Mathematical Biosciences and Engineering, 16(3):1171–1189.
DOI: 10.3934/mbe.2019056
Received: 07 November 2018,
Accepted: 27 December 2018,
Published: 15 February 2019

http://www.aimspress.com/journal/MBE

*Research article*

# Optimal dengue vaccination strategies of seropositive individuals

**Eunha Shim***

Department of Mathematics, Soongsil University, Sangdo-ro 369, Dongjak-gu, Seoul, 156-743, Republic of Korea

*** Correspondence:** Email: alicia@ssu.ac.kr; Tel: +82028200416; Fax: +82028244383.

**Abstract:** The dengue vaccine, CYD-TDV (Dengvaxia), has been licensed in 20 countries in Latin America and Southeast Asia beginning in 2015. In April 2018, the World Health Organization (WHO) advised that CYD-TDV should only be administered to individuals with a history of previous dengue virus infection. Using literature-based parameters, a mathematical model of dengue transmission and vaccination was developed to determine the optimal vaccination strategy while considering the effect of antibody-dependent enhancement (ADE). We computed the optimal vaccination rates under various vaccination costs and serological profiles. We observe that the optimal dengue vaccination rates for seropositive individuals are highest at the initial phase of a vaccination program, requiring intense effort at the early phase of an epidemic. The model shows that even in the presence of ADE, vaccination could reduce dengue incidence and provide population benefits. Specifically, optimal vaccination rates increase with a higher proportion of monotypic seropositive individuals, resulting in a higher impact of vaccination. Even in the presence of ADE and with limited vaccine efficacy, our work provides a population-level perspective on the potential merits of dengue vaccination.

**Keywords:** mathematical model; dengue; vaccine; optimal control; CYD-TDV; seropositive

## 1. Introduction

Dengue is a febrile illness caused by infection with one of the four dengue viruses (DENV) transmitted by Aedes aegypti or Aedes albopictus mosquitoes [1]. When an infected mosquito takes blood from a susceptible host, dengue viruses are transmitted to human cells. Infection may be asymptomatic or result in clinical manifestations, ranging from a mild febrile illness to a life-threatening shock syndrome [1]. The causes of dengue infection also include global trade, lack of interventions, international travel, and urbanization [2–6]. It is estimated that over 390 million dengue

virus (DENV) infections occur worldwide per year, of which approximately 96 million are clinically apparent [7,8]. Furthermore, dengue is the leading cause of fever in returning travelers, and international travel increases the risk of dengue infection as well as geographical heterogeneities [2–6,9]. Recent studies on dengue seroconversion in travelers report an attack rate of around 5%, suggesting that dengue vaccination would be justified for travelers [2,6].

There are four serotypes of DENV: DEN1, DEN2, DEN3, and DEN4. These are closely related but are distinct because the four DENV types have only 60%–75% of their envelope's amino acid level in common [1,10]. Primary infection with one of the DENVs does not result in severe symptoms in general, and upon recovery infected individuals acquire lifelong immunity against the homologous DENV serotype. In addition, there is transient cross-protection among the four dengue serotypes, which wanes and disappears over the months following infection. As a result, individuals living in a dengue-endemic area with multiple types co-circulating are at risk of infection with multiple DENV types, while secondary infection with heterotypic DENV can result in severe dengue [11]. This phenomenon is referred to as antibody-dependent enhancement (ADE) of an infection, where the type of DENV involved in the first infection plays a role in enhancing the replication of the heterologous type of DENV in human cells [12,13].

The immunological interactions of the four DENV serotypes and the risk of ADE have complicated the development of a dengue vaccine [14]. The only approved dengue vaccine to date, CYD-TDV (Dengvaxia), has been licensed in 20 countries in Latin America and Southeast Asia beginning in 2015 [15–17]. Vaccination is considered to be the most effective way of reducing DENV diseases. However, a higher risk of severe dengue disease and hospital admission was reported among recipients that were seronegative before immunization compared with unvaccinated controls, regardless of age at vaccination [2,18]. Such findings have led to the Philippines halting a dengue immunization campaign [17]. In December 2017, the World Health Organization (WHO) also issued a statement indicating that the vaccine was shown to be protective against severe dengue for individuals with dengue seropositivity at the time of vaccination, but that the risk of severe dengue was significantly increased for individuals with dengue seronegativity [19,20]. Such a high probability of fatal symptoms in secondary DENV infections among vaccine recipients makes vaccination in areas of low endemicity a high-risk exercise [16,20]. As a result, in April 2018 the WHO advised that the vaccine should not be utilized until prior dengue infection can be confirmed at the time of administration [17,18,22]. The recommendations on the use of dengue vaccine in the WHO background paper published in the April 2018 included a "pre-vaccination screening strategy" as the preferred option for countries considering vaccination as part of their dengue control program, in which only dengue-seropositive persons are vaccinated [21–23].

To date, some mathematical modeling studies have been published concerning optimal dengue vaccination strategies [24–27]. These prior studies have presented dengue vaccination models, and examined the impact of vaccination for various vaccine efficacy and coverage levels [24–27]. However, none of these models has incorporated the updated WHO recommendations on the use of dengue vaccines, i.e., restricting their use to seropositive individuals in consideration of the potential risks of hospitalization with dengue disease for individuals who are vaccinated when seronegative [23]. Hence, we propose a mathematical model of dengue transmission and vaccination to assess optimal vaccination strategies, which incorporates serostatus-dependent vaccination schemes and multiple dengue serotypes. Specifically, using Yucatan, Mexico as an exemplary region, we applied optimal control theory to a dengue transmission model to determine the optimal

vaccination strategies, taking into account strain-specific vaccine efficacy and the updated vaccination recommendations of the WHO. Furthermore, we calculated the potential risks associated with vaccinating seronegative individuals.

## 2. Method

### *2.1. Mathematical model of dengue transmission and vaccination*

To determine optimal vaccination strategies against dengue considering both primary and secondary infections in the presence of ADE, we present a dynamic model of dengue transmission and vaccination in which only seropositive individuals are eligible to receive vaccines, in line with WHO recommendations. Specifically, our multi-strain model considers the presence of two serotypes, namely serotype-1 and serotype-2, where 1 and 2 indicate DEN1 and DEN2, which are two major co-circulating strains in Mexico [28,29]. It is known that third or fourth dengue infections are often asymptomatic, because the two prior dengue infections provide protective immunity against severe dengue disease [26,30]. Therefore, our model presumes that two dengue infections with different serotypes provide effective permanent immunity. Furthermore, dynamic models implicitly capture the herd protection conferred by vaccination, and thus incorporate vaccine-induced indirect protection.

