Analysis of a model for hepatitis C virus transmission that includes the effects of vaccination and waning immunity

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Abstract: This paper considers a mathematical model based on the transmission dynamics of Hepatitis C virus (HCV) infection. In addition to the usual compartments for susceptible, exposed, and infected individuals, this model includes compartments for individuals who are under treatment and those who have had vaccination for HCV. It is assumed that the immunity provided by the vaccine fades with time. The basic reproduction number, R_0, and the equilibrium solutions of the model are determined. The model exhibits the phenomenon of backward bifurcation where a stable disease-free equilibrium co-exists with a stable endemic equilibrium whenever R_0 is less than unity. It is shown that only the use of a perfect vaccine can eliminate backward bifurcation completely. Furthermore, a unique endemic equilibrium of the model is proved to be globally asymptotically stable under certain restrictions on the parameter values. Numerical simulation results are given to support the theoretical predictions.

Key–Words: epidemiological model; equilibrium solutions; backward bifurcation; global asymptotic stability; Lyapunov function

1 Introduction

The liver of hepatitis patient is one of the most frequently damaged organs in the body, and it is indeed fortunate that it has a very large functional reserve. In the experimental animal, it has been shown that only 10 % of the hepatic parenchyma (the functional part of the liver) is required to maintain normal liver function [1]. The liver can be infected due to a variety of infectious agents such as parasites, viruses, and bacteria, and the diseases of liver have a variety of causes such as obstructive, vascular, metabolic and toxic involvements.

Hepatitis C is the inflammation of the liver caused by hepatitis C virus (HCV), and spreads through contact with contaminated blood. Hepatitis C may be an acute infection, which spans over a period of weeks to a few months, or chronic infection, in which the virus persists for a long time [2, 3]. Acute hepatitis is characterized by moderate liver injury and if symptoms appear, they include fatigue, loss of appetite, abdominal pain, fever and jaundice. However, most of the times, acute hepatitis is asymptomatic. A large percentage of patients with HCV infection recover completely, but some develop the long term chronic hepatitis or massive necrosis of the liver. Chronic HCV infection may damage the liver permanently, it can cause cirrhosis, hepatic failure, and sometimes liver cancer [1].

Today, HCV infects an estimated 170 million people worldwide [4]. Around 150 million people are chronically infected with HCV. HCV infection is a major cause of death of more than 350,000 people every year. Countries with the highest prevalence of chronic liver infection are Egypt (15 %), Pakistan (4.8 %) and China (3.2 %) [5]. Although, treatment for HCV infection does exist, the current drug therapies are ineffective in completely eliminating the virus and patients suffering from chronic illness may require a liver transplant [4]. Unfortunately, there is no effective vaccine yet developed that may help prevent the spread of the disease. At present, various attempts are being made to create such a vaccine [6]. Thus, it is crucial to assess the potential impact of HCV vaccine on the population.

Some mathematical models on HCV infection have been formulated recently, but much work has not been done, since it is a relatively new disease (discovered in 1989) and data is not available on account of the high variability of the HCV. In contrast, more research has been carried out on Hepatitis B virus (HBV) infection. Several epidemiological models have focused on the effects of preventive measures as well as control of HBV infection [7]. This has helped in creating cost effective disease prevention techniques. The modes of transmission of both HCV and HBV are same, i.e. through blood, thus mathematical models on both infections are somewhat inter related. Some mathematical models were formed on HCV infection that considered infected cells, uninfected cells and viral cells in the human host. The basic aim of these models was to study the effects of liver transplant in patients with HCV infection. But in major cases, HCV infection is not completely eliminated even after the transplant. Thus, these models were extended to include more infected compartments [8]. Martcheva and Castillo-Chavez [9] introduced an epidemiologic model of HCV infection with chronic infectious stage in a varying population. Their model does not include a recovered or immune class and it falls within the susceptible-infected- susceptible (SIS) category of models. A susceptible-infected-recovered (SIR) model was used by Kretzschmar and Wiessing [10] to study the transmission of HCV among injecting drug users, while susceptible-infected-removed-susceptible (SIRS) type models that allow waning immunity are presented in Zeiler et al. [11]. Also, a deterministic model for HCV transmission is used by Elbasha, with the objective of assessing the impact of therapy on public health [12].

Our aim is to meticulously analyze the model and examine various parameters to explore their effect on transmission of HCV and its control. The model focuses on studying the effects of imperfect vaccines on the control of HCV infection. The model shows that an imperfect vaccine reduces the number of individuals who are exposed to HCV, while a perfect vaccine completely removes them. We have subdivided the total population into six mutually-exclusive compartments: susceptible, exposed, acutely infectious, chronically infectious, treated and vaccinated individuals. Ordinary differential equations are used to model the HCV infection. This model can help provide insight into the spread of HCV infection and the assessment of the effectiveness of immunization techniques.

This paper is organized as follows: The mathematical model is developed in Section 2. The model is analyzed in Section 3, i.e. stability of disease free and endemic equilibrium is discussed, along with the effects of vaccination on backward bifurcation phenomenon. Numerical simulations are provided in the same section. Section 4 summarizes the final results of the paper.

2 Model Formulation

The total population at time t, denoted by $N(t)$, is divided into sub-populations of susceptible individuals, $S(t)$, exposed individuals with hepatitis C symptoms, $E(t)$, individuals with acute infection, $I(t)$, individuals undergoing treatment, $T(t)$, individuals with chronic infection, $C_h(t)$, and vaccinated individuals, $V(t)$, so that

$$N(t) = S(t) + E(t) + I(t) + T(t) + C_h(t) + V(t).$$

It is assumed that the mode of transmission of HCV infection is horizontal. We further assume that mixing of individual hosts is homogeneous (every person in the population $N(t)$ has an equal chance of getting infected). The following system of ordinary differential equations describes the dynamics of HCV infection:

$$\begin{cases} \frac{dS}{dt} = (1-b)\Lambda + \rho T + \alpha V \\ \qquad -(\beta_1 I + \beta_2 C_h + \beta_3 T)S + \sigma C_h - \mu S, \\ \frac{dE}{dt} = (\beta_1 I + \beta_2 C_h + \beta_3 T)S \\ \quad + (1-\psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)V - (\epsilon + \mu)E, \\ \frac{dI}{dt} = \epsilon E - (\kappa + \mu)I, \\ \frac{dT}{dt} = \pi_1 \kappa I + \pi_2 C_h - (\rho + \mu)T, \\ \frac{dC_h}{dt} = (1-\pi_1)\kappa I - (\pi_2 + \sigma + \mu)C_h, \\ \frac{dV}{dt} = b\Lambda - (\alpha + \mu)V \\ \qquad -(1-\psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)V. \end{cases} \tag{1}$$

The recruitment rate of susceptible humans is Λ. A proportion, b, of these susceptible individuals is vaccinated. The death rate is denoted by μ. The rate of progression from acute infected class to both treated and chronic infected class is given by κ. The acutely infected proportion of individuals who enter the treated class is π_1. The remaining infected proportion, $(1-\pi_1)$, progresses to chronic infectious stage. The rate of progression for treatment from chronic hepatitis is given by π_2. The term ϵ is the rate of progression from exposed class to acute infected class. The recovery rates due to treatment and naturally from the chronic group are ρ and σ, respectively.

The transmission coefficients of HCV infection by individuals with acute hepatitis upper case C, $I(t)$, chronic hepatitis upper case C, $C_h(t)$ and individuals undergoing treatment but not yet cured, $T(t)$ are β_1, β_2, and β_3, respectively. Following effective contact with $I(t)$, $C_(t)$, and $T(t)$, susceptible individuals can acquire HCV at a rate $(\beta_1 I + \beta_2 C_h + \beta_3 T)$. Here, ψ $(0 < \psi \leq 1)$ represents the vaccine efficacy, with $\psi = 1$ representing a perfect vaccine, and $\psi \in (0, 1)$ corresponding to an imperfect vaccine which will wane with time. The term $(1 - \psi)$ corresponds to the decrease in disease transmission in vaccinated individuals, in contrast to susceptible individuals who are not vaccinated. Hence, vaccinated individuals acquire HCV at a reduced rate $(1 - \psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)$. The rate at which the vaccine wanes is denoted by α. The parameter description is described in Table 1.

Table 1: Description of parameters

Para.	Description
Λ	recruitment rate
μ	death rate
α	waning rate of vaccine
ψ	vaccine efficacy
β_i	transmission rate (i=1, 2, 3)
b	proportion of vaccinated individuals
κ	rate of progression from acute state to treated and chronic state
ϵ	rate of transfer from exposed class to acute infected class
π_1	proportion of individuals who enter the treated class from acutely infected class
π_2	rate of progression for treatment from chronic hepatitis
ρ	rate of recovery due to treatment
σ	rate of recovery from the chronic class

In the proposed model (1), the total population is

$$S + E + I + T + C_h + V = \frac{\Lambda}{\mu}, \quad \forall t \geq 0,$$

provided that $S(0) + E(0) + I(0) + T(0) + C_h(0) + V(0) = \frac{\Lambda}{\mu}$. Thus, the biologically feasible region for system (1) given by

$$\Delta = \Big\{(S, E, I, T, C_h, V) \in R^6 : S + E + I + T + C_h + V = \frac{\Lambda}{\mu}\Big\},$$

is positively invariant with respect to the system (1).

2.1 Local stability of disease-free equilibrium (DFE)

For mathematical model (1), the disease free equilibrium (DFE), P_0 is given by

$$(S_0, E_0, I_0, T_0, C_{h0}, V_0) = \Big(\frac{(1-b)\Lambda}{\mu} + \frac{\alpha b \Lambda}{\mu(\alpha+\mu)}, 0, 0, 0, 0, \frac{b\Lambda}{\alpha+\mu}\Big). \tag{2}$$

The local stability of P_0 is determined by the next generation operator method [13] on system (1). For this purpose, the basic reproduction number (the average number of secondary infections produced by an infected individual in a completely susceptible population), denoted by R_0, is first calculated below.

