ECONOMIC EVALUATION AND WILLINGNESS TO PAY (WTP) ELICITATION OF DENGUE VACCINE IN MALAYSIA

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ECONOMIC EVALUATION AND WILLINGNESS TO PAY (WTP) ELICITATION OF DENGUE VACCINE IN MALAYSIA

by

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TABLE OF CONTENTS

ACKNOWLEDGEMENT.....ii

TABLE OF CONTENTS.....iv

LIST OF TABLES.....x

LIST OF FIGURES.....xii

LIST OF ABBREVIATIONS.....xvi

ABSTRAK.....xviii

ABSTRACT.....xx

CHAPTER 1 - INTRODUCTION

1.1 Dengue prevention and control strategy.....1

1.1.1 Vector control and surveillance……...3

1.1.1(a) National Dengue Strategic Plan (NDSP)……3

1.1.2 Dengue vaccine.....4

1.1.2(a) Dengue vaccine development…….5

1.1.3 Health education and community campaign……..12

1.2 Epidemiology of dengue disease.....13

1.3 Health and economic burden of dengue disease.....14

1.4 Problem statement.....16

1.5 Study objectives.....17

1.6 Significance of the study 18

CHAPTER 2 - LITERATURE REVIEW

2.1 Conceptual framework of economic evaluation 19

2.1.1 Economic evaluation using decision-analytic modelling..... 21

2.1.2 Comparative modelling of dengue vaccine public health impact (CMDVI)……..…….23

2.1.3 Current cost-effectiveness/cost-utility studies on dengue vaccine…...25

2.1.4 The dynamic transmission mathematical modelling used in this study.... ……..……..30

2.1.5 Recommendation by the WHO Strategic Advisory Group of Experts on Immunization (WHO-SAGE)……...33

2.2 Elicitation of willingness-to-pay for dengue vaccine..... 35

2.2.1 The strength of contingent valuation method..... 39

2.2.2 Potential biases in contingent valuation study 40

2.2.3 Current willingness-to-pay study on dengue vaccine 42

2.3 Gaps in current knowledge of cost-effectiveness analysis and willingness-to-pay of dengue vaccine…….….43

CHAPTER 3 - METHODS

3.1 Evaluation of the cost-effectiveness and cost-utility of dengue vaccine 46

3.1.1 Model development and study design..... 46

3.1.2 Defining parameter for model calibration input..... 46

3.1.3 Model calibration……..49

3.1.4 Vaccination programmes simulations and parameter input estimation for the programmes.....51

3.1.5 Outcome measures: disease burden, economic burden and vaccine cost-effectiveness.....54

3.1.6 Sensitivity analysis.....56

3.2 The assessment of dengue disease knowledge, household dengue prevention practice, vaccination attitude, dengue vaccine acceptance and willingness-to-pay (WTP) value for hypothetical dengue vaccines……...57

3.2.1 Study design 57

3.2.2 Study location and duration 57

3.2.3 Population, sample size and sampling procedure 58

3.2.4 Study instrument 58

3.2.4(a) Questionnaire design 58

3.2.4(b) Pilot study 1 and 2: validity and reliability of questionnaire.. 59

3.3 Willingness-to-pay measures 60

3.4 Procedures in data collection 63

3.5 Data management and statistical analysis 64

3.5.1 Previous experience with dengue disease measurement 64

3.5.2 Dengue disease knowledge measurement 64

3.5.3 Household dengue prevention practice measurement 64

3.5.4 Vaccination attitude measurement 65

3.5.5 Dengue vaccine acceptance measurement 65

3.5.6 Acceptance for an adult dengue vaccine 66

3.5.7 Willingness to pay for a hypothetical dengue vaccine 66

3.6 Ethical consideration 68

CHAPTER 4 - RESULTS

4.1 Cost-effectiveness/cost-utility of dengue vaccine 69

4.1.1 Dengue treatment and vaccination programme costing estimation .... .69

4.1.2 Health outcome measures: dengue cases, dengue-related deaths, life-year-lost (LYL), and disability-adjusted-life-year (DALY)……...…80

4.1.3 Economic outcome measures: total disease cost, and vaccination programme cost ……..……..83

4.1.4 Highly cost-effective and cost-effective threshold price.. 87

4.1.5 One-Way deterministic sensitivity analysis (DSA) on highly cost-effective and cost-effective threshold price from both public provider and societal perspectives ……..……89

4.1.5(a) Programme 1: THS R13C30 89

4.1.5(b) Programme 2: NW R13C30 91

4.1.5(c) Programme 3: THS R9C30 94

4.1.5(d) Programme 4: NW R9C30 96

4.1.5(e) Programme 5: THS R9C17 99

4.1.5(f) Programme 6: NW R9C17 102

4.1.6 Cost-effectiveness acceptability curve (CEAC) on highly cost-effective threshold and cost-effective threshold……..…..105

4.2 Dengue disease knowledge, household dengue prevention practice, vaccination attitude, dengue vaccine acceptance, and willingness-to-pay (WTP) value for a hypothetical dengue vaccine……108

4.2.1 Descriptive analysis of socio-demographic profile..... 108

4.2.2 Dengue disease knowledge 110

4.2.3 Household dengue prevention practice 111

4.2.4 Vaccination attitude 113

4.2.5 Dengue vaccine acceptance..... 114

4.2.6 Willingness to pay for a hypothetical dengue vaccine..... 118

4.2.6(a) Percentage of not willing to pay and reasons for not willing to pay……..……118

4.2.6(b) Determination of mean willingness-to-pay value and factors affecting the willingness-to-pay by two-part model (TPM) ……...……...……..119

CHAPTER 5 - DISCUSSION

5.1 Potential dengue vaccination programmes to be implemented..... 123

5.2 Calibration of the dynamic transmission model with Malaysia specific epidemiological data ……..……..124

5.3 Cost and benefits of dengue vaccination in Malaysia..... 126

5.4 Probabilistic and deterministic sensitivity analysis..... 128

5.5 Comparison of cost-effectiveness models used in other study.....129

5.6 Limitations: Cost-effectiveness/cost-utility of dengue vaccination.....130

5.7 Acceptance and willingness-to-pay value of dengue vaccine among general population in Penang state determined.....132

5.8 Comparison of WTP with other study.....134

5.9 Limitations: WTP towards hypothetical dengue vaccine.....134

CHAPTER 6 - CONCLUSION

6.1 Conclusions..... 137

6.2 Recommendations……..138

REFERENCES..... 140

APPENDICES

LIST OF PUBLICATIONS

LIST OF SCIENTIFIC PRESENTATIONS

LIST OF AWARD AND ACHIEVEMENTS

LIST OF TABLES

Page

Table 1.1 Dengue vaccine currently available or undergoing rapid clinical development 9

