MATHEMATICAL MODELLING AND OPTIMAL CONTROL OF DENGUE TRANSMISSION WITH SATURATED TREATMENT FUNCTION AND ASYMPTOMATIC IMMIGRATION

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To my family members, lecturers, friends and cats. Thanks for being there.

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ABSTRACT

Dengue fever is a mosquito-borne disease that has been declared as one of the major public health problems in many tropical climate countries. Rising dengue dissemination could be caused by population growth and urbanisation, long-distance travel, lack of sanitation, and ine ective mosquito population control. In light of this issue, this study introduces deterministic models for optimal control problems pertaining to dengue transmission. The rst new model incorporates nonlinear incidence and treatment function since disease occurrences are inherently nonlinear and treatment might be delayed as public health resources are sometimes limited. Although nonlinear incidence functions in dengue transmission models have been proposed in previous studies, the use of both nonlinear incidence and treatment functions are limited. Another model based on a compartment of asymptomatically infected humans with the appearance of constant immigration into the compartment is also introduced. This is in accordance with the fact stated by the World Health Organization, that the majority of dengue disease cases are asymptomatic. Several dengue transmission models with asymptomatic compartment can also be found in the literature, but none have assumed the existence of constant immigration for this compartment model. Subsequently, a threshold governing disease persistence within a population is determined and the existence of endemic equilibrium is identi ed. Then, the analysis of the stability of equilibria and numerical simulations are presented accordingly. Also, the optimal control problems are formulated based on the two new deterministic models in which time-dependent control and prevention measures are used. Then, the optimal control parameters are identi ed, and the corresponding optimality systems are set up. Based on the formed optimality system, numerical simulation is carried out. The results of numerical simulation can be used as a guideline in implementing prevention and control measures for dengue transmission. The results also revealed that self-protection strategy, such as using mosquito repellents and wearing protective clothes, is an important preventive measure in combating dengue transmission.

ABSTRAK

Demam denggi adalah penyakit sebaran nyamuk yang telah diisytiharkan sebagai salah satu masalah kesihatan awam yang utama di banyak negara beriklim tropika. Peningkatan dalam penyebaran denggi boleh disebabkan oleh faktor pertumbuhan penduduk dan urbanisasi, perjalanan jarak jauh, kurang penjagaan sanitasi dan kawalan populasi nyamuk yang tidak berkesan. Disebabkan oleh isu ini, penyelidikan ini memperkenalkan model berketentuan untuk masalah kawalan optimum berkaitan dengan penyebaran denggi. Model baru yang pertama menggunakan fungsi kejadian dan rawatan tak linear berikutan penyebaran penyakit yang tak linear secara semula jadi dan penerimaan rawatan adakalanya lewat akibat kekurangan sumber kesihatan awam. Walaupun fungsi kejadian tak linear dalam model penyebaran denggi telah dicadangkan dalam kajian yang sedia ada, namun penggunaan kedua-dua fungsi kejadian dan rawatan tak linear adalah terhad. Satu lagi model berdasarkan satu kelas populasi manusia yang d angkiti tanpa sebarang gejala, dengan imigrasi secara tetap ke dalam kelas tersebut telah juga telah diperkenalkan. Ini adalah selari dengan fakta daripada Pertubuhan Kesihatan Sedunia, bahawa kebanyakan kes penyakit denggi adalah tidak bergejala. Beberapa model penyebaran denggi dengan kelas pesakit yang tidak bergejala juga boleh didapati dalam kajian sedia ada, namun tiada yang mengandaikan kewujudan imigrasi secara tetap dalam kelas model tersebut. Seterusnya, satu aras yang menjadi tanda kebolehupayaan penyebaran penyakit telah ditentukan dan kewujudan keseimbangan endemik telah dikenal pasti. Kemudian, analisis ke atas kestabilan keseimbangan dan simulasi berangka telah diberikan. Juga, masalah kawalan optimum telah diformulasi berdasarkan dua model berketentuan yang baru tersebut di mana langkah kawalan dan pencegahan yang bergantung-masa telah digunakan. Setelah itu, parameter kawalan optimum dikenal pasti dan sistem optimum berkaitan ditentukan. Berdasarkan sistem optimum yang telah dibentuk, simulasi berangka telah d alankan. Keputusan daripada simulasi berangka boleh d adikan sebagai panduan dalam menjalankan langkah kawalan dan pencegahan dalam penyebaran demam denggi. Keputusan juga menunjukkan bahawa langkah perlindungan-kendiri, seperti penggunaan ubat penghalau nyamuk dan pakaian pelindung, adalah sangat penting dalam membanteras penyebaran demam denggi.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ADE	-	Antibody-Dependent Enhancement
DDT	-	Dichlorodiphenyltrichloroethane
DENV	-	Dengue Virus
DF	-	Dengue Fever
DFE	-	Disease-free Equilibrium
DSS	-	Dengue Shock Syndrome
DHF	-	Dengue Hemorrhagic Fever
EE	-	Endemic Equilibrium
FBSM	-	Forward-backward Sweep Method
IV	-	Intravenous
LHS	-	Latin Hypercube Sampling
ORS	-	Outdoor Residual Spraying
PRCC	-	Partial Rank Correlation Coe cient
SEI	-	Susceptible Exposed Infected
SEIR	-	Susceptible Exposed Infected Recovered
SEIR-SEI	-	Susceptible Exposed Infected Recovered - Susceptible Exposed Infected
SIQR	-	Susceptible Infected Quarantined Recovered
SIQS	-	Susceptible Infected Quarantined Susceptible
SIR	-	Susceptible Infected Recovered
SIR-SI	-	Susceptible Infected Recovered - Susceptible Infected
SIS	-	Susceptible Infected Susceptible
$S_hI_hR_h - S_vI_v$	-	Susceptible human Infected human Recovered human - Susceptible mosquito Infected mosquito
WHO	-	World Health Organization