Using the same notation as in [13], the matrices F and V, evaluated at P_0, the basic reproduction number R_0 is given by

$$R_0 = \frac{\epsilon}{K_1 K_2}\Big(\frac{(1-b)\Lambda}{\mu} + \frac{\alpha b \Lambda}{\mu K_5} + (1-\psi)\frac{b\Lambda}{K_5}\Big) \Big[\beta_1 + \beta_2 \frac{\kappa(1-\pi_1)}{K_4} + \beta_3 \frac{(\pi_1 \kappa K_4 + \pi_2 \kappa(1-\pi_1))}{K_3 K_4}\Big],$$

where $K_1 = \epsilon + \mu,\ K_2 = \kappa + \mu,\ K_3 = \rho + \mu,\ K_4 = \pi_2 + \sigma + \mu$, and $K_5 = \alpha + \mu$.

Using Theorem 2 in [13], the following result is established.

Theorem 1 *The DFE of the model (1) is locally asymptotically stable (LAS) if $R_0 < 1$, and unstable if $R_0 > 1$.*

2.2 Endemic equilibria and backward bifurcation

To calculate the endemic equilibrium, we consider the following reduced system of differential equations:

$$\begin{cases} \frac{dE}{dt} = (\beta_1 I + \beta_2 C_h + \beta_3 T)\times \\ \quad (\frac{\Lambda}{\mu} - E - I - T - C_h - \psi V) - K_1 E, \\ \frac{dI}{dt} = \epsilon E - K_2 I, \\ \frac{dT}{dt} = \pi_1 \kappa I + \pi_2 C_h - K_3 T, \\ \frac{dC_h}{dt} = (1-\pi_1)\kappa I - K_4 C_h, \\ \frac{dV}{dt} = b\Lambda - K_5 V \\ \quad -(1-\psi)(\beta_1 I + \beta_2 C_h + \beta_3 T)V. \end{cases} \quad (3)$$

We will consider the dynamics of the flow generated by (3) in the invariant region

$$\Omega = \{E + I + T + C_h + V \leq \frac{\Lambda}{\mu}\}.$$

The endemic equilibrium for system (3) is $P^*(E^*, I^*, T^*, C_h^*, V^*)$ where

$$\begin{aligned} E^* &= \frac{K_2 I^*}{\epsilon}, \\ T^* &= \frac{(\pi_1 \kappa K_4 + \pi_2(1-\pi_1)\kappa) I^*}{K_4 K_3}, \\ C_h^* &= \frac{(1-\pi_1)\kappa I^*}{K_4}, \\ V^* &= \frac{b\Lambda}{K_5 + (1-\psi)[\beta_1 + \beta_2 \frac{\kappa(1-\pi_1)}{K_4} + \beta_3 \frac{(\pi_1\kappa K_4 + \pi_2 \kappa(1-\pi_1))}{K_3 K_4}] I^*}, \end{aligned} \quad (4)$$

and I^* is the root of the following quadratic equation

$$a_1 {I^*}^2 + a_2 I^* + a_3 = 0, \quad (5)$$

with

$$\begin{aligned} a_1 &= (1-\psi)B^2[\mu K_2 K_3 K_4 + \epsilon\mu\, K_3 K_4 \\ &+ (\pi_1\kappa K_4 + \pi_2\kappa(1-\pi_1))\,\epsilon\mu + \epsilon\kappa\mu(1-\pi_1)K_3], \\ a_2 &= B[\mu K_2 K_3 K_4 K_5 + \epsilon\mu K_3 K_4 K_5 \\ &+ \epsilon\mu K_5(\pi_1\kappa K_4 + \pi_2(1-\pi_1)\kappa) \\ &+ (1-\pi_1)\epsilon\kappa\mu K_3 K_5 + (1-\psi)\mu K_1 K_2 K_3 K_4 \\ &- (1-\psi)\Lambda\epsilon B K_3 K_4], \\ a_3 &= \mu K_1 K_2 K_4 K_3 K_5 (1 - R_0), \end{aligned} \quad (6)$$

where

$$B = \left[\beta_1 + \beta_2 \frac{\kappa(1-\pi_1)}{K_4} + \beta_3 \frac{(\pi_1\kappa K_4 + \pi_2\kappa(1-\pi_1))}{K_3 K_4}\right]. \quad (7)$$

The endemic equilibria of the model (3) can then be obtained by solving for I^* from (5), and substituting the positive values of I^* into the expressions in (4). Hence, S^* can be determined from $\frac{\Lambda}{\mu} - E^* - I^* - T^* - C_h^* - V^*$. From (6), it can be seen that a_1 is always positive (for an imperfect vaccine), and a_3 is positive (negative) if R_0 is less than (greater than) unity. Thus, the following result is established:

Theorem 2 *The HCV model (3) has:*

(i) a unique endemic equilibrium if $a_3 < 0 \Leftrightarrow R_0 > 1$*;*

(ii) a unique endemic equilibrium if $a_2 < 0$*, and* $a_3 = 0$ *or* $a_2^2 - 4a_1 a_3 = 0$*;*

(iii) two endemic equilibria if $a_3 > 0, a_2 < 0$ *and* $a_2^2 - 4a_1 a_3 > 0$*;*

(iv) no endemic equilibrium otherwise.

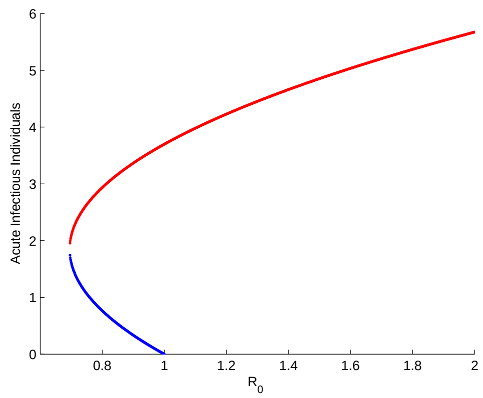


Figure 1: Backward Bifurcation diagram, with parameter values $\beta_2 = 0.09$, $\beta_3 = 0.19$, $\mu = 0.00004$, $\alpha = 0.1$, $\rho = 0.152$, $\pi_1 = .001$, $\pi_2 = 0.02$, $\epsilon = 0.022$, $\kappa = 0.032$, $\Lambda = 0.0052$, $\sigma = 0.2$, $\psi = 0.95$.

Hence, the model has a unique endemic equilibrium (P^*) whenever $R_0 > 1$, as evident from case (i) of the above theorem. Also, case (iii) indicates a possible chance of backward bifurcation (where a locally asymptotically stable DFE exists along with a locally asymptotically stable endemic equilibrium when $R_0 < 1$). Since, for $a_3 > 0$, $R_0 < 1$, the model will have a disease-free equilibrium and two endemic equilibria. To check for this, the discriminant $a_2^2 - 4a_1 a_3$ is set to zero and is solved for the critical value of R_0, denoted by R_c, given by

$$R_c = 1 - \frac{a_2^2}{4a_1\mu K_1 K_2 K_5 K_3 K_4}.$$

Backward bifurcation occurs for those values of R_0 such that $R_c < R_0 < 1$. This is illustrated by simulating the model with these parameter values: $\beta_1 = 0.03$,

$\beta_3 = 0.19$, $\mu = 0.00004$, $\alpha = 0.1$, $\rho = 0.152$, $\pi_1 = 0.001$, $\pi_2 = 0.02$, $\epsilon = 0.022$, $\kappa = 0.032$, $\Lambda = 0.0052$, $\sigma = 0.2$, $\psi = 0.95$. (These values are used merely for illustration purposes, and may not be realistic from epidemiological point of view.) The result is shown in Figure 1. It can be seen that a locally asymptotically stable disease free equilibrium, a locally asymptotically stable endemic equilibrium, and, an unstable endemic equilibrium coexist when $R_0 < 1$.

2.2.1 Proof of backward bifurcation phenomenon

The phenomenon of backward bifurcation can be proved by using center manifold theory on system (1). A theorem (Castillo-Chavez and Song) in [14], will be used here. To apply this method, the following change of variables is made in the model. Let $x_1 = S, x_2 = E, x_3 = I, x_4 = T, x_5 = C_h$, and $x_6 = V$. Let $X = (x_1, x_2, x_3, x_4, x_5, x_6)^T$. Thus, system (1) can now be written as $\frac{dX}{dt} = (f_1, f_2, f_3, f_4, f_5, f_5, f_6)^T$ given below

$$\begin{aligned}\frac{dx_1}{dt} &= f_1 = (1-b)\Lambda + \rho x_4 + \alpha x_6 \\ &\quad -(\beta_1 x_3 + \beta_2 x_5 + \beta_3 x_4)x_1 + \sigma x_5 - \mu x_1, \\ \frac{dx_2}{dt} &= f_2 = (\beta_1 x_3 + \beta_2 x_5 + \beta_3 x_4)x_1 \\ &\quad +(1-\psi)(\beta_1 x_3 + \beta_2 x_5 + \beta_3 x_4)x_6 - K_1 x_2, \\ \frac{dx_3}{dt} &= f_3 = \epsilon x_2 - K_2 x_3, \\ \frac{dx_4}{dt} &= f_4 = \pi_1 k x_3 + \pi_2 x_5 - K_3 x_4, \\ \frac{dx_5}{dt} &= f_5 = (1-\pi_1)k x_3 - K_4 x_5, \\ \frac{dx_6}{dt} &= f_6 = b\Lambda - K_5 x_6 \\ &\quad -(1-\psi)(\beta_1 x_3 + \beta_2 x_5 + \beta_3 x_4)x_6.\end{aligned} \tag{8}$$

Choose β_1 as the bifurcation parameter, and let R_0=1. Solving for β_1=$\bar{\beta}_1$ from R_0=1 gives

$$\beta_1 = \bar{\beta}_1 = \frac{K_1 K_2}{\epsilon A} - \frac{\beta_2(1-\pi_1)\kappa}{K_4} - \frac{\beta_3(\pi_1 k K_4 + \pi_2(1-\pi_1)\kappa)}{K_3 K_4},$$

where

$$A = \frac{(1-b)\Lambda}{\mu} + \frac{\alpha b \Lambda}{\mu K_5} + (1-\psi)\frac{b\Lambda}{K_5}. \tag{9}$$

