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OPTIMAL CONTROL STRATEGIES FOR DENGUE TRANSMISSION IN SELANGOR, MALAYSIA

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OPTIMAL CONTROL STRATEGIES FOR DENGUE TRANSMISSION IN SELANGOR, MALAYSIA

By

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ABSTRACT

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KU YEW SHENG

Dengue is a mosquito-borne viral disease transmitted by Aedes aegypti mosquito. In Malaysia, dengue remains a public health threat. Based on previous dengue data and trends, Ministry of Health Malaysia identified a high increase in dengue cases every four to five years with the surges recorded in 2010, 2015 and 2019. The dengue cases are expected to increase again in 2024 or 2025, with the cases expected to be higher than that recorded in 2019 (130,101 cases). Hence, there is a need to identify effective dengue control strategies to prevent such increase in dengue cases in the future. This study aims to apply optimal control theory to determine the optimal control strategy for reducing dengue cases. For this purpose, a dengue model that links human SIR framework with mosquito ecology is formulated. This model is used to simulate the dengue transmission in Selangor, Malaysia, where suitable modelling data are available and where dengue is prevalent. Curve fitting of dengue data is then performed by using forward difference method to estimate important parameter value such as mosquito biting rate. Next, optimal control theory is applied to illustrate the effects of larvicide, insecticide and vaccination in reducing dengue cases. Seven scenarios, namely i) larvicide, ii) insecticide, iii) vaccination, iv) larvicide and

insecticide, v) larvicide and vaccination, vi) insecticide and vaccination, vii) larvicide, insecticide, and vaccination are analyzed by means of numerical simulations in MATLAB. Based on the simulation results, a combination of larvicide, insecticide and vaccination is identified as the optimal control strategy in Selangor. The simulation results would provide insights on the optimal dengue control strategy in Selangor to assist decision makers in implementing dengue control strategies.

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suggestions and recommendations when I am facing problem. On the other hand, they are also giving supports and encouragements. This is undoubtedly helping me on the way of accomplishing my Final Year Project.

DECLARATION

I hereby declare that the project report is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any degree at UTAR or other institutions.

KU YEW SHENG

APPROVAL SHEET

This project report entitled "**OPTIMAL CONTROL STRATEGIES FOR DENGUE TRANSMISSION IN SELANGOR, MALAYSIA**" was prepared by KU YEW SHENG and submitted as partial fulfilment of the requirements for the degree of Bachelor of Science (HONS) Statistical Computing and Operations Research at Universiti Tunku Abdul Rahman.

Approved by:

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Supervisor

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Date: _____18 /4 /2023_____

PERMISSION SHEET

It is hereby certified that **KU YEW SHENG** (ID No: **19ADB03949**) has completed this final year project entitled "**OPTIMAL CONTROL STRATEGIES FOR DENGUE TRANSMISSION IN SELANGOR, MALAYSIA**" under supervision of Dr. Lim Huai Tein (Supervisor) from the Department Physical and Mathematical Science, Faculty of Science and Dr. Tay Chai Jian (Co-Supervisor) from Centre for Mathematical Sciences, Universiti Malaysia Pahang.

I hereby give permission to the University to upload the softcopy of my final year project in pdf format into the UTAR Institutional Repository, which may be made accessible to the UTAR community and public.

Yours truly,

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(KU YEW SHENG)

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LIST OF SYMBOLS

Symbols		Unit
A_m/A_v	Aquatic mosquito/Pre-adult mosquito population	capita
E_h	Exposed human population	capita
E_m/E_v	Exposed human population	capita
H	Hamiltonian function	-
I_h	Infected human population	capita
I_m/I_v	Infected mosquito population	capita
k	Number of mosquito larvae per human	capita
N_h	Total number human population	capita
N_m	Total adult female population	capita
P_h	Hospitalized human population	capita
R_0	Basic Reproduction Number	-
R_h	Recovered human population	capita
S_h	Susceptible human population	capita
S_m/S_v	Susceptible mosquito population	capita
t	Time	week
u_1	Control Variable for Larvicide	-
u_2	Control Variable for Insecticide	-
u_3	Control Variable for Vaccination	-

V_h	Vaccinated human population	capita
W_1	Importance of reducing the size of infected mosquito population	-
W_2	Importance of reducing the size of infected human population	-
W_3	Costs or efforts required to implement larvicide, u_1	-
W_4	Costs or efforts required to implement insecticide, u_2	-
W_5	Costs or efforts required to implement vaccination, u_3	-
β/B	Mosquito biting rate	$week^{-1}$
β_{hm}	Transmission probability from I_h to S_m	$bite^{-1}$
β_{mh}	Transmission probability from I_m to S_h	$bite^{-1}$
$\eta_h/\eta/\gamma$	Human recovery rate	$week^{-1}$
θ	Vaccine waning rate	$week^{-1}$
λ	Transversality or boundary conditions	-
μ_A	Natural mortality of larvae	$week^{-1}$
μ_h	Natural birth/Mortality of human	$week^{-1}$
μ_m	Natural Mortality of mosquito	$week^{-1}$
σ	Proportion of vaccinated human being infected	capita
ϕ	Oviposition rate	$week^{-1}$
ω	Maturation rate from larvae to adult	$week^{-1}$

LIST OF ABBREVIATIONS

ASEI-SEIR	Aquatic, Susceptible, Exposed, Infected mosquito population and Susceptible, Exposed, Infected, Recovered human population
ASI-SIR	Aquatic, Susceptible, Infected mosquito population and Susceptible, Infected, Recovered human population
ASI-SVIR	Aquatic, Susceptible, Infected mosquito population and Susceptible, Vaccinated, Infected, Recovered human population
CF	Cost Functional
DF	Dengue Fever
EIP	Extrinsic incubation period
GSK	GlaxoSmithKline
IIP	Intrinsic incubation period
NIAID	National Institute of Allergy and Infectious Disease
OC	Optimal Control
OCP	Optimal Control Problem
ODE	Ordinary differential equations
PMP	Pontryagin's Maximum Principle
RK4	Fourth-order Runge-Kutta method

SEIR	Susceptible, Exposed, Infected, Recovered human population
SEI-SEIPR	Susceptible, Exposed, Infected mosquito population and Susceptible, Exposed, Infected, Hospitalized, Recovered human population
SEI-SEIR	Susceptible, Exposed, Infected mosquito population and Susceptible, Exposed, Infected, Recovered human population
SI	Susceptible, Infected mosquito population
SIR	Susceptible, Infected, Recovered human population
SI-SIR	Susceptible, Infected mosquito population and Susceptible, Infected, Recovered human population
SVIR	Susceptible, Vaccinated, Infected, Recovered human population
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research

CHAPTER 1

INTRODUCTION

1.1 Dengue

Dengue fever is a significant infectious disease that poses a threat to around half of the world's population, with an estimated range of 100 to 400 million cases occurring annually, which particularly in tropical countries. In recent decades, there has been a significant increase in the incidence of dengue worldwide. According to the World Health Organization (WHO), the number of reported cases has risen from the year 2000 to 2022. However, it is important to note that the actual number of cases is likely to be much higher, as a large proportion of cases are asymptomatic or mild and are not reported (WHO, 2022). Thus, dengue fever has emerged as a significant epidemic disease in Southeast Asia, which is exacerbated by the lack of knowledge and awareness about the disease among the population. This epidemic is believed to be linked to climate change, and there is a risk that dengue fever may become endemic in the region (Syafruddin et al., 2015).

Mosquito-borne viral disease or commonly known as dengue virus that come from a member of Flaviviridae virus family is transmitted by Aedes aegypti mosquito (Wilder-Smith et al., 2019). Based on CDC (2019), human dengue infection is arisen from serotypes which are DENV-1, DENV-2, DENV-3, and DENV-4. Dengue is typically a mild illness for most individuals, and they may not experience any symptoms or recover within two weeks. However, in some

cases, it can be severe and even deadly. Symptoms usually appear 4-10 days after infection and can persist for up to a week. These symptoms include a high fever of 40°C/104°F, severe headache, pain behind the eyes, muscle and joint pains, nausea, vomiting, swollen glands, and rash. Those who contract dengue for a second time are at a greater risk of severe symptoms. Severe symptoms of dengue often manifest after the fever subsides and may include severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums or nose, fatigue, restlessness, blood in vomit or stool, extreme thirst, pale and cold skin, and weakness (WHO, 2022). Additionally, dengue can be a fatal disease due to the antibody-dependent enhancement (ADE) effect and severe forms of dengue such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Yamanaka et al., 2021).

1.2 Dengue in Malaysia

In Malaysia, the tropical environment creates the perfect breeding grounds for mosquitoes, making dengue a common disease. Dengue cases have been reported in Malaysia, a Southeast Asian nation, since 1902. With its first significant outbreak in 1973, the disease started to pose a threat to public health in the 1970's (Murphy et al., 2020). From 32 cases per 100,000 people in 2000 to 361 cases per 100,000 people in 2014, dengue fever incidence has grown. Dengue affects people most frequently between the ages of 15 and 49, and urban areas account for 80% of cases (Salim et al., 2021). Selangor, one of Malaysia's most populous and urbanised states with 5.79 million residents out of the nation's

31.53 million, is responsible for 90% of all dengue cases nationwide (Salim et al., 2021).

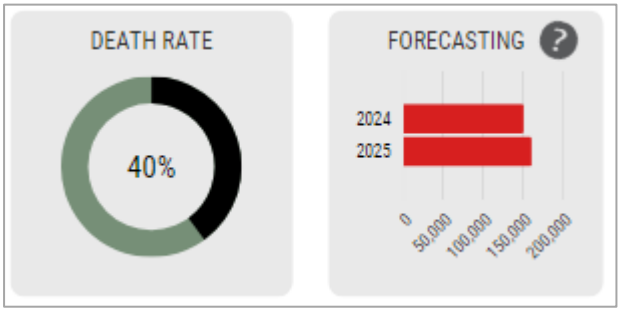

Figure 1.1: Statistic about Dengue in Malaysia

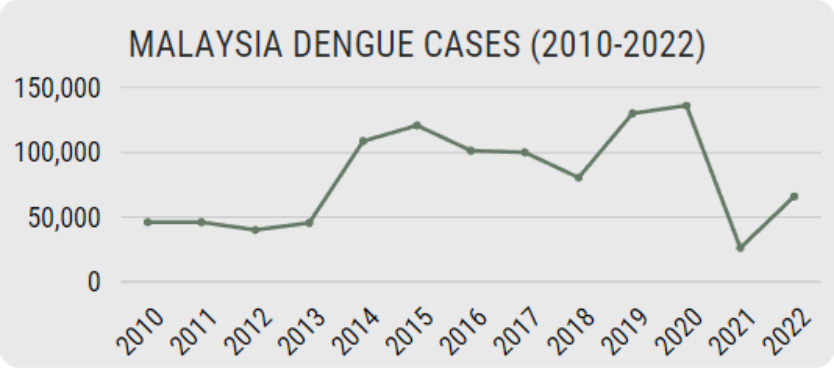

Figure 1.2: Graph for Malaysia Dengue Cases from 2010 to 2022

Table 1.1: Data for Malaysia Dengue Cases from 2010 to 2022

Year	Number of dengue fever cases
2010	46171
2011	46171
2012	40271
2013	45662
2014	108698
2015	120836
2016	101357
2017	100028
2018	80615
2019	130101
2020	136162
2021	26365
2022	66102

According to the research, dengue fever cases are projected to rise once more in 2024 or 2025 (Figure 1.1). According to Dr. Noor Hisham, who is Malaysia Director-General of Health and has stated previously in January of year 2022 that the dengue pandemic in Malaysia is anticipated to record a boom every four to five years. Therefore, based on to the graph above which portraying the dengue cases in Malaysia from 2010 to 2022, we can easily observe that there is an increasing trend for each 5 years. For examples, there was a high peak number of dengue cases in 2015 then, after 5 years in 2019 and 2020, there was another high peak number of dengue case (Figure 1.2 & Table 1.1). Henceforth, they predicted that the next high peak would occur in 2024 or 2025 (CodeBlue, 2022). Aside from that, in 2021, there were approximately 15.7 thousand dengue cases reported in Selangor (Statista, 2023) while in 2022 there is nearly 150% increase compared to the previous year. Table 1.1 is the table of recorded dengue fever cases in Malaysia from year 2010 to 2022 (The Star, 2023). More importantly, the mortality rate of patients with dengue fever is around 40% in Malaysia (Figure 1.1). To summarize, dengue is undoubtedly a serious public health threat to us no matter in ancient times or up to now.

In all, with a prediction on the rise of dengue cases in 2024 or 2025, it's portraying the growing of dengue epidemic. The traditional methods in controlling the dengue disease seem ineffective therefore an effective control for the dengue outbreak through dengue vaccination is studied. Nonetheless, the optimal control strategy which includes the combination of different control strategies is still undetermined. Henceforth, there is a need to apply optimal

control theory to evaluate an optimal dengue control strategy, namely ASI-SVIR model.

1.3 Control Strategies

Optimal control theory is a mathematical field that focuses on identifying the most effective methods for managing a dynamic system. In other words, this theory can be utilized to address numerous issues in the realms of management science and economics that involve systems that change over time. In the field of dengue transmission, there is still room to improve the development of an effective vaccine to immunize the DENV-1, DENV-2, DENV-3, and DENV-4, as Agusto and Khan (2018) claimed that no safe vaccine is readied for the four dengue virus serotypes yet. Therefore, control of Dengue Fever (DF) transmission essentially focuses on its vector mosquitoes through the reduction of population size, and we represent it as vector control strategy. Vector control strategy includes ecological management that is elimination of artificial man-made mosquito breeding sites (such as hollow rocks, puisard, bucket abandoned, used tires, mango trees, bushes, fruits trees and so on), administration of appropriate insecticides or predators to the outdoor water-holding containers, use of personal and household protection (such as window screens, long-sleeved clothes, mosquito repellents, insecticide-treated bed nets, vaporizers and coils), and open space spray of insecticide (Abidemi and Aziz, 2020).

Nevertheless, we are still considering vaccination as one of the control strategies in this research. Sanofi Pasteur has developed the world's first dengue vaccine,

chimeric yellow fever-dengue-tetravalent dengue vaccine, Dengvaxia® (CYD-TDV), which is now available. The vaccine was licensed in Mexico in December 2015 for use in individuals aged 9 to 45 living in areas where dengue fever is endemic. In addition to Sanofi Pasteur, other research laboratories such as Walter Reed Army Institute of Research (WRAIR), Fiocruz, GlaxoSmithKline (GSK), Merck, Takeda, and the National Institute of Allergy and Infectious Diseases (NIAID) are also working on developing a dengue vaccine (Scherwitzl, Mongkolsapaja and Screaton, 2017). Malaysia conditionally registered Dengvaxia on October 31st, 2016, and is currently conducting a phase IV study of the vaccine to further evaluate its efficacy and safety (Anon, 2022).

In this study, we consider the larvicide (that is targeted for pre-adult/Larva which is in aquatic form), insecticide (which is targeted for adult mosquitoes), and vaccination (which is targeted for human) as the control strategies for the dengue fever transmission. The following combinations of different control strategies are considered in this study:

i) Larvicide

ii) Insecticide

iii) Vaccination

iv) Larvicide & Insecticide

v) Larvicide & Vaccination

vi) Insecticide & Vaccination

vii) Larvicide, Insecticide & Vaccination

1.4 Research Questions

The research questions of this study are:

i. How can the dengue cases be reduced based on the optimal control strategy?

ii. What are the effects of the dengue control strategies on the dengue transmission?

iii. What is the optimal dengue control strategy in Selangor, Malaysia?

