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DYNAMICS OF ACUTE HEPATITIS C VIRUS SUBJECT TO RESPONSES OF CYTOTOXIC T LYMPHOCYTES AND ANTIBODIES

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Abstract. Acute hepatitis C virus (HCV) infection is so asymptomatic that it causes the majority of infected people to develop chronic hepatitis and ultimately cirrhotic hepatitis. Although some patients with AHCVI can undergo spontaneous clearance of the virus, most infected people still die of hepatitis C related-complications worldwide. This study proposed a mathematical model to investigate the transmission dynamics of acute hepatitis C virus with responses of cytotoxic T lymphocytes and antibodies. We established the expression for the basic reproductive number, R_{01} and computed the sensitivity indices of R_{01} pertaining to some model parameters. We found that the parameters for the production rate of susceptible hepatocytes, Π; infection rate, ω and virus production rate, β are positively sensitive. Besides, the most negatively sensitive parameter is the natural death rate of hepatocytes, μ while the least negatively sensitive parameter is the natural death rate of the virus, ε. We also performed numerical simulations, which validate the analytical results. Thus, we commend that early strategic intervention should be administered to a patient who is unable to clear the virus spontaneously to fight hepatitis C virus transmission by targeting the most sensitive model parameters. Absolutely, this will prevent disease evolution to more disastrous stages of infection.

Keywords: acute HCV infection; cytotoxic T lymphocytes; antibodies; basic reproductive number; sensitivity analysis.

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1 INTRODUCTION

Hepatitis C infection is a blood borne hepatic disease caused by hepatitis C virus (HCV) initially identified in 1983 (Choo *et al*., 1989; Purcell, 1997). It was recounted by the World Health Organization (WHO) that about 175 million people worldwide were infected with HCV in 2015 (WHO, 2017). HCV infection progresses in two stages, namely acute HCV infection (AHCVI) and chronic HCV infection (CHCVI). AHCVI lasts for six months after infection onset with high degree of asymptomatic state while CHCVI takes place beyond that period. About 20% to 30% of people infected with AHCVI can clear the virus spontaneously (Rehermann, and Nascimbeni, 2005), but many develop chronic liver disease, cirrhosis and hepatocellular carcinoma. To date, a vaccine against HCV infection does not exist and about 50% do not respond to treatment. New treatments are still being developed (Mayer *et al*., 2010). Hepatitis C virus infection has been recognized as a global health problem.

When HCV enters the human body, the immune system responds; and the essential components of a normal immune response to the virus are antibodies, cytokines natural killer cells and T-cells. People infected with HCV generally develop antibodies to react with the core protein as well as several nonstructural protein antigens of HCV; and thus neutralize free virus particles. Besides, in response to the infection, cytotoxic T lymphocytes develop to kill host infected hepatocytes. These immune responses are unable to fully protect the body against new infections and eliminate infections (Lemon and Brown, 1995), but work concurrently to combat the HCV transmission (Ramirez, 2014). At this juncture, we have considered only the immune responses antibodies and cytotoxic T lymphocytes to study the dynamics of AHCVI by mathematical modelling.

Mathematical modelling has generally provided an explicit framework by which we can develop and communicate an understanding of transmission dynamics of an infectious disease. Thus, it has improved our understanding of the T-cell dynamics and the quantitative events that underlies the immune response to HCV. In literature, several models have been formulated to study HCV dynamics with immune system response (Ahmed and El-Saka, 2010; Avendano *et al.,* 2002; Perelson, 2002; Ramirez, 2014). In our model, we consider the transmission dynamics of acute HCV with the responses of antibodies and cytotoxic T lymphocytes and possibility of patient's spontaneous clearance of the virus.

2 MATERIALS AND METHODS

2.1 Model Formulation

Suitable variables and parameters are introduced to represent different populations and describe the population dynamics which institute the model respectively. Certain basic assumptions are also made to support description of the dynamics of the disease. A model flow diagram is employed to show clearly the transmission dynamics of acute HCV. Then a system of non-linear ordinary differential equations is derived. We apply the model to determine the disease free equilibrium point. The basic reproductive number is derived by using the next generation matrix method. Sensitivity analysis is done by using normalized forward sensitivity index method, which produced sensitivity indices of the basic reproductive numbers with reference to certain parameters of the model.

