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Cost 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 sexually transmitted disease. According to the Center for Disease Control and Prevention (CDC), 11.9% of the United States (U.S.) population was infected with HSV–2 in 2015–2016. The HSV–2 pathogen establishes latent infections in neural cells and can reactivate causing lesions later in life, a strategy that increases pathogenicity and allows the virus to evade the immune system. HSV–2 infections are currently treated by Acyclovir only in the non-constitutional stage, marked by genital skin lesions and ulcers. However, patients in the constitutional stage expressing mild and common (with other diseases) symptoms, such as fever, itching and painful urination, remain difficult to detect and are untreated. In this study, we develop and analyze a mathematical model to study the transmission and control of HSV–2 among the U.S. population between the ages of 15–49 when there are options to treat individuals in different stages of their pathogenicity. In particular, the goals of this work are to study the effect on HSV–2 transmission dynamics and to evaluate and compare the cost-effectiveness of treating HSV–2 infections in both constitutional and non-constitutional stages (new strategy) against the current conventional treatment protocol for treating patients in the non-constitutional stage (current strategy). Our results distinguish model parameter regimes where each of the two treatment strategies can optimize the available resources and consequently gives the long-term reduced cost associated with each treatment and incidence. Moreover, we estimated that the public health cost of HSV–2 with the proposed most cost-effective treatment strategy would increase by approximately 1.63% in 4 years of implementation. However, in the same duration, early treatment via the new strategy will reduce HSV–2 incidence by 42.76% yearly and the reproduction number will decrease to 0.84 from its current estimate of 2.5. Thus, the proposed new strategy will be significantly cost-effective in controlling the transmission of HSV–2 if the strategy is properly implemented.

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 [19]. There are two types of HSV (HSV–1 and HSV–2). Type 1 (HSV–1) is less severe than HSV–2 and usu-

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ally transmitted from an infected person to a susceptible person through direct contact with bodily fluids, such as saliva. Meanwhile, type 2 (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 [23]. 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 [31]. Numerous demographical and epidemiological factors affect the acquisition of HSV infection. In less developed countries, seroconversion happens early in life in around 70- 80% by adolescence. In the USA, the incidence of infection among university students is around 5–10% annually [12]. The common risk factors include an increase in population with multiple sexual partners, the presence of other sexually transmitted diseases and non-systematic condom use [12,19]. An epidemiological study of patients seropositive to HSV–1 between 1976 and 2016, shows that a transition occurs in the U.S. with less exposure in childhood and more in adulthood, and less oral infections and more genital acquisition. Hence, HSV–1 is a widely prevalent infection with an increasing genital disease burden [1]. In pregnant women in the U.S., HSV–1 and HSV–2 seroprevalence remained stable between 1999 and 2014. However, a subpopulation of pregnant women with three or fewer sex partners were increasingly seronegative, and as a consequence, an increasing proportion of this subpopulation are vulnerable to primary HSV acquisition in pregnancy, which increased the risk of transmitting HSV to their neonates [13]. HSV–2 also significantly increases the risk of acquisition of human immunodeficiency virus (HIV) [5]. Approximately 417 million individuals between the ages of 15 to 49 years were infected with HSV–2 worldwide in 2012, and nearly 19.2 million of new infections occur each year worldwide [9]. In 2012, global estimates 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%) [9]. Over 10% of the population in European, Eastern Mediterranean, Southeast Asian, and Western Pacific regions are living with HSV–2 [9]. The highest prevalence of HSV–2 was found in Africa with more than 30% of the population being infected with HSV–2 [9]. In the United States, the prevalence of HSV-2 is approximately 12% of the population between 15–49 years of age of sexually active individuals, according to the National Center for Health Statistics (NCHS) in 2015–2016 [10].

1.2. Biological pathway of HSV–2

HSV is a member of the herpesviridae family, that contains a linear double-stranded DNA [8,15,19]. 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. 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 infectious period, the virus ascends through the periaxonal sheath of sensory nerves remaining out of reach of the immune system [15]. The virus establishment can be disrupted if treated quickly (within 24 hours) before it reaches the sensory nerves and evades an immune response. However, the successful disruption of the virus depends on the host health status [24].

Episodes of recurrences can occur throughout the life of the infected individual, promoting the transmission and disease dynamics of HSV–2. HSV remains in a dormant state until the viral replication process is activated again, known as a viral reactivation [8,15]. It is important to note that an HSV recurrence is not reinfection. Several factors, such as stress, fatigue, exposure to heat or sunlight, menstruation, fever, immunosuppression, and others could trigger the recurrence of HSV–2 [8,15,19]. The median number of recurrences is five and two in the first and second year, respectively [8]. The average number of recurrences per year is less than two in 47%, two to five in 36%, and more than five in 16% of patients [16,19].

Symptoms of HSV–2 infections are described in two broad categories: constitutional and non-constitutional symptoms [3]. Constitutional are mild symptoms, such as localized pain, tingling, burning sensation, headache, fever, and others, and are often confused with symptoms of another infection or disease, and thus make it difficult to detect HSV–2 with high accuracy. In contrast, non-constitutional are severe symptoms such as lesions and ulcers which both vary in size and severity but are easily detected.

Two tests used to diagnosis HSV–2 include the routine diagnostic test and the microbiological lab test. The routine diagnostic test refers to a clinical diagnostic evaluation of common symptoms including: painful ulceration in the anogenital region, vaginal or urethral discharge, superficial dyspareunia and external dysuria [26]. Other systemic symptoms such as fever, flu-like illness and malaise are also documented [26]. Signs can vary from multiple ulcers over the anogenital skin to small breaks in the skin, or erythema alone [26].

The clinical diagnosis of genital herpes is made via confirmation through laboratory testing often referred to as the Microbiological lab test. The presence of HSV–2 in the genital area is assessed using techniques like virus isolation and culture, detection of antigen or detection of HSV–2 DNA using molecular diagnostic techniques. In those cases, the sample is obtained from vesicular lesions within the first three days after their appearance [2], when the infection is established and has produce damage.

1.3. Clinical treatment and cost of HSV–2

The antiviral therapy, acyclovir, is one of the most widely used interventions to control the transmission of HSV-2. Acyclovir becomes active only in infected cells, which allows for a safety profile of the treatment and has demonstrated efficacy against mild to severe infections caused by HSV–2 in normal and immunocompromised patients [9]. Treatment with acyclovir depends on whether it is a first infection or recurrent infection. For the first episode of HSV–2, an oral dose of 200 mg of acyclovir is given five times per day, or 400 mg of acyclovir orally three times per day for 7 to 10 days. Treatment reduces the duration of the symptoms by about a week and the healing time of lesions by six days [21]. 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 five days. Topical acyclovir does not provide any additional benefits [21]. 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 [21]. Treatment is currently only applied to patients who exhibit non-constitutional symptoms. Thus, patients with constitutional symptoms are not currently treated. Currently, three drugs are commonly used to treat the symptoms of HSV–2, including acyclovir, famciclovir and valacyclovir.

The clinical diagnosis of genital herpes will be confirmed by laboratory testing, in that case, we refer to Microbiological lab test, in which demonstrates the presence of HSV in the genital area, using techniques like virus isolation and culture, detection of antigen or detection of HSV DNA using molecular diagnostic techniques. In those cases, the sample is obtained from vesicular lesions within the first three days after their appearance [2], when the infection is established and has produce damage.

In 1996, the average economic burden of medical care associated with HSV–2 was an estimated $984 million [16]. Approxi-

mately $470 million is attributed to lab testing and consultations, while $489 million is attributed to treatment [16]. Hospitalization of HSV–2 only attributes $25 million to the public health cost [16]. While this is a large burden, current prevalence rates demonstrate that current control strategies do not effectively reduce the spread of the disease.

In this research, our primary goal is to study the dynamics of HSV–2 transmission and control as the treatment rate of different infected/infectious status individuals are varied. Specifically, we propose and evaluate the impact of a novel treatment policy that targets patients with HSV–2 at the constitutional stage, in addition to the non-constitutional stage. We hypothesize that the proposed approach may be effective in controlling the disease, but the implementation of the new treatment strategy must be modeled to understand the practicality of this approach over different time horizons. The second goal of this study is to develop and analyze the cost and prevalence associated with the proposed treatment policy. Though we realize that there are some costs and benefits that we may not be able to capture in this population-level model, we present findings of a cost-effective analysis in order to mathematically analyze and evaluate whether the proposed program is cost-effective over the long-term in comparison with current strategy to control HSV–2. This paper is organized as follows: the formulation of the mathematical model for the dynamics of the HSV–2 and the cost equation for the proposed model is presented in Section 2. The analytical results of the model studied in Section 3. In Section 4 we present the numerical results for different treatment strategies and their associated cost analysis, and finally a brief discussion of the results and limitations of the model in Section 5.

2. Methods

Previous mathematical models of Herpes have studied the role of various factors and vaccination programs on the transmission dynamics and control of the disease. Tudor [17] evaluated the spread of HSV infection both in humans and animals. In 2005, Blower and Schwartz [15] studied 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 [14] analyzed the qualitative dynamics of HSV–2 with and without vaccination in 2009. Acosta et al. [25], studied the epidemic model of HSV–1 with a vaccination-treatment reproductive number and their sensitivity analysis, and compared different types of treatment and vaccination strategies.

This study investigates the effects of early treatment of HSV–2 on the transmission dynamics and control of HSV–2 using a system of differential equations-based model. Our aim is to estimate and compare the 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. genital lesions. To treat HSV–2 infection early on, we propose a non-conventional treatment which consists of treating patients who present constitutional symptoms, i.e. fever, headache, dysuria, or skin irritation. These symptoms are general and may be confused with other diseases, leading to many misclassifications of the disease. In this study, we propose that treatment should be administered to patients presenting 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, such as having multiple sexual partners, displaying immunodepression, having high frequency of sexual contacts, or unprotected sex. Our proposed mathematical model incorporates both conventional and proposed treatments.

2.1. The proposed model of HSV-2 dynamics

The model consists of a population of sexually active individuals between the ages of 15 and 49 years in the U.S. The population is stratified into HSV-2 infection stages or classes. The S class in the model represents susceptible individuals, 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, but is not infected with HSV-2, a doctor can send him/her to HSV-2 treatment in the X–class at a rate σp; this stage, X, captures false positive individuals. Once the period for the treatment ends, the individual returns to the S class at a rate ϕ_1. Both σp and ϕ_1 correspond to the "first-line" treatment of HSV-2, that is, the recommended initial treatment. If a person is infected with HSV-2, he/she progresses to the I_1 class through the force of infection Ω; an individual in I_1 presents constitutional symptoms and is infectious. If a doctor identifies five constitutional symptoms and risky behavior, the individual progresses to the T_1 class (HSV-2 treatment) at a rate η_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 γ_1; population in this class is infectious. A doctor can send an individual in I_2 to treatment at a rate η_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 γ_2, from T_1 at rate ϕ_1, from T_2 at rate ϕ_2, and directly from I_1 at a rate γ_3 when the infected individual only presents constitutional symptoms before going dormant. The flowchart of the proposed model is shown in Fig. 1. A summary of the relationships between treatments, diagnosis (constitutional and non-constitutional symptoms), and compartments are shown in Table 1. Notice that L individuals do not have any symptoms for HSV–2 and are not infectious. Some of them may have symptoms similar to HSV–2 but since they have serious prior history of HSV–2, they are assumed to be not misdiagnosed by mistake. Since the signs and symptoms of HSV–2 are similar to other pathologies, a misdiagnosis could occur (e.g., Dysuria) which is related to urinary tract infection, lichen sclerosis, thrush, eczema, shingles, and anal fissure; Similarly, urethral discharge is related to chlamydia, gonor-

Table 1
Typical symptoms of the constitutional and non-constitutional stage [3]. The routine diagnostic test consists of an evaluation of common symptoms related to HSV–2 infection. A clinical diagnosis of HSV–2 is confirmed with a Microbiological lab test.

