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MATHEMATICAL MODEL OF HCV TRANSMISSION WITH TREATMENT AND EDUCATIONAL EFFORT

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Abstract: One of the serious health issues around the world is Hepatitis C infection. The hepatitis C virus (HCV) is easily transmitted by drug injection with no hygiene syringe. The HCV transmission often occurs around the uneducated injector and potentially to becomes an epidemic. In this paper, a mathematical model for HVC transmission was proposed with considering educated and uneducated injectors. The purpose is to know how belonging important the role of both educated and uneducated injectors is in virus spreading. We also consider the treatment of the infected population and educational programs on the uneducated injector to control the spreading of the virus. By using the dynamical system theory, we get the equilibrium points and examine their stability. Then we use the control optimal theory to control the disease using interventions with respect to the cost of effort. Finally, through numerical simulation, the prediction of the result of control strategy and sensitivity analysis is obtained to know the most important parameter of the model.

Keywords: HCV; injectors; dynamical theory; optimal control; sensitivity analysis.

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1. INTRODUCTION

Infectious diseases threaten human health and have the potential to become epidemics. One of the serious infectious diseases is hepatitis C which is inflammation of the liver caused by a virus named hepatitis C (HCV). HCV is an RNA virus belonging to the Flaviviridae family that duplicates in the hepatocyte cytoplasm, but it is not directly caused cytopathic effect [10]. The disease is easily infected through contact with contaminated blood. The virus infects about 170 million people worldwide, with 150 million of them potentially chronic infection [2]. In developing countries, the most infection caused by the reuse of needles and syringes for medical injections [14]. Individuals who are infected by the virus may be asymptomatic thus cause the disease more dangerous over time. Hepatitis C has the possibility of becoming an acute infection if it occurs for weeks or a few months and will be a chronic infection if it persists for a longer time [2]. In the chronic stage, HVC infection can attack the liver consistently, which causes cirrhosis and live cancer occasionally.

The HCV is potentially transmitted by the use of drug injection tools, blood transfusions by unchecked donors, unsafe medical injections, and other ways that allow contact with blood. Numerous evidence by developing countries indicates that the dominant source of new infection over the past decades is the drug injection [10]. HCV continues to cause a severe public health enemy. There is a need to understand how injection equipment dynamics play a role in HCV transmission [7]. Although the disease caused by HCV infection has the possibility to cure by some treatment, but it is ineffective to absolutely omit the virus and some infected who are suffering from chronic infection may suppose a liver transplant [2]. There are several interventions that can help to reduce the risk of virus infection, such as vaccination, controlling injectors, media campaign, etc. Vaccination is an effort with a vaccine to produce immunity against a disease, but it is not the only one intervention. The government can control the injectors by educating and enforcing the rules about injections. In addition, media campaigns may be carried out for the public to gain knowledge about infectious disease, hepatitis c, and its potential to become a pandemic. In this paper, we will emphasize how effectively controlling injectors reduces the

potential outbreak caused by HVC infection.

Numerous mathematical models are developed for representing infectious disease mechanisms. Generally, a mathematical model that represents the HCV transmission notable as the SIR model. SIR model represents the Susceptible, Infected, and Recovered populations as compartments. Basically, it describes the path of the disease that spreads from infected person to susceptible person and how they recover. Then, the describe represented by a mathematical equation, usually as a differential equation system. The system will solve analytically to know the equilibrium points and their stability. Numerically is used to confirm the result of the analysis and to see the pattern of the spreading process dynamically based on the resulting graph. It is important to know the pattern of the disease spreading, the government can predict how dangerous it is by the time and make some policies to control it. Many research has done with various intervention on the spread of the hepatitis C disease. Anqi [9] developed a mathematical model for the dynamics of SIR model with both horizontal and vertical transmission, but not specifically to HCV infection. Miller [7] evolved a mathematical model of the HCV transmission as an indirectly transmission and investigated how the injection drug equipment affect the virus spreading. Some researchers investigate epidemic models which consider vaccination with waning immunity as an intervention [2] and hemodialysis affect [3].

Research showed that injection drug equipment play a crucial role in the spread of the virus [7]. Therefore, there needs to be an effort to control the injection activity by controlling injectors and enforce the law. Other than that, media campaign is needed to educate both injector and public about the dangers of indiscriminate injection. In this paper, we build a model of HCV infection with considering treatment and educational effort as interventions. We determine the equilibrium points and their stability. We also discuss basic reproduction number through next generation matrix to know possibility of the epidemics by the spread of the virus. Finally, the numerical solution has been shown to illustrate the spread of the virus dynamically.

