

# A Cost-Effective Analysis of Treatment Strategies for the Control of HSV-2 Infection in the U.S.: A Mathematical Modeling - Based Case Study

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## Abstract

Infection of Herpes Simplex Virus type 2 (HSV-2) is a lifelong disease, which is mainly sexually transmitted, causing genital lesions. According to the Center for Disease Control (CDC), prevalence of HSV-2 in 2015-2016 was estimated at 11.9% of the United States (US) population. The HSV-2 pathogen establishes latent infections in neural cells and can reactivate causing lesions later in life. The latent infection establishment mechanism involves a strategy that not only increases pathogenicity of the disease, but also allows the virus to evade the immune system. HSV-2 infections are treated by a standard therapeutic acyclovir, a synthetic acyclic purine-nucleoside analogue typically prescribed to symptomatic chronic patients, typically referred to a non-constitutional stage. The non-constitutional stage exhibits genital skin lesions and ulcers. The constitutional stage expresses mild symptoms such as fever, skin-redness, itching, headache, and painful urination. In this study, we develop and analyze a mathematical model that considers spread of HSV-2 among the population between the ages of 15-49 in the US and used it to design an optimal treatment distribution strategy. The goal of this research is to evaluate the cost effectiveness of (i) treating HSV-2 infected individuals who are in both constitutional and non-constitutional stages versus (ii) the current conventional treatment protocol for treating only the patients in the non-constitutional stage. Our results distinguish model parameter regimes where each of the two treatment strategy optimizes the available resources and consequently gives the long-term reduced cost associated in effectively handling a patients treatment, while reducing overall incidence. The public health cost of HSV-2 with the newly implemented treatment would increase from \$16 billion to \$20 billion. By considering the proposed strategy for treatment and comparing it with the conventional treatment, it can be observed that early treatment reduces HSV-2 incidence by 38% yearly. The estimated value of the reproductive number decreases by 40% from 2.5 which is based on current conventional treatment protocol.

# 1 Introduction

## 1.1 Epidemiology of HSV

Herpes simplex virus (HSV) is an incurable disease that persists during the lifetime of the human host and produces mucocutaneous infections [17]. There are two types of HSV: type 1 (referred to HSV-1) is less severe and usually transmitted from an infected person to a susceptible person through direct contact with bodily fluids, such as saliva, and type 2 (referred to HSV-2) is more severe than HSV-1 and is considered a sexually transmitted disease. HSV-2 infection in a healthy and non-infected person occurs through sexual contact and direct contact with bodily fluids with an infected person [21]. The present study is focused on HSV-2 and attempts to understand the impact of alternative treatment policy on its transmission dynamics.

Since the 1970s, the prevalence of HSV-2 has increased dramatically and is largely attributed to increased sexual activity. These risk factors include an increase in population with multiple sexual partners, presence of other sexually transmitted disease and a non-systematic condom use [10,17]. HSV-2 also significantly increases the risk of acquisition of human immunodeficiency virus (HIV) [3]. Approximately 417 million people between the ages of 15 to 49 years of age were infected with HSV-2 worldwide, and nearly 19.2 million of new infections occur each year worldwide [7]. Recent global estimations show that the prevalence of HSV-2 varies depending on the geographic region and is approximately 2-fold higher in women (14.8%) than in men (8%) [7]. Over 10% of the population in European, Eastern Mediterranean, Southeast Asian, and Western Pacific regions are living with HSV-2. The highest prevalence of HSV-2 was found in Africa with estimations of more than 30% of the population being infected [7]. In the United States, the prevalence of HSV-2 is approximately 12% of the population between 15-49 years of age of sexually active people according to the National Center for Health Statistics (NCHS) [8].

**Structure and Behavior of HSV-2 Pathogen:** HSV is a member of the herpesviridae family, that contains a linear double-stranded DNA [6,13,17]. The stages of the progression of HSV-2 infection are as follows. The initial exposure of HSV leads to a viral invasion of epithelial cells. Following the invasion, the virus begins intracellular replication at the site of exposure. In severe cases, the virus continues to replicate until it causes a cellular rupture leading to the formation of lesions in the genital areas. In the final stage of the infection period, the virus ascends through the periaxonal sheath of sensory nerves arriving to the trigeminal, cervical, lumbosacral or autonomic ganglia of the host nervous system, remaining out of reach of the immune system [13]. It may be possible to stop virus establishment if treated appropriately before it reaches sensory nerves and evade immune response. However, this window period before virus successful introduction in an individual is small (24 hours) and its length may depends on health condition of an individual [22]. HSV remains in a dormant state until the viral replication process is activated again, known as “viral reactivation” [6,13].

**Pathology of HSV-2:** Episodes of recurrences can occur throughout the life of the infected individual. Recurrence of both mild and severe symptoms following viral reactivation can exacerbate the transmission and disease dynamics of HSV-2. It is important to note that an HSV recurrence is not a reinfection. Once the virus is reactivated, the virus travels through sensory neurons to the mucocutaneous site, infects the cells, undergoes replication and generates clusters of vesicles in the initial site of infection [6,13]. Internal and external factors could trigger the recurrence of HSV-2 causing the virus to transition from a dormant to a replicating state. Several factors trigger viral reactivation

including: stress, fatigue, exposure to heat or sunlight, menstruation, fever, immunosuppression, corticosteroid administration, laser surgery and nerve damage [6, 13, 17]. Periodic recurrences of HSV-2 are common in infected individuals. While recurrence rates may vary based on the region and health of an individual, the median number of recurrences is five in the first year after a primary infection. During the second year of infection, the recurrence rate for HSV-2 decreases to a median of two recurrences per year [6]. Moreover, prior studies suggest that, on average, 47% of infected people present less than two recurrences per year, 36% of infected people two to five recurrences per year, and 16% of the patients presents more than five recurrences per year [14, 17].

The clinical manifestation of HSV-2 infections are described in two broad categories: constitutional and non-constitutional symptoms. Constitutional are mild symptoms, such as localized pain, tingling, burning sensation, headache, fever, dysuria, and inguinal lymphadenopathy who are often confused with symptoms of another infection or disease, and thus make it difficult to detect HSV-2 with high accuracy. Non-constitutional are severe symptoms such as lesions and ulcers who both vary in size and severity and are, in contrast, easily detected because. As the infection progresses, papules and vesicles of varying sizes and erosions appear. These vesicles gradually rupture to form irregular ulcers and erosions of lesions usually crust, re-epithelialize, and heal without scarring. This process can occur within two to six weeks in the absence of antiviral therapy [1, 6, 13, 17]. A summary of constitutional and non-constitutional symptoms are shown in Table 1.

Constitutional	Non-Constitutional
Skin redness	Genital lesions
Dysuria	Development of the lesions
Itching	Ulcerations
Fever	
Headache	
Swollen lymph nodes	
Muscles aches and pain in the groin	

Table 1: Typical of Constitutional and Non-constitutional Stage Symptoms

**Treatment of HSV-2:** One of the most widely used interventions to control the transmission of the disease is antiviral therapy and the recommended treatment for HSV-2 is Acyclovir. Acyclovir is a guanosine analogue that is monophosphorylated by the HSV-2 mechanism encoding for thymidine kinase, with the second and third phosphate groups being added by cellular kinases. The triphosphorylated nucleotide inhibits the viral DNA polymerase producing chain termination. Acyclovir becomes active only in infected cells, which contributes to keep a safety profile of the treatment and has demonstrated efficacy against mild to severe infections caused by HSV-2 in normal and immunocompromised patients [7].

The suggested formulation of the HSV-2 treatment of Acyclovir depends on whether it is a first infection or recurrent infection. Treatment of the first episode of HSV-2 includes an oral dose of 200 mg of Acyclovir five times per day for 7 to 10 days, or 400 mg of Acyclovir orally three times per day for 7 to 10 days. Higher doses of oral acyclovir do not provide any additional benefits. A treatment with Acyclovir in a first HSV episode reduces the duration of the symptoms by about a week and the healing time of lesions by six days [19]. For the recurrences of HSV-2, the recommended treatment is 200 mg orally five times per day, or 800 mg orally two times per day, administered for 5 days. Topical acyclovir does not provide any additional benefits [19]. A recent study indicates that 800 mg three times per day administered for two days is also effective for treating

HSV recurrences if taken within 24 hours of the onset of genital herpes symptoms [19]. Treatment is currently only applied to patients who exhibit non-constitutional symptoms. While treatment is effective for those who are truly infected with HSV-2, it does not allow for much control over the spread of the infection since individuals do not recover.

**Economics of the Treatment of HSV-2 Patient:** In 1996, the average economic burden of medical care associated with HSV-2 was an estimated \$984 million. Approximately \$470 million is attributed to lab testing and consultations, while \$489 million is attributed to treatment. Hospitalization of HSV-2 only attributes \$25 million to the public health cost [14]. While this is a large burden, current prevalence rates demonstrate that current control strategies do not effectively reduce the spread of the disease.

**Review of Modeling Structures:** Previous mathematical models of Herpes have studied the role of various factors on its transmission dynamics. Tudor [15] proposed a SILI population level model (Susceptible-Infective-Latent-Infective) to evaluate the spread of HSV infection both in humans and animals. In 2005, Blower and Schwartz [13] proposed a model incorporating the impact of a vaccine in controlling the prevalence of HSV-2 suggesting that after a decade of the introduction of a vaccine program, 11 million infections would be prevented in the United States. Podder and Gumel [11] analyzed the qualitative dynamics of HSV-2 with and without vaccination in 2009. In 2005, Acosta, Bar-Zohar, Blanco, Luli, and Gao, performed an epidemic model of HSV-1 with Vaccination, the model formulated a simple SVID model studying the disease transmission dynamics with treatment and vaccination [23]. Also Mubayi 2005, develop and analyze a vector-borne epidemic model to study the dynamics of Cutaneous Leishmania in two ecologically distinct affected regions [24]. They showed that the introduction of a vaccine program could lead to improve disease control or eradication if the vaccine efficacy is high.

In this work, we build on the previous studies to evaluate disease transmission and control of HSV-2. We study the impact of a novel treatment that targets patients with HSV-2 at the constitutional stage, in addition to the non-constitutional stage, and perform a cost-effectiveness analysis.

**Research Focus:** In this work, we study the impact of implementing treatment to those who present constitutional symptoms, as well as those who represent non-constitutional symptoms. The proposed approach will be effective in controlling the disease, but the implementation of the new treatment strategy must be modeled to see the practicality of this approach. The cost-effectiveness of the newly implemented treatment will be mathematically analyzed to see if the proposed program is practical and cost effective in comparison with current methods to control the spread of the disease. In other words, Would the novel treatment, that is treating in both constitutional and non-constitutional stage, be more cost-effective in comparison to the conventional treatment?

## 2 Methods

### 2.1 Model Description

In this work, we incorporate early treatment of HSV-2 via a transmission dynamic model and aim to compare cost-effectiveness of non-conventional treatment with conventional treatment strategies. The conventional treatment consists of prescribing Acyclovir pills when a person infected with HSV-2 presents non-constitutional symptoms, i.e. geni-

tal lesions. To treat HSV-2 infection early on, we propose the treatment of patients who present constitutional symptoms (that includes a combination of fever, headache, dysuria, skin irritation, etc.). These symptoms are general and may be confused with other diseases (see Section 1.3); hence, leading to many misclassification of the disease. We proposed that, in order to give treatment to a patient, a medical practitioner should identify at least five constitutional symptoms (shown in Table 1) and a risk factor. A risk factor is any characteristic or exposure of an individual that will increase their likelihood of becoming infected with a disease. Risk factors for HSV-2 include having multiple sexual partners, immuno-depressive patients, frequency of sexual contacts, or unprotected sex. A mathematical model is develop that includes a class for the conventional treatment (when non-constitutional symptoms are only recognized in patients) and two classes for the proposed treatment (when constitutional symptoms appear and a risk factor is identified in a patient; those who present non-constitutional symptoms and access treatment care). During the early phase of an infection, when they present only constitutional symptoms, the likelihood of determining whether an individual is infected with HSV-2 is low. Therefore, this leads to the inclusion of a treatment class for the non-infected population who present similar (but not infected with HSV-2) symptoms and receive treatment, because of incorrect diagnosis. Hence, this extra class for treatment is to keep track of those who receive treatment, but are not infected (false negative).

The flowchart of the proposed model, shown in Figure 1, captures the dynamics of the disease, where the  $S$  class represents susceptible individuals, which includes a sexually active population between the ages of 15 and 49 years in the United States who are not infected with HSV-2. If an individual in the  $S$  class presents at least five of the constitutional symptoms presented in Table 1 and a risky behavior (detailed in the previous paragraph), but is not infected with HSV-2, a doctor can send him/her to HSV-2 treatment in the  $X$ -class at a rate  $\sigma p$ ; this stage,  $X$ , captures false positive individuals. Once the period for the treatment ends, the individual returns to the  $S$  class at a rate  $\phi_1$ . If a person is infected with HSV-2, he/she progresses to the  $I_1$  class through the force of infection  $\Omega$ ; an individual in  $I_1$  presents constitutional symptoms and is infectious. If a doctor identifies five constitutional symptoms and a risky behavior, the individual progresses to the  $T_1$  class (HSV-2 treatment) at a rate  $\eta_1$ . If no treatment is applied during the constitutional stage, the individual proceeds to present non-constitutional symptoms at the  $I_2$  class at a rate  $\gamma_1$ ; population in this class is infectious. A doctor can send an individual in  $I_2$  to treatment at a rate  $\eta_2$ ; this class is  $T_2$  and is the conventional treatment for HSV-2. The latent class  $L$  is the stage where individuals infected with HSV-2 are not infectious because the virus is dormant during this period. There are four ways to enter the  $L$  class: by natural progression of the disease from  $I_2$  at rate  $\gamma_2$ , from  $T_1$  at rate  $\phi_1$ , from  $T_2$  at rate  $\phi_2$ , and directly from  $I_1$  at a rate  $\gamma_3$  when the infected individual only presents constitutional symptoms before going dormant. The variables and parameters definitions are collected in Tables 2 and 3 respectively.

This model has several assumptions. First, there is always a fraction of the  $S$  population who show symptoms similar to HSV-2. Second, individuals in the  $X$  compartment are not infected with HSV-2 but are under going treatment for HSV-2 (window of opportunity). Third, the infected population is symptomatic (except the infected population who are in the latent stage). Fourth, individuals in the  $T_1$  and  $T_2$  compartment are infectious, but they do not engage in risky sexual activity because we assume they are responsible patients and control all risky sexual activities. Fifth, there are no false diagnosis for patients in  $I_2$ . Sixth, the total population is constant. A summary of parameter definitions and values is shown in Table 3. Lastly, for this model all heterogeneity is averaged out, because we are focus in a treatment strategy regardless the gender of pa-

tients, how it is assumed in simple models [25]. More complex models could divide this model in groups to reflect heterogeneity and their interactions between individuals [26].

