Research Article

# Modeling Impacts of Dengue Vaccination on Sequential Epidemics

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**Abstract**
The efficiency of dengue vaccines in preventing the infection from multi strain dengue virus is crucial for public health prevention strategies. To understand how the vaccine interrupts the transmission cycle between strains is an important task leading to the prevention plan. We use a mathematical model to investigate the impact of vaccine on the subsequent spread of two dengue virus serotypes. The model suggests how to maintain sufficient amount of vaccine coverage to prevent the subsequent epidemics and the effect of vaccine on the interaction between strains.

**Keywords**: Epidemic, Dengue, Vaccination, Immunity, Mathematical model

## 1 Introduction

Dengue Fever (DF) has been categorized into the top rank of most important infectious diseases. It is a vector-borne disease that reemerged and is spreading over tropical regions. There are estimated 50 million cases every year and the virulence have considerably increased since the last decade [1]. Several attempts such as the vector control, vaccination program, improved hygiene and medical treatment research have been integrated to epidemic control. However, the theoretical approach is the need for either conducting or contribution the practical operations and has an important role to an aggressive strategic making. A mathematical model has become one of the important tools as well as the field study to contribute the control strategy.

Dengue virus (DEN-virus) belongs to the family Flaviviridae that has four distinct serotypes (DEN-1 to DEN-4) [2]. In some hyperendemicity (Thailand) all 4 serotypes can be observed [3]. Infection with one serotype lead to long lasting of immunity to that serotype but temporary cross-immunity to the others. It is known that co-circulating of multiple serotypes of DEN-virus can result in higher risk to secondary infection that may undergo more severity of disease (DHF) [4]. When this temporary immunity wanes, antibodies can lead to either reduced or enhanced rate of secondary infections. The latter assumption is known as Antibody-Dependent Enhancement (ADE) hypothesis. Although the developing dengue vaccine should prevent infection by all serotypes, it is theoretically assumed that when immunity is waning or between vaccine doses, it can lead to a potential risk of severe dengue to infected individual.

Four serotypes of DEN-virus are possibly assumed to be synchronously persisted in a community [3]. The coexistence of multistrain virus may increase the severity of disease (DHF) or facilitate the infectivity. An important factor is

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indicated to the cross-reactive antibodies or Antibody-Dependent Enhancement (ADE). These effects have been studies in various works through a mathematical model [5]–[8]. The role of such immunological response has been model straightforwardly in terms of degree of enhancement to secondary infection [9]. A few studies have incorporated the effect of cross-immunity into the model [10]. However such models are considered only the transmission in host population dynamics. In 2003, Esteva and Vargas proposed a mathematical model for dengue transmission that the two serotypes are regarded [11]. In 2016, Lourençoa and Reckerb developed a model that regards immune interactions with ADE effects and showed that it can significantly affect the predicted outcome of a dengue vaccination campaign [12]. To simplify an analysis, in this study we propose a simple SIR transmission model with two serotypes without consideration of the dynamics of vectors.

Moreover, assessing potential impact of dengue vaccination at population level becomes difficult when regarding the effects of serotype interactions, i.e., ADE and temporary cross-immunity [10]. Even if the level of immunity at the population scale is high enough to protect the whole population from dengue infection with particular serotype, the question arises whether it could lead to increased transmission of the rest serotypes after some short protection lapses. To address the problem we investigate whether and how the vaccination may indirectly enhance the secondary infection by assuming that the vaccine can effect on only one serotype and induce the cross immunity to the other.

## 2 Methodology

We will analyze the consequence of vaccination programs in population level. We assume that the applied dengue vaccine can perfectly prevent from infection by particular DEN-virus serotype for long lasting period but can create a short time cross-immunity to other different serotypes. Suppose that the proportion of population with acquired immunity is created by vaccination. This presumed mechanism results in such proportion of population can become susceptible to severe dengue infection by other serotype in the later time. The key measure is to quantify the risk of secondary infections at the point of epidemic of different strain taking off.

