Research Article

The Effectiveness of Dengue Vaccine and Vector Control: Model Study

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Abstract
The first of commercial dengue vaccine called Dengvaxia, was approved in Mexico, Brazil and the several countries. The objective of this study is to estimate the effectiveness of the vaccine to number dengue infection by using mathematical model of dengue transmission with multiple serotypes of dengue virus. The vaccine is given to a certain part of population in the community and the number of dengue infections and incidences is then calculated. The combination of vector control methods and vaccination is also evaluated. The results shown that the cooperation between both programs is reduced the number of dengue infection by more than 90% with 50% of vaccine coverage. The vaccination or vector control programs alone are unable to eliminate dengue infection from community.

Keywords: Dengue, Mathematical model, Vaccine

1 Introduction

Dengue virus (DENV) is one of the major causes of illness and death in the tropical and subtropical countries. As many as 400 million people are infected and 20,000 deaths annually. The virus has four distinct serotypes, DENV1-4 [1]. 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 and nutrient for egg laying [2]. Infection with one serotype appears to provide lifelong immunity against reinfection with that particular stereotype but not against the others. The first infection is normally asymptomatic or has only mild symptoms. Severe diseases, including Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) is mostly occurring in individuals who have already recovered from the first infection and are experiencing reinfection with a different serotype [3].

For several decades, many different methods of vector control to eliminate or reduce mosquito population have been implemented with varying degree of success. However, the number of dengue incidences still rising. The vector control is held to be an essential part of the dengue control process, currently available vector control methods have not proven effective in reducing dengue incidences. The control methods such as eliminating containers where rain water can store or install the insect wire screen or bed nets in the residential areas. Other methods include biological control methods such as the use of small fish to eat the mosquito larvae in the water containers or water pools, or use the *Bacillus thuringiensis israelensis* (Bti) bacteria, which release a toxin that kills the mosquito larvae after being ingested. Chemical control through the use of insecticides that kill adult mosquitoes is also effective when used at the right times and places. The most important method is education, instructing people how to prevent from a mosquito bite and eliminate mosquito breeding sites [4]. Until now, there is still no specific method that

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ensures 100% successful control the population of mosquito. The mosquito is quickly adapting to survive the vector control process and the vector control programs require sustainable and expensive efforts to operate.

Therefore, the requirement of vaccination to decrease the number of susceptible humans for virus transmission is an important issue. Vaccination is generally accepted as the most effective method to stop the infectious disease. There is a growing expectation that reducing and eliminating dengue can only be achieved by integrating vector control efforts with dengue vaccines [5]. In late 2015, the first dengue vaccine, Dengvaxia (CYD-TDV), introduced by a French company, Sanofi Pasteur, was approved in Brazil, Mexico, and the Philippines [6]. 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. During the trial tests, Dengvaxia was shown to reduce dengue in all four serotypes in 65.6% of the participants and prevent 80.8% hospitalizations and up to 93.2% of severe dengue cases and 92.9% against the DHF [7]. The vaccine has been approved for use in individuals 9–45 years of age and lives in endemic areas.

We present a mathematical model to demonstrate how the vaccination program and vector control efforts to reduce the number of dengue infections and incidences. The low and high vaccine coverage situation was demonstrated. The vaccine is imperfect and the vector control efforts were integrated into the model simulation.

2 Theory and Methods

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 stereotypes prevents reinfection by the same stereotype, but not by the others. Female mosquitoes contribute the medium vector for dengue fever. The disease cannot spread from human to human or from mosquito to mosquito directly.

The dengue infection can be classified into two categories.

2.1 *The primary infection*

The primary infection or the first time infection with dengue virus is mostly asymptomatic symptoms or mild fever and medical attention is generally not required. The recovery period is short. After recovery from the infection, the lifelong immunity for that serotype is developed in the body [8], [9].

2.2 *The secondary infection*

The secondary infections with a dengue virus serotype that different from the primary infection is increasing the risk for the development of dengue fever to a more life-threatening condition such as DHF or DSS. Most of the severe or hospital incidences are caused by the secondary infection [8], [9].

