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A mathematical model of syphilis transmission in an MSM population

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ABSTRACT

Syphilis is caused by the bacterium *Treponema pallidum* subspecies *pallidum*, and is a sexually transmitted disease with multiple stages. A model of transmission of syphilis in an MSM population (there has recently been a resurgence of syphilis in such populations) that includes infection stages and treatment is formulated as a system of ordinary differential equations. The control reproduction number is calculated, and it is proved that if this threshold parameter is below one, syphilis dies out; otherwise, if it is greater than one, it is shown that there exists a unique endemic equilibrium and that for certain special cases, this equilibrium is globally asymptotically stable. Using data from the literature on MSM populations, numerical methods are used to determine the variation and robustness of the control reproduction number with respect to the model parameters, and to determine adequate treatment rates for syphilis eradication. By assuming a closed population and no return to susceptibility, an epidemic model is obtained. Final outbreak sizes are numerically determined for various parameter values, and its variation and robustness to parameter value changes is also investigated. Results quantify the importance of early treatment for syphilis control.

1. Introduction

Various sexually transmitted diseases are caused by bacteria; for example, *Neisseria gonorrhoeae* causes gonorrhea [26], and *Treponema pallidum* subspecies *pallidum* causes syphilis [21]. *T. pallidum* is classified as a spirochetes (family *Spirochaetaceae*), and measures 6–20 μm in length and 0.18 μm in diameter [25]. It cannot be successfully continually cultured *in vitro* outside of the mammalian host; thus for experimental purposes, *T. pallidum* is usually first obtained from inoculated rabbits. This slows the research process and has been suggested as the greatest setback in terms of syphilis research [21].

In humans, an untreated syphilis infection progresses through multiple stages. After infection, the exposed (infected but not yet infectious) stage lasts an average 28 days [13]. The primary stage is characterized by a single chancre at the source of inoculation (*i.e.*, where *T. pallidum* penetrated dermal microabraisons or mucous membranes) appearing after the exposed period. This painless chancre eventually heals, and the individual progresses to the secondary stage [21,34] after an average of 46 days [13]. The secondary stage is characterized by multiple symptoms, most of which are nonspecific (*i.e.*, sore throat, muscle aches, etc.). Most secondary infections of syphilis also result in copper colored skin lesions that tend to be universally distributed. This rash heals after a few weeks, and the individual progresses to latency [21,34] after an average of about 15 weeks [13]. The latency period of syphilis is divided into two stages: the early latent stage, and the late latent stage. Early latency represents the first year of latency; late latency represents the remainder, until progression to the tertiary stage in 1–46 years [21,34]. The tertiary stage can have multiple presentations, ranging from cardiovascular syphilis to neurosyphilis. Progression to the tertiary stage is poorly understood; only about 30% of untreated cases progress from latency to the tertiary stage [21]. Disease caused mortality also occurs at this stage [34].

Fortunately, treatment for syphilis does exist. For treatment success, usually in the primary, secondary, and early latent stage, a single dose of Benzanthine penicillin G, 2.4 mU is administered; whereas for patients in the late latent stage, treatment is more strenuous, namely three doses of 2.4 mU at 1 week intervals of Benzanthine penicillin G are administered [34,43]. While treatment in the tertiary stage is available, not only is it much more intensive than in previous stages, it often is not as successful [34]. Moreover, the damage (*i.e.*, neurological for neurosyphilis) caused by tertiary syphilis cannot be undone. For appropriate treatment, accurate diagnosis of syphilis and the presenting stage is needed; Smith et al. [36] identified appropriate proteins as diagnostic candidates. It is also important to mention that a human vaccine for syphilis

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does not currently exist on the market, but Cameron and Lukehart [5] outline the needs and potential prospects for a vaccine.

Throughout the 1990s, there had been a decrease in overall cases of syphilis worldwide [15]. In the early 2000s, the homosexual male population (hereafter referred to as the MSM population) has seen resurgence of syphilis; see, for *e.g.*, Heffelfinger et al. [15], Read et al. [30], Simms et al. [33] and Stolte et al. [37]. Moreover, specific outbreaks in MSM communities have been identified and quantified; see, for *e.g.*, Hopkins et al. [16] for study on an outbreak in Ireland; Hourihan et al. [17] for one in East London and Weerakoon et al. [42] for details of syphilis cases in Melbourne. While syphilis itself can be a debilitating disease if not treated early (*i.e.*, allowed to progress to its later stages), it has also been linked to more susceptibility for infection by other serious sexually transmitted diseases such as the Human Immunodeficiency Virus (HIV); see Karp et al. [19], Lynn and Lightman [23] and Tuite et al. [38]. Clearly, control of syphilis is of importance.

Some deterministic mathematical models of syphilis have been formulated and analyzed. Garnett et al. [13] introduced a model that includes the stages of syphilis but does not differentiate between early and late latency. They also include treatment, but treated individuals in the primary and secondary stages do not go into a treated class but return directly to susceptibility; treated individuals in latency and in the tertiary stage flow into the same 'immune' class, from which individuals then return to susceptibility. Pourbohloul et al. [29] formulated an ordinary differential equations (ODE) model with 210 differential equations to model heterosexual syphilis transmission in East Vancouver where they combine the later stages of syphilis but partition the population into multiple groups based on sex, sexual activity and age. The results of published mathematical models of syphilis up to 2008 are reviewed in Fenton et al. [12]. More recently, Milner and Zhao [24] presented an ODE model based on partial immunity and vaccination (assuming a successful vaccine is developed), and showed that there exists backward bifurcation for some parameter values. Their model includes removed classes that contain individuals that have recovered from infection, those that removed themselves from susceptibility, and those that were vaccinated. Recently, Tuite et al. [39] considered an agent based model for the MSM population in Toronto, and concluded that more frequent screening of high-risk males is more effective in reducing syphilis than screening a larger population.

As pointed out by a reviewer, a very recent multistage model for syphilis is formulated and analyzed by Iboi and Okuonghae [18]. Their model includes early and late latent stages as well as individuals who acquire transitory (natural) immunity following successful treatment in an infectious or latent stage. Loss of transitory immunity is shown to allow the possibility of backward bifurcation. If this loss is ignored and individuals in the early latent stage do not revert to the infectious stages, then Iboi and Okuonghae provide a complete global analysis, calculating a basic reproduction number threshold that determines whether syphilis dies out or becomes endemic in the population.

We focus our modeling on an MSM population because of the resurgence of syphilis in such groups. In Section 2, we formulate an ODE model for an MSM population that includes all the stages of syphilis (including exposed, early and late latency), as well as treatment in the latent and infectious stages. Due to different numbers of contact, we assume that the infectivity rates in the primary and secondary infectious stages may be different. Then in Section 3 we calculate the control reproduction number $\mathcal{R}_c$ for our model, which is shown to be a threshold parameter. In Section 4, we address the stability of the disease-free equilibrium, and in Section 5, we show that, for certain parameter values, there exists an endemic equilibrium. We also discuss stability of this equilibrium for various epidemiologically meaningful cases. In Section 6, we give baseline parameter values and perform numerics for our model, including sensitivity analysis by Latin Hypercube Sampling. Final size calculations (assuming constant population) are presented in Section 7. Finally, in Section 8, we draw our conclusions.

2. Formulation of a syphilis model

We first split an MSM population into eleven classes with the numbers in each class given as follows: S denotes susceptible males, E denotes exposed males, I_1 denotes infectious males who are in the primary stage of syphilis, I_2 denotes infectious males who are in the secondary stage of the infection, L_1 denotes males who are in the early latent stage, L_2 denotes males who are in the late latent stage, and X denotes males who are in the tertiary (and final) stage of syphilis. The classes T_1, T_2, T_3 and T_4 denote effectively treated males from the primary, secondary, early latency, and late latency stages of infection, respectively. We assume a constant recruitment Λ into the susceptible class, and m denotes the human natural death rate. We assume that only individuals in the primary and secondary stage of the infection are infectious, and the infectivity rates are denoted β_1, β_2, for the primary and secondary stage, respectively. Note here that β_i, $i = 1, 2,$ is equal to the probability of transmission from one contact between an individual in S and in I_i, times the number of contacts per day per individual. Bilinear incidence is assumed, that is, an average male in I_i makes $\beta_i N$ contacts with other males in the population per unit time, and the probability that such a contact is with a susceptible male is $\frac{S}{N}$. We also assume that treatment only occurs for individuals in I_1, I_2, L_1, L_2, at rates τ_1, τ_2, τ_3, τ_4, respectively and these effectively treated individuals return to susceptibility at rates δ_1, δ_2, δ_3, δ_4, respectively. Since our model is for an MSM population, this return could be due to risky behavior or to loss of immunity. The average incubation time before developing the disease is denoted by $\frac{1}{\eta}$. We assume that the disease progresses from the primary stage to the secondary stage at rate γ_1, from the secondary stage to the early latent stage at rate γ_2, from the early latent stage to late latent stage at rate γ_3, and from the late latent stage to the tertiary stage at rate γ_4. We also consider death due to disease only in the final (tertiary) stage of the infection, where α denotes the death rate due to syphilis of individuals in X. A summary of the parameters used is presented in Table 1.

We formulate the dynamics of the model changing with time as a system of ordinary differential equations, as seen in (1).