We develop a mathematical model for dengue transmission. The assumptions for the model are as follows:

1. The model contains only two dengue virus serotypes.

2. The vector dynamics are omitted for simplicity sake.

3. The standard SIR epidemic model presents the temporal time scale so that the demographic effects are excluded.

4. The total population is constant.

5. The effect of ADE is considered for susceptibility enhancement.

6. The additional class for temporary cross-immunity is presented.

7. No distinction of the characteristic in transmission dynamics between two virus serotypes, i.e., there is no indexing of serotypes for all parameters.

8. All variables are defined by means of the proportion of population.

9. The effects of ADE can be treated as a positive parameter that reflects the extent of risk of exposure to secondary infections.

The explicit model equations is given by

$$\frac{dS}{dt} = -\beta S(I_1 + I_2 + Y_1 + Y_2) \tag{1}$$

$$\frac{dI_i}{dt} = \beta S(I_i + Y_i) - \gamma I_i \tag{2}$$

$$\frac{dT_i}{dt} = \gamma I_j - \delta T_i \tag{3}$$

$$\frac{dS_{ij}}{dt} = \delta T_j - \phi\beta S_{ij}(I_j + Y_j) \tag{4}$$

$$\frac{dY_i}{dt} = \phi\beta S_{ji}(I_i + Y_i) - \gamma Y_i \tag{5}$$

$$\frac{dZ}{dt} = \gamma(Y_1 + Y_2) \tag{6}$$

with $i, j = 1,2 (i \neq j)$,
and $1 = S + I_1 + I_2 + T_1 + T_2 + Y_1 + Y_2 + S_{12} + S_{21} + Z$.
Table 1 presents a list of variables and parameters summary of Equations (1)–(6).

**Table 1**: Variables and parameters summary

| Symbols | Definitions |
|---|---|
| $S$ | Proportion of individuals who is susceptible to both serotypes |
| $I_i$ | Proportion of individuals who infected with serotype |
| $T_i$ | Proportion of individuals who has temporary cross-protection with serotype |
| $S_{ij}$ | Proportion of individuals who had been infected with serotype and is susceptible with serotype |
| $Y_i$ | Proportion of individuals who infected with serotype and has antibody to serotype |
| $Z$ | Proportion of individuals who has permanent immunity to both serotypes |
| $\beta$ | The transmission coefficient |
| $\gamma$ | The recovery rate |
| $\delta$ | The rate of losing temporary cross-immunity |
| $\phi$ | ADE factor (the value is greater than 0) |

## 3 Analysis

According to the observed pattern for serotype-specific epidemics (e.g., in Bangkok, Thailand), there would be a finite time between the initial phase of serotype- specific epidemics say '$t_0$'. Hence, we will separate time line into two phases by supposing that there is only a single particular serotype at the initial time, and after time lapses $t_0$ units, the second distinct serotype will be introduced. Since we are dealing with two serotypes, say DEN-1 and DEN-2, analysis will be performed on two different scenarios:

1. DEN-1 starts at time $t = 0$ then follows by DEN-2 at time $t = t_0$ ;

2. DEN-2 starts at time $t = 0$ then follows by DEN-1 at time $t = t_0$ .

We now suppose that Dengue vaccine prevents infection by DEN-1 for long period but for short period for DEN-2. In the context of vaccine, the parameter also describes the rate of waning. We assume that the vaccination is started at the initial phase of first epidemic ($t = 0$). Suppose that the fraction of population, $\theta$ are vaccinated. They will acquire long term immunity for DEN-1 but short term immunity for DEN-2. We then have $T_2(0) = \theta$.

