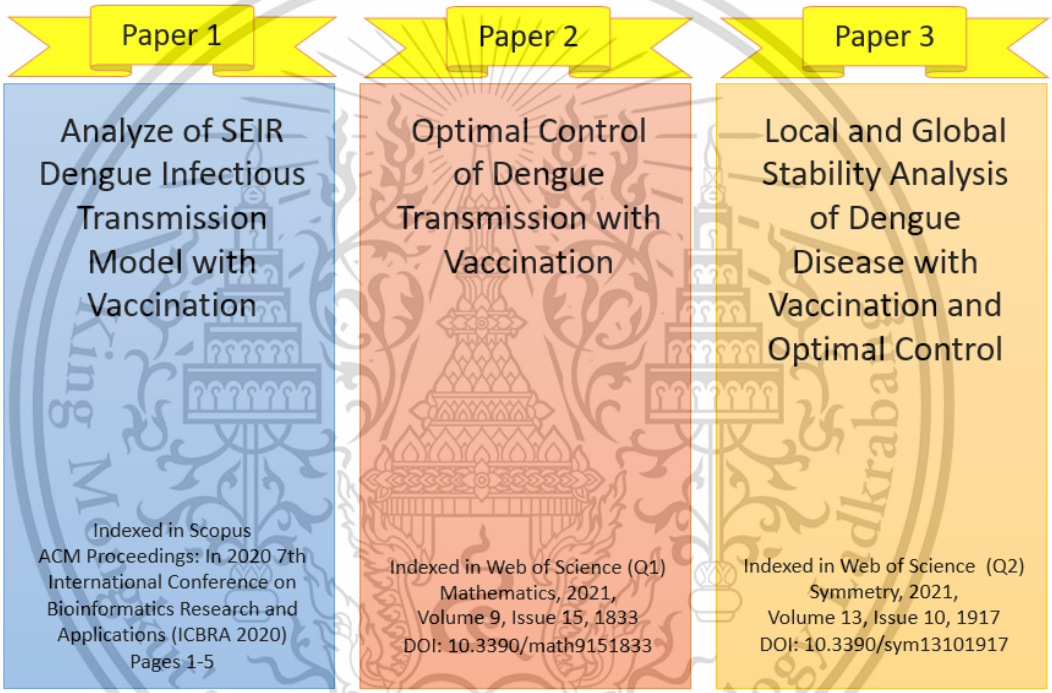


Figure 3.1 Research papers for thesis.

Chapter 4

Analyze of SEIR Dengue Infectious Transmission Model with Vaccination

In this chapter, we focus on the mathematical model of dengue disease with vaccination before the first serotypes infectious of the dengue virus and consider the recurrent infection and death from infection. We will be using the Susceptible-Exposed-Infected-Recovered (SEIR) model for the human population and SI for vector population is used to examine the dynamics of the disease. We will be analyzing the stability of the model using dynamic analysis. The equilibrium states. The reproductive number. The numerical simulation, result, and conclusion are presented.

4.1 Introduction

The dengue virus is disease-causing dengue fever. Which the virus will live in the *Aedes* mosquitoes most are found in *Aedes aegypti* more than the *Aedes albopictus* [36]. Dengue fever (DF) is caused by the dengue virus has four serotypes are DEN-1, DEN-2, DEN-3, and DEN-4 [36,37]. However, severe diseases, along with dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [38,39]. The disease is transmitted from the mosquito bites through the mosquito's saliva. The primary symptoms of dengue fever are high fever, headache, eye socket, muscle pain, and bone pain [3]. Dengue fever is not transmitted from human to human. Can be contagious with *Aedes* mosquitoes contact takes time in patients and mosquitoes. The patients with a high fever around 2-4 days will have a lot of virus in the blood. This period is the period of contact from people to mosquitoes. In addition, the period of increasing the number of viruses in mosquitoes is enough for about 8-10 days, therefore, is the period from mosquito to human [40]. WHO reported vaccination against dengue fever is one of the preventions of dengue fever. For vaccines that have been approved by the Food and Drug Administration of Thailand called Dengvaxia (Chimeric Yellow fever Dengue Tetravalent Dengue Vaccine: CYD-TDV) that covers all 4 serotypes of dengue virus which has been approved for use in people aged 9-45 years by the vaccine in a total of 3 needles, every 6 months [41]. Capeding et al. reported that the vaccine is effective against all dengue serotypes and reduces hospitalization from dengue fever and reduces illness type DHF [19]. Sungchasit et al. proposed the SEIR model for the human and SEI model for mosquitoes of dengue virus with primary and secondary infection [42] and proposed SIR transmission model of dengue virus two age classes in human and two types of mosquitoes (*Aedes Aegypti* and *Aedes Albopictus*) [43]. Massawe et al. [44]

reported that the treatment will have control of dengue fever disease. Analyzed the transmission model of dengue fever with a variable human population size and prove the global asymptotically stability of equilibrium states and consider the relation between two serotypes find that coexistence of both serotypes is possible for a large range of parameters [45,46]. Hossain et al. proposed effects of transient population the transmission dynamics and control the dengue virus effectively and to find the effects of transient population and analyzed a non-linear ODE model [47]. Chanprasopchai et al. [8] proposed the effect of a dengue vaccination model divided into two groups are with vaccine and without vaccine for the human population and SI for vector population. In Thailand, three serotypes are circulating, so the use of the vaccine does not impose additional risks.

In this chapter, we focus on the mathematical model of dengue disease with vaccination before the first serotypes infectious of the dengue virus and considered the recurrent infection and death from infection. We will be using the Susceptible-Exposed-Infected-Recovered (SEIR) model for the human population and SI for vector population is used to examine the dynamics of the disease. We will be analyzing the stability of the model using dynamic analysis. The equilibrium states. The reproductive number. The numerical simulation, result, and conclusion are presented.

4.2 Materials and Methods

4.2.1 Mathematical Model

In this model, we study the Susceptible-Exposed-Infected-Recovered (SEIR) model for the human population and Susceptible-Infected (SI) model for vector population to describe the dynamical transmission of dengue disease with vaccination in Thailand. We assume that the human population has been vaccinated before being infected. The human population is classified into four sub-classes: the number of susceptible individuals $(\overline{S_H})$, exposed individual $(\overline{E_H})$, infected individual $(\overline{I_H})$, and recovered individual $(\overline{R_H})$. The vector population is classified into two sub-classes: the number of susceptible individuals $(\overline{S_V})$, and infected individual $(\overline{I_V})$. The other parameters are defined list in Table 4.1 as follows. The transmission model is shown in Figure 4.1.

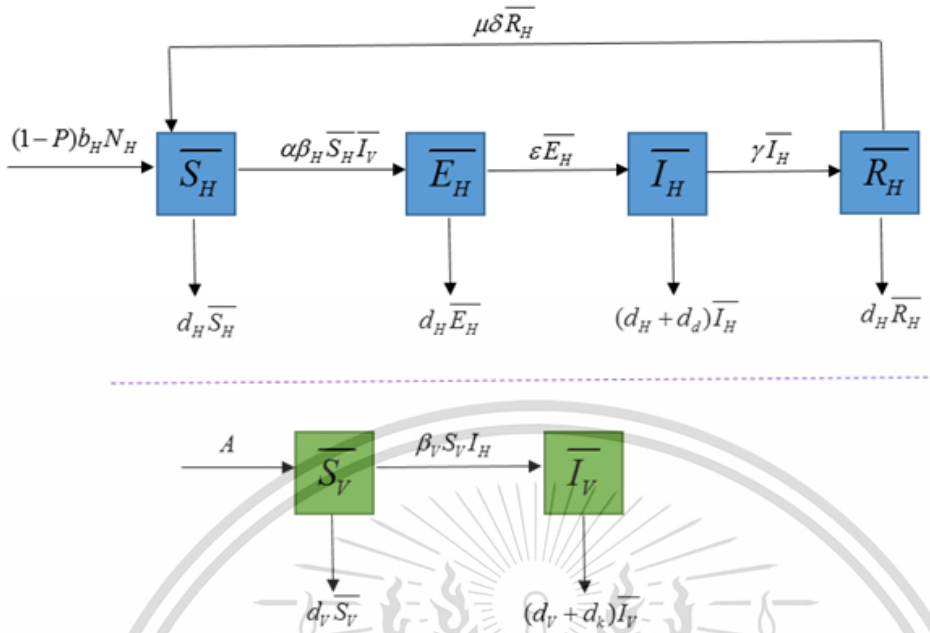


Figure 4.1 Flow chart of transmission model of human and vector population.

Table 4.1 The definition of the parameters.

Parameters	Definition
P	The vaccine efficiency
N_H	The total human population
N_V	The total vector population
b_H	The birth rate
d_H	The natural death rate of human population
d_V	The natural death rate of vector population
d_d	The death rate from infection of human population
d_k	The death rate from infection of vector population
ε	The incubation rate
γ	The recovery rate
α	The biting rate of vector population
A	The constant recruitment rate of vector 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
δ	The recurrent infection rate
μ	The risk of dengue infection in the second round

This model with vaccination, the dynamics of the human and vector population are given by:

$$\frac{d\overline{S_H}}{dt} = (1-P)b_H N_H + \mu\delta\overline{R_H} - \alpha\beta_H \overline{S_H}\,\overline{I_V} - d_H \overline{S_H}, \tag{4.1}$$

$$\frac{d\overline{E_H}}{dt} = \alpha\beta_H \overline{S_H}\,\overline{I_V} - \varepsilon\overline{E_H} - d_H \overline{E_H}, \tag{4.2}$$

$$\frac{d\overline{I_H}}{dt} = \varepsilon\overline{E_H} - (d_H + d_d + \gamma)\overline{I_H}, \tag{4.3}$$

$$\frac{d\overline{R_H}}{dt} = \gamma\overline{I_H} - (\mu\delta + d_H)\overline{R_H}, \tag{4.4}$$

$$\frac{d\overline{S_V}}{dt} = A - \beta_V \overline{S_V}\,\overline{I_H} - d_V \overline{S_V}, \tag{4.5}$$

$$\frac{d\overline{I_V}}{dt} = \beta_V \overline{S_V}\,\overline{I_H} - (d_V + d_k)\overline{I_V}. \tag{4.6}$$

We have assumed that:

$$N_H = \overline{S_H} + \overline{E_H} + \overline{I_H} + \overline{R_H}, \tag{4.7}$$

$$N_V = \overline{S_V} + \overline{I_V}. \tag{4.8}$$

The assumption of our model is the total human and vector populations are constant. This leads to the rate of change for human and vector population being zero, i.e.:

$$\frac{d}{dt}\overline{S_H} + \frac{d}{dt}\overline{E_H} + \frac{d}{dt}\overline{I_H} + \frac{d}{dt}\overline{R_H} = 0, \tag{4.9}$$

$$\frac{d}{dt}\overline{S_V} + \frac{d}{dt}\overline{I_V} = 0. \tag{4.10}$$

From the above equations, we can obtain the following with conditions that:

$$\overline{I_H} = \frac{N_H((1-P)b_H - d_H)}{d_d}, \tag{4.11}$$

$$\overline{I_V} = \frac{A - d_V N_V}{d_k}. \tag{4.12}$$

Normalizing the equations by introducing the following normalized variables:

$$S_H = \frac{\overline{S_H}}{N_H},\ E_H = \frac{\overline{E_H}}{N_H},\ I_H = \frac{\overline{I_H}}{N_H},\ R_H = \frac{\overline{R_H}}{N_H}, \tag{4.13}$$

$$S_V = \frac{\overline{S_V}}{N_H},\ I_V = \frac{\overline{I_V}}{N_H}. \tag{4.14}$$

We also have:

$$S_H + E_H + I_H + R_H = 1, \tag{4.15}$$

$$S_V + I_V = 1. \tag{4.16}$$

The mathematical model of Equations (4.1)-(4.7) is now reduced to the following 4 Equations:

$$\frac{dS_H}{dt} = (1-P)b_H + \mu\delta R_H - \alpha\beta_H S_H I_V N_V - d_H S_H, \tag{4.17}$$

$$\frac{dE_H}{dt} = \alpha\beta_H S_H I_V N_V - \varepsilon E_H - d_H E_H, \tag{4.18}$$

$$\frac{dI_H}{dt} = \varepsilon E_H - (d_H + d_d + \gamma) I_H, \tag{4.19}$$

$$\frac{dI_V}{dt} = \beta_V S_V I_H N_H - (d_V + d_k) I_V. \tag{4.20}$$

4.2.2 Mathematical Model

The equilibrium points are obtained by setting the right hand side of Equations (4.17)-(4.20) to zero. In addition, we get two equilibrium points given by:
The disease-free equilibrium point:

$$E_1 = (\frac{\delta\mu + b_H - Pb_H}{\delta\mu + d_H}, 0, 0, 0). \tag{4.21}$$

The endemic equilibrium point:

$$E_2 = (S_H^*, E_H^*, I_H^*, R_H^*),$$

with

$$S_H^* = \frac{\psi_1\psi_2\left(\left(\gamma\varepsilon + \psi_7 + \gamma d_H + \left(\varepsilon + \psi_3\right)\psi_4\right)\psi_5 + \varepsilon\left(\delta\mu - \psi_6\right)N_H\beta_V\right)}{\varepsilon N_H\left(\psi_1\psi_2\psi_3 + \alpha\left(\gamma\varepsilon + \psi_7 + \gamma d_H + \left(\varepsilon + \psi_3\right)\psi_4\right)N_V\beta_H\right)\beta_V}, \tag{4.22}$$

$$E_H^* = \frac{\psi_2\left(\psi_1\psi_2\psi_3\psi_5 + \alpha\varepsilon\left(\delta\mu - \psi_6\right)N_H N_V\beta_H\beta_V\right)}{\varepsilon N_H\left(\psi_1\psi_2\psi_3 + \alpha\left(\gamma\varepsilon + \psi_7 + \gamma d_H + \left(\varepsilon + \psi_3\right)\psi_4\right)N_V\beta_H\right)\beta_V}, \tag{4.23}$$

$$I_H^* = \frac{\alpha\varepsilon\left(\delta\mu - \psi_6\right)N_H N_V\beta_H\beta_V - \psi_1\psi_2\psi_3\psi_5}{N_H\left(\psi_1\psi_2\psi_3 + \alpha\left(\gamma\varepsilon + \psi_7 + \gamma d_H + \left(\varepsilon + \psi_3\right)\psi_4\right)N_V\beta_H\right)\beta_V}, \tag{4.24}$$

$$I_V^* = \frac{\alpha\varepsilon\left(\delta\mu-\psi_6\right)N_H N_V \beta_H \beta_V - \psi_1\psi_2\psi_3\psi_5}{\alpha N_V \beta_H \left(\left(\gamma\varepsilon+\psi_7+\gamma d_H+\left(\varepsilon+\psi_3\right)\psi_4\right)\psi_5+\varepsilon\left(\delta\mu-\psi_6\right)N_H\beta_V\right)}, \quad (4.25)$$

where

$\psi_1=(\varepsilon+d_H)$, $\psi_2=(\gamma+d_H+d_d)$, $\psi_3=(\delta\mu+d_H)$, $\psi_4=(d_H+d_d)$,
$\psi_5=(d_V+d_k)$, $\psi_6=(P-1)b_H$, $\psi_7=\delta(\gamma+\varepsilon)\mu$.

4.2.3 The Basic Reproductive Number

The basic reproduction number (R_0) of this model is calculated by using next generation matrix method [27]. The disease-free equilibrium point $E_1=(\frac{\delta\mu+b_H-Pb_H}{\delta\mu+d_H},0,0,0)$. From our model, we have considering

$$F=\begin{bmatrix}0 & 0 & \alpha\beta_H S_H N_H\\ 0 & 0 & 0\\ 0 & \beta_V(1-I_V)N_H & -\beta_V I_H N_H\end{bmatrix}, V=\begin{bmatrix}\varepsilon+d_H & 0 & 0\\ -\varepsilon & d_H+d_d+\gamma & 0\\ 0 & 0 & d_V+d_k\end{bmatrix},$$

$$V^{-1}=\begin{bmatrix}\frac{1}{(\varepsilon+d_H)} & 0 & 0\\ \frac{\varepsilon(d_V+d_k)}{(\varepsilon+d_H)(d_H+d_d+\gamma)(d_V+d_k)} & \frac{1}{(d_H+d_d+\gamma)} & 0\\ 0 & 0 & \frac{1}{(d_V+d_k)}\end{bmatrix}.$$

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

$$R=\begin{bmatrix}0 & 0 & \frac{\alpha(\delta\mu+b_H-Pb_H)N_V\beta_H}{(\delta\mu+d_H)(d_V+d_k)}\\ 0 & 0 & 0\\ \frac{\varepsilon(d_V+d_k)N_H\beta_V}{(\varepsilon+d_H)(d_H+d_d+\gamma)(d_V+d_k)} & \frac{N_H\beta_V}{d_H+d_d+\gamma} & 0\end{bmatrix}.$$

R_0 is the dominant eigenvalue of the matrix $R=FV^{-1}$. Then we have

$$R_0=\sqrt{\frac{\alpha\varepsilon N_H N_V\beta_H\beta_V\left(\delta\mu-(P-1)b_H\right)}{(\varepsilon+d_H)(d_H+d_d+\gamma)(d_V+d_k)(\delta\mu+d_H)}}. \quad (4.26)$$

4.2.4 Local stability of equilibrium points

The local stability of each equilibrium point states within this model is determined from the Jacobian matrix at that equilibrium point of the system of Equations (4.17)-(4.20). The Jacobian matrix as:

$$J_{E_i}=\begin{bmatrix} -\mu\delta-\alpha\beta_H I_V N_H-d_H & -\mu\delta & -\mu\delta & -\alpha\beta_H S_H N_V \\ \alpha\beta_H I_V N_H & -(\varepsilon+d_H) & 0 & 0 \\ 0 & \varepsilon & -(d_H+d_d+\gamma) & 0 \\ 0 & 0 & \beta_V(1-I_V)N_H & -\beta_V I_H N_V-(d_V+d_K) \end{bmatrix}.$$

Theorem 4.1 If $R_0<1$, then the disease-free equilibrium point (E_1) is locally asymptotically stable. If $R_0>1$, the disease-free equilibrium point (E_1) is unstable.

Proof. From Jacobian matrix above $J_{E_1}(S_H,E_H,I_H,I_V)$, we set

$$\det\left(J_{E_1}-\lambda I\right)=0. \tag{4.27}$$

The eigenvalues (λ) are obtained by solving the eigenvalue matrix Equation (4.27) where I is identity matrix dimension 4×4 to find the eigenvalues, then we obtain:

$$\lambda_1=-(\varepsilon+d_H),$$
$$\lambda_2=-(\delta\mu+d_H),$$
$$\lambda_3=-(d_H+d_d+\gamma),$$
$$\lambda_4=-(d_V+d_k).$$

Hence, the eigenvalue are have all negative real part. The disease-free equilibrium point (E_1) is locally asymptotically stable. □

Theorem 4.2 If $R_0>1$, the endemic equilibrium point (E_2) is locally asymptotically stable if it conditions satisfies the Routh-Hurwitz criteria.

Proof. From Jacobian matrix above $J_{E_2}(S_H^*,E_H^*,I_H^*,I_V^*)$, we set

$$\det\left(J_{E_2}-\lambda I\right)=0. \tag{4.28}$$

The eigenvalues (λ) are obtained by solving the eigenvalue matrix Equation (4.28) where I is identity matrix dimension 4×4 to find the eigenvalues, we have characteristic equation is considered in the form of

$$\left(-\lambda-d_V-d_K-N_H I_H^*\beta_V\right)\left(\lambda^3+a_1\lambda^2+a_2\lambda+a_3\right)=0, \tag{4.29}$$

where

$$a_1=\gamma+\varepsilon+\delta\mu+d_d+3d_H+\alpha N_V I_V^*\beta_H,$$
$$a_2=\gamma\varepsilon+\delta\mu(\gamma+\varepsilon)+\left(2(\gamma+\varepsilon+\delta\mu)+3d_H\right)+\alpha(\gamma+\varepsilon+\delta\mu+2d_H)N_V I_V^*\beta_H$$
$$+d_d(\varepsilon+\delta\mu+2d_H+\alpha N_V I_V^*\beta_H),$$

$$a_3 = \gamma\varepsilon\delta\mu + \left(\gamma\varepsilon + \delta\mu\left(\gamma+\varepsilon\right) + d_H\left(\gamma+\varepsilon+\delta\mu+d_H\right)\right)\left(d_H + \alpha N_V I_V^* \beta_H\right)$$
$$+ d_d\left(\varepsilon\delta\mu + \left(\gamma+\varepsilon+\delta\mu\right)\left(d_H + \alpha N_V I_V^* \beta_H\right)\right)$$
$$+ \alpha^2 \varepsilon N_H {N_V}^2 S_H^* \left(I_V^* - 1\right) I_V^* {\beta_H}^2 \beta_V .$$

By using Routh-Hurwitz criteria for $n=3$, the endemic equilibrium point is stable if

$$(i)\ a_1 > 0,$$
$$(ii)\ a_3 > 0,$$
$$(iii)\ a_1 a_2 - a_3 > 0.$$

All parameter spaces of endemic equilibrium E_2 are satisfied with the Routh-Hurwitz criteria $(i)-(iii)$ conditions shown as Figure 4.2. The parameter value is defined in Table 4.2. □

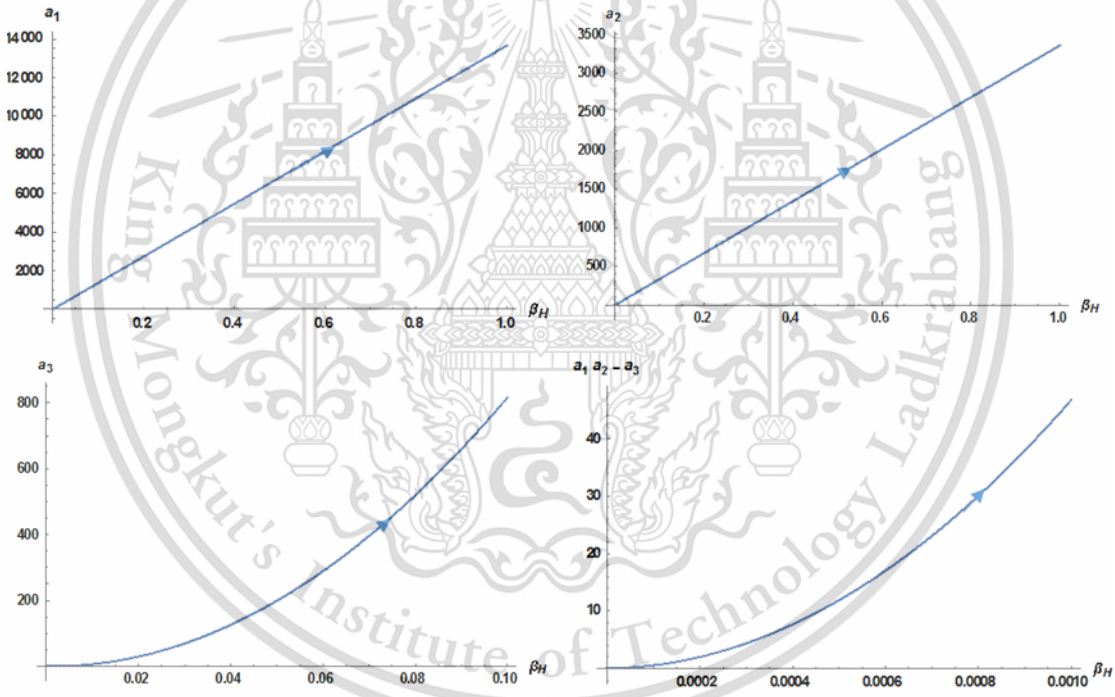


Figure 4.2 The endemic equilibrium are satisfied with the Routh-Hurwitz criteria.

4.2.5 Global stability of equilibrium points

Theorem 4.3 Let $E_1^* = \left(S_H^*, E_H^*, I_H^*, I_V^*\right) = \left(\dfrac{\delta\mu + b_H - Pb_H}{\delta\mu + b_H}, 0, 0, 0\right)$. If $R_0 < 1$ then, the disease-free E_1^* is globally asymptotically stable on Ω_1 where

$$\Omega_1 = \left\{\left(S_H^*, E_H^*, I_H^*, I_V^*\right) \in \mathbb{R}_+^4, N_H = \frac{b_H}{d_H + d_d}, N_V = \frac{A}{d_V + d_K}\right\}.$$

Proof. We consider a Lyapunov function

$$\omega_1(S_H, E_H, I_H, I_V) = \left(S_H - S_H^* \ln S_H\right) + E_H + I_H + I_V.$$

The derivative with respect to time yields:

$$\frac{d\omega_1}{dt} = \left(\frac{dS_H}{dt} - \frac{S_H^*}{S_H}\frac{dS_H}{dt}\right) + \frac{dE_H}{dt} + \frac{dI_H}{dt} + \frac{dI_V}{dt}, \tag{4.30}$$

$$= \left(1 - \frac{S_H^*}{S_H}\right)\frac{dS_H}{dt} + \frac{dE_H}{dt} + \frac{dI_H}{dt} + \frac{dI_V}{dt},$$

$$= \left(1 - \frac{S_H^*}{S_H}\right)\left[(1-P)b_H + \mu\delta R_H - \alpha\beta_H S_H I_V N_V - d_H S_H\right]$$
$$+\left[\alpha\beta_H S_H I_V N_V - \varepsilon E_H - d_H E_H\right] + \left[\varepsilon E_H - (d_H + d_d + \gamma)I_H\right]$$
$$+\left[\beta_V S_V I_H N_H - (d_V + d_k)I_V\right].$$

Substituting the relation in the disease-free E_1^*

$$= \left(1 - \frac{S_H^*}{S_H}\right)\left((1-P)b_H - d_H S_H\right) - d_H E_H - (d_H + d_d + \gamma)I_H - (d_V + d_k)I_V,$$

$$= \left[(1-P)b_H\left(1 - \frac{S_H^*}{S_H}\right) + d_H S_H\left(1 - \frac{S_H^*}{S_H}\right)\right] - d_H E_H - (d_H + d_d + \gamma)I_H - (d_V + d_k)I_V.$$

Substituting with condition $(1-P)b_H = d_H$, we get

$$= \left[(1-P)b_H\left(\left(1 - \frac{S_H^*}{S_H}\right) + \left(1 - \frac{S_H}{S_H^*}\right)\right)\right] - d_H E_H - (d_H + d_d + \gamma)I_H - (d_V + d_k)I_V,$$

$$= \left[(1-P)b_H\left(2 - \frac{S_H^*}{S_H} - \frac{S_H}{S_H^*}\right)\right] - d_H E_H - (d_H + d_d + \gamma)I_H - (d_V + d_k)I_V,$$

$$= (1-P)b_H\left(\frac{2S_H^* S_H - S_H^{*2} - S_H^2}{S_H^* S_H}\right) - d_H E_H - (d_H + d_d + \gamma)I_H - (d_V + d_k)I_V,$$

$$= -(1-P)b_H\left(\frac{S_H^{*2} - 2S_H^* S_H + S_H^2}{S_H^* S_H}\right) - d_H E_H - (d_H + d_d + \gamma)I_H - (d_V + d_k)I_V,$$

$$= -(1-P)b_H\left(\frac{\left(S_H^* - S_H\right)^2}{S_H^* S_H}\right) - d_H E_H - (d_H + d_d + \gamma)I_H - (d_V + d_k)I_V.$$

Simplification yields:

$$\frac{d\omega_1}{dt} = -\left[(1-P)b_H\left(\frac{\left(S_H^* - S_H\right)^2}{S_H^* S_H}\right) + d_H E_H + (d_H + d_d + \gamma)I_H + (d_V + d_k)I_V\right]. \tag{4.31}$$

It is obvious that all the term appearing in Equation (4.31) are always nonpositive. Now, using the Laselle's extension to Lyapunov's theorem, we have $\frac{d\omega_1}{dt} \le 0$ and so the function is to be negative definite. The limit set of each solution is contained in the largest invariant set for which $S_H = S_H^*, E_H = 0, I_H = 0,$ and $I_V = 0$ which is the singleton $\{E_1^*\}$. Then the Laselle's invariant principle implies that the disease-free equilibrium point E_1^* is globally asymptotically stable on Ω_1. □

Next, we consider the global property of the endemic equilibrium point of Equations (4.17)-(4.20).

Theorem 4.4 If $R_0 > 1$ then, the endemic equilibrium point E_2^* is globally asymptotically stable on Ω_1 if and only if

$$\begin{cases} p = \dfrac{b_H - d_H}{b_H}, \\ \beta_H = \dfrac{d_V + d_k}{\alpha S_H N_V}, \\ \beta_V = \dfrac{d_H + d_d + \gamma}{I_H N_H}. \end{cases}$$

Proof. The Lyapunov function is in the form:

$$\zeta_1(S_H, E_H, I_H, I_V) = \left(S_H - S_H^* \ln S_H\right) + E_H + I_H + I_V.$$

The derivative with respect to time yields:

$$\begin{aligned} \frac{d\zeta_1}{dt} &= \left(\frac{dS_H}{dt} - \frac{S_H^*}{S_H}\frac{dS_H}{dt}\right) + \frac{dE_H}{dt} + \frac{dI_H}{dt} + \frac{dI_V}{dt}, \qquad (4.32) \\ &= \left(1 - \frac{S_H^*}{S_H}\right)\frac{dS_H}{dt} + \frac{dE_H}{dt} + \frac{dI_H}{dt} + \frac{dI_V}{dt}, \\ &= \left(1 - \frac{S_H^*}{S_H}\right)\left[(1-P)b_H + \mu\delta R_H - \alpha\beta_H S_H I_V N_V - d_H S_H\right] \\ &\quad + \left[\alpha\beta_H S_H I_V N_V - \varepsilon E_H - d_H E_H\right] + \left[\varepsilon E_H - (d_H + d_d + \gamma) I_H\right] \\ &\quad + \left[\beta_V S_V I_H N_H - (d_V + d_k) I_V\right], \end{aligned}$$

$$= \left(1-\frac{S_H^*}{S_H}\right)(1-P)b_H + \left(1-\frac{S_H^*}{S_H}\right)\mu\delta\left(1-S_H-E_H-I_H\right)$$
$$-\left(1-\frac{S_H^*}{S_H}\right)\alpha\beta_H S_H I_V N_V - \left(1-\frac{S_H^*}{S_H}\right)d_H S_H$$
$$+\alpha\beta_H S_H I_V N_V - d_H E_H - (d_H + d_d + \gamma)I_H + \beta_V S_V I_H N_H - (d_V + d_k)I_V.$$

Substituting with condition $P, \beta_H, \beta_V,$ and simplification yields:

$$= d_H\left[\left(1-\frac{S_H^*}{S_H}\right)+\left(1-\frac{S_H}{S_H^*}\right)\right] - d_H E_H,$$
$$= d_H\left(2-\frac{S_H^*}{S_H}-\frac{S_H}{S_H^*}\right) - d_H E_H,$$
$$= d_H\left(\frac{2S_H S_H^* - S_H^2 - S_H^{*2}}{S_H S_H^*}\right) - d_H E_H,$$
$$= -d_H\left(\frac{S_H^2 - 2S_H S_H^* + S_H^{*2}}{S_H S_H^*}\right) - d_H E_H,$$
$$= -d_H\left(\frac{\left(S_H - S_H^*\right)^2}{S_H S_H^*}\right) - d_H E_H,$$
$$\frac{d\zeta_1}{dt} = -\left[d_H\left(\frac{\left(S_H - S_H^*\right)^2}{S_H S_H^*}\right) + d_H E_H\right]. \qquad (4.35)$$

Therefore, the derivative Equation (4.35) is $\frac{d\zeta_1}{dt} \le 0$ and so the function is to be negative definite. The limit set of each solution is contained in the largest invariant set for which $S_H = S_H^*, I_H = 0, E_H = 0,$ and $I_V = 0$ which is the singleton $\left\{E_2^*\right\}$. Then the Laselle's invariant principle implies that the endemic equilibrium point E_2^* is globally asymptotically stable on Ω_1. □

4.3 Numerical Results

The numerical analysis in this study considers the transmission of dengue disease with vaccination in the model where the values of the parameter value are listed in Table 4.2. The numerical results are shown in Figures 4.3-4.4.

Table 4.2 Parameters used in the numerical simulation.

Parameter	The disease-free	The endemic	References
α	1/7	1/7	[3,8,40-43]
ε	1/10	1/10	[3,8,40-43]
N_H	10,000	10,000	assume
N_V	10,000	10,000	assume
β_H	0.00005	0.08	assume
β_V	0.00003	0.04	assume
δ	1/(30*6)	1/(30*6)	[3,8,40-43]
μ	1/2	1/2	assume
P	0.35	0.35	[3,8,40-43]
b_H	1/(365*70)	1/(365*70)	[3,8,40-43]
d_H	1/(365*70)	1/(365*70)	[3,8,40-43]
d_d	1/14	1/14	[3,8,40-43]
d_V	1/7	1/7	[3,8,40-43]
d_K	1/5	1/5	[3,8,40-43]
γ	1/14	1/14	[3,8,40-43]

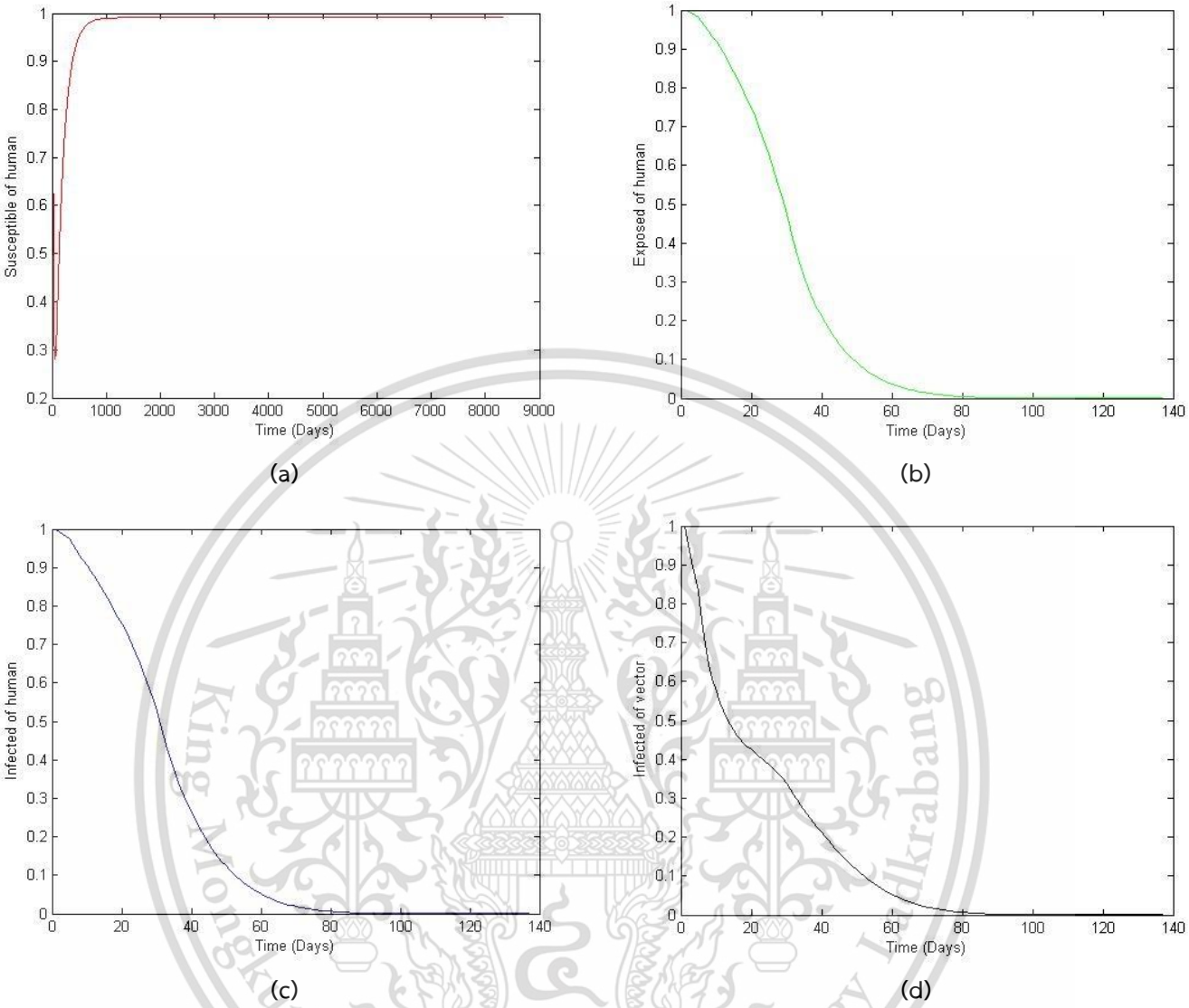


Figure 4.3 The time series of each population group for disease-free.

Figure 4.3 we will see that **(a)** the time rate of change for the susceptible human population, **(b)** the time rate of change for the exposed human population, **(c)** the time rate of change for the infected human population, and **(d)** the time rate of change for the infected vector population.

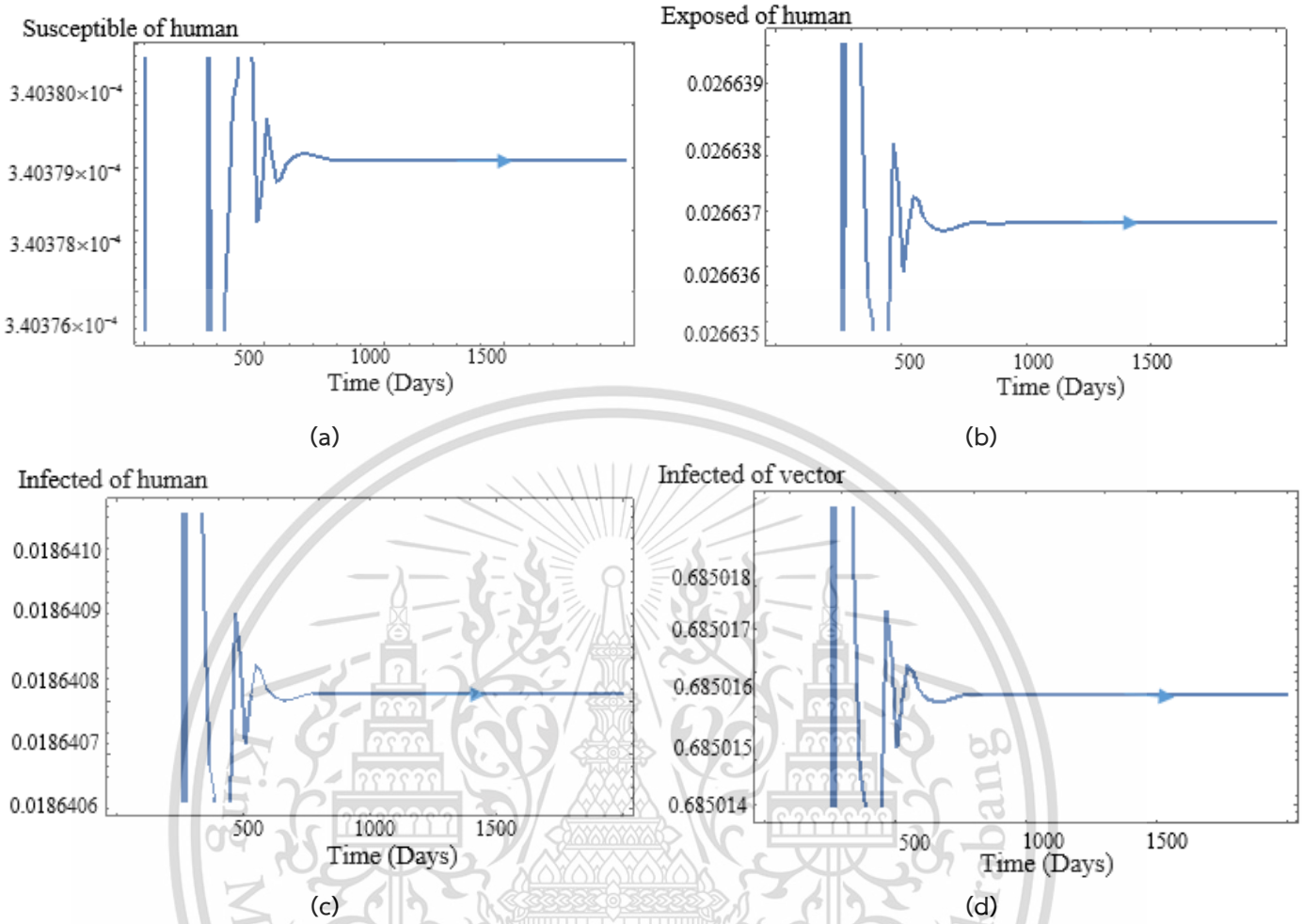


Figure 4.4 The time series of each population group for endemic.

Figure 4.4 we will see that **(a)** the time rate of change for the susceptible human population, **(b)** the time rate of change for the exposed human population, **(c)** the time rate of change for the infected human population, and **(d)** the time rate of change for the infected vector population.

4.4 Discussion and Conclusions

In this chapter, we analyzed the SEIR model for human populations and the SI model for the vector population. In addition, we considered vaccination against dengue fever before the first infection of serotypes. The equilibrium point of all two states is the disease-free and endemic equilibrium point. The reproductive number R_0 using the next generation matrix method. If R_0 less than one the disease-free $E_1 = (1,0,0,0)$ is locally asymptotically stable $R_0 = 0.711$, and unstable if more than one. Similarly, if R_0 more than one the endemic is locally asymptotically stable $R_0 = 90$. We found that the factors

that converge this system of equations are the transmission rate of dengue virus from vector to human and the vaccine efficiency. The numerical solution compares parameters are shown in Figures 4.5-4.6.

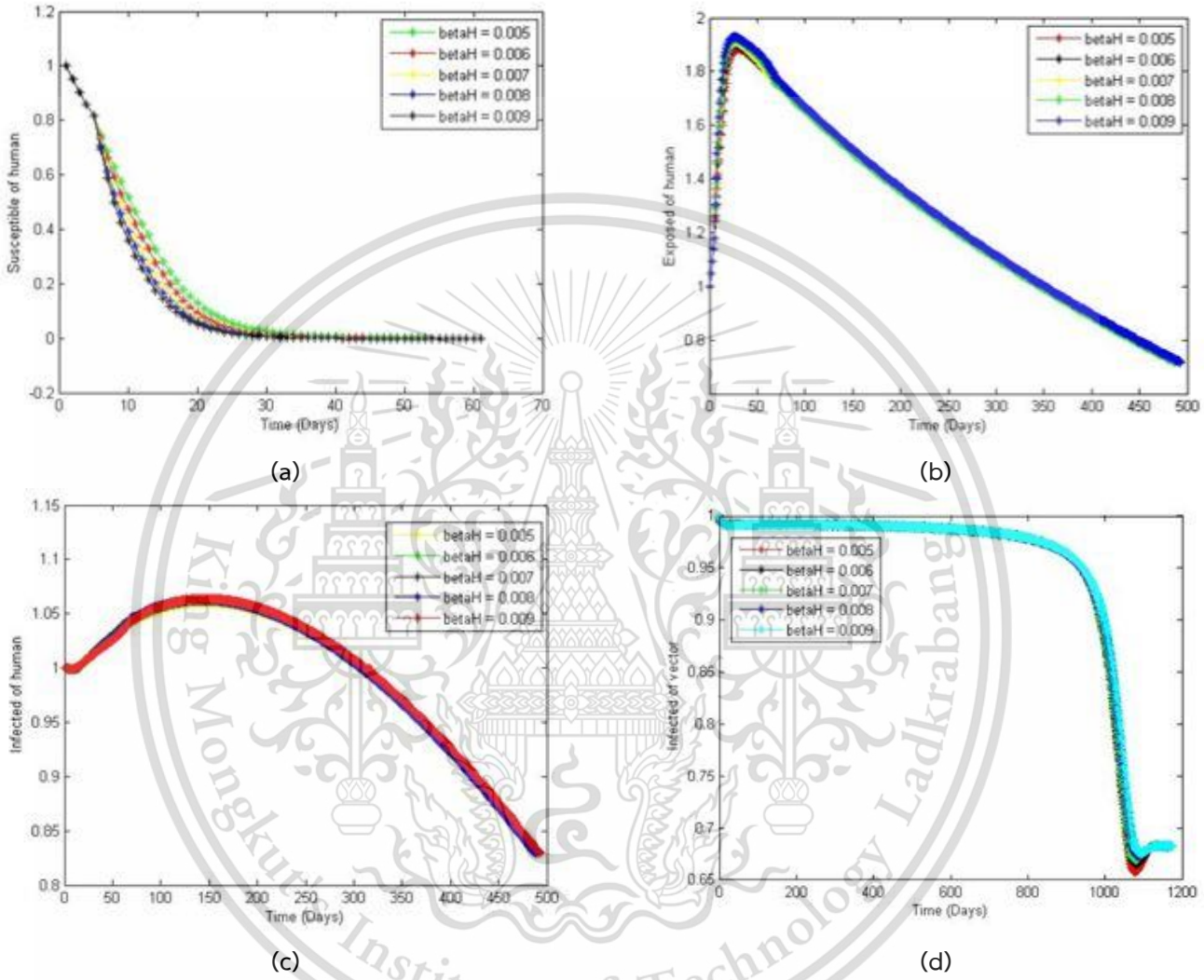


Figure 4.5 The time series of each population group compares parameters the transmission rate of dengue virus from vector to human for endemic.

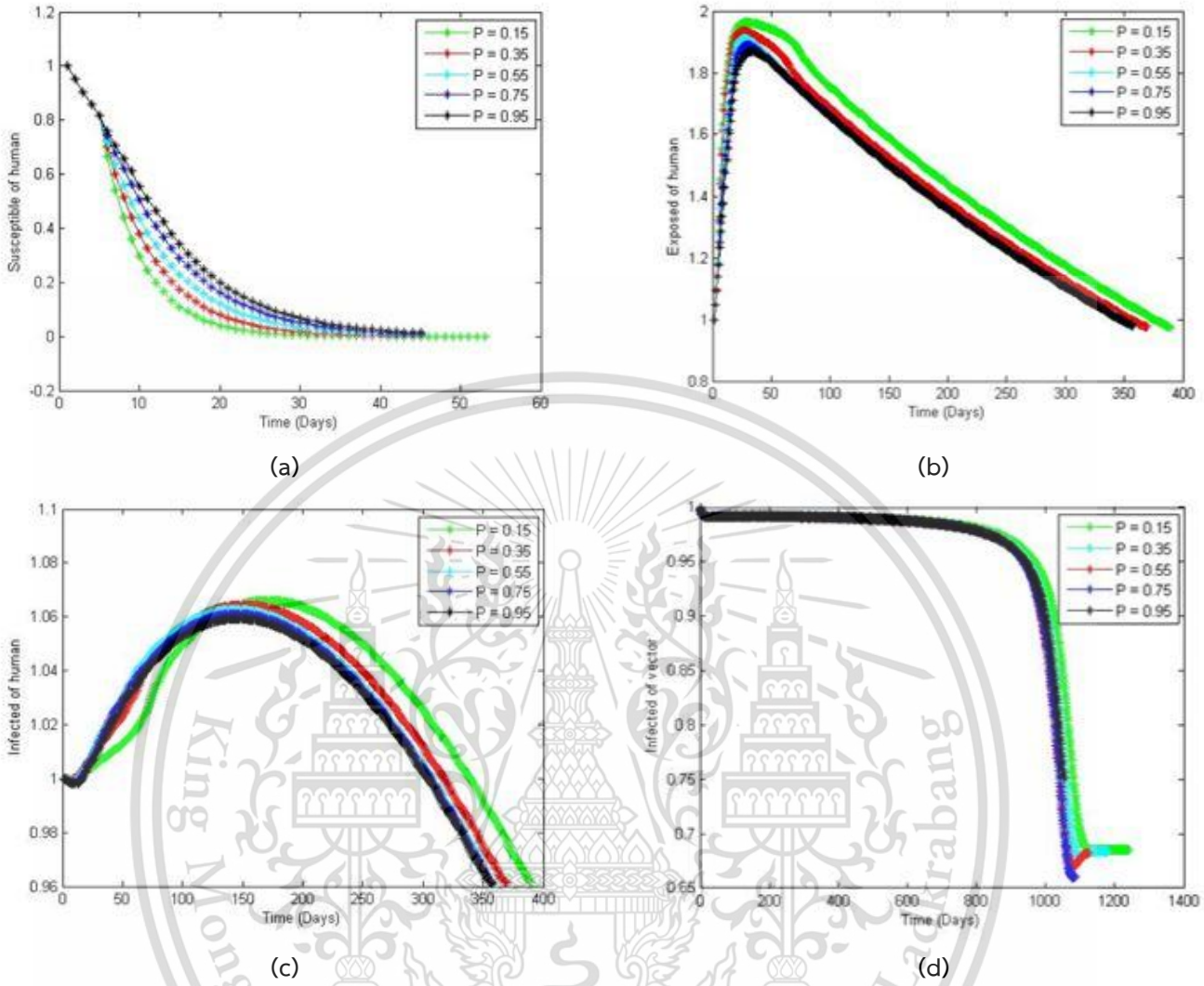


Figure 4.6 The time series of each population group compares parameters the vaccine efficiency for endemic.

From Figure 4.5 we will see that if parameters the transmission rate of dengue virus from vector to human β_H, the more valuable than the time series of each population convergence into the stability, Similarly, if β_H the small value then will make the convergence slow. In addition, from Figure 4.6 we will see that if parameters the vaccine efficiency P, the minimize valuable then the time series of each population convergence into the stability because of the vaccine efficiency form $(1-P)$.

However, there are many ways to prevent dengue fever. Including mosquito bites prevention, restricting mosquito breeding sites, as well as vaccinations, Dengvaxia still not able to completely preventable disease. World Health Organization recommends vaccination of dengue fever in people aged 9-45 years. In the case of never being infected

with dengue before, there is a risk of subsequent severe dengue fever if there is later infection.

Chapter 5

Optimal Control of the Dengue Transmission with Vaccination

This chapter 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.

5.1 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 *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 [1,46,48,49] 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) [51,52]. 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.

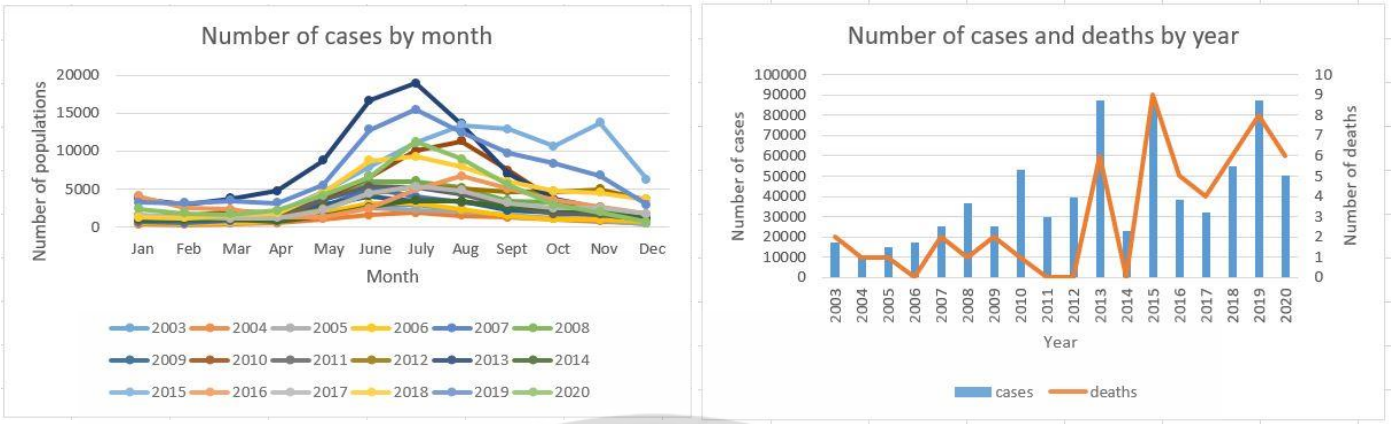
Since millions of people can be infected by the dengue virus, there is an economic cost to these people becoming sick, and vaccines have been developed. Chimeric yellow fever dengue tetravalent dengue vaccine (CYD-TDV) is one of these vaccines. It was first registered as a dengue vaccine in Mexico. It 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 [19,53]. 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% [20,22,54]. In December 2017, the WHO [23] 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 [45,46] 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. [37,55,56] 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 Thai-land. 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. [56], the author used the SIR model to simulate the possible out-comes of vertical transmission of the virus among mosquitos. She and her coworkers [37] included vertical transmission in a SEIR model. Syafruddin and Noorani [57] studied the mathematical model for dengue transmission and applied it to the situations in Indonesia and Malaysia. Yaacob [58] studied the mathematical model of the dengue disease in people who have no immunity.

