Dynamics of a two-sex model for the population ecology of dengue mosquitoes in the presence of Wolbachia

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Abstract

The release of *Wolbachia*-infected mosquitoes into the population of wild mosquitoes is one of the promising biological control method for combating the population abundance of mosquitoes that cause deadly diseases, such as dengue. In this study, a new two-sex mathematical model for the population ecology of dengue mosquitoes and disease is designed and used to assess the population-level impact of the periodic release of *Wolbachia*-infected mosquitoes. Rigorous analysis of the model, which incorporates many of the lifecycle features of dengue disease and the cytoplasmic incompatibility property of *Wolbachia* bacterium in mosquitoes, reveal that the disease-free equilibrium of the model is locally-asymptotically stable whenever a certain epidemiological threshold, known as the *reproduction number* of the model (denoted by $\mathcal{R}_{0W}$), is less than unity. The model is shown, using center manifold theory, to undergo the phenomenon of backward bifurcation at $\mathcal{R}_{0W} = 1$. The consequence of this bifurcation is that *Wolbachia* may not persist, or dengue disease may not be effectively-controlled, when $\mathcal{R}_{0W}$ is less than unity. Such persistence and elimination will depend on the initial sizes of the sub-populations of the model. Two mechanisms were identified for which the backward bifurcation phenomenon can be removed. When backward bifurcation does not occur, the associated non-trivial disease-free equilibrium is shown to be globally-asymptotically stable when the reproduction number of the model is less than unity. Numerical simulations, using data relevant to dengue transmission dynamics in northern Queensland, Australia, shows that releasing *Wolbachia*-infected mosquitoes every three weeks, for a one-year duration, can lead to the effective control of the of the population abundance of the local wild mosquitoes, and that such effective control increases with increasing number of *Wolbachia*-infected mosquitoes released (resulting

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in the reduction of over 90% of the wild mosquito population from their baseline values). Furthermore, simulations show that releasing only adult male *Wolbachia*-infected mosquitoes provide more beneficial population-level impact (in terms of reducing the population abundance of the wild mosquitoes), in comparison to releasing adult female *Wolbachia*-infected mosquitoes. Increasing the frequency of *Wolbachia* release (e.g., from the default release frequency of every three weeks to weekly) does not significantly affect the effectiveness of the *Wolbachia*-based control program in curtailing the local abundance of the wild mosquitoes. Finally, it was shown that the cytoplasmic incompatibility property of *Wolbachia* bacterium does not significantly affect the effectiveness of the *Wolbachia*-based mosquito control strategy implemented in the community.

Keywords: *Wolbachia*; periodic release; backward bifurcation; asymptotic stability; reproduction number.

1 Introduction

Mosquito-borne diseases (MBDs) are infections transmitted to humans *via* the bite of infected adult female mosquitoes. MBDs, such as chikungunya, dengue, malaria, west Nile and Zika, continue to pose major public health challenges globally (particularly in the tropical and subtropical regions [8, 29, 31, 43]). There are over 3,500 species of mosquitoes, of which about 200 are known to be competent vectors of human diseases [5, 30]. Dengue fever, chikungunya and Zika, the most significant and widely spread arthropod-borne viral diseases [27, 34, 86], are vectored by *Aedes* mosquitoes (with the world's prevalent *Aedes aegypti* as the primary vector and the now-expanding *Aedes albopictus* as the secondary vector) [45, 86]. Of the aforementioned three arboviral diseases, dengue poses the heaviest burden (accounting for 50 million cases and 20,000 mortality annually in over 120 countries) [59, 84].

Unfortunately, there is no specific therapy available against dengue fever. Further, the world's first anti-dengue vaccine (Sanofi's *Dengvaxia* licensed in 2016 [83]) proved to be ineffective and had to be withdrawn from the market [21]. Other traditional methods for controlling mosquito population abundance, such as the use of chemical insecticides to kill immature (larvicide) and adult (adulticiding *via* indoor residual spraying IRS) and/or the use of long-lasting insecticidal nets (LLINs), insect repellents etc, have also generally proved to be ineffective, largely due to adult mosquito resistance to the chemicals used in each of the insecticide-based preventive control measures mentioned above [6, 54]. In the context of dengue fever, traditional measures (focused on reducing the population abundance of *Aedes aegypti* mosquitoes) have failed to significantly reduce or slow dengue outbreaks. In fact, as note by Xue *et al.* [47], there has been about 30-fold increase in dengue fever cases over the last 50 years.

The failure of traditional mosquito control methods necessitate a paradigm shift in the effort to control MBDs. Over the years, a range of alternative biological control measures, aimed at suppressing or replacing the mosquito vector *via* the mass release of genetically-modified mosquitoes, have been proposed [2, 25, 41, 60, 70]. These modifications include the sterilization of adult male mosquitoes (sterile insect technology) to reduce the reproduction of adult wild female mosquitoes [2, 11], genetic modification to introduce lethal genes [25, 69]

or introduction of genes that reduce disease transmission [41, 42, 52] into wild adult female mosquito population and the infection of mosquitoes by a second agent, such as the bacterium *Wolbachia*, aimed at suppressing pathogen transmission [60]. As noted by Segoli *et al.* [70], although these alternative methods have potential effect, their success solely depend on the ability of the released modified mosquitoes to survive and reproduce in the field. For instance, the success of sterile insect technology is crucially dependent on the ability of the released sterile male mosquitoes to be competitive and attractive to wild adult female mosquitoes [35]. Similarly, transgenic mosquitoes need to be able to survive and mate in the field in order to induce their novel genes into the wild mosquito population [51].

The release of lab-reared mosquitoes that are infected with the bacterium *Wolbachia pipientis* is considered to be a promising development for the control of dengue [20, 70]. *Wolbachia* is a maternally-transmitted intracellular parasitic infection naturally found in over 60% of insect species, including mosquitoes [65, 75]. Although *Wolbachia* is rarely found in *Aedes aegypti* (the primary vector of dengue), *Wolbachia* strains derived from *Drosophila Melanogaster* artificially introduced into *Aedes* mosquitoes (*via* embryo microinjection) was shown to suppress the development of the dengue virus [3, 23, 70]. Furthermore, *Wolbachia* induces cytoplasmic incompatibility (CI) by disrupting the reproductive cycle between the sperm and the eggs, resulting in the development failure of offsprings in the cross between *Wolbachia*-infected males and uninfected females [79, 80]. In other words, CI occurs when *Wolbachia*-infected males mate with *Wolbachia*-uninfected females to produce fewer or no offspring [79, 80]. This phenomenon causes embryos from *Wolbachia*-uninfected females to die when the females mate with *Wolbachia*-infected males (*Wolbachia*-infected females are not affected in this manner). The overall ecological consequence of CI is that it increases the relative success of *Wolbachia*-infected females in the population, thereby enhancing the spread of the bacterium [70, 76]. In other words, since *Wolbachia* is maternally inherited, the CI effect provides a transmission advantage for the symbiont, resulting in the rapid invasion of the uninfected wild mosquito population [65, 75]. Successful invasion depends on the CI overcoming incomplete maternal transmission of the *Wolbachia* infection, as well as overcoming a loss of fitness of infected hosts [36].

In summary, *Wolbachia* induces resistance to dengue virus in *Aedes aegypti* (and limits transmission of dengue virus in *Aedes albopictus*) [9, 55, 86]. As noted by Xue *et al.* [86], *Wolbachia*-based mosquito control primarily focus on the release of *Wolbachia*-infected mosquitoes aimed at creating sustaining *Wolbachia* infection in the wild (*Wolbachia*-uninfected) mosquito population. If such (*Wolbachia*) infection is sustained, then, the wild *Wolbachia*-infected mosquitoes will be less effective in transmitting dengue virus to humans [42, 52]. Studies have shown that maintaining *Wolbachia* infection in a wild mosquito population requires continually introducing new *Wolbachia*-infected mosquitoes into the wild population [57]. Furthermore, a recent large-scale release of *Wolbachia*-infected mosquitoes in Cairns, Australia, showed that the infected mosquitoes successfully invade and spread through the wild population [42]. On the other hand, smaller releases of *Wolbachia*-infected mosquitoes resulted in the failure of infected mosquitoes to invade (owing to the immigration of *Wolbachia*-free mosquitoes from surrounding areas [42]).

A number of mathematical models, typically of the form of deterministic systems of nonlinear ordinary differential equations (ODEs), have been developed and used to gain insight into the dynamics and impact of large scale release of *Wolbachia*-infected mosquitoes

on the control dengue virus in a population. Caspari and Watson [16] developed the first mathematical model for assessing the dynamics of CI-causing infections, and showed that the frequency of release *Wolbachia*-infected mosquitoes should always tend to increase for infections that impose no fitness cost. Qu and Hyman [62] presented a hierarchy of reduced ODE models for the spread of *Wolbachia* in mosquitoes. Numerical simulations of the ODE models developed by Qu *et al.* [63] and by Xue *et al.* [86] show that, although a small *Wolbachia* infection will die out with time, *Wolbachia* epidemic can be sustained if the fraction of *Wolbachia*-infected mosquitoes exceed a certain threshold (this result, which is supported by a recent large scale field trial in Australia [24, 36], is owing to the presence the phenomenon of backward bifurcation [26, 58]).

Koiller *et al.* [44] presented a 13-dimensional ODE model that included each aquatic stage of the mosquito and fitness cost from *Wolbachia* infection. Li and Liu [49] presented an impulsive differential equation model for *Wolbachia* infection, and showed that factors such as birth and death rates and *Wolbachia* strain type play crucial roles on the persistence of *Wolbachia*-infected mosquitoes in the wild population. Hughes and Britton [39] showed that *Wolbachia* has excellent potential for dengue control in areas where the basic reproduction number for dengue-infected mosquitoes (denoted by $\mathcal{R}_0$) is not too large. Ndii *et al.* [56], using an ODE model that incorporates seasonal forcing, showed that a significant reduction in dengue cases can be achieved *via* the release of wMel strain of *Wolbachia*. Similarly, Ferguson *et al.* [22] showed that wMel *Wolbachia* strain can reduce the basic reproduction number of dengue virus by 66-70%.

The purpose of the current study is to design and analyse a new mathematical model for gaining realistic insight into the dynamics and population-level impact of the large-scale release of *Wolbachia*-infected mosquitoes on the control of dengue virus. The central objective of this project is to determine whether or not a *Wolbachia*-based strategy will lead to the effective control of dengue virus. To achieve this objective, a new mathematical model is designed. The new two-sex model, which takes the form of a deterministic system of nonlinear differential equations, incorporates numerous pertinent aspects of *Wolbachia*-vector-pathogen dynamics, such as the fitness cost of *Wolbachia* infection, dynamics of the aquatic stages of the vector, vertical and horizontal transmission of *Wolbachia* infection and the effects of *Wolbachia* infection in mosquitoes and humans infected with dengue disease. The paper is organized as follows. The model is formulated in Section 2. Its basic qualitative features are also explored. The model is rigorously analysed in Section 3. Numerical simulations are also reported.

2 Model Formulation

The model to be designed in this study is for assessing the population-level impact of the periodic release *Wolbachia*-infected adult mosquitoes on the population abundance of *Aedes aegypti* mosquitoes and dengue fever in a community. The model is formulated as follows. The total population of immature *Aedes aegypti* mosquitoes at time t, denoted by $N_A(t)$, is subdivided into mutually exclusive compartments of *Wolbachia*-uninfected (denoted by $A_U(t)$) and *Wolbachia*-infected ($A_W(t)$) immature *Aedes aegypti* mosquitoes, so that

$$N_A(t) = A_U(t) + A_W(t).$$

Similarly, the total population of adult *Aedes aegypti* mosquitoes at time t, denoted by $N_V(t)$, is subdivided into subpopulation of *Wolbachia*-uninfected (i.e., wild or susceptible) adult female ($F_U(t)$), *Wolbachia*-uninfected adult male ($M_U(t)$), *Wolbachia*-infected adult female ($F_W(t)$), *Wolbachia*-infected adult male ($M_W(t)$) and adult female mosquitoes infected with dengue ($F_D(t)$). Hence,

$$N_V(t) = F_U(t) + M_U(t) + F_W(t) + M_W(t) + F_D(t).$$

Finally, the total human population at time t, denoted by $N_H(t)$, is subdivided into the compartments of susceptible ($S_H(t)$), exposed ($E_H(t)$), infectious ($I_H(t)$) and recovered ($R_H(t)$) humans, so that

$$N_H(t) = S_H(t) + E_H(t) + I_H(t) + R_H(t).$$

2.1 Birth Functions of Mosquitoes

After emergence, adult female *Aedes aegypti* mosquitoes seek male partners to mate. Let $B_{UU}(t)$ be the rate at which offsprings are produced following the mating of *Wolbachia*-uninfected female and *Wolbachia*-uninfected male mosquitoes. The rate $B_{UU}(t)$ is modelled using the logistic growth rate function:

$$B_{UU}(t) = (\phi_u \psi_u) \left(\frac{1 + M_U}{1 + M_U + M_W} \right) \left(1 - \frac{N_A}{K_A} \right)_+ F_U. \tag{2.1}$$

In (2.1), ϕ_u represents the number of eggs laid *per* oviposition, while ψ_u is the oviposition rate of mated *Wolbachia*-uninfected adult female *Aedes aegypti* mosquitoes (F_U). The term $\dfrac{1 + M_U}{1 + M_U + M_W}$ represents the probability that the mating partner is a *Wolbachia*-uninfected male mosquito. The offspring growth rate is modulated by the the logistic term

$$\left(1 - \frac{N_A}{K_A} \right)_+,$$

where $K_A > N_A(t)$, for all $t > 0$, is the carrying capacity of immature mosquitoes. The notation $(x)_+ = \max\{0, x\}$ is used to ensure the non-negativity of the logistic term. Similarly, let B_{WU} represents the rate at which offsprings are produced following mating of *Wolbachia*-infected adult female mosquitoes and a *Wolbachia*-uninfected adult male mosquito. Hence,

$$B_{WU}(t) = (\phi_w \psi_w) \left(\frac{1 + M_U}{1 + M_U + M_W} \right) \left(1 - \frac{N_A}{K_A} \right)_+ F_W, \tag{2.2}$$

where, ϕ_w is the number of eggs laid *per* oviposition by *Wolbachia*-infected adult female mosquitoes (F_W) and ψ_w is the probability of successful mating between *a Wolbachia*-uninfected adult male mosquito (M_U) and a *Wolbachia*-infected adult female mosquito (F_W).

Let B_{WW} represents the birth rate of offsprings between *Wolbachia*-infected adult female and *Wolbachia*-infected adult male mosquitoes. It follows that:

$$B_{WW}(t) = (\phi_w \psi_w) \left(\frac{M_W}{1 + M_U + M_W} \right) \left(1 - \frac{N_A}{K_A} \right)_+ F_W. \tag{2.3}$$

Let $B_{DU}(t)$ represents the rate at which offsprings are produced following the mating of dengue-infected adult female mosquito (F_D) and *Wolbachia*-uninfected adult male mosquito (M_U). Hence,

$$B_{DU}(t) = (\phi_u \psi_u) \left(\frac{1 + M_U}{1 + M_U + M_W} \right) \left(1 - \frac{N_A}{K_A} \right)_+ F_D \tag{2.4}$$

Let B_{UW} represents the rate at which uninfected offsprings are produced following mating of *Wolbachia*-uninfected female and *Wolbachia*-infected male mosquitoes. It follows that

$$B_{UW}(t) = (1 - c_i)(\phi_w \psi_w) \left(\frac{M_W}{1 + M_U + M_W} \right) \left(1 - \frac{N_A}{K_A} \right)_+ F_U,$$

where, ϕ_w and ψ_w are as defined before, and $0 \leq c_i \leq 1$ denotes for proportion of eggs that failed to hatch due to cytoplasmic incompatibility (resulting from the mating between a *Wolbachia*-uninfected female and a *Wolbachia*-infected male mosquito). Finally, let

$$B_{DW}(t) = (1 - c_i)(\phi_w \psi_w) \left(\frac{M_W}{1 + M_U + M_W} \right) \left(1 - \frac{N_A}{K_A} \right)_+ F_D,$$

be the rate at which offsprings are produced following the mating of *Wolbachia*-infected adult male mosquitoes and dengue-infected adult female mosquitoes.

2.2 Equations of the Model

Based on the above derivations and assumptions, the two-sex compartmental model for assessing the population-level impact of *Wolbachia* introduction on the population ecology of *Aedes aegypti* mosquitoes and dengue disease in a community is given by the following deterministic system of nonlinear differential equations:

$$
\begin{aligned}
\frac{dA_U}{dt} &= B_{UU} + (1-v_w)(B_{WU} + B_{WW} + B_{UW} + B_{DW}) + B_{DU} - \sigma_m A_U - \mu_a A_U, \\
\frac{dA_W}{dt} &= v_w(B_{WU} + B_{WW} + B_{UW} + B_{DW}) - \sigma_m A_W - \mu_a A_W, \\
\frac{dF_U}{dt} &= b_f \sigma_m A_U - \left(\frac{a_V \beta_V I_H}{N_H}\right) F_U - q\left(\frac{M_W}{1 + M_U + M_W}\right) F_U - \mu_{uf} F_U, \\
\frac{dF_W}{dt} &= b_f \sigma_m A_W + q\left(\frac{M_W}{1 + M_U + M_W}\right) F_U - \theta_w \mu_{uf} F_W, \\
\frac{dM_U}{dt} &= (1-b_f)\sigma_m A_U - \mu_{um} M_U, \\
\frac{dM_W}{dt} &= (1-b_f)\sigma_m A_W - \mu_{um} M_W, \\
\frac{dF_D}{dt} &= \left(\tfrac{a_V \beta_V I_H}{N_H}\right) F_U - \mu_{uf} F_D, \\
\frac{dS_H}{dt} &= \Pi_H - \left(\tfrac{a_V \beta_H S_H}{N_H}\right) F_D - \mu_H S_H, \\
\frac{dE_H}{dt} &= \left(\tfrac{a_V \beta_H S_H}{N_H}\right) F_D - \sigma_H E_H - \mu_H E_H, \\
\frac{dI_H}{dt} &= \sigma_H E_H - \gamma_H I_H - \mu_H I_H, \\
\frac{dR_H}{dt} &= \gamma_H I_H - \mu_H R_H.
\end{aligned}
\tag{2.5}
$$

In (2.5), the birth functions B_{UU}, B_{WU}, B_{UW},B_{DU} and B_{DW} are defined as before. The parameter $0 < v_w < 1$ is the proportion of offsprings of *Wolbachia*-infected adult female mosquitoes that are born infected with *Wolbachia* (via vertical transmission). The parameter σ_m models the development rate of immature mosquitoes to adulthood, with $0 < b_f < 1$ representing the proportion of new adult mosquitoes that are female. Natural death occurs in all aquatic mosquito stages at a rate μ_a. Adult female (male) mosquitoes die naturally at a rate μ_{uf} (μ_{um}). It is assumed that both *Wolbachia*-uninfected and *Wolbachia*-infected immature mosquitoes mature to adulthood at the same rate σ_m.

