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OPTIMAL STRATEGIES FOR DENGUE CONTROL: WOLBACHIA-INFECTED MOSQUITOES DEPLOYMENT, PUBLIC HEALTH EDUCATION, AND VACCINATION

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ABSTRACT

Wolbachia-infected mosquitoes present a promising method for dengue control by inhibiting viral replication, reducing mosquito reproductive capacity, and shortening the lifespan of Aedes aegypti mosquitoes. This study introduces a novel optimal control model that uniquely integrates two distinct release strategies for Wolbachia-infected mosquitoes—constant and proportional rates. While prior research has explored Wolbachia deployment, our model is the first to directly compare and contrast these two rate types within the same framework to assess their differential impact on dengue transmission dynamics. This provides a more comprehensive understanding of effective release protocols, addressing a critical gap in the literature regarding optimal and adaptive Wolbachia deployment. Based on model simulations for North Kembangan Village, Jakarta, we find that a single-control strategy using Wolbachia mosquito release alone can reduce dengue cases by up to 15%. However, a multiple-control strategy that combines Wolbachia releases with public health education and vaccination is the most effective approach, achieving a substantial reduction of up to 58%. In a cost-effectiveness analysis, the study reveals that the Wolbachia-only strategy (proportional release) is the most cost-effective in terms of cost per infection averted. In terms of release dynamics, the study reveals that a constant release rate provides long-term benefits by establishing a stable Wolbachia-infected mosquito population, whereas a proportional release rate is more effective for achieving a rapid, short-term reduction in dengue cases.

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1. INTRODUCTION

Dengue is a vector-borne infectious disease spread to humans through the bites of infected Aedes mosquitoes. Nearly half of the global population is currently at risk, affecting an estimated 100–400 million people with symptomatic infections annually across more than 125 countries, resulting in 10,000 deaths [1]. Dengue fever presents a significant global health threat, particularly in tropical and subtropical regions where the Aedes mosquito, the primary vector, thrives. The disease has seen a surge in cases due to factors like urbanization, climate change, periodic weather phenomena, vulnerable healthcare systems, and increased travel, which facilitate the spread of the virus [2]. Millions of people are at risk. Severe cases can lead to hospitalization or death, especially among vulnerable populations such as children. By April 2024, more than 7.6 million dengue cases had been reported to the WHO, including 3.4 million confirmed cases, over 16,000 severe cases, and more than 3,000 deaths [3]. Despite ongoing efforts, including vector control measures and vaccine development, dengue continues to challenge healthcare systems, highlighting the need for more robust strategies to prevent outbreaks and mitigate its impact.

In recent years, a multi-faceted approach considering people, animals, and the environment has emerged as a promising framework for reducing virus transmission [4]. One such approach is the use of Wolbachia, a bacterium that can be injected into Aedes aegypti mosquitoes, the primary vector of dengue, Zika, yellow fever, and chikungunya, to inhibit the transmission of the virus [5]. Wolbachia-infected mosquitoes demonstrate a reduced ability to transmit dengue virus to humans because the bacterium interferes with viral replication within the mosquito. Notably, Wolbachia infection is self-sustaining, as it is maternally transmitted, enabling the establishment of Wolbachia-infected mosquito populations through strategic, initial releases [6]. The severity of risks associated with releasing Wolbachia-infected mosquitoes is negligible [7]. Early field trials in countries such as Indonesia, Brazil, and Australia have shown promising reductions in dengue transmission following Wolbachia deployments [8], leading to increased interest in scaling this intervention.

Quantitative analysis, particularly through mathematical modeling, is essential in assessing the effectiveness of Wolbachia technology in dengue management [9]. Wolbachia-infected mosquitoes have shown potential in reducing dengue transmission by limiting the capacity of Aedes aegypti mosquitoes to spread the virus. However, to optimize the deployment of this biocontrol instrument, it is crucial to understand how different factors, such as the release rate of Wolbachia-infected mosquitoes and their interplay with other control strategies, affect overall disease dynamics [10].

The use of Wolbachia-infected mosquitoes in dengue control has been the subject of intense research in recent years, particularly in the context of optimal control models. One of the foundational studies by Abidemi *et al*. [11] explores a control model that includes asymptomatic individuals, isolation, and vigilant compartments. Their model shows that strategically integrating these components with Wolbachia-infected mosquitoes' deployment can significantly reduce dengue transmission, especially when asymptomatic individuals are accounted for, providing a more realistic approach to controlling the epidemic. Another important contribution comes from Yoda *et al*. [12], who analyzed an epidemic model for dengue with optimal control measures. They focused on minimizing the costs associated with different interventions, including mosquito population control and treatment efforts. Their work highlights the importance of a balanced strategy combining vector control with timely treatment of infected individuals, which aligns with similar findings by Kumar *et al*. [13], where the model is extended to include reinfection and treatment, providing valuable insights into how Wolbachia can lower both reinfection rates and overall disease spread.

Studies focusing on the economic optimization of Wolbachia deployment include the work by Hollingsworth *et al*. [14]. This study analyzed different release strategies to minimize costs while maximizing dengue reduction, highlighting the importance of timely and well-scaled releases for long-term economic and public health benefits. Similarly, Almeida *et al*. [15] concluded that carefully timed Wolbachia releases significantly reduce both the economic burden and disease prevalence, emphasizing the need for precise planning in large-scale interventions. Pongsumpun *et al*. [16] contributed by modifying traditional optimal control models for dengue by introducing a vaccination component. They showed that vaccination programs combined with Wolbachia releases provide superior results compared to stand-alone methods. The study provided mathematical proof of the benefits of dual interventions, further supporting the combination approach. Srivastav *et al*. [17] focused on a model that incorporates screening and information campaigns, showing that public awareness and screening efforts are pivotal in maximizing the effectiveness of Wolbachia releases. The study suggested that, in addition to biological control, widespread community engagement is essential for sustained reductions in transmission. The use of biological control through Wolbachia was also explored by Dianavinnarasi *et al*. [18], who applied a Linear Matrix Inequality (LMI) approach to control Aedes aegypti mosquito populations. This method offers a unique mathematical framework for determining optimal release strategies, enhancing the ability to control dengue more effectively.

The objective of this paper is to develop a mathematical model to evaluate the impact of Wolbachia-infected mosquito release rates, both constant and proportional, in controlling the dengue transmission. The combination with existing control measures (public health education and vaccination) is also examined, as they remain important ways to reduce the burden of dengue. We analyze single-control and multiple-control strategies based on their cost-benefit effectiveness in reducing the number of dengue cases, leading to the best strategy for achieving optimal dengue control.

