Research Article

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Economic optimization of *Wolbachia*-infected *Aedes aegypti* release to prevent dengue

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Abstract

BACKGROUND: Dengue virus, primarily transmitted by the *Aedes aegypti* mosquito, is a major public health concern affecting ≈3.83 billion people worldwide. Recent releases of *Wolbachia*-transinfected *Ae. aegypti* in several cities worldwide have shown that it can reduce dengue transmission. However, these releases are costly, and, to date, no framework has been proposed for determining economically optimal release strategies that account for both costs associated with disease risk and releases.

RESULTS: We present a flexible stochastic dynamic programming framework for determining optimal release schedules for *Wolbachia*-transinfected mosquitoes that balances the cost of dengue infection with the costs of rearing and releasing transinfected mosquitoes. Using an ordinary differential equation model of *Wolbachia* and dengue in a hypothetical city loosely describing areas at risk of new dengue epidemics, we determined that an all-or-nothing release strategy that quickly brings *Wolbachia* to fixation is often the optimal solution. Based on this, we examined the optimal facility size, finding that it was inelastic with respect to the mosquito population size, with a 100% increase in population size resulting in a 50–67% increase in optimal facility size. Furthermore, we found that these results are robust to mosquito life-history parameters and are mostly determined by the mosquito population size and the fitness costs associated with *Wolbachia*.

CONCLUSIONS: These results reinforce that *Wolbachia*-transinfected mosquitoes can reduce the cost of dengue epidemics. Furthermore, they emphasize the importance of determining the size of the target population and fitness costs associated with *Wolbachia* before releases occur.

Supporting information may be found in the online version of this article.

Keywords: *Wolbachia*; *Aedes aegypti*; optimal control

1 INTRODUCTION

Dengue virus is a major public health concern worldwide with an estimated 3.83 billion people at risk of infection,[1] resulting in 100 million symptomatic cases and 10 000 deaths per year in ≥125 countries.[2–5] Accounting for fatal and nonfatal infections, dengue was responsible for >2.38 million disability-adjusted life years (DALYs) in 2019 alone.[3,5] Dengue is primarily spread by the vector *Aedes (Stegomyia) aegypti* and to a lesser extent by *Ae. (Stegomyia) albopictus*. Both species are anthropophilic mosquitoes that primarily blood-feed on human hosts, making them highly effective vectors. The risk of dengue infection is expected to increase drastically in coming decades as a consequence of climate change, the spread of *Ae. aegypti*, increasing international travel, and growing urban centers in endemic areas,[1,6,7] with an estimated 6.1 billion people at risk by 2080.[1] Currently, there are no effective drug treatments available and the only available vaccine, Dengvaxia, is controversial,[8] and is only recommended for use in seropositive individuals in endemic regions.[9] Control of dengue outbreaks therefore relies on vector control, historically through the use of chemical adulticides.[6]

Vector control programs successfully eliminated *Ae. aegypti* in >20 countries in the Americas from 1947 to 1962 through the intensive use of chemical adulticides and larvicides, resulting in dengue elimination in previously endemic regions.[6] Since then, *Ae. aegypti* has reinvaded much of its previous range,[7,10] bringing with it risk of dengue outbreaks.[6] The use of adulticides for routine control of *Ae. aegypti* in many of these regions has proven challenging owing to the emergence of insecticide resistance[11,12]

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[Correction added after first online publication on 25 April 2024; Equation 1 has been updated.]

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and concern about their environmental impact. Additionally, the ability of reactive vector control to reduce dengue outbreaks have had mixed results and are likely to be dependent on several factors, including the timing of the control in respect to both the outbreak and season.[13,14]

Several new vector control techniques (e.g. *Wolbachia* transinfection, sterile insect technique and gene drives) have been proposed to help reduce dengue burden worldwide. Many of these methods take advantage of self-spreading elements, either genetic sequences or bacteria, that aim to either reduce the vector population or replace it with a population that is resistant to dengue infection.[15] Currently, the most widely deployed technique relies on *Wolbachia* transinfection, where *Ae.* aegypti are infected with species of *Wolbachia* that do not naturally infect *Ae. aegypti* but do naturally infect other species of insects (e.g. *Drosophila melanogaster*)[16,17] or even mosquitoes (e.g. *Aedes albopictus*).[17] *Wolbachia* are maternally-inherited intracellular bacteria with species that infect >50% of insect species worldwide, but no species of which naturally infect *Ae. aegypti*.[18] *Wolbachia* trans-infections are able to spread quickly through populations as a result of maternal inheritance and cytoplasmic incompatibility,[16,19,20] where females infected with *Wolbachia* are able to successfully mate with both infected and uninfected males, but matings between uninfected females and infected males result in inviable eggs, biasing inheritance towards infected mosquitoes.[16,20,21] *Aedes aegypti* have been successfully transinfected with several strains of *Wolbachia*,[22] resulting in reduced mosquito lifespan and/or reduced susceptibility of the mosquito to dengue,[16,19,23] making it a potentially powerful tool for both stopping dengue transmission in endemic settings and preventing new outbreaks.[24] However, the success of these programs requires the bias in inheritance to overcome any fitness costs, typically defined as the reduction in the expected genetic contribution of an individual to the next generation, associated with *Wolbachia* infection. Although, in general, the expectation is that transinfection results in a fitness cost, counter-examples have been observed,[25] and it has long been observed that the relationship can evolve over time to reduce fitness cost or even provide a fitness benefit.[26] The release of *Wolbachia*-infected mosquitoes for dengue control has now occurred in Australia,[27–29] Vietnam,[30] Indonesia,[31,32] Brazil[33–35] and Malaysia[17] with releases planned or ongoing in at least eight other countries.[36] *Wolbachia* has been able to spread through local *Ae. aegypti* populations in most cases with an estimated 77% reduction in dengue incidence in Yogyakarta, Indonesia.[31,37] However, spread of *Wolbachia* infection was slower than expected in Cairns, Australia owing to unaccounted-for population structure,[38] and lost in Tri Nguyen Village, Vietnam,[30] as a consequence of high temperatures,[30,39] and Brazil, following release of insecticide-susceptible mosquitoes into a highly resistant population.[35]

