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## Interaction between Aedes aegypti Mosquitoes With and Without Wolbachia Bacteria

[Peri Turnip, Dhita S. Y. S. Waluyo, Asep K. Supriatna, and Edy Soewono]

Abstract— Dengue disease is still a serious problem in many tropical countries which risks nearly 40% of the world population. There are some intervention programs to eliminate the disease, however they seem unsuccessful so far. Many creative solutions are explored to overcome the disease since some conventional solution, such as spraying the mosquitoes with insecticides, have created more problems (e.g. resistance to the drug). The introduction of wolbachia-infected mosquitoes into the wild Aedes aegypti population is among the new method to control the transmission of the disease. In this paper we develop a mathematical model to investigate the possibility of non coexistence of these two mosquitoes populations. The analysis of the model shows that the introduction of wolbachia-infected mosquitoes is promising, since it can replace the natural population once they are release into the wild.

*Keywords*—dengue, *Aedes aegypti*, *wolbachia*-infected, coexistence equilibrium, competitive-exclusion equilibrium.

## I. Introduction

Dengue disease, which is transmitted to human by the female *Aedes aegypti* mosquitoes, is still a serious problem in many tropical countries. It risks nearly 40% of the world population and more than 500 million people are infected by the disease every year [WHO - Western Pacific Region, 2014] There are some intervention programs to eliminate the disease, however they seem unsuccessful so far. With vaccines available to protect people from vector-borne disease, it is natural to focus on mosquito control strategy. Not all mosquito controls are effective. The excessive use of insecticide is known create resistance [2,3,4,5]. This resistance to the insecticide sometimes causes an unwanted consequences showing that the program is no more effective [6]

There are some exploration to find an alternative way in overcome the dengue. The introduction of wolbachia-infected mosquitoes into the wild Aedes aegypti population is among the new method to control the transmission of the disease and some experimental researches have been undertaken in proving the potential and the strength of this new method [7,8,9]. Some mathematical approach are also have been done to show the insight of the new method which otherwise could not been able to assess [10,11,16]. The works show that the method (irrespective the strain of the wolbachia) can effectively reduce dengue transmission in a relatively low or moderate dengue transmission [10,11] if the wolbachiainfected mosquitoes can dominate the natural mosquitoes. The work in [16] develop a mathematical model to study the domination between natural and introduced Aedes aegypti mosquitoes. Their model has lump the aquatic stages of the Aedes life cycle.

In this paper we develop a mathematical model to investigate the possibility of non coexistence of these two mosquitoes populations (*wolbachia*-infected mosquitoes and natural mosquitoes) by considering a more complex aquatic stage of the life cycle, i.e. we consider the egg and larva compartments in the mosquitoes aquatic life cycle. To manage the paper we introduce the assumptions and notations used in the model and the model formulation in Section 2. It then followed by the analysis of the model in Section 3, where a standard analysis in mathematical epidemiology is done, i.e. computing the basic reproduction number of the disease, showing the existence of the non-endemic and endemic equilibria, their stability and its relation to the basic reproduction number. Section 4 present a numerical solution to show the behavior of the solution of the model. Finally Section 5 summarizes the results and advises the venue for future research in this area.

# п. Mathematical Model

There are some different views regarding the effect of the introduction of wolbachia into *Aedes aegypti* mosquitoes related to dengue transmission. Some are believe that the bacteria damaged the mosquito proboscis so that they are unable to penetrate human skin, and hence cannot be infected or/and transmit dengue disease [12]. Others believe that there is a *Cytoplasmic Incompatibility* (CI) induced by endosymbiotic *Wolbachia* that make a *wolbachia*-infected mosquitoes cannot be infected by dengue and make the developmental failure of the mosquitoes offspring [13,14] and can be used to sterile males [15]. The authors in [16] summarize the effect of CI in four possibilities occurrences and we make the following assumptions based on this fact, i.e. to formulate our model.

