Vaccine coverage and the cost effectiveness of dengue vaccine in South East Asia

Sittisede Polwiang

Background: Dengue is one of the most important vector-borne diseases, nearly 400000 reported cases in South East Asia and more than 2000 fatalities annually. The first of dengue vaccine called Dengvaxia by the French company, Sanofi Pasteur, was recently approved in Mexico, Brazil and the Philippines to be used for persons who are 9-45 years of age.

Objective: The objective of this study was to estimate the effective of a vaccine to dengue transmission and the cost-effectiveness of the vaccine in South East Asia (SEA).

Methods: The simulation and analysis was carried out using a mathematical model for dengue transmission. The vaccine was given to a certain part of population in the community and the number of dengue infections and incidences was then calculated. The cost effective price of the vaccine was measured as disability adjusted life years (DALYs) averted, and the incremental cost-effectiveness ratio (ICER) of the vaccination was expressed in 2015 US dollars per DALY averted for the countries in SEA.

Results: The herd immunity was observed in the model simulation. The number of dengue incidences was declined with increased vaccine coverage in the community. If a vaccination program would be implemented the highly cost effective of vaccine per person should be 25-28 US dollars in SEA country on the average.

Conclusions: Our results describe effects of the dengue vaccination to infections and incidences. The price of the vaccine has been calculated and and it is different in each SEA country due to several factors such as the number of incidences, the GDP per capita, the hospital costs and the DALYs.

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Vaccine coverage and the cost effective of Dengue vaccine in South East Asia

Sittisede Polwiang[1,2]

[1]**Department of Mathematics, Faculty of Science, Silpakorn University, Thailand**

[2]**Centre of excellence in mathematics, Thailand**

ABSTRACT

Background : Dengue is one of the most important vector-borne diseases, nearly 400000 reported cases in South East Asia and more than 2000 fatalities annually. The first of dengue vaccine called Dengvaxia by the French company, Sanofi Pasteur, was recently approved in Mexico, Brazil and the Philippines to be used for persons who are 9-45 years of age.

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Keywords: Dengue; Cost effectiveness; Mathematical model; Vaccination

INTRODUCTION

The Dengue Fever (DF) is the most frequent mosquito-borne viral disease in humans and it has become a major international public health concern in recent decades. The disease can develop to a life-threatening syndrome called Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Nearly 400000 cases and 2000 deaths annually have been reported in South East Asia (SEA). The dengue fever is caused by one of the four distinct serotypes of dengue virus (DENV), DENV1-4 (World Health Organization, 2014). For the dengue virus, the infection is transmitted through an intermediate vector, the infected mosquitoes. The primary vector of DENV is *Aedes aegypti* and the secondary is *Aedes albopictus*. Only the female mosquito bite to extract blood in order to gain energy for egg laying (Centers for Disease Control and Prevention, 2014). Infection with one serotype appears to provide life-long immunity against reinfection with that particular serotype but not against the others. The first infection is normally asymptomatic or has only mild symptoms. Severe diseases including DHF and DSS is mostly occur to individuals who have already recovered from the first infection and are experiencing reinfection with a different serotype (Murrell et al., 2011). Dengue fever poses a heavy economic burden to the health system in a society. Among hospitalized patients, students lost 5.6 days of school and adults lost 9.9 working days per average dengue episode (Suaya et al., 2009) and over 600 millions US dollars were spend on dengue related issues in SEA (Shepard et al., 2013).

Vaccination is generally known as one of the most effective methods to reduce and control the spread of infectious diseases. Dengue vaccines have been under development for decades but they have been successful only recently. In late 2015, the first dengue vaccine, Dengvaxia, introduced by a French company, Sanofi Pasteur, was approved in Brazil, Mexico, and the Philippines (White, 2016; Sanofi Pasteur, 2015). It is a live recombinant tetravalent dengue vaccine that has been administrated as a 3-dose series on a 6 months interval for each dose. Over 40000 volunteers in 15 countries around the world participated in the dengue vaccine clinical study programme (Phase I, II and III). Of these volunteers, 29000 received the vaccine. Dengvaxia was shown to reduce dengue in all four serotypes in 65.6% of the participants and prevent 80.8% hospitalisations and up to 93.2% of severe dengue cases and 92.9% against the DHF (Guy and Jackson, 2016). The vaccine has been approved for use in individuals 9-45 years of age and live in endemic areas. Therefore only a certain part of the population can receive

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Dengvaxia. The World Health Organization (WHO) has called for development of a dengue vaccine as an essential part of the integrated dengue prevention effort needed to significantly lower the dengue burden and dengue fatalities globally before 2020.