Wolbachia-uninfected adult female mosquito acquire dengue infection, following an effective bite on a dengue-infected human (by a susceptible adult female mosquitoes) at a rate $a_V\beta_V$, where a_V is the *per capita* biting rate of F_U mosquito from infectious human (I_H) and β_V is the probability of transmission (from I_H to F_U *per* bite). Further, *Wolbachia*-uninfected adult female mosquito acquire *Wolbachia* infection following successful mating

with *Wolbachia*-infected adult male mosquitoes at a rate $\frac{qM_W}{1+M_U+M_W}$, where, q is the rate of horizontal *Wolbachia* transmission (following mating between a *Wolbachia*-infected adult male and a *Wolbachia*-uninfected adult female mosquito). The modification parameter θ_w accounts for the assumed increase of natural mortality rate of *Wolbachia*-infected adult female mosquitoes, in comparison to *Wolbachia*-uninfected adult female mosquitoes (i.e., due to fitness cost of *Wolbachia* infection) [79, 80].

Recruitment into the human population (by birth or immigration) occurs at *per capita* rate Π_H. Susceptible humans acquire dengue infection at a rate $a_V\beta_H$, where β_H is the probability of infection *per* bite from a dengue-infected adult female mosquito. Exposed humans develop clinical symptoms of dengue at a rate σ_H. Infectious humans recover at a rate γ_H, and humans in all epidemiological compartments are assumed to die naturally at a rate μ_H (no dengue-induced mortality is assumed).

It is worth noting that, in dengue-endemic areas, adult dengue-competent (*Aedes*) mosquitoes (particularly adult wild mosquitoes) always exist. Hence, it is reasonable to assume, in the formulation of the mating probabilities above, that $M_U(t) \geq 1$ and $M_W(t) \geq 0$ for all $t \geq 0$. In other words, $M_U(t)$ is never zero in dengue-endemic areas. On the other hand, the population of *Wolbachia*-infected adult male mosquitoes ($M_W(t)$) can certainly be zero (e.g., in a dengue-endemic area where the *Wolbachia*-infected mosquitoes are not released or are released in small quantities that they failed to ultimately survive in the community). Hence, based on the assumption that $M_U(t) \geq 1$ and $M_W(t) \geq 0$, our formulation of the mating probabilities guarantee that an adult female mosquito has a higher probability of mating with the adult male mosquito type (wild or *Wolbachia*-infected) that has higher population-level abundance in the community. For example (noting that $M_U(t) > 1$ and $M_W(t) \geq 0$), if $M_W(t) - M_U(t) - 1 > 0$, then an adult female mosquito has a higher probability of mating with an adult *Wolbachia*-infected male mosquito (M_W) than with a *Wolbachia*-uninfected adult male mosquito (M_U) in the community. Similarly, if $1 + M_U(t) - M_W(t) > 0$, then an adult female mosquito has a higher probability of mating with a *Wolbachia*-uninfected male mosquito (M_U) than with a *Wolbachia*-infected male mosquito (M_W) in the community.

The main assumptions made in the formulation of the model (2.5) are:

(i) *Wolbachia*-infected adult female mosquitoes (F_W) do not acquire dengue infection. This is owing to the fact that *Wolbachia* blocks the RNA of dengue virus, making dengue transmission in the *Wolbachia*-infected adult female mosquitoes impossible [10, 78]. In other words, *Wolbachia*-infected adult female mosquito has a fitness advantage of not acquiring dengue infection, as against *Wolbachia*-uninfected adult female mosquito.

(ii) *Wolbachia*-infected adult female mosquitoes have a shorter lifespan ($\theta_w > 1$), in comparison to *Wolbachia*-uninfected adult female female mosquitoes. This is a fitness cost in favour of *Wolbachia*-uninfected adult female mosquitoes. It should be mentioned that such heterogeneity (between *Wolbachia*-infected and *Wolbachia*-uninfected adult female mosquitoes) in lifespan is not assumed in the adult male mosquito population [52, 78].

(iii) No heterogeneity in natural mortality rate (μ_a) and maturation rate (σ_m) in the aquatic stage of the mosquito lifecycle is assumed.

(iv) *Wolbachia* male-killing effect (i.e., feminization) is not accounted for. This is a simplifying assumption [61, 68].

(v) No vertical transmission of dengue disease is assumed. Numerous earlier modeling studies, including the study by Taghikhani and Gumel [73], have shown that vertical transmission has no significant effect on dengue transmission dynamics [28, 66].

Table 1. Description of the state variables of the model (2.5)

State Variables	**Description**
A_U (A_W)	Number of *Wolbachia*-uninfected (infected) immature mosquitoes
F_U (F_W)	Number of *Wolbachia*-uninfected (infected) adult female mosquitoes
M_U (M_W)	Number of *Wolbachia*-uninfected (infected) adult female mosquitoes
F_D	Number of dengue-infected adult female mosquitoes
S_H	Number of susceptible humans
E_H	Number of exposed (infected but not infectious) humans
I_H	Number of symptomatically-infected (infectious) humans
R_H	Number of recovered humans

Table 2. Description of the parameters of the model (2.5)

Parameters	**Description**
K_A	Carrying capacity of aquatic stage of mosquitoes
Π_H	Recruitment rate of humans (*via* birth or immigration)
σ_m	Development rate of immature mosquitoes in aquatic stage
b_f	Proportion of new adult mosquitoes that are female
q	Rate of horizontal transmission of *Wolbachia* from *Wolbachia*-infected adult male mosquitoes to *Wolbachia*-uninfected adult female mosquitoes
c_i	Fraction of unviable offsprings due to cytoplasmic incompatibility
ϕ_u	*Per capita* egg laying rate by *Wolbachia*-free mosquitoes
ψ_u	Probability of successful mating between uninfected adult female and uninfected adult male mosquitoes
ϕ_w	*Per capita* egg laying rate by *Wolbachia*-infected mosquitoes
ψ_w	Probability of successful mating between *Wolbachia*-infected mosquitoes
μ_a	*Per capita* mortality rate of aquatic stage of mosquitoes
μ_{uf}	*Per capita* mortality rate of uninfected adult female mosquitoes
μ_{um}	*Per capita* mortality rate of adult male mosquitoes
v_w	Proportion of offsprings of *Wolbachia*-infected adult female mosquitoes that bear *Wolbachia* infection (*via* vertical transmission)
a_V	Biting rate of *Wolbachia*-free mosquitoes
β_H	Probability of infection of a susceptible human *per* bite by an infected mosquito
β_V	Probability of infection of a susceptible mosquito *per* bite by an infected human
σ_H	Rate of development of clinical symptoms of disease by exposed humans
γ_H	Recovery rate for humans
θ_w	Modification parameter for the assumed increase in the mortality rate of *Wolbachia*-infected adult female mosquitoes, in comparison to *Wolbachia*-uninfected adult female mosquitoes

The model (2.5) is an extension of numerous *Wolbachia*-infected mosquitoes models that include vertical transmission in the vector population (such as those in [1, 17, 22, 26, 28, 33, 39, 86] by (*inter ralia*) :

(a) adding the dynamics of dengue disease in the human and mosquito populations (this was not included in the models in [22, 48, 49, 64, 86]);

(b) allowing for horizontal transmission of *Wolbachia* infection (this was not considered in the models in [22, 39, 48, 49, 56, 64, 86]).

Table 3. Ranges and baseline values of **the parameters** of the model (2.5).

Parameter	**Range**	**Baseline**	**Reference**
b_f	[0.5-0.57]	0.5	[50]
ϕ_u	[0-75]	50	[18]
c_i	[0.95-1]	0.975	[10, 52]
ψ_u	[0-1]	0.8	[87]
ϕ_w	[0-70]	47	[39, 85]
ψ_w	[0-1]	0.8	Assumed
μ_a	[0.01-0.04]	0.02	[37, 53]
μ_{uf}	[1/21-1/14]	1/17	[52, 72]
μ_m	[1/14-1/7]	1/11	[52, 72]
v_w	[0.89-1]	0.95	[78]
β_H	[0.1-0.75]	0.2	[85, 36]
β_V	[0.05-0.35]	0.1	[85, 36]
σ_H	[0.07-0.3]	0.15	[26]
γ_H	[0.09-0.25]	0.2	[26]
θ_w	[1-1.7]	1.1	[39, 85]
a_V	[0-1]	0.12	[4]
q	[0-1]	0.01	Assumed

2.3 Basic Qualitative Analysis of the Model

In this section, the basic qualitative features of the model (2.5) will be explored. The aim is to assess the well-posedness of the model (with respect to the positivity and boundedness properties of the solutions of the model). We claim the following result.

Theorem 2.1. *Let* $\mathbf{X}(t) = (A_U(t),\ A_W(t),\ F_U(t),\ M_U(t),\ F_W(t),\ M_W(t), F_D(t),\ S_H(t),\ E_H(t),\ I_H(t)\ , R_H(t))^T$ *be solutions of the model* (2.5) *at time* t. *If initial data* $\mathbf{X}(0)$ *of the model be strictly positive, then, all solutions of the model remain non-negative and bounded in* $\mathbb{R}^{11}_+$ *for all time* $t > 0$.

Proof. We first show the non-negativity of the state variables $S_H(t)$ and $N_H(t)$ for all $t > 0$. Let $S_H(t_1) = 0$ for some $t = t_1 > 0$. Then, it follows from the eighth equation of (2.5) that (noting that all parameters of the model are assumed to be non-negative)

$$\frac{dS_H}{dt}|_{t=t_1} = \Pi_H > 0.$$

Hence, the solution $S_H(t)$ is increasing at $t = t_1$. Thus, $S_H(t)$ cannot decrease below zero. This shows that $S_H(t) > 0$ for all $t \geq 0$.

For the non-negativity of $N_H(t)$, it is convenient to consider the equation for the rate of change of the total human population (obtained by adding the last four equations of the model (2.5)), given by

$$\frac{dN_H}{dt} = \Pi_H - \mu_H N_H. \tag{2.6}$$

Let $N_H(t_2) = 0$ for some $t = t_2 > 0$. It follows from (2.6) that

$$\frac{dN_H}{dt}|_{t=t_2} = \Pi_H > 0,$$

so that (using similar argument as above) $N_H(t) > 0$ for all $t \geq 0$.

To show the non-negativity of the remaining 10 state variables of the model (2.5), it is convenient to define

$$t^* = \min_{t>0}\{t|\text{at least one of the remaining 10 state variables of the model (2.5) is zero}\}. \tag{2.7}$$

First of all, the case where no such t^* exists (i.e., when each of the remaining 10 state variables of the model is strictly positive) is the trivial case (and no proof is needed).

Suppose such t^* exists. Further, without loss of generality, let $A_U(t^*) = 0$ and the other remaining state variables of the model (2.5) are non-negative at $t = t^*$. Based on the definition of t^* in (2.7), the assumption $A_U(t^*) = 0$ is equivalent to saying $A_U(t) > 0$ for all $t < t^*$. It follows from the first equation of the model (2.5) that

$$\begin{aligned}\frac{dA_U}{dt}|_{t=t^*} &= B_{UU}(t^*) + (1-v_w)\left(B_{WU}(t^*) + B_{WW}(t^*) + B_{UW}(t^*) + B_{DW}(t^*)\right) + B_{DU}(t^*) \\ &= \left(1 - \frac{N_A(t^*)}{K_A}\right)\phi_u\psi_u\left(\frac{M_U(t^*)+1}{1+M_U(t^*)+M_W(t^*)}\right)\left(F_U(t^*)+F_D(t^*)\right) \\ &+ (1-v_w)\left(1-\frac{N_A(t^*)}{K_A}\right)\phi_w\psi_w\left(F_W(t^*) + \frac{(1-c_i)M_W(t^*)\left(F_U(t^*)+F_D(t^*)\right)}{1+M_U(t^*)+M_W(t^*)}\right)\end{aligned} \tag{2.8}$$

To show that $A_U(t) \geq 0$ for all t, we need to show that each of the state variables in (2.8) (namely $F_U(t)$, $F_W(t)$, $M_U(t)$ and $M_W(t)$) is non-negative at $t = t^*$.

Let $M_W(t^*) = 0$. If $A_W(t^*) > 0$, then it follows from the sixth equation of the model (2.5) that, at $t = t^*$,

$$\frac{dM_W}{dt}|_{t=t^*} = (1-b_f)\sigma_m A_W(t^*) > 0.$$

Since $\frac{dM_W}{dt}|_{t=t^*} > 0$, it follows that $M_W(t)$ is an increasing function at $t = t^*$. Hence, $M_W(t)$ is non-negative in a neighbourhood of t^*.

Next, consider the case where $M_W(t^*) = A_W(t^*) = 0$. Since (in this case) $M_W(t^*) = 0$, it follows that, for any $\epsilon_1 > 0$, there exists a $\delta_1 > 0$ such that, for $|t - t^*| < \delta_1$, the inequality $|M_W(t)| < \frac{\epsilon_1}{\mu_{um}}$ holds. It can be seen from the sixth equation of the model (2.5) that the equation for the derivative of $M_W(t)$ in a neighborhood of t^* (where, now, $t \in (t^* - \delta_1, t^*)$ or $(t^*, t^* + \delta_1)$)

$$\frac{dM_W}{dt} \geq (1-b_f)\sigma_m A_W(t) - \epsilon_1. \tag{2.9}$$

Since $A_W(t) > 0$ for $t < t^*$, ϵ_1 can be chosen small enough such that $A_W(t) > \frac{\epsilon_1}{(1-b_f)\sigma_m}$ in a neighbourhood of t^*. Therefore, from equation (2.9), the derivative of M_W is positive in a

neighbourhood of t^*. Hence, M_W is an increasing function at $t = t^*$ and $M_W(t) \geq 0$ in an interval of t^* (i.e., sub-interval of $(t^* - \delta_1)$ or $(t^*, t^* + \delta_1)$). Similarly, it can be shown that $M_U(t) \geq 0$ in an interval of t^*.

Next, we show that $I_H(t) \geq 0$ in a neighbourhood of t^*. Let $I_H(t^*) = 0$. Then, for any $\epsilon_2 > 0$, there exists $\delta_2 > 0$ such that for $|t - t^*| < \delta_2$, the inequality $|I_H(t)| < \frac{\epsilon_2}{\gamma_H + \mu_H}$ holds. It follows from the tenth equation of the model (2.5) that, in the neighbourhood of t^*,

$$\frac{dI_H}{dt} > \sigma_H E_H - \epsilon_2. \tag{2.10}$$

Since $E_H(t) > 0$ for $t < t^*$, ϵ_2 can be chosen small enough such that $E_H(t) > \frac{\epsilon_2}{\sigma_H}$, in a neighbourhood of t^*. Hence, it follows from equation (2.10) that $I_H(t)$ is an increasing function when t is close enough to t^*. Thus, $I_H(t) \geq 0$ in a neighbourhood of t^*. Next we show that $F_U(t) \geq 0$ in a neighbourhood of $t = t^*$. Let $F_U(t^*) = 0$. Then, for any $\epsilon_3 > 0$, there is $\delta_3 > 0$ such that for $|t - t^*| < \delta_3$, the inequality $|F_U(t)| < \epsilon_3$ holds. Since we showed previously that $I_H(t)$, $M_U(t)$ and $M_W(t)$ are all greater or equal to zero in a neighbourhood of $t = t^*$, then it follows from the fourth equation of the model (2.5) that (in a neighbourhood of t^*, and recall that $I_H(t) < N_H(t)$ for all t),

$$\frac{dF_U}{dt} > b_f \sigma_m A_U - a_V \beta_V F_U - q F_U - \mu_{uf} F_U. \tag{2.11}$$

Let $\lambda = \max\{a_V \beta_V, q, \mu_{uf}\}$. Then, equation (2.11) satisfies

$$\frac{dF_U}{dt} > b_f \sigma_m A_U - 3\lambda F_U > b_f \sigma_m A_U - 3\lambda \epsilon_3. \tag{2.12}$$

Since $A_U(t) > 0$ for $t < t^*$, then it follows from (2.12) that ϵ_3 can be chosen small enough such that $A_U(t) > \frac{3\lambda\epsilon_3}{b_f \sigma_m}$ in a neighbourhood of t^*, (i.e., sub-interval of $(t^* - \delta_3, t^*)$ or $(t^*, t^* + \delta_3)$). Hence, $F_U(t)$ is increasing function near t^*. Therefore, $F_U(t) \geq 0$ in a neighbourhood of t^*. Since we showed $I_H(t) > 0$ and $F_U(t) > 0$ in a neighbourhood of t^*, it can be shown that $F_D(t) > 0$ in a neighbourhood of t^* by the same argument. We have shown that all the state variables on the right-hand side of the equation (2.8) are positive. Hence, $A_U(t)$ is an increasing function in a neighbourhood of t^*, which implies that $A_U(t)$ cannot be negative. This proof can be applied for any other state variable of the model (2.5) such that the state variable is zero at $t = t^*$ for the first time. Hence, all the state variables of the model (2.5) are non-negative if the initial vector $\mathbf{X}(0)$ is positive.

For the boundedness of the solutions of the model, it should first be noted that $A_U(t) < K_V$ for all $t \geq 0$. Suppose this assumption is relaxed and $A_U(t)$ can be equal to K_V. Let t_1 be the first time such that $A_U(t)$ equals K_V. That is, define t_1 such that $A_U(t_1) = K_V$. Thus, it follows from the first equation of (2.5) that $\frac{dA_U}{dt}|_{t=t_1} < 0$ (since $\left(1 - \frac{N_A(t_1)}{K_A}\right) < 0$). This implies that $A_U(t)$ is a decreasing function of t in some t_1 neighborhood. Therefore, $A_U(t)$ can not exceed K_V (since $A_U(t)$ is decreasing in a neighbourhood of t_1). Hence, $A_U(t) < K_V$ for all $t > 0$. Using similar argument, it can be shown that $A_W(t) < K_V$ for all $t > 0$.

To show the boundedness for $F_U(t)$, the equation for $\frac{dF_U}{dt}$ in (2.5) can be rewritten as (noting that $A_U(t) < K_V$ for all $t > 0$)

$$\frac{dF_U}{dt} < b_f \sigma_m K_V - \mu_{uf} F_U,$$

from which it follows that

$$F_U(t) < \frac{b_f \sigma_m}{\mu_{uf}} K_V + e^{-\mu_{uf} t} \left(F_U(0) - \frac{b_f \sigma_m}{\mu_{uf}} \right).$$

Hence, $F_U(t)$ is bounded for all $t > 0$. Similarly, it can be shown that the remaining mosquito state variables, $F_W(t)$, $M_U(t)$, $M_W(t)$ and F_D are all bounded for all $t > 0$.

