MODIFIED DETERMINISTIC MODELS FOR DENGUE DISEASE TRANSMISSION AND OPTIMAL CONTROL IN MALAYSIA REGIONS

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To Aminat, Hibatullah and AbdHameed.

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ABSTRACT

Dengue is an acute viral illness caused by RNA virus of the family *Flaviviridae* and spread by *Aedes* mosquitoes. It has imposed significant social, economic and medical burdens which have led to loss of lives in dengue-endemic areas. In order to understand its mode of transmission, dynamics and assess optimal strategies for controlling the disease spread, several researchers have proposed different compartmental deterministic models (single-patch, multi-strain and multi-patch models). However, these models have the shortcomings of either not covering all dengue transmission phases or feature the aquatic stage mosquito. Thus, the existing model is not suitable as model frameworks in assessing different control intervention strategies to effectively control the disease transmission in a homogeneous environment, with coexistence of multiple Dengue Virus (DENV) serotypes in a community, and in a patchy environment. Therefore, the deterministic models that can explain the mechanisms involved in these aspects of dengue transmission and optimal control are needed. This research proposes and analysed single-patch deterministic model featuring all the necessary transmission phases of dengue fever in human, and both the aquatic and adult mosquitoes. This is to facilitate the understanding of the real nature of the dengue spread in a homogeneous environment and reliably use optimal personal protection (u_P), larvicide (u_L) and adulticide (u_A) for its effective control by formulating different optimal control frameworks. By modifying the proposed single-patch model, a two-strain model which groups the four DENV serotypes into two (DENV-1 and DENV-j, $j = 2, 3, 4$) is developed to analyse the transmission dynamics and optimal strategy for the dengue control using Dengvaxia vaccine (u_V) combined with the efforts of controls u_P and u_A. A two-patch model is formulated using the single-patch model to analyse the effect of human travels on the spatial spread and optimal control of dengue using u_P, u_L and u_A controls in two connected patches. Qualitative analysis of the basic properties of the three models is performed. Meanwhile, the associated optimal control problems are analysed using Pontryagin's Maximum Principle. Data from the 2012 dengue outbreaks in Johor and Kuala Lumpur, Malaysia is used in these models. The simulated results of the single-patch model indicate that dengue outbreak can be controlled using a combination strategy of optimal controls u_P, u_L and u_A in Johor and Kuala Lumpur. The results obtained from numerical simulations of the two-strain model reveal that the use of combined efforts of optimal controls u_V, u_P and u_A adequately decreases both the primary and secondary human infections in the population. Numerical results of two-patch model show that the spatial spread of dengue in Johor and Kuala Lumpur can be minimised by implementing optimal controls u_P, u_L and u_A simultaneously during an outbreak in the states.

ABSTRAK

Denggi adalah penyakit virus akut yang disebabkan oleh virus RNA dari famili *Flaviviridae* dan disebarkan oleh nyamuk *Aedes*. Ini telah memberi kesan yang besar terhadap sosial, ekonomi dan beban perubatan yang menyebabkan kehilangan nyawa di kawasan endemik denggi. Untuk memahami cara penyebaran, dinamik dan strategi optimum untuk kawalan penyebaran denggi, beberapa penyelidik telah mencadangkan model penentuan pembahagian yang berbeza (tampalan tunggal, pelbagai regangan dan pelbagai tampalan). Walau bagaimanapun, model ini mempunyai kekurangan sama ada ia tidak merangkumi semua fasa penularan denggi atau tidak mengambil kira nyamuk di peringkat akuatik. Oleh itu, model sedia ada adalah tidak sesuai sebagai kerangka model dalam menilai pelbagai strategi intervensi kawalan penularan denggi secara efektif dalam lingkungan yang homogen, dengan wujudnya serotip pelbagai Virus Denggi (DENV) dalam sebuah komuniti, dan dalam lingkungan yang tidak rata. Oleh itu, model deterministik yang mampu menerangkan mekanisme yang terlibat dalam aspek penularan denggi dan kawalan optimum adalah diperlukan. Kajian ini mencadangkan dan menganalisis model deterministik tampalan tunggal yang menampilkan semua fasa penularan demam denggi kepada manusia, dan kedua-dua nyamuk akuatik dan nyamuk dewasa. Ini bertujuan untuk memudahkan pemahaman mengenai sifat penyebaran denggi di persekitaran yang homogen dan penggunaan perlindungan peribadi yang optimum (u_P), larvisida (u_L), dan pembunuhan nyamuk dewasa (u_A) sebagai kawalan efektif dengan merumuskan pelbagai kerangka kawalan optimum. Dengan mengubahsuai model tampalan tunggal yang dicadangkan, model dua regangan yang mengelompokkan empat serotaip DENV kepada dua (DENV-1 dan DENV-j, $j = 2, 3, 4$) telah dibangunkan untuk menganalisis dinamik penyebaran dan strategi optimal bagi mengawal denggi menggunakan vaksin Dengvaxia (u_V) yang digabungkan dengan usaha kawalan u_P dan u_A. Model dua tampalan dirumuskan menggunakan model tampalan tunggal bagi menganalisis kesan pergerakan manusia terhadap penyebaran ruang dan kawalan optimal denggi menggunakan kawalan u_P, u_L dan u_A dalam dua tampalan yang berhubung. Analisis kualitatif terhadap sifat asas ketiga-tiga model telah dijalankan. Manakala masalah kawalan optimal yang berkaitan pula dianalisis menggunakan Prinsip Maksimum Pontryagin. Data wabak denggi pada tahun 2012 di Johor dan Kuala Lumpur, Malaysia digunakan dalam model-model ini. Hasil simulasi model tampalan tunggal menunjukkan bahawa wabak denggi dapat dikawal dengan menggunakan strategi kombinasi kawalan optimum u_P, u_L dan u_A di Johor dan Kuala Lumpur. Hasil yang diperolehi daripada simulasi berangka model dua regangan pula menunjukkan bahawa penggunaan gabungan usaha kawalan optimum u_V, u_P dan u_A dapat mengurangkan jangkitan manusia primer dan sekunder pada populasi. Keputusan berangka model dua tampalan menunjukkan bahawa penyebaran denggi di Johor dan Kuala Lumpur dapat diminimumkan dengan melaksanakan kawalan optimum u_P, u_L dan u_A secara serentak semasa wabak di negeri terbabit.