For vaccination strategies, the questions arise as to what proportion of the population must be successfully vaccinated and what should the appropriate price of the vaccine in order that cost-effective.

Several mathematical models have been developed to investigate dengue transmission dynamics. We used a specific dengue transmission model to estimate the efficiency of the vaccine coverage for optimal vaccine allocation. The vaccine is given to a certain part of the population in the community and its effects on infection and hospitalization. Also another aim of this study was to estimate the cost-effectiveness of the dengue vaccine in SEA countries.

THEORY AND MODEL

The general concept of the dengue transmission model is that the dengue fever is caused by one of the four serotypes DENV 1-4. Infection with one of the serotypes prevents reinfection by the same serotype but not by the others. Mosquitoes contribute the medium vector for dengue fever. Disease cannot spread from human to human or from mosquito to mosquito directly.

Most of the theory about disease evolution is based on the assumption that the host population is homogeneous. Individual hosts, however, may differ and they may constitute very different persons. In particular, some persons may be more vulnerable to virus infection. The use of mathematical models with imperfect vaccines can describe better this type of human heterogeneity.

The dengue infection can be classified into two categories:

Primary infection

The primary infection or the first time infection with dengue virus has only asymptomatic symptoms or mild fever and medical attention is generally not required. After recovery form the infection, the life-long immunity for that serotype is developed in the body (Screaton et al., 2015).

Secondary infection

The secondary infection means infection by a second serotype. According to the ADE hypothesis, this usually entails larger pain and risk due to DHF and DSS. Most of the severe or hospital

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incidences are caused by the secondary infection (Matheus et al., 2005).

The model

The model in this study is modified from the dengue transmission with multiple serotypes and the secondary infection model by Lee (2015). For simplicity, the role of the climate is ignored in this study. The parameter values correspond to the temperature 28.7°C, which is the most suitable temperature for dengue transmission (Liu-Helmersson et al., 2014; Polwiang, 2015). See Table 1 for description. In Figure 1, i and j represent serotype 1 to 4 of the dengue virus (DENV 1-4). Figure 1 illustrates the flow of population in this model. i is the primary infection with Dengue virus serotype i (DENV i) and j is the secondary infection with Dengue virus serotype j (DENV j). The human population is divided into two categories, non-vaccinated

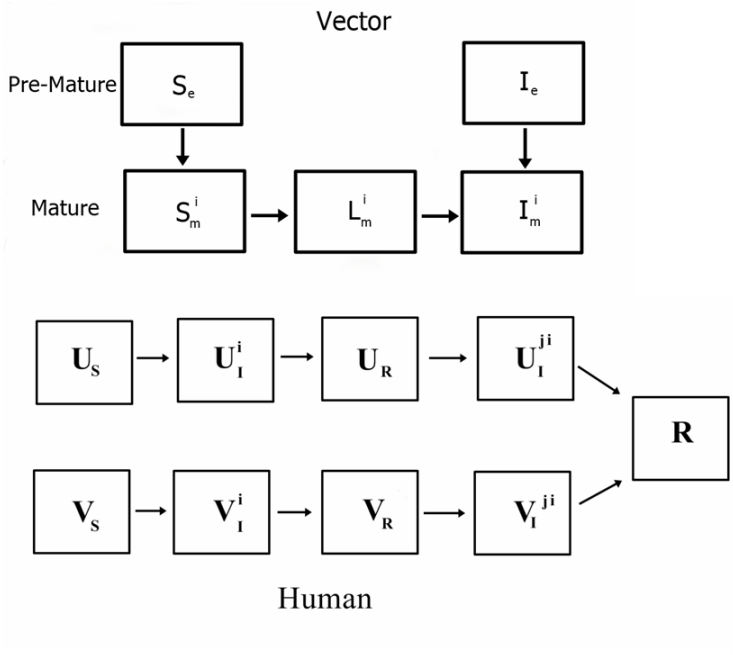

Figure 1. Diagram of the model for mosquito (S, L, I) and human (U, V) population, i is indicate the number of serotype of primary infection and j is serotype number of secondary infection. Note that $j \neq i$. There is no interchange between vaccine, V, and non vaccine, U, population and mosquito is infected with only one serotype.

