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Hepatitis B Optimal Control Model with Vertical Transmission

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Abstract The paper presents a model for the transmission dynamics of hepatitis B disease with vertical transmission incidence. The model is investigated using the tool of dynamical system, which reveals the spreading of the epidemic, when the threshold parameter: The basic reproduction number exceeds one. The model is modified by reformulating as an optimal control problem to assess the effectiveness and impact of treatment on the infective. The optimality is deduced and solved numerically to investigate the cost effective control efforts in reducing the number of exposed and infective.

Keywords Hepatitis B virus (HBV), Lagrangian, Hamiltonain, Boundary conditions

1. Introduction

Disease modeling has been a tool that has led governments, public health organizations and societies out of spiritual mysticism with regards to causes and transmission of infectious diseases [1].

The application of mathematics to the modeling of infectious disease has been the platform where unexplained questions of an epidemic outbreak into a population, its transmission dynamics, the likelihood of the epidemic spreading or dying out in the population of susceptible, the best vaccination strategy that would be efficacious to be embarked on by governments and any treatment possibility of the disease are investigated [2].

The world health organization (WHO, 2016) reported that, Hepatitis B, is a potential life-threatening liver infection caused by the hepatitis B virus (HBV), an enveloped DNA virus that infects the liver and causes hepatocellular necrosis and inflammation. The disease is transmitted by means of exposure to the blood of infected person and various body fluids; saliva, menstral, vaginal and seminal fluid. The disease is also spread sexually in unvaccinated gay men and persons with several sex partners. Furthermore, in highly endemic areas, HBV is transmitted from mother to child at birth from contact with maternal blood and secretions at delivery.

There have been estimated 8 million cases of HBV infection, 240 million chronic carriers and 686,000 deaths globally every year. These estimates render viral hepatitis B to be ranked among the most virulent diseases in the world [3].

Concerning hepatitis B disease, several contributions from mathematical models with deep revelations on transmission dynamics and control intervention decision making have been made. Anderson and May [4], proposed a simple mathematical model that explains the effect of carriers on the transmission of HBV. Zou et al [5], used a mathematical model to examine the transmission dynamics as well as the prevalence of HBV in mainland China. Reza et al [6], studied the dynamics of hepatitis B virus (HBV) infection under administration of a vaccine and treatment with both vertical and horizontal transmission. Eikenbery et al [7], analyzed the dynamics of a model using logistic hepatocyte growth and a standard incidence function governing viral infection. The model also considered an explicit time delays in viral infection. Sacrifice et al [8], formulated a simple SITR treatment model of hepatitis of type B. The model investigated the effect of treatment on the infectives in the treated compartment.

Notwithstanding, optimal control models have been used extensively in identifying the therapeutic strategies that could be used to eradicate or minimize the disease at a minimal cost [9-13]. Forde et al [14], investigated an optimal control problem for a delay differential equation model of immune responses to hepatitis virus B infection. The model investigated the interplay between virological and immunomodulatory effects of therapy, control of viremia and administration of the minimal dosage in a short time frame. Ntaganda [15], used direct approach and Pontryagin's

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maximum principle to solve a hepatitis B virus dynamics optimal control problem. Armbruster and Brandeau [16], developed a mathematical model of a chronic treatable infectious disease and used it to assess the cost and effectiveness of different levels of screening and contact tracing. The model determines the optimal cost-effective equilibrium level of the disease. Hettaf [17], analyzed the optimal efficiency of drug therapy in inhibiting viral protection and preventing new infections. Ntaganda and Gahamanyi [18], presented a fuzzy logic approach to solve a hepatitis B virus Optimal control problem. Elaiw et al [19], considered a nonlinear control system with control input defined to be dependent on the drug dose and drug efficiency. However, treatment schedules for HBV infected patients was developed by using multirate predictive control (mpc). Bhattacharyya and Ghosh [20], studied optimal control of vertically transmitted disease of HBV with regards to its computational and mathematical methods in medicine.

Entrenched in all these mathematical models, backed up by the optimal control models of the viral hepatitis B are the devotees of the achievements of the insightful explanations on the transmission dynamics, therapeutic strategies that could be adopted to enhance the treatment of the disease and the control preventive strategy that could be administered to prevent an invading of epidemic. Yet, none of these works can be completely exhibit all that is observed clinically as well as accounting for the full course of the infection.

In this research article, we consider a basic model for hepatitis B viral infection that includes a fraction of the offspring of the infected and exposed individuals infected with the disease at birth, and hence enter the exposed compartment, giving vertical transmission of the disease as studied in section 2. The model estimates one imperative qualitative threshold parameter, the basic reproduction number. The section 3 formulates an optimal control problem that minimizes the number of exposed and infective and the cost of treatment of the infected persons by incorporating time dependent control functions. The necessary conditions for an optimal and the corresponding states are then derived by employing the Pontryagin's Maximum Principle. Finally, in section 4, the resulting optimality system is numerically solved and interpreted from the epidemiological point of view.