2. RESEARCH METHODS

In this section, we introduce an optimal control model aimed at reducing dengue transmission. The model integrates key interventions, namely the release of Wolbachia-infected mosquitoes, vaccination, and public health education, to effectively control outbreaks. The schematic diagram of the model is presented in Fig. 1. The compartmental model integrates both human and mosquito populations to reflect the dynamics of infection spread. The human population follows an SIR (Susceptible-Infectious-Recovered) framework, and the mosquito population, which is separated into wild and Wolbachia-infected groups, follows an SI (Susceptible-Infectious) structure due to the lack of recovery in mosquitoes. The number of susceptible, infected, and recovered humans at time t are, respectively, denoted by $S_h(t)$, $I_h(t)$, and $R_h(t)$. The total number of humans is given by $N_h(t)$, where $N_h(t) = S_{h(t)} + I_h(t) + R_h(t)$. The number of susceptible wild and susceptible Wolbachia-infected mosquitoes at time t are defined by $S_v(t)$ and $S_w(t)$, respectively. While the number of dengue-positive wild and dengue-positive Wolbachia-infected mosquitoes at time t are denoted by $I_v(t)$ and $I_w(t)$. The total number of mosquitoes in the environment is represented by $N_m(t)$, where $N_m(t) = S_v(t) + S_w(t) + I_v(t) + I_w(t)$.

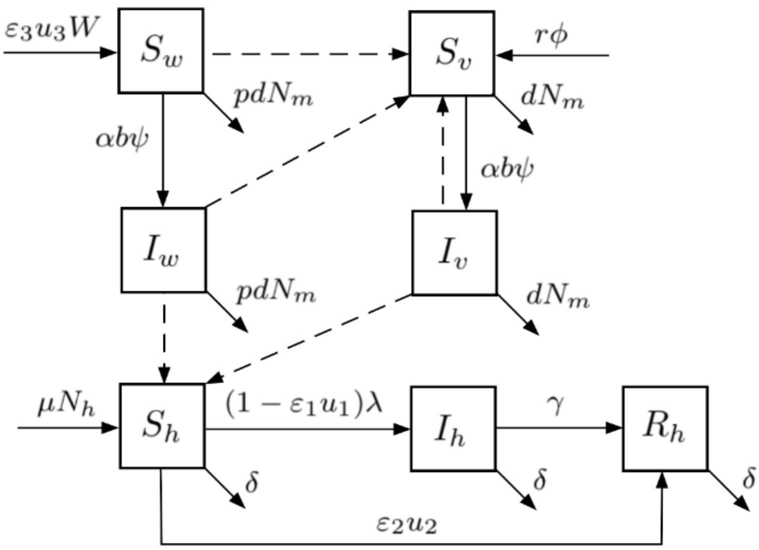


Figure 1. The Schematic Diagram of Dengue Control Consists of Human and Mosquito Populations

2.1 Dengue Control Model

The mathematical model presented in this section describes dengue transmission dynamics, focusing on the interaction between human and mosquito populations. The following key assumptions are imposed.

1. Human migration is assumed to be negligible and not accounted for in this model. New individuals are recruited into the population with a constant per capita birth rate μ.

2. The mortality associated with dengue fever is considered negligible and does not significantly impact the overall assessment of the disease. The per capita natural death rate of humans is denoted by δ.
3. The exposed period of dengue fever patients ranges from 4–5 days, which is relatively short compared to the entire human lifespan and can therefore be considered negligible.
4. After recovering from a dengue infection, individuals generally develop immunity to the specific serotype of the virus that caused their illness. Thus, it is assumed that there is no possibility of reinfection by dengue fever.
5. The rate of dengue virus transmission from mosquitoes to humans and vice versa depends on the proportion of infected mosquitoes and the effectiveness of transmission. The probability of a human contracting dengue fever due to the bite of a dengue-infected mosquito is β and the human-to-mosquito transmission probability is b. The biting rate of Aedes aegypti is α.
6. We assume that natural recovery from dengue fever is possible for infected individuals, reflecting the self-limiting nature of the disease in many cases. The recovery rate is γ.
7. It is assumed that health education can drive behavioral changes, improve community engagement, and complement other disease control strategies. By increasing awareness and promoting preventive practices, education plays a crucial role in reducing dengue transmission and managing public health.
8. It is assumed that the dengue spread can be controlled by vaccination due to the potential for vaccines to provide individual protection, reduce transmission, and decrease disease burden.
9. Susceptible mosquitoes can acquire the dengue virus from biting infected humans, but those of Wolbachia-infected mosquitoes are less susceptible to infection or have reduced transmission capabilities.
10. Dengue-Wolbachia co-infected mosquitoes can transmit dengue virus to susceptible humans, but their ability to infect might be reduced compared to wild mosquitoes. The coefficient of inhibition effect is denoted by $q \in (0,1)$.
11. Wolbachia-infected mosquitoes exhibit a reduced survival rate compared to wild mosquitoes, due to the negative fitness effect imposed by the bacterial infection. The coefficient of fitness effect is given by $p > 1$.
12. The growth of wild susceptible mosquitoes is influenced by both the total population of mosquitoes and the competition from Wolbachia-infected mosquitoes, reflecting the competitive dynamics in the ecosystem. The per capita birth rate of mosquitoes is given by r and the per capita death rate by d.
13. The number of Wolbachia-infected mosquitoes released into a target area is $W(S_v, I_v)$, which can be a constant or vary depending on the number of wild-infected mosquitoes.

In Fig. 1, we define ϕ, ψ, and λ as follows:

$$\phi = \left(1 - \frac{S_w + I_w}{N_m}\right)(S_v + I_v), \qquad \psi = \frac{I_h}{N_h}, \qquad \lambda = \frac{\alpha\beta(I_v + qI_w)}{N_h}. \tag{1}$$

Thus, the modeling equations that describe the dynamics of human and mosquito populations are given by the following ordinary differential equations system:

$$\dot{S}_h = \mu N_h - (1 - \varepsilon_1 u_1)\lambda S_h - (\delta + \varepsilon_2 u_2)S_h, \tag{2}$$

$$\dot{I}_h = (1 - \varepsilon_1 u_1)\lambda S_h - (\delta + \gamma)I_h, \tag{3}$$

$$\dot{R}_h = \gamma I_h + \varepsilon_2 u_2 S_h - \delta R_h, \tag{4}$$

$$\dot{S}_w = \varepsilon_3 u_3 W(S_v, I_v) - \alpha b \psi S_w - pdN_m S_w, \tag{5}$$

$$\dot{S}_v = r\phi - \alpha b \psi S_v - dN_m S_v, \tag{6}$$

$$\dot{I}_w = \alpha b \psi S_w - pdN_m I_w, \tag{7}$$

$$\dot{I}_v = \alpha b\psi S_v - dN_m I_v, \tag{8}$$

with initial conditions

$$S_h(0) = S_h^0, I_h(0) = I_h^0, R_h(0) = R_h^0, S_w(0) = S_w^0, S_v(0) = S_v^0, I_w(0) = I_w^0, I_v(0) = I_v^0, \tag{9}$$

are all non-negative.

