Stability Analysis of a Mathematical Model for the Use of Wolbachia to Stop the Spread of Zika Virus Disease

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SUMMARY

The use of wolbachia-infected mosquitoes to stop the spread of zika virus disease is modeled and analyzed. The model consists of a system of 10 ordinary differential equations which describes the dynamics of the disease in the human population, a wolbachia-free *Aedes aegypti* population, and a wolbachia-infected *Aedes aegypti* population used for disease control. A stability analysis of the disease-free equilibrium is conducted, which shows that it is both locally and globally asymptotically stable when the reproduction number is less than one. The result of the stability analysis shows that the spread of zika virus disease can be stopped, irrespective of the initial sizes of the infected human and mosquito populations, when wolbachia-infected *Aedes aegypti* are introduced in the area where the disease is endemic.

Key words: zika virus disease, *Aedes aegypti*, wolbachia, global stability

1. Introduction

Zika virus disease is one of the flavivirus diseases transmitted to humans mainly through the bites of infected female *Aedes aegypti* mosquitoes (Cao-Lormeau et al., 2014). The virus can equally be transmitted from human to human through sex, blood transfusion and mother-to-fetus transmission (Musso et al., 2014). The disease has a negligible mortality rate; hence, it was not considered a serious disease until its linking with an increase in microcephaly in babies born to mothers who were infected with the virus during pregnancy (Mlakar et al., 2016; Cauchmez et al., 2016). In a recent outbreak of zika in Brazil, there were over 5000 confirmed cases of microcephaly (Gao et al., 2016). In addition to microcephaly, zika has been

linked to the neurological disorder Guillain-Barre Syndrome (GBS) (Cao-Lormeau et al., 2016). These health conditions associated with zika virus disease prompted the World Health Organization (WHO) to declare the disease a Public Health Emergency of International Concern in February 2015 (WHO, 2016). At present, there is no known cure for zika virus disease, and the idea of using bed nets to reduce mosquito bites cannot be applied in this case, because *Aedes aegypti* mosquitoes are day-biters. Also, physical and chemical control methods have not proved to be effective in controlling other mosquito-borne diseases such as malaria and dengue. Hence, it seems that the only feasible option is to adopt biological control by introducing wolbachia-infected *Aedes aegypti* mosquitoes in the area where zika virus disease is endemic.

Wolbachia is a group of bacteria naturally found in the reproductive tissues of some arthropods. They are transmitted maternally through the cytoplasm of eggs of their hosts. Some strains of wolbachia such as *wMel* reduce the ability of the host insects to transmit disease-causing pathogens to humans. This is the idea behind using wolbachia-infected mosquitoes as a bio-control for zika virus disease. Wolbachia are not found naturally in the *Aedes aegypti* mosquitoes that transmit zika virus. In order to use this method to control the spread of zika virus disease, *Aedes aegypti* mosquitoes have to be manually infected with wolbachia in the laboratory (Hughes et al., 2013) and then released into the wild to mate with wolbachia-free insects. When wolbachia is present in infected mosquitoes, it increases the incubation period (or reduces the incubation rate) of the virus, thereby increasing the time it takes the mosquito carrying the virus to become infectious. Since the adult life of the mosquito is short, most of the mosquitoes carrying the virus die before they become infectious. Therefore, the infected wolbachia-carrier mosquitoes may not transmit the virus to humans through bites before they die. In addition, wolbachia induces cytoplasmic incompatibility (CI), which helps its host to invade the wolbachia-free *Aedes aegypti* mosquito population in the wild (Koiller et al., 2014). CI is a phenomenon which prevents the development of embryos (causes non-hatching of eggs) when wolbachia-carrier male mosquitoes mate with wolbachia-free female mosquitoes or with female mosquitoes carrying a different wolbachia strain (Mains et al., 2013). The resultant effect of cytoplasmic incompatibility on the mosquitoes' reproduction process is that wolbachia-carrier female mosquitoes will have the advantage of producing many more offspring than the wild insects, since they can mate with all males in the population

whether infected or not infected with wolbachia, to produce viable eggs that are infected with wolbachia (Hancock et al., 2011). In this work, we present a model for the transmission dynamics of zika virus and its control with wolbachia-carrier *Aedes aegypti* mosquitoes. Essentially, we show that the disease-free equilibrium, that is the state when there is no disease in the populations, is both locally and globally stable when the control reproduction number is less than one. This is essential to ascertain the efficacy of using this method to stop the spread of zika virus disease.

The rest of this work is organized as follows: The model with its basic assumptions is presented in section 2. In section 3, we analyze the model by determining the disease-free and endemic equilibrium points, obtaining the expression for the control reproduction number, and carry out local and global asymptotic stability analyses of the disease-free state. In section 4, some graphical representations of the dynamics of zika virus disease are shown. Section 5 concludes the work.

2. Model assumptions and formulation

In this model, we assume that humans can only contract zika virus when bitten by infectious female *Aedes aegypti* mosquitoes. This means that other modes of transmission of the virus to humans, such as unsafe sex, unsafe blood transfusion or perinatal transmission, are not included in the model. On the other hand, transmission of the zika virus from human to mosquito occurs when an adult, uninfected female *Aedes aegypti* mosquito bites a human to suck blood. If the human is already infected with the virus, it may be passed to the mosquito. The mosquito, once infected, remains so and continues to infect humans throughout its lifetime. Therefore, the model includes three major populations: the human population, the adult female wolbachia-free *Aedes aegypti* population, and the adult female wolbachia-carrier *Aedes aegypti* population used for disease control.