There are significant costs associated with rearing and releasing *Wolbachia*-infected *Ae. aegypti*.[40] These include fixed, capital expenditures – primarily, constructing a mass rearing facility at a given scale – and variable, operational costs of maintaining and deploying the modified organisms.[41] Consequentially, release programs will seek to successfully replace the wild-type (WT) *Ae. aegypti* population with *Wolbachia*-infected *Ae. aegypti*, or to minimize dengue burden, while minimizing the costs associated with the release program. The design of cost-effective release programs will be essential as releases of *Wolbachia*-infected mosquitoes become common and releases begin in resource-limited regions. It is vital for this analysis to account for the interactions between the mosquito population, *Wolbachia* transmission and dengue transmission dynamics. However, previous research has focused on *post hoc* analysis of cost-effectiveness,[40,42] and there has been limited work designing cost-effective release strategies for *Wolbachia*-infected mosquitoes or other self-spreading methods for population reduction or replacement.

Here we present a stochastic dynamic programming (SDP) framework[43] for designing an economically optimal release strategy for *Wolbachia*-infected *Ae. aegypti*. As an example, we use an ordinary differential equation model of *Wolbachia* spread in a panmictic *Ae. aegypti* population that is divided into aquatic juvenile and terrestrial adult life-stages. We determine the economically optimal release strategy for a region at risk of dengue introduction and examine how the strategy varies with key parameter values. The economic optimization implies a strategy of maximal release of *Wolbachia*-infected mosquitoes, followed by rapid tapering and cessation once *Wolbachia* becomes established in the mosquito population. Given that the maximal release rate is determined by facility capacity, we then illustrate how to determine the economically optimal release capacity for a given mosquito population size, given that higher capacity mosquito-rearing facilities are more expensive to build. To do this, we use our SDP framework to estimate the marginal benefits of releases as a function of capacity and compare these to previously published cost-by-capacity estimates. Finally, we examine how results from the SDP and fixed cost analysis are affected by the biological and economic parameters. While our model neglects several biological factors that would be important in real world releases (e.g. spatial population structure in both the human and vector population), the framework that we present here can easily be extended to include these factors and only requires that the biological model can be simulated.

2 MATERIALS AND METHODS

We describe the formulation of the mosquito population, dengue transmission, and *Wolbachia* release and transmission model, define the economic objective of the *Wolbachia* release program, and explain the mathematical and numerical optimization methods used to obtain solutions. Releases are modeled as occurring weekly until the introduction of dengue, with population dynamics between releases following a standard ordinary differential equation model. Table 1 summarizes the key parameters and baseline values in the integrated model. Univariate sensitivity analysis was conducted by varying relevant parameters by ±10%, repeating the analysis, and comparing the optimal facility size to the baseline results.

2.1 Combined dengue and Wolbachia transmission model

We simulated the simultaneous spread of dengue and *Wolbachia* in a region using a previously developed host-vector model that includes *Wolbachia* dynamics [Eqn (1)].[48] The human population is divided into susceptible (S_H), infective (I_H) or recovered (R_H) humans, and is assumed to have equal per-capita birth and mortality rates, μ_H, maintaining a constant population size, N_H. Likewise, the adult mosquito population is divided into susceptible (A_U), *Wolbachia*-infected (A_W) and dengue-infected (A_D). For simplicity, we assume that the ability of *Wolbachia* to block dengue

Table 1. Parameters, notation, estimates and ranges for the model

Parameter	Notation	Value	Range	Units	Source
Human population size	N	2×10^6		Humans	
Human birth rate/death rate (annual)	μ_H	2.75×10^{-4}		$\frac{1}{\text{week}}$	
Transmission parameter (mosq. to human)	B_{MH}	0.278			44
Transmission parameter (human to mosq.)	B_{HM}	0.278			44
Per-capita human recovery rate	γ	0.0168		$\frac{1}{\text{week}}$	
Equilibrium number of female *Ae. Aegypti*	T	2 million	1–4 million	Mosquitoes	
Larvae scaling parameter	k	Value depends on choice of T			
Per-capita adult mosquito recruitment rate	b	3.57		$\frac{1}{\text{week}}$	44
Per-capita adult mosquito mortality rate	μ_M	0.0143		$\frac{1}{\text{week}}$	44
Per-capita larval mortality rate	μ_L	0.00143		$\frac{1}{\text{week}}$	
Wolbachia fitness cost	α	0.15			
Per-capita larval emergence rate	e	0.5		$\frac{1}{\text{week}}$	
Lethality of cytoplasmic Incompatibility	q	1			44
Wolbachia transmission proportion	η	1			
Cost of dengue infection	COI	2900		US$	45
Release capacity	R	300	150–600	$\frac{\text{1000 larvae}}{\text{week}}$	
Marginal cost of release	c	US$458		$\frac{US\$}{\text{1000 larvae}}$	46
Discount rate	r	0.03		$\frac{1}{\text{year}}$	47
Dengue invasion probability	θ	10%		$\frac{1}{\text{year}}$	

Note: Only equilibrium number of mosquitos, release capacity and larvae scaling parameter are varied. All parameters with percentage values are in annual terms. Discount rate and dengue invasion probability given as annual rates for interpretability.

