An Epidemic Model of HSV-1 with Vaccination

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Abstract

The most common type of herpes is Herpes Simplex Virus type 1 (HSV-1), and it is commonly known to cause oral herpes - cold sores and fever blisters. Recent studies show that an HSV-1 vaccine was successful in the lab for animals such as guinea pigs and mice. It is estimated that the vaccine will be available for human use in the next couple of years. Encouraged by those studies, we have formulated a simple SVID model studying the disease transmission dynamics with treatment and vaccination. In this project we find the vaccination-treatment reproductive number, the equilibrium solutions, and their stability. We conduct sensitivity and uncertainty analysis for the reproductive number. We estimate the parameters based on previous works and perform numerical simulations. Finally, we compare different types of treatment and vaccination strategies to find an optimal combination of them and its relative cost in reducing the prevalence of HSV-1 infection in the population.

1 Introduction

Herpes is a disease caused by the Herpes Simplex Virus (HSV). It is estimated that 60% - 95% of the worldwide adult population is or will be infected with some type of herpes [2]. There are two types of herpes that are commonly present in the human population, HSV-1 and HSV-2. HSV-1 is commonly known for causing cold sores or fever blisters; however, it can infect the genital area as well. According to Lin et al. [12], HSV-1 infection is "virtually universal," and up to 90% of adults in the United States will be infected. On the other hand, HSV-2 occurs particularly on the genital area and therefore is normally known as genital herpes.

HSV-1 is transmitted from person to person by direct contact with the infectious individuals' sores or secretions, such as saliva. The virus enters through the mucous membranes and is transported to the ganglia, where it remains in a dormant stage [2] – and sometimes is referred to as *latent* stage. When the virus becomes active, an outbreak may occur (presence of symptoms) [2]. A person may show symptoms 2 – 10 days after being infected with HSV-1. Some of the symptoms are mentioned in [20] and [21], and these include: fever and/or headache, mouth sores, blisters and/or ulcers (which are frequent in the mouth, lips, or gums), and/or enlargement of lymph nodes in the neck.

The outbreaks will usually heal on their own in 7 - 10 days. If a person's immune system is weak, the infection will be more severe and may last longer [20]. At the end of the active period, the virus travels to the end of the spine where it remains dormant until triggered by fever, overexposure to sunlight, stress, or a weak immune system [20]. The frequency and severity of the outbreaks varies from person to person, some people may have one or two outbreaks in a lifetime, while others may have several ones within a single year [21]. One of the features of HSV-1 that facilitates the transmission of the disease is that about half of the infected people are asymptomatic. Hence, a person that does not present symptoms can spread the disease [21].

Since herpes may be asymptomatic, a health care provider would need to do one of the following tests to detect the virus: a blood test, direct fluorescent antibody (DFA) test, Tzanck test, or a viral culture of lesion. Once the infection has been

confirmed and although there is no cure for herpes, there are drugs that reduce the frequency and duration of outbreaks. The most common drug for HSV-1 is Acyclovir (Zovirax®) [20]. Currently, there is an ongoing research for the development of a vaccine that may be available for humans in the next few years. This vaccine will prevent people from getting infected from HSV-1, and it is unlikely that such a vaccine will help people that are already infected.

There has been some work in mathematical modeling of HSV-1 [13], [14], [19]; however, vaccination was not considered. Lipsitch et al. have analyzed the effect of antiviral treatment on the transmission of HSV-1 and the prevalence of drug resistance [13]. Additional laboratory work has been done to study the effects of vaccination on HSV-1; for instance, Itzhaki [10] showed that vaccination prevents dormant HSV-1 infection of mouse brain. Also, Chang et al. [4] demonstrated that glycoprotein gC immunization in mice obstructs completely C3b binding, which is the way that the immune evasion molecule inhibits complement activation in the case of HSV-1. It is believed that this immunization may also induce blocking antibodies that modify HSV-1 in humans. Others have studied the effectiveness of an HSV-1 vaccine; for example, Lin et al. [12] proved that HSV-1 was detected in the brain of 41% of the unvaccinated mice that were infected with HSV-1 versus 7% of the vaccinated mice. On the other hand, many studies have been done about HSV-2 and the impact of a possible vaccine to control the disease; for instance, Schwartz and Blower [16].

Since the trial of an HSV-1 vaccination was successful on guinea pigs and more recently on mice, it leads to believe that a human vaccine for HSV-1 may be available in the near future. Taking into consideration previous studies and events, we formulate an SVID model to study the disease transmission dynamics, and estimate the difference between the cost of treatment and vaccination for HSV-1.

2 The Model

In this section we introduce an epidemiological model that divides the population of interest into four epidemiological classes namely S (Susceptible), V (Vaccinated), I (Infectious), and D (Dormant) as follows:
(i) The Susceptible class S contains all the individuals that are in risk of being infected.
(ii) The Vaccinated class V contains all the individuals that were susceptible, and have been vaccinated. Vaccination does not necessary mean complete immunity.
(iii) The Infectious class I includes all the individuals that have the ability to infect a susceptible or vaccinated individual. An individual in this class *may or may not* present symptoms.
(iv) The dormant class D contains all the individuals who are infected but not infectious.

Now we explain the meaning of the parameters used in the model.
(a) μ is the per capita death and birth rate.
(b) $1/\rho$ is the average time until vaccination.
(c) $1/\omega$ is the average duration of vaccine-induced immunity.
(d) β_1 is the per capita rate of infection for the susceptible class.
(e) p is the proportion of the infectious individuals that are under treatment
(f) ϕ is the per capita rate at which infectious individuals under treatment move into the dormant class. Note that $\phi = p\phi'$, where $1/\phi'$ is the average length of viral shedding episodes for an individual *with* treatment.
(g) γ is the per capita rate at which infectious individuals that are not under treatment move into the dormant class. Similarly to ϕ, $\gamma = (1-p)\gamma'$, where $1/\gamma'$ is the average length of viral shedding episodes for an individual *without* treatment and $1-p$ is the proportion of infectious population under no treatment.
(h) $1/\lambda$ is the average length of time an infected person stays in the dormant class.
(i) α is the proportion of vaccinated individuals that are not protected from the virus.
(i) β_2 is the per capita rate of infection for the vaccinated class, where $\beta_2 = \beta_1\alpha$.

Table 1 summarizes the explanation of the parameters used in the model.

We now discuss the assumptions made in the model. While HSV-1 can be transmitted through oral sex, and consequently causes genital herpes, we are considering oral HSV-1 only. Hence, HSV-1 is transmitted through direct contact, such as a kiss, with the sores or secretions of an individual.

Table 1: Explanation of Parameters.

μ	Per capita death and birth rate.
ρ	Per capita rate of vaccination.
$1/\omega$	Average duration of vaccine-induced immunity
β_1	Per capita rate of infection for the susceptible class
β_2	Per capita rate of infection for the vaccinated class
ϕ	Per capita recovery rate with treatment
γ	Per capita recovery rate without treatment
λ	Per capita recurrence rate

Our model takes into account the presence of a vaccine that protects the susceptibles from getting infected. It is not likely that the vaccine will help people that are already infected with the virus, so we do not consider any movement from I to V but only from V to I. We assume that the vaccine efficacy is less than 100%. Therefore, it is possible for vaccinated people to get infected but not at the same degree as the susceptible people; so $\beta_2 \leq \beta_1$. Another assumption is that, on average, the vaccine induced immunity will wear off in $1/\omega$ years and an average individual stays in the susceptible class $1/\rho$ years before vaccination.

