

Mathematical Assessment of the Role of Pap Screening on  
HPV Transmission Dynamics

by

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# Abstract

Human papillomavirus (HPV), a major sexually-transmitted disease, causes cervical cancer, in addition to numerous other cancers in females and males. This thesis uses mathematical modeling, theory and simulations to study the transmission dynamics of HPV, and associated dysplasia, in a community. A new deterministic model is designed and used to assess the population-level impact of Pap cytology screening on the transmission dynamics of the disease in a community. The model is rigorously analyzed for its dynamical features, *vis-a-vis* determining the conditions for the effective control (or elimination) and persistence of the disease. Furthermore, the effect of uncertainties in the estimates of the parameter values used in the numerical simulations of the model is accounted for *via* uncertainty and sensitivity analysis. Simulations of the model show that Pap screening dramatically reduces the incidence of cervical cancer in the community.

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# Dedication

To my father, Mohammad Javad Javame, who has been a source of encouragement and inspiration to me throughout my life.

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# Glossary

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Abbreviation	Meaning
<i>CIN</i>	<i>Cervical Intraepithelial Neoplasia</i>
<i>DFE</i>	Disease-free Equilibrium
<i>EEP</i>	Endemic Equilibrium Point
<i>GAS</i>	Globally-asymptotically Stable
<i>HPV</i>	Human <i>Papillomavirus</i>
<i>INM</i>	<i>Intraepithelial Neoplasia</i> in Males
<i>LAS</i>	Locally-asymptotically Stable
<i>LHS</i>	Latin Hypercube Sampling
<i>ODE</i>	Ordinary Differential Equation
<i>PRCC</i>	Partial Rank Correlation Coefficients

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# Chapter 1

## Introduction

This chapter provides a brief review of some of the main biological and epidemiological features of HPV disease, and the associated cancers it causes.

### 1.1 *Human Papillomavirus (HPV)*

Human papillomavirus (HPV), a major sexually-transmitted disease, is known to be the causative agent of cervical cancer [1, 14] (in addition to causing many other cancers in both females and males [6, 14, 62, 63]). Each year, about 500,000 women develop cervical cancer (with more than half of those women dying of the disease) globally [4, 62]. In the year 2011, for instance, about 12,000 cervical cancer cases were recorded in the USA (with about 4,000 fatalities) [4]. It is estimated that the annual direct medical costs associated with the prevention and treatment of anogenital warts and cervical HPV-related disease in the US was at least US\$4 billion in 2005 [42]. Figure 1.1 depicts the global cervical cancer incidence.

HPV affects people of all ages, starting in early childhood for some (Figure 1.2) [36, 70]. About 75% of sexually-active males and females will have an HPV infection at some point in their lifetime [14, 19, 61]. There are over 150 related HPV types, categorized as low-risk (such as, HPV-6 and HPV-11 [14, 28]) and high-risk (such as, HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58 and HPV-59 [14, 29])

