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A co-infection model for HPV and syphilis with optimal control and cost-effectiveness analysis

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A co-infection model for human papillomavirus (HPV) and syphilis with cost-effectiveness optimal control analysis is developed and presented. The full co-infection model is shown to undergo the phenomenon of backward bifurcation when a certain condition is satisfied. The global asymptotic stability of the disease-free equilibrium of the full model is shown not to exist when the associated reproduction number is less than unity. The existence of endemic equilibrium of the syphilis-only sub-model is shown to exist and the global asymptotic stability of the disease-free and endemic equilibria of the syphilis-only sub-model was established, for a special case. Sensitivity analysis is also carried out on the parameters of the model. Using the syphilis associated reproduction number, $\mathcal{R}_{0s}$, as the response function, it is observed that the five-ranked parameters that drive the dynamics of the co-infection model are the demographic parameter μ, the effective contact rate for syphilis transmission, β_s, the progression rate to late stage of syphilis σ_2, and syphilis treatment rates: τ_1 and τ_2 for co-infected individuals in compartments H_i and H_l, respectively. Moreover, when the HPV associated reproduction number, $\mathcal{R}_{0h}$, is used as the response function, the five most dominant parameters that drive the dynamics of the model are the demographic parameter μ, the effective contact rate for HPV transmission, β_h, the fraction of HPV infected who develop persistent HPV ρ_1, the fraction of individuals vaccinated against incident HPV infection ϕ and the HPV vaccine efficacy π_h. Numerical simulations of the optimal control model showed that the optimal control strategy which implements syphilis treatment controls for singly infected individuals is the most cost-effective of all the control strategies in reducing the burden of HPV and syphilis co-infections.

Keywords: Human papillomavirus; syphilis; co-infection; optimal control; cost-effectiveness analysis.

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1. Introduction

Syphilis, caused by *Treponema Pallidum*, continues to remain a global threat to life [1]. Although treatment and condom use have proven to be effective in preventing the disease, estimates indicate that every year about 12,000,000 people are infected with the disease [2]. The World Health Organization (WHO) reported that about 2 million pregnant women are infected with syphilis annually [2]. Vertical transmission of syphilis can occur from a pregnant mother to her unborn child, resulting in a very negative outcomes for the pregnancy [2, 3]. The human papillomavirus (HPV) is one of the most prevalent sexually transmitted infections (STIs) worldwide [4]. Globally, the HPV is responsible for roughly 270,000 cervical cancer deaths and 97,000 other cancer deaths yearly [4]. There is no specific treatment for HPV, but the visible symptoms or genital warts due to the disease can be treated, with the goal of reducing the spread of the infection [5]. HPV, like other sexually transmitted infections, can be prevented through the use of condoms. Presently, three major anti-HPV vaccines exist: the bivalent *Cervarix* vaccine (which targets HPV-16 and HPV-18), the quadrivalent *Gardasil* 4 vaccine (which targets the oncogenic HPV types (HPV-16 and HPV-18) and the warts causing HPV types (HPV-6 and HPV-11) and the nonavalent *Gardasil* 9 vaccine (which targets the high-risk HPV types (HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52 and HPV-58) and the low-risk HPV types (HPV-6 and HPV-11) [6].

Epidemiological evidences have shown interactions between HPV, cancer and syphilis [7–12]. Souza *et al.* [7] investigated the incidence of HPV–syphilis co-infection among patients in a hospital at Rio de Janeiro, Brazil. They discovered that many of the patients treated of HPV infections had prior syphilis cases, indicating a strong co-infection between the two infections. Zhang *et al.* [8] studied the risk factors for HPV, human immuno-deficiency virus (HIV) and syphilis infections among men who have sexual interactions with men (MSM) in China. They discovered that HIV infection was high among individuals infected with syphilis or HPV and much higher among individuals co-infected with HPV and syphilis infections. Tseng *et al.* [9] investigated the risk factors for anal cancer in both men and women in a population-based study and showed that prior syphilis infection was associated with persistent HPV infection and increased susceptibility to anal cancer among both genders. The findings in Daling *et al.* [10] reveal that syphilis and anal cancer co-infections were more common among unmarried men than among the married ones. In another report, da Mota *et al.* [11] discussed the prevalence of syphilis and its risk factors among young men presented to the Brazilian Army in 2016 and showed that syphilis infection is mostly preceded by sexually transmitted infections (STIs), especially HPV infection, gonorrhea and HIV. Similar conclusions were made by Miranda *et al.* [12].

Mathematical modeling has extensively been applied in studying the dynamics of infectious diseases [13–17]. In recent times, mathematical models have been formulated to understand the dynamics of syphilis transmission [18–22].

Garnet *et al.* [18] developed a mathematical model for syphilis transmission, capturing the elementary stages of the disease. They assumed infection acquired temporary immunity for infected individuals. In another paper, an susceptible-infected-recovered-susceptible (SIRS) syphilis model was fitted with real-life data [19]. Iboi and Okuonghae [20] rigorously analyzed a deterministic mathematical model, incorporating early latent and late stages of syphilis infection. Saad-Roy *et al.* [21] analyzed a mathematical model for syphilis in an MSM population. More recently, Okuonghae *et al.* [22] developed a syphilis model to assess the impact of disease transmission by individuals in the early latent stage of syphilis infection on the general dynamics and transmission of the disease.

Many mathematical modeling studies have been carried out to understand the dynamics of transmission of the HPV [23–27]. Malik *et al.* [26] studied the optimal control strategies for a vaccination program administering the bivalent *Cervarix*, quadrivalent *Gardasil* 4 and nonavalent *Gardasil* 9 HPV vaccines to the female population. Specifically, they considered the situations where the three vaccines are used concurrently in comparison to the case where the bivalent *cervarix* and quadrivalent *Gardasil* 4 vaccines were initially used and then during the course of the vaccination program, one or two of them are interchanged with the nonavalent vaccine. Omame *et al.* [27] studied a two-sex vaccination model for HPV, to assess the impact of condom use and treatment on the control of HPV in a population. They showed that a vaccine with 75% effectiveness rate for males and about 40% condom compliance level by females could lead to the effective control of HPV in a population.

To understand the co-infections between diseases, mathematical models have been formulated and analyzed [28–39]. Omame *et al.* [28] studied a co-infection model for HPV and tuberculosis (TB), in the presence of HPV vaccination and condom use as well as TB treatment. Their results showed that TB-only treatment strategy can significantly bring down the burden of HPV and the co-infection of the two diseases in a population. Nwankwo and Okuonghae [29] investigated the effect of syphilis treatment in a population where HIV and syphilis are co-circulating and showed that targeted syphilis treatment could significantly curb the burden of the co-infection of the two diseases. Also, an optimal control model for two-strain tuberculosis and HIV/AIDS co-infection with cost-effectiveness analysis was studied by Agusto and Adekunle [30]. They showed that the control strategy that combines prevention of treatment failure in drug-sensitive TB infectious individuals and the treatment of individuals with drug-resistant TB was the most cost-effective in reducing the burden of the co-infection of HIV/AIDS and two strains of tuberculosis.

To the best of the authors' knowledge, no robust optimal control mathematical model has been developed to capture the combined effect of HPV vaccination and syphilis treatment on the control of HPV and syphilis co-infection, despite the availability of epidemiological evidences supporting the co-infections of both

diseases. This study assesses the combined effect of these aforementioned strategies, using optimal control analysis, in order to determine the ways of bringing down the burden of co-infection of the two diseases.

The rest of the paper is organized as follows. The model is formulated in Sec. 2, together with the presentation of its basic properties. The sub-models are analyzed in Sec. 3. Qualitative analyses of the full co-infection model are presented in Sec. 4. Optimal control analyses of the model are presented in Secs. and 5 and 6. Section 7 gives the concluding remarks.

2. Model Formulation

The total sexually active population at time t, denoted by $N(t)$, is divided into 20 mutually exclusive compartments: susceptible individuals ($S(t)$), individuals in early stage of syphilis infection ($I(t)$), individuals in late stage of syphilis infection ($L(t)$), individuals treated of syphilis, ($T(t)$), individuals vaccinated against HPV ($V_h(t)$) , individuals infected with HPV ($H(t)$), individuals with persistent HPV infection ($P(t)$), individuals with anal cancer ($C(t)$), individuals who have recovered from anal cancer ($R_c(t)$), individuals who have recovered from or cleared HPV infection ($R_h(t)$), individuals dually infected with HPV and exposed to syphilis ($H_e(t)$), individuals dually infected with HPV and syphilis in early stage $H_i(t)$, individuals dually infected with HPV and in late stage of syphilis infection, ($H_l(t)$), individuals dually infected with persistent HPV and exposed to syphilis infection ($P_e(t)$), individuals dually infected with persistent HPV and in early stage of syphilis infection ($P_I(t)$), individuals dually infected with persistent HPV and in late stage of syphilis infection ($P_l(t)$), individuals dually infected with anal cancer and exposed to syphilis infection ($C_e(t)$), individuals dually infected with anal cancer and in early stage of syphilis ($C_i(t)$), individuals dually infected with anal cancer and in late stage of syphilis infection ($C_l(t)$).

Thus,

$$N = S + E + I + L + T + V_h + H + P + C + R_c + R_h + H_e + H_i + H_l + P_e + P_i + P_l + C_e + C_i + C_l.$$

The model has the following assumptions:

(i) To avoid model complexity, the primary and secondary stages of syphilis infection are joined together and are referred to as "early stage of syphilis infection". In a similar manner, the latent and tertiary stages of infection are combined together and known as "late stage of syphilis infection".
(ii) Individuals infected with syphilis infection are susceptible to infection with HPV and vice versa. [7].
(iii) Co-infected individuals have higher rate of infectivity than singly infected individuals.
(iv) Co-infected infected individuals can transmit either from HPV or TB but not the mixed infections at the same time,

(v) Co-infected infected individuals can recover either from HPV or TB but not from the mixed infections at the same time,

The population of sexually active unvaccinated susceptible individuals, S, is generated by the recruitment of individuals at a rate Λ_h. This population is decreased as a result of infection with syphilis, following effective contact with both singly and dually infected individuals with syphilis at the rate:

$$\lambda_s = \frac{\beta_s\big[I + C_I + \eta_l(L + C_L) + \theta_h\{H_I + \omega_P P_I + \eta_l(H_L + \omega_P P_L)\}\big]}{N}. \quad (2.1)$$

In a similar manner, the population S is also reduced as a result of infection with HPV, acquired due to effective contact with both singly and dually infected individuals with HPV at the rate:

$$\lambda_h = \frac{\beta_h\big[H + H_E + \omega_P(P + P_E) + \theta_s\{H_I + \omega_P P_I + \eta_l(H_L + \omega_P P_L)\}\big]}{N}. \quad (2.2)$$

The parameter $\theta_h(\theta_h \geq 1)$ is a modification parameter accounting for the increased infectiousness of dually infected individuals due to active HPV, $\eta_l(\eta_l \geq 1)$ is a modification parameter accounting for increased infectiousness of infected individuals in the latent stage of syphilis, in comparison to those in the early stage of syphilis infection. $\omega_p(\omega_p \leq 1)$ is a modification parameter accounting for the reduced infectiousness of infected individuals due to persistent HPV infection while $\theta_s(\theta_s \geq 1)$ is a modification parameter accounting for the increased infectiousness of dually infected individuals due to syphilis infection. In (2.1), β_s is the effective contact rate for the transmission of syphilis infection, while, in (2.2), β_h denotes the effective contact rate for the transmission of HPV infection.

Based on the above formulations and assumptions, the HPV-syphilis co-infection model is given by the following deterministic system of non-linear differential equations (the flow diagram of the model is depicted in Fig. 1 and associated parameters of the model are presented in Table 1.

$$\frac{dS}{dt} = (1-\phi)\Lambda - (\lambda_s + \lambda_h)S - \mu S,$$

$$\frac{dE}{dt} = \lambda_s S + \xi_s\lambda_s T - (\sigma_1 + \mu)E - \lambda_h E + (V_h + R_h + R_C)\lambda_s + \alpha_2 C_E + (1-\rho_2)r_3 H_E + (1-\chi_1)r_6 P_E,$$

$$\frac{dI}{dt} = \sigma_1 E - (\sigma_2 + \tau_1 + \mu)I - \gamma_1\lambda_h I + (1-\rho_3)r_4 H_I + (1-\chi_2)r_7 P_I + \alpha_3 C_I,$$

$$\frac{dL}{dt} = \sigma_2 I - (\tau_2 + \mu + \delta_{s1})L - \gamma_2\lambda_h L + (1-\rho_4)r_5 H_L + (1-\chi_3)r_8 P_L + \alpha_4 C_L,$$

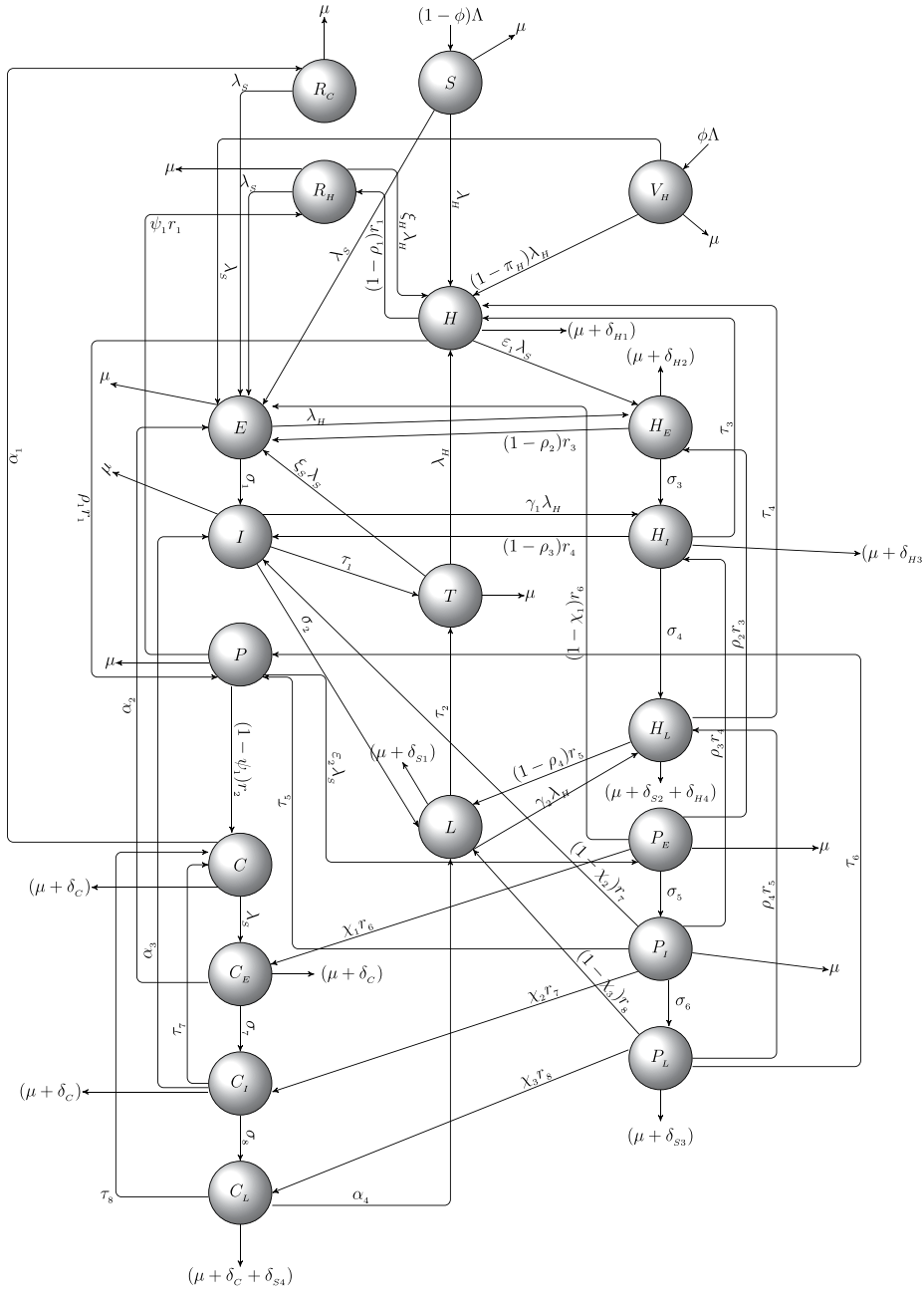


Fig. 1. Schematic diagram of the model (2.3).

