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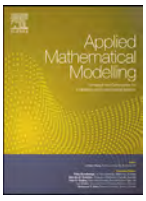

Wolbachia-based biocontrol for dengue reduction using dynamic optimization approach

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ABSTRACT

Aedes aegypti females mosquitoes are the principal transmitters of dengue and other arboviral infections. In recent years, it was disclosed that, when deliberately infected with *Wolbachia* symbiont, this mosquito species loses its vectorial competence and becomes less capable of transmitting the virus to human hosts. Thanks to this important discovery, *Wolbachia*-based biocontrol is now accepted as an ecologically friendly and potentially cost-effective method for prevention and control of dengue and other arboviral infections. In this paper, we propose a dengue transmission model that accounts for the presence of wild *Aedes aegypti* females and those deliberately infected with *wMelPop Wolbachia* strain, which is regarded as the best blocker of dengue and other arboviral infections. However, *wMelPop* strain of *Wolbachia* considerably reduces the individual fitness of mosquitoes, what makes rather challenging to achieve the gradual extrusion of wild mosquitoes and ensure their posterior replacement by *Wolbachia*-carriers. Nonetheless, this obstacle have been overcome by employing the optimal control approach for design of specific intervention programs based on daily releases of *Wolbachia*-carrying mosquitoes. The resulting optimal release programs ensure the population replacement and eventual local extinction of wild mosquitoes in the finite time and also entail a significant reduction in the number of expected dengue infections among human hosts under the long-term settings.

1. Introduction

The invasive peridomestic species of mosquito, *Aedes aegypti*, is widely spread in all tropical and sub-tropical regions worldwide and its abundance is strongly correlated with persistence of dengue and other arboviral infections in human populations [1]. In the absence of effective vaccine against dengue, the disease control efforts are usually centered on reduction of the local mosquito density through the use of chemical substances (larvicides, insecticides) and mechanical elimination of mosquito breeding sites.

On the other hand, dengue virus is transmitted by *Aedes aegypti* females during their blood meals taken on human hosts. Therefore, the infection spread can also be controlled by reducing the virus transmissibility. The latter is possible when

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virus transmitters (i.e., *Aedes aegypti* females) carry an intracellular bacterial symbiont of *Wolbachia*[1] [3–8]. When present in mosquito organism, *Wolbachia* thwarts the virus ability to replicate and to reach the virus concentration sufficient for its transmission towards human hosts during blood-feeding. Additionally, *Wolbachia* is maternally transmitted from female mosquitoes to their eggs, and further to all offspring (males and females). The latter, together with a particular reproductive phenotype induce by *Wolbachia* and known as *cytoplasmic incompatibility*[2], facilitates the spread of *Wolbachia* infection in wild mosquito populations by conferring a certain reproductive advantage to *Wolbachia*-carrying females.

Due to the above mentioned properties, *Wolbachia*-based biocontrol has been proposed by different scholars as an alternative method for reduction of dengue and other arboviral infections among human hosts [3–12].

The essence of *Wolbachia*-based biocontrol consists in reaching the so-called "population replacement", i. e., gradual extrusion of wild mosquitoes (fully capable of transmitting the virus to human hosts) and their posterior substitution by *Wolbachia*-carrying mosquitoes whose vector competence is drastically reduced. Three major *Wolbachia* strains – *wMel, wAlb*, and *wMelPop* – are under test trials for prevention and control of arboviral infections [8,12]. Potential utility of these strains is usually measured in terms of their abilities to reduce the vector competence of mosquitoes versus the underlying fitness costs. Many scholars point out that *wMelPop* strain confers stronger inhibition of virus replication in *Aedes aegypti* mosquitoes than other two strains (*wMel, wAlb*) and, therefore, this strain is regarded as the most beneficial for prevention and control of dengue and other arboviral infections [5,6,8,10,13].

On the other hand, *wMelPop* strain exhibits higher fitness costs since it reduces the female fecundity, the viability of eggs, and the lifespan of its carriers to a greater extent than other two *Wolbachia* strains [14–18]. Therefore, inundative release programs of periodic character (which were originally designed for establishing the more fitful *wMel* strain in wild *Aedes aegypti* populations) may not render the desired result. Indeed, prior attempts to establish *wMelPop*-carrying *Aedes aegypti* mosquitoes in Australia and Vietnam by periodic inundative releases have been reported as unsuccessful [19,20]. Thus, dealing with reduced fitness of mosquitoes transinfected[3] with *wMelPop Wolbachia* strain is a challenging task that inspired us to seek for distinctive release programs capable of establishing *wMelPop Wolbachia* strain in local populations of wild *Aedes aegypti* mosquitoes with the ultimate goal to reduce the morbidity of dengue among local human residents.

In this paper, we propose an ODE model that describes dengue transmission in some locality where wild and *Wolbachia*-carrying mosquitoes are simultaneously present (Section 2). This model can be viewed as a combination of traditional dengue transmission model (introduced by [22]) and competitive population dynamics of wild and *Wolbachia*-carrying female mosquitoes (developed by Campo-Duarte et al. [23]). In the absence of *Wolbachia*-carrying mosquitoes, this model evolves towards its endemic steady state that implies persistence of the disease among human hosts.

For the present study, we have deliberately chosen the simplest dengue transmission model in order to obtain more visible results. However, we are well aware of the existence of more sophisticated models assessing the effects of *Wolbachia* in dengue dynamics. In particular, it is worth mentioning the models with exposed classes for mosquitoes and human hosts that also include time delay in mosquito reproduction [24], models accounting for aquatic stages of mosquitoes [25], and even multi-patch models incorporating human mobility in the presence of wild and *Wolbachia*-carrying mosquitoes [26].

Further, we introduce an exogenous variable (control function) that stands for the number of *Wolbachia*-carrying mosquitoes to be released daily in the target locality. Using this variable we seek to redirect the system evolution towards the disease-free steady state by gradually replacing the wild mosquitoes (capable of transmitting dengue) with *Wolbachia*-carrying ones whose vectorial capacity is very limited. Thus, in Section 3 we formulate the problem of optimal control whose underlying solution should determine the optimal release program that guarantees the population replacement in shortest time. Additionally, we also seek to minimize the disease incidence among human hosts and the total costs of control intervention. In other words, the resultant optimal control problem deals with multi-criteria dynamic optimization where each particular criterion has a certain priority expressed by underlying weight coefficients. The formal solution of the optimal control problem is found by applying the Pontryagin's maximum principle while leaving the weight coefficients unfixed.

Section 4 presents the numerical solution of the optimal control problem formulated in the preceding section, provides the interpretation of simulation results, and discusses several key issues regarding implementation of control intervention programs based on daily releases of *Wolbachia*-carrying mosquitoes. In particular, we address the existence of a certain tradeoff between the expected length of control intervention and the capacity for rearing of *Wolbachia*-carrying mosquitoes. Additionally, we experiment with formalizing priorities for multiple goals and seek for an answer to the following question. To achieve the best result for long-term disease control, is it more urgent to minimize the overall number of dengue-infected human hosts or it would be more rational to reach the population replacement in minimum time? The discussion presented in the final part of Section 4 unfolds a straightforward (albeit a bit unexpected) answer to the above question and provides solid rationale in favor of reaching the population replacement in minimum time.

Finally, Section 5 presents the conclusions and some ideas for practical implementation of our results.

[1] More detailed description of *Wolbachia* pathogen and its interaction with mosquitoes is given in the book by Clements [2].

[2] The phenotype of cytoplasmic incompatibility causes inviability of offspring originated from matings between *Wolbachia*-free females and *Wolbachia*-carrying males. However, the offspring of a *Wolbachia*-carrying female always results *Wolbachia*-infected regardless of her mating with either infected or uninfected male [2,8].

[3] By *transinfection* we understand a deliberate infection of wild mosquitoes with *Wolbachia* pathogen taken from other insect species [14,21].

2. Dengue transmission model involving *Wolbachia*

Traditionally, dengue transmission dynamical models comprise Susceptible-Infected (SI) compartments for female mosquitoes or vectors, which act as transmitters of the dengue virus, and Susceptible-Infected-Recovered (SIR) compartments for human hosts (see, e.g. [22] or similar textbooks). When there are two competing groups of mosquitoes, one consisting of wild insects and another comprising *Wolbachia*-carriers, each group of vectors is divided into Susceptible-Infected compartments. Additionally, these two groups of vectors interact between themselves by competing for the same food resources, breeding sites, and mating opportunities. The latter should be reflected in population dynamics model describing mosquitoes' growth.

In Section 2.1, we provide a concise description of the competitive population dynamics model involving wild and *Wolbachia*-carrying female mosquitoes that was proposed and analyzed by Campo-Duarte et al. [23]. Further, this model is used to lay the basis of dengue transmission dynamics (Section 2.2).

2.1. Modeling framework for female mosquitoes

Let $F(t)$ and $W(t)$ denote, respectively, the densities of wild and *Wolbachia*-carrying female mosquitoes present in the target locality at the day t. For the sake of simplicity, let us suppose that at each $t \geq 0$, the number of living male mosquitoes is proportional to the number of living female mosquitoes since the mosquito sex ratio at birth is about 1: 1 [27]. The competitive population dynamics of $F(t)$ and $W(t)$ can be described, according to [23], by the following stylized mathematical model:

$$\begin{aligned}\frac{dF(t)}{dt} &= \left[\Psi_f - \frac{r_f}{K_f}\big(F(t)+W(t)\big)\right]\left(\frac{F(t)}{K_0}-1\right)F(t) - \delta_f F(t)\\ &= \mathscr{Q}_f\big(F(t),W(t)\big)F(t) - \delta_f F(t),\end{aligned} \tag{1a}$$

$$\begin{aligned}\frac{dW(t)}{dt} &= \left[\Psi_w - \frac{r_w}{K_w}\big(F(t)+W(t)\big)\right]W(t) - \delta_w W(t)\\ &= \mathscr{Q}_w\big(F(t),W(t)\big)W(t) - \delta_w W(t).\end{aligned} \tag{1b}$$

The above model accounts for the frequency-dependent Allee effect with respect to wild females, which is essentially attributed to the reproductive phenotype of *cytoplasmic incompatibility* (CI) induced by *Wolbachia* in wild insect populations [2,8]. The former is modeled by the critical depensation term $\left(\frac{F}{K_0}-1\right)$ in the recruitment part of (1a), which is positive when $F(t) > K_0$ and becomes negative when $F(t) < K_0$. This depensation term helps to mimic the frequency-dependent bistability, which is typical for competitive population dynamics of *Wolbachia* invasion [18,28–32], even though the model (1) is not frequency-based. Furthermore, the quantity $K_0 > 0$ is directly related to the so-called "minimum viable population size" (MVPS) of wild females, which is always present (explicitly or implicitly) in population dynamics models comprising the Allee effect. In the absence of *Wolbachia*-carrying females ($F(t) > 0, W(t) = 0$), it is supposed that $0 < K_0 < 1$, while $K_0 > 1$ is assumed otherwise ($F(t) > 0$, $W(t) > 0$).

In the Eq. (1), we use subindexes f and w for denoting the parameters related to population dynamics of the wild and *Wolbachia*-carrying females, respectively. Thus, $\Psi_{\{f,\,w\}} > 0$ denote the natural birth rates of adult female mosquitoes in the absence of density dependence and $\delta_{\{f,\,w\}} > 0$ express their natural mortality rates. Therefore, $r_{\{f,w\}} = \Psi_{\{f,w\}} - \delta_{\{f,w\}} > 0$ stand for the intrinsic growth rates of female mosquitoes, and both populations $F(t)$ and $W(t)$ have (almost) logistic growth altered by their competition for the same breeding sites and food recourses available in the target locality, as well as for mating opportunities (cf. terms inside square brackets in (1)).

It should be recalled that *Wolbachia* reduces the individual fitness of its hosts [2,8,12,14–17], and this outcome is reflected by the following relationship between mosquito-related parameters:

$$\Psi_w < \Psi_f, \quad \delta_w > \delta_f, \quad r_w < r_f, \quad K_w < K_f. \tag{2}$$

First three conditions in (2) mathematically express that wild females are more fertile and live longer than their *Wolbachia*-carrying coevals, whereas the last relationship in (2) is introduced to keep up with the empirical evidence stating that *Wolbachia* reduces the insect density at steady state [33].

A mere glance at the Eq. (1b) reveals that K_w stands for the carrying capacity of *Wolbachia*-carrying females $W(t)$ since this population group grows logistically without exhibiting Allee effect in presence or absence of wild mosquitoes. On the other hand, it is worth noting that $0 < K_0 < K_f$ in (1a) are the key parameters *related* to the MVPS threshold of wild female mosquitoes (denoted by $K_\flat$, cf. formula (3) below) and to their carrying capacity (denoted by K_*, cf. formula (4)). The detailed explanations are provided by Campo-Duarte et al. [23] and we only state here some cardinal results of that work.

Theorem 1. *Theorem [23]Under the conditions (2), dynamical system (1) has four steady states (see Fig. 1) in the region of biological interest* $\mathbb{R}^2_+ \setminus \{(0,0)\}$[4]*, namely:*

[4] Here, we exclude the origin (0,0) since the total extinction of mosquitoes is unrealistic.