2.1. Zika dynamics in human population

The total human population, $N_H(t)$, at any time t , is divided into 4 compartments or classes, namely, (i) the susceptible class, $S_H(t)$, (ii) the latent or the exposed class, $E_H(t)$, (iii) the infectious class, $I_H(t)$, and (iv) the recovered class, $R_H(t)$. We assume that individuals in the human population are recruited into the susceptible class through migration into the zika endemic area at the rate Π_H . The susceptible class acquires zika virus through

infectious wolbachia-free mosquito bites at the rate b_1 , with transmission probability α_{MH} . Susceptible humans may also contract the virus through the bites of wolbachia-carrier mosquitoes at the rate b_2 , with a very negligible probability of infection, $\alpha_{MwH} \ll \alpha_{MH}$. After the incubation period has elapsed, the exposed class becomes infectious at the incubation rate β_H , but recovers at the rate γ . All of the classes in the human population are subject to the natural mortality rate σ_H , whereas only the infectious class is affected by additional death induced by the disease, at the rate σ'_H , which is negligible.

2.2. Zika dynamics in the *Aedes aegypti* population

The population of wolbachia-free adult female *Aedes aegypti* mosquitoes is grouped into three classes, namely (i) susceptible mosquitoes, $S_M(t)$, (ii) exposed mosquitoes, $E_M(t)$ and (iii) infectious mosquitoes, $I_M(t)$. The wolbachia-free male mosquitoes mate with their female counterparts in the wolbachia-free and wolbachia-carrier mosquito populations to produce wolbachia-free and wolbachia-carrier offspring, respectively. The female wolbachia-free mosquitoes join the susceptible class through migration at the rate Π_M , or through oviposition at the rate μ_M . To model the effect of cytoplasmic incompatibility, we assume that the proportion q of the eggs produced by the female wolbachia-free mosquitoes are viable, while $(1 - q)$ are non-viable. This parameter is responsible for the reduction in the population of the wild mosquitoes. Susceptible mosquitoes contract zika virus when they bite humans in the infectious classes at the biting rate b_1 , with probability of infection α_{HM} , and move to the exposed class. After the incubation period, the exposed mosquitoes become infectious and move to the infectious class at the incubation rate β_M . The mosquitoes remain infectious throughout their lifetime until they die naturally at the rate σ_M . Similarly, the female adult wolbachia-carrier *Aedes aegypti* mosquitoes are grouped in the same manner, with the following compartments: the susceptible wolbachia-carrier class, $S_{Mw}(t)$; the exposed wolbachia-carrier class, $E_{Mw}(t)$; and the infectious wolbachia-carrier class, $I_{Mw}(t)$. The dynamics of zika virus disease in the wolbachia-carrier mosquito population is similar to that in the wolbachia-free mosquitoes, except at the infectious stage, where the probability of the wolbachia-carrier mosquitoes transmitting the virus to susceptible humans is negligible. We also note that susceptible wolbachia-infected mosquitoes are introduced from the laboratory into the zika-endemic area at the constant rate Π_{Mw} . Using the above assumptions

on the transmission dynamics and control of zika, we obtain the following system of nonlinear ordinary differential equations which model the dynamics of the disease.

$$\begin{aligned}
\frac{dS_H(t)}{dt} &= \Pi_H - b_1\alpha_{MH}S_H(t)I_M(t) - b_2\alpha_{MwH}I_{Mw}(t)S_H(t) - \sigma_H S_H(t), \\
\frac{dE_H(t)}{dt} &= b_1\alpha_{MH}I_M(t)S_H(t) + b_2\alpha_{MwH}I_{Mw}(t)S_H(t) - (\beta_H + \sigma_H)E_H(t), \\
\frac{dI_H(t)}{dt} &= \beta_H E_H(t) - (\gamma + \sigma_H + \sigma'_H)I_H(t), \\
\frac{dR_H(t)}{dt} &= \gamma I_H(t) - \sigma_H R_H(t), \\
\frac{dS_M(t)}{dt} &= \Pi_M + q\kappa\mu_M N_M(t) - b_1\alpha_{HM}S_M(t)I_H - \sigma_M S_M(t), \\
\frac{dE_M(t)}{dt} &= b_1\alpha_{HM}S_M(t)I_H(t) - (\beta_M + \sigma_M)E_M(t), \\
\frac{dI_M(t)}{dt} &= \beta_M E_M(t) - \sigma_M I_M(t), \\
\frac{dS_{Mw}(t)}{dt} &= \Pi_{Mw} + \kappa\mu_{Mw} N_{Mw}(t) - b_2\alpha_{HMw}S_{Mw}(t)I_H(t) - \sigma_M S_{Mw}(t), \\
\frac{dE_{Mw}(t)}{dt} &= b_2\alpha_{HMw}S_{Mw}(t)I_H(t) - (\beta_{Mw} + \sigma_M)E_{Mw}(t), \\
\frac{dI_{Mw}(t)}{dt} &= \beta_{Mw} E_{Mw}(t) - \sigma_M I_{Mw}(t)
\end{aligned} \tag{1}$$

The initial conditions are $S_H(0) = S_H^0, E_H(0) = E_H^0, I_H(0) = I_H^0, R_H(0) = R_H^0, S_M(0) = S_M^0, E_M(0) = E_M^0, I_M(0) = I_M^0, S_{Mw}(0) = S_{Mw}^0, E_{Mw}(0) = E_{Mw}^0, I_{Mw}(0) = I_{Mw}^0$, which we assume to be nonnegative quantities. The domain of existence of a solution to this system can be described as $\mathcal{D} = D_1 \cup D_2 \cup D_3$, where $D_1 = \{S_H, E_H, I_H, R_H\} \in \mathbb{R}_+^4 | S_H + E_H + I_H + R_H \leq N_H\}$, $D_2 = \{(S_M, E_M, I_M) \in \mathbb{R}_+^3 | S_M + E_M + I_M \leq N_M\}$, and $D_3 = \{(S_{Mw}, E_{Mw}, I_{Mw}) \in \mathbb{R}_+^3 | S_{Mw} + E_{Mw} + I_{Mw} \leq N_{Mw}\}$.