Singh [4] and Tasman [5] 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 [6,7]. Using a similar model to study the transmission of another disease, melioidosis, Tavaen and Viriyapong [59] 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 [60-63]. 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 5.1 **(a)** The number of cases by month; **(b)** The number of cases and deaths by year. 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 chapter.



(a) (b)

Figure 5.1 The number of cases by month and the number of cases and deaths each year from 2003–2020 [64].

5.2 Materials and Methods

5.2.1 Mathematical Model

The basic mathematical model was the SEIR model presented in ref. [55]. 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 [55] 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 5.1.

Table 5.1 The variables definition of the differential system equation.

Variables	Definition
$\overline{S_{HP}}$	The number of susceptible human population of primary infection
$\overline{I_{HP}}$	The number of infected human population of primary infection
$\overline{R_{HP}}$	The number of recovered human population of primary infection
$\overline{S_{HS}}$	The number of susceptible human population of secondary infection
$\overline{I_{HS}}$	The number of infected human population of secondary infection
$\overline{R_{HS}}$	The number of recovered human population of secondary infection
$\overline{S_V}$	The number of susceptible vector population
$\overline{I_V}$	The number of infected vector population

The dynamic transmission of dengue disease with the vaccination model is shown in Figure 5.2.

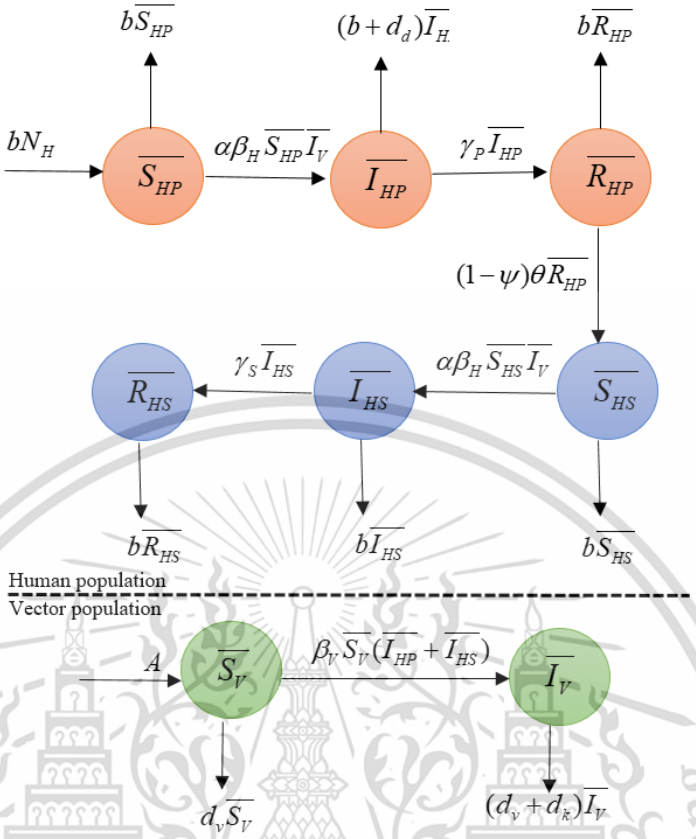


Figure 5.2 Diagram of the transmission model of dengue disease with the vaccination model of human and vector populations.

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

$$\frac{d\overline{S_{HP}}}{dt} = bN_H - \alpha\beta_H\overline{S_{HP}}\overline{I_V} - b\overline{S_{HP}}, \tag{5.1}$$

$$\frac{d\overline{I_{HP}}}{dt} = \alpha\beta_H\overline{S_{HP}}\overline{I_V} - \gamma_P\overline{I_{HP}} - (b+d_d)\overline{I_{HP}}, \tag{5.2}$$

$$\frac{d\overline{R_{HP}}}{dt} = \gamma_P\overline{I_{HP}} - (1-\psi)\theta\overline{R_{HP}} - b\overline{R_{HP}}, \tag{5.3}$$

$$\frac{d\overline{S_{HS}}}{dt} = (1-\psi)\theta\overline{R_{HP}} - \alpha\beta_H\overline{S_{HS}}\overline{I_V} - b\overline{S_{HS}}, \tag{5.4}$$

$$\frac{d\overline{I_{HS}}}{dt} = \alpha\beta_H\overline{S_{HS}}\overline{I_V} - \gamma_P\overline{I_{HS}} - b\overline{I_{HS}}, \tag{5.5}$$

$$\frac{d\overline{R_{HS}}}{dt} = \gamma_S \overline{I_{HS}} - b\overline{R_{HS}}, \tag{5.6}$$

$$\frac{d\overline{S_V}}{dt} = A - \beta_V \overline{S_V}(\overline{I_{HP}} + \overline{I_{HS}}) - d_V \overline{S_V}, \tag{5.7}$$

$$\frac{d\overline{I_V}}{dt} = \beta_V \overline{S_V}(\overline{I_{HP}} + \overline{I_{HS}}) - (d_V + d_k)\overline{I_V}. \tag{5.8}$$

With the conditions

$$\overline{S_{HP}} + \overline{I_{HP}} + \overline{R_{HP}} + \overline{S_{HS}} + \overline{I_{HS}} + \overline{R_{HS}} = N_H, \tag{5.9}$$

$$\overline{S_V} + \overline{I_V} = N_V. \tag{5.10}$$

The parameters of Equations (5.1)-(5.10) are defined as Table 5.2.

Table 5.2 The parameters definition of the differential system.

Parameters	Definition
α	The biting rate of vector population
ψ	The vaccine efficiency
θ	The recurrent infection rate
N_H	The total number of the human population
N_V	The total number of the vector population
β_H	The transmission rate of dengue virus from vector to the human
β_V	The transmission rate of dengue virus from the 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 primary infected
γ_S	The recovery rate of secondary infected

The rate of change of both the total population of human and vector is zero given by:

$$\frac{d\overline{S_{HP}}}{dt} + \frac{d\overline{I_{HP}}}{dt} + \frac{d\overline{R_{HP}}}{dt} + \frac{d\overline{S_{HS}}}{dt} + \frac{d\overline{I_{HS}}}{dt} + \frac{d\overline{R_{HS}}}{dt} = 0, \tag{5.11}$$

$$\frac{d\overline{S_V}}{dt} + \frac{d\overline{I_V}}{dt} = 0. \tag{5.12}$$

With conditions, we get

$$d_d \overline{I_{HP}} = 0, \tag{5.13}$$

$$d_k \overline{I_V} + d_V N_V = A. \tag{5.14}$$

Normalizing the equations by introducing the following normalized variables:

$$S_{HP} = \frac{\overline{S_{HP}}}{N_H},\ I_{HP} = \frac{\overline{I_{HP}}}{N_H}, R_{HP} = \frac{\overline{R_{HP}}}{N_H}, S_{HS} = \frac{\overline{S_{HS}}}{N_H},\ I_{HS} = \frac{\overline{I_{HS}}}{N_H}, R_{HS} = \frac{\overline{R_{HS}}}{N_H}, \tag{5.15}$$

$$S_V = \frac{\overline{S_V}}{N_V},\ I_V = \frac{\overline{I_V}}{N_V}. \tag{5.16}$$

With the additional condition:

$$S_{HP} + I_{HP} + R_{HP} + S_{HS} + I_{HS} + R_{HS} = 1, \tag{5.17}$$

$$S_V + I_V = 1. \tag{5.18}$$

The mathematical model of Equations (5.1)-(5.8) is now reduced to the following equation:

$$\frac{dS_{HP}}{dt} = b - \alpha\beta_H S_{HP} I_V N_V - bS_{HP}, \tag{5.19}$$

$$\frac{dI_{HP}}{dt} = \alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - (b + d_d) I_{HP}, \tag{5.20}$$

$$\frac{dR_{HP}}{dt} = \gamma_P I_{HP} - (1-\psi)\theta R_{HP} - bR_{HP}, \tag{5.21}$$

$$\frac{dS_{HS}}{dt} = (1-\psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - bS_{HS}, \tag{5.22}$$

$$\frac{dI_{HS}}{dt} = \alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - bI_{HS}, \tag{5.23}$$

$$\frac{dI_V}{dt} = \beta_V (1 - I_V)(I_{HP} + I_{HS}) N_H - (d_V + d_k) I_V. \tag{5.24}$$

5.2.2 The Equilibrium Points

Definition 5.1 [57] 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 (5.19)-(5.24) 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:

$$E_1 = (1,0,0,0,0,0). \tag{5.25}$$

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

$$S_{HP}^* = \frac{\tau_1\left(b\left(2\theta(\psi-1)\gamma_P\right)-\tau_2\right)-\tau_7+\sqrt{\tau_3(\tau_4+\tau_5)+\tau_7^{\,2}}}{\tau_6},$$

$$I_{HP}^* = \frac{b\tau_1\tau_2+\tau_7-\sqrt{\tau_3(\tau_4+\tau_5)+\tau_7^{\,2}}}{\tau_6},$$

$$R_{HP}^* = \frac{b\tau_1\tau_2+\tau_7+\sqrt{\tau_3(\tau_4+\tau_5)+\tau_7^{\,2}}}{\tau_6},$$

$$S_{HS}^* = \frac{\tau_7+(\tau_3-\tau_{25}+\tau_{26})\sqrt{\tau_3(\tau_4+\tau_5)+\tau_7^{\,2}}+\tau_{22}}{\tau_{18}\tau_{19}\tau_{20}\tau_{21}},$$

$$I_{HS}^* = \frac{\tau_7+(\tau_3-\tau_{25}+\tau_{26})\sqrt{\tau_3(\tau_4+\tau_5)+\tau_7^{\,2}}-\tau_{22}}{\tau_{18}\tau_{19}\tau_{20}\tau_{21}},$$

$$I_V^* = \frac{\sqrt{\tau_3(\tau_4+\tau_5)+\tau_7^{\,2}}-\tau_{22}-\tau_7}{\tau_{27}+\tau_{28}}, \tag{5.26}$$

where

$\tau_1 = b\alpha N_H N_V \beta_H \beta_V$, $\tau_2 = (b+\theta-\theta\psi)(b+\gamma_S)$, $\tau_3 = b^2\alpha^2 N_H N_V{}^2 \beta_H{}^2 \beta_V$,

$\tau_4 = 4\theta(\psi-1)(d_V+d_k)(b+\alpha N_V\beta_H)(b+d_d+\gamma_P)\gamma_P\tau_2$,

$\tau_5 = N_H\beta_V b\tau_2$, $\tau_6 = 2\alpha\theta(\psi-1)N_H N_V\beta_H(b+\alpha N_V\beta_H)\beta_V\gamma_P(b+d_d+\gamma_P)$,

$\tau_7 = \alpha N_V\beta_H\left(\theta(\psi-1)\gamma_P\right)+\tau_2$, $\tau_8 = 2(b+d_d+\gamma_P)\tau_2$,

$\tau_9 = 2b^2\alpha\theta(\psi-1)(d_V+d_k)N_V\beta_H\gamma_P$,

$\tau_{10} = 2b\alpha^2\theta^2(\psi-1)^2(d_V+d_k)N_V{}^2\beta_H{}^2\gamma_P(d_d+\gamma_P)\gamma_S$,

$\tau_{11} = \theta-\theta\psi+d_d+\alpha N_V\beta_H+\gamma_P+\gamma_S$,

$\tau_{12} = \theta(\psi-1)(\gamma_P+d_d)-\alpha N_V\beta_H-\gamma_S$,

$\tau_{13} = (\theta(\psi-1)-\gamma_P-\gamma_S)(\alpha N_V\beta_H+1)$,

$\tau_{14} = \alpha\theta(\psi-1)N_V\beta_H(d_d+\gamma_P)$, $\tau_{15} = d_d(\theta(\psi-1)-\alpha N_V\beta_H)$,

$\tau_{16} = (2b\alpha N_V\beta_H(\theta-\theta\psi)\gamma_P+(b+\theta-\theta\psi)(b+\gamma_S))^2$,

$\tau_{17} = b^2\left(2\theta^2(\psi-1)^2\gamma_P{}^2-2\theta(\psi-1)\gamma_P\tau_2+\tau_2{}^2\right)$,

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

5.2.3 The Basic Reproductive Number

Definition 5.2 [60] 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 [65-68]. We pick out I_{HP}, I_{HS}, and I_V to be the classes to construct the F and V matrices used in the which are important to this method. For our system, the matrices F and V contain new infection terms and transition terms. Evaluating the Jacobian matrices F and V at the disease-free equilibrium point $E_1 = (1,0,0,0,0,0)$, where F is non-negative and V is a non-singular. The F (Gains) and V (Losess) matrices are:

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

where

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

We have

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

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

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

$$R_0=\sqrt{\frac{\alpha N_H N_V \beta_H \beta_V}{d_k(b+d_d)+d_V(b+d_d)+\gamma_P(d_V+d_k)}}. \quad (5.27)$$

5.2.4 Local stability of equilibrium points

Definition 5.3 [45] 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 part. 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 *(5.19)-(5.25)*. The Jacobian matrix is

$$J_{E_i}=\begin{bmatrix} -\alpha\beta_H I_V N_V - b & 0 & 0 & 0 & 0 & -\alpha\beta_H S_{HP} N_V \\ \alpha\beta_H I_V N_V & -\gamma_P - d_d - b & 0 & 0 & 0 & \alpha\beta_H S_{HP} N_V \\ 0 & \gamma_P & -(1-\psi)\theta - b & 0 & 0 & 0 \\ 0 & 0 & (1-\psi)\theta & -\alpha\beta_H I_V N_V - b & 0 & -\alpha\beta_H S_{HS} N \\ 0 & 0 & 0 & \alpha\beta_H I_V N & -\gamma_S - b & \alpha\beta_H S_{HS} N \\ 0 & \beta_V N_H (1-I_V) & 0 & 0 & \beta_V N_H (1-I_V) & -\beta_V N_H (I_{HP}+I_{HS}) - (d_V+d_k) \end{bmatrix}. \quad (5.28)$$

Theorem 5.1 The equilibrium point E_1, the disease-free state is locally asymptotically stable when $R_0<1$.

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

$$\det(J_{E_1} - \lambda I) = 0, \tag{5.29}$$

where I is 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 are:

$$\lambda_1 = \lambda_2 = -b,\ \lambda_3 = -\left(b + \theta(1+\psi)\right),\ \lambda_4 = -\left(b + \gamma_S\right),$$
$$\lambda_5 = -\left(\frac{1}{2}\varepsilon_1 + \sqrt{\varepsilon_1^2 - 4\varepsilon_2 - \varepsilon_3}\right), \lambda_6 = -\left(\frac{1}{2}\varepsilon_1 - \sqrt{\varepsilon_1^2 - 4\varepsilon_2 - \varepsilon_3}\right),$$

where

$\varepsilon_1 = \left(b + d_d + d_k + d_V + \gamma_P\right), \varepsilon_2 = b\left(d_k + d_V\right) + d_d\left(d_k + d_V\right),$ and

$\varepsilon_3 = \alpha N_H N_V \beta_H \beta_V + \gamma_P\left(d_k + d_V\right)$.

As we see, all the eigenvalue are have negative real part, the disease-free equilibrium point $\left(E_1\right)$ is locally asymptotically stable. □

Theorem 5.2 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 (5.26) is substituted in the Jacobian matrix Equation (5.28)

$J_{E_2} = \left(S_{HP}^*, I_{HP}^*, R_{HP}^*, S_{HS}^*, I_{HS}^*, I_V^*\right)$ where $S_{HP}^*, I_{HP}^*, R_{HP}^*, S_{HS}^*, I_{HS}^*$ and I_V^* defined by equation of the endemic equilibrium point $\left(E_2\right)$, we setting

$$\det(J_{E_2} - \lambda I) = 0. \tag{5.30}$$

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

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0, \tag{5.31}$$

where

$$a_1 = 3b + \theta\left(1-\psi\right) + d_k + d_V + 2\alpha N_V \beta_H I_V^* + N_H\left(I_{HP}^* - I_{HS}^* + \alpha N_V\left(S_{HP}^* - S_{HS}^*\right)\left(I_V^* - 1\right)\beta_H\right)\beta_V,$$
$$a_2 = \left(b + \alpha N_V \beta_H I_V^*\right)\left(3b - 2\theta\left(\psi - 1\right) + \alpha N_V \beta_H I_V^*\right) + d_k\left(3b + \theta - \theta\psi + 2\alpha N_V \beta_H I_V^*\right)$$
$$+ N_H\left(\alpha N_V\left(S_{HP}^* - S_{HS}^*\right)\left(I_V^* - 1\right)\left(3b + \theta - \theta\psi + 2\alpha N_V \beta_H I_V^*\right)\left(\beta_H + I_{HP}^* - I_{HS}^*\right)\right)\beta_V$$
$$+ d_V\left(3b + \theta - \theta\psi + 2\alpha N_V \beta_H I_V^*\right),$$

$$a_3 = b^2\left(b+\theta-\theta\psi\right)+2b\alpha N_V\beta_H I_V^{2*}\left(b+\theta-\theta\psi\right)+\alpha^2 {N_V}^2\beta_H{}^2 I_V^{2*}\left(b+\theta-\theta\psi\right)$$
$$+\left(b+\alpha N_V\beta_H I_V^*\right)\left(3b+2\theta-2\theta\psi+\alpha N_V\beta_H I_V^*\right)\left(d_k+d_V\right)$$
$$+b\alpha N_H N_V\beta_H\beta_V S_{HP}^*\begin{pmatrix}2bI_V^*-2b-2b\theta I_V^*+2\alpha N_V\beta_H-\alpha N_V\beta_H I_V^*+\alpha N_V\psi I_V^*\\+\alpha\theta N_V+2\alpha N_V\beta_H I_V^*+\alpha^2 N_V\beta_H I_V^*+\alpha^2\theta\psi N_V\beta_H I_V^*\end{pmatrix}$$
$$+b\alpha N_H N_V\beta_H\beta_V S_{HS}^*\begin{pmatrix}3b+2b\theta-2b\psi-3b^2-2bI_V^*+2b\psi I_V^*+2\alpha N_V\beta_H I_V^*\\-\alpha\psi N_V I_V^*-3\alpha N_V\beta_H I_V^*+\alpha\psi N_V\beta_H I_V^*\end{pmatrix}$$
$$+b\alpha N_H N_V\beta_H\beta_V I_{HP}^*\left(6I_V^*+2\psi+\alpha N_V\beta_H I_V^*\right)+b\alpha N_H N_V\beta_H\beta_V I_{HS}^* I_V^*\left(6+2\psi-\alpha N_V\beta_H\right),$$

$$a_4 = \left(b+\theta-\theta\psi\right)\left(b+\alpha N_V\beta_H I_V^*\right)^2\left(d_k+d_V\right)+N_H\beta_V\left(b+\theta-\theta\psi\right)\left(b+\alpha N_V\beta_H I_V^*\right)^2\left(I_{HP}^*-I_{HS}^*\right)$$
$$+b\alpha N_V\left(I_V^*-1\right)\beta_H\left(\left(b+\theta-\theta\psi\right)\left(S_{HP}^*-S_{HS}^*\right)\left(b+\alpha N_V\beta_H I_V^*\right)+\alpha\theta\left(\psi-1\right)N_V S_{HP}^* I_V^*\beta_H\gamma_P\right),$$

where $S_{HP}^*, I_{HP}^*, S_{HS}^*, I_{HS}^*$, and I_V^* are defined in section 5.2.2 (The equilibrium point) and all parameter values are defined in Table 5.3. Using Routh-Hurwitz criteria [29] 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 5.3 that conditions $(i)-(iv)$ are indeed satisfied. This means that the polynomial of Equation (5.31) is Hurwitz.

$$(i)\ a_1>0,$$
$$(ii)\ a_3>0,$$
$$(iii)\ a_4>0,$$
$$(iv)\ a_1a_2a_3-a_3{}^2-a_1{}^2a_4>0.$$

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

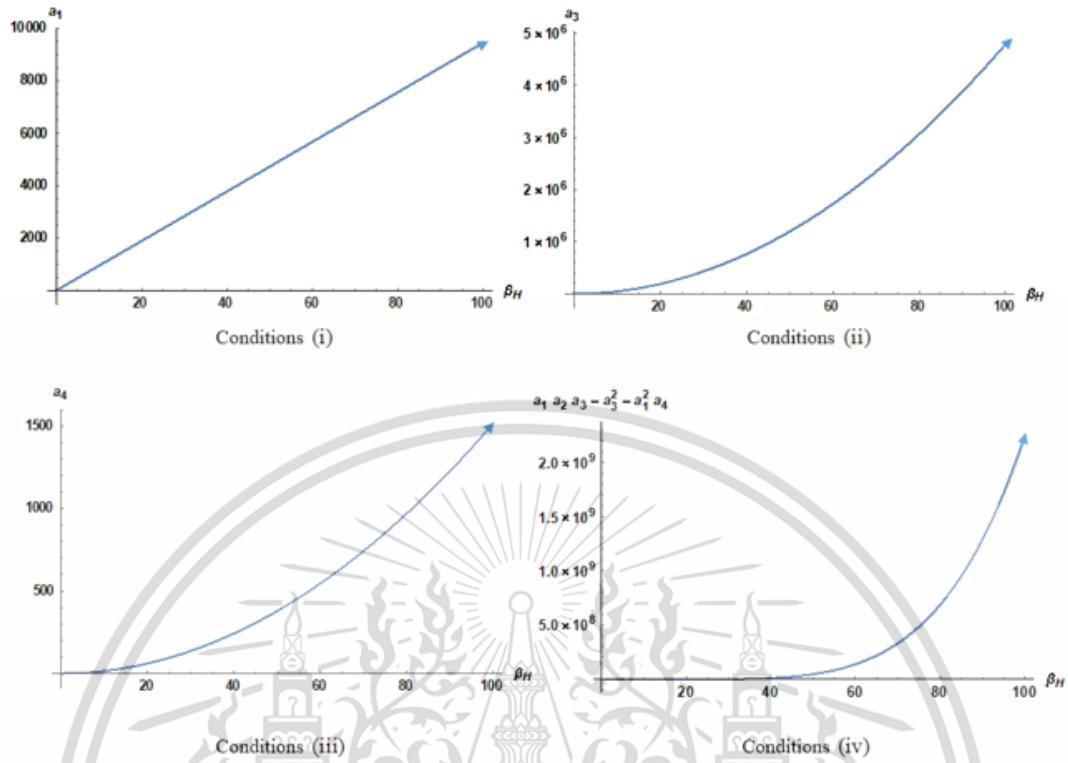


Figure 5.3 All parameter spaces of endemic equilibrium are satisfied with the Routh-Hurwitz criteria.

5.2.5 Global stability of equilibrium points

Theorem 5.3 Let $E_1^* = (S_{HP}^*, I_{HP}^*, R_{HP}^*, S_{HS}^*, I_{HS}^*, I_V^*) = (1,0,0,0,0,0)$. If $R_0 < 1$ then, the disease-free E_1^* is globally asymptotically stable on Ω_2 where

$$\Omega_2 = \left\{ (S_{HP}^*, I_{HP}^*, R_{HP}^*, S_{HS}^*, I_{HS}^*, I_V^*) \in \mathbb{R}_+^6, N_H = \frac{b}{b+d_d}, N_V = \frac{A}{d_V + d_K} \right\}.$$

Proof. We consider a Lyapunov function

$$\omega_2 (S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}, I_V) = (S_{HP} - S_{HP}^* \ln S_{HP}) + I_{HP} + R_{HP} + (S_{HS} - S_{HS}^* \ln S_{HS}) + I_{HS} + I_V.$$

The derivative with respect to time yields:

$$\frac{d\omega_2}{dt} = \left(\frac{dS_{HP}}{dt} - \frac{S_{HP}^*}{S_{HP}} \frac{dS_{HP}}{dt} \right) + \frac{dI_{HP}}{dt} + \frac{dR_{HP}}{dt} + \left(\frac{dS_{HS}}{dt} - \frac{S_{HS}^*}{S_{HS}} \frac{dS_{HS}}{dt} \right) + \frac{dI_{HS}}{dt} + \frac{dI_V}{dt}, \quad (5.32)$$

$$= \left(1 - \frac{S_{HP}^*}{S_{HP}} \right) \frac{dS_{HP}}{dt} + \frac{dI_{HP}}{dt} + \frac{dR_{HP}}{dt} + \left(1 - \frac{S_{HS}^*}{S_{HS}} \right) \frac{dS_{HS}}{dt} + \frac{dI_{HS}}{dt} + \frac{dI_V}{dt},$$

$$=\left(1-\frac{S_{HP}^*}{S_{HP}}\right)\left[b-\alpha\beta_H S_{HP} I_V N_V - bS_{HP}\right]+\left[\alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - (b+d_d) I_{HP}\right]$$

$$+\left[\gamma_P I_{HP} - (1-\psi)\theta R_{HP} - bR_{HP}\right]+\left(1-\frac{S_{HS}^*}{S_{HS}}\right)\left[(1-\psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - bS_{HS}\right]$$

$$+\left[\alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - bI_{HS}\right]+\left[\beta_V (1-I_V)(I_{HP}+I_{HS}) N_H - (d_V+d_k) I_V\right].$$

Substituting the relation in the disease-free E_1^*

$$=\left(b-bS_{HP}\right)\left(1-\frac{S_{HP}^*}{S_{HP}}\right)-(b+d_d) I_{HP} - bR_{HP} - bS_{HS}\left(1-\frac{S_{HS}^*}{S_{HS}}\right)-\left(\gamma_S+b\right) I_{HS} - (d_V+d_k) I_V,$$

$$=\left[b\left(1-\frac{S_{HP}^*}{S_{HP}}\right)+b\left(1-\frac{S_{HP}}{S_{HP}^*}\right)\right]-(b+d_d) I_{HP} - bR_{HP} - \left(\gamma_S+b\right) I_{HS} - (d_V+d_k) I_V,$$

$$=b\left[\left(1-\frac{S_{HP}^*}{S_{HP}}\right)+\left(1-\frac{S_{HP}}{S_{HP}^*}\right)\right]-(b+d_d) I_{HP} - bR_{HP} - \left(\gamma_S+b\right) I_{HS} - (d_V+d_k) I_V.$$

Simplification yields:

$$=-b\left[\frac{\left(S_{HP}-S_{HP}^*\right)^2}{S_{HP} S_{HP}^*}\right]-(b+d_d) I_{HP} - bR_{HP} - \left(\gamma_S+b\right) I_{HS} - (d_V+d_k) I_V,$$

$$\frac{d\omega_2}{dt}=-\left[b\frac{\left(S_{HP}-S_{HP}^*\right)^2}{S_{HP} S_{HP}^*}+(b+d_d) I_{HP} + bR_{HP} + \left(\gamma_S+b\right) I_{HS} + (d_V+d_k) I_V\right]. \quad (5.33)$$

It is obvious that all the term appearing in Equation (5.33) are always nonpositive. Now, using the Laselle's extension to Lyapunov's theorem, we have $\frac{d\omega_2}{dt}\le 0$ and so the function is to be negative definite. The limit set of each solution is contained in the largest invariant set for which $S_{HP}=S_{HP}^*, S_{HS}=S_{HS}^*, I_{HP}=0, R_{HP}=0, I_{HS}=0,$ and $I_V=0$ which is the singleton $\left\{E_1^*\right\}$. Then the Laselle's invariant principle implies that the disease-free equilibrium point E_1^* is globally asymptotically stable on Ω_2. □

Next, we consider the global property of the endemic equilibrium point of Equations (5.19)-(5.24).

Theorem 5.4 If $R_0>1$ then, the endemic equilibrium point E_2^* is globally asymptotically stable on Ω_2 if and only if $\alpha=\frac{\beta_V N_H\left(I_{HP}+I_{HS}\right)\left(I_V-1\right)}{\beta_H I_V N_V\left(S_{HP}+S_{HS}\right)}$.

Proof. The Lyapunov function is in the form:

$$\zeta_2\left(S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}, I_V\right)=\left(S_{HP}-S_{HP}^*\ln S_{HP}\right)+I_{HP}+R_{HP}+\left(S_{HS}-S_{HS}^*\ln S_{HS}\right)+I_{HS}+I_V.$$

The derivative with respect to time yields:

$$\frac{d\zeta_2}{dt} = \left(\frac{dS_{HP}}{dt} - \frac{S^*_{HP}}{S_{HP}}\frac{dS_{HP}}{dt}\right) + \frac{dI_{HP}}{dt} + \frac{dR_{HP}}{dt} + \left(\frac{dS_{HS}}{dt} - \frac{S^*_{HS}}{S_{HS}}\frac{dS_{HS}}{dt}\right) + \frac{dI_{HS}}{dt} + \frac{dI_V}{dt}, \tag{5.34}$$

$$= \left(1 - \frac{S^*_{HP}}{S_{HP}}\right)\frac{dS_{HP}}{dt} + \frac{dI_{HP}}{dt} + \frac{dR_{HP}}{dt} + \left(1 - \frac{S^*_{HS}}{S_{HS}}\right)\frac{dS_{HS}}{dt} + \frac{dI_{HS}}{dt} + \frac{dI_V}{dt},$$

$$= \left(1 - \frac{S^*_{HP}}{S_{HP}}\right)\left[b - \alpha\beta_H S_{HP} I_V N_V - bS_{HP}\right] + \left[\alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - (b + d_d) I_{HP}\right]$$

$$+ \left[\gamma_P I_{HP} - (1-\psi)\theta R_{HP} - bR_{HP}\right] + \left(1 - \frac{S^*_{HS}}{S_{HS}}\right)\left[(1-\psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - bS_{HS}\right]$$

$$+ \left[\alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - bI_{HS}\right] + \left[\beta_V (1 - I_V)(I_{HP} + I_{HS}) N_H - (d_V + d_k) I_V\right].$$

Substituting with condition α and simplification yields:

$$= -b\left[\frac{\left(S_{HP} - S^*_{HP}\right)^2}{S_{HP} S^*_{HP}}\right] - (b + d_d) I_{HP} - \left((1-\psi)\theta + b\right) R_{HP} - \left(\gamma_S + b\right) I_{HS} - (d_V + d_k) I_V,$$

$$\frac{d\zeta_2}{dt} = -\left[\begin{array}{l} b\dfrac{\left(S_{HP} - S^*_{HP}\right)^2}{S_{HP} S^*_{HP}} + (b + d_d) I_{HP} + \left((1-\psi)\theta + b\right) R_{HP} \\ + \left(\gamma_S + b\right) I_{HS} + (d_V + d_k) I_V \end{array}\right]. \tag{5.35}$$

Hence, the derivative Equation (5.35) is $\frac{d\zeta_2}{dt} \le 0$ and so the function is to be negative definite. The limit set of each solution is contained in the largest invariant set for which $S_{HP} = S^*_{HP}, S_{HS} = S^*_{HS}, I_{HP} = 0, R_{HP} = 0, I_{HS} = 0,$ and $I_V = 0$ which is the singleton $\left\{E^*_2\right\}$. Then the Laselle's invariant principle implies that the endemic equilibrium point E^*_2 is globally asymptotically stable on Ω_2. □

5.3 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 5.3. Note that though most of the parameters are taken from the literature, some of the values have to be assumed for the purpose of this investigation. The use of N_H and N_V of 10,000 for both cases reflects a small rural town, for example, Mae Hong Son, with lower socio-economic status, which would be very good to investigate 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 [69]. 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. The numerical results are shown in Figures 5.4-5.7.

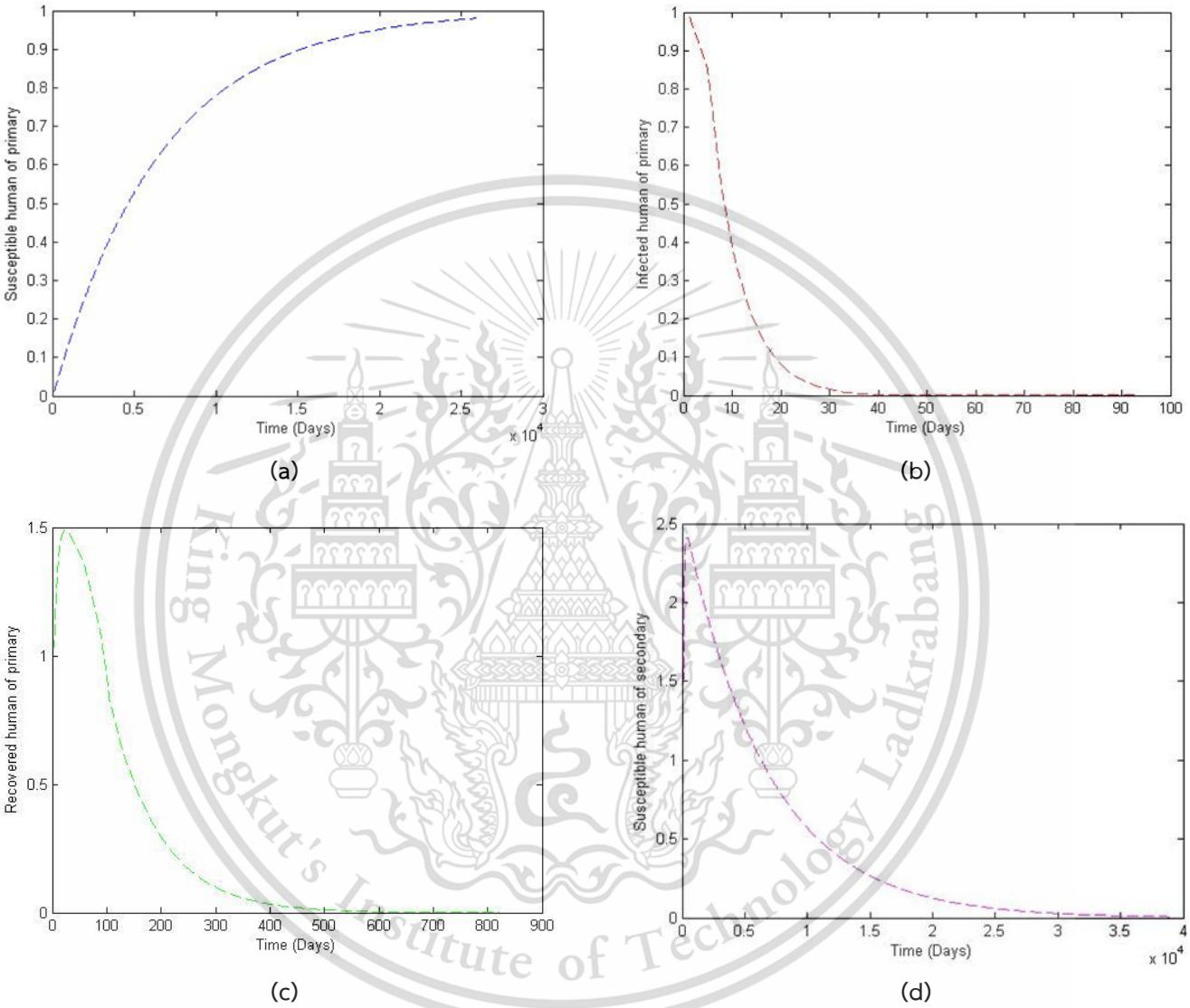
Table 5.3 The parameters used in the numerical simulation.

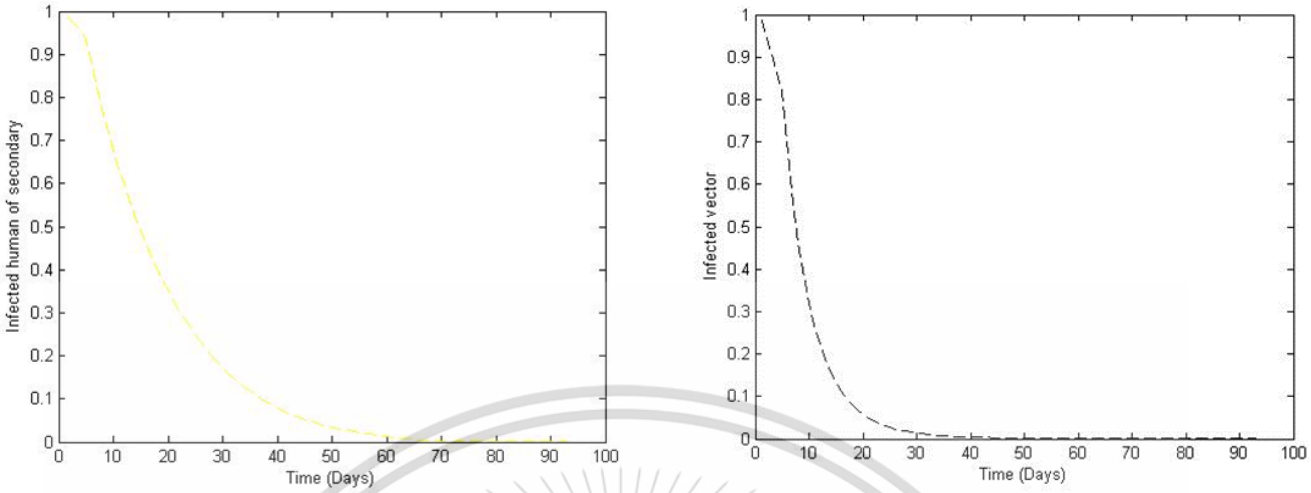
Parameters	The disease-free	The endemic	References
α	1/7	1/7	[1,37,53,56,57],[65-69]
ψ	1/2	1/2	[1,37,53,56,57],[65-69]
θ	1/(30*6)	1/(30*6)	[1,46,48,49]
N_H	10,000	10,000	assumed
N_V	10,000	10,000	assumed
β_H	0.0000080	0.0050	assumed
β_V	0.0000065	0.0030	assumed
b	1/(365*70)	1/(365*70)	[1,37,53,56,57],[65-69]
d_V	1/14	1/14	[1,37,53,56,57],[65-69]
d_d	1/180	1/180	assumed
d_k	1/14	1/14	assumed
γ_P	1/10	1/10	[1,37,53,56,57],[65-69]
γ_S	1/14	1/14	[1,37,53,56,57],[65-69]

For the case of larger cities such as Chiang Mai, Khon Kaen, etc., we assume that
Case 1: the number of the population human $N_H = 500,000$ and the number of the population vector $N_V = 100,000$ while for
Case 2: the number of the population human $N_H = 500,000$ and the number of the population vector $N_V = 100,000e^{(-1/14)t}$ to investigate their implications.

Note that case 2 simulates the situation where the number of 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 is seen from Figures 5.8-5.9, **(a)** Susceptible 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,

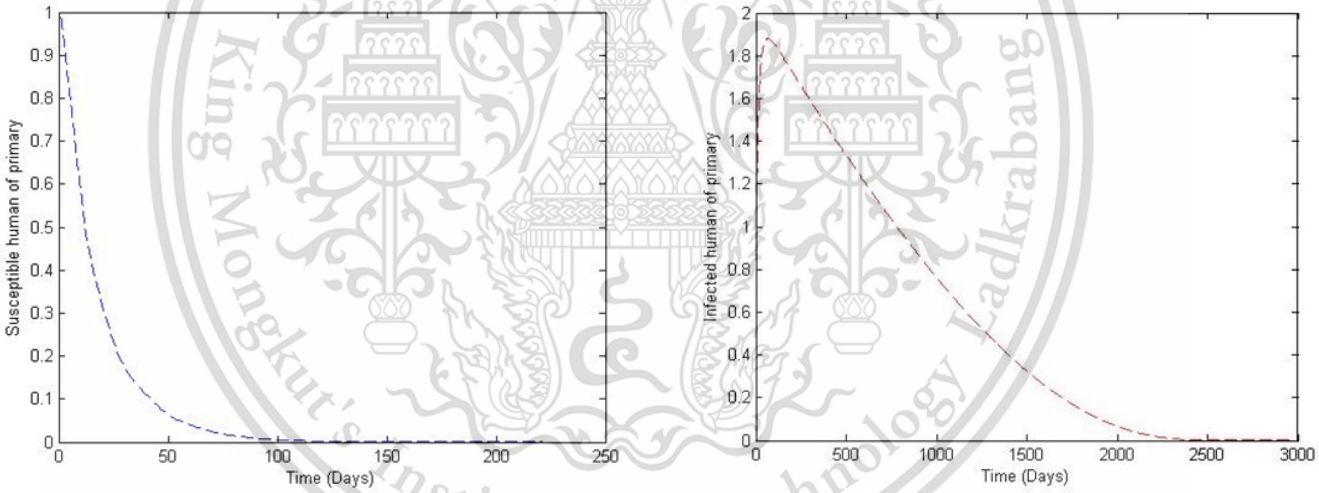
that even though there is a small change in trajectory from case 1 to case 2, which is to be expected since the total vector population slowly decays.





(e) (f)

Figure 5.4 The trajectory of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}, and I_V toward the disease-free equilibrium point for $R_0 < 1$.



(a) (b)

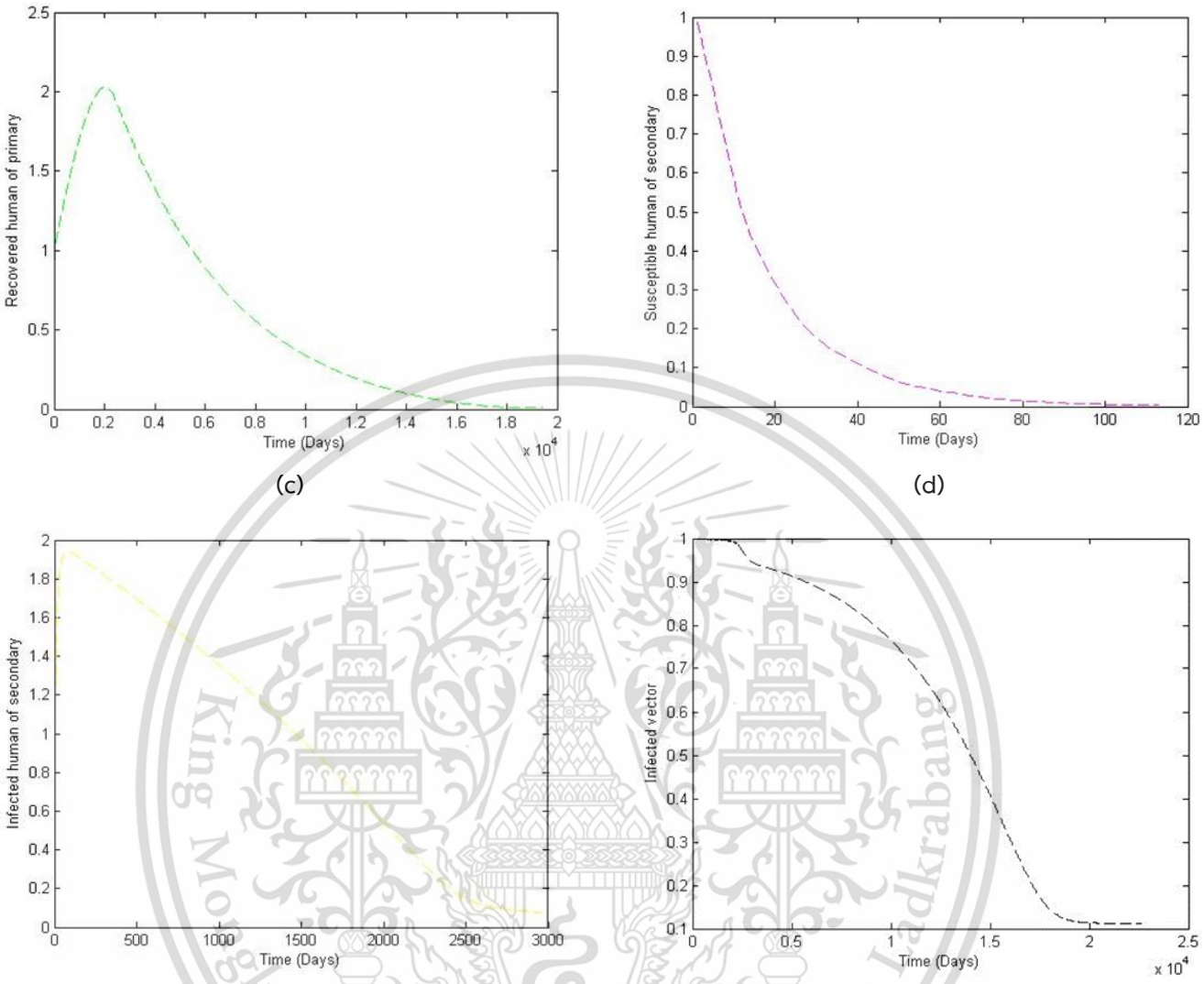
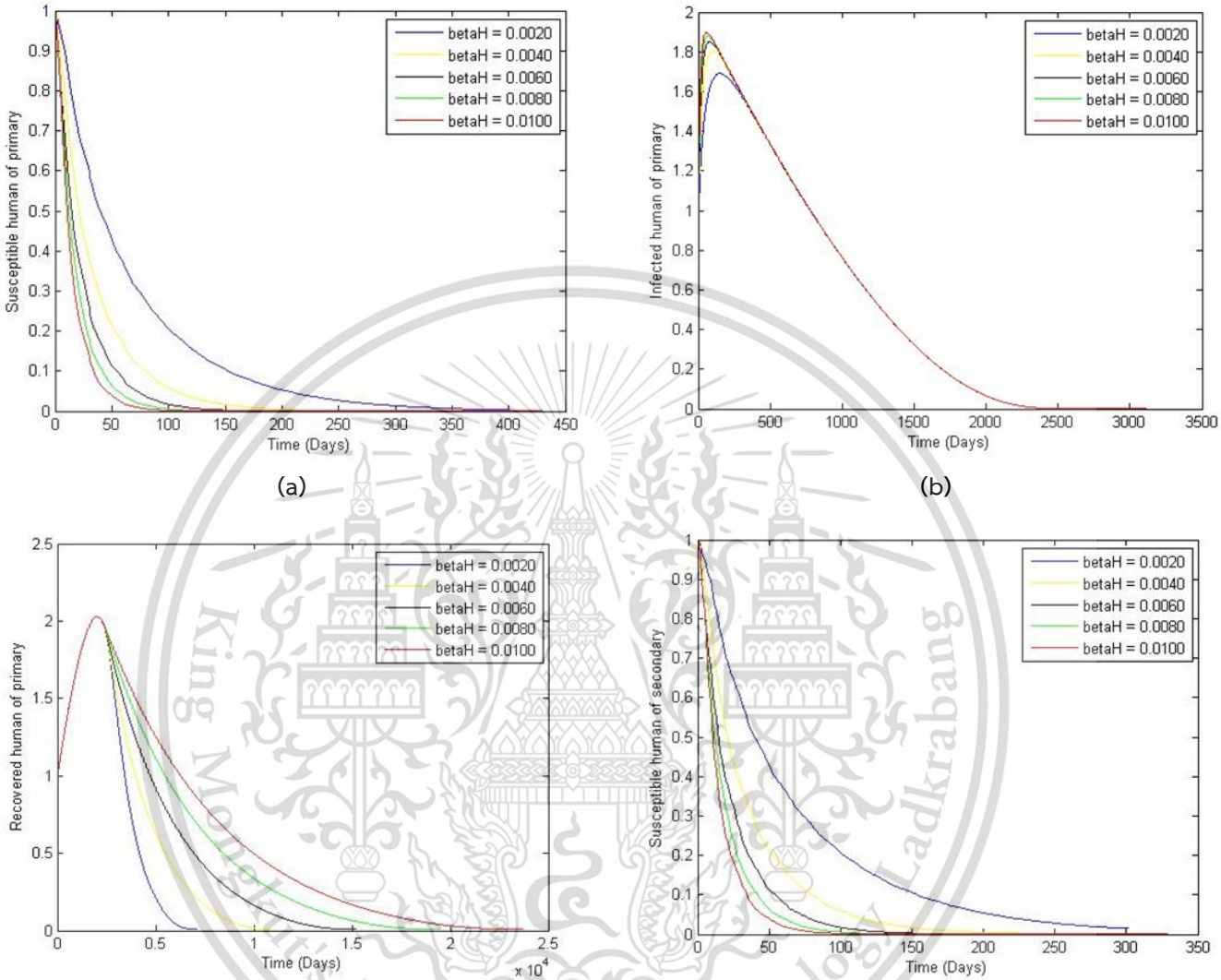
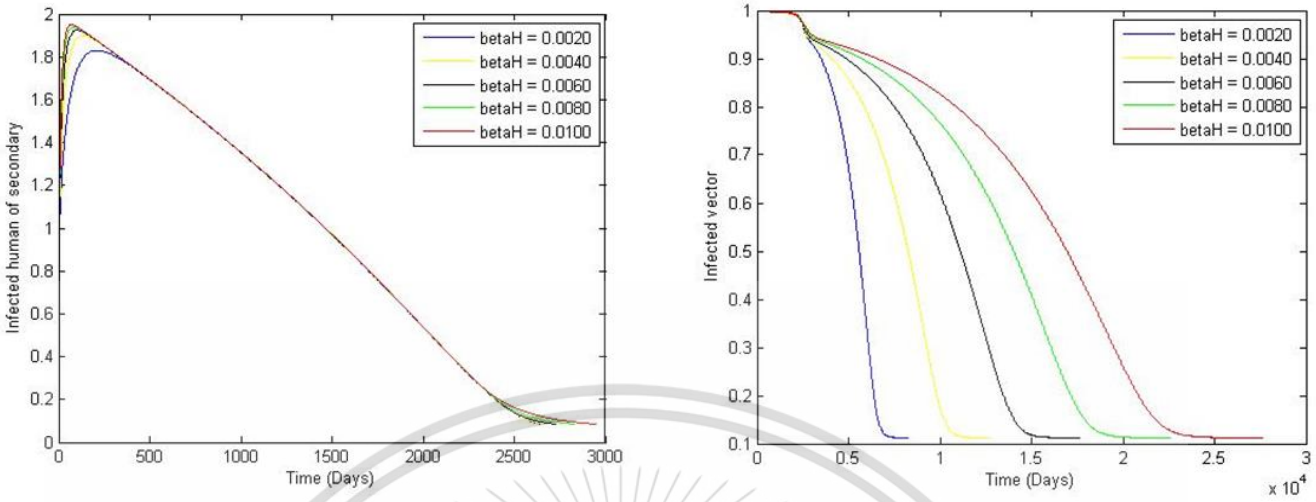


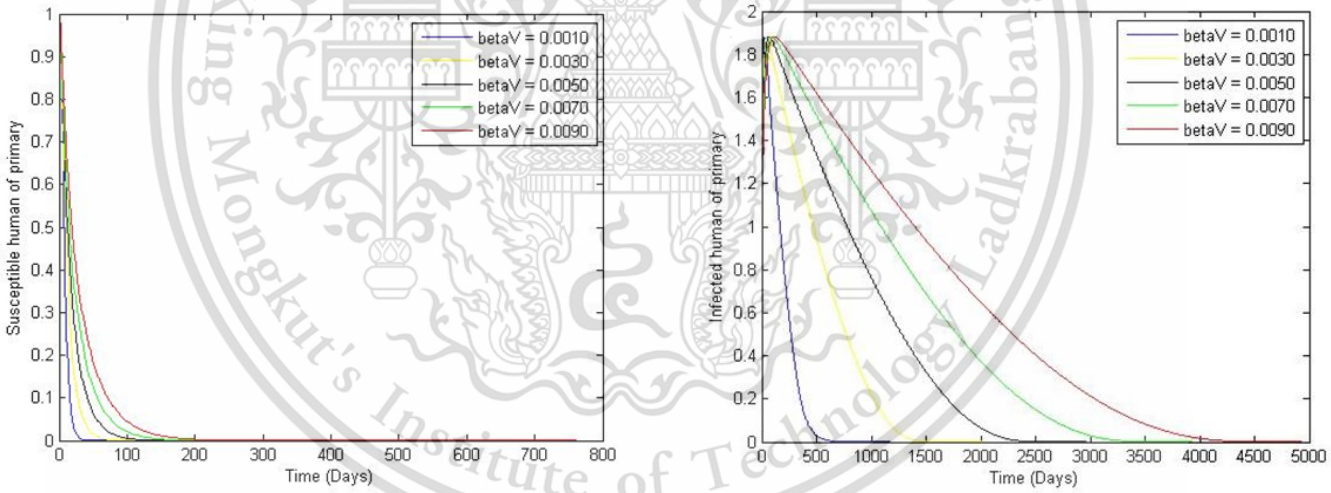
Figure 5.5 The trajectory of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS},$ and I_V toward the endemic equilibrium point for $R_0 > 1$.





(e) (f)

Figure 5.6 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 vector to human, $\beta_H = 0.0020, 0.0040, 0.0060, 0.0080, 0.0100$.