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - mS - (\beta_1 I_1 + \beta_2 I_2)S + \delta_1 T_1 + \delta_2 T_2 + \delta_3 T_3 + \delta_4 T_4 \\
\frac{dE}{dt} &= (\beta_1 I_1 + \beta_2 I_2)S - (\eta + m)E \\
\frac{dI_1}{dt} &= \eta E - (\gamma_1 + \tau_1 + m)I_1 \\
\frac{dI_2}{dt} &= \gamma_1 I_1 - (\gamma_2 + \tau_2 + m)I_2 \\
\frac{dL_1}{dt} &= \gamma_2 I_2 - (\gamma_3 + \tau_3 + m)L_1 \\
\frac{dL_2}{dt} &= \gamma_3 L_1 - (\gamma_4 + \tau_4 + m)L_2 \\
\frac{dT_1}{dt} &= \tau_1 I_1 - (\delta_1 + m)T_1 \\
\frac{dT_2}{dt} &= \tau_2 I_2 - (\delta_2 + m)T_2 \\
\frac{dT_3}{dt} &= \tau_3 L_1 - (\delta_3 + m)T_3 \\
\frac{dT_4}{dt} &= \tau_4 L_2 - (\delta_4 + m)T_4 \qquad (1)
\end{aligned}$$

and

$$\frac{dX}{dt} = \gamma_4 L_2 - (\alpha + m)X \qquad (2)$$

Table 1
Parameters in our model. The units of all (except Λ, β_1, β_2) are per day.

Parameter	Definition
Λ	Recruitment (number per day)
m	Natural death rate
η	Incubation rate
γ_1	Progression rate from primary stage to secondary stage
γ_2	Progression rate from secondary stage to early latent stage
γ_3	Progression rate from early latent stage to late latent stage
γ_4	Progression rate from late latent stage to tertiary stage
β_1	Infectivity rate, males in primary stage to susceptibles (per number per day)
β_2	Infectivity rate, males in secondary stage to susceptibles (per number per day)
τ_1	Treatment rate of males in primary stage
τ_2	Treatment rate of males in secondary stage
τ_3	Treatment rate of males in early latency
τ_4	Treatment rate of males in late latency
δ_1	Rate of return to susceptibility from treatment in primary stage*
δ_2	Rate of return to susceptibility from treatment in secondary stage*
δ_3	Rate of return to susceptibility from treatment in early latency*
δ_4	Rate of return to susceptibility from treatment in late latency*
α	Death rate in tertiary stage
	*This could be due to recovery and return to risky behavior

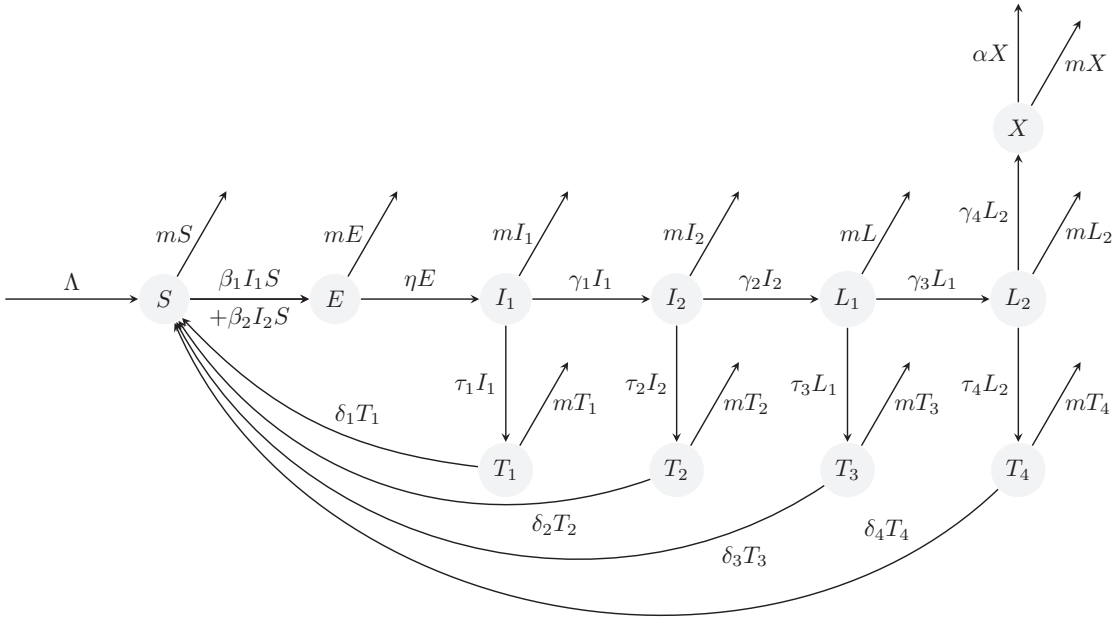


Fig. 1. Flowchart of model.

Note that since the variable X does not appear in (1), it suffices to determine the dynamics of (1), and then those of (2) follow. Letting N denote the population that determines the disease dynamics (*i.e.*, $N = S + E + I_1 + I_2 + L_1 + L_2 + T_1 + T_2 + T_3 + T_4$), it follows from (1) that

$$N' = \Lambda - mN - \gamma_4 L_2 \leq \Lambda - mN \tag{3}$$

Thus, (3) implies that $\limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{m}$. Therefore the feasible region

$$\Gamma = \left\{ (S, E, I_1, I_2, L_1, L_2, T_1, T_2, T_3, T_4) \in \mathbb{R}_+^{10} \mid S + E + I_1 + I_2 + L_1 + L_2 + T_1 + T_2 + T_3 + T_4 \leq \frac{\Lambda}{m} \right\}$$

is positively invariant with respect to (1). The flowchart in Fig. 1 gives a visualization of Model (1).

3. Calculation of the control reproduction number

Note that $P_0 = (S_0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$ with $S_0 = \frac{\Lambda}{m}$ is the disease-free equilibrium of (1). Taking the infected classes

$$(E, I_1, I_2, L_1, L_2, T_1, T_2, T_3, T_4)$$

we follow the next generation matrix approach; see Diekmann and Heesterbeek [11] and van den Driessche and Watmough [41]. We first calculate the Jacobian matrix at P_0, $J(P_0)$, and write $J(P_0) = F - V$ to obtain

$$F = \begin{pmatrix} F_{11} & 0_{3\times 6} \\ 0_{6\times 3} & 0_{6\times 6} \end{pmatrix}, \text{ where } F_{11} = \begin{pmatrix} 0 & \beta_1 S_0 & \beta_2 S_0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

and $V = \begin{pmatrix} V_{11} & 0_{5\times 4} \\ V_{21} & V_{22} \end{pmatrix}$

where

$$V_{11} = \begin{pmatrix} (\eta+m) & 0 & 0 & 0 & 0 \\ -\eta & \kappa_1 & 0 & 0 & 0 \\ 0 & -\gamma_1 & \kappa_2 & 0 & 0 \\ 0 & 0 & -\gamma_2 & \kappa_3 & 0 \\ 0 & 0 & 0 & -\gamma_4 & \kappa_4 \end{pmatrix}$$

$V_{21} = (0_{4\times1} \quad D_{4\times4})$, $D_{4\times4} = diag(-\tau_i)$, and $V_{22} = diag(\delta_i + m)$, with $\kappa_i = \gamma_i + \tau_i + m$ for $i = 1, ..., 4$. Since FV^{-1} is a matrix with rank 1, the control reproduction number

$$\begin{aligned} \mathcal{R}_c &= \rho(FV^{-1}) \\ &= \frac{\beta_1 S_0 \eta}{(\eta+m)(\gamma_1+\tau_1+m)} \\ &\quad + \frac{\beta_2 S_0 \gamma_1 \eta}{(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)(\eta+m)} \\ &= \mathcal{R}_{c_1} + \mathcal{R}_{c_2} \end{aligned} \tag{4}$$

Note that $\frac{\eta}{\eta+m}$ is the probability of surviving the E class, $\frac{1}{\gamma_i+\tau_i+m_i}$ is the average time in I_i, for $i = 1, 2$. Also, $\frac{\gamma_i}{\gamma_i+\tau_i+m_i}$ is the probability of surviving (*i.e.*, not dying and not treated) I_i, for $i = 1, 2$. The formula for $\mathcal{R}_c$ is the sum of the contributions from the primary stage $\mathcal{R}_{c_1}$ and from the secondary stage $\mathcal{R}_{c_2}$. Since L_1 and L_2 individuals are not infectious, τ_3 and τ_4 do not come into $\mathcal{R}_c$; thus $\mathcal{R}_c$ does not depend on the treatment rates of individuals in the latency stages of the disease.

The following remark draws attention to some observations on the effect of τ_1 and τ_2 (which are the parameters that may be controlled by public health measures) on $\mathcal{R}_c$.

Remark 1. If $\tau_2 \to \infty$, $\mathcal{R}_c \to \mathcal{R}_{c_1}$. Setting $\tau_2 \to \infty$ represents treatment immediately upon the completion of the first stage of syphilis; thus biologically, the control reproduction number must only depend on the transmission of infection from individuals in I_1 to S (as none remain in I_2). If $\tau_1 \to \infty$, then it is clear that $\mathcal{R}_c \to 0$, thus meaning that if every single male is treated upon entry in I_1, the disease would not be transmitted further.

The effect of ignoring the short incubation period of syphilis is given in the next remark.

Remark 2. If $\eta \to \infty$, *i.e.*, the incubation period is ignored, then $\mathcal{R}_c \to \frac{\beta_1 S_0}{\gamma_1+\tau_1+m} + \frac{\beta_2 S_0 \gamma_1}{(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)}$ as $\frac{\eta}{\eta+m}$, the probability of surviving incubation, tends to 1. If in addition $\beta_1 = \beta_2$, then $\mathcal{R}_c$ agrees with the effective reproduction number in [18, Eq. (3)].

