American Journal of Computational and Applied Mathematics 2015, 5(1): 11-17
DOI: 10.5923/j.ajcam.20150501.03

Optimal Control Analysis of HCV Disease in a Community with Inflow of Infected Immigrants

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Abstract This paper considers an optimal control analysis for HCV model by incorporating education, health care, immunization, screening of immigrants and treatment in the model. The goal is to minimize the spread of HCV disease in the community with inflow of infected immigrants and to minimize the costs of control strategies. In this context, the existence of an optimal control is proved. The results show that the effective use of optimal screening of immigrants together with education, health care, immunization and treatment has a significant impact in reducing the spread of the disease in the community.

Keywords Infections by Immigrants, Pontryagins maximum principle, Control Strategies, Optimal control of HCV

1. Introduction

Hepatitis C a most common viral infection of the liver is usually caused by hepatitis C virus. Hepatitis C virus (HCV) was first identified in the year 1989 [9]. An estimated 170 million people worldwide (3% of the world's population) are now thought to be HCV chronic carriers. It is also estimated that 85% of the individuals exposed to HCV develop chronic hepatitis C, of which about 15% have the possibility to clear the virus spontaneously within a few months of infection [9] Most common avenues through which HCV is spread are unprotected sex, sharing of contaminated needles among drug addicts and those with other STDs. Some people also get this virus from tattoo and piercing salons. It is also possible to contract HCV at birth, as it can be transmitted from mother to baby. As a matter of fact, Hepatitis C virus in pregnancy is emerging and today it is becoming an increasing source of concern [4].

Mathematical modelling of the spread of infectious diseases continues to become an important tool in understanding the dynamics of diseases and in decision making processes regarding diseases intervention programs for disease in many countries. For instance, [1] formulated and analysed a mathematical model on the effect of Treatment and Infected Immigrants on the spread of Hepatitis C Virus disease at Acute and Chronic stages. [3] investigated the dynamic behaviour of an SEI (Susceptible-Exposed- Infective) model with acute and chronic stages.

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Published online at http://journal.sapub.org/ajcam

Optimal control theory has found wide-ranging applications in biological and ecological problems [6]. Specifically, there have been various studies of epidemiological models where optimal control methods have been applied. [8] used optimal control theory to determine the optimal timing and intensity of an HCV antiviral treatment programme for active injecting drug users (IDUs) with a variety of policy objectives, budget constraints, and prevalence settings. [2] determined an optimal treatment strategy using interferon and ribavirin, through mathematical modelling. [9] considered a deterministic multipatch hepatitis C virus model in order to study the impact of movement between the patches and optimal control movement of infectives and treatments on the transmission dynamics of the disease. Studies conducted so far have not focused on the use of optimal control theory to minimize the cost of the control strategies (education, health care, immunization, screening of immigrants and treatment) of HCV disease. The main outputs of these findings will be minimum spread of HCV disease, costs, contribution to the design of public health policy, suggestion on future research and decision framework for programme implementation.

2. Optimal Control Analysis

The model sub-divides the total human population at time t, denoted by $N(t)$, into sub-populations of susceptible individuals $S(t)$, exposed individuals (infected but not infectious) $E(t)$, individuals with acute infection (initially infected) $A(t)$, chronic infected individuals (infectious individuals) $C(t)$ and recovered individuals $R(t)$. Total

population at time t is given by

$$N(t) = S(t) + E(t) + A(t) + C(t) + R(t) \quad (1)$$

The interaction between the classes will be assumed as follows: exposed (E), acute infected (I) and chronic infected (V) immigrants enter into the population with the rates π_1, π_2, π_3 respectively. Susceptible individuals contacts with acute and chronic infected individuals at rates $\beta_i\ (i = 1,2)$ respectively. Susceptible individuals acquire HCV infection following contact with an active infectious individual at a rate

$$\upsilon = \frac{(\beta_1 A + \beta_2 C)}{N}.$$

The exposed individuals develop to acute infected group at a rate θ while acute infective develop to chronic group at a rate k_1 and exposed individuals move to chronic class at the rate k_2. The infectious individuals recovered at a rate ρ, and recovered individual loses immunity and become immediately susceptible again at a rate σ. Acute and chronic infected individuals undergo death due to the disease at the rate a and d respectively.