(U) and vaccinated members (V). Each category is divided into susceptible (U_S, V_S), primary infected with i serotype (U_I^i, V_I^i), recovery from primary infection (U_R^i, V_R^i), secondary infected with j serotype (U_I^{ji}, V_I^{ji}), and full recovery (R). The third and fourth infections are very rare,

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so we assumed that individuals recovered from the secondary infection become immune to all serotypes.

The total human population is $N = U_S + V_S + U_I^i + V_I^i + U_R^i + V_R^i + U_I^{ji} + V_I^{ji} + R$. We investigate the dengue transmission in the population of 100000 people. The non vaccine population compartment, U, are as follows:

$$\begin{aligned}
\frac{dU_S}{dt} &= \lambda N - \sum_{i=1}^{4} \frac{bb_h I_M^i U_S}{N} - \mu_h U_S \\
\frac{dU_I^i}{dt} &= \frac{bb_h I_M^i U_S}{N} - (\mu_h + r_1) U_I^i \\
\frac{dU_R^i}{dt} &= r_1 U_I^i - \sum_{j \neq i} \frac{bb_h I_M^j U_R^i}{N} - \mu_h U_R^i \\
\frac{dU_I^j}{dt} &= \frac{bb_h I_M^j U_R^i}{N} - (\mu_h + r_2) U_I^j \\
\frac{dR}{dt} &= (1 - \mu_d) r_2 U_I^j - \mu_h R
\end{aligned}$$

The vaccine compartment, V, is based on the imperfect random mass vaccination (Rodrigues et al., 2014). We assume that the vaccine is full function for the vaccine population and ignore the infection during the vaccination process to evaluate the effect of the vaccine coverage. In this study, the vaccine is not administrated to new born children. The vaccine infection rate, v, refers to the infection rate of vaccinated individuals. When $v = 0$, the vaccine works perfectly and when $v = 1$, the vaccine is not effective at all and it is assumed that v is identical for all serotypes. We have the differential equations for vaccine compartment as follows:

$$\begin{aligned}
\frac{dV_S}{dt} &= -\sum_{i=1}^{4} \frac{vbb_h I_M^i V_S}{N} - \mu_h V_S \\
\frac{dV_I^i}{dt} &= \frac{vbb_h I_M^i V_S}{N} - (\mu_h + r_1) V_I^i \\
\frac{dV_R^i}{dt} &= r_1 V_I^i - \sum_{j \neq i} \frac{vbb_h I_M^j V_R^i}{N} - \mu_h U_R^i \\
\frac{dV_I^j}{dt} &= \frac{vbb_h I_M^j V_R^i}{N} - (\mu_h + r_2) V_I^j \\
\frac{dR}{dt} &= (1 - \mu_d) r_2 V_I^j - \mu_h R
\end{aligned}$$

In this study, we assume that vaccine is imperfect. The number of dengue infection means primary infection cases whereas dengue incidence means the number of the secondary infection

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only.

The term mature mosquito refers to a fully developed mosquito. The susceptible mosquito (S_M) bite infected human with dengue virus serotype i and develop to a latent period (L_M^i). At this stage, the dengue virus is still not ready to transmit to human. After the incubation period, mosquitoes become infectious (I_M^i) with dengue virus serotype i. There is no compartment for recovery because the mosquito life span is too short for recovering from the dengue virus and mosquito carries only one serotype of the virus. The differential equations for a mature mosquito are as follows:

$$\frac{dS_M}{dt} = sS_E - \frac{bb_mS_M}{N}\left(\sum_{i=1}^{4} U_I^i + \sum_{j\neq i} U_I^j + \sum_{i=1}^{4} V_I^i + \sum_{j\neq i} V_I^j\right) - \mu_m S_M$$
$$\frac{dL_M^i}{dt} = \frac{bb_mS_M}{N}\left(U_I^i + V_I^i + \sum_{j\neq i} U_I^{ij} + \sum_{j\neq i} V_I^{ij}\right) - (\mu_m + c)L_M^i$$
$$\frac{dI_M^i}{dt} = cL_M^i + sI_E^i - \mu_m I_M^i.$$

