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An Optimal control approach to Transmission Dynamics of Hepatitis B Virus

KEYWORDS: Hepatitis B; Horizontal transmission; optimal control; Vertical transmission.

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ABSTRACT *Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV) and is a major global health problem. In this paper, we focus on the dynamics of HBV by applying optimal control theory for the model by using control policies. The optimal control is obtained by solving the optimality system of nonlinear ordinary differential equations with initial conditions. We take the controls as time dependent and obtain the optimal control strategy to minimize individuals and the associated costs. The results are analyzed and interpreted numerically using MATLAB (R2011a). The results reflect that simultaneous use of two control policies is more effective at reducing the number of secondary infections than the use of single control policies.*

1. Introduction

Hepatitis B is an infectious liver disease. It is characterized by inflammation of the liver and is caused by HBV. Infections of HBV occur only if the virus is able to enter the blood stream and reach the liver. HBVinfection is a global health problem and it is estimated by the World Health Organization (WHO), approximately one-third of the world population has been infected with HBV with serological evidence of past or present infection with HBV. Of the approximately 2 billion people who have been infected worldwide, more than 350 million (5–7% of the world's population) suffer from chronic HBV infection [1-5]. Approximately 15–40% of patients infected with HBV will develop life-threatening liver consequences (including cirrhosis, liver failure and hepatocellular carcinoma) resulting in 600,000 to 1.2 million deaths per year due to HBV.India has over 40 million HBV carriers and accounts for 10–15% of the entire pool of HBV carriers of the world. Of the 25 million infants born every year in India, it is estimated that over 1 million run the lifetime risk of developing chronic HBV infection. Every year over 100,000 Indians die due to illnesses related to HBV infection [6- 8].HBVaffects many people and ranks behind HIV as the tenth leading cause of death in the world.

This infection has two possible phases: (1) acute and (2) chronic. Acute hepatitis B infection lasts less than six months. If the disease is acute, the immune system is usually able to clear the virus from the body, and will recover completely within a few months. Most people who acquire hepatitis B as adults have an acute infection.Chronic hepatitis B infection lasts six months or longer.

Most infants infected with HBV at birth and many children infected between 1 and 6 years of age become chronically infected. About two-thirds of people with chronic HBV infection are chronic carriers. These people do not develop symptoms, even though they harbor the virus and can transmit it to other people.The remaining one-third develops active hepatitis, a disease of the liver that can be very serious. More than 240 million people have chronic liver infections. About 600 000 people die every year due to the acute or chronic consequences of HBV[9].

In highly endemic areas, HBV is most commonly spread from mother to child at birth (vertical transmission), or through horizontal transmission (exposure to infected blood), especially from an infected child to an uninfected child during the first 5 years of life. The development of chronic infection is very common in infants infected from their mothers or before the age of 5 years.

An epidemiological model has become important tool and helps to capture infection or disease transmission by analyzing the spread and control of infectious diseases. Several mathematical models have been formulated on the HBVtransmission.

A mathematical model is developed to eliminate the HBV in NewZealand in 2008 [10]. Simple mathematical model is used to illustrate the effect of carriers on the transmission of HBV [11]. An age structure model was proposed to predict the dynamics of HBVtransmission and evaluate the long-term effectiveness of the vaccination program in China [12]. A model to describe waning of immunity after sometime has been studied by a number of authors [13-16].

The powerful way to target epidemic outbreaks is the optimal control. It is based on defining a strategy to control the system and obtaining the best possibleoutcome. In particular, one can look for the optimal response for a vaccinationschedule that will minimize the disease burden while being mindful of the costs ofthe strategy. The starting point for the applications of optimal control theory to epidemic models has been studied [17-20]. A mathematical model has been developed to explore the impact of vaccination and other controlling measures of HBV infection. Optimal control theory is applied to study the infectiousdiseases [21-23].