Table 1. Description of parameters in the model (2.3).

Parameter	Description	Value	References
Λ_h	Recruitment rate for humans	120895	[46]
μ_h	Natural death rate	0.0135	[46]
ϕ	Fraction of individuals vaccinated against HPV	0.70	Assumed
π_h	HPV vaccine efficacy rate	0.90	[27]
τ_1, τ_2	Syphilis treatment rate for singly infected in compartments I and L, respectively	3.65	[18]
r_1, r_2	HPV natural recovery or clearance rate for individuals in compartments H and P, respectively	0.9	[28]
β_s	Effective contact rate for syphilis infection	7.0	[48]
β_h	Effective contact rate for HPV infection	2.0	[28]
$r_{i\ i=3,..8}$	HPV natural recovery or clearance rates for dually infected individuals in compartments H_E, H_I, H_L, P_E, P_I and P_L, respectively	0.9	[28]
$\tau_{i\ i=3,..8}$	Syphilis treatment rates for dually infected individuals in compartments H_I, H_L, P_I, P_L, C_I and C_L, respectively	1.0	[22]
δ_{s1}	Syphilis-induced death rate for singly infected individuals	0.06849	[20]
$\delta_{s2}, \delta_{s3}, \delta_{s3}$	Syphilis-induced death rates for dually infected individuals in compartments H_L, P_L and C_L, respectively	0.06849	Assumed
δ_{h1}	HPV-induced death rate for singly infected individuals	0.001	[27]
δ_c	Cancer-induced death rate	0.001	[52]
$\delta_{h2}, \delta_{h3}, \delta_{h4}$	HPV-induced death rates for dually infected individuals in compartments H_E, H_I and H_L, respectively	0.001	[28]
$\alpha_{i,\ i=1,2,3,4}$	Anal cancer treatment rates for individuals in compartments C, C_E, C_I and C_L, respectively	0.76	[24]
η_l	Modification parameter accounting for infectiousness of syphilis infected individuals in late latent stage	0.001	[24]
θ_h	Modification parameter accounting for increased infectiousness of dually infected individuals due to HPV infection	1.3	Assumed
θ_s	Modification parameter accounting for increased infectiousness of dually infected individuals due to syphilis infection	1.3	Assumed
ξ_s	Syphilis re-infection rate	0.6	[29]
ξ_h	HPV re-infection rate	0.2	[52]
ω_p	Modification parameter accounting for infectiousness of persistent HPV-infected individuals	0.9	[23]
ω_p	Modification parameter accounting for infectiousness of persistent HPV-infected individuals	0.9	[23]

Table 1. (*Continued*)

Parameter	Description	Value	References
ψ	Fraction of persistent HPV-infected individuals who recover naturally and do not develop anal cancer	0.5	[24]
γ_i $_{i=1,2,3}$	Modification parameter accounting for the susceptibility of syphilis-infected individuals to HPV infection	1.2	[7, 9]
ε_i $_{i=1,2,3}$	Modification parameter accounting for the susceptibility of HPV-infected individuals to syphilis infection	1.3	[11, 12]
ρ_i $_{i=1,2,3}$	Fraction of HPV-infected individuals who develop persistent HPV infection	0.5	Assumed
$\sigma_1, \sigma_3, \sigma_5$	Progression rates to early stage of syphilis infection	0.2	Assumed
$\sigma_2, \sigma_4, \sigma_6$	Progression rates to late stage of syphilis infection	0.2	[18]

$$\frac{dT}{dt} = \tau_1 I + \tau_2 L - \mu T - \xi_s \lambda_s T - \lambda_h T,$$

$$\frac{dV_h}{dt} = \phi\Lambda - (1-\pi_h)\lambda_h V_h - (\mu + \lambda_s)V_h,$$

$$\frac{dH}{dt} = \lambda_h S + (1-\pi_h)\lambda_h V_h - \varepsilon_1 \lambda_s H - (\mu + \delta_{h1} + r_1)H + \tau_3 H_I + \tau_4 H_L + \lambda_h T + \xi_h \lambda_h R_h,$$

$$\frac{dP}{dt} = \rho_1 r_1 H - \varepsilon_2 \lambda_s P - \mu P + \tau_5 P_I + \tau_6 P_L - r_2 P,$$

$$\frac{dC}{dt} = (1-\psi) r_2 P - (\mu + \alpha_1 + \delta_C)C + \tau_7 C_I + \tau_8 C_L - \lambda_s C,$$

$$\frac{dR_C}{dt} = \alpha_1 C - (\mu + \lambda_s)R_C,$$

$$\frac{dR_h}{dt} = (1-\rho_1) r_1 H + \psi r_2 P - \mu R_h - \xi_h \lambda_h R_h - \lambda_s R_h,$$

$$\frac{dH_E}{dt} = \lambda_h E + \varepsilon_1 \lambda_s H - (\sigma_3 + \mu + r_3 + \delta_{h2})H_E,$$

$$\frac{dH_I}{dt} = \sigma_3 H_E + \gamma_1 \lambda_h I - (\sigma_4 + \mu + \tau_3 + r_4 + \delta_{h3})H_I,$$

$$\frac{dH_L}{dt} = \sigma_4 H_I + \gamma_2 \lambda_h L - (\tau_4 + r_5 + \mu + \delta_{s2} + \delta_{h4})H_L,$$

$$\frac{dP_E}{dt} = \varepsilon_2 \lambda_s P - (r_6 + \mu + \sigma_5)P_E + \rho_2 r_3 H_E,$$

$$\begin{aligned}
\frac{dP_I}{dt} &= \sigma_5 P_E - (\tau_5 + r_7 + \mu + \sigma_6)P_I + \rho_3 r_4 H_I,\\
\frac{dP_L}{dt} &= \sigma_6 P_I - (\tau_6 + r_8 + \mu + \delta_{s3})P_L + \rho_4 r_5 H_L,\\
\frac{dC_E}{dt} &= \lambda_s C + \chi_1 r_6 P_E - (\mu + \delta_C + \sigma_7 + \alpha_2)C_E,\\
\frac{dC_I}{dt} &= \chi_2 r_7 P_I - (\mu + \delta_C + \sigma_8 + \alpha_3 + \tau_7)C_I + \sigma_7 C_E,\\
\frac{dC_L}{dt} &= \chi_3 r_8 P_L - (\mu + \delta_C + \delta_{s4} + \alpha_4 + \tau_8)C_L + \sigma_8 C_I.
\end{aligned} \tag{2.3}$$

2.1. *Basic properties of the co-infection model*

The basic dynamical properties of the model (2.3) will now be explored. Particularly, we establish the following positivity and invariance results.

2.1.1. *Positivity and boundedness of solutions*

For the model (2.3) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all times. Following the same approach in Omame *et al.* [27], we establish the following results.

Theorem 2.1. *Let the initial data be* $S(0) > 0$, $E(0) \geq 0$, $I(0) \geq 0$, $L(0) \geq 0$, $T(0) \geq 0$, $V_h(0) \geq 0$, $H(0) \geq 0$, $P(0) \geq 0$, $C(0) \geq 0$, $R_C(0) \geq 0$, $R_h(0) \geq 0$, $H_E(0) \geq 0$, $H_I(0) \geq 0$, $H_L(0) \geq 0$, $P_E(0) \geq 0$, $P_I(0) \geq 0$, $P_L(0) > 0$, $C_E(0) \geq 0$, $C_I(0) \geq 0$, $C_L(0) \geq 0$.

Then the solutions $(S, E, I, L, T, V_h, H, P, C, R_C, R_h, H_E, H_I, H_L, P_E, P_I, P_L, C_E, C_I, C_L)$ *of the model* (2.3) *are non-negative for all time* $t > 0$.

Lemma 2.1. *The region* $\mathcal{D} \subset \mathfrak{R}^{20}_+$ *is positively invariant for the co-infection model* (2.3) *with initial conditions in* $\mathfrak{R}^{20}_+$.

Therefore, $\mathcal{D}$ is positively invariant. Hence, no solution path can leave through any boundary of $\mathcal{D}$ and it is sufficient to consider the dynamics of the model (2.3) in $\mathcal{D}$. Inside this region, the model is considered to be mathematically and epidemiologically well posed.

3. Analysis of the Sub-Models

It is instructive to analyze the sub-models of the co-infection model (2.3), before analyzing the full model.

3.1. *Syphilis-only sub-model*

The syphilis-only sub-model is (obtained by setting $V_h = H = P = C = R_c = R_h = H_e = H_i = H_l = P_e = P_i = P_l = C_e = C_i = C_l = 0$ in the model (2.3)) given by

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - (\lambda_s + \mu)S,\\
\frac{dE}{dt} &= \lambda_s S + \xi_s \lambda_s T - (\mu + \sigma_1)E,\\
\frac{dI}{dt} &= \sigma_1 E - (\sigma_2 + \tau_1 + \mu)I,\\
\frac{dL}{dt} &= \sigma_2 I - (\tau_2 + \delta_{s1} + \mu)L,\\
\frac{dT}{dt} &= \tau_1 I + \tau_2 L - \mu T - \xi_s \lambda_s T,
\end{aligned} \tag{3.1}$$

where now

$$\lambda_s = \frac{\beta_s(I + \eta_l L)}{N} \tag{3.2}$$

with

$$N = S + E + I + L + T.$$

3.1.1. *Basic reproduction number of the syphilis only sub-model*

The syphilis-only sub-model (3.1) has a disease-free equilibrium (DFE), obtained by setting the right-hand sides of the equations in the model (3.1) to zero, given by

$$\begin{aligned}
\xi_{0S} &= (S^*, E^*, I^*, L^*, T^*)\\
&= \left(\frac{\Lambda}{\mu}, 0, 0, 0, 0\right).
\end{aligned} \tag{3.3}$$

The basic reproduction number, using the next generation operator method [40], is given by

$$\mathcal{R}_{0S} = \frac{\beta_s \sigma_1 (K_3 + \eta_l \sigma_2)}{K_1 K_2 K_3}$$

with

$$K_1 = (\sigma_1 + \mu), \quad K_2 = (\sigma_2 + \tau_1 + \mu), \quad K_3 = (\tau_2 + \delta_{s1} + \mu).$$

3.1.2. *Local asymptotic stability of DFE of the syphilis-only submodel*

Lemma 3.1. *The DFE of the syphilis-only sub-model* (3.1) *is locally asymptotically stable (LAS) if* $\mathcal{R}_{0S} < 1$ *and unstable if* $\mathcal{R}_{0S} > 1$.

Proof. The local stability of the syphilis-only sub-model is analyzed by the Jacobian matrix of the system (3.1) at ξ_{0S}, given by

$$J(\xi_{0S}) = \begin{pmatrix} -\mu & 0 & -\beta_s & -\beta_s\eta_l & 0 \\ 0 & -K_1 & \beta_s & \beta_s\eta_l & 0 \\ 0 & \sigma_1 & -K_2 & 0 & 0 \\ 0 & 0 & \sigma_2 & -K_3 & 0 \\ 0 & 0 & \tau_1 & \tau_2 & -\mu \end{pmatrix}, \tag{3.4}$$

where

$$K_1 = \mu + \sigma_1, \quad K_2 = \sigma_2 + \tau_1 + \mu, \quad K_3 = \tau_2 + \sigma_{s1} + \mu. \qquad \square$$

The eigenvalues are $-\mu$, $-\mu$ and the solution of the characteristic polynomial:

$$\lambda^3 + \alpha_1\lambda^2 + \alpha_2\lambda + \alpha_3 = 0, \tag{3.5}$$

where

$$\alpha_1 = (K_1 + K_2 + K_3), \quad \alpha_2 = K_1K_2 + K_1K_3 + K_2K_3 - \beta_s\sigma_1,$$
$$\alpha_3 = K_1K_2K_3(1 - \mathcal{R}_{0S}).$$

Applying the Routh–Hurwitz criterion, the cubic equation (3.5) will have roots with negative real parts if and only if $\alpha_1 > 0$, $\alpha_3 > 0$ and $\alpha_1\alpha_2 > \alpha_3$. Clearly, $\alpha_1 > 0$ and $\alpha_3 > 0$ (if $\mathcal{R}_{0S} < 0$). As a result, the disease-free equilibrium, ξ_{0S} is locally asymptotically stable if $\mathcal{R}_{0S} < 1$.

3.1.3. *Global asymptotic stability of the DFE of the syphilis-only sub-model*

We use the method presented in Castillo-Chavez *et al.* [41] to investigate the global asymptotic stability (GAS) of the disease-free equilibrium of the syphilis-only sub-model.

We list two conditions that if met, also guarantee the GAS of the disease-free state. First, system (3.1) must be written in the form:

$$\begin{aligned} \frac{dX}{dt} &= F(W, Q), \\ \frac{dI}{dt} &= G(W, Q), G(W, 0) = 0, \end{aligned} \tag{3.6}$$

where $W \in R^m$ denotes (its components) the number of uninfected individuals and $Q \in R^n$ denotes (its components) the number of infected individuals including latent, infectious, etc. $U_0 = (W^*, 0)$ denotes the disease-free equilibrium of this system. The following conditions $(H1)$ and $(H2)$ must be met to guarantee local

asymptotic stability:

$(H1)$ For $\frac{dX}{dt} = F(W, 0), W^*$ is globally asymptotically stable (GAS),
$(H2)$ $G(W, Q) = AI - \hat{G}(W, Q)W$, where $G(W, Q) \geq 0$ for $(W, Q) \in \Omega$,

where $A = D_1 G(W^*, 0)$ is an M-matrix (the off-diagonal elements of A are nonnegative) and Ω is the region where the model makes biological sense. If System (3.1) satisfies the above two conditions, then the following theorem holds.

