Modelling the impacts of imperfect maternal transmission on the spread of *Wolbachia* in *Ae. aegypti* population

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Abstract

Dengue continues to be a significant health burden for individuals living in its endemic region. One of the strategies to reduce this burden requires targeting the vector agent, Ae. aegypti, in which intracellular bacterium Wolbachia has proven to be attractive in achieving this aim. Using Wolbachia-infected (WI) mosquitoes to wipe out the Wolbachia-uninfected (WU) ones comes with a maternal-inherited advantage known as cytoplasmic incompatibility, but Wolbachia itself exerts some fitness cost to their host. Also, the effect of imperfect maternal transmission from the WI mosquitoes could be a factor. Despite the successful introduction of WI Ae. aegypti mosquitoes at a small scale, how the method works and the likelihood of success at a larger scale is not fully understood.

In this study, we analyze the invasive prospects of Wolbachia by developing a model that introduces the WI mosquitoes into a wild-type Ae-aegypti population. We study the interactions between key parameters (host fitness and imperfect maternal transmission) that determine whether WI mosquitoes will be suppressed or will dominate. Our analyses show a reproduction fitness threshold exists above which the WI mosquitoes will always dominate, and below which WI mosquitoes may co-exist with the non-Wolbachia infected mosquitoes. We show that cytoplasmic incompatibility alone is not enough for WI mosquitoes to dominate as both its fitness and the possibility of mixed offspring play a critical role. In the absence of WI mosquitoes with greater fitness than the wild-type mosquitoes, small introductions of WI mosquitoes will not lead to invasion. However, under the same circumstances, stable co-existence of both types of mosquito is possible. Hence direct killing of wild-type mosquitoes combined with Wolbachia introduction might be an effective strategy in the fight against dengue.

Keywords: Maternal transmission, Wolbachia, Equilibrium point, Global stability
Introduction

Dengue is one of the major mosquito-borne viral diseases of global health concern. With its widespread geographical distribution, there are around 3.9 billion people at risk of infection with an annual estimate of 390 million new dengue infections [1, 2]. The major vector responsible for the transmission of dengue is the female *Ae. aegypti* mosquito, though the female *Ae. albopictus* mosquitoes also contribute. The risk of mortality due to dengue infection is low but modified by the serotype of the infecting dengue and an individual’s infection history (particularly their immune response to different serotypes) [2]. Despite the low risk of mortality, the large number of confirmed dengue cases and associated morbidity make dengue a substantial contributor to the global health burden. The World Health Organization (WHO) global target for dengue by 2020 is to reduce morbidity and mortality by at least 25% and 50% respectively [3]. An integrated vector management is one among many potential control strategies being considered. Controlling the mosquito vectors appears to be promising but it comes with challenges and great cost [4, 5].

Rather than preventing human-vector contacts, replacing the population of *Ae. aegypti* mosquitoes with another variant that is incapable of dengue transmission has been successfully applied [6]. *Wolbachia*, an intracellular insect bacterium, has the capacity to inhibit dengue virus proliferation inside the *Ae. aegypti* mosquitoes and can spread via maternal (vertical) transmission [7, 8]. Mosquitoes with *Wolbachia* infection have a reproductive advantage over WU mosquitoes via cytoplasmic incompatibility – the mechanism that prevents the embryo maturing following mating between WI males and WU females [9]. This advantage alone may not guarantee that WI mosquitoes will invade the *Ae. aegypti* population, as *Wolbachia* infection leads to a fitness cost to its host [10]. Also, there is the challenge of imperfect maternal transmission which may be overcome by cytoplasmic incompatibility for *Wolbachia* infection to dominate [9, 11, 12]. Hence, having a full understanding of the interplay between key parameters in *Wolbachia* introduction ensures the success of the strategy if it is to be used on a large scale.

Mathematical modelling plays a significant role in understanding the impact of variables involved in the dynamics of a particular infectious disease and has been used in the decision-making process that guides the application of some typical control strategies [13]. Different models have been developed to simulate the introduction of *Wolbachia* into *Ae. aegypti* population [14-17], with each giving the conditions by which WI mosquitoes can dominate. In
this paper, we have assumed imperfect maternal transmission from WI females after mating with WU males. This is not included in the previous models [14, 15]. We also simplify the model in [15] by assuming equal male and female sex proportion. In doing this, we can determine whether *Wolbachia* will invade or not, depending on its reproduction fitness and vertical transmission capabilities.
Material and methods

Minimal model for the persistence of Wolbachia

In this paper, we considered the *Ae. aegypti* mosquito population that is responsible for the transmission of dengue virus. The *Ae. aegypti* mosquito population is divided into two major subpopulations: those with *Wolbachia* infection (\(w\)) and those without *Wolbachia* infection (\(\bar{w}\)). Figure 1 below shows the *Wolbachia* infection status of the offspring as a result of *Wolbachia* infection status of the mating mosquitoes.

![Figure 1. Schematic of maternal transmission of Wolbachia between infected (red) and uninfected (blue) mosquitoes.](image)

(a) WU adult male and female mosquitoes produce offspring that are *Wolbachia* uninfected when they mate. (b) Due to cytoplasmic incompatibility, the offspring from mating between WU female mosquitoes and WI male mosquitoes are not viable. (c) When a WI adult female mates with a WU adult male the offspring could be either WI or WU. (d) Two WI adult mosquitoes produce WI offspring.
Let us denote the number of the mosquitoes that are wildtype in the aquatic stage (egg, larvae, and Pupae), adult male and adult female stage as \( Q_w, M_w \) and \( F_w \), respectively, and those with Wolbachia infection as \( Q_\text{w}, M_\text{w} \) and \( F_\text{w} \). If we assume a logistic growth in the aquatic stage (egg, larvae and Pupae), the dynamics of the \textit{Ae. aegypti} mosquito population is, similar to \([14, 15]\)

\[
\frac{dQ_w}{dt} = \left[ \frac{\phi_w F_w M_w + \rho \phi_w F_w M_w}{M_w + M_\text{w}} \right] \left( 1 - \frac{Q}{K} \right) - (\mu_a + \psi) Q_w, \tag{1}
\]

Wildtype aquatic stage

\[
\frac{dQ_\text{w}}{dt} = \left[ \frac{\phi_w F_w M_w + (1-\rho) \phi_w F_w M_w}{M_\text{w} + M_w} \right] \left( 1 - \frac{Q}{K} \right) - (\mu_a + \psi) Q_\text{w}, \tag{2}
\]