From (1), we see that the total populations of humans and of wolbachia-free and wolbachia-carrier mosquitoes, respectively, satisfy the equations

$$\begin{aligned}
\frac{dN_H}{dt} &= \Pi_H - \sigma_H N_H - \sigma'_H I_H, \\
\frac{dN_M}{dt} &= \Pi_M + (q\kappa\mu_M - \sigma_M) N_M, \\
\frac{dN_{Mw}}{dt} &= \Pi_{Mw} + (\kappa\mu_{Mw} - \sigma_M) N_{Mw}.
\end{aligned} \tag{2}$$

Let $f(X(t))$ represent the right-hand side of (1), where $X(t) = (S_H, E_M, I_H, R_H, S_M, E_M, I_M, S_{Mw}, E_{Mw}, I_{Mw})$. It is easy to show that $f(X(t))$ is continuous, and has continuous partial derivatives with respect to each of the state variables. Hence, there exists a unique solution $X(t)$ to the system (1) that passes through the initial solution, X_0 .

2.3. Positivity of solution

Since the model describes the dynamics of zika virus disease in human and mosquito populations, it will be epidemiologically and mathematically meaningful if all of the state variables (all human and mosquito subpopulations) are nonnegative $\forall t \geq 0$. Moreover, given that the initial conditions are nonnegative in the octant $\mathcal{D}$, we need to establish that the solution remains positive in the set. From the first equation in (1), we have

$$\begin{aligned} \frac{dS_H(t)}{dt} &> -b_1\alpha_{MH}S_HI_M - b_2\alpha_{MwH}I_{Mw}S_H - \sigma_H S_H \\ \implies \frac{dS_H(t)}{S_H(t)} &> -(b_1\alpha_{MH}I_M + b_2\alpha_{MwH}I_{Mw} + \sigma_H) dt \\ \implies S_H(t) &> S_H^0 e^{-\int^t (b_1\alpha_{MH}I_M(s) + b_2\alpha_{MwH}(s)I_{Mw}(s) + \sigma_H) ds} > 0 \end{aligned}$$

Also from the second equation, we have that

$$\begin{aligned} \frac{dE_H(t)}{dt} &> -(\beta_H + \sigma_H)E_H \implies \frac{dE_H(t)}{E_H(t)} > -(\beta_H + \sigma_H)dt \\ \implies E_H(t) &> E_H^0 e^{-(\beta_H + \sigma_H)t} > 0 \end{aligned}$$

A similar argument can be used to show that other component solutions are positive. Therefore, the solution remains positive in $\mathcal{D} \forall t > 0$.

2.4. Positive invariant region

To show that $\mathcal{D}$ is positive invariant with respect to the flow of the model system, we use the total populations in (2). It is easy to show from (2) that

$$\begin{aligned} N_H(t) &\leq \frac{\Pi_H}{\sigma_H} - \left(\frac{\Pi_H}{\sigma_H} - N_H^0 \right) e^{-(\sigma_H - \mu_H)t} \\ N_M(t) &\leq \frac{\Pi_M}{\sigma_M - \mu_M} - \left(N_M^0 - \frac{\Pi_M}{\sigma_M - \mu_M} \right) e^{-(\sigma_M - \mu_M)t} \\ N_{Mw}(t) &\leq \frac{\Pi_{Mw}}{\sigma_M - \mu_{Mw}} - \left(N_{Mw}^0 - \frac{\Pi_{Mw}}{\sigma_M - \mu_{Mw}} \right) e^{-(\sigma_M - \mu_{Mw})t} \end{aligned}$$

Hence, we have that

$$\begin{aligned}\lim_{t \rightarrow \infty} \sup N_H(t) &\leq \frac{\Pi_H}{\sigma_H} \\ \lim_{t \rightarrow \infty} \sup N_M(t) &\leq \frac{\Pi_M}{\sigma_M - qk\mu_M} \\ \lim_{t \rightarrow \infty} \sup N_{Mw}(t) &\leq \frac{\Pi_{Mw}}{\sigma_M - k\mu_{Mw}}\end{aligned}$$

Since the total human and mosquito populations are bounded above, and no population is negative, this implies that all solutions enter and remain in the domain $\mathcal{D}$ $\forall t \geq 0$. This shows that $\mathcal{D}$ is positive invariant. The positivity of other solutions can be shown in a similar manner. Therefore, the solution remains positive $\forall t > 0$.

3. Analysis of the model

3.1. Disease-free equilibrium and the control reproduction number

The disease-free equilibrium, E_0 of the model is the steady state of (1) in the absence of zika virus disease in the population. Hence, it is easy to see that $E_0 = \left(\frac{\Pi_H}{\sigma_H}, 0, 0, 0, \frac{\Pi_M}{\sigma_M - qk\mu_M}, 0, 0, \frac{\Pi_{Mw}}{\sigma_M - k\mu_{Mw}}, 0, 0\right)$. Also, at disease-free equilibrium, $(N_H^0, N_M^0, N_{Mw}^0) = \left(\frac{\Pi_H}{\sigma_H}, \frac{\Pi_M}{\sigma_M - qk\mu_M}, \frac{\Pi_{Mw}}{\sigma_M - k\mu_{Mw}}\right)$. The control reproduction number of a disease outbreak is the average number of persons that can be infected by a single index case when introduced in a purely susceptible population in the presence of control measures. A control measure is effective if the control reproduction number is less than one, otherwise it is ineffective. To determine $\mathcal{R}_c$, we shall adopt the next generation matrix approach introduced by Diekmann et al. (2010), where the reproduction number is found to be the spectral radius of a next generation matrix. If we write (1) in the form