1.5 Objectives of the Study

The objectives of this study are as follows:

i. To formulate a dengue model that links human SIR framework (S-susceptible human, I-infected human, R-recovered human) with mosquito ecology.

ii. To assess the effects of dengue control strategies on dengue transmission.

iii. To identify the optimal dengue control strategy.

1.6 Scope of the Study

A model for dengue fever is developed. It can connect the human SIR framework with mosquito ecology. Aside from that, the effects of dengue control strategies on dengue transmission are illustrated by means of model simulations using MATLAB software. Furthermore, we implement the optimal dengue control strategy to be used in Selangor.

1.7 Significance of the Study

The findings of this study bring about the identification of the optimal control strategy for preventing the spread of the dengue disease when the optimal control theory is applied to it. Apart from that, this study provides some useful insights on the optimal dengue control strategy in Selangor, Malaysia to assist the decision makers in implementing the dengue control strategies.

1.8 Organization of the Study

First and foremost, Chapter 1 introduces the dengue disease and discusses the dengue transmission in Malaysia. Apart from that, the research questions, research objectives, scope, significance of the study and its organization are presented.

The next chapter of the study focuses on Chapter 2, which is a literature review related to the topic. The chapter explains the epidemiological model, including the basic SIR model and the modified SEIR model. It also discusses the vector-host transmission model and how dengue is transmitted between vector and host. The vaccination model also is discussed in this section, with various journals based on different settings such as age groups, vaccination protection, serostatus, and so on. Furthermore, the dengue control strategy model will be discussed, which will cover an article on the ASEI-SEIR model with control variables like personal protection, larvicide, and insecticide, and the SEI-SEIPR model with control variables such as prevention and insecticide spraying.

In Chapter 3, we explore an epidemiological model (i.e., ASI-SVIR), which includes insecticide, larvicide, and vaccination control strategies to describe the transmission of dengue fever. We fit this model to reported dengue incidence data from 2017 to 2019 in Selangor, Malaysia. We also calculate the mosquito biting rate, β by using the forward difference method. To determine the most effective control strategies for managing dengue fever, we will apply optimal control theory and examines the impact of different control measures such as larvicide, insecticide, and vaccination controls on dengue fever dynamics. The study simulates an optimality system by using the fourth-order Runge-Kutta scheme based on the forward-backward sweep method in MATLAB.

In Chapter 4, it covers the numerical outcomes related to the computation of biting rates and execution of a control approach. Furthermore, MATLAB will be utilized with the fourth order Runge-Kutta method to calculate numerical solutions for the optimality system, which includes a non-autonomous model for dengue fever, initial conditions, and the costate system. The forward-backward sweep method procedure will be employed in this method. Then, the results and findings for each of the control strategies will be discussed after the numerical analysis including larvicide, insecticide, and vaccination in Selangor are performed and examined.

Finally, in the Chapter 5, based on the results and findings of this study, there have several conclusions have been drawn. Apart from that, the limitations of

this study and recommendations have been discussed for future research's improvement.

CHAPTER 2

LITERATURE REVIEW

2.1 Epidemiological Model

Epidemiology refers to the examination of how health-related conditions or occurrences are distributed among a particular population, as well as the factors that influence them. The insights gleaned from this study can be applied to managing and preventing health issues (Centers for Disease Control and Prevention, 2019). Henceforth, epidemiologists play a critical role in identifying the origin and most susceptible groups affected by a disease such as dengue fever when it arises in a population. The insights gained through epidemiological research can be utilized to manage the disease's spread and avert subsequent outbreaks (Versus Arthritis, n.d.). Epidemiological modelling is a valuable tool for comprehending the dynamics involved in the spread of infectious diseases. Besides, it helps in identifying the key factors that influence disease transmission and provides guidance on the most effective control strategies. On the other hand, by analysing and simulating various scenarios, epidemiological models assist in identifying the most significant parameters related to the disease and predicting the potential impact of interventions (Skrip and Townsend, 2019). For examples, during the pandemic of COVID-19, epidemiological models have played a significant role in understanding, addressing and managing it. Mathematical epidemiologists have been tasked with predicting the progression of the pandemic and providing insights to help governments make informed decisions on how to control its spread. Hence, this is certainly

becoming a fundamental requirement for epidemiologists throughout the pandemic, as they continue to work towards finding effective solutions for this global health crisis (Jewell, Lewnard and Jewell, 2020).

There are generally two types of models used in epidemiological modelling: stochastic and deterministic. Stochastic models incorporate chance variations in exposure risks, disease outcomes, and other factors, and are therefore probabilistic in nature. On the other hand, deterministic models do not incorporate chance variations and are based solely on the relationships between the different variables, such as the transmission rate, recovery rate, and population demographics. Furthermore, deterministic models divide individuals into different compartments and provide detailed explanations for what happens in each compartment. These models require less data and are easier to set up, which has made them popular in epidemiological research. Despite their relative simplicity, deterministic models have been able to provide valuable insights into disease progression and control strategies and have proven to be an effective tool for understanding how diseases spread and how they can be managed (News-Medical.net, 2021). Therefore, motivated by the above studies, our interest is to develop a compartmental deterministic model to examine the optimal control strategies for dengue transmission in Selangor, Malaysia.

2.1.1 SIR Model

An epidemic is characterized by a rise, often sudden, in the incidence of a disease above the typical occurrence in a specific population and geographic region.

Epidemics happen when there is a sufficient number of susceptible hosts and a pathogen present, and when there is an effective mode of transmission from a source to those hosts. For instance, there are several factors that can contribute to the emergence of an epidemic, such as an increase in the virulence or quantity of the pathogen, the introduction of the pathogen into a new environment, a more efficient mode of transmission, changes in host susceptibility to the pathogen, and factors that increase host exposure or allow for the pathogen to enter through new means (Centers for Disease Control and Prevention, 2019). The SIR model is often used to mathematically express the assumption that infectious diseases, like dengue, follow a typical pattern where the pathogen causes an illness period followed by immunity that is assumed to last for the lifetime of the individual in the scope of the simulations. Henceforth, this situation can be expressed mathematically using a model called SIR.

The SIR model is the most basic type of compartmental model used in epidemiology. It consists of three ordinary differential equations that attempt to describe the rate of change between three distinct compartments in a given population: Susceptible (S_h), Infected and infectious (I_h), and Recovered and no longer able to contract or transmit the disease (R_h). The total human population, (N_h) is $N_h = S_h + I_h + R_h$ (Smith and Moore, 2015). Kermack and McKendrick were the first to propose the initial SIR model in 1927 (Brauer, 2005). As an epidemic progresses, individuals can move from the S compartment to the I compartment, and eventually to the R compartment. The basic model of disease transmission assumes that the rate of spread of the disease is rapid enough to ignore the effects of population demography such as births, deaths, and

migration. In addition, the model assumes a homogeneous population, constant human population due to no disease-induced deaths, and lifelong immunity. The purpose of the equations is to predict how the number of individuals in each compartment will change over time during the course of an epidemic. If the focus is on longer-term persistence and endemic dynamics of a disease, it becomes necessary to take into account the population demography. In such case, this would entail incorporating the human birth rate and natural mortality rate into the SIR model (Gustavo A. Muñoz-Fernández, 2021).

2.1.2 SEIR Model

In Section 2.1.1, there is a limitation of the SIR model that is assuming individuals become infectious immediately after being infected. However, this is not entirely realistic because during the initial infection, the number of pathogen units such as bacteria or virus is very small and that is too low for effective transmission. Therefore, the modified model depends on SIR model is computed which is SEIR model including four compartments: Susceptible (S_h), Exposed (E_h), Infected (I_h), and Recovered (R_h). The SEIR model for dengue involves a process where individuals transition from the susceptible (S) compartment to the exposed (E) compartment once they are bitten by a virus-carrying mosquito. During this period, the individual is infected but remains asymptomatic. Following an incubation period, the individual moves to the infectious (I) compartment and begins displaying symptoms. Eventually, the individual recovers and moves to the recovered (R) compartment. Moreover, the SEIR model for dengue can be used to understand the dynamics of the disease

in a population and to evaluate the effectiveness of different interventions (Side et al., 2018).

2.1.3 Vector-Host Transmission Model

Without any doubt, the original SIR model proposed by Kermack and McKendrick had a significant impact on the advancement of mathematical epidemiological models. The SIR model provides a starting point for comprehending the spread of a disease. Further improvements to the model can be made by enriching it with additional details and refining its formulation. The selection of appropriate compartments for the model depends on factors such as the disease's characteristics, available data, and the goals of the research (Brauer, 2017). On the other hand, vector-borne diseases are a significant category of infectious diseases that are caused by pathogens and spread by a variety of organisms, including insects, ticks, bacteria, and protozoa. These organisms, which are responsible for transmitting the disease, are known as vectors. They can transfer infections from one human to another or from animals to humans, posing a significant threat to public health (Ullah et al., 2020).

Now relating the infectious disease with dengue virus, the main mode of transmission for the dengue virus is through the bite of an infected Aedes aegypti, which can transmit the virus from person to person. Humans are considered the primary host and the primary source of the virus, as female mosquitoes acquire the dengue virus by feeding on the blood of viremic humans

and it is transmitted the virus via bloodsucking arthropods known as vectors (WHO, 2022).

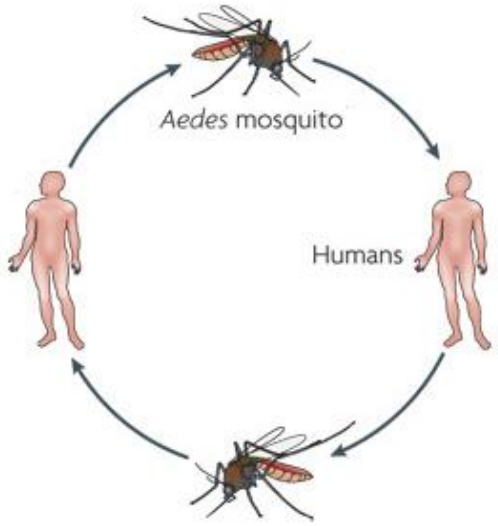

Figure 2.1 Dengue transmission - The dengue virus is spread through a human-to-mosquito-to-human cycle of transmission.

After a mosquito feed on the blood of someone infected with the dengue virus, it can become a vector for the disease, but the mosquito can only acquire the virus if it feeds on the infected person during the period of viremia, i.e., when the person has high levels of the virus in their blood. Once the virus enters the mosquito's body through the blood meal, it takes about eight to twelve days for the virus to replicate and spread throughout the mosquito's body. After this period, the mosquito can transmit the virus to another person when it feeds again (WHO, 2022). The figure 2.1 shows above is a human-to-mosquito-to-human cycle of transmission by the dengue virus (Scitable, 2014). Although the dengue virus can infect and multiply in the mosquito's body, it does not persist there throughout the mosquito's entire lifespan. Typically, the virus remains infectious

in the mosquito’s body for around 14 days after the mosquito has acquired it through a blood meal from an infected person. During this period, the mosquito can transmit the virus to another person by taking another blood meal. However, once this period has passed, the virus is no longer present in the mosquito's body, and the mosquito becomes incapable of transmitting the virus (ECDC, 2021). The lifespan of adult mosquitoes can vary, and it depends on environmental conditions, but it generally ranges from a few weeks to several months (US EPA, OCSPP, 2023).

Therefore, the interplay between the dynamics of mosquito-human populations and the transmission of the dengue virus is a vital factor in the emergence and spread of dengue fever. Moreover, back to the vector-host transmission model, incorporating mathematical models that account for the dynamics of both mosquito and human populations can improve our comprehension of the transmission dynamics of dengue. The entomological parameters of mosquitoes, including their biting rate, virus incubation rate, and population dynamics, are essential factors that contribute to the spread of dengue. It is crucial to understand how changes in these parameters can affect dengue transmission dynamics, which can aid in the planning and implementation of effective control strategies (Polwiang, 2015). Henceforth, to address these issues, a vector-host transmission model has been developed that incorporates both mosquito and human populations.

$$\frac{dS_h}{dt} = \mu_h N_h - \frac{\beta_h b}{N_h} S_h I_v - \mu_h S_h,$$

$$\frac{dI_h}{dt} = \frac{\beta_h b}{N_h} S_h I_v - (\gamma_h + \mu_h) I_h,$$

$$\frac{dR_h}{dt} = \gamma_h I_h - \mu_h R_h,$$

$$\frac{dS_v}{dt} = A - \frac{\beta_v b}{N_h} S_v I_h - \mu_v S_v,$$

$$\frac{dS_v}{dt} = \frac{\beta_v b}{N_h} S_v I_h - \mu_v I_v.$$

Figure 2.2 SI-SIR model

In the past, 1975, Bailey described a vector-host transmission model that serves as the basis for a dengue transmission model, which incorporates both the mosquito population (SI model) and the human population (SIR model). Figure 2.2 shows the SI-SIR model where S_h, I_h and R_h represent the human population for Susceptible, Infectious, and Recovered hosts; S_v and I_v represent the numbers of susceptible and infectious mosquitoes (Andraud et al., 2012). At that, variety of dengue models have been developed based on the original model, with differences in assumptions, dengue epidemiology, and transmission routes.

For examples, SI-SIR model can be extended to SEI-SEIR model by taking consideration on extrinsic incubation period (EIP in mosquito which represent exposed adult female mosquito, E_m and intrinsic incubation period (IIP) in human population which represent exposed human population, E_h (Bhuju, Phaijoo and Gurung, 2020). In dengue transmission models, the EIP in

mosquitoes is a significant factor as it defines the time taken for the mosquito to become infectious after being infected with the virus. This time period is crucial as it is similar to the lifespan of a mosquito that might die before it becomes infectious. Consequently, the EIP is a critical parameter in dengue transmission models and should be considered when developing strategies to control the spread of the virus. On the other hand, including an exposed human compartment in dengue transmission models would better reflect the reality of the disease, as infected humans need to survive the intrinsic incubation period (IIP) before they become infectious. This would allow for a more accurate representation of the transmission dynamics and potential impact of control strategies (WHO, 2022). There were a lot of researchers using SEI-SEIR model to demonstrate the spread of dengue fever and conduct mathematical analysis such as Bhuju et al. (2020).

Moreover, the ASI-SIR or ASEI-SEIR model expands the vector-host transmission model to include the aquatic mosquito population (S. and NOORANI, 2012). By incorporating the aquatic mosquito population into dengue fever transmission models, it can help researchers gain a more comprehensive understanding of the disease's transmission dynamics, as well as the effectiveness of interventions such as vector control measures (Leach et al., 2020). For instance, the effects of vector control for mosquito such as exterminating the breeding sites of mosquitoes, mosquitoes fogging and application of larvicide and insecticide (Chamnan et al., 2021; Fitria et al., 2017; Abidemi and Aziz, 2020) can be evaluated by using ASI-SIR model or ASEI-

SEIR model. All of this can be done by adding the control variable in mosquito compartments.

Since vector-host transmission model is used to simulate and predict the dynamics of dengue transmission in populations that involving mosquitoes and humans as a mathematical tool, the effectiveness of vector control measures can be demonstrated. By comparing the outcomes of different scenarios, it can help in identifying the optimal control strategy for reducing the dengue transmission (Khan and Fatmawati, 2021).

