Research article

Dengue infection modeling and its optimal control analysis in East Java, Indonesia

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ABSTRACT

In this study, we present a mathematical model of dengue fever transmission with hospitalization to describe the dynamics of the infection. We estimated the basic reproduction number for the infected cases in East Java Province for the year 2018 is $\mathcal{R}_0 \approx 1.1138$. The parameters of the dengue model are estimated by using the confirmed notified cases of East Java province, Indonesia for the year 2018. We formulated the model for dengue with hospitalization and present its dynamics in details. Initially, we present the basic mathematical results and then show briefly the stability results for the model. Further, we formulate an optimal control problem with control functions and obtain the optimal control characterization. The optimal control problem is solved numerically and the results comprised of controls system for different strategies. The controls such as prevention and insecticide could use the best role in the disease eradication from the community. Our results suggest that the prevention of humans from the mosquitoes and the insecticide spray on mosquitoes can significantly reduce the infection of dengue fever and may reduce further spread of infection in the community.

1. Introduction

Dengue fever, which is known as vector-borne disease, is caused mainly by the dengue virus. It has the serotypes, such as DENV 1 to DENV4 that belong to *Flavivirus*. Most of the countries of the world are not safe from this disease. The most seriously affected areas of the world due to dengue are Americas, the subtropical regions, Eastern Mediterranean, Africa, and more especially the Western Pacific region and South-East Asia [1, 2, 3]. After Malaria, the dengue fever infection is considered to be the deadliest mosquito-borne or vector-borne disease with thousands of deaths and more than 390 million infections [1, 2] worldwide. A report published in 2012 indicates that more than 100 countries of the world are in risk due to the infection of dengue fever [4]. The dengue disease is spread by many kinds of mosquitoes such as *Aedes* and especially, the *A. Aegypti*. The classical dengue fever or the break bone fever relatively causes both mortality and mild morbidity, and the infected one recovers in a short span of time of one to two weeks from the fever onset [5]. Some individuals develop dengue shock syndrome (DSS) or hemorrhagic fever (DHF) [6]. Worldwide annually, the higher number of dengue hemorrhagic fever (DHF) cases have been reported by World Health Organization (WHO), see for more details [7].

The bites of the mosquitoes carrying the dengue virus (female mosquito) are the main transmission route to the human population [8]. The infection is obtained by taking the blood meal from an infected person and further infected mosquitoes transfer the virus to other healthy individuals. Moreover, the recovery of a person from one particular DENV serotype leads immune permanently and partially or temporarily to the other serotypes [6].

For the dengue virus, until now no such effective treatment is available except some fluid replacement therapy, which can be initiated at the early stage while also there exist some traditional types of treatments [9]. Besides the treatment unavailability for infected people with dengue virus, there is no effective vaccine in market until now to vaccinate the susceptible individuals. The WHO suggested some developments regarding vaccine for the dengue virus, although in the market there is no such effective vaccination against the dengue virus [10]. For the dengue vaccine, a published report in 2015 referred to the development of the first vaccine in Mexico [10].

Mathematical models that addressed the dengue dynamics are numerous in literature [11, 12, 13, 14] and the references therein. All these mentioned references are showing the dynamics of the dengue infections in different perspectives such the dynamical analysis, vacci-

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nation, and their optimal control analysis. Some recent research papers that reported the dengue infection with real data are given in [15]. A mathematical model of dengue infection is constructed in [16] that addressed the dengue infection with real data of Pakistan and presented some useful elimination strategies for mosquitoes infection. The dengue dynamics with the same serotypes and their reinfection have been analyzed in [17]. The dengue modeling in both deterministic and stochastic sense is briefly discussed in [18]. A hybrid methodology for the dengue forecasting is studied in [19]. The authors in [20] studied the dynamics of dengue fever and their coinfection with Zika, where the vaccination effect is shown for the dengue fever. The authors in [21] studied the dengue dynamics in rural Cambodia. A two-strain Tuberculosis model and the dengue virus are proposed in [22]. The dengue model and their optimal control analysis under the effect of Wolbachia Bacterium are studied in [23]. The dynamics of dengue fever modeling in a heterogeneous environment is considered in [24]. The dengue dynamics under the framework of temperature and mosquitoes control, and human mobility are proposed in [25]. The dengue model with the notified cases of humans is considered in [26]. The application of the optimal control technique is also utilized by the researchers in variety of problems, see the published work [27, 28, 29]. For instant, the authors in [27] considered stochastic optimal control problems by using the method of spectral linear filter and presented the results. The dengue dynamics with asymptomatic carriers together with the applications of optimal control strategies have been studied in [28]. An SIR epidemic model with optimal impulse control is considered in [29].

Motivated from the literature above, we wish to consider a new formulation to the dengue fever modeling mathematically with the assumption of hospitalization class. This new idea of the hospitalization of infected cases that are reported has been analyzed through a mathematical model. The data analysis is performed by using the infected cases that hospitalized. In order to find the real statistical values of the parameters for the model, we consider the real data of East Java Province, Indonesia for the year 2018 [30] and the subsequent results are obtained and discussed. We present deeply the dynamics of dengue fever dynamics with control strategies. We provide the recent literature on dengue fever that was conducted previously by researchers and also, a most recent work in Section of introduction. Next, we give a brief overview of the rest of the work of the paper. Brief mathematical modeling of the dengue virus is shown in section 2. The local and global stability at the disease-free equilibrium (DFE) are presented in Section 3. In section 4, we present the endemic equilibria and the backward bifurcation. The parameter estimation of the dengue model and the sensitivity analysis are given in Section 5. We discussed in Section 6 briefly the formulation of an optimal control problem and the associated results. We present the numerical solution of the optimal control problem with control characterization briefly in Section 7. Finally, we summarized the results in Section 8.

2. Dengue model transmission

In this section, we describe a host-vector model for dengue transmission. The host-vector model is divided into three mosquitoes populations, susceptible (S_v), exposed (E_v), and infectious (I_v), and five human (host) populations, susceptible (S_h), exposed (E_h), infectious (I_h), hospitalized and/or notified infectious (P_h) and recovered (R_h). Thus, the total human population denoted by N_h is given as $N_h = S_h + E_h + I_h + P_h + R_h$. Here, we consider the new class known as hospitalized individuals that are notified infected individuals and is shown by P_h. The population in P_h class is assumed to be those who are recorded to the hospital and the people who are identified as confirmed dengue patients. However, we assume that the population in I_h class can also recover without having to enter P_h class. All the human hosts belonging to the class $P_h(t)$ are 100% protected so they do not produce infections in mosquitoes and do not contribute to the disease propagation. With the discussion above, we present the nonlinear system of differential

Table 1. Biological meanings of parameters for dengue model (1).

Parameter	Description
Λ_v	Recruitment rate of mosquito
β	Average biting rate per mosquito per person
α_v	Transmission probability from infected human to susceptible mosquito
μ_v	Natural death rate of mosquito
γ_v	Extrinsic incubation of mosquito
Λ_h	Recruitment rate of human
α_h	Transmission probability from infected mosquito to susceptible human
γ_h	Extrinsic incubation of human
η	Rate of hospitalization and/or notification of infected human
q_1	Natural recovery rate of infected human
q_2	Recovery rate of hospitalized and/or notified infected human
δ	Disease related death rate of human
μ_h	Natural death rate of human

equations describing the dynamics of host-vector dengue fever, which is given by:

$$\frac{dS_v}{dt} = \Lambda_v - \beta \alpha_v S_v \frac{I_h}{N_h} - \mu_v S_v,$$

$$\frac{dE_v}{dt} = \beta \alpha_v S_v \frac{I_h}{N_h} - (\gamma_v + \mu_v) E_v,$$

$$\frac{dI_v}{dt} = \gamma_v E_v - \mu_v I_v,$$

$$\frac{dS_h}{dt} = \Lambda_h - \beta \alpha_h I_v \frac{S_h}{N_h} - \mu_h S_h,$$

$$\frac{dE_h}{dt} = \beta \alpha_h I_v \frac{S_h}{N_h} - (\gamma_h + \mu_h) E_h,$$

$$\frac{dI_h}{dt} = \gamma_h E_h - (\eta + q_1 + \mu_h) I_h,$$

$$\frac{dP_h}{dt} = \eta I_h - (\delta + q_2 + \mu_h) P_h,$$

$$\frac{dR_h}{dt} = q_1 I_h + q_2 P_h - \mu_h R_h, \tag{1}$$

with the initial conditions

$$S_v(0) = S_{v0} \geq 0, E_v(0) = E_{v0} \geq 0, I_v(0) = I_{v0} \geq 0,$$

$$S_h(0) = S_{h0} \geq 0, E_h(0) = E_{h0} \geq 0, I_h(0) = I_{h0} \geq 0,$$

$$P_h(0) = P_{h0} \geq 0, R_h(0) = R_{h0} \geq 0. \tag{2}$$

In the above model, the recruitment rates of vector and host are respectively given by Λ_v and Λ_h. The parameter β is the biting rate of the mosquitoes. The transmission probability among infected humans and susceptible mosquitoes is shown by α_v. The natural mortality rate for humans is given by μ_h while for mosquitoes are μ_v. The parameter γ_v represents the incubation period of mosquitoes populations while for the humans we consider γ_h. The transmission probability among susceptible humans and infected mosquitoes is given by α_h. The notified or hospitalized confirmed dengue infected cases are shown by η. The natural recovery of infected individuals given by q_1 while those are notified confirmed dengue cases recovered at a rate of q_2. The death due infection of dengue fever is shown by δ. The detailed definition of the parameters involved in model (1) is shown briefly in Table 1. In the following section, we explore some of the important properties of the model (1). Next, we show the invariant regions for the given dengue model (1). Consider the feasible region $\Theta = \Theta_v \times \Theta_h \subset \mathbb{R}^3_+ \times \mathbb{R}^5_+$, with

$$\Theta_v = \left\{ (S_v(t), E_v(t), I_v(t)) \in \mathbb{R}^3_+ : N_v(t) \leq \frac{\Lambda_v}{\mu_v} \right\},$$

and

$$\Theta_h = \left\{ (S_h(t), E_h(t), I_h(t), P_h(t), R_h(t)) \in \mathbb{R}^5_+ : N_h(t) \leq \frac{\Lambda_h}{\mu_h} \right\}.$$

We have the following results for this feasible region.

