Available online at http://scik.org

Commun. Math. Biol. Neurosci. 2020, 2020:37

https://doi.org/10.28919/cmbn/4744

ISSN: 2052-2541

STABILITY ANALYSIS AND OPTIMAL CONTROL OF MATHEMATICAL MODEL FOR THE SPREAD OF HEPATITIS E

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Abstract: Hepatitis E disease is caused by hepatitis E virus (HEV). The transmission of hepatitis E from feces to the mouth is mainly through contaminated water and food. This paper proposes the dynamics of HEV transmission through a mathematical model. We analyze stability of equilibria point of the model. In addition, we analyze parameter sensitivity to determine the important role of every single parameter value on the model. Furthermore, we impose treatment and virus extermination on the model as strategy control to reduce HEV transmission. The simulation results indicate that the performance of two controls is effective to minimize the number of infected human and reduce the number of viruses in the environment.

Keywords: mathematical model; hepatitis E; treatment; virus extermination; stability; optimal control.

2010 AMS Subject Classification: 34A34, 37N25, 93D20.

1. INTRODUCTION

Hepatitis is derived from two words, namely hepa (liver) and itis (inflammation). Hepatitis is an inflammation that occurs in liver [1]. There are some kinds of viruses that cause

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Received June 1, 2020

hepatitis and each viruses bring up similar clinical symptoms and some specific symptoms to detect the variety of hepatitis [2]. Generally, there are 5 types of viruses that cause hepatitis, namely: Hepatitis A Virus (HAV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), Hepatitis D Virus (HDV), and Hepatitis E Virus (HEV) [3]. Hepatitis A and E are usually caused by consumption of contaminated food or water. Hepatitis B, C, and D usually occur due to parenteral contact (shared use of the patient's personal tools and syringes) with infected body fluids. Hepatitis B, C, and E can be transmitted vertically, that is transmission from pregnant mother to her fetus. This transmission is most common in hepatitis B [4-7]. Khuroo et al [8] demonstrated fetal outcomes of HEV infection in pregnant mother and found in utero transmission with fetal outcomes ranging from intrauterine fetal death to symptomatic and asymptomatic neonatal liver infection.

Hepatitis E is a heart infectious disease caused by Hepatitis E Virus (HEV). This virus is small size and belong to single strand ribonucleic acid (RNA) virus [9]. Hepatitis E Virus is classified to 4 types of genotype that are genotype 1, 2, 3, and 4. Genotype 1 and 2 have been found only in human body, genotype 3 and 4 are belong to animal (pig, boar, and deer) and can infect human. The virus is shed in the stool of an infected person, and enters the human body through the intestines. The infection in a human body usually occur after 2-10 weeks [2, 10]. Hepatitis E disease is also known as hepatitis fulminant (acute liver failure) which can suffer to death [3]. There are 2.3 billion hepatitis E infections, over 3 million acute cases of hepatitis E, and 70,000 hepatitis E-related deaths in the world. The prevalence is highest in Eastern and Southern Asia [11, 12].

There is no vaccine for Hepatitis E Virus. Recombinant subunit vaccine for preventing Hepatitis E Virus infection had been found in China named Hecolin vaccine, but this is not approved in other countries so that it cannot be published commercially [13]. Keeping the environment clean, especially consuming hygiene foods and drinks is an effective prevention action. Moreover, in current situation, interferon has also been successfully used as a treatment for this disease. For the treatment of acute Hepatitis E can be a special treatment using antiviral

drugs such as ribavirin [9].

Mathematical models have played an essential role in understanding the dynamics of HEV transmission. Several mathematical models and strategies control for HEV transmission have been established in a number of literature to capture the dynamics of the disease in a more effective method (see, for example, [14, 15, 16, 17] and references therein). Mercer and Siddiqui [14] construct the mathematical model of hepatitis E transmission using Holling II and notice four populations that are Susceptible-Infected-Recovered-Viral. Nannyonga et al [15] formulate the SMEIR (Susceptible-Malaria-Exposed-Infected-Recovered) model to explain co-infection between hepatitis E and malaria. Backer et al [16] reviewed transmission model of hepatitis E in pigs with partition of the population of pigs into 3 populations that are Susceptible-Infected-Recovered. Alzahrani and Khan [17] construct the mathematics model of hepatitis E dissemination by noticing parental infection. The population of this model is parted into 2 types of population that are human (Susceptible-Exposed-infected-Recovered) and Hepatitis E Virus. Several researchers have presented the optimal control strategies to explore the effectiveness of the intervention [17, 18, 19]. In the study [17], they extended the model by applying optimal control in the form of prevention and treatment for pregnant women, clean water supply, and spraying of the virus. Khan et al [19] proposed three control strategies: isolation of infected and non-infected individuals, treatment and vaccination to minimize the number of acute infected, chronically infected with hepatitis B individuals and maximize the number of susceptible and recovered individuals.

The present paper will discuss the analysis and optimal control of the spread of Hepatitis E. The mathematical model used refers to the article written by Alzahrani and Khan [17]. We modify the model by ignoring the vertical transmission because the likelihood factor is small. We investigate the dynamics of the model. Furthermore, we demonstrate the effect of optimal control strategy, treatments used to reduce the rate of growth of the human population infected with hepatitis E, and the virus extermination to reduce the causes of Hepatitis E virus in the environment.

The paper is organized as follows: the formulation of HEV model is presented in section 2. The stability analysis are given in section 3 and 4. The parameter sensitivity analysis is highlighted in section 5, which determines key parameters in HEV model equilibria. In section 6, We employ human treatment and virus extermination in the environment as control variables. We then conduct a numerical exploration of HEV model with control in section 7. We conclude by discussing our finding and suggesting future work in section 8.

2. FORMULATION OF HEV MODEL

In this section, the model will be formulated for the spread of hepatitis E. The assumptions for the construction of the model are as follows:

a. The spread of Hepatitis E occurs due to direct and indirect contact.
b. Individuals who recover are considered immune to hepatitis E.
c. The population of exposed individuals can not spread the disease.
d. Deaths due to hepatitis E disease are ignored.