Wolbachia aquatic stage

\[
\frac{dF_w}{dt} = b \psi Q_w - \mu_w F_w, \tag{3}
\]

Susceptible female adult wolbachia free

\[
\frac{dM_\text{w}}{dt} = (1 - b) \psi Q_w - \mu_\text{w} M_\text{w}, \tag{4}
\]

Male adult wolbachia

\[
\frac{dF_w}{dt} = b \psi Q_w - \mu_w F_w, \tag{5}
\]

Susceptible female adult mosquito with Wolbachia

\[
\frac{dM_w}{dt} = (1 - b) \psi Q_w - \mu_w M_w, \tag{6}
\]

Male adult mosquito with Wolbachia

where \( Q = Q_w + Q_\text{w} \) is the total number of aquatic stage mosquitoes which we will assume is less than the carrying capacity \((K)\). The descriptions of the parameters in the system of differential equations (1-6) are given in Table 1.

The system of differential equations (1-6) is very complex, but can be reduced to a simpler model that preserves the key dynamic features. This will enable us to introduce mosquitoes with \textit{Wolbachia} infection in an optimal way to control the spread of dengue. One way to do this is to assume an equal number of male and female mosquitoes. This is reasonable given the experimental work in \([18]\) which estimated the ratio of male to female mosquitoes as 1.02 : 1.

Hence, by setting \( M = F \) (for both \( w \)- and \( \text{w} \)-type mosquitoes) and \( b = \frac{1}{2} \), the system of differential equations (1-6) can be reduced to

\[
\frac{dQ_w}{dt} = \left[ \frac{\phi_w F_w^2 + \rho \phi_w F_w F_w}{F_w + F_w} \right] \left( 1 - \frac{Q}{K} \right) - (\mu_a + \psi) Q_w, \tag{7}
\]
\[ \frac{dQ_w}{dt} = \left[ \frac{\phi_w F_w^2 + (1 - \rho) \phi_w F_w F_\bar{w}}{F_w + F_\bar{w}} \right] \left( 1 - \frac{Q_w}{K} \right) - (\mu_a + \psi) Q_w, \]  
\[ (8) \]

\[ \frac{dF_\bar{w}}{dt} = \frac{\psi}{2} Q_\bar{w} - \mu_\bar{w} F_\bar{w}, \]  
\[ (9) \]

\[ \frac{dF_w}{dt} = \frac{\psi}{2} Q_w - \mu_w F_w. \]  
\[ (10) \]

This system of differential equations (7-10) explicitly includes the possibility of uninfected and infected offspring being produced when a female mosquito with Wolbachia infection mates with male mosquito without Wolbachia infection [6, 9, 11, 12], through the \( \rho \) terms. This possibility is excluded in the models of Wolbachia introduction studied in [14, 15].

We analyse the Wolbachia spread system (equations 7-10) for the conditions that will enable Wolbachia-infected mosquitoes to propagate following their introduction into an Ae. aegypti population that is naïve to Wolbachia infection. This is done as follows:

Given a system of autonomous ordinary differential equations,

\[ \frac{dX}{dt} = F(X), \text{ where } X, F(X) \in \mathbb{R}^n \]  
\[ (11) \]

the asymptotic behavior of the solutions of (11) starting near a known solution \( \bar{X} \) are determined by the eigenvalues of the associated Jacobian matrix defined as \( J = \frac{\partial F}{\partial X} \) evaluated at \( \bar{X} \). We adopt this approach in this paper to understand Wolbachia propagation in the Ae. aegypti population. Also, the simulation of these models using published parameter values was done in MATLAB R2017a (Release M(2017) The MathWorks Inc, Natick, MA, USA).
### Table 1. Parameter description and values for model (7-10)

| Parameter | Description                                                                 | Estimate [Range]       | Unit                | References |
|-----------|----------------------------------------------------------------------------|------------------------|---------------------|------------|
| $K$       | Carrying capacity of the aquatic stage                                      | $10^6 [10^3, 10^8]$   | Aquatic mosquito   | Assume     |
| $\phi_w$  | Per capita egg laying rate for Wolbachia uninfected mosquitoes               | $50 [0 – 75]$          | Eggs per day        | [19]       |
| $\phi_w$  | Per capita egg laying rate for Wolbachia-infected mosquitoes                | $51 [0 – 75]$          | Eggs per day        | [19]       |
| $\rho$    | The fraction of eggs that are Wolbachia-uninfected as result of mating between Wolbachia-uninfected male and Wolbachia-infected female mosquitoes | $0.1 [0 – 1]$          | Dimensionless       | Assume     |
| $b$       | Fractions of eggs that are female                                          | $0.5 [0.34 – 0.6]$     | Dimensionless       | [18-21]    |
| $\psi$    | Maturation rate                                                             | 0.01                   | Per day             | [15]       |
| $\mu_a$   | Aquatic death rate                                                          | 0.02                   | Per day             | [15]       |
| $\mu_w$   | Death rate of Wolbachia-uninfected mosquitoes                               | $0.061 [0.02 – 0.09]$  | Per day             | [19, 22]   |
| $\mu_w$   | Death rate of Wolbachia-infected mosquitoes                                 | $0.068 [0.03 – 0.14]$  | Per day             | [19, 22]   |
**Results**

**No negative mosquitoes (positivity and boundedness of solutions)**

For the *Wolbachia* spread model (7) – (10) to be biologically meaningful, we need to show that the solutions with non-negative initial conditions will remain non-negative for future times.