### 3.1 *Analysis for scenario I*

We assume that at the initial time, the population consists of a certain proportion of infective individuals with DEN-1, $I_1(0)>0$, the vaccinated and unvaccinated individuals. Thus, the proportion of individuals who are susceptible to both serotypes (unvaccinated) at time $t = 0$ is given by

$$S(0)=1-I_1(0)-\theta \tag{7}$$

To examine the transmission dynamic for DEN-1 by the time at which DEN-2 is introduced, we consider

$$\frac{dS}{dt} = -\beta S I_1 \tag{8}$$

$$\frac{dI_1}{dt} = \beta S I_1 - \gamma I_1 \tag{9}$$

$$\frac{dT_2}{dt} = \gamma I_1 - \delta T_2 \tag{10}$$

$$\frac{dS_{12}}{dt} = \delta T_2 \tag{11}$$

for $0 \le t \le t_0$ .

Since we are concerned with the risk of individuals to the secondary infection subject to vaccination, we assume that the herd immunity satisfies

$$R_{vac} = R_0 S(0) < 1 \tag{12}$$

where $R_0 = \beta / \gamma$ is the basic reproduction number. Here, under the absent of vaccination we assume that is greater than one. Under condition Equation (12), however, there will be no epidemic of DEN-1 for, $0 \le t \le t_0$, if

$$\theta > 1 - \frac{1}{R_0} . \tag{13}$$

Figure 1 shows infection of DEN-1 satisfied with Equation (13).

If $I_1(0)$ is sufficiently small, then we can estimate $T_2$ and $S_{12}$ from Equations (10), (11) as

$$T_2(t) = \theta e^{-\delta t}, \; S_{12}(t) = \theta(1 - e^{-\delta t}) \tag{14}$$

for $0 \le t \le t_0$. It is clear from Equation (14) that the susceptibility to subsequent infection with DEN-2 increases with the fraction of vaccinated population and the time between initial phase of epidemics but decreases with the cross-protection period. When DEN-2 is introduced at time $t = t_0$, this implies that

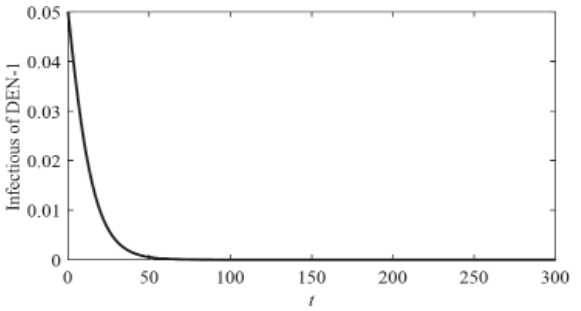


**Figure 1**: Plot of infection of DEN-1obtained from Equations (7)–(11) where $\beta = 0.7$, $\gamma = 1/6$, $\theta = 0.8$.

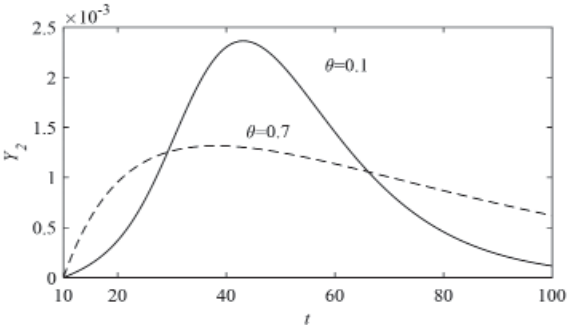


**Figure 2**: Plots of $Y_2(t)$ when $I_1(0) = 0.01$, $t_0 = 10$, $\beta = 0.3$, $\gamma = 0.1$, $\delta = 0.02$, $\phi = 0.4$ and $\theta$ are 0.1 and 0.7.

$I_2(t_0) > 0$. We see that the secondary cases produced by a primary infective individual with DEN-2 among the susceptible population $S_{12}$ occurs if

$$\phi\beta S_{12}(t_0) = \phi\beta\theta(1 - e^{-\delta t_0}) > 0 . \quad (15)$$

We observe from Figure 2 that when Equation (15) is satisfied, the higher vaccination rate will more increase the secondary infection ($Y_2$) at the initial period after $t_0$ (about 30 days) since the vaccine invokes the amount of susceptible to DEN-2.