The transmission dynamics between humans and mosquitoes are described in our mathematical model. To capture the key features of dengue transmission, including multiple strains and ADE, we divide the human population into 14 epidemiologically distinct groups:

$S(t)$—susceptible;

$I_j(t)$—primarily infected with serotype $j$ ($j$ = 1, 2);

$R_j(t)$—recovered from serotype $j$ with temporary cross-immunity against all strains ($j$ = 1, 2);

$S_j(t)$—susceptible with lifelong immunity against serotype $j$ ($j$ = 1, 2);

$X_j(t)$—secondarily infected with serotype $j$ ($j$ = 1, 2 );

$S_j^V(t)$—vaccinated after natural primary infection by strain $j$ ($j$ = 1, 2);

$X_j^V(t)$—secondarily infected with strain $j$ ($j$ = 1, 2) after being vaccinated ($j$ = 1, 2);

$Z(t)$—recovered from secondary infections and immune to both serotypes.

In our model, all epidemiological variables have been normalized, enabling us to deal with population proportions. Here, it is assumed that the total human population ($N(t)$) is constant, i.e., $N(t) = S + Z + \sum_{j=1}^{2}\left(I_j + R_j + S_j + X_j + S_j^V + X_j^V\right) = 1$.

The vector population is divided into three groups:

$S_v(t)$—susceptible;

$I_{vj}(t)$—infected with serotype $j$ ($j$ = 1, 2).

Similarly to the human population, the total vector population ($V(t)$) is assumed to be constant, i.e., $V(t) = S_v + I_{v1} + I_{v2} = 1$.

When seropositive individuals are vaccinated, their force of infection associated with strain $j$ is assumed to be reduced by a factor of $(1-\varepsilon_j)$, where $\varepsilon_j$ is the vaccine efficacy against strain $j$ among seropositive individuals. In line with WHO recommendations, our model assumes that vaccines are

only administered to seropositive individuals, and thus the vaccine efficacy is parameterized using serostatus-dependent data (Table 1).

**Table 1.** Epidemiological parameters.

| Symbol | Parameter | Value | References |
|---|---|---|---|
| $\beta_{hi}$ | Per capita transmission rate of strain *i* from vector to host | 0.20 for $i = 1$<br>0.19 for $i = 2$ | [39,56,57] |
| $\beta_{vi}$ | Per capita transmission rate of strain *i* from host to vector | 0.20 for $i = 1$<br>0.19 for $i = 2$ | [39,56,57] |
| $\rho$ | Rate of recovery from infection | 0.146 $day^{-1}$ | [58] |
| $\alpha$ | Rate of loss of cross-immunity | 0.0055 $day^{-1}$ | [59,60] |
| $\varepsilon_i$ | Vaccine efficacy against infection by strain *i* among seropositive individuals | 0.73 for $i = 1$<br>0.59 for $i = 2$ | [55] |
| $\mu_v$ | Death rate of vector population | 1/10.5 | [39] |
| $u(t)$ | Vaccination rate at time *t* | Varies | Derived from optimization |
| $g_x$ | Proportion of dengue infections that are symptomatic in the epidemiological class $x_k$ | 0.45 for $x_k = I_k$ 0.8 for $x_k = X_j$ 0.14 for $x_k = X_j^V$ | [8,26,61] |
| $h_x$ | Probability of developing DHF/DSS after symptomatic infection among the individuals in the epidemiological class $x_k$ | 0.045 for $x_k = X_k$ or $X_j^V$ $0.25h_Y$ for $x_k = I_k$ | [26] |
| $C_{DF}$ | Average cost estimate per DF (medical and non-medical societal costs) | USD 543 | [31,35,36] |
| $C_{DHF}$ | Average cost estimate per DHF (medical and non-medical societal costs) | USD 1,586 | [31,35,36] |

Based on our assumptions and definitions, the model can be defined through the following nonlinear differential equations:

$$\frac{dS(t)}{dt} = \mu_h - (\beta_{h1} I_{v1} + \beta_{h2} I_{v2})S - \mu_h S,$$

$$\frac{dI_1(t)}{dt} = \beta_{h1} I_{v1} S - (\rho + \mu_h) I_1,$$

$$\frac{dI_2(t)}{dt} = \beta_{h2} I_{v2} S - (\rho + \mu_h) I_2,$$

$$\frac{dR_1(t)}{dt} = \rho I_1 - (\alpha + u(t) + \mu_h) R_1,$$

$$\frac{dR_2(t)}{dt} = \rho I_2 - (\alpha + u(t) + \mu_h) R_2,$$

$$\frac{dS_1(t)}{dt} = \alpha R_1 - \sigma_2 \beta_{h2} I_{v2} S_1 - (u(t) + \mu_h) S_1,$$

$$\frac{dS_2(t)}{dt} = \alpha R_2 - \sigma_1\beta_{h1}I_{v1}S_2 - (u(t)+\mu_h)S_2,$$

$$\frac{dX_1(t)}{dt} = \sigma_1\beta_{h1}I_{v1}S_2 - (\rho+\mu_h)X_1,$$

$$\frac{dX_2(t)}{dt} = \sigma_2\beta_{h2}I_{v2}S_1 - (\rho+\mu_h)X_2,$$

$$\frac{dS_1^V(t)}{dt} = u(t)(R_1+S_1) - (1-\varepsilon_2)\beta_{h2}I_{v2}S_1^V - \mu_h S_1^V,$$

$$\frac{dS_2^V(t)}{dt} = u(t)(R_2+S_2) - (1-\varepsilon_1)\beta_{h1}I_{v1}S_2^V - \mu_h S_2^V,$$

$$\frac{dX_1^V(t)}{dt} = (1-\varepsilon_1)\beta_{h1}I_{v1}S_2^V - (\rho+\mu_h)X_1^V,$$

$$\frac{dX_2^V(t)}{dt} = (1-\varepsilon_2)\beta_{h2}I_{v2}S_1^V - (\rho+\mu_h)X_2^V,$$

