PLOS ONE

RESEARCH ARTICLE

Interplay between vaccines and treatment for dengue control: An epidemic model

Abdoulaye Sow[1☯*], **Cherif Diallo**[1☯], **Hocine Cherifi**[2☯]

1 Department of Computer Science, Algebra Laboratory Cryptography Codes and Applications, Gaston Berger University, Sanit-Louis, Senegal, **2** Department of Computer Science, LIB Burgundy Computer Laboratory -EA 7534, University of Burgundy Franche-Comte, Dijon, France

☯ These authors contributed equally to this work.
* sow.abdoulaye6@ugb.edu.sn

Check for updates

OPEN ACCESS

Citation: Sow A, Diallo C, Cherifi H (2024) Interplay between vaccines and treatment for dengue control: An epidemic model. PLoS ONE 19(1): e0295025. https://doi.org/10.1371/journal.pone.0295025

Editor: Benny Yong, Parahyangan Catholic University: Universitas Katolik Parahyangan, INDONESIA

Received: August 18, 2023

Accepted: November 14, 2023

Published: January 25, 2024

Copyright: © 2024 Sow et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The data used in this study are available at the following url: https://nidss.cdc.gov.tw/en/nndss/disease?id=061.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Assessing public health intervention strategies is crucial for effectively managing dengue. While numerous studies have explored the impact of dengue interventions on its transmission dynamics, limited research has focused on the combined effects of implementing multiple therapeutic interventions for disease control. This study presents an epidemic model for understanding dengue transmission dynamics, incorporating two critical therapeutic measures: vaccination and treatment of infected individuals. The model is characterized by ordinary differential equations involving seven-state variables. The investigation encompasses both disease-free and endemic equilibria of the model. The findings reveal that the disease-free equilibrium (only) is globally stable when the basic reproduction number is below one. Interestingly, when the vaccine's effectiveness is low, treatment emerges as a more successful approach in reducing dengue cases than vaccination. In contrast, a highly effective vaccine alone significantly curtails dengue occurrences. Moreover, the study introduces an optimal control problem, featuring an objective function integrating two control mechanisms: vaccination and treatment. The analysis strongly suggests that implementing two control strategies outweighs the efficacy of a single approach in effectively mitigating the spread of the disease.

Introduction

Dengue fever, caused by a virus prevalent in tropical and subtropical regions globally, presents a significant health concern. Annually, the World Health Organization (WHO) records over 4 million cases of dengue fever, with nearly 500,000 individuals suffering from its severe manifestation [1]. In recent years, authorities have implemented various non-pharmaceutical interventions, including vaccine research, controlling vector mosquitoes in affected areas, and promoting personal protection against mosquito bites. While no specific treatment for dengue fever exists, providing supportive care is crucial for preventing complications and potential fatalities. In severe dengue cases, skilled medical attention by professionals familiar with the disease's effects and progression can drastically reduce the mortality rate from over 20% to less than 1% [2]. A dengue vaccine is available, administered in three doses spread over six months

to individuals aged 9 to 45 [3]. However, recent research indicates potential long-term safety concerns among vaccinated individuals lacking prior exposure to the virus.

Given the virus's ability to infect millions, dengue fever incurs substantial economic costs. Ongoing scientific efforts focus on devising effective intervention strategies to reduce dengue infections and curb the rapid spread of the disease. Consequently, researchers emphasize the need for practical assessments of public health intervention strategies, which are crucial for disease control and informing intervention policies.

Researchers have proposed various models to define disease transmission dynamics and evaluate the evolution or severity of dengue.

Esteva and Vargas [4] were among the first to study dengue transmission. They developed a mathematical model with compartmental models for human and mosquito populations. A susceptible-infected-recovered (SIR) model describes the human population, while an (SI) model describes the mosquito population. Singh et al. [5] and Tasman et al. [6] consider the effects of vaccination on a model dividing the human population into children and adults. They also assume two types of infection, primary and secondary, where people suffering from a secondary condition run a higher risk. Sow et al. [7] build a transmission model for a disease similar to dengue, zika, but considering vector-borne and human-to-human transmission in the disease's transmission dynamics. Meksianis Z. Ndii et al. [8] use a deterministic dynamic model to study the interaction between media publicity of vaccination and disease seasonality and progression. They show that the waning immunity rate is one of the influential factors contributing to the increase in dengue infections, indicating the possibility of a higher number of secondary infections. Anusit Chamnan [9] determines the optimal control when only individuals with a documented history of dengue infection are vaccinated.

Sylvestre Aureliano Carvalho et al. [10] examine the efficacy of vaccination by transferring a proportion of individuals, relative to the vaccination rate, from the susceptible group to the recovered group. Their findings revealed that complete eradication of the dengue epidemic necessitates the implementation of an immunizing vaccine. Vector-targeted control measures alone are inadequate in halting the disease's propagation. Indeed, when removing all infected mosquitoes from the system, susceptible mosquitoes persist. Consequently, human infections contribute to the resurgence of dengue within the human population through the remaining vector population. Ananya Dwivedi et al. [11] investigate the transmission dynamics of the dengue virus using a nonlinear vector-host model. The model considers both vaccination and treatment as control measures. Their research indicates that optimal treatment strategies significantly decrease hospitalizations and the number of infected individuals. MZ Ndii et al. [12] constructed deterministic and stochastic dengue epidemic models involving two age groups. Their findings indicate that vaccinating adult individuals results in fewer instances of infection among adults, offering population-level insights into the potential benefits of dengue vaccination. E Shim [13] develops a model considering antibody-dependent enhancement to find the best vaccination strategy. His findings emphasize the potential benefits of dengue vaccination despite limited vaccine efficacy. Ferguson et al. [14] assess the advantages and risks associated with dengue vaccine usage. They found an elevated risk of hospitalization when vaccination is introduced in regions with low to moderate transmission levels, while benefits emerge in areas with high transmission levels.

A recent review presents a comprehensive analysis of mathematical models for dengue epidemiology, encompassing multi-strain frameworks for transmission dynamics and within-host models [15]. By examining various models' scope, approaches, and validation methods, the study provides insights for disease control strategies and enhances understanding of epidemiological and immunological factors influencing dengue transmission dynamics in real-world scenarios.

Although researchers have formulated numerous mathematical models to investigate dengue transmission dynamics in the context of vaccination, these models have primarily overlooked the potential synergies with treatment.

To the best of current knowledge, no prior work has formulated the issue in this specific manner. It is paramount to compare these interventions' individual and combined performances rigorously. Regrettably, research exploring the combined impact of treatment and vaccination remains relatively scarce. Research investigating the ramifications of both vaccination and treatment on dengue fever underscores the potency of the dengue vaccine, which reduces disease severity by 88.5% and hospitalization by 67.2% [16].

However, there are other diseases for which vaccination and other forms of treatment have been studied jointly. One such example is the paper Modeling the Effects of Vaccination and Treatment on Pandemic Influenza, where Feng et al [17]. studied susceptible, infectious and cured models to assess the efficacy of various control programs using vaccination and antiviral treatment.

This article scrutinizes the effectiveness of vaccination and treatment in curbing dengue transmission. It showcases the outcomes of each strategy in isolation and synergy. To address this issue, we introduce a robust mathematical model. Unlike prior works, our analysis takes a unique angle by considering the intricate interplay between vaccination and treatment within the context of disease dynamics.

This novel perspective sheds light on the combined impact of these interventions and offers fresh insights into potential synergies that might have been overlooked.

By framing the issue this way, we aim to provide a more comprehensive understanding of the strategies' effectiveness against dengue. This approach opens avenues for exploring hitherto unexplored dimensions of dengue control.

In the numerical analysis, we validated and estimated the parameters of the model under consideration by comparing model predictions with reported data on dengue infection in Kaohsiung, the main city in southern Taiwan and Thailand. To explore the robustness of the model to the parameter values used, we have studied sensitivity analysis using PRCC with Latin hypercube sampling. We are also numerically investigating the impact of vaccine efficacy and treatment rate on the epidemic growth rate.

The structure of the paper is as follows. Section 1 presents the proposed model's general description and some dynamic behaviors. Section 2 gives the numerical simulations performed to support the theoretical results of the reference values for the model parameters. Section 3 identifies the influential model parameters that significantly affect the number of basic reproductions through a global sensitivity analysis. Sections 4 and 5 present the formulation and characterization of the control model and numerical simulations for two control strategies. Finally, we conclude with the discussion.

Materials and methods

Formulation of the mathematical model

The compartmental model has two parts: human compartments, denoted h, and vector compartments, subscripted with v. We use an *SVITR* (Susceptible, Vaccination, Infectious, Treatment, Recovered) model to describe the disease spread among the human population. Let $S_h(t)$, $V_h(t)$, $I_h(t)$, $T_h(t)$ and $R_h(t)$ denote the number of individuals in each compartment at time t. The human population at time t is given as

$$N_h(t) = S_h(t) + V_h(t) + I_h(t) + T_h(t) + R_h(t).$$

Moreover, the total mosquito population at time t, denoted by $N_v(t)$, is split into

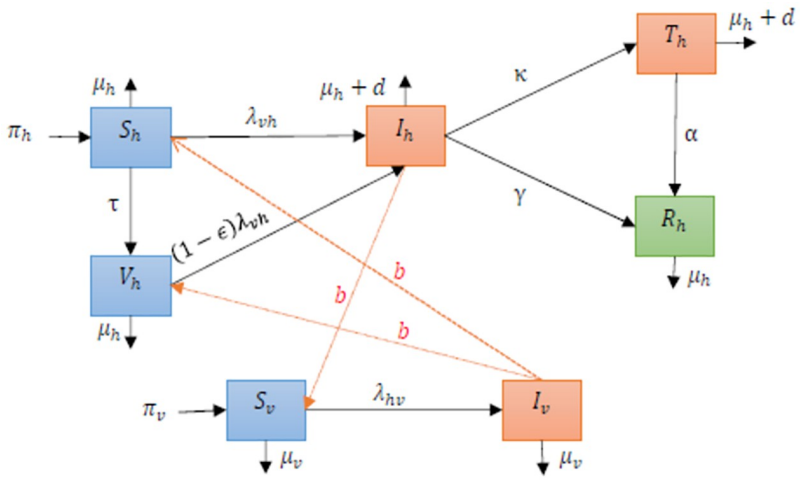


Fig 1. The flow chart represents the dynamical transmission in humans and mosquitoes, incorporating the effect of vaccination and treatment. The host population splits into states: Susceptible (S_h), Vaccinated (V_h), Infectious (I_h), Treatment (T_h) and Rcovered (R_h). The vector population splits into 2 states: Susceptible (S_v), and Infectious (I_v). Dashed arrows show the direction of transmission between humans and mosquitoes.

https://doi.org/10.1371/journal.pone.0295025.g001

subpopulations of susceptible mosquitoes $S_v(t)$ and infected mosquitoes $I_v(t)$, thus

$$N_v(t) = S_v(t) + I_v(t).$$

We will use a single serotype dengue model that does not take into account the effects of secondary infections. Consequently, recovered individuals acquire lifelong immunity against the disease [18]. Transmission from susceptible to infectious state in human and vector populations is associated with mosquito bites b. Fig 1 depicts the schematic model flow. The model variables and parameters are described in Table 1. Since dengue vaccination is available, it is realistic to consider a specific vaccinated class V. The human population is vaccinated at a rate τ. The transmition rates from susceptible and vaccinated to infected is given by, respectively, by the following force of infection λ_{vh} and $(1-\epsilon)\lambda_{vh}$ (ϵ represents the infection reduction of

Table 1. Values of parameters used in the model, and the sources used for the numerical values.