LIST OF SYMBOLS

$u(a)$	-	Number of "susceptible" people who are still alive at age a without having been infected with smallpox.
$w(a)$	-	Number of people who are alive at age a and survived from smallpox.
λ	-	Rate of which susceptible is infected.
β	-	Disease transmission coe cient.
γ	-	Recovery or death rate of infective class.
$\mathcal{R}_0$	-	Basic reproduction number.
c	-	A constant of saturated treatment function.
α	-	A positive constant of saturated incidence function.
E_0	-	Disease-free equilibrium.
E_1	-	Endemic equilibrium.
χ_h	-	Human birth rate.
χ_v	-	Mosquito birth rate.
ι_h	-	Birth and death rate of human.
ι_v	-	Birth and death rate of vector.
A	-	Constant ow of new members into the population in unit time of which a fraction p is infective.
μ	-	Natural death rate constant.
$\mathbf{U}$	-	Control set.
γ_r	-	Recovery rate of infective population.
γ_d	-	Death rate of infective population.
$J[u]$	-	Cost functional or performance criterion.
$h(I)$	-	Treatment function.
$S_h(t)$	-	Susceptible human at time t.
$A_h(t)$	-	Asymptomatically infected human at time t.
$I_h(t)$	-	Symptomatically infected human at time t.
$R_h(t)$	-	Recovered human at time t.
$N_h(t)$	-	Total human population at time t.
$S_v(t)$	-	Susceptible mosquito at time t.

