Effects of vaccination on dengue transmission dynamics

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Abstract. Around 390 million dengue cases happen annually and two thirds of the world’s population are at risk of attracting dengue. Dengue is caused by four distinct serotypes where infection by one of the serotypes provides lifelong immunity to that serotype but has a higher chance of attracting the more dangerous forms of dengue (Dengue Hemorrhagic Fever(DHF) or Dengue Shock Syndrome (DSS)) in subsequent infections. Therefore, a perfect strategy against all dengue serotypes is required to reduce the number of dengue infections. A dengue vaccine with the efficacy of 54–77% has been approved for use in reducing dengue transmission. The use of this ‘imperfect’ vaccine may increase the possibility of individuals to attract DHF or DSS. Using a deterministic mathematical model, we assess the impact of the use of dengue vaccine. The results showed that vaccinating seronegative individuals may increase the number of secondary infections. On the other hand, the number of secondary infections decrease if we vaccinate seropositive individuals. This indicates that the risk of attracting DHF or DSS increases if we vaccinate seronegative individuals. Our results imply that the vaccination program may be successful when we vaccinate seropositive individuals.

1. Introduction
Dengue has been a problem in the world with around 390 million cases annually. The two thirds of the world population are at risk of contracting dengue [1] particularly in tropical and subtropical areas including Indonesia. Dengue is caused by four distinct serotypes where infection by one of the serotypes provides long-life immunity to that serotype although there is a possibility to be reinfected by the same serotype [2]. Individuals may have chance to attract the more dangerous forms of dengue (Dengue Hemorrhagic Fever(DHF) or Dengue Shock Syndrome (DSS)) in the subsequent infections which may be due to the effects of Antibody Dependent Enhancement (ADE) [1]. This means that strategies against dengue should be effective against all dengue serotypes.

The traditional strategies such as insecticides have been implemented but they are not sustainable. A current new strategy is to use the Wolbachia bacterium. The Wolbachia can reduce the number of primary and secondary infections [3, 4, 5]. This is strongly effective in regions with low to moderate transmission levels [3, 4, 5]. The latest strategy that has been proposed is to use vaccine. A dengue vaccine with 54–77% efficacy level has been approved for the
use in reducing dengue transmission. Research showed that the vaccine can be strongly effective in areas with high transmission level [6]. However, due to the imperfect dengue vaccine, the use of dengue vaccine can increase the risk of attracting the DHF or DSS [6, 7]. The question that then arises is “what type of individuals (seropositive or seronegative) should be vaccinated?” Therefore, an analysis is required to understand the dengue transmission dynamics with the use of an ‘imperfect’ dengue vaccine.

Mathematical model can be used to understand complex phenomena such as rumor propagation [8] and disease transmission dynamics [2]. In this paper, using a deterministic mathematical model, we aim to answer the aforementioned question. We also perform a global sensitivity analysis to determine the influential parameters of the model. The remaining parts of the paper is organised as follows. Section 2 presents a two-serotype dengue model with vaccination. Section 3 presents the results which consist of numerical solutions and sensitivity analysis. Section 4 presents the discussion and conclusions.

2. Mathematical Model
A two-serotype dengue model with vaccination has been formulated. The model is in the form of system of differential equations. The variables of the model are given in Table 1. The human population is divided into fully susceptible, seronegative vaccinated, primary infected with serotype $i$, recovered from primary infection, susceptible to the serotypes other than $i$, vaccinated seropositive with serotype $i$, secondary infected with serotype $i$, and fully recovered compartments. The mosquito population is divided into susceptible and infected with serotype $i$ compartments. The $i$ denotes the dengue serotypes ($i = 1, 2$).