2.2 Model Dynamics

The model incorporates five classes: susceptible hepatocytes, S; infected hepatocytes, I; free hepatitis C viruses, V; cytotoxic T lymphocytes, Z and antibodies, W. Susceptible hepatocytes are produced a rate Π and die naturally at a rate μS and are infected by the interaction with the virus at a rate ωSV. Infected hepatocytes recover spontaneously at a rate ΣI, die naturally at a rate μI and are killed by the cytotoxic T lymphocytes response at a rate λIZ. Free virus is produced by infected hepatocytes at a rate βI, die naturally at a rate εV and is neutralized by antibodies at a rate γVW. Cytotoxic T lymphocytes develop in response to viral antigen derived from infected cells at a rate σIZ and die naturally at a rate υZ. In response to free virus, antibodies develop at a rate ηVW and die naturally at a rate αW.

The following assumptions were considered for the formulation of the model:

(i) Susceptible hepatocytes are produced at a constant rate.
(ii) Susceptible hepatocytes are equally likely infected by the virus.
(iii) Susceptible and infected hepatocytes die naturally at equal constant rates.
(iv) Infected hepatocytes recover spontaneously at a constant rate.
(v) Viruses are produced by infected hepatocytes at a constant rate.
(vi) Viruses die naturally at a constant rate.
(vii) Free viruses are neutralized by antibodies at a constant rate.
(viii) Cytotoxic T lymphocytes are produced and die naturally at constant rates.
(ix) Cytotoxic T lymphocytes kill infected hepatocytes at a constant rate.
(x) In response to the virus, antibodies develop at a constant rate .

(xi) Antibodies die naturally at a constant rate.

(xii) The person with HCV infection can either clear the virus spontaneously or not.

The variables and parameters are listed and briefly defined in Table 1 and Table 2 respectively

TABLE 1: Description of state variables

Variable	Description
$S(t)$	Susceptible hepatocytes
$I(t)$	Infected hepatocytes
$V(t)$	Hepatitis C viruses
$Z(t)$	Cytotoxic T lymphocytes ($CD8^+$ T cells)
$W(t)$	Antibodies

Besides, for brevity of formulations and analyses, the model state variables $S(t)$, $I(t)$, $V(t)$, $Z(t)$ and $W(t)$ have simply been represented by the symbols S, I, V, Z and W respectively.

TABLE 2: Description of parameters

Parameter	Description
ω	Infection rate
β	Production rate of free virus by infected hepatocytes
λ	Killing rate of infected hepatocytes by cytotoxic T lymphocytes
Π	Production rate of susceptible hepatocytes
σ	Production rate of cytotoxic T lymphocytes in response to viral antigen derived from infected hepatocytes.
μ	Natural death rate of hepatocytes
ε	Natural death rate of free virus
υ	Natural death rate of cytotoxic T lymphocytes
Σ	Spontaneous recovery rate of infected hepatocytes
δ	Disease-induced death rate of infected hepatocytes
γ	Neutralization rate of free virus by antibodies.
α	Natural death rate of antibodies.
η	Antibodies development rate in response to free virus

2.3 Compartmental Diagram

The description of acute hepatitis C virus dynamics can be summarized by a compartmental diagram as shown in Figure 1.

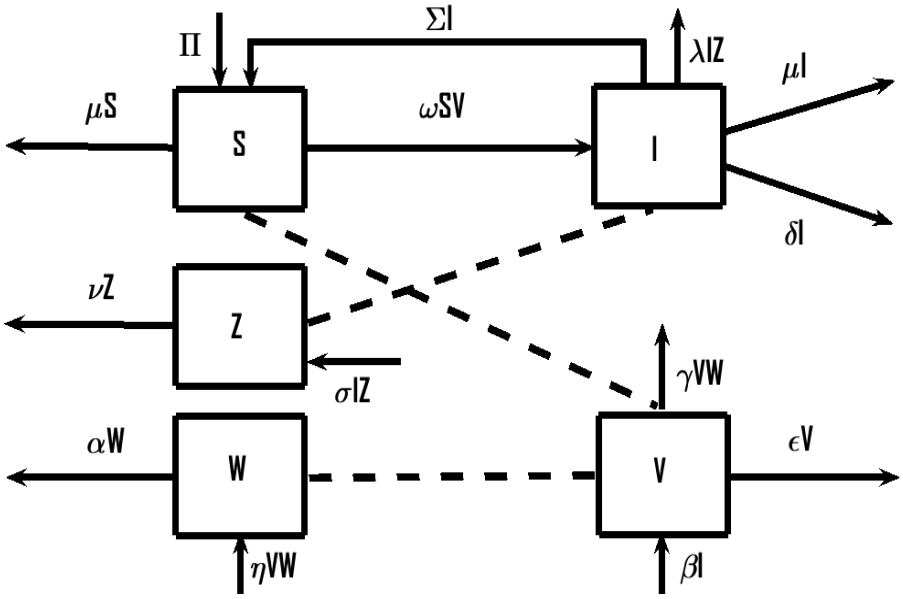

FIGURE 1: Compartmental diagram for transmission dynamics of acute hepatitis C virus