$$X'_i(t) = \mathcal{F}_i(x) - \mathcal{V}_i(x) \quad (3)$$

where $\mathcal{F}_i(x)$ are the terms for the rate of appearance of new infections in compartment i , while $\mathcal{V}_i(x)$ are the terms for the rate of transfer of individuals into and out of compartment i by any other means including death, then the next generation matrix is given by $\mathcal{K} = FV^{-1}$, where $F = \frac{\partial \mathcal{F}(x)}{\partial x}|_{E_0}$ and $V = \frac{\partial \mathcal{V}(x)}{\partial x}|_{E_0}$ and the control reproduction number is therefore the spectral radius of FV^{-1} : $\mathcal{R}_c = \rho(FV^{-1})$.

Theorem 1. *The next generation matrix of the model is of the form*

$$\mathcal{K} = \begin{pmatrix} 0 & \mathcal{K}_{MH} & \mathcal{K}_{MwH} \\ \mathcal{K}_{HM} & 0 & 0 \\ \mathcal{K}_{HMw} & 0 & 0 \end{pmatrix} \quad (4)$$

and the control reproduction number is

$$\mathcal{R}_C = \sqrt{\mathcal{K}_{MH}\mathcal{K}_{HM} + \mathcal{K}_{MwH}\mathcal{K}_{HMw}} \quad (5)$$

where: $\mathcal{K}_{HM}$ = the number of wolbachia-free mosquitoes that one infectious human can infect throughout his infectious lifetime, when introduced in a purely susceptible wolbachia-free mosquito population,

$\mathcal{K}_{HMw}$ = the number of wolbachia-carrier mosquitoes that one infectious human can infect throughout his infectious lifetime, when introduced in a purely susceptible wolbachia-carrier mosquito population,

$\mathcal{K}_{MH}$ = the number of humans that one infectious wolbachia-free mosquito can infect throughout its infectious lifetime, when introduced in a purely susceptible human population,

$\mathcal{K}_{MwH}$ = the number of humans that one infectious wolbachia-carrier mosquito can infect throughout its infectious lifetime, when introduced in a purely susceptible human population, with

$$\begin{aligned} \mathcal{K}_{HM} &= \frac{\beta_H b_1 \alpha_{HM} \Pi_M}{(\sigma_M - qk\mu_M)(\beta_H + \sigma_H)(\gamma + \sigma_H + \sigma'_H)}, \\ \mathcal{K}_{HMw} &= \frac{\beta_H b_2 \alpha_{HMw} \Pi_{Mw}}{(\sigma_M - k\mu_{Mw})(\beta_H + \sigma_H)(\gamma + \sigma_H + \sigma'_H)}, \\ \mathcal{K}_{MH} &= \frac{\beta_M b_1 \alpha_{MH} \Pi_H}{\sigma_H \sigma_M (\beta_M + \sigma_M)}, \quad \mathcal{K}_{MwH} = \frac{\beta_{Mw} b_2 \alpha_{MwH} \Pi_H}{\sigma_H \sigma_M (\beta_{Mw} + \sigma_M)}. \end{aligned}$$

Proof. The shape of the next generation matrix (4) is informed by the major assumptions made in the model. It is assumed that humans can transmit zika virus to wolbachia-free and wolbachia-carrier mosquitoes, and vice versa. Moreover, we have that

$$\mathcal{F}_i = \begin{pmatrix} b_1 \alpha_{MH} I_M S_H + b_2 \alpha_{MwH} I_{Mw} S_H \\ 0 \\ b_1 \alpha_{HM} S_M(t) I_H \\ 0 \\ b_2 \alpha_{HMw} S_{Mw}(t) I_H \\ 0 \end{pmatrix} \text{ and } \mathcal{V}_i = \begin{pmatrix} (\beta_H + \sigma_H) E_H, \\ -\beta_H E_H + (\gamma + \sigma_H + \sigma'_H) I_H, \\ (\beta_M + \sigma_M) E_M(t), \\ -\beta_M E_M(t) + \sigma_M I_M(t), \\ (\beta_{Mw} + \sigma_M) E_{Mw}(t), \\ -\beta_{Mw} E_{Mw}(t) + \sigma_M I_{Mw}(t) \end{pmatrix}$$

from which we obtain

$$F = \begin{pmatrix} 0 & 0 & 0 & b_1 \alpha_{MH} S_H^0 & 0 & b_2 \alpha_{MwH} S_H^0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b_1 \alpha_{HM} S_M^0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & b_2 \alpha_{HMw} S_{Mw}^0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} \beta_H + \sigma_H & 0 & 0 & 0 & 0 & 0 \\ -\beta_H & \gamma + \sigma_H + \sigma'_H & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_M + \sigma_M & 0 & 0 & 0 \\ 0 & 0 & -\beta_M & \sigma_M & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_{Mw} + \sigma_M & 0 \\ 0 & 0 & 0 & 0 & -\beta_{Mw} & \sigma_M \end{pmatrix}$$

Then, with F and V , the next generation matrix is

$$\mathcal{K} = \begin{pmatrix} 0 & 0 & \frac{\beta_M b_1 \alpha_{MH} S_H^0}{\sigma_M (\beta_M + \sigma_M)} & \frac{b_1 \alpha_{MH} S_H^0}{\sigma_M} & \frac{\beta_{Mw} b_2 \alpha_{MwH} S_H^0}{\sigma_M (\beta_{Mw} + \sigma_M)} & \frac{b_2 \alpha_{MwH} S_H^0}{\sigma_M} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_H b_1 \alpha_{HM} S_M^0}{(\beta_H + \sigma_H)(\gamma + \sigma_H + \sigma'_H)} & \frac{b_1 \alpha_{HM} S_M^0}{\gamma + \sigma_H + \sigma'_H} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_H b_2 \alpha_{HMw} S_{Mw}^0}{(\beta_H + \sigma_H)(\gamma + \sigma_H + \sigma'_H)} & \frac{b_2 \alpha_{HMw} S_{Mw}^0}{\gamma + \sigma_H + \sigma'_H} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

