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Mathematics Model Development Deployment of Dengue Fever Diseases by Involve Human and Vectors Exposed Components

Flaviana Priscilla Persulessy[1], Paian Siantur[2] and Jaharuddin[3]
[1]Student, Department of Mathematics, Bogor Agricultural University, INDONESIA
[2,3]Lecturer, epartment of Mathematics, Bogor Agricultural University, INDONESIA

[1]Corresponding Author: priscillaflaviana@gmail.com

ABSTRACT

Dengue virus is one of virus that cause deadly disease was dengue fever. This virus was transmitted through bite of Aedes aegypti female mosquitoes that gain virus infected by taking food from infected human blood, then mosquitoes transmited pathogen to susceptible humans. Suppressed the spread and growth of dengue fever was important to avoid and prevent the increase of dengue virus sufferer and casualties. This problem can be solved with studied important factors that affected the spread and equity of disease by sensitivity index. The purpose of this research were to modify mathematical model the spread of dengue fever be SEIRS-ASEI type, to determine of equilibrium point, to determined of basic reproduction number, stability analysis of equilibrium point, calculated sensitivity index, to analyze sensitivity, and to simulate numerical on modification model. Analysis of model obtained disease free equilibrium (DFE) point and endemic equilibrium point. The numerical simulation result had showed that DFE, stable if the basic reproduction number is less than one and endemic equilibrium point was stable if the basic reproduction number is more than one.

Keywords-- Basic Reproduction Number, Dengue Fever, Mathematical Model, Sensitivity Analysis

I. INTRODUCTION

Dengue virus is a virus can causes death disease that is dengue fever. The virus is transmitted by the bite of female mosquitoes Aedes aegypti. that get viral infections by taking food from infected human blood, then transmit the pathogen to susceptible humans. There are four serotypes of the virus that cause dengue fever DEN1, DEN2, DEN3, and DEN4. A person is infected by one of the four serotypes, the will never be infected again by the same serotype, but a person can infection by another three serotypes in 12 weeks and then becomes more susceptible to developing DHF [6].

Suppressing the spread and growth of dengue fever important thing to avoid and prevent the increase of sufferer and casualties. This can be done by study the important factors affects of the spread and even distribution of the disease through the sensitivity index. Sensitivity index quantify how the basic reproduction number changes when response to the small shifts in the value of a parameter [4]. Sensitivity values can used to see which the parameters are important to measure accuracy and variations in which the parameters will transfer into $\mathcal{R}_0$ variation.

Many research models have been done on mathematical, to study the transmission of dengue fever and sensitivity analysis. [7] develop a SIR-ASI model to perform sensitivity analysis of dengue epidemic models. [3] gives a mathematical model dynamics transmission of dengue fever model epidemic SITR-ASI. [1] elaborated the SIR-MSI model describe the dynamics of dengue fever.

This research discusses modification of SIR-ASI model [7] by adding exposed subpopulations to human and mosquito populations, and assuming that humans will become susceptible again to three other serotypes. So that obtained the model of disease spread SEIRS-ASEI type. The purpose this research is modify mathematical model the spread dengue fever into SEIRS-ASEI type, determine equilibrium point, determine basic reproduction number, execute analysis stability of equilibrium point, numerates sensitivity index, undertake sensitivity analysis, and execute numerical simulation of the modified model.

II. MODIFICATION MATHEMATICAL MODEL

The incubation period is the time when dengue virus enters the body (during transmission) until the onset of the disease. Dengue virus incubation period occurs after humans bitten by mosquitoes infected with dengue virus and mosquitoes are susceptible to bite humans infected with dengue virus. The length of the incubation period depends on the respiration of each body, generally ranges from 4 to 6 days. In this incubation period, population of

susceptible humans and population of susceptible mosquitoes are considered open to virus infection. If case of virus transmission in population of susceptible humans and population of susceptible mosquitoes, then susceptible humans and susceptible mosquitoes are grouped into exposed subpopulations [8]. Therefore, the SIR-ASI model formulated by Rodrigues et al. (2013) are further modified by adding the exposed stages in the human population and mosquito populations.

The added assumption is that infected humans who recover because drug delivery will move to susceptible individuals. This is because medicine only heals and gives immunity to one serotype, nevertheless, not in the other three serotypes. This modification model is SEIRS-ASEI model, where the human population is divided into four classes, that are susceptible human (S_h), exposed human (E_h), infected human (I_h), dan resistant human (R_h). Mosquitoes are divided into three classes, that is aquatic phase (A_v), susceptible vector (S_v), exposed vector (E_v) dan infected vector (I_v).

