Mathematics of a sex-structured model for syphilis transmission dynamics

A. B. Gumel[1]*, J. M. -S. Lubuma [2]†, O. Sharomi [3]‡and Y. A. Terefe[2]§

[1] School of Mathematical and Statistical Sciences, Arizona State University, Tempe, AZ 85287, USA

[2] Department of Mathematics and Applied Mathematics, University of Pretoria, Pretoria 0002, South Africa

[3] Department of Applied Mathematics and Sciences, Khalifa University of Science and Technology, Abu Dhabi, 127788, UAE

Abstract

Syphilis, a major sexually-transmitted disease, continues to pose major public health burden in both under-developed and developed nations of the world. This study presents a new two-group sex-structured model for assessing the community-level impact of treatment and condom use on the transmission dynamics and control of syphilis. Rigorous analysis of the model shows that it undergoes the phenomenon of backward bifurcation. In the absence of this phenomenon (which is shown to arise due to the re-infection of recovered individuals), the disease-free equilibrium of the model is shown to be globally-asymptotically stable (GAS) when the associated reproduction number is less than unity. Furthermore, the model can have multiple endemic equilibria when the reproduction threshold exceeds unity. Numerical simulations of the model, using data relevant to the transmission dynamics of the disease in Nigeria, show that, with the assumed 80% condom efficacy, the disease will continue to persist (i.e., remain endemic) in the population regardless of the level of compliance in condom usage by males. Furthermore, detailed optimal control analysis (using Pontraygin's Maximum

*email: agumel@asu.edu

†Corresponding author email: jean.lubuma@up.ac.za

‡email: oluwaseun.sharomi@kustar.ac.ae

§email: yibeltal.terefe@up.ac.za

Principle) reveals that, for situations where the cost of implementing the controls (treatment and condom-use) considered in this study is low, channelling resources to a treatment-only strategy is more effective than channelling them to a condom-use only strategy. Furthermore, as expected, the combined condom-treatment strategy provides a higher population-level impact than the treatment-only strategy or the condom-use only strategy. When the cost of implementing the controls is high, the three strategies are essentially equally as ineffective.

Keywords: Syphilis; reproduction number; re-infection; stability; bifurcation.
AMS Subject Classification: 34A34, 37N25, 92B05, 92D30

1 Introduction

Syphilis, a sexually-transmitted disease (STD), caused by the bacteria *Treponema Pallidum* continues to pose a major public health challenge in both the developing and developed parts of the world [1, 2, 4, 8]. The disease accounts for about 12-13 million infections globally [8] and close to 200,000 fatalities every year [63] (the incidence rate for syphilis varies from country -to-country, ranging from 3.5 to 30 *per* 100,000 in countries like Denmark, Germany, The Netherlands and the United Kingdom [10]) (Data for developing countries are hardly available, though we could find some for Nigeria in [11]). Furthermore, studies from the World Health Organization (WHO) show that a significant number of pregnant women (about 2 million) acquire syphilis infection every year [8] (and mother-to-fetus transmission occurs in 80% of cases [3, 5, 6, 8]).

Syphilis, tagged the "*great imitator*" by Sir William Olser [46], spreads through direct contact with sores created by the bacteria. The infection progresses through multiple stages when left untreated, namely primary stage of infection (usually lasting between 3 and 6 weeks), secondary stage (usually lasting between 4 and 10 weeks), latent stage (usually lasting between 10 weeks and 2 years) and the late (tertiary) stage of infection (usually lasting over two years) [10, 27]. The point of syphilis contamination is portrayed by an ulcerative chancre flagging the start of the primary stage of the disease [10]. The secondary stage of infection is characterized by multiple symptoms, especially fever, lymphadenopathy, skin rash and genital or perinea condyloma latum [10]. The latent stage of infection is where damage to internal organ is possible, causing serious health complications which can lead to death [10]. In the latent stage, all clinical manifestations subside and the infection is apparent only on serologic testing [10]. The late (tertiary) stage of infection can manifest as gummatous disease, cardiovascular disease or central nervous system involvement [10]. Syphilis infection can be treated by using antibiotics, such as *penicillin*, at any stage of the infection [10] (in fact, in its early stages, the disease can be cured with a single injection of this drug. Infected individuals who have syphilis longer than a year may require additional doses).

Infected individuals who recovered from syphilis infection do not acquire permanent immunity against re-infection [9, 24, 35] (hence, re-infection and relapse of infected individuals who have recovered from syphilis infection after treatment, can occur at any stages of the infection [32, 61, 65].

Mathematical and statistical models of infectious diseases have, historically, provided useful insight into the transmission dynamics and control of infectious diseases. However, for syphilis, very few such models have been designed and used to help to understand its complex transmission dynamics and to evaluate the contribution of any proposed interventions before they are implemented [18]. A basic mathematical model that assumes infected individuals acquire temporary immunity only after recovery from the latent and tertiary infections was designed and analysed by Garnett *et.al.* [18]. Grassly *et. al.* [38] were able to fit an SIR model for syphilis for more than 65 US cities between 1941-2002 using realistic data set. Another mathematical model that includes inoculation and behavioral patterns as control while emphasizing that secondary and later syphilis infections confer immunity was designed and analysed by Milner and Zhao [25]. Oxman *et. al.* [28] used multicompartment iterative computer simulation with empirically derived input data to simulate and ascertain behavioral and sociological features necessary to produce epidemic transmission. Iboi and Okuonghae [20] designed and analysed a mathematical model for the transmission dynamics of syphilis that incorporates early and late latent stages of syphilis infection, reversions of early latent syphilis to the primary and secondary stages as well as the three potential outcomes that emanate from the late latent stage of infection while Saad-Roy *et.al.* [29] developed a deterministic model for syphilis transmission in gay men population. This study presents a new, two-group, deterministic, sex-structured mathematical model for gaining insight into the transmission dynamics of syphilis in a population. The model is based on the following main assumptions:

1. For mathematical convenient, the primary and secondary stages of infection are lumped together (and are referred to as "early stage of infection"). Furthermore, the latent and tertiary stages of infection are lumped together (and are referred to as "late stage of infection").

2. Individuals in both ("early" and "late") disease stages, including those who failed treatment, are assumed to be capable of transmitting the disease.

3. Re-infection and disease relapse in recovered individuals occur [**9, 10, 24, 32, 35, 61, 65**].

The paper is organized as follows. The model is formulated in Section 2, and its qualitative features are analysed in Section 3. Detailed sensitivity and uncertainty analyses of the reproduction number of the model are carried out in Section 4. Similarly, optimal control analysis is carried out in Section 5. This is followed by discussion and concluding remarks in Section 6.

2 Model Formulation

The total sexually-active population at time t, denoted by $N(t)$, is divided into the total male ($N_m(t)$) and female ($N_f(t)$) population. The total female population is further sub-divided into five mutually-exclusive compartments of susceptible females ($S_F(t)$), infected females in the early stage ($I_{FE}(t)$), infected females in the late stage ($I_{FL}(t)$), treated females who failed treatment ($Q_F(t)$) and treated females who recovered from the infection ($R_F(t)$). Similarly, the total male population is sub-divided into susceptible males ($S_M(t)$), infected males in the early stage ($I_{ME}(t)$), infected males in the late stage ($I_{ML}(t)$), treated males who failed treatment ($Q_M(t)$) and treated males who recovered from the infection ($R_M(t)$). Thus,

$$\begin{aligned} N(t) &= N_F(t) + N_M(t), \\ N_F(t) &= S_F(t) + I_{FE}(t) + I_{FL}(t) + Q_F(t) + R_F(t), \\ N_M(t) &= S_M(t) + I_{ME}(t) + I_{ML}(t) + Q_M(t) + R_M(t). \end{aligned}$$

The susceptible populations (for both males and females) are increased by the recruitment of new sexually-active individuals (assumed susceptible) into the population at a rate $\Lambda_M(\Lambda_F)$ for males(females). Susceptible males acquire syphilis infection, following effective contact with infected females (i.e., those in the I_{FE}, I_{FL} and Q_F classes), at a rate λ_M, given by

$$\lambda_M(t) = (1-\epsilon_M c_M)\frac{p_M \beta_M}{N_F(t)}[I_{FE}(t) + \nu_F I_{FL}(t) + \xi_F Q_F(t)]. \tag{2.1}$$

Similarly, susceptible females acquire syphilis infection following effective contact with infected males (i.e., those in the I_{ME}, I_{ML} and Q_M classes) at a rate

$$\lambda_F(t) = (1-\epsilon_F c_F)\frac{p_F \beta_F}{N_M(t)}[I_{ME}(t) + \nu_M I_{ML}(t) + \xi_M Q_M(t)], \tag{2.2}$$

where the parameters ϵ_F and ϵ_M (with $0 < \epsilon_F, \epsilon_M < 1$) are the efficacy of condom use for females and males, respectively, while c_F and c_M (with $0 < c_F, c_M < 1$) represent, respectively, the proportion of females and males that use condoms consistently (i.e., they are compliance proportions). Hence, the terms $\epsilon_F c_F$ and $\epsilon_M c_M$ represent the overall effectiveness of condom use for susceptible females and males, respectively. The terms p_F and p_M are the probabilities of transmitting syphilis from male-to-female and female-to-male *per* contact, respectively. The parameters β_F and β_M are the average number of sexual partners for females and males, respectively. Thus, the terms $\kappa_F = \beta_F p_F$ and $\kappa_M = \beta_M p_M$ represent the effective contact rates for male-to-female and female-to-male transmission of syphilis, respectively. Furthermore, the modification parameters ν_F

and ν_M account for the assumed variability in the relative infectiousness of individuals in the I_{FL} and I_{ML} classes, in comparison to infected individuals in the I_{FE} and I_{ME} classes for females and males, respectively. Similarly, the modification parameters ξ_F and ξ_M account for the assumed variability in the relative infectiousness of individuals in the Q_F and Q_M classes, in comparison to infected individuals in the I_{FE} and I_{ME} classes for females and males, respectively.

Individuals in the I_{FE} and I_{ME} classes progress to the corresponding late stage (I_{FL} and I_{ML}) classes at rates σ_F and σ_M, respectively. Males and females are treated at rates τ_M and τ_F, respectively. A fraction, $f_F(f_M)$, of the treated individuals from the early stage of infection will recover, and move to the $R_F(R_M)$ class, while the remaining fraction, $(1-f_F)((1-f_M))$, will fail treatment and move to the $Q_F(Q_M)$ class. Individuals in the late stage of infection who eventually show symptoms of the disease are treated at a rate $\alpha_T\tau_F$ ($\alpha_T\tau_M$) for females (males), where α_T is the modification parameter for the variability in the treatment rate of individuals in the late stage of infection, in comparison to those in the early stage of infection. A fraction, $g_F(g_M)$, of the treated individuals in the late stage of infection, will recover and move to the class R_F (R_M), while the remaining fraction, $(1-g_F)((1-g_M))$, will fail treatment and move to the Q_F (Q_M) class. Individuals who have failed treatment will eventually be treated successfully at a rate $\eta_T\tau_F$ ($\eta_T\tau_M$) for females (males), and move to the R_F (R_M) class. The parameter $\eta_T < 1$ accounts for the assumed decrease in the recovery rate of individuals in the Q_F and Q_M classes, in comparison to successfully-treated individuals. Recovered individuals acquire re-infected at rates $\theta_F\lambda_F(t)$ and $\theta_M\lambda_M(t)$ for males and females, respectively (with $\theta_F > 0$ and $\theta_M > 0$ representing the re-infection parameters for males and females, respectively). Recovered individuals can relapse, and become infectious again, at a rate γ_F (γ_M).

Furthermore, natural mortality occurs in all epidemiological classes at a rate μ, while individuals in the I_{FL} and I_{ML} classes suffer an additional disease-induced mortality at rates δ_F and δ_M, for females and males, respectively. Combining all these definitions and assumptions, it follows that the model for the transmission of syphilis in a sexually-active population is given by the following system of differential equations (a flow diagram of the model is depicted in Figure 1, and the state variables and parameters of the model are tabulated in Table 1):

$$
\begin{aligned}
\frac{dS_F}{dt} &= \Lambda_F - (\lambda_F + \mu)S_F, \\
\frac{dI_{FE}}{dt} &= \lambda_F(S_F + \theta_F R_F) + \gamma_F R_F - (\sigma_F + \tau_F + \mu)I_{FE}, \\
\frac{dI_{FL}}{dt} &= \sigma_F I_{FE} - (\alpha_T \tau_F + \delta_F + \mu)I_{FL}, \\
\frac{dQ_F}{dt} &= (1 - f_F)\tau_F I_{FE} + (1 - g_F)\alpha_T \tau_F I_{FL} - (\eta_T \tau_F + \mu)Q_F, \\
\frac{dR_F}{dt} &= f_F \tau_F I_{FE} + g_F \alpha_T \tau_F I_{FL} + \eta_T \tau_F Q_F - \theta_F \lambda_F R_F - (\mu + \gamma_F)R_F, \\
\frac{dS_M}{dt} &= \Lambda_M - (\lambda_M + \mu)S_M, \\
\frac{dI_{ME}}{dt} &= \lambda_M(S_M + \theta_M R_M) + \gamma_M R_M - (\sigma_M + \tau_M + \mu)I_{ME}, \\
\frac{dI_{ML}}{dt} &= \sigma_M I_{ME} - (\alpha_T \tau_M + \delta_M + \mu)I_{ML}, \\
\frac{dQ_M}{dt} &= (1 - f_M)\tau_M I_{ME} + (1 - g_M)\alpha_T \tau_M I_{ML} - (\eta_T \tau_M + \mu)Q_M, \\
\frac{dR_M}{dt} &= f_M \tau_M I_{ME} + g_M \alpha_T \tau_M I_{ML} + \eta_T \tau_M Q_M - \theta_M \lambda_M R_M - (\mu + \gamma_M)R_M,
\end{aligned}
\tag{2.3}
$$

where λ_M and λ_F are as given in Equations (2.1) and (2.2), respectively. For the model (2.3), the following conservation law of sexual contacts holds:

$$
\beta_F N_F \;=\; \beta_M N_M, \text{so that, } \beta_M = \frac{\beta_F N_F}{N_M}. \tag{2.4}
$$

The analysis of the model (2.3) will be carried out with β_M replaced by the equation in (2.4). The model (2.3) complements other models for syphilis transmission dynamics in the literature (such as those in [18, 20, 25]), by, *inter alia*:

(i) Splitting the total population in terms of gender (males and females).

(ii) Allowing for the re-infection of individuals who recovered from the infection.

