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MODELLING THE INTRODUCTION OF *WOLBACHIA* INTO *AEDES AEGYPTI* MOSQUITOES TO REDUCE DENGUE TRANSMISSION

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Abstract

Infecting *Aedes aegypti* mosquitoes with the bacteria *Wolbachia* has been proposed as an innovative new strategy to reduce the transmission of dengue fever. Field trials are currently being undertaken in Queensland, Australia. However, few mathematical models have been developed to consider the persistence of *Wolbachia*-infected mosquitoes in the wild. This paper develops a mathematical model to determine the persistence of *Wolbachia*-infected mosquitoes by considering the competition between *Wolbachia*-infected and non-*Wolbachia* mosquitoes. The model has four steady states that are biologically feasible: all mosquitoes dying out, only non-*Wolbachia* mosquitoes surviving, and two steady states where non-*Wolbachia* and *Wolbachia*-infected mosquitoes coexist. The stability of the steady states is determined with respect to the key parameters in the mosquito life cycle. A global sensitivity analysis of the model is also conducted. The results show that the persistence of *Wolbachia*-infected mosquitoes is dominated by the reproductive rate, death rate, maturation rate and maternal transmission. For the parameter values where *Wolbachia* persists, it dominates the population, and hence the introduction of *Wolbachia* has great potential to reduce dengue transmission.

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1. Introduction

Dengue, a vector-borne disease, is a public health problem worldwide and poses a risk to two-thirds of the world's population [1]. There are four distinct serotype viruses of dengue: DENV1, DENV2, DENV3 and DENV4. Infection with dengue is divided

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into three categories: dengue fever, dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS). DHF and DSS are the most severe forms of dengue, with fatality rates greater than 20% [17]. If individuals are infected by one serotype of the virus, they become immune to that serotype. However, they are more likely to contract the much more severe DHF and DSS if they are subsequently infected with any of the other three serotypes.

Aedes aegypti is the mosquito that is responsible for most dengue transmission globally. Its lifespan is 10–22 days, depending on the temperature and humidity of the region [19]. It is common in urban areas, has a preference for laying eggs in small artificial water sources such as pot plant holders, water tanks, and discarded tyres [10], and is thought to move approximately 120 m during its lifetime [9]. It is highly anthropophilic, preferring to feed on humans over animals.

Various strategies have been implemented to reduce dengue transmission by controlling the mosquito vector, but these have been largely ineffective. For example, the use of insecticide has become largely ineffective as the mosquitoes have developed resistance to the chemicals [8]. Environmental measures such as house-to-house removal of breeding sites are effective in the short term but are expensive and require continuous application.

An alternative approach of infecting *Aedes aegypti* mosquitoes with *Wolbachia* has been proposed as a new strategy for reducing dengue transmission [7]. *Wolbachia* is a bacterium that can inhibit the ability of *Aedes aegypti* to transmit dengue in different ways depending on its strain. One strain of *Wolbachia* achieves this by shortening the lifespan of the mosquitoes, resulting in the dengue virus not having sufficient time to replicate in the mosquito to a level where it is infectious [3]. This strain bends the proboscis [15], so that it is unable to pierce the skin. Another strain of *Wolbachia* reduces how much dengue virus is present in the saliva of the mosquito [16]. Experimental results and current field trials show that the ability of *Aedes aegypti* mosquitoes infected with *Wolbachia* to transmit dengue is reduced [2, 7, 16].

On its own, the reduction in the mosquito lifespan would result in *Wolbachia*-infected mosquitoes being unable to compete in the wild with non-*Wolbachia* mosquitoes. That is, the *Wolbachia*-infected mosquitoes would not persist. However, *Wolbachia* gives female mosquitoes a reproductive advantage known as "cytoplasmic incompatibility" (CI). CI is the condition where *Wolbachia* causes incompatibility between *Wolbachia*-infected males and non-*Wolbachia* females, such that a cross between the two produces embryos that die before hatching. To summarize the effect of CI, there are four possibilities to consider:

(1) Non-*Wolbachia* males and non-*Wolbachia* females produce uninfected offspring.
(2) Non-*Wolbachia* males and *Wolbachia*-infected females produce both *Wolbachia*-infected and uninfected offspring in a certain ratio.
(3) *Wolbachia*-infected males and non-*Wolbachia* females *cannot* produce offspring successfully (although an embryo is formed), further blocking reproduction of non-*Wolbachia* females.

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(4) *Wolbachia*-infected males and *Wolbachia*-infected females produce both infected and uninfected offspring in a certain ratio.

There is, therefore, a complex interplay between lifespan shortening and CI that gives rise to potentially complex dynamics in the mosquito population. If the *Wolbachia*-infected mosquitoes can dominate the population, a reduction in dengue transmission can be attained.