infection is perfect, so that no individuals are simultaneously infected with both dengue and *Wolbachia*. To account for density-dependent dynamics, we included an aquatic larval stage, which is divided into uninfected (L_U) and *Wolbachia* infected (L_W) mosquitoes. Larvae are recruited into the population at per-adult rate, b, and either emerge as adults of the corresponding class, at per-capita rate e, or die at a density-dependent rate that increases proportionally to the larval population size, according to the carrying capacity term (k). Despite being a simplification, the inclusion of density-dependent mortality in the aquatic larval stage is a standard assumption based on the observation that larval populations are constrained by resource competition, whereas the adult population has no such constraint.[49] Naturally, the existence of a larval carrying capacity constrains the size of the adult population. (Supplementary information in Appendix S1) In the presence of *Wolbachia*, larval recruitment into the uninfected and infected classes is determined by the proportion of *Wolbachia*-infected mosquitoes, the proportion of offspring from matings between *Wolbachia*-infected males and uninfected females that fail to develop as a result of cytoplasmic incompatibility (q), the proportion of offspring that inherit *Wolbachia* infections from their mother (ξ) and the reproductive fitness cost of *Wolbachia* (α). While our model allows for imperfect maternal inheritance and cytoplasmic incompatibility, we assume perfect inheritance and cytoplasmic incompatibility ($\eta=1$, $q=1$) for simplicity. Dengue transmission is modeled using a standard form, where transmission from humans to mosquito is determined by transmission parameter B_{HM} and from mosquito to human by transmission parameter B_{MH}, which account for biting rates and transmission probabilities.[50] Following infection, humans are assumed to be infectious for an average of $1/\gamma$ weeks before recovering, at which time they are immune to additional infections, corresponding to only one serotype of dengue circulating.

$$
\begin{aligned}
\frac{dS_H}{dt} &= \mu_H(N_H - S_H) - B_{MH}\frac{S_H A_D}{N_H} \\
\frac{dI_H}{dt} &= B_{MH}\frac{S_H A_D}{N_H} - (\gamma + \mu_H) I_H \\
\frac{dR}{dt} &= \gamma I_H - \mu_H R_H \\
\frac{dL_U}{dt} &= \left(1 - q\frac{A_W}{A_U + A_W + A_D}\right) b A_U + (1-\eta)[A_W(1-\alpha)b] \\
&\quad - eL_U - \mu_L[1 + k(L_U + L_W)]L_U \\
\frac{dL_W}{dt} &= \eta[A_W(1-\alpha)b] - eL_W - \mu_L[1 + k(L_U + L_W)]L_W \\
\frac{dA_U}{dt} &= eL_U - \mu_M A_U - B_{HM}\frac{A_U I_H}{N_H} \\
\frac{dA_W}{dt} &= eL_W - \mu_M A_W \\
\frac{dA_D}{dt} &= B_{HM}\frac{A_U I_H}{N_H} - \mu_M A_D
\end{aligned}
\tag{1}
$$

A sufficiently high larval recruitment rate, $b > \mu_M\left(1 + \frac{\mu_L}{e}\right)$, in this model ensures persistence of the (WT) mosquito population. In the absence of dengue, the model has two stable equilibria, the *Wolbachia*-free equilibrium and an equilibrium where the *Wolbachia* prevalence is between 0 and 1, and two unstable equilibria, the mosquito-free equilibrium and an internal equilibrium (Appendix S1). Importantly, the unstable internal equilibrium results in an invasion threshold, above which *Wolbachia* will self-spread to fixation and below which the prevalence of *Wolbachia* will decline to zero.

For our analysis, we consider a scenario in which a 'virgin soil' dengue outbreak occurs in an immuno-naïve population of 2 million people. This represents a worst-case scenario in terms of dengue control as pre-existing immunity leads to an increased short-term impact of controls.[51,52] *Wolbachia* releases are

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conducted preventively to reduce the capability of the mosquito population to transmit dengue of the mosquito population at the time of dengue introduction. For the dengue transmission model, the human population is further assumed to be well-mixed and homogeneous with regard to infection. In the human population, the expected lifespan is 70 years, the average length of infection is taken to be 1.21 weeks, and any deaths resulting from dengue infection are assumed to be negligible.[44]

In order to calculate the economic damages from an outbreak, we simulated the dynamics of an epidemic for 1 year (52 weeks) following the introduction of dengue, which was sufficient for the initial epidemic to run its course. The outbreak cost was calculated as the total number of unique infection events in that year multiplied by the cost of infection (COI). Where the total number of unique infection events was found by integrating the transmission term over the length of the outbreak. [Eqn (2)]

$$D(\cdot) = \mathrm{COI} \times \int_0^{52} B_{\mathrm{MH}} \frac{S_{\mathrm{H}}(t) A_{\mathrm{D}}(t)}{N_{\mathrm{H}}(t)} dt \tag{2}$$

Damages $D(\cdot)$, resulting from the costs of the outbreak, are a function of state variables at the onset of the outbreak, as well as model parameters, because in general a higher number of uninfected mosquitoes facilitates higher dengue transmission rates, whereas higher prevalence of *Wolbachia* reduces transmission. To apply the SDP technique described below, we simulate the model and calculate (2) across a $20 \times 20 \times 20 \times 20$ grid of values for initial conditions on L_{U}, L_{W}, A_{U} and A_{W} at the time of disease introduction and use linear interpolation to obtain a continuous damage function.

2.2 Economic optimization

We applied stochastic dynamic programming (SDP) methods[43] to compute the *Wolbachia* release policy that minimizes the expected net present value (ENPV) of dengue damage and the recurring costs of rearing and releasing *Wolbachia*-infected mosquitoes. The ENPV[43] is the standard economic efficiency criterion in the presence of uncertainty and accounting for time discounting (i.e. that a given payoff earlier in time is valued more than the same amount later). This is done to account for the added benefits of an earlier payoff (e.g. being able to reinvest). Fixed costs are excluded from this part of the analysis, as they are assumed have already been incurred, cannot be recovered and are constant across all release strategies. We address these fixed costs and optimal capacity decisions regarding rear-and-release facility at the end of this section.

