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Qualitative Study of the Role of Pap Screening on HPV Transmission Dynamics

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ABSTRACT. A new deterministic model is designed and used to assess the population-level impact of Pap cytology screening on the transmission dynamics of human papillomavirus (HPV), and associated dysplasia, in a community. In the absence of Pap screening, the disease-free equilibrium (DFE) of the resulting model is shown to be globally-asymptotically stable whenever the associated reproduction number ($\mathcal{R}_0$) is less than unity. Furthermore, the model has a unique endemic equilibrium, which is locally- and globally- asymptotically stable for special cases. The disease-free equilibrium of the Pap screening model is also shown to be globally-asymptotically stable when its reproduction number ($\mathcal{R}_{0s}$) is less than unity. The effect of uncertainties in the estimates of the parameter values used in the numerical simulations of the Pap screening model is accounted for *via* uncertainty and sensitivity analysis. Numerical simulations of the Pap screening model show that HPV transmission models that do not incorporate disease transmission by individuals in the pre-cancerous stages may under-estimate the burden of HPV (and associated dysplasia) in the community. Although Pap screening significantly reduces the incidence of cervical cancer (for instance, detecting 50% of sexually-active females with cervical intraepithelial neoplasia resulted in 95% reduction of cervical cancer cases over 10 years), its singular use is insufficient to lead to the effective control of the spread of HPV in the community.

Keywords and phrases: HPV, cervical cancer, equilibria, stability, reproduction number.

1. Introduction

Human papillomavirus (HPV), a major sexually-transmitted disease, is known to be the causative agent of cervical cancer [1, 13] (in addition to causing many other cancers in both females and males [6, 13, 49, 50]). Each year, about 500,000 women develop cervical cancer (with more than half of those women dying of the disease) globally [4, 49]. In the year 2011, for instance, about

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12,000 cervical cancer cases were recorded in the USA (with about 4,000 fatalities) [4]. HPV targets epithelial basal cells, and HPV-associated diseases are transmitted *via* skin-to-skin contact [29]. It is known that $70\% - 90\%$ of HPV cases clear their infections naturally within two years [1, 13, 15]. In women who do not clear their HPV infection (typically those infected with high-risk HPV types [6, 13, 61]), pre-cancerous lesions (cervical intraepithelial neoplasia (CIN)) may persist for many years (and, consequently, progress to cervical cancer [13, 45, 49, 50]). Furthermore, high-risk HPV types cause pre-cancerous *intraepithelial neoplasia* in males (INM), resulting in various cancers (such as anal and penile cancers) [5, 19]. Pap screening has played an essential role in the early detection of CIN and, consequently, reduce cervical cancer incidence and mortality [45, 50] (for instance, it is known that regular Pap screening decreases the incidence of cervical cancer by 70% over the last five decades [28, 43]). Pap screening detects abnormal cervical cells, including pre-cancerous cervical lesions and early cervical cancers [13, 17, 50]. Once detected, pre-cancerous lesions can be treated successfully (using, for instance, loop electrosurgical excision procedure, which involves the removal of a cancerous tissue using a wire loop, or using laser therapy [14, 50, 53]). Cervical cancer screening consists of two screening tests, namely cytology-based screening (known as the Pap test (or Pap smear or Pap cytology), and HPV testing [50]. The major goal of the screening is to detect abnormal cells that may develop into cancer if left untreated, while HPV testing is used to check for the presence of DNA or RNA of high-risk HPV types in cervical cells [36, 50]. It has recently been recommended that women have their Pap test at the age of 21 [50] (and such test should be administered every 3 years for women of age 21 through 29 [50]; women of age 30 through 65 can be screened every 5 years with Pap and HPV co-testing or every 3 years with a Pap test alone [15, 50]). Pap screening is not administrated for males.

Although three anti-HPV vaccines, namely *Cervarix*® (GlaxoSmithKline), *Gardasil*® and *Gardasil 9*® (Merck Inc.), have been approved for use to protect new sexually-active males and females against some of the most common HPV types [37, 49, 51, 57, 60], Pap screening remains a critically important preventive measure against HPV infection (this is largely due to the low coverage, high cost, and the side-effects associated with the use of the two anti-HPV vaccines [7, 25, 31, 38, 49, 56]).

Mathematical models, typically of the form of deterministic system of non-linear differential equations, have been developed and used to study the transmission dynamics of HPV and associated dysplasia in a community [2, 3, 16, 19, 20, 21, 22, 35, 40, 44, 45, 48]. Myers *et al.* [48] modeled the natural history of HPV infection and cervical carcinogenesis using a deterministic model. Models for assessing the impact of vaccination on HPV dynamics were presented in [2, 3, 10, 11, 16, 19, 21, 22, 40]. Malik *et al.* [45], Kulasingam and Myers [40] and Bosch *et al.* [9] investigated the combined impact of an anti-HPV vaccine and Pap screening on the dynamics of HPV and associated dysplasia. The purpose of the current study is to extend prior Pap screening models for HPV transmission in the literature by developing, and rigorously analyzing, a more realistic model for assessing the population-level impact of Pap screening. Some of the notable features of the novel model to be designed include adding the dynamics of pre-cancerous and HPV-related cancers in males, HPV transmission by individuals in the pre-cancerous stages and including the dynamics of exposed (asymptomatic) individuals (i.e., HPV-infected individuals with no clinical symptoms of the disease). The paper is organized as follows. The new Pap screening model is formulated in Section 2. The model in the absence of Pap screening is analyzed in section 3. The full model is analyzed in Section 4. Uncertainty and sensitivity analyses, as well as numerical simulations of the Pap screening model, are also reported.

2. Mathematical Model

The new model for the transmission dynamics of HPV in a community, in the presence of the Pap cytology screening, is designed by stratifying the total sexually-active female population at time t (denoted by $N_f(t)$) into twelve mutually-exclusive sub-populations of susceptible females ($S_f(t)$), exposed (asymptomatic) females ($E_f(t)$), symptomatic (infected with clinical symptoms of HPV) females ($I_f(t)$), females with persistent HPV infection ($P_f(t)$), females with undetected low-grade CIN ($L_{fu}(t)$), females with detected low-grade CIN ($L_{fd}(t)$), females with undetected high-grade CIN ($H_{fu}(t)$), females with detected high-grade CIN ($H_{fd}(t)$), females with undetected cervical cancer ($C_{fu}(t)$), females with detected cervical cancer ($C_{fd}(t)$), females who recovered from cervical cancer ($R_{fc}(t)$) and females who recovered from HPV infection without developing

cervical cancer ($R_f(t)$), so that

$$\begin{aligned} N_f(t) &= S_f(t) + E_f(t) + I_f(t) + P_f(t) + L_{fu}(t) + L_{fd}(t) \\ &+ H_{fu}(t) + H_{fd}(t) + C_{fu}(t) + C_{fd}(t) + R_{fc}(t) \\ &+ R_f(t). \end{aligned} \tag{2.1}$$

Similarly, the total sexually-active male population at time t (denoted by $N_m(t)$) is sub-divided into nine mutually-exclusive sub-populations of susceptible males ($S_m(t)$), exposed (asymptomatic) males ($E_m(t)$), symptomatic males ($I_m(t)$), males with persistent HPV infection ($P_m(t)$), males with low-grade INM ($L_m(t)$), males with high-grade INM ($H_m(t)$), males with HPV-related cancer ($C_m(t)$), males who recovered from HPV-related cancer ($R_{mc}(t)$) and males who recovered from HPV infection without developing HPV-related cancer ($R_m(t)$). Thus,

$$\begin{aligned} N_m(t) &= S_m(t) + E_m(t) + I_m(t) + P_m(t) + L_m(t) + H_m(t) \\ &+ C_m(t) + R_{mc}(t) + R_m(t). \end{aligned} \tag{2.2}$$

It follows from (2.1) and (2.2) that the total sexually-active (heterosexual) population, at time t, is given by $N(t) = N_f(t) + N_m(t)$. The model for the transmission dynamics of HPV (and associated dysplasia) in a community, in the presence of Pap screening, is given by the following deterministic system of non-linear differential equations (a flow diagram of the model is depicted in Figure 1; the associated state variables and parameters are tabulated in Tables 1, 2 and 3):

$$
\text{Females}\begin{cases}
\frac{dS_f}{dt} = \pi_f + \xi_f R_f - (\lambda_m + \mu_f)S_f,\\
\frac{dE_f}{dt} = \lambda_m S_f - (\sigma_f + \mu_f)E_f,\\
\frac{dI_f}{dt} = \sigma_f E_f - (\psi_f + \mu_f)I_f,\\
\frac{dP_f}{dt} = (1-b_f)\psi_f I_f + d_{f2}g_f L_{fu} + q_{f4}z_f H_{fu} - (\alpha_f + \mu_f)P_f,\\
\frac{dL_{fu}}{dt} = (1-k_f)\alpha_f P_f + q_{f2}z_f H_{fu} - (g_f + \mu_f)L_{fu},\\
\frac{dL_{fd}}{dt} = d_{f3}g_f L_{fu} - (r_1 + \mu_f)L_{fd},\\
\frac{dH_{fu}}{dt} = [1-(d_{f1}+d_{f2}+d_{f3})]g_f L_{fu} + j_{f2}\gamma_f C_{fu} - (z_f + \mu_f)H_{fu},\\
\frac{dH_{fd}}{dt} = q_{f3}z_f H_{fu} - (r_2 + \mu_f)H_{fd},\\
\frac{dC_{fu}}{dt} = [1-(q_{f1}+q_{f2}+q_{f3}+q_{f4})]z_f H_{fu} - (\gamma_f + \mu_f + \delta_{fu})C_{fu},\\
\frac{dC_{fd}}{dt} = j_{f1}\gamma_f C_{fu} - (r_3 + \mu_f + \delta_{fd})C_{fd},\\
\frac{dR_{fc}}{dt} = [1-(j_{f1}+j_{f2})]\gamma_f C_{fu} + r_3 C_{fd} - \mu_f R_{fc},\\
\frac{dR_f}{dt} = b_f\psi_f I_f + k_f\alpha_f P_f + d_{f1}g_f L_{fu} + r_1 L_{fd} + q_{f1}z_f H_{fu} + r_2 H_{fd} - (\xi_f + \mu_f)R_f,
\end{cases}
$$

$$
\text{Males}\begin{cases}
\frac{dS_m}{dt} = \pi_m + \xi_m R_m - (\lambda_f + \mu_m)S_m,\\
\frac{dE_m}{dt} = \lambda_f S_m - (\sigma_m + \mu_m)E_m,\\
\frac{dI_m}{dt} = \sigma_m E_m - (\psi_m + \mu_m)I_m,\\
\frac{dP_m}{dt} = (1-b_m)\psi_m I_m + d_{m2}g_m L_m + q_{m3}z_m H_m - (\alpha_m + \mu_m)P_m,\\
\frac{dL_m}{dt} = (1-k_m)\alpha_m P_m + q_{m2}z_m H_m - (g_m + \mu_m)L_m,\\
\frac{dH_m}{dt} = [1-(d_{m1}+d_{m2})]g_m L_m + j_m\gamma_m C_m - (z_m + \mu_m)H_m,\\
\frac{dC_m}{dt} = [1-(q_{m1}+q_{m2}+q_{m3})]z_m H_m - (\gamma_m + \mu_m)C_m,\\
\frac{dR_{mc}}{dt} = (1-j_m)\gamma_m C_m - \mu_m R_{mc},\\
\frac{dR_m}{dt} = b_m\psi_m I_m + k_m\alpha_m P_m + d_{m1}g_m L_m + q_{m1}z_m H_m - (\xi_m + \mu_m)R_m.
\end{cases}
\tag{2.3}
$$

The description of the derivation of the equations for the Pap screening model (2.3) is given in Appendix A. The model (2.3) is an extension of many HPV Pap screening models in the literature (such as those in [2, 3, 11, 20, 22, 45]) by, *inter alia*,

(i) incorporating the dynamics of exposed females (E_f) and males (E_m), and allowing for HPV transmission by exposed males and females (this is not included in the models developed in [11, 20, 22, 45]);
(ii) incorporating the dynamics of individuals (females and males) in the pre-cancerous *intraepithelial neoplasia* stages (CIN and INM), as well as the dynamics of HPV-related cancers in males (which are not included in the models developed in [3, 11, 20, 22, 45]; it should, however, be stated that three CIN stages for females are included in the model developed in [45]);
(iii) allowing for the loss of infection-acquired immunity by recovered individuals (this is not included in the models considered in [11, 20, 22, 45]);
(iv) incorporating the regression from cervical (for females) and other HPV-related cancers (for males) to high-grade *intraepithelial neoplasia* stages and from low- and high-grade *intraepithelial neoplasia* stages to persistent infection (this is not included in the models considered in [3, 11, 20, 22, 45]); it should, however, be stated that only regression from high-grade *intraepithelial neoplasia* stage to persistent infection is included in the model developed in [2]);
(v) allowing for HPV transmission by individuals (females and males) in the various *intraepithelial neoplasia* stages (this is not included in the models considered in [2, 3, 11, 20, 22, 45]).

2.1. **Basic Properties.** Since the Pap screening model (2.3) monitors human populations, all its associated parameters and state variables are non-negative for $t \geq 0$.

Theorem 2.1. *Let the initial data be* $S_f(0) > 0$, $E_f(0) \geq 0$, $I_f(0) \geq 0$, $P_f(0) \geq 0$, $L_{fu}(0) \geq 0$, $L_{fd}(0) \geq 0$, $H_{fu}(0) \geq 0$, $H_{fd}(0) \geq 0$, $C_{fu}(0) \geq 0$, $C_{fd}(0) \geq 0$, $R_{fc}(0) \geq 0$, $R_f(0) \geq 0$, $S_m(0) > 0$, $E_m(0) \geq 0$, $I_m(0) \geq 0$, $P_m(0) \geq 0$, $L_m(0) \geq 0$, $H_m(0) \geq 0$, $C_m(0) \geq 0$, $R_{mc}(0) \geq 0$, $R_m(0) \geq 0$. *Then the solutions* $(S_f(t), E_f(t), I_f(t), P_f(t), L_{fu}(t), L_{fd}(t), H_{fu}(t), H_{fd}(t), C_{fu}(t), C_{fd}(t), R_{fc}(t), R_f(t), S_m(t), E_m(t), I_m(t), P_m(t), L_m(t),$

$H_m(t), C_m(t), R_{mc}(t), R_m(t)$) of the model (3.1), with positive initial data, will remain positive for all time $t > 0$.

Proof. Let

$$\begin{aligned} t_1 \;=\; & sup\ \{\ t > 0 : S_f(0) > 0, E_f(0) \geq 0, I_f(0) \geq 0, P_f(0) \geq 0, \\ & L_{fu}(0) \geq 0, L_{fd}(0) \geq 0, H_{fu}(0) \geq 0, H_{fd}(0) \geq 0, C_{fu}(0) \geq 0, \\ & C_{fd}(0) \geq 0, R_{fc}(0) \geq 0, R_f(0) \geq 0, S_m(0) > 0, E_m(0) \geq 0, \\ & I_m(0) \geq 0, P_m(0) \geq 0, L_m(0) \geq 0, H_m(0) \geq 0, C_m(0) \geq 0, \\ & R_{mc}(0) \geq 0, R_m(0) \geq 0\} > 0. \end{aligned}$$

The first equation of the model (2.3) can be re-written as

$$\frac{d}{dt}\left\{S_f(t)\exp\left[\int_0^t \lambda_m(u)du\right]\right\} \geq \pi_m \exp\left[\int_0^t \lambda_m(u)du + \mu_m(t)\right],$$

so that,

$$S_f(t_1)\exp\left[\int_0^{t_1} \lambda_m(u)du + \mu_f)t_1\right] - S_f(0)$$

is equal to:

$$\int_0^{t_1} \pi_f \exp\left[\int_0^z \lambda_m(u)du + \mu_f z\right] dz.$$

Thus,

$$\begin{aligned} S_f(t_1) \;\geq\; & S_f(0)\exp\left[-\int_0^{t_1} \lambda_m(u)du - \mu_f t_1\right] \\ + \;& \exp\left[-\int_0^{t_1} \lambda_m(u)du - \mu_f t_1\right] \\ \times \;& \int_0^{t_1} \pi_f \exp\left[\int_0^z \lambda_m(u)du + (\xi + \mu_f)z\right] dz > 0. \end{aligned}$$

Similarly, it can be shown that $E_f(t) \geq 0$, $I_f(t) \geq 0$, $P_f(t) \geq 0$, $L_{fu}(t) \geq 0$, $L_{fd}(t) \geq 0$, $H_{fu}(t) \geq 0$, $H_{fd}(t) \geq 0$, $C_{fu}(t) \geq 0$, $C_{fd}(t) \geq 0$, $R_{fc}(t) \geq 0$, $R_f(t) \geq 0$, $S_m(t) \geq 0$, $E_m(t) \geq 0$, $I_m(t) \geq 0$, $P_m(t) \geq 0$, $L_m(t) \geq 0$, $H_m(t) \geq 0$, $C_m(t) \geq 0$, $R_{mc}(t) \geq 0$ and $R_m(t) \geq 0$ for all time $t > 0$. Hence, all solutions of the Pap screening model (2.3) remain positive for all non-negative initial conditions. □

Lemma 2.1. *The closed set*

$$\mathcal{D}_s = \mathcal{D}_f \cup \mathcal{D}_m \subset \mathbb{R}_+^{12} \times \mathbb{R}_+^9,$$

with,

$$\mathcal{D}_f = \left\{(S_f, E_f, I_f, P_f, L_{fu}, L_{fd}, H_{fu}, H_{fd}, C_{fu}, C_{fd}, R_{fc}, R_f) \in \mathbb{R}_+^{12} : N_f \leq \frac{\pi_f}{\mu_f}\right\},$$

and,

$$\mathcal{D}_m = \left\{(S_m, E_m, I_m, P_m, L_m, H_m, C_m, R_{mc}, R_m) \in \mathbb{R}_+^9 : N_m \leq \frac{\pi_m}{\mu_m}\right\},$$

is positively-invariant and attracting for the Pap screening model (2.3).

Proof. Adding the first twelve equations of the model (3.1) gives

$$\frac{dN_f}{dt} = \pi_f - \mu_f N_f - (\delta_{fu} C_{fu} + \delta_{fd} C_{fd}) \leq \pi_f - \mu_f N_f. \tag{2.4}$$

It follows from (2.4) that $\frac{dN_f}{dt} < 0$ if $N_f(t) > \frac{\Pi_f}{\mu_f}$. Further, it follows, using Comparison Theorem [41], that

$$N_f(t) \leq N_f(0) e^{-\mu_f(t)} + \frac{\pi_f}{\mu_f}[1 - e^{-\mu_f(t)}].$$

In particular, $N_f(t) \leq \frac{\pi_f}{\mu_f}$ if $N_f(0) \leq \frac{\pi_f}{\mu_f}$. Similarly, it follows from the last nine equations of the model (3.1) that

$$N_m(t) \leq N_m(0) e^{-\mu_m(t)} + \frac{\pi_m}{\mu_m}[1 - e^{-\mu_m(t)}].$$

Thus, $N_m(t) \leq \frac{\pi_m}{\mu_m}$ if $N_m(0) \leq \frac{\pi_m}{\mu_m}$. Therefore, the region $\mathcal{D}_s$ is positively-invariant for the Pap screening model (2.3). Furthermore, if $N_f(0) > \frac{\pi_f}{\mu_f}$ and $N_m(0) > \frac{\pi_m}{\mu_m}$, then either the solution enters the region $\mathcal{D}_s$ in finite time, or $N_f(t)$ approaches $\frac{\pi_f}{\mu_f}$ and $N_m(t) \to \frac{\pi_m}{\mu_m}$ asymptotically [45]. Hence, the region $\mathcal{D}_s$ attracts all solutions in $\mathbb{R}_+^{21}$. □

Since the region $\mathcal{D}_s$ is positively-invariant, the usual existence, uniqueness, continuation results hold for the system (hence, it is sufficient to consider the dynamics of the flow generated by the Pap screening model (2.3) in this region [30]).