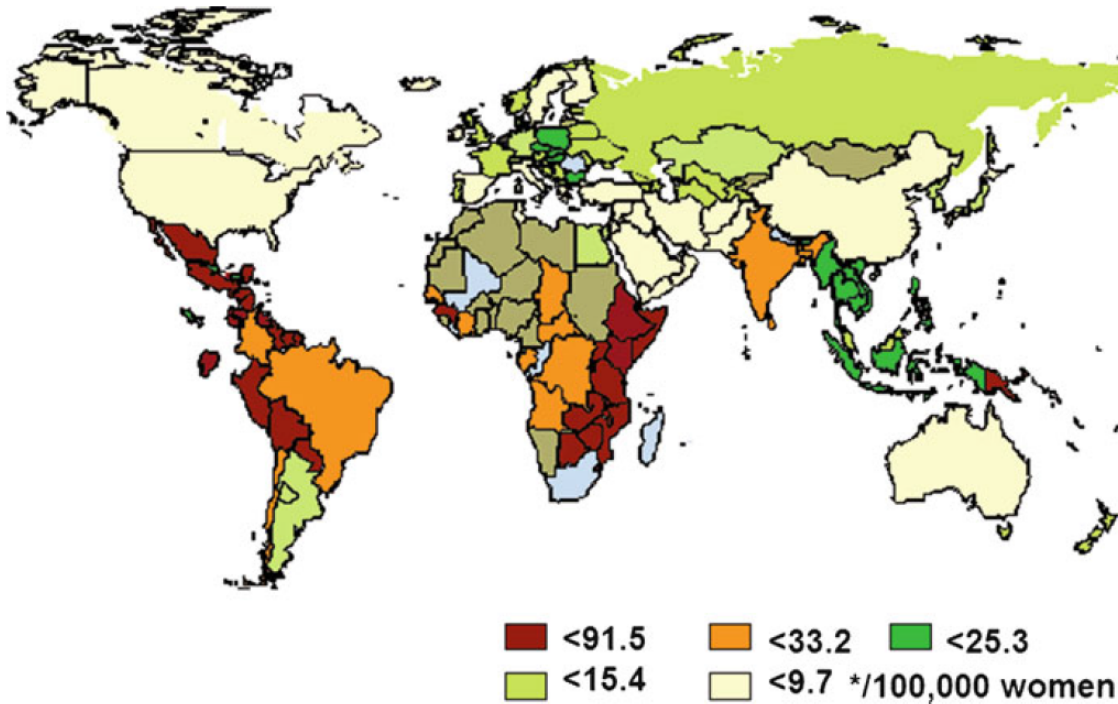


Figure 1.1: Worldwide cervical cancer incidence [8].

types (based on the degree of risk of developing cancer after HPV infection). While the low-risk HPV types do not cause cancers (but cause genital warts) [14, 61, 85], the high-risk HPV types cause various cancers, such as cervical, anal, vulvar, vaginal, and penile cancers [14, 61, 65, 85]. For instance, the high-risk HPV-16 and HPV-18 types cause about 70% of cervical cancers [14, 61] (other high-risk HPV types, such as HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58 and HPV-59, also cause cervical cancer [14, 61, 65]). Furthermore, HPV-16 and HPV-18 are known to cause about half of vaginal, vulvar, penile cancer and, most recently, cancer of oropharynx [14, 61, 65]. Risk factors for HPV infection include having multiple sexual partners, unprotected sex, weakened immune system and tobacco use [14, 61, 85].

HPV targets epithelial basal cells, and HPV-associated diseases are transmitted *via* skin-to-skin contact [36]. It is known that 70%–90% of HPV cases clear their infections naturally within two years [1, 14, 20]. In women who do not clear their HPV infection (typically