To date, few mathematical models have been developed to determine the persistence of *Wolbachia*-infected *Aedes aegypti* mosquitoes. Previous models have not considered the competition for persistence between non-*Wolbachia* and *Wolbachia*-infected mosquitoes [16]. Therefore, in this paper, a deterministic model for a mosquito population including the introduction of *Wolbachia*-infected mosquitoes into the wild is developed and analysed.

This paper is organized as follows. The model is developed and the key mosquito life-cycle parameters are explained in Section 2. The steady states of the model are found and their stability is determined in Section 3. Numerical solutions are calculated and discussed in Section 4. A sensitivity analysis is conducted in Section 5 to determine which parameters dominate the mosquito population dynamics. Finally, conclusions are presented in Section 6.

2. Model development

The model is a deterministic compartment model with the mosquito population represented by six compartments, as shown in Figure 1. The compartments represent non-*Wolbachia* aquatic mosquitoes (A_N), non-*Wolbachia* male and female mosquitoes (M_N and F_N, respectively), *Wolbachia*-infected aquatic mosquitoes (A_W), and *Wolbachia*-infected male and female mosquitoes (M_W and F_W, respectively). The total adult population is the sum of non-*Wolbachia* and *Wolbachia*-infected adult male and female mosquitoes, $P = M_N + F_N + M_W + F_W$. The model assumes homogeneous mixing and does not capture the dispersal of mosquitoes. As the model aims to investigate whether *Wolbachia*-infected mosquitoes can persist in competition with non-*Wolbachia* mosquitoes, these assumptions do not have an impact on the model outcomes. Eggs, larvae and pupae are grouped into one aquatic stage instead of dividing them into different compartments since *Wolbachia* does not influence the immature stage. The adult stage is divided into two compartments, male and female, to enable the inclusion of CI in reproduction.

The lines in Figure 1 show how mosquitoes progress through the system as they mature. Non-*Wolbachia* aquatic mosquitoes only become non-*Wolbachia* adults. Maternal transmission of *Wolbachia* is not 100%, hence *Wolbachia*-infected aquatic mosquitoes can mature to become either *Wolbachia*-infected adults with the proportion α_W or non-*Wolbachia* adults with the proportion $1 - \alpha_W$. The unlabelled arrows into A_N and A_W represent the reproductive rate, indicating birth, which is influenced by the size of the male and female adult populations.

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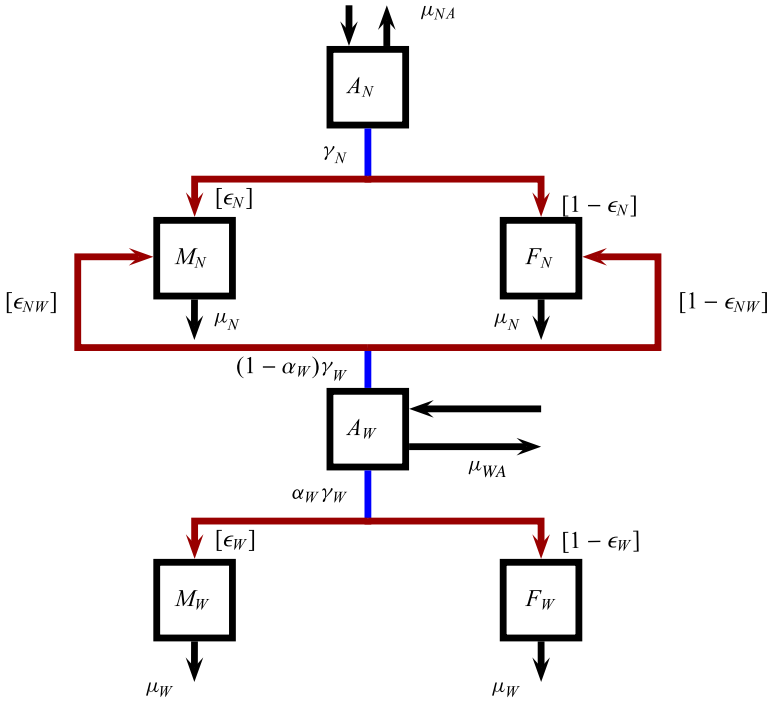

FIGURE 1. Schematic representation of the model (2.1). Unbracketed labels are rates and bracketed labels are proportions. The unlabelled arrows into A_N and A_W represent the reproductive rate, indicating birth, which is influenced by the size of the male and female adult populations.