The Jacobian matrix (J) of system (8) calculated at the DFE, P_0, with $\beta_1 = \bar{\beta}_1$ is given as follows

$$J = \begin{pmatrix} -\mu & 0 & -\beta_1 K_h & \rho - \beta_3 K_h & \sigma - \beta_2 K_h & \alpha \\ 0 & -K_1 & \beta_1 A & \beta_3 A & \beta_2 A & 0 \\ 0 & \epsilon & -K_2 & 0 & 0 & 0 \\ 0 & 0 & \pi_1 \kappa & -K_3 & \pi_2 & 0 \\ 0 & 0 & (1-\pi_1)\kappa & 0 & -K_4 & 0 \\ 0 & 0 & -\beta_1 K_m & -\beta_3 K_m & -\beta_2 K_m & -K_5 \end{pmatrix} \tag{10}$$

where $K_h = (\frac{\Lambda}{\mu} - \frac{b\Lambda}{K_5})$ and $K_m = \frac{(1-\psi)\Lambda b}{K_5}$. The characteristic equation (in λ) of the Jacobian matrix, J, is given as

$$(-\mu-\lambda)(-K_5-\lambda)(\lambda^4 + D_1\lambda^3 + D_2\lambda^2 + D_3\lambda + D_4) = 0 \tag{11}$$

where

$$\begin{aligned} D_1 &= K_1 + K_2 + K_3 + K_4, \\ D_2 &= K_3K_4 + K_1K_3 + K_2K_3 + K_1K_4 + K_2K_4 \\ &\quad + K_1K_2 - \beta_1 \epsilon A, \\ D_3 &= K_1K_3K_4 + K_2K_3K_4 + K_1K_2K_3 + K_1K_2K_4 \\ &\quad -\beta_1\epsilon A(K_3 + K_4) - \beta_3\kappa\pi_1\epsilon A - (1-\pi_1)\beta_2\kappa\epsilon A, \\ D_4 &= K_1K_2K_3K_4(1 - R_0). \end{aligned} \tag{12}$$

For R_0=1, the characteristic equation (11) becomes

$$\lambda(-\mu-\lambda)(-K_5-\lambda)(\lambda^3 + D_1\lambda^2 + D_2\lambda + D_3) = 0 \tag{13}$$

Hence, the equation (13) has a zero eigenvalue and two negative eigenvalues, $-\mu$ and $-K_5$. The remaining three eigenvalues are given by the following cubic equation in λ

$$\lambda^3 + D_1\lambda^2 + D_2\lambda + D_3 = 0 \tag{14}$$

D_1 is clearly positive, and D_2 and D_3 can easily be shown to be positive when β_1 is replaced with $\bar{\beta}_1$. Similarly, $D_1D_2 - D_3 > 0$. Hence, using Routh-Hurwitz criterion [15], all roots of the characteristic equation (14) have negative real parts. Therefore, the Jacobian matrix of the linearized system has a simple zero eigenvalue, with all other eigenvalues having negative real parts. Hence, the Center Manifold Theory [14] can be used to analyze the dynamics of system (8). Corresponding to the zero eigenvalue, Jacobian matrix $J\mid_{\beta_1=\bar{\beta}_1}$ can be shown to have a right eigenvector given by $w = (w_1, w_2, w_3, w_4, w_5, w_6)^T$, where

$$\begin{aligned} w_1 &= \tfrac{1}{\mu}\Big(\rho\left(\tfrac{\pi_1\kappa K_4+\pi_2(1-\pi_1)\kappa}{K_3K_4}\right)+\sigma\tfrac{(1-\pi_1)\kappa}{K_4} \\ &-\tfrac{K_1K_2}{\epsilon A}\left(\tfrac{(1-b)\Lambda}{\mu}+\tfrac{\alpha b\Lambda}{\mu K_5}+\tfrac{\alpha(1-\psi)b\Lambda}{K_5^2}\right)\Big)w_3, \\ w_2 &= \tfrac{K_2}{\epsilon}w_3, \\ w_3 &= w_3, \\ w_4 &= \tfrac{\pi_1\kappa}{K_3}w_3+\tfrac{\pi_2(1-\pi_1)\kappa}{K_3K_4}w_3, \\ w_5 &= \tfrac{-(1-\psi)b\Lambda K_1K_2}{K_5^2\epsilon A}w_3. \end{aligned} \tag{15}$$

Similarly, corresponding to the zero eigenvalue, $J\mid_{\beta_1=\bar{\beta}_1}$ has a left eigenvector given by $v=(v_1,v_2,v_3,v_4,v_5,v_6)$, where $v_1=0$, $v_2=\frac{\epsilon}{K_1}v_3$, $v_3=v_3$, $v_4=\frac{\epsilon\beta_3 A}{K_1K_3}v_3$, $v_5=\frac{\epsilon\beta_2 A}{K_1K_4}v_3+\frac{\epsilon\beta_3\pi_2 A}{K_1K_4K_3}v_3$, $v_6=0$.

Calculation of a. For the system (8), the corresponding non-zero partial derivatives of f_i $(i=1,2,...,6)$ calculated at the disease free equilibrium, P_0, are given by

$$\begin{aligned} &\frac{\partial^2 f_1}{\partial x_1\partial x_3}=-\beta_1, && \frac{\partial^2 f_1}{\partial x_1\partial x_5}=-\beta_2, \\ &\frac{\partial^2 f_1}{\partial x_1\partial x_4}=-\beta_3, && \frac{\partial^2 f_2}{\partial x_1\partial x_3}=\beta_1, \\ &\frac{\partial^2 f_2}{\partial x_1\partial x_5}=\beta_2, && \frac{\partial^2 f_2}{\partial x_1\partial x_4}=\beta_3, \\ &\frac{\partial^2 f_2}{\partial x_3\partial x_6}=(1-\psi)\beta_1, && \frac{\partial^2 f_2}{\partial x_5\partial x_6}=(1-\psi)\beta_2, \\ &\frac{\partial^2 f_2}{\partial x_4\partial x_6}=(1-\psi)\beta_3, && \frac{\partial^2 f_6}{\partial x_3\partial x_6}=-(1-\psi)\beta_1, \\ &\frac{\partial^2 f_6}{\partial x_3\partial x_6}=-(1-\psi)\beta_2, && \frac{\partial^2 f_6}{\partial x_4\partial x_6}=-(1-\psi)\beta_3. \end{aligned}$$

Consequently, the associated bifurcation coefficient, a, is given by

$$\begin{aligned} a &= \sum_{k,i,j=1}^{6} u_k w_i w_j \frac{\partial^2 f_k}{\partial x_i\partial x_j}(0,0) \\ &= \frac{\epsilon u_3 w_3^2}{K_1\mu}\Big(\beta_1+\beta_2\frac{\kappa(1-\pi_1)}{K_4} \\ &\quad+\beta_3\frac{(\pi_1\kappa K_4+\pi_2\kappa(1-\pi_1))}{K_3K_4}\Big) \\ &\quad\Big(\rho\left(\frac{\pi_1\kappa K_4+\pi_2(1-\pi_1)\kappa}{K_3K_4}\right)+\sigma\frac{(1-\pi_1)\kappa}{K_4} \\ &\quad-\frac{K_1K_2}{\epsilon A}\left(\frac{(1-b)\Lambda}{\mu}+\frac{\alpha b\Lambda}{\mu K_5}+\frac{\alpha(1-\psi)b\Lambda}{K_5^2}\right) \\ &\quad-\frac{(1-\psi)^2\mu b\Lambda K_1K_2}{K_5^2\epsilon A}\Big). \end{aligned} \tag{16}$$

Calculation of b. The required partial derivative, for the computation of b, is calculated at the disease free equilibrium, i.e. $\frac{\partial^2 f_2}{\partial x_3\partial\beta_1}=A$. Hence, the associated bifurcation coefficient, b, is given as

$$b=\sum_{k,i=1}^{6}u_k w_i\frac{\partial^2 f_k}{\partial x_i\partial\phi}(0,0)=\frac{A\epsilon u_3 w_3}{K_1}>0. \tag{17}$$

Since the coefficient b is always positive, it follows from Theorem 3.3 that the system (3) will undergo backward bifurcation if the coefficient a is positive.

The phenomenon of backward bifurcation poses a lot of problems, since it jeopardizes the possibility of total disease eradication from the population, when the basic reproduction number is less than unity. Hence, it is instructive to try to eliminate the backward bifurcation effect. Since, this effect requires the existence of at least two endemic equilibria when $R_0<1$ [16, 17], it may be removed by considering such a model, in which positive endemic equilibria cease to exist.

2.2.2 Use of perfect vaccine to eliminate backward bifurcation

The backward bifurcation behavior of the proposed HCV infection model (1), can be eliminated by using a perfect vaccine, i.e., when ψ=1. For ψ=1, the original model now becomes

$$\begin{aligned} \tfrac{dS}{dt} &= (1-b)\Lambda+\rho T+\alpha V-(\beta_1 I+\beta_2 C_h \\ &+\beta_3 T)S+\sigma C_h-\mu S, \\ \tfrac{dE}{dt} &= (\beta_1 I+\beta_2 C_h+\beta_3 T)S-K_1 E, \\ \tfrac{dI}{dt} &= \epsilon E-K_2 I, \\ \tfrac{dT}{dt} &= \pi_1\kappa I+\pi_2 C_h-K_3 T, \\ \tfrac{dC_h}{dt} &= (1-\pi_1)\kappa I-K_4 C_h, \\ \tfrac{dV}{dt} &= b\Lambda-K_5 V. \end{aligned} \tag{18}$$

The system (18) has a DFE, $P_0(S_0,0,0,0,0,V_0)$, which is the same as the original model given in equation (1). The corresponding *vaccinated reproduction number*, $\bar{R}_0$, for model (18) is given as

$$\begin{aligned} &\bar{R}_0 = R_0\mid_{\psi=1}= \\ &\frac{\epsilon}{K_1K_2}\Big(\frac{(1-b)\Lambda}{\mu}+\frac{\alpha b\Lambda}{\mu K_5}\Big)\times \\ &\Big(\beta_1+\beta_2\frac{\kappa(1-\pi_1)}{K_4}+\beta_3\frac{(\pi_1\kappa K_4+\pi_2\kappa(1-\pi_1))}{K_3K_4}\Big). \end{aligned}$$

Consider the quadratic equation (5), rewritten below for convenience

$$a_1 I^{*2}+a_2 I^*+a_3=0. \tag{19}$$

For $\psi = 1$, using the values given in equation (6), the coefficients a_1, a_2, and a_3 of the above quadratic equation reduce to $a_1 = 0, a_2 > 0$, and $a_3 \geq 0$ (whenever $\bar{R}_0 = R_0 \mid_{\psi=1} \leq 1$). In this case, the quadratic equation (5) will have just a single non positive solution

$$I^* = -\frac{a_3}{a_2} \leq 0.$$

Hence, whenever $\bar{R}_0 \leq 1$, the model (18), with perfect vaccine, has no positive endemic equilibrium. This clearly suggests the impossibility of backward bifurcation (because for backward bifurcation to occur, there must exist at least two endemic equilibria whenever $\bar{R}_0 \leq 1$).