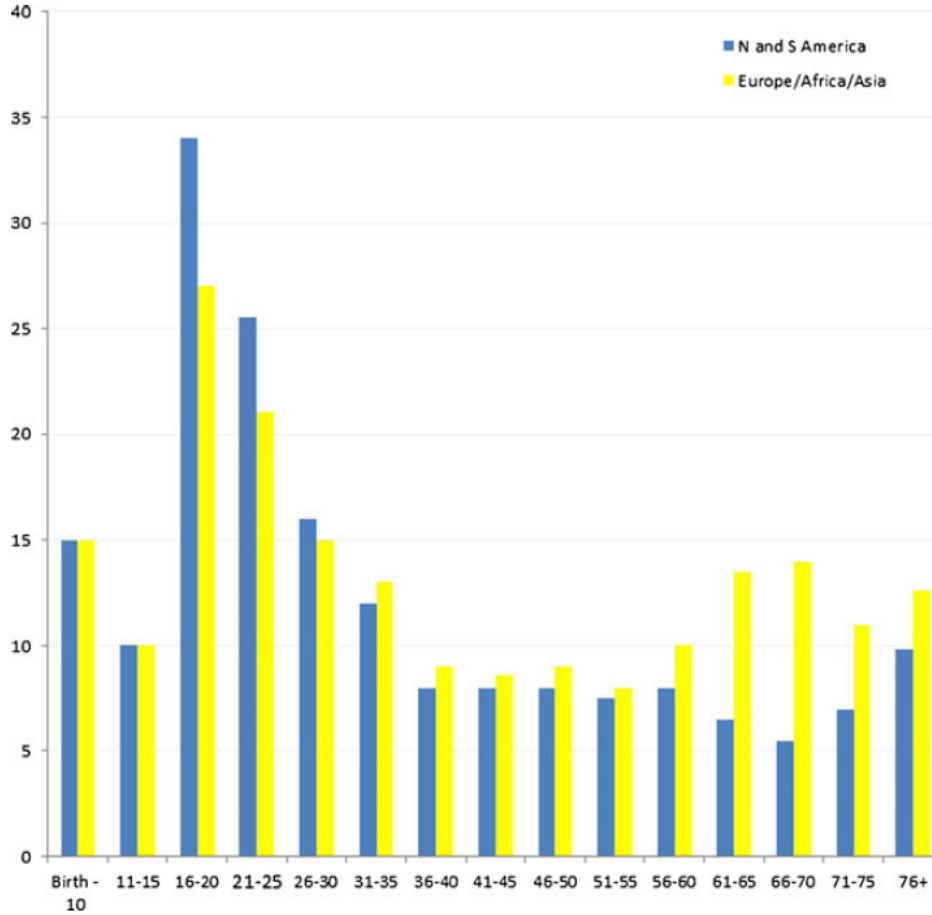


Figure 1.2: HPV prevalence by age. HPV prevalence exists at all ages [36].

those infected with the high-risk HPV types [6, 14, 83]), pre-cancerous lesions (*cervical intraepithelial neoplasia* (CIN)) may persist for many years and, consequently, progress to cervical cancer [14, 55, 62, 63]. Furthermore, high-risk HPV types cause pre-cancerous *intraepithelial neoplasia* in males (INM), resulting in various cancers (such as anal and penile cancers) [5, 27]. Figure 1.3 depicts the natural history of HPV infection and the various *dysplasia* stages.

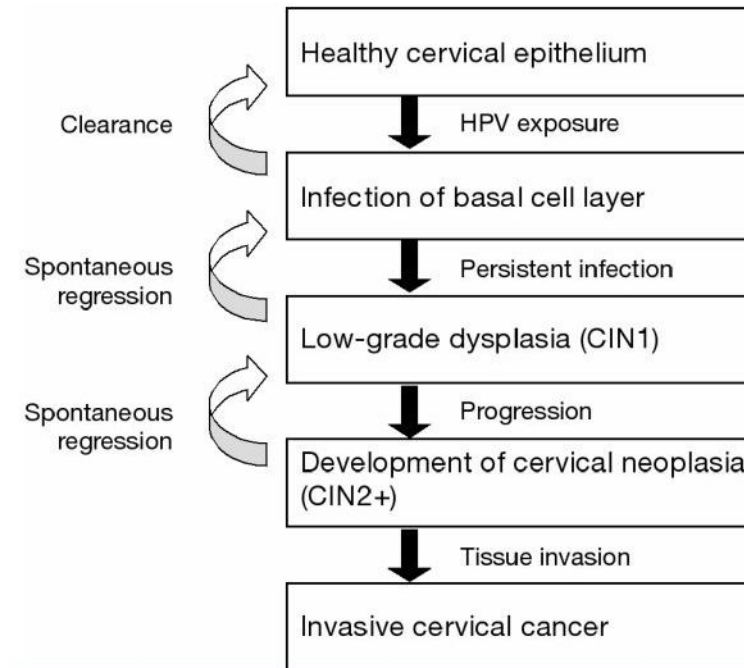


Figure 1.3: Progression and regression of HPV for various stages of cervical dysplasia and cervical cancer [44].

## 1.2 Control Strategies

### 1.2.1 Pap screening, HPV testing and treatment

Pap screening has played an essential role in the early detection of CIN and, consequently, reduce cervical cancer incidence and mortality [55, 63]. For instance, it is known that regular Pap screening decreases the incidence of cervical cancer by 70% over the last five decades [35, 54]. Pap screening detects abnormal cervical cells, including pre-cancerous cervical lesions and early cervical cancers [14, 23, 63]. 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 [15, 63, 69]). 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 [63].