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ADE	-	Antibody-Dependent Enhancement
AMPL	-	A Mathematical Programming Language
BC	-	Boundary Condition
BE	-	Boundary Equilibrium
BRDFE	-	Biologically Realistic Disease-Free Equilibrium
Bti	-	*Bacillus thuringiensis israelensis*
CF	-	Cost Functional
COMBI	-	Communication for Behavioural Impact
DENV	-	Dengue Virus
DF	-	Dengue Fever
DFE	-	Disease-Free Equilibrium
DHF	-	Dengue Hemorrhagic Fever
DOTcvp	-	Dynamic Optimisation Toolbox with control vector parameterisation
DSS	-	Dengue Shock Syndrome
DYNOPT	-	Dynamic Optimisation Toolbox
E	-	Exposed/latent
EE	-	Endemic Equilibrium
FBSM	-	Forward-Backward-Sweep Method
GAS	-	Globally Asymptotically Stable
I	-	Infectious
IC	-	Initial Condition
IPOPT	-	Interior Point OPTimizer
KNITRO	-	Nonlinear Interior Point Trust Region Optimisation
LAS	-	Locally Asymptotically Stable
M	-	Immune humans

MOH	-	Ministry of Health
NGM	-	Next Generation Matrix
OCP	-	Optimal Control Problem
OCT	-	Optimal Control Theory
ODE	-	Ordinary Differential Equation
PMP	-	Pontryagin's Maximum Principle
R	-	Recovered
S	-	Susceptible
SNOPT	-	Sparse Nonlinear OPTimiser
SPDDM	-	Single-Patch Deterministic Dengue Model
TE	-	Trivial Equilibrium
TPDDM	-	Two-Patch Deterministic Dengue Model
TSDDM	-	Two-Strain Deterministic Dengue Model
RK-4	-	Fourth-Order Runge-Kutta
WHO	-	World Health Organisation
ULV	-	Ultra-Low Volume
USD	-	United States Dollar

LIST OF SYMBOLS

α	-	Saturation rate
$\bar{\alpha}$	-	Constant parameter
$\bar{\beta}$	-	Constant parameter
μ_{ai}	-	Natural mortality rate of larva in patch i
μ_{bi}	-	Per capita oviposition rate of mosquito in patch i
μ_h	-	Human natural birth and death rate
μ_{hi}	-	Birth and death rate of humans in patch i
η_{hi}	-	Incubation rate of human in patch i
μ_v	-	Mosquito mortality rate
μ_{vi}	-	Natural mortality rate of mosquito in patch i
μ_{vj}	-	Mortality rate of mosquito in Patch j
ξ_h	-	Human recovery rate
$\vec{\lambda}$	-	Adjoint vector
$\vec{x}$	-	State vector
$\vec{u}$	-	Control vector
$\mathcal{U}$	-	Control set
$\vec{u}_{\text{old}}$	-	Immediate preceding iterate of control vector
β_h	-	Rate of effective contacts between the infectious and susceptible humans
λ_v	-	Force of infection of mosquitoes
σ_1	-	Susceptibility index for secondary infection with virus serotype 1
σ_j	-	Susceptibility index for secondary infection with virus serotype j, $j \in \{2, 3, 4\}$
t	-	Time
t_0	-	Initial time

t_f	-	Final time
t_*	-	Least upper bound of the time interval $[0, t]$
ϵ_t	-	Tolerance
J	-	Jacobian matrix
μ_a	-	Natural mortality rate of larvae
μ_b	-	Mosquito oviposition rate
μ_{dhf}	-	Dengue disease-induced death rate
η_a	-	Maturity rate of larvae
η_{ai}	-	Development rate of larva to female mosquito in patch i
η_h	-	Intrinsic incubation period
η_{h_1}	-	Incubation period of virus serotype 1 in humans
η_{h_j}	-	Incubation period of virus serotype j in humans
η_v	-	Extrinsic incubation period
η_{v_1}	-	Incubation period of virus serotype 1 in mosquitoes
η_{vi}	-	Incubation rate of mosquito in patch i
η_{v_j}	-	Incubation period of virus serotype j in mosquitoes
η_{vj}	-	Mosquito incubation period in patch j
ξ_h	-	Human recovery rate
ξ_{h_1}	-	Period of infection with virus serotype 1 in human
ξ_{hi}	-	Recovery rate of human in Patch i
ξ_{h_j}	-	Period of infection with virus serotype j in human
Θ	-	Vector of parameters
$\mathcal{H}$	-	Hamiltonian
$\lambda(t)$	-	Adjoint or costate variable
ϕ_{ij}	-	Human travel/movement rate from patch j to patch i
$\bar{\phi}_{ij}$	-	Mosquito travel/movement rate from patch j to patch i
$\mathcal{M}$	-	Net reproduction number of mosquitoes
$\mathcal{M}_i$	-	Net reproduction number of mosquitoes in patch i ($i = 1, 2$)

