Dynamics of Two Strain Dengue Transmission with Hypothetical Vaccination Strategies

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Abstract

Dengue fever is a mosquito-borne tropical disease caused by the DENV virus. Dengue disease has currently emerged as a major public health concern in the world with the mounting number of cases reported annually. This situation has led to a growing concern among medical scientists over effective vaccination as a measure of disease prevention. Strikingly, understanding the dynamics of dengue is of vital importance in the introduction of vaccination. This study, thus, attempts to examine some important simulations in order to understand the usefulness of vaccination strategies. A classical compartmental model is used here to simulate the dynamics of dengue under the effect of hypothetical vaccination. Also, a numerical simulation is carried out so as to identify the impact of vaccine efficacy and vaccination coverage on the infected population.

Keywords: dengue disease dynamics; hypothetical vaccination; two strain SIR models; secondary dengue infections.

1 Introduction

A study which was carried out by the WHO reveals that an estimated 3.9 billion people in 128 countries are presently at risk for being infected with the dengue virus [2]. Dengue has posed a significant threat to the social and economic life of most of the urban areas in Africa, Asia and South America over the years since the Second World War. Dengue is a mosquito borne flavivirus disease transmitted by the female Aedes aegypti mosquito [2]. WHO statistics indicate that 390 million dengue infections are reported per year of which 96 million manifest clinically severe forms of the disease such as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [2]. If the disease aggravates to the life-threatening DHF or DSS states characterized by such symptoms as blood plasma leakage, fluid accumulation, severe muscle and joint pain, extreme bleeding, organ deficiency and respiratory distress, etc. hospitalization or professional medical care is necessary to avoid the risk of extreme complications or death [1,2].

Dengue is caused by four different serotypes of the DENV virus namely DENV-1, DENV-2, DENV-3 and DENV-4. An individual infected with one serotype acquires life-long immunity against that particular serotype, but it confers only a transient protection against the three remaining serotypes, known as the Temporary Cross Immunity (TCI) which is developed by the antibodies in the infected host due to the genetic relatedness of the serotypes [2,5,6]. Because of the phenomenon known as Antibody-Dependent Enhancement (ADE), more severe forms of the dengue disease can be commonly observed in secondary heterogonous infections [5, 9, 10]. ADE refers to the increase in virulence caused by the cross-reactive non-neutralizing antibodies from a previous heterotypic infection [9,10]. This largely accounts for the need for the introduction of an effective vaccine in order to reduce the disease burden in endemic areas that are affected by multiple DENV subtypes.
Owing to the unavailability of specific clinical treatments for dengue, a productive vaccine is considered to be of timely importance in controlling the spread of the disease. Therefore, medical scientists have been conducting thorough research on the production of a tetravalent vaccine that will provide a considerable level of protection against all the DENV serotypes. It is important to note that the world’s first dengue vaccine, Dengvaxia (CYD-TDV) developed by Sanofi Pasteur, was first registered in Mexico in the year 2015, and is currently used in several other endemic countries with the recommendation of the Strategic Advisory Group of Experts (SAGE) of WHO. In addition to Dengvaxia which is a live recombinant tetravalent vaccine, there are many other vaccine candidates for dengue (such as DENVax/TAK-003, TetraVax-DV, TDENV PIV, V180, etc.) currently under evaluation in clinical trials or pre-clinical studies which are based on diverse technologies in vaccine development [1,3,15,16].

According to the research carried out by Augiar et al. in [6], it is shown that these vaccinations work best for seropositive individuals (those who have previously had a DENV infection), and might have an adverse effect on the seronegative individuals (those who have not yet been affected by the virus) due to the impact of vaccine sensitization resulting in Vaccine Disease Enhancement (VDE) (where a vaccinated seronegative individual experiences in their primary infection an acute form of the disease which is similar to the severity of a secondary infection).

As is clear from the above explanation, it seems to be of paramount importance to analyze which factors are most sensitive towards aggravating the effect of the dengue virus within an infected human. Thus, we used an SIR (Susceptible-Infected-Recovered) model in the two strain structure (based on the models used by Augiar et al. [5] and Augiar et al. [6]) which consists of various important parameters including TCI, VDE, vaccination coverage, and vaccine efficacy. In the literature, the use of multi strain dengue models becomes prominent in the works of Ferguson et al. [7], Billings et al. [8], Augiar et al. [9], Augiar et al. [10], Feng et al. [11] and Nuraini et al. [12].