Wolbachia-infected mosquitoes have a reduced lifespan [19], which can contribute to a decline in Aedes aegypti populations over time. This effect is represented by the coefficient of fitness effect $p > 1$, which influences the Wolbachia-infected mosquitoes S_w and I_w in Eqs. (5) and (7), respectively. Wolbachia bacteria can also suppress virus replication [20], thus reducing the transmission potential of dengue, as represented by $q \in (0,1)$ through transmission rate λ in Eqs. (2) and (3). Term $1 - (S_w + I_w)/N_m$ within ϕ in Eq. (6) represents the competition for resources among the mosquitoes. It shows that as the proportion of Wolbachia-infected mosquitoes $(S_w + I_w)$ increases relative to the total mosquito population N_m, the growth rate of susceptible wild mosquitoes S_v is proportionally reduced. When Wolbachia-infected mosquitoes are few, this fraction approaches 1, allowing near-full reproduction; as Wolbachia-infected mosquitoes increase, competition intensifies, reducing the growth of S_v. Meanwhile, term $(S_v + I_v)$ indicates that the reproduction potential applies to all wild mosquitoes, regardless of their infection status.

In this model, both susceptible S_v and infectious I_v wild mosquitoes contribute to new wild mosquito births. Overall, the expression of ϕ suggests that the population of susceptible wild mosquitoes increases based on the total wild mosquito population, subject to a decreasing factor as Wolbachia-infected mosquitoes make up a larger portion of the population. This competitive effect reflects how Wolbachia-carrying mosquitoes indirectly limit the growth of wild mosquito populations by reducing their reproduction potential [21].

2.2 Control Measures

Dengue model Eqs. (2)–(8) is featured with three control variables, namely public health education, vaccination, and Wolbachia-infected mosquito release. Raising public awareness and educating communities about the mosquito vector's habitat, life cycle, and both physical and cultural control methods are essential for managing mosquito populations effectively [22]. Programs like Integrated Dengue Education and Learning (iDEAL) equip communities with knowledge and practical skills for effective prevention [23]. Knowledge, Attitude, and Practice (KAP) studies further enhance these efforts by evaluating people's understanding, attitudes, and behaviors toward dengue, allowing for adjustments in education strategies to address specific needs [23]. The proportion of susceptible individuals who receive dengue-related education at time t is denoted by $u_1(t)$ with effectiveness ε_1. Vaccination is a key component in reducing the global dengue burden, yet developing a safe and effective dengue vaccine has proven highly challenging. For over 75 years, scientists and developers have worked to create effective dengue vaccines, but they have faced significant and persistent obstacles [24]. There are three licensed vaccines against the DENVs, namely Dengvaxia (CYD-TDV) by Sanofi Pasteur, France, Qdenga (TAK-003) by Takeda, Japan, and Butantan-Dengue Vaccine (Butantan-DV) by Instituto Butantan, Brazil [25]. The primary distinction between them lies in the type of backbone and the degree of chimerization. The available vaccines have an efficacy of 71–81 percent [26]. In the model, the proportion of susceptible individuals who receive the dengue vaccine at time t is represented by $u_2(t)$ with effectiveness ε_2.

As depicted in Fig. 1, new wild mosquitoes are born and added to the susceptible wild mosquito population S_v as many as $r\phi$, where r is the per capita birth rate and ϕ is given in Eq. (1). Wolbachia-infected mosquitoes are deliberately introduced into the susceptible population S_w as many as $\varepsilon_3 u_3(t) W(S_v, I_v)$, where W is the number of Wolbachia-infected mosquitoes released, u_3 is the control intensity, and ε_3 is the control effectiveness. In this work, we consider two methods of release, namely by constant and proportional release rates. In the former case, we set $W(S_v, I_v) = \overline{W}$ (a fixed value) and $u_3(t) = 1$ for all $t \in [0, T]$ with T is the control period. While in the latter case, we define $W(S_v, I_v) = S_v + I_v$, which means that the number of Wolbachia-infected mosquitoes released is proportional to that of wild infected mosquitoes. In this case, $u_3(t) \in [0,1]$ with $t \in [0, T]$, should optimally be determined by the model. By this approach, we allow the model to simulate both consistent and adaptive strategies for Wolbachia-infected mosquito release in dengue control programs.

2.3 Control Problem

The control problem considered in this study is to determine the control measures $u_1(t)$, $u_2(t)$, and $u_3(t)$, such that minimize the performance objective.

$$J(u_1,u_2,u_3)=\int_0^T\left(w_0I_h(t)+w_1u_1^2(t)+w_2u_2^2(t)+w_3u_3^2(t)\right)dt, \tag{10}$$

representing the combined costs of dengue infection cases and control interventions, subject to the dynamics of the system in Eq. (2)–(8). In Eq. (10), w_0 is the unit cost of human infections, which refers to the economic, social, and health-related impacts associated with individuals contracting dengue. Weights w_1, w_2, and w_3 reflect the unit costs associated with education, vaccination, and Wolbachia-infected mosquito release, respectively [36]. Control variables are formulated in quadratic form in Eq. (10) for three key reasons: it represents a non-linear cost where larger control efforts are disproportionately more expensive; the quadratic form ensures the objective functional is smooth and differentiable, which is essential for mathematical optimization; and it encourages a more realistic, spread-out allocation of control resources over time by penalizing a single, large intervention. The control variables are bounded to reflect resource and practical limitations:

$$0\le u_1(t)\le \bar{u}_1,\qquad 0\le u_2(t)\le \bar{u}_2,\qquad 0\le u_3(t)\le \bar{u}_3, \tag{11}$$

for all $t\in[0,T]$, where $\bar{u}_1$, $\bar{u}_2$, and $\bar{u}_3$, represent the maximum feasible proportions for each control function.