We assume that HSV-1 is not drug resistant. A person that has had treatment does not develop any protection from the virus in the future. Finally, we consider that the infected people seek treatment *only* when they are having an outbreak. Such a treatment consists of ointments and pills that lessen the pain and make the sores disappear faster.

2.1 Compartmental model

The box diagram in Figure 1 clearly illustrates the flow of individuals as an HSV-1 epidemic progresses.

Using the assumptions, definitons, and the box diagram, we can easily describe the dynamics of HSV-1 among the human population by the following system of

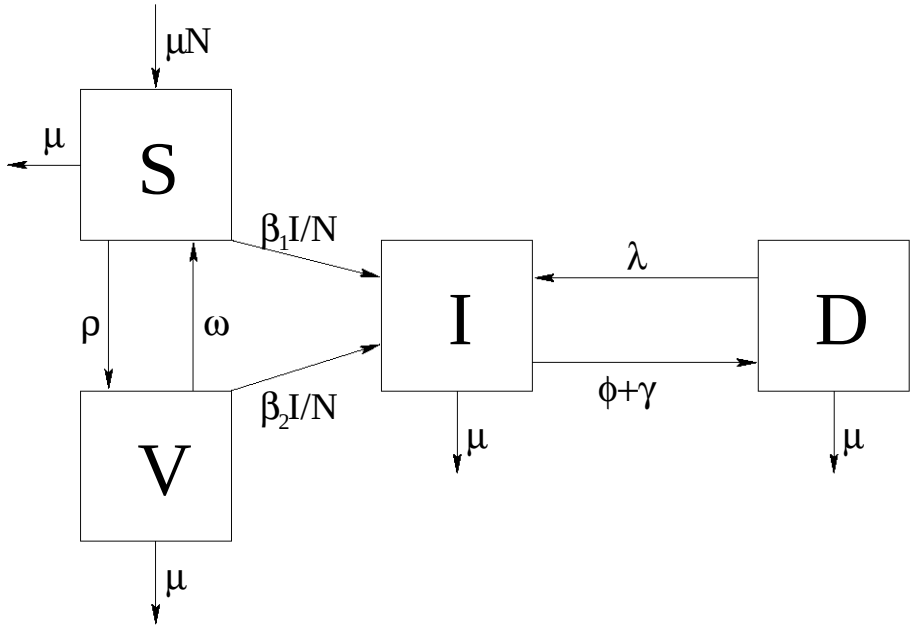

Figure 1: Compartmental model of HSV-1 with vaccination

nonlinear differential equations:

$$\frac{dS}{dt} = \mu N - \beta_1 S\frac{I}{N} + \omega V - (\rho + \mu)S \tag{1}$$

$$\frac{dI}{dt} = \beta_1 S\frac{I}{N} + \beta_2 V\frac{I}{N} + \lambda D - (\phi + \gamma + \mu)I \tag{2}$$

$$\frac{dD}{dt} = (\phi + \gamma)I - (\lambda + \mu)D \tag{3}$$

$$\frac{dV}{dt} = \rho S - \beta_2 V\frac{I}{N} - (\mu + \omega)V, \text{ where} \tag{4}$$

$$N = S + I + D + V \tag{5}$$

As we can see, equation 5 implies that $N' = S' + I' + D' + V'$. Direct computation yields that $S' + I' + D' + V' = 0$, which shows that N, the population size, is constant. Also, since N is constant, there is no harm in assuming $N = 1$. However, we chose not to do so.

3 Model analysis

In this section we analyze the system presented in Equations (1) – (5). We first find the vaccination-treatment reproductive number, $\mathcal{R}(\rho, \phi)$, and deduce from it the basic reproductive number $\mathcal{R}_0$. We also discuss the relationship between $\mathcal{R}(\rho, \phi)$ and $\mathcal{R}_0$. $\mathcal{R}$ is a function of ρ and ϕ that fits our goal of evaluating the importance of vaccination and treatment in the disease dynamics. We analyze the equilibria of the system, and carry out sensitivity and uncertainty analysis. We perform sensitivity analysis in order to determine which parameter would have a greater effect on the vaccination-treatment reproductive number. We also perform uncertainty analysis in the vaccination-treatment reproductive number because of the uncertainty in estimating the parameter values.

3.1 Reproductive Numbers

Using standard methods (see Appendix), we calculate the vaccination-treatment reproductive number $\mathcal{R}(\rho, \phi)$,

$$\mathcal{R}(\rho, \phi) = \frac{1}{\gamma + \mu + \phi}\left(\beta_1 \frac{\mu + \omega}{\mu + \rho + \omega} + \beta_2 \frac{\rho}{\mu + \rho + \omega} + \frac{\lambda(\gamma + \phi)}{\lambda + \mu}\right)$$

A possible explanation for $\mathcal{R}(\rho, \phi)$ is as follows, $\frac{1}{\gamma+\mu+\phi}$ is the average time that an infected individual spent in class I. $\frac{\beta_1(\mu+\omega)}{\mu+\omega+\rho}$ is the rate at which susceptible individuals enter class I. $\frac{\beta_2\rho}{\mu+\omega+\rho}$ is the rate at which vaccinated individuals enter class I. $\frac{\lambda(\phi+\gamma)}{\lambda+\mu}$ is the rate at which dormant individuals enter class I and infected individuals enter class D.

When ρ and ϕ equal to zero we have

$$\mathcal{R}(0, 0) = \frac{1}{\gamma + \mu}\left(\beta_1 + \frac{\lambda\gamma}{\lambda + \mu}\right)$$

Notice that $\mathcal{R}(0, \phi)$ does not depend on ω. This is in agreement with our expectation, that if the population is not vaccinated, the period of immunization is zero.

Also, note that $\rho = \phi = 0$ implies that the dynamics of HSV-1 will not be affected by any external intervention – all the movement of individuals from one class to

another will only depend on the dynamics of the population and the disease. Hence, $\mathcal{R}(0,0)$ is the basic reproductive number of the disease. We write it as $\mathcal{R}_0 = \mathcal{R}(0,0)$.

This number offers the following meaning: $\frac{\beta_1}{\gamma+\mu}$ is the rate at which susceptible individuals enter the infectious class in the absence of treatment or vaccination. Furthermore, $\frac{\lambda\gamma}{(\gamma+\mu)(\lambda+\mu)}$ is the contribution that the D class makes to the I class. The products $\lambda\gamma$, and $\frac{1}{\lambda+\mu}\frac{1}{\gamma+\mu}$, emphasize the cycle of in-flow and out-flow between I and D, as $\frac{1}{\lambda+\mu}$ is the average time spent in the D class and $\frac{1}{\gamma+\mu}$ is the average time spent in I, without treatment or vaccination.

3.2 Disease-free equilibrium

The model has the following disease-free equilibrium,

$$E_0 = \left(\frac{N(\mu+\omega)}{\mu+\rho+\omega}, 0, 0, \frac{\rho N}{\mu+\rho+\omega}\right)$$

The computation of this equilibrium point is included in the Appendix.

According to previous work [8], E_0 is locally asymptotically stable whenever the vaccination-treatment reproductive number of the system is less than one.

3.3 Endemic equilibrium

We now show the existence of at least one endemic equilibrium, when $\mathcal{R}(\rho,\phi) > 1$.