Class	Description
$S$	Sexually active people between 15 and 49 in the U.S. who are not infected with HSV-2.
$X$	Non-infected people with HSV-2 who present mild symptoms and are under treatment.
$I_1$	Infected and infectious people of HSV-2 who present mild symptoms.
$I_2$	Infected and infectious people of HSV-2 who present severe symptoms.
$L$	Infected and non-infectious people of HSV-2.
$T_1$	Infected and infectious people of HSV-2 with mild symptoms under treatment.
$T_2$	Infected and infectious people of HSV-2 with severe symptoms under treatment.

Table 2: Stages of the proposed model.

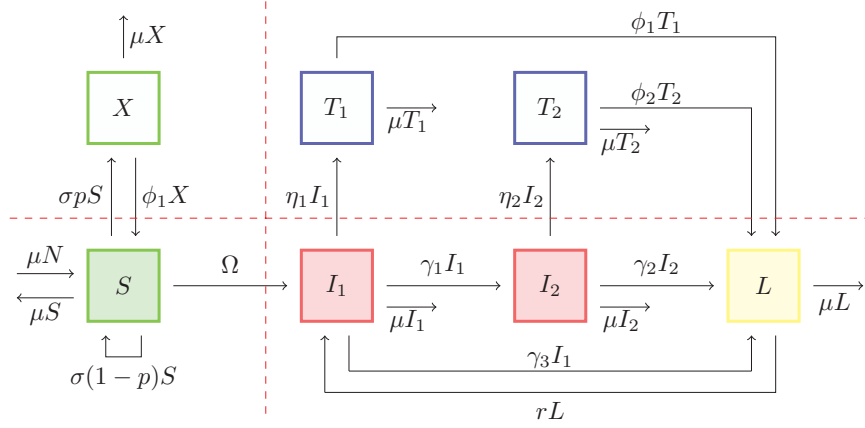


Figure 1: The diagram illustrates the susceptible ( $S$ ), infected ( $I_1$  and  $I_2$ ), latent ( $L$ ) and treatment classes ( $T_1$ ,  $T_2$ , and  $X$ ). The compartments in green are non-infectious, whereas the other compartments include individuals with HSV-2. The compartments with no shading (e.g.,  $X$ ,  $T_1$ ,  $T_2$ ) represent treatment groups, whereas the others are non-treatment classes (e.g.,  $S$ ,  $I_1$ ,  $I_2$ , and  $L$ ). The parameter definitions are shown in Table 3.

The proposed model is governed by the following system of equations:

PARAM	Description	Value	Ref.
$\mu$	Rate of non-active sexually population between 15 to 49.	$6.328 \times 10^{-5} \text{ days}^{-1}$	[20]
$\beta_1$	Transmission probability of a susceptible individual from contact of an infected individual in $I_i$ .	$0.0027 \text{ days}^{-1}$	Estimated
$\beta_2$	Transmission probability of a susceptible individual from contact of an infected individual in $I_i$ .	$0.00135 \text{ days}^{-1}$	Estimated
$\frac{1}{\gamma_1}$	Avg. time it takes an infected individual showing mild symptoms to develop severe symptoms without treatment.	6 days	[4]
$\frac{1}{\gamma_2}$	Average time it takes an infected individual with severe symptoms to relapse.	14 days	[4]
$\frac{1}{\gamma_3}$	Average time it takes an infected individual with mild symptoms to relapse.	13 day	[20]
$\frac{1}{\phi_1}$	Treatment length for patients presenting mild symptoms.	4 days	[17]
$\frac{1}{\phi_2}$	Treatment length for patients presenting severe symptoms.	6 days	[19]
$r$	Activation from latency.	$0.0127 \text{ days}^{-1}$	[2, 20]
$\eta_1$	Per-capita rate of infected $I_1$ patients going for treatment.	Variable	Estimated
$\eta_2$	Per-capita rate of infected $I_2$ patients going for treatment.	$0.25 \text{ days}^{-1}$	[14]
$\sigma$	Per-capita rate of $S$ patients w/ mild symptoms (no HSV-2).	$1.34 \text{ days}^{-1}$	Estimated
$p$	Proportion of people w/ mild symptoms who get treatments.	0.01	Estimated

Table 3: Description and units of the model parameters.

$$\frac{dS}{dt} = \mu N + \phi_1 X - \sigma p S - \Omega - \mu S, \quad (2.1)$$

$$\frac{dX}{dt} = \sigma p S - (\phi_1 + \mu) X, \quad (2.2)$$

$$\frac{dI_1}{dt} = \Omega + r L - (\eta_1 + \gamma_1 + \gamma_3 + \mu) I_1, \quad (2.3)$$

$$\frac{dT_1}{dt} = \eta_1 I_1 - (\phi_1 + \mu) T_1, \quad (2.4)$$

$$\frac{dI_2}{dt} = \gamma_1 I_1 - (\eta_2 + \gamma_2 + \mu) I_2, \quad (2.5)$$

$$\frac{dT_2}{dt} = \eta_2 I_2 - (\phi_2 + \mu) T_2, \quad (2.6)$$

$$\frac{dL}{dt} = \gamma_3 I_1 + \gamma_2 I_2 + \phi_2 T_2 + \phi_1 T_1 - (r + \mu) L, \quad (2.7)$$

where  $N = N_1 + N_2$  with  $N_1 = S + I_1 + I_2 + L$  and  $N_2 = X + T_1 + T_2$ . The force of infection term is denoted  $\Omega = \frac{\beta_1 S I_1 + \beta_2 S I_2}{N_1}$  and the entry rate is  $\Lambda = \mu N$ . Also,  $\sigma p = \kappa \eta_1$ , where  $\kappa$  is a proportion.

## 2.2 Cost Effectiveness of Proposed Treatment

The total cost acquired by the public health department is analyzed for the implementation of early treatment strategy for HSV-2. The cost function of the proposed strategy is denoted by  $C_p(t)$  and computed as follows:

$$C_p(t) = C_1 \int_0^t \sigma(1-p)S(s)ds + C_2 \int_0^t \sigma p S(s)ds + C_2 \int_0^t \eta_1 I_1(s)ds + C_3 \int_0^t \eta_2 I_2(s)ds, \quad (4.1)$$

where  $C_1$  denotes the average cost incurred by the public health department to evaluate a single patient.  $C_2$  is the average cost incurred by the public health department to di-

agnose and prescribe treatment to one patient, and  $C_3$  denotes the average cost incurred by the public health department to diagnose the patient, carry out microbiological and antibody test, and drug treatment to one patient.

The expressions  $\sigma(1-p)S(t)$ ,  $\sigma pS(t)$ ,  $\eta_1 I_1(t)$ ,  $\eta_2 I_2(t)$  denote the cumulative number of individuals treated, while being susceptible, mildly infected, or severely infected during a period of  $T$  days. We compare the cost of the proposed early treatment with the cost of the current strategy of treatment to control HSV-2, denoted by  $C_c(t)$ :

$$C_c(t) = C_3 \int_0^t \eta_2 I_2(s) ds \quad (4.2)$$

Our study is motivated by previous research which indicates that treating patients within the first 24 hours of onset symptoms of genital herpes could control a recurrence episode in two days [19]. Considering this fact, we want to evaluate how a different strategy (early treatment to HSV-2) could affect the incidence of the disease and its public health cost. In other words, we compare strategies in terms of cost per the effect in health achieved through the implementation of a specific strategy [9].

In this study we evaluate, whether or not an early treatment to HSV-2 as a proposed strategy is more cost effective than the current treatment strategy. Also, we evaluate the cost effectiveness of combined strategies in order to reduce the incidence of HSV-2 in the population. Cost per health-effect is evaluated by calculating the variation in cost-effectiveness through the Incremental Cost-Effectiveness Ratio (ICER) [18]:

$$\text{ICER}(t) = \frac{C_p(t) - C_c(t)}{I_p(t) - I_c(t)} = \frac{\Delta C}{\Delta I}.$$

Type of Cost	Description	Value (\$)	Ref.
$C_1$	Consultation + Clinical Examination + Routine lab test	161.85	[14]
$C_2$	$C_1$ + Antiviral treatment	248.1833	[14]
$C_3$	$C_2$ + HSV lab test	328.35	[14]

Table 4: Description of type of costs per person

The ICER ratio takes into account the relationship between the change in cost over the change in incidence.  $C_p(t)$  is defined by the proposed cost of implementing early treatment, while  $C_c(t)$  is defined by current cost.  $I_p(t)$  is defined by incidence level after implementing early treatment, while  $I_c(t)$  is defined by current incidence level.

### 3 Analysis

To better understand the transmission dynamics and control of HSV-2, we study the dynamics of the model analytically by calculating the equilibria and evaluating the conditions for their existence. The equilibria are calculated by setting equations (2.1) to (2.7) to zero. There are in fact two equilibria in our system; the disease free and the endemic equilibria.

#### 3.1 Existence of Disease-Free Equilibrium

The disease-free equilibrium (DFE) is defined as the case where the disease is not present in the population. In our model the infected classes ( $I_1$ ,  $I_2$  and  $L$ ) must be zero when no disease is present. Since there would be no disease, then it is not necessary to consider any treatment for HSV-2 patients, and thus,  $T_1$ , and  $T_2$  are also set to zero.



The DFE is given by  $E_0 = (S^*, X^*, I_1^*, T_1^*, I_2^*, T_2^*, L^*)$ , which is

$$(S^* = \frac{\mu z_1 N}{\kappa \eta_1 z_1 + \mu z_1 - \kappa \eta_1 \phi_1}, X^* = \frac{\kappa \eta_1 \mu N}{\kappa \eta_1 z_1 + \mu z_1 - \kappa \eta_1 \phi_1}, I_1^* = 0, T_1^* = 0, I_2^* = 0, T_2^* = 0, L^* = 0),$$

where  $z_1 = \mu + \phi_1$ ,  $z_2 = \mu + \eta_1 + \gamma_1 + \gamma_3$ ,  $z_3 = \mu + \eta_2 + \gamma_2$ ,  $z_4 = \mu + \phi_2$ , and  $z_5 = \mu + r$ . Each  $z_i$  represents the sum of all the possible rates at which an individual can leave the  $T_1, I_1, I_2, T_2$ , and  $L$  compartments, respectively.

### 3.2 Basic and Control Reproductive Numbers of Simple Models

The Basic Reproductive Number, denoted  $\mathcal{R}_0$ , is defined as the expected number of secondary cases produced by a typical infected individual during its entire period of infectiousness in a completely susceptible population [5, 16]. Similarly  $\mathcal{R}_c$  denotes the control reproductive number which incorporates control measures, such as treatment, quarantine, or isolation. In order to obtain  $\mathcal{R}_0$  from  $\mathcal{R}_c$ , we set the parameters associated with the control measures to zero. The Next Generation Operator method (see Appendix) is applied to calculate  $\mathcal{R}_c$  and  $\mathcal{R}_0$ . In order to understand our model's  $\mathcal{R}_c$  and  $\mathcal{R}_0$ , we first analyze simple models and their respective thresholds of reproduction. We begin with a simple three-compartment model and build on this model by expanding the number of infection and treatment classes with the purpose of understanding the behavior of the disease. We present  $\mathcal{R}_c$  and  $\mathcal{R}_0$  in Models 1 to 4 and discuss the patterns observed as the model becomes more complex due to the introduction of infection and treatment classes, and recurrence of infection.

#### 3.2.1 Model 1 (SILI; Simple Transmission Dynamic Model)

We start with the *SILI* model (Susceptible–Infectious–Latent–Infectious), the reproductive number is:

$$\mathcal{R}_{1,0} = \sum_{n=0}^{\infty} \frac{\beta}{\mu + \gamma} \left( \frac{\gamma}{\mu + \gamma} \cdot \frac{r}{\mu + r} \right)^n = \frac{\frac{\beta}{\mu + \gamma}}{1 - \frac{\gamma}{\mu + \gamma} \cdot \frac{r}{\mu + r}}.$$

This expression can be interpreted as the product of the transmission rate,  $\beta$ , and the average time spent in  $I$ ,  $\frac{1}{\mu + \gamma}$ , related to the probability of progressing into the cycle of the disease. The  $\mathcal{R}_{1,0}$  of this model is the convergent sum of the geometric series associated with the cyclic recurrent behavior of infection in patients. Notice that the denominator has the form  $1 - \Theta$ , where  $\Theta$  is the proportion through the cyclic path out of  $I$ . Details of these calculations are summarized in Appendix A.

#### 3.2.2 Model 2 (SITLI; Transmission Dynamic Model with Treatment)

The *SITLI* Model (Susceptible–Infectious–Treated–Latent–Infectious) incorporates treatment to some individuals in the infectious class and the rest progress to the latent stage (see the flowchart in Appendix A. The control reproductive number is:

$$\mathcal{R}_{2,c} = \frac{\frac{\beta}{\mu + \gamma + \eta}}{1 - \left( \frac{\gamma}{\mu + \gamma + \eta} \cdot \frac{r}{\mu + r} + \frac{\eta}{\mu + \gamma + \eta} \cdot \frac{\phi}{\mu + \phi} \cdot \frac{r}{\mu + r} \right)}.$$

Setting the treatment parameters to zero, that is,  $\phi = 0$  or  $\eta = 0$ , we obtain basic reproductive number:

$$\mathcal{R}_{2,0} = \sum_{n=0}^{\infty} \frac{\beta}{\mu + \gamma} \left( \frac{\gamma}{\mu + \gamma} \cdot \frac{r}{\mu + r} \right)^n = \frac{\frac{\beta}{\mu + \gamma}}{1 - \frac{\gamma}{\mu + \gamma} \cdot \frac{r}{\mu + r}}.$$

For  $\mathcal{R}_{2,c}$  the progression into the cycle of the disease is based on two different paths:  $I-T-L-I$  and  $I-L-I$ . Therefore, the associated  $\hat{\Theta}$  of  $\mathcal{R}_{2,c}$ , where  $\mathcal{R}_{2,c} = \frac{\frac{\beta}{\mu+\gamma}}{1-\hat{\Theta}}$ , contains the sum of these two paths. Details of these analysis are show in Appendix A.