Table 2.1 Summary of CEA/CUA of dengue vaccine 28

Table 2.2 Model input parameters 32

Table 2.3 Questions and considerations for a contingent valuation study of a health care programme 37

Table 3.1 Calibration input parameters 47

Table 4.1 Dengue treatment and dengue vaccination programme cost estimates from public provider perspective 71

Table 4.2 Dengue treatment and dengue vaccination programme cost estimates from societal perspective 74

Table 4.3 Vaccination programmes and parameters estimation 77

Table 4.4 Parameter and input values for probabilistic and one-way deterministic sensitivity analyses 79

Table 4.5 Summary of health outcome measures 82

Table 4.6 Summary of economic outcome measures 84

Table 4.7 Summary of highly cost-effective and cost-effective prices for all vaccination programmes 88

Table 4.8 Socio-demographic status of the respondents 109

Table 4.9 Respondents' dengue knowledge 110

Table 4.10 Respondents' household dengue prevention practice..... 112

Table 4.11 Respondents' attitude towards vaccination 113

Table 4.12 Respondents' acceptance towards dengue vaccine 114

Table 4.13 Simple logistic regression results associated with adult dengue vaccine acceptance..... 117

Table 4.14 Reasons for not willing to pay for the hypothetical vaccine scenario..... 119

Table 4.15 Estimated coefficients of the Two-Parts Model for WTP per dose of dengue vaccine 121

LIST OF FIGURES

Page

Figure 2.1 Dynamic transmission mathematical model of dengue disease transmission 31

Figure 3.1 Flow chart of the processes involved in the phase 1 study……45

Figure 3.2 Observed (green) versus projected (blue) dengue incidence in Selangor state over the period of 2003 – 2017 51

Figure 3.3 Description of hypothetical dengue vaccine scenarios of 5 years (vaccine A) and 10 years (vaccine B) protection duration 61

Figure 3.4 Double-bound dichotomous choice and bidding approach used for elicitation of WTP amount 62

Figure 3.5 The description of the contingent valuation scenario 63

Figure 4.1 Annual dengue cases with and without vaccination programme 1 (THS R13C30) 80

Figure 4.2 One-way DSA on the vaccine highly cost-effective threshold price from provider perspective (THS R13C30) 89

Figure 4.3 One-way DSA on the vaccine cost-effective threshold price from provider perspective (THS R13C30) 90

Figure 4.4 One-way DSA on the vaccine highly cost-effective threshold price from societal perspective (THS R13C30) 91

Figure 4.5 One-way DSA on the vaccine cost-effective threshold price from societal perspective (THS R13C30) 91

Figure 4.6 One-way DSA on the vaccine highly cost-effective threshold price from provider perspective (NW R13C30) 92

Figure 4.7 One-way DSA on the vaccine cost-effective threshold price from provider perspective (NW R13C30) 92

Figure 4.8 One-way DSA on the vaccine highly cost-effective threshold price from societal perspective (NW R13C30) 93

Figure 4.9 One-way DSA on the vaccine cost-effective threshold price from societal perspective (NW R13C30) 93

Figure 4.10 One-way DSA on the vaccine highly cost-effective threshold price from provider perspective (THS R9C30) 94

Figure 4.11 One-way DSA on the vaccine cost-effective threshold price from provider perspective (THS R9C30) 95

Figure 4.12 One-way DSA on the vaccine highly cost-effective threshold price from societal perspective (THS R9C30) 96

Figure 4.13 One-way DSA on the vaccine cost-effective threshold price from societal perspective (THS R9C30) 96

Figure 4.14 One-way DSA on the vaccine highly cost-effective threshold price from provider perspective (NWR9C30) 97

Figure 4.15 One-way DSA on the vaccine highly cost-effective threshold price from provider perspective (NWR9C30) 97

Figure 4.16 One-way DSA on the vaccine highly cost-effective threshold price from societal perspective (NW R9C30) 98

Figure 4.17 One-way DSA on the vaccine cost-effective threshold price from societal perspective (NW R13C30) 99

Figure 4.18 One-way DSA on the vaccine highly cost-effective threshold price from provider perspective (THS R9C17) 100

Figure 4.19 One-way DSA on the vaccine cost-effective threshold price from provider perspective (THS R9C17) 100

Figure 4.20 One-way DSA on the vaccine highly cost-effective threshold price from societal perspective (THS R9C17) 101

Figure 4.21 One-way DSA on the vaccine highly cost-effective threshold price from societal perspective (THS R9C17) 102

Figure 4.22 One-way DSA on the vaccine cost-effective threshold price from provider perspective (NW R9C17) 103

Figure 4.23 One-way DSA on the vaccine highly cost-effective threshold price from societal perspective (NW R9C17) 103

Figure 4.24 One-way DSA on the vaccine cost-effective threshold price from societal perspective (NW R9C17) 104

Figure 4.25 One-way DSA on the vaccine highly cost-effective threshold price from provider perspective (NW R9C17) 104

Figure 4.26 Cost-effectiveness acceptability curve for vaccine's price on highly cost-effective threshold from provider perspective 105

Figure 4.27 Cost-effectiveness acceptability curve for vaccine's price on cost-effective threshold from provider perspective 106

Figure 4.28 Cost-effectiveness acceptability curve for vaccine's price on highly cost-effective threshold from societal perspective 106

Figure 4.29 Cost-effectiveness acceptability curve for vaccine's price on cost-effective threshold from societal perspective 107

Figure 4.30 Respondents' dengue knowledge level 111

Figure 4.31 Respondents' household dengue prevention practice level 112

Figure 4.32 Respondents' vaccination attitude level 113

Figure 4.33 Respondents' acceptance towards adult dengue vaccine 115

Figure 4.34 Respondents' acceptance towards children dengue vaccine 115

LIST OF ABBREVIATIONS

CEA	Cost-Effectiveness Analysis
CFR	Case Fatality Rate
COMBI	Communication for Behavioural Impact
CUA	Cost-Utility Analysis
CV	Contingent Valuation
CVM	Contingent Valuation Method
DALY	Disability-Adjusted-Life-Year
DF	Dengue Fever
DHF	Dengue Haemorrhagic Fever
DSA	Deterministic Sensitivity Analysis
DSS	Dengue Shock Syndrome
GDP	Gross Domestic Product
ICER	Incremental Cost-Effectiveness Ratio
IVM	Integrated Vector Management
KAP	Knowledge, Attitude and Practice
LMIC	Low and Middle Income Countries
LYL	Life-Year-Lost
MOH	Ministry of Health
NDSP	National Dengue Strategic Plan
NW	Nationwide
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted-Life-Year
SIR	Susceptible-Infected-Recovered
THS	Targeted Hotspot