Proposition 1. *If $R(\rho,\phi) > 1$, then the system described in (1) – (5) has a unique endemic equilibrium point.*

Proof. See the Appendix. ■

In the proof included in the appendix, we define

$$a = \frac{\beta_1\beta_2}{N}\left(1 + \frac{\phi+\gamma}{\lambda+\mu}\right),$$
$$b = \beta_1\left((\mu+\omega)(1+\frac{\phi+\gamma}{\lambda+\mu}) - \beta_2\right) + \beta_2\left((\phi+\gamma+\mu) - \lambda\frac{\phi+\gamma}{\lambda+\mu} + \rho\left(1+\frac{\phi+\gamma}{\lambda+\mu}\right)\right)$$
$$c = N(\gamma+\phi+\mu)(\mu+\rho+\omega)(1-\mathcal{R}(\rho,\phi)).$$

With this in mind, one has

Proposition 2. *Let b and Δ be defined as before, then if $b > 0$ and $R(\rho, \phi) < 1$ there is no endemic equilibrium point.*

Proof. Since $\mathcal{R}(\rho, \phi) < 1$ we have that $c > 0$. So, from the Vièta relations, we have that $r_1 r_2 > 0$ and $r_1 + r_2 < 0$. Thus, both non-zero roots of (7) are negative. ■

Proposition 3. *Let b and Δ be defined as before, then if $b < 0$, $\Delta > 0$, and $\mathcal{R}(\rho, \phi) < 1$ there are two endemic equilibria points.*

Proof. If $\mathcal{R}(\rho, \phi) < 1$, then $c > 0$. This implies that $r_1 r_2 > 0$ and $r_1 + r_2 > 0$. In this case, there are two positive solutions to (7), and so two endemic equilibria. ■

Since $\mathcal{R}(\rho, \phi) > 1 \iff c < 0$, in this case $\Delta > 0$. Hence, the positive solution to (7) is given by

$$\frac{-b + \sqrt{b^2 - 4ac}}{2a}$$

Similarly, whenever the conditions of Proposition 3 are given, the two endemic states are

$$\frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

Whenever the conditions of Proposition 3 are satisfied, the model defined in (1) – (5) presents a backward bifurcation behavior. This implies that, depending on the initial conditions, $R(\rho, \phi) < 1$ is not enough to control the prevalence of HSV-1 infection. Figure 2(b) is a schematic representation of a backward bifurcation behavior; in contrast with Figure 2(a) which represents a forward bifurcation behavior.

Note that in the case of Figure 2(a) there is only one bifurcation point to know, $\mathcal{R}(\rho, \phi) = 1$. On the other hand, in the case of Figure 2(b), we have two bifurcation points to know, $\mathcal{R}(\rho, \phi) = C$, where $C < 1$, and $\mathcal{R}(\rho, \phi) = 1$. We summarize the results of propositions 1 – 3 in Table 2. We use the expression "NA" to indicate: (1) that once some conditions have been fixed to certain parameters, the rest can be inferred; (2) that the conditions on the parameters that have been assigned "NA" do not matter for the result to hold. For instance, in the second row of Table 2, once we have $\mathcal{R}(\rho, \phi) < C$, the conditions upon b and Δ do not matter. Also, in row 4, one only needs $\mathcal{R}(\rho, \phi) > 1$ for a unique endemic equilibrium to exist.

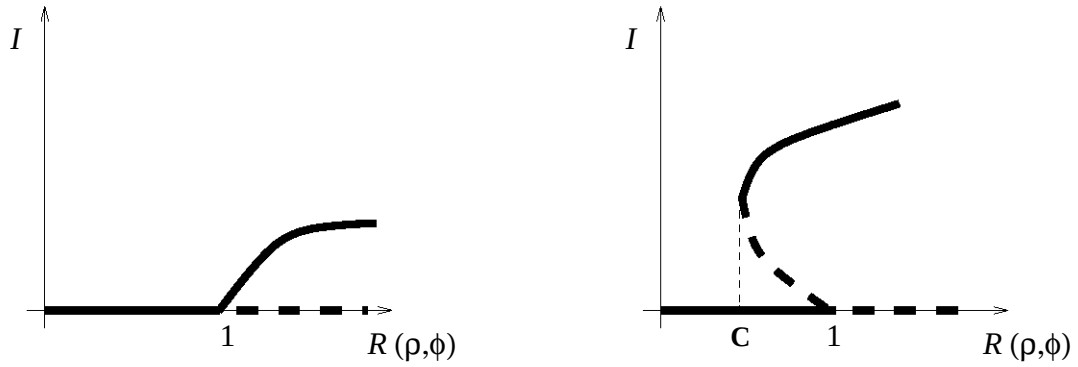

Figure 2: (a) Forward bifurcation (b) Backward bifurcation

Table 2: Existence of Equilibria.

$\mathcal{R}(\rho,\phi)$	b	Δ	Number of Equilibria
$\mathcal{R}(\rho,\phi) < C$	NA	NA	One: DFE only
$C < \mathcal{R}(\rho,\phi) < 1$	< 0	> 0	Three: DFE and two endemic equilibria
$\mathcal{R}(\rho,\phi) = C$	NA	$= 0$	Two: DFE and one endemic equilibrium
$\mathcal{R}(\rho,\phi) > 1$	NA	NA	One: Unique endemic equilibrium

Proposition 3 only gives conditions for the existence of two endemic equilibria points. However, one usually uses the term "backward bifurcation" to refer to the case of Figure 2(b). In order to guarantee that, we use Theorem 4.1 in [3] .

Proposition 4. *The system described in (1) – (4) presents a backward bifurcation when* $\mathcal{R}(\rho,\phi) < 1$ *and*

$$\frac{(\beta_1-\beta_2)\rho}{\rho+\mu+\omega}\left(1+\frac{\beta_2}{\mu+\omega+\rho}+\frac{\phi+\gamma}{\lambda+\mu}\right)-\beta_1\left(1+\frac{\phi+\gamma}{\lambda+\mu}\right)>0$$

Proof. See the Appendix. ■

3.4 Sensitivity Analysis of $\mathcal{R}(\rho,\phi)$

We calculate the sensitivity index of $\mathcal{R}(\rho,\phi)$ with respect to all our parameters, as can be seen in Table 3. The values of all the parameters were fixed to determine their sensitivity index. A negative sensitivity index means that an increase in the value of parameters, in our case γ, μ, ϕ, and ρ would decrease $\mathcal{R}(\rho,\phi)$. On the

other hand, a positive sensitivity index means that an increase in the value of a parameter, in our case, β_1, ω, and λ, and β_2 would increase $\mathcal{R}(\rho, \phi)$. We notice that the sensitivity index of our parameters are small in value, and as a result, a perturbation in the values of our parameters would have little effect on $\mathcal{R}(\rho, \phi)$.

Table 3: Calculated sensitivity index of $\mathcal{R}(\rho, \phi)$ with respect to the parameters.

Parameters	Sensitivity Index
γ	-0.003529
μ	-0.006736
ϕ	-0.003395
β_1	0.005047
ω	0.001642
ρ	-0.001993
λ	0.006386
β_2	0.002510

Since we are interested in the combination of vaccination and treatment to control the prevalence and incidence of HSV-1 in the population, we focus on the sensitivity analysis of ρ and ϕ. These are the only parameters that can be influenced by exterior forces, such as vaccination and treatment policies.

Let S_q be the sensitivity index of $\mathcal{R}(\rho, \phi)$ with respect to the parameter q. We are going to compare S_ρ and S_ϕ. For that, we fix all the other parameters using values from Table 4 except for ρ and ϕ. Since $\mathcal{R}_0 \geq \mathcal{R}(\rho, \phi)$, S_ρ and S_ϕ must be both negative. This is confirmed experimentally. Furthermore, as expected, the relation between S_ρ and S_ϕ depends heavily on the chosen parameters. In figure 3 we plot $S_\rho = S_\phi$ in the $\rho - \phi$ plane. We notice that $|S_\phi| \leq |S_\rho|$ below the curve meaning that, in that region, an increase in the value of ρ would have a slightly greater impact in decreasing $\mathcal{R}(\rho, \phi)$ compared to ϕ. On the other hand, $|S_\rho| \leq |S_\phi|$ above the curve meaning that, in that region, an increase in the value of ϕ would have a slightly greater impact in decreasing $\mathcal{R}(\rho, \phi)$ compared to ρ.

