HiLL PUBLISHING

Journal of Applied Mathematics and Computation, 2024, 8(3), 227-237
https://www.hillpublisher.com/journals/JAMC/
ISSN Online: 2576-0653
ISSN Print: 2576-0645

Optimal Control Strategies for Reducing Herpes Simplex Virus Type 2 (HSV-2) Infections

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How to cite this paper: Samiha Islam Tanni, Chandra Nath Podder. (2024) Optimal Control Strategies for Reducing Herpes Simplex Virus Type 2 (HSV-2) Infections. *Journal of Applied Mathematics and Computation*, 8(3), 227-237.
DOI: 10.26855/jamc.2024.09.005

Received: August 20, 2024
Accepted: September 18, 2024
Published: October 15, 2024

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Abstract

Genital herpes, caused by the herpes simplex viruses (HSVs) is a globally sexually transmitted disease that has been more drastic in recent years. In this work, we have studied the epidemiological model applied to Herpes Simplex Virus Type 2 (HSV-2) infection in an optimal control perspective. The mathematical model that is developed in this work representing the disease dynamics is based on ordinary differential equations. Here we have employed the optimal control strategies to study the necessary mathematical analysis such as the existence and characterization of optimal control including some necessary conditions of the model. Our goal is to find a strategy using which we can prevent this disease by reducing HSV-2 infection. For this purpose, we have applied Pontryagin's maximum principle and adopted vaccination as the control measure. We have examined the model both analytically and numerically, and the analytical findings have been illustrated using numerical simulations. After illustrating the graphs in different types of situations, we conclude that vaccination could be the most effective measure to reduce the number of infected individuals.

Keywords

Herpes Simplex Virus Type-2 (HSV-2); Mathematical model; Optimal control; Existence of the state; Existence of the objective functional; Pontryagin's Maximum Principle; Optimality system; Hamiltonian (H)

1. Introduction

Optimal control theory is an area of mathematics that involves finding optimal ways to control the spread of infectious diseases. It is such type of mathematical optimization method from which we can derive the control policies for a specific disease easily. At first Lev Pontryagin and Richard Bellma [1] worked on this method. Nowadays, it has become very popular and is playing a significant role in controlling the spread of infections. In any kind of complex biological situation [2], optimal control theory is recently using which we can easily find a control law for a disease if the nature of the disease is known to us. The nature of all diseases is not the same. For some diseases, either vaccination or treatment is available. Controlling such types of diseases for which either vaccination or treatment is available, optimal control theory can play an important role.

Herpes simplex virus type 2 (HSV-2) is such type of virus that is transmitted by sexual contact or via the maternal-neonatal relationship. It is a linear double-stranded DNA virus of the Herpesviridae family and Alphaherpesvirinae subfamily. In recent times around the world, at least 500 million people have been infected by this virus worldwide [3]. The prevalence of HSV-2 is higher in the USA than in Europe, Australia, and New Zealand. Most people are not aware of the infection and may transmit the virus during periods of subclinical shedding.

An effective preventive measure for controlling the spread of infectious disease is necessary and also it is of great concern

worldwide. It is known to all that the most efficient control strategy to control the spreading of infection or infectious disease is vaccination. For some diseases, treatment is necessary to control the spread of infection. We will design a mathematical modeling framework for gaining insights into the spread of HSV-2 in the body of an infected host, based on an existing model [4], and use this model using optimal control theory to propose effective strategies for controlling its spread. Optimal control technique represents vaccination schedule easily for a finite time period, so we choose this technique to gain insight into HSV-2 disease dynamics. We consider vaccination strategies defined by a fraction of the current susceptible population to be targeted for vaccination. The optimal vaccination strategy is to control the total number of susceptible and exposed individuals and also to minimize the probability that the infected individuals spread the disease in the population. Then we demonstrate how the optimal control of the vaccination variable $u(t)$ can be applied to minimize the number of infected individuals.

2. Formulation of HSV-2 Mathematical Model

To design the HSV-2 transmission model, we can sub-divide all population such as homogeneously- mixed, heterosexual, sexually active population at time t, denoted by $N(t)$, into four mutually exclusive compartments which are susceptible $S(t)$, exposed to HSV-2 but there is clinical symptoms of the disease $Q(t)$, infectious containing the clinical symptoms of HSV-2 $H(t)$ and infectious but whose infection is quiescent state $Q(t)$, so that $N(t) = S(t) + E(t) + H(t) + Q(t)$.

The increase of the susceptible population by the contact of new sexually-active individuals which is assumed susceptible into the population at a rate β and it indicates the birth rate. The rate δ indicates the diminishment of population by death and the acquisition of infection, following effective contact with infectious individuals (in the H and Q classes), at a rate c. The modification parameter $0 \leq \theta < 1$ is introduced for assuming the lower infection of infectious individuals in the quiescent class Q in comparison to those in the H class. The development of symptoms in exposed individuals is expressed as the progression rate ϵ and γ is the rate at which the infected individuals activate in the quiescent state. In a certain time, the infectious individuals revert to a quiescent state at the rate ρ. μ_1, μ_2 are the disease-induced death rates for infectious non-quiescent individuals and quiescent individuals respectively.

