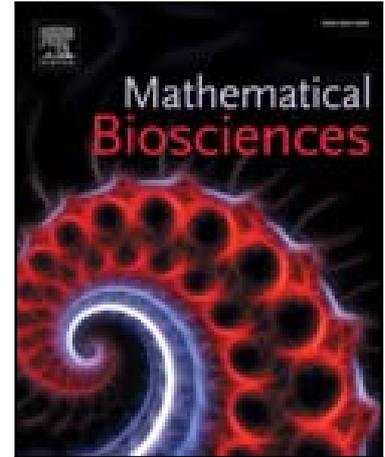


## Accepted Manuscript

Models to assess the effects of non-identical sex ratio augmentations of Wolbachia-carrying mosquitoes on the control of dengue disease

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**Highlights**

- *Wolbachia*-infected mosquitoes are released to break the cycle of dengue transmission.
- Modelling mosquitoes with stage structure and non-identical sex ratio augmentation is proposed.
- Bifurcation diagrams and the basin of attractions of equilibria are obtained.
- Three possible results for mosquito augmentation in parameter space are summarized.
- The study will be helpful to design proper mosquito augmentation plans.

ACCEPTED MANUSCRIPT

# Models to assess the effects of non-identical sex ratio augmentations of *Wolbachia*-carrying mosquitoes on the control of dengue disease

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## Abstract

The introduction of endosymbiont *Wolbachia* into laboratory-reared mosquito populations, which are then released to mix with natural populations to prevent the mosquito vectors from reproducing and thus break the transmission cycle of dengue disease, is an innovative new technology. Field trials of *Wolbachia*-carrying mosquitoes have now been implemented in many countries where there have been the outbreaks of dengue disease. A mathematical model is proposed to investigate the effects of non-identical sex ratio releases of *Wolbachia*-carrying mosquitoes on the control of dengue transmission. Firstly, we analyzed the existence and stability of equilibria for the system and proved the existence of forward and backward bifurcations. Secondly, bifurcation diagrams, the basins of attraction of the equilibria and the effects of mosquito augmentation for the system with imperfect and perfect transmission rates were obtained. Thirdly, three possible results for mosquito augmentation were summarized for different parameter regions. Further we explored an uncertainty and sensitivity analysis of solutions to estimate the effects of different parameter values on the success or failure of population replacement. Based on the above analysis, we considered a series of relevant issues such as (a) whether or not mosquito augmentation can ensure the success of population replacement? (b) If not, what are the parameter regions for the success or possible success of population replacement? (c) How does the initial density of natural mosquitoes and the quantity of mosquito augmentations affect the success of population replacement? (d) Whether all population replacements are effective for reducing the spread of dengue virus in the end? The results of this study will be helpful for public health authorities in designing proper strategies of mosquito augmentations for the control of dengue disease.

*Keywords:* *Wolbachia*, Dengue disease, Mosquito augmentation, Backward bifurcation

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## 1. Introduction

Dengue disease has rapidly become one of the most common widespread mosquito-borne diseases (MBDs) prevalent throughout the tropics and subtropics. It is estimated that around two-thirds of the world's population lives under the threat of dengue disease and almost 400 million infections occur each year [1, 2]. Dengue virus is transmitted to humans by mosquitoes, especially *Aedes aegypti*. There exist at least five different serotypes of dengue viruses (DENV 1-5) [3, 4], so people may be infected with dengue virus more than once [5]. There is no licensed

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vaccine and specific prophylactic or therapeutic drug for dengue disease. Infected individuals can gain lifelong immunity to the particular serotype that they are exposed to, but only temporary immunity to the others, which indicates that re-infection with another serotype will lead to a higher chance of developing the more severe forms of the disease: dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) [6, 7]. Thus it is very challenging to develop effective vaccines against all serotypes of dengue virus simultaneously. The control of the vector mosquitoes is therefore an appropriate method for preventing the spread of dengue disease [8, 9]. However, traditional strategies to reduce vector mosquitoes are usually unsuccessful or unsustainable. For example, extensive use of insecticides to reduce the number of adult or larval mosquitoes is often prohibitively expensive, may cause major toxicological effects on human health, and even lead to insecticide resistance [8, 10]. The destruction and removal of mosquito breeding sites can reduce oviposition sites for mosquitoes, but it is impractical for scaling up successfully over large geographical areas and in modern mega-cities [2, 11].

The introduction of *Wolbachia* bacteria into mosquitoes and widespread releases of such laboratory-reared insects, to mix with natural populations of mosquitoes to fight against MBDs, especially dengue disease, is an innovative technology that is now used in a variety of contexts [12, 13, 14, 15]. It has been estimated that up to 65% of insect species and approximately 28% of the surveyed mosquito species can carry *Wolbachia* [16]. *Wolbachia* typically emerge in the testes, ovaries and eggs of their host. Thus, they can interfere with the reproduction of the hosts through some remarkable mechanisms such as maternal inheritance, cytoplasmic incompatibility (CI), parthenogenesis, feminization of genetic males and so on. Moreover, the phenotype expressed depends on host species and *Wolbachia* strains. For instance, CI results in embryos from *Wolbachia*-free (or natural) females dying when they mate with *Wolbachia*-carrying males, whereas others are not affected [17, 18].

There are two main strategies for the control of dengue disease by using *Wolbachia*-carrying mosquito releases. One is based on CI mechanism to realize population suppression (reduction of mosquito numbers) through the inundative release of *Wolbachia*-carrying males [17]. China and Singapore are trying this approach [19]. Another is based on matrilineal inheritance and CI to realize population replacement (*Wolbachia*-carrying mosquitoes becoming established and replacing natural ones) through the mixture and inoculative releases of *Wolbachia*-carrying females and males [14, 15, 20, 21]. Ten countries, including Australia, Brazil, Colombia, Indonesia, Sri Lanka, India, Vietnam, Kiribati, Fiji and Vanuatu, have signed up for this approach [19]. The introduction of different *Wolbachia* strains or different tactics of augmentation may lead to different strategies of mosquito controls. The *Wolbachia* strain known as *wMelPop* can halve the lifespan of adult mosquitoes so that the mosquitoes will die before the completion of their extrinsic incubation period [13, 22, 23]. The *wMelPop-CLA* strain can halve the lifespan of adult mosquitoes and inhibit replication and transmission of some MBDs [24]. However, two other strains (*wMel* and *wAlbB*) have little influence on the lifespan of adult mosquitoes which contributes to the success of population replacement. Thus they can act as a 'vaccine' to prevent the mosquitoes from replicating and transmitting dengue viruses [14, 12, 25].

At present, *Wolbachia* strains as potential agents for the biological control of pathogen transmission have drawn attention from both biological and mathematical researchers. Since the first successful open augmentations (releases) of *wMel*-carrying mosquitoes in Yorkeys Knob and Gordonvale, Australia, in 2011 [15], mosquitoes implanted with different *Wolbachia* strains have been released to block the spread of dengue virus in other countries. For example, *wMelPop*- and *wMel*-carrying mosquitoes are augmented into natural populations in Tri Nguyen Island, Vietnam. At first, the experiment failed in April 2013 but was successful in May 2014 [26]. *wMel*-carrying mosquitoes were used in augmentations in the north of Rio de Janeiro, Brazil, in September 2014. Releases also began in Niteroi, Brazil, in August 2015 [27].

There have been several modelling studies investigating the population dynamics of natural

and *Wolbachia*-carrying mosquitoes, including discrete time models [28, 29, 30], continuous time ordinary differential equation models [31, 32, 33, 34], continuous time partial differential equation models [35, 36, 37, 38], stochastic dynamical models [39] and impulsive differential equation models [40, 26, 41]. The spread of *Wolbachia*, and how *Wolbachia* strains can affect the transmission of dengue disease has also been investigated [42, 43]. Haygood et. al. [30] developed both deterministic and stochastic models to analyze the evolutionary consequences of incompatibility in a sub-divided host population. They revealed that if population density is regulated locally, variation among patches in infection frequencies may induce change in the relative frequencies of the strains, and whether this change favours stronger incompatibility depends on the initial frequencies. Farkas et al. [31] studied the competition between mutually incompatible *Wolbachia* strains and developed an age-structured model with different fertility and mortality rates at different stages of the mosquitoes' life cycle. Zheng et al. [34] developed a delay differential equation model and proved that there exists a threshold for the success of *Wolbachia* invasion. Then they investigated the relationships of the minimal releasing of infected mosquitoes and the waiting time (the first time when the ratio of *Wolbachia* infected to total mosquitoes reaches 95%) with a time delay, and the waiting time in relation to the sex ratio of the released populations. Zhang et al. [40, 26, 41] developed impulsive differential equation models to investigate the effects of birth-pulse, different density-dependent death rates and different mosquito augmentations on the success of population replacement and suppression. An epidemic model with the presence of *Wolbachia* and seasonal forcing in the mosquito population was proposed to explore how the augmentations of *Wolbachia*-carrying mosquitoes affect human dengue cases in [44]. Farkas et al. [45] introduced sex-structured models with CI and male killing for the spread of *Wolbachia* in mosquito population, and extended the model to incorporate West Nile virus (WNV) dynamics among birds and mosquitoes by using an epidemic modelling approach. A basic reproduction number was computed for the WNV infection. The results suggested that, if the mosquito population consists mainly of *Wolbachia*-carrying individuals, WNV eradication is likely if WNV replication in *Wolbachia*-carrying individuals is sufficiently reduced.

In practice, *Wolbachia*-carrying mosquitoes are not necessarily augmented with identical sex ratio in some field trials, so it is important to explore the effects on population suppression or replacement of *Wolbachia*-carrying mosquito releases with different sex-ratios. The most severe outbreak of dengue disease in Guangzhou in China occurred in 2014, with more than 47,000 reported cases [46, 47, 48], so *Wolbachia*-carrying mosquitoes were released in Shazai Island, in Guangzhou by two separate procedures since Mar. 12, 2015 to fight against dengue disease. First, only *Wolbachia*-carrying male mosquitoes were released three times a week, with about 70,000 – 100,000 mosquitoes involved each time, to significantly reduce the density of female mosquitoes (population suppression). Next *Wolbachia*-carrying female mosquitoes were to be released for population replacement [48]. Note that not all the releases of *Wolbachia*-carrying mosquitoes succeed in suppressing or replacing the target population in open field trials [49]. Experience following the outbreak of Zika virus in Brazil provides an indirect evidence for the failure of open releases [50]. In addition, whether the strategy of population suppression or replacement is chosen has partly to do with costs. Unlike the replacement approach, the suppression approach is more expensive because it involves sorting males from females in the lab and requires sustained release of males [19]. We are therefore focusing on the second approach in this work. Clearly, it is essential to study how *Wolbachia*-carrying mosquito releases with different sex-ratios affect the dynamics of the mosquito population. Even though there have been many studies on the dynamics of population replacement and suppression, the appropriate threshold conditions to guide a successful practice remain unclear. Therefore, we developed a mathematical model to investigate how non-identical sex ratio releases of *Wolbachia*-carrying mosquitoes and specific parameter spaces affect the success of population suppression or re-

placement. We will consider a series of relevant issues such as (a) whether or not mosquito augmentation can ensure the success of population replacement? (b) If not, what are the parameter regions for the success or possible success of population replacement? (c) How does the initial density of natural mosquitoes and the quantity of mosquito augmentation affect the success of population replacement? (d) Whether or not all population replacements are effective in reducing the spread of dengue virus in the end? The results of this study will be helpful for public health authorities in designing proper plans on mosquito augmentation for the control of dengue transmission.

The paper is organized as follows. First, in Section 2, we develop a deterministic mathematical model to investigate how releases of non-identical sex-ratios of *Wolbachia*-carrying mosquitoes affect the success or failure of population suppression or replacement. In Section 3, we investigate the existence and stability of equilibria of the system, and prove the existence of forward and backward bifurcation. Then we give some numerical simulations and sensitivity analysis. In the final section, some discussions and conclusions are given.

