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Genetic algorithm to optimization mobility-based dengue mathematical model

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ABSTRACT

Implementation of vaccines, mosquito repellents and several Wolbachia schemes have been proposed recently as strategies against dengue. Research showed that the use of vaccine and repellent is highly effective when implemented to individuals who are in area with high transmission rates, while the use of Wolbachia bacteria is strongly effective when implemented in area with low transmission rates. This research is to show a three-strategy combination to cope with the dengue using mathematical model. In dengue mathematical model construction, several parameters are not yet known, therefore a genetic algorithm method was used to estimate dengue model parameters. Numerical simulation results showed that the combination of three strategies were able to reduce the number of infected humans. The dynamic of the human population with the combination of three strategies on average was able to reduce the infected human population by 45.2% in immobility aspect. Furthermore, the mobility aspect in dengue model was presented by reviewing two areas; Yogyakarta and Semarang in Indonesia. The numerical solutions showed that the trend graph was almost similar between the two areas. With the maximum effort given, the combination control values decreased slowly until the 100th day.

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1. INTRODUCTION

Dengue is an infectious disease caused by dengue virus and becomes one health issue predominantly found in tropical and sub-tropical area. This disease is a mosquito-borne infection from dengue-infected female Aedes aegypti. The dengue virus consists of 4 serotypes called DEN-1, DEN-2, DEN-3 and DEN-4 [1]–[3]. These serotypes can cause yearly epidemic in the tropical and sub-tropical area. Since 1943 when the dengue-virus serotypes were first isolated in Japan, the number of dengue transmissions is raising in all of the tropical countries [4]. Indonesia as one of the tropical countries in the world, is now classified as endemic country with category-A for dengue-virus infections in Southeast Asia.

One of the most effective ways to cope with the mosquito bites is through personal protection, including the use of diethyltoluamide (DEET)-based mosquito repellent. DEET-based mosquito repellents can cause the central nervous system of the mosquito. Within 1 meter, DEET ingredient is effective to deter mosquito up to 60% [5]. Moreover, researchers have investigated some medication to treat dengue infections but the result was not optimum [6]. One most common treatment conducted in the past research was to use living vector to create vaccine. Vaccine use can reduce the dengue case up to 80% in one area identified as high transmission rate [7].

In recent years, there have been several studies conducted for vector control by genetic modification. In addition, several methods of biological control to replace wild mosquitoes by releasing genetically modified mosquitoes have also been tried by several researchers. The methods of biological control are sterilization of male mosquitoes [8] and genetic modification to reduce reproduction and increase the life-shortening Wolbachia bacteria [9]. The use of intracellular Wolbachia symbionts has attracted much attention. This indicates that Wolbachia can inhibit dengue virus replication in mosquitoes. One prominent strategy proposed over the some last years to reduce the dengue transmission is by infecting mosquito population using the Wolbachia bacteria [10]–[12]. Wolbachia is generally transmitted maternally, i.e., only females infected with Wolbachia can pass it on to their offspring. Wolbachia intervention has been proved to reduce the chance of being infected in the areas with low and medium rate of transmission [13]. Moreover, Wolbachia intervention can slow down the dengue-virus developed inside Aedes aegypti [14]. If the male Wolbachia-carrying Aedes aegypti mates the female non Wolbachia-carrying Aedes aegypti, the dengue virus in the egg is terminated. On the other hand, if the female Wolbachia-carrying Aedes aegypti mates the male non-Wolbachia-carrying Aedes aegypti, all the eggs will be Wolbachia-infected. This results in the Wolbachia mosquito population. Wolbachia-carrying mosquito bites will not cause dengue virus infections. The Wolbachia bacteria being used in areas with low and medium rate of transmission can reduce the dengue transmission up to 86% [15]. In Indonesia, specifically in Yogyakarta, Wolbachia mosquitoes have begun to be developed which are members of the Eliminate Dengue Project-Yogyakarta program which is collaborative research between the Faculty of Medicine Gadjah Mada University (UGM) and Monash University, Australia. This study focused on producing Aedes aegypti mosquitoes with Wolbachia through the cross-breeding method to be spread in the Yogyakarta area [16].

Several modeling efforts focusing on dengue control strategies have been carried out in recent years. The application of mathematical models in disease epidemiology studies has a considerable impact on public health in general. Mathematical models are tools that can understand and interpret complex case studies so that they can be translated easily. It can be used to understand population dynamics [17], virus transmission dynamics [18] and others [19]. For the spread of dengue virus, mathematical models involving mosquitoes and human populations have been studied [20]. Similarly, many researchers have previously dengue model mathematical compartment deterministic to recognize the dynamic pattern of the dengue spread in several areas [21], [22]. The study of mathematical models of dengue fever cases has been carried out using the suspected, infected, and recovered (SIR) and suspected, exposed, infected, and recovered (SEIR) models. The SIR model studied assumes that individuals who recover from the disease will not become infected again. The facts show that the possibility of recovered patients has a chance to be reinfected. This is the main reason for modifying SIR to SIRS [23]. One model of human population control using repellents has been studied in [24]. Another study in [22] developed a model involving eight mutually exclusive compartments by repellent personal protection, larvicide, and adult control strategies that describe the population dynamics of dengue transmission. Zhou *et al.* [25] built a dengue model with the assumption of vertical transmission in mosquitoes and concluded that dengue virus can be significantly reduced by controlling the growth of the mosquito population. O'Reilly [15] also studied and used mathematical models to assess Wolbachia's performance in reducing dengue transmission in Indonesia and found an 80% reduction in dengue cases. In addition, the long-term application of Wolbachia provides a higher reduction in the incidence of dengue fever [26].

Although various mathematical models have been studied and developed to obtain strategies to reduce the spread of dengue fever, studies on the use of combination vaccination, repellent and Wolbachia are rarely considered. Therefore, this study will investigate the optimization of controlled design for dengue model with and without the mobility aspects using the combination of vaccination and repellent to human and Wolbachia bacteria injected to non-Wolbachia mosquito eggs. This research will focus on formulating a mathematical dengue model with and without the mobility aspect. The model will then be analyzed to estimate the parameters using genetics algorithm method to formulate a model simulation. The combination effect of all the controlled groups will be compared and concluded based on the numerical results.