2. Model Framework

In this section, viral hepatitis B transmission epidemic model in a constant population where natural birth rate equals death rate (μ) is presented. The population at time t is categorized into the populations of susceptible, S, Exposed, E, Infective, I, and Removed, R. The exposed individual becomes infected with a constant rate ψ, and infected individuals recover with rate δ_1. β is assumed to be the contact rate between the susceptible and the infective. The model assumes that a fraction of the offspring of the exposed and infected individuals are infected with the disease at birth and so enters the exposed compartment, giving vertical transmission of the disease. Thus a fraction t_1 of the offspring from the exposed individuals and a fraction t_2 of the offspring from the infective individuals are born into the exposed class. The model is a version of the model proposed by [24]. The compartmental mathematical model is represented by the following system of four differential equations:

$$\begin{aligned}\frac{dS}{dt} &= \mu - \beta SI - t_1\mu E - t_2\mu I - \mu S\\ \frac{dE}{dt} &= \beta SI + t_1\mu E + t_2\mu I - (\psi+\mu)E\\ \frac{dI}{dt} &= \psi E - (\delta_1+\mu)I\\ \frac{dR}{dt} &= \delta_1 I - \mu R\end{aligned} \tag{1}$$

with initial conditions

$$S(0) \geq 0,\ E(0) \geq 0,\ I(0) \geq 0,\ R(0) \geq 0 \tag{2}$$

2.1. The Basic Reproduction Ratio and the Stability of the Disease-free equilibrium

There exist a unique disease-free equilibrium (DFE) of hepatitis model (1) and is given by $E_0 = (1,0,0,0)$. The basic reproduction number, R_0, is deduced by the next generation matrix [2]. This is given by

$$F = \begin{pmatrix}0 & \beta\\ 0 & 0\end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix}((\psi+\mu)-t_1\mu) & -t_2\mu\\ -\psi & (\delta_1+\mu)\end{pmatrix}$$

$$R_0 = \rho(FV^{-1}) = \frac{\beta\psi}{((\psi+\mu)-t_1\mu)(\delta_1+\mu)-\psi t_2\mu)} \tag{3}$$

The DFE, is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.

3. Optimal Control Strategies

In system (1), we modified the transmission rate by reducing the factor by $(1 - V_h(t))$, where $V_h(t)$ measures the effort to reduce the contact between the susceptible and the infective individuals. The control variable $V_\gamma(t)$ represents the rate at which infected individuals are treated at each time. We further assume that $V_\gamma I$ individuals at any time (t) are removed from the infective class and added to the removed class. With regards to these assumptions, the dynamics of system (1) are modified into the following system of equations:

$$\begin{aligned}\frac{dS}{dt} &= \mu - (1-V_h)\beta SI - t_1\mu E - t_2\mu I - \mu S\\ \frac{dE}{dt} &= (1-V_h)\beta SI + t_1\mu E + t_2\mu I - (\psi+\mu)E\\ \frac{dI}{dt} &= \psi E - \left(\delta_1+\mu+V_\gamma\right)I\\ \frac{dR}{dt} &= \delta_1 I - \mu R + V_\gamma I\end{aligned} \tag{4}$$

with initial conditions (2), our objective functional for the state system (4) is given by

$$J(V_h, V_\gamma) = \int_{t_0}^{t_f}\left(B_1E(t) + B_2I(t) + \frac{a_1}{2}{V_h}^2(t) + \frac{a_2}{2}{V_\gamma}^2(t)\right)dt \tag{5}$$

subject to the state system (4). Our objective for the work is to minimize the number of exposed and infective in the population and the cost of treatment of the infected individual by using the minimum control variables V_h and V_γ respectively. The quantities B_1 and B_2 denote the weight constants of the exposed and infective human population. Also, the quantities V_h and V_γ are weight constant for reducing the number of exposed and infective and treatment of infective. The term $\frac{1}{2}a_1{V_h}^2(t)$ and $\frac{1}{2}a_2{V_\gamma}^2(t)$ represent the cost associated with the reduction in the exposed and infective and treatment of infective. The cost associated with treatment could be offering the hepatitis B infected person with drugs such as Tenofovir.

Here, we seek to find a control functions such that

$$J(V_h^*, V_\gamma^*) = \min\{J(V_h, V_\gamma): (V_h, V_\gamma)\epsilon V\} \quad (6)$$

subject to system (4), where

$$V = \{(V_h, V_\gamma)|\ 0 \le V_h, V_\gamma \le 1, lebesgue\ measurable\} \quad (7)$$

For the optimal solution, we first introduce the Lagrangian and the Hamiltonain for the optimal problem (4)-(5) by

$$L = B_1E + B_2I + \frac{a_1}{2}{V_h}^2 + \frac{a_2}{2}{V_\gamma}^2$$

Here, we seek the minimal value of the Lagrangian. This is done by defining the Hamiltonian H for the control problem as

$$H = B_1E + B_2I + \tfrac{a_1}{2}{V_h}^2 + \tfrac{a_2}{2}{V_\gamma}^2 + \lambda_1\tfrac{dS}{dt} + \lambda_2\tfrac{dE}{dt} + \lambda_3\tfrac{dI}{dt} + \lambda_4\tfrac{dR}{dt} \quad (8)$$

3.1. Existence of Control Problem

For the existence of the optimal control problem, we state and prove the following theorem.