In this study, the vaccine has given to a certain portion of the population in the community to simulate the number of infections and it is assumed that the vaccine is effective at the time of the start of the simulation.

2.3 *Vaccine program*

The efficiency of the vaccine varies in each stereotype. 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 [7]. Another concern is changing patterns of dengue virus serotypes. For example, the major sereotypes were inconsistent in Thailand: DENV-1 in 2004 (56.41%), DENV-4 in 2007 (50%), DENV-1 in 2008 (57.41%), and DENV-3 in 2010 (38.7%) [10]. These studies have shown that the dengue vaccine is far under 100% efficiency and the reason to simulate the imperfect vaccination in the dengue transmission model. Vaccine efficacy and coverage are the most important parameters to decide the achievement of the vaccine program. Vaccine efficacy is represented in this study as vaccine infection rate. The vaccine infection rate is the rate at which vaccinated members may infect with the virus compared to non-vaccinated members. The number 0 means vaccine is perfect protection and 1 means the vaccine is not working at all. The vaccine coverage is the percentage of members in the population received the vaccine. The Dengvaxia target group is the persons age 9–45 years. Therefore, only part of the population will receive the vaccine.

2.4 *The mathematical model*

The model in this study is modified from the dengue

transmission model with multiple serotypes and the secondary infection by Lee *et al*. [11]. For simplicity, the roles of the climate are ignored in this study. The parameter values are derived from Liu-*Helmersson et al*. [12]. 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*). Note that $i \neq j$ represent different serotype of primary and secondary dengue infection.

Table 1: Description of the symbols in this study

Parameters	Meaning	Values
λ	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_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	0.345
c	Inverse of extrinsic incubation period	0.1105
K	Egg carrying capacity	100,000
t	Time	-
p	Proportional vaccine coverage	-
v	Vaccine infection rate	-

The human population in this model is divided into two categories, non-vaccinated (U) and vaccinated population (V). Each category is divided into susceptible (U_S, V_S), the primary infection of i dengue serotype (U_I^i, V_I^i), recovery from the primary infection (U_R^i, V_R^i), secondary infected with j serotype (U_I^{ij}, V_I^{ij}), and full recovery (R). The third and fourth infection of dengue virus are very rare [13]. Hence we can assumed that individuals recovered from the secondary infection become immune to all serotypes.

The total human population is the combination of two population groups. The compartments for non-vaccinated population, U, are as follows:

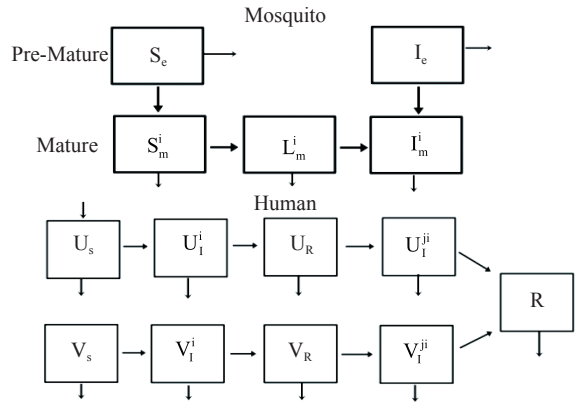

Figure 1: Diagram of the model for mosquito (S, L, I) and human (U, V) population, i is indicate the number of serotype of primary infection and j is serotype number of secondary infection. Note that $i \neq j$. There is no interchange between vaccine, V, and non-vaccine, U, population and mosquito is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

$$\frac{dU_S}{dt} = \lambda N - \sum_{i=1}^{4} \frac{bb_h I_M^i U_S}{N} - \mu_h U_S,$$

$$\frac{dU_I^i}{dt} = \frac{bb_h I_M^i U_S}{N} - (\mu_h + r_1) U_I^i,$$

$$\frac{dU_R^i}{dt} = r_1 U_I^i - \sum_{j \neq i} \frac{bb_h I_M^j U_R^i}{N} - \mu_h U_R^i,$$