2. MATERIALS AND METHODS

In developing a mathematical model to describe the HCV transmission, there are several assumptions needed, which are:

- Susceptible population being infected if injected by uneducated injectors.
- Uneducated injectors have a role to spread the disease trough injection.
- Uneducated injector can be educated if get knowledge through educational program.
- Mortality risk of infected population is higher than the others.

The schematic diagram of the HCV transmission with injectors both educated and uneducated as in Figure 1, with the definition of parameters and variable used in Table 1.

TABLE 1. Parameter value and initial condition

Variable / Parameter	Definition	Value
S	Susceptible Population	10
I	Infected Population	4
R	Recovered Population	0
U	Uneducated Injector Population	3
E	Educated Injector Population	2
Λ	Birthrate of Susceptible	2
μ	Mortality Rate	0.009
μ_H	Mortality Rate Caused by HCV Infection	0.035
α	Infection Rate of Susceptible	0.072
λ_1	Uneducated Injectors Growth Rate	2
λ_2	Educated Injectors Growth Rate	1
r	Recovery Rate	0.082
ζ	Treatment Rate	0.085
η	Education Rate	0.0025
γ	Injection Rate	0.4

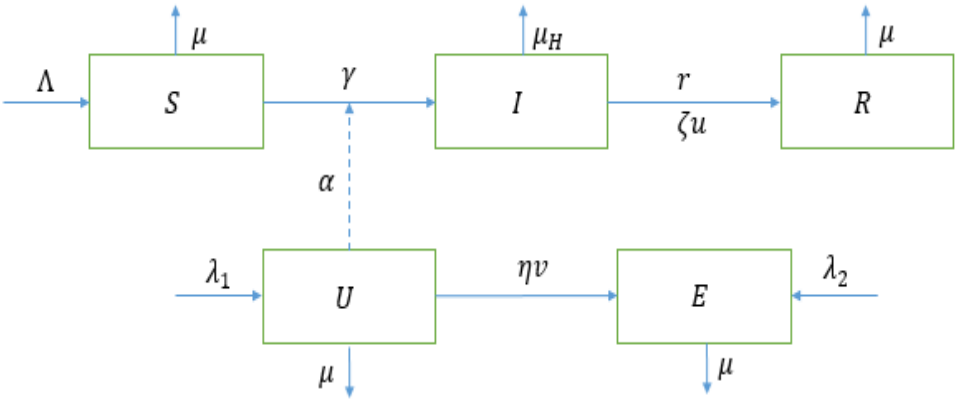


Figure 1. Schematic diagram of the HCV transmission with injectors both educated and uneducated

According to the schematic diagram in Figure 1, the mathematical model of the HCV transmission can be represented as follows:

$$\frac{dS}{dt} = \Lambda - \mu S - \alpha\gamma\left(\frac{U}{U+E}\right)SI \quad (1)$$

$$\frac{dI}{dt} = \alpha\gamma\left(\frac{U}{U+E}\right)SI - \mu_H I - rI - \zeta I \quad (2)$$

$$\frac{dR}{dt} = \zeta I + rI - \mu R \quad (3)$$

$$\frac{dU}{dt} = \lambda_1 - \mu U - \eta U \quad (4)$$

$$\frac{dE}{dt} = \lambda_2 + \eta U - \mu E \quad (5)$$

3. Results and Discussions

3.1 Equilibrium Point

Disease-free state is defined as the absence of disease infection in a system. To get the non-endemic equilibrium point, we set the infected be zero $(I^* = 0)$. Based on Model 1, a non-endemic point is obtained as follow:

$$Eq_0 = \{S^*, I^*, R^*, U^*, E^*\} = \left\{\frac{\Lambda}{\mu}, 0, 0, \frac{\lambda_1}{\eta+\mu}, \frac{(\lambda_1+\lambda_2)\eta + \mu\lambda_2}{\mu(\mu+\eta)}\right\} \quad (6)$$