**Claim 1:** For any given non-negative initial conditions, the solutions of (7-10) are non-negative for all $t \geq 0$.

**Proof:**

We prove by contradiction that whenever a solution enters the feasible region $\mathbb{R}^4_+$, it stays there forever. Consider the following four cases:

i. there exists a first time $t_1 > 0$ such that whenever $Q_w(t_1) = 0, \frac{dQ_w(t_1)}{dt} < 0, Q_w(t) \geq 0, F_w(t) \geq 0, 0 \leq t \leq t_1$

ii. there exists a first time $t_2 > 0$ such that whenever $Q_w(t_2) = 0, \frac{dQ_w(t_2)}{dt} < 0, Q_w(t) \geq 0, F_w(t) \geq 0, 0 \leq t \leq t_2$

iii. there exists a first time $t_3 > 0$ such that whenever $F_w(t_3) = 0, \frac{dF_w(t_3)}{dt} < 0, Q_w(t) \geq 0, 0 \leq t \leq t_3$

iv. there exists a first time $t_4 > 0$ such that whenever $F_w(t_4) = 0, \frac{dF_w(t_4)}{dt} < 0, Q_w(t) \geq 0, 0 \leq t \leq t_4$

First, it can be shown that $Q(t) \leq K$ provided $Q(0) < K$. Then, for the first case:

$$\frac{dQ_w(t_1)}{dt} = \left[\frac{\phi_w F_w^2(t_1) + \rho \phi_w F_w(t_1) F_w(t_1)}{F_w(t_1) + F_w(t_1)} \right] \left(1 - \frac{Q_w(t_1)}{K}\right) \geq 0,$$

which contradicts that $\frac{dQ_w(t_1)}{dt} < 0$. For all the remaining cases, we have:

$$\frac{dQ_w(t_1)}{dt} = \left[\frac{\phi_w F_w^2(t_1) + (1-\rho) \phi_w F_w F_w}{F_w(t_1) + F_w(t_1)} \right] \left(1 - \frac{Q_w(t_1)}{K}\right) \geq 0,$$

$$\frac{dF_w(t_1)}{dt} = \frac{\psi}{2} Q_w(t_1) \geq 0,$$

$$\frac{dF_w(t_1)}{dt} = \frac{\psi}{2} Q_w(t_1) \geq 0.$$

Hence, the solutions are non-negative for all future times given non-negative initial data.
Claim 2: Let \( (t) = Q_w(t) + Q_w(t) + F_w(t) + F_w(t) \), there exists a constant \( \tau > 0 \) such that \( \limsup_{t \to \infty} M(t) \leq \tau \).

Proof:

Adding equations (7) to (10), we have

\[
\frac{dM}{dt} = \left[ \frac{\phi_w F_w^2 + \phi_w F_w F_w + \phi_w F_w}{F_w + F_w} \right] \left( 1 - \frac{Q}{K} \right) - \mu_a (Q_w + Q_w) - \frac{\psi}{2} (Q_w + Q_w) - \mu_w F_w - \mu_w F_w.
\]

Since \( Q_w \leq K \), \( Q_w \leq K \), then from equations (9) and (10), \( F_w \leq \frac{\psi K}{2 \mu_1} \) and \( F_w \leq \frac{\psi K}{2 \mu_1} \), where \( \mu_1 = \min(\mu_w, \mu_w, \mu_a) \). Thus, equation (12) becomes

\[
\frac{dM}{dt} \leq \frac{\psi K (\phi_u + 2 \phi_w)}{4 \mu_1} - \mu_1 M.
\]

Hence, it follows from the inequality that there exists a constant \( \tau \) such that

\[
\limsup_{t \to \infty} M(t) \leq \tau.
\]

Equilibrium points

The Wolbachia spread model (7-10) has four steady states: \( E_1 = (0, 0, 0, 0) \) – where there are no mosquitoes; \( E_2 = (Q_w, 0, 0) \) – where the WU mosquitoes dominate and which leads to the extinction of infected ones; \( E_3 = (0, Q_w, 0) \) – where only the WI mosquitoes exist; and \( E_4 = (Q_w, Q_w, 0, 0) \) – where both WU and infected mosquitoes coexist. It is important for the control of dengue or other arboviruses that are transmitted by Ae. aegypti mosquitoes to determine how the dynamics of the Wolbachia spread model behave near and far from these equilibrium points.

No mosquitoes

Now, we determine the nature of the stability points of the model (7-10). One of its equilibrium points is the no mosquito point \( E_1 = (0, 0, 0, 0) \). Establishing the stability of this point is critical for the control of any mosquito borne disease [23]. The general Jacobian of the models (7-10) is given as

\[
J(E_1) = \begin{pmatrix}
-F_1 & -T_1 & A_1 & A_2 \\
-T_2 & -F_2 & B_1 & B_2 \\
\frac{\psi}{2} & 0 & -\mu_w & 0 \\
0 & \frac{\psi}{2} & 0 & -\mu_w
\end{pmatrix}
\]

(13)
where

\[ T_1 = \frac{\phi_w F_w^* + \rho \phi_w F_w^* F_w^*}{(F_w^* + F_w^*)K} \geq 0, \]  

(14)

\[ T_2 = \frac{\phi_w F_w^* + (1-\rho) \phi_w F_w^* F_w^*}{(F_w^* + F_w^*)K} \geq 0, \]  

(15)

\[ A_1 = \left(1 - \frac{Q^*}{K}\right) \left[\left(\frac{F_w^* (\phi_w - \rho \phi_w)}{(F_w^* + F_w^*)^2}\right)\right] \geq 0, \]  

(16)

\[ A_2 = \left(1 - \frac{Q^*}{K}\right) \left[\left(\frac{\rho \phi_w F_w^*}{(F_w^* + F_w^*)^2}\right)\right] \leq 0, \]  

(17)

\[ B_1 = \left(1 - \frac{Q^*}{K}\right) \left[\left(\frac{\phi_w F_w^*}{(F_w^* + F_w^*)^2}\right)\right] \leq 0, \]  

(18)

\[ B_2 = \left(1 - \frac{Q^*}{K}\right) \left[\left(\frac{(1-\rho) \phi_w F_w^* + 2 \phi_w F_w^* F_w^* + \phi_w F_w^*}{(F_w^* + F_w^*)^2}\right)\right] \geq 0, \]  

(19)

\[ F_1 = \mu_\alpha + \psi + T_1, \]  

(20)

\[ F_2 = \mu_\alpha + \psi + T_2. \]  

(21)

The limits as \( F_w^* \to 0 \) and \( F_w^* \to 0 \) in any direction for \( T_1 \) and \( T_2 \) are zero. However, \( T_1 \) and \( T_2 \) are undefined at \( F_w^* = 0 \) and \( F_w^* = 0 \). The limits of \( A_1, A_2, B_1 \) and \( B_2 \) do not exist as \( Q_w^* \to 0, Q_w^* \to 0, F_w^* \to 0, F_w^* \to 0 \). With this, we cannot evaluate the Jacobian at this point. However, we can gain insights from a situation where there is no interaction between WU mosquitoes and WI mosquitoes, by defining

\[ R_{0\bar{w}} = \frac{\phi_{\bar{w}}\psi}{2\mu_{\bar{w}}(\mu_\alpha + \psi)}, \]  