Pre-mature mosquito means the combination of egg, larva and pupae stages of a mosquito. Generally, the dengue virus passes from an infected mature mosquito to egg. This is called a vertical transmission, γ. We assume that the infected pre mature mosquitoes carry only one serotype. S_E denoted non-infected pre-mature mosquito and I_E^i designated infected pre-mature mosquito with DENV i. We assume that pre-mature mosquitoes are infect with only one serotype. The differential equations for a pre-mature mosquito is as follow:

$$\frac{dS_E}{dt} = a\left(1 - \frac{S_E + \sum_{i=1}^{4} I_E^i}{K}\right)(S_M + L_M + (1-\gamma)I_M) - (s+\mu_e)S_E$$
$$\frac{dI_E^i}{dt} = a\left(1 - \frac{S_E + I_E^i}{K}\right)\gamma I_M^i - (s+\mu_e)I_E^i.$$

Initial values

In this study, the population is assumed to have no immunity against any serotype of the dengue virus at the beginning. The number of mosquitoes with dengue virus serotype DENV 1-4 are distributed equally. The total population is assumed to be 100000. The initial values are shown in table 2. All calculations are carried out by matlab with ode45 function.

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Table 1. Description of the symbols in this study

Parameters	Meaning	Values
λ_h	Human birth rate	0.000044
μ_h	Mortality rate of the humans	0.00004
r_1	Recovery rate of primary infection	0.333
r_2	Recovery rate of secondary infection	0.143
γ	Infection rate in mosquito's egg	0.028
μ_e	Mortality rate of the aquatic stage mosquito	0.143
μ_d	Death due to dengue	0.001
μ_m	Mortality rate of the mosquitoes	0.026
a	Oviposition rate	7.75
s	Pre-adult mosquito maturation rate	0.1307
b	Daily biting rate	0.2177
b_m	Probability of infection from human to mosquito per bite	0.2
b_h	Probability of transmission of dengue virus from infected mosquitoes to humans per bite	0.345
c	Inverse of extrinsic incubation period	0.1105
K	Egg carrying capacity	100000
t	Time	-
p	Proportional vaccine coverage	see text
v	Vaccine infection rate	see text

The parameters in this study are set to optimise transmission capability for the dengue virus at constant temperature 28.7°C (Liu-Helmersson et al., 2014; Polwiang, 2015).

Table 2. Initial values for differential equations

Parameters	value
U_S	$100000(1-p)$
V_S	$100000p$
S_e	18000
I_e^i	100
S_M	100000
L_M^i	300
I_M^i	300
otherwise	0

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Table 3. Field studies and simulation results

Study site	Study period	Population	Dengue infection	Dengue incidence
Rayong, Thailand (Sangkawibha et al., 1984)	1980-1981	1056	9.4%	0.4%
Bangkok, Thailand (Burke et al., 1988)	1980-1981	1757	11.8%	0.8%
Yogyakarta, Indonesia (Graham et al., 1999)	1995-1996	1837	29.2%	0.8%
Kamphaneng Phet, Thailand (Endy et al., 2002)	1998-2002	2119	7.3%	1.6%
Managua, Nicaragua (Balmaseda et al., 2006)	2001-2002	1186	9.0%	n/a
This simulation	2 years	100000	13.35%	0.69%

Dengue incidence is the combination of severe and hospitalized dengue.

RESULTS

Table 3 shows the numbers of dengue infections (primary infections) and hospitalized dengue (secondary infections) compared to several field studies. The period of simulation is 2 years and the initial values are shown in Table 2. When no vaccine is being administrated, we measure the numbers of dengue infections and dengue incidences and compare them to previous studies (Sangkawibha et al., 1984; Burke et al., 1988; Graham et al., 1999; Endy et al., 2002; Balmaseda et al., 2006). The term dengue incidence refers to a severe and hospitalized dengue in the field studies. The simulations show that 13.4%, 13350 infections, of the total population are infected with dengue virus and 0.69%, 687 incidences, are reinfected. The results given by the model are of the same magnitude as field studies, 9.4-29.2% for dengue infections and 0.4-1.6% for dengue incidences.