$$\frac{dZ(t)}{dt} = \rho(X_1+X_2+X_1^V+X_2^V) - \mu_h Z,$$

$$\frac{dS_v(t)}{dt} = \mu_v - \beta_{v1}(I_1+X_1+X_1^V)S_v - \beta_{v2}(I_2+X_2+X_2^V)S_v - \mu_v S_v,$$

$$\frac{dI_{v1}(t)}{dt} = \beta_{v1}(I_1+X_1+X_1^V)S_v - \mu_v I_{v1},$$

$$\frac{dI_{v2}(t)}{dt} = \beta_{v2}(I_2+X_2+X_2^V)S_v - \mu_v I_{v2}.$$

Because the time scale of interest in our study is relatively short, we ignore the demographics of humans (births and deaths). However, for the vector population birth and deaths rates are not ignored, and are assumed to be equal, meaning that the vector population does not change significantly. Susceptible vectors may acquire infections through contact with infected humans with strain *i* at a per-capita rate of $\beta_{vi}$ per infected host. In addition, susceptible individuals may acquire infections via contact with infected vectors with strain *i* at a per-capita rate $\beta_{hi}$ per infected vector. We account for ADE by assuming that the probabilities of developing dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) after a secondary infection are greater than those after a primary infection.

Because the total human and vector populations are constant ($N(t) = S + I_1 + I_2 + R_1 + R_2 + S_1 + S_2 + X_1 + X_2 + Z = 1$ and $V(t) = S_v + I_{v1} + I_{v2} = 1$), Model 1 can be reduced to a system consisting of the following 15 equations:

$$\frac{dS(t)}{dt} = \mu_h - (\beta_{h1}I_{v1} + \beta_{h2}I_{v2})S - \mu_h S,$$

$$\frac{dI_1(t)}{dt} = \beta_{h1}I_{v1}S - (\rho+\mu_h)I_1,$$

$$\frac{dI_2(t)}{dt} = \beta_{h2} I_{v2} S - (\rho + \mu_h) I_2,$$

$$\frac{dR_1(t)}{dt} = \rho I_1 - (\alpha + u(t) + \mu_h) R_1,$$

$$\frac{dR_2(t)}{dt} = \rho I_2 - (\alpha + u(t) + \mu_h) R_2,$$

$$\frac{dS_1(t)}{dt} = \alpha R_1 - \sigma_2 \beta_{h2} I_{v2} S_1 - (u(t) + \mu_h) S_1,$$

$$\frac{dS_2(t)}{dt} = \alpha R_2 - \sigma_1 \beta_{h1} I_{v1} S_2 - (u(t) + \mu_h) S_2,$$

$$\frac{dX_1(t)}{dt} = \sigma_1 \beta_{h1} I_{v1} S_2 - (\rho + \mu_h) X_1,$$

$$\frac{dX_2(t)}{dt} = \sigma_2 \beta_{h2} I_{v2} S_1 - (\rho + \mu_h) X_2,$$

$$\frac{dS_1^V(t)}{dt} = u(t)(R_1 + S_1) - (1 - \varepsilon_2)\beta_{h2} I_{v2} S_1^V - \mu_h S_1^V,$$

$$\frac{dS_2^V(t)}{dt} = u(t)(R_2 + S_2) - (1 - \varepsilon_1)\beta_{h1} I_{v1} S_2^V - \mu_h S_2^V,$$

$$\frac{dX_1^V(t)}{dt} = (1 - \varepsilon_1)\beta_{h1} I_{v1} S_2^V - (\rho + \mu_h) X_1^V,$$

$$\frac{dX_2^V(t)}{dt} = (1 - \varepsilon_2)\beta_{h2} I_{v2} S_1^V - (\rho + \mu_h) X_2^V,$$

$$\frac{dI_{v1}(t)}{dt} = \beta_{v1}(I_1 + X_1 + X_1^V)(1 - I_{v1} - I_{v2}) - \mu_v I_{v1},$$

$$\frac{dI_{v2}(t)}{dt} = \beta_{v2}(I_2 + X_2 + X_2^V)(1 - I_{v1} - I_{v2}) - \mu_v I_{v2}.$$

### *2.2. Calibration*

To expresses the cumulative fraction of symptomatic infections among humans per year, we introduce an additional variable $P_S(t)$. In mathematical terms, this additional variable can be defined through the following differential equation with the corresponding initial condition:

$$\frac{dP_S(t)}{dt} = g_I(1 - h_I)(\beta_{h1} I_{v1} + \beta_{h2} I_{v2}) S + g_X(1 - h_X)\sigma_2 \beta_{h2} I_{v2} S_1 + g_X(1 - h_X)\sigma_1 \beta_{h1} I_{v1} S_2 + g_V(1 - h_V)(1 - \varepsilon_2)\beta_{h2} I_{v2} S_1^V + g_V(1 - h_V)(1 - \varepsilon_1)\beta_{h1} I_{v1} S_2^V,$$

$$P_S(0) = 0.$$

Similarly, the incidence of DHF can be expressed by another variable $P_{DHF}(t)$, where:

$$\frac{dP_{DHF}(t)}{dt} = g_I h_I(\beta_{h1} I_{v1} + \beta_{h2} I_{v2})S + g_X h_X \sigma_2 \beta_{h2} I_{v2} S_1 + g_X h_X \sigma_1 \beta_{h1} I_{v1} S_2 + g_V h_V (1-\varepsilon_2)\beta_{h2} I_{v2} S_1^V + g_V h_V (1-\varepsilon_1)\beta_{h1} I_{v1} S_2^V,$$

$$P_{DHF}(0) = 0.$$

Here, we define $g_I$, $g_X$, and $g_V$ as the proportions of dengue infections that are symptomatic in the epidemiological classes $I_j$, $X_j$, and $X_j^V$, respectively ($j$ = 1, 2) (Table 1). In addition, $h_I$, $h_X$, and $h_V$ are defined as the probabilities of developing DHF/DSS following symptomatic infection among individuals in the epidemiological classes $I_j$, $X_j$, and $X_j^V$, respectively ($j$ = 1, 2) (Table 1). Using the baseline parameters, we generated country-specific epidemiological profiles of dengue infection. Specifically, the per-capita transmission rates of serotype $i$, $\beta_{hi}$ and $\beta_{vi}$, were set such that the annual incidence of symptomatic dengue infection in Yucatan, Mexico is 719 per 100,000, which is comparable with empirical estimates [31–33]. The annual incidence of DHF in Yucatan, Mexico is estimated to be 13 per 100,000, with adjustments that account for underreporting [32,34–36].

