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Releasing *Wolbachia*-infected *Aedes aegypti* to prevent the spread of dengue virus: A mathematical study

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ABSTRACT

Wolbachia is a bacterium that is present in 60% of insects but it is not generally found in *Aedes aegypti*, the primary vector responsible for the transmission of dengue virus, Zika virus, and other human diseases caused by RNA viruses. *Wolbachia* has been shown to stop the growth of a variety of RNA viruses in *Drosophila* and in mosquitoes. *Wolbachia*-infected *Ae. aegypti* have both reproductive advantages and disadvantages over wild types. If *Wolbachia*-infected females are fertilized by either normal or infected males, the offspring are healthy and *Wolbachia*-positive. On the other hand, if *Wolbachia*-negative females are fertilized by *Wolbachia*-positive males, the offspring do not hatch. This phenomenon is called cytoplasmic incompatibility. Thus, *Wolbachia*-positive females have a reproductive advantage, and the *Wolbachia* is expanded in the population. On the other hand, *Wolbachia*-infected mosquitoes lay fewer eggs and generally have a shorter lifespan. In recent years, scientists have successfully released these *Wolbachia*-adapted mosquitoes into the wild in several countries and have achieved a high level of replacement with *Wolbachia*-positive mosquitoes. Here, we propose a minimal mathematical model to investigate the feasibility of such a release method. The model has five steady-states two of which are locally asymptotically stable. One of these stable steady-states has no *Wolbachia*-infected mosquitoes while for the other steady-state, all mosquitoes are infected with *Wolbachia*. We apply optimal control theory to find a release method that will drive the mosquito population close to the steady-state with only *Wolbachia*-infected mosquitoes in a two-year time period. Because some of the model parameters cannot be accurately measured or predicted, we also perform uncertainty and sensitivity analysis to quantify how variations in our model parameters affect our results.

1. Introduction

Dengue virus is a leading cause of illness and death in the tropics and subtropics. Global incidence of dengue has grown dramatically in recent decades. About half of the world's population is now at risk. According to World Health Organization (WHO, 2019), as many as 390 million people are infected yearly and an estimated half million people with severe dengue require hospitalization each year, a large proportion of whom are children. About 2.5% of those affected die. Although a

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dengue vaccine has been registered in several countries for use in people 9–45 years of age living in endemic settings, at present, the key method to prevent the transmission of dengue virus is still to control vector mosquitoes (WHO, 2019).

Dengue, Zika and many other diseases such as chikungunya and yellow fever are mosquito-borne and the primary vector is *Ae. aegypti*, although *Aedes albopictus* is also a possible carrier. *Ae. aegypti* can be found in the tropical and subtropical areas across the world. It is a day-biting mosquito very well adapted to humans. Only the female bites to obtain blood to mature their eggs.

It is very difficult to eliminate *Ae. aegypti* because they can lay their eggs in many places such as one's backyard with very little water. The eggs can survive months without water and hatch immediately once water is available. They are also resistant to common insecticides (Lima et al., 2011; Marcombe et al., 2012). These make the control of *Ae. aegypti* using conventional methods very difficult (Achee et al., 2015).

There are currently two novel approaches that showed considerable promise in limiting the spread of dengue by *Ae. aegypti* (Yakob & Walker, 2016). One approach is genetic control by releasing mosquitoes that are engineered with lethal or flightless trait (Labbé, Scaife, Morgan, Curtis, & Alphey, 2012; Thomas, Donnelly, Wood, & Alphey, 2000), and the other approach is development of mosquitoes that are resistant to arbovirus. This paper is concerned with the second approach.

It is known that *Wolbachia* can stop the growth of dengue in mosquitoes (Ferguson et al., 2015; Kamtchum-Tatuene, Joseph, Benjamin, Baylis, & Solomon, 2017). The idea here is to release *Wolbachia*-infected mosquitoes into the mosquito population. Due to cytoplasmic incompatibility, the bacteria are passed on from generation to generation and the percentage of mosquitoes carrying *Wolbachia* grows until it remains high without any further releases. This method is tried in several countries for field release experiments (Frentiu et al., 2014; Hoffmann et al., 2011; O'Neill et al., 2018). Recently, it is found that this method may also be able to stop the spread of Zika virus (Aliota, Peinado, Velez, & Osorio, 2016).

Since releasing *Wolbachia*-infected mosquitoes can be time-consuming and costly to implement, a few mathematical models have been proposed to understand the impact of *Wolbachia* on the transmission of arboviruses (Dorigatti, McCormack, Nedjati-Gilani, & Ferguson, 2018). In this most recent review paper, the authors noted that Hughes and Britton (Hughes & Britton, 2013) investigated the "potential impact of a *Wolbachia* strain with perfect material transmission and CI on the transmission of a single-strain arbovirus", as well as gave other references (Supriatna & Padjadjaran, 2012), (Ndii, Hickson, Allingham, & Mercer, 2015),(Ndii, Allingham, Hickson, & Glass, 2016a), (Ndii, Allingham, Hickson, & Glass, 2016b) that "used simplified compartmental models of dengue transmission to examine similar issues".

In our mathematical model, we consider the bistability of disease-free vs endemic states, proposed a releasing method that utilized optimal control theory and conducted a sensitivity analysis for model parameters. To our knowledge, there has not been a study regarding impact of *Wolbachia* on dengue transmission that contains all three parts. The mathematical model we propose has no analytical solutions but it has five steady state solutions, two of which are locally asymptotically stable and the others are unstable. One of these stable steady-states contains no *Wolbachia*-infected mosquitoes and represents an unfavorable outcome, while all mosquitoes are infected with *Wolbachia* for the other stable steady-state and represents a favorable outcome. We then add a control, $u(t)$, to our model, which represents a *Wolbachia*-infected mosquitoes release method. Applying optimal control theory, we find a release method, $u^*(t)$, which will drive the solutions of the mathematical model close to the favorable steady-state at the end of two years. After that, the *Wolbachia*-infected mosquitoes will continue to expand in the population and eventually all mosquitoes are infected with *Wolbachia*, thus preventing the spread of dengue.

The organization of the paper is as follows. In Section 2, we present our minimal model, parameter values and justify the assumptions we made. In Section 3, we analyze the model and prove that it has five steady-states, two of which are locally asymptotically stable. In Section 4, we explain how to find the optimal control, $u^*(t)$, and illustrate the results with numerical examples. In order to ensure that the release method is feasible in practice, we restrict ourselves to bang-bang control.

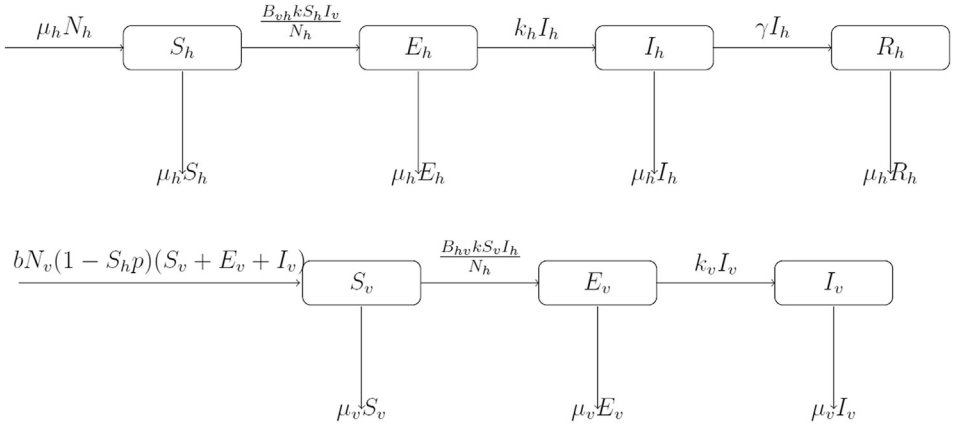

Fig. 1. Transmission diagram of dengue virus among *Ae. aegypti* and humans.

Because there is considerable uncertainty in measuring or estimating some of the model parameters, in Section 5, we perform uncertainty and sensitivity analysis to quantify these uncertainties in our model. The last section is discussion. Additional references will be provided as we move through the technical parts of the paper.

2. Mathematical model

Our model consists of a system of ordinary differential equations, (2.1) illustrated in Fig. 1, with seven state variables: S_h, E_h, I_h, S_v, E_v, I_v and W. We only model female mosquitoes because only female mosquitoes bite to obtain protein to develop and lay their eggs. We assume that there are equal number of male and female mosquitoes and homogeneous mixing.

$$\begin{aligned}
\dot{S}_h &= \mu_h N_h - \frac{B_{vh} k S_h I_v}{N_h} - \mu_h S_h,\\
\dot{E}_h &= \frac{B_{vh} k S_h I_v}{N_h} - \kappa_h E_h - \mu_h E_h,\\
\dot{I}_h &= \kappa_h E_h - \gamma I_h - \mu_h I_h,\\
\dot{S}_v &= b(N_v)(1 - s_h p)(S_v + E_v + I_v) - \frac{B_{hv} k S_v I_h}{N_h} - \mu_v S_v,\\
\dot{E}_v &= \frac{B_{hv} k S_v I_h}{N_h} - \kappa_v E_v - \mu_v E_v,\\
\dot{I}_v &= \kappa_v E_v - \mu_v I_v\\
\dot{W} &= b(N_v)\Big(1 - s_f\Big) W - (\mu_v + D) W + u(t),
\end{aligned} \tag{2.1}$$

In the above model, S_h denotes susceptible humans, E_h denotes exposed but not infectious humans, and I_h denotes infectious humans. The infected humans eventually recover from the illness and form another class R_h. But the recovered humans are permanently immune from the virus, and since the human population size is assumed to be a constant, N_h, there is no need to model R_h separately. The first three equations of (2.1) is a classic SEIR model except that the virus is transmitted by mosquito bites so I_h in the S_h equation is replaced by I_v.

The next three equations form an SEI model for mosquitoes. S_v denotes susceptible mosquitoes, E_v denotes exposed but not infectious mosquitoes, and I_v denotes mosquitoes infected with dengue (but not *Wolbachia*). Mosquitoes do not recover from dengue virus. The last state variable W represents mosquitoes that are infected by *Wolbachia* (but not dengue). We assume there is no co-infection by *Wolbachia* and dengue. (2.1) is a minimal model that includes interactions between mosquitoes and humans and *Wolbachia*-infected mosquitoes.

In our model, we assume per capita emergence rate of mosquitoes (fecundity) is given by the logistic growth function (Edelstein-Keshet, 2005)

$$b(N_v) = max\left\{ b_0\left(1 - \frac{N_v}{K}\right) + \mu_v \frac{N_v}{K},\ 0 \right\}, \tag{2.2}$$

where K is the constant carrying capacity of mosquitoes and $N_v := S_v + E_v + I_v + W$. This is because all mosquitoes compete for resources. Note that unlike N_h, N_v is not a constant and changes over time.

The term $1 - s_h p$ in the equation for S_v, where $p := W/N_v$, models cytoplasmic incompatibility (CI). It is known that offspring of *Wolbachia*-infected females are also infected with *Wolbachia* and viable. CI means that a fraction, s_h, of eggs produced by *Wolbachia*-infected male and uninfected female is not viable. We follow (Hughes & Britton, 2013) to explain how this equation is derived.

We ignore life-cycle (aquatic stages) of mosquitoes. Let

$$\dot{S}_v = birth - rate - \left(\frac{k B_{hv}}{N_h}\right) S_v I_h - \mu_v S_v.$$

Then the rate of addition to wild type mosquitoes is $b(N_v)(S_v + E_v + I_v) + (1 - v) b(N_v)(1 - s_f) W$, where v is fraction of offspring from *Wolbachia*-infected female that are also *Wolbachia*-infected. But not all eggs are going to hatch because of CI. Assuming random mating and equal number of male and female mosquitoes, the probability of inviability is $s_h I_w / N_v$. Therefore,

$$birth - rate = \left(1 - s_h \frac{I_w}{N_v}\right) b(N_v) \left(S_v + E_v + I_v + (1 - v)\Big(1 - s_f\Big) W\right).$$

if we assume CI is 100% successful so that $v = 1$, we obtain the equation for $\dot{S}_v$ in (2.1).