In Figure 4 we graph $S_\phi = S_\rho$ in the $\rho - \phi$ plane with different values of β_2. Note how the curve dividing the two regions changes in each case. One verifies the dependence of the sensitivity index on the parameters given.

Figure 5 represents the equation $\mathcal{R}(\rho, \phi) = 1$. $\mathcal{R}(\rho, \phi)$ is greater than 1 below the curve. $\mathcal{R}(\rho, \phi)$ is less than 1 above the curve.

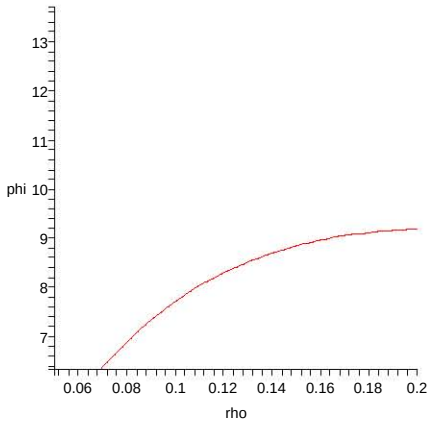

Figure 3: $S_\phi = S_\rho$

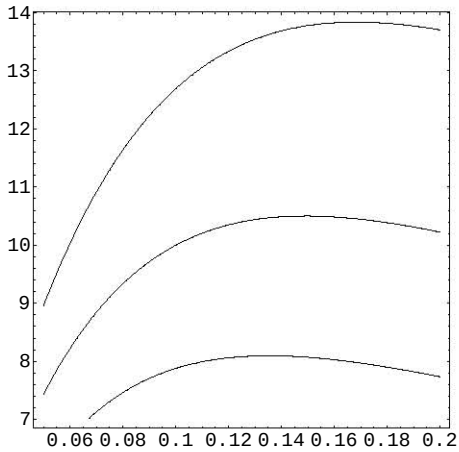

Figure 4: $|S_\phi| = |S_\rho|$ in the $\rho - \phi$ plane with different values of β_2. From bottom up, $\beta_2 = 0.0435, 0.094, 0.1305$

4 Numerical Simulations

We now present the numerical results obtained. The first experiment that we performed is to see the long-time behavior of our model when $\rho = \phi = 0$. Using the parameters estimated in Table 4, we get the the graphs presented in Figure **??**.

In the simulation, $V = 0$, as there is no in-flow to V. Also, the infectious and dormant class attain a steady state quite fast. Furthermore, the susceptible class

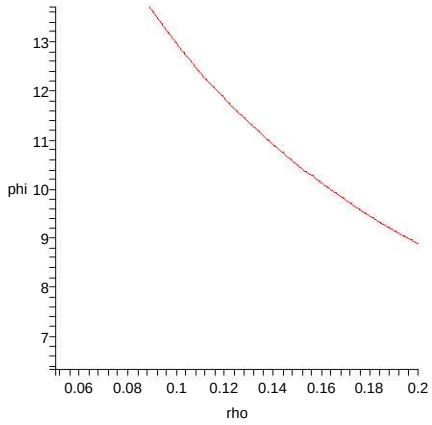

Figure 5: $\mathcal{R}(\rho, \phi) = 1$

decays almost linearly. Figure 6 shows that HSV-1 infection is more or less stable with the current parameter values, which is in agreement with the information found in current literature [5], [13], [15], [16], [22].

4.1 Parameter Values

To run the numerical simulations, we use estimations included in previous works (See Table 4). We now explain the values given to the parameters.

1. μ. The life expectancy of an American individual is estimated to be between 70 – 77.2 years. We use the estimation for United States in 2001, provided by the National Center for Health Statistics [13], and [22].

2. ρ. This parameter does not depend on the epidemiology of the disease or the dynamics of the American population. In our model, $1/\rho$ is estimated to be between 5 – 20 years.

3. $1/\omega$. It is estimated to be between 10 – 20 years. Since HSV-1 and HSV-2 are closely related, we use the same estimations as in [16].

4. λ. Recurrent oral herpes affects about 20% of the adult population in the United States [17]. Most people have two to three sores a year [5]. Since our class I includes people that may or may not show symptoms, we consider that

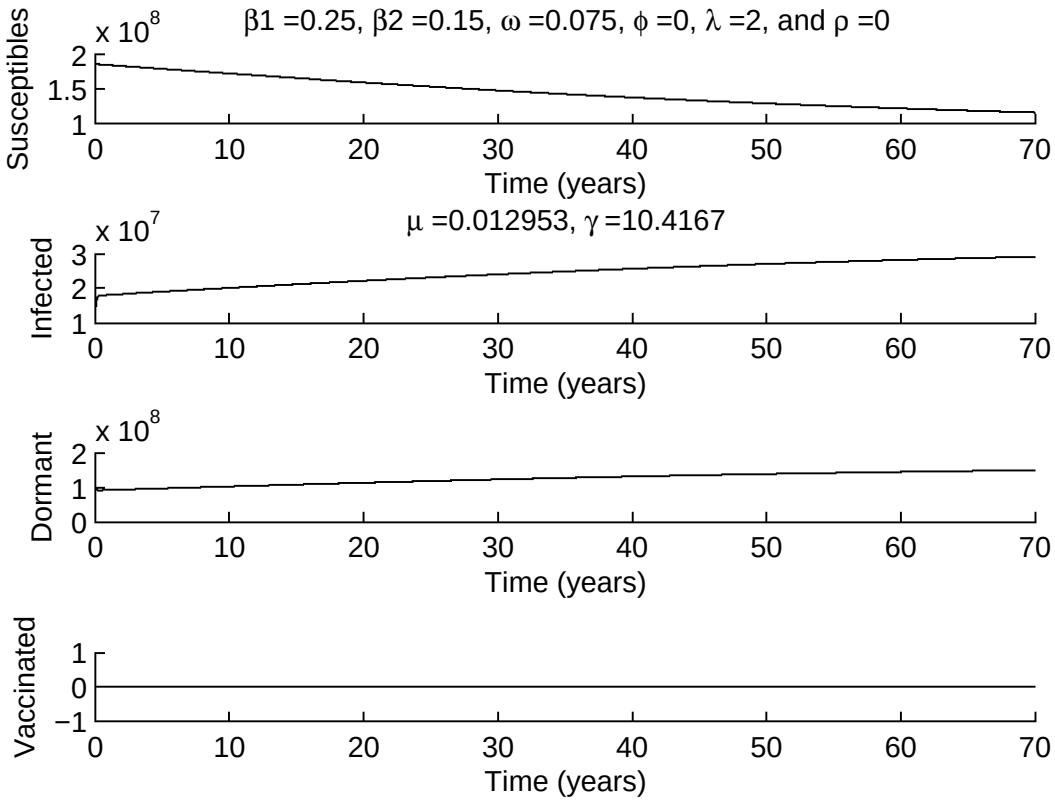

Figure 6: Dynamics of HSV-1 with $\rho = \phi = 0$.

the virus becomes active (whether it shows symptoms or not) between two and three times a year. Hence, λ is in the range between 1/(0.5 year) and 1/(0.4 year)

5. β_1. As pointed out by Malkin [15], due to the asymptomatic infection in certain individuals, it is difficult to estimate the rate of infection. We follow Malkin's suggestion and let β_1 range from 5% to 24%.