The population of humans is divided into four compartments as the following; susceptible population (S), exposed population (E) that is the human population that has been exposed to the virus but has not been able to transmit the virus, infected population (I), and recover population (R). The virus populations in the environments are denoted as (P). The definition of parameters can be seen in Table 2.1 as follows.

Table 2.1 Definition of Model Parameters.

Notation	Definition
Λ	Human birth rate
β	Contact rate with infected individuals
α	Transmission parameter of P and S
μ	Natural death rate of humans
ρ	Rate of infectious of exposed individuals
τ	Natural recovery rate
θ	Shedding of virus by the infected individuals to the environment
μ_v	Natural death rate of viruses

Based on the assumptions and descriptions of parameters and variables, a transmission diagram of hepatitis E transmission model is presented in Figure 2.1 as follows.

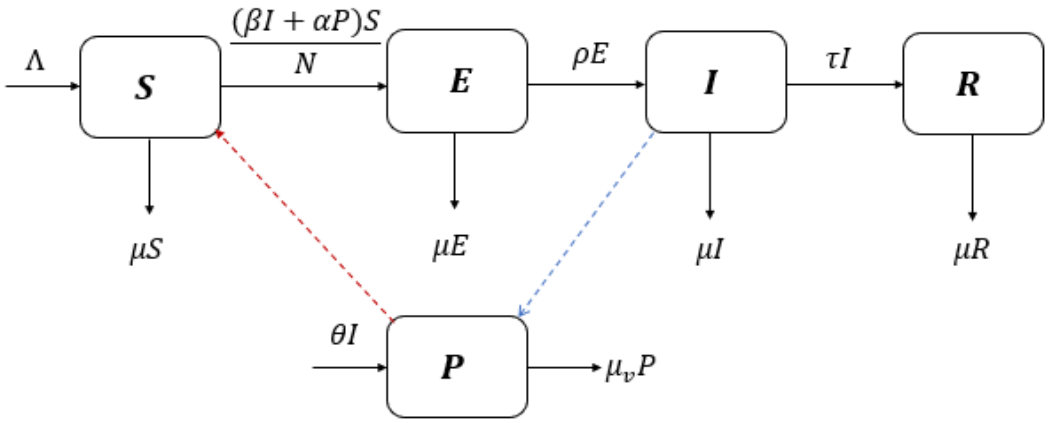

Figure 2.1 Transmission Diagram of HEV Model.

⟶ : Reduce the original population number and increase the intended population number.

⇢ : Increase the intended population number, but do not reduce the original population number.

⇢ : There is interaction between the two populations, but neither increases nor decreases both number.

The transmission diagram in Figure 2.1 is formulated as follows:

$$\frac{dS}{dt} = \Lambda - \frac{(\beta I+\alpha P)S}{N} - \mu S \quad (2.1a)$$

$$\frac{dE}{dt} = \frac{(\beta I+\alpha P)S}{N} - (\mu + \rho)E \quad (2.1b)$$

$$\frac{dI}{dt} = \rho E - (\mu + \tau)I \quad (2.1c)$$

$$\frac{dR}{dt} = \tau I - \mu R \quad (2.1d)$$

$$\frac{dP}{dt} = \theta I - \mu_v P \quad (2.1e).$$

with $S, E, I, R, P \geq 0$ and $\Lambda, \beta, \alpha, \mu, \rho, \tau, \theta, \mu_v > 0$.

Total population stated with $N = S + E + I + R$. Then rate of change of total population is

$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt}$,

by using equation (2.1a) - (2.1b), we obtained

$\frac{dN}{dt} = \Lambda - \mu N$.

From the calculation results we obtained

$\lim_{t\to\infty} N(t) = \frac{\Lambda}{\mu}$.

and then, N variable will be $N = \frac{\Lambda}{\mu}$.

Therefore, for analysis of the model in equation $(2.1a) - (2.1e)$, the following model can be used:

$$\frac{dS}{dt} = \Lambda - \frac{\mu(\beta I + \alpha P)S}{\Lambda} - \mu S \quad (2.1f)$$

$$\frac{dE}{dt} = \frac{\mu(\beta I + \alpha P)S}{\Lambda} - (\mu + \rho)E \quad (2.1g)$$

$$\frac{dI}{dt} = \rho E - (\mu + \tau)I \quad (2.1h)$$

$$\frac{dR}{dt} = \tau I - \mu R \quad (2.1i)$$

$$\frac{dP}{dt} = \theta I - \mu_v P \quad (2.1j)$$

3. MODEL ANALYIS

Mathematical model for the spread of hepatitis E has two equilibria: the non endemic equilibrium point (E_0) and endemic equilibrium point (E_1). The non endemic equilibrium point of the model is $E_0 = (S, E, I, R, P) = (\frac{\Lambda}{\mu}, 0,0,0,0)$.

Next, we will determine the basic reproduction number (R_0) which has the important role in the disease modelling [20, 21]. The basic reproduction number R_0 can be computed using the next generation matrix on the HEV model.

Consider the infected compartments in HEV model (1) are E; I; and P. Using the approach in [22], the matrices $\mathbb{F}$ and $\mathbb{Z}$ at DFE are given as follows

$$\mathbb{F} = \begin{pmatrix} 0 & \beta & \alpha \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \text{ and } \mathbb{Z} = \begin{pmatrix} \mu+\rho & 0 & 0 \\ -\rho & \tau+\mu & 0 \\ 0 & -\theta & \mu_v \end{pmatrix}.$$

The basic reproduction number of the model (1) is obtained through the spectral radius of the matrix $\mathbb{F}\mathbb{Z}^{-1}$ which is given by

$$R_0 = \frac{\rho(\mu_v\beta+\alpha\theta)}{\mu_v(\mu+\tau)(\mu+\rho)}.$$

From the calculation we obtained the endemic equilibrium point of the model is as follows. $E_1 = (S^*, E^*, I^*, R^*, P^*)$

$$S^* = \frac{\Lambda^2\mu_v}{\mu(\mu_v\beta I^*+\alpha\theta I^*+\Lambda\mu_v)} \quad (3.1a)$$

$$E^* = \frac{(\mu_v\beta I^*+\alpha\theta I^*)\Lambda}{(\mu+\rho)(\mu_v\beta I^*+\alpha\theta I^*+\Lambda\mu_v)} \quad (3.1b)$$

$$I^* = \frac{\rho\Lambda}{(\mu+\tau)(\mu+\rho)} - \frac{\Lambda\mu_v}{(\mu_v\beta+\alpha\theta)} \quad (3.1c)$$

$$R^* = \frac{\tau}{\mu} I^* \quad (3.1d)$$

$$P^* = \frac{\theta}{\mu_v} I^* \quad (3.1e)$$

Based on the description above, the endemic equilibrium point (E_1) will exist if it fulfills the condition $R_0 - 1 > 0$ or $R_0 > 1$.