Variable	Symptoms	Diagnosis	Treatment Class (Treatment Type)
I_1	Constitutional (caused by HSV–2)	Routine diagnostic test	T_1 (nonconventional)
I_2	Non-constitutional (caused by HSV–2)	Microbiological lab test	T_2 (conventional)
S	Constitutional (not caused by HSV-2)	Routine diagnostic test	X (nonconventional)
L	None	Routine diagnostic test	None

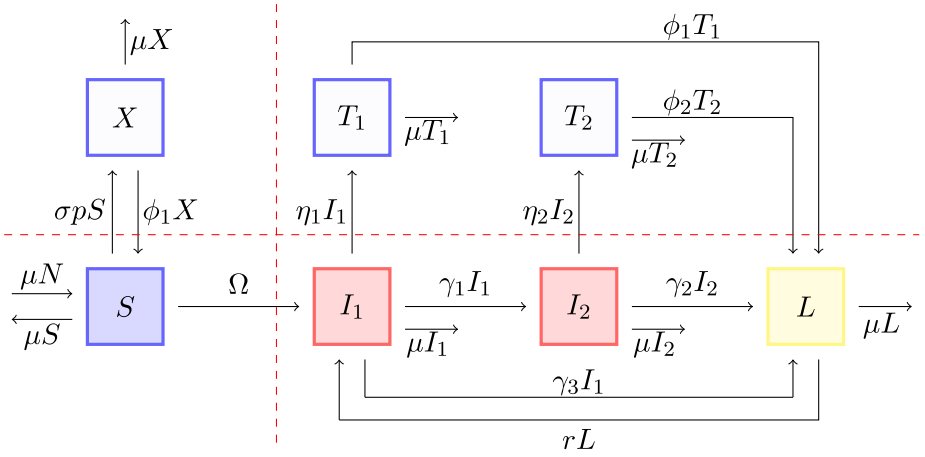

Fig. 1. The diagram illustrates the susceptible (S), infected (I_1 and I_2), latent (L) and treatment classes (T_1, T_2, and X). The compartments S, X, T_1 and T_2 include individual with HSV-2. The compartments X, T_1, and T_2 represent treatment groups, where as S, I_1, I_2, and L are non-treatment classes. The parameter definitions are shown in Table 3. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Stages of the proposed model.

Class	Description
S	Sexually active 15 and 49 year-olds in the U.S. who are not infected with HSV-2.
X	Non-HSV–2 infected individuals who present nonspecific mild symptoms and hence, are put under treatment for HSV–2 by mistake but only with first line treatment.
I_1	Infected and infectious individuals who present HSV–2 specific mild symptoms.
I_2	Infected and infectious individuals of HSV-2 who present its severe symptoms.
L	Infected and non-infectious individuals of HSV-2.
T_1	Infected and infectious individuals with mild symptoms and are under HSV–2 treatment with any of three drugs available that work.
T_2	Infected and infectious individuals with severe symptoms and are under HSV–2 treatment.
I_p	Cumulative incidence over time after implementing early treatment.
I_c	Cumulative incidence over time with current treatment strategy.

rhea, non-specific urethritis, urinary tract infection. The most common sign of HSV–2 is genital ulceration, which could also be related to Syphilis, Behcetâs disease, Crohnâs disease, tropical ulcers, and malignancy [26]. Hence, the similarities of symptoms make distinguishing HSV–2 from other infections challenging.

This model is constructed based on 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 undergoing availing interventions related to HSV–2 (window of opportunity for reducing HSV–2, that is, their risk of developing HSV–2 is reduced or delayed due to interventions. 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 is no false diagnosis for patients in I_2. Sixth, the total population is constant. While more complex models could divide the population into groups to capture for differences in mixing patterns based on gender or sexual activity [29], here all heterogeneity is averaged out. That is, we focus on a treatment strategy regardless of the gender of patients, which has also been assumed in a prior simple model [28]. The variables and parameter definitions are collected in Tables 2 and 3, respectively.

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

$$\frac{dS}{dt} = \mu N + \phi_1 X - \sigma pS - \Omega - \mu S, \tag{2.1}$$

$$\frac{dX}{dt} = \sigma pS - (\phi_1 + \mu)X, \tag{2.2}$$

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

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

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

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

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

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 $\Omega = \frac{\beta_1 SI_1 + \beta_2 SI_2}{N_1}$ and the entry rate is $\Lambda = \mu N$. Also, σp is assumed to be $\sigma = \kappa\eta_1$ approximately, where κ is a scaling coefficient (between 0 and 1) which captures the effect of efficiency of testing positive for HSV-2 given presence of pathogens.

The baseline parameter values were defined based on prior studies or published data. The annual per-capita death rate estimated by Wang et al. [22] and is the assumed average entry rate of new sexually active individuals between 15 to 49 years old, which yields an average daily rate of 0.0231 per unit time. The transmission rate of individuals who present constitutional (I_1) and non-constitutional (I_2) symptoms denoted β_1 and β_2, respectively, were estimated based on reported number of sexual partners and self-reported HSV-2 cases [20], and the approximate value 2.5 of $\mathcal{R}_c$. In the following Section we discuss the steps taken for fixing the values of η_1 and ϕ_1 as zero, and we calculate the control reproductive

Table 3
Description and units of the model parameters, where d denotes day.

Parameter	Description	Point estimate	Ref.
μ	Per capita rate of removal/entry sexually active population	$6.310^{-5} d^{-1}$	[22]
β_1	Transmission coefficient related to infection spread from I_1 to S	$0.0027\ d^{-1}$	[20]
β_2	Transmission coefficient related to infection spread from I_2 to S	$0.00135\ d^{-1}$	[20]
γ_1^{-1}	Duration of mild symptoms stage	$6\ d$	[6]
γ_2^{-1}	Duration of severe symptoms stage before relapse	$14\ d$	[6]
γ_3^{-1}	Duration of mild symptoms stage before relapse	$13\ d$	[22]
ϕ_1^{-1}	Duration of mild symptoms	$4\ d$	[19]
ϕ_2^{-1}	Duration of severe symptoms	$6\ d$	[21]
r	Per capita activation rate from latency	$0.0127\ d^{-1}$	[4,22]
η_1	Per capita treatment rate of I_1 after routine diagnostic test	Varies	Estimated
η_2	Per capita treatment rate of I_2 after microbiological lab test	$0.25\ d^{-1}$	[16]
σ	Per capita treatment rate of non-HSV–2 individuals	$1.34\ d^{-1}$	Estimated
p	Proportion of S who develops symptoms of other diseases	0.01	Estimated

Table 4
Description of type of costs where value is defined per person. Parameters in C_c and C_p are defined as follows: τ represents the time period, η_1 is the per capita rate of early treatment, η_2 is the per capita rate of the conventional treatment, and $\tilde{\eta}_2$ is the baseline value of η_2.

Type of Cost	Description	Value	Ref.
C_1	Consultation + Clinical Examination + Routine diagnostic test	161.85	[16]
C_2	C_1 + Antiviral treatment	248.18	[16]
C_3	C_2 + HSV-2 microbiological lab test	328.35	[16]
$C_p(\tau;\, \eta_1,\, \eta_2)$	Cost of implementing early treatment		
$C_c(\tau;\, \tilde{\eta}_2)$	Cost of the current strategy		

number for this model to compare with $\mathcal{R}_c$ values of the proposed model. Solving an equation for β_1 and β_2, using the known values for the others parameters, we derived an equation which depends on β_1 and β_2. In the first 6 days of infection (average time an infected individual takes to develop severe symptoms), the viral load is twice compared with the next 14 days. This means the value of β_1 is twice the value of β_2. However, this may be underestimated due to bias in self-reported data or due to undiagnosed cases. The average time an infected individual takes to develop severe symptoms is 6 days. Individuals manifest mild or severe symptoms before relapsing for an average duration of 13 and 14 days, respectively [6,22]. The number of days spent for treatment for mild or severe symptoms is 4 and 6 days, respectively [19,21]. The time it takes for HSV-2 virus cells to reactivate from the latency stage is 0.0127 per unit time of days [4,22]. The treatment rate of I_1 individuals varies since many are unaware that they have HSV-2. In contrast, individuals with some mild or severe symptoms have an average daily treatment rate of 0.25 day^{-1} [16]. The rate of false-positives and symptomatic period of non-HSV-2 diseases were estimated based on the literature.

2.2. Cost model

The total cost incurred by the healthcare system is estimated from the model and analyzed over time. The cost that consists of consultation, diagnosis and treatment of HSV–2 is evaluated when early treatment strategy for HSV–2 is implemented in addition to the conventional treatment. The cost of the proposed strategy, in terms of treatment rates of individuals with constitutional symptoms (η_1) and non-constitutional symptoms (η_2), over τ years is denoted by $C_p(\tau;\, \eta_1,\, \eta_2)$.

Total Cost = Cumulative cost of (
routine diagnostic testing of pS population with negative result at rate $\tilde{\sigma}$
+ routine diagnostic testing of pS population with positive result and treatment at rate σ
+ routine diagnostic testing of I_1 population with positive result and treatment at rate η_1
+ microbiological lab testing of I_2 population with positive result and treatment at rate η_2
+ routine diagnostic testing of pL population with negative result at rate $\tilde{\sigma}$)

$$\begin{aligned} C_p(\tau;\, \eta_1,\, \eta_2) = C_1 \int_0^\tau \tilde{\sigma}\, pS(t)dt + C_2 \int_0^\tau \sigma\, pS(t)dt \\ + C_2 \int_0^\tau \eta_1 I_1(t)dt + C_3 \int_0^\tau \eta_2 I_2(t)dt \\ + \int_0^\tau \tilde{\sigma}\, pL(t)dt \end{aligned} \tag{2.8}$$

where C_1 denotes the average cost incurred to evaluate (includes consultation, clinical examination and a routine diagnostic test) a single patient, C_2 is the average cost incurred to evaluate as well as provide basic treatment to a patient, and C_3 denotes the average cost incurred to evaluate, carry out microbiological and antibody tests, and provide specialized treatment to a patient (see Table 4). The expressions $\sigma\, pS(t)$, $\eta_1 I_1(t)$ and $\eta_2 I_2(t)$ represent the rates of individuals getting treated, while being susceptible, mildly infected, and severely infected, respectively, on t-th day. The expressions $\tilde{\sigma}\, pS(t)$ and $\tilde{\sigma}\, pL(t)$ represent the rates of consultation and routine diagnostic tests of p proportion of susceptible and latent individuals respectively that present HSV-2 like symptoms but are not diagnosed positive for HSV-2. The rate $\tilde{\sigma} \geq \sigma$ is assumed to be the rate of diagnostic testing only where σ includes both testing and treatment. Note that, using the relation $\sigma = \kappa \eta_1$ mentioned above, and assuming $\tilde{\sigma}$ to be σ scaled up by a factor q, all the components of the cost C_p will be functions of either η_1 or η_2.