It has recently been recommended that women have their Pap test at the age of 21 [63] (and such test should be administered every 3 years for women of age 21 through 29 [63];

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Age	ACS	ACOG	USPSTF
<b>21 to 29</b>	Every two years with a liquid-based test or annually with a conventional test	Annual Pap tests	Pap tests at least every three years
<b>Over 30</b>	Every two or three years if you have had three negative tests in a row	Every two or three years if you have had three negative tests in a row	Pap tests at least every three years

---

Table 1.1: Recommendations by American Cancer Society (ACS), the American College of Obstetricians and Gynecologists (ACOG) and the U.S. Preventive Services Task Force (USPSTF) regarding when a woman should have a Pap smear [56].

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 [20, 63]) (Table 1.1). Figure 1.4 depicts Pap screening process for females. While the major goal of the screening is to detect abnormal cells that may develop into cancer if left untreated, HPV testing is used to check for the presence of DNA or RNA of high-risk HPV types in cervical cells [63]. Pap screening is not administrated for males.

### 1.2.2 Vaccination

Two anti-HPV vaccines, namely *Cervarix*®(GlaxoSmithKline) and *Gardasil*®(Merck Inc.), have been approved, by the U.S. Food and Drug Administration (in 2005 and 2009, respectively), for use to protect new sexually-active males and females against some of the most common HPV types [45, 62, 64, 82]. The vaccines are implemented *via* a three-dose strategy [14, 29, 62]. These licensed vaccines are very efficacious (with efficacy of at least 90%) [26, 28, 82]. Furthermore, while *Gardasil* costs about US \$400 for the three required doses [54, 77], *Cervarix* costs about US \$300 for the three doses [59]. Thus, these vaccines are, un-