### *2.3. Parameterization of weight constants*

We parameterized the weight constants of infection based on the costs associated with symptomatic infection. By combining these data with the distribution of cases, we derived an average cost estimate per day associated with dengue fever (DF) and DHF. The weight constants associated with primary and secondary infection among unvaccinated individuals are calculated as follows:

$$W_1 = \rho(g_I(1-h_I)C_{DF} + g_I h_I C_{DHF}),$$

$$W_2 = \rho(g_X(1-h_X)C_{DF} + g_X h_X C_{DHF}),$$

$$W_3 = \rho(g_V(1-h_V)C_{DF} + g_V h_V C_{DHF}).$$

Where $W_1$ and $W_2$ are the weight constants associated with primary and secondary infection among unvaccinated individuals, respectively. In addition, $W_3$ is the weight constant associated with secondary infection among vaccinated individuals. Here, $C_{DF}$ and $C_{DHF}$ are defined as the average cost estimates per DF and DHF (Table 1). $C_{DF}$ and $C_{DHF}$ include indirect costs, medical costs, and direct non-medical costs, which were obtained from prior studies based on patient interviews [31]. We also included indirect costs based on productivity losses from the number of school days and workdays lost [31,36] (Table 1).

### *2.4. Optimal dengue vaccination strategies*

Using our dynamic model of dengue transmission, we investigate the optimal vaccination rates $u(t)$ where the vaccination rate $u(t)$ is considered to be the control variable to reduce or even eradicate the disease. The optimal control problem for the dengue vaccination model is formulated to minimize the cost associated with dengue infection as well as vaccination for a finite time. The objective functional to be minimized is given by:

$$J(u(t)) = \int_0^{t_f} W_1\big(I_1(t) + I_2(t)\big) + W_2\big(X_1(t) + X_2(t)\big) + W_3\big(X_1^V(t) + X_2^V(t)\big) + \frac{1}{2}W_4 u(t)^2\, dt$$

Where the control effect is modeled by quadratic terms in $u(t)$. The control efforts are modeled by quadratic terms to incorporate the societal cost associated with the implementation of vaccination [24,37,38]. Here, $W_4$ is the weight constant for the cost of vaccination, and as the baseline value $W_4$ is assumed to be 200.

The optimal vaccination strategies against dengue infection can be obtained by determining optimal control functions $u^*(\mathrm{t})$ such that:

$$J(u^*(\mathrm{t})) = \min_{\Theta} J\big(u(t)\big)$$

Subject to our model, where $\Theta = \big\{u(t) \in L^1(0, t_f) |\ 0 \le u(t) \le M, t \in [0, t_f]\big\}$. The control upper bound for vaccination $M$ represents the maximum daily vaccination rate, which has been previously estimated as 0.02 [39].

The existence of optimal controls is guaranteed by standard results from optimal control theory [40–44]. The necessary conditions of optimal solutions are derived from Pontryagin's maximum principle [45]. This principle converts the system into the problem of minimizing the Hamiltonian $H$ given by:

$$\begin{aligned}
H = {} & W_1\big(I_1(t) + I_2(t)\big) + W_2\big(X_1(t) + X_2(t)\big) + W_3\big(X_1^V(t) + X_2^V(t)\big) + \frac{W_4 u(t)^2}{2} \\
& + \lambda_1[\mu_h - (\beta_{h1} I_{v1} + \beta_{h2} I_{v2})S - \mu_h S] + \lambda_2[\beta_{h1} I_{v1} S - (\rho + \mu_h) I_1] \\
& + \lambda_3[\beta_{h2} I_{v2} S - (\rho + \mu_h) I_2] + \lambda_4[\rho I_1 - \{\alpha + u(t) + \mu_h\} R_1] \\
& + \lambda_5[\rho I_2 - \{\alpha + u(t) + \mu_h\} R_2] + \lambda_6[\alpha R_1 - \sigma_2 \beta_{h2} I_{v2} S_1 - \{u(t) + \mu_h\} S_1] \\
& + \lambda_7[\alpha R_2 - \sigma_1 \beta_{h1} I_{v1} S_2 - \{u(t) + \mu_h\} S_2] + \lambda_8[\sigma_1 \beta_{h1} I_{v1} S_2 - (\rho + \mu_h) X_1] \\
& + \lambda_9[\sigma_2 \beta_{h2} I_{v2} S_1 - (\rho + \mu_h) X_2] + \lambda_{10}[u(t)(R_1 + S_1) - (1 - \varepsilon_2)\beta_{h2} I_{v2} S_1^V - \mu_h S_1^V] \\
& + \lambda_{11}[u(t)(R_2 + S_2) - (1 - \varepsilon_1)\beta_{h1} I_{v1} S_2^V - \mu_h S_2^V] \\
& + \lambda_{12}[(1 - \varepsilon_1)\beta_{h1} I_{v1} S_2^V - (\rho + \mu_h) X_1^V] + \lambda_{13}[(1 - \varepsilon_2)\beta_{h2} I_{v2} S_1^V - (\rho + \mu_h) X_2^V] \\
& + \lambda_{14}[\beta_{v1}(I_1 + X_1 + X_1^V)(1 - I_{v1} - I_{v2}) - \mu_v I_{v1}] \\
& + \lambda_{15}[\beta_{v2}(I_2 + X_2 + X_2^V)(1 - I_{v1} - I_{v2}) - \mu_v I_{v2}]
\end{aligned}$$

From this Hamiltonian and Pontryagin's maximum principle, we obtain the following theorem:

**Theorem 1.** There exists an optimal control $U^*(t)$ and corresponding state solutions $X^*(t)$ that minimize $J(u(t))$ over $U$. For the above statement to be true, it is necessary that there exist continuous functions $\lambda_i(t)$ for $i = 1, 2, 3, \cdots, 15$ such that:

$$\lambda_1^{'} = -\frac{\partial H}{\partial S} = (\lambda_1 - \lambda_2)\beta_{h1} I_{v1} + (\lambda_1 - \lambda_3)\beta_{h2} I_{v2} + \lambda_1 \mu_h,$$

$$\lambda_2^{'} = -\frac{\partial H}{\partial I_1} = -W_1 + (\lambda_2 - \lambda_4)\rho - \lambda_{14}\beta_{v1}(1 - I_{v1} - I_{v2}) + \lambda_2\mu_h,$$

$$\lambda_3^{'} = -\frac{\partial H}{\partial I_2} = -W_1 + (\lambda_3 - \lambda_5)\rho - \lambda_{15}\beta_{v2}(1 - I_{v1} - I_{v2}) + \lambda_3\mu_h,$$

$$\lambda_4^{'} = -\frac{\partial H}{\partial R_1} = (\lambda_4 - \lambda_6)\alpha + (\lambda_4 - \lambda_{10})u \quad (t \quad) + \lambda_4\mu_h,$$

$$\lambda_5^{'} = -\frac{\partial H}{\partial R_2} = (\lambda_5 - \lambda_7)\alpha + (\lambda_5 - \lambda_{11})u(t) + \lambda_5\mu_h,$$

$$\lambda_6^{'} = -\frac{\partial H}{\partial S_1} = (\lambda_6 - \lambda_{10})u(t) + (\lambda_6 - \lambda_9)\sigma_2\beta_{h2}I_{v2} + \lambda_6\mu_h,$$

$$\lambda_7^{'} = -\frac{\partial H}{\partial S_2} = (\lambda_7 - \lambda_{11})u(t) + (\lambda_7 - \lambda_8)\sigma_1\beta_{h1}I_{v1} + \lambda_7\mu_h,$$

$$\lambda_8^{'} = -\frac{\partial H}{\partial X_1} = -W_2 - \lambda_{14}\beta_{v1}(1 - I_{v1} - I_{v2}) + \lambda_8(\rho + \mu_h),$$

$$\lambda_9^{'} = -\frac{\partial H}{\partial X_2} = -W_2 - \lambda_{15}\beta_{v2}(1 - I_{v1} - I_{v2}) + \lambda_9(\rho + \mu_h),$$

$$\lambda_{10}^{'} = -\frac{\partial H}{\partial S_1^V} = (\lambda_{10} - \lambda_{13})(1 - \varepsilon_2)\beta_{h2}I_{v2} + \lambda_{10}\mu_h,$$

$$\lambda_{11}^{'} = -\frac{\partial H}{\partial S_2^V} = (\lambda_{11} - \lambda_{12})(1 - \varepsilon_1)\beta_{h1}I_{v1} + \lambda_{11}\mu_h,$$

$$\lambda_{12}^{'} = -\frac{\partial H}{\partial X_1^V} = -W_3 - \lambda_{14}\beta_{v1}(1 - I_{v1} - I_{v2}) + \lambda_{12}(\rho + \mu_h),$$

$$\lambda_{13}^{'} = -\frac{\partial H}{\partial X_2^V} = -W_3 - \lambda_{15}\beta_{v2}(1 - I_{v1} - I_{v2}) + \lambda_{13}(\rho + \mu_h),$$

$$\lambda_{14}^{'} = -\frac{\partial H}{\partial I_{v1}} = (\lambda_1 - \lambda_2)\beta_{h1}S + (\lambda_7 - \lambda_8)\sigma \quad {}_1\beta_{h1}S_2 + (\lambda_{11} - \lambda_{12})(1 - \varepsilon_1)\beta_{h1}S_2^V + \lambda_{14}\beta_{v1}(I_1 + X_1 + X_1^V) + \lambda_{14}\mu_v,$$

$$\lambda_{15}^{'} = -\frac{\partial H}{\partial I_{v2}} = (\lambda_1 - \lambda_3)\beta_{h2}S + (\lambda_6 - \lambda_9)\sigma \quad {}_2\beta_{h2}S_1 + (\lambda_{10} - \lambda_{13})(1 - \varepsilon_2)\beta_{h2}S_1^V + \lambda_{15}\beta_{v2}(I_2 + X_2 + X_2^V) + \lambda_{15}\mu_v,$$

Satisfying the transversality conditions $\lambda_i(t_f) = 0$ for $i = 1, 2, \ldots, 15$, and the optimality conditions:

$$u^* = \min\left\{\max\left\{0, \frac{1}{W_4}\{(\lambda_4 - \lambda_{10})R_1 + (\lambda_5 - \lambda_{11})R_2 + (\lambda_6 - \lambda_{10})S_1 + (\lambda_7 - \lambda_{11})S_2\}\right\}, M\right\}$$

The numerical solutions to the optimality system, our model, and the adjoint equations were

obtained using the forward-backward scheme [37,46]. Starting with an initial guess for the optimal control $u(t)$, the state variables were solved forward in time from our model using the forward Euler method. Next, state variables and the transversality conditions were employed to solve the adjoint equations backward in time. The control $u(t)$ was updated, and the error between the old and updated values was calculated. This iterative process terminates when the error is less than a pre-assigned value of 0.00001. The final values of the vaccination rate $u(t)$ obtained via the above method were used as our numerical approximations for the optimal control solutions.

## 3. Dengue transmission dynamics in the absence of vaccination: The basic reproduction number

In this section, we present our results for the dengue transmission dynamics in the absence and presence of vaccination. We also present numerical simulations of the optimal vaccination strategy applied to our model of dengue transmission with two serotypes [29], and illustrate the impact of dengue vaccination on the reduction of symptomatic dengue incidence, as well as the incidence of DHF.

### *3.1. Dengue transmission dynamics in the absence of vaccination: the basic reproductive number*

Through direct calculation, it is easy to determine that for our model there always exists a disease-free equilibrium $E_{V0} = (1,0,0,0,0,0,0,0,0,0,0,0,0,0,0)$. By employing the next generation matrix approach [47] we calculate the basic reproductive number ($R_0$). We let $\mathbf{x_V} = (I_1, I_2, X_1, X_2, I_{v1}, I_{v2})^T$ and $\mathcal{F}_V(\mathbf{x_V})$ and $\mathcal{V}_V(\mathbf{x_V})$ represent all the new rate of appearance of new infections in compartments. To calculate the basic reproduction number $R_0$ considering vaccination, we set:

$$\mathcal{F}_V(\mathbf{x_V}) = \begin{pmatrix} \beta_{h1} I_{v1} S \\ \beta_{h2} I_{v2} S \\ \sigma_1 \beta_{h1} I_{v1} S_2 \\ \sigma_2 \beta_{h2} I_{v2} S_1 \\ \beta_{v1}(I_1 + X_1 + X_1^V)(1 - I_{v1} - I_{v2}) \\ \beta_{v2}(I_2 + X_2 + X_2^V)(1 - I_{v1} - I_{v2}) \end{pmatrix}, \quad \mathcal{V}_V(\mathbf{x_V}) = \begin{pmatrix} (\rho + \mu_h) I_1 \\ (\rho + \mu_h) I_2 \\ (\rho + \mu_h) X_1 \\ (\rho + \mu_h) X_2 \\ \mu_v I_{v1} \\ \mu_v I_{v2} \end{pmatrix}$$