Lemma 1. *The region given by $\Theta = \Theta_v \times \Theta_h \subset \mathbb{R}^3_+ \times \mathbb{R}^5_+$ is positively invariant for the dengue model (1) with the non-negative initial conditions in (2).*

Proof. The summation of the mosquitoes and human populations of the dengue model (1) leads to

$$\frac{dN_v}{dt} = \Lambda_v - \mu_v N_v$$

and

$$\frac{dN_h}{dt} = \Lambda_h - \mu_h N_h - \delta P_h \leq \Lambda_h - \mu_h N_h.$$

Hence, $\frac{dN_v(t)}{dt} \leq 0$, if $N_v(0) \geq \frac{\Lambda_v}{\mu_v}$ and $\frac{dN_h(t)}{dt} \leq 0$, if $N_h(0) \geq \frac{\Lambda_h}{\mu_h}$. So, $N_v(t) \leq N_v(0)e^{-\mu_v t} + \frac{\Lambda_v}{\mu_v}\left(1 - e^{-\mu_v t}\right)$ and $N_h(t) \leq N_h(0)e^{-\mu_h t} + \frac{\Lambda_h}{\mu_h}\left(1 - e^{-\mu_h t}\right)$. Thus, the region given by Θ is positively invariant. Also, if $N_v(0) > \frac{\Lambda_v}{\mu_v}$ and $N_h(0) > \frac{\Lambda_h}{\mu_h}$, then either the solutions enter Θ in finite time, or $N_v(t)$ tends to $\frac{\Lambda_v}{\mu_v}$ and $N_h(t)$ tends to $\frac{\Lambda_h}{\mu_h}$ asymptotically. So, the regions given by Θ attract all the solutions in $\mathbb{R}^8_+$. $\square$

3. Stability analysis disease free case

This section explores the stability results for the dengue model given by at the disease free equilibrium (DFE) E_0. We set the right hand side of the dengue model (1) equals to zero and obtain the following expressions

$$E_0 = \left(S_v^0, 0, 0, S_h^0, 0, 0, 0, 0\right) = \left(\frac{\Lambda_v}{\mu_v}, 0, 0, \frac{\Lambda_h}{\mu_h}, 0, 0, 0, 0\right).$$

We compute the basic reproduction number $\mathcal{R}_0$ by using the next generation matrix approach for the dengue model (1). Consider the infected compartments in dengue model (1) are E_v, I_v, E_h, I_h, P_h and follow the instruction given in [31] and also its applications in [32, 33], the matrices F and V are obtained as follows:

$$F = \begin{pmatrix} 0 & 0 & 0 & \frac{\beta\alpha_v\mu_h\Lambda_v}{\Lambda_h\mu_v} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & \beta\alpha_h & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \text{ and } V = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 \\ -\gamma_v & \mu_v & 0 & 0 & 0 \\ 0 & 0 & k_2 & 0 & 0 \\ 0 & 0 & -\gamma_h & k_3 & 0 \\ 0 & 0 & 0 & -\eta & k_4 \end{pmatrix},$$

where $k_1 = (\gamma_v + \mu_v)$, $k_2 = (\gamma_h + \mu_h)$, $k_3 = (\eta + q_1 + \mu_h)$ and $k_4 = (\delta + q_2 + \mu_h)$. The required basic reproduction to the given model is obtained through the spectral radius of the matrix $\mathcal{R}_0 = \rho(FV^{-1})$, which is given by the following equation

$$\mathcal{R}_0^2 = \frac{\beta^2\alpha_h\gamma_h\mu_h\alpha_v\gamma_v\Lambda_v}{k_1k_2k_3\Lambda_h\mu_v^2}.$$

The basic reproduction number $\mathcal{R}_0$ expresses an average number of secondary human infections produced by one infective human individual during his/her infectious period. It expresses an average number of secondary infections in mosquitoes and human hosts produced by one infective individual (either mosquito or human) during their infectious period. It determines that an emerging infectious disease spread in a community or population and determines that what proportion of the population should be immunized by vaccination for the disease eradication. In biological models if $\mathcal{R}_0 > 1$, the infection will be spread in the population otherwise no when $\mathcal{R}_0 < 1$. In general, when the value of $\mathcal{R}_0$ is large then it is harder to control the epidemic. Next, we demonstrate the local stability of the disease free equilibrium (DFE) at E_0 in the following:

Theorem 1. *The DFE E_0 is a locally asymptotically stable equilibrium of the system (1) whenever $\mathcal{R}_0 < 1$.*

Proof. In order to prove the given theorem, we need to obtain the Jacobian matrix by evaluated the model (1) at the DFE E_0, and we have

$$J(E_0) = \begin{pmatrix} -\mu_v & 0 & 0 & 0 & 0 & -\frac{\beta\alpha_v\Lambda_v\mu_h}{\Lambda_h\mu_v} & 0 & 0 \\ 0 & -k_1 & 0 & 0 & 0 & \frac{\beta\alpha_v\Lambda_v\mu_h}{\Lambda_h\mu_v} & 0 & 0 \\ 0 & \gamma_v & -\mu_v & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\beta\alpha_h & -\mu_h & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta\alpha_h & 0 & -k_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_h & -k_3 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \eta & -k_4 & 0 \\ 0 & 0 & 0 & 0 & 0 & q_1 & q_2 & -\mu_h \end{pmatrix}.$$

It can be seen from the above matrix $J(E_0)$, the eigenvalues $-\mu_v$, $-\mu_h$, $-\mu_h$, and $-k_4$ are obviously negative while the remaining four eigenvalues with negative reals parts can be obtained through the following equations:

$$\lambda^4 + \varpi_1\lambda^3 + \varpi_2\lambda^2 + \varpi_3\lambda + \varpi_4 = 0,$$

where

$$\varpi_1 = k_1 + k_2 + k_3 + \mu_v,$$

$$\varpi_2 = k_3\mu_v + k_2(k_3 + \mu_v) + k_1(k_2 + k_3 + \mu_v),$$

$$\varpi_3 = k_2k_3\mu_v + k_1\left(k_3\mu_v + k_2(k_3 + \mu_v)\right),$$

$$\varpi_4 = k_1k_2k_3\mu_v\left(1 - \mathcal{R}_0^2\right).$$

The coefficients given by ϖ_i for $i = 1, 2..., 4$ are positive for obviously for ϖ_i, for, $i = 1, 2, 3$ while ϖ_4 can be positive or negative based on the value of the $\mathcal{R}_0$. For the DFE case, the value of the basic reproduction number should be less than 1, so the last coefficient is positive when $\mathcal{R}_0 < 1$. So, all coefficients ϖ_i for $i = 1, 2..., 4$ positive, then they should satisfy the Rough-Hurtwiz criteria, which can be easily satisfied, for the conditions supplied $\varpi_1\varpi_2\varpi_3 > \varpi_3^2 + \varpi_1^2\varpi_4$, where $\varpi_i > 0$ for all $i = 1, 2, ...4$. This conditions say $\Phi = \varpi_1\varpi_2\varpi_3 - \varpi_3^2 - \varpi_1^2\varpi_4 > 0$ is satisfied and is given by,

$$\Phi = k_1^2(k_2 + k_3 + \mu_v)\left[k_2\left(2k_3(1 + \mathcal{R}_0^2)\mu_v + k_3^2 + \mu_v^2\right) + k_2^2(k_3 + \mu_v)\right.$$

$$\left. + k_3\mu_v(k_3 + \mu_v)\right]$$

$$+ k_1^3\left[k_2\left(k_3(2 + \mathcal{R}_0^2)\mu_v + k_3^2 + \mu_v^2\right) + k_2^2(k_3 + \mu_v) + k_3\mu_v(k_3 + \mu_v)\right]$$

$$+ k_1\left(k_2^3\left(k_3(2 + \mathcal{R}_0^2)\mu_v + k_3^2 + \mu_v^2\right) + k_3k_2(2 + \mathcal{R}_0^2)\mu_v(k_3 + \mu_v)^2\right.$$

$$+ k_3^2\mu_v^2(k_3 + \mu_v)) + k_1k_2^2(k_3 + \mu_v)\left(k_3(2\mathcal{R}_0^2 + 3)\mu_v + k_3^2 + \mu_v^2\right)$$

$$+ k_2k_3(k_2 + k_3)\mu_v(k_2 + \mu_v)(k_3 + \mu_v) > 0.$$

Thus, the condition of Rough-Hurtwiz criteria ensures the local asymptotical stability of the dengue model given by (1) at the DFE E_0. $\square$