## 2. Model formulation

Mosquitoes pass through four stages in their life cycles: egg, larva, pupa and adult, and the densities of each stage may have different dynamics. For convenience, the first three aquatic stages (egg, larva and pupa) are treated together as one stage termed larvae or aquatic ( $L$ ). Then *Wolbachia*-free (or natural) mosquitoes are divided into aquatic female ( $L_{NF}$ ), aquatic male ( $L_{NM}$ ), adult female ( $F_N$ ) and adult male ( $M_N$ ). Similarly, we divide *Wolbachia*-carrying mosquitoes into aquatic female ( $L_{WF}$ ), aquatic male ( $L_{WM}$ ), adult female ( $F_W$ ) and adult male ( $M_W$ ). Denote  $N_L = L_{NF} + L_{NM} + L_{WF} + L_{WM}$ . *Wolbachia* is mostly passed from *Wolbachia*-carrying adult females to their offspring with a probability  $\tau \in (0, 1]$ . The effect of the CI mechanism results in zygotic death of potential offspring with a probability  $q \in [0, 1]$  when a *Wolbachia*-carrying male mosquito mates with a *Wolbachia*-free female.  $d_i$  (or  $\tilde{d}_i$ ),  $i = 1, 2, 3, 4$ , denote the natural death rate of the corresponding female (or male) aquatic and adult populations, respectively.  $\beta_i$  (or  $\tilde{\beta}_i$ ) and  $\delta_i$  (or  $\tilde{\delta}_i$ ),  $i = 1, 2$ , denote the maturation rate and the density-dependent death rates of corresponding female (or male) aquatic populations, respectively. The natural birth rates of *Wolbachia*-free and -carrying mosquitoes are denoted as  $\tilde{b}_1$  and  $\tilde{b}_2$ , respectively.  $\eta_i$  ( $i=1,2,3$ ) denote the proportions of female offspring of *Wolbachia*-free females and of *Wolbachia*-carrying females with and without maternal inheritance, respectively.

It follows from numerical analysis (Figures 8, 10 and 11) in [41] that by decreasing the release period and increasing the release amount of mosquitoes, it is easier and faster to realize the strategy of population replacement. It indicates that sufficient release amount with high frequency is beneficial to the success of population replacement and then to dengue control. In practice, when mosquito clusters spring up, even along with the outbreak of dengue disease, we desire the successful control of mosquito population, such as the success of population replacement, within a short time. In this situation, it requires more amount of mosquito releases with more frequency, such as in each day, to control mosquito population, so we involve the daily average release quantities of *Wolbachia*-carrying females and males, which are denoted as

$\theta_1$  and  $\theta_2$ , respectively. By extending from [32, 34], we have the following model:

$$\left\{ \begin{array}{l} \frac{dL_{NF}}{dt} = \eta_1 \tilde{b}_1 F_N \left(1 - \frac{qM_W}{M_N + M_W}\right) + \eta_3 (1 - \tau) \tilde{b}_2 F_W - \beta_1 L_{NF} - d_1 L_{NF} \\ \quad - \delta_1 L_{NF} N_L, \\ \frac{dL_{NM}}{dt} = (1 - \eta_1) \tilde{b}_1 F_N \left(1 - \frac{qM_W}{M_N + M_W}\right) + (1 - \eta_3) (1 - \tau) \tilde{b}_2 F_W - \tilde{\beta}_1 L_{NM} \\ \quad - \tilde{d}_1 L_{NM} - \tilde{\delta}_1 L_{NM} N_L \\ \frac{dF_N}{dt} = \beta_1 L_{NF} - d_2 F_N, \\ \frac{dM_N}{dt} = \tilde{\beta}_1 L_{NM} - \tilde{d}_2 M_N, \\ \frac{dL_{WF}}{dt} = \eta_2 \tau \tilde{b}_2 F_W - \beta_2 L_{WF} - d_3 L_{WF} - \delta_2 L_{WF} N_L, \\ \frac{dL_{WM}}{dt} = (1 - \eta_2) \tau \tilde{b}_2 F_W - \tilde{\beta}_2 L_{WM} - \tilde{d}_3 L_{WM} - \tilde{\delta}_2 L_{WM} N_L, \\ \frac{dF_W}{dt} = \beta_2 L_{WF} - d_4 F_W + \theta_1, \\ \frac{dM_W}{dt} = \tilde{\beta}_2 L_{WM} - \tilde{d}_4 M_W + \theta_2. \end{array} \right. \quad (1)$$

Since only adult female mosquitoes bite and transmit dengue virus, we focus on the dynamics of aquatic and adult female mosquitoes. For system (1), denote  $\eta_i = 1/2$ , ( $i = 1, 2, 3$ ),  $b_i = \tilde{b}_i/2$ ,  $\beta_i = \tilde{\beta}_i$ , ( $i = 1, 2$ ) and  $d_j = \tilde{d}_j$ , ( $j = 1, 2, 3, 4$ ). Then the ratio of *Wolbachia*-free male and female mosquitoes is approximately 1 : 1 after several generations since system (1) will tend to a stable state, so we assume that the densities of *Wolbachia*-free males and females are identical, i.e.,  $F_N = M_N$ . In this paper, we aim to study the effects of *Wolbachia*-carrying mosquito releases with different sex ratios on the densities of natural mosquitoes during their outbreak season. Hence, we assume that there is no competition among the aquatic, i.e, there is a suitable environment for their development, such as abundant nutrition, temperature and humidity. Then we can disregard the effect of density dependence among aquatic, i.e.,  $\delta_i = \tilde{\delta}_i = 0$ , ( $i = 1, 2$ ). Therefore, system (1) can be simplified to:

$$\left\{ \begin{array}{l} \frac{dL_{NF}}{dt} = b_1 F_N \left(1 - \frac{qM_W}{F_N + M_W}\right) + (1 - \tau) b_2 F_W - \beta_1 L_{NF} - d_1 L_{NF}, \\ \frac{dF_N}{dt} = \beta_1 L_{NF} - d_2 F_N, \\ \frac{dL_{WF}}{dt} = \tau b_2 F_W - \beta_2 L_{WF} - d_3 L_{WF}, \\ \frac{dF_W}{dt} = \beta_2 L_{WF} - d_4 F_W + \theta_1, \\ \frac{dM_W}{dt} = \beta_2 L_{WF} - d_4 M_W + \theta_2. \end{array} \right. \quad (2)$$

The definitions of variables are the same as for system (1). The definition of parameters and the ranges of their values are shown in Table 1. It can be verified that for system (2) without the introduction of *Wolbachia*-carrying mosquitoes, there exists a stable (or unstable) equilibrium  $(0, 0)$  provided that  $d_2 > b_1 \beta_1 / (\beta_1 + d_1)$  (or  $d_2 < b_1 \beta_1 / (\beta_1 + d_1)$ ), which indicates the success (or failure) of population suppression. In the following, we mainly study the existence and stability of equilibria and bifurcation analysis of system (2).

### 3. Results

#### 3.1. The existence of equilibria

Equilibria of system (2) are nonnegative roots of the algebraic equations obtained by setting the right hand side of system (2) equal to zero. By simple calculation, equilibria of system (2) satisfy the following equations:

$$F_N = \frac{\beta_1 L_{NF}}{d_2}, \quad F_W = \frac{\beta_2 L_{WF} + \theta_1}{d_4}, \quad M_W = \frac{\beta_2 L_{WF} + \theta_2}{d_4}.$$

Then we obtain the interior equilibria of system (2) as follows

$$E_i^* = \left( L_{NF}^{(i)}, \frac{\beta_1 L_{NF}^{(i)}}{d_2}, L_{WF}^*, \frac{\beta_2 L_{WF}^* + \theta_1}{d_4}, \frac{\beta_2 L_{WF}^* + \theta_2}{d_4} \right), \quad i = 1, 2,$$

Table 1: Parameter descriptions, values and sources for the models. (*W*: *Wolbachia*)

Para.	Description	Value(Range)	Unit	Source
$\eta$	Proportion of aquatic born female	0.5(0.4,0.6)	N/A	[32, 34]
$b_1$	Birth rate of <i>W</i> -free adult females $b_1 = \eta \bar{b}_1$	0.3976(0.01,0.85)	day <sup>-1</sup>	[14, 34]
$\beta_1$	Maturation rate of <i>W</i> -free mosquitoes	0.1(0.01, 0.85)	day <sup>-1</sup>	[44, 51]
$d_1$	Natural death rate of <i>W</i> -free aquatic	0.0714(0.01, 0.85)	day <sup>-1</sup>	[44, 51]
$d_2$	Natural death rate of <i>W</i> -free adults	0.0714(0.01, 0.85)	day <sup>-1</sup>	[51]
$b_2$	Birth rate of <i>W</i> -carrying adult females $b_2 = (1 - \eta)b_2$	0.3777(0.01,0.85)	day <sup>-1</sup>	[14]
$\beta_2$	Maturation rate of <i>W</i> -carrying mosquitoes	0.1(0.01, 0.85)	day <sup>-1</sup>	[51]
$d_3$	Natural death rate of <i>W</i> -carrying aquatic	0.0714(0.01, 0.85)	day <sup>-1</sup>	[51]
$d_4$	Natural death rate of <i>W</i> -carrying adults	0.0785(0.01, 0.85)	day <sup>-1</sup>	[14, 21]
$\tau$	Maternal transmission rate	0.9(0.5, 1)	N/A	[14, 44]
$q$	CI rate	0.9(0.5, 1)	N/A	[15, 43]
$\theta_1$	The quantity of <i>W</i> -carrying adult females augmented	(0.1, 30)	Capita	Assume
$\theta_2$	The quantity of <i>W</i> -carrying adult males augmented	(0.1, 30)	Capita	Assume

where

$$L_{WF}^* = \frac{\tau b_2 \theta_1}{P_1}, \quad P_1 = d_4(\beta_2 + d_3) - \tau b_2 \beta_2.$$

If  $P_1 > 0$ , then  $L_{WF}^* > 0$ .  $L_{NF}^{(i)}$  ( $i = 1, 2$ ) is the positive root of the following equation

$$AL_{NF}^2 + BL_{NF} + C = 0, \quad (3)$$

where

$$\begin{aligned} A &= \beta_1 d_4^2 P_2, \\ B &= d_2 d_4 ((1 - \tau) b_2 \beta_1 (\beta_2 L_{WF}^* + \theta_1) + P_3 (\beta_2 L_{WF}^* + \theta_2)), \\ C &= (1 - \tau) b_2 d_2^2 (\beta_2 L_{WF}^* + \theta_1) (\beta_2 L_{WF}^* + \theta_2) \geq 0, \\ P_2 &= b_1 \beta_1 - d_2 (\beta_1 + d_1) > P_3 = (1 - q) b_1 \beta_1 - d_2 (\beta_1 + d_1). \end{aligned} \quad (4)$$

Solving the above equation with respect to  $L_{NF}$  yields

$$L_{NF}^{(i)} = \frac{-B \mp \sqrt{B^2 - 4AC}}{2A}.$$

In practice, different environments may induce different values of parameters related to mosquito dynamics. We aim to explore, in a large interval of these parameters, the effects of mosquito augmentation as control parameters on the three outcomes of population replacement (unsuccessful, possibly successful and successful replacement) which will be clear in subsection 3.4.2). Therefore, we first choose  $d_2$  and  $d_4$  as the first layer of bifurcation parameters to determine parameter regions related to different environment settings, and then explore under each parameter regions how do the second layer of control parameters  $(\theta_1, \theta_2)$  impact the existence of equilibria for system (2). To provide valuable explanation from biology, the three equations  $P_i = 0$  ( $i = 1, 2, 3$ ) are recompounded, respectively, as follows:

$$\begin{aligned} \Gamma_1 : d_4 &= \frac{\tau b_2 \beta_2}{\beta_2 + d_3} \triangleq B_W, \\ \Gamma_2 : d_2 &= \frac{b_1 \beta_1}{\beta_1 + d_1} \triangleq B_N, \\ \Gamma_3 : d_2 &= \frac{(1-q) b_1 \beta_1}{\beta_1 + d_1} \triangleq B_{NW}, \end{aligned} \quad (5)$$

where  $B_W$  is defined as an effective maturation rate of *Wolbachia*-carrying mosquitoes from aquatic to adult female. While  $B_N$  and  $B_{NW}$  are defined as a total maturation rate and an effective maturation rate of *Wolbachia*-free aquatic mosquitoes, respectively.