Before analyzing the Pap screening model (2.3), it is instructive to explore the dynamics of the model in the absence of Pap screening (since Pap screening is not generally implemented in resource-poor countries [26] and older, as well as poor, women, who are at the highest risk of developing cervical cancer, are less likely to be screened [26, 27]), as below.

3. Analysis of Screening-free Model

In the absence of Pap screening, the model (2.3) can be re-written as (denoted by screening-free (or basic) model):

$$\text{Females}\begin{cases}\dfrac{dS_f}{dt} = \pi_f - (\lambda_m + \mu_f)S_f,\\ \dfrac{dE_f}{dt} = \lambda_m S_f - (\sigma_f + \mu_f)E_f,\\ \dfrac{dI_f}{dt} = \sigma_f E_f - (r_{f1} + \psi_f + \mu_f)I_f,\\ \dfrac{dP_f}{dt} = \psi_f I_f - (r_{f2} + \alpha_f + \mu_f)P_f,\\ \dfrac{dQ_f}{dt} = \alpha_f P_f - (r_{f3} + g_f + \mu_f)Q_f,\\ \dfrac{dC_f}{dt} = g_f Q_f - (r_{f4} + \mu_f + \delta_f)C_f,\\ \dfrac{dR_{fc}}{dt} = r_{f4}C_f - \mu_f R_{fc},\\ \dfrac{dR_f}{dt} = r_{f1}I_f + r_{f2}P_f + r_{f3}Q_f - \mu_f R_f,\end{cases} \tag{3.1}$$

$$\text{Males}\begin{cases}\dfrac{dS_m}{dt} = \pi_m - (\lambda_f + \mu_m)S_m,\\ \dfrac{dE_m}{dt} = \lambda_f S_m - (\sigma_m + \mu_m)E_m,\\ \dfrac{dI_m}{dt} = \sigma_m E_m - (r_{m1} + \psi_m + \mu_m)I_m,\\ \dfrac{dP_m}{dt} = \psi_m I_m - (r_{m2} + \alpha_m + \mu_m)P_m,\\ \dfrac{dQ_m}{dt} = \alpha_m P_m - (r_{m3} + g_m + \mu_m)Q_m,\\ \dfrac{dC_m}{dt} = g_m Q_m - (r_{m4} + \mu_m)C_m,\\ \dfrac{dR_{mc}}{dt} = r_{m4}C_m - \mu_m R_{mc},\\ \dfrac{dR_m}{dt} = r_{m1}I_m + r_{m2}P_m + r_{m3}Q_m - \mu_m R_m,\end{cases}$$

where $N(t) = N_f(t) + N_m(t)$, with $N_f(t) = S_f(t) + E_f(t) + I_f(t) + P_f(t) + Q_f(t) + C_f(t) + R_{fc}(t) + R_f(t)$ and $N_m(t) = S_m(t) + E_m(t) + I_m(t) + P_m(t) + Q_m(t) + C_m(t) + R_{mc}(t) + R_m(t)$. The variables and parameters of the screening-free model (3.1) are described in Tables

4 and 5, respectively. It is assumed, for mathematical convenience, that, for the model (3.1), only infected individuals in the symptomatic (I_f and I_m) and persistent infection (P_f and P_m) classes can transmit the disease. Thus, the forces of infection, λ_m and λ_f, are now re-written, respectively, as

$$\lambda_m = \frac{\beta_m c_f \left(I_m + \theta_m P_m\right)}{N_m} \quad \text{and} \quad \lambda_f = \frac{\beta_f c_f \left(I_f + \theta_f P_f\right)}{N_m}. \quad (3.2)$$

The result below can be established using the approach in Section 2.

Lemma 3.1. *The closed set*

$$\mathcal{D} = \mathcal{D}_f \cup \mathcal{D}_m \subset \mathbb{R}_+^8 \times \mathbb{R}_+^8,$$

with,

$$\mathcal{D}_f = \left\{ (S_f, E_f, I_f, P_f, Q_f, C_f, R_{fc}, R_f) \in \mathbb{R}_+^8 : N_f \leq \frac{\pi_f}{\mu_f} \right\},$$

and,

$$\mathcal{D}_m = \left\{ (S_m, E_m, I_m, P_m, Q_m, C_m, R_{mc}, R_m) \in \mathbb{R}_+^8 : N_m \leq \frac{\pi_m}{\mu_m} \right\},$$

is positively-invariant and attracting for the screening-free model (3.1).

3.1. **Asymptotic Stability of Disease-free Equilibrium (DFE).** The DFE of the screening-free model (3.1), obtained by setting the right-hand sides of the equations of the model to zero, is given by,

$$\begin{aligned} \mathcal{E}_0 &= (S_f^*, E_f^*, I_f^*, P_f^*, Q_f^*, C_f^*, R_{fc}^*, R_f^*, S_m^*, E_m^*, I_m^*, P_m^*, Q_m^*, C_m^*, \\ &\quad R_{mc}^*, R_m^*) \\ &= \left(\frac{\pi_f}{\mu_f}, 0, 0, 0, 0, 0, 0, 0, \frac{\pi_m}{\mu_m}, 0, 0, 0, 0, 0, 0, 0 \right). \end{aligned}$$

The local asymptotic stability of the DFE ($\mathcal{E}_0$) can be established using the next generation operator method [18, 58]. Using the notation in [58], the non-negative matrix $\mathcal{F}$ (of new infection terms), and the M-matrix $\mathcal{V}$ (of the transition terms) associated with the model (3.1), evaluated at $\mathcal{E}_0$, are given, respectively, by:

$$\mathcal{F} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_m c_f S_f^*}{N_m^*} & \frac{\beta_m c_f S_f^* \theta_m}{N_m^*} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_f c_f & \beta_f c_f \theta_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

and,

$$\mathcal{V} = \begin{bmatrix} h_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_f & h_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\psi_f & h_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\alpha_f & h_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -g_f & h_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & h_6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\sigma_m & h_7 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\psi_m & h_8 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\alpha_m & h_9 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -g_m & h_{10} \end{bmatrix},$$

with, $h_1 = \sigma_f + \mu_f$, $h_2 = r_{f1} + \psi_f + \mu_f$, $h_3 = r_{f2} + \alpha_f + \mu_f$, $h_4 = r_{f3} + g_f + \mu_f$, $h_5 = r_{f4} + \mu_f + \delta_f$, $h_6 = \sigma_m + \mu_m$, $h_7 = r_{m1} + \psi_m + \mu_m$, $h_8 = r_{m2} + \alpha_m + \mu_m$, $h_9 = r_{m3} + g_m + \mu_m$ and $h_{10} = r_{m4} + \mu_m$.

It follows from [58] that the *basic reproduction number* of the model (3.1) [30], denoted by $\mathcal{R}_0$, is given by (where ρ is the spectral radius of the next generation matrix $\mathcal{F}\mathcal{V}^{-1}$)

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\mathcal{R}_m \mathcal{R}_f}, \tag{3.3}$$

with,

$$\mathcal{R}_m = \frac{\pi_f \mu_m \beta_m c_f \sigma_m}{\mu_f \pi_m h_6 h_7}\left(1+\frac{\theta_m \psi_m}{h_8}\right) \text{ and } \mathcal{R}_f = \frac{\beta_f c_f \sigma_f}{h_1 h_2}\left(1+\frac{\theta_f \psi_f}{h_3}\right).$$

The result below follows from Theorem 2 of [58].

Lemma 3.2. *The DFE, $\mathcal{E}_0$, of the model (3.1) is locally-asymptotically stable (LAS) if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The epidemiological consequence of Lemma 3.2 is that HPV can be effectively-controlled in the community (when $\mathcal{R}_0 < 1$) if the initial sizes of the sub-populations of the model (3.1) are in the basin of attraction of the DFE ($\mathcal{E}_0$). The threshold quantity, $\mathcal{R}_0$, represents the average number of secondary HPV infections generated by one infected male (female) in a completely-susceptible male (female) population [30]. It is epidemiologically interpreted as follows.

Interpretation of the basic reproduction number. Consider the screening-free model (3.1). Susceptible males acquire HPV infection, following effective contacts with symptomatic females (I_f) or females with persistent HPV infection (P_f). The number of male infections generated by symptomatic females is the product of the infection rate of symptomatic females $\left(\frac{\beta_f c_f S_m^*}{N_m^*}\right)$, the probability that an exposed female survives the exposed class and move to the symptomatic stage $\left(\frac{\sigma_f}{\sigma_f+\mu_f} = \frac{\sigma_f}{h_1}\right)$ and the average duration in the symptomatic class $\left(\frac{1}{r_{f1}+\psi_f+\mu_f} = \frac{1}{h_2}\right)$. Furthermore, the number of male infections generated by females with persistent HPV infection is the product of the infection rate of females with persistent HPV infection $\left(\frac{\beta_f c_f \theta_f S_m^*}{N_m^*}\right)$, the probability that an exposed female survives the exposed class and moves to the persistent infection class $\left(\frac{\psi_f}{r_{f1}+\psi_f+\mu_f} = \frac{\psi_f}{h_2}\right)$ and the average duration in the persistent infection class $\left(\frac{1}{r_{f2}+\alpha_f+\mu_f} = \frac{1}{h_3}\right)$. Hence, the average number of new male infections generated by infected females (symptomatic or those with persistent HPV infection) is given by (it is worth noting that $N_m^* = S_m^* = \frac{\pi_m}{\mu_m}$)

$$\left(\frac{\mu_m \beta_f c_f \sigma_f}{\pi_m h_1 h_2} + \frac{\mu_m \beta_f c_f \sigma_f \theta_f \psi_f}{\pi_m h_1 h_2 h_3}\right) S_m^* = \frac{\beta_f c_f \sigma_f}{h_1 h_2}\left(1+\frac{\theta_f \psi_f}{h_3}\right). \quad (3.4)$$

The terms in the left-hand side of (3.4) represent the number of new male infections generated by symptomatic females (I_f) and females with persistent HPV infection (P_f).

Similarly, susceptible females acquire HPV infection, following effective contacts with symptomatic males (I_m) or males with persistent HPV infection (P_m). The number of female infections generated by symptomatic males is the product of the infection rate of symptomatic males $\left(\frac{\beta_m c_f S_m^*}{N_m^*}\right)$, the probability that an exposed male survives the exposed class and move to the symptomatic stage $\left(\frac{\sigma_m}{\sigma_m+\mu_m} = \frac{\sigma_m}{h_6}\right)$ and the average duration in the symptomatic class $\left(\frac{1}{r_{m1}+\psi_m+\mu_m} = \frac{1}{h_7}\right)$. Furthermore, the number of female infections generated by males with persistent HPV infection is the product of the infection rate of males with persistent HPV infection $\left(\frac{\beta_m c_f \theta_m S_f^*}{N_m^*}\right)$, the probability that an exposed male survives the exposed class and moves to the persistent HPV infection class $\left(\frac{\psi_m}{r_{m1}+\psi_m+\mu_m} = \frac{\psi_m}{h_7}\right)$ and the average duration in the persistent infection class $\left(\frac{1}{r_{m2}+\alpha_m+\mu_m} = \frac{1}{h_8}\right)$. Thus, the average number of new female infections generated by infected males (symptomatic or those with persistent HPV infection) is given by (noting that $S_f^* = \frac{\pi_f}{\mu_f}$)

$$\left(\frac{\mu_m\beta_m c_f\sigma_m}{\pi_m h_6 h_8} + \frac{\mu_m\beta_m c_f\sigma_m\theta_m\psi_m}{\pi_m h_6 h_7 h_8}\right) S_f^* = \frac{\pi_f\mu_m\beta_m c_f\sigma_m}{\mu_f\pi_m h_6 h_7}\left(1 + \frac{\theta_m\psi_m}{h_8}\right). \tag{3.5}$$

The terms in the left-hand side of (3.5) represent the number of new female infections generated by symptomatic males (I_m) and males with persistent HPV infection (P_m). Since two generations are needed in the female-male-female HPV transmission cycle, the geometric mean of (3.4) and (3.5) gives the basic reproduction number, $\mathcal{R}_0$, of the screening-free model (3.1).

Lemma 3.2 shows that the effective control of HPV in the community (when $\mathcal{R}_0 < 1$) is dependent on the initial sizes of the sub-populations of the model. In order to show that such control is independent of the initial sizes of the sub-populations, a global asymptotic stability result should be established for the DFE ($\mathcal{E}_0$) of the screening-free model (3.1). This is done below.

Theorem 3.1. *The DFE, $\mathcal{E}_0$, of the screening-free model (3.1) is GAS in $\mathcal{D}$ whenever $\mathcal{R}_0 < 1$.*

The proof of Theorem 3.1, based on using a comparison theorem, is given in Appendix B. The epidemiological implication of Theorem 3.1 is that HPV will be eliminated from the community whenever the associated basic reproduction threshold ($\mathcal{R}_0$) is less than unity (in other words, the requirement $\mathcal{R}_0 < 1$ is necessary and sufficient for the effective control or elimination of HPV from the community). Figure 2 shows the solution profiles of the screening-free model (3.1), generated by simulating the model using various initial conditions, showing convergence to the DFE ($\mathcal{E}_0$) for the case when $\mathcal{R}_0 < 1$ (in line with Theorem 3.1).

3.2. **Existence and Stability of Endemic Equilibrium Point: Special Case.** In this section, the existence and stability of endemic equilibria (i.e., equilibria where the infected components of the screening-free model (3.1) are non-zero) will be explored. Let,

$$\begin{aligned}\mathcal{E}_1 \;=\; & (S_f^{**}, E_f^{**}, I_f^{**}, P_f^{**}, Q_f^{**}, C_f^{**}, R_{fc}^{**}, R_f^{**}, S_m^{**}, E_m^{**}, I_m^{**}, P_m^{**}, Q_m^{**}, \\ & C_m^{**}, R_{mc}^{**}, R_m^{**}),\end{aligned}$$

represents an arbitrary EEP of the model (3.1). Furthermore, let

$$\lambda_m^{**} = \frac{\beta_m c_f \mu_m \left(I_m^{**} + \theta_m P_m^{**}\right)}{\pi_m} \quad \text{and} \quad \lambda_f^{**} = \frac{\beta_f c_f \mu_m \left(I_f^{**} + \theta_f P_f^{**}\right)}{\pi_m}, \tag{3.6}$$

be the *force of infection* for males and females at endemic steady-state, respectively (it should be mentioned that $N_m(t)$ is now replaced by its limiting value $N_m^* = \frac{\pi_m}{\mu_m}$). Solving the equations of the screening-free (3.1) at the endemic steady-state gives:

$$\begin{aligned}
&S_f^{**} = \frac{\pi_f}{\lambda_m^{**} + \mu_f}, \quad E_f^{**} = \frac{\lambda_m^{**} S_f^{**}}{h_1}, \quad I_f^{**} = \frac{\sigma_f E_f^{**}}{h_2}, \quad P_f^{**} = \frac{\psi_f I_f^{**}}{h_3}, \\
&Q_f^{**} = \frac{\alpha_f P_f^{**}}{h_4}, \quad C_f^{**} = \frac{g_f Q_f^{**}}{h_5}, \quad R_{fc}^{**} = \frac{r_{f4} C_f^{**}}{\mu_f}, \\
&R_f = \frac{r_{f1} I_f^{**} + r_{f2} P_f^{**} + r_{f3} Q_f^{**}}{\mu_f} \quad S_m^{**} = \frac{\pi_m}{\lambda_f^{**} + \mu_m}, \quad E_m^{**} = \frac{\lambda_f^{**} S_m^{**}}{h_6}, \\
&I_m^{**} = \frac{\sigma_m E_m^{**}}{h_7}, \quad P_m^{**} = \frac{\psi_m I_m^{**}}{h_8}, \quad Q_m^{**} = \frac{\alpha_m P_m^{**}}{h_9}, \\
&C_m^{**} = \frac{g_m Q_m^{**}}{h_{10}}, \quad R_{mc}^{**} = \frac{r_{m4} C_m^{**}}{\mu_m}, \quad R_m = \frac{r_{m1} I_m^{**} + r_{m2} P_m^{**} + r_{m3} Q_m^{**}}{\mu_m}.
\end{aligned} \tag{3.7}$$

Substituting the expressions in (3.7) into (3.6) gives

$$\lambda_m^{**} = \frac{\beta_m c_f \mu_m \sigma_m (\theta_m \psi_m + h_8) \lambda_f^{**}}{h_6 h_7 h_8 (\lambda_f^{**} + \mu_m)}, \tag{3.8}$$

$$\lambda_f^{**} = \frac{\pi_f \beta_f c_f \mu_m \sigma_f (\theta_f \psi_f + h_3) \lambda_m^{**}}{\pi_m h_1 h_2 h_3 (\lambda_m^{**} + \mu_f)}. \tag{3.9}$$

Substituting (3.8) into (3.9), and simplifying, gives

$$\lambda_f^{**} = \frac{\mu_m \left[(\mathcal{R}_0)^2 - 1 \right]}{\pi_m h_1 h_2 h_3 \left[\beta_m c_f \mu_m (\psi_m \sigma_m \theta_m + \sigma_m h_8) + \mu_f h_6 h_7 h_8 \right]}. \tag{3.10}$$

It follows from (3.10) that (since all the parameters of the model (3.1) are positive) λ_f^{**} is positive whenever $\mathcal{R}_0 > 1$ (so that the screening-free model (3.1) has a unique EEP whenever $\mathcal{R}_0 > 1$). The components of the unique EEP can then be obtained by substituting (3.10) into the steady-state expressions in (3.7). Furthermore, if $\mathcal{R}_0 = 1$, then $\lambda_f^{**} = 0$ (which corresponds to the DFE, $\mathcal{E}_0$, of the model (3.10)). For $\mathcal{R}_0 < 1$, $\lambda_f^{**} < 0$ (which is biologically meaningless). These results are summarized below.