$$\frac{dU_I^{ji}}{dt} = \frac{bb_h I_M^j U_R^i}{N} - (\mu_h + r_2) U_I^{ij},$$

$$\frac{dR}{dt} = r_2 U_I^{ji} - \mu_h R$$

The vaccine compartment, V, is based on the imperfect random mass vaccination. 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 [14]. 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 [14]. We have the differential equations for vaccine compartment as follows:

$$\frac{dV_S}{dt} = \lambda N - \sum_{i=1}^{4} \frac{vbb_h I_M^i V_S}{N} - \mu_h V_S,$$

$$\frac{dV_I^i}{dt} = \frac{vbb_h I_M^i V_S}{N} - (\mu_h + r_1)V_I^i,$$

$$\frac{dV_R^i}{dt} = r_1 V_I^i - \sum_{j \neq i} \frac{vbb_h I_M^j V_R^i}{N} - \mu_h V_R^i,$$

$$\frac{dV_I^{ji}}{dt} = \frac{bb_h I_M^j V_R^i}{N} - (\mu_h + r_2)V_I^{ji},$$

$$\frac{dR}{dt} = r_2 V_I^{ji} - \mu_h R$$

The term mature or adult mosquito refers to a fully developed mosquito. The susceptible mosquito (S_M) bite an 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 (L_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 mature mosquito compartment are as follows:

$$\frac{dS_M}{dt} = sS_M - \mu_m S_M - \frac{bb_m S_M}{N}\left(\sum_{i=1}^{4} U_I^i + \sum_{j \neq i} U_I^{ji} + \sum_{i=1}^{4} V_I^i + \sum_{j \neq i} V_I^{ji}\right),$$

$$\frac{dL_M^i}{dt} = \frac{bb_m S_M}{N}\left(\sum_{i=1}^{4} U_I^i + \sum_{j \neq i} U_I^{ji} + \sum_{i=1}^{4} V_I^i + \sum_{j \neq i} V_I^{ji}\right) - (\mu_m + c)L_M^i,$$

$$\frac{dI_M^i}{dt} = cL_M^i + sI_E^i - \mu_m I_M^i$$

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. We assume that the infected pre mature mosquitoes carry only one serotype. S_E is the non-infected pre-mature mosquito and I_E^i is the infected pre-mature mosquito with DENV serotype i. We assume that pre-mature mosquitoes are infect with only one serotype. The differential equations for a pre-mature mosquito compartment are as follow:

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

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

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 100,000. All calculations are carried out by Matlab with ode45 function.

3 Results

In this study, we report our results in three scenarios. Vaccine program scenario (vaccine program without vector control efforts), vector control process (vector control efforts without vaccine program) and integration program (combination of vaccine programs and vector control efforts). The results illustrate as the percentage number of primary dengue infections and secondary dengue infection of the human population. We assume that the population in this study do not have dengue immunity at the beginning.

3.1 *The effectiveness of vaccine programs*

The vaccine only administrated to the vaccinated members only once. The vaccine infection rate and coverage are very important parameters affecting the number of the primary and secondary dengue infections. In this study, the vaccine infection rate is 0.1–0.4 to represent the imperfect vaccine protection. The vaccine coverage is 0–100% of the total population.

Figure 2 shows the percentage of the primary and secondary dengue infections in the total population as a