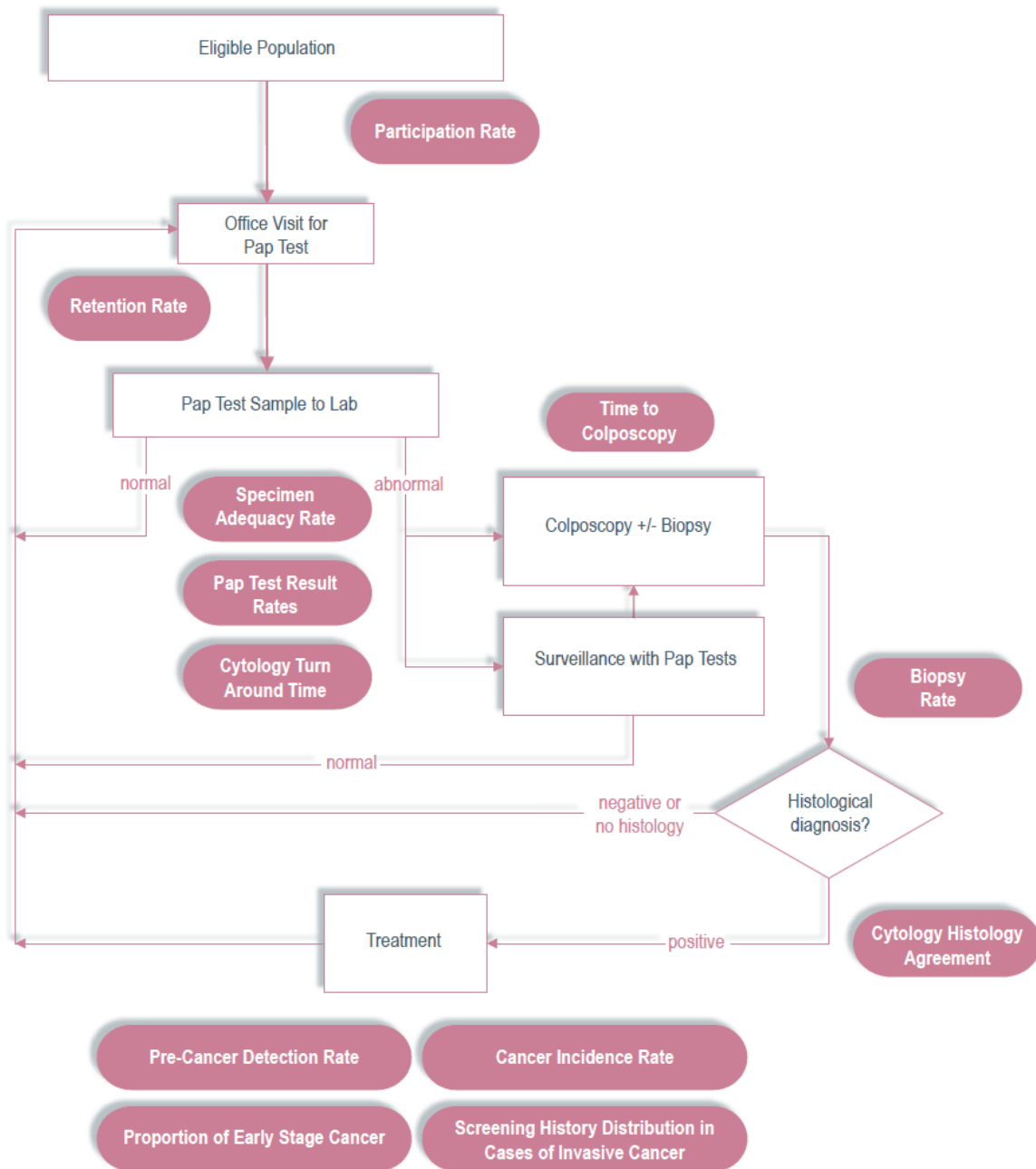


Figure 1.4: General Pap screening process for females [67].

doubtedly, among the most expensive in the market [13, 77], and countries with the heaviest burden of cervical cancer mortality (i.e., Ghana, Nigeria and Uganda [77]) are less likely to afford implementing a routine mass vaccination program using these vaccines. Additionally, the coverage associated with these vaccines (in countries that offer them routinely) is not as high as is needed [77, 86] due to side-effects, poor compliance to the three doses [74, 77], and other factors. Hence, for these reasons, Pap screening remains a viable (and affordable) option for combating HPV (and related cancers) in many (developing) nations of the world. Consequently, the main motivation of this thesis is to use mathematical approaches to qualitatively and quantitatively assess the impact of Pap screening in curtailing the spread of HPV in a community.

### 1.3 Thesis Outline

Mathematical models, typically of the form of deterministic systems of non-linear differential equations, have been developed and used to study the role of Pap screening on the transmission dynamics of HPV and associated dysplasia in a community [28, 50, 55, 60]. Myers *et al.* [60] modeled the natural history of HPV infection and cervical carcinogenesis using a deterministic model. Malik *et al.* [55] investigated the combined impact of an anti-HPV vaccine and Pap screening on the dynamics of HPV and associated dysplasia. The purpose of this thesis is to extend prior HPV transmission models in the literature (that incorporate Pap screening) by developing, and rigorously analyzing, a more realistic model for assessing the population-level impact of Pap screening on the dynamics of HPV and its related cancers in the community. 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 HPV).

The thesis is organized as follows. Some of the basic mathematical definitions, theories and techniques used in the thesis are briefly introduced in Chapter 2. In Chapter 3, a basic model for HPV transmission (and associated dysplasia) is formulated and rigorously analyzed. In Chapter 4, the basic model developed in Chapter 3 is extended to include the routine implementation of Pap screening to sexually-active females. This entails adding two CIN and INM stages (for females and males, respectively), as well as classes for detected females with pre-cancerous lesions and cervical cancer.

Some of the main questions to be addressed in the thesis are:

1. What are the main qualitative features of a realistic basic (in the absence of anti-HPV intervention) model for the transmission dynamics of HPV (and associated dysplasia) in a community? In particular, emphasis will be on determining conditions for the existence and asymptotic (both local and global) stability of the associated disease-free equilibrium of the model.
2. What is the distribution of the values of the *reproduction number* of a realistic HPV transmission model (in the absence of any intervention strategy)? This distribution will provide insight into the persistence or effective control of the disease in the community.
3. What are the main parameters (of the model) that influence the values of the associated reproduction number (hence, drive the disease transmission dynamics):
  - (a) for a basic model for HPV transmission dynamics in a population (in the absence of Pap screening);
  - (b) for a model for HPV transmission dynamics in the presence of Pap screening.
4. What is the population-level impact of HPV transmission by individuals (females and males) with pre-cancerous CIN and INM lesions?
5. Does the community-wide implementation of routine Pap screening offer a quantifiable community-wide impact in minimizing cervical cancer cases in females?