Theorem 3.1. *The fixed point $U_{0S} = (W^*, 0)$ is a globally asymptotic stable (GAS) equilibrium of (3.1) provided that $R_0 < 1$ (LAS), and that assumptions $(H1)$ and $(H2)$ are satisfied.*

Proof.

$$\frac{dW}{dt} = F(W, Q) = \begin{pmatrix} \Lambda - (\lambda_s + \mu)S \\ \tau_1 I + \tau_2 L - \mu T - \xi_s \lambda_s T \end{pmatrix}, \quad F(W, 0) = \begin{pmatrix} \Lambda - \mu S \\ 0 \end{pmatrix}, \tag{3.7}$$

where W denotes the number of non-infectious individuals and Q denotes the number of infected individuals

$$G(W, Q) = \begin{pmatrix} \lambda_s S + \xi_s \lambda_s T - K_1 E \\ \sigma_1 E - K_2 I \\ \sigma_2 I - K_3 L \end{pmatrix},$$

$$A = D_Q G(W^*, 0) = \begin{pmatrix} -K_1 & \beta_s & \beta_s \eta_l \\ \sigma_1 & -K_2 & 0 \\ 0 & \sigma_2 & -K_3 \end{pmatrix},$$

$$AQ = \begin{pmatrix} -K_1 E + \beta_s (I + \eta_L L) \\ \sigma_1 E - K_2 I \\ \sigma_2 I - K_3 L \end{pmatrix},$$

$$\hat{G}(W, Q) = \begin{pmatrix} \beta_s (I + \eta_l L) \left(1 - \dfrac{S}{N}\right) - \xi_s \lambda_s T \\ 0 \\ 0 \end{pmatrix}.$$

It is clear from the above that $\hat{G}(W, Q) \ngeq 0$. Hence, the DFE, U_{0S}, may not be globally asymptotically stable, suggesting the possibility of a backward bifurcation. This supports the backward bifurcation analysis in Sec. 3.1.5. □

3.1.4. *Endemic equilibrium point (EEP) of the syphilis-only sub-model*

We now obtain the endemic equilibrium point (EEP) of the syphilis-only sub-model (3.1). The endemic equilibrium point (EEP) of the syphilis-only sub-model (3.1) is given by

$$\xi_{eS} = (S^{**}, E^{**}, I^{**}, L^{**}, T^{**}),$$

where

$$\begin{aligned}
S^{**} &= \frac{\Lambda}{\lambda_s^{**} + \mu},\\
E^{**} &= \frac{\Lambda K_2 K_3 \lambda_s^{**}\big(\mu + \xi_s \lambda_s^{**}\big)}{\big(\mu + \lambda_s^{**}\big)\big[\mu K_1 K_2 K_3 + \xi_s\big(\mu K_2 K_3 + \sigma_1 \mu K_3 + \sigma_1\sigma_2\big(\mu + \delta_{s1}\big)\big)\lambda_s^{**}\big]},\\
I^{**} &= \frac{\Lambda \sigma_1 K_3 \lambda_s \big(\mu + \xi_s \lambda_s^{**}\big)}{\big(\mu + \lambda_s^{**}\big)\big[\mu K_1 K_2 K_3 + \xi_s\big(\mu K_2 K_3 + \sigma_1 \mu K_3 + \sigma_1\sigma_2\big(\mu + \delta_{s1}\big)\big)\lambda_s^{**}\big]},\\
L^{**} &= \frac{\Lambda \sigma_1\sigma_2 \lambda_s^{**}\big(\mu + \xi_s \lambda_s^{**}\big)}{\big(\mu + \lambda_s^{**}\big)\big[\mu K_1 K_2 K_3 + \xi_s\big(\mu K_2 K_3 + \sigma_1 \mu K_3 + \sigma_1\sigma_2(\mu + \delta_{s1})\big)\lambda_s^{**}\big]},\\
T^{**} &= \frac{\Lambda \sigma_1\big(\tau_1 K_3 + \tau_2\sigma_2\big)\lambda_s^{**}}{\big(\mu + \lambda_s^{**}\big)\big[\mu K_1 K_2 K_3 + \xi_s\big(\mu K_2 K_3 + \sigma_1 \mu K_3 + \sigma_1\sigma_2(\mu + \delta_{s1})\big)\lambda_s^{**}\big]}.
\end{aligned} \tag{3.8}$$

Substituting the right-hand sides of (3.8) into the force of infection (3.2) at steady states, we obtain the polynomial equation

$$a_1 \lambda_s^{**2} + a_2 \lambda_s^{**} + a_3 = 0, \tag{3.9}$$

where

$$\begin{aligned}
a_1 &= (K_2K_3 + \sigma_1 K_3 + \sigma_1\sigma_2)\xi_s,\\
a_2 &= (\mu K_2K_3 + \sigma_1\sigma_2(\mu + \delta_{s1}) + \sigma_1\mu K_3)\xi_s + \mu K_2K_3 + \mu\sigma_1 K_3 + \mu\sigma_1\sigma_2\\
&\quad + \sigma_1(\tau_1 K_3 + \tau_2\sigma_2) - \beta_s\sigma_1\xi_s(K_3 + \eta_l\sigma_2),\\
a_3 &= \mu K_1K_2K_3(1 - \mathcal{R}_{0S}).
\end{aligned}$$

It is worthy of note from Eq. (3.9) that $a_1 > 0$, while a_3 is greater than zero (less than zero) if $\mathcal{R}_{0S} < 1 (> 1)$. Hence, the following result can be established:

Theorem 3.2. *The model* (3.1) *has*

(i) *a unique endemic equilibrium if* $a_3 < 0 \Longleftrightarrow \mathcal{R}_{0S} > 1$;
(ii) *a unique endemic equilibrium if* $a_2 < 0$ *and* $a_1 = 0$ *or* $a_2^2 - 4a_3a_1 = 0$;
(iii) *two endemic equilibria if* $a_1 > 0$, $a_2 < 0$ *and* $a_2^2 - 4a_3a_1 > 0$ *and* $\mathcal{R}_{0S} < 1$;
(iv) *no endemic equilibrium otherwise.*

It is also interesting to note that setting the re-infection term $\xi_s = 0$ reduces the quadratic (3.9) to $a_2\lambda_s^{**} + a_3 = 0$, resulting in no sign changes in the polynomial equation (3.9), as $a_2 > 0$ and $a_3 > 0$ (for $\mathcal{R}_{0S} < 1$). Hence, no existence of an endemic equilibrium for $\mathcal{R}_{0S} < 1$, ruling out the existence of backward bifurcation in the syphilis only sub-model (3.1) in the absence of re-infection of treated individuals. This is consistent with the proof in Theorem 3.1.

3.1.5. *Bifurcation analysis of the syphilis-only sub-model*

Using the same approach as in Castillo–Chavez and Song [42], we shall investigate the possibility of a backward bifurcation for the syphilis-only sub-model. The linearized system evaluated at the DFE is given as

$$\begin{pmatrix} -\mu & 0 & -\beta_s & -\beta_s\eta_l & 0 \\ 0 & -K_1 & \beta_s & \beta_s\eta_l & 0 \\ 0 & \sigma_1 & -K_2 & 0 & 0 \\ 0 & 0 & \sigma_2 & -K_3 & 0 \\ 0 & 0 & \tau_1 & \tau_2 & -\mu \end{pmatrix}, \tag{3.10}$$

where

$$K_1 = \mu + \sigma_1, \quad K_2 = \sigma_2 + \tau_1 + \mu, \quad K_3 = \tau_2 + \sigma_{s1} + \mu,$$

The components of the right eigenvector are given as

$$\begin{aligned} \omega_1 &= -(K_3 + \eta_l)\frac{\omega_5\beta_s^*}{\sigma_2\tau_2 + K_3\tau_1} < 0, \quad \omega_2 = \frac{\mu K_3\omega_5 K_2}{\sigma_1(\sigma_2\tau_2 + K_2\tau_1)} > 0, \\ \omega_3 &= \frac{\mu K_3\omega_5}{(\sigma_2\tau_2 + K_3\tau_1)} > 0, \quad \omega_4 = \frac{\mu\omega_5}{(\sigma_2\tau_2 + K_3\tau_1)} > 0, \quad \omega_5 = \omega_5 > 0. \end{aligned} \tag{3.11}$$

The components of the left eigenvector are equally given by

$$\begin{aligned} \nu_2 &= \frac{\sigma_1}{K_1K_2}, \quad \nu_3 = \frac{1}{K_2}, \quad \nu_4 = \frac{\eta_l}{K_3 + \eta_l\sigma_2}, \\ a &= \sum_{k,i,j=1}^{n} \nu_k\omega_i\omega_j\frac{\partial^2 f_k}{\partial x_i\partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{n} \nu_k\omega_i\frac{\partial^2 f_k}{\partial x_i\partial\phi}(0,0), \\ a &= -\frac{2\beta_s^*\nu_2}{N^*}(\omega_3 + \eta_l\omega_4)(\omega_2 + \omega_3 + \omega_4 + \omega_5) + \frac{2\beta_s^*\xi_s\nu_2\omega_5}{N^*}(\omega_3 + \eta_l\omega_4), \\ b &= \nu_2(\omega_3 + \omega_4\eta_l) = \frac{\mu\sigma_1\omega_5}{K_1K_3(\omega_2\tau_2 + K_3\tau_1)}(K_3 + \eta_l) > 0. \end{aligned} \tag{3.12}$$

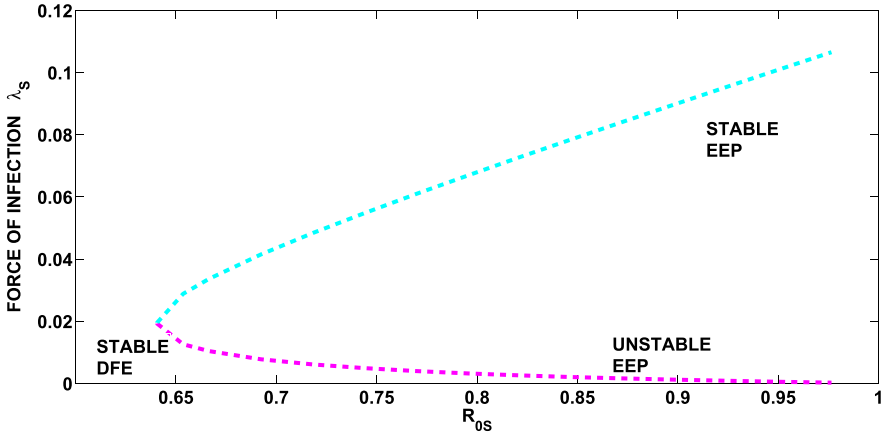


Fig. 2. Bifurcation diagram for the syphilis-only sub-model (3.1). Parameter values used are $2.48 \leq \beta_s \leq 3.865, \xi_s = 2.6142$. All other parameters are given in Table 1.

It can be observed from (3.12) that setting the re-infection parameter, $\xi_s = 0$, results in $a < 0$. Thus, re-infection induced the phenomenon of backward bifurcation in the syphilis-only sub-model (3.1). This is consistent with the results obtained in the analyses in Secs. 3.1 and 3.1.4. An associated backward bifurcation diagram is depicted in Fig. 2.

3.1.6. *GAS of EEP of the syphilis-only sub-model: special case ($\xi_s = \delta_s = 0$)*

We seek to prove the GAS of the unique endemic equilibrium of the sub-model, for a special case when re-infection term $\xi_s = 0$ and disease-induced death rate is negligible, that is, $\delta_s = 0$.

The syphilis-only sub-model (3.1) has an endemic equilibrium given by

$$\xi_{eS} = (S^{**}, E^{**}, I^{**}, L^{**}, T^{**}).$$

It should be noted that setting $\delta_s = 0$ in (3.1) gives us $N \to \frac{\Lambda}{\mu}$ as $t \to \infty$. Let $\bar{\beta}_s = \frac{\mu\beta_s}{\Lambda}$ so that

$$\lambda_s = \bar{\beta}_s(I + \eta_l L). \tag{3.13}$$

Theorem 3.3. *Consider the sub-model* (3.1) *with* $\xi_s = 0$. *The DFE is GAS in* $\mathcal{D}\backslash\mathcal{D}_0$ *whenever* $\bar{\mathcal{R}}_{0S} = \mathcal{R}_{0S}|_{\xi_s=0} > 1$, *where*

$$\mathcal{D}_0 = \{(S, E, I, L, T) \in \mathcal{D} : E = I = L = T = 0\}.$$

Proof. Consider the syphilis-only sub-model (3.1) with (3.13) and $\xi_s = 0$ and $\bar{\mathcal{R}}_0 > 1$, so that the associated unique endemic equilibrium exists. Also, consider the Lyapunov functional similar to the Goh–Volterra type considered

in [43]:

$$\mathcal{L} = \int_{S^{**}}^{S} \left(1 - \frac{S^{**}}{w}\right) dw + \int_{E^{**}}^{E} \left(1 - \frac{E^{**}}{w}\right) dw + \frac{\bar{\beta}_s S^{**}(K_3 + \sigma_2\eta_l)}{K_2K_3} \int_{I^{**}}^{I} \left(1 - \frac{I^{**}}{w}\right) dw + \frac{\bar{\beta}_s \eta_l S^{**}}{K_3} \int_{L^{**}}^{L} \left(1 - \frac{L^{**}}{w}\right) dw.$$

The time derivative, using the Leibniz rule for integration as illustrated in Adams [44], is given by

$$\dot{\mathcal{L}} = \left(1 - \frac{S^{**}}{S}\right)\dot{S} + \left(1 - \frac{E^{**}}{E}\right)\dot{E} + \frac{\bar{\beta}_s S^{**}(K_3 + \eta_l\sigma_2)}{K_2K_3}\left(1 - \frac{I^{**}}{I}\right)\dot{I} + \frac{\bar{\beta}_s \eta_l S^{**}}{K_3}\left(1 - \frac{L^{**}}{L}\right)\dot{L}.$$

Substituting the expressions for the derivatives, $\dot{S}$, $\dot{E}$, $\dot{I}$ and $\dot{L}$ from (3.1), into the Lyapunov derivative, $\dot{\mathcal{L}}$, and carrying out certain algebraic manipulations, we have that

$$\dot{\mathcal{L}} = \mu S^{**}\left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}}\right) + 3\bar{\beta}_s I^{**}S^{**} + 4\bar{\beta}_s\eta_l L^{**}S^{**} - \frac{\bar{\beta}_s(S^{**})^2}{S}(I^{**} + \eta_l L^{**}) - \frac{\bar{\beta}_s S E^{**}(I + \eta_l L)}{E} - \frac{\bar{\beta}_s S^{**}E(I^{**})^2}{E^{**}I} - \frac{\bar{\beta}_s S^{**}\eta_l E I^{**}L^{**}}{IE^{**}} - \frac{\bar{\beta}_s\eta_l(L^{**})^2 I S^{**}}{I^{**}L} \tag{3.14}$$

(3.14) can be further simplified into

$$\dot{\mathcal{L}} = \mu S^{**}\left(2 - \frac{S^{**}}{S} - \frac{S}{S^{**}}\right) + \bar{\beta}_s S^{**}I^{**}\left(3 - \frac{S^{**}}{S} - \frac{SIE^{**}}{S^{**}I^{**}E} - \frac{I^{**}E}{IE^{**}}\right) + \bar{\beta}_s S^{**}\eta_l L^{**}\left(4 - \frac{S^{**}}{S} - \frac{SLE^{**}}{S^{**}L^{**}E} - \frac{I^{**}E}{IE^{**}} - \frac{L^{**}I}{LI^{**}}\right). \tag{3.15}$$

Thus, $\dot{\mathcal{L}} \leq 0$ for $\bar{\mathcal{R}}_0 > 1$. Hence, $\mathcal{L}$ is a Lyapunov function in $\mathcal{D}$ and it follows from La Salle's Invariance principle [45] that every solution to the equations of the syphilis-only sub-model (3.1) with (3.13) and initial conditions in $\mathcal{D}\setminus\mathcal{D}_0$ approaches the associated unique endemic equilibrium ξ_{es} of the syphilis-only sub-model as $t \to \infty$ for $\bar{\mathcal{R}}_{0S} > 1$. □

The epidemiological implication of Theorem 3.3 is that if a previous infection with syphilis confers lifetime protection against re-infection, then syphilis infection will persist in the population if the threshold quantity $\bar{\mathcal{R}}_0 > 1$.

3.2. *HPV-only sub-model*

The HPV-only sub-model is (obtained by setting $E = I = L = T = H_e = H_i = H_l = P_e = P_i = P_l = C_e = C_i = C_l = 0$ in the model (2.3)) given by

$$\begin{aligned}
\frac{dS}{dt} &= (1-\phi)\Lambda - (\lambda_h + \mu)S,\\
\frac{dV_h}{dt} &= \phi\Lambda - (1-\pi_h)\lambda_h V_h - \mu_f V_h,\\
\frac{dH}{dt} &= \lambda_h S + (1-\pi_h)\lambda_h V_h - (\mu + \delta_{h1} + r_1)H + \xi_h\lambda_h R_h\\
\frac{dP}{dt} &= \rho_1 r_1 H - (\mu + r_2)P,\\
\frac{dC}{dt} &= (1-\psi)r_2 P - (\alpha_1 + \delta_c + \mu)C,\\
\frac{dR_c}{dt} &= \alpha_1 C - \mu R_c,\\
\frac{dR_h}{dt} &= (1-\rho_1)r_1 H + \psi r_2 P - (\mu + \xi_h\lambda_h)R_h,
\end{aligned} \tag{3.16}$$

where now

$$\lambda_h = \frac{\beta_h(H + \omega_p P)}{N}$$

with

$$N = S + V_h + H + P + C + R_c + R_h.$$

3.2.1. *Basic reproduction number of the HPV-only sub-model*

The HPV-only sub-model (3.16) has a DFE, obtained by setting the right-hand sides of the equations in the model (3.16) to zero, given by

$$\begin{aligned}
\xi_{0H} &= (S^*, V_h^*, H^*, P^*, C^*, R_c^*, R_h^*)\\
&= \left(\frac{(1-\phi)\Lambda}{\mu}, \frac{\phi\Lambda}{\mu}, 0, 0, 0, 0, 0\right).
\end{aligned} \tag{3.17}$$

The basic reproduction number using the next generation operator method [40] is given by

$$\mathcal{R}_{0H} = \frac{\beta_h(1-\phi\pi_h)(K_5 + \omega_p\rho_1 r_1)}{K_4 K_5}$$

with

$$K_4 = \mu + \delta_{h1} + r_1, \quad K_5 = \mu + r_2.$$

The local asymptotic stability and GAS analyses of the HPV-only sub-model (3.16) were well explored by Omame *et al.* [28].