In this model, vaccination has been implemented in seronegative and seropositive individuals. The individuals birth at rate $\mu_h$ and the proportion of $p$ is vaccinated and move to the vaccinated class ($V$). The susceptible and vaccinated individuals are infected with dengue after being bitten by mosquitoes with serotype $i$ at a rate $\beta_h$ and $(1 - \epsilon)\beta_h$ for susceptible and vaccinated individuals respectively. They are then recovered from dengue. After certain period, the recovered individuals are susceptible to the serotype that they are not previously infected with. The recovered and susceptible individuals (seropositive) are then vaccinated at a rate $c$ and move to the vaccinated compartment. They may be reinfected with dengue when the vaccine loses its efficacy at rate $1 - \epsilon_2$ and are bitten by the mosquitoes carrying serotypes that they are not previously infected with. The process continues until they are fully recovered.

The mosquitoes obtain dengue virus after they bite infected individuals (primary or secondary infections). When mosquitoes bite the secondary infected individuals, the probability of obtaining dengue is higher due to the antibody-dependent enhancement (ADE). The ADE rate is represented by the parameter $\sigma$. The descriptions of the model’s variables are given in Table 1. The model is governed by a system of differential equation as given in Equation (1).
Table 1. The description of the variables. $i = 1, 2$.

| Variable | Description |
|----------|-------------|
| $S$      | Susceptible individuals |
| $V$      | Vaccinated individuals (seronegative) |
| $I_i$    | Primary infected individuals with serotype $i$ |
| $R_i$    | Recovered individuals from primary infection with serotype $i$ |
| $S_i$    | Susceptible individuals who are immune to serotype $i$ |
| $V_i$    | Vaccinated individuals (seropositive) with serotype $i$ |
| $X_i$    | Individuals with secondary infection of serotype $i$ |
| $Z$      | Recovered individuals |
| $S_v$    | Susceptible mosquitoes |
| $I_{vi}$ | Infected mosquitoes with serotype $i$ |

\[
\begin{align*}
S' &= (1 - p)\mu_hN_h - \frac{\beta_h S (I_{v1} + I_{v2})}{N_h} - \mu_h S, \\
V' &= p\mu_hN_h - \frac{(1 - \epsilon)\beta_h V (I_{v1} + I_{v2})}{N_h} - \mu_h V, \\
I'_1 &= \frac{\beta_h S I_{v1}}{N_h} - \gamma_h I_1 - \mu_h I_1, \\
I'_2 &= \frac{\beta_h S I_{v2}}{N_h} - \gamma_h I_2 - \mu_h I_2, \\
R'_1 &= \gamma_h I_1 - (\alpha + c + \mu_h) R_1, \\
R'_2 &= \gamma_h I_2 - (\alpha + c + \mu_h) R_2, \\
S'_1 &= \alpha R_1 - \frac{\beta_h I_{v2} S_1}{N_h} - (c + \mu_h) S_1, \\
S'_2 &= \alpha R_2 - \frac{\beta_h I_{v1} S_2}{N_h} - (c + \mu_h) S_2, \\
V'_1 &= c (S_1 + R_1) - \frac{(1 - \epsilon_2)\beta_h I_{v2} V_1}{N_h} - \mu_h V_1, \\
V'_2 &= c (S_2 + R_2) - \frac{(1 - \epsilon_2)\beta_h I_{v1} V_2}{N_h} - \mu_h V_2, \\
X'_1 &= \frac{(1 - \epsilon)\beta_h I_{v1} V}{N_h} + \frac{(1 - \epsilon_2)\beta_h I_{v2} V_1}{N_h} + \frac{\beta_h I_{v1} S_2}{N_h} - \gamma_h X_1 - \mu_h X_1, \\
X'_2 &= \frac{(1 - \epsilon)\beta_h I_{v2} V}{N_h} + \frac{(1 - \epsilon_2)\beta_h I_{v1} V_1}{N_h} + \frac{\beta_h I_{v2} S_1}{N_h} - \gamma_h X_2 - \mu_h X_2, \\
Z' &= \gamma_h (X_1 + X_2) - \mu_h Z, \\
S'_v &= \mu_v N_v - \frac{\beta_v (I_1 + I_2) S_v}{N_h} - \sigma \beta_v (X_1 + X_2) S_v - \mu_v S_v, \\
I'_{v1} &= \frac{\beta_v I_1 S_v}{N_h} + \frac{\sigma \beta_v X_1 S_v}{N_H} - \mu_v I_{v1}, \\
I'_{v2} &= \frac{\beta_v I_2 S_v}{N_h} + \frac{\sigma \beta_v X_2 S_v}{N_H} - \mu_v I_{v2}.
\end{align*}
\]
3. Results
This section presents numerical solutions and sensitivity analysis. Since the model is complex and the analytical calculations cannot be easily done, we present the numerical solutions of the models. Furthermore, we also conducted the global sensitivity analysis by combining the Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC).