4. Endemic equilibria

This section presents the endemic equilibria of the dengue model (1) denoted by E_1^* and is given

$$E_1 = (S_v^*, E_v^*, I_v^*, S_h^*, E_h^*, I_h^*, P_h^*, R_h^*),$$

where

$$S_v^* = \frac{\Lambda_v}{\lambda_v^* + \mu_v}, \quad E_v^* = \frac{\lambda_v^*\Lambda_v}{k_1(\lambda_v^* + \mu_v)}, \quad I_v^* = \frac{\gamma_v\lambda_v^*\Lambda_v}{k_1\mu_v(\lambda_v^* + \mu_v)},$$

$$S_h^* = \frac{\Lambda_h}{\lambda_h + \mu_h}, \quad E_h^* = \frac{\Lambda_h\lambda_h}{k_2(\lambda_h^* + \mu_h)}, \quad I_h^* = \frac{\Lambda_h\gamma_h\lambda_h^*}{k_2k_3(\lambda_h^* + \mu_h)},$$

$$P_h^* = \frac{\eta\Lambda_h\gamma_h\lambda_h^*}{k_2k_3k_4(\lambda_h^* + \mu_h)}, \quad R_h^* = \frac{\Lambda_h\gamma_h\lambda_h^*(k_4q_1 + \eta q_2)}{k_2k_3k_4\mu_h(\lambda_h^* + \mu_h)}, \tag{3}$$

where

$$\lambda_v^* = \frac{\beta\alpha_v I_h^*}{N_h^*}, \quad \lambda_h^* = \frac{\beta I_v^*\alpha_h}{N_h^*}. \tag{4}$$
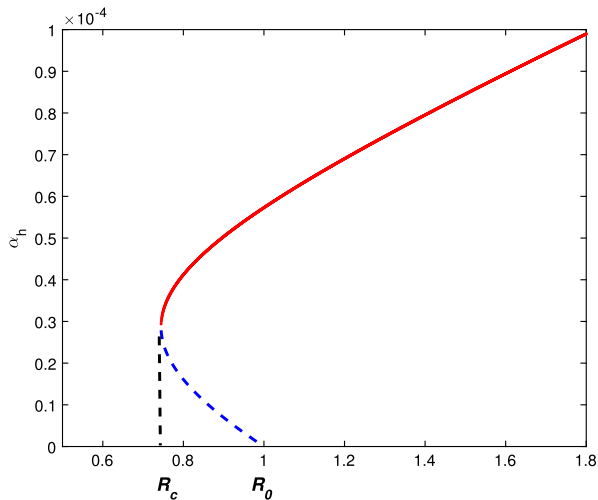
Fig. 1. Backward bifurcation plot for the dengue model (1).

Inserting the expression in (3) into (4), we get the following,

$$g_1 \lambda_h^{*2} + g_2 \lambda_h^* + g_3 = 0,$$

where

$$g_1 = k_1 \Lambda_h \mu_v \Big(k_4 \left[\mu_h (\gamma_h + k_3) + q_1 \gamma_h \right] + \eta \gamma_h (\mu_h + q_2) \Big) \times$$
$$\Big(k_4 \left(\beta \alpha_h \gamma_h \mu_h + \mu_v (\mu_h (\gamma_h + k_3) + q_1 \gamma_h) \right) + \eta \gamma_h \mu_v (\mu_h + q_2) \Big),$$

$$g_2 = k_2 k_3 k_4 \mu_h \Big(k_4 \Big[2 k_1 \Lambda_h \mu_v^2 (\mu_h (\gamma_h + k_3) + q_1 \gamma_h)$$
$$+ \beta \alpha_h \gamma_h \mu_h (k_1 \Lambda_h \mu_v - \beta \alpha_v \gamma_v \Lambda_v)) \Big] \Big)$$
$$+ 2 k_2 k_3 k_4 \mu_h \eta k_1 \Lambda_h \gamma_h \mu_v^2 (\mu_h + q_2),$$

$$g_3 = k_1 k_2^2 k_3^2 k_4^2 \Lambda_h \mu_h^2 \mu_v^2 \left(1 - \mathcal{R}_0^2 \right).$$

Here, $g_1 > 0$, g_3 depends on the sign of $\mathcal{R}_0$, and is positive when $\mathcal{R}_0 < 1$ and is negative for the case when $\mathcal{R}_0 > 1$. We establish the following result:

Theorem 2. *The dengue model given by (1) has:*

(i) *if $g_3 < 0 \Longleftrightarrow \mathcal{R}_0 > 1$, then there exists a unique endemic equilibrium,*
(ii) *if $g_2 < 0$ and $g_3 = 0 \longrightarrow \mathcal{R}_0 = 1$, then we have a unique endemic equilibrium,*
(iii) *if $g_3 > 0 \longrightarrow \mathcal{R}_0 < 1$, $g_2 < 0$ and their discriminant is positive, then two endemic equilibria exist*
(iv) *no possibilities of equilibria otherwise*

Remark 1. It can be seen from the first point (i) of Theorem (2) that for the case of $\mathcal{R}_0 > 1$, we have clearly a unique positive endemic equilibrium. The third item of the above Theorem (2) shows the possible existence of the backward bifurcation when $\mathcal{R}_0 < 1$. In order to determine this possibility of backward bifurcation for the dengue model (1), we set $g_2^2 - 4g_1 g_3 = 0$, and then solving for the critical values of $\mathcal{R}_0$ described by $\mathcal{R}_c$ which is given through the following expression

$$\mathcal{R}_c = \sqrt{1 - \frac{g_2^2}{4g_1 k_1 k_2^2 k_3^2 k_4^2 \Lambda_h \mu_h^2 \mu_v^2}}.$$

Thus, the backward bifurcation can occur for the values of $\mathcal{R}_0$ such that $\mathcal{R}_c < \mathcal{R}_0 < 1$. Using the values given in Table 2, except $\delta = 0.01932$, $\eta = 0.0272$, we give the backward bifurcation diagram in Fig. 1.

5. Parameter estimation and global sensitivity analysis of dengue model

5.1. Parameter estimation

In this subsection, we estimate the parameters of the model (1) to the cases of dengue fever in East Java, Indonesia. Based on data obtained from the East Java Provincial Health Office, it was reported that the incidence rate of Dengue Hemorrhagic Fever (DHF) in East Java in 2016 was 64.8 per 100,000 population, an increase compared to 2015 which was 54.18 per 100,000 population, while the incidence rate of DHF in 2017 was 20 per 100,000 population [34]. Although in 2017, cases of DHF have decreased compared to the previous year, but awareness of the surge in cases in the next year needs to be improved. However, in 2017 the total number of DHF in East Java reached 7,854 people, while in 2018 it reached 9,452 people [30]. From this, it appears that there is an increase in the number of DHF in 2018 compared to 2017. Hence, the cumulative monthly reported of DHF cases from January to December 2018 are used to parameterize the model (1).

In order to get a good fit to the real data, we estimate the parameters using the least square curve fitting technique except for the recruitment rate of human Λ_h and the natural death rate of human μ_h. The parameter μ_h is calculated as the inverse of the average lifespan of the population in East Java so that $\mu_h = 1/70.97$ per year, where 70.97 years is the average lifespan the population of East Java Province [35]. The parameter Λ_h is computed as follows. Since the total population of East Java province was 39,507,370, in 2018, we have $\Lambda_h/\mu_h = 39,507,370$ is the maximum human population without the disease, therefore $\Lambda_h = 556,677.0466$ per year. The other parameters are obtained using least-square curve fitting method. The fitted and estimated parameter values of the model (1) are set out in Table 2. The result of fitting model (1) to the actual data of dengue incidence is displayed in Fig. 2. The red-circle shows the monthly dengue cases reported in East Java Indonesia while the solid line denotes the model fit. These infected cases are the hospitalized reported cases that have been hospitalized in East Java Indonesia for the year 2018. Using the parameter values stated in Table 2, the basic reproduction number in East Java is $\mathcal{R}_0 \approx 1.1138$. The application and uses of the least square curve fitting technique has been used by many researchers for epidemiological models, see for example [32, 36]. Our computed reproduction number has a closed value to those published work in [36] (see $\mathcal{R}_0^2 = 1.1104$) and [32] (see $\mathcal{R}_0^2 = 1.014$). Some of the parameter such μ_v, μ_h are related closely to [32] but in other parameters obtained in this paper have a little up and down but considered to be close to [32]. Our estimated parameters such as μ_v, α_v are related closely to the work published in [16] but for the other values there is not a big difference except for the case of bitting rate β.
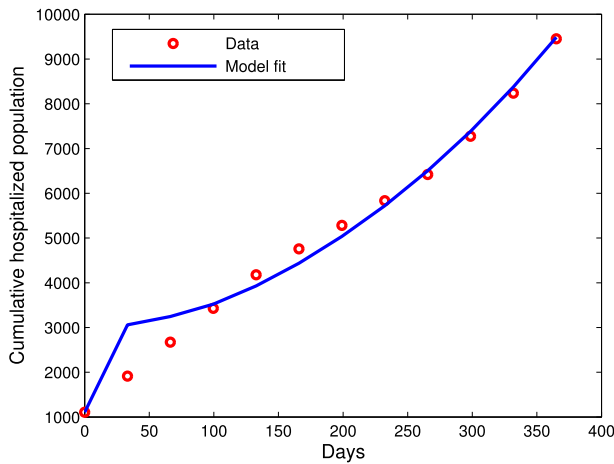
Fig. 2. Data fitting of cumulative hospitalized humans using model (1).