One of the main reasons for studying HBV is to improve control and decreases the infectious individuals which include vaccination, education, screening of blood and blood products; and treatment. In this paper, we study the transmission dynamics of HBV infection considering the vaccination and treatment control policies where HBV infection is transmitted in two ways through vertical and horizontal transmission. The horizontal transmission can be reduced through vaccination control strategy for the susceptible individuals, while the vertical transmission can be reduced by giving treatment control for the infectious individuals. Therefore vaccination and treatment policies play different role in controlling the spread of HBV.

In this study, we mainly focus on the changes in HBV by applying optimal control as vaccination and treatment for the model which explains the spread of disease in both horizontal and vertical directions. The optimal control is obtained by solving the optimality system of nonlinear ordinary differential equations with initial conditions. We take the controls as time dependent and obtain the

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optimal control strategy to minimize the acute and carrier individuals and also the associated costs.

The paper is organized as follows. In section 2 optimal control HBV model is formulated. Section 3 is devoted to optimal control analysis of the model. Numerical illustrations have been discussed in section 4.Finally section 5 deals with the conclusion.

2. Model Formulation

In the present paper, we consider an optimal control compartmental model based on the characteristics of Hepatitis B Virus model with vertical and horizontal transmission [24]. We have considered two optimal control strategies i.e. vaccination and treatment controls to prevent the spread of HBV. We divide the total population into five compartments, susceptible individuals $S(t)$,exposed $E(t)$,Acute $A(t)$, Carrier $C(t)$, Immunity class $Z(t)$,with control measures as $V(t)$ as vaccinated individuals and $M(t)$ as treated individuals. The flow chart of compartmental model is shown in Fig.1. The optimal control of HBV model with two control strategies is given by the following nonlinear differential equations

$$\frac{dS(t)}{dt} = \delta\pi\big(1-\eta C(t)\big) - \delta S(t) - \beta\big(A(t)+\kappa C(t)\big)S(t) + \delta_0 Z(t) - u_1 S(t)$$
$$\frac{dE(t)}{dt} = \beta\big(A(t)+\kappa C(t)\big)S(t) - \delta E(t) + \delta\pi\,\eta C(t) - \gamma_1 E(t)$$
$$\frac{dA(t)}{dt} = \gamma_1 E(t) - \delta A(t) - q\gamma_2 A(t) - (1-q)\gamma_1 A(t) \qquad (1)$$
$$\frac{dC(t)}{dt} = q\gamma_2 A(t) - \delta C(t) - \gamma_3 C(t) - u_2(t)C(t)$$
$$\frac{dZ(t)}{dt} = \gamma_3 C(t) + (1-q)\gamma_1 A(t) - \delta_0 Z(t) - \delta Z(t) + \delta(1-\pi) + u_1 S(t) + u_2(t)C(t)$$

Subject to the initial conditions,

$$S(0) \geq 0, \quad E(0) \geq 0, \qquad A(0) \geq 0, \quad C(0) \geq 0, \quad Z(0) \geq 0$$

In the above equations, we assume the population is stable with same birth rate and death rate as δ and disease induced death rate is not considered. γ_1 is the rate of exposed individuals becoming infectious. γ_2 is the rate at which exposed individuals move to acute infectious class. γ_3 is the flow of carrier to Immunity class, β transmission coefficient, κ represents the carrier infectiousness to acute infection q is the proportion of acute individuals that become carrier, δ_0 represent the loss of immunity rate and the individual become the susceptible again, η is the unimmunized children born to carriermothers, π represents the failure of immunization $\delta(1-\pi)$ measures the successful immunization ofnewborn babies, and the term $\delta\pi(1-\eta\ C(t)$ shows that thenewborns are unimmunized and become susceptible again.We assume that the total population size is equal to 1,The sum of the totalpopulation is *S(t) + E(t) + A(t) + C(t) + V(t) + M(t) = 1.*