#### **Model Assumptions:**

- 1. Wolbachia-infected males and Wolbachia-infected females produce both infected and uninfected offspring with ratio  $\eta\%$  uninfected and  $(1-\eta)\%$  infected by the wolbachia
- 2. Non-*Wolbachia* males and *Wolbachia*-infected females produce both *Wolbachia*-infected and uninfected offspring with ratio  $\gamma$ % uninfected and  $(1-\gamma)$ % infected by the *wolbachia*
- 3. Non-*Wolbachia* males and non-*Wolbachia* females produce 100% uninfected offspring.
- 4. *Wolbachia*-infected males and non-*Wolbachia* females cannot produce offspring successfully, 100% of the offspring die
- 5. There are three stages of the mosquitoes life cycle: two stages in aquatic phase, i.e. egg and larva, and one stage of adult phase
- 6. There are six compartments of the mosquitoes:  $E_1, E_2, L_1, L_2, M_1$ , and  $M_2$  representing the uninfected and *wolbachia*-infected eggs, larva, and adult mosquitoes, respectively.



| TABLE 1. NOTATIONS AND THEIR DECRIPTIONS |
|--|
|--|

| Notation                   | Description  |  |  |
|----------------------------|--|--|--|
| <i>E</i> <sub>1</sub>      | Normal (uninfected) mosquito's eggs  |  |  |
| <i>E</i> <sub>2</sub>      | Infected mosquito's eggs   |  |  |
| L <sub>1</sub>             | Normal (uninfected) mosquito's larva   |  |  |
| L <sub>2</sub>             | Infected mosquito's larva  |  |  |
| <i>M</i> <sub>1</sub>      | Normal mosquitoes  |  |  |
| <i>M</i> <sub>2</sub>      | Infected mosquitoes  |  |  |
| A <sub>2</sub>             | Wolbachia-infected mosquito recruitment rate   |  |  |
| λ                          | Normal egg recruitment   |  |  |
| $\lambda_1$<br>$\lambda_2$ | Infected egg recruitment   |  |  |
| $\beta_1$                  | Egg hatching rate to larva   |  |  |
| $\alpha_1$                 | Larva aging rate to adult mosquitoes   |  |  |
| $\mu_{l}$                  | Natural death rate of normal mosquitoes  |  |  |
| $\mu_2$                    | Natural death rate of infected mosquitoes  |  |  |
| a                          | Larval competition rate  |  |  |
| η                          | Proportion of <i>Wolbachia</i> -infected males and <i>Wolbachia</i> -infected females produce new uninfected offspring |  |  |
| Ŷ                          | Proportion of Non-Wolbachia males and Wolbachia-<br>infected females produce new uninfected offspring                  |  |  |

To formulate the model we use the notations described in Table 1 and a digramatic transmission in Figure 1.

Using these notations and the diagrammatic *wolbachia* transmission shown in Figure 1, we obtain the model of our *wolbachia* transmission in the mosquitoes in the form of a system of six differential equations.

$$\frac{dE_{1}}{dt} = \frac{1}{2} \frac{\lambda_{1} M_{1}^{3}}{(M_{1} + M_{2})^{2}} + \frac{1}{2} \frac{\eta \lambda_{2} M_{1} M_{2}^{2}}{(M_{1} + M_{2})^{2}} + \frac{1}{2} \frac{\eta \lambda_{2} M_{2}^{2}}{(M_{1} + M_{2})^{2}} - \beta_{1} E_{1}$$

$$\frac{dL_{1}}{dt} = \beta_{1} E_{1} - \alpha_{1} L_{1} - a_{1} L_{1} (L_{1} + L_{2})$$

$$\frac{dM_{1}}{dt} = \alpha_{1} L_{1} - \mu_{1} M_{1}$$

$$\frac{dE_{2}}{dt} = \frac{1}{2} \frac{(1 - \eta) \lambda_{2} M_{1} M_{2}^{2}}{(M_{1} + M_{2})^{2}} + \frac{1}{2} \frac{(1 - \gamma) \lambda_{2} M_{2}^{2}}{(M_{1} + M_{2})^{2}} - \beta_{1} E_{2}$$

$$\frac{dL_{2}}{dt} = \beta_{1} E_{2} - \alpha_{1} L_{2} - a_{1} L_{2} (L_{1} + L_{2})$$

$$\frac{dM_{2}}{dt} = A_{2} + \alpha_{1} L_{2} - \mu_{2} M_{2}$$
(1)