(iii) Allowing for the relapse of individuals who recovered from the infection.

The result below holds for the model (2.3).

Theorem 2.1 *All solutions of the model system* (2.3) *with positive initial data remain positive for all time* $t > 0$. *Furthermore, the model is a dynamical system on the region* $\Omega = \Omega_1 \cup \Omega_2 \subset \mathbb{R}^5_+ \times \mathbb{R}^5_+$

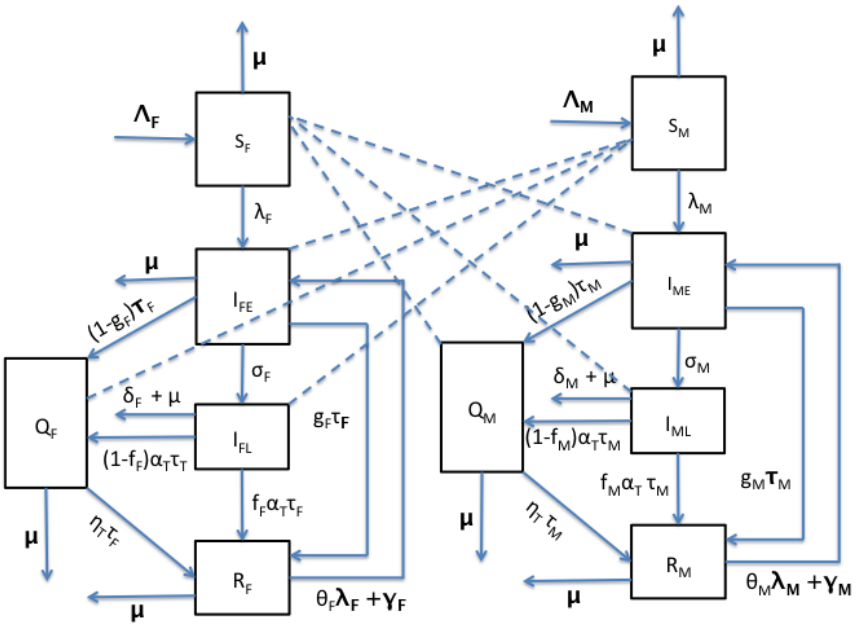

Figure 1: Schematic diagram of the model (2.3)

with,

$$\Omega_1 = \Big\{(S_F, I_{FE}, I_{FL}, Q_F, R_F) : S_F + I_{FE} + I_{FL} + Q_F + R_F = N_F \leq \Lambda_F/\mu\Big\},$$

$$\Omega_2 = \Big\{(S_M, I_{ME}, I_{ML}, Q_M, R_M) : S_M + I_{ME} + I_{ML} + Q_M + R_M = N_M \leq \Lambda_M/\mu\Big\},$$

and the region Ω *is attracting with respect to the model (2.3) with initial conditions in* $\mathbb{R}^{10}_+$.

The proof of Theorem 2.1 is given in Appendix A. Thus, it is sufficient to consider the dynamics of the flow generated by the model (2.3) in Ω ([64]).

3 Mathematical Analysis

3.1 Asymptotic Stability of Disease-free Equilibrium (DFE)

The DFE of the model (2.3) is given by

$$\mathcal{E}_0 = (S_F^*, I_{FE}^*, I_{FL}^*, Q_F^*, R_F^*, S_M^*, I_{ME}^*, I_{ML}^*, Q_M^*, R_M^*) = \left(\frac{\Lambda_F}{\mu}, 0, 0, 0, 0, \frac{\Lambda_M}{\mu}, 0, 0, 0, 0\right).$$

The local stability of $\mathcal{E}_0$ will be explored using the next generation operator method [34]. Using the notation in [34, 37], the non-negative matrix, F, of new infection terms and the M-matrix, V, of transition terms associated with the model (2.3) are

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & x_F & x_F\nu_M & x_F\xi_M & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ x_M & x_M\nu_F & x_M\xi_F & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$V = \begin{pmatrix} k_1 & 0 & 0 & -\gamma_F & 0 & 0 & 0 & 0 \\ -\sigma_F & k_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ -(1-f_F)\tau_F & -(1-g_F)\alpha_T\tau_F & k_3 & 0 & 0 & 0 & 0 & 0 \\ -f_F\tau_F & -g_F\alpha_T\tau_F & -\eta_T\tau_F & k_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & k_5 & 0 & 0 & -\gamma_M \\ 0 & 0 & 0 & 0 & -\sigma_M & k_6 & 0 & 0 \\ 0 & 0 & 0 & 0 & -(1-f_M)\tau_M & -(1-g_M)\alpha_T\tau_M & k_7 & 0 \\ 0 & 0 & 0 & 0 & -f_M\tau_M & -g_M\alpha_T\tau_M & -\eta_T\tau_M & k_8 \end{pmatrix},$$

where,

$$\begin{aligned} x_F &= \frac{(1-\epsilon_F c_F)p_F\beta_F\Lambda_F}{\Lambda_M}, \quad x_M = \frac{(1-\epsilon_M c_M)p_M\beta_M\Lambda_M}{\Lambda_F}. \\ k_1 &= \sigma_F + \tau_F + \mu, \quad k_2 = \alpha_T\tau_F + \delta_F + \mu, \quad k_3 = \eta_T\tau_F + \mu, \quad k_4 = \mu + \gamma_F, \\ k_5 &= \sigma_M + \tau_M + \mu, \quad k_6 = \alpha_T\tau_M + \delta_M + \mu, \quad k_7 = \eta_T\tau_M + \mu, \quad k_8 = \mu + \gamma_M. \end{aligned}$$

It follows that the *basic reproduction number* of the model (2.3), denoted by $\mathcal{R}_0 = \rho(FV^{-1})$ (where ρ denotes the spectral radius), is given by

$$\mathcal{R}_0 = \sqrt{\mathcal{R}_F\mathcal{R}_M},$$

where,

$$\mathcal{R}_F = \frac{(1-\epsilon_F c_F)p_F\beta_F k_4 T_F}{T_{F1}+T_{F2}} \text{ and } \mathcal{R}_M = \frac{(1-\epsilon_M c_M)p_M\beta_M k_8 T_M}{T_{M1}+T_{M2}},$$

with,

$$\begin{aligned}
T_F &= \tau_F\xi_F[k_2(1-f_F)+\alpha_T\sigma_F(1-g_F)]+k_3(k_2+\nu_F\sigma_F),\\
T_{F1} &= k_2\{\mu^3+[\sigma_F+\gamma_F+\tau_F(1+\eta_T)]\mu^2+[\eta_T(\tau_F+\sigma_F+\gamma_F)+\gamma_F(1-f_F)]\tau_F\mu\},\\
T_{F2} &= \gamma_F\sigma_F\{\mu^2+[\delta_F+\eta_T\tau_F+\tau_F\alpha_T(1-g_F)]\mu+\eta_T\tau_F\delta_F\},\\
T_M &= \tau_M\xi_M[k_6(1-f_M)+\alpha_T\sigma_M(1-g_M)]+k_7(k_6+\nu_M\sigma_M),\\
T_{M1} &= k_6\{\mu^3+[\sigma_M+\gamma_M+\tau_M(1+\eta_T)]\mu^2+[\eta_T(\tau_M+\sigma_M+\gamma_M)+\gamma_M(1-f_M)]\tau_M\mu\},\\
T_{M2} &= \gamma_M\sigma_M\{\mu^2+[\delta_M+\eta_T\tau_M+\tau_M\alpha_T(1-g_M)]\mu+\eta_T\tau_M\delta_M\}.
\end{aligned}$$

The result below follows from Theorem 2 in [34].

Lemma 3.1 *The DFE of the model* (2.3)*, given by* $\mathcal{E}_0$*, is locally-asymptotically stable (LAS) if* $\mathcal{R}_0 < 1$*, and unstable if* $\mathcal{R}_0 > 1$*.*

The threshold quantity $\mathcal{R}_0$ measures the average number of new syphilis infections generated by a single infected individual in a completely susceptible population [14, 30, 34]. It is the geometric mean of the reproduction numbers for females ($\mathcal{R}_F$) and males ($\mathcal{R}_M$). In particular $\mathcal{R}_F$ ($\mathcal{R}_M$) represents the average number of new syphilis infections in the female (male) population generated by a single infected male (female) introduced into a completely susceptible female (male) population. The square root in the expression for $\mathcal{R}_0$ in (3.1) is due to the fact that two generations (males-females-males) are needed to complete the syphilis transmission cycle.

Lemma 3.1 implies that syphilis can be effectively controlled in (or eliminated from) the community (when $\mathcal{R}_0 < 1$) if the initial sizes of the subpopulations of the model are in the basin of attraction of the DFE ($\mathcal{E}_0$). To ensure that disease elimination is independent of the initial sizes of the sub-populations, it is necessary to show that the DFE is globally-asymptotically stable (GAS) if $\mathcal{R}_0 < 1$. This is explored, for a special case, in Section 3.2.2.

3.2 Backward Bifurcation Analysis

3.2.1 Existence of backward bifurcation

Before investigating the global asymptotic stability of the DFE, it is instructive to determine the number of equilibrium solutions the model (2.3) can have. Let

$$\mathcal{E}_1 = (S_F^{**}, I_{FE}^{**}, I_{FL}^{**}, Q_F^{**}, R_F^{**}, S_M^{**}, I_{ME}^{**}, I_{ML}^{**}, Q_M^{**}, R_M^{**})$$

be any arbitrary equilibrium of the model (2.3). Furthermore, let

$$\begin{aligned} \lambda_F^{**} &= (1-\epsilon_F c_F)\frac{p_F \beta_F}{N_M^{**}}\left(I_{ME}^{**} + \nu_M I_{ML}^{**} + \xi_M Q_M^{**}\right), \\ \lambda_M^{**} &= (1-\epsilon_M c_M)\frac{p_M \beta_M}{N_F^{**}}\left(I_{FE}^{**} + \nu_F I_{FL}^{**} + \xi_F Q_F^{**}\right), \end{aligned} \tag{3.1}$$

be the associated infection rates ("*force of infection*") for females and males, respectively, at steady-state. To find conditions for the existence of an equilibrium for which syphilis infection is endemic in the population (i.e., the scenario where at least one of $I_{FE}^{**}, I_{FL}^{**}, Q_F^{**}, I_{ME}^{**}, I_{ML}^{**}$ and Q_M^{**} is non-zero), the equations of the model (2.3) are solved in terms of the aformentioned infection rates at steady-state (λ_F^{**} and λ_M^{**}). Setting the right-hand sides of the equations of the model (2.3) to zero (at steady-state) gives:

$$\begin{aligned} S_F^{**} &= \frac{\Lambda_F}{\lambda_F^{**}+\mu}, \quad I_{FE}^{**} = \frac{\lambda_F^{**}(a_{11}\lambda_F^{**}+a_{12})}{(\lambda_F^{**}+\mu)(C_1\lambda_F^{**}+C_2)}, \quad I_{FL}^{**} = \frac{\lambda_F^{**}(a_{21}\lambda_F^{**}+a_{22})}{(\lambda_F^{**}+\mu)(C_1\lambda_F^{**}+C_2)}, \\ Q_F^{**} &= \frac{\lambda_F^{**}(a_{31}\lambda_F^{**}+a_{32})}{(\lambda_F^{**}+\mu)(C_1\lambda_F^{**}+C_2)}, \quad R_F^{**} = \frac{a_{41}\lambda_F^{**}}{(\lambda_F^{**}+\mu)(C_1\lambda_F^{**}+C_2)}, \\ S_M^{**} &= \frac{\Lambda_M}{\lambda_M^{**}+\mu}, \quad I_{ME}^{**} = \frac{\lambda_M^{**}(b_{11}\lambda_M^{**}+b_{12})}{(\lambda_M^{**}+\mu)(D_1\lambda_F^{**}+D_2)}, \quad I_{ML}^{**} = \frac{\lambda_M^{**}(b_{21}\lambda_M^{**}+b_{22})}{(\lambda_M^{**}+\mu)(D_1\lambda_M^{**}+D_2)}, \\ Q_M^{**} &= \frac{\lambda_M^{**}(b_{31}\lambda_M^{**}+b_{32})}{(\lambda_M^{**}+\mu)(D_1\lambda_M^{**}+D_2)}, \quad R_M^{**} = \frac{b_{41}\lambda_M^{**}}{(\lambda_M^{**}+\mu)(D_1\lambda_M^{**}+D_2)}, \end{aligned} \tag{3.2}$$

where,

$$
\begin{aligned}
&a_{11} = k_2k_3\Lambda_F\theta_F,\ \ a_{12} = k_2k_3\Lambda_Fk_4,\ \ a_{21} = k_3\sigma_F\Lambda_F\theta_F,\ \ a_{22} = k_3\sigma_F\Lambda_Fk_4,\\
&a_{31} = \Lambda_F\tau_F[k_2(1-f_F)+\sigma_F\alpha_T(1-g_F)]\theta_F,\ \ a_{32} = \Lambda_F\tau_F[k_2(1-f_F)+\sigma_F\alpha_T(1-g_F)]k_4,\\
&a_{41} = \Lambda_F\tau_F[\alpha_T\eta_T\sigma_F\tau_F(1-g_F)+\eta_T\tau_Fk_2(1-f_F)+f_Fk_2k_3+g_F\alpha_T\sigma_Fk_3],\ \ D_b = T_{M1}+T_{M2},\\
&b_{11} = k_6k_7\Lambda_M\theta_M,\ \ b_{12} = k_6k_7\Lambda_Mk_8,\ \ b_{21} = k_7\sigma_M\Lambda_M\theta_M,\ \ b_{22} = k_7\sigma_M\Lambda_Mk_8,\\
&b_{31} = \Lambda_M\tau_M[k_6(1-f_M)+\sigma_M\alpha_T(1-g_M)]\theta_M,\ \ b_{32} = \Lambda_M\tau_M[k_6(1-f_M)+\sigma_M\alpha_T(1-g_M)]k_8,\\
&b_{41} = \Lambda_M\tau_M[\alpha_T\eta_T\sigma_M\tau_M(1-g_M)+\eta_T\tau_Mk_6(1-f_M)+f_Mk_6k_7+g_M\alpha_T\sigma_Mk_7],\ \ C_b = T_{F1}+T_{F2},\\
&C_a = \theta_F[k_1k_2k_3+f_Fk_2k_3\tau_F+g_F\alpha_Tk_3\sigma_F\tau_F-\alpha_T\eta_T\sigma_F\tau_F^2(1-g_F)-\eta_Tk_2\tau_F(1-f_F)],\\
&D_a = \theta_M[k_5k_6k_7+f_Mk_6k_7\tau_M+g_M\alpha_Tk_7\sigma_M\tau_M-\alpha_T\eta_T\sigma_M\tau_M^2(1-g_M)-\eta_Tk_6\tau_M(1-f_M)].
\end{aligned}
\tag{3.3}
$$