It is assumed that the rate of contact of susceptibles with chronic individuals is much less than acute infectives $(\beta_2 \le \beta_1)$ because on chronic stage people become aware of their infection and may choose to use control measures and change their behaviour and thus may contribute little in spreading the infection.

Taking into account the above considerations, the model will be governed by the following system of equations:

$$\begin{aligned}
\frac{dS}{dt} &= Q(1-\pi_1-\pi_2-\pi_3) - \upsilon S + \sigma R - \mu S \\
\frac{dE}{dt} &= Q\pi_1 + \upsilon S - (\theta + k_2 + \mu)E \\
\frac{dA}{dt} &= Q\pi_2 + \theta E - (k_1 + \rho_1 + a + \mu)A \\
\frac{dC}{dt} &= Q\pi_3 + k_2 E + k_1 A - (\rho_2 + d + \mu)C \\
\frac{dR}{dt} &= \rho_1 A + \rho_2 C - (\sigma + \mu)R
\end{aligned} \quad (2)$$

with nonnegative initial conditions and $N(0) > 0$.

We introduce into the model (2), time dependent preventive (u_1, u_2, u_3) efforts as controls to minimize the spread of the disease. We wish to minimize the spread of HCV disease, as well as minimizing the cost associated with control strategies. For effective control to be achievable in a finite time, we need to consider time dependent controls. We then proceed by applying Pontryagins maximum principle to determine the conditions for effective control in finite time. We introduce into the model (2), education, health care, immunization (u_1), screening of immigrants (u_2) and treatment (u_3) as time dependent controls to curtail the spread of HCV disease. The model (2) becomes

$$\begin{aligned}
\frac{dS}{dt} &= Q(1-u_2\pi_1-u_2\pi_2-u_2\pi_3) - (1-u_1)\upsilon S + \sigma R - \mu S \\
\frac{dE}{dt} &= Qu_2\pi_1 + (1-u_1)\upsilon S - (\theta + k_2 + \mu)E \\
\frac{dA}{dt} &= Qu_2\pi_2 + \theta E - (k_1 + u_3\rho_1 + a + \mu)A \\
\frac{dC}{dt} &= Qu_2\pi_3 + k_2 E + k_1 A - (u_3\rho_2 + d + \mu)C \\
\frac{dR}{dt} &= u_3\rho_1 A + u_3\rho_2 C - (\sigma + \mu)R
\end{aligned} \quad (3)$$

Here,

$$\upsilon = \frac{(\beta_1 A + \beta_2 C)}{N}$$

where $0 \le u_2 \le 1$, is the screening control, $0 \le u_1 \le 1$ is the control on education, healthcare and immunization and $0 \le u_3 \le 1$, is the treatment control for $t \in [0,T]$. To investigate the optimal level of efforts that would be needed to control the disease, we form the objective function J, which is to minimize the spread of the disease and the cost of applying the control u_1 ,u_2 and u_3.

$$J = \min \int_0^T \left(B_1 E + B_2 A + B_3 C + \frac{A_1 {u_1}^2}{2} + \frac{A_2 {u_2}^2}{2} + \frac{A_3 {u_3}^2}{2} \right) dt \quad (4)$$

where B_1, B_2, B_3, A_1, A_2 and A_3 are positive weights. The terms $A_1 {u_1}^2$, $A_2 {u_2}^2$ and $A_3 {u_3}^2$ are the costs associated with u_2 (screening of immigrants), u_1 (education, health care and immunization) and u_3 (treatment). With the given objective function $J(u_1, u_2, u_3)$, our goal is to minimize the spread of the disease, while minimizing the cost of controls $u_1(t), u_2(t)$ and $u_3(t)$. We thus seek an optimal control triple ${u_1}^*$, ${u_2}^*$and ${u_3}^*$ such that

$$J({u_1}^*, {u_2}^*, {u_3}^*) = \min \{ J(u_1, u_2, u_3) \mid u_1, u_2, u_3 \in u \} \quad (5)$$

Here $u = \{u_1, u_2, u_3\}$ such that u_1, u_2, u_3 are measurable with $0 \le u_1 \le 1$, $0 \le u_2 \le 1$ and $0 \le u_3 \le 1$ for $t \in [0,T]$ is the control set. The necessary conditions that an optimal control problem must satisfy come from Pontryagin's maximum principle [10]. This principle converts (3)-(4) into a problem of minimizing pointwise a