3.1. Numerical Simulations
In this section, we present the numerical solutions of the model. The parameters are given in Table 2.

Table 2. Parameter descriptions and values of the parameters. The unit of the parameters is year$^{-1}$. The parameters are given in literature [1, 3, 4, 5, 7, 9, 11, 12].

| Symbol | Description | Value |
|--------|-------------|-------|
| $p$    | The proportion of vaccinated individual at birth | 0.5   |
| $\mu_h$ | Natural human death rate | 1/65  |
| $\beta_h$ | Transmission rate from mosquito to human | 200   |
| $\gamma_h$ | Recovery rate from primary and secondary infection | 52    |
| $\alpha$ | Progression rate from recovered class (primary infection) to susceptible class of other serotype | 2     |
| $c$    | Vaccination rate of seropositive individuals | 1     |
| $\epsilon$ | Vaccine efficacy for seronegative individuals | 0.4   |
| $\epsilon_2$ | Vaccine efficacy for seropositive individuals | 0.8   |
| $\mu_v$ | Mosquito death rate | 26.07 |
| $\sigma$ | The rate of antibody-dependent enhancement | 1.1   |
| $\beta_v$ | Transmission rate from human to mosquito | 200   |

Figure 1. The number of primary and secondary infections for the last 100 years when the values of $p = 0.1$ (top) and $p = 0.5$ (bottom). The plot starts from year five.
Figure 1 shows that the number of secondary infections is higher than that of primary infections when the proportion of vaccinated individuals at birth ($p$) is 0.5 and is lower than that of primary infections when the value of $p$ is 0.1. This indicates that vaccinating seronegative individuals increases the probability of attracting the secondary infections. Furthermore, there is a fluctuation in the number of infected individuals in the first 20 years before reaching the steady state.

3.2. Sensitivity analysis
We will conduct a sensitivity analysis by combining Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficient (PRCC). The details of the method can be seen in [13, 15]. The method is the following.

Suppose there are $K$ parameters and $N$ samples. Then the LHS matrix, $L$, and the output, $O$, are

$$L = \begin{bmatrix} p_{11} & p_{12} & \cdots & p_{1K} \\ p_{21} & p_{22} & \cdots & p_{2K} \\ \vdots & \vdots & \ddots & \vdots \\ p_{N1} & p_{N2} & \cdots & p_{NK} \end{bmatrix}, \quad O = \begin{bmatrix} O_1 \\ O_2 \\ \vdots \\ O_N \end{bmatrix}. $$

The output is the solutions of the mathematical model using the input parameters as in LHS matrix. The next step is to rank the samples of each parameter and the output $O$, in order of increasing size and obtain the matrices

$$L_R = \begin{bmatrix} l_{11} & l_{12} & \cdots & l_{1K} \\ l_{21} & l_{22} & \cdots & l_{2K} \\ \vdots & \vdots & \ddots & \vdots \\ l_{N1} & l_{N2} & \cdots & l_{NK} \end{bmatrix}, \quad O_R = \begin{bmatrix} o_1 \\ o_2 \\ \vdots \\ o_N \end{bmatrix},$$

where the elements of matrix $L_R = [l_{ij}]$ and $O_R = [o_i]$, where $l_{ij} \in \{1, \ldots, K\}$ is the rank of parameter $p_{ij}$ in our parameter sample ordering and $o_i \in \{1, \ldots, N\}$ is the rank of output $O_i$ in the ordering of our output values.