4. Disease free equilibrium and stability

As mentioned in Section 3, Model (1) has a disease-free equilibrium $P_0 = (S_0, 0, 0, 0, 0, 0, 0, 0, 0, 0)$. The following theorem addresses the global stability of this equilibrium.

Theorem 3. *If $\mathcal{R}_c < 1$, then the disease-free equilibrium P_0 is globally asymptotically stable in the feasible region Γ.*

Proof. Algebraic operation gives

$$V^{-1}F = \begin{pmatrix} 0 & A_{12} & A_{13} & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{5}$$

with

$$A_{1,i+1} = \begin{pmatrix} \frac{\beta_i S_0}{\eta+m} \\ \frac{\eta\beta_i S_0}{(\eta+m)\kappa_1} \\ \frac{\eta\gamma_1\beta_i S_0}{(\eta+m)\kappa_1\kappa_2} \\ \frac{\eta\gamma_1\gamma_2\beta_i S_0}{(\eta+m)\kappa_1\kappa_2\kappa_3} \\ \frac{\eta\gamma_1\gamma_2\gamma_3\beta_i S_0}{(\eta+m)\kappa_1\kappa_2\kappa_3\kappa_4} \\ \frac{\eta\tau_1\beta_i S_0}{(\eta+m)\kappa_1\sigma_1} \\ \frac{\eta\gamma_1\tau_2\beta_i S_0}{(\eta+m)\kappa_1\kappa_2\sigma_2} \\ \frac{\eta\gamma_1\gamma_2\tau_3\beta_i S_0}{(\eta+m)\kappa_1\kappa_2\kappa_3\sigma_3} \\ \frac{\eta\gamma_1\gamma_2\gamma_3\tau_4\beta_i S_0}{(\eta+m)\kappa_1\kappa_2\kappa_3\kappa_4\sigma_4} \end{pmatrix}$$

for $i = 1, 2$, where $\kappa_i = (\gamma_i + \tau_i + m)$ and $\sigma_i = (\delta_i + m)$ for $i = 1, ..., 4$.

Since $V^{-1}F$ is reducible, we construct a Lyapunov function Q as in Theorem 5.1 of Shuai and van den Driessche [35] by identifying a left Perron eigenvector w^T of $V^{-1}F$ for the eigenvalue $\mathcal{R}_c$, namely,

$$\begin{aligned} &(0 \quad w_2 \quad w_3 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0)V^{-1}F \\ &= \mathcal{R}_c(0 \quad w_2 \quad w_3 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0 \quad 0) \end{aligned}$$

This gives

$$\begin{aligned} \mathcal{R}_c w_2 &= w_2 \frac{\eta\beta_1 S_0}{(\eta+m)(\gamma_1+\tau_1+m)} \\ &\quad + w_3 \frac{\eta\gamma_1\beta_1 S_0}{(\eta+m)(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)} \\ \mathcal{R}_c w_3 &= w_2 \frac{\eta\beta_2 S_0}{(\eta+m)(\gamma_1+\tau_1+m)} \\ &\quad + w_3 \frac{\eta\gamma_1\beta_2 S_0}{(\eta+m)(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)} \end{aligned}$$

A solution to the above system is $w_2 = 1$ and $w_3 = \frac{\beta_2}{\beta_1}$, and so

$$w^T = \begin{pmatrix} 0 & 1 & \frac{\beta_2}{\beta_1} & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Now, as in [35], let $Q = w^T V^{-1} x$, where

$$x = \begin{pmatrix} E & I_1 & I_2 & L_1 & L_2 & T_1 & T_2 & T_3 & T_4 \end{pmatrix}^T$$

Simple calculations lead to

$$\begin{aligned} Q &= \left(\frac{\eta}{(\eta+m)(\gamma_1+\tau_1+m)} \right. \\ &\quad \left. + \frac{\beta_2}{\beta_1} \frac{\eta\gamma_1}{(\eta+m)(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)} \right) E \\ &\quad + \left(\frac{1}{(\gamma_1+\tau_1+m)} + \frac{\beta_2}{\beta_1} \frac{\gamma_1}{(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)} \right) I_1 \\ &\quad + \left(\frac{\beta_2}{\beta_1} \frac{1}{\gamma_2+\tau_2+m} \right) I_2 \end{aligned}$$

Differentiating Q along solutions of the system (1) and rearranging leads to

$$\begin{aligned} Q' &= \left(\frac{\eta\beta_2\gamma_1 S}{(\eta+m)(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)} + \frac{\eta\beta_1 S}{(\eta+m)(\gamma_1+\tau_1+m)} - 1 \right) I_1 \\ &\quad + \frac{\beta_2}{\beta_1} \left(\frac{\eta\beta_1 S}{(\eta+m)(\gamma_1+\tau_1+m)} \right. \\ &\quad \left. + \frac{\eta\beta_2\gamma_1 S}{(\eta+m)(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)} - 1 \right) I_2 \end{aligned} \tag{6}$$

Since $S \le S_0$ (because $N \le S_0 = \frac{\Lambda}{m}$),

$$Q' \le \Big(\frac{\eta\beta_2\gamma_1 S_0}{(\eta+m)(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)} + \frac{\eta\beta_1 S_0}{(\eta+m)(\gamma_1+\tau_1+m)} - 1\Big)I_1 + \frac{\beta_2}{\beta_1}\Big(\frac{\eta\beta_1 S_0}{(\eta+m)(\gamma_1+\tau_1+m)} + \frac{\eta\beta_2\gamma_1 S_0}{(\eta+m)(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)} - 1\Big)I_2$$

Using (4)

$$Q' \le (\mathcal{R}_c - 1)I_1 + \frac{\beta_2}{\beta_1}(\mathcal{R}_c - 1)I_2$$

Thus, if $\mathcal{R}_c < 1$, $Q' \le 0$ and by an application of LaSalle's invariance principle [22], since the singleton $\{P_0\}$ is the largest invariant subset of Γ where $Q' = 0$, P_0 is globally asymptotically stable if $\mathcal{R}_c < 1$. From (2), it follows that $X \to 0$ also. □

Remark 4. Since global asymptotic stability of P_0 follows from Theorem 3 if $\mathcal{R}_c < 1$, it becomes interesting to calculate values of τ_1 and τ_2 for which this occurs. First, if $\tau_1 > \frac{\eta}{\eta+m}(\beta_1 S_0 + \frac{\beta_2 S_0\gamma_1}{\gamma_2+\tau_2+m}) - \gamma_1 - m$, then $\mathcal{R}_c < 1$ and the disease will be eventually eradicated. If $\frac{\eta}{\eta+m}(\beta_1 S_0 + \frac{\beta_2 S_0\gamma_1}{\gamma_2+\tau_2+m}) < \gamma_1 + m$, then treatment of individuals in I_1 is not necessary as $\tau_1 = 0$ results in $\mathcal{R}_c < 1$. Second, if $\mathcal{R}_{c_1} < 1$, then $\tau_2 > \frac{\beta_2\gamma_1}{\frac{(\gamma_1+\tau_1+m)(\eta+m)}{S_0\eta} - \beta_1} - \gamma_2 - m$ results in $\mathcal{R}_c < 1$ and thus in eventual eradication of the disease. Otherwise, if $\mathcal{R}_{c_1} > 1$, there is no such τ_2 value that will result in disease eradication, and thus it is necessary to treat individuals in the primary stage.

5. Endemic equilibrium and stability

We now address the existence of an endemic equilibrium (EE) with a positive number of males in each class.

Theorem 5. *If $\mathcal{R}_c > 1$, then the disease persists. Moreover, if $\mathcal{R}_c > 1$, there exists a unique endemic equilibrium $P^* = (S^*, E^*, I_1^*, I_2^*, L_1^*, L_2^*, T_1^*, T_2^*, T_3^*, T_4^*)$.*

Proof. Using the Lyapunov function Q of Theorem 3 and (6), $Q' > 0$ in a neighborhood of P_0 provided $\mathcal{R}_c > 1$. Then as in Theorem 2.2 of Shuai and van den Driessche [35], since P_0 is the only equilibrium on the boundary of Γ and is isolated, the instability of P_0 implies uniform persistence if $\mathcal{R}_c > 1$. The uniqueness of the endemic equilibrium follows by setting each derivative equal to zero in (1). Straightforward calculations result in

$$S^* = \frac{\eta+m}{\frac{\beta_1\eta}{\gamma_1+\tau_1+m} + \frac{\beta_2\eta\gamma_1}{(\gamma_1+\tau_1+m)(\gamma_2+\tau_2+m)}} = \frac{S_0}{\mathcal{R}_c}$$

and it follows that

$$E^* = \frac{\Lambda}{\eta+m-A}\Big(1 - \frac{1}{\mathcal{R}_c}\Big), I_1^* = \frac{\eta}{\gamma_1+\tau_1+m}E^*$$

$$I_2^* = \frac{\gamma_1}{\gamma_2+\tau_2+m}I_1^*, L_1^* = \frac{\gamma_2}{\gamma_3+\tau_3+m}I_2^*, L_2^* = \frac{\gamma_3}{\gamma_4+\tau_4+m}L_1^*$$

$$T_1^* = \frac{\tau_1}{\delta_1+m}I_1^*, T_2^* = \frac{\tau_2}{\delta_2+m}I_2^*, T_3^* = \frac{\tau_3}{\delta_3+m}L_1^*, T_4^* = \frac{\tau_4}{\delta_4+m}L_2^*$$

where

$$A = \frac{\delta_2\tau_2\gamma_1\eta}{(\delta_2+m)\kappa_2\kappa_1} + \frac{\delta_1\tau_1\eta}{(\delta_1+m)\kappa_1} + \frac{\delta_3\tau_3\gamma_2\gamma_1\eta}{(\delta_3+m)\kappa_3\kappa_2\kappa_1} + \frac{\delta_4\tau_4\gamma_3\gamma_2\gamma_1\eta}{(\delta_4+m)\kappa_4\kappa_3\kappa_2\kappa_1}$$

and $\kappa_i = \gamma_i + \tau_i + m$, $i = 1, ..., 4$. The denominator of E^* is positive, thus if $\mathcal{R}_c > 1$ then $E^* > 0$, and it follows that if $\mathcal{R}_c > 1$ then $I_1^*, I_2^*, L_1^*, L_2^*, T_1^*, T_2^*, T_3^*, T_4^* > 0$. From (2), it follows that $X^* > 0$. □

The following remark draws observation to the effects of the treatment rates of the early and late latent classes, τ_3 and τ_4, on the endemic equilibrium.