4. Analysis of the Full Co-Infection Model

We now qualitatively analyze the full co-infection model.

4.1. *Basic reproduction number of the full co-infection model*

The model (2.3) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\begin{aligned}\xi_0 &= (S^*, E^*, I^*, L^*, T^*, V_h^*, H^*, P^*, C^*, R_c^*, R_h^*, H_e^*, H_i^*, H_l^*, P_e^*,\\ &\quad P_i^*, P_l^*, C_e^*, C_i^*, C_l^*)\\ &= (S^*, 0, 0, 0, 0, V_H^*, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0)\end{aligned}$$

with $S^* = \frac{(1-\phi)\Lambda}{\mu}$, $\quad V_H^* = \frac{\phi\Lambda}{\mu}$.

The linear stability of ξ_0 will be investigated using the next generation operator method [40] on the system (2.3).

The basic reproduction number of the model (2.3) is given by $\mathcal{R}_0 = \max\{\mathcal{R}_{0S}, \mathcal{R}_{0H}\}$ where $\mathcal{R}_{0S}$ and $\mathcal{R}_{0H}$ are the associated reproduction numbers for syphilis and HPV transmissions, respectively, given by

$$\mathcal{R}_{0S} = \frac{\beta_S \sigma_1 (K_3 + \eta_l \sigma_2)}{K_1 K_2 K_3},$$

$$\mathcal{R}_{0H} = \frac{\beta_H (1 - \phi\pi_h)(K_5 + \omega_p \rho_1 r_1)}{K_4 K_5}$$

with

$$K_1 = (\sigma_1 + \mu), \quad K_2 = (\sigma_2 + \tau_1 + \mu), \quad K_3 = (\tau_2 + \delta_{s1} + \mu),$$

$$K_4 = \mu + \delta_{h1} + r_1, \quad K_5 = \mu + r_2.$$

4.2. *Local asymptotic stability of disease-free equilibrium co-infection model*

Lemma 4.1. *The DFE,* ξ_0*, of the HPV–syphilis co-infection model* (2.3) *is locally asymptotically stable* (*LAS*) *if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

The epidemiological implication of Lemma 4.1 is that when $\mathcal{R}_0 < 1$, a small influx of HPV or syphilis-infected individuals into the population will not generate large HPV or syphilis outbreaks, and the diseases will die out.

4.3. *GAS of the disease-free equilibrium of the full co-infection model*

Using the same approach as in Sec. 3.1.3, we can establish the following result.

Consider the following conditions:

$(H1)$ For $\frac{dW}{dt} = F(W, 0), W^*$is globally asymptotically stable (GAS),
$(H2)$ $G(W, Q) = AQ - \hat{G}(W, Q)W$, where $G(W, Q) \geq 0$ for $(W, Q) \in \Omega$,

where $A = D_Q G(W^*, 0)$ is an M-matrix (the off-diagonal elements of A are nonnegative) and Ω is the region where the model makes biological sense. If system (2.3) satisfies the above two conditions, then the following theorem holds.

Theorem 4.1. *The fixed point $U_0 = (W^*, 0)$ is a globally asymptotic stable (GAS) equilibrium of* (2.3) *provided that $R_0 < 1$ (LAS) and that assumptions* $(H1)$ *and* $(H2)$ *are satisfied.*

The proof follows as in Sec. 3.1, where

$$\hat{G}(X, I) = \begin{bmatrix} \lambda_h E + \beta_s\big[I + C_I + \eta_l(L + C_L) + \theta_h\{H_I + \omega_P P_I \\ + \eta_l(H_L + \omega_P P_L)\}\big]\left[1 - \dfrac{S + V_h + R_h + R_c}{N}\right] - \xi_s\lambda_s T \\ \gamma_1\lambda_h I \\ \gamma_2\lambda_h L \\ \varepsilon_1\lambda_s H + \beta_h\big[H + H_E + \omega_P(P + P_E) + \theta_s\{H_I + \omega_P P_I \\ + \eta_l(H_L + \omega_P P_L)\}\big]\left[\dfrac{S^* + (1-\pi_h)V^*}{N^*} - \dfrac{(S + (1-\pi_h)V_h)}{N}\right] - \xi_h\lambda_h R_h \\ \varepsilon_2\lambda_s P \\ \lambda_s C \\ -[\lambda_h E + \varepsilon_1\lambda_s H] \\ -\gamma_1\lambda_h I \\ -\gamma_1\lambda_h L \\ -\varepsilon_2\lambda_s P \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}.$$

It is evident from the above that $\hat{G}(W, Q) \ngeq 0$, which means that the condition $(H2)$ is not satisfied. Hence, the DFE, $U_0 = (W^*, 0)$ may not be globally asymptotically stable, suggesting the possibility of a backward bifurcation. This supports

the backward bifurcation analysis for the full-co-infection model (2.3) in the next section.

4.4. *Backward bifurcation analysis of the full co-infection model*

We shall investigate the type of bifurcation the model (2.3) may undergo, using the Centre Manifold Theory as discussed in [42]. The following result can be obtained using the approach in [42].

Theorem 4.2. *If* $\mathcal{R}_0 < 1$ *and a backward bifurcation coefficient* $a > 0$, *where*

$$\begin{aligned} a = &-\frac{2\beta_s^*(\omega_3+\eta_l\omega_4)\nu_2}{N^*}\{\omega_3+\omega_4+\omega_5-\xi_s\omega_5+\omega_7+\omega_8+\omega_9\} \\ &-\frac{2\beta_s^*(\omega_3+\eta_l\omega_4)}{N^*}\{\varepsilon_1\omega_7(\nu_7-\nu_{12})+\varepsilon_2\omega_8(\nu_8-\nu_{15})\} \\ &-\frac{2\beta_h\{x_1^*+(1-\pi_h)x_6^*\}(\omega_7+\omega_p\omega_8)\nu_7}{N^*}\{\omega_1+\omega_2+\omega_3 \\ &+\omega_4+\omega_5+\omega_6+\omega_7+\omega_8+\omega_9+\omega_{10}+\omega_{11}\}-\frac{2\beta_h(\omega_7+\omega_p\omega_8)}{N^*}\{\omega_2(\nu_2-\nu_{12}) \\ &+\gamma_1\omega_3(\nu_3-\nu_{13})+\gamma_2\omega_4(\nu_4-\nu_{14})-(\omega_1+\omega_5+(1-\pi_h)\omega_6-\xi_h\omega_{11})\nu_7\}, \end{aligned}$$

then model (2.3) *exhibits backward bifurcation at* $\mathcal{R}_0 = 1$. *If* $a < 0$, *then the system* (2.3) *exhibits a forward bifurcation at* $\mathcal{R}_0 = 1$.

Proof. Suppose

$$\begin{aligned} \xi_e = \big(&S^{**}, E^{**}, I^{**}, L^{**}, T^{**}, V_h^{**}, H^{**}, P^{**}, C^{**}, R_c^{**}, R_h^{**}, H_e^{**}, \\ &H_i^{**}, H_l^{**}, P_e^{**}, P_i^{**}, P_l^{**}, C_e^{**}, C_i^{**}, C_l^{**}\big) \end{aligned}$$

represents any arbitrary endemic equilibrium of the model (i.e. an endemic equilibrium in which at least one of the infected components is non-zero). To apply the Centre Manifold Theory, it is necessary to carry out the following change of variables.

Let

$$\begin{aligned} &S = x_1, \quad E = x_2, \quad I = x_3, \quad L = x_4, \quad T = x_5, \quad V_h = x_6, \quad H = x_7, \quad P = x_8, \\ &C = x_9, \quad R_c = x_{10}, \quad R_h = x_{11}, \quad H_e = x_{12}, \quad H_i = x_{13}, \quad H_l = x_{14}, \quad P_e = x_{15}, \\ &P_i = x_{16}, \quad P_l = x_{17}, \quad C_e = x_{18}, \quad C_i = x_{19}, \quad C_l = x_{20}, \end{aligned}$$

so that

$$N = \sum_{i=1}^{20} x_i.$$

Further, using the vector notation

$$X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}, x_{11}, x_{12}, x_{13}, x_{14}, x_{15}, x_{16}, x_{17}, x_{18}, x_{19}, x_{20})^T,$$

the model (2.3) can be re-written in the form

$$\frac{dX}{dt} = f = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10}, f_{11}, f_{12}, f_{13}, f_{14}, f_{15}, f_{16}, f_{17}, f_{18}, f_{19}, f_{20})^T$$

as follows:

$$\begin{aligned}
\dot{x}_1 &= (1-\phi)\Lambda - (\lambda_s + \lambda_h)x_1 - \mu x_1,\\
\dot{x}_2 &= \lambda_s x_1 + \xi_s \lambda_s x_5 + (x_6 + x_{11} + x_{10})\lambda_s + \alpha_2 x_{18} + (1-\rho_2) r_3 x_{12}\\
&\quad + (1-\chi_1) r_6 x_{15} - (\sigma_1 + \mu) x_2 - \lambda_h x_2,\\
\dot{x}_3 &= \sigma_1 x_2 + (1-\rho_3) r_4 x_{13} + (1-\chi_2) r_7 x_{16} + \alpha_3 x_{19} - (\sigma_2 + \tau_1 + \mu) x_3 - \gamma_1 \lambda_h x_3,\\
\dot{x}_4 &= \sigma_2 x_3 + (1-\rho_4) r_5 x_{14} + (1-\chi_3) r_8 x_{17} + \alpha_4 x_{20} - (\tau_2 + \mu + \delta_{s1}) x_4 - \gamma_2 \lambda_h x_4,\\
\dot{x}_5 &= \tau_1 x_3 + \tau_2 x_4 - \mu x_5 - \xi_s \lambda_s x_5 - \lambda_h x_5,\\
\dot{x}_6 &= \phi\Lambda - (1-\pi_h)\lambda_h x_6 - (\mu + \lambda_s) x_6,\\
\dot{x}_7 &= \lambda_h x_1 + (1-\pi_h)\lambda_h x_6 - \varepsilon_1 \lambda_s x_7 + \tau_3 x_{13}\\
&\quad + \tau_4 x_{14} + \lambda_h x_5 + \xi_h \lambda_h x_{11} - (\mu + \delta_{h1} + r_1) x_7,\\
\dot{x}_8 &= \rho_1 r_1 x_7 + \tau_5 x_{16} + \tau_6 x_{17} - \varepsilon_2 \lambda_s x_8 - \mu x_8 - r_2 x_8,\\
\dot{x}_9 &= (1-\psi) r_2 x_8 + \tau_7 x_{19} + \tau_8 x_{20} - \lambda_s x_9 - (\mu + \alpha_1 + \delta_C) x_9,\\
\dot{x}_{10} &= \alpha_1 x_9 - (\mu + \lambda_s) x_{10},\\
\dot{x}_{11} &= (1-\rho_1) r_1 x_7 + \psi r_2 x_8 - \mu x_{11} - \xi_h \lambda_h x_{11} - \lambda_s x_{11},\\
\dot{x}_{12} &= \lambda_h x_2 + \varepsilon_1 \lambda_s x_7 - (\sigma_3 + \mu + r_3 + \delta_{h2}) x_{12},\\
\dot{x}_{13} &= \sigma_3 x_{12} + \gamma_1 \lambda_h x_3 - (\sigma_4 + \mu + \tau_3 + r_4 + \delta_{h3}) x_{13},\\
\dot{x}_{14} &= \sigma_4 x_{13} + \gamma_2 \lambda_h x_4 - (\tau_4 + r_5 + \mu + \delta_{s2} + \delta_{h4}) x_{14},\\
\dot{x}_{15} &= \varepsilon_2 \lambda_s x_8 + \rho_2 r_3 x_{12} - (r_6 + \mu + \sigma_5) x_{15},\\
\dot{x}_{16} &= \sigma_5 x_{15} + \rho_3 r_4 x_{13} - (\tau_5 + r_7 + \mu + \sigma_6) x_{16},\\
\dot{x}_{17} &= \sigma_6 x_{16} + \rho_4 r_5 x_{14} - (\tau_6 + r_8 + \mu + \delta_{s3}) x_{17},
\end{aligned}$$

$$\begin{aligned}
\dot{x}_{18} &= \lambda_s x_9 + \chi_1 r_6 x_{15} - (\mu + \delta_C + \sigma_7 + \alpha_2)x_{18},\\
\dot{x}_{19} &= \chi_2 r_7 x_{16} + \sigma_7 x_{18} - (\mu + \delta_C + \sigma_8 + \alpha_3 + \tau_7)x_{19},\\
\dot{x}_{20} &= \chi_3 r_8 x_{17} + \sigma_8 x_{19} - (\mu + \delta_C + \delta_{s4} + \alpha_4 + \tau_8)x_{20},
\end{aligned} \tag{4.1}$$

where

$$\begin{aligned}
\lambda_s &= \frac{\beta_s\big[x_3 + x_{19} + \eta_l(x_4 + x_{20}) + \theta_h\{x_{13} + \omega_P x_{16} + \eta_l(x_{14} + \omega_P x_{17})\}\big]}{N},\\
\lambda_h &= \frac{\beta_h\big[x_7 + x_{12} + \omega_P(x_8 + x_{15}) + \theta_s\{x_{13} + \omega_P x_{16} + \eta_l(x_{14} + \omega_P x_{17})\}\big]}{N}.
\end{aligned} \tag{4.2}$$

Consider the case when $\mathcal{R}_{0S} = 1$. Suppose, further, that β_s is chosen as a bifurcation parameter. Solving for $\beta_s = \beta_s^*$ from $\mathcal{R}_{0S} = 1$ gives

$$\beta_s = \beta_s^* = \frac{K_1K_2K_3}{\sigma(K_3 + \eta_l\sigma_2)}.$$

Evaluating the Jacobian of the system (4.1) at the DFE, $J(\xi_0)$, and using the approach in [42], we have that $J(\xi_0)$ has a right eigenvector (associated with the simple zero eigenvalue of $J(\xi_0)$) given by

$$\begin{aligned}
\mathbf{w} = [&\omega_1, \omega_2, \omega_3, \omega_4, \omega_5, \omega_6, \omega_7, \omega_8, \omega_9, \omega_{10}, \omega_{11}, \omega_{12}, \omega_{13}, \omega_{14},\\
&\omega_{15}, \omega_{16}, \omega_{17}, \omega_{18}, \omega_{19}, \omega_{20}]^T,
\end{aligned}$$

where

$$\begin{aligned}
\omega_1 &= -\frac{1}{\mu}\left[\frac{K_1K_2x_1^*}{\sigma_1\sigma_2N^*} + \frac{\beta_h x_1^*(K_5 + \omega_p\rho_1 r_1)}{K_5N^*}\right] < 0, \quad \omega_2 = \frac{K_2}{\sigma_1\sigma_2} > 0,\\
\omega_3 &= \frac{1}{\sigma_2} > 0, \quad \omega_4 = \frac{1}{K_3} > 0, \quad \omega_5 = \frac{\tau_1K_3 + \tau_2\sigma_2}{\mu\sigma_2K_3} > 0,\\
\omega_6 &= -\frac{1}{\mu}\left[\frac{K_1K_2x_6^*}{\sigma_1\sigma_2N^*} + \frac{(1-\pi_h)\beta_h x_6^*(K_5 + \omega_p\rho_1 r_1)}{K_5N^*}\right] < 0, \quad \omega_7 = \omega_7 > 0,\\
\omega_8 &= \frac{\rho_1 r_1}{K_5}\omega_7 > 0, \quad \omega_9 = \frac{G_1\rho_1 r_1}{K_5K_6}\omega_7 > 0, \quad \omega_{10} = \frac{\alpha_1G_1\rho_1 r_1}{\mu K_5K_6}\omega_7 > 0,\\
\omega_{11} &= \frac{(K_5G_8 + \psi r_1r_2\rho_1)}{\mu K_5}\omega_7 > 0,\\
\omega_{12} &= \omega_{13} = \omega_{14} = \omega_{15} = \omega_{16} = \omega_{17} = \omega_{18} = \omega_{19} = \omega_{20} = 0.
\end{aligned}$$