For the boundedness of the state variables for the human components of the model (2.5), it is convenient to consider the equation for the rate of change of total human population ($N_H(t)$), given by

$$\frac{dN_H}{dt} = \Pi_H - \mu_H N_H,$$

from which it follows that $N_H(t) < \dfrac{\Pi_H}{\mu_H} + N_H(0)$ for all $t > 0$. Hence, $N_H(t)$ is bounded. Thus, since $N_H(t) = S_H(t) + E_H(t) + I_H(t) + R_H(t)$, it follows that $S_H(t)$, $E_H(t)$, $I_H(t)$ and $R_H(t)$ are bounded for all $t > 0$.

□

3 Mathematical Analysis

It is convenient, first of all, to define the following quantity

$$\mathcal{R}_U = (\phi_u \psi_u) \left(\frac{\sigma_m}{\sigma_m + \mu_a} \right) (b_f) \left(\frac{1}{\mu_{uf}} \right), \tag{3.1}$$

which represents the average number of new *Wolbachia*-uninfected adult female *Aedes* mosquitoes produced by a *Wolbachia*-uninfected adult female *Aedes* mosquito during its lifetime. Ecologically-speaking, it is product of the eggs laying rate of *Wolbachia*-uninfected adult *Aedes* female mosquitoes ($\phi_u \psi_u$), the probability that these eggs survived to become adult mosquitoes $\left(\frac{\sigma_m}{\sigma_m + \mu_a} \right)$, the proportion of new adult mosquitoes that are females (b_f), and the average lifespan of *Wolbachia*-uninfected adult female mosquitoes $\left(\frac{1}{\mu_{uf}} \right)$.

3.1 Existence of Disease-free and Boundary Equilibria

The model (2.5) has the following disease-free (i.e., dengue-free) and boundary equilibria.

(i) Trivial (mosquito-free and dengue-free) equilibrium ($\mathcal{T}_0$)

$$\begin{aligned} \mathcal{T}_0 &= (A_U^*, A_W^*, F_U^*, F_W^*, M_U^*, M_W^*, F_D^*, S_H^*, E_H^*, I_H^*, R_H^*) \\ &= \left(0, 0, 0, 0, 0, 0, 0, \frac{\Pi_H}{\mu_H}, 0, 0, 0 \right). \end{aligned}$$

This equilibrium is ecologically unrealistic, since mosquitoes always exist. Hence, this equilibrium will not be considered in the analysis of the model (**recall that** $M_U(t) \geq 1$ **and** $M_W(t) \geq 0$ **for all** $t \geq 0$).

(ii) *Wolbachia*-free and dengue-free equilibrium ($\mathcal{T}_1$)

$$\begin{aligned}\mathcal{T}_1 &= (A_U^*, A_W^*, F_U^*, F_W^*, M_U^*, M_W^*, F_D^*, S_H^*, E_H^*, I_H^*, R_H^*)\\ &= \left(A_U^*, 0, \frac{b_f\sigma_m A_U^*}{\mu_{uf}}, 0, \frac{(1-b_f)\sigma_m A_U^*}{\mu_{um}}, 0, 0, \frac{\Pi_H}{\mu_H}, 0, 0, 0\right),\end{aligned}$$

with $A_U^* = K_A(1-\frac{1}{\mathcal{R}_U})$. Clearly, this equilibrium exists if and only if $\mathcal{R}_U > 1$ (since $A_U^* > 0$ if and only if $\mathcal{R}_U > 1$).

(iii) *Wolbachia*-free and dengue-present boundary equilibrium ($\mathcal{T}_2$)

$$\begin{aligned}\mathcal{T}_2 &= (A_U^*, A_W^*, F_U^*, F_W^*, M_U^*, M_W^*, F_D^*, S_H^*, E_H^*, I_H^*, R_H^*)\\ &= \left(A_U^*, 0, \frac{\mu_H\mu_{uf}F_D^*}{a_V\beta_V I_H^*}, 0, \frac{(1-b_f)\sigma_m A_U^*}{\mu_{um}}, 0, F_D^*, \frac{\Pi_H\mu_H}{a_V\beta_H F_D^* + \mu_H N_H^*}, \frac{a_V\beta_H F_D^* S_H^*}{N_H^*(\sigma_H+\mu_H)}, \frac{\sigma_H E_H^*}{\gamma_H+\mu_H}, \frac{\gamma_H I_H^*}{\mu_H}\right),\end{aligned}$$

where,

$$A_U^* = \frac{K_A\phi_u\psi_u(F_U^*+F_D^*)}{\phi_u\psi_u(F_U^*+F_D^*)+K_A(\sigma_m+\mu_a)}, \text{ and, } \quad F_D^* = \frac{A-B-C}{D},$$

with,

$$\begin{aligned}A &= \sigma_m K_A\Pi_H a_V^2 b_f\beta_H\beta_V\phi_u\psi_u\sigma_H,\\ B &= \phi_u\psi_u N_H^2\mu_H(\mu_H+\sigma_H)(\gamma_H+\mu_H)\mu_{uf}^2,\\ C &= \Pi_H a_V^2 K_A\sigma_H\beta_V\beta_H(\sigma_m+\mu_a)\mu_{uf},\\ D &= a_V(N_H(\mu_H+\sigma_H)(\gamma_H+\mu_H)\mu_{uf} + \Pi_H a_V\beta_V\sigma_H)\phi_u\beta_H\mu_{uf}\psi_u.\end{aligned}$$

It follows that this equilibrium ($\mathcal{T}_2$) exists (i.e., $F_D^* > 0$) if and only if

$$\frac{\sigma_m K_A\Pi_H {a_V}^2 b_f\beta_H\beta_V\phi_u\psi_u\sigma_H}{\phi_u\psi_u {N_H}^2\mu_H(\mu_H+\sigma_H)(\gamma_H+\mu_H){\mu_{uf}}^2 + \Pi_H {a_V}^2 K_A\sigma_H\beta_V\beta_H(\sigma_m+\mu_a)\mu_{uf}} > 1. \qquad (3.2)$$

The results above are summarized below.

Theorem 3.1. *The model* (2.5) *has the following equilibria:*

(i) *A trivial mosquito-free and dengue-free equilibrium ($\mathcal{T}_0$), which always exists.*

(ii) *A Wolbachia-free and dengue-free equilibrium ($\mathcal{T}_1$), which exists if and only if $\mathcal{R}_U > 1$.*

(iii) *A Wolbachia-free and dengue-present boundary equilibrium ($\mathcal{T}_2$), which exists whenever Inequality* (3.2) *holds.*

It should be mentioned that the model (2.5) has at least one co-existence equilibrium (where both *Wolbachia*-uninfected and *Wolbachia*-infected mosquitoes are present, as well as humans and dengue). However, expressing this equilibrium in closed form is difficult (and not given here).

3.2 Asymptotic Stability of Disease-free Equilibria

In this section, the local asymptotic stability of the disease-free equilibria $\mathcal{T}_0$ and $\mathcal{T}_1$ will be explored.

3.2.1 Asymptotic Mosquito-free and Dengue-free Equilibrium ($\mathcal{T}_0$)

The linear stability of the trivial equilibrium ($\mathcal{T}_0$) can be established by linearizing the model (2.5) around $\mathcal{T}_0$. In particular, the Jacobian of the linearized system (2.5) around $\mathcal{T}_0$ is given by

$$\mathcal{J}(\mathcal{T}_0) = \begin{bmatrix} j_{1,1} & 0 & \phi_u\psi_u & j_{1,4} & 0 & 0 & \phi_u\psi_u & 0 & 0 & 0 & 0 \\ 0 & j_{2,2} & 0 & v_w\phi_w\psi_w & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ b_f\lambda & 0 & -\mu_{uf} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b_f\lambda & 0 & -\theta_w\mu_{uf} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ j_{5,1} & 0 & 0 & 0 & -\mu_{um} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & j_{6,2} & 0 & 0 & 0 & -\mu_{um} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_{uf} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -a_V\beta_H & -\mu_H & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & a_V\beta_H & 0 & j_{9,9} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_H & j_{10,10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_H & -\mu_H \end{bmatrix},$$

where, $j_{1,1} = j_{2,2} = -(\sigma_m + \mu_a)$, $j_{1,4} = (1 - v_w)\,\phi_w\psi_w$, $j_{5,1} = (1 - b_f)\,\sigma_m$, $j_{6,2} = (1 - b_f)\,\sigma_m$, $j_{9,9} = -(\sigma_H + \mu_H)$, $j_{10,10} = -(\gamma_H + \mu_H)$. The associated eigenvalues of $\mathcal{J}(\mathcal{T}_0)$ are given by

$$\begin{aligned} \lambda_1 &= -\frac{1}{2}\left[\theta_w\mu_{uf} + \sigma_m + \mu_a + \sqrt{(\sigma_m + \mu_a - \theta_w\mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_w\psi_w v_w}\right], \\ \lambda_2 &= -\frac{1}{2}\left[\theta_w\mu_{uf} + \sigma_m + \mu_a - \sqrt{(\sigma_m + \mu_a - \theta_w\mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_w\psi_w v_w}\right], \\ \lambda_3 &= -\frac{1}{2}\left[\mu_{uf} + \sigma_m + \mu_a + \sqrt{(\sigma_m + \mu_a - \mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_u\psi_u}\right], \\ \lambda_4 &= -\frac{1}{2}\left[\mu_{uf} + \sigma_m + \mu_a - \sqrt{(\sigma_m + \mu_a - \mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_u\psi_u}\right], \\ \lambda_5 &= -\mu_{uf},\ \lambda_6 = \lambda_7 = -\mu_{um},\ \lambda_8 = \lambda_9 = -\mu_H,\ \lambda_{10} = -(\sigma_H + \mu_H), \\ \lambda_{11} &= -(\gamma_H + \mu_H). \end{aligned} \tag{3.3}$$

It follows from (3.3) that the eigenvalues λ_1, λ_3, λ_5, λ_6, λ_7, λ_8, λ_9, λ_{10} and λ_{11} all have negative real part. Furthermore, it can be seen that the eigenvalue $\lambda_2 < 0$ if and only if

$$\mathcal{R}_W = \frac{v_w b_f \sigma_m\,\phi_w\psi_w}{\theta_w\mu_{uf}(\sigma_m + \mu_a)} < 1. \tag{3.4}$$

Similarly, the eigenvalue $\lambda_4 < 1$ if and only if

$$\mathcal{R}_U = \frac{b_f \sigma_m \, \phi_u \psi_u}{\mu_{uf}(\sigma_m + \mu_a)} < 1. \tag{3.5}$$

These results are summarized below.

Theorem 3.2. *The trivial equilibrium ($\mathcal{T}_0$) of the model* (2.5) *is locally-asymptotically stable whenever $\mathcal{R}_U < 1$ and $\mathcal{R}_W < 1$, and unstable if $\mathcal{R}_U > 1$ or $\mathcal{R}_W > 1$.*

The ecological implication of Theorem 3.2 is that a small influx of mosquitoes (both wild and *Wolbachia*-infected) into the community will not lead to the persistence of the mosquito population whenever both $\mathcal{R}_U$ and $\mathcal{R}_W$ are less than unity. In other words, for small initial number of mosquitoes (both wild and *Wolbachia*-infected), the mosquito population will go extinct whenever $\mathcal{R}_U$ and $\mathcal{R}_W$ are less than unity.

3.2.2 Asymptotic Stability of Wolbachia-free and Dengue-free Equilibrium ($\mathcal{T}_1$)

The *Wolbachia*-free and dengue-free equilibrium ($\mathcal{T}_1$) is the more realistic (in nature) of the disease-free (i.e., dengue-free) equilibria discussed above. Hence, it will be solely considered for the asymptotic stability analysis of the model (2.5). The *next generation operator* method [19, 77] will be used for the analysis. Using the notation in van den Driessche and Watmough [77], the associated matrices F and V, for the new infection and transmission terms, respectively, are given by

$$F = \begin{bmatrix} 0 & v_m\phi_w\psi_w\left(1-\frac{A_U^*}{K_A}\right) & v_m\phi_w\psi_w(1-c_i)\frac{F_U^*}{1+M_U^*}\left(1-\frac{A_U^*}{K_A}\right) & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{qF_U^*}{(1+M_U^*)} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{a_V\beta_V F_U^*}{N_H^*} & 0 \\ 0 & 0 & 0 & a_V\beta_H & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$V = \begin{bmatrix} \sigma_m + \mu_a & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_m\, b_f & \mu_{uf}\theta_w & 0 & 0 & 0 & 0 & 0 \\ -(1-b_f)\,\sigma_m & 0 & \mu_{um} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \mu_{uf} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma_H + \mu_H & 0 & 0 \\ 0 & 0 & 0 & 0 & -\sigma_H & \gamma_H + \mu_H & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma_H & \mu_H \end{bmatrix}.$$

It follows that the *reproduction number* of the model (2.5), denoted by $\mathcal{R}_0$, is given by (where, ρ is the spectral radius; that is, ρ is the dominant eigenvalue of FV^{-1})

$$\mathcal{R}_0 = \rho(FV^{-1}) = \max\{\mathcal{R}_{0W}, \mathcal{R}_{0D}\}, \tag{3.6}$$

where,

$$\mathcal{R}_{0W} = \frac{Z}{2} + \sqrt{\frac{Z^2}{4} + \frac{k_1 k_3 \phi_w \sigma_m (1 - b_f)}{(\sigma_m + \mu_a)\theta_w \mu_{um} \mu_{uf}}} \tag{3.7}$$

and,

$$\mathcal{R}_{0D} = \sqrt{\frac{a_V a_V \beta_H \beta_V \sigma_H F_U^*}{\mu_{uf}(\sigma_H + \mu_H)(\gamma_H + \mu_H) N_H^*}} \tag{3.8}$$

with,

$$Z = \frac{\phi_w \sigma_m [k_1 b_f \mu_{um} + \theta_w \mu_{uf} k_2 (1 - b_f)]}{(\sigma_m + \mu_a)\theta_w \mu_{uf} \mu_{um}}, \quad k_1 = v_m \psi_w \left(1 - \frac{A_U^*}{K_A}\right),$$
$$k_2 = k_1 (1 - c_i) \frac{F_U^*}{1 + M_U^*}, \quad k_3 = \frac{q F_U^*}{1 + M_U^*}.$$

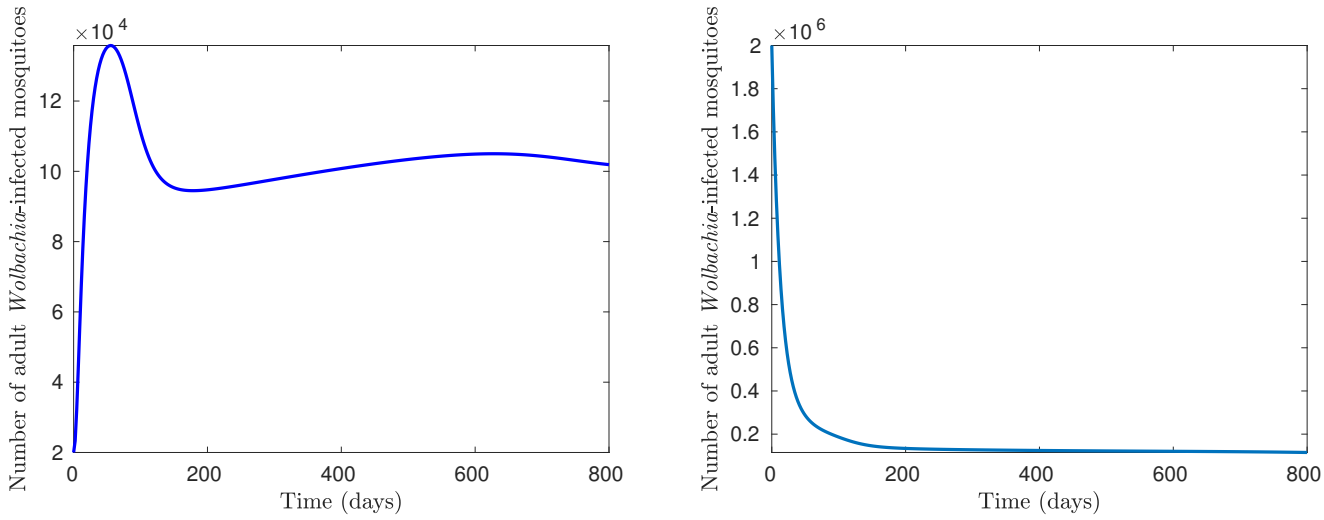
The quantity $\mathcal{R}_{0W}$ represents the average number of *Wolbachia*-infected mosquitoes produced by one *Wolbachia*-infected adult female mosquito introduced into a mosquito population with only the wild adult mosquitoes present (near to the *Wolbachia*-free and dengue-free equilibrium $\mathcal{T}_1$). Similarly, $\mathcal{R}_{0D}$ is the average number of new dengue cases generated by one dengue-infected human (dengue-infected and *Wolbachia*-uninfected adult female mosquito) introduced into a population of susceptible adult female *Wolbachia*-uninfected mosquitoes (susceptible humans) near the *Wolbachia*-free and dengue-free equilibrium $\mathcal{T}_1$. The result below follows from Theorem 2 of [77].

Theorem 3.3. *Consider the model* (2.5) *with* $\mathcal{R}_U > 1$. *The Wolbachia-free and dengue-free equilibrium* $\mathcal{T}_1$ *is locally-asymptotically stable whenever* $\mathcal{R}_0 < 1$, *and unstable if* $\mathcal{R}_0 > 1$.

The epidemiological implication of Theorem 3.3 is that releasing small number of *Wolbachia* or dengue-infected mosquitoes into the wild mosquito population will not lead to the persistence (or dominance) of the *Wolbachia*-infected mosquitoes or dengue disease in the community when $\mathcal{R}_U > 1$ and $\mathcal{R}_0 < 1$.

The result of Theorem 3.3 is numerically illustrated by simulating the model (2.5) using various combinations of $\mathcal{R}_{0W}$ and $\mathcal{R}_{0D}$ (here, various combinations of $\mathcal{R}_0$). The results obtained are tabulated in Table 4. Items (i) and (iii) of Table 4 suggest the possibility of backward bifurcation in the model (2.5) (see [12, 13] and some of the references therein). This is owing to the fact that these two items show that *Wolbachia*-infected mosquitoes may die out or persist when $\mathcal{R}_0 < 1$. Backward bifurcation is a dynamic phenomenon associated with the co-existence of multiple asymptotically-stable equilibrium (namely, the locally-asymptotically stable $\mathcal{T}_1$ and a locally-asymptotically stable co-existence equilibrium)

when $\mathcal{R}_{0W} < 1$ [12, 13]. In particular, Figure 1 shows such persistence (Figure 1a) or decay (Figure 1b) of *Wolbachia*-infected mosquitoes when $\mathcal{R}_0 < 1$ for two different sets of initial conditions.