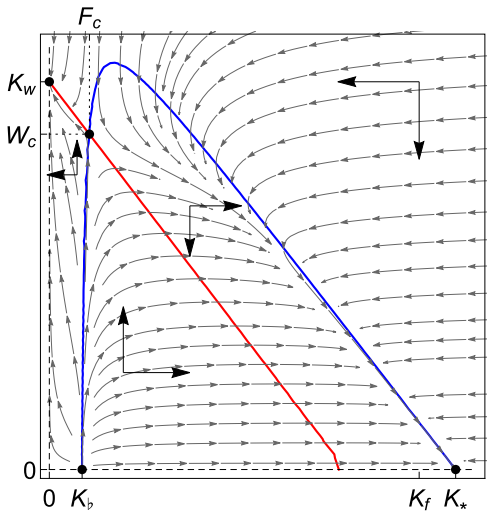


Fig. 1. Directional vector field and phase diagram of the dynamical system (1) in the plane (F, W) and its four steady state (black points); F-isocline is drawn in blue color and W-isocline is given in red color (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

- *one nodal repeller* $(K_\flat, 0)$ *where*

$$K_\flat = \frac{r_f K_0 + \Psi_f K_f - \sqrt{(r_f K_0 + \Psi_f K_f)^2 - 4 r_f K_0 K_f (\Psi_f + \delta_f)}}{2 r_f} > 0 \tag{3}$$

  indicates the MVPS threshold of wild mosquitoes;
- *one saddle point* (F_c, W_c) *of unstable coexistence of both mosquito groups with coordinates given by*

$$F_c = \frac{K_0\left[\Psi_f (K_f - K_w) + \delta_f (K_f + K_w)\right]}{\Psi_f (K_f - K_w) + \delta_f K_w} > 0,$$
$$W_c = K_w - F_c > 0;$$

- *two nodal attractors* $(0, K_w)$ *and* $(K_*, 0)$, *where*

$$K_* = \frac{r_f K_0 + \Psi_f K_f + \sqrt{(r_f K_0 + \Psi_f K_f)^2 - 4 r_f K_0 K_f (\Psi_f + \delta_f)}}{2 r_f} \tag{4}$$

  defines the carrying capacity of wild females.

As shown in Fig. 1, only one of two nodal attractors can be eventually reached according to the choice of initial conditions $F(0) > 0$, $W(0) > 0$ assigned to the system (1), namely:

- If $F(0) > K_\flat$ and $W(0) > 0$ then $(K_*, 0)$ is reachable when $t \to \infty$ and wild mosquitoes persist while *Wolbachia*-carriers become extinct.
- If $F(0) < K_\flat$ and $W(0) > 0$ then $(0, K_w)$ is reachable when $t \to \infty$ and *Wolbachia*-carriers persist while wild mosquitoes become extinct.

The latter fully agrees with the *principle of competitive exclusion* (see, e.g., [34] or other similar textbooks) according to which only one of two competing groups of mosquitoes should ultimately survive.

Additionally, [23] have shown that the following relationships are valid

$$0 < K_0 < K_\flat < K_w < K_f < K_* \tag{5}$$

and it was also detected that the competition system (1) exhibits stiffness.

In the next section we propose a vector-host dengue transmission model where the competitive model (1) describes the population dynamics of two interacting groups of *Aedes aegypti* female mosquitoes.

2.2. *Vector-host model involving* Wolbachia

Dengue virus (DENV) is transmitted when a female mosquito feeds on an infectious human individual and then bites another (susceptible) person. Male mosquitoes never become infected with dengue virus since they do not ingest human blood; therefore, male mosquito populations are usually ignored in the models describing dengue transmission. There is

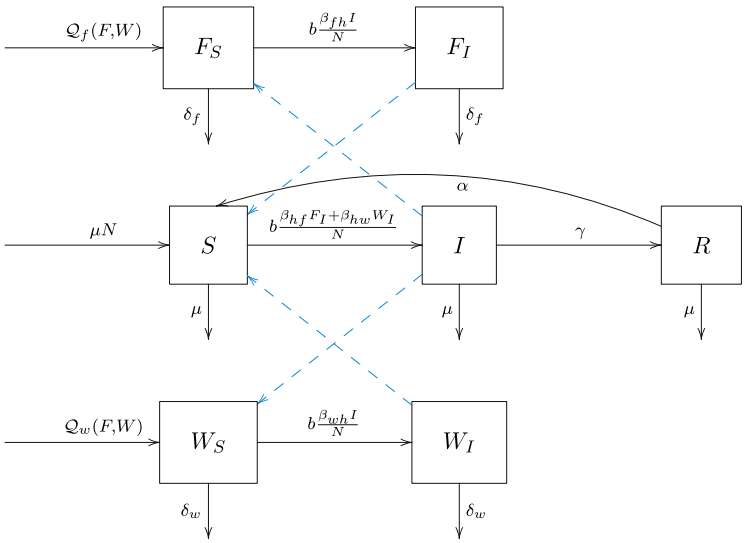


Fig. 2. Block diagram of the dengue transmission model (6) involving wild and *Wolbachia*-carrying vectors

evidence that some *Wolbachia* strains induce resistance to DENV in *Aedes aegypti* [3,5], while other strains may even block this virus [6,10]. In other words, *Wolbachia* slows down (or inhibits) the virus replication within mosquito and reduces the rate of *effective contacts* (i.e., infectious bites) between *Aedes aegypti* females and human hosts.

Suppose that in some target locality, two group of female mosquitoes with variable sizes $F(t)$ and $W(t)$ are present at the day $t \geq 0$ together with a population of human hosts, N, which is assumed essentially invariant in time, that is,

$$N = S(t) + I(t) + R(t) \quad \text{and} \quad \frac{dN}{dt} = 0 \quad \text{for all} \quad t \geq 0.$$

In the above expression, three disjoint compartments of human hosts represent the numbers of susceptible, infectious, and recovered individuals which are denoted by $S(t)$, $I(t)$, and $R(t)$, respectively.

In order to develop the modeling framework of dengue transmission that involves wild and *Wolbachia*-carrying vectors, we suppose that each mosquito subpopulation can be subdivided into two disjoint compartments:

$$F(t) = F_S(t) + F_I(t), \qquad W(t) = W_S(t) + W_I(t),$$

where the subscript S indicates susceptible females mosquitoes (not infected with dengue) and the subscript I indicates dengue-infected females mosquitoes that are capable of transmitting the virus.

Thus, our modeling framework can be regarded as SI-SIR(S) dengue transmission model and its formulation relies upon the following general assumptions:

(i) All populations are homogeneously mixed within the limits of target locality.
(ii) There is no mortality due to the disease neither for human hosts nor for mosquitos.
(iii) Recovered human hosts may get infected only with heterologous DENV strains after losing the temporary cross-immunity.
(iv) Once infected with DENV, the mosquitoes do not recover and die being infectious.
(v) Transovarial or vertical transmission of DENV is ignored.[5]

Under the above assumptions, the combination of traditional vector-host transmission [22] with competitive population dynamics of wild and *Wolbachia*-carrying females (1) results in the dengue transmission model involving wild and *Wolbachia*-carrying vectors which appears in Fig. 2 and can be described by the following system of seven ordinary differential equations:

$$\frac{dS}{dt} = \mu N - b\frac{\beta_{hf}F_I(t) + \beta_{hw}W_I(t)}{N}S(t) + \alpha R(t) - \mu S(t), \tag{6a}$$

$$\frac{dI}{dt} = b\frac{\beta_{hf}F_I(t) + \beta_{hw}W_I(t)}{N}S(t) - (\mu + \gamma)I(t), \tag{6b}$$

[5] A thorough review performed in [35] has failed to find convincing evidence of transovarial DENV transmission in *Aedes aegypti* females claimed by some scholars. Therefore, it is unlikely that an occasionally observed vertical transmission is important for the epidemiological DENV persistence at a local or regional level.

$$\frac{dR}{dt} = \gamma I(t) - (\alpha + \mu)R(t), \tag{6c}$$

$$\frac{dF_S}{dt} = \mathscr{Q}_f(F(t), W(t))F(t) - b\frac{\beta_{fh} I(t)}{N} F_S(t) - \delta_f F_S(t), \tag{6d}$$

$$\frac{dW_S}{dt} = \mathscr{Q}_w(F(t), W(t))W(t) - b\frac{\beta_{wh} I(t)}{N} W_S(t) - \delta_w W_S(t), \tag{6e}$$

$$\frac{dF_I}{dt} = b\frac{\beta_{fh} I(t)}{N} F_S(t) - \delta_f F_I(t), \tag{6f}$$

$$\frac{dW_I}{dt} = b\frac{\beta_{wh} I(t)}{N} W_S(t) - \delta_w W_I(t). \tag{6g}$$

Eq. (6a)–(6c) describe evolution of three human compartments with $\mu > 0$ denoting the demographic inflow and outflow (human birth and death rates) and $\alpha \geq 0$ expressing the rate of loss of the temporary cross-immunity. According to Eq. (6c), human hosts recover from the disease after $1/\gamma$ days and may become susceptible to heterologous DENV strains after $1/\alpha$ days when various DENV serotypes circulate simultaneously in the environment. Thus, $\alpha > 0$ implies the possibility of re-infection and gradual loss of cross-immunity, while $\alpha = 0$ should be supposed in case of strong predominance of one particular DENV strain.[6]

Parameter $b > 0$ plays the key role in the disease transmission and stands for the biting rate, i.e., the number of blood meals (or successful bites) that a female mosquito needs to take on human hosts in average per day for maturing her eggs. There is evidence that aging *Wolbachia*-carrying females may experience difficulties in obtaining a blood meal; however, such difficulties are "compensated" by an increase in the number of attempting bites [37]. Additionally, [38] found out that the presence of dengue virus within mosquitoes does not affect their biting habits. Therefore, we assume the same biting rate b for all effective contacts between vectors and human hosts (that is, bites taken by either wild or *Wolbachia*-carrying *Aedes aegypti* females and bites received by human hosts).

The DENV pathogen is passed from infectious female mosquitoes F_I and W_I to susceptible human hosts (cf. Eq. (6a)–(6b)) with effective contact rates β_{hf} and β_{hw}, respectively. It is worth noting that the probability for a human individual to become infected after being bitten by an infectious vector (either with or without *Wolbachia*) is basically the same; therefore, it is safe to assume that

$$\beta_{hf} \approx \beta_{hw}. \tag{7}$$

On the other hand, *Wolbachia* reduces or blocks the DENV replication within mosquito and thus suppresses the development of viral load sufficient for transmission. Therefore, the DENV pathogen is passed from infectious human hosts to susceptible mosquitoes F_S and W_S with different probabilities or effective contact rates β_{fh} and β_{wh} (cf. Eq. (6d)–(6g)), and it is plausible to assume that

$$\beta_{fh} > \beta_{wh} \tag{8}$$

since *Wolbachia* reduces the virus transmission ability in mosquitoes [3,5,6,8,10].

From the mathematical standpoint, it is easy to see that state variables $\mathbf{X}(t) = \big(S(t), I(t), R(t), F_S(t), W_S(t), F_I(t), W_I(t)\big)$ of the model (6) are defined over the closed and bounded domain $\Omega_{\mathbf{X}} \subset \mathbb{R}^7_+$ given by

$$\Omega_{\mathbf{X}} = \left\{ \mathbf{X} \in \mathbb{R}^7_+ : \quad S(t) + I(t) + R(t) = N, \ 0 \leq F_S(t) + F_I(t) \leq K_*, 0 \leq W_S(t) + W_I(t) \leq K_w \quad \text{for all} \quad t \geq 0 \right\}$$

which is invariant in the sense that all trajectories of (6) parting from $\mathbf{X}(0) \in \Omega_{\mathbf{X}}$ remain in $\Omega_{\mathbf{X}}$ for all $t > 0$. Therefore, it is plausible to affirm that epidemiological system (6) is mathematically well-posed.

In the following section we derive the basic reproductive number for the dengue transmission model (6) and briefly study the asymptotic behavior of its trajectories.

2.3. Analysis of the vector-host model (6)

In epidemiology, the *basic reproduction number* $\mathscr{R}_0$ is a key metric that characterizes the speed of infection spread through a host population. In general terms, $\mathscr{R}_0$ expresses the expected number of secondary infections produced, in a completely susceptible population, by a "typical" infective individual during his/her entire infectiousness period [39].

For compartmental epidemiological models, $\mathscr{R}_0$ can be calculated by identifying the largest eigenvalue or spectral radius of the next-generation matrix evaluated at the disease-free steady state [40,41]. Our dengue transmission model (6) is compartmental, and the next-generation approach is applicable for finding its basic reproductive number $\mathscr{R}_0$.

[6] Thorough rationale of this modeling feature has been provided in [36] (see Remark 1 in that work).

However, system (6) possesses *two* disease-free equilibria engendered by the bistable nature of competitive population dynamics of two mosquito groups (1). As explained in Section 2.1, only one of two mosquito groups $F(t)$, $W(t)$ should ultimately persist in the target locality, whereas either $(0, K_w)$ or $(K_*, 0)$ attracting steady state of (1) can be eventually reached. Using $\phi \in \{0, 1\}$ as a binary variable, two disjoint disease-free steady states of the dengue transmission system (6) can be expressed in the following way:

$$\mathbf{E}_0 = \big(N, 0, 0, \phi K_*, (1-\phi)K_w, 0, 0\big) = \begin{cases} \mathbf{E}_0^F = \big(N, 0, 0, K_*, 0, 0, 0\big) & \text{when} \quad \phi = 1, \\ \mathbf{E}_0^W = \big(N, 0, 0, 0, K_w, 0, 0\big) & \text{when} \quad \phi = 0. \end{cases} \tag{9}$$

Further, application of the next-generation method [41] yields the closed form of the basic reproductive number:

$$\mathscr{R}_0 = \phi \frac{b^2 \beta_{hf} \beta_{fh} \dfrac{K_*}{N}}{(\mu+\gamma)\delta_f} + (1-\phi) \frac{b^2 \beta_{hw} \beta_{wh} \dfrac{K_w}{N}}{(\mu+\gamma)\delta_w} = \phi \mathscr{R}_0^F + (1-\phi)\mathscr{R}_0^W \tag{10}$$

where $\phi \in \{0, 1\}$ is the same binary variable as in (9). Precise details regarding the calculation of $\mathscr{R}_0$ are available in Appendix A.