Endemic state is defined that the epidemic happened by the disease and exist if $\mathfrak{R}_0 > 1$. Based

on Model 1, an endemic equilibrium point is obtained follow:

$$S^* = \frac{(\mu_H + r)\big(\lambda_1(\gamma\rho + c) + \lambda_2(\gamma\rho + c + \mu)\big)}{\lambda_1\alpha(1-\gamma)\mu} \tag{7}$$

$$I^* = \frac{\big((\alpha\Lambda + r\rho + \rho\mu_H)\gamma + \mu r + \mu\mu_H - \alpha\Lambda\big)\lambda_1 + (\mu_H + r)(\gamma\rho + c + \mu)\lambda_2}{(\gamma - 1)(\mu_H + r)\alpha\lambda_1} \tag{8}$$

$$R^* = \frac{\Big(\big((\gamma\rho + \mu)r + (\alpha\Lambda + \rho\mu_H)\gamma + \mu\mu_H - \alpha\Lambda\big)\lambda_1 + (\mu_H + r)(\gamma\rho + c + \mu)\lambda_2\Big)r}{\mu(\gamma - 1)(\mu_H + r)\lambda_1\alpha} \tag{9}$$

$$U^* = \frac{\lambda_1}{\gamma\rho + c + \mu} \tag{10}$$

$$E^* = \frac{(\gamma\rho + c + \mu)\lambda_2 + \rho\gamma\lambda_1}{(\gamma\rho + c + \mu)\mu} \tag{11}$$

3.2 Basic Reproduction Ratio

In epidemiology, basic reproduction ratio ($\mathfrak{R}_0$) is a necessary thing to know [14]. It is important because by knowing the value we know how the potential epidemics of the disease. To get the basic reproduction ratio, we use the next generation matrix [14], with f as the new infection matrix and v as the change in compartment matrix (including decrease by death or immunity acquisition). The f and v matrix follow:

$$f = \left[\alpha\gamma\left(\frac{U}{U+E}\right)SI\right] \text{ dan } v = [\mu_H I + rI + \zeta I]$$

We look for F dan V^{-1} as the jacobian matrix of f and v, then determine the radius spectral (dominant eigenvalue) of FV^{-1} matrix at non-endemic equilibrium point. So we get:

$$\mathfrak{R}_0 = \frac{\gamma\Lambda\alpha\lambda_1}{(\lambda_1 + \lambda_2)(\eta + \mu)(\zeta + r + \mu_H)}$$

3.3 Stability Analysis

Jacobian matrix for the model is

$$J = \begin{bmatrix} -\mu - \frac{\alpha\gamma UI}{U+E} & -\frac{\alpha\gamma SU}{U+E} & 0 & -\frac{\alpha\gamma SI}{U+E} + \frac{\alpha\gamma SUI}{(U+E)^2} & \frac{\alpha\gamma SUI}{(U+E)^2} \\ \frac{\alpha\gamma UI}{U+E} & \frac{\alpha\gamma SU}{U+E} - \mu_H - r - \zeta & 0 & \frac{\alpha\gamma SI}{U+E} - \frac{\alpha\gamma SUI}{(U+E)^2} & -\frac{\alpha\gamma SUI}{(U+E)^2} \\ 0 & \zeta + r & -\mu & 0 & 0 \\ 0 & 0 & 0 & -\eta - \mu & 0 \\ 0 & 0 & 0 & \mu & -\mu \end{bmatrix}$$

The local stability of the non-endemic and endemic equilibrium points are given through the theorem as follow as:

Theorem 1

The non-endemic equilibrium of the model is locally asymptotically stable if $\mathfrak{R}_0 < 1$.

Proof

By following [1], substitute the disease-free equilibrium point into the Jacobian matrix for non-endemic equilibrium points, so we get the following characteristic polynomial of $J(Eq_0)$ is

$$\frac{1}{(\eta+\mu)(\lambda_1+\lambda_2)}\Big((x+\mu)^3(x+\mu+\eta)\big((\lambda_1+\lambda_2)(\zeta+r+\mu_H+x)(\eta+\mu)-\Lambda\alpha\gamma\lambda_1\big)\Big)=0$$

From the characteristic polynomial, the eigenvalues are obtained as follows :

$$x_{1,2,3}=-\mu, x_4=-(\mu+\eta)$$

based on the eigenvalues, for $x_1, x_2, x_3,$ and x_4 are negative, so the model is stable, then x_5 must be negative. By considering the characteristic polynomial, we get

$$(\lambda_1+\lambda_2)(\zeta u+r+\mu_H+x)(\eta v+\mu)-\Lambda\alpha\gamma\lambda_1=0$$

