PHARMACOECONOMIC MODEL OF DENGUE VACCINE IN MALAYSIA

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PHARMACOECONOMIC MODEL OF DENGUE VACCINE IN MALAYSIA

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		Unit
a	Age of death	years
A	Mean age of acquiring dengue disease	years
A_m	Pre-adult mosquito (aquatic form)	capita
B	Average daily biting	day^{-1}
β	Age weighting constant	—
β_{hm}	Transmission probability from I_h to S_m	$bite^{-1}$
β_{mh}	Transmission probability from I_m to S_h	$bite^{-1}$
c	Insecticide control term	day^{-1}
C	Adjustment constant for age-weights	—
$CostD_{nv}$	Costs associated with dengue infection before vaccination	USD
$CostD_v$	Costs associated with dengue infection after vaccination	USD
$CostV$	Vaccination cost	USD
$DALY_{no\ vaccine}$	DALY without vaccination	years
$DALY_{vaccine}$	DALY with vaccination	years
DW	Disability weight	—
E_1	Disease-free equilibrium	—
E_2	Endemic equilibrium	—
E_h	Exposed human population	capita
E_m	Exposed adult female mosquito (wing form)	capita
f	Rate of appearance of new infections	—
$F_i(x)$	Rate of appearance of new infections in compartment i	—

I	Number of cases	—
I_h	Infected human population	capita
I_m	Infected adult female mosquito (wing form)	capita
k	Number of mosquito larvae per human	capita /capita
K	Age-weighting modulation constant	—
l	Mean lifetime	years
L	Standard life expectancy at age death	years
L_1	Average duration of disability	years
N	Number of deaths	—
N_h	Total human population	capita
N_m	Total adult female mosquito population	capita
η_h	Inverse of viremic period	day^{-1}
η_m	Inverse of extrinsic incubation period	day^{-1}
p	Proportion of eligible vaccinated per day (vaccination rate)	day^{-1}
P_m	Maximum price	USD
P_n	Cost neutral price	USD
r	Correlation coefficient	—
r_1	Discount rate	—
R_h	Recovered human population	capita
R_{hm}	Dengue infection from host to vector	—
R_{mh}	Dengue infection from vector to host	—
R_o	Basic reproduction number	—
$R_{o,vac}$	Basic reproduction number of MOSSEIR-Vaccine model	—
S_h	Susceptible human population	capita

S_m	Susceptible adult female mosquito (wing form)	capita
t	Time	day
μ_A	Natural mortality of larvae	day^{-1}
μ_h	Natural birth/mortality of human	day^{-1}
μ_m	Natural mortality of mosquito	day^{-1}
v	Rate of transfer of individuals from one compartment to another	—
V_h	Vaccinated human population	capita
$V_i^+(x)$	Rate of transfer of individuals into compartment i	—
$V_i^-(x)$	Rate of transfer of individuals out of compartment i	—
v_h	Inverse of intrinsic incubation period	day^{-1}
x_i	Number of individuals in each compartment i	—
X_s	Set of disease free states	—
λ_h	Force of infection in human population	—
λ_m	Force of infection in mosquito population	—
ω	Maturation rate from larvae to adult	day^{-1}
ϕ	Oviposition rate (number of eggs at each deposit per capita)	day^{-1}
ϕ_1	Fraction of the population that are vaccinated	—
ϕ_c	Critical vaccinated fraction	—
σ	Proportion of vaccinated being infected (vaccine efficacy = $1 - \sigma$)	—
θ	Vaccine waning rate	day^{-1}

LIST OF ABBREVIATIONS

ADE	Antibody dependent enhancement
ASEI-SEIR	Aquatic, susceptible, exposed and infected mosquito; susceptible, exposed, infected and recovered human
ASEI-SIR	Aquatic, susceptible, exposed and infected mosquito; susceptible, infected and recovered human
ASI-SIR	Aquatic, susceptible and infected mosquito; susceptible, infected and recovered human
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CMA	Cost-minimization analysis
COMBI	Communication for Behavioral Impact
CUA	Cost-utility analysis
DALY	Disability-adjusted life year
DENV	Dengue virus
DF	Dengue fever
DFE	Disease-free equilibrium
DHF	Dengue haemorrhagic fever
DNA	Deoxyribonucleic acid
DSS	Dengue shock syndrome
DVIT	Dengue Volunteer Inspection Team
DW	Disability weight
EE	Endemic equilibrium
EIP	Extrinsic incubation period
GDP	Gross domestic product
GSK	GlaxoSmithKline
GUI	Graphical user interface

HCE	Highly cost-effective
ICER	Incremental cost-effectiveness ratio
IIP	Intrinsic incubation period
IVM	Integrated vector management
JB	Johor Bahru
MBSA	Shah Alam City Council
MOH	Malaysian Ministry of Health
NGM	Next generation method
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
ODE	Ordinary differential equations
PSO	Particle swarm optimization
QALY	Quality-adjusted life-years
SA	Sensitivity analysis
SARS	Severe acute respiratory syndrome
SEIR	Susceptible, exposed, infected and recovered human
SEI-SEIR	Susceptible, exposed and infected mosquito; susceptible, exposed, infected and recovered human
SI	Susceptible and infected mosquito
SIR	Susceptible, infected and recovered human
SI-SIR	Susceptible and infected mosquito; susceptible, infected and recovered human
ULV	Ultra low volume
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research
YLD	Years lost due to disability