Theorem 3.1: There exists an optimal control $V^* = (V_h^*, V_\gamma^*)\epsilon V$ such that

$$J(V_h^*, V_\gamma^*) = \min_{(V_h, V_\gamma)\in V} J(V_h, V_\gamma)$$

Subject to the control system (4) with the initial conditions (2)

Proof: corollary 4.1 of [21] gives the existence of an optimal control due to the convexity of the integrand of J with respect to V_h, V_γ, a priori boundedness of the solutions of both the state and adjoint equations and the Lipchitz property of the state system with respect to the state variables.

To find the optimal solution, we apply Pontryagin's maximum principle [22] to the Hamiltonian (8), such that if (x, v) is an optimal solution of an optimal control problem, then there exists a non trivial vector function $\lambda = (\lambda_1, \lambda_2, \dots, \lambda_n)$ which satisfies the inequalities

$$\frac{dx}{dt} = \frac{\partial H(t,x,v,\lambda)}{\partial \lambda}$$
$$0 = \tfrac{\partial H(t,x,v,\lambda)}{\partial v} \quad (9)$$
$$\lambda' = -\frac{\partial H(t,x,v,\lambda)}{\partial x}$$

Now, we apply the necessary conditions to the Hamiltonian H in (8).

Theorem 3.2: Given that (S^*, E^*, I^*, R^*) are optimal state solutions and (V_h, V_γ) are associated optimal control variables for the optimal control problem (4)-(5), then, there exist adjoint variables λ_i, for $i = 1,2,\dots,4$ satisfying

$$\begin{aligned}
\tfrac{d\lambda_1}{dt} &= \lambda_1\,\mu + (\lambda_1 - \lambda_2)(1 - {V_h}^*)\beta I^* \\
\tfrac{d\lambda_2}{dt} &= -B_1 + \lambda_2\,(\psi + \mu) + (\lambda_1 - \lambda_2)t_1\mu - \lambda_3\,\psi \quad (10)\\
\tfrac{d\lambda_3}{dt} &= -B_2 + (\lambda_1 - \lambda_2)t_2\mu + (\lambda_1 - \lambda_2)(1 - {V_h}^*)\beta S + \\
&\lambda_3\,(\delta_1 + \mu + {V_\gamma}^*) - \lambda_4\,(\delta_1 + {V_\gamma}^*) \\
\tfrac{d\lambda_4}{dt} &= \lambda_4\,\mu
\end{aligned}$$

with the boundary conditions

$$\lambda_i\,(t_f) = 0, \text{ for } \ i = 1, 2, \dots.4. \quad (11)$$

with the optimal control pair given by

$${V_h}^*(t) = min\left\{max\left\{0, \tfrac{\beta S^* I^*(\lambda_2 - \lambda_1)}{a_1}\right\}, 1\right\} \quad (12)$$

$${V_\gamma}^*(t) = min\left\{max\left\{0, \tfrac{(\lambda_3 - \lambda_4)I^*}{a_2}\right\}, 1\right\} \quad (13)$$

Proof: To find the adjoint equations and boundary conditions, we employ the Hamiltonian (8).

Setting $S(t) = S^*(t)$, $E(t) = E^*(t)$, $I(t) = I^*(t)$ and $R(t) = R^*(t)$, and differentiating the Hamiltonian (8) with respect to S, E, I and R respectively gives equation (8). By solving the equations

$$\frac{\partial H}{\partial V_h} = 0 \quad \text{and} \quad \frac{\partial H}{\partial V_\gamma} = 0$$

On the interior of the control set and using the optimality conditions and the property of the control space V, we obtain equations (12)-(13).

Further, we infer from equation (12)-(13) for $V^* = (V_h^*, V_\gamma^*)$, the characterization of the optimal control. The optimal control and the state variables are found by solving the optimality system, which includes the state system (4), the adjoint system (10), the boundary conditions (11), and the characterization of the optimal control (12)- (13). Thus the optimality system is solved by the use of the boundary conditions together with the characterization of the optimal control (V_h^*, V_γ^*) given by (12)-(13).