Parameter	Definition	Value	Source
π_h	Recruitment rate of human	2.5	[19]
b	Mosquito biting rate	0.786	Estimated
β_{vh}	Probability of mosquito infectiousness	0.84	Estimated
β_{hv}	Probability of mosquito infection	0.78	Estimated
γ	Recovery rate for humans rate	0.2	[19]
τ	Vaccination rate	0.25	Assumed
μ_h	Natural mortality rate of humans	0.000039	[19]
ϵ	Vaccine efficacy	0.538	[20]
κ	treatement rate of Infectious humans	0.12	[21]
α	Recovery rate of hospitalized individuals	0.4	[21]
d	Disease-induced mortality rate of humans	0.001	[19]
π_v	Recruitment rate of vector	5000	[19]
μ_v	Natural mortality rate of adult mosquitoes	0.17	Estimated

https://doi.org/10.1371/journal.pone.0295025.t001

vaccinated individuals), thus

$$\lambda_{vh} = \frac{b\beta_{vh}I_h}{N_h}$$

The transmition rate from susceptible mosquitoes to infected mosquitoes is given by,

$$\lambda_{hv} = \frac{b\beta_{hv}I_v}{N_h}$$

Infectious humans are treated at a rate κ, recover naturally at a rate γ and suffer disease-induced death at a rate d. Treated humans recover at a rate α. The features of transmission are illustrated in Fig 1, and the mathematical model is described by the following ordinary differential equations with the initial conditions

$$\begin{aligned}
\frac{dS_h}{dt} &= \pi_h - \lambda_{vh}S_h - (\tau + \mu_h)S_h \\
\frac{dV_h}{dt} &= \tau S_h - (1-\varepsilon)\lambda_{vh}V_h - \mu_h V_h \\
\frac{dI_h}{dt} &= \lambda_{vh}S_h + (1-\varepsilon)\lambda_{vh}V_h - (\gamma + \kappa + d + \mu_h)I_h \\
\frac{dT_h}{dt} &= \kappa I_h - (\alpha + d + \mu_h)T_h \\
\frac{dR_h}{dt} &= \gamma\ I_h + \alpha T_h - \mu_h R_h \\
\frac{dS_v}{dt} &= \pi_v - \lambda_{hv}S_v - \mu_v S_v \\
\frac{dI_v}{dt} &= \lambda_{hv}S_v - \mu_v I_v
\end{aligned} \tag{1}$$

$$S_h(0) \geq 0, V_h(0) \geq 0, I_h(0) \geq 0, T_h(0) \geq 0, R_h(0) \geq 0, S_v(0) \geq 0, I_v(0) \geq 0 \tag{2}$$

Properties of solutions

The model proposed (1) is a system of non-linear ordinary differential equations with initial conditions (2). To be meaningful from an epidemiological and mathematical point of view, all solutions with the given initial conditions must remain non-negative and bounded for all finite time. The model must be analyzed in a biologically meaningful realizable region defined by a positive invariant set.

Lemma 1 *Let* $F(t) = (S_h, V_h, I_h, T_h, R_h, S_v, I_v)$ *such that* $F(0) \geq 0$. *Then the solutions* $F(t)$ *of the model* (1) *are non negative for all* $t \geq 0$.

Proof 1 *Let* $T = \sup\{t > 0 : F(t) > 0\}$. *In model* (1) *we have*:

$$\frac{dS_h}{dt} = \pi_h - \lambda_{vh}S_h(t) - (\tau + \mu_h)S_h(t)$$

with $\lambda_{vh} = \frac{b\beta_{vh}I_v}{N_h}$ *we can write the* λ_{vh} *as a function of* I_v *and* N_h. *This gives*:

$$\frac{dS_h}{dt} = \pi_h - \lambda_{vh}(I_v, N_h)S_h(t) - (\tau + \mu_h)S_h(t)$$

By integration we obtain

$$\frac{d}{dt}\left\{S_h(t)\left[\exp\left(\int_0^T \lambda_{vh}(I_v(x),N_h(x))dx\right)+(\tau+\mu_h)T\right]\right\}$$

$$=\pi\exp\left(\int_0^T \lambda_{vh}(I_v(x),N_h(x))dx+(\tau+\mu_h)T\right)$$

Therefore

$$S_h(T)\exp\left[\left(\int_0^T \lambda_{vh}(I_v(x),N_h(x))dx+(\tau+\mu_h)T\right)\right]-S_h(0)$$

$$=\int_0^T \pi\exp\left(\int_0^y \lambda_{vh}(I_v(x),N_h(x))dx+(\tau+\mu_h)y\right)dy$$

Or

$$S_h(T)=S_h(0)\exp\left[-\left(\int_0^T \lambda_{vh}(I_v(x),N_h(x))dx+(\tau+\mu_h)T\right)\right]$$

$$+exp\left[-\left(\int_0^T \lambda_{vh}(I_v(x),N_h(x))dx+(\tau+\mu_h)T\right)\right]$$

$$\times\int_0^T \pi exp\left(\int_0^y \lambda_{vh}(I_v(x),N_h(x))dx+(\tau+\mu_h)y\right)dy>0$$

Similarly, we can prove that $V_h(T)$, $I_h(T)$, $T_h(T)$, $R_h(T)$, $S_v(T)$ *and* $I_v(t)$ *all are psitive for all* $T>0$ *therefore* $F>0$ *for all* $t>0$

Theorem 2 *The closed region* $\Omega=\left\{(S_h,V_h,I_h,T_h,R_h,S_v,I_v)\in\mathbb{R}_+^7, N_h\leq\frac{\pi_h}{\mu_h}, N_v\leq\frac{\pi_v}{\mu_v}\right\}$ *is a positively invariant set for the model (1) with non-negative initial condition in* $\mathbb{R}_+^7$

Proof 2 *here we use the basic theory of dynamical systems as described in* [22]
As the total population sizes are

$$N_h(t)=S_h(t)+V_h(t)+I_h(t)+T_h(t)+R_h(t)\geq 0\quad\forall t>0$$

and

$$N_v(t)=S_v(t)+I_v(t)\geq 0\quad\forall t>0$$

we get

$$\frac{dN_h}{dt} = \pi_h - \mu_h N_h - d(I_h + T_h) \text{ and } \frac{dN_v}{dt} = \pi_v - \mu_v N_v$$

$$\frac{dN_h}{dt} \leq \pi_h - \mu_h N_h$$

$$\frac{dN_v}{dt} \leq \pi_v - \mu_v N_v$$

$$N_h \leq N_h(0)e^{-\mu_h(t)} + \frac{\pi_h}{\mu_h}\left(1 - e^{-\mu_h(t)}\right)$$

$$N_v \leq N_v(0)e^{-\mu_v(t)} + \frac{\pi_v}{\mu_v}\left(1 - e^{-\mu_v(t)}\right)$$

which shows that

$$\limsup_{t\to\infty} N_h \leq \frac{\pi_h}{\mu_h}$$

$$\limsup_{t\to\infty} N_v \leq \frac{\pi_v}{\mu_v}$$

The initial conditions given (2) ensure that $N_h(0) \geq 0$ *and* $N_v(0) \geq 0$. *Thus* $N_h(t)$ *and* $N_v(t)$ *are positively-bounded for all* $t \geq 0$

Disease-free equilibrium and basic reproduction number

The basic reproduction ratio, R_0, gives the average number of secondary cases of infection resulting from a single primary infection in a population where everyone is susceptible. In epidemic models, it is worthy of consideration as it indicates the persistence or eradication of diseases by giving a threshold depending on epidemiological parameters. Indeed, an epidemic is said to be under control (cannot persist in the population) when $R_0 < 1$.

The disease-free equilibrium (DFE) of the model (1) is obtained by using $I_h = 0$, $T_h = 0$ and $I_v = 0$ in the steady state conditions:

$$E_0 = \left(\frac{\pi_h}{\tau + \mu_h}, \frac{\tau\pi_h}{\mu_h(\tau + \mu_h)}, 0, 0, 0, 0, \frac{\pi_v}{\mu_v}\right)$$

We use the following generation operator method on model (1) to calculate the basic reproduction number.

Consider the infected compartments I_h; T_h; I_v at the disease-free equilibrium (DFE) and applying [23] technique, the Jacobian matrices F and V for the new infection terms and the

remaining transfer terms respectively are given by

$$F = \begin{pmatrix} 0 & 0 & \frac{b\beta_{vh}S_h^0 + b(1-\varepsilon)\beta_{vh}V_h^0}{N_h^0} \\ 0 & 0 & 0 \\ \frac{b\beta_{hv}S_v^0}{N_h^0} & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \gamma + \kappa + d_h + \mu_h & 0 & 0 \\ -\kappa & \alpha + \mu_h + d_h & 0 \\ 0 & 0 & \mu_v \end{pmatrix}$$

Thus, the effective reproduction number is given by

$$R_0 = \sqrt{\frac{b^2\beta_{vh}\beta_{hv}\mu_h^2\pi_v}{\pi_h\mu_v^2(\tau+\mu_h)(\gamma+\kappa+d+\mu_h)}\left[1+\frac{\tau(1-\varepsilon)}{\mu_h}\right]} \tag{3}$$

Global asymptotic stability of the disease-free equilibrium

In this section, we study the global asymptotic stability of the disease-free equilibrium (DFE) to assure the eradication of the Dengue virus. We consider the feasible region

$$\Gamma = \{(S_h, V_h, I_h, T_h, R_h, S_v, I_v) \in \mathbb{R}_+^7, S_h \leq S_h^0, S_v \leq S_v^0\}$$

Lemma 3 Γ *is a positively invariant set for the model (1) with non- negative initial condition in* $\mathbb{R}^7$

Proof 3 *From model (1) we have*

$$\frac{dS_h}{dt}(t) = \pi_h - \lambda_{vh}S_h(t) - (\mu_h+\tau)S_h(t) \leq \pi_h - (\mu_h+\tau)S_h(t) = (\mu_h+\tau)\left(\frac{\pi_h}{(\mu_h+\tau)} - S_h(t)\right)$$

and we know that $S_h(0) = \frac{\pi_h}{\mu+\tau}$ *therefore* $S_h(t) \leq S_h(0) - (S_h^0 - S_h(0))e^{-(\mu_h+\tau)t}$.

So, if $S_h(0) \leq S_h^0 \forall t \geq 0 S_h(t) \leq S_h^0 \quad \forall t \geq 0$. *and also*

$$\frac{dS_v}{dt}(t) = \pi_v - \lambda_{vh}S_v(t) - \mu_v S_v(t) \leq \pi_v - \mu_v S_v(t) = \mu_v\left(\frac{\pi_v}{\mu_v} - S_v(t)\right) = \mu_v(S_v(0) - S_v(t))$$

$S_v(0) = \frac{\pi_v}{\mu_v}S_v(t) \leq S_v(0) - (S_v^0 - S_v(0))e^{-\mu_v t}$. *Thus if* $S_v(0) \leq S_v^0 \quad \forall t \geq 0 S_v(t) \leq S_v^0 \quad \forall t \geq 0$

Lemma 4 *Let* $(X_1^0, \vec{0})$ *such that* X_1^0 *is a globally stable equilibrium. If* $G(X_1, X_2)$ *satisfies the following two conditions given in* [24], *namely*
$G(X_1, \vec{0}) = \vec{0}$ *and* $\hat{G}(X_1, X_2) = D_{X_2}G(X_1^0, \vec{0})X_2 - G(X_1, X_2), \vec{G}(X_1, X_2) \geq 0$, *then the disease free equilibrium is globally asymptotically stable*

Theorem 5 *(global asymptotic stability of the DFE). The DFE* Γ *of model (1) is globally asymptotically stable if* $R_0 < 1$:

Proof 4 *Let*

$$X_1 = (S_h, V_h, R_h, S_v), \qquad X_2 = (I_h, T_h, I_v)$$

and by grouping model (1) into

$$\frac{dX_1}{dt} = F(X_1, 0), \frac{dX_2}{dt} = G(X_1, X_2)$$

where $F(X_1, 0)$ is obtained from the right-hand side of the first, second, fifth and sixth equations of model (1) with $I_h = T_h = Iv = 0$ and $G(X_1;X_2)$ is obtained from the right-hand side of the third, fourth and seventh equations of model (1).