YLL	Years of life lost due to premature mortality

MODEL FARMAKOEKONOMI UNTUK VAKSIN DENGGI DI MALAYSIA

ABSTRAK

Lebih kurang dua bilion orang terdedah kepada jangkitan denggi di kawasan tropika dan subtropika, di mana kira-kira 50 hingga 100 juta jangkitan denggi berlaku setiap tahun, yang menyebabkan 20000 hingga 30000 kematian setiap tahun. Denggi ialah penyakit virus bawaan nyamuk yang disebarkan kepada manusia melalui gigitan nyamuk betina yang membawa virus. Kawalan wabak denggi sukar dicapai, terutamanya kerana kegagalan untuk mengawal habitat pembiakan nyamuk di persekitaran bandar. Vaksin denggi yang selamat, berkesan dan kos-efektif masih dalam ujian. Model yang menghubungkan dinamik penularan virus dari nyamuk kepada manusia adalah kunci kepada penilaian telus harga vaksin denggi. Dalam kajian ini, satu model dalaman bernama MOSSEIR dibangunkan dan digunakan untuk simulasi dinamik penularan denggi di Shah Alam dan Selangor. Kemudian, dinamik penularan denggi dikenal pasti dengan menerbitkan nombor pembiakan asas R_o. Analisis kepekaan untuk R_o menunjukkan bahawa kadar kematian semula jadi dan kadar gigitan nyamuk betina dewasa adalah parameter penting dalam penularan denggi. Strategi kawalan, iaitu penghapusan kawasan pembiakan nyamuk, semburan kabus nyamuk dan vaksinasi, dinilai melalui model MOSSEIR. Dari segi teori, hasil simulasi menunjukkan bahawa ketiga-tiga strategi kawalan ini dapat, secara ketaranya, mengurangkan penularan denggi. Sebenarnya, keberkesanan kaedah kawalan tradisional seperti penghapusan kawasan pembiakan nyamuk dan semburan kabus nyamuk adalah di bawah jangkaan kerana ketidakpatuhan. Oleh itu, penggunaan vaksin yang selamat,

berkesan dan berpatutan harganya masih merupakan prospek terbaik untuk kawalan denggi. Suatu model farmakoekonomi dibangunkan dengan menghubungkan hasil model MOSSEIR dengan mekanisme harga vaksin untuk menilai ambang harga yang sangat kos-efektif untuk Malaysia. Ambang harga vaksin yang sangat kos-efektif untuk pelbagai senario vaksinasi di Shah Alam, Selangor dan Malaysia ditunjukkan. Berpandukan hasil simulasi, bagi vaksin denggi yang selamat dan berkesan, ambang harga yang berpatutan dan lestari sebanyak USD5.00 setiap dos untuk Malaysia disokong.

PHARMACOECONOMIC MODEL OF DENGUE VACCINE IN MALAYSIA

ABSTRACT

Around two billion people are vulnerable to dengue infections in tropical and subtropical regions, where about 50 to 100 million dengue infections occur each year, leading to 20000 to 30000 deaths annually. Dengue is a mosquito-borne viral disease that is transmitted to humans through the bites of female mosquitoes carrying the virus. Control of dengue epidemic has been elusive, mainly because of the failure to control mosquito breeding habitats in urban environments. Safe, efficacious and cost-effective dengue vaccine is still under testing. The model that links the virus transmission dynamics between mosquito and human is the key to a transparent valuation of dengue vaccine pricing. In this study, an in-house mathematical model named MOSSEIR is developed and used to simulate the dengue transmission dynamics in Shah Alam and Selangor. The dengue transmission dynamics are then examined by deriving the basic reproduction number R_o. Sensitivity analysis for R_o shows that the natural mortality and the biting rate of adult female mosquito are significant parameters in dengue transmission. Control strategies, namely elimination of mosquito breeding sites control, fogging and vaccination, are evaluated by means of the MOSSEIR model. Simulation results indicate that these three control strategies can significantly reduce dengue transmission, in theory. In reality, the effectiveness of traditional control methods such as elimination of mosquito breeding sites and fogging is below expectation due to non-compliance. Therefore, the adoption of a safe, effective and affordable vaccine remains the best prospect for controlling dengue. A pharmacoeconomic

model is developed by linking the MOSSEIR model results with the vaccine pricing mechanism to evaluate a highly cost-effective price threshold for Malaysia. A highly cost-effective vaccine price threshold for various vaccination scenarios in Shah Alam, Selangor and Malaysia are demonstrated. Based upon the simulation results, for a safe and effective dengue vaccine, an affordable and sustainable pricing threshold of USD5.00 per dose for Malaysia is advocated.

CHAPTER 1

INTRODUCTION

1.1 Introduction to Dengue

Dengue is a mosquito-borne viral disease transmitted by *Aedes aegypti* mosquito and it is one of the most important arboviral disease affecting human. Dengue virus (DENV) is classified under Flaviviridae virus family and it includes four distinct serotypes, namely DENV-1, DENV-2, DENV-3 and DENV-4 (Back and Lundkvist, 2013). Dengue is endemic in more than 128 countries and 3.97 billion people living in areas are exposed to the risk of dengue transmission (Brady et al., 2012). It is suggested that the number of global dengue incidence is close to 400 million per year (Murray et al., 2013) and it is ranked second to Malaria amongst deadly mosquito-borne diseases (Khan et al., 2014). Dengue transmission occurs when an infected female mosquito bites an individual, following a virus incubation for 4–10 days. Infected human serves as a source of virus for uninfected mosquitoes and the virus is transmitted when mosquitoes feed on an infected individual. *Aedes aegypti* bites to obtain blood for laying eggs and breeds in artificial water containers such as tyres, tin cans and ceramic pots. Dengue fever (DF) is the most common clinical syndrome accompanied by high fever (40°C), severe headache, and muscle and joint pains (WHO, 2009). In less than 5% of dengue cases, the disease develops into a more severe clinical syndrome, known as dengue haemorrhagic fever (DHF). The DHF together with plasma leakage results in circulatory failure which causes life-threatening dengue shock syndrome (Luz et al., 2009).

1.2 Dengue in Malaysia

The first dengue case was reported in year 1902 in Penang, Malaysia (Pang and Loh, 2016). The first epidemic outbreak occurred in year 1973, with a total number of 969 dengue cases and 54 dengue deaths. The dengue transmission continues to circulate in the population and there is an upward trend in the total number of dengue cases in Malaysia (Mia et al., 2013). For example, there is an increment of 250% dengue infections in year 2014 (Pang and Loh, 2016). The total number of dengue cases in Malaysia in year 1995 is 6,543 and increased to 101,357 in year 2016 as shown in Figure 1.1 (MOH, 2016a). Figure 1.2 shows the number of dengue cases by states in Malaysia year 2016. In year 2016, Selangor has the highest number of dengue cases, which is 51,652 or 50.96% of total number of dengue cases in Malaysia.