We can recover (4) by pre- and post-multiplying the next generation matrix above using an auxiliary matrix of the form $A = \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \end{pmatrix}^T$ to get

$$\mathcal{K}_s = A \mathcal{K} A^T = \begin{pmatrix} 0 & \frac{\beta_M b_1 \alpha_{MH} S_H^0}{\sigma_M (\beta_M + \sigma_M)} & \frac{\beta_{Mw} b_2 \alpha_{MwH} S_H^0}{\sigma_M (\beta_{Mw} + \sigma_M)} \\ \frac{\beta_H b_1 \alpha_{HM} S_M^0}{(\beta_H + \sigma_H)(\gamma + \sigma_H + \sigma'_H)} & 0 & 0 \\ \frac{\beta_H b_2 \alpha_{HMw} S_{Mw}^0}{(\beta_H + \sigma_H)(\gamma + \sigma_H + \sigma'_H)} & 0 & 0 \end{pmatrix}. \quad (6)$$

We see that (5) is the spectral radius of (6) or the control reproduction number of the disease. $\square$

3.2. Local asymptotic stability of the disease-free equilibrium

The linearization of the model system (1) around the equilibrium point E_0 gives the Jacobian matrix:

$$J(E_0) = \begin{pmatrix} -J_{11} & 0 & 0 & 0 & 0 & 0 & -J_{12} & 0 & 0 & -J_{13} \\ 0 & -J_{21} & 0 & 0 & 0 & 0 & J_{22} & 0 & 0 & J_{23} \\ 0 & J_{31} & -J_{32} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & J_{41} & -J_{42} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -J_{51} & 0 & -J_{52} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & J_{61} & 0 & 0 & -J_{62} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & J_{71} & -J_{72} & 0 & 0 & 0 \\ 0 & 0 & -J_{81} & 0 & 0 & 0 & 0 & -J_{82} & 0 & 0 \\ 0 & 0 & J_{91} & 0 & 0 & 0 & 0 & 0 & -J_{92} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & J_{101} & -J_{102} \end{pmatrix} \quad (7)$$

where:

$J_{11} = \sigma_H, J_{12} = b_1\alpha_{MH}S_H^0, J_{13} = b_2\alpha_{MwH}S_H^0, J_{21} = (\beta_H + \sigma_H), J_{22} = b_1\alpha_{MH}S_H^0, J_{23} = b_2\alpha_{MwH}S_H^0, J_{31} = \beta_H, J_{32} = (\gamma + \sigma_H + \sigma'_H), J_{41} = \gamma, J_{42} = \sigma_H, J_{51} = b_1\alpha_{HM}S_M^0, J_{52} = (\sigma_M - qk\mu_M), J_{61} = b_1\alpha_{HM}S_M^0, J_{62} = (\beta_M + \sigma_M), J_{71} = \beta_M, J_{72} = \sigma_M, J_{81} = b_2\alpha_{HMw}S_{Mw}^0, J_{82} = (\sigma_M - k\mu_{Mw}), J_{91} = b_2\alpha_{HMw}S_{Mw}^0, J_{92} = (\beta_{Mw} + \sigma_M), J_{101} = \beta_{Mw}, J_{102} = \sigma_M.$ The eigenvalues of $J(E_0)$ are $-J_{11} < 0, -J_{42} < 0, -J_{52} < 0, -J_{82} < 0$ and the eigenvalues of the 6×6 submatrix $J'(E_0)$:

$$J'(E_0) = \begin{pmatrix} -(\beta_H + \sigma_H) & 0 & 0 & b_1\alpha_{MH}S_H^0 & 0 & b_2\alpha_{MwH}S_H^0 \\ \beta_H & -(\gamma + \sigma_H + \sigma'_H) & 0 & 0 & 0 & 0 \\ 0 & b_1\alpha_{HM}S_M^0 & -(\beta_M + \sigma_M) & 0 & 0 & 0 \\ 0 & 0 & \beta_M & -\sigma_M & 0 & 0 \\ 0 & b_2\alpha_{HMw}S_{Mw}^0 & 0 & 0 & -(\beta_{Mw} + \sigma_M) & 0 \\ 0 & 0 & 0 & 0 & \beta_{Mw} & -\sigma_M \end{pmatrix}.$$

It is easy to transform the submatrix $J'(E_0)$ to a lower triangular matrix to obtain

$$J''(E_0) = \begin{pmatrix} (\beta_H + \sigma_H)(\mathcal{R}_C^2 - 1) & 0 & 0 & 0 & 0 & 0 \\ \beta_H & -(\gamma + \sigma_H + \sigma'_H) & 0 & 0 & 0 & 0 \\ 0 & b_1\alpha_{HM}S_M^0 & -(\beta_M + \sigma_M) & 0 & 0 & 0 \\ 0 & 0 & \beta_M & -\sigma_M & 0 & 0 \\ 0 & b_2\alpha_{HMw}S_{Mw}^0 & 0 & 0 & -(\beta_{Mw} + \sigma_M) & 0 \\ 0 & 0 & 0 & 0 & \beta_{Mw} & -\sigma_M \end{pmatrix}. \quad (8)$$