$$x=\frac{\Lambda\alpha\gamma\lambda_1}{(\lambda_1+\lambda_2)(\mu+\eta)}-(\zeta+r+\mu_H)=\frac{\Lambda\alpha\gamma\lambda_1-(\zeta+r+\mu_H)(\lambda_1+\lambda_2)(\mu+\eta)}{(\lambda_1+\lambda_2)(\mu+\eta)}<0$$

$$\frac{(\mathfrak{R}_0-1)(\zeta+r+\mu_H)(\lambda_1+\lambda_2)(\mu+\eta)}{(\lambda_1+\lambda_2)(\mu+\eta)}<0\rightarrow(\mathfrak{R}_0-1)(\zeta+r+\mu_H)<0$$

$$\mathfrak{R}_0-1<0\rightarrow\mathfrak{R}_0<1$$

it can be seen that $\mathfrak{R}_0 < 1$. This completes the proof.

Theorem 2

The endemic equilibrium point of the model is locally asymptotically stable if $\mathfrak{R}_0 > 1$.

Proof

Since we have a basic reproduction ratio, we get the new form equilibrium point for S^* and I^* which

$$Eq_1=\{S^*,I^*,R^*,U^*,E^*\}=\left\{\frac{1}{\mathfrak{R}_0}\frac{\Lambda}{\mu},\frac{(\mathfrak{R}_0-1)(\eta+\mu)(\lambda_1+\lambda_2)}{\alpha\gamma\lambda_1},R^*,U^*,E^*\right\}$$

Substitute endemic equilibrium into the Jacobian matrix, so we get the following characteristic polynomial of $J(E_1)$ is

$$\frac{1}{\mathfrak{R}_0(\eta+\mu)(\lambda_1+\lambda_2)}\left((x+\mu)^2(x+\mu+\eta)\left(\frac{\Lambda\alpha\gamma\lambda_1}{\zeta+r+\mu_H}x^2+\left(\frac{\mu\Lambda\alpha\gamma\lambda_1}{(\zeta+r+\mu_H)}\mathfrak{R}_0\right)x\right.\right.$$

$$\left.\left.+(\mathfrak{R}_0-1)\mu\Lambda\alpha\gamma\lambda_1\right)\right)=0$$

From the characteristic polynomial, the eigenvalues are obtained as follows:

$$x_{1,2}=-\mu, x_3=-\mu-\eta$$

Based on the eigenvalues for $x_1, x_2,$ and x_3 are negative, so the model is stable, then x_4 and x_5 must be negative. By considering the characteristic polynomial, we get

$$a_1=\frac{\Lambda\alpha\gamma\lambda_1}{\zeta+r+\mu_H}>0$$

$$a_2=\frac{\mu\Lambda\alpha\gamma\lambda_1}{(\zeta+r+\mu_H)}\mathfrak{R}_0>0$$

$$a_3=(\mathfrak{R}_0-1)\mu\Lambda\alpha\gamma\lambda_1>0\rightarrow\mathfrak{R}_0-1>0\rightarrow\mathfrak{R}_0>1$$

It can be seen that $\mathfrak{R}_0>1$. This completes the proof.

3.4 Problem of Optimal Control

In an effort to control the disease spreads, our aim is to minimize the total of infected population and uneducated injector population, so that the uneducated injector population who has the potential to spread the disease is reduced. To minimize the total of infected and uneducated injector population and optimize the treatment and education used with regard to the control cost. We will remodel the system (1)-(5) with adding control parameters u and v, then we get

$$\frac{dS}{dt}=\Lambda-\mu S-\alpha\gamma\left(\frac{U}{U+E}\right)SI \quad (12)$$

$$\frac{dI}{dt}=\alpha\gamma\left(\frac{U}{U+E}\right)SI-\mu_H I-rI-u\zeta I \quad (13)$$

$$\frac{dR}{dt}=u\zeta I+rI-\mu R \quad (14)$$

$$\frac{dU}{dt}=\lambda_1-\mu U-\eta vU \quad (15)$$

$$\frac{dE}{dt}=\lambda_2+\eta vU-\mu E \quad (16)$$

We will look for the treatment and education effort with the objective function as follow:

$$J^*(u,v) = \min \int_0^{tf} [AI + BU + Cu^2 + Dv^2]\, dt \tag{17}$$

Parameters $A, B, C,$ and D defines the weight of infected population, uneducated injector, treatment cost, and education cost in the performance index that satisfies $A, B, C, D \geq 0$. We solve the optimal control model through the Pontryagin Maximum Principle the control u and v with the variable state $y(t) = \begin{bmatrix} S(t) \\ I(t) \\ R(t) \\ U(t) \\ E(t) \end{bmatrix}$ and the constraint:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \mu S - \alpha\gamma\left(\frac{U}{U+E}\right)SI \\
\frac{dI}{dt} &= \alpha\gamma\left(\frac{U}{U+E}\right)SI - \mu_H I - rI - u\zeta I \\
\frac{dR}{dt} &= u\zeta I + rI - \mu R \\
\frac{dU}{dt} &= \lambda_1 - \mu U - v\eta U \\
\frac{dE}{dt} &= \lambda_2 + v\eta U - \mu E
\end{aligned} \tag{18}$$