2. METHOD

The problem with mathematical model epidemiology is that it is difficult to find parameter estimates that fit the data. In this regard, we have successfully applied a genetic algorithm to estimate the unknown parameters in the formed epidemiological mathematical model that affect the optimization results of numerical simulation results. The explanation of the research methodology to be carried in this study shown in Figure 1.

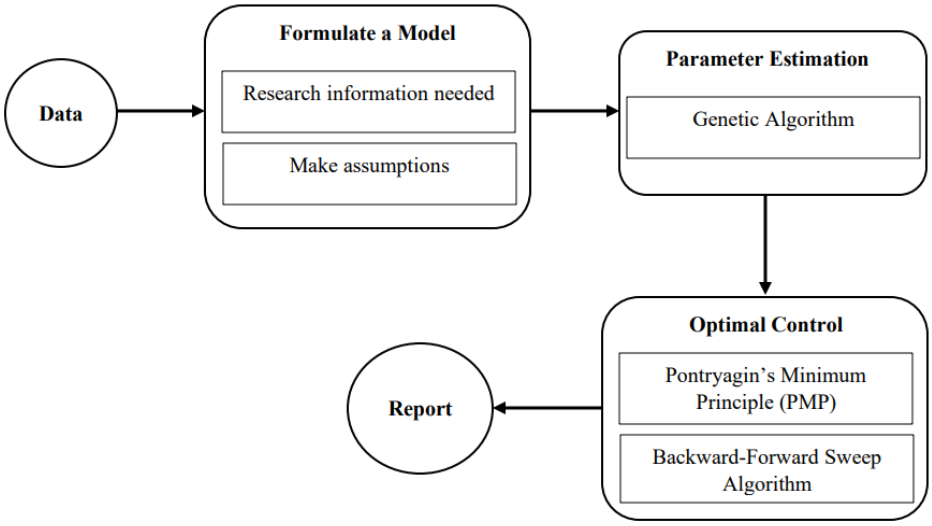

Figure 1. Research methodology in optimization of mobility-based dengue mathematical model

2.1. Data

At this stage, data is collected from the Semarang and Yogyakarta City Health Offices, the data will be used to validate and visualize the epidemiological trends of each compartment of dengue model based on the mobility formed. In addition, at this stage also collected several facts of the spread of dengue disease that has been mentioned in the introduction. The choice of data in the cities of Semarang and Yogyakarta is because the distance between the two cities is quite close, which is about 90 km, so that it affects the mobility aspect which is quite high. In addition, in the city of Yogyakarta, research on the development of Wolbachia bacteria in mosquitoes has been carried out in collaboration with the Yogyakarta Health Government with the World Mosquito Program, Monash University and Gadjah Mada University since 2016.

2.2. Formulate a model

At this stage, we formulate a mathematical dengue model based on mobility with some reasonable assumptions with the problem of the spread of dengue virus in the real world. The assumptions in this study are i) mosquito eggs could change locations by assuming the eggs were transported by fairly calm water; ii) the observed locations were close within the mosquito flight distance allowing the mosquito to move between locations; iii) the birth rate is the same as the death rate, so the human and mosquito populations remain constant; iv) infected humans will transmit the virus and mosquitoes will become infected if they interact with infected humans; v) mosquitoes that have been infected with the dengue virus will remain infected for the rest of their lives; vi) there is no vertical transmission from parent to offspring; vii) in Wolbachia and non-Wolbachia mosquito populations, the mass of eggs to pupae and larvae is negligible; viii) the use of repellents in humans is carried out routinely; ix) the bite of a Wolbachia mosquito does not cause dengue virus infection; and x) in this model, random vaccination and repellent are used with transient immunity.

2.3. Parameter estimation

In the formulated dengue mathematical model, several parameters were unknown. To be able to simulate a mathematical model accurately, the unknown parameters needed to be estimated. In this research, the genetic algorithm method was used to find the parameters estimation. During the genetic algorithm process, several program parameter values were determined. Parameter $(nvar)$ states the number of parameters estimated, meaning the value depended on the number of variables estimated. Parameter value $(npop)$ was not determined specifically, so it is necessary to look for value which gave result close to the optimum results. Like the parameter $(npop)$, parameter $(mutate)$, values giving result close to the optimum results in parameter, or the mutation probability needed to be determined. Moreover, parameter value $(xrate)$ was not determined specifically, so it is necessary to look for value with the result close to the optimum results. The genetic algorithm steps for parameter estimation in the dengue epidemic model are as:

a. Determine the parameters used. In this case, the parameters used were the size of the population, $(npop)$, number of generations $(ngen)$, mutation probability $(mutate)$, selection rate $(xrate)$, number of parameters estimated $(nvar)$ and real data input.

b. Generate chromosomes randomly $[0,1]$ with the size$(npop \times nvar)$.
c. Count $(nparent = npop \times xrate)$, the calculation result to be rounded up.
d. Create a rank order of $(nparent)$.
e. Count the cumulative rank: $f = \frac{nparent(nparent+1)}{2}$.
f. Create a cumulative probability matrix of $(nparent)$ in size which the k^{th} element is $\frac{\sum_{x=1}^{k} rank\ x}{f}$.
g. Compute the numerical solution of dengue mathematical model with $ode45$.
h. Evaluate the objective function value for each chromosome in the population. The objective function value used is to minimize the average of mean of magnitude relative error (MMRE) is defined $\frac{1}{n}\sum_{i=1}^{n}\left(\sum_{m=1}^{k}\left|\frac{x_{mi}-x_{mi}^{ode45}}{x_{mi}}\right|\right)$ with n states the number of data and k states the number of model compartment. From the number of the compartment model, x_{mi} states the number of compartment population to m based on real data at a time of i and x_{mi}^{ode45} states the result of $ode45$ compartment calculation to m at a time of i. Equation MMRE is chosen as the formula to determine the objective function to be implemented in the program.
i. Rank the population based on the objective function value of each chromosome with MMRE minimum value in the first rank and it continuous on.
j. Select the population into a number of $(nparent)$.
k. Select the parent that will do the crossover.
l. Cross over between two parents using a linear combination method from both parents. This process will result in two offspring being obtained, then place the offspring from the cross into the chromosome population.
m. Perform elitism so that the chromosome with the best objective function value does not undergo mutation.
n. Perform mutation to several gens from the chromosome randomly by changing the value of the chosen gen with the random value.
o. Create a new population by combining the chromosomes from the elitism process in the step (m) the chromosome from the mutation process in the step (n).
p. Choose the chromosome with the minimum objective function value.
q. Check the termination criteria to $ngen$. If this is not fulfilled, return to the step (g). If fulfilled, show the results in the step (p).