4. LOCAL STABILITY OF EQUILIBRIUM POINT

In this section, stability analysis will be applied on both equilibrium points, non endemic equilibrium point (E_0) and endemic equilibrium point (E_1).

4.1 LOCAL STABILITY OF NON-ENDEMIC EQUILIBRIUM POINT

Local stability analysis of non endemic equilibrium point begins by substituting the non endemic equilibrium point $E_0 = (S, E, I, R, P) = (\frac{\Lambda}{\mu}, 0,0,0,0)$ into the Jacobian matrix, thus obtained

$$J_{E_0} = \begin{pmatrix} -\mu & 0 & -\beta & 0 & -\alpha \\ 0 & -\rho-\mu & \beta & 0 & \alpha \\ 0 & \rho & -\tau-\mu & 0 & 0 \\ 0 & 0 & \tau & -\mu & 0 \\ 0 & 0 & \theta & 0 & -\mu_v \end{pmatrix}.$$

Based on the J_{E_0} Jacobian matrix, a characteristic equation is made as follows:

$$\det\left(J_{E_0} - \lambda I\right) = 0.$$

$$det\begin{pmatrix} -\mu-\lambda & 0 & -\beta & 0 & -\alpha \\ 0 & -\rho-\mu-\lambda & \beta & 0 & \alpha \\ 0 & \rho & -\tau-\mu-\lambda & 0 & 0 \\ 0 & 0 & \tau & -\mu-\lambda & 0 \\ 0 & 0 & \theta & 0 & -\mu_v-\lambda \end{pmatrix} = 0 \ ,$$

$$\Leftrightarrow (-\mu-\lambda)(-\mu-\lambda)[\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3] = 0, \qquad (4.1a)$$

with

$a_1 = 2\mu + \rho + \tau + \mu_v,$

$a_2 = \mu^2 + \rho\mu + \tau\mu + \tau\rho + 2\mu\mu_v + \mu_v\rho + \mu_v\tau - \rho\beta,$

$a_3 = (\mu^2\mu_v + \rho\mu\mu_v + \tau\mu\mu_v + \tau\rho\mu_v) - \rho(\beta\mu_v + \alpha\theta).$

Based on the equation (4.1a), we obtained eigen values $\lambda_1 = \lambda_2 = -\mu$, and roots of equation as follows,

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 \quad . \qquad (4.1b)$$

The non endemic equilibrium point will be asymptotically stable if and only if the characteristic equation (4.1a) has the roots part of negative real number. It is clear that λ_1 and λ_2 are negative because all parameters as described are positive. Then equation (4.1b) will have the roots part of negative real number with Routh-Hurwitz criteria. Based on Routh-Hurwitz criteria, the non endemic equilibrium point will be asymptotically stable if and only if $R_i < 1$, with $i = 0,1,2$.

$R_0 = \frac{\rho(\mu_v\beta + \alpha\theta)}{\mu_v(\mu+\tau)(\mu+\rho)}$,

$R_1 = \frac{\rho\beta}{\mu^2+\rho\mu+\tau\mu+\tau\rho+2\mu\mu_v+\mu_v\rho+\mu_v\tau}$,

$R_2 = \frac{a_3}{a_1 a_2}$,

This shows that if all conditions are fulfilled, then there is no further transmission of the disease.

4.2 LOCAL STABILITY OF ENDEMIC EQUILIBRIUM POINT

Substitute endemic equilibrium point $E_1 = (S^*, E^*, I^*, R^*, P^*)$ to the Jacobian matrix as

follow,

$$J_{E_1} = \begin{pmatrix} b_1 & 0 & b_6 & 0 & b_7 \\ b_8 & b_2 & b_9 & 0 & b_{10} \\ 0 & b_{11}\rho & b_3 & 0 & 0 \\ 0 & 0 & b_{12} & b_4 & 0 \\ 0 & 0 & b_{13} & 0 & b_5 \end{pmatrix},$$

with

$b_1 = \frac{\alpha\mu\theta I^*}{\Lambda\mu_v} - \mu$ $\quad$ $b_8 = \frac{\alpha\mu\theta I^*}{\Lambda\mu_v}$

$b_2 = -\rho - \mu$ $\quad$ $b_9 = \frac{\beta\mu\Lambda^2\mu_v}{\Lambda\mu(\mu_v\beta I^* + \alpha\theta I^* + \Lambda\mu_v)}$

$b_3 = -\tau - \mu$ $\quad$ $b_{10} = \frac{\alpha\mu\Lambda^2\mu_v}{\Lambda\mu(\mu_v\beta I^* + \alpha\theta I^* + \Lambda\mu_v)}$

$b_4 = -\mu$ $\quad$ $b_{11} = \rho$

$b_5 = -\mu_v$ $\quad$ $b_{12} = \tau$

$b_6 = \frac{-\beta\mu\Lambda^2\mu_v}{\Lambda\mu(\mu_v\beta I^* + \alpha\theta I^* + \Lambda\mu_v)}$ $\quad$ $b_{13} = \theta$

$b_7 = \frac{-\alpha\mu\Lambda^2\mu_v}{\Lambda\mu(\mu_v\beta I^* + \alpha\theta I^* + \Lambda\mu_v)}$ $I^* = \frac{\rho\Lambda}{(\mu+\tau)(\mu+\rho)} - \frac{\Lambda\mu_v}{(\mu_v\beta+\alpha\theta)}$.