# Chapter 2

## Mathematical Preliminaries

This chapter introduces some of the basic mathematical definitions, theories and methodologies relevant to the thesis.

### 2.1 Equilibria of Linear and Non-linear Autonomous Systems

This thesis considers *autonomous* systems of *ordinary differential equations* (ODEs) given by (where a dot represents differentiation with respect to time  $t$ )

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n. \quad (2.1)$$

That is, *non-autonomous* ODE systems of the form,

$$\dot{x} = f(x, t), \quad x \in \mathbb{R}^n, \quad \text{and} \quad t \in \mathbb{R}, \quad (2.2)$$

where the vector field  $f \in C^r$  (with  $r \geq 1$ ) depends on the independent variable  $t$ , are not considered in this thesis.

**Definition 2.1.** *A point  $\bar{x} \in \mathbb{R}^n$  is called an equilibrium point of the autonomous system*

(2.1) if  $f(\bar{x}) = 0$ .

**Definition 2.2.** The Jacobian matrix of the vector field  $f$ , of the system (2.1), at the equilibrium  $\bar{x}$ , denoted by  $Df(\bar{x})$ , is the matrix,

$$J(\bar{x}) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1}(\bar{x}) & \cdots & \frac{\partial f_1}{\partial x_n}(\bar{x}) \\ \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial x_1}(\bar{x}) & \cdots & \frac{\partial f_n}{\partial x_n}(\bar{x}) \end{pmatrix},$$

of partial derivatives of  $f$  evaluated at  $\bar{x}$ .

**Definition 2.3.** The linear system  $\dot{x} = Ax$ , with the matrix  $A = Df(\bar{x})$ , is called the linearization of the autonomous system (2.1) at  $\bar{x}$ .

## 2.2 Stability Theory

**Definition 2.4.** [84]. The equilibrium  $\bar{x}$  is said to be stable if given  $\epsilon > 0$ , there exists a  $\delta = \delta(\epsilon) > 0$  such that, for any solution  $y(t)$  of (2.1) satisfying  $|\bar{x} - y(t_0)| < \delta$ ,  $|\bar{x} - y(t)| < \epsilon$  for  $t > t_0, t_0 \in \mathbb{R}$ .

**Definition 2.5.** [84]. The equilibrium  $\bar{x}$  is said to be asymptotically-stable if it is stable and there exists a constant  $c > 0$  such that, for any solution  $y(t)$  of (2.1) satisfying  $|\bar{x} - y(t_0)| < c$ , then  $\lim_{t \rightarrow \infty} |\bar{x} - y(t)| = 0$ .

**Definition 2.6.** An equilibrium solution which is not stable is said to be unstable.

**Theorem 2.1.** [84]. Suppose all the eigenvalues of  $Df(\bar{x})$  have negative real parts. Then, the equilibrium solution  $x = \bar{x}$  of the system (2.1) is locally-asymptotically stable (LAS). It is unstable if at least one of the eigenvalues has positive real part.

**Definition 2.7.** If all solutions in the feasible (and invariant) region  $(\Omega)$  of the model converge to the equilibrium  $\bar{x}$  as  $t \rightarrow \infty$ , then  $\bar{x}$  is globally-asymptotically stable (GAS) in  $\Omega$ .



**Definition 2.8.** [84]. *An equilibrium point  $\bar{x}$  is called a hyperbolic if none of the eigenvalues of  $Df(\bar{x})$  has zero real part.*

**Definition 2.9.** [84]. *An equilibrium point that is not hyperbolic is called non-hyperbolic.*

## 2.3 Lyapunov Function Theory

**Definition 2.10.** [84]. *Let  $S \subset \mathbb{R}^n$  be a set. Then,  $S$  is said to be invariant under the flow  $\phi$  generated by  $\dot{x} = f(x)$  if for any  $x_0 \in S$ , we have  $\phi(t, x_0) \in S$  for all  $t \in \mathbb{R}$ .*

**Definition 2.11.** [84]. *A function  $V : \mathbb{R}^n \rightarrow \mathbb{R}$  is said to be positive-definite at  $\bar{x}$  if:*

(i)  $V(x) > 0$  for all  $x \neq \bar{x}$ ,

(ii)  $V(x) = 0$  if and only if  $x = \bar{x}$ .