2.4. Optimal control

In this section, we solve the optimal control problem in a dengue model constructed using Pontryagin's minimum principle (PMP) to determine a more optimal control strategy in minimizing infected humans and minimizing the costs. The optimal control problem with PMP can be solved numerically, by designing an algorithm that produces an estimate of the optimal control value. Note that the optimal system consists of a state equation with initial conditions, a co-state equation with a transversality condition, and an optimal control characteristic. This optimal control problem is solved by a backward-forward sweep algorithm as:

a. Time interval $[0, t_f]$ divided into $\mathbb{N}$ uniform subintervals. Vector form $\vec{x} = (x_1, x_2, \dots, x_{18})$ and vector $\vec{\lambda} = (\lambda_1, \lambda_2, \dots, \lambda_{18})$ are a vector approximation for state and co-state.
b. Make an initial value for $\vec{u}_{1p}, \vec{u}_{1r}, \vec{u}_{2p}, \vec{u}_{2r}, \vec{u}_{3p}, \vec{u}_{3r}$ during the time interval, with $\vec{u}_{1p}(0) = 0$, $\vec{u}_{1r}(0) = 0$, $\vec{u}_{2p}(0) = 0$, $\vec{u}_{2r}(0) = 0$, $\vec{u}_{3p}(0) = 0$, $\vec{u}_{3r}(0) = 0$ based on the differential equation of state on the optimal system using the Runge-Kutta 4th method. $\vec{u}_{1p}(t), \vec{u}_{1r}, \vec{u}_{2p}, \vec{u}_{2r}, \vec{u}_{3p}, \vec{u}_{3r}$ are a control approximation $\vec{u}_{1p}, \vec{u}_{1r}, \vec{u}_{2p}, \vec{u}_{2r}, \vec{u}_{3p}, \vec{u}_{3r}$ at the time t.
c. With the initial state $x_1 = x(t_0) = x_0$ and value at $\vec{u}_{1p}, \vec{u}_{1r}, \vec{u}_{2p}, \vec{u}_{2r}, \vec{u}_{3p}, \vec{u}_{3r}$ doing state solution value $(\vec{x})$ by forward against time t based on the co-state differential equation on the optimal system using the Runge-Kutta method of order 4.
d. With the condition of transversality $\lambda_{\mathbb{N}+1} = \lambda(t_f) = 0$ and value $\vec{u}_{1p}, \vec{u}_{1r}, \vec{u}_{2p}, \vec{u}_{2r}, \vec{u}_{3p}, \vec{u}_{3r}, \vec{x}$, doing solve $\vec{\lambda}$ by backward at the time.
e. Update value $\vec{u}_{1p}, \vec{u}_{1r}, \vec{u}_{2p}, \vec{u}_{2r}, \vec{u}_{3p}, \vec{u}_{3r}$ with value subtitutions $\vec{x}$ and $\vec{\lambda}$ to the optimal control characteristics.
f. Check convergence. If the variable values in the current and previous iterations are close enough, then the current value is the solution. Otherwise, return to step (b).

3. RESULT AND DISCUSSION

3.1. Result of the mobility dengue mathematical model formulation

In the real situation, the mobility aspect significantly influences in the dengue virus transmission, therefore, it is necessary to formulate mobility-based dengue mathematical model. It was assumed that there were two clusters observed: cluster p and r. The human population was divided into susceptible $(S_{h\{p,r\}})$, infected $(I_{h\{p,r\}})$, and recovered $(R_{h\{p,r\}})$. The non Wolbachia-carrying mosquito population was divided into aquatic egg $(A_{v\{p,r\}})$, susceptible $(S_{v\{p,r\}})$, infected $(I_{v\{p,r\}})$, and protected $(P_{v\{p,r\}})$. The Wolbachia mosquito population was divided into aquatic egg $(A_{w\{p,r\}})$ and susceptible $(S_{w\{p,r\}})$. The assumptions used in the model formed have been given previously in the methods section. Beside that in mosquito population, there was no recovered class because the mosquito would remain infectious for its entire life. It was also assumed that Wolbachia-carrying Aedes aegypti mosquitoes would be released and mate the non-Wolbachia-carrying Aedes aegypti. In this case, the Wolbachia bacteria in the Wolbachia-carrying Aedes aegypti would be transmitted to the other Aedes aegypti and killed the dengue virus in the mosquito. As a result, the mosquito would not be able to transmit the dengue virus to human. Therefore, the researchers assumed that mosquitoes mating the Wolbachia-carrying Aedes aegypti would also be infected with the bacteria causing the mosquito population changing to the protected human population compartment. Based on these assumptions, the researchers also modeled the Wolbachia mosquito compartment, although the model has less effect on the human and non-Wolbachia-carrying mosquito compartments, but the researchers assumed that it was important to model the Wolbachia mosquito compartment so that the contact rate of Wolbachia-carrying and non-Wolbachia-carrying mosquitoes could be realized and became plausible. As the aim of this research is to gain general insight into the possible effectiveness of using vaccines, repellents and Wolbachia, the use of a combination of three strategies is more effective in reducing dengue cases than implementing only one strategy. Thus, the formulated model can be seen in system (1) and explanations on the parameters and variables are given in Table 1.