### 3.2.3 Model 3 ( $SI_1I_2LI_1$ ; Transmission Dynamic Model with Heterogeneous Infection Stages)

In the  $SI_1I_2LI_1$  Model (Susceptible; first Infectious period; second Infectious period; Latent; first Infectious period), the reproduction number is:

$$\mathcal{R}_{3,0} = \sum_{n=0}^{\infty} \left( \frac{\beta_1}{\mu+\gamma_1} + \frac{\gamma_1}{\mu+\gamma_1} \cdot \frac{\beta_2}{\mu+\gamma_2} \right) \left( \frac{\gamma_1}{\mu+\gamma_1} \cdot \frac{\gamma_2}{\mu+\gamma_2} \cdot \frac{r}{\mu+r} \right)^n = \frac{\frac{\beta_1}{\mu+\gamma_1} + \frac{\gamma_1}{\mu+\gamma_1} \cdot \frac{\beta_2}{\mu+\gamma_2}}{1 - \frac{\gamma_1}{\mu+\gamma_1} \cdot \frac{\gamma_2}{\mu+\gamma_2} \cdot \frac{r}{\mu+r}}.$$

In this case,  $\mathcal{R}_0$  is the sum of the contribution of new infections and average time spent in each infection class, and also, the probability of progressing from  $I_1$  to  $I_2$ . That is  $\frac{\beta_1}{\mu+\gamma_1}$  represents the product of the transmission rate to  $I_1$ , ( $\beta_1$ ), and the time spent in  $I_1$ , ( $\frac{1}{\mu+\gamma_1}$ ). Similarly,  $\frac{\gamma_1}{\mu+\gamma_1}$  represents the probability of progressing to  $I_2$  and  $\frac{\beta_2}{\mu+\gamma_2}$  represents the transmission rate to  $I_2$  ( $\beta_2$ ) and the time spent in  $I_2$ , ( $\frac{1}{\mu+\gamma_2}$ ). The term  $\Theta := \frac{\gamma_1}{\mu+\gamma_1} \cdot \frac{\gamma_2}{\mu+\gamma_2} \cdot \frac{r}{\mu+r}$  represents the proportion being out of  $I_1$  and returning by recurrence. Thus,  $1 - \Theta$  is the proportion in  $I_1$ .

### 3.2.4 Model 4 ( $SI_1I_2TLI_1$ ; Transmission Dynamic Model with Current Conventional Treatment)

In the  $SI_1I_2TLI_1$  Model (Susceptible; first Infectious period; second Infectious period; Treated; Latent; first Infectious period). The control reproductive number is:

$$\mathcal{R}_{4,c} = \frac{\frac{\beta_1}{\mu+\gamma_1+\gamma_3} + \frac{\gamma_1}{\mu+\gamma_1+\gamma_3} \cdot \frac{\beta_2}{\mu+\gamma_2+\eta}}{1 - \left( \frac{\gamma_1}{\mu+\gamma_1+\gamma_3} \cdot \frac{\gamma_2}{\mu+\gamma_2+\eta} \cdot \frac{r}{\mu+r} + \frac{\gamma_1}{\mu+\gamma_1+\gamma_3} \cdot \frac{\eta}{\mu+\gamma_2+\eta} \cdot \frac{\phi}{\mu+\phi} \cdot \frac{r}{\mu+r} + \frac{\gamma_3}{\mu+\gamma_1+\gamma_3} \cdot \frac{r}{\mu+r} \right)}.$$

To obtain  $\mathcal{R}_{4,0}$ , we set treatment parameters  $\phi = 0$  or  $\eta = 0$ . The reproductive number is:

$$\mathcal{R}_{4,0} = \frac{\frac{\beta_1}{\mu+\gamma_1+\gamma_3} + \frac{\gamma_1}{\mu+\gamma_1+\gamma_3} \cdot \frac{\beta_2}{\mu+\gamma_2}}{1 - \left( \frac{\gamma_1}{\mu+\gamma_1+\gamma_3} \cdot \frac{\gamma_2}{\mu+\gamma_2} + \frac{\gamma_3}{\mu+\gamma_1+\gamma_3} \cdot \frac{r}{\mu+r} \right)} \quad \text{and}$$

$$\mathcal{R}_{4,0} = \sum_{n=0}^{\infty} \left( \frac{\beta_1}{\mu+\gamma_1+\gamma_3} + \frac{\gamma_1}{\mu+\gamma_1+\gamma_3} \cdot \frac{\beta_2}{\mu+\gamma_2} \right) \left( \frac{\gamma_1}{\mu+\gamma_1+\gamma_3} \cdot \frac{\gamma_2}{\mu+\gamma_2} + \frac{\gamma_3}{\mu+\gamma_1+\gamma_3} \cdot \frac{r}{\mu+r} \right)^n.$$

The interpretation of  $\mathcal{R}_{4,c}$  is similar to Model 3 with the inclusion of the time spent in the treatment compartment. Here  $\frac{\beta_1}{\mu+\gamma_1+\gamma_3}$  represents the transmission rate due to  $I_1$ , multiplied by the average time spent in  $I_1$ . Next,  $\frac{\beta_2}{\mu+\gamma_2+\eta}$  represents the probability of progressing to  $I_2$  multiplied by the time spent in  $I_2$ ; this is related with the progression into the cycle of the disease, considering three different paths: ( $I_1-I_2-T-L-I_1$ ), ( $I_1-I_2-L-I_1$ ) and ( $I_1-L-I_1$ ). In the case of  $\mathcal{R}_{4,0}$ , the dynamics are similar to  $\mathcal{R}_{4,c}$ , except there are only two paths because the treatment is not considered. These paths are the associated  $\Theta$  and  $\hat{\Theta}$  representing the population leaving  $I_1$  returning by recurrence. Details are shown in Appendix A.

### 3.3 Control and Basic Reproductive Numbers of the Proposed Model

For the proposed model,  $\mathcal{R}_c$  and  $\mathcal{R}_0$  show the same behavior as the previous models. For simplicity, we substitute  $z_i$ , where  $i = 1, \dots, 5$ , as follows:  $z_1 = \mu + \phi_1$ ,  $z_2 = \mu + \eta_1 + \gamma_1 + \gamma_3$ ,  $z_3 = \mu + \eta_2 + \gamma_2$ ,  $z_4 = \mu + \phi_2$ , and  $z_5 = \mu + r$ . The control reproductive number is:

$$\mathcal{R}_c = \sum_{n=0}^{\infty} \left( \frac{\beta_1}{z_2} + \frac{\gamma_1}{z_2} \cdot \frac{\beta_2}{z_3} \right) \left( \frac{\gamma_1}{z_2} \cdot \frac{\gamma_2}{z_3} \cdot \frac{r}{z_5} + \frac{\eta_1}{z_2} \cdot \frac{\phi_1}{z_1} \cdot \frac{r}{z_5} + \frac{\gamma_1}{z_2} \cdot \frac{\eta_2}{z_3} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5} + \frac{\gamma_3}{z_2} \cdot \frac{r}{z_5} \right)^n.$$

Notice that  $\mathcal{R}_c$  is the convergent sum of the geometric series:

$$\mathcal{R}_c = \frac{\frac{\beta_1}{z_2} + \frac{\gamma_1}{z_2} \cdot \frac{\beta_2}{z_3}}{1 - \left( \frac{\gamma_1}{z_2} \cdot \frac{\gamma_2}{z_3} \cdot \frac{r}{z_5} + \frac{\eta_1}{z_2} \cdot \frac{\phi_1}{z_1} \cdot \frac{r}{z_5} + \frac{\gamma_1}{z_2} \cdot \frac{\eta_2}{z_3} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5} + \frac{\gamma_3}{z_2} \cdot \frac{r}{z_5} \right)}.$$

This  $\mathcal{R}_c$  can be interpreted as the transmission rate due to  $I_1$  individuals,  $\beta_1$  multiplied by the time spent in the  $I_1$  compartment,  $\frac{1}{z_2}$ . This value is added to the probability of progressing to the  $I_2$  compartment,  $\frac{\gamma_1}{z_2}$ , multiplied by the transmission rate due to the  $I_2$  compartment,  $\beta_2$ , multiplied again by the time spent in the  $I_2$  compartment,  $\frac{1}{z_3}$ . This is related to the progression into the cyclic paths of the disease (let it be  $\hat{\Theta}$ ). There are four cyclic paths:  $(I_1-I_2-L-I_1)$ ,  $(I_1-T_1-L-I_1)$ ,  $(I_1-I_2-T_2-L-I_1)$ , and  $(I_1-L-I_1)$ . We observe that  $\mathcal{R}_c$  has the form:

$$\mathcal{R}_c = \frac{\mathcal{R}_1 + \mathcal{R}_2}{1 - \hat{\Theta}},$$

where  $\mathcal{R}_1$  and  $\mathcal{R}_2$  are the contributions of  $I_1$  and  $I_2$  respectively to  $\mathcal{R}_c$ , and  $1 - \hat{\Theta}$  is the proportion at  $I_1$ .

$\mathcal{R}_0$  has a similar dynamic as  $\mathcal{R}_c$ , except that the two paths related to treatments are not considered. The basic reproductive number is:

$$\mathcal{R}_0 = \frac{\frac{\beta_1}{\mu + \gamma_1 + \gamma_3} + \frac{\gamma_1}{\mu + \gamma_1 + \gamma_3} \cdot \frac{\beta_2}{\mu + \gamma_2}}{1 - \left( \frac{\gamma_1}{\mu + \gamma_1 + \gamma_3} \cdot \frac{\gamma_2}{\mu + \gamma_2} \cdot \frac{r}{\mu + r} + \frac{\gamma_3}{\mu + \gamma_1 + \gamma_3} \cdot \frac{r}{\mu + r} \right)}.$$

### 3.4 Existence of Endemic Equilibrium

For our original model, we have calculated the Jacobian, see Appendix A.7. Due to the complexity of our model, to analyze the endemic equilibrium, we consider the reduced system shown in Appendix A with  $I = I_1 + I_2$ ,  $T = T_1 + T_2$ ,  $\eta_1 = \eta_2 = \eta$ ,  $\gamma_2 = \gamma_3 = \gamma$ ,  $\beta_1 = \beta_2 = \beta$ , and  $\phi_1 = \phi_2 = \phi$ . The system of equations corresponding to this model are the following:

$$\frac{dS}{dt} = \mu N + \phi X - \frac{\beta SI}{N_1} - (\mu + \kappa \eta) S, \quad (3.4.1)$$

$$\frac{dX}{dt} = \kappa \eta S - (\phi + \mu) X, \quad (3.4.2)$$

$$\frac{dI}{dt} = \frac{\beta SI}{N_1} + rL - (\eta + \gamma + \mu) I, \quad (3.4.3)$$

$$\frac{dT_1}{dt} = \eta I - (\phi_1 + \mu) T, \quad (3.4.4)$$

$$\frac{dL}{dt} = \gamma I + \phi T - (r + \mu) L, \quad (3.4.5)$$

where  $N_1 = S + I + L$ .

To simplify the endemic equilibrium we have calculated the  $\mathcal{R}_c$ .

$$\mathcal{R}_c = \frac{\frac{\beta}{z_2}}{1 - \frac{\gamma}{z_2} \frac{r}{z_5} - \frac{\phi}{z_1} \frac{\eta}{z_2} \frac{r}{z_5}}$$

where  $z_1 = \phi + \mu$ ,  $z_2 = \eta + \gamma + \mu$ , and  $z_5 = r + \mu$ . We define the following expressions:

$$p_1 = \frac{\phi}{z_1}, \quad p_2 = \frac{\eta}{z_2}, \quad p_5 = \frac{r}{z_5}, \quad \pi_c = \pi_1 + \pi_2.$$

$$q_2 = \frac{\gamma}{z_2}, \quad \pi_1 = \frac{\phi}{z_1} \frac{\eta}{z_2} \frac{r}{z_5}, \quad \pi_2 = \frac{r}{z_5} \frac{\gamma}{z_2}, \quad \text{and}$$

Analyzing the model gives the endemic equilibrium  $E_1 = (S^*, X^*, I^*, T^*, L^*)$ ; where:

$$S^* = \frac{N z_1 \mu (r + z_2 \pi_c)}{z_2 (\alpha_1 \mu + r \alpha_2 + r z_1 (-1 + \pi_2))},$$

$$X^* = \frac{N r \mu \kappa \eta (\beta + z_2 (-1 + \pi_c))}{z_2^2 (\alpha_1 \mu + r \alpha_2 + r z_1 (-1 + \pi_2)) (-1 + \pi_c)},$$

$$I^* = \frac{N r z_1 \mu (\beta + z_2 (-1 + \pi_1 + \pi_2))}{z_2^2 (\alpha_1 \mu + r \alpha_2 + r z_1 (-1 + \pi_2)) (-1 + \pi_c)},$$

$$T^* = \frac{N r \mu \eta (\beta + z_2 (-1 + \pi_1 + \pi_2))}{z_2^2 (\alpha_1 \mu + r \alpha_2 + r z_1 (-1 + \pi_2)) (-1 + \pi_c)},$$

$$L^* = \frac{N r \mu (\beta + z_2 (-1 + \pi_1 + \pi_2)) (z_1 \gamma + \eta \phi)}{z_2^2 z_5 (\alpha_1 \mu + r \alpha_2 + r z_1 (-1 + \pi_2) (-1 + \pi_c))},$$

with  $\alpha_1 = z_1 (\pi_1 + \pi_2) + \eta \kappa \pi_2$  and  $\alpha_2 = \frac{z_1 (\beta + \mu) + \eta \kappa \mu}{z_2}$ . Evaluating  $E_1$  with the current conventional treatment, we can show that there exists an endemic equilibrium for the system in Figure 2. Since this system is reduced from our original system,  $E_1$  has a different quantitative meaning related with the treated population but the same qualitative meaning, because of the treatment. Therefore, for our original model, there exists an endemic equilibrium with the parameters in Table 3.

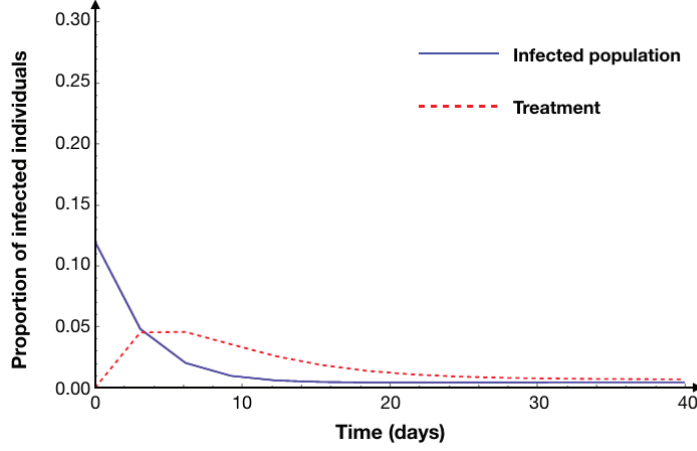


Figure 2: The blue curve represents the  $I$  class and red curve represent the  $T$  class. Time is measured in days.