(a) (b)

Figure 1: Simulation of the model (2.5) showing the persistence or decay of the total population of adult *Wolbachia*-infected mosquitoes ($F_W + M_W$) as a function of time, using two different set of initial conditions. Parameter values used are: $\sigma_m = 0.25$, $q = 0.1$, $K_A = 120000$, $b_f = 0.5$, $\mu_a = 0.001$, $\mu_{uf} = 1/18$, $\mu_{um} = 1/11$, $v_w = 0.5$, $\phi_u = 3$, $\psi_u = 0.8$, $\phi_w = 3$, $\psi_w = 0.6$, $\theta_w = 1.1$, $a_V = 0.3$, $\beta_H = 0.8$, $\beta_V = 0.8$, $\sigma_H = 0.15$, $\gamma_H = 0.2$, $\Pi_H = 100$, and $\mu_H = 0.00005$, such that $\mathcal{R}_U = 21.51$, $\mathcal{R}_{\mathcal{W}} = 7.82$, $\mathcal{R}_{0W} = 0.95$ and $\mathcal{R}_{0D} = 0.94$. The initial values used are: **(a)** $A_U(0) = 100$, $A_W(0) = 0$, $F_U(0) = 10,000$, $F_W(0) = 10,000$, $M_U(0) = 100$, $M_W(0) = 10,000$, $F_D(0) = 1,000$, $S_H(0) = 100,000$, $E_H(0) = 10$, $I_H(0) = 2$, and $R_H(0) = 0$. **(b)** $A_U(0) = 10,000$, $A_W(0) = 1,000$, $F_U(0) = 10,000$, $F_W(0) = 100,000$, $M_U(0) = 10,000$, $M_W(0) = 1,000,000$, $F_D(0) = 1,000$, $S_H(0) = 100,000$, $E_H(0) = 10$, $I_H(0) = 2$, and $R_H(0) = 0$.

Table 4.

Item	$\mathcal{R}_{0W}$	$\mathcal{R}_{0D}$	$\mathcal{R}_0$	outcome
(i)	< 1	< 1	< 1	*Wolbachia* dies out or persists
(ii)	> 1	< 1	$\mathcal{R}_{0W}$	*Wolbachia* persists
(iii)	< 1	> 1	$\mathcal{R}_{0D}$	*Wolbachia* dies out or persists
(iv)	$1 < \mathcal{R}_{0W} < \mathcal{R}_{0D}$	> 1	$\mathcal{R}_{0D}$	*Wolbachia* dies out or persists
(v)	> 1	$1 < \mathcal{R}_{0D} < \mathcal{R}_{0W}$	$\mathcal{R}_{0W}$	*Wolbachia* persists
(vi)	$\mathcal{R}_{0W} = \mathcal{R}_{0D} > 1$	$\mathcal{R}_{0W} = \mathcal{R}_{0D} > 1$	$\mathcal{R}_{0W}$ or $\mathcal{R}_{0D}$	*Wolbachia* persists

The epidemiological implication of backward bifurcation is that the classical requirement of having $\mathcal{R}_0 < 1$, while necessary, is no longer sufficient for the effective control of mosquitoes in the community [12, 13]. In such a backward bifurcation scenario (in the context of the model (2.5)), the effective control of mosquitoes and dengue disease (including the persistence of *Wolbachia*-infected mosquitoes) depend on the initial size of the sub-populations of the model (2.5). Although some earlier studies for *Wolbachia*-dengue dynamics, such

as those in [1, 17, 22, 26, 28, 33, 39, 86], have illustrated the presence of backward bifurcation numerically, there has been, to our knowledge, no such studies that established the phenomenon rigorously. Consequently, we will explore the presence of the phenomenon of backward bifurcation rigorously. This is done for a special case of the model (2.5), as discussed below.

3.3 Backward Bifurcation Analysis

For simplicity, the phenomenon of backward bifurcation will be explored for a special case of the model (2.5) with mosquitoes only (i.e., no humans and dengue disease). This special case of the model (2.5) is given by (where the expressions for $B_{UU}(t)$, $B_{WU}(t)$ and $B_{WW}(t)$ in Section 2.1 are used)

$$\begin{aligned}
\frac{dA_U}{dt} &= B_{UU} + (1-v_w)(B_{WU} + B_{WW} + B_{UW}) - \sigma_m A_U - \mu_a A_U,\\
\frac{dA_W}{dt} &= v_w(B_{WU} + B_{WW} + B_{UW}) - \sigma_m A_W - \mu_a A_W,\\
\frac{dF_U}{dt} &= b_f \sigma_m A_U - \left(\frac{a_V \beta_V I_H}{N_H}\right) F_U - q\left(\frac{M_W}{1+M_U+M_W}\right) F_U - \mu_{uf} F_U,\\
\frac{dF_W}{dt} &= b_f \sigma_m A_W + q\left(\frac{M_W}{1+M_U+M_W}\right) F_U - \theta_w \mu_{uf} F_W,\\
\frac{dM_U}{dt} &= (1-b_f)\sigma_m A_U - \mu_{um} M_U,\\
\frac{dM_W}{dt} &= (1-b_f)\sigma_m A_W - \mu_{um} M_W.
\end{aligned} \tag{3.9}$$

The model (3.9) will be studied in the following invariant region:

$$\mathcal{D} = \{(A_U, A_W, F_U, F_W, M_U, M_W) \in \mathbb{R}^6_+ | A_U, A_W, F_U, F_W, M_U, M_W < K_A\}.$$

For the model (3.9), the equilibria $\mathcal{T}_0$ and $\mathcal{T}_1$ now, respectively, reduce to

$$\mathcal{T}_{0\diamond} = (A^*_U, A^*_W, F^*_U, F^*_W, M^*_U, M^*_W) = (0,0,0,0,0,0),$$

and,

$$\mathcal{T}_{1\diamond} = (A^*_U, A^*_W, F^*_U, F^*_W, M^*_U, M^*_W) = (A^*_U, 0, \frac{b_f \sigma_m A^*_U}{\mu_{uf}}, 0, \frac{(1-b_f)\sigma_m A^*_U}{\mu_{um}}, 0),$$

with $A^*_U = K_A(1 - \frac{1}{\mathcal{R}_U})$. The equilibrium $\mathcal{T}_{1\diamond}$ exists if and only if $\mathcal{R}_U > 1$. We claim the following result for the trivial equilibrium $\mathcal{T}_{0\diamond}$ of the model (3.9).

Theorem 3.4. *The trivial equilibrium ($\mathcal{T}_{0\diamond}$) of the model* (3.9) *is locally-asymptotically stable whenever $\mathcal{R}_U < 1$ and $\mathcal{R}_W < 1$, and unstable if $\mathcal{R}_U > 1$ or $\mathcal{R}_W > 1$.*

The proof of Theorem 3.4, based on using standard linearization, is given in Appendix A. Further, we claim the the following result.

Theorem 3.5. *The model* (3.9) *with* $\mathcal{R}_U > 1$ *undergoes a backward bifurcation at* $\mathcal{R}_{0W} = 1$ *whenever a certain bifurcation coefficient, denoted by* $a(\phi_w^*)$ *and defined in Equation* (B.5)*, is positive.*

The proof of Theorem 3.5, based on using Center Manifold theory [13, 15], is given in Appendix B. Figure 2 depicts the backward bifurcation diagram of the model (3.9). As stated above, this may be the first time the presence of backward bifurcation is shown rigorously in a model for mosquito and dengue dynamics that incorporates *Wolbachia*-based mosquito control in a dengue-endemic community. The presence of backward bifurcation in the transmission dynamics of a disease emphasize the importance of initial conditions in determining the disease outcome when the reproduction number of the model is less than unity. In other words, the presence of backward bifurcation phenomenon makes the effective disease control more difficult. Consequently, it is instructive to explore the mechanism(s) that may cause the presence of backward bifurcation in the model (3.9) (or, equivalently, to determine sufficient conditions for the removal of backward bifurcation in the model). This is done below.

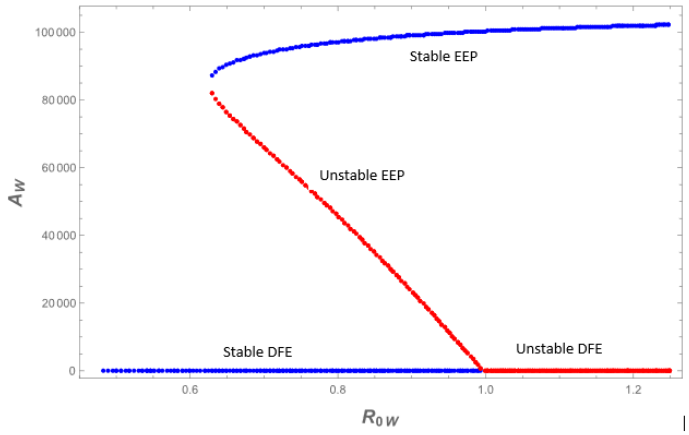


Figure 2: Backward bifurcation diagram of the model (3.9), showing a plot of A_W^* as a function of the reproduction umber $\mathcal{R}_{0W}$. Parameter values used to generate this bifurcation diagram are: $\sigma_m = 1/5, q = 0.01, K_A = 1.2 \times 10^5, b_f = 1/2, \mu_a = 0.001, c_i = 0.96, \mu_{uf} = 1/18, \mu_{um} = 1/9, \phi_u = 17, v_w = 0.88076, \psi_u = 1, \psi_w = 0.42, \theta_w = 0.997$ and $\phi_w = 8$ (so that, $a = 2.777351 \times 10^{-6}$ and $\mathcal{R}_{0W} = 1$). Red and blue lines indicate unstable and stable endemic equilibrium points (EEP), respectively.

It is convenient to consider the special case of the model (3.9) with no horizontal transmission of *Wolbachia* (i.e., $q = 0$) and with fixed mating probabilities, $\frac{M_W}{1+M_U+M_W}$ and $\frac{1+M_U}{1+M_U+M_W}$. That is, let $q = 0$ in (3.9) and

$$m_w = \frac{M_W}{1 + M_U + M_W} = \bar{m}_w \text{ and } \quad m_u = 1 - m_w = \frac{1 + M_U}{1 + M_U + M_W} = \bar{m}_u.$$

with $\bar{m}_u \in$ **(0,1]**, $\bar{m}_w \in$ **[0,1)**, $M_U \geq 1$ **and** $M_W \geq 0$ **for all** $t \geq 0$. Using the fixed values of m_u and m_w (given by $\bar{m}_u$ and $\bar{m}_w$ above, respectively) in the model (3.9), it follows that the equilibria $\mathcal{T}_{0\diamond}$ and $\mathcal{T}_{1\diamond}$ now have the forms:

$$\mathcal{T}_{0c} = (A_U^*, A_W^*, F_U^*, F_W^*, M_U^*, M_W^*) = (0, 0, 0, 0, 0, 0),$$

and,

$$\mathcal{T}_{1c} = (A_U^*, A_W^*, F_U^*, F_W^*, M_U^*, M_W^*) = (A_U^*, 0, \frac{b_f \sigma_m A_U^*}{\mu_{uf}}, 0, \frac{(1-b_f)\sigma_m A_U^*}{\mu_{um}}, 0),$$

with $A_U^* = K_A(1 - \frac{1}{\mathcal{R}_U})$. Furthermore, let

$$\bar{\mathcal{R}}_{0W} = \frac{\mathcal{R}_W}{\bar{m}_u \mathcal{R}_U},$$

be the associated reproduction number of the model (3.9). Note that whenever $\bar{m}_u = 1$ and $\bar{m}_w = 0$,

$$\bar{\mathcal{R}}_{0W} = \frac{\mathcal{R}_W}{\mathcal{R}_U}.$$

We claim the following result.

Theorem 3.6. *Consider the model* (3.9) *with* $m_w = \bar{m}_w = 0$, $m_u = \bar{m}_u = 1$ *and* $q = 0$. *The trivial equilibrium* $\mathcal{T}_{0c}$ *of the model is locally-asymptotically stable if* $\mathcal{R}_W < 1$ *and* $\mathcal{R}_U < 1$.

The proof of Theorem 3.6, based on using standard linearization, is given in Appendix C. We claim the following result.

Theorem 3.7. *Let* $\mathcal{R}_U > 1$. *The model* (3.9) *does not undergo a backward bifurcation at* $\tilde{\bar{\mathcal{R}}}_{0W} = 1$ *whenever any of the following conditions hold*

(a) $m_w = \bar{m}_w = 0$, $m_u = \bar{m}_u = 1$ *and* $q = 0$*;*

(b) $c_i = 1$, $m_w = \bar{m}_w \in [0, 1)$, $m_u = \bar{m}_u \in \left[\frac{1}{\mathcal{R}_U}, 1\right]$, *and* $q = 0$.

The proof of Theorem 3.7, based on using Center Manifold theory [13, 15], is given in Appendix D. Theorem 3.7 guarantees the non-existence of backward bifurcation in the model (3.9) when $\mathcal{R}_U > 1$, $m_w = \bar{m}_w = 0$, $m_u = \bar{m}_u = 1$ and $q = 0$ or $\mathcal{R}_U > 1$, $c_i = 1$, $m_w = \bar{m}_w \in [0, 1)$, $m_u = \bar{m}_u \in (0, 1]$, $q = 0$. Thus, this study identifies two sufficient conditions for the removal of backward bifurcation in the model (2.5), namely

(i). No horizontal transmission of *Wolbachia* from a *Wolbachia*-infected male mosquito to a *Wolbachia*-uninfected female mosquito (i.e., $q = 0$) and *Wolbachia*-infected adult male mosquitoes do not mate with adult female mosquitoes (so that $m_w = 0$ and $m_u = 1$).

(ii). No horizontal transmission of *Wolbachia* from adult *Wolbachia*-infected male mosquitoes to *Wolbachia*-uninfected adult female mosquitoes (i.e., $q = 0$), cytoplasmic incompatibility is perfect (i.e., $c_i = 1$) and mating probabilities for *Wolbachia*-infected adult male mosquitoes are fixed (i.e., $m_w = \bar{m}_w \in [0, 1)$ and $m_u = \bar{m}_u \in \left[\frac{1}{\mathcal{R}_U}, 1\right]$).

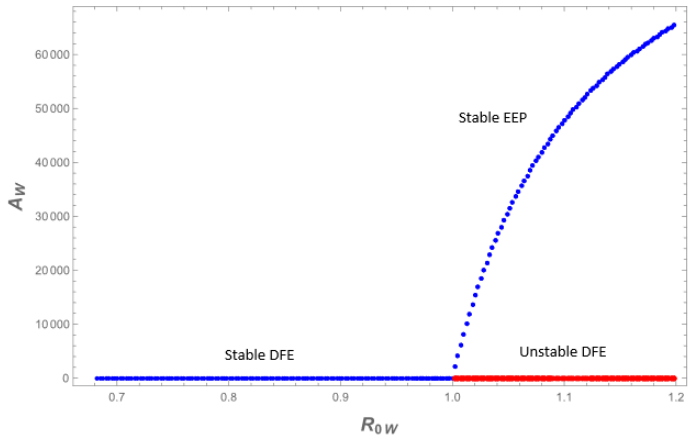


Figure 3: Transcritical (forward) bifurcation diagram of the special case of the model (3.9), with $c_i = 1$, $m_w = \bar{m}_w = 0.5$, $m_u = \bar{m}_u = 0.5$ and $q = 0$. Parameter values used to generate this bifurcation diagram are: $\sigma_m = 1/5$, $K_A = 120000$, $b_f = 1/2$, $\mu_a = 0.001$, $\mu_{uf} = 1/17$, $\mu_{um} = 1/9$, $\phi_u = 17$, $\psi_u = 1$, $\psi_w = 0.42$, $\theta_w = 0.997$, $c_i = 1$, $\bar{m}_u = 0.5$, $\bar{m}_w = 0.5$, $v_w = .88076$ and $\phi_w = 25.2$ (so that $a = -5.565182480 \times 10^{-7}$, $\bar{\mathcal{R}}_{0W} = 1$, $w_2 = 1$ and $v_2 = 1$). Red and blue lines indicate unstable and stable endemic equilibrium, respectively.

It is instructive to explore whether or not the *Wolbachia*-free equilibrium of the model (3.9), given by $\mathcal{T}_{1c}$, is globally-asymptotically stable when the aforementioned conditions for backward bifurcation are relaxed (i.e., when $q = 0$, $m_u = \bar{m}_u = 1$ and $m_w = \bar{m}_w = 0$ or $c_i = 1$, $m_w = \bar{m}_w \in [0, 1)$, $m_u = \bar{m}_u \in (0, 1]$, $q = 0$). This is done below and we claim the following result.

Theorem 3.8. *Let $\mathcal{R}_U > 1$. The Wolbachia-free equilibrium of the model (3.9), given by $\mathcal{T}_{1c}$, is globally-asymptotically stable in $\mathcal{D}\backslash\{\mathcal{T}_{0\diamond}\}$ whenever any of the following conditions hold*

(a) $m_w = \bar{m}_w = 0$, $m_u = \bar{m}_u = 1$, $q = 0$, *and* $\mathcal{R}_W < 1$;

(b) $c_i = 1$, $m_w = \bar{m}_w \in [0, 1)$, $m_u = \bar{m}_u \in (0, 1]$, $q = 0$, *and* $\mathcal{R}_W < 1$.

The proof of Theorem 3.8, based on using Lyapunov function theory, is given in Appendix E. The epidemiology implication of Theorem 3.8 is that under certain conditions, the *Wolbachia*-infected mosquito population will not survive in the community regardless of the initial number of *Wolbachia*-infected mosquitoes released into the wild mosquito population (if $\mathcal{R}_W < 1$).

3.4 Periodic Release of *Wolbachia*-infected Mosquitoes

To allow for the impulsive/periodic release of mosquitoes in the reduced model (2.5), the equations for dynamics of the *Wolbachia*-infected females (F_W) and males (M_W) will now

be re-defined as [38, 40, 71]

$$\begin{aligned}
\frac{dF_W}{dt} &= b_f\sigma_m A_W + q\left(\frac{M_W}{1+M_U+M_W}\right)F_U - \theta_w\mu_{uf}F_W, \quad t \neq n\tau, \\
\frac{dM_W}{dt} &= (1-b_f)\sigma_m A_W - \mu_{um}M_W, \qquad t \neq n\tau, \\
F_W(n\tau^+) &= F_W(n\tau^+) + W_{Rf}, \qquad t = n\tau, \\
M_W(n\tau^+) &= M_W(n\tau^+) + W_{Rm}, \qquad t = n\tau, \\
F_W(0^+) &\geq 0, \;\; M_W(0^+) \geq 0,
\end{aligned} \tag{3.10}$$

where, $\tau > 0$ is the time lag between successive releases of adult *Wolbachia*-infected mosquitoes (either males or females or both), $n\tau^+$ is the moment immediately after the nth *Wolbachia*-infected mosquitoes release and W_{Rf} and W_{Rm} denote for the number of *Wolbachia*-infected female and male mosquitoes released, respectively, at each release time $n\tau$.

