Understanding resistant effect of mosquito on fumigation strategy in dengue control program

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Abstract. A mathematical model of dengue disease transmission will be introduced in this talk with involving fumigation intervention into mosquito population. Worsening effect of uncontrolled fumigation in the form of resistance of mosquito to fumigation chemicals will also be included into the model to capture the reality in the field. Deterministic approach in a 9 dimensional of ordinary differential equation will be used. Analytical result about the existence and local stability of the equilibrium points followed with the basic reproduction number will be discussed. Some numerical result will be performed for some scenario to give a better interpretation for the analytical results.

1. Introduction
Dengue is an infectious disease, which caused by a DEN virus. This virus has 4 different serotypes, i.e. DEN-1, DEN-2, DEN-3 and DEN-4 [5]. The virus is transmitted from mosquitos’ bites, i.e. Aedes aegypti. Actually, there is another mosquito that could spread this virus, i.e. Aedes albopictus. Unfortunately, majority reported infected case of Dengue in Indonesia is caused by Aedes aegypti bites [4].

There are three types of dengue depend on their infectious stages in human body, i.e. dengue fever, dengue hemorrhagic fever and dengue shock syndrome. The symptoms of this disease are fever, headache, vomiting, pain in the muscle, bleeding under the skin, nosebleeds, and many more [5].

Until today, there is no medicine that can cure people from dengue infection. Vaccines of dengue have been implemented in the last 10 years in many dengue potential countries like Brazil, Thailand, Indonesia, etc. [6]. The most popular policies to control dengue spread that has been implemented in many countries are fumigation and mechanical control. These both policies are to control the mosquito population. Fumigation is given to control adult mosquito population, while mechanical control (promote the clean environment) done in purpose to control mosquitoes breeding site [6].

Unfortunately, implementations of fumigation with chemical material trigger the evolution of mosquito to resist in the effect of this fumigation strategy. According to WHO, resistant define as capability of the organism to be resisting to the toxin that might kill another organism in the same species [7]. The resistant to insecticide is defined as the increase of proportion of insecticide that survives after exposed by an insecticide. This individual enhancement is primarily due to the death of insensitive individuals, providing an opportunity for resistant individuals to continue to breed and pass on resistance genes in off spring. Since first report in 1914 about the resistance to insecticide in San Jose, California [8], the number of cases of insecticide resistant mosquito resistance cases continues to increase like in Indonesia.
Many mathematical model have been introduced to understand how dengue might spread among human and mosquito population with many kind of mathematical approach, such as with deterministic approach [1], [2], [3], statistical approach [9], [10], [11], data analyzing [12], [13], [14]. In this article, mathematical model of dengue with intervention of fumigation to kill adult mosquito will be discussed. Resistant effect of the fumigation strategy in to mosquito population will be involved in to the model to capture previous introduction in the third paragraph.

The paper will be organized as follows. Section 2 introduced the mathematical model along with the assumptions that used to construct the model. Mathematical analysis about the equilibrium points and basic reproduction number will be given in the 3rd section and followed with some numerical experiment in the 4th section. Some conclusions will be given in the last section of the article.

2. The Construction of the Mathematical Model

Let human population divided in to 3-sub population, let call it as susceptible human \( S_h \), infected human \( I_h \) and recovered human \( R_h \). In the other hand, mosquito population divided into 6-subpopulation, i.e. normal and resistant mosquito in aquatic stage \( (E_m \) and \( E_r \), respectively), normal and resistant susceptible adult mosquito \( (S_m \) and \( S_r \), respectively), normal and resistant infected adult mosquito \( (I_m \) and \( I_r \), respectively). We assume that recruitment rate of human only coming from newborn with constant rate \( A_h \) and \( A_v \) for mosquito population. A constant proportion will separate new born of the mosquito between the natural and the resistant mosquito. This is because we assume that resistant effect of mosquito can be transmitted vertically from newborn process. We also assume that a constant rate of fumigation is given to adult mosquito to control their population with effectiveness rate of the fumigation is \( \zeta_m \) for natural mosquito and \( \zeta_r \) for resistant mosquito. Mosquito which not death caused by the fumigation intervention will instantly transferred in to resistant mosquitoes population. Using the transmission dynamic given in figure 1, the mathematical model of dengue spread with fumigation strategy and their resistant effect is given by:

\[
\begin{align*}
\frac{dS_h}{dt} &= A_h - \beta_h S_h I_m - \mu_S S_h + \delta_S R_h \\
\frac{dI_h}{dt} &= \beta_h S_h I_m - (\gamma_S + \mu_S + \alpha_S) I_h \\
\frac{dR_h}{dt} &= \gamma_S I_h - (\mu_S + \delta_S) R_h \\
\frac{dE_m}{dt} &= -\eta_m E_m - \mu_m E_m + p A_v \\
\end{align*}
\]