**Definition 2.12.** [84]. *Consider the system (2.1). Let,  $\bar{x}$  be an equilibrium solution of (2.1) and let  $V : U \rightarrow \mathbb{R}$  be a  $C^1$  function defined on some neighborhood  $U$  of  $\bar{x}$  such that*

(a)  $V$  is positive-definite,

(b)  $\dot{V}(x) \leq 0$  in  $U \setminus \{\bar{x}\}$ .

*Any function,  $V$ , that satisfies Conditions (a) and (b) above is called a Lyapunov function.*

**Theorem 2.2.** (LaSalle's Invariance Principle [53]). *Suppose that there exists a positive-definite  $C^1$  function  $V : \mathbb{R}^n \rightarrow \mathbb{R}$  whose derivative along solutions of the system (2.1) satisfies the inequality  $\dot{V}(x) \leq 0, \forall x$ . Let  $M$  be the largest invariant set contained in the set  $\{x \mid \dot{V}(x) = 0\}$ . Then the system is stable and every solution that remains bounded for  $t \geq 0$  approaches  $M$  as  $t \rightarrow \infty$ .*

**Corollary 2.1.** *If  $M$  contains no trajectory of the system except the trajectory  $x(t) = \bar{x}$  for  $t \geq 0$ , then the solution is globally-asymptotically stable.*

Lyapunov Function Theory and LaSalle's Invariance Principle are used to prove the global asymptotic stability of an equilibrium in Chapter 3.

## 2.4 Comparison Theorem

**Definition 2.13.** [75]. An open subset  $D \subset \mathbb{R}^n$  is said to be  $p$ -convex if  $tx + (1 - t)y \in D$  for all  $t \in [0, 1]$  whenever  $x, y \in D$  and  $x \leq y$ .

**Definition 2.14.** [75]. If  $D$  is a  $p$ -convex subset of  $\mathbb{R}^n$  and

$$\frac{\partial f_i}{\partial x_j} \geq 0, \quad i \neq j, \quad x \in D,$$

then a continuously-differentiable function  $f$  is of Type  $K$  in  $D$ .

**Theorem 2.3.** (Comparison Theorem [51]). Let  $f$  be continuous on  $D$  and of Type  $K$ . Suppose that  $x(t)$  be a solution of  $\dot{x} = f(x)$  defined on  $[a, b]$ .

- If  $z(t)$  is a continuous function on  $[a, b]$  satisfying  $\dot{z} \leq f(z)$  on  $(a, b)$ , with  $z(a) \leq x(a)$ , then  $z(t) \leq x(t)$  for all  $t \in [a, b]$ ;
- If  $y(t)$  is a continuous function on  $[a, b]$  satisfying  $\dot{y} \geq f(y)$  on  $(a, b)$ , with  $y(a) \geq x(a)$ , then  $y(t) \geq x(t)$  for all  $t \in [a, b]$ .

Comparison Theorem is used to prove the global asymptotic stability of the disease-free equilibria of the models developed in Chapters 3 and 4.

## 2.5 Next Generation Operator Method

One of the most popularly-used methods for computing the reproduction number ( $\mathcal{R}_0$ ) of disease transmission models is the next generation operator method [24, 80]. The reproduction number measures the average number of new cases of infections generated by a typical infected individual if introduced in a susceptible population [37]. The formulation (for computing  $\mathcal{R}_0$ ) given in [80] is described below.

Suppose the given disease transmission model, with non-negative initial conditions, can be written in terms of the following autonomous system [80]:

$$\dot{x}_i = f(x_i) = F_i(x) - V_i(x), \quad i = 1, \dots, n, \quad (2.3)$$

where  $V_i^- - V_i^+$  and the functions satisfy the following axioms ( $V_i^+(x)$  is the rate of transfer of individuals into compartment  $i$  by all other means and  $V_i^-(x)$  is the rate of transfer of individuals out of compartment  $i$ ) [80]. First of all,  $\{X_s = x \geq 0 | x_i = 0, i = 1, \dots, m\}$  is defined as the disease-free states (non-infected state variables) of the model, where  $x = (x_1, \dots, x_n)^T$ ,  $x_i \geq 0$  represents the number of individuals in each compartment of the model and  $m$  is the number of the compartments correspond to infected individuals.