## ш. Model Analysis

In this section we provide a standard analysis in mathematical epidemiology, i.e. computing the basic reproduction number of the disease ( $R_0$ ), showing the existence of the non-endemic and endemic equilibria, their

stability and its relation to the basic reproduction number. We look at two different cases, i.e. (a) natural case  $(A_2=0)$  when there is no *wolbachia*-infected mosquito recruitment and (b) artificial case  $(A_2 \neq 0)$  when there is *wolbachia*-infected mosquitoes introduction to the wild.

#### Equilibria for $A_2 = 0$

We obtain two equilibria, the normal equilibrium  $X_1 = (E_1, 0, L_1, 0, M_1, 0)$  and the coexistence equilibrium  $X_3 = (E_1^*, E_2^*, L_1^*, L_2^*, M_1^*, M_2^*)$ . In the first equilibrium all normal mosquitoes compartments exist and all infected mosquitoes vanish, where the size of each compartment is given in (2). In the second equilibrium both normal and infected mosquitoes are present where the size of each compartment cannot be easily shown explicitly.

$$E_{1} = \frac{1}{4} \frac{\lambda_{1} \alpha_{1}^{2} (\lambda_{1} - 2\mu_{1})}{a_{1} \mu_{1}^{2} \beta_{1}},$$

$$L_{1} = \frac{1}{2} \frac{\alpha_{1} (\lambda_{1} - 2\mu_{1})}{\alpha_{1} \mu_{1}}, \quad (2)$$

$$M_{1} = \frac{1}{2} \frac{\alpha_{1}^{2} (\lambda_{1} - 2\mu_{1})}{a_{1} \mu_{1}^{2}}$$

1

It is easy to see that the condition for the existence of normal mosquito population is its egg recruitment rate should be twice larger than its natural death rate, i.e.  $\frac{1}{2}\lambda_1 > \mu_1$ , which is plausable.

Here we also perform dynamic analysis for the equilibria. If we substitute the equilibrium point (2) into the Jacobian

$$\frac{1}{2} \frac{\lambda_{i} M_{i}^{j}}{(M_{1} + M_{2})^{2}} + \frac{1}{2} \frac{\eta \lambda_{i} M_{i} M_{2}^{2}}{(M_{1} + M_{2})^{2}} + \frac{1}{2} \frac{\eta \lambda_{i} M_{2} M_{2}^{2}}{(M_{1} + M_{2})^{2}} \xrightarrow{\beta_{i} E_{1}} \xrightarrow{\beta_{i} E_{1}} \xrightarrow{\alpha_{i} L_{1}} \xrightarrow{\alpha_{$$

Figure 1. Disease transmission diagram

matrix of Equation (1) then we have the matrix

$$\mathbf{f}_{1} = \begin{pmatrix} -\beta_{1} & 0 & \frac{1}{2}\lambda_{1} & 0 & 0 & -\lambda_{1} \\ \beta_{1} & -\alpha_{1} - \frac{\alpha_{1}(\lambda_{1} - 2\mu_{1})}{\mu_{1}} & 0 & 0 & -\frac{1}{2}\frac{\alpha_{1}(\lambda_{1} - 2\mu_{1})}{\mu_{1}} & 0 \\ 0 & \alpha_{1} & -\mu_{1} & 0 & 0 & 0 \\ 0 & 0 & 0 & -\beta_{1} & 0 & 0 \\ 0 & 0 & 0 & \beta_{1} & -\alpha_{1} - \frac{\alpha_{1}(\lambda_{1} - 2\mu_{1})}{\mu_{1}} & 0 \\ 0 & 0 & 0 & 0 & \alpha_{1} & -\mu_{1} \end{pmatrix}$$

Further from the Jacobian matrix  $J_1$  we obtain a characteristic polynomial in the form of