$$
\begin{aligned}
\frac{dS_{h\{p,r\}}}{dt} &= \mu_{h\{p,r\}}N_{h\{p,r\}} + \left(\theta_{\{p,r\}}u_{1\{p,r\}} + \alpha_{\{p,r\}}u_{2\{p,r\}}\right)R_{h\{p,r\}} + \delta_{\{rp,pr\}}S_{h\{r,p\}} - S_{\{p,r\}1},\\
\frac{dI_{h\{p,r\}}}{dt} &= \frac{\beta_{h\{p,r\}}I_{v\{p,r\}}S_{h\{p,r\}}}{N_{h\{p,r\}}} + \delta_{\{rp,pr\}}I_{h\{r,p\}} - \left(\mu_{h\{p,r\}} + \gamma_{\{p,r\}} + \delta_{\{pr,rp\}}\right)I_{h\{p,r\}},\\
\frac{dR_{h\{p,r\}}}{dt} &= \gamma_{\{p,r\}}I_{h\{p,r\}} + \left(u_{1\{p,r\}} + u_{2\{p,r\}}\right)S_{h\{p,r\}} + \delta_{\{rp,pr\}}R_{h\{r,p\}} - R_{\{p,r\}1},\\
\frac{dA_{v\{p,r\}}}{dt} &= \mu_{v\{p,r\}}N_{v\{p,r\}} + \alpha_{\{rp,pr\}}A_{v\{r,p\}} - \left(\mu_{v\{p,r\}} + \epsilon_{\{p,r\}} + u_{3\{p,r\}} + \alpha_{\{pr,rp\}}\right)A_{v\{p,r\}},\\
\frac{dS_{v\{p,r\}}}{dt} &= \epsilon_{\{p,r\}}A_{v\{p,r\}} + \alpha_{\{rp,pr\}}S_{v\{r,p\}} - \left(\mu_{v\{p,r\}} + \beta_{1\{p,r\}} + \frac{\beta_{v\{p,r\}}I_{h\{p,r\}}}{N_{h\{p,r\}}} + \alpha_{\{pr,rp\}}\right)S_{v\{p,r\}},\\
\frac{dI_{v\{p,r\}}}{dt} &= \frac{\beta_{v\{p,r\}}I_{h\{p,r\}}S_{v\{p,r\}}}{N_{h\{p,r\}}} + \alpha_{\{rp,pr\}}I_{v\{r,p\}} - \left(\mu_{v\{p,r\}} + \beta_{0\{p,r\}} + \alpha_{\{pr,rp\}}\right)I_{v\{p,r\}},\\
\frac{dP_{v\{p,r\}}}{dt} &= \beta_{0\{p,r\}}I_{v\{p,r\}} + \beta_{1\{p,r\}}S_{v\{p,r\}} + u_{3\{p,r\}}A_{v\{p,r\}} + \alpha_{\{rp,pr\}}P_{v\{r,p\}} - \left(\mu_{v\{p,r\}} + \alpha_{\{pr,rp\}}\right)P_{v\{p,r\}},\\
\frac{dA_{w\{p,r\}}}{dt} &= \mu_{w\{p,r\}}N_{w\{p,r\}} + \theta_{\{rp,pr\}}A_{w\{r,p\}} - \left(\mu_{w\{p,r\}} + \eta_{\{p,r\}} + \theta_{\{pr,rp\}}\right)A_{w\{p,r\}},\\
\frac{dS_{w\{p,r\}}}{dt} &= \eta_{\{p,r\}}A_{w\{p,r\}} + \theta_{\{rp,pr\}}S_{w\{r,p\}} - \left(\mu_{w\{p,r\}} + \theta_{\{pr,rp\}}\right)S_{w\{p,r\}}. \qquad (1)
\end{aligned}
$$

$$
\begin{aligned}
&with\, S_{\{p,r\}1} = \left(u_{1\{p,r\}} + u_{2\{p,r\}} + \mu_{h\{p,r\}} + \frac{\beta_{h\{p,r\}}I_{v\{p,r\}}}{N_h\{p,r\}} + \delta_{\{pr,rp\}}\right)S_{h\{p,r\}},\\
&R_{\{p,r\}1} = \left(\mu_{h\{p,r\}} + \alpha_{\{p,r\}}u_{2\{p,r\}} + \theta_{\{p,r\}}u_{1\{p,r\}} + \delta_{\{pr,rp\}}\right)R_{h\{p,r\}}.
\end{aligned}
$$

Basic reproduction number (R_0) stating the average of secondary cases per primary cases when the dengue infection was given to susceptible population [27]. In this research, (R_0) was formulated using the next generation matrix (NGM) method in correspondence to the virus-free equilibrium point. Therefore, (R_0) is obtained as (2):

$$
R_0 = \sqrt{\frac{N_{v\{p,r\}}\epsilon_{\{p,r\}}\beta_{h\{p,r\}}\beta_{v\{p,r\}}\mu_{v\{p,r\}}}{N_{h\{p,r\}}\left(\mu_{h\{p,r\}}+\gamma_{\{p,r\}}\right)\left(\mu_{v\{p,r\}}+\beta_{1\{p,r\}}\right)\left(\mu_{v\{p,r\}}+\beta_{0\{p,r\}}\right)\left(\mu_{v\{p,r\}}+\epsilon_{\{p,r\}}\right)}} \qquad (2)
$$

based on the value of R_0 in the uncontrolled model (1), it can be concluded that a virus-free condition occured when the virus was not epidemic or there had never been any infection case; that is when $R_0 < 1$. In

this case, $N_{v\{p,r\}}\epsilon_{\{p,r\}}\beta_{h\{p,r\}}\beta_{v\{p,r\}}\mu_{v\{p,r\}}$ represented parameters relevant to the virus infection in the population. While $N_{h\{p,r\}}(\mu_{h\{p,r\}}+\gamma_{\{p,r\}})(\mu_{v\{p,r\}}+\beta_{1\{p,r\}})(\mu_{v\{p,r\}}+\beta_{0\{p,r\}})(\mu_{v\{p,r\}}+\epsilon_{\{p,r\}})$ represented the parameters relevant to the infection decline in the population. Thus, condition reflecting the virus was not epidemic or there had never been any occurrence of infection case when the rate of virus infection is smaller than the recovery and death rate. While the endemic condition occurred when a virus was epidemic; that is when $R_0 > 1$. Therefore, it can be concluded that a virus was epidemic when the rate of virus infection was higher than the recovery and death rate.

To confirm the validity of the model that has been made, model validation was done by comparing the numerical simulation results with the original data obtained. Data compared was the numerical simulation of virus-infected population with the virus-infected patients in Yogyakarta based on the database from the local Public Health Office. Yogyakarta was chosen since this area had monthly recapitulation of virus-infected patients and was the first city for Wolbachia-carrying mosquito trial. Based on Figure 2, it can be seen that the real data plot (*) had a fairly small error approaching the graph of infected population within the uncontrolled system. Thus, it can be concluded that the dengue model formulated was sufficient to depict the real situation using the aforementioned parameters.