Furthermore, the second derivative of the Langrangian with respect to ${V_h}^*$ and ${V_\gamma}^*$ are positive, which implies, the optimal problem is minimum at controls ${V_h}^*, {V_\gamma}^*$. Hence, substituting the values of ${V_h}^*$ and ${V_\gamma}^*$ in the control system (4) gives

$$\begin{aligned}
\tfrac{ds}{dt} &= \mu - \left(1 - min\left\{max\left\{0, \tfrac{\beta S^* I^*(\lambda_2 - \lambda_1)}{a_1}\right\}, 1\right\}\right)(\beta SI) - \\
&t_1\mu E - t_2\mu I - \mu S \\
\tfrac{dE}{dt} &= \left(1 - min\left\{max\left\{0, \tfrac{\beta S^* I^*(\lambda_2 - \lambda_1)}{a_1}\right\}, 1\right\}\right)(\beta SI) + \\
&t_1\mu E + t_2\mu I - (\psi + \mu)E \\
\tfrac{dI}{dt} &= \psi E - \left(\delta_1 + \mu + min\left\{max\left\{0, \tfrac{(\lambda_3 - \lambda_4)I^*}{a_2}\right\}, 1\right\}\right)I \quad (14)
\end{aligned}$$

$$\frac{dR}{dt} = \delta_1 I - \mu R + \left(min\left\{max\left\{0, \frac{(\lambda_3-\lambda_4)I^*}{a_2}\right\}, 1\right\}\right) I$$

with H^* at $\left(t, S^*, E^*, I^*, R^*, {V_h}^*, {V_\gamma}^*, \lambda_1, \lambda_2, \lambda_3, \lambda_4\right)$:

$$H^* = B_1 E + B_2 I + \frac{1}{2}\left(a_1\left(min\left\{max\left\{0, \frac{\beta S^* I^* (\lambda_2-\lambda_1)}{a_1}\right\}, 1\right\}\right)\right)^2 + \frac{1}{2}\left(a_2\left(min\left\{max\left\{0, \frac{(\lambda_3-\lambda_4)I^*}{a_2}\right\}, 1\right\}\right)\right)^2 + \lambda_1 \frac{dS^*}{dt} + \lambda_2 \frac{dE^*}{dt} + \lambda_3 \frac{dI^*}{dt} + \lambda_4 \frac{dR^*}{dt} \quad (15)$$

Solving numerically the above systems (14) and (15) gives the optimal control and the state.

4. Numerical Results and Discussion

Here, we numerically investigate the effect of the optimal control strategies on the transmission dynamics of hepatitis B epidemic model with vertical transmission. The optimal control is obtained by solving the optimality system; state system and adjoint system. We then apply an iterative scheme in solving the optimality system. First, we solve the state systems of equations with a guess for the controls over the simulated time frame using fourth order Runge-Kutta scheme. Due to the boundary conditions (11), the adjoint system is solved by backwards fourth order Runge-Kutta by employing the current iterative solutions of the state equation. The controls are then updated by means of a convex combination of the previous controls as well as the characterizations (12) and (13). The whole process is repeated until the values of the unknowns at the previous iterations are closed to the one at the current iterations [23].

The model investigates the transmission dynamics of Hepatitis B virus with vertical transmission incidence. We study the control effects of prevention of the interaction between the susceptible and the infectives and treatment control on the spread of the disease. We investigate the effects of the control strategies by comparing numerically the results of the stated scenarios with simulated values taken from [20]: $a_1 = 5000$, $a_2 = 10$, $B_1 = 1$ and $B_2 = 1$, with the initial condition $S(0) = 950$, $E(0) = 10$, $I(0) = 3$, $R(0) = 2$.

Here, we assume that the wight factor, a_1, associated with control V_h is greater than B_1, B_2 and a_2 respectively, which are association of control V_γ. This is due to the fact that the cost of implementing V_h includes, the cost of screening and surveillance and educational campaign of educating the public against such practices of receiving blood from untested individuals and the need to avoid if possible, becoming exposed to various bodily fluids of infected persons and the need of pregnant women having safe sex with outsiders and even long term partners. The cost of treatment includes hospitalization, medical examination and the administration of antiviral drugs for Hepatitis B. Here, we illustrate the effect of various optimal control strategies on the spread of Hepatitis B epidemic model in an endemic population. The parameter values used in the simulations are estimated based on a Hepatitis B disease as given in Table 1. Other parameters were chosen arbitrary for the numerical simulation.

Table 1. Description of variables and parameters of the Hepatitis B Model (1)

Parameter	Parameter Name	Estimated Value	Reference
μ	birth rate	0.00004	[Assumed]
β	contact rate	0.009	[20]
ψ	rate at which the exposed becomes infected	0.0385	[6]
δ_1	recovery rate	0.002	[20]
t_1	exposed infected fraction	0.0002	[Assumed]
t_2	fraction of the infected	0.0003	[Assumed]

Figures 1-2 represent the number of susceptible individuals (S) without and with controls for different values of a_2. In the absence of control, the susceptible (solid curve) decreases sharply in the first ten years until all the susceptible population are infected with the disease and leaves no population of susceptible. In the presence of controls, the susceptible (dashed curve) decreases slowly, and their population are maintained until about thirty five years where all their population degenerated due to being infected.