Next is a characteristic equation by using $\det(J_{E_1} - \lambda I) = 0$.

$$\det\begin{pmatrix} b_1 - \lambda & 0 & b_6 & 0 & b_7 \\ b_8 & b_2 - \lambda & b_9 & 0 & b_{10} \\ 0 & b_{11} & b_3 - \lambda & 0 & 0 \\ 0 & 0 & b_{12} & b_4 - \lambda & 0 \\ 0 & 0 & b_{13} & 0 & b_5 - \lambda \end{pmatrix} = 0.$$

Thus, we obtain the characteristics equation

$$\Leftrightarrow (b_4 - \lambda)(\lambda^4 + c_1\lambda^3 + c_2\lambda^2 + c_3\lambda + c_4) = 0 \qquad (4.2a)$$

Because $c_1, c_2, c_3,$ dan c_4 contain many parameter values that are difficult to be simplified analytically, so it will be analyzed through numerical simulation using the phase field.

The Simulation is by giving parameters value and three initial value for $(S(0), E(0), I(0), R(0), P(0))$, which are different. The parameters value are presented in Table 4.1

Table 4.1 Parameters Value of Model

Parameter	Value	Unit	Source
Λ	100	$\frac{orang}{hari}$	Assume
β	0003	$\frac{1}{hari}$	Alzahrani and Khan (2018)
α	0.8	$\frac{1}{hari}$	Assume
μ	0004	$\frac{1}{hari}$	Alzahrani and Khan (2018)
ρ	0:02	$\frac{1}{hari}$	Alzahrani and Khan (2018)
τ	0:02	$\frac{1}{hari}$	Alzahrani and Khan (2018)
θ	0:06	$\frac{1}{hari}$	Assume
μ_v	0:02	$\frac{1}{hari}$	Alzahrani and Khan (2018)

The three initial values are presented in Table 4.2.

Table 4.2 Initial Value

Initial value	$\boldsymbol{S(0)}$	$\boldsymbol{E(0)}$	$\boldsymbol{I(0)}$	$\boldsymbol{R(0)}$	$\boldsymbol{P(0)}$	Colour
Initial Value 1	500	200	150	90	2000	Blue
Initial Value 2	750	400	100	80	3000	Green
Initial value 3	1000	750	500	150	2500	Red

The results of the phase field simulation at the endemic equilibrium point in the spread of Hepatitis E are shown in Figure 4.1

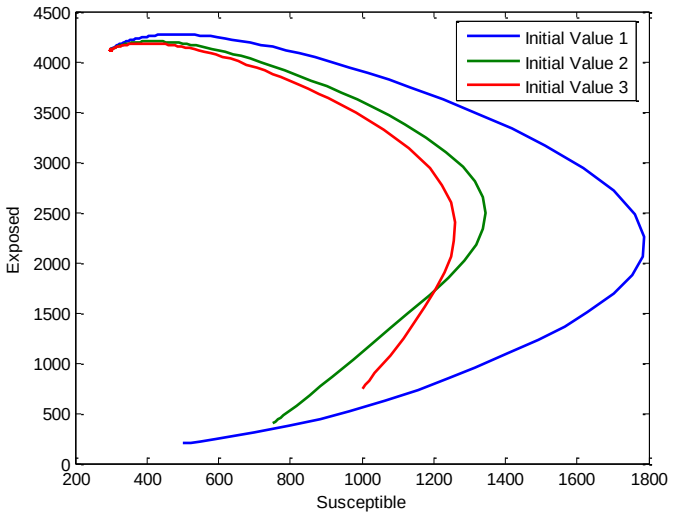

Figure 4.1 Phase Field Simulation on $S - E$ Population for Endemic Equilibrium Model

Figure 4.1 shows phase field simulation for susceptible human population $S(t)$ with exposed human population $E(t)$. Based on three different initial values have been given, it shows that all graphs of population tend to converge to a point $(S, E) = (299{,}62\ ,\ 4116{,}72)$ which is an endemic equilibrium point $E_1 = (299{,}62\ ;\ 4116{,}72\ ;\ 3430{,}61\ ;\ 17153{,}03\ ;\ 10291{,}82)$. In addition, based on the given parameter values we obtained value $R_0 = 83{,}43750000 > 1$.

Based on the explanation above, the endemic equilibrium point $E_1 = (S^*, E^*, I^*, R^*, P^*)$ on the mathematical model of the spread of hepatitis E will tend to be asymptotically stable if and only if $R_0 > 1$. This shows transmission of hepatitis E disease.

5. ANALYSIS OF PARAMETERS SENSITIVITY

The analysis sensitivity aims to determine the parameters that have a large influence in terms of stability of the equilibrium point, non endemic and endemic. The parameters considered are only the parameter contained in R_0 because these parameter indicate the condition whether the spread of the disease is occured or not. This can be known through sensitivity index (e_m) of each parameter. Using the approach in [23], the parameter sensitivity index is formulated as

follows,

$$e_m = \left(\frac{\partial R_0}{\partial m}\right)\frac{m}{R_0},$$

with:

m : Parameters to be analyzed

e_m : Sensitivity index parameter.

The R_0 value is influenced by 7 parameters. These are $\rho, \mu_v, \beta, \alpha, \theta, \tau,$ and μ. The following is the example of the sensitivity index calculation for α parameter. By substituting the parameters value in Table 4.1 we obtained:

$$e_\alpha = \left(\frac{\partial R_0}{\partial \alpha}\right)\frac{\alpha}{R_0} = \frac{\rho\theta}{\mu_v(\mu+\tau)(\mu+\rho)}\frac{\alpha\mu_v(\mu+\tau)(\mu+\rho)}{\rho(\mu_v\beta+\alpha\theta)} = \frac{\alpha\theta}{\rho(\mu_v\beta+\alpha\theta)} = 0.99.$$

The results of the calculation of the sensitivity index parameters can be seen in Table 5.1 below:

Table 5.1 Parameter Sensitivity Index Calculation Results

Parameter	Sensitivity Index
α	0.99
θ	0.99
μ_v	-0.99
τ	-0.83
μ	-0.33
ρ	0.17
β	0.0012

Based on Table 5.1 it can be seen that the sensitivity of the index α and θ is 0.99. This can be interpreted that if the transmission parameter of *P* and *S* (α) and shedding of virus by the infected individuals to the environment (θ) increased by 10%, then the R_0 value will increase by 9.9% and as well as vice versa. The analysis also applies to the parameters ρ dan β. This shows that for positive sensitivity index, if the parameter value increases, the R_0 value will also increase. On the other hand, for the negative sensitivity index, if the value of the parameter increases, the R_0 value will be reduced. For example, if the Natural death rate of viruses (μ_v) increase by 10%, then the R_0 value will be reduced by 9.9%. The analysis also applies to the parameter τ dan μ.