We ignore thefifth equation in system (1); so, the new model becomes

$$\frac{dS(t)}{dt} = \delta\pi\big(1-\eta C(t)\big) - \delta S(t) - \beta\big(A(t)+\kappa C(t)\big)S(t) + \delta_0(1 - S(t) + E(t) + A(t) + C(t)) - u_1 S(t)$$
$$\frac{dE(t)}{dt} = \beta\big(A(t)+\kappa C(t)\big)S(t) - \delta E(t) + \delta\pi\,\eta C(t) - \gamma_1 E(t)$$
$$\frac{dA(t)}{dt} = \gamma_1 E(t) - \delta A(t) - q\gamma_2 A(t) - (1-q)\gamma_1 A(t) \qquad (2)$$
$$\frac{dC(t)}{dt} = q\gamma_2 A(t) - \delta C(t) - \gamma_3 C(t) - u_2(t)C(t)$$

3. Optimal Control Analysis

In the above model we have considered two control measures that is vaccination and treatment controls. $u_1(t)$ is the proportion of the susceptible individuals that are vaccinated per unit time. Here we are considering only proportion of individuals get vaccinated and some proportion becomes susceptible again. $u_2(t)$ is the proportion of chronic carriers getting antiviral treatment per unit time. Here the control functions $u_1(t)$ and $u_2(t)$ are bounded by Lebesgueintegral functions. Here, we investigate the prevention policies to minimize the total number of acute and carrier individuals keeping total cost of the policies low during the spread. The time-dependentoptimal prevention policies can be obtained by minimizing the following objectivefunctional:

$$J = \int_0^T (B_1 S(t) + B_2 E(t) + B_3 A(t) + B_4 C(t) + \frac{W_1}{2}u_1^2 + \frac{W_2}{2}u_2^2)\,dt \qquad (3)$$

The costs of the control policies are nonlinear and take quadraticforms. Here the coefficients $B_1, B_2, B_3, B_4, W_1, W_2$ respectively, are the weight constants of the individuals and control measures.They can be chosen to balance the units in the integrand and change the relative importance ofminimizing of infected individuals and intervention efforts.

Our goal is to find (u_1^*, u_2^*) such that

$$J(u_1^*, u_2^*) = \min_U J(u_1(t), u_2(t))$$

Subject to system (1), where the control set is defined as

$$U = \{(u_1(t), u_2(t)) \text{ are measurable}, 0 \leq ((u_1(t), u_2(t)) \leq 1\}$$

3 Existence of control problem

In this section, we consider the control system (2) with initial conditions to show the existence of the control problem. Note that for the bounded lebesgue measurable controls and non-negative initial conditions, non-negative bounded solutions to the state system exists [25].In order to find an optimal solution, first we should find the Lagrangian and Hamiltonian for the optimal control problem. The minimal value of the Lagrangian is given by $= B_1 S(t) + B_2 E(t) + B_3 A(t) + B_4 C(t) + \frac{W_1}{2}u_1^2 + \frac{W_2}{2}u_2^2$. We define the Hamiltonian H for the control problem, where $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ are adjoint variables:

$$\begin{aligned} H = {} & B_1 S(t) + B_2 E(t) + B_3 A(t) + B_4 C(t) + \frac{W_1}{2}u_1^2 + \frac{W_2}{2}u_2^2 \\ & + \lambda_1\big[\delta\pi\big(1-\eta C(t)\big) - \delta S(t) - \beta\big(A(t)+\kappa C(t)\big)S(t) \\ & + \delta_0(1 - S(t) + E(t) + A(t) + C(t) - u_1 S(t)] \\ & + \lambda_2\big[\beta\big(A(t)+\kappa C(t)\big)S(t) - \delta E(t) + \delta\pi\,\eta C(t) - \gamma_1 E(t)\big] + \lambda_3\gamma_1 E(t) \\ & - \delta A(t) - q\gamma_2 A(t) - (1-q)\gamma_1 A(t)\big] \\ & + \lambda_4[q\gamma_2 A(t) - \delta C(t) - \gamma_3 C(t) \\ & - u_2(t)C(t)] \end{aligned} \qquad (4)$$

For the existence of our control system (2), we state and prove the following theorem.