Hamiltonian H , with respect to u_1, u_2 and u_3

$$\begin{aligned} H &= B_1E + B_2A + B_3C + \frac{A_1{u_1}^2}{2} + \frac{A_2{u_2}^2}{2} + \frac{A_3{u_3}^2}{2} + \\ &\lambda_S\left\{Q\left(1-u_2\pi_1-u_2\pi_2-u_2\pi_3\right)-\left(1-u_1\right)\upsilon S+\sigma R-\mu S\right\} \\ &+\lambda_E\left\{Qu_2\pi_1+\left(1-u_1\right)\upsilon S-\left(\theta+k_2+\mu\right)E\right\} \\ &+\lambda_A\left\{Qu_2\pi_2+\theta E-\left(k_1+u_3\rho_1+a+\mu\right)A\right\} \\ &+\lambda_C\left\{Qu_2\pi_3+k_2E+k_1A-\left(u_3\rho_2+d+\mu\right)C\right\} \\ &+\lambda_R\left\{u_3\rho_1A+u_3\rho_2C-\left(\sigma+\mu\right)R\right\} \end{aligned} \quad (6)$$

Where the λ_S, λ_E, λ_A, λ_C and λ_R are the adjoint variables or co-state variables. By applying Pontryagin's maximum principle [10] and the existence result for the optimal control from [3], we obtain

Proposition1. For optimal control triple ${u_1}^*, {u_2}^*$ and ${u_3}^*$ that minimizes $J\left(u_1,u_2,u_3\right)$ over u , then there exist adjoint variables λ_S, λ_E, λ_A, λ_C and λ_R satisfying.

$$\begin{aligned} -\frac{d\lambda_S}{dt} &= \left(\left(1-u_1\right)\upsilon+\mu\right)\lambda_s-\left(1-u_1\right)\upsilon\lambda_E \\ -\frac{d\lambda_E}{dt} &= -\beta_1+\left(\theta+k_2+\mu\right)\lambda_E-\theta\lambda_A-k_2\lambda_C \\ -\frac{d\lambda_A}{dt} &= -\beta_2+\left(k_1+u_3\rho_1+a+\mu\right)\lambda_A-k_1\lambda_C-u_3\rho_1\lambda_R \\ &+\left(1-u_1\right)\frac{\beta_1}{N}S\lambda_S-\left(1-u_1\right)\frac{\beta_1}{N}S\lambda_E \\ -\frac{d\lambda_C}{dt} &= -\beta_3+\left(u_3\rho_2+d+\mu\right)\lambda_C \\ &+\left(1-u_1\right)\frac{\beta_2}{N}S\lambda_S-\left(1-u_1\right)\frac{\beta_2}{N}S\lambda_E-u_3\rho_2\lambda_R \\ -\frac{d\lambda_R}{dt} &= -\sigma\lambda_S+\left(\sigma+\mu\right)\lambda_R \end{aligned} \quad (5)$$

and with transversality conditions

$$\lambda_S(T)=\lambda_E(T)=\lambda_A(T)=\lambda_C(T)=\lambda_R(T)=0 \quad (6)$$

and by optimality conditions;

$${u_1}^* = \max\left\{0,\min\left(1,\ \bar{u}_1\right)\right\},$$

$${u_2}^* = \max\left\{0,\min\left(1,\ \bar{u}_2\right)\right\}.\ \text{and}$$

$${u_3}^* = \max\left\{0,\min\left(1,\ \bar{u}_3\right)\right\}.$$

To find $\bar{u}_1$, $\bar{u}_2$ and $\bar{u}_3$ we first solve the optimality conditions given by

$$\frac{\partial H}{\partial u_1}=0,\ \ \frac{\partial H}{\partial u_2}=0 \text{ and } \frac{\partial H}{\partial u_3}=0 \quad (7)$$

We differentiate equestion (6) with respect to u_1, u_2 and u_3 to get

$$\frac{\partial H}{\partial u_1} = A_1u_1+\lambda_s\left(\frac{\beta_1A+\beta_2C}{N}\right)S-\lambda_E\left(\frac{\beta_1A+\beta_2C}{N}\right)S \quad (8)$$

$$\frac{\partial H}{\partial u_2} = A_2u_2-\lambda_SQ\left(\pi_1+\pi_2+\pi_3\right)+\lambda_E\pi_1Q+\lambda_A\pi_2Q+\lambda_C\pi_3Q$$

$$\frac{\partial H}{\partial u_3} = A_3u_3-\rho_1A\lambda_A-\rho_2C\lambda_C+\rho_1A\lambda_R+\rho_2C\lambda_R$$