Similarly, figures 3-4 represent the number of Exposed individuals (E) without and with controls for different values of a_2. When there are no controls, the exposed (solid curve) increases sharply in the first nine years, and decreases sharply for the rest of the years. In the presence of control, the number E (dashed curve) increases gradually in the first twenty years and decreases slowly for the rest of the years.

Figures 5-6 compare the number of Infective individuals (I) without and with controls for a set of values of a_2. In the absence of control, the infective (solid curve) increases highly and maintains its equilibrium for the rest of the years. The presence of control resulted in the number of infective (dashed line) increased in the first twenty month. However, the control strategy proposed was effective in minimizing the infective population drastically.

Figures 7-8 presents the optimal control plots of the efforts to prevent the susceptible individual from becoming exposed to the infective V_h and the treatment control V_γ for $a_1 = 5000$. We see that the preventive control V_h is at the upper bound till $t = 52$, when it slowly drops to the lower bound, while the optimal treatment V_γ is at the peak of 100% for $t = 95$, before is drops sharply to the lower bound at $t = 100$. This implies that least effort would be required in employing the strategy of treatment of the infected individuals for $a_1 = 5000$.

In figures 9-10, again the optimal control plots of the efforts to prevent the susceptible individual from becoming exposed to the infective V_h and the treatment control V_γ are presented for $a_1 = 10000$. The plots show that the preventive control is at the upper bound for $t = 50$, when it gradually ebb off to the lower bound. The treatment control V_γ however stayed at the upper bound for $t = 95$, till it

drops to the lower bound. This also suggest that a smaller effort is need ed for treatment of infected individual than the prevention of the susceptible from becoming infected when $a_1 = 10000$.

Figures 11-12 presents the optimal control plots of the efforts to prevent the susceptible individual from becoming exposed to the infective V_h and the treatment control V_γ for $a_2 = 5000$. Here, we notice that the preventive control V_h is at the upper bound till $t = 82$, before it ebbs away gradually to the lower bound at $t = 98$, while the optimal treatment V_γ maintains the maximum of 100% for $t = 44$, when it drops slowly to the lower bound at $t = 91$. This suggest that a minimal effort is required for the prevention of the disease than treatment under $a_2 = 5000$.

Finally, in figures 13-14, when $a_2 = 10000$. The optimal control plots indicate that the preventive control V_h is at the upper bound till $t = 81$, when it slowly falls to the lower bound at $t = 99$. The optimal treatment V_γ however drops from the upper bound when t was at 41 and moves gradually to the lower bound at $t = 90$. This also suggest a requirement of a smaller effort for the prevention of the disease than treatment when $a_2 = 10000$.

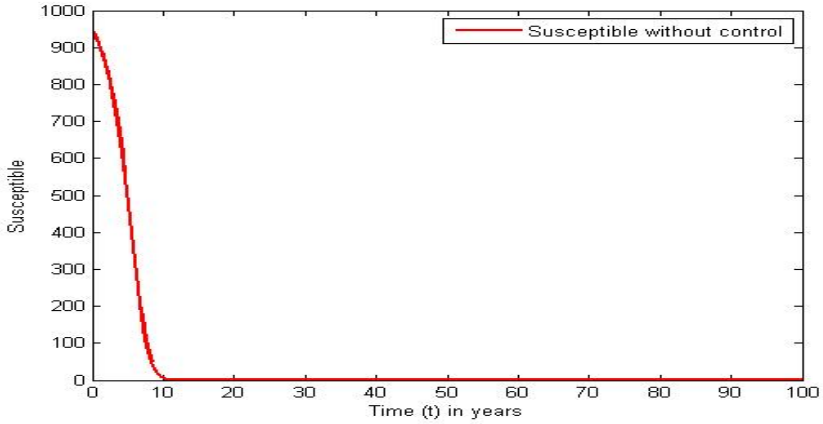

Figure 1. The plot represents population of susceptible individuals without control