Theorem 3.1 There existsan optimal control $u^* = (u_1^*, u_2^*) \in U$ such that

$$J(u_1^*, u_2^*) = \min_U J(u_1(t), u_2(t))$$

Proof: to prove the existence of an optimal control we use the result in [26, 27, 38]. Here the control and state variables are non-negative values. In this minimizing problem, the necessary convexity of the objective function in u_1, u_2 are satisfied. The set of all the control variables $(u_1, u_2) \in U$ is also convex and closed by definition. The optimal system is bounded which determines the compactness needed for the existence of an optimal control. In addition the integrand in the functional (3) $B_1S(t) + B_2E(t) + B_3A(t) + B_4C(t) + \frac{W_1}{2}u_1^2 + \frac{W_2}{2}u_2^2$ is convex on the control set U. Also we can see that, there exists a constant $\rho > 1$ and positive numbers ω_1, ω_2such that

$$J(u_1, u_2) \geq c_1\,(|u_1|^2 + |u_2|^2)^{\rho/2} - \omega_2$$

Because, the state variables are bounded, this completes the existence of optimal control.

In order to derive the necessary conditions, we use Pontryagin's Maximum Principle as follows. If (x,u) is an optimal solution of an optimal control problem, then there exists a non trivial vector function $\lambda = (\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ satisfying the following equations:

$$\frac{dx}{dt} = \frac{\partial H(t,x,u,\lambda)}{\partial \lambda},$$

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$$0 = \frac{\partial H(t,x,u,\lambda)}{\partial u}, \qquad \frac{d\lambda}{dt} = \frac{\partial H(t,x,u,\lambda)}{\partial x}. \tag{5}$$

We now derive the necessary conditions that optimal control functions and corresponding states must satisfy. The following theorem, we present the adjoint system and control characterization.

Theorem 3.2 Let S*, E*, A* and C* be optimal state with associated optimal control variables $(u_1^*(t), u_2^*(t))$ respectively for the optimal control problem. Then there exist adjoint variables $\lambda_i(t)(i = 1,2,3,4,)$ satisfying

$$\dot{\lambda}_1(t) = -B_1 + \lambda_1[\delta + \delta_0 + u_1] - (\lambda_2 - \lambda_1)\beta(A(t) + \kappa C(t))$$

$$\dot{\lambda}_2(t) = -B_2 + \lambda_1\delta_0 + (\lambda_2 - \lambda_3)\gamma_1 + \lambda_2\delta)$$

$$\dot{\lambda}_3(t) = -B_3 - (\lambda_2 - \lambda_1)\beta S(t) + \delta_0\lambda_1 + \lambda_3(\delta + (1-q)\gamma_1) - (\lambda_4 - \lambda_3)q\gamma_2$$

$$\dot{\lambda}_4(t) = -B_3 + (\lambda_1 - \lambda_2)\delta\pi\,\eta - (\lambda_2 - \lambda_1)\beta\kappa S(t) + \delta_0\lambda_1 + \lambda_4(\delta + \gamma_3 + u_2) \tag{6}$$

With transversality conditions,

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = 0 \tag{7}$$

Furthermore the control functions $u_1^*(t), u_2^*(t)$ are given by,

$$u_1^*(t) = \min\left\{\max\left\{LB_1, \frac{\lambda_1 S(t)}{W_1}\right\}, UB_1\right\}$$

$$u_2^*(t) = \min\left\{\max\left\{LB_2, \frac{\lambda_4 C(t)}{W_2}\right\}, UB_2\right\} \tag{8}$$

Proof: To determine the adjoint equations and the transversality conditions, we use the Hamiltonian H in equation (4). The form of the adjoint equations and transversality conditions are standard results from Pontryagin's Maximum Principle. We differentiate the Hamiltonian with respect to each state (respectively as stated above), then the adjoint system can be written as:

$$\dot{\lambda}_1(t) = -\frac{\partial H}{\partial S}, \dot{\lambda}_2(t) = -\frac{\partial H}{\partial E}, \dot{\lambda}_3(t) = -\frac{\partial H}{\partial A}, \dot{\lambda}_4(t) = -\frac{\partial H}{\partial C}$$