Fig. 3. Global sensitivity analysis and PRCC results for $\mathcal{R}_0$.

Table 3. Partial rank correlation coefficient (PRRC) values of $\mathcal{R}_0$ with corresponding p-values.

Parameter	PRCC values	p values
β	0.7386	0.0000
α_h	0.4565	0.0000
γ_h	0.3013	0.0000
μ_h	0.1782	0.0002
α_v	0.4494	0.0000
γ_v	0.3217	0.0000
Λ_v	0.5208	0.0000
μ_v	-0.7876	0.0000
Λ_h	-0.4826	0.0010
η	-0.1352	0.1963
q_1	-0.1746	0.0003

5.2. Global sensitivity analysis

We performed the global sensitivity analysis using Partial rank correlation coefficient (PRRC) in order to determine the most important value that affect the basic reproduction number $\mathcal{R}_0$. Using the parameters values given in Table 2, the sensitivity analysis is performed and the values are obtained and have been given in Table 3 while the PRCC plot is shown in Fig. 3. It can be seen from Table 3 that the most sensitive parameter is μ_v while the other sensitive parameters are β, Λ_v, Λ_h, α_h etc. Increasing the death rate of the mosquitoes can reduce the dengue infection. Further, the bite of mosquitoes can be reduced by closing the doors when entering the room and use air conditioner to cool the room. The practical and the recommended environmental management strategy is to eliminate unnecessary container habitats that collect water (such as plastic jars, bottles, cans, tires, and buckets) in which *Aedes aegypti* can lay their eggs. The bite of the mosquito can be reduced when using the bet net and other necessary measure.

The effect of some sensitive parameters such as β, α_h and μ_v that can decrease the number of infected and hospitalized individuals in the long run are plotted in Figs. 4, 5 and 6. Decreasing the value of the rate of mosquitoes by making use of bed nets and some other preventive measure the population of infected and hospitalized people are decreased, see Fig. 4. Similarly the parameter α_h which denotes the probability of transmission among susceptible and infected humans, and the parameter μ_v the death rate of mosquitoes also reduces rapidly the infection in the infected and hospitalized population, see Figs. 5 and 6.

6. Optimal control problem

The optimal control formulation for the epidemic models is to use proper control measure to identify the possible elimination of the disease from the society. In mathematical biology, the epidemic models
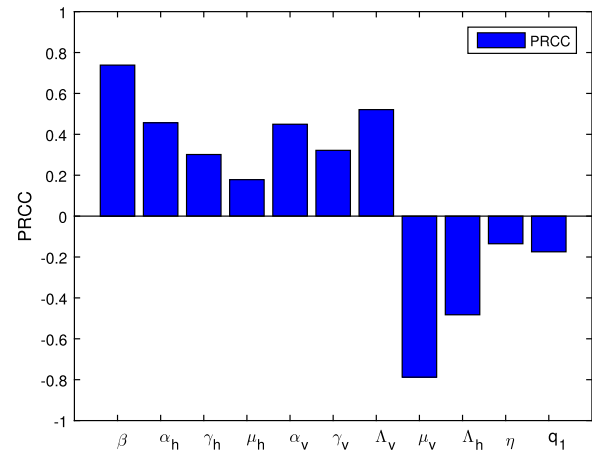
and their controls have been documented with considering different diseases, see for example [37, 38, 39, 40]. In order to have an optimal control problem for our considered model (1), we, in this section, describe an extension for dengue model (1) with control variables. We incorporate two intervention strategies, namely, prevention (u_1) and insecticide (u_2) efforts as control variables in the model. The use of the control for dengue infection as a prevention only has been considered in the work [33, 41]. The control u_2 insecticide spraying only has been considered in dengue control model given in [42]. The use of both the control for dengue control in the population is considered in [36, 43]. The prevention efforts include the use of mosquito nets, mosquito repellent like DEET, and treat clothes with repellent, while insecticide includes spraying and fogging against mosquitoes. The system of differential equations describing the controlled model is written as,

$$\frac{dS_v}{dt} = \Lambda_v - (1-u_1)\beta\alpha_v S_v \frac{I_h}{N_h} - \mu_v S_v - bu_2 S_v,$$

$$\frac{dE_v}{dt} = (1-u_1)\beta\alpha_v S_v \frac{I_h}{N_h} - (\gamma_v + \mu_v)E_v - bu_2 E_v,$$

$$\frac{dI_v}{dt} = \gamma_v E_v - \mu_v I_v - bu_2 I_v,$$

$$\frac{dS_h}{dt} = \Lambda_h - (1-u_1)\beta\alpha_h I_v \frac{S_h}{N_h} - \mu_h S_h,$$

$$\frac{dE_h}{dt} = (1-u_1)\beta\alpha_h I_v \frac{S_h}{N_h} - (\gamma_h + \mu_h)E_h,$$

$$\frac{dI_h}{dt} = \gamma_h E_h - (\eta + q_1 + \mu_h)I_h,$$

$$\frac{dP_h}{dt} = \eta I_h - (\delta + q_2 + \mu_h)P_h,$$

$$\frac{dR_h}{dt} = q_1 I_h + q_2 P_h - \mu_h R_h, \tag{5}$$

where the parameter b represents the death rate of mosquito due to insecticide.

This case study seeks to minimize the number of dengue-infected hosts and vector while keeping the costs of implementing the controls u_1 and u_2 as low as possible. This goal can be represented by the following objective function as

$$J(u_1,u_2) = \int_0^{t_f} \left(E_v + I_v + E_h + I_h + \frac{c_1}{2}u_1^2 + \frac{c_2}{2}u_2^2 \right) dt, \tag{6}$$