Theorem 3.2. *The screening-free model (3.1) has a unique endemic equilibrium (of the form $\mathcal{E}_1$) whenever $\mathcal{R}_0 > 1$, and no endemic equilibrium otherwise.*

The local asymptotic stability property of the unique EEP ($\mathcal{E}_1$) of the screening-free model (3.1) will now be explored, for a special case with no disease-induced mortality for the females (i.e., $\delta_f = 0$). It is convenient to define $\Delta = \mu_f \mu_m (D_1 D_2 - D_3)$, where,

$$\begin{aligned}
D_1 &= \alpha_m g_m \lambda_f^{**} \mu_m \psi_m \sigma_m + \alpha_m g_m \lambda_f^{**} \psi_m r_{m4} \sigma_m \\
&\quad + \alpha_m \lambda_f^{**} \mu_m \psi_m \sigma_m h_{10} + \alpha_m \lambda_f^{**} \psi_m r_{m3} \sigma_m h_{10} \\
&\quad + \mu_m h_6 h_7 h_8 h_9 h_{10} + \lambda_f^{**} \mu_m h_7 h_8 h_9 h_{10} + \lambda_f^{**} \mu_m \sigma_m h_8 h_9 h_{10} \\
&\quad + \lambda_f^{**} r_{m1} \sigma_m h_8 h_9 h_{10} + \lambda_f^{**} \mu_m \psi_m \sigma_m h_9 h_{10} \\
&\quad + \lambda_f^{**} \psi_m r_{m2} \sigma_m h_9 h_{10}, \\
D_2 &= \alpha_f g_f \lambda_m^{**} \mu_f \psi_f \sigma_f + \alpha_f g_f \lambda_m^{**} \psi_f r_{f4} \sigma_f + \alpha_f h_5 \lambda_m^{**} \mu_f \psi_f \sigma_f \\
&\quad + \alpha_f h_5 \lambda_m^{**} \psi_f r_{f3} \sigma_f + \mu_f h_1 h_2 h_3 h_4 h_5 + \lambda_m^{**} \mu_f h_2 h_3 h_4 h_5 \\
&\quad + \lambda_m^{**} \mu_f \sigma_f h_3 h_4 h_5 + \lambda_m^{**} r_{f1} \sigma_f h_3 h_4 h_5 + \lambda_m^{**} \mu_f \psi_f \sigma_f h_4 h_5 \\
&\quad + \lambda_m^{**} \psi_f r_{f2} \sigma_f h_4 h_5, \\
D_3 &= \frac{1}{(N_m^*)^2} \left(S_f^{**} S_m^{**} \mu_f \mu_m \sigma_f \sigma_m \beta_f \beta_m {c_f}^2 h_4 h_5 h_9 h_{10} \right) (\psi_m \theta_m + h_8) \\
&\quad (\psi_f \theta_f + h_3),
\end{aligned}$$

with,

$$\begin{aligned} S_f^{**} &= N_f^* - E_f^{**} - I_f^{**} - P_f^{**} - Q_f^{**} - C_f^{**} - R_{fc}^{**} - R_f^{**} \geq 0, \\ S_m^{**} &= N_m^* - E_m^{**} - I_m^{**} - P_m^{**} - Q_m^{**} - C_m^{**} - R_{mc}^{**} - R_m^{**} \geq 0, \end{aligned}$$

and,

$$\lambda_m^{**} = \frac{\beta_m c_f (I_m^{**} + \theta_m P_m^{**})}{N_m^*}, \quad \lambda_f^{**} = \frac{\beta_f c_f (I_f^{**} + \theta_f P_f^{**})}{N_m^*}.$$

Theorem 3.3. *The EEP ($\mathcal{E}_1$) of the model (3.1) is LAS if $\mathcal{R}_0 > 1$, $\delta_f = 0$ and $\Delta \neq 0$.*

The proof of Theorem 3.3, based on using a Krasnoselskii argument [23, 24, 55], is given in Appendix C. The epidemiological implication of Theorem 3.3 is that, for the screening-free (3.1) with $\mathcal{R}_0 > 1$ and negligible cancer-induced mortality in females ($\delta_f = 0$), HPV will persist in the community whenever the initial sizes of the sub-populations of the model (3.1) are in the basin of attraction of the unique EEP ($\mathcal{E}_1$). The equilibrium ($\mathcal{E}_1$) is now shown to be globally-asymptotically stable for a special case (below).

It is convenient to define $\mathcal{R}_1 = \mathcal{R}_0|_{\theta_m = \theta_f = 0}$ and the region (stable manifold of the DFE of the screening-free model (3.1))

$$\mathcal{D}_0 = \mathcal{D}_{f_0} \cup \mathcal{D}_{m_0} \subset \mathbb{R}_+^8 \times \mathbb{R}_+^8,$$

with,

$$\begin{aligned} \mathcal{D}_{f_0} &= \left\{ (S_f, E_f, I_f, P_f, Q_f, C_f, R_{fc}, R_f) \in \mathbb{R}_+^8 : \right. \\ &\quad \left. E_f = I_f = P_f = Q_f = C_f = 0 \right\}, \\ \mathcal{D}_{m_0} &= \left\{ (S_m, E_m, I_m, P_m, Q_m, C_m, R_{mc}, R_m) \in \mathbb{R}_+^8 : \right. \\ &\quad \left. E_m = I_m = P_m = Q_m = C_m = 0 \right\}. \end{aligned}$$

Theorem 3.4. *The unique EEP ($\mathcal{E}_1$) of the screening-free model (3.1), with $\theta_m = \theta_f = 0$, is GAS in $\mathcal{D} \backslash \mathcal{D}_0$ whenever $\mathcal{R}_1 > 1$, $S_f(t) \leq S_f^{**}$ and $S_m(t) \leq S_m^{**}$ for all t.*

The proof of Theorem 3.4, based on using a nonlinear Lyapunov function of Goh-Volterra type, is given in Appendix D. Theorem 3.4 shows that, for the case of the model (3.1) where individuals with persistent HPV infection do not transmit infection (i.e., $\theta_m = \theta_f = 0$), HPV will always persist in the population whenever the associated reproduction threshold ($\mathcal{R}_1$) exceeds unity, and that $S_f(t) \leq S_f^{**}$ and $S_m(t) \leq S_m^{**}$ for all time t. Figure 3 depicts solution profiles of the screening-free model, showing convergence to the unique EEP ($\mathcal{E}_1$) for the case when $\mathcal{R}_1 > 1$ (in agreement with Theorem 3.4). It is worth stating that although the conditions

$S_f(t) \leq S_f^{**}$ and $S_m(t) \leq S_m^{**}$ for all t are somewhat restrictive, extensive numerical simulations of the screening-free model (3.1) suggest that the conditions always hold (all the extensive simulations carried out support this claim).

The screening-free model (3.1) contains numerous parameters. Hence, uncertainties can arise in the estimates of the values of these parameters used in the numerical simulations of the model. To account for the effect of such uncertainties in the numerical simulations of the screening-free model (3.1), a detailed uncertainty analysis (using Latin Hypercube Sampling (LHS) [8, 32, 33, 34, 46, 47]) is carried out. The implementation of the LHS technique entails defining each parameter of the model as a distribution, and, subsequently, generating numerous LHS runs for a given output (which, in this study, is the basic reproduction threshold, $\mathcal{R}_0$). Sensitivity analysis (using Partial Rank Correlation Coefficients (PRCC) [32, 33, 34]) is also carried out to determine the key parameters of the model that most influence the disease transmission dynamics (i.e., parameters of the model (3.1) that most affect the value of the basic reproduction threshold $\mathcal{R}_0$). Figure 4 depicts the box plots of the basic reproduction number ($\mathcal{R}_0$), as a function of the 1000 LHS runs carried out, using the baseline parameter values and ranges in Table 5. For any given number of runs (N_R), each box plot displays the lower and upper quartile ranges of $\mathcal{R}_0$ (denoted by the lower and upper horizontal lines on a box, respectively). The horizontal line within a box denotes the median value (middle quartile) of $\mathcal{R}_0$. The upper and lower whiskers denote the most extreme values for $\mathcal{R}_0$ [47]. Values for $\mathcal{R}_0$ plotted beyond the whiskers are classified as outliers. Figure 4 shows that the distribution of $\mathcal{R}_0$ lies in the range $\mathcal{R}_0 \in [3.55, 4.20]$, with a mean of $\mathcal{R}_0 = 3.90$ (which is in line with the $\mathcal{R}_0$ values reported in [22, 45]). Furthermore, Table 6 shows the PRCC values of the parameters of the screening-free model (3.1), from which it is clear that the most dominant parameters are the average number of female sexual partners for males *per* unit time (c_f), the average duration of sexual activity for females and males (μ_f and μ_m), the infection probability for females and males (β_f and β_m), the recruitment rate of new sexually-active individuals (π_f and π_m), modification parameter for the infectiousness of individuals with persistent infection, relative to those in the corresponding symptomatic class (θ_f and θ_m) and the natural recovery rate of infected females (r_{f1}).

In summery, the screening-free model (3.1) has the following dynamic features:

i) The disease-free equilibrium of the screening-free model (3.1) is locally- and globally- asymptotically stable whenever the associated reproduction number ($\mathcal{R}_0$) is less than unity. The epidemiological implication of this result is that the community-wide control (or elimination) of HPV (and related dysplasia) is feasible if the basic reproduction number ($\mathcal{R}_0$) of the screening-free model (3.1) can be reduced to (and maintained at) a value less than unity. This can be achieved *via* the use of intervention strategies, such as Pap cytology screening.
ii) The screening-free model (3.1) has a unique endemic equilibrium point whenever the basic reproduction number ($\mathcal{R}_0$) exceeds unity. This equilibrium is shown to be locally- and globally- asymptotically stable for special cases.
iii) It is determined (based on the detailed uncertainty and sensitivity analyses) that the most dominant parameters that affect the disease transmission dynamics (as measured in terms of increase in the value of the associated basic reproduction threshold, $\mathcal{R}_0$) are:
   (a) the average number of female sexual partners for males *per* unit time (c_f);
   (b) the average duration of sexual activity for females and males (μ_f and μ_m);
   (c) the infection probability for females and males (β_f and β_m);
   (d) the recruitment rate of new sexually-active individuals for females and males (π_f and π_m);
   (e) the modification parameters for the infectiousness of individuals with persistent infection (in relation to those in the respective symptomatic class) (θ_f and θ_m);
   (f) the natural recovery rate of infected females (r_{f1}).

4. Analysis of Pap Screening Model

4.1. **Asymptotic stability.** The DFE of the Pap screening model (2.3) is given by,

$$\begin{aligned}\mathcal{E}_{0s} &= (S_f^*, E_f^*, I_f^*, P_f^*, L_{fu}^*, L_{fd}^*, H_{fu}^*, H_{fd}^*, C_{fu}^*, C_{fd}^*, R_{fc}^*, R_f^*, S_m^*,\\ &\quad E_m^*, I_m^*, P_m^*, L_m^*, H_m^*, C_m^*, R_{mc}^*, R_m^*)\\ &= \left(\frac{\pi_f}{\mu_f}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, \frac{\pi_m}{\mu_m}, 0, 0, 0, 0, 0, 0, 0, 0\right).\end{aligned}$$

Using the next generation operator method (as in Section 3), it follows that the associated next generation matrices, $\mathcal{F}_s$ and $\mathcal{V}_s$, are given, respectively, by:

$$\mathcal{F}_s = \begin{bmatrix}\mathbf{0}_{9\times 9} & \mathcal{F}_1\\ \mathcal{F}_2 & \mathbf{0}_{6\times 6}\end{bmatrix} \quad \text{and} \quad \mathcal{V}_s = \begin{bmatrix}\mathcal{V}_1 & \mathbf{0}_{6\times 6}\\ \mathbf{0}_{10\times 10} & \mathcal{V}_2\end{bmatrix},$$

where (with $\mathbf{0}_{n\times n}$ being the zero matrix of order n),

$$\mathcal{F}_1 = \begin{bmatrix}\frac{\beta_m c_f S_f^* \eta_m}{N_m^*} & \frac{\beta_m c_f S_f^*}{N_m^*} & \frac{\beta_m c_f S_f^* \theta_m}{N_m^*} & \frac{\beta_m c_f S_f^* \theta_m}{N_m^*} & \frac{\beta_m c_f S_f^* \theta_m \theta_{mh}}{N_m^*} & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\end{bmatrix},$$

$$\mathcal{F}_2 = \begin{bmatrix}\beta_f c_f \eta_f & \beta_f c_f & \beta_f c_f \theta_f & 0 & \beta_f c_f & \beta_f c_f \theta_f \theta_{fh} & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\end{bmatrix},$$

$$\mathcal{V}_1 = \begin{bmatrix}h_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ -\sigma_f & h_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\ 0 & -(1-b_f)\psi_f & h_3 & -d_{f2}g_f & 0 & -q_{f4}z_f & 0 & 0 & 0\\ 0 & 0 & -(1-k_f)\alpha_f & h_4 & 0 & -q_{f2}z_f & 0 & 0 & 0\\ 0 & 0 & 0 & -d_{f3}g_f & h_5 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & -b_1 & 0 & h_6 & 0 & -j_{f2}\gamma_f & 0\\ 0 & 0 & 0 & 0 & 0 & -q_{f3}z_f & h_7 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & -b_2 & 0 & h_8 & 0\\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -j_{f1}\gamma_f & h_9\end{bmatrix},$$

$$\mathcal{V}_2 = \begin{bmatrix} h_{10} & 0 & 0 & 0 & 0 & 0 \\ -\sigma_m & h_{11} & 0 & 0 & 0 & 0 \\ 0 & -(1-b_m)\psi_m & h_{12} & -d_{m2}g_m & -q_{m3}z_m & 0 \\ 0 & 0 & -(1-k_m)\alpha_m & h_{13} & -q_{m2}z_m & 0 \\ 0 & 0 & 0 & -b_3 & h_{14} & -j_m\gamma_m \\ 0 & 0 & 0 & 0 & -b_4 & h_{15} \end{bmatrix},$$

with, $b_1 = [1-(d_{f1}+d_{f2}+d_{f3})]g_f$, $b_2 = [1-(q_{f1}+q_{f2}+q_{f3}+q_{f4})]$, $b_3 = [1-(d_{m1}+d_{m2})]g_m$, $b_4 = [1-(q_{m1}+q_{m2}+q_{m3})]z_m$, $h_1 = \sigma_f+\mu_f$, $h_2 = \psi_f+\mu_f$, $h_3 = \alpha_f+\mu_f$, $h_4 = g_f+\mu_f$, $h_5 = r_1+\mu_f$, $h_6 = z_f+\mu_f$, $h_7 = r_2+\mu_f$, $h_8 = \gamma_f+\mu_f+\delta_{fu}$, $h_9 = r_3+\mu_f+\delta_{fd}$, $h_{10} = \sigma_m+\mu_m$, $h_{11} = \psi_m+\mu_m$, $h_{12} = \alpha_m+\mu_m$, $h_{13} = g_m+\mu_m$, $h_{14} = z_m+\mu_m$ and $h_{15} = \gamma_m+\mu_m$.

It follows from [58] that the *effective reproduction number* (i.e., reproduction number in the presence of Pap screening) of the model (2.3) is given by

$$\mathcal{R}_{0s} = \rho(FV^{-1}) = \sqrt{\mathcal{R}_f\ \mathcal{R}_m}, \tag{4.1}$$

where, $\mathcal{R}_f = \rho(F_1V_2^{-1}) = \frac{A_1}{A_2}$ and $\mathcal{R}_m = \rho(F_2V_1^{-1}) = \frac{B_1}{B_2}$ and,

$$\begin{aligned}
A_1 &= \beta_m c_f \pi_f \mu_m (a_3b_3c_{10}h_{15}\sigma_m\theta_m + a_3b_4c_{11}h_{13}\sigma_m\theta_m \\
&\quad -a_3h_{13}h_{14}h_{15}\sigma_m\theta_m + a_4b_3c_9\eta_m h_{11}h_{15} - a_4b_4c_8c_{11}\eta_m h_{11} \\
&\quad +a_4c_8\eta_m h_{11}h_{14}h_{15} + b_3c_{10}\eta_m h_{11}h_{12}h_{15} + b_4c_{11}\eta_m h_{11}h_{12}h_{13} \\
&\quad -\eta_m h_{11}h_{12}h_{13}h_{14}h_{15} + a_4b_3c_9h_{15}\sigma_m - a_4b_4c_8c_{11}\sigma_m \\
&\quad +a_4c_8h_{14}h_{15}\sigma_m + b_3c_{10}h_{12}h_{15}\sigma_m + b_4c_{11}h_{12}h_{13}\sigma_m \\
&\quad -h_{12}h_{13}h_{14}h_{15}\sigma_m), \\
A_2 &= \mu_f\pi_m h_{10}h_{11}(a_4b_3c_9h_{15} - a_4b_4c_8c_{11} + a_4c_8h_{14}h_{15} \\
&\quad +b_3c_{10}h_{12}h_{15} + b_4c_{11}h_{12}h_{13} - h_{12}h_{13}h_{14}h_{15}), \\
B_1 &= \beta_f c_f (a_1b_1c_3h_8\sigma_f\theta_f + a_1b_2c_5h_4\sigma_f\theta_f - a_1h_4h_6h_8\sigma_f\theta_f \\
&\quad +a_2b_1c_2\eta_f h_2h_8 - a_2b_2c_1c_5\eta_f h_2 + a_2c_1\eta_f h_2h_6h_8 \\
&\quad +b_1c_3\eta_f h_2h_3h_8 + b_2c_5\eta_f h_2h_3h_4 - \eta_f h_2h_3h_4h_6h_8 \\
&\quad +a_2b_1c_2h_8\sigma_f - a_2b_2c_1c_5\sigma_f + a_2c_1h_6h_8\sigma_f + b_1c_3h_3h_8\sigma_f \\
&\quad +b_2c_5h_3h_4\sigma_f - h_3h_4h_6h_8\sigma_f), \\
B_2 &= (a_2b_1c_2h_8 - a_2b_2c_1c_5 + a_2c_1h_6h_8 + b_1c_3h_3h_8 \\
&\quad +b_2c_5h_3h_4 - h_3h_4h_6h_8)h_1h_2,
\end{aligned}$$

with $a_1 = (1-b_f)\,\psi_f$, $a_2 = (1-k_f)\,\alpha_f$, $a_3 = (1-b_m)\,\psi_m$, $a_4 = (1-k_m)\,\alpha_m$, $c_1 = d_{f2}g_f$, $c_2 = q_{f4}z_f$, $c_3 = q_{f2}z_f$, $c_4 = d_{f3}g_f$, $c_5 = j_{f2}\gamma_f$, $c_6 = q_{f3}z_f$, $c_7 = j_{f1}\gamma_f$, $c_8 = d_{m2}g_m$, $c_9 = q_{m3}z_m$, $c_{10} = q_{m2}z_m$, $c_{11} = j_m\gamma_m$. It can be shown that the quantities A_1, A_2, B_1

and B_2 are positive (the calculations are lengthy, thus, not reported here). Hence, the reproduction number, $\mathcal{R}_{0s}$, is positive. The result below follows from Theorem 2 of [58].

Lemma 4.1. *The DFE, $\mathcal{E}_{0s}$, of the Pap screening model (2.3) is LAS if $\mathcal{R}_{0s} < 1$, and unstable if $\mathcal{R}_{0s} > 1$.*

The associated threshold quantity, $\mathcal{R}_{0s}$, represents the average number of secondary HPV infections generated by one infected male (female) in a susceptible male (female) population where a certain fraction of susceptible females undergo routine Pap screening [30]. We claim the following result.

Theorem 4.1. *The DFE, $\mathcal{E}_{0s}$, of the Pap screening model (2.3) is GAS in $\mathcal{D}_s$ whenever $\mathcal{R}_{0s} < 1$.*

Proof. The proof of Theorem 4.1 is given in Appendix E. □

The epidemiological implication of Theorem 4.1 is that HPV will be eliminated from the community whenever the community-wide implementation of the routine Pap screening program is effective enough to bring (and maintain) the associated effective reproduction threshold ($\mathcal{R}_{0s}$) to a value less than unity. Figure 5 shows the solution profiles of the model (2.3) converging to the DFE ($\mathcal{E}_{0s}$) when $\mathcal{R}_{0s} < 1$ (in line with Theorem 4.1).

In summary, the analyses in Sections 3 and 4 show that the screening-free model (3.1) and the Pap screening model (2.3) have the same qualitative dynamics with respect to the asymptotic stability of the respective disease-free equilibrium (since the DFE of each of the two models is GAS whenever its associated reproduction number is less than unity). Thus, this study shows that Pap screening does not alter the asymptotic dynamics of the screening-free model for HPV spread (with respect to the dynamics of the disease-free equilibrium).

4.2. **Simulations.** Figure 6 depicts the box plots of the effective reproduction number ($\mathcal{R}_{0s}$), as a function of the LHS runs carried out, using the parameter values and ranges in Tables 2 and 3. This figure shows the distribution of $\mathcal{R}_{0s}$ to be in the range $\mathcal{R}_{0s} \in [1.45, 2.70]$ (which is in line with those reported in [16, 22, 45]). Thus, although Pap screening reduces the range of the basic reproduction number ($\mathcal{R}_0$) of the screening-free HPV transmission model (3.1) (from $\mathcal{R}_0 \in [2.80, 4.95]$ to $\mathcal{R}_{0s} \in [1.45, 2.70]$), the community-wide implementation of a routine Pap screening program for females is insufficient (*albeit* it greatly reduces HPV burden) to lead to the

effective control of HPV in the community (since the distribution of $\mathcal{R}_{0s}$, depicted in Figure 6, exceed unity; and the disease will persist in this case). Table 7 depicts the PRCC values of the parameters of the Pap screening model (2.3), from which it is clear that the most dominant parameters (that govern the dynamics of the Pap screening model (2.3), with respect to the threshold quantity, $\mathcal{R}_{0s}$) are the average number of female sexual partners for males *per* unit time (c_f), the fraction of symptomatic females (males) who recovered naturally from HPV ($b_f(b_m)$), the infection probability for individuals (β_m and β_f), the recruitment rate of new sexually-active individuals (π_f and π_m), the average duration of sexual activity (μ_f and μ_m) and the transition rate out of the $I_f(I_m)$ class ($\psi_f(\psi_m)$).

