Development of Two-Serotype Dengue Model with Vaccination Impacts for Predicting Transmission of Dengue in Thailand

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Abstract: In this study, the mathematical model of dengue disease with two serotype of standard incidence rate is developed by taking into account an impact of dengue vaccination, i.e., vaccination rate, vaccine efficacy and vaccine wanes. The developed model named dengue-vaccine model is based on Susceptible-Exposed-Infected-Recovered (SEIR) epidemic model paying attention to a latent period after infection before becoming infectious. The mathematical analyze revealed that the model exhibit the phenomenon of backward bifurcation where the stable diseases free equilibrium coexists with a stable endemic equilibrium. And the backward bifurcation is removed when the disease-induced death rate is zero. To validate the developed model, the real data of dengue outbreak in Thailand 2013 is employed to study and verify the model efficiency. It shows that three vaccination parameters values of vaccination rate (\( \xi \)), vaccine efficacy (\( \epsilon \)) and waning rate of vaccine (\( \alpha \)), respectively are critically important in controlling the transmission of dengue with two serotypes. The comparing results demonstrated that the predicted data produced by the developed dengue-vaccine model fit well to the actual data. These demonstrated that the developed model can be used as a suitable tool for predicting the dengue transmission in Thailand.

Key words: Backward bifurcation, dengue, secondary infection, two-serotype, vaccination, transmission

INTRODUCTION

A viral mosquito-borne infection, known as dengue has become a major international public health concern in recent years. It is cause of illness leading to death with more than 50 million dengue fever cases per year in the tropical and subtropical regions (Kauther et al., 1997; Halstead, 2007) and 400 million dengue infection cases year in the world (Bhatt et al., 2013). Although, the fifth strain of the dengue virus has been discovered (Normile, 2013), there are four the dengue serotypes closely coexisting in many endemic areas (Gubler, 1998; Gibbons et al., 2007), i.e., DEN 1, DEN 2, DEN 3 and DEN 4. Infection with one serotype provides life-long immunity to that serotype (WHO., 2015) but only temporary partial immunity to the other three serotypes (WHO., 2015; Dejnirattisai et al., 2010). Reinfection with a different serotype of patients is called secondary infection leading to increase at the risk of Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). The multiple serotype of dengue virus can result in more severe disease (DHF) (Gubler, 1998) and facilitating infectivity.

Nowadays, the efficacious dengue vaccine for the secondary infection which has been registered and evaluated in clinical trials is CYD-TDV (Chimeric Yellow Fever Dengue Tetravalent Dengue Vaccine) (CDC., 2019; WHO., 2019). The vaccine includes of 3-doses which each dose is apart spaced 6 months. After 3-dose of vaccination, the epidemic of dengue disease will be reduced and it can reduce high disease severity leading to death of the infected human. The point that is the control of infected population can inhibit the spread of dengue disease. No patient means no common source of epidemic, consequently, the dengue disease can be controlled by controlling the infection of population. The results by Halstead (2007) point out that a dengue vaccine, Dengvaxia, seems to induce dengue infection-enhancing Antibodies (ADE). Thus, the dengue vaccination plays a crucial role in the epidemic of dengue disease with two serotypes.

Recently, a Mathematical model called epidemic model has been generally employed as an important tool for understanding communicable diseases epidemiology, taking to great development for epidemic disease control.
predicting the potential of the epidemic disease transmission. For the dengue disease, many mathematical models have been studied and developed by many researchers with the significantly different aspects for great advance in representing of dengue behavior. To achieve that some researchers have tried to incorporate various factors focusing on several effects, e.g., patent age, sequence of infection, dengue serotype, incidence rate, immunity, vaccination and so forth. However, it may become too much in mathematical difficulty in the modeling formulation and determination of its parameters. For dengue vaccine efficiency in preventing the infection, an influence of vaccination on dengue model has been investigated by several researchers during the recent decade. Garba et al. (2008) have extended the model incorporate an imperfect vaccine against the strain of dengue. The results shown that an imperfect vaccine influences on the efficiency of dengue disease control in a community if the vaccine coverage and vaccine efficacy are high enough. A set of simulations with different efficacy and different ways of distributing the vaccine being a useful tool for reducing disease spread within the community have presented by Rodrigues et al. (2014). Likewise, the dengue model with two-serotype has been extended by developing an age structured model and with vaccinated individuals age 9-45 years in dengue endemic countries following the WHO recommendation (Aguir et al., 2011). Nevertheless, the model have been assumed that persons of any age will benefit from vaccination (e.g., high rates of decreasing hospitalizations) when they have experienced at least one dengue infection for seropositive individuals only. Whereas vaccination of seronegative individuals increases the risk of vaccine disease enhancement and hospitalization. Moreover, vaccine efficacy in prevention for hospitalized dengue cases have been estimated by using available hospitalized dengue data (Stollenwerk et al., 2012; Mateu et al., 2013). The parameter was obtained by matching the last 5 years the dengue data for Chiang Mai Thailand. The results indicated that reserving vaccine for seropositive persons should provide a high level of protection whereas indiscriminately vaccinating could increase the number of hospitalizations on the population level. Similarly, Aguir et al. (2016a, b) have estimated vaccine efficacy via Bayesian’s approach by using the trial data of public available vaccine. As a result of an age structured model analysis, a significant reduction of hospitalizations have found only when the vaccine is provided to seropositive individuals. However, although these studies have given great contributions in the dengue transmission, some aspects are still inadequate for modelling the dengue transmission. For instance, Most of those dengue models are based on the Susceptible-Infected-Recovered (SIR) epidemic model which ignores a latent period. It is incubation period before the hosts become infectious and very important because of the unpredictable climate change nowadays. Likewise, the occurring of backward bifurcation phenomenon in dengue model playing a crucial role for disease control and transmission has not been investigated in some of them.