The system must satisfy the condition: $0 < t < t_f, 0 \leq u(t) \leq Up, 0 \leq v(t) \leq Vp, S(t), I(t), R(t), U(t), E(t) \geq 0$, where Up and Vp is the upper limit of control. Remind that the control u and v represent the percentage of the control we can do. This value describes the maximum effort in managing the control and then it is determined $u = 1$ and $v = 1$. We create the function of Hamiltonian as $H = f(y,u,v,t) + \lambda' g(y,u,v,t)$, which equal to

$$H = AI + BU + Cu^2 + Dv^2 + \beta_1\left[\Lambda - \mu S - \alpha\gamma\left(\tfrac{U}{U+E}\right)SI\right] + \beta_2\left[\alpha\gamma\left(\tfrac{U}{U+E}\right)SI - \mu_H I - rI - u\zeta I\right] + \beta_3[u\zeta I + rI - \mu R] + \beta_4[\lambda_1 - \mu U - v\eta U] + \beta_5[\lambda_2 + v\eta U - \mu E]$$

where $\beta_1(t), \beta_2(t), \beta_3(t), \beta_4(t)$ and $\beta_5(t)$ are the Lagrange multiplier of the problem of optimization or mostly known as the co-state variables in optimal control theory. The necessary conditions than an optimal control is noted, it should satisfies the Pontryagin Maximum Principle as follow:

- State equations for this model rewrite with the condition

  $S(t) \geq 0, I(t) \geq 0, R(t) \geq 0, U(t) \geq 0, E(t) \geq 0$

- Co-state equation

$$\dot{\beta}_1 = -\beta_1(t)\left(-\alpha\gamma\left(\frac{U(t)}{U(t)+E(t)}\right)I(t) - \mu\right) - \beta_2(t)\left(\alpha\gamma\left(\frac{U(t)}{U(t)+E(t)}\right)I(t)\right)$$

$$\dot{\beta}_2 = -A - \beta_1(t)\left(-\alpha\gamma\left(\frac{U(t)}{U(t)+E(t)}\right)S(t)\right) - \beta_2(t)\left(\alpha\gamma\left(\frac{U(t)}{U(t)+E(t)}\right)S(t) - \mu_H - r - \zeta u(t)\right) - \beta_3(t)\big(r + \zeta u(t)\big)$$

$$\dot{\beta}_3 = -\beta_3(t)(-\mu)$$

$$\dot{\beta}_4 = -B - \beta_1(t)\left(-\alpha\gamma\left(\frac{E(t)}{\big(U(t)+E(t)\big)^2}\right)S(t)I(t)\right) - \beta_2(t)\left(-\alpha\gamma\left(\frac{E(t)}{\big(U(t)+E(t)\big)^2}\right)S(t)I(t)\right) - \beta_4(t)\big(\mu - \eta v(t)\big) - \beta_5(t)\big(\eta v(t)\big)$$

$$\dot{\beta}_5 = -\beta_5(t)(-\mu)$$

- Stationer condition $\frac{\partial H}{\partial u} = 0$ and $\frac{\partial H}{\partial v} = 0$, with respect that $0 \leq u, v \leq 1$ then we get

$$u^* = \min\left\{\max\left[0, \frac{1}{2}\left(\frac{\beta_2(t)\zeta I(t) - \beta_3(t)\zeta I(t)}{C}\right)\right], 1\right\}$$

$$v^* = \min\left\{\max\left[0, \frac{1}{2}\left(\frac{\beta_4(t)\eta U(t) - \beta_5(t)\eta U(t)}{D}\right)\right], 1\right\}$$

because $\frac{\partial^2 H}{\partial u^2} = 2C > 0$ and $\frac{\partial^2 H}{\partial v^2} = 2D > 0$ satisfies the minimization problem of the optimal control with u^* and v^* as the optimal control of the system.