Where we define $6 \times 6$ matrices $F_V = \left[\frac{\partial \mathcal{F}_V}{\partial x_j}(E_{V0})\right]$ and $V_V = \left[\frac{\partial \mathcal{V}_V}{\partial x_j}(E_{V0})\right]$ evaluated at the disease-free equilibrium $\boldsymbol{x_{V0}}$. Then, we can determine $\mathfrak{R}_0$ by calculating the spectral radius of $F_V {V_V}^{-1}$, which amounts to $\mathfrak{R}_0 = \max\{\sqrt{\mathfrak{R}_{01}}, \sqrt{\mathfrak{R}_{02}}\}$, where $\mathfrak{R}_{01} = \frac{\beta_{h1}\beta_{v1}}{(\rho+\mu_h)\mu_v}$ and $\mathfrak{R}_{02} = \frac{\beta_{h2}\beta_{v2}}{(\rho+\mu_h)\mu_v}$.

The basic reproductive ratio $R_0$ represents the expected number of secondary cases resulting from introducing a typical infected individual to a completely susceptible population. Here, $R_0^2$ is a measure of two-stage infection, formulated as follows. A mosquito infected by strain $i$ successfully infects $\beta_{hi}$ humans per day during the time $1/\mu_v$ that they are infectious. Each infected human then infects $\beta_{vi}$ mosquitoes per day during the time $1/(\rho + \mu_h)$ that they are infected. Furthermore, the disease-free equilibrium $E_0$ of our model is locally asymptotically stable if $\mathfrak{R}_0 < 1$ and unstable if $\mathfrak{R}_0 > 1$. With our baseline parameters, our basic reproduction ratios of serotypes 1 and 2 are estimated at $R_{01}$ = 2.65 and $R_{02}$ = 2.44, which are consistent with prior estimates [48,49].

## 4. Optimal vaccination strategies

In this section, we present numerical simulations of the optimal vaccination strategy applied to our model of dengue transmission with two serotypes [29], and illustrate the impact of dengue vaccination on the reduction of symptomatic dengue incidence, as well as the incidence of DHF.

We show numerical simulations associated with implementing optimal vaccination, as well as the effects on dengue incidence under different serological profiles. We compared the incidence and cumulative curves in the presence of optimal vaccination with the results in the absence of vaccination (Figure 2). As a baseline, we considered the case that 75% of the population are seropositive, with 25% monotypic and 50% multitypic, which is consistent with recent observations [50,51]. In Figure 2, we illustrate the cumulative incidences of symptomatic infection and DHF with and without optimal vaccination strategies. Optimal vaccination efforts should be implemented with an increasing vaccination rate, with a peak around day 50, resulting in a final vaccine coverage level of 8.4% (Figure 2). The size of an outbreak was shown to be reduced under an optimal vaccination scenario, averting 35 symptomatic infections annually per 100,000 (Figure 2). Vaccination reduces the incidence by both serotypes, with a slightly greater impact on the prevalence of serotype 1 (Figure 3). It is difficult to stop epidemics, because only seropositive individuals with a monotypic response, i.e. 25% of total population, were eligible to receive vaccines. Under the alternative scenario where the proportion of seropositive individuals whose immune response is monotypic is increased to 35% while keeping the total seropositive population constant (i.e., 75%), the larger epidemic size occurs. Therefore, this requires more intensive controls, i.e., a higher vaccination rate (Figure 4). In this case, our simulation shows that a yearly incidence of 971 symptomatic infections per 100,000 would result without vaccination, but when the optimal vaccination strategy is applied 165 symptomatic infections are expected to be averted per year (Figure 4). In addition, in the presence of an optimal vaccination rate the yearly incidence of DHF is expected to decrease from 20 to 14 per 100,000.

We also evaluated how the vaccination costs affect the optimal vaccination rate (Figure 5). Under various values for the weight constant associated with vaccination, the final epidemic sizes and the incidences of DHF under optimal vaccination scenarios were compared. Recently, the WHO suggested that the vaccine against dengue should only be utilized after testing individuals to assess whether they have ever been exposed to the infection. Therefore, it is worthwhile considering a range of costs associated with vaccination, including slightly higher values to account for the additional costs of testing. In the case with a higher weight constant for vaccination ($W_4$ = 400), the optimal vaccination rates decreased, with an eventual vaccination coverage level of 5.63%. On the contrary, when the cost associated with vaccination was lowered to $W_4$ = 100, the optimal vaccination strategies obtained an eventual vaccine coverage level of 11.72%, reducing the incidence of symptomatic dengue infection by 24 per 100,000. Therefore, the impact of an optimal vaccination strategy increased with the monotypic seropositivity level and a lower associated vaccination cost.