Note that there is no density competition in system (2), so except for the two interior equilibria, the system may exist infinite singular point(s). In order to further investigate the existence of backward bifurcation for system (2) in subsection 3.3, it is necessary to introduce the Poincare transformation  $V = L_{NF}/F_N$  and  $Z = 1/F_N$ , and study the existence and stability of equilibria corresponding to infinite singular points in system (2). We obtain the Poincare transformation system as follows:

$$\begin{cases} \frac{dV}{dt} = b_1 \left(1 - \frac{qM_W Z}{1+M_W Z}\right) + (1 - \tau) b_2 F_W Z - \beta_1 V^2 - (\beta_1 + d_1 - d_2) V \triangleq f(V, Z), \\ \frac{dZ}{dt} = -Z(\beta_1 V - d_2), \\ \frac{dL_{WF}}{dt} = \tau b_2 F_W - \beta_2 L_{WF} - d_3 L_{WF}, \\ \frac{dF_W}{dt} = \beta_2 L_{WF} - d_4 F_W + \theta_1, \\ \frac{dM_W}{dt} = \beta_2 L_{WF} - d_4 M_W + \theta_2. \end{cases} \quad (6)$$

Solving equation  $f(V, 0) = 0$  with respect to  $V$  yields

$$V_{1,2}^* = \frac{-(\beta_1 + d_1 - d_2) \mp \sqrt{(\beta_1 + d_1 - d_2)^2 + 4b_1 \beta_1}}{2\beta_1}.$$

Then the positive infinite singular point of system (6) is

$$\tilde{E}_\infty = \left( V_2^*, 0, L_{WF}^*, \frac{\beta_2 L_{WF}^* + \theta_1}{d_4}, \frac{\beta_2 L_{WF}^* + \theta_2}{d_4} \right).$$

Thus, there exists one positive infinity equilibrium of system (2), denoted as

$$E_\infty = \left( +\infty, +\infty, L_{WF}^*, \frac{\beta_2 L_{WF}^* + \theta_1}{d_4}, \frac{\beta_2 L_{WF}^* + \theta_2}{d_4} \right).$$

Note that the last three variables of system (2) are independent to the first two, so the existence of positive equilibria is determined by the first two variables. Moreover when parameter values are fixed, the last three coordinates of the interior and infinity equilibria have the same values, which indicates that the density of *Wolbachia*-carrying mosquitoes tends to a constant after a long enough time.

With system (2) de-coupled, we can study the dynamics of the first two equations. Based on (3), there may exist zero, one or even two positive equilibria for system (2) with an imperfect transmission rate  $\tau \in (0, 1)$  depending on the values of  $A$ ,  $B$  and  $B^2 - 4AC$ . When  $A < 0$ , i.e., the natural death rate of *Wolbachia*-free adult mosquitoes is larger than the total maturation rate of *Wolbachia*-free aquatic mosquitoes, then there just exists one positive equilibrium  $E_1^*$  for system (2). In the following, we focus on investigating the existence of positive equilibria with  $A > 0, C > 0$ . Then whether equation (3) exists with positive roots or not is determined by the sign of  $B$ .

Solving the equation  $B = 0$  with respect to  $\theta_2$  obtains

$$L_1 : \theta_2^{(1)} = \frac{-b_2(\tau\beta_2 P_3 + P_4)}{P_1 P_3} \theta_1 \triangleq G_1 \theta_1, \quad (7)$$

with

$$P_4 = \beta_1 d_4 (1 - \tau)(\beta_2 + d_3) > 0.$$

Then we rearrange the discriminant  $B^2 - 4AC = 0$  as follows

$$A_1 \theta_2^2 + B_1 \theta_1 \theta_2 + C_1 \theta_1^2 = 0, \quad (8)$$

with

$$\begin{aligned} A_1 &= P_3^2 > 0, \\ B_1 &= \frac{2b_2(\tau\beta_2 P_3^2 - P_4(P_2 + b_1\beta_1 q))}{P_1^2}, \\ C_1 &= \frac{b_2^2((\tau\beta_2 P_3 + P_4)^2 - 4\tau\beta_2 P_2 P_4)}{P_1^2}. \end{aligned} \quad (9)$$

Solving equation (8) with respect to  $\theta_2$  yields

$$\begin{aligned} L_2 : \theta_2^{(2)} &= \frac{-B_1 P_1 - 4b_2 P_4 \sqrt{b_1 \beta_1 q P_2}}{2A_1 P_1} \theta_1 \triangleq G_2 \theta_1, \\ L_3 : \theta_2^{(3)} &= \frac{-B_1 P_1 + 4b_2 P_4 \sqrt{b_1 \beta_1 q P_2}}{2A_1 P_1} \theta_1 \triangleq G_3 \theta_1, \text{ with } G_2 < G_3. \end{aligned} \quad (10)$$

From (7) and (10), we have

$$G_3 - G_1 = \frac{2b_2 P_2 P_4 (1 + P_1 \sqrt{q b_1 \beta_1})}{P_1 P_3^2} > 0,$$

so the slope of  $L_3$  is larger than that of  $L_1$  and  $L_2$ . Because the location of three curves  $L_i$  is determined by  $G_i$  ( $i = 1, 2, 3$ ), it is necessary to consider the equations  $\tau\beta_2 P_3 + P_4 = 0$ ,  $B_1 = 0$  and  $C_1 = 0$ , which are equivalent to

$$\begin{aligned} \Gamma_4 : \Phi_1(d_2, d_4) &= \tau\beta_2 P_3 + P_4 = 0 \Leftrightarrow d_4 = \frac{-\tau\beta_2 P_3}{\beta_1(1-\tau)(\beta_2+d_3)} \triangleq B(d_2), \\ \Gamma_5 : \Phi_2(d_2, d_4) &= \tau\beta_2 P_3^2 - P_4(P_2 + b_1\beta_1 q) = 0, \\ \Gamma_6 : \Phi_3(d_2, d_4) &= (\tau\beta_2 P_3 + P_4)^2 - 4\tau\beta_2 P_2 P_4 = 0. \end{aligned} \quad (11)$$

Moreover the three curves  $\Gamma_4, \Gamma_5$  and  $\Gamma_6$  intersect at the following two points

$$(B_{NW}, 0) \text{ and } \left( B_N, \frac{q\tau b_1 \beta_2}{(1-\tau)(\beta_2 + d_3)} \right).$$

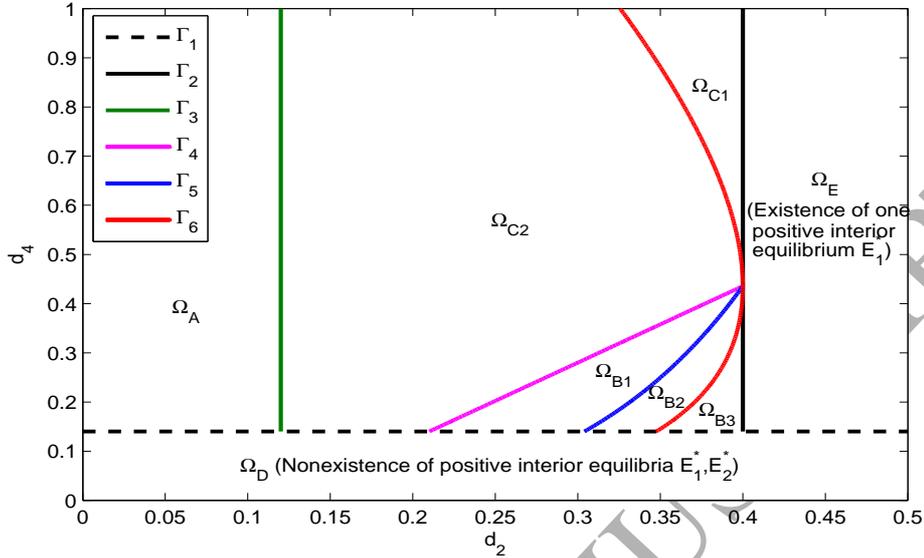


Figure 1: The regions for the existence of equilibria of system (2) with an imperfect transmission rate. The parameter values are fixed as follows:  $b_1 = 0.8, b_2 = 0.6, \beta_1 = 0.3, \beta_2 = 0.2, \tau = 0.7, q = 0.7, d_1 = 0.3, d_3 = 0.4$ .

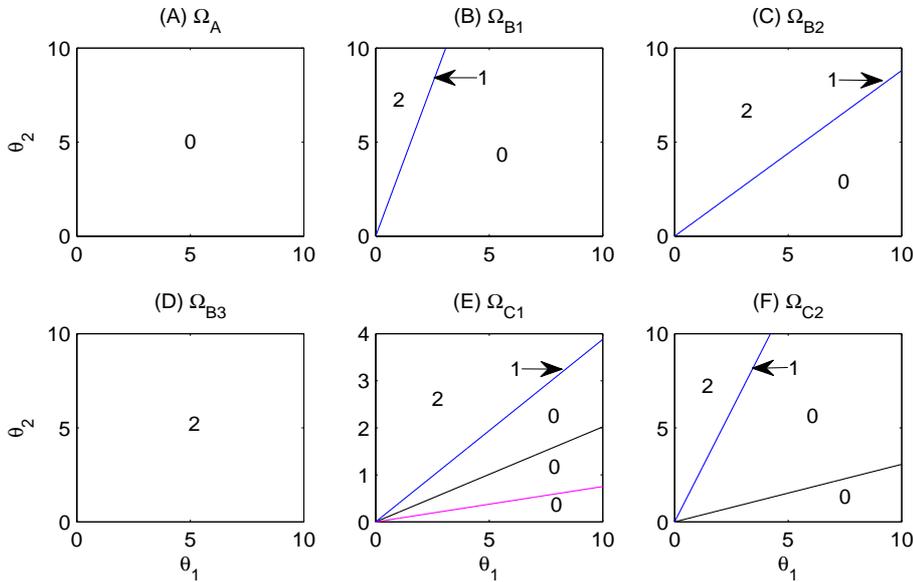


Figure 2: The existence of interior equilibria in different regions. (A)  $d_2 = 0.1, d_4 = 0.3$ ; (B)  $d_2 = 0.3, d_4 = 0.25$ ; (C)  $d_2 = 0.35, d_4 = 0.2$ ; (D)  $d_2 = 0.38, d_4 = 0.2$ ; (E)  $d_2 = 0.39, d_4 = 0.85$ ; (F)  $d_2 = 0.3, d_4 = 0.5$ . The other parameter values are the same as in Fig 1. Black, magenta and blue lines denote the three lines  $L_1, L_2$  and  $L_3$ , respectively. The items 0, 1 and 2 mean that in the corresponding regions there is zero, one interior equilibrium and two interior equilibria, respectively. Especially, in (E) and (F), there is no interior equilibrium in the regions below blue line, including on the black and magenta lines.

The six curves  $(\Gamma_i, i = 1, 2, 3, 4, 5, 6)$  divide the  $d_2$  and  $d_4$  parameter space into eight regions as shown in Fig 1. We choose  $d_2$  and  $d_4$  as the first layer of bifurcation parameters to investigate how the number of positive interior equilibria for system (2) in different regions is affected by

the second layer of control parameters (*i.e.*  $\theta_1, \theta_2$ ), as shown in Fig 2. When  $d_4 < B_W$ , there is no positive interior equilibrium, as shown in region  $\Omega_D$  of Fig 1. When  $A < 0$ , *i.e.*,  $d_2 > B_N$ , there only exists one positive interior equilibrium, as shown in region  $\Omega_E$  of Fig 1. Next, we mainly discuss the existence of positive interior equilibria in the following three cases. For convenience, interior equilibria stand for positive interior equilibria below.

**Case A:**  $(d_2, d_4) \in \Omega_A \Leftrightarrow d_2 < B_{NW}, d_4 > B_W$

In this case, parameter values lie in region  $\Omega_A$  of Fig 1, we have  $G_1 < 0$ , and  $B > 0$  is well defined in the first quadrant of  $\theta_1 - \theta_2$  plane. Thus there is no interior equilibrium in the first quadrant. This indicates that the strategy of population replacement cannot be achieved for any mosquito augmentation (see Fig 2 (A)).

**Case B:**  $(d_2, d_4) \in \Omega_{B_i}, i = 1, 2, 3 \Leftrightarrow d_2 > B_{NW}, B_W < d_4 < B(d_2)$

In this case, parameter values may lie in one of the regions  $\Omega_{B_i} (i = 1, 2, 3)$  of Fig 1, we have  $G_1 < 0$ , and  $B < 0$  is well defined in the first quadrant of the  $\theta_1 - \theta_2$  plane. This indicates that there may exist zero, one or two interior equilibria depending on the value of  $B^2 - 4AC$ . Based on (8),  $A_1 > 0$  and  $B_1^2 - 4A_1C_1 > 0$  are well defined.

**Case  $B_1$ :** When  $B_1 < 0$  and  $C_1 < 0$  (see  $\Omega_{B_1}$  in Fig 1), we have  $G_2 < 0$  and  $G_3 > 0$ . There are two interior equilibria provided  $\theta_2 > \theta_2^{(3)}$ ; the two interior equilibria coincide as one provided that  $\theta_2 = \theta_2^{(3)}$ ; there is no interior equilibrium provided that  $\theta_2 < \theta_2^{(3)}$ , as shown in Fig 2 (B).

**Case  $B_2$ :** When  $B_1 > 0$  and  $C_1 < 0$  (see  $\Omega_{B_2}$  in Fig 1), we have  $G_2 < 0$  and  $G_3 > 0$ . There are similar results as in Case  $B_1$ , as shown in Fig 2 (C).

**Case  $B_3$ :** When  $B_1 > 0$  and  $C_1 > 0$  (see  $\Omega_{B_3}$  in Fig 1), we have  $G_2 < 0$  and  $G_3 < 0$ . There exist two interior equilibria in the  $\theta_1 - \theta_2$  plane, as shown in Fig 2 (D).