The mosquito population model is governed by the following system of differential equations:

$$\begin{aligned}
\frac{dA_N}{dt} &= \rho_N \frac{F_N M_N}{P}\left(1 - \frac{A_N + A_W}{K}\right) - \mu_{NA} A_N - \gamma_N A_N,\\
\frac{dM_N}{dt} &= \epsilon_N \gamma_N A_N - \mu_N M_N + \epsilon_{NW}(1-\alpha_W)\gamma_W A_W,\\
\frac{dF_N}{dt} &= (1-\epsilon_N)\gamma_N A_N - \mu_N F_N + (1-\epsilon_{NW})(1-\alpha_W)\gamma_W A_W,\\
\frac{dA_W}{dt} &= \rho_W \frac{F_W(M_W + M_N)}{P}\left(1 - \frac{A_N + A_W}{K}\right) - \mu_{WA} A_W - \gamma_W A_W,\\
\frac{dM_W}{dt} &= \epsilon_W \alpha_W \gamma_W A_W - \mu_W M_W,\\
\frac{dF_W}{dt} &= (1-\epsilon_W)\alpha_W \gamma_W A_W - \mu_W F_W.
\end{aligned} \tag{2.1}$$

An increase in non-*Wolbachia* aquatic mosquitoes (A_N) is determined by the reproductive rate ρ_N and occurs when non-*Wolbachia* female and male mosquitoes

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mate and produce offspring. A decrease in non-*Wolbachia* aquatic mosquitoes occurs due to maturation of non-*Wolbachia* aquatic mosquitoes at rate γ_N and their death at rate μ_{NA}. The number of *Wolbachia*-infected aquatic mosquitoes (A_W) increases as *Wolbachia*-infected females (F_W) mate with non-*Wolbachia* and *Wolbachia*-infected males (M_N and M_W) and produce offspring at rate ρ_W. This number decreases due to death at rate μ_{WA} and maturation at rate γ_W.

The number of non-*Wolbachia* adult mosquitoes increases as non-*Wolbachia* aquatic mosquitoes mature at rate γ_N and some proportion ϵ_N become male and the rest $(1-\epsilon_N)$ become female. This is similar for *Wolbachia*-infected adults. In addition, a proportion α_W of infected aquatic mosquitoes mature to become *Wolbachia*-infected adults and a proportion $1-\alpha_W$ mature to become non-*Wolbachia* adults. The death rates of *Wolbachia*-infected and non-*Wolbachia* adults are denoted by μ_W and μ_N, respectively.

The effect of CI is evident in the equations for the aquatic stages, with the difference being the $F_N M_N/P$ term for non-*Wolbachia* aquatics compared to $F_W(M_W+M_N)/P$ for *Wolbachia*-infected aquatics. The parameter K is the carrying capacity, which is the capacity of the environment to sustain the aquatic mosquitoes. The populations can be nondimensionalized with respect to this value, which is equivalent to setting $K=1$.

3. Steady states and stability

This section presents the steady states of the model (2.1) and their stability. As the ratio between male and female mosquitoes is approximately 1:1 [12], and letting $K=1$, (2.1) can be reduced to

$$\begin{aligned}
\frac{dA_N}{dt} &= \rho_N \frac{M_N^2}{2(M_N+M_W)}[1-(A_N+A_W)] - \mu_{NA}A_N - \gamma_N A_N,\\
\frac{dM_N}{dt} &= \frac{\gamma_N A_N}{2} - \mu_N M_N + \frac{(1-\alpha_W)\gamma_W A_W}{2},\\
\frac{dA_W}{dt} &= \frac{\rho_W M_W}{2}[1-(A_N+A_W)] - \mu_{WA}A_W - \gamma_W A_W,\\
\frac{dM_W}{dt} &= \frac{\alpha_W \gamma_W A_W}{2} - \mu_W M_W.
\end{aligned}$$

The model has four steady-state solutions:

$$E_1 = (0,0,0,0), \quad E_2 = (A_N^*, M_N^*, 0, 0), \quad E_3, E_4 = (A_N^+, M_N^+, A_W^+, M_W^+),$$

where

$$\begin{aligned}
A_N^* &= 1 - \frac{4\mu_N(\mu_{NA}+\gamma_N)}{\rho_N \gamma_N},\\
M_N^* &= \frac{\gamma_N A_N^*}{2\mu_N} = \frac{\gamma_N}{2\mu_N}\left(1 - \frac{4\mu_N(\mu_{NA}+\gamma_N)}{\rho_N\gamma_N}\right),
\end{aligned}$$

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and

$$M_N^+ = \frac{1}{2\mu_N}(B_4 A_N^+ + B_5), \quad M_W^+ = B_3 B_2 - B_3 A_N^+, \quad A_W^+ = B_2 - A_N^+,$$

with A_N^+ given by the nonnegative roots of $K_1 A_N^{+2} + K_2 A_N^+ + K_3 = 0$, where

$$K_1 = \left(\frac{1}{B_1} - \frac{B_4}{2\mu_N}\right)\frac{B_4}{2\mu_N} - \frac{B_3}{B_1},$$
$$K_2 = \left(\frac{1}{B_1} - \frac{B_4}{2\mu_N}\right)\frac{B_5}{2\mu_N} + \frac{B_3 B_2}{B_1} - \frac{B_4 B_5}{4\mu_N^2}, \quad K_3 = -\frac{B_5^2}{4\mu_N^2},$$