Substituting (3.2) with (3.3) into the expressions for λ_F^{**} and λ_M^{**} in (3.1), and simplifying, gives

$$
\lambda_M^{**} = \frac{\lambda_F^{**}(c_{11}\lambda_F^{**}+c_{12})}{c_{13}(\lambda_F^{**})^2+c_{14}\lambda_F^{**}+c_{15}}\ \text{ and }\ \lambda_F^{**} = \frac{\lambda_M^{**}(c_{21}\lambda_M^{**}+c_{22})}{c_{23}(\lambda_M^{**})^2+c_{24}\lambda_M^{**}+c_{25}},
\tag{3.4}
$$

where,

$$
\begin{aligned}
&c_{11} = (1-\epsilon_Mc_M)p_M\beta_M(a_{11}+\nu_Fa_{21}+\xi_Fa_{31}),\ \ c_{12} = (1-\epsilon_Mc_M)p_M\beta_M(a_{12}+\nu_Fa_{22}+\xi_Fa_{32}),\\
&c_{13} = a_{11}+a_{21}+a_{31},\ \ c_{14} = \Lambda_FC_a+a_{12}+a_{22}+a_{32}+a_{41},\ \ c_{15} = \Lambda_FC_b,\\
&c_{21} = (1-\epsilon_Fc_F)p_F\beta_F(b_{11}+\nu_Mb_{21}+\xi_Mb_{31}),\ \ c_{22} = (1-\epsilon_Fc_F)p_F\beta_F(b_{12}+\nu_Mb_{22}+\xi_Mb_{32}),\\
&c_{23} = b_{11}+b_{21}+b_{31},\ \ c_{24} = \Lambda_MD_a+b_{12}+b_{22}+b_{32}+b_{41},\ \ c_{25} = \Lambda_MD_b,
\end{aligned}
\tag{3.5}
$$

so that the non-zero (endemic) equilibria of the model (2.3) satisfy:

$$
D_1(\lambda_M^{**})^4+D_2(\lambda_M^{**})^3+D_3(\lambda_M^{**})^2+D_4\lambda_M^{**}+D_5 = 0,
\tag{3.6}
$$

where,

$$
\begin{aligned}
D_1 &= c_{13}c_{21}^2+c_{14}c_{21}c_{23}+c_{15}c_{23}^2,\\
D_2 &= c_{23}(c_{14}c_{22}+2c_{15}c_{24})+c_{21}(c_{14}c_{24}+2c_{13}c_{22})-c_{11}c_{21}^2-c_{12}c_{23}c_{21},\\
D_3 &= c_{15}(c_{24}^2+2c_{23}c_{25})+c_{22}(c_{14}c_{24}-c_{12}c_{23})+c_{13}c_{22}^2+c_{21}(c_{14}c_{25}-2c_{11}c_{22}-c_{12}c_{24}),\\
D_4 &= 2c_{24}c_{25}c_{15}+c_{22}(c_{14}c_{25}-c_{12}c_{24})-c_{11}c_{22}^2-c_{25}c_{12}c_{21},\\
D_5 &= c_{15}c_{25}^2\left(1-\frac{c_{12}c_{22}}{c_{15}c_{25}}\right) = c_{15}c_{25}^2(1-\mathcal{R}_0^2).
\end{aligned}
\tag{3.7}
$$

It can be seen from (3.5) and (3.7) that $D_1 > 0$ (since all the model parameters are non-negative). Furthermore, $D_5 > 0$ whenever $\mathcal{R}_0^2 < 1$ ($\mathcal{R}_0 < 1$). Thus, the number of possible positive real roots the polynomial (3.6) can have depends on the signs of D_2, D_3 and D_4. This can be analyzed using the Descartes' Rule of Signs on the quartic $f(x) = D_1x^4 + D_2x^3 + D_3x^2 + D_4x + D_5$ (with $x = \lambda_M^{**}$). Hence, the following results are established.

Theorem 3.2 *The model* (2.3)

(a) *has a unique endemic equilibrium if* $\mathcal{R}_0 > 1$ *and either of the following holds*

- **(i)** $D_2 > 0, D_3 > 0, D_4 > 0$;
- **(ii)** $D_2 < 0, D_3 < 0, D_4 < 0$;
- **(iii)** $D_2 > 0, D_3 < 0, D_4 < 0$;
- **(iv)** $D_2 > 0, D_3 > 0, D_4 < 0$;

(b) *could have more than one endemic equilibrium if* $\mathcal{R}_0 > 1$ *and either of the following holds*

- **(i)** $D_2 < 0, D_3 > 0, D_4 < 0$;
- **(ii)** $D_2 < 0, D_3 < 0, D_4 > 0$;
- **(iii)** $D_2 > 0, D_3 < 0, D_4 > 0$;
- **(iv)** $D_2 < 0, D_3 > 0, D_4 > 0$;

(c) *could have 2 or more endemic equilibria if* $\mathcal{R}_0 < 1$ *and any, or all, of* D_2, D_3 *and* D_4 *are negative.*

Item (c) of Theorem 3.2 suggests the existence of multiple endemic equilibria when $\mathcal{R}_0 < 1$ (which is typically a signature for the existence of the phenomenon of backward bifurcation [10, 14, 20, 26]). The phenomenon of backward bifurcation, which is characterized by the co-existence of a stable DFE and a stable endemic equilibrium when the associated reproduction number of the model is less than unity, has been observed in numerous disease transmission models, such as those for (or with) vector-borne diseases [19, 30, 44, 45, 47, 48, 49], imperfect vaccination [39, 40, 41, 42, 43], multi-groups [50, 51] etc. The presence of this phenomenon in the model (2.3) is now formally explored.

Theorem 3.3 *The model* (2.3) *undergoes a backward bifurcation at* $\mathcal{R}_0 = 1$ *whenever (where the eigenvectors* v_2, v_7, $w_2, w_3, w_4, w_5, w_7, w_8, w_9, w_{10}$ *are defined in Appendix B)*

$$\theta_F(v_2 - v_5)w_5 - v_2\sum_{i=2}^{5} w_i > 0 \text{ and } \theta_M(v_7 - v_{10})w_{10} - v_7\sum_{i=7}^{10} w_i > 0.$$

The proof of Theorem 3.3, based on using center manifold theory [15, 32], is given in Appendix B (the associated backward bifurcation diagram is depicted in Figure 2). The epidemiological implication of Theorem 3.3 is that the classical epidemiological requirement of having $\mathcal{R}_0 < 1$, while necessary, is no longer sufficient for the effective control of (or elimination of) the disease in the community.

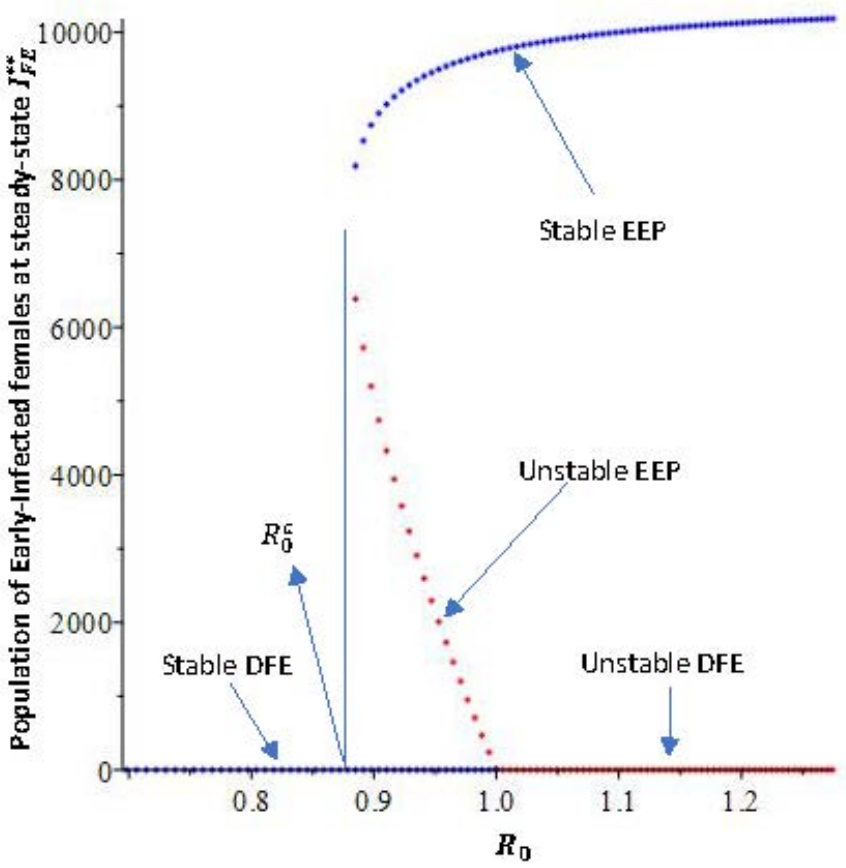

Figure 2: Backward bifurcation diagram of the model (2.3), showing the profile of I_{FE}^{**} as a function of $\mathcal{R}_0$. Parameter values used are: $\Lambda_F = 160, \mu = 0.1/70, \beta_F = 0.085, p_F = 0.9, c_F = 0.1, \nu_F = 1, \xi_F = 1, \theta_F = 0.4, \gamma_F = 0.975, \sigma_F = 0.012, \tau_F = 0.975, f_F = 0.975, g_F = 0.965, \alpha_T = 0.08, \eta_T = 1.5, \epsilon_F = 0.51, \delta_F = 10.9, \Lambda_M = 160, c_M = 0.1, \nu_M = 1, \xi_M = 1, \theta_M = 0.4, \gamma_M = 0.975, \sigma_M = 0.12, \tau_M = 0.975, \epsilon_M = 0.91, f_M = 0.975, g_M = 0.965, \delta_M = 10.9, \beta_M = \dfrac{0.085\Lambda_F}{\Lambda_M}$ (so that, $p_M^* = 0.2690300627$ and $a = 5.85501984 \times 10^5 > 0$).

3.2.2 Non-existence of backward bifurcation

Models that incorporate re-infection of recovered individuals are known to lose their backward bifurcation property when the re-infection parameters are set to zero (see, for instance, [19, 30, 51]). In this section, the role of the re-infection of recovered females (θ_F) and males (θ_M) on the backward bifurcation phenomenon of the model (2.3) will be investigated. It is convenient to define $\tilde{\mathcal{R}}_0 = \mathcal{R}_0|_{\theta_F=\theta_M=0}$.

Theorem 3.4 *The special case of the model* (2.3) *in the absence of re-infection of recovered individuals (i.e., $\theta_F = \theta_M = 0$) does not undergo a backward bifurcation at $\tilde{\mathcal{R}}_0 = 1$.*

The proof of Theorem 3.4, based on using center manifold theory, is given in Appendix C. The consequence of Theorem 3.4 is that this study confirms the fact that re-infection (of recovered individuals) does, indeed, cause backward bifurcation in syphilis transmission dynamics. To further confirm the absence of backward bifurcation in the model (when $\tilde{\mathcal{R}}_0 < 1$) for the special case of the model (2.3) with $\theta_F = \theta_M = 0$, a global asymptotic stability result is given for the DFE ($\mathcal{E}_0$).

Theorem 3.5 *The DFE of the special case of the model* (2.3) *with $\theta_F = \theta_M = 0$ is GAS in Ω whenever $\tilde{\mathcal{R}}_0 < 1$.*

The proof of Theorem 3.5, based on using a Comparison Theorem [22], is given in Appendix D (the result in Theorem 3.5 is numerically illustrated in Figure 3). The epidemiological implication of Theorem 3.5 is that, in the absence of re-infection (i.e., $\theta_F = \theta_M = 0$), syphilis will be effectively controlled in (or eliminated from) the community if the threshold quantity $\tilde{\mathcal{R}}_0$ can be brought to (and maintained at) a value less than unity.

3.3 Existence of Unique Endemic Equilibrium: Special Case

In this section, the possible existence of a unique endemic equilibrium of the model (2.3) will be explored, for the special case with no re-infection (i.e., $\theta_F = \theta_M = 0$). In the absence of re-infection of recovered individuals (i.e., $\theta_F = \theta_M = 0$), the coefficients D_i ($i = 1 \ldots 5$) in (3.7) reduce to

$$\begin{aligned} &D_1 = D_2 = 0, \quad D_3 = c_{15}c_{24}^2 + c_{22}c_{14}c_{24}, \\ &D_4 = 2c_{24}c_{25}c_{15} + c_{22}(c_{14}c_{25} - c_{12}c_{24}), \\ &D_5 = c_{15}c_{25}^2\left(1 - \frac{c_{12}c_{22}}{c_{15}c_{25}}\right) = c_{15}c_{25}^2[1 - (\tilde{\mathcal{R}}_0)^2]. \end{aligned} \tag{3.8}$$

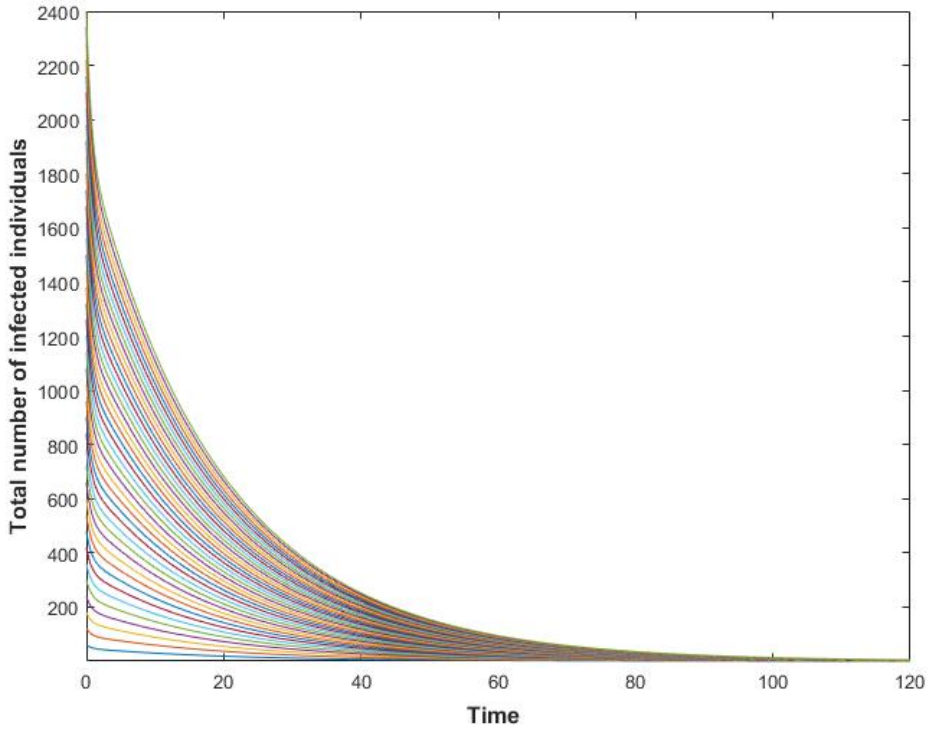

Figure 3: Simulation of the model, showing the total number of infected individuals as a function of time, using multiple initial conditions. Parameter values used are: $\Lambda_F = 160, \mu = 1/70, \beta_F = 0.1, p_F = 0.9, c_F = 0.5, \nu_F = 1, \xi_F = 1, \theta_F = 0, \gamma_F = 0.975, \sigma_F = 0.12, \tau_F = 0.5, f_F = 0.75, g_F = 0.65, \alpha_T = 0.08, \eta_T = 1.5, \epsilon_F = 0.51, \delta_F = 0.9, \Lambda_M = 160, c_M = 0.5, \nu_M = 1, \xi_M = 1, \theta_M = 0, \gamma_M = 0.975, \sigma_M = 0.12, \tau_M = 0.5, \epsilon_M = 0.91, f_M = 0.75, g_M = 0.65, \delta_M = 0.9, \beta_M = \dfrac{0.1\Lambda_F}{\Lambda_M}$ (so that, $\tilde{\mathcal{R}}_0 = 0.3975 < 1$).