The effect of the uncertainty in the estimates of the aforementioned eleven dominant (PRCC-ranked) parameters is further assessed by simulating the Pap screening model (2.3) for the following two scenarios:

(i) the baseline value of each of the top-eleven PRCC-ranked parameters in Table 7 is increased by 10%;
(ii) the baseline value of each of the top-eleven PRCC-ranked parameters in Table 7 is decreased by 10%.

It follows from Figure 7 that an increase (decrease) in the baseline values of these top PRCC-ranked parameters lead to a corresponding increase (decrease) in the numerical simulation results obtained (cumulative number of HPV cases over a 10-year period), confirming the sensitivity of the simulation results on these parameters. Figures 8 and 9 show similar sensitivities of these parameters on the cumulative cervical cancer (for females) and HPV-related cancers (for males) cases, respectively.

The effect of the HPV transmission by individuals (sexually-active females and males) in the pre-cancerous stages (both CIN and INM) on the dynamics of HPV is assessed by simulating the Pap screening model (2.3) in the presence, and absence, of such transmission. Figure 10 shows that HPV transmission by individuals with CIN and INM increases (in the long run) the cumulative number of HPV cases. Thus, these simulations suggests that HPV transmission models that do not incorporate HPV transmission by individuals in the pre-cancerous (CIN and INM) stages may underestimate HPV (and, consequently, cancer) burden in the community.

A contour plot of the effective reproduction number ($\mathcal{R}_{0s}$), as a function of the fraction of symptomatic females who recovered

naturally from HPV (b_f) and the fraction of symptomatic males who recovered naturally from HPV (b_m), is depicted in Figure 11. As expected, the plot shows a decrease in $\mathcal{R}_{0s}$ values with increasing values of the fractions b_f and b_m. Furthermore, it shows that, based on the parameter values in Tables 2 and 3 used in the simulations, even if 100% of symptomatic females and males recover naturally from HPV, the disease will still persist in the population (since such recovery fails to reduce the effective reproduction number, $\mathcal{R}_{0s}$, to a value less than unity; which is needed to eliminate the disease, in line with Theorem 4.1).

Finally, the effect of Pap screening on the cumulative number of cervical cancer cases is assessed by simulating the model (2.3) with different values of the fraction of females with CIN detected. Figure 12 confirms the effectiveness of Pap screening on minimizing cervical cancer cases. For example, while detecting 25% of females with CIN leads to about 65% reduction of cervical cancer cases in the community over a 10-year period, detecting 50% of females with CIN results in a 95% reduction of cervical cancer in the community over the same time period.

Conclusions

A new deterministic model for the transmission dynamics of HPV and related cancers in a community, where routine Pap cytology screening is administrated for sexually-active females, is designed. The model extends numerous other HPV transmission models in the literature by incorporating more crucial aspects of HPV dynamics, such as the dynamics of individuals (females and males) in the pre-cancerous (CIN and INM) and cancerous stages. Furthermore, the new model allows for the loss of infection-acquired immunity by recovered individuals, and incorporates the regression from cervical (for females) and other HPV-related cancers (for males) to high-grade intraepithelial neoplasia stages (and from low- and high-grade intraepithelial neoplasia stages to persistent infection). Some of the main theoretical and numerical results obtained are summarized below:

i) In the absence of Pap screening, the DFE of the resulting screening-free (basic) model is shown to be globally-asymptotically stable whenever the associated reproduction

number ($\mathcal{R}_0$) is less than unity. This model has a unique endemic equilibrium, which is shown to be locally- and globally-asymptotically stable for special cases, whenever the associated reproduction number ($\mathcal{R}_0$) exceeds unity.

ii) The disease-free equilibrium of the Pap screening model (2.3) is locally- and globally-asymptotically stable whenever the associated reproduction number is less than unity. Thus, the community-wide control or elimination of HPV (and related dysplasia) is feasible if the community-wide implementation of routine Pap screening could reduce (and maintain) the associated reproduction number ($\mathcal{R}_{0s}$) to a value less than unity.

iii) The parameters of the Pap screening model (2.3) that most influence the disease transmission dynamics (with respect to the effective reproduction threshold, $\mathcal{R}_{0s}$) are:
   (a) the average number of female sexual partners for males *per* unit time (c_f);
   (b) the fraction of symptomatic females (males) who recovered naturally from HPV ($b_f(b_m)$);
   (c) the infection probability for females and males (β_f and β_m);
   (d) the recruitment rate of new sexually-active individuals (π_f and π_m);
   (e) the average duration of sexual activity (μ_f and μ_m);
   (f) the average duration of sexual activity and the transition rate out of the I_f (I_m) class ($\psi_f(\psi_m)$).

iv) Adding Pap screening to the screening-free model does not alter the qualitative dynamics of the screening-free model (with respect to the asymptotic stability of the disease-free equilibrium).

v) Numerical simulations of the Pap screening model (3.1) suggest that:
   (a) HPV transmission by individuals with CIN and INM increases (in the long run) the cumulative number of new HPV cases;
   (b) Pap screening is very effective in minimizing cervical cancer cases. For instance, detecting 50% of females with CIN results in a 95% reduction of cervical cancer cases in the community over a 10-year period;

(c) Pap screening alone is insufficient to lead to effective control of HPV in the community (since it fails to reduce $\mathcal{R}_{0s}$ to a value less than unity);
(d) HPV transmission models that do not include disease transmission by individuals in the pre-cancerous stages may underestimate HPV-associated burden in the community.

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APPENDICES

Appendix A. Description of the Pap Screening Model (2.3)

The derivation of the equations of the Pap screening model (2.3) is described below.

The population of susceptible females ($S_f(t)$) is generated by the recruitment of new sexually-active females (at a rate π_f). This population is increased by the loss of infection-acquired immunity by infected females who recovered from HPV-infection without developing cervical cancer (at a rate ξ_f). The population is decreased by the acquisition of HPV infection, following effective contact with infected males (i.e., males in the E_m, I_m, P_m, L_m and H_m classes), at a rate λ_m, given by

$$\lambda_m = \frac{\beta_m c_f(N_m, N_f)\left[\eta_m E_m + I_m + \theta_m(P_m + L_m + \theta_{mh} H_m)\right]}{N_m}. \tag{A.1}$$

In (A.1), β_m is the probability of transmission of HPV infection from infected males to susceptible females *per* contact, and $c_f(N_m, N_f)$ is the average number of female partners *per* male *per* unit time (hence, $\beta_m c_f(N_m, N_f)$ is the effective contact rate for male-to-female transmission of HPV). Furthermore, $0 \leq \eta_m < 1$ is a modification parameter accounting for the assumption that exposed males (in the E_m class) are less infectious than symptomatically-infected males, and $\theta_m > 0$ models the assumed variability of the infectiousness of HPV-infected males in the P_m, L_m and H_m classes in relation to HPV-infected males in the E_m and I_m classes. Furthermore, $\theta_{mh} \geq 1$ accounts for the assumed increase of the infectiousness of males with high-grade INM in comparison to infected males in the P_m and L_m classes. The population of susceptible females is further diminished by natural death (at a rate μ_f; it is assumed that females in all epidemiological compartments suffer natural death at this rate). Thus,

$$\frac{dS_f}{dt} = \pi_f + \xi_f R_f - (\lambda_m + \mu_f) S_f. \tag{A.2}$$

The population of females exposed to HPV ($E_f(t)$) is generated by the infection of susceptible females (at the rate λ_m). Exposed females develop clinical symptoms of HPV (at a rate σ_f) and suffer natural death. Thus,

$$\frac{dE_f}{dt} = \lambda_m S_f - (\sigma_f + \mu_f) E_f. \tag{A.3}$$

The class of infected females with clinical symptoms of HPV ($I_f(t)$) is populated by the development of clinical symptoms of HPV by exposed females (at the rate σ_f). It is assumed that a fraction, $0 \leq b_f \leq 1$, of members of this class recovers (at a rate $b_f \psi_f$), while the remaining fraction, $1 - b_f$, develops persistent HPV infection (at a rate $(1 - b_f)\psi_f$). This population is further decreased by natural death. Thus,

$$\frac{dI_f}{dt} = \sigma_f E_f - (\psi_f + \mu_f) I_f. \tag{A.4}$$

The population of females with persistent HPV infection ($P_f(t)$) is generated by the development of persistent HPV infection by symptomatic females (at the rate $(1 - b_f)\psi_f$) as well as by the reversion of individuals with low-grade and high-grade CIN (at a rate $d_{f2} g_f$ and $q_{f4} z_f$, respectively; where the fractions d_{f2} and q_{f4} are defined below). It is assumed that detected individuals with CIN do not develop persistent HPV infection (since they are expected to be effectively treated). Individuals move out of this class through recovery (at a rate $k_f \alpha_f$; where k_f is the fraction of females with persistent HPV infection that recovers; the remaining fraction, $1 - k_f$, progress to low-grade CIN stage), development of pre-cancerous CIN lesions (at a rate $(1 - k_f)\alpha_f$) and natural death. Hence,

$$\frac{dP_f}{dt} = (1 - b_f)\psi_f I_f + d_{f2} g_f L_{fu} + q_{f4} z_f H_{fu} - (\alpha_f + \mu_f) P_f. \tag{A.5}$$

The population of females with undetected low-grade CIN ($L_{fu}(t)$) is generated by the development of CIN lesions by females with persistent HPV infection (at the rate $(1 - k_f)\alpha_f$) or by the regression of females with high-grade CIN (at a rate $q_{f2} z_f$; where the fraction q_{f2} is defined below). Transition out of this class occurs at a rate g_f (where a fraction, d_{f1}, recovers; another fraction, d_{f2}, reverts to P_f class; yet another fraction, d_{f3}, is detected and

the remaining fraction, $1-(d_{f1}+d_{f2}+d_{f3})$, progresses to the high-grade CIN 2/3 stage). Furthermore, this population is decreased by natural death. Thus,

$$\frac{dL_{fu}}{dt} = (1-k_f)\alpha_f P_f + q_{f2} z_f H_{fu} - (g_f + \mu_f) L_{fu}. \tag{A.6}$$

The population of females with detected low-grade CIN ($L_{fd}(t)$) is populated by the detection of females in the $L_{fu}(t)$ class (at the rate $d_{f3}g_f$). It is decreased by recovery (at a rate r_1) and natural death. Hence,

$$\frac{dL_{fd}}{dt} = d_{f3} g_f L_{fu} - (r_1 + \mu_f) L_{fd}. \tag{A.7}$$

The population of females with undetected high-grade CIN 2/3 ($H_{fu}(t)$) is generated by the progression of females with low-grade CIN (at the rate $[1-(d_{f1}+d_{f2}+d_{f3})]g_f$) or by the regression of individuals in the C_{fu} class (at a rate $j_{f2}\gamma_f$; where the fraction j_{f2} is defined below). Transition out of this class occurs at a rate z_f (where a fraction, q_{f1}, recovers; a fraction, q_{f2}, reverts to the L_{fu} class; a fraction, q_{f3}, is detected; another fraction, q_{f4}, reverts to the P_f class and the remaining fraction, $1-(q_{f1}+q_{f2}+q_{f3}+q_{f4})$, progresses to the C_{fu} class). Furthermore, this population is decreased by natural death. Thus,

$$\frac{dH_{fu}}{dt} = [1-(d_{f1}+d_{f2}+d_{f3})] g_f L_{fu} + j_{f2}\gamma_f C_{fu} - (z_f + \mu_f) H_{fu}. \tag{A.8}$$

The population of females with detected high-grade CIN 2/3 ($H_{fd}(t)$) is populated by the detection of females in the $H_{fu}(t)$ class (at the rate $q_{f3}z_f$). It is decreased by recovery (at a rate r_2) and natural death. Hence,

$$\frac{dH_{fd}}{dt} = q_{f3} z_f H_{fu} - (r_2 + \mu_f) H_{fd}. \tag{A.9}$$

The population of females with undetected cervical cancer ($C_{fu}(t)$) is generated by females in the H_{fu} class who develop cervical cancer (at the rate $[1-(q_{f1}+q_{f2}+q_{f3}+q_{f4})]z_f$). Transition out of this class occurs at a rate γ_f (where a fraction, j_{f1}, is detected; another fraction, j_{f2}, reverts to the H_{fu} class and the remaining fraction, $1-(j_{f1}+j_{f2})$, recovers). Furthermore, it is decreased by natural death and cancer-related mortality (at a rate δ_{fu}). Thus,

$$\frac{dC_{fu}}{dt} = [1-(q_{f1}+q_{f2}+q_{f3}+q_{f4})] z_f H_{fu} - (\gamma_f + \mu_f + \delta_{fu}) C_{fu}. \tag{A.10}$$

The population of females with detected cervical cancer ($C_{fd}(t)$) is populated by the detection of females in the $C_{fu}(t)$ compartment (at the rate $j_{f1}\gamma_f$). It is diminished by the recovery (at a rate r_3), natural death and cancer-related mortality (at a rate δ_{fd}). Hence,

$$\frac{dC_{fd}}{dt} = j_{f1}\gamma_f C_{fu} - (r_3 + \mu_f + \delta_{fd}) C_{fd}. \tag{A.11}$$

The population of females who recovered from cervical cancer ($R_{fc}(t)$) is generated by the recovery of females with undetected (at the rate $[1-(j_{f1}+j_{f2})]\gamma_f$) and detected (at the rate r_3) cervical cancer. Like in other epidemiological classes, females in this class also suffer natural death (at the rate μ_f). Hence,

$$\frac{dR_{fc}}{dt} = [1-(j_{f1}+j_{f2})]\gamma_f C_{fu} + r_3 C_{fd} - \mu_f R_{fc}. \tag{A.12}$$

The population of females who recovered from HPV infection without developing cervical cancer ($R_f(t)$) is populated by the recovery of females in the I_f, P_f, L_{fu}, L_{fd}, H_{fu} and H_{fd} classes (at the rates $b_f\psi_f$, $k_f\alpha_f$, $d_{f1}g_f$, r_1, $q_{f1}z_f$ and r_2, respectively). It is decreased by the loss of infection acquired immunity (at the rate ξ_f) and natural death, so that

$$\frac{dR_f}{dt} = b_f\psi_f I_f + k_f\alpha_f P_f + d_{f1} g_f L_{fu} + r_1 L_{fd} + q_{f1} z_f H_{fu} + r_2 H_{fd} - (\xi_f + \mu_f) R_f. \tag{A.13}$$

The population of susceptible males ($S_m(t)$) is generated by the recruitment of new sexually-active males (at a rate π_m). This population is further increased by the loss of infection-acquired immunity by infected males who recovered from HPV infection without developing HPV-related cancer (at a rate ξ_m). The population is decreased by the acquisition

of HPV infection, following effective contact with infected females (in the E_f, I_f, P_f, L_{fu}, L_{fd}, H_{fu} and H_{fd} classes), at a rate λ_f, given by

$$\lambda_f = \frac{\beta_f \; c_m(N_m, N_f) \left\{ \eta_f E_f + I_f + \theta_f \left[(P_f + L_{fu} + \theta_{fh} H_{fu} + \nu \left(L_{fd} + \theta_u H_{fd} \right) \right] \right\}}{N_f}. \tag{A.14}$$

In (A.14), β_f is the probability of transmission of HPV infection from infected females to susceptible males *per* contact, and $c_m(N_m, N_f)$ is the average number of male partners *per* female *per* unit time. Similarly, $0 \leq \eta_f < 1$ is a modification parameter accounting for the assumption that exposed females (in the E_f class) are less infectious than symptomatically-infected females, and $\theta_f > 0$ models the assumed variability of the infectiousness of HPV-infected females in the P_f, L_{fu}, L_{fd}, H_{fu} and H_{fd} classes in relation to the infectiousness of females in the E_f and I_f classes. Furthermore, $\theta_{fh} > 1 (\theta_u > 1)$ accounts for the assumed increase of the infectiousness of females with undetected (detected) high-grade CIN, in comparison to those in the P_f and L_{fu} (L_{fd}) classes. The parameter $\nu > 0$ models the variability of the infectiousness of females with detected CIN, in relation to the infectiousness of females with undetected CIN. The population of susceptible males is further diminished by natural death (at a rate μ_m; it is assumed that males in all epidemiological compartments suffer natural death at this rate). Thus,

$$\frac{dS_m}{dt} = \pi_m + \xi_m R_m - (\lambda_f + \mu_m) S_m. \tag{A.15}$$

The population of exposed males ($E_m(t)$) is generated by the infection of susceptible males (at the rate λ_f). Exposed males develop clinical symptoms of HPV (at a rate σ_m) and suffer natural death. Thus,

$$\frac{dE_m}{dt} = \lambda_f S_m - (\sigma_m + \mu_m) E_m. \tag{A.16}$$

The class of infected males with clinical symptoms of HPV ($I_m(t)$) is populated by the development of clinical symptoms of HPV by exposed males (at the rate σ_m). It is assumed that a fraction, $0 \leq b_m \leq 1$, of individuals in this class recovers (at a rate $b_m \psi_m$), while the remaining fraction, $1 - b_m$, develops persistent HPV infection (at the rate $(1 - b_m)\psi_m$). This population is further decreased by natural death. Thus,

$$\frac{dI_m}{dt} = \sigma_m E_m - (\psi_m + \mu_m) I_m. \tag{A.17}$$

The population of males with persistent HPV infection ($P_m(t)$) is generated by the development of persistent HPV infection by symptomatic males (at the rate $(1 - b_m)\psi_m$) as well as by the reversion of males with low-grade and high-grade INM (at a rate $d_2 g_m$ and $q_{m3} z_m$, respectively; where the fractions d_2 and q_{m3} are defined below). Individuals move out of this class through recovery (at a rate $k_m \alpha_m$; where k_m is the fraction of males in this class that recovers; the remaining fraction, $1 - k_m$, progresses to low grade INM stage), development of pre-cancerous INM lesions (at a rate $(1 - k_m)\alpha_m$) and natural death. Hence,

$$\frac{dP_m}{dt} = (1 - b_m)\psi_m I_m + d_{m2} g_m L_m + q_{m3} z_m H_m - (\alpha_m + \mu_m) P_m. \tag{A.18}$$

The population of males with the low-grade INM ($L_m(t)$) is generated by the development of INM lesions by males with persistent infection (at the rate $(1 - k_m)\alpha_m$) or by the regression of males in the H_m class (at a rate $q_{m2} z_m$). Transition out of this class occurs at a rate g_m (where a fraction, d_{m1}, recovers; another fraction, d_{m2}, reverts to P_m class and the remaining fraction, $1 - (d_{m1} + d_{m2})$, progresses to the high-grade INM 2/3 stage). Furthermore, this population is decreased by natural death. Thus,

$$\frac{dL_m}{dt} = (1 - k_m)\alpha_m P_m + q_{m2} z_m H_m - (g_m + \mu_m) L_m. \tag{A.19}$$

The population of males with the high-grade INM 2/3 ($H_m(t)$) is generated by the progression of infected males with INM (at the rate $[1 - (d_{m1} + d_{m2})] g_m$) or regression of males in the C_m class (at a rate $j_m \gamma_m$; where the fraction j_m is defined below). Transition out of this class occurs at a rate z_m (where a fraction, q_{m1}, recovers; a fraction, q_{m2}, reverts to the L_m class;

another fraction, q_{m3}, reverts to P_m class and the remaining fraction, $1-(q_{m1}+q_{m2}+q_{m3})$, progresses to class C_m). Furthermore, the population is decreased by natural death. Thus,

$$\frac{dH_m}{dt} = [1-(d_{m1}+d_{m2})]g_m L_m + j_m\gamma_m C_m - (z_m+\mu_m)H_m. \tag{A.20}$$