Remark 6. If $\tau_3 \to \infty$, it follows that $L_1^* \to 0$, $L_2^* \to 0$, and $X^* \to 0$. However, $\frac{\tau_3}{\kappa_3} \to 1$, thus the denominator of E^* becomes smaller, and E^* becomes larger. This implies that I_1^* and I_2^* also grow. If $\tau_4 \to \infty$, it follows that $L_2^* \to 0$, and $X^* \to 0$. Similarly to the previous case, $\frac{\tau_4}{\kappa_4} \to 1$, thus the denominator of E^* becomes smaller, and once again E^* becomes larger; but now, I_1^*, I_2^* and also L_1^* become larger. Thus, increasing τ_3 and τ_4 can lead to increases in individuals in the primary and secondary stages of the infection. This exemplifies the need for early treatment (*i.e.*, in the primary and secondary stages), as the goal is to reduce the number of infectious individuals (*i.e.*, individuals in the primary and secondary stages of the disease).

Theorems 3 and 5 imply that $\mathcal{R}_c$ is a sharp threshold, with syphilis dying out if $\mathcal{R}_c < 1$, but becoming endemic if $\mathcal{R}_c > 1$. We now focus on the dynamical behavior of Model (1) for $\mathcal{R}_c > 1$. Consider the case with $\Lambda = m = \tau_1 = \tau_2 = \tau_3 = \gamma_4 = \beta_2 = 0$ and $\eta \to \infty$. Then, Model (1) behaves as an $SIR_1R_2R_3R_4S$ epidemiological model, where I_2 acts as the first, L_1 as the second, L_2 as the third, and T_4 as the fourth removed subclass. This model has been studied in Hethcote et al. [14] (and again mentioned in Bodine et al. [2]) and found to have periodic solutions about the endemic equilibrium for some parameter values. Taking parameter values $\frac{\gamma_1}{50} = \gamma_2 = \gamma_3 = \tau_4 = \delta_4 = \frac{1}{100}$, $\beta_1 = 1.34\gamma_1$, giving $\mathcal{R}_c = 3.048$, we have numerically verified periodic solutions for our model. Thus, global asymptotic stability of the endemic equilibrium for Model (1) for all parameter values with $\mathcal{R}_c > 1$ is impossible. We remark that Breban et al. [4] examined the hypothesis that syphilis epidemics cycle, but concluded that CDC syphilis data show no evidence of this.

However, for $\mathcal{R}_c > 1$, global asymptotic stability of the endemic equilibrium (EE) can be proved in some special cases. The following three theorems address this, each with different assumptions, that may be appropriate in some situations. In the first two results where $\gamma_2 > 0$ (*i.e.*, the disease progresses to the latent stages), if the variables in (1) are globally asymptotically stable, the global stability of X^* follow from (2).

The first of these theorems addresses global stability of the endemic equilibrium under the condition that $\delta_1 = \delta_2 = \delta_3 = \delta_4 = 0$. Biologically, this represents the case that treated individuals do not return to susceptibility. This could be due to recovery and the adoption of safe behavior. For example, from data in San Francisco, reinfection with syphilis in an MSM population (without HIV coinfection) is only 2% within a year [27].

Theorem 7. *Suppose that $\delta_1 = \delta_2 = \delta_3 = \delta_4 = 0$. If $\mathcal{R}_c > 1$, then the endemic equilibrium P^* is globally asymptotically stable in int(Γ).*

Proof. With the theorem assumptions, Model (1) becomes

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - mS - (\beta_1 I_1 + \beta_2 I_2)S\\ \frac{dE}{dt} &= (\beta_1 I_1 + \beta_2 I_2)S - (\eta+m)E\\ \frac{dI_1}{dt} &= \eta E - (\gamma_1+\tau_1+m)I_1\\ \frac{dI_2}{dt} &= \gamma_1 I_1 - (\gamma_2+\tau_2+m)I_2\end{aligned} \tag{7}$$

The L_1, L_2, T_1, T_2, T_3, T_4 equations uncouple from the system, and thus their behavior follows from the behavior of (7).

Consider $D_1 = S - S^* - S^*\ln(\frac{S}{S^*}) + E - E^* - E^*\ln(\frac{E}{E^*})$, $D_2 = I_1 - I_1^* - I_1^*\ln(\frac{I_1}{I_1^*})$ and $D_3 = I_2 - I_2^* - I_2^*\ln(\frac{I_2}{I_2^*})$. Differentiating along solutions of the system (7) and using the inequality $1 - x \leq -\ln x$ for $x > 0$ lead to

$$\begin{aligned}
D_1' &= \left(\frac{S-S^*}{S}\right)\frac{dS}{dt} + \left(\frac{I_1 - I_1^*}{I_1}\right)\frac{dI_1}{dt} \\
&= -\frac{m(S-S^*)^2}{S} + \beta_1 S^* I_1^*\left(2 - \frac{S^*}{S} + \frac{I_1}{I_1^*} - \frac{SI_1E^*}{S^*I_1^*E} - \frac{E}{E^*}\right) \\
&\quad + \beta_2 S^* I_2^*\left(2 - \frac{S^*}{S} + \frac{I_2}{I_2^*} - \frac{SI_2E^*}{S^*I_2^*E} - \frac{E}{E^*}\right) \\
&\leq \beta_1 S^* I_1^*\left(\frac{I_1}{I_1^*} - \ln\left(\frac{I_1}{I_1^*}\right) - \frac{E}{E^*} + \ln\left(\frac{E}{E^*}\right)\right) \\
&\quad + \beta_2 S^* I_2^*\left(\frac{I_2}{I_2^*} - \ln\left(\frac{I_2}{I_2^*}\right) - \frac{E}{E^*} + \ln\left(\frac{E}{E^*}\right)\right) \\
&= a_{12}G_{12} + a_{13}G_{13} \text{ where } a_{12} = \beta_1 S^* I_1^*, a_{13} = \beta_2 S^* I_2^*
\end{aligned}$$

$$\begin{aligned}
D_2' &= \left(\frac{I_1 - I_1^*}{I_1}\right)\frac{dI_1}{dt} \\
&= \eta E^*\left(\frac{E}{E^*} - \frac{EI_1^*}{E^*I_1} - \frac{I_1}{I_1^*} + 1\right) \\
&\leq \eta E^*\left(\frac{E}{E^*} - \ln\left(\frac{E}{E^*}\right) - \frac{I_1}{I_1^*} + \ln\left(\frac{I_1}{I_1^*}\right)\right) \\
&= a_{21}G_{21} \text{ where } a_{21} = \eta E^*
\end{aligned}$$

$$\begin{aligned}
D_3' &= \left(\frac{I_2 - I_2^*}{I_2}\right)\frac{dI_2}{dt} \\
&= \gamma_1 I_1^*\left(\frac{I_1}{I_1^*} - \frac{I_1I_2^*}{I_1^*I_2} - \frac{I_2}{I_2^*} + 1\right) \\
&\leq \gamma_1 I_1^*\left(\frac{I_1}{I_1^*} - \ln\left(\frac{I_1}{I_1^*}\right) - \frac{I_2}{I_2^*} + \ln\left(\frac{I_2}{I_2^*}\right)\right) \\
&= a_{32}G_{32} \text{ where } a_{32} = \gamma_1 I_1^*
\end{aligned}$$

Since $G_{12} + G_{21} = 0$ and $G_{13} + G_{21} + G_{32} = 0$, an application of Theorems 3.3 and 3.5 of [35], gives the Lyapunov function $D = c_1D_1 + c_2D_2 + c_3D_3$, where $c_1 = a_{21}a_{32}, c_2 = a_{12}a_{32} + a_{32}a_{13}$ and $c_3 = a_{13}a_{21}$. The use of this Lyapunov function for (1) along with LaSalle's invariance principle [22] completes the proof of the global asymptotic stability of the EE P^* if $\delta_1 = \delta_2 = \delta_3 = \delta_4 = 0$ and $\mathcal{R}_c > 1$. □

Sometimes data on primary and secondary syphilis are combined [6,10], so in our model with $\gamma_2 \to \infty$, I_1 denotes these infectious men. Assuming that the time scale for the loss of immunity from T_3 and T_4 is large compared with that from T_1, we take $\delta_3 = \delta_4 = 0$, and in addition we ignore the exposed class in the next result.