Thus, the polynomial (3.6) now becomes

$$D_3(\lambda_M^{**})^2 + D_4\lambda_M^{**} + D_5 = 0. \tag{3.9}$$

Solving the quadratic (3.9) gives the roots $\lambda_M^{**} = -\dfrac{c_{25}}{c_{24}} < 0$ and $\lambda_M^{**} = \dfrac{c_{15}c_{25}[(\tilde{\mathcal{R}}_0)^2 - 1]}{c_{15}c_{24} + c_{14}c_{22}} < 0$ whenever $(\tilde{\mathcal{R}}_0)^2 < 1$ ($\tilde{\mathcal{R}}_0 < 1$). Hence, in this case (with $\theta_F = \theta_M = 0$), no endemic equilibrium exists whenever $(\tilde{\mathcal{R}}_0)^2 < 1$ ($\tilde{\mathcal{R}}_0 < 1$). Further, for $(\tilde{\mathcal{R}}_0)^2 > 1$ ($\tilde{\mathcal{R}}_0 > 1$), the roots $\lambda_M^{**} = -\dfrac{c_{25}}{c_{24}} < 0$ and $\lambda_M^{**} = \dfrac{c_{15}c_{25}[(\tilde{\mathcal{R}}_0)^2 - 1]}{c_{15}c_{24} + c_{14}c_{22}} > 0$ confirm the existence of a unique endemic equilibrium when $\tilde{\mathcal{R}}_0 > 1$. This result is summarised below.

Theorem 3.6 *In the absence of re-infection of recovered individuals (i.e., $\theta_F = \theta_M = 0$), the model (2.3) has a unique endemic equilibrium whenever $\tilde{\mathcal{R}}_0 > 1$, and no endemic equilibrium*

otherwise.

The result below follows from Theorem 3.4, Theorem 3.6 and Item (iv) of Theorem 4.1 in [15].

Theorem 3.7 *The unique endemic equilibrium of the special case of the model* (2.3)*, with* $\theta_F = \theta_M = 0$*, is LAS whenever* $\hat{\mathcal{R}}_0 > 1$ *and* $\hat{\mathcal{R}}_0$ *near 1.*

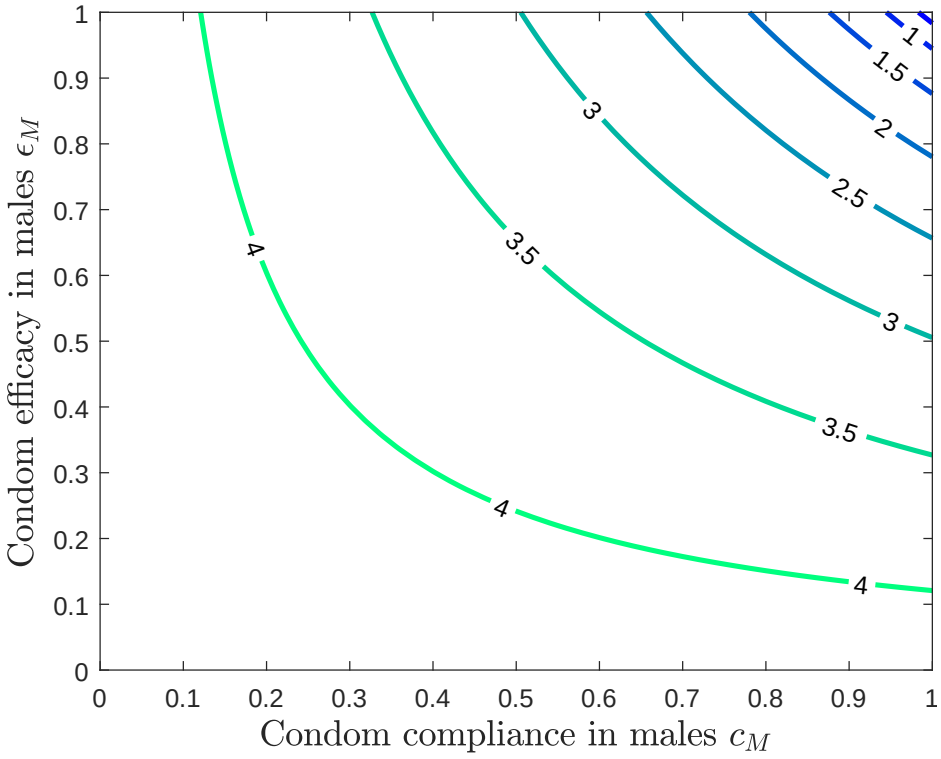

Figure 4: Contour plot of $\hat{\mathcal{R}}_0$ as a function of condom compliance (c_M) and efficacy (ϵ_M) in males.

4 Uncertainty and Sensitivity Analysis

The asymptotic analysis of most epidemiological models have dependably been based on the threshold quantity called the basic reproduction number, which can lead to uncertainties particularly when the model consists of many parameters. Another reason for uncertainties in these models is the absence of precision in the estimation of all associated parameters, error in collecting and interpreting data and natural variations. Thus, to determine the impact of the model parameters on

the transmission dynamics of the syphilis, an uncertainty and sensitivity analysis will be conducted using Latin Hypercube Sampling (LHS) and Partial Rank Correlation Coefficients (PRCCs) [60].

LHS is a statistical method for generating a sample of plausible collections of parameter values from a multidimensional distribution [60]. Using the range of plausible values for the thirty-one parameters of the model (2.3) (see Table 2 for the mean and associated distributions of these parameters), a sample of size $n = 10,000$ is obtained through LHS. LHS treats the model inputs (i.e., the model parameters), as random variables. Thus, appropriate probability distributions will be associated with each parameter. The analysis below assumes that the model inputs can take the form of uniform, gamma or normal distributions. The LHS procedure is implemented by dividing the range of values for each given parameter into equally probable, intervals and one selected at random from each interval with the objective of uniformly filling the input space [60].

PRCC is a robust sensitivity measure for nonlinear but monotonic relationships between input and output, as long as little to no correlation exists between the inputs [54]. PRCC is considered to be more powerful at determining the sensitivity of a parameter that is strongly monotonic yet highly nonlinear [55]. The analysis below uses PRCCs to assess the sensitivity of the output ($\mathcal{R}_0$) to that of the model input parameters. The magnitude, as well as the statistical significance, of the PRCC value of a parameter indicates that parameters contribution to the models prediction imprecision [60]. The parameters with large PRCC values (> 0.5 or < -0.5) are the most important [56]. Thus, a PRCC approaching -1 to +1 indicates a strong effect of the corresponding parameter to $\mathcal{R}_0$. The sign indicates the qualitative relationship between the parameter inputs and $\mathcal{R}_0$. A negative sign indicates that the LHS parameter is inversely proportional to the $\mathcal{R}_0$.

The analysis is completed using parameter values relevant to syphilis transmission dynamics in Nigeria [11], given in Table 2. The distribution of the mean value of $\mathcal{R}_0$ as a function of distributions of various parameters of the model reveals that the estimate of $\mathcal{R}_0$ for syphilis is approximately 4.44 with 95% CI. The probability that $\mathcal{R}_0 > 1$ for syphilis is given by 1. Hence, under the assumed conditions, syphilis will become endemic in the population.

Results from the sensitivity analyses of the model, using $\mathcal{R}_0$ as the response function, show (Figure 5) that the top five dominant parameters of the model are effective contact rate for females ($\kappa_F = \beta_F p_F$) and males ($\kappa_M = \beta_M p_M$), proportion of treated females(males) in the early stage who recovered from infection ($f_F(f_M)$), condom compliance in males (c_M) and the modification parameter for the assumed decrease in the recovery rate of individuals in the Q_F and Q_M classes, in comparison to successfully-treated individuals (η_T). **The implication of these analyses is that effective community-wide control of the disease can be achieved by minimizing the contact rates κ_F and κ_M (perhaps by implementing an effective public health education campaign to encourage safer sex practices within the sexually-active population), early**

detection and treatment of infected individuals (this can be achieved by devoting resources to monitoring infected individuals *via* contact tracing), encouraging and increasing condom compliance in the sexually-active male population (this can also be achieved *via* effective public health education campaign) and increase the recovery rate of individuals who failed treatment (by, perhaps, using better drugs and encouraging treated individuals to adhere to the prescribed treatment regimen). Thus, this study identifies key parameters that should be targeted for the design of effective public health strategy or policy for combatting the spread of syphilis in the community.

5 Optimal Control Analysis

In this section, an analysis to determine an optimal intervention strategy, based on the two controls (treatment and compliance to condom use), will be carried out. It is assumed that the treatment rate $\tau_F(\tau_M)$ and condom compliance rate $c_F(c_M)$ for females (males), are now time-dependent, and will therefore act as the control variables. Using these controls, the model (2.3) now becomes

$$\begin{aligned}
\frac{dS_F}{dt} &= \Lambda_F - (\lambda_F + \mu)S_F, \\
\frac{dI_{FE}}{dt} &= \lambda_F(S_F + \theta_F R_F) + \gamma_F R_F - k_1 I_{FE}, \\
\frac{dI_{FL}}{dt} &= \sigma_F I_{FE} - k_2 I_{FL}, \\
\frac{dQ_F}{dt} &= (1 - f_F)\tau_F(t) I_{FE} + (1 - g_F)\alpha_T \tau_F(t) I_{FL} - k_3 Q_F, \\
\frac{dR_F}{dt} &= f_F \tau_F(t) I_{FE} + g_F \alpha_T \tau_F(t) I_{FL} + \eta_T \tau_F(t) Q_F - \theta_F \lambda_F R_F - k_4 R_F, \\
\frac{dS_M}{dt} &= \Lambda_M - (\lambda_M + \mu)S_M, \\
\frac{dI_{ME}}{dt} &= \lambda_M(S_M + \theta_M R_M) + \gamma_M R_M - k_5 I_{ME}, \\
\frac{dI_{ML}}{dt} &= \sigma_M I_{ME} - k_6 I_{ML}, \\
\frac{dQ_M}{dt} &= (1 - f_M)\tau_M(t) I_{ME} + (1 - g_M)\alpha_T \tau_M(t) I_{ML} - k_7 Q_M, \\
\frac{dR_M}{dt} &= f_M \tau_M(t) I_{ME} + g_M \alpha_T \tau_M(t) I_{ML} + \eta_T \tau_M(t) Q_M - \theta_M \lambda_M R_M - k_8 R_M,
\end{aligned} \tag{5.1}$$

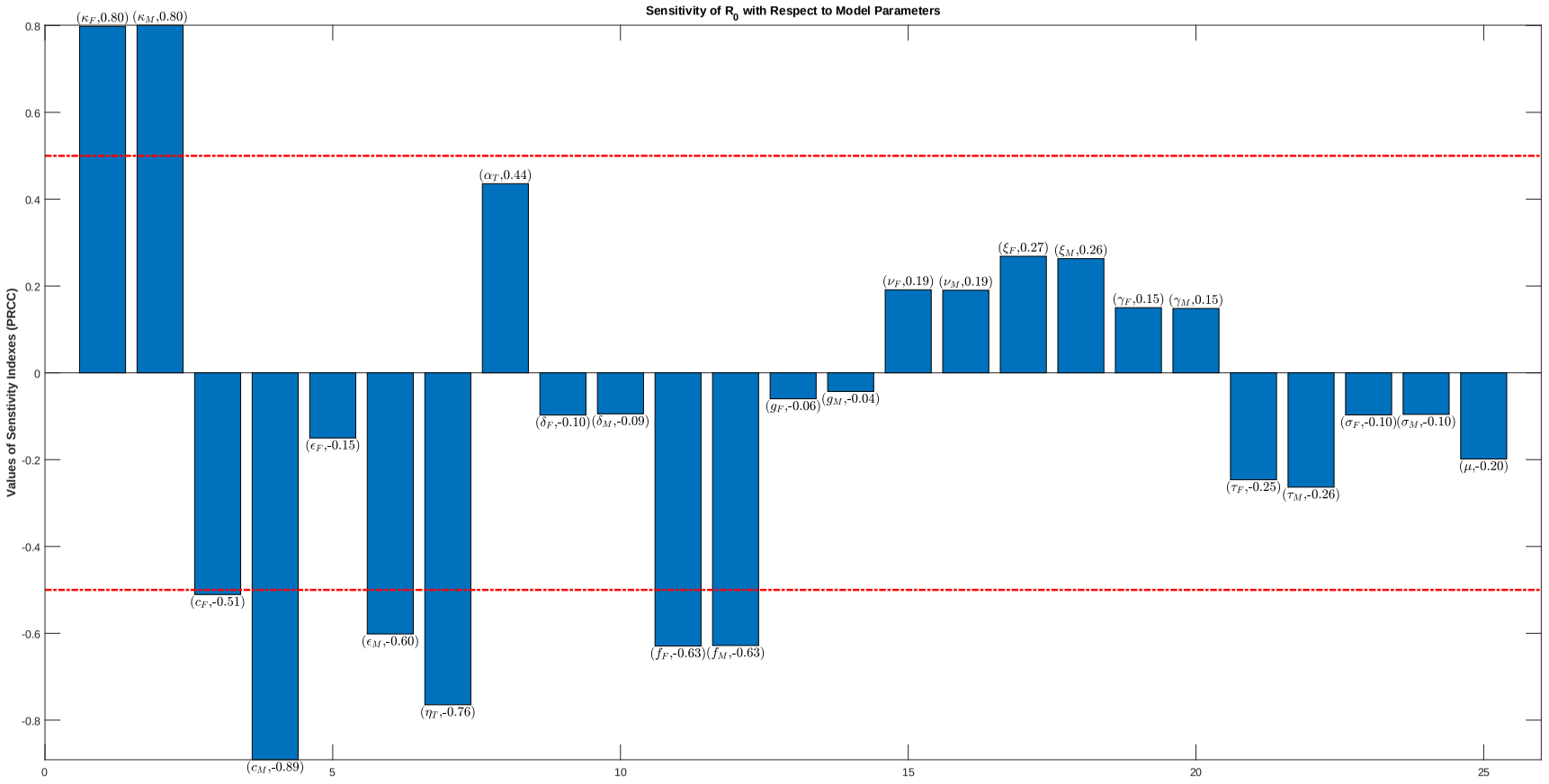

Figure 5: PRCC plots of the various parameters of the model sensitivity indexes of $\mathcal{R}_0$ with respect to the model parameters.