(a) (b)

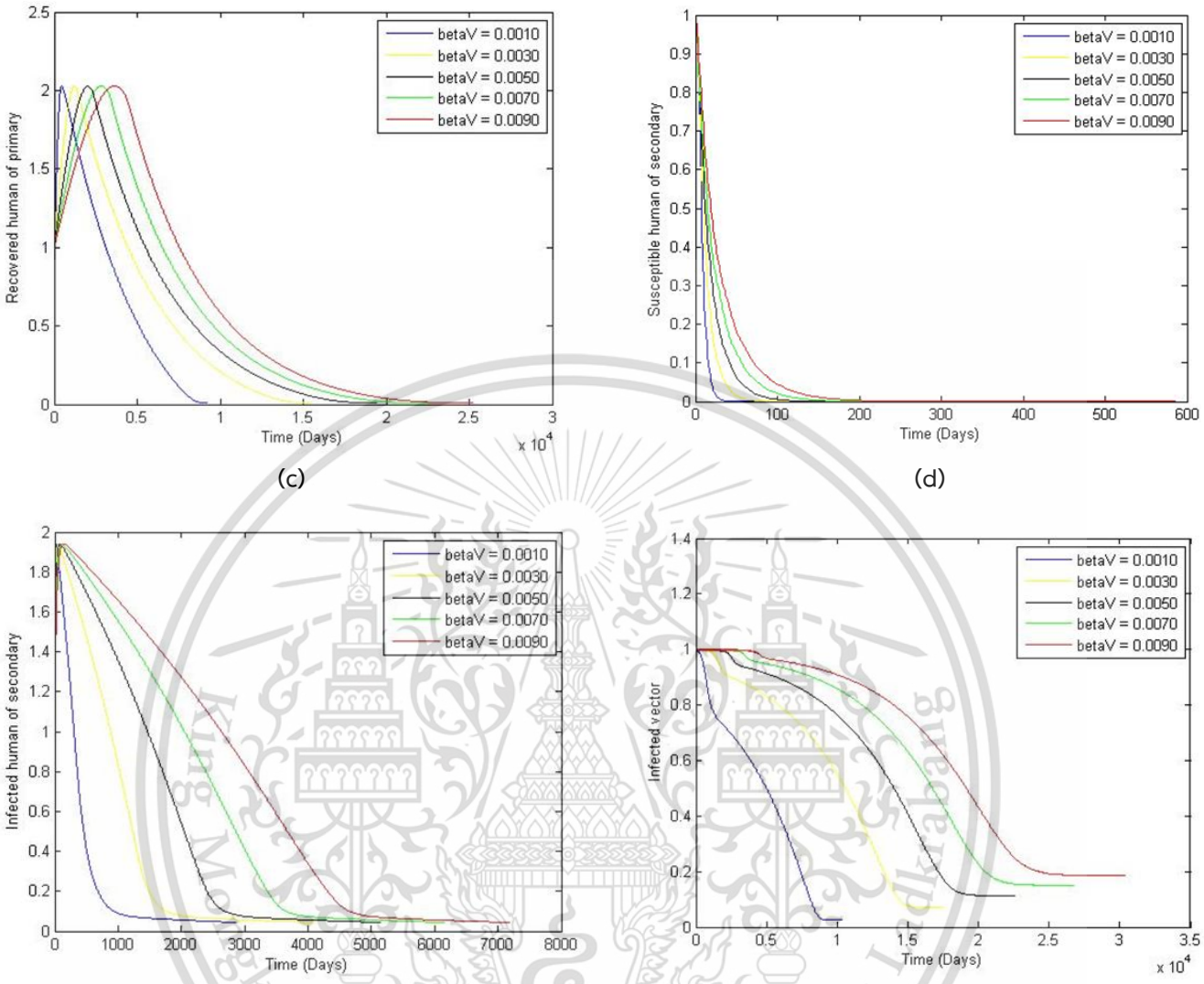
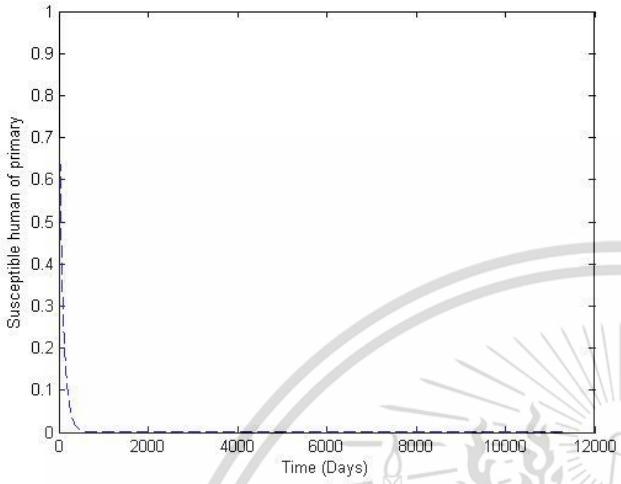
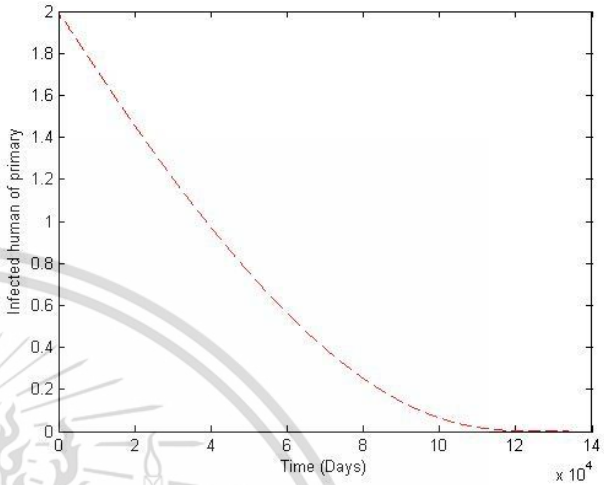


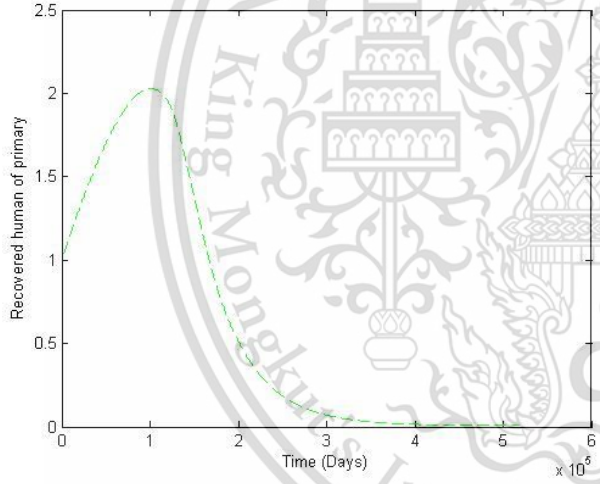
Figure 5.7 The trajectory of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}, and I_V toward the endemic equilibrium point for $R_0 > 1$ with a comparison of the transmission rate of the dengue virus from vector to human, $\beta_V = 0.0010, 0.0030, 0.0050, 0.0070, 0.0090$.



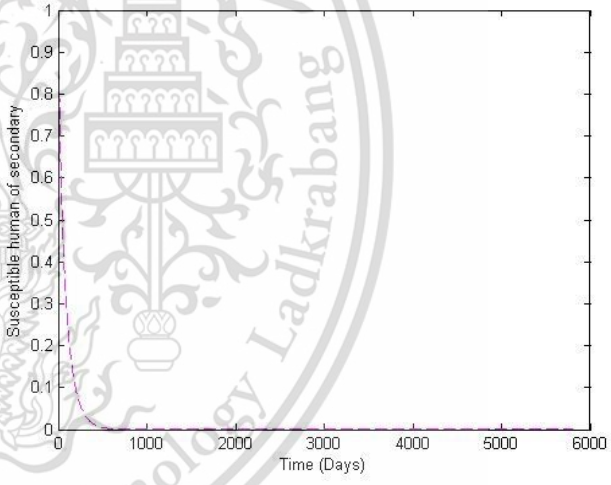
(a)



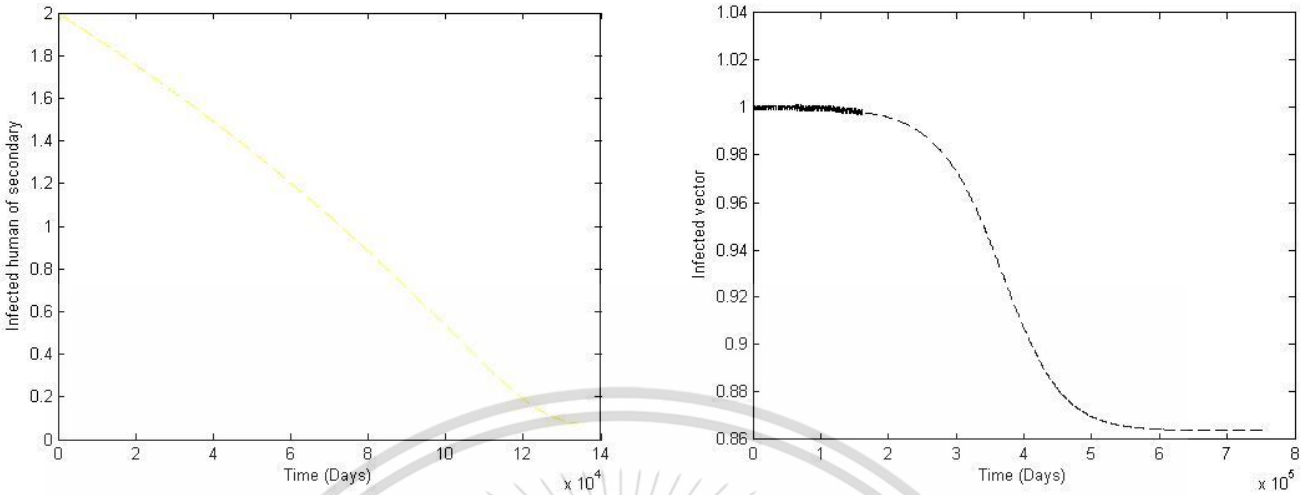
(b)



(c)

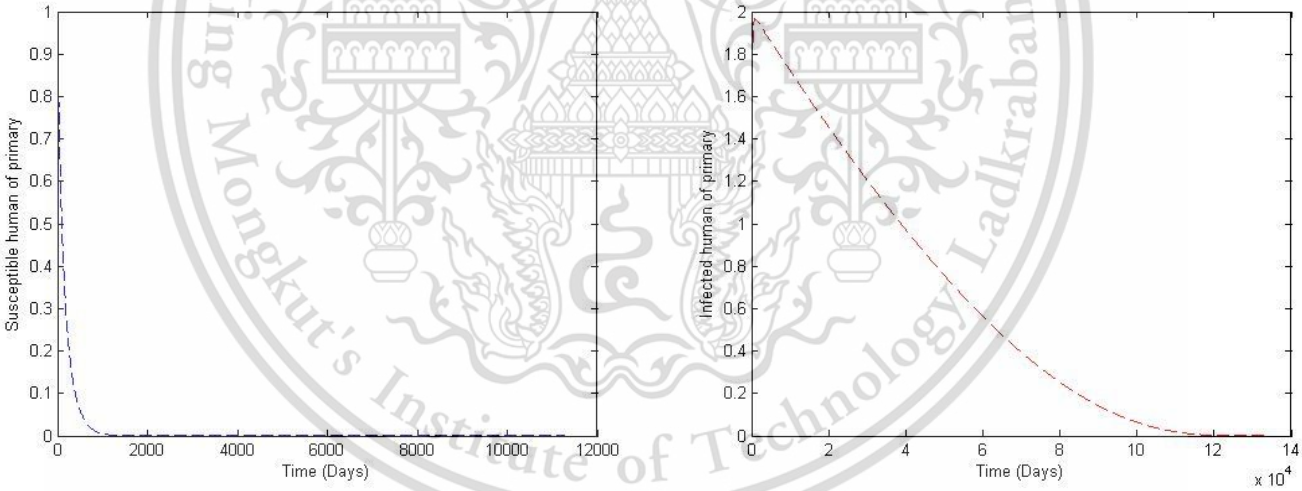


(d)



(e) (f)

Figure 5.8 The trajectory of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS},$ and I_V toward the endemic equilibrium point respectively. For $R_0 > 1$ with parameter values changes $N_H = 500,000$ and $N_V = 100,000$.



(a) (b)

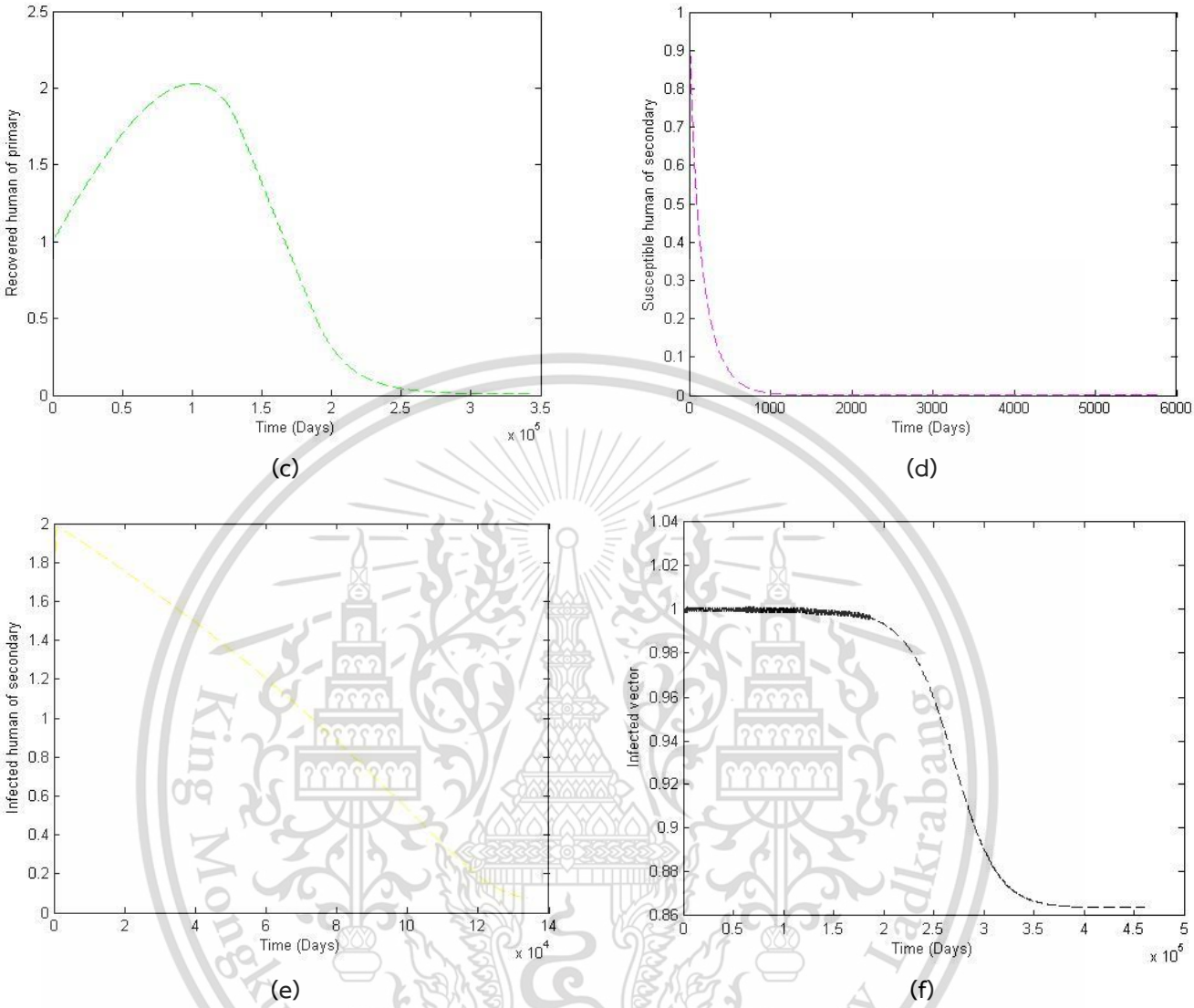


Figure 5.9 The trajectory of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}, and I_V toward the endemic equilibrium point respectively. For $R_0 > 1$ with parameter values changes $N_H = 500,000$ and $N_V = 100,000e^{(-1/14)t}$.

5.4 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 (5.19)–(5.24) will be recast as a control problem. The purpose of this is to recast the problem as one of minimizing the number of infected human populations 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 breeding

of the *Aegypti* mosquitoes is destroyed. This model can be written as the system of the equation as follows:

$$\frac{dS_{HP}}{dt} = b - \alpha\beta_H S_{HP} I_V N_V - bS_{HP}, \tag{5.36}$$

$$\frac{dI_{HP}}{dt} = \alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - (b + d_d) I_{HP}, \tag{5.37}$$

$$\frac{dR_{HP}}{dt} = \gamma_P I_{HP} - (1-\psi)\theta R_{HP} - bR_{HP}, \tag{5.38}$$

$$\frac{dS_{HS}}{dt} = (1-\psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - bS_{HS} - u_1(\mathrm{t}) I_{HS}, \tag{5.39}$$

$$\frac{dI_{HS}}{dt} = \alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - bI_{HS}, \tag{5.40}$$

$$\frac{dR_{HS}}{dt} = \gamma_S I_{HS} - bR_{HS}, \tag{5.41}$$

$$\frac{dS_V}{dt} = \frac{A}{N_V} - \beta_V S_V (I_{HP} + I_{HS}) N_H - d_V S_V - u_2(\mathrm{t}) S_V, \tag{5.42}$$

$$\frac{dI_V}{dt} = \beta_V S_V (I_{HP} + I_{HS}) N_H - (d_V + d_k) I_V - u_2(\mathrm{t}) \beta_V S_V (I_{HP} + I_{HS}) N_H. \tag{5.43}$$

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

$$\frac{dS_{HP}}{dt} = b - \alpha\beta_H S_{HP} I_V N_V - bS_{HP}, \tag{5.44}$$

$$\frac{dI_{HP}}{dt} = \alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - (b + d_d) I_{HP}, \tag{5.45}$$

$$\frac{dR_{HP}}{dt} = \gamma_P I_{HP} - (1-\psi)\theta R_{HP} - bR_{HP}, \tag{5.46}$$

$$\frac{dS_{HS}}{dt} = (1-\psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - bS_{HS} - u_1(\mathrm{t}) I_{HS}, \tag{5.47}$$

$$\frac{dI_{HS}}{dt} = \alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - bI_{HS}, \tag{5.48}$$

$$\frac{dI_V}{dt} = \beta_V S_V (I_{HP} + I_{HS}) N_H - (d_V + d_k) I_V - u_2(\mathrm{t}) \beta_V S_V (I_{HP} + I_{HS}) N_H. \tag{5.49}$$

All parameters have the same definitions as before. The optimal control problems of Equations (5.44) – (5.49), require a definition of the objective function given as:

$$J(u_1, u_2) = \min \int_0^T \left[X_1 I_{HP} + X_2 I_{HS} + \frac{1}{2}\left(X_3 u_1^{\,2}(t) + X_4 u_2^{\,2}(t) \right) \right] dt, \tag{5.50}$$

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 term $X_3 u_1^{\ 2}(t)$ 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 the Lagrangian and the Hamiltonian of the problems. The Lagrangian of the optimal control problem is given by

$$L\left(I_H, I_V, u_1, u_2\right) = X_1 I_{HP} + X_2 I_{HS} + \frac{1}{2}\left(X_3 u_1^{\ 2}(t) + X_4 u_2^{\ 2}(t)\right). \qquad (5.51)$$

Theorem 5.5 We consider the objective function J given by Equation *(5.50)* with $(u_1, u_2) \in U$ subjecting to the control system of Equations *(5.44)-(5.49)* 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 [8,71]
The control set U is closed and convex by its definition above and the integrand of the function Equations (5.44)-(5.49) is also convex in U. It is obvious that these states and control variable are nonnegative. Since, the solution to the systems given by Equations (5.44)-(5.49) 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

$$\begin{aligned} L(I_{HP}, I_{HS}, u_1, u_2) &= X_1 I_{HP} + X_2 I_{HS} + \frac{1}{2}(X_3 u_1^2(t) + X_4 u_2^2(t)), \\ &\geq q_2(I_{HP} + I_{HS}) + q_1(|u_1|^2 + |u_2|^2), \\ &= q_2 + q_1(|u_1|^2 + |u_2|^2). \end{aligned} \qquad (5.52)$$

The optimal control of this model is obtained by applying Pontryagin's Minimum Principle [29]. □

Theorem 5.6 There exists the adjoint variables $\lambda_1,\ \lambda_2,\ \lambda_3, \lambda_4,\ \lambda_5,$ and λ_6 under the control that satisfy the following*:*

$$\begin{aligned} \frac{d\lambda_1}{dt} &= \lambda_1(\mathrm{t})\left(\alpha\beta_H I_V N_V + b\right) - \lambda_2(\mathrm{t})\left(\alpha\beta_H I_V N_V\right), \\ \frac{d\lambda_2}{dt} &= -X_1 + \lambda_2(\mathrm{t})\left(\gamma_P + d_d + b\right) - \lambda_3(\mathrm{t})\gamma_P - \lambda_6(\mathrm{t})\left(\beta_V N_H\left(1 - I_V - u_2^{\ *}(\mathrm{t}) + I_V u_2^{\ *}(\mathrm{t})\right)\right), \\ \frac{d\lambda_3}{dt} &= \lambda_3(\mathrm{t})\left((1-\psi)\theta + b\right) - \lambda_4(\mathrm{t})\left((1-\psi)\theta\right), \end{aligned} \qquad (5.53)$$

$$\frac{d\lambda_4}{dt} = \lambda_4(t)\left(\alpha\beta_H I_V N_V + b\right) - \lambda_5(t)\left(\alpha\beta_H I_V N_V\right),$$

$$\frac{d\lambda_5}{dt} = -X_2 + \lambda_4(t)\left(u_1^*(t)\right) + \lambda_5(t)\left(\gamma_S + b\right) - \lambda_6(t)\left(\beta_V N_H\left(1 - I_V - u_2^*(t) + I_V u_2^*(t)\right)\right),$$

$$\frac{d\lambda_6}{dt} = \lambda_1(t)\left(\alpha\beta_H S_{HP} N_V\right) - \lambda_2(t)\left(\alpha\beta_H S_{HP} N_V\right) + \lambda_4(t)\left(\alpha\beta_H S_{HS} N_V\right)$$
$$-\lambda_5(t)\left(\alpha\beta_H S_{HS} N_V\right) + \lambda_6(t)\left(\beta_V N_H (1 - u_2^*(t))(I_{HP} + I_{HS}) + (d_V + d_k)\right).$$

With the boundary conditions

$$\lambda_1(t) = \lambda_2(t) = \lambda_3(t) = \lambda_4(t) = \lambda_5(t) = \lambda_6(t) = 0. \tag{5.54}$$

Also, the optimal control variables are given by

$$u_1^*(t) = \max\left(\min\left(\frac{\lambda_4 I_{HS}^*}{X_3}, u_1^{\max}\right), 0\right), \tag{5.55}$$

$$u_2^*(t) = \max\left(\min\left(\frac{\lambda_6\left(1 - I_V^*\right)\beta_V\left(I_{HP}^* + I_{HS}^*\right)N_H}{X_4}, u_2^{\max}\right), 0\right). \tag{5.56}$$

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

$$H = L\left(I_{HP}, I_{HS}, u_1, u_2\right) + \lambda_1\frac{dS_{HP}}{dt} + \lambda_2\frac{dI_{HP}}{dt} + \lambda_3\frac{dR_{HP}}{dt} + \lambda_4\frac{dS_{HS}}{dt} + \lambda_5\frac{dI_{HS}}{dt} + \lambda_6\frac{dI_V}{dt}, \tag{5.57}$$

$$\begin{aligned} H = {} & X_1 I_{HP} + X_2 I_{HS} + \frac{1}{2}\left(X_3 u_1^2(t) + X_4 u_2^2(t)\right) \\ & + \lambda_1\left[b - \alpha\beta_H S_{HP} I_V N_V - bS_{HP}\right] \\ & + \lambda_2\left[\alpha\beta_H S_{HP} I_V N_V - \gamma_P I_{HP} - \left(b + d_d\right) I_{HP}\right] \\ & + \lambda_3\left[\gamma_P I_{HP} - (1 - \psi)\theta R_{HP} - bR_{HP}\right] \\ & + \lambda_4\left[(1 - \psi)\theta R_{HP} - \alpha\beta_H S_{HS} I_V N_V - bS_{HS} - u_1(t) I_{HS}\right] \\ & + \lambda_5\left[\alpha\beta_H S_{HS} I_V N_V - \gamma_S I_{HS} - bI_{HS}\right] \\ & + \lambda_6\left[\left(1 - u_2(t)\right)\beta_V\left(1 - I_V\right)\left(I_{HP} + I_{HS}\right)N_H - \left(d_V + d_k\right) I_V\right]. \end{aligned} \tag{5.58}$$

The adjoint associated system is obtained as follows:

$$\frac{d\lambda_1}{dt} = \lambda_1(t)\left(\alpha\beta_H I_V N_V + b\right) - \lambda_2(t)\left(\alpha\beta_H I_V N_V\right),$$

$$\frac{d\lambda_2}{dt} = -X_1 + \lambda_2(t)(\gamma_P + d_d + b) - \lambda_3(t)\gamma_P - \lambda_6(t)\left(\beta_V N_H\left(1 - I_V - u_2^*(t) + I_V u_2^*(t)\right)\right),$$

$$\frac{d\lambda_3}{dt} = \lambda_3(t)\left((1-\psi)\theta + b\right) - \lambda_4(t)\left((1-\psi)\theta\right), \tag{5.59}$$

$$\frac{d\lambda_4}{dt} = \lambda_4(t)\left(\alpha\beta_H I_V N_V + b\right) - \lambda_5(t)\left(\alpha\beta_H I_V N_V\right),$$

$$\frac{d\lambda_5}{dt} = -X_2 + \lambda_4(\mathrm{t})\left(u_1^*(t)\right) + \lambda_5(t)(\gamma_S + b) - \lambda_6(t)\left(\beta_V N_H\left(1 - I_V - u_2^*(t) + I_V u_2^*(t)\right)\right),$$

$$\frac{d\lambda_6}{dt} = \lambda_1(t)\left(\alpha\beta_H S_{HP} N_V\right) - \lambda_2(t)\left(\alpha\beta_H S_{HP} N_V\right) + \lambda_4(t)\left(\alpha\beta_H S_{HS} N_V\right)$$
$$-\lambda_5(t)\left(\alpha\beta_H S_{HS} N_V\right) + \lambda_6(t)\left(\beta_V N_H\left(1 - u_2^*(t)\right)\left(I_{HP} + I_{HS}\right) + \left(d_V + d_k\right)\right).$$

Using the optimal conditions, we find that

$$\frac{\partial H}{\partial u_1} = \frac{\partial H}{\partial u_2} = 0 \text{ at } u_1 = u_1^* \text{ and } u_2 = u_2^*. \tag{5.60}$$

Therefore,

$$\frac{\partial H}{\partial u_1} = X_3 u_1 - \lambda_4 I_{HS} = 0,$$
$$u_1^* = \frac{\lambda_4 I_{HS}}{X_3}, \tag{5.61}$$

$$\frac{\partial H}{\partial u_2} = X_4 u_2 - \lambda_6\left(1 - I_V\right)\beta_V\left(I_{HP} + I_{HS}\right)N_H = 0,$$
$$u_2^* = \frac{\lambda_6\left(1 - I_V\right)\beta_V\left(I_{HP} + I_{HS}\right)N_H}{X_4}. \tag{5.62}$$

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

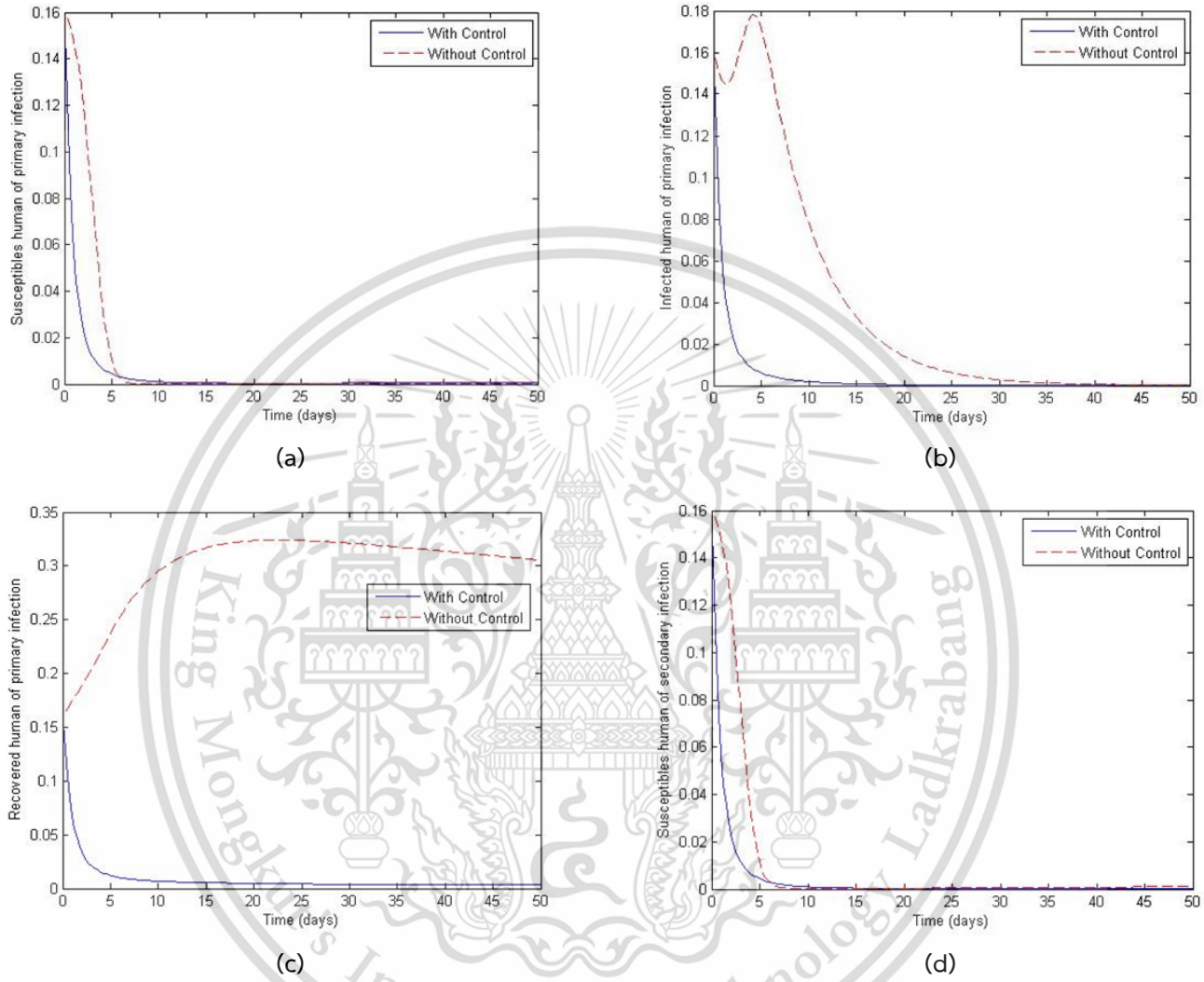
$$u_1^* = \begin{cases} 0 & if\ \frac{\lambda_4 I_{HS}}{X_3} \le 0, \\ \frac{\lambda_4 I_{HS}}{X_3} & if\ \frac{\lambda_4 I_{HS}}{X_3} < u_1^{\max}, \\ u_1^{\max} & if\ \frac{\lambda_4 I_{HS}}{X_3} \ge u_1^{\max}. \end{cases} \tag{5.63}$$

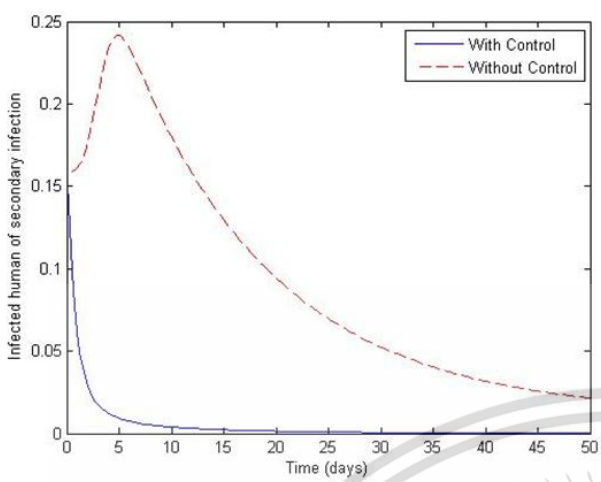
$$u_2^* = \begin{cases} 0 & if \ \dfrac{\lambda_6 (1-I_V)\beta_V (I_{HP}+I_{HS})N_H}{X_4} \le 0, \\ \dfrac{\lambda_6 (1-I_V)\beta_V (I_{HP}+I_{HS})N_H}{X_4} & if \ \dfrac{\lambda_6 (1-I_V)\beta_V (I_{HP}+I_{HS})N_H}{X_4} < u_2^{\max}, \\ u_2^{\max} & if \ \dfrac{\lambda_6 (1-I_V)\beta_V (I_{HP}+I_{HS})N_H}{X_4} \ge u_2^{\max}. \end{cases} \quad (5.64)$$

The simulation results for the optimal states are presented in Figures 5.10-5.14 and the optimal controls are shown in Figure 5.15. □

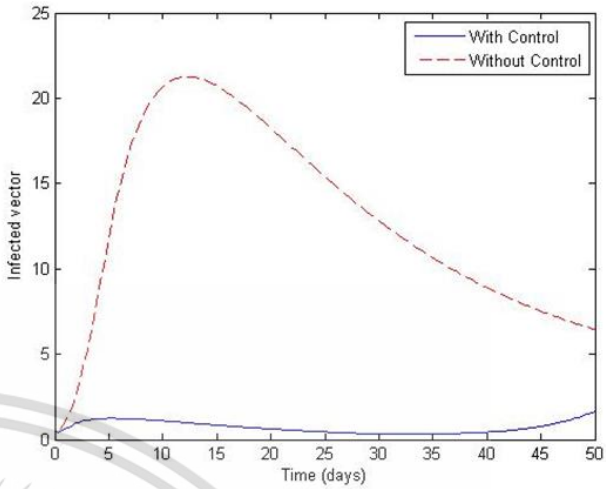
The simulation results for the optimal states are presented in Figures 5.10-5.14 and the optimal controls are shown in Figure 5.15 and parameter values according to Table 5.3.

Figures 5.10-5.14, **(a)** Susceptible of primary infection **(b)** Infected population with primary infection **(c)** Recovered human of primary infection **(d)** Susceptible of secondary infection **(e)** Infected human of secondary infection **(f)** Infected vector, shows the simulation results of system of Equations (5.44)-(5.49) with and without controls of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS},$ and I_V. The plot of Figure 5.10 is obtained by setting the weight X_1 to be equal to X_2. Figure 5.11 presents the case in which the weight X_1 less than X_2. Figure 5.12 presents the case where X_1 is at least 10 times greater than X_2. Figure 5.13 presents the case in which the weight X_1 greater than X_2. Figure 5.14 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 human population 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 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, respectively. Moreover, as the weight X_1 increases, the steady state 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 appears to be flooring to zero for a large weight of 100. With no control measures, it will take longer for equilibrium to be reached.



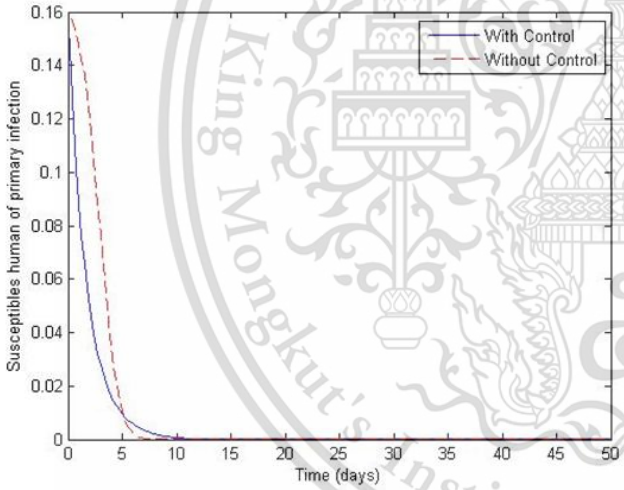


(e)

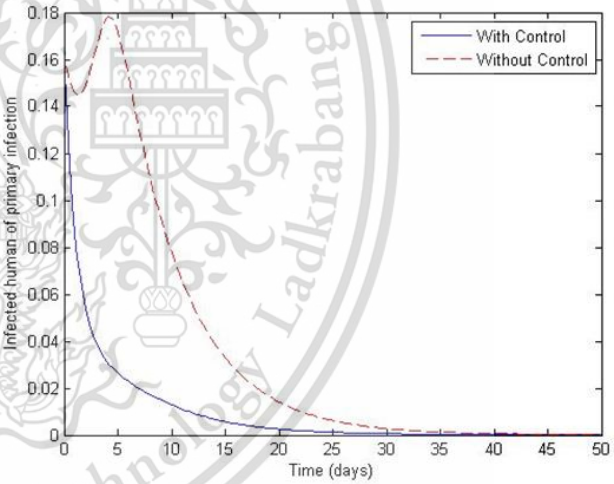


(f)

Figure 5.10 Simulation results of system of Equations (5.44)-(5.49) with and without controls of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}$, and I_V. Using $X_1 = 100,\ X_2 = 100$.



(a)



(b)

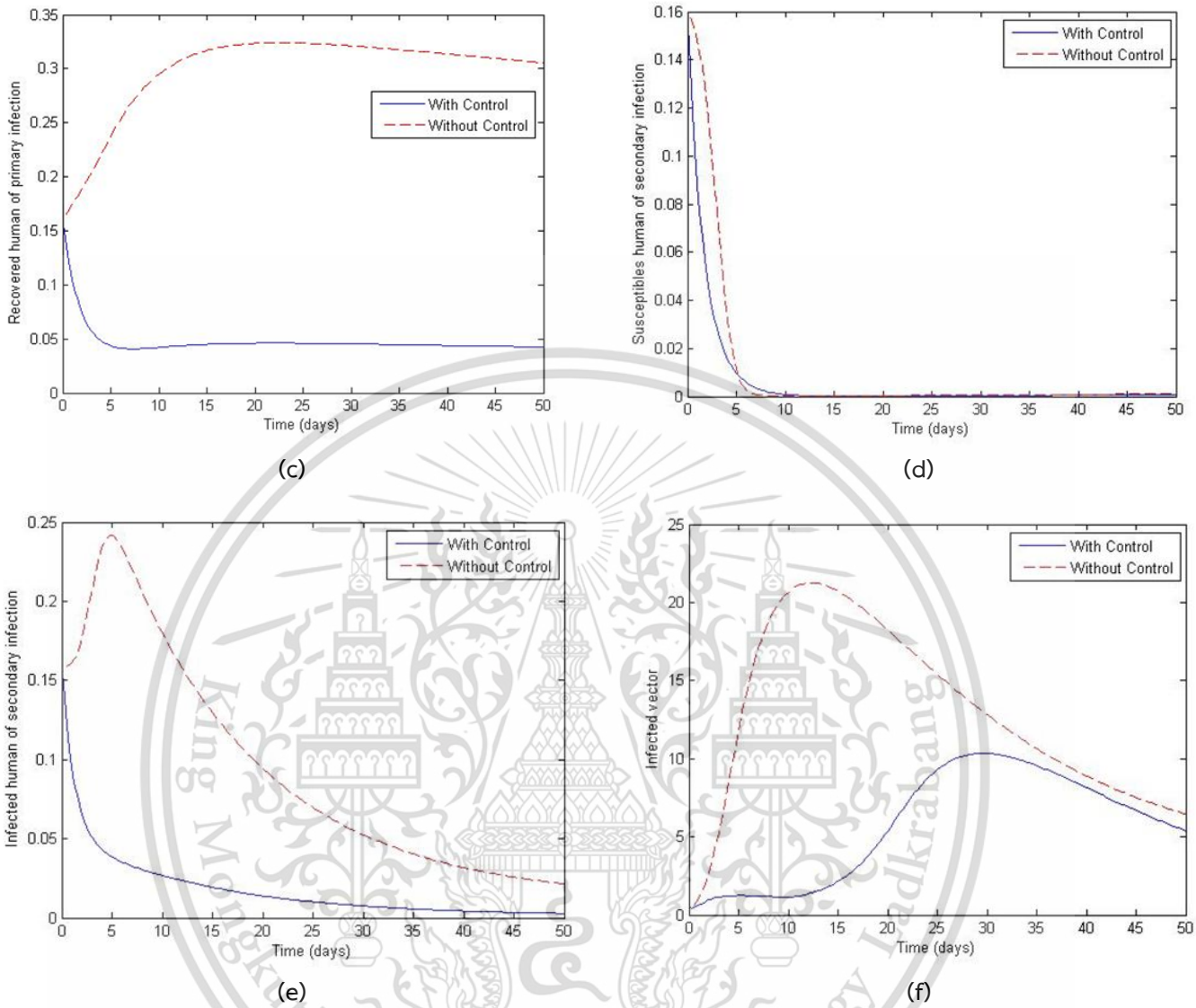
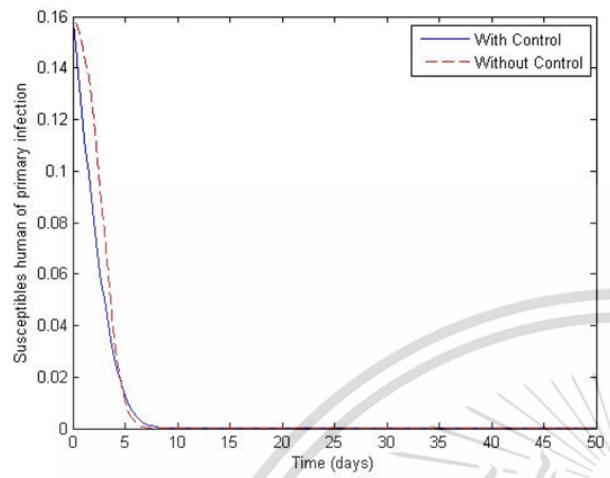
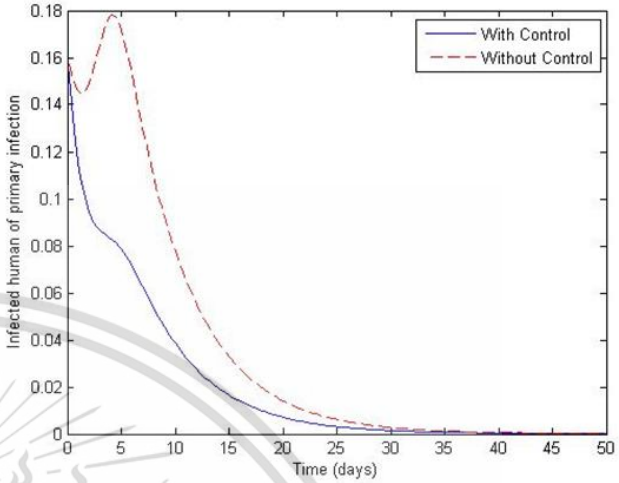


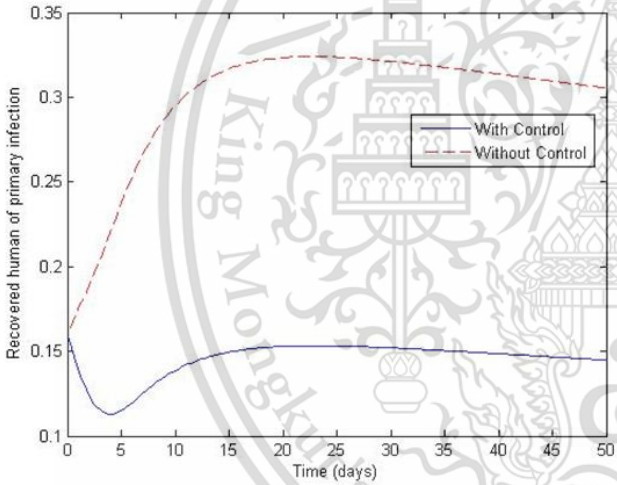
Figure 5.11 Simulation results of system of Equations (5.44)-(5.49) with and without controls of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}$, and I_V. Using $X_1 = 50, X_2 = 100$.



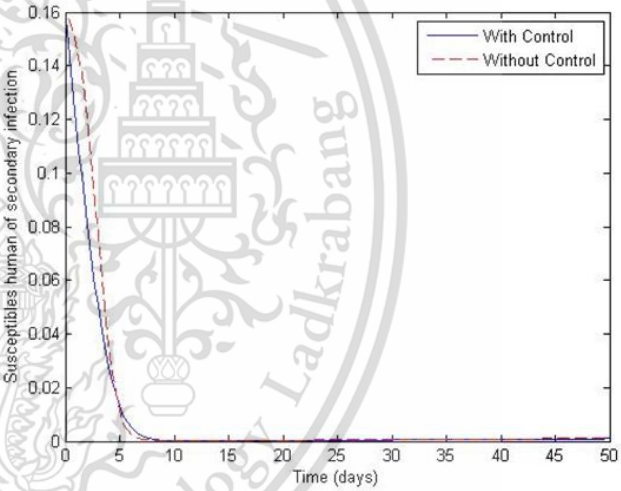
(a)



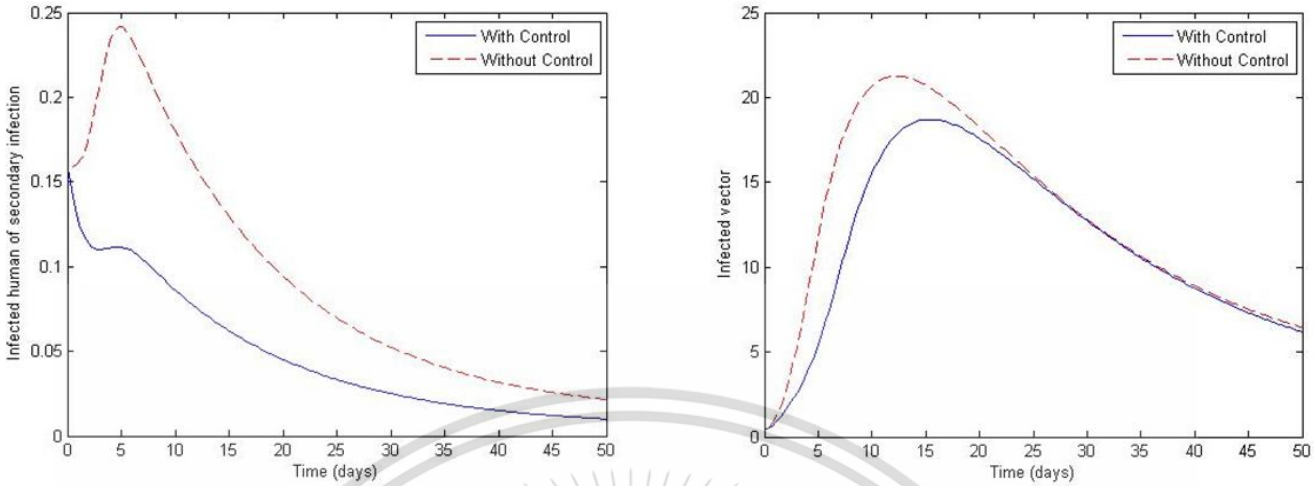
(b)



(c)

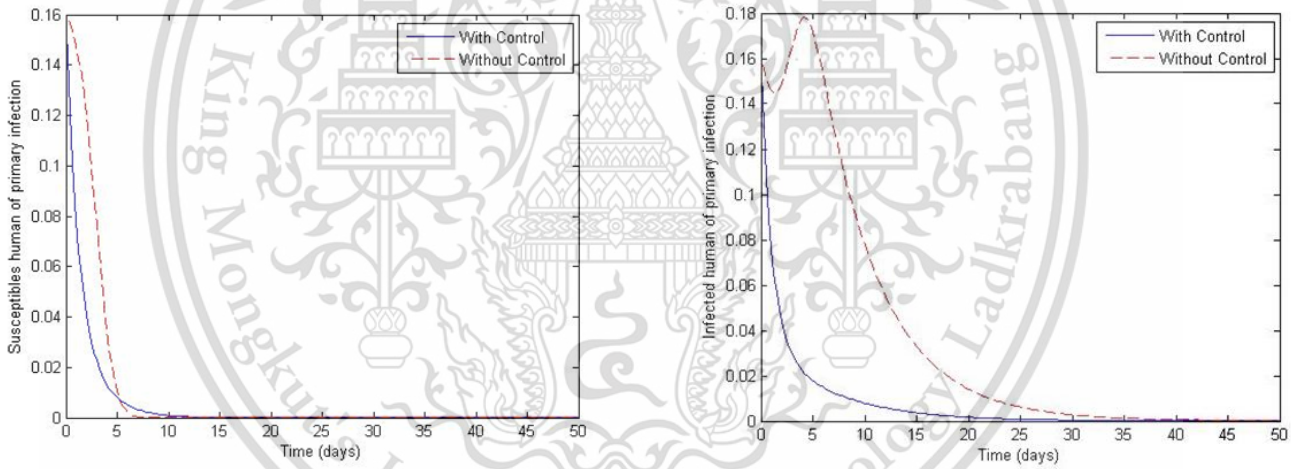


(d)



(e) (f)

Figure 5.12 Simulation results of system of Equations (5.44)-(5.49) with and without controls of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}$, and I_V. Using $X_1 = 0.00001$, $X_2 = 100$.



(a) (b)

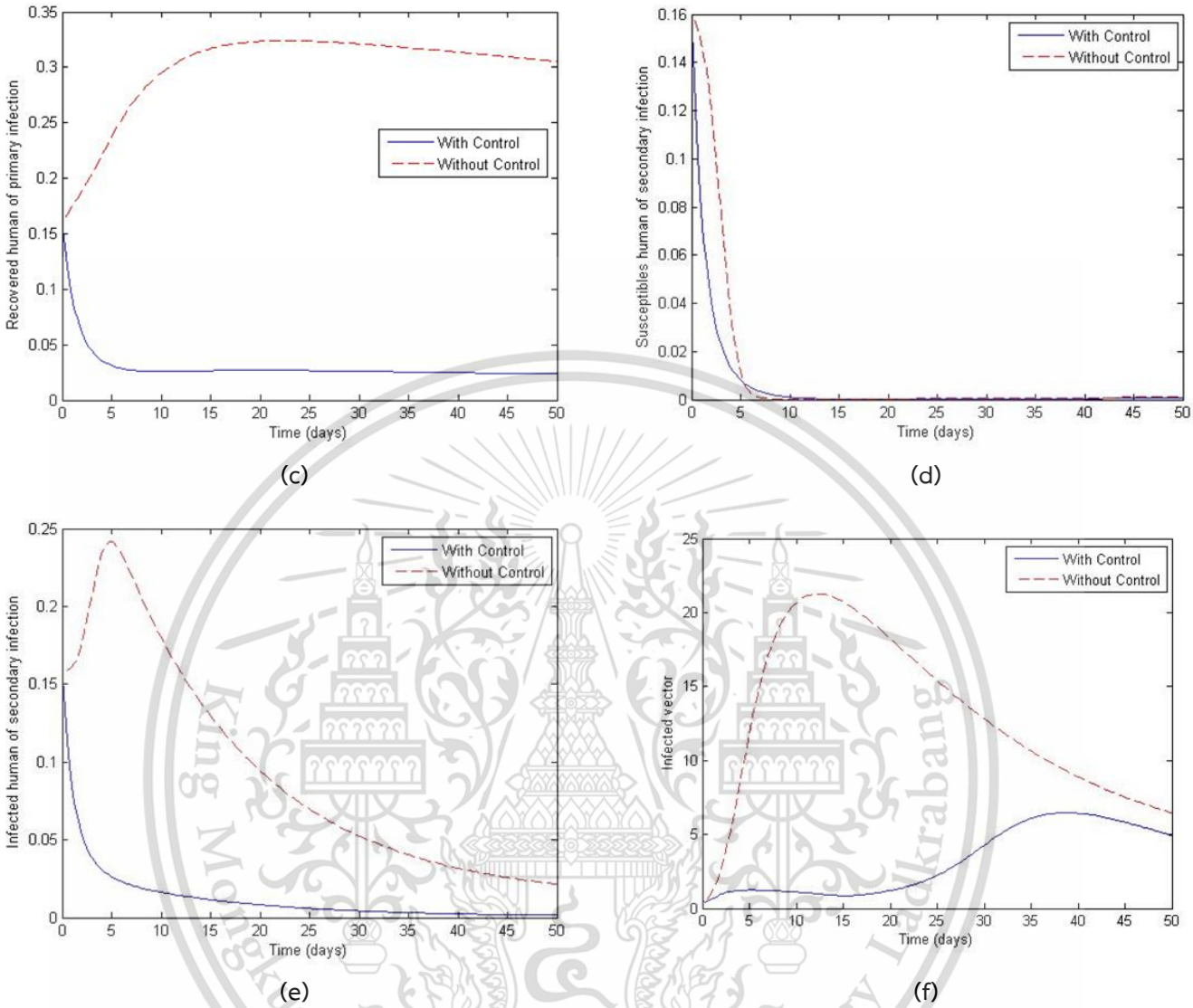
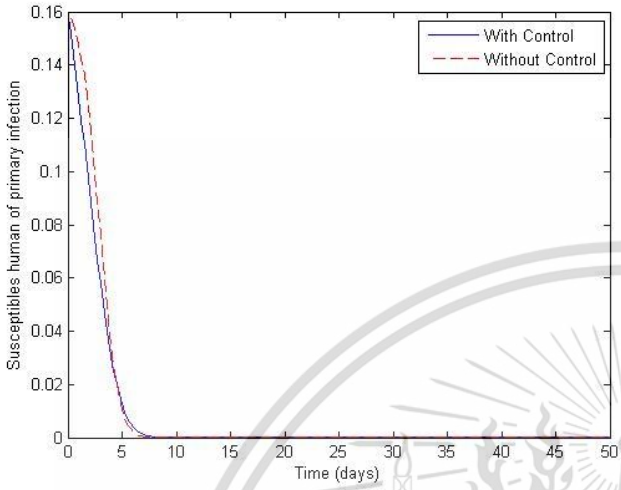
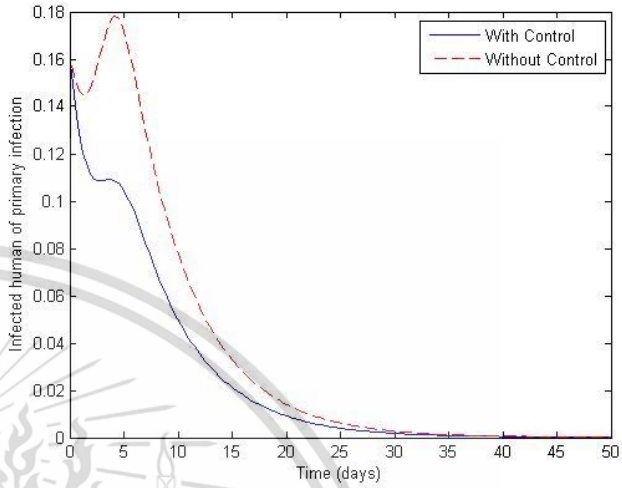


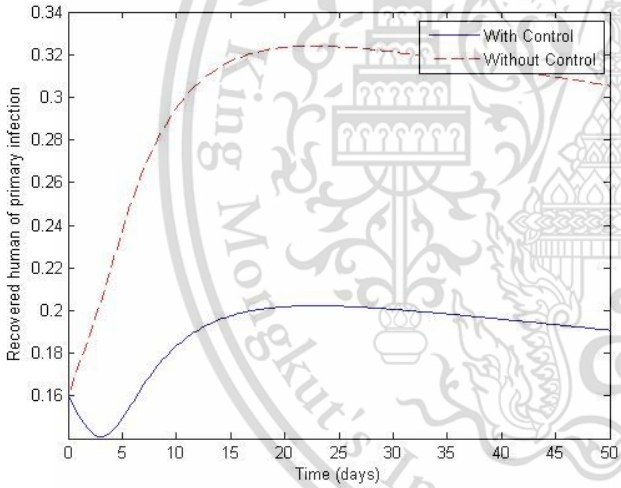
Figure 5.13 Simulation results of system of Equations (5.44)–(5.49) with and without controls of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}$, and I_V. Using $X_1 = 100,\ X_2 = 50$.