We compare the cost of the proposed early treatment with the cost of the current strategy of treatment to control HSV–2. The cost of the current strategy of treatment, $C_c(\tau,\, \eta_2)$ is calculated as the total cost of evaluation, diagnosis and treatment (at a rate $\eta_2 = 0.25\ day^{-1}$) of only the HSV–2 infected individuals showing non-constitutional symptoms over the period of τ days.

$$C_c(\tau;\, \tilde{\eta}_2) = C_3 \int_0^\tau \eta_2 I_2(t)dt \tag{2.9}$$

Our study is motivated by previous research which indicates that treating of patients within the first 24 hours of onset symp-

toms of genital herpes could control a recurrence episode in two days [21]. Considering this fact, we want to evaluate how a different strategy (early treatment to HSV–2) could affect the cumulative incidence of the disease over τ days and its public health cost. In other words, we compare strategies in terms of their cost per the effect in health achieved through the implementation of a specific strategy [11]. Cost per health-effect is evaluated by calculating the variation in cost-effectiveness through the Average Cost-Effectiveness Ratio (ACER) [20]. The incremental health effect will be measured in terms of the reduction in the cumulative incidence, that is, the total number of new cases of HSV–2 prevented in τ days. The cumulative incidence over τ days is calculated as $\int_0^\tau \Omega(t;\eta_1,\eta_2)dt$ where

$$\Omega(t;\eta_1,\eta_2) = \frac{\beta_1 S(t;\eta_1,\eta_2)I_1(t;\eta_1,\eta_2) + \beta_2 S(t;\eta_1,\eta_2)I_2(t;\eta_1,\eta_2)}{N_1(t;\eta_1,\eta_2)}$$

Therefore, the cumulative incidences during τ days in the current strategy and the proposed strategy for treating HSV–2, denoted by $I_c(\tau;\tilde{\eta}_2)$ and $I_p(\tau;\eta_1,\eta_2)$ respectively are

$$I_c(\tau;\tilde{\eta}_2) = \int_0^\tau \Omega(t;0,\eta_2)dt,$$

$$I_p(\tau;\eta_1,\eta_2) = \int_0^\tau \Omega(t;\eta_1,\eta_2)dt$$

Therefore the ACER will be calculated as

$$\text{ACER}(\tau;\eta_1,\eta_2) = \frac{C_p(\tau;\eta_1,\eta_2) - C_c(\tau;\tilde{\eta}_2)}{I_p(\tau;\eta_1,\eta_2) - I_c(\tau;\tilde{\eta}_2)} \tag{2.10}$$

The ACER calculates the incremental cost over the incremental health effect, which here is defined as prevented cumulative number of cases, of proposed treatment with respect to the current treatment. $C_p(\tau;\eta_1,\eta_2)$ is defined by the proposed cost of implementing early treatment at per capita rate η_1 along with conventional treatment at per capita rate η_2 (both varied from 0 to 1 day^{-1} for analysis), while $C_c(\tau;\tilde{\eta}_2$ is related to the current treatment strategy with per capita rate of conventional treatment is $\eta_2 = \tilde{\eta}_2$=0.25 day^{-1}. We use the notation $\tilde{\eta}_2$ to refer to a baseline value of η_2. $I_p(\tau;\eta_1,\eta_2)$ is defined by cumulative incidence level over τ time period when implementing early treatment at per capita rate η_1 along with conventional treatment at per capita rate η_2 (both varied from 0 to 1 day^{-1} for analysis), while $I_c(\tau;\tilde{\eta}_2)$ is defined by cumulative incidence level τ time period related to current treatment strategy with per capita rate of conventional treatment is $\eta_2 = \tilde{\eta}_2$=0.25 day^{-1}.

3. Analysis

To better understand the transmission dynamics and control of HSV-2, we study the dynamics of the model analytically. We derive the threshold term $\mathcal{R}_0$, which represents the basic reproduction number, and the steady states of the proposed model. The equilibria are calculated by setting Eqs. (2.1) to (2.7) to zero.

Remark: There are two equilibria in our system: the disease-free equilibrium and the endemic equilibrium. The general analysis suggests that if $R_c < 1$ then HSV-2 can be controlled (that is, the disease-free equilibrium is locally stable). However, when $R_c > 1$ the disease becomes endemic (that is, the endemic equilibrium is locally stable and the disease free equilibrium exists but becomes unstable).

3.1. The reproduction number of the model

The basic reproduction number, $\mathcal{R}_0$, 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 [7,18,27]. The $\mathcal{R}_c$ denotes the control reproduction number which incorporates control measures, such as treatment, quarantine, or isolation. Since the derivation of $\mathcal{R}_c$ is complex we have attempted to show the steps of the derivation by varying different model assumptions and generating special cases of the model in Appendix A. The Next Generation Operator method (shown in Appendix B using methodology in [30]) is applied to calculate $\mathcal{R}_c$ of the model. In order to obtain $\mathcal{R}_0$ from $\mathcal{R}_c$, we set the parameters associated with the control programs to zero [30].

For simplicity, we substitute z_i, where $i = 1,\ldots,5$, 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 $z_5 = \mu + r$. Notice that the convergent sum of the geometric series is the control reproduction number ($\mathcal{R}_c$):

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

Hence, $\mathcal{R}_c$ is:

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

This $\mathcal{R}_c$ can be interpreted as the transmission rate due to I_1 individuals, β_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, β_2, multiplied again by the time spent in the I_2 compartment, $\frac{1}{z_3}$. The reproduction number is typically related to the disease progression via a cyclic path (through reinfection). There are four cyclic paths, which are captured by a parameter $\hat{\Theta}$ as shown in the equation of $\mathcal{R}_c$. The four cyclic paths are: (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. The derivation of the $\mathcal{R}_c$ is shown in Appendix B.

The basic reproduction number is:

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

Details of this analysis is shown in Appendix A.5.

3.2. Equilibria and stability

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

$$E_0 = (S^*, X^*, I_1^*, T_1^*, I_2^*, T_2^*, L^*) = \left(S^* = \frac{\mu z_1 N}{\kappa\eta_1 z_1 + \mu z_1 - \kappa\eta_1\phi_1}, X^* = \frac{\kappa\eta_1\mu N}{\kappa\eta_1 z_1 + \mu z_1 - \kappa\eta_1\phi_1}, I_1^* = 0, T_1^* = 0, I_2^* = 0, T_2^* = 0, L^* = 0\right),$$

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.

3.3. Endemic equilibrium

The Jacobian of the model is given in Appendix Appendix C. Due to the complexity of our model, we consider a special case of the model. The reduced system shown in Appendix A.5 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:

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

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

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

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

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

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: $p_1 = \frac{\phi}{z_1}$, $p_2 = \frac{\eta}{z_2}$, $p_5 = \frac{r}{z_5}$, $q_2 = \frac{\gamma}{z_2}$, $\pi_1 = \frac{\phi}{z_1}\frac{\eta}{z_2}\frac{r}{z_5}$, $\pi_2 = \frac{r}{z_5}\frac{\gamma}{z_2}$, and $\pi_c = \pi_1 + \pi_2$. The endemic equilibrium is given by $E_1 = (S^*, X^*, I^*, T^*, L^*)$; where:

$$S^* = \frac{Nz_1\mu(r + z_2\pi_c)}{z_2(\alpha_1\mu + r\alpha_2 + rz_1(-1 + \pi_2))},$$

$$X^* = \frac{Nr\mu\kappa\eta(\beta + z_2(-1 + \pi_c))}{z_2^2(\alpha_1\mu + r\alpha_2 + rz_1(-1 + \pi_2))(-1 + \pi_c)},$$

$$I^* = \frac{Nrz_1\mu(\beta + z_2(-1 + \pi_1 + \pi_2))}{z_2^2(\alpha_1\mu + r\alpha_2 + rz_1(-1 + \pi_2))(-1 + \pi_c)},$$

$$T^* = \frac{Nr\mu\eta(\beta + z_2(-1 + \pi_c))}{z_2^2(\alpha_1\mu + r\alpha_2 + rz_1(-1 + \pi_2))(-1 + \pi_c)},$$

$$L^* = \frac{Nr\mu(\beta + z_2(-1 + \pi_c))(z_1\gamma + \eta\phi)}{z_2^2z_5(\alpha_1\mu + r\alpha_2 + rz_1(-1 + \pi_2(-1 + \pi_c))},$$

with $\alpha_1 = z_1\pi_c + \eta\kappa\pi_2$ 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 (Fig. 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.

4. Results

To evaluate the effectiveness of the proposed treatment strategy, we perform a local sensitivity analysis of $\mathcal{R}_c$ with respect to the control parameters η_1 and η_2 shown in Section 4.1 of the proposed model. The effects of treatments on the prevalence of infected individuals (I_1 and I_2) is shown in Section 4.2.

4.1. Sensitivity analysis of $\mathcal{R}_c$ with respect to parameters

The $\mathcal{R}_c$ considers the case when the two treatment strategies are implemented, that is, $\eta_1, \eta_2 > 0$. To understand the effects of the treatment strategy on controlling HSV–2 transmission, we perform a local sensitivity analysis of $\mathcal{R}_c$ with respect to η_1 and η_2. The proof can be found in Appendix D.1.

