Evaluating the Impact of a Tetravalent Vaccine in Populations with High-Incidence of Dengue: A Mathematical Model

Irma Pérez C., Maria E. Cardenas P., Miguel A. Enriquez G., Alejandro Juárez D.

Facultad de Medicina
Benemérita Universidad Autónoma de Puebla
Puebla, Puebla, México

Anibal Muñoz L.

Facultad de Educación
Grupo de Modelación Matemática en Epidemiología (GMME)
Universidad del Quindío
Armenia, Colombia

Abstract

We have formulated a simulation model for different tetravalent vaccination strategies by using an integral equations system. This one interprets the dynamics of the Dengue vector-host infectious process.

Keywords: Simulation model, tetravalent vaccine, host-vector, integral equations, Dengue

1 Introduction

Dengue is an infectious febrile disease, of systemic viral etiology that is transmitted by *Aedes* sp mosquitoes. It has a variable clinical symptomatology, a little-predictive evolution, self-limited, and temporarily disabling. Dengue
presents several clinical manifestations: as fever, hemorrhagic fever, and shock syndrome.

It is an arbovirus (arthropod-borne virus) with four serotypes; these ones have been grouped together using biologic, immunological, and molecular criteria, as follows: Denv-1, Denv-2, Denv-3, and Denv-4. The virus has immunological and antigenic properties that are given by structural (P, M, E) and non-structural (NS1, NS2) antigens. It is present in blood (viremia) within the first five days of the fever onset [6].

Actually, the main efforts have been done principally in the development of vaccines against Dengue. This research has focused in live attenuated vaccines, inactivated ones, and with sub-unities. The live-attenuated-vaccines have afforded several questions since the disease in the second infection may cause severe clinical signs, as: hemorrhagic fever or shock syndrome.

The antibodies produced by an infection help to protect people in a new infection. However, existence of heterologous antibodies increases the infected cells by bonding with the virus (infection enhancement). The complex virus-antibody binds with Fc receptors at the cell’s surface to trigger severe clinical manifestations. It is highly important to have tetravalent live-attenuated-vaccines that produce antibodies for all serotypes of Dengue [1].

In the past decades it has increased the Dengue incidence around the world. The real number of cases is not documented enough and a lot of these cases are badly classified. In a recent estimation it has been reported 390 million of infections each year (this interval with 95% of certainty, 284 to 528 million), from which, 96 million (67 to 136 million) are clinically manifested [16]. People cares about this growing worldwide epidemic, that is why, an effective and safe vaccination plan necessary is. The World Health Organization (WHO) has taken the vaccines as an integral prevention and control strategy in the entire world (from 2012 to 2020) [19, 20, 21]. So then, the evaluation of the vaccination impact in Dengue virus for different scenarios, using mathematical models, allows us to have an improvement of the prevention strategies against this disease.

In this context, we have evaluated the impact of a tetravalent vaccine in a population with high Dengue incidence in Mexico by using a host-vector-like mathematical model. With this evaluation it is possible to set valid strategies for the vaccine application.

Some other models treating transmission and incidence of Dengue as func-
tion of the Temperature are reported in [5, 10, 18] and models applied to vaccination strategies in [4, 7, 9, 13, 14, 15, 17].

2 The Model

We have formulated a simulation model that plays the Dengue transmission and incidence dynamics using integral equations, with the following assumptions:

- Risk group (susceptible persons) until an age $a$.
- The vaccine is given to people who recently meet the age $a$.
- Prevention is given to susceptible people by means of vaccination.
- The vaccine is given to infected people.
- We have considered the infected-people recovery to one of the virus serotypes.
- The vaccine is 100% effective against all virus serotypes.
- Demography is not considered.
- We have considered the vector’s life-cycle.
- We consider a biological stage that includes: eggs, larvae, and pupas.
- Control of the mosquito population growth.