2.4 Equations of the Model

From the compartmental diagram, illustrative of the transmission dynamics of acute hepatitis C virus, a system of five non-linear ordinary differential equations is derived. Equation (1) models the susceptible hepatocytes sub-population; (2), the infected hepatocytes sub-population; (3), the free hepatitis C virus population; (4), the cytotoxic T lymphocytes ($CD8^+$ T cells**)** population and (5), the antibodies with initial conditions of the respective variables: $S(0) = S_0$, $I(0) = I_0$, $V(0) = V_0$, $Z(0) = Z_0$ and $W(0) = W_0$. Thus, the system of equations is as follows:

$$\frac{dS}{dt} = \Pi + \Sigma I - \omega SV - \mu S \tag{1}$$

$$\frac{dI}{dt} = \omega SV - \mu I - \lambda IZ - \delta I - \Sigma I \tag{2}$$

$$\frac{dV}{dt} = \beta I - \varepsilon V - \gamma VW \tag{3}$$

$$\frac{dZ}{dt} = \sigma IZ - \upsilon Z \tag{4}$$

$$\frac{dW}{dt} = \eta VW - \alpha W \tag{5}$$

and $S \geq 0, I \geq 0, V \geq 0, Z \geq 0$ and $W \geq 0$..

2.5 Basic Properties of the Model

(i) Positivity of Solutions

Since the model system of equations involves modeling of populations, then all state variables and parameters of the model must be non-negative for all $t \geq 0$. In this case, we prove that the state variables $S(t), I(t), V(t), Z(t)$ and $W(t)$ are non-negative $\forall t \geq 0$, which is achieved by Theorem 1.

Theorem 1: *Suppose the initial values of the variables are:* $S(0), I(0), V(0), Z(0)$ *and* $W(0)$. *Then the solution set* $\{S(t), I(t), V(t), Z(t), W(t)\}$ *contains non-negative numerical values* $\forall t \geq 0$

Proof:

From (5), we have:

$$\frac{1}{W}\frac{dW}{dt} = \eta V - \alpha, \tag{6}$$

Integrating (6) we get:

$$\ln\left(\frac{W}{W_0}\right) = \int_0^t (\eta V(s) - \alpha) ds$$

Thus,
$$W(t) = \exp\left[\int_0^t (\eta V(s) - \alpha) ds\right] \geq 0 \text{ for } W_0 \geq 0 \tag{7}$$

Similarly,

$$V(t) \geq V_0 \exp\left[-\int_0^t (\varepsilon t + W(s)) ds\right] \text{ for } V_0 \geq 0 \tag{8}$$

$$S(t) \geq S_0 \exp\left[-\int_0^t (\mu t + V(s)) ds\right] \geq 0 \text{ for } S_0 \geq 0 \tag{9}$$

$$I(t) \geq I_0 \exp\left[-\int_0^t ((\mu + \delta + \Sigma)t + \lambda Z(s)) ds\right] \geq 0 \text{ for } I_0 \geq 0 \tag{10}$$

and
$$Z(t) \geq Z_0 \exp(-\upsilon t) \geq 0 \text{ for } Z_0 \geq 0 \tag{11}$$

The results (7), (8), (9), (10) and (11) indicate that the set $\{S(t), I(t), V(t), Z(t), W(t)\}$ contains only non-negative values $\forall t \geq 0$. Thus, we have proved Theorem 1.

(ii) Invariant Regions

In this section, we determine the invariant region that contains feasible solutions of the model. We initially determine the invariant region for individual populations since the model system has heterogeneous populations. To achieve this, we assumed that the state variables and parameters are non-negative $\forall t \geq 0$ and used the following theorem:

Theorem 2: *All forward solutions of the model system* (1)-(5) *are contained in the region* $\Omega \subset R_+^5, \Omega = \theta_L \times \theta_V \times \theta_Z \times \theta_W$, *where*

$$\theta_L = (S, I) \in R_+^2 : S + I \leq N$$

$$\theta_V = \{V \in R_+^1 : (4) \text{ and } (5) \text{ are satisfied}\}$$

$$\theta_Z = \{Z \in R_+^1 : (4) \text{ and } (5) \text{ are satisfied}\}$$

$$\theta_W = \{W \in R_+^1 : (4) \text{ and } (5) \text{ are satisfied}\}$$

$\forall t \geq 0$. and Ω is the invariant region (bounded region) for the whole model system (1)-(5).