The partial rank correlation coefficient between $L_R$ and $O_R$ is calculated using the formula [15]

$$\gamma_{xy} = \frac{\text{Cov}(l_j, o_i)}{\sqrt{(\text{Var}(l_j)\text{Var}(o))}} = \frac{\sum_{i=1}^{N} (l_{ij} - \mu_l)(o_i - \mu_o)}{\sqrt{\sum_{i=1}^{N} (l_{ij} - \mu_l)^2 \sum_{i=1}^{N} (o_i - \mu_o)^2}}, \quad (2)$$

where $\mu_l$ and $\mu_o$ are the sample average, and $j = 1, 2, \ldots, K$.

The value of PRCC is used to identify the sensitivity of the parameters. If the values of PRCC of the parameter is close to 1 or -1, the parameter is more influential. The negative and positive values indicates the relationship between the parameter and the output.

Figure 2 shows the PRCC values over time. It is measured against the increasing number of primary infection which is the solution of

$$\frac{dC_{IP}}{dt} = \frac{\beta_h SI_{v1}}{N_h} + \frac{\beta_v SI_{v2}}{N_h}. \quad (3)$$

It shows that the transmission rate from human to mosquitoes and mosquito to human ($\beta_h$ and $\beta_v$), and the proportion of vaccinated individuals at birth ($p$) are the most influential
parameters with the latter being negative relationships. This means that when the $p$ is higher, the number of primary infection decreases. If the transmission rates are high, the number of primary infection is higher. The antibody-dependent enhancement rate ($\sigma$) can also contribute to the increasing number of primary infections. It also gives positive relationship. When the ADE rate increases, the number of primary infection also increases. Furthermore, the mosquito death rate is also influential and has negative relationship to the increasing number of primary infection. If the death rate of mosquitoes increases, the number of primary infection decreases.

Figure 3 shows the PRCC values against time for the secondary infections. It is measured against the increasing number of secondary infection which is the solution of the equation

$$
\frac{dC_{IS}}{dt} = \frac{(1 - \epsilon) \beta_h I_{e1} S}{N_h} + \frac{(1 - \epsilon_2) \beta_h I_{V1} V_2}{N_h} + \frac{\beta_h I_{e1} S_2}{N_h} + \frac{(1 - \epsilon_2) \beta_h I_{V2} S_1}{N_h}. \tag{4}
$$

The results show that in general the most influential parameters are similar to that of secondary infections. However, the parameter $p$ has positive relationship. This means that when the proportion of vaccination individuals at birth (seronegative) increases, the number of secondary infections also increases. Furthermore, the efficacy of vaccine has negative relationship. The vaccine efficacy for seropositive individuals is more influential that that for seronegative individuals. The vaccination rate of seropositive individuals has negative relationship to the increasing number of secondary infection. This means that an increase in this parameter leads to a decrease in the number of secondary infection.
4. Discussion and Conclusions
This paper presents a two-serotype dengue model with vaccination. The results show that although the decrease in seronegative vaccinated individuals decreases the number of primary infections, it increases the number of secondary infections. On the other hand, an increase in vaccination rate of seropositive individuals may decrease the number of secondary infection. The results are similar that that found by Aguiar et al. [10], Ferguson et al. [6], Flasche et al. [14]. The results may imply that vaccination benefits the population in high-transmission areas [6] because the population may have possibility to be infected with dengue before vaccination has been implemented.

The numerical solutions are in line with the results of sensitivity analysis. When \( p \) is higher, the number of secondary infection is higher. On the other hand, the number of secondary infection decreases when we decrease the value of \( p \). Note that the fluctuation in the early period before reaching the steady state may need to be investigated further. This may indicate the risk of the use of dengue vaccine in the early period. The results indicate that the vaccination program may be successful if we vaccinate the seropositive individuals, which is individuals who have dengue before they are vaccinated.

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