(22)

and

\[ R_{0w} = \frac{\phi_w\psi}{2\mu_w(\mu_\alpha + \psi)}, \]  

(23)

which are the thresholds that determine whether each population will persist or extinguish in the absence of interactions. The thresholds in (22) and (23) are derived from the stability conditions of the associated Jacobian matrix when no interaction exists between the uninfected and infected mosquitoes. Equivalent expressions were given in [15] for the dynamics that explicitly include the male mosquito compartments. Hence, as we shall see later, the two populations are extinguished whenever \( R_{0\bar{w}} < 1 \) and \( R_{0w} < 1 \), as the contributing terms cannot sustain the
populations and also, since the solutions are always non-negative for non-negative initial data, the solutions tend to the no-mosquito equilibrium point.

One question is how that equilibrium point is approached considering that the elements of the Jacobian matrix is undefined at that point? If we follow a similar argument to [24], this equilibrium point is attained if either $F_w$ goes to zero faster than $F_w$ or the other way round. Thus, we can reduce the mosquito population to a no-mosquito situation using efforts targeting reproductive rate such as the use of insecticides and destroying breeding sites.

**WU mosquitoes-only**

The WU equilibrium point is given as $E_2 = (Q_w^*, 0, F_w^*, 0)$ where

$$Q_w^* = K \left(1 - \frac{1}{R_0w}\right),$$  \hspace{1cm} (23)

$$F_w^* = \frac{\psi K}{2\mu_w} \left(1 - \frac{1}{R_0w}\right),$$  \hspace{1cm} (24)

Hence $R_0w > 1$ is necessary for the existence of this equilibrium point. Otherwise, there will be no WU mosquitoes.

Let us define the basic reproduction number $R_{0w|w}$ associated with the number of secondary offspring that would be *Wolbachia* infected due to the introduction of a typical WI adult mosquito into a population of WU adult mosquitoes. In a similar way to [15], we derive $R_{0w|w}$ as follows:

The WI compartments can be divided into the rate of appearance of new mosquitoes with *Wolbachia* infection ($\mathcal{F}$) and other transition rates such as progression into adult mosquitoes with *Wolbachia* infection and death rates ($\mathcal{V}$):

$$\mathcal{F} = \left(\frac{\phi_w F_{w}^2 + (1 - \rho)\phi_w F_w F_w}{F_w + F_w} 1 - \frac{Q_w}{K}\right),$$  \hspace{1cm} (25)

$$\mathcal{V} = \left(\frac{\mu_a + \psi}{2} Q_w 0 \right) + \left(\frac{\mu_w}{2} + \mu_w F_w\right).$$  \hspace{1cm} (26)

Next, we introduce the matrices $F$ and $V$ with components $F_{ij} = \frac{\partial \mathcal{F}_i}{\partial x_j} \bigg|_{E_2}$ and $V_{ij} = \frac{\partial \mathcal{V}_i}{\partial x_j} \bigg|_{E_2}$, where the $x_j$s represent the infected compartments $Q_w$ and $F_w$. Hence,

$$F = \begin{pmatrix} 0 & \phi_w (K - Q_w^*) (1 - \rho) \\ 0 & \frac{\phi_w (K - Q_w^*) (1 - \rho)}{K} \\ 0 & 0 \end{pmatrix},$$  \hspace{1cm} (27)

$$V = \begin{pmatrix} \mu_a + \psi & 0 \\ -\frac{\psi}{2} & \mu_w \end{pmatrix}.$$  \hspace{1cm} (28)
and the next-generation matrix is

\[
FV^{-1} = \begin{pmatrix}
\frac{\psi \phi_w (K - Q \bar{w}^*) (1 - \rho)}{2(\mu_a + \psi) \mu_w K} & \frac{\phi_w (K - Q \bar{w}^*) (1 - \rho) \phi_w}{\mu_w K} \\
0 & 0
\end{pmatrix}.
\] (29)

Hence the basic reproduction number is

\[
R_0 = \frac{\phi_{\bar{w}}}{\phi_{\bar{w}} \phi_{\bar{w}}},
\] (30)

\((1 - \rho)\) shows the effect of the proportion of aquatic stage mosquitoes that are WI as a result of mating between WU male mosquitoes and WI female mosquitoes.

The Jacobian at \(E_2\) is given as

\[
J(E_2) = \begin{pmatrix}
-(\mu_a + \psi) R_{0\bar{w}} & (\mu_w + \psi)(1 - R_{0\bar{w}}) & \frac{\phi_{\bar{w}}}{R_{0\bar{w}}} & \frac{\phi_{\bar{w}} (\phi_{\bar{w}} - \rho \phi_{\bar{w}})}{R_{0\bar{w}}} \\
0 & -(\mu_a + \psi) & 0 & \frac{\phi_{\bar{w}} (1 - \rho) \phi_{\bar{w}}}{R_{0\bar{w}}} \\
\psi & 0 & -\mu_{\bar{w}} & 0 \\
0 & \psi / 2 & 0 & -\mu_{\bar{w}}
\end{pmatrix}.
\] (31)

The characteristic equation for this Jacobian is given as

\[
P(\lambda) = (\lambda^2 + a_1 \lambda + a_2)(\lambda^2 + b_1 \lambda + b_2) = 0,
\] (32)

where

\[
a_1 = \frac{2 \mu_{\bar{w}}^2 + \phi_{\bar{w}} \psi}{2 \mu_{\bar{w}}} > 0,
\] (33)

\[
a_2 = \mu_{\bar{w}} (\mu_a + \psi)(R_{0\bar{w}} - 1),
\] (34)

\[
b_1 = \mu_a + \psi + \mu_w > 0,
\] (35)

\[
b_2 = \mu_w (\mu_a + \psi)(1 - R_{0\bar{w}})\bar{w}.
\] (36)

The equilibrium point \(E_2\) is locally asymptotically stable whenever \(R_{0\bar{w}} < 1\) and \(R_{0\bar{w}} > 1\). This implies that WI mosquitoes will not spread following their introduction if those conditions are satisfied and if the amount of WI mosquitoes introduced is not large enough to change the present state of the \textit{Ae. aegypti} mosquitoes (see later).