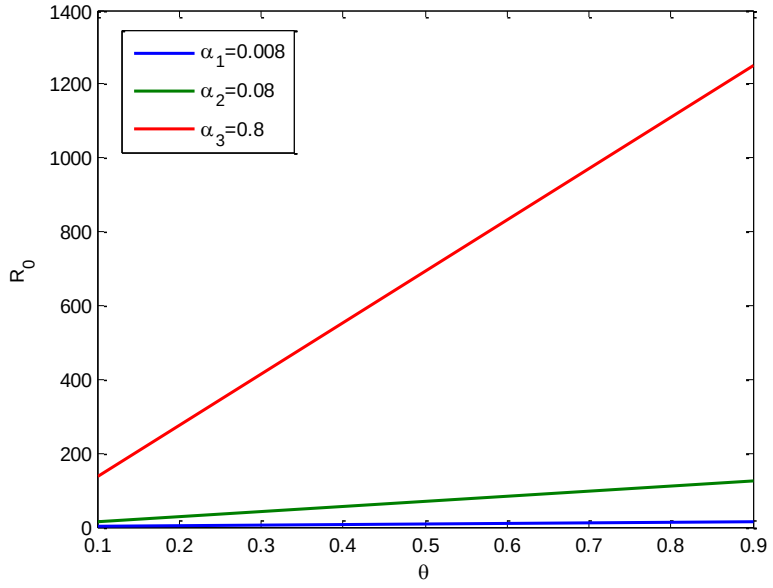

Figure 5.1 Sensitivity θ against R_0 values in three different α values

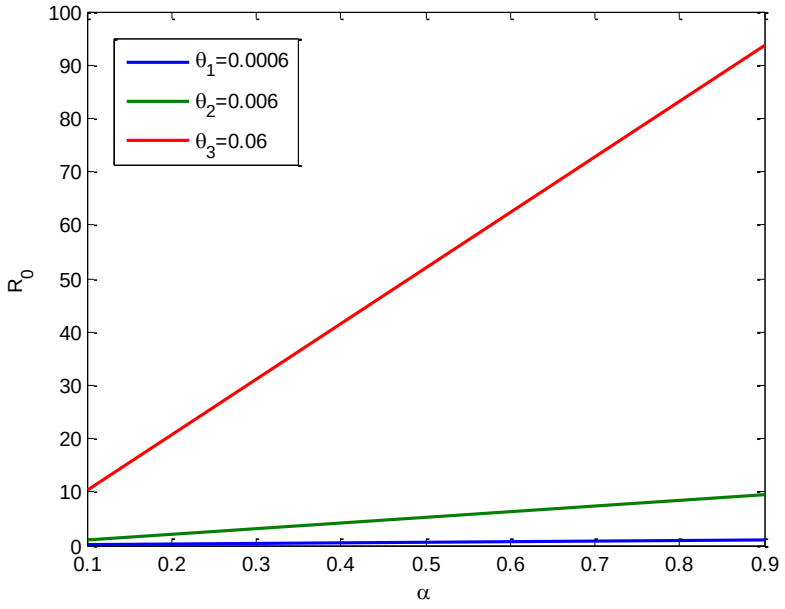

Figure 5.2 Sensitivity α against R_0 values in three different θ values

Furthermore, sensitivity parameters of α and θ are simulated against R_0. In the first simulation, we selected $\alpha = 0{,}008, \alpha = 0{,}08$ and $\alpha = 0{,}8$, while the θ value is in the interval $0{,}1 \leq \theta \leq 0{,}9$. The second simulation, we selected $\theta = 0{,}0006, \theta = 0{,}006,$ and $\theta = 0{,}06$, while the α value is in the interval $0{,}1 \leq \alpha \leq 0{,}9$. The results of the simulation can be seen in

Figure 5.1 and Figure 5.2.

Figure 5.1 and 5.2 describe that if parameters α and θ increase, then the R_0 value will also increase, meaning that the spread of hepatitis E disease will become more prevalent. This because the sensitivity index of parameters α and θ are positive, so that when the value is increase, the R_0value will also increase.

6. FORMULATION OF OPTIMAL CONTROL

We examine the application of optimal control in HEV model to reduce the spread of HEV. There are two control variables applied to the model, namely treatment (u_1) and virus extermination in the environment (u_2). The following is the mathematical model for the spread of hepatitis E with control variables

$$\frac{dS}{dt} = \Lambda - \frac{\mu(\beta I+\alpha P)S}{\Lambda} - \mu S \qquad (6.1a)$$

$$\frac{dE}{dt} = \frac{\mu(\beta I+\alpha P)S}{\Lambda} - (\mu + \rho)E \qquad (6.1b)$$

$$\frac{dI}{dt} = \rho E - (\mu + \tau)I - \varepsilon_1 u_1 I \qquad (6.1c)$$

$$\frac{dR}{dt} = \tau I - \mu R + \varepsilon_1 u_1 I \qquad (6.1d)$$

$$\frac{dP}{dt} = \theta I - \mu_v P - \varepsilon_2 u_2 P \qquad (6.1e)$$

The variable and parameter have been described in detail in section 4. From the model, it can be seen there are additional variable in the form of control variables $u_1$and u_2. The cost function or objective function which might be formed based on the explanation above are as follows:

$$Min\, J = \int_0^{t_f} \left(I + P + \frac{W_1}{2} {u_1}^2 + \frac{W_2}{2} {u_2}^2 \right) dt$$

with W_1, W_2 are weighting constants in the form of costs for the controls. The optimal control is at $0 \le u_i(t) \le 1$, with $i = 1,2$, $0 \le t \le t_f$ and t_f is the final time. We take a quadratic form to quantify the control costs [24, 25, 26].