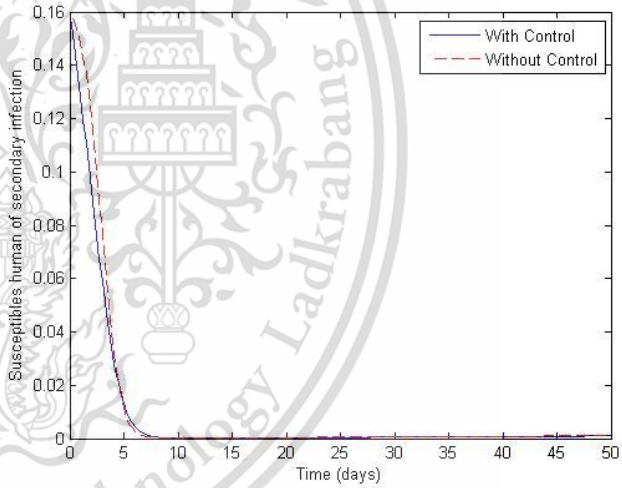
(a)



(b)



(c)



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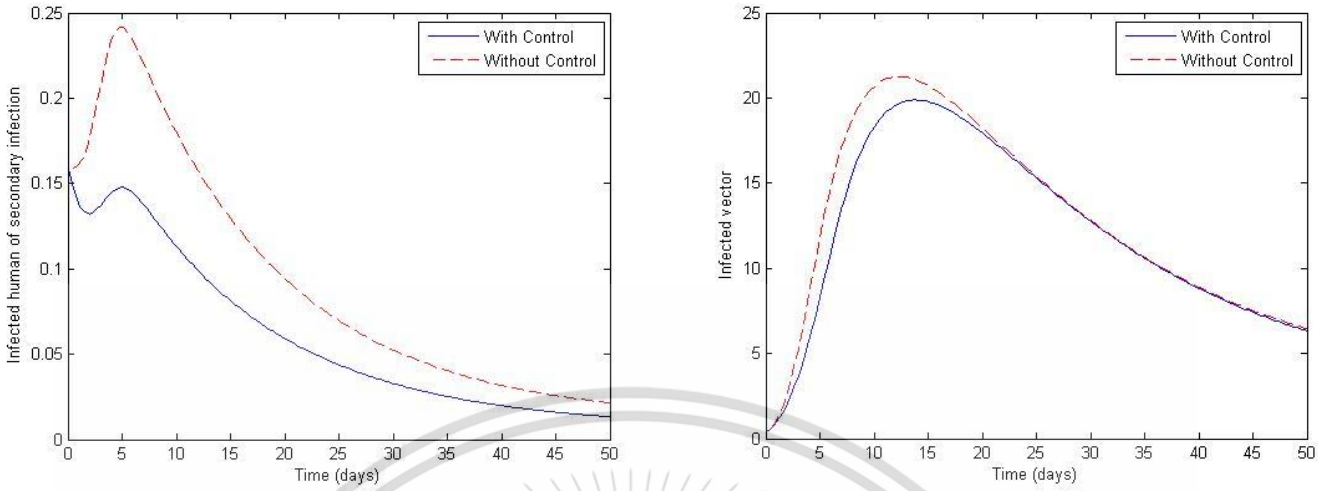
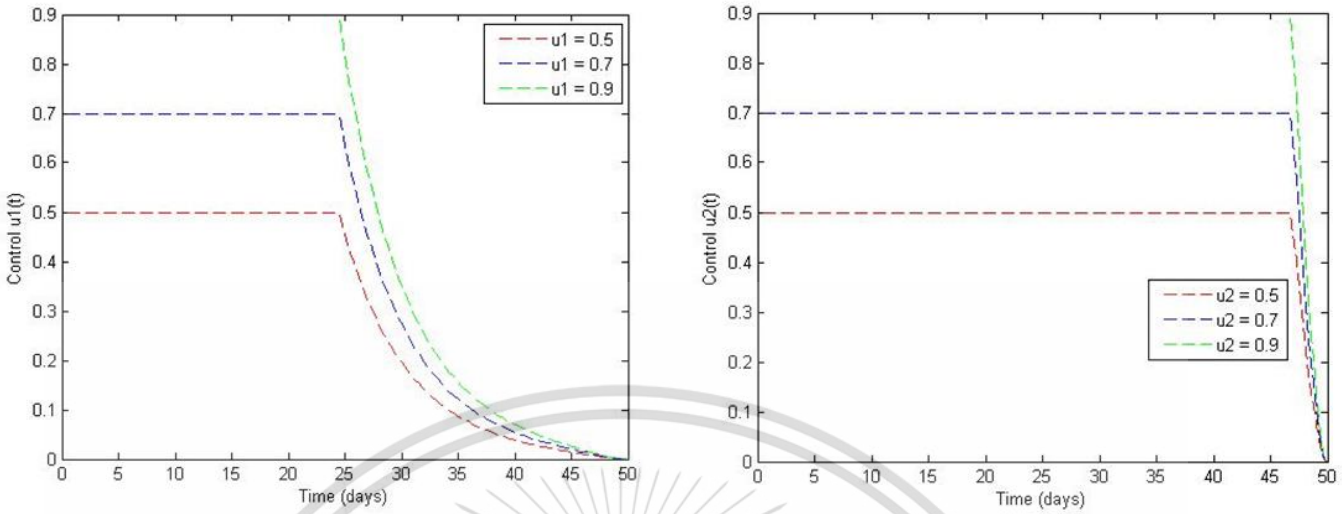


(e) (f)

Figure 5.14 Simulation results of system of Equations (5.44)–(5.49) with and without controls of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}$, and I_V. Using $X_1 = 100,\ X_2 = 0.00001$.

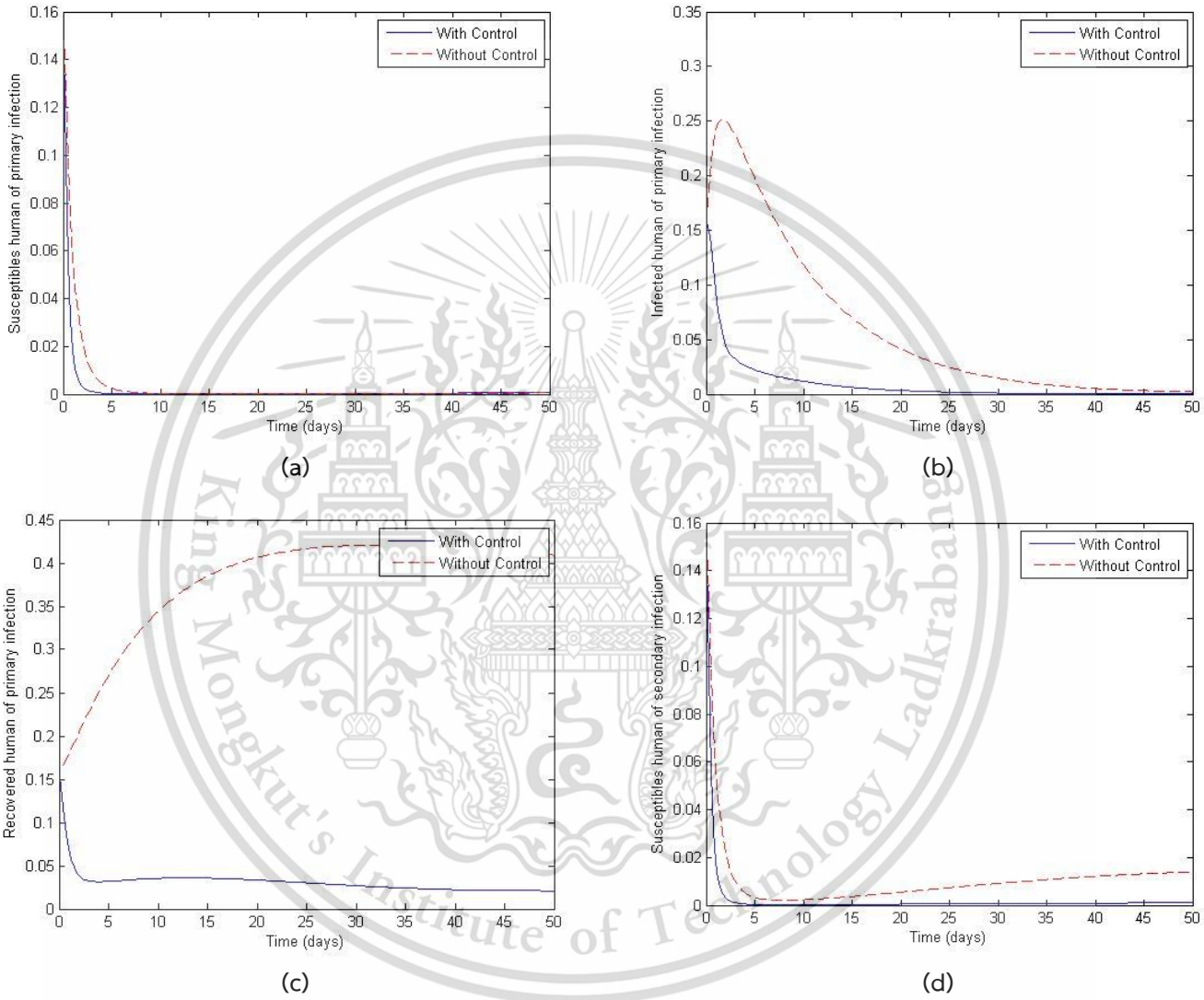
Figure 5.15 **(a)** The vaccination rate $u_1(t)$ and **(b)** The *Aegypti* breeding destroying rate $u_2(t)$, Figure 5.15(a) shows that to maintain the optimal control of the infected population, $u_1(t)$ would have to be at 50%, 70%, and 90% for the first 25 days, after which the control required will show an exponential decline to zero. Figure 5.15(b) 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.

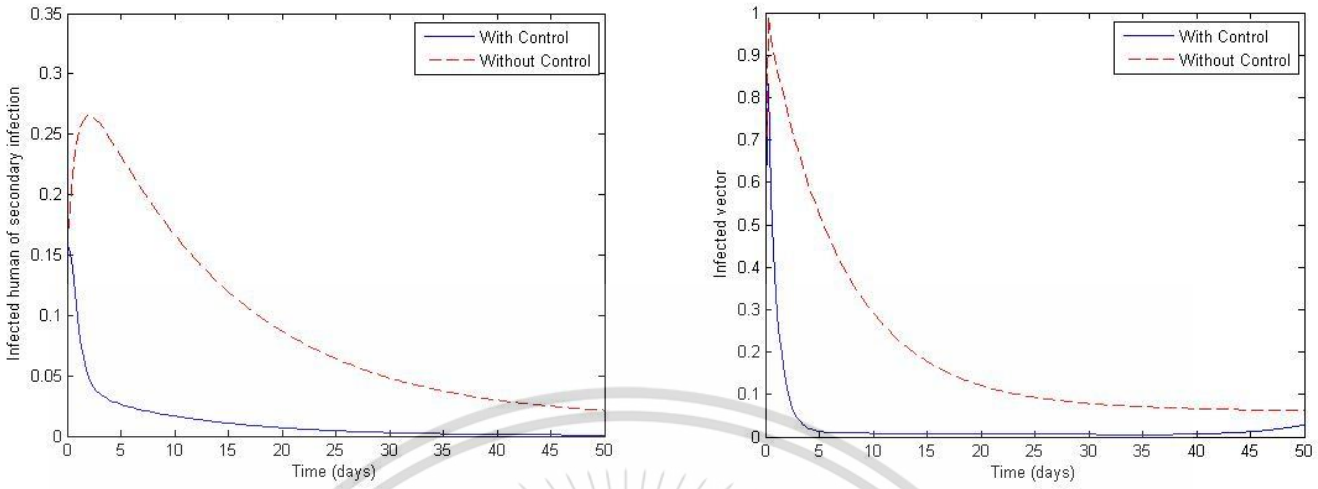


(a) (b)

Figure 5.15 Simulation results of the control using $X_1 = 100,\ X_2 = 100.$

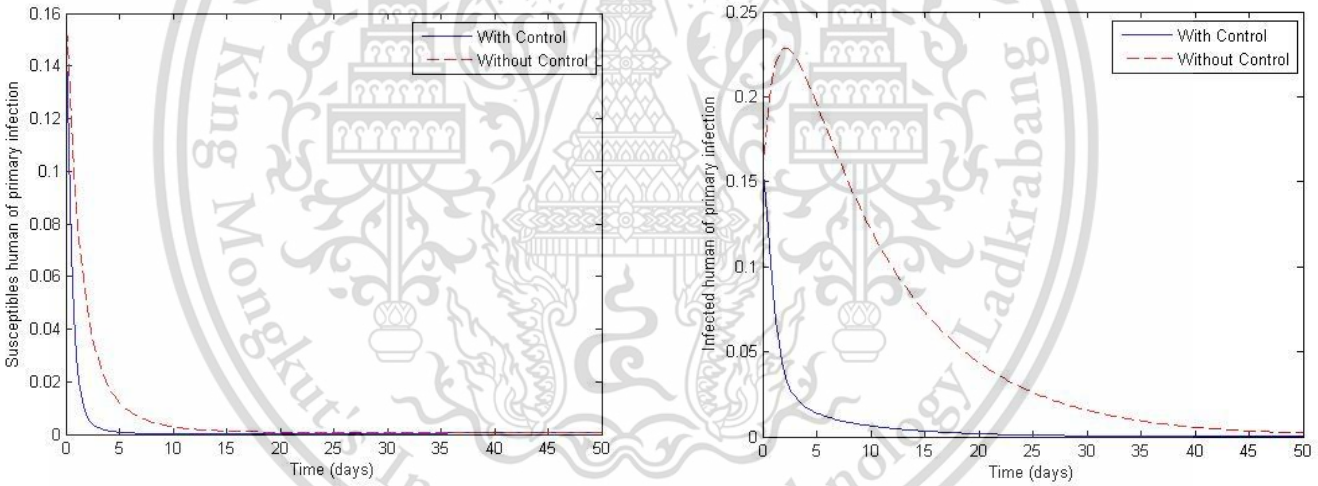
Figures 5.16-5.17, **(a)** Susceptible of primary infection **(b)** Infected population with primary infection **(c)** Recovered human of primary infection **(d)** Susceptible of secondary infection **(e)** Infected human of secondary infection **(f)** Infected vector, now plot the cases of $N_H = 500,000$ and $N_V = 100,000$ and of $N_H = 500,000$ and $N_V = 100,000e^{(-1/14)t}$. The later values which again 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 5.16 to Figure 5.17, which is to be expected since the total number of vector population is slowly decayed as a function of time.





(e) (f)

Figure 5.16 Simulation results of system with and without controls of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}$, and I_V. Using $X_1 = 100,\ X_2 = 100,\ N_H = 500000,\ N_V = 100000.$



(a) (b)

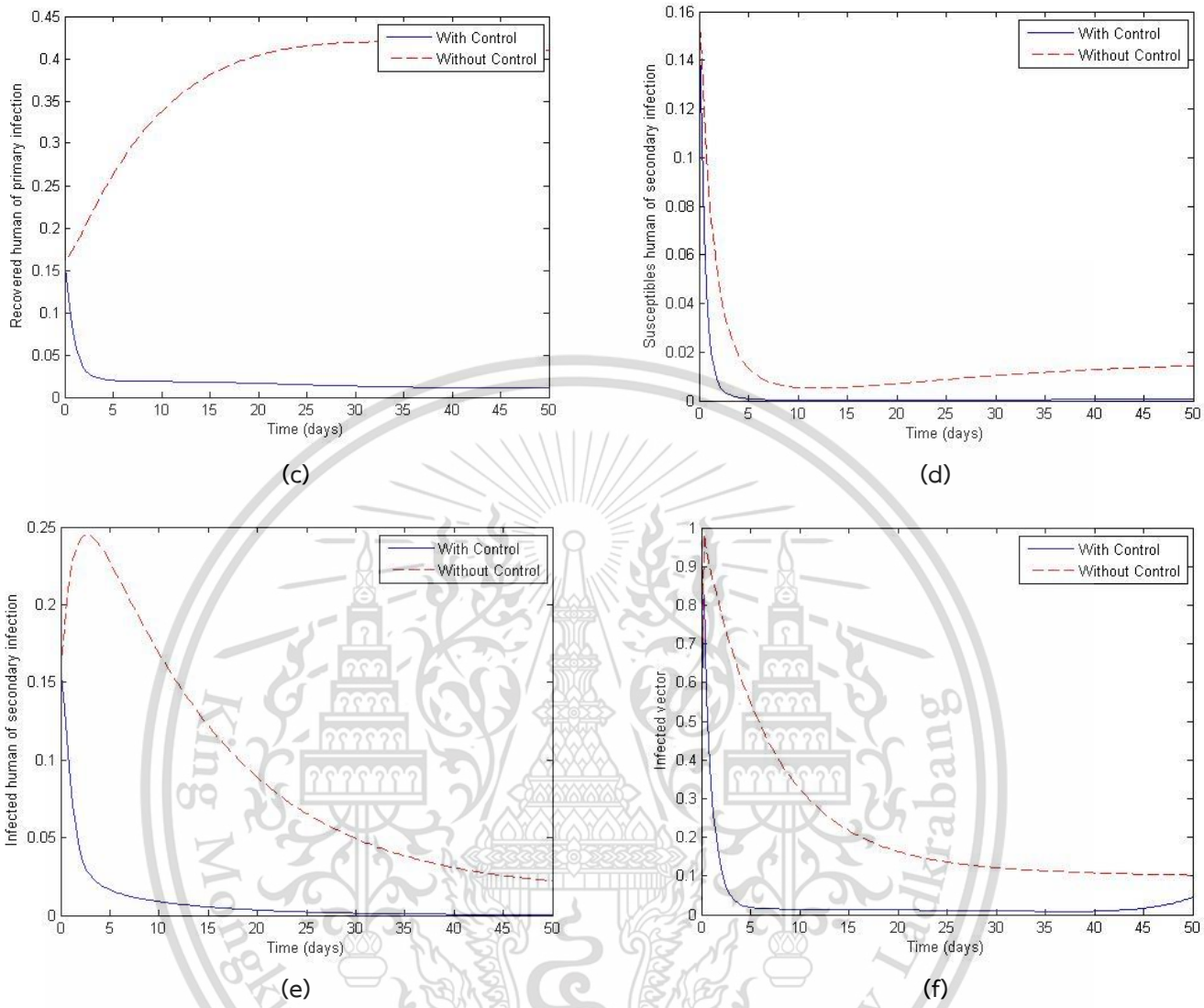


Figure 5.17 Simulation results of system with and without controls of $S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS}$, and I_V. Using $X_1 = 100,\ X_2 = 100,\ N_H = 500000,\ N_V = 100000e^{(-1/14)t}$.

5.5 Discussion and Conclusions

In this chapter, we have 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 is based on the use of the Routh-Hurwitz criteria to establish the local asymptotically stability. The equilibrium point that we found are disease-free converge to $E_1 = (1,0,0,0,0,0)$ and endemic equilibrium point. The basic reproductive number is defined as R_0. If R_0 is less than one then the disease-free state exits and is local asymptotically stable and unstable when R_0 is greater than one. We

simulate the numerical solution of the parameters with different values which is shown in Figure 5.6 We can see that if the transmission rate of dengue virus from vector to the human β_H is large, the slower the convergence to an equilibrium point of susceptible human of primary and secondary infection becomes. The recovered human of primary infection, infected human of primary and secondary infection, and infected vector will converge to an equilibrium point more rapidly. Likewise, in Figure 5.7, we see if the transmission rate of the dengue virus from human to vector β_V is large, the slower the convergence to an equilibrium point of the susceptible humans becomes. Similarly, recovered human of primary infection, infected human of primary and secondary infection, and infected human will converge to an equilibrium point more quickly, i.e., $E_2\left(S_{HP}=0.00003, I_{HP}=0.00022, R_{HP}=0.00810, S_{HS}=0.00002, I_{HS}=0.00031\right).$ However, the infected vector will converges to a different equilibrium point. In addition, this will also make the basic reproductive number R_0 greater than one. Changing N_V to a different value which affects the convergence time for reaching the equilibrium point as shown in Figures 5.8-5.9. 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 larges N_V of 100,000. The second case kept N_H the same, whilst the N_V being treated as an exponential function of time. Results show that although having a non-constant N_V does have some effect on the trajectories, such change will be quite small compared to the constant vector population case.

We have 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 the infected human population of primary and secondary infection to the cost of controlling the epidemic. 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 infected human population of primary and secondary infection will increase. 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 5.10-5.17.

Chapter 6

Stability Analysis of Dengue Disease with Vaccination and Optimal Control

This chapter research presents optimal control which studies the vaccination only in individuals with a documented past dengue infection (seropositive), regardless of the serotypes of infection causing the initial infection by the disease. The analysis of dengue transmission model is used to establish the local asymptotically stabilities. The property of symmetry in the Lyapunov function an import role in achieving this global asymptotically stabilities. The optimal control systems are shown in numerical solutions and conclusions. The result shows that the control resulted in a significant reduction in the number of infected humans and infected vectors.

6.1 Introduction

Mosquito-borne dengue fever viral disease infects hundreds of millions of people in tropical and subtropical areas every year [72]. Thailand has reported outbreaks of dengue fever for more than 60 years. At present, dengue fever has spread throughout the country, every province, and every districts [73]. Dengue hemorrhagic fever is contagious with the *Aedes aegypti* mosquito being an important disease-carrying insect in many rural areas. The *Aedes albopictus* is a second disease-carrying mosquito. The four virus serotypes that cause dengue virus (DENV) are DENV-1, DENV-2, DENV-3, and DENV-4 [1,74,75]. In Thailand, the *Aedes aegypti* mosquito is considered to be the primary vector of the dengue virus. Infection with dengue serotype provides lifelong immunity to that serotype and will have cross-protection against other species heterotypic immunity for a short period of time [23,76]. The clinical symptoms of dengue virus infection range from being asymptomatic to severe illness that can lead to death if not properly treated. In most cases involving young children, there is a mild fever with a red rash and the child is said to be suffering from blood fever. In older children teenagers and adults, the symptoms may be worse, i.e., they may come down with high fevers, thrombocytopenia, leukopenia, rashes, myalgia, and arthralgia. Dengue fever (DF) is more common in children under 15 years of age. In areas in which hyperemia is also occurring, there may be recurrent dengue infections during which the more severe symptoms are occurring and the patients may be suffering from Dengue Hemorrhagic Fever (DHF). If the plasma leakage becomes extremely severe, the illness develops into Dengue Shock Syndrome (DSS) [12,13,50] and the patient might die.

The incidence of dengue fever infection appears to be age dependent. Pongsumpun and Tang [77] reported that in one province in Thailand in 1998, mentioned that most of the cases occurred in children below the age of 15. Sriprom et al. [78] mentioned that this did not change much. What changed over time was the dengue strain responsible for the infection, very few of the dengue infections were due to DENV-4. In the last few years, the greatest number of infections is caused by the DENV-4 strain. We have not taken this change into account. Most infections caused by the dengue virus and other viruses lead are either asymptomatic or minimally symptomatic with no way to tell whether the patients were infected or not. Burke et al. [79] reported that 87 % of the tested infected children in Bangkok Thailand in 1980-1981 belong to these two groups. We do not expect much had changed over the years except for the strain of the dengue virus.

A vaccine to prevent dengue fever has recently being developed. The vaccine efficacy of the dengue vaccine was moderate 56.5%, meaning it could prevent more than half the number of dengue infections. The dengue vaccine reductions in hospital admissions by 80.3% [22], and 67.2% [20]. The CYD-TDV vaccine is highly effective among children with serological evidence of prior DENV infection. A phase 3 study of dengue vaccine found that dengue vaccine was able to reduce the severity of the disease by 88.5% and prevent dengue by 90.0% [80]. A cautionary note should be mentioned, there is an increased risk of hospitalization of the vaccinated individual among groups without prior infections. Mass vaccination with the CYD-TDV vaccine should not be done in countries that do not have a history of dengue infections by most of the strains of the DENV. This is why the vaccination programs involving this vaccine have been stopped in countries such as Thailand, where there is a prior history of infections by multiple strains of the DENV's.

The chimeric yellow fever dengue virus tetravalent dengue vaccine (CYD-TDV) covers 4 serotypes of dengue. The Dengue vaccination program requires a total of 3 injections, 6 months apart are 0, 6, and 12 months. The optimal age for injection is over 9 years [41]. A single dose of dengue vaccination is as effective as the three-dose vaccination program. This may be due to the fact that 79% of the cohort in the study had dengue seropositivity at baseline in countries with dengue-endemic areas [81]. The immunization obtained from vaccination gradually loses as time goes on. Once infected with any serotypes, the body will always be immune to that serotypes. However, they are temporarily immune to other serotypes, thus there is a chance of re-infecting dengue in other serotypes until all are complete.

The World Health Organization (WHO) aims to reduce the mortality and morbidity of dengue by at least 50% and 25%, respectively, by 2020 [82]. Esteva and Vargus [83]

studied local stability and global stability of models with the Susceptible-Infected-Recovery (SIR) model of dengue transmission and assumed that the human population and the vector population are constant. Chanprasopchai et al. [8] studied dengue fever and the effect of vaccination with analyzed of stable conditions of an equilibrium point of the model using Routh-Hurwitz criteria. A mathematical model of dengue with and without awareness in the host population [30] assumes that some hosts do not interact with infected mosquitoes. This is because they take different preventive measures due to their perception of the disease. Wu and Wong [66] studied the mathematical model with two delays to reflect the extrinsic and intrinsic incubation periods of virus in the dengue disease transmission model. The stability analysis of two equilibrium points is carried out and a simulation is given for different parameter settings and to simulate the succession of two epidemics with variable human populations [84]. Khan and Fatmawati [9] described changes in dengue infection from basic reproductive values which defines a model with hospitalization and presents the changes in detail. The results suggest that spraying insecticides on mosquitoes can significantly reduce dengue infection. Pongsumpun et al. [10] studied a mathematical model of the dengue model with a vertical transmission control mechanism based on the dengue model. The two policy control models were insecticide and vaccinations which simulated the parameters affecting this model control. The authors [85] study a dynamic basic mathematical model for dengue transmission in Thailand, by including infection of different serotypes to analyze the effects of different vaccination strategies. With an interest in the optimal control between primary and secondary infection. There are many studies about applying to solve the optimal control problem of dengue fever [63,71,86-88].

In Thailand, data dengue hemorrhagic fever (DHF) from the department of disease control the ministry of health. It is seen that dengue hemorrhagic fever is prevalent in 2013 per 100,000 which is the highest and the number of morbidities will trend fluctuated each year from 2003 to 2020. Likewise, when the number of mortality direct variation with the number of morbidities, but this is a very small percentage compared to the infected as shown in Figure 6.1.

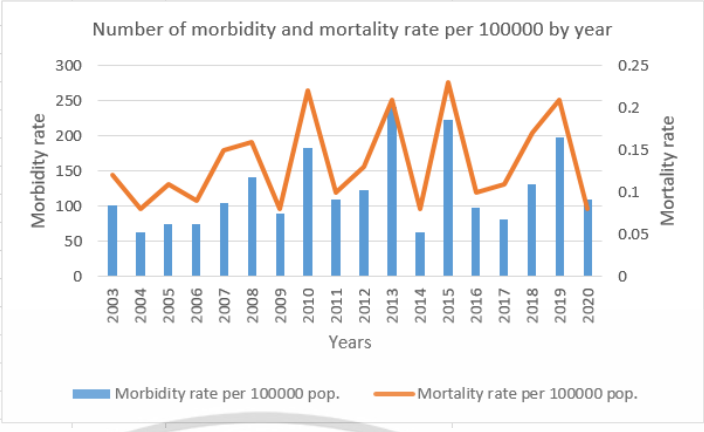


Figure 6.1 The number of morbidity and mortality rate per 100,000 by year from 2003-2020 [64].

In this chapter, we study the vaccination only in individuals with a documented past dengue infection (seropositive), regardless of the serotypes of infection, with a simplified model. This model focused on the population of Thailand for the provinces with high morbidity rates, such as Mae Hong Son, Rayong, Nakhon Ratchasima, Chaiyaphum, Chainat, and the regions with the highest morbidity rates were the Northeast, North, Central, Southern regions, respectively, where there were outbreaks of dengue hemorrhagic fever, resulting in people who have been infected with dengue fever being re-infected. The human population is modeled through the SEIRS framework, and the vector population is modeled using the SI model. Local and global stability analyses are given with the basic reproduction number being the bifurcation point. The property of symmetry in the Lyapunov function an important role in achieving this global asymptotically stabilities. The optimal control is applied in the spreading model to minimize the number of infected human and infected vector populations. The results are then given numerically to demonstrate the analyses.

6.2 Materials and Methods

6.2.1 Mathematical Model

The mathematical model of the dengue transmission is for the vector population and the human population. The Susceptible-Infected (SI) and Susceptible-Exposed-Infected-Recovered (SEIRS) model for vector and human population respectively. In Thailand, some regions are densely populated with a high prevalence of *Aedes* mosquitoes. This model of dengue outbreak considers vaccination only in previously infected populations as it reduces the severity of the disease and reduces the rate of hospitalization for the next infection. Note that dengue fever has four different serotypes,

and we can get infected up to four times. Vaccination should be administered after each injection to minimize the risk of hospitalization and the severity of the disease in following infections. Once infected with any dengue serotype, the person is immune to that serotype for life and only has a short period of time of cross-protection against other species, as advised by the World Health Organization. In this model, the transmission of the dengue virus when vaccinated after each infection is described. The human and vector population is divided into four and two individuals respectively. The variables and parameters are defined listed in Table 6.1. The dynamic dengue fever model with vaccination after each infectious is shown in Figure 6.2.

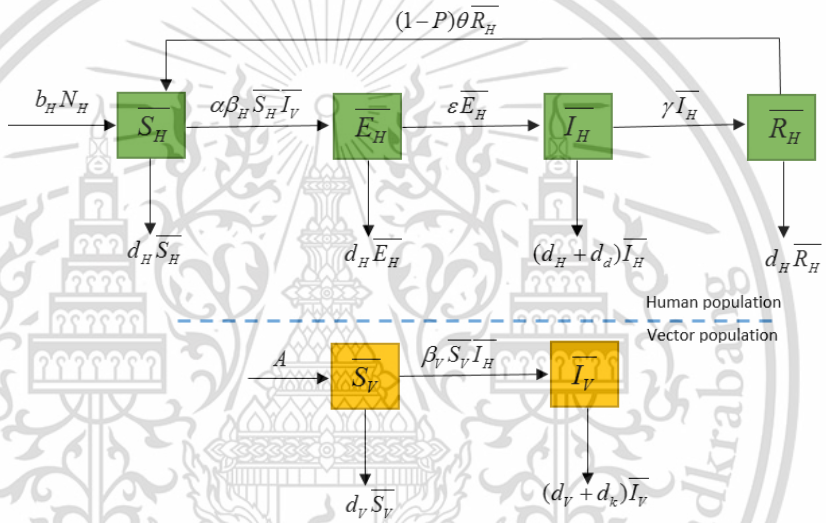


Figure 6.2 Schematic diagram representation compartments vector and human population after each infectious dengue fever.

The dynamics behavior model of human and vector population is encapsulated in the following systems of differential equations:

$$\frac{d\overline{S_H}}{dt} = b_H N_H + (1-P)\theta\overline{R_H} - \alpha\beta_H\overline{S_H}\overline{I_V} - d_H\overline{S_H}, \tag{6.1}$$

$$\frac{d\overline{E_H}}{dt} = \alpha\beta_H\overline{S_H}\overline{I_V} - \varepsilon\overline{E_H} - d_H\overline{E_H}, \tag{6.2}$$

$$\frac{d\overline{I_H}}{dt} = \varepsilon\overline{E_H} - \gamma\overline{I_H} - (d_H + d_d)\overline{I_H}, \tag{6.3}$$

$$\frac{d\overline{R_H}}{dt} = \gamma\overline{I_H} - (1-P)\theta\overline{R_H} - d_H\overline{R_H}, \tag{6.4}$$

$$\frac{d\overline{S_V}}{dt} = A - \beta_V \overline{S_V}\,\overline{I_H} - d_V \overline{S_V}, \tag{6.5}$$

$$\frac{d\overline{I_V}}{dt} = \beta_V \overline{S_V}\,\overline{I_H} - (d_V + d_k)\overline{I_V}. \tag{6.6}$$

With the conditions

$$\overline{S_H} + \overline{E_H} + \overline{I_H} + \overline{R_H} = N_H, \tag{6.7}$$

$$\overline{S_V} + \overline{I_V} = N_V. \tag{6.8}$$

Table 6.1 The parameters used in the numerical simulation.

Variables and parameters	Biological meaning
$\overline{S_H}$	The number of susceptible human population
$\overline{S_V}$	The number of susceptible vector population
$\overline{E_H}$	The number of exposed human population
$\overline{I_H}$	The number of infected human population
$\overline{I_V}$	The number of infected vector population
$\overline{R_H}$	The number of recovered vector population
P	The vaccine efficiency
β_H	The transmission rate of dengue virus from vector to the human
β_V	The transmission rate of dengue virus from the human to vector
α	The biting rate of vector population
θ	The recurrent infection rate
ε	The incubation rate
γ	The recovery rate
A	The constant recruitment rate
d_H	The natural mortality rate of the human population
d_d	The mortality rate from infection of the human population
d_V	The natural mortality rate of the vector population
d_k	The mortality rate from infection of the vector population
b_H	The birth rate
N_H	The total number of the human population
N_V	The total number of the vector population

The rate of change of the total population of human and vector are:

$$\frac{d\overline{S_H}}{dt}+\frac{d\overline{E_H}}{dt}+\frac{d\overline{I_H}}{dt}+\frac{d\overline{R_H}}{dt}=0, \tag{6.9}$$

$$\frac{d\overline{S_V}}{dt}+\frac{d\overline{I_V}}{dt}=0. \tag{6.10}$$

The conditions of Equations (6.7) and (6.8) employ:

$$\overline{I_H}=\frac{(b_H-d_H)N_H}{d_d}, \tag{6.11}$$

$$\overline{I_V}=\frac{A-d_V N_V}{d_k}. \tag{6.12}$$

Normalizing the equations with assuming the proportion number of the individual following as:

$$S_H=\frac{\overline{S_H}}{N_H},\ E_H=\frac{\overline{E_H}}{N_H},\ I_H=\frac{\overline{I_H}}{N_H},R_H=\frac{\overline{R_H}}{N_H}, \tag{6.13}$$

$$S_V=\frac{\overline{S_V}}{N_V},\ I_V=\frac{\overline{I_V}}{N_V}. \tag{6.14}$$

We also have

$$S_H+E_H+I_H+R_H=1, \tag{6.15}$$

$$S_V+I_V=1. \tag{6.16}$$

The normalized system of equations are:

$$\left.\begin{aligned}
\frac{dS_H}{dt}&=b_H+(1-P)(1-S_H-E_H-I_H)\theta-\alpha\beta_H S_H I_V N_V-d_H S_H\\
\frac{dE_H}{dt}&=\alpha\beta_H S_H I_V N_V-\varepsilon E_H-d_H E_H\\
\frac{dI_H}{dt}&=\varepsilon E_H-\gamma I_H-(d_H+d_d)I_H\\
\frac{dI_V}{dt}&=\beta_V(1-I_V)I_H N_H-(d_V+d_k)I_V
\end{aligned}\right\}. \tag{6.17}$$

Proposition 6.1 [89] Let $\left(S_H(t),E_H(t),I_H(t),R_H(t),S_V(t),I_V(t)\right)$ be the solution of Equations (6.1)-(6.6) with positive initial conditions $S_H(0),E_H(0),I_H(0),R_H(0),S_V(0),I_V(0)$. Denoting also invariant set $\phi=\left\{(S_H,E_H,I_H,R_H,S_V,I_V)\in\mathbb{R}_+^6 : N_H\le\frac{b_H}{d_H},N_V\le\frac{A}{d_V}\right\}$ then the closed set ϕ is positive invariant that attracts all solutions in the space $\mathbb{R}_+^6$.

Proof. We begin by setting

$$N_T(t) = \left(N_H(t), N_V(t)\right) = \left(S_H + E_H + I_H + R_H, S_V + I_V\right).$$

The differentiation yields:

$$\frac{dN_T(t)}{dt} = \left(\frac{dN_H(t)}{dt}, \frac{dN_V(t)}{dt}\right),$$

$$= \left(b_H - d_H S_H - d_H E_H - d_H I_H - d_d I_H - d_H R_H, \mathrm{A} - d_V S_V - d_V I_V - d_k I_V\right),$$

$$= \left(b_H - d_H N_H - d_d I_H, A - d_V N_V - d_k I_V\right),$$

$$\leq \left(b_H - d_H N_H, A - d_V N_V\right).$$

Hence, $\frac{dN_H(t)}{dt} = b_H - d_H N_H \leq 0$ for $N_H(t) \geq \frac{b_H}{d_H}$, and $\frac{dN_V(t)}{dt} = A - d_V N_V \leq 0$ for $N_V(t) \geq \frac{A}{d_V}$. Then $\frac{dN_T(t)}{dt} \leq 0$ wherever $N_H(t) \geq \frac{b_H}{d_H}$, and $N_V(t) \geq \frac{A}{d_V}$.

Integrating the above equation, it follows that $\frac{dN_T(t)}{dt} \leq 0$ on

$$0 \leq N_H(t), N_V(t) \leq \left(\frac{b_H}{d_H} + N_H(0)\mathrm{e}^{-d_H t}, \frac{A}{d_V} + N_V(0)\mathrm{e}^{-d_V t}\right).$$

As $t \to \infty, e^{-d_H t} \to 0, e^{-d_V t} \to 0,$ and then $0 \leq N_H(t), N_V(t) \leq \left(\frac{b_H}{d_H}, \frac{A}{d_V}\right)$.

Since the epidemiological parameters are assumed to be positive, it follows that the region of all solutions of ϕ will be in $\mathbb{R}^6_+$. Thus ϕ is a positively invariant set. Note that all equations described by Equations (6.1)-(6.6) in the non-negative octant $\mathbb{R}^6_+$ are positively invariant [67,89,90]. □

6.2.2 The Equilibrium Points

Let us find equilibrium points of system Equations (6.17) that describe the model. Note that by setting the right-hand side of system Equations (6.17) to zero yields two equilibrium points, namely:

The disease-free equilibrium point:

$$E_1 = (1, 0, 0, 0).$$

The endemic equilibrium point:

$$E_2^* = \left(S_H^*, E_H^*, I_H^*, I_V^*\right),$$

with

$$S_H^* = \frac{\left(\pi_1\pi_2\left(\left(\gamma\varepsilon - \pi_3\theta + \gamma d_H + \left(\varepsilon + \pi_4\right)\pi_5\right)d_K - \left(\gamma\varepsilon - \pi_3\theta + \gamma d_H + \left(\varepsilon + \pi_4\right)\pi_5\right)d_V - \varepsilon\pi_8 N_H\beta_V\right)\right)}{\varepsilon N_H\left(\left(\pi_7 - d_H\right)\pi_1\pi_2 - \alpha\left(\gamma\varepsilon - \pi_3\theta + \gamma d_H + \left(\varepsilon + \pi_4\right)\pi_5\right)N_V\beta_H\right)\beta_V},$$

$$E_H^* = \frac{\pi_2\left(\pi_1\pi_2\pi_4\pi_6 - \alpha\varepsilon\left(\pi_7 - b_H\right)N_H N_V\beta_H\beta_V\right)}{\varepsilon N_H\left(\pi_1\pi_2\pi_4 + \alpha\left(\gamma\varepsilon - \pi_3\theta + \gamma d_H + \left(\varepsilon + \pi_4\right)\pi_5\right)N_V\beta_H\right)\beta_V}, \tag{6.18}$$

$$I_H^* = \frac{\pi_1\pi_2\pi_4\pi_6 - \alpha\varepsilon\left(\pi_7 - b_H\right)N_H N_V\beta_H\beta_V}{N_H\left(\pi_1\pi_2\pi_4 + \alpha\left(\gamma\varepsilon - \pi_3\theta + \gamma d_H + \left(\varepsilon + \pi_4\right)\pi_5\right)N_V\beta_H\right)\beta_V},$$

$$I_V^* = \frac{\left(\pi_7 - d_H\right)\pi_1\pi_2\pi_6 + \alpha\varepsilon\pi_8 N_H N_V\beta_H\beta_V}{\alpha N_V\beta_H\left(\left(\gamma\varepsilon - \pi_3\theta + \gamma d_H + \left(\varepsilon + \pi_4\right)\pi_5\right)\pi_6 + \varepsilon\pi_8 N_H\beta_V\right)},$$

where

$\pi_1 = \left(\varepsilon + d_H\right)$, $\pi_2 = \left(\gamma + d_H + d_d\right)$, $\pi_3 = \left(P-1\right)\left(\gamma + \varepsilon\right)$, $\pi_4 = \left(\theta - P\theta + d_H\right)$,
$\pi_5 = \left(d_H + d_d\right)$, $\pi_6 = \left(d_V + d_k\right)$, $\pi_7 = \left(P-1\right)\theta$, $\pi_8 = \left(\theta - P\theta + b_H\right)$.

6.2.3 The Basic Reproductive Number

The next-generation matrix method of the works in [91,92] is used to compute the basic reproductive number $\left(R_0\right)$ for the dengue model of system Equation (6.17). The classes E_H, I_H, and I_V are identified as influencing the new infections. The F and V matrices are obtained as follows:

$$F = \begin{bmatrix} 0 & 0 & \alpha\beta_H S_H N_V \\ 0 & 0 & 0 \\ 0 & \beta_V S_V N_H & 0 \end{bmatrix}, V = \begin{bmatrix} d_H + \varepsilon & 0 & 0 \\ -\varepsilon & d_H + d_d + \gamma & 0 \\ 0 & 0 & d_V + d_k \end{bmatrix},$$

$$V^{-1} = \begin{bmatrix} \frac{1}{(d_H + \varepsilon)} & 0 & 0 \\ \frac{\varepsilon d_V + \varepsilon d_k}{(\varepsilon + d_H)(\gamma + d_H + d_d)(d_V + d_k)} & \frac{1}{(\gamma + d_H + d_d)} & 0 \\ 0 & 0 & \frac{1}{(d_V + d_k)} \end{bmatrix}.$$

The basic reproductive number is obtained through the spectral radius of the matrix $R_0 = \rho FV^{-1}$ is called the reproductive number and given by

$$R_0 = \sqrt{\frac{\alpha\varepsilon\left(\left(P-1\right)\theta - b_H\right)N_H N_V\beta_H\beta_V}{\left(\left(P-1\right)\theta - d_H\right)(\gamma + d_H + d_d)(\varepsilon + d_H)(d_V + d_k)}}. \tag{6.19}$$

6.2.4 Local stability of equilibrium points

In this section, we are going to analyze the stability condition of two equilibrium points, namely the disease-free E_1 and the endemic E_2 equilibrium points. The outcome of stability condition analysis of these equilibria is shown in the following Theorem 6.1 and Theorem 6.2. The obtained Jacobian matrix is:

$$J_{E_i} = \begin{bmatrix} (P-1)\theta - d_H - \alpha\beta_H I_V N_V & (P-1)\theta & (P-1)\theta & -\alpha\beta_H S_H N_V \\ \alpha\beta_H I_V N_V & -\varepsilon - d_H & 0 & 0 \\ 0 & \varepsilon & -\gamma - d_H - d_d & 0 \\ 0 & 0 & \beta_V N_H - \beta_V N_H I_V & -\beta_V N_H I_H - d_V - d_k \end{bmatrix}. \quad (6.20)$$

Theorem 6.1 If $R_0 < 1$, then the disease-free equilibrium point E_1 of system Equation (6.17) is locally asymptotically stable and unstable otherwise

Proof. The characteristic polynomial of the Jacobian matrix of Equation (6.20) evaluated at the disease-free equilibrium is:

$$\det(J_{E_1} - \lambda I) = 0. \quad (6.21)$$

The eigenvalues (λ) are obtained from the roots of Equation (6.21) where I is identity matrix (4×4) the matrix is:

$$\lambda_1 = -(\varepsilon + d_H),$$
$$\lambda_2 = -((P+1)\theta + d_H),$$
$$\lambda_3 = -(d_H + d_d + \gamma),$$
$$\lambda_4 = -(d_V + d_k).$$

It is obvious that all the eigenvalues have negative real part. So, E_1 is locally asymptotically stable [92]. □

Theorem 6.2 The endemic equilibrium point E_2 is locally asymptotically stable if $R_0 > 1$ and unstable otherwise.

Proof. The characteristic equation of the Jacobian matrix evaluated at the endemic equilibrium is:

$$\det(J_{E_2} - \lambda I) = 0. \quad (6.22)$$

One eigenvalue of the above matrix is $\lambda = -(d_H + d_d + \gamma) < 0$. The rest of the characteristic equation is considered in the form of

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \quad (6.23)$$

where

$$a_1 = \varepsilon + \theta + P\theta + 2d_H + d_k + d_V + \alpha N_V I_V^* \beta_H + N_H I_H^* \beta_V,$$

$$a_2 = d_H^2 + (1-P)\varepsilon\theta + d_V(\varepsilon + \theta - P\theta) + a_{21}(\alpha\varepsilon + \alpha\theta + P\alpha\theta + \alpha\varepsilon\theta + P\alpha\varepsilon\theta + \alpha d_V)$$
$$+ d_k(a_{22}) + N_H I_H^*(a_{22})\beta_V + d_H\left(a_{22} + 2(d_k + d_V + N_H I_H^* \beta_V)\right),$$

$$a_3 = d_k\left(a_{31} - \alpha\left(\varepsilon + (P-1)(\varepsilon-1)\theta + d_H\right)a_{21}\right) + d_V\left(a_{31} - a_{32}\right)$$
$$+ N_H\left(\alpha^2\varepsilon N_V^2 S_H^*\left(I_V^* - 1\right)I_V^*\beta_H^* + I_H^*\left(a_{31} - a_{32}\right)\right)\beta_V,$$

$a_{21} = N_V I_V^* \beta_H, a_{22} = \varepsilon + \theta - P\theta + \alpha,\ a_{31} = \left((P-1)\theta - d_H\right)(\varepsilon + d_H),$
$a_{32} = \alpha\left(\varepsilon + (P-1)(\varepsilon-1)\theta + d_H\right)a_{21},$ $S_H^*, I_H^*,$ and I_V^* are defined Equation (6.18). By using Routh-Hurwitz criteria [89,91,92] for $n = 3$, then E_2 is stable if conditions $(i) - (iv)$ are satisfied. Since algebraic proofs may be a little difficult to verify these conditions, we then resort to numerical simulations. We plot the values of the conditions against the changes in β_H, which is shown in Figure 6.3. It is seen that these conditions are indeed satisfied

$$(i)\ a_1 > 0,$$
$$(ii)\ a_2 > 0,$$
$$(iii)\ a_3 > 0,$$
$$(iv)\ a_1 a_2 - a_3 > 0.$$

It then follows that the polynomial of Equation (6.23) will indeed be Hurwitz, which thus implies the stability of the endemic equilibrium E_2. □

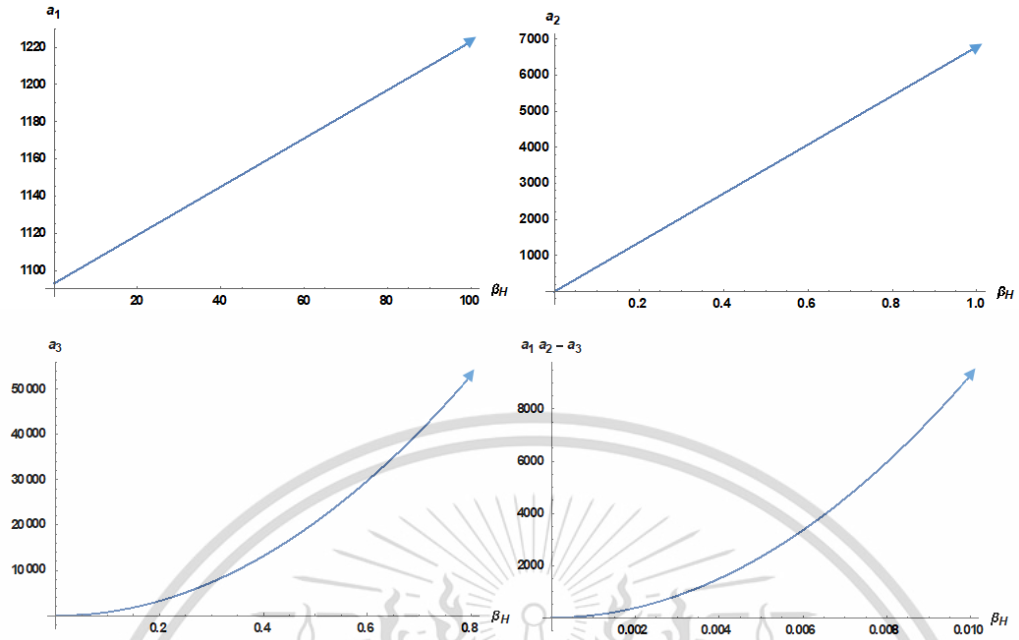


Figure 6.3 The Routh-Hurwitz criteria conditions satisfied for the endemic equilibrium point.

6.2.5 Global stability of equilibrium points

The global stability of each equilibrium point of the model in system Equation (6.17) is investigated in this section. To serve this purpose, we hereby derive two theorems.

Theorem 6.3 Let $E_1^* = (S_H^*, E_H^*, I_H^*, S_H^*, I_V^*) = (1,0,0,0)$ the disease-free E_1^* is globally asymptotically stable on ϕ if and only if $R_0 < 1$ where ϕ are defined as Proposition 6.1.

Proof. Consider the following Lyapunov function candidate [93-96]:

$$\omega_3(S_H, E_H, I_H, I_V) = \left(S_H - S_H^* \ln S_H\right) + E_H + I_H + I_V.$$

This function satisfies the positive definiteness condition as required for a Lyapunov function since the positive invariances. It should provide ease in the proving of the negative definiteness in its time derivative, as compared to say a quadratic candidate, which is more prominently used as one such candidate.