**WI mosquitoes-only**

The equilibrium point associated with WI mosquitoes only is

\[
E_3 = \left(0, K \left(1 - \frac{1}{R_{0\bar{w}}} \right), 0, \frac{\psi K}{2 \mu_w} \left(1 - \frac{1}{R_{0\bar{w}}} \right)\right).
\] (37)

As pointed out earlier that no-mosquito equilibrium point holds when both \(R_{0\bar{w}}\) and \(R_{0\bar{w}}\) are less than one, this equilibrium point does not exist when \(R_{0\bar{w}} \leq 1\). Thus, the corresponding Jacobian is defined as
\[ J(E_3) = \begin{pmatrix} - (\mu_a + \psi) & 0 & \rho \Phi_w \frac{1}{R_{0w}} \frac{\phi_w}{R_{0w}} \\ \frac{\psi}{2} & - (\mu_a + \psi) R_{0w} & 0 \\ 0 & 0 & - \mu_w \end{pmatrix} \]  

(38)

Hence, the characteristic equation is

\[ P(\lambda) = (\lambda^2 + c_1 \lambda + c_2)(\lambda^2 + d_1 \lambda + d_2) = 0, \]

where

\[ c_1 = \frac{2 \mu_a^2 + \phi_w \psi}{2 \mu_w} > 0, \]

\[ c_2 = \mu_w (\mu_a + \psi) (R_{0w} - 1), \]

\[ d_1 = \mu_a + \psi + \mu \bar{\omega} > 0, \]

\[ d_2 = (\mu_a + \psi) (\mu \bar{\omega} - \rho \mu_w). \]

The eigenvalues of the quartic characteristic equation are negative or have negative real parts if \( R_{0w} > 1 \) and \( \mu \bar{\omega} > \rho \mu_w \). The condition \( \mu \bar{\omega} > \rho \mu_w \) gives the fitness level of the adult WI that is sufficient for spread. This boils down to the mechanism by which Wolbachia bacteria control the proliferation of dengue virus in the mosquitoes, and if conferring greater fitness to WI mosquitoes will be needed for it to propagate [10].

Following from the expression of the basic reproduction number (equation (30)), the equilibrium point for adult female mosquitoes can be written as

\[ F_{w}^* = \frac{\psi K}{2 \mu_w} \left( 1 - \frac{(1-\rho)}{R_{0w \mid \omega}} \right), \]  

(39)

The expression above shows that the WI-mosquito-only equilibrium can exist when \( R_{0w \mid \omega} < 1 \).

The existence of endemic equilibria for \( R_{0w \mid \omega} < 1 \) is an indicator of a backward bifurcation in the conventional infectious diseases modeling papers [25, 26]. We are not considering that in this paper. However, it is interesting to know that this equilibrium point is unstable whenever \( R_{0w \mid \omega} < \frac{(1-\rho)}{R_{0w}} \) (\( \Rightarrow R_{0w} < 1 \)) and it is locally asymptotically stable even if \( R_{0w \mid \omega} < 1 \), in as much as \( R_{0w} > 1 \) and \( \mu \bar{\omega} > \rho \mu_w \). Thus, since the term \( \frac{(1-\rho)}{R_{0w}} \) can be a small value for some realistic estimates, then establishing Ae. aegypti with Wolbachia requires introducing a substantial number of mosquitoes with Wolbachia to force the state of the Ae. aegypti to near the WI mosquitoes only state. For \( R_{0w \mid \omega} < 1 \), both the \( E_2 \) and \( E_3 \) equilibrium points are locally asymptotically stable in as much as \( R_{0w} > 1 \) for \( E_2 \), and \( R_{0w} > 1 \) and \( \mu \bar{\omega} > \rho \mu_w \) for \( E_3 \).
Claim 3. The WI mosquitoes only equilibrium point is globally asymptotically stable for $Q_w < Q_w^*$ when $R_{0w|\bar{w}} > 1$ and $R_{0w} > 1$, provided $\mu\bar{w} > \rho\mu_w$.

Proof:

When $R_{0w|\bar{w}} > 1$ then $R_{0w} > \frac{R_{0w}}{1-p}$ and this implies $R_{0w} > R_{0\bar{w}}$. Define a Lyapunov function $V$ as

$$V = \frac{\psi}{2\mu_w(\mu_\alpha + \psi)} \int_0^{Q_w} (1 - \frac{Q_w^*}{y}) d\gamma + \frac{1}{\mu_w} \int_{F_w}^{F_w^*} (1 - \frac{F_w^*}{y}) d\gamma. \tag{40}$$

Differentiating equation (40) with respect to time, we have

$$\frac{dV}{dt} = \frac{\psi}{2\mu_w(\mu_\alpha + \psi)} \left(1 - \frac{Q_w^*}{Q_w}\right) \frac{dQ_w}{dt} + \frac{1}{\mu_w} \left(1 - \frac{F_w^*}{F_w}\right) \frac{dF_w}{dt}. \tag{41}$$

Substituting the expression for the differential equations (8) and (10) we have,

$$\frac{\psi}{2\mu_w(\mu_\alpha + \psi)} \left(1 - \frac{Q_w^*}{Q_w}\right) \frac{dQ_w}{dt} = \frac{\psi}{2\mu_w(\mu_\alpha + \psi)} \left(1 - \frac{Q_w^*}{Q_w}\right) \left(U_1 \left(1 - \frac{Q}{K}\right) - (\mu_\alpha + \psi)Q_w\right), \tag{42}$$

where

$$U_1 = \left(\frac{\phi_{w}F_w^{\frac{5}{2}}(1-p)\psi_{w}F_{w}F_w}{F_{w}+F_{w}}\right), \tag{43}$$

and

$$\frac{1}{\mu_w} \left(1 - \frac{F_w^*}{F_w}\right) \frac{dF_w}{dt} = \frac{1}{\mu_w} \left(1 - \frac{F_w^*}{F_w}\right) \left(\psi Q_w - \frac{\psi}{2}\mu_w\right). \tag{44}$$