Now consider the model in reduced form:

$$\begin{aligned}\frac{dS_h}{dt} &= \pi_h - (\tau + \mu_h)S_h \\ \frac{dV_h}{dt} &= \tau S_h - \mu_h V_h \\ \frac{dR_h}{dt} &= -\mu_h R_h \\ \frac{dS_v}{dt} &= \pi_v - \mu_v S_v\end{aligned} \tag{4}$$

This equation has a unique equilibrium point

$$X_1^0 = \left(\frac{\pi_h}{\tau + \mu_h}, \frac{\tau\pi_h}{\mu_h(\tau + \mu_h)}, 0, \frac{\pi_v}{\mu_v}\right)$$

which is globally asymptotically stable

Next, we check $G(X_1, X_2)$ satisfies two conditions of lemme 2 where

$$(X_1^0, \vec{0}) = \left(\frac{\pi_h}{\tau + \mu_h}, \frac{\tau\pi_h}{\mu_h(\tau + \mu_h)}, 0, 0, 0, \frac{\pi_v}{\mu_v}, 0\right)$$

and

$$D_{X_2}G(X_1^0, \vec{0}) = \begin{pmatrix} -\gamma - \kappa - d - \mu_h & 0 & \frac{b\beta_{vh}S_h + b(1-\varepsilon)\beta_{vh}V_h}{N_h^0} \\ k & -\alpha - d = \mu_h & 0 \\ \frac{b\beta_{hv}S_v}{N_h^0} & 0 & -\mu_v \end{pmatrix}$$

is the Jacobian of $G(X_1, X_2)$ with respect to $(I_h;T_h;I_v)$ is calculated at $(X_1^0, \vec{0})$ It is an M-matrix with off-diagonal elements that are non-negative. The relation

$$\hat{G}(X_1, X_2) = D_{X_2}G(X_1^0, \vec{0})X_2 - G(X_1, X_2)$$

gives

$$\hat{G}(X_1, X_2) = \begin{pmatrix} \frac{b\beta_{vh}S_h^0}{N_h^0}\left(1 - \frac{N_h^0 S_h}{S_h^0 N_h}\right) + \frac{b\beta_{vh}V_h^0(1-\epsilon)}{N_h^0}\left(1 - \frac{N_h^0 V_h}{V_h^0 N_h}\right) \\ 0 \\ \frac{b\beta_{hv}S_v^0}{N_h^0}\left(1 - \frac{N_h^0 S_v}{S_v^0 N_h}\right) \end{pmatrix}$$

In the region Γ, we have $\hat{G}(X_1, X_2) \geq 0$ So by the theorem in [24], the global stability of the DFE is obtained.

The above theorem indicates that the dengue virus can be eradicated from the population if R_0 can be reduced to a value less than or equal to unity, regardless of the size of the initial sub-population in each class.

Stability of the endemic equilibrium

The state of endemic equilibrium is the state in which the disease cannot be totally eradicated but persists in the population.

Let

$$E^* = (S_h^*, V_h^*, I_h^*, T_h^*, R_h^*; S_v^*, I_v^*)$$

After some algebraic manipulations, the endemic equilibrium of model system (3) is obtained as

$$S_h^* = \frac{\pi_h}{\lambda_{vh}^* + (\tau + \mu_h)},$$

$$V_h^* = \frac{\tau\pi_h}{(\lambda_{vh}^* + (\tau + \mu_h))((1-\varepsilon) + \mu_h)},$$

$$I_h^* = \left[\frac{\lambda_{vh}^*\pi_h}{\lambda_{vh}^* + (\tau + \mu_h)} + \frac{(1-\varepsilon)\tau\pi_h}{(\lambda_{vh}^* + (\tau + \mu_h))((1-\varepsilon) + \mu_h)}\right] \cdot \frac{1}{(\gamma + \kappa + d + \mu_h)},$$

$$S_v^* = \frac{\pi_v}{\lambda_{hv}^* + \mu_v},$$

$$I_v^* = \frac{\lambda_{hv}^*\pi_v}{(\lambda_{hv}^* + \mu_v)\mu_v}$$

with

$$\lambda_{vh}^* = \frac{b\beta_{vh}I_v^*}{N_h} = \frac{b\beta_{vh} \cdot \frac{\lambda_{hv}^*\pi_v}{(\lambda_{hv}^* + \mu_v)\mu_v}}{N_h} \tag{5}$$

and

$$\lambda_{hv}^* = \frac{b\beta_{hv}I_h^*}{N_h} = \frac{b\beta_{hv}\left[\frac{\lambda_{vh}^*\pi_h}{\lambda_{vh}^* + (\tau + \mu_h)} + \frac{(1-\varepsilon)\tau\pi_h}{(\lambda_{vh}^* + (\tau + \mu_h))((1-\varepsilon) + \mu_h)}\right]}{N_h(\gamma + \kappa + d + \mu_h)} \tag{6}$$

From the Eq (5) and using Eq (6) we obtain the following quadratic equation;

$$\lambda_{hv}^*(c_3\lambda_{hv}^{*3} + c_2\lambda_{hv}^{*2} + c_1\lambda_{hv}^* + c_0) = 0 \tag{7}$$

If $\lambda_{hv}^* = 0$, then $I_h = 0$, which represents the disease-free equilibrium. Otherwise

$$c_3\lambda_{hv}^{*3} + c_2\lambda_{hv}^{*2} + c_1\lambda_{hv}^* + c_0 = 0$$

Now by the Routh-Hurtwiz criteria, the eigenvalues of the endemic equilibrium state will have negative real parts if c_3, c_2 and c_1 are positive constants and $c_1c_2 > c_0c_3$,

$$c_0 = \pi_h(\gamma + \kappa + d + \mu_h)(\tau + \mu_h)^2\mu_v^3(R_0^2 - 1) \tag{8}$$

and c_1, c_2 and c_3 given in the appendix S1 Appendix. All these conditions will be satisfied if $R_0 > 1$

Theorem 6 *The equilibrium point E^* is locally asymptotically stable when If $R_0 > 1$.*

Table 2. Summary table of initial state values.

Parameter	Definition	Value
$S_h(0)$	initial susceptible human	1767970
$V_h(0)$	initial vaccinated human	20
$I_h(0)$	initial infected human	10
$T_h(0)$	initial treatement human	0
$R_h(0)$	initial recovered human	0
$S_v(0)$	initial susceptible vector	$3 \times S_h(0)$
$I_v(0)$	initial infected vector	100

https://doi.org/10.1371/journal.pone.0295025.t002

Model fitting and parameter estimation

This section concerns parameter estimation (using least squares regression) of the dengue model based on weekly dengue case data from 2014–2015 in Kaohsiung, the main city in southern Taiwan [25]. In this paper, the values of parameters such as mosquito infection probability, human infection probability, mosquito bite rate and adult mosquito natural mortality rate are estimated, while the values of other parameters are chosen from the literature. The corresponding values of the estimated parameters are given in Table 1. In 2014–2015, the total population of Kaohsiung was estimated at 1768000 [26]. The initial total population is therefore $N_h(0) = 1768000$. The initial number of infected populations is 10 and the initial density of the remaining populations is arbitrarily assumed Table 2.

Fig 2 shows that the model captures the general behavior of dengue cases in this municipality.

Numerical simulations

In this section, we conduct a numerical analysis of dengue transmission through vaccination and treatment using several distinct scenarios. The model's parameter values are listed in Table 1.

We perform numerical simulations to illustrate the dynamic behavior of the diseases. Fig 3 demonstrates the cure rate's influence on the disease's transmission dynamics. As the treatment strategy intensifies, the infected population diminishes. Fig 4 shows the effect of transmission of vaccination efficacy. the transmission effect of vaccination efficacy. As vaccination efficiency increases, the infected population decreases.

Here, we present the dengue reduction with three scenarios: vaccination, treatment, and both vaccination and treatment. We also show the numerical solutions of the model with different vaccination rates and vaccine efficacy.

Fig 5 depicts the numerical solutions of the model with a vaccine efficacy of 0.536 and a vaccination rate of 0.2. Here, the vaccine efficacy of 0.536 reflects its effectiveness on seronegative individuals. The findings reveal that treatment alone significantly reduces dengue cases more than the vaccine. Specifically, using vaccination alone, treatment alone, and a combination of both strategies can curtail the number of dengue cases by approximately 74%, 89%, and 98%, respectively. It underscores that relying solely on treatment is sufficient to reduce dengue cases when the vaccine efficacy is low.

Fig 6 illustrates that despite a high vaccination rate, the effectiveness of treatment surpasses that of the vaccine. This outcome could potentially be influenced by a low vaccine efficacy, resulting in the reinfection of vaccinated individuals.

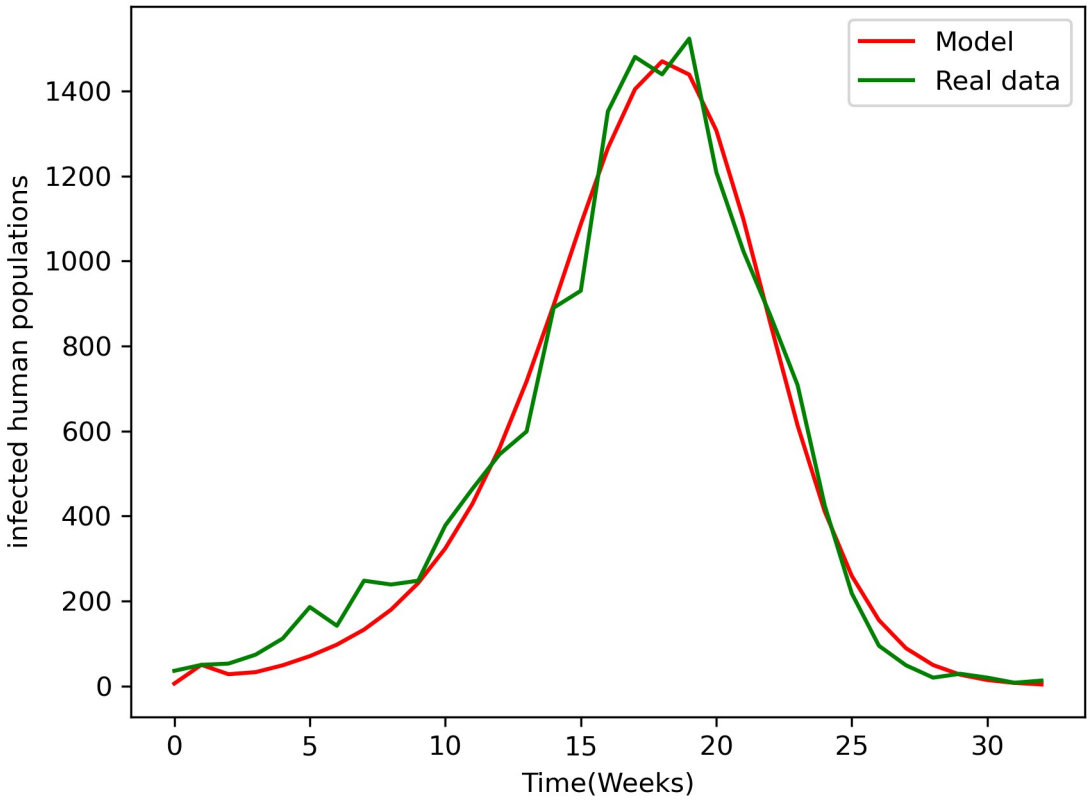


Fig 2. Best fit of models to reported dengue cases in Kaohsiung. The real data corresponds to the number of reported cases for the dengue outbreak occurred in Kaohsiung 2014–2015.