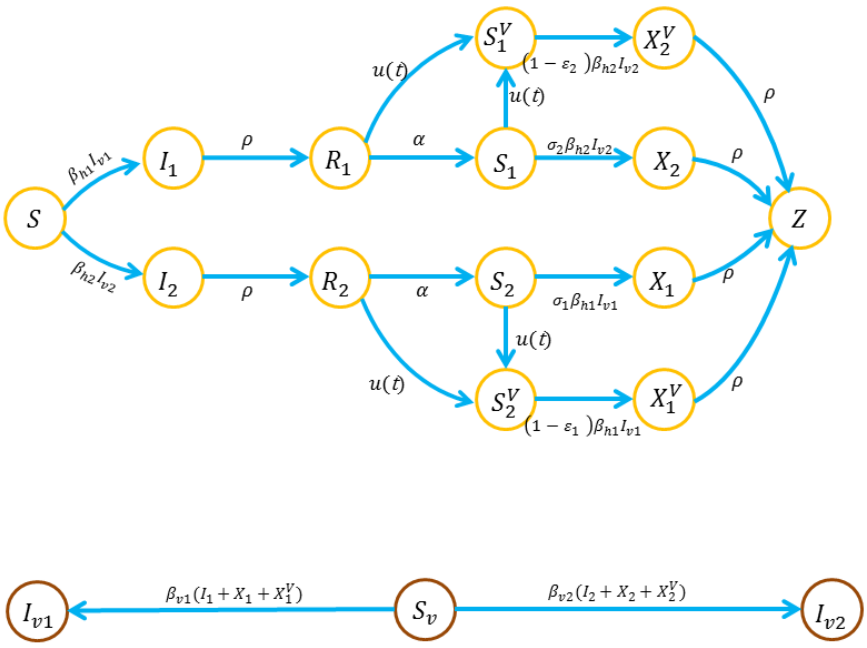


**Figure 1.** Model diagram. The host and vector populations are divided into dengue-related epidemiological classes.

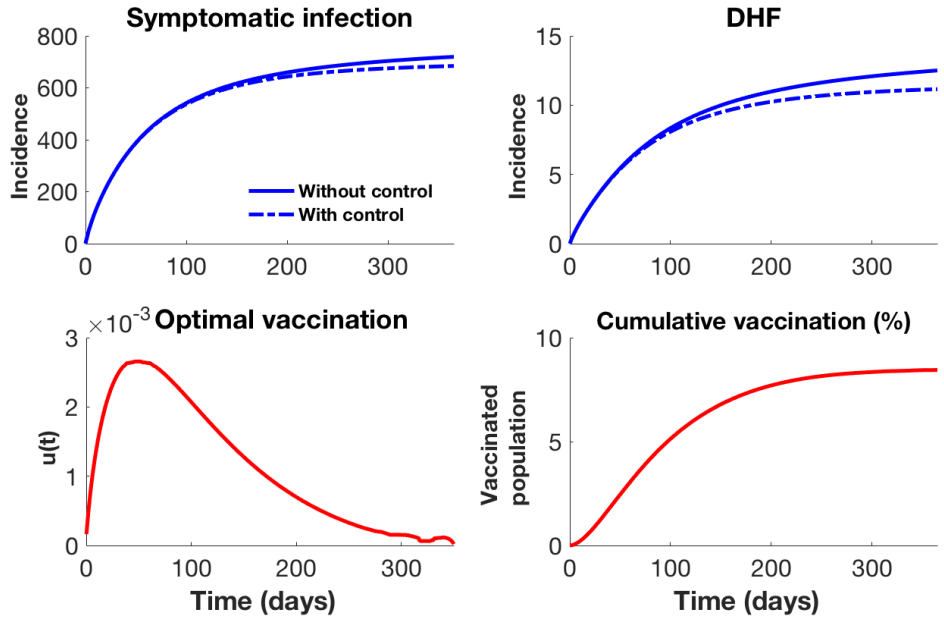


**Figure 2.** Optimal dengue vaccination and its impact. Top left: The corresponding cumulative incidences of symptomatic dengue cases per 100,000, under no vaccination with those generated with optimal vaccination control are compared. Top right: The corresponding cumulative incidence of DHF cases per 100,000, under no vaccination with those generated with optimal vaccination control are compared. Bottom left: Time-dependent optimal vaccination rate per day is presented. Bottom right: The corresponding cumulative vaccine coverage levels under optimal vaccination strategy is presented.

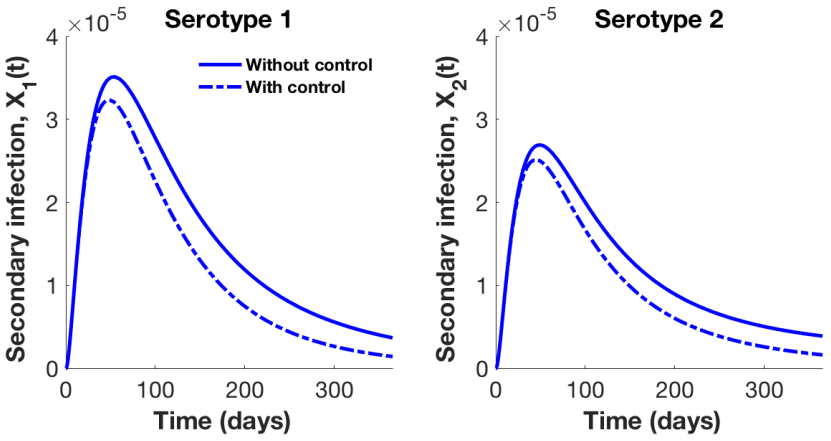


**Figure 3.** Serotype-specific impact of optimal dengue vaccination. Left: We compare an incidence of secondary dengue infections by serotype 1 under no vaccination (i.e. without control) with those when implementing optimal vaccination strategies. Right: We compare an incidence of secondary dengue infections by serotype 2 under no vaccination (i.e. without control) with those when implementing optimal vaccination strategies.

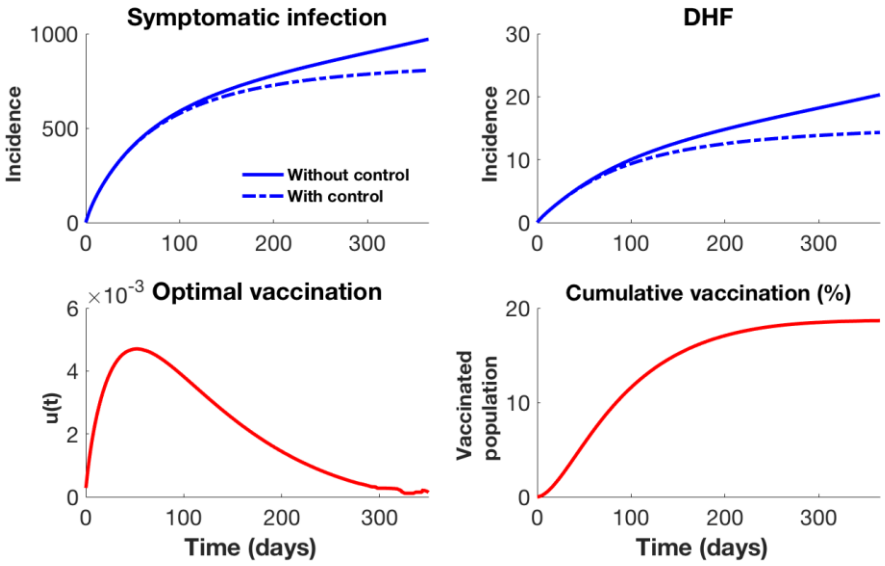


**Figure 4.** Optimal dengue vaccination when the proportion of seropositive individuals whose immune response is monotypic is increased. For sensitivity analysis, we examined the alternative scenario where the proportion of seropositive individuals whose immune response is monotypic is increased to 35% while keeping the total seropositive population constant (i.e., 75%). Top left: The corresponding cumulative incidences of symptomatic dengue cases per 100,000, under no vaccination with those generated with optimal vaccination control are compared. Top right: The corresponding cumulative incidence of DHF cases per 100,000, under no vaccination with those generated with optimal vaccination control are compared. Bottom left: Time-dependent optimal vaccination rate per day is presented. Bottom right: The corresponding cumulative vaccine coverage levels under optimal vaccination strategy is presented.