All the four distinct dengue serotypes coexist in Malaysia and the prevalent dengue serotype changes from year to year as shown in Figure 1.3 (Mudin, 2015). From Figure 1.3, DENV-3 is predominant from year 1992 to 1995 and 2001 to 2002. From year 1996 to 2012, the prevalent dengue serotype changes between DENV-1, DENV-2 and DENV-3. DENV-1 is predominant between year 1996 to 1998 and 2002 to 2006. DENV-2 is predominant between year 1998 to 2000 and 2006 to 2009. The percentage of DENV-4 is found to be small as compared to other three serotypes. From year 2013 to 2015, DENV-1 and DENV-2 are more prevalent compared to the other two serotypes.

With the upward trend of dengue cases in Malaysia, efforts have been taken by the government to lower dengue transmission. It is estimated that the government of Malaysia has spent USD73.5 million on dengue vector control activities in year 2010 (Packierisamy et al., 2015). However, limited success is achieved by current control methods (Ong, 2016). The dengue incidence would continue to increase if no effective control strategies are implemented (Pang and Loh, 2016). This urges the development of dengue vaccine, where vaccine is thought to be one of the most cost-effective public health interventions and as a long-term dengue control measure (Marimuthu and Ravinder, 2016). Following this, the world's first dengue vaccine is developed by Sanofi Pasteur and several dengue vaccine candidates are undergoing clinical trial phases (Pang and Loh, 2017; Wichmann et al., 2017). Therefore, dengue vaccination could be a key approach for effective dengue outbreak control in Malaysia.

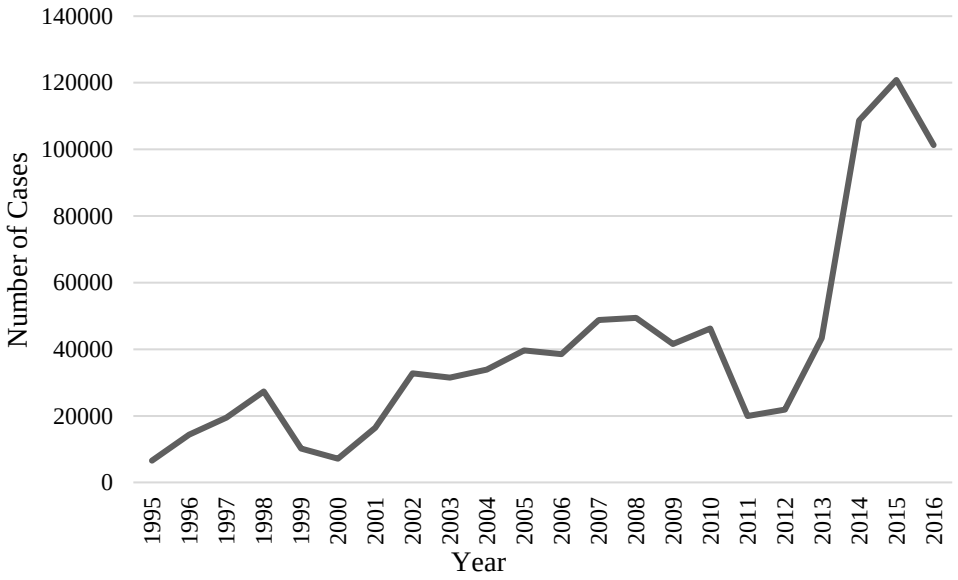

Figure 1.1: Dengue cases in Malaysia from year 1995 to 2016.

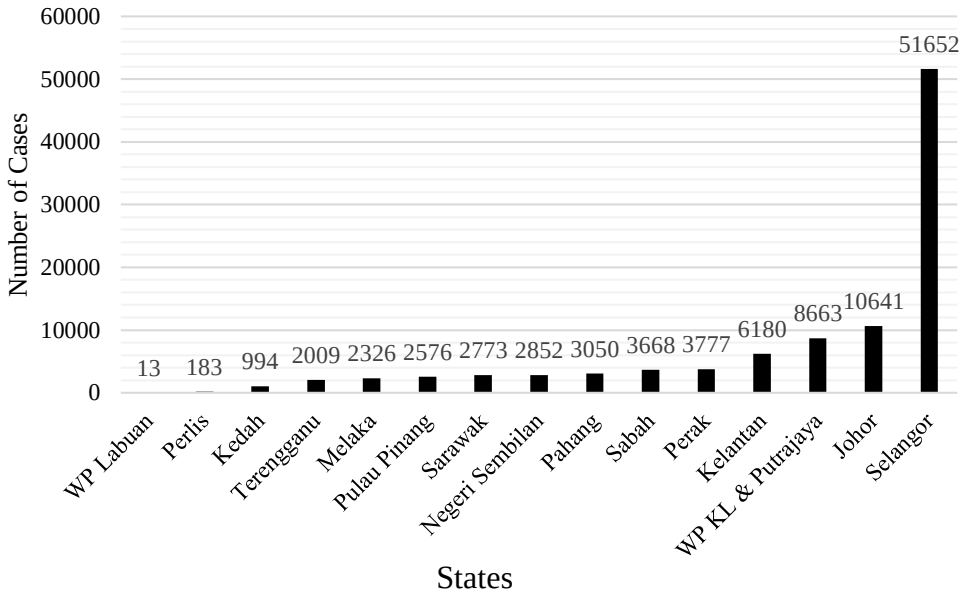

Figure 1.2: Number of dengue cases by states in Malaysia year 2016.