Proof:

To prove Theorem 2, we initially determine the bounded regions for individual populations.

Liver Cells Population

Here, we determine the bounded region for the liver cells population that contains feasible solutions. Let θ_L be the bounded region and $\theta_L = (S, I) \in R_+^2$ be the solution of the population with non-negative initial conditions. Then, we have:

Total hepatic cells population at time t *is* given by

$$N(t) = S(t) + I(t)$$

This implies that

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} \tag{15}$$

Substitution of (1) and (2) into (15) yields:

$$\frac{dN}{dt} = \Pi - \mu N - \lambda IZ - \delta I \tag{16}$$

From (16), we have:

$$\frac{dN}{dt} \le \Pi - \mu N \tag{17}$$

Then the general solution of the differential inequality (17) is

$$N(t) \le \frac{\Pi}{\mu} + \left(N_0 - \frac{\Pi}{\mu} \right) \exp(-\mu t) \tag{18}$$

where N_0 is the initial size of the hepatic cells population evaluated at the initial conditions $S_0 = S(0) \ge 0$ and $I_0 = I(0) \ge 0$.

From (18), we deduce two cases for all $\forall t \ge 0$.

Case 1: When $N_0 > \frac{\Pi}{\mu}$, the largest value of the right hand side (RHS) of the inequality (18) is obtained at $t = 0$; and the value is N_0. Hence $N(t) \le N_0$

Case 2: When $N_0 < \frac{\Pi}{\mu}$, the value $\left(N_0 - \frac{\Pi}{\mu} \right) \exp(-\mu t)$ is negative and approaches zero as $t \to \infty$. So, the largest value in the RHS of the inequality (18) is $\frac{\Pi}{\mu}$. Hence $N(t) \le \frac{\Pi}{\mu}$

In respect of this, we deduce that

$$N(t) \le \max\left\{ N_0, \frac{\Pi}{\mu} \right\} = N^* \quad \forall t \ge 0 \text{ and whatever value of } N_0,$$

Thus, $N(t)$ is bounded above.

Hence all feasible solutions for the hepatic cells population are contained in the region.

$$\theta_L = \left\{ N(t) : N(t) \le N^* \right\}. \tag{20}$$

Cytotoxic T Lymphocytes Population

From (4), we have:

$$\frac{1}{Z}\frac{dZ}{dt} = \sigma I - \upsilon$$

Thus, we have:

$$\frac{1}{Z}\frac{dZ}{dt} \le \sigma N^* - \upsilon \tag{21}$$

Then the general solution of the differential inequality (21) is

$$Z(t) \le Z_0 \exp\left[(\sigma N^* - \upsilon) t \right] \tag{22}$$

where Z_0 is the initial size of the cytotoxic T lymphocytes population.

According to (22), $Z(t)$ is bounded above only if $\sigma N^* \le \nu$ .Thus, we have:

$$Z(t) \le Z_0 \ \forall t \ge 0$$

Hence all feasible solutions for the cytotoxic T lymphocytes population are contained in the region.

$$\theta_Z = \{Z(t) : Z(t) \le Z_0\} \tag{23}$$

Hepatitis C Virus Population

From (3) and (20), we have:

$$\frac{dV}{dt} \le \beta N^* - \varepsilon V - \gamma V W \le \beta N^* - \varepsilon V \tag{24}$$

From (24), we deduce that

$$\frac{dV}{dt} \le \beta N^* - \varepsilon V$$

It implies that

$$\frac{dV}{dt} + \varepsilon V \le \beta N^* \tag{25}$$

Then the general solution of the differential inequality (25) is

$$V(t) \le \frac{\beta N^*}{\varepsilon} + \left(V_0 - \frac{\beta N^*}{\varepsilon}\right)\exp(-\varepsilon t) \tag{26}$$

where V_0 is the initial size of the hepatitis C virus population.

It follows that for all $t \ge 0$, we obtain:

$$V(t) \le \max\left\{V_0, \frac{\beta N^*}{\varepsilon}\right\} = V^* \ \forall t \ge 0 \text{ and whatever value of } V_0.$$

Thus, $V(t)$ is bounded above.

Hence all feasible solutions for the hepatitis C virus population are contained in the region.

$$\theta_V = \left\{V(t) : V(t) \le \max\left\{V_0, \frac{\beta N^*}{\varepsilon}\right\} = V^*\right\} \tag{27}$$

Antibody Load

From (4), we have:

$$\frac{1}{W}\frac{dW}{dt} = \eta V - \alpha \tag{28}$$

From (27), we deduce that

$$V(t) \le V^* \tag{29}$$

Substitution of (29) into (28) produces:

$$\frac{1}{W}\frac{dW}{dt} \le \eta V^* - \alpha \tag{30}$$

Then the general solution of the differential inequality (30) is

$$W(t) \le W_0 \exp\left[(\eta V^* - \alpha)t\right] \tag{31}$$

where W_0 is the initial size of the antibodies load.