where t_f is the final time and c_1 and c_2 are positive weights. We do not include the hospitalized and/or notified infectious individuals (P_h) explicitly in the objective function due to it has assumed that the P_h population is not going to infect the others. However, the P_h population will decrease if the I_h population decreases.
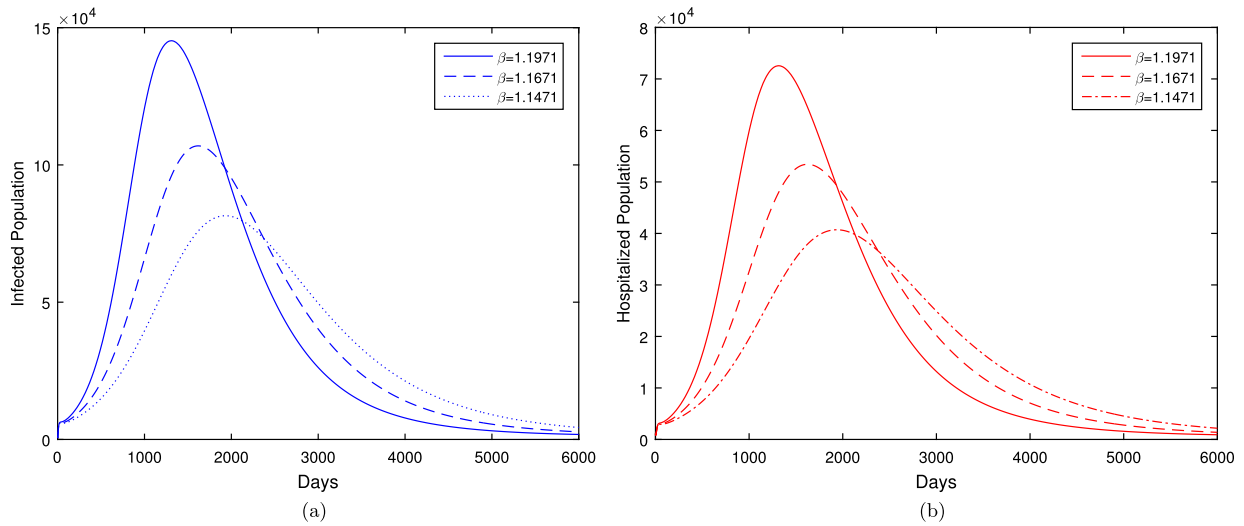
Fig. 4. Effect of parameter β on the infected and hospitalized individuals.
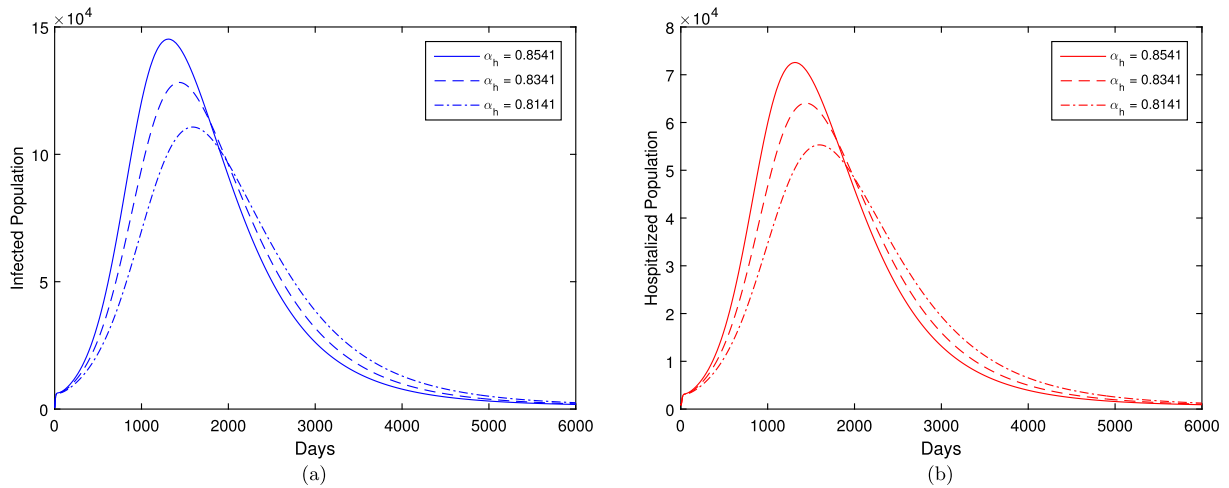

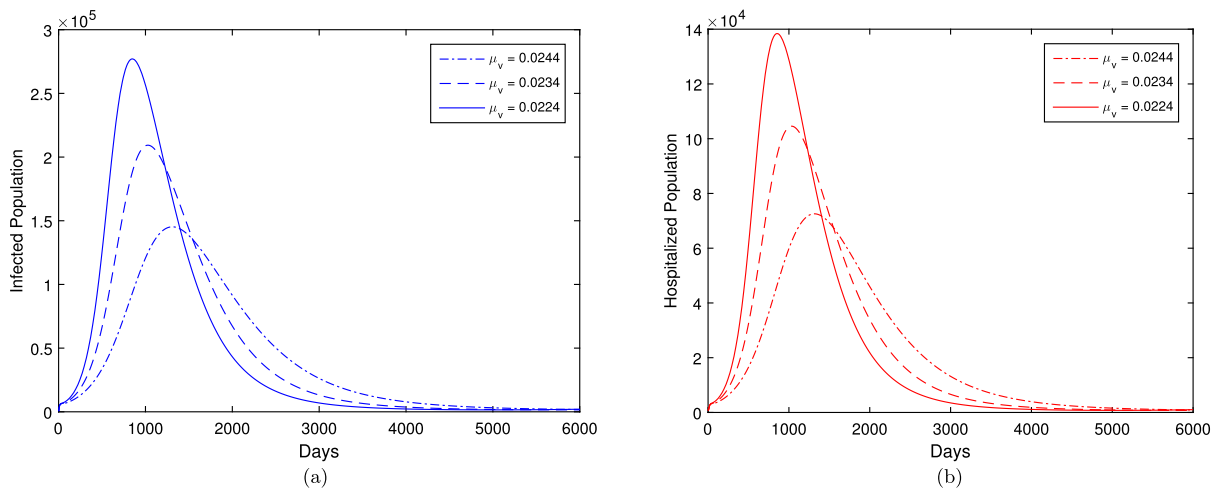**Fig. 5.** Effect of parameter α_h on the infected and hospitalized individuals.

Fig. 6. Effect of parameter μ_v on the infected and hospitalized individuals.

In the present work, we implement a quadratic objective functional in order to measure the control cost, since the costs of the intervention are nonlinear. This assumption is based on the fact that there are no linear relationship among the effects of intervention and the cost of intervention of the infective populations, such quadratic costs have been widely used by the authors, see for more details [44, 45]. Some more related work where the authors considered the quadratic objective functional, see [46, 47, 48] and the references therein. The term $c_1 u_1^2$ and $c_2 u_2^2$ describe the cost of control efforts on minimizing the prevention and insecticide respectively.

Our aim is to find an optimal control pair u_1^* and u_2^* such that

$$J(u_1^*, u_2^*) = \underbrace{min}_{\Gamma} J(u_1, u_2), \tag{7}$$

where $\Gamma = \{(u_1, u_2) \,|\, 0 \leq u_1 \leq u_1^{\max}, 0 \leq u_2 \leq u_2^{\max}\}$. In this region, when the value of a control is zero, then no investment in control has been made. Moreover, when the values of the controls are $u_i^{\max}, i = 1, 2$, then the control effort have been carried out maximally.

The conditions are necessary for determining the optimal controls u_1^* and u_2^* that satisfy condition (7) with constraint model (5) will be found via Pontryagin's Maximum Principle [49]. This principle converts equations (5), (6), and (7) into a problem of minimizing the Hamiltonian function H, pointwise with respect to (u_1, u_2), i.e.,

$$H = E_v + I_v + E_h + I_h + \frac{c_1}{2} u_1^2 + \frac{c_2}{2} u_2^2 + \sum_{i=1}^{8} \rho_i g_i,$$

where g_i denotes the right-hand side of model (5). The adjoint variables ρ_i for $i = 1, 2, \dots, 8$ satisfy the following co-state system.

6.1. The existence of the optimal control

The existence of the optimal control problem (5) can be analysed by using the result established in [50]. It is clear that the system (5) is bounded above. Hence, we can use the result in [50] for the control system (5) if the following conditions are satisfied.

N_1: The state variables and the corresponding set of the controls are non-empty.

N_2: The control set Γ is closed and convex.

N_3: The right side of the control system (5) is linear with respect to control variables.

N_4: There exist nonnegative constants l_1 and l_2 and $n > 1$ such that the integrand $L(\mathbf{x}, u_1, u_2)$ of (6) is convex and satisfies

$$L(\mathbf{x}, u_1, u_2) \geq l_2 + l_1(|u_1|^2 + |u_2|^2)^{\frac{n}{2}}, \tag{8}$$

with $L(\mathbf{x}, u_1, u_2) = E_v + I_v + E_h + I_h + \frac{c_1}{2} u_1^2 + \frac{c_2}{2} u_2^2$.

In order to prove the existence of system (5), we refer to the Theorem 9.2.1 from Lukes [51]. The condition N_1 is satisfied with the compliance of the state and the controls variables which is non-empty and bounded. The condition N_2 can be fulfilled by definition of the control set Γ. The condition N_3 is valid due to the linear dependence of the state system on controls u_1 and u_2. Finally, the integrand L is clearly convex with respect to the controls u_1 and u_2. To prove the bound on L, let $l_2 = \min(E_v + I_v + E_h + I_h)$ and $l_1 = \min(c_1, c_2)$ and $n = 2$, then we have

$$L(\mathbf{x}, u_1, u_2) = E_v + I_v + E_h + I_h + \frac{c_1}{2} u_1^2 + \frac{c_2}{2} u_2^2 \geq l_2 + l_1(|u_1|^2 + |u_2|^2)^{\frac{n}{2}}, \tag{9}$$

where $c_1, c_2, l_1, l_2 > 0$ and $n > 1$. Therefore, we obtain the following result.

Theorem 3. *There exists an optimal control pair $u_1^*(t)$ and $u_2^*(t)$ such that*

$$J(u_1^*, u_2^*) = \underbrace{min}_{\Gamma} J(u_1, u_2),$$

subject to the control system (5) with the initial conditions (2).

6.2. Characterization of the optimal control

In this present section, we apply the Pontryagin's Maximum Principle to solve the optimal control problem [49]. The consequence of the maximum principle is stated by the following theorem.