We therefore solve for u_1, u_2 and u_3 by equating $\frac{\partial H}{\partial u_1}=0$, $\frac{\partial H}{\partial u_2}=0$ and $\frac{\partial H}{\partial u_3}=0$ as described by Lenhart and Workman (2002).

By equating system (8) to zero we obtain

$$u_1 = \left(\lambda_E-\lambda_S\right)\left(\frac{\beta_1A+\beta_2C}{NA_1}\right)S$$

$$u_2 = \frac{\lambda_SQ\left(\pi_1+\pi_2+\pi_3\right)-\lambda_E\pi_1Q-\lambda_A\pi_2Q-\lambda_C\pi_3Q}{A_2} \quad (9)$$

$$u_3 = \frac{\rho_1A\lambda_A+\rho_2C\lambda_C-\rho_1A\lambda_R-\rho_2C\lambda_R}{A_3}$$

From the system (9) then $\bar{u}_1=u_1$, $\bar{u}_2=u_2$ and $\bar{u}_3=u_3$. Hence the optimality conditions is written as

$${u_1}^* = \max\left\{0,\min\left(1,\left(\lambda_E-\lambda_E\right)\left(\frac{\beta_1A+\beta_2C}{NA_1}\right)S\right)\right\}$$

$${u_2}^* = \max\left\{0,\min\left(1,\left(\frac{\lambda_SQ\left(\pi_1+\pi_2+\pi_3\right)-\lambda_E\pi_1Q}{-\lambda_A\pi_2Q-\lambda_C\pi_3Q}\right)\right)\right\}$$

$${u_3}^* = \max\left\{0,\min\left(1,\left(\frac{\rho_1A\lambda_A+\rho_2C\lambda_C-\rho_1A\lambda_R-\rho_2C\lambda_R}{A_3}\right)\right)\right\} \quad (10)$$

By standard control arguments involving the bounds on the controls, we conclude similarly as Okosun (2012) that

$${u_1}^* = \begin{cases} 0 & \text{if} \quad \bar{u}_1\le 0 \\ \bar{u}_1 & \text{if} \quad 0<\bar{u}_1<1 \\ 1 & \text{if} \quad \bar{u}_1\ge 1 \end{cases}, {u_2}^* = \begin{cases} 0 & \text{if} \quad \bar{u}_2\le 0 \\ \bar{u}_2 & \text{if} \quad 0<\bar{u}_2<1 \\ 1 & \text{if} \quad \bar{u}_2\ge 1 \end{cases} \text{ and}$$

$${u_3}^* = \begin{cases} 0 & \text{if} \quad \bar{u}_3\le 0 \\ \bar{u}_3 & \text{if} \quad 0<\bar{u}_3<1 \\ 1 & \text{if} \quad \bar{u}_3\ge 1 \end{cases} \quad (11)$$

According to the prior boundedness of the state system, the adjoint system and the resulting Lipschitz structure of the ODEs, we obtain the uniqueness of the optimal control for small T. The uniqueness of the optimal control follows from the uniqueness of the optimality system, which consist of equations (5) and (6) and transversality condition with characterization (10).

There is a restriction on the length of time interval in order to guarantee the uniqueness of the optimality system. This smallness restriction of the length on the time due to the opposite time orientations of (5) and (6); the state problem has initial values and the adjoint problem has final values. This restriction is common in control problems [see 5, 6, 7]

3. Simulation for the Optimal Control Problem

In this section, we study numerically an optimal transmission parameter control for the HCV model. In order to study the effects of control u_2 (screening rate) and control u_1 (education, health care and immunization) and u_3 (treatment) on transmission dynamics of HCV infection, the numerical simulations of the model (3) are carried out using the following set of estimated values: β_1=0.38, β_2 =0.001, θ =0.5, k_1 =0.5, k_2 =0.34, ρ_1 =[0.02-0.5], ρ_2 =[0.002-0.45], σ =[0.13-0.5], a =0.0034, d =0.5, μ =[0.0001-0.09], Q = [5-85], π_1 = [0.4-0.6], π_2 =0.2, π_3 =0.03, N = [2-15]. Assume the weights at final time are being kept fixed as, $B_1 = 5$, $B_2 = 20$, $B_3 = 15$, $A_1 = 10$, $A_2 = 7$, to illustrate the effect of various optimal strategies on the transmission dynamics of HCV.