With transversality conditions,

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = 0$$

To get the characterization of the optimal control we have to solve the equations,

$$\frac{\partial H}{\partial u_1(t)} = 0, \qquad \frac{\partial H}{\partial u_2(t)} = 0,$$

For $u_1^*(t), u_2^*(t)$ subject to the constraints, the characterization (8) can be derived and we have

$$\frac{\partial H}{\partial u_1} = W_1 u_1(t) - \lambda_1 S(t) = 0$$

$$\frac{\partial H}{\partial u_2} = W_2 u_2(t) - \lambda_4 C(t) = 0$$

Then by standard variation arguments with the control bounds, we obtain the properties (8)

4. Simulation results and Discussions.

This section discusses the numerical simulations of the optimality system and the corresponding results of varying the optimal controls u_1 and u_2 using the below parameter values.

Numerical solutions to the optimality system composing the state equation (2) and adjoint equation (6) are carried out in MATLAB 7.12.0 (R2011a). We have plotted Susceptible,exposed, acute, and carriers individuals with and without control by considering real parameter values given in Table 1, for the simulation purpose we have considered initial values $S(0) = 930,\ E(0) = 10,\ A(0) = 9,\ C(0) = 1.$ The weight constant of the objective functional are $W_1 = 1,\ W_2 = 1,$ $B_1 = 10,\ B_2 = 10,\ B_3 = 10,\ B_4 = 10.$ The algorithm is the forward-backward scheme; starting with an initial guess for the optimal controls. The state variables are then solved forward in time using Runge-Kutta method of the fourth order. Then, those state variables and initial guess for the controls are used to solve the adjoint Equation backward in time with given final conditions (7), again employing a fourth order Runge-Kutta method. The controls are updated and used to solve the state and then the adjoint system. This iterative process terminates when current state, adjoint, and control values converge sufficiently [29, 30]. The results from our simulations are displayed in the following figures. We investigate and compare the numerical results in the following scenario. The vaccination control for the susceptible individuals and treatment control for the carrier individuals are used to optimize the objective functional.

We assumed time in years. The time dependent optimal control strategies are shown in Fig.3 and Fig.4, the control profile u_1 is at the upper bound for some time and dropped gradually from upper bound to lower bound after 22 days and similarly the countrol profile u_2 is at the upper bound for some time and gradually drops to lower bound after 11 days and suddenly increases to upper bound and remain at the upper bound till the final time. When both the control efforts are optimized i.e. vaccination control and the treatment control. In Fig.7, We observe that this control strategy results in significant decrease in number of carrier individuals compared with the case without control. Similarly, when compared to exposed and acute individuals there is also significant decrease in number of individuals when both the controls are optimized.

5. Conclusion

In our present study, we performed optimal control analysis for the transmission dynamics of Hepatitis B virus model with effective use of vaccination and treatment control strategies. Using Pontryagin's Maximum Principle, the control system is analyzed to determine the necessary conditions for the existence of an optimal control. The control plots we developed indicate that the number of exposed, acute and carrier individuals decreased in the optimality system. We conclude that successful use of control measures has a significant impact in reducing the infectious diseases. The simultaneous use of two control policies is more effective at reducing the number of secondary infections than the use of single control policies.

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Table 1: Parameter values used for numerical simulations.

Notation	Parameter description	Range
δ	Natural death and birth rate	0.0143
π	The failure immunization	0.1
γ_1	The rate at which the Exposed individuals become infectious	6
γ_2	The rate at which the acute individuals move to the carrier class	4
γ_3	The rate of flow from carrier to the vaccinated class	0.34
β	The transmission coefficient	1.5
q	The proportion of individuals become carrier	0.005
δ_0	Represent the loss of immunity	0.05
κ	The infectiousness of carriers related to acute Infection	0.1

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