Theorem 4. *Assumed that S_v^*, E_v^*, I_v^*, S_h^*, E_h^*, I_h^*, P_h^* and R_h^* be the optimal solution with controls u_i^* for $i = 1, 2$ for the control system (5). Then there exists adjoint variables ρ_i for $i = 1, 2, \dots 8$ that satisfying*

$$\dot{\rho}_1 = \rho_1 \left(\frac{(1 - u_1)\beta \alpha_v I_h}{N_h} + \mu_h + b u_2 \right) - \frac{\rho_2(1 - u_1)\beta \alpha_v I_h}{N_h},$$

$$\dot{\rho}_2 = -1 + \rho_2 \left(b u_2 + \gamma_v + \mu_v \right) + \rho_3 \gamma_v,$$

$$\dot{\rho}_3 = -1 + \rho_3(b u_2 + \mu_v) + \frac{\rho_4(1 - u_1)\beta \alpha_h S_h}{N_h} - \frac{\rho_5(1 - u_1)\beta \alpha_h S_h}{N_h}$$

$$\dot{\rho}_4 = (\rho_2 - \rho_1)\frac{(1 - u_1)\beta \alpha_v S_v I_h}{N_h^2} + (\rho_4 - \rho_5)\frac{(1 - u_1)\beta \alpha_h I_v}{N_h}$$
$$+ (\rho_5 - \rho_4)\frac{(1 - u_1)\beta \alpha_h I_v S_h}{N_h^2} + \mu_h \rho_4$$

$$\dot{\rho}_5 = -1 + (\rho_2 - \rho_1)\frac{(1 - u_1)\beta \alpha_v S_v I_h}{N_h^2} + (\rho_5 - \rho_4)\frac{(1 - u_1)\beta \alpha_h I_v S_h}{N_h^2}$$
$$+ (\rho_5 - \rho_6)\gamma_h + \mu_h \rho_5, \tag{10}$$

$$\dot{\rho}_6 = -1 + (\rho_1 - \rho_2)\frac{(1 - u_1)\beta \alpha_v S_v}{N_h} + (\rho_2 - \rho_1)\frac{(1 - u_1)\beta \alpha_v S_v I_h}{N_h^2}$$
$$+ (\rho_5 - \rho_4)\frac{(1 - u_1)\beta \alpha_h I_v S_h}{N_h^2} - \rho_7 \eta - \rho_8 q_1 + \rho_6(\eta + q_1 + \mu_h),$$

$$\dot{\rho}_7 = (\rho_2 - \rho_1)\frac{(1 - u_1)\beta \alpha_v S_v I_h}{N_h^2} + (\rho_5 - \rho_4)\frac{(1 - u_1)\beta \alpha_h I_v S_h}{N_h^2}$$
$$+ \rho_7(\delta + q_2 + \mu_h) - \rho_8 q_2,$$

$$\dot{\rho}_8 = (\rho_2 - \rho_1)\frac{(1 - u_1)\beta \alpha_v S_v I_h}{N_h^2} + (\rho_5 - \rho_4)\frac{(1 - u_1)\beta \alpha_h I_v S_h}{N_h^2} + \rho_8 \mu_h, \tag{11}$$

where the transversality conditions

$$\rho_i(t_f) = 0, \tag{12}$$

where $i = 1, 2, \dots, 8$, and the optimal control variables,

$$u_1^* = \max \left\{ 0, \min \left(u_1^{\max}, \frac{(\rho_2 - \rho_1)\beta \alpha_v S_v I_h + (\rho_5 - \rho_4)\beta \alpha_h I_v S_h}{c_1 N_h} \right) \right\}$$

$$u_2^* = \max \left\{ 0, \min \left(u_2^{\max}, \frac{b(\rho_1 S_v + \rho_2 E_v + \rho_3 I_v)}{c_2} \right) \right\}. \tag{13}$$

Proof. We follow the result in [50] to prove the existence, convexity, *Lipschitz* and boundedness of the optimal control solution. The co-state equations (10) are determined by taking the time derivative of the Hamiltonian function H to the state variables: $\frac{\partial \rho_1}{\partial t} = -\frac{\partial H}{\partial S_v}$, $\frac{\partial \rho_2}{\partial t} = -\frac{\partial H}{\partial E_v}$, $\frac{\partial \rho_3}{\partial t} = -\frac{\partial H}{\partial I_v}$, $\frac{\partial \rho_4}{\partial t} = -\frac{\partial H}{\partial S_h}$, $\frac{\partial \rho_5}{\partial t} = -\frac{\partial H}{\partial E_h}$, $\frac{\partial \rho_6}{\partial t} = -\frac{\partial H}{\partial I_h}$, $\frac{\partial \rho_7}{\partial t} = -\frac{\partial H}{\partial P_h}$, $\frac{\partial \rho_8}{\partial t} = -\frac{\partial H}{\partial R_h}$, with $\rho_i(t_f) = 0$, $i = 1, \dots, 8$. To obtain the optimal control characterization that given in (13), we apply $\frac{\partial H}{\partial u_i} = 0$, for $i = 1, 2$. □

7. Numerical results of the control problem

This section sets out to explore the numerical results of the model without control (1) and with optimal control (5). The optimal solution of the model (5) is simulated using the forward-backward sweep method [52]. The optimal control problem is solved numerically by the fourth-order Runge-Kutta method.

We consider the initial values of the simulation based on the number of population in East Java province in 2018. The initial value of the total population as given in the data is $N(0) = 39,507,370$. We assume that the initial populations of exposed human and infectious human are $E_h(0) = 10,000$ and $I_h(0) = 100$, respectively. The initial value of the
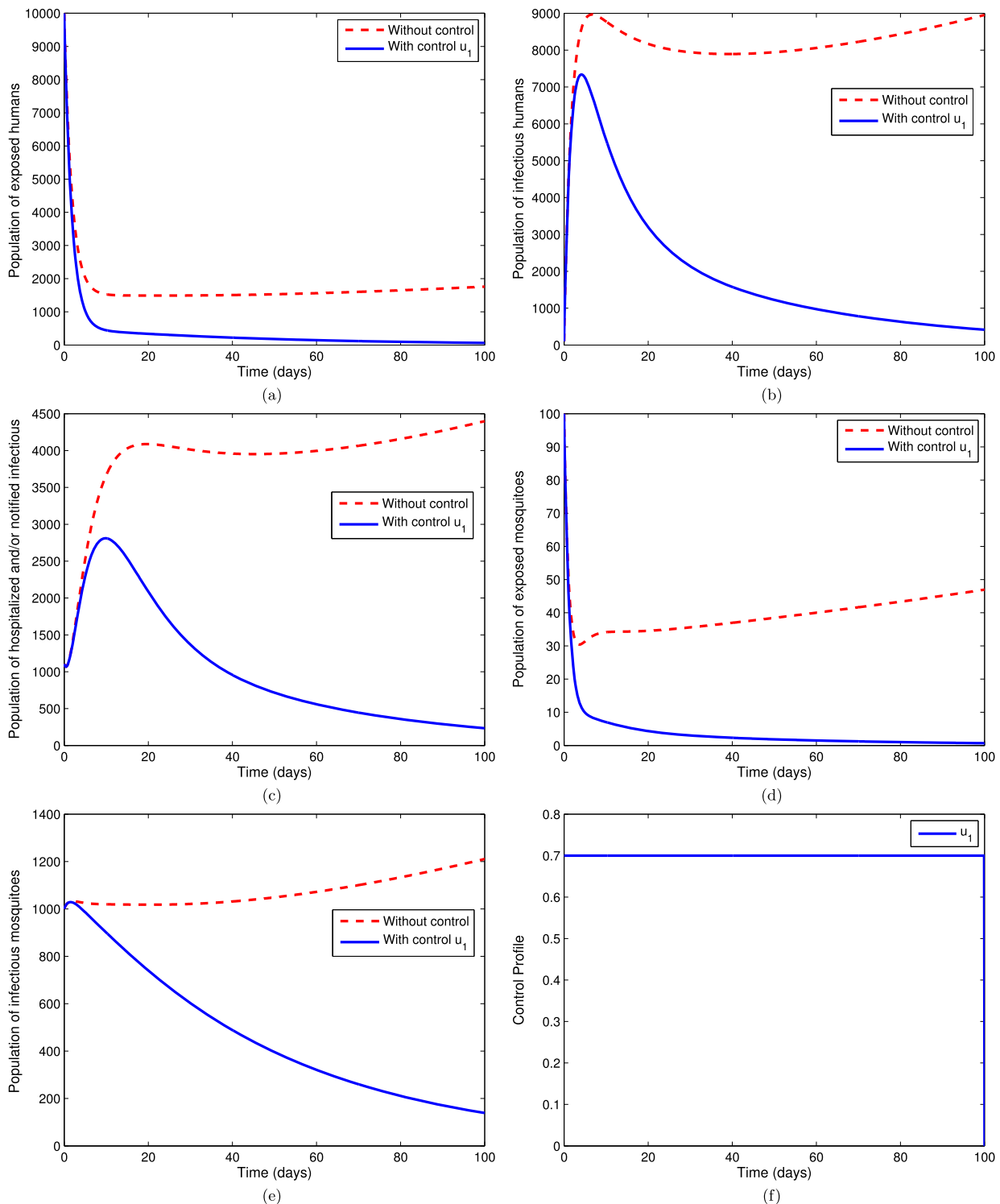
Fig. 7. Numerical results of the model using prevention only.

hospitalized and/or notified infectious population as stated in the data is $P_h = 1106$. The initial of the recovered human population is taken as $R_h(0) = 1095$ [30]. Hence, the initial susceptible human population is given as $S_h(0) = N_h(0) - E_h(0) - I_h(0) - P_h(0) - R_h(0) = 39,495,069$. We assume the initial population for the mosquitoes are given as $S_v(0) = 10^5$, $E_v(0) = 100$ and $I_v(0) = 1000$. We also employed parameter value $b = 0.5$ as the maximum of the death rate in mosquito due to insecticide. The weight factors in the objective function are $c_1 = 1$ and $c_2 = 0.1$. The upper bound of u_1 and u_2 are assumed equal to $u_1^{max} = 0.7$ and $u_2^{max} = 0.8$, respectively, as stated in [33, 36]. For the simulations, we adopt

the estimated parameter values that are given in Table 2. Using this parameter values, the basic reproduction number is $\mathcal{R}_0 \approx 1.1138$, which indicates that the disease will be epidemic in the province.