Table 2
Parameter Values. The table shows the range of the parameter values and their meanings used in (2.1). They will be used in our numerical simulations in Sections 4 and 5.

Parameter (unit)	Range	Meaning
B_{vh}	(0.10, 0.75)	Probability of infection from infected mosquito to susceptible human
B_{hv}	(0.10, 0.75)	Probability of infection from infected human to susceptible mosquito
k	(0.33, 1)	Biting rate
K/N_h	(1, 5)	Ratio of mosquitoes population to human population
μ_h (1/years)	(1/76, 1/60)	Human death-rate
μ_v (1/days)	(1/42, 1/8)	Mosquito death-rate
γ (1/days)	(1/12, 1/4)	Human recovery rate
κ_h (days)	(1/10, 1/3)	IIP for humans
κ_v (days)	(1/15, 1/2)	EIP for mosquitoes at 30 °C
b_0 (1/days)	(0.5, 1)	Intrinsic growth rate of mosquitoes
s_f	(0, 0.25)	Reduction in birth-rate for *Wolbachia*-infected mosquitoes
s_h	(0.75, 1)	Reduction in birth-rate due to CI
D (1/days)	(1/20, 1/10)	Death-rate of *Wolbachia*-infected mosquitoes
a	(0.01, 0.10)	Rate of release of *Wolbachia* in fraction of K

There are fitness disadvantages of *Wolbachia*-infected mosquitoes over the wild types: females lay a fraction, $1 - s_f$, of eggs compared to wild types, and encounter an additional per capita mortality rate D. These are reflected in the equation for W in (2.1). The dengue model (first six equations with $W = 0$) and its analysis may be found in the papers (Derouich, Boutayeb, & Twizell, 2003; Manore, Hickmann, Xu, Helen, & Hyman, 2014). See also chapter 2 of (Antonelli, 2015).

Although we strive to construct a minimal model, it is important to include the exposed classes, E_h and E_v, in our model because dengue virus takes some time after the initial infection before it reaches levels in the host when it can be transmitted again to a susceptible agent. This time in humans is known as the intrinsic incubation period (IIP) and ranges from 3 to 10 days for dengue (Chan & Johansson, 2012). The time until the virus is transmissible in mosquitoes is known as the extrinsic incubation period (EIP) and has been found to range from 2 to 15 days (Chan & Johansson, 2012). These incubation periods are significant when compared to the life-span of a mosquito, which for female mosquito is estimated to be between 8 and 48 days. One can avoid exposed classes by using delay equations but delay equations are harder to analyze (Smith, 2011) and the results are the same as using exposed classes.

We have made several simplifications in our model. There are four distinct serotypes of the virus that cause dengue. Recovery from infection by one provides lifelong immunity against that particular serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infection by other serotypes increase the risk of developing severe dengue due to antibody-dependent enhancement (Katzelnick et al., 2017). In this paper, we restrict our consideration to only one serotype. References to models that study two or more serotypes may be found in the review article (Andraud, Niel Hens, Marais, & Beutels, 2012). We do not include life-cycle of mosquitoes in our study to keep the number of equations to a minimum. Otherwise, we will need to build an age-structured model, which will significantly increase the complexity of our model. We also assume that our model parameters are constant, hence no seasonal effects are included in our model. One way to take temperature or rainfall into account is to allow the carrying capacity, K, to be a periodic function of time. Studies suggest that most female *Ae. aegypti* spend their lifetime in or around the places where they emerge as adults and they usually fly an average of 400 m (WHO, 2016). This means that people, rather than mosquitoes, rapidly move the virus within and between communities and places. We ignore spatial migration of humans because its effect is small compared to other environmental factors.

Our model contains 13 parameters: B_{vh}, B_{hv}, k, K/N_h, μ_h, μ_v, γ, κ_h, κ_v, b_0, s_f, s_h and D. The range of values for these parameters are given in Table 2. They are taken from Table 3 of (Manore et al., 2014) except for b_0, s_f, s_h and D, which we estimated. We chose the values for *Ae. aegypti* in (Manore et al., 2014) although *Ae. albopictus* is also a possible carrier. Values of IIP and EIP are taken from (Chan & Johansson, 2012).

The release of *Wolbachia*-infected mosquitoes is model by the bounded piecewise continuous function, $u(t)$, in the last equation of (2.1). We restrict our consideration to the case $u(t)$ takes on only two values: 0 or $a > 0$. This is called a bang-bang control.

Table 3
Parameter values for example 1 with $\alpha = 0.5$.

$\beta_1 = 0.94225366$	$\beta_2 = 0.08016039$	$k = 0.70788728$	$K/N_h = 3.53413624$
$\mu_h = 0.00003904$	$\mu_v = 0.09749953$	$\gamma = 0.14075889$	$\kappa_h = 0.21466300$
$\kappa_v = 0.12951257$	$b_0 = 0.69182424$	$s_f = 0.05536627$	$s_h = 0.98174721$
$D = 0.06030220$	$a = 0.03043562$	$\mathscr{R}_0 = 1.77156218$	$\theta = 0.90$

3. Analysis of the model

We first non-dimensionalize (2.1) by letting $\overline{S}_h = S_h/N_h$, $\overline{E}_h = E_h/N_h$, $\overline{I}_h = I_h/N_h$, $\overline{S}_v = S_v/K$, $\overline{E}_v = E_v/K$, $\overline{I}_v = I_v/K$ and $\overline{W} = W/K$. In terms of these newly defined state variables, (2.1) becomes

$$\begin{aligned}
\dot{S}_h &= \mu_h - \beta_1 S_h I_v - \mu_h S_h,\\
\dot{E}_h &= \beta_1 S_h I_v - \kappa_h E_h - \mu_h E_h,\\
\dot{I}_h &= \kappa_h E_h - \gamma I_h - \mu_h I_h,\\
\dot{S}_v &= b(N_v)(1 - s_h p)(S_v + E_v + I_v) - \beta_2 S_v I_h - \mu_v S_v,\\
\dot{E}_v &= \beta_2 S_v I_h - \kappa_v E_v - \mu_v E_v,\\
\dot{I}_v &= \kappa_v E_v - \mu_v I_v,\\
\dot{W} &= b(N_v)\Big(1 - s_f\Big)W - (\mu_v + D)W + u(t)\ ,
\end{aligned} \tag{3.1}$$

where we have omitted the bar above the state variables for convenience. Also, in (3.1), $\beta_1 = B_{vh}\, kK/N_h$, $\beta_2 = B_{hv}k$ *and* $b(N_v) = \max\{b_1(N_v), 0\}$, where $b_1(N_v) = b_0(1 - N_v) + \mu_v N_v$. This means only the ratio of mosquito carrying capacity to human population size is relevant in our study. The rate of release of *Wolbachia*-infected mosquitoes, a, is also expressed as a fraction of K in (3.1).

We assume that there exists $T > 0$ such that $u(t) = 0$ for $t \geq T$. Let $\mathrm{x}(t)$ be the solutions of (3.1). Then $\mathrm{x}_1(t) = \mathrm{x}(t + T)$ satisfies (3.1) with $u(t)$ replaced by $u(t + T) = 0$ and initial condition $\mathrm{x}_1(0) = \mathrm{x}(T)$. Therefore, we assume that $u(t) = 0$ in the following analysis.

Let $b_0 > \mu_v$ (see Table 2). Then $\frac{db_1(N_v)}{dt} = (\mu_v - b_0)\dot{N}_v = (b_0 - \mu_v)(\mu_v N_v + DW) > 0$ when $b_1(N_v) = 0$. Thus, $b_1(N_v) > 0$ if it is positive initially. Henceforth, we assume that $b(N_v) = b_0(1 - N_v) + \mu_v N_v$.

Since we assume no co-infection, W does not contribute to the spread of dengue. The basic reproduction number is

$$\mathscr{R}_0 = \sqrt{\frac{\beta_1\beta_2\kappa_h\kappa_v}{\mu_v(\mu_h + \kappa_h)(\mu_v + \kappa_v)(\gamma + \mu_h)}}. \tag{3.2}$$

This is proved in Appendix A. The basic reproduction number, $\mathscr{R}_0$, is defined as the expected number of secondary cases produced by a typical infection in a completely susceptible population $\overline{E}_1$ defined below. There is outbreak of the disease if $\mathscr{R}_0 > 1$. The standard method of finding $\mathscr{R}_0$ is the next generation matrix method (Van den Driessche and Watmough, 2002). $\mathscr{R}_0$ was estimated to be around 5 in (Sanches & Massad, 2016) for dengue outbreak. If we allow co-infection, then the basic reproduction number should be smaller. One can argue that μ_v should be replaced by $\mu_v + D$ and B_{hv} is smaller in (3.2) (Hughes & Britton, 2013).

System (3.1) has five steady-states, $\overline{E}_i := (S_h^i, E_h^i, I_h^i, S_v^i, E_v^i, I_v^i, W^i)$, $i = 1, \ldots, 5$. They are constant solutions of (3.1) and are obtained by setting the right hand side of (3.1) to zero and finding all non-negative roots of the system of equations. To define them, let

$$\begin{aligned}
J &:= b_0\Big(1 - s_f\Big) - \mu_v - D,\\
A_1 &:= \mu_h(\beta_1\beta_2\kappa_h\kappa_v - (\mu_h + \kappa_h)(\mu_v + \kappa_v)(\mu_h + \gamma)\mu_v),\\
A_2 &:= \beta_2(\mu_h + \kappa_h)(\beta_1\kappa_v + \mu_h\kappa_v + \mu_h\mu_v),\\
A_3 &:= (\kappa_v + \mu_v)(\beta_2\kappa_h\mu_h + \mu_v(\gamma + \mu_h)(\kappa_h + \mu_h)),\\
\sigma &:= \frac{s_h(D + \mu_v) - \mu_v s_f - D}{s_h\Big(1 - s_f\Big)},\\
B_1 &:= \textit{numerator of second component of } \overline{E}_5,\\
B_2 &:= \textit{denominator of second component of } \overline{E}_5,\\
B_3 &:= \beta_1 s_h\kappa_v\Big(s_f - 1\Big)(\kappa_v + \mu_v)(b_0 - \mu_v)(\mu_v + D) \times \Big(\beta_2\kappa_h\mu_h + \gamma\kappa_h\mu_v + \gamma\mu_h\mu_v + \kappa_h\mu_h\mu_v + \mu_h^2\mu_v\Big).
\end{aligned}$$

then,

$$\begin{aligned}
\overline{E}_1 :=&\quad (1,\ 0,\ 0,\ 1,\ 0,\ 0,\ 0),\\
\overline{E}_2 :=&\quad \left(1,\ 0,\ 0,\ 0,\ 0,\ 0,\ \frac{J}{\left(b_0-\mu_v\right)\left(1-s_f\right)}\right),\\
\overline{E}_3 :=&\quad \left(1,\ 0,\ 0,\ \frac{J\sigma}{(D+\mu_v)(b_0-\mu_v)},\ 0,\ 0,\ \frac{\left(\mu_v s_f+D\right)J}{s_h\left(b_0-\mu_v\right)\left(1-s_f\right)\left(\mu_v+D\right)}\right),\\
\overline{E}_4 :=&\quad \left(\frac{A_3(\mu_h+\kappa_h)}{A_2\kappa_h},\ \frac{A_1}{A_2\kappa_h},\ \frac{A_1}{(\gamma+\mu_h)A_2},\ \frac{(\mu_v+\kappa_v)(\mu_h+\gamma)\mu_v A_2}{A_3\kappa_v\beta_1\beta_2},\ \frac{\mu_v A_1}{A_3\beta_1\kappa_v},\ \frac{A_1}{A_3\beta_1},\ 0\right),\\
\overline{E}_5 :=&\quad \left(\frac{B_3(\kappa_h+\mu_h)}{B_2\beta_1\kappa_v},\frac{B_1}{B_2},\frac{B_1\kappa_h}{B_2(\gamma+\mu_h)},\frac{B_2\mu_v(\gamma+\mu_h)(\kappa_v+\mu_v)}{B_3\kappa_h\beta_2},\frac{\mu_v B_1}{B_3},\frac{B_1\kappa_v}{B_3},\quad \frac{\left(\mu_v s_f+D\right)J}{s_h\left(1-s_f\right)\left(b_0-\mu_v\right)\left(\mu_v+D\right)}\right).
\end{aligned}$$