Table 1. Explanation of parameter and variable

Symbol	Description	Unit
$\mu_{w\{p,r\}}$	Death rate of Wolbachia-carrying mosquito due to natural cause in cluster *p* or *r*	Day^{-1}
$\eta_{\{p,r\}}$	Breeding time for Wolbachia-carrying egg to adult mosquito in cluster *p* or *r*	Day^{-1}
$\mu_{v\{p,r\}}$	Death rate of non-Wolbachia-carrying mosquito due to natural cause in cluster *p* or *r*	Day^{-1}
$\epsilon_{\{p,r\}}$	Breeding time for non-Wolbachia-carrying egg to adult mosquito in cluster *p* or *r*	Day^{-1}
$\mu_{h\{p,r\}}$	Death rate of human due to natural cause in cluster *p* or *r*	Day^{-1}
$\beta_{h\{p,r\}}$	Proportion of dengue virus transmission from dengue-infected mosquito to human in cluster *p* or *r*	N/A
$\beta_{v\{p,r\}}$	Proportion of dengue virus transmission from dengue-infected human to mosquito in cluster *p* or *r*	N/A
$\beta_{0\{p,r\}}$	Proportion of contact between dengue-infected mosquito and Wolbachia-carrying mosquito in cluster *p* or *r*	N/A
$\beta_{1\{p,r\}}$	Proportion of contact between susceptible Wolbachia-carrying mosquito and susceptible non Wolbachia-carrying mosquito in cluster *p* or *r*	N/A
$\gamma_{\{p,r\}}$	Rate of human recovered from the virus in cluster *p* or *r*	Day^{-1}
$\theta_{\{p,r\}}$	Rate of immunity decline of human being vaccinated in cluster *p* or *r*	Day^{-1}
$\alpha_{\{p,r\}}$	Rate of repellent drop out human getting repellent treatment in cluster *p* or *r*	Day^{-1}
$u_{1\{p,r\}}$	Control stating the proportion of susceptible human being vaccinated at time *t* with $0 \le u_{1\{p,r\}}(t) \le 1$ in cluster *p* or *r*	Day^{-1}
$u_{2\{p,r\}}$	Control stating the proportion of susceptible human getting repellent treatment at time *t* with $0 \le u_{2\{p,r\}}(t) \le 1$ in cluster *p* or *r*	Day^{-1}
$u_{3\{p,r\}}$	Control stating the proportion of mosquito eggs getting the Wolbachia injection at time *t* with $0 \le u_{3\{p,r\}}(t) \le 1$ in cluster *p* or *r*	Day^{-1}
$\alpha_{\{pr,rp\}}$	Transfer rate of non-Wolbachia mosquitoes from cluster $\{p,r\}$ to cluster $\{r,p\}$	Day^{-1}
$\delta_{\{pr,rp\}}$	Transfer rate of human from cluster $\{p,r\}$ to cluster $\{r,p\}$	Day^{-1}
$\theta_{\{pr,rp\}}$	Transfer chance of Wolbachia mosquitoes from cluster $\{p,r\}$ to cluster $\{r,p\}$	Day^{-1}

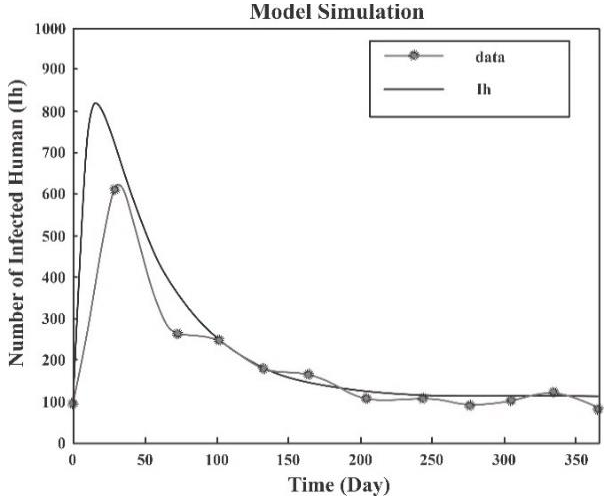

Figure 2. Dengue model simulation matching graph with data

3.2. Result of parameter estimation using genetic algorithm

In this estimation studies, the researchers divided the data into 2 area; they were p cluster which consisted of Yogyakarta Indonesia area and r cluster which consisted of Semarang Indonesia area and the required data used were weekly data of dengue cases in Yogyakarta and Semarang City, Indonesia in 2020. The parameters to be estimated were $\beta_{hp}, \beta_{hr}, \gamma_p, \gamma_r, \epsilon_p, \epsilon_r, \beta_{1p}, \beta_{1r}, \beta_{vp}, \beta_{vr}, \beta_{0p}, \beta_{0r}, \eta_p$ and η_r. In genetic algorithm scheme, 30 iterations were used with the input of parameter estimation, the population size was 200, the mutation rate was 0.04 and the selection rate was 0.5. The parameters are presented in Table 2.

Table 2. Parameter estimation with genetic algorithm

Parameter Estimation	Result Genetic Algorithm	Parameter Estimation	Result Genetic Algorithm
β_{hp}	0.00278	β_{1p}	0.0087
γ_p	0.069108	β_{0p}	0.01976
ϵ_p	0.2382	η_p	0.0854
β_{hr}	0.003454	γ_r	0.05346
ϵ_r	0.439	β_{1r}	0.00675
β_{vr}	0.18634	β_{0r}	0.01976
η_r	0.03211	β_{vp}	0.17181

$\eta_p = 0.0854$ means on average, 854 mosquito eggs would hatch into Wolbachia-carrying mosquitoes after 10.000 days in area cluster p. $\epsilon_p = 0.238$ means on average, 238 mosquito eggs would hatch into non Wolbachia-carrying mosquitoes after 1,000 days in area cluster p. $\beta_{vp} = 0.17181$ means on average 17,181 mosquitoes would be infected if there were 100,000 dengue virus transmissions from infected human to one mosquito by susceptible mosquito bites to infected human in area cluster p. $\beta_{0p} = 0.0195$ means on average, 195 infected mosquitoes would get Wolbachia bacteria if there were 10,000 contacts between the infected mosquitoes and Wolbachia-carrying mosquitoes in area cluster p. $\beta_{1p} = 0.0087$ means on average 87 susceptible mosquitoes would get Wolbachia bacteria if there were 10,000 contacts between the susceptible Wolbachia-carrying mosquitoes and susceptible non Wolbachia-carrying mosquitoes in area cluster p. $\beta_{hp} = 0.00278$ means on average 278 humans would be dengue-infected if there were 100,000 dengue virus transmissions from one infected mosquito to human by infected mosquito bites to susceptible human in cluster p. $\gamma_p = 0.069108$ means on average 69,108 humans would recover after 1,000,000 days in area cluster p.