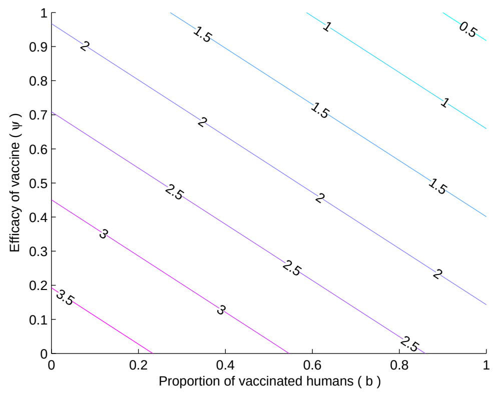


Figure 2: Simulation of the model (18), showing a contour plot of $\bar{R}_0$ as a function of proportion of vaccinated humans (b) and vaccine efficacy (ψ).

A contour plot of vaccinated reproduction number ($\bar{R}_0$) as a function of proportion of vaccinated humans (b) and vaccine efficacy (ψ) is shown in Fig. 2. The parameter values used to generate this diagram are as given in Table (1). The contours illustrate a significant decrease in the vaccinated reproduction number, $\bar{R}_0$, with increasing vaccine efficacy, ψ, and proportion of vaccinated humans, b. It can be seen that very high vaccine efficacy and vaccine coverage is required to control HCV infection effectively in the population. Almost all of the susceptible individuals should have had vaccination, and vaccine efficacy must be 100% for $\bar{R}_0$ to be less than one, so that the spread of HCV infection is controlled effectively. The global stability of the disease free equilibrium can be proved in the region Δ as follows.

Theorem 3 *The disease-free equilibrium (DFE) is globally asymptotically stable in Δ whenever $\bar{R}_0 \leq 1$*

Proof: Let the Lyapunov function be

$$V = A_1 E + A_2 I + A_3 T + A_4 C_h, \qquad (20)$$

where

$$\begin{aligned} A_1 &= \tfrac{S_0\mu}{\Lambda}, \\ A_2 &= \tfrac{S_0 K_1 \mu}{\epsilon\Lambda}, \\ A_3 &= \tfrac{\beta_3 S_0}{K_3}, \\ A_4 &= \tfrac{\beta_2 S_0}{K_4} + \tfrac{\beta_3 S_0 \pi_2}{K_3 K_4}. \end{aligned} \qquad (21)$$

Then,

$$\begin{aligned} V' &= A_1 E' + A_2 I' + A_3 T' + A_4 C_h' \\ &= A_1((\beta_1 I + \beta_2 C_h + \beta_3 T)S - K_1 E) \\ &\quad + A_2(\epsilon E - K_2 I) + A_3(\pi_1 \kappa I + \pi_2 C_h - K_3 T) \\ &\quad + A_4((1-\pi_1)\kappa I - K_4 C_h). \end{aligned} \qquad (22)$$

Since $S + E + I + T + C_h + V \leq \frac{\Lambda}{\mu}$ implies that $S \leq \frac{\Lambda}{\mu}$. Therefore V' becomes

$$\begin{aligned} V' &\leq A_1\Big((\beta_1 I + \beta_2 C_h + \beta_3 T)\frac{\Lambda}{\mu} - K_1 E\Big) \\ &\quad + A_2(\epsilon E - K_2 I) + A_3(\pi_1 \kappa I + \pi_2 C_h - K_3 T) \\ &\quad + A_4((1-\pi_1)\kappa I - K_4 C_h) \\ &= E(-K_1 A_1 + \epsilon A_2) \\ &\quad + I\Big(\beta_1 A_1 \frac{\Lambda}{\mu} - K_2 A_2 + \pi_1 \kappa A_3 + A_4 \kappa (1-\pi_1)\Big) \\ &\quad + T\Big(\beta_3 A_1 \frac{\Lambda}{\mu} - K_3 a_3\Big) \\ &\quad + C_h\Big(\beta_2 A_1 \frac{\Lambda}{\mu} + \pi_2 A_3 - K_4 A_4\Big) \\ &= I\Big(S_0(\beta_1 + \beta_2 \frac{\kappa(1-\pi_1)}{K_4} \\ &\quad + \beta_3 \frac{(\pi_1 \kappa K_4 + \pi_2 \kappa (1-\pi_1))}{K_3 K_4}) - \frac{S_0 K_2 K_1 \mu}{\epsilon\Lambda}\Big) \\ &= \frac{I K_1 K_2}{\epsilon}\Big(\bar{R}_0 - \frac{S_0\mu}{\Lambda}\Big) \leq 0, \end{aligned} \qquad (23)$$

whenever,

$$\bar{R}_0 \leq \frac{S_0 \mu}{\Lambda} < 1. \qquad (24)$$

Hence, $V' \leq 0$ for $\bar{R}_0 \leq \frac{S_0\mu}{\Lambda}$. It should also be noted that $\frac{S_0\mu}{\Lambda} = \frac{\frac{\Lambda}{\mu} - \frac{b\Lambda}{\alpha+\mu}}{\frac{\Lambda}{\mu}} < 1$ and $V' = 0$ only when $E + I + T + C_h = 0$. System (18) then becomes

$$\begin{aligned} \tfrac{dS}{dt} &= (1-b)\Lambda + \alpha V - \mu S, \\ \tfrac{dE}{dt} &= \tfrac{dI}{dt} = \tfrac{dT}{dt} = \tfrac{dC_h}{dt} = 0, \\ \tfrac{dV}{dt} &= b\Lambda - (\alpha+\mu)V. \end{aligned} \qquad (25)$$

When $t \to \infty$, the solution of the last equation in the system (25) becomes

$$V = \frac{b\Lambda}{\alpha + \mu}. \qquad (26)$$

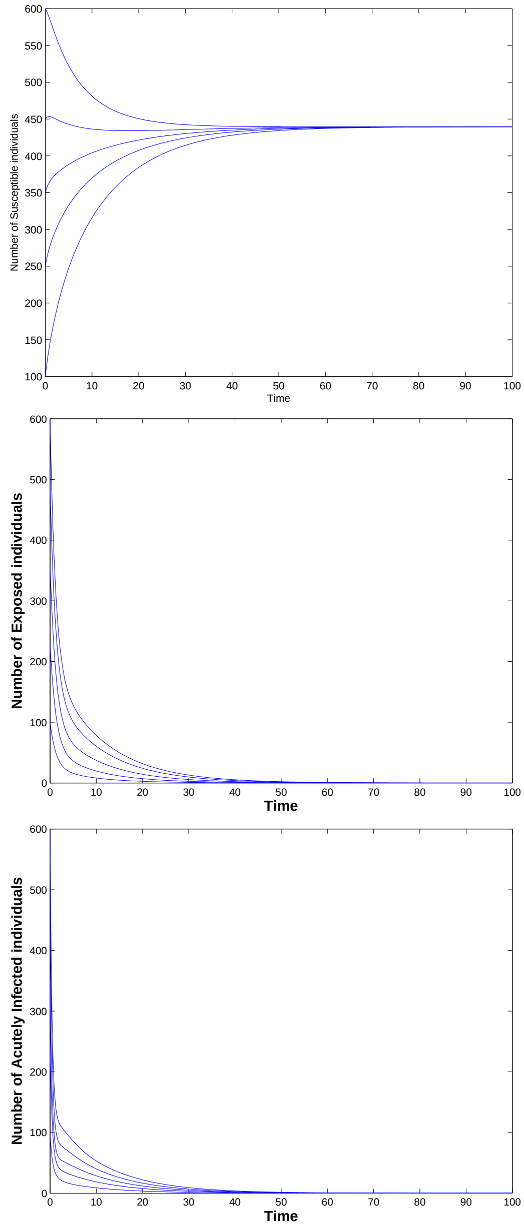
Putting this value back into the equation

$$\frac{dS}{dt} = (1-b)\Lambda + \alpha V - \mu S, \tag{27}$$

and letting $t \to \infty$ gives

$$S = \frac{(1-b)\Lambda}{\mu} + \frac{\alpha b \Lambda}{\mu(\alpha+\mu)}. \tag{28}$$

The solution to the remaining equations in (25) is obviously zero. Clearly, when $t \to \infty$, the solution to system (25) approaches the DFE, $P_0(S_0, 0, 0, 0, 0, V_0)$. By using LaSalle's invariance principle [18], P_0 is found to be globally asymptotically stable in Δ. This result is illustrated by simulating the model (18) using a reasonable set of parameter values given in Table 1. The plot shows that the disease is eliminated from the population (Fig. 3).