### 3.5 Local sensitivity of $\mathcal{R}_c$ with respect to $\eta_1$ and $\eta_2$

**Proposition 1:** Consider  $\mathcal{R}_c$  as the control reproductive number and  $\eta_2$  a parameter. We show that  $\frac{\partial \mathcal{R}_c}{\partial \eta_2} \rightarrow 0$  when  $\eta_2 \rightarrow \infty$  and  $\mathcal{R}_c$  converges to  $\mathcal{R}_c^* > 1$  when  $\eta_2 \rightarrow \infty$  where

$$\mathcal{R}_c = \frac{\frac{\beta_1}{z_2}}{(1 - (\alpha_1 + \alpha_4 + \frac{\gamma_1 \cdot \phi_2 \cdot r}{z_2 \cdot z_4 \cdot z_5}))}.$$

**Proof:**

Consider the change of variables with respect to the partial derivatives:

$$\begin{aligned} \frac{\partial \alpha_1}{\partial \eta_2} &= -\frac{\gamma_1}{z_2} \cdot \frac{r}{z_5} \cdot \frac{\gamma_2}{z_3} & \alpha_1 &:= \frac{\gamma_1}{z_2} \cdot \frac{\gamma_2}{z_3} \cdot \frac{r}{z_5}, \\ \frac{\partial \alpha_2}{\partial \eta_2} &= 0 & \alpha_2 &:= \frac{\eta_1}{z_2} \cdot \frac{\phi_1}{z_1} \cdot \frac{r}{z_5}, \\ \frac{\partial \alpha_3}{\partial \eta_2} &= \frac{\gamma_1}{z_2} \cdot \frac{\phi_2}{z_4} \cdot \left( \frac{z_3 - \eta_2}{z_3} \right) & \alpha_3 &:= \frac{\gamma_1}{z_2} \cdot \frac{\eta_2}{z_3} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5}, \text{ and} \\ \frac{\partial \alpha_4}{\partial \eta_2} &= 0 & \alpha_4 &:= \frac{\gamma_3}{z_2} \cdot \frac{r}{z_5}. \end{aligned}$$

We now rewrite  $\mathcal{R}_c$  as:

$$\mathcal{R}_c = \frac{\frac{\beta_1}{z_2} + \frac{\gamma_1}{z_2} \cdot \frac{\beta_2}{z_3}}{1 - (\alpha_1 + \alpha_2 + \alpha_3 + \alpha_4)},$$

to observe the change of  $\mathcal{R}_c$  when  $\eta_2$  varies, we will reference the derivative of  $\mathcal{R}_c$  with respect to  $\eta_2$ , since  $\mathcal{R}_c$  depends on many parameters we must calculate the partial derivative with respect to  $\eta_2$ , which yields:

$$\frac{\partial \mathcal{R}_c}{\partial \eta_2} = \frac{-\frac{\gamma_1 \beta_2}{z_2 z_3^2} (1 - (\alpha_1 + \alpha_2 + \alpha_3 + \alpha_4)) + \left( \frac{\beta_1}{z_2} + \frac{\gamma_1 \beta_2}{z_2 z_3} \right) \left( \frac{\partial \alpha_1}{\partial \eta_2} + \frac{\partial \alpha_3}{\partial \eta_2} \right)}{(1 - (\alpha_1 + \alpha_2 + \alpha_3 + \alpha_4))^2}.$$

Calculating the limit of  $\mathcal{R}_c$  as  $\eta_2$  approaches infinity, we get:

$$\lim_{\eta_2 \rightarrow \infty} \frac{\partial \mathcal{R}_c}{\partial \eta_2} = \lim_{\eta_2 \rightarrow \infty} \frac{-\frac{\gamma_1 \beta_2}{z_2 z_3^2} (1 - (\alpha_1 + \alpha_2 + \alpha_3 + \alpha_4)) + \left( \frac{\beta_1}{z_2} + \frac{\gamma_1 \beta_2}{z_2 z_3} \right) \left( \frac{\partial \alpha_1}{\partial \eta_2} + \frac{\partial \alpha_3}{\partial \eta_2} \right)}{(1 - (\alpha_1 + \alpha_2 + \alpha_3 + \alpha_4))^2} = 0.$$

Since  $\lim_{\eta_2 \rightarrow \infty} \left( -\frac{\gamma_1 \beta_2}{z_2 z_3^2} \right) = 0$ ,  $\lim_{\eta_2 \rightarrow \infty} \left( \frac{\partial \alpha_1}{\partial \eta_2} + \frac{\partial \alpha_3}{\partial \eta_2} \right) = 0$ , and  $\lim_{\eta_2 \rightarrow \infty} \left( 1 - (\alpha_1 + \alpha_2 + \alpha_3 + \alpha_4) \right) = \left( 1 - \left( \alpha_1 + \alpha_4 + \frac{\gamma_1}{z_2} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5} \right) \right)$ .

Then  $\mathcal{R}_c$  will converge to a specific  $\mathcal{R}_c^*$

$$\lim_{\eta_2 \rightarrow \infty} \mathcal{R}_c = \lim_{\eta_2 \rightarrow \infty} \frac{\frac{\beta_1}{z_2} + \frac{\gamma_1}{z_2} \cdot \frac{\beta_2}{z_3}}{1 - (\alpha_1 + \alpha_2 + \alpha_3 + \alpha_4)} = \frac{\frac{\beta_1}{z_2}}{\left( 1 - (\alpha_1 + \alpha_4 + \frac{\gamma_1}{z_2} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5}) \right)} = \mathcal{R}_c^*.$$

To  $\mathcal{R}_c^* > 1$  if and only if  $\eta_1 < 0.2588$  this result was obtained numerically, and is consistent with the results obtained in Figure 4. This shows that no matter how much  $\eta_2$  is increased,  $\mathcal{R}_c^*$  will not decrease enough to control the epidemic unless  $\eta_1$  is increased. In other words, the change in  $\mathcal{R}_c$  with respect to  $\eta_2$  will stabilize asymptotically and converge to a number greater than zero if and only if  $\eta_1 < 0.2588$ .

**Proposition 2:** Consider  $\mathcal{R}_c$  as the control reproductive number and  $\eta_1$  a parameter for which we have control. We now show that  $\frac{\partial \mathcal{R}_c}{\partial \eta_1} < 0$  when  $\eta_1 \rightarrow \infty$  and  $\mathcal{R}_c \rightarrow 0$  when  $\eta_1 \rightarrow \infty$ .

**Proof:**

Let

$$\mathcal{R}_c = \frac{\frac{\beta_1}{z_2} + \frac{\gamma_1}{z_2} \cdot \frac{\beta_2}{z_3}}{1 - \left( \frac{\gamma_1}{z_2} \cdot \frac{\gamma_2}{z_3} \cdot \frac{r}{z_5} + \frac{\eta_1}{z_2} \cdot \frac{\phi_1}{z_1} \cdot \frac{r}{z_5} + \frac{\gamma_1}{z_2} \cdot \frac{\eta_2}{z_3} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5} + \frac{\gamma_3}{z_2} \cdot \frac{r}{z_5} \right)},$$

be the control reproductive number. Due to  $z_2$  being the only term including  $\eta_1$ , we rewrite  $\mathcal{R}_c$  as follows:

$$\mathcal{R}_c = \frac{\left( \frac{1}{z_2} \right) \left( \beta_1 + \frac{\gamma_1 \beta_2}{z_3} \right)}{\left( \frac{1}{z_2} \right) \left[ z_2 - \left( \frac{\gamma_1 \gamma_2}{z_3} \cdot \frac{r}{z_5} + \frac{\eta_1 \phi_1}{z_1} \cdot \frac{r}{z_5} + \frac{\gamma_1 \eta_2}{z_3} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5} + \frac{\gamma_3 r}{z_5} \right) \right]}.$$

Calculating the partial derivative of  $\mathcal{R}_c$  with respect to  $\eta_1$  we have:

$$\frac{\partial \mathcal{R}_c}{\partial \eta_1} = - \frac{\left( \beta_1 + \frac{\gamma_1 \beta_2}{z_3} \right) \left( 1 - \frac{\phi_1 \cdot r}{z_1 z_5} \right)}{\left( z_2 - \left( \frac{\gamma_1 \gamma_2}{z_3} \cdot \frac{r}{z_5} + \frac{\eta_1 \phi_1}{z_1} \cdot \frac{r}{z_5} + \frac{\gamma_1 \eta_2}{z_3} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5} + \frac{\gamma_3 r}{z_5} \right) \right)^2}.$$

Note that the denominator is always positive. The first term of the numerator is also positive. It is enough to show that for any value of the parameters, the second term is always positive. We see that

$$0 < \left( 1 - \frac{\phi_1 \cdot r}{z_1 z_5} \right) \leq 1.$$

This term is equal to 1 only when  $\phi_1 = 0$  and in this case it is seen that  $\frac{\partial \mathcal{R}_c}{\partial \eta_1} < 0$ . Since  $z_1 = \mu + \phi_1$  and  $z_5 = \mu + r$ , then  $\frac{\phi_1}{\mu + \phi_1}$  and  $\frac{r}{\mu + r}$  represent probabilities, therefore, the values are between 0 and 1. We have seen the case when the reproductive number is equal to zero, now it will never be equal to zero. We can write the product as  $\frac{\phi_1 r}{\mu^2 + \mu(\phi_1 + r) + \phi_1 r}$ . Therefore, we confirm that this denominator is always between 0 and 1.

We see now that  $\mathcal{R}_c \rightarrow 0$  when  $\eta_1 \rightarrow \infty$ ,

$$\lim_{\eta_1 \rightarrow \infty} \mathcal{R}_c = \lim_{\eta_1 \rightarrow \infty} \frac{(\beta_1 + \frac{\gamma_1 \beta_2}{z_3})}{z_2 - \left( \frac{\gamma_1 \cdot \gamma_2}{z_3} \cdot \frac{r}{z_5} + \frac{\eta_1 \cdot \phi_1}{z_1} \cdot \frac{r}{z_5} + \frac{\gamma_1 \cdot \eta_2}{z_3} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5} + \frac{\gamma_3 \cdot r}{z_5} \right)} = 0.$$

Notice that the numerator is a fixed value and the denominator tends to infinity when  $\eta_1$  tends to infinity, then  $z_2 \gg \eta_1 \cdot \frac{\phi_1 \cdot r}{z_1 z_5}$ .

Finally,  $\frac{\partial \mathcal{R}_c}{\partial \eta_1} < 0$  for whichever parameter values. therefore,  $\mathcal{R}_c$  is always decreasing when  $\eta_1$  is increasing. This suggest that it is necessary to implement early treatment to reduce incidence rates of HSV-2.

## 4 Numerical Results

### 4.1 Effect of Control Measures on the Reproductive Number

This section evaluates the impact of new treatment rates on  $\mathcal{R}_c$ . More specifically, we examine how  $\mathcal{R}_c$  changes as parameters  $\eta_1$  and  $\eta_2$  are varied. Figure 3 shows the effect  $\eta_1$  and  $\eta_2$  have on the control reproductive number. It can be seen that  $\eta_1$  is more effective in reducing the control reproductive number than  $\eta_2$ . The plot also shows that when  $\eta_1 = 0$ , the control reproductive number remains above 1 for all values of  $\eta_2$ .

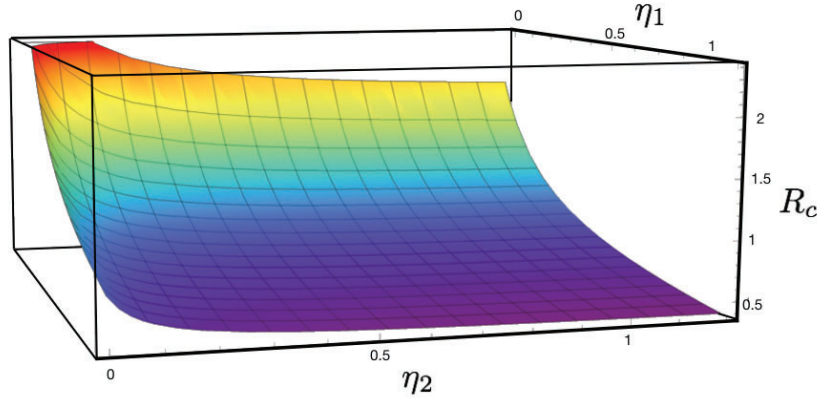


Figure 3: Surface of  $\mathcal{R}_c$  generated as  $\eta_1$  and  $\eta_2$  change.

Figure 4 is a contour plot of Figure 2 when  $\mathcal{R}_c = 1$ . This plot represents the treatment parameter threshold for disease control. As seen, the graph is asymptotic as  $\eta_2$  is increased, and  $\eta_1$  is decreased below 0.2588 (Proposition 1). This shows that no matter how much effort is put into getting people from  $I_2$  into  $T_2$  the epidemic will not be controlled. The graph also shows that the disease is better controlled as  $\eta_1$  increases and  $\eta_2$  decreases. This shows that as more people are removed from  $I_1$  the more likely it is to control HSV-2.

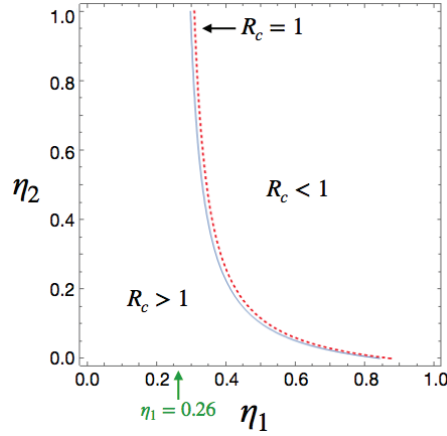


Figure 4: Contour plot when  $\mathcal{R}_c = 1$ .

Figure 5 shows the relationship  $\eta_1$  has on  $\mathcal{R}_c$ . We can conclude that as  $\eta_1$  increases  $\mathcal{R}_c$  decreases enough to control the epidemic. The constant line at  $\mathcal{R}_c = 1$  shows the point needed to cross the threshold of controlling the epidemic. The minimum rate needed for  $\eta_1$  to cross this threshold is 0.39. If this is reached, the epidemic will be controlled effectively.

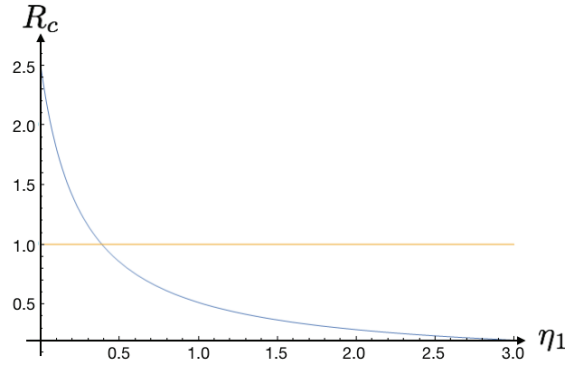


Figure 5:  $\mathcal{R}_c$  function as  $\eta_1$  increases.