TPM	Two-Part Model
WHO	World Health Organization
WTA	Willingness-To-Accept
WTP	Willingness-To-Pay
YLD	Years Lived with Disability
YLL	Years of Life Lost

PENILAIAN EKONOMIK DAN NILAI KESANGGUPAN UNTUK MEMBAYAR UNTUK VAKSIN DENGGI DI MALAYSIA

ABSTRAK

Penyakit denggi menyumbang kepada beban kesihatan dan ekonomik yang tinggi di Malaysia. Kajian ini dibahagikan kepada dua fasa. Fasa-1 menilai impak dan kos keberkesanan vaksin denggi dengan menggunakan satu model matematik transmisi dinamik dari perspektif pembekal awam dan masyarakat. Model tersebut menggabungkan data epidemiologi yang khusus kepada Malaysia, data keberkesanan bersepadu dan keselamatan jangka panjang dari kajian klinikal fasa-III, dan analisa kepekaan untuk memperbaiki anggaran daripada kajian-kajian sebelumnya. Fasa-2 menilai penerimaan dan nilai kesanggupan-untuk-membayar (WTP) untuk vaksin denggi di antara masyarakat umum di Pulau Pinang dengan menggunakan kaedah keratarentas dan penilaian kontingen. Kaedah pembahagian dua-tahap dengan teknik pembidaan telah digunakan untuk memperolehi jumlah WTP. Nilai purata WTP dan faktor-faktor yang mempengaruhi nilai WTP ditentukan dengan kaedah parametrik permodalan dua tahap (TPM). Hubungan antara penerimaan vaksin denggi dengan faktor-faktor yang mempengaruhinya dianalisa dengan modal regresi logistik univariat. Dalam kajian fasa-1, keenam-enam program vaksinasi denggi menghasilkan manfaat yang positif dalam aspek pengurangan kes-kes denggi, kematian, kelangsungan hidup terlaras hilang upaya (DALY), dan kos rawatan denggi. Kos keberkesanan vaksin denggi dianalisa dengan pengiraan nilai ambang untuk sangat kos-berkesan (ICER<1x GDP/kapita) dan kos-berkesan (ICER=1–3x GDP/kapita). Kajian mendapati bahawa program pemvaksinasi denggi adalah kos berkesan sehingga harga maksimum US$28.59-87.49 dan sangat kos berkesan

sehingga harga maksimum US$12.60-42.27 dari perspektif pembekal awam. Kos keberkesanan adalah peka terhadap faktor kurang lapor, tempoh perlindungan vaksin, dan tempoh masa model. Vaksinasi rutin untuk orang awam berumur 13 tahun dengan tangkapan di antara golongan orang awam berumur 14–30 tahun di kawasan titik sasaran merupakan program yang paling bernilai. Dalam kajian fasa-2, hasil kajian menunjukkan bahawa 88.4% responden menerima vaksin denggi untuk dewasa. Analisis regresi menunjukkan bahawa penerimaan vaksin dipengaruhi oleh pengetahuan denggi (OR 1.426), sikap terhadap vaksinasi (OR 1.909), dan etnik Cina (OR 0.359). Nilai purata WTP adalah RM83.19 (US$18.80). Anggaran logit daripada TPM menunjukkan bahawa responden yang mempunyai anak, dengan peringkat pendidikan yang tinggi, dan pesara adalah lebih cenderung untuk membayar untuk vaksin denggi. Regresi kedua dalam model TPM menganggarkan nilai WTP yang lebih tinggi dalam kalangan pesara dan responden dengan skor amalan pencegahan denggi yang lebih tinggi. Vaksin denggi adalah pelaburan yang berpotensi tinggi jika pembeli boleh berunding untuk membelinya dengan harga yang kurang daripada nilai ambang kos-berkesan. Vaksin denggi didapati amat diterima oleh orang awam, di mana ia menunjukkan nilai yang tinggi untuk vaksin denggi di Malaysia.

ECONOMIC EVALUATION AND WILLINGNESS TO PAY (WTP) ELICITATION OF DENGUE VACCINE IN MALAYSIA

ABSTRACT

Dengue disease poses great health and economic burden in Malaysia. This study was divided into two phases. Phase-1 evaluated the impact and cost-effectiveness of dengue vaccine employing a dynamic-transmission mathematical model from both public provider and societal perspective. The model integrated Malaysia-specific epidemiological data, pooled efficacy and long-term safety data from phase-III clinical studies, and sensitivity analyses to refine the estimates from previous studies. Phase-2 assessed the acceptance and willingness-to-pay (WTP) value of dengue vaccine among Penang general population utilizing a cross-sectional, contingent-valuation approach. A double-bounded dichotomous-choice approach was applied in eliciting the WTP amount via bidding game method. The mean WTP value and the factors affecting the WTP value were determined by a parametric two-part model (TPM). The association between dengue vaccine acceptance and its determinants was analysed by a univariate logistic regression model. In phase-1 study, all six vaccination programmes produced positive benefits expressed in the reduction in dengue cases, dengue-related-deaths, disability-adjusted-life-years (DALY), and treatment cost. The cost-effectiveness of dengue vaccination was evaluated by calculating the threshold values for highly cost-effective (ICER<1x GDP/capita) and cost-effective (ICER=1–3x GDP/capita). The study found that dengue vaccination is cost-effective up to a price of US$28.59-87.49 and highly cost-effective up to a price of US$12.60-42.27 from provider perspective. The cost-

effectiveness is sensitive to underreporting factor, vaccine protection duration, and model time horizon. Routine vaccination for 13-year-old with catch-up cohort 14–30-year-old in targeted hotspot appeared to be the best-valued programme. In phase-2 study, results showed that 88.4% of the respondents accepted the adult vaccine. The regression analysis showed that the vaccine's acceptance was affected by dengue knowledge (OR 1.426), vaccination attitude (OR 1.909), and Chinese ethnicity (OR 0.359). The mean WTP was RM83.19 (US$18.80). The logit estimation from TPM showed that respondents with children, with higher education level, and pensioners were more likely to pay for the vaccine. The second-stage regression of TPM estimated a significant higher WTP amount from pensioners and respondents with higher household dengue prevention practice score. Dengue vaccination is a potentially good investment if the purchaser could negotiate a price below the cost-effective threshold price. Dengue vaccine is highly acceptable by the public, which indicates its high value among Malaysian.