The derivative with respect to time yields:

$$\frac{d\omega_3}{dt} = \left(1 - \frac{S_H^*}{S_H}\right)\frac{dS_H}{dt} + \frac{dE_H}{dt} + \frac{dI_H}{dt} + \frac{dI_V}{dt},$$

$$= \left(1-\frac{S_H^*}{S_H}\right)\left(b_H + (1-P)(1-S_H-E_H-I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H\right)$$
$$+\left(\alpha\beta_H S_H I_V N_V - \varepsilon E_H - d_H E_H\right) + \left(\varepsilon E_H - \gamma I_H - (d_H + d_d) I_H\right)$$
$$+\left(\beta_V (1-I_V) I_H N_H - (d_V + d_k) I_V\right),$$

$$= \left(1-\frac{S_H^*}{S_H}\right)\left(b_H + (1-P)(1-S_H-E_H-I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H\right)$$
$$- d_H E_H - (d_H + d_d) I_H + \left(\beta_V (1-I_V) I_H N_H - (d_V + d_k) I_V\right).$$

Substituting the relation of disease-free $E_1^* = (1,0,0,0)$, we get

$$= \left(1-\frac{S_H^*}{S_H}\right)\left(b_H - d_H S_H\right) - d_H E_H - (d_H + d_d) I_H - (d_V + d_k) I_V,$$

$$= \left[d_H\left(1-\frac{S_H}{S_H^*}\right) + b_H\left(1-\frac{S_H^*}{S_H}\right)\right] - d_H E_H - (d_H + d_d) I_H - (d_V + d_k) I_V.$$

From Equation (6.11) at the disease-free, we get $b_H = d_H$ thus

$$= \left[d_H\left(1-\frac{S_H}{S_H^*}\right) + d_H\left(1-\frac{S_H^*}{S_H}\right)\right] - d_H E_H - (d_H + d_d) I_H - (d_V + d_k) I_V,$$

$$= d_H\left(2-\frac{S_H}{S_H^*}-\frac{S_H^*}{S_H}\right) - d_H E_H - (d_H + d_d) I_H - (d_V + d_k) I_V,$$

$$= -d_H\left(\frac{\left(S_H^* - S_H\right)^2}{S_H^* S_H}\right) - d_H E_H - (d_H + d_d) I_H - (d_V + d_k) I_V,$$

$$\frac{d\omega_3}{dt} = -\left[d_H\left(\frac{\left(S_H^* - S_H\right)^2}{S_H^* S_H}\right) + d_H E_H + (d_H + d_d) I_H + (d_V + d_k) I_V\right]. \qquad (6.24)$$

As can be seen, all of the terms in Equation (6.24) are always negative. Now, using LaSalle's invariance principle [93], we have $\frac{d\omega_3}{dt} \le 0$ and so the function $\frac{d\omega_3}{dt}$ is to be negative definite. Each solution's limit set is included in the biggest invariant set for which $S_H = S_H^*, E_H = 0, I_H = 0,$ and $I_V = 0$ which is the singleton $\{E_1^*\}$. The disease-free equilibrium point E_1^* is then globally asymptotically stable on ϕ according to LaSalle's invariant principle. □

Theorem 6.4 When $R_0 > 1$, the endemic equilibrium point E_2^* is defined as Equation (6.18). Then Equation (6.18) is globally asymptotically stable on ϕ if and only if

$$\begin{cases} b_H = d_H S_H, \\ I_V = \dfrac{\beta_V I_H N_H}{\beta_V I_H N_H + d_V + d_k}. \end{cases} \tag{6.25}$$

Proof. The Lyapunov function is in the form:

$$\zeta_3(\mathrm{S}_H, E_H, I_H, I_V) = (S_H - S_H^* \ln S_H) + E_H + I_H + I_V.$$

The derivative with respect to time yields:

$$\frac{d\zeta_3}{dt} = \left(1 - \frac{S_H^*}{S_H}\right)\frac{dS_H}{dt} + \frac{dE_H}{dt} + \frac{dI_H}{dt} + \frac{dI_V}{dt},$$

$$= \left(1 - \frac{S_H^*}{S_H}\right)\left(b_H + (1-P)(1-S_H - E_H - I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H\right)$$
$$- d_H E_H - (d_H + d_d) I_H + \left(\beta_V (1 - I_V) I_H N_H - (d_V + d_k) I_V\right),$$

$$= \left(b_H - b_H \frac{S_H^*}{S_H} - d_H S_H + d_H S_H^* + (1-P)(1-S_H - E_H - I_H)\theta - (1-P)(1-S_H - E_H - I_H)\theta \frac{S_H^*}{S_H}\right)$$
$$- d_H E_H - (d_H + d_d) I_H + \left(\beta_V (1 - I_V) I_H N_H - (d_V + d_k) I_V\right),$$

$$= \left(b_H \left(1 - \frac{S_H^*}{S_H}\right) + d_H S_H^* \left(1 - \frac{S_H}{S_H^*}\right) + (1-P)(1-S_H - E_H - I_H)\theta \left(1 - \frac{S_H^*}{S_H}\right)\right)$$
$$- d_H E_H - (d_H + d_d) I_H + \left(\beta_V (1 - I_V) I_H N_H - (d_V + d_k) I_V\right).$$

Substituting the expressions for d_H and I_V, we get:

$$= b_H \left(\left(1 - \frac{S_H^*}{S_H}\right) + \left(1 - \frac{S_H}{S_H^*}\right)\right) - d_H E_H - (d_H + d_d) I_H,$$

$$= -b_H \left(\frac{\left(S_H^* - S_H\right)^2}{S_H^* S_H}\right) - d_H E_H - (d_H + d_d) I_H,$$

$$\frac{d\zeta_3}{dt} = -\left(b_H \frac{\left(S_H^* - S_H\right)^2}{S_H^* S_H} + d_H E_H + (d_H + d_d) I_H\right). \tag{6.26}$$

Hence, the condition of Equation (6.26) shows that $\frac{d\zeta_3}{dt} \le 0$ for $\left(\mathrm{S}_H, E_H, I_H, I_V\right) \in \phi$, and the strict quality holds only for $S_H = S_H^*, E_H = 0, I_H = 0,$ and $I_V = 0$. Then the endemic equilibrium point E_2^* is globally asymptotically stable in ϕ. □

Note that the exact solution of the system may also be revived by using the powerful tool of Lie algebra. For further information, see the works of Shang [97,98]

6.3 Numerical simulation

In this section, we investigate the impact of the transmission of dengue consider only re-infectious, regardless of individual serotypes each time they were infected. The initial values for the parameter are listed in Table 5.2. The parameter values of dengue cases in Thailand are estimated. The information was gathered from the Ministry of Public Health's Department of Disease Control. Note that although most parameter's initial values are taken from the source literature. However, certain values must be estimated and assumed for the purposes of this model. There are four parameters to be estimated: $N_H, N_V, d_d,$ and d_k and two parameters to be assumed: β_H and β_V . The model of system Equation (6.17) is then simulated with the use of a differential equation. The results of our present numerical simulation are shown in Figures 6.4-6.7, **(a)** Susceptible human **(b)** Exposed human **(c)** Infected human and **(d)** Infected vector.

The model of Equation (6.17) is solved using the differential solver ode45. This solver employs the fourth-order Runge-Kutta method with adjustable step size to solve the system of differential equations.

Table 6.2. The initial value for the parameters.

Parameters	The disease-free	The endemic	Source
α	1/7	1/7	[6,99-103]
ε	1/10	1/10	[6,99-103]
P	0.5	0.5	[6,99-103]
θ	1/(30*6)	1/(30*6)	[6,99-103]
N_H	250,000	250,000	estimated
N_V	200,000	200,000	estimated
β_H	0.00000025	0.005	assumed
β_V	0.00000012	0.003	assumed
b_H	1/(365*70)	1/(365*70)	[6,99-103]
d_H	1/(365*70)	1/(365*70)	[6,99-103]
d_V	1/14	1/14	[6,99-103]
d_d	1/14	1/14	estimated
d_k	1/7	1/7	estimated
γ	1/14	1/14	[6,99-103]

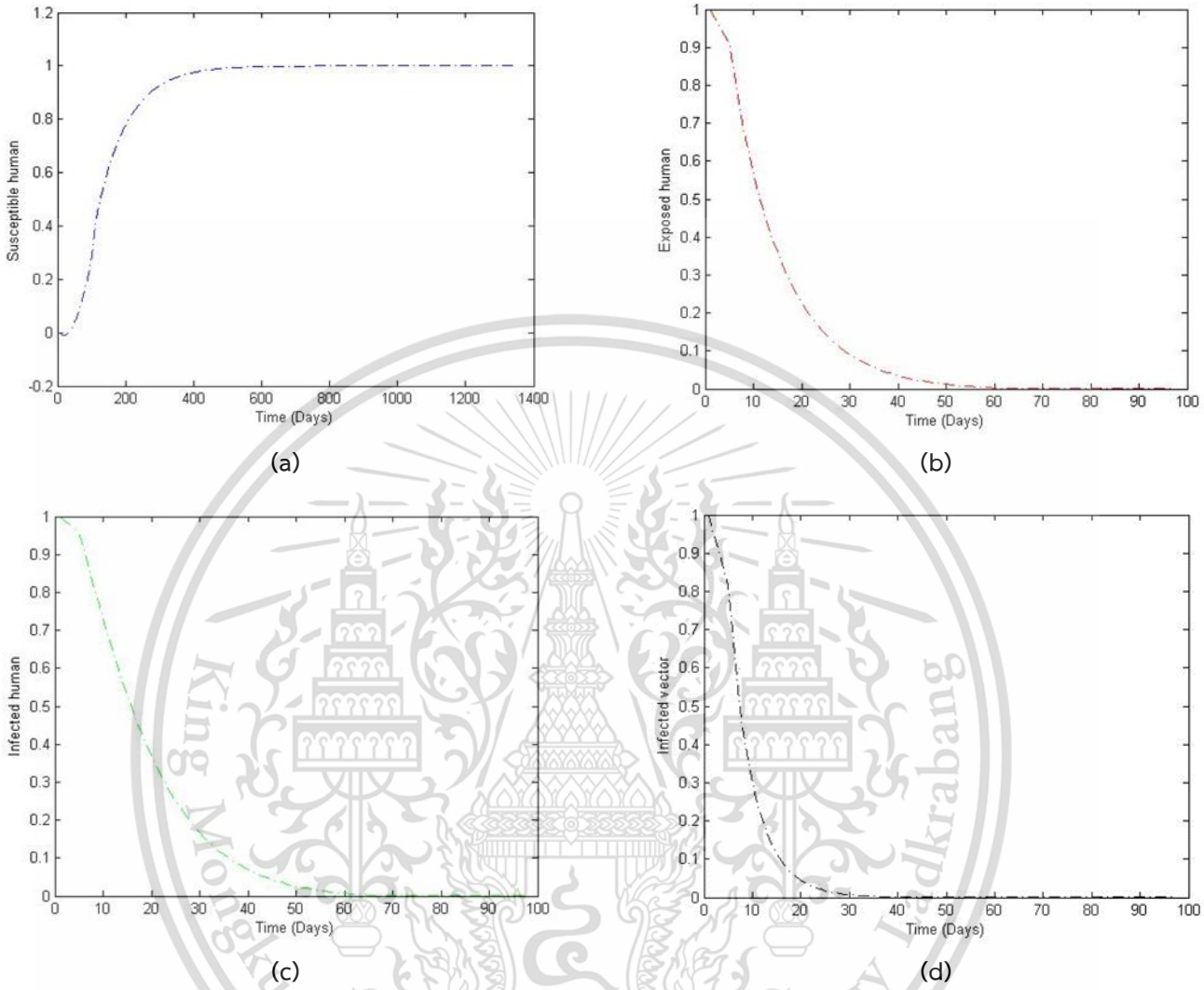


Figure 6.4 Graphs of system Equation (6.17) at the disease-free equilibrium point of S_H, E_H, I_H, and I_V for $R_0 < 1$.

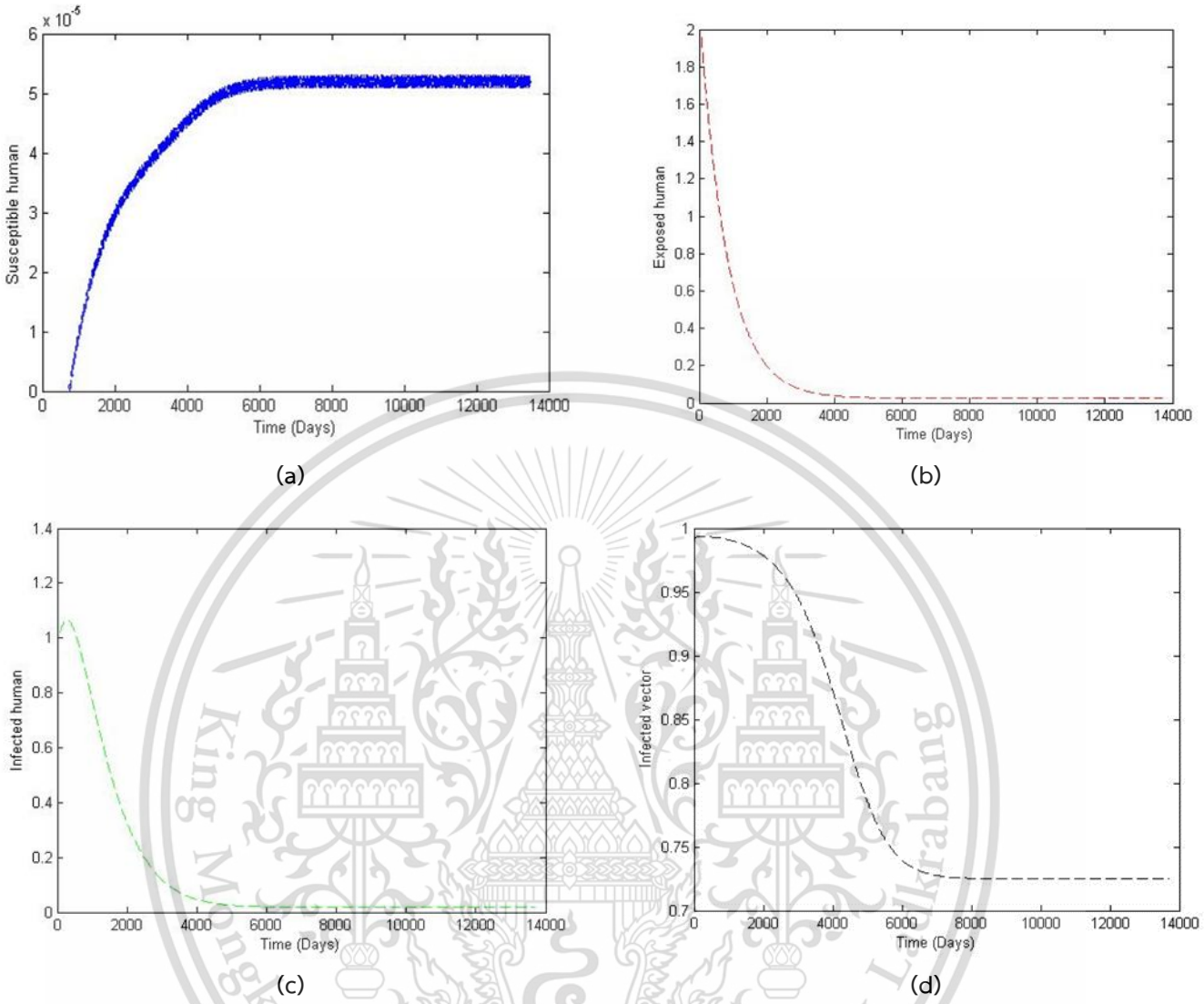


Figure 6.5 Graphs of system Equation (6.17) at the endemic equilibrium point of S_H, E_H, I_H, and I_V for $R_0 > 1$.

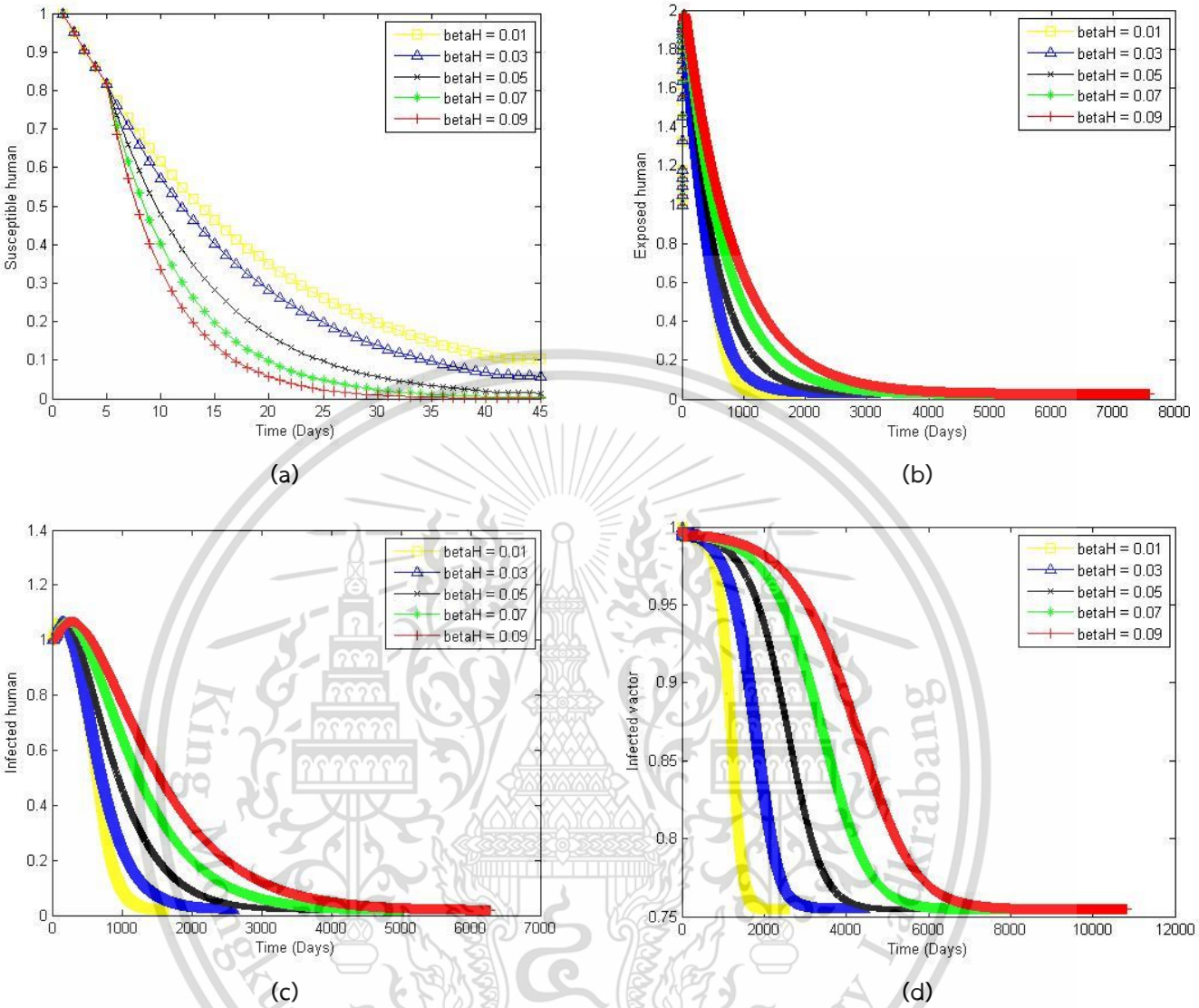


Figure 6.6 Graphs of system Equation (6.17) at the endemic equilibrium point of S_H, E_H, I_H, and I_V for $R_0 > 1$, with compares parameter β_H.

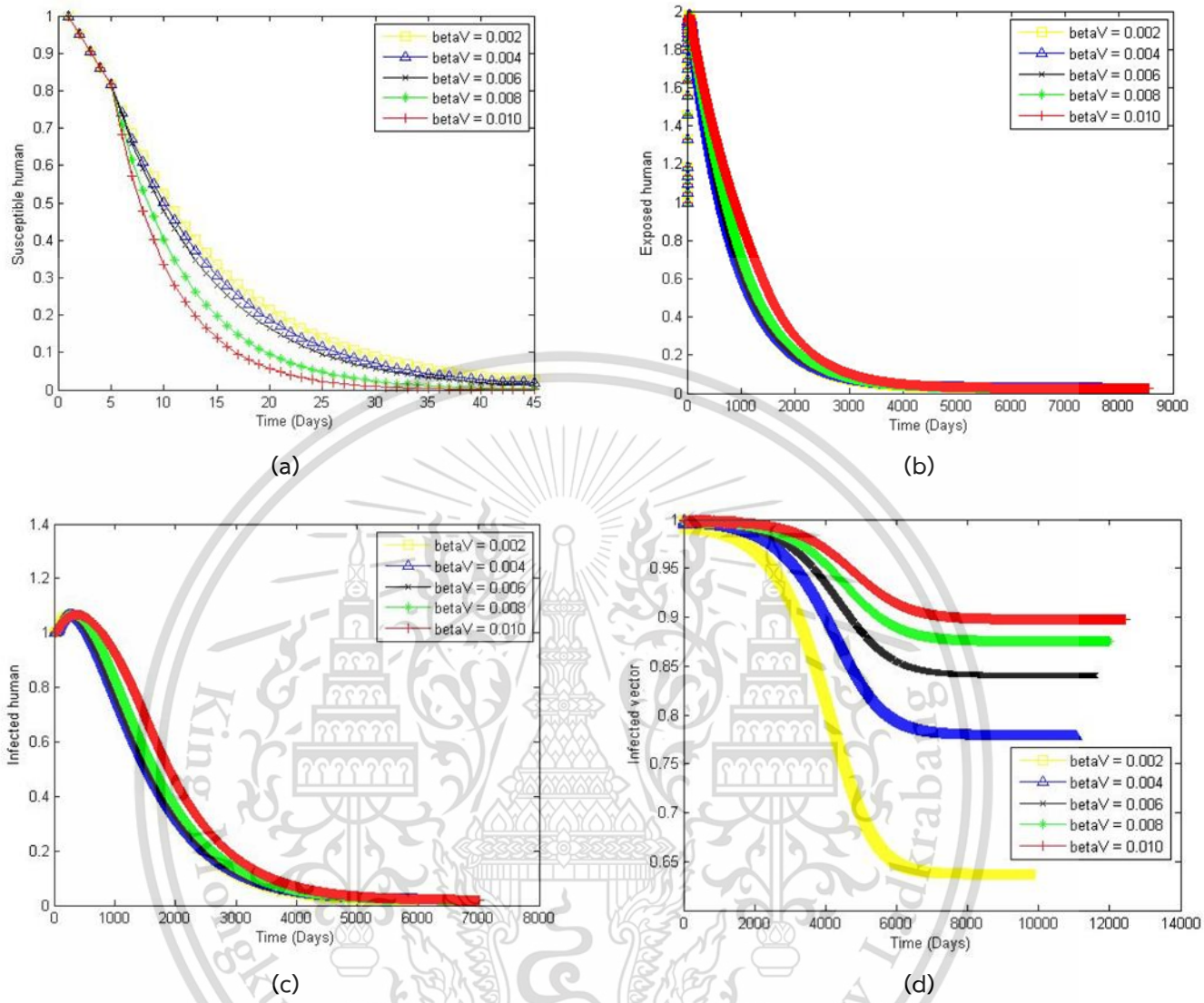


Figure 6.7 Graphs of system Equation (6.17) at the endemic equilibrium point of S_H, E_H, I_H, and I_V for $R_0 > 1$, with compares parameter β_V.

Figure 6.4 shows the numerical solution of the disease-free equilibrium where $R_0 < 1$ after about 500, 60, 65, and 30 days for the susceptible human, exposed human, infected human, and infected vector it converges to $E_1 = (1,0,0,0)$, respectively. Figure 6.5 shows the numerical solution of the endemic equilibrium where $R_0 > 1$ after about 6500, 4000, 5000, and 7000 days for the susceptible human, exposed human, infected human, and infected vector it converges to $E_2 = (0.00005, 0.02689, 0.01881, 0.73048)$, respectively. Figures 6.6-6.7 show the numerical solution of the endemic equilibrium with compares parameters the dengue virus transmission rate from vector to human $\beta_H = 0.01, 0.03, 0.05, 0.07, 0.09$ and the dengue virus transmission rate from human to

vector $\beta_V = 0.002, 0.004, 0.006, 0.008, 0.010$ for the susceptible human, exposed human, infected human, and infected vector. We can observe that the higher the dengue virus transmission rate from vector to human β_H and the dengue virus transmission rate from human to vector β_V, the slower the convergence to a susceptible human equilibrium point. The exposed human, infected human, and infected vector all rapidly reach a point of equilibrium, respectively.

6.4 The Optimal Control Problem

In this section, we apply the Pontryagin's Maximum Principle (PMP) to derive the necessary conditions for the solution for the existence of optimal control. Equations (6.17) can be rewritten as an optimal control problem with the goal of reducing the number of infected human populations. Two control inputs may be assigned to the system since they include the dynamics of both human and vector populations, namely u_1 where this control input represents an effort to reduce the number of infected humans by giving vaccinations to humans, and u_2 for the vector population represents the administration of repellents to mosquitoes and destroying mosquito breeding sites. The system of equations with control is written as:

$$\frac{dS_H}{dt} = b_H + (1-P)R_H\theta - \alpha\beta_H S_H I_V N_V - d_H S_H - u_1(t)I_H, \tag{6.27}$$

$$\frac{dE_H}{dt} = \alpha\beta_H S_H I_V N_V - \varepsilon E_H - d_H E_H, \tag{6.28}$$

$$\frac{dI_H}{dt} = \varepsilon E_H - \gamma I_H - (d_H + d_d)I_H, \tag{6.29}$$

$$\frac{dR_H}{dt} = \gamma I_H - (1-P)\theta R_H - d_H R_H, \tag{6.30}$$

$$\frac{dS_V}{dt} = \frac{A}{N_V} - \beta_V S_V I_H N_H - d_V S_V - u_2(t)S_V, \tag{6.31}$$

$$\frac{dI_V}{dt} = \beta_V S_V I_H N_H - (d_V + d_k)I_V - u_2(t)\beta_V S_V I_H N_H. \tag{6.32}$$

In normalized compartments Equations (6.27)-(6.32) are:

$$\frac{dS_H}{dt} = b_H + (1-P)(1-S_H - E_H - I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H - u_1(t)I_H, \tag{6.33}$$

$$\frac{dE_H}{dt} = \alpha\beta_H S_H I_V N_V - (\varepsilon + d_H)E_H, \tag{6.34}$$

$$\frac{dI_H}{dt} = \varepsilon E_H - (d_H + d_d + \gamma) I_H, \tag{6.35}$$

$$\frac{dI_V}{dt} = (1-u_2(t))\beta_V I_H N_H (1-I_V) - (d_V + d_k) I_V. \tag{6.36}$$

All parameter definitions retain their meanings from the uncontrolled system. For non-negative bounded initial conditions, this system has non-negative bounded solution (Lukes 1982 [70]). The objective function to be minimized is written:

$$J(u) = \int_0^T \left[C_1 I_H + C_2 I_V + \frac{1}{2}\left(D_1 u_1^2(t) + D_2 u_2^2(t) \right) \right] dt. \tag{6.37}$$

With initial condition $S_H, E_H, I_V \geq 0,$ and $I_H \geq 0$. The weight constants are C_1 and C_2 for the number of infected humans and the infected vector populations. The weights D_1 and D_2 are measures of the costs associated with the control variables u_1 and u_2 respectively. The Hamiltonian for the Lagrangian problem of the optimal control problem and the optimal control problem by Lagrangian was defined as follows:

$$L = C_1 I_H + C_2 I_V + \frac{1}{2}\left(D_1 u_1^2(t) + D_2 u_2^2(t) \right). \tag{6.38}$$

Theorem 6.5. There exists an optimal control $u_1^*(t)$ and $u_2^*(t)$ such that $J\left(u_1^*, u_2^*\right) = \min\left\{ J\left(u_1, u_2\right) | \left(u_1, u_2\right) \in U \right\}$.

Proof. The existence of the optimal control problem Equations (6.33)-(6.36) we apply results from [101,102] to prove the analyzed existence results of the optimal control problem.

The existence of the system in Equations (6.33)-(6.36) is given which is non-empty and bounded, according to Theorem 9.2.1 from Lukes [70]. The control set U is closed and convex. The right side of the control system Equations (6.33)-(6.36) is linear in u_1 and u_2. The integrand L is convex on U. To prove the bound on L, let $m_2 = \min\left(I_H(t), I_V(t) \right), m_1 = \left(D_1, D_2 \right),$ and $\psi = 2$. Then the Lagrangian function L defined as:

$$\begin{aligned} L(I_H, I_V, u_1, u_2) &= C_1 I_H + C_2 I_V + \frac{1}{2}(D_1 u_1^2(t) + D_2 u_2^2(t)), \\ &\geq m_2(I_H + I_V) + m_1(|u_1|^2 + |u_2|^2), \\ &= m_2 + m_1(|u_1|^2 + |u_2|^2), \end{aligned} \tag{6.39}$$

where $m_1, m_2, C_1, C_2, D_1, D_2 > 0,$ and $\psi > 1$. Therefore, there exists an optimal control for the system of Equations (6.33)-(6.36) satisfying the Pontryagin's Minimum Principle [29,70,71,86]. □

Theorem 6.6 Let u_1^* and u_1^* be optimal controls, and let $S_H, E_H, I_H,$ and I_V be the solutions of the optimal control problem Equations (6.33)-(6.36) that minimize $J(u_1, u_2) \in \mathrm{U}$. Then there are adjoint variables $\lambda_1 = \lambda_{S_H}, \lambda_2 = \lambda_{E_H}, \lambda_3 = \lambda_{I_H},$ and $\lambda_4 = \lambda_{I_V}$ satisfying the adjoint system of equations:

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -\lambda_1(t)\left((P-1)\theta - \alpha\beta_H I_V N_V - d_H\right) - \lambda_2(\alpha\beta_H I_V N_V),\\
\frac{d\lambda_2}{dt} &= -\lambda_1(t)(P-1)\theta - \lambda_2(-\varepsilon - d_H) - \lambda_3(\varepsilon),\\
\frac{d\lambda_3}{dt} &= -\lambda_1(t)\left((P-1)\theta - u_1^*(\mathrm{t})\right) - \lambda_3(-d_H - d_d - \gamma) - \lambda_4\left(\left(1-u_2^*(\mathrm{t})\right)\beta_V N_H\left(1-I_V\right)\right) - C_1,\\
\frac{d\lambda_4}{dt} &= -\lambda_1(t)\left(-\alpha\beta_H S_H N_V\right) - \lambda_2(\alpha\beta_H S_H N_V) - \lambda_4\left(-\beta_V I_H N_H + u_2^*(\mathrm{t}) I_H \beta_V N_H - d_V - d_k\right) - C_2.
\end{aligned} \tag{6.40}$$

Where $S_H, E_H, I_H,$ and I_V are the adjoint variables, and the controls u_1^* and u_2^* obey the optimality conditions

$$u_1^*(t) = \max\left(\min\left(\frac{\lambda_1 I_H^*}{D_1}, u_1^{\max}\right), 0\right), \tag{6.41}$$

$$u_2^*(t) = \max\left(\min\left(\frac{\left(1-I_V^*\right)\beta_V I_H^* N_H}{D_2}, u_2^{\max}\right), 0\right). \tag{6.42}$$

Proof. The corresponding Hamiltonian is defined as:

$$H = L\left(I_H, I_V, u_1, u_2\right) + \lambda_1\frac{dS_H}{dt} + \lambda_2\frac{dE_H}{dt} + \lambda_3\frac{dI_H}{dt} + \lambda_4\frac{dI_V}{dt}, \tag{6.43}$$

$$\begin{aligned}
H = {} & C_1 I_H + C_2 I_V + \frac{1}{2}\left(D_1 u_1^2(\mathrm{t}) + D_2 u_2^2(\mathrm{t})\right)\\
& + \lambda_1\left[b_H + (1-P)(1-S_H - E_H - I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H - u_1(t) I_H\right]\\
& + \lambda_2\left[\alpha\beta_H S_H I_V N_V - (\varepsilon + d_H)E_H\right] + \lambda_3\left[\varepsilon E_H - (d_H + d_d + \gamma) I_H\right]\\
& + \lambda_4\left[(1-u_2(t))\beta_V I_H N_H (1-I_V) - (d_V + d_k) I_V\right].
\end{aligned} \tag{6.44}$$

The associated adjoint system is as follows:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_H} = -\lambda_1(t)\left((P-1)\theta - \alpha\beta_H I_V N_V - d_H\right) - \lambda_2(\alpha\beta_H I_V N_V),$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial E_H} = -\lambda_1(t)(P-1)\theta - \lambda_2(-\varepsilon - d_H),$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I_H} = -\lambda_1(t)\left((P-1)\theta - u_1^*(\mathrm{t})\right) - \lambda_3(-d_H - d_d - \gamma)$$
$$-\lambda_4\left(\left(1-u_2^*(\mathrm{t})\right)\beta_V N_H\left(1-I_V\right)\right) - C_1,$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial I_V} = -\lambda_1(t)\left(-\alpha\beta_H S_H N_V\right) - \lambda_2(\alpha\beta_H S_H N_V) \tag{6.45}$$
$$-\lambda_4\left(-\beta_V I_H N_H + u_2^*(\mathrm{t}) I_H \beta_V N_H - d_V - d_k\right) - C_2.$$

With the boundary conditions

$$\lambda_1(t) = 0, \lambda_2(t) = 0, \lambda_3(t) = 0, \lambda_4(t) = 0. \tag{6.46}$$

Using the properties of optimal set optimality conditions, we find that

$$\frac{\partial H}{\partial u_1} = \frac{\partial H}{\partial u_2} = 0 \text{ at } u_1 = u_1^* \text{ and } u_2 = u_2^*. \tag{6.47}$$

Therefore,

$$\frac{\partial H}{\partial u_1} = D_1 u_1 - \lambda_1 I_H = 0,$$
$$u_1^* = \frac{\lambda_1 I_H}{D_1}. \tag{6.48}$$

$$\frac{\partial H}{\partial u_2} = D_2 u_2 - (1-I_V)\beta_V I_H N_H = 0,$$
$$u_2^* = \frac{(1-I_V)\beta_V I_H N_H}{D_2}. \tag{6.49}$$

The optimal controls u_1^* and u_2^* are then given by:

$$u_1^* = \begin{cases} 0 & ; \frac{\lambda_1 I_H}{D_1} \le 0, \\ \frac{\lambda_1 I_H}{D_1} & ; \frac{\lambda_1 I_H}{D_1} < u_1^{\max}, \\ u_1^{\max} & ; \frac{\lambda_1 I_H}{D_1} \ge u_1^{\max}. \end{cases} \tag{6.50}$$

$$u_2^* = \begin{cases} 0 & ;\frac{(1-I_V)\beta_V I_H N_H}{D_2} \le 0, \\ \frac{(1-I_V)\beta_V I_H N_H}{D_2} & ;\frac{(1-I_V)\beta_V I_H N_H}{D_2} < u_2^{\max}, \\ u_2^{\max} & ;\frac{(1-I_V)\beta_V I_H N_H}{D_2} \ge u_2^{\max}. \end{cases} \quad (6.51)$$

□

The fourth-order Runge-Kutta method, in conjunction with the forward-backward method, is used to solve the optimal control problem numerically. The solution results for optimal strategies control are shown in Figures 6.8-6.13 the initial values parameter according to listed in Table 6.2.

Figures 6.8-6.12 show the results of Equation (6.17) with and without control of $S_H, E_H, I_H,$ and I_V. We have divided the weight simulations into 5 cases as follows: Case 1 represents the case of C_1 being much less than C_2; Case 2 represents the case of C_1 being less than C_2; Case 3 represents the case where both C_1 and C_2 are equal; Case 4 is where C_1 is greater than C_2 and Case 5 is where C_1 is much greater than C_2. The results of these cases are plotted in Figures 6.8-6.12, for case 1-5 respectively.

Figures 6.8-6.12, **(a)** Susceptible human **(b)** Exposed human **(c)** Infected human and **(d)** Infected vector, shows that after effective control such as for the human population is an effort to reduce the number of infected humans by giving vaccinations to humans and for the vector population is control by giving repellent to mosquitoes and destroying mosquito breeding sites. The number of the susceptible human S_H, exposed human E_H, infected human I_H, and infected vector I_V is significantly reduced compared with that without control. The results of numerical simulation show that vaccination and the elimination of disease-carrying mosquitoes have a positive effect. The control, in particular, resulted in a significant reduction in the number of infected humans and vectors.

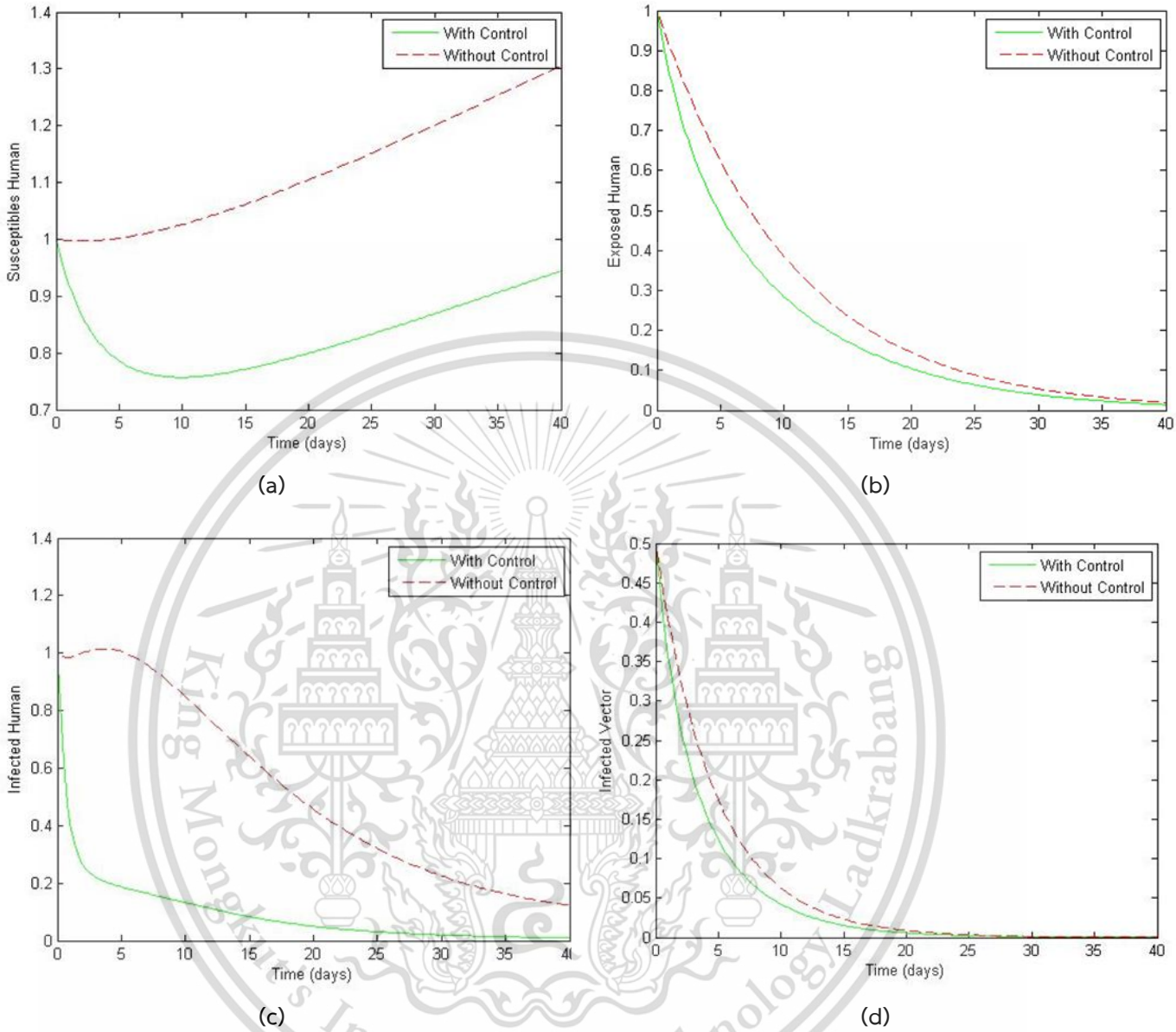


Figure 6.8 Comparison of behaviors with and without of system of Equations (6.33)-(6.36) of S_H, E_H, I_H, and I_V when using $C_1 = 0.000005, C_2 = 50.$

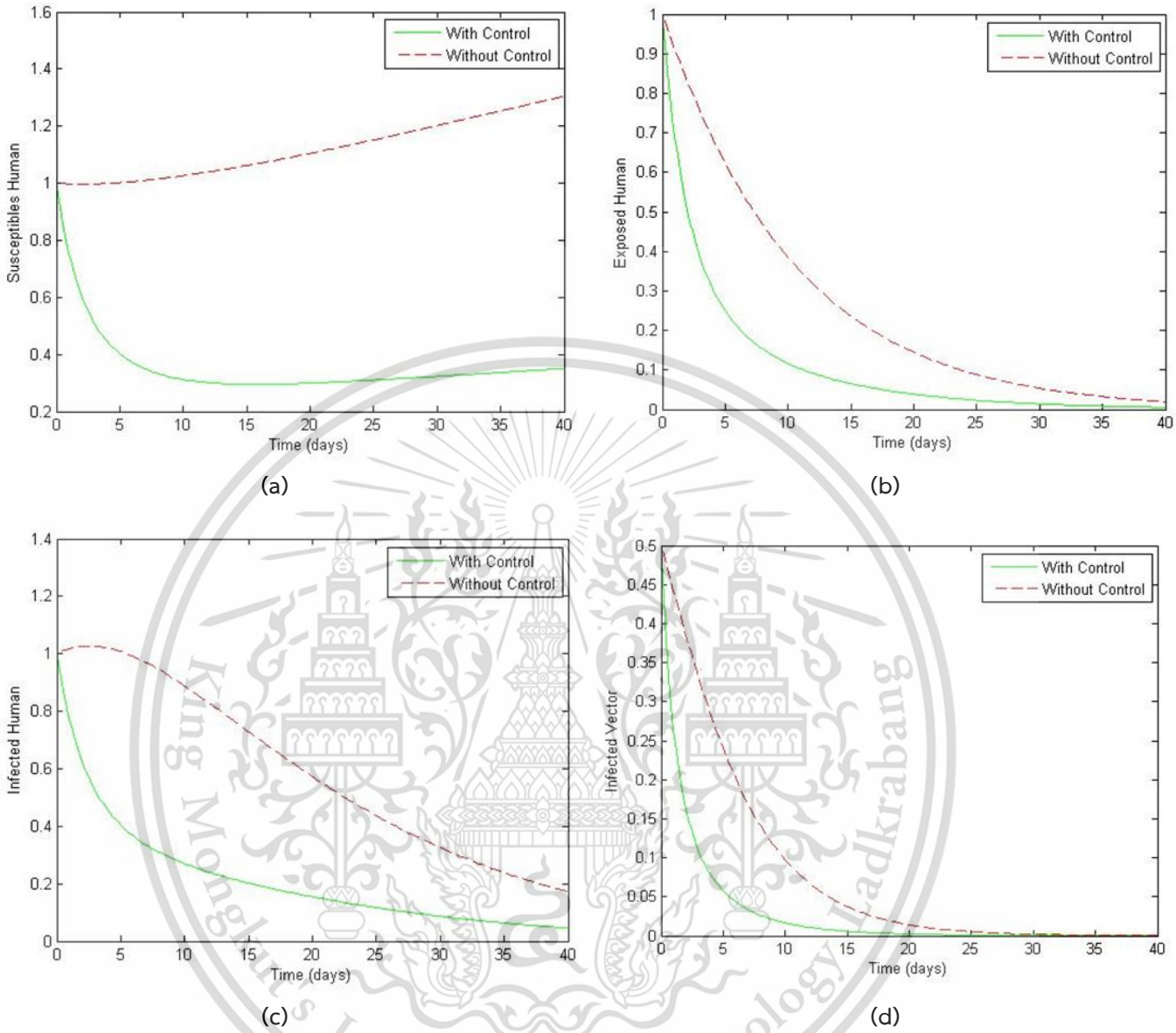


Figure 6.9 Comparison of behaviors with and without of system of Equations (6.33) – (6.36) of S_H, E_H, I_H, and I_V when using $C_1 = 5, C_2 = 50$.

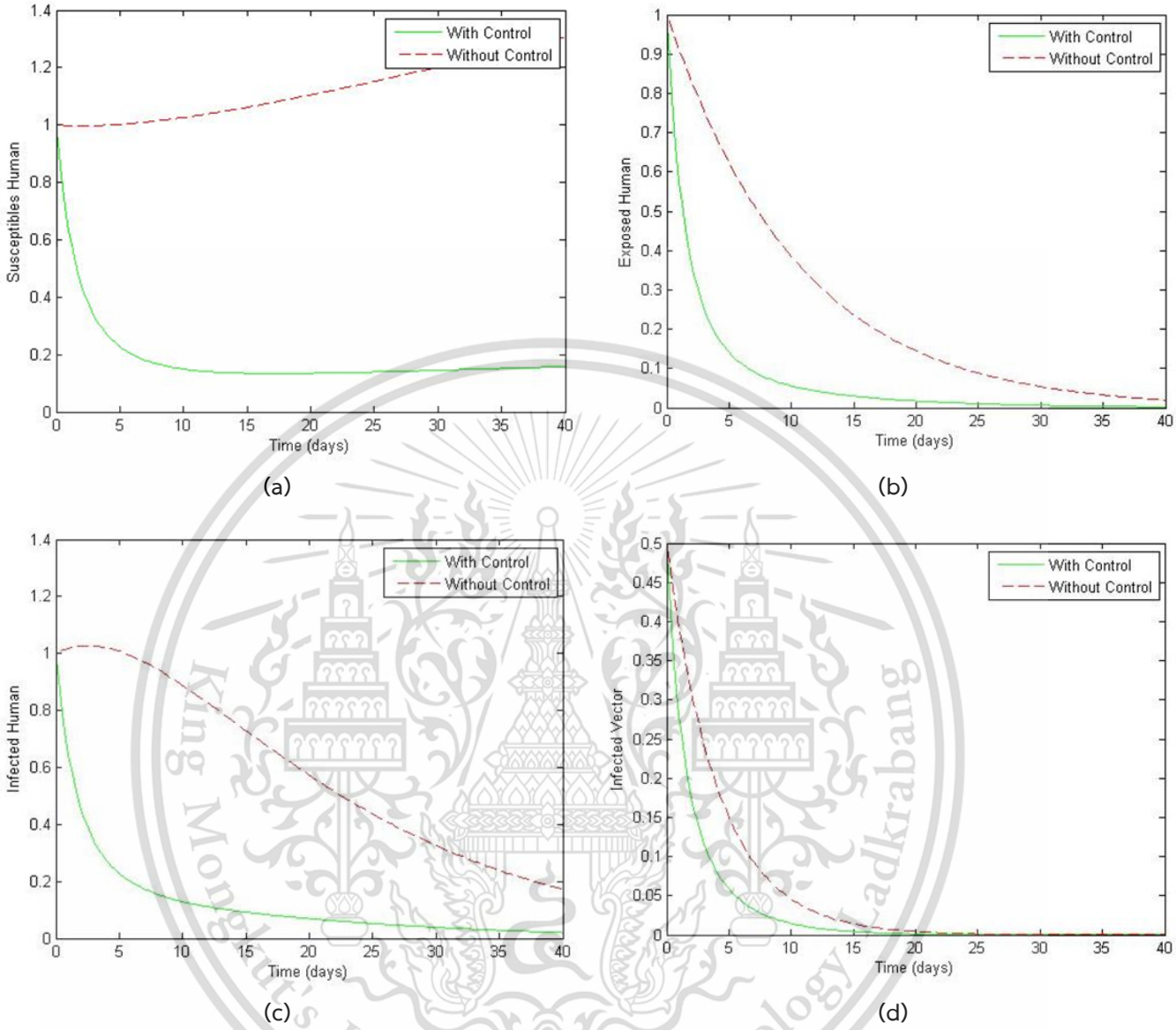


Figure 6.10 Comparison of behaviors with and without of system of Equations (6.33)–(6.36) of S_H, E_H, I_H, and I_V when using $C_1 = 50, C_2 = 50$.

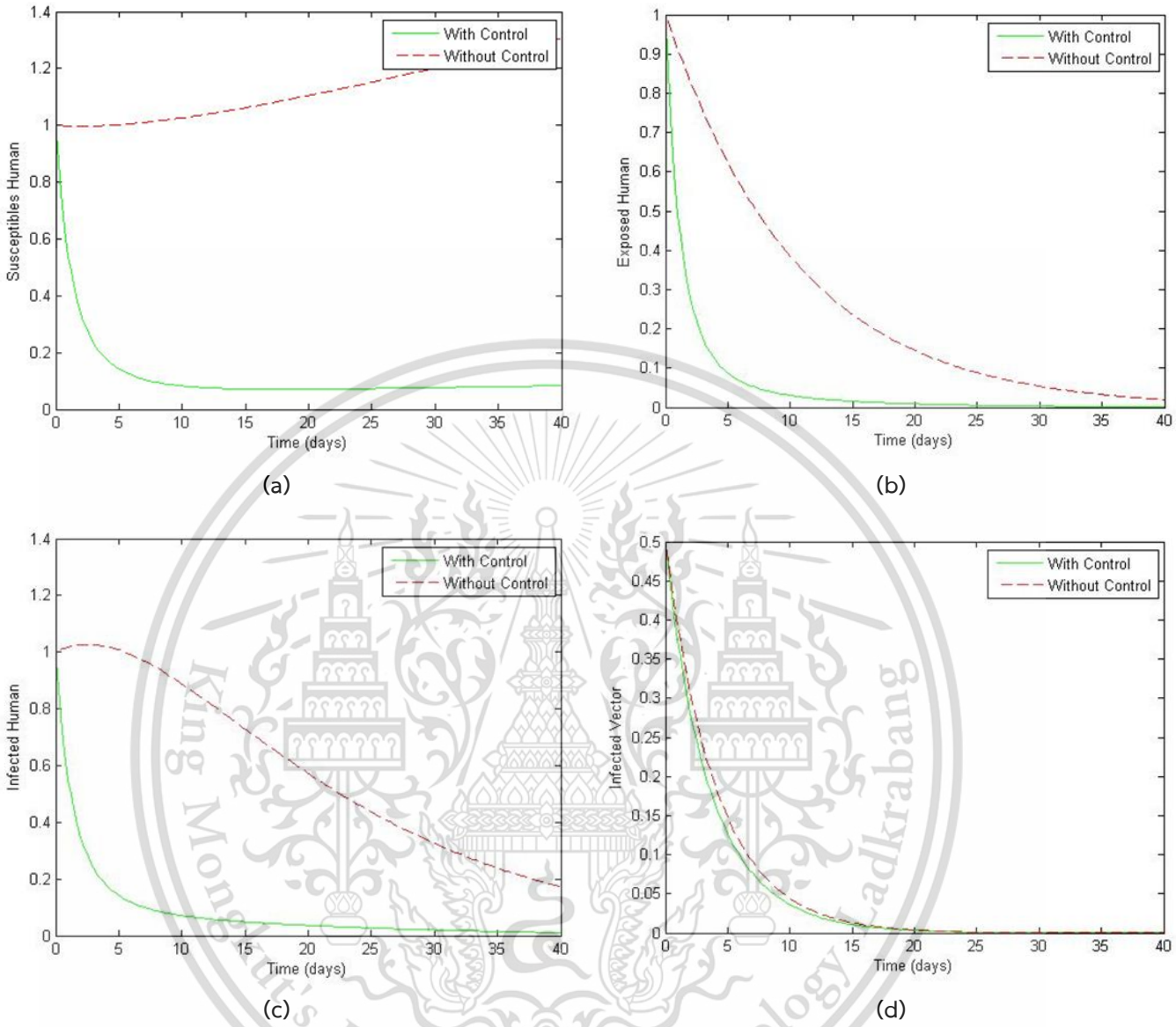


Figure 6.11 Comparison of behaviors with and without of system of Equations (6.33)–(6.36) of S_H, E_H, I_H, and I_V when using $C_1 = 50, C_2 = 5$.