Theorem 8. *Suppose that η, $\gamma_2 \to \infty$ and $\delta_3 = \delta_4 = 0$. If $\mathcal{R}_c = \frac{\beta_1 S_0}{\gamma_1+\tau_1+m} > 1$, then the EE P^* is globally asymptotically stable in int(Γ).*

Proof. Setting η, $\gamma_2 \to \infty$ (giving $E, I_2 = 0$) and $\delta_3 = \delta_4 = 0$, system (1) becomes

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - mS - \beta_1 I_1 S + \delta_1 T_1 \\
\frac{dI_1}{dt} &= \beta_1 I_1 S - (\gamma_1 + \tau_1 + m)I_1 \\
\frac{dT_1}{dt} &= \tau_1 I_1 - (\delta_1 + m)T_1
\end{aligned} \tag{8}$$

Since all other variables do not appear in (8), the behavior of them follow directly from (8). Now, as in [20] and [40], consider $N_1 = S + I_1 + T_1$, and thus $N_1^* = S^* + I_1^* + T_1^*$ and

$$\frac{dN_1}{dt} = \Lambda - mN_1 - \gamma_1 I_1$$

Now consider the following equivalent system:

$$\begin{aligned}
\frac{dN_1}{dt} &= \Lambda - mN_1 - \gamma_1 I_1 \\
\frac{dI_1}{dt} &= \beta_1 I_1(N_1 - I_1 - T_1) - (\gamma_1 + \tau_1 + m)I_1 \\
\frac{dT_1}{dt} &= \tau_1 I_1 - (m + \delta_1)T_1
\end{aligned}$$

Let $D_1 = \frac{1}{2}(N_1 - N_1^*)^2$, $D_2 = I_1 - I_1^* - I^*\ln(\frac{I_1}{I_1^*})$ and $D_3 = \frac{1}{2}(T_1 - T_1^*)^2$. Differentiating along solutions and after rearrangements,

$$\begin{aligned}
D_1' &= -m(N_1 - N_1^*)^2 - \gamma_1(I_1 - I_1^*)(N_1 - N_1^*) \leq -\gamma_1(I_1 - I_1^*)(N_1 - N_1^*) \\
&= a_{12}G_{12} \text{ where } a_{12} = \gamma_1 \\
D_2' &= \beta_1[(I_1 - I_1^*)(N_1 - N_1^*) - (I_1 - I_1^*)^2 - (I_1 - I_1^*)(T_1 - T_1^*)] \\
&\leq \beta_1(I_1 - I_1^*)(N_1 - N_1^*) - \beta_1(I_1 - I_1^*)(T_1 - T_1^*) \\
&= a_{21}G_{21} + a_{23}G_{23} \text{ where } a_{21} = a_{23} = \beta_1 \\
D_3' &= \gamma_1(I_1 - I_1^*)(T_1 - T_1^*) - (m + \delta_1)(T_1 - T_1^*)^2 \\
&\leq \gamma_1(I_1 - I_1^*)(T_1 - T_1^*) \\
&= a_{32}G_{32} \text{ where } a_{32} = \gamma_1
\end{aligned}$$

An application of Theorems 3.3 and 3.5 of [35] results in the Lyapunov function $D = c_1D_1 + c_2D_2 + c_3D_3$ where $c_1 = c_3 = \beta_1$ and $c_2 = \gamma_1$, and this function, along with an application of LaSalle's invariance principle [22], proves the global asymptotic stability of (N_1^*, I_1^*, T_1^*). Under the above assumptions, the global asymptotic stability of (S^*, I_1^*, T_1^*) for (8) and thus of P^* for (1) follows provided $\mathcal{R}_c > 1$. □

Another possible case is if the disease does not progress to its secondary stage, thus $\gamma_1 = 0$ and our model becomes an SEI_1T_1S model. This could model the case of complete surveillance and treatment in the primary stage. Enhanced surveillance is currently underway in several locations, for *e.g.* in inner Sydney, Australia [3] and in China [7]. More specifically with regards to an MSM population, the Los Angeles County started a social marketing campaign to increase surveillance of syphilis within the MSM community [28]. The next theorem addresses global stability of the endemic equilibrium under these conditions, and we also assume constant population size, thus the variables can be regarded as fractions of the population.

Theorem 9. *Suppose $\Lambda = m$, and $\gamma_1 = 0$. If $\mathcal{R}_c > 1$, then (S^*, E^*, I_1^*, T_1^*) is globally asymptotically stable in int(Γ).*

Proof. Since $\gamma_1 = 0$, system (1) becomes

$$\begin{aligned}
\frac{dS}{dt} &= m - mS - \beta_1 I_1 S + \delta_1 T_1 \\
\frac{dE}{dt} &= \beta_1 I_1 S - (\eta + m)E \\
\frac{dI_1}{dt} &= \eta E - (\tau_1 + m)I_1 \\
\frac{dT_1}{dt} &= \tau_1 I_1 - (\delta_1 + m)T_1
\end{aligned}$$

Clearly, this is just like an *SEIRS* epidemiological model having constant population size and with the T_1 acting as the R class. Thus, an application of Theorems 6 and 7 in [8] completes the proof. These theorems utilize well chosen Lyapunov functions and compound matrices to show asymptotic global stability of an *SEIRS* model with constant population. □

Table 2
Baseline parameter values for MSM populations as estimated from various sources in the literature, all normalized to be per day.

Parameter	Value ($\frac{1}{\text{day}}$)	Reason
m	0.0000498	$\frac{1}{m} = 55$ years
Λ	0.0000498	$\Lambda = m$
η	0.0476190	$\frac{1}{\eta} = 28$ days [13]
γ_1	0.0217391	$\frac{1}{\gamma_1} = 46$ days [13]
γ_2	0.0092593	$\frac{1}{\gamma_2} = 108$ days [13]
β_1	0.0353888	[16,32]
β_2	0.0353888	[16,32]
τ_1	0.0100000	Estimated guess
τ_2	0.0100000	Estimated guess

6. Numerics: sensitivity and control measures

6.1. Elasticity indices

With the goal of quantifying disease control, we calculate the elasticity indices of each parameter present in $\mathcal{R}_c$. This linearization allows us to see which parameter variation has the greatest impact on $\mathcal{R}_c$ when all other parameters are at baseline values. These indices have been used in other epidemiological models (see, for *e.g.*, Chitnis et al. [9] and Saad-Roy et al. [31]) and are denoted as

$$\Upsilon_p^{\mathcal{R}_c} = \frac{\partial \mathcal{R}_c}{\partial p} \times \frac{p}{\mathcal{R}_c}$$

where p is a parameter. Computing this for the parameters present in $\mathcal{R}_c$, gives

$$\Upsilon_{\beta_1}^{\mathcal{R}_c} = \frac{\mathcal{R}_{c_1}}{\mathcal{R}_c},\ \Upsilon_{\beta_2}^{\mathcal{R}_c} = \frac{\mathcal{R}_{c_2}}{\mathcal{R}_c},\ \Upsilon_{\gamma_1}^{\mathcal{R}_c} = -\frac{\gamma_1}{\gamma_1+\tau_1+m} + \frac{\mathcal{R}_{c_2}}{\mathcal{R}_c},$$
$$\Upsilon_{\gamma_2}^{\mathcal{R}_c} = -\frac{\mathcal{R}_{c_2}}{\mathcal{R}_c}\frac{\gamma_2}{\gamma_2+\tau_2+m},\ \Upsilon_{\tau_1}^{\mathcal{R}_c} = -\frac{\tau_1}{\gamma_1+\tau_1+m},$$
$$\Upsilon_{\tau_2}^{\mathcal{R}_c} = -\frac{\mathcal{R}_{c_2}}{\mathcal{R}_c}\frac{\tau_2}{\gamma_2+\tau_2+m},\ \text{and}\ \Upsilon_{\eta}^{\mathcal{R}_c} = \frac{m}{\eta+m}$$

Baseline disease parameter values are estimated from various sources in the literature on syphilis in MSM populations. For our baseline parameters, m is calculated based on an average time in the MSM population of 55 years, and for simplicity, we assume that $\Lambda = m$, thus recruitment is equal to death, and so numbers in each class can be thought of as fractions. Parameter β_i, $i = 1, 2$, is the probability of transmission from a male in the I_i class times the number of his partners, all normalized per day, thus $\beta_i = 0.49 \times 0.07222$ since 0.49 is the probability of transmission [32, Table III] and 0.07222 is the average number of partners per day per male [16, Table 2]. In this calculation, β_i is probably underestimated, as we consider that an individual has only one contact per partner. However this may not be the case, and repeated exposure to the same infected partner would increase likelihood of successful transmission of the disease. Data is lacking on the values of β_i, $i = 1, 2$, so we assume $\beta_1 = \beta_2$. The average primary incubation period is taken as $\frac{1}{\eta} = 28$ days, the average times in the primary stage and secondary stage as $\frac{1}{\gamma_1} = 46$ days and $\frac{1}{\gamma_2} = 3.6$ months, all obtained from data in Garnett et al. [13]. Using the baseline parameters as given in Table 2, $\mathcal{R}_{c_1} = 1.11$ and $\mathcal{R}_{c_2} = 1.25$ giving $\mathcal{R}_c = 2.36$, and we compute the elasticity indices given above, presenting the results in Table 3. Note that every elasticity index is sign determined except for $\Upsilon_{\gamma_1}^{\mathcal{R}_c}$; for this index, if $(\tau_1+m)\mathcal{R}_{c_2} > \gamma_1\mathcal{R}_{c_1}$, namely $\beta_2(m+\tau_1) - \beta_1(\gamma_2+\tau_2+m) > 0$, then $\Upsilon_{\gamma_1}^{\mathcal{R}_c} > 0$; otherwise if $\beta_2(m+\tau_1) - \beta_1(\gamma_2+\tau_2+m) < 0$, then $\Upsilon_{\gamma_1}^{\mathcal{R}_c} < 0$ as in Table 3. The calculations in Table 3 indicate the importance of early treatment and the need to have good estimates of β_i, $i = 1, 2$, which have the largest elasticity indices.