## 4.2 Local Sensitivity on Endemic Prevalence Levels

A local sensitivity analysis is performed in order to evaluate the effects of the treatment parameters of  $I_1(\eta_1)$  and  $I_2(\eta_2)$  individuals. We discuss the role of small changes in  $\eta_1$  and  $\eta_2$  on  $I_1$  and  $I_2$  over time.

Figure 6 shows the effects of  $\eta_1$  and  $\eta_2$  on the infected population with constitutional symptoms  $I_1$ . It is observed that as  $\eta_1$  (blue-solid curve) increases the infected population with non-constitutional symptoms  $I_2$  decreases as  $I_2$  individuals leave the compartment, and after some time  $I_1$  stabilizes. It is also seen that as  $\eta_2$  (red-dashed curve) increases, it has a little effect on the change of  $I_1$ , since individuals enter in the  $I_1$  compartment before transition into the  $I_2$  class. This slight increase is due to the higher number of recurrences due to the people entering the latent stage.



Figure 7 shows the effects of  $\eta_1$  and  $\eta_2$  on the  $I_2$  compartment. It is seen that  $\eta_2$  (blue-solid curve) has a larger effect on the  $I_2$  compartment than  $\eta_1$  (red-dashed curve) since  $\eta_2$  is directly removing individuals from the  $I_2$  compartment. The plots also show that changes in  $\eta_1$  also have a significant effect on  $I_2$  since this rate does not allow individuals to reach the  $I_2$  class. This shows that  $I_2$  is more sensitive to  $\eta_2$  than  $\eta_1$ .

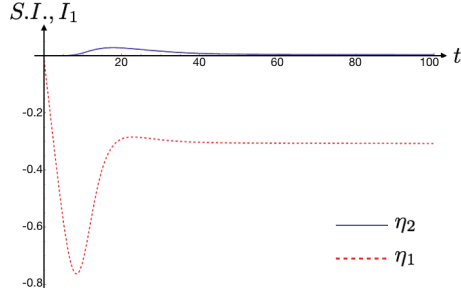


Figure 6: Local sensitivity analysis of class  $I_1$  with respect to  $\eta_1$  (blue curve) and  $\eta_2$  (red curve).

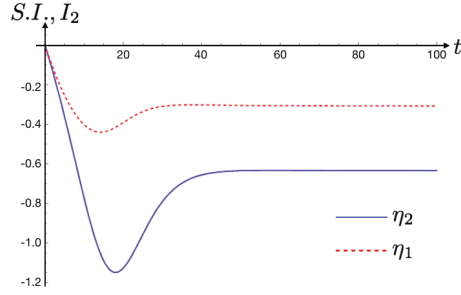


Figure 7: Local sensitivity analysis of class  $I_2$  with respect to  $\eta_1$  (red curve) and  $\eta_2$  (blue curve).

### 4.3 Impact of Treatment Parameters on Cost of Implementation of Treatment Strategies

Figure 8 and Figure 9 compare the incidence, at a proportional level of the US population, of HSV-2 infections between conventional treatment (Figure 9) and proposed treatment (Figure 8). It is seen that incidence levels drop drastically as  $\eta_1$  is varied.

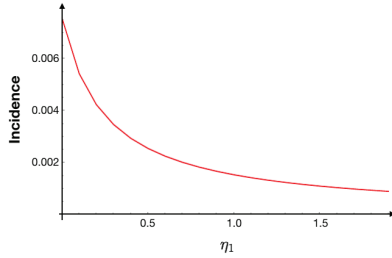


Figure 8: Incidence proportion as  $\eta_1$  varies while  $\eta_2 = 0.25$  (proposed treatment method)

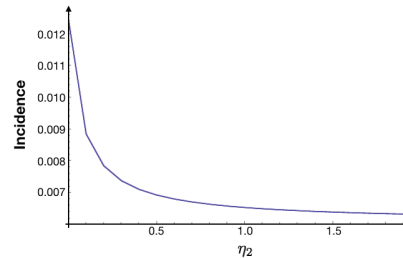


Figure 9: Incidence proportion as  $\eta_2$  varies while  $\eta_1 = 0$  (conventional treatment method)

### 4.4 Cost Effectiveness Analysis

According to the literature we set  $\eta_2 = 0.25$ , and from this we computed the current public health cost and incidence level [14]. Figure 10 shows the components of the ICER as functions of  $\eta_1$  normalized by the current  $C_c(t)$  and  $I_c(t)$  respectively. It is seen that as  $\eta_1$  increases benefit proportion of cost increases while incidence levels decrease.

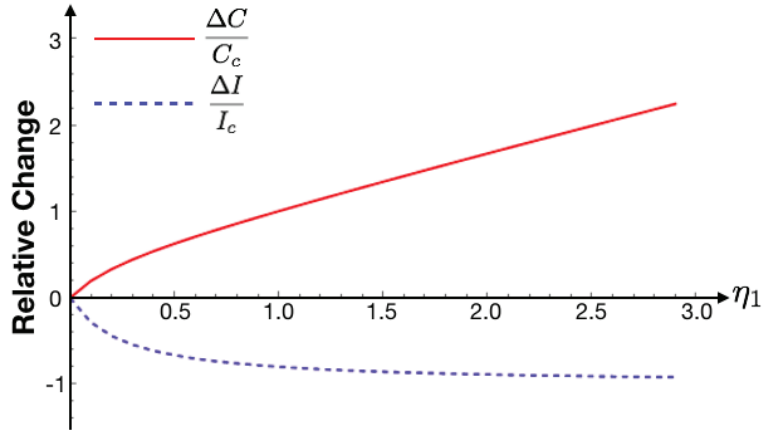


Figure 10: The Upper red-solid curve represents  $\Delta C$ , while the lower blue-dashed curve represents  $\Delta I$ .

Figure 11 shows the relationship between cost as a function of conventional and proposed treatment rates, the combined effect of treatment rates, and the cost implicated. We observe in both plots that as the proposed treatment  $\eta_1$  increases, the cost also increases. Although conventional treatment is less expensive. By incorporating proposed treatment plan its possible to find feasible diseases control strategies, under the constraints of available resources.

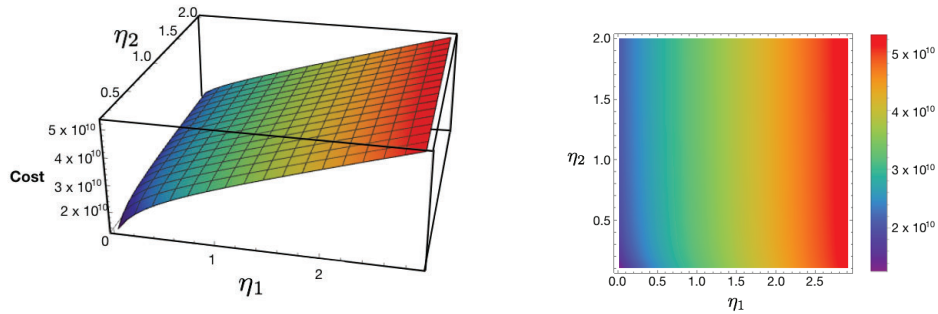


Figure 11: Relationship between  $\eta_1$ ,  $\eta_2$ , and cost

Figure 12 demonstrates the range of cost as  $\eta_1$  and  $\eta_2$  increase. The range of the plot begins at \$15 billion and ranges to \$50 billion. The practical amount of monetary expenses is between \$20 billion and \$25 billion.

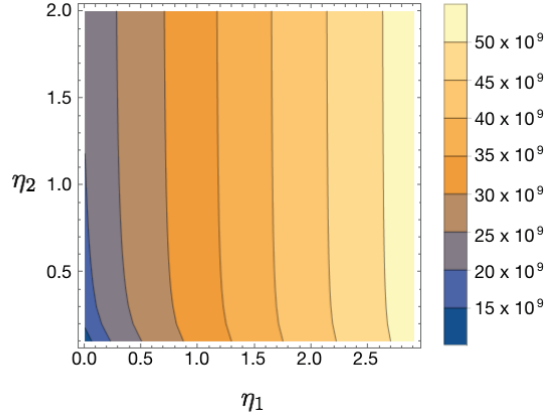


Figure 12: Level curves of cost  $(\eta_1, \eta_2)$ .

Figure 13 shows the relationship of the ICER as  $\eta_1$  and  $\eta_2$  vary. It is seen that as  $\eta_1$  and  $\eta_2$  become very large, it is extremely beneficial, but not practical because the ICER decreases by such a large cost.

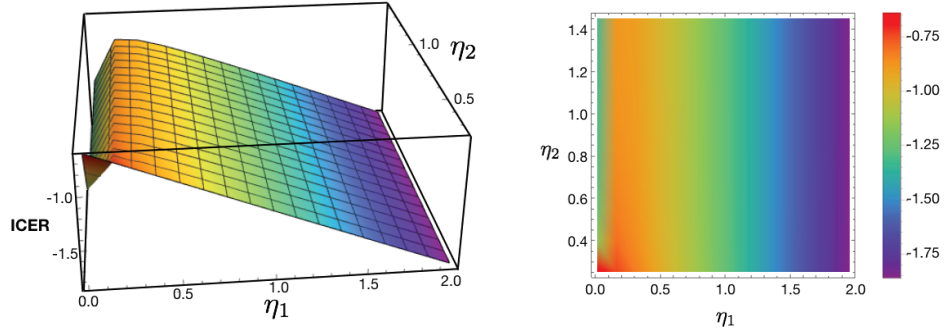


Figure 13: Plot of  $\eta_1$ ,  $\eta_2$ , and ICER

From Figure 13 we obtain many possible combinations of treatment strategies. Some of these combinations are ideal in control of the epidemic but not practical due to the cost needed to support these strategies. Practical strategies were found by analyzing Figure 5 as well as Figure 12. Optimal values of  $\eta_1$  and  $\eta_2$  were estimated by analyzing Figure 12. This analysis gave a range of values for  $\eta_1$  and  $\eta_2$  for a given cost range. From these  $\eta_1$  and  $\eta_2$  values two examples were chosen to come close to crossing the  $\mathcal{R}_c$  threshold of  $\mathcal{R}_c=1$ . Two examples of strategies were created through this method an optimal strategy and an Ideal strategy, both are analyzed in Table 5.

Current treatment	Optimal strategy	Ideal strategy
$\eta_1 = 0$	$\eta_1 = 0.2145$	$\eta_1 = 0.4$
$\eta_2 = 0.25$	$\eta_2 = 0.1407$	$\eta_2 = 0.3$
$\mathcal{R}_c = 2.506$	$\mathcal{R}_c = 1.509$	$\mathcal{R}_c = 0.956$
ICER = N/A	ICER = $-0.6672$	ICER = $-0.8923$
Cost = \$16.14 B.	$\$20.4 \text{ B.} \leq \text{Cost} \leq \$20.5 \text{ B.}$	$\$24 \text{ B.} \leq \text{Cost} \leq \$24.1 \text{ B.}$
Incidence = 1, 146, 200 (0.76%)	Incidence = 683, 467 (0.45%)	Incidence = 432, 146 (0.28%)

Table 5: Comparison between Treatment Strategies.

In Table 5 we compare examples of optimal and ideal treatment strategies with the

current treatment strategy. In the current treatment with  $\mathcal{R}_c = 2.506$ , applying the conventional treatment, the total public health cost is \$16.14 billion with an incidence of about 1.15 million of newly infected individuals. Applying a combined strategy and considering  $\mathcal{R}_c = 0.956$  the total public health cost is about 24 billion dollars. However, the incidence is reduced to approximately 714,054 new infected individuals, this represents an important incremental cost on public health. This is why, the optimal strategy, where we slightly increase the effort of  $\eta_1$  and  $\eta_2$  to obtain  $\mathcal{R}_c = 1.509$  will generate a total public health cost of \$20.4-20.5 billion meanwhile reducing the incidence to 462,733 newly infected individuals.

From Proposition 1 and Figure 4, we realize that an  $\eta_1 > 0.2588$  is required in order to cross the threshold  $\mathcal{R}_c = 1$ . According to Figure 12, the minimum budget of public health cost for HSV-2 (marginal cost) is given by \$12.56 Billion, but this budget does not guarantee the control of the disease.

#### 4.5 Wasted Cost of Treatment of Non-Infected Individuals

Figure 14 shows functions of total cost (red-solid) as well as wasted cost (blue-dashed) as  $\eta_1$  varies, with  $\eta_2 = 0.25$  and cost being on a logarithmic scale.  $p_1$  and  $p_2$  represent the percentage of total cost that is attributed to waste cost. When  $\eta_1 = 0.5$ , the percentage of total cost attributed to waste cost ( $p_1$ ) is 18.15%. When  $\eta_1 = 2$ , the percentage of total cost attributed to waste cost ( $p_2$ ) is 44.31%. This suggests that it would be impractical to choose the largest value of  $\eta_1$  possible, since much of the total cost would be attributed to waste cost.

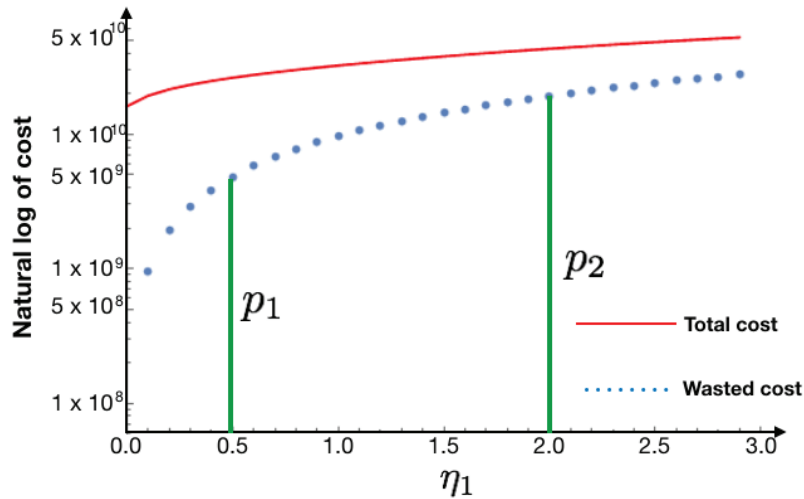


Figure 14: Wasted Cost Functions

## 5 Discussion

### 5.1 Conclusions

The purpose of this study was to investigate optimal treatment strategies for reducing HSV-2 infections in the United States. We proposed that treatment in the constitutional stage would be more cost effective than the conventional treatment, which only applies treatment in the non-constitutional stage. To test this, we developed and analyzed a

mathematical model that modeled treatment at the constitutional stage, in addition to treatment of the non-constitutional stage, and we also tracked the treatment of false positive cases.