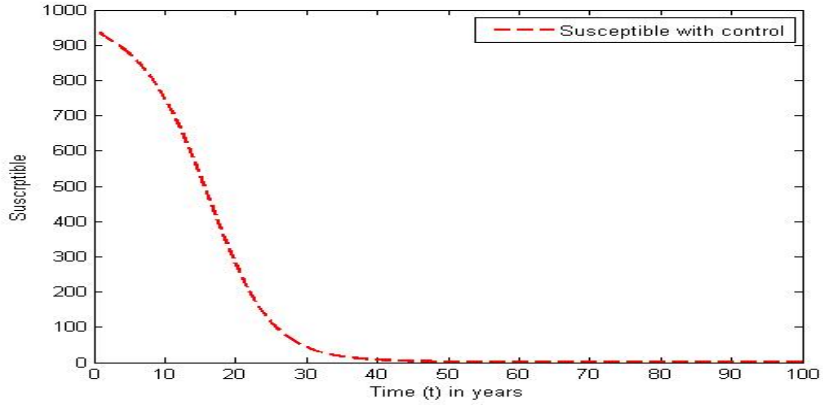

Figure 2. The plot represents population of susceptible individuals with control

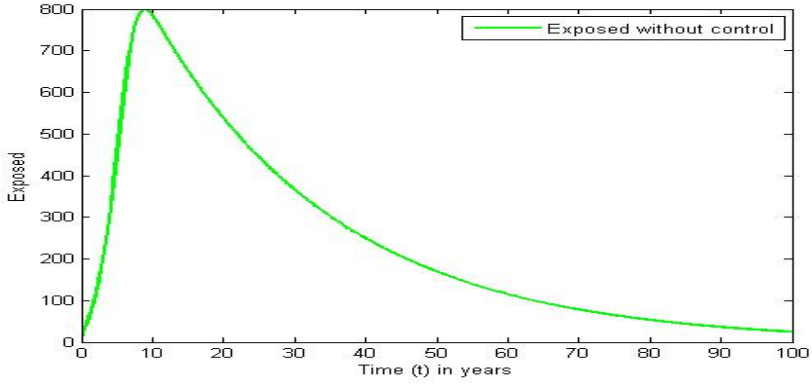

Figure 3. The plot represents population of Exposed individuals without control

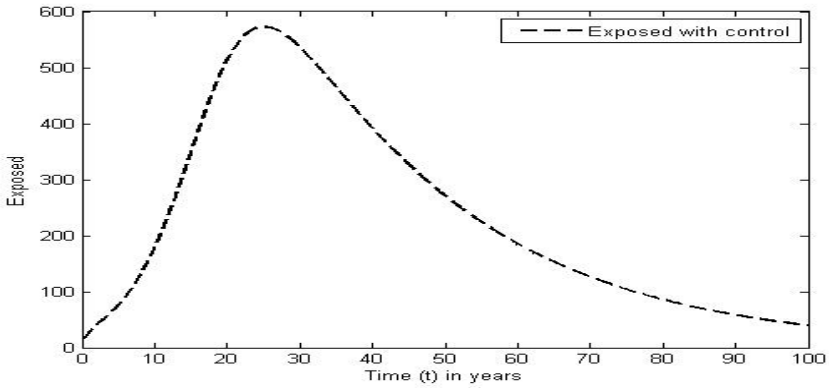

Figure 4. The plot represents population of Exposed with control

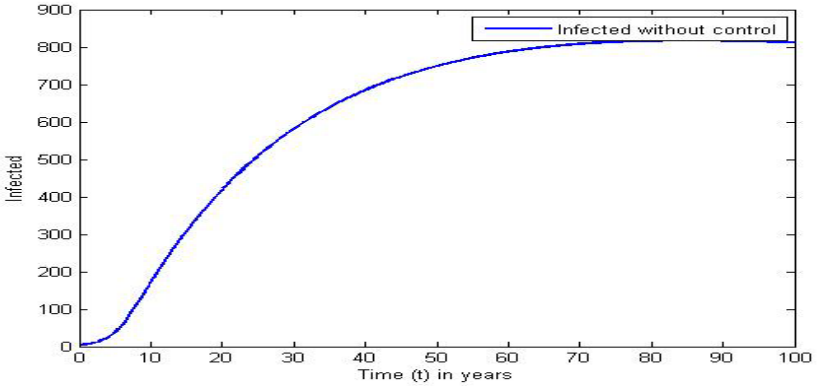

Figure 5. The plot represents population of Infected individuals without control

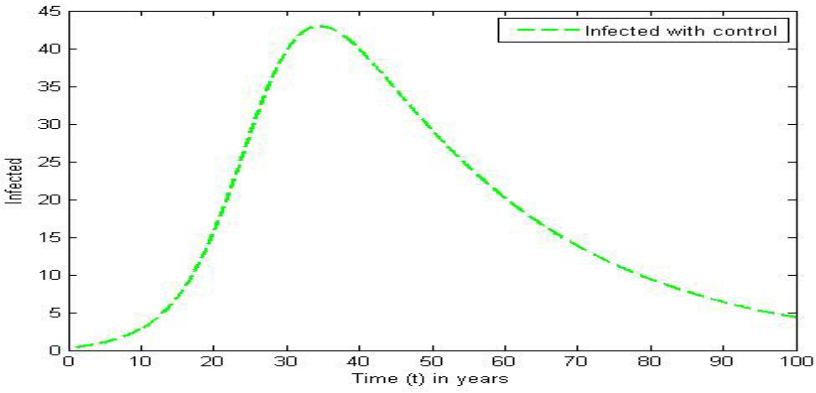

Figure 6. The plot represents population of Infected individuals with control

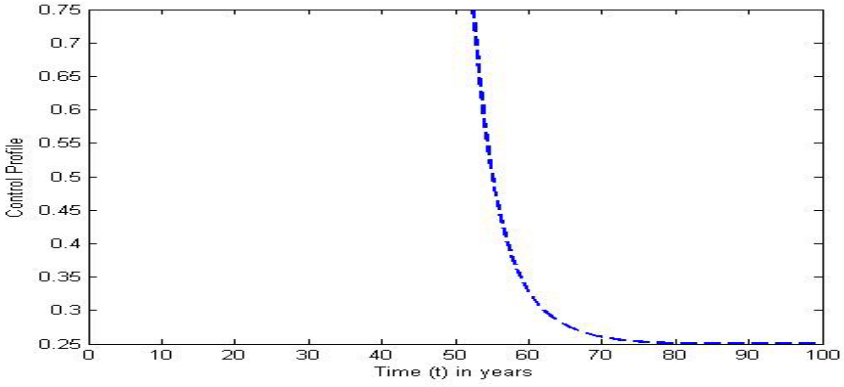

Figure 7. The plot represents optimal control V_h with $a_1 = 5000$

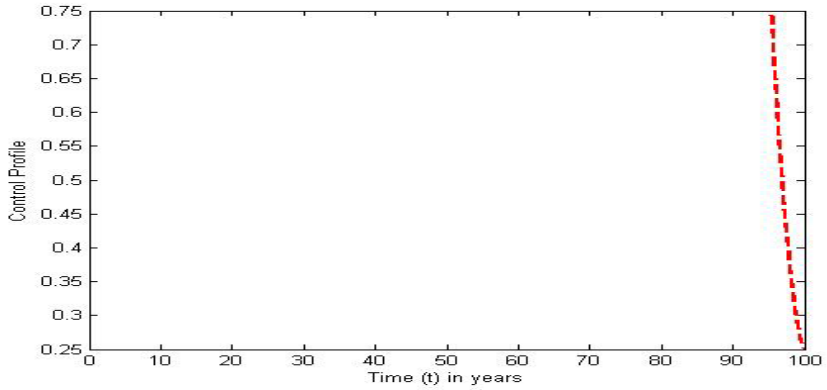

Figure 8. The plot represents optimal control V_γ with $a_1 = 5000$

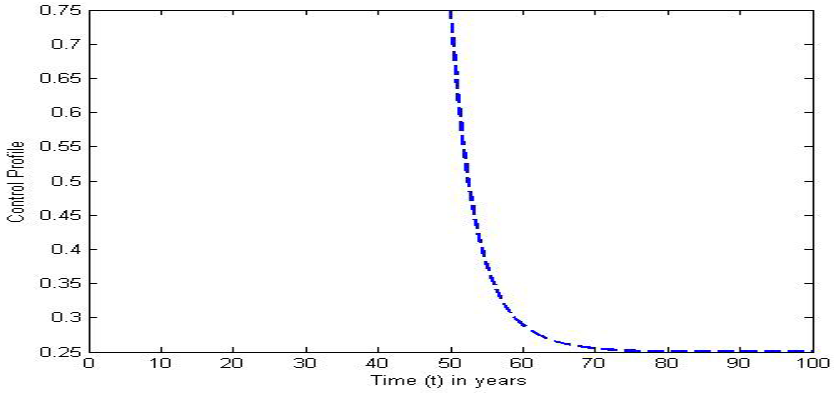