2.3 Global stability of the endemic equilibrium

Theorem 4 *The endemic equilibrium $P^*(S^*, E^*, I^*, T^*, C_h^*, V^*)$, of the system (1) with $\rho = 0$ and $\sigma = 0$ is globally asymptotically stable whenever it exists.*

In order to prove the above theorem, we have used the method given in [19, 20]. At the endemic equilibrium P^*, with $\rho = 0$ and $\sigma = 0$, the following equations are satisfied:

$$\begin{aligned}
0 &= (1-b)\Lambda + \alpha V^* - (\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)S^* \\
&\quad -\mu S^* \\
0 &= (\beta_1 I^* + \beta_2 C_h^* + \beta_3 T^*)S^* + (1-\psi)(\beta_1 I^* \\
&\quad + \beta_2 C_h^* + \beta_3 T^*)V^* - (\epsilon+\mu)E^* \\
0 &= \epsilon E^* - (\kappa+\mu)I^* \\
0 &= \pi_1 \kappa I^* + \pi_2 C_h^* - \mu T^* \\
0 &= (1-\pi_1)\kappa I^* - (\pi_2+\mu)C_h^* \\
0 &= \Lambda - (\alpha+\mu)V^* - (1-\psi)(\beta_1 I^* + \beta_2 C_h^* \\
&\quad +\beta_3 T^*)V^*.
\end{aligned} \tag{29}$$

Let

$$x_1 = \frac{S}{S^*},\ x_2 = \frac{E}{E^*},\ x_3 = \frac{I}{I^*},\ x_4 = \frac{T}{T^*}, \tag{30}$$

$$x_5 = \frac{C_h}{C_h^*}, \quad x_6 = \frac{V}{V^*}. \tag{31}$$

Then (1) can be rewritten as

$$\begin{aligned}
x_1' &= x_1\Big[\tfrac{(1-b)\Lambda}{S^*}(\tfrac{1}{x_1} - 1) + \tfrac{\alpha V^*}{S^*}(\tfrac{x_6}{x_1} - 1) \\
&\quad -\beta_1 I^*(x_3 - 1) - \beta_2 C_h^*(x_5 - 1) \\
&\quad -\beta_3 T^*(x_4 - 1)\Big],
\end{aligned}$$

$$\begin{aligned}
x_2' &= x_2\Big[\tfrac{\beta_1 I^* S^*}{E^*}(\tfrac{x_3 x_1}{x_2} - 1) \\
&\quad +\tfrac{\beta_2 C_h^* S^*}{E^*}(\tfrac{x_1 x_5}{x_2} - 1) - 1) \\
&\quad +(1-\psi)\tfrac{\beta_1 I^* V^*}{E^*}(\tfrac{x_3 x_6}{x_2} - 1) \\
&\quad +(1-\psi)\tfrac{\beta_2 C_h^* V^*}{E^*}(\tfrac{x_5 x_6}{x_2} - 1) \\
&\quad +(1-\psi)\tfrac{\beta_3 T^* V^*}{E^*}(\tfrac{x_4 x_6}{x_2} - 1) \\
&\quad +\tfrac{\beta_3 T^* S^*}{E^*}(\tfrac{x_1 x_4}{x_2}\Big],
\end{aligned}$$

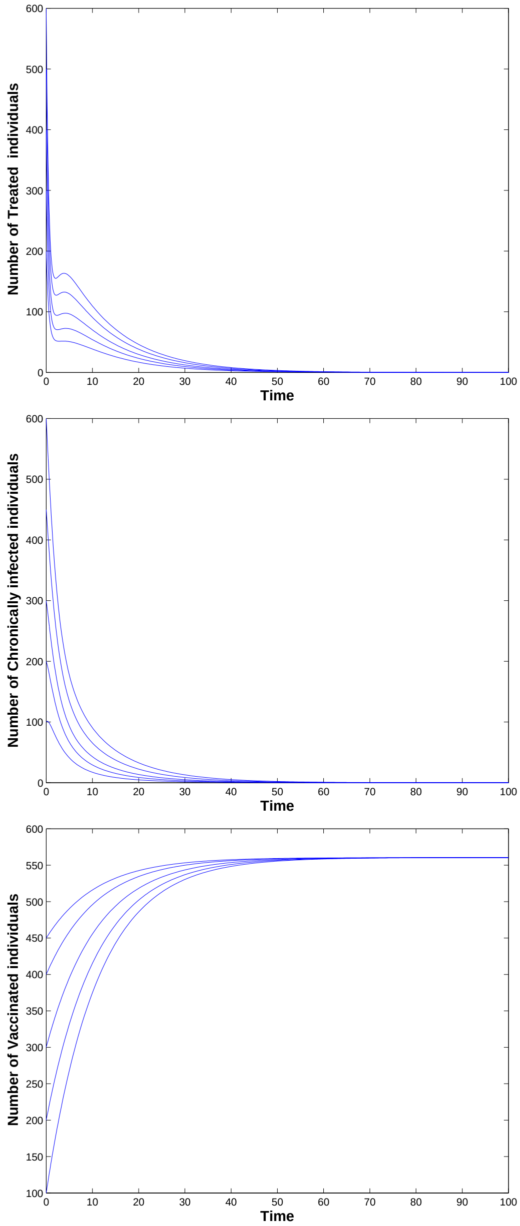


Figure 3: Simulation of system (18), showing the total number of susceptible, exposed, acutely infected, chronically infected, treated and vaccinated individuals as a function of time (years). Parameter values are given in Table 1, with $\psi = 1$ for perfect vaccine, $\beta_1 = 0.0009$, $\beta_2 = 0.0006$, $\beta_3 = 0.0001$ and $\bar{R}_0 = 0.654 < 1$. The numerical simulation shows that the disease is eliminated when $\bar{R}_0 < 1$. It is assumed that the acute phase is more infectious than the chronic stage which is in turn more infectious than the treatment phase. So $\beta_1 > \beta_2 > \beta_3$.

$$
\begin{aligned}
x_3' &= x_3\Big[\tfrac{\epsilon E^*}{I^*}(\tfrac{x_2}{x_3} - 1)\Big],\\
x_4' &= x_4\Big[\tfrac{\pi_1 \kappa I^*}{T^*}(\tfrac{x_3}{x_4} - 1) + \tfrac{\pi_2 C_h^*}{T^*}(\tfrac{x_5}{x_4} - 1)\Big],\\
x_5' &= x_5\Big[(1-\pi_1)\tfrac{\kappa I^*}{C_h^*}(\tfrac{x_3}{x_5} - 1)\Big],\\
x_6' &= x_6\Big[\tfrac{b\Lambda}{V^*}(\tfrac{1}{x_6} - 1) - (1-\psi)\beta_1 I^*(x_3 - 1)\\
&\quad -(1-\psi)\beta_2 C_h^*(x_5 - 1)\\
&\quad -(1-\psi)\beta_3 T^*(x_4 - 1)\Big].
\end{aligned} \tag{32}
$$

The endemic equilibrium $P^*(S^*, E^*, I^*, T^*, C_h^*, V^*)$ corresponds to the positive equilibrium $\bar{P}^*(1, 1, 1, 1, 1, 1)$ of (32). Since, the global stability of $\bar{P}^*$ is the same as that of P^*, the global stability of $\bar{P}^*$ is described below instead of P^*. We define the Lyapunov function as follows

$$
\begin{aligned}
L = {} & a_1 S^*(x_1 - 1 - \ln x_1) + a_2 E^*(x_2 - 1 - \ln x_2)\\
& + a_3 I^*(x_3 - 1 - \ln x_3) + a_4 T^*(x_4 - 1 - \ln x_4)\\
& + a_5 C_h^*(x_5 - 1 - \ln x_5) + a_6 V^*(x_6 - 1 - \ln x_6).
\end{aligned}
$$

where a_1, a_2, a_3, a_4, a_5 and a_6 are positive numbers which are to be determined. Using (29), the time derivative of L along the solutions of system (1) is given as

$$
\begin{aligned}
\frac{dL}{dt} = {} & a_1\Big(2(1-b)\Lambda + \alpha V^* - \beta_1 I^* S^* - \beta_2 C_h^* S^*\\
& -\beta_3 T^* S^*\Big) + a_2\Big(\beta_1 I^* S^* + \beta_2 C_h^* S^*\\
& +\beta_3 T^* S^* + (1-\psi)\beta_1 I^* V^* + (1-\psi)\beta_2 C_h^* V^*\\
& +(1-\psi)\beta_3 T^* V^*\Big) + a_3\epsilon E^* + a_4 \pi_1 \kappa I^*\\
& +a_5(1-\pi_1)\kappa I^* + a_6\Big(2b\Lambda - (1-\psi)\beta_1 I^* V^*\\
& -(1-\psi)\beta_2 C_h^* V^* - (1-\psi)\beta_3 T^* V^*\Big)\\
& -x_1\Big(a_1(1-b)\Lambda + a_1\alpha V^* - a_1\beta_1 I^* S^*\\
& -a_1\beta_2 C_h^* S^* - a_1\beta_3 T^* S^*\Big)\\
& +x_2\Big(-a_2\beta_1 I^* S^* - a_2\beta_2 C_h^* S^* - a_2\beta_3 T^* S^*\\
& -a_2(1-\psi)\beta_1 I^* V^* - a_2(1-\psi)\beta_2 C_h^* S^*\\
& -a_2(1-\psi)\beta_3 T^* V^* + a_3\epsilon E^*\Big)\\
& +x_3\Big(a_1\beta_1 I^* S^* - a_3\epsilon E^* + a_4\pi_1\kappa I^*\\
& +a_5(1-\pi_1\kappa I^* + a_6(1-\psi)\beta_1 I^* V^*)\Big)\\
& +x_4\Big(a_1\beta_3 T^* S^* - a_4\pi_1\kappa I^* - a_4\pi_2 C_h^*\\
& +a_6(1-\psi)\beta_3 T^* V^*\Big)\\
& +x_5\Big(a_1\beta_2 C_h^* S^* + a_4\pi_2 C_h^* - a_5(1-\pi_1)\kappa I^*\\
& +a_6(1-\psi)\beta_2 C_h^* V^*\Big)
\end{aligned}
$$

$$
\begin{aligned}
&-x_6\Big(-a_1\alpha V^*+a_6b\Lambda-a_6(1-\psi)\beta_1I^*V^*\\
&-a_6(1-\psi)\beta_2C_h^*V^*-a_6(1-\psi)\beta_3T^*V^*\Big)\\
&+x_5x_6\Big(a_2(1-\psi)\beta_2C_h^*V^*-a_6(1-\psi)\beta_2C_h^*V^*\Big)\\
&+x_1x_3\Big(-a_1\beta_1I^*S^*+a_2\beta_1I^*S^*\Big)\\
&+x_1x_5\Big(-a_1\beta_2C_h^*S^*+a_2\beta_2C_h^*S^*\Big)\\
&+x_1x_4\Big(-a_1\beta_3T^*S^*+a_2\beta_3T^*S^*\Big)\\
&+x_3x_6\Big(a_2(1-\psi)\beta_1I^*V^*-a_6(1-\psi)\beta_1I^*V^*\Big)\\
&+x_4x_6\Big(a_2(1-\psi)\beta_3T^*V^*-a_6(1-\psi)\beta_3T^*V^*\Big)\\
&+\frac{1}{x_1}(-a_1(1-b)\Lambda)\\
&+\frac{1}{x_6}(-a_6b\Lambda)+\frac{x_6}{x_1}(-a_1\alpha V^*)\\
&+\frac{x_3}{x_5}(-a_5(1-\pi_1\kappa I^*))+\frac{x_5}{x_4}(-a_4\pi_2C_h^*)\\
&+\frac{x_3}{x_4}(-a_4\pi_1\kappa I^*)+\frac{x_2}{x_3}(-a_3\epsilon E^*)\\
&+\frac{x_3x_6}{x_2}(-a_2(1-\pi)\beta_1I^*V^*)\\
&+\frac{x_3x_1}{x_2}(-a_2\beta_1I^*S^*)+\frac{x_5x_1}{x_2}(-a_2\beta_2C_h^*S^*)\\
&+\frac{x_1x_4}{x_2}(-a_2\beta_3T^*S^*)\\
&+\frac{x_4x_6}{x_2}(-a_2(1-\pi)\beta_3T^*V^*)\\
&+\frac{x_5x_6}{x_2}(-a_2(1-\pi)\beta_2C_h^*V^*)\\
&=: F(x_1,x_2,x_3,x_4,x_5,x_6).
\end{aligned}
\tag{33}
$$