Now, we introduce a control $u(t)$ into the HSV-2 basic model which represents the percentage of susceptible individuals being vaccinated at time t for controlling the spread of HSV-2 infection. A piecewise continuous function which is defined on $[0, t_f]$ is considered as our control class and it has the bound $0 \leq u(t) \leq 1$. It is to be noted that, for the highest use of vaccination as a control, we consider $u(t) = 1$ and for the case of absence of the vaccination $u(t) = 0$.

So, the controlled mathematical system is represented by using the following system of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \beta N(t) - \delta S(t) - cS(t)(H + \theta Q)(t) - u(t)S(t) \\
\frac{dE}{dt} &= cS(t)(H + \theta Q)(t) - (\epsilon + \delta)E(t) + \theta u(t)S(t) \\
\frac{dH}{dt} &= \epsilon E(t) + \gamma Q(t) - \rho H(t) - \delta H(t) - \mu_1 H(t) + (1 - \theta)u(t)S(t) \\
\frac{dQ}{dt} &= \rho H(t) - \gamma Q(t) - \delta Q(t) - \mu_2 Q(t) \\
\frac{dN}{dt} &= (\beta - \delta)N(t) - (\mu_1 + \mu_2)(H(t) + Q(t))
\end{aligned} \tag{1}$$

with initial conditions,

$$S(0) = S_0 \geq 0, E(0) = E_0 \geq 0, H(0) = H_0 \geq 0, Q(0) = Q_0 \geq 0, N(0) = N_0 \tag{2}$$

2.1 Formulation of Our Optimal Control Problem

We define our objective functional as

$$J(u) = \int_0^{t_f} (A(H + \theta Q)(t) + u(t)^2)dt \tag{3}$$

subject to the system of equation (1) while the control set U is Lebesgue measurable and is defined

$$U = \{u(t)\ is\ piecewise\ continuous\ function\ | 0 \leq u(t) \leq 1, t \in [0, t_f]\}$$

Here A is considered as a weight parameter and it describes the relative importance of the two terms in the functional. By the term $A(H + \theta Q)(t)$ in the objective functional indicates the individuals who are infected and is taken as a measure

of the death associated with the outbreak.

2.2 Existence of the Controlled System

For existence, we consider the controlled system (1) with initial condition (2), which can be written in the form

$$\emptyset_t = B\emptyset + F(\emptyset), \tag{4}$$

where

$$\emptyset = \begin{bmatrix} S(t) \\ E(t) \\ H(t) \\ Q(t) \\ N(t) \end{bmatrix},\ \emptyset_t = \begin{bmatrix} \frac{dS}{dt} \\ \frac{dE}{dt} \\ \frac{dH}{dt} \\ \frac{dQ}{dt} \\ \frac{dN}{dt} \\ 0 \end{bmatrix},\ F(\emptyset) = \begin{bmatrix} -cS(H+\theta Q) \\ cS(H+\theta Q) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}$$

$$B = \begin{bmatrix} -(\delta+u) & 0 & 0 & 0 & 0 \\ \theta u & -(\varepsilon+\delta) & 0 & 0 & 0 \\ (1-\theta)u & \varepsilon & -(\rho+\mu_1+\delta) & \gamma & 0 \\ 0 & 0 & q & -(\gamma+\mu_2+\delta) & 0 \\ 0 & 0 & -(\mu_1+\mu_2) & -(\mu_1+\mu_2) & (\beta-\delta) \end{bmatrix}$$

here $\emptyset_t$ denote derivative of $\emptyset$ with respect to time t. Equation (4) is a non-linear system with a bounded coefficient. We set $D(\emptyset) = \emptyset_t = B\emptyset + F(\emptyset)$.

The boundedness of solution of the system for finite time is needed to obtain the existence of an optimal control and optimality system.

Now taking

$$N(t) \leq (\beta - \delta)N(t)$$

So, we have

$$N(t) \leq N_0 e^{(\beta-\delta)t_f} = V_1 \in R_+$$

And $\limsup_{t\to\infty} N(t) \leq V_1$

Which conclude $S(t), E(t), H(t), Q(t) \leq V_1\ as\ t \to \infty$

Again we have,

$$F(\emptyset_1) - F(\emptyset_2) = \begin{bmatrix} -cS_1(H_1+\theta Q_1) \\ cS_1(H_1+\theta Q_1) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} - \begin{bmatrix} -cS_2(H_2+\theta Q_2) \\ cS_2(H_2+\theta Q_2) \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{5}$$