2.2 Vaccination Model

An epidemiological model for dengue vaccination focused on disease transmission would likely employ a compartmental model to categorize individuals based on their disease status, such as susceptible, infected, or recovered. Besides, the model would incorporate various parameters, including the transmission rate of the virus, the length of time an infected individual remains infectious, and the effectiveness of the vaccine. A new compartment for vaccinated individuals would be added to the model. Vaccinated individuals would be considered immune to the virus, and the vaccine efficacy parameter would indicate how well the vaccine can prevent infection. The transmission rate for vaccinated individuals would be adjusted based on the vaccine efficacy, allowing for the simulation of the impact of vaccination on the spread of dengue in a population. Besides, the vaccination coverage parameter would reflect the proportion of the population that has been vaccinated (Abidemi and Aziz, 2020).

2.2.1 Setting for Vaccination

Several epidemiological studies have incorporated vaccination into their models. These studies have made assumptions about the vaccine's effectiveness based on several factors, such as age group, vaccination coverage, and the individual's serostatus. For instance, some studies have taken into account the age-dependency of the vaccine's efficacy, as it is known to vary among different age groups. Other studies have considered the vaccine's protection rate, which is affected by various factors, including the number of doses administered, the duration between doses, and the time since the last dose. Furthermore, vaccination coverage is a critical factor in determining the vaccine's effectiveness at the population level. Lastly, the individual's serostatus, or pre-existing immunity to the disease, can impact the vaccine's effectiveness. By incorporating these factors into their epidemiological models, researchers can better understand the potential impact of the vaccine on disease prevention and control.

For examples, based on the age group, Maier et al. (2020) was examines the most appropriate age for administering dengue vaccination, taking into consideration the varying rates at which mosquitoes bite people at different ages. By utilizing an epidemiological model, the writers evaluated the best age for vaccination in Brazil and concluded that vaccinating kids aged between 9 and 12 would have the most significant effect in minimizing dengue transmission. They also discovered that vaccinating older people may not have much of an impact because they have fewer opportunities to be bitten by mosquitoes. From

this research, the significance of considering both individuals' age and mosquitoes' age-dependent biting rate while introducing dengue vaccination campaigns can be determined. However, in this study, the age group for taking dengue vaccination will not be limited.

On the other hand, some of the studies will consider the the waning rate of the vaccination used. For instances, Salje et al. (2021) assesses how effective the Dengvaxia vaccine is in preventing symptomatic and subclinical (i.e., not showing obvious symptoms) dengue infections. The findings demonstrated that the vaccine was effective in protecting against both types of infections among those who had already contracted dengue before. Nevertheless, among those who had not been exposed to dengue previously, the vaccine was observed to escalate the chances of severe disease. The study emphasizes the significance of screening people for dengue exposure before administering the vaccine to identify those who might be susceptible to severe dengue and guarantee the vaccine's safe and efficient use. According to the findings, the vaccine was 61.0% effective in preventing symptomatic infections in baseline seropositive individuals in the year after receiving the third dose, but this efficacy reduced to 39.4% after six years. Similarly, the cumulative efficacy of the vaccine in preventing subclinical infections declined from 50.3% to 36.2% during the same period. The research indicates that the vaccine's protective efficacy is mainly concentrated in the early years after vaccination and suggests that a booster dose given after the initial vaccination series could extend the duration of protection (CDC, 2021). Despite the varying rates of waning reported by different researchers, and some authors suggesting that the vaccine being used does not

exhibit any waning rate, I have decided to use a vaccine efficacy of 82% (CDC, 2021) for my study without taking into consideration on the number of doses administered, the duration between doses, and the time since the last dose.

Apart from that, it is assumed that the vaccination coverage of the population is 100%. In this scenario, the vaccinated population is calculated as the remaining portion of the total population, excluding those who are susceptible to the dengue, currently infected, or have recovered from the infection. Therefore, the vaccinated population (V_h) can be derived as the difference between the total population (N_h) and the susceptible population (S_h), infected population (I_h), and recovered population (R_h). Aside from that, the dengue vaccine's safety and effectiveness may be influenced by the dengue serostatus of individuals. Research has demonstrated that individuals who have never been infected with dengue and have a negative serostatus when vaccinated have a greater chance of developing severe dengue if they become infected with the virus later. This is because the vaccine can provoke an intense immune response against the dengue virus, which may be too aggressive in those without prior exposure to the virus. In contrast, those who have been previously infected with dengue and have a positive serostatus at the time of vaccination generally have a lower risk of severe dengue after immunization. This is because their immune system has already been primed to the virus, and the vaccine functions as a booster to improve their immune response. Hence, prior dengue infection may increase the risk of severe side effects following vaccination but also enhance vaccine efficacy (Sridhar et al., 2018; Luo et al., 2019).

2.3 Dengue Control Strategy Model

Control variables for dengue refer to the various factors that can be manipulated or controlled to prevent the transmission of dengue virus. There were a lot of articles applying different control variables. These variables include mosquito control measures, such as the use of insecticides, mosquito nets, and elimination of mosquito breeding sites. Other control variables include vaccination, surveillance and monitoring of dengue outbreaks, community education and engagement, and early detection and treatment of dengue cases. Effective control of these variables can help to reduce the incidence of dengue and prevent outbreaks. However, control strategies for dengue involve various measures to prevent the transmission of the virus and reduce the number of cases. A comprehensive approach that combines multiple control measures is usually most effective in reducing the burden of dengue.

For examples, Abidemi and Aziz, 2020 presents a mathematical model namely ASEI-SEIR that describes the transmission dynamics of dengue fever, incorporating personal protection, larvicide and adulticide control strategies. The mathematical model used in the study incorporates three populations: humans, aquatic and female mosquitoes. There are four classes in human population which are susceptible individuals (S_h), exposed individuals (infected but not yet infectious, E_h), infectious individuals (I_h), and recovered individuals (R_h). The size of the aquatic mosquito population is according to the proportion of a total human population, while the female mosquito population is divided into four compartments: aquatic form (A_m), susceptible (S_m), exposed (E_m), and

infectious mosquitoes (I_m). The result of the most cost-effective strategy in their proposed model is a combination of the adulticide controls and personal protection.

Aside from that, Khan and Fatmawati (2021) also develops a mathematical model (SEI-SEIPR) to describe the transmission dynamics of dengue fever with hospitalization and estimates the basic reproduction number (R_0=1.1138) for infected cases in East Java Province, Indonesia in 2018. The model parameters are estimated using confirmed notified cases. Optimal control strategies are also formulated, and the results suggest that prevention measures for humans and insecticide spraying on mosquitoes can significantly reduce the infection of dengue fever and further spread in the community. The mathematical model describes dengue transmission which includes three populations of mosquito's classes: susceptible (S_m), exposed (E_m), and infectious (I_m) and five populations of humans' classes: susceptible (S_h), exposed (E_h), infectious (I_h), hospitalized/notified infectious (P_h), and recovered (R_h). The total human population is denoted by a variable $N_h=S_h+E_h+I_h+P_h+R_h$. The model includes a new class for hospitalized individuals, denoted as P_h, which consists of those who have been recorded as confirmed dengue patients. All individuals in this class are assumed to be 100% protected and do not contribute to disease transmission. Also, the basic reproduction number (R_0) is calculated using the next generation matrix method and the MATLAB simulation for the optimality system involves a fourth-order Runge-Kutta scheme that is based on the forward-backward sweep method. The control strategies are set as:

i. Implementation of control variable for prevention.

ii. Implementation of control variable for insecticide.

iii. Implementation of control variables for prevention and insecticide.

As a result, optimal control strategies are applied, and a combination of prevention and insecticide is found to be the most effective in reducing dengue transmission, while implementing insecticide alone is also effective.

CHAPTER 3

METHODOLOGY

3.1 Introduction

This chapter will discuss the use of an epidemiological model with seven compartments, which includes insecticide, larvicide, and vaccination control strategies to describe the transmission of dengue fever. The model is fitted to the incidence data related to reported dengue cases from 2017 to 2019 in Selangor, Malaysia. Additionally, we will calculate the biting rate of the mosquito, β, by using the forward difference method. To optimally control the spread of dengue fever, we will apply optimal control theory to investigate the effect of different control strategies, including combinations of larvicide, insecticide, and vaccination controls on dengue fever dynamics. Then, the fourth-order Runge-Kutta scheme based on the forward-backward sweep method is used to simulate the resulting optimality system in MATLAB. The study's findings and conclusions will be presented and may prove valuable to authorities in Malaysia seeking to evaluate the effectiveness of mosquito interventions in reducing the incidence of dengue.

3.2 ASI-SVIR Model Formulation

In this section, we will describe a vector-host model for dengue transmission involving seven compartments. The vector-host transmission model is divided into three mosquitoes (vector) compartments which is Aquatic form/Pre-adult mosquito population (A_m), Susceptible adult female mosquito population (S_m), and Infected adult female mosquito population (I_m), and four human (host)

compartments which is Susceptible human population (S_h), Vaccinated human population (V_h), Infected human population (I_h), and Recovered human population (R_h). Therefore, the total mosquito population will denote by N_m given that $N_m = S_m + I_m$ while the total human population will be denoted as N_h where $N_h = S_h + V_h + I_h + R_h$ (N_h will be assumed as 6517500, average human population in Selangor from 2018-2021, which taken from Dosm.gov.my, 2021**.** In this study, we will consider the new class known as vaccinated individuals which is defined as V_h. For the vaccination, we are not limiting the age group which means the human populations are involving all age groups. Besides, the vaccination coverage will be 100% compared to the total human population in Selangor. The vaccine efficacy will be pre-assumed to be 82% and there will not have any side effects for the positive serostatus individuals (CDC, 2021).

In addition, certain assumptions were made in this research. The research focused on Aedes aegypti, a particular type of mosquito, and a single variant of dengue virus. According to the model, individuals who recover from dengue are assumed to have lifelong immunity, while infected mosquitoes are assumed to never recover (Khan, Hassan and Imran, 2014). However, it should be noted that the dengue vaccine is not completely effective, and there is a chance that vaccinated individuals may still get infected. Furthermore, the vaccine's immunity is temporary, and its effectiveness reduces over time, with a protection period of only 6 to 10 years (Thisyakorn et al., 2022; CDC, 2022). These assumptions are essential to consider when developing strategies for dengue prevention and management.

With the discussion above, we have presented the nonlinear system of differential equations describing the dynamics of host-vector dengue fever. The set of ordinary differential equations (ODEs) and compartment model that describe how the numbers of individuals in each compartment change over time and the definition and unit of the parameters list are illustrated below:

Mosquito Compartment:

Pre $-$ $adult/Larva$: $\frac{dA_m}{dt} = \Phi\left(1 - \frac{A_m}{kN_h}\right)(S_m + I_m) - \omega A_m - \mu_A A_m - u_1 A_m$

Susceptible Adult: $\frac{dS_m}{dt} = \omega A_m - B\beta_{hm} S_m \left(\frac{I_h}{N_h}\right) - \mu_m S_m - u_2 S_m$

Infected Adult: $\frac{dI_m}{dt} = B\beta_{hm} S_m \left(\frac{I_h}{N_h}\right) - \mu_m I_m - u_2 I_m$

Human Compartment:

Susceptible: $\frac{dS_h}{dt} = \mu_h N_h + \theta V_h - B\beta_{mh} S_h \left(\frac{I_m}{N_h}\right) - u_3 S_h - \mu_h S_h$

Vaccinated: $\frac{dV_h}{dt} = u_3 S_h - \theta V_h - \sigma B\beta_{mh}(I_m/N_h)V_h - \mu_h V_h$

Infected: $\frac{dI_h}{dt} = B\beta_{mh} S_h \left(\frac{I_m}{N_h}\right) + \sigma B\beta_{mh}(I_m/N_h)V_h - \eta_h I_h - \mu_h I_h$

Recovered: $\frac{dR_h}{dt} = \eta_h I_h - \mu_h R_h$

Figure 3.1 Set of Differential Equations

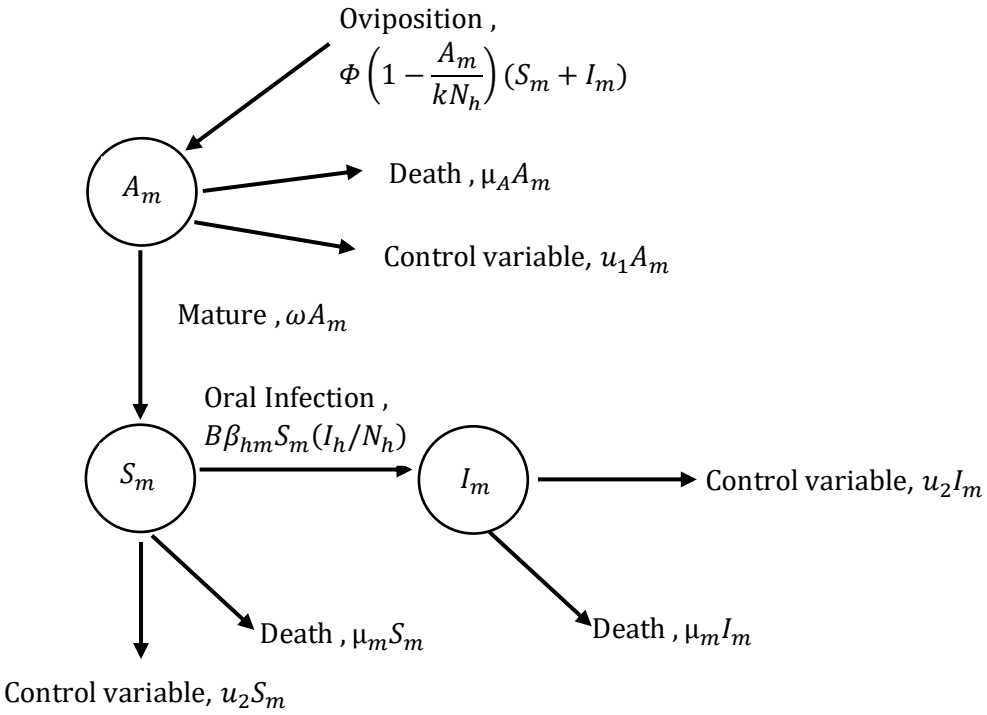

Figure 3.2 Compartment model for Mosquitoes

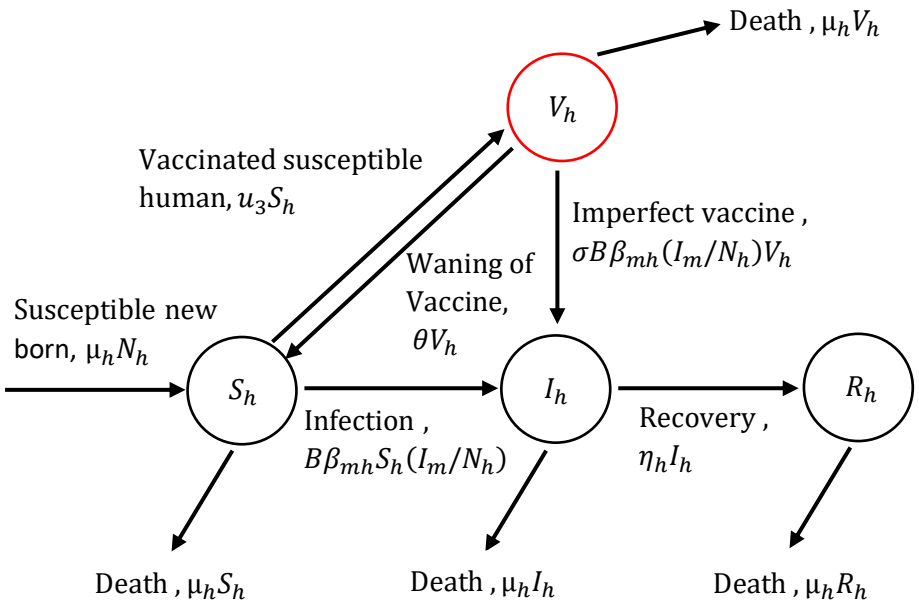

Figure 3.3 Compartment model for Human

Table 3.1 Definition and unit of parameters

No	Parameter	Definition	Unit	Value	Source
1	A_m	Pre-adult mosquito (aquatic form)	capita	-	-
2	S_m	Susceptible adult female mosquito (wing form)	capita	-	-
3	I_m	Infected adult female mosquito (wing form)	capita	-	-
4	N_m	Total adult female population mosquito ($N_m = S_m + I_m$)	capita	(1/5)*N_h	Assumed
5	S_h	Susceptible human population	capita	-	-
6	V_h	Vaccinated human population	capita	-	-
7	I_h	Infected human population	capita	-	-
8	R_h	Recovered human population	capita	-	-
9	N_h	Total human population ($N_h = S_h + V_h + I_h + R_h$)	capita	(5*N_m)	Assumed