3.4.1 Release effect statistic

Following White *et al* [81], we define the *release effect statistic*, denoted by $R(t)$, given by

$$R(t) = \frac{\int_\tau^{t+\tau} N_1(s)ds}{\int_\tau^{t+\tau} N_0(s)ds}, \tag{3.11}$$

where, N_1 is the total abundance of uninfected adult female mosquitoes over a period of time with the release of *Wolbachia*-infected mosquitoes and N_0 is the total abundance of un-infected adult female mosquitoes over that same period without the release of *Wolbachia*-infected mosquitoes. The time-dependent measure $R(t)$ in Equation (3.11) gives the relative effect of the *Wolbachia*-infected mosquitoes release at different time points in the population cycle of the wild-type mosquitoes [81]. Equation (3.11) gives the following three ecological explanation for the release statistic R [81]:

1. If $R = 1$, then there is no relative effect of the control strategy on the wild-type mosquito population.
2. If $R < 1$, then the release have a negative (desirable) effect on the wild-type mosquito population.
3. If $R > 1$, then the release have a positive (not desirable) effect on the wild-type mosquito population.

3.4.2 Simulations: effect of periodic release of *Wolbachia*-infected mosquitoes

The model (2.5), with (3.10), will now be simulated, using the baseline values tabulated in Table 3 (unless otherwise stated), to assess the population-level impact of the release of

certain quantities of adult *Wolbachia*-infected mosquitoes on the population abundance of the local wild adult mosquitoes. The model (2.5), with (3.10), will, first of all, be simulated in the absence of the release of *Wolbachia*-infected mosquitoes (i.e., $A_W = F_W = M_W = 0$), for a period of two years, to determine the baseline worse-case abundance of the local wild adult mosquito population (Figure 4). The adult *Wolbachia*-infected mosquitoes are then released periodically for a one year duration. The model (2.5), with (3.10), is now simulated to assess the impact of the periodic release of *Wolbachia*-infected mosquitoes on the population abundance of the wild adult mosquitoes. In particular, the model will be simulated using a frequency release period of three weeks (i.e., $\tau = 21$ days) and various values of W_{Rf} and W_{Rm}. The chosen 3-week release period is consistent with what was done in Australia during the period 2014-2017 [67]. Releasing $10,000$ Wolbachia-infected female and male mosquitoes (i.e., $W_{Rf} = W_{Rm} = 10,000$), for the 3-week release period for a one-year duration (Figure 5), shows that the implementation of *Wolbachia*-based mosquito control resulted in a significant decrease in the wild adult mosquito population (in comparison to the baseline worse-case scenario, Figure 4). In particular, Figure 5 shows that the populations of un-infected adult female (F_U) and adult male (M_U) mosquitoes decreased by 85% and 70%, respectively, in comparison to the worst-case scenario in Figure 4. It should be mentioned that, for the number of *Wolbachia*-infected mosquitoes released and frequency of release in this simulation (i.e., $W_{Rf} = W_{Rm} = 10,000$ and $\tau = 21$ days), the associated release effect statistic of the model is $R = 0.79$ (from which it follows that the release of *Wolbachia*-infected mosquitoes will lead to the effective control or elimination of the wild mosquitoes[81]).

When the number of *Wolbachia*-infected adult mosquitoes released is increased to $100,000$ (i.e., $W_{Rf} = W_{Rm} = 100,000$), for the same 3-week ($\tau = 21$ days) release period and the same one year duration, the results obtained (depicted in Figure 6) show a decrease of 93% (from the baseline worse-case scenario) for the un-infected adult female mosquitoes (F_U) and 73% for the un-infected adult male mosquitoes (M_U). The corresponding larger release effect statistic of the model is $R = 0.66 < 1$. Finally, when the number of *Wolbachia*-infected mosquitoes released is increased to $200,000$ (i.e., $W_{Rf} = W_{Rm} = 200,000$, with the same $\tau = 21$ days frequency of release and one year duration), our simulations show an increase in the reduction in the in the wild adult mosquito population (Figure 7). In particular, the populations of un-infected adult female and male mosquitoes decreased by 96% and 76%, respectively. For this case, the corresponding release effect statistic of the model is $R = 0.64 < 1$.

The model (2.5), with (3.10), is further simulated for the case where *Wolbachia*-infected mosquitoes of one gender are released. In particular, when $200,000$ *Wolbachia*-infected male mosquitoes are released (i.e., $W_{Rm} = 200,000$) and no Wolbachia-infected female mosquitoes are released (i.e., $W_{Rf} = 0$), our simulations (for the 3-week release period over a one-year duration) show a reduction (from their baseline values) of 95% and 75% in the population of adult wild mosquitoes, respectively (Figure 8). Similarly, when only $200,000$ adult female mosquitoes are released, and no adult male mosquitoes are released ($W_{Rf} = 200,000$ and $W_{Rm} = 0$), the simulation results obtained, depicted in Figure 9, show a reduction (from baseline) of 90% and 70% in the population of the wild adult mosquitoes. Thus, this study shows that releasing adult male *Wolbachia*-infected mosquitoes is more beneficial than releasing adult female Wolbachia-infected mosquitoes. For these simulations, the release effect statistic (R) is given by $R = 0.65$ if only adult male Wolbachia-infected mosquitoes are re-

leased, and 0.68 if only adult females are released. This result can be ecologically explained based on the fact that the *Wolbachia*-infected adult male mosquitoes significantly affect the cytoplasmic incompatibility aspect of *Wolbachia* implementation [79, 80] (thereby reducing the population abundance of the wild mosquitoes).

It is worth stating that if the release frequency is increased, for instance from the default release frequency of every three weeks to weekly (i.e., τ is decreased from $\tau = 21$ days to $\tau = 7$ days), the simulation results obtained for the case with $W_{Rf} = W_{Rm} = 100,000$ (depicted in Figure 10) show similar dynamics as those obtained in Figure 7. Thus, increasing the frequency of release from the default value of every three weeks to weekly does not significantly affect the effectiveness of the *Wolbachia*-based control program in curtailing the local abundance of the wild mosquitoes. This is contrary to other studies for biological control of mosquitoes, such as sterile insect technology, where the effectiveness of the intervention increase with more frequent releases [7, 14, 74].

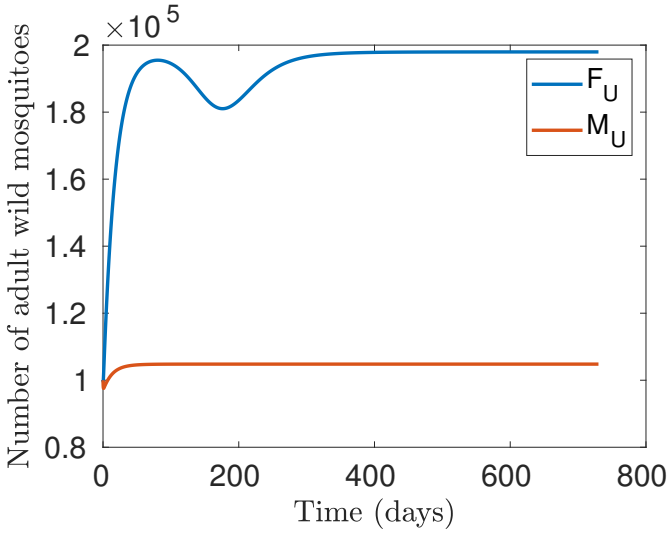
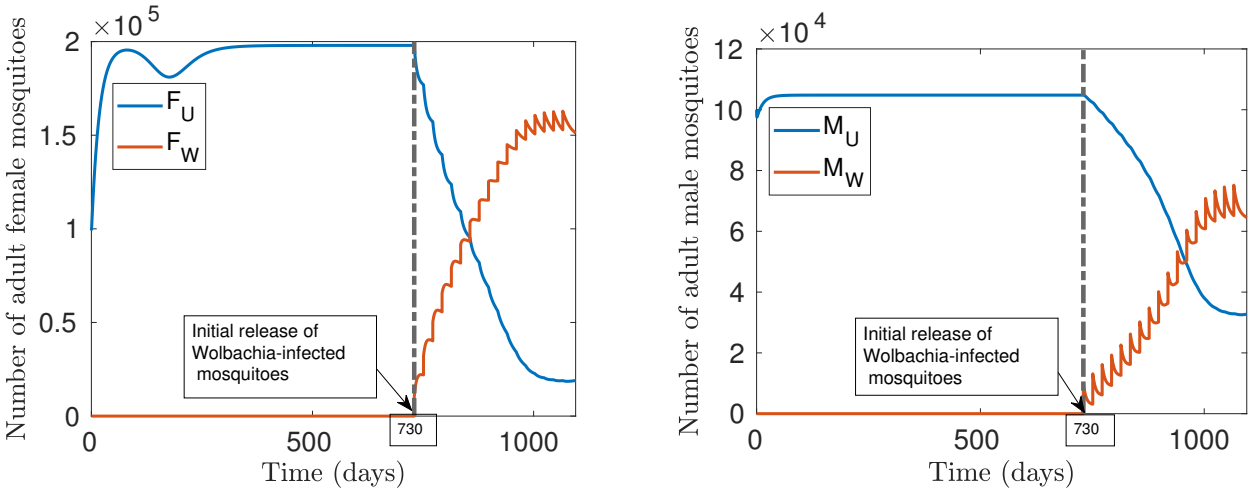
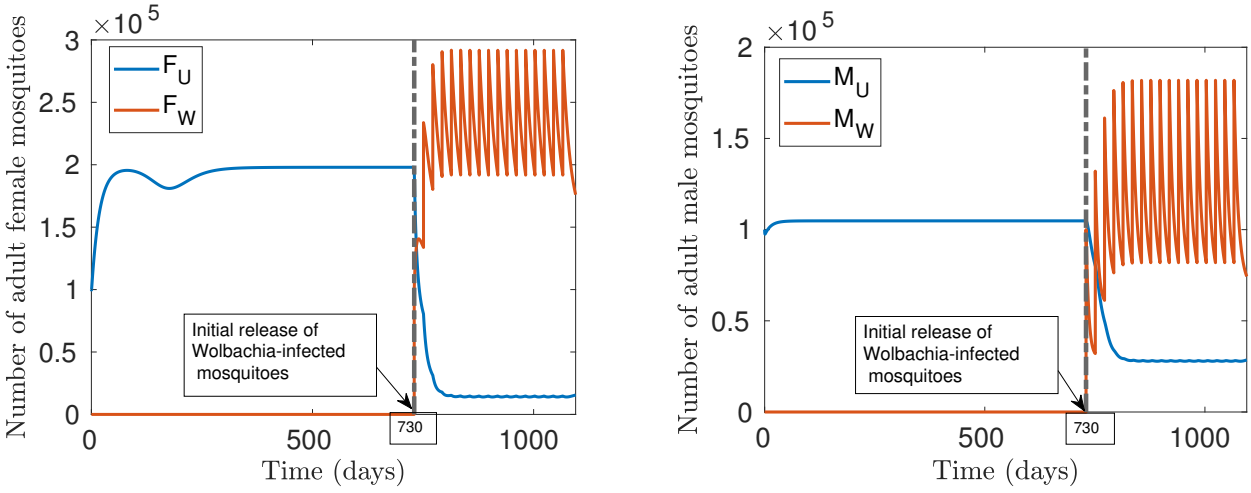


Figure 4: Simulations of the model (2.5), with (3.10), showing the dynamics of wild adult wild male and female mosquitoes, in the absence of the release of *Wolbachia*-infected mosquitoes, over a two-year period (this is needed to generate baseline values for the number of wild mosquitoes prior to the release of Wolbachia-infected mosquitoes). Parameter values used are as given in Table 3 (with this set of parameter values, the reproduction number ($\mathcal{R}_0$) takes the value $\mathcal{R}_0 = 1.24$).



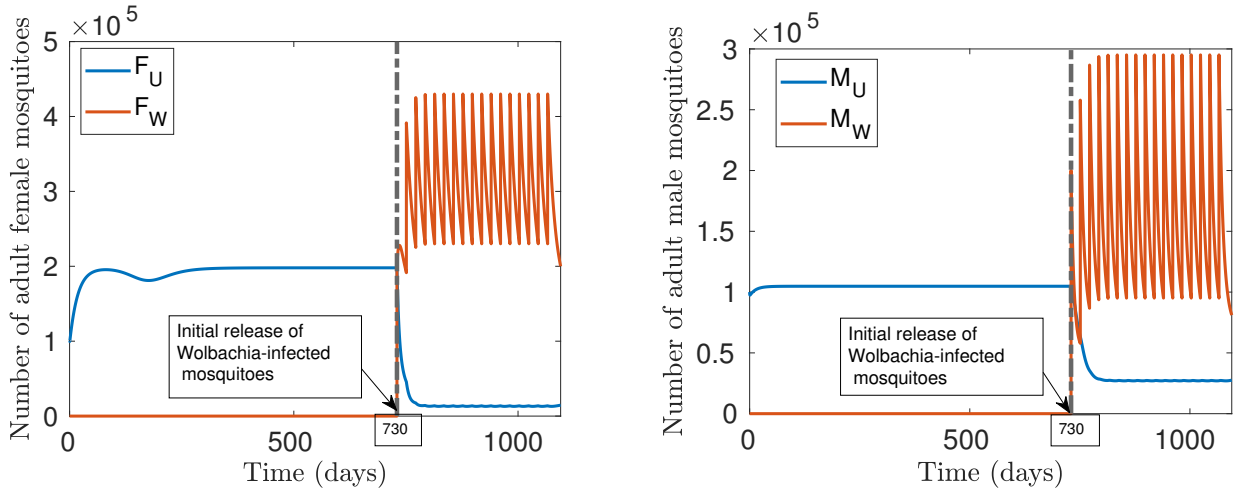
(a) (b)

Figure 5: Simulations of the model (2.5), with (3.10), showing the dynamics of *Wolbachia*-infected and *Wolbachia*-uninfected (wild) adult mosquitoes. The simulations were ran for two years without the release of the *Wolbachia*-infected mosquitoes, following which the *Wolbachia*-infected mosquitoes are released every three weeks (i.e., $\tau = 21$ days) for a period of one year. A total of 10,000 Wolbachia-infected female ($W_{Rf} = 10,000$) and male ($W_{Rm} = 10,000$) mosquitoes are released *per* release period. Parameter values used are as given in Table 3. Notation: the dashed vertical lines represent the time for the onset of the release of the *Wolbachia*-infected mosquitoes.



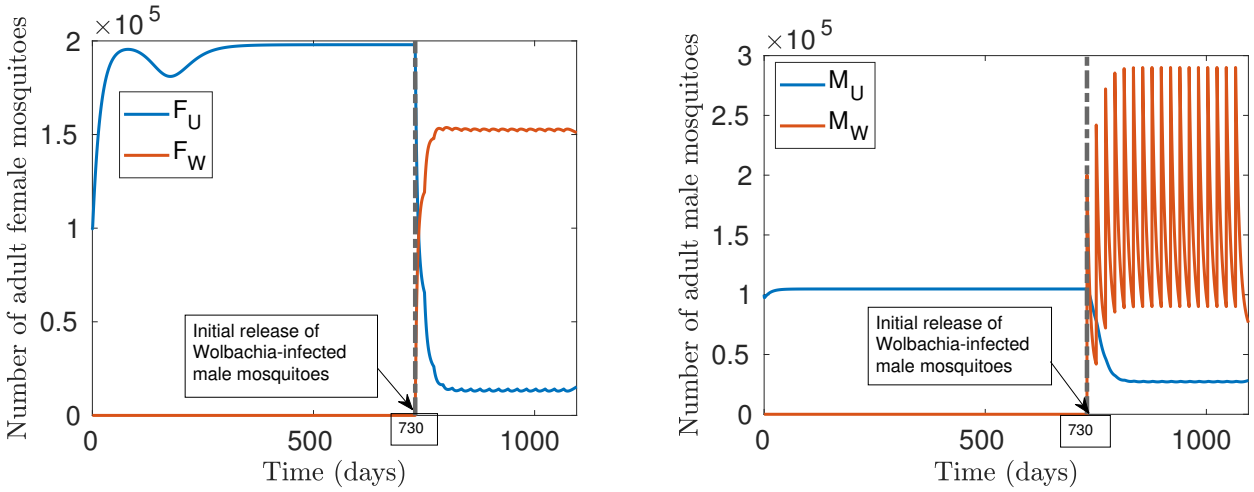
(a) (b)

Figure 6: Simulations of the model (2.5), with (3.10), showing the dynamics of *Wolbachia*-infected and *Wolbachia*-uninfected (wild) adult mosquitoes. The simulations were ran for two years without the release of the *Wolbachia*-infected mosquitoes, following which the *Wolbachia*-infected mosquitoes are released every three weeks (i.e., $\tau = 21$ days) for a period of one year. A total of 100,000 *Wolbachia*-infected female ($W_{Rf} = 100,000$) and male ($W_{Rm} = 100,000$) mosquitoes are released *per* release period. Parameter values used are as given in Table 3. Notation: the dashed vertical lines represent the time for the onset of the release of the *Wolbachia*-infected mosquitoes.



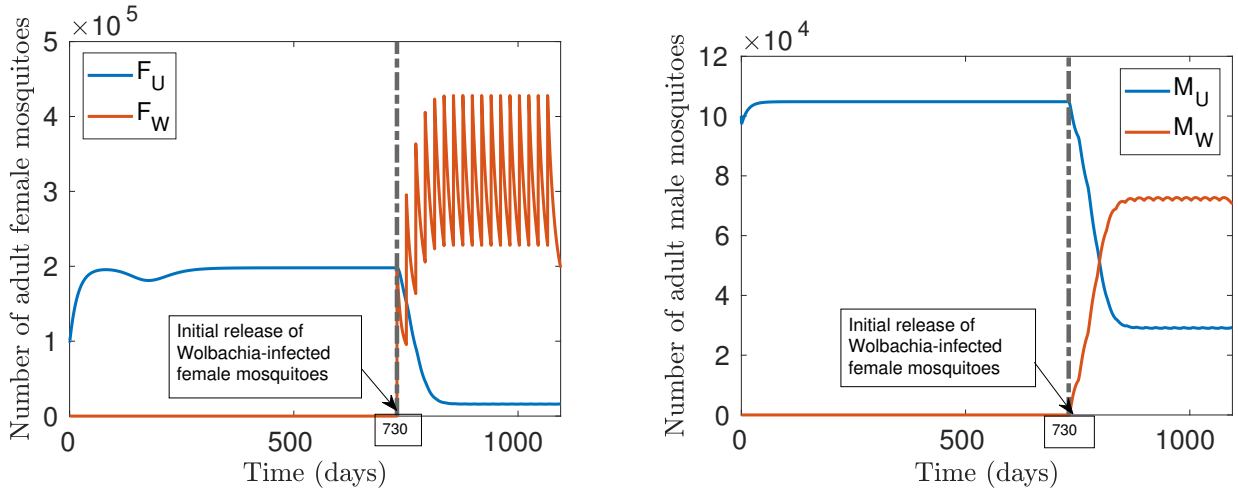
(a) (b)

Figure 7: Simulations of the model (2.5), with (3.10), showing the dynamics of *Wolbachia*-infected and *Wolbachia*-uninfected (wild) adult mosquitoes. The simulations were ran for two years without the release of the *Wolbachia*-infected mosquitoes, following which the *Wolbachia*-infected mosquitoes are released every three weeks (i.e., $\tau = 21$ days) for a period of one year. A total of 200,000 *Wolbachia*-infected female ($W_{Rf} = 200,000$) and male ($W_{Rm} = 200,000$) mosquitoes are released *per* release period. Parameter values used are as given in Table 3. Notation: the dashed vertical lines represent the time for the onset of the release of the *Wolbachia*-infected mosquitoes.