https://doi.org/10.1371/journal.pone.0295025.g002

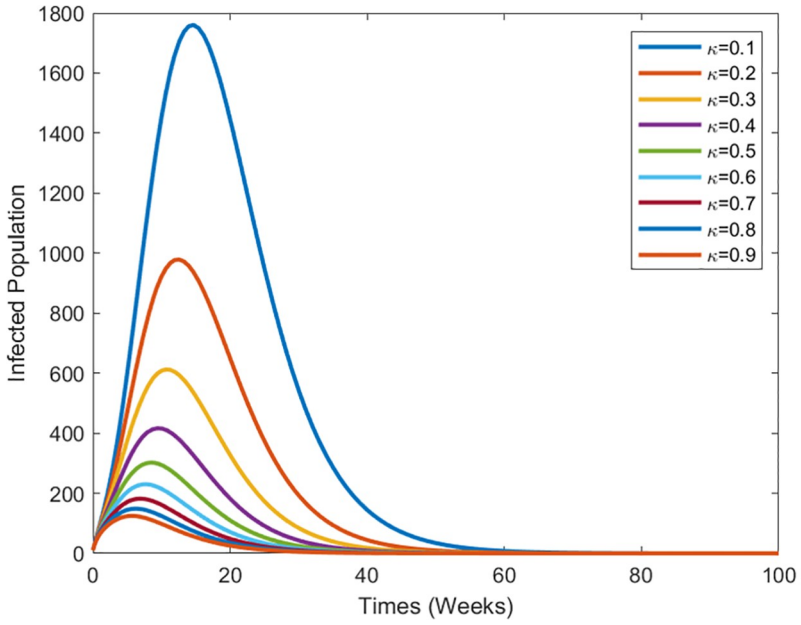


Fig 3. Evolution of the epidemic spreading in the human population for various values of the cure rate κ.

https://doi.org/10.1371/journal.pone.0295025.g003

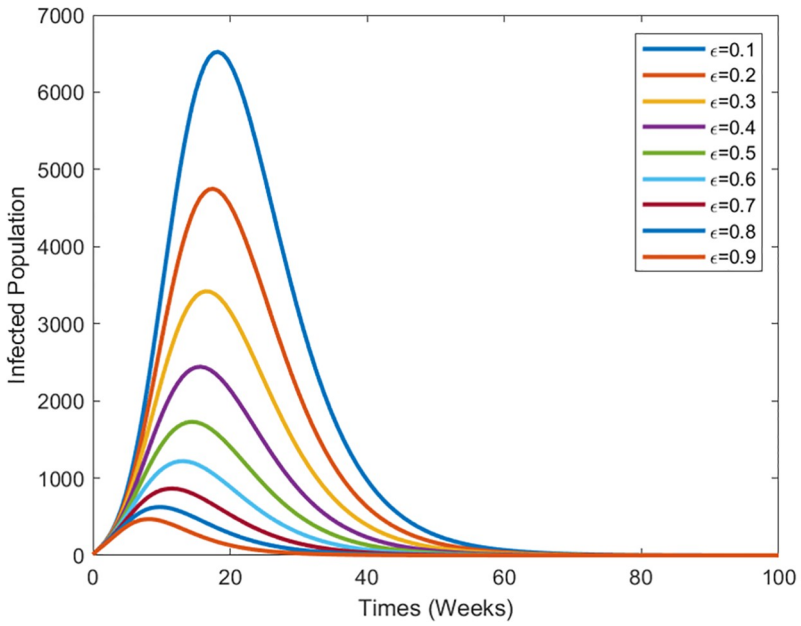


Fig 4. Evolution of the epidemic spreading in the human population for various values of the vaccine efficacy rate ϵ.

https://doi.org/10.1371/journal.pone.0295025.g004

At a vaccination rate of 0.5 and vaccine efficacy of 0.8, Fig 7 demonstrates that the reduction in the number of dengue cases achieved through vaccination outweighs that achieved through treatment. It emphasizes the significance of factoring in vaccine efficacy and vaccination rate when devising a vaccination strategy.

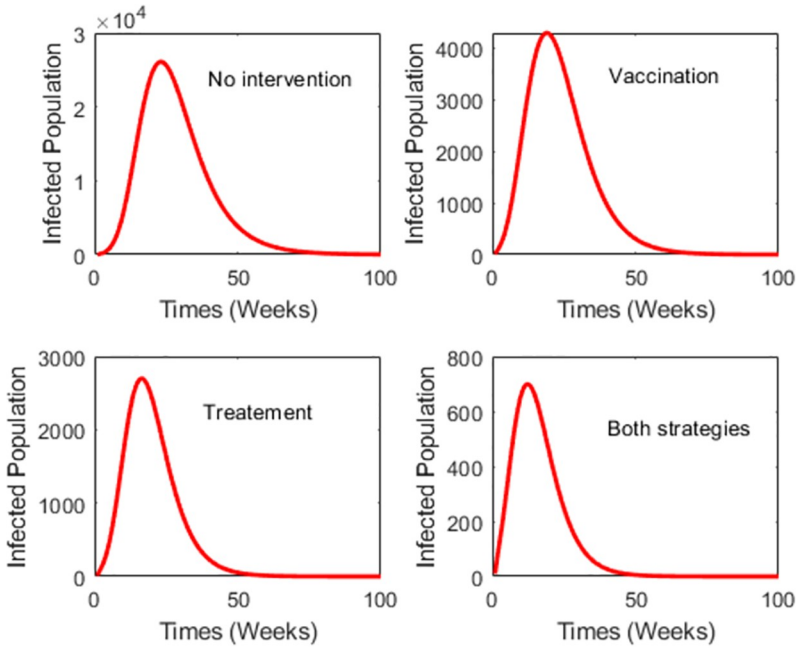


Fig 5. Numerical simulations of the model with no intervention, vaccine only, treatement only, and both vaccine and treatement. The vaccine efficacy is 0.536 and the vaccination rate is 0.2.

https://doi.org/10.1371/journal.pone.0295025.g005

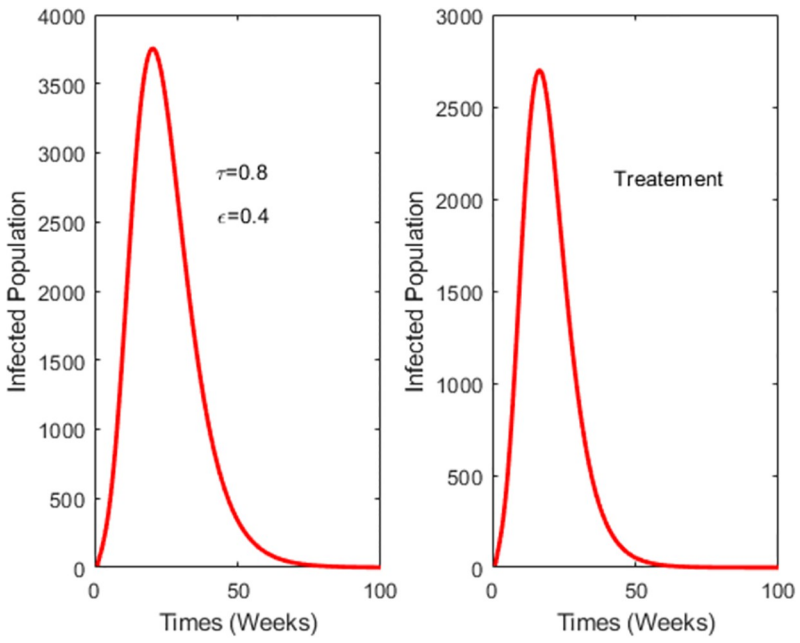


Fig 6. Comparing the performance of vaccination and treatment with high vaccination rates. $\tau = 0.8$ and the vaccine efficacy is 0.4.

https://doi.org/10.1371/journal.pone.0295025.g006

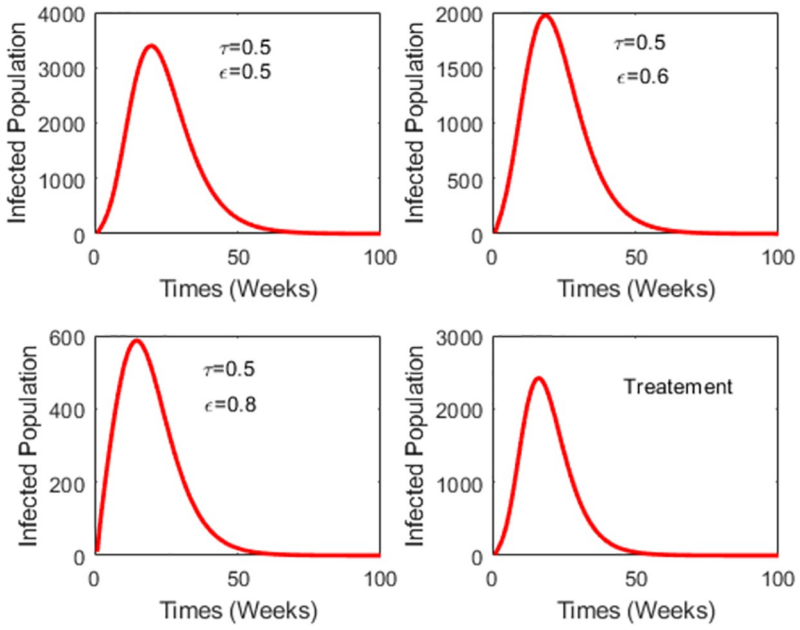


Fig 7. Comparing the performance of vaccination and treatment with different vaccine efficacy.

https://doi.org/10.1371/journal.pone.0295025.g007

Vaccination campaign

We analyze the crucial vaccination coverage rate necessary for disease eradication. In the absence of vaccination within the community, the number of effective reproductions is:

$$r_0 = \sqrt{\frac{b^2\beta_{vh}\beta_{hv}\mu_h^2\pi_v}{\pi_h\mu_v^2\mu_h(\gamma+\kappa+d+\mu_h)}} \tag{9}$$

We know

$$R_0 = \sqrt{\frac{b^2\beta_{vh}\beta_{hv}\mu_h^2\pi_v}{\pi_h\mu_v^2(\tau+\mu_h)(\gamma+\kappa+d+\mu_h)}\left[1+\frac{\tau(1-\varepsilon)}{\mu_h}\right]} \tag{10}$$

After some rearrangement,

$$\frac{R_0^2}{r_0^2} = \frac{\mu_h}{\tau+\mu_h} + \frac{\tau}{\tau+\mu_h}(1-\epsilon)$$

$$R_0 = r_0\sqrt{\left[\frac{\mu_h}{\tau+\mu_h} + \frac{\tau}{\tau+\mu_h}(1-\epsilon)\right]} \tag{11}$$

$$R_0^\infty = \lim_{\tau\to\infty} R_0 = r_0\sqrt{1-\epsilon} \tag{12}$$

$$R_0(\infty) < 1 \Leftrightarrow r_0\sqrt{1-\epsilon} < 1 \Leftrightarrow \epsilon > 1 - \frac{1}{r_0^2} \tag{13}$$

$$\epsilon^* = 1 - \frac{1}{r_0^2} \Leftrightarrow \epsilon > \epsilon^*$$

An average infected individual causing R_0 secondary cases prompts us to consider immunizing at least $r_0^2 - 1$ of them to halt epidemic spread. It establishes a critical vaccination level for population protection. This value, derived from the differential equation model, represents the threshold against preventing a newly introduced infectious disease and eradicating an existing contagious one (see Fig 8). Notably, disease control does not require complete population vaccination. Indeed, each vaccinated individual contributes to collective immunity, reducing the likelihood of disease transmission to others they might have infected. Moreover, Fig 8 shows that additional efforts is necessary to reduce R_0 below unity even when vaccination coverage τ is high.

Global sensitivity analysis

The input parameters determine the results of the compartmental mathematical models, which may be subject to uncertainty. A global sensitivity analysis is therefore carried out to examine the effect of uncertainty and the sensitivity of numerical simulation results to changes in each parameter of our model. Therefore, a global sensitivity analysis is performed to determine the most influential model parameters using a combination of Latin Hypercube Sampling (LHS) and Partial Rank Coefficient (PRCC).