where,

$$\begin{aligned}
\lambda_F(t) &= [1-\epsilon_F c_F(t)]\frac{p_F\beta_F}{N_M(t)}[I_{ME}(t)+\nu_M I_{ML}(t)+\xi_M Q_M(t)],\ \ \beta_M=\frac{\beta_F N_F}{N_M},\\
\lambda_M(t) &= [1-\epsilon_M c_M(t)]\frac{p_M\beta_M}{N_F(t)}[I_{FE}(t)+\nu_F I_{FL}(t)+\xi_F Q_F(t)],\\
k_1 &= \sigma_F+\tau_F(t)+\mu,\ \ k_2=\alpha_T\tau_F(t)+\delta_F+\mu,\ \ k_3=\eta_T\tau_F(t)+\mu,\ \ k_4=\mu+\gamma_F,\\
k_5 &= \sigma_M+\tau_M(t)+\mu,\ \ k_6=\alpha_T\tau_M(t)+\delta_M+\mu,\ \ k_7=\eta_T\tau_M(t)+\mu,\ \ k_8=\mu+\gamma_M.
\end{aligned}$$

Consider the cost function:

$$\begin{aligned}
J[\tau_F,\tau_M,c_F,c_M] = \int_0^T \Big[&\omega_1 I_{FE}+\omega_2 I_{FL}+\omega_3 Q_F+\omega_4 I_{ME}+\omega_5 I_{ML}+\omega_6 Q_M\\
&+\frac{1}{2}\omega_7[\tau_F(t)]^2+\frac{1}{2}\omega_8[\tau_M(t)]^2+\frac{1}{2}\omega_9[c_F(t)]^2+\frac{1}{2}\omega_{10}[c_M(t)]^2\Big]dt.
\end{aligned} \tag{5.2}$$

Here, the parameters $\omega_i, (i=1,2,\ldots,10)$ are the weight factors to help balance each term in the integrand in (5.2), so that none of the terms dominates. The terms in the integrand in (5.2) are explained as follows:

(i) The term $\omega_1 I_{FE}+\omega_2 I_{FL}+\omega_3 Q_F+\omega_4 I_{ME}+\omega_5 I_{ML}+\omega_6 Q_M$ represents the cost associated with monitoring infected individuals in all stages.

(ii) The term $\omega_7[\tau_F(t)]^2+\omega_8[\tau_M(t)]^2$ represents the cost associated with all forms of treatment for all infected individuals.

(iii) The term $\omega_9[c_F(t)]^2+\omega_{10}[c_M(t)]^2$ represents the cost associated with the public health education campaign to educate the public on safer sex practice (condom compliance; correct and consistent usage).

The aim is to minimize the total number of infected females and males, while ensuring that the cost associated with the controls (condom use and treatment) are minimized. It is assumed that the costs of the controls are nonlinear and take quadratic form. The goal is to find an optimal quadruple $(\tau_F^*(t),\ \tau_M^*(t),\ c_F^*(t),\ c_M^*(t))$, such that

$$J[\tau_F^*,\tau_M^*,c_F^*,c_M^*] = \min_{\tau_F,\tau_M,c_F,c_M\in W} J[\tau_F,\tau_M,c_F,c_M],$$

where the control set (W) is defined as:

$$\begin{aligned}
W = \{&(\tau_F(t),\tau_M(t),c_F(t),c_M(t))\in L^1(0,t_f)|a_{11}\le\tau_F(t)\le a_{12}, a_{21}\le\tau_M(t)\le a_{22},\\
&b_{11}\le c_F(t)\le b_{12}, b_{21}\le c_M(t)\le b_{22}\}.
\end{aligned}$$

5.1 Analysis of Optimal Control

The Pontryagins Maximum Principle [53] gives the necessary conditions that the optimal control quadruple must satisfy. This principle converts Equations (5.1) and (5.2) into a problem of minimizing pointwise a Hamiltonian (H), with respect to the controls τ_F, τ_M, c_F and c_M, defined by:

$$\begin{aligned} H =& \omega_1 I_{FE} + \omega_2 I_{FL} + \omega_3 Q_F + \omega_4 I_{ME} + \omega_5 I_{ML} + \omega_6 Q_M \\ &+ \frac{1}{2}\omega_7[\tau_F(t)]^2 + \frac{1}{2}\omega_8[\tau_M(t)]^2 + \frac{1}{2}\omega_9[c_F(t)]^2 + \frac{1}{2}\omega_{10}[c_M(t)]^2 + \lambda_{S_F} g_1 + \lambda_{I_{FE}} g_2 \\ &+ \lambda_{I_{FL}} g_3 + \lambda_{Q_F} g_4 + \lambda_{R_F} g_5 + \lambda_{S_M} g_6 + \lambda_{I_{ME}} g_7 + \lambda_{I_{ML}} g_8 + \lambda_{Q_M} g_9 + \lambda_{R_M} g_{10}, \end{aligned} \tag{5.3}$$

where,

$$\begin{aligned} g_1 &= \Lambda_F - (\lambda_F + \mu)S_F, \\ g_2 &= \lambda_F(S_F + \theta_F R_F) + \gamma_F R_F - k_1 I_{FE}, \\ g_3 &= \sigma_F I_{FE} - k_2 I_{FL}, \\ g_4 &= (1 - f_F)\tau_F(t) I_{FE} + (1 - g_F)\alpha_T \tau_F(t) I_{FL} - k_3 Q_F, \\ g_5 &= f_F \tau_F(t) I_{FE} + g_F \alpha_T \tau_F(t) I_{FL} + \eta_T \tau_F(t) Q_F - \theta_F \lambda_F R_F - k_4 R_F, \\ g_6 &= \Lambda_M - (\lambda_M + \mu)S_M, \\ g_7 &= \lambda_M(S_M + \theta_M R_M) + \gamma_M R_M - k_5 I_{ME}, \\ g_8 &= \sigma_M I_{ME} - k_6 I_{ML}, \\ g_9 &= (1 - f_M)\tau_M(t) I_{ME} + (1 - g_M)\alpha_T \tau_M(t) I_{ML} - k_7 Q_M, \\ g_{10} &= f_M \tau_M(t) I_{ME} + g_M \alpha_T \tau_M(t) I_{ML} + \eta_T \tau_M(t) Q_M - \theta_M \lambda_M R_M - k_8 R_M, \end{aligned}$$

and $\lambda_{S_F}, \lambda_{I_{FE}}, \lambda_{I_{FL}}, \lambda_{Q_F}, \lambda_{R_F}, \lambda_{S_M}, \lambda_{I_{ME}}, \lambda_{I_{ML}}, \lambda_{Q_M}, \lambda_{R_M}$ are adjoint functions. By applying Pontryagin's Maximum Principle [53], and the existence result for the optimal control quadruple ($\tau_F^*(t)$, $\tau_M^*(t)$, $c_F^*(t)$, $c_M^*(t)$) [52], the following result holds:

Theorem 5.1 *There exists an optimal control quadruple $(\tau_F^*, \tau_M^*, c_F^*, c_M^*)$ and corresponding solution, $S_F^*, I_{FE}^*, I_{FL}^*, Q_F^*, R_F^*, S_M^*, I_{ME}^*, I_{ML}^*, Q_M^*$ and R_F^*, that minimizes $J[\tau_F, \tau_M, c_F, c_M]$ over W. Furthermore, there exists adjoint functions $\lambda_{S_F}, \lambda_{I_{FE}}, \lambda_{I_{FL}}, \lambda_{Q_F}, \lambda_{R_F}, \lambda_{S_M}, \lambda_{I_{ME}}, \lambda_{I_{ML}}, \lambda_{Q_M}, \lambda_{R_M}$, such that*

$$-\frac{d\lambda_j}{dt} = \frac{\partial H}{\partial j}, \tag{5.4}$$

with transversality conditions

$$\lambda_j(t_f) = 0, \text{ where } j = S_F, I_{FE}, I_{FL}, Q_F, R_F, S_M, I_{ME}, I_{ML}, Q_M, R_M. \tag{5.5}$$

Furthermore, the optimal control quadruple $(\tau_F^*, \tau_M^*, c_F^*, c_M^*)$ *satisfy the optimality conditions*

$$\begin{aligned} \tau_F^* &= \min\left\{a_{12}, \max\left(a_{11}, Z_1\right)\right\}, \quad \tau_M^* = \min\left\{a_{22}, \max\left(a_{21}, Z_2\right)\right\}, \\ c_F^* &= \min\left\{b_{11}, \max\left(b_{12}, Z_3\right)\right\}, \quad c_M^* = \min\left\{b_{21}, \max\left(b_{22}, Z_4\right)\right\}, \end{aligned} \tag{5.6}$$

where,

$$\begin{aligned} Z_1 &= \frac{I_{FE}[\lambda_{I_{FE}} - \lambda_{Q_F} + f_F(\lambda_{Q_F} - \lambda_{R_F})] + \alpha_T I_{FL}(\lambda_{I_{FL}} - \lambda_{Q_F}) + (\alpha_T I_{FL} g_F + \eta_T Q_F)(\lambda_{Q_F} - \lambda_{R_F})}{\omega_7}, \\ Z_2 &= \frac{I_{ME}[\lambda_{I_{ME}} - \lambda_{Q_M} + f_M(\lambda_{Q_M} - \lambda_{R_M})] + \alpha_T I_{ML}(\lambda_{I_{ML}} - \lambda_{Q_M}) + (\alpha_T I_{ML} g_M + \eta_T Q_M)(\lambda_{Q_M} - \lambda_{R_M})}{\omega_8}, \\ Z_3 &= \frac{\epsilon_F p_F \beta_F (I_{ME} + \nu_M I_{ML} + \xi_M Q_M)[S_F(\lambda_{I_{FE}} - \lambda_{S_F}) + \theta_F R_F(\lambda_{I_{FE}} - \lambda_{R_F})]}{\omega_9 N_M}, \\ Z_4 &= \frac{\epsilon_M p_M \beta_M (I_{FE} + \nu_F I_{FL} + \xi_F Q_F)[S_M(\lambda_{I_{ME}} - \lambda_{S_M}) + \theta_M R_M(\lambda_{I_{ME}} - \lambda_{R_M})]}{\omega_{10} N_F}. \end{aligned} \tag{5.7}$$

The proof of this theorem is postponed to Appendix E.

5.2 Numerical Results

In this section, numerical simulations for the optimal control solution will be carried out using the parameter values in Table 2, and initial data relevant to syphilis transmission dynamics in Nigeria [11]. In particular, we set $S_F(0) = 91,186,775$, $I_{FE}(0) = 4,582$, $I_{FL}(0) = 366,580$, $Q_F(0) = 87,063$, $R_F(0) = 0$, $S_M(0) = 91,186,775$, $I_{ME}(0) = 4,582$, $I_{ML}(0) = 366,580$, $Q_M(0) = 87,063$ and $R_M(0) = 0$ [11]. The optimal control solution is obtained by solving the optimality system, consisting of 20 ordinary differential equations [62] (i.e., a combination of the equations of the model (2.3) and the associated adjoint equations given in (5.4)). The equations of the model (2.3) are solved forward in time with MATLAB ODE45, first of all, using any initial guess for control. Using the transversality conditions (5.5), the adjoint equations are solved backward in time using the same MATLAB ODE45 routine. This process is done iteratively until the control variables converges. Numerical simulations are then carried out based on the following assumptions:

1. It is assumed that $0 \leq \tau_F(t),\ \tau_M(t) \leq 1, 0.1 \leq c_F(t) \leq 0.3, 0.4 \leq c_M(t) \leq 0.8$.

2. The weights $\omega_i (i = 1, 2, \ldots, 6)$ are assumed to be equal. This ensures the same cost for monitoring infected and recovered individuals in any class.

3. The weights ω_7 and ω_8 are greater than the weights ω_9 and ω_{10}. This assumes that the cost associated with treatment τ_F and τ_M exceeds the cost associated with condom compliance c_F and c_M since treatment usually takes up to 90 days to clear infection.

4. The weights associated with the cost of controls always exceeds that for monitoring individuals in any class (i.e., $\omega_i < \omega_j,\ i = 1, 2, \ldots, 6,\ j = 7, 8, 9, 10$).