**Case C:**  $(d_2, d_4) \in \Omega_{C_i}, i = 1, 2 \Leftrightarrow d_2 > B_{NW}, d_4 > \max\{B_W, B(d_2)\}$

In this case, parameter values may lie in one of the regions  $\Omega_{C_i} (i = 1, 2)$  of Fig 1, we have  $G_1 > 0$ , and the first quadrant of the  $\theta_1 - \theta_2$  plane is divided into the regions of  $B > 0$  and  $B < 0$ . There is no interior equilibrium for  $B > 0$ . While there may exist zero, one or two interior equilibria for  $B < 0$  depending on the value of  $B^2 - 4AC$  and the relationship among  $G_1, G_2$  and  $G_3$ .

**Case  $C_1$ :** When  $B_1 < 0$  and  $C_1 > 0$  (see  $\Omega_{C_1}$  in Fig 1), we have  $G_3 > G_2 > 0$ . If  $G_3 > G_2 > G_1$ , then there are two interior equilibria provided that  $\theta_2 > \theta_2^{(3)}$  or  $\theta_2 < \theta_2^{(2)}$ ; the two interior equilibria coincide as one provided that  $\theta_2 = \theta_2^{(2)}$  or  $\theta_2 = \theta_2^{(3)}$ ; there is no interior equilibrium provided that  $\theta_2^{(2)} < \theta_2 < \theta_2^{(3)}$  or  $\theta_2 < \theta_2^{(1)}$ . If  $G_3 > G_1 > G_2$ , then there are two interior equilibria provided that  $\theta_2 > \theta_2^{(3)}$ ; the two interior equilibria coincide as one provided that  $\theta_2 = \theta_2^{(3)}$ ; there is no interior equilibrium provided that  $\theta_2 < \theta_2^{(3)}$ , as shown in Fig 2(E).

**Case  $C_2$ :** When  $B_1 < 0$  and  $C_1 < 0$  (see  $\Omega_{C_2}$  in Fig 1), we have  $G_2 < 0$  and  $G_3 > G_1 > 0$ . There are two interior equilibria provided that  $\theta_2 > \theta_2^{(3)}$ ; the two interior equilibria coincide as one provided that  $\theta_2 = \theta_2^{(3)}$ ; there is no interior equilibrium provided that  $\theta_2 < \theta_2^{(3)}$ , as shown in Fig 2(F).

We summarize the above discussion about the existence of equilibria for system (2) as follows.

**Theorem 1.** For system (2) with imperfect transmission rate  $\tau \in (0, 1)$ .

- (i) When  $d_4 < B_W$  (*i.e.*,  $\Omega_D$ ), there is no interior equilibrium.
- (ii) When  $d_2 < B_{NW}$  and  $d_4 > B_W$  (*i.e.*,  $\Omega_A$ ), there exists infinity equilibrium  $E_\infty$ ;
- (iii) When  $B_{NW} < d_2 < B_N$  (*i.e.*,  $\Omega_B$  and  $\Omega_C$ ), there always exists infinity equilibrium  $E_\infty$ . In regions  $\Omega_{B_i} (i = 1, 2)$ ,  $\Omega_{C_1}$  with  $G_3 > G_1 > G_2$  and  $\Omega_{C_2}$ , there are two interior equilibria  $E_1^*$  and

$E_2^*$  provided that  $\theta_2 > \theta_2^{(3)}$ ; the two interior equilibria coalesce as  $E^*$  provided that  $\theta_2 = \theta_2^{(3)}$ ; there is no interior equilibrium provided that  $\theta_2 < \theta_2^{(3)}$ . In region  $\Omega_{B3}$ , there are two interior equilibria  $E_1^*$  and  $E_2^*$ . In region  $\Omega_{C1}$  with  $G_3 > G_2 > G_1$ , there are two interior equilibria provided that  $\theta_2 > \theta_2^{(3)}$  or  $\theta_2 < \theta_2^{(2)}$ ; the two interior equilibria coincide as one provided that  $\theta_2 = \theta_2^{(2)}$  or  $\theta_2 = \theta_2^{(3)}$ ; there is no interior equilibrium provided that  $\theta_2^{(2)} < \theta_2 < \theta_2^{(3)}$  or  $\theta_2 < \theta_2^{(1)}$ . (iv) When  $d_2 > B_N$  and  $d_4 > B_W$  (i.e.,  $\Omega_E$ ), there exists one interior equilibrium  $E_1^*$ .

When the transmission from mother to offspring is perfect, i.e.,  $\tau = 1$ , then we have  $A = \beta_1 d_4^2 P_2$ ,  $B = d_2 d_4 P_3 (\beta_2 L_{WF}^* + \theta_2)$  and  $C = 0$  with

$$P_1 = d_4(\beta_2 + d_3) - b_2 \beta_2 > 0, P_4 = 0 \text{ and } L_{WF}^* = \frac{b_2 \theta_1}{P_1}.$$

The existence of infinite equilibrium  $E_\infty^*$  is similar to that for system (2) with an imperfect transmission rate. While for the existence of finite equilibria, if  $A > 0$ , i.e.,  $d_2 < B_N$  (or  $A < 0$ , i.e.,  $d_2 > B_N$ ), then  $L_{NF}^{(1)}$  (or  $L_{NF}^{(2)}$ ) is replaced by zero. Moreover, three curves  $\Gamma^4, \Gamma^5$  and  $\Gamma^6$  coincide with  $\Gamma^3$ . The other three curves  $L_i$  ( $i = 1, 2, 3$ ) also coincide together and  $G_i = -b_2 \beta_2 / P_1 < 0$ . When  $P_3 > 0$ , i.e.,  $d_2 < B_{NW}$ , then  $B > 0$  is well defined in the first quadrant of the  $\theta_1 - \theta_2$  plane. This indicates that there is one boundary equilibrium  $E_2^*$  for any possibility of mosquito augmentation, where

$$E_2^* = (0, 0, L_{WF}^*, \frac{\beta_2 L_{WF}^* + \theta_1}{d_4}, \frac{\beta_2 L_{WF}^* + \theta_2}{d_4}) \triangleq E_0^*.$$

When  $B_{NW} < d_2 < B_N$ , then  $B < 0$  is well defined in the first quadrant of  $\theta_1 - \theta_2$  plane. It indicates that boundary equilibrium  $E_1^*$  and interior equilibrium  $E_2^*$  coexist for any possibility of mosquito augmentation, where

$$E_1^* = (0, 0, L_{WF}^*, \frac{\beta_2 L_{WF}^* + \theta_1}{d_4}, \frac{\beta_2 L_{WF}^* + \theta_2}{d_4}) \triangleq E_0^*,$$

$$E_2^* = (L_{NF}^{(2)}, \frac{\beta_1 L_{NF}^{(2)}}{d_2}, L_{WF}^*, \frac{\beta_2 L_{WF}^* + \theta_1}{d_4}, \frac{\beta_2 L_{WF}^* + \theta_2}{d_4}),$$

with  $L_{NF}^{(2)} = -B/A > 0$ . When  $d_2 > B_N$ , then  $B < 0$  is well defined in the first quadrant of the  $\theta_1 - \theta_2$  plane. This indicates that there is one boundary equilibrium  $E_1^*$  for any possibility of mosquito augmentation, where

$$E_1^* = (0, 0, L_{WF}^*, \frac{\beta_2 L_{WF}^* + \theta_1}{d_4}, \frac{\beta_2 L_{WF}^* + \theta_2}{d_4}) \triangleq E_0^*.$$

Similarly,  $d_2$  and  $d_4$  are chosen as first layer of bifurcation parameters to investigate the existence of equilibria for system (2) with perfect transmission rate, and the six degenerative curves (i.e.,  $\Gamma_i, i = 1, 2, 3, 4, 5, 6$ ) divide the two parameter space into many regions as shown in Fig 3. Based on the above, we have the following theorem.

**Theorem 2.** For system (2) with a perfect transmission rate  $\tau = 1$ .

- (i) When  $d_4 < B_W$  (i.e.,  $\Omega_D$ ), there is no interior equilibrium.
- (ii) When  $d_2 < B_{NW}$  and  $d_4 > B_W$  (i.e.,  $\Omega_A$ ), there exists infinity equilibrium  $E_\infty$ , while interior equilibrium  $E_2^*$  is degenerated as boundary equilibrium  $E_0^*$ .
- (iii) When  $B_{NW} < d_2 < B_N$  and  $d_4 > B_W$  (i.e.,  $\Omega_B$  and  $\Omega_C$ ), there exist infinite equilibrium  $E_\infty$  and interior equilibrium  $E_2^*$ , while interior equilibrium  $E_1^*$  is degenerated as boundary equilibrium  $E_0^*$ .
- (iv) When  $d_2 > B_N$  (i.e.,  $\Omega_E$ ), there exists infinite equilibrium  $E_\infty$ , while interior equilibrium  $E_1^*$  is degenerated as boundary equilibrium  $E_0^*$ .

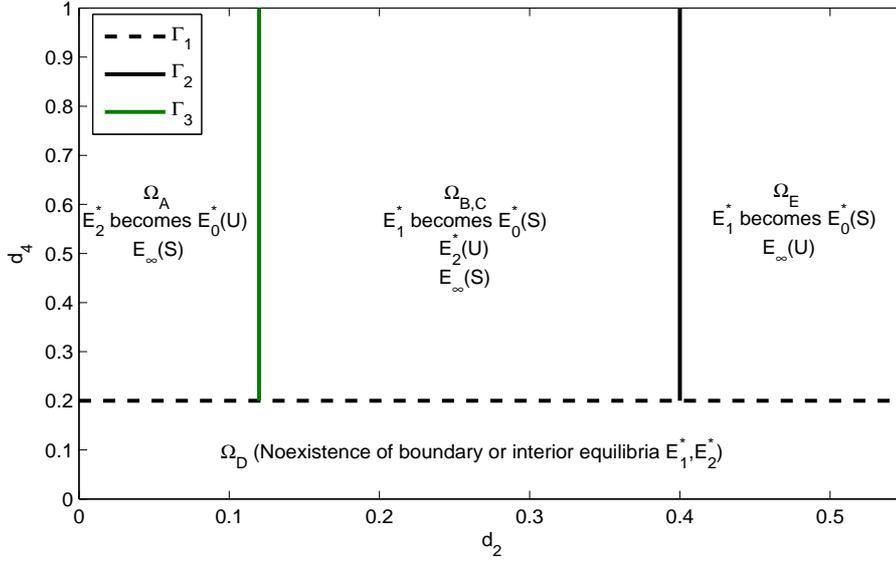


Figure 3: The regions for the existence of equilibria of system (2) with perfect transmission rate. Except for  $\tau = 1$ , the other parameter values are the same as in Fig 1.

### 3.2. The stability analysis of equilibria

From Theorems 1 and 2, the existence of interior equilibria of system (2) in different parameter regions is discussed in detail. The success (or failure) of population replacement means *Wolbachia*-carrying mosquitoes (or not) becoming established and replacing natural ones, which is determined by the stability of interior equilibria  $E_i^*$ ,  $i = 1, 2$  (or infinity equilibrium  $E_\infty$ ). It therefore is important to analyze the stability of these equilibria, and we have the following main results.

**Theorem 3.** For system (2) with imperfect transmission rate  $\tau \in (0, 1)$  and suppose  $d_4 > B_W$ .

- (i) When  $d_2 < B_{NW}$  (i.e.,  $\Omega_D$ ), then  $E_\infty$  is locally stable.
- (ii) When  $B_{NW} < d_2 < B_N$  (i.e.,  $\Omega_B$  and  $\Omega_C$ ), then the interior equilibrium may be locally stable or not. In regions  $\Omega_{Bi}$  and  $\Omega_{Ci}$ ,  $i = 1, 2$ ,  $E_1^*$  and  $E_2^*$  are locally stable and unstable, respectively, provided that  $\theta_2 > \theta_2^{(3)}$ ;  $E^*$  is a center provided  $\theta_2 = \theta_2^{(3)}$ . In region  $\Omega_{B3}$ ,  $E_1^*$  and  $E_2^*$  are locally stable and unstable, respectively.
- (iii) When  $d_2 > B_N$  (i.e.,  $\Omega_E$ ), then  $E_1^*$  and  $E_\infty$  are locally stable and unstable, respectively.