Figure (1) shows the simulation of the model with control u_1 (education, health care and immunization) and screening of immigrants (u_2)

The screening control u_2 and the education, health care, immunization (u_1) are used to optimize the objective functional J while we set the treatment u_3, to zero . We observed in figure 1(A) that due to the control strategies, the number of exposed population decreases while the population of exposed increases when there is no control. A similar decrease is observed in figure 1 (B) and (C) for infectious population in the presence of control strategies while an increased number is observed for the uncontrolled case. The control profile is shown in figure 1(D) we see that the optimal education, health care, immunization u_1 is at the upper bound, till the time $T = 4.7$ years before dropping to the lower bound while the optimal screening u_2 is at the lower bound till the final time. It observed that u_2 did not contribute meaningfully to the elimination of the disease except that it increases the control operational cost. Hence for cost effectiveness and disease optimal control strategy u_1 seems sufficient. These results show that in the presence of screening rate without education, health care and immunization, the community is not disease free and a stable endemic situation exists. Therefore, an effective and optimal screening in the population together with education, health care and immunization will be beneficial to the community for the control of HCV disease.

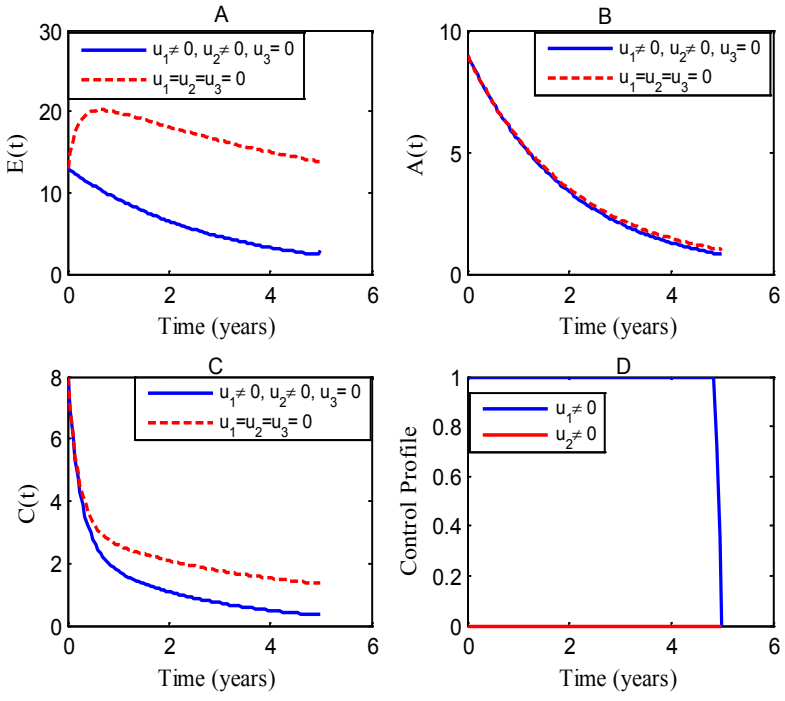

Figure 1. Simulations of the model showing the effects of education, health care, immunization (u_1) and screening (u_2) on the spread of HCV

Figure (2) shows the simulation of the model with screening u_2 and treatment (u_3)