3. RESULTS AND DISCUSSION

3.1 Optimality Conditions

To address the optimal control problem for dengue control using education, vaccination, and Wolbachia-infected mosquitoes, Pontryagin's maximum principle is applied to derive the necessary conditions for an optimal solution. Further, to connect the system dynamics, cost function, and control variables, we introduce adjoint variables to capture the sensitivity of the cost to state variables, which are incorporated into the Hamiltonian H as follows

$$\begin{aligned}H={}&w_0I_h+w_1u_1^2+w_2u_2^2+w_3u_3^2+a_1(\mu N_h-(1-\varepsilon_1u_1)\lambda S_h-(\delta+\varepsilon_2u_2)S_h)\\&+a_2\big((1-\varepsilon_1u_1)\lambda S_h-(\delta+\gamma)I_h\big)+a_3(\gamma I_h+\varepsilon_2u_2S_h-\delta R_h)\\&+a_4(\varepsilon_3u_3W(S_v,I_v)-\alpha b\psi S_w-pdN_mS_w)+a_5(r\phi-\alpha b\psi S_v-dN_mS_v)\\&+a_6(\alpha b\psi S_w-pdN_mI_w)+a_7(\alpha b\psi S_v-dN_mI_v),\end{aligned} \tag{12}$$

where $a_i=a_i(t)$, $i=1,2,\dots,7$, are the adjoint functions. Let x denote the vector of state variables given by $x=(S_h,I_h,R_h,S_w,S_v,I_w,I_v)^T$. The Pontryagin maximum principle then specifies conditions under which the Hamiltonian is minimized with respect to the control variables as follows:

$$\frac{\partial H}{\partial u_j}=0,\qquad j=1,2,3, \tag{13}$$

$$\frac{da_i}{dt}=-\frac{\partial H}{\partial x_i},\qquad i=1,2,\dots,7, \tag{14}$$

$$\frac{dx_i}{dt}=\frac{\partial H}{\partial a_i},\qquad i=1,2,\dots,7. \tag{15}$$

We assume the terminal time T is fixed, but the terminal state $x(T)$ is free. This setup is common in systems where achieving an exact final condition is less critical than optimizing a performance index over the duration. With this assumption, Pontryagin's maximum principle introduces a transversality condition

$$a_i(T)=0,\qquad i=1,2,\dots,7. \tag{16}$$

Note that the condition in Eq. (13) will produce optimal controls, the condition in Eq. (14) will provide the adjoint system with a terminal time restriction in Eq. (16), and the condition in Eq. (15) will reformulate the state system in Eq. (2)–(8), with initial time restrictions in Eq. (9). Altogether, they create a set of differential equations with boundary conditions that can be solved to determine the optimal control strategies over time. Optimal controls and adjoint system are presented in the following theorems.

Theorem 1. *The optimal controls u_1, u_2, and u_3, which minimize* Eq. (10), *are given by*

$$u_1 = \min\left\{\bar{u}_1, \max\left\{0, \frac{\varepsilon_1 \alpha\beta(a_2 - a_1)(I_v + qI_w)S_h}{2w_1 N_h}\right\}\right\}, \tag{17}$$

$$u_2 = \min\left\{\bar{u}_2, \max\left\{0, \frac{\varepsilon_2(a_1 - a_3)S_h}{2w_2}\right\}\right\}, \tag{18}$$

$$u_3 = \min\left\{\bar{u}_3, \max\left\{0, -\frac{\varepsilon_3 a_4 W(S_v, I_v)}{2w_3}\right\}\right\}, \tag{19}$$

where $W(S_v, I_v) = \bar{W}$ for a constant release rate and $W(S_v, I_v) = S_v + I_v$ for proportional release rate.

Proof. Application of Eq. (13) provides $2w_1u_1 + \varepsilon_1(a_1 - a_2)\lambda = 0$, $2w_2u_2 - \varepsilon_2 a_1 S_h + \varepsilon_2 a_3 S_h = 0$, and $2w_3u_3 + \varepsilon_3 a_4 W(S_v, I_v) = 0$. Optimal controls in Eq. (17)–(19) are obtained by considering bounded controls in Eq. (11). ■

Theorem 2. *Given the optimal state variable $x = (S_h, I_h, R_h, S_w, S_v, I_w, I_v)^T$ associated with the optimal control pair $u = (u_1, u_2, u_3)^T$ in* Theorem 1, *the adjoint variables a_i $(i = 1,2, \dots, 7)$ satisfy the following differential equations system:*

$$\begin{aligned} \dot{a}_1 = {} & (\delta - \mu)a_1 + (1 - \varepsilon_1 u_1)\lambda(a_1 - a_2)\left(1 - \frac{S_h}{N_h}\right) + \varepsilon_2 u_2(a_1 - a_3) \\ & - \frac{\alpha b\psi}{N_h}\big(S_w(a_4 - a_6) + S_v(a_5 - a_7)\big), \end{aligned} \tag{20}$$

$$\begin{aligned} \dot{a}_2 = {} & -w_0 - \mu a_1 - (1 - \varepsilon_1 u_1)\lambda(a_1 - a_2)\frac{S_h}{N_h} + (\delta + \gamma)a_2 - \gamma a_3 \\ & + \frac{\alpha b(1 - \psi)}{N_h}\big(S_w(a_4 - a_6) + S_v(a_5 - a_7)\big), \end{aligned} \tag{21}$$

$$\dot{a}_3 = -\mu a_1 - (1 - \varepsilon_1 u_1)\lambda(a_1 - a_2)\frac{S_h}{N_h} + \delta a_3 - \frac{\alpha b\psi}{N_h}\big(S_w(a_4 - a_6) + S_v(a_5 - a_7)\big), \tag{22}$$

$$\dot{a}_4 = a_4\big(\alpha b\psi + pd(S_w + N_m)\big) + a_5\left(\frac{r\phi}{N_m} + dS_v\right) - a_6(\alpha b\psi - pdI_w) + da_7 I_v, \tag{23}$$

$$\begin{aligned} \dot{a}_5 = {} & -a_4\left(\varepsilon_3 u_3 \frac{\partial W}{\partial S_v} - pdS_w\right) - a_5\left(\frac{2r(S_v + I_v) - r\phi}{N_m} - d(S_v + N_m) - \alpha b\psi\right) \\ & + pda_6 I_w - a_7(\alpha b\psi - dI_v), \end{aligned} \tag{24}$$

$$\dot{a}_6 = \alpha\beta q(1 - \varepsilon_1 u_1)\lambda(a_1 - a_2)\frac{S_h}{N_h} + pda_4 S_w + a_5\left(\frac{r\phi}{N_m} + dS_v\right) + pda_6(I_w + N_m) + da_7 I_v, \tag{25}$$

$$\begin{aligned} \dot{a}_7 = {} & \alpha\beta(1 - \varepsilon_1 u_1)\lambda(a_1 - a_2)\frac{S_h}{N_h} - a_4\left(\varepsilon_3 u_3 \frac{\partial W}{\partial S_v} - pdS_w\right) \\ & - a_5\left(\frac{2r(S_v + I_v) - r\phi}{N_m} - d(S_v + N_m) - \alpha b\psi\right) + pda_6 I_w + da_7(I_v + N_m), \end{aligned} \tag{26}$$

where $\frac{\partial W}{\partial S_v} = \frac{\partial W}{\partial I_v} = 0$ for Wolbachia-infected mosquito deployment with a constant release rate, and $\frac{\partial W}{\partial S_v} = \frac{\partial W}{\partial I_v} = 1$ for proportional release rate, with terminal time conditions in Eq. (16).