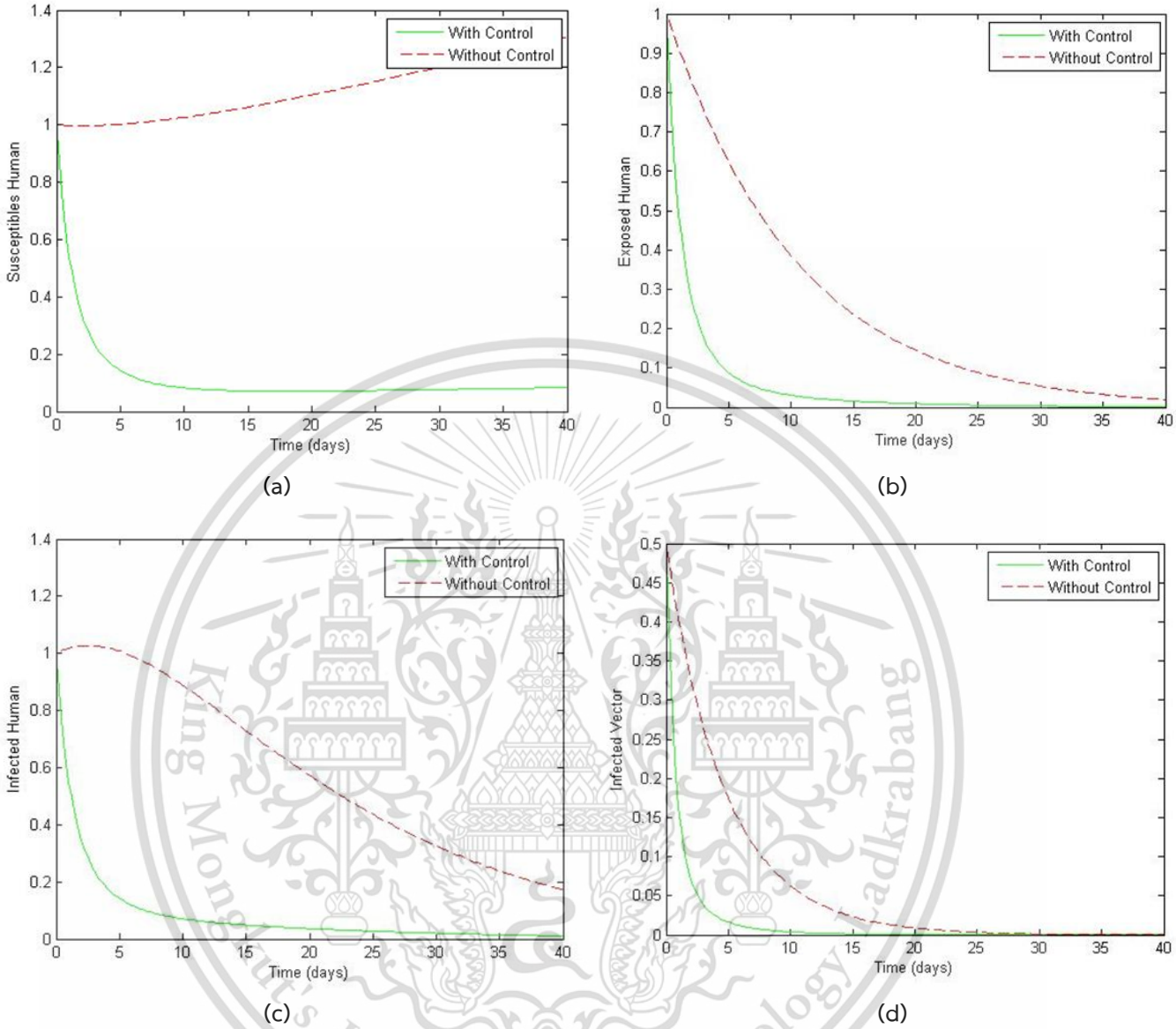
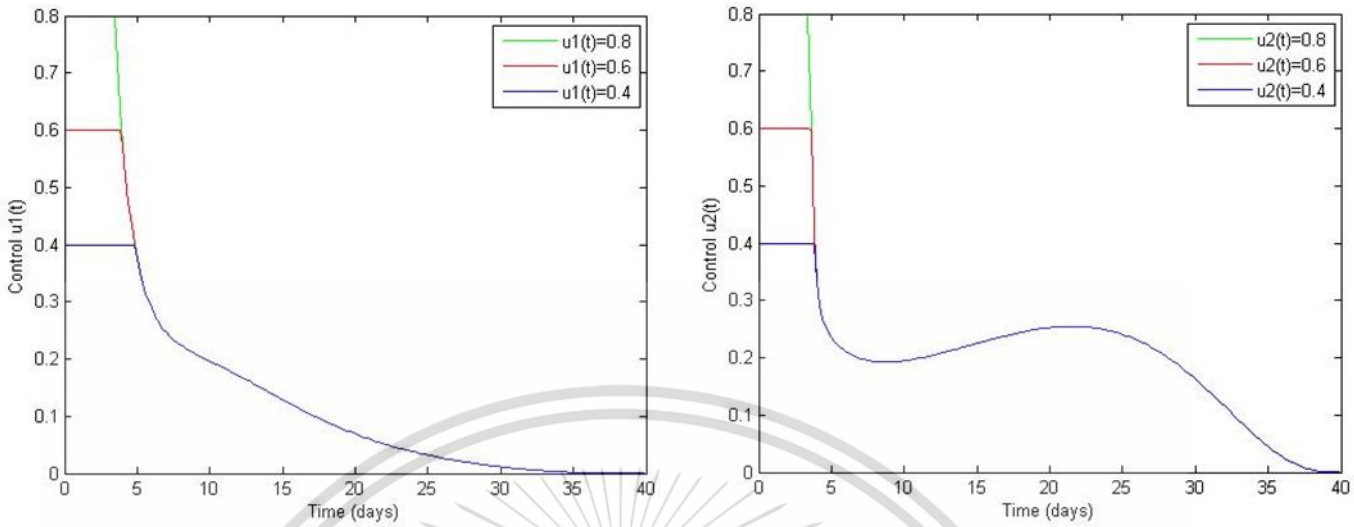


Figure 6.12 Comparison of behaviors with and without of system of Equations (6.33)–(6.36) of S_H, E_H, I_H, and I_V when using $C_1 = 50, C_2 = 0.000005$.



(a) (b)

Figure 6.13 Control variables using $C_1 = 50,\ C_2 = 50.$

Figure 6.13**(a)** illustrates maintaining optimal control of vaccination rates in the human population $u_1(t)$ at initial value differences as follows: 40%, 60%, and 80% in approximately the first 4 days control is maintained, then the control gradually decreases to zero. Figure 6.13**(b)** shows the control values of the second control effort $u_2(t)$ at 40%, 60%, and 80% initiation to achieve control. It is seen that the optimal level of control is maintained in the first 4 days, then gradually increases and reaches the plateau on Day 22, after which the control dosage is reduced to zero.

6.5 Discussion and Conclusions

In this article, we analyzed the impact of post-reinfection vaccination strategies for the $2^{nd}, 3^{rd}$, and 4^{th} times, without regarding the serotype sequence during infection, for regions with high dengue outbreaks, in order to reduce the hospitalization rates and disease severity in the subsequent infections. This model is optimal for densely populated areas and abundant *Aedes* mosquitoes, which are carriers of dengue fever and there is a chance of re-infection with dengue fever multiple times. According to the 2020 report in Thailand, the region with the highest morbidity rate is the Northeastern region, with 127.53 per 100,000 inhabitants. The Routh-Hurwitz criterion for determining local asymptotically stability and the Lyapunov function for determining global asymptotically stability are used in the study. The equilibrium point that we found two states are disease-free converge to $E_1 = (1,0,0,0)$ and endemic equilibrium point converge to $E_2 = (S_H = 0.00005,\ E_H = 0.02689,\ I_H = 0.01881,\ I_V = 0.73048)$.

The basic reproductive number is defined as R_0 . The disease-free equilibrium point there exists locally asymptotically stable if R_0 is less than one and locally asymptotically stable when R_0 greater than one for the endemic equilibrium point. Similarly, the disease-free and endemic equilibrium point exists locally and globally asymptotically stable if and only if according to conditions of Theorem 6.1 to Theorem 6.4. We simulated the numerical results solution of the compare two parameters with different values that affect the basic reproductive number value of this model as shown in Figures 6.6 and 6.7, where we can observe that the higher the dengue virus transmission rate from vector to human β_H and the dengue virus transmission rate from human to vector β_V , the slower the convergence to a susceptible human equilibrium point. The exposed human, infected human, and infected vector all rapidly reach a point of equilibrium.

We developed the optimal control strategies using the elimination of mosquitoes that carry diseases rate and the vaccination rate to minimize the number of infected human population and infected vector population to cost controlling effort. The Pontryagin Minimum Principle (PMP) approach is used to solve the optimum control issue in this situation. We can see that effective measures such as vaccinations to humans and the annihilation of mosquito breeding sites represent powerful measures that effectively controlled the spread of the dengue virus. In comparison to those without control, the number of susceptible humans exposed, infected humans, and infected vectors are significantly reduced. The numerical simulation results show that the number of infections decreases over time. Figures 6.8-6.12 show that the control resulted in a significant reduction in the number of infected humans and infected vectors. Finally, the effective control and prevention of dengue fever rely on three components: Improved vector control, improved case management, and effective vaccine development.

Chapter 7
Conclusions and Suggestions

7.1 Conclusions

Dengue fever is a disease that has spread all over the world, including Thailand. Dengue is caused by a virus and there are four distinct serotypes of the virus that cause dengue DENV-1, DENV-2, DENV-3, and DENV-4. The dengue viruses are transmitted by two species of *Aedes* mosquitoes, *Aedes aegypti*, and the *Aedes albopictus*. Currently, the dengue vaccine used in Thailand is chimeric yellow tetravalent dengue (CYD-TDV). In Thailand, there are different outbreaks of dengue fever in different areas. In this research, the mathematical model has been developed and designed to cover all 3 models:

Model 1: A simple mathematical model for low-infected endemic areas.

Model 2: The mathematical model for the outbreak area focuses on regions to reduce the severity of the second infection and is controlled by vaccination.

Model 3: The mathematical model for outbreak areas focused on provinces with high outbreaks and at risk of re-infection more than 2 serotypes to reduce the severity of re-infection and control it through vaccination.

In each model, the stability analysis of the dengue transmission model is used to establish the local asymptotically stabilities by Routh-Hurwitz. The property of symmetry in the Lyapunov function an important role in achieving this global asymptotically stabilities. The optimal control is applied in the spreading model to minimize the number of infected human and infected vector populations. The results are then given numerically to demonstrate the analyses. The results of the study showed that the three models reduced the number of dengue cases and were able to reduce the severity of the disease when the vaccine provided immunity and the control resulted in a significant reduction in the number of infected humans and infected vectors.

7.2 Suggestions

We suggest that future guidelines for this thesis should consider the serotypes of infection and provide a more complete age range for vaccination. However, there are many ways to prevent dengue fever. Including mosquito bites prevention, restricting mosquito breeding sites, as well as vaccinations, Dengvaxia is still not able to completely preventable a disease. World Health Organization recommends vaccination of dengue fever in people aged 9- 45 years for individuals with a documented past dengue infection

(seropositive). In the case of never being infected with dengue before, there is a risk of subsequent severe dengue fever if there is a later infection.

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Appendix

Appendix A

Paper 1

Analyze of SEIR Dengue Infectious Transmission Model with Vaccination

Analyze of SEIR Dengue Infectious Transmission Model with Vaccination

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ABSTRACT

Dengue infection is caused by dengue virus. The virus live in the *Aedes* mosquitoes. Dengue fever (DF) is caused by the dengue virus. They have four serotypes such that DEN-1, DEN-2, DEN-3, and DEN-4. The disease is transmitted from the biting of mosquito through the mosquito's saliva. We focus on the mathematical model of dengue disease with vaccination before the first serotypes infections of the dengue virus and considered the recurrent infection and death from infection. We used SEIR model (Susceptible-Exposed-Infected-Recovered) for the human population and SI for vector population. This is used to examine the dynamics of the disease. We analyzed the stability of the model by using dynamic analysis. The equilibrium states and the reproductive number of our model are found. The numerical simulations are used for compare the parameters that affect this model, result, and conclusion are presented.

CCS CONCEPTS

• **Applied computing**; • **Computational biology**;

KEYWORDS

dengue virus, mathematical model, vaccination

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1 INTRODUCTION

The dengue virus is the disease-causing dengue fever. The virus live in the *Aedes* mosquitoes most are found in *Aedes aegypti* more than the *Aedes albopictus* [1]. Dengue fever (DF) is caused by the dengue virus has four serotypes are DEN-1, DEN-2, DEN-3, and DEN-4 [1, 2], However, severe diseases, along with dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [3, 4]. The disease is transmitted from the mosquito bites through the mosquito's saliva. The primary symptoms of dengue fever are high fever, headache, eye socket, muscle pain, and bone pain [5]. Dengue fever is not transmitted from human to human. It can be contagious with *Aedes* mosquitoes contact takes time in patients and mosquitoes. The patients with a high fever around 2-4 days will have a lot of virus in the blood. This period is the period of contact from people to mosquitoes. In addition, the period of increasing the number of viruses in mosquitoes is enough for about 8-10 days [6]. WHO reported vaccination against dengue fever is one of the preventions of dengue fever. For vaccines that have been approved by the Food and Drug Administration of Thailand called Dengvaxia (Chimeric Yellow fever Dengue Tetravalent Dengue Vaccine: CYD-TDV) that covers all 4 serotypes of dengue virus which has been approved for use in people aged 9-45 years by the vaccine in a total of 3 needles, every 6 months [7]. Capeding et al. reported that the vaccine is effective against all dengue serotypes and reduces hospitalization from dengue fever and reduces illness type DHF [8]. Sungchasit et al. proposed the SEIR model for the human and SEI model for mosquitoes of dengue virus with primary and secondary infection [9] and proposed SIR transmission model of dengue virus two age classes in human and two types of mosquitoes (*Aedes Aegypti* and *Aedes Albopictus*) [10]. Massawe et al. reported that the treatment will have control of dengue fever disease [11]. Analyzed the transmission model of dengue fever with a variable human population size and prove the global asymptotically stability of equilibrium states and consider the relation between two serotypes find that coexistence of both serotypes is possible for a large range of parameters [12-13]. Hossain et al. proposed effects of transient population the transmission dynamics and control the dengue virus effectively and to find the effects of transient population and analyzed a non-linear ODE model [14]. Chanprasopchai et al. proposed the effect of a dengue vaccination model divided into two groups are with vaccine and without vaccine for the human population and SI for vector population. In Thailand, three serotypes are circulating, so the use of the vaccine does not impose additional risks [15]. In Bangkok, Thailand, the number of people infected with dengue fever is high during the rainy season from July to September and the highest in the year 2019 as Figure 1. In this paper, we focus on the mathematical model of dengue disease with vaccination before the first serotypes infectious of the dengue virus and considered the recurrent infection and death from infection.

2 MATHEMATICAL MODEL

In this model, we study the Susceptible-Exposed-Infected-Recovered (SEIR) model for the human population and Susceptible-

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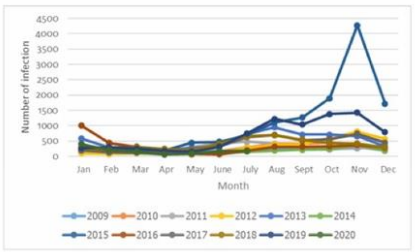

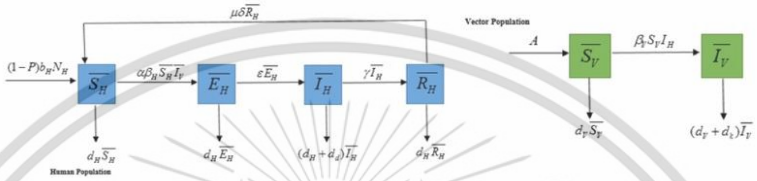

Figure 1: The number of people infected with dengue each month from 2009 to 2020 [5] and flow chart of transmission model of human and vector population.

Infected (SI) model for vector population to describe the dynamical transmission of dengue disease with vaccination in Thailand. We assume that the human population has been vaccinated before being infected. The human population is classified into four sub-classes; the number of susceptible individuals $\overline{S_H}$, exposed individual $\overline{E_H}$, infected individual $\overline{I_H}$, and recovered individual $\overline{R_H}$. The vector population is classified into two sub-classes: the number of susceptible individuals $\overline{S_V}$, and infected individual $\overline{I_V}$. The other parameters are defined as follows; P is the vaccine efficiency, N_H and N_V are the total human and vector population, b_H is the birth rate, d_H and d_V are the natural death rate of human and vector population, d_d and d_k are the death rate from infection of human and vector population, ϵ is the incubation rate, γ is the recovery rate, α is the biting rate of vector population, A is the constant recruitment rate of vector population β_H, and β_V are the transmission rate of dengue virus from vector to human and human to vector, δ is the recurrent infection rate and μ is the risk of dengue infection in the second round. The diagram of our model is shown in Figure 1

This model with vaccination, the dynamics of the human and vector population are given by:

$$\begin{aligned}
\overline{S_H'} &= (1-P)\,b_H\,N_H + \mu\delta\overline{R_H} - \alpha\beta_H\overline{S_H}I_V - d_H\overline{S_H},\\
E_H' &= \alpha\beta_H\overline{S_H}I_V - \epsilon\overline{E_H} - d_H\overline{E_H},\\
\overline{I_H'} &= \epsilon\overline{E_H} - (d_H + d_d + \gamma)\,\overline{I_H}\,,\\
\overline{R_H'} &= \gamma\overline{I_H} - (\mu\delta + d_H)\,\overline{R_H},\quad \overline{S_V} = A - \beta_V\overline{S_V}\,\overline{I_H} - d_V\overline{S_V},\quad \overline{I_V}\\
&= \beta_V\overline{S_V}\,\overline{I_H} - (d_V + d_k)\overline{I_V}.
\end{aligned} \tag{1}$$

We have assumed that: $N_H = \overline{S_H} + \overline{E_H} + \overline{I_H} + \overline{R_H}$, *and* $N_V = \overline{S_V} + \overline{I_V}$. The assumption of our model is the total human and vector populations are constant. This leads to the rate of change for human and vector population being zero, i.e.: $\overline{S_H}' + \overline{E_H}' + \overline{I_H}' + \overline{R_H}' = 0$ and $\overline{S_V}' + \overline{I_V}' = 0$. From the above equations, we can obtain the following with conditions that: $S_H = \overline{S_H}/N_H$, $E_H = \overline{E_H}/N_H$, $I_H = \overline{I_H}/N_H$, $R_H = \overline{R_H}/N_H$, $S_V = \overline{S_V}/N_V$, and $I_H = \overline{I_V}/N_V$. Normalizing the equations by introducing the following normalized variables:
$I_H = (b_H - d_H)N_H/d_d$ *and* $I_V = A - d_V N_V/d_k$ The mathematical model of Equation (1) is now reduced to the following four equations:

$$\begin{aligned}
S_H' &= (1-P)\,b_H\ + \mu\delta R_H - \alpha\beta_H S_H I_V N_V - d_H S_H,\quad E_H'\\
&= \alpha\beta_H S_H I_V N_V - \epsilon E_H - d_H E_H,\quad I_H'\\
&= \epsilon E_H - (d_H + d_d + \gamma)I_H,\ I_V'\\
&= \beta_V S_V I_H N_H - (d_V + d_k)I_V
\end{aligned} \tag{2}$$

The equilibrium points are obtained by setting the right hand side of Equation (2) to zero. In addition, we get two equilibrium points given by: The disease-free equilibrium point $E_1 = ((\delta\mu + b_H - Pb_H)/(\delta\mu + b_H), 0, 0, 0)$.

The endemic equilibrium point $E_2 = (S_H^*, E_H^*, I_H^*, I_V^*)$ with

$$\begin{aligned}
S_H^* &= \frac{\psi_1\psi_2((\gamma\,\delta+\psi_7+\gamma\,d_H+(\epsilon+\psi_3)\psi_4)\psi_5+\epsilon(\delta\mu-\psi_6)N_H\beta_V}{\epsilon N_H(\psi_1\psi_2\psi_3+\alpha(\gamma\epsilon+\psi_7+\gamma\,d_H+(\epsilon+\psi_3)\psi_4)N_H\beta_H)\beta_V},\\
E_H^* &= \frac{\psi_2((\psi_1\psi_2\psi_3\psi_5+\alpha\epsilon(\delta\mu-\psi_6)N_H N_V\beta_H\beta_V)}{\epsilon N_H(\psi_1\psi_2\psi_3+\alpha(\gamma\epsilon+\psi_7+\gamma\,d_H+(\epsilon+\psi_3)\psi_4)N_H\beta_H)\beta_V},\\
I_H^* &= \frac{\alpha\epsilon(\delta\mu-\psi_6)N_H N_V\beta_H\beta_V-\psi_1\psi_2\psi_3\psi_5}{\epsilon N_H(\psi_1\psi_2\psi_3+\alpha(\gamma\epsilon+\psi_7+\gamma\,d_H+(\epsilon+\psi_3)\psi_4)N_H\beta_H)\beta_V},\\
I_V^* &= \frac{\alpha\epsilon(\delta\mu-\psi_6)N_H N_V\beta_H\beta_V-\psi_1\psi_2\psi_3\psi_5}{\alpha N_V\beta_H((\gamma\epsilon+\psi_7+\gamma\,d_H+(\epsilon+\psi_3)\psi_4)\psi_5+\epsilon(\delta\mu-\psi_6)N_H\beta_V)},
\end{aligned}$$

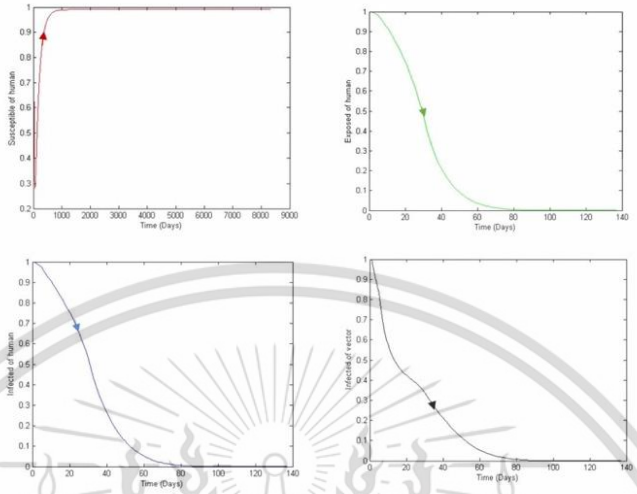

Figure 2: The time series of each population group for disease-free (S_H, E_H, I_H, I_V), $R_0 = 0.711$.

where $\psi_1 = (\varepsilon + d_H)$, $\psi_2 = (\gamma + d_H + d_d)$, $\psi_3 = (\delta\mu + d_H)$, $\psi_4 = (d_H + d_d)$, $\psi_5 = (d_V + d_k)$, $\psi_6 = (P-1)b_H$ *and* $\psi_7 = \delta(\gamma + \varepsilon)\mu$ The basic reproduction number of this model is calculated by using next generation matrix method [16] $R_0 = \sqrt{\frac{\alpha\varepsilon N_H N_V \beta_H \beta_V (\delta\mu - (P-1)b_H)}{(\varepsilon + d_H)(d_H + d_d + \gamma)(d_V + d_k)(\delta\mu + d_H)}}$

3 NUMERICAL RESULTS

The numerical analysis in this study considers the transmission of dengue disease with vaccination in the model where the values of the parameter value are: $\alpha = 1/7$, $\epsilon = 1/10, N_H = N_V = 10,000$, $\delta = 1/(30 * 6), \mu = 1/2$, $b_H = d_H = 1/(365 * 70), d_d = \gamma = 1/14, d_V = 1/7, d_k = 1/5, P = 0.35$ for the disease-free $\beta_H = 0.00005$ and endemic $\beta_H = 0.08$ [5–7, 9, 10, 15]. The numerical results are shown in Figure 2 and Figure 3

We will see that the solution converge to the disease-free equilibrium point for $R_0 < 1$ as show in figure 2 and the solution oscillate to the endemic point for $R_0 > 1$ as show in figure 3

4 DISCUSSION AND CONCLUSIONS

In this paper, we analyzed the SEIR model for human populations and the SI model for the vector population. In addition, we considered vaccination against dengue fever before the first infection of serotypes. The equilibrium point of all two states is the disease-free and endemic equilibrium point. The reproductive number R_0 is found by using the next generation matrix method. If R_0 less than one the disease-free state is locally asymptotically stable. Similarly, if R_0 more than one the endemic equilibrium point is locally asymptotically stable. We found that the factors that converge this system of equations are the transmission rate of dengue virus from vector to human and the vaccine efficiency. The numerical solutions compare parameters as shown in Figure 4 and Figure 5. From Figure 4, we will see that if the transmission rate of dengue virus from vector to human (β_H) is large, the slower of the convergence to an equilibrium point of susceptible human. Exposed human, infectious human and infectious vector converge to an equilibrium point quickly. In addition, from figure 5, we will see that if the vaccine efficiency (P) has a very small value, then the slower of the convergence of susceptible population to an equilibrium point. The faster of the convergence of exposed human, infectious human and infectious vector to an equilibrium point. However, there are many ways to prevent dengue fever. Including mosquito bites prevention, restricting mosquito breeding sites, as well as vaccinations, Dengvaxia still not able to completely preventable disease. World Health Organization recommends vaccination of dengue fever in people aged 9-45 years. In the case of never being infected with dengue virus before, there is a risk of subsequent severe dengue fever if there is later infection.

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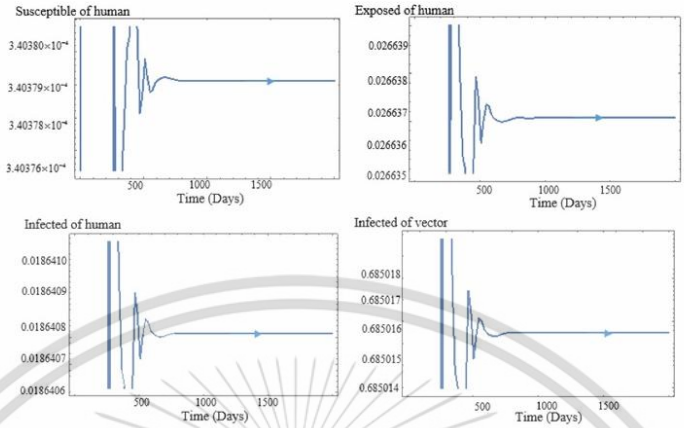

Figure 3: The time series of each population group for endemic (S_H, E_H, I_H, I_V), $R_0 = 90$.

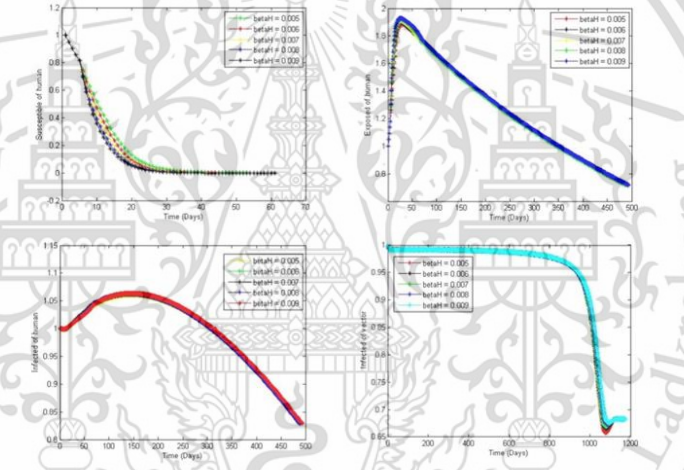

Figure 4: The time series of each population group compares parameters the transmission rate of dengue virus from vector to human for endemic equilibrium point (S_H, E_H, I_H, I_V).

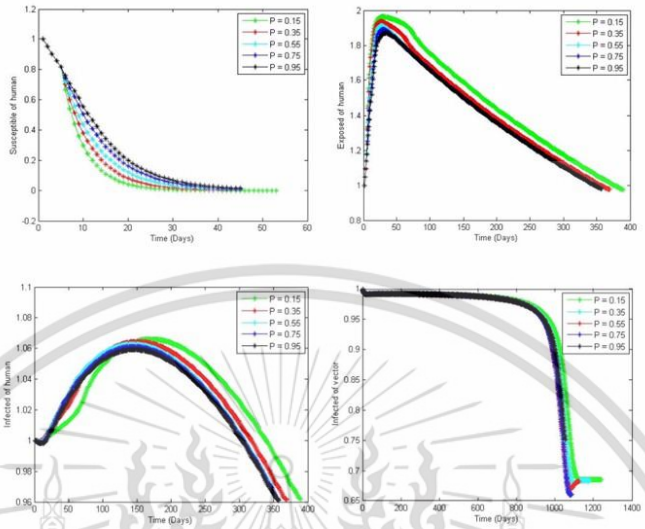

Figure 5: The time series of each population group compares parameters the vaccine efficiency for endemic (S_H, E_H, I_H, I_V).

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Appendix B

Paper 2

Optimal Control of Dengue Transmission with Vaccination

mathematics

MDPI

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 mosquitos. 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.

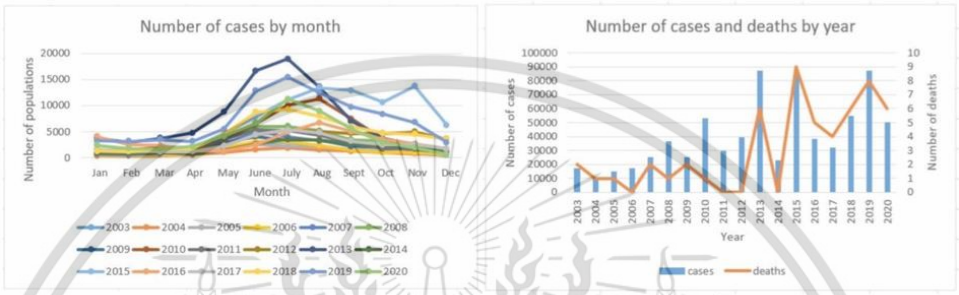


Figure 1. The number of cases by month and the number of cases and deaths each year from 2003–2020 [29]: (**a**) the number of cases by month; (**b**) the number of cases and deaths by year.

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.

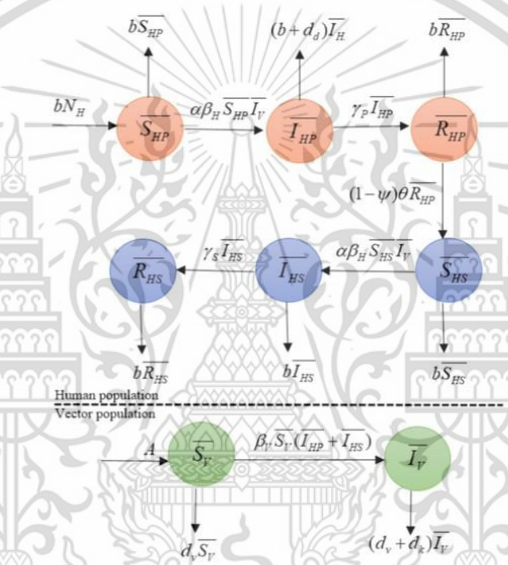


Figure 2. Diagram of the transmission model of dengue disease with the vaccination model of human and vector populations.

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

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

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

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

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

$$\frac{d\overline{I_{HS}}}{dt} = \alpha\beta_H\overline{S_{HS}}\overline{I_V} - \gamma_P\overline{I_{HS}} - b\overline{I_{HS}} \quad (5)$$

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

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

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

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 $f\left(t, \tilde{X}\right) = 0$ 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:

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

The endemic equilibrium point $E_2 = \left(S^*_{HP}, I^*_{HP}, R^*_{HP}, S^*_{HS}, I^*_{HS}, I^*_V\right)$ 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:

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

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 $E_1 = (1,0,0,0,0,0)$, where F is non-negative and V is non-singular. The F (gains) and V (losses) matrices are:

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

where:

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

The required matrices are:

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

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

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:

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

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 $d_{\hat{d}}$ 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]
$d_{\hat{d}}$	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.

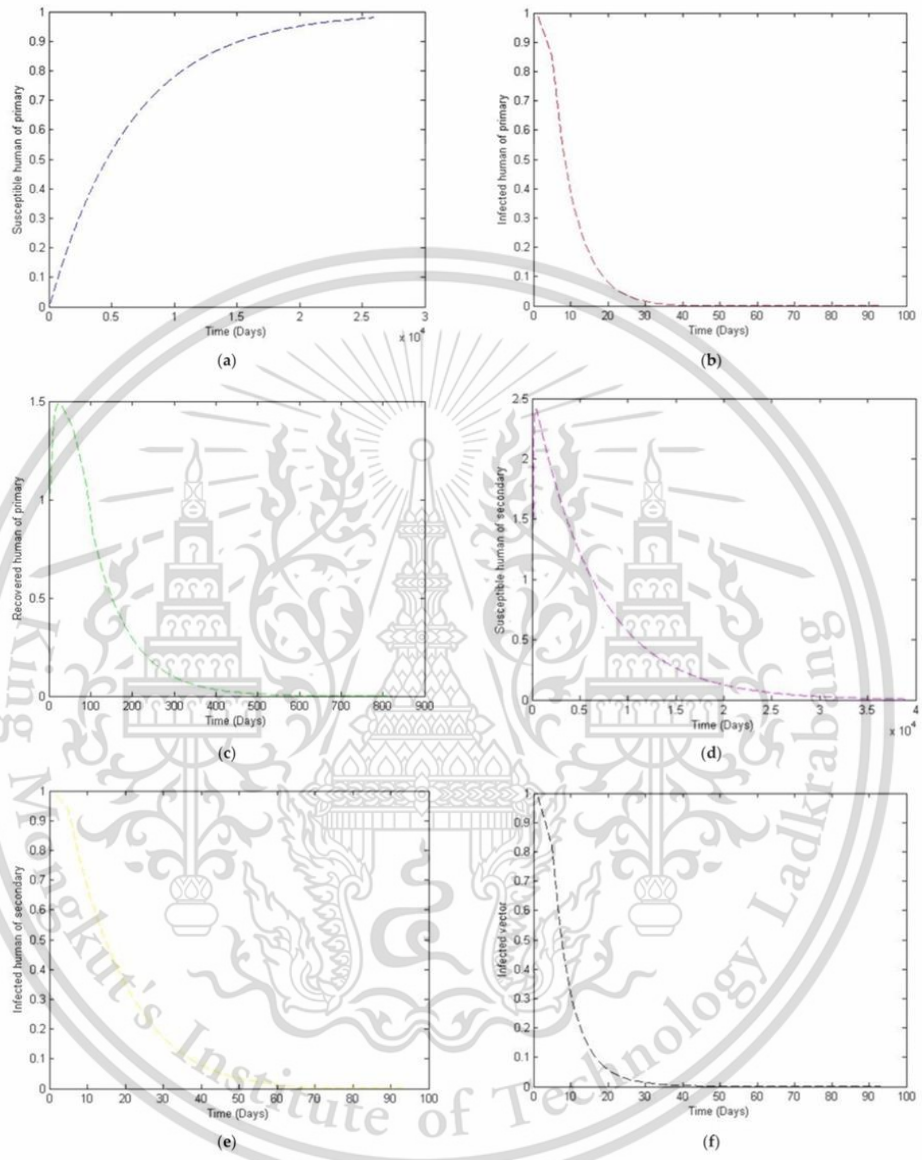


Figure 3. The trajectory of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V toward the disease-free equilibrium point for $R_0 < 1$ with parameter values according to Table 1. (**a**) Susceptibles of primary infection (**b**) Infected population with primary infection (**c**) Recovered human of primary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

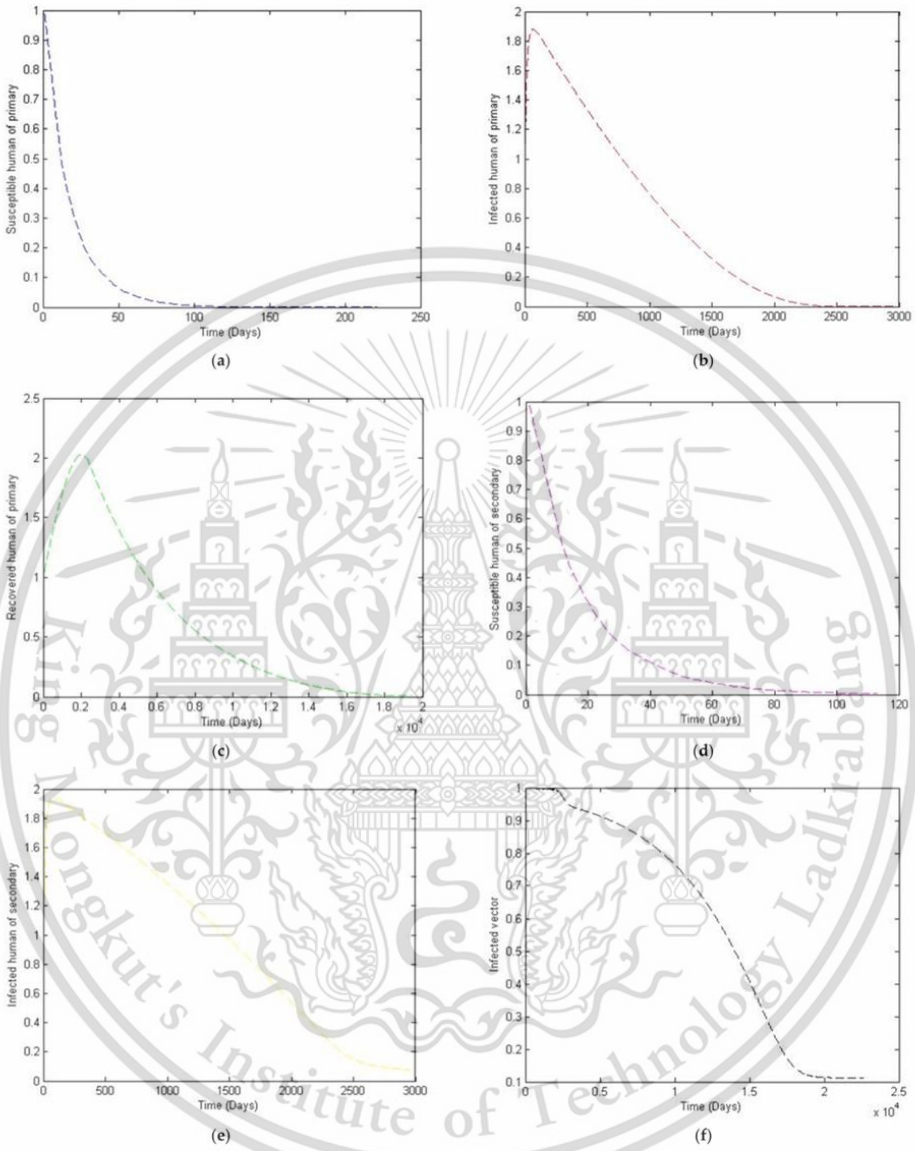


Figure 4. The trajectory of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V toward the endemic equilibrium point, for $R_0 > 1$ with parameter values according to Table 3. (**a**) Susceptibles of primary infection (**b**) Infected population with primary infection (**c**) Recovered human of primary infection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

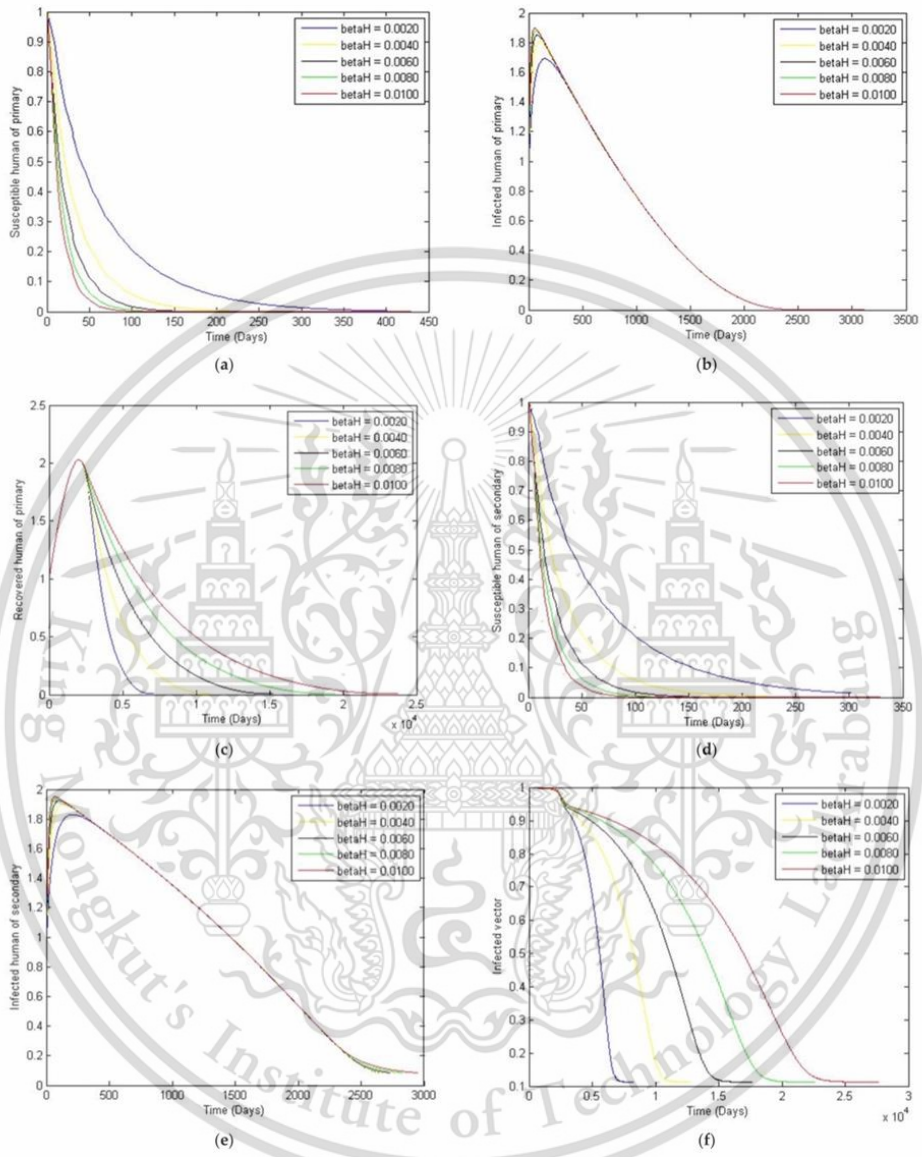


Figure 5. The trajectory of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V toward the endemic equilibrium point for $R_0 > 1$ with a comparison of the transmission rate of the dengue virus from vector to human, $\beta_H = 0.0020, 0.0040, 0.0060, 0.0080, 0.0100$, and parameter values according to Table 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.

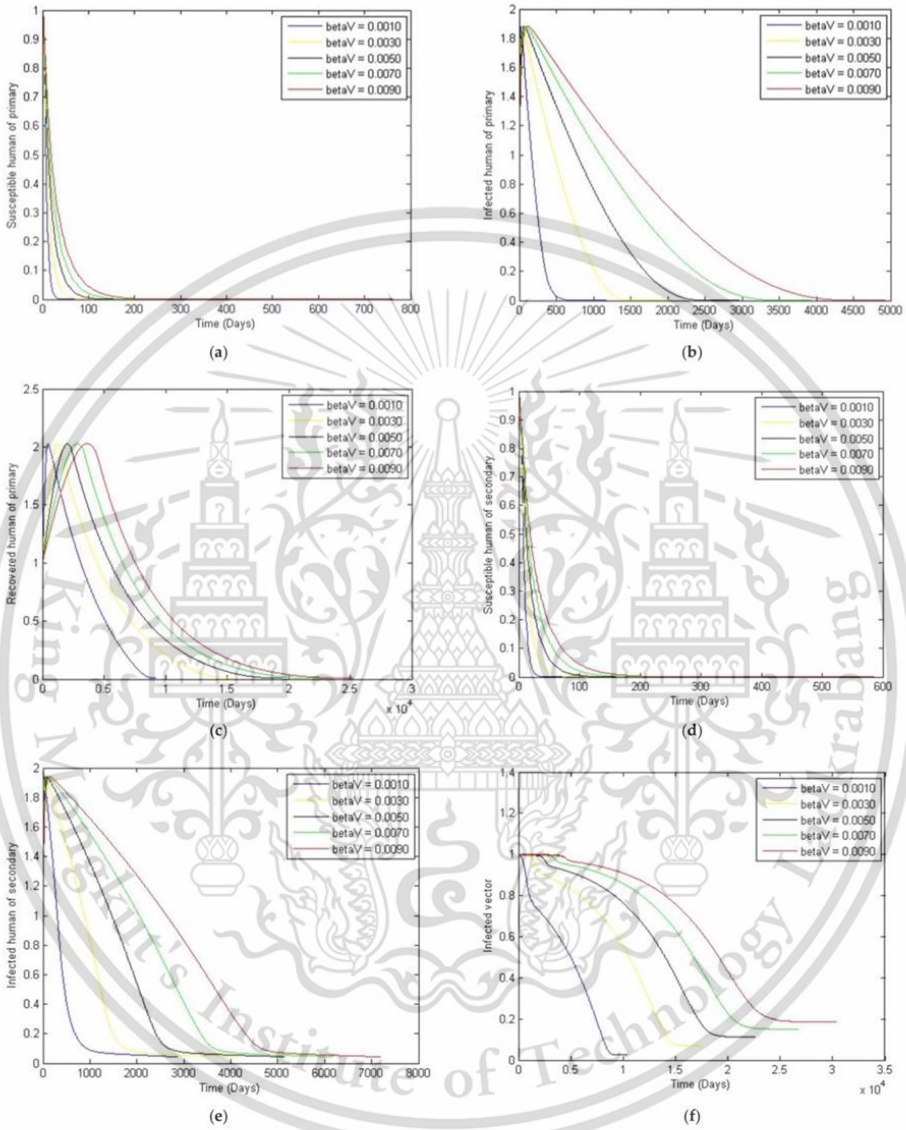


Figure 6. The trajectory of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V toward the endemic equilibrium point for $R_0 > 1$ with a comparison of the transmission rate of the dengue virus from human to vector, $\beta_V = 0.0010, 0.0030, 0.0050, 0.0070, 0.0090$, and parameter values according to Table 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.

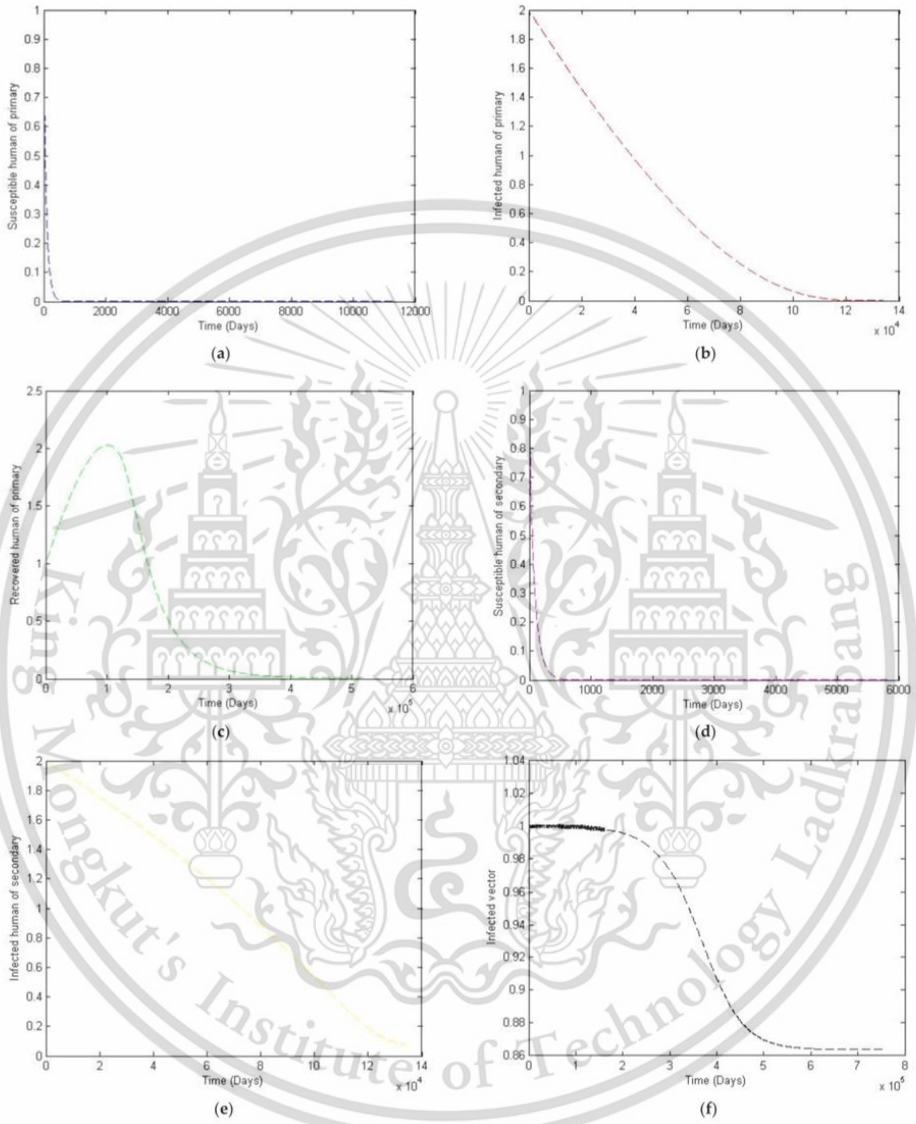


Figure 7. The trajectory of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V toward the endemic equilibrium point for $R_0 > 1$ with parameter values according to Table 3; changes N_H = 500,000, and N_V = 100,000 . (**a**) Susceptibles of primary infection (**b**) Infected population with primary infection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

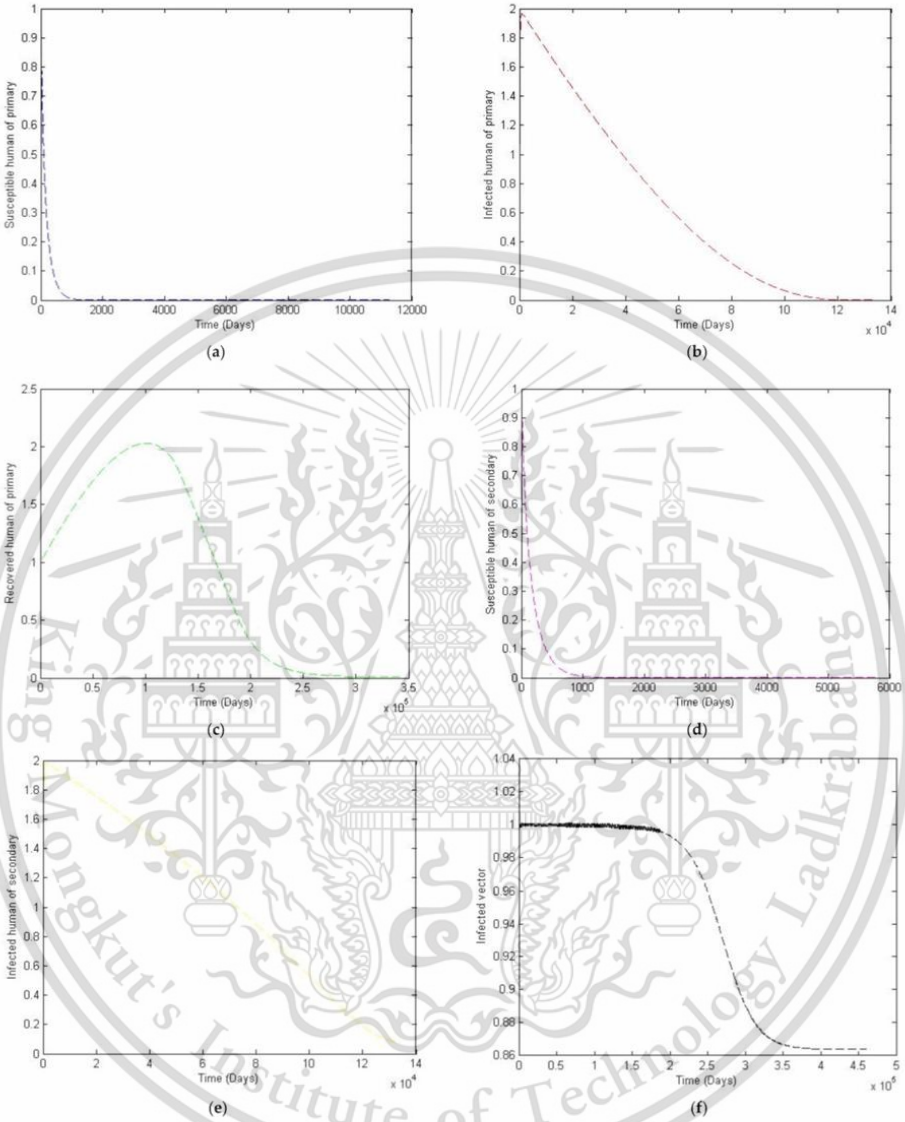


Figure 8. The trajectory of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V toward the endemic equilibrium point for $R_0 > 1$ with parameter values according to Table 3; changes N_H = 500,000, and $N_V = 100{,}000e^{(-1/14)t}$. (**a**) Susceptibles of primary infection (**b**) Infected population with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

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

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 $\overset{R_0}{p}$ 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
$d_{\hat{d}}$	−0.20825858
d_k	−0.3333333
γ_P	−0.2916001

Figure 9 plots a comparison of the R_0 values against the changes in $d_{\hat{d}}$ and γ_P. It can be seen that as the $d_{\hat{d}}$ and γ_P values change, the increment of R_0 in $d_{\hat{d}}$ is more pronounced than that of γ_P. This is reflected in the $\overset{R_0}{p}$ index, where $\overset{R_0}{d_{\hat{d}}}$ is significantly larger than $\overset{R_0}{\gamma_P}$. 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.