Reduction of dengue infections and incidences

Ignoring the time for vaccine receivers to develop immunity or the possibility for them to be infected may lead to over evaluating the effects of vaccination. In this study, the vaccine has given to certain portion of the population in the community to simulate the number of infections and it was assumed that the vaccine was effective at the time of the start of the simulation. The initial population for susceptible humans is $100000(1-p)$ and the vaccinated population is $100000p$, where p designates the proportion of the human population with vaccine. The rate $p = 0.1$ means that 10% of the total population has been given vaccine.

The vaccine only administrated to the vaccinated members only once. The vaccine infection rate

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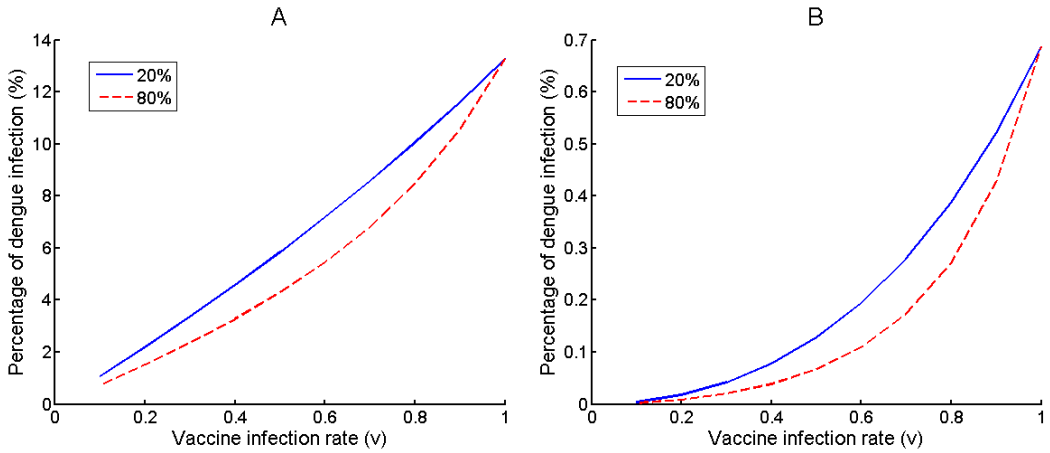

Figure 2. Percentage of the dengue infections and incidences among the vaccinated population (V) as a function of vaccine infection rate (v). A: Dengue infection or primary infection. B: Dengue incidence or secondary infection.

and coverage are very important parameters affecting the number of the dengue infections and incidences. Figure 2 shows the percentage of the dengue infections and incidences in vaccinated members as a function of the vaccine infection rate, v. The vaccine is given to 20% and 80% of the population, 20000 and 80000 persons, respectively. The simulations show that the percentage of dengue infection among the vaccinated members falls linearly and the dengue incidences drop sharply. When $v = 0.4$, the percentage of the dengue incidences declined from 0.69% to 0.078% among vaccinated members which translates into 88% reduction of dengue incidences from the control condition (non-vaccine program) of the vaccine coverage 20%, and the dengue incidences drop to 0.039% or 94% reduction, of the vaccine coverage is 80%. When $v = 0.1$, the percentage of incidences is only 0.004% or prevent 99% of dengue incidences and 0.002% or prevent 99% of the vaccine coverage is 20% and 80%, respectively. The difference of dengue incidence with vaccine coverage 20% and 80% is small for very low vaccine infection rate (< 0.2) and relatively high otherwise.