In this study, the two-serotype dengue model is developed by based on Susceptible-Exposed-Infected-Recovered (SEIR) epidemic model taking in to account the incubation in the transmission process. Since, it is more realistic than the SIR model as a result of life cycle consideration of the dengue disease. Then the model is extended to include vaccine factors i.e., vaccination rate, vaccine efficacy and vaccine wanes. The impact of vaccination is also studied by using sensitivity analysis. Moreover, the backward bifurcation phenomenon relating to the stability of the developed model is investigated as well. The developed model is validated by applying to the real data of dengue outbreak in Thailand 2013. Set of vaccine parameters significantly controlling the transmission of dengue with two serotypes is also identified as a useful tool for predicting dengue transmission in Thailand.

MATERIALS AND METHODS

Model formulation: The dengue disease can spread to humans by bite of Aedes mosquitoes. Two populations are considered as human population and mosquito population, respectively. It is known that once a person is infected and recovers from one serotype, lifelong immunity to that serotype is conferred while it may also confer temporary cross immunity to the other serotypes. However, it is postulated that individuals with secondary infection are more infectious than during their first infection and they have at greater risk of developing a severe form of the disease. This study, thus, aims to formulate the dengue vaccine model with two serotypes for study the impact of vaccine on the dynamics of the dengue. The dengue vaccine model based on assuming a homogenous mixture of both human and mosquito populations, so that, each mosquito bite is as likely to transmit the virus to humans regardless of the type of the virus is formulated under the following assumptions:

Human population: Consider the transmission of dengue in the primary and secondary infections, the total human population at time t denoted by \( N_h(t) \), represented by a state flow diagram in Fig. 1 is divided into thirteen sub-populations: Susceptible Human \( (S_h(t)) \) who is susceptible to both serotypes, i.e., serotype-I and
serotype-II, vaccinated human (P_v(t)) who are vaccinated against the dengue fever, the population in primary infection consisting of exposed human with serotype-I (E_{v1}(t)), infected human with serotype-i, (I_{v1}(t)) and recovered human from the first infection with serotype-I (R_{v1}(t)), for i = 1, 2, the population in secondary infection when the first infection was caused by serotype-i, consisting of exposed human for second time exposed with serotype-j when the first infection was caused by serotype-I, (E_{v1}(t)), infected human for second time infected with serotype-j when the first infection was caused by serotype-i (I_{v1}(t)) for i ≠ j, i, j = 1, 2 and recovered human population who recovers from infection with both serotypes (R_{v12}(t)). Therefore, the total human population, N_{h}(t) is given by Eq. 1:

\[ N_{h}(t) = S_{h}(t) + P_{v}(t) + \sum_{i=1}^{2} (E_{v1}(t) + I_{v1}(t) + R_{v1}(t)) + \sum_{i=1}^{2} \sum_{j=1, j ≠ i} (E_{v1}(t) + I_{v1}(t) + R_{v1}(t)) + \sum_{i=1}^{2} (E_{v1}(t) + I_{v1}(t) + R_{v12}(t)) \] (1)

Susceptible individuals are generated by birth or by immigration at a rate \( II_{r} \) and by vaccinated individuals who lose immunity acquired by preventive vaccine due to vaccine wane at the rate \( \omega \). This population is reduced through vaccination (moving to vaccinated class P_v) at a rate, \( \varphi_p \), infection (moving to exposed class by infected dengue with serotype-i \( (E_{v1}) \) at a rate \( \varphi_i \), i = 1, 2 and natural death at a rate \( \mu_{v1} \).

The vaccinated human population is increased with the vaccination of susceptible at a rate. Since, dengue vaccine is developed in clinical development, dengue vaccine would be imperfect. It is assumed that vaccinated individuals acquire via effective contact with an infectious mosquito at the rate \( \varphi_{v}(1-\varepsilon) \) where, \( 0 < \varepsilon < 1 \) is the vaccine efficacy and \( \varphi_{v}, i = 1, 2 \) are the force of infection of humans with serotype-i, given by Eq. 2:

\[ \varphi_{r} = \frac{b_{r}I_{v}}{N_{h, r}} \] (2)

where, \( b_{r}(i = 1 \text{ or } i = 2) \) is the transmission probability from an infected mosquito with serotype-i to a susceptible human. The vaccinated class is reduced by the infection with serotype-i (moving to the class of exposed with serotype-i \( (E_{v1}) \) at the rate \( \varphi_{i}(1-\varepsilon) \), natural death at the rate \( \mu_{v} \) and waning of vaccine-based immunity at the rate \( \omega \).
### Table 1: Estimated parameter values used in the models (Eq. 4) and (5)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Descriptions</th>
<th>Value (range)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Pi_H$</td>
<td>Recruitment rate of human, 1/day</td>
<td>55</td>
<td>-</td>
</tr>
<tr>
<td>$\Pi_0$</td>
<td>Recruitment rate of mosquito, 1/day</td>
<td>16000</td>
<td>-</td>
</tr>
<tr>
<td>$\mu_H$</td>
<td>Natural death rate of human, 1/day</td>
<td>0.0143 (0.0133-0.0154)</td>
<td>-</td>
</tr>
<tr>
<td>$\mu_0$</td>
<td>Natural death rate of mosquito, 1/day</td>
<td>0.0714 (0.0714-0.1667)</td>
<td>-</td>
</tr>
<tr>
<td>$\delta_i$</td>
<td>Disease-induced death rate for infected human with serotype-i, 1/day</td>
<td>0.0005</td>
<td>0.2 (0.1-0.25)</td>
</tr>
<tr>
<td>$\sigma_i$</td>
<td>Rate at which an infected human with serotype-i becomes infectious, 1/day</td>
<td>0.1667 (0.1667-0.3333)</td>
<td>0.2 (0.1-0.25)</td>
</tr>
<tr>
<td>$\gamma_i$</td>
<td>Recovery rate from serotype-i, 1/day</td>
<td>0.1667 (0.1667-0.3333)</td>
<td>0.2 (0.1-0.25)</td>
</tr>
<tr>
<td>$\lambda_i$</td>
<td>Temporary cross-immunity with serotype</td>
<td>0.01 (0-1)</td>
<td>-</td>
</tr>
<tr>
<td>$\eta_{bi}$</td>
<td>Modification parameters with serotype</td>
<td>0.3 (0-1)</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_i$</td>
<td>Transmission probability rate from infected mosquito with serotype-i to susceptible human, 1/day</td>
<td>0.75 (0.1-0.75)</td>
<td>-</td>
</tr>
<tr>
<td>$\beta_{ni}$</td>
<td>Transmission probability rate from infected mosquito with serotype-i to susceptible human, 1/day</td>
<td>0.75 (0.1-0.75)</td>
<td>-</td>
</tr>
<tr>
<td>$b$</td>
<td>Biting rate, 1/day</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>$e$</td>
<td>Vaccine efficacy</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>$\xi$</td>
<td>Vaccination rate</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Waning rate of vaccine</td>
<td>0.3</td>
<td>-</td>
</tr>
</tbody>
</table>