Figure 9. The plot represents Optimal control V_h with $a_1 = 10000$

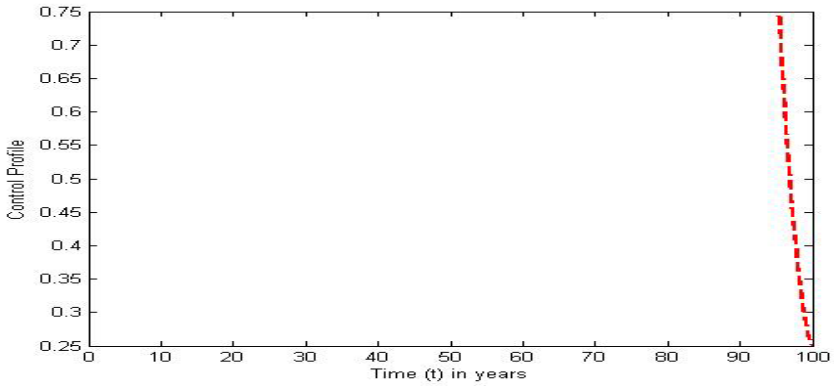

Figure 10. The plot represents Optimal control V_γ with $a_1 = 10000$

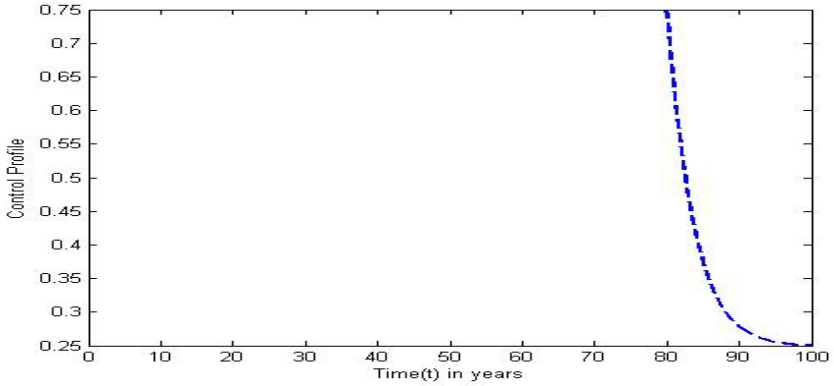

Figure 11. The plot represents Optimal control V_h with $a_2 = 5000$

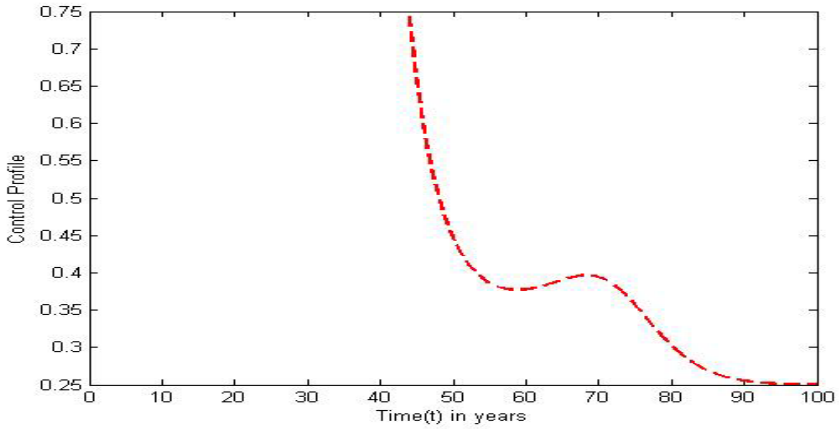

Figure 12. The plot represents Optimal control V_γ with $a_2 = 5000$

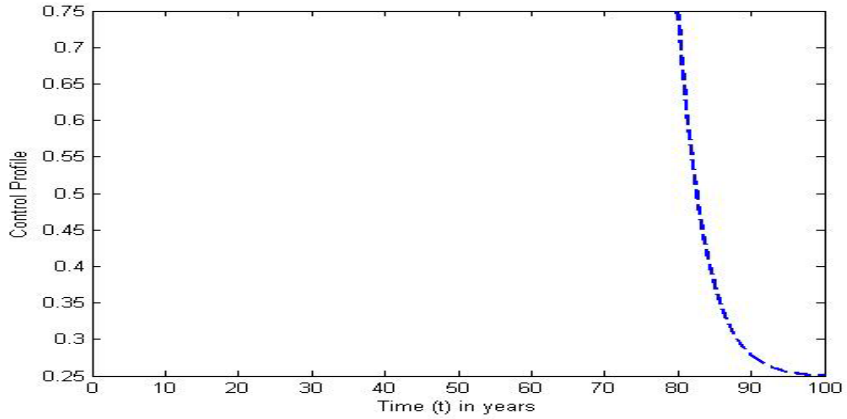

Figure 13. The plot represents Optimal control V_h with $a_2 = 10000$

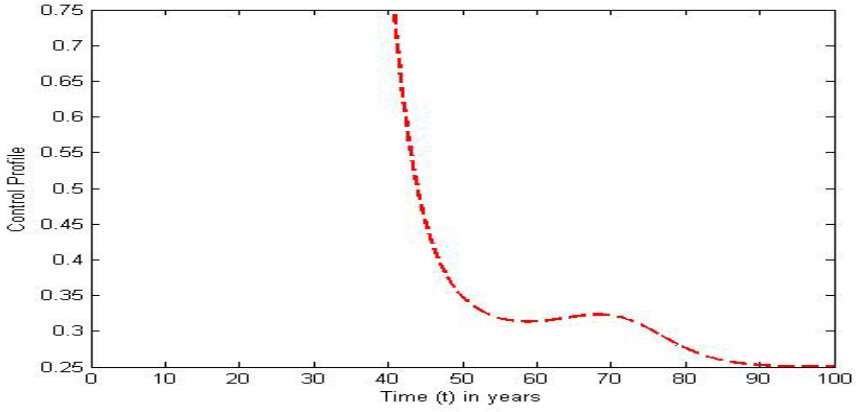

Figure 14. The plot represents Optimal control V_γ with $a_2 = 10000$

5. Conclusions

In this paper, we formulated and studied the transmission dynamics of hepatitis B disease that employs preventive and treatment controls for optimal control analysis of the model. The necessary conditions for the optimal control of the disease was derived and analyzed. Two types of control functions associated with the reduction of the exposed and the infective and treatment of infective strategies were considered. The control plots that were plotted showed that the number of exposed and infected human decreased in the optimality system. The control analysis indicates that the optimal control strategies have an incomparable effect for the reduction of the infected individuals as compared to the model without control as shown in the plot of figures for the models with control and without control. The simulation results showed that despite the vertical transmission incidence, the proposed control strategy is effective in the reduction of the number of the infective of the disease.

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