The components of the left eigenvector of $J(\xi_0)|_{\beta_s=\beta_s^*}$, $\mathbf{v} = (\nu_1, \nu_2, \ldots, \nu_{20})$ satisfying $\mathbf{v}.\mathbf{w} = 1$ are

$$\nu_2 = \frac{\sigma_1(K_3 + \eta_l\sigma_2)}{K_1K_2K_3\eta_l} > 0, \quad \nu_3 = \frac{K_3 + \eta_l\sigma_2}{K_2K_3\eta_l} > 0,$$

$$\nu_4 = \frac{1}{K_3} > 0, \quad \nu_7 = \nu_7 > 0, \quad \nu_8 = \frac{\omega_p \beta_h (x_1^* + x_6^*)}{K_5 N^*} \nu_7 > 0,$$

$$\nu_{12} = \frac{\begin{array}{l} N^* G_1 \sigma_1 (K_3 + \eta_l \sigma_2) + \eta_l K_1 K_2 K_3 \beta_h \{x_1^* + (1 - \pi_h x_6^*)\} \nu_7 \\ + \eta_l N^* K_1 K_2 K_3 (\sigma_3 \nu_{13} + \rho_2 r_3 \nu_{15}) \end{array}}{\eta_l N^* K_1 K_2 K_3} > 0,$$

$$\nu_{13} = \frac{\begin{array}{l} N^* \theta_h K_2 K_3 + N^* G_3 (K_3 + \eta_l \sigma_2) + K_2 K_3 \eta_l N^* [\rho_3 r_4 \nu_{16} + \sigma_4 \nu_{14}] \\ + [\theta_s \beta_h \{x_1^* + (1 - \pi_h) x_6^*\} \tau_3 N^*] K_1 K_3 \eta_l \nu_7 \end{array}}{K_2 K_3 K_8 \eta_l N^*},$$

$$\nu_{14} = \frac{\begin{array}{l} N^* \theta_h K_3 + N^* G_5 + [\tau_7 K_3 N^* + \theta_s \sigma_L \beta_h K_3 \{x_1^* \\ + (1 - \pi_h x_6^*)\}] \nu_7 + K_3 N^* \rho_4 r_5 \nu_{17} \end{array}}{K_3 K_9 N^*} > 0,$$

$$\nu_{15} = \frac{\begin{array}{l} G_2 \sigma_1 (K_3 + \eta_l \sigma_2) N^* + [\omega_p \beta_h \{x_1^* + (1 - \pi_h) x_6^*\} \nu_7 \\ + \sigma_5 N^* \nu_{16} + \chi_1 r_6 N^* \nu_{18}] \eta_l K_1 K_2 K_3 \end{array}}{\eta_l K_1 K_2 K_3 K_{10} N^*} > 0,$$

$$\nu_{16} = \frac{\begin{array}{l} \theta_h \omega_p K_3 K_5 K_{14} K_{15} K_{16} N^* + \eta_l G_4 K_5 K_{14} K_{15} K_{16} N^* \\ + \omega_p \eta_l K_3 K_{14} K_{15} K_{16} (\theta_s K_5 + \tau_5) \{x_1^* + (1 - \pi_h) x_6^*\} \nu_7 \end{array}}{\eta_l K_3 K_5 K_{14} K_{15} K_{16} N^*},$$

$$+ \frac{\eta_l K_3 K_5 K_{14} K_{15} K_{16} \sigma_6 \nu_{17} + \chi_2 r_7 K_5 [K_3 K_{15} + \eta_l (K_3 + \alpha_4) \sigma_8]}{\eta_l K_3 K_5 K_{14} K_{15} K_{16} N^*} > 0,$$

$$\nu_{17} = \frac{\theta_h \omega_p K_3 K_5 K_{12} K_{15} N^* + G_6 K_5 K_{12} K_{15} N^* + K_5 K_{12} N^* \chi_3 r_8 (K_3 + \alpha_4)}{K_3 K_5 K_{12} K_{15} N^*},$$

$$+ \frac{K_3 K_{12} K_{15} \beta_h \omega_p \{x_1^* + (1 - \pi_h x_6^*)\} (K_5 \theta_s \eta_l + \tau_6) \nu_7}{K_3 K_5 K_{12} K_{15} N^*} > 0,$$

$$\nu_{18} = \frac{\alpha_2 \sigma_1 K_{14} K_{15} (K_3 + \eta_l \sigma_2) + \sigma_7 K_1 K_2 [K_3 K_{15} + \eta_l \sigma_8 (K_3 + \alpha_4)]}{\eta_l K_1 K_2 K_3 K_{13} K_{14} K_{15}} > 0,$$

$$\nu_{19} = \frac{K_3 K_{15} + \eta_l \sigma_8 (K_3 + \alpha_4)}{\eta_l K_3 K_{14} K_{15}} > 0,$$

$$\nu_{20} = \frac{K_3 + \alpha_4}{K_3 K_{15}} > 0, \quad \nu_1 = \nu_5 = \nu_6 = \nu_9 = \nu_{10} = \nu_{11} = 0,$$

where

$$K_1 = \sigma_1 + \mu, \quad K_2 = \sigma_2 + \tau_1 + \mu, \quad K_3 = \tau_2 + \mu + \delta_{s1},$$

$$K_4 = \mu + \delta_{h1} + r_1, \quad K_5 = \mu + r_2, \quad K_6 = \mu + \alpha_1 + \delta_c,$$

$$K_7 = \sigma_3 + \mu + r_3 + \delta_{h2}, \quad K_8 = \sigma_4 + \mu + \tau_3 + r_4 + \delta_{h3}$$

$$K_9 = \tau_4 + r_5 + \mu + \delta_{s2} + \delta_{h4}, \quad K_{10} = r_6 + \mu + \sigma_5,$$

$$K_{11} = \tau_5 + r_7 + \mu + \sigma_6, \quad K_{12} = \tau_6 + r_8 + \mu + \delta_{s3},$$

$$K_{13} = \mu + \delta_C + \sigma_7 + \alpha_2, \quad K_{14} = \mu + \delta_C + \sigma_8 + \alpha_3 + \tau_7,$$
$$K_{15} = \mu + \delta_C + \delta_{s4} + \alpha_4 + \tau_8, \quad G_1 = (1-\rho_2)r_3,$$
$$G_2 = (1-\chi_1)r_6, \quad G_3 = (1-\rho_3)r_4, \quad G_4 = (1-\chi_2)r_7,$$
$$G_5 = (1-\rho_4)r_5, \quad G_6 = (1-\chi_3)r_8, \quad G_7 = (1-\psi_1)r_2,$$
$$G_8 = (1-\rho_1)r_1, \quad X_2^* = [x_1^* + (1-\pi_h)x_6^*].$$

It follows from Theorem 4.1 in [42], by computing the non-zero partial derivatives of $f(x)$ (evaluated at the disease-free equilibrium, (ξ_0)) that the associated bifurcation coefficients is defined by a and b, given by

$$a = \sum_{k,i,j=1}^{n} \nu_k \omega_i \omega_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \quad \text{and} \quad b = \sum_{k,i=1}^{n} \nu_k \omega_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_S^*}(0,0),$$

are computed to be

$$\begin{aligned} a = &-\frac{2\beta_s^*(\omega_3 + \eta_l\omega_4)\nu_2}{N^*}\{\omega_3 + \omega_4 + \omega_5 - \xi_s\omega_5 + \omega_7 + \omega_8 + \omega_9\} \\ &+ \frac{2\beta_s^*(\omega_3 + \eta_l\omega_4)}{N^*}\{\varepsilon_1\omega_7(\nu_{12} - \nu_7) + \varepsilon_2\omega_8(\nu_{15} - \nu_8)\} \\ &- \frac{2\beta_h\{x_1^* + (1-\pi_h)x_6^*\}(\omega_7 + \omega_p\omega_8)\nu_7}{N^{*2}}\{\omega_1 + \omega_2 + \omega_3 + \omega_4 + \omega_5 + \omega_6 + \omega_7 \\ &+ \omega_8 + \omega_9 + \omega_{10} + \omega_{11}\} + \frac{2\beta_h(\omega_7 + \omega_p\omega_8)}{N^*}\{\omega_2(\nu_{12} - \nu_2) + \gamma_1\omega_3(\nu_{13} - \nu_3) \\ &+ \gamma_2\omega_4(\nu_{14} - \nu_4) + (\omega_1 + \omega_5 + (1-\pi_h)\omega_6 + \xi_h\omega_{11})\nu_7\} \end{aligned} \tag{4.3}$$

and

$$b = \sum_{k,i=1}^{20} \nu_k \omega_i \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) = (\omega_3 + \eta_l\omega_4)\nu_2 > 0.$$

Since the bifurcation coefficient b is positive, it follows from Theorem 4.1 in [42] that model (2.3), or the transformed model (4.1), will undergo a backward bifurcation if the backward bifurcation coefficient, a, given by (4.3) is positive. The public health implication of the phenomenon of backward bifurcation is that the classical epidemiological requirement of having the reproduction number $\mathcal{R}_0$ to be less than unity, while necessary, is no longer sufficient for the effective control of the disease in the population. In other words, the backward bifurcation property of the model (2.3) makes effective control of the diseases in the population very difficult. □

5. Analysis of Optimal Control Problem

We apply Pontryagin's Maximum Principle to determine the necessary conditions for the optimal control of the HPV–Syphilis co-infection model. We assume that

the proportion of vaccinated individuals, ϕ for HPV and the syphilis treatment rates $u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8$ are now time dependent and will therefore act as the control variables. Hence, we have

$$\begin{aligned}
\dot{S} &= (1-\phi(t))\Lambda - (\lambda_s + \lambda_h)S - \mu S,\\
\dot{E} &= \lambda_s S + \xi_s \lambda_s T - (\sigma_1 + \mu)E - \lambda_h E + (V_h + R_h + R_C)\lambda_s + \alpha_2 C_E\\
&\quad + (1-\rho_2) r_3 H_E + (1-\chi_1) r_6 P_E,\\
\dot{I} &= \sigma_1 E - (\sigma_2 + u_1(t) + \mu)I - \gamma_1 \lambda_h I + (1-\rho_3) r_4 H_I + (1-\chi_2) r_7 P_I + \alpha_3 C_I,\\
\dot{L} &= \sigma_2 I - (u_2(t) + \mu + \delta_{s1})L - \gamma_2 \lambda_h L + (1-\rho_4) r_5 H_L + (1-\chi_3) r_8 P_L + \alpha_4 C_L,\\
\dot{T} &= u_1(t) I + u_2(t) L - \mu T - \xi_s \lambda_s T - \lambda_h T,\\
\dot{V_h} &= \phi(t)\Lambda - (1-\pi_h)\lambda_h V_h - (\mu + \lambda_s)V_h,\\
\dot{H} &= \lambda_h S + (1-\pi_h)\lambda_h V_h - \varepsilon_1 \lambda_s H - (\mu + \delta_{h1} + r_1)H + u_3(t) H_I\\
&\quad + u_4(t) H_L + \lambda_h T + \xi_h \lambda_h R_h,\\
\dot{P} &= \rho_1 r_1 H - \varepsilon_2 \lambda_s P - \mu P + u_5(t) P_I + u_6(t) P_L - r_2 P,\\
\dot{C} &= (1-\psi) r_2 P - (\mu + \alpha_1 + \delta_C) C + u_7(t) C_I + u_8(t) C_L - \lambda_s C,\\
\dot{R_C} &= \alpha_1 C - (\mu + \lambda_s) R_C,\\
\dot{R_h} &= (1-\rho_1) r_1 H + \psi r_2 P - \mu R_h - \xi_h \lambda_h R_h - \lambda_s R_h,\\
\dot{H_E} &= \lambda_h E + \varepsilon_1 \lambda_s H - (\sigma_3 + \mu + r_3 + \delta_{h2}) H_E,\\
\dot{H_I} &= \sigma_3 H_E + \gamma_1 \lambda_h I - (\sigma_4 + \mu + u_3(t) + r_4 + \delta_{h3}) H_I,\\
\dot{H_L} &= \sigma_4 H_I + \gamma_2 \lambda_h L - (u_4(t) + r_5 + \mu + \delta_{s2} + \delta_{h4}) H_L,\\
\dot{P_E} &= \varepsilon_2 \lambda_s P - (r_6 + \mu + \sigma_5) P_E + \rho_2 r_3 H_E,\\
\dot{P_I} &= \sigma_5 P_E - (u_5(t) + r_7 + \mu + \sigma_6) P_I + \rho_3 r_4 H_I,\\
\dot{P_L} &= \sigma_6 P_I - (u_6(t) + r_8 + \mu + \delta_{s3}) P_L + \rho_4 r_5 H_L,\\
\dot{C_E} &= \lambda_s C + \chi_1 r_6 P_E - (\mu + \delta_C + \sigma_7 + \alpha_2) C_E,\\
\dot{C_I} &= \chi_2 r_7 P_I - (\mu + \delta_C + \sigma_8 + \alpha_3 + u_7(t)) C_I + \sigma_7 C_E,\\
\dot{C_L} &= \chi_3 r_8 P_L - (\mu + \delta_C + \delta_{s4} + \alpha_4 + u_8(t)) C_L + \sigma_8 C_I,
\end{aligned} \tag{5.1}$$

where

$$\lambda_s = \frac{\beta_s[I + C_I + \eta_l(L + C_L) + \theta_h\{H_I + \omega_P P_I + \eta_l(H_L + \omega_P P_L)\}]}{N},$$
$$\lambda_h = \frac{\beta_h[H + H_E + \omega_P(P + P_E) + \theta_s\{H_I + \omega_P P_I + \eta_l(H_L + \omega_P P_L)\}]}{N}. \tag{5.2}$$

For this, we consider the objective functional

$$\begin{aligned} J[u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8, \phi] &= \int_0^T [E(t) + I(t) + L(t) + H(t) + P(t) + C(t) + H_E(t) + H_I(t) \\ &\quad + H_L(t) + P_E(t) + P_I(t) + P_l(t) + C_E(t) + C_I(t) + C_l(t) \\ &\quad \frac{1}{2}w_1\phi^2 + \frac{1}{2}w_2u_1^2 + \frac{1}{2}w_3u_2^2 + \frac{1}{2}w_4u_3^2 + \frac{1}{2}w_5u_4^2 + \frac{1}{2}w_6u_5^2 + \frac{1}{2}w_7u_6^2 \\ &\quad + \frac{1}{2}w_8u_7^2 + \frac{1}{2}w_9u_8^2\Big]\, dt. \end{aligned} \tag{5.3}$$