In the absence of *Wolbachia*-infected mosquitoes ($\phi = 1$) we have from the closed form (10) that

$$\mathscr{R}_0 = \mathscr{R}_0^F = \frac{b^2 \beta_{hf} \beta_{fh} \dfrac{K_*}{N}}{(\mu+\gamma)\delta_f} \tag{11}$$

which is the basic reproductive number for traditional dengue transmission models of SIR(S)-SI type (see, e.g., [42] or similar textbooks). Here, the numerator and denominator contain parameters referring to the disease transmission and transition, respectively. It should be noted that $\frac{K_*}{N}$ represents the so-called "vectorial density" that expresses the average number of female mosquitoes per one human host.

Alternatively, in the absence of wild mosquitoes ($\phi = 0$), relationship (10) renders

$$\mathscr{R}_0 = \mathscr{R}_0^W = \frac{b^2 \beta_{hw} \beta_{wh} \dfrac{K_w}{N}}{(\mu+\gamma)\delta_w} \tag{12}$$

with a similar interpretation and $\frac{K_w}{N}$ expressing the vectorial density with regards to *Wolbachia*-carrying female mosquitoes. In addition, it holds that

$$\mathscr{R}_0^F > \mathscr{R}_0^W$$

in virtue of the relationships (2), (5), (7), (8).

It is worth recalling that $\mathscr{R}_0$ plays the role of the threshold value governing the stability of disease-free and endemic equilibria of dengue transmission models.[7] Thus, fair assessment of $\mathscr{R}_0$ is helpful for predicting whether or not the disease can spread through a population and, broadly speaking, $\mathscr{R}_0$ marks a certain threshold value in the following conventional sense:

- If $\mathscr{R}_0 < 1$, then an infective human individual produces, in average, less than one secondary infection over the course of his/her infectious period, and the disease eventually dies out.
- If $\mathscr{R}_0 > 1$, then an infective human individual produces, in average, more than one secondary infection, and the disease persists in the host population.

When dealing with two group of vectors capable of transmitting the disease, and taking into account their bistable population dynamics (cf. system (1)), it is expected to have two disjoint endemic equilibria $\mathbf{E}_\sharp^F$ and $\mathbf{E}_\sharp^W$ of the dengue transmission model (6), corresponding to persistence of either $F(t)$ or $W(t)$.

When wild mosquitoes persist in the target locality and *Wolbachia*-carrying mosquitoes become extinct (that is, $F_S + F_I \to K_*, W_S + W_I \to 0$ and $\phi = 1$), the dengue transmission system (6) evolves towards one of the following equilibria:

- A disease-free equilibrium $\mathbf{E}_0^F = (N, 0, 0, K_*, 0, 0, 0)$ if $\mathscr{R}_0 = \mathscr{R}_0^F < 1$.
- An endemic equilibrium $\mathbf{E}_\sharp^F = \big(S_F^\sharp, I_F^\sharp, R_F^\sharp, F_S^\sharp, 0, F_I^\sharp, 0\big)$ if $\mathscr{R}_0 = \mathscr{R}_0^F > 1$.

The components of $\mathbf{E}_\sharp^F$ satisfy the relations $S_F^\sharp + I_F^\sharp + R_F^\sharp = N$, $F_S^\sharp + F_I^\sharp = K_*$ and $\mathbf{E}_\sharp^F$ exists only if its coordinates

$$S_F^\sharp = N - \frac{\alpha+\mu+\gamma}{\alpha+\mu} I_F^\sharp \tag{13a}$$

$$I_F^\sharp = \frac{(\alpha+\mu)N\big(\mathscr{R}_0^F - 1\big)}{C_f(\alpha+\mu) + \mathscr{R}_0^F(\alpha+\mu+\gamma)} \tag{13b}$$

[7] See an exhaustive review on dengue transmission models performed in [43] and references therein.

$$R_F^\sharp = \frac{\gamma}{\alpha+\mu} I_F^\sharp \tag{13c}$$

$$F_S^\sharp = \frac{K_*}{1 + C_f I_F^\sharp / N} \tag{13d}$$

$$F_I^\sharp = \frac{K_* C_f I_F^\sharp / N}{1 + C_f I_F^\sharp / N} \tag{13e}$$

are strictly positive. The latter is true only if $\mathscr{R}_0^F > 1$. Detailed calculations of the coordinates (13) of $\mathbf{E}_\sharp^F$ are presented in Appendix B, and it is worth pointing out that

$$C_f = \frac{b\beta_{fh}}{\delta_f}$$

in expressions (13b), (13d), (13e) stands for the average number of infectious bites $b\beta_{fh}$ taken by a susceptible wild female mosquito on infectious human hosts during her lifespan $1/\delta_f$.

Alternatively, when *Wolbachia*-carrying mosquitoes persist in the target locality and wild mosquitoes become extinct (that is, $F_S + F_I \to 0, W_S + W_I \to K_w$ and $\phi = 0$), the dengue transmission system (6) evolves towards one of the following equilibria:

- A disease-free equilibrium $\mathbf{E}_0^W = (N, 0, 0, 0, K_w, 0, 0)$ if $\mathscr{R}_0 = \mathscr{R}_0^W < 1$.
- An endemic equilibrium $\mathbf{E}_\sharp^W = \left(S_W^\sharp, I_W^\sharp, R_W^\sharp, 0, W_S^\sharp, 0, W_I^\sharp\right)$ if $\mathscr{R}_0 = \mathscr{R}_0^W > 1$.

The components of $\mathbf{E}_\sharp^W$ satisfy the relations $S_W^\sharp + I_W^\sharp + R_W^\sharp = N$, $W_S^\sharp + W_I^\sharp = K_w$ and $\mathbf{E}_\sharp^W$ exists only if its coordinates

$$S_W^\sharp = N - \frac{\alpha+\mu+\gamma}{\alpha+\mu} I_W^\sharp \tag{14a}$$

$$I_W^\sharp = \frac{(\alpha+\mu)N\left(\mathscr{R}_0^W - 1\right)}{C_w(\alpha+\mu) + \mathscr{R}_0^W(\alpha+\mu+\gamma)} \tag{14b}$$

$$R_W^\sharp = \frac{\gamma}{\alpha+\mu} I_W^\sharp \tag{14c}$$

$$W_S^\sharp = \frac{K_w}{1 + C_w I_W^\sharp / N} \tag{14d}$$

$$W_I^\sharp = \frac{K_w C_w I_W^\sharp / N}{1 + C_w I_W^\sharp / N} \tag{14e}$$

are strictly positive. The latter is true only if $\mathscr{R}_0^W > 1$. Detailed calculations of the coordinates (14) of the endemic steady state $\mathbf{E}_\sharp^W$ are given in Appendix B, and it is worth pointing out that

$$C_w = \frac{b\beta_{wh}}{\delta_w}$$

in expressions (14b), (14d), (14e) stands for the average number of infectious bites $b\beta_{wh}$ taken by a susceptible *Wolbachia*-carrying female mosquito on infectious human hosts during her lifespan $1/\delta_w$.

To analyze local stability of four possible equilibria of the dengue transmission model (6), the direct calculation of Jacobian eigenvalues results rather knotty and cumbersome from the computational standpoint. Alternatively, we propose to use Monte Carlo method (see, e.g. [44,45]).

Let us recall that K_* in (13) can be directly calculated from the mosquito population dynamic model (1) using its positive constant parameters Ψ_f, δ_f, K_0, and K_f (cf. formula (4) where $r_f = \Psi_f - \delta_f$). Therefore, the coordinates of all four steady states can be expressed explicitly in terms of fifteen parameters

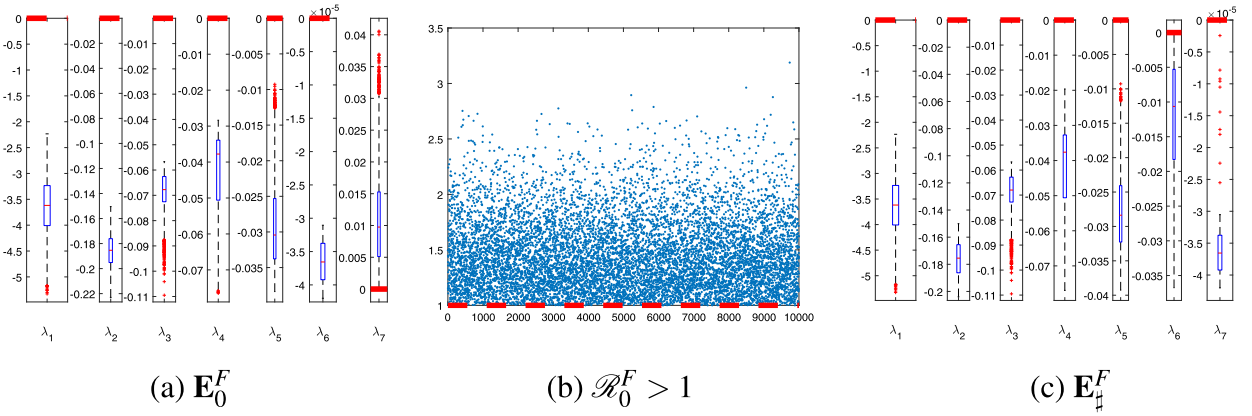
$$\left(\Psi_f, \Psi_w, \delta_f, \delta_w, K_f, K_0, K_w, N, \beta_{hf}, \beta_{hw}, \beta_{fh}, \beta_{wh}, \mu, \gamma, \alpha\right)$$

of the vector-host model (6) whose baseline values are given in Table 1.

The sampling pool $\mathbb{S} = \prod_{i=1}^{15} P_i \in \mathbb{R}_+^{15}$ is defined by a Cartesian product of fifteen closed intervals of the form $P_i = [p_i - \theta p_i, p_i + \theta p_i]$ where each $p_i, i = 1, \ldots, 15$ stands for the baseline value of one parameter (see Table 1) and $\theta > 0$ defines the variation range. Our sampling comprised 10^4 confounding scenarios $S = (s_1, \ldots, s_{15}) \in \mathbb{S}$ where each $s_i \in P_i, i = 1, \ldots 15$ was randomly chosen for $\theta = 0.15$ (that is, with 15% deviation from the baseline values) under uniform distribution with no correlation between parameters. The result of numerical calculations are given in Figs. 3 and 4.

Table 1
Reference values for parameters of the vector-host model (6).

Values	Ranges	Reference
$\mu = 1/(75 * 365)$	$72 - 78$ years	[56]
$N = 2,244,668$		size of Cali, Colombia [57]
$b = 1/3$	[0.15,2]	[46,58,59]
$\Psi_f = 0.326$	[0.2,0.35]	[23,58,60]
$\Psi_w = 0.217$	$\frac{2}{3}\Psi_f$	[14,18,23]
$\delta_f = 0.03$	$[\frac{1}{45}, \frac{1}{15}]$	[46,58,60]
$\delta_w = 0.06$	$2\delta_f$	[14,18,23]
$K_f = 3,367,002$	$[N, 3N]$	assumed as $1.5N$ [36]
$K_w = 3,142,535$		assumed as $1.4N$ [23]
$K_0 = 314,254$		assumed as $0.1K_w$ [23]
$K_\natural = 346,085$		calculated from the expression (3)
$K_* = 3,675,654$		calculated from the expression (4)
$\beta_{hf} = 0.063$	[0,1]	[36,46,61]
$\beta_{hw} = 0.063$	[0,1]	[4,7,37]
$\beta_{fh} = 0.52$	[0,1]	[36,46,61]
$\beta_{wh} = 0.026$	$[0.05\beta_{fh}, 0.1\beta_{fh}]$	[4,7,37]
$\gamma = \frac{1}{7}$	[0.08,0.25]	[36,46,62]
$\alpha = \frac{1}{30}$	$[\frac{1}{56}, \frac{1}{14}]$	[36,63,64]



(a) $\mathbf{E}_0^F$ (b) $\mathscr{R}_0^F > 1$ (c) $\mathbf{E}_\sharp^F$

Fig. 3. *Left and right charts:* Eigenvalue distribution (real parts) corresponding to the disease-free $\mathbf{E}_0^F$ and endemic $\mathbf{E}_\sharp^F$ equilibria when only wild mosquitoes persist. *Central chart:* basic reproduction number $\mathscr{R}_0^F$ in function of trials $n = 1, 2, \ldots, 10^4$.