In order to apply SDP methods, we evaluate mosquito population dynamics and *Wolbachia* spread at weekly intervals. Let us denote the vector x_t as containing all state variables in the model at week t, and summarize the dynamics of our system as the discrete-time state-transition equation:

$$x_{t+1} = F(x_t, r_t) \tag{3}$$

where $F(\cdot)$ is the function specifying the weekly transition dynamics and $r_t \geq 0$ is the control (i.e. releases of *Wolbachia*-infected mosquitoes). This transition function simply consists of evaluating the continuous time model in (1) for 1 week, starting from x_t and with the release rate r_t constant over that week.

We assume that dengue is absent from the system until a random time $\tau > 0$, when a dengue outbreak occurs, at which point we assume releases cease and monetized ENPV damages $D(x_\tau) \geq 0$ from the outbreak are assessed [Eqn (2)]. In the context of *Wolbachia* releases for dengue control, this is equivalent to assuming that *Wolbachia* releases are conducted only before the onset of a dengue epidemic, at which point releases cease. This assumption is motivated by the premise that *Wolbachia* is unlikely to be used as a reactive control measure and that resources would shift to more immediate control and treatment strategies during an outbreak, and it greatly facilitates mathematical optimization.

We assume a constant per-unit cost c of *Wolbachia* releases r_t with a maximum release capacity, the number of female *Ae. aegypti* larvae that the facility is able to produce, of R (which we include in the optimization in subsequent analysis). Future costs and damages are weighted according to a discount factor $\beta \in (0,1)$. Lower β reflects a greater preference on the part of the decision-maker for near-term over long-term payoffs. The optimal release policy $r(x_t)$, as a function of the current mosquito population state, seeks to minimize expected NPV (ENPV) of costs and damages, given an initial biological state, x_0:

$$V(x_0) \equiv \min_{r(\cdot) \in [0,R]} \mathbb{E}\left\{ D(x_\tau)\beta^\tau + \sum_{t=0}^{\tau-1} c \cdot r(x_t) \cdot \beta^t \,\middle|\, x_0 \right\} \tag{4}$$

subject to the state transition dynamics in: (1). The function $V(x_0)$ is the minimized ENPV of costs and damages yielded by the above optimization, conditional on the initial conditions x_0 in the biological model. SDP methods use a recursive approach to solve (4).[43] Assuming that the random dengue introduction time τ is distributed according to a geometric distribution with a constant introduction probability, θ, (conditional on dengue not having arrived earlier) and that all other model components are deterministic [as per Eqn (3)], the function $V(\cdot)$ (4) can be shown to satisfy the following recursive equation[43]:

$$V(x_t) = \min_{r \in [0,R]} \left\{ cr + \beta \left[\theta D\left(\underbrace{F(x_t, r)}_{x_{t+1}} \right) + (1-\theta) V\left(\underbrace{F(x_t, r)}_{x_{t+1}} \right) \right] \right\} \tag{5}$$

This equation says that the ENPV of costs and damages in the current week t is equal to the current release costs $c \cdot r$ plus the discounted ENPV in the *next period*. In turn, if dengue arrives next period with probability θ, the conditional NPV in the next period is equal to the damages $D(x_{t+1})$. Otherwise, if with probability $1-\theta$ dengue does not arrive, the next-period ENPV is given by $V(x_{t+1})$. Equation (5) represents a functional equation for the ENPV function $V(\cdot)$. Under standard regularity conditions that exist in our model, existence and uniqueness of the solution is guaranteed. The solution $V(\cdot)$ can then be used to obtain the optimal policy $r^*(x_t)$ for any current biological state x_t, by solving the optimization problem on the right-hand-side of (5), as shown in Eqn (6):

$$r^*(x_t) \equiv \arg \min_{r \in [0,R]} \{ cr + \beta[\theta D(F(x_t, r)) + (1-\theta) V(F(x_t, r))] \} \tag{6}$$

In our model, Eqn (4) can only be solved numerically. Function approximation, for example using a piecewise linear interpolation, with different iterative procedures is the standard numerical solution method.[53] To implement this method, we use the open-source CompEcon software toolkit[54] in Matlab.[55]

The optimal release policy $r^*(\cdot)$ and ENPV function $V(\cdot)$ depend on the rearing facility capacity constraint R, and so R can be included as an argument in both functions: $r^*(R, x_t)$ and $V(R, x_t)$.

It is easy to see mathematically that the ENPV of total costs – both damages and recurring costs – of the release program is nonincreasing in the capacity constraint, $V(R',x_t) \le V(R,x_t)$ for any $R'>R>0$, because R does not affect total costs in our model and any release level that is feasible with capacity constraint R must still be feasible for any higher capacity $R'>R$. Therefore, the benefits of increased capacity are given by reductions in the ENPV of total costs.

In order to analyze economically optimal facility capacity, we repeatedly solve the dynamic optimization problem in (5) across a dense grid of values for R, to analyze how ENPV improves with increased capacity. For a given *Wolbachia*-free initial state of the mosquito population given by x_0, the benefits of a given capacity R are defined as:

$$B(R,x_0) \equiv V(0,x_t) - V(R,x_t) \ge 0 \quad (R \ge 0) \tag{7}$$

We compare these benefits to estimates of the fixed costs of facility construction at different capacity sizes. We follow Brown *et al.*[56] and employ a power-law relationship, $C(R) \equiv \kappa R^{\xi}$ $(\kappa,\xi>0)$ to model fixed costs.[56] The economically optimal facility level R^* therefore solves the optimization problem to achieve maximal net benefits (NB^*), given the costs $[C(R)]$ and benefits $[B(R,x_0)]$ associated with building a facility with a given capacity R:

$$NB^* \equiv \max_{R \ge 0} B(R,x_0) - C(R) \tag{8}$$

Equation (8) is a simple univariate optimization problem which we solve numerically. In general, there exists a finite capacity R^* solving this optimization problem: this is because the cost function is unbounded as $R \to \infty$, the benefits function is bounded (i.e. the most an arbitrarily capacious facility could hope to achieve is zero dengue damage), and both functions are continuous over the relevant domain for R.