Figure 3 shows the percentage of dengue infections and incidences in the total population as a function of the vaccine coverage, v, with various vaccine infection rates (0.1-0.4). When the vaccine coverage is 10%, the percentage of dengue infections among the total population reduce to 10.56-11.22% or 15.96-20.90% reduction from the control value depend on vaccine infection rate and the dengue incidences reduce to 0.46-0.50% or 27.3-33.2% reduction. When the vaccine coverage is 80%, then the percentage of incidence reduce to 0.04-0.06% or 91.3-94.2% reduction

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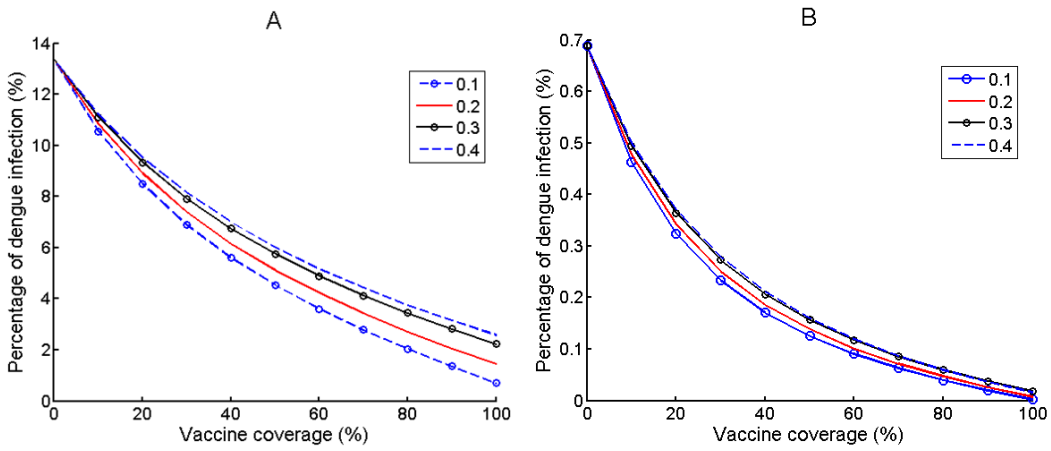

Figure 3. Percentage of dengue infections and incidences in total population (N) as a function of proportional of vaccine coverage (p). The value is adjusted to ratio with original value (without vaccine introducing). A: Dengue infection or primary inflection. B: Dengue Incidence or secondary infection. The vaccine infection rate (v) is 0.1-0.4.

of dengue incidences. The outcome of dengue incidences for equal vaccine coverage with different vaccine infection rate (0.1-0.4) is small.

Cost effectiveness of the vaccine

The cost of the dengue treatment is different in each country. For example, 3273 US dollars in Singapore compared to 690 US dollars in Thailand and 314 US dollars in Indonesia as shown in Table 4. The costs are based on the US dollar rate in 2015 with direct and indirect hospital costs derived from Shepard et al. (2013). One important factor in infection control to consider is the price of the vaccine. Dengue fever is generally not a life threatening disease, with approximately 0.1% fatality rate. If the price is too high, the vaccine target may not be reached and the disease control may not be successful. In this section, we calculate the cost effectiveness of the dengue vaccine for countries in South East Asia. In order to calculate the cost effectiveness of the vaccine, we use the formula of the incremental cost-effectiveness ratio (ICER) or the cost per DALY (disability adjusted life year) averted of vaccination. The formula of ICER for as follow:

$$\mathrm{ICER} = \frac{\mathrm{Cost}_{\mathrm{vaccine}} - \mathrm{Cost}_{\mathrm{no\ vaccine}}}{\mathrm{DALYs}_{\mathrm{no\ vaccine}} - \mathrm{DALYs}_{\mathrm{vaccine}}} \quad (1)$$

The cost effectiveness threshold was based on the gross domestic product per capita (GDP). Vaccination was considered to be highly cost effective when ICER was less than the GDP per capita, cost effective when the ICER was between one and three times the GDP per capita, and

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Table 4. Cost effectiveness of the vaccine in South East Asia