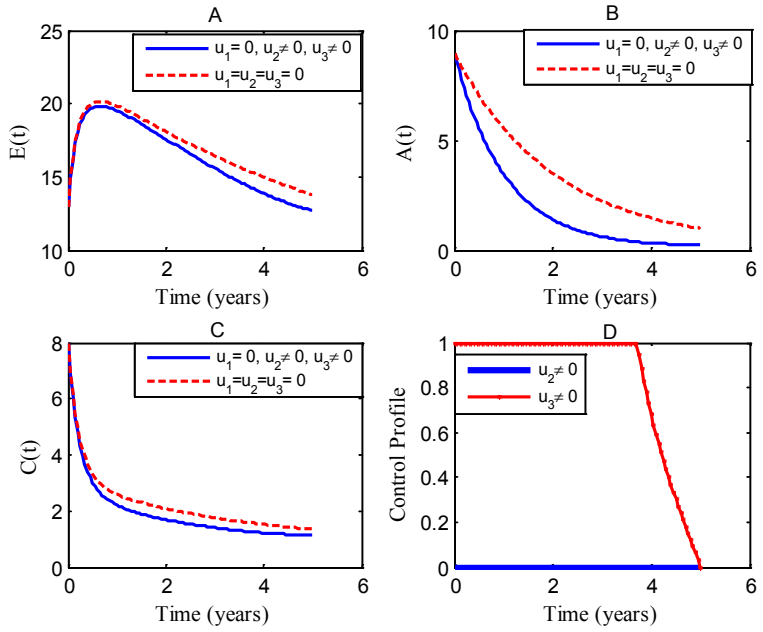

Figure 2. Simulations of the model showing the effects of screening (u_2) and treatment (u_3) on the spread of HCV

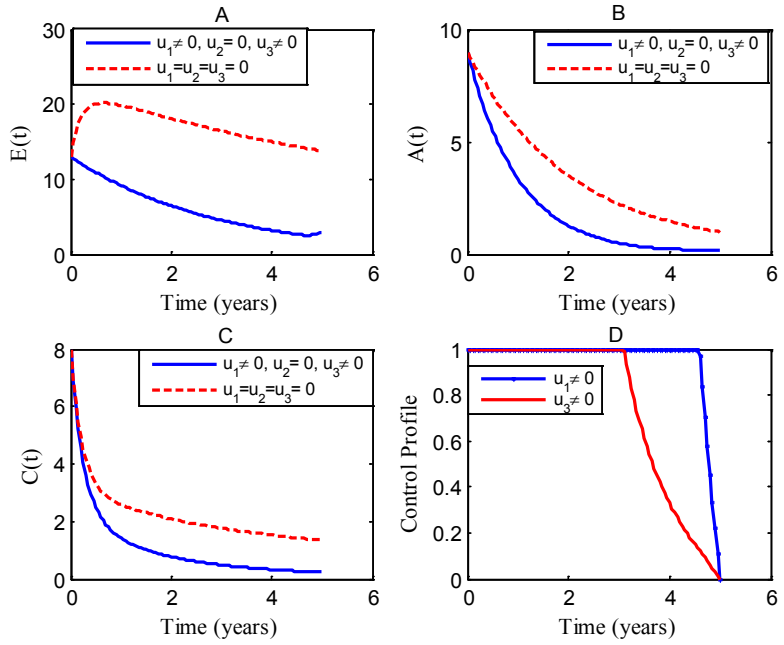

Figure 3. Simulations of the model showing the effects of education, health care, immunization (u_1) and treatment (u_3) on the spread of HCV

The use of screening control u_2 and the treatment u_3 are used to optimize the objective functional J while we set, education, health care, immunization u_1 to zero. In figure (2), the results show a significant difference in the number of exposed humans E, acute infected humans A and chronic infected humans C with optimal strategy compared to E, A and C without control. Specifically, we observed in fig. 2(A) that the control strategies lead to a decrease in the number of exposed humans E as against increases in the uncontrolled case. Similarly in figure 2(B) and (C), the uncontrolled case resulted in increased number of acute infected humans A and chronic infected humans while the control strategy lead to a decrease in the number of infected humans.

Figure (3) shows the simulation of the model where by

controls u_1 and u_3 are optimized.

We optimize the objective function J using the education, health care, immunization u_1 and treatment u_3 while the screening of immigrants control u_2 is set to zero. The results in figure 3(A-C) show a significance difference in the numbers of exposed and infectious humans with optimal strategy compared to the number without controls. Due to the control strategies, the number of exposed population decreses while the population of exposed increases when there is no control. In figure 3(B) and (C), the infectious population decrease in the presence of control strategies while an incresed number is observed for the uncontrolled case. From the control profile shown in figure 3(D), the results suggests control on education, health care, immunization u_1 to be at the upper bound for 4.5 years before dropping gradually to the lower bound while the control on treatment u_3 to be at the upper bound for 3.7 yrs before dropping gradually to the lower bound at final time.