From equation (42),

$$\frac{\psi}{2\mu_w(\mu_\alpha + \psi)} \left(1 - \frac{Q_w^*}{Q_w}\right) \frac{dQ_w}{dt} = \frac{\psi}{2\mu_w(\mu_\alpha + \psi)} \left(1 - \frac{Q_w}{Q_w}\right) U_1 \left(1 - \frac{Q}{K}\right) - \frac{\psi Q_w}{2\mu_w} + \frac{\psi Q_w^*}{2\mu_w}, \tag{45}$$

and from equation (44),

$$\frac{1}{\mu_w} \left(1 - \frac{F_w^*}{F_w}\right) \frac{dF_w}{dt} = \frac{\psi Q_w}{2\mu_w} - \frac{\psi Q_w F_w}{2\mu_w F_w} - F_w + F_w^*. \tag{46}$$

Adding equations (45) and (46) yields

$$\frac{dV}{dt} = \frac{\psi}{2\mu_w(\mu_\alpha + \psi)} \left(1 - \frac{Q_w}{Q_w}\right) U_1 \left(1 - \frac{Q}{K}\right) + \frac{\psi Q_w^*}{2\mu_w} - \frac{\psi Q_w F_w}{2\mu_w F_w} - F_w + F_w^*. \tag{47}$$

Rearrangement and some manipulations give,

$$\frac{dV}{dt} = \frac{\psi}{2\mu_w(\mu_\alpha + \psi)} \left(1 - \frac{Q_w}{Q_w}\right) U_1 \left(1 - \frac{Q}{K}\right) + F_w^* \left(2 - \frac{Q_w F_w}{Q_w F_w} - \frac{Q_w F_w}{Q_w F_w}\right) - F_w \left(1 - \frac{Q_w^*}{Q_w}\right). \tag{48}$$

Thus,

$$\frac{dV}{dt} = R_{0w} F_w \left(1 - \frac{Q_w}{Q_w}\right) \left(\frac{F_w + (1-p)F_w}{F_w + F_w} \left(1 - \frac{Q}{K}\right) - \frac{1}{R_{0w}}\right) + F_w^* \left(2 - \frac{Q_w F_w}{Q_w F_w} - \frac{Q_w F_w}{Q_w F_w}\right), \tag{49}$$

15
\[
\frac{dV}{dt} \leq F_w \left(1 - \frac{Q_w}{Q_w^*}\right)(R_{0w} - 1) + F_w^* \left(2 - \frac{Q_wF_w}{Q_w^*F_w^*} - \frac{Q_w}{Q_w^*F_w^*}\right).
\]  

(50)

From equation (50), \(2 - \frac{Q_wF_w}{Q_w^*F_w^*} - \frac{Q_w}{Q_w^*F_w^*} \leq 0\) and \(\frac{dV}{dt} < 0\) for all \((Q_w, F_w) \neq (Q_w^*, F_w^*)\) whenever \(Q_w < Q_w^*\) and \(R_{0w} > 1\), and \(\frac{dV}{dt} = 0\) for \((Q_w, F_w) = (Q_w^*, F_w^*)\). It follows from the Krasovskii-Lasalle theorem \([27, 28]\) that

\[(Q_w, F_w) \rightarrow (Q_w^*, F_w^*) \text{ as } t \rightarrow \infty.\]  

(51)

It remains to show that \((Q_w, F_w) \rightarrow (0, 0)\) as \(t \rightarrow \infty\). In this case, \(\limsup_{t \rightarrow \infty} Q_w = Q_w^*\) and \(\limsup_{t \rightarrow \infty} F_w = F_w^*\). Hence, there exist a sufficiently small number \(\epsilon > 0\) and \(t_1 > 0\), such that \(\limsup_{t \rightarrow t_1} F_w \leq F_w^* + \epsilon\) and \(\limsup_{t \rightarrow t_1} Q_w \leq Q_w^* + \epsilon\) for all \(t > t_1\). It follows from equation (7) that for \(t > t_1\),

\[
\frac{dQ_w(t)}{dt} \leq \left[\phi_F^{F_w^{\infty}} + \rho\phi_F(F_w^{\infty} + \epsilon)F_w^{\infty}\right]
\left[1 - \frac{Q_w^{\infty} + \epsilon}{K}\right] - (\mu + \psi)Q_w(t),
\]  

(52)

where \(F_w^{\infty} = \limsup_{t \rightarrow \infty} F_w(t)\). Hence, by the comparison theorem \([29]\) and letting \(\epsilon \rightarrow 0\)

\[
Q_w^{\infty} = \limsup_{t \rightarrow \infty} Q_w(t) \leq \frac{\phi_F^{F_w^{\infty}} + \rho\phi_F(F_w^{\infty} + F_w^{\infty})}{(F_w^{\infty} + F_w^{\infty})(\mu + \psi)R_{0w}}.
\]  

(53)

If \(F_w^{\infty} = \limsup_{t \rightarrow \infty} F_w(t) = 0\) then \(Q_w^{\infty} \leq 0\). Otherwise,

\[
\limsup_{t \rightarrow \infty} F_w(t) \leq \frac{\psi Q_w^{\infty}}{2\mu \bar{w}}
\]  

(54)

and

\[
Q_w^{\infty} \left(\frac{\psi}{2\mu \bar{w}}\left[1 - \frac{R_{0w}}{R_{0w}^*}\right]\right) + Q_w^{\infty} F_w^{\infty} \left(1 - \frac{\rho \mu w}{\mu \bar{w}}\right) \leq 0
\]  

(55)

Hence,

\[
\frac{-2\mu w F_w^{\infty}\left(1 - \frac{\rho \mu w}{\mu \bar{w}}\right)}{\psi(1 - R_{0w}^*)} \leq Q_w^{\infty} \leq 0.
\]  

(56)

Thus, it is immediate that \(Q_w^{\infty} = \limsup_{t \rightarrow \infty} Q_w(t) = 0\) and \(\limsup_{t \rightarrow \infty} F_w(t) = 0\). Hence, \((Q_w, F_w) \rightarrow (0, 0)\) as \(t \rightarrow \infty\). This concludes the proof.