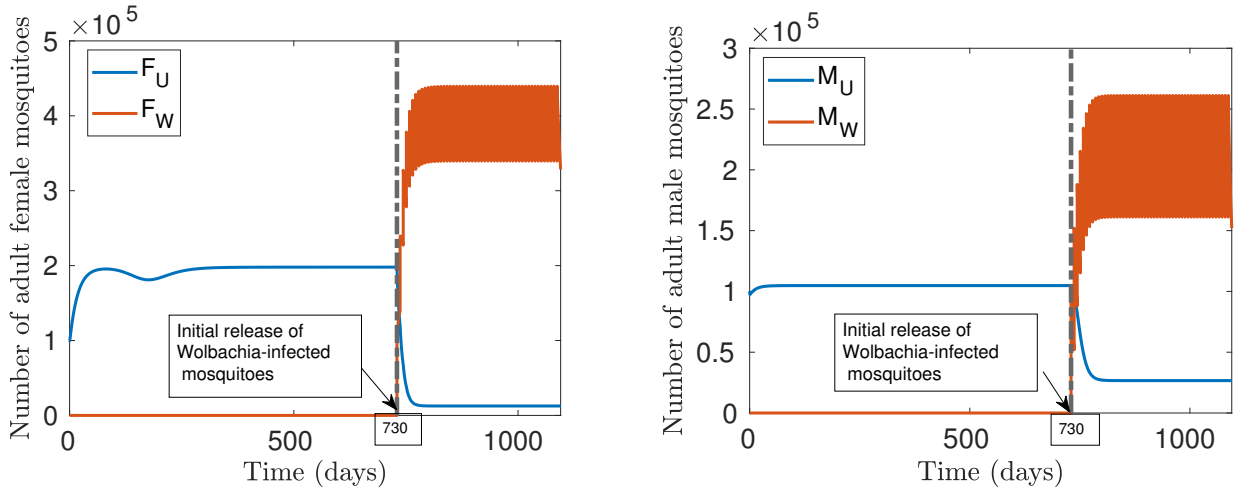
(a) (b)

Figure 8: Simulations of the model (2.5), with (3.10), showing the dynamics of *Wolbachia*-infected and *Wolbachia*-uninfected (wild) adult mosquitoes. The simulations were ran for two years without the release of the *Wolbachia*-infected mosquitoes, following which the *Wolbachia*-infected mosquitoes are released every three weeks (i.e., $\tau = 21$ days) for a period of one year. A total of 200,000 *Wolbachia*-infected male mosquitoes only (i.e., $W_{Rm} = 200,000$ and $W_{Rf} = 0$) are released *per* release period. Parameter values used are as given in Table 3. Notation: the dashed vertical lines represent the time for the onset of the release of the *Wolbachia*-infected mosquitoes.



(a) (b)

Figure 9: Simulations of the model (2.5), with (3.10), showing the dynamics of *Wolbachia*-infected and *Wolbachia*-uninfected (wild) adult mosquitoes. The simulations were ran for two years without the release of the *Wolbachia*-infected mosquitoes, following which the *Wolbachia*-infected mosquitoes are released every three weeks (i.e., $\tau = 21$ days) for a period of one year. A total of 200,000 *Wolbachia*-infected female mosquitoes only (i.e., $W_{Rf} = 200,000$ and $W_{Rm} = 0$) are released *per* release period. Parameter values used are as given in Table 3. Notation: the dashed vertical lines represent the time for the onset of the release of the *Wolbachia*-infected mosquitoes.



(a) (b)

Figure 10: Simulations of the model (2.5), with (3.10), showing the dynamics of *Wolbachia*-infected and *Wolbachia*-uninfected (wild) adult mosquitoes. The simulations were ran for two years without the release of the *Wolbachia*-infected mosquitoes, following which the *Wolbachia*-infected mosquitoes are released every one-week (i.e., $\tau = 7$ days) for a period of one year. A total of 100,000 *Wolbachia*-infected female ($W_{Rf} = 100,000$) and male ($W_{Rm} = 100,000$) mosquitoes are released *per* release period. Parameter values used are as given in Table 3. Notation: the dashed vertical lines represent the time for the onset of the release of the *Wolbachia*-infected mosquitoes

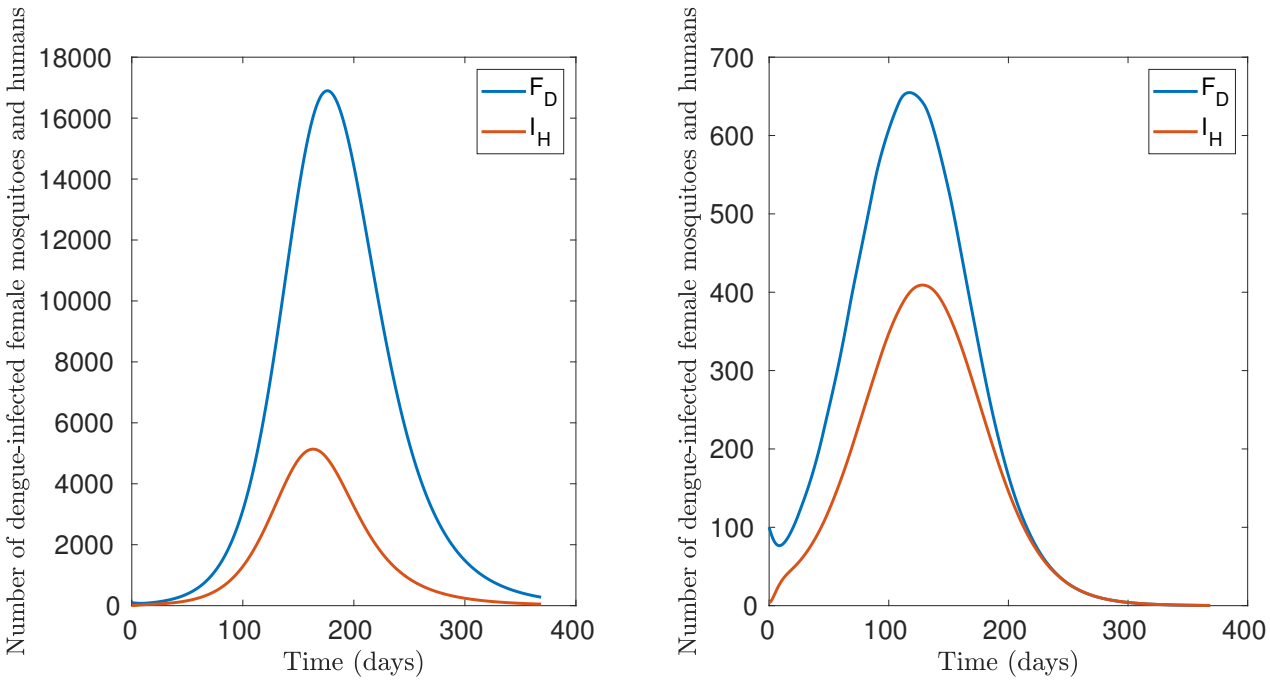


Figure 11: Simulations of the model (2.5), with (3.10), showing the temporal dynamics of dengue-infected adult female mosquitoes (F_D) and dengue-infected humans (I_H) in the absence and presence of *Wolbachia* release. (a) no release of *Wolbachia*-infected mosquitoes. (b) A total of 100,000 *Wolbachia*-infected adult male ($W_{Rm} = 100,000$) and 100,000 *Wolbachia*-infected adult female ($W_{Rf} = 100,000$) mosquitoes are released every three weeks (i.e., $\tau = 21$ days for one year). Parameter values used are as given in Table 3.

The effect of *Wolbachia*-based mosquito control strategy on dengue disease in the vector and humans is monitored by simulating the model (2.5), with (3.10), in the absence and presence of *Wolbachia* implementation. For these simulations, 100,000 *Wolbachia*-infected adult mosquitoes of both gender (i.e., $W_{Rf} = W_{Rm} = 100,000$) are released every three weeks (so that $\tau = 21$ days) for a one year period. The results obtained, depicted in Figure 11, show a marked decrease in the number of dengue-infected mosquitoes and infectious humans when the *Wolbachia*-based control strategy is implemented (Figure 11 (b)), in comparison to when the strategy is not implemented (Figure 11 (a)). In particular, Figure 11 (b) shows a 95% reduction in the population of dengue-infected adult female mosquitoes, in comparison to the case when *Wolbachia* control is not implemented. Similarly, a 90% reduction in population of dengue-infectious humans is also recorded. For these simulations, the R release effect statistic takes the value $R = 0.042 < 1$, indicating a very positive effect of the *Wolbachia*-based control strategy on reducing the population abundance of dengue-infected mosquitoes and infectious humans.

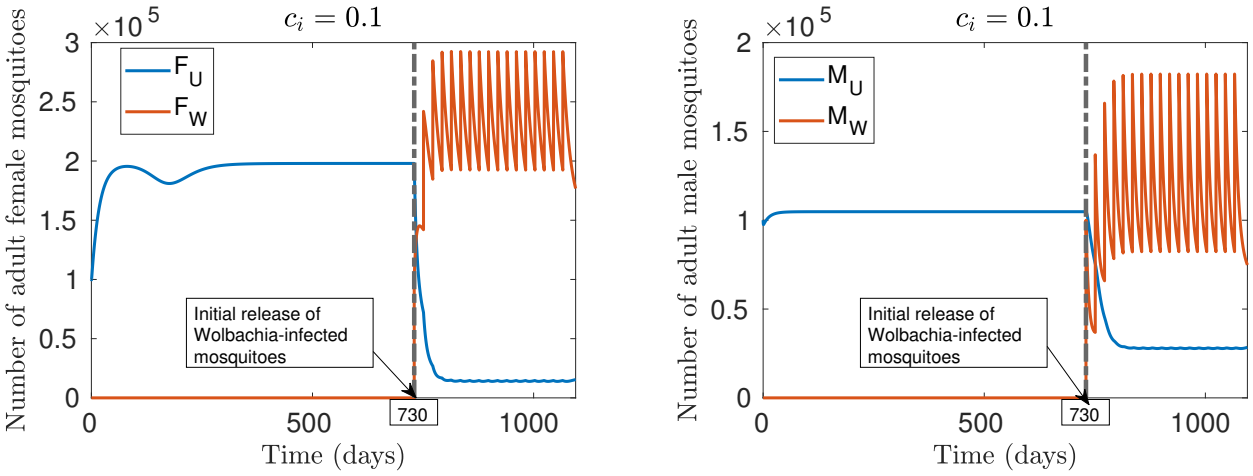
3.5 Simulations for Effect of Cytoplasmic Incompatibility (CI)

In this section, the model (2.5), together with with (3.10), will be simulated to numerically assess the impact of CI on the effectiveness of the *Wolbachia*-based mosquito control strategy.

The baseline parameter values tabulated in Table 3 are used in these simulations. The specific objective of these simulations is to assess the impact of CI on the population abundance of the local wild (i.e., *Wolbachia*-uninfected adult female and male) adult mosquitoes. We first considered the case where CI is at a low level. In particular, we first simulated the model (2.5), with (3.10), where CI is set at 10% (i.e., $c_i = 0.1$). This means 90% of the eggs laid by the *Wolbachia*-uninfected adult female mosquito that mated with a *Wolbachia*-infected adult male mosquito will hatch into larvae. For this simulation, $100,000$ *Wolbachia*-infected adult female and male mosquitoes are released for the 3-week release period (i.e., we set $W_{Rf} = W_{Rm} = 100,000$, $\tau = 21$) for a one-year duration.

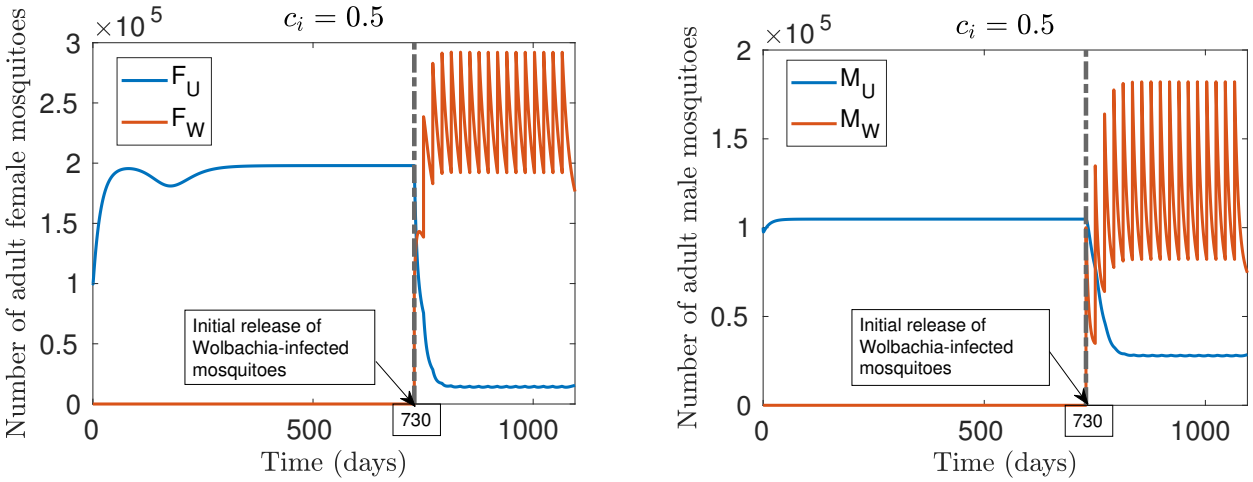
The simulation results obtained, depicted in Figure 12, show a dramatic decrease in the local abundance of the *Wolbachia*-uninfected adult mosquito population (by about 92% for the adult female and 72% for the adult male mosquitoes, from the baseline worse-case scenario shown in Figure 4, respectively). It should, however, be recalled that almost exactly the same dramatic reductions in the population abundance of the *Wolbachia*-uninfected adult mosquito population were achieved for the same scenario but with perfect CI (Figure 6). In other words, this simulation shows that CI (at the low level of $c_i = 0.1$) has no significant effect on the effectiveness of *Wolbachia*-based mosquito control strategy.

Additional simulation was carried out, for the same setting (i.e., the model (2.5) with $W_{Rf} = W_{Rm} = 100,000$, $\tau = 21$) but with CI increased to 50% (i.e., $c_i = 0.5$). The simulation results obtained show a 93% and 73% reduction in the population abundance of the *Wolbachia*-uninfected adult female and male mosquitoes, respectively. Again, these numbers are similar to those recorded in Figure 6 with perfect CI. In summary, our simulations clearly show (by comparing Figures 12 and 13, where CI is set at 10% and 50%, respectively, with Figure 6, where CI is set at 100%) that CI has no significant effect on the effectiveness of *Wolbachia* introduction to curtail the local abundance of the wild adult mosquito population in the community.



(a) (b)

Figure 12: Simulations of the model (2.5), with (3.10), showing the dynamics of *Wolbachia*-infected and *Wolbachia*-uninfected (wild) adult mosquitoes. The simulations were ran for two years without the release of the *Wolbachia*-infected mosquitoes, following which the *Wolbachia*-infected mosquitoes are released every three weeks (i.e., $\tau = 21$ days) for a period of one year. A total of 100,000 *Wolbachia*-infected female ($W_{Rf} = 100,000$) and male ($W_{Rm} = 100,000$) mosquitoes are released *per* release period with $c_i = 0.1$. Parameter values used are as given in Table 3. Notation: the dashed vertical lines represent the time for the onset of the release of the *Wolbachia*-infected mosquitoes.



(a) (b)

Figure 13: Simulations of the model (2.5), with (3.10), showing the dynamics of *Wolbachia*-infected and *Wolbachia*-uninfected (wild) adult mosquitoes. The simulations were ran for two years without the release of the *Wolbachia*-infected mosquitoes, following which the *Wolbachia*-infected mosquitoes are released every three weeks (i.e., $\tau = 21$ days) for a period of one year. A total of 100,000 *Wolbachia*-infected female ($W_{Rf} = 100,000$) and male ($W_{Rm} = 100,000$) mosquitoes are released *per* release period with $c_i = 0.5$. Parameter values used are as given in Table 3. Notation: the dashed vertical lines represent the time for the onset of the release of the *Wolbachia*-infected mosquitoes.

Discussion and Conclusions

Dengue fever is one of the most important vector-borne diseases affecting mankind. The disease, which is spread between humans *via* the bite of adult female *Aedes* mosquitoes (its main vector), affects over one-third of the world's population (particularly those residing in the tropical and sub-tropical regions) [46, 82]. In general, there are no safe and effective vaccine or drug therapy for use against diseases caused by mosquitoes, such as dengue. Consequently, control measures against mosquito-borne diseases are mostly limited to implementing strategies that target the mosquito population. The traditional methods for controlling mosquito population abundance, such as the use of chemical insecticides to kill immature and adult mosquitoes, the use of long-lasting insecticidal nets (LLINs), insect repellents etc. Unfortunately, the widespread use of these insecticides in endemic areas has resulted in the emergence of insecticide resistance in the adult mosquito population [6, 54]. Consequently, other alternative methods for mosquito control are needed. One of such methods is the implementation of biological measures, such as the release of *Wolbachia*-infected mosquitoes in the endemic areas [7, 14, 74]).