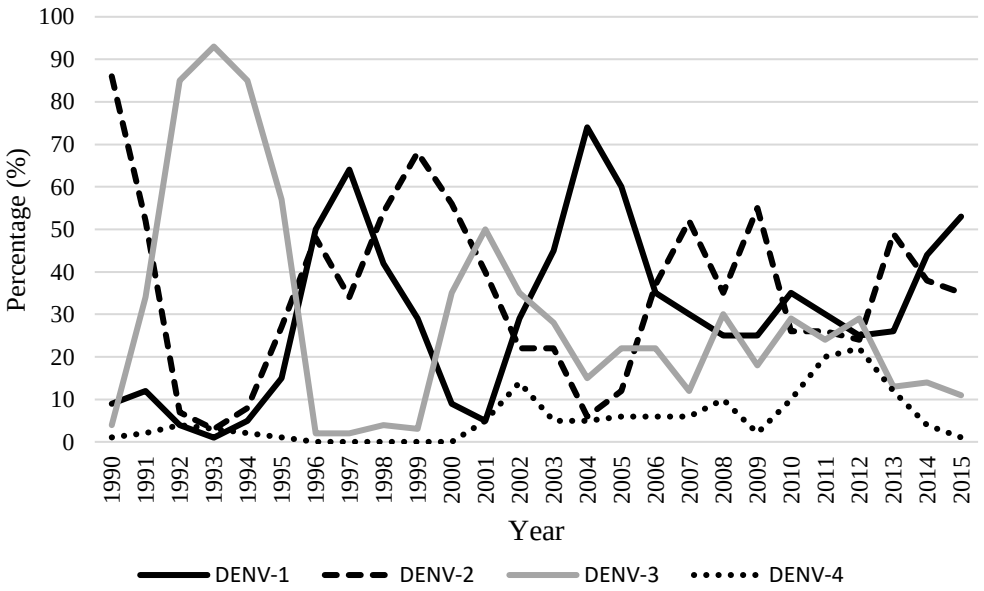

Figure 1.3: Circulation of dengue serotypes in Malaysia from year 1990 to 2015.

1.3 Dengue Vaccine

The world's first dengue vaccine, Dengvaxia which is developed by Sanofi Pasteur, is now available and first licensed in Mexico on December 2015 for the use in individuals 9–45 years of age living in endemic areas (Vannice et al., 2016). To date, Dengvaxia has been approved in more than 10 countries (Lyon, 2016).

Dengvaxia is a tetravalent, recombinant, live-attenuated vaccine which provides protection by neutralising antibodies that are claimed to be equally effective against all the four dengue serotypes (Wichmann et al., 2017). An equal protection against all four dengue serotypes is important to prevent antibody dependent enhancement (ADE) which results in a higher risk of severe dengue such as DHF or dengue shock syndrome (DSS) during a secondary infection (Guzman and Vazquez, 2010; Pang and Loh, 2017). The administration of Dengvaxia in seropositive individuals (individuals who has previous dengue infection with at least one serotype) would boost the recipients' immunity to levels comparable to individuals who experienced two natural infections (infected by dengue twice). The next infection would behave as post-secondary infection with a much lower risk of severe disease (Figure 1.4). Conversely, vaccination in seronegative individuals (individuals who has no previous dengue infection) acts as a "primary-like" infection. The subsequent infection (first natural infection) behaves as a "secondary-like" infection with a higher risk of severe disease (Ferguson et al., 2016; Flasche et al., 2016).

Aside from Sanofi Pasteur, many research laboratories are developing dengue vaccine, including Walter Reed Army Institute of Research (WRAIR), Fiocruz, GlaxoSmithKline (GSK), Merck, Takeda and National Institute of Allergy and Infectious Diseases (NIAID) (Schwartz et al., 2015). The current stages of clinical trials of other vaccine candidates with predicted earliest licensure are shown in Table 1.1 (Pang and Loh, 2017). From Table 1.1, Dengvaxia, TV003 or TV005 and TDV are live attenuated chimeric vaccines. A live attenuated virus vaccine which contains attenuated pathogenic microorganisms, is known to produce a robust, long-lasting and broad immune response (Briggs et al., 2014). There is a higher

chance of developing an efficacious tetravalent vaccine by using a live attenuated virus vaccine. Currently on trial, the vaccine TV003 or TV005 is given as single dose which induces tetravalent responses in 74%–92% (TV003) and 90% (TV005) of flavivirus seronegative adults (Whitehead, 2016). Phase III trial is scheduled to begin in the early of 2016 to evaluate the long-term efficacy of TV003 (Pang and Loh, 2017).

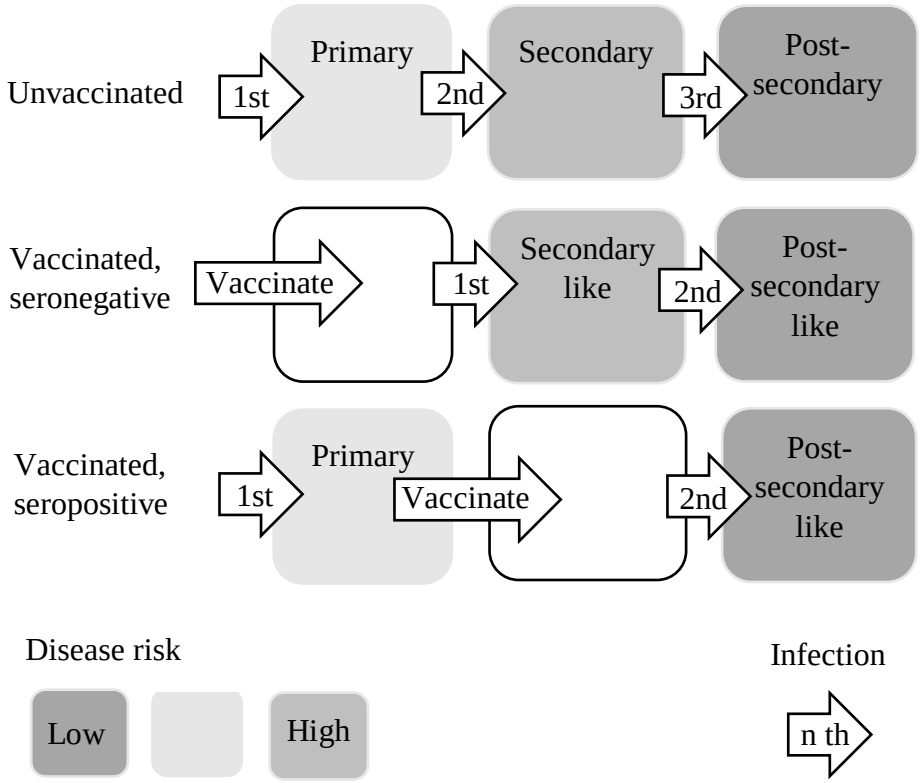

Figure 1.4: Illustration of the assumed mode of action of vaccine Dengvaxia (Flasche et al., 2016).