We define the function $H=\sum_{i=1}^{14}P_i$, where $P_i(i=1,2,...,14)$ is given as

$$
\begin{aligned}
&P_1=b_1\Big(2-x_1-\tfrac{1}{x_1}\Big),\\
&P_2=b_2\Big(2-x_6-\tfrac{1}{x_6}\Big),\\
&P_3=b_3\Big(3-x_1-\tfrac{1}{x_6}-\tfrac{x_6}{x_1}\Big),\\
&P_4=b_4\Big(3-\tfrac{1}{x_1}-\tfrac{x_1x_3}{x_2}-\tfrac{x_2}{x_3}\Big),\\
&P_5=b_5\Big(4-\tfrac{1}{x_1}-\tfrac{x_1x_4}{x_2}-\tfrac{x_3}{x_4}-\tfrac{x_2}{x_3}\Big),\\
&P_6=b_6\Big(4-\tfrac{1}{x_1}-\tfrac{x_1x_5}{x_2}-\tfrac{x_3}{x_5}-\tfrac{x_2}{x_3}\Big),\\
&P_7=b_7\Big(5-\tfrac{1}{x_1}-\tfrac{x_1x_4}{x_2}-\tfrac{x_5}{x_4}-\tfrac{x_2}{x_3}-\tfrac{x_3}{x_5}\Big),\\
&P_8=b_8\Big(3-\tfrac{1}{x_6}-\tfrac{x_3x_6}{x_2}-\tfrac{x_2}{x_3}\Big),\\
&P_9=b_9\Big(4-\tfrac{1}{x_6}-\tfrac{x_4x_6}{x_2}-\tfrac{x_3}{x_4}-\tfrac{x_2}{x_3}\Big),\\
&P_{10}=b_{10}\Big(5-\tfrac{1}{x_6}-\tfrac{x_4x_6}{x_2}-\tfrac{x_5}{x_4}-\tfrac{x_2}{x_3}-\tfrac{x_3}{x_5}\Big),\\
&P_{11}=b_{11}\Big(4-\tfrac{1}{x_6}-\tfrac{x_5x_6}{x_2}-\tfrac{x_3}{x_5}-\tfrac{x_2}{x_3}\Big),\\
&P_{12}=b_{12}\Big(4-\tfrac{1}{x_6}-\tfrac{x_1x_3}{x_2}-\tfrac{x_6}{x_1}-\tfrac{x_2}{x_3}\Big),\\
&P_{13}=b_{13}\Big(5-\tfrac{1}{x_6}-\tfrac{x_1x_5}{x_2}-\tfrac{x_6}{x_1}-\tfrac{x_2}{x_3}-\tfrac{x_3}{x_5}\Big),\\
&P_{14}=b_{14}\Big(5-\tfrac{1}{x_6}-\tfrac{x_1x_4}{x_2}-\tfrac{x_6}{x_1}-\tfrac{x_2}{x_3}-\tfrac{x_3}{x_4}\Big).
\end{aligned}
\tag{34}
$$

To determine all the coefficients, ($a_i>0$ $(i=1,2,...,6)$, $b_i\geq 0$ $(i=1,2,...,14)$) we let $F(x_1,x_2,x_3,x_4,x_5,x_6)=H$. Comparing coefficients of F and H, we see that the terms $x_2,\ x_4,\ x_5,\ x_5x_6,\ x_1x_3,\ x_1x_5,\ x_1x_4,\ x_3x_6$, and x_4x_6 of F do not appear in H. Hence their coefficients will be equal to zero, i.e.,

$$
\begin{aligned}
-a_2\beta_1I^*S^*-a_2\beta_2C_h^*S^*-a_2\beta_3T^*S^*\\
-a_2(1-\psi)\beta_1I^*V^*-a_2(1-\psi)\beta_2C_h^*S^*\\
-a_2(1-\psi)\beta_3T^*V^*+a_3\epsilon E^*=0,
\end{aligned}
\tag{35}
$$

$$
\begin{aligned}
a_1\beta_1I^*S^*-a_3\epsilon E^*+a_4\pi_1\kappa I^*\\
+a_5(1-\pi_1\kappa I^*+a_6(1-\psi)\beta_1I^*V^*)=0,
\end{aligned}
\tag{36}
$$

$$
\begin{aligned}
a_1\rho T^*+a_1\beta_3T^*S^*-a_4\pi_1\kappa I^*\\
-a_4\pi_2C_h^*+a_6(1-\psi)\beta_3T^*V^*=0,
\end{aligned}
\tag{37}
$$

$$
\begin{aligned}
a_1\beta_2C_h^*S^*+a_1\sigma C_h^*+a_4\pi_2C_h^*\\
-a_5(1-\pi_1)\kappa I^*+a_6(1-\psi)\beta_2C_h^*V^*=0,
\end{aligned}
\tag{38}
$$

$$a_2(1-\psi)\beta_2C_h^*V^*-a_6(1-\psi)\beta_2C_h^*V^*=0, \tag{39}$$

$$a_2(1-\psi)\beta_1I^*V^*-a_6(1-\psi)\beta_1I^*V^*=0, \tag{40}$$

$$a_2(1-\psi)\beta_3T^*V^*-a_6(1-\psi)\beta_3T^*V^*=0, \tag{41}$$

$$-a_1\beta_1I^*S^*+a_2\beta_1I^*S^*=0, \tag{42}$$

$$-a_1\beta_2C_h^*S^*+a_2\beta_2C_h^*S^*=0, \tag{43}$$

$$-a_1\beta_3T^*S^*+a_2\beta_3T^*S^*=0. \tag{44}$$

The above equations have the following solution

$$
\begin{aligned}
&a_1=1,a_2=1,a_6=1,\\
&a_3=\frac{\epsilon+\mu}{\epsilon},\\
&a_4=\frac{\beta_3S^*+(1-\psi)\beta_3V^*}{\mu},\\
&a_5=\frac{(S^*+(1-\psi)V^*)(\beta_2+\frac{\beta_3\pi_2}{\mu})}{\pi_2+\mu}.
\end{aligned}
$$

Substituting these values into $L'=F(x_1,x_2,x_3,x_4,x_5,x_6)$, and using equations (29) gives

$$
\begin{aligned}
&F(x_1,x_2,x_3,x_4,x_5,x_6)\\
&=\Big(2\Lambda+\alpha V^*+(\epsilon+\mu)E^*\\
&+\beta_3(S^*+(1-\psi)V^*\Big)T^*\\
&+\Big(S^*+(1-\psi)V^*\Big)\Big(\beta_2+\frac{\beta_3\pi_2}{\mu}\Big)C_h^*\Big)\\
&-x_1(\mu S^*)-x_6(\mu V^*)\\
&-\frac{1}{x_1}((1-b)\Lambda)-\frac{1}{x_6}(b\Lambda)-\frac{x_6}{x_1}(\alpha V^*)\\
&-\frac{x_3}{x_5}\Big((S^*+(1-\psi)V^*)(\beta_2+\frac{\beta_3\pi_2}{\mu})C_h^*\Big)
\end{aligned}
$$

$$
\begin{aligned}
&-\frac{x_5}{x_4}\Big(\frac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*\Big)\\
&-\frac{x_3}{x_4}\Big(\frac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_1\kappa I^*\Big)\\
&-\frac{x_2}{x_3}\Big((\epsilon+\mu)E^*\Big)-\frac{x_3x_6}{x_2}\Big((1-\psi)\beta_1I^*V^*\Big)\\
&-\frac{x_1x_3}{x_2}(\beta_1I^*S^*)-\frac{x_1x_5}{x_2}(\beta_2C_h^*S^*)\\
&-\frac{x_1x_4}{x_2}(\beta_3T^*S^*)-\frac{x_4x_6}{x_2}\Big((1-\psi)\beta_3T^*V^*\Big)\\
&-\frac{x_5x_6}{x_2}\Big((1-\psi)\beta_2C_h^*V^*\Big). \qquad (45)
\end{aligned}
$$

Comparing the remaining coefficients of F and H gives

$$
\begin{aligned}
&b_1=\mu S^*-\alpha V^*+b_{12}+b_{13}+b_{14},\\
&b_2=\mu V^*\geq 0,\\
&b_3=\alpha V^*-b_{12}-b_{13}-b_{14},\\
&b_4=\beta_1I^*S^*-b_{12},\\
&b_5=\beta_3T^*S^*-\tfrac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*\\
&+b_{10}-b_{14}, \qquad (46)\\
&b_6=\beta_2C_h^*S^*-b_{13},\\
&b_7=\tfrac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*-b_{10},\\
&b_8=(1-\psi)\beta_1I^*V^*\geq 0,\\
&b_9=(1-\psi)\beta_3T^*V^*-b_{10},\\
&b_{11}=(1-\psi)\beta_2C_h^*V^*\geq 0.
\end{aligned}
$$