All the eigenvalues of $J''(E_0)$ are negative or have negative real part if $\mathcal{R}_C^2 < 1$, or equivalently when $\mathcal{R}_C < 1$, where

$$\begin{aligned} \mathcal{R}_C^2 &= \frac{\beta_H b_2 \beta_{Mw} \alpha_{MwH} b_2 \alpha_{HMw} S_H^0 S_{Mw}^0}{\sigma_M (\beta_H + \sigma_H) (\beta_{Mw} + \sigma_M) (\gamma + \sigma_H + \sigma'_H)} \\ &\quad + \frac{\beta_H b_1 \beta_M \alpha_{MH} b_1 \alpha_{HM} S_H^0 S_M^0}{\sigma_M (\beta_H + \sigma_H) (\beta_M + \sigma_M) (\gamma + \sigma_H + \sigma'_H)}. \end{aligned}$$

Therefore, the disease-free equilibrium E_0 is locally asymptotically stable if $\mathcal{R}_C < 1$. This implies that zika virus disease can be eliminated from the zika-endemic area, when $\mathcal{R}_C < 1$, by using this control measure, if the initial sizes of the compartments are within the basin of attraction of the disease-free equilibrium.

3.3. Existence of endemic equilibrium

Let $E_1 = (S_H^*, E_H^*, I_H^*, R_H^*, S_M^*, E_M^*, I_M^*, S_{Mw}^*, E_{Mw}^*, I_{Mw}^*)$ where

$$S_H^* = \frac{\Pi_H}{b_1\alpha_{MH}I_M^* + b_2\alpha_{MwH}I_{Mw}^* + \sigma_H}, \quad E_H^* = \frac{b_1\alpha_{MH}I_M^* + b_2\alpha_{MwH}I_{Mw}^*}{\beta_H + \sigma_H}, \quad I_H^* = \frac{\beta_H E_H^*}{\gamma + \sigma_H + \sigma_H'},$$

$$R_H^* = \frac{\gamma I_H^*}{\sigma_H}, \quad S_M^* = \frac{\Pi_M + qk\mu_M N_M^*}{b_1\alpha_{HM}I_H^* + \sigma_M}, \quad E_M^* = \frac{b_1\alpha_{HM}S_M^* I_H^*}{(\beta_M + \sigma_M)},$$

$$I_M^* = \frac{b_1\beta_M\alpha_{HM}(\Pi_M + qk\mu_M N_M^*)I_H^*}{\sigma_M(\beta_M + \sigma_M)(b_1\alpha_{HM}I_H^* + \sigma_M)}, \quad S_{Mw}^* = \frac{\Pi_{Mw} + qk\mu_{Mw} N_{Mw}^*}{b_1\alpha_{HMw}I_H^* + \sigma_M},$$

$$E_{Mw}^* = \frac{b_2\alpha_{HMw}S_{Mw}^* I_H^*}{(\beta_{Mw} + \sigma_M)}, \quad I_{Mw}^* = \frac{b_2\beta_{Mw}\alpha_{HMw}(\Pi_{Mw} + k\mu_{Mw} N_{Mw}^*)I_H^*}{\sigma_M(\beta_{Mw} + \sigma_M)(b_2\alpha_{HMw}I_H^* + \sigma_M)},$$

$$N_M^* = \frac{\Pi_M}{\sigma_M - qk\mu_M}, \quad N_{Mw}^* = \frac{\Pi_{Mw}}{\sigma_M - k\mu_{Mw}}, \quad N_H^* = \frac{\Pi_H - \sigma_H' I_H^*}{\sigma_H}.$$

This means that E_1 satisfies the following set of equations:

$$\Pi_H - b_1\alpha_{MH}S_H I_M - b_2\alpha_{MwH}I_{Mw}S_H - \sigma_H S_H = 0, \quad (9)$$

$$b_1\alpha_{MH}I_M S_H + b_2\alpha_{MwH}I_{Mw}S_H - (\beta_H + \sigma_H)E_H = 0, \quad (10)$$

$$\beta_H E_H - (\gamma + \sigma_H + \sigma_H')I_H = 0, \quad (11)$$

$$\gamma I_H - \sigma_H R_H = 0, \quad (12)$$

$$\Pi_M + qk\mu_M N_M - b_1\alpha_{HM}S_M(t)I_H - \sigma_M S_M(t) = 0, \quad (13)$$

$$b_1\alpha_{HM}S_M(t)I_H - (\beta_M + \sigma_M)E_M(t) = 0, \quad (14)$$

$$\beta_M E_M(t) - \sigma_M I_M(t) = 0, \quad (15)$$

$$\Pi_{Mw} + k\mu_{Mw} N_{Mw} - b_2\alpha_{HMw}S_{Mw}(t)I_H - \sigma_M S_{Mw}(t) = 0, \quad (16)$$

$$b_2\alpha_{HMw}S_{Mw}(t)I_H - (\beta_{Mw} + \sigma_M)E_{Mw}(t) = 0, \quad (17)$$

$$\beta_{Mw} E_{Mw}(t) - \sigma_M I_{Mw}(t) = 0, \quad (18)$$

Let I_M^* and I_{Mw}^* be written in the forms $I_M^* = \frac{A_1 I_H^*}{A_2 I_H^* + A_3}$ and $I_{Mw}^* = \frac{B_1 I_H^*}{B_2 I_H^* + B_3}$, respectively, where, $A_1 = b_1\beta_M\alpha_{HM}(\Pi_M + qk\mu_M N_M^*)$, $A_2 = \sigma_M(\beta_M + \sigma_M)b_1\alpha_{HM}$, $A_3 = \sigma_M^2(\beta_M + \sigma_M)$, $B_1 = b_2\beta_{Mw}\alpha_{HMw}(\Pi_{Mw} + k\mu_{Mw} N_{Mw}^*)$, $B_2 = \sigma_M(\beta_{Mw} + \sigma_M)b_2\alpha_{HMw}$, $B_3 = \sigma_M^2(\beta_{Mw} + \sigma_M)$. Substituting these into (11) and simplifying, we obtain