**Proof.** Note that  $d_4 > B_W$  is a necessary condition for the existence of  $E_\infty$  and  $E_i^*$  ( $i = 1, 2$ ). In order to determine the stability of  $E_i^*$  ( $i = 1, 2$ ) of system (2) with an imperfect transmission rate, the Jacobian matrix at  $E_i^*$  is given as

$$J(E_i^*) = \begin{pmatrix} -(\beta_1 + d_1) & b_1 \left(1 - \frac{qM_W^{2*}}{(F_N^{(i)} + M_W^*)^2}\right) & 0 & (1 - \tau)b_2 & 0 \\ \beta_1 & -d_2 & 0 & 0 & 0 \\ 0 & 0 & -(\beta_2 + d_3) & \tau b_2 & 0 \\ 0 & 0 & \beta_2 & -d_4 & 0 \\ 0 & 0 & \beta_2 & 0 & -d_4 \end{pmatrix}. \quad (12)$$

The eigenfunction of  $E_i^*$  is obtained as follows:

$$(\lambda + d_4)(\lambda^2 + (\beta_2 + d_3 + d_4)\lambda + P_1) \left( \lambda^2 + (\beta_1 + d_1 + d_2)\lambda + \frac{b_1\beta_1qM_W^{2*}}{(F_N^{(i)} + M_W^*)^2} - P_2 \right) = 0. \quad (13)$$

From  $d_4 > B_W$ , we have  $P_1 > 0$ , so the real parts of the first three eigenvalues are negative. Then the stability of  $E_i^*$  ( $i = 1, 2$ ) is determined by the value of

$$\Psi(\theta_1, \theta_2) \triangleq \frac{b_1\beta_1qM_W^{2*}}{(F_N^{(i)} + M_W^*)^2} - P_2.$$

Similarly, for the stability of  $\tilde{E}_\infty$ , its eigenfunction is obtained as follows:

$$(\lambda + 2\beta_1V_2^* + (\beta_1 + d_1 - d_2))(\lambda + \beta_1V_2^* - d_2)(\lambda + d_4)(\lambda^2 + (\beta_2 + d_3 + d_4)\lambda + P_1) = 0. \quad (14)$$

(i) When  $d_2 < B_{NW}$ , based on the analysis on the above section, there is no interior equilibrium in this case. Solving the roots of (14) with respect to  $\lambda$ , we have

$$\lambda_1 = -\sqrt{(\beta_1 + d_1 - d_2)^2 + 4b_1\beta_1} < 0, \lambda_3 = -d_4 < 0,$$

and

$$\lambda_2 = d_2 - \beta_1V_2^* < 0$$

provided that  $d_2 < B_N$ . The other two roots of (14) are negative provided that  $d_4 > B_W$ . Thus when  $d_4 > B_W$  and  $d_2 < B_{NW} < B_N$ , then  $\tilde{E}_\infty$  is locally stable which indicates that  $E_\infty$  is locally stable.

(ii) When  $B_{NW} < d_2 < B_N$ , based on the proof in (i),  $E_\infty$  is locally stable. Suppose that  $E_i^*$  ( $i = 1, 2$ ) exist, then it is obvious that  $\Psi(\theta_1, \theta_2) > 0$  is equivalent to

$$\frac{b_1\beta_1qM_W^*}{F_N^{(i)} + M_W^*} - \sqrt{b_1\beta_1qP_2} > 0 \quad (15)$$

or

$$\frac{b_1\beta_1qM_W^*}{F_N^{(i)} + M_W^*} + \sqrt{b_1\beta_1qP_2} < 0. \quad (16)$$

It is not valid for (16), so only (15) is considered in this case. If  $B^2 - 4AC = 0$ , then  $E_1^*$  and  $E_2^*$  overlap as  $E^* = (L_{WF}^*, F_N^*, L_W^*, F_W^*, M_W^*)$ . Thus

$$\begin{cases} \frac{b_1\beta_1qM_W^*}{F_N^* + M_W^*} - \sqrt{b_1\beta_1qP_2} = 0 \Leftrightarrow \theta_2 = G_3\theta_1, \\ \frac{b_1\beta_1qM_W^*}{F_N^* + M_W^*} + \sqrt{b_1\beta_1qP_2} = 0 \Leftrightarrow \theta_2 = G_2\theta_1. \end{cases} \quad (17)$$

Then in regions  $\Omega_{Bi}$  and  $\Omega_{Ci}$ ,  $i = 1, 2$ , if  $\theta_2 = \theta_2^{(3)}$ , then we have  $\Psi(\theta_1, \theta_2) = 0$ , which indicates that the linearized system around the coalesced equilibrium  $E^*$  of  $E_1^*$  and  $E_2^*$  has a pair of pure imaginary roots. Therefore,  $E^*$  is a centre. Note that

$$\begin{aligned} \frac{b_1\beta_1qM_W^*}{F_N^{(1)} + M_W^*} - \sqrt{b_1\beta_1qP_2} &> \frac{b_1\beta_1qM_W^*}{F_N^* + M_W^*} - \sqrt{b_1\beta_1qP_2} = 0, \\ \frac{b_1\beta_1qM_W^*}{F_N^{(2)} + M_W^*} - \sqrt{b_1\beta_1qP_2} &< \frac{b_1\beta_1qM_W^*}{F_N^* + M_W^*} - \sqrt{b_1\beta_1qP_2} = 0, \end{aligned} \quad (18)$$

then the real parts of the eigenvalues of  $E_1^*$  are all negative, while for  $E_2^*$ , there exists one positive eigenvalue. Therefore, we can prove the results in case (ii).

(iii) When  $d_2 > B_N$ , from the proof of case (i),  $E_\infty$  is unstable. Based on Theorem 1 and the proof in (ii), only  $E_1^*$  exists and  $\Psi(\theta_1, \theta_2) > 0$  is well defined. Therefore, all the roots of (13) with respect to  $\lambda$  are negative, which indicates that  $E_1^*$  is locally stable. We complete the proof of Theorem 3.

**Theorem 4.** For system (2) with perfect transmission rate  $\tau = 1$  and suppose  $d_4 > B_W$ .

(i) When  $d_2 < B_{NW}$  (i.e.,  $\Omega_D$ ), then  $E_0^*$  is unstable, and  $E_\infty$  is locally stable.

- (ii) When  $B_{NW} < d_2 < B_N$  (i.e.,  $\Omega_B, \Omega_C$ ), then both  $E_0^*$  and  $E_\infty$  are locally stable, and  $E_2^*$  is unstable.  
 (iii) When  $d_2 > B_N$  (i.e.,  $\Omega_E$ ), then  $E_\infty$  is unstable, and  $E_0^*$  is locally stable.

**Proof.** The proof of the stability of  $E_\infty$  is similar to that for Theorem 1. In order to investigate the stability of  $E_0^*$  of system (2) with a perfect transmission rate  $\tau = 1$ , based on (12), the eigenvalues of  $J(E_0^*)$  and  $J(E_1^*) = J(E_2^*)$  satisfy the following equation

$$(\lambda + d_4) (\lambda^2 + (\beta_2 + d_3 + d_4)\lambda + P_1) (\lambda^2 + (\beta_1 + d_1 + d_2)\lambda - P_3) = 0. \quad (19)$$

Thus,  $E_0^*$  is locally stable provided that  $P_3 < 0$ , i.e.,  $d_2 > B_{NW}$ , while it is unstable provided that  $P_3 > 0$ , i.e.,  $d_2 < B_{NW}$ .

Similarly, the eigenvalues of the Jacobian matrix at the interior equilibrium satisfy the following equation

$$(\lambda + d_4) (\lambda^2 + (\beta_2 + d_3 + d_4)\lambda + P_1) \left( \lambda^2 + (\beta_1 + d_1 + d_2)\lambda + \frac{P_2 P_3}{b_1 \beta_1 q} \right) = 0. \quad (20)$$

Thus, the interior equilibrium is locally stable provided that  $d_2 < B_{NW}$  or  $d_2 > B_N$ , while it is unstable provided that  $B_{NW} < d_2 < B_N$ . We complete the proof of Theorem 4.

### 3.3. Backward bifurcation

From Theorem 3, the stability of infinite equilibrium  $E_\infty$  is determined by  $d_2 = B_N$ . Denote

$$R_0 = \frac{d_2(\beta_1 + d_1)}{b_1 \beta_1},$$

then the equation  $R_0 = 1$  holds if and only if  $d_2 = B_N$ . Based on Theorem 4.1 in [52], we analyze whether system (2) undergoes either a forward or a backward bifurcation when  $R_0 = 1$ . Then we have the following result.

**Lemma 5.** System (6) with  $d_4 > B_W$  undergoes a backward bifurcation at  $R_0 = 1$ .

**Proof.** According to Theorem 4.1 in [52], we need to compute the two quantities, labelled as  $\mathcal{A}$  and  $\mathcal{B}$ , which depend on the higher order terms in the Taylor expansion of system (6) and the left and right eigenvectors of the Jacobian  $J(\tilde{E}_\infty)$  with respect to the eigenvalue equal zero. By simple calculation, the right and left eigenvectors of Jacobian  $J(\tilde{E}_\infty)$  are

$$\begin{aligned} w &= (w_1, w_2, w_3, w_4, w_5)' = \left( -\frac{b_1 q (\tau b_2 \beta_2 \theta_1 + P_1 \theta_2)}{P_1 d_4 \sqrt{(\beta_1 + d_1 - d_2)^2 + 4b_1 \beta_1}}, 1, 0, 0, 0 \right), \\ v &= (v_1, v_2, v_3, v_4, v_5)' = (0, 1, 0, 0, 0), \end{aligned} \quad (21)$$

respectively, with  $w \cdot v = 1$ .

In order to follow the notation involved in Theorem 4.1 of [52], introducing  $x_1 = V - V_2^*$ ,  $x_2 = Z$ ,  $x_3 = L_{WF}$ ,  $x_4 = F_W$ ,  $x_5 = M_W$ ,  $\phi = d_2 - B_N$  and denote the left side of the transformed system (6) as  $f_i = (x_1, x_2, x_3, x_4, x_5)$ ,  $i = 1, 2, 3, 4, 5$ , then the Taylor expansion of system (6) is calculated as

$$\frac{\partial^2 f_1}{\partial x_1^2}(O, 0) = -2\beta_1, \quad \frac{\partial^2 f_1}{\partial x_2^2}(O, 0) = 2b_1 q (M_W^*)^2, \quad \frac{\partial^2 f_1}{\partial x_2 \partial x_5}(O, 0) = -b_1 q,$$

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_2}(O, 0) = \frac{\partial^2 f_2}{\partial x_2 \partial x_1}(O, 0) = -\beta_1,$$

$$\frac{\partial^2 f_1}{\partial x_1 \partial \phi}(O, 0) = \frac{\partial^2 f_2}{\partial x_2 \partial \phi}(O, 0) = 1,$$

with  $O$  denoting the vector  $(0, 0, 0, 0, 0)$  and all other partial derivatives equal to zero. Based on the definitions of  $\mathcal{A}$  and  $\mathcal{B}$ , we can calculate them by substituting the vectors  $w$  and  $v$  into the expressions

$$\mathcal{A} = \sum_{k,i,j=1}^5 v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(O, 0) = \frac{2b_1 \beta_1 q (\tau b_2 \beta_2 \theta_1 + P_1 \theta_2)}{P_1 d_4 \sqrt{(\beta_1 + d_1 - d_2)^2 + 4b_1 \beta_1}} > 0$$

$$\mathcal{B} = \sum_{k,i=1}^5 v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(O, 0) = 1 > 0.$$

Therefore, we can prove that both  $\mathcal{A}$  and  $\mathcal{B}$  are larger than zero, which indicates the existence of a backward bifurcation provided that  $R_0 = 1$ . We complete the proof of Lemma 5.

Based on the equivalence between systems (2) and (6), we have following results.

**Theorem 6.** System (2) with  $d_4 > B_W$  undergoes a backward bifurcation at  $R_0 = 1$ .

For system (2) with an imperfect transmission rate, in order to further investigate the thresholds for the existence of a forward and a backward bifurcation, we denote

$$R_0^c = 1 - \frac{1}{q} \left( \frac{2A_1 P_1 \theta_2 + B_1 P_1 \theta_1}{4b_1 b_2 \beta_1 P_4 \theta_1} \right)^2,$$

which is determined by  $B^2 - 4AC = 0$ . For system (2) with a perfect transmission rate and  $d_4 > B_W$ , we have  $R_0^c = 1 - q$ . Then we have the following results.

**Theorem 7.** For system (2) with  $d_4 > B_W$ , given  $d_2$  and  $d_4$ , there exists a backward bifurcation provided  $R_0^c < R_0 < 1$ ; there exists a forward bifurcation provided that  $R_0 > 1$ .

### 3.4. Numerical simulations

In this part, we first obtain a bifurcation diagram of the transformed system (6) with imperfect and perfect transmission rates, which corresponds with the bifurcation analysis of system (2). Then basin of attraction of equilibria for system (6) with imperfect and perfect transmission rates is considered. Second, we analyze the possible cases of population replacement for system (2) with imperfect and perfect transmission rates in different regions of parameter space and then explore the effects of mosquito augmentation on the outcomes of population replacement. Further we explore the parameter space by performing an uncertainty and sensitivity analysis to understand the effects of different parameters on the success or failure of population replacement. Note that the initial density of *Wolbachia*-free mosquitoes is determined by the habitats of the mosquito populations. In our numerical simulations, we focus on showing possible distributions of mosquito populations, so we just suppose the numbers of natural aquatic and adult females as 260 and 200, respectively. Meanwhile we assume that before the releases of *Wolbachia*-carrying mosquitoes, their initial density is assumed to be zero.