CHAPTER 1

INTRODUCTION

Dengue disease is the most common arthropod-borne viral illness affecting human population found in major tropical and subtropical areas worldwide. Malaysia has been experiencing a surge of dengue cases in recent years; with 43,346 cases in 2013 that doubled to 111,285 cases in 2015 (World Health Organization, 2016b). However, existing studies have shown that dengue cases in Malaysia could be under-reported (Shepard et al., 2012, Undurraga et al., 2013). Several studies found that the annual economic burden of dengue in Malaysia ranges from US$78 million to US$311 million (Lee Han et al., 2010, Shepard et al., 2012, Shepard et al., 2013a, Shepard, 2013b). WHO Global strategy for dengue prevention and control has identified dengue vaccine implementation as one of the key elements in combating dengue disease (World Health Organization, 2012b). Nevertheless, the potential impact and cost-effectiveness of dengue vaccine have yet to be assessed in Malaysia. A country-specific economic evaluation of a new healthcare intervention is crucial to inform decision making and facilitate its implementation. In addition, the determination of the public's willingness to pay for a hypothetical dengue vaccine explores its potential for selling in the private markets. This would help the public healthcare decision makers as well as vaccine manufacturers to devise strategies in the implementation of vaccination campaign.

1.1 Dengue prevention and control strategy

The WHO Global strategy for dengue prevention and control (2012–2020) (World Health Organization, 2012b) aimed to reduce 50% of the dengue-related mortality and 25% of the morbidity by 2020 . The strategy advocated 5 technical elements:

1) Diagnosis and case management: the implementation of a timely and appropriate clinical management, which involves early clinical and laboratory diagnosis, intravenous rehydration, staff training and hospital reorganization, aims to reduce dengue-related mortality to almost zero.

2) Integrated surveillance and outbreak preparedness: the surveillance system for dengue should be a part of the national health information system. In addition, a harmonized effort across national dengue surveillance systems is needed for to obtain the critical data of the disease's burden. A well-prepared outbreak handling should be based on well-developed contingency plans that are broadly disseminated and thoroughly understood and pre-tested before an epidemic.

3) Sustainable vector control: effective vector control measures are critical to achieving and sustaining reduction of morbidity attributable to dengue. Since the preventive and vector control interventions aim to reduce dengue transmission, thereby decreasing the incidence of the infection and preventing outbreaks of the disease. This element also advised that countries should adopt the integrated vector management approach to vector control as promoted by WHO and define it as a rational decision-making process to optimize the use of resources for vector control. The approach aims to improve efficacy, cost effectiveness, ecological soundness, and sustainability of vector control interventions. Dengue vector control is most amenable to the implementation of the principles of integrated vector management, which ensure judicious use of insecticides in combination with other prevention and control interventions.

4) Future vaccine implementation: the current dengue prevention and control strategies should include vaccines as an essential element to anticipate and prepare for. This includes preparing for future decision-making on vaccine introduction and use,

considering the integration of vaccines with other tools for dengue prevention and control, and investments in surveillance systems and safety monitoring of vaccines.

5) Basic operational and implementation research: this element emphasized the importance of research, and recommended that all party should promote and support the efforts.

1.1.1 Vector control and surveillance

As described above, the second and third elements of the WHO Global strategy for dengue prevention and control (2012–2020) advocate the integrated surveillance and sustainable vector control. However, currently, the only method to control the disease transmission in Malaysia is through active dengue surveillance and vector control interventions, as there are no specific treatment or licensed vaccine in Malaysia to protect against the disease. The Ministry of Health (MOH) Malaysia regards vector control as a gold standard for the prevention of dengue outbreaks although vector control has been shown to be only partially effective in reducing the disease burden (Horstick et al., 2010). Malaysia spent US$73.5 million or 0.03% of the country's GDP on its National Dengue Vector Control Program on year 2010 (Packierisamy et al., 2015). However, vector control effort is often constrained due to the lack of community support and involvement.

1.1.1(a) National Dengue Strategic Plan (NDSP)

In a continuous effort to combat dengue illness, MOH Malaysia has introduced and implemented NDSP in 2011 to enhance the dengue control strategies. The employed strategies include enhancing dengue surveillance, vector control, case and outbreak management, population mobilization and research in innovative dengue control tools

and strategies (Mudin, 2015). Moving forward, NDSP (2015-2020) adopted 7 new strategies to combat dengue including dengue surveillance, national cleanliness policy and integrated vector management, management of dengue cases, social mobilization and communication for dengue, dengue outbreak response, dengue research, and reduction of dengue burden in the Klang Valley (Ministry of Health Malaysia, 2015). In addition, new tool and strategy including residual sprays (a deltamethrin-based insecticide) in hotspot area and vaccination programme have been proposed in the updated NDSP. Deltamethrin is a synthetic compound that is currently used to control pests in agriculture, gardens, and pets. It has a broad-spectrum effect, which means that it would also be effective in killing most species of mosquitoes and other insects.

1.1.2 Dengue vaccine

Element 4 of the WHO Global strategy for dengue prevention and control (2012–2020) advocates the use of dengue vaccine as a tool for dengue prevention. Dengue vaccine appears to be a promising supplementary tool in controlling dengue disease as current dengue prevention strategies are limited to mosquito control. In most settings, such strategies have been proven to be partially effective or difficult to sustain due to the expansion of *A.aegypti* populations, mosquito and virus dispersal through extensive human travel networks, fragile vector control system, insufficient resources, lack of political will, and ineffective implementation of existing tools and strategies (Horstick et al., 2010, Reiner et al., 2016). At individual level, dengue vaccine could be beneficial to reduce the probability of infection after bitten by an infected mosquito, thus reducing the probability of severe disease or the probability to transmit the virus to a mosquito to bite him/her. On the other hand, at population level, dengue vaccine could reduce the overall transmission, thus providing herd immunity even to

unvaccinated people. WHO Global strategy for dengue prevention and control has identified dengue vaccine implementation as one of the five technical elements in combating dengue disease (World Health Organization, 2012b).

Ideally, a successful dengue vaccine should be minimally reactogenic and elicit strong, balanced and durable immune responses simultaneously to all 4 DENV serotypes upon one or two administrations. However, in reality, some or all these ideals could not be met due to immune enhancement and vaccine induced antibodies may predispose recipients to severe disease in the case of imbalanced responses against the four serotypes. As dengue is a human disease, the absence of satisfactory dengue animal disease model further complicates the study of the dengue pathogenesis and the immune response to the vaccine. Furthermore, the difficulties in the design and conduct of the dengue efficacy studies present challenges to the vaccine development (Wallace et al., 2013).

1.1.2(a) Dengue vaccine development

The first dengue vaccine, Sanofi Pasteur tetravalent chimeric yellow-fever dengue (CYD-TDV or Dengvaxia®) vaccine, was licensed in Mexico in December 2015 and subsequently registered in 4 countries including the Philippines, Brazil, El Salvador, and Costa Rica. Dengvaxia® uses the yellow fever 17D vaccine as its backbone as the live, attenuated yellow fever 17D vaccine was previously deemed to be the world's safest and the model for the development of other live virus vaccines including polio, measles, mumps and varicella. As such, live vaccines against other flaviviruses, such as Japanese encephalitis virus, West Nile virus, and dengue viruses, based on the yellow fever 17D virus vaccine began to be developed (Monath et al., 2015). At least

eight other countries in Asia and Latin America including Singapore, Malaysia, Thailand and Indonesia are actively considering its licensure (Pang, 2016).