$$\frac{\beta_H \Pi_H}{\beta_H + \sigma_H} \frac{G_1 I_H^{*2} + G_2 I_H^*}{G_3 I_H^{*2} + G_4 I_H^* + G_5} - (\gamma + \sigma_H + \sigma_H')I_H^* = 0 \quad (19)$$

where,

$$G_1 = b_1\alpha_{MH}A_1B_2 + b_2\alpha_{MwH}B_1A_2, \quad G_2 = b_1\alpha_{MH}A_1B_3 + b_2\alpha_{MwH}B_1A_3, \\ G_3 = G_1 + \sigma_H A_2B_2, \quad G_4 = G_2 + \sigma_H(A_2B_3 + A_3B_2), \quad G_5 = \sigma_H A_3B_3$$

Rearranging (19) gives the cubic equation

$$-C_1 I_H^{*3} + C_2 I_H^{*2} + C_3 I_H^* = 0 \quad (20)$$

where $C_1 = (\beta_H + \sigma_H)(\gamma + \sigma_H + \sigma'_H)G_3$, $C_2 = (\beta_H \Pi_H G_1 - (\beta_H + \sigma_H)(\gamma + \sigma_H + \sigma'_H))G_4$, $C_3 = (\beta_H + \sigma_H)(\gamma + \sigma_H + \sigma'_H)[\mathcal{R}_C^2 - 1]$. The trivial solution, $I_H^* = 0$, of (20) corresponds to the disease-free equilibrium, which is locally asymptotically stable if $\mathcal{R}_C < 1$. Applying the Descartes rule of signs, we have

- case I: If $C_2 < 0$ and $\mathcal{R}_C > 1$, a unique endemic equilibrium exists in the model.
- case II: If $C_2 > 0$ and $\mathcal{R}_C > 1$, a unique endemic equilibrium exists in the model.
- case III: If $C_2 < 0$ and $\mathcal{R}_C < 1$, no endemic equilibrium exists in the model.
- case IV: If $C_2 > 0$ and $\mathcal{R}_C < 1$, two positive endemic equilibria exist in the model.

The first two cases indicate the absence of backward bifurcation in the model, since backward bifurcation involves at least two endemic equilibria. Case III, which is rare, indicates that only disease-free equilibrium exists in the model; it is an indication that the disease has been totally eradicated in the population. Case IV may be an indication of backward bifurcation in the model.

3.4. Global asymptotic stability of the disease-free equilibrium

We investigate the global stability of the disease-free equilibrium by using the two conditions (H1) and (H2) from Castillo-Chavez et al. (2012), which must be satisfied for $\mathcal{R}_C < 1$. To do this, we rewrite the model equations in the form

$$\frac{dX}{dt} = F_1(X, Y) \quad (21)$$

$$\frac{dY}{dt} = F_2(X, Y), F_2(X, 0) \geq 0, \quad (22)$$

where $X = (S_H, R_H, S_M, S_{Mw})^T$ and $Y = (E_H, I_H, E_M, I_M, E_{Mw}, I_{Mw})^T$ denote the uninfected and infected populations, respectively. The first condition (H1) requires that for $\frac{dX}{dt} = F_1(X, 0)$, the disease-free equilibrium

$E_0 = \left(\frac{\Pi_H}{\sigma_H}, 0, \frac{\Pi_M}{\sigma_M - qk\mu_M}, \frac{\Pi_{Mw}}{\sigma_M - k\mu_{Mw}} \right)$ must be globally asymptotically stable. The second condition (H2) requires that $\bar{F}_2(X, Y) := AY - F_2(X, Y) \geq 0$, where A is the Jacobian matrix of $F_2(X, Y)$ evaluated at the disease-free equilibrium. Using the first condition (H1), we solve

$$\frac{dX}{dt} = F_1(X, 0) = \begin{pmatrix} \Pi_H - \sigma_H S_H \\ -\sigma_H R_H \\ \Pi_M + qk\mu_M S_M - \sigma_M S_M \\ \Pi_{Mw} + k\mu_{Mw} S_{Mw} - \sigma_M S_{Mw} \end{pmatrix}. \quad (23)$$

The solution to (23) is

$$\begin{aligned} S_H(t) &= \frac{\Pi_H}{\sigma_H} (1 - e^{-\sigma_H t}) + S_H(0)e^{-\sigma_H t} \\ R_H(t) &= R_H(0)e^{-\sigma_H t} \\ S_M(t) &= \frac{\Pi_M}{\sigma_M - qk\mu_M} (1 - e^{(\sigma_M - qk\mu_M)t}) + S_M(0)e^{(\sigma_M - qk\mu_M)t} \\ S_{Mw}(t) &= \frac{\Pi_{Mw}}{\sigma_M - k\mu_{Mw}} (1 - e^{(\sigma_M - k\mu_{Mw})t}) + S_{Mw}(0)e^{(\sigma_M - k\mu_{Mw})t}. \end{aligned} \quad (24)$$

Therefore, as

$$t \rightarrow \infty, (S_H(t), R_H(t), S_M(t), S_{Mw}(t)) \rightarrow \left(\frac{\Pi_H}{\sigma_H}, 0, \frac{\Pi_M}{\sigma_M - qk\mu_M}, \frac{\Pi_{Mw}}{\sigma_M - k\mu_{Mw}} \right)$$

irrespective of the size of the initial populations.