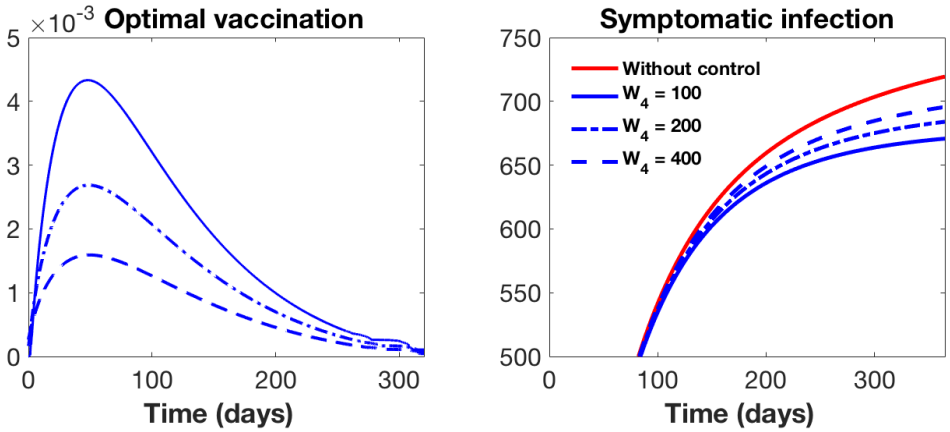


**Figure 5.** Impact of various vaccination costs on optimal vaccination rates. Left: Under various values for the weight constant associated with vaccination ($W_4$ = 100, 200, and 400), optimal vaccination rates were computed. Right: The corresponding curves illustrating the cumulative number of symptomatic infections with optimal vaccination (where $W_4$ = 100, 200, and 400) and no control are presented.

## 5. Discussion

Beginning in 2015, the dengue vaccine CYD-TDV (Dengvaxia) was licensed in 20 countries in Latin America and Southeast Asia, and it was originally licensed for use for individuals aged 9–45 years or 9–60 years, depending on the country [17,52,53]. However, CYD-TDV was found to have a paradoxical effect on patients who have not previously been infected by dengue virus [52]. Specifically, in a case-cohort study where data from three vaccine efficacy trials were reanalyzed, the vaccine increased the risk of severe dengue infection among dengue-seronegative children, although it protected against severe dengue infection among dengue-seropositive children [52]. Therefore, in April 2018 the WHO's Strategic Advisory Group of Experts recommended that in countries considering the introduction of vaccination with CYD-TDV, the vaccine should only be given to people who are dengue seropositive, and pre-vaccination screening should be preferred to assess dengue virus serostatus [17,19,53]. It is also suggested that CYD-TDV is not suitable for a mass immunization program that does not screen for previous dengue infection [54].

To evaluate optimal strategies of dengue vaccination, we employed a mathematical model of the transmission dynamics of dengue that accounted for vector dynamics, coexisting strains, and the serological status of the host population. Our model also incorporated the updated WHO recommendations and thus assumes that only seropositive individuals are eligible to receive dengue vaccines. Our mathematical framework incorporated time-dependent vaccination rates into the optimal control framework.

We computed optimal vaccination policies and analyzed them in the presence of two coexisting dengue serotypes. For a higher proportion of individuals with monotypic seropositivity with the proportion of total seropositive population kept constant, vaccination has greater effect in terms of the reduction of infected individuals. Furthermore, vaccination was more efficient at reducing the prevalence of DENV-1 than DENV-2, partially owing to a higher vaccine efficacy against DENV-1. The simulation of the model indicated that increasing the basic reproductive ratio would result in

higher optimal vaccination rates (not shown).

Our results further indicate that the optimal dengue vaccination strategy with consideration of seropositivity of target population can potentially decrease the incidence of dengue infection as well as DHF, resulting in minimizing the cost associated with infection and vaccination. The eligible vaccine recipients are now limited to seropositive individuals to avoid a paradoxical effect of CYD-TDV; thus on a similar note, it is also suggested that in a region with no indication of high endemicity a mass vaccination program against dengue should be suspended to minimize the vaccination of seronegative individuals [54]. For instance, CYD-TDV is being utilized in a mass vaccination program in Paraná, Brazil, where dengue is not highly endemic, and it has been proposed that the mass vaccination program in this region should be halted [54].

Although these results are only presented in the context of the CYD-TDV dengue vaccine, it would be worthwhile incorporating the use of pre-vaccination screening into the model in future studies. To this end, the WHO has also encouraged the urgent development of rapid diagnostic tests to determine the serostatus before vaccination [17]. Furthermore, the vaccine efficacy were shown to vary widely depending on serotypes and seropositivity, although we only considered two serotypes (i.e., DENV-1 and DENV-2). The pooled serotype-specific vaccine efficacies were lowest against serotype 2, but ranged up to 83.2% (95% CI, 76.2 to 88.2) for serotype 4 among participants who were 9 years of age or older [55]. Based on serotype-specific vaccine efficacy data, it was recently estimated that the serotype 4 would have the most favorable vaccine-preventable disease incidence, followed by serotype 1 [56]. Future studies on the impact of vaccination on four serotype-specific dengue incidences and also shifting age patterns as measures of vaccine impact would be invaluable.

In addition, further efforts to increase the sensitivity and specificity of RTDs for diagnosing serostatus would potentially facilitate the success of a dengue vaccination program. Finally, the considerations for optimal vaccination strategies highlighted here can be extended not just to dengue, but also more broadly to vaccine-preventable vector-borne infectious diseases in general.

## Acknowledgments

This work was supported by the Soongsil University Research Fund of 2015.

## Conflict of interest

All authors declare no conflicts of interest in this paper.

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