The population of males with HPV-related cancer ($C_m(t)$) is generated by males in the H_m class who develop HPV-related cancer (at the rate $[1-(q_{m1}+q_{m2}+q_{m3})]z_m$). Transition out of the class occurs at a rate γ_m (where a fraction, j_m, reverts to the H_m class and the remaining fraction, $1-j_m$, recovers). Furthermore, it is decreased by natural death (it should be mentioned that since HPV-related cancer, such as penile cancer, is rare in males [59], no mortality due to HPV-related cancer is assumed for males). Thus,

$$\frac{dC_m}{dt} = [1-(q_{m1}+q_{m2}+q_{m3})]z_m H_m - (\gamma_m+\mu_m)C_m. \tag{A.21}$$

The population of males who recovered from HPV-related cancer ($R_{mc}(t)$) is generated by the recovery of males with HPV-related cancer (at the rate $(1-j_m)\gamma_m$). It is reduced by natural death. Hence,

$$\frac{dR_{mc}}{dt} = (1-j_m)\gamma_m C_m - \mu_m R_{mc}. \tag{A.22}$$

The population of males who recovered from HPV infection without developing HPV-related cancer ($R_m(t)$) is populated by the recovery of males in the I_m, P_m, L_m and H_m classes (at the rates $b_m\psi_m$, $k_m\alpha_m$, $d_{m1}g_m$, and $q_{m1}z_m$, respectively). It is decreased by the loss of infection acquired immunity (at the rate ξ_m) and natural death, so that

$$\frac{dR_m}{dt} = b_m\psi_m I_m + k_m\alpha_m P_m + d_{m1}g_m L_m + q_{m1}z_m H_m - (\xi_m+\mu_m)R_m. \tag{A.23}$$

It is worth stating, from the equations given in $\{(A.15)-(A.23)\}$, that

$$\frac{dN_m(t)}{dt} = \pi_m - \mu_m N_m(t), \text{ so that } N_m(t) \longrightarrow \frac{\pi_m}{\mu_m}, \text{ as } t \longrightarrow \infty. \tag{A.24}$$

Furthermore, since the model {(A.2) - (A.23)} is a sex-structured one, it is crucial that the conservation law of sexual contacts (i.e., the total number of sexual contacts made by males balances that made by females) is preserved in the heterosexual community [45]. Hence, for the model {(A.2) - (A.23)},

$$c_m(N_m,N_f)\ N_m = c_f(N_m,N_f)\ N_f. \tag{A.25}$$

It is assumed that male sexual partners are abundant, and that females can have enough number of male sexual partners *per* unit time (so that it is reasonable to assume that $c_f(N_m,N_f)=c_f$ a constant). Hence, (A.25) can be re-written as

$$c_m(N_m,N_f) = \frac{c_f N_f}{N_m}. \tag{A.26}$$

It is assumed (for mathematical convenience), from the now on, that only undetected infected females with low- or high-grade CIN can transmit HPV infection to males (i.e., $\nu=0$). Consequently, using (A.25) in (A.1) and (A.14), the force of infections, λ_m and λ_f, are now re-written, respectively, as

$$\begin{aligned} \lambda_m &= \frac{\beta_m c_f\left[\eta_m E_m + I_m + \theta_m(P_m+L_m+\theta_{mh}H_m)\right]}{N_m}, \\ \lambda_f &= \frac{\beta_f c_f\left[\eta_f E_f + I_f + \theta_f(P_f+L_{fu}+\theta_{fh}H_{fu})\right]}{N_m}. \end{aligned} \tag{A.27}$$

Appendix B. Proof of Theorem 3.1

Proof. Consider the screening-free model (3.1). The proof is based on using a Comparison Theorem [41]. It is worth mentioning, first of all, that since the off-diagonal entries of the Jacobian matrix of the infected components of the screening-free (3.1), at the DFE ($\mathcal{E}_0$), are non-negative, the system (3.1) satisfies the Type K condition [41]. Hence, comparison theorem can be used.

Let $\mathcal{R}_0 < 1$ (so that the DFE, $\mathcal{E}_0$, of the screening-free model (3.1) is LAS, in line with Lemma 3.2). The infected components of the model (3.1) can be re-written as:

$$\frac{d\boldsymbol{x}}{dt} = (\mathcal{F} - \mathcal{V})\boldsymbol{x} - J\boldsymbol{x}, \tag{B.1}$$

where, $\boldsymbol{x} = [E_f(t), I_f(t), P_f(t), Q_f(t), C_f(t), R_{fc}(t), R_f(t), E_m(t), I_m(t), P_m(t), Q_m(t), C_m(t), R_{mc}(t), R_m(t)]^T$,

where the matrices $\mathcal{F}$ and $\mathcal{V}$ are as defined in Section 3.1, and

$$J = \left[1 - \frac{\mu_f S_f(t)}{\pi_f}\right] J_1 + \left[1 - \frac{\mu_m S_m(t)}{\pi_m}\right] J_2,$$

where,

$$J_1 = \begin{pmatrix} 0_{7\times 7} & \mathcal{J}_1 \\ 0_{7\times 7} & 0_{7\times 7} \end{pmatrix}, \quad J_2 = \begin{pmatrix} 0_{7\times 7} & 0_{7\times 7} \\ \mathcal{J}_2 & 0_{7\times 7} \end{pmatrix},$$

with,

$$\mathcal{J}_1 = \begin{pmatrix} 0 & \frac{\beta_m c_f \pi_f \mu_m}{\pi_m \mu_f} & \frac{\beta_m c_f \theta_m \pi_f \mu_m}{\pi_m \mu_f} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\mathcal{J}_2 = \begin{pmatrix} 0 & \beta_f c_f & \beta_f c_f \theta_f & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

It is worth noting that J_1 and J_2 are non-negative matrices. Furthermore, since, for all $t \geq 0$ in $\mathcal{D}_s$, $S_f(t) \leq N_f(t) \leq \frac{\pi_f}{\mu_f}$ and $S_m(t) \leq N_m(t) \leq \frac{\pi_m}{\mu_m}$, it follows that, $\frac{\mu_f S_f(t)}{\pi_f} \leq 1$ and $\frac{\mu_m S_m(t)}{\pi_m} \leq 1$. Hence, J is a non-negative matrix. Thus, it follows, from (B.1), that

$$\frac{d\boldsymbol{x}}{dt} \leq (\mathcal{F} - \mathcal{V})\boldsymbol{x}. \tag{B.2}$$

Using the fact that the eigenvalues of the matrix $\mathcal{F} - \mathcal{V}$ all have negative real parts when $\mathcal{R}_0 < 1$ (based on the local asymptotic stability result given in Lemma 3.2), it follows that the linear differential inequality system (B.2) is stable whenever $\mathcal{R}_0 < 1$. Hence, by Comparison Theorem [41],

$$\lim_{t\to\infty} (E_f(t), I_f(t), P_f(t), Q_f(t), C_f(t), R_{fc}(t), R_f(t), E_m(t), I_m(t), P_m(t), Q_m(t), C_m(t), R_{mc}(t), R_m(t)) = (0,0,0,0,0,0,0,0,0,0,0,0,0,0).$$

Substituting $E_f(t) = I_f(t) = P_f(t) = Q_f(t) = C_f(t) = R_{fc}(t) = R_f(t) = E_m(t) = I_m(t) = P_m(t) = Q_m(t) = C_m(t) = R_{mc}(t) = R_m(t) = 0$ into the first and ninth equations of the model (3.1) shows that $S_f(t) \to S_f^*$ and $S_m(t) \to S_m^*$ as $t \to \infty$ (for $\mathcal{R}_0 < 1$). Thus,

$$\lim_{t\to\infty} \quad (S_f(t), E_f(t), I_f(t), P_f(t), Q_f(t), C_f(t), R_{fc}(t), R_f(t), S_m(t)E_m(t), I_m(t), P_m(t), Q_m(t), C_m(t), R_{mc}(t), R_m(t)) = \mathcal{E}_0.$$

□

Appendix C. Proof of Theorem 3.3

Proof. Consider the screening-free model (3.1). Let $\mathcal{R}_0 > 1$ (so that the unique EEP ($\mathcal{E}_1$) of the screening-free (3.1) exists, by Theorem 3.2), $\delta_f = 0$ (hence, $N_f(t) = N_f^* = \frac{\pi_f}{\mu_f}$ at steady-state) and $\Delta \neq 0$. Thus (using $N_f^* = \frac{\pi_f}{\mu_f}$), and $S_f(t) = N_f^*(t) - E_f(t) - I_f(t) - P_f(t) - Q_f(t) - C_f(t) - R_{fc}(t) - R_f(t)$ and $S_m(t) = N_m^*(t) - E_m(t) - I_m(t) - P_m(t) - Q_m(t) - C_m(t) - R_{mc}(t) - R_m(t)$, it is sufficient to study the following limiting system (instead of the system (3.1)):

$$\begin{aligned}
\frac{dE_f}{dt} &= \lambda_m(N_f^* - E_f - I_f - P_f - Q_f - C_f - R_{fc} - R_f) - (\sigma_f + \mu_f)E_f,\\
\frac{dI_f}{dt} &= \sigma_f E_f - (r_{f1} + \psi_f + \mu_f)I_f,\\
\frac{dP_f}{dt} &= \psi_f I_f - (r_{f2} + \alpha_f + \mu_f)P_f,\\
\frac{dQ_f}{dt} &= \alpha_f P_f - (r_{f3} + g_f + \mu_f)Q_f,\\
\frac{dC_f}{dt} &= g_f Q_f - (r_{f4} + \mu_f + \delta_f)C_f,\\
\frac{dR_{fc}}{dt} &= r_{f4}C_f - \mu_f R_{fc},\\
\frac{dR_f}{dt} &= r_{f1}I_f + r_{f2}P_f + r_{f3}Q_f - \mu_f R_f,\\
\frac{dE_m}{dt} &= \lambda_f(N_m^* - E_m - I_m - P_m - Q_m - C_m - R_{mc} - R_m) - (\sigma_m + \mu_m)E_m,\\
\frac{dI_m}{dt} &= \sigma_m E_m - (r_{m1} + \psi_m + \mu_m)I_m,\\
\frac{dP_m}{dt} &= \psi_m I_m - (r_{m2} + \alpha_m + \mu_m)P_m,\\
\frac{dQ_m}{dt} &= \alpha_m P_m - (r_{m3} + g_m + \mu_m)Q_m,\\
\frac{dC_m}{dt} &= g_m Q_m - (r_{m4} + \mu_m)C_m,\\
\frac{dR_{mc}}{dt} &= r_{m4}C_m - \mu_m R_{mc},\\
\frac{dR_m}{dt} &= r_{m1}I_m + r_{m2}P_m + r_{m3}Q_m - \mu_m R_m.
\end{aligned} \tag{C.1}$$

Consider, next, the model (C.1) with $\mathcal{R}_0 > 1$. The proof is based on showing that the linearization of the model (C.1), around the associated EEP ($\mathcal{E}_1$), has no solution of the form [23, 24, 55]

$$\bar{Z}(t) = \bar{Z}_0 e^{wt}, \tag{C.2}$$

with $\bar{Z}_0 = (Z_1, Z_2, \cdots, Z_{14})$, $Z_i \in \mathbb{C}$, $w \in \mathbb{C}$, and $\mathrm{Re}(w) \geq 0$. The consequence of this is that the eigenvalues of the characteristic polynomial associated with the linearized version of model (C.1) will have negative real part (in which case, the EEP ($\mathcal{E}_1$) is LAS).

Let $E_f^{**}, I_f^{**}, P_f^{**}, Q_f^{**}, C_f^{**}, R_{fc}^{**}, R_f^{**}, E_m^{**}, I_m^{**}, P_m^{**}, Q_m^{**}, C_m^{**}, R_{mc}^{**}, R_m^{**}$ denote the coordinates of the endemic equilibrium, EEP. Substituting the solution of the form (C.2), into the linearized system of (C.1) around $(\mathcal{E}_1)$, gives the following system of linear equations:

$$\begin{aligned}
wZ_1 &= -(\lambda_m^{**}+h_1)Z_1 - \lambda_m^{**}Z_2 - \lambda_m^{**}Z_3 - \lambda_m^{**}Z_4 - \lambda_m^{**}Z_5 - \lambda_m^{**}Z_6 - \lambda_m^{**}Z_7 \\
&\quad + A_1^{**}Z_9 + \theta_m A_1^{**}Z_{10}, \\
wZ_2 &= \sigma_f Z_1 - h_2 Z_2, \\
wZ_3 &= \psi_f Z_2 - h_3 Z_3, \\
wZ_4 &= \alpha_f Z_3 - h_4 Z_4, \\
wZ_5 &= g_f Z_4 - h_5 Z_5, \\
wZ_6 &= r_{f4} Z_5 - \mu_f Z_6, \\
wZ_7 &= r_{f1} Z_2 + r_{f2} Z_3 + r_{f3} Z_4 - \mu_f Z_7, \\
wZ_8 &= A_2^{**}Z_2 + \theta_f A_2^{**}Z_3 - (\lambda_f^{**}+h_6)Z_8 - \lambda_f^{**}Z_9 - \lambda_f^{**}Z_{10} - \lambda_f^{**}Z_{11} - \lambda_f^{**}Z_{12} \\
&\quad - \lambda_f^{**}Z_{13} - \lambda_f^{**}Z_{14}, \\
wZ_9 &= \sigma_m Z_8 - h_7 Z_9, \\
wZ_{10} &= \psi_m Z_9 - h_8 Z_{10}, \\
wZ_{11} &= \alpha_m Z_{10} - h_9 Z_{11}, \\
wZ_{12} &= g_m Z_{11} - h_{10} Z_{12}, \\
wZ_{13} &= r_{m4} Z_{12} - \mu_m Z_{13}, \\
wZ_{14} &= r_{m1} Z_9 + r_{m2} Z_{10} + r_{m3} Z_{11} - \mu_m Z_{14},
\end{aligned} \tag{C.3}$$

where,

$$\begin{aligned}
A_1^{**} &= \frac{\beta_m c_f (N_f^* - E_f^{**} - I_f^{**} - P_f^{**} - Q_f^{**} - C_f^{**} - R_{fc}^{**} - R_f^{**})}{N_m^{**}}, \\
A_2^{**} &= \frac{\beta_f c_f (N_m^* - E_m^{**} - I_m^{**} - P_m^{**} - Q_m^{**} - C_m^{**} - R_{mc}^{**} - R_m^{**})}{N_m^{**}}.
\end{aligned}$$

Solving for Z_2 from the second equation of and also for Z_9 from the ninth equation of (C.3) and substituting the results into the remaining equations of (C.3), gives the following system

$$
\begin{aligned}
\left\{1+\frac{1}{h_1}\left[w+\lambda_m^{**}\left(1+\frac{\sigma_f}{w+h_2}\right)\right]\right\}Z_1 &= -\frac{\lambda_m^{**}}{h_1}Z_3-\frac{\lambda_m^{**}}{h_1}Z_4-\frac{\lambda_m^{**}}{h_1}Z_5-\frac{\lambda_m^{**}}{h_1}Z_6\\
&\quad -\frac{\lambda_m^{**}}{h_1}Z_7+\frac{A_1^{**}}{h_1}Z_9+\frac{\theta_m A_1^{**}}{h_1}Z_{10},\\
\left(1+\frac{w}{h_2}\right)Z_2 &= \frac{\sigma_f}{h_2}Z_1,\\
\left(1+\frac{w}{h_3}\right)Z_3 &= \frac{\psi_f}{h_3}Z_2,\\
\left(1+\frac{w}{h_4}\right)Z_4 &= \frac{\alpha_f}{h_4}Z_3,\\
\left(1+\frac{w}{h_5}\right)Z_5 &= \frac{g_f}{h_5}Z_4,\\
\left(1+\frac{w}{\mu_f}\right)Z_6 &= \frac{r_{f4}}{\mu_f}Z_5,\\
\left(1+\frac{w}{\mu_f}\right)Z_7 &= \frac{r_{f1}}{\mu_f}Z_2+\frac{r_{f2}}{\mu_f}Z_3+\frac{r_{f3}}{\mu_f}Z_4,\\
\left\{1+\frac{1}{h_6}\left[w+\lambda_f^{**}\left(1+\frac{\sigma_m}{w+h_7}\right)\right]\right\}Z_8 &= \frac{A_2^{**}}{h_6}Z_2+\frac{\theta_f A_2^{**}}{h_6}Z_3-\frac{\lambda_f^{**}}{h_6}Z_{10}-\frac{\lambda_f^{**}}{h_6}Z_{11}\\
&\quad -\frac{\lambda_f^{**}}{h_6}Z_{12}-\frac{\lambda_f^{**}}{h_6}Z_{13}-\frac{\lambda_f^{**}}{h_6}Z_{14},\\
\left(1+\frac{w}{h_7}\right)Z_9 &= \frac{\sigma_m}{h_7}Z_8,\\
\left(1+\frac{w}{h_8}\right)Z_{10} &= \frac{\psi_m}{h_8}Z_9,\\
\left(1+\frac{w}{h_9}\right)Z_{11} &= \frac{\alpha_m}{h_9}Z_{10},\\
\left(1+\frac{w}{h_{10}}\right)Z_{12} &= \frac{g_m}{h_{10}}Z_{11},\\
\left(1+\frac{w}{\mu_m}\right)Z_{13} &= \frac{r_{m4}}{\mu_m}Z_{12},\\
\left(1+\frac{w}{\mu_m}\right)Z_{14} &= \frac{r_{m1}}{\mu_m}Z_9+\frac{r_{m2}}{\mu_m}Z_{10}+\frac{r_{m3}}{\mu_m}Z_{11}.
\end{aligned}
$$