The constants B_1 and B_2 are defined in Appendix D. One can easily verify $\overline{E}_5$ by showing that $\frac{E_h}{I_h}=\frac{\gamma+\mu_h}{\kappa_h}$, $S_hS_v=\frac{1}{\mathscr{R}_0^2}$, $\frac{S_hE_v}{E_h}=\frac{\mu_v(\kappa_h+\mu_h)}{\beta_1\kappa_v}$ and $\frac{I_v}{E_v}=\frac{\kappa_v}{\mu_v}$. Since $B_3<0$, we need B_1,B_2 to be both negative in order for $\overline{E}_5$ to exist. This is not always true for parameters chosen according to Table 2. Note that $\mathscr{R}_0>1$ is equivalent to $A_1>0$. The last four components of $\overline{E}_1$ and $\overline{E}_4$ add up to 1. The last four components of $\overline{E}_2,\overline{E}_3$ and $\overline{E}_5$ add up to $\frac{J}{(1-s_f)(b_0-\mu_v)}$. For the rest of this paper, we assume that

$$b_0\left(1-s_f\right)-\mu_v-D>0, \tag{H1}$$

$$s_h(D+\mu_v)-\mu_v s_f-D>0. \tag{H2}$$

Condition (H1) is stronger than $b_0>\mu_v$, which was used to show that $b(N_v)>0$ for $t>0$ if it holds at time $t=0$. Condition (H2) will be satisfied if CI is 100% successful ($s_h=1$). Otherwise, it will depend on the reduction in birthrate of *Wolbachia*-infected mosquitoes. If the birthrate is very low ($s_f\approx 1$), then (H2) may not be satisfied. (H1) is equivalent to $J>0$ and (H2) implies that $\sigma>0$.

Lemma 3.1. (*i*) *B_1 is negative for sufficiently small μ_h if*

$$\mathscr{R}_0^2>\frac{(b_0-\mu_v)(\mu_v+D)}{\sigma J}. \tag{3.3}$$

(ii) *B2 is negative for sufficiently small μ_h.*

Proof. Through some calculations, one can obtain

$$\begin{aligned}
B_1 =&\quad \left(t_1+t_2\mu_h+t_3\mu_h^2\right)\mu_h,\\
t_1 =&\quad s_h\left(1-s_f\right)\left[\kappa_h\gamma\mu_v(\kappa_v+\mu_v)(b_0-\mu_v)(\mu_v+D)-\kappa_h\kappa_v\beta_1\beta_2\sigma J\right],\\
t_2 =&\quad (\gamma+\kappa_h)t_3,\\
t_3 =&\quad \mu_v s_h\left(1-s_f\right)(\kappa_v+\mu_v)(b_0-\mu_v)(\mu_v+D).
\end{aligned}$$

Then (*i*) *follows from t_1 and* (3.2). *Again, through some calculations, we can show that*

$$B_2=k_h\beta_v(k_h+\mu_h)\left[B_{20}+B_{21}\mu_h+O\left(\mu_h^2\right)\right],$$

where $B_{20}=-\beta_h k_v J(s_h(D+\mu_v)-\mu_v s_f-D)$ and $B_{21}=s_h(s_f-1)(k_v+\mu_v)(b_0-\mu_v)(\mu_v+D)$ are both negative from our hypotheses above. Thus (*ii*) *holds. The proof of the lemma is completed.*

Note that if $s_h=1$, then condition (3.3) *becomes*

$$\mathscr{R}_0^2>\frac{b_0-\mu_v}{b_0\left(1-s_f\right)-\mu_v s_f-D}\,\frac{\mu_v+D}{\mu_v}.$$

Lemma 3.2. *The set* $\boldsymbol{R}^+ = \{S_h > 0, E_h > 0, I_h > 0,\ S_v > 0,\ E_v > 0,\ I_v > 0,\ W > 0\}$ *is invariant under the flow* (3.1). *The same is true for the set where all components are positive except* $W = 0$.

Proof. Suppose $S_h(t_1) = 0$. *Then* $\dot{S}_h(t_1) = \mu_h > 0$ *so* S_h *immediately turns around and reenter* $\boldsymbol{R}^+$. *The same argument may be applied to the other equations except for W. But the system with no Wolbachia is an invariant set so W(t) cannot be zero in finite time t. The proof of the lemma is completed.*

Lemma 3.3. *Let* (*H*1) *be replaced by the weaker condition* $b_0 > \mu_v$. *Suppose there is no Wolbachia-infected mosquito, then the reduced system has three possible steady-states*: $\tilde{E}_1 = [1, 0, 0, 0, 0, 0], \tilde{E}_2 = [1, 0, 0, 1, 0, 0]$ *and* $\tilde{E}_3$, *which is the same as* $\overline{E}_4$ *without the last component.* $\tilde{E}_1$ *is always unstable. If* $\mathscr{R}_0 < 1$, *then* $\tilde{E}_2$ *is stable and* $\tilde{E}_3$ *does not exist. If* $\mathscr{R}_0 > 1$, *then* $\tilde{E}_2$ *is unstable and* $\tilde{E}_3$ *exists and is locally asymptotically stable.*

Proof. The eigenvalues of $\tilde{E}_1$ *are* $\{-\mu_h, -\mu_v, -\kappa_h - \mu_h, -\kappa_v - \mu_v, -\gamma - \kappa_h, b_0 - \mu_v\}$. *From our assumption* $\tilde{E}_1$ *is unstable. The characteristic polynomial at* $\tilde{E}_2$ *is* $(\lambda + \mu_h)(\lambda + b_0 - \mu_v)p(\lambda)$, *where* $p(\lambda) = \lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0$. *It can be shown that*

$$
\begin{aligned}
b_0 = \ & -\beta_1\beta_2\kappa_1\kappa_2 + \mu_2(\kappa_2 + \mu_2)(\kappa_1 + \mu_1)(\gamma + \mu_1),\\
b_1 = \ & \gamma\,\kappa_1\,\kappa_2 + 2\,\gamma\,\kappa_1\,\mu_2 + \gamma\,\kappa_2\,\mu_1 + \gamma\,\kappa_2\,\mu_2 + 2\,\gamma\,\mu_1\,\mu_2 + \gamma\,\mu_2^2,\\
& + \kappa_1\,\kappa_2\,\mu_1 + \kappa_1\,\kappa_2\,\mu_2 + 2\,\kappa_1\,\mu_1\,\mu_2 + \kappa_1\,\mu_2^2 + \kappa_2\,\mu_1^2 + 2\,\mu_1\,\mu_2\,\kappa_2 + 2\,\mu_1^2\mu_2 + 2\,\mu_1\,\mu_2^2,\\
b_2 = \ & \gamma\,(\kappa_1 + \kappa_2) + \gamma\,\mu_1 + 2\,\gamma\,\mu_2 + \kappa_1\,\kappa_2 + \kappa_1\,\mu_1 + 2\,\kappa_1\,\mu_2 + 2\,\kappa_2\,\mu_1 + \kappa_2\,\mu_2 + \mu_1^2 + 4\,\mu_1\,\mu_2 + \mu_2^2,\\
b_3 = \ & \gamma + \kappa_1 + \kappa_2 + 2\,\mu_1 + 2\,\mu_2.
\end{aligned}
$$

According to the Routh-Hurwitz criterion (Edelstein-Keshet, 2005), $\tilde{E}_2$ *is stable if and only if* b_0, b_1, b_2, b_3 *are all positive and* $\Delta = (b_1b_2 - b_0b_3)b_3 - b_1^2b_4 > 0$. *Now* $\Delta = w_1 + w_2$, *where*

$$
\begin{aligned}
w_2 = \ & (\kappa_2 + 2\,\mu_2)(\kappa_1 + \mu_1 + \mu_2)(\kappa_1 + \kappa_2 + \mu_1 + \mu_2)(\gamma + \mu_1 + \mu_2)(\gamma + \kappa_2 + \mu_1 + \mu_2)(\gamma + \kappa_1 + 2\,\mu_1)\,,\\
w_1 = \ & \beta_1\,\beta_2\,\kappa_1\,\kappa_2\,(\gamma + \kappa_1 + \kappa_2 + 2\,\mu_1 + 2\,\mu_2)^2.
\end{aligned}
$$

Thus, $\tilde{E}_2$ *is stable if and only if* $b_0 > 0$, *or equivalently,* $\mathscr{R}_0 < 1$. *Finally, since* $\overline{E}_4$ *is stable,* $\tilde{E}_3$ *must also be stable. The proof of the lemma is completed.*

The system will have no Wolbachia-infected mosquitoes if $u(t) = 0$ *and there is no Wolbachia-infected mosquitoes initially.*

Lemma 3.4. *Suppose* $\mathscr{R}_0 > 1, B_1 < 0$ *and* $B_2 < 0$, *then all five steady-states exist.* $\overline{E}_1, \overline{E}_3, \overline{E}_5$ *are unstable and* $\overline{E}_2, \overline{E}_4$ *are locally asymptotically stable for sufficiently small* μ_h.

Proof. The existence part is obvious from the definitions above. The stability part is more delicate and is given in Appendix B. *The idea, which originates from* (Chung & Lui, 2016), *is when* $\mu_h = 0$, *the characteristic polynomial at* $\overline{E}_4$ *has two zero roots. We show that when we turn on* $\mu_h > 0$, *these two zero eigenvalues move to the negative complex plane. The proof of the lemma is completed.*

The five steady-states defined above represent possible long-term behavior of the human and mosquito populations. For example, if solutions of (3.1) *converge to* $\overline{E}_1$ *as time goes to infinity, then eventually the population consists of mostly susceptible humans and mosquitoes. Assuming that there are no periodic solutions, Lemma* 3.4 *implies that depending on the initial conditions, solutions of* (3.1) *approach either* $\overline{E}_2$ *or* $\overline{E}_4$ *as time goes to infinity. This bistability phenomenon is quite interesting and is similar to strong competition in population ecology* (Edelstein-Keshet, 2005).

The steady-state $\overline{E}_2$ *is desirable because all mosquitoes carry Wolbachia;* S_v, E_v *and* I_v *components of* $\overline{E}_2$ *are all zero. On the other hand,* $\overline{E}_4$ *is undesirable because no mosquitoes carry Wolbachia; the last component of* $\overline{E}_4$ *is* 0. *Since* $\overline{E}_4$ *exists if there is an epidemic, solutions of* (3.1) *may approach it depending on the initial condition. The idea here is to release Wolbachia-infected mosquitoes into the mosquito population until the percentage of Wolbachia-infected mosquitoes is high enough to sustain itself. Once the release stops, the solutions of* (3.1) *will converge to* $\overline{E}_2$ *as time goes to infinity, thus preventing the spread of dengue.*

We give an example to illustrate the bistability phenomenon. Let $B_{vh} = 0.60715$, $B_{hv} = 0.15273$, $k = 0.95269$, $N_h/K = 3$, $\mu_1 = 0.00159$, $\mu_2 = 0.07307$, $\gamma = 0.15598$, $\kappa_1 = 0.29078$, $\kappa_2 = 0.41109$, $b_0 = 0.7233919$, $D = 0.06532$, $s_h = 1.00000$, $s_f = 0.12713$, *and* $T = 5$ *years. Then,*

$$
\begin{array}{lcl}
y_1(0) & = & [0.993398\quad 0.000000\quad 0.006602\quad 0.220499\quad 0.000000\quad 0.002870\quad 0.062834],\\
y_1(T) & = & [0.055014\quad 0.005133\quad 0.009472\quad 0.981487\quad 0.002794\quad 0.015719\quad 0.000000],\\
\overline{E}_4 & = & [0.055014\quad 0.005133\quad 0.009472\quad 0.981487\quad 0.002794\quad 0.015719\quad 0.000000],\\
y_2(0) & = & [1.004709\quad 0.002305\quad 0.008443\quad 0.001948\quad 0.002259\quad 0.001707\quad 0.870846],\\
y_2(T) & = & [0.995562\quad 0.000000\quad 0.000000\quad 0.000000\quad 0.000000\quad 0.000000\quad 0.868570],\\
\overline{E}_2 & = & [1.000000\quad 0.000000\quad 0.000000\quad 0.000000\quad 0.000000\quad 0.000000\quad 0.868570]\,.
\end{array}
$$

From the above, we *see that after* 5 *years, solutions for the first set of initial conditions converge to* $\overline{E}_4$, *while solutions for the second set of initial conditions converge to* $\overline{E}_2$. *Distance between* $y_1(T)$ *and* $\overline{E}_4$ *is approximately* 4.0223×10^{-7}, *while distance between* $y_2(T)$ *and* $\overline{E}_2$ *is approximately* 0.0043833. *Thus, which stable steady-state solutions converge to depends on the initial conditions.*

4. Optimal control

In this section, we assume that $u(t)$ is a piecewise continuous function that lies between 0 and $a > 0$. We want to find the control that minimizes the total number of infected humans and cost of releasing *Wolbachia* over T days.