For our proposed model we defined a system of ordinary differential equations, and performed computer simulations to analyze the behavior of HSV-2 infections. With the reduction of our model, we showed that with the given parameters in Table 3, there exists an endemic equilibrium with the current conventional treatment. Since  $R_c$  considers control strategies, the rate at which infected individuals initiate treatment is considered in the calculation of this threshold. Thus,  $\eta_1$  and  $\eta_2$  form part of the cyclic paths of progression through the disease observed in  $\mathcal{R}_c$ .

To study the optimal strategy, we developed a cost function to evaluate the cost effectiveness of the proposed treatment. The total public cost in one year, i.e,  $T = 365$ , we numerically solved equations (4.1) and (4.2). Our results have shown that, it does not matter how much effort we put on getting infected individuals into treatment when they are in the non-constitutional stage (conventional treatment), the disease persist because there is a period of time in which the person is infectious with constitutional symptoms but is not getting treatment. Also, if we focus only on a strategy that involves early treatment, it will be efficient in terms of decreasing  $\mathcal{R}_c$ , but the monetary effect is not practical because when a doctor treat patients who show mild symptoms, he/she can not know for sure if the patient has HSV-2, which is why the cost will increase. This is why, to optimize the cost effectiveness, we need a combination of the two treatments, that is, we need to put effort in both  $\eta_1$  and  $\eta_2$ . This combined strategy not only bring  $\mathcal{R}_c(\eta_1, \eta_2)$  less than one but also reduces the cost by approximately 20% of a possible ideal strategy.

The cost required to decrease the  $\mathcal{R}_c$  by this much was found by calculating the ICER. It was found that as more monetary effort is invested into implementation of early treatment, incidence of new HSV-2 cases is expected to decrease drastically. Optimal implementation, as seen in Table 5, would require an ICER value of -0.6, which would relate to annual costs between \$18 to \$20 billion. The implementation of early treatment is strongly recommended to decrease incidence of HSV-2 infections in a cost effective manner.

## 5.2 Future Work

Future work would include to study the impact this proposed strategy has in the US population but with HSV-1 instead of HSV-2. Analyze different strategies to see which one is more effective, for example, analyze the effect on vaccination and compare it with our proposed strategy for this research. A limitation in this work was finding data over the constitutional stage, since patients are not treated here. If early treatment was implemented, it would be interesting to study the impact of implemented treatment through data.

## 5.3 Acknowledgements

We would like to thank Dr. Carlos Castillo-Chavez, Founding and Co-Director of the Mathematical and Theoretical Biology Institute (MTBI), for giving us the opportunity to participate in this research program. We would also like to thank Co-Director Dr. Anuj Mubayi as well as Coordinator Ms. Rebecca Perlin and Management Intern Ms. Sabrina Avila for their efforts in planning and executing the day to day activities of MTBI. We also want to give special thanks to Baltazar Espinoza, Anarina Murillo, Rohan Patil, Leon Arriola, Arunchalam Viswanathan, and Anuj Mubayi for their help in developing and executing this project. This research was conducted as part of 2018

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## A Appendix: Simple Models

All of these models represent a modification of the proposed model. We begin with a simple 3 compartment model and continue to build, or add more complexity, and calculate the reproductive number. We compare and show the behavior of  $\mathcal{R}_0$  and  $R_c$  through an inductive way.

### A.1 Model 1

In this model we only consider susceptible, infectious and latent classes shown in figure 13.

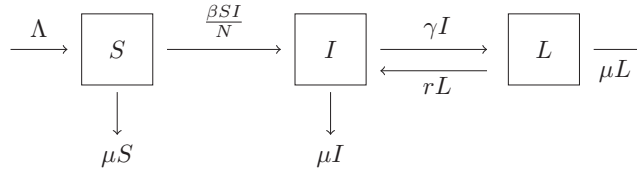


Figure 15: *SILLI* Model

The differential equations that represent this model are the following:

$$\frac{dS}{dt} = \Lambda - \frac{\beta SI}{N} - \mu S \quad (3.1.1)$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - (\mu + \gamma)I + rL \quad (3.1.2)$$

$$\frac{dL}{dt} = \gamma I - (r + \mu)L \quad (3.1.3)$$

#### Calculation of $\mathcal{R}_{1,0}$ :

$$\text{DFE} = \left( \frac{\Lambda}{\mu}, 0, 0 \right) \text{ where } N = \frac{\Lambda}{\mu}.$$

$$\text{Infected classes: } X = \begin{bmatrix} I \\ L \end{bmatrix}$$

Thus,  $\mathcal{F}$  and  $\mathcal{V}$  are as follows:

$$\mathcal{F} = \begin{bmatrix} \frac{\beta SI}{N} \\ 0 \end{bmatrix} \quad \mathcal{V} = \begin{bmatrix} (\mu + \gamma)I - rL \\ -\gamma I + (\mu + r)L \end{bmatrix}$$

The Jacobian matrices for  $\mathcal{F}$  and  $\mathcal{V}$  with respect to  $I$  and  $L$  are respectively the following:

$$F = \begin{bmatrix} \beta & 0 \\ 0 & 0 \end{bmatrix} \quad V = \begin{bmatrix} \mu + \gamma & -r \\ -\gamma & \mu + \gamma \end{bmatrix}$$

The spectral radius  $\rho(FV^{-1})$  of  $FV^{-1}$  is the largest eigenvalue and it represents the basic reproductive number  $\mathcal{R}_{1,0}$ . For this model is as follows:

$$\mathcal{R}_{1,0} = \rho(FV^{-1}) = \rho\left(\frac{1}{(\mu + \gamma)(\mu + r) - r\gamma} \begin{bmatrix} \beta(\mu + r) & \beta r \\ 0 & 0 \end{bmatrix}\right) = \frac{\beta(\mu + r)}{(\mu + \gamma)(\mu + r) - r\gamma}$$

We consider a geometric series because this represents the  $n$  cycles that a infected person can do in the model, the geometric series of this case is:

$$\frac{\frac{\beta}{(\mu + \gamma)}}{1 - \frac{\gamma}{\mu + \gamma} \cdot \frac{r}{\mu + r}} = \sum_{n=0}^{\infty} \frac{\beta}{\mu + \gamma} \left(\frac{\gamma}{\mu + \gamma} \cdot \frac{r}{\mu + r}\right)^n$$

It is enough to show that the ratio of the series is less than 1 to justify that the series actually converges,

$$\frac{\gamma}{\mu + \gamma} \cdot \frac{r}{\mu + r} = \frac{\gamma \cdot r}{\mu^2 + \mu(\gamma + r) + \mu r}$$

The first two factors are probabilities therefore they are between zero and one, now note that in the denominator of the right side the terms  $\mu^2$  and  $\mu(\gamma + r)$  are positive non null so the denominator is greater than the numerator, then the ratio is less than one. Therefore the geometric series converges to  $\mathcal{R}_{1,0}$ .

## A.2 Model 2

In this model we only contemplate susceptible, infectious, treatment and latent state shown in figure 14.

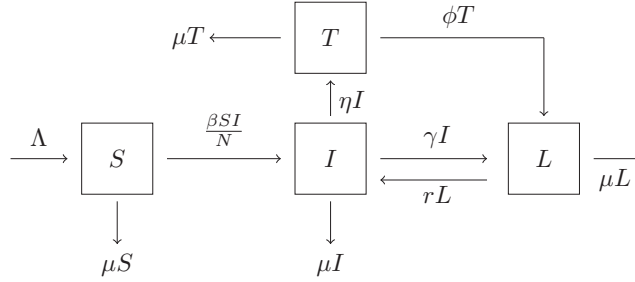


Figure 16: *SITLI* Model

The differential equations that represent this model are the following:

$$\frac{dS}{dt} = \Lambda - \frac{\beta SI}{N} - \mu S \quad (1)$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} + rL - (\eta + \gamma + \mu)I \quad (2)$$

$$\frac{dT}{dt} = \eta I - (\mu + \phi)T \quad (3)$$

$$\frac{dL}{dt} = \phi T + \gamma I - (\mu + r)L \quad (4)$$

Calculation of  $\mathcal{R}_{2,0}$ :

DFE =  $(\frac{\Lambda}{\mu}, 0, 0, 0)$ , where  $N = \frac{\Lambda}{\mu}$

Infected classes:  $X = \begin{bmatrix} I \\ T \\ L \end{bmatrix}$

Thus,  $\mathcal{F}$  and  $\mathcal{V}$  are as follows:

$$\mathcal{F} = \begin{bmatrix} \frac{\beta SI}{N} \\ 0 \\ 0 \end{bmatrix} \quad \mathcal{V} = \begin{bmatrix} -rL + (\eta + \gamma + \mu)I \\ -\eta I + (\mu + \phi)T \\ -\phi T - \gamma I + (\mu + r)L \end{bmatrix}$$

The Jacobian matrices for  $\mathcal{F}$  and  $\mathcal{V}$  with respect to  $I$ ,  $T$  and  $L$  are respectively the following:

$$F = \begin{bmatrix} \beta & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad V = \begin{bmatrix} \eta + \gamma + \mu & 0 & -r \\ -\eta & \mu + \phi & 0 \\ -\gamma & -\phi & \mu + r \end{bmatrix}$$

Thus,

$$FV^{-1} = \frac{1}{(\eta + \gamma + \mu)(\mu + \phi)(\mu + r) - r(\eta\phi + \gamma(\mu + \phi))} \begin{bmatrix} \beta(r + \mu)(\mu + \phi) & \beta r\phi & \beta r(\mu + \phi) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

The spectral radius  $\rho(FV^{-1})$  of  $FV^{-1}$  is the largest eigenvalue and it represents the control reproductive number  $\mathcal{R}_{2,c}$  because of the consideration of the treatment compartment ( $T$ ). For this model is as follows:

$$\mathcal{R}_{2,c} = \frac{\frac{\beta}{\mu + \gamma + \eta}}{1 - \left( \frac{\gamma}{\mu + \gamma + \eta} \cdot \frac{r}{\mu + r} + \frac{\eta}{\mu + \gamma + \eta} \cdot \frac{\phi}{\mu + \phi} \cdot \frac{r}{\mu + r} \right)}$$

By setting  $\phi = \eta = 0$ , the parameters associated to treatment, we are able to find  $\mathcal{R}_{2,0}$ . Thus,

$$\mathcal{R}_{2,0} = \frac{\frac{\beta}{\mu + \gamma}}{1 - \frac{\gamma}{\mu + \gamma} \cdot \frac{r}{\mu + r}}$$

Geometric Series for  $\mathcal{R}_{2,0}$ :

$$\mathcal{R}_{2,0} = \sum_{n=0}^{\infty} \frac{\beta}{\mu + \gamma} \left( \frac{\gamma}{\mu + \gamma} \cdot \frac{r}{\mu + r} \right)^n,$$

this geometric series converges because the ratio is less than 1, we prove that for the Model 1.



### A.3 Model 3

In this model we only contemplate susceptible, latent and two infectious classes shown in figure 15.

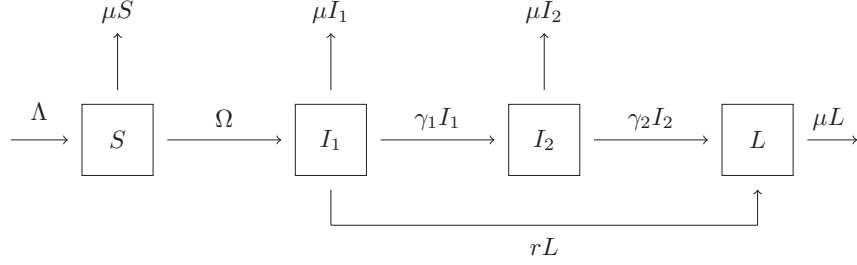


Figure 17:  $SI_1I_2LI_1$  Model

Note:  $\Omega = \frac{\beta_1SI_1 + \beta_2SI_2}{N}$ .

$$\frac{dS}{dt} = \Lambda + \mu S - (\beta_1I_1 + \beta_2I_2) \frac{S}{N} \quad (5)$$

$$\frac{dI_1}{dt} = (\beta_1I_1 + \beta_2I_2) \frac{S}{N} + rL - (\gamma_1 + \mu)I_1 \quad (6)$$

$$\frac{dI_2}{dt} = \gamma_1I_1 - (\mu + \gamma_2)I_2 \quad (7)$$

$$\frac{dL}{dt} = \gamma_2I_2 - (\mu + r)L \quad (8)$$

**Calculation of  $\mathcal{R}_{3,0}$ :**

DFE =  $(\frac{\Lambda}{\mu}, 0, 0, 0)$ , where  $N = \frac{\Lambda}{\mu}$

Infected classes:  $X = \begin{bmatrix} I_1 \\ I_2 \\ L \end{bmatrix}$

Thus,  $\mathcal{F}$  and  $\mathcal{V}$  are as follows:

$$\mathcal{F} = \begin{bmatrix} (\beta_1I_1 + \beta_2I_2) \frac{S}{N} \\ 0 \\ 0 \end{bmatrix} \quad \mathcal{V} = \begin{bmatrix} (\gamma_1 + \mu)I_1 - rL \\ (\mu + \gamma_2)I_2 - \gamma_1I_1 \\ (\mu + r)L - \gamma_2I_2 \end{bmatrix}$$

The Jacobian matrices for  $\mathcal{F}$  and  $\mathcal{V}$  with respect to  $I_1, I_2$  and  $L$  are respectively the following:

$$F = \begin{bmatrix} \beta_1 & \beta_2 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad V = \begin{bmatrix} \gamma_1 + \mu & 0 & -r \\ -\gamma_1 & \mu + \gamma_2 & 0 \\ 0 & -\gamma_2 & \mu + r \end{bmatrix}$$

Thus,

$$FV^{-1} = \frac{1}{\det(V)} \begin{bmatrix} \beta_1(r + \mu)(\gamma_2 + \mu) + \beta_2(r\gamma_1 + \gamma_1\mu) & r\beta_1\gamma_2 + \beta_2(r + \mu)(\gamma_1 + \mu) & r\beta_2\gamma_2 + \beta_1(r\gamma_2 + r\mu) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

where  $\det(V) = (r + \mu)(\gamma_1 + \mu)(\gamma_2 + \mu) - r\gamma_1\gamma_2$

Therefore, the basic reproductive number  $\mathcal{R}_{3,0}$  is as follows:

$$\mathcal{R}_{3,0} = \frac{\frac{\beta_1}{\mu + \gamma_1} + \frac{\gamma_1}{\mu + \gamma_1} \cdot \frac{\beta_2}{\mu + \gamma_2}}{1 - \frac{\gamma_1}{\mu + \gamma_1} \cdot \frac{\gamma_2}{\mu + \gamma_2} \cdot \frac{r}{\mu + r}}$$

Geometric series for  $\mathcal{R}_{3,0}$ :

$$\mathcal{R}_{3,0} = \sum_{n=0}^{\infty} \left( \frac{\beta_1}{\mu + \gamma_1} + \frac{\gamma_1}{\mu + \gamma_1} \cdot \frac{\beta_2}{\mu + \gamma_2} \right) \left( \frac{\gamma_1}{\mu + \gamma_1} \cdot \frac{\gamma_2}{\mu + \gamma_2} \cdot \frac{r}{\mu + r} \right)^n$$

Ahora debemos probar que el ratio es menor que 1,

$$\frac{\gamma_1}{\mu + \gamma_1} \cdot \frac{\gamma_2}{\mu + \gamma_2} \cdot \frac{r}{\mu + r} = \frac{\gamma_1 \cdot \gamma_2 \cdot r}{\mu^3 + \mu^2(\gamma_1 + \gamma_2 + r) + \mu(\gamma_1\gamma_2 + r(\gamma_1 + \gamma_2)) + \gamma_1\gamma_2r}$$

Each of the first three factors represents the probability that a person moves from  $I_1$  to  $I_2$ ,  $I_2$  to  $L$  and  $L$  to  $I_1$  respectively for each of the terms. Therefore each one is between zero and one, the product will also be between zero and one. The terms of the denominator of the fraction of the right side  $\mu^3$ ,  $\mu^2(\gamma_1 + \gamma_2 + r)$  and  $\mu(\gamma_1\gamma_2 + r(\gamma_1 + \gamma_2))$  are positive non null, then the denominator is greater than the numerator. Therefore the ratio is less than one and so the geometric series converges.