where $B_1, \ldots, B_5$ are defined in terms of the parameter values as

$$B_1 = \frac{2\rho_N}{\mu_{NA} + \gamma_N}\frac{\mu_W(\mu_{WA} + \gamma_W)}{\rho_W \gamma_W \alpha_W}, \quad B_2 = 1 - \frac{4\mu_W(\mu_{WA} + \gamma_W)}{\rho_W \gamma_W \alpha_W},$$
$$B_3 = \frac{\gamma_W \alpha_W}{2\mu_W}, \quad B_4 = \gamma_N - (1 - \alpha_W)\gamma_W, \quad B_5 = (1 - \alpha_W)\gamma_W B_2.$$

As A_N^+ is calculated from a quadratic equation, there are two possible values, resulting in two possible steady states (E_3 and E_4). Whether A_N^+ is physically realistic or not depends on the parameter values.

The steady state E_1, where all mosquitoes die out, is not an interesting case as this does not occur in reality. The steady state E_2 is where non-*Wolbachia* mosquitoes persist and *Wolbachia*-infected mosquitoes die out. This is one of the steady states of interest as it means that non-*Wolbachia* mosquitoes dominate the population and hence transmission of dengue continues at the unreduced level. The steady states E_3 and E_4 are when both non-*Wolbachia* and *Wolbachia*-infected mosquitoes persist. It is required that the steady states be physically realistic, which implies that they should be nonnegative as they represent a proportion of the carrying capacity. There is a special case if perfect maternal transmission $\alpha_W = 1$ occurs. That is, only *Wolbachia*-infected mosquitoes persist ($A_N = M_N = 0$). When maternal transmission is perfect ($\alpha_W = 1$), $B_5 = 0$ and $K_3 = 0$ and hence $A_N^+ = 0$ is the only realistic solution. However, this is not biologically realistic as in reality perfect maternal transmission cannot happen [16].

The stability of the steady states is determined by calculating the Jacobian matrix and finding the eigenvalues. If the real parts of all the eigenvalues are negative, then the steady state is locally stable; otherwise, it is unstable. For biologically sensible parameter values, the steady state where all mosquitoes die out (E_1) was found to be unstable. The steady state where *Wolbachia*-infected mosquitoes die out and non-*Wolbachia* mosquitoes persist (E_2) was found to be stable for a range of biologically sensible parameter values. As the *Wolbachia*-infected mosquitoes die out, the model is reduced to a simple mosquito population model without *Wolbachia*-infected mosquitoes. It is straightforward to show that E_2 is stable if

$$\rho_N > \frac{(\mu_{NA} + \gamma_N)\mu_N}{\gamma_N \epsilon_N (1 - \epsilon_N)}.$$

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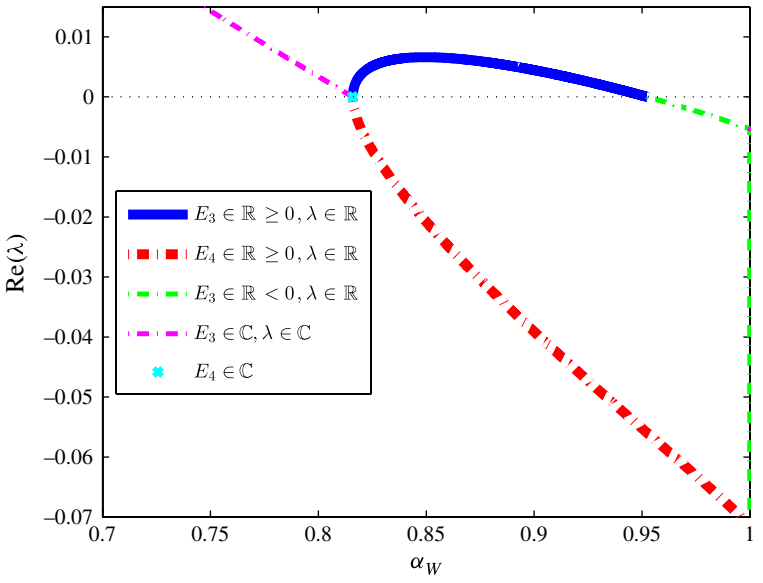

FIGURE 2. Stability of steady states E_3 and E_4. The largest real parts of the eigenvalues are plotted against the maternal transmission α_W, with $\rho_N = 1.25$, $\rho_W = 2.1\rho_N$ and the other parameter values given by Table 1. A steady state must be real and positive to be physically realistic. (Colour available online.)