Modification model is a modification of Rodrigues et al. (2013) by adding the E_h compartment is the exposed human population and E_v is the exposed mosquito population. Exposed human populations can experience natural death at μ_h rate and exposed mosquito populations can die naturally at rates μ_v. Furthermore, modification of the model is also done by adding the assumption that susceptible humans given the vaccine will have immunity to one serotype at a rate of ψ, after the immunity is reduced then the recovered human can return to being susceptible to the rate χ because immunity only applies to one serotype only. Schematically, the dispersion pattern of dengue fever type SEIRS-ASEI is illustrated in Figure 1, with (→) representing individual displacements and (⇢) expressing the influence between compartments. The blue color shows the modification of Rodrigues et al. (2013).

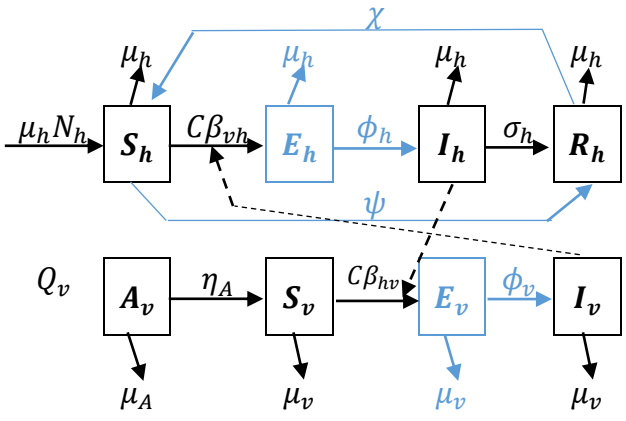


Figure 1 Diagram of Dengue Model Type SEIRS-ASEI

Based on the compartment diagram in Figure 1, we obtain a system of differential equations for each compartment as follows:

$$
\begin{aligned}
\frac{dS_h}{dt} &= \mu_h N_h - \left(C\beta_{vh}\frac{I_v}{N_h} + \mu_h + \psi\right)S_h + \chi R_h,\\
\frac{dE_h}{dt} &= \frac{C\beta_{vh}}{N_h}S_h I_v - (\mu_h + \phi_h)E_h,\\
\frac{dI_h}{dt} &= \phi_h E_h - (\sigma_h + \mu_h)I_h,\\
\frac{dR_h}{dt} &= \sigma_h I_h + \psi S_h - (\mu_h + \chi)R_h\,,\\
\frac{dA_v}{dt} &= \varphi\left(1 - \frac{A_v}{kN_h}\right)(S_v + E_v + I_v) - (\eta_A + \mu_A)A_v,\\
\frac{dS_v}{dt} &= \eta_A A_v - \left(C\beta_{hv}\frac{I_h}{N_h} + \mu_v\right)S_v,\\
\frac{dE_v}{dt} &= \frac{C\beta_{hv}}{N_h}S_v I_h - (\mu_v + \phi_v)E_v,\\
\frac{dI_v}{dt} &= \phi_v E_v - \mu_v I_v,
\end{aligned}
\tag{1}
$$

with $S_h + E_h + I_h + R_h = N_h$ is the total human population and $A_v + S_v + E_v + I_v = N_v$ total population of mosquitoes.

The transformations used for each compartment are: $S^h = \frac{S_h}{N_h}$, $E^h = \frac{E_h}{N_h}$, $I^h = \frac{I_h}{N_h}$, $R^h = \frac{R_h}{N_h}$, $A^v = \frac{A_v}{N_v}$, $S^v = \frac{S_v}{N_v}$, $E^v = \frac{E_v}{N_v}$, $I^v = \frac{I_v}{N_v}$. Thus, the equation of human population and mosquitoes can be written in the following differential equation system:

$$
\begin{aligned}
\frac{dS^h}{dt} &= \mu_h - (nC\beta_{vh}I^v + \mu_h + \psi)S^h + \chi\,(1 - S^h - E^h - I^h),\\
\frac{dE^h}{dt} &= nC\beta_{vh}S^h I^v - (\mu_h + \phi_h)E^h\,,\\
\frac{dI^h}{dt} &= \phi_h E^h - (\sigma_h + \mu_h)I^h,\\
\frac{dS^v}{dt} &= \eta_A(1 - S^v - E^v - I^v) - (C\beta_{hv}I^h + \mu_v)S^v,\\
\frac{dE^v}{dt} &= C\beta_{hv}S^v I^h - (\mu_v + \phi_v)E^v\,,\\
\frac{dI^v}{dt} &= \phi_v E^v - \mu_v I^v.
\end{aligned}
\tag{2}
$$

where $n = \frac{N_v}{N_h}$.