Proof. The proof is immediate from Eq. (14). ■

From the numerical point of view, optimal control problem posed by state system in Eqs (2)–(8), optimal controls in Eqs. (17)–(18), and the adjoint system Eqs. (20)–(26) is very challenging. This requires the simultaneous satisfaction of conditions at both ends, which is computationally sensitive to initial guesses and prone to instability. Additionally, coupled state-adjoint dynamics and high-dimensional systems further increase complexity, requiring robust numerical techniques, such as the forward-backward sweep method in combination with the well-known Runge-Kutta algorithms, and careful tuning of parameters for convergence and stability.

3.2 Implementation of Model

In this section, we implement our optimal control model to the local demographics and epidemiological conditions of North Kembangan Village, situated in Kembangan Sub-district, West Jakarta, Indonesia, a densely populated urban area of 3.65 kilometer squares with approximately 70,000 residents. It has been identified as a high-risk area for dengue fever outbreaks due to its dense population and environmental factors conducive to mosquito breeding. In response, an integrated dengue control program, including the deployment of Wolbachia-infected mosquitoes, was initiated in October 2024 [27]. The parameter values used in the model simulations were derived from various relevant literature sources to ensure the reliability and validity of the findings and are summarized in Table 1.

Table 1. Parameter Values

Parameter	Description	Value	Unit	Reference
μ	per capita birth rate of humans	3.24×10^{-5}	per day	[28]
δ	per capita natural death rate of humans	1.75×10^{-5}	per day	[28]
γ	per capita recovery rate	0.14	per day	[29]
α	biting rate of Aedes aegypti	0.38	per day	[30]
β	probability of mosquito-to-human infection	0.27	–	[31]
b	probability of human-to-mosquito infection	0.45	–	[31]
q	inhibition effect	0.127	–	[20]
p	fitness effect	1.05	–	[32]
r	per capita birth rate of mosquitoes	0.25	per day	[31]
d	per capita death rate of mosquitoes	2.85×10^{-5}	per day	[31]
ε_1	effectiveness of dengue-related education	0.774	–	[33]
ε_2	effectiveness of vaccination	0.71	–	[26]
ε_3	effectiveness of Wolbachia-infected mosquito release	0.77	–	[8]
u_1	proportion of susceptible humans who receive education	[0,0.8]	–	
u_2	proportion of susceptible humans who receive vaccination	[0,0.25]	–	[34]
u_3	intensity of Wolbachia-infected mosquito release (constant)	1	–	
	intensity of Wolbachia-infected mosquito release (proportional)	[0,1]	–	
w_0	unit cost of human infection	99.145	US$	[35]
w_1	unit cost of education	0.35	US$	[36]
w_2	unit cost of vaccination	48.07	US$	[36]
w_3	unit cost of Wolbachia-infected mosquito release	2.41×10^{-4}	US$	[37]
T	control period	60	days	
$\overline{W}$	number of Wolbachia-infected mosquitoes released	15,000	per day	[27]

3.2.1 Parameter Values

Per capita birth rate of humans μ is set to 3.24×10^{-5} per day, representing a realistic demographic growth rate in urban areas with stable populations, and per capita natural death rate of humans δ is chosen as 1.75×10^{-5} per day, reflecting a typical life expectancy in the regions [28]. The biting rate of Aedes aegypti mosquitoes α is assumed to be 0.38 bites per day, average of Thailand and Puerto Rico cases [30]. The probability of a human contracting dengue fever due to an infected mosquito bite β is 0.27, and the human-to-mosquito transmission probability b is set to 0.45, aligns with empirical estimates in dengue literature [31]. While the transmission efficacy of Wolbachia-infected mosquitoes q is 0.127, accounts for Wolbachia's known reduction in viral transmission [20]. The rate of recovery γ is assumed to be 0.14, represents an average recovery period for dengue cases [29]. The effectiveness of the dengue-related education ε_1 is 0.774 [33] and that of vaccination ε_2 is 0.71 based on [26] showing moderate to high impacts of health interventions. The effectiveness of the Wolbachia-infected mosquito release ε_3 is 0.77, reflects findings from pilot programs demonstrating high suppression of wild mosquito populations [8]. Per capita birth rate of mosquitoes r is 0.25, and per capita death rate of wild mosquitoes d is 2.85×10^{-5}, calibrated to match the reproductive and survival dynamics of Aedes aegypti in tropical conditions [31].

The reduction in the lifespan of Wolbachia-infected mosquitoes compared to uninfected ones typically ranges from 5 percent to 16 percent, depending on the strain of Wolbachia used and the mosquito species [38]. Therefore, the fitness effect p, which exhibits a reduced survival rate compared to wild mosquitoes, is assumed to be 1.05. A modest decrease in the lifespan of adult mosquitoes, combined with Wolbachia's direct ability to suppress pathogen growth within the mosquito, results in a significantly larger reduction in the overall transmission of the pathogen. This dual mechanism—shortened mosquito life expectancy and direct inhibition of the pathogen—works together to amplify the impact on disease control.

To estimate the unit cost of human infection, we use the average data of dengue costs for Yogyakarta, Indonesia, presented in [34] and [35], i.e., $w_0 = 99.124$ US dollars. Meanwhile, the per capita cost of public health education is $w_1 = 0.35$ US dollar as suggested by [36]. It is also reported in [34] that the cost for 3-dose of vaccine per child was estimated to be 72.11 dollars. Thus, by assuming a 60-day program, the unit cost of vaccination is $w_2 = 24.04$ US dollars. The cost per person covered by the Wolbachia program in Yogyakarta is US$1.27 per year [37], equivalent to US$$3.48 \times 10^{-3}$ per day. The release of Wolbachia-infected mosquitoes was conducted every 14 days, for a total of 12 rounds. With Yogyakarta's population at 0.46 million and an area of 37.24 kilometer squares, and assuming 2–3 mosquitoes were released per square meter [8], the total number of Wolbachia-infected mosquitoes released during the program amounted to 14.46 mosquitoes per person per day. Therefore, the cost of releasing a Wolbachia-infected mosquito is $w_3 = 2.41 \times 10^{-4}$ US dollar.