It can be verified that \(\mu \bar{w} > \rho \mu w\) implies \(Q_w \leq Q_w^{\infty}\) provided \(Q_w(0) \leq Q_w^{\infty}\). \(\mu \bar{w} > \rho \mu w\) was also used in equation (55) above. We examine claim 3 by simulating equations (7)-(10) with parameters that satisfy these conditions (see Figure 2).
Both mosquitoes

An interesting situation is to have both WI and uninfected mosquitoes in the *Ae. aegypti* population. In such case, we will want the majority of the mosquitoes to be infected with *Wolbachia*. For the systems of differential equations (7)-(10), the co-existence equilibrium point is given as

\[
E_4 = (d_1 F_w^*, d_2 F_w^*, d_3 F_w^*, F_w^*)
\]

where,

\[
F_w^* = \frac{K \psi}{2(\mu_w d_3 + \mu_w)} \left[ \frac{R_{0w}(1+\rho d_3) - (1+d_3)}{R_{0w}(1+\rho d_3)} \right], \quad d_1 = \frac{2 \mu_w}{\psi}, \quad d_2 = \frac{2 \mu_w}{\psi}, \quad d_3 = \frac{R_{0w}(\mu_w - \rho \mu_w)}{\mu_w(1-\rho)(1-R_{0w}/\mu_w)}.
\]

From (57), it can be observed immediately that there exist two conditions for which either must be true for the existence of this equilibrium point:

i. \( \rho < 1, R_{0w}/\mu_w < 1, R_{0w} > 1, R_{0w} > 1 \) and \( \mu_w > \rho \mu_w \)
ii. \( \rho < 1, R_{0w}/\mu_w > 1, R_{0w} > 1, R_{0w} > 1 \) and \( \mu_w < \rho \mu_w \)

Condition (i) describes a situation in which both WI and uninfected mosquitoes have sufficient fitness to sustain themselves, and WI is not able to disrupt uninfected mosquitoes at uninfected
mosquito equilibrium. Furthermore the life span of WI mosquitoes \((1/\mu_w)\) must be shorter than that of uninfected mosquitoes multiplied by the proportion of incomplete maternal transmission.

Hence all of the equilibrium points of the Wolbachia spread model (7)-(10) can co-exist when \(R_{0w|\bar{w}} < 1\) [15] and only the co-existence and WI-mosquito-only equilibrium points can be stable for \(R_{0w|\bar{w}} > 1\). To establish whether this equilibrium point is stable or not, we use the general Jacobian expressions (13)-(21) to derive its corresponding characteristic equation.

The characteristic equation is

\[
P(\lambda) = \lambda^4 + e_1\lambda^3 + e_2\lambda^2 + e_3\lambda + e_4 = 0,
\]

where the coefficients are given by the following expressions:

\[
e_1 = (F_1 + \mu_{\bar{w}}) + (F_2 + \mu_w),
\]

\[
e_2 = (F_2\mu_w - \frac{\psi B_2}{2}) + (F_1 + \mu_{\bar{w}})(F_2 + \mu_w) + \left(F_1\mu_{\bar{w}} - \frac{\psi A_1}{2}\right) - T_1T_2,
\]

\[
e_3 = \left(F_2\mu_w - \frac{\psi B_2}{2}\right)(F_1 + \mu_{\bar{w}}) + (F_2 + \mu_w)\left(F_1\mu_{\bar{w}} - \frac{\psi A_1}{2}\right) - T_2\left(T_1\mu_w - \frac{\psi A_2}{2}\right) - T_1\left(T_2\mu_w - \frac{\psi B_1}{2}\right),
\]

\[
e_4 = \left(F_1\mu_w - \frac{\psi A_1}{2}\right)\left(F_2\mu_w - \frac{\psi B_2}{2}\right) - \left(T_1\mu_w - \frac{\psi A_2}{2}\right)\left(T_2\mu_w - \frac{\psi B_1}{2}\right).
\]

One way to establish the nature of the equilibrium point is to apply the Lienard and Chipart criterion [30], or the popular Routh-Hurwitz Criteria [13]. For this criterion, it is necessary and sufficient to show that the coefficients of the quartic equation (51) are greater than zero and that \(e_1e_2e_3 > e_3^2 + e_1^2e_4\) for the equilibrium point to be locally asymptotically stable. We investigate this equilibrium point by using a randomization method to show that there exists a parameter set for which the conditions above are satisfied and the quartic equation (58) has negative roots (i.e. the eigenvalues of the associated Jacobian have negative real parts). For the parameters in Table 1, we sample 10000 parameter combinations assuming uniform distributions for the ranges listed in Table 1 and checked whether the equilibrium point is asymptotically stable or not when condition (i) or (ii) is satisfied. We found that for either condition (i) or (ii), the equilibrium point can be asymptotically stable or unstable depending on the parameter set. This shows that there are conditions for which the equilibrium point is locally asymptotically stable. For instance, and given a particular parameter set that satisfies condition (ii) above, the equilibrium point moves from being unstable to become asymptotically stable as we vary \(\rho\) (Figure 3a).

We have verified numerically that if condition (ii) above is satisfied and it is stable then it is globally asymptotically stable (see Figure 3b). Also, Table 2 below lists the conditions for local asymptotic stability of the equilibrium points.

**Table 2: Conditions for stability of the equilibrium points**

| Equilibrium point                  | Stability conditions                                      |
|------------------------------------|----------------------------------------------------------|
| \(E_1\) (No Mosquitoes)           | \(R_{0w} < 1\) and \(R_{0\bar{w}} < 1\)                  |
| \(E_2\) (Only WU Mosquitoes)      | \(R_{0w|\bar{w}} < 1\) and \(R_{0w} > 1\)                |
| \(E_3\) (Only WI Mosquitoes)      | \(R_{0w} > 1\) and \(\mu_w < \rho\mu_w\)                |
| \(E_4\) (Both Mosquitoes)         | Either \(\rho < 1\), \(R_{0w|\bar{w}} < 1\), \(R_{0w} > 1\), \(R_{0w} > 1\), and \(\mu_w > \rho\mu_w\), or \(\rho < 1\), \(R_{0w|\bar{w}} > 1\), \(R_{0w} > 1\), \(R_{0w} > 1\), and \(\mu_w < \rho\mu_w\). |
Figure 3. The stability conditions of the co-existence equilibrium point. The nature of the stability point changes with $\rho$. The Routh-Hurtwitz conditions were evaluated at the dotted point for the following parameters: $R_{0W|\bar{w}} = 2.5$, $R_{0w} = 125$, $R_{0\bar{w}} = 12.5$, $\rho = 0.75$, $\mu_w = 0.04$, $\mu_w = 0.1$, $K = 2000000$ and the co-existence point is characterized by $(F_{\bar{w}}^*, F_{w}^*) = (3.42 \times 10^6, 5.87 \times 10^5)$. The initial data in (b) are $Q_{\bar{w}}(0) = 5000000, Q_{w}(0) = 0, F_{\bar{w}}(0) = 1000000$, and $F_{w}(0) = 1$.