Table 1 Parameter of SEIRS-ASEI Model and its dimensions

Paramater	Description	Parameter Value	Unit
C	Average number of bites	0.8*	day^{-1}
μ_h	Average humans mortality	1/ (71x365)*	days
β_{vh}	Transmission probability from I_v	0. 375*	bite^{-1}
ϕ_h	Intrinsic incubation rate	1/5**	time unit
σ_h	Average healing period	1/3*	day^{-1}
ψ	The proportion of susceptible humans who were given the vaccine was immune	0.1***	no units
χ	Rate of loss of infection-acquired immunity	0.1***	no units
η_A	Maturation rate from larvae to adult	0.08*	day^{-1}

β_{hv}	Transmission probability from I_h	0. 375*	bite^{-1}
μ_A	Natural mortality of larvae	¼*	day^{-1}
μ_v	Average lifespan of adult mosquitoes	1/10*	days
ϕ_v	Extrinsic incubation rate	1/10**	time unit
φ	Number of eggs at each deposit per capita	6	day^{-1}
k	Number of larvae per human	3	no units
N_h	Total human population	480000	no units
n	$\frac{N_v}{N_h}$	1***	n/a

Assumption***)
Source: Rodrigues. *Et al*.2013*) and Newton and Reiter, 1992**)

III. RESULTS AND DISCUSSION

The equilibrium point determination of the system in equation (2) has a positive solution region, with $S^h \geq 0, E^h \geq 0, I^h \geq 0, S^v \geq 0, E^v \geq 0$, and $I^v \geq 0$.

The Equilibrium Points Determination

The Disease Free Equilibrium (DFE) is a point where all individuals are suspectibles An endemic equilibrium is a point condition when the diseases there in human population.

From the system of equation (2), obtained two equilibrium points are disease free equilibrium point (T_0) and endemic equilibrium point (T_1) as follows $T_0(S^{h*}, E^{h*}, I^{h*}, S^{v*}, E^{v*}, I^{v*}) = \left(\frac{\chi+\mu_h}{\chi+\psi+\mu_h}, 0,0, \frac{\eta_A}{\eta_A+\mu_v}, 0,0\right)$ and $T_1(S^{h**}, E^{h**}, I^{h**}, S^{v**}, E^{v**}, I^{v**}) = \left(\frac{-(-1+E_h+I_h)\chi+\mu_h}{cI_v n\beta_{vh}+\chi+\psi+\mu_h}, \frac{cnS_h\beta_{vh}}{\phi_h+\mu_h}, \frac{E_h\phi_h}{\sigma_h+\mu_h}, -\frac{(-1+E_v+I_v)\eta_A}{cI_h\beta_{hv}+\eta_A+\mu_v}, \frac{cI_hS_v\beta hv}{\phi_v+\mu_v}, \frac{E_v\phi_v}{\mu_v}\right)$.

Basic Reproduction Number

The basic reproduction number is defined as the expected number of secondary infections produced by a single infected individual in a completely susceptible population [2]. The basic reproduction number is determined by using the next generation matrix G defined

$$G = FV^{-1}$$

The matrix F and V for the DFE point (T_0) were obtained based on the system of differential equations (2) as follows:

$$F = \begin{pmatrix} 0 & 0 & 0 & nc\beta_{vh}\frac{\chi+\mu_h}{\chi+\psi+\mu_h} \\ 0 & 0 & 0 & 0 \\ 0 & c\beta_{hv}\frac{\eta_A}{\eta_A+\mu_v} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \mu_h+\phi_h & 0 & 0 & 0 \\ -\phi_h & \sigma_h+\phi_h & 0 & 0 \\ 0 & 0 & \mu_v+\phi_v & 0 \\ 0 & 0 & -\phi_v & \mu_v \end{pmatrix}$$

The basic reproduction number $(\mathcal{R}_0)$ is largest nonnegative eigenvalue of matrix $G = FV^{-1}$. Based on the system of equation (2), $\mathcal{R}_0$ is obtained as follows:

$$\mathcal{R}_0 = \frac{c^2 n\beta_{hv}\beta_{vh}\eta_A\phi_h\phi_v(\chi+\mu_h)}{(\sigma_h+\mu_h)(\phi_h+\mu_h)(\chi+\psi+\mu_h)\mu_v(\eta_A+\mu_v)(\phi_v+\mu_v)}.$$