### 3.2 *Analysis for scenario II*

Suppose that there is a fraction of infective individuals with DEN-2 at time $t = 0$ namely, $I_2(0) > 0$. Similarly to the first scenario, the susceptible at $t = 0$ is $S(0) = 1 - I_2(0) - \theta$. Since vaccine coverage is assumed to be high enough for preventing infection, fraction of infected with DEN-2 is exponentially decay,

$$I_2(t) = I_2(0)e^{-\gamma t} \quad (16)$$

We consider that as time passes the temporary cross-immunity to DEN-2 wanes with the rate $\delta$. How mach chance for the fraction of population who vaccinated at the initial time will be infected with DEN-2 by the time depends on how fast for the infective individuals recover relative to the rate of lost immunity. If $\gamma$ is much greater than $\delta$, then the infective recovers before the cross-immunity loses. Thus, the secondary infection cannot occur since the proportion of susceptible is too small. The transmission dynamic before that DEN-1 is introduced is described by

$$T_2(t) = \theta e^{-\delta t} \quad (17)$$

$$\frac{dS_{12}}{dt} = \delta T_2 \quad (18)$$

$$\frac{dT_1}{dt} = \gamma I_2(0)e^{-\gamma t} - \delta T_1 \quad (19)$$

$$\frac{dS_{21}}{dt} = \delta T_1 . \quad (20)$$

From Equations (16)–(20), we are able to calculate the susceptible to the secondary infection with DEN-1 at the time $t = t_0$ as

$$S_{21}(t_0) = \left(\frac{\delta\gamma I_2(0)}{\gamma - \delta}\right)\left(\frac{1}{\delta}(1 - e^{-\delta t_0}) - \frac{1}{\gamma}(1 - e^{-\gamma t_0})\right). \quad (21)$$

We observe from Equation (21) that there is nothing to do with the vaccinated group. Also, the susceptibility is small if either $I_2(0)$ or $\delta$ is small.

If the rate of recovery is not much greater than the rate of losing temporary cross-immunity to DEN-2, the secondary infection with DEN-1 emerges as shown in Figure 3 while the individuals who infected with serotype 2 and has antibody to serotype 1 is very small since the influence of vaccine converage at the initial time.

## 4 Conclusions

In the first scenario, we see that the high vaccine coverage can prevent the subsequent spread. However, it will lead to the high secondary infection at the beginning time of the second phase as well. We note

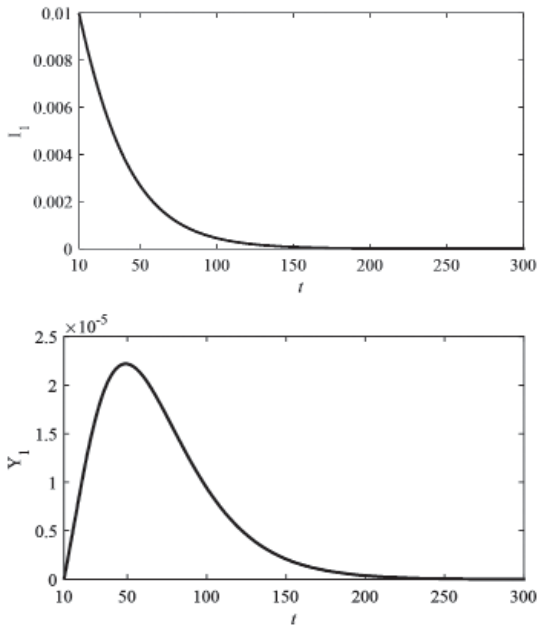


**Figure 3**: Plots of $I_1(t)$ and $Y_1(t)$, respectively when $I_2(0) = 1$, $t_0 = 10$, $\beta = 0.3$, $\gamma = 0.1$, $\delta = 0.02$, $\phi = 0.4$ and $\theta = 0.75$.

however that the result is based on the small fraction of infective at the initial time so that the susceptible to secondary infection is proportional to the vaccine coverage.

In the second scenario, if vaccine coverage is high enough and the rate of recovery is much greater than the rate of losing temporary cross-immunity to DEN-2, the secondary infection to DEN-1 will not occur.

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