The baseline economic parameter values (varied in later sensitivity analyses) are as follows: The COI is assumed to be US$2900 per dengue case.[45] Unit release costs are set at US$458 per thousand larvae based on rearing facility cost estimates.[46] Following a previous publication,[56] we used fixed costs for 17 different sterile insect technique (SIT) programs worldwide, 11 targeting the Mediterranean fruit fly, *Ceratitis capitata* (Medfly) and six targeting various other species. For the full 17-observation sample, $\kappa=0.13, \xi=0.6713$, whereas restricting to only Medfly facilities changes these estimates to $\kappa=0.232, \xi=0.6194$.[56] For the discount factor, we use the World Health Organization (WHO)'s recommended discount rate of 3% per year, resulting in a weekly discount factor of $\beta=(1+0.03/52)^{-1} \approx 0.999$.[47]

3 RESULTS

As examples, we calculated optimal release (OR) strategies and their resulting ENPV of costs and dengue damages for all combinations of three different equilibrium population sizes of adult female *Ae. aegypti* (1 million, 2 million and 4 million) and three different representative release capacities (150 000, 300 000 and 600 000 larvae per week).

3.1 Optimal release strategies and expected net present value

Minimization of Eqn (5) allows for the calculation of the ENPV of releasing 1000 female larvae, given an observed population density and *Wolbachia* prevalence in adult and larval mosquitoes (Appendix S1). Because ENPV is a function of all four state variables (L_U, L_W, A_U and A_W), we choose to show ENPV as a function of adult population density and *Wolbachia* prevalence, as these are the most likely to be measured in the field. To do this, we assume that the larval population is 1.4-fold larger than that of the adult population (the relationship that occurs at equilibrium) with equal *Wolbachia* prevalence. Although the ENPV is not calculated for the optimal release, it illustrates how the ENPV of releasing a number of individuals changes drastically depending on the state variables, which drives the optimal release strategy. The ENPV of releases is high (>US$100 000), driven by the cost of a potentially large dengue outbreak, when *Wolbachia* prevalence is low (<25%), but drops quickly as *Wolbachia* prevalence increases above 25% (Fig. S1 in Appendix S1). This corresponds to *Wolbachia* prevalence surpassing the invasion threshold (25.7%; Table S1 in Appendix S1), reducing the benefit of additional releases. ENPV of releases is higher at intermediate (25%–40%) *Wolbachia* prevalence for larger equilibrium population sizes, owing to the increased *Wolbachia* prevalence necessary to prevent a dengue outbreak when mosquito population sizes are high.

The OR surfaces, based on the ENPV and cost of releases, show that the optimal release size is 100% of the maximum capacity when *Wolbachia* prevalence is low and mosquito population sizes are high, a direct result of the high NPV of releases from a dengue epidemic (Fig. 1). Sizes of OR decrease sharply as *Wolbachia* prevalence increases and more gradually as the mosquito population size decreases compared to its equilibrium, reflecting the reduced number of *Wolbachia*-infected mosquitoes required to surpass the invasion threshold. Notably, additional releases are optimal even after *Wolbachia* prevalence surpasses the invasion threshold (25.7%) until ≈50%. This is a consequence of the slow spread of *Wolbachia* near the invasion threshold and the potential for a dengue outbreak occurring before *Wolbachia* spread. Furthermore, the region of state space where intermediate release sizes are optimal increases with higher maximum release capacity and lower equilibrium mosquito population size, as intermediate release sizes are sufficient for speeding *Wolbachia* fixation. Whereas this region of state space increases with maximum release capacity, intermediate releases are rarely seen in simulations (discussed below) owing to initial releases being sufficient to overcome the invasion threshold. This means that although intermediate release sizes are optimal across a large range of the state space in these situations, they are rarely seen in the simulations. However, intermediate-sized releases may be more common in practice owing to stochastic fluctuations.

3.2 Optimal release simulations

For cases where the release facility was small (150 000 larvae per week), the OR strategy was to release the maximum number of larvae for between 3 and 17 weeks, depending on the mosquito population size. As the facility size increases, the number of weeks at 100% maximum release size decreased from between two and nine for the intermediate facility size, and one and six for the largest facility size. Several optimal release strategies included one release below the maximum release size, but no simulation called for a second, suggesting that an all-or-nothing approach will be optimal, or near-optimal, in most cases (Fig. 2). In simulations, *Wolbachia* prevalence increased nearly linearly with time in the population as releases occurred. Once releases stopped, *Wolbachia* continued to spread to fixation, albeit slowly at first (Fig. 2).