The model has the following variables: $x_1(t)$ average number of susceptible persons, $x_2(t)$ average number of infectious persons, $x_3(t)$ average number of immune people to all virus serotypes, $x_4(t)$ average number of immune people to one virus serotype, $N = x_1 + x_2 + x_3 + x_4$ : the total population, $y_1(t)$ average number of non-carrier mosquitoes, $y_2(t)$ average number of virus - carrier mosquitoes, $M = y_1 + y_2$ : is the total mosquito population, and $z(t)$ average number of immature stages at time $t$, respectively.

The parameters are: $K(t)$ the charge capacity of the immature stages, $\rho$ the constant flux of people who recently meets the age $a$, $\beta_h$ the virus transmission probability from mosquito to human, $\beta_v$ the virus transmission probability from people to non-carrier mosquitoes, $\theta$ the infectious people recovery rate by treatment, $\eta$ : increasing flux of the adult mosquitoes population, $r$ increasing - fraction in the number of non-carrier mosquitoes, $\pi$ the adult mosquitoes’ natural mortality rate, $\omega$ the developing rate from pupa to adult stage, $\epsilon$ the immature stages’ mortality rate, $\phi$ the oviposition rate, and $g$ the eggs fraction.
that turns to female mosquito.

We implement the following strategies:

- \( f \) : the vaccinated people fraction of age \( a \) and \( 1 - f \) : the susceptible non-vaccinated people fraction of age \( a \).

- \( j \) : the susceptible people fraction that are protected by vaccination, after that, \( 1 - j \) : is the susceptible people fraction that are not vaccinated.

- \( \sigma \) : the infected people fraction that are vaccinated and \( 1 - \sigma \) : the non-vaccinated infected people fraction that recovers from one of the virus serotypes.

The integral equations’ system that interprets the infectious process is,

\[
\begin{align*}
    x_1(t) &= x_1(0) + (1 - f)\rho \int_0^t N(s)ds - \beta_h(1 - j) \int_0^t \frac{y_2(s)}{M(s)} x_1(s)ds \\
x_2(t) &= x_2(0) + \beta_h(1 - j) \int_0^t \frac{y_2(s)}{M(s)} x_1(s)ds - \theta \int_0^t x_2(s)ds \\
x_3(t) &= x_3(0) + f\rho \int_0^t N(s)ds + \sigma \theta \int_0^t x_2(s)ds \\
x_4(t) &= x_4(0) + (1 - \sigma)\theta \int_0^t x_2(s)ds \\
y_1(t) &= y_1(0) + r\eta t + \omega \int_0^t z(s)ds - \beta_v \int_0^t \frac{x_2(s)}{N(s)} y_1(s)ds - \pi \int_0^t y_1(s)ds \\
y_2(t) &= y_2(0) + (1 - r)\eta t + \beta_v \int_0^t \frac{x_2(s)}{N(s)} y_1(s)ds - \pi \int_0^t y_2(s)ds \\
z(t) &= z(0) + g\phi \int_0^t (y_1(s) + y_2(s)) \left(1 - \frac{z(s)}{K}\right) ds - \epsilon \int_0^t z(s)ds \\
N(t) &= N(0) + \rho \int_0^t N(s)ds \\
M(t) &= M(0) + \eta t - \pi \int_0^t M(s)ds + \omega \int_0^t z(s)ds
\end{align*}
\]
Fig 1. Flux diagram of the dynamics, with $\Omega = g(\phi y_1(t) + y_2(t)) \left(1 - \frac{z(t)}{k}\right)$.

where, $\rho, \theta, \omega, \epsilon, \eta, \phi, K, \pi > 0$, $0 < \beta_h, \beta_v, \sigma, f, r, j < 1$ and initial conditions $x_1(0) = x_{10}$, $x_2(0) = x_{20}$, $x_3(0) = x_{30}$, $x_4(0) = x_{40}$, $y_1(0) = y_{10}$, $y_2(0) = y_{20}$, $z(0) = z_0$.