$I_v(t)$	-	Infected mosquito at time t.
$N_v(t)$	-	Total mosquito population at time t.
$I_h'(t)$	-	Derivative of $I_h(t)$.
$I_v'(t)$	-	Derivative of $I_v(t)$.
$N_h'(t)$	-	Derivative of $N_h(t)$.
$N_v'(t)$	-	Derivative of $N_v(t)$.
$u_1(t)$	-	Personal protection or self-prevention by human at time t.
$u_2(t)$	-	Supportive treatment of symptomatic patients at time t.
$u_3(t)$	-	Intervention used for vector control at time t.
$u_4(t)$	-	Screening of immigrant at time t.
$\lambda_h(t), \lambda_v(t)$	-	Incidence function.
$h(I_h)$	-	Treatment function for population of infected human.
Λ_h	-	Recruitment rate of human population.
b	-	Mosquito biting rate.
β_v	-	Transmission probability from infectious mosquito to susceptible human.
α_h	-	Saturation constant which determine the level at which the force of infection saturates.
μ_h	-	Natural death rate of human.
r	-	Recovery rate of infected human.
γ_m	-	Maximal medical resources supplied per unit time.
α_r	-	Delayed constant of treatment.
Λ_v	-	Recruitment rate of mosquito population.
β_h	-	Transmission probabilty from infectious human to susceptible mosquito.
α_v	-	Saturation constant which determine the level at which the force of infection saturates.
μ_v	-	Mortality rate of mosquito.
ϕ	-	Fraction of immigrants that are asymptomatically infected with DENV.
r_1	-	Recovery rate of asymptomatically infected human.
r_2	-	Recovery rate of symptomatically infected human.
η	-	Modi cation parameter.
$\nu(t)$	-	Integrating factor.

H	-	Hamiltonian function.
$\bar{Y}$	-	Vector of state variables.
$\mathbf{U}$	-	Vector of control variables.
$\boldsymbol{\lambda}$	-	Vector of adjoint variables.
m_i	-	Upper bound for control variables.
T_f	-	Final time.

LIST OF APPENDICES

CHAPTER 1

INTRODUCTION

1.1 Motivation

Pathogenic microorganisms such as bacteria, viruses, parasites or fungi are the common causes of infectious diseases. Some common infectious diseases include HIV and AIDS, measles, ebola virus disease (EVD), tuberculosis, malaria and dengue fever. These diseases can be transmitted from one person to another, either directly or indirectly. By direct transmission, disease can be passed on from one person to another by direct physical contact with blood or body fluids. On the other hand, airborne transmission, contaminated food and water, and animal-to-person contact are some of the mechanisms for indirect transmission of infectious diseases.

Dengue fever is a type of infectious disease that is indirectly transmitted from one host to another where mosquitoes act as the mechanism transmitting the virus. Virus transmission from infected human occurs through the bite of a female mosquito of *Aedes aegypti*, which then may be transmitted to another healthy individual through an effective bite. As far as dengue is concerned, Malaysia is listed as one of the countries located within dengue endemic regions (Shepard *et al.*, 2013; Pang and Loh, 2016). Due to this, prevention and eradication of dengue transmission is always a priority and is becoming a major public health problem.

In the case of an outbreak of infectious disease, health authorities, other than the individual itself, are amongst the people in the community who are affected the most. These authorities need to evaluate appropriate treatment and prevention programmes and, at the same time, need to consider the incurring cost. This is so that affected individuals can receive appropriate treatment and prevention measures without further infecting other susceptible individuals, and eventually disease can efficiently be eradicated.

Cost is one of the main factors that is usually considered in implementing a prevention and control strategy for infectious diseases. Prevention measures might include treatment, vaccination (if any, for a speci c disease), quarantine, and others. In some cases, resources needed to implement prevention measures might be scarce and eventually lead to a higher incurred cost. Moreover, as in the case of infectious diseases in animals and plants, the prevention measures usually involve culling of the a ected population. Nonetheless, it is not always practical to remove all of them.

Therefore, consideration of cost and other decisive factors in disease control, such as the optimal use of limited resources for treatment and prevention, has become one of the motivations for the study of mathematical modelling of infectious disease. It has been acknowledged that the study of mathematical modelling of infectious disease assists in the attempts to describe and analyse the behaviour of disease spread through a population in order to make predictions, to evaluate control programs, and to suggest prevention strategies (Hethcote, 2000; Zaman et al., 2008; Huang and Li, 2009; Kar and Batabyal, 2011). With regard to this matter, deterministic models consisting of systems of ordinary di erential equations and optimal control problems pertaining to dengue transmission will be formulated in this study.