Let $J_1[u] = \int_0^T AI_h^2(t)\, N_h^2 + Bu(t)\, Kdt + \Psi_1(\mathrm{x}(T))$, where A, B are positive constants. Dividing J_1 by the constant $AN_h^2 + BK$, we can reduce J_1 to the form

$$J[u] = \int_0^T \theta I_h^2(t) + (1-\theta)u(t)\, dt + \Psi(\mathrm{x}(T)), \tag{4.1}$$

where $\theta = AN_h^2/(AN_h^2 + BK)$, $0 < \theta < 1$, and $0 \le u \le a$.

Let $\mathrm{x} = [S_h, E_h, I_h, S_v, E_v, I_v, W]$. Given a set of parameters chosen according to Table 2, we want to find u which minimizes $J[u]$. Pontryagin minimum principle gives a necessary condition for finding such a minimizer (Lenhart & Workman, 2007). To implement Pontryagin minimum principle, we first form the Hamiltonian:

$$\begin{aligned} H = {} & \theta I_h^2(t) + (1-\theta)u(t) \\ & +\lambda_1(t)[\mu_h - \beta_1 S_h I_v - \mu_h S_h] \\ & +\lambda_2(t)[\beta_1 S_h I_v - \kappa_h E_h - \mu_h E_h] \\ & +\lambda_3(t)[\kappa_h E_h - \gamma I_h - \mu_h I_h] \\ & +\lambda_4(t)[b(N_v)(1-s_h p)(S_v + E_v + I_v) - \beta_2 S_v I_h - \mu_v S_v] \\ & +\lambda_5(t)[\beta_2 S_v I_h - \kappa_v E_v - \mu_v E_v] \\ & +\lambda_6(t)[\kappa_v E_v - \mu_v I_v] \\ & +\lambda_7(t)\left[b(N_v)\left(1-s_f\right)W - (\mu_v + D)W + u(t)\right], \end{aligned} \tag{4.2}$$

where the adjoint variable, $\boldsymbol{\lambda}(t)$, satisfies the equations

$$\frac{d\lambda_j}{dt} = -\frac{\partial H}{\partial x_j}, \quad j = 1, 2, \ldots, 7, \tag{4.3}$$

and terminal transversality condition $\boldsymbol{\lambda}(\mathrm{T}) = \Psi_x(\mathrm{x}(T))$. Explicit form of equation (4.3) is given in Appendix C.

The optimal control, $u^*(t)$, satisfies the equation $0 = \frac{\partial H}{\partial u}$. Since H is linear in u, this equation yields no information on u. In order to minimize H, we set u to be the maximum ($= a$) if the coefficient of u in H, $\psi(t) = (1 - \theta) + \lambda_7(t)$, is negative and set $u = 0$ otherwise. The result is a bang-bang control and $\psi(t)$ is called the switching function.

To solve this set of necessary conditions numerically, we use the method of forward backward sweep (Lenhart & Workman, 2007). We start with a guess control, say $u_1(t) = 0$, and solve the state equation (3.1) with $u = u_1$ forward in time until T. We then solve (4.3) backward in time with the adjoint variable satisfying the transversality condition at time T. Then we update u_1 to u_2 by setting it equals to either 0 or a depending on the sign of the switching function. This is one iteration and then we repeat the process. We set an exit criterion and in our case we exit the loop when we reach 20 iterations or when an iteration does not produce any changes in u. Since $\overline{E}_2$ is the desirable stable steady state, we want to choose the terminal condition, Ψ, such that the solution under the optimal control is close to $\overline{E}_2$ at time T. Hence, we let $\Psi(\mathrm{x}(T)) = -\alpha W(T)$, $\alpha > 0$.

The choice of a bang-bang control is by design. In actual application, *Wolbachia* is collected from other insects such as fruit flies and injected into the larvae of *Aedes* in a laboratory. When the mosquitoes hatch, the *Wolbachia*-infected mosquitoes are released into the wild (Soares, 2016). Not all larvae are successfully infected with *Wolbachia* this way. This process may also need to be repeated, such as in example 2.

There are a large number of papers on applying optimal control to control the spread of dengue but they deal with different aspects of the problem. For example, in a recent paper (Agusto & Khan, 2018), the authors used vaccination and insecticides as control and include an immunized class in the model. In the paper (Campo-Duarte, Doris, Vasilieva, Cardona-Salgado, & Svinin, 2018), the authors studied a sex-structured model which describes the interaction between uninfected mosquitoes and those infected with the *wMelPop* strain of *Wolbachia*. The purpose of their study is to find a trade-off between reaching replacement by *Wolbachia* and minimum time with minimum cost of control effort. Their model also exhibits bistability and they conclude that periodic release is necessary to establish *Wolbachia* in mosquito populations. It is unclear if Pontryagin maximum principle still holds if we replace bounded control by periodic control. Below we present two examples using our method.

Example 1. Parameter values are given in Table 3. Initial condition is

$$x(0) = [1,\ 0,\ 0,\ 0.24284960,\ 0,\ 0.04587122,\ 0.01345308].$$

Basic reproduction number is $\mathscr{R}_0 = 1.71156218$. If there is no control, then after $T = 2$ years, x(T) = [0.06479510, 0, 0, 1, 0, 0, 0] so most humans belong to the recovered class. Note that μ_h is relatively small so S_h has not reached its equilibrium after 2 years.

We perform forward-backward sweep. Simulations stopped after 6 iterations. The graph of the optimal control obtained numerically is given in Fig. 2.

The limit of the solutions of (3.1) after 2 years with optimal control and modified optimal control are:

$$\bar{E}_2 = [1.00000000,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0.88297444],$$

$$x(T) = [0.33468947,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0.93197956],$$

$$x_s(T) = [0.33468947,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0.88297456].$$

Solutions of (3.1) with and without optimal control for this set of parameter values are given in Fig. 3.

Example 2. In this example u_s^* attains the value a twice, see Fig. 4. Parameter values are given in Table 6. Initial condition is

$$x(0) = [1,\ 0,\ 0,\ 0.24361241,\ 0,\ 0.03118208,\ 0.02162989].$$

Basic reproduction number is $\mathscr{R}_0 = 7.45627458$. After $T = 2$ years,

$$\bar{E}_2 = [1.00000000,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0.87543420],$$

$$x(T) = [0.02589060,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0.97307461],$$

$$x_s(T) = [0.02589060,\ 0,\ 0,\ 0,\ 0,\ 0,\ 0.87543425].$$

Solutions of (3.1) with and without optimal control for this set of parameter values are given in Fig. 5. It should be pointed out that in our simulations, for a small set of parameter values, the control fails to drive the solutions close to $\bar{E}_2$ at the end of 2 years.

5. Sensitivity analysis

In this section, we conduct uncertainty and sensitivity analysis using Latin Hypercube Sampling (LHS) (Blower & Dowlatabadi, 1994; Marino, Hogue, Ray, & E Kirschner, 2008; McKay, Beckman, & Conover, 1979) and partial rank correlation coefficients (PRCC) (Blower & Dowlatabadi, 1994; Kendall, 1942; Marino et al., 2008) to examine the variability of various important outcomes and their association with input variables. LHS, or stratified sampling without replacement, is an efficient implementation of Monte Carlo simulation that requires fewer samples than random sampling. PRCC is partial correlation coefficient (PCC) (Fisher, 1924; Marino et al., 2008) calculated on the ranks instead of values. PCC is the correlation between a

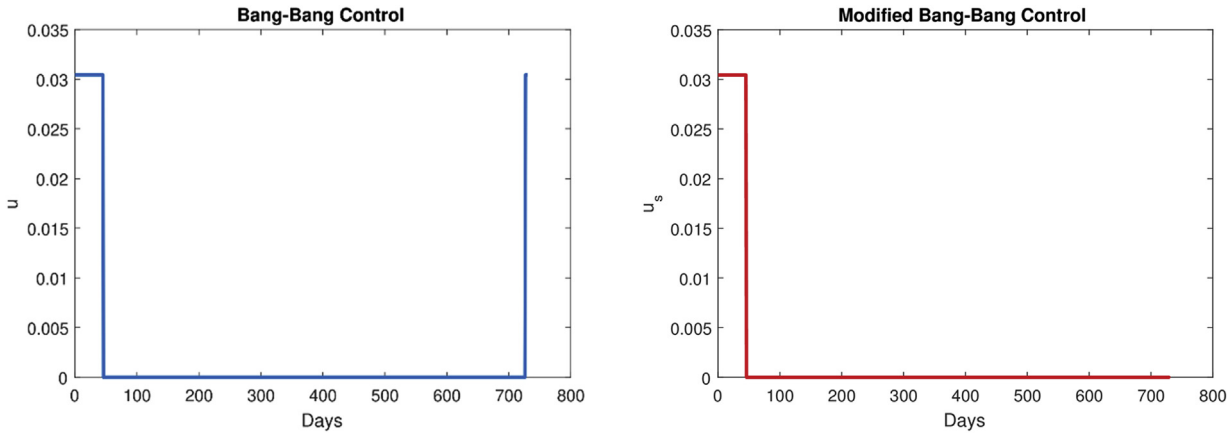

Fig. 2. Graph of optimal control $u^*(t)$ on the left and modified optimal control $u_s^*(t)$ on the right. The modified optimal control is obtained by setting the last part of $u^*(t)$ to zero.