To assure that $b_1, b_3, b_4, b_5, b_6, b_7$ and b_9 are non negative, $b_{10}, b_{12}, b_{13}, b_{14}$ must satisfy the following inequalities :

$$
\begin{aligned}
&\alpha V^*-\mu S^*\leq b_{12}+b_{13}+b_{14}\leq\alpha V^*,\\
&b_{10}\leq\min\left\{\begin{array}{l}(1-\psi)\beta_3T^*V^*,\\ \frac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*\end{array}\right\},\\
&b_{14}-b_{10}\leq\beta_3T^*S^*-\tfrac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*,\\
&b_{12}\leq\beta_1I^*S^*, b_{13}\leq\beta_2C_h^*S^*.
\end{aligned} \qquad (47)
$$

Finally, using equations (29), the equality for the constant terms between $F(x_1,x_2,x_3,x_4,x_5,x_6)$ and H is verified, as follows

$$
\begin{aligned}
&2b_1+2b_2+3b_3+3b_4+4b_5+4b_6+5b_7+3b_8\\
&+4b_9+5b_{10}+4b_{11}+4b_{12}+5b_{13}+5b_{14}\\
=\;&2\Big[\mu S^*-\alpha V^*+b_{12}+b_{13}+b_{14}\Big]+2\mu V^*\\
&+3\Big[\alpha V^*-b_{12}-b_{13}-b_{14}\Big]+3\Big[\beta_1I^*S^*-b_{12}\Big]\\
&+4\Big[\beta_3T^*S^*-\frac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*\Big]\\
&+4\Big[b_{10}-b_{14}\beta_2C_h^*S^*-b_{13}\Big]\\
&+5\Big[\frac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*-b_{10}\Big]\\
&+3(1-\psi)\beta_1I^*V^*+4\Big[(1-\psi)\beta_3T^*V^*-b_{10}\Big]\\
&+5b_{10}+4(1-\psi)\beta_2C_h^*V^*+4b_{12}\\
&+5b_{13}+5b_{14}\\
=\;&2\mu S^*+2\mu V^*+\alpha V^*+3\beta_1I^*S^*+4\beta_2C_h^*S^*\\
&+4\beta_3T^*S^*+3(1-\psi)\beta_1I^*V^*\\
&+4(1-\psi)\beta_2C_h^*V^*+4(1-\psi)\beta_3T^*V^*\\
&+\frac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*\\
=\;&4(1-b)\Lambda+4\alpha V^*\\
&-4(\beta_1I^*+\beta_2C_h^*+\beta_3T^*)S^*\\
&+4\mu V^*+\alpha V^*+4\beta_1I^*S^*+4\beta_2C_h^*S^*\\
&+4\beta_3T^*S^*+4(1-\psi)\beta_1I^*V^*\\
&+4(1-\psi)\beta_2C_h^*V^*+4(1-\psi)\beta_3T^*V^*\\
&+\frac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*-2\mu S^*\\
&-\beta_1I^*S^*-(1-\psi)\beta_1I^*V^*-2\mu V^*\\
=\;&\alpha V^*+\frac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^*-2\mu S^*\\
&-2\mu V^*+4\Lambda-(\epsilon+\mu)E^*\\
&+(\beta_2C_h^*+\beta_3T^*)(S^*+(1-\psi)V^*)\\
=\;&\alpha V^*+2\Lambda+(\epsilon+\mu)E^*\\
&+\beta_3(S^*+(1-\psi)V^*)T^*\\
&+(S^*+(1-\psi)V^*)\Big(\beta_2+\frac{\beta_3\pi_2}{\mu}\Big)C_h^*\\
&+2\Big[(\Lambda-\mu S^*)-(\mu V^*)-(\epsilon+\mu)E^*\Big]\\
=\;&\alpha V^*+2\Lambda+(\epsilon+\mu)E^*\\
&+\beta_3(S^*+(1-\psi)V^*)T^*\\
&+\Big(S^*+(1-\psi)V^*\Big)\Big(\beta_2+\frac{\beta_3\pi_2}{\mu}\Big)C_h^*
\end{aligned} \qquad (48)
$$

which is the same as the constant term of $F(x_1,x_2,x_3,x_4,x_5,x_6)$.

The constrained conditions in (47) show that the available values of b_{10}, b_{12}, b_{13}, and b_{14} are not unique. Since, $b_1, b_3, b_4, b_5, b_6, b_7$ and b_9 depend on b_{10}, b_{12}, b_{13}, and b_{14}, their values will also be non unique. Using inequalities (47), we can assign different values to $b_i (i = 1, 3, ...14, i \neq 2, 8, 11)$, and hence H can have different forms in following three subregions:

Case 1: $\mu S > \alpha V$, and $\frac{\beta_3}{\mu}(S^*+(1-\psi)V^*)\pi_2C_h^* \leq (1-\psi)\beta_3T^*V^*$.

For Case 1, using equations (46) and (47), choose $b_1 = \mu S^* - \alpha V^*$, $b_3 = \alpha V^*$, $b_4 = \beta_1 I^* S^*$,

$b_5 = \beta_3 T^* S^*$, $b_6 = \beta_2 C_h^* S^*$, $b_7 = 0$, $b_9 = (1-\psi)\beta_3 T^* V^* - \frac{\beta_3}{\mu}(S^* + (1-\psi)V^*)\pi_2 C_h^*$, $b_{10} = \frac{\beta_3}{\mu}(S^* + (1-\psi)V^*)\pi_2 C_h^*$, $b_{12} = 0$, $b_{13} = 0$ and $b_{14} = 0$.

Using these values, and the values of b_2, b_8 and b_{11}, the function $F(x_1, x_2, x_3, x_4, x_5, x_6)$ becomes

$$\begin{aligned}
&F(x_1,x_2,x_3,x_4,x_5,x_6)\\
&= (\mu S^* - \alpha V^*)\Big(2 - x_1 - \frac{1}{x_1}\Big)\\
&+\mu V^*\Big(2 - x_6 - \frac{1}{x_6}\Big)\\
&+\alpha V^*\Big(3 - x_1 - \frac{1}{x_6} - \frac{x_6}{x_1}\Big)\\
&+\beta_1 I^* S^*\Big(3 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_3}{x_2}\Big)\\
&+\beta_3 T^* S^*\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_4}{x_2} - \frac{x_3}{x_4}\Big)\\
&+\beta_2 C_h^* S^*\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_5}{x_2} - \frac{x_3}{x_5}\Big)\\
&+(1-\psi)\beta_1 I^* V^*\Big(3 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_3 x_6}{x_2}\Big)\\
&+\Big((1-\psi)\beta_3 T^* V^*\\
&-\frac{\beta_3}{\mu}(S^* + (1-\psi)V^*)\pi_2 C_h^*\Big) \times\\
&\Big(4 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_4 x_6}{x_2} - \frac{x_3}{x_4}\Big)\\
&+\frac{\beta_3}{\mu}(S^* + (1-\psi)V^*)\pi_2 C_h^*\Big(5 - \frac{1}{x_6} - \frac{x_2}{x_3}\\
&-\frac{x_4 x_6}{x_2} - \frac{x_3}{x_5} - \frac{x_5}{x_4}\Big)\\
&+(1-\psi)\beta_2 C_h^* V^*\Big(4 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_5 x_6}{x_2} - \frac{x_3}{x_5}\Big).
\end{aligned}$$

Case 2: $\mu S = \alpha V$, $\frac{\beta_3}{\mu}(S^* + (1-\psi)V^*)\pi_2 C_h^* \geq (1-\psi)\beta_3 T^* V^*$.

For Case 2, using equations (46) and (47), choose $b_1 = 0$, $b_3 = \alpha V^*$, $b_4 = \beta_1 I^* S^*$, $b_5 = \beta_3(S^* + (1-\psi)V^*)\frac{\pi_1 \kappa I^*}{\mu}$, $b_6 = \beta_2 C_h^* S^*$, $b_7 = \frac{\beta_3}{\mu}(S^* + (1-\psi)V^*)\pi_2 C_h^* - (1-\psi)\beta_3 T^* V^*$, $b_9 = 0$, $b_{10} = (1-\psi)\beta_3 T^* V^*$, $b_{12} = 0$, $b_{13} = 0$ and $b_{14} = 0$.
Using the above values, and the values of b_2, b_8 and b_{11}, the function $F(x_1, x_2, x_3, x_4, x_5, x_6)$ becomes

$$\begin{aligned}
&F(x_1,x_2,x_3,x_4,x_5,x_6)\\
&= \mu V^*\Big(2 - x_6 - \frac{1}{x_6}\Big)\\
&+\alpha V^*\Big(3 - x_1 - \frac{1}{x_6} - \frac{x_6}{x_1}\Big)\\
&+\beta_1 I^* S^*\Big(3 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_3}{x_2}\Big)\\
&+\beta_3 (S^* + (1-\psi)V^*)\frac{\pi_1 \kappa I^*}{\mu} \times\\
&\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_4}{x_2} - \frac{x_3}{x_4}\Big)\\
&+\beta_2 C_h^* S^*\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_5}{x_2} - \frac{x_3}{x_5}\Big)\\
&+\Big(\frac{\beta_3}{\mu}(S^* + (1-\psi)V^*\Big)\pi_2 C_h^*\\
&-(1-\psi)\beta_3 T^* V^*) \times\\
&\Big(5 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_4}{x_2} - \frac{x_3}{x_5} - \frac{x_5}{x_4}\Big)\\
&+(1-\psi)\beta_1 I^* V^*\Big(3 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_3 x_6}{x_2}\Big)\\
&+(1-\psi)\beta_3 T^* V^*\Big(5 - \frac{1}{x_6} - \frac{x_2}{x_3}\\
&-\frac{x_4 x_6}{x_2} - \frac{x_3}{x_5} - \frac{x_5}{x_4}\Big)\\
&+(1-\psi)\beta_2 C_h^* V^*\Big(4 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_5 x_6}{x_2}\frac{x_3}{x_5}\Big).
\end{aligned}$$

Case 3: $\mu S < \alpha V$, $\frac{\beta_3}{\mu}(S^* + (1-\psi)V^*)\pi_2 C_h^* \geq (1-\psi)\beta_3 T^* V^*$.