This study presents a new sex-structured mathematical model for assessing the community-wide impact of the release of *Wolbachia*-infected mosquitoes on the population abundance of the local wild (i.e., *Wolbachia*-uninfected) *Aedes* mosquitoes, as well as on the transmission dynamics of dengue disease. The model incorporates many of the many pertinent aspects of *Wolbachia* transmission in mosquito populations. Rigorous analysis of the special case of the model showed that the *Wolbachia*-free and dengue-free equilibrium of the model is locally-asymptotically stable whenever a certain epidemiological threshold, known as the *reproduction number* of the model, is less than unity. Furthermore, using Center Manifold theory, it was shown that the model undergoes the dynamic phenomenon of backward bifurcation (when this threshold is less than unity). This bifurcation is characterized by the co-existence of the locally-asymptotically stable *Wolbachia*-free and dengue-free equilibrium with a locally-asymptotically stable endemic equilibrium. The epidemiological implication of this phenomenon is that the effective control of the wild mosquito population (using the *Wolbachia*-based control intervention) will depend on the initial size of the sub-populations of the model. In other words, the presence of the phenomenon of backward bifurcation makes the prospects for the effective control of the wild mosquito population, using *Wolbachia*-based control, more difficult. This, to the authors', knowledge is the first time this phenomenon is rigorous established for a model for the transmission dynamics of a mosquito-borne disease that employs a *Wolbachia*-based anti-mosquito intervention. Further, two sufficient conditions for the removal of such bifurcation have been identified (in other words, we have identified two possible mechanisms that cause backward bifurcation in a dynamic model for dengue mosquitoes and disease that incorporate *Wolbachia*-based mosquito control). We showed that, in the absence of the backward bifurcation phenomenon of the model, the associated non-trivial disease-free equilibrium of the model is globally-asymptotically stable whenever a certain epidemiological quantity (denoted by $\mathcal{R}_{0W}$) is less than unity. The implication of this result is that both the population abundance of the dengue mosquito and disease can be effectively controlled in (or eliminated from) the community when the threshold quantity is less than unity. In other words, such effective control or elimination can be achieved if the *Wolbachia*-based intervention can bring (and maintain) $\mathcal{R}_{0W}$) to a value less

than unity.

Numerous numerical simulations were carried out to assess the impact of the number of *Wolbachia*-infected mosquitoes released into the wild, as well as the frequency of such releases. Based on the reasonable set of parameter values used in the numerical simulations, our study shows, for instance, that releasing 10,000 each of *Wolbachia*-infected adult male and adult female mosquitoes every three weeks for a one year duration can lead to a dramatic reduction of up to 85% and 70% of the local wild adult female and male mosquito populations, respectively. These reductions increase to 93% for adult female and 73%, respectively, for adult male mosquitoes if the number of *Wolbachia*-infected mosquitoes is increased to 100,000 each for adult female and adult male mosquitoes. Further reductions (by 96% for adult female and 76% for adult male) are achieved if the number of *Wolbachia*-infected mosquitoes released is increased to 200,000 for each gender. We observed (generally) qualitatively similar results when the release frequency is decreased from every three weeks to every two weeks or even weekly. Thus, these simulations show that the *Wolbachia*-based intervention can significantly reduce the local population abundance of the wild adult *Aedes* mosquitoes if the number of *Wolbachia*-infected mosquitoes periodically released into the wild is high enough. In particular, our study shows that up to 90%-95% of the local wild adult female *Aedes* mosquito population can be eliminated using the aforementioned *Wolbachia*-based intervention. Reducing such a huge number of the local wild adult female *Aedes* mosquitoes certainly imply a great reduction in the burden of dengue disease in the community.

This study further showed that if only *Wolbachia*-infected mosquitoes of one gender (e.g., only males or only females) can be released, it is more beneficial if *Wolbachia*-infected male mosquitoes, rather than *Wolbachia*-infected female mosquitoes, are released into the wild. This is intuitive ecologically, since the *Wolbachia*-infected adult male mosquitoes significantly affect the cytoplasmic incompatibility property of the *Wolbachia* implementation (thereby reducing the population abundance of the wild mosquitoes in the community). Our study further shows that cytoplasmic incompatability (CI) does not significantly affect the effectiveness of the *Wolbachia*-based strategy to reduce the local population abundance of the wild mosquito population.

In summary, this study aimed to provide insight into the effectiveness of the *Wolbachia*-based biological control strategy in combating the population abundance of the targeted mosquito population (i.e., wild adult *Aedes* mosquitoes) in the community. This was achieved *via* the development, analysis and simulations of a novel, two-sex, mathematical model for the population dynamics of the *Aedes* mosquito (both immature and adult) in a community. In addition to incorporating many relevant features of the mosquito population dynamics (such as vertical and horizontal transmission in *Wolbachia*-infected mosquito population), the model developed in this study also incorporated the effect of cytoplasmic incompatibility (CI) in the mosquito dynamics (to account for the fact CI significantly affects the population abundance of the local wild mosquito population [65, 75]). Our study showed the prospects for the effective control (or elimination) of dengue disease in a community using *Wolbachia*-based mosquito control are promising provided a relatively large number of the *Wolbachia*-infected mosquitoes (both males and females) are released into the wild at reasonable frequency (e.g., every three weeks or biweekly, or even weekly). We showed that if resources are limited, and only *Wolbachia*-infected mosquitoes of one gender (e.g., only males or only females) can be released, then male *Wolbachia*-infected mosquitoes must be

chosen.

Acknowledgments

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Appendix A Proof of Theorem 3.4

Proof. Consider the model (3.9) with $\mathcal{R}_U < 1$ and $\mathcal{R}_W < 1$. The Jacobian of the model (3.9) at the trivial equilibrium $\mathcal{T}_{0\diamond}$ is given by

$$\mathcal{J}(\mathcal{T}_{0\diamond}) = \begin{bmatrix} -\sigma_m - \mu_a & 0 & \phi_u\psi_u & (1-v_w)\,\phi_w\psi_w & 0 & 0 \\ 0 & -\sigma_m - \mu_a & 0 & v_w\phi_w\psi_w & 0 & 0 \\ b_f\sigma_m & 0 & -\mu_{uf} & 0 & 0 & 0 \\ 0 & b_f\sigma_m & 0 & -\theta_w\mu_{uf} & 0 & 0 \\ (1-b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} & 0 \\ 0 & (1-b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} \end{bmatrix}.$$

The associated eigenvalues of the matrix $\mathcal{J}(\mathcal{T}_{0\diamond})$ are

$$\begin{aligned} \lambda_1 &= -\frac{1}{2}\left[\theta_w\mu_{uf} + \sigma_m + \mu_a + \sqrt{(\sigma_m + \mu_a - \theta_w\mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_w\psi_w v_w}\right], \\ \lambda_2 &= -\frac{1}{2}\left[\theta_w\mu_{uf} + \sigma_m + \mu_a - \sqrt{(\sigma_m + \mu_a - \theta_w\mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_w\psi_w v_w}\right], \\ \lambda_3 &= -\frac{1}{2}\left[\mu_{uf} + \sigma_m + \mu_a + \sqrt{(\sigma_m + \mu_a - \mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_u\psi_u}\right], \\ \lambda_4 &= -\frac{1}{2}\left[\mu_{uf} + \sigma_m + \mu_a - \sqrt{(\sigma_m + \mu_a - \mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_u\psi_u}\right], \\ \lambda_5 &= \lambda_6 = -\mu_{uf}. \end{aligned} \tag{A.1}$$

It is clear from (A.1) that eigenvalues λ_1, λ_3, λ_5 and λ_6 are automatically negative. Furthermore, it can be shown easily, using similar argument as in the proof of Theorem 3.2, that the eigenvalue $\lambda_2 < 0$ whenever $\mathcal{R}_W < 1$ and the eigenvalue $\lambda_4 < 0$ whenever $\mathcal{R}_U < 1$. □

Appendix B Proof of Theorem 3.5

Proof. Consider the model (3.9) with $\mathcal{R}_U > 1$. It is convenient to define the following change of variables for the model (3.9), $A_U = x_1$, $A_W = x_2$, $F_U = x_3$, $F_W = x_4$, $M_U = x_5$ and $M_W = x_6$. Furthermore, by using the vector notation $\mathbf{x} = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, the model (3.9) can be written in form $\frac{d\mathbf{x}}{dt} = \mathbf{f} = (f_1, f_2, f_3, f_4, f_5, f_6)^T$, as follows,

$$\begin{aligned}
\frac{dx_1}{dt} =& \left(1 - \frac{x_1 + x_2}{K_A}\right)\left[\phi_u\psi_u\left(\frac{1 + x_5}{1 + x_5 + x_6}\right)x_3 + \phi_w\psi_w(1 - v_w)\left\{x_4 + \right.\right. \\
& \left.\left.(1 - c_i)\left(\frac{1 + x_5}{1 + x_5 + x_6}\right)x_3\right\}\right] - (\sigma_m + \mu_a)x_1, \\
\frac{dx_2}{dt} =& v_w\phi_w\psi_w\left(1 - \frac{x_1 + x_2}{K_A}\right)\left[x_4 + (1 - c_i)\left(\frac{1 + x_5}{1 + x_5 + x_6}\right)x_3\right] - (\sigma_m + \mu_a)x_2, \\
\frac{dx_3}{dt} =& b_f\sigma_m x_1 - q\left(\frac{x_6}{1 + x_5 + x_6}\right)x_3 - \mu_{uf}x_3, \\
\frac{dx_4}{dt} =& b_f\sigma_m x_2 + q\left(\frac{x_6}{1 + x_5 + x_6}\right)x_3 - \theta_w\mu_{uf}x_4, \\
\frac{dx_5}{dt} =& (1 - b_f)\sigma_m x_1 - \mu_{um}x_5, \\
\frac{dx_6}{dt} =& (1 - b_f)x_2 - \mu_{um}x_6.
\end{aligned} \tag{B.1}$$

The proof is based on using Center Manifold theory [13, 15]. In particular, the following Theorem from [13] will be used.

Theorem B.1 ([13]). *Consider a system of ordinary differential equations*

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n \tag{B.2}$$

with a parameter ϕ, assumed such that:

1. *0 is an equilibrium of the system, $f(0, \phi) = 0$ for all $\phi \in \mathbb{R}$;*
2. *0 is a simple eigenvalue of $\mathcal{J} = D_x f(0, 0) = [\frac{\partial f_i}{\partial x_i}(0, 0)]$ and all other eigenvalues of $\mathcal{J}$ have negative real parts.*

Let $W = [w_1, w_2, \ldots, w_n]^T$ and $V = [v_1, v_2, \ldots, v_n]$ be a right and a left eigenvector matrix $\mathcal{J}$, respectively, associated to eigenvalues 0 and $f_k(x, \phi)$ be the kth component of $f(x, \phi)$. Then the local dynamics of system around the equilibrium point 0 is totally determined by the signs of a and b below:

$$a = \sum_{k=1}^{n}\sum_{j=1}^{n}\sum_{k=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0, 0),$$

$$b = \sum_{k=1}^{n}\sum_{i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial\phi\partial x_i}(0,0),$$

Then local dynamics of (B.2) *around* 0 *are totally determined by* a *and* b.

(i). $a > 0$, $b > 0$. *When* $\phi < 0$ *with* $|\phi| < 1$, *0 is locally asymptotically stable, and there exists a positive unstable equilibrium; when* $0 < \phi < 1$, *0 is unstable and there exists a negative and locally asymptotically stable equilibrium;*

(ii). $a < 0$, $b < 0$. *When* $\phi < 0$ *with* $|\phi| < 1$, *0 is unstable; when* $0 < \phi < 1$, *0 is locally asymptotically stable, and there exists a positive unstable equilibrium;*

(iii). $a > 0$, $b < 0$. *When* $\phi < 0$ *with* $|\phi| < 1$, *0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi < 1$, *0 is stable, and a positive unstable equilibrium appears;*

(iv). $a < 0$, $b > 0$. *When* ϕ *changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally-asymptotically stable.*

If $a > 0$ *and* $b > 0$, *then a backward bifurcation occurs at* $\phi = 0$ *for the system* (B.2).

It can be seen that the Jacobian of the model (B.1) at $\mathcal{T}_1$ is given by:

$$\mathcal{J}(\mathcal{T}_1) = \begin{bmatrix} j_{11} & -\frac{\phi_u\psi_u F_U^*}{K_A} & j_{13} & j_{14} & 0 & j_{16} \\ 0 & -\sigma_m - \mu_a & 0 & j_{24} & 0 & j_{26} \\ b_f\sigma_m & 0 & -\mu_{uf} & 0 & 0 & -\frac{qF_U^*}{\left(M_U^*+1\right)} \\ 0 & b_f\sigma_m & 0 & -\theta_w\mu_{uf} & 0 & \frac{qF_U^*}{\left(M_U^*+1\right)} \\ (1-b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} & 0 \\ 0 & (1-b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} \end{bmatrix},$$

where, $j_{11} = -\frac{\phi_u\psi_u F_U^*}{K_A} - \sigma_m - \mu_a$, $j_{13} = \phi_u\psi_u\left(1 - \frac{A_U^*}{K_A}\right)$, $j_{14} = (1-v_w)\,\phi_w\psi_w\left(1 - \frac{A_U^*}{K_A}\right)$, $j_{16} = -\frac{\phi_u\psi_u F_U^*}{\left(M_U^*+1\right)}\left(1 - \frac{A_U^*}{K_A}\right) + (1-v_w)(1-c_i)\phi_w\psi_w\frac{F_U^*}{1+M_U^*}\left(1 - \frac{A_U^*}{K_A}\right)$, $j_{24} = v_w\phi_w\psi_w\left(1 - \frac{A_U^*}{K_A}\right)$, $j_{26} = v_w(1-c_i)\phi_w\psi_w\frac{F_U^*}{1+M_U^*}\left(1 - \frac{A_U^*}{K_A}\right)$. Consider the case where $\mathcal{R}_{0W} = 1$. Suppose, further, that ϕ_w be chosen as a bifurcation parameter. Solving for ϕ_w from $\mathcal{R}_{0W} = 1$ gives

$$\phi_w^* = \left\{\frac{\sigma_m}{\sigma_m + \mu_a}\frac{(k_1k_3 + \theta_w\mu_{uf}k_2)(1-b_f) + k_1b_f\mu_{um}}{\theta_w\mu_{uf}\mu_{um}}\right\}^{-1}.$$

Let $\mathbf{w} = [w_1, \ldots, w_6]^T$ and $\mathbf{v} = [v_1, \ldots, v_6]$ be the right and left eigenvectors of $\mathcal{J}(\mathcal{T}_1)$, respectively, given by:

$$w_1 = \frac{\mu_{uf}}{\mu_{uf}j_{11} + j_{13}b_f\sigma_m}\left(\frac{\phi_u\psi_u F_U^* w_2}{K_A} + \frac{j_{13}qF_U^*}{1+M_U^*}\frac{\sigma_m(1-b_f)w_2}{\mu_{uf}\mu_{um}} - j_{14}w_4 - j_{16}w_6\right), \quad w_2 > 0,$$

$$
\begin{aligned}
&w_3 = \frac{b_f\sigma_m w_1}{\mu_{uf}} - \frac{qF_U^*}{1+M_U^*}\frac{\sigma_m(1-b_f)w_2}{\mu_{uf}\mu_{um}}, \quad w_4 = \frac{b_f\sigma_m w_2}{\theta_w\mu_{uf}} + \frac{qF_U^*}{1+M_U^*}\frac{\sigma_m(1-b_f)w_2}{\theta_w\mu_{uf}\mu_{um}},\\
&w_5 = \frac{\sigma_m(1-b_f)w_1}{\mu_{um}}, \quad w_6 = \frac{\sigma_m(1-b_f)w_2}{\mu_{um}},\\
&v_1 = 0, \quad v_2 > 0, \quad v_3 = 0, \quad v_4 = \frac{\psi_w\phi_w^* v_w v_2}{\theta_w\mu_{uf}\mathcal{R}_U},\\
&v_5 = 0, \quad v_6 = \frac{\psi_w\phi_w^* v_w v_2 F_U^*[q+\theta_w\mu_{uf}(1-c_i)]}{\theta_w\mu_{um}\mu_{uf}M_U^*\mathcal{R}_U}.
\end{aligned} \tag{B.3}
$$

Applying Theorem B.1, it can be shown, by computing the non-zero partial derivatives of $\mathbf{f}$, that the associated backward bifurcation coefficients, a and b, are given, respectively, by

$$
a = \sum_{k=1}^{6}\sum_{j=1}^{6}\sum_{k=1}^{6} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\mathcal{T}_1), \text{ and } b = \sum_{k=1}^{6}\sum_{i=1}^{6} v_k w_i \frac{\partial^2 f_k}{\partial \phi_w \partial x_i}(\mathcal{T}_1), \tag{B.4}
$$

where, (with the eigenvectors w_i and v_i, $i = 1, 2, \ldots, 6$, are as given in (B.3))

$$
\begin{aligned}
a(\phi_w^*) = &-2qw_6\frac{[F_U^*(w_5+w_6) - w_3(1+M_U^*)]}{(1+M_U^*)^2}\\
&- 2v_m\phi_w^*\psi_w\frac{(w_1+w_2)[F_U^* w_6(1-c_i) + w_4(1+M_U^*)]}{(1+M_U^*)K_A}\\
&- 2v_m\phi_w^*\psi_w w_3\frac{w_6(1-c_i)(A_U^*-K_A)}{(1+M_U^*)K_A}\\
&+ 2v_m\phi_w^*\psi_w\frac{F_U^* w_6(w_5+w_6)(1-c_i)(A_U^*-K_A)}{(1+M_U^*)^2K_A}
\end{aligned} \tag{B.5}
$$

and

$$
b(\phi_w^*) = \frac{v_2\phi_w^*\psi_w[F_U^* w_6(1-c_i) + w_4(1+M_U^*)](A_U^*-K_A)}{(1+M_U^*)K_A} > 0, \tag{B.6}
$$

Hence, it follows from Theorem B.1 that, the model (3.9) undergoes a backward bifurcation whenever $a(\phi_w^*)$, given in (B.5), is positive. □

Appendix C Proof of Theorem 3.6

Proof. Consider the model (3.9) with $m_w = \bar{m}_w = 0$, $m_u = \bar{m}_u = 1$, $q = 0$, $\mathcal{R}_W < 1$ and $\mathcal{R}_U < 1$. The Jacobian of the model (B.1) at the trivial equilibrium $\mathcal{T}_{0\diamond}$ is given by

$$\mathcal{J}(\mathcal{T}_{0\diamond}) = \begin{bmatrix} -\sigma_m - \mu_a & 0 & \phi_u\psi_u & (1-v_w)\,\phi_w\psi_w & 0 & 0 \\ 0 & -\sigma_m - \mu_a & 0 & v_w\phi_w\psi_w & 0 & 0 \\ b_f\sigma_m & 0 & -\mu_{uf} & 0 & 0 & 0 \\ 0 & b_f\sigma_m & 0 & -\theta_w\mu_{uf} & 0 & 0 \\ (1-b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} & 0 \\ 0 & (1-b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} \end{bmatrix}.$$