10	t	Time	week	-	-
11	Φ	Oviposition rate (number of eggs at each deposit per capita)	week^{-1}	4.9	Abidemi and Aziz, (2020)
12	k	Number of mosquito larvae per human (Larvae capacity)	capita	3	Rodrigues et al. (2012)
13	ω	Maturation rate from larvae to adult	week^{-1}	0.14	Abidemi and Aziz, (2020)
14	μ_A	Natural mortality of larvae	week^{-1}	0.42	Abidemi and Aziz, (2020)
15	$B \text{ or } \beta$	Mosquito biting rate	week^{-1}	From curve fitting result	-
16	β_{hm}	Transmission probability from I_h to S_m	bite^{-1}	0.95	Andraud et al., (2012)
17	μ_m	Natural mortality of mosquito	week^{-1}	0.7	Rodrigues et al. (2014)

18	μ_h	Natural birth/mortality of human	$week^{-1}$	0.00026	MOHD UZIR MAHIDIN (2018)
19	β_{mh}	Transmission probability from I_m to S_h	$bite^{-1}$	0.95	Andraud et al., (2012)
20	$\eta \; or \; \eta_h$	Human recovery rate (or gamma, γ)	$week^{-1}$	0.7	Abidemi and Aziz, (2020)
21	θ	Vaccine waning rate	$week^{-1}$	0.00189	Shafie et al. (2017)
22	σ	Proportion of vaccinated human being infected (vaccine efficacy = 1 - σ)	capita	0.18	CDC, (2021)
23	u_1	Control variables for larvicide	-	0.001	-
24	u_2	Control variables for insecticide	-	0.001	-
25	u_3	Control variables for vaccination	-	0.001	-

3.2.1 Pre-intervention Dengue Fever Model

To parameterize the DF model described in Figure 3.1, we examine a scenario where none of the three controls are utilized (i.e., when $u_1(t) = u_2(t) = u_3(t) = 0$). In this case, Equations in Figure 3.1 transform from a non-autonomous DF model to an autonomous system of ODEs as shown in below:

Mosquito Compartment:

Pre − adult/Larva: $\frac{dA_m}{dt} = \Phi\left(1 - \frac{A_m}{kN_h}\right)(S_m + I_m) - \omega A_m - \mu_A A_m$

Susceptible Adult: $\frac{dS_m}{dt} = \omega A_m - B\beta_{hm} S_m \left(\frac{I_h}{N_h}\right) - \mu_m S_m$

Infected Adult: $\frac{dI_m}{dt} = B\beta_{hm} S_m \left(\frac{I_h}{N_h}\right) - \mu_m I_m$

Human Compartment:

Susceptible: $\frac{dS_h}{dt} = \mu_h N_h + \theta V_h - B\beta_{mh} S_h \left(\frac{I_m}{N_h}\right) - \mu_h S_h$

Vaccinated: $\frac{dV_h}{dt} = -\theta V_h - \sigma B\beta_{mh}(I_m/N_h)V_h - \mu_h V_h$

Infected: $\frac{dI_h}{dt} = B\beta_{mh} S_h \left(\frac{I_m}{N_h}\right) + \sigma B\beta_{mh}(I_m/N_h)V_h - \eta_h I_h - \mu_h I_h$

Recovered: $\frac{dR_h}{dt} = \eta_h I_h - \mu_h R_h$

Figure 3.4 Autonomous system of ODEs ($u_1(t) = u_2(t) = u_3(t) = 0$)

3.3 Estimation of Biting Rate

Here, the biting rates, β in Selangor is estimated based upon the 2017 to 2019 data. From the differential equation of I_h, the forward difference method is used to calculate the value of biting rate through MATLAB, β based on the dengue data, as indicated in equation below:

$$\beta_i = \left[\frac{I_{h,i+1}-I_{h,i}}{\Delta t} + (\boldsymbol{\eta_h} + \boldsymbol{\mu_h})I_{h,i}\right] \times \frac{N_h}{(I_{m,i}\times S_{h,i})} \qquad (3.1)$$

The forward difference method approximates the derivative of a function at a specific point by utilizing values of the function at two neighbouring points. Typically, these points are the given point and a point to the right. The technique estimates the slope of the function's tangent line at the given point. The reason for its name is that it employs the function value at the current point and a point to the right to perform the estimation. This numerical method is popular in numerical analysis and can be applied to discrete and continuous functions of various kinds (BrainKart, 2019). Therefore, the equation uses I_h to denote the data on the number of humans infected with dengue, and β is determined for each point in time where β should always greater or equal to 0. The graph for the biting rate will be presented in next chapter, Chapter 4.

3.4 Optimal Control Problem Formulation

This section examines the optimal control problem (OCP) formulation of the non-autonomous system described by Figure 3.1 for Dengue Fever transmission dynamics. To analyse the problem in detail, Pontryagin's Maximum Principle (PMP) is utilized, which has been widely used in other studies that involve optimal control (OC) in dynamical systems (Abidemi and Aziz, 2020; Ndii,

2022). In this formulation, the cost functional (CF) is quadratic in relation to the control terms, which is consistent with other studies (Abidemi and Aziz, 2020; Ndii, 2022). Therefore, the problem is formulated as:

$$Minimize\ J(u_1, u_2, u_3) = \int_0^{t_f} \left(W_1 I_m + W_2 I_h + \frac{W_3}{2} u_1^2 + \frac{W_4}{2} u_2^2 + \frac{W_5}{2} u_3^2 \right) dt \qquad (3.2)$$

where W_i, i = 1, 2, 3…5 are positive weight constants which means $W_i > 0$. Besides, W_1 and W_2 measure the importance of reducing the size of infected mosquito and infected human populations in dengue transmission. Then, W_3, W_4 and W_5 are the relative measures of the costs or efforts required to implement the respective controls.

3.4.1 Characterization of Optimal Controls

Next, let H to be the Hamiltonian which associated with optimal control problem, and it is determined as follow:

$$H = W_1 I_m + W_2 I_h + \frac{W_3}{2} u_1^2 + \frac{W_4}{2} u_2^2 + \frac{W_5}{2} u_3^2 + \lambda_1 \frac{dA_m}{dt} + \lambda_2 \frac{dS_m}{dt} + \lambda_3 \frac{dI_m}{dt}$$
$$+ \lambda_4 \frac{dS_h}{dt} + \lambda_5 \frac{dV_h}{dt} + \lambda_6 \frac{dI_h}{dt} + \lambda_7 \frac{dR_h}{dt} \qquad (3.3)$$

For optimal solution, there exists a non-trivial vector function (adjoint functions), and it is derived as follow:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial A_m}$$
$$= -\left[\lambda_1 \left(-u_1 - \frac{(S_m + I_m)}{kN_h} \varphi - \omega - \mu_A \right) + \lambda_2 \omega \right]$$
$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial S_m}$$
$$= -\left[\lambda_2 \left(-u_2 - \mu_m - \frac{\beta I_h \beta_{hm}}{N_h} \right) + (1 - \frac{A_m}{kN_h}) \lambda_1 \varphi + (\frac{\beta I_h \beta_{hm}}{N_h}) \lambda_3 \right]$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial I_m}$$

$$= -\left[\lambda_3(-u_2-\mu_m) + \lambda_6\left(\frac{\sigma\beta V_h\beta_{mh}}{N_h} + \frac{\beta S_h\beta_{mh}}{N_h}\right) - \lambda_5\left(\frac{\sigma\beta V_h\beta_{mh}}{N_h}\right)\right.$$

$$\left. + (1-\frac{A_m}{kN_h})\lambda_1\varphi - \lambda_4\left(\frac{\beta S_h\beta_{mh}}{N_h}\right) + W_1\right]$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial S_h}$$

$$= -\left[\lambda_5 u_3 + \lambda_4\left(-u_3-\mu_h - \frac{\beta I_m\beta_{mh}}{N_h}\right) + \lambda_6\left(\frac{\beta I_m\beta_{mh}}{N_h}\right)\right]$$

$$\frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial V_h}$$

$$= -\left[\lambda_4\theta + \lambda_5\left(-\theta - \frac{\sigma\beta I_m\beta_{mh}}{N_h} - \mu_h\right) + \lambda_6\left(\frac{\sigma\beta I_m\beta_{mh}}{N_h}\right)\right]$$

$$\frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial I_h}$$

$$= -\left[\lambda_6(-u_h - \boldsymbol{\eta_h}) + \lambda_7\boldsymbol{\eta_h} + \lambda_3\left(\frac{\beta S_m\beta_{hm}}{N_h}\right) + \lambda_2\left(\frac{\beta S_m\beta_{hm}}{N_h}\right) + W_2\right]$$

$$\frac{d\lambda_7}{dt} = -\frac{\partial H}{\partial I_h} = \lambda_7\boldsymbol{\eta_h}$$

The following transversality or boundary conditions are used in the simulation:

$$\lambda_i(t_f) = 0,\ i = 1,2,3,...,7$$

where t_f is the final time.

The optimality condition is derived as follow:

$$\frac{\partial H}{\partial u_1} = 0$$

$$\frac{\partial H}{\partial u_2} = 0$$

$$\frac{\partial H}{\partial u_3} = 0$$

Therefore, the u_1, u_2, u_3 will be solved as:

$$u_1 = \frac{\lambda_1 A_m}{W_3}$$

$$u_2 = \frac{\lambda_3 I_m + \lambda_2 S_m}{W_4}$$

$$u_2 = \frac{\lambda_4 S_h - \lambda_5 S_h}{W_5}$$

Then, Forward-backward sweep method is used in MATLAB to obtain the solution. The aim of this part is to investigate the numerical outcomes of the model with and without control, and to simulate the optimal solution of the model using the forward-backward sweep method. The optimal control problem is solved numerically with the fourth order Runge-Kutta method. The RK4 method, also known as the fourth-order Runge-Kutta method, is a commonly employed numerical technique for solving ordinary differential equations. To calculate the estimated solution of an ODE at each time step, this method employs four stages that include determining the slopes at the starting point, the midpoint, and the endpoint. The subsequent time step's estimated solution is achieved by weighting the average of these slopes. Due to its ease, precision, and effectiveness, RK4 is a fourth-order approach that is well-known (Mukhsar et al., 2023).

CHAPTER 4

RESULTS

4.1 Introduction

In this section, the numerical results for the estimation of biting rates and implementation of a control strategy will be discussed. In addition, numerical solutions for the optimality system, which consists of a non-autonomous dengue fever model, initial conditions, and the costate system, are computed using MATLAB with the fourth order Runge-Kutta scheme. This method employs the forward-backward sweep method procedure.

4.2 Parameter values

Before implementing the numerical simulation, the state and control balancing weight values shown in the previous chapter are taken as:

$$Minimize\, J(u_1, u_2, u_3) = \int_0^{t_f} \left(W_1 I_m + W_2 I_h + \frac{W_3}{2} u_1^2 + \frac{W_4}{2} u_2^2 + \frac{W_5}{2} u_3^2 \right) dt$$

$$H = W_1 I_m + W_2 I_h + \frac{W_3}{2} u_1^2 + \frac{W_4}{2} u_2^2 + \frac{W_5}{2} u_3^2 + \lambda_1 \frac{dA_m}{dt} + \lambda_2 \frac{dS_m}{dt} + \lambda_3 \frac{dI_m}{dt}$$
$$+ \lambda_4 \frac{dS_h}{dt} + \lambda_5 \frac{dV_h}{dt} + \lambda_6 \frac{dI_h}{dt} + \lambda_7 \frac{dR_h}{dt}$$

where $W_i > 0$, i =1, 2, 3, 4, 5.

Table 4.1 Definition and Value of control balancing weight constant

Respective With	**Weight constant, W_i**	**Value**
Infected mosquito population, I_m	W_1	100
Infected human population, I_h	W_2	100
Larvicide, u_1	W_3	1000000000
Insecticide, u_2	W_4	2500000000
Vaccination, u_3	W_5	100000000000

The W_1 and W_2 are assumed to be 100 and measured the importance of reducing the size of infected mosquito, I_m and infected human population, I_h in dengue transmission (Pongsumpun, Tang and Wongvanich, 2019). Then, for the W_3, W_4 and W_5 are representing the measure of cost or efforts required to implement the respective controls. Based on some of studies and assume that the latest science and technology are utilized, we set the W_3=1000000000, W_4=2500000000 and W_5=100000000000 which are in MYR (Lee et al., 2010; Packierisamy et al., 2015; Suwantika et al., 2021; España et al., 2021).

4.3 Estimation of Biting Rate, β

Using the incidence data on dengue and mathematical model, the rate at which mosquitoes bite and infect people in Selangor was estimated through the forward difference method, as depicted in Figure 4.2. Figure 4.1 illustrates how well the model is fitted to infected human data. Additionally, all compartments of the epidemiological model were computed in this estimation, as illustrated in Figures 4.1 and 4.3 to 4.7.