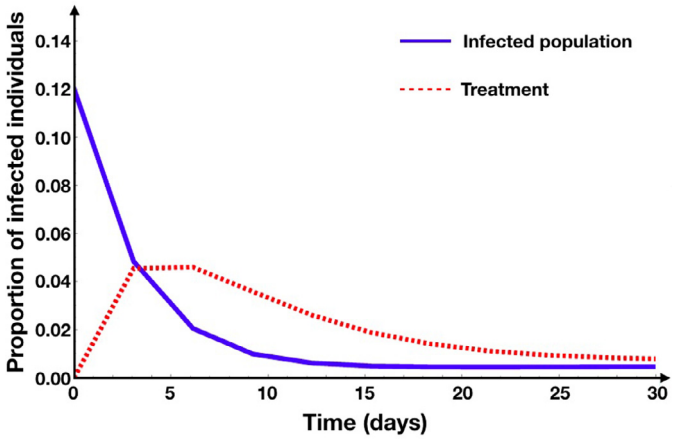

Fig. 2. The solid (blue) curve represents the I class and dashed (red) curve represents the T class. Time is measured in days. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Proposition 1. *Consider $\mathcal{R}_c$ as the control reproduction number and η_2 a parameter. We show that $\frac{\partial \mathcal{R}_c}{\partial \eta_2} \to 0$ when $\eta_2 \to \infty$ and $\mathcal{R}_c$ converges to $\mathcal{R}_c^*$ when $\eta_2 \to \infty$ where $\mathcal{R}_c^* = \frac{\frac{\beta_1}{z_2}}{(1-(\alpha_1+\alpha_4+\frac{\gamma_1}{z_2}\cdot\frac{\phi_2}{z_4}\cdot\frac{r}{z_5}))}$.*

Remark 1. It can be shown that calculating the limit of $\mathcal{R}_c$ as η_2 approaches infinity, $\mathcal{R}_c$ will converge to a specific $\mathcal{R}_c^*$. Then $\mathcal{R}_c^* > 1$ if and only if $\eta_1 < 0.2588$ as illustrated in Fig. 6. This shows that no matter how much η_2 is increased, $\mathcal{R}_c^*$ will not decrease enough to control the epidemic unless η_1 is increased. In other words, the change in $\mathcal{R}_c$ with respect to η_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 reproduction number and η_1 a parameter for which we have control. We now show that $\frac{\partial \mathcal{R}_c}{\partial \eta_1} < 0$ when $\eta_1 \to \infty$ and $\mathcal{R}_c \to 0$ when $\eta_1 \to \infty$.*

Remark 2. It can be shown that for a set of fixed parameter values $\frac{\partial \mathcal{R}_c}{\partial \eta_1} < 0$, and therefore, $\mathcal{R}_c$ is always decreasing when η_1 is increasing. This result illustrates that it is necessary to implement early treatment in order to reduce the incidence of HSV–2 at the population-level. The proof is shown in Appendix D.2.

4.2. Sensitivity analysis of 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 η_1 and η_2 on I_1 and I_2 over time.

Fig. 3 shows the effects of η_1 and η_2 on the infected population with constitutional symptoms I_1. It is observed that as η_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 η_2 (red-dashed curve) increases, it has a little effect on the change of I_1, since individuals enter into the I_1 compartment before transitioning into the I_2 class. This slight increase is due to the higher number of recurrences due to the individuals entering the latent stage.

Fig. 4 shows the effects of η_1 and η_2 on the I_2 compartment. It is seen that η_2 (blue-solid curve) has a larger effect on the I_2 compartment than η_1 (red-dashed curve) since η_2 is directly removing individuals from the I_2 compartment. The plots also show that changes in η_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 η_2 than η_1.

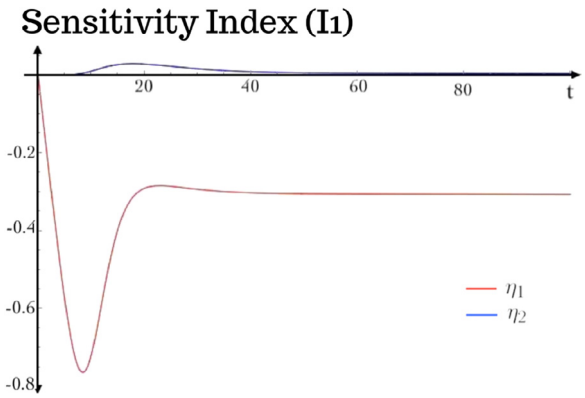

Fig. 3. Local sensitivity analysis of class I_1 with respect to η_1 (red curve) and η_2 (blue curve). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

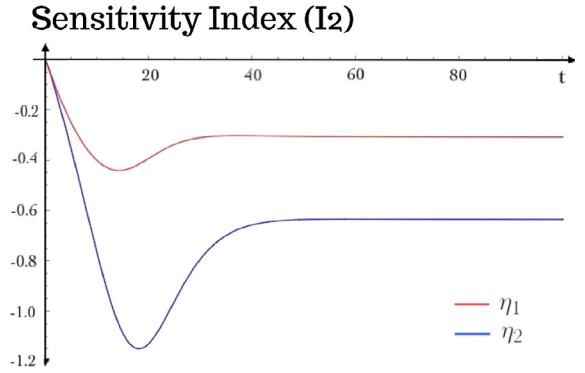

Fig. 4. Local sensitivity analysis of class I_2 with respect to η_1 (red curve) and η_2 (blue curve). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4.3. The impact of variations in control measure-Related parameters on $\mathcal{R}_c$

This section evaluates the impact of new treatment rates on $\mathcal{R}_c$. More specifically, we examine how $\mathcal{R}_c$ changes as parameters η_1 and η_2 are varied. Fig. 5 shows the effect η_1 and η_2 have on the control reproduction number. It can be seen that η_1 is more effective in reducing the control reproduction number than η_2. The plot also shows that when $\eta_1 = 0$, then $\mathcal{R}_c > 1$ for all values of η_2.

The parameter threshold for disease control is explored. Fig. 6 shows a contour plot of Fig. 2 when $\mathcal{R}_c = 1$. This plot represents the treatment parameter threshold for disease control. As seen, the graph is asymptotic as η_2 is increased, and η_1 is decreased below 0.2588 (Proposition 1). This shows that no matter how much effort is put into getting individuals from I_2 into T_2 the epidemic will not be controlled. The disease is better controlled as η_1 increases and η_2 decreases. Hence, this shows that as more individuals are removed from I_1 the more likely it is to control HSV–2.

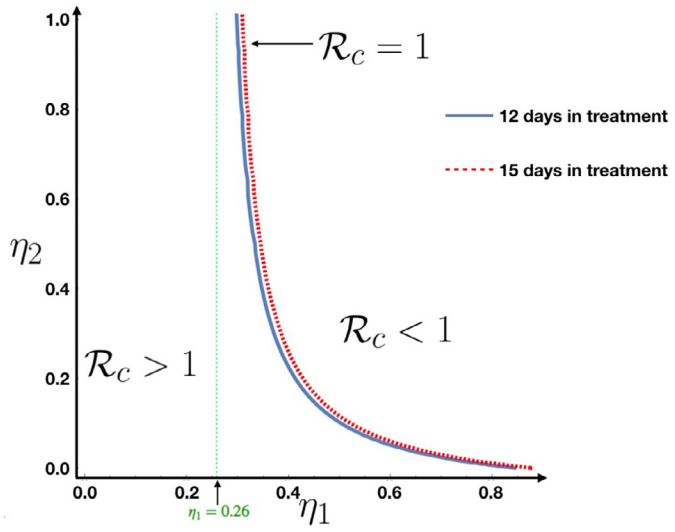

Fig. 6. Contour plot when $\mathcal{R}_c(\eta_1, \eta_2) = 1$. This graph shows two different scenarios, an endemic region when $\mathcal{R}_c > 1$, and a control region when $\mathcal{R}_c < 1$. Dashed lines represent the effect of different length treatments over the control reproduction number.

The relationship between η_1 and $\mathcal{R}_c$ is shown in Fig. 7. We can conclude that as η_1 increases 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 η_1 to cross this threshold is 0.39. If this is reached, the epidemic will be controlled effectively.

4.4. Cost-effectiveness analysis of control strategies

We investigated the impact of treatment control programs (η_1 and η_2 parameters) on the cost of the implementation of treatment strategies and on the cumulative incidence (that is, total number of new cases over a time period). The cumulative cost and incidence were numerically computed over implementation of treatment strategy for 1, 2, 3 and 4 years. The initial conditions and parameters for the dynamical model were thoroughly estimated before performing cost-effectiveness analysis.

For the numerical simulations, the total population in the system (~ 0.15 billion) was assumed to be the total at-risk U.S.

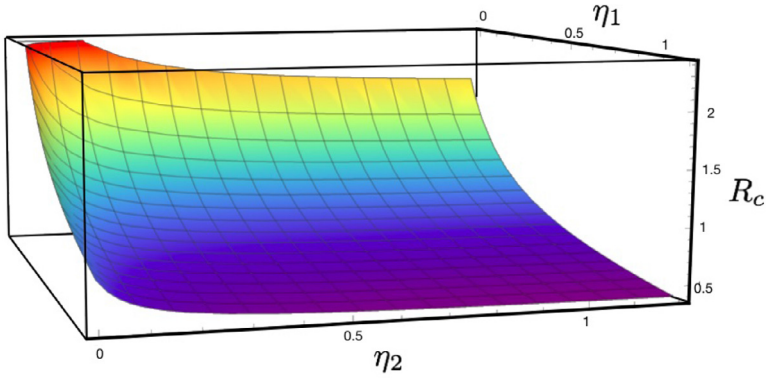

Fig. 5. Surface of $\mathcal{R}_c$ generated as η_1 and η_2 change.

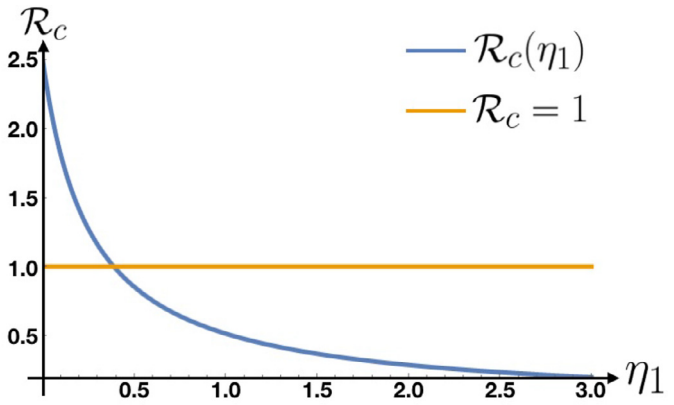

Fig. 7. $\mathcal{R}_c$ function as η_1. Here η_2 is fixed to the actual value. The yellow line presents $\mathcal{R}_c = 1$. The blue line represents how $\mathcal{R}_c$ changes when η_1 increases. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

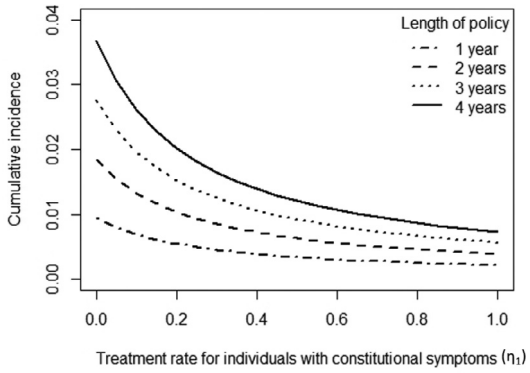

Fig. 8. Incidence proportion as η_1 varies while $\tilde{\eta_2} = 0.25\ day^{-1}$ for different lengths of policy implementation as shown.

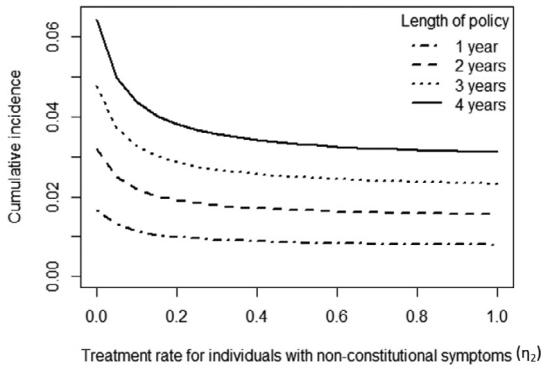

Fig. 9. Incidence proportion as η_2 varies while $\eta_1 = 0$ for different lengths of policy implementation as shown.