Dengvaxia® is licensed in individuals age 9-45 years living in endemic areas administered on a 0/6/12-month schedule. The safety and efficacy of CYD-TDV has been evaluated in 2 parallel Phase 3 randomized clinical trials, i.e. CYD14 and CYD 15. CYD 14 was conducted at sites in 5 countries in Asia (Indonesia, Malaysia, Philippines, Thailand and Vietnam) with 10,275 participants aged 2-14 years at first vaccination while CYD 15 was conducted at sites in 5 countries in Latin America (Brazil, Colombia, Honduras, Mexico and Puerto Rico) (Capeding et al., Villar et al., 2015).

The recent review states that the pooled vaccine efficacy against symptomatic virologically-confirmed dengue (VCD) of any serotype in the year starting 1 month after the third dose was 59.2% (95%CI 52.3 – 65.0) (Hadinegoro et al., 2015). Vaccine efficacy was found to be higher against DENV-3 (71.6%) and DENV-4 (76.9%) than against DENV-1 (54.7%) and DENV-2 (43.0%). Pooled vaccine efficacy for symptomatic dengue during the first 25 months were 60.3% (95% CI, 55.7 to 64.5) for all participants. Surprisingly, the efficacy for those 9 years of age or older were higher (65.6%) than for those younger than 9 years of age (44.6%). The results of long-term safety follow up showed an unexplained increased risk of hospitalization and severe dengue among participants younger than 9 years old in the third year after receipt of the first dose (RR = 7.45, 95% CI 1.15, 313.80), though this is dissipated in year 4 and 5. The biologic mechanism behind this increased risk is currently not understood but may be related to naïve vaccine serostatus and/or age.

Nevertheless, a lower risk of hospitalization was observed among children between the ages of 9 and 16 years compared to control group for up to 2 years after

completion of the three-dose vaccination schedule. There was no other safety signal has been identified.

Dengue vaccine candidates in phase III and phase II clinical trials

Several other dengue vaccine candidates are currently undergoing various phases of rapid development, including the 2 most advanced candidates (Takeda's DENVax-TDV and Butantan Institute's TetraVax-DV-TV003) which are under evaluation in Phase 3 trials. The properties of these vaccine candidates are summarized in Table 1.1. TV003 and TV005 developed by the US National Institutes of Health (NIH) are based on wild-type strains with genetic mutations to attenuate the virus (Schwartz et al., 2015). Both the vaccines have been licensed to several manufacturers, including Butantan, VaBiotech, and Merck. Phase 2 studies are currently ongoing in Brazil and Thailand, and a Phase 3 trial led by Butantan began in February 2016 (Whitehead, 2016, Butantan Institute).

TDV developed by Takeda is also a tetravalent live recombinant vaccine with a wildtype DEN2 strain attenuated in primary dog kidney cells and further attenuated by mutation in NS3 gene with whole virus DENV2 and recombinant DENV1/3/4 in DENV2 backbone (Schwartz et al., 2015). Various ongoing and completed Phase 1 and Phase 2 trials have evaluated the variation of the 2 doses formulations and routes of administration (George et al., 2015, Osorio et al., Rupp et al., 2015). An ongoing Phase 3 trial has being carried out since April 2016 (Takeda).

Dengue vaccine candidates in phase I clinical trials and pre-clinical development

There are 4 candidates currently under development in Phase 1 trial (Table 1.1) including a tetravalent purified-inactivated vaccine by GSK (Martinez et al., 2015), a

tetravalent recombinant subunit vaccine based on the dengue wild-type pre-membrane and truncated envelope protein by Merck (Coller et al., 2011, Govindarajan et al., 2015), a monovalent plasmid DNA vaccine by US Navy Medical Research Center (NMRC) (Beckett et al., 2011), and an inactivated vaccine/live attenuated vaccine heterologous prime boost by Walter Reed Army Institute of Research (WRAIR) (U.S. Army Medical Research and Materiel Command).

There are currently 16 vaccines undergoing rapid pre-clinical development (Vannice et al., 2016) (Table 1.1) including 3 recombinant subunit vaccines, a tetravalent DNA vaccine, a virus-like particles (VLP) vaccine, 2 virus-vectored vaccines, 3 tetravalent purified-inactivated virus vaccines, 4 live-attenuated virus vaccines, a heterologous prime-boost and a simultaneously administered vaccine.

Table 1.1: Dengue vaccines currently available or undergoing rapid clinical development

Vaccine Candidate	Developer	Vaccine Type	Mechanism of attenuation or inactivation	Status	References
Dengvaxia ®	Sanofi Pasteur	Tetravalent live recombinant/attenuated	Yellow fever 17D vaccine backbone, pre-membrane and envelope proteins from wildtype dengue virus	Completed Phase III, and registered in 10 countries	(Vannice et al., 2016, Schwartz et al., 2015)
TetraVax-DV-TV003/TV005	US NIH and Butantan Institute	Tetravalent live recombinant/attenuated	Wildtype strains with genetic mutations to attenuate the virus. DENV1, 3, and 4 are based on whole virus whereas DENV 2 is recombined in DENV4 backbone	Phase III	(Vannice et al., 2016, Butantan Institute, Schwartz et al., 2015)
TDV (Formerly DENVax)	Takeda	Tetravalent live recombinant/attenuated	Wildtype DEN2 strain attenuated in primary dog kidney cells and further attenuated by mutation in NS3 gene with whole virus DENV2 and recombinant DENV1/3/4 in DENV2 backbone	Phase III	(Vannice et al., 2016, Takeda, Schwartz et al., 2015)
TDENV PIV	GSK, U.S. WRAIR and Fiocruz	Tetravalent purified inactivated	Non-attenuated viruses of the 4 virus strains (DENV-1 to DENV-4), propagated in Vero cells, purified, and inactivated with formalin	Phase I	(Vannice et al., 2016, U.S. Army Medical Research and Materiel Command, Schwartz et al., 2015, Martinez et al., 2015)
DEN-80E	Merck	Tetravalent recombinant subunit	Wildtype pre-membrane and truncated envelope protein via expression in the Drosophila S2 cell expression system	Phase I	(Vannice et al., 2016, Schwartz et al., 2015, Coller et al., 2011, Govindarajan et al., 2015)
D1ME100	US NMRC	Tetravalent DNA	Pre-membrane and envelope proteins of DENV1 are expressed under control of the human cytomegalovirus promoter/enhancer of the plasmid vector VR1012	Phase I	(Vannice et al., 2016, Schwartz et al., 2015, Beckett et al., 2011)
TLAV-TPIV	U.S. WRAIR	Tetravalent live attenuated/purified inactivated	Heterologous prime-boost with live attenuated tetravalent, live attenuated vaccine and tetravalent alum-adjuvanted purified inactivated vaccine	Phase I	(Vannice et al., 2016, U.S. Army Medical Research and Materiel Command)