6. γ'. It is estimated that when active, the virus remains so from 1 to 2 weeks.

7. ϕ'. With treatment, the virus remains active in average one day less than without treatment. This data is available for users of Valtrex®, and we assume that other treatments such as ointments have a similar effect.

8. p. This is the effective treatment rate. The numerical simulations performed in 6 suggest that p varies between 23% and 3% of the whole population. We were not able to obtain real data for this parameter.

Table 4: Estimation of parameters.

Parameters	Minimum value	Maximum value
μ	$(1/77.2)$ yr^{-1} [22]	$(1/70)$ yr^{-1} [13]
ρ	$1/20$	$1/5$
ω	$1/20$ [16]	$1/10$ [16]
β_1	0.05 [15]	0.24 [15]
ϕ'	$(1/0.0356)$ yr^{-1}	$(1/0.0164)$ yr^{-1}
γ'	$(1/0.0384)$ yr^{-1}	$(1/0.0192)$ yr^{-1}
p	0.2	0.25
λ	$1/0.5$ yr^{-1} [5]	$1/0.4$ yr^{-1} [5]
α	0.3 [16]	0.9 [16]

5 Uncertainty Analysis

We perform uncertainty analysis in $\mathcal{R}(\rho, \phi)$ to estimate the variability of $\mathcal{R}(\rho, \phi)$ as a result of the uncertainty in estimating the parameter values. We use the values for $\beta_1, \beta_2, \omega, \phi, \gamma, \rho, \mu$, and λ from Table 4 and use Monte Carlo simulations (simple random sampling) to determine the uncertainty of $\mathcal{R}(\rho, \phi)$. We assume that

$$\mu \sim \exp(\mu = 1/70) \qquad \lambda \sim \text{Unif}(a = 2, b = 3)$$
$$\omega \sim \exp(\mu = 1/20) \qquad \phi \sim \exp(\mu = 0.04)$$
$$\beta_1 \sim \text{Unif}(a = 0.05, b = 0.24) \qquad \beta_2 \sim \text{Unif}(a = 0.01, b = 0.21)$$
$$\gamma \sim \exp(\mu = 0.04) \qquad \rho \sim \exp(\mu = 1/5)$$

We compute $\mathcal{R}(\rho, \phi)$ by sampling the parameters 10000 times from different probability distributions. This sampling generates a histogram of the frequencies from the different values obtained for $\mathcal{R}(\rho, \phi)$. Figure 7 collects the results for one realization, which looks like a Gamma distribution.

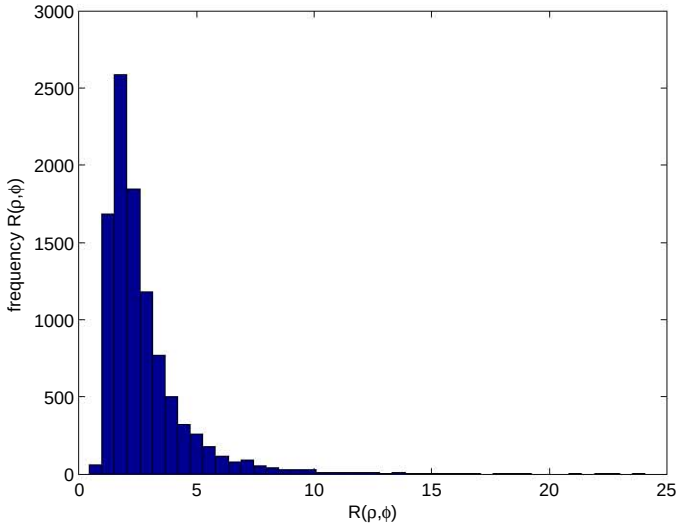

Figure 7: Histogram of $\mathcal{R}(\rho, \phi)$ for one realization of 10000 samplings.

6 Estimating the Cost of Vaccination and Treatment

Taking into consideration the work done by Daley et al. [6], we formulate a cost function that can be used to compare the cost of the vaccine and the treatment over a certain time interval,

$$\mathbf{Cost}(\rho, \phi) = P_v \rho S(\infty) + P_{tr} \phi I(\infty) \tag{6}$$

where P_v is the price of the vaccine, $\rho S(\infty)$ is the flow from susceptible to vaccinated per unit time, P_{tr} is the amount of money that is spent on treatment per infected per unit time, and $\phi I(\infty)$ is the flow from infectious to dormant who go through treatment per unit time.

The details of computing the cost function $\mathbf{Cost}(\rho, \phi)$ are described in Algorithm 1, which is included in the appendix. One detail to notice is that our goal is to reduce $\mathcal{R}_0$ by 1%. At first glance, such a goal does not seem an ambitious one. However, considering the sensitivity analysis performed on $\mathcal{R}(\rho, \phi)$, one sees that changing ρ and ϕ actually exerts little change to $\mathcal{R}(\rho, \phi)$. Therefore, 1% is an achievable goal.

We perform three different kind of experiments to graph the cost function.

In the first case, we look at the trivial vaccination strategy of vaccinating all the susceptible. This is optimal when, for instance, $P_{tr} \approx 50\%$ of P_v. We can see in Figure 8 that **Cost** is minimal when $\rho = 1$. The same behavior occurs when $P_{tr} \geq 0.5 \times P_{tr}$. In this case, one observes that the higher the vaccination rate, the lower the treatment rate, and the lower the cost obtained. This means that the majority of the resources should be devoted to vaccination.

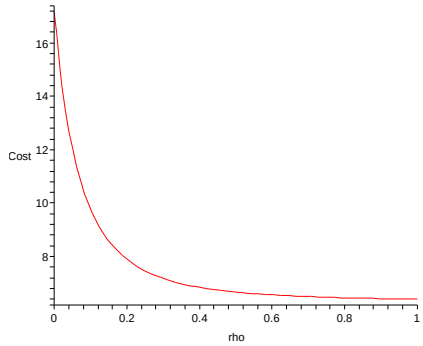

Figure 8: **Cost** when $P_{tr} = 0.5 \times P_v$

In the second case, we look at the vaccination strategy of not vaccinating any individual. This is optimal, for instance, when P_{tr} equals 10% of P_v. We can see in Figure 9 that **Cost** is minimal when $\rho = 0$. The same behavior occurs when $P_{tr} \leq 0.1 \times P_v$. This implies that all resources should be spent on treatment rather than vaccination.

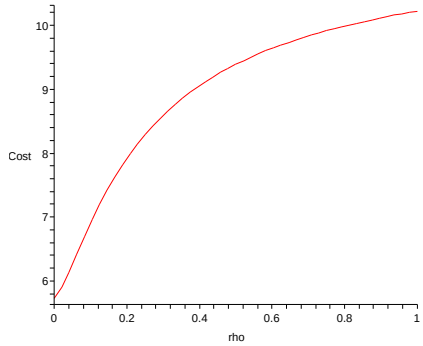

Figure 9: **Cost** when $P_{tr} = 0.1 \times P_v$

In the third case, we study $0.1 \times P_v < P_{tr} < 0.45 P_v$. Here we obtain a non trivial vaccination-treatment strategy. For instance, $P_{tr} \approx 25\%$ of P_v. We can see in

Figure 10 that the optimal vaccination-treatment strategy in this case is to vaccinate about 24% of the susceptible population. Table 5 presents different values for this case. Note that the optimal vaccination-strategy – in terms of cost – depends on the actual price of the vaccine, which is difficult to estimate at this time, since it is not available yet.