Therefore,

$$|F(\emptyset_1) - F(\emptyset_2)| = |-cS_1(H_1+\theta Q_1) + cS_2(H_2+\theta Q_2)| + |cS_1(H_1+\theta Q_1) - cS_2(H_2+\theta Q_2)|$$
$$= c|S_1(H_1+\theta Q_1) - S_2(H_2+\theta Q_2)| + c|S_1(H_1+\theta Q_1) - S_2(H_2+\theta Q_2)|$$
$$= 2c|S_1(H_1+\theta Q_1) - S_2(H_2+\theta Q_2)|$$
$$= 2c|S_1(H_1+\theta Q_1) - S_2(H_1+\theta Q_1) + S_2(H_1+\theta Q_1) - S_2(H_2+\theta Q_2)|$$
$$= 2c|(H_1+\theta Q_1)(S_1-S_2) + S_2(H_1+\theta Q_1 - H_2 - \theta Q_2)|$$
$$\leq 2c(|(H_1+\theta Q_1)||S_1-S_2| + |S_2||H_1-H_2| + |\theta S_2||Q_1-Q_2|)$$
$$\Rightarrow |F(\emptyset_1) - F(\emptyset_2)| \leq M[|S_1-S_2| + |H_1-H_2| + |Q_1-Q_2|] \leq M|\emptyset_1 - \emptyset_2|$$

Since H_1, Q_1 and S_2 are bounded, we consider

$$M = 2c\ max\{|(H_1 + \theta Q_1)|, |S_2|, |\theta S_2|\}$$

Then we get, $|\mathrm{F}(\emptyset_1) - \mathrm{F}(\emptyset_2)| \leq \mathrm{M}|\emptyset_1 - \emptyset_2|$

Also, we get,

$$|D(\emptyset_1) - D(\emptyset_2)| \leq \|B\||\emptyset_1 - \emptyset_2| + M|\emptyset_1 - \emptyset_2| \leq V|\emptyset_1 - \emptyset_2|$$

Where, $V = \max(M, \|B\|) < \infty$

Thus, it follows that the function D is uniformly Lipschitz continuous. From the definition of the control $u(t)$ *and* the restriction on S, E, H, Q *and* $N \geq 0$, we see that a solution of the system (4) exists.

2.3 Existence of Objective Functional

To prove existence, we will use the theory from Fleming and Rishel [5].

Theorem 1. *Let*

$$\bar{x}(t) = \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

be a system of n state variables, and let $\mathrm{u(t)}$ be a control variable with set of admissible control U, satisfying the differential equation

$$x_i'(t) = g_i\big(t, x_i(t), u(t)\big),\ for\ i = 1, \ldots \ldots n,$$

with associated objective functional

$$J(u) = \int f\big(t, \bar{x}(t), u(t)\big)dt$$

There exists an optimal control minimizing $\mathrm{J(u)}$ if the following conditions are satisfied:

1) The set U of control and corresponding state variables defined by F is nonempty.
2) The control set U is closed and convex.
3) The right-hand side of the state system is continuous, is bounded above by a linear combination of the control and the state, and can be written as a linear function of u with coefficients defined by the time and the state.
4) The integrand of the objective functional is convex on U and is bounded below by

$$-\mathrm{C}_2 + \mathrm{C}_1(\mathrm{u})^{\eta}, \text{with } \mathrm{C}_1 > 0 \text{ and } \eta > 1.$$

To prove that F is nonempty, we will use a simplified version of an existence result in Boyce and DiPrima ([6], Theorem 7.1.1), which is given below.

Theorem 2. Let each of the functions $\mathrm{F}_1 \ldots \ldots \mathrm{F}_n$ and the partial derivatives $\frac{\partial \mathrm{F}_1}{\partial \mathrm{x}_1}, \ldots \ldots, \frac{\partial \mathrm{F}_1}{\partial \mathrm{x}_n}, \ldots \ldots \frac{\partial \mathrm{F}_n}{\partial \mathrm{x}_1}, \ldots \ldots, \frac{\partial \mathrm{F}_n}{\partial \mathrm{x}_n}$ be continuous in a region R of $\{\mathrm{t}, \mathrm{x}_1, \mathrm{x}_{2 \ldots\ldots} \mathrm{x}_n\}$ space defined by $\alpha < \mathrm{t} < \beta$, $\alpha_1 < \mathrm{x}_1 < \beta_1 \ldots . \alpha_n < \mathrm{x}_1 < \beta_n$, and let the point $(\mathrm{t}_0, \mathrm{x}_1^0, \mathrm{x}_2^0, \ldots \ldots \mathrm{x}_n^0)$ be in $\mathfrak{R}$. Then, there is an interval $[\mathrm{t} - \mathrm{t}_0] < \mathrm{h}$ in which there exists a unique solution $\mathrm{x}_1 = \emptyset_1(\mathrm{t}), \ldots . . \mathrm{x}_n = \emptyset_n(\mathrm{t})$ of the system of differential equations

$$\mathrm{x}_1' = \mathrm{F}_1(\mathrm{t}, \mathrm{x}_1, \ldots \ldots, \mathrm{x}_n)$$
$$\mathrm{x}_2' = \mathrm{F}_2(\mathrm{t}, \mathrm{x}_1, \ldots \ldots, \mathrm{x}_n)$$
$$\mathrm{x}_n' = \mathrm{F}_n(\mathrm{t}, \mathrm{x}_1, \ldots \ldots, \mathrm{x}_n)$$