1.2 Background of the Study

"Vector-borne diseases" is a general term that is used to describe the types of infectious diseases which are transmitted by organisms that carry infectious pathogens from one host to another. These organisms can be mosquitoes, sand ies, ticks, snails and others. Malaria, West Nile virus, yellow fever, dengue fever, Zika and Chikungunya viruses are the types of diseases that are caused by vector transmission. According to WHO, dengue fever and severe dengue haemorrhagic fever (DHF) are the world's fastest growing vector-borne diseases (WHO, 2009). A majority of dengue cases are asymptomatic, which leads to an underreported and misclassi ed dengue incidence.

Dengue fever is a type of vector-borne disease that is transmitted by female mosquitoes, mainly the *Aedes aegypti* mosquito, and in some occasional occurrences, may also be transmitted by *Aedes albopictus*. Mammals' blood is needed in the maturity of the mosquitoes' eggs and therefore only the female bites for blood, which eventually be the ones that transmit the disease (Nevai and Soewono, 2014). It is reported by the WHO that approximately 3.9 billion people in 128 countries are at risk of dengue virus infection (WHO, 2019). More than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Paci c have been declared as endemic regions for dengue by WHO. Amongst these, the Americas, South-East Asia and Western Paci c regions are the most greatly a ected.

People infected with dengue virus experience symptom of u-like illness and some of the common symptoms include sudden high fever, severe headaches, joint and muscle pain and skin rash which may appear two to ve days after the onset of fever.For a more serious case, known as dengue hemorrhagic fever (DHF), it may cause lymph and blood vessel damage, nose and gum bleeding, liver enlargement and circulatory system failure. It can also progress to a stage of dengue shock syndrome (DSS) where it causes massive bleeding, shock and fatality.

Dengue virus (DENV) can be classi ed into four distinct serotypes (also known as strains), DENV-1, DENV-2, DENV-3 and DENV-4, which belong to the genus of Flavivirus, a family of Flaviviridae (WHO, 2009). Recovery from infection by one type provides lifelong immunity against that serotype but confers only partial and temporary protection against subsequent infection by the other three (Rodenhuis-Zybert *et al.*, 2010). Moreover, studies have shown that secondary infection increases the risk of more serious disease, resulting in dengue hemorrhagic fever (DHF). Therefore, it should be noted that complex antibody-mediated occurrences, such as cross-protection and infection enhancement, can be generated from the co-circulation of the four di erent dengue viruses (Halstead, 2007).

Once a mosquito acquires the virus from an infected human, it will go through an extrinsic incubation period ranging from 8 to 12 days (Rodenhuis-Zybert *et al.*, 2010). The extrinsic incubation period is de ned as the time required for the mosquito to become infective (Pooja *et al.*, 2014). Humans also undergo an incubation period once the virus is transmitted to them, which ranges from 3 to 15 days (usually 5 to

8 days), and will afterwards experience symptoms of the fever (Henchal and Putnak, 1990).

It is mentioned by WHO that a vast majority of dengue incidences are asymptomatic (also known as inapparent, subclinical), which implies a situation where a person is infected with dengue virus but exhibits inapparent symptoms. The prevalence of asymptomatic infection has been reported in several studies including, M ndez *et al.* (2006); Yoon *et al.* (2012); Gordon *et al.* (2013); Wang *et al.* (2015); Ra que *et al.* (2017); Castro-Bonilla *et al.* (2018). Cases of asymptomatic dengue infection have also been detected in blood donors (Stramer *et al.*, 2012; Harif *et al.*, 2014; Slavov *et al.*, 2019).