To guarantee well-posedness of the model, the following conditions

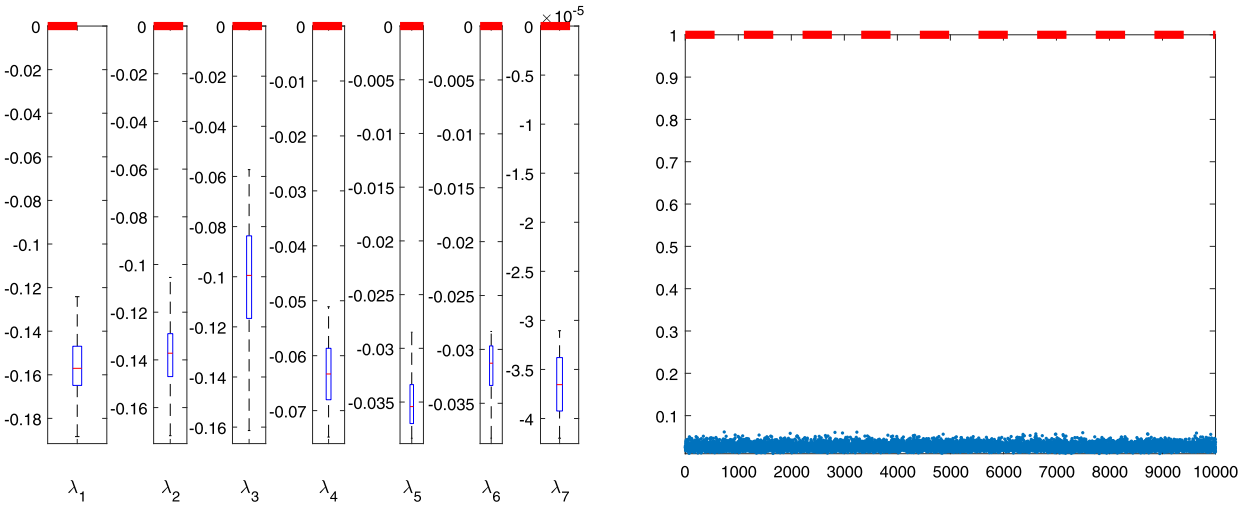
$$K_f > K_w > K_0, \quad \Psi_f > \Psi_w, \quad \delta_f < \delta_w, \quad r_f > r_w > 0, \quad \beta_{fh} > \beta_{wh}$$

have been repeatedly verified before each trial, and 10^4 attested trials were performed. For each trial $n = 1, 2, \ldots, 10^4$ the following actions have been accomplished:

1. Values of $\mathscr{R}_0^F$ and $\mathscr{R}_0^W$ were evaluated according to formulas (11) and (12) and then plotted versus the trial number $n = 1, 2, \ldots, 10^4$ (see Figs. 3(b) and 4(b), respectively).
2. For Jacobian matrices of (6) evaluated in two disease-free steady states, $\mathbf{E}_0^F$ and $\mathbf{E}_0^W$, the real parts of seven eigenvalues were calculated and their distributions were plotted (see Figs. 3(a) and 4(a), respectively).
3. Coordinates of two endemic steady states $\mathbf{E}_\sharp^F$ and $\mathbf{E}_\sharp^W$ were calculated according to formulas (13) and (14) and then tested for positiveness. For attested points, the Jacobian of (6) was evaluated, the real parts of its eigenvalues were calculated, and their distributions were plotted in Fig. 3(c).

It is worth pointing out that only the components of $\mathbf{E}_\sharp^F$ have passed the positiveness test albeit with few exceptions (5 out of 10^4 trials, which can be attributed to rounding errors or numerical precision loss and thus discarded), while the components of $\mathbf{E}_\sharp^W$ completely failed this test for all trials. The latter was quite expectable since for all trial it was obtained that $\mathscr{R}_0^W < 1$.

As shown in the left chart of Fig. 3, one eigenvalue (λ_7) of the Jacobian evaluated in the disease-free equilibrium $\mathbf{E}_0^F$ has strictly positive real part, while the others six $\lambda_i, i = 1, \ldots, 6$ have strictly negative real parts. Therefore, $\mathbf{E}_0^F$ is unstable (saddle point). For endemic equilibrium $\mathbf{E}_\sharp^F$ the situation is different, and it is safe to affirm that $\mathbf{E}_\sharp^F$ is locally asymptotically stable since all its eigenvalues have strictly negative real part (see left chart in Fig. 3). Therefore, when wild mosquitoes conquer the grounds ($W_S(t) + W_I(t) \to 0$), it is expected that solutions of the vector-host model (6) evolve towards $\mathbf{E}_\sharp^F$,



(a) $\mathbf{E}_0^W$ (b) $\mathscr{R}_0^W$

Fig. 4. *Left chart:* Eigenvalue distribution (real parts) corresponding to the disease-free equilibrium $\mathbf{E}_0^W$ when only *Wolbachia*-carrying mosquitoes persist. *Right chart:* basic reproduction number $\mathscr{R}_0^W$ in function of trials $n = 1, 2, \ldots, 10^4$.

which implies persistence of the disease. The latter is corroborated by the fact that $\mathscr{R}_0^F > 1$ for all trials (cf. central chart in Fig. 3).

On the other hand, if *Wolbachia*-carrying mosquitoes manage to invade the target locality by vanquishing the wild ones ($F_S(t) + F_I(t) \to 0$), solutions of the vector-host model (6) would converge towards the disease-free equilibrium $\mathbf{E}_0^W$ which is a unique steady state in such situation due to $\mathscr{R}_0^W < 1$ (cf. right chart in Fig. 4). This steady state is locally asymptotically stable since its underlying eigenvalues have strictly negative real parts as displayed in the left chart of Fig. 4.

From the foregoing, it stems that the disease evolution among human hosts is defined by the type of mosquitoes dominating in the target locality. Namely, the disease persists when wild mosquitoes are dominant ($\mathscr{R}_0 = \mathscr{R}_0^F > 1$ with $\phi = 1$), whereas the predominance of *Wolbachia*-carrying mosquitoes should induce extinction of the disease ($\mathscr{R}_0 = \mathscr{R}_0^W < 1$ with $\phi = 0$). The latter gives a clear idea for reduction of the dengue morbidity and eventual disease eradication in the target locality that consists in the so-called "population replacement" by means of *Wolbachia*-based biocontrol. In other words, the population of wild *Aedes aegypti* is sought to be replaced by *Wolbachia*-carriers within the limits of target locality.

In the following section, we propose the method for reaching the population replacement and local disease eradication in finite time. Our method is based on the dynamic optimization approach and it allows to change the natural evolution of the system (6) from its endemic steady state $\mathbf{E}_\sharp^F$ to the desirable disease-free equilibrium $\mathbf{E}_0^W$ by employing external control intervention measures that consist in inoculative releases of *Wolbachia*-carrying mosquitoes.

3. Optimal control approach and release policies

The optimal control approach requires to define the control variable that mathematically expresses the control action. In our case, let $u(t)$: $[0, T] \mapsto [0, u_{\max}]$ be the number of *Wolbachia*-carriers to be released at the day t in the target locality. Here, $u_{\max} > 0$ stands for the maximum number of *Wolbachia*-infected female mosquitoes available for a daily releases, and this number naturally depends on the production capacity of a laboratory where *Wolbachia*-carrying insects are reared. We also suppose that the overall time $T > 0$ of control action is finite and is left free.

The goal of control intervention consists in reducing the dengue incidence among human residents of the target locality in shortest time and at minimal cost. This can be done by performing daily releases of *Wolbachia*-carrying mosquitoes and thus finally replacing the population of wild *Aedes aegypti* with *Wolbachia*-carrying mosquitoes whose vectorial capacity is very limited. It is worth recalling that population replacement will be reached when *Wolbachia*-carrying mosquitoes invade the target locality while total population of wild mosquitoes drops below its minimum viable population size (or MVPS threshold $K_\flat$ given by formula (3)).

We also know that $K_\flat$ is related to the critical depensation parameter $K_0 > 0$ of the model (1) that describes the population dynamics of wild and *Wolbachia*-carrying mosquitoes. Moreover, it holds that $K_0 < K_\flat$ in virtue of (5). Therefore, it seems reasonable to seek for a minimum time $T^* > 0$ that fulfills the following equality constraint:

$$F(T^*) = F_S(T^*) + F_I(T^*) = K_0 < K_\flat \tag{15}$$

in order to be sure that $F(t) = F_S(t) + F_I(t) < K_\flat$ for all $t \geq T^*$.

In mathematical terminology, the purpose of control action based on inoculative releases of *Wolbachia*-carrying mosquitoes can be formulated in the form of the optimal control problem. Thus, we seek to find an optimal release program

$$u^*(t) \in [0, u_{\max}], \quad t \in [0, T^*] \tag{16}$$

and a minimum time $T^* \in (0, \infty)$ which minimize the objective functional

$$\min_{\substack{0 \le u(t) \le u_{\max} \\ 0 < T < \infty}} J(u,T) = \min_{\substack{0 \le u(t) \le u_{\max} \\ 0 < T < \infty}} \upsilon \Phi\left(F_S(T), F_I(T)\right) + \int_0^T \left[C_1 I(t) + \frac{1}{2}u^2(t) + C_2\right] dt \tag{17}$$

over the set of all possible solutions to the dynamical system

$$\frac{dS}{dt} = \mu N - b\frac{\beta_{hf} F_I(t) + \beta_{hw} W_I(t)}{N} S(t) + \alpha R(t) - \mu S(t) \tag{18a}$$

$$\frac{dI}{dt} = b\frac{\beta_{hf} F_I(t) + \beta_{hw} W_I(t)}{N(t)} S(t) - (\mu + \gamma) I(t) \tag{18b}$$

$$\frac{dR}{dt} = \gamma I(t) - (\alpha + \mu) R(t) \tag{18c}$$

$$\frac{dF_S}{dt} = \mathscr{Q}_F(F(t), W(t)) F(t) - b\frac{\beta_{fh} I(t)}{N} F_S(t) - \delta_f F_S(t) \tag{18d}$$

$$\frac{dW_S}{dt} = \mathscr{Q}_W(F(t), W(t)) W(t) - b\frac{\beta_{wh} I(t)}{N} W_S(t) - \delta_w W_S(t) + u(t) \tag{18e}$$

$$\frac{dF_I}{dt} = b\frac{\beta_{fh} I(t)}{N} F_S(t) - \delta_f F_I(t) \tag{18f}$$

$$\frac{dW_I}{dt} = b\frac{\beta_{wh} I(t)}{N} W_S(t) - \delta_w W_I(t) \tag{18g}$$

with initial conditions

$$S(0) = S_F^0, I(0) = I_F^0, R(0) = R_F^0, \tag{19a}$$

$$F_S(0) = F_S^0, W_S(0) = W_S^0, F_I(0) = F_I^0, W_I(0) = W_I^0 \tag{19b}$$

satisfying the relationships

$$S(0) + I(0) + R(0) = N, \quad F_S(0) + F_I(0) \le K_*.$$

Let us briefly address the meaning of the objective functional $J(u, T)$ given by (17). The scalar function $\Phi : \mathbb{R}_+^2 \mapsto \mathbb{R}_+$ in the terminal part of (17) has the following form:

$$\Phi\left(F_S(T), F_I(T)\right) = \left(F_S(T) + F_I(T) - K_0\right)^2. \tag{20}$$

Thus, the global minimum of Φ is obviously zero and it is attained exactly at $t = T^* > 0$ that satisfies the endpoint constraint (15). The penalty parameter $\upsilon > 0$ in the terminal part of $J(u, T)$ must be sufficiently large in order to assign the highest priority to the population replacement and thus guarantee eventual extinction of wild mosquitoes within the limits of target locality.

The integral part of $J(u, T)$ refers to minimization of three different objectives, namely:

- all dengue infections acquired during $[0, T]$ by human hosts residing in the target locality $\left(\int_0^T I(t)dt\right)$;
- the cumulative control effort over the period $[0, T]$ that basically refers to the rearing of *Wolbachia*-carrying mosquitoes in laboratory conditions $\left(\int_0^T \frac{1}{2}u^2(t)dt\right)$;
- the overall time of control intervention, $\left(\int_0^T dt\right)$.

Additionally, there are two weight coefficients (C_1, $C_2 > 0$) in the integrand of (17), and by varying their values together with that of $\upsilon > 0$ in the terminal part of $J(u, T)$, one can reflect different priorities of the decision-making.

It is worth pointing out that in the formulation of optimal control problem (16)–(19) we have assumed no linear relationship between the coverage of control actions and their underlying costs. Under this assumption, the integrand function in (17) is quadratic with respect to $u(t)$. The latter implies that the *marginal cost* of the control action is proportional to the number of Wolbachia-carriers $u(t)$ to be released at day t in the target locality. This approach is rather common in dynamic optimization engaging population dynamics, and its justifications can be consulted in numerous works (see, e.g., [23,29,30,46]).

The problem of minimizing the objective functional (17) subject to dynamical constraints (18) with initial conditions (19) can be solved by applying the variant of Pontryagin maximum principle adopted for optimal control problems with free terminal time [47,48]. Moreover, existence of the optimal control for sufficiently large $u_{\max}$ can be assured by virtue of three important features of the problem (16)–(19): linearity of the ODE system (18) in u, convexity of the integrand in (17) with respect to u, and compactness of state domain $\Omega_{\mathbf{X}} \subset \mathbb{R}^7_+$ for any finite $0 < T < \infty$ (see formal proofs and further details in the book [49]).