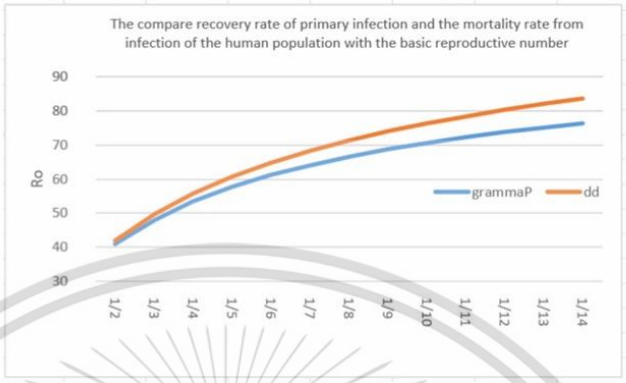


Figure 9. A comparison of parameters between d_d and γ_P with R_0.

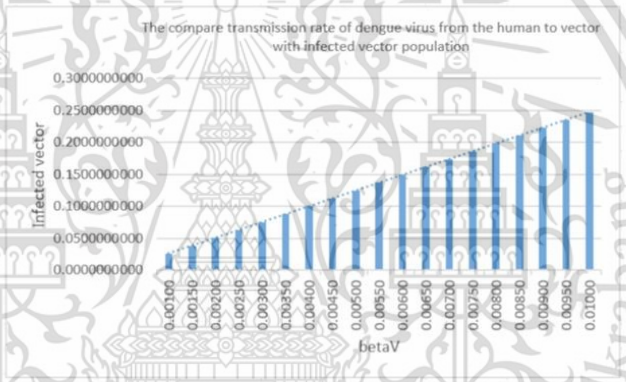


Figure 10. A comparison of parameters between β_V with $I_V{}^*$.

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:

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

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:

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

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* λ_1, λ_2, λ_3, λ_4, λ_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.

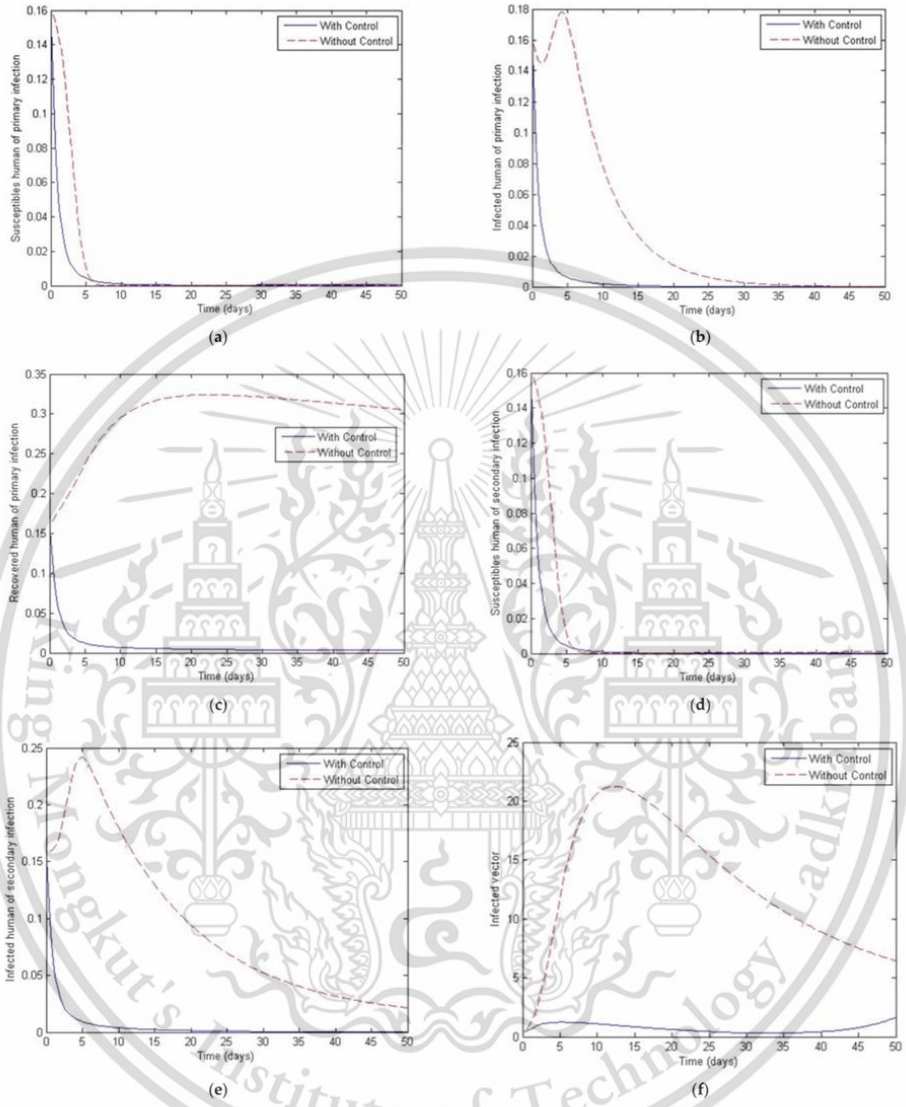


Figure 11. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V for $X_1 = 100$, $X_2 = 100$. (**a**) Susceptibles of primary infection (**b**) Infected population with primary infection (**c**) Recovered human of primary infection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

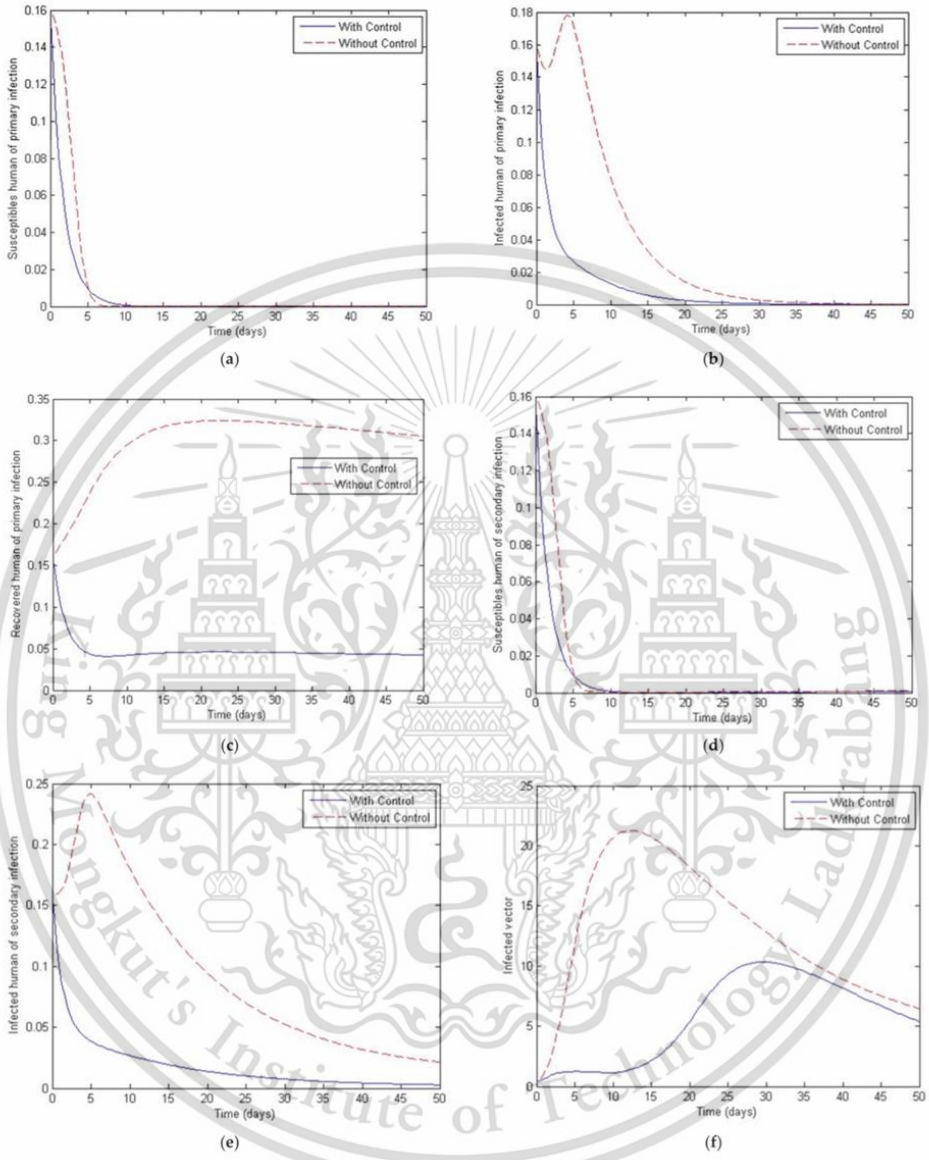


Figure 12. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V with $X_1 = 50$, $X_2 = 100$. (**a**) Susceptibles of primary infection (**b**) Infected population with primary infection (**c**) Recovered human of primary infection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

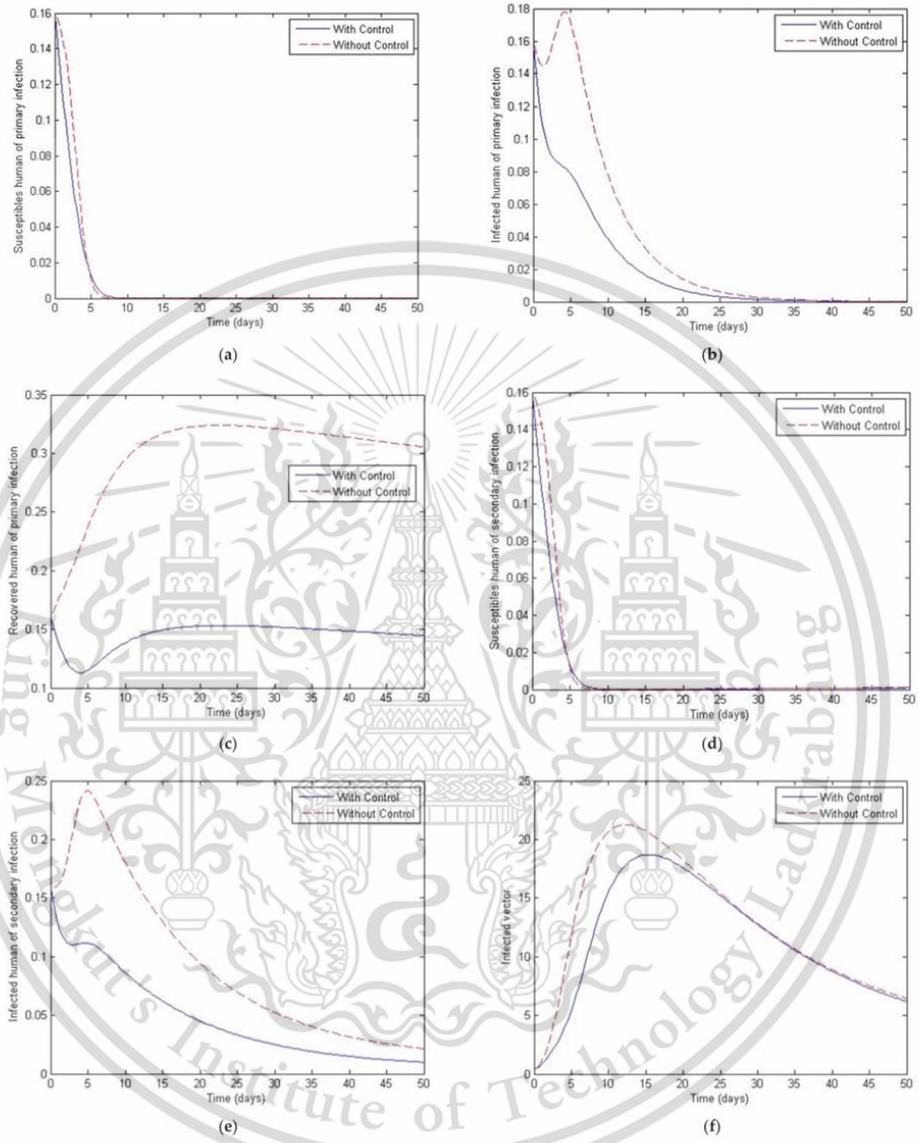


Figure 13. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V when $X_1 = 0.00001$, $X_2 = 100$. (**a**) Susceptibles of primary infection (**b**) Infected population with primary infection (**c**) Recovered human of primary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

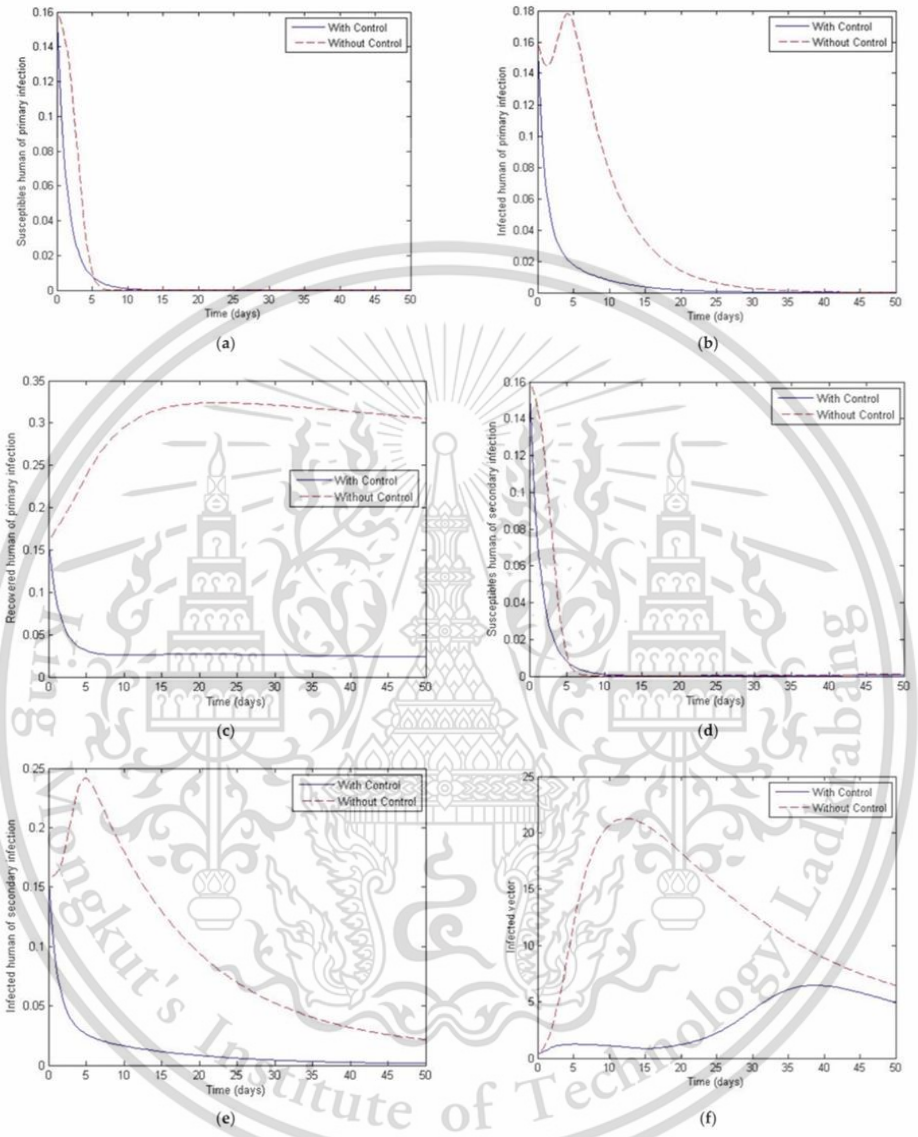


Figure 14. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V when $X_1 = 100$, $X_2 = 50$. (**a**) Susceptibles of primary infection (**b**) Infected population with primary infection (**c**) Recovered human of primary infection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

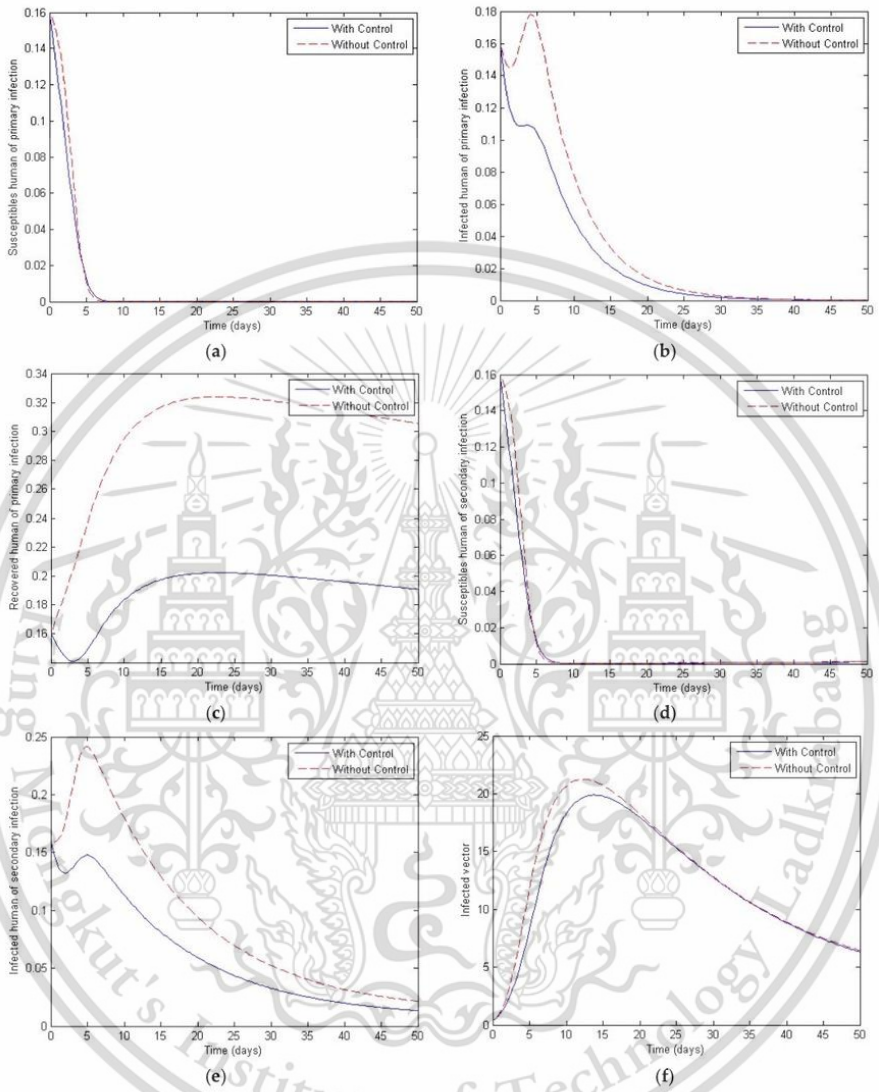
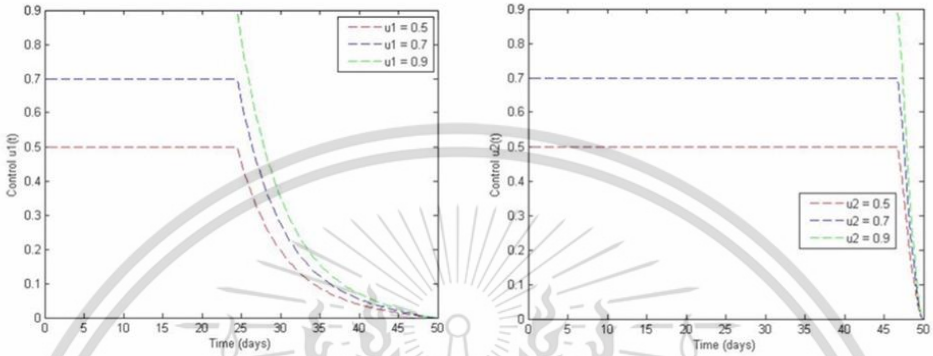


Figure 15. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V when $X_1 = 100$, $X_2 = 0.00001$. **(a)** Susceptibles of primary infection **(b)** Infected population with primary infection **(c)** Recovered human of primary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



(**a**) (**b**)

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.

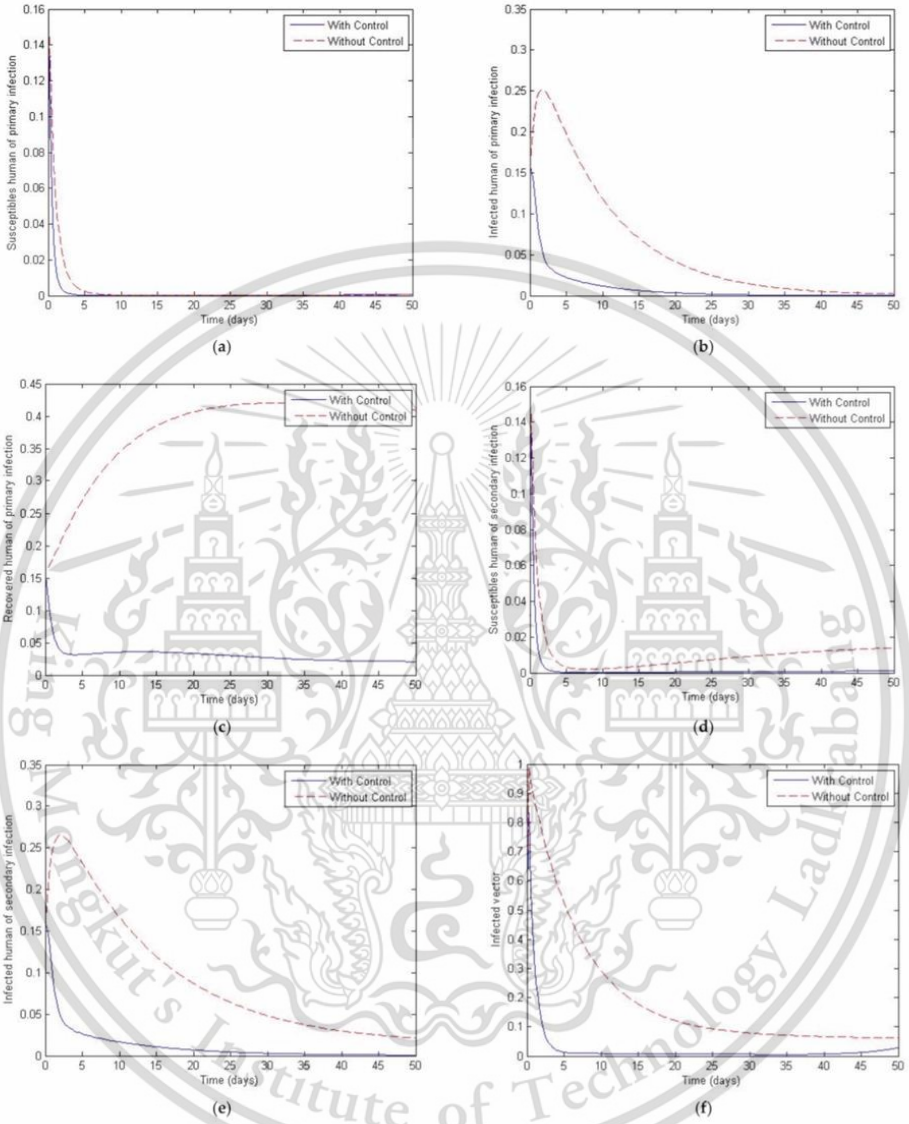


Figure 17. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V with $X_1 = 100$, $X_2 = 100$, $N_H = 500{,}000$, $N_V = 100{,}000$. (**a**) Susceptibles of primary infection (**b**) Infected population with primary infection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

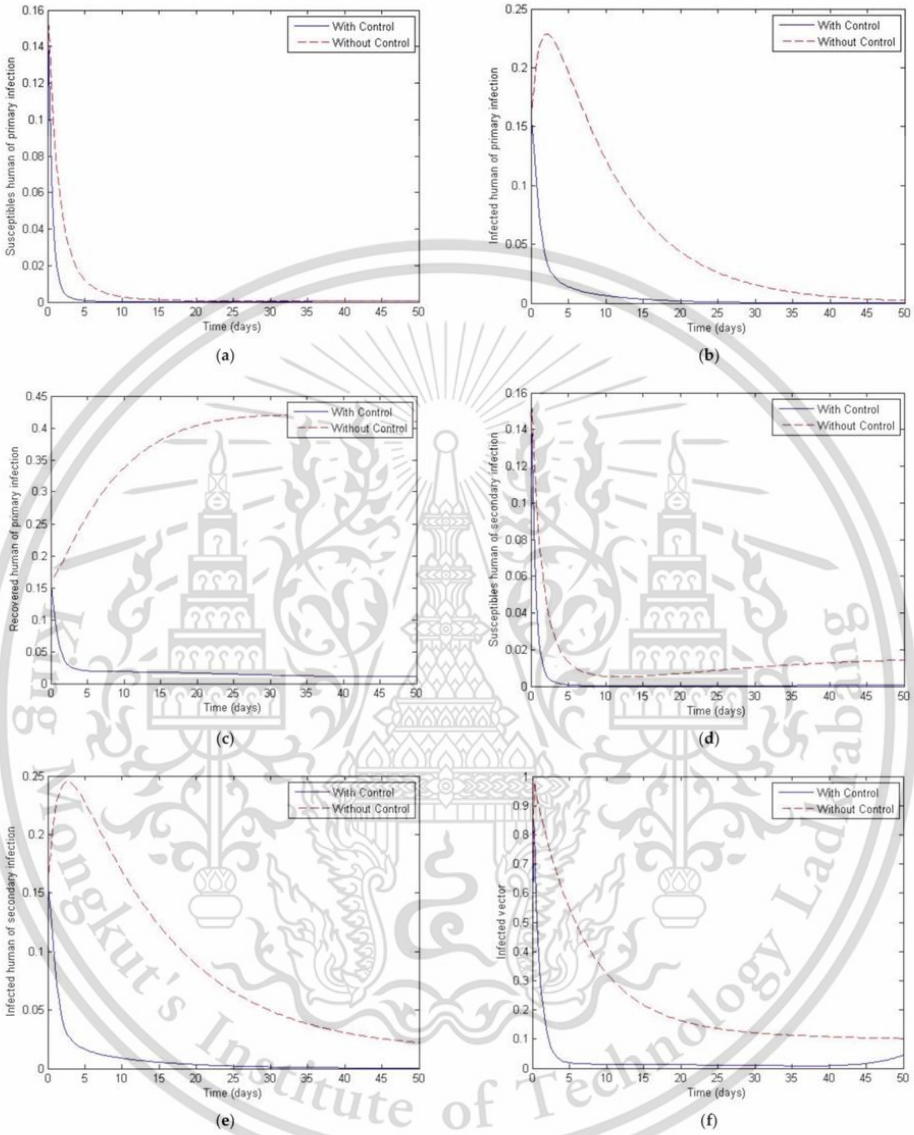


Figure 18. Simulation results of system of Equations (38)–(43) with and without controls of S_{HP}, I_{HP}, R_{HP}, S_{HS}, I_{HS} and I_V with $X_1 = 100$, $X_2 = 100$, $N_H = 500{,}000$, $N_V = 100{,}000e^{(-1/14)t}$. (**a**) Susceptibles of primary infection (**b**) Infected population with primary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

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Conflicts of Interest: The authors declare no conflict of interest.

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:

$$\lambda_1 = \lambda_2 = -b,\ \lambda_3 = -(b + \theta(1 + \psi)),\ \lambda_4 = -(b + \gamma_S),$$
$$\lambda_5 = -\left(\tfrac{1}{2}\varepsilon_1 + \sqrt{\varepsilon_1^2 - 4\varepsilon_2 - \varepsilon_3}\right), \text{ and } \lambda_6 = -\left(\tfrac{1}{2}\varepsilon_1 - \sqrt{\varepsilon_1^2 - 4\varepsilon_2 - \varepsilon_3}\right).$$

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. □

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:

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

$$\begin{aligned} a_2 =& \left(b + \alpha N_V \beta_H I^*_V\right)\left(3b - 2\theta(\psi - 1) + \alpha N_V \beta_H I^*_V\right) + d_k(3b + \theta - \theta\psi + 2\alpha N_V \beta_H I^*_V) \\ &+ N_H\left(\alpha N_V\left(S^*_{HP} - S^*_{HS}\right)\left(I^*_V - 1\right)\left(3b + \theta - \theta\psi + 2\alpha N_V \beta_H I^*_V\right)\left(\beta_H + I^*_{HP} - I^*_{HS}\right)\right)\beta_V \\ &+ d_V(3b + \theta - \theta\psi + 2\alpha N_V \beta_H I^*_V), \end{aligned}$$

$$\begin{aligned} a_3 =& b^2(b + \theta - \theta\psi) + 2b\alpha N_V \beta_H I^{2*}_V(b + \theta - \theta\psi) + \alpha^2 N_V^2 \beta_H^2 I^{*2}_V(b + \theta - \theta\psi) \\ &+ \left(b + \alpha N_V \beta_H I^*_V\right)\left(3b + 2\theta - 2\theta\psi + \alpha N_V \beta_H I^*_V\right)(d_k + d_V) \\ &+ b\alpha N_H N_V \beta_H \beta_V S^*_{HP}\begin{pmatrix} 2bI^*_V - 2b - 2b\theta I^*_V + 2\alpha N_V \beta_H - \alpha N_V \beta_H I^*_V + \alpha N_V \psi I^*_V \\ + \alpha\theta N_V + 2\alpha N_V \beta_H I^*_V + \alpha^2 N_V \beta_H I^*_V + \alpha^2 \theta\psi N_V \beta_H I^*_V \end{pmatrix} \\ &+ b\alpha N_H N_V \beta_H \beta_V S^*_{HS}\begin{pmatrix} 3b + 2b\theta - 2b\psi - 3b^2 - 2bI^*_V + 2b\psi I^*_V + 2\alpha N_V \beta_H I^*_V \\ - \alpha\psi N_V I^*_V - 3\alpha N_V \beta_H I^*_V + \alpha\psi N_V \beta_H I^*_V \end{pmatrix} \\ &+ b\alpha N_H N_V \beta_H \beta_V T^*_{HP}(6I^*_V + 2\psi + \alpha N_V \beta_H I^*_V) + b\alpha N_H N_V \beta_H \beta_V I^*_{HS} I^*_V(6 + 2\psi - \alpha N_V \beta_H), \end{aligned}$$

$$\begin{aligned} a_4 =& (b + \theta - \theta\psi)\left(b + \alpha N_V \beta_H I^*_V\right)^2(d_k + d_V) + N_H \beta_V(b + \theta - \theta\psi)\left(b + \alpha N_V \beta_H I^*_V\right)^2\left(I^*_{HP} - I^*_{HS}\right) \\ &+ b\alpha N_V\left(I^*_V - 1\right)\beta_H\left(\left(b + \theta - \theta\psi\right)\left(S^*_{HP} - S^*_{HS}\right)\left(b + \alpha N_V \beta_H I^*_V\right) + \alpha\theta(\psi - 1)N_V S^*_{HP} I^*_V \beta_H \gamma_P\right). \end{aligned}$$

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. □

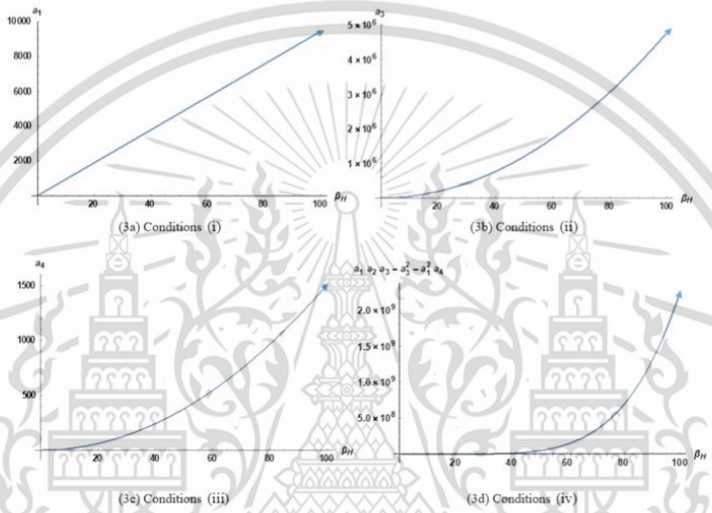

Figure A1. All parameter spaces of endemic equilibrium are satisfied with the Routh–Hurwitz criteria.

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:

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

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

Theorem A4. *There exists the adjoint variables λ_1, λ_2, λ_3, λ_4, λ_5 and λ_6 under the control that satisfies the following:*

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

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:

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

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

The adjoint associated system is obtained as follows:

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

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:

$$\frac{\partial H}{\partial u_1} = X_3 u_1 - \lambda_4 I_{HS} = 0 \qquad u_1^*(t) = \frac{\lambda_4 I_{HS}}{X_3} \tag{A13}$$

$$\frac{\partial H}{\partial u_2} = X_4 u_2 - \lambda_6 (1 - I_V)\beta_V (I_{HP} + I_{HS}) N_H = 0 \qquad u_2^*(t) = \frac{\lambda_6 (1-I_V)\beta_V (I_{HP}+I_{HS}) N_H}{X_4} \tag{A14}$$

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

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

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

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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Appendix C

Paper 3

Local and Global Stability Analysis of Dengue Disease with Vaccination and Optimal Control

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Local and Global Stability Analysis of Dengue Disease with Vaccination and Optimal Control

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Abstract: Dengue fever is a disease that has spread all over the world, including Thailand. Dengue is caused by a virus and there are four distinct serotypes of the virus that cause dengue DENV-1, DENV-2, DENV-3, and DENV-4. The dengue viruses are transmitted by two species of the *Aedes* mosquitoes, the *Aedes aegypti*, and the *Aedes albopictus*. Currently, the dengue vaccine used in Thailand is chimeric yellow tetravalent dengue (CYD-TDV). This research presents optimal control which studies the vaccination only in individuals with a documented past dengue infection (seropositive), regardless of the serotypes of infection causing the initial infection by the disease. The analysis of dengue transmission model is used to establish the local asymptotically stabilities. The property of symmetry in the Lyapunov function an import role in achieving this global asymptotically stabilities. The optimal control systems are shown in numerical solutions and conclusions. The result shows that the control resulted in a significant reduction in the number of infected humans and infected vectors.

Keywords: dengue fever; global asymptotically stabilities; local asymptotically stabilities; optimal control; vaccination

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1. Introduction

Mosquito-borne dengue fever viral disease infects hundreds of millions of people in tropical and subtropical areas every year [1]. Thailand has reported outbreaks of dengue fever for more than 60 years. At present, dengue fever has spread throughout the country, every province, and every district [2]. Dengue hemorrhagic fever is contagious with the *Aedes aegypti* mosquito being an important disease-carrying insect in many rural areas. The *Aedes albopictus* is a second disease-carrying mosquito. The four virus serotypes that cause dengue virus (DENV) are DENV-1, DENV-2, DENV-3, and DENV-4 [3–5]. In Thailand, the *Aedes aegypti* mosquito is considered to be the primary vector of the dengue virus. Infection with dengue serotype provides lifelong immunity to that serotype and will have cross-protection against other species heterotypic immunity for a short period of time [6,7]. The clinical symptoms of dengue virus infection range from being asymptomatic to severe illness that can lead to death if not properly treated. In most cases involving young children, there is a mild fever with a red rash and the child is said to be suffering from blood fever. In older children teenagers and adults, the symptoms may be worse, i.e., they may come down with high fevers, thrombocytopenia, leukopenia, rashes, myalgia, and arthralgia. Dengue fever (DF) is more common in children under 15 years of age. In areas in which hyperemia is also occurring, there may be recurrent dengue infections during which the more severe symptoms are occurring, and the patients may be suffering from dengue hemorrhagic fever (DHF). If the plasma leakage becomes extremely severe, the illness develops into dengue shock syndrome (DSS) [8–10] and the patient might die.

The incidence of dengue fever infection appears to be age dependent. Pongsumpun and Tang [11] reported that in one province in Thailand in 1998, mentioned that most of the cases occurred in children below the age of 15. Sriprom et al. [12] mentioned that this did not change much. What changed over time was the dengue strain responsible for the infection, very few of the dengue infections were due to DENV-4. In the last few years, the greatest number of infections is caused by the DENV-4 strain. We have not taken this change into account. Most infections caused by the dengue virus and other viruses lead are either asymptomatic or minimally symptomatic with no way to tell whether the patients were infected or not. Burke et al. [13] reported that 87% of the tested infected children in Bangkok Thailand in 1980–1981 belong to these two groups. We do not expect much had changed over the years except for the strain of the dengue virus.

A vaccine to prevent dengue fever has recently been developed. The vaccine efficacy of the dengue vaccine was moderate at 56.5%, meaning it could prevent more than half the number of dengue infections. The dengue vaccine reductions in hospital admissions by 80.3% [14], and 67.2% [15]. The CYD-TDV vaccine is highly effective among children with serological evidence of prior DENV infection. A Phase 3 study of dengue vaccine found that dengue vaccine was able to reduce the severity of the disease by 88.5% and prevent dengue by 90.0% [16]. A cautionary note should be mentioned, there is an increased risk of hospitalization of the vaccinated individual among groups without prior infections. Mass vaccination with the CYD-TDV vaccine should not be undertaken in countries that do not have a history of dengue infections by most of the strains of the DENV. This is why the vaccination programs involving this vaccine have been stopped in countries such as Thailand, where there is a prior history of infections by multiple strains of the DENV's.

The chimeric yellow fever dengue virus tetravalent dengue vaccine (CYD-TDV) covers four serotypes of dengue. The Dengue vaccination program requires a total of three injections, 6 months apart at 0, 6, and 12 months. The optimal age for injection is over 9 years [17]. A single dose of dengue vaccination is as effective as the three-dose vaccination program. This may be due to the fact that 79% of the cohort in the study had dengue seropositivity at baseline in countries with dengue-endemic areas [18]. The immunization obtained from vaccination gradually loses as time goes on. Once infected with any serotypes, the body will always be immune to those serotypes. However, they are temporarily immune to other serotypes, thus there is a chance of re-infecting dengue in other serotypes until all are complete.

The World Health Organization (WHO) aims to reduce the mortality and morbidity of dengue by at least 50% and 25%, respectively, by 2020 [19]. Esteva and Vargus [20] studied local stability and global stability of models with the susceptible-infected-recovery (SIR) model of dengue transmission and assumed that the human population and the vector population are constant. Chanprasopchai et al. [21] studied dengue fever and the effect of vaccination with analyzed of stable conditions of an equilibrium point of the model using Routh–Hurwitz criteria. A mathematical model of dengue with and without awareness in the host population [22] assumes that some hosts do not interact with infected mosquitoes. This is because they take different preventive measures due to their perception of the disease. Wu and Wong [23] studied the mathematical model with two delays to reflect the extrinsic and intrinsic incubation periods of virus in the dengue disease transmission model. The stability analysis of two equilibrium points is carried out and a simulation is given for different parameter settings and to simulate the succession of two epidemics with variable human populations [24]. Khan and Fatmawati [25] described changes in dengue infection from basic reproductive values which defines a model with hospitalization and presents the changes in detail. The results suggest that spraying insecticides on mosquitoes can significantly reduce dengue infection. Pongsumpun et al. [26] studied a mathematical model of the dengue model with a vertical transmission control mechanism based on the dengue model. The two policy control models were insecticide and vaccinations which simulated the parameters affecting this model control. The authors [27] study a dynamic basic mathematical model for dengue transmission in Thailand, by including infection of

different serotypes to analyze the effects of different vaccination strategies. With an interest in the optimal control between primary and secondary infection. There are many studies about applying to solve the optimal control problem of dengue fever [28–32].

In Thailand, data on dengue hemorrhagic fever (DHF) comes from the Department of Disease Control, the Ministry of Health. It is seen that dengue hemorrhagic fever is prevalent in 2013 per 100,000 which is the highest and the number of morbidities will trend fluctuated each year from 2003 to 2020. Likewise, when the number of mortality direct variation with the number of morbidities, but this is a very small percentage compared to the infected as shown in Figure 1.

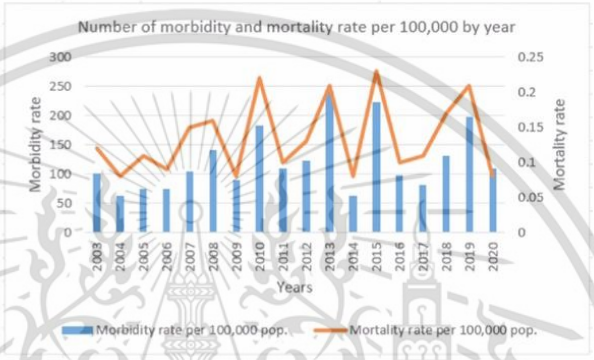

Figure 1. The number of morbidity and mortality rate per 100,000 by year from 2003–2020 [33].

In this paper, we study the vaccination only in individuals with a documented past dengue infection (seropositive), regardless of the serotypes of infection, with a simplified model. This model focused on the population of Thailand for the provinces with high morbidity rates, such as Mae Hong Son, Rayong, Nakhon Ratchasima, Chaiyaphum, Chainat, and the regions with the highest morbidity rates were the Northeast, North, Central, Southern regions, respectively, where there were outbreaks of dengue hemorrhagic fever, resulting in people who have been infected with dengue fever being re-infected. The human population is modeled through the SEIRS framework, and the vector population is modeled using the SI model. Local and global stability analyses are given with the basic reproduction number being the bifurcation point. The property of symmetry in the Lyapunov function an important role in achieving this global asymptotically stabilities. The optimal control is applied in the spreading model to minimizes the number of infected human and infected vector populations. The results are then given numerically to demonstrate the analyses.

2. Materials and Methods

The mathematical model of the dengue transmission is for the vector population and the human population. The susceptible–infected (SI) and susceptible–exposed–infected–recovered (SEIRS) model for vector and human population, respectively. In Thailand, some regions are densely populated with a high prevalence of *Aedes* mosquitoes. This model of dengue outbreak considers vaccination only in previously infected populations as it reduces the severity of the disease and reduces the rate of hospitalization for the next infection. Note that dengue fever has four different serotypes, and we can get infected up to four times. Vaccination should be administered after each injection to minimize the risk of hospitalization and the severity of the disease in following infections. Once infected with any dengue serotype, the person is immune to that serotype for life and only has a short period of time of cross-protection against other species, as advised by the World

Health Organization. In this model, the transmission of the dengue virus when vaccinated after each infection is described. The human and vector populations are divided into four and two individuals, respectively. The variables and parameters are defined listed in Table 1. The dynamic dengue fever model with vaccination after each infectious is shown in Figure 2.

Table 1. The parameters used in the numerical simulation.

Variables and Parameters	Biological Meaning
$\overline{S_H}$	The number of susceptible human population
$\overline{S_V}$	The number of susceptible vector population
$\overline{E_H}$	The number of exposed human population
$\overline{I_H}$	The number of infected human population
$\overline{I_V}$	The number of infected vector population
$\overline{R_H}$	The number of recovered vector population
P	The vaccine efficiency
β_H	The transmission rate of dengue virus from vector to the human
β_V	The transmission rate of dengue virus from the human to vector
α	The biting rate of vector population
θ	The recurrent infection rate
ε	The incubation rate
γ	The recovery rate
A	The constant recruitment rate
d_H	The natural mortality rate of the human population
d_d	The mortality rate from infection of the human population
d_V	The natural mortality rate of the vector population
d_k	The mortality rate from infection of the vector population
b_H	The birth rate
N_H	The total number of the human population
N_V	The total number of the vector population

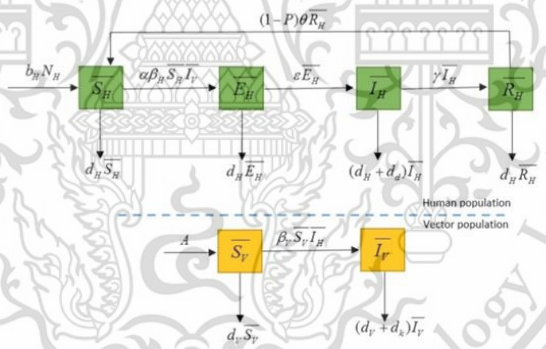

Figure 2. Schematic diagram representation compartments vector and human population after each infectious dengue fever.

The dynamics behavior model of human and vector population is encapsulated in the following systems of differential equations:

$$\frac{d\overline{S_H}}{dt} = b_H N_H + (1-P)\theta\overline{R_H} - \alpha\beta_H\overline{S_H I_V} - d_H\overline{S_H} \quad (1)$$

$$\frac{d\overline{E_H}}{dt} = \alpha\beta_H\overline{S_H I_V} - \varepsilon\overline{E_H} - d_H\overline{E_H} \quad (2)$$

$$\frac{d\overline{I_H}}{dt} = \varepsilon\overline{E_H} - \gamma\overline{I_H} - (d_H + d_d)\overline{I_H} \tag{3}$$

$$\frac{d\overline{R_H}}{dt} = \gamma\overline{I_H} - (1-P)\theta\overline{R_H} - d_H\overline{R_H} \tag{4}$$

$$\frac{d\overline{S_V}}{dt} = A - \beta_V\overline{S_V}\overline{I_H} - d_V\overline{S_V} \tag{5}$$

$$\frac{d\overline{I_V}}{dt} = \beta_V\overline{S_V}\overline{I_H} - (d_V + d_k)\overline{I_V} \tag{6}$$

with the conditions

$$\overline{S_H} + \overline{E_H} + \overline{I_H} + \overline{R_H} = N_H \tag{7}$$

$$\overline{S_V} + \overline{I_V} = N_V \tag{8}$$

The rate of change of the total population of human and vector are as follows:

$$\frac{d\overline{S_H}}{dt} + \frac{d\overline{E_H}}{dt} + \frac{d\overline{I_H}}{dt} + \frac{d\overline{R_H}}{dt} = 0 \tag{9}$$

$$\frac{d\overline{S_V}}{dt} + \frac{d\overline{I_V}}{dt} = 0 \tag{10}$$

The conditions of Equations (7) and (8) employ:

$$\overline{I_H} = \frac{(b_H - d_H)N_H}{d_d} \tag{11}$$

$$\overline{I_V} = \frac{A - d_V N_V}{d_k} \tag{12}$$

Normalizing the equations with assuming the proportion number of the individual following as:

$$S_H = \frac{\overline{S_H}}{N_H}, E_H = \frac{\overline{E_H}}{N_H}, I_H = \frac{\overline{I_H}}{N_H}, R_H = \frac{\overline{R_H}}{N_H} \tag{13}$$

$$S_V = \frac{\overline{S_V}}{N_V}, I_V = \frac{\overline{I_V}}{N_V} \tag{14}$$

we also have

$$S_H + E_H + I_H + R_H = 1 \tag{15}$$

$$S_V + I_V = 1 \tag{16}$$

The normalized system of equations is:

$$\left.\begin{array}{l} \frac{dS_H}{dt} = b_H + (1-P)(1 - S_H - E_H - I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H \\ \frac{dE_H}{dt} = \alpha\beta_H S_H I_V N_V - \varepsilon E_H - d_H E_H \\ \frac{dI_H}{dt} = \varepsilon E_H - \gamma I_H - (d_H + d_d) I_H \\ \frac{dI_V}{dt} = \beta_V (1 - I_V) I_H N_H - (d_V + d_k) I_V \end{array}\right\} \tag{17}$$

3. Analysis of the Model

3.1. Positivity Invariant Sets of the Model

Proposition 1. *From [34], let $(S_H(t), E_H(t), I_H(t), R_H(t), S_V(t), I_V(t))$ be the solution of Equations (1)–(6) with positive initial conditions $S_H(0), E_H(0), I_H(0), R_H(0), S_V(0), I_V(0)$. Denoting also the invariant set $\phi = \left\{(S_H, S_V, E_H, I_H, I_V, R_H) \in \mathbb{R}^6_+ : N_H \leq \frac{b_H}{d_H}, N_V \leq \frac{A}{d_V}\right\}$ then the closed set ϕ is positive invariant that attracts all solutions in the space $\mathbb{R}^6_+$.*

Proof. We begin by setting $N_T(t) = (N_H(t), N_V(t)) = (S_H + E_H + I_H + R_H, S_V + I_V)$.