#### A.4 Model 4

For this model we only contemplate susceptible, latent states, two infectious states and one treatment state, shown in figure 16.

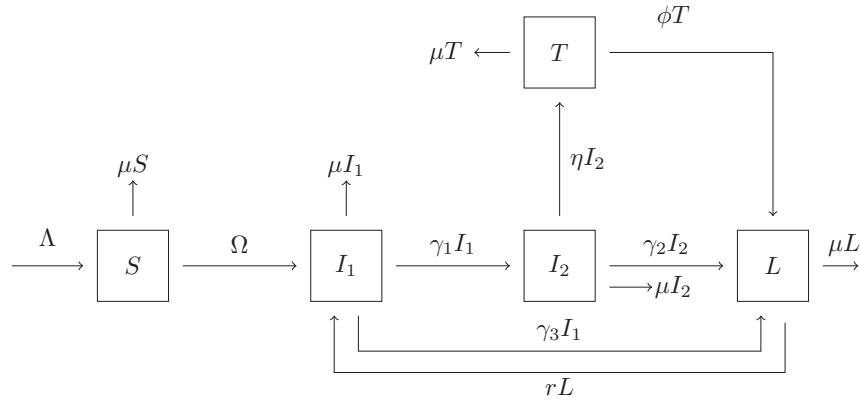


Figure 18:  $SI_1I_2TLI_1$  Model

$$\frac{dS}{dt} = \Lambda - (\beta_1 I_1 + \beta_2 I_2) \frac{S}{N} - \mu S \quad (9)$$

$$\frac{dI_1}{dt} = (\beta_1 I_1 + \beta_2 I_2) \frac{S}{N} - (\mu + \gamma_1 + \gamma_3) I_1 + rL \quad (10)$$

$$\frac{dI_2}{dt} = \gamma_1 I_1 - (\mu + \gamma_2 + \eta) I_2 \quad (11)$$

$$\frac{dT}{dt} = \eta_2 I_2 - (\mu + \phi) T \quad (12)$$

$$\frac{dL}{dt} = \phi T + \gamma_2 I_2 + \gamma_3 I_1 - (\mu + r) L \quad (13)$$

**Calculation of  $\mathcal{R}_{4,0}$ :**

DFE =  $(\frac{\Lambda}{\mu}, 0, 0, 0, 0)$ , where  $N = \frac{\Lambda}{\mu}$ .

Infected classes:  $X = \begin{bmatrix} I_1 \\ I_2 \\ T \\ L \end{bmatrix}$

Thus,  $\mathcal{F}$  and  $\mathcal{V}$  are as follows:

$$\mathcal{F} = \begin{bmatrix} (\beta_1 I_1 + \beta_2 I_2) \frac{S}{N} \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \mathcal{V} = \begin{bmatrix} (\mu + \gamma_1 + \gamma_3) I_1 - rL \\ -\gamma_1 I_1 + (\mu + \gamma_2 + \eta) I_2 \\ -\eta_2 I_2 + (\mu + \phi) T \\ -\phi T - \gamma_2 I_1 - \gamma_3 I_1 + (\mu + r) L \end{bmatrix}$$

The Jacobian matrices for  $\mathcal{F}$  and  $\mathcal{V}$  with respect to  $I_1, I_2, T$  and  $L$  are respectively the following:

$$F = \begin{bmatrix} \beta_1 & \beta_2 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad V = \begin{bmatrix} \gamma_1 + \gamma_3 + \mu & 0 & 0 & -r \\ -\gamma_1 & \gamma_2 + \eta + \mu & 0 & 0 \\ 0 & -\eta & \mu + \phi & 0 \\ -\gamma_3 & -\gamma_2 & -\phi & r + \mu \end{bmatrix}$$

where  $\det(V) = (\gamma_1 + \gamma_3 + \mu)(\gamma_2 + \eta + \mu)(\mu + \phi)(r + \mu) - r\gamma_1[\eta\phi + \gamma_2(\mu + \phi)] - r\gamma_3(\gamma_2 + \eta + \mu)(\mu + \phi)$

$$a_1 = \beta_1(r + \mu)(\gamma_2 + \eta + \mu)(\mu + \phi) - \beta_2(r + \mu)(\gamma_1\mu - \gamma_1\phi)$$

$$a_2 = \beta_2(r\gamma_1 + r\mu + \gamma_1\mu + \gamma_3\mu + \mu^2)(\mu + \phi) + \beta_1(r\gamma_2\mu + r\gamma_2\phi + r\eta\phi)$$

$$a_3 = r\beta_2\gamma_1\phi + r\beta_1(\gamma_2 + \eta + \mu)\phi$$

$$a_4 = r\beta_1(\gamma_2 + \eta + \mu)(\mu + \phi) + \beta_2(r\gamma_1\mu + r\gamma_1\phi)$$

$$FV^{-1} = \frac{1}{\det(V)} \begin{bmatrix} a_1 & a_2 & a_3 & a_4 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\mathcal{R}_{4,c} = \frac{\frac{\beta_1}{\mu + \gamma_1 + \gamma_3} + \frac{\gamma_1}{\mu + \gamma_1 + \gamma_3} \cdot \frac{\beta_2}{\mu + \gamma_2 + \eta}}{1 - \left( \frac{\gamma_1}{\mu + \gamma_1 + \gamma_3} \cdot \frac{\gamma_2}{\mu + \gamma_2 + \eta} \cdot \frac{r}{\mu + r} + \frac{\gamma_1}{\mu + \gamma_1 + \gamma_3} \cdot \frac{\eta}{\mu + \gamma_2 + \eta} \cdot \frac{\phi}{\mu + \phi} \cdot \frac{r}{\mu + r} + \frac{\gamma_3}{\mu + \gamma_1 + \gamma_3} \cdot \frac{r}{\mu + r} \right)}$$

Thus,

$$\mathcal{R}_{4,0} = \frac{\frac{\beta_1}{\mu+\gamma_1+\gamma_3} + \frac{\gamma_1}{\mu+\gamma_1+\gamma_3} \cdot \frac{\beta_2}{\mu+\gamma_2}}{1 - \left( \frac{\gamma_1}{\mu+\gamma_1+\gamma_3} \cdot \frac{\gamma_2}{\mu+\gamma_2} + \frac{\gamma_3}{\mu+\gamma_1+\gamma_3} \cdot \frac{r}{\mu+r} \right)}$$

## A.5 Proposed Model

In order to calculate the  $\mathcal{R}_c$  of the proposed model, the Next Generation Operator is used. Let  $\hat{X} = (I_1, I_2, T_1, T_2, L)^T$  be the vector of the infected classes with HSV-2. Now,  $\hat{X}$  is re-written as  $\hat{X} = \mathcal{F} - \mathcal{V}$ , where  $\mathcal{F}$  are new infection cases and  $\mathcal{V}$  are composed of the other terms. Thus,

$$\mathcal{F} = \begin{bmatrix} \frac{(\beta_1 I_1 + \beta_2 I_2)S}{S + I_1 + I_2 + L} \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{and} \quad \mathcal{V} = \begin{bmatrix} -rL + z_2 + I_1 \\ -\gamma_1 I_1 + z_3 I_2 \\ -\eta_1 I_1 + z_1 T_1 \\ \eta_2 I_2 + z_4 T_2 \\ -\gamma_3 I_1 - \gamma_2 I_2 - \phi_2 T_2 - \phi_1 T_1 + z_5 L \end{bmatrix}$$

For simplicity, we substitute  $z_i$ , where  $i = 1, \dots, 5$ , as follows:

$$z_1 = \mu + \phi_1, \quad z_2 = \mu + \eta_1 + \gamma_1 + \gamma_3, \quad z_3 = \mu + \eta_2 + \gamma_2, \quad z_4 = \mu + \phi_2, \quad \text{and} \quad z_5 = \mu + r.$$

Next we calculate the Jacobian matrices for  $\mathcal{F}$  and  $\mathcal{V}$  are the following:

$$F = \begin{bmatrix} \beta_1 & \beta_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} z_2 & 0 & 0 & 0 & -r \\ -\gamma_1 & z_3 & 0 & 0 & 0 \\ -\eta_1 & 0 & z_1 & 0 & 0 \\ 0 & -\eta_2 & 0 & z_4 & 0 \\ -\gamma_3 & -\gamma_2 & -\phi_1 & -\phi_2 & z_5 \end{bmatrix}$$

Next, we find the eigenvalues of  $FV^{-1}$ , which is,

$$FV^{-1} = \frac{1}{\det(V)} \begin{bmatrix} b_1 & b_2 & b_3 & b_4 & b_5 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

where  $\det(V) = z_1 z_2 z_3 z_4 z_5 - r z_3 z_4 \eta_1 \phi_1 - r z_1 (z_4 \gamma_1 \gamma_2 + z_2 z_3 \gamma_3 + \gamma_1 \eta_2 \phi_2)$ , and

$$b_1 = z_1 z_3 z_4 z_5 \beta_1 + z_1 z_4 z_5 \beta_2 \gamma_1,$$

$$b_2 = \beta_2 (z_1 z_2 z_4 z_5 - r z_1 z_4 \gamma_3 - r z_4 \eta_1 \phi_1) + \beta_1 (r z_1 z_4 \gamma_2 + r z_1 \eta_2 \phi_2),$$

$$b_3 = r z_3 z_4 \beta_1 \phi_1 + r z_4 \beta_2 \gamma_1 \phi_1,$$

$$b_4 = r z_1 z_3 \beta_2 \phi_2 + r z_1 \beta_2 \gamma_1 \phi_2, \quad \text{and}$$

$$b_5 = r z_1 z_3 z_4 \beta_1 + r z_1 z_4 \beta_2 \gamma_1.$$

The  $\mathcal{R}_c$  is mathematically defined as the spectral radius (the largest eigenvalue) of the matrix  $FV^{-1}$ . Therefore,

$$\mathcal{R}_c = \frac{\frac{\beta_1}{z_2} + \frac{\gamma_1}{z_2} \cdot \frac{\beta_2}{z_3}}{1 - \left( \frac{\gamma_1}{z_2} \cdot \frac{\gamma_2}{z_3} \cdot \frac{r}{z_5} + \frac{\eta_1}{z_2} \cdot \frac{\phi_1}{z_1} \cdot \frac{r}{z_5} + \frac{\gamma_1}{z_2} \cdot \frac{\eta_2}{z_3} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5} + \frac{\gamma_3}{z_2} \cdot \frac{r}{z_5} \right)}.$$

Notice that  $\mathcal{R}_c$  is the convergent sum of the geometric series:

$$\mathcal{R}_c = \sum_{n=0}^{\infty} \left( \frac{\beta_1}{z_2} + \frac{\gamma_1}{z_2} \cdot \frac{\beta_2}{z_3} \right) \left( \frac{\gamma_1}{z_2} \cdot \frac{\gamma_2}{z_3} \cdot \frac{r}{z_5} + \frac{\eta_1}{z_2} \cdot \frac{\phi_1}{z_1} \cdot \frac{r}{z_5} + \frac{\gamma_1}{z_2} \cdot \frac{\eta_2}{z_3} \cdot \frac{\phi_2}{z_4} \cdot \frac{r}{z_5} + \frac{\gamma_3}{z_2} \cdot \frac{r}{z_5} \right)^n$$

By setting to zero the parameters associated to treatment, i.e.  $\eta_1$ ,  $\eta_2$ ,  $\phi_1$ , and  $\phi_2$ , we obtain  $\mathcal{R}_0$ :

$$\mathcal{R}_0 = \frac{\frac{\beta_1}{\mu + \gamma_1 + \gamma_3} + \frac{\gamma_1}{\mu + \gamma_1 + \gamma_3} \cdot \frac{\beta_2}{\mu + \gamma_2}}{1 - \left( \frac{\gamma_1}{\mu + \gamma_1 + \gamma_3} \cdot \frac{\gamma_2}{\mu + \gamma_2} \cdot \frac{r}{\mu + r} + \frac{\gamma_3}{\mu + \gamma_1 + \gamma_3} \cdot \frac{r}{\mu + r} \right)}.$$

## A.6 Reduced model

Due to the complexity of our original model, we reduced it to a five-equation model. The following flow chart was made to be able to analyze the endemic equilibrium of our original system, shown in figure 17.