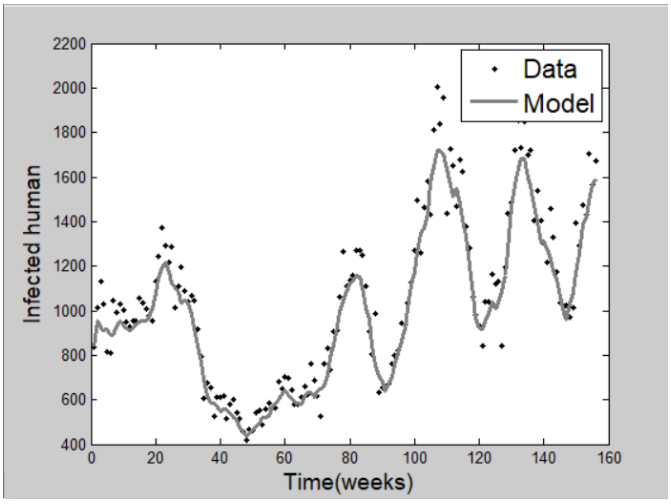

Figure 4.1 Curve fitting with Infected Human Population, I_h

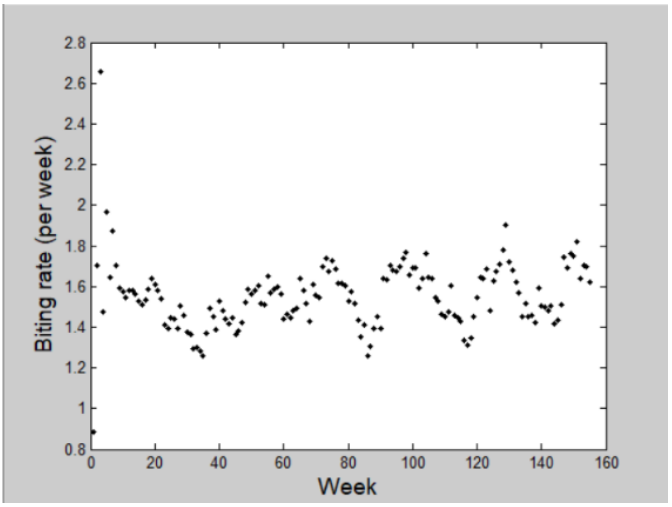

Figure 4.2 Estimation of mosquito biting rate, β

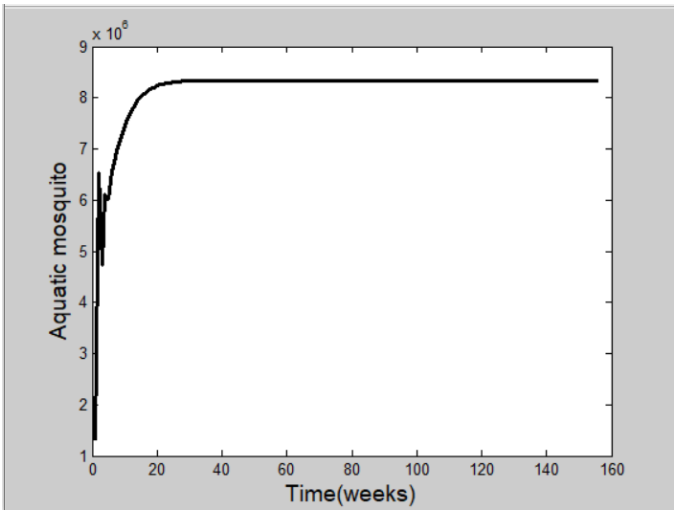

Figure 4.3 Aquatic Mosquitoes Populations, A_m

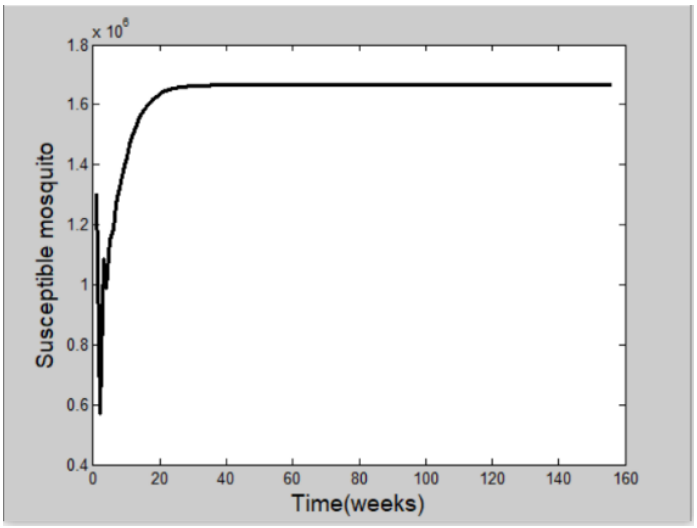

Figure 4.4 Susceptible Mosquitoes Populations, S_m

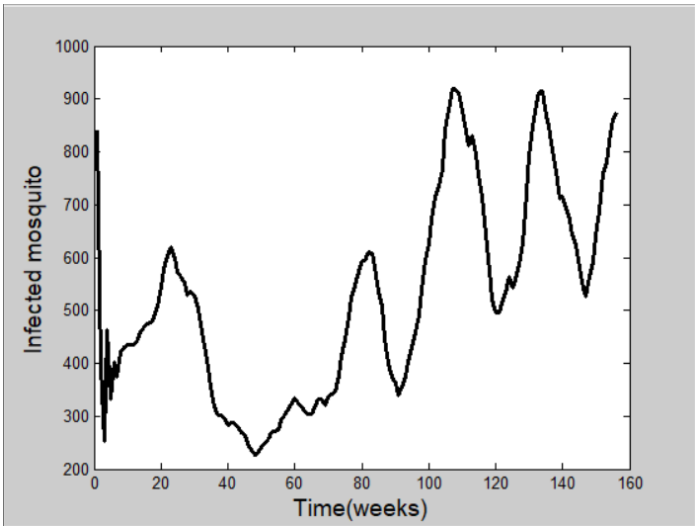

Figure 4.5 Infected Mosquitoes Populations, I_m

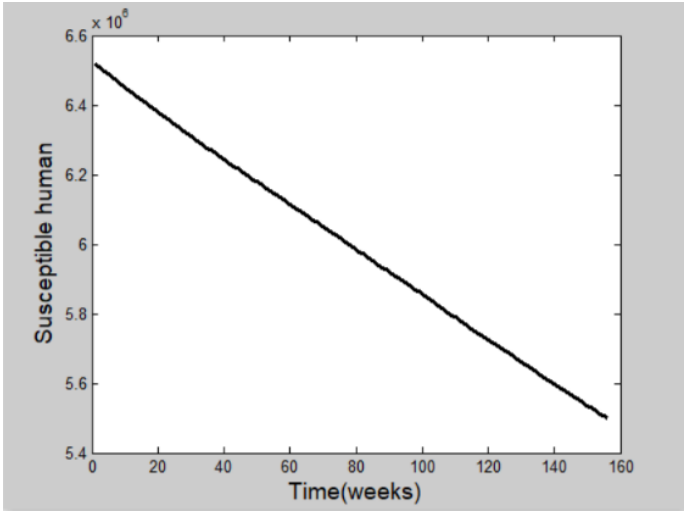

Figure 4.6 Susceptible Human Populations, S_h

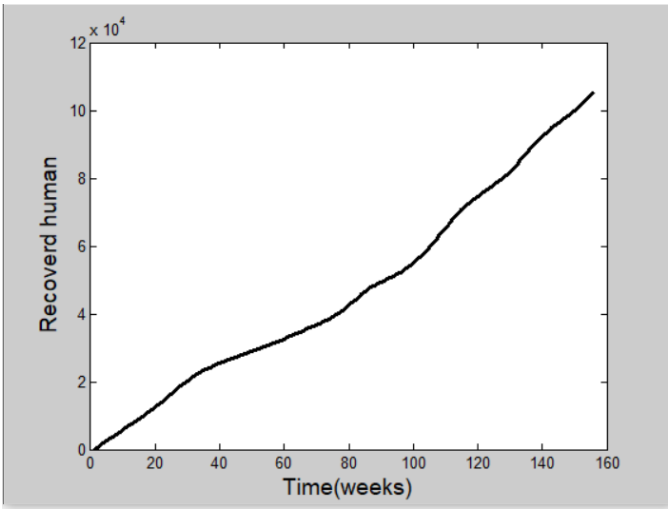

Figure 4.7 Recovered Human Populations, R_h

From the Figure 4.1, we can clearly observe that the curve is well fitted to the model. Hence, the estimation of mosquito biting rate that vary over the time are qualified.

4.4 Several Control Strategies

There were several control strategies involved in the numerical simulation which incorporate with the control variable such as larvicide (u_1), insecticide (u_2), vaccination (u_3). [Note: The "Ori" in the figures below means original dengue data reported from 2017-2019]

4.4.1 Strategy 1: Implementation of optimal larvicide (u_1)

This strategy for intervention demonstrates how larvicide (u_1) impact the transmission dynamics of dengue fever within a population. The findings from applying this intervention strategy are visualized in Figures below:

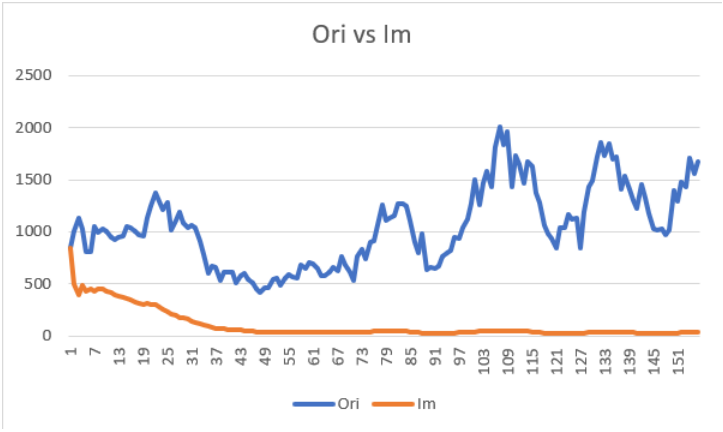

Figure 4.8 Original data vs Infected Mosquito Population, I_m

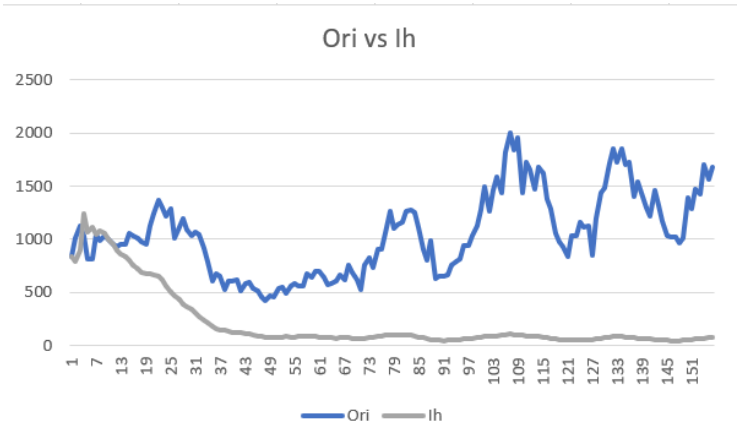

Figure 4.9 Original data vs Infected Human Population, I_h

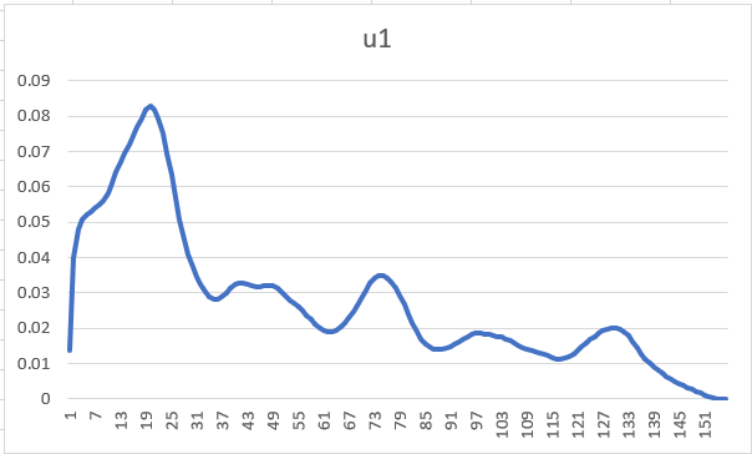

Figure 4.10 Control measures of Larvicide (u_1)

4.4.2 Strategy 2: Implementation of optimal insecticide (u_2)

This strategy for intervention demonstrates how insecticide (u_2) impact the transmission dynamics of dengue fever within a population. The findings from applying this intervention strategy are visualized in Figures below:

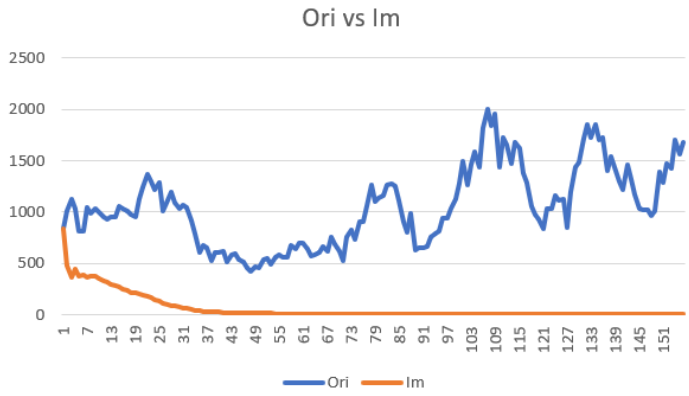

Figure 4.11 Original data vs Infected Mosquito Population, I_m

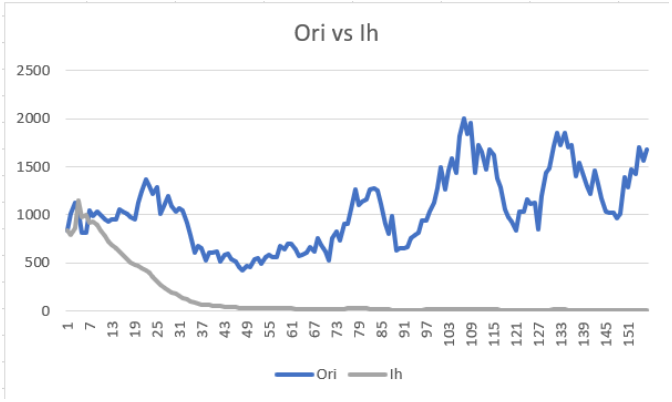

Figure 4.12 Original data vs Infected Human Population, I_h

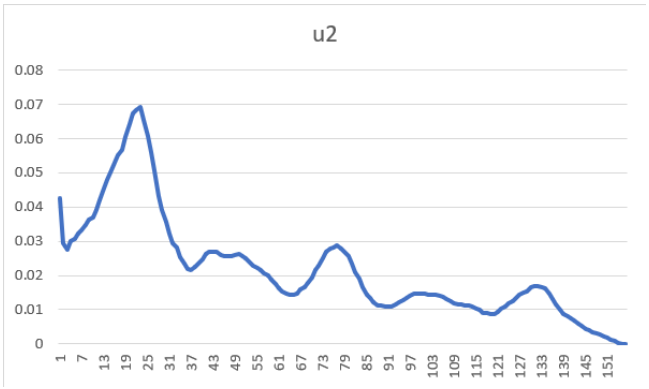

Figure 4.13 Control measures of Insecticide (u_2)

4.4.3 Strategy 3: Implementation of optimal vaccination (u_3)

This strategy for intervention demonstrates how vaccination (u_3) impact the transmission dynamics of dengue fever within a population. The findings from applying this intervention strategy are visualized in Figures below:

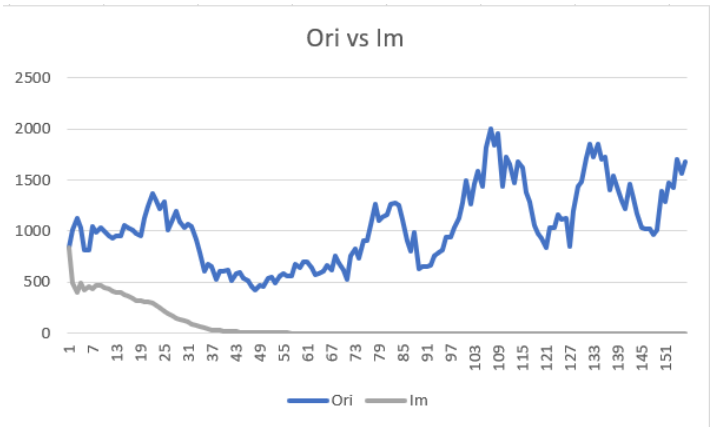

Figure 4.14 Original data vs Infected Mosquito Population, I_m

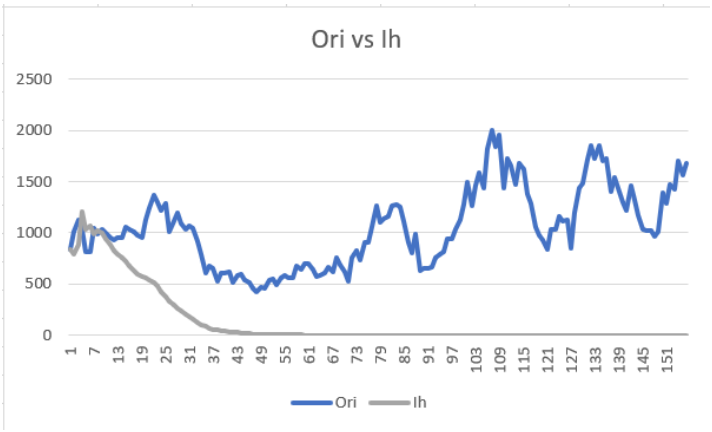

Figure 4.15 Original data vs Infected Human Population, I_h

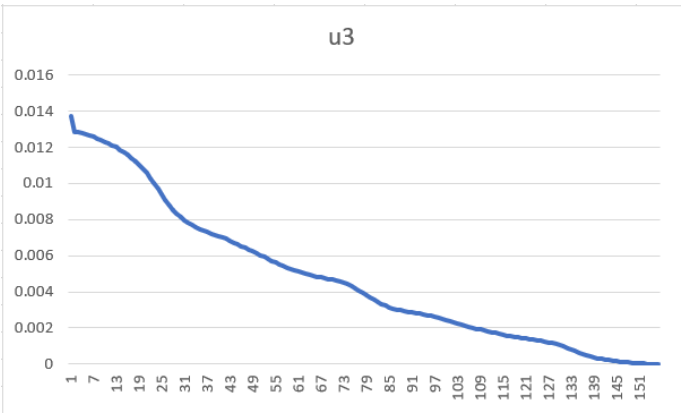

Figure 4.16 Control measures of Vaccination (u_3)

4.4.4 Strategy 4: Implementation of optimal larvicide (u_1) and insecticide (u_2)

This strategy for intervention demonstrates how the joint actions of larvicide (u_1) and insecticide (u_2) impact the transmission dynamics of dengue fever within a population. The findings from applying this intervention strategy are visualized in Figures below:

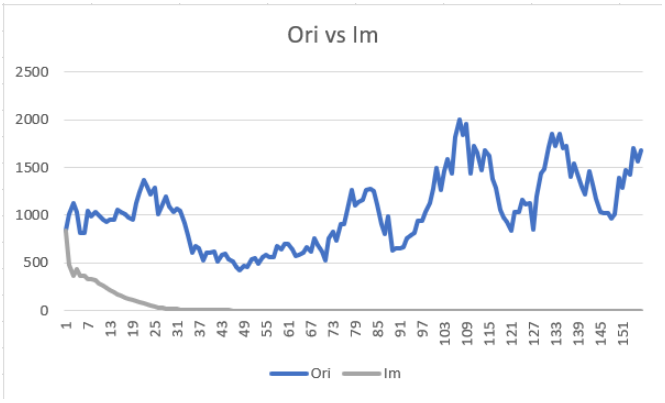

Figure 4.17 Original data vs Infected Mosquito Population, I_m

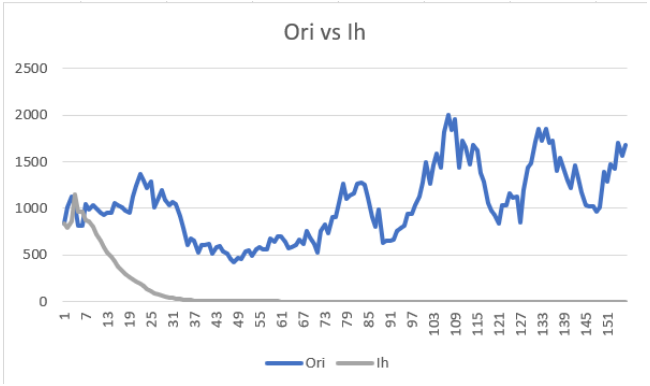

Figure 4.18 Original data vs Infected Human Population, I_h

4.4.5 Strategy 5: Implementation of optimal larvicide (u_1) and vaccination (u_3)

This strategy for intervention demonstrates how the joint actions of larvicide (u_1) and vaccination (u_3) impact the transmission dynamics of dengue fever within a

population. The findings from applying this intervention strategy are visualized in Figures below:

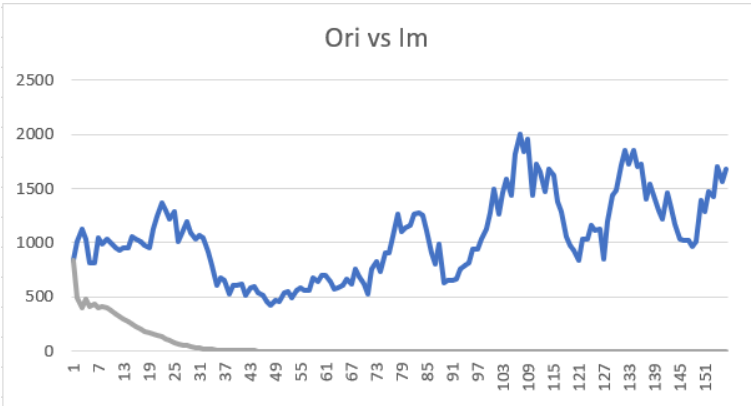

Figure 4.19 Original data vs Infected Mosquito Population, I_m

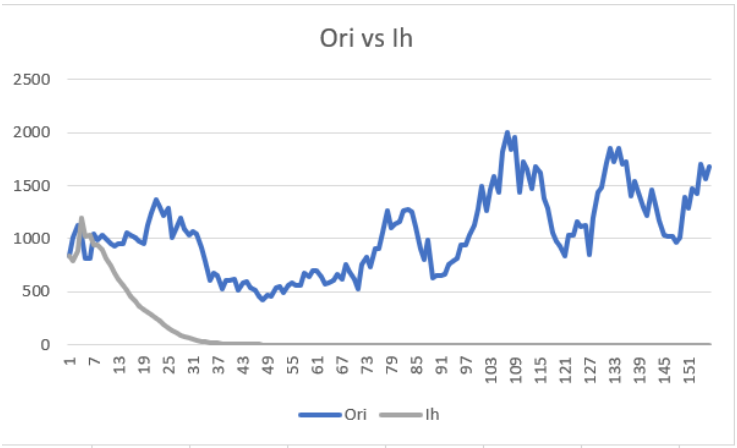

Figure 4.20 Original data vs Infected Human Population, I_h

4.4.6 Strategy 6: Implementation of optimal insecticide (u_2) and vaccination (u_3)

This strategy for intervention demonstrates how the joint actions of insecticide (u_2) and vaccination (u_3) impact the transmission dynamics of dengue fever within a population. The findings from applying this intervention strategy are visualized in Figures below:

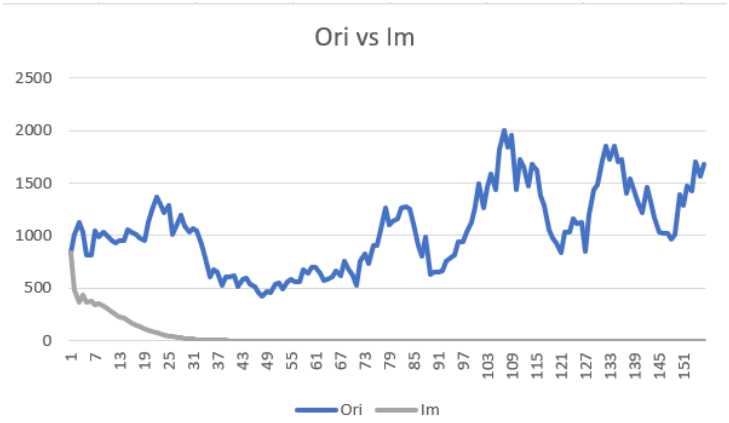

Figure 4.21 Original data vs Infected Mosquito Population, I_m

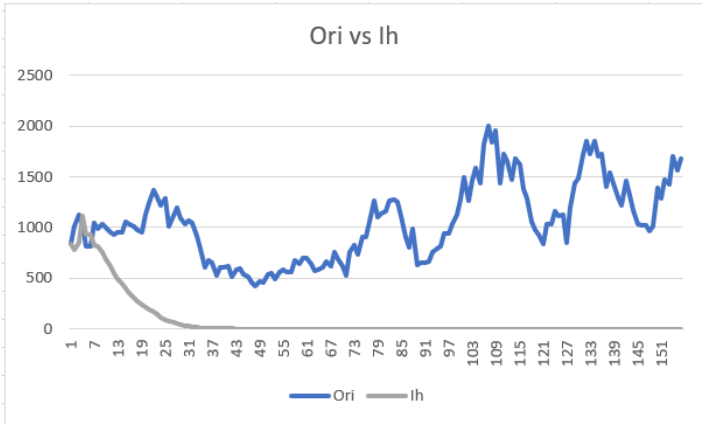

Figure 4.22 Original data vs Infected Human Population, I_h

4.4.7 Strategy 7: Implementation of optimal larvicide (u_1), insecticide (u_2) and vaccination (u_3)

This strategy for intervention demonstrates how the joint actions of larvicide (u_1), insecticide (u_2) and vaccination (u_3) impact the transmission dynamics of dengue fever within a population. The findings from applying this intervention strategy are visualized in Figures below:

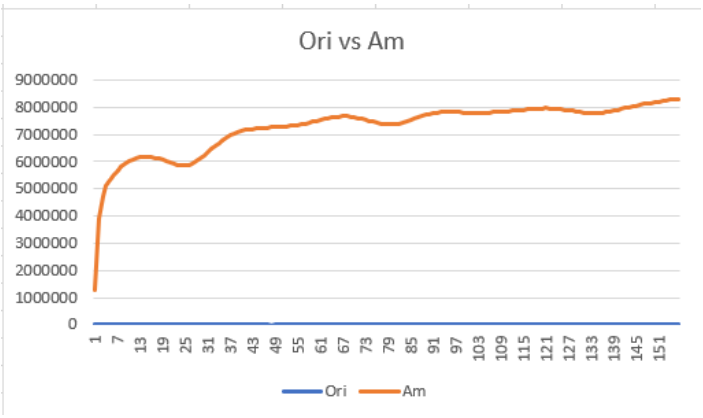

Figure 4.23 Original data vs Aquatic Mosquito Population, A_m

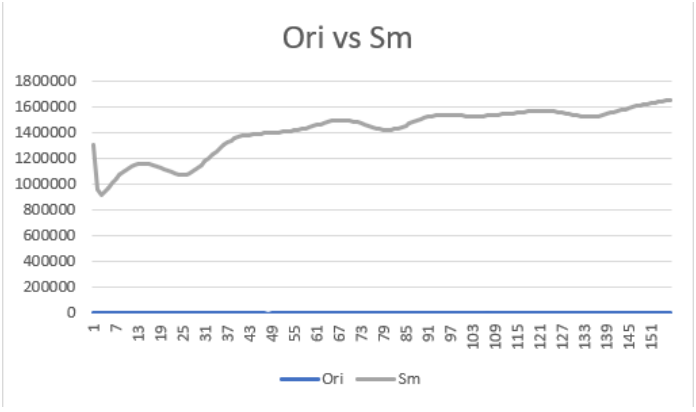

Figure 4.24 Original data vs Susceptible Mosquito Population, S_m

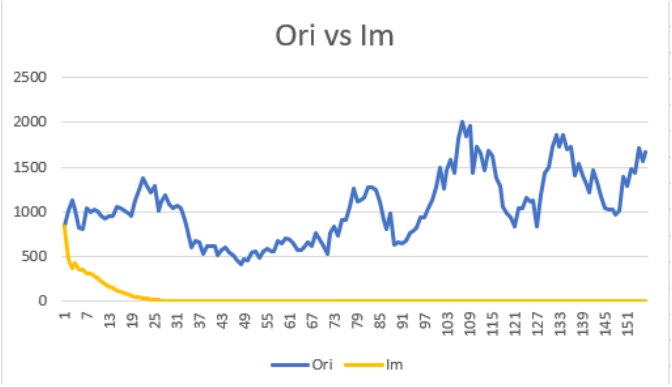

Figure 4.25 Original data vs Infected Mosquito Population, I_m

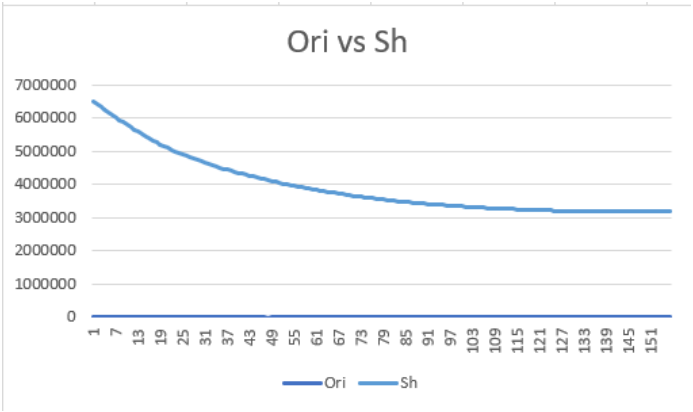

Figure 4.26 Original data vs Susceptible Human Population, S_h

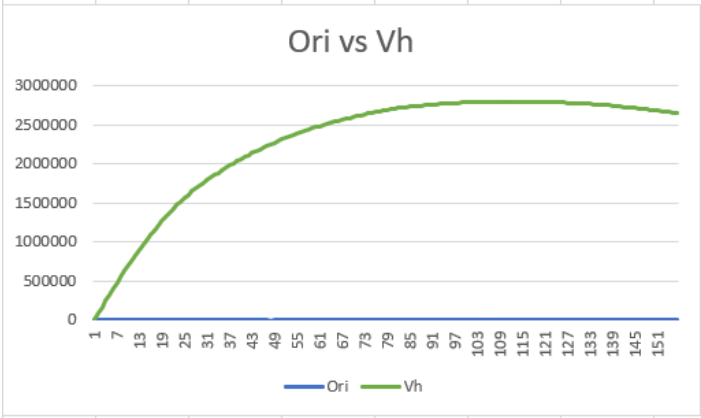

Figure 4.27 Original data vs Vaccinated Human Population, V_h

Figure 4.28 Original data vs Infected Human Population, I_h

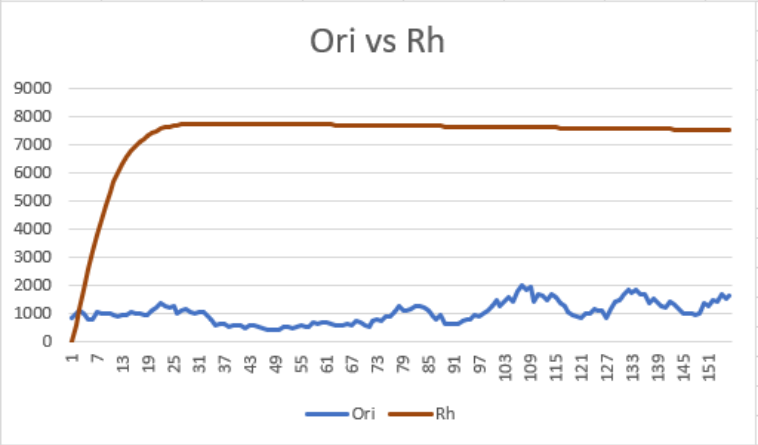

Figure 4.29 Original data vs Recovered Human Population, R_h

Overall, all the seven strategies have been applied and the compartments in the ASI-SVIR model such as A_m, S_m, I_m, S_h, V_h, I_h, and R_h populations are computed over the time and compared with the original infected human population incidence data. The findings of the graphs will be explained in the next section.