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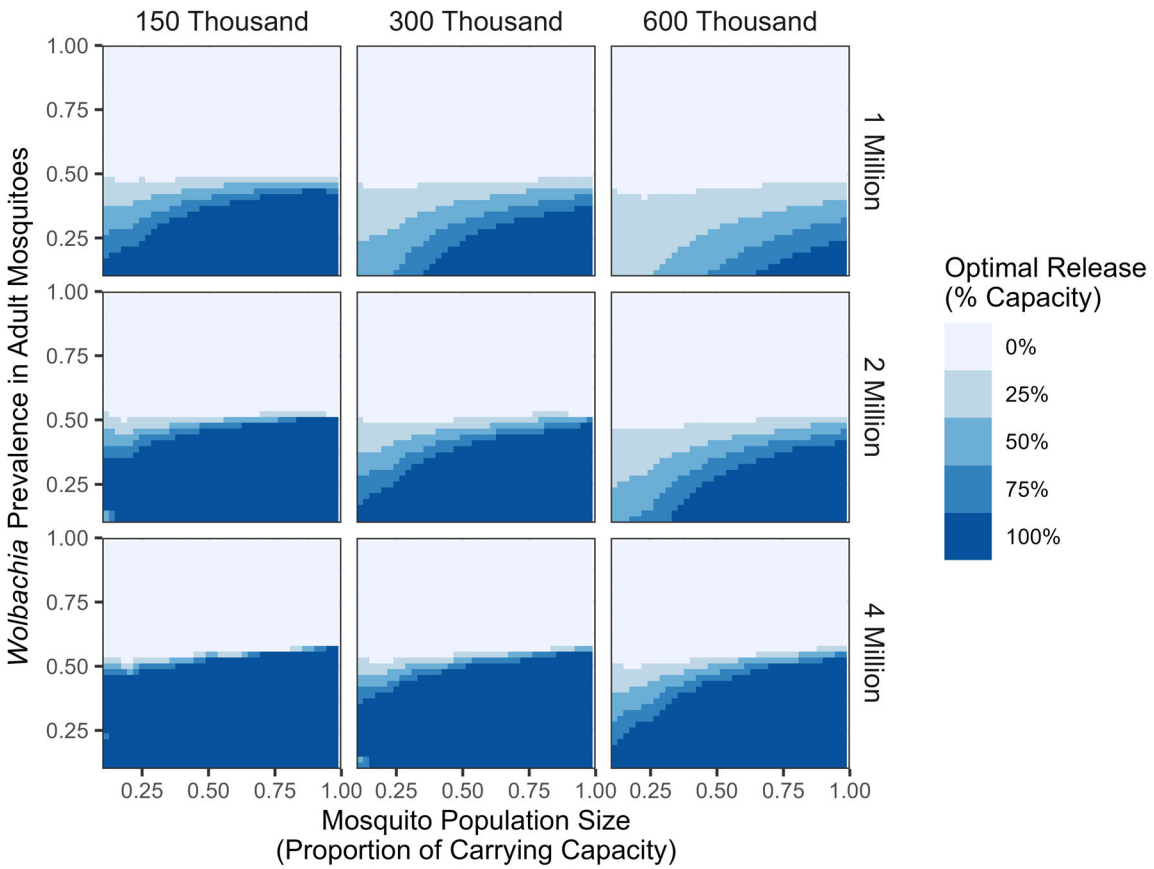

Figure 1. Optimal release size (as proportion of maximum) for a given proportion of carrying capacity and prevalence of *Wolbachia*. Rows represent three different population sizes (1 million, 2 million and 4 million) of adult mosquitoes and columns depict three different release capacities (150 000, 300 000 and 600 000 larvae); these are shown to illustrate their effects on our results. Larval populations are assumed to be 1.4-fold larger than that of the adult population, with equal *Wolbachia* prevalence. Intermediate releases are only optimal in a small region when the maximum release rate is high compared to the population size. This suggests that all-or-nothing strategies will be optimal, or nearly optimal, in most cases.

Mosquito population density decreased monotonically and stabilized at the *Wolbachia*-fixed equilibrium (Fig. 2).

3.3 Fixed cost analysis and optimal scale of mass-rearing facility

Calculating the net benefit of optimal releases from varying sizes of facilities showed that the marginal benefit associated with increasing facility size decreased rapidly as facility size increased (Fig. 3). Expectedly, marginal benefits were higher for situations when the mosquito population was larger. Comparing the marginal benefits associated with facility size to the marginal costs of a larger facility, we found that the optimal facility size was between 120 000–300 000 and 150 000–400 000 larvae, depending on the mosquito population size, for marginal costs resembling Medfly and non-Medfly SIT facilities, respectively (Fig. 3). The large range of possible optimal facility sizes highlights the importance of accurate estimates of the target mosquito population sizes. Further sensitivity analysis, to examine how these results depend on our parameter choices, suggests that the optimal facility size is most sensitive to the dengue invasion probability, θ, and the fitness cost associated with *Wolbachia*, α (Table 2).

4 DISCUSSION

We presented a highly flexible framework for designing an optimal release strategy for *Wolbachia*-infected *Ae. aegypti* that minimizes the impact of an expected dengue outbreak when the precise timing of the outbreak is unknown. This framework calculates the NPV and OR surfaces and determines the optimal release strategies by simulating the spread of *Wolbachia*. Herein we present a simple model of *Wolbachia* spread, yet this framework can incorporate any level of biological realism deemed appropriate, assuming sufficient computational resources are available. Our results show that an all-or-nothing release strategy for *Wolbachia*-infected mosquitoes is often optimal, owing to high costs associated with a dengue outbreak. This suggests that care should be taken in determining the size of the rearing facility, and thus the number of *Wolbachia*-infected mosquitoes that can be released weekly, before construction. We found that the optimal size of the rearing facility was highly dependent on mosquito population size and fitness costs associated with *Wolbachia* infection, suggesting that an upper bound on these parameters for the target population should be determined before a rearing facility is constructed. However, mosquito population size is difficult to accurately estimate and can fluctuate significantly through time.[57,58] Finally, we have shown that these results are driven by the high cost associated with dengue outbreaks and are relatively insensitive to parameters associated with mosquito life history.

Several modeling studies have presented frameworks for determining an optimal release strategy for *Wolbachia*-infected mosquitoes.[59–64] These studies also found that the optimal release strategy was to release the maximum number of *Wolbachia*-