$\eta_r = 0.03211$ means on average 3211 mosquito eggs would hatch to Wolbachia-carrying mosquitoes after 100,000 days in cluster r. $\epsilon_r = 0.439$ means on average 439 mosquito eggs hatch to non-Wolbachia-carrying mosquitoes after 1,000 days in cluster r. $\beta_{vr} = 0.18634$ means on average 18,634 mosquitoes are infected if there are 100,000 dengue virus transmissions from infected human to one mosquito by the susceptible mosquito bites to the infected human cluster r. $\beta_{0r} = 0.01976$ means on average 1,976 infected mosquitoes get Wolbachia bacteria if there are 100,000 contacts between the infected mosquitoes and Wolbachia-carrying mosquitoes in r. $\beta_{1r} = 0.00675$ means on average 675 susceptible mosquitoes get Wolbachia bacteria if there are 100,000 contacts between the susceptible Wolbachia-carrying mosquitoes and the susceptible non Wolbachia-carrying mosquitoes in cluster r. $\beta_{hr} = 0.003454$ means on average 278 humans are dengue virus infected if there are 100,000 dengue virus transmissions from one infected mosquito to human by the infected mosquito bites to the susceptible human in cluster r. $\gamma_r = 0.05346$ means on average 5,346 humans would recover after 100,000 days in area cluster r.

After obtaining the parameters, it is necessary to conduct a sensitivity analysis to determine the most influencing model parameters in the population dynamics. Sensitivity analysis is an analysis used to examine the parameters existing in a model and is useful for identifying parameters that have more influence on the stability of the equilibrium point of each population. The analysis can be performed by changing the value of one of the parameters on the next simulation, thus it can be analyzed how much one parameter can influence. In this case, the sensitivity analysis reviewed the number (R_0) towards $\left(I_{h\{p,r\}}\right)$ to analyze which parameters influenced the most to $\left(I_{h\{p,r\}}\right)$. Parameters analyzed were β_{hp} and δ_{pr}. The results of sensitivity index are presented in Table 3.

Table 3. Sensitivity index results

Parameter	Value
β_{hp}	0.0000197694768
δ_{pr}	0.0247083072

Based on the results above, it is clear that the most influencing parameter of endemic occurrence was the rate of human mobility δ_{pr}. In other words, if one area has high risk of dengue transmission, the migration level in the area was to be reduced to avoid the dengue transmission to other areas.

3.3. Result of optimal control

At this stage, the researchers analyzed the implementation of optimal control on mobility dengue model with the aim of minimizing the infected human population. Thus, the objective function formula is as (3):

$$J = \min_{u_{1\{p,r\}},u_{2\{p,r\}},u_{3\{p,r\}}} \int_0^{t_f} \left(I_{h\{p,r\}} + B_{1\{p,r\}}u_{1\{p,r\}}^2 + B_{2\{p,r\}}u_{2\{p,r\}}^2 + B_{3\{p,r\}}^2 u_{3\{p,r\}}^2\right)dt \quad (3)$$

where $0 \le t \le t_f, 0 \le u_{1\{p,r\}}(t), u_{2\{p,r\}}(t), u_{3\{p,r\}}(t) \le 1, t_f$ is the final time $I_{h\{p,r\}}$ is the number of dengue infected human in area cluster p or r. $B_{1\{p,r\}}, B_{2\{p,r\}}$, and $B_{3\{p,r\}}$ are positive constants which represent the vaccination, repellent and Wolbachia bacteria weight in area cluster p and r.

To solve the system (1) and minimize the objective function (3), the Pontryagin's minimum principle was used. Thus, the Hamiltonian function can easily be obtained as:

$$\begin{aligned}
H = {} & I_{h\{p,r\}} + B_{1\{p,r\}}u_{1\{p,r\}}^2 + B_{2\{p,r\}}u_{2\{p,r\}}^2 + B_{3\{p,r\}}^2 u_{3\{p,r\}}^2 + \lambda_1\left[\mu_{w\{p,r\}}N_{w\{p,r\}} + \theta_{\{rp,pr\}}A_{w\{r,p\}}\right. \\
& + \lambda_2\left[\left[\mu_{w\{p,r\}}N_{w\{p,r\}} + \theta_{\{rp,pr\}}A_{w\{r,p\}} - \left(\mu_{w\{p,r\}} + \eta_{\{p,r\}} + \theta_{\{pr,rp\}}\right)A_{w\{p,r\}}\right]\right. \\
& + \lambda_3\left[\mu_{v\{p,r\}}N_{v\{p,r\}} + \alpha_{\{rp,pr\}}A_{v\{r,p\}} - \left(\mu_{v\{p,r\}} + \epsilon_{\{p,r\}} + u_{3\{p,r\}} + \alpha_{\{pr,rp\}}\right)A_{v\{p,r\}}\right] \\
& + \lambda_4\left[\epsilon_{\{p,r\}}A_{v\{p,r\}} + \alpha_{\{rp,pr\}}S_{v\{r,p\}}\right. \\
& \left.\left.\left.- \left(\mu_{v\{p,r\}} + \beta_{1\{p,r\}} + \frac{\beta_{v\{p,r\}}I_{h\{p,r\}}}{N_{h\{p,r\}}} + \alpha_{\{pr,rp\}}\right)S_{v\{p,r\}}\right]\right. \\
& + \lambda_5\left[\frac{\beta_{v\{p,r\}}I_{h\{p,r\}}S_{v\{p,r\}}}{N_{h\{p,r\}}} + \alpha_{\{rp,pr\}}S_{v\{r,p\}}\right. \\
& \left.- \left(\mu_{v\{p,r\}} + \beta_{1\{p,r\}} + \frac{\beta_{v\{p,r\}}I_{h\{p,r\}}}{N_{h\{p,r\}}} + \alpha_{\{pr,rp\}}\right)S_{v\{p,r\}}\right] \\
& + \lambda_5\left[\frac{\beta_{v\{p,r\}}I_{h\{p,r\}}S_{v\{p,r\}}}{N_{h\{p,r\}}} + \alpha_{\{rp,pr\}}I_{v\{r,p\}} - \left(\mu_{v\{p,r\}} + \beta_{0\{p,r\}} + \alpha_{\{pr,rp\}}\right)I_{v\{p,r\}}\right] \\
& + \lambda_6\left[\beta_{0\{p,r\}}I_{v\{p,r\}} + \beta_{1\{p,r\}}S_{v\{p,r\}} + u_{3\{p,r\}}A_{v\{p,r\}} + \alpha_{\{rp,pr\}}P_{v\{r,p\}} - \left(\mu_{v\{p,r\}} + \alpha_{\{pr,rp\}}\right)P_{v\{p,r\}}\right] \\
& + \lambda_7\left[\mu_{h\{p,r\}}N_{h\{p,r\}} + \left(\theta_{\{p,r\}}u_{1\{p,r\}} + \alpha_{\{p,r\}}u_{2\{p,r\}}\right)R_{h\{p,r\}} + \delta_{\{rp,pr\}}S_{h\{r,p\}} - S_{\{p,r\}1}\right] \\
& + \lambda_8\left[\frac{\beta_{h\{p,r\}}I_{v\{p,r\}}S_{h\{p,r\}}}{N_{h\{p,r\}}} + \delta_{\{rp,pr\}}I_{h\{r,p\}} - \left(\mu_{h\{p,r\}} + \gamma_{\{p,r\}} + \delta_{\{pr,rp\}}\right)I_{h\{p,r\}}\right] \\
& + \lambda_9\left[\gamma_{\{p,r\}}I_{h\{p,r\}} + \left(u_{1\{p,r\}} + u_{2\{p,r\}}\right)S_{h\{p,r\}} + \delta_{\{rp,pr\}}R_{h\{r,p\}} - R_{\{p,r\}1}\right].
\end{aligned}$$