$\mathcal{R}_0$	-	Basic reproduction number
$\mathcal{R}_t$	-	Basic reproduction number in a partially susceptible human population
$\mathcal{R}_{01}^s$	-	Basic reproduction number of isolated patch 1
$\mathcal{R}_{02}^s$	-	Basic reproduction number of isolated patch 2
$\mathcal{R}_{10}$	-	Basic reproduction number of patch 1 with human travel rates
$\mathcal{R}_{20}$	-	Basic reproduction number of patch 2 with human travel rates
$\mathcal{R}_{01}$	-	Basic reproduction number associated with virus serotype 1
$\mathcal{R}_{0j}$	-	Basic reproduction number associated with virus serotype j
$\mathcal{F}_i$	-	Rate of appearance of new infections in compartment i
A	-	Constant mosquito recruitment rate
$\bar{a}$	-	Lower bound imposed on the control variable $u(t)$
b	-	Mosquito biting rate
$\bar{b}$	-	Upper bound imposed on the control variable $u(t)$
b_i	-	Biting rate of mosquito in patch i
b_j	-	Mosquito biting rate in Patch j
c	-	Rate of contacts
m	-	Number of *Aedes aegypti* female mosquitoes per human
m_c	-	Number of infected compartments in the model
m_i	-	Number of female mosquitoes per human in patch i $(i = 1, 2)$
n_c	-	Total number of compartments in the model
m_s	-	Number of alternative hosts available as blood sources
F	-	Infection matrix
M	-	Metzler matrix

p	-	Probability of making contact with an infectious individual
p_{ij}	-	The fraction of time a human resident in Patch i spends in Patch j
q_{ij}	-	The fraction of time a mosquito resident in Patch i spends in Patch j
X_s	-	The set of disease-free states
$x(t)$	-	State variable
$u(t)$	-	Control variable
v	-	Rate of effective contact
V	-	Transition matrix
$\mathcal{J}$	-	Cost functional
β_{hv}	-	Transmission probability of virus from infectious human to susceptible mosquito
β_{hv_1}	-	Transmission probability of virus serotype 1 from infectious human to susceptible mosquito
β_{hvi}	-	Probability of virus transmission from an infectious human to susceptible mosquito in Patch i
β_{hvj}	-	Probability of virus transmission from an infectious human to mosquito in Patch j
β_{hv_j}	-	Transmission probability of virus serotype j from infectious human to susceptible mosquito
β_{vh}	-	Transmission probability of virus from infectious mosquito to susceptible human
β_{vh_1}	-	Transmission probability of virus serotype 1 from infectious mosquito to susceptible human
β_{vhi}	-	Probability of virus transmission from an infectious mosquito to susceptible human in Patch i
β_{vhj}	-	Probability of virus transmission from an infectious

		mosquito to susceptible human in Patch j
β_{vh_j}	-	Transmission probability of virus serotype j from infectious mosquito to susceptible human
$\mathcal{V}_i^+(x)$	-	Transfer rate of individuals into compartment i by all other means
$\mathcal{V}_i(x)^-$	-	Transfer rate of individuals out of compartment i by all other means
$\mathcal{V}_i(x)$	-	Difference between $\mathcal{V}_i^-(x)$ and $\mathcal{V}_i^+(x)$
$\mathcal{E}$, $\mathcal{E}_i$	-	Equilibrium points, where $i = 0, 1, \ldots, 5$
λ_h, $\lambda_h(t)$	-	Force of infection of humans
A_v, $A_v(t)$	-	Aquatic mosquito population at time t
A_{vi}, $A_{vi}(t)$	-	Aquatic mosquitoes in patch i ($i = 1, 2$) at time t
E_h, $E_h(t)$	-	Exposed humans at time t
E_{hi}, $E_{hi}(t)$	-	Exposed individuals in patch i ($i = 1, 2$) at time t
E_{h_j}, $E_{h_j}(t)$	-	Exposed individuals to virus serotype j at time t
E_{h_1}, $E_{h_1}(t)$	-	Exposed individuals to virus serotype 1 at time t
$E_{h_{j1}}$, $E_{h_{j1}}(t)$	-	Recovered individuals from virus serotype j and exposed to serotype 1 at time t
$E_{h_{1j}}$, $E_{h_{1j}}(t)$	-	Recovered individuals from virus serotype 1 and exposed to serotype j at time t
E_v, $E_v(t)$	-	Exposed mosquitoes at time t
E_{v_1}, $E_{v_1}(t)$	-	Number of mosquitoes exposed to virus serotype 1 at time t
E_{v_j}, $E_{v_j}(t)$	-	Number of mosquitoes exposed to virus serotype j at time t
E_{vi}, $E_{vi}(t)$	-	Exposed mosquitoes in patch i ($i = 1, 2$) at time t
I_h, $I_h(t)$	-	Infectious humans at time t
I_{hi}, $I_{hi}(t)$	-	Infectious individuals in patch i ($i = 1, 2$) at time t
I_{hj}	-	Number of infectious humans in Patch j

I_{h_j}, $I_{h_j}(t)$	-	Infectious individuals by serotypes j at time t
I_{h_1}, $I_{h_1}(t)$	-	Infectious individuals by serotype 1 at time t
$I_{h_{1j}}$, $I_{h_{1j}}(t)$	-	Infectious individuals by serotype j having recovered from infection by serotype 1 at time t
$I_{h_{j1}}$, $I_{h_{j1}}(t)$	-	Infectious individuals by serotype 1 having recovered from infection by serotype j at time t
I_v, $I_v(t)$	-	Infectious mosquitoes at time t
I_{vi}, $I_{vi}(t)$	-	Infectious mosquitoes in patch i ($i = 1, 2$) at time t
I_{vj}	-	Number of infectious mosquitoes in Patch j
I_{v_1}, $I_{v_1}(t)$	-	Infectious mosquitoes by serotypes 1 at time t
I_{v_j}, $I_{v_j}(t)$	-	Infectious mosquitoes by serotypes j at time t
k	-	Number of larvae per human
k_i	-	Number of larvae per human in patch i ($i = 1, 2$)
K_L	-	Larvae carrying capacity
K_{Li}	-	Carrying capacity of larvae in patch i ($i = 1, 2$)
N_{hj}	-	Total human population in Patch j
N_h, $N_h(t)$	-	Total human population at time t
N_{hi}, $N_{hi}(t)$	-	Total human population in patch i ($i = 1, 2$) at time t
N_v, $N_v(t)$	-	Total mosquito population at time t
N_{vi}, $N_{vi}(t)$	-	Total mosquito population in patch i ($i = 1, 2$) at time t
R_h, $R_h(t)$	-	Recovered humans at time t
R_{hi}, $R_{hi}(t)$	-	Recovered individuals in patch i ($i = 1, 2$) at time t
S_h, $S_h(t)$	-	Susceptible humans at time t
S_{hi}, $S_{hi}(t)$	-	Susceptible individuals in patch i ($i = 1, 2$) at time t
$S_{h_{j1}}$, $S_{h_{j1}}(t)$	-	Recovered individuals from infection by serotype j and susceptible to serotype 1 at time t
$S_{h_{1j}}$, $S_{h_{1j}}(t)$	-	Recovered individuals from infection by serotype 1 and susceptible to serotype j at time t
S_v, $S_v(t)$	-	Susceptible mosquitoes at time t