Table 1.1 Current stages of clinical trials of some dengue vaccine candidates.

Vaccine	Company	Type	Stage	Earliest Licensure
CYD-TDV (Dengvaxia)	Sanofi Pasteur	Live attenuated chimeric	Completed	2015
TV003/ TV005	NIH/NIAID/ Butantan Institute	Live attenuated chimeric	Phase III	2018–2019
TDV	Inviragen/ Takeda	Live attenuated chimeric	Phase III	2017–2018
TDEN	GSK/WRAIR	Purified inactivated whole virus	Phase II	2018
V180	Merck/ NIAID	Subunit	Phase I	—
D1ME100	U.S. Naval Medical Institute	DNA	Phase I	—

The vaccine TDV is another live attenuated chimeric vaccine which is undergoing phase III clinical trial. The results of phase II trial of TDV imply that it is immunogenic for all four dengue serotypes in all age groups after 1 or 2 doses, irrespective of pre-vaccination dengue serostatus (Sirivichayakul et al., 2016). Phase III clinical trial of TDV involves 20,000 healthy children to assess the efficacy of TDV in averting symptomatic dengue fever of any severity (Pang and Loh, 2017). Consisting of purified inactivated whole virus, the vaccine TDEN is considered safer compared to the live dengue vaccine. However, the development of TDEN is hindered by a low immunogenicity and hence requires the use of certain adjuvants to strengthen TDEN for long-term protection (Liu et al., 2016). The examination of safety and immunogenicity of TDEN is scheduled to begin in December 2016. In phase II trial, the effectiveness of a prime-boost strategy with TDEN and a live attenuated dengue vaccine is under evaluation (Schwartz et al., 2015). The vaccine V180 is an E-based recombinant subunit vaccine, which has completed the evaluation of safety and immunogenicity in phase I trial (Liu et al., 2016; Pang and Loh, 2017). Developed by U.S. Naval Medical Institute, D1ME100

is a monovalent plasmid DNA vaccine, which completed phase I study and the work to improve its immunogenicity is ongoing (Liu et al., 2016).

On 31st October 2016, Malaysia had conditionally registered Dengvaxia and phase IV study of Dengvaxia in Malaysia is currently conducted to further examine the vaccine efficacy and safety. This is because the results of the two phase III clinical trials of Dengvaxia indicates a modest protection to seronegative individuals in Asia (56.5%) and Latin America (60.8%) (Pang and Loh, 2017). Further, the vaccine efficacy against DENV-2 is the lowest, i.e., 35% and 42.3% in Asia and Latin America, respectively. Since DENV-2 is prevalent in Malaysia, a more conclusive data on the vaccine effectiveness and duration of protection is needed. The phase IV study would address questions such as safety according to age and serostatus of vaccinated population, adverse events after vaccination and overall effects on dengue incidence and hospitalized dengue (Wichmann et al., 2017).

1.4 Vaccine Pricing

Before the introduction of a new vaccine, the decision makers should consider its safety, cost-effectiveness, affordability and sustainability (WHO, 2014a). Demographic, clinical, epidemiological, economic data and the use of modelling approaches to simulate disease transmission dynamics should be considered in cost-effectiveness analyses (Tozan, 2015). Since the price of dengue vaccine is unknown, a transparent pharmacoeconomic model of dengue vaccine is needed to assess the vaccine price. Price transparency would assist decision makers to evaluate the affordability in introducing a new vaccine, provide knowledge on how

to obtain lower price by changing procurement practices and provide comparative price information between countries (WHO, 2017).

1.5 Research Questions

The research questions of this study are:

i. What are the vaccination effects on dengue transmission in Malaysia?
ii. What are the economic and disease burden of dengue before and after vaccination in Malaysia?
iii. What is the highly cost-effective price threshold of dengue vaccine in Malaysia?

1.6 Objectives of the Study

The objectives of this study are as follows:

i. To develop a pharmacoeconomic model based on the dengue virus transmission model;
ii. To assess the effectiveness of vaccination and other dengue mitigation measures;
iii. To compare the highly cost-effective price threshold for dengue vaccine in Malaysia with that in other papers.

1.7 Scope of the study

A pharmacoeconomic model will be developed by coupling the dengue virus dynamic transmission model that links human SEIR framework with mosquito ecology model (Koh and Teh, 2011; Rodrigues et al., 2012) with the pricing mechanism demonstrated in Coudeville and Garnet (2012) and Shepard et al. (2012). The vaccination impacts on dengue transmission model, economic and disease burden of dengue will be determined by means of model simulations. A highly cost-effective price threshold for dengue vaccine in Malaysia will be proposed.

1.8 Significance of the Study

The pharmacoeconomic model can help in advocating a transparent mechanism to evaluate highly cost-effective price threshold for dengue vaccine in Malaysia, following WHO guidelines. The country's overall immunization and health care system could be improved with the use of a safe, efficacious and affordable dengue vaccine.

1.9 Organization of Thesis

This thesis begins with Chapter 1 which introduce the dengue disease and discuss the dengue transmission in Malaysia. With the growing dengue epidemic and ineffective control by traditional methods, the need of dengue vaccination is discussed for effective dengue outbreak control. However, the price of dengue vaccine is still undetermined so there is a need to evaluate the price of vaccine by

using a pharmacoeconomic model. Then, the research questions, objectives, scope, significance and organization of this study are presented.