The differentiation yields:

$$\begin{aligned}\frac{dN_T(t)}{dt} &= \left(\frac{dN_H(t)}{dt}, \frac{dN_V(t)}{dt}\right)\\ &= (b_H - d_H S_H - d_H E_H - d_H I_H - d_d I_H - d_H R_H, A - d_V S_V - d_V I_V - d_k I_V)\\ &= (b_H - d_H N_H - d_d I_H, A - d_V N_V - d_k I_V)\\ &\leq (b_H - d_H N_H, A - d_V N_V)\end{aligned}$$

Hence, $\frac{dN_H(t)}{dt} = b_H - d_H N_H \leq 0$ for $N_H(t) \geq \frac{b_H}{d_H}$ and $\frac{dN_V(t)}{dt} = A - d_V N_V \leq 0$ for $N_V(t) \geq \frac{A}{d_V}$. Then $\frac{dN_T(t)}{dt} \leq 0$ wherever $N_H(t) \geq \frac{b_H}{d_H}$ and $N_V(t) \geq \frac{A}{d_V}$. Integrating the above equation, it follows that $\frac{dN_T(t)}{dt} \leq 0$ on $0 \leq N_H(t), N_V(t) \leq (\frac{b_H}{d_H} + N_H(0)e^{-d_H t}, \frac{A}{d_V} + N_V(0)e^{-d_V t})$. As $t \to \infty, e^{-d_H t} \to 0, e^{-d_V t} \to 0,$ and then $0 \leq N_H(t), N_V(t) \leq \left(\frac{b_H}{d_H}, \frac{A}{d_V}\right)$. Since the epidemiological parameters are assumed to be positive, it follows that the region of all solutions of ϕ will be in $\mathbb{R}^6_+$. Thus ϕ is a positively invariant set. Note that all equations described by Equations (1)–(6) in the non-negative octant $\mathbb{R}^6_+$ are positively invariant [34–36]. □

3.2. Equilibrium Points of the Model

Let us find equilibrium points of system Equation (17) that describe the model. Note that by setting the right-hand side of system Equation (17) to zero yields two equilibrium points, namely:

The disease-free equilibrium point:

$$E_1 = (1, 0, 0, 0)$$

The endemic equilibrium point:
$E_2 = (S^*_H, E^*_H, I^*_H, I^*_V)$ with

$$\begin{aligned}S^*_H &= \frac{(\pi_1\pi_2((\gamma\varepsilon - \pi_3\theta + \gamma d_H + (\varepsilon + \pi_4)\pi_5)d_K - (\gamma\varepsilon - \pi_3\theta + \gamma d_H + (\varepsilon + \pi_4)\pi_5)d_V - \varepsilon\pi_8 N_H\beta_V))}{\varepsilon N_H((\pi_7 - d_H)\pi_1\pi_2 - \alpha(\gamma\varepsilon - \pi_3\theta + \gamma d_H + (\varepsilon + \pi_4)\pi_5)N_V\beta_H)\beta_V}\\ E^*_H &= \frac{\pi_2(\pi_1\pi_2\pi_4\pi_6 - \alpha\varepsilon(\pi_7 - b_H)N_H N_V\beta_H\beta_V)}{\varepsilon N_H(\pi_1\pi_2\pi_4 + \alpha(\gamma\varepsilon - \pi_3\theta + \gamma d_H + (\varepsilon + \pi_4)\pi_5)N_V\beta_H)\beta_V}\\ I^*_H &= \frac{\pi_1\pi_2\pi_4\pi_6 - \alpha\varepsilon(\pi_7 - b_H)N_H N_V\beta_H\beta_V}{N_H(\pi_1\pi_2\pi_4 + \alpha(\gamma\varepsilon - \pi_3\theta + \gamma d_H + (\varepsilon + \pi_4)\pi_5)N_V\beta_H)\beta_V}\\ I^*_V &= \frac{(\pi_7 - d_H)\pi_1\pi_2\pi_6 + \alpha\varepsilon\pi_8 N_H N_V\beta_H\beta_V}{\alpha N_V\beta_H((\gamma\varepsilon - \pi_3\theta + \gamma d_H + (\varepsilon + \pi_4)\pi_5)\pi_6 + \varepsilon\pi_8 N_H\beta_V)}\end{aligned} \tag{18}$$

where

$$\pi_1 = (\varepsilon + d_H),\ \pi_2 = (\gamma + d_H + d_d),\ \pi_3 = (P-1)(\gamma + \varepsilon),\ \pi_4 = (\theta - P\theta + d_H),$$
$$\pi_5 = (d_H + d_d),\ \pi_6 = (d_V + d_k),\ \pi_7 = (P-1)\theta,\ \pi_8 = (\theta - P\theta + b_H).$$

3.3. Basic Reproductive Number

The next-generation matrix method of the works in [37,38] is used to compute the basic reproductive number (R_0) for the dengue model of system Equation (17). The classes E_H, I_H, and I_V are identified as influencing the new infections. The F and V matrices are obtained as follows:

$$F = \begin{bmatrix} 0 & 0 & \alpha\beta_H S_H N_V \\ 0 & 0 & 0 \\ 0 & \beta_V S_V N_H & 0 \end{bmatrix},\ V = \begin{bmatrix} d_H + \varepsilon & 0 & 0 \\ -\varepsilon & d_H + d_d + \gamma & 0 \\ 0 & 0 & d_V + d_k \end{bmatrix}$$

$$V^{-1} = \begin{bmatrix} \frac{1}{(d_H+\varepsilon)} & 0 & 0 \\ \frac{\varepsilon d_V + \varepsilon d_k}{(\varepsilon+d_H)(\gamma+d_H+d_d)(d_V+d_k)} & \frac{1}{(\gamma+d_H+d_d)} & 0 \\ 0 & 0 & \frac{1}{(d_V+d_k)} \end{bmatrix}$$

The basic reproductive number is obtained through the spectral radius of the matrix $R_0 = \rho FV^{-1}$ is called the reproductive number and given by:

$$R_0 = \sqrt{\frac{\alpha\varepsilon((P-1)\theta - b_H)N_H N_V \beta_H \beta_V}{((P-1)\theta - d_H)(\gamma + d_H + d_d)(\varepsilon + d_H)(d_V + d_k)}} \tag{19}$$

3.4. Local Stability Analysis

In this section, we are going to analyze the stability condition of two equilibrium points, namely the disease-free E_1 and the endemic E_2 equilibrium points. The outcome of stability condition analysis of these equilibria is shown in the following—Theorems 1 and 2. The obtained Jacobian matrix is:

$$J_{E_i} = \begin{bmatrix} (P-1)\theta - d_H - \alpha\beta_H I_V N_V & (P-1)\theta & (P-1)\theta & -\alpha\beta_H S_H N_V \\ \alpha\beta_H I_V N_V & -\varepsilon - d_H & 0 & 0 \\ 0 & \varepsilon & -\gamma - d_H - d_d & 0 \\ 0 & 0 & \beta_V N_H - \beta_V N_H I_V & -\beta_V N_H I_H - d_V - d_k \end{bmatrix} \tag{20}$$

Theorem 1. *If $R_0 < 1$, then the disease-free equilibrium point E_1 of Equations (17)–(20) is locally asymptotically stable and unstable otherwise.*

Proof. The characteristic polynomial of the Jacobian matrix of Equation (20) evaluated at the disease-free equilibrium is:

$$\det(J_{E_1} - \lambda I) = 0 \tag{21}$$

The eigenvalues (λ) are obtained from the roots of Equation (21) where I is identity matrix (4×4) the matrix is:

$$\begin{aligned} \lambda_1 &= -(\varepsilon + d_H), \\ \lambda_2 &= -((P+1)\theta + d_H), \\ \lambda_3 &= -(d_H + d_d + \gamma), \\ \lambda_4 &= -(d_V + d_k). \end{aligned}$$

It is obvious that all the eigenvalues have negative real part. Therefore, E_1 is locally asymptotically stable [38]. □

Theorem 2. *The endemic equilibrium point E_2 is locally asymptotically stable if $R_0 > 1$ and unstable otherwise.*

Proof. The characteristic equation of the Jacobian matrix evaluated at the endemic equilibrium is:

$$\det(J_{E_2} - \lambda I) = 0 \tag{22}$$

One eigenvalue of the above matrix is $\lambda = -(d_H + d_d + \gamma) < 0$. The rest of the characteristic equation is considered in the form of

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \tag{23}$$

where

$$a_1 = \varepsilon + \theta + P\theta + 2d_H + d_k + d_V + \alpha N_V I_V^* \beta_H + N_H I_H^* \beta_V$$
$$a_2 = d_H^2 + (1-P)\varepsilon\theta + d_V(\varepsilon + \theta - P\theta) + a_{21}(\alpha\varepsilon + \alpha\theta + P\alpha\theta + \alpha\varepsilon\theta + P\alpha\varepsilon\theta + \alpha d_V)$$
$$+ d_k(a_{22}) + N_H I_H^*(a_{22})\beta_V + d_H(a_{22} + 2(d_k + d_V + N_H I_H^* \beta_V))$$
$$a_3 = d_k(a_{31} - \alpha(\varepsilon + (P-1)(\varepsilon-1)\theta + d_H)a_{21}) + d_V(a_{31} - a_{32})$$
$$+ N_H(\alpha^2 \varepsilon N_V^2 S_H^*(I_V^* - 1) I_V^* \beta_H^* + I_H^*(a_{31} - a_{32}))\beta_V.$$

where $a_{21} = N_V I_V^* \beta_H$, $a_{22} = \varepsilon + \theta - P\theta + \alpha a_{21}$, $a_{31} = ((P-1)\theta - d_H)(\varepsilon + d_H)$, $a_{32} = \alpha(\varepsilon + (P-1)(\varepsilon-1)\theta + d_H)a_{21}$ and S_H^*, I_H^*, and I_V^* are defined Equation (21).

By using Routh–Hurwitz criteria [37,38] for $n = 3$, then E_2 is stable if conditions (i)–(iv) are satisfied. Since algebraic proofs may be a little difficult to verify these conditions, we then resort to numerical simulations. We plot the values of the conditions against the changes in β_H, which is shown in Figure 3. It is seen that these conditions are indeed satisfied (i) $a_1 > 0$, (ii) $a_2 > 0$, (iii) $a_3 > 0$, and (iv) $a_1 a_2 - a_3 > 0$.

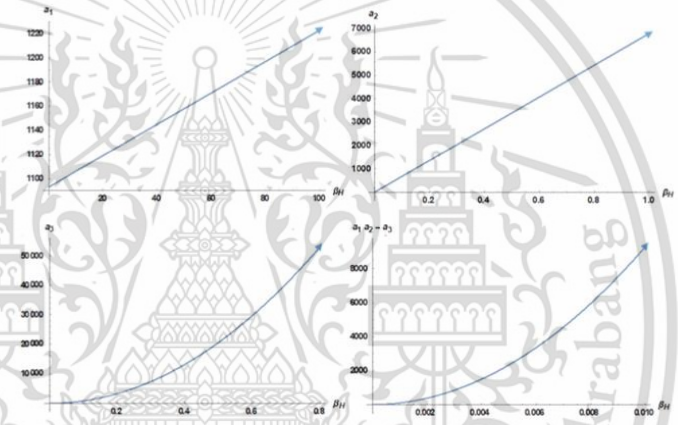

Figure 3. The Routh–Hurwitz criteria conditions satisfied (i)–(iv) for the endemic equilibrium point.

It then follows that the polynomial of Equation (23) will indeed be Hurwitz, which thus implies the stability of the endemic equilibrium E_2. □

3.5. Global Stability Analysis

The global stability of each equilibrium point of the model in system Equation (17) is investigated in this section. To serve this purpose, we hereby derive two theorems.

Definition 1. *(Lyapunov) Let $x = 0$ be an equilibrium point $\dot{x} = f(x)$ and $f(x) : \phi \subset \mathbb{R}^n$. Let $V(x) : \phi \to \mathbb{R}$ be a continuously differentiable function such that:*

(i) $V(0) = 0$
(ii) $V(x) > 0$ *in* ϕ, *except at* $x = 0$
(iii) $\dot{V}(0) = 0$
(iv) $\dot{V}(x) < 0$ *in* ϕ, *except at* $x = 0$

If $\dot{V}(x) < 0$ in $\phi - \{0\}$, then $x = 0$ is globally asymptotically stable.

Theorem 3. *Let $E_1^* = (S_H^*, E_H^*, I_H^*, S_H^*, I_V^*) = (1,0,0,0)$ the disease-free E_1^* is globally asymptotically stable on ϕ if and only if $R_0 < 1$ where ϕ are defined as Proposition 1.*

Proof. Consider the following Lyapunov function candidate [39–42]:

$$\omega(S_H, E_H, I_H, I_V) = (S_H - S_H^* ln S_H) + E_H + I_H + I_V$$

This function satisfies the positive definiteness condition as required for a Lyapunov function since the positive invariances have been proven in Proposition 1. Furthermore, it should provide ease in the proving of the negative definiteness in its time derivative, as compared to say a quadratic candidate, which is more prominently used as one such candidate.

The derivative with respect to time yields:

$$\frac{d\omega}{dt} = \left(1 - \frac{S_H^*}{S_H}\right)\frac{dS_H}{dt} + \frac{dE_H}{dt} + \frac{dI_H}{dt} + \frac{dI_V}{dt}$$

$$= \left(1 - \tfrac{S_H^*}{S_H}\right)(b_H + (1-P)(1 - S_H - E_H - I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H)$$
$$+(\alpha\beta_H S_H I_V N_V - \varepsilon E_H - d_H E_H) + (\varepsilon E_H - \gamma I_H - (d_H + d_d)I_H)$$
$$+(\beta_V(1 - I_V)I_H N_H - (d_V + d_k)I_V)$$

$$= \left(1 - \tfrac{S_H^*}{S_H}\right)(b_H + (1-P)(1 - S_H - E_H - I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H)$$
$$-d_H E_H - (d_H + d_d)I_H + (\beta_V(1 - I_V)I_H N_H - (d_V + d_k)I_V)$$

Substituting the relation of disease-free $E_1^* = (1,0,0,0)$, we obtain:

$$= \left(1 - \frac{S_H^*}{S_H}\right)(b_H - d_H S_H) - d_H E_H - (d_H + d_d)I_H - (d_V + d_k)I_V$$

$$= \left[d_H\left(1 - \frac{S_H}{S_H^*}\right) + b_H\left(1 - \frac{S_H^*}{S_H}\right)\right] - d_H E_H - (d_H + d_d)I_H - (d_V + d_k)I_V$$

From Equation (11) at the disease-free, we obtain $b_H = d_H$ thus

$$= \left[d_H\left(1 - \frac{S_H}{S_H^*}\right) + d_H\left(1 - \frac{S_H^*}{S_H}\right)\right] - d_H E_H - (d_H + d_d)I_H - (d_V + d_k)I_V$$

$$= d_H\left(2 - \frac{S_H}{S_H^*} - \frac{S_H^*}{S_H}\right) - d_H E_H - (d_H + d_d)I_H - (d_V + d_k)I_V$$

$$= -d_H\left(\frac{(S_H^* - S_H)^2}{S_H^* S_H}\right) - d_H E_H - (d_H + d_d)I_H - (d_V + d_k)I_V$$

$$\frac{d\omega}{dt} = -\left[d_H\left(\frac{(S_H^* - S_H)^2}{S_H^* S_H}\right) + d_H E_H + (d_H + d_d)I_H + (d_V + d_k)I_V\right] \quad (24)$$

As can be seen, all of the terms in Equation (24) are always negative. Now, using LaSalle's invariance principle [39], we have $\frac{d\omega}{dt} \leq 0$ and so the function $\frac{d\omega}{dt}$ is to be negative definite. Each solution's limit set is included in the biggest invariant set for which $S_H = S_H^*, E_H = E_H^*, I_H = I_H^*$, and $I_V = I_V^*$ which is the singleton $\{E_1^*\}$. The disease-free equilibrium point E_1^* is then globally asymptotically stable on ϕ according to LaSalle's invariant principle. □

Theorem 4. *When $R_0 > 1$, the endemic equilibrium point E_2^* is defined as Equation (18). Then Equation (21) is globally asymptotically stable on ϕ if and only if*

$$\begin{cases} b_H = d_H S_H^* \\ I_V = \frac{\beta_V I_H N_H}{\beta_V I_H N_H + d_V + d_k} \end{cases} \tag{25}$$

Proof. The Lyapunov function is in the form:

$$\zeta(S_H, E_H, I_H, I_V) = (S_H - S_H^* ln S_H) + E_H + I_H + I_V$$

The derivative with respect to time yields:

$$\frac{d\xi}{dt} = \left(1 - \frac{S_H^*}{S_H}\right)\frac{dS_H}{dt} + \frac{dE_H}{dt} + \frac{dI_H}{dt} + \frac{dI_V}{dt}$$

$$= \left(1 - \tfrac{S_H^*}{S_H}\right)(b_H + (1-P)(1 - S_H - E_H - I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H)$$
$$-d_H E_H - (d_H + d_d)I_H + (\beta_V(1 - I_V)I_H N_H - (d_V + d_k)I_V)$$

$$= \begin{pmatrix} b_H - b_H\frac{S_H^*}{S_H} - d_H S_H + d_H S_H^* + (1-P)(1 - S_H - E_H - I_H)\theta \\ -(1-P)(1 - S_H - E_H - I_H)\theta\frac{S_H^*}{S_H} \end{pmatrix} - d_H E_H - (d_H + d_d)I_H$$
$$+(\beta_V(1 - I_V)I_H N_H - (d_V + d_k)I_V)$$

$$= \left(b_H\left(1 - \tfrac{S_H^*}{S_H}\right) + d_H S_H^*\left(1 - \tfrac{S_H}{S_H^*}\right) + (1-P)(1 - S_H - E_H - I_H)\theta\left(1 - \tfrac{S_H^*}{S_H}\right)\right)$$
$$-d_H E_H - (d_H + d_d)I_H + (\beta_V(1 - I_V)I_H N_H - (d_V + d_k)I_V)$$

Substituting the expressions for d_H and I_V, we obtain:

$$= b_H\left(\left(1 - \frac{S_H^*}{S_H}\right) + \left(1 - \frac{S_H}{S_H^*}\right)\right) - d_H E_H - (d_H + d_d)I_H$$

$$= -b_H\left(\frac{(S_H^* - S_H)^2}{S_H^* S_H}\right) - d_H E_H - (d_H + d_d)I_H$$

$$\frac{d\xi}{dt} = -\left(b_H\frac{(S_H^* - S_H)^2}{S_H^* S_H} + d_H E_H + (d_H + d_d)I_H\right) \tag{26}$$

Hence, the condition of Equation (26) shows that $\frac{d\xi}{dt} \leq 0$ for $(S_H, E_H, I_H, I_V) \in \phi$, and the strict quality holds only for $S_H = S_H^*$, $E_H = E_H^*$, $I_H = I_H^*$, and $I_V = I_V^*$. Then the endemic equilibrium point E_2^* is globally asymptotically stable in ϕ. □

Note that the exact solution of the system may also be revived by using the powerful tool of Lie algebra. For further information, see the works of Shang [43,44].

4. Numerical Simulation

In this section, we investigate the impact of the transmission of dengue consider only re-infectious, regardless of individual serotypes each time they were infected. The initial values for the parameter are listed in Table 2. The parameter values of dengue cases in Thailand are estimated. The information was gathered from the Ministry of Public Health's Department of Disease Control. Note that although most parameter's initial values are taken from the source literature. However, certain values must be estimated and assumed for the purposes of this model. There are four parameters to be estimated: N_H, N_V, d_d, and d_k and two parameters to be assumed: β_H and β_V. The model of system Equation (17) is

then simulated with the use of a differential equation solver in MATLAB. The results of our present numerical simulation are shown in Figures 4–7.

Table 2. The initial value for the parameters.

Parameters	The Disease-Free	The Endemic	Source
α	1/7	1/7	[45–50]
ε	1/10	1/10	[45–50]
P	0.5	0.5	[45–50]
θ	$1/(30 \times 6)$	$1/(30 \times 6)$	[45–50]
N_H	250,000	250,000	estimated
N_V	200,000	200,000	estimated
β_H	0.00000025	0.005	assumed
β_V	0.00000012	0.003	assumed
b_H	$1/(365 \times 70)$	$1/(365 \times 70)$	[45–50]
d_H	$1/(365 \times 70)$	$1/(365 \times 70)$	[45–50]
d_V	1/14	1/14	[45–50]
d_d	1/14	1/14	estimated
d_k	1/7	1/7	estimated
γ	1/14	1/14	[45–50]

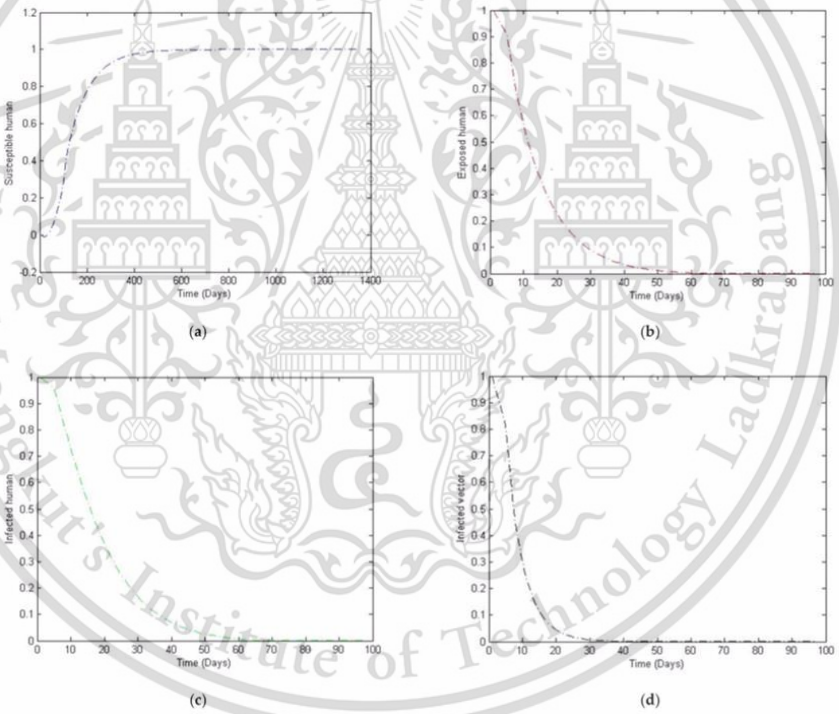

Figure 4. Graphs of system Equation (17) at the disease-free equilibrium point of S_H, E_H, I_H, and I_V for $R_0 < 1$. (**a**) Susceptible human, (**b**) exposed human, (**c**) infected human, and (**d**) infected vector.

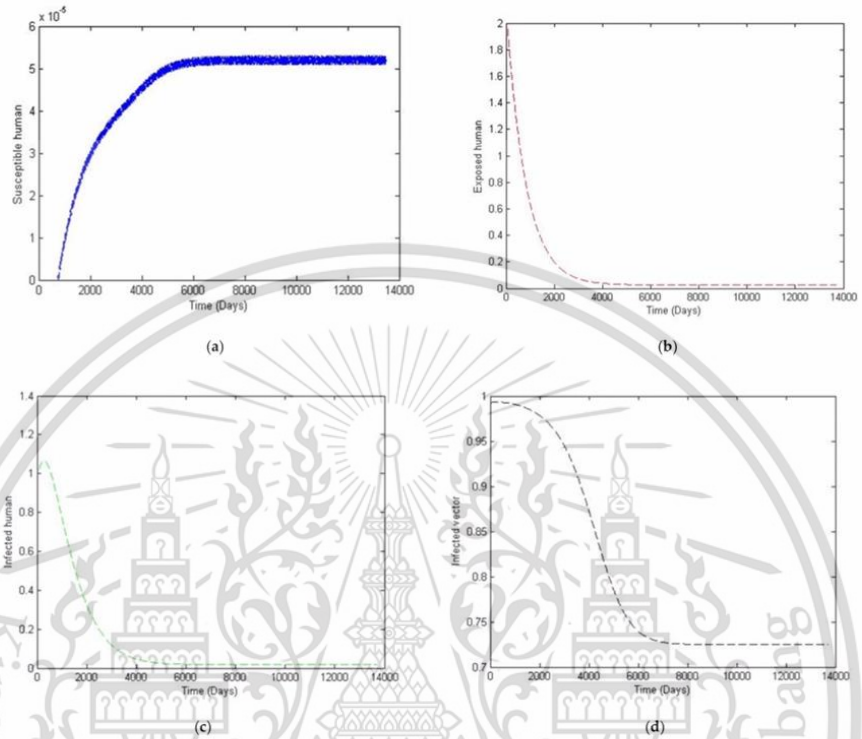

Figure 5. Graphs of system Equation (17) at the endemic equilibrium point of S_H, E_H, I_H, and I_V for $R_0 > 1$. (**a**) Susceptible human, (**b**) exposed human, (**c**) infected human, and (**d**) infected vector.

The model of Equation (17) is solved using the differential solver ode45 in MATLAB. This solver employs the fourth-order Runge-Kutta method with adjustable step size to solve the system of differential equations.

Figure 4 shows the numerical solution of the disease-free equilibrium where $R_0 < 1$ after about 500, 60, 65, and 30 days for the susceptible human, exposed human, infected human, and infected vector it converges to $E_1 = (1, 0, 0, 0)$, respectively. Figure 5 shows the numerical solution of the endemic equilibrium where $R_0 > 1$ after about 6500, 4000, 5000, and 7000 days for the susceptible human, exposed human, infected human, and infected vector it converges to $E_2 = (0.00005, 0.02689, 0.01881, 0.73048)$, respectively. Figures 6 and 7 show the numerical solution of the endemic equilibrium with compares parameters the dengue virus transmission rate from vector to human $\beta_H = 0.01, 0.03, 0.05, 0.07, 0.09$ and the dengue virus transmission rate from human to vector $\beta_V = 0.002, 0.004, 0.006, 0.008, 0.010$ for the susceptible human, exposed human, infected human, and infected vector. We can observe that the higher the dengue virus transmission rate from vector to human β_H and the dengue virus transmission rate from human to vector β_V, the slower the convergence to a susceptible human equilibrium point. The exposed human, infected human, and infected vector all rapidly reach a point of equilibrium, respectively.

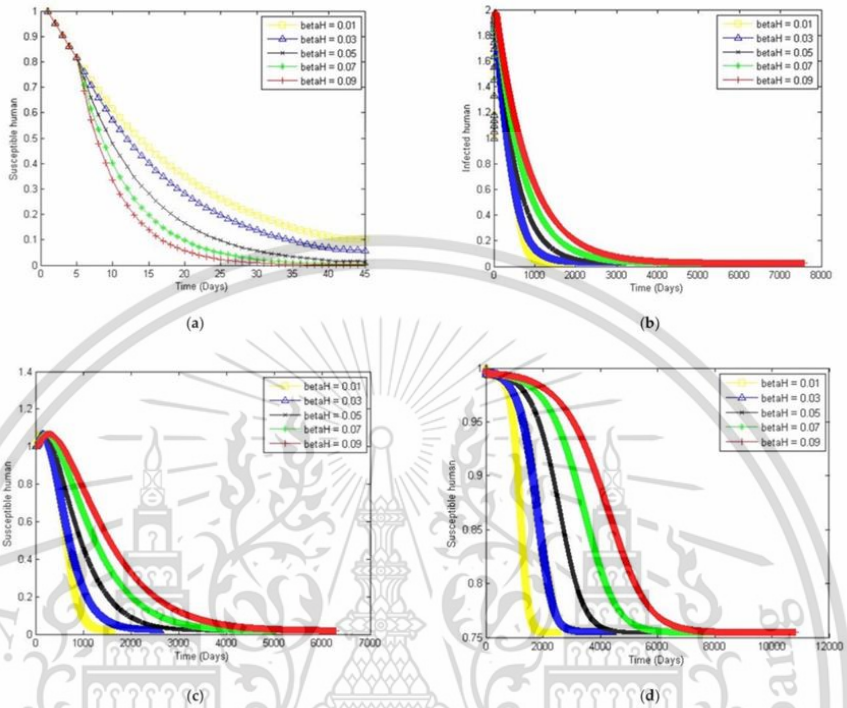

Figure 6. Graphs of system Equation (17) at the endemic equilibrium point of S_H, E_H, I_H, and I_V for $R_0 > 1$ with compares parameter $\beta_H = 0.01, 0.03, 0.05, 0.07, 0.09$. (**a**) Susceptible human, (**b**) exposed human, (**c**) infected human, and (**d**) infected vector.

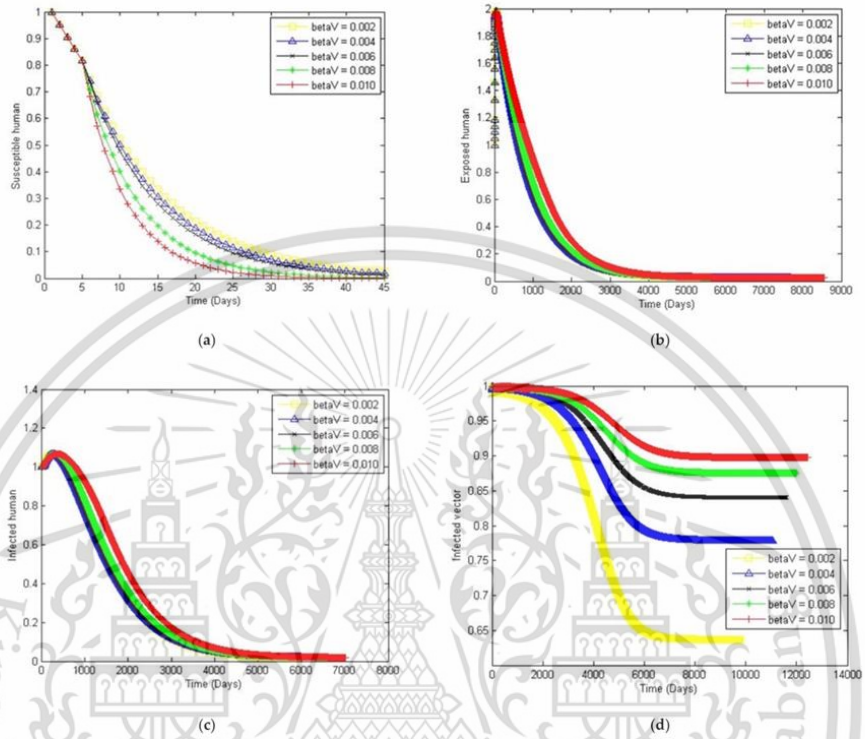

Figure 7. Graphs of system Equation (17) at the endemic equilibrium point of S_H, E_H, I_H, and I_V for $R_0 > 1$ with compares parameter $\beta_V = 0.002, 0.004, 0.006, 0.008, 0.010$. (**a**) Susceptible human, (**b**) exposed human, (**c**) infected human, and (**d**) infected vector.

5. Optimal Control Strategies

In this section, we apply the Pontryagin's maximum principle (PMP) to derive the necessary conditions for the solution for the existence of optimal control. Equations (17) can be rewritten as an optimal control problem with the goal of reducing the number of infected human populations. Two control inputs may be assigned to the system since they include the dynamics of both human and vector populations, namely u_1 where this control input represents an effort to reduce the number of infected humans by giving vaccinations to humans, and u_2 for the vector population represents the administration of repellents to mosquitoes and destroying mosquito breeding sites. The system of equations with control is written as:

$$\frac{dS_H}{dt} = b_H + (1-P)R_H\theta - \alpha\beta_H S_H I_V N_V - d_H S_H - u_1(t) I_H \tag{27}$$

$$\frac{dE_H}{dt} = \alpha\beta_H S_H I_V N_V - \varepsilon E_H - d_H E_H \tag{28}$$

$$\frac{dI_H}{dt} = \varepsilon E_H - \gamma I_H - (d_H + d_d) I_H \tag{29}$$

$$\frac{dR_H}{dt} = \gamma I_H - (1-P)\theta R_H - d_H R_H \tag{30}$$

$$\frac{dS_V}{dt} = \frac{A}{N_V} - \beta_V S_V I_H N_H - d_V S_V - u_2(t) S_V \tag{31}$$

$$\frac{dI_V}{dt} = \beta_V S_V I_H N_H - (d_V + d_k) I_V - u_2(t) \beta_V S_V I_H N_H \tag{32}$$

In normalized compartments Equations (27)–(32) are:

$$\frac{dS_H}{dt} = b_H + (1-P)(1 - S_H - E_H - I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H - u_1(t) I_H \tag{33}$$

$$\frac{dE_H}{dt} = \alpha\beta_H S_H I_V N_V - (\varepsilon + d_H) E_H \tag{34}$$

$$\frac{dI_H}{dt} = \varepsilon E_H - (d_H + d_d + \gamma) I_H \tag{35}$$

$$\frac{dI_V}{dt} = (1 - u_2(t))\beta_V I_H N_H (1 - I_V) - (d_V + d_k) I_V \tag{36}$$

All parameter definitions retain their meanings from the uncontrolled system. For non-negative bounded initial conditions, this system has non-negative bounded solution (Lukes 1982 [51]). The objective function to be minimized is written:

$$J(u) = \int_0^T \left[C_1 I_H + C_2 I_V + \frac{1}{2}\left(D_1 u_1^2(t) + D_2 u_2^2(t) \right) \right] dt \tag{37}$$

with initial condition S_H, E_H, $I_V \geq 0$, and $I_H \geq 0$. The weight constants are C_1 and C_2 for the number of infected humans and the infected vector populations. The weights D_1 and D_2 are measures of the costs associated with the control variables u_1 and u_2 respectively. The Hamiltonian for the Lagrangian problem of the optimal control problem and the optimal control problem by Lagrangian was defined as follows:

$$L = C_1 I_H + C_2 I_V + \frac{1}{2}\left(D_1 u_1^2(t) + D_2 u_2^2(t) \right) \tag{38}$$

Theorem 5. *There exists an optimal control $u_1^*(t)$ and $u_2^*(t)$ such that $J(u_1^*, u_2^*) = \min\{J(u_1, u_2) | (u_1, u_2) \in U)\}$.*

Proof. The existence of the optimal control problem Equations (33)–(36) we apply results from [48,49] to prove the analyzed existence results of the optimal control problem.

The existence of the system in Equations (33)–(36) is given which is non-empty and bounded, according to Theorem 9.2.1 from Lukes [51]. The control set U is closed and convex. The right side of the control system Equations (33)–(36) is linear in u_1 and u_2. The integrand L is convex on U. To prove the bound on L, let $m_2 = \min(I_H(t), I_V(t))$, $m_1 = (D_1, D_2)$, and $\psi = 2$. Then the Lagrangian function L defined as:

$$\begin{aligned} L(I_H, I_V, u_1, u_2) &= C_1 I_H + C_2 I_V + \tfrac{1}{2}(D_1 u_1^2(t) + D_2 u_2^2(t)) \\ &\geq m_2(I_H + I_V) + m_1(|u_1|^2 + |u_2|^2) \\ &= m_2 + m_1(|u_1|^2 + |u_2|^2) \end{aligned} \tag{39}$$

where $m_1, m_2, C_1, C_2, D_1, D_2 > 0$, and $\psi > 1$. Therefore, there exists an optimal control for the system of Equations (33)–(36) satisfying the Pontryagin's minimum principle [25–29,51,52]. □

Theorem 6. *Let u_1^* and u_1^* be optimal controls, and let S_H, E_H, I_H, and I_V be the solutions of the optimal control problem Equations (33)–(36) that minimize $J(u_1, u_2) \in U$. Then there are adjoint variables $\lambda_1 = \lambda_{S_H}, \lambda_2 = \lambda_{E_H}, \lambda_3 = \lambda_{I_H}$, and $\lambda_4 = \lambda_{I_V}$ satisfying the adjoint system of equations:*

$$\begin{aligned}
\tfrac{d\lambda_1}{dt} &= -\lambda_1(t)((P-1)\theta - \alpha\beta_H I_V N_V - d_H) - \lambda_2(\alpha\beta_H I_V N_V) \\
\tfrac{d\lambda_2}{dt} &= -\lambda_1(t)(P-1)\theta - \lambda_2(-\varepsilon - d_H) - \lambda_3(\varepsilon) \\
\tfrac{d\lambda_3}{dt} &= -\lambda_1(t)\big((P-1)\theta - u_1^*(t)\big) - \lambda_3(-d_H - d_d - \gamma) - \lambda_4((1-u_2^*(t))\beta_V N_H(1-I_V)) - C_1 \\
\tfrac{d\lambda_4}{dt} &= -\lambda_1(t)(-\alpha\beta_H S_H N_V) - \lambda_2(\alpha\beta_H S_H N_V) - \lambda_4(-\beta_V I_H N_H + u_2^*(t) I_H \beta_V N_H - d_V - d_k) - C_2
\end{aligned} \tag{40}$$

where S_H, E_H, I_H, and I_V are the adjoint variables, and the controls u_1^* and u_2^* obey the optimality conditions

$$u_1^*(t) = \max\left(\min\left(\frac{\lambda_1 I_H^*}{D_1}, u_1^{\max}\right), 0\right), \tag{41}$$

$$u_2^*(t) = \max\left(\min\left(\frac{(1-I_V^*)\beta_V I_H^* N_H}{D_2}, u_2^{\max}\right), 0\right). \tag{42}$$

Proof. The corresponding Hamiltonian is defined as:

$$H = L(I_H, I_V, u_1, u_2) + \lambda_1 \frac{dS_H}{dt} + +\lambda_2 \frac{dE_H}{dt} + \lambda_3 \frac{dI_H}{dt} + \lambda_4 \frac{dI_V}{dt} \tag{43}$$

$$\begin{aligned}
H = {} & C_1 I_H + C_2 I_V + \tfrac{1}{2}(D_1 u_1^2(t) + D_2 u_2^2(t)) \\
& + \lambda_1[b_H + (1-P)(1 - S_H - E_H - I_H)\theta - \alpha\beta_H S_H I_V N_V - d_H S_H - u_1(t) I_H] \\
& + \lambda_2[\alpha\beta_H S_H I_V N_V - (\varepsilon + d_H) E_H] + \lambda_3[\varepsilon E_H - (d_H + d_d + \gamma) I_H] \\
& + \lambda_4[(1 - u_2(t))\beta_V I_H N_H (1 - I_V) - (d_V + d_k) I_V]
\end{aligned} \tag{44}$$

The associated adjoint system is as follows:

$$\begin{aligned}
\tfrac{d\lambda_1}{dt} &= -\tfrac{\partial H}{\partial S_H} = -\lambda_1(t)((P-1)\theta - \alpha\beta_H I_V N_V - d_H) - \lambda_2(\alpha\beta_H I_V N_V) \\
\tfrac{d\lambda_2}{dt} &= -\tfrac{\partial H}{\partial E_H} = -\lambda_1(t)(P-1)\theta - \lambda_2(-\varepsilon - d_H) \\
\tfrac{d\lambda_3}{dt} &= -\tfrac{\partial H}{\partial I_H} = -\lambda_1(t)((P-1)\theta - u_1^*(t)) - \lambda_3(-d_H - d_d - \gamma) \\
&\quad -\lambda_4((1-u_2^*(t))\beta_V N_H(1-I_V)) - C_1 \\
\tfrac{d\lambda_4}{dt} &= -\tfrac{\partial H}{\partial I_V} = -\lambda_1(t)(-\alpha\beta_H S_H N_V) - \lambda_2(\alpha\beta_H S_H N_V) \\
&\quad -\lambda_4(-\beta_V I_H N_H + u_2^*(t) I_H \beta_V N_H - d_V - d_k) - C_2
\end{aligned} \tag{45}$$

with the boundary conditions

$$\lambda_1(t) = 0, \lambda_2(t) = 0, \lambda_3(t) = 0, \lambda_4(t) = 0 \tag{46}$$

Using the properties of optimal set optimality conditions, we find that

$$\frac{\partial H}{\partial u_1} = \frac{\partial H}{\partial u_2} = 0 \text{ at } u_1 = u_1^* \text{ and } u_2 = u_2^* \tag{47}$$

Therefore,

$$\begin{aligned}
\tfrac{\partial H}{\partial u_1} &= D_1 u_1 - \lambda_1 I_H = 0 \\
u_1^* &= \tfrac{\lambda_1 I_H}{D_1}
\end{aligned} \tag{48}$$

$$\begin{aligned}
\tfrac{\partial H}{\partial u_2} &= D_2 u_2 - (1 - I_V)\beta_V I_H N_H = 0 \\
u_2^* &= \tfrac{(1-I_V)\beta_V I_H N_H}{D_2}
\end{aligned} \tag{49}$$

The optimal controls u_1^* and u_2^* are then given by:

$$u_2^* = \begin{cases} 0 & ; \frac{\lambda_1 I_H}{D_1} \leq 0, \\ \frac{\lambda_1 I_H}{D_1} & ; \frac{\lambda_1 I_H}{D_1} < u_1^{\max}, \\ u_1^{\max} & ; \frac{\lambda_1 I_H}{D_1} \geq u1\max. \end{cases} \tag{50}$$

$$u_2^* = \begin{cases} 0 & ; \frac{(1-I_V)\beta_V I_H N_H}{D_2} \leq 0, \\ \frac{(1-I_V)\beta_V I_H N_H}{D_2} & ; \frac{(1-I_V)\beta_V I_H N_H}{D_2} < u_2^{\max}, \\ u_2^{\max} & ; \frac{(1-I_V)\beta_V I_H N_H}{D_2} \geq u_2^{\max}. \end{cases} \tag{51}$$

□

The fourth-order Runge-Kutta method, in conjunction with the forward-backward method, is used to solve the optimal control problem numerically. The solution results for optimal strategies control are shown in Figures 8–13 the initial values parameter according to listed in Table 2.

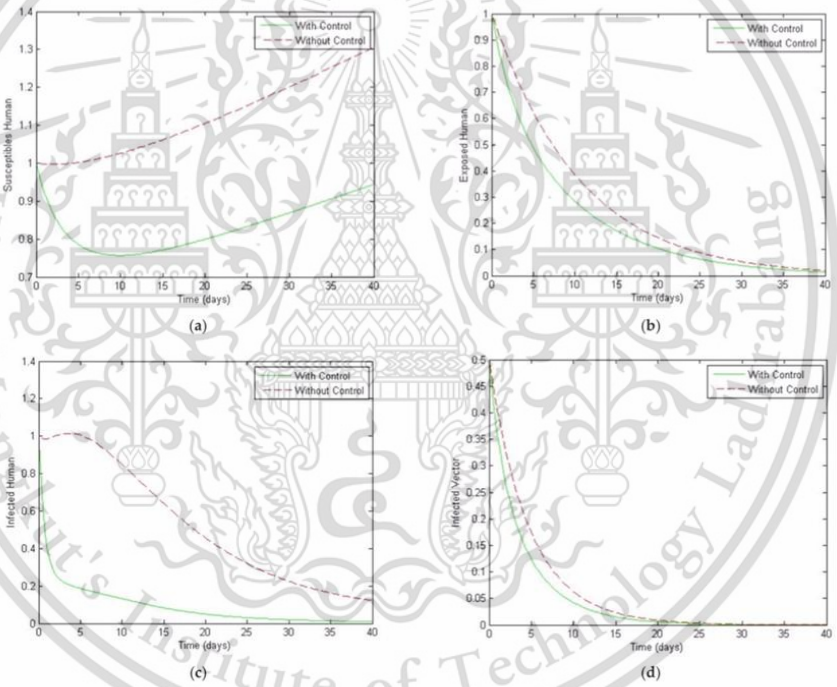

Figure 8. Comparison of behaviors with and without of system of Equations (33)–(36) of S_H, E_H, I_H, and I_V when using $C_1 = 0.000005, C_2 = 50$. (**a**) Susceptible human (**b**) exposed human (**c**) infected human and (**d**) infected vector.

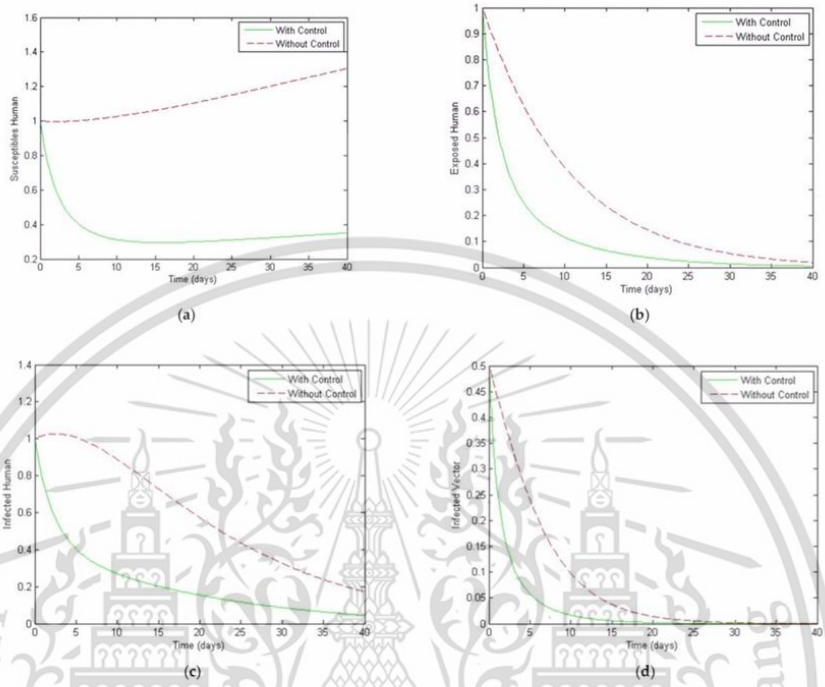

Figure 9. Comparison of behaviors with and without of system of Equations (33)–(36) of S_H, E_H, I_H, and I_V when using $C_1 = 5, C_2 = 50$. (**a**) Susceptible human, (**b**) exposed human, (**c**) infected human, and (**d**) infected vector.

Figures 8–12 show the results of Equation (17) with and without control of S_H, E_H, I_H, and I_V. We have divided the weight simulations into five cases as follows: Case 1 represents the case of C_1 being much less than C_2; Case 2 represents the case of C_1 being less than C_2; Case 3 represents the case where both C_1 and C_2 are equal; Case 4 is where C_1 is greater than C_2 and Case 5 is where C_1 is much greater than C_2. The results of these cases are plotted in Figures 8–12, for Cases 1–5 respectively.

Figures 8–12 shows that after effective control such as for the human population is an effort to reduce the number of infected humans by giving vaccinations to humans and for the vector population is control by giving repellent to mosquitoes and destroying mosquito breeding sites. The number of the susceptible human S_H, exposed human E_H, infected human I_H, and infected vector I_V is significantly reduced compared with that without control. The results of numerical simulation show that vaccination and the elimination of disease-carrying mosquitoes have a positive effect. The control, in particular, resulted in a significant reduction in the number of infected humans and vectors.

Figure 13a illustrates maintaining optimal control of vaccination rates in the human population $u_1(t)$ at initial value differences as follows: 40%, 60%, and 80% in approximately the first 4 days control is maintained, then the control gradually decreases to zero. Figure 13b shows the control values of the second control effort $u_2(t)$ at 40%, 60%, and 80% initiation to achieve control. It is seen that the optimal level of control is maintained in the first 4 days, then gradually increases and reaches the plateau on Day 22, after which the control dosage is reduced to zero.

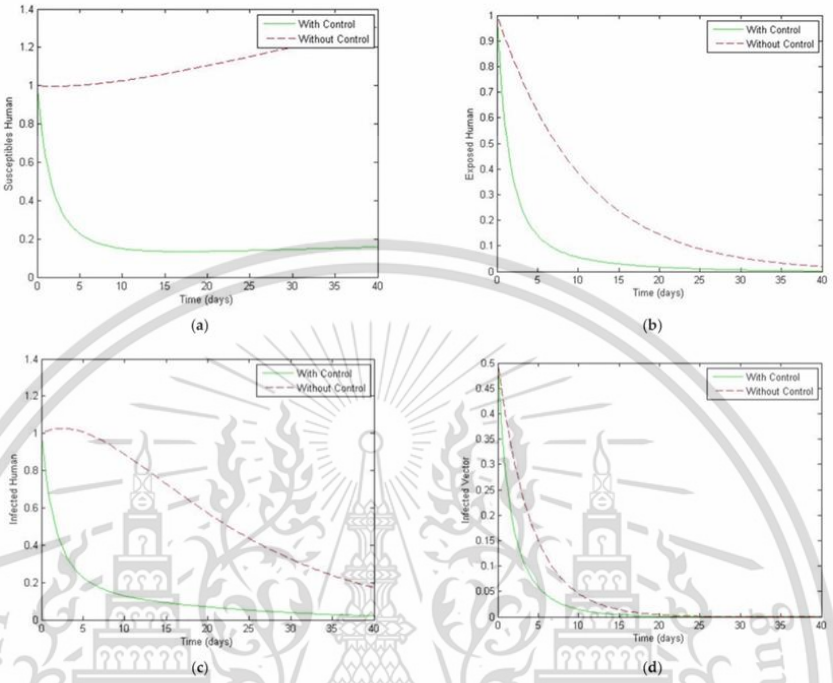

Figure 10. Comparison of behaviors with and without of system of Equations (33)–(36) of S_H, E_H, I_H, and I_V when using $C_1 = 50, C_2 = 50$. (**a**) Susceptible human, (**b**) exposed human, (**c**) infected human, and (**d**) infected vector.

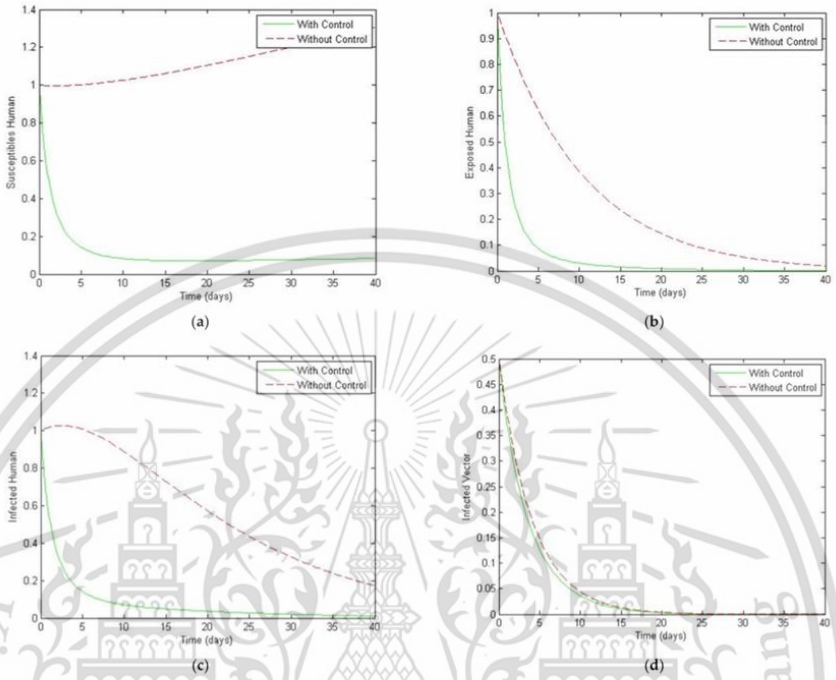

Figure 11. Comparison of behaviors with and without of system of Equations (33)–(36) of S_H, E_H, I_H, and I_V when using $C_1 = 50, C_2 = 5$. (**a**) Susceptible human, (**b**) exposed human, (**c**) infected human, and (**d**) infected vector.

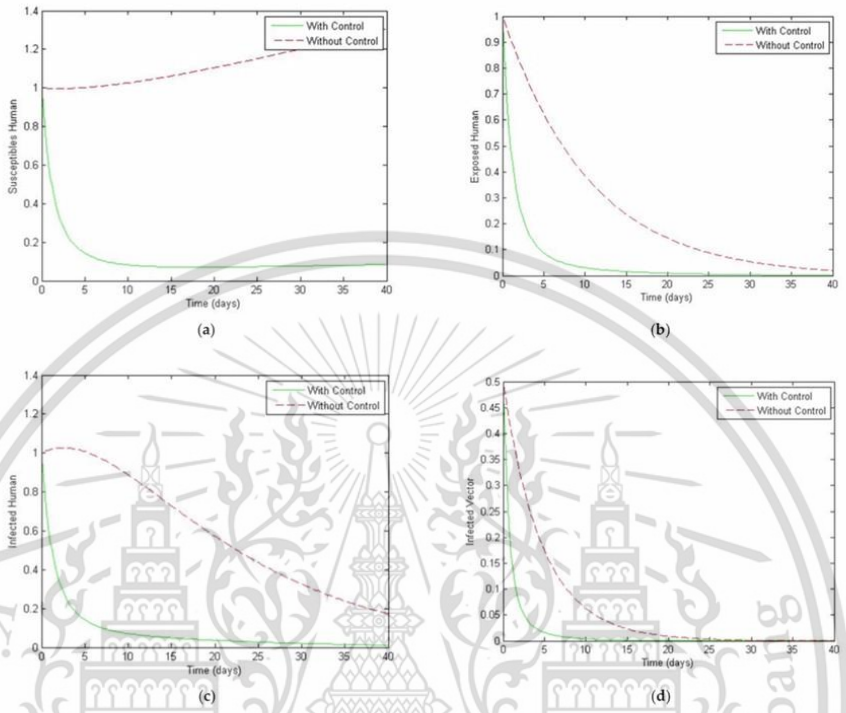

Figure 12. Comparison of behaviors with and without of system of Equations (33)–(36) of S_H, E_H, I_H, and I_V when using $C_1 = 50, C_2 = 0.000005$. (**a**) Susceptible human, (**b**) exposed human, (**c**) infected human, and (**d**) infected vector.

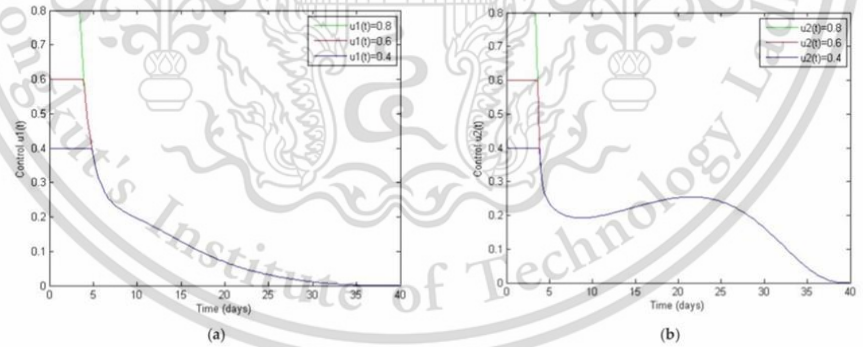

Figure 13. Control variables: (**a**) the vaccination rate $u_1(t)$ and (**b**) the elimination of mosquitoes that carry diseases rate $u_2(t)$. Using $C_1 = 50, C_2 = 50$.

6. Conclusions

In this article, we analyzed the impact of post-reinfection vaccination strategies for the second, third and fourth times, without regarding the serotype sequence during infection, for regions with high dengue outbreaks, in order to reduce the hospitalization rates and disease severity in the subsequent infections. This model is optimal for densely populated areas and abundant *Aedes* mosquitoes, which are carriers of dengue fever and there is a chance of re-infection with dengue fever multiple times. According to the 2020 report in Thailand, the region with the highest morbidity rate is the Northeastern region, with 127.53 per 100,000 inhabitants. The Routh–Hurwitz criterion for determining local asymptotically stability and the Lyapunov function for determining global asymptotically stability are used in the study. The equilibrium point that we found two states are disease-free converge to $E_1 = (1, 0, 0, 0)$ and endemic equilibrium point converge to $E_2 = (S_H = 0.00005,\ E_H = 0.02689,\ I_H = 0.01881,\ I_V = 0.73048)$. The basic reproductive number is defined as R_0. The disease-free equilibrium point there exists locally asymptotically stable if R_0 is less than one and locally asymptotically stable when R_0 greater than one for the endemic equilibrium point is. Similarly, the disease-free and endemic equilibrium point exists globally asymptotically stable if and only if according to conditions of Theorems 3 and 4. We simulated the numerical results solution of the compare two parameters with different values that affect the basic reproductive number value of this model as shown in Figures 6 and 7, where we can observe that the higher the dengue virus transmission rate from vector to human β_H and the dengue virus transmission rate from human to vector β_V, the slower the convergence to a susceptible human equilibrium point. The exposed human, infected human, and infected vector all rapidly reach a point of equilibrium.

We developed the optimal control strategies using the elimination of mosquitoes that carry diseases rate and the vaccination rate to minimize the number of infected human population and infected vector population to cost controlling effort. The Pontryagin minimum principle (PMP) approach is used to solve the optimum control issue in this situation. We can see that effective measures such as vaccinations to humans and the annihilation of mosquito breeding sites represent powerful measures that effectively controlled the spread of the dengue virus. In comparison to those without control, the number of susceptible humans exposed, infected humans, and infected vectors are significantly reduced. The numerical simulation results show that the number of infections decreases over time. Figures 8–12 show that the control resulted in a significant reduction in the number of infected humans and infected vectors. Finally, the effective control and prevention of dengue fever rely on three components: improved vector control, improved case management, and effective vaccine development.

We suggest that future guidelines for this model should consider the serotypes of infection and provide a more complete age range for vaccination.

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