S_{vi}, $S_{vi}(t)$	-	Susceptible mosquitoes in patch i ($i = 1, 2$) at time t
V_h	-	Number of vaccinated humans
$\rho\left(FV^{-1}\right)$	-	Spectral radius of matrix FV^{-1}
$Df(x_{DFE})$	-	Derivative $\left[\frac{\partial f_i}{\partial x_j}(x_{DFE})\right]$ evaluated at the disease-free equilibrium point x_{DFE} for $1 \leq i,\ j \leq m_c$
Ω	-	Spatial domain
∇	-	Diffusion of human population in spatial dimension x
$N_h(x)$	-	Density of human population on spatial domain, Ω
$\bar{d}(x)$	-	Diffusion rate/coefficient
$\bar{p}(x)$	-	Advection
$\mathbb{R}$, $\mathbb{R}^n$	-	Real numbers
$\delta(x(t_f))$	-	A continuously differentiable function accounting for the terminal cost of maximising the state variable x at final time t_f
$x(t_0)$	-	Initial condition for the state variable $x(t)$
$u_{i\max}$	-	Maximum effort invested on control u_i
u_V	-	Vaccination control parameter
u_P	-	Personal protection control parameter
u_T	-	Treatment control parameter
u_L	-	Larvicide control parameter
u_A	-	Adulticide control parameter
$1 - u_M$	-	Mechanical control parameter
u_A^*	-	Optimal control u_A
u_L^*	-	Optimal control u_L
u_P^*	-	Optimal control u_P
u_V^*	-	Optimal control u_V
u^*, $u^*(t)$	-	Optimal control $u(t)$
x^*, $x^*(t)$	-	Optimal state variable $x(t)$

$u_A(t)$	-	Time-dependent control variable representing adulticide
$u_L(t)$	-	Time-dependent control variable representing larvicide
$u_P(t)$	-	Time-dependent control variable accounting for personal protection
$u_V(t)$	-	Time-dependent control variable representing Dengvaxia vaccine
$I_h(t_i)$	-	Number of infected humans at time t_i predicted by the compartmental model for data point i, $i = 1, 2, \ldots N$
$\hat{I}_{h_i}$	-	Number of infected humans for N data points
$\mathcal{D}$	-	Positively invariant set
$\mathcal{D}_i$	-	Positively invariant sets for $i = 0, 1, 2$
$\mathcal{D}_h$, $\mathcal{D}_v$	-	Positively invariant sets with respect to human and mosquito compartments, respectively
$\mathbb{R}^n_+$	-	n-tuppled positive real numbers
$D_I G(Y^*, 0)$	-	Jacobian of $G(Y, I)$ evaluated at the disease-free equilibrium $(Y^*, 0)$
ϑ	-	Amplitude of seasonal variation
$p_i(\lambda)$	-	Polynomials with terms in eigenvalues λ for $i = 1, j$ $(j = 2, 3, 4)$
ρ	-	Rate of waning immunity process
σ	-	Proportion of effective treatment
W_1, A_i	-	Weight constant associated with exposed human subpopulation where $i = 1, 2$
W_2, B_i	-	Weight constant associated with infectious human subpopulation with $i = 1, 2$
W_3, C_i	-	Weight constant associated with aquatic mosquito population, where $i = 1, 2$
D_i, $\bar{W}_3$, W_4	-	Weight constant associated with female mosquito population, for $i = 1, 2$

$\bar{W}_1$	-	Weight constant for primary and secondary infected humans by virus serotype 1
$\bar{W}_1$	-	Weight constant for primary and secondary infected humans by virus serotype j (where $j = 2, 3, 4$)
γ_P	-	Weight constant for personal protection
γ_L	-	Weight constant for larvicide control
γ_A	-	Weight constant for adulticide control
γ_V	-	Weight constant for Dengvaxia vaccination
$\mathcal{L}$	-	Lagrangian
$\| (\cdot) \|$	-	Norm of $(\cdot)$
$\|(\cdot)\|$	-	Absolute value of $(\cdot)$
$\alpha_1, \alpha_2, \varphi$	-	Constants
Time^{-1}	-	Per time
$\mathcal{F}(w)$,	-	Representation of the components associated with new dengue cases in the infected compartments
$\mathcal{V}(w)$	-	Representation of the remaining components in the infected compartments
$\mathcal{F}(y)$	-	Representation of the components related to new dengue cases in the infected compartments
$\mathcal{V}(y)$	-	Representation of the remaining components in the infected compartments
$\mathcal{F}(z)$,	-	Representation of the components associated with new dengue cases in the infected compartments
$\mathcal{V}(z)$	-	Representation of the remaining components in the infected compartments
$D_I G(Z^*, 0)$	-	Jacobian of $G(Z, I)$ evaluated at the disease-free equilibrium $(Z^*, 0)$
Φ	-	Sensitivity variable
ω	-	Vector of sensitivity parameters

Φ^S	-	Non-negative migration matrix of susceptible individuals
Φ^E	-	Non-negative migration matrix of exposed individuals
Φ^I	-	Non-negative migration matrix of infectious individuals
Φ^R	-	Non-negative migration matrix of recovered individuals
ϕ^S_{ji}	-	Travel rate of susceptible individuals from patch i to patch j $(i, j = 1, 2, i \neq j)$
ϕ^E_{ji}	-	Travel rate of exposed individuals from patch i to patch j $(i, j = 1, 2, i \neq j)$
ϕ^I_{ji}	-	Travel rate of infectious individuals from patch i to patch j $(i, j = 1, 2, i \neq j)$
ϕ^R_{ji}	-	Travel rate of recovered individuals from patch i to patch j $(i, j = 1, 2, i \neq j)$
$\mathcal{W}, \mathcal{X}$	-	Lyapunov functions
$D_I G(W^*, 0)$	-	Jacobian of $G(W, I)$ evaluated at the disease-free equilibrium $(W^*, 0)$
X_u	-	Class of every pairs $(x(t), u(t))$
S	-	Compact set
S_{t_f}	-	Terminal set