### Mosquito population:

For mosquito population, due to life cycle of Aedes aegypti is short (approximated one and a-half to 5 weeks), it is assumed that once a mosquito is infected with one serotype it never recovers from the infection and it cannot be re-infected with a different serotype (Garba et al., 2008), so that, secondary infection may take place only in human population. The total mosquito population at time $t$, therefore, denoted by $N_v(t)$ is split into five sub-populations: susceptible mosquito, ($S_v(t)$) exposed mosquito with serotype-i ($E_v(t)$) and infected mosquito with serotype-i ($I_v(t)$), so that, Eq. 3:

$$N_v(t) = S_v(t) + \sum_{i=1}^{2} (E_v(t) + I_v(t))$$

The susceptible mosquito population is increased by birth at a constant rate $\Pi_0$. This population is decreased by the infection with serotype-i (moving to the class of exposed with serotype-i ($E_v(t)$) at the rate $\varphi_v$ and natural death at the rate $\mu_v$. The force of infection of mosquito with serotype-i ($\varphi_v$) are given by Eq. 4:

$$\varphi_v = b\beta_{vi}\left(\eta_{vi}(E_v(t) + I_v(t)) + I_{hi}(t)\right) / N_{bre}$$

For $i = j, i, j = 1, 2$ where $\beta_{vi}$ is the transmission probability from infected human with serotype-i to a susceptible mosquito and the parameter $\eta_{vi}\in(0, 1)$ accounts for the reduction in transmissibility with serotype-i of exposed human relative to infected human. The model of human population with vaccination, therefore, can be described by the following system of nonlinear differential equations:

### Human population:

$$\begin{align*}
\frac{dS_h}{dt} &= \Pi_h + \alpha P_h - \sum_{i=1}^{2} \varphi_h S_h - \left(\xi + \mu_h\right) S_h \\
\frac{dE_h}{dt} &= \xi S_h - \sum_{i=1}^{2} \varphi_i \left(1 - e\right) P_h - \left(\sigma_i + \mu_h\right) E_h \\
\frac{dI_h}{dt} &= \varphi_i S_h - \varphi_i \left(1 - e\right) P_h - \left(\sigma_i + \mu_h\right) I_h \\
\frac{dR_h}{dt} &= \gamma_i I_h - \left(\gamma_i + \delta_i + \mu_h\right) R_h
\end{align*}$$

### Mosquito population:

$$\begin{align*}
\frac{dS_v}{dt} &= \Pi_v - \sum_{i=1}^{2} \varphi_v S_v - \mu_v S_v \\
\frac{dE_v}{dt} &= \sum_{i=1}^{2} \varphi_v S_v - K_{i+1} E_v \\
\frac{dI_v}{dt} &= \sigma_v E_v - \mu_v I_v
\end{align*}$$

where $K_i = \sigma_i + \mu_h, K_{i+2} = \gamma_i + \delta_i + \mu_h, K_{i+4} = \sigma_i + \mu_v$ The systems (Eq. 5) and (6) are called dengue vaccine model. The compartmental model which shows the mode of transmission of dengue between the two interacting populations is depicted in Fig. 1. Equation 5 and 6 is called dengue-vaccine model. All parameters and state
variables of dengue-vaccine model are assumed to be positive. Using similar approach in Table 1, the dynamical behaviors of the systems (Eq. 5) and (6) are studied in the positive invariant set \( \Omega \) Eq. 7:

\[
\Omega = \Omega_1 \cup \Omega_2 \subset \mathcal{R}_+^3 \times \mathcal{R}_+^3
\]

Where:

\[
\Omega_1 = \left\{ \left( \begin{array}{c}
S_0, \ P_0, \ E_0, \ I_{h1}, \ R_{h1}, \ E_{h12}, \ I_{h12}, \ R_{h12}, \\
E_{h2}, \ I_{h2}, \ R_{h2}, \ E_{h21}, \ I_{h21}, \ R_{h21}, \ R_{h22}
\end{array} \right) \in \mathcal{R}_+^3, \ N_{thres} \leq \frac{\Pi_{h}}{\mu_h} \right\}
\]

\[
\Omega_2 = \left\{ \left( \begin{array}{c}
S_v, \ E_v, \ I_{v1}, \ V_{v2}, \ I_{v1}, \ V_{v2}
\end{array} \right) \in \mathcal{R}_+^3, \ N_v \leq \frac{\Pi_v}{\mu_v} \right\}
\]

**Equilibrium and stability:** This section demonstrates the acquisition of the threshold value called the basic reproductive number to present the condition for the existence of positive equilibria. Stabilities of equilibria of the model are analyzed for understanding the dynamics of the dengue vaccine model and investigated the phenomenon of backward bifurcation.