According to (31), $W(t)$ is bounded above only if $\eta\beta N^* \le \alpha\varepsilon$ .Thus, we have:

$$W(t) \le W_0 \text{ for } t \ge 0$$

Hence all feasible solutions for the antibodies load are contained in the region.

$$\theta_W = \{W(t) : W(t) \le W_0\} \tag{32}$$

From the results (20), (23), (27) and (32), we deduce the invariant region for the whole model system (1) - (5) is

$\Omega = \theta_L \times \theta_V \times \theta_Z \times \theta_W$, where

$$\theta_L = \{N(t) : N(t) \le N^*\},$$
$$\theta_V = \{\{V(t) : V(t) \le V^*\},$$
$$\theta_Z = \{Z(t) : Z(t) \le Z_0\}$$

and

$$\theta_W = \{W(t) : W(t) \le W_0\}$$

Since Ω is positively invariant, it is appropriate to consider solutions within it. Thus, the model (1)-(5) is epidemiologically and mathematically realistic (Hethcote, 2000)

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3 RESULTS AND DISCUSSION

In this section, we present and discuss the analytical results of the model system (1) - (5) in order to get more insights into its dynamic features for better understanding of the impact of Cytotoxic T lymphocytes and antibodies on the transmission dynamics of acute hepatitis C virus

3.1 The Disease Free Equilibrium (DFE)

We usually obtain the equilibria of a model by setting its time derivatives equal are zero. Then solving the resulting system in the absence of infection yields the disease free equilibrium. Thus, we obtain the disease free equilibrium, E_0 of the model system (1)-(5) by setting the right hand side of its equations equal to zero, i.e.

$$\frac{dS}{dt}=\frac{dI}{dt}=\frac{dV}{dt}=\frac{dZ}{dt}=\frac{dW}{dt}=0$$

This implies that

$$\begin{cases}\Pi+\Sigma I-\omega SV-\mu S=0\\ \omega SV-\mu I-\lambda IZ-\delta I-\Sigma I=0\\ \beta I-\varepsilon V-\gamma VW=0\\ \sigma IZ-\upsilon Z=0\\ \eta VW-\alpha W=0\end{cases} \tag{33}$$

From (33), we deduce:

$$E_0=(S_0,I_0,V_0,T_0)=\left(\frac{\Pi}{\mu},0,0,0,0\right).$$

3.2 The Basic Reproductive Number

The basic reproductive number, denoted by R_{01}, is well-defined as the average number of new infected hepatocytes instigated by an infected hepatocyte in a completely susceptible hepatocytes population during infection period (Dietz, 1975; Diekmann and Heesterbeek., 1990; Van den Driessche and Watmough, 2002)., which can be applied as a metric to determine whether or not an infection will spread through the hepatic cells population. If $R_{01}>1$, the HCV infection establishes in the population, but the virus will not spread in it if $R_{01}<1$ (Nowk and May, 2000; Wodarz, 2005).

Mathematically, R_{01} is the spectral radius of the next generation matrix (Van den Driessche and Watmough, 2002) and obtained by taking the largest (dominant) eigenvalue, (spectral radius) of the matrix FY^{-1}. Then, we have:

$$FY^{-1}=\left[\frac{\partial F_i(E_0)}{\partial X_j}\right]\left[\frac{\partial Y_i(E_0)}{\partial X_j}\right]^{-1},$$

where

$$F_i = \begin{bmatrix} \omega SV \\ \beta I \end{bmatrix} ; \; Y_i = \begin{bmatrix} \lambda IZ + \mu I + \delta I + \Sigma I \\ \varepsilon V + \gamma VW \end{bmatrix};$$

$$F = \left[\frac{\partial F_i(E_0)}{\partial X_j} \right] = \begin{bmatrix} 0 & \frac{\omega \Pi}{\mu} \\ \beta & 0 \end{bmatrix};$$

$$Y = \left[\frac{\partial Y_i(E_0)}{\partial X_j} \right] = \begin{bmatrix} \mu + \delta + \Sigma & 0 \\ 0 & \varepsilon \end{bmatrix}$$

and

$$Y^{-1} = \begin{bmatrix} \frac{1}{\varepsilon} & 0 \\ 0 & \frac{1}{\mu + \delta + \Sigma} \end{bmatrix}$$