3.5 Numerical Simulations

In this section, we show some simulations of the model. To know how the probability of the spread happens dynamically, we need to use values sample in Table 1 with some parameter determined hypothetically.

Firstly, we discuss the population dynamics for all compartments showed in Figure 2.

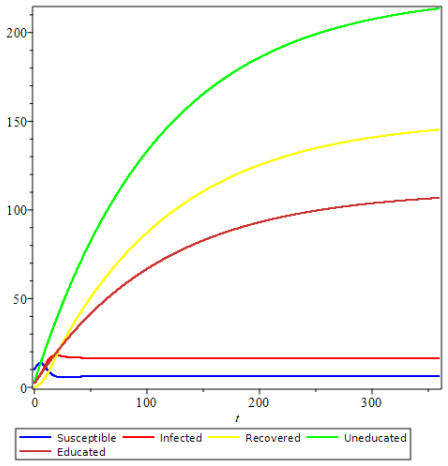
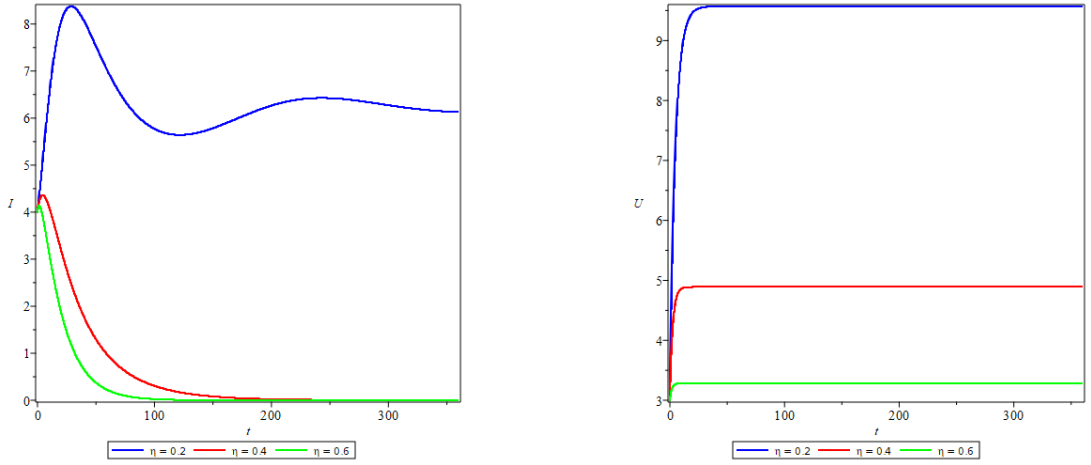


Figure 2. Dynamical population of the system without treatment and educational effort

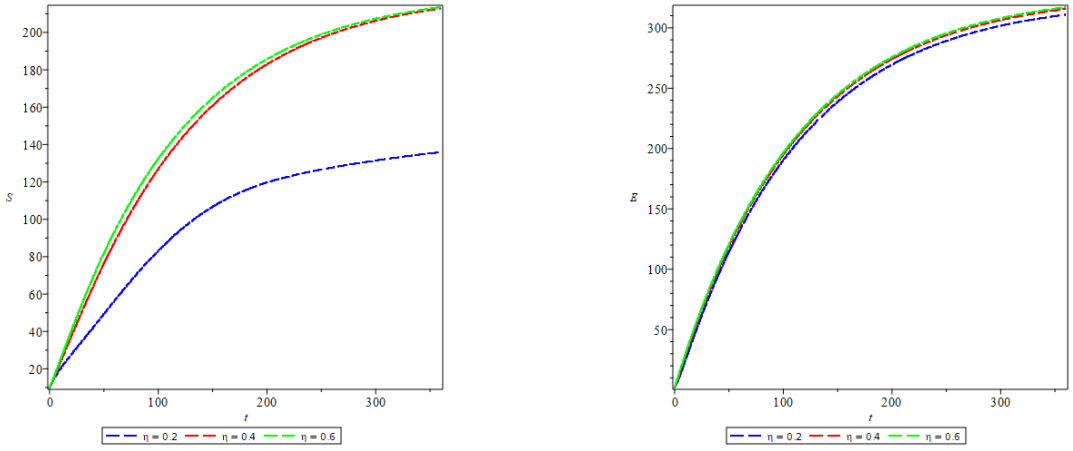
3.5.1 Impact of Education Effort

Then some scenarios will be used up to control the spread of the disease with considering the educational effort. The different of each scenarios is represented by the difference value of parameter η, we use three value for it to see how the parameter impacts the system behavior.