**Local stability of disease-free equilibrium:** The dengue-vaccine model has a Disease-Free Equilibrium (DFE), \( P_{vke}^0 \), given by Eq. 8:

\[
P_{vke}^0 = \left( \begin{array}{c}
S_0^0, \ P_0^0, \ E_0^0, \ I_{h1}^0, \ R_{h1}, \ E_{h12}, \ I_{h12}, \ R_{h12}, \\
E_{h2}^0, \ I_{h2}, \ R_{h2}^0, \ E_{h21}, \ I_{h21}, \ R_{h21}, \ R_{h22}
\end{array} \right)
\]

\[
= \left( \begin{array}{c}
\Pi_h \left( \alpha + \mu_h \right) \\
\mu_h \left( \alpha + \xi + \mu_h \right) \\
0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0
\end{array} \right)
\]

Similarly as described in Theorem 2.2, by using the next generation (Carr, 1981), the reproduction number of dengue-vaccine model is given by:

\[
R_{ve} = \max \{R_{ve1}, R_{ve2}\}
\]

where, \( R_{ve1} \) and \( R_{ve2} \) are the vaccine-induced reproduction numbers for serotype-I and serotype-II, respectively, given by Eq. 10:

\[
\begin{aligned}
R_{ve1} &= \frac{\Pi_h b \beta_h \sigma_h \mu_h \left( \alpha + \xi + \mu_h \right)}{\mu_h \mu_r K_{h1} K_{h2} K_{h12}} \bigg( \alpha + \xi + \mu_h \bigg) \\
R_{ve2} &= \frac{\Pi_h b \beta_h \sigma_h \mu_h \left( \alpha + \xi + \mu_h \right)}{\mu_h \mu_r K_{h1} K_{h2} K_{h12}} \bigg( \alpha + \xi + \mu_h \bigg)
\end{aligned}
\]

Hence, using theorem 2.2 of van den Driessche and Watmough (2002), the following lemma is established.

**Lemma 1:** The DFE, given in Eq. 8, of the system (Eq. 5) and (6) is Locally Asymptotically Stable (LAS) in \( \Omega \) whenever \( R_{ve1} < 1 \) and unstable if \( R_{ve1} > 1 \). The threshold quantity, \( R_{ve} \), represents the average number of secondary cases that one case can produce if introduced into a human community where a fraction of the susceptible population has been vaccinated. Lemma 1 verifies that if \( R_{ve1} < 1 \), vaccination has a positive impact on disease control by decreasing dengue prevalence because of the DFE is LAS.

The concept of reproductive number, \( R_{ve} \), introduced by van den Driessche and Watmough is defined in epidemiological modelling as the average number of infected individuals produced by one infected individual introduced completely in a population susceptible. Thus, if \( R_{ve} < 1 \), the disease dies out and if \( R_{ve} > 1 \), the disease spreads in the population and goes to an endemic level. For a disease that confers immunity in which the susceptible population is vaccinated it has been demonstrated that under certain parameter conditions there is a dependence of the reproduction number on the vaccination rate. In such a case, the reproduction ratio, \( R_{ve} \) which is the basic reproduction ratio \( R_0 \) modified by vaccination, must be reduced below one in order to ensure that the disease dies out. If there is no vaccination, then \( R_{ve} = R_0 \). Therefore, \( R_{ve} \) the basic reproductive number under vaccination is the number of secondary cases caused by one primary case introduced into a population in which a proportion of vaccinated humans.

**Positive equilibria and backward bifurcation:** Let:

\[
P_{vke}^* = \left( \begin{array}{c}
S_1^*, \ P_1^*, \ E_1^*, \ I_{h1}^*, \ R_{h1}^*, \ E_{h12}^*, \ I_{h12}^*, \ R_{h12}^*, \\
E_{h2}^*, \ I_{h2}^*, \ R_{h2}^*, \ E_{h21}^*, \ I_{h21}^*, \ R_{h21}^*, \ R_{h22}^*
\end{array} \right)
\]

Be an arbitrary positive endemic equilibrium at steady-state. Further, let:

\[
\phi_i^* = \frac{b_i \beta_i}{N_{thres}}
\]

Be the force of infection of human with serotype-i at steady-state and:

\[
\phi_i^* = \frac{\beta_{h_i} b_i \eta_i \left( E_{h_i}^* \right) + I_{l_i}^* \left( I_{h_i}^* + I_{l_i}^* \right)}{N_{thres}}
\]

Be the force of infection of mosquito with serotype-i at steady-state, respectively, for \( i = 1, 2 \), and \( i, j \). Setting all derivative in Eq. 5 and 6 equal to zero and solving for the state variables at steady-state, yield Eq. 14:
\[ S^*_n = \frac{\prod_{i=1}^{n} \sum_{i=1}^{n} \phi_i^*(1 - \epsilon) + \sigma_i \mu_i}{\sum_{i=1}^{n} \sum_{i=1}^{n} \phi_i^*(1 - \epsilon) + \sigma_i \mu_i + \zeta} \]

\[ P^*_n = \frac{\xi S^*_n}{\sum_{i=1}^{n} \phi_i^*(1 - \epsilon) + \sigma_i \mu_i}, \quad E^*_n = \frac{\phi_i^*(S^*_n - (1 - \epsilon)P^*_n)}{K_i} \]

\[ I_{1n}^* = \frac{\sigma_i E^*_n}{K_{1n}}, \quad R_{1n}^* = \frac{\gamma_i I_{1n}^* + \sigma_i \phi_i^*}{\mu_i} \]

\[ R_{2n}^* = \frac{\gamma_i I_{2n}^* + \sigma_i \phi_i^*}{\mu_i} \]

(14)

For positive fixed points \( \phi_i^* \) and \( \phi_i^* \) and then substitute them into expression (Eq. 14 and 15). Analysis of the positive endemic equilibria are summarized in the following lemma.