6.1 SOLVING OF OPTIMAL CONTROL

Based on Pontryagin's Maximum Principle [27], the first step taken is to form the Hamiltonian function in the model as follows:

$$\mathcal{H} = I + P + \frac{W_1}{2}{u_1}^2 + \frac{W_2}{2}{u_2}^2 + \gamma^T(t)(f(x(t), u(t), t)) \qquad (6.1f)$$

with $f(x(t), u(t), t)$ is at the right hand side of the mathematical model of the spread of hepatitis E, while $\gamma^T(t)$ expresses the Lagrange multiplier or co-state variable.

Next, in order to obtain the optimal condition, the Hamiltonian function must in the stationary condition of

$$\frac{\partial H}{\partial u} = 0 \Leftrightarrow \frac{\partial H}{\partial u_1} = 0 \text{ , dan } \frac{\partial H}{\partial u_2} = 0$$

i. $\frac{\partial H}{\partial u_1} = 0$

$\Leftrightarrow W_1 u_1 - \gamma_3 \varepsilon_1 I + \gamma_4 \varepsilon_1 I = 0$

$\Leftrightarrow u_1 = \frac{\varepsilon_1 I(\gamma_3 - \gamma_4)}{W_1}$,

ii. $\frac{\partial H}{\partial u_2} = 0$

$\Leftrightarrow W_2 u_2 - \gamma_5 \varepsilon_2 P = 0$

$\Leftrightarrow u_2 = \frac{\varepsilon_2 \gamma_5 P}{W_2}$,

due to $0 \le u_i(t) \le 1$, with $i = 1,2$ the following possible value of u are:

$${u_1}^* = \begin{cases} 0 & \text{for } {u_1}^* \le 0 \\ \frac{\varepsilon_1 I(\gamma_3 - \gamma_4)}{W_1} & \text{for } 0 < {u_1}^* < 1 \\ 1 & \text{for } {u_1}^* \ge 1, \end{cases}$$

$${u_2}^* = \begin{cases} 0 & \text{for } {u_2}^* \le 0 \\ \frac{\varepsilon_2 \gamma_5 P}{W_2} & \text{for } 0 < {u_2}^* < 1 \\ 1 & \text{for } {u_2}^* \ge 1 \text{ .} \end{cases}$$

Based of the probability above, the optimal of control value is obtained as follows

$${u_1}^* = min\left(1, max\left(0, \frac{\varepsilon_1 I(\gamma_3 - \gamma_4)}{W_1}\right)\right) \qquad (6.1g)$$

$$u_2{}^* = min\left(1, max\left(0, \frac{\varepsilon_2 \gamma_5 P}{W_2}\right)\right) \qquad (6.1h).$$

Next, due to the controller $u_1{}^*$ and $u_2{}^*$ there are state variables, $= (S, E, I, R, P)^T$, therefore the state equation and co-state equation need to be resolved to obtain these variables. Thus it will be determined the completion of the state equation to obtain the variable $\dot{x} = \frac{\partial H}{\partial \gamma}$.

Furthermore, co-state equation on controller $u_1{}^*$ and $u_2{}^*$ will be determined, from the following formula

$$\dot{\gamma} = -\frac{\partial H}{\partial x}.$$

which resulted in

$$\dot{\gamma_1} = -\frac{\partial \mathcal{H}}{\partial S} = -\left[\frac{-\mu(\beta I + \alpha P)(\gamma_2 - \gamma_1) - \gamma_1 \mu \Lambda}{\Lambda}\right],$$

$$\dot{\gamma_2} = -\frac{\partial \mathcal{H}}{\partial E} = -[-\gamma_2(\mu + \rho) + \gamma_3 \rho],$$

$$\dot{\gamma_3} = -\frac{\partial \mathcal{H}}{\partial I} = -\left[1 + \frac{\beta \mu S(\gamma_2 - \gamma_1)}{\Lambda} - \gamma_3(\mu + \tau + \varepsilon_1 u_1) + \gamma_3(\tau + \varepsilon_1 u_1) + \gamma_5 \theta\right],$$

$$\dot{\gamma_4} = -\frac{\partial \mathcal{H}}{\partial R} = -[-\gamma_4 \mu],$$

$$\dot{\gamma_5} = -\frac{\partial \mathcal{H}}{\partial P} = -\left[1 + \frac{\alpha \mu S(\gamma_2 - \gamma_1)}{\Lambda} + \gamma_5(\mu_v + \varepsilon_2 u_2)\right].$$

7. NUMERICAL RESULTS

We address the numerical solution of the control model (4) with and without control. We utilize the fourth- order Runge-Kutta (RK4) algorithm to obtain the numerical solution of the control model. The forward RK4 algorithm is employed to solve the state systems. Thus, the backward RK4 algorithm is used to solve the co-state system [28].

Simulation is conducted for the following $t = 0$ to $t = 100$ days with the initial value for each condition is $S(0) = 500,\ E(0) = 200,\ I(0) = 150, R(0) = 90,\ P(0) = 2000$. The parameter value used is the same as the parameter value when simulating the phase field for the endemic equilibrium point. Weighting constants for the controls is $W_1 = 100$ and $W_2 = 70$.

Simulation is in four condition. The first simulation is without any control. The second simulation is only the treatment (u_1). The third simulation is only virus extermination (u_2). The last simulation is the treatment (u_1) and virus extermination (u_2).