The solution profiles of the four optimal controls ($\tau_F^*, \tau_M^*, c_F^*$ and c_M^*) are depicted in Figure 6. Furthermore, Figure 7 shows, as expected, a marked reduction in the disease burden in the presence of the optimal control (as against the case with no such control). This figure also shows a corresponding increase in the number of recovered individuals. Further numerical simulations are carried out to illustrate the impact of the cost of implementing the four controls on the number of new cases of infections in females (**i.e.,** $\lambda_F S_F$) and males (**i.e.,** $\lambda_M S_M$)generated over a 30-day period. For these simulations, three control strategies are considered, namely the condom-only strategy (where the treatment controls are set to zero), the treatment-only strategy (where the condom controls are set to zero) and the combined treatment-condom strategy. The weights w_7 and w_8 correspond to the cost associated with all forms of treatment for all infected females and males whiles, the weights w_9 and w_{10}, corresponding to the cost associated with the public health education campaign to educate the public on safer sex practice (condom compliance; correct and consistent usage), are chosen for this purpose. The weights values 10, 100 and 1000 are considered low as compared to the weights ($\omega_i (i = 1, \ldots, 6)$) which are set to 1 while the weight values $10^4, 10^5, 10^6$ and 10^7 are regarded as high. The results obtained, tabulated in Table 3, show that, for low cost of controls, the treatment-only strategy resulted in 629,330 new cases, while the condom-only strategy accounted for over 1 million new cases, over the 30-day period. Thus, for situations where control resources are limited, investment in treatment programs is far more effective than investment in condom use as prevention. Furthermore, as expected, the combined treatment-condom strategy provides an even more effective population-level impact than the treatment-only strategy. For situations where the cost of implementing the controls is high, the three strategies are equally ineffective (close to 2 million new cases).

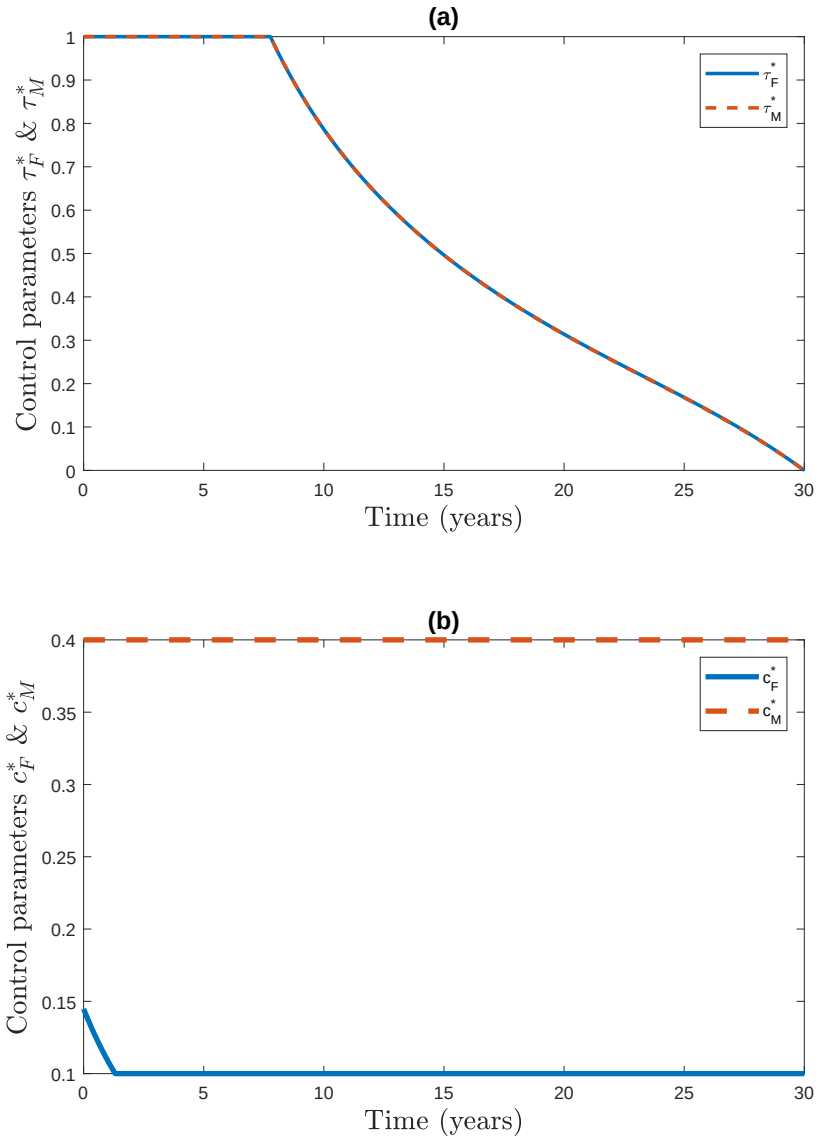

Figure 6: The controls parameters, (a) $\tau_F(t)$ and $\tau_M(t)$, (b) $c_F(t)$ and $c_M(t)$, are plotted as functions of time for $\omega_i = 1 (i = 1, 2, \ldots, 6)$, $\omega_7 = \omega_8 = 10^5$, $\omega_9 = \omega_{10} = 10^4$. All parameter value used are as given in Table 2.

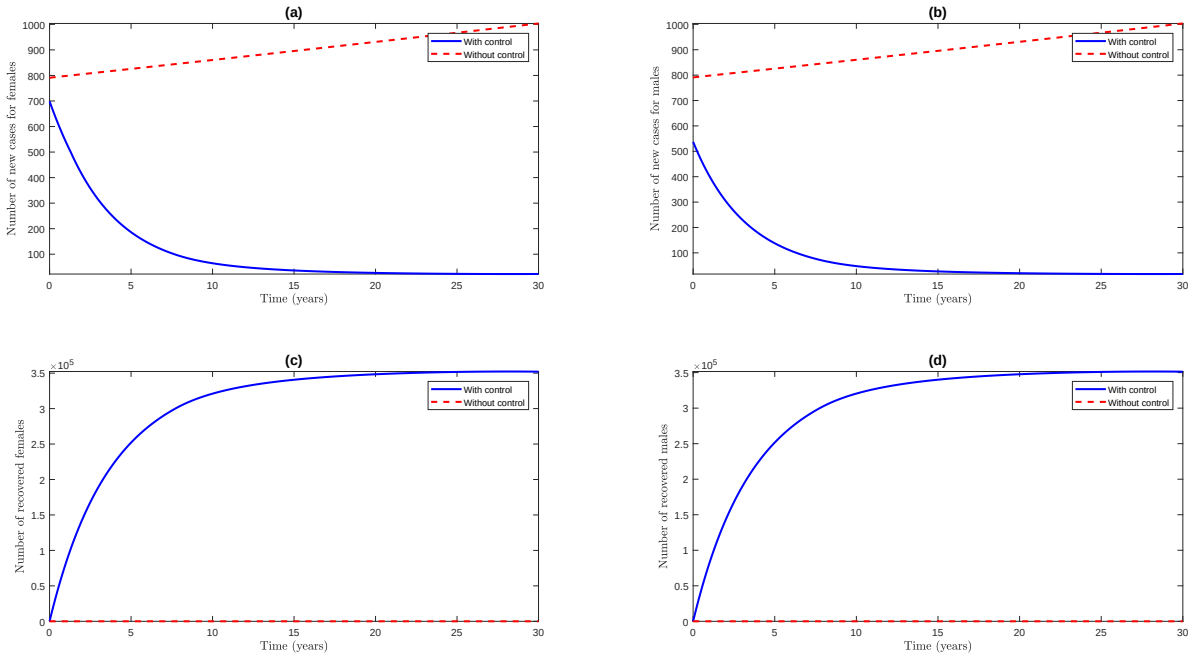

Figure 7: Number of (a) new cases for females (b) new cases for males (c) recovered females and (d) recovered males as a function of time in the presence and absence of optimal control. All parameter value used are as given in Table 2.

Discussion and Conclusions

Syphilis is one of the most deadly sexually-transmitted diseases. Every year, it accounts for over 12 million cases and over 200,000 fatalities globally (inflicting major public health burden in both developing and developed of the world) [1, 2, 4, 8, 10, 63]. Control against syphilis include rapid diagnosis of suspected cases, treatment of confirmed cases and condom use.

This study presents a new deterministic model for gaining insight into the transmission dynamics of syphilis in a population. In addition to allowing for the assessment of the population-level impact of treatment and condom use strategies, the model includes some pertinent features of the disease, such as the multiple stages of infection in untreated patients (represented by "early" and "late" stage of infection) [10] and allowing for reinfection of, and disease relapse from, recovered individuals.

Rigorous qualitative analysis of the model shows that it undergoes the phenomenon of backward bifurcation when the associated reproduction number of the model (denoted by $\mathcal{R}_0$) is less than unity. The epidemiological consequence of backward bifurcation, a dynamic phenomenon characterised by the co-existence of the stable disease-free equilibrium and a stable endemic equilibrium when $\mathcal{R}_0$ is less than unity, is that the classical epidemiological requirement of bringing (and maintaining) $\mathcal{R}_0$ to a value less than unity, while necessary, is no longer sufficient for the effective control (or elimination) of the disease [10, 14, 20, 26]. In a backward bifurcation situation, effective disease control is dependent on the initial sizes of the sub-populations of the model. In other words, the presence of backward bifurcation in the transmission dynamics of a disease makes its effective control difficult. It is shown that the backward bifurcation phenomenon of the model is caused by the reinfection of recovered individuals.

It is worth emphasizing that, although the reinfection of recovered individuals is an important and well-known feature of syphilis transmission dynamics [32], many of the published modeling studies in the literature do not incorporate such property [18, 38, 28, 20, 29] (and, as a consequence, fail to capture the reinfection-induced backward bifurcation property of the disease). This study is **one of the very first to theoretically illustrate the phenomenon of backward bifurcation in syphilis transmission dynamics (Milner and Zhao [25] also showed the presence of backward bifurcation in syphilis dynamics, and used this property to explain the resurgence of syphilis in recent decades)**. It is shown that, in the absence of backward bifurcation (i.e., when reinfection of recovered individuals does not occur), the disease-free equilibrium of the model is globally asymptotically stable whenever the associated reproduction number is less than unity. Thus, for the case when reinfection of recovered individuals is small enough, the implementation of the two control strategies adopted (condom use and treatment of confirmed cases) can lead to the effective control (or elimination) of the disease from the community if they can

result in bringing (and maintaining) the associated reproduction number of the model to a value less than unity. Thus, this study suggests that the prospects of the effective control of syphilis in a population, using treatment and condom strategies, are promising.

The model developed in this study consists of numerous parameters, and uncertainties were expected to exist in the estimate of their values used in the numerical simulations of the model. The effect of such uncertainties (on the simulation results obtained) was assessed using Latin Hypercube Sampling [60], with the reproduction number of the model as the response function. It is shown, using data relevant to the transmission dynamics of the model in Nigeria [11], that the reproduction number of the model lie within the range $(3.19, 6.15)$, with a mean of 4.44. Thus, this study suggests that the current level of treatment and condom strategies are inadequate to effectively contain the spread of the disease in the country (since they fail to bring the mean value of $\mathcal{R}_0$ to a value less than unity). In other words, more needs to be done in terms of increasing compliance in condom use, rapid diagnosis and treatment of confirmed cases and public health education and counselling to encourage safer sex practices.

Detailed sensitivity analysis of the model shows that the most important parameters that affect the reproduction number of the model (hence, disease burden) are the condom efficacy, condom compliance, proportion of treated individuals in the early stage who recovered and the modification parameter associated with the decrease in recovery rate for individuals who failed treatment. This suggests (as expected) that increasing condom compliance and recovery rate of those who failed treatment will decrease syphilis burden in the community.

Optimal control analysis, using Pontraygin's Maximum Principle, was carried out to assess the impact of the cost of implementing the controls (singular and combined administration of condom use and treatment strategies). The simulation results obtained show that, when the cost of implementing the controls is low, treatment-only strategy is significantly more effective than the condom-use only strategy. In particular, while the treatment-only strategy accounted for 642,360 new cases over a 30-day period, the condom-only strategy resulted in 1.3 million cases over the same time period. In other words, these simulation suggests that, in this scenario (with low cost of implementation), the control resources should be targeted towards encouraging/enhancing treatment use in the community. The combined condom-treatment strategy is, expectedly, shown to be more effective than the treatment-only strategy (it accounted for new cases over the 30-day period). However, for the case when the cost of implementation of the controls is high, the three strategies are equally as ineffective (each resulting in nearly 2 million new cases over 30 days). Thus, this study suggests emphasizing treatment ahead of condom use if the cost of implementation of controls is low. This study is perhaps the first to apply optimal control to syphilis transmission dynamics (the models in [18, 38, 28, 20, 29] do not include such analysis). Overall, this study

shows that effective control of syphilis in a population, using condom and treatment strategies, is feasible if their effectiveness level (especially condom compliance rate) are high enough.

The study is preliminary, and can be extended in numerous ways, such as including the effect of vertical transmission, testing of pregnant women and their sexual partners and public health education and counselling for safer sex practices. Moreover, the study can be extended to include the effect of age structure and account for all four stages of syphilis disease. Further theoretical results, such as the global asymptotic stability of the unique endemic equilibrium (which exists for $\tilde{\mathcal{R}}_0 > 1$ in the absence of reinfection), can also be explored.

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Appendix A: Proof of Theorem 2.1

Proof. It is easy to check that the equations for male and female susceptible individuals in the model (2.3) lead to the following first-order inequalitity equations:

$$\frac{dS_F}{dt} + (\lambda_F + \mu)S_F > 0 \text{ and } \frac{dS_M}{dt} + (\lambda_M + \mu)S_M > 0.$$

Multiplying these inequalities by the integrating factors $\rho_F(t) = \exp(\int_0^t (\lambda_F(s) + \mu)ds$ and $\rho_M(t) = \exp(\int_0^t (\lambda_M(s) + \mu)ds$ and observing that

$$\rho_F[\frac{dS_F}{dt} + (\lambda_F + \mu)S_F] = \frac{d(S_F\rho_F)}{dt} \text{ and } \rho_F[\frac{dS_F}{dt} + (\lambda_M + \mu)S_M] = \frac{d(S_M\rho_M)}{dt},$$

then integration with respect to time from 0 to t gives $S_F(t) \geq 0$ and $S_M(t) \geq 0$ at all times, respectively. However, this direct approach does not apply to the remaining equations. Nevertheless, having the nonnegativity of S_F and S_M in mind, it can be shown that the remaining eight equations in the model (2.3) form a monotone system. Consequently, all its solutions corresponding to positive initial data remain positive at all times $t \geq 0$ (see [64]).