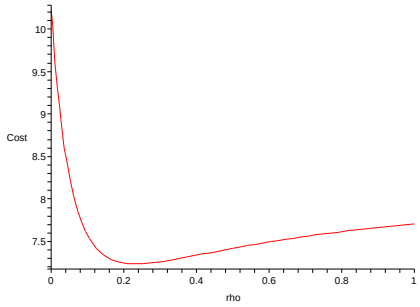

Figure 10: **Cost** when $P_{tr} = 0.25 \times P_v$

Table 5 presents different optimal vaccination-treatment strategies depending on the relationship between P_v and P_{tr}.

Table 5: Optimal values of vaccination and treatment.

P_{tr}	percentage vaccinated	Percentage treated
10% of P_v	0	$\approx 23\%$
11% of P_v	< 0.01	$\approx 22\%$
25% of P_v	0.23	$\approx 7\%$
42% of P_v	0.85	$\approx 3.3\%$
43% of P_v	0.91	$\approx 3.2\%$
44% of P_v	0.97	$\approx 3.1\%$
45% of P_v	1	$\approx 3\%$

As one can see from Table 5, there are two trivial vaccination-treatment strategies – either vaccinating the whole susceptible population or none. This happens, approximately, when $P_{tr} \geq 0.45 \times P_v$, and $P_{tr} < 0.11 \times P_v$, respectively. For other values of P_{tr}, Table 5 presents the approximate optimal solution.

7 Discussion and Conclusions

The purpose of this study was to develop a mathematical model for HSV-1 with a combination of treatment and vaccination. This model is a "future model" and will be more accurate for the population in the next couple of years, when the vaccine becomes available. We want to show with a function of cost, what vaccination-treatment strategy will be more effective to reduce $\mathcal{R}_0$. To do this we formulated an SVID model which has ϕ as the treatment rate and ρ as the vaccination rate.

We only consider oral HSV-1 that causes blisters and cold sores on the lips. We take under consideration that only a susceptible person can be vaccinated and that the vaccine is not a 100% efficient. Vaccine induced-immunity waines after $1/\omega$ years and HSV-1 is not drug -resistant. We consider that the infected people are under treatment only when they have an outbreak. We computed the reproductive number, our equilibria, which are the DFE and the endemic, and discussed their stability.

From the sensitivity analysis, we saw that if we change our vaccination and treatment rate, $\mathcal{R}(\rho, \phi)$ does not change dramatically. From our uncertainty analysis, by choosing mostly exponential or uniform distribution for the parameters which appear in $\mathcal{R}(\rho, \phi)$, we obtain the histogram presented in Figure 7. From such a histogram, it seems as though $\mathcal{R}(\rho, \phi)$ has a Gamma distribution.

Our results are similar to the ones obtained by [16] that the vaccine will have limited impact on the prevalence of the infection. In fact, in some cases, the treatment is more effective. These results were obtained from a simpler model than the one presented in [16]. Some of the possible reasons why HSV-1 cannot be easily reduced are: (1) it is a disease that is already widespread, (2) the fact that HSV-1 is an asymptomatic disease does not help to reduce its spread, as a person may transmit the disease without knowing, and (3) the disease is life-lasting, and so once a person is infected, he or she will carry the disease all his or her life.

We plotted the cost function given in Equation (6) for certain parameter values, and as a result we conclude that the optimal vaccination-treatment strategy depends on the relationship between P_v and P_{tr}. When $P_{tr} \approx 50\%$ of P_v, the optimal strategy is to vaccinate 100% of the susceptible population. When $P_{tr} \approx 10\%$ of P_v, the optimal strategy is to use treatment. Finally, when $P_{tr} \approx 25\%$ of P_v, the optimal strategy is to vaccinate about 20% of the susceptible population.

8 Future Work

As future work we would like to compare our results with similar ones obtained for HSV-2.

Also, a bifurcation analysis needs to be done on the system.

Since there is no vaccine nowadays, it would be interesting to see the effect of increasing the length of the dormant period on the disease by improving treatment.

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10 Appendix

Sensitivity index of the parameters

Table 6 presents the sensitivity index of $\mathcal{R}(\rho, \phi)$ with respect to all the parameters.

Finding the disease-free equilibrium

We now find the disease free equilibrium (DFE) of the system, which we represent by (S_0, I_0, D_0, V_0), where $I_0 = 0$. Under this condition, from (3) we get that

$$(\lambda + \mu)D_0 = 0, \text{ or } D_0 = 0$$

Table 6: Sensitivity Analysis of $\mathcal{R}(\rho, \phi)$.

Parameters	Sensitivity Index
γ	$\frac{\gamma}{\gamma+\mu+\phi} + \frac{\lambda\gamma(\mu-\phi)}{\mathcal{R}(\rho,\phi)(\gamma+\mu)^2(\gamma+\mu+\phi)}$
μ	$\mu\big(\frac{-1}{\gamma+\mu+\phi} + \frac{\beta_1}{(\mu+\rho+\omega)(\gamma+\mu+\phi)\mathcal{R}(\rho,\phi)} - \frac{\lambda(\gamma+\phi)}{(\gamma+\mu)^2(\gamma+\mu+\phi)\mathcal{R}(\rho,\phi)} - \frac{\beta_1(\mu+\omega)-\beta_2\rho}{(\mu+\rho+\omega)^2(\gamma+\mu+\phi)\mathcal{R}(\rho,\phi)}\big)$
ϕ	$\phi\big(\frac{-1}{\gamma+\mu+\phi} + \frac{\lambda}{(\gamma+\mu+\phi)(\gamma+\mu)\mathcal{R}(\rho,\phi)}\big)$
β_1	$\frac{\beta_1(\mu+\omega)}{(\gamma+\mu+\phi)(\mu+\rho+\omega)\mathcal{R}(\rho,\phi)}$
ω	$\omega\big(\frac{\beta_1}{(\mu+\rho+\omega)\mathcal{R}(\rho,\phi)(\gamma+\mu+\phi)} - \frac{\beta_1(\mu+\omega)+\beta_2\rho}{(\mu+\rho+\omega)^2\mathcal{R}(\rho,\phi)(\gamma+\mu+\phi)}\big)$
β_2	$\frac{\rho\beta_2}{(\gamma+\mu+\phi)(\mu+\rho+\omega)\mathcal{R}(\rho,\phi)}$
λ	$\frac{(\gamma+\phi)\lambda}{(\gamma+\mu+\phi)(\gamma+\mu)\mathcal{R}(\rho,\phi)}$
ρ	$\frac{\rho(-\frac{\beta_1(\mu+\omega)}{(\mu+\rho+\omega)^2}+\frac{\beta_2}{\mu+\rho+\omega}-\frac{\beta_2\rho}{(\mu+\rho+\omega)^2})}{(\gamma+\mu+\phi)\mathcal{R}(\rho,\phi)}$

Now, from equations (1), and (4), we get that

$$\begin{aligned}\omega V_0 - \rho S_0 - \mu S_0 &= -\mu N\\ \rho S_0 - \omega V_0 - \mu V_0 &= 0\end{aligned}$$

One can solve the system above using Cramer's rule to obtain

$$S_0 = \frac{\det\begin{bmatrix}-\mu N & \omega\\ 0 & -(\omega+\mu)\end{bmatrix}}{\det\begin{bmatrix}-(\rho+\mu) & \omega\\ \rho & -(\omega+\mu)\end{bmatrix}} = \frac{N(\mu+\omega)}{\mu+\rho+\omega}$$

$$V_0 = \frac{\det\begin{bmatrix}-(\rho+\mu) & -\mu N\\ \rho & 0\end{bmatrix}}{\det\begin{bmatrix}-(\rho+\mu) & \omega\\ \rho & -(\omega+\mu)\end{bmatrix}} = \frac{\rho N}{\mu+\rho+\omega}$$

and so, the DFE state is $E_0 = (S_0, 0, 0, V_0)$.