Table 3
Elasticity indices as calculated for the baseline parameter values given in Table 2.

Parameter	Value ($\frac{1}{\text{day}}$)	Elasticity index
β_2	0.0353888	0.5296001
β_1	0.0353888	0.4703999
τ_1	0.0100000	−0.3145748
τ_2	0.0100000	−0.2742752
γ_2	0.0092593	−0.2539586
γ_1	0.0217391	−0.1542582
η	0.0476190	0.00139283

Table 4
Ranges of all parameters that we assume to follow uniform distributions. Units of γ_i are per day, and units of β_i are per number per day, for $i = 1, 2$.

Parameter	Upper limit	Lower limit
γ_1	$\frac{1}{14}$	$\frac{1}{84}$
γ_2	$\frac{1}{90}$	$\frac{1}{120}$
β_1	0.3×0.07222	0.7×0.07222
β_2	0.3×0.07222	0.7×0.07222

6.2. Effect of treatment rates on $\mathcal{R}_c$

Since τ_1 and τ_2 are the parameters in $\mathcal{R}_c$ that may be controlled if syphilis is identified early, it is interesting to see what happens to $\mathcal{R}_c$ as these two parameters are varied. Moreover, the aim is to predict values of τ_1 and τ_2 that would result in disease eradication; *i.e.*, to bring $\mathcal{R}_c$ below 1 in accordance with Theorem 3. This expands on the comments stated in Remarks 1 and 4, as these considered appropriate values of τ_i, $i = 1, 2$, for fixed τ_j, $j = 1, 2$, $j \neq i$. In order to consider treatment rates, we first need to fix other parameters at their baseline values as estimated from data found in the literature; see Table 2.

With the other parameter values fixed as in Table 2, we vary τ_1 and τ_2 from their baseline values of 0.01 and calculate the change in $\mathcal{R}_c$ as defined in (4). The results are given in Fig. 2(a), and plotting the contour lines of this graph gives Fig. 2(b).

Fig. 2(a) and (b) illustrate the effect of both τ_1 and τ_2 on $\mathcal{R}_c$ while all other parameters are at baseline values. However, parameter baseline values are estimates found in the literature, and these are inexact values depending on location and sampling techniques.

Fixing m and Λ at their baseline value, to help identify the robustness of $\mathcal{R}_c$ to the baseline parameters, we sample the γ_1, γ_2, β_1, β_2, η parameter space using Latin Hypercube Sampling (LHS) maximin criteria, see, for *e.g.*, Blower et al. [1] and references therein. We then compute $\mathcal{R}_c$ at all these parameter values for fixed values of τ_2 and a range of τ_1, and generate box plots at each τ_1 value. We assume that $\frac{1}{\eta} \sim Gamma(\alpha = 1.5, \beta = 18.6667)$, since Singh and Romanowski [34] state that the range of $\frac{1}{\eta}$ (we take this as the 95% confidence interval) is 3–90 days. We assume that γ_1, γ_2, β_1, β_2 follow uniform independent distributions, with their ranges presented in Table 4. These ranges are estimated from data presented in [34], or (for the infectivity rates), estimated using approximately symmetric intervals about the baseline value as mean. For fixed τ_2, we present different curves of $\mathcal{R}_c$ as a function of τ_1. This presentation is chosen as τ_1 and τ_2 values depend on the public health initiatives and not on the biology of the disease. Fig. 3 confirms that our baseline parameters are relatively accurate, especially for larger treatment rates. Interestingly, this figure also illustrates that with lower treatment rates, values of $\mathcal{R}_c$ vary more and have more outliers present (see Appendix). These outliers are probably due to low γ_1 values present for certain data points chosen by LHS, as very low γ_1 and τ_1 values would greatly increase

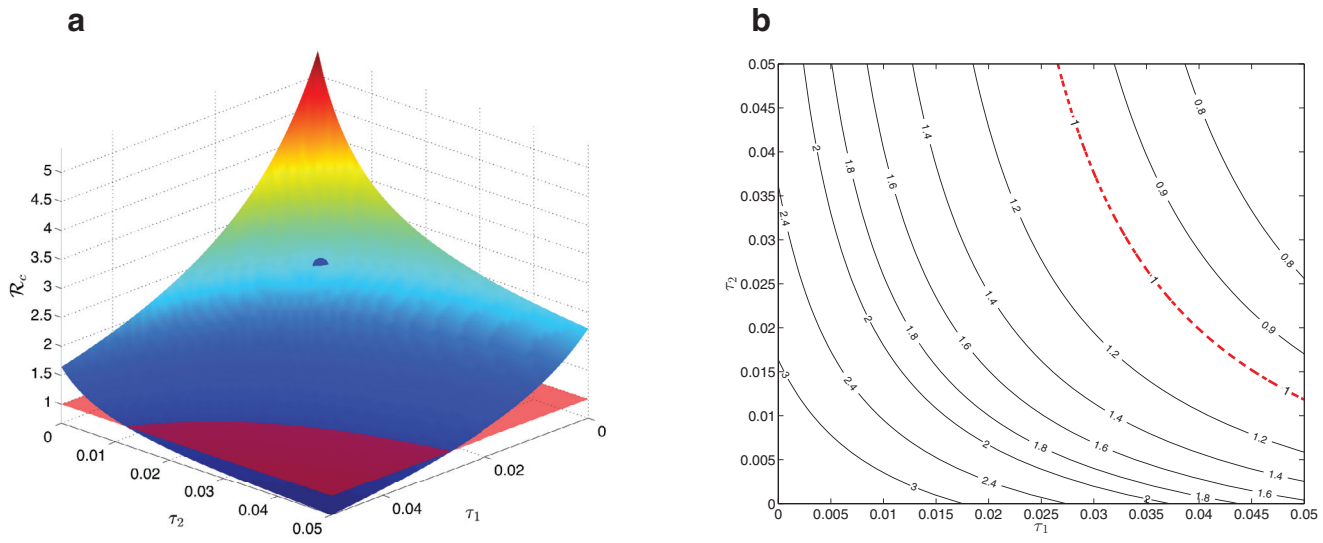


Fig. 2. (a) Values of $\mathcal{R}_c$ as τ_1 and τ_2 are varied within a feasible region. The blue circular marker represents the baseline values of τ_1 and τ_2. The red plane represents $\mathcal{R}_c = 1$. (b) Contour curves of the values of $\mathcal{R}_c$ as τ_1 and τ_2 are varied within a feasible region. The dashed red line represents $\mathcal{R}_c = 1$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