A literature review on the epidemiological models is provided in Chapter 2. The basic human SIR and SEIR models are described and the need of using a vector-host model to illustrate the spread of dengue in Malaysia is highlighted. Several methods to derive the basic reproduction number, a key concept in the study of epidemiology, are reviewed. This is followed by a discussion on the importance of sensitivity analysis and the methods in doing so for basic reproduction number. Then, a review on vaccination models is provided to identify the most suitable vaccination model in Malaysia. Methods to calculate the disease and economic burden of dengue before and after vaccination are presented. Lastly, pharmacoeconomic studies involving the evaluation of dengue vaccine price are reviewed to determine the most suitable approach in assessing the vaccine price for Malaysia.

Next, three types of vector-host dengue transmission model, ASI-SIR, ASEI-SIR and ASEI-SEIR models are introduced in Chapter 3. A comparison of basic reproduction number for each of these models is performed to determine the most suitable model. Then, MOSSEIR, which is developed based on ASEI-SEIR model is discussed and used to illustrate dengue transmission dynamics in Malaysia. Model validation is carried out by comparing the simulation results to the results reported in Rodrigues et al. (2012). Bifurcation and sensitivity analysis of basic reproduction number are also performed. Finally, curve fitting analysis is

performed to estimate the parameter values that reflect the dengue transmission dynamics in Shah Alam and Selangor for the year 2010. These parameter values are critical to illustrate the vaccination effects and evaluate the vaccine pricing in later chapters.

Several dengue control strategies such as breeding sites reduction, mosquito fogging and public education which have been implemented in Malaysia are described in Chapter 4. Since dengue vaccination would be a new approach to reduce dengue transmission in Malaysia, a vaccination model, known as MOSSEIR-Vaccine is introduced to illustrate the effects of vaccination. Then, the basic reproduction number of MOSSEIR-Vaccine is derived and stability analyses at disease-free and endemic equilibria are performed to determine the conditions for the equilibria to be stable. After that, numerical analysis of control strategies, including breeding sites reduction, mosquito fogging and vaccination in Shah Alam are performed and examined. These simulation results on vaccination effects will be used to assess and project the price of vaccine for Malaysia in Chapter 5.

In Chapter 5, a pharmacoeconomic model which links the MOSSEIR-Vaccine model and vaccine pricing model is developed. Dengue vaccination in Selangor is chosen to demonstrate the pricing mechanism due to data availability. Both the disease and economic burden of dengue before and after vaccination are calculated. This information will be needed in cost-effectiveness analysis of dengue vaccine. The relationship between vaccine price and incremental cost-effectiveness ratio is also described. After that, a highly cost-effective price threshold for Malaysia is

estimated. A highly cost-effective vaccine price threshold for different vaccination scenarios in Shah Alam, Selangor and Malaysia are also compared and analyzed.

Finally, several conclusions are drawn in Chapter 6 based on the results of this study. The limitations of this study and recommendations for future research are also discussed.

CHAPTER 2

LITERATURE REVIEW

2.1 Epidemiological Models

Epidemiology is the study of the distribution and determinant of health-related states or events in specified population, and the application of this study to control of health problems (Kramer et al., 2010). The purposes of epidemiology study are to explain the aetiology of a disease, to determine the risk and protective factors, to estimate the disease burden, to forecast disease trends and to examine the effectiveness of interventions. Epidemiology modelling helps to identify the process involved in epidemiology of an infectious disease, to determine the most significant parameter and to provide guidance on control strategies. The knowledge provided by epidemiological models also assist in analysing the control strategies for newly emerging and re-emerging pathogens. For example, during the outbreak of severe acute respiratory syndrome (SARS), mathematical modelling was used to analyse the infectious disease data and evaluate the effectiveness of control strategies (Wallinga and Teunis, 2004).

In general, there are two types of models which can be used to study epidemiology modelling, i.e., stochastic and deterministic models. Stochastic model depends on chance variation in risks of exposure, disease and other factors (Kipruto et al., 2013). This model considers human heterogeneities and provides more understanding on individual-level modelling. However, the model could be laborious to set up and could become mathematically complex (Hori et al., 2003).

Deterministic model divides individuals into different compartments and explains what happens in each compartment with some degree of details. Requiring less data and is easier to set up, the deterministic models have become popular as they are able to provide useful insights to disease progression and control strategy (Kipruto et al., 2013). Therefore, deterministic model will be used to study dengue transmission in Malaysia. In the following section, three types of deterministic models will be discussed, i.e. SIR model, SEIR model and vector-host transmission model.

2.1.1 SIR Model

An epidemic may be described as a sudden outbreak of a disease that infects a substantial portion of the population in a region before it disappears (Keeling and Rohani, 2008). Consistent with most infectious diseases including dengue, it is assumed appropriately that the pathogen causes illness for a period, followed by immunity, which can be considered as lifelong over the duration of the simulations. This scenario can be formulated mathematically in a model called SIR, which describes three different states or groups of individuals in the population in terms of a system of differential equations. In SIR model, the human population is categorized into three groups: (a) S_h, the number of individuals who are susceptible to the disease, (b) I_h, the number of infected individuals and (c) R_h, the number of infected individuals who is removed from the possibility of being infected again or of spreading infection. The total human population (N_h) is $N_h = S_h + I_h + R_h$. The initial SIR model is proposed by Kermack and McKendrick in year 1927 (Chowell and Brauer, 2009).

In the simplest case, the population demography (births, deaths and migration) is ignored because it is assumed that the time scale of disease spread is sufficiently fast and not to be affected by human births and deaths. Other assumptions include homogeneous human population, no disease-induced deaths (which means constant total human population) and lifelong immunity. There are only two transitions, i.e., $S_h \rightarrow I_h$ and $I_h \rightarrow R_h$. The transition from S_h to I_h involves the disease transmission while the transition from I_h to R_h involves the movement of infected individuals to recovered class once they have recovered from the infection. If a longer-term persistence and endemic dynamics need to be explored, then the population demography is important. In this case, the human birth rate and natural mortality rate need to be included in SIR model (Chowell and Brauer, 2009; Keeling and Rohani, 2008).