The associated eigenvalues of the matrix $\mathcal{J}(\mathcal{T}_{0\diamond})$ are

$$\begin{aligned} \lambda_1 &= -\frac{1}{2}\left[\theta_w\mu_{uf} + \sigma_m + \mu_a + \sqrt{(\sigma_m + \mu_a - \theta_w\mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_w\psi_w v_w}\right], \\ \lambda_2 &= -\frac{1}{2}\left[\theta_w\mu_{uf} + \sigma_m + \mu_a - \sqrt{(\sigma_m + \mu_a - \theta_w\mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_w\psi_w v_w}\right], \\ \lambda_3 &= -\frac{1}{2}\left[\mu_{uf} + \sigma_m + \mu_a + \sqrt{(\sigma_m + \mu_a - \mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_u\psi_u}\right], \\ \lambda_4 &= -\frac{1}{2}\left[\mu_{uf} + \sigma_m + \mu_a - \sqrt{(\sigma_m + \mu_a - \mu_{uf})^2 + 4\,b_f\sigma_m\,\phi_u\psi_u}\right], \\ \lambda_5 &= \lambda_6 = -\mu_{um}. \end{aligned} \tag{C.1}$$

It is clear from (C.1) that eigenvalues λ_1, λ_3, λ_5 and λ_6 are automatically negative. Furthermore, it can be shown that the eigenvalue $\lambda_2 < 0$ whenever $\mathcal{R}_W < 1$ and the eigenvalue $\lambda_4 < 0$ whenever $\mathcal{R}_U < 1$. □

Appendix D Proof of Theorem 3.7

Proof. (a) Consider the model (3.9) with $m_w = \bar{m}_w = 0,\ m_u = \bar{m}_u = 1$, $q = 0$ and $\mathcal{R}_U > 1$. Further, let

$$m_w = \frac{M_W}{1 + M_U + M_W} = \bar{m}_w = 0, \text{ and } m_u = 1 - m_w = \frac{1 + M_U}{1 + M_U + M_W} = 1.$$

In this case, the *Wolbachia*-free and dengue-free equilibrium ($\mathcal{T}_{1c}$) is given by

$$\mathcal{T}_{1c} = (A_U^*, A_W^*, F_U^*, F_W^*, M_U^*, M_W^*) = (A_U^*, 0, \frac{b_f \sigma_m A_U^*}{\mu_{uf}}, 0, \frac{(1-b_f)\sigma_m A_U^*}{\mu_{um}}, 0),$$

with $A_U^* = K_A(1 - \frac{1}{\mathcal{R}_U})$. This equilibrium exists if and only if $\mathcal{R}_U > 1$. Let

$$\bar{\mathcal{R}}_{0W} = \frac{\mathcal{R}_W}{\mathcal{R}_U}, \tag{D.1}$$

be the associated reproduction number of the model (3.9), with $m_w = \bar{m}_w = 0,\ m_u = \bar{m}_u = 1$ and $q = 0$. Solving $\bar{\mathcal{R}}_{0W} = 1$ for ϕ_w (chosen as the bifurcation parameter) gives

$$\phi_w^* = \frac{\theta_w \mu_{uf}(\sigma_m + \mu_a)\mathcal{R}_U}{v_w \sigma_m b_f \psi_w}.$$

The Jacobian of the model (3.9), with $m_w = \bar{m}_w,\ m_u = \bar{m}_u$ and $q = 0$, at $\mathcal{T}_{1c}$, is given by

$$\mathcal{G}(\mathcal{T}_{1c}) = \begin{bmatrix} j_{11} & -\frac{\phi_u \psi_u F_U^*}{K_A} & j_{13} & j_{14} & 0 & 0 \\ 0 & -\sigma_m - \mu_a & 0 & j_{24} & 0 & 0 \\ b_f \sigma_m & 0 & -\mu_{uf} & 0 & 0 & 0 \\ 0 & b_f \sigma_m & 0 & -\theta_w \mu_{uf} & 0 & 0 \\ (1-b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} & 0 \\ 0 & (1-b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} \end{bmatrix},$$

The right and left eigenvectors of the matrix $\mathcal{G}$ are given, respectively, by

$$w_1 = \frac{(B_1 + B_2)\,w_2}{\theta_w\left(K_A \mu_{uf}\,(\sigma_a + \mu_a)\,(1 - \mathcal{R}_U)\right)}, \quad w_2 > 0, \quad w_3 = \frac{\sigma_m w_1}{\mu_{uf}}, \ w_4 = \frac{\sigma_a b_f w_2}{\theta_w \mu_{uf}}, \ w_5 = 0$$
$$w_6 = \frac{\lambda\,(1-b_f)\,w_2}{\mu_{um}}, \ v_1 = 0, \ v_2 > 0, \ v_3 = 0, \ v_4 = \frac{v_w \phi_w \psi_w v_2}{\theta_w \mu_{uf} \mathcal{R}_U} \ v_5 = 0, \ v_6 = 0, \tag{D.2}$$

where,

$$B_1 = \frac{K_A b_f \sigma_a \psi_w \phi_w\,(1 - v_w)}{R_U}, \text{ and } B_2 = K_A b_f \phi_u \psi_u \theta_w \mu_{uf} \sigma_a \left(1 - \frac{1}{\mathcal{R}_U}\right).$$

The associated backward bifurcation coefficients, a and b, are given, respectively, by (where the eigenvectors w_i and v_i, $i = 1, 2, \ldots, 6$, are given in (D.5))

$$a(\phi_w^*) = \frac{2v_2{w_2}^2\sigma_m\, b_f v_w \phi_w \psi_w \mathcal{R}_W\,(1 - v_w)}{\theta_w \mu_{uf} K_A \mathcal{R}_U\,(1 - \mathcal{R}_U)}, \tag{D.3}$$

and,

$$b = \frac{v_2 w_2 b_f v_w \psi_w \sigma_m}{\theta_w \mu_{uf} \mathcal{R}_U} > 0.$$

It follows from Equation (D.6) that, $a(\phi^*) < 0$, (since $\mathcal{R}_U > 1$ and $0 < v_w < 1$). Thus, it follows from item (iv) of Theorem B.1 [13] that the model (3.9) does not undergo a backward bifurcation at $\bar{\mathcal{R}}_{0W} = 1$ whenever $\mathcal{R}_U > 1$.

(b) Consider the model (3.9) with $c_i = 1$, $m_w = \bar{m}_w \in [0, 1)$, $m_u = \bar{m}_u \in (0, 1]$, $q = 0$ and $\mathcal{R}_U > 1$. In this case, the *Wolbachia*-free and dengue-free equilibrium ($\mathcal{T}_{1c}$) is given by

$$\mathcal{T}_{1c} = (A_U^*, A_W^*, F_U^*, F_W^*, M_U^*, M_W^*) = (A_U^*, 0, \frac{b_f \sigma_m A_U^*}{\mu_{uf}}, 0, \frac{(1 - b_f)\sigma_m A_U^*}{\mu_{um}}, 0),$$

with $A_U^* = K_A(1 - \frac{1}{\bar{m}_u \mathcal{R}_U})$. This equilibrium exists if and only if $\bar{m}_u \mathcal{R}_U > 1$. Let

$$\bar{\mathcal{R}}_{0W} = \frac{\mathcal{R}_W}{\bar{m}_u \mathcal{R}_U}, \tag{D.4}$$

be the associated reproduction number of the model (3.9), with $c_i = 1$, $m_w = \bar{m}_w$, $m_u = \bar{m}_u$ and $q = 0$. Solving $\bar{\mathcal{R}}_{0W} = 1$ for ϕ_w (chosen as the bifurcation parameter) gives

$$\phi_w^* = \frac{\theta_w \mu_{uf}(\sigma_m + \mu_a)\mathcal{R}_U}{v_w \sigma_m b_f \psi_w}.$$

The Jacobian of the model (3.9), with $c_i = 1$, $m_w = \bar{m}_w$, $m_u = \bar{m}_u$ and $q = 0$, at $\mathcal{T}_{1c}$, is given by

$$\mathcal{G}(\mathcal{T}_{1c}) = \begin{bmatrix} g_{11} & -\frac{\phi_u \psi_u \bar{m}_u F_U^*}{K_A} & g_{13} & j_{14} & 0 & 0 \\ 0 & -\sigma_m - \mu_a & 0 & j_{24} & 0 & 0 \\ b_f \sigma_m & 0 & -\mu_{uf} & 0 & 0 & 0 \\ 0 & b_f \sigma_m & 0 & -\theta_w \mu_{uf} & 0 & 0 \\ (1 - b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} & 0 \\ 0 & (1 - b_f)\,\sigma_m & 0 & 0 & 0 & -\mu_{um} \end{bmatrix},$$

where, $g_{11} = -\frac{\phi_u \psi_u \bar{m}_u F_U^*}{K_A} - \sigma_m - \mu_a$, $g_{13} = \phi_u \psi_u \bar{m}_u \left(1 - \frac{A_U^*}{K_A}\right)$. The associated right and left eigenvectors of the matrix $\mathcal{G}$ are given, respectively, by

$$w_1 = \frac{(B_1 + B_2)\, w_2}{\theta_w \left(K_A \mu_{uf} \left(\sigma_a + \mu_a\right)\left(1 - \bar{m}_u \mathcal{R}_U\right)\right)}, \quad w_2 > 0, \quad w_3 = \frac{\sigma_m w_1}{\mu_{uf}}, \ w_4 = \frac{\sigma_a b_f w_2}{\theta_w \mu_{uf}}, \ \ w_5 = 0$$
$$w_6 = \frac{\lambda\ (1 - b_f)\, w_2}{\mu_{um}}, \ \ v_1 = 0, \ \ v_2 > 0, \ v_3 = 0, \ v_4 = \frac{v_w \phi_w \psi_w v_2}{\theta_w \mu_{uf} \bar{m}_u \mathcal{R}_U} \ \ v_5 = 0, \ \ v_6 = 0, \tag{D.5}$$

where,

$$B_1 = \frac{K_A b_f \sigma_a \psi_w \phi_w \left(1 - v_w\right)}{\bar{m}_u \mathcal{R}_U}, \text{ and } \ B_2 = K_A b_f \phi_u \psi_u \theta_w \mu_{uf} \sigma_a \bar{m}_u \left(1 - \frac{1}{\bar{m}_u \mathcal{R}_U}\right).$$

The associated backward bifurcation coefficients, a and b, are given, respectively, by (where the eigenvectors w_i and v_i, $i = 1, 2, \ldots, 6$, are given in (D.5))

$$a(\phi_w^*) = \frac{2 v_2 {w_2}^2 \sigma_m\, b_f v_w \phi_w \psi_w \mathcal{R}_W \left(1 - v_w\right)}{\theta_w \mu_{uf} K_A \bar{m}_u \mathcal{R}_U \left(1 - \bar{m}_u \mathcal{R}_U\right)}, \tag{D.6}$$

and,

$$b = \frac{v_2 w_2 b_f v_w \psi_w \sigma_m}{\theta_w \mu_{uf} \bar{m}_u \mathcal{R}_U} > 0.$$

It follows from Equation (D.6) that, $b > 0$. Hence, $a(\phi^*) < 0$ whenever $\bar{m}_u > \frac{1}{\mathcal{R}_U}$. Thus, it follows from item (iv) of Theorem B.1 [13] that the model (3.9) does not undergo a backward bifurcation at $\bar{\mathcal{R}}_{0W} = 1$ whenever $\bar{m}_u > \frac{1}{\mathcal{R}_U}$. □

Appendix E Proof of Theorem 3.8

Proof. (a.) Consider the model (3.9) with $m_w = \bar{m}_w = 0,\ m_u = \bar{m}_u = 1$, $q = 0$ and $\mathcal{R}_U > 1$. Also, let $\mathcal{R}_W < 1$. Further, consider the Lyapunov function

$$V = b_f\sigma_m A_W + (\sigma_m + \mu_a)F_W.$$

so that the derivative of V with respect to t is given by

$$\begin{aligned}
\frac{dV}{dt} &= b_f\sigma_m\frac{dA_W}{dt} + (\sigma_m + \mu_a)\frac{dF_W}{dt} \\
&= b_f\sigma_m v_w\phi_w\psi_w\left(1 - \frac{A_U + A_W}{K_A}\right)F_W - b_f\sigma_m(\sigma_m + \mu_a)F_W \\
&+b_f\sigma_m(\sigma_m + \mu_a)F_W - (\sigma_m + \mu_a)\theta_w\mu_{uf}F_W \\
&< b_f\sigma_m v_w\phi_w\psi_w\left(1 - \frac{A_U}{K_A}\right)F_W - (\sigma_m + \mu_a)\theta_w\mu_{uf}F_W \\
&= \theta_w\mu_{uf}(\sigma_m + \mu_a)F_W\left[\frac{b_f\sigma_m v_w\phi_w\psi_w}{\theta_w\mu_{uf}(\sigma_m + \mu_a)}\left(1 - \frac{A_U}{K_A}\right) - 1\right] \\
&= \theta_w\mu_{uf}(\sigma_m + \mu_a)F_W\left[\frac{b_f\sigma_m\phi_u\psi_u}{\mu_{uf}(\sigma_m + \mu_a)}\frac{v_w\phi_w\psi_w}{\theta_w\phi_u\psi_u}\left(1 - \frac{A_U}{K_A}\right) - 1\right] \\
&= \theta_w\mu_{uf}(\sigma_m + \mu_a)F_W\left[\bar{\mathcal{R}}_{0W}\mathcal{R}_U\left(1 - \frac{A_U}{K_A}\right) - 1\right] \\
&< \theta_w\mu_{uf}(\sigma_m + \mu_a)F_W\left[\bar{\mathcal{R}}_{0W}\mathcal{R}_U - 1\right] \\
&= \theta_w\mu_{uf}(\sigma_m + \mu_a)F_W\left[\mathcal{R}_W - 1\right] \\
&\leq 0 \ \text{ for } \ \mathcal{R}_W < 1.
\end{aligned}$$

Thus, $\dfrac{dV}{dt} \leq 0$ whenever $\mathcal{R}_W < 1$ with $\dfrac{dV}{dt} = 0$ if and only if $F_W = 0$. Let

$$\mathcal{L} = \{\mathbf{x} \in \mathcal{D} | \frac{dV}{dt}(\mathbf{x}) = 0\}\backslash\{\mathcal{T}_{0\diamond}\} = \{\mathbf{x} \in \mathcal{D} | F_W = 0\}\backslash\{\mathcal{T}_{0\diamond}\}.$$

Since V is positive definite function and the set $\mathcal{L}$ does not contain any equilibria of the system besides the equilibria $\mathcal{T}_{1\diamond}$ when $\mathcal{R}_U > 1$ ($\mathcal{T}_{0\diamond}$ is unstable, by Theorem 3.6) then by the LaSalle's invariance principle [32] as $t \to \infty$, then $A_W \to 0$, $F_W \to 0$, $M_W \to 0$, $A_U \to A_U^*$, $F_U \to F_U^*$ and $M_U \to M_U^*$. Hence, the equilibria $\mathcal{T}_{1\diamond}$ is globally asymptotically stable when $\mathcal{R}_W < 1$.

(b) Consider the model (3.9) with $c_i = 1$, $m_w = \bar{m}_w \in [0, 1)$, $m_u = \bar{m}_u \in (0, 1]$, $q = 0$ and $\mathcal{R}_U > 1$. Also, let $\mathcal{R}_W < 1$. Further, consider the Lyapunov function

$$V = b_f\sigma_m A_W + (\sigma_m + \mu_a)F_W.$$

so that the derivative of V with respect to t is given by

$$\begin{aligned}
\frac{dV}{dt} &= b_f\sigma_m\frac{dA_W}{dt} + (\sigma_m+\mu_a)\frac{dF_W}{dt} \\
&= b_f\sigma_m v_w\phi_w\psi_w\left(1-\frac{A_U+A_W}{K_A}\right)F_W - b_f\sigma_m(\sigma_m+\mu_a)F_W \\
&+ b_f\sigma_m(\sigma_m+\mu_a)F_W - (\sigma_m+\mu_a)\theta_w\mu_{uf}F_W \\
&< b_f\sigma_m v_w\phi_w\psi_w\left(1-\frac{A_U}{K_A}\right)F_W - (\sigma_m+\mu_a)\theta_w\mu_{uf}F_W \\
&= \theta_w\mu_{uf}(\sigma_m+\mu_a)F_W\left[\frac{b_f\sigma_m v_w\phi_w\psi_w}{\theta_w\mu_{uf}(\sigma_m+\mu_a)}\left(1-\frac{A_U}{K_A}\right)-1\right] \\
&= \theta_w\mu_{uf}(\sigma_m+\mu_a)F_W\left[\frac{b_f\sigma_m\phi_u\psi_u}{\mu_{uf}(\sigma_m+\mu_a)}\frac{v_w\phi_w\psi_w}{\theta_w\phi_u\psi_u}\left(1-\frac{A_U}{K_A}\right)-1\right] \\
&= \theta_w\mu_{uf}(\sigma_m+\mu_a)F_W\left[\bar{\mathcal{R}}_{0W}\mathcal{R}_U\bar{m}_u\left(1-\frac{A_U}{K_A}\right)-1\right] \\
&< \theta_w\mu_{uf}(\sigma_m+\mu_a)F_W\left[\bar{\mathcal{R}}_{0W}\mathcal{R}_U\bar{m}_u-1\right] \\
&= \theta_w\mu_{uf}(\sigma_m+\mu_a)F_W\left[\mathcal{R}_W-1\right] \\
&\leq 0 \text{ for } \mathcal{R}_W<1.
\end{aligned}$$

Thus, $\frac{dV}{dt}\leq 0$ whenever $\mathcal{R}_W<1$ with $\frac{dV}{dt}=0$ if and only if $F_W=0$. Let

$$\mathcal{L}=\{\mathbf{x}\in\mathcal{D}|\frac{dV}{dt}(\mathbf{x})=0\}\backslash\{\mathcal{T}_{0\diamond}\}=\{\mathbf{x}\in\mathcal{D}|F_W=0\}\backslash\{\mathcal{T}_{0\diamond}\}.$$

Since V is positive definite function and the set $\mathcal{L}$ does not contain any equilibria of the system besides the equilibria $\mathcal{T}_{1\diamond}$ when $\mathcal{R}_U>1$ ($\mathcal{T}_{0\diamond}$ is unstable, by Theorem 3.6) then by the LaSalle's invariance principle [32] as $t\to\infty$, then $A_W\to 0$, $F_W\to 0$, $M_W\to 0$, $A_U\to A_U^*$, $F_U\to F_U^*$ and $M_U\to M_U^*$. Hence, the equilibria $\mathcal{T}_{1\diamond}$ is globally asymptotically stable when $\mathcal{R}_W<1$. □

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