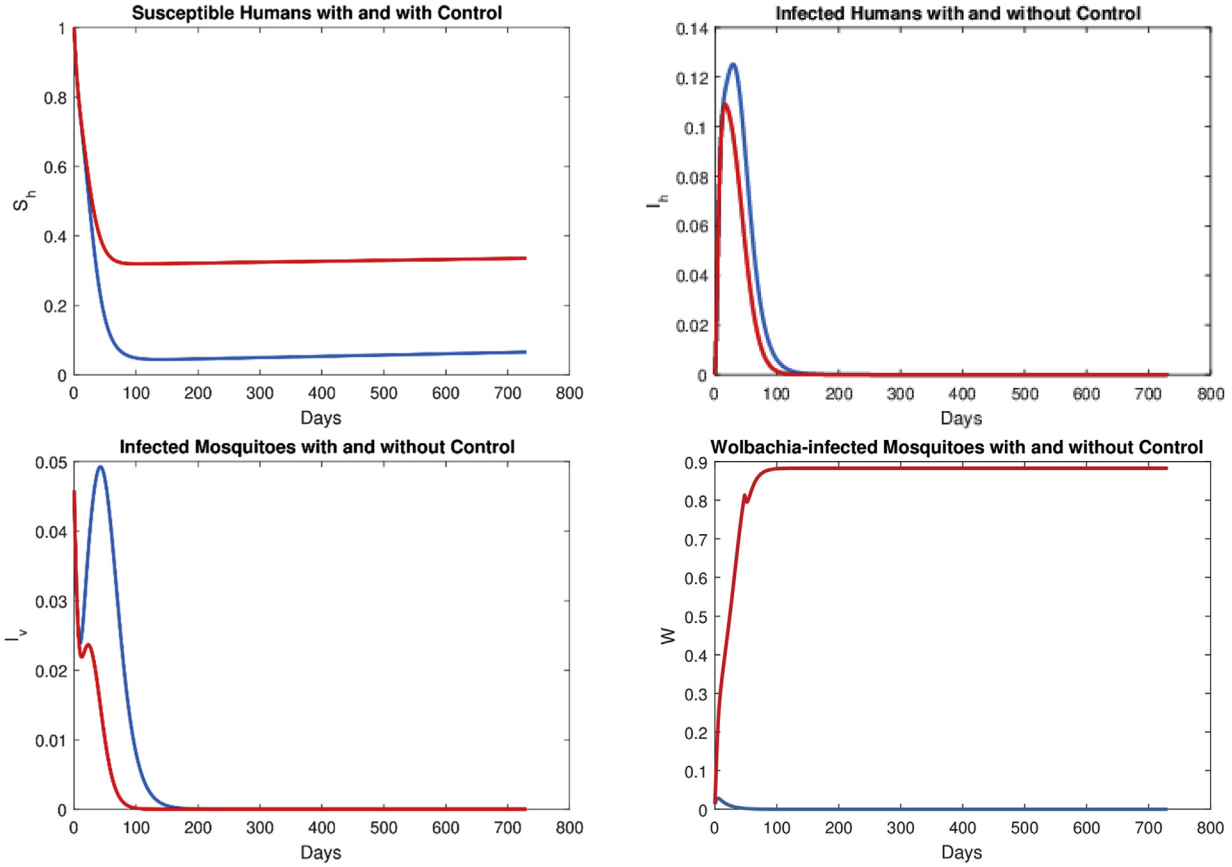

Fig. 3. Graph of solutions of (3.1) with (red) and without (blue) control u_s^*. Parameters values are given in Table 3. Maximum values of infected humans, I_h, are 0.1088 and 0.1251 and occur on days 18 and 30 for the cases with and without control, respectively. Maximum values of infected mosquitoes, I_v are 0.0459 and 0.0492 and occur on days 1 and 43 for the cases with and without control, respectively.

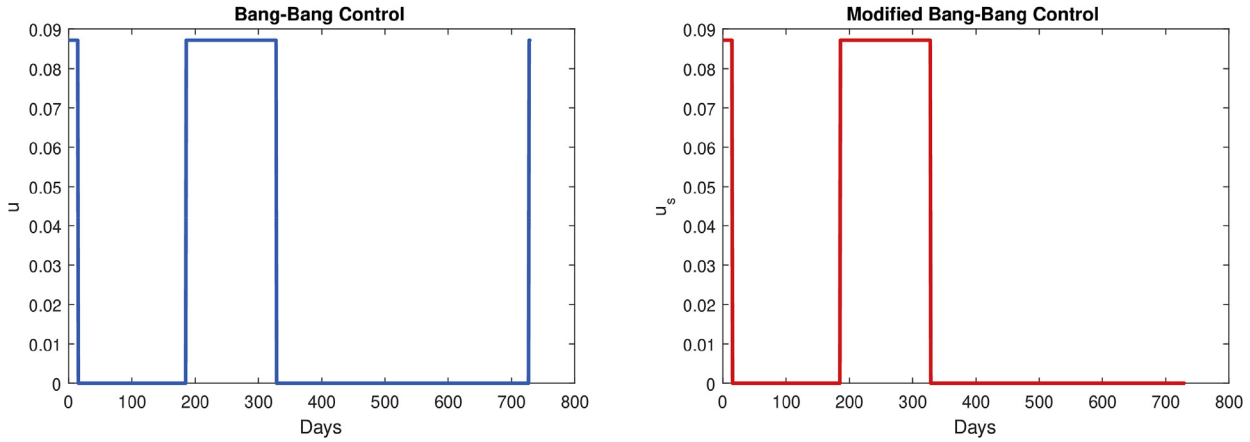

Fig. 4. Graph of optimal control $u^*(t)$ on the left and modified optimal control $u_s^*(t)$on the right. The modified optimal control is obtained by setting the last part of $u^*(t)$ to zero. Unlike the first example, the controls achieve the value $a = 0.0872$ twice.

given outcome and an input while discounting the linear effects of all other inputs. PCC measures the 'genuine' association between the outcome and the input by excluding the impact of other inputs on the outcome and input of interest. When performed on the ranks, PRCC is robust against potentially non-linear effects.

To perform uncertainty analysis, we use LHS to generate 17 input variables 1, 000 times independently from uniform distributions with ranges defined in Table 2. These 17 input variables include those from Table 2 and initial conditions $S_{v,0}$, $I_{v,0}$

Table 6
Parameter values for example 2 with $\alpha = 0.5$.

$\beta_1 = 1.08983733$	$\beta_2 = 0.32748506$	$k = 0.73155980$	$K/N_h = 2.55101907$
$\mu_h = 0.00004209$	$\mu_v = 0.05244734$	$\gamma = 0.10915675$	$\kappa_h = 0.25036073$
$\kappa_v = 0.43447502$	$b_0 = 0.86062658$	$s_f = 0.02594910$	$s_h = 0.92287205$
$D = 0.09669820$	$a = 0.08719785$	$\mathscr{R}_0 = 7.45627458$	$\theta = 0.90$

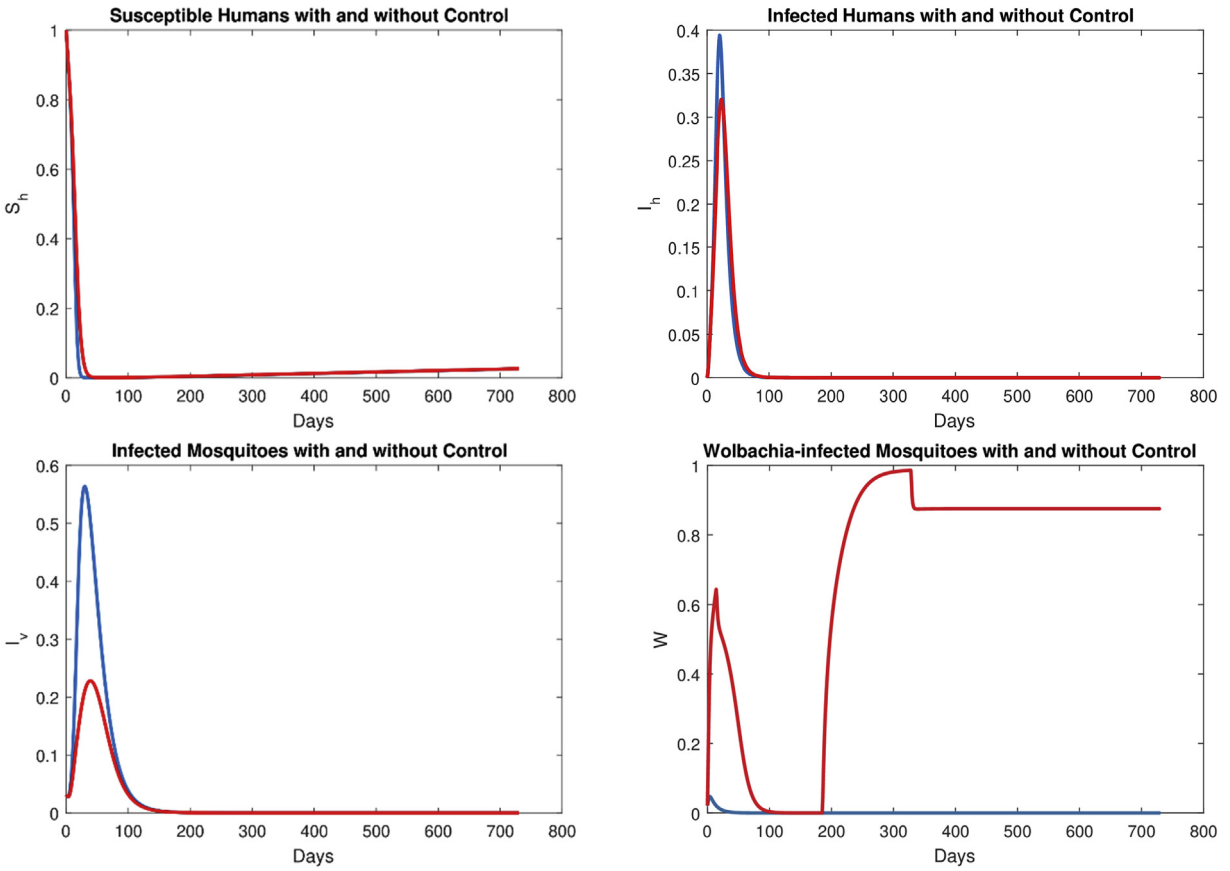

Fig. 5. Graph of solutions of (3.1) with (red) and without (blue) optimal control u_s^*. Parameters values are given in Table 6. Maximum values of infected humans, I_h, are 0.3943 and 0.3200 and occur on days 21 and 24 for the cases with and without control, respectively. Maximum values of infected mosquitoes, I_v, are 0.5637 and 0.2281 and occur on days 31 and 40 for the cases with and without control, respectively.

and W_0 which are randomly chosen from the intervals (0, 1), (0, 0.05) and (0, 0.05), respectively. Because of the conditions in Lemma 3.4, only 798 sets of data were selected. With the simulated data, we summarize the descriptive statistics of important outcomes and use PRCC and the corresponding t-test to determine the sensitivity of the outcomes to the input variables.

Fig. 6 shows that the empirical distributions of $\mathscr{R}_0$, max I_h, and max I_v are all right-skewed. This means that the majority of the values lie on the left side of the scale. An overly right-skewed distribution means that even though median is smaller than the mean, the chance of getting large outcomes, i.e., the right-tail probability, is not negligible.

Fig. 7 shows the PRCC between the state variables at the end of two years and maximum values of infected humans and infected mosquitoes against the 14 parameters given in Table 2. We observe that (1) E_h, I_h, E_v and I_v are sensitive to the same set of inputs: B_{vh}, B_{hv}, μ_v, γ and a. The magnitude of the associations for each input remains stable across the outcomes. (2) S_h and S_v are influenced by B_{vh}, B_{hv}, μ_v, κ_h, s_f, s_h, D and a. These associations are in opposite directions. It is also worth mentioning that μ_h appears to be associated with S_h but not with S_v while γ is associated with S_v but not with S_h. (3) The outcome variables max I_h and max I_v are strongly associated with B_{vh}, B_{hv}, μ_v and a but only weakly associated with κ_h, κ_v, b_0, s_h and D. The parameter γ has large influence over max I_h but almost no influence over max I_v.

The scatter plots of the top PRCC in Fig. 8 show that this approach indeed identifies the input variables that have large impact on the outcomes. We observe that as in (1) above, E_h, I_h, E_v and I_v are similarly correlated with μ_v since they are, in fact, highly correlated with each other. The large clusters near the bottom in their PRCC plots with μ_v correspond to the cases that

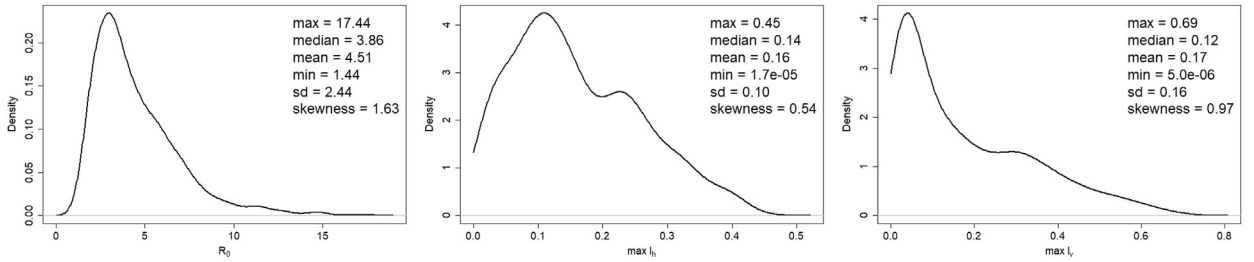

Fig. 6. Empirical densities and summary statistics of $\mathscr{R}_0$ (left), max I_h (center), and max I_v (right).