that also satisfies the initial conditions

$$x_1(t_0) = x_1^0, x_2(t_0) = x_2^0, \ldots \ldots x_n(t_0) = x_n^0$$

Theorem 3. *Let* $x_i = F_i(t, x_1, \ldots \ldots, x_n)$ *for* $i \in [1, n]$ be a system of n differential equations with initial conditions $x_i(t_0) = x_1^0$ for $i \in [1, n]$. If each of the functions, $F_1, \ldots \ldots, F_n$ and the partial derivatives

$$\frac{\partial F_1}{\partial x_1}, \ldots \ldots, \frac{\partial F_1}{\partial x_n}, \ldots \ldots \frac{\partial F_n}{\partial x_1}, \ldots \ldots, \frac{\partial F_n}{\partial x_n}$$

are continuous in $\mathfrak{R}^{n+1}$ space, then there exists a unique solution $x_1 = \sigma_1(t), \ldots \ldots, x_n = \sigma_n(t)$. that satisfies the initial conditions.

With these theorems in place, we can proceed to prove existence.

Proof. (i) To prove that F is nonempty, let

$$\frac{dS}{dt} = F_1(t,S,E,H,Q,N)$$
$$\frac{dE}{dt} = F_2(t,S,E,H,Q,N)$$
$$\frac{dH}{dt} = F_3(t,S,E,H,Q,N)$$
$$\frac{dQ}{dt} = F_4(t,S,E,H,Q,N)$$
$$\frac{dN}{dt} = F_5(t,S,E,H,Q,N)$$

where F_1, F_2, F_3, F_4 and F_5 form the RHS of system (1). Let $u(t) = C$ for some constant C, and since all other parameters are constant, F_1, F_2, F_3, F_4 and F_5 are linear. Thus, they are continuous everywhere. Additionally, the partial derivatives of F_1, F_2, F_3, F_4 and F_5 with respect to all state are constants, and so they are also continuous everywhere.

Therefore, there exists a unique solution $\{S = \sigma_1(t), E = \sigma_2(t), H = \sigma_3(t), Q = \sigma_4(t), N = \sigma_5(t)\}$ that satisfies the initial conditions. Therefore, the set of controls and corresponding state variables is non-empty, and condition (i) is satisfied.

(ii) By definition, U is closed. Take any controls $u_1, u_2 \in U$ and $\emptyset \in [0,1]$. Then,

$$0 \leq \emptyset u_1 + (1-\emptyset)u_2$$

Additionally, observe that $\emptyset u_1 \leq \emptyset$ and $(1-\emptyset)u_2 \leq (1-\emptyset)$. Then

$$\emptyset u_1 + (1-\emptyset)u_2 \leq \emptyset + (1-\emptyset) = 1$$

Hence,
$0 \leq \emptyset u_1 + (1-\emptyset)u_2 \leq 1$ for all $u_1, u_2 \in U$ and $\emptyset \in [0,1]$. Therefore, U is convex and condition (ii) is satisfied.

(iii) As stated previously, the RHS of the state system is continuous. Consider,

$$F_1 \leq bN - uS$$
$$F_2 \leq K_1 E + \theta uS$$
$$F_3 \leq eE + rQ + (1-\theta)uS$$
$$F_4 \leq qH$$
$$F_5 \leq bN$$

Given the state system,

$$\frac{dS}{dt} = F_1(t,S,E,H,Q,N)$$
$$\frac{dE}{dt} = F_2(t,S,E,H,Q,N)$$
$$\frac{dH}{dt} = F_3(t,S,E,H,Q,N)$$
$$\frac{dQ}{dt} = F_4(t,S,E,H,Q,N)$$
$$\frac{dN}{dt} = F_5(t,S,E,H,Q,N)$$

we can rewrite the system in matrix form:

$$\bar{F}(t,\bar{X},u) \leq \bar{m}\left(t,\begin{bmatrix}S\\E\\H\\Q\\N\end{bmatrix}\right)\bar{X}(t) + \bar{n}\left(t,\begin{bmatrix}S\\E\\H\\Q\\N\end{bmatrix}\right)u(t) \leq \begin{bmatrix}0&0&0&0&\beta\\0&K_1&0&0&0\\0&\epsilon&0&\gamma&0\\0&0&\rho&0&0\\0&0&0&0&\beta\end{bmatrix}\begin{bmatrix}S\\E\\H\\Q\\N\end{bmatrix} + \begin{bmatrix}-S\\\theta S\\(1-\theta)S\\0\\0\end{bmatrix}u(t) \quad (6)$$

$$\text{Where } \bar{m}\left(t,\begin{bmatrix}S\\E\\H\\Q\\N\end{bmatrix}\right)=\begin{bmatrix}0&0&0&0&\beta\\0&K_1&0&0&0\\0&\epsilon&0&\gamma&0\\0&0&\rho&0&0\\0&0&0&0&\beta\end{bmatrix} \tag{7}$$

$$\text{And } \bar{n}\left(t,\begin{bmatrix}S\\E\\H\\Q\\N\end{bmatrix}\right)=\begin{bmatrix}-S\\\theta S\\(1-\theta)S\\0\\0\end{bmatrix} \tag{8}$$

giving us a linear function of u with coefficients determined by time and state variables. We can then determine the bound of the RHS. Note that all parameters are constant and greater than or equal to zero. So, we can write,

$$|\bar{F}(t,\bar{X},u|\leq|\bar{m}|\big||\bar{X}|+|\bar{S}||u(t)|\big|\leq C(|\bar{X}|)+|u(t)|$$

since $\bar{S}$ is bounded, incorporates the upper bound of the constant matrix. Thus, we see that the RHS is bounded by a sum of the state and the bounded control. Condition (iii) is now satisfied.