For Case 3, using equations (46) and (47), we assume that $\alpha V^* \leq \beta_3(S^* + (1-\psi)V^*)\frac{\pi_1 \kappa I^*}{\mu}$ and choose $b_1 = \mu S^*$, $b_3 = 0$, $b_4 = \beta_1 I^* S^*$, $b_5 = \beta_3(S^* + (1-\psi)V^*)\frac{\pi_1 \kappa I^*}{\mu} - \alpha V^*$, $b_6 = \beta_2 C_h^* S^*$, $b_7 = \frac{\beta_3}{\mu}(S^* + (1-\psi)V^*)\pi_2 C_h^* - (1-\psi)\beta_3 T^* V^*$, $b_9 = 0$, $b_{10} = (1-\psi)\beta_3 T^* V^*$, $b_{12} = 0$, $b_{13} = 0$ and $b_{14} = \alpha V^*$.
Using the above values, and the values of b_2, b_8 and b_{11}, the function $F(x_1, x_2, x_3, x_4, x_5, x_6)$ becomes

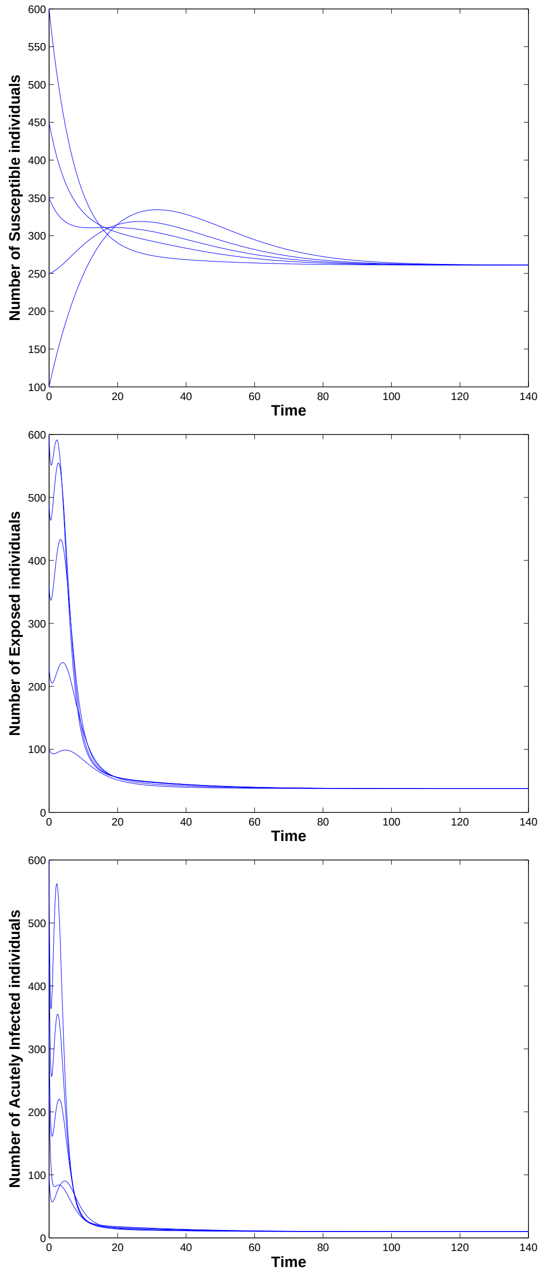
$$\begin{aligned}
&F(x_1,x_2,x_3,x_4,x_5,x_6)\\
&= \mu S^*\Big(2 - x_1 - \frac{1}{x_1}\Big) + \mu V^*\Big(2 - x_6 - \frac{1}{x_6}\Big)\\
&+\beta_1 I^* S^*\Big(3 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_3}{x_2}\Big)\\
&+\Big(\beta_3(S^* + (1-\psi)V^*)\frac{\pi_1 \kappa I^*}{\mu} - \alpha V^*\Big) \times\\
&\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_4}{x_2} - \frac{x_3}{x_4}\Big)\\
&+\beta_2 C_h^* S^*\Big(4 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_5}{x_2} - \frac{x_3}{x_5}\Big)\\
&+\frac{\beta_3}{\mu}(S^* + (1-\psi)V^*)\pi_2 C_h^* - (1-\psi)\beta_3 T^* V^*\\
&\Big(5 - \frac{1}{x_1} - \frac{x_2}{x_3} - \frac{x_1 x_4}{x_2} - \frac{x_5}{x_4} - \frac{x_3}{x_5}\Big)
\end{aligned}$$

$$+(1-\psi)\beta_1 I^* V^* \Big(3 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_3 x_6}{x_2}\Big)$$
$$+(1-\psi)\beta_3 T^* V^* \times$$
$$\Big(5 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_4 x_6}{x_2} - \frac{x_3}{x_5} - \frac{x_5}{x_4}\Big)$$
$$+(1-\psi)\beta_2 C_h^* V^* \times$$
$$\Big(4 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_5 x_6}{x_2} - \frac{x_3}{x_5}\Big)$$
$$+\alpha V^* \Big(5 - \frac{1}{x_6} - \frac{x_2}{x_3} - \frac{x_1 x_4}{x_2} - \frac{x_3}{x_4} - \frac{x_6}{x_1}\Big).$$

Since, the arithmetic mean is greater than or equal to the geometric mean, $F(x_1, x_2, x_3, x_4, x_5, x_6) \leq 0$ in each of the above three cases. The equality holds only when $x_1 = 1, x_6 = 1$, and $x_2 = x_3 = x_4 = x_5$, i.e.,

$$\{(x_1, x_2, x_3, x_4, x_5, x_6) \in \Delta : \\ F(x_1, x_2, x_3, x_4, x_5, x_6) = 0\} \\ = \left\{ (x_1, x_2, x_3, x_4, x_5, x_6) \mid \begin{array}{l} x_1 = x_6 = 1, \\ x_2 = x_3 \\ = x_4 = x_5 \end{array} \right\}.$$

This corresponds to the set $\Delta' = \{(S, E, I, T, C_h, V) : S = S^*, V = V^*, E/E^* = I/I^* = T/T^* = C_h/C_h^*\} \in \Delta$. Hence, the maximum invariant set of (1) on the set Δ' is the singleton $\{P^*\}$. Therefore, by LaSalle's Invariance principle, the endemic equilibrium P^* is globally stable in Δ when $\rho = 0$ and $\sigma = 0$. This result is illustrated by simulating the model (1) using a reasonable set of parameter values given in Table 1. The plot shows that the disease persists in the population (Fig. 4).



3 Conclusion

This paper presents a deterministic model for the transmission dynamics of Hepatitis C virus infection. The formulated model, realistically, allows HCV transmission by acutely and chronically infected individuals. Most importantly, the model includes a compartment of vaccinated individuals, and considers the effect of a waning vaccine on the transfer of individuals from one compartment to another. The model was rigorously analyzed to gain insights into its qualitative dynamics. We obtained the following results:

1. The model has a locally stable disease free equilibrium whenever the associated reproduction number is less than unity.
2. The model exhibits the phenomenon of backward bifurcation, suggesting a case where stable disease-free equilibrium co-exists with a stable endemic equilibrium whenever the basic reproductive number is less than unity.
3. Using an imperfect vaccine would have no positive epidemiological impact to reduce disease burden in the community.
4. Using a perfect vaccine can result in effective elimination of HCV infection in a community, that is, the efficacy of the vaccine should be 100% for complete removal of the disease.

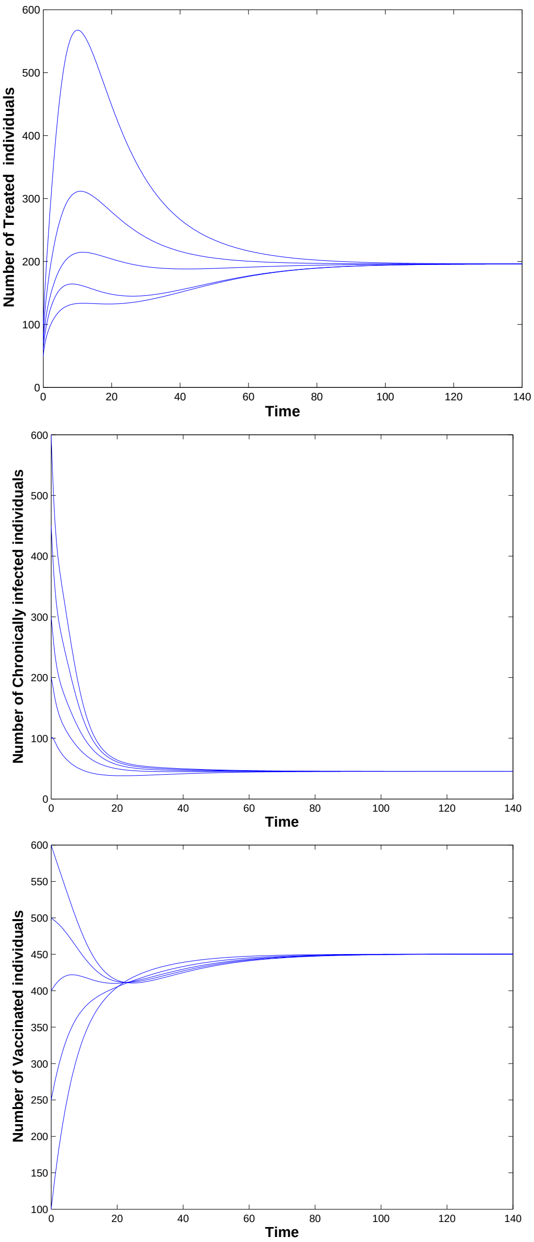


Figure 4: Simulation of system (1), showing the total number of susceptible, exposed, acutely infected, chronically infected, treated and vaccinated individuals as a function of time (years) when $R_0 > 1$. Parameter values are given in Table 1, with $\psi = 0.6$, $\rho = 0$, $\sigma = 0$, $\beta_1 = 0.0009$, $\beta_2 = 0.0006$, and $\beta_3 = 0.0001$. The numerical simulation shows that the disease persists when $R_0 > 1$.

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