We examine the model (5) with prevention (u_1) and insecticide (u_2) as control variables to investigate the effects of the transmission of dengue disease in the population. We consider three control scenarios, which are explained as follows.

Scenario 1. In this scenario, we set $u_1 \neq 0$ and $u_2 = 0$ to optimize the objective function J. The numerical results are given in Fig. 7.
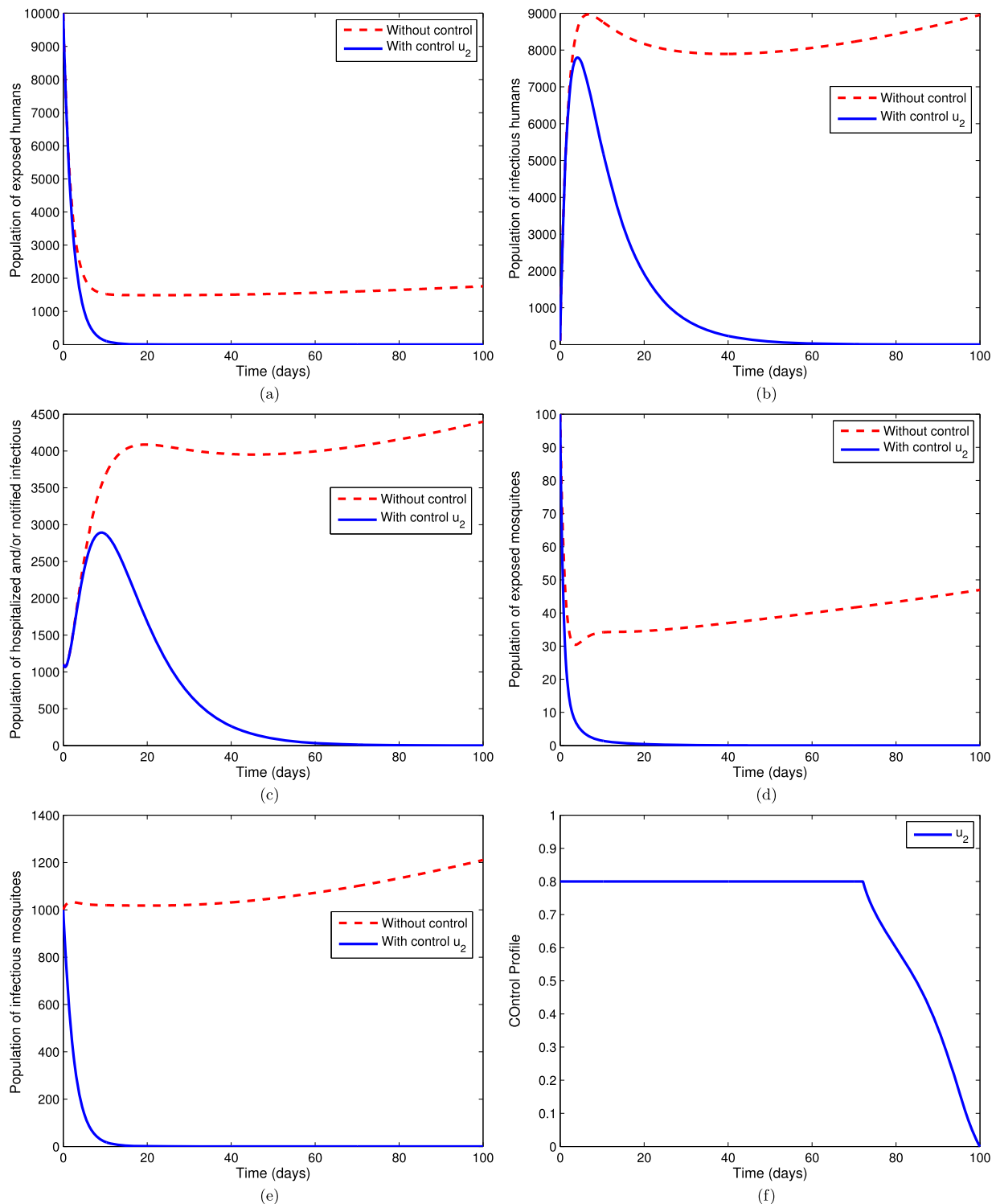
Fig. 8. Numerical results of the model using insecticide only.

From Fig. 7(a)-7(c), the number of the exposed, infectious, and hospitalized and/or notified infectious humans decrease significantly using this scenario control compared to the case without control. Also, in Fig. 7(d)-7(e), the number of the exposed and infectious mosquitoes decreases more compared to without the control. The profile control for this scenario is depicted in Fig. 7(f). In Fig. 7(f), we can see that the prevention is kept at full effort for 100 days and then drastically reduces at the end of the intervention. The previous studies showed that optimal preventive efforts should be implemented with the maximum level [33,

36, 41]. Results of our study show similar effort of the prevention on dengue control in East Java, Indonesia. In other words, the human population must maintain a strong level of awareness about the presence of dengue fever and continue to take all available measures for personal protection from mosquito bites.

Scenario 2. In this scenario, we set $u_2 \neq 0$ and $u_1 = 0$ to optimize the objective function J. The numerical results are displayed in Fig. 8. From Fig. 8(a)-8(e), there is a difference in the number of the population between the controlled case and the case without control. Using this sce-
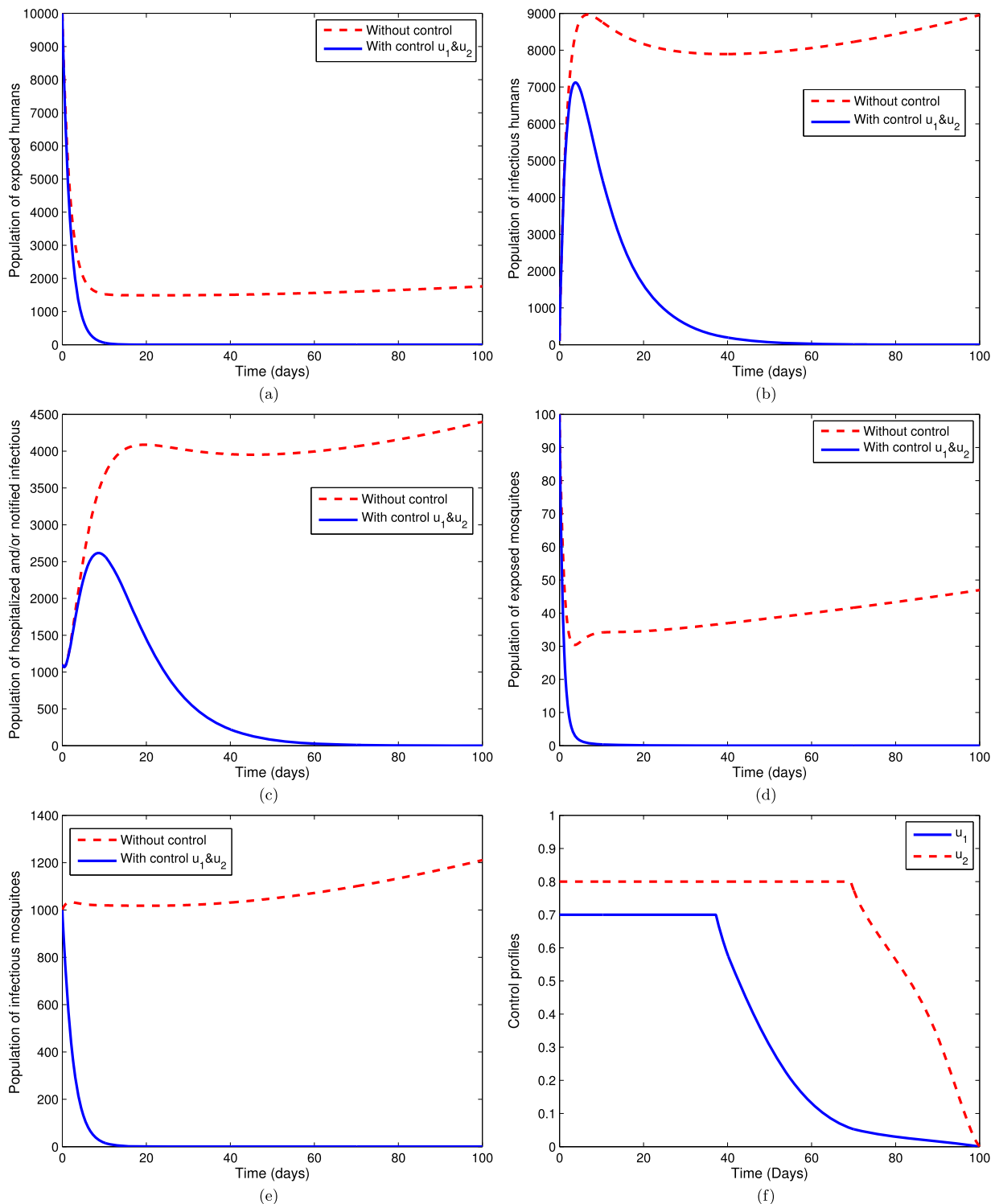
Fig. 9. Numerical results of the model using prevention and insecticide.