4.5 Effect of Dengue Interventions

Considering control strategies 1 to 3 which is implementing only one of the control interventions (u_1, u_2, u_3) are carried. The figure 4.10, 4.13, and 4.16 showing the interventions of the control variables over the times from 2017 to 2019. Aside from that, from the figure 4.8, 4.11, and 4.14 (original dengue data versus infected mosquito population, I_m), it's showing that insecticide (u_2) will have a better effect on controlling the dengue fever than larvicide (u_1), since the peak of the infected mosquito population of u_2 is 476 week^{-1} which is less than u_1, 496 week^{-1}. Then, for vaccination (u_3), its peak is around 497 week^{-1} same with u_1 so this showing that insecticide has the most effectiveness in controlling dengue fever but only in short term (not considering the first week of the number since there are initial value). Besides, comparing u_1, u_2, and u_3, implementing insecticide give the least total number of infected mosquitoes (I_m=9831), for u_1 and u_3, the total number of infected mosquitoes are 16014 and 10606. While from figure 4.9, 4.12, and 4.15, the results are showing the total infected humans population comparing with original dengue data. Based on those graphs in section 4.4, the peak number of infected humans for u_1, u_2 and u_3 are 1240, 1155, and 1206 week^{-1} respectively. Hence, the effectiveness of dengue interventions is ordered ascendingly as u_2, u_3, u_1.

Despite of the findings above showing the insecticide is the most effective dengue intervention, the vaccination (u_3) will be the most effective control variables compared to others (u_1, u_2) in long term. This is because the total number of infected humans, I_h from 2017 to 2019 for u_3 is the least, which is 20771 compared with u_1 and u_3, 33815 and 21394. Furthermore, in contrast of

figure 4.9 (u_1), 4.12 (u_2) and 4.15 (u_3), the graph for u_3 clearly showing the infected human decreased to around 0 at the 65th weeks but for u_1 and u_2, both are only fluctuated over the time. The reason of u_3 still having a quite high amount of total infected humans from 2017 to 2019 even it decreased to 0 at 65th but still consider as the most effective control variable is because of the body may take several weeks to generate antibodies against the dengue virus after being vaccinated. The time it takes for this process to occur can vary depending on the type of vaccine and the individual receiving it. However, most people should have detectable levels of antibodies within a period of a few weeks to a month after vaccination. Then, the vaccine can provide protection against dengue for at least 6 years (Rosa, Cunha and Medronho, 2019; CDC, 2022).

Now considering the combination of u_1, u_2, and u_3 (strategies 4 to 7), the results will be discussed based on the findings above. From the figure 4.17, 4.19, 4.21, and 4.25, the results showing the peak number of infected mosquitoes for a week is ordered ascendingly as strategies 4,7,6, and 5 (475.8, 475.9, 476, and 497 per week respectively) but the 4, 7 and 6 are approximately same. However, the total number for infected mosquitoes for strategies 4 to 7 can be ordered ascendingly as 7, 4, 6 and 5 (5422, 6439, 6584 and 8084 respectively). Hence, based on the infected mosquito population, I_m, the strategy 7 which is the combination of larvicide, insecticide and vaccination (u_1, u_2, u_3) is the most effective control strategy.

Aside from that, from the figure 4.18, 4.20, 4.22, and 4.28, the results showing the peak number of infected humans for a week is ordered ascendingly as strategies 7, 6, 4, and 5 (1112, 1118, 1147, and 1199 per week respectively) but their differences are less than 52. However, the total number for infected humans for strategies 4 to 7 can be ordered ascendingly as 7, 4, 6 and 5 (11543, 13549, 14558 and 16254 respectively). Hence, based on the infected human population, I_h, the strategy 7 which is the combination of larvicide, insecticide and vaccination (u_1, u_2, u_3) is the most effective control strategy.

4.6 Discussion

According to the research, the overtime and repeated use of larvicide, and insecticide will cause the mosquito resistant to them. For examples, insecticide resistance refers to the decreased effectiveness of an insecticide in eliminating mosquitoes. This implies that the product fails to work as intended or works only to a limited extent (CDC, 2021). Therefore, in long term, vaccination (u_3) will give the best controlling of dengue fever.

Henceforth, based on the results of findings for infected mosquitoes and infected humans, the strategy 7 will be the most effective control strategy. From the other graph under the intervention of strategy 7 (Figure 4.23, 4.24, 4.26, 4.27 and 4.29), the aquatics mosquitoes and susceptible mosquitoes are controlled constantly, and we cannot directly kill all of them since this will affect the ecosystem. This is because mosquitoes play various roles in their respective ecosystems. For examples, mosquito eggs and larvae are a significant part of the

biomass found in lakes and streams, serving as food for fish, turtles, amphibians, and other insects like dragonflies. Besides, mosquitoes flying in the air are easy prey for birds and bats in land-based environments. Other creatures like lizards, frogs, spiders, and insects depend mainly on adult mosquitoes for their food (Rafferty, J. P., 2022). Therefore, the extinction of mosquito will cause the imbalance of ecosystem. While for the Susceptible, Vaccinated, and Recovered human populations, all will also remain constant after a certain time since the presence of the vaccine and the controlled number of mosquitoes.

Nowadays, Malaysia has implemented a lot of dengue control strategies including larvicide, insecticide and vaccination but it seems like the dengue outbreak is not under control. Hence, the result get from the findings above are so ideal since the findings all are generated through simulation. There are too much of uncertainty that causing the dengue fever not under control such as the carelessness of human, the resistant to larvicide and insecticide for mosquito, the loose management of control strategies and so on. Overall, the ideal result just provides an insight on the optimal dengue control strategy in Selangor to assist decision makers in implementing dengue control strategies.

CHAPTER 5

CONCLUSION

5.1 Summary

All in all, in this study, a new mathematical model of dengue fever with vaccination compartment has been formulated. The mosquito biting rates are estimated by using the weekly real incidence data of Selangor, Malaysia from 2017 to 2019. To avoid the spread of dengue virus in Selangor, we applied the optimal control strategies to investigate the effect of larvicide, insecticide, and vaccination. The numerical simulation was performed with different control strategies. Then, the numerical results indicate that the implementation of larvicide, insecticide and vaccination is the optimal control strategy to minimize the number of dengue-infected hosts and vector in the population.

In addition, the optimal control variable is implementing vaccination (u_3). This result does not claim that larvicide (u_1) and insecticide (u_2) are not effective in controlling the dengue fever, but vaccination is more effective than them. This is because the long period of protection against dengue virus at least 6 years. Therefore, the infected human can be reduced to 0 after 65 weeks and having the least total number of infected humans among the three years under the interventions of vaccination by comparing with u_1 and u_2. However, our body will need a period of times maybe a few weeks or a month (the times vary depend on individuals or several factor) to generate the antibodies against the dengue virus after being vaccinated. Hence, the effect of dengue control for vaccination

might not be effective compared to larvicide and insecticide in the early period. So, the combination of dengue control variables will be considered.

Furthermore, seven control strategies are discussed and analysed in this study. After the investigation, the optimal control strategy is the combination of larvicide, insecticide, and vaccination (u_1, u_2 and u_3). From the findings, it shows that this optimal strategy gives the lowest total number of infected mosquitoes and total number of infected humans. Apart from that, the population of aquatics mosquitoes (A_m) and susceptible mosquitoes (S_m) are controllable since the presence of u_1 and u_2. Besides, the Susceptible, Vaccinated, and Recovered human populations (S_h, V_h and R_h), all will also remain constant after a certain time since the presence of the u_3. As a results, the intervention of larvicide and insecticide controlled the mosquito population in the early period where the larvicide targeted to aquatic mosquitoes (used to kill the aquatic mosquitoes) and insecticide targeted the adult mosquitoes (used to kill adult mosquitoes). Then, the implementation of vaccination help to protect human from dengue virus in the long term (humans will generate antibodies to kill the dengue virus in their body and also the mosquito will do that). This combination of control variables helps to preventing the spread of dengue disease in each of the period. Henceforth, the optimal dengue control strategy in Selangor, Malaysia undeniable will be the combination of larvicide, insecticide and vaccination and this study will help the researchers and government to design a program in the future to control the dengue disease further spread.

5.2 Limitation and Future Research

Despite that this study reviewed a lot of previous literature and journal article and analysed the incidence data using a numerical approach, there are several limitations in this study.

First and foremost, the outcome and results of this study are only for Selangor and thus not able to represent the whole Malaysia or other countries. This is due to this study is taking the real incidence data for Selangor, Malaysia. Therefore, there might be several factors that differentiate the results. For examples, the capabilities of the targeted place to implement the optimal control strategy, the level of cooperation of citizens, the population of the focused place and so on. Besides, for foreign country, since Malaysia is a multicultural race so the findings may be different when encountered different culture and ethnicity. Hence, the model and results of this study are only for Selangor, Malaysia and so it only can take as a reference. However, it might be possible to extend the analysis to other states in Malaysia.

On the other hands, the incidence data from 2017 to 2019 is used in this study. Therefore, the simulated parameters might be outdated and possible to give a different outcome. So, the results from this study can only be taken as a reference. However, we may use the latest incidence data to repeat the simulation and analysis if there are no other new statistical and numerical approaches are proposed.

Apart from that, for the future research, the control strategy can consider the application of Wolbachia to reduce dengue transmission. As in the study of Mustafa et al., (2016), Wolbachia can prevent the transmission of dengue in two ways: it can either directly hinder the virus, or it can shorten the lifespan of the mosquito vector.

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APPENDICES

Coding for Generating graph for A_m, S_m, I_m, S_h, I_h, R_h, β against time, t (week)

```
clear all
format long

% data for the model
n=156;
tdata=1:1:1*n;
Ih1 = xlsread('SData.xlsx','B2:B157'); %need to change data
Ih2 = smooth(Ih1);

Ih(1) = Ih2(1);
Sh(1) = 6517500-Ih(1);   %change from 6345814
Rh(1) = 0;
%Vh(1) = 6517500-Sh(1)-Ih(1)-Rh(1);
Am(1) = 6517500/5;
Sm(1) = (6517500/5)-Ih(1);
Im(1) = Ih(1);

%unit of time: week^-1
deltat = 1;
phi = (0.7)/(1/7);  %2018 ASEI-SEIR article changed from 0.7 to 6 ##confirmed 6/(1/7)
w = 0.02/(1/7); %2018... article ##confirmed 0.56 from 0.14
mua = 0.06/(1/7); %2018... article changed from 0.06 to 0.25 ##confirmed 0.25/(1/7)
gamma = 0.1*7; %2022_Dengue epidemiological... in KL and Selangor article %human recovery rate/Inverse of viremic period/eta h %SI-SIR model ##confirmed
Nh = 6517500;  %2018-2021 average population
mum = 0.1*7; %remains unchanged 2018... ##confirmed
muh = 1./(75*52); %original value = 1./(75*52)
k = 3; %remains unchanged 2018...
%sigma = 0.18; %refer to latest information
theta = 0.00027/(1/7);
Bmh = 0.95;%0.75
Bhm = 0.95;%0.5
u1 = 0.001; %0.95
u2 = 0.001; %0.95
u3 = 0.001; %0.95

for i = 1:length(tdata)-1

    Beta(i) = (((Ih2(i+1)-Ih2(i))/deltat)+((gamma+muh)*Ih2(i)))*(Nh/(Im(i)*Sh(i)));

    Ih(i+1) = Ih(i)+deltat*(Beta(i)*Bmh*Sh(i)*(Im(i)/Nh)-gamma*Ih(i)-muh*Ih(i));
    Rh(i+1) = Rh(i)+deltat*(gamma*Ih(i)-muh*Rh(i));


end

figure;
plot(tdata,Ih1,'.k','LineWidth',2.25)
hold on
plot(tdata,Ih,'k','color', [0.5 0.5 0.5],'LineWidth',2.25)
hold off
xlabel('Time(weeks)','FontSize',14)
ylabel('Infected human','FontSize',14)
legend({'Data','Model'},'FontSize',16)
drawnow

%Im
figure;
plot(tdata,Im,'k','LineWidth',2.25)
xlabel('Time(weeks)','FontSize',14)
ylabel('Infected mosquito','FontSize',14)

%Am
figure;
plot(tdata,Am,'k','LineWidth',2.25)
xlabel('Time(weeks)','FontSize',14)
ylabel('Aquatic mosquito','FontSize',14)

%Sm
figure;
plot(tdata,Sm,'k','LineWidth',2.25)
xlabel('Time(weeks)','FontSize',14)
ylabel('Susceptible mosquito','FontSize',14)

%Sh
figure;
plot(tdata,Sh,'k','LineWidth',2.25)
xlabel('Time(weeks)','FontSize',14)
ylabel('Susceptible human','FontSize',14)

%Vh
%figure;
%plot(tdata,Vh,'k','LineWidth',2.25)
%xlabel('Time(weeks)','FontSize',14)
%ylabel('Vaccinated human','FontSize',14)

%Ih
figure;
plot(tdata,Ih,'k','LineWidth',2.25)
xlabel('Time(weeks)','FontSize',14)
ylabel('Infected human','FontSize',14)

%Rh
figure;
plot(tdata,Rh,'k','LineWidth',2.25)
xlabel('Time(weeks)','FontSize',14)
ylabel('Recoverd human','FontSize',14)

figure;
for i = 1:length(tdata)-1
    B = Beta(i);
    plot(i,B,'k.')
    hold on

end
hold on
xlabel('Week','FontSize',14)
ylabel('Biting rate (per week)','FontSize',14)
drawnow
```

Coding for Generating graph for V_h against time, t (week)

```
clear all
format long

% data for the model
n=155;
tdata=1:1:1*n;
Beta = xlsread('BetaValue.xlsx','B2:B156');


Ih(1) = 839;
Sh(1) = 6517500-Ih(1);
Rh(1) = 0;
Vh(1) = 6517500-Sh(1)-Ih(1)-Rh(1);
Am(1) = 6517500/5;
Sm(1) = (6517500/5)-Ih(1);
Im(1) = Ih(1);

%unit of time: week
deltat = 1;
phi = (0.7)/(1/7);  %2018 ASEI-SEIR article changed from 0.7 to 6 ##confirmed 6/(1/7)
w = 0.02/(1/7); %2018... article ##confirmed 0.56 from 0.14
mua = 0.06/(1/7); %2018... article changed from 0.06 to 0.25 ##confirmed 0.25/(1/7)
gamma = 0.1*7; %2022_Dengue epidemiological... in KL and Selangor article %human recovery rate/Inverse of viremic period/eta h %SI-SIR model ##confirmed
Nh = 6517500;  %2018-2021 average population
mum = 0.1*7; %remains unchanged 2018... ##confirmed
muh = 1./(75*52); %original value = 1./(75*52)
k = 3; %remains unchanged 2018...
sigma = 0.18; %refer to latest information
theta = 0.00027/(1/7);
Bmh = 0.95;%0.75
Bhm = 0.95;%0.5
u1 = 0.001; %0.95
u2 = 0.001; %0.95
u3 = 0.001; %0.95

for i = 1:length(tdata)-1

    Am(i+1) = Am(i)+deltat*(phi*(1-(Am(i)/(k*Nh)))*(Sm(i)+Im(i))-w*Am(i)-mua*Am(i)-u1*Am(i));
    Sm(i+1) = Sm(i)+deltat*(w*Am(i)-(Beta(i)*Bhm*Sm(i)*(Ih(i)/Nh))-mum*Sm(i)-u2*Sm(i));
    Im(i+1) = Im(i)+deltat*((Beta(i)*Bhm*Sm(i)*(Ih(i)/Nh))-mum*Im(i)-u2*Im(i));

    Sh(i+1) = Sh(i)+deltat*(muh*Nh+theta-Beta(i)*Bmh*Sh(i)*(Im(i)/Nh)-u3*Sh(i)-muh*Sh(i));
    Vh(i+1) = Vh(i)+deltat*(u3*Sh(i)-theta*Vh(i)-sigma*Beta(i)*Bmh*(Im(i)/Nh)*Vh(i)-muh*Vh(i));
    Ih(i+1) = Ih(i)+deltat*(Beta(i)*Bmh*Sh(i)*(Im(i)/Nh)+sigma*Beta(i)*Bmh*(Im(i)/Nh)-gamma*Ih(i)-muh*Ih(i));
    Rh(i+1) = Rh(i)+deltat*(gamma*Ih(i)-muh*Rh(i));


end

figure;
plot(tdata,Ih,'k','LineWidth',2.25)
xlabel('Time(weeks)','FontSize',14)
ylabel('Infected human','FontSize',14)
drawnow

%Vh
figure;
plot(tdata,Vh,'k','LineWidth',2.25)
xlabel('Time(weeks)','FontSize',14)
ylabel('Vaccinated human','FontSize',14)


figure;
plot(tdata,Im,'k','LineWidth',2.25)
xlabel('Time(weeks)','FontSize',14)
ylabel('Infected mosquito','FontSize',14)


drawnow
```