The parameters, $w_1, w_2, w_3, w_4, w_5, w_6, w_7$ and w_8, are the weight on the benefit and cost of implementing the optimal control measure, where W_1 balances the cost factors as a result of the size and the relevance of the terms making up the objective functional. T is the final time. We seek to find an optimal control, $\phi^*, u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*, u_7^*$, and u_8^* such that

$$\begin{aligned} &J(\phi^*, u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*, u_7^*, u_8^*) \\ &\quad = \min\{J(\phi, u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8)| \\ &\qquad \phi, u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8 \in U\}, \end{aligned} \tag{5.4}$$

where $U = \{(\phi, u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8)\}$ such that $\phi, u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8$ are measurable with $0 \le \phi \le 1, 0 \le u_1 \le 1, 0 \le u_2 \le 1, 0 \le u_3 \le 1, 0 \le u_4 \le 1, 0 \le u_5 \le 1, 0 \le u_6 \le 1, 0 \le u_7 \le 1, 0 \le u_8 \le 1$, for $t \in [0, T]$ is the control set. Pontryagin's Maximum Principle [53] gives the necessary conditions which an optimal control set must satisfy. This principle transforms (5.1), (5.3) and (5.4) into a problem of minimizing a Hamiltonian, $\mathcal{H}_{am}$, pointwisely with regard to the control functions, $\phi, u_1, u_2, u_3, u_4, u_5, u_6, u_7$ and u_8:

$$\begin{aligned} \mathcal{H}_{am} &= E(t) + I(t) + L(t) + H(t) + P(t) + C(t) + H_E(t) + H_I(t) + H_L(t) \\ &\quad + P_E(t) + P_I(t) + P_l(t) + C_E(t) + C_I(t) + C_l(t) + \frac{1}{2}w_1\phi^2 + \frac{1}{2}w_2u_1^2 \\ &\quad + \frac{1}{2}w_3u_2^2 + \frac{1}{2}w_4u_3^2 + \frac{1}{2}w_5u_4^2 + \frac{1}{2}w_6u_5^2 + \frac{1}{2}w_7u_6^2 + \frac{1}{2}w_8u_7^2 + \frac{1}{2}w_9u_8^2 \\ &\quad + \lambda_S\big[(1 - \phi(t))\Lambda - (\lambda_s + \lambda_h)S - \mu S\big] + \lambda_E\big[\lambda_s S + \xi_s\lambda_s T - (\sigma_1 + \mu)E \end{aligned}$$

$$
\begin{aligned}
&- \lambda_h E + (V_h + R_h + R_C)\lambda_s + \alpha_2 C_E + (1-\rho_2) r_3 H_E + (1-\chi_1) r_6 P_E \big] \\
&+ \lambda_I \big[\sigma_1 E - (\sigma_2 + u_1 + \mu) I - \gamma_1 \lambda_h I + (1-\rho_3) r_4 H_I \\
&+ (1-\chi_2) r_7 P_I + \alpha_3 C_I \big] + \lambda_L \big[\sigma_2 I - (u_2 + \mu + \delta_{s1}) L - \gamma_2 \lambda_h L \\
&+ (1-\rho_4) r_5 H_L + (1-\chi_3) r_8 P_L + \alpha_4 C_L \big] \\
&+ \lambda_T \big[u_1 I + u_2 L - \mu T - \xi_s \lambda_s T - \lambda_h T \big] \\
&+ \lambda_{V_H} \big[\phi(t)\Lambda - (1-\pi_h)\lambda_h V_h - (\mu + \lambda_s) V_h \big] \\
&+ \lambda_H \big[\lambda_h S + (1-\pi_h)\lambda_h V_h - \varepsilon_1 \lambda_s H - (\mu + \delta_{h1} + r_1) H \\
&+ u_3 H_I + u_4 H_L + \lambda_h T + \xi_h \lambda_h R_h \big] \\
&+ \lambda_P \big[\rho_1 r_1 H - \varepsilon_2 \lambda_s P - \mu P + u_5 P_I + u_6 P_L - r_2 P \big] \\
&+ \lambda_C \big[(1-\psi) r_2 P - (\mu + \alpha_1 + \delta_C) C + u_7 C_I + u_8 C_L - \lambda_s C \big] \\
&+ \lambda_{R_C} \big[\alpha_1 C - (\mu + \lambda_s) R_C \big] \\
&+ \lambda_{R_H} \big[(1-\rho_1) r_1 H + \psi r_2 P - \mu R_h - \xi_h \lambda_h R_h - \lambda_s R_h \big] \\
&+ \lambda_{H_E} \big[\lambda_h E + \varepsilon_1 \lambda_s H - (\sigma_3 + \mu + r_3 + \delta_{h2}) H_E \big] \\
&+ \lambda_{H_I} \big[\sigma_3 H_E + \gamma_1 \lambda_h I - (\sigma_4 + \mu + u_3 + r_4) H_I \big] \\
&+ \lambda_{H_L} \big[\sigma_4 H_I + \gamma_2 \lambda_h L - (u_4 + r_5 + \mu + \delta_{s2} + \delta_{h3}) H_L \big] \\
&+ \lambda_{P_E} \big[\varepsilon_2 \lambda_s P - (r_6 + \mu + \sigma_5) P_E + \rho_2 r_3 H_E \big] \\
&+ \lambda_{P_I} \big[\sigma_5 P_E - (u_5 + r_7 + \mu + \sigma_6) P_I + \rho_3 r_4 H_I \big] \\
&+ \lambda_{P_L} \big[\sigma_6 P_I - (u_6 + r_8 + \mu + \delta_{s3}) P_L + \rho_4 r_5 H_L \big] \\
&+ \lambda_{C_E} \big[\lambda_s C + \chi_1 r_6 P_E - (\mu + \delta_C + \sigma_7 + \alpha_2) C_E \big] \\
&+ \lambda_{C_I} \big[\chi_2 r_7 P_I - (\mu + \delta_C + \sigma_8 + \alpha_3 + u_7) C_I + \sigma_7 C_E \big] \\
&+ \lambda_{C_L} \big[\chi_3 r_8 P_L - (\mu + \delta_C + \delta_{s4} + \alpha_4 + u_8) C_L + \sigma_8 C_I \big].
\end{aligned} \tag{5.5}
$$

Theorem 5.1. *For an optimal control set $\phi, u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8$ that minimizes J over U, there are adjoint variables, $\lambda_1, \lambda_2, ..., \lambda_{20}$ satisfying*

$$-\frac{\partial \lambda_i}{\partial t} = \frac{\partial \mathcal{H}_{am}}{\partial i}$$

and with transversality conditions

$$\lambda_i(t_f) = 0,$$

where

$$i = S, E, I, L, T, V_h, H, P, C, R_C, R_h, H_E, H_I, H_L, P_E, P_I, P_L, C_E, C_I, C_L. \tag{5.6}$$

Furthermore,

$$\begin{aligned}
&\phi^* = \max\left\{0, \min\left(1, \frac{\Lambda(\lambda_1 - \lambda_6)}{w_1}\right)\right\}, \quad u_1^* \max\left\{0, \min\left(1, \frac{(\lambda_3 - \lambda_5)I^*}{w_2}\right)\right\},\\
&u_2^* = \max\left\{0, \min\left(1, \frac{(\lambda_4 - \lambda_5)L^*}{w_3}\right)\right\}, \quad u_3^* = \max\left\{0, \min\left(1, \frac{(\lambda_{13} - \lambda_3)H^*}{w_4}\right)\right\},\\
&u_4^* = \max\left\{0, \min\left(1, \frac{(\lambda_{14} - \lambda_7)H_L^*}{w_5}\right)\right\}, \quad u_5^* = \max\left\{0, \min\left(1, \frac{(\lambda_{16} - \lambda_8)P_I^*}{w_6}\right)\right\},\\
&u_6^* = \max\left\{0, \min\left(1, \frac{(\lambda_{17} - \lambda_8)P_L^*}{w_7}\right)\right\}, \quad u_7^* = \max\left\{0, \min\left(1, \frac{(\lambda_{19} - \lambda_9)C_I^*}{w_8}\right)\right\},\\
&u_8^* = \max\left\{0, \min\left(1, \frac{(\lambda_{20} - \lambda_9)C_L^*}{w_9}\right)\right\}.
\end{aligned} \tag{5.7}$$

Proof of Theorem 5.1. Suppose $U^* = \left(\phi^*, u_1^*, u_2^*, \ldots, u_8^*\right)$ is an optimal control and $S^*, E^*, I^*, L^*, T^*, V_h^*, H^*, P^*, C^*, R_C^*, R_h^*, H_I^*, H_L^*, P_E^*, P_I^*, P_L^*, C_E^*, C_I^*, C_L^*$ are the corresponding state solutions. Applying Pontryagin's Maximum Principle [53], there exist adjoint variables satisfying

$$\begin{aligned}
&-\frac{d\lambda_S}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial S}, \quad \lambda_s(t_f) = 0, \quad -\frac{d\lambda_E}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial E}, \quad \lambda_E(t_f) = 0,\\
&-\frac{d\lambda_I}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial I}, \quad \lambda_I(t_f) = 0, \quad -\frac{d\lambda_L}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial L}, \quad \lambda_L(t_f) = 0,\\
&-\frac{d\lambda_T}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial T}, \quad \lambda_T(t_f) = 0, \quad -\frac{d\lambda_{V_H}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial V_H}, \quad \lambda_{V_H}(t_f) = 0,\\
&-\frac{d\lambda_H}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial H}, \quad \lambda_h(t_f) = 0, \quad -\frac{d\lambda_P}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial P}, \quad \lambda_P(t_f) = 0,\\
&-\frac{d\lambda_C}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial C}, \quad \lambda_C(t_f) = 0, \quad -\frac{d\lambda_{R_C}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial R_C}, \quad \lambda_{R_C}(t_f) = 0,\\
&-\frac{d\lambda_{R_H}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial R_H}, \quad \lambda_{R_H}(t_f) = 0, \quad -\frac{d\lambda_{H_E}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial H_E}, \quad \lambda_{H_E}(t_f) = 0,\\
&-\frac{d\lambda_{H_I}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial H_I}, \quad \lambda_{H_I}(t_f) = 0, \quad -\frac{d\lambda_{H_L}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial H_L}, \quad \lambda_{H_L}(t_f) = 0,\\
&-\frac{d\lambda_{P_E}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial P_E}, \quad \lambda_{P_E}(t_f) = 0, \quad -\frac{d\lambda_{P_I}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial P_I}, \quad \lambda_{P_I}(t_f) = 0,\\
&-\frac{d\lambda_{P_L}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial P_L}, \quad \lambda_{P_L}(t_f) = 0, \quad -\frac{d\lambda_{C_E}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial C_E}, \quad \lambda_{C_E}(t_f) = 0,\\
&-\frac{d\lambda_{C_I}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial C_I}, \quad \lambda_{C_I}(t_f) = 0, \quad -\frac{d\lambda_{C_L}}{dt} = \frac{\partial \mathcal{H}_{am}}{\partial C_L}, \quad \lambda_{CL}(t_f) = 0
\end{aligned} \tag{5.8}$$

with transversality conditions;

$$\begin{aligned}\lambda_S(t_f) &= \lambda_E(t_f) = \lambda_I(t_f) = \lambda_L(t_f) = \lambda_T(t_f) = \lambda_{V_H}(t_f) = \lambda_H(t_f) = \lambda_P(t_f)\\ &= \lambda_C(t_f) = \lambda_{R_C}(t_f) = \lambda_{R_H}(t_f) = \lambda_{H_E}(t_f) = \lambda_{H_I}(t_f) = \lambda_{H_L}(t_f) = \lambda_{P_E}(t_f)\\ &= \lambda_{P_E}(t_f) = \lambda_{P_I}(t_f) = \lambda_{P_L}(t_f) = \lambda_{C_E}(t_f) = \lambda_{C_I}(t_f) = \lambda_{C_L}(t_f) = 0.\end{aligned}$$

We can determine the behavior of the control by differentiating the Hamiltonian, $\mathcal{H}_{am}$ with respect to the controls $(\phi, u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8)$. On the interior of the control set, where $0 < u_j < 1$ for all $(j = 1, \ldots, 8)$ and $0 < \phi < 1$, we obtain

$$\begin{aligned}&0 = \frac{\partial \mathcal{H}_{am}}{\partial \phi} = w_1\phi - (\lambda_1 - \lambda_6), \quad 0 = \frac{\partial \mathcal{H}_{am}}{\partial u_1} = w_2u_1^* - (\lambda_3 - \lambda_5)I^*,\\ &0 = \frac{\partial \mathcal{H}_{am}}{\partial u_2} = w_3u_2^* - (\lambda_4 - \lambda_5)L^*, \quad 0 = \frac{\partial \mathcal{H}_{am}}{\partial u_3} = w_4u_3^* - (\lambda_{13} - \lambda_3)H^*,\\ &0 = \frac{\partial \mathcal{H}_{am}}{\partial u_4} = w_5u_4^* - (\lambda_4 - \lambda_5)H_L^*, \quad 0 = \frac{\partial \mathcal{H}_{am}}{\partial u_5} = w_6u_5^* - (\lambda_{16} - \lambda_8)P_I^*,\\ &0 = \frac{\partial \mathcal{H}_{am}}{\partial u_6} = w_7u_6^* - (\lambda_{17} - \lambda_8)P_L^*, \quad 0 = \frac{\partial \mathcal{H}_{am}}{\partial u_7} = w_8u_7^* - (\lambda_{19} - \lambda_9)C_I^*,\\ &0 = \frac{\partial \mathcal{H}_{am}}{\partial u_8} = w_9u_8^* - (\lambda_{20} - \lambda_9)C_L^*.\end{aligned} \tag{5.9}$$

Therefore, we have that [51]

$$\begin{aligned}&\phi^* = \frac{(\lambda_1 - \lambda_6)}{w_1}, \quad u_1^* = \frac{(\lambda_3 - \lambda_5)I^*}{w_2}, \quad u_2^* = \frac{(\lambda_4 - \lambda_5)L^*}{w_3},\\ &u_3^* = \frac{(\lambda_{13} - \lambda_3)H^*}{w_4}, \quad u_4^* = \frac{(\lambda_4 - \lambda_5)H_L^*}{w_5}, \quad u_5^* = \frac{(\lambda_{16} - \lambda_8)P_I^*}{w_6},\\ &u_6^* = \frac{(\lambda_{17} - \lambda_8)P_L^*}{w_7}, \quad u_7^* = \frac{(\lambda_{19} - \lambda_9)C_I^*}{w_8}, \quad u_8^* = \frac{(\lambda_{20} - \lambda_9)C_L^*}{w_9},\end{aligned} \tag{5.10}$$

$$\begin{aligned}&\phi^* = \max\left\{0, \min\left(1, \frac{(\lambda_1 - \lambda_6)}{w_1}\right)\right\}, \quad u_1^* = \max\left\{0, \min\left(1, \frac{(\lambda_3 - \lambda_5)I^*}{w_2}\right)\right\},\\ &u_2^* = \max\left\{0, \min\left(1, \frac{(\lambda_4 - \lambda_5)L^*}{w_3}\right)\right\}, \quad u_3^* = \max\left\{0, \min\left(1, \frac{(\lambda_{13} - \lambda_3)H^*}{w_4}\right)\right\},\\ &u_4^* = \max\left\{0, \min\left(1, \frac{(\lambda_4 - \lambda_5)H_L^*}{w_5}\right)\right\}, \quad u_5^* = \max\left\{0, \min\left(1, \frac{(\lambda_{16} - \lambda_8)P_I^*}{w_6}\right)\right\},\\ &u_6^* = \max\left\{0, \min\left(1, \frac{(\lambda_{17} - \lambda_8)P_L^*}{w_7}\right)\right\}, \quad u_7^* = \max\left\{0, \min\left(1, \frac{(\lambda_{19} - \lambda_9)C_I^*}{w_8}\right)\right\},\\ &u_8^* = \max\left\{0, \min\left(1, \frac{(\lambda_{20} - \lambda_9)C_L^*}{w_9}\right)\right\}.\end{aligned} \tag{5.11}$$

6. Simulations

Uncertainty and sensitivity analyses of the parameters of the model are hereby carried out on the parameters of the model. It is appropriate to state that we have very limited data on the co-infection of HPV and syphilis. Numerical simulations are also carried out on the optimal control model in order to assess the impact of various control strategies on the dynamics syphilis and HPV co-infections.

6.1. *Uncertainty and sensitivity analyses*

As a result of the uncertainties in some of the parameter values used for the numerical simulations, a Latin Hypercube Sampling (LHS) [47] is implemented on the parameters of the model. For the sensitivity analysis, a Partial Rank Correlation Coefficient (PRCC) was carried out. 1000 simulations of the co-infection model (2.3) *per* LHS were run. Using the syphilis associated reproduction number, $\mathcal{R}_{0s}$, as the response function, it is observed from Table 2 that the five-ranked parameters that drive the dynamics of the co-infection model are the demographic parameter μ, the effective contact rate for syphilis transmission, β_s, the progression rate to late stage of syphilis σ_2, and syphilis treatment rates: τ_1 and τ_2 for co-infected individuals in compartments H_i and H_l, respectively. Moreover, when the HPV associated reproduction number, $\mathcal{R}_{0h}$, is used as the response function, the five most dominant parameters that drive the dynamics of the model are the demographic parameter μ, the effective contact rate for HPV transmission, β_h, the fraction of HPV infected who develop persistent HPV ρ_1, the fraction of individuals vaccinated against incident HPV infection ϕ and the HPV vaccine efficacy π_h.