For the initial condition of human populations in Eq. (9), we assume $S_h(0) = 65{,}000$, $I_h(0) = 440$, and $R_h(0) = 60$ individuals. The total mosquito population is assumed to be 1 million, with 10 percent infected with the dengue virus, i.e., we set $S_v(0) = 0.9$ million and $I_v(0) = 0.1$ million. No Wolbachia-infected mosquitoes are assumed to be present in the population, i.e., $S_w(0) = I_w(0) = 0$. This setup establishes a baseline for assessing the potential impact of introducing Wolbachia mosquitoes on disease transmission dynamics. The Jakarta Health Office has prepared 800 Wolbachia buckets, each containing 300 Aedes aegypti eggs with a hatching rate of 90 percent [27]. The buckets will be replaced every two weeks to ensure continuous release. Based on these numbers, approximately $\overline{W} = 15{,}000$ Wolbachia-carrying mosquitoes were deployed into the environment daily.

3.2.2 Simulation Results

The simulation study will evaluate the dynamics of dengue infection under four distinct scenarios based on the optimal control model in Eq. (2)–(8). The first scenario involves only the release of Wolbachia-infected mosquitoes at a constant rate, denoted by Wolbachia (C), while the second scenario considers a proportional release rate based on specific population metrics, namely S_v and I_v, denoted by Wolbachia (P). The third scenario integrates multiple control measures, including constant-rate release of Wolbachia-infected mosquitoes, public health education to raise awareness and encourage preventive behaviors, and dengue vaccination programs, denoted by All controls (C). Lastly, the fourth scenario combines the proportional release of Wolbachia-infected mosquitoes with public health education and vaccination efforts, denoted by All controls (P).

Fig. 2 depicts the dynamics of dengue-infected individuals under various control scenarios. Both Wolbachia-only scenarios, involving constant and proportional releases of Wolbachia-infected mosquitoes, show a modest reduction in infections compared to the no-control scenario. However, the decrease is not particularly significant, highlighting the limited impact of Wolbachia releases alone. These scenarios reduce the number of incidents by merely 13 percent and 15 percent, respectively. In contrast, the scenarios integrating Wolbachia releases with public health education and vaccination, i.e., All controls (C) and All controls (P), result in a substantial reduction in dengue cases by 58 percent, emphasizing the importance of combining multiple intervention strategies for effective disease control. Furthermore, the results reveal no significant difference in the reduction of infections between constant and proportional release rates, whether applied as single control measures or as part of multiple controls.

The limited effectiveness of a single Wolbachia release (only achieving a 13-15% reduction in cases) can be attributed to key biological and ecological factors. First, achieving complete mosquito population replacement is challenging and time-consuming, meaning a portion of the wild mosquito population may remain uninfected and continue to transmit the virus. Second, the intervention primarily targets the mosquito vector but does not directly prevent persistent human-to-human transmission once the virus is circulating within a community. Finally, while Wolbachia significantly reduces vector competence, its effect is not always absolute, which can allow for a low but continuous level of viral transmission. These factors collectively highlight why Wolbachia releases are most effective when integrated into a comprehensive strategy that also includes human-focused interventions like vaccination and public health education.

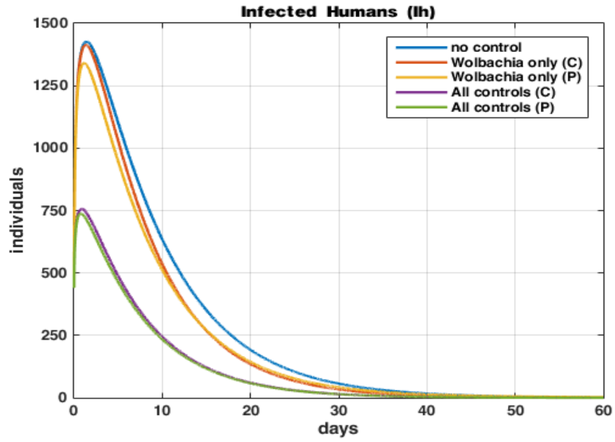


Figure 2. Dynamics of Dengue Infections I_h: Comparing Scenarios with and without Control Measures

With the constant release rate, 15,000 Wolbachia-infected mosquitoes are deployed daily. In the case of the proportional release rate, the intensity reaches a maximum of 100 percent over nearly 60 days as illustrated in Fig. 3. However, the number of Wolbachia-infected mosquitoes released proportionally depends on the population of wild mosquitoes, represented by S_v (susceptible mosquitoes) and I_v (dengue-infected mosquitoes). In the case of multiple controls with constant release of Wolbachia mosquitoes, public health education is implemented with a maximum intensity of 80 percent of the susceptible population during the first 26 days, after which the intensity is gradually reduced for the remainder of the period. Vaccination is applied with a maximum intensity of 25 percent during the first 15 days. If the Wolbachia-infected mosquitoes are released proportionally, both education and vaccination efforts maintain their maximum intensity for longer durations, lasting about 41 days and 25 days, respectively. After these periods, the intensity is gradually reduced in a controlled manner for the remainder of the simulation period.

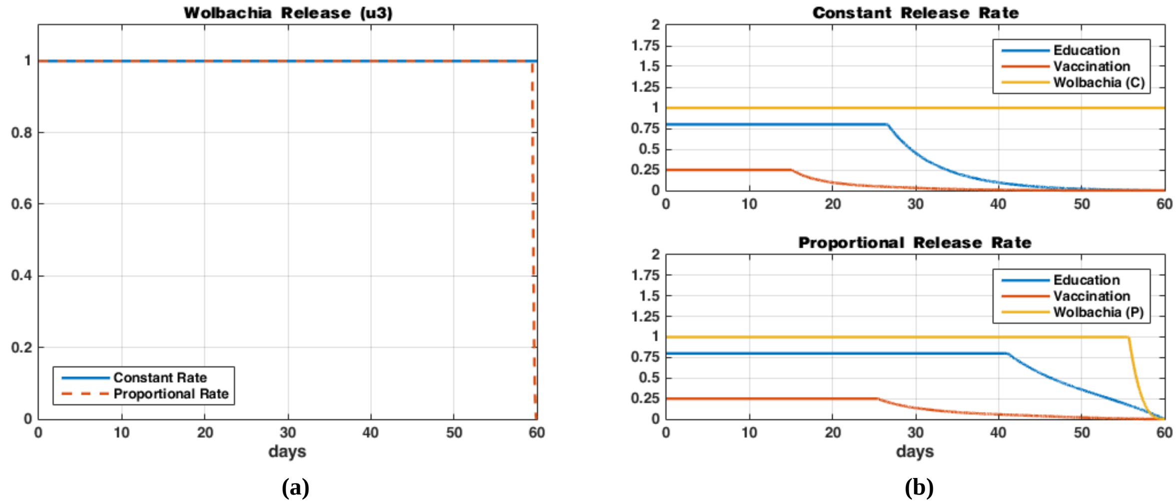
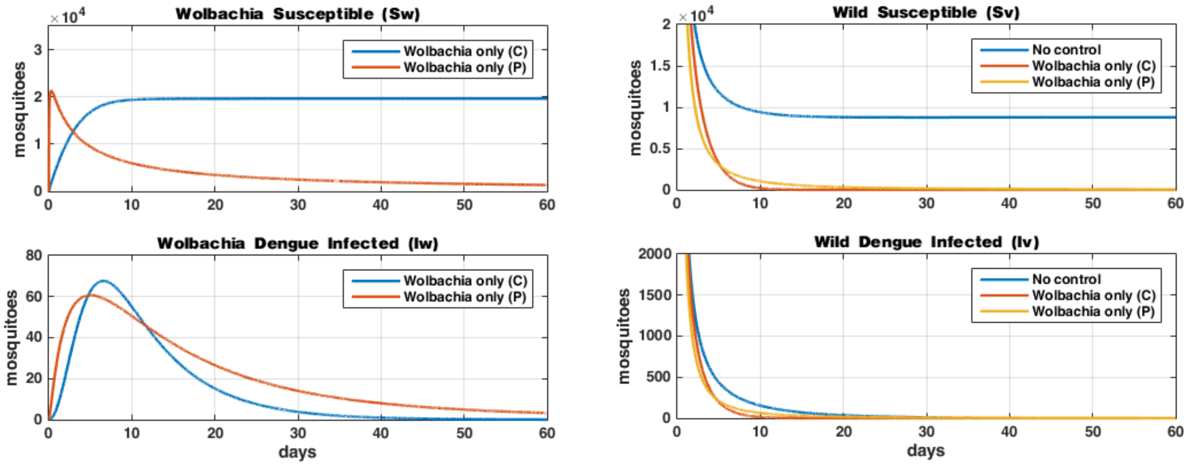