nario, the number of exposed, infectious, hospitalized and/or notified infectious humans, exposed mosquitoes, and also infectious mosquitoes is less than the first scenario in the end of intervention. The profile control for this scenario is given in Fig. 8(f). In Fig. 8(f), it can be seen that the insecticide is maintained at full effort for 72 days before drastically reduces for the rest of the intervention. These results seem to be consistent with previous research [36, 42] which found that the insecticide spraying alone had the effect of rapidly reducing the number of infectious humans, almost enabling eradication of disease.

Scenario 3. In this scenario, we set $u_1 \neq 0$ and $u_2 \neq 0$ to optimize the objective function J. The numerical results are depicted in Fig. 9. As depicted in Fig. 9(a)-9(c), it can be observed that the implementation of both controls at the same time, the number of the exposed, infectious, and hospitalized and/or notified infectious humans more decreases compared to the scenario 1 and 2. While the number of the exposed and infectious mosquitoes remain the same with the scenario 2. The profile controls for this scenario is depicted in Fig. 9(f). As depicted in Fig. 9(f), the prevention is kept at full effort for approximately
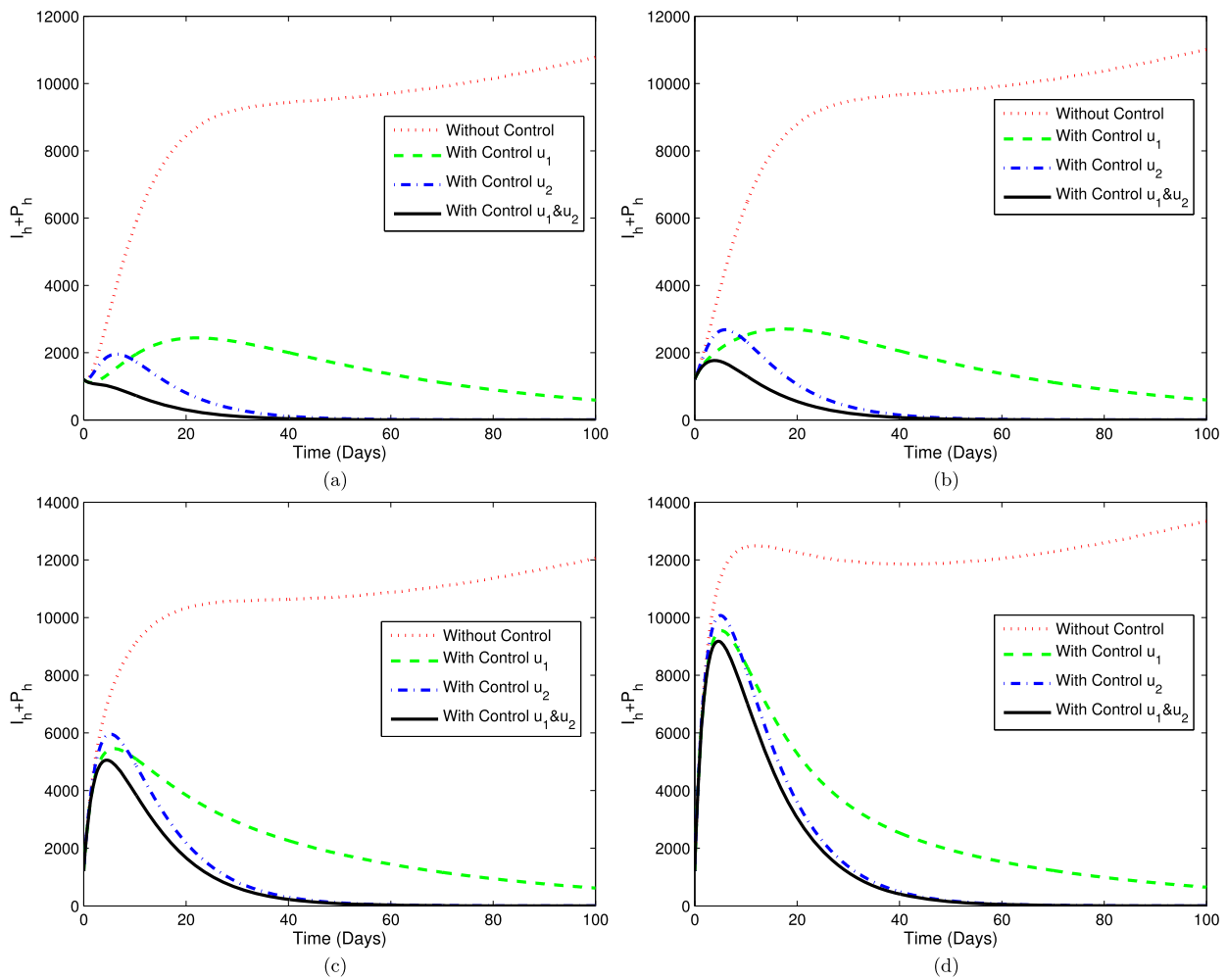
Fig. 10. The total of infective human with initial conditions (a) $E_h(0) = 100$, (b) $E_h(0) = 1000$, (c) $E_h(0) = 5000$, and (d) $E_h(0) = 10000$, using various control scenarios.

37 days and then reduces gradually till the end of the intervention, while the insecticide is maintained at maximal effort during 69 days and then reduces rapidly for the rest of the intervention. These results are in accord with earlier studies [36, 43] which showed when the two controls were combined, the impact of insecticide spraying appeared to be dominant over preventive measures alone. Moreover, the prevalence timing was similar to that of insecticide-only interventions.

Next, we perform the comparison for the total of infective human $(I_h + P_h)$ using the all scenario of the strategy controls. We vary the initial values of the exposed human population by $E_h(0) = 100$, $E_h(0) = 1000$, $E_h(0) = 5000$ and $E_h(0) = 10^4$. The total of the infective human for different initial conditions of the exposed human population using three control scenarios is displayed in Fig. 10. It is apparent from the Fig. 10 that the number of the infective human population more decrease by applying the third scenario compared to the other scenario.

From the scenario 1 to 3, we conclude that the scenario 3 is the best strategy to minimize the number of dengue-infected hosts and vector in the community.

8. Conclusion

In this paper, we have proposed a new mathematical model of dengue fever with hospitalization. The model parameters are estimated using the monthly real data of East Java province, Indonesia for the year 2018. The fundamental properties of the model are analyzed as well as the basic reproduction number $(\mathcal{R}_0)$ of the model. The disease-free equilibrium (DFE) is locally asymptotically stable when $\mathcal{R}_0 < 1$. The model has a unique endemic equilibrium whenever $\mathcal{R}_0 > 1$. Using the value of the estimated parameters, the basic reproduction number in East Java Province is $\mathcal{R}_0 \approx 1.1138$. This finding confirms that the dengue fever is still endemic in the province. We have further investigated the global sensitivity analysis using Partial rank correlation coefficient in order to identify the most influence parameters on the dengue disease transmission. The sensitivity analysis shows that the death rate of the mosquitoes (μ_v) and the biting rate of the mosquitoes (β) are the most sensitive parameters. The increasing of the death rate of the mosquitoes can reduce rapidly the dengue infection. However, the bite of mosquitoes can be reduced by using the bet net, mosquito repellent and other necessary measure. Hence, we applied the optimal control strategies to investigate the impact of prevention and insecticide to reduce the dengue transmission in East Java Province. The existence and the optimal control characterization were derived and analyzed. The numerical simulation was performed with different control strategies. The numerical results indicate that the integration of the prevention and insecticide is the best strategy to minimize the number of dengue-infected hosts and vector in the population. In addition, the implementation of the insecticide only is also an effective way in reducing the dengue transmission in the population. These results are in keeping with the sensitivity analysis which shows that the death rate of the mosquitoes are the significant parameters. This study will help the government to design a program in the future to control the disease further spread.

Declarations

Author contribution statement

M. A. Khan, Fatmawati: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

Data availability statement

The data that has been used is confidential.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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