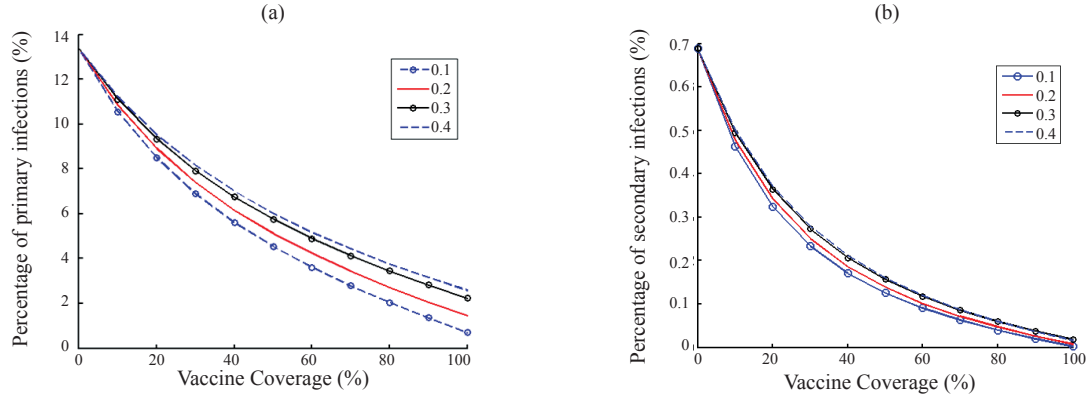

Figure 2: Percentage of dengue infections and incidences in total population (N) as a function of proportional of vaccine coverage (p). The value is adjusted to ratio with original value (without vaccine introducing). A: The primary inflection. B: The secondary infection. The vaccine infection rate (v) is 0.1, 0.2, 0.3 and 0.4.

function of the vaccine coverage. Figure 2(a) illustrates the primary infection. Without a vaccine program, approximately 13.3% of the total population will be infected. When the vaccine coverage is 20%, the percentage of primary dengue infections among the total population reduce to 8.5–9.5% of the total population depend on vaccine infection rate. Figure 2(b) displays that the secondary dengue infection without vaccine program, 0.7% of total the population are infected. For the vaccine coverage 20%, the number reduces to only 0.32–0.37% of the total population. When the vaccine coverage is 80%, then the percentage of secondary infections reduces to less than 0.1%. The simulations show that even though the vaccine coverage is 100%, but there is existing dengue infection due to imperfect vaccine efficacy.

3.2 *The Effectiveness of Vector Control Efforts*

The dengue transmission parameters are suppressed by vector control programs. Several actions have a direct impact on the mosquito population. The biting rate is reduced by using bed nets or chemical repellent. Removal of containers that may capable of mosquito's egg laying is reducing the egg capacity. Using chemical insect killers will direct kill the mosquito and shorten the mosquito lifespan or increase the mortality rate of mosquito. The vector controls are added to the model by applying a multiplier to the transmission parameters. In this study, three transmission parameters, biting rate, egg capacity and mosquito mortality, are suppressed by a multiplier to represent the vector control efforts. That is the vector controls are constant at all times. Figure 3 displays the effects of the vector controls to dengue infection. Adding a multiplier 0.5–1 to biting rate means the daily biting rate of mosquito is constantly reduced to a multiplier value. If the biting rate drops to half of control condition. The percentage of primary dengue infection decline to 3.7% of total population [Figure 3(a)] and secondary dengue infection, reduce to 0.04% [Figure 3(d)]. Also, the same multiplier applied to egg capacity. If the egg capacity is reduced to half of control condition. The percentage of the primary dengue infection decline to 8.4% of total population [Figure 3(b)] and the secondary dengue infection, reduce to 0.27% [Figure 3(e)]. When the mosquito mortality rate is high means the life span of an adult mosquito is short. The multiplier for being mosquito mortality rate is 1–1.5. The results are similar to reducing the biting rate. At the multiplier equal to 1.5, the primary dengue infection is 4.8% of total population and the secondary dengue infection is declining to 0.08%.

3.3 *The Integration of Vaccination and Vector Control Program*

When considered together, vaccine program can be enhanced by vector control efforts. Figure 4 displays the effects of integration of vaccination and vector control program to primary [Figure 4(a)–(c)] and secondary [Figure 4(d)–(f)] dengue infection. The levels of vaccine coverage are 25%, 50% and