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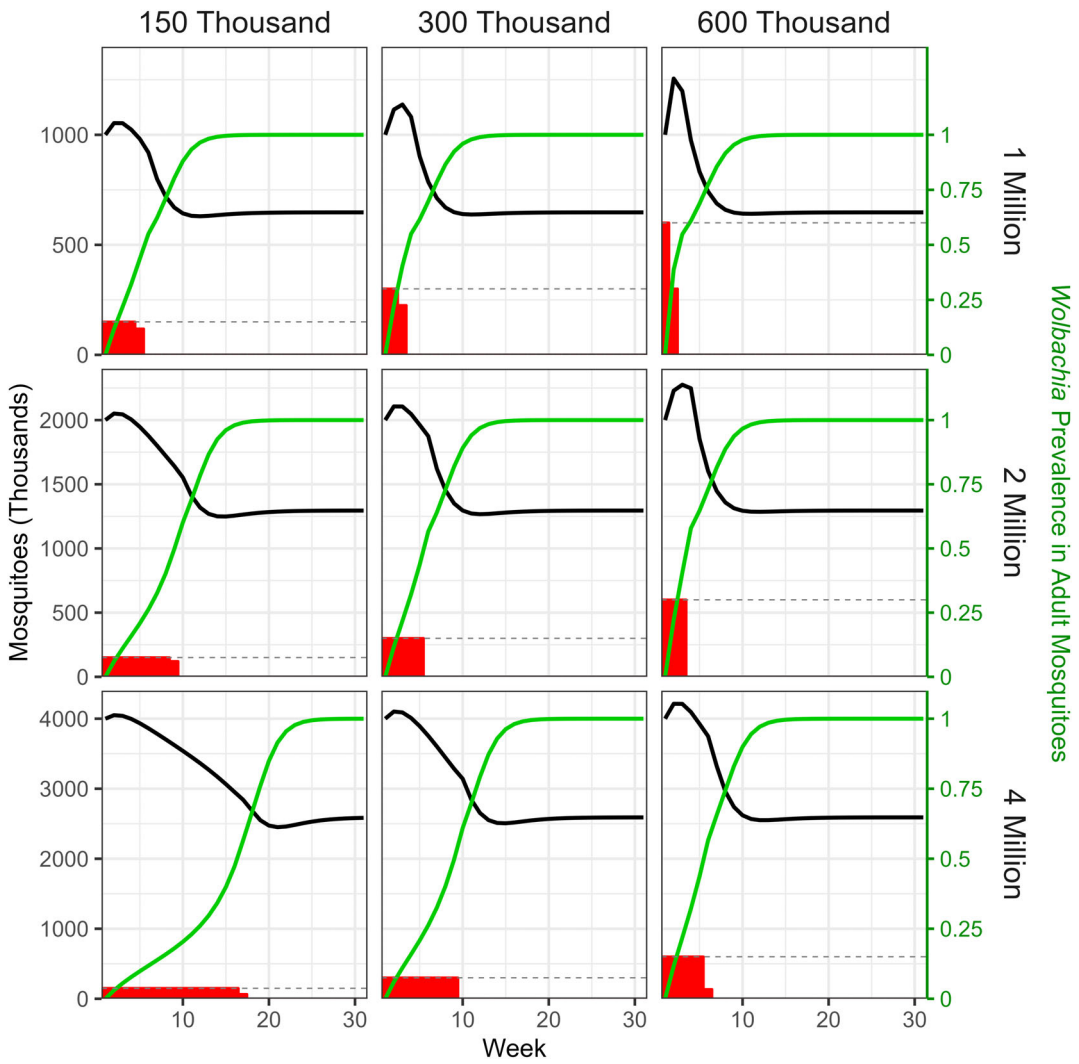

Figure 2. Simulated optimal releases. Simulations show that the optimal release strategy (red bars) involves the release of larvae at the maximum release rate (grey dashed line) to bring *Wolbachia* prevalence above the threshold for self-spread, followed by a sharp decrease in releases until they are stopped. Mosquito population size (black line) and *Wolbachia* prevalence in adults (green line) are also shown. Three different equilibrium population sizes (1 million, 2 million and 4 million) and three different release capacities (150 000, 300 000 and 600 000 larvae) are shown to illustrate their effects on our results. In all cases, optimal releases involve releases at the maximum release rate and at most one intermediate release. Releases are then stopped once *Wolbachia* is capable of self-spreading at sufficiently high rates.

infected mosquitoes possible until the invasion threshold was surpassed. However, the aims of these papers were either to minimize the number of dengue cases in a dengue endemic region,[59,60] or to minimize mosquito densities.[61–63] Further, none of these studies compared the cost associated with releases to the benefits they provide. One additional study examined the optimal allocation of resources for controlling dengue with a constrained budget[64] and found that a mixture of childhood vaccine and *Wolbachia* releases were optimal, but did not examine how interventions should be deployed over time. *Post hoc* quantification of the cost-effectiveness of dengue control through releases of *Wolbachia*-infected mosquitoes in Yogyakarta found that releases were cost-effective, costing approximately US$1500 per DALY averted.[40] Additional modeling studies examining the potential cost-effectiveness of theoretical releases in Singapore and Thailand found that programs would be cost-effective, costing US$50 000–100 000[42] and US$343–420[65,66] per DALY averted, respectively. While these results are not directly comparable with the results presented here, and come from a dengue-endemic region, it highlights the low costs associated with *Wolbachia* releases compared to the cost of dengue infection. Although our results show that, if undertaken, releases of *Wolbachia*-infected mosquitoes should occur as quickly as possible, there are other important considerations when determining if the release of *Wolbachia*-infected mosquitoes is appropriate. For this reason, we are not advocating for or against future releases.

The results we present here come from an extremely simplified model of *Wolbachia* and dengue spread. The spread of both *Wolbachia* and dengue are likely to vary both seasonally and spatially across a region. *Wolbachia* spread is known to be heavily influenced by temperature, particularly when high,[39] and mosquito population structure,[38,67] which is likely to be seasonally varying and affected by spatial variation in microclimate and environment. Likewise, dengue incidence is known to cluster at relatively small spatial scales[68–72] and is known to be affected by local variation in mosquito population density,[69] mosquito dispersal

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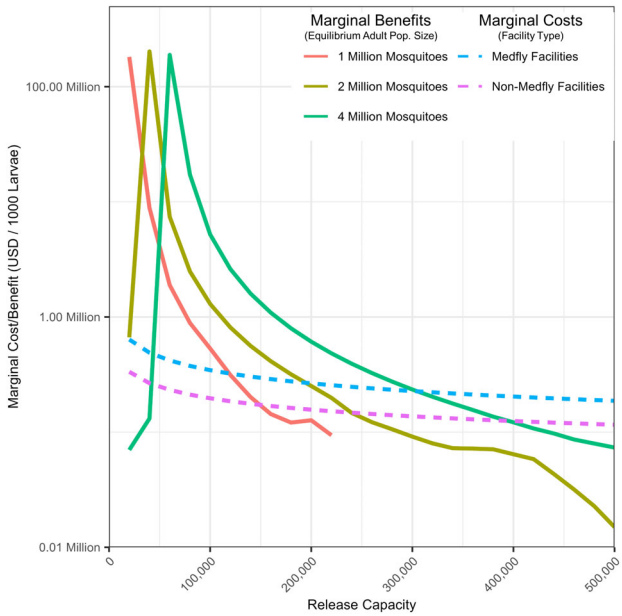