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$$p_1(X) = \frac{1}{4} \frac{1}{\mu_1^2} ((X + \beta_1)(2X\mu_1 + \alpha_1\lambda_1)(X + \mu_2)(q_1(X) + q_2(X)))$$

with  $q_1(X) = 2\mu_1 X^3 + (2\alpha_1\lambda_1 - 2\alpha_1\mu_1 + 2\beta_1\mu_1 + 2\mu_1^2)X^2$  and  $q_2(X) = 2((\lambda_1 - \mu_1)(\beta_1 + \mu_1)\alpha_1 + 2\beta_1\mu_1^2)X + \alpha_1\beta_1\mu_1(\lambda_1 - 2\mu_1).$ 

Again, if  $\lambda_1 - 2\mu_1 > 0$  all of the eigen values are negative giving the local stability of the normal equilibrium.

An example show that when there is no *wolbachia*-infected mosquitoes are introduced into natural system, with

 $\lambda_1 = 5, \lambda_2 = 4, \alpha_1 = 1/12, \beta_1 = 1/2, \alpha_1 = 0.1, \mu_1 = 1/30, \mu_2 = 1/15, \eta = 0.15, \gamma = 0.1$ 

we obtain three different equilibria:

$$X_1 = (E_1 = 770.8333, E_2 = 0, L_1 = 61.666,$$
  
 $L_2 = 0, M_1 = 154.1667, M_2 = 0)$ 

$$\begin{split} X_2 = (E_1 &= 12.95488975, \, E_2 &= 39.87044217, \, L_1 &= 3.884762048, \\ L_2 &= 11.95588566, \, M_1 &= 9.711905121, \, M_2 &= 14.94485708) \\ X_3 = (E_1 &= 11.37114447, \, E_2 &= 76.92422330, \, L_1 &= 2.652824286, \\ L_2 &= 17.94599024, \, M_1 &= 6.632060715, \, M_2 &= 22.43248781) \end{split}$$

In this case, by evaluating each Jacobian matrix it can be shown that the only stable equilibrium is  $X_1$  and  $X_3$ .

The following section provides a numerical example to illustrate the effect of *wolbachia*-infected mosquitoes introduction  $(A_2 \neq 0)$  on the stability/unstability of those equilibria and its consequences in term of dengue control. We can also expect some insight regarding the behavior of the co-existence equilibrium (since it is difficult to find analytically) and the possibility of the existence of complete replacement of natural mosquitoes by the introduce mosquitoes.

# **IV.** Numerical Simulation

For the simulation we use the following two data set of parameters values representing high rate and moderate rate *wolbachia*-infected mosquitoes introduction into the natural system:

(1). High rate introduction

$$A_2 = 1, \lambda_1 = 5, \lambda_2 = 4, \alpha_1 = 1/12, \beta_1 = 1/2, \alpha_1 = 0.1, \mu_1 = 1/30, \mu_2 = 1/15, \eta = 0.2, \gamma = 0.2$$

(2). Modest rate introduction

$$A_2 = 3/30, \lambda_1 = 5, \lambda_2 = 4, \alpha_1 = 1/12, \beta_1 = 1/2, \alpha_1 = 0.1, \mu_1 = 1/30,$$
  
$$\mu_2 = 1/15, \eta = 0.15, \gamma = 0.1$$

We note that the first data set is more favorable for the establishment of *wolbachia*-infected mosquitoes since it has a higher rate of recruitment and high proportion in inheriting *wolbachia* infection to their offspring. We expect that this can be confirmed in the following results of simulation.