Stability Analysis of Equilibrium Point

Stability analysis of disease free equilibrium point (T_0) and endemic equilibrium point (T_1) obtained the following conclusions.

a. The disease free equilibrium point (T_0) of the system of equation (2) is locally asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

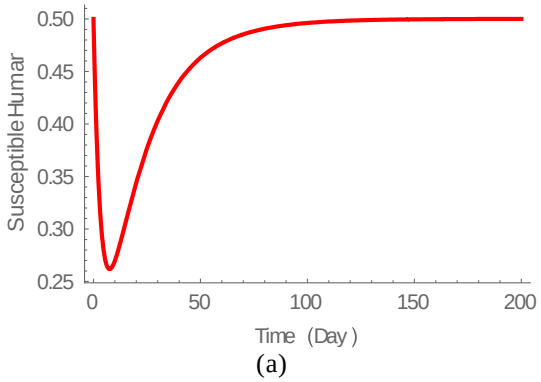
b. The endemic equilibrium point (T_1) of the system of equation (2) is stable if $\mathcal{R}_0 > 1$, and unstable if $\mathcal{R}_0 < 1$.

Numerical Simulation

Simulations were performed to demonstrate the stability characteristics for each equilibrium point using the Wolfram Mathematica® 11.0 software. The parameter values for the model is listed in Table 1, with initial conditions are $S_{h_0} = 0.5$, $E_{h_0} = 0.3$, $I_{h_0} = 0.2$, $S_{v_0} = 0.4$, $E_{v_0} = 0.3$, $I_{v_0} = 0.3$.

Dynamic Population for Disease Free Equilibrium Point (T_0)

Based on the parameter values listed in Table 1 , we obtained the basic reproduction number $\mathcal{R}_0 = 0.299965 < 1$ and the disease free equilibrium point $T_0(S^{h*}, E^{h*}, I^{h*}, S^{v*}, E^{v*}, I^{v*}) = (0.500096,0,0,0.444444,0,0)$. Numerical simulation for the dynamics of human population when $\mathcal{R}_0 < 1$ stable at the disease free equilibrium point T_0, is presented in Figure 2.



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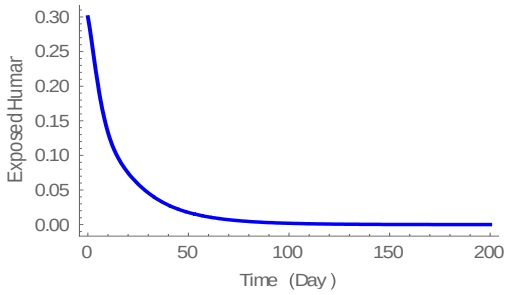

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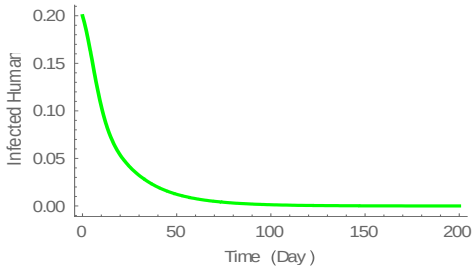
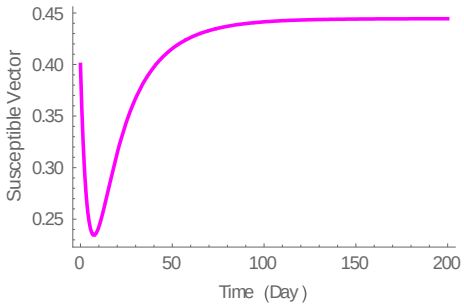


(c)

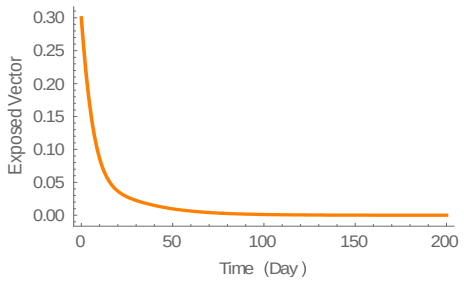
Figure 2 Human population dynamics for disease free quilibrium point (T_0)

Simulation results show that the susceptible human population decreased to $S^h = 0.26$, then increased to stable at point $S^h = 0.500096$ (Figure 2a). Exposed human population experienced in population numbers until stablized at the point $E^h = 0$ (Figure 2b). The infected human population has decreased to become stable at the point $I^h = 0$ (Figure 2c).