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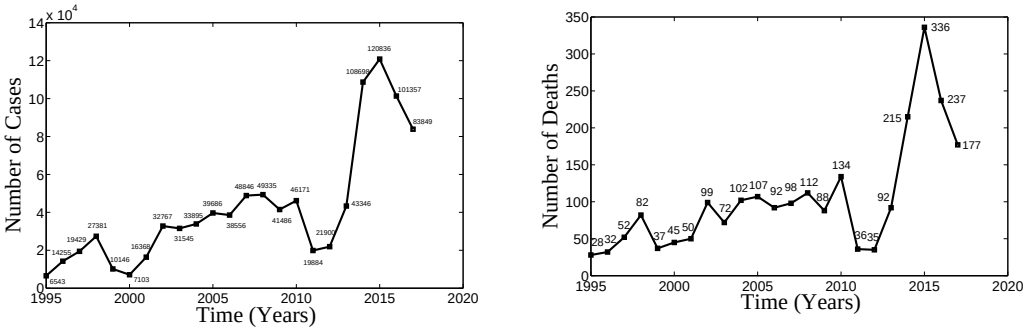
CHAPTER 1

INTRODUCTION

1.1 Motivation

Malaysia has continued to experience annual increase in number of dengue cases. Dengue Fever (DF) is presently recognised as a noteworthy general health issue in the country [1, 2]. An increasing trend of number of dengue cases and deaths during the last decades in Malaysia is alarming. Figure 1.1 presents the record of dengue in Malaysia for the years 1995–2017. The data showed a noteworthy fluctuation in annual dengue-induced deaths between 2000 and 2010. In 2000 and 2001, an average of 48 deaths was reported annually. However, 99 deaths in 2002 and 72 deaths in 2003 showed a remarkable variation in the subsequent two years. The number of deaths increased from 102 to 107 in 2004 and 2005, respectively. Between 2006 and 2007, an average of 95 deaths was recorded. Also, 112 deaths was reported in 2008 and an average of 111 deaths was reported for the period 2009–2010. There was a significant rise in the number of reported deaths between 2012 and 2015. Observing the trend of reported deaths in the last two decades, it could be observed that the total number of deaths reported between 2001 and 2010 was 954 while a total number of 1122 deaths was reported for the years 2011–2017. This study of dengue trend from 2001–2017 shows that dengue has imposed more burdens to the population as well as claimed more lives just between 2011–2017 than during the years 2001–2010.

Figures 1.1(a) and 1.1(b) show that there exists a linear relationship between the reported dengue cases and deaths for the period of 1995–2017 in Malaysia. It is observed that both Figures 1.1(a) and 1.1(b) exhibit an upward trend. In other words, as long as high number of dengue cases is reported for Malaysia, high number of deaths is expected. Consequently, endeavours to decrease the number of dengue cases is presently a high need of different internal and external agencies in Malaysia, particularly, Ministry of Health (MOH), Malaysia [4]. Today, it is the obligation of



(a) Number of Reported Dengue Cases (b) Number of Reported Deaths

Figure 1.1 Record of Dengue in Malaysia for the Years 1995–2017 [3]

every medical practitioners in Malaysia to report each case of DF to the closest local health office within twenty-four hours from the time of diagnosis [4, 5]. Through the developed reporting systems, the trend of recorded dengue cases and dengue-induced deaths has been reported on weekly basis by MOH, Malaysia [3]. However, this practice is very insensitive because doctors have a low threshold to diagnose dengue during inter-epidemic periods. In most cases, recognition of dengue outbreaks only occur when the disease transmission is already at its peak. At this time, implementing preventive and control measures to alter the transmission dynamics of the disease is too late [6]. Therefore, there is the need to conduct a study in order to come up with a better way to minimise dengue-induced burdens through integrated human protection and vector management for effective prevention and control of dengue epidemics in Malaysia.

Another concern about dengue outbreaks in Malaysia is the economic burden it imposes on the Government and individuals in general. Endemicity and hyper-endemicity (that is, the state of continuous circulation of various dengue virus serotypes in the same area) of dengue disease transmission in Malaysia have adversely affected the economy of the country. According to Liang *et al.* [7], about USD 73.45 million (United States Dollar) was estimated as the cost incurred on dengue-related vector control by Malaysian government in 2010. This is about USD 2.63 per capita population of the country during this year. Pang and Loh [8] also revealed that approximately USD 56 million is allocated as management fee for dengue on annual basis by the government. Hence, devising a control strategy that minimises dengue outbreak, and

possibly eliminates the disease spread at low costs of control implementation would be appealing to the Malaysian government and the general public.

1.2 Background of the Study

Dengue is the most widespread mosquito-borne disease in the world [9, 10, 11, 12]. The disease is a major public health issue throughout tropical and sub-tropical areas of the globe [13, 14] where the disease is now endemic, including Central and South America, South Asia, South-East Asia and the Pacific region countries [14]. The spectrum of dengue disease ranges from DF to more severe Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [15]. During the last decades, dengue disease has become the major cause of deaths and hospitalisations by DHF and DSS in most tropical nations [16]. According to the World Health Organisation (WHO) [17], over 40% of the world's population is presently at the risk of dengue, and it is estimated that about 50–100 million dengue infections with over 20,000 deaths related to DF is likely to occur per annum across the globe. In addition, up to 0.5 million people develop DHF or DSS [17]. While dengue is a worldwide health concern, with a relentless increment in the number of nations announcing the disease, presently near 75% of the worldwide population at dengue risk are in Asia Pacific region countries [18]. Since the 1950s, dengue has become a serious health problem in the South-East Asia region [19], including Malaysia. Hence, dengue prevention and management has become a major concern to the world at large.