**Lemma 2:** The dengue vaccine model has: (i) serotype-I boundary equilibrium whenever \( R_{1v} < 1 < R_{2v} \), denoted by Eq. 17:

\[ P_{1v}^* = \left( S_{1v}^*, P_{1v}^*, E_{1v}^*, I_{1v}^*, R_{1v}^*, 0, 0, 0 \right) \]

And serotype-II boundary equilibrium whenever \( R_{1v} < 1 < R_{2v} \), denoted by:

\[ P_{2v}^* = \left( S_{2v}^*, P_{2v}^*, 0, 0, 0, 0, E_{2v}^*, I_{2v}^*, 0, 0 \right) \]

(17)

Where:

\[ S_{1v}^* = \frac{\prod_{i=1}^{n} \phi_i^* \left( (1 - \epsilon) + \sigma_i \mu_i \right)}{K_i \left( \sum_{i=1}^{n} \phi_i^* \left( (1 - \epsilon) + \sigma_i \mu_i \right) \right)} \]

\[ P_{1v}^* = \frac{\xi S_{1v}^*}{\phi_i^* \left( (1 - \epsilon) + \sigma_i \mu_i \right)}, \quad E_{1v}^* = \frac{\phi_i^* \left( S_{1v}^* + (1 - \epsilon) P_{1v}^* \right)}{K_i} \]

\[ I_{1v}^* = \frac{\sigma_i E_{1v}^*}{K_{1v}}, \quad R_{1v}^* = \frac{\gamma_i I_{1v}^* + \sigma_i \phi_i^*}{\mu_i} \]

\[ S_{2v}^* = \frac{\prod_{i=1}^{n} \phi_i^* \left( (1 - \epsilon) + \sigma_i \mu_i \right)}{K_i \left( \sum_{i=1}^{n} \phi_i^* \left( (1 - \epsilon) + \sigma_i \mu_i \right) \right)} \]

\[ P_{2v}^* = \frac{\xi S_{2v}^*}{\phi_i^* \left( (1 - \epsilon) + \sigma_i \mu_i \right)}, \quad E_{2v}^* = \frac{\phi_i^* \left( S_{2v}^* + (1 - \epsilon) P_{2v}^* \right)}{K_i} \]

\[ I_{2v}^* = \frac{\sigma_i E_{2v}^*}{K_{2v}}, \quad R_{2v}^* = \frac{\gamma_i I_{2v}^* + \sigma_i \phi_i^*}{\mu_i} \]

(ii) Co-existence equilibrium \( P_{1v}^* \) given in Eq. 10 and 13, 14 whenever \( R_{1v} > 1 \) and \( R_{2v} > 1 \) for \( i, j = 1, 2 \) (i.e.) Further, the phenomenon of backward bifurcation is explored as follows. Since, two serotypes are mathematically symmetric and for mathematical convenience, the serotype-boundary equilibrium is investigated under the assumption \( \phi_i = 0 \). Substituting \( \phi_i = 0 \) into (Eq. 16) gives the fixed point problem \( \phi_i(\psi, 0) = 0 \), for which its fixed point, denoted \( \phi_i^* \), the positive root of Eq. 19:

\[ A_{ii} \left( \phi_i \right)^3 + B_{ii} \left( \phi_i \right)^3 + C_{ii} \left( \phi_i \right)^3 + D_{ii} \phi_i + E_{ii} = 0 \]  

(19)

Where:

\[ A_{ii} = \frac{\prod_{i=1}^{n} \left( (1 - \epsilon) \right) A_i A_i \left( A_i + A_i \right) \geq 0}{\mu_i K_i} \]

\[ B_{ii} = \frac{\prod_{i=1}^{n} \left( (1 - \epsilon) \right) A_i A_i \left( B K_i A_i \left( (1 - \epsilon) \right) \right) + \left( \prod_{i=1}^{n} \left( (1 - \epsilon) \right) A_i A_i \left( (1 - \epsilon) \right) \geq 0 \]

9877
\[ C_{11} = \Pi_{hi} (1-\varepsilon) C_{1} \frac{\Pi_{hi} (1-\varepsilon) A_{i} C_{2}}{\mu_{hi} K_{i}} + \]  
\[ \Pi_{hi} (A_{i} + A_{j}) (1-\varepsilon) B_{i} - \mu_{hi} (1-\varepsilon) A_{i} A_{j} + \]  
\[ \left( \frac{\Pi_{hi}}{\mu_{hi}} A_{j} \right) C_{2} B_{j} - 2(1-\varepsilon) A_{i} A_{j} B_{j} \geq 0 \]  
\[ D_{1i} = \frac{\Pi_{hi}}{\mu_{hi}} \left( R_{i}^{C} - R_{i}^{E} \right), \quad E_{1i} = \frac{\Pi_{hi}}{\mu_{hi}} \mu_{i} K_{i} B_{i} \left( 1 - R_{i}^{C} \right) \]

\[ A_{1} = b \beta_{1} \left( \eta_{i} K_{i} + \sigma_{i} \right) K_{i}, \quad A_{2} = \]  
\[ \mu_{hi} \left( \mu_{i} K_{i} + \sigma_{i} \mu_{hi} + \gamma_{i} \right) K_{i}, \quad A_{3} = \frac{\Pi_{hi} b \beta_{1} \sigma_{i} K_{i}}{\mu_{hi} K_{i}}, \quad A_{4} = \frac{\Pi_{hi} \sigma_{i} K_{i}}{\mu_{hi} K_{i}} \]

\[ B_{2} = \omega_{1} \xi_{1} (1-\varepsilon) + \mu_{hi}, \quad B_{3} = \omega_{1} \xi_{1} + \mu_{hi}, \quad C_{1} = \]  
\[ (A_{i} + A_{j}) B_{i} + \mu_{hi} (1-\varepsilon) K_{i}, \quad C_{2} = \mu_{hi} K_{i} \]

\[ R_{i}^{C} = \frac{\Pi_{hi} \delta_{i} \xi_{i} C_{1} B_{i} - \mu_{hi} K_{i} B_{i}}{\Pi_{hi} \mu_{hi} K_{i} B_{i} \left( B_{i} + \mu_{hi} (1-\varepsilon) \right)} \geq 0 \]