The Jacobian of our system is

$$J = \begin{bmatrix}-\beta_1\frac{I}{N} - \rho - \mu & -\beta_1\frac{S}{N} & 0 & \omega\\ \beta_1\frac{I}{N} & \beta_1\frac{S}{N} + \beta_2\frac{V}{N} - \phi - \gamma - \mu & \lambda & \beta_2\frac{I}{N}\\ 0 & \phi+\gamma & -(\lambda+\mu) & 0\\ \rho & -\beta_2\frac{V}{N} & 0 & -\left(\omega + \beta_2\frac{I}{N} + \mu\right)\end{bmatrix}$$

Evaluating the reproductive number

We will use the second generation operator method, as described in van den Diekmann and Heesterbeek [7], and van den Driessche and Watmough [8]. Let X be the vector whose components are the functions that represent the classes that are not infected; Y be the vector whose component is the dormant class, and Z be the vector whose component is the function representing the infectious class. In the case of this model

$$X = \begin{bmatrix} S \\ V \end{bmatrix}, \quad Y = \begin{bmatrix} D \end{bmatrix}, \quad Z = \begin{bmatrix} I \end{bmatrix}$$

the disease-free equilibrium is

$$\left(\frac{N(\omega + \mu)}{\mu + \omega + \rho}, 0, 0, \frac{N\rho}{\mu + \omega + \rho} \right)$$

From equation (3) we know that

$$D = \frac{I(\gamma + \phi)}{\lambda + \mu}$$

and so

$$Y^*(X^*, Z) = \frac{I(\gamma + \phi)}{\lambda + \mu}$$

Now, we obtain

$$\frac{\partial}{\partial Z} \frac{dZ}{dt} \bigg|_{X=X^*, Y=Y^*(X^*,Z)} = \beta_1 \frac{\mu + \omega}{\mu + \rho + \omega} + \beta_2 \frac{\rho}{\mu + \rho + \omega} + \frac{\lambda(\gamma + \phi)}{\lambda + \mu} - (\gamma + \mu + \phi)$$

We find that

$$\mathcal{R}(\rho, \phi) = \frac{1}{\gamma + \mu + \phi} \left(\beta_1 \frac{\mu + \omega}{\mu + \rho + \omega} + \beta_2 \frac{\rho}{\mu + \rho + \omega} + \frac{\lambda(\gamma + \phi)}{\lambda + \mu} \right)$$

When ρ and ϕ equal to zero we have

$$\mathcal{R}(0, 0) = \frac{1}{\gamma + \mu} \left(\beta_1 + \frac{\lambda\gamma}{\lambda + \mu} \right)$$

Proof of Proposition 1

Proof. Since we know that N is constant, we ignore equation (1) and express (3)

and (4) in terms of I^*. From equation (3) and (4), we get that

$$D = \frac{\phi+\gamma}{\lambda+\mu}I, \quad V = \frac{\rho(N-I-D)}{\beta_2\frac{I}{N}+\mu+\omega+\rho}$$

Substituting V and I into, we get a cubic equation that can be factored as

$$I(aI^2+bI+c) = Ip(I) \tag{7}$$

where $p(I) = aI^2+bI+c$.

$$a = \frac{\beta_1\beta_2}{N}\left(1+\frac{\phi+\gamma}{\lambda+\mu}\right),$$
$$b = \beta_1\left((\mu+\omega)(1+\frac{\phi+\gamma}{\lambda+\mu})-\beta_2\right)+\beta_2\left((\phi+\gamma+\mu)-\lambda\frac{\phi+\gamma}{\lambda+\mu}+\rho\left(1+\frac{\phi+\gamma}{\lambda+\mu}\right)\right)$$
$$c = N(\gamma+\phi+\mu)(\mu+\rho+\omega)(1-\mathcal{R}(\rho,\phi)).$$

Note that a is always positive and $R(\rho,\phi) > 1$ implies $c < 0$. Also note that D^* and V^* exist and are positive whenever I^* exists and is positive, since we managed to write them in terms of I^*. We considered the case $I^* = 0$ in Section 3.2, so we assume that $I^* \neq 0$; this implies that $ax^2+bx+c = 0$. Now, if r_1, r_2 are the roots of ax^2+bx+c, by Viète's Theorem, one has $r_1+r_2 = -b/a$ and $r_1r_2 = c/a$. Let $\Delta = b^2-4ac$, and note that $\Delta \geq 0$ whenever $R(\rho,\phi) > 1$. So when $R(\rho,\phi) > 1$ r_1, r_2 would be real numbers. Hence, from $r_1r_2 < 0$ we get that there is exactly one positive root, and so there is a unique endemic equilibrium point. ■

Proof of bifurcation

We verify the conditions of Theorem 4.1 in [3]. First,

$$\frac{dI}{dt} = \beta_1(N-I-D-V)\frac{I}{N}+\beta_2V\frac{I}{N}+\lambda D-(\phi+\gamma+\mu)I$$
$$\frac{dD}{dt} = (\phi+\gamma)I-(\lambda+\mu)D$$
$$\frac{dV}{dt} = \rho(N-I-D-V)-\beta_2V\frac{I}{N}-(\mu+\omega)V$$

In those equations we substitute the following, $I = X_1, D = X_2, V = X_3$. So our equations are $f_1 = \beta_1(N-X_1-X_2-X_3)\frac{X_1}{N}+\beta_2X_3/N+\lambda X_2-(\phi+\gamma+\mu)X_1$,

$f_2 = (\phi+\gamma)X_1 - (\lambda+\mu)X_2$, and $f_3 = \rho(N - X_1 - X_2 - X_3) - \beta_2 X_3/N - (\mu+\omega)X_3$. The Jacobian Matrix of the system is

$$A = \begin{bmatrix} \beta_2\frac{X_3}{N} + \beta_1\frac{N-2(X_1)-X_2-X_3}{N} - \phi - \gamma - \mu & -\beta_1\frac{X_1}{N} + \lambda & -\beta_1\frac{X_1}{N} + \beta_2\frac{X_1}{N} \\ \phi + \gamma & -\mu - \lambda & 0 \\ -\rho - \beta_2\frac{X_3}{N} & -\rho & -\rho - \omega - \beta_2\frac{X_1}{N} - \mu \end{bmatrix}$$

and now we will use the DFE, which is

$$\left(0, 0, \frac{N\rho}{\mu+\omega+\rho}\right)$$

and substitute $X_1 = 0, X_2 = 0, X_3 = \frac{N\rho}{\mu+\omega+\rho}$ in A to obtain

$$B = \begin{bmatrix} \beta_2\frac{\rho}{\mu+\omega+\rho} - 2\beta_1\frac{\rho}{\mu+\omega+\rho} + \beta_1 - \phi - \gamma - \mu & \lambda & 0 \\ +\phi + \gamma & -\mu - \lambda & 0 \\ -\rho - \beta_2\frac{\rho}{\mu+\omega+\rho} & -\rho & -\rho - \omega - \mu \end{bmatrix}$$

We find the eigenvalues y_1, y_2, and y_3 of A. Simple inspection shows that $y_1 = -(\rho+\omega+\mu)$, and y_2, y_3 are the eigenvalues of

$$\begin{bmatrix} \beta_1 - (\phi+\gamma+\mu) + \frac{(\beta_2-\beta_1)\rho}{\mu+\omega+\rho} & \lambda \\ \phi + \gamma & -\mu - \lambda \end{bmatrix}$$

when $\mathcal{R}(\rho, \phi) = 1$, i.e.,

$$\beta_1\frac{\mu+\omega}{\rho+\omega+\mu} + \frac{\beta_2\rho}{\rho+\omega+\mu} + \lambda\frac{\lambda(\gamma+\phi)}{\lambda+\mu} = \gamma + \mu + \phi$$

$$\beta_1 - (\phi+\gamma+\mu) = \frac{(\beta_1-\beta_2)\rho}{\rho+\omega+\mu} - \frac{\lambda(\gamma+\omega)}{\lambda+\mu}$$

We get that $y_2 = 0$ and $y_3 = -\beta_1 - (\phi+\gamma+\mu) + \frac{(\beta_2-\beta_1)\rho}{\rho+\omega+\mu} - (\lambda+\mu)$. Note that y_3 is negative. So one has a simple zero eigenvalue and two negative ones.