Table 1.1-1 continued: Dengue vaccines currently available or undergoing rapid clinical development

Vaccine Candidate	Developer	Vaccine Type	Mechanism of attenuation or inactivation	Status	References
DIII-C	IPK/CIGB	Recombinant subunit	EDIII-p64k fusion proteins and EDIII-capsid fusion proteins expressed in E. coli	Pre-clinical	(Vannice et al., 2016)
-	VaxInnate	Recombinant subunit	Bivalent 80E-STF2 fusion proteins expressed in baculovirus/insect cells	Pre-clinical	
-	NHRI	Recombinant subunit	Tetravalent consensus EDIII protein expressed in E. coli	Pre-clinical	
-	US CDC	Tetravalent DNA	prM/E expressed from plasmid vector DNA vaccine	Pre-clinical	
-	ICGEB	VLP	EDIII-HBsAg VLPs or ectoE-based VLPs expressed in P. pastoris	Pre-clinical	
-	Themis Bioscience/ Institute Pasteur	Virus-vectored	Tetravalent EDIII and DENV-1 ectoM expressed from live-attenuated measles virus vector	Pre-clinical	
-	Global Vaccines	Virus-vectored	E85 expressed from single-cycle VEE virus vector	Pre-clinical	
-	US NMRC	Purified inactivated	Psoralen-inactivated DENV	Pre-clinical	
-	FIOCRUZ	Purified inactivated	Purified inactivated DENV	Pre-clinical	
-	Global Vaccines	Purified inactivated	Inactivated virus (+VEE-particle adjuvant)	Pre-clinical	

Table 1.1-2 continued: Dengue vaccines currently available or undergoing rapid clinical development

Vaccine Candidate	Developer	Vaccine Type	Mechanism of attenuation or inactivation	Status	References
-	Chiang Mai University, Mahidol University, NSTDA and BioNet-Asia	Live attenuated	DEN/DEN chimeric viruses, live, attenuated	Pre-clinical	(Vannice et al., 2016)
-	Arbovax	Live attenuated	DEN host range mutations, live, attenuated	Pre-clinical	
-	Beijing Institute	Live attenuated	DEN-SA 14 14 2, live, attenuated	Pre-clinical	
-	Novartis Institute for Tropical Diseases/ Agency for Science, Technology and Research, Singapore	Live attenuated	DEN targeted mutation (2′-O-methyltransferase mutant), live, attenuated	Pre-clinical	
-	NMRC/WRAIR	Heterologous prime-boost	Plasmid vector expressing prM/E (prime) and live attenuated DENV (boost)	Pre-clinical	
-	FIOCRUZ	Simultaneous administration	DENV prM/E expressed from live attenuated chimeric YF 17D/DEN virus with DNA vaccine	Pre-clinical	

1.1.3 Health education and community campaign

Primary prevention of dengue disease is a very important objective in combating the virus transmission. The strategy in primary prevention mainly revolves around health education and active participation from the community. Various studies have highlighted the importance of community health education and campaigns in vector reducing strategy. The health education and community-based dengue control approach were found to be at least as effective or cost-effective as chemicals larvicides (Espinoza-Gómez et al., 2002, Baly et al., 2009, Sanchez et al., 2009).

The WHO, in its Handbook for Integrated Vector Management (IVM) (World Health Organization, 2012c), recommends the frequent communication with the general public to create awareness. This will drive behavioural change and empower people to become involved in the analysis and decision-making and adopt good dengue prevention practices. Among the tools advocated in the WHO-IVM handbook for reaching the public include the media, educational interventions, communication and farmer field schools to increase knowledge and skills. In the other hand, the WHO also developed the Communication for Behavioural Impact (COMBI) programme to promote communication, advocacy and social mobilisation in neighbourhoods, educational and workplace settings (World Health Organization and UNICEF, 2012). COMBI emphasises the role of knowledge, attitude and practice (KAP) surveys in recognizing key barriers to favourable behaviours regarding dengue.

Nevertheless, existing literatures on KAP among Malaysian show mixed results and conclusions. Aung et al found 54.6% of the rural Terengganu population had good dengue-related knowledge and 91.7% performed good practices against dengue infection (Aung et al. 2016). However, only 18.6% of them had good attitude against dengue infection. In contrast, Al-Zurfi et al found that majority of the students

from Shah Alam high school had good knowledge and attitude but only 26% of them performed good practice against dengue infection (Al-Zurfi et al., 2015).

1.2 Epidemiology of dengue disease

The World Health Organization (WHO) reported a 30-fold increase in annual dengue cases in the last 50 years with a mortality rate of 2.5% among severe dengue cases. Approximately 3.9 billion people globally are at risk, with 390 million infections occurring annually, and 68% of cases occurring in Asia (Bhatt et al., 2013). Malaysia has been experiencing a surge of dengue cases in recent years; with 43,346 cases in 2013 that doubled to 111,285 cases in 2015 (World Health Organization, 2016b). Local epidemiology study found that states in west peninsular Malaysia are most affected by dengue, with dengue hotspot concentrated in Klang Valley, Kelantan, Penang, and Hulu Langat (Hii et al., 2016). Nevertheless, existing studies have shown that dengue cases in Malaysia could be under-reported (Shepard et al., 2012, Undurraga et al., 2013).

Dengue is mainly caused by dengue viruses transmitted by female *Aedes aegypti* mosquitoes and to a lesser extent *Aedes albopictus* and *Aedes polynesiensis* (Halstead, 2007). The dengue transmission dynamics are influenced by multiple complex risk factors including host immunity, vector capacity, circulating dengue virus serotypes, weather or climate, dengue control capacity, increasing urbanization and population movement (Ooi and Gubler, 2009, Hii et al., 2016). There are currently 4 known dengue virus serotypes which are antigenically distinct but immunologically closely related; namely DENV-1, DENV-2, DENV-3 and DENV-4 (World Health Organization, 2009). Early studies have shown that Malaysia is dengue hyper-endemic, with all four serotypes circulating concurrently and with an abundance of

both *Aedes aegypti* and *Aedes albopictus* (Chen et al., 2006, Chew et al., 2012). Over the past few decades, major dengue outbreaks occurred in a cyclical pattern of approximately 8 years, involving mainly DENV-1, DENV-2, and DENV-3 serotypes (Hii et al., 2016).