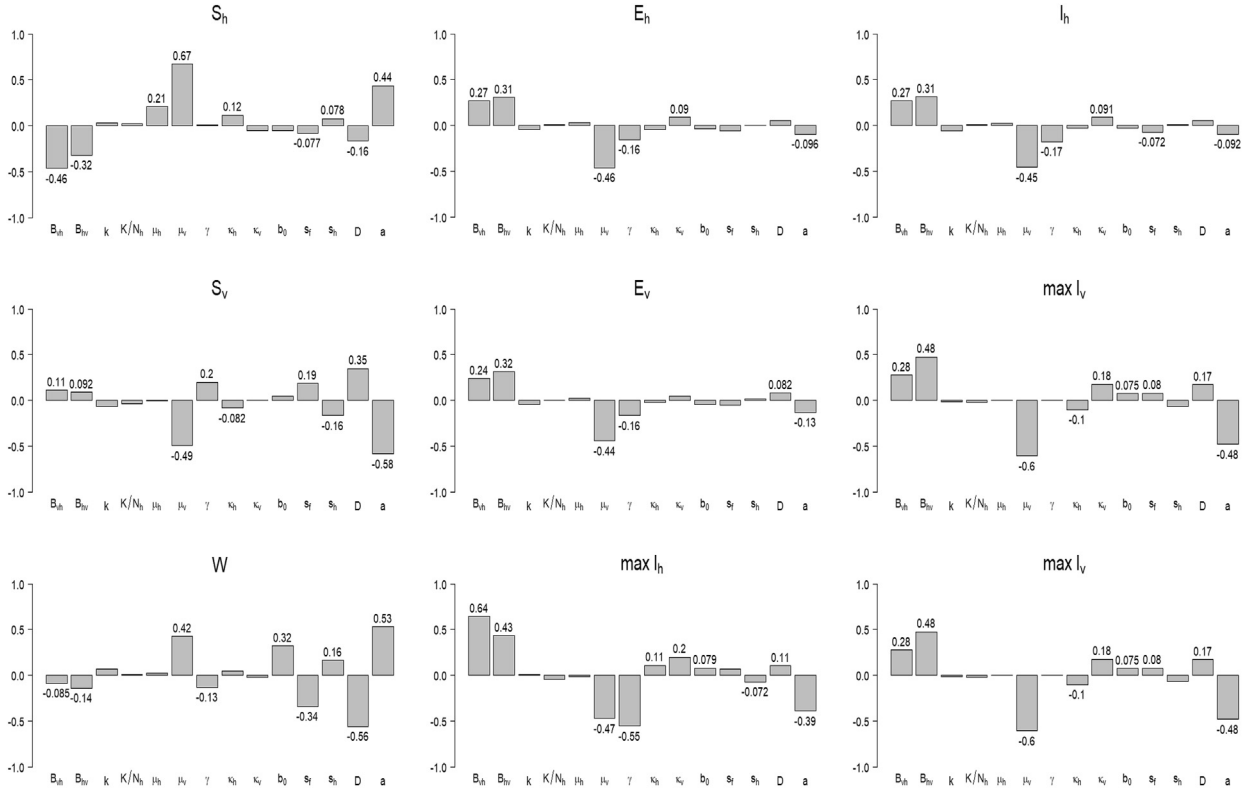

Fig. 7. The PRCC between input variables and outcomes for model (3.1). The PRCCs that pass the statistical significance threshold of 0.01 are labeled.

at the end of two years, E_h, I_h, E_v and I_v are equal to 0. Occasionally, the release method fails to drive the solutions close to $\overline{E}_2$ and they are partially responsible for the small clusters near the top left of the scatter plots. These clusters also show that a relatively small μ_v can increase the likelihood of getting large outcomes, i.e., a failed optimal control.

Fig. 9 shows that B_{vh}, μ_v and a are significantly associated with all the outcomes. On the other hand, k, K/N_h and b_0 are not associated with any of the outcomes. From (2.2), b_0 is the fecundity of mosquito when the density is very low and its value is estimated. Our global sensitivity analysis also implicates that death-rate of mosquitoes, μ_v, is the most important factor in controlling the spread of dengue.

6. Discussions

Dengue is a mosquito-borne viral infection which normally causes flu-like symptoms that go away in a few days. However, occasionally, it may lead to something more serious called severe dengue, which is a leading cause of illness and death among children in some Asian and Latin American countries (WHO, 2019).

Wolbachia is a bacterium commonly found in insects but not in *Ae. aegypti*, the mosquito that carries the dengue virus. There is strong evidence that *Wolbachia*-infected *Ae. aegypti* can resist infection by dengue virus. In the paper (Ferguson et al.,

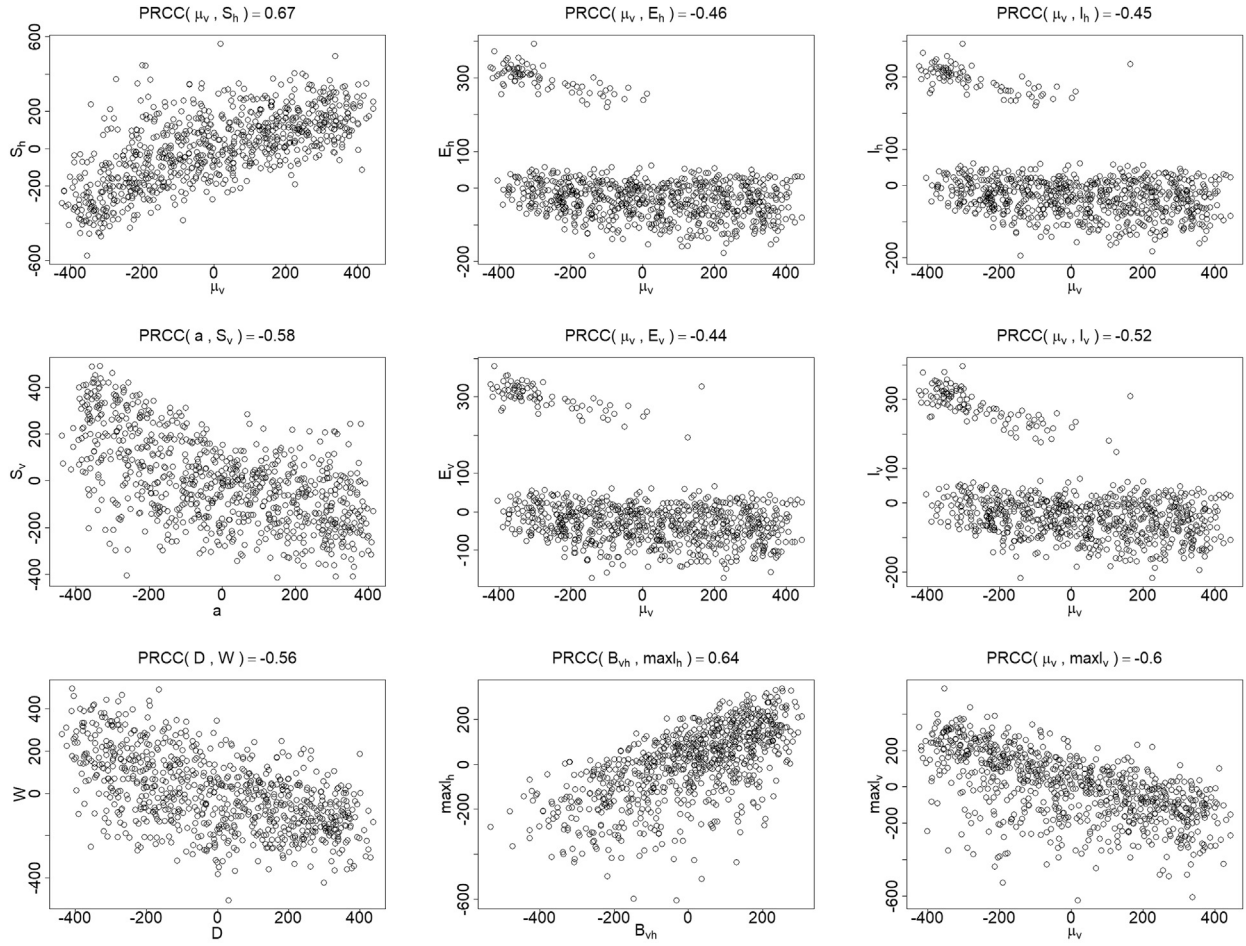

Fig. 8. The scatter plots of the largest PRCC between each outcome and input variables for model (3.1). Each dot represents a pair of residuals from regressing the outcome and the input variable against other input variables on rank values.

2015), the authors performed field experiments and used a mathematical model to conclude that the strain of *Wolbachia*, *wMelPop*, can reduce the basic reproduction number of dengue transmission by 66–75 percent. This strain of *Wolbachia* is considered to be the best blocker of dengue (Ant, Herd, Geoghegan, Hoffmann, & Sinkins, 2018).

The purpose of this paper is to use mathematical modeling and optimal control theory to find a release method that will be effective in controlling the spread of dengue. Without release, our model exhibits bistability, which is interesting because absent *Wolbachia*-infected mosquito, there is only one interior steady-state which is stable when it exists, see Lemma 3.3.

Our release of *Wolbachia*-infected mosquitoes is modeled by the forcing function $u(t)$ in (2.1). We employ optimal control theory to find $u(t)$ that will drive the solutions of (2.1) close to the stable steady-state, $\overline{E}_2$, at the end of two years. When the release stops, since $\overline{E}_2$ is locally asymptotically stable, solutions of (2.1) will converge to $\overline{E}_2$ as time goes to infinity. All mosquitoes are then infected with *Wolbachia*, preventing the spread of dengue.

The control is optimal in the sense that it minimizes a functional within certain class of functions. However, it is by no means the best release method. For example, if medical resources are limited in a community, then one might want to find a control that minimizes max I_h. It is not clear if such a control can be found by minimizing a functional. In practice, it is not possible to continuously adjust the amount of release. Hence, we design a functional so that the control is a bang-bang control; its value is either zero or $a > 0$.

The last part of our paper deals with uncertainty and sensitivity analysis. Uncertainty analysis means quantifying variability of the output due to the variability of the input; in other words, propagation of error. For us, the uncertainty of input comes from random selection of the 14 model parameters each assume to be uniformly distributed on an interval suggested by experimental data. Some researchers chose to use other distributions such as triangular or normal distribution, or a mix of them. The uncertainty of our output is quantified by the probability distribution function (pdf) of the outcome variables we want to measure plus their associated statistics.

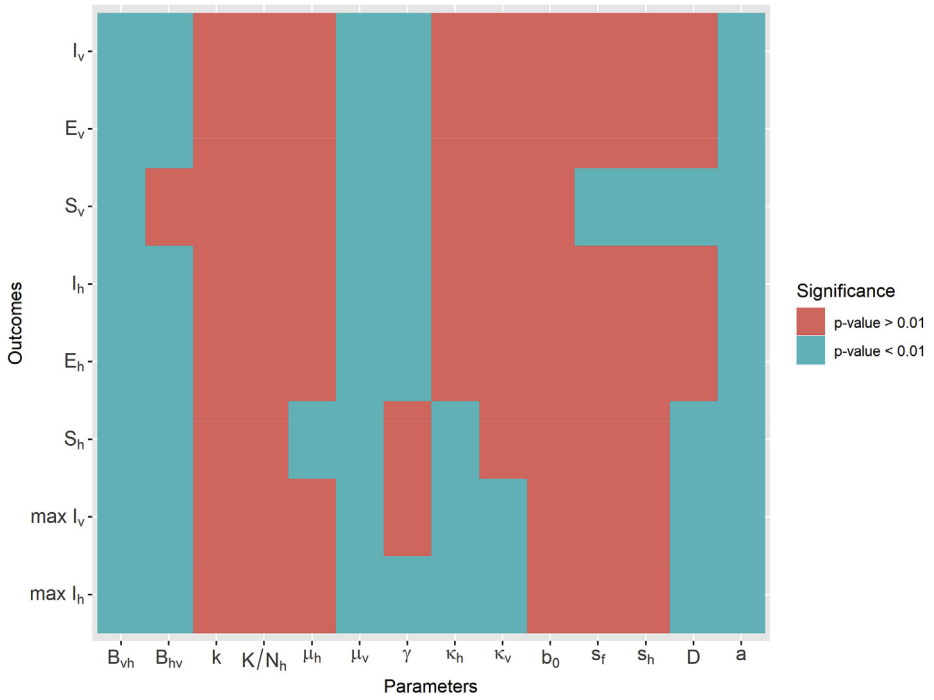

Fig. 9. The heatmap for the statistical significance of PRCC between input variables and outcomes under model (3.1).