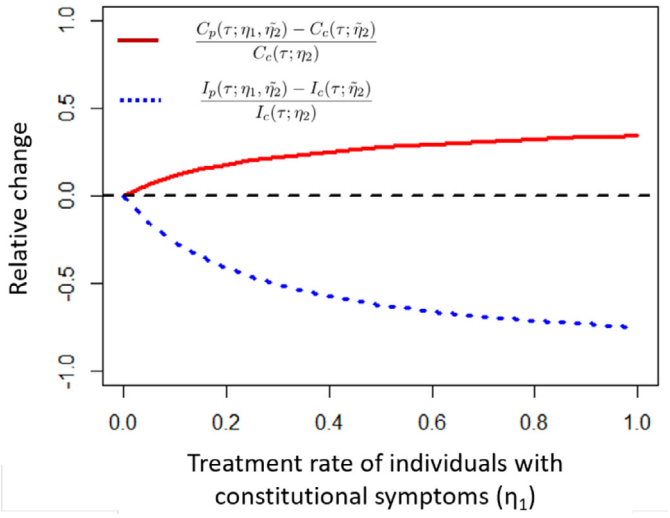

Fig. 10. The solid red curve represents relative increase in cost of proposed treatment strategy (treating constitutional and non-constitutional symptomatic individuals), while the dotted blue curve represents relative change in the cumulative incidence for 1 year of policy implementation ($\tau = 1$ year). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

population (ages 15–49 years). Fraction of individuals with non-constitutional symptoms was estimated to be 12% of the population since it is the reported prevalence [10]. According to [3], 50% of the clinically identified HSV–2 infected individuals reported having similar symptoms before. Therefore, initial conditions for prevalence of HSV–2 infection with constitutional symptoms and latent individuals were assumed to be 25% of the ones with non-constitutional symptoms each. Population size in every other class (i.e. treatment classes) of the model at time $t = 0$ was assumed to be zero. In this section, η_1 and η_2 are varied from 0 to 1 in increments of 0.05 to build various combinations of treatment policies. The parameter values used are shown in Table 3.

The trend in cumulative incidence (represented as a proportion of the at-risk U.S. population) as the rate of conventional treatment (η_2; Fig. 9) and the rate of proposed treatment (η_1; Fig. 8) are varied, for different lengths of policy implementation. It can be seen that incidence levels drop drastically as η_1 is varied for $\tilde{\eta_2} = 0.25$ day^{-1} (Fig. 8) [16].

It can be seen that increasing η_1 decreases cumulative incidence more consistently and smoothly than that seen in case of increasing η_2. Increasing η_2 beyond a certain threshold have negligible impact on the cumulative incidence.

For a fixed rate of conventional treatment, $\tilde{\eta_2} = 0.25$ day^{-1} approximately, we computed the current public health cost and cumulative incidence level for varying rate of proposed treatment (η_1). Fig. 10 shows the increment in cost and increment in effect, as functions of η_1 and normalized by the cost, $C_c(t;\tilde{\eta_2})$, and the cumulative incidence, $I_c(t;\tilde{\eta_2})$, respectively of the conventional treatment strategy. It is seen that as η_1 increases, the proportion of cost increases slower as compared to the increase in effect (in terms of reduced cumulative incidence proportion) for lower values of η_1. The qualitative behaviors observed for all the 4 years of implementation, were similar.

Using the cost and incidence for all treatment strategy by simultaneously varying η_1 and η_2, we generate the cost-effectiveness plane, that is, a plot of incremental cost ($C_p - C_c$, in \$) vs. incremental effect ($I_c - I_p$, in terms of number of new cases prevented) as compared to current policy. Shown in Fig. 11 are the cost-effectiveness planes for 1, 2, 3, and 4 years of policy implementation. The plot only shows the points corresponding to treatment policies yielding reproduction numbers under 1 since the goal is to control the disease. From this plane, we perform cost-effectiveness analysis only on the policies corresponding to points in the first quadrant. The second and third quadrant are not included in the analysis since they correspond to the policies giving increased cumulative incidence as compared to current policy. In quadrant 4, policies corresponding to the points here qualify for adoption (since cost and cumulative incidence both are lower). However, these points (shown in red) correspond to $\eta_2 = 0$, denoting no treatment for HSV–2 infected individuals with severe non-constitutional symptoms which is biologically impractical.

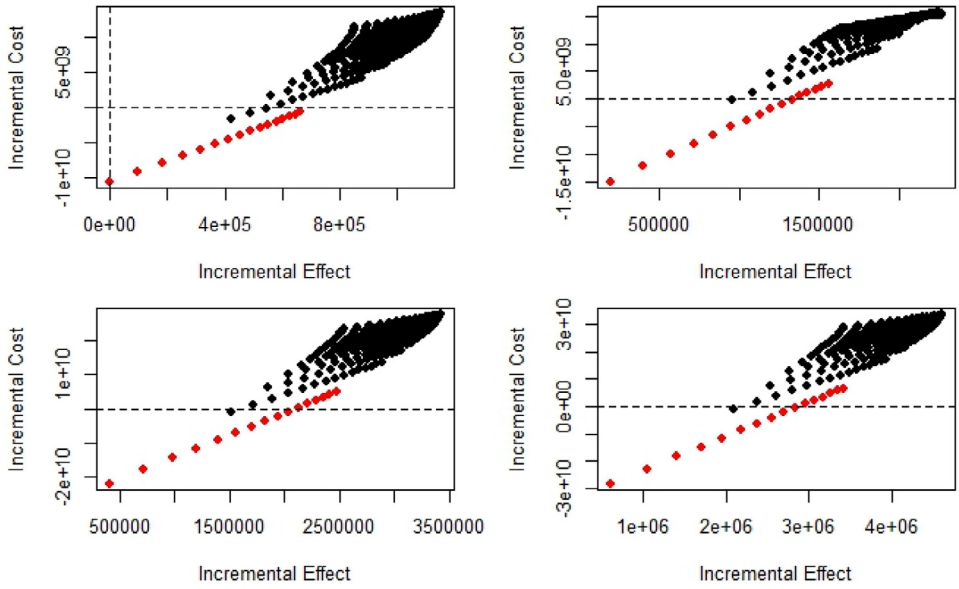

Fig. 11. Cost-effectiveness plane. A plot of incremental cost ($C_p - C_c$, in \$) vs. incremental effect ($I_c - I_p$, in terms of number of new cases prevented) of various combinations of rates of conventional and proposed treatment policies against the current treatment policy corresponding to different years of implementation (τ) is shown. Note that only the combinations that yield reproduction number to be less than 1 are shown since the goal is to control HSV-2 in a cost-effective manner.

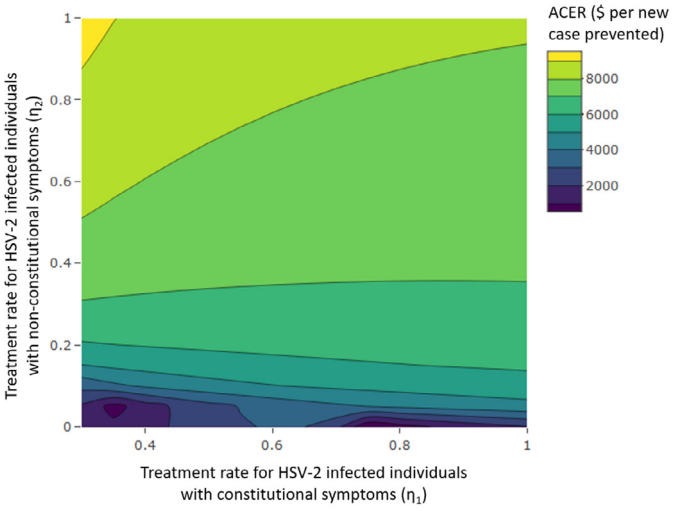

Fig. 12. Effect of proposed treatment rate (η_1) and conventional treatment rate (η_2) on the cost per reduced incidence (ACER) for 3 year duration. Most cost-effective combinations of treatment rates would correspond to the darkest blue regions in the contour plot. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We compute the ACER (as described in the methods section) for policies corresponding to the points in the first quadrant shown in Fig. 11 in terms of USD per reduced cumulative incidence. The policy corresponding to the minimum incremental cost per reduced incidence is said to be most cost-effective. Fig. 12 represents the cost per reduced incidence for different combinations of treatment rates implemented for 3 years; the qualitative properties of the plots were similar for all other durations. From Fig. 12, we see that the minimum cost per reduced prevalence is achieved for lower values of conventional treatment rate (η_2) and a fairly wide range for the proposed treatment rate (η_1). This is indirectly reflecting that if faster is, the constitutional symptomatic infectious individuals treated it is more cost-effective because fewer individuals will be maintained in the non-constitutional symptomatic infection class, and hence smaller η_2 suffices. The minimum value of cost per reduced prevalence obtained (for different durations of policy implementation) was for the following treatment rate combinations with τ defined in terms of years

$\tau = 1$: $\eta_1 = 0.45$; $\eta_2 = 0.05$
$\tau = 2$: $\eta_1 = 0.35$; $\eta_2 = 0.05$
$\tau = 3$: $\eta_1 = 0.35$; $\eta_2 = 0.05$
$\tau = 4$: $\eta_1 = 0.35$; $\eta_2 = 0.05$

As compared to the current treatment strategy, the public health cost of treating HSV–2 to control it with the proposed most cost-effective treatment strategy ($\eta_1 = 0.35$ day^{-1}; $\eta_2 = 0.05$day^{-1}) would increase by approximately 1.63% in 4 years. However, in the same duration, early treatment via the proposed strategy will reduce HSV–2 incidence by 42.76% and the reproduction number will decrease to 0.84 from its current estimate of 2.5.

5. Discussion

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 the 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, η_1 and η_2 form part of the cyclic paths of progression through the disease observed in $\mathcal{R}_c$.

Although the earlier we treat individuals (with mild symptoms), the lower the incidence will be, the cost incurred can be very high. We observed that for a fixed rate of conventional treatment, the amount of the effect of the increasing proposed treatment rate

on the cumulative incidence depends on how long the treatment policy is implemented and assessed. To identify the optimal strategy, we developed a cost function to evaluate the cost effectiveness of the proposed treatment in combination with the conventional treatment. We aim to minimize the cost per reduced incidence such that $\mathcal{R}_c < 1$ (that is, the disease dies out eventually), we found the optimal combination of treatment rates based on the length of the policy implementation.

The most cost-effective policy among all various combinations against the current treatment turned out to be a positive treatment rate for individuals with constitutional symptoms and a close to zero rates of non-constitutional symptomatic individuals. This holds because for a high treatment early on, the number of individuals in severe symptomatic individuals will be less and hence favored. But practically, treating individuals with mild symptoms might not be economically feasible given it might be any other infection than HSV–2. Also, this optimal combination gave a reproduction number greater than 1 means the disease will persist.