Country	Reported dengue cases	Hospital cost	GDP per capita	DALY	$v = 0.4$ Expected cases	$v = 0.4$ Highly effective cost	$v = 0.4$ Effective cost	$v = 0.1$ Expected cases	$v = 0.1$ Highly effective cost	$v = 0.1$ Effective cost
Brunei	18.00	2698	40776	3.55	4.74	28.58	71.43	3.27	31.40	78.30
Cambodia	105.00	126.70	1084	113.00	27.63	20.09	56.35	19.08	22.02	61.71
Indonesia	45.00	314.90	3514	41.00	11.84	23.41	66.06	8.18	25.66	72.34
Laos	144.00	116.30	1707	40.20	37.89	12.62	32.94	26.16	13.86	36.09
Malaysia	140.00	939	10829	30.80	36.83	68.74	167.46	25.44	75.55	183.61
Myanmar	33.00	88.50	1203	29	8.68	5.59	15.92	6.00	6.13	17.43
Philippines	51.00	230.60	2872	42.50	13.42	19.80	55.93	9.27	21.70	61.25
Singapore	141.00	3273.00	56284	20.10	37.10	235.45	570.32	25.62	258.80	625.34
Thailand	115.00	690.40	5977	42.10	30.26	48.94	123.43	20.90	53.76	135.29
Vietnam	90.00	83.80	2052	12.35	23.68	4.86	12.36	16.35	5.34	13.55
ASEAN	67.22	422.8	3911	37.26	17.69	25.76	68.89	12.21	28.26	75.47

The reported dengue case designates incidences per 100000 (Shepard et al., 2013).
Hospital cost is 2015 US dollar and DALY per 100000 is derived from Shepard et al. (2013).
GDP per capita in 2014 is taken from The world bank (2015).
The expected cases number is annual dengue incidence predicted by the model after the vaccine program starts with 0.4 and 0.1 vaccine infection rates and the vaccine is given to 50% of the population.
ASEAN means all countries in SEA. Timor-Leste was excluded due to insufficient data.

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not effective when the ICER exceeded three times the GDP per capita (Lee et al., 2011). Table 4 demonstrates the dengue incidences in the countries of South East Asia per 100000 population, the hospital costs for dengue, the GDP per capita and the DALY (Shepard et al., 2013; The world bank, 2015). The expected cases after the vaccine introduction and the highly effective cost and the effective cost for vaccination also calculated and displayed in the table. The cost for vaccine is the total cost for all doses required for a full function of the vaccine. In this study, we assumed that the mass vaccine required 3 doses and conferred immunity for 10 years. The vaccine infection rate 0.4 was chosen because its efficiency is close to that of Dengvaxia (approximately 90% incidence reduction) and 0.1 was almost eradicates the dengue incidences in vaccinated members as shown in Figure 2. The conclusion of the cost effective thresholds for a 50% vaccine coverage with 0.1 and 0.4 vaccine infection rate are shown in Table 4. The highly effective cost threshold is different in each country from 4.86-5.34 US dollar per person for Vietnam compare to 235-258 US dollar for Singapore. The average highly effective costs threshold for South East Asia are 25.76 and 28.6 US dollars for vaccine programs with 0.4 and 0.1 vaccine infection rates, respectively. The effective costs threshold with infection rate 0.4 is 68.89 US dollars and infection rates 0.1 is 75.47 US dollars for average ASEAN country. For full detail of every countries, see the Table 4. If the vaccine covers a larger population, the price will lower and vice versa.

DISCUSSION

We studied the dengue vaccination effects via vector-host model with multi serotypes dengue virus. The vaccine was given to a population in the age group 9-45. Thus only a portion of the population received vaccine protection. We investigated the effects of vaccine coverage to the number of dengue infections and incidences and cost effectiveness of the vaccine.

Our simulation set the parameters for dengue transmission to correspond to the optimal condition at temperature 28.7°C to maximize the number of dengue incidence and other climate factors were excluded. The dengue infections and incidences are represent all age groups in this simulation but the field studies focused on children age. The children are more vulnerable to dengue fever than adult. Hence by averaging both condition, the result is acceptable.

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The herd immunity

The simulation shows that the dengue vaccine with vaccine infection rate lower than 0.5 can prevent hospitalization for more than 80% of those who received vaccine (Figure 2) thereby also reducing the number of dengue incidences in the non vaccinated population. Our results indicate that if the vaccine coverage is 20% (low coverage), this will reduce the dengue primary infection by 29-36% and the severe dengue (secondary infection) by 46-53% (Figure 3). More over, if the vaccine coverage is 80% (high coverage), the dengue primary infection is reduced by 72-85% and the severe dengue (secondary infection) by 91-94%. Dengue incidence reduction is exhibiting the herd immunity in this study, particularly in the low coverage ($< 30\%$). The percentage of reduction of the secondary infections is higher than the percentage of the vaccine coverage. When a critical portion of the population is vaccinated and immunized against the dengue virus, most members of the community are protected against that virus because there will be fewer opportunities for mosquitoes to contact infected persons and for infectious mosquitoes to bite non-vaccinated members. Therefore fewer mosquitoes are capable of transmitting the virus and this leads to an overall decline of the transmission risk for all people in the community.