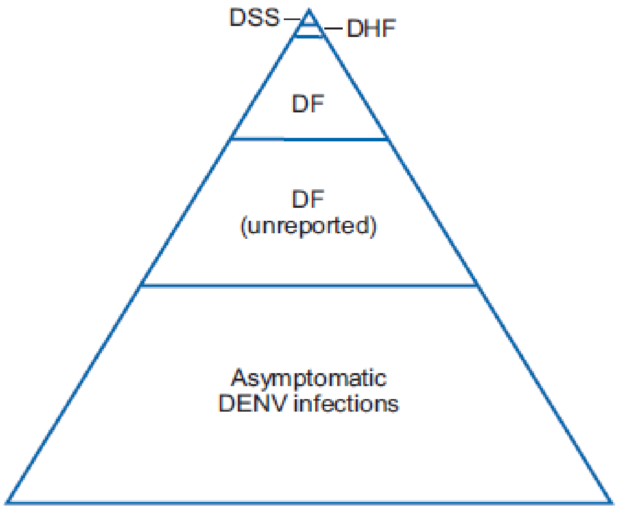

Figure 1.1 Representation of clinical manifestation of DENV infection in a pyramid form. Source: Kyle and Harris (2008).

Figure 1.1 is extracted from Kyle and Harris (2008) where it classi es the prevalence of dengue cases according to clinical manifestation. This is in line with the fact published by WHO that a vast majority of dengue incidences are asymptomatic, also known as inapparent or subclinical (WHO, 2019). It is also indicated by Chastel (2012) that a proportion of asymptomatic cases may pass the dengue virus to competent mosquitoes if it reaches a su cient viraemia level. Moreover, it is stated in the study by Duong *et al.* (2015) that dengue virus can be transmitted to mosquitoes by people with natural DENV infections but exhibit no clinical symptoms. It is also mentioned that asymptomatic and presymptomatic infections may result in an increment of transmission potential. From these findings, it can be seen that asymptomatic infection may contribute to a major part of the worldwide dengue burden.

Even though mosquitoes are the medium that is responsible for transmitting dengue virus from one human to another, humans might be a major contributing factor in the worldwide dissemination of the disease. Rather than mosquitoes, humans, acting as the host of dengue virus, rapidly move the virus within and between communities. New vectors and pathogens are constantly introduced into novel geographic areas by human migration and international trade and travel (Grange *et al.*, 2014). Furthermore, studies found that mosquitoes, in this case, *Aedes aegypti*, have a limited flying range, which further strengthened the fact that humans may be the major contributing factor in the spread of the virus (Maidana and Yang, 2008; Stoddard *et al.*, 2013).

In consideration of this particular issue, infected human, especially the one who has inapparent symptoms (asymptomatic or presymptomatic), may travel to a non-endemic region and eventually results in the spread of the disease. Returned travellers from dengue endemic regions may also be the cause of dengue virus transmission in their country of origin. It has been reported by Punzel *et al.* (2014) that dengue virus has been detected in a blood stem cell donor who recently travelled to Sri Lanka. The reported case happened in Germany, and the transmission of dengue virus to the recipient of the blood stem cells is confirmed. As mentioned in Ratnam *et al.* (2013), the incidence rate of dengue infection in short-term travellers to dengue-endemic countries is of considerable importance. The prevalence of dengue infection amongst returned travellers has also been reported in Olivero *et al.* (2016). Therefore, this thesis is going to investigate the effect of asymptomatically infected immigrants on the dynamic of dengue virus transmission.

There is no specific antiviral treatment available for dengue infection. People are usually advised to take acetaminophen (also known as paracetamol) and to drink plenty of fluids if they develop symptoms of dengue fever. In the case of severe dengue fever, hospitalisation may be needed. People with severe dengue fever will usually be treated by intravenous (IV) uid and electrolyte replacement, blood pressure monitoring and transfusion to replace blood loss. As for prevention, one way is to isolate dengue patients so that the virus cannot be transmitted to mosquitoes. Personal protection and environmental management are some of the other methods that can be implemented to prevent dengue infection. In account of personal protection, people can wear repellent and suitable clothing to avoid mosquito bites. As for environmental management, possible breeding areas for mosquitoes need to be properly eliminated and disposed of. Also, dengue transmission is usually being controlled by health authorities using mosquito fogging and another more recent technique called outdoor residual spraying (ORS).