Then we deduce:

$$FY^{-1} = \begin{bmatrix} 0 & \frac{\omega \Pi}{\varepsilon \mu} \\ \frac{\beta}{\mu + \delta + \Sigma} & 0 \end{bmatrix},$$

Hence the basic reproductive number of the model system (1) - (5) is given by

$$R_{01} = \sqrt{\frac{\beta \omega \Pi}{\varepsilon \mu (\mu + \delta + \Sigma)}} \qquad (34)$$

The result (34) clearly shows that the number of new infected hepatocytes is determined by the liver cells population and HCV population as all parameters instituting R_{01} are derived from these populations. This indicates that the transmission of HCV in the hepatic cells population can be combated once control measures are targeted to these populations. Conversely, the immune system response does not determine occurrence of new infections as no parameter embedded in R_{01} is derived from it.

In the absence of spontaneous hepatitis C viral clearance $(\Sigma = 0)$, the basic reproductive number R_{01} reduces to R_{02}, which is given by

$$R_{02} = \sqrt{\frac{\beta \omega \Pi}{\varepsilon \mu (\mu + \delta)}}$$

where R_{02} signifies the basic reproductive number derived when there is no spontaneous viral clearance.

Analytically, we have:

$$\sqrt{\varepsilon\mu(\mu+\delta)} < \sqrt{\varepsilon\mu(\mu+\delta+\Sigma)} \Rightarrow R_{02} = \sqrt{\frac{\beta\omega\Pi}{\varepsilon\mu(\mu+\delta)}} > \sqrt{\frac{\beta\omega\Pi}{\varepsilon\mu(\mu+\delta+\Sigma)}} = R_{01}$$

Hence $R_{02} > R_{01}$. This implies that more hepatocytes are infected for a patient with AHCVI who is incapable of clearing the virus spontaneously.

3.3 Sensitivity Analysis

Sensitivity analysis in mathematical epidemiology is a systematic procedure that helps to identify sites in a model for possible deliberate intervention. This is typically accomplished by computing sensitivity indices of the basic reproductive number relating to the parameters of the model using the method of Chitnis *et al.* (2008). The sensitivity index significantly describes how influential each parameter is on the transmission dynamics and incidence of an infection; and it refers to as the relative change in a state variable subject to a parameter change (Chitnis *et al.*, 2008).

For our case, the sensitivity indices of basic reproductive number R_{01} relating to the HCV model parameter were determined by using parameter values from literatures while certain parameter values were simply estimated. All parameter values are listed in Table 3.

TABLE 3: Parameter values used to calculate the sensitivity indices of R_{01}.

Parameter	Value	Units	Source
μ	0.02	day^{-1}	Avendano *et al*. (2002)
ω	0.00003	$virus^{-1}day^{-1}$	
β	100	$cell^{-1}day^{-1}$	
ε	5	day^{-1}	
υ	0.02	day^{-1}	
Π	100	$cells\ day^{-1}$	
δ	0.48	day^{-1}	
λ	0.00064	$cell^{-1}day^{-1}$	Ramirez (2014)
γ	2	$molecule^{-1}day^{-1}$	
η	0.00001	$virus^{-1}day^{-1}$	
α	0.2	day^{-1}	
σ	0.0000003	$cell^{-1}day^{-1}$	
Σ	1	day^{-1}	Dahari *et al*. (2005)

Definition 1: According to Chitnis *et al*. (2008), the forward normalized sensitivity index of a variable K that depends on a parameter L is defined as

$$X_L^K = \frac{\partial K}{\partial L} \times \frac{L}{K} \tag{35}$$

Replacing K by R_{01} in equation (35), we obtain the expression for $X_L^{R_{01}}$ is given by

$$X_Q^{R_{01}} = \frac{\partial R_{01}}{\partial L} \times \frac{L}{R_{01}} \tag{36}$$

Replacing L by a parameter in (36), we obtained the sensitivity index of R_{01} relating to each parameter. Henceforth, the sensitivity indices of R_{01} relating to the parameters μ, ω and δ are given by

$$X_\mu^{R_{01}} = \frac{\partial R_{01}}{\partial \mu} \times \frac{\mu}{R_{01}} = -0.5029,\ X_\omega^{R_{01}} = \frac{\partial R_{01}}{\partial \omega} \times \frac{\omega}{R_{01}} = +0.5000 \text{ and } X_\delta^{R_{01}} = \frac{\partial R_{01}}{\partial \delta} \times \frac{\delta}{R_{01}} = -0.1305$$

Other indices

$$X_\beta^{R_{01}}, X_\Pi^{R_{01}}, X_\varepsilon^{R_{01}} \text{ and } X_\Sigma^{R_{01}},$$

are determined by using the same method; and all indices are listed in Table 4.