Figure 3. Control Intensity Dynamics of Education (u_1), Vaccination (u_2), and Wolbachia-infected Mosquito Release (u_3): (a) Single Control, (b) Multiple Controls

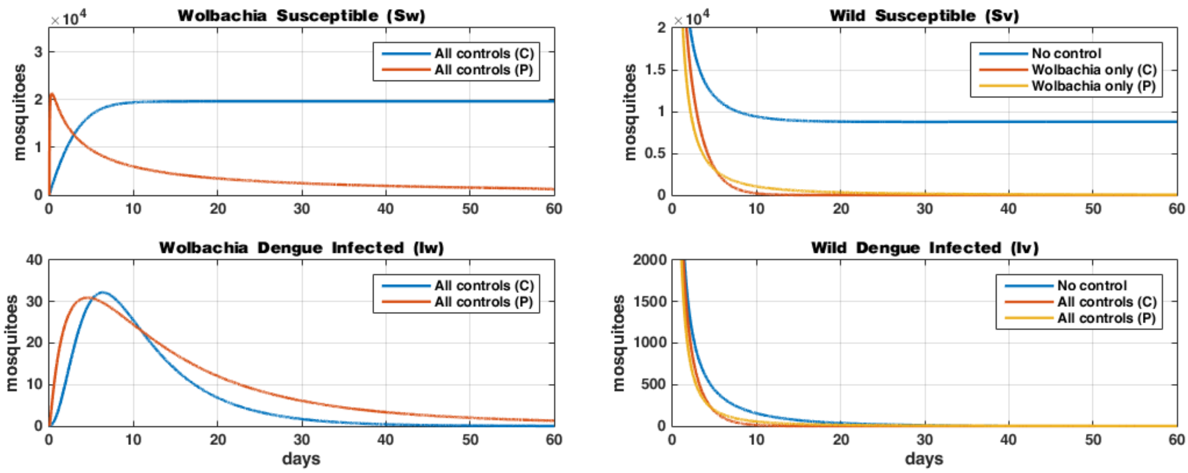
Fig. 4 and Fig. 5 describe that, in both single control and multiple control scenarios, the constant release of Wolbachia-infected mosquitoes rapidly establishes a population of 20,000 Wolbachia mosquitoes within the first 10 days, reaching a steady state condition by the end of the simulation period. In contrast, the proportional release strategy initially introduces 20,000 Wolbachia mosquitoes at the onset. However, the number of released mosquitoes then declines drastically, in response to the reduction in the wild mosquito population (right figures). This demonstrates the adaptive nature of the proportional release approach, where the intensity of mosquito release is dynamically adjusted according to the changing dynamics of the wild mosquito population. The 20,000 is the result of the initial calculation of the proportional release rate at time $t = 0$, based on the initial wild mosquito population, rather than a fixed assumption.



(a) **(b)**

Figure 4. Dynamics of Mosquito Populations under Single Control Intervention: (a) Wolbachia-infected Mosquito, (b) Wild Mosquito

When released at a constant rate, Wolbachia-infected mosquitoes will dominate the overall mosquito population, comprising 86 percent of the total population. With proportional release, the proportion of Wolbachia-infected mosquitoes in the environment is 58 percent. This difference illustrates the varying effects of the two release strategies, with the constant release method resulting in a higher prevalence of Wolbachia-infected mosquitoes compared to the proportional release approach. Wolbachia-infected mosquito was found to be stable and established at consistent levels in local mosquito populations (more than 60 percent prevalence) in the majority (67 percent) of areas [39].



(a) **(b)**

Figure 5. Dynamics of Mosquito Populations under Multiple Control Intervention: (a) Wolbachia-infected Mosquito, (b) Wild Mosquito

The proportional release strategy exhibits a distinct behavioral shift between early and late time horizons, a dynamic that is absent in the constant release approach, see Fig. 4 (a) and Fig. 5 (a) for S_w. In the initial phases, when the native *Aedes aegypti* population is high, the proportional rate is similarly high, effectively overwhelming the wild mosquito population to accelerate the spread of Wolbachia. As the intervention takes effect and the target mosquito population density declines, the proportional release rate automatically decreases. This makes the strategy highly adaptable and resource-efficient, as it requires a large input only when necessary and a minimal one for long-term maintenance. This adaptive behavior is what allows the proportional release to be a more sustainable and cost-effective long-term solution.

3.3 Cost-Effectiveness Analysis

A single control strategy yields results that are not significantly different in terms of reducing dengue infection cases. Despite the difference in the number of Wolbachia-infected mosquitoes released, which consequently leads to varying costs, the impact on infection reduction remains similar. This situation is also observed in multiple control cases. The lack of a substantial difference in infection reduction, even when varying the release intensity and associated costs, suggests that factors beyond the quantity of released mosquitoes may be influencing the effectiveness of the interventions. This highlights the importance of optimizing the release strategy and considering the cost-effectiveness of different control measures.