Clearly, \( A_{1i}, B_{1i}, C_{1i} \) are always positive while \( D_{1i} \) and \( E_{1i} \) are positive or negative depending on \( R_{i}^{C} \) and \( R_{i}^{E} \). From the analysis of the coefficients and using Descartes' Rule of Signs (DRS), the following result is established:

**Theorem 1:** Assume that \( \phi_{i} \geq 0 \) and \( R_{i}^{C} \geq 1 \). The system (Eq. 5) and (6) has:

i. Two serotype-i boundary equilibria if \( R_{i}^{C} < R_{i}^{C} < 1 \).

ii. An unique serotype-i boundary equilibrium if \( R_{i}^{C} > 1 \).

Theorem 1 reveals that it is instructive to determine whether dengue vaccine model undergoes the phenomenon of backward bifurcation. Therefore, the Centre Manifold theory (Carr, 1981) is used to determine backward bifurcation threshold conditions at which the dengue vaccine model exhibits. Thus, the following result is established:

**Theorem 2:** When \( R_{i} = \max \{ R_{i}^{C}, R_{i}^{E} \} = R_{i}^{C} = 1 \), \( R_{i}^{C} = 1 \), \( R_{i}^{C} = 2 \), the dengue-vaccine model exhibits a backward bifurcation if \( R_{i}^{E} \geq R_{i}^{C} < 0 \) and \( R_{i}^{E} < 0 \) and a forward bifurcation if \( R_{i}^{E} > 0 \) and \( R_{i}^{C} > 0 \).

Proof: Consider \( R_{i} = \max \{ R_{i}^{C}, R_{i}^{E} \} = 1 \) when \( R_{i}^{C} = 1 \) and \( R_{i}^{E} < 1 \) (the approach to be applied also work if we set \( R_{i}^{E} = 1 \) when \( R_{i}^{C} < 1 \)). Taking \( \beta_{i} = \beta_{i}^{*} \) as a bifurcation parameter. To apply Centre Manifold theory, the bifurcation coefficients \( \alpha \) and \( \delta \) of the dengue-vaccine model are computed in form as follow:

\[ \alpha_{i} = \sum_{k, \ell, m = 1}^{n} \frac{\partial^{2} f_{i}}{\partial x_{k} \partial x_{l}} \left( 0, 0 \right) = \frac{2 \mu_{hi} K_{i} \left( \eta_{i} K_{i} + \sigma_{i} \right)}{\mu_{hi} K_{i} K_{j} \left( 1 - R_{i}^{C} \right)^{2}} \]

And:

\[ \delta_{i} = \sum_{k, \ell, m = 1}^{n} \frac{\partial^{2} f_{i}}{\partial x_{k} \partial x_{l}} \left( 0, 0 \right) = \frac{\Pi_{hi} b \beta_{1} \sigma_{i} K_{i}}{\mu_{hi} K_{i} K_{j}} \left( \mu_{hi} K_{i} + \sigma_{i} \right) \left( \mu_{hi} K_{i} + \sigma_{i} \right) \]

where, \( \omega_{i} > 0 \), \( w_{i} > 0 \) and \( R_{i}^{C} = B_{i}^{2} [A_{i} + A_{j}] \mu_{hi} K_{i} / \mu_{hi} \sigma_{i} K_{i} + \mu_{hi} K_{i} K_{j} \xi_{i}^{2} \). (1-\varepsilon).

Since, the coefficient \( \delta \) is automatically positive, it follows that the dengue-vaccine model will undergo backward bifurcation if the coefficient, \( \alpha \), given by Eq. 19 is positive, that is \( R_{i}^{C} < 1 \). If \( R_{i}^{C} > 1 \), then \( \delta = 0 \). Since, two serotypes are mathematically symmetric. Then we can implies that the dengue vaccine model (Eq. 5) and (6) will undergo backward bifurcation with serotype-i boundary equilibrium when \( R_{i}^{E} < 1 \) and \( R_{i}^{C} < 1 \). If \( R_{i}^{C} > 1 \), then the serotype-i boundary equilibrium is LAS for \( R_{i}^{C} < 1 < R_{i}^{E} \) and \( \beta_{i}^{*} < \beta_{i} \) with \( \beta_{i}^{*} \) close to \( \beta_{i}^{*} \).

It follows from theorem 2 that the dengue vaccine model (Eq. 5) and (6) exhibits the backward bifurcation under the condition \( R_{i}^{C} < R_{i}^{E} < 1 \) and \( R_{i}^{E} < 1 \). On the other hand, the dengue-i vaccine model (Eq. 5) and (6) has an unique serotype-i boundary equilibrium whenever \( R_{i}^{C} < 1 < R_{i}^{E} < 1 \), for \( i = 1 \) and \( i = 2 \).

The backward bifurcation phenomenon of the dengue vaccine model is illustrated by simulating the dengue vaccine model with various initial conditions and the parameter values used: \( \beta_{i} = 0.45 \), \( \delta_{i} = 0.3 \) and the other model parameter values in Table 1. With this set of parameter values, \( R_{i}^{C} = 0.9776 \), \( R_{i}^{E} = 0.9652 \), \( R_{i}^{E} = 0.2838 \) and \( R_{i}^{E} = 0.5581 \), so that, \( R_{i}^{C} = R_{i}^{C} < 1 \), \( R_{i}^{C} < 1 \), and \( R_{i}^{E} < 1 \), respectively which satisfy the conditions in theorem 2. The results are shown in Fig. 2.