The state equation, co-state equation and stationery condition can be solved by completing:

$$\dot{x} = \frac{\partial H}{\partial \lambda_p}, p = 1,2,\dots,9;\ -\dot{\lambda} = \frac{\partial H}{\partial x};\ \text{and}\ \frac{\partial H}{\partial u_{k\{p,r\}}} = 0, k = 1,2,3.$$

with $x = \left(S_{h\{p,r\}}, I_{h\{p,r\}}, R_{h\{p,r\}}, A_{v\{p,r\}}, S_{v\{p,r\}}, I_{v\{p,r\}}, P_{v\{p,r\}}, A_{w\{p,r\}}, S_{w\{p,r\}}\right)$.

The solutions obtained are:

$$\begin{aligned}
u_{1\{p,r\}}^*(t) &= \min\left(1, \max\left(0, \frac{(\lambda_1 - \lambda_3)S_{h\{p,r\}} + (\lambda_3 - \lambda_1)\theta_{\{p,r\}}R_{h\{p,r\}}}{2B_{1\{p,r\}}}\right)\right) \\
u_{2\{p,r\}}^*(t) &= \min\left(1, \max\left(0, \frac{(\lambda_1 - \lambda_3)S_{h\{p,r\}} + (\lambda_3 - \lambda_1)\alpha_{\{p,r\}}R_{h\{p,r\}}}{2B_{2\{p,r\}}}\right)\right) \\
u_{3\{p,r\}}^*(t) &= \min\left(1, \max\left(0, \frac{(\lambda_4 - \lambda_7)A_{v\{p,r\}}}{2B_{3\{p,r\}}}\right)\right)
\end{aligned} \quad (5)$$

Table 4 show the results that during the observation time, the dynamics of the human population due to vaccination control was able to reduce the infected human population by 24.2% on average. The dynamics of the human population with repellent control was able to reduce the infected human population by 19.2% on average. The dynamics of the human population with Wolbachia control was able to reduce the infected human population by 30.4% on average. The dynamics of the human population with vaccination and repellent control on average was able to reduce the infected human population by 31.9%. The dynamics of the human population with vaccination and Wolbachia control on average was able to reduce the infected human population by 40%. The dynamics of the human population with repellent and Wolbachia control on average was able to reduce the infected human population by 34.7%. The dynamics of the human population with vaccination, repellent and Wolbachia bacteria control on average was able to reduce the infected human population by 45.2%.

Table 4. Comparison of infected human population on day 100

Condition	Number of Infected Human Population
Without control	420
Vaccination control	318
Repellent control	338
Wolbachia control	292
Vaccination and repellent control	286
Vaccination and Wolbachia control	252
Repellent and Wolbachia control	272
Vaccination, repellent, and Wolbachia control	230

Figure 3 presents the results of the numerical solution in three combination strategies model where it shows that the trend graph is almost similar between Yogyakarta and Semarang areas. At first the combination control value of vaccination, repellent and Wolbachia were given with maximum effort, then the combination control value decreased slowly until the 100^{th} day. It means that at first the combination control of vaccination, repellent and Wolbachia were carried out optimally, then the value of combination control of vaccination, repellent and Wolbachia decreased slowly as the number of infected individuals decreased. Figure 3 also explains that Yogyakarta area and the Semarang area had similar trend graph in the cases of the infected human population. It can be seen that at first the size of the infected human population increased, this was due to the increase in the population of humans susceptible to dengue virus, and the increase in displacement between the two regions. Then the graph of the size of the human population that has decreased, this is due to the reduction in humans caused by natural deaths or caused by humans recovered from infection after the treatment process, natural deaths, and reductions occurred due to displacement between regions. The dynamics of the human population with vaccination, repellent and Wolbachia bacteria combination on average was able to reduce the infected human population by 45.2%. In Figure 3, plot (A1) is controlling simulation for Yogyakarta area, plot (A2): control simulation for Semarang area, Plot (B1) is the dynamics of the infected human population in Yogyakarta area, and plot (B2) is the dynamics of the infected human population in Semarang area.

3.4. Discussion

Mathematical models of dengue transmission using the strategy of vaccinations, repellent and Wolbachia have been developed and the sensitivity analysis have been conducted to determine the most influencing model parameter. The results of the sensitivity index showed that the most influencing parameter in the occurrence of endemic was the rate of human mobility δ_{pr}. In other words, if there is an area that is at high risk of dengue, the migration rate in that area can be reduced in order to avoid the dengue transmission to other areas. Not only will it reduce the mobility of the dengue transmission, the migration rate reduction also will impact the suppressing number of COVID-19 transmission to prevent the COVID-19 epidemic. In addition, high self-efficacy and decision to take action are good practices to dengue prevention during the COVID-19 pandemic [28].