Adding the first, third, fourth, fifth, sixth and seventh and then the eighth, tenth, eleventh, twelfth, thirteenth and fourteenth equations of (C.3), and finally moving all the negative terms to the left-hand sides gives

$$
\begin{aligned}
&[1+F_1(w)]\,Z_1+[1+F_3(w)]\,Z_3+[1+F_4(w)]\,Z_4+[1+F_5(w)]\,Z_5+[1+F_6(w)]\,Z_6\\
&+[1+F_7(w)]\,Z_7=\left(H\bar{Z}\right)_1+\left(H\bar{Z}\right)_3+\left(H\bar{Z}\right)_4+\left(H\bar{Z}\right)_5+\left(H\bar{Z}\right)_6+\left(H\bar{Z}\right)_7,\\
&[1+F_2(w)]\,Z_2=\left(H\bar{Z}\right)_2,\\
&[1+F_8(w)]\,Z_8+[1+F_{10}(w)]\,Z_{10}+[1+F_{11}(w)]\,Z_{11}+[1+F_{12}(w)]\,Z_{12}+[1+F_{13}(w)]\,Z_{13}\\
&+[1+F_{14}(w)]\,Z_{14}=\left(H\bar{Z}\right)_8+\left(H\bar{Z}\right)_{10}+\left(H\bar{Z}\right)_{11}+\left(H\bar{Z}\right)_{12}+\left(H\bar{Z}\right)_{13}+\left(H\bar{Z}\right)_{14},\\
&[1+F_9(w)]\,Z_9=\left(H\bar{Z}\right)_9,
\end{aligned}
\tag{C.4}
$$

where,

$$F_1(w)=\frac{1}{h_1}\left[w+\lambda_m^{**}\left(1+\frac{\sigma_f}{w+h_2}\right)\right],\quad F_2(w)=\frac{w}{h_2},$$
$$F_3(w)=\frac{1}{h_3}\left(w+\frac{h_3\lambda_m^{**}}{h_1}\right),\quad F_4(w)=\frac{1}{h_4}\left(w+\frac{h_4\lambda_m^{**}}{h_1}\right),$$
$$F_5(w)=\frac{1}{h_5}\left(w+\frac{h_5\lambda_m^{**}}{h_1}\right),\quad F_6(w)=\frac{1}{\mu_f}\left(w+\frac{\mu_f\lambda_m^{**}}{h_1}\right),$$
$$F_7(w)=\frac{1}{\mu_f}\left(w+\frac{\mu_f\lambda_m^{**}}{h_1}\right),\quad F_8(w)=\frac{1}{h_6}\left[w+\lambda_f^{**}\left(1+\frac{\sigma_m}{w+h_7}\right)\right],$$
$$F_9(w)=\frac{w}{h_7},\quad F_{10}(w)=\frac{1}{h_8}\left(w+\frac{h_8\lambda_f^{**}}{h_6}\right),$$
$$F_{11}(w)=\frac{1}{h_9}\left(w+\frac{h_9\lambda_f^{**}}{h_6}\right),\quad F_{12}(w)=\frac{1}{h_{10}}\left(w+\frac{h_{10}\lambda_f^{**}}{h_6}\right),$$
$$F_{13}(w)=\frac{1}{\mu_m}\left(w+\frac{\mu_m\lambda_f^{**}}{h_6}\right),\quad F_{14}(w)=\frac{1}{\mu_m}\left(w+\frac{\mu_m\lambda_f^{**}}{h_6}\right),$$

with H equals to:

$$\begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{A_1^{**}}{h_1} & \frac{\theta_m A_1^{**}}{h_1} & 0 & 0 & 0 & 0\\
\frac{\sigma_f}{h_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & \frac{\psi_f}{h_3} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & \frac{\alpha_f}{h_4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & \frac{g_f}{h_5} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & \frac{r_{f4}}{\mu_f} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & \frac{r_{f1}}{\mu_f} & \frac{r_{f2}}{\mu_f} & \frac{r_{f3}}{\mu_f} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & \frac{A_2^{**}}{h_6} & \frac{\theta_f A_2^{**}}{h_6} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\sigma_m}{h_7} & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\psi_m}{h_8} & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\alpha_m}{h_9} & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{g_m}{h_{10}} & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{r_{m4}}{\mu_m} & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{r_{m1}}{\mu_m} & \frac{r_{m2}}{\mu_m} & \frac{r_{m3}}{\mu_m} & 0 & 0 & 0
\end{bmatrix}.$$

It should be noted note that the notation $H(\bar{Z})_i$ (with $i=1,\ldots,14$) denotes the ith coordinate of vector $H(\bar{Z})$. Furthermore, the matrix H has no negative entries, and the EEP $\mathcal{E}_1=(E_f^{**},I_f^{**},P_f^{**},Q_f^{**},C_f^{**},R_{fc}^{**},R_f^{**},E_m^{**},I_m^{**},P_m^{**},Q_m^{**},C_m^{**},R_{mc}^{**},R_m^{**})$ satisfies $\mathcal{E}_1=H\mathcal{E}_1$. Furthermore, since the coordinates of the EEP, $\mathcal{E}_1$, are all positive, it follows that if $\bar{Z}$ is a solution of (C.4), then it is possible to find a minimal positive real number, s, such that

$$|\bar{Z}|\leq s\,\mathcal{E}_1,$$

where $|\bar{Z}|=(|Z_1|,\ldots,|Z_9|)$, and $|.|$ is a norm in $\mathbb{C}$. The task ahead is to show that $\mathrm{Re}(w)<0$. It will be proved by contradiction. Assume the first case $w=0$ then, (C.3) is a homogeneous linear system in the variables Z_i $(i=1,\ldots,14)$. The determinant of this system corresponds to that of the Jacobian of the system (C.1), evaluated at $\mathcal{E}_1$, given by, $\Delta=\mu_f\mu_m(D_1D_2-D_3)$. It should be recalled that $\Delta\neq 0$ (Theorem 3.3). Hence, the linear system (C.3) can only have the trivial solution which contradicts the existence of the EEP, $\mathcal{E}_1$. Now consider the case when $w\neq 0$ for which $\mathrm{Re}\,(F_i(w))\geq 0$ $(i=1,\ldots,14)$ since, by assumption, Re $w\geq 0$. It means that $|1+F_i(w)|>1$ for all i. Now, by defining $F(w)=\min|1+F_i(w)|$, $i=1,\ldots,14$, we obtain $F(w)>1$. Hence, $\frac{s}{F(w)}<s$. The minimality of s implies that $|\bar{Z}|>\frac{s}{F(w)}\mathcal{E}_1$. On the other hand, taking norms of both sides of the forth equation of (C.4), and using the fact that all the entries of H are non-negative, gives,

$$F(w)|Z_9|\leq H(|Z|)_9\leq s(H|\mathcal{E}_1|)_9\leq sI_m^{**}.$$

Hence, $|Z_9| \leq \frac{s}{F(w)} I_m^{**}$ which is a contradiction. Thus, Re $w < 0$. Hence, the unique endemic equilibrium ($\mathcal{E}_1$) of the model (3.1) is LAS whenever $\mathcal{R}_0 > 1$, $\delta_f = 0$ and $\Delta \neq 0$. □

Appendix D. Proof of Theorem 3.4

Proof. Consider the screening-free model (3.1), with $\mathcal{R}_1 > 1$ (so that its unique EEP ($\mathcal{E}_1$) exists, by Theorem 3.2). Furthermore, let $S_f(t) \leq S_f^{**}$ and $S_m(t) \leq S_m^{**}$ for all t. It should be noted, first of all, that none of the state variables $R_{fc}(t)$, $R_f(t)$, $R_{mc}(t)$ and $R_m(t)$ feature in any of the other equations of the model (3.1). Thus, the equations for $R_{fc}(t)$, $R_f(t)$, $R_{mc}(t)$ and $R_m(t)$ can be temporarily removed from the analysis.

Consider, next, the following non-linear Lyapunov function for the sub-model (consisting of the equations for the variables S_f, E_f, I_f, P_f, Q_f, C_f, E_m, I_m, P_m, Q_m and C_m) of the screening-free model (3.1):

$$\begin{aligned}
\mathcal{F} \quad = \quad & \left(S_f - S_f^{**} - S_f^{**} \ln \frac{S_f}{S_f^{**}}\right) + \left(E_f - E_f^{**} - E_f^{**} \ln \frac{E_f}{E_f^{**}}\right) \\
& + b_1 \left(I_f - I_f^{**} - I_f^{**} \ln \frac{I_f}{I_f^{**}}\right) + b_2 \left(P_f - P_f^{**} - P_f^{**} \ln \frac{P_f}{P_f^{**}}\right) \\
& + b_3 \left(Q_f - Q_f^{**} - Q_f^{**} \ln \frac{Q_f}{Q_f^{**}}\right) + b_4 \left(C_f - C_f^{**} - C_f^{**} \ln \frac{C_f}{C_f^{**}}\right) \\
& \left(S_m - S_m^{**} - S_m^{**} \ln \frac{S_m}{S_m^{**}}\right) + \left(E_m - E_m^{**} - E_m^{**} \ln \frac{E_m}{E_m^{**}}\right) \\
& + b_5 \left(I_m - I_m^{**} - I_m^{**} \ln \frac{I_m}{I_m^{**}}\right) + b_6 \left(P_m - P_m^{**} - P_m^{**} \ln \frac{P_m}{P_m^{**}}\right) \\
& + b_7 \left(Q_m - Q_m^{**} - Q_m^{**} \ln \frac{Q_m}{Q_m^{**}}\right) + b_8 \left(C_m - C_m^{**} - C_m^{**} \ln \frac{C_m}{C_m^{**}}\right),
\end{aligned} \tag{D.1}$$

where,

$$b_1 = \frac{\beta_m c_f \mu_m S_f^{**} I_m^{**}}{\sigma_f \pi_m E_f^{**}}, \quad b_2 = \frac{\beta_m c_f \mu_m S_f^{**} I_m^{**}}{\psi_f \pi_m I_f^{**}}, \quad b_3 = \frac{\beta_m c_f \mu_m S_f^{**} I_m^{**}}{\alpha_f \pi_m P_f^{**}}, \quad b_4 = \frac{\beta_m c_f \mu_m S_f^{**} I_m^{**}}{g_f \pi_m Q_f^{**}},$$

$$b_5 = \frac{\beta_f c_f \mu_m S_m^{**} I_f^{**}}{\sigma_m \pi_m E_m^{**}}, \quad b_6 = \frac{\beta_f c_f \mu_m S_m^{**} I_f^{**}}{\psi_m \pi_m I_m^{**}}, \quad b_7 = \frac{\beta_f c_f \mu_m S_m^{**} I_f^{**}}{\alpha_m \pi_m P_m^{**}}, \quad b_8 = \frac{\beta_f c_f \mu_m S_m^{**} I_f^{**}}{g_m \pi_m Q_m^{**}}.$$

The Lyapunov derivative of (D.1) is given by

$$
\begin{aligned}
\dot{\mathcal{F}} \;=\; & \left(1-\frac{S_f^{**}}{S_f}\right)\left[\pi_f-\left(\frac{\beta_m c_f \mu_m I_m}{\pi_m}+\mu_f\right)S_f\right] \\
& +\left(1-\frac{E_f^{**}}{E_f}\right)\left[\frac{\beta_m c_f \mu_m I_m}{\pi_m}S_f-(\sigma_f+\mu_f)E_f\right] \\
& +b_1\left(1-\frac{I_f^{**}}{I_f}\right)\left[\sigma_f E_f-(r_{f1}+\psi_f+\mu_f)I_f\right] \\
& +b_2\left(1-\frac{P_f^{**}}{P_f}\right)\left[\psi_f I_f-(r_{f2}+\alpha_f+\mu_f)P_f\right] \\
& +b_3\left(1-\frac{Q_f^{**}}{Q_f}\right)\left[\alpha_f P_f-(r_{f3}+g_f+\mu_f)Q_f\right] \\
& +b_4\left(1-\frac{C_f^{**}}{C_f}\right)\left[g_f Q_f-(r_{f4}+\mu_f+\delta_f)C_f\right] \\
& +\left(1-\frac{S_m^{**}}{S_m}\right)\left[\pi_m-\left(\frac{\beta_f c_f \mu_m I_f}{\pi_m}+\mu_m\right)S_m\right] \\
& +\left(1-\frac{E_m^{**}}{E_m}\right)\left[\frac{\beta_f c_f \mu_m I_f}{\pi_m}S_m-(\sigma_m+\mu_m)E_m\right] \\
& +b_5\left(1-\frac{I_m^{**}}{I_m}\right)\left[\sigma_m E_m-(r_{m1}+\psi_m+\mu_m)I_m\right] \\
& +b_6\left(1-\frac{P_m^{**}}{P_m}\right)\left[\psi_m I_m-(r_{m2}+\alpha_m+\mu_m)P_m\right] \\
& +b_7\left(1-\frac{Q_m^{**}}{Q_m}\right)\left[\alpha_m P_m-(r_{m3}+g_m+\mu_m)Q_m\right] \\
& +b_8\left(1-\frac{C_m^{**}}{C_m}\right)\left[g_m Q_m-(r_{m4}+\mu_m)C_m\right].
\end{aligned}
\tag{D.2}
$$

The following relations, at the endemic steady-state (obtained from the associated sub-model of the model (3.1)), will be used to simplify (D.2):

$$
\begin{aligned}
&\pi_f=\frac{\beta_m c_f \mu_m}{\pi_m}I_m^{**}S_f^{**}+\mu_f S_f^{**},\quad \sigma_f+\mu_f=\frac{\beta_m c_f \mu_m}{\pi_m}\frac{I_m^{**}S_f^{**}}{E_f^{**}},\quad r_{f1}+\psi_f+\mu_f=\sigma_f\frac{E_f^{**}}{I_f^{**}},\\
&r_{f2}+\alpha_f+\mu_f=\psi_f\frac{I_f^{**}}{P_f^{**}},\quad r_{f3}+g_f+\mu_f=\alpha_f\frac{P_f^{**}}{Q_f^{**}},\quad r_{f4}+\mu_f+\delta_f=g_f\frac{Q_f^{**}}{C_f^{**}},\\
&\pi_m=\frac{\beta_f c_f \mu_m}{\pi_m}I_f^{**}S_m^{**}+\mu_m S_m^{**},\quad \sigma_m+\mu_m=\frac{\beta_f c_f \mu_m}{\pi_m}\frac{I_f^{**}S_m^{**}}{E_m^{**}},\quad r_{m1}+\psi_m+\mu_m=\sigma_m\frac{E_m^{**}}{I_m^{**}},\\
&r_{m2}+\alpha_m+\mu_m=\psi_m\frac{I_m^{**}}{P_m^{**}},\quad r_{m3}+g_m+\mu_m=\alpha_m\frac{P_m^{**}}{Q_m^{**}},\quad r_{m4}+\mu_m=g_m\frac{Q_m^{**}}{C_m^{**}}.
\end{aligned}
\tag{D.3}
$$

Substituting (D.3) into (D.2), and simplifying, gives

$$
\begin{aligned}
\dot{\mathcal{F}} \;\leq\; & \mu_f S_f^{**}\left(2-\frac{S_f^{**}}{S_f}-\frac{S_f}{S_f^{**}}\right)+\mu_m S_m^{**}\left(2-\frac{S_m^{**}}{S_m}-\frac{S_m}{S_m^{**}}\right) \\
+\;& M_1\left(7-\frac{S_f^{**}}{S_f}-\frac{I_m S_f E_f^{**}}{I_m^{**}S_f^{**}E_f}-\frac{E_f I_f^{**}}{E_f^{**}I_f}-\frac{I_f P_f^{**}}{I_f^{**}P_f}-\frac{P_f Q_f^{**}}{P_f^{**}Q_f}-\frac{C_f}{C_f^{**}}-\frac{Q_f C_f^{**}}{Q_f^{**}C_f}\right) \\
+\;& M_2\left(7-\frac{S_m^{**}}{S_m}-\frac{I_f S_m E_m^{**}}{I_f^{**}S_m^{**}E_m}-\frac{E_m I_m^{**}}{E_m^{**}I_m}-\frac{I_m P_m^{**}}{I_m^{**}P_m}-\frac{P_m Q_m^{**}}{P_m^{**}Q_m}-\frac{C_m}{C_m^{**}}-\frac{Q_m C_m^{**}}{Q_m^{**}C_m}\right),
\end{aligned}
\tag{D.4}
$$

where,

$$M_1 = \frac{\beta_m c_f \mu_m}{\pi_m} S_f^{**} I_m^{**} > 0 \quad \text{and} \quad M_2 = \frac{\beta_f c_f \mu_m}{\pi_m} S_m^{**} I_f^{**} > 0.$$

Since the arithmetic mean exceeds the geometric mean, it follows that the parentheses of (D.4) are negative. Hence, $\dot{\mathcal{F}} \leq 0$. Furthermore,

$$\begin{aligned} \lim_{t\to\infty} \quad & (S_f(t), E_f(t), I_f(t), P_f(t), Q_f(t), C_f(t), S_m(t), E_m(t), I_m(t), P_m(t), Q_m(t), C_m(t)) \\ \to \quad & (S_f^{**}, E_f^{**}, I_f^{**}, P_f^{**}, Q_f^{**}, C_f^{**}, S_m^{**}, E_m^{**}, I_m^{**}, P_m^{**}, Q_m^{**}, C_m^{**}). \end{aligned}$$

Substituting $\big(I_f(t), P_f(t), Q_f(t), I_m(t), P_m(t), Q_m(t)\big) = \Big(I_f^{**}, P_f^{**}, Q_f^{**}, I_m^{**}, P_m^{**}, Q_m^{**}\Big)$ into the model (3.1) shows that $\big(R_{fc}(t), R_f(t), R_{mc}(t), R_m(t)\big) \to \Big(R_{fc}^{**}, R_f^{**}, R_{mc}^{**}, R_m^{**}\Big)$ as $t \to \infty$. Hence, the unique endemic equilibrium of the screening-free model (3.1), with $\theta_m = \theta_f = 0$, is GAS in $\mathcal{D}\backslash\mathcal{D}_0$ whenever $\mathcal{R}_1 > 1$, $S_f(t) \leq S_f^{**}$ and $S_m(t) \leq S_m^{**}$ for all t. □

Appendix E. Proof of Theorem 4.1

Proof. Consider the Pap screening model (2.3). The proof is based on using a Comparison Theorem [41]. As in Appendix B, it can be shown that the system (2.3) satisfies Type K condition (hence, Comparison theorem can be used).

Let $\mathcal{R}_{0s} < 1$ (so that the DFE, $\mathcal{E}_{0s}$, is LAS, in line with Lemma 4.1). The infected components of the model (2.3) can be re-written as:

$$\frac{d\boldsymbol{x}_s}{dt} = (\mathcal{F}_s - \mathcal{V}_s)\boldsymbol{x}_s - J_s \boldsymbol{x}_s, \tag{E.1}$$

where,

$$\begin{aligned} \boldsymbol{x}_s \quad = \quad & [E_f(t), I_f(t), P_f(t), L_{fu}(t), L_{fd}(t), H_{fu}(t), H_{ft}(t), C_{fu}(t), C_{fd}(t), R_{fc}(t), R_f(t), \\ & E_m(t), I_m(t), P_m(t), L_m(t), H_m(t), C_m(t), R_{mc}(t), R_m(t)]^T, \end{aligned}$$

with the matrices $\mathcal{F}_s$ and $\mathcal{V}_s$ are as defined in Section 4, and

$$J_s = \left[1 - \frac{\mu_f S_f(t)}{\pi_f}\right] J_1 + \left[1 - \frac{\mu_m S_m(t)}{\pi_m}\right] J_2,$$

where,

$$J_1 = \begin{bmatrix} \mathbf{0}_{11\times 11} & \mathcal{J}_1 \\ \mathbf{0}_{11\times 8} & \mathbf{0}_{8\times 8} \end{bmatrix} \quad \text{and} \quad J_2 = \begin{bmatrix} \mathbf{0}_{11\times 11} & \mathbf{0}_{8\times 11} \\ \mathcal{J}_2 & \mathbf{0}_{8\times 8} \end{bmatrix},$$

with,

$$\mathcal{J}_1 = \begin{bmatrix} u_1 & u_2 & u_3 & u_4 & u_5 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

where $u_1 = \frac{\beta_m c_f \eta_m \pi_f \mu_m}{\mu_f \pi_m}$, $u_2 = \frac{\beta_m c_f \pi_f \mu_m}{\mu_f \pi_m}$, $u_3 = \frac{\beta_m c_f \theta_m \pi_f \mu_m}{\mu_f \pi_m}$, $u_4 = \frac{\beta_m c_f \theta_m \pi_f \mu_m}{\mu_f \pi_m}$ and $u_5 = \frac{\beta_m c_f \theta_m \theta_{mh} \pi_f \mu_m}{\mu_f \pi_m}$,

$$\mathcal{J}_2 = \begin{bmatrix} \beta_f c_f \eta_f & \beta_f c_f & \beta_f c_f \theta_f & \beta_f c_f \theta_f & 0 & \beta_f c_f \theta_f \theta_{fh} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

It is worth noting that J_1 and J_2 are non-negative matrices. Furthermore, since, for all $t \geq 0$ in $\mathcal{D}$,

$$S_f(t) \leq N_f(t) \leq \frac{\pi_f}{\mu_f} \quad \text{and} \quad S_m(t) \leq N_m(t) \leq \frac{\pi_m}{\mu_m},$$

it follows that,

$$\frac{\mu_f S_f(t)}{\pi_f} \leq 1 \quad \text{and} \quad \frac{\mu_m S_m(t)}{\pi_m} \leq 1.$$