Table 2. PRCC values for the model parameters using the associated reproduction numbers $\mathcal{R}_{0s}$ and $\mathcal{R}_{0h}$.

Parameters	$\mathcal{R}_{0S}$	$\mathcal{R}_{0H}$
μ	**0.9886**	**0.97778**
β_h	–	**0.9378**
β_s	**0.9330**	–
δ_{s1}	−0.0095	–
δ_{h1}	–	−0.2802
σ_1	0.1057	–
σ_2	**0.8695**	–
τ_1	**−0.4515**	–
τ_2	**−0.4601**	–
η	0.2329	–
ρ_1	–	**0.4001**
ω_p	–	0.1527
r_1	–	0.0573
r_2	–	−0.0311
ϕ	–	**−0.6743**
π	–	**−0.6711**

6.2. *Numerical simulations*

We now simulate the optimal control model (5.1) numerically using the parameter estimates in Table 1, so that the reproduction number, $\mathcal{R}_0 = 1.80842$ (unless otherwise stated), to assess the potential impact of various targeted control strategies on the transmission dynamics of HPV and syphilis in the population. Demographic parameters relevant to the city of Rio de Janeiro in Brazil were chosen. Specifically, since the total population of sexually active susceptible individuals (15–64 years) in the State of Rio de Janeiro in Brazil are estimated to be 12,850,804, at disease-free equilibrium, $\frac{\Lambda}{\mu} = 8,946,246$ ([46]). In Brazil, the life expectancy is estimated at 74 years [46]. Hence, we have that $\mu = 0.0135$, so that $\Lambda = 12,0895$ per year.

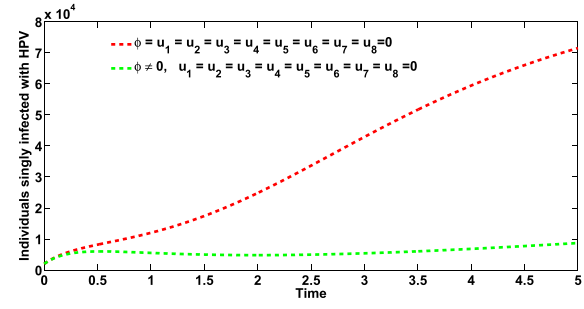
Numerical simulations of the optimal control problem (5.1), adjoint equations (5.8) and characterizations of the control (5.11) are implemented by the Runge Kutta method using the forward backward sweep (carried out in MATLAB). The balancing factor $w_1 = 10^3$ (The Centres for Disease Control cost per dose of the pediatric *Gardasil* 4, the *Gardasil* 9, and the *Cervarix*, respectively, is \$121.03, \$134.26 and \$107.97 [26, 49]. Since the associated costs considered are combinations of price per dose, storage/administration-related costs and transportation, etc, we will assume $w_1 = 10^3$). Following the estimates for syphilis treatment in [50], the balancing factors for syphilis-infected individuals are $w_2 = w_3 = 200, w_4 = w_5 = w_6 = w_7 = w_8 = w_9 = 220$. Here, we assume that the cost of treatment for co-infected individuals is more than the cost of treatment for singly infected individuals. Following the reported prevalence of syphilis and HPV as well as the co-infection prevalence in [7, 54] and the demographic data obtained from [46], we set the initial conditions at $S(0) = 100,000$, $E(0) = 10,000$, $I(0) = 20,000$, $L(0) = 2000, T(0) = 0, V_H = 100,000, H(0) = 2000$, $P(0) = 1000$, $C(0) = 2000$, $R_C(0) = 0, R_H(0) = 0, H_E(0) = 2000, H_I(0) = 10,000, H_L(0) = 10.000, P_E(0) = 1000, P_I(0) = 1000, P_L(0) = 1000, C_E(0) = 1000, C_I(0) = 10,000, C_L(0) = 5000$. We implement the following four different control strategies for numerical simulations of the co-infection model 5.1:

(I) Optimal HPV vaccination strategy ($\phi \neq 0$).
(II) Syphilis treatment controls for singly infected individuals ($u_1 \neq u_2 \neq 0$).
(III) Syphilis treatment controls for dually infected individuals only ($u_3 \neq u_4 \neq u_5 \neq u_6 \neq u_7 \neq u_8 \neq 0$).
(IV) Universal strategy ($\phi \neq u_1 \neq u_2 \neq u_3 \neq u_4 \neq u_5 \neq u_6 \neq u_7 \neq u_8 \neq 0$).

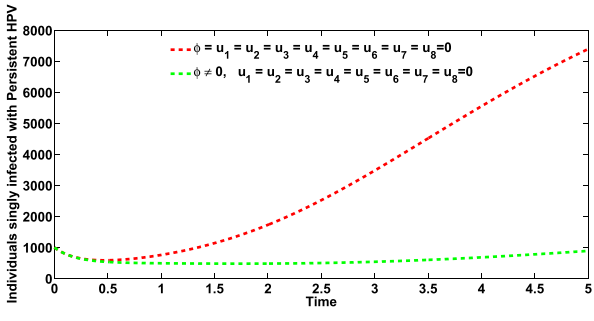
6.2.1. *Strategy I*: *Optimal HPV vaccination strategy ($\phi \neq 0$)*

Applying this strategy, we note in Figs. 3(a) and 3(b) that the total number of individuals singly infected with HPV and persistent HPV, respectively, is less than the total number when no control is applied. It can equally be observed that optimal HPV vaccination strategy has a high positive population level impact on the populations of infected individuals dually infected with HPV and syphilis in early

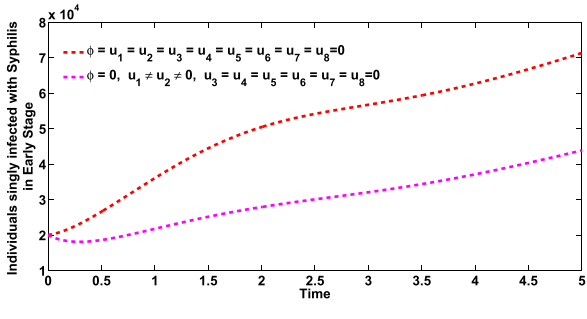
and late stages of infection, respectively (Figs. 4(a) and 4(b)), infected individuals dually infected with persistent HPV and syphilis in early and late stages of infection, respectively (Figs. 5(a) and 5(b)) and infected individuals dually infected with cancer and syphilis in early and late stages of infection, respectively (Figs. 6(a) and 6(b)). The results of the simulations agree with the epidemiological reports in



(a)

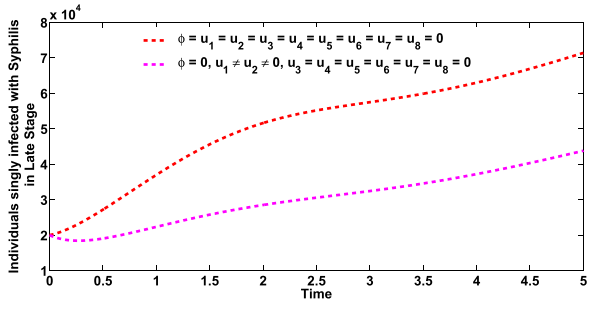


(b)



(c)

Fig. 3. Plots of the total number of individuals singly infected with HPV and persistent HPV, respectively (Figs. 3(a) and 3(b)) in the presence of optimal vaccination control only ($\phi \neq 0$) and total number of individuals singly infected with syphilis in early and late stages of infection, respectively (Figs. 3(c) and 3(d)) in the presence of treatment controls for singly infected only ($u_1 \neq u_2 \neq 0$). Here, $\beta_S = 7.0$, $\beta_H = 2.0$. All other parameters are given in Table 1.



(d)

Fig. 3. (*Continued*)

[11, 12] that prior HPV infections are risk factors for syphilis infection. Therefore, controlling HPV infections through vaccination can bring down the burden of co-infection of the two diseases.

6.2.2. *Strategy II*: *Syphilis treatment controls for singly infected individuals only* ($u_1 \neq u_2 \neq 0$)

Using this control strategy, we observe in Figs. 3(c) and 3(d) that the number of individuals singly infected with syphilis in early and late stages of infection, respectively, is less than the number when no control strategy is applied. Likewise, the syphilis only treatment controls for singly infected with syphilis have positive population level impact on the populations of infected individuals dually infected with HPV and syphilis in early and late stages of infection, respectively (Figs. 4(c) and 4(d)). Treatment controls for singly infected with syphilis equally have positive population level impact on the population of individuals dually infected with persistent HPV and syphilis in early and late stages of infection as observed in Figs. 5(c) and 5(d). The total number of individuals dually infected with cancer and syphilis in early and late stages of infection is lesser when treatment controls are applied to individuals singly infected with syphilis than when no treatment control is applied (Figs. 6(c) and 6(d)).

6.2.3. *Strategy III*: *Syphilis treatment controls for dually infected individuals only* ($u_3 \neq u_4 \neq u_5 \neq u_6 \neq u_7 \neq u_8 \neq 0$)

The simulations of the total number of dually infected individuals in the presence of syphilis treatment controls are depicted in Figs. 6(a)–6(d). Applying this control, we observe that the total number of individuals dually infected with HPV and syphilis in early and late stages of infection, respectively, is less than the total population when no control is applied as expected (Figs. 6(a) and 6(b)). Similarly, it is noted from Figs. 6(c) and 6(d) that the total number of individuals dually infected with persistent HPV and syphilis in early and late stages of infection, respectively, is

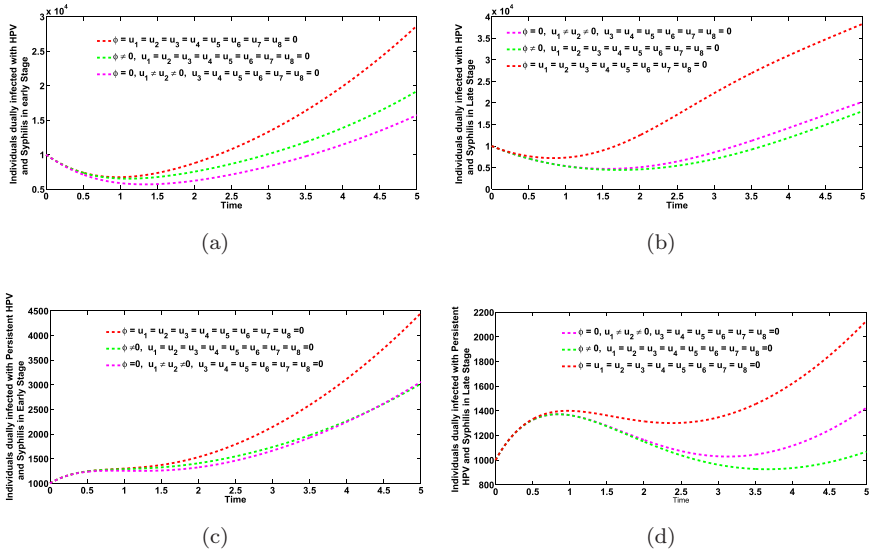


Fig. 4. Plots of the co-infection cases for individuals dually infected with HPV and syphilis in early and late stages of infection, respectively (Figs. 4(a) and 4(b)) and co-infection cases for individuals dually infected with persistent HPV and syphilis in early and late stages of infection, respectively (Figs. 4(c) and 4(d)) when optimal vaccination control only strategy ($\phi \neq 0$) and syphilis treatment controls for singly infected ($u_1 \neq u_2 \neq 0$) are administered. Here, $\beta_S = 7.0$, $\beta_H = 2.0$. All other parameters are given in Table 1.

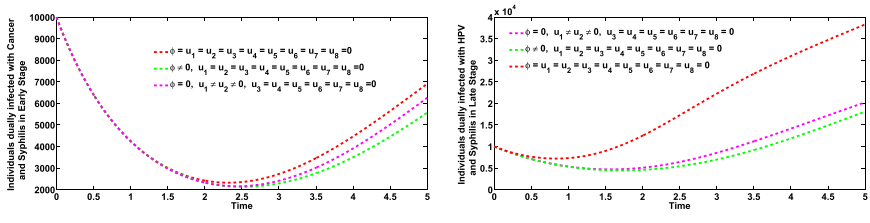


Fig. 5. Plots of the co-infection cases for individuals dually infected with anal cancer and syphilis in early and late stages of infection, respectively (Figs. 5(a) and 5(b)) when optimal vaccination control only strategy ($\phi \neq 0$) and syphilis treatment controls for singly infected ($u_1 \neq u_2 \neq 0$) are administered. Here, $\beta_S = 7.0$, $\beta_H = 2.0$. All other parameters are given in Table 1.

lesser when this control is applied. In addition, high population level impact is noted on the total number of individuals dually infected with cancer and syphilis in early and late stages of infection, respectively, as shown in Figs. 7(a) and 7(b). This supports the epidemiological report in the introduction section that syphilis is a risk factor for HPV infection [7]. Hence, if we focus on syphilis treatment controls, it can significantly bring down the burden of the co-infection of HPV and syphilis in a population. The simulations equally agree with the findings in Tseng *et al.* [9] that prior syphilis infection was associated with persistent HPV

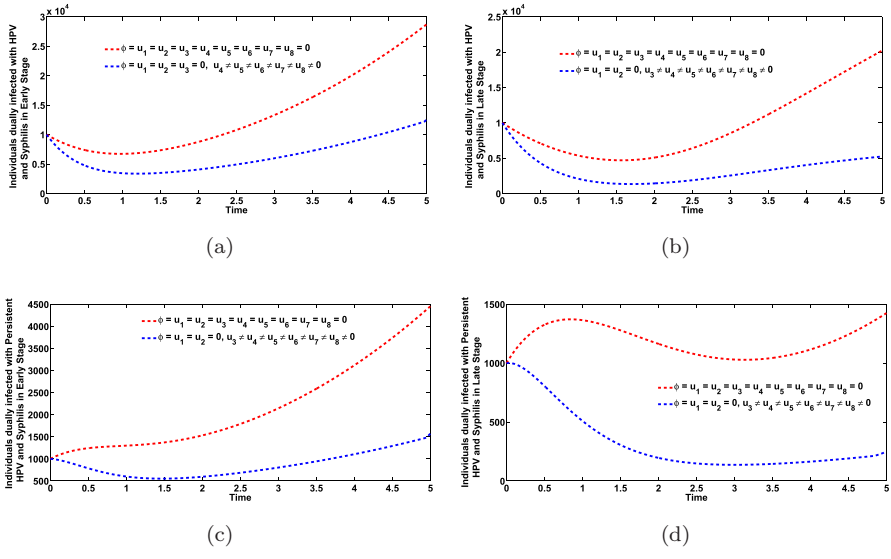


Fig. 6. Plots of the co-infection cases for individuals dually infected with HPV and syphilis in early and late stages of infection, respectively (Figs. 6(a) and 6b) as well as co-infection cases for individuals dually infected with persistent HPV and syphilis in early and late stages of infection, respectively (Figs. 6(c) and 6(d)). Here, $\beta_S = 7.0$, $\beta_H = 2.0, \phi = u_1 = u_2 = 0, u_3 \neq u_4 \neq u_5 \neq u_6 \neq u_7 \neq u_8 \neq 0$. All other parameters are given in Table 1.