There is a large amount of work done on sensitivity analysis (Chitnis, Hyman, & Cushing, 2008; Saltelli et al., 2008; Wu, Dhingra, Gambhir, & Remais, 2013). We use PRCC to perform global sensitivity analysis on the 14 parameters and find out which parameters have strong influence on the outcomes we are interested in. They are reported in Figs. 7 and 9. The parameter values that we estimated are b_0, s_f, s_h and D. Fig. 9 shows that b_0, s_f, s_h are not strongly associated with any outcome variables except s_f, s_h are associated with S_v.

It was pointed out in (Marino et al., 2008) that PRCC may produce erroneous results if the outcome variables we measure do not depend monotonically on the model parameters. In such cases, a different test, eFAST (Extended Fourier Amplitutde Sensitivity Test), is necessary. However, from the descriptions given in Table 2, it is reasonable to assume that the monotonicity conditions are satisfied.

The idea in this paper may be applicable to other mosquito-borne diseases such as malaria and Zika. In improve our model, we plan to introduce rainfall into our model because mosquito aquatic stages all require water. We also plan to distinguish between male and female mosquitoes to better model CI and include multiple serotype in our next model.

Dengue is considered as the world's fastest spreading tropical disease. It is estimated about 50% of the world's population is at risk of getting dengue (WHO, 2019). Since 2011, the World Mosquito Program has been breeding *Wolbachia*-carrying mosquitoes and in partnerships with local communities release them into areas affected by mosquito-borne diseases. This method is self-sustaining in almost all international project sites operated by the World Mosquito Program. This agrees with our analysis in Section 3, as solutions of our model converge to the stable steady-state, $\overline{E}_2$, even after the release is stopped. The results in Section 4 may be useful in finding the optimal way to release the *Wolbachia*-carrying mosquitoes. Hopefully, this method can be safe and effective to stop *A. aegypti* from spreading viruses such as dengue, Zika, chikungunya and yellow fever to humans.

Declaration of competing interest

None.

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Appendix

A. Proof of (3.2).

We follow the recipe in (Van den Driessche and Watmough, 2002) and write the model equation as

$$\begin{aligned}
\dot{E}_h &= \beta_1 S_h I_v - \kappa_h E_h - \mu_h E_h,\\
\dot{E}_v &= \beta_2 S_v I_h - \kappa_v E_v - \mu_v E_v,\\
\dot{I}_h &= \kappa_h E_h - \gamma I_h - \mu_h I_h,\\
\dot{I}_v &= \kappa_v E_v - \mu_v I_v.
\end{aligned}$$

Let $x_i = \mathscr{F}_i(\mathrm{x}) - \mathscr{V}_i(\mathrm{x})$, $\mathrm{x} = (E_h, E_v, I_h, I_v)$, where $\mathscr{F}_i$ is rate of new infection in compartment i and $\mathscr{V}_i$ is rate of transfer of infected humans and mosquitoes in and out of compartment i.

$$\mathscr{F} = \begin{pmatrix} \beta_1 S_h I_v \\ \beta_2 S_v I_h \\ 0 \\ 0 \end{pmatrix}, \qquad \mathscr{V} = \begin{pmatrix} \kappa_h E_h + \mu_h E_h \\ \kappa_v E_v + \mu_v E_v \\ \gamma I_h + \mu_h I_h - \kappa_h E_h \\ \mu_v I_v - \kappa_v E_v \end{pmatrix}.$$

We then compute the Jacobian of $\mathscr{F}$ and $\mathscr{V}$.

$$J\mathscr{F} = \begin{pmatrix} 0 & 0 & 0 & \beta_1 S_h \\ 0 & 0 & \beta_2 S_v & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \qquad J\mathscr{V} = \begin{pmatrix} \kappa_h + \mu_h & 0 & 0 & 0 \\ -\kappa_h & \kappa_v + \mu_v & 0 & 0 \\ 0 & 0 & \gamma + \mu_h & 0 \\ 0 & -\kappa_v & 0 & \mu_v \end{pmatrix},$$

$$(J\mathscr{F})(J\mathscr{V})^{-1} = \begin{pmatrix} 0 & \dfrac{\beta_1 S_h \kappa_v}{(\kappa_v + \mu_v)\mu_v} & 0 & \dfrac{\beta_1 S_h}{\mu_v} \\ \dfrac{\beta_2 S_v \kappa_h}{(\kappa_h + \mu_h)(\mu_h + \gamma)} & 0 & \dfrac{\beta_2 S_v}{\gamma + \mu_h} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

The basic reproduction number, $\mathscr{R}_0$, is the spectral radius of the matrix $(J\mathscr{F})(J\mathscr{V})^{-1}$ evaluated at the disease-free stage $S_h = 1$, $S_v = 1$. This will yield formula (3.2).

B. Proof of Lemma 3.4.

A steady-state is locally asymptotically stable if all the eigenvalues of the Jacobian matrix evaluated at the steady-state are negative or have negative real-parts. Otherwise, the steady-state is said to be unstable (Edelstein-Keshet, 2005). Eigenvalues are the roots of the characteristic equation of the Jacobian matrix. Let J_i be the Jacobian matrix evaluated at $\overline{E}_i$. To avoid excessive algebra, we assume that $s_h = 1$ so that $\sigma > 0$. Condition $J > 0$ is equivalent to

$$b_0 > \frac{\mu_v + D}{1 - s_f}. \tag{7.1}$$

The following calculations were performed using the mathematical software Maple.

Lemma 7.1. *$\overline{E}_1, \overline{E}_3$ and $\overline{E}_5$ are unstable, while $\overline{E}_2$ and $\overline{E}_4$ are locally asymptotically stable for sufficiently small $\mu_h > 0$.*

Proof.

(i) *Eigenvalues of J_1 are $\{-\mu_h, -(b_0 - \mu_v), -D - \mu_v s_f\}$, which are all negative, plus the roots of a fourth degree polynomial. The leading coefficient of this polynomial is one and the constant term is $t_0 := -\theta + O(\mu_h)$, where*

$$\theta := \beta_1\beta_2\kappa_h\kappa_v - \gamma\kappa_h\kappa_v\mu_v - \gamma\kappa_h\mu_v^2.$$

Now $A_1 = \theta\,\mu_h - O(\mu_h^2)$. *Since we assume* $A_1 > 0$ *in order for* $\overline{E}_4$ *to exist, we have* $\theta > 0$ *and* $t_0 < 0$ *for sufficiently small* $\mu_h > 0$. *Since* t_0 *is the product of the eigenvalues of* J_1, *one of these eigenvalues must be positive when* μ_h *is sufficiently small. Thus,* $\overline{E}_1$ *is unstable.*

(ii) *The eigenvalues of* J_2 *are* $\{-\mu_h, -\mu_v, -\mu_v, -\mu_h-\gamma, -\mu_h-\kappa_h, -\mu_v-\kappa_v, -J\}$, *which are all negative. Thus,* $\overline{E}_2$ *is locally asymptotically stable.*

(iii) *The characteristic polynomial of* J_3 *is* $(\lambda+\mu_h)\,p_1(\lambda)\,p_2(\lambda)$, *where* $p_1(\lambda)$ *is a quadratic polynomial and* $p_2(\lambda)$ *is fourth degree polynomial. The leading term of* $p_1(\lambda)$ *is* $(1-s_f)(\mu_v+D)^2 > 0$ *and the constant term is* $-\mu_v(1-s_f)(\mu_v+D)(\mu_v s_f+D)J < 0$. *Thus,* $p_1(\lambda)$ *has one positive and one negative root and* $\overline{E}_3$ *is unstable.*

(iv) *The characteristic polynomial of* J_4 *when* $\mu_h = 0$ *is*

$$\lambda^2(\lambda+b_0-\mu_v)\Big(\mu_v s_f + D + \lambda\Big)p_3(\lambda).$$

where $p_3(\lambda)$ *is a third degree polynomial. Using Routh-Hurwitz stability criterion* (Edelstein-Keshet, 2005), *one can show that the roots of* $p_3(\lambda)$ *are either negative or have negative real parts. We only need to determine the sign of the real parts of the two zero roots* (λ^2) *when* μ_h *turns positive. To accomplish that, we let the characteristic polynomial of* J_4 *be*

$$p_4(\lambda) := \lambda^7 + a_6(\mu_h)\lambda^6 + \ldots + a_1(\mu_h)\lambda + a_0(\mu_h).$$

We look for a pair of complex conjugate roots of (7.3), *which vanish when* $\mu_h = 0$. *Let* $a_i(\mu_h) = a_{i0} + a_{i1}\mu_h + a_{i2}\mu_h^2 \ldots$ *It can be shown that* $a_{i0} \neq 0$ *for* $i = 2, \ldots, 6$ *while*

$$\begin{aligned} a_0(\mu_h) &= a_{01}\,\mu_h + o(\mu_h), \quad a_{01} \neq 0, \\ a_1(\mu_h) &= a_{11}\,\mu_h + o(\mu_h), \quad a_{11} \neq 0. \end{aligned}$$

Let $\lambda := \sqrt{\mu_h}\,\lambda_1 + \mu_h\,\lambda_2 + O\left(\mu_h^{\frac{3}{2}}\right)$. *Substitute this into* $p_4(\lambda) = 0$ *and expanding in terms of* μ_h,

$$p_4 = \Big(a_{20}\lambda_1^2 + a_{01}\Big)\mu_h + \Big(a_{30}\lambda_1^3 + 2a_{20}\lambda_1\lambda_2 + a_{11}\lambda_1\Big)\mu_h^{\frac{3}{2}} + \textit{higher order terms of } \mu_h.$$

therefore,

$$\lambda_1^2 = -\frac{a_{01}}{a_{20}} = -\left(\frac{\theta}{\gamma\kappa_h\kappa_v + 2\gamma\kappa_h\mu_v + \gamma\kappa_v\mu_v + \gamma\mu_v^2 + \kappa_h\kappa_v\mu_v + \kappa_h\mu_v^2}\right),$$

$$\lambda_2 = -\left(\frac{a_{30}\lambda_1^2 + a_{11}}{2a_{20}}\right) = \frac{a_{30}a_{01} - a_{11}a_{20}}{2a_{20}^2}.$$

Since $\theta > 0$, λ_1 *is pure imaginary. The sign of* λ_2 *is determined by the sign of its numerator. Expanding the numerator as a series in* β_2, *one can show that numerator* $= A + B\,\beta_2$, *where* $B < 0$ *and* A, B *are too complicated to be displayed here. From* $\theta > 0$, *we have* $\beta_2 > (\gamma\kappa_v\mu_v + \gamma\mu_v^2)/(\beta_1\kappa_v)$ *so that*

$$\begin{aligned} \textit{numerator of } \lambda_2 &< A + B\,\frac{\gamma\kappa_v\mu_v + \gamma\mu_v^2}{\beta_1\kappa_v} \\ &= -(b_0-\mu_v)^2\Big(\mu_v s_f + D\Big)^2\Big(\gamma\kappa_h\kappa_v + 2\gamma\kappa_h\mu_v + \gamma\kappa_v\mu_v + \gamma\mu_v^2 + \kappa_h\kappa_v\mu_v + \kappa_h\mu_v^2\Big)^2. \end{aligned}$$

therefore, $\lambda_2 < 0$ *and* λ^2 *in* (7.2) *turns into a pair of complex conjugate eigenvalues with negative real parts when* μ_h *turns positive.* E_4 *is locally asymptotically stable when* $\mu_h > 0$ *is sufficiently small.*

(v) *When* $\mu_h = 0$, *the characteristic polynomial of* J_5 *is of the form* $\lambda^2\,p_5(\lambda)\,p_6(\lambda)$, *where* $p_5(\lambda)$ *is a quadratic polynomial with leading coefficient* $(\mu_v+D)^2$ *and constant term* $-\mu_v(\mu_v s_f + D)(\mu_v+D)J < 0$. *Thus,* $p_5(\lambda)$ *has one positive and one negative*

root. It can be shown using Routh-Hurwitz stability criterion that all roots of $p_6(\lambda)$ are negative or have negative real parts. One can use the method presented in (iv) to investigate the behavior of λ^2 when $\mu_h > 0$ but J_5 has at leaset one positive eigenvalue and $\bar{E}_5$ is therefore unstable. The proof of the lemma is complete.