(1)

| Parameter | Description | Value | Dimension |
|-----------|-------------|-------|-----------|
| \( N_h \) | The total of human population | \( N_h(t) \geq 0 \) | human |
| \( A_h \) | Human newborn population | \( A_h \geq 0 \) | human day |
| \( A_v \) | Mosquitoes recruitment rate | \( A_v \geq 0 \) | egg day |
| \( \beta_h \) | Transmission rate of infection probability from mosquito to human per mosquito | \( \beta_h(t) \in [0,1] \) | human mosquito day |
| \( \beta_m \) | Transmission rate of infection probability from human to mosquito | \( \beta_m(t) \in [0,1] \) | 1 day |
| \( \mu_h \) | Humans natural mortality rate | \( \mu_h \in [0,1] \) | 1 day |
\[ \frac{dS_m}{dt} = \eta_m E_m - \frac{\beta_m S_m(I_h)}{S_h + I_h + R_h} - \mu_m S_m - \zeta_m u S_m - (1 - \zeta_m) u S_m \]
\[ \frac{dI_m}{dt} = \frac{\beta_m S_m(I_h)}{S_h + I_h + R_h} - \mu_m I_m - \zeta_m u I_m - (1 - \zeta_m) u I_m - \mu I_h + (1 - \eta) A_v \]
\[ \frac{dE_r}{dt} = -\eta_m E_r - \mu_m E_r + (1 - p)A_v \]
\[ \frac{dS_r}{dt} = \eta_m E_r - \frac{\beta_m S_r I_h}{S_h + I_h + R_h} - \mu_m S_r - \zeta_r u S_r + (1 - \zeta_m) u S_m \]
\[ \frac{dI_r}{dt} = \frac{\beta_m S_r I_h}{S_h + I_h + R_h} - \mu_m I_r - \zeta_r u I_r + (1 - \zeta_m) u I_m \]

with initial condition of each compartment are non-negative. Please see table 1 for the interpretation of each parameter in system (1).
In the next section, mathematical analysis for the equilibrium points and basic reproduction number will be discussed.

3. Equilibrium Points and Basic Reproduction Number

To find the equilibrium points, first we set all the right hand side of system (1) equal to 0, i.e.

\[
\begin{align*}
\frac{dS_h}{dt} &= 0, \quad \frac{dI_h}{dt} = 0, \quad \frac{dR_h}{dt} = 0, \\
\frac{dS_m}{dt} &= 0, \quad \frac{dI_m}{dt} = 0, \quad \frac{dE_m}{dt} = 0, \\
\frac{dS_r}{dt} &= 0, \quad \frac{dI_r}{dt} = 0, \quad \frac{dE_r}{dt} = 0,
\end{align*}
\]

and then solve it to each variable. There are 2 different equilibrium points here, i.e. mosquito free equilibrium point (MFE), disease free equilibrium point (DFE) and the endemic equilibrium point (EE).

The MFE is given by

\[
\begin{align*}
E_m = 0, I_m = 0, S_r = 0, I_r = 0, E_m = 0, E_r = 0, I_h = 0, R_h = 0, S_h = \frac{A_h}{\mu_h},
\end{align*}
\]

This equilibrium represents a situation where no mosquitoes exist in the population, which result in to non-existence of the dengue disease. Using the Jacobian matrix of system (1) and evaluate MFE in it, we find that this equilibrium point is always locally stable without any stability criteria.