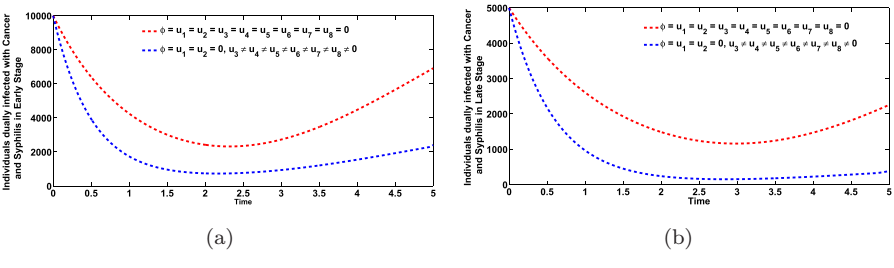


Fig. 7. Plots of the co-infection cases for individuals dually infected with anal cancer and syphilis in early and late stages of infection, respectively (Figs. 7(a) and 7(b)). Here, $\beta_S = 7.0$, $\beta_H = 2.0, \phi = u_1 = u_2 = 0, u_3 \neq u_4 \neq u_5 \neq u_6 \neq u_7 \neq u_8 \neq 0$. All other parameters are given in Table 1.

and increased susceptibility to anal cancer. As a result, treating syphilis infection in individuals dually infected with persistent HPV and anal cancer or focusing on syphilis treatment among individuals dually infected with syphilis and anal cancer will significantly curb the mixed infections.

6.2.4. *Strategy IV*: *Universal strategy* $(\phi \neq u_1 \neq u_2 \neq u_3 \neq u_4 \neq u_5 \neq u_6 \neq u_7 \neq u_8 \neq 0)$

The simulations of the optimal control model (5.1) in the presence of combined optimal HPV vaccination strategy and syphilis treatment controls are depicted

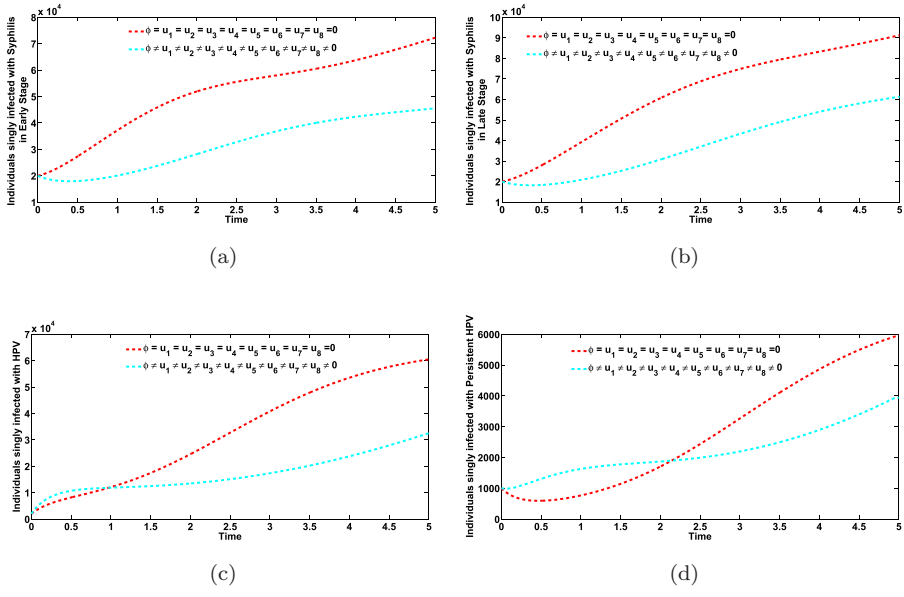


Fig. 8. Plots of the total number of infected individuals singly infected with syphilis in early and late stages of infection, respectively (Figs. 8(a) and 8(b)) and total number of infected individuals infected with HPV and persistent HPV, respectively (Figs. 8(c) and 8(d)) when the universal control strategy is implemented and when there is no control administered. Here, $\beta_S = 7.0$, $\beta_H = 2.0$. All other parameters are given in Table 1.

in Figs. 8–10. It is observed in Fig. 8 that the combined control strategy has a high population level impact on the populations of individuals singly infected with syphilis in early stage (Fig. 8(a)), individuals singly infected with syphilis in late stage (Fig. 8(b)), individuals singly infected with HPV (Fig. 8(c)) and individuals singly infected with persistent HPV (Fig. 8(d)). In a similar manner, the total number of individuals dually infected with HPV and syphilis in early and late stages of infection, respectively (Figs. 9(a) and 9(b)), total number of individuals dually infected with persistent HPV and syphilis in early and late stages of infection, respectively (Figs. 9(c) and 9(d)) and total number of individuals dually infected with anal cancer and syphilis in early and late stages of infection, respectively (Figs. 10(a) and 10(b)) all recorded lesser population number when the universal strategy is implemented than when no control is administered.

6.3. *Cost-effectiveness analysis*

We seek to determine the most cost-effective intervention strategy in combating HPV and syphilis co-infection. To achieve this, two methods are employed, *viz*, the average cost-effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER). The cost-effectiveness analysis is used to evaluate the health interventions related benefits so as to justify the costs of the strategies [30]. This is obtained

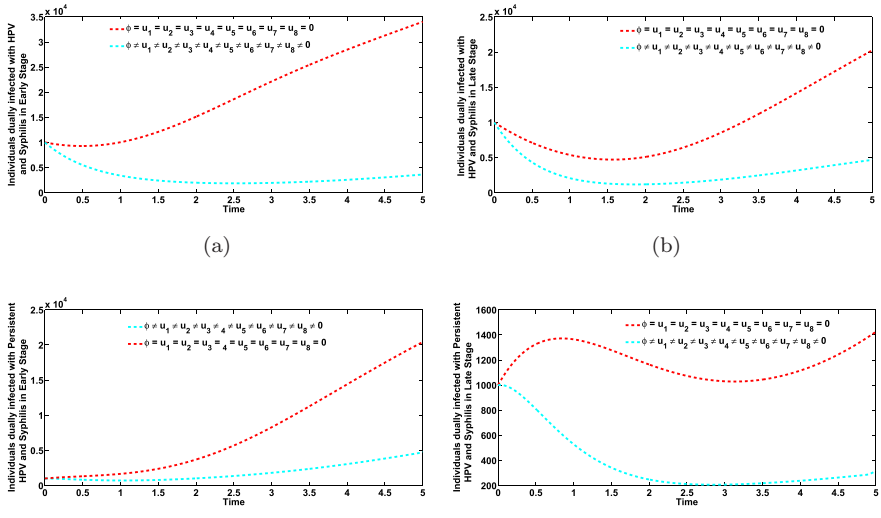


Fig. 9. Plots of the co-infection cases for individuals dually infected with HPV and syphilis in early and late stages of infection, respectively (Figs. 9(a) and 9(b)) and co-infection cases for individuals dually infected with persistent HPV and syphilis in early and late stages of infection, respectively (Figs. 9(c) and 9(d)) when the universal control strategy is implemented and when there is no control administered. Here, $\beta_S = 7.0$, $\beta_H = 2.0$. All other parameters are given in Table 1.

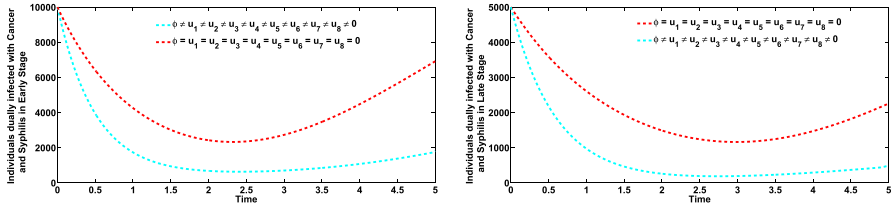


Fig. 10. Plots of the co-infection cases for individuals dually infected anal cancer and syphilis in early and late stages of infection, respectively (Figs. 10(a) and 10(b) when there is universal control strategy and when there is no control administered. Here, $\beta_S = 7.0$, $\beta_H = 2.0$. All other parameters are given in Table 1.

by comparing the differences among the health outcomes and costs of those interventions. ACER is concerned with a single intervention strategy and weighing the intervention against its baseline option. It is the ratio of the total cost of the intervention to the total number of infection averted by the intervention. The formula is given thus

$$\text{ACER} = \frac{\text{Total cost produced by intervention}}{\text{Total number of infection averted}}.$$

In a similar manner, ICER is concerned with the comparison of the differences between the costs and health outcomes of two alternative intervention strategies competing for the same resources. It is the ratio of the change in costs of two alternative strategies to the change in the total number of infection averted by the two strategies [43]. The ICER formula is given by

$$\text{ICER} = \frac{\text{Difference in costs between strategies}}{\text{Difference in health effects between strategies}}.$$

We calculated the total number of co-infection cases averted and the total cost of the strategies applied in Table 3. This is equally presented in Fig. 11. The total number of co-infection cases prevented is obtained by calculating the total number of individuals when controls are implemented and the total number when there is no control applied. Similarly, we apply the cost functions $\frac{1}{2}w_1\phi^2, \frac{1}{2}w_2u_1^2, \frac{1}{2}w_3u_2^2, \frac{1}{2}w_4u_3^2, \frac{1}{2}w_5u_4^2, \frac{1}{2}w_6u_5^2, \frac{1}{2}w_7u_6^2, \frac{1}{2}w_8u_7^2, \frac{1}{2}w_9u_8^2$, over time, to compute the total cost for the various strategies implemented. We compared the cost-effectiveness of strategy I (optimal HPV vaccination strategy for sexually active susceptible individuals) and strategy II (syphilis treatment controls for singly

Table 3. Increasing order of the total infection averted due to the control strategies.

Strategy	Total infection averted	Total cost	ACER	ICER
II: $u_1(t), u_2(t)$	34,302	3996	0.1165	0.1165
I: $\phi(t)$	34,425	4996.5	0.1451	8.1341
III: $u_3(t), u_4(t), u_5(t), u_6(t), u_7(t), u_8(t)$	41,372.6	5954.5	0.1439	0.1379
IV: $\phi(t), u_1(t), u_2(t), u_3(t), u_4(t), u_5(t), u_6(t), u_7(t), u_8(t)$	69,380	10,286	0.1483	0.1547

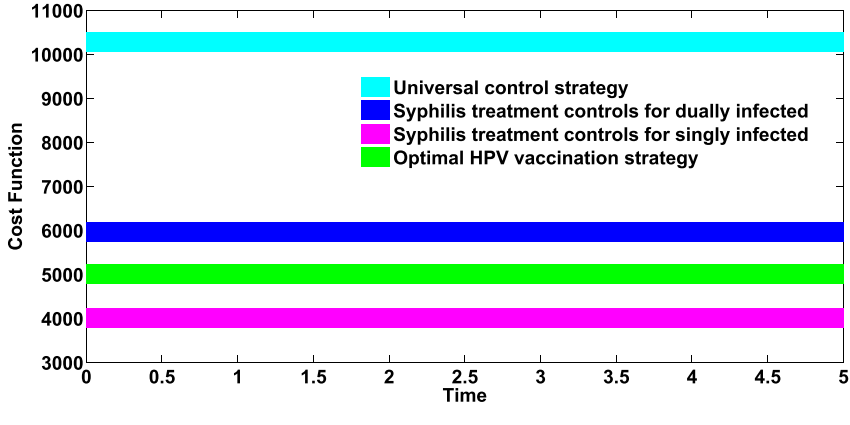


Fig. 11. Cost functions of the different control strategies.

Table 4. Increasing order of the total infection averted due to the control strategies.

Strategy	Total infection averted	Total cost	ACER	ICER
II: $u_1(t), u_2(t)$	34,302	3 996	0.1165	0.1165
III: $u_3(t), u_4(t), u_5(t), u_6(t), u_7(t), u_8(t)$	41,372.6	5 954.5	0.1439	0.2770
IV: $\phi(t), u_1(t), u_2(t), u_3(t), u_4(t), u_5(t), u_6(t), u_7(t), u_8(t)$	69,380	10,286	0.1483	0.1547

infected individuals).

$$\text{ICER (II)} = \frac{3996}{34,302} = 0.1165.$$

$$\text{ICER (I)} = \frac{4996.5 - 3996}{34,425 - 34,302} = 8.1341.$$

From ICER (I) and ICER(II), we see a cost saving of 0.1165 observed for strategy II over strategy I. This implies that strategy I is more costly and less effective compared to strategy II. Hence, strategy I is removed from subsequent ICER computations, as shown in Table 4. We now compare strategy II and strategy III.

$$\text{ICER (II)} = \frac{3996}{34,302} = 0.1165.$$

$$\text{ICER (III)} = \frac{5954.5 - 3996}{41,372.6 - 34,302} = 0.2770.$$

Comparing strategy II and strategy III, we observe that ICER (III) is greater than ICER (II), showing that strategy III is more expensive and less effective compared to strategy II. Therefore, strategy III is removed from the list of next alternative strategies and we re-calculate ICER for the remaining competing strategies II and IV, as shown in Table 5.

$$\text{ICER (II)} = \frac{3996}{34,302} = 0.1165.$$

$$\text{ICER (IV)} = \frac{10286 - 3996}{69380 - 34,302} = 0.1793.$$

Comparing strategy II and strategy IV, it can be observed that ICER (IV) is greater than ICER (II), showing that strategy IV is more costly and less effective compared to strategy III. As a result, strategy II (the strategy that implements syphilis treatment controls for singly infected individuals) has the least ICER and

Table 5. Increasing order of the total infection averted due to the control strategies.

Strategy	Total infection averted	Total cost	ACER	ICER
II: $u_1(t), u_2(t)$	34,302	3996	0.1165	0.1165
IV: $\phi(t), u_1(t), u_2(t), u_3(t), u_4(t), u_5(t), u_6(t), u_7(t), u_8(t)$	69,380	10,286	0.1483	0.1793

is the most cost-effective of all the control strategies for the control of HPV and syphilis co-infections. This is clearly illustrated in Fig. 11, which also agrees with the results obtained from both ACER and ICER methods that strategy II is the most cost-effective strategy.

7. Conclusion

A co-infection model for HPV and syphilis with cost-effectiveness optimal control analysis has been developed and presented. The full co-infection model was shown to undergo the phenomenon of backward bifurcation when a certain condition was satisfied. The GAS of the disease-free equilibrium of the full model was shown not to exist when the associated reproduction number was less than unity. The existence of endemic equilibrium of the syphilis-only sub-model was shown to exist and the GAS of the disease-free and endemic equilibria of the syphilis-only sub-model was established, for a special case (when syphilis re-infection term is set to zero).

Based on the qualitative analysis of the model, it was observed that syphilis re-infection $\xi_s \neq 0$ caused the phenomenon of backward bifurcation in the syphilis only sub-model. The epidemiological significance is that if syphilis treatment does not confer lifelong immunity, then the control of syphilis becomes difficult in the population, even when the associated reproduction number $\mathcal{R}_{0s} < 1$. Hence, it is appropriate that policies to prevent re-infection with syphilis should be strictly put in place in order to bring down the burden of syphilis and its co-infection with HPV at the community level.

Sensitivity analysis was also carried out on the parameters of the model. Using the syphilis associated reproduction number, $\mathcal{R}_{0s}$, as the response function, it is observed from Table 2 that the five-ranked parameters that drive the dynamics of the co-infection model are the demographic parameter μ, the effective contact rate for syphilis transmission, β_s, the progression rate to late stage of syphilis σ_2, and syphilis treatment rates: τ_1 and τ_2 for co-infected individuals in compartments H_i and H_l, respectively. Moreover, when the HPV associated reproduction number, $\mathcal{R}_{0h}$, is used as the response function, the five most dominant parameters that drive the dynamics of the model are the demographic parameter μ, the effective contact rate for HPV transmission, β_h, the fraction of HPV infected who develop persistent HPV ρ_1, the fraction of individuals vaccinated against incident HPV infection ϕ and the HPV vaccine efficacy π_h.

Numerical simulations of the optimal control model showed that

(i) HPV vaccination control has a positive population level impact in reducing the burden of HPV and the co-infection cases in a population.
(ii) Syphilis treatment controls for singly infected individuals not only help bring down the burden of syphilis infection, but also reduce the burden of the HPV and syphilis co-infections.

(iii) The control strategy which implements syphilis treatment for singly infected individuals is the most cost-effective of all the control strategies in reducing the burden of HPV and syphilis co-infections.

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