(a) Compartment I (b) Compartment U

Figure 3. The impact of education on the compartment I and U



(c) Compartment S (d) Compartment E

Figure 4. The impact of education on the compartment S and E

Based on the Figure 3 and Figure 4, it is clear that various number of η on the third case give the different impact to the system. The simulation shows that higher value of η can be more suppress the infected and uneducated injector population significantly, despite we can see that on the susceptible and educated injector the different level on η is not significant to increase the number. Generally, we can conclude that the difference level on η give the different impact to the system. In this case, the higher value of η give the higher impact on the system.

3.5.2 Impact of Optimal Control

Respective to the objective function on (17), our aim is to minimize the number of infected population, uneducated injector population, treatment effort, and educational effort given. Optimal function graph is shown in following figure

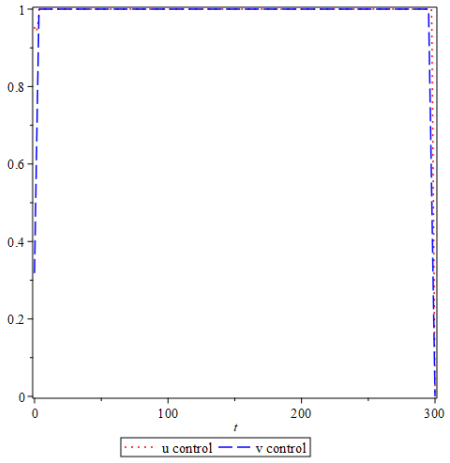
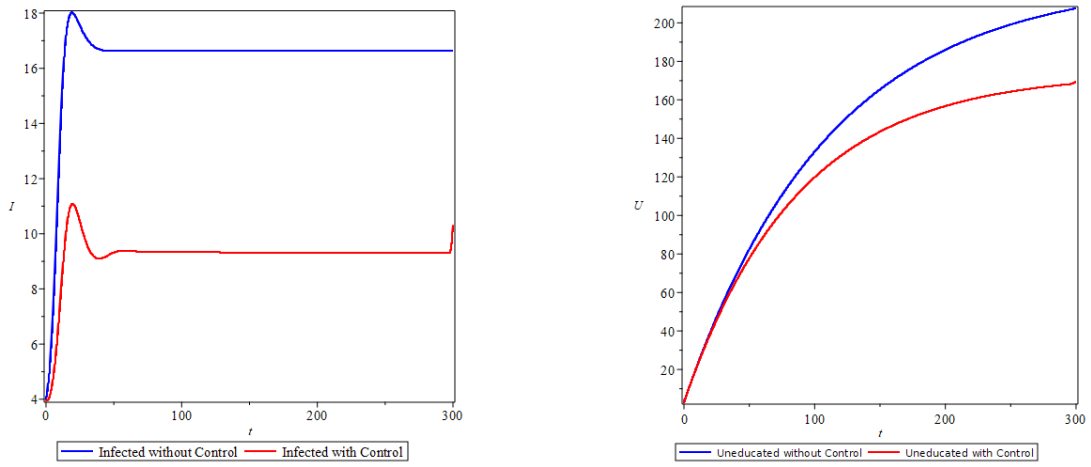
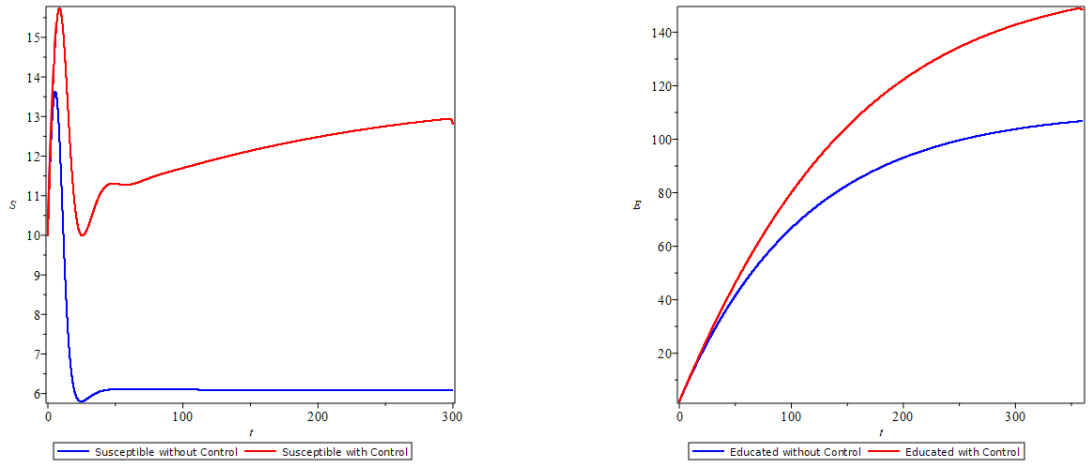