There is no specific treatment for both DF and DHF or DSS presently. Dengue preventive action and control completely rely upon viable vector control measures [13]. The use of interventions targeting the vector population has been the only approach for the prevention and control of dengue virus spread for which integrated vector management was suggested until a vaccine was introduced [20]. The vaccine Dengvaxia (CYD-TDV) manufactured by Sanofi Pasteur was recently licensed, and has been approved in 11 countries [17]. The vaccine protects against three Dengue Virus (DENV) serotypes DENV-1, DENV-3 and DENV-4 but only confers imperfect protection against DENV-2 serotype [21]. Therefore, an integrated strategy which

combines Dengvaxia vaccine, human self-protection and vector control measures (such as larvicide and adulticide) has been suggested for use in dengue-endemic region countries (which include Malaysia) by WHO [17]. However, cost associated with the implementation of vector control and prevention mechanisms for dengue is often expensive and limited financial and health resources are usually available. Thus, it is necessary to derive an optimal strategy for distributing the available limited resources. The quest to gain insights into the dynamics of dengue disease transmission and optimal control strategies by applying Optimal Control Theory (OCT) has attracted the interest of many researchers to formulate various compartmental dengue models.

In the late 1920s, the pioneering work of Kermack and McKendrick established the deterministic SIR (Susceptible-Infectious-Recovered) epidemic model as stated in [22]. Since then, several extensions of this basic model have been proposed to investigate different aspects of dengue by many researchers [12, 21, 23, 24, 25, 26, 27, 28, 29, 30]. For instance, Rodrigues *et al.* [23] developed a single-patch $S_hI_hR_h+A_vS_vI_v$ model (where S_h, I_h and R_h denote the susceptible, infectious and recovered humans, respectively, and A_v, S_v and I_v are the subpopulations of aquatic, susceptible and infectious mosquitoes, respectively) to examine the impact of adulticide and ecological controls on dengue disease transmission and control dynamics in Madeira Island. However, the model excludes the latent periods in human and mosquito, and covered limited control measures. Agusto and Khan [24] developed single-patch $S_hV_hE_hI_hR_h + S_vE_vI_v$ mathematical model (where V_h, E_h and E_v are the vaccinated humans, exposed or latent humans and mosquitoes, respectively) for dengue. Optimal Control Problem (OCP) formulation of the model was discussed, and the problem was qualitatively analysed to derive the optimal strategy for the use of vaccination and adulticide controls in preventing and controlling dengue disease spread in Pakistan by employing OCT. A similar investigation on optimal control of dengue using vaccination and adulticide controls was carried out by formulating single-patch $S_hE_hI_hR_h + S_vE_vI_v$ deterministic model in [25]. However, the use of only vaccination and adulticide controls considered in [24, 25] impacts the disease prevalence in human and adult mosquito populations, but not directly affects the size of aquatic stage mosquito which is also necessary to focus on in dengue control plan. Consequently, all the transmission phases related to DF are not well described by the models proposed in [23, 24, 25]. In addition, the models are not suitable to explore several available human prevention and vector control measures,

and explain the optimal strategy for the disease control using the control intervention measures.

Further, compartmental models have been used to describe the transmission dynamics and control of dengue with coexistence of multiple DENV serotypes. Particularly, Rocha *et al.* [12] constructed a two-strain model based on $S_hI_hR_h + A_vS_vI_v$ framework to forecast the impact of adulticide control on the dynamics of dengue disease spread when two DENV strains coexist in Madeira Island. However, open space spraying of adulticide is only applied as a short time control measure when a dengue outbreak occurs. Morales *et al.* [21] used a two-strain $S_hE_hI_hR_h + S_vI_v$ based deterministic model to describe the transmission dynamics and control of dengue using different scenarios of Dengvaxia vaccine administered on the susceptible humans. However, the model does not incorporate Dengvaxia vaccine according to the suggestion on the use of the vaccine as well as the integrated control strategy recommended by WHO [17]. Zheng and Nie [26] formulated an OCP for a two-strain $S_hI_hR_h + S_vI_v$ dengue model capturing susceptible human awareness and adulticide controls. By employing Pontryagin's Maximum Principle (PMP), the problem was theoretically analysed to derive the optimal awareness campaign and adulticide controls needed to reduce or even eradicate the disease. However, it is necessary to extend this model structure and integrate the control strategies with Dengvaxia vaccine in order to derive a more realistic deterministic model framework and better control strategy for preventing and controlling dengue disease transmission when multiple DENV serotypes coexist in a population.

The role of host mobility on spatial dissemination of dengue have been studied using deterministic models. Mishra and Gakkhar [27] used a two-patch $S_hI_hR_h + S_vI_v$ based mathematical model to examine the impacts of human travel on dengue epidemic dynamics using the states Rio de Jenerio and Ceara of Brazil as case studies. Phaijoo and Gurung [28] constructed an n-patch dengue model based on $S_hE_hI_hR_h + S_vE_vI_v$ modelling framework to assess the impacts of human movements and seasonal variation on dengue disease transmission dynamics in a patchy environment. Also, Bock and Jayathunga [29] constructed n-patch $S_hI_hR_h+S_vI_v$ model in order to examine the optimal strategy for dengue disease control in a patchy environment by applying personal

protection control. In a similar study, Kim *et al.* [30] used two-patch $S_hE_hI_hR_h + S_vE_vI_v$ deterministic model to derive an optimal strategy for controlling dengue disease spread using personal protection. However, none of these spatial models includes the aquatic stage mosquito, which plays important roles in dengue disease spread and management. In addition, the idea of optimal control introduced to the model formulation in [29, 30] only considers personal protection which is not sufficient to decrease human infections of the two connected patches to zero simultaneously.