C. Explicit form of the Adjoint Equation

$$\lambda_1'(t) = -\frac{\partial H}{\partial S_h} = \lambda_1(t)\beta_1 I_v + \lambda_1(t)\mu_h - \lambda_2(t)\beta_1 I_v,$$

$$\lambda_2'(t) = -\frac{\partial H}{\partial E_h} = \lambda_2(t)(\kappa_h + \mu_h) - \lambda_3(t)\kappa_h,$$

$$\lambda_3'(t) = -\frac{\partial H}{\partial I_h} = -2\theta I_h + \lambda_3(t)(\gamma + \mu_h) + \lambda_4(t)\beta_2 S_v - \lambda_5(t)\beta_2 S_v,$$

$$\lambda_4'(t) = -\frac{\partial H}{\partial S_v}$$

$$= -\lambda_4(t)\left[b'(N_v)(1 - s_h p)(S_v + E_v + I_v) + b(N_v)\left(s_h\frac{W}{N_v^2}\right)(S_v + E_v + I_v)\right]$$

$$-\lambda_4(t)[\, b(N_v)(1 - s_h p) - \beta_2 I_h - \mu_v] - \lambda_5(t)\beta_2 I_h - \lambda_7(t)b'(N_v)\left(1 - s_f\right)W,$$

$$\lambda_5'(t) = -\frac{\partial H}{\partial E_v}$$

$$= -\lambda_4(t)\left[b'(N_v)(1 - s_h p)(S_v + E_v + I_v) + b(N_v)\left(s_h\frac{W}{N_v^2}\right)(S_v + E_v + I_v)\right]$$

$$-\lambda_4(t)b(N_v)(1 - s_h p) + \lambda_5(t)(\kappa_v + \mu_v) - \lambda_6(t)\kappa_v - \lambda_7(t)b'(N_v)\left(1 - s_f\right)W,$$

$$\lambda_6'(t) = -\frac{\partial H}{\partial I_v}$$

$$= \lambda_1(t)\beta_1 S_h - \lambda_2(t)\beta_1 S_h$$

$$-\lambda_4(t)\left[b'(N_v)(1 - s_h p)(S_v + E_v + I_v) + b(N_v)\left(s_h\frac{W}{N_v^2}\right)(S_v + E_v + I_v)\right]$$

$$-\lambda_4(t)b(N_v)(1 - s_h p) + \lambda_6(t)\mu_v - \lambda_7(t)b'(N_v)\left(1 - s_f\right)W,$$

$$\lambda_7'(t) = -\frac{\partial H}{\partial W}$$

$$= -\left\{\lambda_4(t)(S_v + E_v + I_v)\left[b'(N_v)(1 - s_h p) + b(N_v)\left(-s_h\frac{S_v + E_v + I_v}{N_v^2}\right)\right]\right\}$$

$$-\lambda_7(t)\left[b'(N_v)\left(1 - s_f\right)W + b(N_v)\left(1 - s_f\right) - (\mu_v + D)\right].$$

D. Explicit form of B_1 and B_2 in the definition of $\bar{E}_5$.

$$
\begin{aligned}
B_1 := \mu_1\Big(&Db_0\beta_1\beta_2\kappa_1\kappa_2 s_f s_h - Db_0\gamma\kappa_1\kappa_2\mu_2 s_f s_h - Db_0\gamma\kappa_1\mu_2^2 s_f s_h - Db_0\gamma\kappa_2\mu_1\mu_2 s_f s_h\\
&- Db_0\gamma\mu_1\mu_2^2 s_f s_h - Db_0\kappa_1\kappa_2\mu_1\mu_2 s_f s_h - Db_0\kappa_1\mu_1\mu_2^2 s_f s_h - Db_0\kappa_2\mu_1^2\mu_2 s_f s_h\\
&- Db_0\mu_1^2\mu_2^2 s_f s_h + D\gamma\kappa_1\kappa_2\mu_2^2 s_f s_h + D\gamma\kappa_1\mu_2^3 s_f s_h + D\gamma\kappa_2\mu_1\mu_2^2 s_f s_h\\
&+ D\gamma\mu_1\mu_2^3 s_f s_h + D\kappa_1\kappa_2\mu_1\mu_2^2 s_f s_h + D\kappa_1\mu_1\mu_2^3 s_f s_h + D\kappa_2\mu_1^2\mu_2^2 s_f s_h\\
&+ D\mu_1^2\mu_2^3 s_f s_h - b_0\beta_1\beta_2\kappa_1\kappa_2\mu_2 s_f^2 + b_0\beta_1\beta_2\kappa_1\kappa_2\mu_2 s_f s_h - b_0\gamma\kappa_1\kappa_2\mu_2^2 s_f s_h\\
&- b_0\gamma\kappa_1\mu_2^3 s_f s_h - b_0\gamma\kappa_2\mu_1\mu_2^2 s_f s_h - b_0\gamma\mu_1\mu_2^3 s_f s_h - b_0\kappa_1\kappa_2\mu_1\mu_2^2 s_f s_h\\
&- b_0\kappa_1\mu_1\mu_2^3 s_f s_h - b_0\kappa_2\mu_1^2\mu_2^2 s_f s_h - b_0\mu_1^2\mu_2^3 s_f s_h + \gamma\kappa_1\kappa_2\mu_2^3 s_f s_h\\
&+ \gamma\kappa_1\mu_2^4 s_f s_h + \gamma\kappa_2\mu_1\mu_2^3 s_f s_h + \gamma\mu_1\mu_2^4 s_f s_h + \kappa_1\kappa_2\mu_1\mu_2^3 s_f s_h\\
&+ \kappa_1\mu_1\mu_2^4 s_f s_h + \kappa_2\mu_1^2\mu_2^3 s_f s_h + \mu_1^2\mu_2^4 s_f s_h + D^2\beta_1\beta_2\kappa_1\kappa_2 s_h\\
&- Db_0\beta_1\beta_2\kappa_1\kappa_2 s_f - Db_0\beta_1\beta_2\kappa_1\kappa_2 s_h + Db_0\gamma\kappa_1\kappa_2\mu_2 s_h + Db_0\gamma\kappa_1\mu_2^2 s_h\\
&+ Db_0\gamma\kappa_2\mu_1\mu_2 s_h + Db_0\gamma\mu_1\mu_2^2 s_h + Db_0\kappa_1\kappa_2\mu_1\mu_2 s_h + Db_0\kappa_1\mu_1\mu_2^2 s_h\\
&+ Db_0\kappa_2\mu_1^2\mu_2 s_h + Db_0\mu_1^2\mu_2^2 s_h - D\beta_1\beta_2\kappa_1\kappa_2\mu_2 s_f + 2D\beta_1\beta_2\kappa_1\kappa_2\mu_2 s_h\\
&- D\gamma\kappa_1\kappa_2\mu_2^2 s_h - D\gamma\kappa_1\mu_2^3 s_h - D\gamma\kappa_2\mu_1\mu_2^2 s_h - D\gamma\mu_1\mu_2^3 s_h\\
&- D\kappa_1\kappa_2\mu_1\mu_2^2 s_h - D\kappa_1\mu_1\mu_2^3 s_h - D\kappa_2\mu_1^2\mu_2^2 s_h - D\mu_1^2\mu_2^3 s_h\\
&+ b_0\beta_1\beta_2\kappa_1\kappa_2\mu_2 s_f - b_0\beta_1\beta_2\kappa_1\kappa_2\mu_2 s_h + b_0\gamma\kappa_1\kappa_2\mu_2^2 s_h + b_0\gamma\kappa_1\mu_2^3 s_h\\
&+ b_0\gamma\kappa_2\mu_1\mu_2^2 s_h + b_0\gamma\mu_1\mu_2^3 s_h + b_0\kappa_1\kappa_2\mu_1\mu_2^2 s_h + b_0\kappa_1\mu_1\mu_2^3 s_h\\
&+ b_0\kappa_2\mu_1^2\mu_2^2 s_h + b_0\mu_1^2\mu_2^3 s_h - \beta_1\beta_2\kappa_1\kappa_2\mu_2^2 s_f + \beta_1\beta_2\kappa_1\kappa_2\mu_2^2 s_h\\
&- \gamma\kappa_1\kappa_2\mu_2^3 s_h - \gamma\kappa_1\mu_2^4 s_h - \gamma\kappa_2\mu_1\mu_2^3 s_h - \gamma\mu_1\mu_2^4 s_h - \kappa_1\kappa_2\mu_1\mu_2^3 s_h\\
&- \kappa_1\mu_1\mu_2^4 s_h - \kappa_2\mu_1^2\mu_2^3 s_h - \mu_1^2\mu_2^4 s_h - D^2\beta_1\beta_2\kappa_1\kappa_2 + Db_0\beta_1\beta_2\kappa_1\kappa_2 - D\beta_1\beta_2\kappa_1\kappa_2\mu_2\Big)
\end{aligned}
$$

$$
\begin{aligned}
B_2 := \beta_2\kappa_1\Big(\kappa_1+\mu_1\Big)\Big(&Db_0\beta_1\kappa_2 s_f s_h + Db_0\kappa_2\mu_1 s_f s_h + Db_0\mu_1\mu_2 s_f s_h - D\kappa_2\mu_1\mu_2 s_f s_h\\
&- D\mu_1\mu_2^2 s_f s_h - b_0\beta_1\kappa_2\mu_2 s_f^2 + b_0\beta_1\kappa_2\mu_2 s_f s_h + b_0\kappa_2\mu_1\mu_2 s_f s_h\\
&+ b_0\mu_1\mu_2^2 s_f s_h - \kappa_2\mu_1\mu_2^2 s_f s_h - \mu_1\mu_2^3 s_f s_h + D^2\beta_1\kappa_2 s_h\\
&- Db_0\beta_1\kappa_2 s_f - Db_0\beta_1\kappa_2 s_h - Db_0\kappa_2\mu_1 s_h - Db_0\mu_1\mu_2 s_h\\
&- D\beta_1\kappa_2\mu_2 s_f + 2D\beta_1\kappa_2\mu_2 s_h + D\kappa_2\mu_1\mu_2 s_h + D\mu_1\mu_2^2 s_h\\
&+ b_0\beta_1\kappa_2\mu_2 s_f - b_0\beta_1\kappa_2\mu_2 s_h - b_0\kappa_2\mu_1\mu_2 s_h - b_0\mu_1\mu_2^2 s_h\\
&- \beta_1\kappa_2\mu_2^2 s_f + \beta_1\kappa_2\mu_2^2 s_h + \kappa_2\mu_1\mu_2^2 s_h + \mu_1\mu_2^3 s_h\\
&- D^2\beta_1\kappa_2 + Db_0\beta_1\kappa_2 - D\beta_1\kappa_2\mu_2\Big)
\end{aligned}
$$

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