The numerical simulation for the population dynamic vector when $\mathcal{R}_0 < 1$ stable at the disease free equilibrium point T_0, is presented in Figure 3.



(a)



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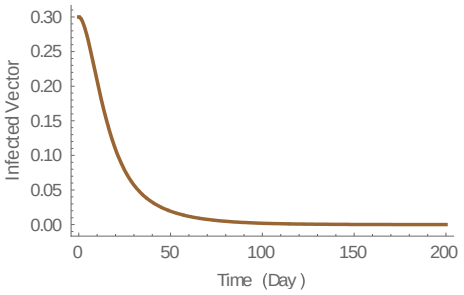


(c)

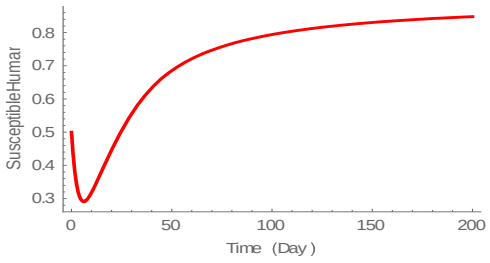
Figure 3 Dynamics population vectors for disease free equilibrium point (T_0)

The simulation results showed that the susceptible mosquito population decreased from $S^v = 0.40$ then increased steadyly at the point $S^v = 0.444444$ (Figure 3a). The exposed mosquitoes population decreased to a stable condition at point $E^v = 0$ (Figure 3b). Infected mosquito population decreased until stable at point $I^v = 0$ (Figure 3c).

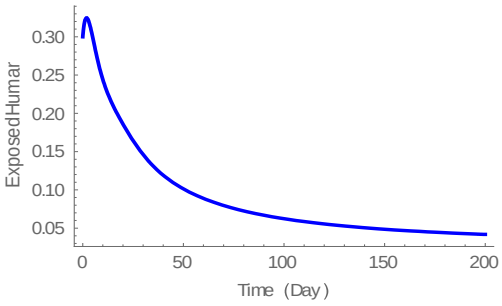
The simulation results presented in figures 2 and 3 correspond to Theorem 1 The disease free equilibrium point of equation system (2) is local asymptotic stablity if $\mathcal{R}_0 < 1$. The disease free equilibrium point (T_0) is unstable if $\mathcal{R}_0 > 1$.

Population Dynamics Endemic Equilibrium Point (T_1)

Based on the parameter values listed in Table 1, and the following parameters values $\psi = 0.01$, $\chi = 0.2$, $n = 2$ which were assigmend to the different with the listed in Table 1. We obtained the basic reproduction numbers are $\mathcal{R}_0 = 1.14251 > 1$ and endemic equilibrium point
$T_1(S^{h**}, E^{h**}, I^{h**}, S^{v**}, E^{v**}, I^{v**}) =$
(0.878416,0.029878,0.017925,0.421764,0.01143, 0.01134). Numerical simulation for the dynamics of human population when $\mathcal{R}_0 > 1$ stable at the endemic equilibrium point T_1 is presented in Figure 4.



(a)



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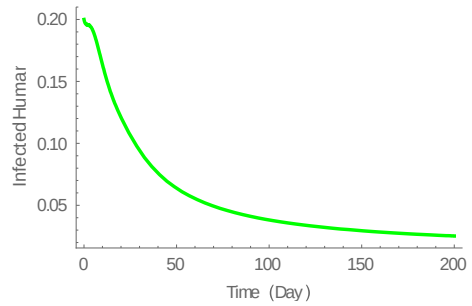
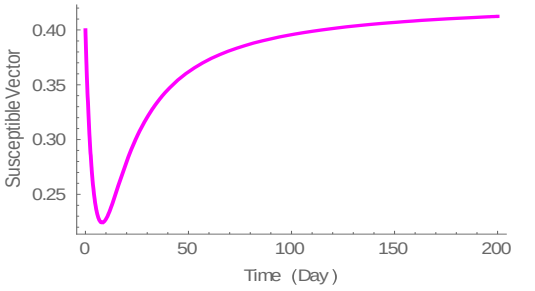


(c)

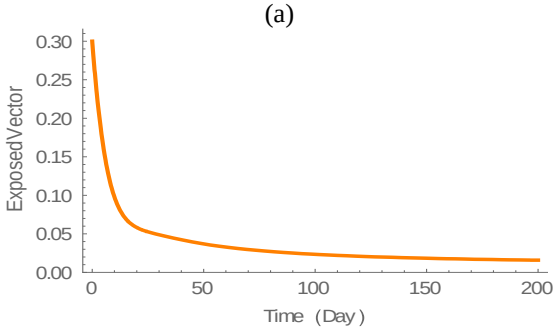
Figure 4 Human population dynamics for endemic equilibrium point (T_1)

The simulation result shows that susceptible human population is stable at point $S^h = 0.878416$ (Figure 4a), exposed human population is stable at point $E^h = 0.029878$ (Figure 4b), and the infected human population is stable at point $I^h = 0.0179247$ (Figure 4c).