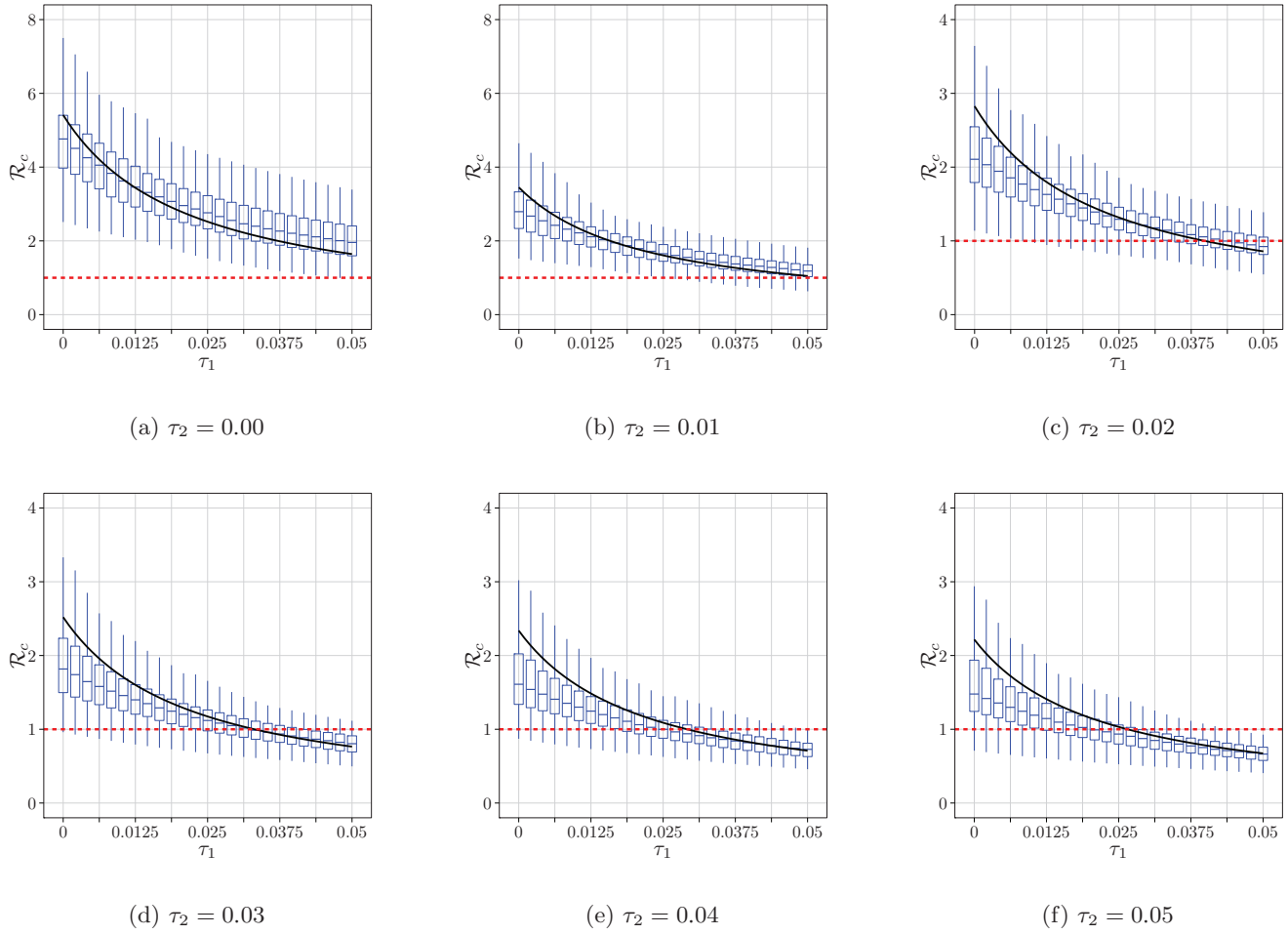


Fig. 3. Values of $\mathcal{R}_c$ as of function of τ_1 for fixed τ_2. The black line represents the $\mathcal{R}_c$ values at the baseline values for the parameters γ_1, γ_2, β_1, β_2, m, Λ, η. The box plots represent 250 parameter points obtained by LHS maximin criteria for γ_1, γ_2, β_1, β_2 and η, based on their associated probability distributions. The red dotted line is at $\mathcal{R}_c = 1$; values of $\mathcal{R}_c$ below this result in disease eradication. Note that outliers are omitted, and that the $\mathcal{R}_c$ scales changes from (b) to (c). The outside lines in the boxplots represent the first and third quartiles while the middle line represents the median, and the bottom and top whiskers respectively represent the smallest value within 1st quartile $- 1.5 \times$ inter-quartile range (IQR) and the largest value within 3rd quartile $+ 1.5 \times$ IQR. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

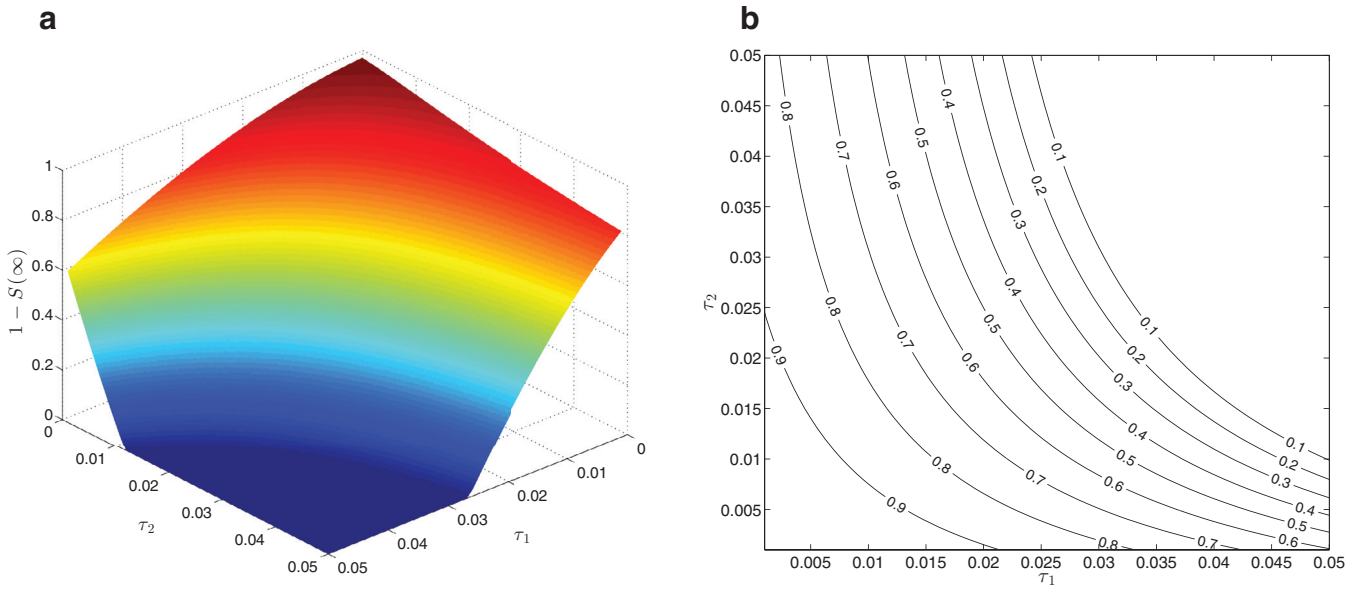


Fig. 4. (a) Values of $1-S(\infty)$ as τ_1 and τ_2 are varied. (b) Contour curves of the values of $1-S(\infty)$ as τ_1 and τ_2 are varied.

$\mathcal{R}_c$. In conjunction with Fig. 2 treatment rates needed for disease control can be estimated.

7. Final size calculations

The previous sections dealt with an open population with recruitment and death, and thus if $\mathcal{R}_c > 1$ Model (1) admits an endemic equilibrium with positive values for all of the population classes. Now, however, we ignore recruitment and death (*i.e.*, $\Lambda = m = \alpha = 0$), as well as return to susceptibility after treatment (*i.e.*, $\delta_i = 0,\ i = 1, ..., 4$) giving an epidemic model instead of an endemic one. Taking a time scale of about 12–18 months for an epidemic, the late latent and tertiary stages can be ignored, and T_3 becomes a terminal class. Thus, we can study the final disease outbreak size of syphilis as predicted from our model, given that the population is a closed one and there is no return to susceptibility after treatment. Model (1) then becomes

$$\begin{aligned}
\frac{dS}{dt} &= -(\beta_1 I_1 + \beta_2 I_2)S \\
\frac{dE}{dt} &= (\beta_1 I_1 + \beta_2 I_2)S - \eta E \\
\frac{dI_1}{dt} &= \eta E - (\gamma_1 + \tau_1)I_1 \\
\frac{dI_2}{dt} &= \gamma_1 I_1 - (\gamma_2 + \tau_2)I_2 \\
\frac{dL_1}{dt} &= \gamma_2 I_2 - \tau_3 L_1 \\
\frac{dT_1}{dt} &= \tau_1 I_1 \\
\frac{dT_2}{dt} &= \tau_2 I_2 \\
\frac{dT_3}{dt} &= \tau_3 L_1
\end{aligned} \tag{9}$$

Thus, $\mathcal{R}_c = \frac{\beta_1 S(0)}{\gamma_1+\tau_1} + \frac{\beta_2 S(0)\gamma_1}{(\gamma_1+\tau_1)(\gamma_2+\tau_2)}$ where $S(0)$ is the fraction of susceptible individuals at time $t = 0$. This control reproduction number now represents the epidemic threshold; as in the proof of Theorem 3, syphilis dies out if $\mathcal{R}_c < 1$; whereas if $\mathcal{R}_c > 1$, then there is an epidemic with final size given below. Note that since the total population $N_{FS} = S + E + I_1 + I_2 + L_1 + T_1 + T_2 + T_3$ is constant, the populations in each class can be thought of as a fraction such that $N_{FS} = 1$.

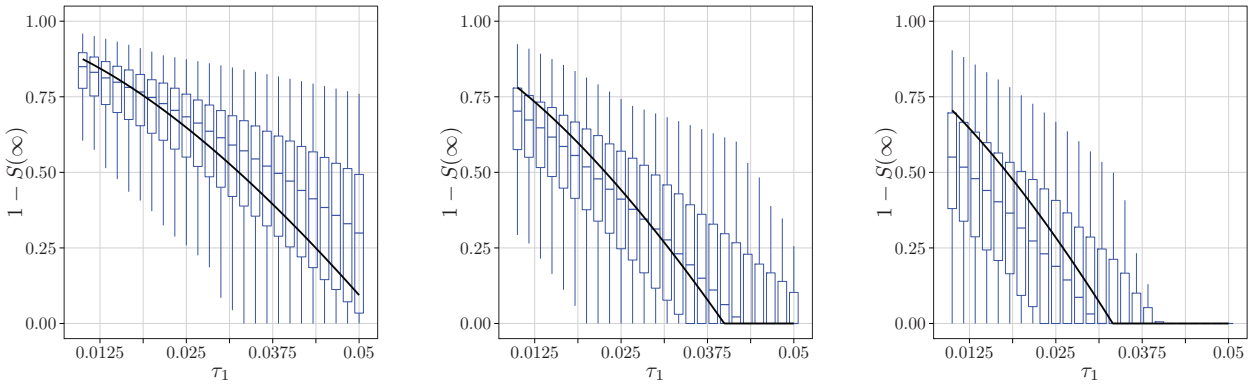
Theorem 10. *As $t \to \infty$ in system (9), the disease burns out; i.e., $I_1(\infty) = I_2(\infty) = L_1(\infty) = 0$. Moreover, $S(\infty)$, $T_1(\infty)$, $T_2(\infty)$ and $T_3(\infty)$ are nonnegative constants such that $S(\infty) + T_1(\infty) + T_2(\infty) + T_3(\infty) = 1$. The final size relations with $\tau_1,\ \tau_2 > 0$ are given by*

$$\begin{aligned}
\ln S(\infty) &= -\frac{\mathcal{R}_c(\gamma_1+\tau_1)(\gamma_2+\tau_2)}{\gamma_1\gamma_2} T_3(\infty) \\
\ln S(\infty) &= -\frac{\beta_2\gamma_1 + \beta_1(\gamma_2+\tau_2)}{\gamma_1\tau_2} T_2(\infty) \\
\ln S(\infty) &= -\frac{\beta_1}{\tau_1} T_1(\infty) - \frac{\beta_2}{\tau_2} T_2(\infty) \\
1 - S(\infty) &= T_1(\infty) + T_2(\infty) + T_3(\infty)
\end{aligned}$$