To formulate the maximum principle, let us define the Hamiltonian function:

$$\begin{aligned} H(\mathbf{X}, u, \lambda) = & -C_1 I - \frac{1}{2}\, u^2 - C_2 \\ & + \lambda_1 \cdot \left[\mu N - b\frac{\beta_{hf} F_I + \beta_{hw} W_I}{N} S(t) + \alpha R - \mu S) \right] \\ & + \lambda_2 \cdot \left[b\frac{\beta_{hf} F_I + \beta_{hw} W_I}{N(t)} S - (\mu + \gamma) I \right] \\ & + \lambda_3 \cdot [\gamma I - (\alpha + \mu) R] \\ & + \lambda_4 \cdot \left[\mathscr{Q}_F(F, W) F - b\frac{\beta_{fh} I}{N} F_S - \delta_f F_S \right] \\ & + \lambda_5 \cdot \left[\mathscr{Q}_W(F, W) W - b\frac{\beta_{wh} I}{N} W_S - \delta_w W_S + u \right] \\ & + \lambda_6 \cdot \left[b\frac{\beta_{fh} I}{N} F_S - \delta_f F_I \right] \\ & + \lambda_7 \cdot \left[b\frac{\beta_{wh} I}{N} W_S - \delta_w W_I \right] \end{aligned} \tag{21}$$

where $\mathbf{X} = (S, I, R, F_S, W_S, F_I, W_I)' = (X_1, X_2, \ldots X_7)' \in \Omega_{\mathbf{X}}$ is the vector of state variables and $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7)' \in \mathbb{R}^n$ stands for the vector of adjoint variables or Lagrange multipliers.

Let (u^*, T^*) be an optimal pair in the sense that $u^*(t)$ is a piecewise continuous real function with domain $[0, T^*]$ and range $[0, u_{\max}]$ and $J(u^*, T^*) \leq J(u, T)$ for all other controls u and times T. Let $\mathbf{X}^*(t) = \mathbf{X}(t, u^*(t))$ be the corresponding state defined for all $t \in [0, T^*]$. Then there exists a piecewise differentiable adjoint function $\lambda : [0, T^*] \mapsto \mathbb{R}^7, i = 1, 2, \ldots 7$ satisfying the adjoint ODE system

$$\frac{d\lambda}{dt} = -\frac{\partial H(\mathbf{X}, u^*, \lambda)}{\partial \mathbf{X}}, \tag{22}$$

with seven transversality conditions

$$\lambda(T^*) = -\upsilon \frac{\partial \Phi}{\partial \mathbf{X}}\bigg|_{T=T^*} \tag{23}$$

while $0 < T^* < \infty$ fulfills that

$$H\Big(\mathbf{X}^*(T^*), u^*(T^*), \lambda(T^*)\Big) = 0. \tag{24}$$

Furthermore, the Hamiltonian (21) has a critical point (maximum[8]) at $u = u^*(t)$, i.e,

$$H\Big(\mathbf{X}^*(t), u^*(t), \lambda(t)\Big) \geq H\Big(\mathbf{X}^*(t), u(t), \lambda(t)\Big)$$

for any admissible $u(t)$: $[0, T^*] \mapsto [0, u_{\max}]$ and for almost all $t \in [0, T^*]$.

[8] One can easily verify that $\frac{\partial^2 H}{\partial u^2} = -1 < 0$ for all admissible $u \in [0, u_{\max}]$.

According to [48], the above condition can be written more comprehensively as

$$\left.\begin{array}{lll} u^*(t) = 0 & \text{if} & \dfrac{\partial H}{\partial u} < 0 \\ 0 < u^*(t) < u_{\max} & \text{if} & \dfrac{\partial H}{\partial u} = 0 \\ u^*(t) = u_{\max} & \text{if} & \dfrac{\partial H}{\partial u} > 0 \end{array}\right\} \tag{25}$$

which is equivalent to the closed form

$$u^*(t) = \max\left\{0, \min\left\{\lambda_5, u_{\max}\right\}\right\} \tag{26}$$

known as the *characterization of optimal control*.

Remark 1. From the economics standpoint, the Pontryagin maximum principle formulated in the form (25) has an interesting interpretation. Effectively, the necessary condition of optimality

$$\frac{\partial H}{\partial u} = -u + \lambda_5 = 0$$

implies that, under optimal release program u^*, the marginal cost of control action (expressed by u, i.e., the number of released *Wolbachia*-carriers) is equal to its marginal benefit (given by λ_5). When marginal cost of the control action becomes higher than its marginal benefit (that is, $\frac{\partial H}{\partial u} < 0$ in (25)), it is optimal to take no action, so we have $u^*(t) = 0$. Alternatively, when marginal cost of the control action is lower than its marginal benefit (that is, $\frac{\partial H}{\partial u} > 0$ in (25)), it is optimal to use all available resources, and we have $u^*(t) = u_{\max}$.

Using the compact form of $u^*(t)$ from (26) we can reduce the original optimal control problem (17)–(19) to a two-point boundary value problem which is also known as *optimality system*. The latter is conformed by fourteen differential equations with fourteen endpoint conditions, namely:

- seven *direct* Eq. (18) where $u(t)$ in (18e) is replaced by its characterization (26);
- seven *adjoint* Eq. (22) with $u(t)$ replaced by its characterization (26);
- seven initial conditions (19) specified at $t = 0$;
- seven transversality conditions (23) specified at $t = T^*$.

The optimal time $0 < T^* < \infty$ is then determined from the optimality condition (24).

The optimality system described above can only be solved numerically due to its non-linearity and high dimension. Traditional techniques[9] for solving the optimality systems and other two-point boundary value problems cannot guarantee the convergence of the numerical algorithm when the final time T is left free. However, the next-generation optimal software package GPOPS-II solver[10] designed for MATLAB platform [52] is fully capable of dealing with free terminal time problems (see a brief description of this feature in Appendix B of the work [30]). This solver does not rely on numerical integration and implements an adaptive combination of direct and orthogonal collocation techniques known as *Radau pseudospectral method* [53]. Due to its adaptiveness, the GPOPS-II algorithm is also applicable of dealing with stiff systems. Therefore, this solver is the most suitable software tool for solving our optimal control problem (17)–(19) whose dynamics (18) exhibits stiffness inherited from the model (1).

4. Numerical results and discussion

In this paper, we will be dealing with *wMelPop* strain of *Wolbachia* which is regarded as the best one for prevention and control of arboviral infections [5,6,10,13]. On the other hand, many scholars have claimed that *wMelPop* strain of *Wolbachia* is difficult to establish in wild *Aedes aegypti* populations because its fitness cost is substantially high [2,8,12,14–18]. The latter makes far more challenging our task of solving the optimal control problem (17)–(19).

4.1. Preliminary settings

In accordance with scientific evidence available in literature with regards to *wMelPop Wolbachia* strain, Table 1 displays numerical values assigned to all constant parameters of the dengue transmission model (18), including those corresponding

[9] Here we understand by "traditional techniques" the so-called *forward-backward sweep methods* [48], *shooting methods* [50], and *direct collocation methods* [51].

[10] For more information regarding GPOPS-II solver please visit http://gpops2.com/

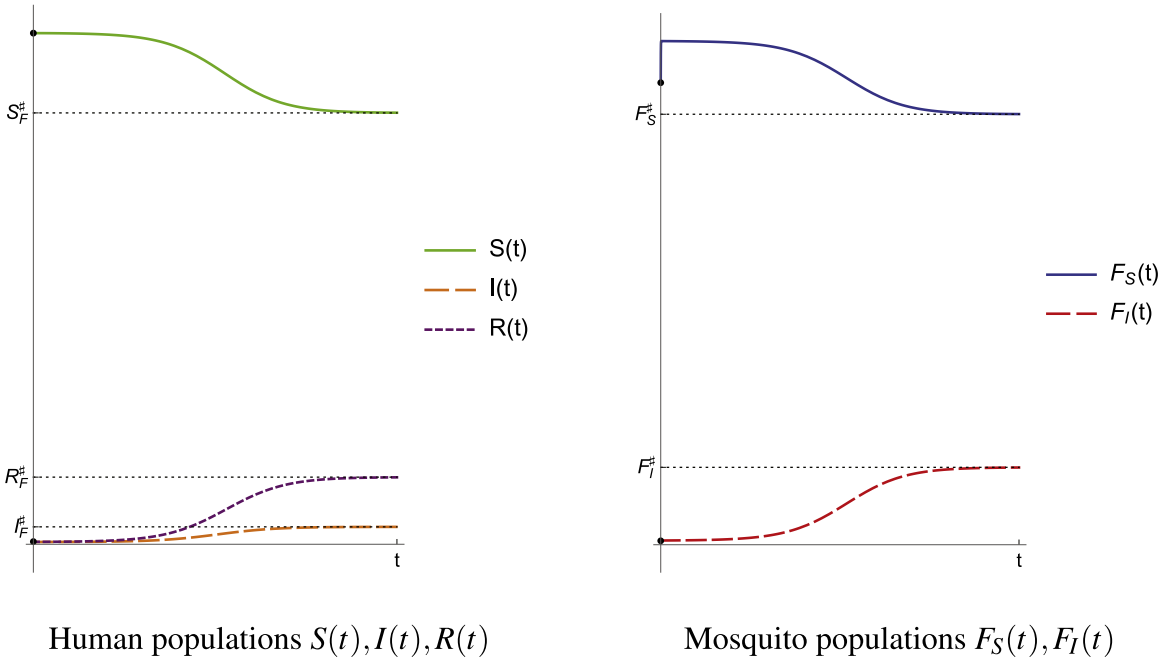


Fig. 5. Asymptotic behavior of the vector-host model (18) with initial conditions (27) and $u = 0$

to the competition system (1). Here, birth and death rates (Ψ_f, Ψ_w, δ_f, δ_w, μ), and the rates related to dengue transmission and transition (β_{hf}, β_{hw}, β_{fh}, β_{wh}, α, γ) are measured in day^{-1} while N, K_f, K_0, and K_w are expressed in terms of the numbers of individuals (human hosts and mosquitoes).

To make our simulations more realistic, we assume that N matches exactly the total size of Santiago de Cali, one of the principal Colombian cities which is considered hyperendemic with regards to dengue morbidity [54,55]. Additionally, we choose initial conditions for human-related states $S(0)$, $I(0)$, $R(0)$ in accordance with average daily prevalence of dengue in Santiago de Cali[11] and suppose that only wild mosquitoes are present in the city before the control intervention. In summary, initial conditions (19) have the following form:

$$S(0) = N - I(0) - R(0), I(0) = 410, R(0) = 494, \tag{27a}$$

$$F_S(0) = K_f - F_I(0), W_S(0) = 0, F_I(0) = 1.5I(0), W_I(0) = 0. \tag{27b}$$

Here, we have assumed that wild mosquitoes are not at equilibrium K_* but reasonably close to it: $F(0) = F_S(0) + F_I(0) = K_f < K_*$. When $t \to \infty$, the model (18) with initial conditions (27) and $u = 0$ predicts asymptotic persistence of the disease and displays that all system trajectories are attracted to the endemic steady state $\mathbf{E}_\sharp^F$ defined by (13) (see Fig. 5). The latter stays in line with the fact that $\mathscr{R}_0 = \mathscr{R}_0^F = 1.39043 > 1$ for numerical values of parameters given in Table 1.

The purpose of control intervention consist in re-directing the system evolution from the endemic steady state $\mathbf{E}_\sharp^F$ to the disease-free steady state $\mathbf{E}_0^W$ by releasing an adequate number of *Wolbachia*-carriers $u(t) \le u_{\max}$ at each day $t \in [0, T^*]$ in the target locality. Here, the maximum capacity $u_{\max}$ of daily releases must be high enough in order to guarantee the existence of solution of the optimal control problem (17)–(19). If $u_{\max}$ is not ample enough, then *Wolbachia*-carriers, due to their reduced fitness, will never reach the frequencies sufficient for their proliferation and eventual invasion.

This situation is illustrated in Fig. 6(a) where $F(t) = F_S(t) + F_I(t)$ and $W(t) = W_S(t) + W_I(t)$ correspond to the populations of wild and *Wolbachia*-carrying mosquitoes, respectively, and they were obtained by running the system (18) with small constant daily releases $u(t) = u_{\max} = 5 \times 10^4$ and $t \to \infty$. Thus, Fig. 6(a) plainly indicates that the population of wild mosquitoes will never reach the threshold $K_\flat$ of minimum viable population size (represented by lower dotted line in Fig. 6(a)) no matter for how long the releases are carried on. In this case, the optimal control problem (17)–(19) does not have feasible solution, and higher values of $u_{\max}$ should be tried over.

It is worthwhile to recall that inundative abundant releases of mosquitoes carrying *WmelPop Wolbachia* strain have not rendered desirable results [19,20]. Therefore, the control intervention program $u(t)$ should seek to increase the frequency of *Wolbachia*-carrying insects, not only the total size of population $W(t)$, and this must be done in a more gradual way in order to guarantee the population replacement.

[11] Here, the disease prevalence refers to the number of human hosts who are infectious at an average day t.