From a mathematical modelling point of view, dengue transmission is often formulated as an interaction between the a ected population, particularly between human and mosquito. The population for each of them is then categorized into several distinct classes, also known as compartments, with each of them portraying human and mosquito disease status. The most common classes that are frequently used are susceptible (S), infected and infectious (I), and recovered or removed (R). Based on a review of the literature, some authors, such as Esteva and Vargas (1998), developed dengue transmission model in the form of SIR-SI (for human and mosquito respectively), while others, such as Garba *et al.* (2008), developed the transmission model as $SEIR$-SEI, where E represents the compartment of exposed human and mosquito. Several other formulations have also been established and will be further discussed in Chapter 2.

One of the important concerns that should be considered in formulating a mathematical model of infectious disease is the incidence rate. The occurrence of new cases of disease within a population over a particular time period is referred to as incidence. In other words, it is a rate that implicates susceptible becoming infectious (Esteva and Matias, 2001; Ujjainkar *et al.*, 2012). It should be noted that bilinear and standard incidence rates are frequently used in modelling the dynamics of dengue transmission (Esteva and Vargas, 1998; Pongsumpun and Tang, 2003; Derouich and Boutayeb, 2006; Garba *et al.*, 2008; Tewa *et al.*, 2009; Syafruddin and Noorani, 2013;

Sardar *et al.*, 2015; Agusto and Khan, 2018). Nevertheless, due to the fact that susceptible individuals may be taking preventive measures or due to crowding of infective individuals at high infectious levels, the rate of effective contact between infective and susceptible individuals may saturate (Ruan and Wang, 2003). Therefore, Capasso and Serio (1978) introduced a saturated incidence rate to address the phenomena of saturation which may arise at large numbers of infectives. With regard to this matter, Cai *et al.* (2009) used the combination of saturating and bilinear incidence rate to investigate the dynamics of dengue transmission. However, it is necessary to extend this model by integrating saturated incidence rate to both human and mosquito population.

Constant sufficiency of medical resources for disease treatment is another assumption that is usually made in epidemiology modelling (Zhou and Fan, 2012). In the language of mathematical modelling, removal or recovery rate of infectives is frequently assumed to be in proportion to the number of infectives (Wang and Ruan, 2004). However, this is not always true in reality as each community may have limited capacity of medical resources (Eckalbar and Eckalbar, 2011). Therefore, it is also necessary to employ saturated treatment function as it can describe the effect of delayed treatment to infected individuals (Zhang and Lu, 2008). The issue of asymptomatic dengue infection has been addressed using mathematical model in studies by Pongsumpun and Samana (2006); Sriprom *et al.* (2007); Pongsumpun (2009); Vargas (2009); Anggriani *et al.* (2013) and Jan *et al.* (2020). Nevertheless, it is necessary to extend these studies as the usage of saturated incidence rate was not considered by these authors.

Optimal control theory deals with the notion of determining a law of control for a dynamical system over a period of time in a way that an objective function is optimized. It is frequently being used in mathematical models of infectious disease as an approach to determine the optimal strategies in controlling disease transmission. Amongst the earliest studies on the application of optimal control theory in the field of infectious disease model are done by Gupta and Rink (1973) and Sethi and Staats (1978). As far as dengue is concerned, several authors including Caetano and Yoneyama (2001); Thomé *et al.* (2010); Aldila *et al.* (2013); Rodrigues *et al.* (2014); Agusto and Khan

(2018); Zheng and Nie (2018) and Jan and Xiao (2019) have applied the theory of optimal control to dengue transmission model. Although the works by these authors have considered the use of optimal control theory in dengue transmission models, the utilization of saturated incidence rate and saturated treatment function have not been taken into account which then motivate the studies done in this thesis.