TABLE 4: Numerical values of sensitivity indices of R_{01}

Parameter	Sensitivity index
μ	-0.5029
ε	-0.5000
β	$+0.5000$
ω	$+0.5000$
Π	$+0.5000$
Σ	-0.3666
δ	-0.1305

In Table 4, we observe that if the parameters β, ω and Π are increased while others are kept constant, the value of R_{01} increases because these parameters have positive sensitivity indices. This implies that the increase of R_{01} increases of the disease transmission whereas the decrease

of R_{01} can decrease the disease transmission. Conversely, it is observed that the parameters μ, ε, Σ and δ increase the value of R_{01} when they are decreased as they are negative. This implies endemicity of hepatitis C virus infection increases when the values of these parameters are with decreased.

Besides, we observe that the most sensitive parameter is the natural death rate of hepatocytes μ; followed by the natural death rate of the free virus, ε virus production rate β, infection rate ω and production rate of susceptible hepatocytes Π; followed by noncytolytic recovery rate of infected hepatocytes Σ and the disease-induced death rate of infected hepatocytes δ, which is the least sensitive parameter.

3.4 Numerical Simulations

In this section, we verify the analytical results of the study by performing numerical solutions of the model system $(1)-(5)$ by using the parameter values listed in Table 3. The symbols R_{01} and R_{02} in the simulations legends signify the value of basic reproductive number with and without spontaneous viral clearance respectively. We used Maple-12 software tools to evaluate the basic reproductive numbers R_{01} and R_{02} at these parameter values and obtained 7.0711 and 12.1474 respectively, which explicitly shows that $R_{O2} > R_{01}$. Thus, this connotes that the hepatitis C virus is more epidemic in the hepatocytes population for a patient who cannot clear the virus spontaneously.

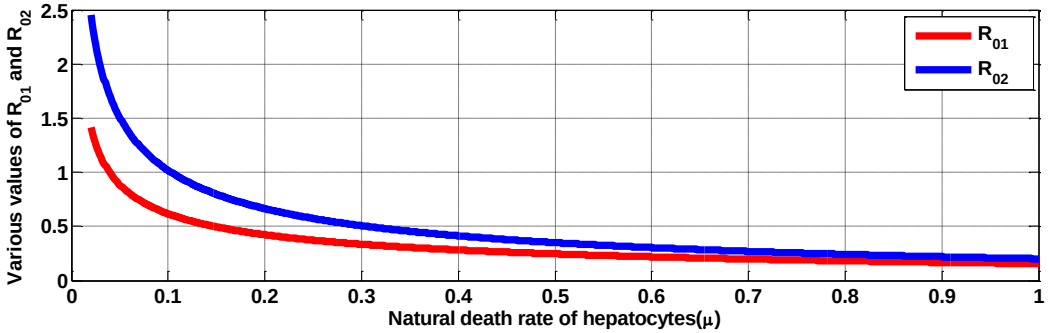

FIGURE 2: Variation of basic reproductive numbers with natural death rate of hepatocytes

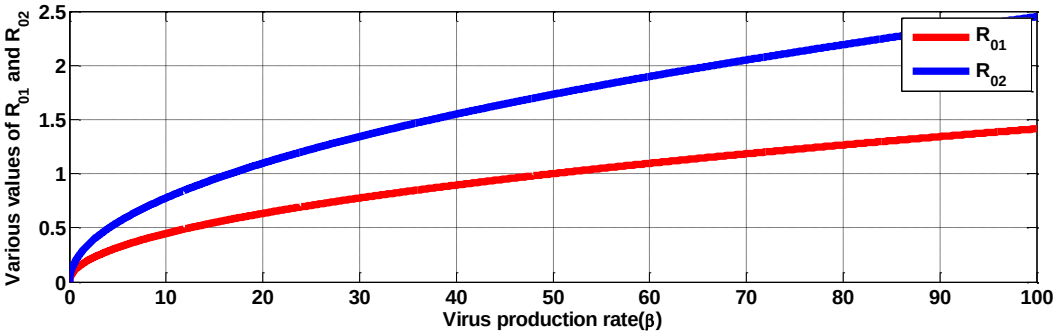

FIGURE 3: Variation of basic reproductive numbers with virus production rate.