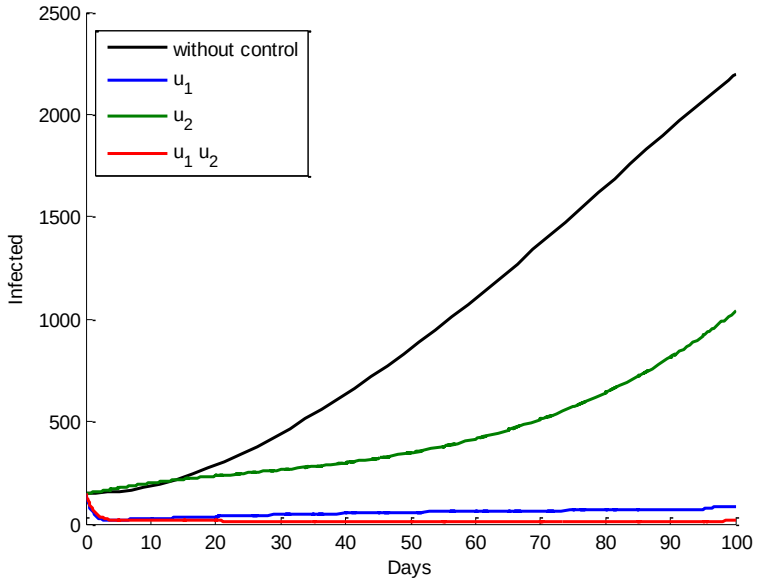

Figure 7.1 Comparison Simulation of Infected Human Population for 100 Days.

Table 7.1 Comparison of Total Individuals Infected for 100 days.

Scenario	Total population of infected individuals at day 100
Without control	2200
Control u_1	85
Control u_2	1039
Control u_1 and u_2	16

Figure 7.1 shows that there is a significant difference between the number of infected individuals population when without and with the control variables. The number of infected individuals with the control u_1 population decreased significantly. When given a control u_2, the number of infected individuals decreased by about 50% of the total population with no control. When given the control u_1 and u_2, it decreased even dramatically. This is as presented in Table 7.1 shows that at the end of the observation the number of infected individuals population has the least amount compared to other scenarios.

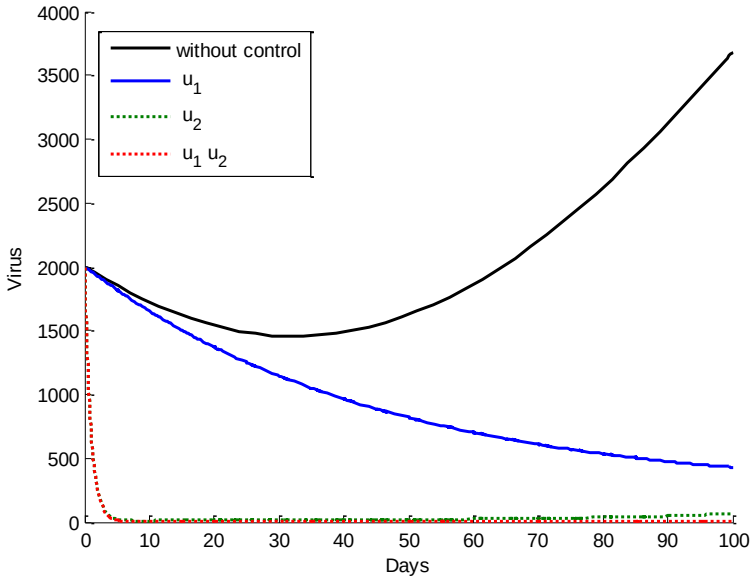

Figure 7.2 Comparison Simulation of Virus in the Environment for 100 Days

Table 7.2 Comparison of virus in the environment for 100 days.

Scenario	Total population of virus in the environment at day 100
Without control	3684
Control u_1	430
Control u_2	69
Control u_1 and u_2	4

Figure 7.2 shows that there is a siginificant difference between the number of virus when without and with the control variables. The number of viruses with control u_1 decreased until the last day. When given control u_2, the number of viruses decreased quite dramatically until day 5, and then remained constant until the last day of observation. When given the control u_1 and u_2, it also decreased the amount of the virus that is similar to the second scenario, but the amount of the virus in this scenario is a little more at the last day. This is as presented in Table 7.2 shows that at the end of the observation, the number of viruses in the environment has the least amount compared to other scenarios.

Furthermore, the simulation of the control profile for u_1 and u_2 are presented in Figure 7.3, Figure 7.4 and Figure 7.5 below:

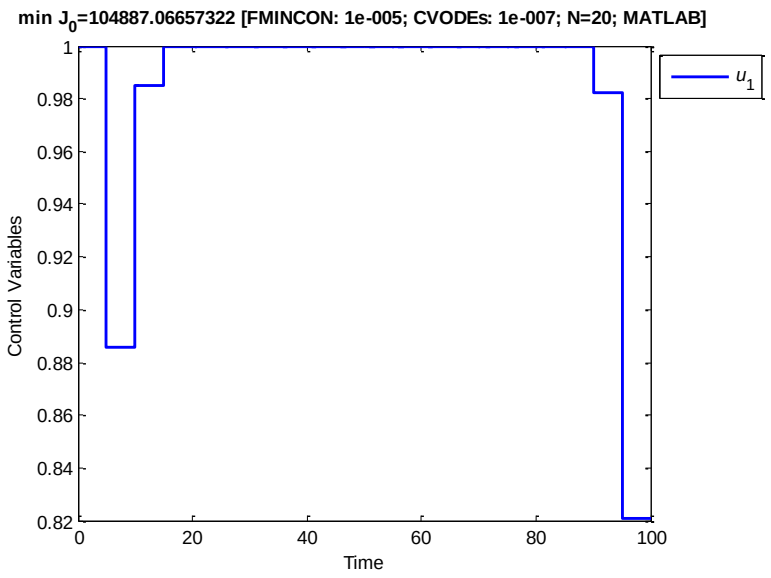

Figure 7.3 Control Profile of Treatment (u_1)

Figure 7.3 shows that the control variables of the treatment (u_1), on the day 1 to day 5, the effort is done maximally. When the observation is on the day 5 to day 10, the effort fell to 0.88 or 88%. Then, when the observation is on the day 10 to day 90, the effort increased up to 0.98 or 98% until the maximum effort. Furthermore, on the day 90 until the last day, the effort decreased gradually until around 0.82 or 82%.