Cost-effectiveness analysis can be an essential tool to fairly compare the four scenarios by evaluating the costs relative to the health outcomes achieved [36], [37]. In this context, the goal is to identify which intervention strategy provides the greatest reduction in dengue infections for the least number of resources. Following [40], two cost-effectiveness measures known as the average cost-effectiveness ratio (ACER) and the Incremental Cost-Effectiveness Ratio (ICER) are employed. ACER represents the average cost incurred per infection averted for a single strategy compared to the no-control option, while ICER is defined as the additional cost required to achieve an additional unit of benefit. In the context of health interventions, ICER represents the ratio of the difference in total costs incurred between one strategy and the next most effective strategy to the difference in the total number of infections prevented by each strategy. Benefit contributed by Strategy k is defined by

$$B_k = \int_0^T w_0 \left(I_{h,0}(t) - I_{h,k}(t) \right) \, dt, \tag{27}$$

where $I_{h,k}$ is the number of infected humans due to strategy k and $I_{h,0}$ is that under no control strategy. While the total cost associated with implementing the strategy k using constant release and proportional release rates of Wolbachia-infected mosquitoes are, respectively, defined as

$$C_k = \int_0^T \left(w_1 u_1(t) S_{h,k}(t) + w_2 u_2(t) S_{h,k}(t) + w_3 u_3(t) \bar{W} \right) \, dt, \tag{28}$$

and

$$C_k = \int_0^T \left(w_1 u_1(t) S_{h,k}(t) + w_2 u_2(t) S_{h,k}(t) + w_3 u_3(t) \left(S_{v,k}(t) + I_{v,k}(t) \right) \right) \, dt, \tag{29}$$

where $S_{h,k}$ is the number of susceptible humans, $S_{v,k}$ and $I_{v,k}$ respectively are the number of wild susceptible and dengue-infected mosquitoes, all produced by Strategy k. ACER and ICER are then calculated according to

$$\text{ACER}_k = \frac{C_k}{B_k}, \qquad \text{ICER}_k = \frac{C_k - C_{k-1}}{B_k - B_{k-1}}, \tag{30}$$

for $k = 0,1,2,3,4$, with $k = 0$ refers to the no-control strategy. For the calculation of ICER, the strategy must be arranged in ascending order based on the total number of infections averted, as illustrated in Table 2. In this context, B_0 and C_0 represent the total number of infections averted and the total cost incurred under a no-control strategy, both of which are equal to zero. A lower ACER indicates a strategy that provides for reducing infections at a lower average cost per unit, and a lower ICER suggests that the additional health benefit is achieved at a relatively low cost. This strategy is likely cost-effective.

Table 2. Calculation of ACER and ICER

k	Strategy	Benefit	Cost	ACER	ICER
0	No control	0	0	NA	NA
1	Wolbachia only (C)	2,025.36	224.91	0.11	D
2	Wolbachia only (P)	2,457.24	42.96	0.02	0.02
3	All controls (C)	9,230.04	2,259,434.98	244.79	333.60
4	All controls (P)	9,507.18	2,304,127.55	242.36	161.27

NA: not available, D: dominated

Table 2 shows that Strategy 2 (Wolbachia-infected mosquitoes release with a proportional rate) dominates Strategy 1 (Wolbachia-infected mosquitoes release with a constant rate) as it is both cheaper ($C_2 < C_1$) and more effective ($B_2 > B_1$). Thus, Strategy 1 is eliminated. Wolbachia only (P) is the most cost-effective option, with an ICER of US\$0.02 per infection averted, offering a low-cost intervention for significant benefits. Moving to All controls (C) from Wolbachia only (P) results in a substantial increase in cost (US\$333.83 per infection averted) but also provides significantly higher effectiveness. Shifting to All controls (P) from All controls (C) incurs an additional cost of US\$161.27 per infection averted, representing a more efficient upgrade than the prior jump in cost-effectiveness. While Wolbachia only (P) is the most cost-effective in terms of cost per infection averted, All controls (C) and All controls (P) provide greater overall benefits at higher costs. Decision-makers should weigh the budget constraints and willingness-to-pay thresholds to choose the best strategy. By comparing ICER values to a certain threshold, e.g., the per capita GDP of Indonesia, decision-makers can determine the economic viability and prioritize the most efficient public health strategy.

4. CONCLUSION

In this study, our conclusions are:

1. A proportional release strategy, which adjusts the number of Wolbachia mosquitoes based on the wild mosquito population, emerged as the most economical option, optimizing resources while maintaining effectiveness.
2. A constant release strategy incurs higher costs due to the larger volume of mosquitoes released; it ensures long-term Wolbachia dominance, offering greater potential for sustained dengue transmission suppression.
3. Combining Wolbachia release with public health education and dengue vaccination substantially reduced cases, achieving a reduction of more than 50 percent. However, this integrated approach is limited by high costs, mainly due to the expensive dengue vaccine and the relatively higher per-unit cost of education campaigns compared to mosquito release.
4. These findings underscore the importance of strategic planning to achieve the optimal balance between immediate cost efficiency and long-term disease control. Decision-makers should tailor the Wolbachia release rate to the specific objective: a proportional rate for rapid reduction in outbreaks and a constant rate for sustained, long-term control in endemic areas.

Based on our findings, we provide the following actionable recommendations for public health agencies. First, while a Wolbachia-only strategy is the most cost-effective per infection averted, a combined approach incorporating public health education and vaccination is essential for achieving a substantial, long-term reduction in dengue cases. Therefore, a balanced investment across these three control measures is crucial for maximizing public health outcomes. Second, the choice between constant and proportional release rates should be guided by specific objectives. For areas experiencing an outbreak, a proportional release is ideal for a rapid, short-term impact. For endemic areas aiming for sustained control, a constant release is recommended to maintain a stable Wolbachia presence. These insights can help optimize resource allocation and improve the effectiveness of dengue control programs.

Author Contributions

Toni Bakhtiar: Conceptualization, Formal Analysis, Investigation, Methodology, Project Administration, Supervision, Validation, Writing - Original Draft, Writing - Review and Editing. Jaharuddin: Conceptualization, Formal Analysis, Funding Acquisition, Investigation, Methodology, Supervision, Validation, Writing - Original Draft, Writing - Review and Editing. Farida Hanum: Data Curation, Formal Analysis, Investigation, Software, Visualization, Writing - Original Draft, Writing - Review and Editing. All authors contributed significantly to this manuscript, with each bringing distinct expertise to the research process, and collectively, they discussed the results and refined the final manuscript.

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Declarations

The authors declare that they have no conflicts of interest.

Declaration of Generative AI and AI-assisted Technologies

Generative AI tools (e.g., ChatGPT) were used solely for language refinement, including grammar, spelling, and clarity. The scientific content, analysis, interpretation, and conclusions were developed entirely by the authors. All final text was reviewed and approved by the authors.

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