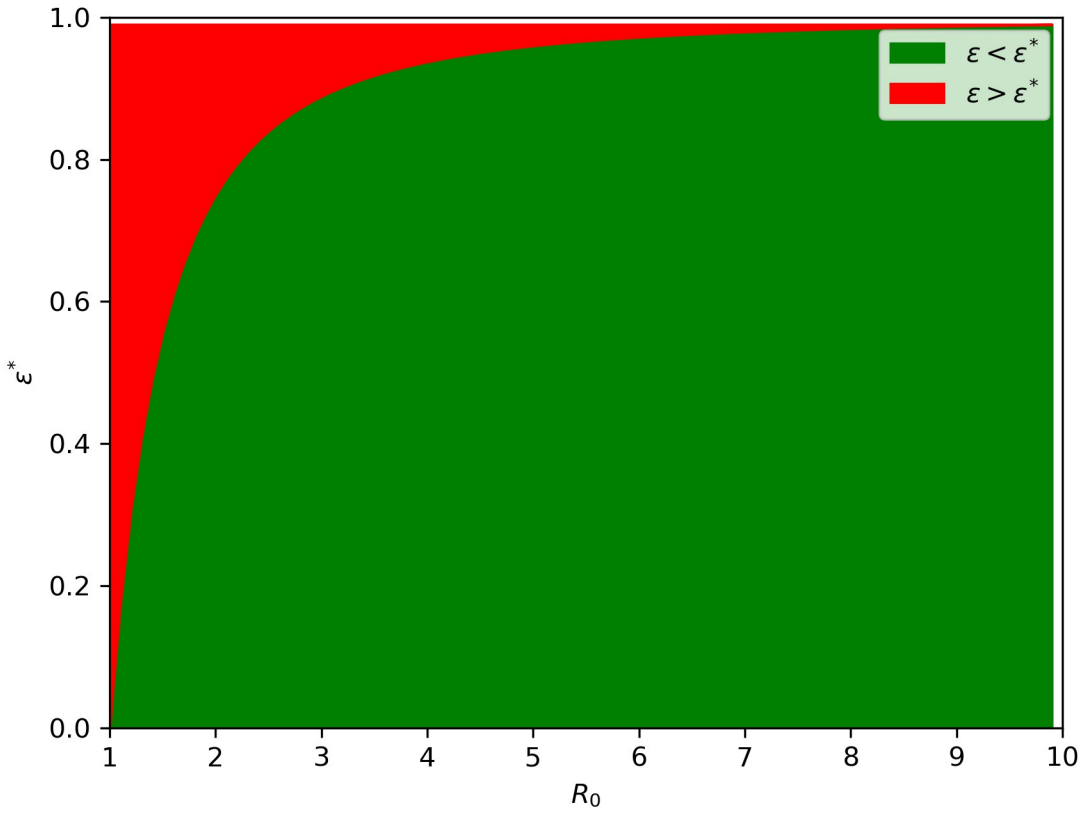


Fig 8. Theoretical impact of perfect vaccination. The graph shows the relationship between the critical level of vaccination required to eradicate infection and the basic reproduction rate, R_0.

https://doi.org/10.1371/journal.pone.0295025.g008

Fig 9 illustrates the sensitivity analysis results. It indicates that transmission probability, biting rates, vaccine efficacy, Recovery rate for humans rate, and mosquito mortality rates hold the most significant sway over the rise in infections. The first two parameters exhibit negative correlations, while the latter exhibit positive ones. It implies that higher mosquito mortality rates, vaccine, and treatment efficacy contribute to fewer infections. Similarly, reduced biting rates and transmission probabilities lead to fewer dengue cases.

Figs 10–14 confirm the impact of these key parameters on R_0.

Optimal control model

In the previous section, we investigated the impact of vaccine efficacy and treatment on the dynamics of the infectious disease dengue. In this section, we develop an optimal control problem to address dengue mitigation. We introduce two time-dependent controls, denoted as $u_1(t)$ and $u_2(t)$ in model (1), to examine how their temporal variations influence dengue dynamics. Eq (14) defines the control problem. To analyze the effect of enhanced vaccine efficacy, we consider the time-dependent control variable $u_1(t)$. Similarly, the control variable $u_2(t)$ is chosen to assess the improvement in infection treatment. The dengue control model

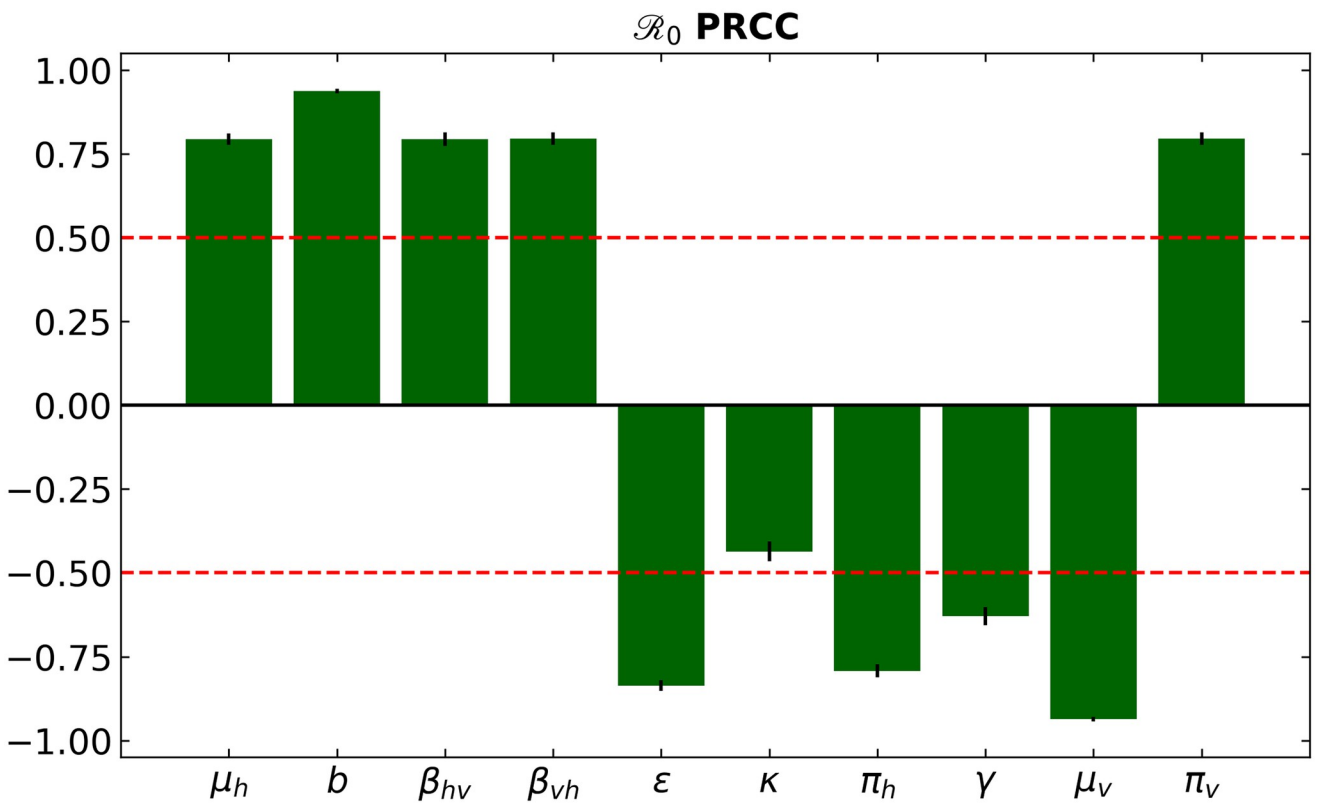


Fig 9. Global sensitivity indices for R_0 against the parameter values in Table 1. This analysis highlights the intercorrelated sensitivities of each of the model parameters. Green bars indicate the mean value of each PRCC, with error bars corresponding to one standard deviation. The red line marks the PRCC values +/- 0.50 and identifies the most influential parameters (greater than 0.50 or less than—0.50).

https://doi.org/10.1371/journal.pone.0295025.g009

that emerges incorporates these control variables as follows:

$$\begin{aligned}
\frac{dS_h}{dt} &= \pi_h - \lambda_{vh} S_h - (u_1 + \mu_h) S_h \\
\frac{dV_h}{dt} &= u_1 S_h - (1-\varepsilon)\lambda_{vh} V_h - \mu_h V_h \\
\frac{dI_h}{dt} &= \lambda_{vh} S_h + (1-\varepsilon)\lambda_{vh} V_h - (\gamma + \kappa + d + \mu_h) I_h \\
\frac{dT_h}{dt} &= \kappa I_h - (u_2 + d + \mu_h) T_h \\
\frac{dR_h}{dt} &= \gamma\ I_h + u_2 T_h - \mu_h R_h \\
\frac{dS_v}{dt} &= \pi_v - \lambda_{hv} S_v - \mu_v S_v \\
\frac{dI_v}{dt} &= \lambda_{hv} S_v - \mu_v I_v
\end{aligned} \quad . \tag{14}$$

The functional objective for a fixed final time T is given below:

$$J(u_1, u_2) = \int_0^T (A_1 I_h + A_2 T_h + B_1 u_1^2(t) + B_2 u_2^2(t))dt \tag{15}$$

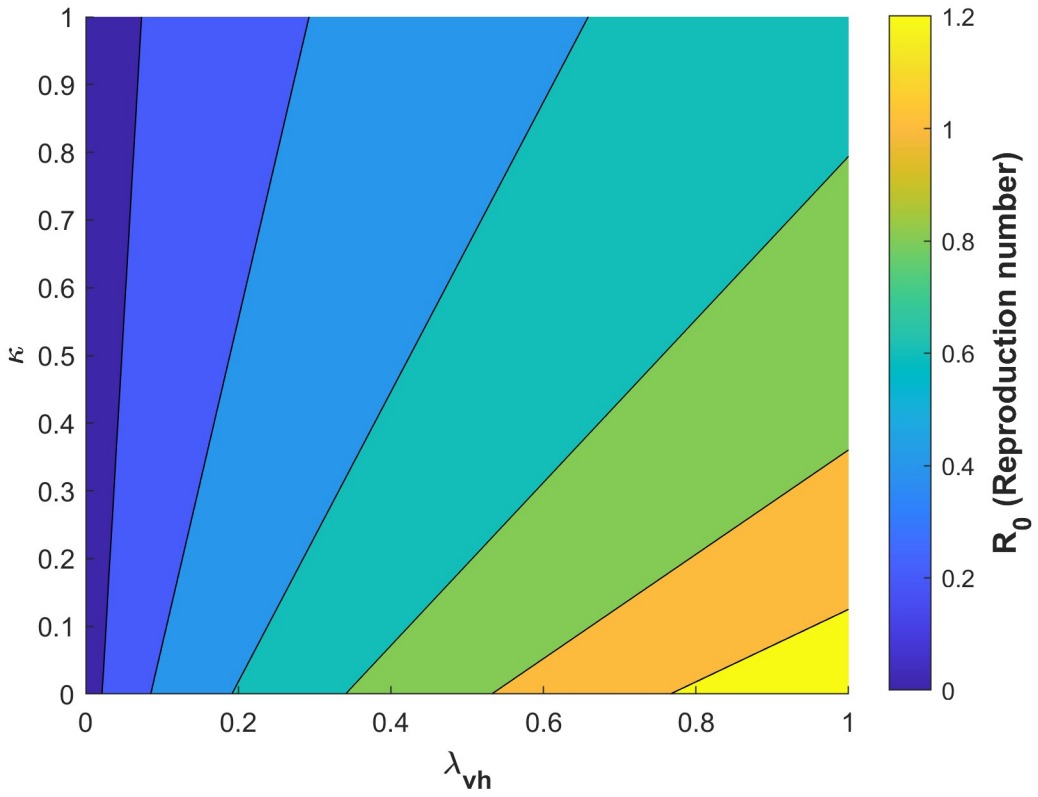


Fig 10. Contour plot of R_0 concerning probability of infection of a susceptible mosquito per bite on an infected human λ_{vh} and treatement rate of infectious humans κ.