By adding the first five and the last five equations of the model (2.3), we obtain the conservation

law

$$\begin{aligned}\frac{dN_F}{dt} &= \Lambda_F - \mu N_F - \delta_F I_{FL} \leq \Lambda_F - \mu N_F,\\ \frac{dN_M}{dt} &= \Lambda_M - \mu N_M - \delta_M I_{ML} \leq \Lambda_M - \mu N_M.\end{aligned}$$

Thus, a standard comparison theorem or Gronwall inequality can be used to show that the general a priori estimates below hold.

$$\begin{aligned}0 \leq N_F(t) &\leq N_F(0)e^{-\mu t} + \frac{\Lambda_F}{\mu}(1 - e^{-\mu t})\\ 0 \leq N_M(t) &\leq N_M(0)e^{-\mu t} + \frac{\Lambda_M}{\mu}(1 - e^{-\mu t}).\end{aligned}$$

In particular, we have a priori estimates

$$\begin{aligned}0 \leq N_F(t) &\leq \frac{\Lambda_F}{\mu} \text{ if } N_F(0) \leq \frac{\Lambda_F}{\mu}\\ 0 \leq N_M(t) &\leq \frac{\Lambda_M}{\mu} \text{ if } N_M(0) \leq \frac{\Lambda_M}{\mu}.\end{aligned}$$

Combining these a priori estimates and the fact that the right-hand side of the model (2.3) is locally Lipschitz, we conclude that there exists a unique global solution in the domain Ω (see Theorem 2.1.5 in [33]). Thus, the model (2.3) is a dynamical system on Ω. On the other hand, if a solution is outside the region Ω, that is

$$N_F(t) \geq \frac{\Lambda_F}{\mu} \text{ and } N_M(t) \geq \frac{\Lambda_M}{\mu},$$

then, it follows from the above conservation law that $\frac{dN_F}{dt} \leq 0$ and $\frac{dN_M}{dt} \leq 0$. Hence, the above general a priori estimates show that $N_F(t)$ tends to $\frac{\Lambda_F}{\mu}$ and $N_M(t)$ tends $\frac{\Lambda_M}{\mu}$ as $t \to \infty$. Thus, the region Ω is attracting.

Appendix B: Proof of Theorem 3.3

Proof. It is convenient to define the following change of variables $x_1 = S_F,\ x_2 = I_{FE},\ x_3 = I_{FL},\ x_4 = Q_F,\ x_5 = R_F,\ x_6 = S_M,\ x_7 = I_{ME},\ x_8 = I_{ML},\ x_9 = Q_F$ and $x_{10} = R_M$, so that $N_f = x_1 + x_2 + x_3 + x_4 + x_5$ and $N_m = x_6 + x_7 + x_8 + x_9 + x_{10}$. Furthermore, by using the vector notation $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10})^T$, the model (2.3) can be written in the

form $\dfrac{dX}{dt} = F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10})^T$, as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &= \Lambda_F - (\lambda_F + \mu)x_1, \\
\frac{dx_2}{dt} &= \lambda_F(x_1 + \theta_F x_5) + \gamma_F x_5 - k_1 x_1, \\
\frac{dx_3}{dt} &= \sigma_F x_2 - k_2 x_3, \\
\frac{dx_4}{dt} &= (1 - f_F)\tau_F x_2 + (1 - g_F)\alpha_T \tau_F x_3 - k_3 x_4, \\
\frac{dx_5}{dt} &= f_F \tau_F x_2 + g_F \alpha_T \tau_F x_3 + \eta_T \tau_F x_4 - \theta_F \lambda_F x_5 - k_4 x_5, \\
\frac{dx_6}{dt} &= \Lambda_M - (\lambda_M + \mu)x_6, \\
\frac{dx_7}{dt} &= \lambda_M(x_6 + \theta_M x_{10}) + \gamma_M x_{10} - k_5 x_7, \\
\frac{dx_8}{dt} &= \sigma_M x_7 - k_6 x_8, \\
\frac{dx_9}{dt} &= (1 - f_M)\tau_M x_7 + (1 - g_M)\alpha_T \tau_M x_8 - k_7 x_9, \\
\frac{dx_{10}}{dt} &= f_M \tau_M x_7 + g_M \alpha_T \tau_M x_8 + \eta_T \tau_M x_9 - \theta_M \lambda_M x_{10} - k_8 x_{10},
\end{aligned} \tag{B.1}$$

where (as before),

$$\begin{aligned}
k_1 &= \sigma_F + \tau_F + \mu, \;\; k_2 = \alpha_T \tau_F + \delta_F + \mu, \;\; k_3 = \eta_T \tau_F + \mu, \;\; k_4 = \mu + \gamma_F, \\
k_5 &= \sigma_M + \tau_M + \mu, \;\; k_6 = \alpha_T \tau_M + \delta_M + \mu, \;\; k_7 = \eta_T \tau_M + \mu, \;\; k_8 = \mu + \gamma_M,
\end{aligned}$$

and, now,

$$\begin{aligned}
\lambda_F &= (1 - \epsilon_F c_F)\frac{p_F \beta_F}{N_M}\left(x_7 + \nu_M x_8 + \xi_M x_9\right), \\
\lambda_M &= (1 - \epsilon_M c_M)\frac{p_M \beta_M}{N_F}\left(x_2 + \nu_F x_3 + \xi_F x_4\right).
\end{aligned}$$

The Jacobian of the system (B.1), at the associated DFE ($\mathcal{E}_0$), is given by

$$J(\mathcal{E}_0) = \begin{pmatrix} A_{5\times 5} & B_{5\times 5} \\ C_{5\times 5} & D_{5\times 5} \end{pmatrix},$$

where,

$$A=\begin{pmatrix} -\mu & 0 & 0 & 0 & 0 \\ 0 & -k_1 & 0 & 0 & \gamma_F \\ 0 & \sigma_F & -k_2 & 0 & 0 \\ 0 & (1-f_F)\tau_F & (1-g_F)\alpha_T\tau_F & -k_3 & 0 \\ 0 & \tau_F f_F & \alpha_T\tau_F g_F & \eta_T\tau_F & -k_4 \end{pmatrix},\quad B=\begin{pmatrix} 0 & -x_F & -x_F\nu_M & -x_F\xi_M & 0 \\ 0 & x_F & x_F\nu_M & x_F\xi_M & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$C=\begin{pmatrix} 0 & -x_M & -x_M\nu_F & -x_M\xi_F & 0 \\ 0 & x_M & x_M\nu_F & x_M\xi_F & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \text{ and } D=\begin{pmatrix} -\mu & 0 & 0 & 0 & 0 \\ 0 & -k_5 & 0 & 0 & \gamma_M \\ 0 & \sigma_M & -k_6 & 0 & 0 \\ 0 & (1-f_M)\tau_M & (1-g_M)\alpha_T\tau_M & -k_7 & 0 \\ 0 & \tau_M f_M & \alpha_T\tau_M g_M & \eta_T\tau_F & -k_8 \end{pmatrix},$$

with,

$$x_F=\frac{(1-\epsilon_F c_F)p_F\beta_F\Lambda_F}{\Lambda_M},\quad x_M=\frac{(1-\epsilon_M c_M)p_M\beta_M\Lambda_M}{\Lambda_F}.$$

Consider, next, the case when $\mathcal{R}_0=1$, and choose p_M as a bifurcation parameter. Solving for p_M from $\mathcal{R}_0=1$ gives

$$p_M=p_M^*=\frac{(T_{F1}+T_{F2})(T_{M1}+T_{M2})}{p_F\beta_F\beta_M k_4 k_8(1-\epsilon_M c_M)(1-\epsilon_F c_F)T_F T_M}, \tag{B.2}$$

where (as before),

$$\begin{aligned} T_F &= \tau_F\xi_F[k_2(1-f_F)+\alpha_T\sigma_F(1-g_F)]+k_3(k_2+\nu_F\sigma_F), \\ T_{F1} &= k_2\{\mu^3+[\sigma_F+\gamma_F+\tau_F(1+\eta_T)]\mu^2+[\eta_T(\tau_F+\sigma_F+\gamma_F)+\gamma_F(1-f_F)]\tau_F\mu\}, \\ T_{F2} &= \gamma_F\sigma_F\{\mu^2+[\delta_F+\eta_T\tau_F+\tau_F\alpha_T(1-g_F)]\mu+\eta_T\tau_F\delta_F\}, \\ T_M &= \tau_M\xi_M[k_6(1-f_M)+\alpha_T\sigma_M(1-g_M)]+k_7(k_6+\nu_M\sigma_M), \\ T_{M1} &= k_6\{\mu^3+[\sigma_M+\gamma_M+\tau_M(1+\eta_T)]\mu^2+[\eta_T(\tau_M+\sigma_M+\gamma_M)+\gamma_M(1-f_M)]\tau_M\mu\}, \\ T_{M2} &= \gamma_M\sigma_M\{\mu^2+[\delta_M+\eta_T\tau_M+\tau_M\alpha_T(1-g_M)]\mu+\eta_T\tau_M\delta_M\}. \end{aligned}$$

It can be verified that the transformed system (B.1), with $p_M=p_M^*$, has a non hyperbolic equilibrium point such that the linearized system has a simple eigenvalue with zero real part, and all other eigenvalues have negative real parts. Hence, the centre manifold theory [13, 15, 34] can be used to analyse the dynamics of the model (B.1) near $p_M=p_M^*$. Using the notation in [15], the following computations are carried out.

Eigenvectors of $J(\mathcal{E}_0)\Big|_{p_M=p_M^*}$

It can be shown that the Jacobian, $J(\mathcal{E}_0)$ at $p_M = p_M^*$ (denoted by $J_{p_M^*}$) has a right eigenvector (associated with the zero eigenvalue), given by

$$\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}]^T,$$

where,

$$\begin{aligned}
w_1 &= -\frac{p_F\beta_F\Lambda_F w_7(1-\epsilon_F c_F)[\alpha_T\sigma_M\tau_M\xi_M(1-g_M)+\tau_M\xi_M k_6(1-f_M)+k_7(k_6+\nu_M\sigma_M)]}{\mu\Lambda_M k_6 k_7},\\
w_2 &= \frac{p_F\beta_F\Lambda_F k_2k_3k_4 w_7(1-\epsilon_F c_F)[\alpha_T\sigma_M\tau_M\xi_M(1-g_M)+\tau_M\xi_M k_6(1-f_M)+k_7(k_6+\nu_M\sigma_M)]}{\Lambda_M k_6 k_7 T_{F1}},\\
w_3 &= \frac{\sigma_F w_2}{k_2},\quad w_4 = \frac{(1-f_F)\tau_F w_2+(1-g_F)\alpha_T\tau_F w_3}{k_4},\quad w_5 = \frac{f_F\tau_F w_2+g_F\alpha_T\tau_F w_3+\eta_T\tau_F w_4}{k_4},\\
w_6 &= -(1-\epsilon_M c_M)p_M\beta_F(w_2+\nu_F w_3+\xi_F w_4),\quad w_7 = w_7 > 0,\quad w_8 = \frac{\sigma_M w_7}{k_6},\\
w_9 &= \frac{(1-f_M)\tau_M w_7+(1-g_M)\alpha_T\tau_M w_8}{k_7},\quad w_{10} = \frac{f_M\tau_M w_7+g_M\alpha_T\tau_M w_8+\eta_T\tau_M w_9}{k_8}.
\end{aligned}$$

Furthermore, $J_{p_M^*}$ has a left eigenvector (associated with the zero eigenvalue), given by

$$\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}],$$

with,

$$\begin{aligned}
v_1 &= 0,\\
v_2 &= \frac{p_M\beta_F k_4 v_7(1-\epsilon_M c_M)[\alpha_T\sigma_F\tau_F\xi_F(1-g_F)+\tau_F\xi_F k_2(1-f_F)+k_3(k_2+\nu_F\sigma_F)]}{T_{F1}},\\
v_3 &= \frac{(1-g_F)\alpha_T\tau_F v_4}{k_2}+\frac{g_F\alpha_T\tau_F\gamma_F v_2}{k_2k_4}+\frac{p_M\beta_F\nu_F(1-c_M\epsilon_M)v_7}{k_2},\\
v_4 &= \frac{p_M\beta_F v_7(1-\epsilon_M c_M)\{\eta_T\gamma_F\tau_F(k_2+\nu_F\sigma_F)+\xi_F[k_1k_2k_4-\gamma_F\tau_F(f_Fk_2+g_F\alpha_T\sigma_F)]\}}{T_{F1}},
\end{aligned}$$

$$\begin{aligned}
v_5 &= \frac{\gamma_F v_2}{k_4},\quad v_6 = 0,\quad v_7 = v_7 > 0,\\
v_8 &= \frac{p_F\beta_F(1-c_F\epsilon_F)\nu_M\Lambda_F v_2}{\Lambda_M k_6}+\frac{(1-g_M)\alpha_T\tau_M v_9}{k_6}+\frac{g_M\alpha_T\tau_M\gamma_M v_7}{k_6k_8},\\
v_9 &= \frac{p_F\beta_F(1-c_F\epsilon_F)\xi_M\Lambda_F v_2}{\Lambda_M k_7}+\frac{\eta_T\tau_M\gamma_M v_7}{k_7k_8},\quad v_{10} = \frac{\gamma_M v_7}{k_8}.
\end{aligned}$$

Computations of bifurcation coefficients a and b

It can be shown, by computing the non-zero partial derivatives of F at the DFE ($\mathcal{E}_0$) and simplifying, that

$$\begin{aligned} a =& \sum_{k,i,j=1}^{10} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\mathcal{E}_0), \\ =& \frac{2\mu}{\Lambda_F}(1-\epsilon_F c_F) p_F \beta_M \left[\theta_F(v_2 - v_5)w_5 - v_2 \sum_{i=2}^{5} w_i\right](w_7 + \nu_M w_8 + \xi_M w_9) \\ &+ \frac{2\mu}{\Lambda_M}(1-\epsilon_M c_M) p_M \beta_F \left[\theta_M(v_7 - v_{10})w_{10} - v_7 \sum_{i=7}^{10} w_i\right](w_2 + \nu_F w_3 + \xi_F w_4). \end{aligned} \tag{B.3}$$

Thus, the bifurcation coefficient, a, is positive whenever

$$\theta_F(v_2 - v_5)w_5 - v_2 \sum_{i=2}^{5} w_i > 0 \ \text{ and } \ \theta_M(v_7 - v_{10})w_{10} - v_7 \sum_{i=7}^{10} w_i > 0.$$

Furthermore, it can be shown that:

$$\begin{aligned} b &= \sum_{k,i=1}^{10} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial p_M^*}(\mathcal{E}_0), \\ &= \beta_F v_7 (1-\epsilon_M c_M)(w_2 + \nu_F w_3 + \xi_F w_4) > 0. \end{aligned}$$