Hence, J is a non-negative matrix. Thus, it follows, from (E.1), that

$$\frac{d\boldsymbol{x}_s}{dt} \leq (\mathcal{F}_s - \mathcal{V}_s)\boldsymbol{x}_s. \tag{E.2}$$

Using the fact that the eigenvalues of the matrix $\mathcal{F}_s - \mathcal{V}_s$ all have negative real parts when $\mathcal{R}_{0s} < 1$ (based on the local asymptotic stability result given in Lemma 4.1), it follows that the linear differential inequality system (E.2) is stable whenever $\mathcal{R}_{0s} < 1$. Hence, by Comparison Theorem [41],

$$\begin{aligned} \lim_{t\to\infty} \quad & (E_f(t), I_f(t), P_f(t), L_{fu}(t), L_{fd}(t), H_{fu}(t), H_{fd}(t), C_{fu}(t), C_{fd}(t), R_{fc}(t), \\ & R_f(t), E_m(t), I_m(t), P_m(t), L_m(t), H_m(t), C_m(t), R_{mc}(t), R_m(t)) \\ = \quad & (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0). \end{aligned}$$

Substituting $E_f(t) = I_f(t) = P_f(t) = L_{fu}(t) = L_{fd}(t) = H_{fu}(t) = H_{fd}(t) = C_{fu}(t) = C_{fd}(t) = R_{fc}(t) = R_f(t) = E_m(t) = I_m(t) = P_m(t) = L_m(t) = H_m(t) = C_m(t) = R_{mc}(t) = R_m(t) = 0$ into the first and thirteenth equations of the model (2.3) shows that $S_f(t) \to S_f^*$ and $S_m(t) \to S_m^*$ as $t \to \infty$ (for $\mathcal{R}_{0s} < 1$). Thus,

$$\begin{aligned} \lim_{t\to\infty} \quad & (S_f(t), E_f(t), I_f(t), P_f(t), L_{fu}(t), L_{fd}(t), H_{fu}(t), H_{fd}(t), C_{fu}(t), C_{fd}(t), R_{fc}(t), \\ & R_f(t), S_m(t)E_m(t), I_m(t), P_m(t), L_m(t), H_m(t), C_m(t), R_{mc}(t), R_m(t)) = \mathcal{E}_{0s}. \end{aligned}$$

□

Variable	Description
$S_f(t)$	Population of susceptible females
$E_f(t)$	Population of exposed (asymptomatic) females
$I_f(t)$	Population of symptomatic (infected with clinical symptoms of HPV) females
$P_f(t)$	Population of females with persistent HPV infection
$L_{fu}(t)$	Population of females with undetected low-grade CIN
$L_{fd}(t)$	Population of females with detected low-grade CIN
$H_{fu}(t)$	Population of females with undetected high-grade CIN
$H_{fd}(t)$	Population of females with detected high-grade CIN
$C_{fu}(t)$	Population of females with undetected cervical cancer
$C_{fd}(t)$	Population of females with detected cervical cancer
$R_{fc}(t)$	Population of females who recovered from cervical cancer
$R_f(t)$	Population of females who recovered from HPV infection without developing cervical cancer
$S_m(t)$	Population of susceptible males
$E_m(t)$	Population of exposed (asymptomatic) males
$I_m(t)$	Population of symptomatic males
$P_m(t)$	Population of males with persistent HPV infection
$L_m(t)$	Population of males with low-grade INM
$H_m(t)$	Population of males with high-grade INM
$C_m(t)$	Population of males with HPV-related cancer
$R_{mc}(t)$	Population of males who recovered from HPV-related cancer
$R_m(t)$	Population of males who recovered from HPV infection without developing HPV-related cancer

TABLE 1. Description of the state variables of the Pap screening model (2.3).

Parameter	Description	Baseline Value *per* year	Ranges	Ref.
$\pi_f(\pi_m)$	Recruitment rate of new sexually-active females (males)	10000	[9000,11000]	[52]
$\frac{1}{\mu_f}(\frac{1}{\mu_m})$	Average duration of sexual activity for females (males)	65	[59.5,71.5]	[10]
$\beta_m(\beta_f)$	Infection probability for females (males)	0.4/contact	[0.34,0.44]	[12]
$c_m(c_f)$	Average number of male (female) sexual partners for females (males) per unit time	2 ($2\ \frac{N_f}{N_m}$)	[1.8,2.2]	[52]
$\xi_f(\xi_m)$	Rate of loss of infection-acquired immunity for females (males)	0.5	[0.45,0.55]	[39]
$\sigma_f(\sigma_m)$	Rate of symptoms development for exposed females (males)	5	[4.5,5.5]	A
$b_f(b_m)$	Fraction of symptomatic females (males) who recover naturally from HPV (but do not develop persistent infection)	0.95	[0.75,0.95]	[54]
$\psi_f(\psi_m)$	Transition rate out of the I_f (I_m) class for females (males)	0.5	[0.45,0.55]	[22]
$k_f(k_m)$	Fraction of symptomatic females (males) who recover naturally from persistent infection with HPV	0.5	[0.45,0.55]	[45]
$\alpha_f(\alpha_m)$	Transition rate out of the P_f (P_m) class for females (males)	0.25	[0.2,0.3]	[21]
$d_{f1}(d_{m1})$	Fraction of infected females (males) with low-grade low-grade CIN (INM) who recover naturally from HPV infection	0.04	[0.01,0.1]	[45]
$d_{f2}(d_{m2})$	Fraction of females (males) with undetected low-grade CIN (INM) who revert to the P_f] (P_m) class	0.28	[0.2,0.35]	[21]
d_{f3}	Fraction of females with low-grade CIN who is detected	0.64	[0.6,0.7]	[45]
$g_f(g_m)$	Transition rate out of L_{fu} (L_m) class for females (males)	1.18	[1,1.5]	[45]
r_1	Recovery rate of detected females with low-grade CIN	0.13	[0.1,0.2]	[48]
$q_{f1}(q_{m1})$	Fraction of infected females (males) with high-grade CIN 2/3 (INM 2/3) who recover naturally from HPV infection	0.24	[0.2,0.3]	[45]
$q_{f2}(q_{m2})$	Fraction of females (males) with undetected high-grade CIN 2/3 (INM 2/3) who revert to the L_{fu} (L_m) class	0.04	[0.03,0.05]	[48]

TABLE 2. Description of parameters of the Pap screening model (2.3). "A" denotes "assumed".

Parameter	Description	Baseline Value *per* year	Ranges	Ref.
q_{f3}	Fraction of females with high-grade CIN 2/3 who is detected	0.47	[0.4,0.55]	[45]
$q_{f4}(q_{m3})$	Regression rate from the H_{fu} (H_m) class to P_f (P_m) class	0.17	[0.1,0.25]	[35]
$z_f(z_m)$	Transition rate out of the $H_{fu}(H_m)$ class for females (males)	2.08	[2,2.2]	[45]
r_2	Recovery rate of detected females with high-grade CIN 2/3	0.13	[0.1,0.2]	[48]
j_{f1}	Fraction of females with cervical cancer who is detected	0.62	[0.5,0.7]	[42]
$j_{f2}(j_m)$	Fraction of females (males) with cervical (HPV-related) cancer who revert to the H_{fu} (H_m) class	0.23	[0.15,0.3]	[21]
$\gamma_f(\gamma_m)$	Transition rate out of the $C_{fu}(C_m)$ class for females (males)	1.31	[1.2,1.4]	[42]
r_3	Recovery rate of females with detected cancer	0.75	[0.65,0.85]	[21]
$\eta_f(\eta_m)$	Modification parameter for infectiousness of exposed females (males) in the E_f (E_m) class, relative to those in the I_f (I_m) class	0.5	[0.45,0.55]	A
$\theta_f(\theta_m)$	Modification parameter for infectiousness of females (males) in the P_f, L_{fu}, L_{fd}, H_{fu}, H_{fd} (P_m, L_m, H_m) classes, relative to those in the E_f, I_f (E_m, I_m) classes	0.9	[0.8,1]	[45]
$\theta_{fh}(\theta_{mh})$	Modification parameter for infectiousness of females (males) in the H_{fu} (H_m) class, relative to those in the P_f, L_{fu} (P_m, L_m) classes	1.5	[1.35,1.65]	A
$\delta_{fu}(\delta_{fd})$	Cancer-induced mortality rate for undetected (detected) females	0.01 (0.001)	[0.009,0.02] ([0.0009,0.002])	[45]

TABLE 3. Description of parameters of the Pap screening model (2.3) continued. "A" denotes "assumed".

Variable	Description
$S_f(t)$	Population of susceptible females
$E_f(t)$	Population of exposed (asymptomatic) females
$I_f(t)$	Population of symptomatic (infected with clinical symptoms of HPV) females
$P_f(t)$	Population of females with persistent HPV infection
$Q_f(t)$	Population of females with CIN
$C_f(t)$	Population of females with cervical cancer
$R_{fc}(t)$	Population of females who recovered from cervical cancer
$R_f(t)$	Population of females who recovered from HPV infection without developing cervical cancer
$S_m(t)$	Population of susceptible males
$E_m(t)$	Population of exposed (asymptomatic) males
$I_m(t)$	Population of symptomatic males
$P_m(t)$	Population of males with persistent HPV infection
$Q_m(t)$	Population of males with INM
$C_m(t)$	Population of males with HPV-related cancer
$R_{mc}(t)$	Population of males who recovered from HPV-related cancer
$R_m(t)$	Population of males who recovered from HPV infection without developing HPV-related cancer

TABLE 4. Description of the state variables of the screening-free model (3.1).

Parameter	Description	Baseline Value *per* year	Ranges	Ref.
$\pi_f(\pi_m)$	Recruitment rate of new sexually-active females (males)	10000	[9000,11000]	[52]
$\frac{1}{\mu_f}(\frac{1}{\mu_m})$	Average duration of sexual activity for females (males)	65	[59.5,71.5]	[10]
$\beta_m(\beta_f)$	HPV infection probability from males to females (females to males)	0.8/contact (0.7/contact)	[0.72,0.88] [0.63,0.77]	[22]
$c_m(c_f)$	Average number of male (female) sexual partners for females (males) per unit time	2 (2 $\frac{N_f}{N_m}$)	[1.8,2.2]	[52]
$\sigma_f(\sigma_m)$	Rate of symptoms development for exposed females (males)	5	[4.5,5.5]	A
$\psi_f(\psi_m)$	Rate of development of persistent infection for females (males)	0.5	[0.45,0.55]	[22]
$\alpha_f(\alpha_m)$	Progression rate from HPV to CIN (INM) for females (males)	0.1	[0.09,0.11]	[21]
$g_f(g_m)$	Progression rate from CIN (INM) to cancer for females (males)	0.08	[0.079, 0.081]	[21]
$r_{f1}(r_{m1})$	Natural recovery rate of infected females (males)	0.495 (0.9)	[0.446,0.545] [0.89, 0.91]	[22]
$r_{f2}(r_{m2})$	Natural recovery rate of females (males) with persistent HPV infection	0.1	[0.09,0.11]	[45]
$r_{f3}(r_{m3})$	Natural recovery rate of females with CIN (males with INM)	0.05	[0.045,0.055]	[48]
$r_{f4}(r_{m4})$	Natural recovery rate of females with cervical cancer (males with HPV-related cancer)	0.76	[0.68,0.84]	[21]
$\theta_f(\theta_m)$	Modification parameter for the infectiousness of females (males) with persistent infection, relative to those in the I_f (I_m) class	0.9	[0.8,1]	[45]
δ_f	Cancer-induced mortality rate for females	0.01	[0.009,0.011]	[45]

TABLE 5. Description of parameters of the screening-free model (3.1). "A" denotes "assumed".

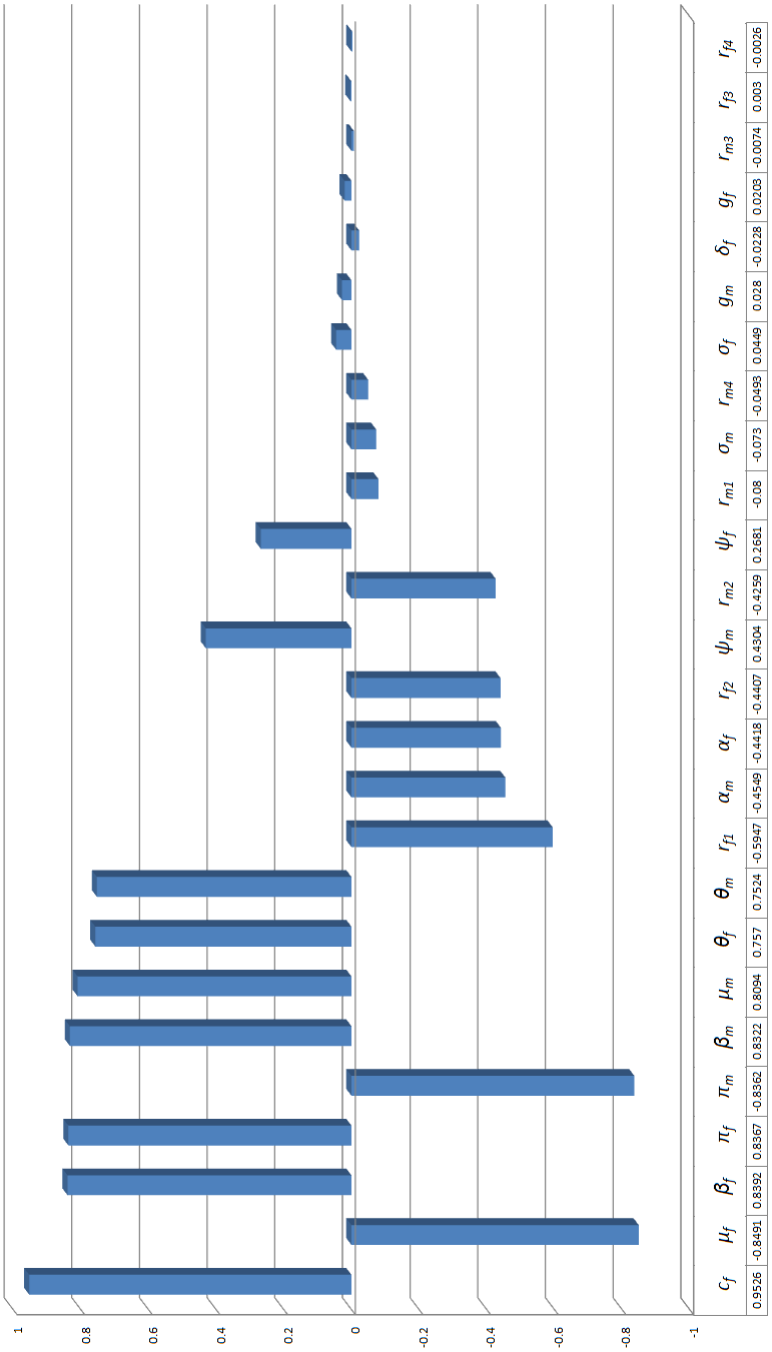

TABLE 6. PRCC values of the parameters of the screening-free model (3.1) using $\mathcal{R}_0$ as output. Baseline parameter values and ranges used are as given in Table 5.

Parameter	PRCC value	Parameter	PRCC value
c_f	0.9123	r_2	0.0348
b_m	−0.8571	σ_m	−0.0340
b_f	−0.8494	g_f	−0.0300
β_f	0.8133	k_f	−0.0274
β_m	0.8128	j_{f1}	−0.0269
π_m	−0.7373	ξ_f	0.0262
π_f	0.7281	d_{f3}	0.0223
μ_f	−0.7258	ξ_m	−0.0200
μ_m	0.7098	r_1	0.0192
ψ_m	−0.6151	δ_{fd}	0.0182
ψ_f	−0.5868	θ_{fh}	0.0178
α_m	−0.4380	j_{f2}	0.0173
α_f	−0.4110	η_m	0.0166
θ_m	0.2732	d_{f1}	−0.0152
θ_f	0.2257	d_{m1}	−0.0141
d_{m2}	0.1199	δ_{fu}	0.0123
q_{m3}	0.0986	z_m	−0.0101
η_f	0.0984	γ_m	−0.0090
d_{f2}	0.0773	z_f	−0.0068
g_m	0.0690	q_{f3}	−0.0066
j_m	0.0668	γ_f	0.0059
q_{f4}	−0.0563	σ_f	0.0051
k_m	−0.0473	θ_{mh}	−0.0028
r_3	0.0472	q_{f1}	0.0010
q_{m1}	0.0376	q_{f2}	0.0007
q_{m2}	−0.0355		

TABLE 7. PRCC values of the parameters of the Pap screening model (2.3), using $\mathcal{R}_{0s}$ as output. Baseline parameter values and ranges used are as given in Tables 2 and 3.

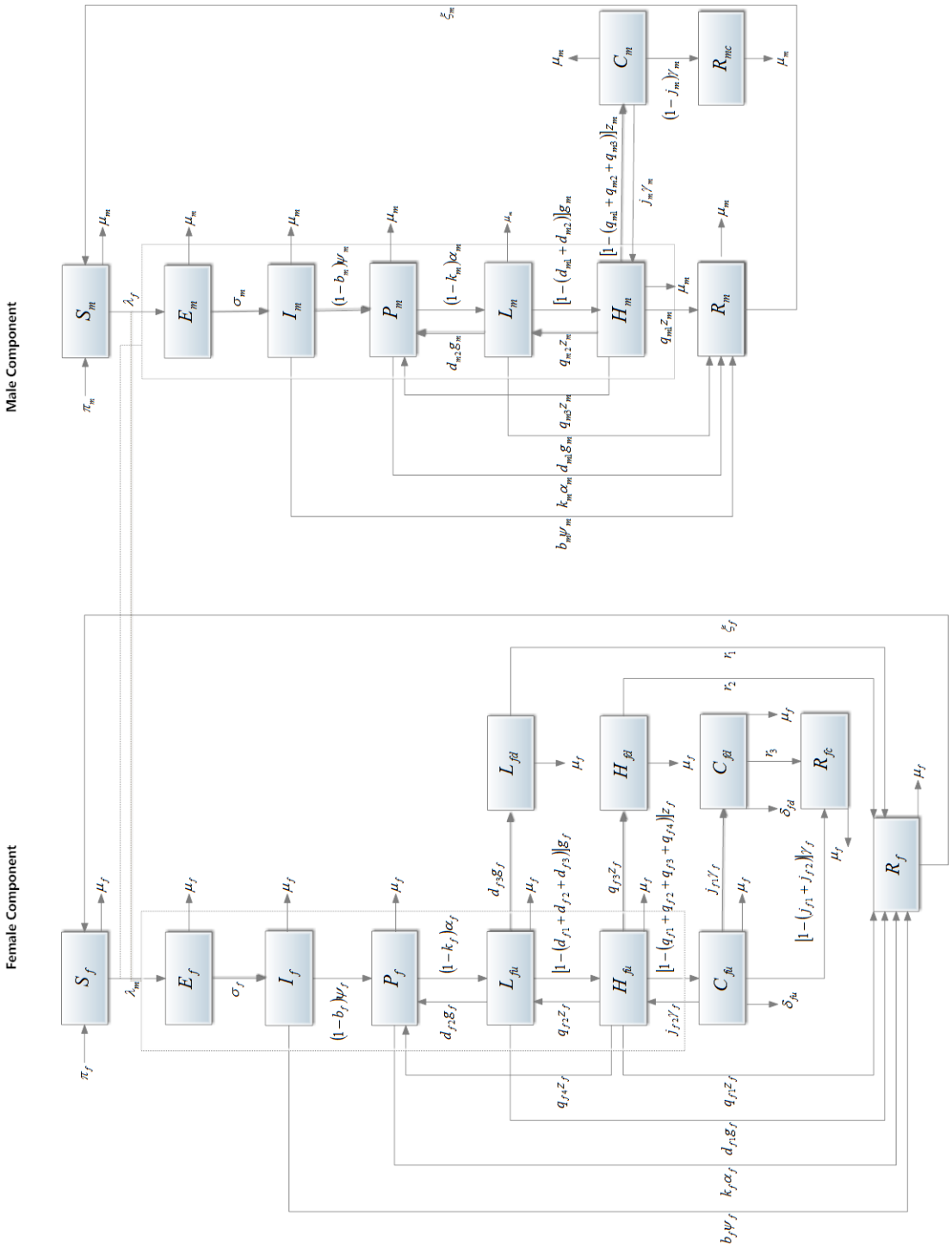

FIGURE 1. Schematic diagram of the Pap screening model (2.3).