The DFE is given by

\[
\begin{align*}
E_m &= \frac{pA_v}{\eta_m + \mu_m}, I_r = -\frac{(p-1)A_v}{\eta_m + \mu_m}, I_h = 0, I_m = 0, R_h = 0, S_h = \frac{A_h}{\mu_h}, \\
S_r &= \frac{S_m}{\eta_m A_v p(R_1 - 1)}
\end{align*}
\]

where \( R_1 = \frac{p(\zeta_m + \mu_m)}{(u + \mu_m)} \). It can be seen that this equilibrium point will always have a biological meaning (positiveness of each non infected sub-population) if \( R_1 < 1 \). Using a Jacobian matrix, which evaluated in DFE, the local stability of this equilibrium point is investigated. The characteristic polynomial of the eigenvalues is given by

\[
\lambda^2 + \alpha \lambda + \beta = 0,
\]

where \( \alpha \) and \( \beta \) are given by

\[
\begin{align*}
\alpha &= \frac{1}{R_1} \left( \frac{1}{\eta_m A_v} + \frac{p}{\eta_m + \mu_m} \right), \\
\beta &= \frac{1}{R_1} \left( \frac{1}{\eta_m A_v} \right).
\end{align*}
\]
\[\frac{1}{A_ha_{10}}((\lambda + \mu_m + \eta_m)^2(\lambda + \mu_h + u)(\lambda + \mu_h + \delta_h)(\lambda + \mu_h + \zeta_r u))(A_ha_{10}^3 \\
+ a_{10}(\mu_h + u\zeta_r + u + \gamma_h + 2\mu_m + \alpha_h)\lambda^2 + c_{10}\lambda + d_{10}) = 0,\]

where \(a_{10}, c_{10}, d_{10}\) are the function of parameters in table 1 which are not in a simple form to be written in this article. However, according to Routh-Hurwitz criteria [15], the DFE will locally stable if and only if

\[\frac{(\mu_h + u\zeta_r + u + \gamma_h + 2\mu_m + \alpha_h)}{A_h} > 0, \frac{c_{10}}{A_ha_{10}} > 0 \text{ and } \frac{d_{10}}{A_ha_{10}} > 0.\]

The endemic equilibrium point (EE) is given by

\[\left( S^*_h, I^*_h, R^*_h, E^*_m, S^*_m, I^*_m, E^*_r, S^*_r, I^*_r \right),\]

where

- \(S^*_h = -\frac{a_1I_h - b_1}{c_1},\)
- \(R^*_h = \frac{I_h\gamma_h}{\mu_h + \delta_h},\)
- \(E^*_m = \frac{pA_v}{\eta_m + \mu_m},\)
- \(S^*_m = -\frac{a_2I_h^3 + b_2I_h^2 + c_2I_h + d_2}{a_3I_h^2 + b_3I_h},\)
- \(I^*_m = -\frac{a_4I_h^2 + b_4I_h + c_4}{(1 - p)A_v},\)
- \(E^*_r = \frac{-1}{a_5I_h^2 + b_5I_h},\)
- \(S^*_r = -\frac{a_6I_h^3 + b_6I_h^2 + c_6I_h + d_6}{(a_7I_h^2 + b_7I_h)},\)

with \(a_1, a_2, a_3, a_4, a_5, a_6, a_7, b_1, b_2, b_3, b_4, b_5, b_6, c_2, c_3, c_4, c_5, d_2, d_3, d_4\) are a function of parameters in table (1) and \(I_r\), which are not in simple form to be written in this article. It can be seen that all sub population in EE is given as a function of \(I_h\) and \(I_r\).

### 3.1. Basic Reproduction Number

Basic reproduction number \(R_0\) is defined as an expected number of secondary cases from one primary infection in a virgin population during one infection period [16]. There is several ways that can be used to find the Basic reproduction number, such as with next-generation matrix approach [17], graph theory approach [16], and many more. In this article, next-generation matrix approach will be used to find the basic reproduction number of system (1), which give us

\[R_0 = \frac{\beta_mA_v\eta_m\mu_h\beta_h(pu^2\zeta_m\zeta_r - pu^2\zeta_r^2 + pu^2\zeta_m - pu^2\zeta_r + 2pu\zeta_m\mu_m - 2pu\zeta_r\mu_m - u^2 - 2u\mu_m - \mu_m^2)}{A_h(\gamma_h + \mu_h + \alpha_h)(\eta_m + \mu_m)(\mu + \mu_m)^2(\mu_r + \mu_m)^2}.\]

We find that the endemic equilibrium point will locally stable if \(R_0 > 1\) and unstable otherwise. Therefore, controlling the value of \(R_0\) can be use as the scientific reason about strategy to controlling the spread of dengue. In figure 2, sensitivity analysis of \(R_0\) respect to proportion of non-resistant new born \((p)\) and fumigation rate \((u)\). It can be seen that enlarging fumigation intervention will reduce basic reproduction number significantly. In the other hand, larger value of proportion of non-resistant new born \((p)\) will reduce basic reproduction number.
Figure 2. Sensitivity analysis of basic reproduction number respect to rate of fumigation and proportion of non-resistant new born.