The numerical simulation for population vector dynamics when $\mathcal{R}_0 > 1$ stable at the endemic equilibrium point T_1, is presented in Figure 5.



(a)



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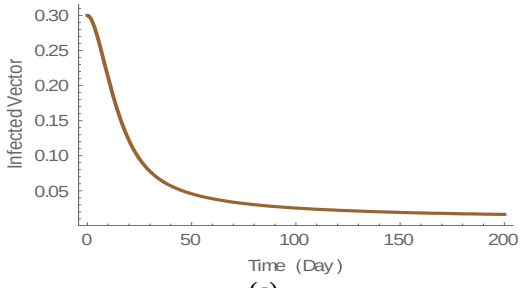

(c)

Figure 5 Population dynamics vectors for endemic equilibrium point (T_1)

The simulation results show that the susceptible mosquito population is stable at the point $S^v = 0.421764$ (Figure 5a), exposed mosquitoes population is stable at point $E^v = 0.01134$ (Figure 5b), and infected mosquitoes population is stable at point $I^v = 0.01134$ (Figure 5c).

The simulation results presented in figures 4 and 5 correspond to Theorem 2 The endemic equilibrium point of the system of equation (2) is stable if $\mathcal{R}_0 > 1$.

Sensitivity Analysis

This task is intended to assess the effect of changing particular parameter values on $\mathcal{R}_0$. The sensitivity index of the basic reproduction number of the $\mathcal{R}_0$ depending on the parameter p is obtained by

$$\Upsilon_p^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial p} \times \frac{p}{\mathcal{R}_0}.$$

The sensitivity index of each parameter of the model is presented in Table 2.

Referring to Table 1 also the values of the parameters ψ, χ, n for conditions without disease and endemic, two basic reproduction values are obtained as presented previously. The sensitivity index value that will be presented in Table 2 is the sensitivity index value for the parameters in conditions without disease and endemic.

Table 2 The Sensitivity Index of Parameter

Paramater	Sensitivity Index Value	
	$\mathcal{R}_0 < 1$	$\mathcal{R}_0 > 1$
C	2	2
μ_h	-0.000115824	-0.0000515319
β_{vh}	1	1
ϕ_h	0.000192901	0.000192901
σ_h	$-\frac{25915}{25918}$	$-\frac{25915}{25918}$
ψ	-0.499904	-0.666581
χ	0.499711	0.666324
η_A	0.555556	0.555556
β_{hv}	1	1
μ_A	0	0
μ_v	-2.05556	-2.05556
ϕ_v	0.5	0.5
n	1	1

Based on Table 2, there are three group sensitivity index values, which are positive, negative and zero. The positive values indicate that the increase of that particular parameter will increase the values of $\mathcal{R}_0$. The negative values indicate that the increase of that particular parameter will descrease the values of $\mathcal{R}_0$. Whereas, the sensitivity index is zero meaning the parameter p has no effect on the value of $\mathcal{R}_0$.

In adddition, computer simulations was also conducted to show the effect of changing parameter values C, β_{vh}, σ_h, ψ, and χ on $\mathcal{R}_0$.

The Effect of Average Daily Biting (C)

The daily rate of mosquito bites in humans is also an important factor to be observed. Numerical simulation results are shown in Figure 6 to see the effect of changing

parameter value C on exposed human population and infected human population.