1.3 Statement of the Problem

The occurrence of saturation phenomena which may arise at a high number of infectives has led to the establishment of a saturated incidence rate proposed by Capasso and Serio (1978). Another concern which often occurs in the event of epidemic outbreak is de ciency of treatment resources. The implication of health authorities having limited medical resources, particularly at a non-endemic region, need to be evaluated. To address this situation, Zhang and Lu (2008) has proposed a type of saturated treatment function which characterizes a situation of treatment delay. Though there are numerous published works regarding dengue transmission model, only a part of these studies have utilized this type of saturated incidence rate (Cai *et al.*, 2009; Ozair *et al.*, 2012), nonlinear recovery rate (Abdelrazec *et al.*, 2016) and piecewise linear treatment function (Nugraha *et al.*, 2019). Motivated by these factors, a formulation of a dengue transmission model with saturated incidence and saturated treatment function, which is an extension and modi cation to the model by Cai *et al.* (2009), will be presented in this study. With this formulation, theoretical analysis, including investigation on local and global stability of disease-free and endemic equilibrium will be presented.

The issue of clinically inapparent dengue infection or asymptomatic infection has been a major worldwide burden. Though asymptomatically infected human exhibit clinically inapparent symptoms, a high viraemia level in their body may cause dengue virus to be transmitted to mosquito (Duong *et al.*, 2015). Therefore, another issue that will be addressed in this thesis is the existence of asymptomatically infected immigrants. This will be integrated into the model through the inclusion of asymptomatically infected class.

Furthermore, considering the fact that curtailing dengue transmission highly depends on prevention, supportive treatment and mosquito control, optimal control problems should be formulated so that an optimal trajectories of control and prevention measures with corresponding implication on the dynamic of human and mosquito population within a speci c time period can be determined.

1.4 Objectives of the Study

The aim of this study is to develop deterministic models implying dynamics of dengue transmission and identifying optimal prevention, treatment and control strategies through the application of optimal control theory. The main objectives are as listed below.

1. To develop a deterministic model for dengue transmission with saturated incidence and saturated treatment function.
2. To develop a deterministic model for dengue transmission with saturated incidence and inclusion of asymptomatically infected class with constant immigration.
3. To formulate optimal control problems for models in Objective 1 and 2 respectively by introducing time dependent prevention, treatment and control strategies.

1.5 Scope of the Study

Mathematical models in this study are formulated based on the notion of deterministic compartmental model. A deterministic model implies that the predictions of these models are entirely determined by the initial conditions, input parameter values and the underlying set of equations. The formulated deterministic compartmental models are made up of ordinary di erential equations system. These models focus on the interaction between human and mosquito population in a way that the dynamic of dengue transmission can be investigated and explored.

For the rst deterministic model, human population is categorized into compartments of susceptible, infective and recovered while mosquito population consists of susceptible and infected compartment. A nonlinear incidence and treatment function of saturating form will be integrated into this model. A saturated incidence rate imitates a situation where preventive measures are taken by susceptible individuals or crowding of infectives which may happen at high number of infections. On the other hand, a saturated treatment function mimics a situation of treatment delay or limited public health resources.

In view of the second deterministic model, human population is classi ed into four compartments which are susceptible, asymptomatic and symptomatic infective and recovered. Whereas, mosquito population is categorized into compartments of susceptible and infected. A fraction of immigrants is assumed to be asymptomatically infected. A nonlinear incidence rate of saturating form is integrated into this model which signi es a crowding e ect of the infective individuals.

Computing an exact solution of models involving a high degree of nonlinearity is commonly analytically intractable. Instead of determining a general solution, which is often di cult to accomplish, stability analysis is conducted as a way to get a sense of solution behaviour. Particularly, long term behaviour of the underlying dynamical system can be predicted from the results of stability analysis. With regards to this, analysis of local and global stability of equilibrium points are often investigated in literatures.