(iv) Let $f(u)=A(H+\theta Q)(t)+u^2$ be the integrand of the objective functional.

Take $u_1,u_2\in U$ and $0<\psi<1$. Clearly

$$u_1^2-2u_1u_2+u_2^2=(u_1-u_2)^2\geq 0$$
$$\Rightarrow\ u_1^2+u_2^2\geq 2u_1u_2$$
$$\Rightarrow\psi(1-\psi)u_1^2+\psi(1-\psi)u_2^2\geq\psi(1-\psi)2u_1u_2$$
$$\Rightarrow(\psi-\psi^2)u_1^2+[(1-\psi)-(1-\psi)^2]u_2^2\geq 2\psi(1-\psi)u_1u_2$$
$$\Rightarrow\ \psi u_1^2+(1-\psi)u_2^2\geq\psi^2u_1^2+(1-\psi)^2u_2^2+2\psi(1-\psi)u_1u_2$$
$$\Rightarrow\psi u_1^2+(1-\psi)u_2^2\geq[\psi u_1+(1-\psi)u_2]^2$$
$$\Rightarrow A(H+\theta Q)+\psi u_1^2+(1-\psi)u_2^2\geq A(H+\theta Q)+[\psi u_1+(1-\psi)u_2]^2$$
$$\Rightarrow A(H+\theta Q)[\psi+(1-\psi)]+\psi u_1^2+(1-\psi)u_2^2\geq A(H+\theta Q)+[\psi u_1+(1-\psi)u_2]^2$$
$$\Rightarrow\psi A(H+\theta Q)+A(H+\theta Q)(1-\psi)+\ \psi u_1^2+(1-\psi)u_2^2\geq A(H+\theta Q)(t)+[\psi u_1+(1-\psi)u_2]^2$$
$$\Rightarrow\psi f(u_1)+(1-\psi)f(u_2)\geq f(\psi u_1+(1-\psi)u_2)$$

This implies that $f(u)$ is convex on U.

And we have to prove that $J(\mathrm{u})\geq -C_2+C_1(u)^{\eta}$, with $\eta>1, C_1\geq 0$

$$J(\mathrm{u})=A(H+\theta Q)(t)+(u)^2$$
$$J(\mathrm{u})\geq -A(H+\theta Q)(t)+(u)^2$$
$$=-C_2+C_1(u)^2$$

where $C_2>0$, depends upper bounds on $(H+\theta Q)(t)$ with $\eta=2>1, C_1>0$

Since all the conditions of Theorem 1 is satisfied, so we can say that the proof of existence is completed.

Now we can characterize the form of the optimal control u^*.

2.4 Characterization of an Optimal Control

In the previous section we showed the existence of an optimal control, which minimize the functional (3) subject to the system (1). In order to derive the necessary conditions for this optimal control, we apply Pontryagin's maximum principle to the Hamiltonian H.

If $(x^*(t),u^*(t))$ is an optimal solution of an optimal control problem, then there exists a non-trivial vector function

$$\lambda(\mathrm{t})=\lambda_1(t),\ldots\ldots,\lambda_n(t)$$

satisfying the following equalities:

$$\mathrm{x}'(t)=\frac{\partial H\big(t,\ x^*,u^*,\lambda(\mathrm{t})\big)}{\partial\lambda}$$

$$0 = \frac{\partial H\big(t,\ x^*, u^*, \lambda(\mathrm{t})\big)}{\partial \mathrm{u}}$$

$$\lambda'(t) = -\frac{\partial H(t,\ x^*, u^*, \lambda(\mathrm{t}))}{\partial \mathrm{x}}$$

which gives after derivation

$$\begin{cases} u^*(t) = 0, if\ \frac{\partial H}{\partial u} < 0 \\ u^*(t) \in [0, u_{max}], if\ \frac{\partial H}{\partial u} = 0 \\ u^*(t) = u_{max}, if\ \frac{\partial H}{\partial u} > 0 \end{cases} \tag{9}$$