#### 3.4.1. Backward bifurcation and basin of attraction

Based on Theorems 6 and 7, system (2) naturally undergoes a backward bifurcation at  $R_0 = 1$ . When the natural death rate of *Wolbachia*-carrying adult females  $d_4$  is fixed and the other parameter values are the same as in Fig 1, it follows from Fig 4 (A) that we can first show the bifurcation diagram of system (6) with perfect transmission rate with respect to the formula  $R_0(d_2)$  and the variable  $V(t)$ , which corresponds with that of system (2) because of the equivalence between the two systems. When backward bifurcation occurs, there exists a saddle-node (here denote SN) bifurcation point  $R_0^c$ . There exists a unique locally stable infinite

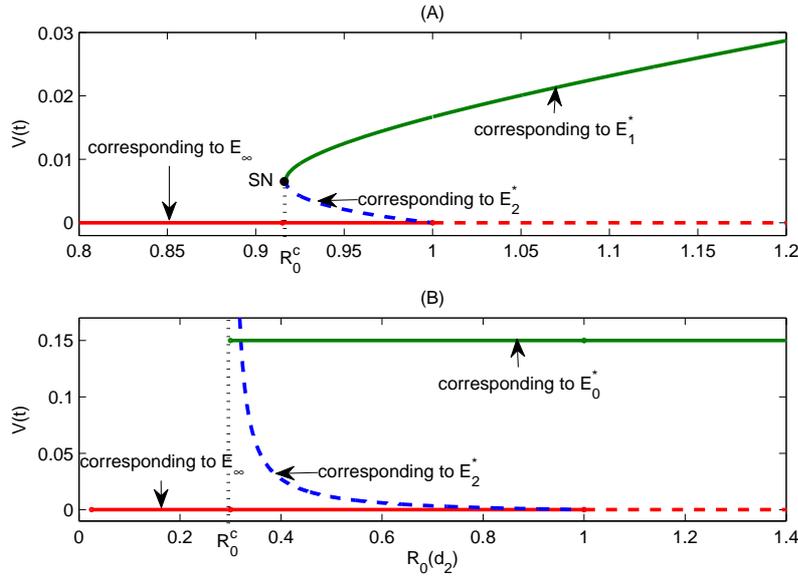


Figure 4: Bifurcation diagram of system (6). (A) For imperfect transmission rate  $\tau = 0.7, \theta_1 = 11.7, \theta_2 = 5$ ; (B) For perfect transmission rate  $\tau = 1, \theta_1 = 12.5, \theta_2 = 5$ . Expect for  $d_4 = 0.25$ , the other parameter values are the same as in Fig 1.

equilibrium  $E_\infty$  provided that  $R_0 < R_0^c$ , which indicates that we fail to realize partial population replacement for any mosquito augmentation. The locally stable infinite equilibrium  $E_\infty$  coexists with two interior equilibria  $E_1^*$  (locally stable) and  $E_2^*$  (unstable) provided that  $R_0^c < R_0 < 1$ , which indicates the success of partial population depending on the initial density of mosquitoes. The unstable infinite equilibrium  $E_\infty$  coexists with interior equilibrium  $E_1^*$  (locally stable) provided that  $R_0 > 1$ , which indicates that partial population replacement can be realized for any mosquito augmentation. Similarly, for system (2) with perfect transmission rate, based on Theorems 4 and 7, the bifurcation diagram of system (6) (corresponding to system (2)) is shown in Fig 4 (B). Note that boundary equilibrium  $E_0^*$  of system (2) corresponds with an infinite one in system (6), so here the green line just describes the existence of equilibrium  $E_0^*$  for system (2), not the exact change of variable  $V(t)$  with respect to  $R_0(d_2)$ . Especially, in this case, if  $R_0^c < R_0 < 1$ , we may realize complete population replacement from some initial densities of natural mosquitoes, while if  $R_0 > 1$ , we can realize complete population replacement from any initial density of natural mosquitoes.

From (8), line  $L_3$  is determined by  $R_0 = R_0^c$ . When  $R_0 < 1$  and parameter values of  $d_2$  and  $d_4$  are fixed in different regions, Fig 2 shows the effect of different mosquito augmentation on the existence of interior equilibria of system (2). Moreover, the slope of the blue line (i.e.,  $L_3$  dividing the regions between nonexistence and coexistence of two interior equilibria of system (2)) is distinctly diverse on different parameter regions of  $d_2$  and  $d_4$ . If the augmentation of *Wolbachia*-carrying females (or males) is fixed, with the increase (or decrease) of the augmentation of *Wolbachia*-carrying males (or females), there exist zero, one or two interior equilibria sequentially, as shown in Fig 2 (B), (C), (E) and (F), so partial population replacement may be fulfilled by the increase (decrease) of the augmentation of *Wolbachia*-carrying males (females). Especially, if the parameter values of  $d_2$  and  $d_4$  lie in region  $\Omega_{B3}$ , then two interior equilibria coexist for any mosquito augmentation, so the success of population replacement is determined by both the initial density of natural mosquitoes and the quantity of mosquitoes in the augmentation.

When backward bifurcation occurs for system (2), it is important to analyze the effect of the initial density of natural mosquitoes on the success or failure of population replacement. For example, in region  $\Omega_{B2}$  (see Fig 2 (C)), when mosquito augmentation is fixed in the region

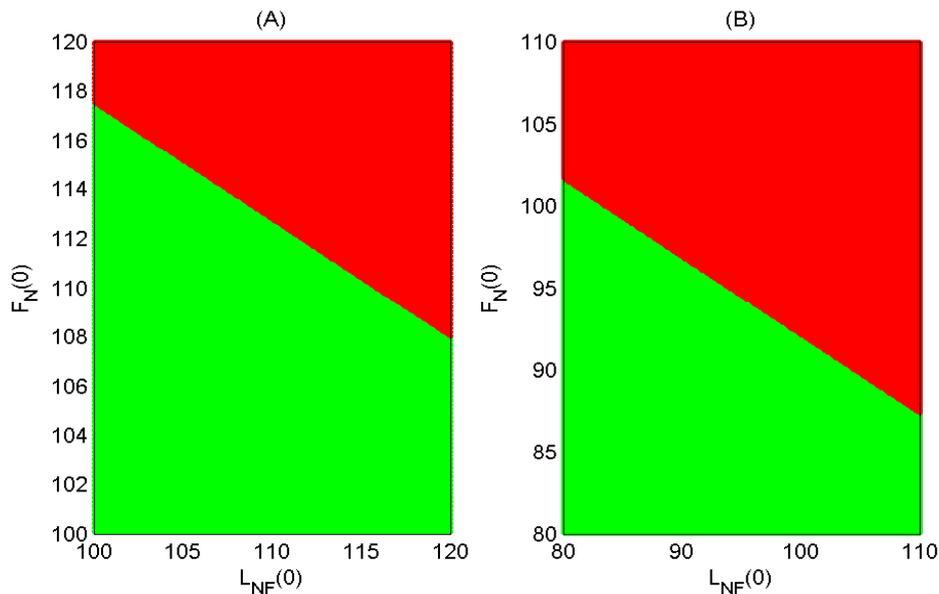


Figure 5: Basin of attraction of equilibria for system (2) with respect to the initial density of mosquitoes. (A) for imperfect transmission rate  $\tau = 0.7$ ; (B) for perfect transmission rate  $\tau = 1$ . Green and red regions denote the basins of attraction for the success and failure of population replacement, respectively. Except for  $\theta_1 = 1$  and  $\theta_2 = 5$ , the other parameter values are the same as in Fig 2(C).

$\theta_2 > \theta_2^{(3)}$ , the basin of attraction of equilibria (here  $E_\infty^*$  and  $E_1^*$ ) for system (2) is shown in Fig 5 (A). When the initial density of natural mosquitoes lies in the green region, we can achieve partial population replacement, otherwise, we fail to achieve the replacement. Similarly, for other regions with two interior equilibria, we can also obtain the corresponding basin of attraction of equilibria. Moreover, for system (2) with a perfect transmission rate, the basin of attraction of equilibria (here  $E_\infty^*$  and  $E_0^*$ ) is shown in Fig 5 (B). Although a perfect transmission rate may lead to complete population replacement, the basin of attraction of the boundary equilibrium is significantly shrunk, which implies that from the same initial density of natural mosquitoes, partial population replacement may be achieved for system (2) with an imperfect transmission rate, but a complete population replacement may fail for the system with a perfect transmission rate.

#### 3.4.2. The possible cases for population replacement

From Theorems 1-4, there exist three possible cases for population replacement as follows. For convenience, in the following figures, solid and dashed lines denote the solutions of system (2) about the density of *Wolbachia*-free (natural) and *Wolbachia*-carrying adult females, respectively. Magenta, blue and red curves denote the solutions of system (2) with different tactics of mosquito augmentation in sequence.

- *The regions for unsuccessful population replacement*

Based on Theorems 1 and 3, if parameter values lie in regions  $\Omega_A$ ,  $\Omega_D$  or in the regions  $\Omega_B$  and  $\Omega_C$  with nonexistence of interior equilibria of system (2) (see Figs 1 and 2), then any mosquito augmentation cannot realize the strategy of population replacement at all in the end, as shown in Figs 6(A) and 7. It is remarkable that from Fig 7 (B), when mosquito augmentation is fixed as (6, 18) (blue curve) or (4, 20) (red curve), the density of natural adult females increases in a short time interval, and then it decreases in the next time interval, but it significantly increases in the end. And the increased part in the beginning of the time interval is removed in Fig 7(C). Therefore, in practice, some releases of *Wolbachia*-carrying mosquitoes in field trials can plausibly reduce the density of *Wolbachia*-free females at the beginning, but the density of *Wolbachia*-free females could rebound in the end, which might provide misleading

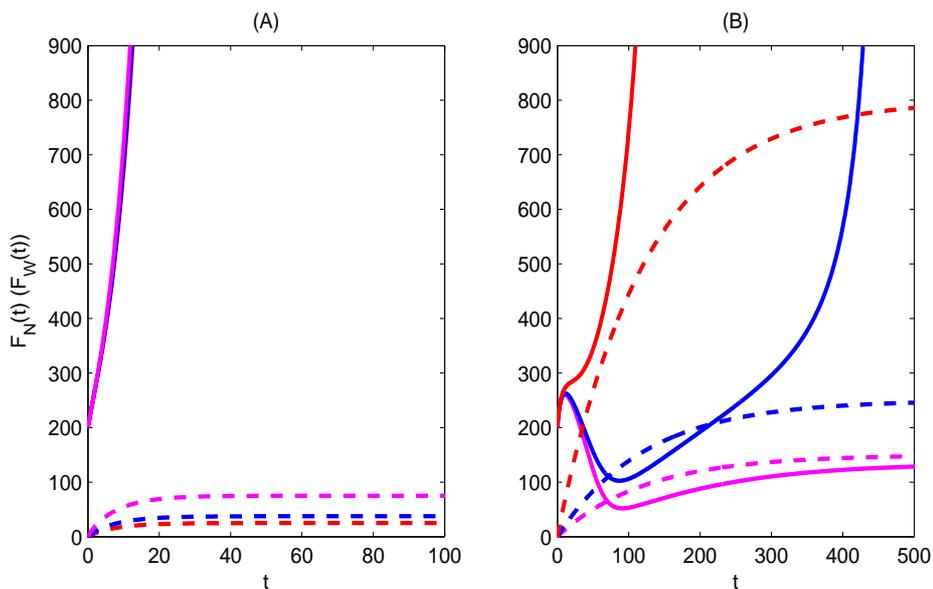


Figure 6: The solutions of system (2) in different regions. (A) In region  $\Omega_A$  with  $d_2 = 0.1, d_4 = 0.3, (\theta_1, \theta_2) = (12, 12), (6, 18), (4, 20)$ ; (B) in region  $\Omega_{B1}$  with  $d_2 = 0.3, d_4 = 0.15, (\theta_1, \theta_2) = (1.5, 30), (2.5, 30), (8, 30)$ . The other parameter values are the same as in Fig 1. For explanations of the different coloured lines see the first paragraph of section 3.4.2.