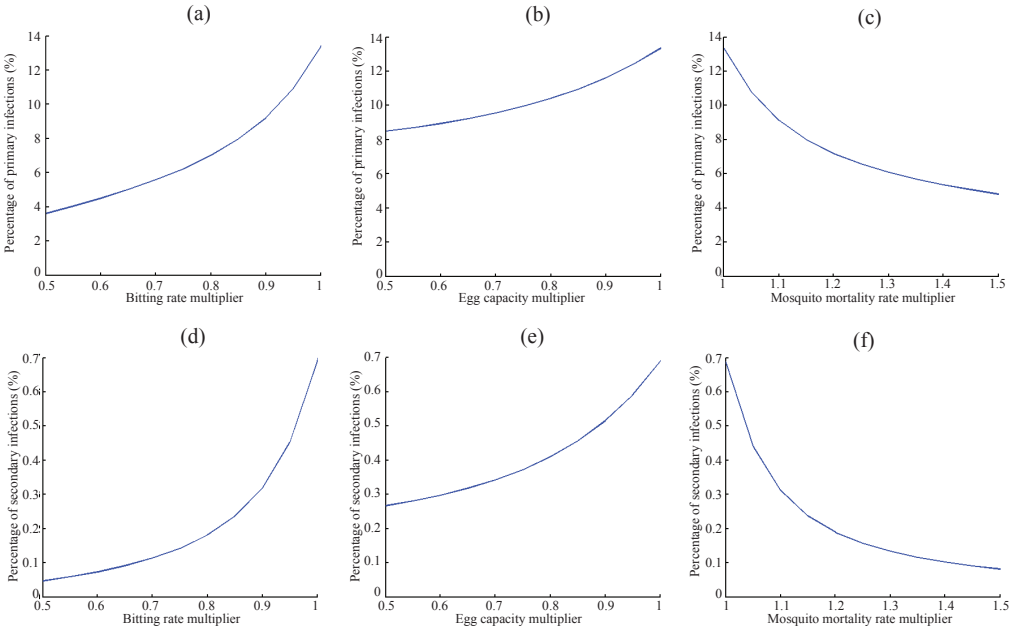

Figure 3: percentage of the primary (a)–(c) and secondary (d)–(f) dengue infection as a function of dengue transmission parameter multipliers. (a), (d): biting rate multiplier, (b), (e): egg capacity multiplier, (c), (f): mosquito mortality rate multiplier.

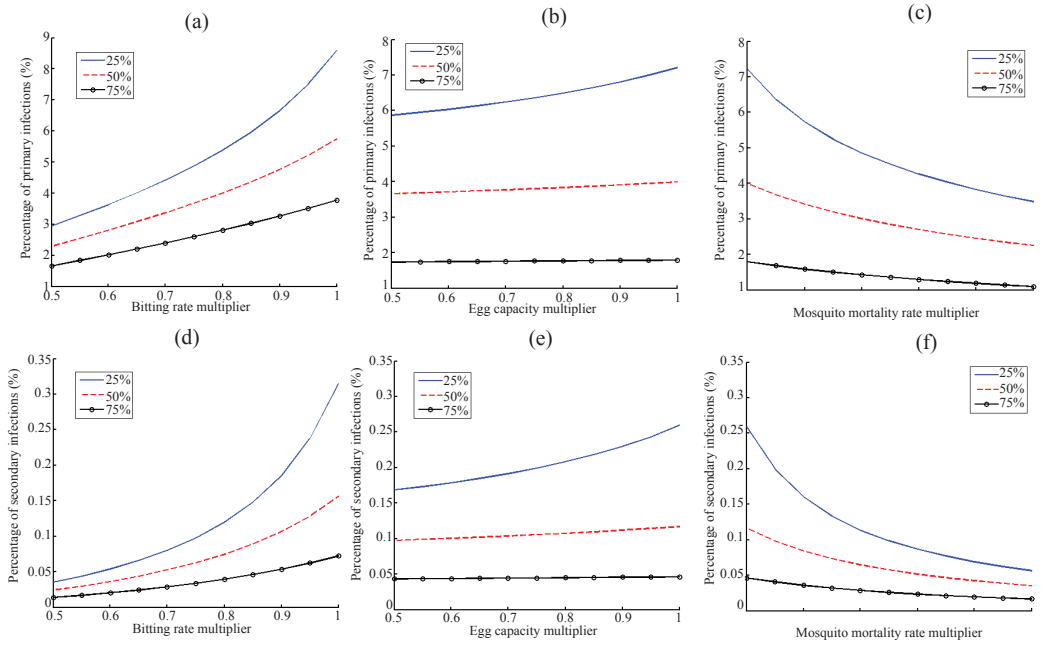

Figure 4: percentage of primary (a)–(c) and secondary (d)–(f) dengue infection as a function of dengue transmission parameter multipliers and vaccine implementation with vaccine infection rate 0.3. The vaccine coverages are 25% (blue), 50% (broken red) and 75% (black cycle). (a), (d): biting rate multiplier, (b), (e): egg capacity multiplier, (c), (f): mosquito mortality rate multiplier.