The stability of the two steady states where both non-*Wolbachia* and *Wolbachia*-infected mosquitoes persist (E_3 and E_4) is obtained numerically. Figure 2 shows the stability of the surviving steady states by plotting the largest real part of the eigenvalues (denoted by λ) against the maternal transmission parameter values (α_W). The thick lines are physically realistic steady states and the thin lines are unrealistic (negative). When the steady states are real and positive, hence realistic, the eigenvalues can be real or complex. The stability of the steady states is determined by the sign of the real part of the eigenvalues: if it is negative, the steady state is stable; otherwise, it is unstable.

There are two realistic steady states. As shown by the sign of the largest real part of the eigenvalues, only one of them is stable. For $\alpha_W \lessapprox 0.816$, the steady state E_3 is real but negative, and further analysis shows that in this case the *Wolbachia*-free steady state E_2 is stable. This is biologically sensible as for low maternal transmission (α_W), the number of *Wolbachia*-infected offspring produced is low and hence the number of non-*Wolbachia* mosquitoes is high. Therefore, *Wolbachia*-infected mosquitoes die out. Furthermore, when $0.816 \lessapprox \alpha_W < 1$, the E_4 steady state is real, positive and stable, whereas E_3 is either real, positive and unstable, or negative (physically unrealistic) but stable. Therefore, there is only one physically realistic stable steady state where both non-*Wolbachia* and *Wolbachia*-infected mosquitoes coexist. A similar approach can be implemented to determine the stability of the steady states in terms of the other parameters.

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TABLE 1. Parameter descriptions, values and sources for the model (2.1) for introducing *Wolbachia*-infected mosquitoes into the wild.

Parameter	Description	Value	Unit	Source
ρ_N	Non-*Wolbachia* reproductive rate	1.25	day^{-1}	Estimated
ρ_W	*Wolbachia* reproductive rate	$2.1\rho_N$	day^{-1}	Estimated
μ_{NA}	Non-*Wolbachia* aquatic death rate	1/7.78	day^{-1}	[19]
μ_{WA}	*Wolbachia* aquatic death rate	1/7.78	day^{-1}	[2, 16, 19]
γ_N	Non-*Wolbachia* maturation rate	1/6.67	day^{-1}	[5, 19]
γ_W	*Wolbachia* maturation rate	1/6.67	day^{-1}	[2, 5, 16]
ϵ_N	Proportion of non-*Wolbachia* adults that are male	0.5	N/A	[12, 19]
ϵ_W	Proportion of *Wolbachia*-infected adults that are male	0.5	N/A	[2]
μ_N	Non-*Wolbachia* adult death rate	1/14	day^{-1}	[4]
μ_W	*Wolbachia* adult death rate	1/7	day^{-1}	[11, 16]
ϵ_{NW}	Proportion of non-*Wolbachia* males hatched from a *Wolbachia*-infected mother	0.5	N/A	[12]
α_W	Maternal transmission	0.8–0.9	N/A	[13, 16, 18, 20]
P	Total population	$M_N + M_W + F_N + F_W$	N/A	N/A
K	Carrying capacity	1	N/A	N/A

4. Numerical solutions

Numerical solutions of the model (2.1) are calculated using the routine ODE15s in MATLAB. The parameter values are taken from the available literature and summarized in Table 1. As no data is currently available to the authors, validation and calibration of the model against data will be conducted as it becomes available. Initial values for the numerical simulations are obtained from calculation of the steady state of the model without the introduction of *Wolbachia*-infected mosquitoes. The initial population of *Wolbachia*-infected mosquitoes ($A_W + M_W + F_W$) is 20% of the total population of non-*Wolbachia* mosquitoes. This was done to replicate the experiments of Xi et al. [18]. The rate ρ_W is estimated to be higher than ρ_N because *Wolbachia*-infected mosquitoes have higher fecundity rates [12]. The estimated value of the non-*Wolbachia* reproductive rate, $\rho_N = 1.25$, is used because this value in combination with other parameter values ensures that non-*Wolbachia* mosquitoes persist in the wild before the introduction of *Wolbachia*-infected mosquitoes, so as to reflect reality.

Figure 3 shows a case where *Wolbachia*-infected mosquitoes die out and non-*Wolbachia* mosquitoes persist, using $\alpha_W = 0.8$. Of interest in terms of the experimental results and seasonal factors is how long this takes. For this example, it takes approximately 300 days for the *Wolbachia*-infected mosquitoes to die out. Figure 3 shows that the number of non-*Wolbachia* mosquitoes decreases in the early period due to competition with the added *Wolbachia*-infected mosquitoes, before increasing and approaching the steady state.