Figure 3. Fixed costs analysis (log-scale). Fixed costs analysis was performed for three different equilibrium population sizes (1 million, 2 million and 4 million). Without estimates for *Wolbachia* rearing facilities, fixed costs from both Mediterranean fruit fly (MedFly) SIT facilities (blue dashed line) and other facilities (purple dashed line) are used for comparison. For facility costs resembling medFly facilities, the optimal facility size has a release capacity of between 120 000 (1 million adult females, red line) and 300 000 (4 million adult females, green line) larvae. For costs resembling non-Medfly facilities, the optimal release capacity is between 150 000 (1 million adult females, red line) and 400 000 (4 million adult females, green line) larvae.

Table 2. Sensitivity of optimal facility capacity to variation in key parameter values, assuming facility costs similar to either Medfly or non-Medfly SIT facilities

Parameter	Low	High
Wolbachia transmission proportion (η) (*Default value* = 1)		
Medfly	**220 000** (0.9)	**260 000** (0.95)
Non-Medfly	**300 000** (0.9)	**340 000** (0.95)
Dengue invasion probability (θ) (*Default value* = 10% per year)		
Medfly	**260 000** (5%)	**140 000** (20%)
Non-Medfly	**400 000** (5%)	**180 000** (20%)
Transmission parameter (mosq. to human) (B_{MH}) (*Default value* = 0.278)		
Medfly	**200 000** (0.2502)	**200 000** (0.3058)
Non-Medfly	**240 000** (0.2502)	**240 000** (0.3058)
Wolbachia fitness cost (α) (*Default value* = 0.15)		
Medfly	**190 000** (0.135)	**240 000** (0.165)
Non-Medfly	**200 000** (0.135)	**250 000** (0.165)
Marginal cost of release (*mc*) (*Default value* = $458)		
Medfly	**200 000** ($412.2)	**200 000** ($503.8)
Non-Medfly	**240 000** ($412.2)	**240 000** ($503.8)

Note: The transmission parameter (B_{MH}), fitness cost (α), and marginal cost of release (*mc*) are varied by ±10%, imperfect Wolbachia transmission (τ) is considered at 90% and 95%, and the dengue invasion probability is increased/decreased by a factor of 2. The equilibrium number of female *Ae. aegypti* was set equal to the human population. For baseline parameters, optimal facility sizes are 200 000 larvae per week (Medfly) and 240 000 (non-Medfly facility costs).

rates[70–73] and human movement patterns.[74,75] Although our model neglects this variation, our key conclusions that *Wolbachia* releases should occur as rapidly as possible and that the size of the local mosquito population should be carefully considered when determining the size of a rearing facility would be expected to hold. We also make the simplifying assumption that releases are occurring in a dengue-free location. Finally, our assumption of a constant hazard rate for dengue introduction is unlikely to be realistic. A nonconstant hazard rate (e.g. seasonally varying) could be included using a more general, nonautomonous form of the Bellman equation. Although this extension deserves follow-up, we expect that the likely effect would be accelerated releases before high-risk seasons and more intermediate releases if risk was sufficiently reduced. However, this would not affect our overall conclusions. Additionally, how risk of dengue introduction changes with time is likely to be context-dependent. These assumptions would affect the cost associated with any dengue outbreak but would again be unlikely to affect our key conclusions. Importantly, the framework that we present is sufficiently flexible to include any level of realism future researchers or policymakers deem appropriate. The only constraint on realism presented by our framework is the computational resources necessary for the large number of simulations required.

Releases of *Wolbachia*-infected *Ae. aegypti* are either ongoing or planned in more than a dozen countries worldwide.[36] The number of regions where releases occur is likely to increase rapidly in the coming years, as evidence of its effectiveness and cost-effectiveness builds and as dengue risk increases in the coming decades.[1,6,10] Evaluation of current release programs has suggested that they were cost-efficient for dengue reduction according to WHO guidelines,[76] cost-effectiveness can be further improved through the design of optimal release strategies that are tailored to, and informed by the ecology of, the targeted area. Reducing costs will be even more important as releases begin in more economically constrained regions and when deployed at larger scales. The framework presented here represents a significant step towards designing release programs that can reduce incidence while also minimizing costs, and the flexibility of the modeling framework allows for its adaptation to a variety of settings. We have also shown that, as these programs are being set-up, a key consideration will be the choice of facility size, which should be tailored to the size of the local mosquito population.

We have presented a framework for designing an optimal release strategy for *Wolbachia*-infected mosquitoes for dengue control. Using an example of releases occurring in a city where the expected time until a dengue outbreak is 10 years, we have shown that the optimal strategy is to release *Wolbachia*-infected mosquitoes as quickly as possible to thwart the potential outbreak. Additionally, we have shown that the choice of facility size is key for designing a cost-effective release program. These results highlight the low costs associated with releases of *Wolbachia*-transinfected mosquitoes, especially compared to potential dengue outbreaks. Although this framework represents a significant advancement in the design of optimal release programs, it should be further improved through the inclusion of biological realism tailored to potential release areas. In addition, the importance placed on the choice of facility size, combined with the short timeframe for releases, suggests that the design of nonpermanent or movable facilities will be vital to reducing costs associated with releases.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in OpenICPSR at https://www.openicpsr.org, reference number 198746.

SUPPORTING INFORMATION

Supporting information may be found in the online version of this article.

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