Theorem 4. Given an optimal control u^* and a solution $X^*(t) = \big(S^*(t), E^*(t), H^*(t), Q^*(t), N^*(t)\big)$ of the corresponding system (1), there exist adjoint variables $\lambda_S(t), \lambda_E(t), \lambda_H(t), \lambda_Q(t), \lambda_N(t)$ which satisfies the following:

$$\begin{aligned} \lambda_S' &= \lambda_S(\delta + c(H + \theta Q) + u) - \lambda_E(c(H + \theta Q) + \theta u) - \lambda_H(1 - \theta)u \\ \lambda_E' &= \lambda_E(\epsilon + \delta) - \lambda_H E \\ \lambda_H' &= -A + (\lambda_S - \lambda_E)cS + \lambda_H(\rho + \mu_1 + \delta) - \lambda_Q\rho + \lambda_N(\mu_1 + \mu_2) \\ \Lambda_Q' &= -A\theta + (\lambda_S - \lambda_E)cS\theta - \lambda_H\gamma + \lambda_Q(\gamma + \mu_2 + \delta) + \lambda_N(\mu_1 + \mu_2) \\ \lambda_N' &= \lambda_N(\delta - \beta) - \lambda_S\beta \end{aligned} \tag{10}$$

with transversality conditions

$$\lambda_i\big(t_f\big) = 0, i = S, E, H, Q, N$$

Furthermore, the optimal control $u^*(t)$ is given by

$$u^* = min\left[1, max\left[0, \frac{S(\lambda_S - \lambda_H) - \theta S(\lambda_E - \lambda_H)}{2}\right]\right] \tag{11}$$

Proof. Using Pontryagin's Maximum Principle [7], to find the optimal vaccination schedule we first define the Hamiltonian as

$$\begin{aligned} H = A(H + \theta Q) + u^2 + \lambda_S(\beta N - cS(H + \theta Q) - uS) + \lambda_E(cS(H + \theta Q) - (\epsilon + \delta)E + \theta uS) \\ + \lambda_H(\epsilon E + \gamma Q - (\rho + \mu_1 + \delta)H + (1 - \theta)uS) + \lambda_Q(\rho H - (\gamma + \mu_2 + \lambda)Q \\ + \lambda_N\big((\beta - \delta)N - (\mu_1 + \mu_2)(H + Q)\big) \end{aligned}$$

The values $\lambda_S, \lambda_E, \lambda_H, \lambda_Q, \lambda_N$ are associated adjoints for the state S, E, H, Q, N respectively. By differentiating the Hamiltonian with respect to each state variable, we find the differential equation for the associated adjoints Also, because S, E, H, Q, N do not have fixed values at the final time, the values of the associated adjoints at the final time are zero. Therefore, the adjoint system is

$$\begin{aligned} \lambda_S' &= \lambda_S(\delta + c(H + \theta Q) + u) - \lambda_E(c(H + \theta Q) + \theta u) - \lambda_H(1 - \theta)u \\ \lambda_E' &= \lambda_E(\epsilon + \delta) - \lambda_H E \\ \lambda_H' &= -A + (\lambda_S - \lambda_E)cS + \lambda_H(\rho + \mu_1 + \delta) - \lambda_Q\rho + \lambda_N(\mu_1 + \mu_2) \\ \lambda_Q' &= -A\theta + (\lambda_S - \lambda_E)cS\theta - \lambda_H\gamma + \lambda_Q(\gamma + \mu_2 + \delta) + \lambda_N(\mu_1 + \mu_2) \\ \lambda_N' &= \lambda_N(\delta - \beta) - \lambda_S\beta \end{aligned} \tag{12}$$

with transversality conditions

$$\lambda_i\big(t_f\big) = 0, i = S, E, H, Q, N$$

By optimal condition we have

$$\frac{\partial H}{\partial u}|\mathrm{u} = u^* = 0$$

$$\Rightarrow\ 2u^* - \lambda_S S + \lambda_E\theta S + (1 - \theta)\lambda_H S = 0$$

$$\Rightarrow 2u^* = \lambda_S S - \lambda_E \theta S + (1-\theta)\lambda_H S$$
$$\Rightarrow 2u^* = \lambda_S S - \lambda_E \theta S - \lambda_H S + \theta \lambda_H S$$
$$\Rightarrow 2u^* = S(\lambda_S - \lambda_H) - \theta S(\lambda_E - \lambda_H)$$
$$\Rightarrow u^* = \frac{S(\lambda_S - \lambda_H) - \theta S(\lambda_E - \lambda_H)}{2}$$

So on the interior set where u^* denotes the optimal control, solving for u^*on the interior of the control set gives

$$u^* = \frac{S(\lambda_S - \lambda_H) - \theta S(\lambda_E - \lambda_H)}{2} \tag{13}$$

By standard control agreement involving bounds on the controls (using equation 9), we conclude

$$u^* = \begin{cases} 0, \ if \ \frac{S(\lambda_S - \lambda_H) - \theta S(\lambda_E - \lambda_H)}{2} < 0 \\ \frac{S(\lambda_S - \lambda_H) - \theta S(\lambda_E - \lambda_H)}{2}, if \ 0 \leq \frac{S(\lambda_S - \lambda_H) - \theta S(\lambda_E - \lambda_H)}{2} \leq 1 \\ 1, if \ \frac{S(\lambda_S - \lambda_H) - \theta S(\lambda_E - \lambda_H)}{2} > 1 \end{cases} \tag{14}$$

In compact notion:

$$u^* = min\left[1, max\left[0, \frac{S(\lambda_S - \lambda_H) - \theta S(\lambda_E - \lambda_H)}{2}\right]\right] \tag{15}$$

3. Numerical Simulation and Discussion

In this section, the numerical simulations for the HSV-2 model demonstrating the theoretical results are discussed which helps us to predict the evolution of infectious diseases in the population at host. As our target is to control the total number of susceptible individuals by using an optimal control strategy, we have to minimize the probability that the infected individuals spread the disease to the host population.