Coding for Generating graph for A_m, S_m, I_m, S_h, V_h, I_h, R_h against time, t (week) under the control of u_1, u_2, or u_3

```
clear all
format long
clearvars global

%n-total number of data in EXCEL
%tdata-matrix
%Beta-Beta value read from excel file (is a large size of array)
%x0-initial value of Am,Sm,Im,Sh,Vh,Ih,Rh
%lambdafinal-final value of lambda
%T = 1000;
%N = 100000;
%t = linspace(0,T,N+1);
%hRK4-used in forward and backward RK method

n=155;
tdata=1:1:1*n;
BETA0=xlsread('BetaValue.xlsx','B2:B156');

x0=[1303500;1302661;839;6516661;0;839;0];
lambdafinal =[0;0;0;0;0;0;0];

T = 155;
N = 155;
t = linspace(1,T,N+1);
hRK4 = T/N;


%unit of time : week
%deltat = 1;
phi = (0.7)/(1/7);
w = 0.02/(1/7);
mua = 0.06/(1/7);
gamma = 0.1*7;
Nh = 6517500;
mum = 0.1*7;
muh = 1./(75*52);
k = 3;
sigma = 0.18;
theta = 0.00027/(1/7);
Bmh = 0.95;
Bhm = 0.95;
%u1 = 0.001;
%u2 = 0.001;
%u3 = 0.001;
W1=100;
W2=100;
W3=1000000000; %cost
W4=2500000000; %cost
W5=100000000000; %cost

u1_0 = 0.001;
u2_0 = 0.001;
u3_0 = 0.001;

x = zeros(7,N+1);
u1 = zeros(1,N+1);
u2 = zeros(1,N+1);
u3 = zeros(1,N+1);
lambda = zeros(7,N+1);

x(:,1) = x0;
u1(1) = u1_0;
u2(1) = u2_0;
u3(1) = u3_0;
lambda(:,N+1) = lambdafinal;

z = 1;%counter of the iteration %change from k to z
delta = 0.001; %error bound
test = -1; %error

    oldx = x;
    oldu1 = u1;
    oldu2 = u2;
    oldu3 = u3;  %change to u3
    oldlambda = lambda;

    %forward Runge-Kutta
    for i = 1:N
        if i>155
            B_V=0;
        else
            B_V=BETA0(i);
        end
        u1 = zeros(1,N+1);
        u2 = zeros(1,N+1);
        %u3 = zeros(1,N+1);
        k1(1:7,1) = state(t(i) , x(:,i) , u1(i),u2(i),u3(i),B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
        k2(1:7,1) = state(t(i)+hRK4/2 , x(:,i)+hRK4*k1/2 , (u1(i)+u1(i+1))/2,(u2(i)+u2(i+1))/2,(u3(i)+u3(i+1))/2,B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
        k3(1:7,1) = state(t(i)+hRK4/2 , x(:,i)+hRK4*k2/2 ,(u1(i)+u1(i+1))/2,(u2(i)+u2(i+1))/2, (u3(i)+u3(i+1))/2,B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
        k4(1:7,1) = state(t(i)+hRK4 , x(:,i)+hRK4*k3 ,u1(i+1),u2(i+1), u3(i+1),B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
        x (:,i+1) = x(:,i)+ (hRK4/6)*(k1+2*k2+2*k3+k4);
    end

    %backward Runge-Kutta
    for i = 1:N
        j = N+2-i;
        if i>155
            B_V=0;
        else
            B_V=BETA0(i);
        end
        u1 = zeros(1,N+1);
        u2 = zeros(1,N+1);
        %u3 = zeros(1,N+1);
        k1(1:7,1) = adjoint(t(j) , lambda(:,j) , x(:,j) ,u1(:,j) ,u2(:,j) ,u3(:,j) ,B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
        k2(1:7,1) = adjoint(t(j)-hRK4/2, lambda(:,j)-hRK4*k1/2,(x(:,j)+x(:,j-1))/2,(u1(:,j)+u1(:,j-1))/2,(u2(:,j)+u2(:,j-1))/2,(u3(:,j)+u3(:,j-1))/2,B_V,phi,w,mua,gamma,Nh,mum,muh
        k3(1:7,1) = adjoint(t(j)-hRK4/2, lambda(:,j)-hRK4*k2/2,(x(:,j)+x(:,j-1))/2,(u1(:,j)+u1(:,j-1))/2,(u2(:,j)+u2(:,j-1))/2,(u3(:,j)+u3(:,j-1))/2,B_V,phi,w,mua,gamma,Nh,mum,muh
        k4(1:7,1) = adjoint(t(j)-hRK4/2, lambda(:,j)-hRK4*k3/2,x(:,j-1),u1(:,j-1),u2(:,j-1),u3(:,j-1),B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
```

```
        lambda(:,j-1) = lambda(:,j) -(hRK4/6) *(k1+2*k2+2*k3+k4);
    end

    %Find controls (optimality conditions)
    for i = 1:N+1
        u1(1,i)=(lambda(1,i)*x(1,i))/W3;
        u2(1,i)=(lambda(3,i)*x(3,i)+lambda(2,i)*x(2,i))/W4;
        u3(1,i) = (lambda(4,i)*x(4,i)-lambda(5,i)*x(4,i))/W5;
    end

    %updates control
    c = 0.8;
    u1 = (1-c)*u1 + c*oldu1;
    u2 = (1-c)*u2 + c*oldu2;
    u3 = (1-c)*u3 + c*oldu3;

for i = 1:N
        if i>155
            B_V=0;
        else
            B_V=BETA0(i);
        end
        u1 = zeros(1,N+1);
        u2 = zeros(1,N+1);
        %u3 = zeros(1,N+1);
        k1(1:7,1) = state(t(i) , x(:,i) , u1(i),u2(i) ,u3(i) ,B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
        k2(1:7,1) = state(t(i)+hRK4/2 , x(:,i)+hRK4*k1/2 ,u1(i),u2(i), u3(i),B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
        k3(1:7,1) = state(t(i)+hRK4/2 , x(:,i)+hRK4*k2/2 ,u1(i), u2(i),u3(i),B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
        k4(1:7,1) = state(t(i)+hRK4 , x(:,i)+hRK4*k3 ,u1(i),u2(i), u3(i),B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm);
        x (:,i+1) = x(:,i)+ (hRK4/6)*(k1+2*k2+2*k3+k4);
end

% %Graph
% figure;
% plot(t,x(1,:),'.k','LineWidth',2.25)
% axis([1 155 0 90000000])
% xlabel('Time, t (week)','FontSize',14)
axis([1 155 0 90000000])
xlabel('Time, t (week)','FontSize',14)
ylabel('Aquatic mosquito, Am (capita)','FontSize',14)
xt = get(gca, 'XTick');
set(gca, 'FontSize', 14)

figure;
plot(t,x(2,:),'.k','LineWidth',2.25)
axis([1 155 0 20000000]);
xlabel('Time, t (week)','FontSize',14)
ylabel('Susceptible mosquito, Sm (capita)','FontSize',14)
xt = get(gca, 'XTick');
set(gca, 'FontSize', 14)

figure;
plot(t,x(3,:),'.k','LineWidth',2.25)
axis([1 155 0 1000]);
xlabel('Time, t (week)','FontSize',14)
ylabel('Infected mosquito, Im (capita)','FontSize',14)
xt = get(gca, 'XTick');
set(gca, 'FontSize', 14)

figure;
plot(t,x(4,:),'.k','LineWidth',2.25)
axis([1 155 0 7000000]);
xlabel('Time, t (week)','FontSize',14)
ylabel('Susceptible human, Sh (capita)','FontSize',14)
xt = get(gca, 'XTick');
set(gca, 'FontSize', 14)

figure;
plot(t,x(5,:),'.k','LineWidth',2.25)
axis([1 155 0 20000000]);
xlabel('Time, t (week)','FontSize',14)
ylabel('Vaccinated human, Vh (capita)','FontSize',14)
xt = get(gca, 'XTick');
set(gca, 'FontSize', 14)

figure;
plot(t,x(7,:),'.k','LineWidth',2.25)
axis([1 155 0 10000]);
xlabel('Time, t (week)','FontSize',14)
ylabel('Recovered human, Rh (capita)','FontSize',14)
xt = get(gca, 'XTick');
set(gca, 'FontSize', 14)

%change h to control variable

figure;
plot(t,u1(1,:),'.k','LineWidth',2.25)
axis([1 155 0 0.09]);
xlabel('Time, t (week)','FontSize',14)
ylabel('Control Variable 1, u1 (no unit)','FontSize',14)
xt = get(gca, 'XTick');
set(gca, 'FontSize', 14)

figure;
plot(t,u2(1,:),'.k','LineWidth',2.25)
axis([1 155 0 0.09]);
xlabel('Time, t (week)','FontSize',14)
ylabel('Control Variable 2, u2 (no unit)','FontSize',14)
xt = get(gca, 'XTick');
set(gca, 'FontSize', 14)

figure;
plot(t,u3(1,:),'.k','LineWidth',2.25)
axis([1 155 0 0.02]);
xlabel('Time, t (week)','FontSize',14)
ylabel('Control Variable 3, u3 (no unit)','FontSize',14)
xt = get(gca, 'XTick');
set(gca, 'FontSize', 14)
```

Coding for the State Function

```
%include dengue model here
function dxdt = state(t,x,u1,u2,u3,B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm)

    %dH/dlambda(i) for all 7 lambda (so here we will have total 7 equations
    %remember to change the Am,...,Rh to x(1),...,x(7)

    %change to dxdt = zeros(7,1)
    dxdt = zeros(7,1);

    %dxdt(1) = b*x(1)*((x(2)-pa*x(1))/(ha+x(2)-pa*x(1)))-la*x(1);
    %dxdt(2) = l+r*((x(2)^q)/(x(2)^q+n^q))-lp*x(2)-g*x(3)*pw*(1-(x(3)/K))*(x(2)/(x(2)+hw));
    %dxdt(3) = g*x(3)*(1-(x(3)/K))*(x(2)/(x(2)+hw))-h(1)*x(3);

    dxdt(1)= phi*(1-(x(1)/(k*Nh)))*(x(2)+x(3))-w*x(1)-mua*x(1)-u1*x(1);
    dxdt(2)=w*x(1)-(B_V*Bhm*x(2)*(x(6)/Nh))-mum*x(2)-u2*x(2);%B_V(i)
    dxdt(3)=(B_V*Bhm*x(2)*(x(6)/Nh))-mum*x(3)-u2*x(3);
    dxdt(4)=muh*Nh+theta-B_V*Bmh*x(4)*(x(3)/Nh)-u3*x(4)-muh*x(4);
    dxdt(5)=u3*x(4)-theta*x(5)-sigma*B_V*Bmh*(x(3)/Nh)*x(5)-muh*x(5);
    dxdt(6)=B_V*Bmh*x(4)*(x(3)/Nh)+sigma*B_V*Bmh*(x(3)/Nh)-gamma*x(6)-muh*x(6);
    dxdt(7)=gamma*x(6)-muh*x(7);

end
```

Coding for the Adjoint Function

```
%The adjoint functions
function dlambdadt = adjoint(t,lambda,x,u1,u2,u3,B_V,phi,w,mua,gamma,Nh,mum,muh,k,sigma,theta,Bmh,Bhm)

    %change all Am,Sm,...,Rh to x(1),...,x(7)
    %change 3 to 7 (dlambdadt=zeros(7,1)
    dlambdadt = zeros(7,1);
    W1=1000; %Im
    W2=1000; %Ih
    W3=1000000000; %Larvicide
    W4=2500000000; %Insecticide
    W5=100000000000; %Vaccination
    %dlambdadt(1) = lambda(1)*(la - (b*(x(2) - pa*x(1)))/(ha + x(2) - pa*x(1)) + (b*pa*x(1))/(ha + x(2) - pa*x(1)) - (b*pa*x(1)*(x(2) - pa*x(1)))/(ha + x(2) - pa*x(1))^2) - A;
    %dlambdadt(2) = lambda(2)*(lp - (q*r*x(2)^(q - 1))/(n^q + x(2)^q) - (g*pw*x(3)*(x(3)/K - 1))/(hw + x(2)) + (q*r*x(2)^q*x(2)^(q - 1))/(n^q + x(2)^q)^2 + (g*pw*x(2)*x(3)*(x(3)/K -
    %dlambdadt(3) = lambda(3)*(h(1) + (g*x(2)*(x(3)/K - 1))/(hw + x(2)) + (g*x(2)*x(3))/(K*(hw + x(2)))) - lambda(2)*((g*pw*x(2)*x(3)/K - 1))/(hw + x(2)) + (g*pw*x(2)*x(3))/(K*(hw +

    dlambdadt(1)=-(lambda(1)*(-u1-phi*((x(2)+x(3))/(Nh*k))-w-mua)+lambda(2)*w);
    dlambdadt(2)=-(lambda(2)*((-u2-mum-((B_V*x(6)*Bhm)/Nh)))+lambda(1)*phi*(1-(x(1)/(k*Nh)))+lambda(3)*((B_V*x(6)*Bhm)/Nh));
    dlambdadt(3)=-(lambda(3)*(-u2-mum)+lambda(6)*(((sigma*B_V*Bmh*x(5))/Nh)+((B_V*Bmh*x(4))/Nh))-lambda(5)*((sigma*B_V*Bmh*x(5))/Nh)+lambda(1)*phi*(1-(x(1)/(k*Nh)))-lambda(4)*((B_V*B
    dlambdadt(4)=-(lambda(4)*(-u3-muh-((B_V*Bmh*x(3))/Nh))+(lambda(5)*u3)+lambda(6)*((B_V*Bmh*x(3))/Nh));
    dlambdadt(5)=-(lambda(4)*theta+(lambda(5)*(-theta-(sigma*B_V*Bmh*x(3))/Nh)-muh)+(lambda(6)*((sigma*B_V*Bmh*x(3))/Nh)));
    dlambdadt(6)=-(lambda(6)*(-muh-gamma)+(lambda(7)*(gamma))+(lambda(3)*((B_V*Bhm*x(2))/Nh))-(lambda(2)*((B_V*Bhm*x(2))/Nh))+W2);
    dlambdadt(7)= lambda(7)*muh;

end
```