75% to represent low, medium and high coverage, respectively, combined with the vector control efforts. The combination of biting rate and vaccination, almost eradicate the dengue infection, the primary infection reduces to 1.6–2.9% with half of the biting rate and the numbers of secondary dengue infection are lower than 0.05% of all vaccine coverages. In other words, the number of dengue infection is reduced more than 90% before interference program. For the combination of egg capacity multiplier and vaccination, the primary infection is reduced to 1.7–5.9% of total population and the secondary infection is reduced to 0.04–0.17%. However, the combination programs with egg capacity multiplier display slightly effect on medium and high vaccine coverage. For the combination of mosquito mortality rate multiplier and vaccination, the primary infection is reduced to 1.1–3.5% of total population and the secondary infection is reduced to 0.02–0.06%.

4 Discussions

We investigated the effects of a combination of vaccine programs and vector control efforts to dengue transmission by using a mathematical model. The model represents the dengue transmission with multiple serotypes.

The vaccine infection rate has little effect on the secondary infection as shown in Figure 2(b). The percentage numbers of the population are repeat infected with dengue virus are nearly equal to vaccine infection rate 0.1–0.4. The herd immunity also observed in this simulation. For example, Figure 2 display that 20% of vaccine coverage reduce the number of the primary infection from 14% to 8.5–9.5% of total population or the number of incidences reduce 27–36% from its original value and the secondary infection reduce from 0.7% to 0.32–0.37% or the number of incidences decline 47–54%. The simulation also illustrates that with 100% of vaccine coverage, the dengue infection remains to occur because the imperfect vaccine efficiency.

It is clear from the simulation results that biting rate is the main factor of dengue transmission. These results are supported by sensitivity analysis in Massad *et al*. study [15]. With low vaccine coverage (25%), the vector controls play a significant role. The combination of 25% vaccine coverage and 34% of the biting rate reduction has reduced the number of dengue infection to equal to 75% vaccine coverage only [Figure 4 (a), (d)]. Additionally, the combination of 25% vaccine coverage and 18%, increasing by the mosquito mortality rate achieve the same number of reductions of dengue infection as 50% vaccine coverage only. However, reducing the egg capacity shows a minor effect on dengue infections under vaccination. For high vaccine coverage, the role of vector controls are still important. This results have shown that, even the 75% vaccine coverage is still unable to prevent all dengue incidences, but the vector controls are fulfilling the gap.

In this study, we demonstrate that the integration of vector controls and vaccination can almost entirely eliminate the dengue incidence. The vaccination and vector controls have limitations. The dengue vaccine is required a lot of research and development to achieve the target efficacy, and providing vaccine to individuals in the community to cover appropriate number is a difficult task. After decades of vector control programs, the number of dengue incidences is still enormous and the infectious disease expanded to several countries. There are several reasons for the unsuccessful program. The mosquito population rebounds to normal level within a matter of weeks after massive vector control implementations. Mosquitoes are quickly adapt to human-made environments. This is the reason that controlling the population is very difficult work. An insufficient cooperation and communication between the various levels of public and private health services or inadequate of education about the importance of dengue control awareness are also a significant burden for dengue control [16]. The combination could reduce such limitations of both methods. Therefore, the integration between vaccine and vector control programs are essential tools to combat the dengue virus. The combination of both methods would ultimately decrease the number of dengue infection in the community.

5 Conclusions

In this study, a mathematical model for dengue transmission simulates the situation where the dengue vaccines are given to a population to evaluate the efficiency of the vaccine coverage. Our model study has shown that the combination of vaccination and vector control efforts would dramatically reduce the number of dengue infections.

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