Establishing WI Mosquitoes

In a population with WU mosquitoes, we will expect the mosquitoes to be at the WU equilibrium point. Let us assume that $\frac{R_{0w}}{R_{0\bar{w}}} = 1$. That is, both WU and infected mosquitoes have equal reproductive capacities. We consider the effect of the proportion of offspring $(1 - \rho)$ that become Wolbachia infected as a result of mating between WU male and infected female mosquitoes on the effort of introducing Wolbachia into the Ae. aegypti population. We ask, in a deterministic fashion, what percentage of $F_{\bar{w}}^*$ should be introduced for WI mosquitoes to dominate the Ae. aegypti population. It is seen from Figure 4 that the time taken for the WI mosquitoes to dominate since their introduction decreases as we increase the number of WI mosquitoes at the starting point, for $\rho = 0$, $\rho = 0.1$ and $\rho = 0.25$. As the proportion of offspring that retains Wolbachia infection $(1 - \rho)$ increases, the time required for WI mosquitoes to dominate decreases. When $\rho = 0.5$ the WI mosquitoes never persist for this choice of parameter set, despite the advantage of cytoplasmic incompatibility.
Figure 4. The time gap before WI mosquitoes dominates the *Ae. aegypti* population. In this simulation, $\phi_{\bar{w}} = \phi_{w} = 50$, $\psi = 0.01$, $\mu_{a} = 0.02$, $\mu_{\bar{w}} = \mu_{w} = 0.061$, and $K = 2000000$. 
Discussion and conclusions

In this study, we developed and analysed a simplified version of a complex dynamical system of a two-type-mosquito population to examine the necessary conditions for the propagation of *Wolbachia* infection in an *Ae. aegypti* population. Our analytic results showed that mosquitoes with *Wolbachia* infection can dominate, co-exist or die out in the mosquito population depending on whether they are fitter than mosquitoes without *Wolbachia* infection. Our results show clearly which factors and conditions that are necessary and sufficient for WI mosquitoes to persist.

Our results show that even with perfect maternal transmission of *Wolbachia* and complete cytoplasmic incompatibility, *Wolbachia* infected mosquitoes will not disrupt and outbreed existing populations unless they also have higher reproductive fitness, if introduced in small numbers. Given the current situation, in which *Wolbachia* infected mosquitoes are shorter-lived than uninfected mosquitoes, it seems likely that *Wolbachia* infected mosquitoes are less reproductively fit than uninfected mosquitoes. One solution is to develop intracellular *Wolbachia* bacteria that limits the proliferation of dengue virus inside the *Ae. aegypti* mosquitoes while also conferring greater fitness. Alternatively, if *Wolbachia* infected mosquitoes are introduced in larger numbers, or if uninfected mosquito numbers are reduced at the same time, both types of mosquito may coexist under realistic circumstances as described in our model.

Many strategies are involved in controlling a particular infectious disease, but the ultimate goal is to eradicate such disease [31]. One such strategy is targeting the vector agent, which was first suggested by Ross for malaria [23] and has been adopted for the control of dengue through the usage of insecticide and treatment of established breeding sites [4, 5, 32]. However, eradicating the *Ae. aegypti* population is not realistic due to the many challenges involved [33] and so, alternative options need to be considered.

A more complex model in [15] derived the conditions for WI mosquitoes to invade the *Ae. aegypti* population and showed that the *Wolbachia* can still spread despite the fact that the number of *Wolbachia*-infected offspring due to WI adult mosquitoes in the next generation was less than one. By assuming an equal sex ratio between male and female *Ae. aegypti* mosquitoes and assuming that the maternal transmission of *Wolbachia* to offspring following mating between *Wolbachia*-infected female and uninfected male *Ae. aegypti* is not perfect, we were able to find the threshold at which *Wolbachia* will not spread. The *Wolbachia*-infected
mosquitoes can dominate if they have a greater reproductive fitness. More importantly, if the defined basic reproduction number is greater than one (this is the reproduction number of WI mosquitoes introduced into a WU population) then in a deterministic fashion, the introduction of a single WI mosquito is enough for Wolbachia to invade the Ae. aegypti population and eliminate the WU mosquitoes. For this to occur cytoplasmic incompatibility is necessary but not sufficient.

Another interesting result in our work is establishing the condition for co-existence of the two Ae. aegypti populations. The similar models in [14, 15] have variable conclusions on the nature of this equilibrium point but they were not able to determine explicitly the conditions for the existence of the co-existence point. Our analysis shows that this point can be reached depending on the parameter choice and it can be globally stable. Hence, if this is the goal, we will want more WI mosquitoes than mosquitoes without Wolbachia infection.

Our study has some limitations that may affect our conclusions. One, we assumed that the ratio of male to female Ae. aegypti mosquitoes is the same. This has been shown under a laboratory study and may not be necessarily true in a real-life situation [18]. Whatever the ratio of males to females in the number of eggs laid by either WU or infected female Ae. aegypti mosquitoes, the main factor that determines Wolbachia take-over is the proportion of WI eggs in the next generation. Two, all the important parameters in the associated basic reproduction number are seasonally dependent [34, 35]. The dependency of key parameters on temperature is likely to affect Wolbachia-uninfected and infected mosquitoes in a similar way. This means that we are likely to have Ae. aegypti populations with any of three possibilities: without Wolbachia; with Wolbachia; and co-existence. Adverse conditions for the female Ae. aegypti mosquitoes are likely to reduce the ability to reproduce and fertilize their eggs, and this is likely to push the population into the no-mosquito equilibrium point rather than changing the proportion of the Ae. aegypti population with Wolbachia infection.

In general, controlling dengue epidemics with Wolbachia is promising but implementing the strategy comes at a cost that requires careful evaluation. Our modelling work has shown the potential outcomes of implementing such a strategy and the key parameters that could be targeted to achieve the desired objectives. If Wolbachia has a strong and sustained effect in the Ae. aegypti population, it remains to be seen whether the Ae. albopictus will take over as a key vector agent for dengue transmission or whether climate change can negate all gains from such an introduction. These are questions for future research.
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