The results obtained is suggested that owing to the phenomenon of backward bifurcation in the dengue-vaccine model, dengue elimination when would depends on the initial sizes of the sub-populations of the dengue-vaccine model.
Fig. 2: The dengue-vaccine model

Furthermore, it can be shown that the backward bifurcation is removed when the disease-induced death rate ($\delta_i$) is zero. Thus, the effect of the vaccine efficacy and $\delta_i$ on this phenomenon is investigate by substituting $\delta_i=0$ into $R_{\text{net}}^*$. It can be shown that:

$$R_{\text{net}}^* = \left( \frac{(\xi+\xi)(1-e)+\mu_h}{\mu_h(1-e)} \right)^{1-\frac{\mu_h\beta_h(\gamma_1+\mu_h)+\sigma_i}{\mu_hK_1(\gamma_1+\mu_h)}} > 1$$

(22)

It is clear, from (Eq. 20) that if the parameter $\delta_i=0$ then $R_{\text{net}}^*>1$. These results indicate that the backward bifurcation is removed when the disease-induced death rate ($\delta_i$) is zero.

Dependence on vaccination rate ($z$), vaccine efficacy ($\varepsilon$) and vaccine wanes ($\omega$): The impact of vaccination is investigated by using sensitivity analysis (i.e., differentiating $R_{\text{net}}$ partially with respect to control parameters vaccination rate ($\xi$), vaccine efficacy ($\varepsilon$) and vaccine wanes ($\omega$), respectively. It is found that:

$$\frac{\partial R_{\text{net}}}{\partial z} = \frac{1}{2} \frac{\varepsilon (\omega+\mu_h) R_0}{(\omega+\xi)(1-e)+\mu_h} < 0$$

$$\frac{\partial R_{\text{net}}}{\partial \varepsilon} = \frac{1}{2} \frac{\xi R_0}{(\omega+\xi)(1-e)+\mu_h} < 0$$

$$\frac{\partial R_{\text{net}}}{\partial \omega} = \frac{1}{2} \frac{e \xi R_0}{(\omega+\xi)(1-e)+\mu_h} < 0$$

(23)

Where:

$$R_{\text{net}} = R_0 \sqrt{\frac{\omega+\xi(1-e)+\mu_h}{\omega+\xi+\mu_h}}$$

$$R_0 = \frac{\prod_i b_i \beta_i \sigma_i \mu_i}{\prod_i \mu_i K_i K_i K_i K_i}$$

(24)

It is clear from Eq. 23 that increasing values of $\xi$ and $\varepsilon$ reduce $R_{\text{net}}$ while $R_{\text{net}}$ increases as increasing $\omega$.

The study results indicate that in controlling the disease, vaccination rate must be increasing, vaccine efficacy must be high and no vaccine wane. The critical values of $\xi$, $\varepsilon$ and $\omega$ denoted by $\xi_c$, $\varepsilon_c$ and $\omega_c$, respectively are obtained by setting (Eq. 24) equal to one and solving, given by:

$$\xi_c = \frac{(\omega+\mu_h)(R_0-1)}{1-(1-e)R_0}$$

$$\varepsilon_c = \frac{(\xi+\xi+\mu_h)(R_0-1)}{\xi R_0}$$

$$\omega_c = \frac{(\varepsilon+\mu_h)(\xi+\xi+\mu_h)R_0}{R_0}$$

(25)

For these requirements, vaccination has a positive impact on dengue control. It follows from Eq. 25 and the parameters $\xi$, $\omega$, $\varepsilon[0,1]$ that if $R_{\text{net}}<1$ that is $\xi>\xi_c$, $\varepsilon>\varepsilon_c$ and $\omega>\omega_c$.

RESULTS AND DISCUSSION

The impact factor of vaccination for controlling disease control: Dengue vaccination policies aim to produce immunity to provide long-term protection against all four serotypes. In addition, vaccine creates the immune to vaccinated individual. It can also create herd immunity too. Herd immunity is a form of immunity that occurs when a part of portion population is vaccinated then provides the protection for individuals who have not developed immunity. Therefore, the number of individuals vaccinated and vaccine efficacy are a part of important factor for controlling disease. From Lemma 1, the disease-free equilibrium ($P_{DFE}$) of dengue-vaccine model is LAS whenever $R_{\text{net}}<1$ (see in lemma 2.1). This enables to determine the disease will be eradicated from community without vaccination whenever $R_0<1$ and the disease dies.
out with vaccine if \( R_{ve} < 1 \). For controlling disease in dengue vaccine model must consider only case of \( R_{ve} > 1 \) because if \( R_{ve} < 1 \), then disease dies out without vaccination. Hence, the fraction of individuals vaccinated at steady-state is investigated as follows. Let \( p \) be the fraction of individuals vaccinated at steady-state that is \( p = P^{\text{h}}_{\text{V}}/N^{\text{h}}_{\text{tot}} \). The expression, Eq. 24 can be written as:

\[
R_{ve} = R_{e} \sqrt{1-p} \tag{26}
\]

From Eq. 26, the reproduction number under vaccine (\( R_{ve} \)) is changed according to the reproduction number (\( R_{e} \)), the fraction of individuals vaccinated (\( p \)) and vaccine efficacy (\( e \)). The relation of \( R_{ve} \), \( R_{e} \), \( p \) and \( e \) is described by contour plot. A contour plot of reproduction number under vaccine (\( R_{ve} \)) as function vaccine efficacy (\( e \)) and the fraction of individuals vaccinated at steady state (\( p \)) is depicted in Fig. 3.

It is seen that if the values of \( e \) and \( p \) increase then \( R_{ve} \) decrease. When the reproduction number (\( R_{e} \)) are high, the values of \( e \) and \( p \) are closed to unity as show in Fig. 3a-e. The basic reproduction number for dengue transmission in Thailand is estimated from low values of range 1-3 to higher values of 10-12 (Feng and Velasco-Hernandez, 1997). The example for controlling disease, for \( R_{e} = 1.3516 \) (low levels). Hence, it followed that if the vaccine efficacy is 60\%, the fraction of vaccinated individuals should be >75\% to eliminate dengue from the community.