Therefore, we assessed only those combinations which will ensure the disease dies out. Our results have shown that, for a cost-effective policy, proposed treatment rate must be at least 0.35 day^{-1}. For treatment implementation duration of 2 years and above the outcomes were consistent; the most cost-effective policy is a moderate rate, that is the number of people per day, for the proposed treatment, and a lower rate, that is the number of people per day, for conventional treatment. This means, if the treatment is implemented for long enough and proposed treatment rate is a little higher, a lower conventional treatment rate suffices to remove disease in a cost-effective way. Future work would include studying the impact of this proposed strategy in the U.S. population but with HSV–1 instead of HSV–2. Through analyzing different strategies we can determine 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. Also, in future, the economic costs (quality of life) can also be incorporated in the cost analysis.

Declaration of Competing Interest

The authors have no interests to declare.

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Appendix A. Simple Models

Here we build simplified models of the proposed model in order to fully understand the impact of the non-conventional treatment strategy considered in this study. In Model 1, a simple transmission dynamic model of HSV–2, defined as Susceptible–Infectious–Latent–Infectious (*SILI*) is considered, where susceptible (S) individuals can become infected (I), and then transition to a latent (L) state where they carry the virus but are not infectious before they experience recurrence of symptoms (or return to the I-state). Next, we consider the scenario where HSV–2 infected receive treatment. In Model 2, a simple HSV–2 transmission dynamic model with treatment is proposed, defined as Susceptible–Infectious–Treated–Latent–Infectious (*SITLI*) where infectious individuals can receive treatment (T), to expedite their transition to the L-state. However, in Models 1 and 2, we take a simplistic approach to modeling the infected class. That is, we consider only individuals who show severe (or constitutional) symptoms. To track individuals with non-constitutional symptoms we improve on Models 1 and 2 next. In Model 3, an HSV–2 transmission dynamic model with heterogeneous infection stages is studied, defined as Susceptible–first Infectious period–second Infectious period–Latent–first Infectious period ($SI_1I_2LI_1$), where now the individual transitions through two infectious periods, with non-constitutional (I_1) and constitutional symptoms (I_2), and there is no treatment. In Model 4, we expand Model 3 by including a treatment (T) class, the model is defined as Susceptible–first Infectious period–second Infectious period–Treated–Latent–first Infectious period ($SI_1I_2TLI_1$). In Model 5, we consider Model 4 with one infectious period and a new class X which captures false positive individuals, false positive means non-infected individuals with HSV-2 who present mild symptoms and are under treatment. Model 5 is defined as Susceptible–False Positive–Infectious period–Treated–Latent–Infectious period (*SXITLI*).

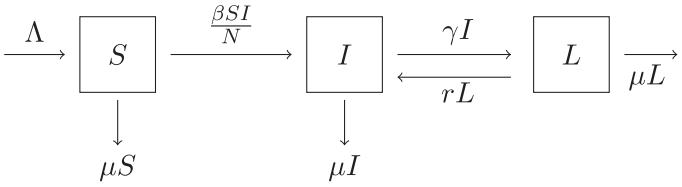

Fig. 13. *SILI* Model.

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 reproduction number. We compare and show the behavior of $\mathcal{R}_0$ and R_c through an inductive way.

*A1. Model 1 (*SILI*; simple transmission dynamic model)*

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

The differential equations that represent this model are the following:

$$\frac{dS}{dt} = \Lambda - \frac{\beta SI}{N} - \mu S \tag{A1.1}$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - (\mu + \gamma)I + rL \tag{A1.2}$$

$$\frac{dL}{dt} = \gamma I - (r + \mu)L \tag{A1.3}$$

Calculation of $\mathcal{R}_{1,0}$: We will use the Next Generation Matrix (NGM) method to derive the Basic Reproduction Number [30].

First we calculate the Disease Free Equilibrium (DFE). This point is obtained when the equations A.1.1, A.1.2 and A.1.3 are equal to zero and solving for S, I and L. In this model the DFE is $\left(\frac{\Lambda}{\mu}, 0, 0\right)$ where $N = \frac{\Lambda}{\mu}$.

Now, we define an infected class $\hat{X}$ which represents those individuals who can infect others. They are the only individuals who are infected. In this model the infected class is given by: $\hat{X} = \begin{bmatrix} I \\ L \end{bmatrix}$.

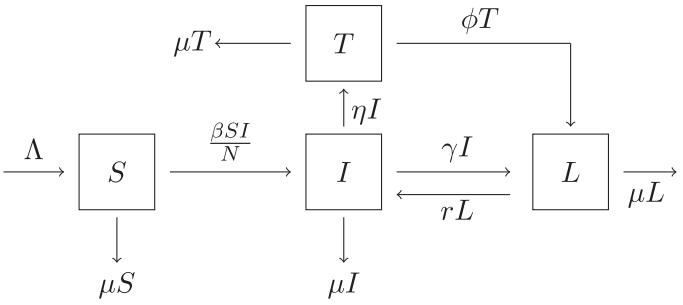

Fig. 14. *SITLI* Model.

Consider the change in $\hat{X}$ with respect to time, $\frac{d\hat{X}}{dt}$, represented by equations A.1.2 and A.1.3. Then $\frac{d\hat{X}}{dt}$ can be expressed as a difference between $\mathcal{F}$, all terms relating to new infections, and $\mathcal{V}$, transfers of infections from one compartment to another. Thus, $\mathcal{F}$ and $\mathcal{V}$ are as follows:

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

Calculated the Jacobian matrices for $\mathcal{F}$ and $\mathcal{V}$ (F and V respectively) with respect to I and L evaluated at the DFE are the following:

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

The spectral radius $\rho(FV^{-1})$ of FV^{-1} is the largest eigenvalue and it represents the Basic Reproduction Number $\mathcal{R}_{1,0}$. For this model we have:

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

This expression can be interpreted as the product of the transmission rate, β, 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. Other interpretations for the Basic Reproduction Number can be to consider a geometric series because this represents the n cycles that an infected person can have 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 μ^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 $\mathcal{R}_{1,0}$.

*A2. Model 2 (*SITLI*; transmission dynamic model with treatment)*

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

The differential equations that represent this model are the following:

$$\frac{dS}{dt} = \Lambda - \frac{\beta SI}{N} - \mu S \tag{A2.1}$$
$$\frac{dI}{dt} = \frac{\beta SI}{N} + rL - (\eta + \gamma + \mu)I \tag{A2.2}$$
$$\frac{dT}{dt} = \eta I - (\mu + \phi)T \tag{A2.3}$$
$$\frac{dL}{dt} = \phi T + \gamma I - (\mu + r)L \tag{A2.4}$$

Calculation of $\mathcal{R}_{2,0}$: We will use the Next Generation Matrix (NGM) method to derive the Basic Reproduction Number [30].

First we calculate the Disease Free Equilibrium (DFE). This point is obtained when the equations A.2.1, A.2.2, A.1.3 and A.2.4 are equal to zero and solving for S, I, T and L. In this model the DFE $= (\frac{\Lambda}{\mu}, 0, 0, 0)$, where $N = \frac{\Lambda}{\mu}$.

In this model the infected class is given by: $\hat{X} = \begin{bmatrix} I \\ T \\ L \end{bmatrix}$.

Now, $\frac{d\hat{X}}{dt}$ can be expressed by the difference between $\mathcal{F}$ and $\mathcal{V}$.In this case $\mathcal{F}$ and $\mathcal{V}$ are as follows:

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

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

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

Thus, the Next Generation Matrix is:

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

The spectral radius $\rho(FV^{-1})$ of FV^{-1} is the largest eigenvalue and it represents the Control Reproduction Number $\mathcal{R}_{2,c}$ because of the consideration of the treatment compartment (T). For this model it is defined 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,

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

Considering all possible paths for a individual in the disease, we are able to express the 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 Model 2 shown in Fig. 14.

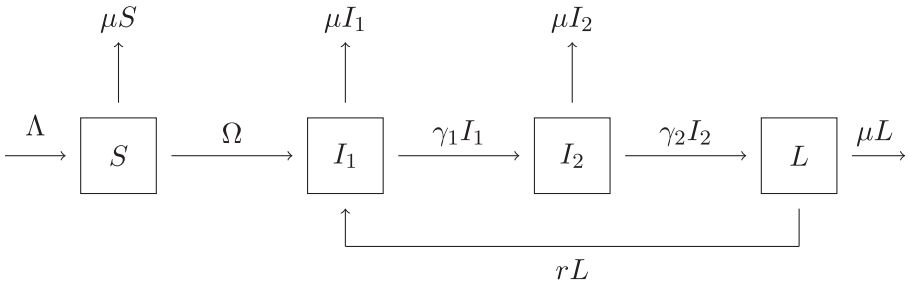

Fig. 15. $SI_1I_2LI_1$ Model.

A3. Model 3($SI_1I_2LI_1$; transmission dynamic model with heterogeneous infection stages)

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

Note: $\Omega = \frac{\beta_1 SI_1 + \beta_2 SI_2}{N}$.

$$\frac{dS}{dt} = \Lambda + \mu S - (\beta_1 I_1 + \beta_2 I_2)\frac{S}{N} \tag{A3.1}$$

$$\frac{dI_1}{dt} = (\beta_1 I_1 + \beta_2 I_2)\frac{S}{N} + rL - (\gamma_1 + \mu)I_1 \tag{A3.2}$$

$$\frac{dI_2}{dt} = \gamma_1 I_1 - (\mu + \gamma_2)I_2 \tag{A3.3}$$

$$\frac{dL}{dt} = \gamma_2 I_2 - (\mu + r)L \tag{A3.4}$$

Calculation of $\mathcal{R}_{3,0}$: We will use the Next Generation Matrix (NGM) method to derive the Basic Reproduction Number [30].

First we calculate the Disease Free Equilibrium (DFE). This point is obtained when the equations A.3.1, A.3.2, A.3.3 and A.3.4 are equal to zero and solving for S, I_1, I_2 and L. In this model the DFE $= (\frac{\Lambda}{\mu}, 0, 0, 0)$, where $N = \frac{\Lambda}{\mu}$.

For this model the infected class is given by: $\hat{X} = \begin{bmatrix} I_1 \\ I_2 \\ L \end{bmatrix}$.

To express $\frac{d\hat{X}}{dt}$ as a difference $\mathcal{F}$ and $\mathcal{V}$ are as follows:

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

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

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

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 largest eigenvalue is the Basic Reproduction Number $\mathcal{R}_{3,0}$. It is as follows:

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

With all possible paths for a individual in the disease we can express the geometric series for $\mathcal{R}_{3,0}$:

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

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, (β_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 (β_2) and the time spent in I_2, $(\frac{1}{\mu+\gamma_2})$.

Now, we have to proof that the ratio is less than 1,

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

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 μ^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.

A4. Model 4 ($SI_1I_2TLI_1$; transmission dynamic model with current conventional treatment)

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

$$\frac{dS}{dt} = \Lambda - \left(\beta_1 I_1 + \beta_2 I_2\right)\frac{S}{N} - \mu S \tag{A4.1}$$

$$\frac{dI_1}{dt} = \left(\beta_1 I_1 + \beta_2 I_2\right)\frac{S}{N} - (\mu + \gamma_1 + \gamma_3)I_1 + rL \tag{A4.2}$$

$$\frac{dI_2}{dt} = \gamma_1 I_1 - (\mu + \gamma_2 + \eta)I_2 \tag{A4.3}$$

$$\frac{dT}{dt} = \eta_2 I_2 - (\mu + \phi)T \tag{A4.4}$$

$$\frac{dL}{dt} = \phi T + \gamma_2 I_2 + \gamma_3 I_1 - (\mu + r)L \tag{A4.5}$$

Calculation of $\mathcal{R}_{4,0}$: We will use the Next Generation Matrix (NGM) method to derive the Basic Reproduction Number [30].