https://doi.org/10.1371/journal.pone.0295025.g010

The principal aim of our observations is to find the optimal control variables u_1^* and u_2^* respectively associated with vaccination efficacy and treatment improvement, such that

$$J(u_1^*, u_2^*) = \min_{\Omega} J(u_1, u_2)$$

The Lagrangian and Hamiltonian associated with the dengue control system developed Eq (14) are defined as follows

$$H = A_1 I_h + A_2 T_h + B_1 u_1^2 + B_2 u_2^2 + \delta_{S_h}\frac{dS_h}{dt} + \delta_{V_h}\frac{dV_h}{dt} + \delta_{I_h}\frac{dI_h}{dt} + \delta_{T_h}\frac{dT_h}{dt} + \delta_{R_h}\frac{dR_h}{dt} + \delta_{S_v}\frac{dS_v}{dt} + \delta_{I_v}\frac{dI_v}{dt}$$

where $\delta_{S_h}, \delta_{V_h}, \delta_{I_h}, \delta_{T_h}, \delta_{R_h}, \delta_{S_v}$ and δ_{i_v} are the adjoint variables. The following result presents the adjoint system and control characterization. satisfies

$$\frac{d\delta_i}{dt} = -\frac{dH}{d_i} \tag{16}$$

where $i = S_h, V_h, I_h, T_h, R_h, S_v, I_v$

Theorem 7 *For the optimal control* u_1 and u_2 *and the solutions of* $S_h, V_h, I_h, T_h, R_h, S_v$ and I_v *of the associated systems that minimizes the objective functional* $J(u_1, u_2)$ *over U there exists adjoint variables* $\delta_{S_h}, \delta_{V_h}, \delta_{I_h}, \delta_{T_h}, \delta_{R_h}, \delta_{S_v}, \delta_{I_v}$ *and with transversality condition* $\delta_i(T) = 0$ *and*

$$u_1 = \min\left\{1, \max\left(0, \frac{S_h(\delta_{S_h} - \delta_{V_h})}{2B_1}\right)\right\} \qquad u_2 = \min\left\{1, \max\left(0, \frac{T_h(\delta_{V_h} - \delta_{R_h})}{2B_2}\right)\right\}$$

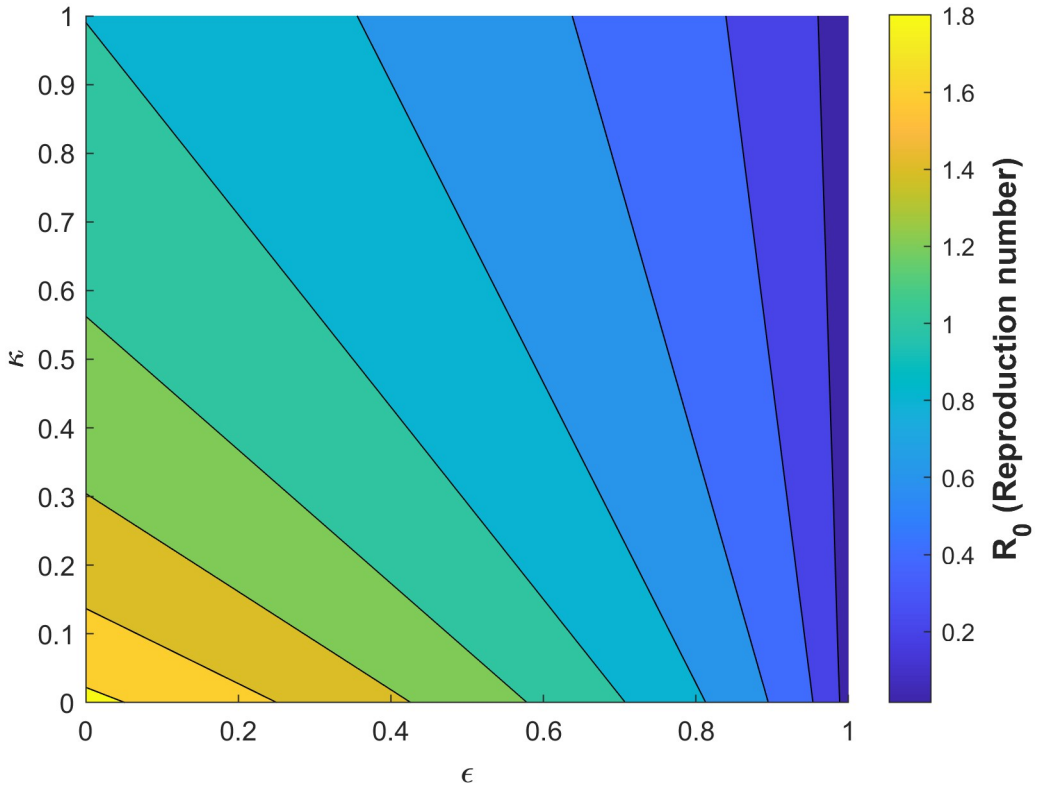


Fig 11. Contour plot of R_0 with respect to vaccine efficacy ϵ and treatment rate of infectious humans κ.

https://doi.org/10.1371/journal.pone.0295025.g011

Proof 5 *The adjoint equations are obtained by taking partial derivatives of the Hamiltonian $\mathcal{H}$ with respect to the associated state variables, so that we obtain*

$$\begin{aligned}
\frac{d\delta_{S_h}}{dt} &= \delta_{S_h}\left(\frac{b\beta_{vh}I_v}{N_h} + u_1 + \mu_h\right) - \delta_{V_h}u_1 - \delta_{I_h}\frac{b\beta_{vh}I_v}{N_h}\\
\frac{d\delta_{V_h}}{dt} &= \delta_{V_h}\left((1-\epsilon)\frac{b\beta_{vh}I_v}{N_h} + \mu_h\right) - \delta_{I_h}\left((1-\epsilon)\frac{b\beta_{vh}I_v}{N_h}\right)\\
\frac{d\delta_{I_h}}{dt} &= -A_1 + \delta_{I_h}(\gamma + \kappa + d + \mu_h) - \delta_{T_h}\kappa - \delta_{R_h}\gamma + \delta_{S_v}\frac{b\beta_{hv}S_v}{N_h}(\delta_{S_v} - \delta_{I_v})\\
\frac{d\delta_{T_h}}{dt} &= -A_2 + \delta_{T_h}(\mu_2 + d + \mu_h) - \delta_{R_h}\mu_h\\
\frac{d\delta_{R_h}}{dt} &= \delta_{R_h}\mu_h\\
\frac{d\delta_{S_v}}{dt} &= \delta_{S_v}\frac{b\beta_{hv}I_h}{N_h}(\delta_{S_v} - \delta_{I_v}) + \delta_{S_v}\mu_v\\
\frac{d\delta_{I_v}}{dt} &= \delta_{S_h}\frac{b\beta_{vh}}{N_h}S_h + \delta_{V_h}(1-\epsilon)\frac{b\beta_{vh}}{N_h}V_h - \delta_{I_h}\left(\frac{b\beta_{vh}}{N_h}S_h + (1-\epsilon)\frac{b\beta_{vh}}{N_h}V_h\right) + \delta_{I_v}\mu_v
\end{aligned} \tag{17}$$

Furthermore, taking the derivative of Hamiltonian with respect to control variables to obtain

$$\frac{dH}{u_1} = 2B_1u_1 - \delta_{S_h}S_h + \delta_{V_h}S_h, \quad \frac{dH}{u_2} = 2B_1u_2 - \delta_{V_h}T_h + \delta_{R_h}T_h \tag{18}$$

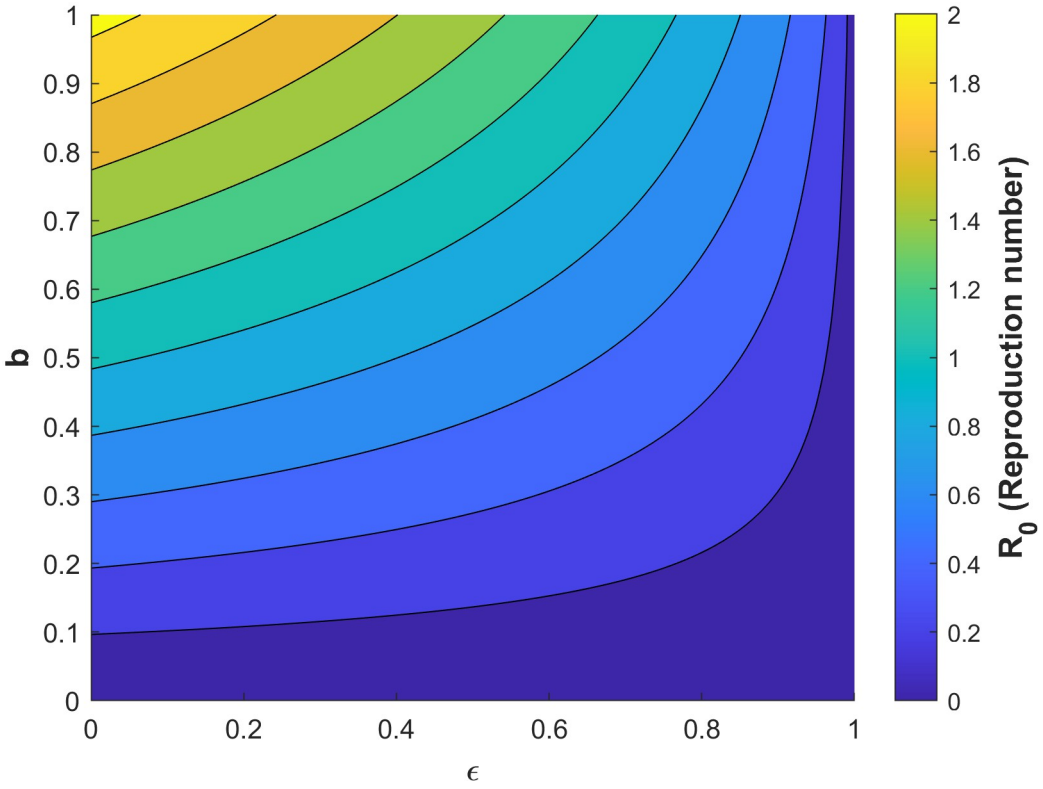


Fig 12. Contour plot of R_0 with respect to vaccine efficacy ϵ biting rate b.

https://doi.org/10.1371/journal.pone.0295025.g012

Solving the equation for u_1 and u_2 to obtain

$$u_1 = \frac{S_h(\delta_{S_h} - \delta_{V_h})}{2B_1} \qquad u_2 = \frac{T_h(\delta v_h - \delta_{R_h})}{2B_2} \tag{19}$$

Using the bounds, we obtain the optimal control characterization as given in Eq (14). This completes the proof.

Numerical simulations of the optimal controls

In this section, we demonstrate the simulations of our optimal control model using MATLAB. The parameter values remain consistent with those discussed in Section 2. The time interval considered is [0, 100]. To solve the adjoint equations, we explore various strategies to gauge the impact of optimal control on the number of infected individuals. We aim to determine the most effective type of optimal control in reducing the infected population. These scenarios are based on two control intervention approaches: single and paired control variables. The first scenario employs a single control, allowing only one control to be utilized at a time. All controls are applied to the model's state variables in the second scenario. We delve into each scenario's impact in greater detail as follows:

Strategy 1: Using only one control at a time

In this scenario, the two control strategies, u_1 (vaccination) and u_2 (treatment), are examined separately to study their impact on disease dynamics.