Therefore, $E_0 = \left(\frac{\Pi_H}{\sigma_H}, 0, \frac{\Pi_M}{\sigma_M - qk\mu_M}, \frac{\Pi_{Mw}}{\sigma_M - k\mu_{Mw}} \right)$ is globally asymptotically stable. For the second condition, we have that

$$A = \begin{pmatrix} -(\beta_H + \sigma_H) & 0 & 0 & b_1 \alpha_{MH} S_H^0 & 0 & b_2 \alpha_{MwH} S_H^0 \\ \beta_H & -(\gamma + \sigma_H + \sigma'_H) & 0 & 0 & 0 & 0 \\ 0 & b_1 \alpha_{HM} S_M^0 & -(\beta_M + \sigma_M) & 0 & 0 & 0 \\ 0 & 0 & \beta_M & -\sigma_M & 0 & 0 \\ 0 & b_2 \alpha_{HMw} S_{Mw}^0 & 0 & 0 & -(\beta_{Mw} + \sigma_M) & 0 \\ 0 & 0 & 0 & 0 & \beta_{Mw} & -\sigma_M \end{pmatrix}$$

and

$$F_2(X, Y) = \begin{pmatrix} b_1 \alpha_{MH} I_M S_H + b_2 \alpha_{MwH} I_{Mw} S_H - (\beta_H + \sigma_H) E_H(t) \\ \beta_H E_H - (\gamma + \sigma_H + \sigma'_H) I_H(t) \\ b_1 \alpha_{HM} S_M(t) I_H - (\beta_M + \sigma_M) E_M(t) \\ \beta_M E_M(t) - \sigma_M I_M(t), \\ b_2 \alpha_{HMw} S_{Mw}(t) I_H - (\beta_{Mw} + \sigma_M) E_{Mw}(t) \\ \beta_{Mw} E_{Mw}(t) - \sigma_M I_{Mw}(t) \end{pmatrix}.$$

Then,

$$\bar{F}_2(X, Y) = \begin{pmatrix} (b_1\alpha_{MH}I_M + b_2\alpha_{MwH}I_{Mw})(S_H^0 - S_H(t)) \\ 0 \\ b_1\alpha_{HM}(t)I_H(S_M^0 - S_M(t)) \\ 0 \\ b_2\alpha_{HMw}(t)I_H(S_{Mw}^0 - S_{Mw}(t)) \\ 0 \end{pmatrix}.$$

This shows that $\bar{F}_2(X, Y) \geq 0$, since from (24), we have that $S_H(t) \leq S_H^0$, $S_M(t) \leq S_M^0$, $S_{Mw}(t) \leq S_{Mw}^0$. Hence, the disease-free equilibrium, E_0 , is globally asymptotically stable. This result confirms the existence of a unique endemic equilibrium when $\mathcal{R}_C > 1$. Therefore, backward bifurcation does not occur in the model.

4. Numerical simulations

Table 1. Parameter values used in this model

Parameter	Value	Source	Parameter	Value	Source
Π_H	250	assumed	σ'_H	0.00001	assumed
Π_M	500	assumed	σ_H	0.0005	assumed
α_{HM}	0.175	Gao et al.	Π_{Mw}	250	assumed
α_{HMw}	0.0005	assumed	μ_M	0.03	assumed
μ_{Mw}	0.03	assumed	σ_M	0.15	Ndii et al.
β_H	$\frac{1}{3}$	Kucharski et al.	κ	0.5	Ndii et al.
b_1	0.0075	assumed	γ	0.5	assumed
b_2	0.7	assumed	α_{MwH}	0.001	assumed
β_M	1/9	Dantas et al.	α_{MH}	0.0175	assumed
β_{Mw}	1/18	assumed	q	0.017	assumed

Numerical simulations are performed in this section to visualize the dynamics of zika virus disease in the presence of wolbachia-carrier mosquitoes used for disease control. The parameter values used in the simulations are given in Table 1. The initial solutions used are $S_H^0 = 1500$, $E_H^0 = 200$, $I_H^0 = 500$, $R_H^0 = 100$, $S_M^0 = 1500$, $E_M^0 = 300$, $I_M^0 = 400$, $S_{Mw}^0 = 2400$, $E_{Mw}^0 = 0$, $I_{Mw}^0 = 0$. The results of the numerical simulation are presented graphically in Figures 1–4. In Figure 2, we see that the wolbachia-carrier mosquitoes suppress and replace the wild wolbachia-free mosquitoes in the wild. This replacement is achieved through cytoplasmic incompatibility, which prevents eggs of wolbachia-free mosquitoes from hatching. The effect of cytoplasmic incompatibility is visible in Figure 3, where the size

Figure 1. Total population of mosquitoes

Figure 2. Mosquitoes susceptible to zika virus

Figure 3. Mosquitoes exposed to zika virus

Figure 4. Mosquitoes that are infectious

of the population of wolbachia-free mosquitoes that are susceptible to the virus is prevented from increasing. The same feature is seen in Figure 3 and Figure 4, where the wolbachia-free mosquitoes that are exposed to the zika virus and those that are infectious are seen to diminish over time, thereby reducing the rate at which zika virus spreads in the population.

5. Conclusion

In this paper, we have modeled the use of wolbachia-carrier *Aedes aegypti* mosquitoes to stop the spread of zika virus disease. We showed that the disease-free equilibrium of the model is both locally and globally asymptotically stable when the control reproduction number $\mathcal{R}_C < 1$. Essentially, the global stability of the disease-free equilibrium entails that any sudden outbreak of zika virus disease will eventually subside over time, even when the initial sizes of the infected human and mosquito populations are high. Therefore, we conclude that this bio-control method is an effective and efficient method for controlling the spread of zika virus disease and other mosquito-borne diseases such as dengue, yellow fever and malaria.

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