Proof. Consider $S + E$. From (9), it follow that $\frac{d}{dt}(S+E) = -\eta E$. Thus, $S + E$ is a monotonically nonincreasing function, as $E(t) \geq 0$ by definition. But $0 \leq S + E \leq 1$, so $S + E$ is bounded. By the monotone convergence theorem, this implies that $\lim_{t\to\infty}(S(t) + E(t)) = c \in [0, 1]$. But then it follows that $\lim_{t\to\infty} \frac{d}{dt}(S(t) + E(t)) = \lim_{t\to\infty}(-\eta E(t)) = 0$, so clearly $\lim_{t\to\infty} E(t) = 0$, and $\lim_{t\to\infty}(S(t) + E(t)) = \lim_{t\to\infty} S(t) = c = S(\infty) \in [0, 1]$ since $0 \leq S(t) \leq 1$ for all t. A similar approach with first the S, E, I_1 equations, then with the S, E, I_1, I_2, T_1 equations, and lastly with the S, E, I_1, I_2, L_1, T_1, T_2 equations results in $I_1(\infty) = I_2(\infty) = L_1(\infty) = 0$ and in $T_1(\infty)$, $T_2(\infty)$, $T_3(\infty)$ being nonnegative constants. Since these are nonnegative constants, and $N_{FS} = 1$ it follows that $S(\infty) + T_1(\infty) + T_2(\infty) + T_3(\infty) = 1$. Notice that

$$\begin{aligned}
J_1 &= \ln S + \frac{\beta_1}{\gamma_1} I_2 + \frac{\mathcal{R}_c(\gamma_1+\tau_1)(\gamma_2+\tau_2)}{S(0)\gamma_1\gamma_2}(L_1 + T_3) \\
J_2 &= \ln S + \frac{\beta_1}{\gamma_1} I_2 + \frac{\beta_2\gamma_1 + \beta_1(\gamma_2+\tau_2)}{\gamma_1\tau_1} T_2 \\
J_3 &= \ln S + \frac{\beta_1}{\tau_1} T_1 + \frac{\beta_2}{\tau_2} T_2
\end{aligned} \tag{10}$$

are all first integrals for (9); *i.e.*, $\frac{dJ_i}{dt} = 0$ for $i = 1, 2, 3$.



(a) $\tau_2 = 0.01$ (b) $\tau_2 = 0.02$ (c) $\tau_2 = 0.03$

Fig. 5. Values of the final disease outbreak size $1 - S(\infty)$ as of function of τ_1 for fixed τ_2. The black curve represents $1 - S(\infty)$ values at the baseline values for the parameters γ_1, γ_2, β_1, β_2. The box plots represent 250 parameter points obtained by LHS maximin criteria for these parameters, based on their associated probability distributions. The nonlinear equations for the final size relations are solved using the nleqslv of R. The outside lines on the boxplots represent the first and third quartiles, while the middle line represents the median; the bottom and top whiskers represent the smallest value within 1st quartile $- 1.5 \times$ IQR and the largest value within 3rd quartile $+ 1.5 \times$ IQR respectively, and outliers are omitted from this plot.

Using the final size relationships above, the final size $1 - S(\infty)$ of the outbreak is obtained, in the case that a few infectious individuals are introduced into a completely susceptible population; thus, we assume that $E(0) = I_1(0) = I_2(0) = L_1(0) = T_1(0) = T_2(0) = T_3(0) \approx 0$. Since very few infectious individuals are introduced to a susceptible population, $S(0) \approx 1$. Thus, (10) results in the system of four equations in four unknowns as given in the theorem statement. □

Solving the final size relations given in Theorem 10 using parameter values presented in Table 2, $S(\infty) = 0.12547$, $T_1(\infty) = 0.27553$, $T_2(\infty) = 0.31102$ and $T_3(\infty) = 0.28798$. However, as previously mentioned, since the values of τ_1 and τ_2 may be controlled, we generate surface and contour plots of $1 - S(\infty)$ (which represents the final outbreak size). The values of $1 - S(\infty)$ as τ_1, τ_2 are varied are given in Fig. 4.

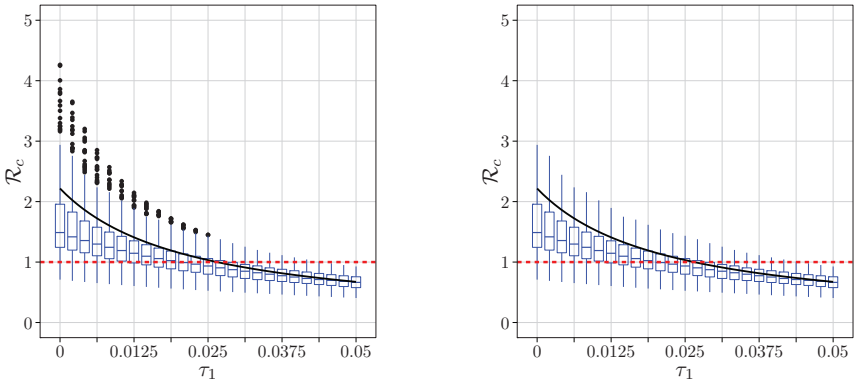
Fig. 4 illustrates how the final disease outbreak size $1 - S(\infty)$ changes as τ_1 and τ_2 are varied, while all other parameters are kept at baseline values (presented in Table 2). However, these parameter values are estimates; thus, using LHS maximin criteria (as in the previous section), we perform uncertainty analyses. We assign probability distributions to parameters, as previously done, and use LHS maximin criteria to obtain 250 samples from the feasible parameter region. Then, since we are especially interested in how $1 - S(\infty)$ changes as τ_1 varies (*i.e.*, the impact of early treatment on the epidemic), we compute $1 - S(\infty)$ at each sample point for fixed τ_1 values, and generate box plots at subsequent τ_1 values to illustrate the distribution of the sample points. This is presented in Fig. 5. Note that no data points are presented for $\tau_1 = 0$ or $\tau_2 = 0$ because the final size equations require that both τ_1, $\tau_2 > 0$. Fig. 5 (b) and (c) show values of τ_1, τ_2 for syphilis eradication; see also Fig. 4, and confirm the importance of treatment in the primary stage. Although there is considerable variation in the final size values, Fig. 5 confirms that our baseline parameter values are reasonable.

8. Concluding remarks

We first formulated an ODE model for the transmission of syphilis by the bacterium *Treponema pallidum* subspecies *pallidum* in an MSM population. We separated the males based on their stage of infection, and included the primary, secondary, early latency, late latency, and the tertiary stages of syphilis. We also incorporated treated classes at all stages except the tertiary one. We then proceeded to calculate the control reproduction number $\mathcal{R}_c$, which is a threshold parameter for our model. If $\mathcal{R}_c < 1$, we proved that the disease-free equilibrium is globally asymptotically stable; that is, the disease dies out. Otherwise, if $\mathcal{R}_c > 1$, the disease persists and admits a unique endemic equilibrium. We showed that for any fixed parameter values, there always exists a treatment rate for the primary stage that results in disease eradication; however this may not be the case for the secondary stage. Moreover, if the treatment rates in the later stages of the disease (*i.e.*, early and late latency) are higher, then the endemic equilibrium has more individuals present in the primary and secondary stages, which is the opposite of public health aims. While we show that global asymptotic stability for all parameter values is impossible, for certain parameter restrictions (for various possible biological cases) we prove the global asymptotic stability of this endemic equilibrium with $\mathcal{R}_c$ acting as a sharp threshold.

We then proceeded to various numerical approaches. First, we computed elasticity indices of $\mathcal{R}_c$ for each parameter, to determine local behavior of $\mathcal{R}_c$ at the baseline parameters, estimated from the literature. We also investigated the effect of treatment rates in the primary and secondary stages on $\mathcal{R}_c$, and this provided possible treatment rates that would lead to the eradication of syphilis, given that the baseline estimates are accurate. We also investigated the robustness of $\mathcal{R}_c$ to our baseline values by using Latin Hypercube Sampling maximin criteria to sample the parameter space for all disease parameters in $\mathcal{R}_c$ with fixed treatment rates. This showed that, while variation was present, our baseline estimates were reasonably accurate.

Lastly, we modified our endemic model into an epidemic one; that is, we assumed the population was closed and there was no return to susceptibility. With this model, the disease eventually dies out, and we numerically simulated the final outbreak size for varying treatment rates. Graphical results illustrated the greater benefit of increasing treatment in the primary stage compared to that of increasing treatment in the secondary stage. This reinforces results from our endemic model showing that early treatment is important to control syphilis in an MSM population. This conclusion agrees with those found from other models in the literature, for example, Garnett et al. [13] and Iboi and Okuonghae [18]. Thus reliable diagnostic tests to detect syphilis in its primary stage are crucial to disease control.



(a) With outliers (b) Without outliers

Fig. 6. Values of $\mathcal{R}_c$ as of function of τ_1 for fixed $\tau_2 = 0.05$. These graphs are identical to Fig. 3 (f), however (a) has outliers present. These outliers represent values that lie outside the whiskers. Note the scale change in $\mathcal{R}_c$ from Fig. 3 (f) to include all outliers.

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Appendix

As mentioned in Section 6, using LHS lower treatment rates in the primary stage give more outliers for $\mathcal{R}_c$. These outliers are shown in Fig. 6(a), with Fig. 6(b) given for comparison.

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