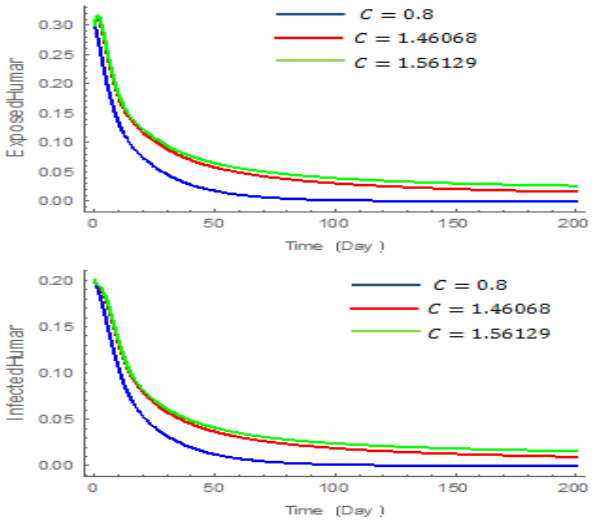

Figure 6 Effect of E_h and I_h from variation C

Figure 6 shows that with an average daily bite increased, it will increase the number of exposed human populations (Figure 6a) and infected human population (Figure 6b). This shows that if the average mosquito bites infected in humans can not be pressed from 1.46068 per day then the disease will not disappear from the population. If parameter value C = 0.8 then the graph will be stable at the disease free equilibrium point. Whereas, if parameter C = 1.56129 then the graph will be stable at endemic equilibrium point.

The Effect Transmission Probability from Infected Mosquito

Transmission infected mosquitoes is transmission of virus from infected mosquitoes to susceptible humans. Numerical simulation results are shown in Figure 7 to see the effect of changing parameter value β_{vh} on exposed human population and infected human population.

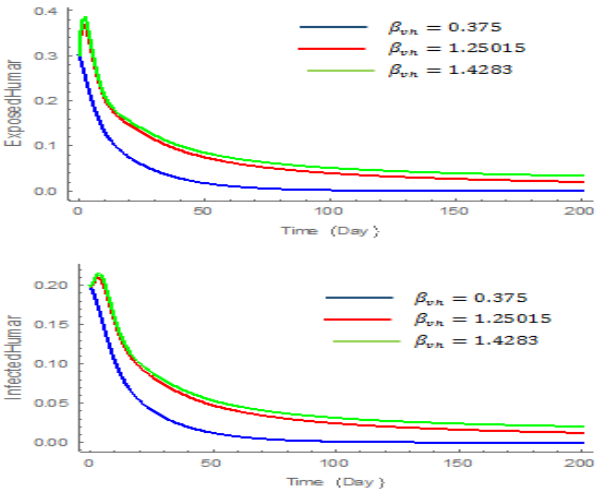

Figure 7 Effect of E_h and I_h from variation β_{vh}

Figure 7 shows that the greater the transmission rate I_v occurs, will increase the number of exposed human populations (Figure 7a) and the number of infected populations. This indicates that if the transmission rate I_v is not suppressed to less than 1.25015 per day then the disease will not disappear from the population. If parameter value β_{vh} = 0.375 then the graph will be stable at the disease free equilibrium point. Whereas, if parameter β_{vh}= 1.4283 then the graph will be stable at endemic equilibrium point.

Effect of Healing Period from Dengue Fever

The healing period observed in this study is the period of healing of dengue fever in the human population. Numerical simulation results are shown in Figure 8 to see the effect of changing parameter value σ_h on exposed human population and infected human population.

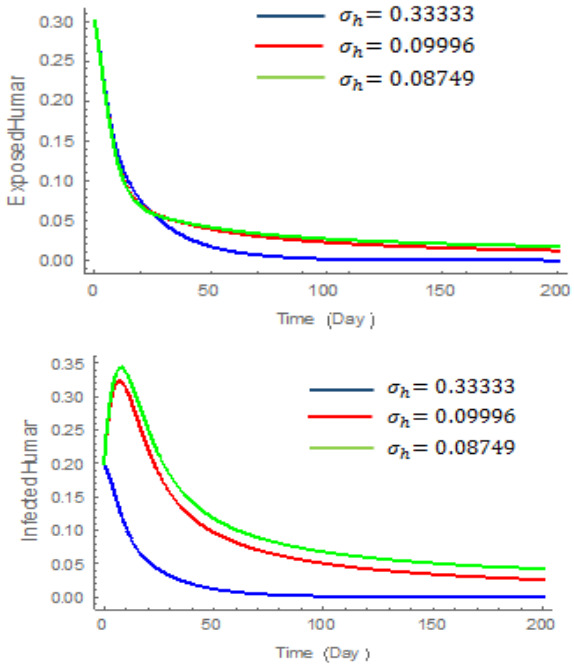

Figure 8 Effect of E_h and I_h of variation σ_h

Figure 8 shows that the greater the healing period (σ_h), will decrease the exposed human population (Figure 8a) and the number of infected human populations (Figure 8b). This suggests that if medical treatment is done well to increase healing to 0.09996 per day, then the disease will still exist in the population. If parameter value σ_h = 0.33333 then the graph will be stable at the disease free equilibrium point. Whereas, if parameter σ_h = 0.08749 then the graph will be stable at equilibrium point endemic.