First we calculate the Disease Free Equilibrium (DFE). This point is obtained when the equations A.4.1, A.4.2, A.4.3, A.4.4 and A.4.5

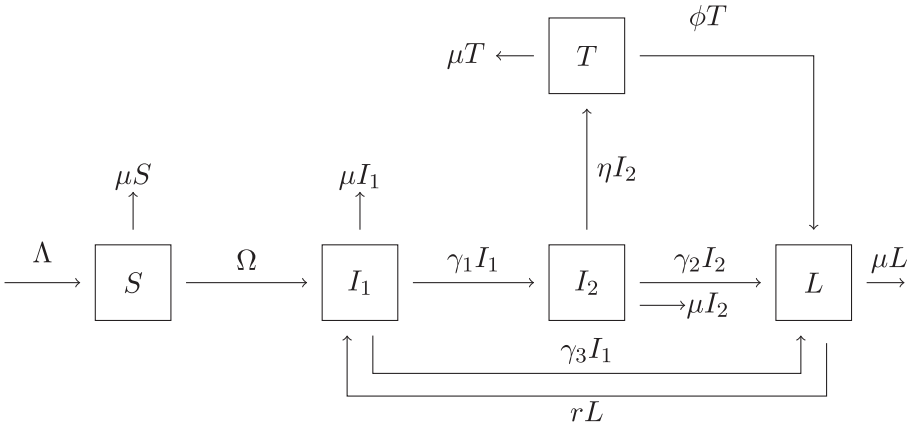

Fig. 16. $SI_1I_2TLI_1$ Model.

are equal to zero and solving for S, I_1, I_2, T and L. In this model the DFE $= (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$, where $N = \frac{\Lambda}{\mu}$.

In this model the infected class is given by: $\hat{X} = \begin{bmatrix} I_1 \\ I_2 \\ T \\ L \end{bmatrix}$.

$\frac{d\hat{X}}{dt}$ can be expressed by the difference between $\mathcal{F}$ and $\mathcal{V}$, these are as follows:

$$\mathcal{F} = \begin{bmatrix} \left(\beta_1 I_1 + \beta_2 I_2\right)\frac{S}{N} \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{and}$$

$$\mathcal{V} = \begin{bmatrix} (\mu+\gamma_1+\gamma_3)I_1 - rL \\ -\gamma_1 I_1 + (\mu+\gamma_2+\eta)I_2 \\ -\eta_2 I_2 + (\mu+\phi)T \\ -\phi T - \gamma_2 I_1 - \gamma_3 I_1 + (\mu+r)L \end{bmatrix}.$$

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

$$F = \begin{bmatrix} \beta_1 & \beta_2 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} \quad \text{and}$$

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

where

$$\begin{aligned} \det(V) &= (\gamma_1+\gamma_3+\mu)(\gamma_2+\eta+\mu)(\mu+\phi)(r+\mu) \\ &\quad + -r\gamma_1[\eta\phi + \gamma_2(\mu+\phi)] - r\gamma_3(\gamma_2+\eta+\mu)(\mu+\phi), \\ a_1 &= \beta_1(r+\mu)(\gamma_2+\eta+\mu)(\mu+\phi) - \beta_2(r+\mu)(\gamma_1\mu - \gamma_1\phi), \\ a_2 &= \beta_2(r\gamma_1 + r\mu + \gamma_1\mu + \gamma_3\mu + \mu^2)(\mu+\phi) \\ &\quad + \beta_1(r\gamma_2\mu + r\gamma_2\phi + r\eta\phi), \\ a_3 &= r\beta_2\gamma_1\phi + r\beta_1(\gamma_2+\eta+\mu)\phi, \qquad \text{and} \\ a_4 &= r\beta_1(\gamma_2+\eta+\mu)(\mu+\phi) + \beta_2(r\gamma_1\mu + r\gamma_1\phi). \end{aligned}$$

Then the Next Generation Matrix is:

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

With the spectral radius $\rho(FV^{-1})$ of the NGM we obtain the control reproduction number $\mathcal{R}_{4,c}$:

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

When the treatment parameters are zero, $\eta = \phi = 0$, we get the Basic Reproduction Number $\mathcal{R}_{4,0}$:

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

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.

Hence, the Basic Reproduction Number in this model is similar with Model 3 shown in Fig. 15, but the difference is that we do not have the possibility to progress to latent period from I_1.

*A5. Model 5 (*SXITLI*; transmission dynamic model with* X *class and treatment)*

For this model we only consider susceptible, false positive, infectious, treated and latent classes, the compartmental model is shown in Fig. 17.

For this model the differential equations are the following:

$$\frac{dS}{dt} = \Lambda + \phi X - \frac{\beta SI}{N} - \kappa\eta S - \mu S \tag{A5.1}$$

$$\frac{dX}{dt} = \kappa\eta S - (\phi+\mu)X \tag{A5.2}$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} + rL - (\eta+\gamma+\mu)I \tag{A5.3}$$

$$\frac{dT}{dt} = \eta I - (\phi+\mu)T \tag{A5.4}$$

$$\frac{dL}{dt} = \gamma I + \phi T - (r+\mu)L \tag{A5.5}$$

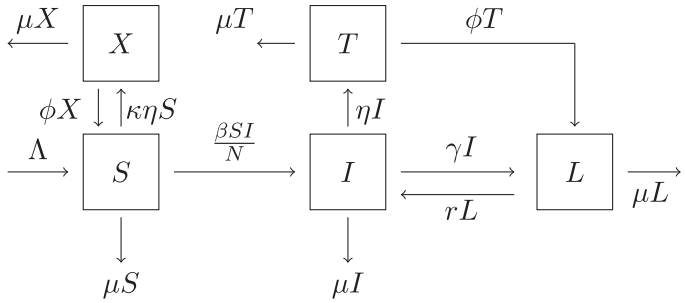

Fig. 17. *SXITLI* Model.

Calculation of $\mathcal{R}_{5,0}$: We will use the Next Generation Matrix (NGM) method to derive the Basic Reproduction Number [30].

First we calculate the Disease Free Equilibrium (DFE). This point is obtained when the equations A.5.1, A.5.2, A.5.3, A.5.4 and A.5.5 are equal to zero and solving for S, X, I, T and L. In this model the DFE $= (\frac{\Lambda(\mu+\phi)}{\mu(\kappa\eta+\mu+\phi)}, \frac{\Lambda\kappa\eta}{\mu(\kappa\eta+\mu+\phi)}, 0, 0, 0)$, where $N = \frac{\Lambda}{\mu}$.

In this model the infected class is given by: $\hat{X} = \begin{bmatrix} I \\ T \\ L \end{bmatrix}$.

In this case $\frac{d\hat{X}}{dt}$ can be expressed by the difference between $\mathcal{F}$ and $\mathcal{V}$, these are as follows:

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

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

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

Then the Next Generation Matrix FV^{-1} is:

$$FV^{-1} = \frac{1}{(\kappa\eta+\phi+\mu)(-z_1z_2z_5+z_1\gamma r+r\eta\phi)} \begin{bmatrix} z_1z_5\beta(\phi+\mu) & r\beta\phi(\phi+\mu) & z_1r\beta(\phi+\mu) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Where $z_1 = (\phi+\mu)$, $z_2 = (\gamma+\eta+\mu)$ and $z_5 = (\mu+r)$. The largest spectral radius $\rho(FV^{-1})$ for this NGM is:

$$\mathcal{R}_{5,c} = \frac{\frac{\beta}{\mu+\eta+\gamma} \cdot \frac{\mu+\phi}{\eta\kappa+\mu+\phi}}{1 - \left(\frac{\gamma}{\eta+\mu+\gamma} \cdot \frac{r}{\mu+r} + \frac{\phi}{\mu+\phi} \cdot \frac{\eta}{\eta+\mu+\gamma} \cdot \frac{r}{\mu+r}\right)}.$$

To obtain the Basic Reproduction Number we set the treatment parameters equals to zero, $\eta = \phi = 0$. Then $\mathcal{R}_{5,0}$ is:

$$\mathcal{R}_{5,0} = \sum_{n=0}^{\infty} \left(\frac{\beta}{\mu+\gamma}\right)\left(\frac{\gamma}{\mu+\gamma} \cdot \frac{r}{\mu+r}\right)^n = \frac{\frac{\beta}{\mu+\gamma}}{1 - \frac{\gamma}{\mu+\gamma} \cdot \frac{r}{\mu+r}} = \mathcal{R}_{2,0}.$$

The interpretation of $\mathcal{R}_{5,c}$ is similar to Model 3 and Model 4, we need to consider all different paths into the cycle of the disease. For this model, $\frac{\beta}{\mu+\eta+\gamma}$ represents the transmission rate multiplied by the average time spent in I. If $\frac{\mu+\phi}{\eta\kappa+\mu+\phi} < 1$ then $\mathcal{R}_{5,c}$ is a proportion of $\mathcal{R}_{2,c}$ due to the X compartment. With treatment, we have two different paths $(I-T-L-I)$ and $(I-L-I)$. Without treatment, the unique path is $(I-L-I)$. Hence, Model 5 is important because we will analyze the endemic equilibrium for this, due to the complexity of our proposed model and the relationship between them. When we consider all possible paths that one individual can do in the model, the Basic Reproduction Number matches with the Basic Reproduction Number of the Model 2. Then in A.2 we proof that the geometric series converges.

Appendix B. 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,

$$\mathcal{F} = \begin{bmatrix} \frac{(\beta_1 I_1 + \beta_2 I_2)S}{S+I_1+I_2+L} \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad \text{and}$$

$$\mathcal{V} = \begin{bmatrix} -rL + z_2 + I_1 \\ -\gamma_1 I_1 + z_3 I_2 \\ -\eta_1 I_1 + z_1 T_1 \\ \eta_2 I_2 + z_4 T_2 \\ -\gamma_3 I_1 - \gamma_2 I_2 - \phi_2 T_2 - \phi_1 T_1 + z_5 L \end{bmatrix}.$$

For simplicity, we substitute z_i, where $i = 1, \ldots, 5$, 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 $z_5 = \mu + r$.