We use an iterative method to solve the optimality system, consisting of the system of ODEs (1) and the adjoint system (12). Specifically, a forward fourth-order Runge–Kutta scheme [8] is used for this. For the transversality conditions, the adjoint equation is solved by a backward fourth-order Runge-Kutta scheme using the current iteration solution of the state equations. A convex combination is used to update the controls and the value from the characterizations derived by (14). This process is repeated and iteration is stopped if the values of unknowns at the previous iterations are close enough to the ones at the present iteration [9, 10]. We considered the numerical value of the control u in between zero (0) and one (1) as they are not 100 percent effective [11][12].

The table below shows the parameters used in the simulations and the parameters are chosen arbitrarily.

Vaccination is simulated for 20 years in the case.

Table 1. Description and parameter values of the HSV-2 model

Variable	Description	Values	Source
S_0	initial susceptible individuals	1700	[Assumed]
E_0	initial exposed individuals	250	[Assumed]
H_0	initial infectious individuals	60	[Assumed]
Q_0	initial quiescent individuals	60	[Assumed]
Parameters	**Description**	**Values**	**Source**
β	Natural birth rate	0.625	[Assumed]
δ	Natural death rate	0.6	[Assumed]
c	incidence coefficient	.001	[13]
ϵ	Progression rate to symptoms development of exposed individuals	0.5	[Assumed]
γ	Activation rate of infectious individuals in the quiescent state	0.6	[Assumed]
ρ	Rate at which infectious individuals revert to quiescent state	0.7	[Assumed]
μ_1, μ_2	Disease-induced death rate for infectious individuals	0.25, 0.20	[14]
θ	Modification parameter for lower infectiousness of infectious individuals	0.5	[15]
A	weight parameter	0.1	[16]
t_f	number of years	20	[Assumed]

The graphs below, allow us to compare changes in the number of infectious, quiescent infectious, exposed and susceptible individuals before and after the introduction of vaccination control.

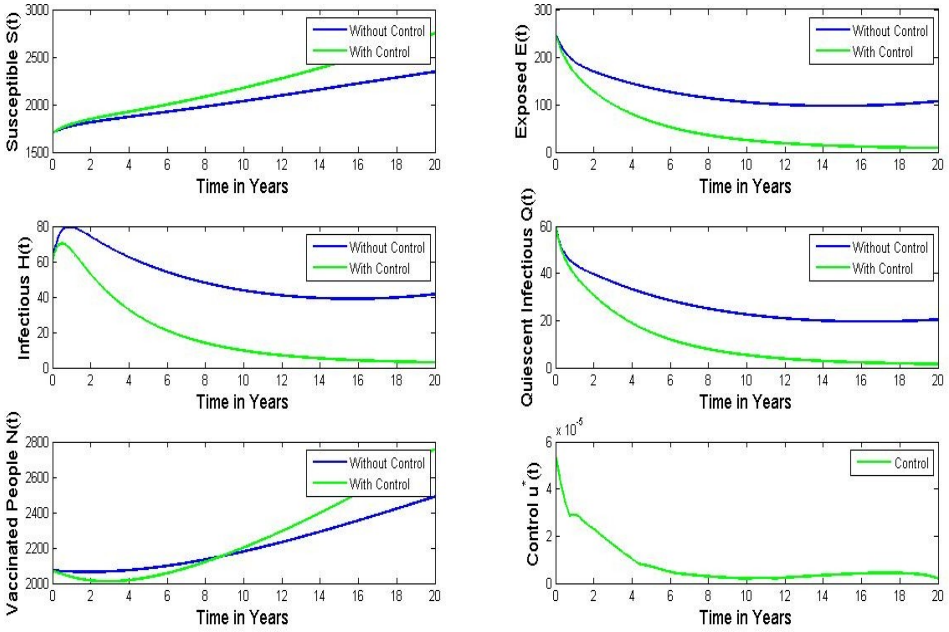

Figure 1. HSV-2 model with and without control, parameter values are taken from Table 1.

From Figure 1, we observe that the population in the exposed, infectious and quiescent infectious classes decreases significantly after implementation of vaccination control and susceptible individuals increase. As a result, the total population decreased when vaccination control was introduced in the population. This also demonstrates the impact that vaccination has had on the population.

It is worth noting that the control yields positive results after a period of 20 years, hence the vaccination control has a positive impact in controlling HSV-2 infection.

Now we will discuss the impact of incidence level for vaccination schedule. Here we consider two cases for vaccination schedule (low incidence and high incidence).