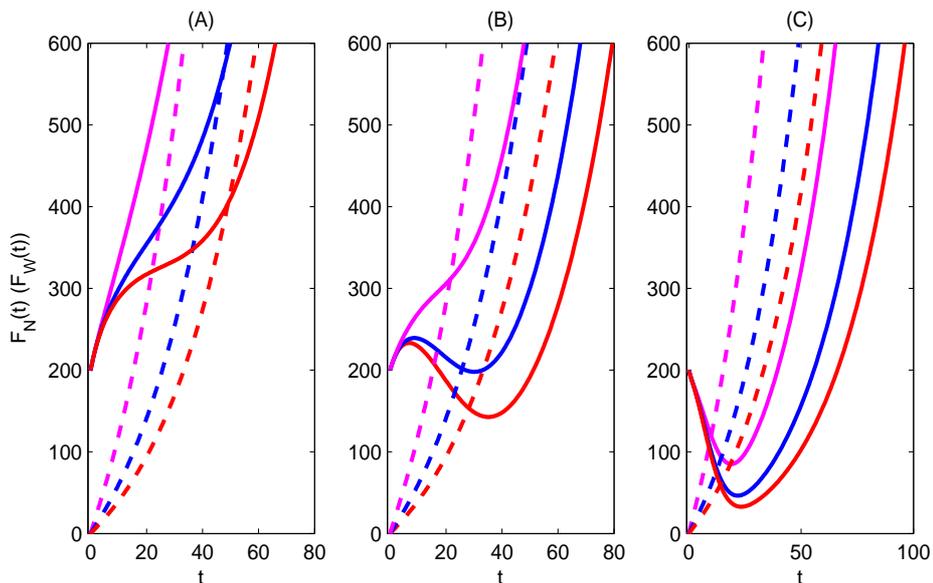


Figure 7: The solutions of system (2) in the region  $\Omega_D$ . (A)  $d_2 = 0.3, d_4 = 0.1$ ; (B)  $d_2 = 0.33, d_4 = 0.1$ ; (C)  $d_2 = 0.45, d_4 = 0.1$ . Except for  $(\theta_1, \theta_2) = (12, 12), (6, 18), (4, 20)$ , the other parameter is the same as in Fig 1. For explanations of the different coloured lines see the first paragraph of section 3.4.2.

guidance on the success of population replacement.

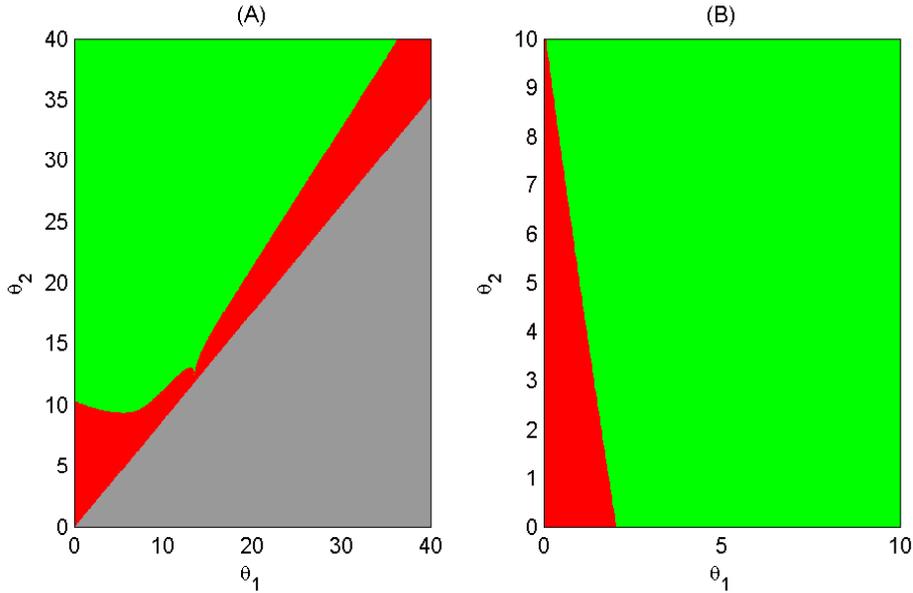


Figure 8: The effects of mosquito augmentation on the success or failure of population replacement for system (2). (A) for imperfect transmission rate  $\tau = 0.7$ ; (B) for perfect transmission rate  $\tau = 1$ . Initial density of mosquitoes fixed as  $(260, 200, 0, 0, 0)$ , and the other parameter values are the same as in Fig 5.

- *The regions for possibly successful population replacement*

Based on Theorems 1 and 3, if parameter values lie in the regions  $\Omega_B$  and  $\Omega_C$  with coexistence of two interior equilibria  $E_i^*$ ,  $i = 1, 2$  and infinite equilibrium  $E_\infty^*$  for system (2) (see Figs 1 and 2), then there exists a backward bifurcation such that both  $E_1^*$  and  $E_\infty^*$  are locally stable, which indicates that it is possible to realize the strategy of population replacement depending on both the initial density of natural mosquitoes and the quantity of mosquitoes in the augmentation, as shown in Figs 5, 6(B) and 8. The effect of the initial density of natural mosquitoes on the success or failure of population replacement has been shown in the basin of attraction of equilibria with respect to the initial density of *Wolbachia*-free aquatic and adult females (see Fig 5).

In region  $\Omega_{B1}$ , it follows from Fig 6(B), that the three curves (magenta, blue and red) are the solutions of system (2) with different mosquito augmentations (here  $(1.5, 30)$ ,  $(2.5, 30)$  or  $(8, 20)$ ). It is worth noting that although population replacement can be fulfilled in the end (magenta curve), the density of *Wolbachia*-free females slightly increases at first. Moreover, with the increase of the release of *Wolbachia*-carrying females to some extent (see blue curve), the density of natural adult females can also increase in a narrow time interval, next it may be plausibly reduced, then it sharply rebounds in the end. Therefore, both of the two curves might give erroneous indications about the control of mosquitoes.

Further based on Fig 6(B), when the initial density of natural mosquitoes is fixed, then some mosquito augmentation may lead to the failure of population replacement in the end (red and blue curves), while others may lead to the success of population replacement (magenta curve), which indicates that the success of population replacement is determined by the quantity of mosquitoes in the augmentation. Therefore, it is necessary to obtain the effects of the mosquito augmentation on the success or failure of population replacement (see Fig 8). Only if the quantity of mosquitoes included in the augmentation lies in the green region, does the population replacement get achieved. If it lies in the red or grey region, then population replacement cannot be achieved at all. For system (2) with imperfect and perfect transmission rates, there are obvious differences between the effects of mosquito augmentation on the success

or failure of population replacement, as shown in Fig 8. For system (2) with an imperfect transmission rate, when  $\theta_1$  is fixed, then only a large enough  $\theta_2$  can lead to the success of population replacement. When  $\theta_2$  is fixed at less than 9.3, then any  $\theta_1$  causes the failure of population replacement; when  $\theta_2$  is fixed between 9.3 and 10.2, with the increase of  $\theta_1$ , population replacement may fail, succeed and fail again in sequence; when  $\theta_2$  is fixed higher than 10.2, even a small enough  $\theta_1$  can lead to the success of population replacement. While for system (2) with a perfect transmission rate, no grey region exists. When  $\theta_1$  is fixed less than 2, only a large enough  $\theta_2$  can cause the success of population replacement; when  $\theta_1$  is fixed larger than 2, even a small enough  $\theta_2$  can also cause the success of population replacement. When  $\theta_2$  is fixed less than 10, only a large enough  $\theta_1$  can lead to the success of population replacement; when  $\theta_2$  is fixed larger than 10, then even a small enough  $\theta_1$  can also lead to the success of population replacement. These results indicate that the success of population replacement is determined by both  $\theta_1$  and  $\theta_2$ . Similarly, for other regions with coexistence of interior equilibria and different initial densities of natural mosquitoes, the effects of mosquito augmentation on the success or failure of population replacement can also be obtained.

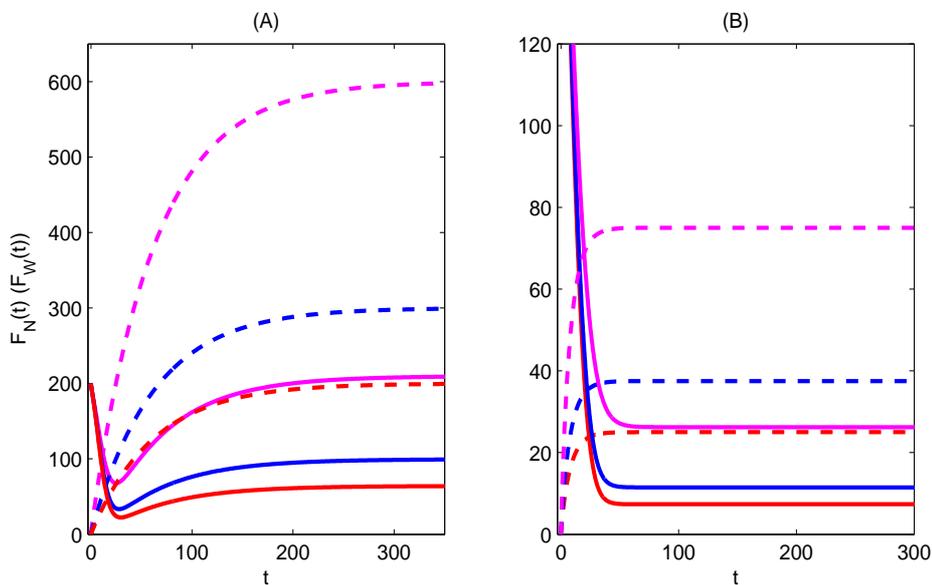


Figure 9: The solutions of system (2) in the region of  $\Omega_E$ . (A)  $d_2 = 0.45, d_4 = 0.16$ ; (B)  $d_2 = 0.45, d_4 = 0.3$ . Except for  $(\theta_1, \theta_2) = (12, 12), (6, 18), (4, 20)$ , the other parameter is the same as in Fig 1. For explanations of the different coloured lines see the first paragraph of section 3.4.2.

- *The regions of successful population replacement*

Based on Theorems 1 and 3, if parameter values lie in region  $\Omega_E$  (see Figs 1 and 2), then the strategy of population replacement may be achieved for any mosquito augmentation, as shown in Fig 9. It follows from Fig 9 that, with the increase of the ratio (male to female) of mosquito augmentation, we can increase the spread and level of population replacement. However, in region  $\Omega_E$ , if the natural death rate of *Wolbachia*-carrying adult females is too low, although the density of natural females may significantly reduce in the beginning and population replacement can be realized in the end, the density of natural females may increase again such that its density is just moderately reduced (blue curve), even slightly increased in the end, which is not an expected result for the control of dengue disease. Therefore, it is possible to effectively decrease the transmission rate of dengue virus, if both successful population replacement and a significant decrease of the density of natural adult females occur.

### 3.4.3. Uncertainty and sensitivity analysis

Uncertainty analysis is explored by using a Latin hypercube sampling (LHS) method, an extension of Latin square sampling. Sensitivity analysis is studied by evaluating partial rank correlation coefficients (PRCCs) [53, 54] for various input parameter values (generated from the LHS method with 2000 samples) against the output parameters (here  $F_N(t)$ ,  $F_W(t)$  and  $F_W(t)/(F_N(t) + F_W(t))$ ) over time, which can determine the importance of each parameters contribution to the value of the outcome variable over an entire time interval during progression of the model dynamics. Positive (or negative) values of the PRCC mean positive (or negative) correlations between the input parameters and the output variables. Absolute values of PRCCs which belong to  $(0.4, 1)$ ,  $(0.2, 0.4)$ , and  $(0, 0.2)$  indicate very important, moderate correlations and relationships that are not significantly different from zero between input parameters and output variables, respectively.

In the absence of available data on the distribution functions, we choose a uniform distribution for all input parameters. In practice, parameter values for mosquito populations are obviously determined by differences in the environment, such as temperature, humidity and light, which lead to different parameter values for mosquito populations. In order to analyze all possible solutions of system (2) in different environments, each parameter value is chosen from within a reasonable parameter range, which is larger than that in some publications, as shown in Table 1. In order to consider how each parameter value affects the dynamics of mosquito populations in the season of them emerging, here we consider the mosquito releases performed from March to October.