1.3 Problem Statement

DF or DHF imposes significant social, economic and medical burdens in Malaysia [31] and other countries in dengue-endemic areas. The disease causes 50-100 million infections worldwide every year [18], and has also caused increased significant numbers of infections and dengue-related deaths in Malaysia in recent years [3, 5]. A number of single-patch deterministic models have been proposed for necessary assessment of the transmission dynamics of DF and impact of various control interventions on ways to handle the disease outbreak in a homogeneous environment by many researchers. However, the transmission phases related to DF are not all covered by these models, and hence, not suitable to represent the reality of dengue disease transmission and control. In several studies, two-strain or multi-strain compartmental deterministic models have been developed and analysed for dengue disease transmission in a population with coexistence of two or multiple DENV serotypes, and various strategies for effective control of the disease, particularly by using the recently licensed Dengvaxia vaccine, have also been examined. However, these models do not capture all the disease transmission phases to appropriately integrate the vaccine with other control intervention measures in accordance with the guideline on its usage. The effect of human movement on spatial transmission and control of DF in a patchy environment has been examined using n-patch deterministic models in other studies. However, these models do not feature the aquatic stage mosquito, and consequently not suitable as a compartmental model framework to assess different control intervention strategies (particularly those that target the aquatic stage mosquito) to effectively control and prevent the spatial spread of the disease outbreak. Until the complex relationship

between infectiousness, symptom severity as a result of different DENV serotypes co-circulating, and human mobility are extensively explored and well-understood in a way to improve on the control strategies in curtailing the spread of dengue, the disease will continue to be a national health threat in dengue endemic countries such as Malaysia. Therefore, deterministic models that are capable of explaining the mechanisms involved in dengue disease transmission and optimal control in a homogeneous environment, with coexistence of multiple DENV serotypes, and with spatial effect are needed.

Owing to different complex phenomena, such as distinct phases of infectiousness, coexistence of multiple DENV serotypes and human dispersal, that influence the severity of dengue infections, emergence and re-emergence of the disease as well as the existing dengue control intervention measures, this research proposes single-patch deterministic model based on $S_hE_hI_hR_h + A_vS_vE_vI_v$ structure featuring all the transmission phases of DF in human, both the aquatic and adult mosquitoes, and consideration of integrated vector management involving vaccination, personal protection, treatment based on drug therapy, larvicide, adulticide and ecological control measures in order to comprehend the real nature of the disease spread in a homogeneous environment and analyse different control strategies for its effective control in Malaysia. To facilitate the understanding of mechanisms involved in the dynamics of dengue disease transmission with coexistence of two DENV serotypes in the interacting human and mosquito population and control, the single-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ dengue model is modified to two-strain $S_hE_hI_hR_h + S_vE_vI_v$ by grouping the four DENV serotypes into two, namely, DENV-1 and DENV-j (for $j = 2, 3, 4$), to analyse the transmission dynamics of dengue when two virus serotypes coexist in a population. By constructing a suitable control dynamical system, the optimal strategy for dengue prevention and control using Dengvaxia vaccine, personal protection and adulticide controls is examined in line with the guideline on the use of Dengvaxia vaccine in dengue-endemic country like Malaysia by WHO [17]. This focus on the co-circulation of two DENV serotypes is based on the evidence that secondary infection triggers the risk of developing DHF than any subsequent post-secondary infections [12, 21, 32]. Finally, the single-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ model proposed in this study is modified to a two-patch model to describe and analyse the effect of human travels on the spatial dissemination of dengue disease, and derive an optimal strategy for curtailing the disease transmission in two interconnected patches.

1.4 Research Questions

Based on the problem statement highlighted in Section 1.3, several research challenges are raised. Providing answers to the questions highlighted below consequently addresses these challenges.

1. How would a deterministic model capturing all the phases of DF transmission and stages of *Aedes aegypti* female mosquito be formulated and analysed for the disease spread and control in a homogeneous environment?
2. How would dengue disease transmission with coexistence of two DENV serotypes in the interacting human and mosquito populations and control be modelled and analysed mathematically using two-strain $S_hE_hI_hR_h + S_vE_vI_v$ model based on single-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ dengue model?
3. How would single-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ dengue model be used as a building block in formulating and analysing two-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ deterministic model for spatial dissemination and control of DF in two connected patches?

1.5 Research Objectives

The aim of this study is to develop deterministic models to describe and analyse the dynamics of transmission and control of dengue in homogeneous and patchy environments. The main objectives are:

1. To develop and analyse single-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ deterministic model describing dengue disease transmission and control in a homogeneous environment.
2. To modify the developed single-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ model for the formulation and analysis of two-strain $S_hE_hI_hR_h + S_vE_vI_v$ deterministic model for dengue disease spread with coexistence of two DENV serotypes and control.

3. To modify the developed single-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ model for the development and analysis of two-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ deterministic model describing the dynamics of transmission and control of dengue in a patchy environment.

1.6 Research Scope

Deterministic models will be developed to examine the dynamics of transmission and control of dengue disease in homogeneous and patchy environments. Single-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ dengue model which accommodates the necessary transmission phases of DENV between the interacting human and mosquito populations will be developed, solved and analysed. The model will be modified to assess the impact of seasonal variations as well as the efficacy of several control measures (that are personal protection, vaccination, treatment of infectious humans, ecological control, larvicide and adulticide) on dengue disease spread and derive optimal strategy for the disease control. Also, two-strain $S_hE_hI_hR_h + S_vE_vI_v$ dengue model capturing the coexistence of two DENV serotypes will be formulated, solved and analysed, and used to investigate the influence of seasonal variation, impacts of control measures (Dengvaxia vaccine, human self-protection and adulticide) on the dynamics of dengue disease transmission in the presence of two DENV strains co-circulating and derive optimal strategy for controlling the disease spread. Moreover, the role of human movement (without the consideration of mosquito dispersal) on dengue disease transmission between only two interconnected patches, efficacy of different control measures (personal protection, larvicide and adulticide) and optimal control strategies will be examined by constructing, solving and analysing two-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ based model. In each case, PMP will be applied to OCP in order to prove the existence and characterise optimal controls.

Furthermore, the study will consider Malaysia, a country in South-East Asia region, with focus on only two of the most affected states Johor and the Federal Territory Kuala Lumpur/Putrajaya, particularly during the 2012 dengue outbreaks in the country. The weekly reported dengue cases data documented by the MOH, Malaysia [33] will

be used in parameterising and estimating the initial state variable values of the models proposed in this research.