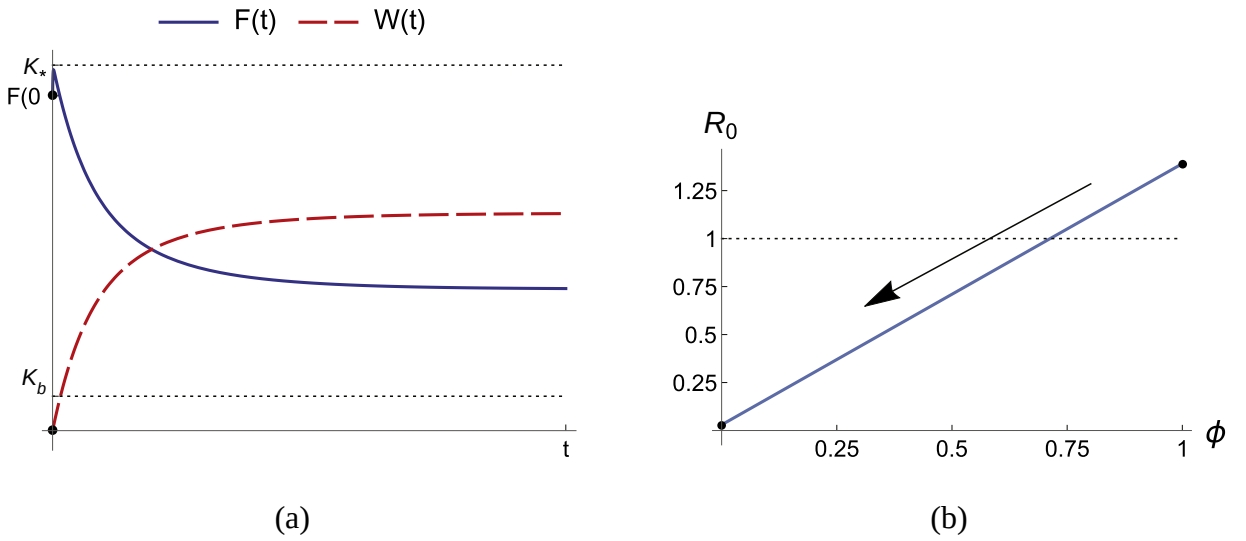


Fig. 6. (a) Evolution of $F(t) = F_S(t) + F_I(t)$ and $W(t) = W_S(t) + W_I(t)$ under constant control $u(t) = u_{\max} = 5 \times 10^4$ when $u_{\max}$ is not high enough; (b) expected changes in $\mathscr{R}_0$ due to releases of *Wolbachia*-carrying mosquitoes.

As *Wolbachia*-carrying mosquitoes are gradually released in the target locality, the overall dengue transmission is expected to slow down, and less number of secondary infections should be produced by each infective human host. In other words, under the release program $u(t)$, the basic reproductive number $\mathscr{R}_0$ given by (10) will be gradually reduced from $\mathscr{R}_0^F = 1.39043 > 1$ (when $\phi = 1$) to $\mathscr{R}_0^W = 0.0297191 < 1$ (when $\phi = 0$). The latter should guarantee eventual evolution of the controlled system (18) towards the disease-free steady state $\mathbf{E}_0^W$ followed by the local extinction of the disease. This situation is schematically[12] illustrated in Fig. 6(b) where the value of $\mathscr{R}_0$ declines with an increase in frequency of *Wolbachia*-carrying mosquitoes. This is exactly the outcome we seek to obtain by solution of the optimal control problem, and we aspire to reach this outcome in the minimum time and with minimum number of *Wolbachia*-carrying mosquitoes to be released.

Since the population replacement is the primary goal of the control intervention, we assign the highest priority to this goal by setting

$$\upsilon = 1000$$

in the terminal part of the objective functional (17) for all scenarios, which are described further on.

As mentioned in Section 3, the choice of positive weights C_1 and C_2 in the integral part of the objective functional (17) defines other priorities of the decision-making, and our analysis will be focused on two alternative options that seem the most reasonable in the context of decision-making, namely:

Option A: Reduction of the overall number of human infections is more important than minimization of the total time to reach the population replacement

$$C_1 = 100, \quad C_2 = 10 \quad \text{with} \quad C_1 > C_2.$$

Option B: Time to reach the population replacement is more important than reduction of the overall number of human infections

$$C_1 = 10, \quad C_2 = 100 \quad \text{with} \quad C_1 < C_2.$$

It is worthwhile to note that for both options described above, we suppose that the rearing cost of *Wolbachia*-carrying mosquitoes is normalized to unity for being far less than υ and $C_i, i = 1, 2$.

It can be intuitively perceived that there must exist a certain tradeoff between the expected length T^* of control intervention period and the maximal available capacity $u_{\max}$ of daily releases. In order to identify such a tradeoff, it is plausible to consider four different cases defined in the following way:

Case 1: $u_{\max} = 6 \times 10^4$; **Case 2:** $u_{\max} = 9 \times 10^4$;
Case 3: $u_{\max} = 12 \times 10^4$; **Case 4:** $u_{\max} = 20 \times 10^4$.

[12] Illustration given in Fig. 6(b) is regarded as "schematic" because in this figure the binary variable $\phi \in \{0, 1\}$ is "synthetically" extended to a continuous one, and its domain [0,1] includes all intermediate values.

Ultimately, by coupling two options and four cases we can set up eight different scenarios. Under this setting, **Scenario 1A** combines **Option A** with **Case 1**. All eight scenarios are simulated with the same values of constant parameters given in Table 1 and with the same initial conditions (27).

It is worth noting that GPOPS-II algorithm automatically scales all input intervals $[0, T]$ to the interval $[-1, 1]$ thus allowing to cope with free final time T^* [52]. Therefore, for all internal calculations we have assumed the standard numerical tolerance of 10^{-6} with respect to scaling.

The GPOPS-II solver does not deliver solution to an optimal control problem with unfixed final time unless the optimality condition (24) is satisfied. We acknowledge here that for all numerical experiments presented in Section 4.2 GPOPS-II has found the underlying optimal solutions.

4.2. Numerical solutions of the optimal control problem

Since we deal here with minimum-time problems, it is clear that T^* will delivered by the numerical algorithm together with underlying optimal release program $u^*(t)$ defined on $[0, T^*]$. However, the value of T^* will be different for each scenario. Therefore, we need to establish a "uniformed" observation interval $[0, \hat{T}]$ with $\hat{T}$ greater than any other T^* obtained for all eight scenarios. The optimal release programs $u^*(t)$ defined for $t \in [0, T^*]$ for each particular T^* can be extended to the uniformed observation interval $[0, \hat{T}]$ by the following transformation:

$$\hat{u}^*(t) = \begin{cases} u^*(t), & t \in [0, T^*], \\ 0, & t \in [T^*, \hat{T}]. \end{cases} \tag{28}$$

Here we have accounted for the fact that optimal release program $u^*(t)$ is suspended exactly at $t = T^*$, i.e., when the endpoint condition (15) is fulfilled, and terminal function Φ in $J(u, T)$ achieves its global minimum. Further, optimal state trajectories (. $S^*(t)$, $I^*(t)$, $R^*(t)$, $F_S^*(t)$, $F_I^*(t)$, $W_S^*(t)$, $W_I^*(t)$.) initially delivered by the numerical algorithm as real functions defined for $t \in [0, T^*]$ can also be extended to the uniformed interval $[0, \hat{T}]$ by running the system (18) with corresponding (28).

Using the uniformed interval $[0, \hat{T}]$ we can compare the effects of the optimal release programs on dengue transmission during and after the control intervention.

For better visualization of the control intervention impact on reduction and prevention of dengue morbidity, it is convenient to introduce an auxiliary variable known as *cumulative incidence* and defined as

$$\mathscr{I}_c(t) = \int_0^t I(\tau)d\tau, \tag{29}$$

where $I(\cdot)$ corresponds to the state profile of the system (18) without control intervention. Formula (29) implies that $\mathscr{I}_c(t)$ effectively sums up all new dengue infections acquired by human hosts within the time lapse $[0, t]$ and regardless of their posterior recuperation.

Similarly, we can define

$$\mathscr{I}_c^*(t) = \int_0^t I^*(\tau)d\tau. \tag{30}$$

where $I^*(\cdot)$ corresponds to the state profile of the system (18) under optimal release program $u^*(t)$ or $\hat{u}^*(t)$ expressed by (28). Formula (30) indicates that $\mathscr{I}_c^*(t)$ give the total number of human infections acquired within $[0, t]$ when optimal release program $u^*(t)$ is in action.

Remark 2. An alternative way to evaluate the current value of $\mathscr{I}_c(t)$ is to amend the system (18) with an additional equation and underlying initial condition of the form

$$\frac{d\mathscr{I}_c}{dt} = b\frac{\beta_{hf}F_I(t) + \beta_{hw}W_I(t)}{N(t)}S(t), \quad \mathscr{I}_c(0) = 0 \tag{31}$$

and then solve numerically the system composed by eight ODEs with assigned initial conditions (18), (27), (31).

Using formulas (29) and (30), it is possible to estimate the total number of dengue infections that can be avoided or prevented when optimal release program $u^*(t)$ is implemented. We are interested to assess the number of averted dengue infections, denoted by $\mathrm{ADI}(\hat{u}^*)$, that can be prevented in human hosts during the uniformed observation period $[0, \hat{T}]$:

$$\mathrm{ADI}(\hat{u}^*) = \int_0^{\hat{T}} [I(\tau) - I^*(\tau)]d\tau = \mathscr{I}_c(\hat{T}) - \mathscr{I}_c^*(\hat{T}). \tag{32}$$

This number $\mathrm{ADI}(\hat{u}^*)$ will be the core feature characterizing the *benefit* of the optimal release program corresponding to each scenario, and will help us to perform evaluation and comparison of all scenarios. It is worthwhile to emphasize that, in virtue of formula (32), $\mathrm{ADI}(\hat{u}^*)$ accounts for the number of human infections that are expected to be avoided during and after implementation of the release program $u^*(t)$. In other words, cumulative incidences $\mathscr{I}_c^*(t)$ are solutions of the amended ODE system (18), (27), (31) with control function given by (28) and defined on the uniformed observation interval $[0, \hat{T}]$.

On the other hand, it is also useful to estimate the costs associated with optimal release programs $u^*(t)$ designed for each scenario. Unfortunately, we do not possess any reliable information regarding the costs of the mass-rearing and releases of *Wolbachia*-infected mosquitoes. For that reason, we are unable to compare such costs with conventional outlays for traditional vector control interventions, (e.g., insecticide spraying, mechanical elimination of mosquito breeding sites, etc.). However, a reasonable cost estimation can be done by assessing the total (cumulative) number of *Wolbachia*-carrying mosquitoes that are needed for implementation of the optimal release program $u^*(t)$. This quantity, denoted by NWC(u^*), can be assessed as

$$\mathrm{NWC}(u^*) = \int_0^{T^*} u^*(t)dt = \int_0^{\hat{T}} \hat{u}^*(t)dt. \tag{33}$$

Using an indicator NWC(u^*) and taking into account the maximal daily rearing capacity $u_{\max}$ along with the overall time of factual release campaign T^*, the healthcare managers will be able to assess the underlying costs and then compare them with the costs of traditional measures for mosquito control.

Thus, for each scenario, the optimal release program $u^*(t)$ will be characterized by three important quantities: factual duration of the releases T^*, number of averted dengue infections ADI($\hat{u}^*$), and underlying costs NWC(u^*).

The length of uniformed observation interval $[0, \hat{T}]$ was set as 350 day, that is, $\hat{T} = 350$ for all scenarios. The total number of expected human infections without releasing *Wolbachia*-carrying mosquitoes ($u(t) = 0$) during this observation interval was assessed by calculating the cumulative incidence according to the formula (29): $\mathscr{I}_c(\hat{T}) = 58,283$ dengue cases.

Let us consider first **Option A** which seems more reasonable and thoughtful since this option prioritizes reduction of dengue morbidity among human hosts over the length of intervention. The results of numerical solutions of the optimal control problem (17)-(27), (31) for **Scenarios 1A-3A** are displayed in Fig. 7 by rows.

Charts in the left column present the population dynamics of wild mosquitoes $F^*(t) = F_S^*(t) + F_I^*(t)$ (blue curves) and *Wolbachia*-carrying mosquitoes $W^*(t) = W_S^*(t) + W_I^*(t)$ (red curves), charts in the middle column display the form of optimal release program $\hat{u}^*$, and charts in the right column show the cumulative incidences in absence of control intervention ($\mathscr{I}_c(t)$, red curves) and under optimal release program $\hat{u}^*(t)$ ($\mathscr{I}_c^*(t)$, blue curves).

The outcome of **Scenario 4A** is omitted here since it coincides exactly with that of **Scenario 3A**. The latter has a rational explanation: the optimal control profile designed for **Scenario 3A** never attains its upper border $u_{\max} = 9 \times 10^4$ (see middle chart in last row of Fig. 7). Therefore, any enhancement in the maximum capacity of daily releases $u_{\max}$ is unnecessary for it does not change the optimal release program.

In all charts of Fig. 7 the vertical dashed line $t = T^*$ marks the optimal time of control intervention, meaning that factual releases are suspended for all $t > T^*$. It is worth noting that the population trajectory of wild mosquitoes $F^*(t)$ fulfills the constraint (15) and then declines towards zero. This occurs after suspension of the releases, and it takes about 50 days till eventual extinction of wild mosquito population. Additionally, one can observe that all blue curves in the left column of Fig. 7 (corresponding $F^*(t)$) exhibit inflexion between $t = 50$ and $t = 100$. In other words, the rate of decrease in $F^*(t)$ is higher in the beginning of the intervention than in the end.

Charts in the middle column of Fig. 7 indicate that the initial release has about the same size for all considered values of $u_{\max}$, namely $u^*(0) \approx 5.3 \times 10^4$. Additionally, these charts display that all optimal release programs u^* designed for **Option A** are bell-shaped. The latter agrees with optimal release policies designed in [23] for two-dimensional model (1) that did not involve the dynamics of dengue transmission. Furthermore, optimal release programs designed in [30] for a sex-structured model of mosquito evolution have also resulted bell-shaped.