#### Simulation in a high rate of introduction

Using the first data set of parameters we obtain three equilibria for Equation (1), i.e.:

$$\begin{split} X_1 &= (E_1 \ = \ 463.1802865, \ E_2 = 5.916744847, \ L_1 = 47.40971495, \\ L_2 &= \ 0.6056198736, \ M_1 = \ 118.5242874, \ M_2 = \ 15.75702484) \\ X_2 &= (E_1 \ = \ 52.11869128, \ E_2 = \ 39.35408543, \ L_1 = \ 11.95010468, \\ L_2 &= \ 9.023354752, \ M_1 = \ 29.87526171, \ M_2 = \ 26.27919344) \\ X_3 &= (E_1 \ = \ 26.92998374, \ E_2 = \ 87.67355324, \ L_1 = \ 5.527936356, \\ L_2 &= \ 17.99681080, \ M_1 = \ 13.81984089, \ M_2 = \ 37.49601350) \end{split}$$

We illustrate the stability of each equilibrium by giving different initial values close to the equilibrium as follows:  $I_1(0) = \{E_1(0) = 460, E_2(0) = 5, L_1(0) = 45, L_2(0) = 1, M_1(0) = 50, M_2(0) = 50\}$   $I_2(0) = \{E_1(0) = 40, E_2(0) = 50, L_1(0) = 10, L_2(0) = 10, M_1(0) = 20, M_2(0) = 20\}$  $I_3(0) = \{E_1(0) = 20, E_2(0) = 80, L_1(0) = 5, L_2(0) = 15, M_1(0) = 5, M_2(0) = 2\}$ 

Furthermore, we also show the orbit of Natural and *Wolbachia*-infected Mosquitoes in figure 5.

#### The first equilibrium $(X_1)$

Linearization of the system evaluated in this equilibrium gives six negative eigenvalues which means that the equilibrium is stable. Figure 2 show the trajectori of the solution from the initial value  $I_1(0)$  which close to  $X_1$ . The solution suggests a coexistence steady state with the natural population exceed the introduced population.

#### The second equilibrium $(X_2)$

Linearization of the system evaluated in this equilibrium gives six negative eigenvalues with one of them positive which means that the equilibrium is not stable. Figure 3 show the trajectori of the solution from the initial value  $I_2(0)$ . The solution suggests that the introduced *wolbachia*-infected mosquitoes out competes the natural mosquitoes population, which is a desirable condition in terms of dengue control problem.

#### The third equilibrium $(X_3)$

Linearization of the system evaluated in this equilibrium gives six negative eigenvalues which means that the equilibrium is stable. Figure 4 shows the trajectori of the solution from the initial value  $I_3(0)$ . The solution suggests a co-existence steady state with the natural population size below the size of the introduced population, which is better than the situation in Figure 2 in terms of dengue control problem.

#### Simulation in a modest rate of introduction

Using the second data set of parameters we obtain three equilibria for Equation (1), i.e.  $X_1 = (E_1 = 740.6344119, E_2 = 0.05050655604, L_1 = 60.43640712, L_2 = 0.004121378556, M_1 = 151.0910178, M_2 = 1.505151723)$   $X_2 = (E_1 = 11.10017185, E_2 = 32.00612639, L_1 = 3.674685034, L_2 = 10.59555071, M_1 = 9.186712585, M_2 = 14.74443838)$  $X_3 = (E_1 = 8.658414914, E_2 = 58.90338617, L_1 = 2.302651092, L_2 = 15.66498578, M_1 = 5.756627730, M_2 = 21.08123222$ 

The stability of these equilibria is exactly the same as in the first case. Further, using the same initial values as in the first



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case to perturb the equilibrium we obtain Figures 6 to 8 as follows. Also show the orbit of Natural and *Wolbachia*-infected Mosquitoes in figure 9.

In this numerical examples we obtain that complete replacement of natural mosquitoes population is possible by releasing relatively high rate of *wolbachia*-infected mosquitoes (data set 1). A relatively modest release rate is able to make the introduced mosquitoes establish and co-exists