In the present paper, Section 2 describes the development of the model, and Section 3 presents the numerical simulations and a discussion of the results of those model simulations. Finally, the conclusion of the paper is presented in Section 4.

2 Model Development

In this study, we investigate how a hypothetical vaccine would affect the dynamics of dengue disease by using a two-strain minimalistic epidemiological model which is able to capture the phenomenon of multi-strain interaction. We expand the two-strain dengue model presented by Augiar et al. in [5] using the model with vaccination proposed by Augiar et al. in [6]. It is quite important to note that we assume our hypothetical vaccine to possess most of the features of Dengvaxia which seems to be a reasonable assumption given the fact that Dengvaxia is the only dengue vaccine available in the world at present. Basically, we probe into the models used in [5] and [6] with some modifications (as explained in Section 2.1 and Section 2.2), and analyze how the variations in the chosen parameters lead to certain important changes in the dynamics of dengue.

2.1 Model with only seropositives vaccinated (Model I)

![Figure 2.1: The state flow diagram for the two infection dengue model with only seropositives vaccinated.](image-url)
The systematic flow diagram of Model I is shown in Figure 2.1. This model is based on the model presented in [5] with the modifications of the constant force of infection, and the introduction of hypothetical vaccination. The complete set of ordinary differential equations for the model with only seropositives vaccinated is as follows:

\[
\begin{align*}
\frac{ds}{dt} &= \mu N - \frac{\beta}{N} S(l_1 + \theta l_{12}) - \frac{\beta}{N} S(l_2 + \theta l_{12}) - \mu S \\
\frac{dl_1}{dt} &= \frac{\beta}{N} S(l_1 + \theta l_{12}) - (r + \mu)l_1 \\
\frac{dl_2}{dt} &= \frac{\beta}{N} S(l_2 + \theta l_{12}) - (r + \mu)l_2 \\
\frac{dR_1}{dt} &= r l_1 - (\alpha + \mu)R_1 \\
\frac{dR_2}{dt} &= r l_2 - (\alpha + \mu)R_2 \\
\frac{ds_1}{dt} &= \alpha R_1 - \frac{\beta}{N} S_1(l_2 + \theta l_{12}) - \mu S_1 - \theta P v S_1 \\
\frac{ds_2}{dt} &= \alpha R_2 - \frac{\beta}{N} S_2(l_1 + \theta l_{21}) - \mu S_2 - \theta P v S_2 \\
\frac{dl_{21}}{dt} &= \frac{\beta}{N} S_2(l_1 + \theta l_{21}) - (r + \mu)l_{21} \\
\frac{dl_{12}}{dt} &= \frac{\beta}{N} S_1(l_2 + \theta l_{12}) - (r + \mu)l_{12} \\
\frac{dR}{dt} &= r(l_{12} + l_{21}) + \theta P v S_1 + \theta P v S_2 - \mu R
\end{align*}
\]

Now we non-dimensionalize these equations using,

\[
S^* = \frac{S}{N}, \quad I_1^* = \frac{l_1}{N}, \quad I_2^* = \frac{R_1}{N}, \quad S_1^* = \frac{S_1}{N}, \quad I_1^* = \frac{l_{12}}{N}, \quad I_2^* = \frac{l_{21}}{N}, \quad R^* = \frac{R}{N}
\]

Substituting the above into the complete system of equations yields,

\[
\begin{align*}
\frac{ds}{dt} &= \mu - \beta S(l_1 + \theta l_{12}) - \beta S(l_2 + \theta l_{12}) - \mu S \\
\frac{dl_1}{dt} &= \beta S(l_1 + \theta l_{12}) - (r + \mu)l_1 \\
\frac{dl_2}{dt} &= \beta S(l_2 + \theta l_{12}) - (r + \mu)l_2 \\
\frac{dR_1}{dt} &= r l_1 - (\alpha + \mu)R_1 \\
\frac{dR_2}{dt} &= r l_2 - (\alpha + \mu)R_2 \\
\frac{ds_1}{dt} &= \alpha R_1 - \beta S_1(l_2 + \theta l_{12}) - \mu S_1 - \theta P v S_1 \\
\frac{ds_2}{dt} &= \alpha R_2 - \beta S_2(l_1 + \theta l_{21}) - \mu S_2 - \theta P v S_2 \\
\frac{dl_{21}}{dt} &= \beta S_2(l_1 + \theta l_{21}) - (r + \mu)l_{21} \\
\frac{dl_{12}}{dt} &= \beta S_1(l_2 + \theta l_{12}) - (r + \mu)l_{12} \\
\frac{dR}{dt} &= r(l_{12} + l_{21}) + \theta P v S_1 + \theta P v S_2 - \mu R
\end{align*}
\]