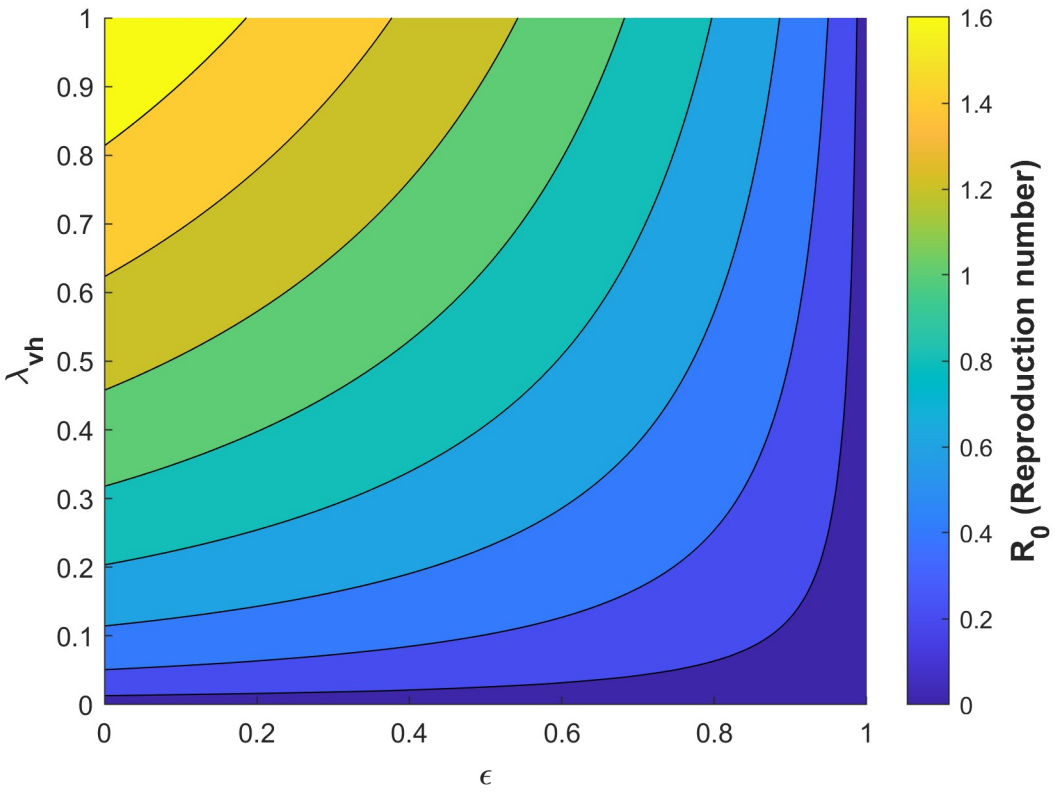


Fig 13. Contour plot of R_0 with respect to vaccine efficacy ϵ and treatment rate of infectious humans λ_{vh}.

https://doi.org/10.1371/journal.pone.0295025.g013

Fig 15 illustrates the different types of optimal control when applied alone and the corresponding effects on the total number of infected individuals. This figure clearly shows that vaccination is more effective in reducing the incidence of infection.

Strategy 2: Implementing all Controls In the second scenario, we examine the collective impact of vaccination and treatment control measures on the dynamics of infectious dengue disease. This exploration aims to elucidate the combined biological implications of simultaneously implementing all control measures for disease incidence. By utilizing the optimal controls within system (14), we present the graphical outcomes in Fig 16 through Fig 18. These figures illustrate the dynamic changes in distinct population compartments under controlled and uncontrolled conditions. Notably, within this dual-control scenario, the susceptible population experiences a rapid decline (Fig 16). Furthermore, the sizes of the infected and hospitalized people (Figs 17 and 18) also witness significant reductions. In summary, simulating this scenario indicates that the simultaneous application of the proposed control measures is more suitable and impactful for reducing infection within a community. This comprehensive approach can potentially protect the population from future disease outbreaks.

Discussion

This paper introduces a mathematical model for dengue virus disease, considering vaccination and treatment. We calculate the basic reproduction number R_0. The disease-free equilibrium (DFE) is globally asymptotically stable when $R_0 < 1$ under specific conditions. We estimate the

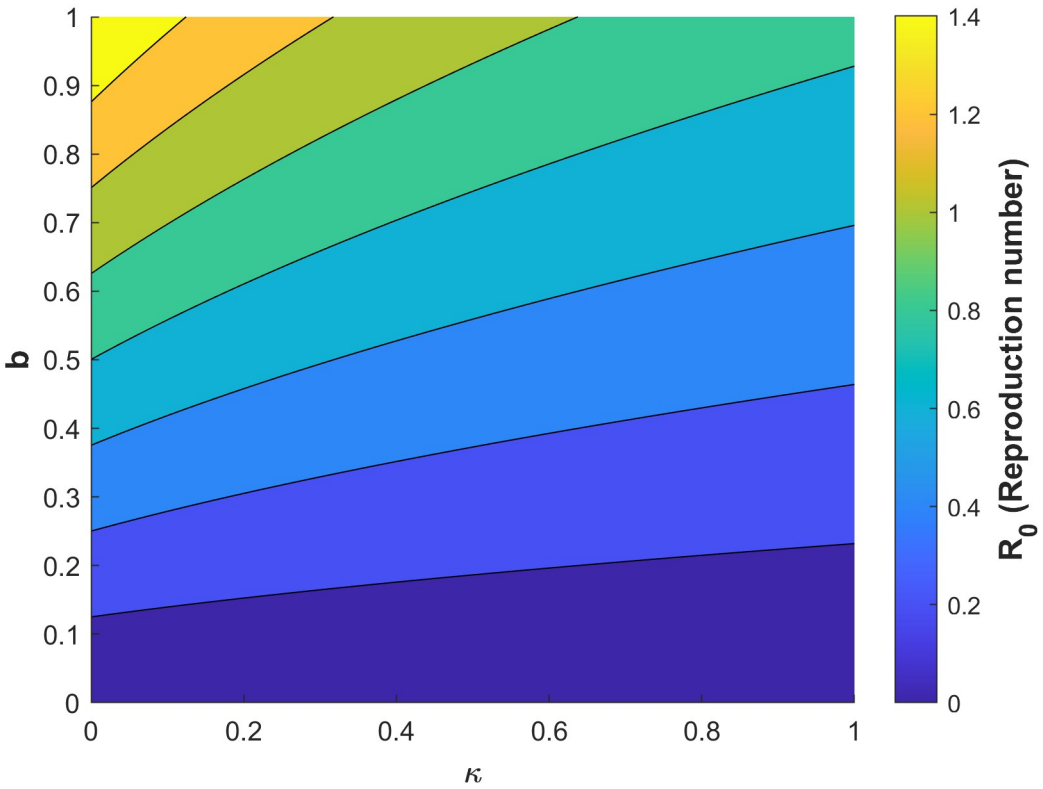


Fig 14. Contour plot of R_0 with respect to biting rate b and treatment rate of infectious humans κ.

https://doi.org/10.1371/journal.pone.0295025.g014

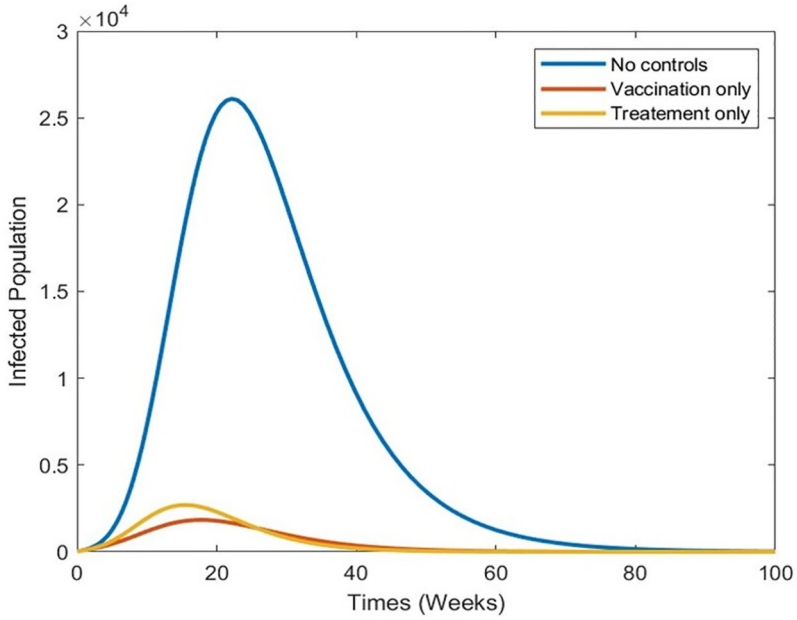


Fig 15. Simulation results of the system of Eq (14) with without controls, vaccination only and treatment only of the infected population.

https://doi.org/10.1371/journal.pone.0295025.g015

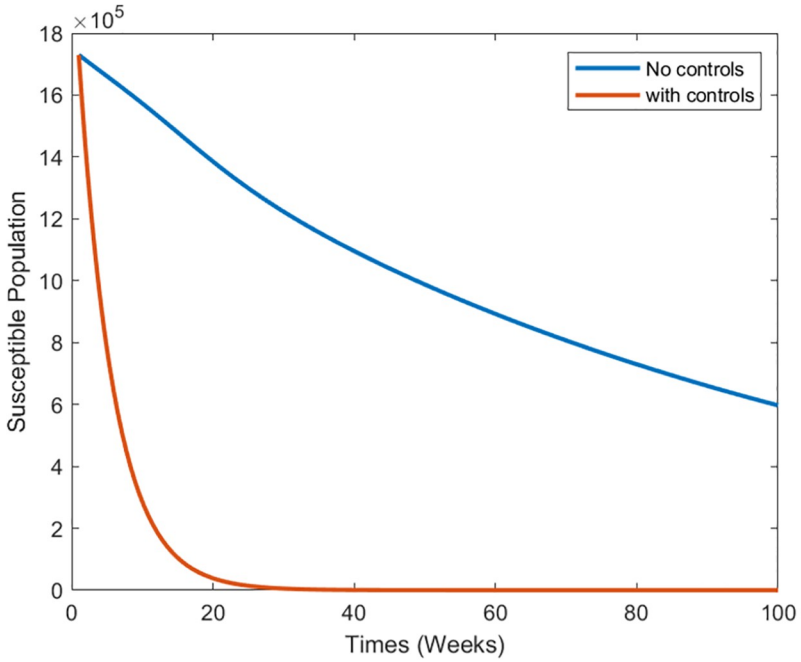


Fig 16. Simulation results of the system of Eq (14) with and without controls of the susceptible population.

https://doi.org/10.1371/journal.pone.0295025.g016

model parameters and validate the model by using the reported dengue infection data in Kaohsiung of the year 2014–2015

Furthermore, treatment performs better than vaccination in reducing dengue transmission when the vaccine's efficacy is low. However, reducing the disease doesn't equate to eradicating

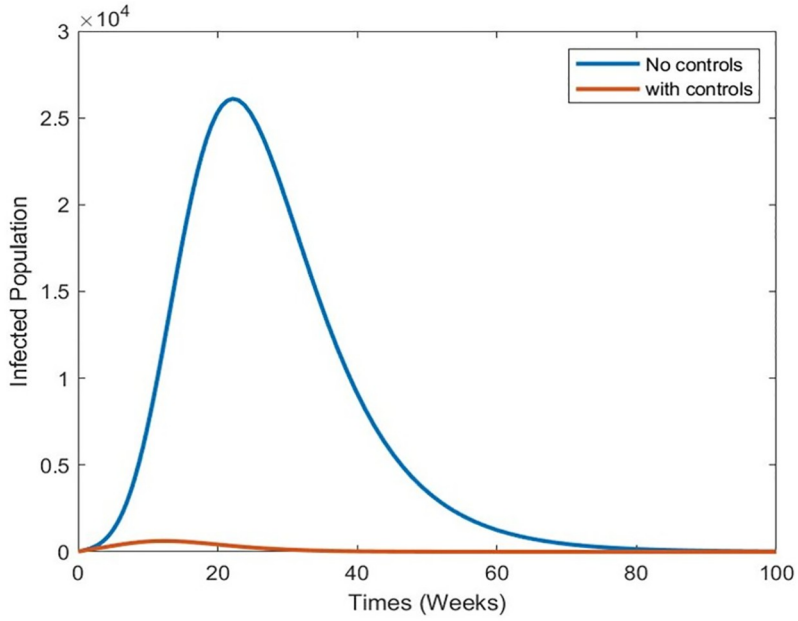


Fig 17. Simulation results of the system of Eq (14) with and without controls of the infected population.

https://doi.org/10.1371/journal.pone.0295025.g017

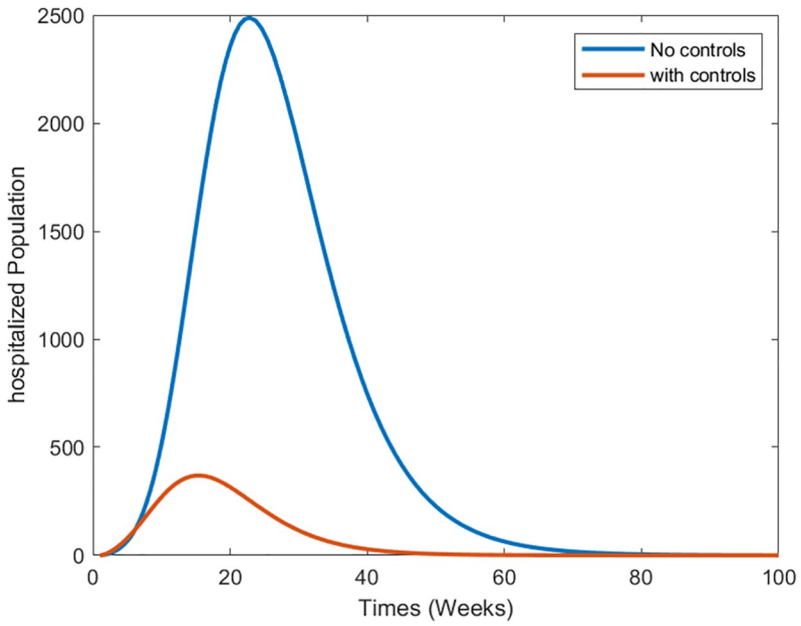


Fig 18. Simulation results of the system of Eq (14) with and without controls of the hospitalized population.

https://doi.org/10.1371/journal.pone.0295025.g018

it. A highly effective vaccine significantly reduces dengue cases if its efficacy is very high. The findings imply that a high vaccine efficacy and vaccination rate make the vaccine alone sufficient. Nonetheless, even with high vaccine effectiveness and vaccination rate, combining it with treatment remains essential. Notably, vaccines with high efficacy aren't always available. Moreover, the hospitalization of infected patients helps prevent critical cases linked to diseases such as breast cancer.