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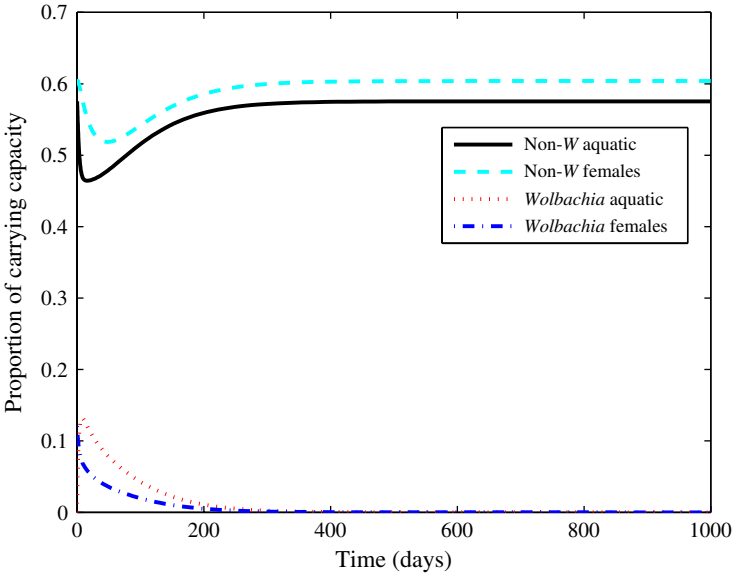

FIGURE 3. Numerical solution where the *Wolbachia*-infected mosquitoes die out, with $\alpha_W = 0.8$ and the other parameter values given by Table 1. The initial *Wolbachia*-infected population is 20% of the total population of non-*Wolbachia* mosquitoes.

Figure 4 shows a case where persistence of both non-*Wolbachia* mosquitoes and *Wolbachia*-infected mosquitoes occurs, using $\alpha_W = 0.9$. It takes approximately 450 days for the mosquito population to approach this steady state. The number of *Wolbachia*-infected female mosquitoes declines slightly in the early period due to competition for resources, but after that they increase and dominate the population.

In comparing Figures 3 and 4, the only change in the parameter values is that the maternal transmission has been increased from $\alpha_W = 0.8$ in Figure 3 to $\alpha_W = 0.9$ in Figure 4. The result confirms the stability analysis of the steady state as given in Figure 2, where the *Wolbachia*-infected mosquitoes die out if $\alpha_W \lessapprox 0.816$, and otherwise both non-*Wolbachia* and *Wolbachia*-infected mosquitoes persist. Furthermore, this result indicates the sensitivity of the model to the parameter, where a slight change of the parameter value can lead to a different model outcome. Further investigation of this is conducted in Section 5.

Experimental results conducted in far north Queensland for approximately 90–120 days [16] show that *Wolbachia*-infected mosquitoes persist. Our numerical results show that *Wolbachia*-infected mosquitoes persist longer than approximately 120 days, but over a longer period the population dies out (see Figure 3). Furthermore, when the maternal transmission is high, $\alpha_W = 0.9$, *Wolbachia*-infected mosquitoes persist, but it takes around 450 days to approach the steady state. This is longer than the 120 days in the aforementioned experiments [16], meaning that the steady state shown here is not likely to be reached in far north Queensland given seasonality. Therefore, our results

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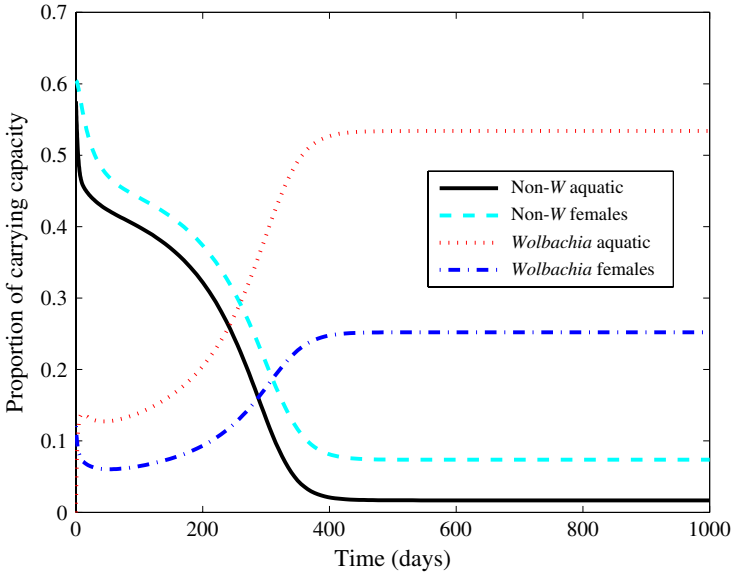

FIGURE 4. Numerical solution where the *Wolbachia*-infected mosquitoes persist, with $\alpha_W = 0.9$ and the other parameter values given by Table 1. The initial *Wolbachia*-infected population is 20% of the total population of non-*Wolbachia* mosquitoes.

reveal that there is a possibility for *Wolbachia*-infected mosquitoes to die out in the long term, something that cannot be determined by experimental trials conducted for a relatively short period of approximately 90–120 days.