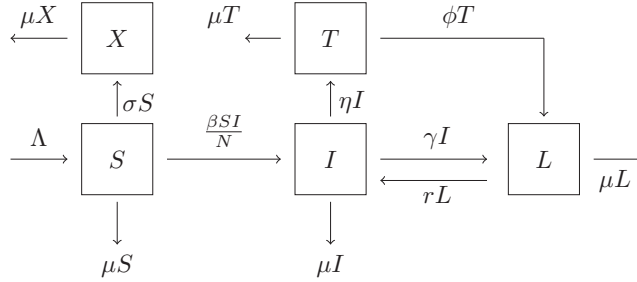


Figure 19: Reduced Model

## A.7 Jacobian of original model

$$J = \begin{bmatrix} c_{11} & \phi_1 & c_{13} & 0 & c_{15} & 0 & c_{17} \\ \kappa\eta_1 & -(\phi_1 + \mu) & 0 & 0 & 0 & 0 & 0 \\ c_{31} & 0 & c_{33} & 0 & c_{35} & 0 & r - c_{17} \\ 0 & 0 & \eta_1 & -(\phi_1 + \mu) & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -(\eta_1 + \gamma_1 + \mu) & 0 & 0 \\ 0 & 0 & 0 & 0 & \eta_2 & -(\phi_2 + \mu) & 0 \\ 0 & 0 & \gamma_3 & \phi_1 & \gamma_2 & \phi_2 & -(r + \mu) \end{bmatrix}$$

Where,

$$\begin{aligned}
c_{11} &= -\kappa\eta_1 - \frac{N1(\beta_1I_1 + \beta_2I_2) - (\beta_1SI_1 + \beta_2SI_2)}{N_1^2} - \mu, \\
c_{13} &= -\frac{N1(\beta_1S) - (\beta_1SI_1 + \beta_2SI_2)}{N_1^2}, \\
c_{15} &= -\frac{N1(\beta_2S) - (\beta_1SI_1 + \beta_2SI_2)}{N_1^2}, \\
c_{17} &= \frac{S(I_1\beta_1 + I_2\beta_2)}{N_1^2}, \\
c_{31} &= \frac{N1(\beta_1I_1 + \beta_2I_2) - (\beta_1SI_1 + \beta_2SI_2)}{N_1^2}, \\
c_{33} &= \frac{N1(\beta_1S) - (\beta_1SI_1 + \beta_2SI_2)}{N_1^2} - (\eta_1 + \gamma_3 + \gamma_1 + \mu), \\
c_{35} &= \frac{N1(\beta_2S) - (\beta_1SI_1 + \beta_2SI_2)}{N_1^2}.
\end{aligned}$$

### A.8 Sensitivity Analysis on stages with respect to $\eta_1$ and $\eta_2$

The following fourteen equations were calculated in order to use them for forward sensitivity equations with respect to parameters  $\eta_1$  and  $\eta_2$ . We made a numerical solution to obtain the sensitivity of  $I_1$  and  $I_2$  with respect of both parameters.

$$\begin{aligned}
\frac{d}{dt} \left[ \frac{\partial S}{\partial \eta_1} \right] &= \phi_1 \frac{\partial X}{\partial \eta_1} - \eta_1 \kappa \frac{\partial S}{\partial \eta_1} - \kappa S - \frac{(\beta_1 I_1 + \beta_2 I_2)(N_1 \frac{\partial S}{\partial \eta_1} - S \frac{\partial N_1}{\partial \eta_1}) + (\beta_1 \frac{\partial I_1}{\partial \eta_1} + \beta_2 \frac{\partial I_2}{\partial \eta_1}) S N_1}{N_1^2} - \mu \frac{\partial S}{\partial \eta_1} \\
\frac{d}{dt} \left[ \frac{\partial X}{\partial \eta_1} \right] &= \eta_1 \kappa \frac{\partial S}{\partial \eta_1} + \kappa S - (\phi_1 + \mu) \frac{\partial X}{\partial \eta_1} \\
\frac{d}{dt} \left[ \frac{\partial I_1}{\partial \eta_1} \right] &= \frac{(\beta_1 I_1 + \beta_2 I_2)(N_1 \frac{\partial S}{\partial \eta_1} - S \frac{\partial N_1}{\partial \eta_1}) + (\beta_1 \frac{\partial I_1}{\partial \eta_1} + \beta_2 \frac{\partial I_2}{\partial \eta_1}) S N_1}{N_1^2} + r \frac{\partial L}{\partial \eta_1} - \eta_1 \frac{\partial I_1}{\partial \eta_1} - I_1 \\
&\quad - (\gamma_1 + \gamma_3 + \mu) \frac{\partial I_1}{\partial \eta_1} \\
\frac{d}{dt} \left[ \frac{\partial T_1}{\partial \eta_1} \right] &= \eta_1 \frac{\partial I_1}{\partial \eta_1} + I_1 - (\phi_1 + \mu) \frac{\partial T_1}{\partial \eta_1} \\
\frac{d}{dt} \left[ \frac{\partial I_2}{\partial \eta_1} \right] &= \gamma_1 \frac{\partial I_1}{\partial \eta_1} - (\eta_2 + \gamma_2 + \mu) \frac{\partial I_2}{\partial \eta_1} \\
\frac{d}{dt} \left[ \frac{\partial T_2}{\partial \eta_1} \right] &= \eta_2 \frac{\partial I_2}{\partial \eta_1} - (\phi_2 + \mu) \frac{\partial T_2}{\partial \eta_1} \\
\frac{d}{dt} \left[ \frac{\partial L}{\partial \eta_1} \right] &= \gamma_3 \frac{\partial I_1}{\partial \eta_1} + \gamma_2 \frac{\partial I_1}{\partial \eta_1} + \phi_2 \frac{\partial T_2}{\partial \eta_1} + \phi_1 \frac{\partial T_1}{\partial \eta_1} - (r + \mu) \frac{\partial L}{\partial \eta_1} \\
\frac{d}{dt} \left[ \frac{\partial S}{\partial \eta_2} \right] &= \phi_1 \frac{\partial X}{\partial \eta_2} - \kappa \eta_1 \frac{\partial S}{\partial \eta_2} - \frac{(\beta_1 I_1 + \beta_2 I_2)(N_1 \frac{\partial S}{\partial \eta_2} - S \frac{\partial N_1}{\partial \eta_2}) + (\beta_1 \frac{\partial I_1}{\partial \eta_2} + \beta_2 \frac{\partial I_2}{\partial \eta_2}) S N_1}{N_1^2} - \mu \frac{\partial S}{\partial \eta_2} \\
\frac{d}{dt} \left[ \frac{\partial X}{\partial \eta_2} \right] &= \kappa \eta_1 \frac{\partial S}{\partial \eta_2} - (\phi_1 + \mu) \frac{\partial X}{\partial \eta_2} \\
\frac{d}{dt} \left[ \frac{\partial I_1}{\partial \eta_2} \right] &= \frac{(\beta_1 I_1 + \beta_2 I_2)(N_1 \frac{\partial S}{\partial \eta_2} - S \frac{\partial N_1}{\partial \eta_2}) + (\beta_1 \frac{\partial I_1}{\partial \eta_2} + \beta_2 \frac{\partial I_2}{\partial \eta_2}) S N_1}{N_1^2} + r \frac{\partial L}{\partial \eta_2} \\
&\quad - (\eta_1 + \gamma_1 + \gamma_3 + \mu) \frac{\partial I_1}{\partial \eta_2} \\
\frac{d}{dt} \left[ \frac{\partial T_1}{\partial \eta_2} \right] &= \eta_1 \frac{\partial I_1}{\partial \eta_2} - (\phi_1 + \mu) \frac{\partial T_1}{\partial \eta_2} \\
\frac{d}{dt} \left[ \frac{\partial I_2}{\partial \eta_2} \right] &= \gamma_1 \frac{\partial I_1}{\partial \eta_2} - \eta_2 \frac{\partial I_2}{\partial \eta_2} - I_2 - (\gamma_2 + \mu) \frac{\partial I_2}{\partial \eta_2} \\
\frac{d}{dt} \left[ \frac{\partial T_2}{\partial \eta_2} \right] &= \eta_2 \frac{\partial I_2}{\partial \eta_2} + I_2 - (\phi_2 + \mu) \frac{\partial T_2}{\partial \eta_2} \\
\frac{d}{dt} \left[ \frac{\partial L}{\partial \eta_2} \right] &= \gamma_3 \frac{\partial I_1}{\partial \eta_2} + \gamma_2 \frac{\partial I_1}{\partial \eta_2} + \phi_2 \frac{\partial T_2}{\partial \eta_2} + \phi_1 \frac{\partial T_1}{\partial \eta_2} - (r + \mu) \frac{\partial L}{\partial \eta_2}
\end{aligned}$$

## References

- [1] Beauman, J. G. (2005). Genital herpes: a review. *American Family Physician*, 72(8), 1527–1534. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16273819>
- [2] Benedetti J, Corey L, Ashley R. Recurrence Rates in Genital Herpes after Symptomatic First-Episode Infection. *Ann Intern Med*. 1994;121(11):847. doi:10.7326/0003-4819-121-11-199412010-00004
- [3] Burn, C., Ramsey, N., Garforth, S. J., Almo, S., Jacobs, W. R., & Herold, B. C. (2017). An HSV-2 single- cycle candidate vaccine deleted in glycoprotein D,  $\Delta gD-2$ , protects male mice from lethal skin challenge with clinical isolates of HSV-1 and HSV-2. *The Journal of Infectious Diseases*, 217(5), 754–758. <https://doi.org/10.1093/infdis/jix628>
- [4] Corey L, Adams HG, Brown ZA, Holmes KK. Genital Herpes Simplex Virus Infections: Clinical Manifestations, Course, and Complications. *Ann Intern Med*. 1983;98(6):958. doi:10.7326/0003-4819-98-6-958

- [5] Diekmann, O., Heesterbeek, J. A. P., & Metz, J. A. (1990). On the definition and the computation of the basic reproduction ratio  $R_0$  in models for infectious diseases in heterogeneous populations. *Journal of mathematical biology*, 28(4), 365-382.
- [6] Fatahzadeh, M., Schwartz, R. A. (2007). Human herpes simplex virus infections: Epidemiology, pathogenesis, symptomatology, diagnosis, and management. *Journal of the American Academy of Dermatology*, 57(5), 737-763. <https://doi.org/10.1016/J.JAAD.2007.06.027>
- [7] Johnston, C., & Corey, L. (2016). Current Concepts for Genital Herpes Simplex Virus Infection: Diagnostics and Pathogenesis of Genital Tract Shedding. *Clinical Microbiology Reviews*, 29(1), 149-161. <https://doi.org/10.1128/CMR.00043-15>
- [8] McQuillan G, e. (2018). Prevalence of Herpes Simplex Virus Type 1 and Type 2 in Persons Aged 14-49: United States, 2015-2016. - PubMed - NCBI. [online] Ncbi.nlm.nih.gov. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29442994>.
- [9] Mubayi A, Zaleta CK, Martcheva M, Castillo-Chávez C. A cost-based comparison of quarantine strategies for new emerging diseases. *Eng.* 2010;7(3):687-717. doi:10.3934/mbe.2010.7.687
- [10] Nakubulwa, S., Kaye, D. K., Bwanga, F., Tumwesigye, N. M., Nakku-Joloba, E., & Mirembe, F. M. (2016). Incidence and risk factors for herpes simplex virus type 2 seroconversion among pregnant women in Uganda: A prospective study. *The Journal of Infection in Developing Countries*, 10(10), 1108. <https://doi.org/10.3855/jidc.6874>
- [11] Podder, C. N., & Gumel, A. B. (2009). Qualitative dynamics of a vaccination model for HSV-2. *IMA Journal of Applied Mathematics*, 75(1), 75-107.
- [12] Almonte-Vega L., Ramos-Soto L., Rosado-Perez M., Roman-Melendez E., & Rios-Soto K. A Mathematical Epidemiological Model to Study the Impact of the Prodromal Stages on Herpes Simplex Viruses Epidemics. *Center for Undergraduate Research in Mathematics (CURM)*. Technical report. 2016.
- [13] Schwartz, E. J., & Blower, S. (2005). Predicting the potential individual-and population-level effects of imperfect herpes simplex virus type 2 vaccines. *Journal of Infectious Diseases*, 191(10), 1734-1746.
- [14] Szucs, T. D., Berger, K., Fisman, D. N., & Harbarth, S. (2001). The estimated economic burden of genital herpes in the United States. An analysis using two costing approaches. *BMC Infectious Diseases*, 1(1), 5. <https://doi.org/10.1186/1471-2334-1-5>
- [15] Tudor, D. (1990). A deterministic model for herpes infections in human and animal populations. *SIAM review*, 32(1), 136-139.
- [16] Van den Driessche, P., & Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical biosciences*, 180(1-2), 29-48.
- [17] Whitley, R. J., & Roizman, B. (2001). Herpes simplex virus infections. *The Lancet*, 357(9267), 1513-1518. [https://doi.org/10.1016/S0140-6736\(00\)04638-9](https://doi.org/10.1016/S0140-6736(00)04638-9)
- [18] D Wonderling RG and NB. *Introduction to Health Economics*. (Open University Press, ed.). United Kingdom: Mc Graw - Hill Education ; 2005. <http://bayanbox.ir/view/409603433922021820/Introduction-to-Health-Economics.pdf>.
- [19] Workowski, K. A., Bolan, G. A., & Centers for Disease Control and Prevention. (2015). Sexually transmitted diseases treatment guidelines, 2015. *MMWR. Recommendations and Reports : Morbidity and Mortality Weekly Report. Recommendations and Reports*, 64(RR-03), 1-137. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/26042815>
- [20] Wang J, Yu X, Tessmer HL, Kuniya T, Omori R. Modelling infectious diseases with relapse: a case study of HSV-2. *Theor Biol Med Model*. 2017;14(1):13. doi:10.1186/s12976-017-0059-4
- [21] Magaret, A. S., Mujugira, A., Hughes, J. P., Lingappa, J., Bukusi, E. A., DeBruyn, G., ... Mugo, N. R. (2015). Effect of Condom Use on Per-act HSV-2 Transmission Risk in HIV-1, HSV-2-discordant Couples. *Clinical Infectious Diseases*, 62(4), civ908. <https://doi.org/10.1093/cid/civ908>



- [22] Fields, S. A., Bhatia, G., Fong, J. M., Liu, M., & Shankar, G. N. (2015). SR-2P vaginal microbicide gel provides protection against Herpes Simplex virus 2 when 1 administered as a combined prophylactic/post exposure therapeutic. 2. AAC Accepted Manuscript Posted Online. <https://doi.org/10.1128/AAC.00690-15>
- [23] Acosta, A., Bar-Zohar, E., Blanco, S., Luli, D., & Gao, L. Q. (2005). An Epidemic Model of HSV-1 with Vaccination. Retrieved from <http://homes.sice.indiana.edu/sblancor/papers/hsv1.pdf>
- [24] Mubayi, A., Paredes, M., & Ospina, J. (2018). A Comparative Assessment of Epidemiologically Different Cutaneous Leishmaniasis Outbreaks in Madrid, Spain and Tolima, Colombia: An Estimation of the Reproduction Number via a Mathematical Model. *Tropical Medicine and Infectious Disease*, 3(2), 43. <https://doi.org/10.3390/tropicalmed3020043>
- [25] Baggaley, R. F., & Fraser, C. (2010). Modelling sexual transmission of HIV: testing the assumptions, validating the predictions. *Current Opinion in HIV and AIDS*, 5(4), 269–276. <https://doi.org/10.1097/COH.0b013e32833a51b2>
- [26] Granich, R. M., Gilks, C. F., Dye, C., De Cock, K. M., & Williams, B. G. (2009). Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *The Lancet*, 373(9657), 48–57. [https://doi.org/10.1016/S0140-6736\(08\)61697-9](https://doi.org/10.1016/S0140-6736(08)61697-9)