Regarding the charts in the right column of Fig. 7, it is clear that all release strategies have very positive impact on reduction of dengue morbidity. However, better results are expected when higher capacities $u_{\max}$ of daily releases are available.

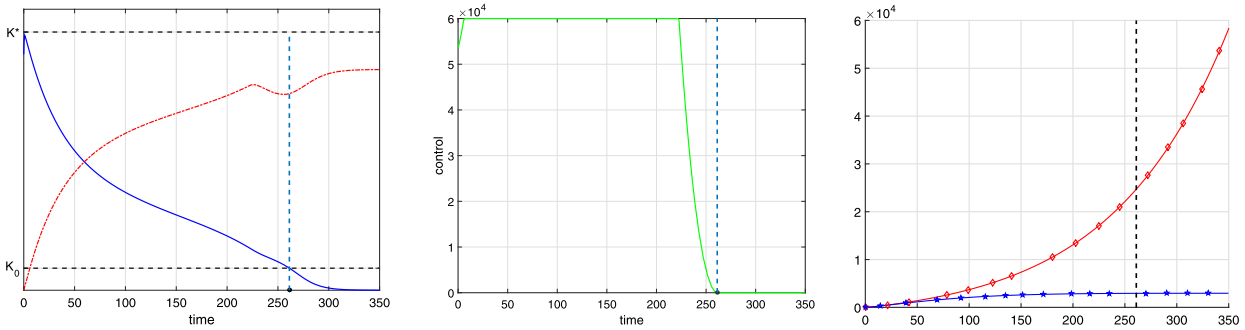
Now let us consider **Option B** that values the promptness of intervention over the reduction of dengue incidence. The results of numerical solutions of the optimal control problem (17)–(27), (31) for **Scenarios 1B-4B** presented in Fig. 8 are organized in a similar way to Fig. 7 and bear the same notations.

The effect of optimal intervention policies over the mosquito population $F^*(t)$ is shown on four charts in the left column of Fig. 8. Note that for $u_{\max} \geq 9 \times 10^4$, the population of wild mosquitoes $F^*(t)$ (blue curves) exhibits a steadier decrease towards the critical value of K_0 than in case of **Scenarios 2A** and **3A**, and this critical value is reached sooner. Moreover, optimal release programs $u^*(t)$ designed for **Option B** have better effect on reduction of dengue transmission than those obtained for **Option A** (see estimations of the expected benefits ADI($\hat{u}^*$) provided in Table 2 for both options). In addition, Table 2 reveals that optimal release programs $u^*(t)$ designed for **Option B** have lower costs than those corresponding to **Option A**, both in term of optimal time T^* and the number of *Wolbachia*-carriers to be reared for intervention.

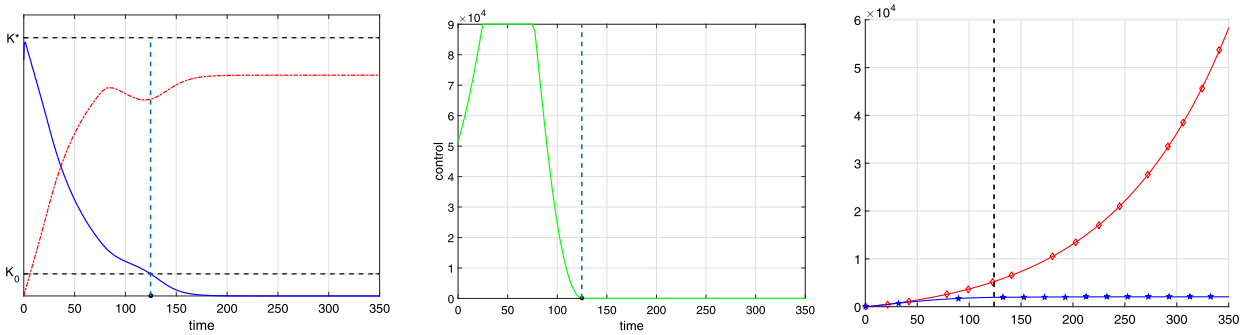
On the other hand, it is easy to observe that by changing the priorities of decision-making from **Option A** to **Option B** the form of optimal release programs $u^*(t)$ is transformed from the bell-shaped to trapezoidal while taking the same values of $u_{\max}$ (cf. shapes of $u^*(t)$ for **Scenarios 1A-3A** versus **Scenarios 1B-3B** in Figs. 7 and 8).

However, the form of $u^*(t)$ corresponding to **Scenario 4B** is still bell-shaped (see the lower chart in the middle column of Fig. 8), while the initial release size is rather large, namely, $u^*(0) \approx 14.2 \times 10^4$. Actually, the mentioned transformation in the form of $u^*(t)$ is quite deceptive and easily explainable if we bear in mind that **Option B** seeks the reduction in the effective time of releases and the latter is attained by increasing the sizes of daily releases. In fact, trapezoidal forms of

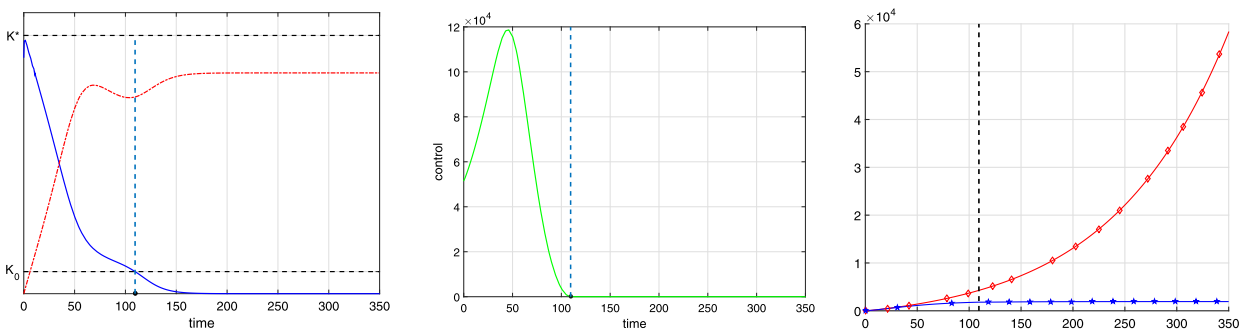
Mosquito dynamics $F^*(t)$ and $W^*(t)$ | *Release program* $\hat{u}^*(t)$ | *Cumulative incidences* $\mathscr{I}_c(t)$ and $\mathscr{I}_c^*(t)$



Scenario 1A: $u_{max} = 6 \times 10^4$, $T^* = 261$



Scenario 2A: $u_{max} = 9 \times 10^4$, $T^* = 124$



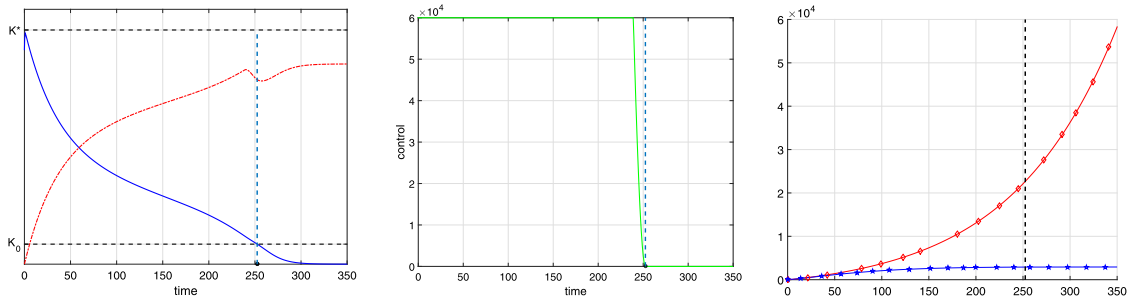
Scenario 3A: $u_{max} = 12 \times 10^4$, $T^* = 109$

Fig. 7. Numerical solutions for **Option A**: $C_1 = 100$ and $C_2 = 10$.

$u^*(t)$ can be viewed as "flattened" bell-shaped mode of the release program when maximum daily release capacity $u_{\max}$ is limited.

The results of numerical experiments displayed by Figs. 7, 8, and Table 2 attest the existence of a certain tradeoff between the effective length of control intervention T^* and the maximal available capacity $u_{\max}$ of daily releases. Namely, higher values of $u_{\max}$ guarantee shorter time T^*. However, this tendency vanishes when the optimal release program $u^*(t)$ becomes plainly bell-shaped as in **Scenarios 3A** and **4B**. In other words, there exists a certain value of $u_{\max}$ above which any additional enhancement in the daily capacity of releases cannot guarantee further reduction of the effective length of control intervention T^*. This value was identified as $u_{\max} = 12 \times 10^4$ for **Option A**, and as $u_{\max} = 20 \times 10^4$ for **Option B**.

Mosquito dynamics $F^*(t)$ and $W^*(t)$ | *Release program* $\hat{u}^*(t)$ | *Cumulative incidences* $\mathscr{I}_c(t)$ and $\mathscr{I}_c^*(t)$



Scenario 1B: $u_{max} = 6 \times 10^4$, $T^* = 252$

Scenario 2B: $u_{max} = 9 \times 10^4$, $T^* = 104$

Scenario 3B: $u_{max} = 12 \times 10^4$, $T^* = 74$

Scenario 4B: $u_{max} = 20 \times 10^4$, $T^* = 54$

Fig. 8. Numerical solutions for **Option B**: $C_1 = 10$ and $C_2 = 100$.

Table 2
Estimations of optimal time T^*, expected benefits (averted dengue infections, ADI), and underlying costs (NWC) for all considered scenarios.

Option A: $C_1 = 100$ and $C_2 = 10$				
Scenario	u_{max}	Time (days)	Benefit (ADI)	Cost (NWC)
1A	6×10^4	261	55,335	1.4098×10^7
2A	9×10^4	124	56,326	7.8666×10^6
3A	12×10^4	109	56,481	7.1447×10^6
Option B: $C_1 = 10$ and $C_2 = 100$				
Scenario	u_{max}	Time (days)	Benefit (ADI)	Cost (NWC)
1B	6×10^4	252	55,358	1.4631×10^7
2B	9×10^4	104	56,505	8.3515×10^6
3B	12×10^4	74	56,888	7.2878×10^6
4B	20×10^4	54	57,167	6.5661×10^6

Let us now analyze the results given in Table 2. First, we compare the outcomes of optimal control programs $u^*(t)$ designed for each option, while considering different values of the maximum capacity of daily releases $u_{\max}$. It is easy to see that an enhancement of $u_{\max}$ has a very positive impact on the performance of optimal release programs $u^*(t)$ which is expressed in lower costs, shorter time of effective intervention, and higher expected numbers of averted human infections for enlarged values of $u_{\max}$. Therefore, mosquito rearing capacity plays the key role for successful and timely interventions under both considered options of decision-making.

On the other hand, it is worthwhile to recall that **Option A** prioritizes the reduction of human dengue infections over the effective time of intervention, while **Option B** has the opposite priorities. Notwithstanding the described priorities, **Scenarios 1A-3A** do not display better results than **Scenarios 1B-3B** in terms of the expected number of averted infections when they are compared for each particular value of $u_{\max} = 12 \times 10^4$ or lower (i.e., **Option A** versus **Option B**). In other words, **Option B** that favors time minimization is more rational and farseeing even though it may seem less heedful than **Option A** at the first glance. Moreover, for $u_{\max} = 20 \times 10^4$ (**Scenario 4B**, bottom row of Table 2) we obtain the best result in term of all considered quantities, that is, the shortest time of intervention, the highest number of avoided human infections, and the lowest cost.

From the foregoing analysis, we can conclude that optimal release programs $u^*(t)$ obtained under **Option B** are trapezoidal and render greater benefits and shorter effective times of intervention, albeit slightly elevated costs, when maximum capacity of daily releases is $u_{\max} = 12 \times 10^4$ or lower. Furthermore, for $u_{\max} = 20 \times 10^4$ or higher the form of optimal release program $u^*(t)$ becomes bell-shaped and this release program provides the best outcomes with regards to the promptness of control intervention, capability for avoiding human infections, and underlying costs.

5. Conclusions

In this paper we have presented a dengue transmission model that accounts for the presence of wild and *Wolbachia*-carrying vector transmitters of DENV pathogen (*Aedes aegypti* female mosquitoes). This model keeps the key properties of other models describing *Wolbachia* invasion in wild mosquito populations, such as bistable dynamics and frequency-dependent Allee effect attributed to the reproductive phenotype of cytoplasmic incompatibility [18,28–32].

On the other hand, our vector-host model agrees with other epidemiological models describing dengue transmission [43] and also allows for natural introduction of *Wolbachia*-based control intervention measures. The latter is modeled by daily releases of mosquitoes carrying *wMelPop* strain of *Wolbachia*, which is considered the most beneficial for prevention and control of dengue infections [5,6,8,10,13], and also the most challenging to establish in wild mosquito populations [16,18–20].

Using the optimal control approach, we have considered several scenarios and designed underlying programs for optimal releases of *Wolbachia*-carrying mosquitoes transinfected with *wMelPop* strain, while varying the daily capacities of releases and considering two alternatives for decision-making priorities. Our simulation results have provided rather interesting and potentially useful insights regarding the practical implementation of release programs, namely:

1. Maximal capacity of daily releases, $u_{\max}$ is virtually related to the effective time of intervention T^*, in the sense that higher $u_{\max}$ ensures shorter T^* (up to some extent, as disclosed by **Scenarios 3A** and **4A**).
2. Optimal release programs $u^*(t)$ that are plainly bell-shaped (neither “truncated” nor “flattened”) ensure shortest intervention time T^* and better “cost-effectiveness” in the sense that a greater number of human infections can be prevented by releasing a smaller quantity of *Wolbachia*-carrying mosquitoes.
3. Promptness of intervention purports a higher number of prevented human infection under the long-term settings, that is, during and after implementation of the release programs.