Comparison predicted data and epidemiological dengue data in Thailand 2013: Thailand is the tropical country confronting the dengue outbreak every years. In 2013, Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand reported that there are 151,502 of dengue cases, an incidence of 235.74 per 100,000 population and especially, 133 deaths from DF, DHF and DSS. Therefore, in this section the model (5-6) is applied for predicting the transmission of Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) in Thailand 2013.

For the simulation, the parameters based on real data for dengue in Table 1 are used with \( \kappa_1 = \kappa_2 = 0.037 \). By these values, the associated reproduction numbers are \( R_1 = R_2 = 1.3516 \) in the range from 1.15-3 (Carr, 1981). The initial conditions are chosen as:

\[
S_{h1}(0) = 900000, E_{h1}(0) = 1000, I_{h1}(0) = 1500, R_{h1}(0) = 7000, E_{h2}(0) = 500
\]
\[
I_{h2}(0) = 2500, E_{v1}(0) = 1000, I_{v1}(0) = 1500, R_{h2}(0) = 7000, E_{v1}(0) = 500
\]
\[
I_{h1}(0) = 110000, S_{v1}(0) = 100000, E_{v1}(0) = 100, I_{v1}(0) = 500
\]
\[
E_{v2}(0) = 100, I_{v2}(0) = 500, C(0) = 8085
\]

With above parameter values and initial conditions, the dengue model is simulated for predicting the cumulative number of dengue cases and they are compared with the actual data as shown in Fig. 4. The value of \( R^2 \) is 0.9983 which confirms that the predicted
data produced by the dengue model fit well to the actual data. Therefore, the dengue model can be used to predict the occurrence of dengue in Thailand, 2013.

As stated earlier, the dengue is caused by the dengue viruses I-IV. Infection by one of the four dengue virus serotypes has been shown to confer lasting protection against the other serotype reinfecion but only transient protection against a secondary infection. Moreover, secondary infection is associated with an increased risk of severe disease which is referred to as immune enhancement of disease. The study result in Fig. 4 supports this fact. Due to these dengue-specific complexities, vaccine development is to focus at providing long-term protection against all virus serotypes.

The dengue-vaccine model is simulated with $\xi = \varepsilon = 0.5$, $\omega = 0.3$, $P_0(0) = 1000$, the other parameters and initial conditions as used in simulating the dengue model. It is seen that the reproduction number of the dengue-vaccine model is less than the reproduction number of the dengue model that is $R_{re} = 1.1705$ and $R_0 = 1.3516$. The simulated results are compared with both actual data and predicted data produced by the dengue model (Fig. 5). It is found that if people have vaccinated, the cumulative number of dengue cases decrease. This result verifies that a dengue vaccine would be a major advance in controlling the spread of dengue in a community.

Further, the effect of vaccination parameters are investigated by simulating the dengue-vaccine model with simulations various values of vaccination rate ($\xi$), vaccine efficacy ($\varepsilon$) and waning rate of vaccine ($\omega$), respectively. It is clear, from Table 2 that increasing values of $\xi$ and $\varepsilon$ reduce $R_{re}$ while $R_{re}$ increase as $\omega$ increases. However, all cases give $R_{re}<R_0$.

It is important to note that the vaccine efficacy is the most influential factor in decreasing $R_{re}$. The simulated results are compared with both actual data and predicted data produced by the dengue model as shown in Fig. 6. This figure indicates that increasing the values of $\xi$, $\varepsilon$ and decreasing the value of $\omega$ lead to the reduction of dengue cases.

![Fig. 4: The cumulative number of dengue cases](image1)

![Fig. 5: The simulated results are compared with both actual data and predicted data produced by the dengue model](image2)

<table>
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<th>$\xi$</th>
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<th>$\varepsilon$</th>
<th>$R_{re}$</th>
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Table 2: Effect of vaccination parameters on the reproduction numbers
CONCLUSION

The two-serotype dengue model with the impact of vaccine factors called the dengue-vaccine model is developed in this study. It is based on Susceptible-Exposed-Infected-Recovered (SEIR) epidemic model being realistic with life cycle of the dengue disease. Analysis of the developed dengue-vaccine model reveals the existence of four equilibrium points which belong to the region of biological interest. One of the equilibrium points corresponds to the disease-free state, the other three equilibria correspond to the two states i.e., one serotype is present and both serotypes coexist, respectively. This developed dengue-vaccine has a locally asymptotically stable disease-free equilibrium whenever the associated reproduction number is less than unity. The state when one serotype is present, the developed dengue-vaccine model exhibits the phenomenon of backward bifurcation where the stable disease-free equilibrium coexists with a stable endemic equilibrium. It is shown that the developed model can have endemic equilibria if infection with one serotype confers partial cross immunity against the other serotype in which disease elimination, competitive exclusion or co-existence of the two serotypes can occur. The stability region of secondary coexistence equilibrium is reduced by strong cross immunity. Further, the developed model is compared with the real data to showing the impact of vaccination parameters in controlling the transmission of dengue with two serotypes in Thailand 2013. It is verified that three vaccination parameters values of vaccination rate ($\xi$), vaccine efficacy ($\varepsilon$) and waning rate of vaccine ($\omega$), respectively are critically important in controlling the transmission of dengue with two serotypes. The comparing results demonstrated that the predicted data produced by the developed dengue-vaccine model fit well to the actual data. Therefore, the developed model can be used as a suitable tool for predicting the occurrence of dengue in Thailand.

At present, the dengue vaccine is only provided to the primary infected persons for acquiring high effectiveness. However, the symptom of dengue fever for primary infection is similar to common cold leading to disregard of the best treatment for dengue fever. Consequently, the patients are the severe disease by the secondary infection and then leading to death. Therefore, if we can develop the dengue vaccine being able to prevent dengue virus, since, the persons have no infection, severe disease and death by the secondary infection of patient may be reduced.

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REFERENCES