Therefore, for the given underlying dynamical system of Model 1 and Model 2 which will later be formulated in Chapter 3 and 4 respectively, qualitative analysis which includes nding the existence and stability of equilibria will be carried out. The existence of two types of equilibria, named as disease-free and endemic for each model will be investigated. Several established methods will be used to perform the analysis of stability and also bifurcation including the theory of centre manifold (Castillo-Chavez and Song, 2004) and geometric approach (Li and Muldowney, 1996). Computation of a threshold parameter which rules the spread of disease will be demonstrated. This threshold parameter, known as the basic reproduction number, denoted as $\mathcal{R}_0$ will be computed based on the approach of next generation operator (Van den Driessche and Watmough, 2002) and done with the help of MAPLE software.

In the second part of this study, optimal control theory will be applied to both rst and second models to formulate optimal control problems. Time dependent prevention and control strategies, which include personal protection, supportive treatment for symptomatic patients, mosquito control and immigrant screening in eradicating the spread of infectious disease are incorporated into the respective models. Necessary conditions for the optimal control problems which are part of the qualitative analysis of optimal control problems will be identi ed. Also, respective optimality systems which consist of ordinary di erential equations from the state and adjoint equations are determined through the use of Pontryagin's maximum principle.

For the purpose of numerical simulation, value of parameters and initial conditions are extracted from related literatures and some are being assumed. This is due to limitations in securing actual data for the related parameters. In the rst part of this study, numerical simulations are executed in MATLAB by utilizing a built-in function known as `ode45` where it employs a type of Runge-Kutta method. For the second part, numerical results for optimal control problems are solved using an indirect approach known as forward-backward sweep method (FBSM).

1.6 Thesis Organization

This thesis is made up of six di erent parts with three parts of them presenting the original contribution of this study. The rst part, which is as presented in this chapter, introduced motivation, a brief background, objectives, research problems and scope related to this study.

The second part concerns the review of literatures which will be presented in Chapter 2. In this chapter, discussion on a brief history of the mathematical model of infectious diseases is presented. Subsequently, topics on current progression in mathematical models and optimal control of infectious disease particularly on vector-borne disease and dengue transmission are reviewed.

The third and the fourth part, which will be presented in Chapter 3 and Chapter 4 respectively, concern the formulation of dengue transmission models. The rst model describes dengue transmission dynamics using nonlinear incidence and treatment function. Meanwhile, the second model introduces a class of asymptomatically infected human with constant immigration. Respectively, for each of this model, a threshold governing disease persistence is determined. Then, the existence of equilibria is identi ed and eventually stability analysis of equilibria and numerical simulation are presented.

The fth part, as will be presented in Chapter 5, concerns the formulation of optimal control problems based on the proposed model presented in Chapter 3 and Chapter 4 respectively. Time-dependent prevention, treatment and control measures are incorporated into respective models. Then, investigation on the existence of optimal control is presented and an optimality systems for each of the problem is established. Thereafter, numerical simulation is executed to study the e ect of di erent possible combinations of prevention and control measures.

This study concludes in the sixth part which will be presented in Chapter 6. In this chapter, discussion on research summary, contributions and some possible direction of future works are provided.

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LIST OF PUBLICATIONS

Indexed Journal (SCOPUS)

1. Nordin, N. A., Ahmad, R., & Ahmad, R. (2015). Optimal control of vector-borne disease with direct transmission. *Jurnal Teknologi*, 76(13), 53-60. doi:10.11113/jt.v76.5822

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1. Nurul Aida Nordin, Rohanin Ahmad and Rashidah Ahmad, Optimal Control of Vector-borne Disease with Direct Transmission. *Proceeding of 3rd International Science Postgraduate Conference 2015(ISPC2015)*, Faculty of Science, Universiti Teknologi Malaysia, Johor, Malaysia. 24 25 February 2015.