Last item basically states that it is more reasonable to prioritize the minimization of intervention time T^* over the reduction of the total number of human infections during the period of intervention $[0, T^*]$. Therefore, the rational choice

between **Options A** and **B** should be in favor of **Option B**. The rationale behind this choice is very prudential. As shown in the left columns of Figs. 7 and 8, wild mosquitoes (both susceptible $F_S(t)$ and infected $F_I(t)$) remain in the system for about 50 days after suspension of releases at $t = T^*$ when $F(t) = F_S(t) + F_I(t)$ drops below the MVPS threshold and the terminal-time constraint (15) becomes active. Thus, wild mosquitoes remain in the system for about $T^* + 50$ days until their eventual extinction, and during these $T^* + 50$ days they actively transmit the virus to human hosts. This explains why for shorter T^* it is reasonable to expect less number of human infections under the long-term setting, that is, during the total observation period $[0, \hat{T}] = [0, 350]$.

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Appendix A. Basic reproductive number for vector-host model (6)

To calculate the basic reproductive number for dengue transmission system (6), we employ the next-generation matrix approach, which was originally proposed in [41] and then adapted in [42]. Following this methodology, we define the state sub-vector $\mathbf{Z} \in \mathbb{R}^3_+$ that contains the infective compartments of vectors and human hosts, that is,

$$\mathbf{Z} = \left(I, F_I, W_I\right).$$

Further, we extract from system (6) three differential equations corresponding to the components of $\mathbf{Z}$ writing them as the following sub-system:

$$\frac{d\mathbf{Z}}{dt} = \mathscr{F}(\mathbf{Z}) - \mathscr{V}(\mathbf{Z})$$

where $\mathscr{F}(\mathbf{Z}) \geq \mathbf{0}$ and $\mathscr{V}(\mathbf{Z}) \geq \mathbf{0}$ represent the rates of the disease transmission and transition, respectively:

$$\mathscr{F} = \begin{pmatrix} b\dfrac{\beta_{hf}F_I + \beta_{hw}W_I}{N}S \\ b\dfrac{\beta_{fh}I}{N}F_S \\ b\dfrac{\beta_{wh}I}{N}W_S \end{pmatrix}, \qquad \mathscr{V} = \begin{pmatrix} (\mu+\gamma)I \\ \delta_f F_I \\ \delta_w W_I \end{pmatrix} \tag{A-1}$$

Further, we denote by $F = \mathscr{F}_{\mathbf{Z}}(\mathbf{E}_0)$ and $V = \mathscr{V}_{\mathbf{Z}}(\mathbf{E}_0)$ the Jacobian matrices of (A-1) evaluated at the disease-free steady state $\mathbf{E}_0$ (cf. formula (9)) and thus obtain the following numerical matrices:

$$F = \begin{pmatrix} 0 & b\beta_{hf} & b\beta_{hw} \\ \phi b\beta_{fh}\dfrac{K_*}{N} & 0 & 0 \\ (1-\phi)b\beta_{wh}\dfrac{K_w}{N} & 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \mu+\gamma & 0 & 0 \\ 0 & \delta_f & 0 \\ 0 & 0 & \delta_w \end{pmatrix}$$

According to [39,41], FV^{-1} defines the so-called "next generation matrix" for the dengue transmission model (6):

$$FV^{-1} = \begin{pmatrix} 0 & \dfrac{b\beta_{hf}}{\delta_f} & \dfrac{b\beta_{hw}}{\delta_w} \\ \dfrac{\phi b\beta_{fh}K_*}{(\mu+\gamma)N} & 0 & 0 \\ \dfrac{(1-\phi)b\beta_{wh}K_w}{(\mu+\gamma)N} & 0 & 0 \end{pmatrix}. \tag{A-2}$$

and its dominant eigenvalue (or spectral radius) determines the average number of secondary infections produced by one infective individual at each stage (or generation) of the disease transmission.

In effect, the characteristic polynomial of FV^{-1} is given by

$$\lambda^3 - \left((1-\phi)\frac{b^2\beta_{hw}\beta_{wh}K_w}{\delta_w(\mu+\gamma)N} + \phi\frac{b^2\beta_{hf}\beta_{fh}K_*}{\delta_f(\mu+\gamma)N}\right)\lambda = 0$$

and its three eigenvalues are

$$\lambda_1 = 0,\ \ \lambda_2 = \sqrt{\phi\frac{b^2\beta_{hf}\beta_{fh}K_*}{\delta_f(\mu+\gamma)N} + (1-\phi)\frac{b^2\beta_{hw}\beta_{wh}K_w}{\delta_w(\mu+\gamma)N}},\ \ \lambda_3 = -\lambda_2,$$

whereas spectral radius of (A-2) is

$$\rho(FV^{-1}) = \sqrt{\phi\frac{b^2\beta_{hf}\beta_{fh}}{\delta_f(\mu+\gamma)}\frac{K_*}{N} + (1-\phi)\frac{b^2\beta_{hw}\beta_{wh}}{\delta_w(\mu+\gamma)}\frac{K_w}{N}}.$$

In case of vector-borne diseases, there are two stages involved in the pathogen transmission from one human host to another (human $\rightarrow$ vector and vector $\rightarrow$ human), whereas the largest eigenvalue of the next-generation matrix (A-2) expresses the geometric mean of two secondary infection numbers generated at each stage [42]. Therefore, the basic reproductive number $\mathscr{R}_0$ for the dengue transmission system (6) is calculated as a square of $\rho(FV^{-1})$, that is,

$$\mathscr{R}_0 = \rho(FV^{-1})^2 = \phi\frac{\beta_{hf}\beta_{fh}b^2}{(\mu+\gamma)\delta_f}\frac{K_*}{N} + (1-\phi)\frac{\beta_{hw}\beta_{wh}b^2}{(\mu+\gamma)\delta_w}\frac{K_w}{N} = \phi\mathscr{R}_0^F + (1-\phi)\mathscr{R}_0^W$$

where $\phi \in \{0, 1\}$ is a binary variable.

Appendix B. Endemic steady states of the dynamical system (6)

The coordinates of endemic steady state $\mathbf{E}_\sharp^F = \left(S_F^\sharp, I_F^\sharp, R_F^\sharp, F_S^\sharp, 0, F_I^\sharp, 0\right)$ are positive solutions of the following algebraic system:

$$0 = \mu N - \frac{b\beta_{hf}F_I^\sharp}{N}S_F^\sharp + \alpha R_F^\sharp - \mu S_F^\sharp \tag{B-1a}$$

$$0 = \frac{b\beta_{hf}F_I^\sharp}{N}S_F^\sharp - (\mu+\gamma)I_F^\sharp \tag{B-1b}$$

$$0 = \gamma I_F^\sharp - (\alpha+\mu)R_F^\sharp \tag{B-1c}$$

$$0 = \mathscr{D}_f\left(F_S^\sharp + F_I^\sharp, 0\right)(F_S^\sharp + F_I^\sharp) - \frac{b\beta_{fh}I_F^\sharp}{N}F_S^\sharp - \delta_f F_S^\sharp \tag{B-1d}$$

$$0 = \frac{b\beta_{fh}I_F^\sharp}{N}F_S^\sharp - \delta_f F_I^\sharp \tag{B-1e}$$

Let us express $S_F^\sharp, R_F^\sharp, F_S^\sharp$, and $F_I^\sharp$ as functions of $I_F^\sharp$ and then use Eq. (B-1b) to find the value of $I_F^\sharp$ in terms of the model's parameters.

From Eq. (B-1c) we directly obtain that

$$R_F^\sharp = \frac{\gamma}{\alpha+\mu}I_F^\sharp. \tag{B-2}$$

By summing up Eqs. (B-1a) and (B-1b) and using (B-2) we have

$$S_F^\sharp = N - \frac{\alpha+\mu+\gamma}{\alpha+\mu}I_F^\sharp. \tag{B-3}$$

From Eq. (B-1e) we obtain

$$F_I^\sharp = \frac{b\beta_{fh}}{\delta_f}\frac{I_F^\sharp}{N}F_S^\sharp. \tag{B-4}$$

On the other hand, using $F_S^\sharp + F_I^\sharp = K_*$ together with (B-4) we have

$$K_* = F_S^\sharp + \frac{b\beta_{fh}}{\delta_f}\frac{I_F^\sharp}{N}F_S^\sharp = \left(1 + C_f\frac{I_F^\sharp}{N}\right)F_S^\sharp, \tag{B-5}$$

where $C_f = b\beta_{fh}/\delta_f$ stands for the average number of infectious bites $b\beta_{fh}$ taken by a susceptible wild female mosquito on infectious human hosts during her lifespan $1/\delta_f$. From (B-4) and (B-5) it results that

$$F_S^\sharp = \frac{K_*}{1 + C_f I_F^\sharp/N}, \qquad F_I^\sharp = \frac{K_* C_f I_F^\sharp/N}{1 + C_f I_F^\sharp/N} \tag{B-6}$$

Let us recall that

$$\mathscr{R}_0^F = \frac{b^2\beta_{hf}\beta_{fh}}{(\gamma+\mu)\delta_f}\frac{K_*}{N} = \frac{b\beta_{hf}C_f}{\gamma+\mu}\frac{K_*}{N}$$

and then use expressions (B-3) and (B-6) for $S_F^\sharp$ and $F_I^\sharp$, respectively, within Eq. (B-1b) in order to find the value of $I_F^\sharp \neq 0$ in terms of the model's parameters:

$$I_F^\sharp = \frac{b\beta_{hf}}{\gamma+\mu}S_F^\sharp F_I^\sharp = \frac{b\beta_{hf}}{\gamma+\mu}\left(N - \frac{\alpha+\mu+\gamma}{\alpha+\mu}I_F^\sharp\right)\frac{K_*C_fI_F^\sharp/N}{1+C_fI_F^\sharp/N}.$$

After some computations we finally obtain

$$I_F^\sharp = \frac{(\alpha+\mu)N\left(\mathscr{R}_0^F-1\right)}{C_f(\alpha+\mu)+\mathscr{R}_0^F(\alpha+\mu+\gamma)} \tag{B-7}$$

so that all components of $\mathbf{E}_\sharp^F$ given by formulas (B-3), (B-7), (B-2), and (B-6) coincide with (13) presented in the main text.

The same approach can be used for finding the coordinates of an alternative endemic steady state $\mathbf{E}_\sharp^W = \left(S_W^\sharp, I_W^\sharp, R_W^\sharp, 0, W_S^\sharp, 0, W_I^\sharp\right)$, which are positive solutions of the following algebraic system:

$$0 = \mu N - b\frac{\beta_{hw}W_I^\sharp}{N}S_W^\sharp + \alpha R_W^\sharp - \mu S_W^\sharp \tag{B-8a}$$

$$0 = b\frac{\beta_{hw}W_I^\sharp}{N}S_W^\sharp - (\mu+\gamma)I_W^\sharp \tag{B-8b}$$

$$0 = \gamma I_W^\sharp - (\alpha+\mu)R_W^\sharp \tag{B-8c}$$

$$0 = \mathscr{Q}_w\left(0, W_S^\sharp + W_I^\sharp\right)\left(W_S^\sharp + W_I^\sharp\right) - b\frac{\beta_{wh}I_W^\sharp}{N}W_S^\sharp - \delta_w W_S^\sharp \tag{B-8d}$$

$$0 = b\frac{\beta_{wh}I_W^\sharp}{N}W_S^\sharp - \delta_w W_I^\sharp \tag{B-8e}$$

Here we have expressed $S_W^\sharp, R_W^\sharp, W_S^\sharp$, and $W_I^\sharp$ as functions of $I_W^\sharp$, that is,

$$S_W^\sharp = N - \frac{\alpha+\mu+\gamma}{\alpha+\mu}I_W^\sharp, R_W^\sharp = \frac{\gamma}{\alpha+\mu}I_W^\sharp, \tag{B-9a}$$

$$W_S^\sharp = \frac{K_w}{1+C_wI_W^\sharp/N}, W_I^\sharp = \frac{K_wC_wI_W^\sharp/N}{1+C_wI_W^\sharp/N} \tag{B-9b}$$

and then used Eq. (B-8b) to find the value of $I_W^\sharp \neq 0$ in terms of the model's parameters:

$$I_W^\sharp = \frac{(\alpha+\mu)N\left(\mathscr{R}_0^W-1\right)}{C_w(\alpha+\mu)+\mathscr{R}_0^W(\alpha+\mu+\gamma)}. \tag{B-10}$$

It is worth pointing out that $C_w = b\beta_{wh}/\delta_w$ in (B-9b) and (B-10) expresses the average number of infectious bites $b\beta_{wh}$ taken by a susceptible *Wolbachia*-carrying female on infectious human hosts during her lifespan $1/\delta_w$, and it should be recalled that

$$\mathscr{R}_0^W = \frac{b^2\beta_{hw}\beta_{wh}}{(\gamma+\mu)\delta_w}\frac{K_w}{N} = \frac{b\beta_{hw}C_w}{\gamma+\mu}\frac{K_w}{N}.$$

The final outcome summarized by expressions (B-9) and (B-10) coincide with (14) presented in the main text.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.apm.2020.01.032.

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