Our model classifies the human population at time \( t \) into 10 groups: susceptible to both strain 1 and strain 2 (\( S \)), primarily infected with strain 1 (\( I_1 \)), primarily infected with strain 2 (\( I_2 \)), recovered from the primary infection with strain 1 (\( R_1 \)), recovered from the primary infection with strain 2 (\( R_2 \)), susceptible to a secondary infection with strain 2 (\( S_2 \)), susceptible to a secondary infection with strain 1 (\( S_1 \)), secondarily infected with strain 1 (\( I_{12} \)), secondarily infected with strain 2 (\( I_{21} \)), and recovered from the secondary infection with strain 1 or 2 (\( R \)).

The effective infection rate is denoted by \( \beta \) and, unlike in [5] and [6], we consider it as a constant in our study thus avoiding the effect of seasonal forcing in dengue incidence. It is very important that in this model, the dynamics of the vector population are taken into account only in the effective infection rate (\( \beta \)), rather than explicitly dividing the mosquito population into different compartments as in many models used in the literature, for instance in [13] and [14]. The parameter \( \varphi \) represents the ratio of infection contribution to the Force of Infection (FOI) by those who are undergoing a secondary infection. The parameters \( \alpha \) and \( \gamma \) represent the temporary cross immunity and the recovery rate respectively. That is, those who are infected with one strain recover by the recovery rate \( \gamma \) while acquiring complete lifelong immunity against that strain. However, after a certain period of TCI (\( \alpha \)) against the remaining strains, they become susceptible again for an infection with one of those strains.

The population size (\( N \)) is taken to be constant whereas the demography rate (birth and death rate) is denoted by \( \mu \). The parameter \( p \) represents the vaccination coverage (i.e. the proportion of the
population that is vaccinated). The vaccine efficacy factor (θ) parameterizes the effectiveness of the vaccine as a percentage of the level of protection that it delivers a vaccinated individual. Also, we assume that the vaccine is implemented with vaccination rate \( v \) so that the vaccination period is \( \frac{1}{v} \).

### 2.2 Model with both seropositives and seronegatives vaccinated (Model II)

![Figure 2.2: The state flow diagram for the two strain dengue model with both seropositives and seronegatives vaccinated.](image)

The state flow diagram for Model II is shown in Figure 2.2. The complete set of ordinary differential equations for the model with both seropositives and seronegatives vaccinated is given below,

\[
\begin{align*}
\frac{dR_2}{dt} &= rI_2 - (\alpha + \mu)R_2 \\
\frac{dS_1}{dt} &= aR_1 - \frac{\beta}{N} S_1(I_2 + \phi I_{12} + \phi v I_{v2}) - \mu S_1 - \theta P v S_1 \\
\frac{dS_2}{dt} &= aR_2 - \frac{\beta}{N} S_2(I_1 + \phi I_{21} + \phi v I_{v1}) - \mu S_2 - \theta P v S_2 \\
\frac{dI_{12}}{dt} &= \frac{\beta}{N} S_1(I_2 + \phi I_{12} + \phi v I_{v2}) - (r + \mu)I_{12} \\
\frac{dI_{21}}{dt} &= \frac{\beta}{N} S_2(I_1 + \phi I_{21} + \phi v I_{v1}) - (r + \mu)I_{21} \\
\frac{dS_v}{dt} &= \theta P v S - \frac{\beta}{N} \psi S_v(I_1 + \phi I_{21} + \phi v I_{v1}) \\
&\quad - \frac{\beta}{N} \psi S_v(I_2 + \phi I_{12} + \phi v I_{v2}) - \mu S_v \\
\frac{dI_{v1}}{dt} &= \frac{\beta}{N} \psi S_v(I_1 + \phi I_{21} + \phi v I_{v1}) - (r + \mu)I_{v1} \\
\frac{dI_{v2}}{dt} &= \frac{\beta}{N} \psi S_v(I_2 + \phi I_{12} + \phi v I_{v2}) - (r + \mu)I_{v2} \\
\frac{dR}{dt} &= r(I_{12} + I_{21} + I_{v1} + I_{v2}) + \theta P v S_1 + \theta P v S_2 - \mu R
\end{align*}
\]