The persistence of *Wolbachia*-infected mosquitoes is possible, as in the experimental trials, weekly supplementation of *Wolbachia*-infected mosquitoes was undertaken [2, 16]. However, the experimental trials did not present the number of non-*Wolbachia* mosquitoes, only showing that *Wolbachia*-infected mosquitoes persist. It may happen that the number of *Wolbachia*-infected mosquitoes is smaller than the number of non-*Wolbachia* mosquitoes. This means that non-*Wolbachia* mosquitoes still dominate the population, and hence the transmission of dengue continues. The numerical results presented in this paper clearly show the numbers of non-*Wolbachia* and *Wolbachia*-infected mosquitoes when competing in the wild.

5. Sensitivity analysis

Sensitivity of the model outcome to the parameters is investigated in this section. Latin hypercube sampling is used in conjunction with partial rank correlation coefficient (PRCC) multivariate analysis [6] to investigate which parameters most contribute to the model outcome. The parameters are sampled from a triangular probability distribution since a most likely value (peak), a minimum and a maximum value for each parameter are estimable [14]. A negative PRCC indicates a negative correlation between parameters and the outcome of interest. This means that an

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increase in the parameter value leads to a decrease in the outcome of interest. On the other hand, a positive PRCC indicates a positive correlation between parameters and the outcome of interest, meaning that an increase in the parameter value leads to an increase in the outcome of interest. The larger the magnitude of the PRCC value, the more dominant that parameter is in the outcome.

The parameters are chosen in such a way that for one group of parameter values, the steady state is usually the *Wolbachia*-free steady state, which is where *Wolbachia*-infected mosquitoes die out and non-*Wolbachia* mosquitoes persist (E_2). For the other group of parameter values, the steady state is where both *Wolbachia*-infected and non-*Wolbachia* mosquitoes persist (E_4). The sensitivity of the model outcome to the parameters is measured against a monotonically increasing function. Of interest is the cumulative number of female mosquitoes, since they are responsible for dengue transmission and hence are a proxy for dengue activity. For the range of parameters where the model outcome tends to the *Wolbachia*-free steady state (E_2), the parameters are measured against the cumulative number of non-*Wolbachia* female mosquitoes, which is the solution of

$$\frac{dC_{FN}}{dt} = (1-\epsilon_N)\gamma_N A_N + \epsilon_{NW}(1-\alpha_W)\gamma_W A_W. \tag{5.1}$$

For the range of parameters where the model outcome tends to the *Wolbachia*-surviving steady state (E_4), the parameters are measured against both the cumulative number of non-*Wolbachia* female mosquitoes (the solution of (5.1)) and the cumulative number of *Wolbachia*-infected female mosquitoes, which is the solution of

$$\frac{dC_{FW}}{dt} = (1-\epsilon_W)\alpha_W\gamma_W A_W. \tag{5.2}$$

Over 2000 runs of the model are performed, with at least 95% of the runs tending to one of the steady states of interest. Only samples resulting in the correct steady state are kept for each PRCC analysis, resulting in at least 2000 samples. The range of parameter values used for each steady-state analysis is given in Table 2. In addition, ρ_N and ρ_W are not correlated. They are sampled randomly from the defined range of parameter values. Note that only μ_W and ρ_W are changed to alternate between E_2 and E_4.

As summarized in Table 3, when *Wolbachia*-infected mosquitoes die out and non-*Wolbachia* mosquitoes persist (E_2), non-*Wolbachia* related parameters are dominant (larger magnitude) when the parameters are measured against the cumulative number of non-*Wolbachia* female mosquitoes. This is biologically sensible, as only non-*Wolbachia* mosquitoes persist. The parameters μ_{NA} and μ_N have negative PRCC values, meaning that an increase in the death rates of non-*Wolbachia* aquatics and non-*Wolbachia* adults reduces the population of non-*Wolbachia* mosquitoes. On the other hand, the parameters ρ_N and γ_N have positive PRCC values, indicating that as the reproductive rate or the maturation rate of non-*Wolbachia* mosquitoes increases, the population increases. In contrast, when both non-*Wolbachia* and *Wolbachia*-infected

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TABLE 2. Parameter descriptions, minimum, mode and maximum values and references. Where two ranges of parameters are given, the first is for the *Wolbachia*-free steady state (E_2), and the second is for the steady state where *Wolbachia*-infected mosquitoes survive (E_4).