We conduct a sensitivity analysis to identify the parameter with the most impact on the basic reproduction number R_0. A comprehensive global sensitivity analysis reveals that transmission probability, bite rate, vaccine effectiveness, cure rate, treatment, and mosquito mortality rate significantly affect the increase in infected individuals. Furthermore, the parameters ϵ and κ, connected to the transmission, hold substantial influence, especially when combined. This synergy is particularly pronounced when both control strategies, vaccination, and treatment, are implemented together.

Moreover, we've expanded our model to address the optimal control challenge, incorporating two distinct types of optimal control. We analyze the optimal control problem employing Pontryagin's maximum principle. We conduct numerical simulations, exploring various combinations of optimal controls. Two scenarios are investigated to minimize infection: strategies involving a single control variable and strategies encompassing all control variables. Notably, using the individual $u_2(t)$ (treatment) control strategy alone isn't effective in reducing infection. However, the simultaneous application of all proposed control measures considerably decreases the overall number of infected individuals.

Conclusion

This section summarizes the main theoretical results of our study. In this paper, a deterministic compartmental model is developed with a system of seven ODEs that describe vector-host

interactions in the presence of vaccination and treatment. After introducing the model, some of its fundamental properties are discussed. In addition, some parameters of the model have been estimated using real data in order to validate it based on the 2014 dengue epidemic in Kaohsiung, Taiwan. To evaluate the impact of different strategies involving the use of vaccination and treatment, an optimal control analysis was established. Theoretical analysis and numerical simulations led the following results.

The disease-free equilibrium (only) is globally stable when the basic reproduction number is less than one. Sensitivity analysis of the models suggests that transmission probability, biting rates, vaccine efficacy, human recovery rates and mosquito mortality rates, among other parameters, are the most important parameters influencing R_0 epidemiological thresholds. By studying the impact of the control measures of vaccination (u_1), and treatment (u_2) on the transmission and spread of the disease in the population, we observe that the combination of the two controls considerably reduces the spread of the disease. Thus, the most effective of the different control strategies analyzed in this work is the strategy combining vaccination and treatment.

In conclusion, our study sheds light on the potential synergies between vaccination and treatment as strategies to mitigate dengue transmission. We have provided valuable insights into how these interventions can work in tandem to curb the spread of the disease. However, it's important to acknowledge the limitations of our current model, such as the omission of seasonality effects, the impact of age on vaccine efficacy, and the consideration of only one dengue serotype. To enhance the robustness of our findings and provide a more comprehensive understanding of dengue control strategies, future work will delve into incorporating seasonality into the model [27, 28] and exploring the interplay of age [29, 30] and vaccine interventions [11]. Additionally, we have used a single-serotype dengue model that does not take into account the effects of secondary infections. It is therefore advisable to extend this work by considering several dengue serotypes and examining the effects of vaccination and treatment on the dynamics of disease transmission. By continuously refining our model and accounting for these complex factors, we hope to contribute further to developing effective and tailored approaches for managing dengue transmission and ultimately reducing its burden on public health.

Supporting information

S1 Appendix. Presents the value of c_1, c_2 and c_3 in Eq 8.
(PDF)

Author Contributions

Conceptualization: Abdoulaye Sow, Cherif Diallo, Hocine Cherifi.

Data curation: Abdoulaye Sow.

Methodology: Abdoulaye Sow.

Supervision: Cherif Diallo, Hocine Cherifi.

Validation: Cherif Diallo, Hocine Cherifi.

Writing – original draft: Abdoulaye Sow.

Writing – review & editing: Cherif Diallo, Hocine Cherifi.

References

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 2013; 496(7446):504–507. https://doi.org/10.1038/nature12060 PMID: 23563266
2. WHO. Dengue and severe dengue. 2019. Available https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue/
3. Dengue Available: https://www.afro.who.int/health-topics/dengue
4. Esteva L, Vargas C. Analysis of a dengue disease transmission model. Mathematical biosciences. 1998; 150(2):131–151. https://doi.org/10.1016/S0025-5564(98)10003-2 PMID: 9656647
5. Singh B, Jain S, Khandelwal R, Porwal S, Ujjainkar G. Analysis of a dengue disease tramission model with vaccination. Advances in Applied Science Research. 2014; 5(3):237–242.
6. Tasman H, Supriatna AK, Nuraini N, Soewono E, et al. A dengue vaccination model for immigrants in a two-age-class population. International Journal of Mathematics and Mathematical Sciences. 2012; 2012. https://doi.org/10.1155/2012/236352
7. Sow A, Diallo C, Cherifi H, et al. Effects of Vertical Transmission and Human Contact on Zika Dynamics. Complexity. 2022; 2022. https://doi.org/10.1155/2022/5366395
8. Ndii MZ. The effects of vaccination, vector controls and media on dengue transmission dynamics with a seasonally varying mosquito population. Results in Physics. 2022; 34:105298. https://doi.org/10.1016/j.rinp.2022.105298
9. Chamnan A, Pongsumpun P, Tang IM, Wongvanich N. Optimal control of dengue transmission with vaccination. Mathematics. 2021; 9(15):1833. https://doi.org/10.3390/math9151833
10. Carvalho SA, da Silva SO, Charret IdC. Mathematical modeling of dengue epidemic: control methods and vaccination strategies. Theory in Biosciences. 2019; 138:223–239. https://doi.org/10.1007/s12064-019-00273-7 PMID: 30740641
11. Dwivedi A, Keval R, Khajanchi S. Modeling optimal vaccination strategy for dengue epidemic model: a case study of India. Physica Scripta. 2022; 97(8):085214. https://doi.org/10.1088/1402-4896/ac807b
12. Ndii MZ, Adi YA, Djahi BS. DETERMINISTIC AND STOCHASTIC DENGUE EPIDEMIC MODEL: EXPLORING THE PROBABILITY OF EXTINCTION. BAREKENG: Jurnal Ilmu Matematika dan Terapan. 2022; 16(2):583–596. https://doi.org/10.30598/barekengvol16iss2pp583-596
13. Shim E. Optimal dengue vaccination strategies of seropositive individuals. Mathematical Biosciences and Engineering. 2019; 16(3):1171–1189. https://doi.org/10.3934/mbe.2019056 PMID: 30947414
14. Ferguson NM, Rodríguez-Barraquer I, Dorigatti I, Mier-y Teran-Romero L, Laydon DJ, Cummings DA. Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment. Science. 2016; 353(6303):1033–1036. https://doi.org/10.1126/science.aaf9590 PMID: 27701113
15. Aguiar M, Anam V, Blyuss KB, Estadilla CDS, Guerrero BV, Knopoff D, et al. Mathematical models for dengue fever epidemiology: A 10-year systematic review. Physics of Life Reviews. 2022; 40:65–92. https://doi.org/10.1016/j.plrev.2022.02.001 PMID: 35219611
16. Torresi J, Ebert G, Pellegrini M. Vaccines licensed and in clinical trials for the prevention of dengue. Human vaccines & immunotherapeutics. 2017; 13(5):1059–1072. https://doi.org/10.1080/21645515.2016.1261770 PMID: 28281864
17. Feng Z., Towers S., & Yang Y. (2011). Modeling the effects of vaccination and treatment on pandemic influenza. The AAPS journal, 13, 427–437. https://doi.org/10.1208/s12248-011-9284-7 PMID: 21656080
18. Le virus de la dengue et sa transmission. Available https://www.inspq.qc.ca/en/node/1172
19. Musa S. S., Zhao S., Chan H. S., Jin Z., & He D. H. (2019). A mathematical model to study the 2014-2015 large-scale dengue epidemics in Kaohsiung and Tainan cities in Taiwan, China. Mathematical Biosciences and Engineering: MBE, 16(5), 3841–3863. https://doi.org/10.3934/mbe.2019190 PMID: 31499639
20. Villar L, Dayan GH, Arredondo-García JL, Rivera DM, Cunha R, Deseda C, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. New England Journal of Medicine. 2015; 372(2):113–123. https://doi.org/10.1056/NEJMoa1411037 PMID: 25365753
21. Seadawy A, Jun W, et al. New mathematical model of vertical transmission and cure of vector-borne diseases and its numerical simulation. Advances in Difference Equations. 2018; 2018(1):1–15.
22. Mtisi E, Rwezaura H, Tchuenche JM. A mathematical analysis of malaria and tuberculosis co-dynamics. Discrete and Continuous Dynamical Systems-B. 2009; 12(4):827–864. https://doi.org/10.3934/dcdsb.2009.12.827

23. Van den Driessche P, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Mathematical biosciences. 2002; 180(1-2):29–48. https://doi.org/10.1016/S0025-5564(02)00108-6 PMID: 12387915

24. C. Castillo-Chavez, Z. Feng, and W. Huang, "On the computation of R0 and its role in global stability," IMA Volumes in Mathematics and Its Applications, vol. 125, pp. 229–250, 2002.

25. Centers for Disease Control Taiwan. Taiwan National Infectious Disease Statistics System;. Available from: http://nidss.cdc.gov.tw/en/SingleDisease.aspx?dc=1&dt=4&disease=061&position=1.

26. 2015 population estimate for Kaohsiung, China. Available from: https://books.mongabay.com/population_estimates/2015/Kaohsiung-China.html

27. Arquam M, Singh A, Cherifi H. Integrating environmental temperature conditions into the sir model for vector-borne diseases. In: Complex Networks and Their Applications VIII: Volume 1 Proceedings of the Eighth International Conference on Complex Networks and Their Applications COMPLEX NETWORKS 2019 8. Springer International Publishing; 2020. p. 412–424.

28. Arquam M, Singh A, Cherifi H. Impact of seasonal conditions on vector-borne epidemiological dynamics. IEEE Access. 2020; 8:94510–94525. https://doi.org/10.1109/ACCESS.2020.2995650

29. Annan E, Treviño J, Zhao B, Rodriguez-Morales AJ, Haque U. Direct and indirect effects of age on dengue severity: The mediating role of secondary infection. PLOS Neglected Tropical Diseases. 2023; 17 (8):e0011537. https://doi.org/10.1371/journal.pntd.0011537 PMID: 37556473

30. Prattay KMR, Sarkar MR, Shafiullah AZM, Islam MS, Raihan SZ, Sharmin N. A retrospective study on the socio-demographic factors and clinical parameters of dengue disease and their effects on the clinical course and recovery of the patients in a tertiary care hospital of Bangladesh. PLoS neglected tropical diseases. 2022; 16(4):e0010297. https://doi.org/10.1371/journal.pntd.0010297 PMID: 35377886