Now we transform these equations into the dimensionless form using,

\[
S^* = \frac{S}{N}, \quad I_{1}^* = \frac{I_{1}}{N}, \quad R_{1}^* = \frac{R_{1}}{N}, \quad S_{1}^* = \frac{S_{1}}{N}, \quad I_{12}^* = \frac{I_{12}}{N}, \quad I_{2}^* = \frac{I_{2}}{N}, \quad R_{2}^* = \frac{R_{2}}{N}, \quad S_{2}^* = \frac{S_{2}}{N}, \quad I_{21}^* = \frac{I_{21}}{N}, \quad S_{v}^* = \frac{S_{v}}{N}, \quad I_{v1}^* = \frac{I_{v1}}{N}, \quad I_{v2}^* = \frac{I_{v2}}{N}, \quad R_{v}^* = \frac{R}{N}.
\]

Substituting the above into the complete system of equations gives,

\[
\begin{align*}
\frac{ds}{dt} &= \mu - \beta S(I_1 + \phi I_{12} + \phi v I_{v1}) \\
&\quad - \beta S(I_2 + \phi I_{21} + \phi v I_{v2}) - \mu S - \theta P v S \\
\frac{dI_{1}}{dt} &= \frac{\beta}{N} S(I_1 + \phi I_{12} + \phi v I_{v1}) - (r + \mu)I_1 \\
\frac{dI_{2}}{dt} &= \frac{\beta}{N} S(I_2 + \phi I_{12} + \phi v I_{v2}) - (r + \mu)I_2 \\
\frac{dR_{1}}{dt} &= rI_1 - (\alpha + \mu)R_1 \\
\frac{dR_{2}}{dt} &= rI_2 - (\alpha + \mu)R_2 \\
\frac{dS_{1}}{dt} &= \alpha R_1 - \beta S(I_2 + \phi I_{12} + \phi v I_{v2}) - \mu S_1 - \theta P v S_1
\end{align*}
\]
\[
\frac{dS}{dt} = \alpha R - \beta S(I_1 + \phi I_2 + \phi v I_v) - \mu S - \theta P v S
\]

\[
\frac{dI_1}{dt} = \beta S(I_2 + \phi I_1 + \phi v I_v) - (r + \mu)I_1
\]

\[
\frac{dI_2}{dt} = \beta S_2(I_1 + \phi I_2 + \phi v I_v) - (r + \mu)I_2
\]

\[
\frac{dS_v}{dt} = \theta P v S - \beta S_v(I_1 + \phi I_2 + \phi v I_v) - \mu S_v - \beta S_v(I_2 + \phi I_1 + \phi v I_v) - \mu S_v
\]

\[
\frac{dI_v}{dt} = \beta S_v(I_1 + \phi I_2 + \phi v I_v) - (r + \mu)I_v
\]

\[
\frac{dI_v}{dt} = \beta S_v(I_2 + \phi I_1 + \phi v I_v) - (r + \mu)I_v
\]

\[
\frac{dR}{dt} = r(I_1 + I_2 + I_v) + \theta P v S_1 + \theta P v S_2 - \mu R
\]

In this model, following Augiar et al. [6], we introduce a new compartment to the previous structure; the new class \(S_v\) embodies vaccinated seronegatives. Further, we have the additional parameter, vaccine disease enhancement factor \(\Psi\) which parameterizes the phenomenon of vaccine sensitization. So, here we assume that both seropositive and seronegative individuals in the population are vaccinated without an immunological screening prior to vaccination. The reason is that the Dengvaxia vaccine, when administered, mimics the characteristics of a primary infection in a vaccine-sensitized seronegative individual thus leading to vaccine disease enhancement [6].

### 3 Numerical Results and Discussion

The numerical simulations in this paper are carried out using MATLAB \textit{ode45} solver. The \textit{ode45} solver is based on a Runge-Kutta method which uses a variable time step. For the analysis, we vary the parameters \(p\) and \(\theta\) in the model, and then observe the consequent effect on the spread, prevalence and magnitude of potential epidemic outbreaks. First, we observe the changing behavior of the curves of infected humans \(I_h\) subject to the variation of vaccination coverage \(p\) and vaccine efficacy \(\theta\).