Hence, it follows, from Theorem 4.1 in [15], that the model (2.3) exhibits a backward bifurcation at $\mathcal{R}_0 = 1$ whenever

$$\theta_F(v_2 - v_5)w_5 - v_2 \sum_{i=2}^{5} w_i > 0 \ \text{ and } \ \theta_M(v_7 - v_{10})w_{10} - v_7 \sum_{i=7}^{10} w_i > 0.$$

□

Appendix C: Proof of Theorem 3.4

Proof. Setting $\theta_F = \theta_M = 0$ in the expression for the bifurcation coefficient a, given in (B.3) above, gives (it should be noted that the eigenvectors $v_2, v_7, w_2, w_3, w_4, w_5, w_7, w_8, w_9, w_{10}$ are all positive)

$$\begin{aligned} a &= \sum_{k,i,j=1}^{10} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(\mathcal{E}_0), \\ &= -\left[\frac{2\mu}{\Lambda_F}(1-\epsilon_F c_F) p_F \beta_M v_2 (w_7 + \nu_M w_8 + \xi_M w_9) \sum_{i=2}^{5} w_i \right. \\ &\quad \left. + \frac{2\mu}{\Lambda_M}(1-\epsilon_M c_M) p_M \beta_F v_7 (w_2 + \nu_F w_3 + \xi_F w_4) \sum_{i=7}^{10} w_i \right] < 0. \end{aligned} \tag{C.1}$$

Thus, it follows from Theorem 4.1 in [15] that the model (2.3) with $\theta_F = \theta_M = 0$ will not undergo a backward bifurcation at $\tilde{\mathcal{R}}_0 = 1$. □

Appendix D: Proof of Theorem 3.5

Proof. It is worth noting, first of all, that the equations for the infected components of the model (2.3) with $\theta_F = \theta_M = 0$ can be written in matrix-vector form:

$$\frac{dX(t)}{dt} = \left[(F - V) - \left(1 - \frac{S_F}{N_F}\right) K_1 - \left(1 - \frac{S_M}{N_M}\right) K_2\right] X(t), \tag{D.1}$$

where $X(t) = (I_{FE}(t), I_{FL}(t), Q_F(t), R_F(t), I_{ME}(t), I_{ML}(t), Q_M(t), R_M(t))^T$ and the matrices F and V are given in Section 3, Furthermore,

$$K_1 = \begin{pmatrix} 0 & 0 & 0 & 0 & x_F & x_F\nu_M & x_F\xi_M & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad K_2 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ x_M & x_M\nu_F & x_M\xi_F & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Since K_1 and K_2 are non-negative matrices and $S_F(t) \leq N_M(t)$ and $S_M(t) \leq N_M(t)$ in Ω, it follows that

$$\frac{dX(t)}{dt} \leq (F - V)X(t). \tag{D.2}$$

Using the fact that the eigenvalues of the matrix $F-V$ all have negative real parts (i.e., $\rho(FV^{-1}) < 1$ if $\tilde{\mathcal{R}}_0 < 1$), it follows that the linearized differential inequality system (2.3) is stable whenever $\tilde{\mathcal{R}}_0 < 1$. Thus, by Comparison Theorem [22],

$$\lim_{t\to\infty}(I_{FE}(t), I_{FL}(t), Q_F(t), R_F(t), I_{ME}(t), I_{ML}(t), Q_M(t), R_M(t)) = (0,0,0,0,0,0,0,0). \tag{D.3}$$

Substituting (D.3) into (2.3), it can be shown that $S_F(t) \to \dfrac{\Lambda_F}{\mu}$ and $S_M(t) \to \dfrac{\Lambda_M}{\mu}$, as $t \to \infty$. Hence,

$$\begin{aligned}&\lim_{t\to\infty}(S_F(t), I_{FE}(t), I_{FL}(t), Q_F(t), R_F(t), S_M(t), I_{ME}(t), I_{ML}(t), Q_M(t), R_M(t))\\ &= (\frac{\Lambda_F}{\mu}, 0, 0, 0, 0, \frac{\Lambda_M}{\mu}, 0, 0, 0, 0) = \mathcal{E}_0.\end{aligned}$$

Thus, every solution to the equations of the model (2.3), with $\theta_F = \theta_M = 0$ and initial conditions in Ω, approaches the DFE ($\mathcal{E}_0$) as $t \to \infty$ whenever $\tilde{\mathcal{R}}_0 < 1$. □

Appendix E: Proof of Theorem 5.1

Proof. Corollary 4.1 of [52] gives the existence of an optimal control quadruple ($\tau_F(t)$, $\tau_M(t)$, $c_F(t)$, $c_M(t)$) due to the convexity of the integrand of J with respect to ($\tau_F(t)$, $\tau_M(t)$, $c_F(t)$, $c_M(t)$), a priori boundedness of the state solutions, and the **local** Lipschitz property of the model (2.3) with respect to the state variables. Applying the Pontryagin's Maximum Principle [53], gives

$$\begin{aligned}
&\frac{d\lambda_{S_F}}{dt} = -\frac{\partial H}{\partial S_F}, \ \ \lambda_{S_F}(t_f) = 0, \ \ \frac{d\lambda_{I_{FE}}}{dt} = -\frac{\partial H}{\partial I_{FE}}, \ \ \lambda_{I_{FE}}(t_f) = 0,\\
&\frac{d\lambda_{I_{FL}}}{dt} = -\frac{\partial H}{\partial I_{FL}}, \ \ \lambda_{I_{FL}}(t_f) = 0, \ \ \frac{d\lambda_{Q_F}}{dt} = -\frac{\partial H}{\partial Q_F}, \ \ \lambda_{Q_F}(t_f) = 0,\\
&\frac{d\lambda_{R_F}}{dt} = -\frac{\partial H}{\partial R_F}, \ \ \lambda_{R_F}(t_f) = 0, \ \ \frac{d\lambda_{S_M}}{dt} = -\frac{\partial H}{\partial S_M}, \ \ \lambda_{S_M}(t_f) = 0,\\
&\frac{d\lambda_{I_{ME}}}{dt} = -\frac{\partial H}{\partial I_{ME}}, \ \ \lambda_{I_{ME}}(t_f) = 0, \ \ \frac{d\lambda_{I_{ML}}}{dt} = -\frac{\partial H}{\partial I_{ML}}, \ \ \lambda_{I_{ML}}(t_f) = 0,\\
&\frac{d\lambda_{Q_M}}{dt} = -\frac{\partial H}{\partial Q_M}, \ \ \lambda_{Q_M}(t_f) = 0, \ \ \frac{d\lambda_{R_M}}{dt} = -\frac{\partial H}{\partial R_M}, \ \ \lambda_{R_M}(t_f) = 0.
\end{aligned} \tag{E.1}$$

Evaluating (E.1) at the optimal control quadruple $(\tau_F(t), \tau_M(t), c_F(t), c_M(t))$ and the corresponding state variables results in the stated adjoint system (5.4) and (5.5). In the interior of the control set W, where $a_{11} < \tau_F(t) < a_{12}, a_{21} < \tau_M(t) < a_{22}, b_{11} < c_F(t) < b_{12}, b_{21} < c_M(t) < b_{22}$, the optimality conditions give

$$\begin{aligned}
\frac{\partial H}{\partial \tau_F} &= \omega_9 \tau_F - I_{FE}[\lambda_{I_{FE}} - \lambda_{Q_F} + f_F(\lambda_{Q_F} - \lambda_{R_F})] - \alpha_T I_{FL}(\lambda_{I_{FL}} - \lambda_{Q_F}) \\
&\quad - (\alpha_T I_{FL} g_F + \eta_T Q_F)(\lambda_{Q_F} - \lambda_{R_F}) = 0, \\
\frac{\partial H}{\partial \tau_M} &= \omega_{10} \tau_M - I_{ME}[\lambda_{I_{ME}} - \lambda_{Q_M} + f_M(\lambda_{Q_M} - \lambda_{R_M})] - \alpha_T I_{ML}(\lambda_{I_{ML}} - \lambda_{Q_M}) \\
&\quad - (\alpha_T I_{ML} g_M + \eta_T Q_M)(\lambda_{Q_M} - \lambda_{R_M}) = 0, \\
\frac{\partial H}{\partial c_F} &= \omega_{11} c_F - \frac{\epsilon_F p_F \beta_F (I_{ME} + \nu_M I_{ML} + \xi_M Q_M)[S_F(\lambda_{I_{FE}} - \lambda_{S_F}) + \theta_F R_F(\lambda_{I_{FE}} - \lambda_{R_F})]}{N_M} = 0, \\
\frac{\partial H}{\partial c_M} &= \omega_{12} c_M - \frac{\epsilon_M p_M \beta_M (I_{FE} + \nu_F I_{FL} + \xi_F Q_F)[S_M(\lambda_{I_{ME}} - \lambda_{S_M}) + \theta_M R_M(\lambda_{I_{ME}} - \lambda_{R_M})]}{N_F} = 0.
\end{aligned} \tag{E.2}$$

The optimal control quadruple $(\tau_F^*, \tau_M^*, c_F^*, c_M^*)$ can be obtained by solving the optimality conditions above, to obtain $\tau_F^* = Z_1, \tau_M^* = Z_2, c_F^* = Z_3, c_M^* = Z_4$, where, Z_1, Z_2, Z_3 and Z_4 are defined in (5.7). Using the bounds for the control variables in the control set W, the controls $\tau_F^*, \tau_M^*, c_F^*$ and c_M^* can be re-written in the form (5.6), as required. □

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State Variable	Description
$S_F(S_M)$	Susceptible females (males)
$I_{FE}(I_{ME})$	Infected females (males) in the early stage
$I_{FL}(I_{ML})$	Infected females (males) in the late stage
$Q_F(Q_M)$	Treated females (males) who fail treatment
$R_F(R_M)$	Treated females (males) who recover from infection
Parameters	**Description**
$\Lambda_F(\Lambda_M)$	Recruitment rate of new sexually-active females (males)
μ	Natural death rate
$\sigma_F(\sigma_M)$	Progression rate from early to late stage for females (males)
$\tau_F(\tau_M)$	Treatment rate for females (males)
α_T	Modification parameter for the variability in the treatment rate of individuals in the late stage of infection, in comparison to those in the early stage of infection.
η_T	Modification parameter for the assumed decrease in the recovery rate of individuals in the Q_F and Q_M classes, in comparison to successfully-treated individuals.
$\gamma_F(\gamma_M)$	Relapse rate for females (males) in $R_F(R_M)$ class
$\theta_F(\theta_M)$	Re-infection rate for females (males) in $R_F(R_M)$ class
$f_F(f_M)$	Proportion of treated females(males) in the early stage who recovered
$g_F(g_M)$	Proportion of treated females(males) in the late stage who recovered
$\delta_F(\delta_M)$	Syphilis-induced mortality for females (males) in $I_{FL}(I_{ML})$ class
$\epsilon_F(\epsilon_M)$	Efficacy of condoms in preventing infection in susceptible females (males)
$c_F(c_M)$	Condom compliance for females (males)
$\kappa_F(\kappa_M)$	Effective contact rate for females (males)
$\nu_F(\nu_M)$	Modification parameter for the assumed increase in infectiousness of individuals in the $I_{FL}(I_{ML})$ class in comparison to those in the (I_{ME}) class
$\xi_F(\xi_M)$	Modification parameter for the assumed reduction of infectiousness of individuals in the $Q_F(Q_M)$ class in comparison to those in the (I_{ME}) class

Table 1: Description of state variables and parameters of the model (2.3).

Table 2: Mean values of the model parameters with their assigned distributions.

Parameters	Distribution	Range	Baseline values	References
μ	Normal	5.08×10^{-5} - 5.89×10^{-5}	5.48×10^{-5} day^{-1}	[57]
$\sigma_F,\ \sigma_M$	Normal	3.89×10^{-2} - 5.73×10^{-2}	4.762×10^{-2} day^{-1}	[58]
$\tau_F,\ \tau_M$	Normal	2.75×10^{-1} - 4.51×10^{-1}	3.6×10^{-1} day^{-1}	Implied from [58]
η_T	Normal	1.99×10^{-2} - 1.79×10^{-1}	0.1	Assumed
α_T	Normal	2.35×10^{-2} - 4.49×10^{-1}	$2.5\eta_T$	Implied from [58]
$f_F,\ \ f_M$	Normal	8.5×10^{-1} - 9.5×10^{-1}	0.9	Assumed
$g_F,\ \ g_M$	Gamma	8.5×10^{-1} - 9.5×10^{-1}	0.9	Assumed
$\delta_F,\ \ \delta_M$	Normal	5.8×10^{-2} - 7.68×10^{-2}	6.849×10^{-2} day^{-1}	Implied from [20]
$\epsilon_F,\ \ \epsilon_M$	Uniform	2.5×10^{-1} - 9.5×10^{-1}	0.8	[59]
c_M	Uniform	4×10^{-1} - 8×10^{-1}	0.6	Assumed
c_F	Uniform	1×10^{-1} - 3×10^{-1}	0.15	Assumed
$\kappa_F,\ \ \kappa_M$	Gamma	1.86×10^{-1} - 4.54×10^{-1}	0.3	[58]
$\nu_F,\ \ \nu_M$	Gamma	1 - 1.4	1.2	Assumed
$\xi_F,\ \ \xi_M$	Gamma	3.15×10^{-1} - 7.39×10^{-1}	0.5	Assumed
$\Lambda_F,\ \ \Lambda_M$	-	-	1.0203×10^{3} day^{-1}	[11, 57]
$\theta_F,\ \ \theta_M$	-	-	0.9	Assumed
$\gamma_F,\ \ \gamma_M$	Normal	6×10^{-4} - 7.6436×10^{-4}	6.8×10^{-4} day^{-1}	Implied from [58]

Table 3: Number of new cases of infections for various control strategies using different weights

$\omega_9, \omega_{10}, \omega_{11}, \omega_{12}$	$c_F^* = c_M^* = 0$	$\tau_F^* = \tau_M^* = 0$	$\tau_F^*, \tau_M^*, c_F^*, c_M^*$
10^1	6.3217×10^5	1.2927×10^6	3.5408×10^5
10^2	6.3217×10^5	1.2952×10^6	3.6376×10^5
10^3	6.3220×10^5	1.3188×10^6	4.1798×10^5
10^4	6.3447×10^5	1.5012×10^6	5.0647×10^5
10^5	6.8244×10^5	1.8544×10^6	5.4578×10^5
10^6	1.2124×10^6	1.8611×10^6	9.6992×10^5
10^7	2.0147×10^6	1.8611×10^6	1.6071×10^6