Now we find the right and left eigenvector corresponding to $y_2 = 0$.

To find the right eigenvalue we calculate

$$\begin{bmatrix} -\lambda\frac{\gamma+\phi}{\lambda+\mu} & \lambda & 0 \\ \phi + \gamma & -\mu - \lambda & 0 \\ -\phi - \frac{\beta_2\rho}{\rho+\omega+\mu} & -\rho & -(\rho+\omega+\mu) \end{bmatrix} \begin{bmatrix} u_1 \\ u_2 \\ u_3 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

So the right eigenvector is

$$U = \begin{bmatrix} 1 \\ \frac{\phi+\gamma}{\lambda+\mu} \\ -\frac{\rho}{\rho+\omega+\mu}(1+\frac{\beta_2}{\mu+\omega+\rho}+\frac{\phi+\gamma}{\lambda+\mu}) \end{bmatrix}$$

To find the left eigenvector we calculate

$$\begin{bmatrix} -\lambda\frac{\gamma+\phi}{\lambda+\mu} & \phi+\gamma & -\rho-\frac{\beta_2\rho}{\rho+\omega+\mu} \\ \lambda & -\mu-\lambda & -\rho \\ 0 & 0 & -(\rho+\omega+\mu) \end{bmatrix} \begin{bmatrix} v_1 \\ v_2 \\ v_3 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}$$

So the left eigenvalue is

$$V = \begin{bmatrix} 1 \\ \frac{\lambda}{\mu+\lambda} \\ 0 \end{bmatrix}$$

Now we find a and b

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{(\partial)(x_i)(\partial)(x_j)}(0,0)$$
$$b = \sum_{k,i=1}^{n} v_k w_j \frac{\partial^2 f_k}{(\partial)(x_i)(\partial\phi)}(0,0)$$

It is easy to see that $b > 0$. So whenever $a > 0$ we have backward bifurcation.

We have five nonzero terms in a,

$$a = v_1u_2u_1\frac{\delta^2 f_1}{\delta x_2 \delta x_1} + v_1u_1u_1\frac{\delta^2 f_1}{\delta x_1 \delta x_1}(0,0) + v_1u_2u_1\frac{\delta^2 f_1}{\delta x_2 \delta x_1}(0,0) + \\ + v_1u_3u_1\frac{\delta^2 f_1}{\delta x_3 \delta x_1}(0,0) + v_1u_1u_3\frac{\delta^2 f_1}{\delta x_1 \delta x_3}(0,0)$$

Finally we have

$$a = -\frac{\beta_1}{N} - \frac{\beta_1(\phi+\gamma)}{N(\lambda+\mu)} + \frac{\rho}{N(\rho+\mu+\omega)}\left(1+\frac{\beta_2}{\mu+\omega+\rho}+\frac{\phi+\gamma}{\lambda+\mu}\right)(\beta_1-\beta_2)$$

By theorem 4.1, [3], one has backward bifurcation if $a > 0$. ■

Calculating C for the backward bifurcation

We can analytically compute C by noting that at this point, we only have one positive solution to (7). Since $\mathcal{R}(\rho, \phi) < 1$, to guarantee a unique positive solution, one needs $\Delta = 0$ and $b < 0$. Assuming that these conditions holds, we find that

$$C = 1 - \frac{1}{N} \frac{\beta_1 \Phi_1 + \beta_2 \Phi_2}{4\beta_1\beta_2\left(1 + \frac{\phi+\gamma}{\lambda+\mu}\right)(\gamma + \phi + \mu)(\mu + \rho + \omega)}$$

where

$$\Phi_1 = (\mu + \omega)(1 + \frac{\phi + \gamma}{\lambda + \mu}) - \beta_2 \text{ and } \Phi_2 = \phi + \gamma + \mu + \rho\left(1 + \frac{\phi + \gamma}{\lambda + \mu}\right) - \lambda\frac{\phi + \omega}{\lambda + \mu}$$

MATLAB code for the uncertainty analysis

```
% uncertainty analysis for basic repruduction number of svid-model
clear all

dim=1e4; reali=150; fname='sis-logistic_uncrt.mat';

%matrices storing data

r0im=zeros(dim,reali);

for j=1:reali

%distributions for parameters and sampling

%names of distributions to be used

name1='exponential'; name2='uniform';

par1=1/70; mu=random(name1,par1,dim,1);

par2=2;par14=3; lambda=random(name2,par2,par14,dim,1);

par3=1/20; ommega=random(name1,par3,dim,1);


par5=0.04; phi=random(name1,par5,dim,1);

par6=0.05; par7=0.24; beta_1=random(name2,par6,par7,dim,1);

par8=0.01; par9=0.21; beta_2=random(name2,par8,par9,dim,1);


par11=0.04; gamma=random(name1,par11,dim,1);

par12=1/5; rho=random(name1,par12,dim,1);

%basic reproductive numbers
```

```
r0im(:,j)=(1./(gamma+mu+rho)).*(beta_1.*(mu+ommega)./(mu+rho+ommega)+
beta_2.*(rho./(mu+rho+ommega))+lambda.*(phi+gamma)./(lambda+mu));

end
%for␣loop␣over␣realizations

%mean,median,std,iqr

mean_r0i=␣mean(r0im)';␣median_r0i=median(r0im)';␣std_r0i=std(r0im)';

for␣k=1:length(r0im(1,:))␣t1=r0im(:,k);
pg1r0i(k)=1-length(t1(find(t1<=1)))/length(t1);␣end

pg1r0i=pg1r0i';

%save␣sampled␣data

save(fname,'r0im')

%histograms␣for␣r0

nbins=100;␣edg=linspace(min(r0im(:,end)),max(r0im(:,end)),nbins);

bar(edg,histc(r0im(:,end),edg),'histc')␣xlabel('r0')
ylabel('frequency␣r0')␣axis([0,25,0,3000])
```

Algorithm 1 Finding the cost function

Input

parameters P_v, $P_{tr}, \mu, \gamma, \beta_1, \beta_2, \omega, \lambda$ such that $\mathcal{R}_0 > 1$.

Output

Cost function

$$\mathbf{Cost}(\rho, \phi) = P_v \rho S(\infty) + P_{tr} \phi I(\infty)$$

1: Solve $\mathcal{R}(\rho, \phi) = 0.99 \times \mathcal{R}_0$. This gives an expression for ϕ in terms of ρ; that is, $\phi = F(\rho)$.
2: Substitute $\phi = F(\rho)$ into $p(I)$ and solve $p(I) = 0$. This will give a unique positive solution, as $\mathcal{R}(\rho, \phi) > 1$. This solution is $I(\infty)$.
3: Find $S(\infty)$.
4: Plot $\mathbf{Cost}(\rho, \phi) = P_v \rho S(\infty) + P_{tr} F(\rho) I(\infty)$.

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