Then, we use the \textit{rand()} function in MATLAB in order to observe the distribution of the mean and standard deviation of the infected human population with respect to the variation of the vaccine efficacy \(\theta\). The descriptions of the parameters and their respective values used in our simulations are given in Table 3.1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\mu)</td>
<td>Human birth and death rate</td>
<td>1/75y</td>
<td>Assumed</td>
</tr>
<tr>
<td>(\beta)</td>
<td>Effective infection rate</td>
<td>0.5y</td>
<td>Assumed</td>
</tr>
<tr>
<td>(\emptyset)</td>
<td>The ratio of infection contribution to the FOI by those who are secondarily infected</td>
<td>0.9</td>
<td>[6]</td>
</tr>
<tr>
<td>(r)</td>
<td>Recovery rate</td>
<td>1/14 d</td>
<td>Assumed</td>
</tr>
<tr>
<td>(P)</td>
<td>Vaccination coverage</td>
<td>varying</td>
<td>Assumed</td>
</tr>
<tr>
<td>(V)</td>
<td>Vaccination rate</td>
<td>1/1y</td>
<td>[6]</td>
</tr>
<tr>
<td>(\theta)</td>
<td>Vaccine efficacy</td>
<td>varying</td>
<td>Assumed</td>
</tr>
<tr>
<td>(\alpha)</td>
<td>Temporary cross immunity period</td>
<td>0.5y</td>
<td>[6]</td>
</tr>
<tr>
<td>(\Psi)</td>
<td>Vaccine disease enhancement factor</td>
<td>0.1</td>
<td>[6]</td>
</tr>
<tr>
<td>(\phi_V)</td>
<td>The ratio of infection contribution to the FOI by vaccine sensitized seronegatives</td>
<td>0.9</td>
<td>[6]</td>
</tr>
</tbody>
</table>

**Figure 3.1: Model I Simulation:** The variation of the number of individuals primarily infected with strain 1 (top left) and strain 2 (top right); the variation of the individuals secondarily infected with strain 1 (bottom left) and strain 2 (bottom right). The parameter \(p\) is increased from 0 to 1 with equal increments of length 0.2 while \(\emptyset\) remains constant at 0.8.
According to Figure 3.1 (top left and top right), it becomes apparent that the vaccination of only seropositive individuals (i.e. those who have already had an infection with strain 1 or strain 2) has a very slight effect on the reduction of primary infection cases, though it substantially helps reduce secondary infections. That is, a vaccine like Dengvaxia (which is recommended only for seropositive hosts) may not be very effective as a method of prevention against primary dengue infections, as it works only to decrease the Force of Infection to a certain extent. The reason, in clearer terms, is that the vaccination of seropositives helps in the reduction of secondary dengue infections which consequently contributes to a drop in the Force of Infection. This fact, then, serves to reduce the susceptibility of seronegative individuals to the dengue virus infection, and hence to a decrease in dengue cases.

Moreover, Figure 3.1 (bottom left and bottom right) clearly reflects the fact that by vaccinating only seropositive individuals, the burden of the epidemic can be reduced to a greater extent as far as secondary infections are considered. This consequence can be viewed as of great importance given the fact that secondary infections intensify the vulnerability of dengue patients to the chronic DHF or DSS states which are characterized by an acute level of clinical burden. Also, it is prominent from Figure 3.1 (bottom left and bottom right), that the higher the vaccination coverage (p), the lower the number of dengue cases throughout the duration of an epidemic situation.

Further, in an observation of the mean curves (with error bars) in Figure 3.2 (which capture the behavior of the size of the infective reservoirs subject to the random variation of θ), the variation at the peak point is relatively large, though restrained to a very short interval around the mean. It accounts for a slight variability of the number of infected hosts at the peak of a potential outbreak. These mean curves provide us with a better understanding of the behavior of the size of the particular compartments over time. In addition, the lower deviation in the mean values on the curves enhances the reliability of the results generated by the model under consideration.

Figure 3.3 (top left and top right) shows that the number of infected humans decreases as the vaccination coverage (p) increases. Another important revelation that comes out for examination in Figure 3.3 (top left and top right) is that there is an unavoidable delay in the incidence of the epidemic outbreak as the value of the parameter p increases. It is, therefore, evident that the greater the vaccination coverage, the lower the intensity of the epidemic, and the later that it occurs. Here, Figure 3.3 (bottom left and bottom right) clarifies that the higher the vaccination coverage (p) without immunological screening, the larger the number of vaccine sensitization cases ($I_{v1}$ and $I_{v2}$).