2.1.2 SEIR Model

One unrealistic feature of SIR model described in Section 2.1.1 is that the individuals become infectious immediately upon infection. This is because at the initial inoculation of a very small number of pathogen units (bacteria or virus), the virus abundance is too low for active transmission. These individuals are infected but not yet infectious and are referred to as exposed individuals, represented by E_h. In this latent period, the virus multiples inside the body of a susceptible individual until a certain level, at which the infected individual becomes infectious. The addition of a latent period may act to introduce a slight time delay into the system (Keeling and Rohani, 2008). Therefore, the epidemic growth after the introduction of latent period in SEIR model may be slower due to the transition of susceptible

human population to exposed class before they can contribute to the transmission process.

2.1.3 Vector-host Transmission Model

The initial SIR model by Kermack and McKendrick has a great influence in the development of mathematical epidemiology models (Rodrigues, 2016). The SIR model is a beginning point to understand how the disease spreads. Refinement is possible in enriching the model and in adding more details in the model formulation. The choice of appropriate compartments of the model depends on the properties of the disease, data availability and the purposes of the study (Verelst et al., 2016). Dengue fever is a vector-borne disease which is transmitted via blood-sucking arthropods known as vectors (Keeling and Rohani, 2008). It cannot be passed between primary hosts (person to person) but through an intermediate insect host or vector. The interactions between coupled mosquito-human population dynamics and dengue transmission play an important role in the development of dengue fever (Liao et al., 2015). Mathematical models which include both the mosquito and human population dynamics would enhance the understanding on the spread of this mosquito-borne disease. The mosquito entomological parameters such as the biting rate, virus incubation rate in mosquito and mosquito population dynamics are some of the key factors in dengue transmission. There is a need to understand the effects of changes in these parameters that would help in the planning of effective control strategies (Manore et al., 2014). For such purposes, a vector-host transmission model which includes both mosquito and human population is developed.

A vector-host transmission model described by Bailey (1975) provides the basis for a dengue transmission model that includes both the mosquito (SI model) and human populations (SIR model). Many models have been derived from this basic dengue model, depending on the assumptions of the model, the dengue epidemiology and/or transmission routes (Andraud et al., 2012). For example, the SI-SIR model may be extended to SEI-SEIR model to include both extrinsic incubation period (EIP) in mosquito and intrinsic incubation period (IIP) in human population. The EIP in mosquito is important because it is about the same duration as the mosquito lifespan and because the mosquito might die before it becomes infectious (Manore et al., 2014). The inclusion of exposed human compartment would reflect the reality that the infected human has to survive the IIP before he or she becomes infectious. Garba et al. (2008), Lashari and Zaman (2011) and Manore et al. (2014) use SEI-SEIR model to illustrate the dengue transmission and perform mathematical analysis.

The ASI-SIR or ASEI-SEIR model includes the aquatic mosquito population in the vector-host transmission model (Chen and Hsieh, 2012; Liao et al., 2015; Rodrigues et al., 2013). This would assist in the analysis of effects of aquatic mosquito entomological parameters such as the oviposition rate, maturation rate from larvae to adult and natural mortality of larvae in dengue transmission (Esteva and Yang, 2015). The effects of vector control such as mosquito breeding sites control, application of larvicides and mosquito fogging can also be evaluated by using ASI-SIR or ASEI-SEIR model (Barmak et al., 2014; Burattini et al., 2008; Rodrigues et al., 2013). This can be done by adding a control variable in mosquito compartments

(Rodrigues et al., 2013) or increasing the mosquitoes' mortality rate (Burattini et al., 2008).

Since the impacts of vector control can be demonstrated by using a vector-host transmission model, the most efficient control strategy could be identified from the model. For example, Amaku et al. (2014) suggests that the control of adult mosquitoes is the most effective control measure by performing sensitivity analysis. Therefore, an understanding on the life cycle of adult mosquitoes and the seasonal cycle of disease transmission would assist in a successful vector control. A two-treatment cycle of mosquito fogging is based on the life cycle of adult mosquito and the EIP of mosquito (Lam, 1993). It is recommended that mosquito fogging be applied at the peak biting time especially during rainy season (Pang and Loh, 2016). Oki et al. (2011) suggests that the seasonality and the level of transmission intensity should be considered during mosquito fogging. Burattini et al. (2008) opines that a discrete application of fogging would be more feasible from the practical point of view and the impact of consistent fogging (four weekly fogging applications) is more durable when seasonality is considered in the dengue model.

Moreover, the mosquito compartment can be extended to incorporate different dengue serotypes to assist in the analysis of a severe form of the dengue disease such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). Such analysis would require at least two different dengue serotypes in the mosquito compartment (Kooi et al., 2014; Morales et al., 2017). There are also papers that consider four dengue serotypes to illustrate the immunological interactions between

the four dengue serotypes such as cross-protection and cross enhancement, which are the features of dengue transmission (Coudeville and Garnett, 2012; Hladish et al., 2016; Reich et al., 2013). For the human population, it can be extended to include heterogeneities in age. This can be done by dividing the human population into several age groups. Since dengue disease spreads differently in different age groups and the data from WHO shows that the majority of dengue patients are children (Aldila et al., 2013; Vicente et al., 2017), several papers consider human age groups in developing dengue model (Aldila et al., 2013; Cochran and Xu, 2014; Mello and Castilho, 2014).

In general, both simple and complex models have been developed to explore dengue transmission (Ellis et al., 2011). One of the limitations of deterministic model is the assumption of homogeneous population, where each individual has the same amount of contacts. The spread of disease depends on the age groups, contact pattern and geographic location (Chao et al., 2013; Valle et al., 2013). These factors could be incorporated in a stochastic model but the model might become complex. A more complex model tends to be more realistic if the parameters are known but the behavior of a complex model might be difficult to investigate analytically (Ellis et al., 2011). After considering the availability of dengue data and the complexity of a model, a deterministic model consisting of the mosquito and human population will be used to demonstrate the dengue transmission dynamics in Malaysia. This model will be discussed in Chapter 3. The mosquito population is needed to provide deeper insight into the underlying mechanisms for the spread of dengue disease and suggest effective control strategies. The human age groups and multi-serotypes of

dengue are not considered because they are beyond the scope of this study and because of the limitation of data.