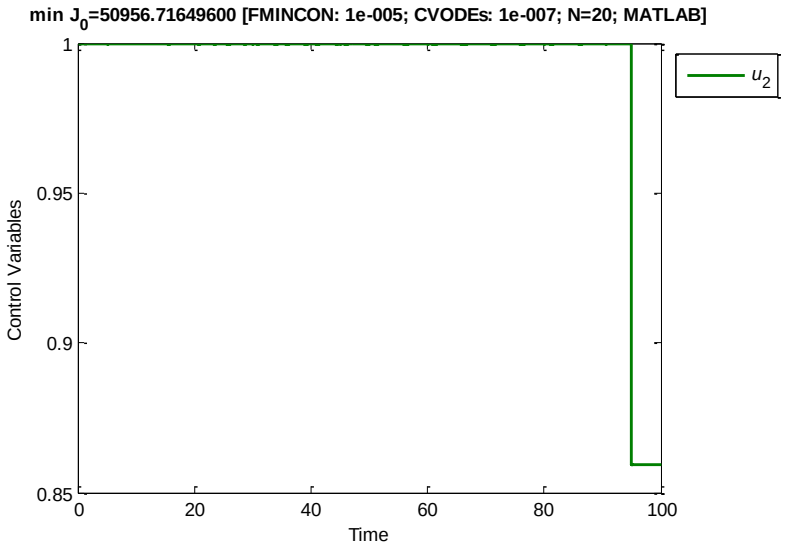

Figure 7.4 Control Profile of Virus Extermination (u_2)

Figure 7.4 shows that the control variables of virus extermination (u_2), on day 1 to day 95, the effort is done maximally. When the observation is on the day 95 until the last day, the effort decreased to 0.85 or 85%.

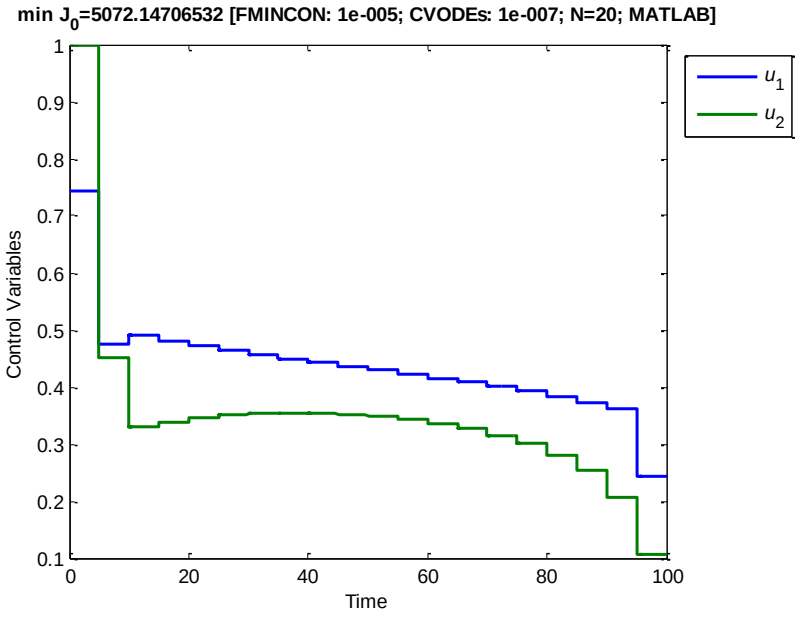

Figure 7.5 Control Profile of Treatment (u_1) and Virus Extermination (u_2)

Figure 7.5 shows that the control variables u_1 and u_2 are given simultaneously. On the day 1 to day 5, the effort is given around 0.74 or 74%, while for control u_2 is given a maximum. When the observation is on the day 5 to day 10, the effort of u_1 and u_2 decreased respectively to 0.47 and 0.45 or 47% or 45%. Then, when the observations is on the day 10 to day 15 control u_1 increased up to 0.49 or 49%, while for control u_2 decreased to 0.33 or 33%. Next, control u_1 on the day 15 to day 95 with a difference of once every 5 day decreased by about 0.01 or 1%, but on the day 95 to the last day, the effort exerted fell up again to 0.24 or 24%, whereas for control u_2 it decreased gradually once every 5 days up to day of 45 for 0.01 or 1%. Next, at the day of 45 to day 90 the effort given is decline gradually into a 0.2 or 20% and at the last day of the observation, control u_2 given was just 0.1 or 10%. The cost function value of each control can be seen in Table 7.3 below:

Table 7.3 The cost function of each control on a given.

Scenario	Cost Function Value
Control u_1	104,887.07
Control u_2	50956.72
Control u_1 and u_2	5072.15

Based on Table 7.3 it can be concluded that, in the 100 days, to minimize the number of infected individuals and populations of viruses in the environment as well as to minimize the cost of controlling the application of the most effective control, is to perform the treatment (u_1) and virus extermination (u_2) that are given simultaneously.

8. CONCLUSION

Based on the results and observations described, the following conclusions are derived:

1. The mathematical model for the spread of hepatitis E as control variables has two equilibria, non endemic equilibrium point(E_0) and endemic equilibrium point(E_1). Non endemic equilibrium point will be asymptotically stable if and only if $R_0 < 1$ and fulfill several conditions. Endemic equilibrium point will tend to be locally asymptotically stable if and only if $R_0 > 1$, with
$$R_0 = \frac{\rho(\mu_v\beta + \alpha\theta)}{\mu_v(\mu+\tau)(\mu+\rho)}.$$
2. The form of optimal control on a mathematical model for the spread of hepatitis E with control treatment(u_1) and virus extermination(u_2) is
$$u_1^* = min\left(1, max\left(0, \frac{\varepsilon_1 I(\gamma_3 - \gamma_4)}{W_1}\right)\right)$$
$$u_2^* = min\left(1, max\left(0, \frac{\varepsilon_2\gamma_5 P}{W_2}\right)\right)$$
3. Based on numerical simulation results on the mathematical model for the spread of hepatitis E before and after being given control, the form of treatment (u_1) and virus

extermination(u_2) are the most effective way to minimize the infected individuals and the population of virus in the environment.

Further research can modify the mathematical model for the spread of hepatitis E by adding control variable in the form of prevention given in susceptible individuals. Furthermore, it also can investigate the most effective effort to reduce the spread of hepatitis E.

ACKNOWLEDGMENTS

This research is funded by Research Grants from Faculty of Science and Technology, Universitas Airlangga, Indonesia.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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