This depicts the negative effect of vaccination on the seronegative individuals because the number of vaccine sensitized individual’s increases with the vaccination coverage (p). So, this finding indicates the need for a proper immunological screening prior to vaccination as far as Dengvaxia or any other vaccine with similar characteristics is concerned. All these simulations stress the importance of a strong tetravalent vaccine against dengue which could provide protection against all the four serotypes unlike Dengvaxia which is recommended for administration only in seropositive individuals.
Figure 3.3: Model II Simulation: The graph of the individuals primarily infected with strain 1 (top left), secondarily infected with strain 2 (top right), vaccine-sensitized seronegatives primarily infected with strain 1 (bottom left), and strain 2 (bottom right). The parameter $p$ is increased from 0 to 1 with equal increments of length 0.2 while $\theta$ remains constant at 0.8.

Figure 3.4: Model II Simulation: The graph of the mean value (with error bars) of the individuals primarily infected with strain 1 (top) and secondarily infected with strain 2 (bottom), where $p = 0.8$ and $\theta$ is varied randomly over the interval $[0.6, 0.8]$.

The mean curves (with error bars) in Figure 3.4 and Figure 3.5 (which portray the behavior of the size of the pool of infective subject to the random variation of $\theta$) lead to a better estimate of the average number of infected individuals along with the level of variability associated with each point of time. There, in Figure 3.4 (top), it can be perceived that the variation is somewhat higher before the peak point of the epidemic, and then it declines promptly thus dying out after a few days. Nevertheless, in Figure 3.4 (bottom), the variation at the peak point appears to be comparatively large, although it is limited to a relatively short interval around the mean.

These mean curves are so important that they contribute to a more accurate representation of the behavior of the number of the infected individuals over time. In fact, the lower variation of the mean values on the curves enriches the accuracy and consistency of the results obtained.

4 Conclusion

As specified in the introduction, our main purpose in the present paper was to investigate the changing dynamics of dengue disease in the presence of hypothetical vaccination in order to emphasize the vitality of a promising vaccine in the worldwide attempts towards the eradication of dengue.

Models I and II are based on a minimalistic two strain dengue model simulation which is more realistic than the single strain structure due to the co-existence of multiple strains in an endemic geographic area. In the numerical analysis section, we studied the behavior of the size of the infected human population with respect to the changes of the two parameters, vaccination coverage ($p$) and vaccine efficacy ($\theta$). The numerical simulations of Model I indicated that the higher the proportion of the host population vaccinated, the lower the magnitude of the epidemic. Also, it was observed that a highly effective vaccine can have a better impact on disease control. Further, the mean curves with error bars obtained through the random variation of $\theta$ provided more reliable results with respect to the distribution of infectives.

Two very important parameters used in these models are the temporary cross immunity period ($\alpha$), and the...
vaccine disease enhancement factor ($\psi$) which are pivotal in understanding the complicated dynamics of secondary dengue infections. We observed that the vaccination of only seropositives could contribute to a substantial reduction in disease burden in general. Nevertheless, we also discovered the fact that vaccination of only seropositives has merely a minor effect on the reduction of primary dengue infections. We, thus, emphasize the need for a vaccine which is effective in controlling primary dengue infections too.

Moreover, the simulations pertaining to Model II stressed the importance of serological testing of the individuals prior to vaccination, especially if the vaccine is likely to have a negative effect on seronegative individuals as in the case of Dengvaxia (CYD-TDV). The incorporation of the vaccine disease enhancement factor ($\psi$) clearly depicted how the phenomenon of vaccine sensitization in seronegative individuals leads to worsen the epidemic. Further, this suggests the need for a strong tetravalent vaccine against dengue which could provide a high level of immunity against all the four serotypes unlike Dengvaxia which is recommended for administration only in seropositive individuals.

Most importantly, the models and analysis used in this study may be modified or improved appropriately so as to evaluate the progress of the vaccine trials that are currently undertaken in several countries. The important results derived herein also provide implications to future research opportunities that may be carried out to scrutinize the way in which these parameters have an effect on the changing dynamics of dengue.

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