Figure 5. Control Function



(a) Compartment I (b) Compartment U

Figure 6. The impact of control on the compartment I and U



(a) Compartment S (b) Compartment E

Figure 7. The impact of control on the compartment S and E

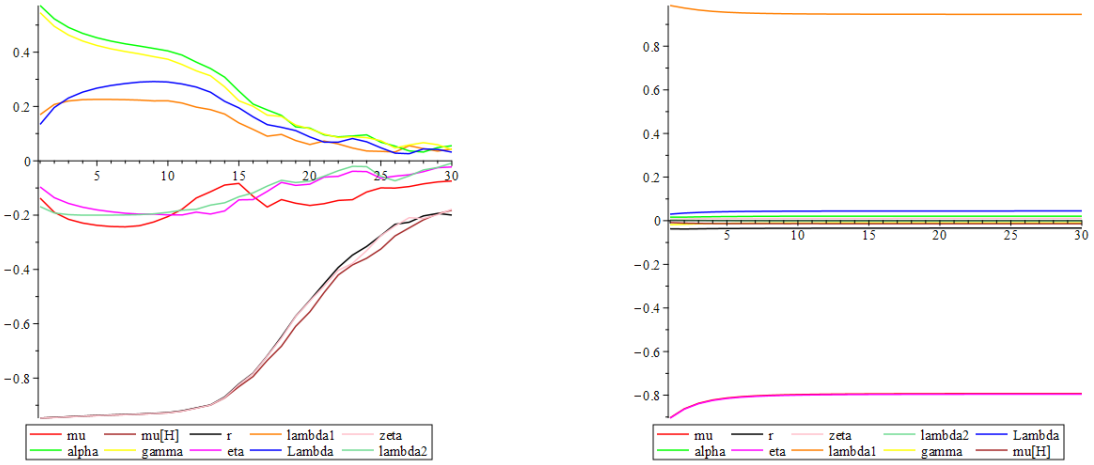
Based on Figure 6, the system with optimal control shows that it is success to suppress the infected and uneducated injector population. While on Figure 7, optimal control give the impact to the system as we see that the number of susceptible and educated injector population increase. It means that the optimal control success to reach the aim of objective function which to minimization the population of infected and uneducated injector with respective to cost of control.

3.5.3 Sensitivity Analysis

In this section, we show the analysis of sensitivity for the HCV transmission model through the combination of Latin Hypercube Sampling (LHS) with using 5000 samples and Partial Rank Correlation Coefficient (PRCC). Then, we operate the infection and uneducated injector, and the result is

Figure 8.a shows that the most dominant parameter r. The r parameter a has negative relationship, it represents that when the r value increases, then the total of infected population decreases. The other parameters such as μ_H and ζ significantly effect the number of infected population but it all decreases over the time.

Figure 8.b shows that the most dominant parameter λ_1 and η. The λ_1 parameter has a positive relationship, it means that if λ_1 increases, then the total of uneducated injector population increases. But the negative relationship of η parameter, it represents that when the value r increase, the total of infected population decreases.



(a) Analysis on I Compartment (b) Analysis on U Compartment

Figure 8. Sensitivity Analysis on Each Compartment

4. CONCLUSION

In this paper, we propose to develop a mathematical model for the HCV transmission with treatment and educational effort. Analysis result on the model shows that non-endemic equilibrium point is asymptotically stable if $\mathfrak{R}_0 < 1$ and endemic equilibrium point is asymptotically stable

if $\mathfrak{R}_0 > 1$. Through the theory of optimal control and Pontryagin maximum principle, the optimal conditions of the HCV transmission model obtained. The numerical simulation shows that the intervention with respect to the control has impact on suppressing the number of infected and uneducated injector, then increase the recovered and educated injector at the same time. By sensitivity analysis, we show that there are some parameters has the most influence on the model of each compartment, such as r on the I compartment and λ_1, η on the U compartment.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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