Parameter	Min	Mode	Max	Unit	Source
ρ_N	1	1.25	2.5	day^{-1}	Estimated
μ_{NA}	1/16.84	1/7.78	1/3.5	day^{-1}	[19]
γ_N	1/13.51	1/6.67	1/5	day^{-1}	[5, 19]
μ_N	1/22.77	1/14	1/10	day^{-1}	[12, 19]
μ_{WA}	1/16.84	1/7.78	1/3.5	day^{-1}	[2, 16, 19]
μ_W	1/11	1/7	1/5	day^{-1}	[11, 16]
	1/20	1/12	1/8		
ρ_W	ρ_N	$1.25\rho_N$	$1.5\rho_N$	day^{-1}	Estimated
	$2\rho_N$	$2.5\rho_N$	$6\rho_N$		
γ_W	1/13.51	1/6.67	1/5	day^{-1}	[2, 5, 16]
α_W	0.8	0.9	1	N/A	[13, 16, 18, 20]

TABLE 3. PRCC values for the *Wolbachia*-free steady state (E_2) and for the both-surviving steady state (E_4) after 1000 days, using parameter ranges given in Table 2. Here C_{FN} is the cumulative number of non-*Wolbachia* female mosquitoes from equation (5.1), and C_{FW} is the cumulative number of *Wolbachia*-infected female mosquitoes from equation (5.2).

Parameter	E_2	E_4	
	C_{FN}	C_{FN}	C_{FW}
ρ_N	0.8854	0.4279	−0.0158
μ_{NA}	−0.8303	−0.3523	0.1575
γ_N	0.9644	0.2952	−0.0150
μ_N	−0.8297	−0.4206	0.1454
μ_{WA}	−0.0051	0.0133	−0.6142
μ_W	0.0708	0.0132	−0.6902
ρ_W	0.0071	0.0736	0.8000
γ_W	0.0053	0.7499	0.9717
α_W	−0.0225	−0.9499	0.7790

mosquitoes persist (E_4), *Wolbachia*-infected related parameters are dominant. For example, when measured against the cumulative number of non-*Wolbachia* female mosquitoes (C_{FN}), the parameters α_W and γ_W have the highest magnitudes. This means that if the maternal transmission rate or the maturation rate increases, the population of *Wolbachia*-infected mosquitoes increases. The *Wolbachia*-related parameters are also dominant when measured against the cumulative number of *Wolbachia*-infected mosquitoes (C_{FW}).

The results of the sensitivity analysis reveal that once the *Wolbachia*-infected mosquitoes persist, they dominate the mosquito population. This confirms that the introduction of *Wolbachia*-infected mosquitoes can be a powerful strategy in reducing dengue transmission. Furthermore, a greater reduction in non-*Wolbachia* female

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mosquitoes can be obtained if the proportion of *Wolbachia*-infected offspring from a *Wolbachia*-infected mother (α_W) is high, as given by the PRCC value of α_W (-0.9499) when measured against the cumulative number of non-*Wolbachia* female mosquitoes.

6. Conclusions

Research conducted by Hoffman et al. [2] and Walker et al. [16] found that *Wolbachia*-infected mosquitoes will dominate the population. Hence a *Wolbachia* intervention would be a potential strategy to reduce dengue spread. These findings are compatible with what the proposed model has demonstrated. The numerical solutions, stability analysis and sensitivity analysis show that once the *Wolbachia*-infected mosquitoes persist, they can ultimately dominate the population. The model also reveals that the persistence of *Wolbachia*-infected mosquitoes mostly depends on the death rate of *Wolbachia*-infected adults (μ_W), the maturation rate of *Wolbachia*-infected adults (γ_W), their reproductive rate (ρ_W) and maternal transmission (α_W). The non-*Wolbachia* mosquitoes would dominate the population only if the *Wolbachia*-infected mosquitoes die out. This means that once the *Wolbachia*-infected mosquitoes can persist in the wild, the non-*Wolbachia* mosquitoes cannot dominate the population.

The results indicate that the introduction of *Wolbachia*-infected mosquitoes can be a powerful strategy if the *Wolbachia*-infected mosquitoes can dominate the population in the long term. This is because in dengue endemic countries, the dengue season lasts for more than 90–120 days, the approximate time duration in which the experiments on *Wolbachia* intervention have been conducted in far north Queensland [2, 16].

Future work stemming from this model can be conducted, such as including seasonality effects in the model. Several parameters such as the maturation rate, death rate and reproductive rate are temperature dependent [19], hence including seasonality effects could improve the model provided adequate data on the temperature dependence is available. By including seasonal variation in all temperature-dependent parameters, the model outcome would give detailed information about the mosquito population dynamics as temperature varies. This would aid the understanding of the effectiveness of this intervention, particularly in the areas where the temperature is extreme, such as Queensland.

Another interesting extension that can be undertaken is modelling the mosquito *(Aedes aegypti)* dispersal dynamics. The aim is to predict the areas that mosquitoes disperse to and their concentration, and hence determine the dengue endemic areas in which a *Wolbachia* intervention could work effectively. For this, distance and time are required and hence partial differential equations are needed. A travelling wave approach, coupled with the underlying population dynamics, would be both novel and interesting. It could be used to help predict where further releases of Wolbachia-infected mosquitoes would be most effective.

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