3 Results and conclusions

We carry out all simulations with the Maple software, using literature values for the parameters and some other hypothetical ones. $\pi = 0.1$, $\eta = 10$, $g = 0.6$, $\beta_h = 0.75$, $\beta_v = 0.75$, $\phi = 8$, $K = 3000$, $\theta = 0.8$, $\epsilon = 0.096$, $\omega = 0.904$, $\rho = 0.01$ and $r = 0.1$. Figures 1, 2, and 3 correspond to the following strategies

- $E_0 : f = 0$, $j = 0$ and $\sigma = 0$ (straight line)
- $E_1 : f = 0$, $j = 0.3$ and $\sigma = 0.4$ (dashed line)
- $E_2 : f = 0.4$, $j = 0$ and $\sigma = 0.4$ (dotted line)
• $E_3 : f = 0.4$, $j = 0.3$ and $\sigma = 0$ (dash-dot-dash line).

![Figure 1: The infected people behavior ($x_2(t)$) for each strategy.](image)

Comparing the parameters $(x_2(t), x_3(t), x_4(t))$ and $(y_2(t))$ with the ones obtained without vaccination, it is possible to observe that the infected people number in strategy $E_3$ is higher than that the ones obtained with strategies $(E_1, E_2)$ and without vaccination $(E_0)$, see Figure 1. Taking into account that this strategy $(E_3)$ includes a 40% of vaccination to 9-years-old susceptible population and a 30% of vaccination applied to people as prevention.

The virus-carrier mosquito behavior remains almost unchanged even after application of all treated strategies $(E_0, E_1, E_2)$ and $(E_3)$, as seen in Figure 2.

The immune-people behavior to all virus serotypes shows that there exists a higher average number of immune people to all virus serotypes with strategy $E_2$ (upper part of Figure 3). Also, in second place it is found the strategy $E_3$ and the last one, with values under 350, strategy $E_1$. In Figure 3 (bottom part) is showed the immune people behavior to only one virus serotype, it is clear that the highest values are obtained when there is not vaccine application.

We have determined the key parameters in a mathematical model that are
related with the effectiveness of a tetravalent vaccine against dengue. It has been used three different vaccination strategies in a 9 to 23 years old population from an endemic zone in México.

Our results have in some sense an agreement with other studies applied to populations with this similar issue. As example, a study realized in 5 countries of Latin America, where, it was evaluated the effectiveness of a tetravalent vaccine (CYD-TDV) in a population of 20,869 children (from 9 to 16 years old). This analysis consist of a phase III essay, the obtained results showed an efficacy of 60.8% after three vaccine shots. Also, in this study has been found a high efficacy in seropositive children to one of the four virus serotypes [2, 3, 8, 11, 12].

Other study realized in 5 Asian countries, where it was applied a phase-III essay in 10,275 healthy children (from 12 to 14 years old). These children have received three doses (0, 6, and 12 months) of a live attenuated virus recombinant vaccine (CYD-TDV). Results show that the symptomatology, fever by Dengue, and some other adverse effects were minimum compared with the control group, showing a 56.5% of vaccine effectiveness. Finally, in other phase-II essay in a children cohort in Brasil (from 9 to 16 years old), the obtained results with the same vaccine (CYD-TDV) show that it was also effective for all four virus serotypes, being well admitted by children. Reinforcing the findings for phase-I and phase-II vaccines [4].
Figure 3: Upper part, immune people behavior to all virus serotypes \( (x_3(t)) \), and bottom part, immune people behavior to only one virus serotype in each strategy \( (x_4(t)) \).

Acknowledgements. AML thanks to: Facultad de Medicina de la Benemérita Universidad Autónoma de Puebla, México; Al grupo de Modelación
Matemática en Epidemiología (GMME), Facultad de Educación de la Universidad de Quindío, Colombia.

References


Received: December 15, 2015; Published: February 11, 2016