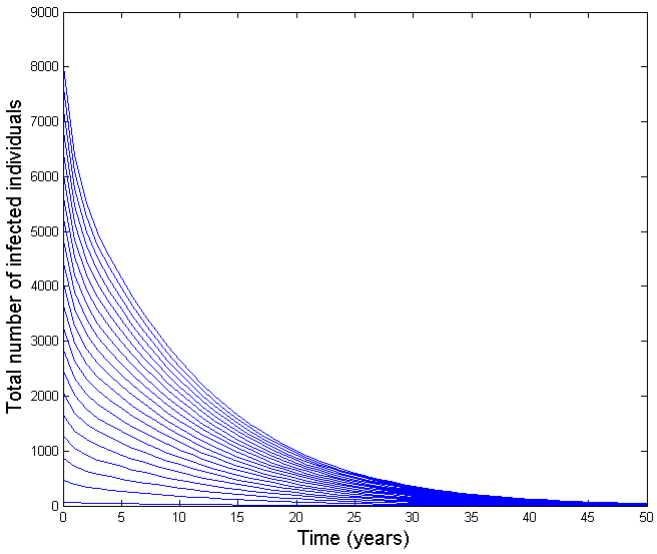

FIGURE 2. Solution profiles of the screening-free model (3.1), showing the total number of HPV-infected individuals (females and males) as a function of time using various initial conditions. Parameter values used are as given in Table 5, with $c_f = 1$, $\beta_f = 0.2$ and $\beta_m = 0.2$ (so that, $\mathcal{R}_0 = 0.5159 < 1$).

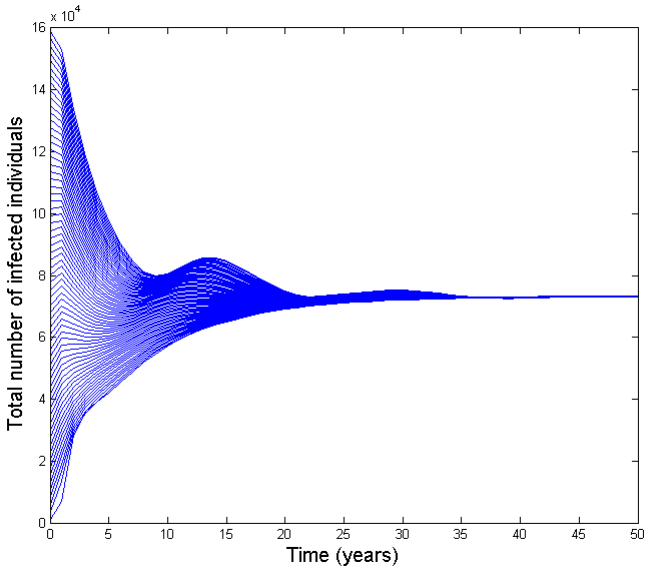

FIGURE 3. Solution profiles of the screening-free model (3.1), showing the total number of HPV-infected individuals (females and males) with $\theta_m = \theta_f = 0$ as a function of time using various initial conditions. Parameter values used are as given in Table 5, with $c_f = 3$, $\beta_f = 2.5$ and $\beta_m = 2.5$ (so that, $\mathcal{R}_1 = 6.2549 > 1$).

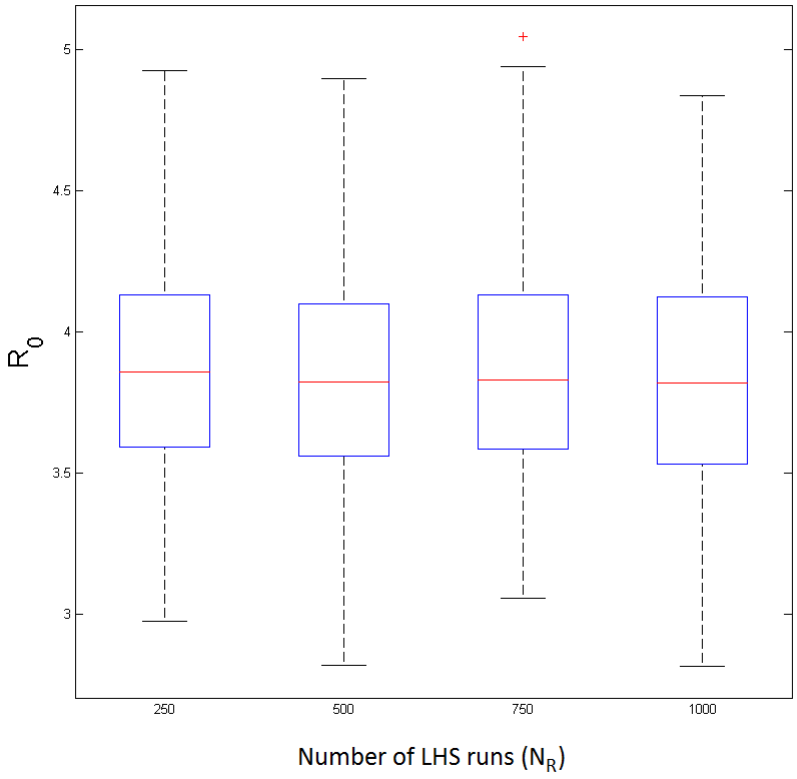

FIGURE 4. Box plot of the basic reproduction number ($\mathcal{R}_0$) as a function of the number of runs (N_R) for the screening-free model (3.1), using the baseline parameter values and ranges given in Table 5.

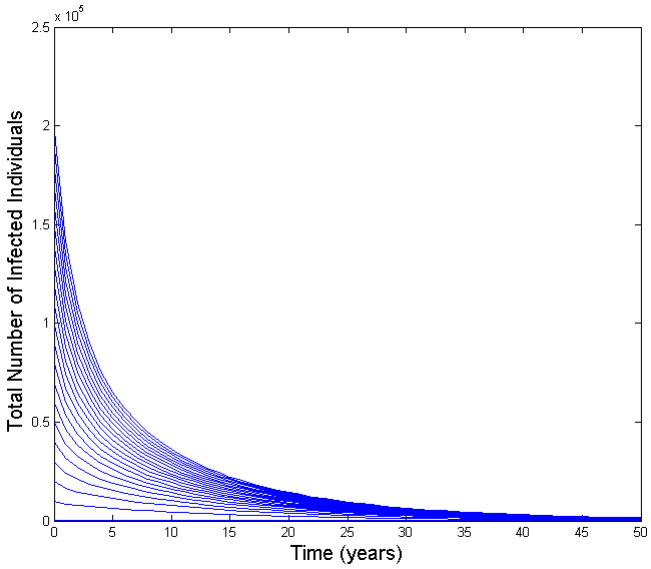

FIGURE 5. Solution profiles of the Pap screening model (2.3), showing the total number of HPV-infected individuals (females and males) as a function of time, using various initial conditions. Parameter values used are as given in Tables 2 and 3, with $c_f = 1.3$, $\beta_m = 0.25$ and $\beta_f = 0.25$ (so that, $\mathcal{R}_{0s} = 0.8111 < 1$).

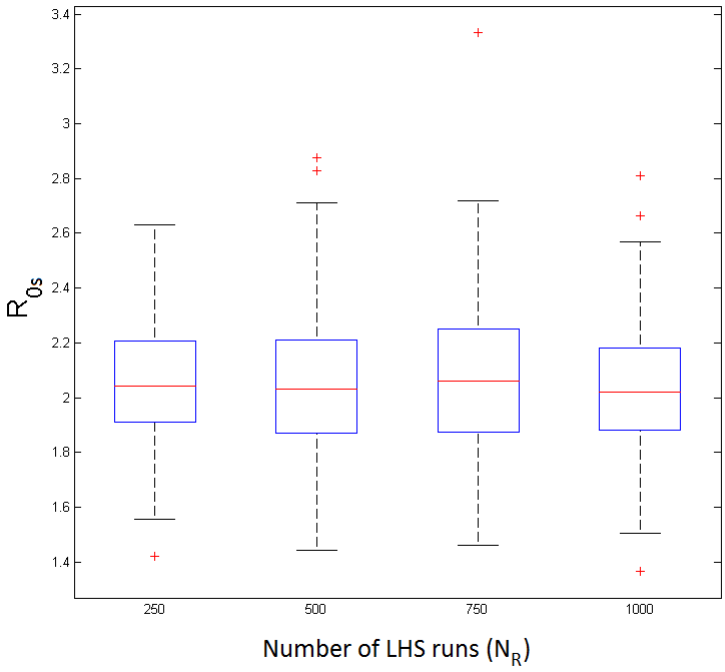

FIGURE 6. Box plot of the effective reproduction number ($\mathcal{R}_{0s}$) of the Pap screening model (2.3) as a function of the number of runs (N_R), using the parameter values and ranges given in Tables 2 and 3.

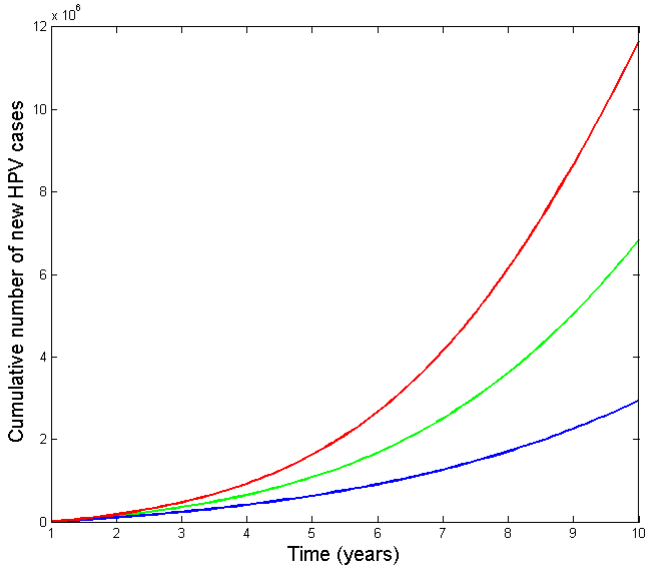

FIGURE 7. Simulations of the Pap screening model (2.3), showing the cumulative number of new HPV cases (for females and males) as a function of time. Parameter values used are as given in Tables 2 and 3 (with the top-eleven PRCC-ranked parameters modified accordingly). Green color: baseline parameters as in Tables 2 and 3 ($\mathcal{R}_{0s}$=2.1019). Blue color: top-eleven PRCC-ranked parameters in Table 7 decreased by 10% ($\mathcal{R}_{0s}$=1.8537). Red color: top-eleven PRCC-ranked parameters in Table 7 increased by 10% ($\mathcal{R}_{0s}$=2.1734).

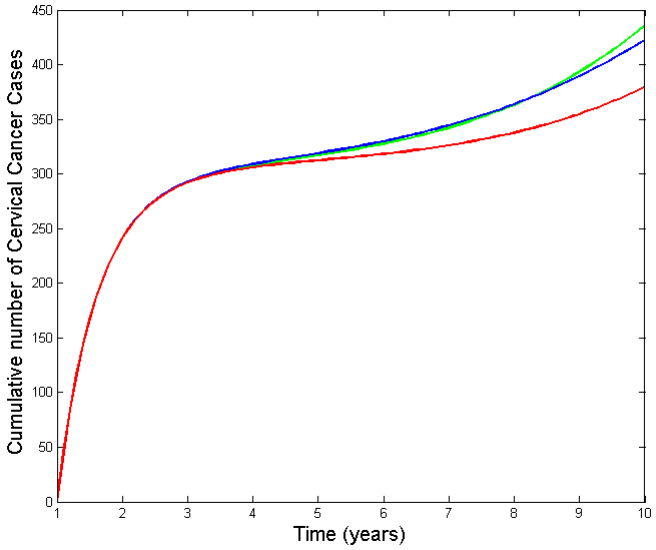

FIGURE 8. Simulations of the Pap screening model (2.3), showing the cumulative number of cervical cancer cases as a function of time. Parameter values used are as given in Tables 2 and 3 (with the top-eleven PRCC-ranked parameters modified accordingly). Green color: baseline parameters as in Tables 2 and 3 ($\mathcal{R}_{0s}$=2.1019). Blue color: top-eleven PRCC-ranked parameters in Table 7 decreased by 10% ($\mathcal{R}_{0s}$=1.8537). Red color: top-eleven PRCC-ranked parameters in Table 7 increased by 10% ($\mathcal{R}_{0s}$=2.1734).

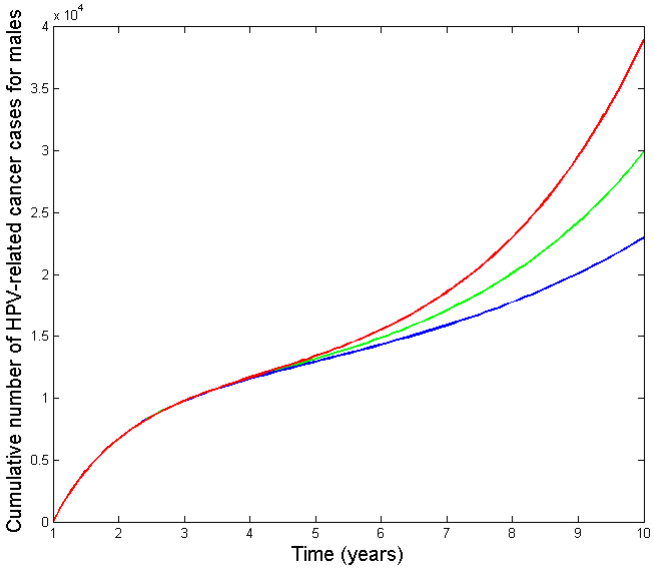

FIGURE 9. Simulations of the Pap screening model (2.3), showing the cumulative number of HPV-related cancer cases for males as a function of time. Parameter values used are as given in Tables 2 and 3 (with the top-eleven PRCC-ranked parameters modified accordingly). Green color: baseline parameters as in Tables 2 and 3 ($\mathcal{R}_{0s}$=2.1019). Blue color: top-eleven PRCC-ranked parameters in Table 7 decreased by 10% ($\mathcal{R}_{0s}$=1.8537). Red color: top-eleven PRCC-ranked parameters in Table 7 increased by 10% ($\mathcal{R}_{0s}$=2.1734).

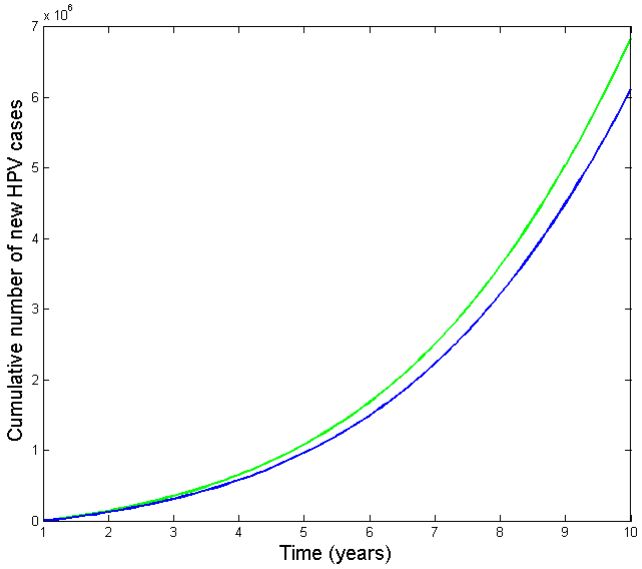

FIGURE 10. Simulations of the Pap screening model (2.3), showing the cumulative number of new HPV cases (for females and males) as a function of time in the presence (green color) and absence (blue color) of the HPV transmission by individuals in the pre-cancerous stages (both CIN and INM). Parameter values used are as given in Tables 2 and 3 ($\mathcal{R}_{0s} = 2.1019 > 1$).

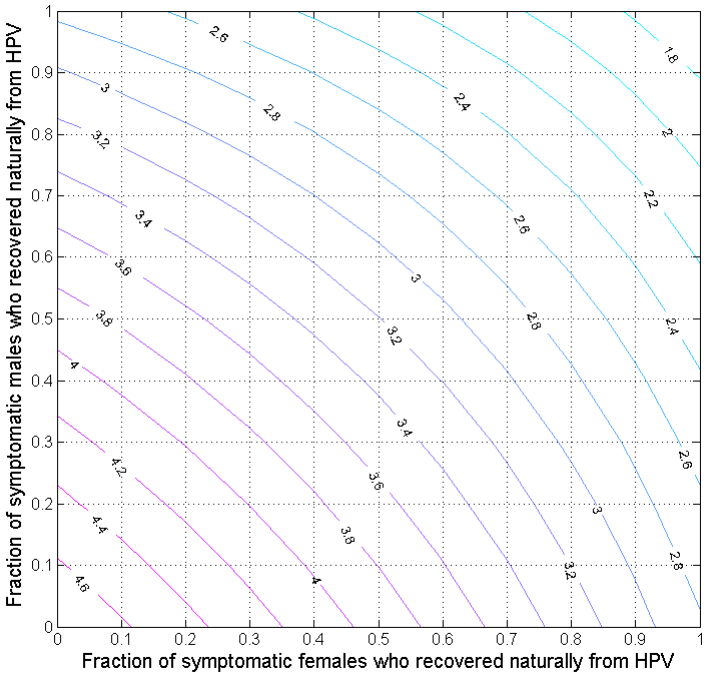

FIGURE 11. Simulations of the Pap screening model (2.3), showing a counter plot of $\mathcal{R}_{0s}$, as a function of the fraction of symptomatic females who recovered naturally from HPV (b_f) and the fraction of symptomatic males who recovered naturally from HPV (b_m). Parameter values used are as given in Tables 2 and 3.

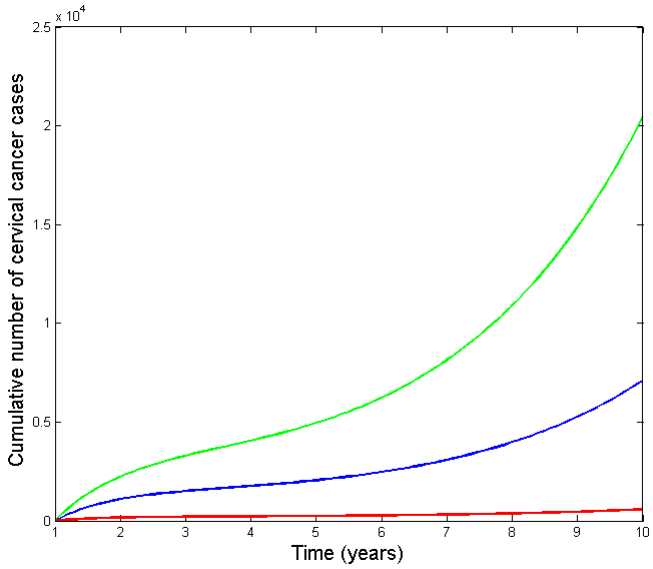

FIGURE 12. Simulations of the Pap screening model (2.3), showing the cumulative number of cervical cancer cases for females as a function of time. Green color: 0% of females with CIN detected ($\mathcal{R}_{0s}$=2.1201). Blue color: 25% of females with CIN detected ($\mathcal{R}_{0s}$=2.1118). Red color: 50% of females with CIN detected ($\mathcal{R}_{0s}$=2.1051).