Figure (4) shows the simulation of the model where by both controls u_1, u_2 and u_3 are optimized.

We use all the three controls, education, health care, immunization (u_1), screening of immigrants u_2 and treatment u_3 to optimize the objective functional J. We observed in figure 4(A-C) that the control strategies resulted in a decrease in the numbers of exposed E, acute infected A and chronic infected C while there is increases in the numbers of E, A and C in the uncontrolled cases. The control profile in figure 4(D) suggests that education, health care, immunization u_1 to be at the upper bound for 4.5 years before dropping gradually to the lower bound while the control on treatment u_3 to be at the upper bound for 3.7 years before dropping gradually to the lower bound at final time. The optimal screening u_2 is at the lower bound till the final time. These results show that in the presence of screening rate without education, health care, immunization and treatment, the community is not disease free and a stable endemic situation exists. Therefore, an effective and optimal screening in the population with education, health care, immunization and treatment will be beneficial to the community for the control of HCV disease.

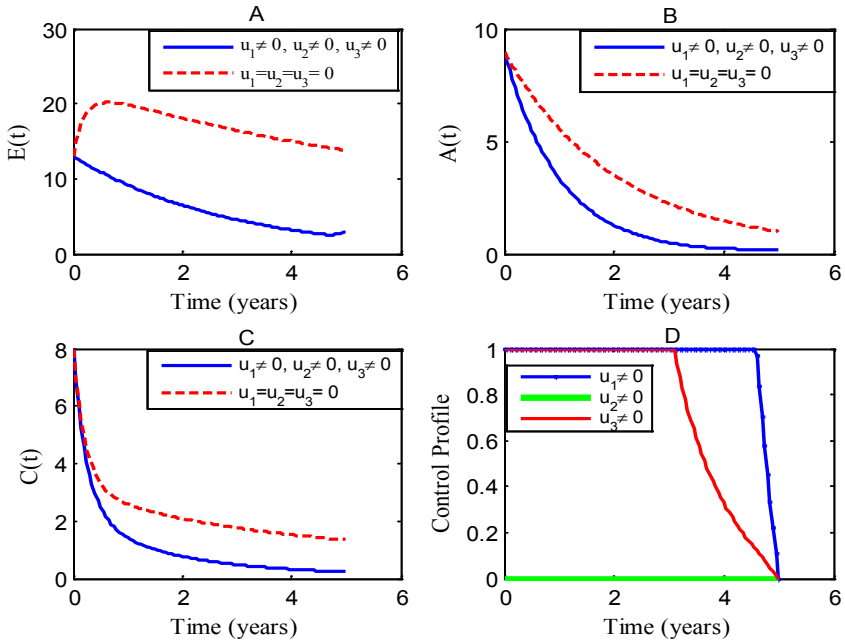

Figure 4. Simulations of the model showing the effects of all controls on spread of HCV

Table 1. The different final states and total cost

Strategy	$E(t)$	$A(t)$	$C(t)$	$R(t)$	Total Cost
$J(0,0,0)$	13.7829	0.9890	1.3460	0.6591	$1.0997e^{+004}$
$J(u_1^*, u_2^*, u_3^*)$	2.9999	0.1522	0.2555	2.3383	$3.0003e^{+003}$

From figures (1-4) and table 1, it is clear that the spread of the disease decreased and the total cost is also decreased by the optimal control policy.

From Table (1), it is noted that when both controls are set to zero $(u_1 = u_2 = 0)$, the cost of the objective function is much ($1.0997e^{+004}$) while the total cost is small ($3.0003e^{+003}$) when all controls $(u_1 \ u_2 \text{ and } u_3)$ are used to optimize the objective function J. It is shown that the spread of the decreses when all controls are optimized decreases at final time compared to the case without control. All controls $(u_1 \ u_2 \text{ and } u_3)$ result in a significant increase in the number of recovered individuals at the final time compared to the uncontrolled case.

4. Conclusions

In this paper, we performed optimal control analysis for HCV model. Using Pontryagin's maximum principle we derived and analyzed the conditions for optimal control of the disease with effective use of education, health care, immunization, screening of immigrants and treatment. The results suggest that the effective optimal screening of immigrants together with education, health care, immunization and treatment has a significant impact in reducing the spread of the disease.

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