Price of the vaccine

A price that is lower than the highly effective cost is the most preferable for the vaccine programs. Although, any price is not exceeding the effective cost is acceptable. The highly cost effective price of the vaccine in this study is more expensive than the previous study by Carrasco et al. (2011) which was calculated to be 150 US dollars for 3 doses with 10 years immunity compared to 235-258 US dollars in our study. However, in Carrasco et al. (2011), a lower DALY was used than in our study, 9-14 compared to 20.1. Lee et al. (2011) calculated that the highly cost effective price for a dengue vaccine in Thailand would be 60-100 US dollars which is more costly than our results (48-54 US dollars). The reason is the herd immunity excluded and the vaccine assumed lifetime immunity in Lee et al. (2011) study. Another calculation in Orellano et al. (2016) estimated that the highly cost effective price for vaccine in endemic areas in Argentina is 84 US dollars for 3 doses vaccine. Currency exchange and inflation would affect the calculation of the vaccine price. Young children are more vulnerable to dengue infection than the adults (Guzman et al., 2002). In order to eradicate the dengue fever, some improvements in the vaccine are required to allow applicable for children under 9.

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An important reason for considering the cost effectiveness of the vaccine is that a higher price of the vaccine may discourage people to purchase the vaccine. Another reason is that a higher price could encourage more manufacturers to develop the vaccine. The cost effectiveness of the vaccine varies from country to country in South East Asia. For Dengvaxia, full immunization requires 3 doses. The price is still undisclosed. Our calculation suggests that if the vaccine price is too high, the vaccination target may not be reached in poor countries. Simultaneous application of vector control methods and the vaccine program can have a positive effect by further reducing the number of dengue infections (Christofferson and Mores, 2015).

Limitations of this study

There are limitations in this study. The parameters in the dengue transmission were set to correspond to optimal temperature conditions. The number of infections may be overestimated. Also the parameter values may be different in each country. Efficiency of the vaccine is varies in each serotype (Guy and Jackson, 2016). During the phase III, CYD-TDV efficiency is 50.0% against DENV 1; 35.0% against DENV 2; 78.4% against DENV 3; 75.3% against DENV 4 (Screaton et al., 2015). Moreover, the effect of the vaccine also depends on the age of the vaccine receivers. The country demographic is another important factor in the dengue transmission(Mbah et al., 2014). Another concern is changing pattern of dengue virus serotypes. For example, the major serotypes were inconsistent in Thailand: DENV1 in 2004 (56.41%), DENV4 in 2007 (50%), DENV1 in 2008 (57.41%), and DENV3 in 2010 (38.7%) (Pongsiri et al., 2012). However, further medical investigation may be required to develop a more accurate model. Sanofi claimed that Dengvaxia work better for persons experienced primary infections but in this study primary and secondary infection share identical transmission probabilities.

CONCLUSION

In this study, a mathematical model for dengue transmission simulates the situation where the dengue vaccines given to a population to evaluate the efficiency of the vaccine coverage. The model demonstrates that the vaccine greatly reduces the number of dengue infections in vaccinated population and that also the number of infections among non vaccinated members is declined. In order to cover 50% of the population, the highly effective costs for dengue vaccine in South East Asia 25.76 and 28.26 US dollars with vaccine infection rates 0.4 and 0.1, respectively.

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The overall cost in the region is close to the cost in Indonesia. Indonesia is the most populous country in South East Asia and it also has the highest DALY in the region.

Several countries have approved the initial phases of Dengvaxia in December 2015. The vaccination has not just reduced the number of infections among vaccinated members but also in the non vaccinated individuals. Researchers predict that it will take several years before the current vaccine is fully analysed, clinically tested and proven to be efficacious on the field to be administered to all age groups. This study provides guidelines how the vaccine will affect the dengue infections and incidences. It also estimates the cost effectiveness of the vaccine.

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