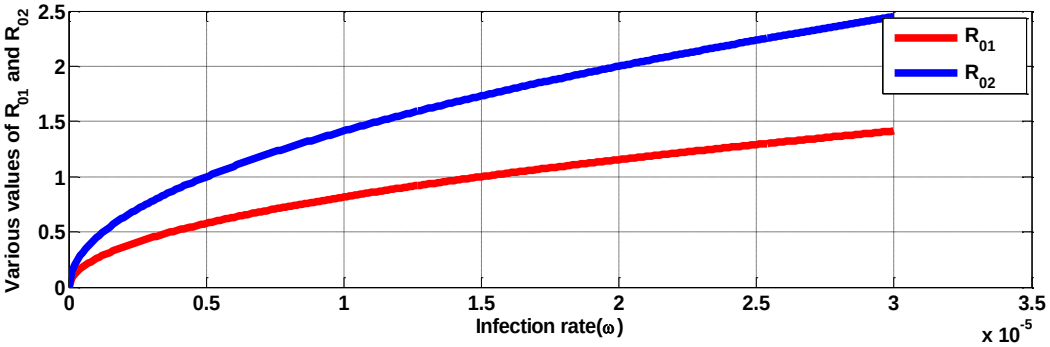

FIGURE 4: Variation of basic reproductive numbers with infection rate

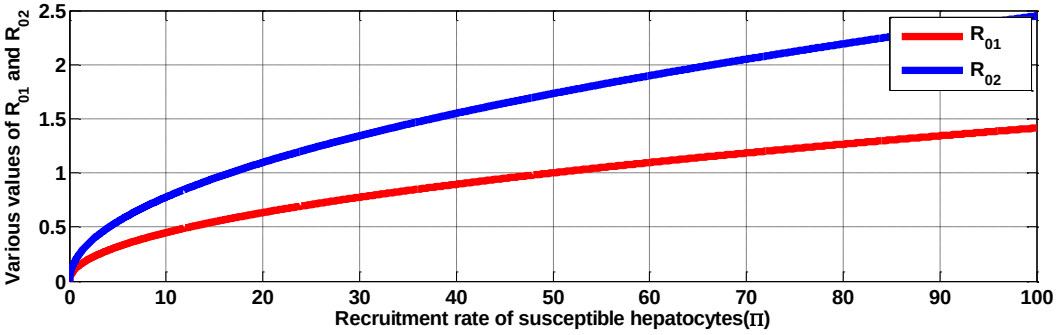

FIGURE 5: Variation of basic reproductive numbers with recruitment rate of susceptible hepatocytes

Figure 2 shows simulations for the basic the reproductive number R_{01} with natural death rate of hepatocytes μ, where it is observed that R_{01} decreases with increase of μ and vice versa. This implies that the number of secondary-new- infections reduces with increase of μ and increases with increase of μ. In Figures 3-5, the simulations indicate the basic reproductive number R_{01} increases with the virus production rate β, the infection rate ω and the recruitment rate of

susceptible hepatocytes Π; and vice versa. This implies that the number of secondary infections increases with increase of β, ω and Π. Besides, we observe that in the absence of spontaneous HCV clearance, variations of basic reproductive number R_{02} with μ, β, ω and Π follows the same trend though $R_{02} > R_{01}$ at any particular values of these parameters (Figures 2, 3, 4 and 5 respectively). It should be noted that the parameters μ and Π never become zero as hepatocytes continuously undergo natural death and new susceptible hepatocytes are endlessly being produced.

4 CONCLUSION

In this paper, we have formulated a deterministic mathematical model for transmission dynamics of acute hepatitis C virus with responses of cytotoxic T lymphocytes and antibodies. In this case, we have assumed that the patient can either clear the virus spontaneously or not. From the model system of equations, we have determined the disease free equilibrium E_0, indicative of the state of no disease; and derived the basic reproductive number R_{01}, indicative of the number of new infections triggered by a single infectious hepatocyte in the completely hepatic cells population. We also noted that as R_{01} does not incorporate parameters from the cytotoxic T lymphocytes and antibody populations, the immune system does not determine the occurrence of new hepatitis C virus infections in the hepatic cells population. Besides, we have noted that if the patient cannot clear the virus spontaneously hepatitis C virus is highly epidemic in the hepatic cells population, which may cause disastrous consequences if strategic intervention is not implemented.

Moreover, we have performed the sensitivity analysis on the basic reproductive number relating to some model parameters and noted that the most sensitive parameter is the natural death rate of hepatocytes μ; followed by the recruitment rate of new susceptible hepatocytes Π, the infection rate ω and the virus production rate β; and the virus natural death rate ε is the least sensitive parameter. We executed numerical simulations of the model to verify the analytical result, which absolutely suggests that the disease transmission in the hepatic cells population can be reduced, or rather eradicated, if the most sensitive parameters are deliberately targeted for intervention.

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Conflict of Interests

The authors declare that there is no conflict of interests.

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