| Parameter<br>A <sub>2</sub> | Equilibria (M <sub>1,</sub> M <sub>2</sub> ) | Stability | Perturbation<br>in initial<br>condition |
|-----------------------------|--|-----------|---|
| 0                           | (154,0)                                      | Stable    | (6,13)                                  |
|                             | (9,14)                                       | Unstable  | stablelizes to                          |
|                             | (6,17)                                       | Stable    | (6,17)                                  |
| 3/30                        | (151,2)                                      | Stable    | (6,13)                                  |
|                             | (9,15)                                       | Unstable  | stablelizes to                          |
|                             | (6,21)                                       | Stable    | (151,2)                                 |
| 6/30                        | (147,3)                                      | Stable    | (10,14)                                 |
|                             | (14,16)                                      | Unstable  | stablelizes to                          |
|                             | (6,24)                                       | Stable    | (6,24)                                  |
| 1                           | (118,16)                                     | Stable    | (33,25)                                 |
|                             | (34,25)                                      | Unstable  | stablelizes to                          |
|                             | (8,46)                                       | Stable    | (8,46)                                  |

TABLE 2. SENSITIVITY ANALYSIS OF  $A_2$ 

with the natural population (data set).

## v. Conclusion

We have provided a mathematical model of the introduction of *wolbachia*-infected mosquitoes into a virgin mosquitoes population. The analysis of the model shows that there exist a competitive-exclusion equilibrium in which the introduced *wolbachia*-infected mosquitoes completely replaces the natural mosquitoes population. Hence, the introduction of *wolbachia*-infected mosquitoes is promising in controlling the spread of dengue disease in human population, even to eliminate it. Further research can be done by investigating the optimal release rate of *wolbachia*-infected mosquitoes considering that the program will be costly to implement.

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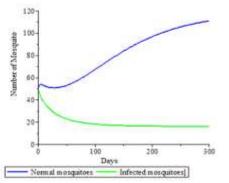


Figure 2. Small perturbation near  $X_1$ : Coexistence Equilibrium between the Natural and *Wolbachia*-infected Mosquitoes with the former dominates the later

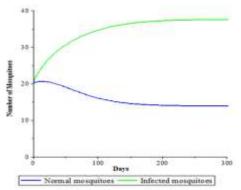


Figure 3. Small perturbation near X<sub>2</sub>: Competitive Exclusion of the Natural Mosquitoes by the *wolbachia*-infected mosquitoes

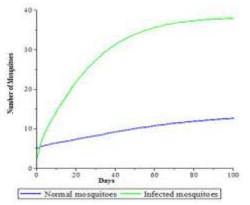


Figure 4. Small perturbation near  $X_3$ : Coexistence Equilibrium between the Natural and *Wolbachia*-infected Mosquitoes with the former dominated by the later

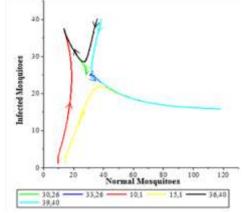


Figure 5. An orbit of Natural and Wolbachia-infected Mosquitoes

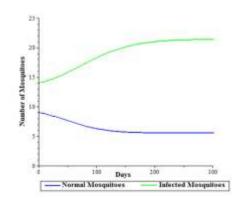


Figure 6. Small perturbation near  $X_1$ : Coexistence Equilibrium between the Natural and *Wolbachia*-infected Mosquitoes with the former dominates the later

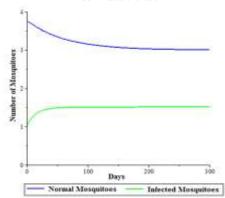


Figure 7. Small perturbation near  $X_2$ : Coexistence Equilibrium between the Natural and *Wolbachia*-infected Mosquitoes with the former dominated by the later. Compared to Figure 3, here Competitive Exclusion of the Natural Mosquitoes by the *wolbachia*-infected mosquitoes is not observed

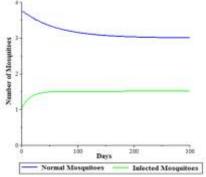


Figure 8. Small perturbation near  $X_3$ : Coexistence Equilibrium between the Natural and *Wolbachia*-infected Mosquitoes with the former dominated by the later

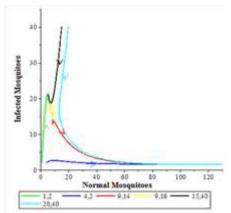


Figure 9. An orbit of Natural and Wolbachia-infected Mosquitoes