The Effect of The Proportion of Humans Given The Vaccine Directly Immune

The vaccine is an antigenic agent used to produce active immunity against a disease. Numerical simulation results are shown in Figure 9 to see the effect of changing parameter value ψ on exposed human population and infected human population.

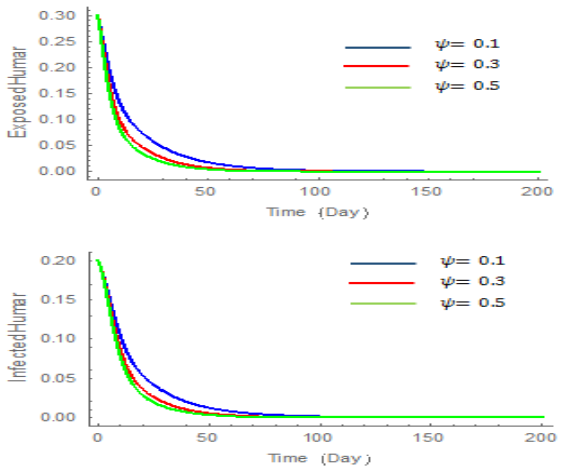

Figure 9 Effect of E_h and I_h of variation ψ

In Figure 9 it shows that the more human populations given the vaccine (ψ), the lower the exposed human population (Figure 9a) and the infected human population (Figure 9b). This suggests that the more humans are vaccinated the system will stabilize at disease free equilibrium point.

The Effect of Constant Rate of Immune Loss In Humans After Healing

Immunity is a system of protection of outside biological influences by specialized cells and organs in an organism. Numerical simulation results are shown in Figure 10 to see the effect of changing parameter value χ on exposed human population and infected human population.

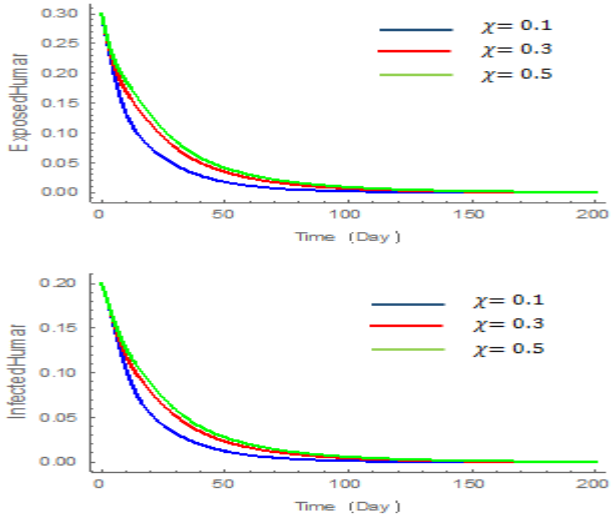

Figure 10 Effect of E_h and I_h of variation χ

In Figure 10 it is seen that the greater the χ, resulting in an expanding human population number so that the human population is infected will also increase. This suggests that if the level of constant immune loss in humans after recovery increases, exposed human populations and infected human populations will increase. If parameter value χ = 0.1 then the graph will be stable at disease free equilibrium point. Whereas if parameter χ increases more than 0.1 then the graph will be stable at endemic equilibrium point.

CONCLUSIONS

In this research, modified mathematical model of dengue fever distribution by adding exposed stages on mosquito and human population and some assumptions as model parameters. The result of the analysis performed on the modified model obtained two equilibrium points, i.e equilibrium point without disease and endemic equilibrium point. Equilibrium point without disease locally asymptotic stable at condition $\mathcal{R}_0 < 1$, whereas endemic equilibrium point stable at condition $\mathcal{R}_0 > 1$. The numerical simulation results for $\mathcal{R}_0 < 1$ indicate that the local asymptotic population of humans and mosquitoes is stable at the equilibrium point without disease, whereas for $\mathcal{R}_0 > 1$ shows that the human and mosquito populations are stable at endemic equilibrium point. The sensitivity analysis performed on the parameters shows that each parameter has a different influence on $\mathcal{R}_0$ depending on its sensitivity. The average daily bite parameters, healing rate from dengue fever, infected mosquito transmission rate, and loss of immunity in humans after healing when increased will increase the $\mathcal{R}_0$ value that affects the dengue epidemic. If vaccination is increased then it causes a decrease in $\mathcal{R}_0$ value so as to help suppress disease growth rate.

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