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

$$F = \begin{bmatrix} \beta_1 & \beta_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \quad \text{and}$$

$$V = \begin{bmatrix} z_2 & 0 & 0 & 0 & -r \\ -\gamma_1 & z_3 & 0 & 0 & 0 \\ -\eta_1 & 0 & z_1 & 0 & 0 \\ 0 & -\eta_2 & 0 & z_4 & 0 \\ -\gamma_3 & -\gamma_2 & -\phi_1 & -\phi_2 & z_5 \end{bmatrix}.$$

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 $\det(V) = z_1z_2z_3z_4z_5 - rz_3z_4\eta_1\phi_1 - rz_1(z_4\gamma_1\gamma_2 + z_2z_3\gamma_3 + \gamma_1\eta_2\phi_2)$, and

$b_1 = z_1z_3z_4z_5\beta_1 + z_1z_4z_5\beta_2\gamma_1$,
$b_2 = \beta_2(z_1z_2z_4z_5 - rz_1z_4\gamma_3 - rz_4\eta_1\phi_1) + \beta_1(rz_1z_4\gamma_2 + rz_1\eta_2\phi_2)$,
$b_3 = rz_3z_4\beta_1\phi_1 + rz_4\beta_2\gamma_1\phi_1$,
$b_4 = rz_1z_3\beta_2\phi_2 + rz_1\beta_2\gamma_1\phi 2$, and
$b_5 = rz_1z_3z_4\beta_1 + rz_1z_4\beta_2\gamma_1$.

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. η_1, η_2, ϕ_1, and ϕ_2, we obtain $\mathcal{R}_0$:

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

Appendix C. 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,

$$c_{11} = -\kappa\eta_1 - \frac{N_1(\beta_1 I_1+\beta_2 I_2) - (\beta_1 S I_1+\beta_2 S I_2)}{N_1^2} - \mu,$$
$$c_{13} = -\frac{N_1(\beta_1 S) - (\beta_1 S I_1+\beta_2 S I_2)}{N_1^2},$$
$$c_{15} = -\frac{N_1(\beta_2 S) - (\beta_1 S I_1+\beta_2 S I_2)}{N_1^2},$$
$$c_{17} = \frac{S(I_1\beta_1+I_2\beta_2)}{N_1^2},$$
$$c_{31} = \frac{N_1(\beta_1 I_1+\beta_2 I_2) - (\beta_1 S I_1+\beta_2 S I_2)}{N_1^2},$$
$$c_{33} = \frac{N_1(\beta_1 S) - (\beta_1 S I_1+\beta_2 S I_2)}{N_1^2} - (\eta_1+\gamma_3+\gamma_1+\mu),$$
$$c_{35} = \frac{N_1(\beta_2 S) - (\beta_1 S I_1+\beta_2 S I_2)}{N_1^2}.$$

Appendix D. Sensitivity Analysis on stages with respect to η_1 and η_2

The following fourteen equations were calculated in order to use them for forward sensitivity equations with respect to parameters η_1 and η_2. We made a numerical solution to obtain the sensitivity of I_1 and I_2 with respect of both parameters.

$$\frac{d}{dt}\left[\frac{\partial S}{\partial\eta_1}\right] = \phi_1\frac{\partial X}{\partial\eta_1} - \eta_1\kappa\frac{\partial S}{\partial\eta_1} - \kappa S - \frac{(\beta_1 I_1+\beta_2 I_2)(N_1\frac{\partial S}{\partial\eta_1} - S\frac{\partial N_1}{\partial\eta_1}) + (\beta_1\frac{\partial I_1}{\partial\eta_1}+\beta_2\frac{\partial I_2}{\partial\eta_1})SN_1}{N_1^2} - \mu\frac{\partial S}{\partial\eta_1}$$

$$\frac{d}{dt}\left[\frac{\partial X}{\partial\eta_1}\right] = \eta_1\kappa\frac{\partial S}{\partial\eta_1} + \kappa S - (\phi_1+\mu)\frac{\partial X}{\partial\eta_1}$$

$$\frac{d}{dt}\left[\frac{\partial I_1}{\partial\eta_1}\right] = \frac{(\beta_1 I_1+\beta_2 I_2)(N_1\frac{\partial S}{\partial\eta_1} - S\frac{\partial N_1}{\partial\eta_1}) + (\beta_1\frac{\partial I_1}{\partial\eta_1}+\beta_2\frac{\partial I_2}{\partial\eta_1})SN_1}{N_1^2} + r\frac{\partial L}{\partial\eta_1} - \eta_1\frac{\partial I_1}{\partial\eta_1} - I_1 - (\gamma_1+\gamma_3+\mu)\frac{\partial I_1}{\partial\eta_1}$$

$$\frac{d}{dt}\left[\frac{\partial T_1}{\partial\eta_1}\right] = \eta_1\frac{\partial I_1}{\partial\eta_1} + I_1 - (\phi_1+\mu)\frac{\partial T_1}{\partial\eta_1}$$

$$\frac{d}{dt}\left[\frac{\partial I_2}{\partial\eta_1}\right] = \gamma_1\frac{\partial I_1}{\partial\eta_1} - (\eta_2+\gamma_2+\mu)\frac{\partial I_2}{\partial\eta_1}$$

$$\frac{d}{dt}\left[\frac{\partial T_2}{\partial\eta_1}\right] = \eta_2\frac{\partial I_2}{\partial\eta_1} - (\phi_2+\mu)\frac{\partial T_2}{\partial\eta_1}$$

$$\frac{d}{dt}\left[\frac{\partial L}{\partial\eta_1}\right] = \gamma_3\frac{\partial I_1}{\partial\eta_1} + \gamma_2\frac{\partial I_1}{\partial\eta_1} + \phi_2\frac{\partial T_2}{\partial\eta_1} + \phi_1\frac{\partial T_1}{\partial\eta_1} - (r+\mu)\frac{\partial L}{\partial\eta_1}$$

$$\frac{d}{dt}\left[\frac{\partial S}{\partial\eta_2}\right] = \phi_1\frac{\partial X}{\partial\eta_2} - \kappa\eta_1\frac{\partial S}{\partial\eta_2} - \frac{(\beta_1 I_1+\beta_2 I_2)(N_1\frac{\partial S}{\partial\eta_2} - S\frac{\partial N_1}{\partial\eta_2}) + (\beta_1\frac{\partial I_1}{\partial\eta_2}+\beta_2\frac{\partial I_2}{\partial\eta_2})SN_1}{N_1^2} - \mu\frac{\partial S}{\partial\eta_2}$$

$$\frac{d}{dt}\left[\frac{\partial X}{\partial\eta_2}\right] = \kappa\eta_1\frac{\partial S}{\partial\eta_2} - (\phi_1+\mu)\frac{\partial X}{\partial\eta_2}$$

$$\frac{d}{dt}\left[\frac{\partial I_1}{\partial\eta_2}\right] = \frac{(\beta_1 I_1+\beta_2 I_2)(N_1\frac{\partial S}{\partial\eta_2} - S\frac{\partial N_1}{\partial\eta_2}) + (\beta_1\frac{\partial I_1}{\partial\eta_2}+\beta_2\frac{\partial I_2}{\partial\eta_2})SN_1}{N_1^2} + r\frac{\partial L}{\partial\eta_2} - (\eta_1+\gamma_1+\gamma_3+\mu)\frac{\partial I_1}{\partial\eta_2}$$

$$\frac{d}{dt}\left[\frac{\partial T_1}{\partial\eta_2}\right] = \eta_1\frac{\partial I_1}{\partial\eta_2} - (\phi_1+\mu)\frac{\partial T_1}{\partial\eta_2}$$

$$\frac{d}{dt}\left[\frac{\partial I_2}{\partial\eta_2}\right] = \gamma_1\frac{\partial I_1}{\partial\eta_2} - \eta_2\frac{\partial I_2}{\partial\eta_2} - I_2 - (\gamma_2+\mu)\frac{\partial I_2}{\partial\eta_2}$$

$$\frac{d}{dt}\left[\frac{\partial T_2}{\partial\eta_2}\right] = \eta_2\frac{\partial I_2}{\partial\eta_2} + I_2 - (\phi_2+\mu)\frac{\partial T_2}{\partial\eta_2}$$

$$\frac{d}{dt}\left[\frac{\partial L}{\partial\eta_2}\right] = \gamma_3\frac{\partial I_1}{\partial\eta_2} + \gamma_2\frac{\partial I_1}{\partial\eta_2} + \phi_2\frac{\partial T_2}{\partial\eta_2} + \phi_1\frac{\partial T_1}{\partial\eta_2} - (r+\mu)\frac{\partial L}{\partial\eta_2}$$

D1. Local sensitivity analysis of $\mathcal{R}_c$

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

$$\frac{\partial\alpha_1}{\partial\eta_2} = -\frac{\gamma_1}{z_2}\cdot\frac{r}{z_5}\cdot\frac{\gamma_2}{z_3^2} \qquad \alpha_1 := \frac{\gamma_1}{z_2}\cdot\frac{\gamma_2}{z_3}\cdot\frac{r}{z_5},$$
$$\frac{\partial\alpha_2}{\partial\eta_2} = 0 \qquad \alpha_2 := \frac{\eta_1}{z_2}\cdot\frac{\phi_1}{z_1}\cdot\frac{r}{z_5},$$
$$\frac{\partial\alpha_3}{\partial\eta_2} = \frac{\gamma_1}{z_2}\cdot\frac{\phi_2}{z_4}\cdot\left(\frac{z_3-\eta_2}{z_3^2}\right) \qquad \alpha_3 := \frac{\gamma_1}{z_2}\cdot\frac{\eta_2}{z_3}\cdot\frac{\phi_2}{z_4}\cdot\frac{r}{z_5}, \qquad \text{and}$$
$$\frac{\partial\alpha_4}{\partial\eta_2} = 0 \qquad \alpha_4 := \frac{\gamma_3}{z_2}\cdot\frac{r}{z_5}.$$

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 η_2 varies, we will reference the derivative of $\mathcal{R}_c$ with respect to η_2, since $\mathcal{R}_c$ depends on many parameters we must calculate the partial derivative with respect to η_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 η_2 approaches infinity, we get:

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

Since

$$\lim_{\eta_2\to\infty}\left(-\frac{\gamma_1\beta_2}{z_2z_3^2}\right)=0,\ \lim_{\eta_2\to\infty}\left(\frac{\partial\alpha_1}{\partial\eta_2}+\frac{\partial\alpha_3}{\partial\eta_2}\right)=0,$$

and

$$\lim_{\eta_2\to\infty}(1-(\alpha_1+\alpha_2+\alpha_3+\alpha_4)=\left(1-\left(\alpha_1+\alpha_4+\frac{\gamma_1}{z_2}\cdot\frac{\phi_2}{z_4}\cdot\frac{r}{z_5}\right)\right).$$

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

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

□

D2. Local sensitivity analysis of $\mathcal{R}_c$ considering η_1

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 reproduction number. Due to z_2 being the only term including η_1, we rewrite $\mathcal{R}_c$ as follows:

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

Calculating the partial derivative of $\mathcal{R}_c$ with respect to η_1 we have:

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

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 reproduction 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 $\mathcal{R}_c\to 0$ when $\eta_1\to\infty$,

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

Notice that the numerator is a fixed value and the denominator tends to infinity when η_1 tends to infinity, then $z_2>>\eta_1\cdot\frac{\phi_1\cdot r}{z_1\ z_5}$.

Finally, $\frac{\partial\mathcal{R}_c}{\partial\eta_1}<0$ for whichever parameter values. therefore, $\mathcal{R}_c$ is always decreasing when η_1 is increasing. This suggest that it is necessary to implement early treatment to reduce incidence rates of HSV–2. □

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