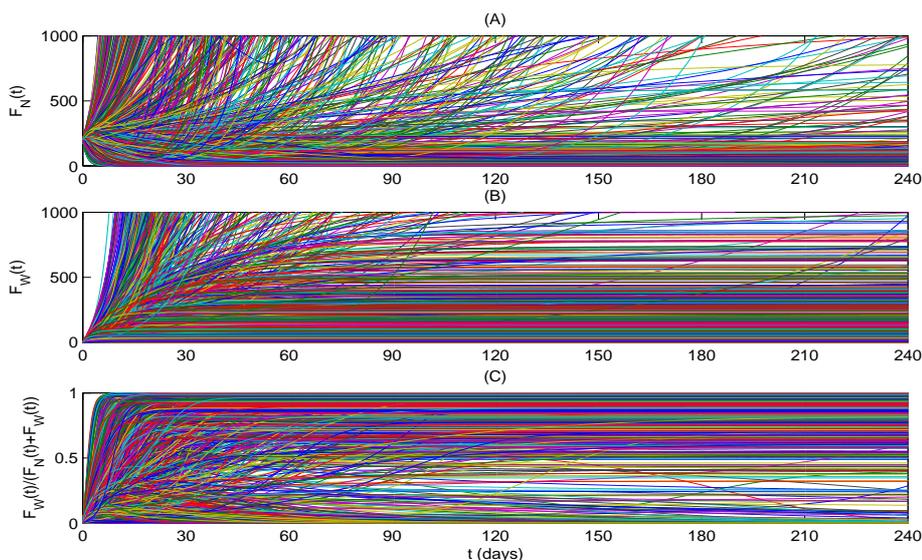


Figure 10: The solutions of system (2) with 2000 runs of the LHS method. (A) The densities of *Wolbachia*-free adult females; (B) the densities of *Wolbachia*-carrying adult females; (C) the ratio of *Wolbachia*-carrying adult females to the total number of adult females. The regions of parameter values for the LHS method are shown in Table 1.

Fig 10 shows the 2000 simulations for the densities of *Wolbachia*-free and *Wolbachia*-carrying adult females and the ratio  $F_W(t)/(F_N(t) + F_W(t))$  to the LHS matrix, and the scheme is defined by varying each input parameter. It is consistent with Theorems 1-4 that there exist three possible cases for population replacement as above. Fig 11 performs the sensitive analysis of each parameter against the solutions of system (2). Shortly after the first 60 days, the effect of each parameter on the solutions of the system tends to stability. From Fig 11(A), for most of the time interval, the most influential parameters are the birth rate of *Wolbachia*-carrying adults ( $b_2$ ), the natural death rate of *Wolbachia*-free adults ( $d_2$ ) and the natural death rate

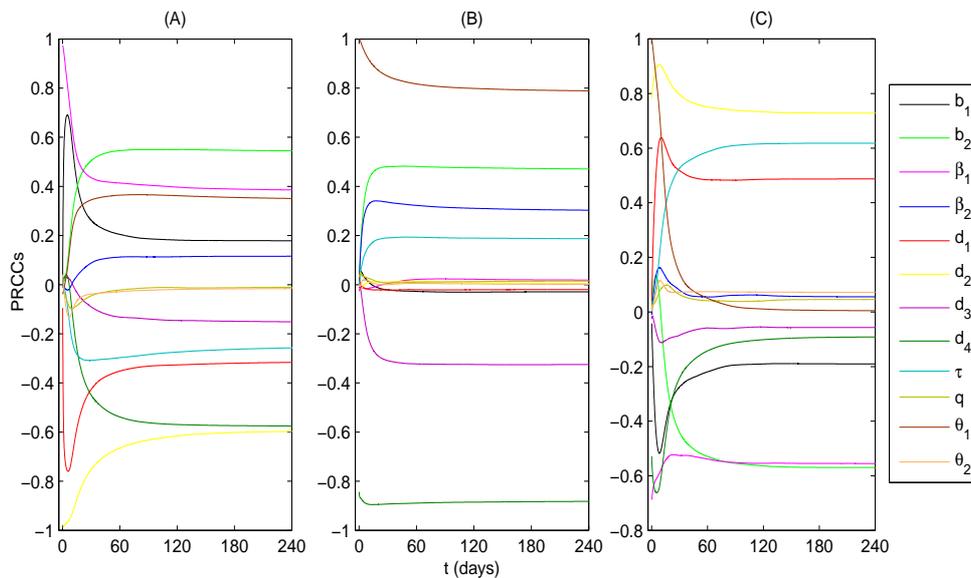


Figure 11: PRCCs involving the solutions of system (2) with respect to each parameter over time. (A) PRCCs for the density of *Wolbachia*-free adult females; (B) PRCCs for the density of *Wolbachia*-carrying adult females; (C) PRCCs for the ratio of *Wolbachia*-carrying adult females to the total of adult females.

of *Wolbachia*-carrying adults ( $d_4$ ). As  $b_2$  and  $d_4$  change, they are positively and negatively correlated with small PRCCs, respectively, in the early time interval, and then have increased correlations in short time intervals, and later keep steady correlations in the rest of the time interval. While for  $d_2$ , there is a strong negative correlation with large PRCCs at the early time point, and then there is a reduced correlation until it keeps a steady correlation value for the rest of the time interval. As the birth rate of *Wolbachia*-free adult females ( $b_1$ ) and the natural death rate of *Wolbachia*-free aquatic ( $d_1$ ) change, they are positively and negatively correlated with small PRCCs, respectively, in the early time points, and significantly correlated with large PRCCs until the peak, and then they have reduced correlations with decreasing PRCCs in a short time interval. Finally, they keep a steady correlation value with a constant PRCC value.

It follows from Fig 11(B) that, for most time intervals, the most influential parameters are  $d_4$ ,  $\theta_1$  and  $b_2$ . Comparing 11(B) with Fig 11(A), parameters related to *Wolbachia*-free mosquitoes (here  $b_1, \beta_1, d_1, d_2$ ) have insignificant correlations for  $F_W(t)$ . For other parameters related to *Wolbachia*-carrying mosquitoes (here  $b_2, \beta_2, d_3, d_4, \theta_1$ ), although there are different correlations between  $F_N(t)$  and  $F_W(t)$  in the early time interval, they show similar positive or negative correlations in the rest of the time interval. While for the quantity of *Wolbachia*-carrying males augmented ( $\theta_2$ ), maternal transmission rate ( $\tau$ ) and CI rate ( $q$ ), they perform weak and opposite correlations between the densities of *Wolbachia*-free (negative) and carrying (positive) adult females.

Similarly, from Fig 11(C), the most influential parameters are  $b_2, \beta_1, d_2, \tau, d_1$  in most of the time interval. Comparing Fig 11(C) with Fig 11(A), there exist opposite correlations for most of the parameters (except for  $\theta_1, \beta_2, d_3, d_4$ ) against  $F_N(t)$  and  $F_W(t)/(F_N(t) + F_W(t))$ . Comparing Fig 11(C) with Fig 11(B), most of the parameters (except for  $b_2$ ) possess the consistent correlation between  $F_W(t)$  and  $F_W(t)/(F_N(t) + F_W(t))$ . The special four parameters (here  $\theta_1, \beta_2, d_3, d_4$ ) cannot be deduced directly, because the correlation of the parameters against  $F_W(t)/(F_N(t) + F_W(t))$  is determined to weigh the corresponding correlations of the parameters against  $F_N(t)$  and  $F_W(t)$ . Especially, in the beginning, augmenting the quantity of *Wolbachia*-carrying females can contribute to the increase of the density of *Wolbachia*-carrying females and the ratio of *Wolbachia*-carrying females to the total ones, and lead to an increase of *Wolbachia*-free females, but later, there is a weak correlation for the ratio, which indicates that

in order to realize population replacement, it is beneficial to augment with a large quantity of *Wolbachia*-carrying females in the beginning, and later with a smaller quantity.

#### 4. Discussion and conclusion

In this paper, a deterministic mathematical model was formulated to investigate the effect of non-identical sex ratio augmentation of *Wolbachia*-carrying mosquitoes on the control of dengue virus. Our model incorporates the effect of CI, aquatic (egg, larvae and pupae combined) and adult stages for mosquitoes. We assumed that mosquito augmentation is done daily, that there is no competition among aquatic and adult mosquitoes in suitable environments, that half of the mosquito population mature into adult females, that before mosquito augmentation, the density of *Wolbachia*-carrying mosquitoes is zero, because the bacterium is not naturally carried in *Aedes aegypti*. There are two main differences between our work with that of Farkas et al. [45]. One is that they are different species of vectors for the spread of WNV (*Culex* mosquitoes) and dengue virus (*Aedes* mosquitoes), for example, they have different strategies of surviving the winter. Another one is that the two works focus on different issues. Suppose that there are some *Wolbachia*-carrying mosquitoes lived with natural mosquitoes, but without further mosquito augmentation, Farkas et al. [45] explored the existence and stability of equilibria which is related with the success of population replacement. The most interesting is that the authors extended the model to incorporate WNV dynamics among birds and mosquitoes by using an epidemic modelling approach, and computed a basic reproduction number for the WNV infection, which give some hints for the eradication of WNV. While in our work, suppose that there exists further mosquito augmentation, we aimed to explore parameter thresholds for the existence and stability of equilibria based on two layers of parameters, the first layer is related to mosquito dynamics, which are determined by different environment settings, the second layer is mosquito augmentations, regarded as control parameters. Then we proved the existence of forward and backward bifurcations, and obtained the basin of attractions and the effects of mosquito augmentation on the success of population replacement. Furthermore, we performed the global uncertain and sensitive analysis to explore the effects of different parameters on the success or failure of population replacement (see Figs 10 and 11), and we have answered the series of related issues mentioned in the introduction.

Based on this work, we learn that mosquito augmentation cannot ensure the success of population replacement. It follows from 6(A) that any mosquito augmentation can fail to achieve population replacement, and the density of natural mosquitoes could dramatically increase in the end. Then we summarize the cases for the failure, possible success, and success of population replacement in section 3.4. Note that the existence of backward bifurcation indicates the possible success of population replacement, which could cause diametrically opposite results (here success or failure of population replacement) depending on the initial density of natural mosquitoes and the quantity of mosquitoes in the augmentations. The basins of attraction and the effects of mosquito augmentation show the regions concerning the above two indices (here  $(L_{NF}(0), F_N(0))$  and  $(\theta_1, \theta_2)$ ) on the success and failure of population replacement, as shown in Figs 5 and 8, respectively.

Compared with the system with an imperfect transmission, the system with a perfect transmission rate can achieve complete population replacement. It also narrows the region of initial density for the success of population replacement (see Fig 5). There exist obvious differences in the regions for the quantity of mosquitoes in the augmentations between the system with imperfect and perfect transmission rates (see Fig 8). For an imperfect transmission rate, note that *Wolbachia*-carrying females can give birth of *Wolbachia*-free offspring. This indicates that the abundance of *Wolbachia*-carrying females will increase the density of natural female mosquitoes. Thus, in practice, augmentation with a small quantity of *Wolbachia*-carrying females and a

large number of *Wolbachia*-carrying males will be beneficial to the success of partial population replacement. While for a perfect transmission rate, it is necessary to augment moderate quantities of *Wolbachia*-carrying females and males for the success of population replacement. Especially, in this case, if the augmentation of *Wolbachia*-carrying females or males is larger than some threshold values (for example 2 and 10, respectively, in Fig 8(B)), then the success of complete population replacement can be achieved even though there is no augmentation of *Wolbachia*-carrying males or females, respectively. Also, it is remarkable that the success of population replacement cannot certainly reduce the spread of dengue virus in the end, as shown in 9(A), because the success of replacement cannot guarantee the decrease in the density of natural adult females. Therefore, for open releases of *Wolbachia*-carrying mosquitoes in field trials, one should first realize population replacement, while also making sure that the density of natural female mosquitoes is significantly reduced.

In conclusion, compared with available modelling results, we obtained the subregions in parameter space for unsuccessful, possibly successful and successful population replacement. We show that different natural death rates of mosquitoes, the quantity of mosquitoes used in augmentations and the initial density of natural mosquitoes could affect the success of population replacement. For open releases of *Wolbachia*-carrying mosquitoes in field trials, the increase or decrease of the density of natural mosquitoes, in the beginning, may give misleading clues about the success or failure of population replacement in the end, and misguide plans for the control of mosquitoes. Also, our analysis was based on the assumption that there is no density dependence amongst developing stages but such density dependence and competition for food does occur in field cage populations, as shown by Hancock et al. [55]. Therefore future models may need to take these factors into account by, for instance, retaining the variables dropped from system (1) for the formulation of system (2).

In order to fight against dengue disease, *Wolbachia*-carrying mosquitoes have been released to fulfill the strategies of population replacement or suppression in some field trials. However, *Wolbachia*-carrying females may transmit diseases and are responsible for nuisance biting, while *Wolbachia*-carrying males do not blood feed or transmit MBDs and do not pose a health threat. The ethics of mosquito releases from the Chinese Center for Disease Control and Prevention (CDCP) allows the augmentation of male mosquitoes. Therefore, it is essential to minimise or even avoid the numbers of females released, but only *Wolbachia*-carrying males are being released in the Guangdong province of China. Currently, some laboratory experiments are underway, and we will study the augmentation strategy (frequency, quantity, cost and so on) of *Wolbachia*-carrying males, when the relevant data are available.

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