2.2 Basic Reproduction Number

An understanding on the potential spread of dengue disease and significant parameters influencing dengue transmission that could aid dengue control strategies can be derived from the dengue transmission model. This can be done by using basic reproduction number, R_o which is a key concept in the study of epidemiology and within-host pathogen dynamics. Developed for the study of vector-borne diseases, infectious diseases and in-host population dynamics, R_o is an indicator of transmissibility in a completely susceptible population. In general, R_o is the number of secondary cases produced by a single infected individual during his or her entire infectious period in a completely susceptible population (Chen et al., 2007; Heffernan et al., 2005). From this definition, when $R_o < 1$, each infected individual produces less than one new infected individual, indicating the disease cannot invade the population. If $R_o > 1$, the cases increase and epidemic may occur. In an endemic infection, R_o can be used to determine the most effective control measure in reducing R_o below one. The magnitude of R_o is used to estimate the potential risk of infectious disease such as SARS, foot and mouth disease, dengue, malaria and Ebola. Table 2.1 shows examples of R_o for some infectious diseases.

Table 2.1: Basic reproduction number, R_o of some infectious diseases.

Diseases	R_o	References
Measles	12-18	Fine (1993)
Smallpox	5-7	Fine (1993)
Rubella	6-7	Fine (1993)
Malaria	5-100	Fine (1993)
SARS	3.5	Gumel et al. (2004)
H1N1	1.33	White et al. (2013)
Ebola	1.5-2.5	Althaus (2014)
Zika	2.06	Gao et al. (2016)

There are several methods to derive R_o, such as the survival function, final size equation, intrinsic growth rate, average age at infection, the Jacobian method and the next generation method (NGM) (Heffernan et al., 2005). The final size equation, intrinsic growth rate and average age at infection are methods to estimate R_o from incidence data. The final size equation is applicable to closed populations only in which the infection leads either to immunity or death. In this case, the number of susceptible human population can only decrease and the final fraction of susceptible human is used to estimate R_o. The intrinsic growth rate is the rate at which the infected human population grows and the R_o can be estimated based on this rate. However, this method depends on the accuracy of incidence data and the estimation of R_o is highly model dependent. Average at infection is a method based on the endemic equilibrium and R_o can be estimated as l/A, where l is the mean lifetime and A is the mean age of acquiring the disease.

The survival function, the Jacobian method and the NGM method are methods to derive R_o in terms of the parameters of some deterministic model. The Jacobian is used to derive a parameter that reflects the stability of the disease-free equilibrium. The parameter obtained may or may not reflect the biologically meaning value of R_o. For a more complex model with more infected compartments, it is difficult to

apply Jacobian method to derive R_o (Driessche, 2017). The Jacobian method is sufficient to predict whether the disease will persist or be eliminated. The survival function is used to handle situations in which infectivity depends on time. This method can be extended to describe models in which a series of states are involved in the production of newly infected individuals. However, this method becomes cumbersome when the infection cycles involve three or more states (Heffernan et al., 2005). In this situation, the NGM method will be more suitable in deriving R_o. The NGM method can be used to derive R_o when more than one class of infective is involved. In this method, the infection process is viewed as the generations of infected individuals (Diekmann et al., 2010). Subsequent generations growing in size indicates an epidemic and the growth factor per generation implies the potential for growth. This growth factor is given by the largest eigenvalue of the next-generation matrix and is the mathematical characterization of R_o. The NGM method has been applied by a majority of papers on epidemiological modelling (Abboubakar et al., 2016; Aldila et al., 2013; Liao et al., 2015; Manore et al., 2014; Mishra et al., 2018; Morales et al., 2017; Rodrigues et al., 2013; Yang, 2014).

Deriving R_o for a disease system could be a complex problem due to the involvement of several species, different epidemiological reactions at different life-history stages and multiple transmission routes. The NGM method can be used to characterize R_o even in systems with such complexity (Hartemink et al., 2008). The R_o is one of the most important concepts in epidemiology modelling and NGM method provides a convenient way to perform such calculations (Hurford et al., 2010). Hence, in this study, the NGM method will be used to derive R_o for dengue model to identify significant parameters in dengue transmission.

2.3 Sensitivity Analysis

To control dengue transmission and to reduce dengue mortality, it is necessary to understand the relative importance of different factors responsible for dengue transmission and prevalence. Sensitivity analysis (SA) studies the variation of outputs of a model caused by variations in the inputs. It is usually performed as a series of tests where a different sets of input parameters is used to observe the change in dynamical behavior of the system. It helps to determine which parameters are the key drivers of a model's results, to interpret the reasonable range of system outcomes and to identify the robustness of a modelling study's qualitative conclusions (Wu et al., 2013). A highly sensitive parameter should be carefully estimated as a small variation in that parameter will result in a large change to outputs, while an insensitive parameter does not require as much effort to estimate as a small variation in that parameter will not produce a large change to results. Since the R_o represents the nature of disease transmission, sensitivity analysis (SA) is performed for R_o to determine the impact of model parameters on dengue transmission.

There are several methods to perform SA which have been discussed by Hamby (1994), Wu et al. (2013) and Pianosi et al. (2016). In our study, SA using partial differentiation technique—the most fundamental technique of SA—is chosen because it is computationally efficient (Hamby, 1994) and has been applied by several studies (Burattini et al., 2008; Chitnis et al., 2008; Manore et al., 2014; Nie and Xue, 2017; Samsuzzoha et al., 2013; Toro et al., 2017). The results of SA in some studies suggest that the mosquito biting rate or/and mosquito mortality rate are major factors influencing R_o (Abboubakar et al., 2016; Burattini et al., 2008;