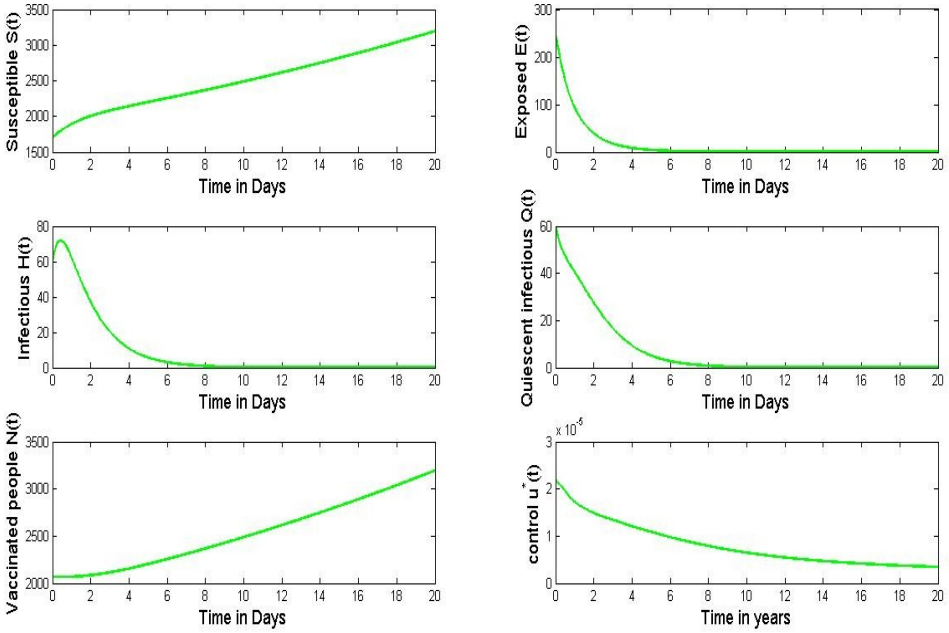

Figure 2. HSV-2 model with control, parameter values are taken from Table 1, with $c = 0.0001$.

Figure 2 depicts scenarios for low incidence levels. When the incidence level is low the number of infectious and quiescent infectious individuals quickly decreases to zero, this shows that the disease dies out and only the susceptible remain in the population. Also, the population of exposed individuals for low incidence decreases to zero.

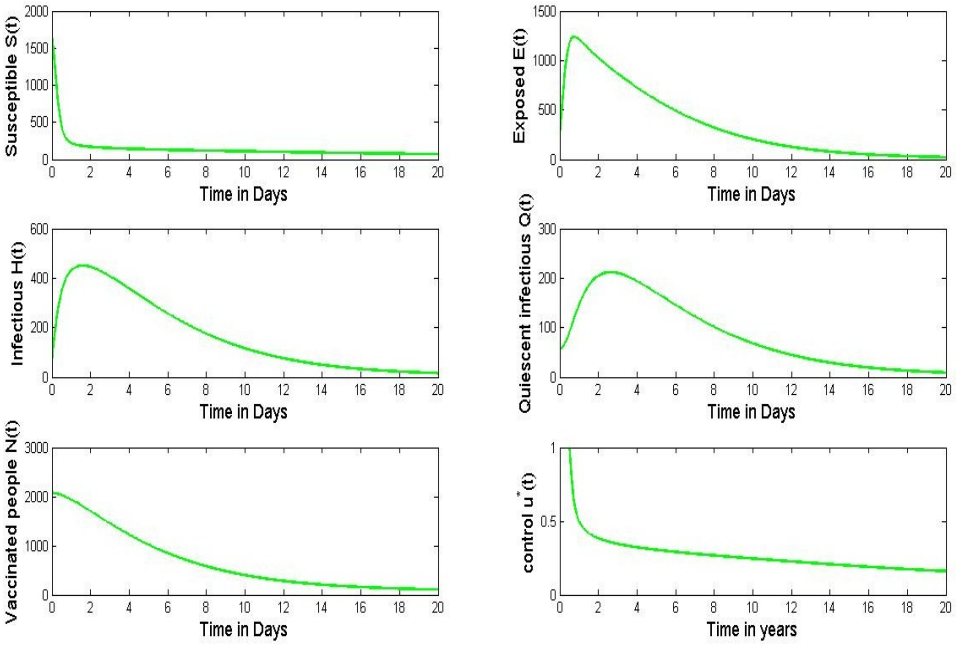

Figure 3. HSV-2 model with vaccination and parameter values are taken from Table 1, with $c = 0.01$.

Now we are considering a much higher incidence rate. For higher incidence, we observe that the population of the exposed, infectious, and quiescent infectious individuals increases greatly for the first few years and then decreases to zero around the year 14th. Here, the susceptible individuals sharply decrease in the first year after that begin to go to a stable state.

4. Conclusion

We have monitored that after implementing optimal control techniques, the infected and quiescent infected individuals are notably reduced which is helpful to control the spread of disease dynamics. For a lower incidence rate, the control is effective for a longer period compared to the higher incidence rate. The graphs here illustrate various types of situations from which we can get a clear idea about the effectiveness of introducing vaccination as a control parameter for lessening the infectious and quiescent infectious individuals. We conclude that the optimal control technique represents a vaccination schedule successfully for a finite time period.

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