In the next section, some numerical simulation will be given to give an interpretation of the analytical results.

4. Numerical Experiments

To perform all simulations in this section, the value of all parameters are \( N_h = 10000; A_v = \frac{10000}{65 \times 365}; A_r = \frac{1000}{30}; \beta_h = 0.65; \beta_m = 0.675; \mu_h = \frac{1}{65 \times 365}; \mu_m = 0.09; \delta_h = \frac{1}{60}; \eta_m = 0.15; \gamma_h = 0.143; p = 0.5; u = 0.8; \alpha_h = 3.5 \times 10^{-3}; \zeta_m = 0.95; \zeta_r = 0.75 \), which gave us the magnitude of basic reproduction number is \( 0.01101066873 \).

The initial conditions is \( S_h = 10000; R_h = 40; I_h = 0; S_m = 30; I_m = 80; S_r = 180; I_r = 300; E_r = 50; E_m = 60 \). The first simulation is given to see how rate of fumigation will affect the reduce of infected human and mosquito as shown in figure 3 where x-axis is time for day while y-axis is for number of human/mosquitoes. It can be seen that intervention of fumigation could suppress the number of infected human and mosquito in all of the time of simulation. The number of infected people is only slightly different in figure 3(c) since the value of basic reproduction number is less than 1.

![](image)

(a) Trajectory of Infected human
Figure 3. Trajectories of infected human and mosquito for \( t \in [0,200] \).

The next simulation is given in figure 4 and 5 which is performed to show how the intervention of fumigation which implemented not in whole of time simulation, but implemented as an impulse function which is given in two different scenario of periodic time. First scenario is when intervention of fumigation is implemented 10 times with rate of \( u=1 \) for each day of intervention. In the other hand, second scenario is implemented 5 times with rate of \( u=2 \) for each day. Choosing the 1\textsuperscript{st} scenario implemented 10 times while 2\textsuperscript{nd} scenario implemented 5 times, the total rate of fumigation for both scenario are the same, i.e. \( u = 10 \).

Figure 4. Trajectories of control for 1\textsuperscript{st} scenario (top-left), infected human (top-right), susceptible human (bottom-left) and the total of infected mosquito (bottom-right).
Figure 5. Trajectories of control for 2nd scenario (top-left), infected human (top-right), susceptible human (bottom-left) and the total of infected mosquito (bottom-right).

It can be seen from figure 4 and 5 that both scenario of intervention succeed to reduce number of infected human and mosquito and increase number of susceptible human. However, the successful rate of infection reduction for both scenarios is slightly different as shown in table 2. From this results, we can see that more often the fumigation intervention implemented will give a better result to reduce number of infection in human and mosquito.

Table 2. Numerical result for figure 4 and 5.

| Scenario | Number of intervention | Fumigation rate (u) | Number of infected human reduced | Total number of infected mosquito reduced |
|----------|-----------------------|---------------------|----------------------------------|------------------------------------------|
| 1st      | 10 times              | 1                   | 0.3951                           | 0.7587                                   |
| 2nd      | 5 times               | 2                   | 0.3765                           | 0.7476                                   |

5. Conclusions
A mathematical model of dengue spread with intervention of fumigation has been intervention in this article. Resistant effect of fumigation is given in to the model to see how the effect of this resistant in mosquito population affects the success of dengue control program. From analytic and numerical result, it can be seen that larger effect of mosquito resistant will make the dengue control program become more difficult to be success. Also we find that more often the intervention is given (periodic-daily intervention) will give a better result in controlling dengue spread. For further research, implementation of fumigation could be reconstruct as an optimal control problem to see how the fumigation change respect to time such that the cost of intervention could be minimized rather than choosing a constant intervention.

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