Dengue exhibits a broad spectrum of clinical manifestation and its clinical evolution and outcome are often unpredictable. There are currently 3 known manifestation of dengue; namely dengue fever (DF), dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) (World Health Organization, 2009). DF and DHF are identified as the major cause of mortality and morbidity in tropical and subtropical countries (Gubler, 1998). Fatality rate of DHF can be as high as more than 20% without proper facility or treatment, however, if adequately treated, it could be reduced to less than 1% (World Health Organization, 2015). On the other hand, DSS accounts for more than 72% of common cause of death in dengue patients in Malaysia (2013-2014), followed by severe organ dysfunction (69%) and severe bleeding (29.7%) (Woon et al., 2016). Dengue case fatality rate (CFR) was found to be relatively constant at 0.2-0.3% although the number of death due to dengue disease increases from 45 to 134 from year 2000 to 2010. However, it was also found that there was an unusual spike of CFR in 2000 (0.63%) (Mohd-Zaki et al., 2014).

1.3 Health and economic burden of dengue disease

The social and economic impact concerning dengue disease is relatively high, thus, quantifying its health and economic burden is crucial for decision makers to prioritize policy setting and to form strategic control implementation based on informed decisions about the disease.

Suaya et al presented the first multicounty estimate of the direct and indirect cost of dengue cases in 8 countries across America and Asia including Malaysia. The total estimated average annual dengue cases were 574,000 for these 8 countries during 2001–2005. The estimated total economic burden associated with dengue was US$238 million, with Brazil and Thailand responsible for 94% and 60% of the aggregate cost in the American and Asian study countries, respectively. The estimated average annual dengue cases and deaths for Malaysia over the study period were 31,000 and 86, respectively. The estimated economic burden of dengue in Malaysia totalled up to US$38.2 million annually (Suaya et al., 2009). Nevertheless, subsequent studies found that the annual economic burden of dengue in Malaysia ranges from US$78 million to US$311 million with annual 143,891 dengue cases and 162 deaths (Lee Han et al., 2010, Shepard et al., 2012, Shepard et al., 2013a, Shepard, 2013b).

1.4 Problem statement

The huge dengue disease economic and health burden in Malaysia poses a growing challenge to both the public health officials as well as the policymakers. Success in tackling this global threat is contingent on strengthening the evidence base on which control planning decisions and their impact are evaluated (Bhatt et al., 2013).

The newly introduced dengue vaccine marks a new era in the humankind long battling with dengue disease. Dengue vaccine has been perceived as a promising solution for combating dengue, in view with the rising tide of dengue fever and its associated morbidities and mortalities. Furthermore, the vector control has not shown effective results in the prevention of dengue virus transmission, probably due to operational constraints as well as the inherent weakness in the programme delivery method (Shepard et al., 2004).

Nevertheless, the potential impact and cost-effectiveness of dengue vaccine have yet to be assessed in Malaysia. At present, there is no clear decision framework on the uptake of new healthcare interventions in the country. Therefore, the issue of arbitrariness consideration might arise which will in turn affect the consistency and effectiveness of the decision. A country-specific economic evaluation of a new healthcare intervention is crucial to inform decision making. Therefore, the evaluation of the Malaysia-specific dengue vaccination impact, cost-effectiveness, and acceptance is crucial to inform decision making and facilitate its implementation. In addition, the determination of the public's willingness to pay for a hypothetical dengue vaccine explores its potential for selling in the private markets. This would help the public healthcare decision makers as well as vaccine manufacturers to devise strategies in the implementation of vaccination campaign.

1.5 Study objectives

Main objective: To evaluate the potential cost-effectiveness and to elicit the willingness-to-pay (WTP) value of dengue vaccine in Malaysia.

Specific objective:

1) To determine the potential health impact (dengue cases, dengue related deaths, life year lost and disability-adjusted-life-year) and economic impact (ambulatory dengue disease cost, hospitalized dengue disease cost, and productivity loss due to dengue disease) of dengue vaccination from both public provider and societal perspectives in Malaysia.
2) To estimate the cost-effective threshold value of dengue vaccine in Malaysia employing cost-utility and cost-effectiveness analysis from both public provider and societal perspectives in Malaysia.
3) To evaluate the acceptance of the hypothetical dengue vaccines among the general population in Penang state, Malaysia.
4) To determine the willingness-to-pay (WTP), estimate the WTP values and evaluate the factors affecting the WTP towards the hypothetical dengue vaccines among the general population in Penang state, Malaysia.

1.6 Significance of the study

This study serves as the first empirical estimates of dengue vaccine's impact, cost-effective threshold value, and willingness-to-pay value in Malaysia. It acts as a valuable piece of evidence for the stakeholder and policy makers in the decision making when considering the integration of dengue vaccine into the National Dengue Strategic Plan (NDSP). This study also provides vaccine manufacturers a better picture of Malaysian's perceptions of dengue fever and dengue vaccines which would assist them in the proper planning of the marketing strategies.

CHAPTER 2

LITERATURE REVIEW

The objective of this review is to review the state of the art for economic evaluation evidences of dengue vaccines focusing on the cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and willingness-to-pay (WTP). In addition, the relationship between acceptance and WTP towards dengue vaccine, dengue disease knowledge, dengue prevention practice, and vaccination attitude will also be reviewed.

2.1 Conceptual framework of economic evaluation

The conventional approach for a systematic comparison of cost and effects of health-care interventions is through economic evaluation. CEA is a type of economic evaluation that involves the measurement of health effectiveness by natural units of health (number of cases/death averted) of an intervention in relative to cost. Though the measures of effectiveness by natural units might be helpful in comparing the effectiveness of different treatment, they lack the flexibility to compare across different programmes or diseases. CUA is a subset of CEA that utilizes composite index of health (reduction in Disability-Adjusted-Life-Year (DALY)/increase in Quality-Adjusted-Life-Year (QALY)) as a measurement of effectiveness (Drummond et al., 2005).

Results of CEA and CUA are commonly summarized in Incremental Cost-Effectiveness Ratio (ICER). ICER is a ratio calculated by dividing the incremental cost (the difference in cost) to the incremental effects (the difference in effects) between two alternatives (Berger et al., 2003). The numerator (cost) in ICER is expressed as monetary unit whereas the denominator (effect) is expressed in appropriate health

units. For example, life-year-lost (LYL) or death averted in CEA whereas QALY or DALY in CUA (Drummond et al., 2005). In short, ICER measures the additional cost per unit of health benefits gained in comparison between 2 interventions. The ICER formula is shown below:

$$ICER = \frac{Cost\ of\ Intervention\ A - Cost\ of\ Intervention\ B}{Effect\ of\ Intervention\ A - Effect\ of\ Intervention\ B}$$

QALY and DALY are universal health outcome measure used to quantify the impact of both changes in quality of life (morbidity) and quantity of life (mortality) in a single unit of measurement (Berger et al., 2003). QALY is a function of health-related quality of life weight attached to the relevant year of life. Therefore, it is used primarily to correct someone's life expectancy based on the levels of health-related quality of life predicted to experience throughout the course or part of their life (Drummond et al., 2005). On the other hand, DALY is a function of disability-related quality of life weight attached to the relevant year of life, calculated by the summation of years of life lost (YLL) due to premature mortality and years lived with disability (YLD) due to disease incidence (Drummond et al., 2005). A higher DALY score signifies a worst health. DALY is primarily a measure of disease burden incorporating the disability weight and was first introduced and applied in the 1990 Global Burden of Disease study (Salomon et al., 2013).