The results showed that the use of vaccination, repellent and vector control such as Wolbachia was necessary to reduce dengue cases. Even thought if the effectiveness of vaccination and repellent is higher, the performance of this strategy in reducing the number of dengue cases will be more effective than using only Wolbachia mosquitoes. However, the results of our study suggest that the use of vaccination, vector control and vector control such as Wolbachia carried out together is very important in order to reduce dengue fever cases very significantly. In fact, higher vaccine and repellent efficacy can be obtained when 9–45 years of age seropositive individuals are vaccinated [4], [15] and vector control such as using Wolbachia is needed to suppress dengue cases [16]. The dynamics of the human population with vaccination, repellent and

Wolbachia bacteria combination strategy on average was able to reduce the infected human population by 45.2% in immobility aspect. Then in mobility dengue model, the numerical solutions showed that the trend graph is almost the same between Yogyakarta and Semarang areas. In two area, it showed that the combination control value of vaccination, repellent and Wolbachia were given with maximum effort, then the combination control value decreased slowly until the 100th day. This would cause the trend of the graph of infected individuals to decrease when control is given.

The aim of our research is to gain general insight into possible optimization of combination of vaccine, repellent and Wolbachia strategies in reducing dengue transmission, and therefore a single dengue serotype model is sufficient. The researchers used a single dengue serotype model that did not take into account the effects of secondary infection and it is therefore preferable to extend this study to consider multiple dengue serotypes. Reducing the mosquito model for the model with the mobility aspect is needed to continue further research due to the fact that mosquitoes are not very adventurous in the mobility aspect model because mosquitoes have a fairly short flight ability. In addition, because population dynamics are necessary during the season, the effect is considered because it can affect the dynamics of virus transmission. The age-dependent effect of the three combinations described is not considered. The issues we have outlined may help further research in the future.

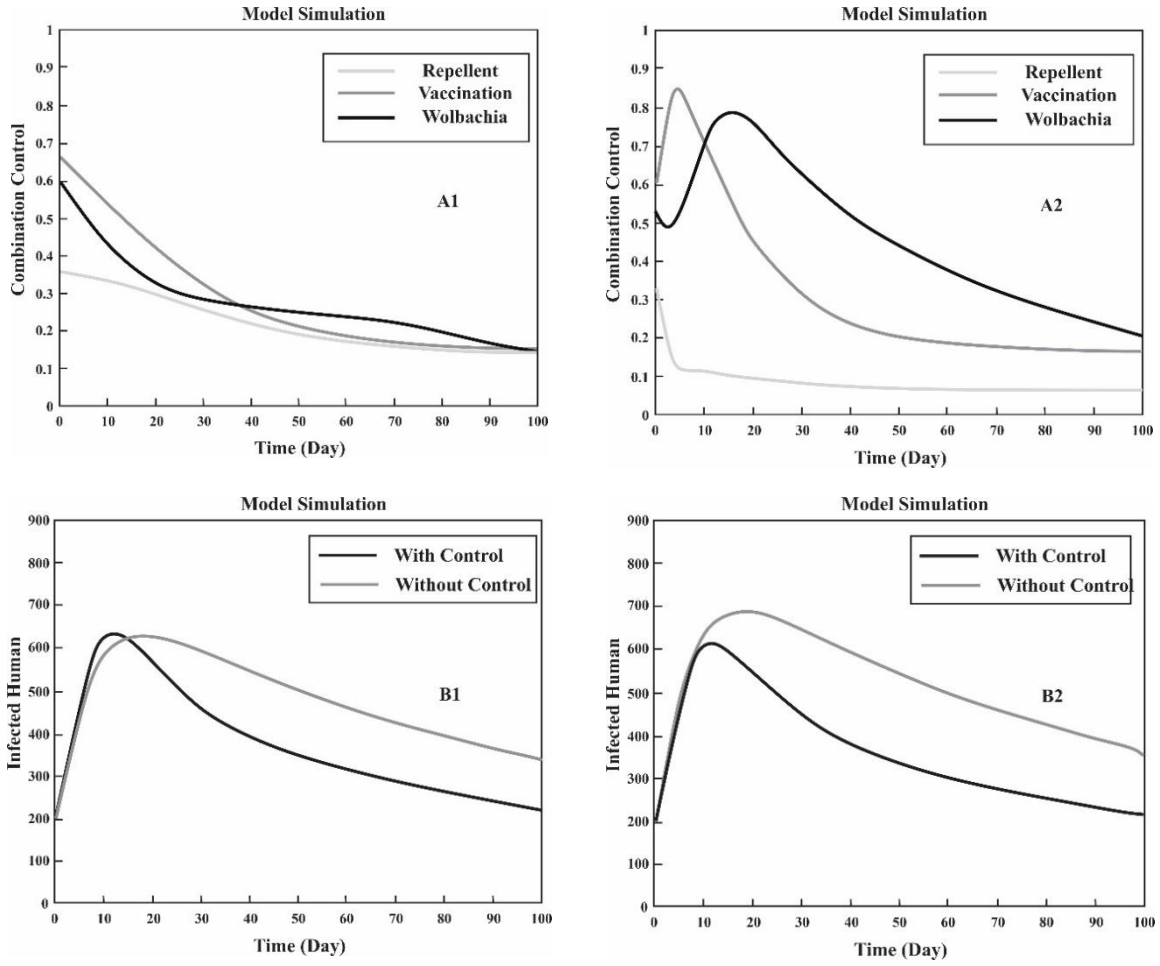

Figure 3. Numerical simulation of mobility-based dengue mathematical model

4. CONCLUSION

This study examines the dengue model with mobility aspects. In dengue model there are 3 main populations, namely the human population, non-Wolbachia mosquitoes and Wolbachia mosquitoes. Controls are carried out in the form of vaccination proportions, repellent to humans per unit time and injecting Wolbachia bacteria into non-Wolbachia mosquito eggs with the rule that one Wolbachia bacterium can only fill one egg. Genetic algorithm is used to estimate the unknown parameters in the model. Optimal control is

solved by Pontryagin's minimum principle. Backward-forward sweep algorithm was used to simulate the optimal control. The simulation results were then compared with the time without control. Based on the simulation results during the observation time, the dynamics of the human population with a combination of vaccination control, repellent and Wolbachia bacteria were able to reduce the infected human population by an average of 45.2%.

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