1.7 Significance of the Research

In many previous studies, $S_hI_hR_h+S_vI_v$, $S_hI_hR_h+A_vS_vI_v$ and $S_hE_hI_hR_h+S_vE_vI_v$ mathematical model structures were used to describe the vector-host interactions for dengue disease transmission dynamics and control in a homogeneous landscape. This study proposes a single-patch model based on $S_hE_hI_hR_h + A_vS_vE_vI_v$ framework. The new framework allows for investigating the efficacy of several control measures on the dynamics of dengue disease spread. Also, $S_hI_hR_h + S_vI_v$ and $S_hI_hR_h + A_vS_vI_v$ based deterministic models have been used to examine dengue disease transmission dynamics and control when multiple DENV serotypes co-circulate. This study will formulate two-strain deterministic model based on $S_hE_hI_hR_h + S_vE_vI_v$ structure to forecast the impacts of integrated control strategy through the use of Dengvaxia vaccine, personal protection and adulticide. Furthermore, several mathematical models based on $S_hI_hR_h + S_vI_v$ and $S_hE_hI_hR_h + S_vE_vI_v$ frameworks have been proposed by previous researchers to investigate the role of human travel on the epidemics of dengue. However, these models did not capture the aquatic stage of mosquitoes which is important to be considered in any dengue control plan. Hence, this study will develop a two-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ based deterministic model to describe the transmission dynamics and control of dengue in a patchy environment.

Various aspects of dengue disease (such as transmission dynamics and control) are comprehended through the use of the proposed models. The models are used to forecast the transmission dynamics and control of the disease. WHO, South-East Asia countries, particularly Malaysia, and other dengue affected regions worldwide will benefit from these findings.

The findings of this research form part of essential dengue database for MOH Malaysia. The Malaysian government as well as the public health practitioners will

make reference to the information provided in the research findings in taking decisions concerning the prevention and control of the future dengue outbreak whenever it occurs.

The models can be adapted by nations at dengue risk regions worldwide, especially South-East Asian countries to understand the dynamics of dengue disease transmission, control of new epidemic and prevention of future outbreak of the disease.

The findings of this research would be of benefit to higher institutions of learning. The suggested directions for future work provided in this research will be a foundation for further study.

1.8 Thesis Organisation

The organisation of the remainder of this thesis is as follows:

Chapter 2 presents the review of literature related to the research topic. The review captures the general overview on vector-borne diseases. Brief history of dengue in global and Malaysia perspectives is described. How dengue virus transmits, the symptoms and measures to prevent and control it are discussed. A brief description of Malaysia in terms of geographical location, distribution, population and climate is given. Further, a review of related works on compartmental modelling of vector-borne diseases and optimal control is considered. The chapter also provides a detail review of recent works on compartmental modelling of different aspects of dengue.

In Chapter 3, the methodology adopted in this research is provided. The chapter presents the research design and procedure, operational framework in addition to the theoretical framework. The chapter discusses the theoretical analysis of the general approach adopted as well as the specific tools employed for the numerical implementations of the proposed compartmental deterministic models and the formulated OCPs.

The single-patch deterministic dengue models developed in this study are discussed in Chapter 4. The formulation of single-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ deterministic dengue model and the theoretical analysis of its basic properties are conducted. The model serves as basis for the other single-patch models with seasonal variation and control interventions presented in this chapter. In addition, OCP is formulated based on the non-autonomous version of the model using five different strategies, and PMP is used for its qualitative analysis. The model developed in the first part is parametrised using data from the state of Johor and Kuala Lumpur/Putrajaya dengue outbreaks in 2012. Graphical method is used to validate the model. Numerical simulations of all the proposed models and OCP are also considered in the chapter.

Chapter 5 covers the construction and analysis of two-strain $S_hE_hI_hR_h + S_vE_vI_v$ based deterministic models proposed in this research. The development of two-strain model for dengue disease transmission dynamics with coexistence of two DENV serotypes is discussed. Qualitative analysis of the basic properties of the model is carried out. The model is parametrised using information from the 2012 DF and DHF outbreaks in Johor and Kuala Lumpur/Putrajaya. Furthermore, modification of the model to two two-strain dengue models, one incorporating seasonal forcing mosquito birthrate and the other involving three control parameters (that account for Dengvaxia vaccine, personal protection and adulticide controls) is considered. OCP of the two-strain model capturing three time-dependent control functions is formulated by employing OCT. Lastly, the proposed two-strain compartmental models and the optimality system obtained from OCP analysis are numerically solved.

In Chapter 6, the two-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ deterministic models formulated in this study are discussed. Two-patch $S_hE_hI_hR_h + A_vS_vE_vI_v$ mathematical model describing the effect of host mobility on dengue disease spread between two interconnected patches is formulated and analysed. The model is first modified to examine the impact of personal protection, larvicide and adulticide control measures on dengue disease transmission dynamics in two connected patches via human unidirectional and bidirectional movements. Later, the model is modified to include three patch-specific time-dependent control functions accounting for human self-

protection, larvicide and adulticide controls for OCP formulation. The models as well as the optimality system derived from OCP analysis are numerically simulated.

Finally, the summary of the research and the conclusion of the whole study based on the results obtained in Chapters 4, 5 and 6 are discussed in Chapter 7. The chapter also provides the contributions to knowledge, limitation of the research, and directions for future work.

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2. **Abidemi, A.** and Aziz, N. A. B. Optimal Control Strategies for Dengue Fever Spread in Johor, Malaysia. Computer Methods and Programs in Biomedicine, 2020. 196: 105585
3. **Abidemi, A.**, Ahmad, R. and Aziz, N. A. B. Controlling the Spread of Dengue Disease in Two Interconnected Patches: Modelling and Simulation. *Applied Mathematics and Computation*, (Submitted).
4. **Abidemi, A.** and Aziz, N. A. B. Mathematical Modelling and Simulation of Dengue Disease Transmission, Prevention and Control: A Case Study of Johor, Malaysia. *Ecological Complexity*, (Submitted).
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