The measurement of dengue disease burden using DALY was reported differently in different studies due to several factors. Firstly, in early studies, the DALY calculation only considered the DHF incidence and excluded the less severe DF; which leads to the underestimation of dengue cases by 2 to 10-fold (Beatty et al., 2011). Second factor is the inconsistency in the application of disability scores and

duration of illness. Some early studies applied a very low disability scores (0.172 to 0.211) and long duration of illness (30 days) (Beatty et al., 2011). In view of this, WHO revised the dengue disease burden estimates in 2004, where the disability score for DHF was increased to 0.5 but the duration of illness was shortened to 11 days. Furthermore, DF was included in the new estimates, with an assigned disability score of 0.211 and duration of illness of 5.5 days (Mathers et al., 2008).

Economic evaluation has become an important tool for health policy decisions making for healthcare providers, payers and planners in evaluating the value for healthcare expenditure. In healthcare budget allocation, reimbursement decisions in vaccination are often weighted against other preventive and therapeutic interventions due to scarcity of health care budgets. This situation is especially common in low-and-middle income countries (LMIC) which comprise almost 80% of the world population (Burchett et al., 2012). The design of economic evaluation before a vaccine has been fully introduced requires assumptions about variables such as efficacy, effectiveness, safety, dosage and costs. Furthermore, healthcare policy makers should consider country-specific demographic, epidemiological, clinical, and economic data in the modelling approaches to simulate disease transmission dynamics.

2.1.1 Economic evaluation using decision-analytic modelling

Decision-analytic modelling offers a framework for decision-making under conditions of uncertainty. Specifically, it defines a set of mathematical relationship between entities characterizing the range of possible disease prognoses and the impacts of alternative interventions (Drummond et al., 2015). Several types of model are used for economic evaluation, including decision tree, Markov, discrete event simulation and dynamic transmission models. Identifying an appropriate model type is a very crucial

stage in the decision modelling process. The decision to select a model in a study should depend on the overall objective of the economic evaluation, the nature of the disease process, and impacts of the interventions (Drummond et al., 2015). In the context of selecting an appropriate model to represent the dengue disease process in this study, 2 models will be discussed in this review, i.e. the Markov model and the dynamic transmission model.

Markov models are based on a series of "states" that a patient can occupy at a given point in time. Time elapses explicitly with a Markov model, with the probability of a patient occupying a given state assessed over a series of discrete time periods, called "cycles". The length of each cycle will depend on the disease and interventions being evaluated. The speed with which patients move between the states in the model is determined by a set of transition probabilities. Each state in the model generally has a cost and an outcome associated with it. The costs and values of each Markov state are weighted by the time a patient spends in that state. This is made up of 2 stages. Stage 1 calculates the probability of a patient being in each state for each cycle; stage 2 calculates the expected costs and effects. A cohort simulation is undertaken for each option being evaluated (Drummond et al., 2015). Markov model assumes that the individual being modelled are independent from each other with respect to their health. This independence assumption may be untenable in the context of infectious disease where the incidence of new infections depends on the existing number of individuals who are infected. Furthermore, the incidence of an infection changes dynamically during an epidemic. Therefore, models relating to infectious diseases may need to consider a dynamic transmission model (Drummond et al., 2015).

The transmissible nature of infectious diseases is what sets them apart from other disease models. The probability of a susceptible individual becoming infected at

any one point in time (the force of infection) is related to the number of infectious individuals in the population, will change over time, and will feed back into the future force of infection. These nonlinear interactions produce transmission dynamics that require specific consideration when modelling an intervention that has an impact on the transmission of a pathogen. Dynamic transmission models can reproduce the direct and indirect effects (individuals not reached by the program can still benefit by experiencing a lower infection risk) that may arise from a communicable disease control program (Pitman et al., 2012).

A dynamic transmission model can be deterministic or stochastic. Deterministic models, in which every state variable is uniquely determined by the parameter values and previous state-variable values, always give the same results for the same starting conditions and parameter values. They approximate a system's average behaviour and are most appropriate when all subgroups are large. They are comparatively easy to fit to data and thus are easier to calibrate. In a stochastic model, the state variables are described by probability distributions, incorporating the role of chance. This often occurs in small populations or when a subgroup is small (e.g. at an epidemic's beginning or ends) that is, when local extinction is likely (Pitman et al., 2012).

2.1.2 Comparative modelling of dengue vaccine public health impact (CMDVI)

The WHO initiated the “Comparative modelling of dengue vaccine public health impact” (CMDVI) consortium (World Health Organization, 2016a) in April 2015 to develop model based predictions of the long-term safety, health and economic impact of Dengvaxia®, and to inform recommendations to the WHO Strategic Advisory Group of Experts on Immunization (WHO-SAGE). Any group that has a dynamic

transmission model of dengue vaccination that had been used to examine the potential public health impact of vaccination and where results and key features have been documented (in either a peer reviewed journal article, or an unpublished technical documentation to the standard of a journal article) was invited to join.

Four out of eight of the models in the evaluation were stochastic simulation models (University of Florida, University of Western Australia, University of Notre Dame, and Exeter University/Oxford University) while the other four were deterministic compartmental models (Sanofi Pasteur, Johns Hopkins University/University of Florida, Imperial College, and Duke University). All the models mentioned above have been described in detail in their respective publications (Nagao and Koelle, 2008, Lourenço and Recker, 2013, Rodriguez-Barraquer et al., 2014, Rodriguez-Barraquer et al., 2013, Coudeville et al., 2015, Hladish et al., 2016, Karl et al., 2014).

CMDVI found that all models predicted a routine vaccination of children age 9 years old with Dengvaxia® at 80% vaccine coverage would reduce dengue disease in moderate to high transmission intensity settings (i.e. where seroprevalence of children age 9 years old more than 50%). The reduction in dengue-related hospitalization was highest in high transmission intensity settings (i.e. where seroprevalence of children age 9 years old more than 70%). Besides, all the models predicted that the optimal age for routine vaccination decreased as the transmission intensity increased.

All models measured the health effects in terms of DALY. The cost-effectiveness evaluation revealed that vaccination will only be cost-effective if the total cost of full vaccination per person is below US$40 from the public payer