(A1) If  $x \geq 0$ , then  $F_i, V_i^+, V_i^- \geq 0$  for  $i = 1, \dots, m$ .

(A2) If  $x_i = 0$ , then  $V_i^- = 0$ . In particular, if  $x \in X_s$  then  $V_i^- = 0$  for  $i = 1, \dots, m$ .

(A3)  $F_i = 0$  if  $i > m$ .

(A4) If  $x \in X_s$ , then  $F_i(x) = 0$  and  $V_i^+(x) = 0$  for  $i = 1, \dots, m$ .

(A5) If  $F(x)$  is set to zero, then all eigenvalues of  $D(f(x_0))$  have negative real parts.

In the above,  $F_i(x)$  represents the rate of appearance of new infections in compartment  $i$ ,  $V_i^+(x)$  represents the rate of transfer of individuals into compartment  $i$ . It is assumed that these functions are at least twice continuously-differentiable in each variable [80].

**Definition 2.15.** [21]. A matrix  $A = (a_{ij}) \in \mathbb{R}^{n \times n}$  is called an  $M$ -matrix if  $a_{ij} \leq 0$  for  $i \neq j$  and  $A^{-1} > 0$  (i.e.  $(A^{-1})_{ij} > 0$ ).

**Lemma 2.1.** (van den Driessche and Watmough [80]). If  $\bar{x}$  is a DFE of (2.3) and  $f_i(x)$  satisfy (A1) – (A5), then the derivative  $DF(\bar{x})$  and  $DV(\bar{x})$  are partitioned as

$$DF(\bar{x}) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \quad DV(\bar{x}) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where  $F$  and  $V$  are the  $m \times m$  matrices defined by,

$$F = \left[ \frac{\partial F_i}{\partial x_j}(\bar{x}) \right] \quad \text{and} \quad V = \left[ \frac{\partial V_i}{\partial x_j}(\bar{x}) \right] \quad \text{with} \quad 1 \leq i, j \leq m.$$

Furthermore,  $F$  is non-negative,  $V$  is non-singular  $M$ -matrix and  $J_3$  and  $J_4$  are matrices associated with the transition terms of the model, and all eigenvalues of  $J_4$  have positive real parts.

**Theorem 2.4.** (van den Driessche and Watmough [80]). Consider the disease transmission model given by (2.3) with  $f(x)$  satisfying axioms (A1)-(A5). If  $\bar{x}$  is a DFE of the model, then  $\bar{x}$  is LAS if  $\mathcal{R}_0 = \rho(FV^{-1}) < 1$  (where  $\rho$  is the spectral radius), and unstable if  $\mathcal{R}_0 > 1$ .

This technique is used to prove the local asymptotic stability of the disease-free equilibria of the models developed in Chapters 3 and 4.

## 2.6 Krasnoselskii Sub-linearity Argument

**Definition 2.16.** [48]. A Banach space  $X$  is a complete normed vector space. For example, the Cartesian space  $\mathbb{R}^n$  is a Banach space with

$$\|(x_1, \dots, x_n)\|_p = \left( \sum_{i=1}^n |x_i|^p \right)^{\frac{1}{p}}, \quad \text{when } 1 \leq p \leq \infty.$$

**Definition 2.17.** [47]. Let  $E$  be a real Banach space. A set  $K \subset E$  is called a cone if the following conditions are satisfied:

- the set  $K$  is closed;
- if  $u, v \in K$ , then  $\alpha u + \beta v \in K$  for all  $\alpha, \beta \geq 0$ ;
- for each pair of points  $x, -x$ , at least one does not belong to  $K$ , provided  $x \neq \theta$ , where  $\theta$  is the zero of the space  $E$ .

**Definition 2.18.** [47]. Let  $u_0$  be some fixed non-zero element of  $K$ . If for every  $x \in K$  ( $x \neq \theta$ )

$$\alpha u_0 \leq A^n x \leq \beta u_0,$$

for some positive  $\alpha, \beta$  and  $n$ , then the operator  $A$  is called  $u_0$ -positive.

**Theorem 2.5.** (Krasnoselskii [47]). Let  $u_0 \in K$ . If  $A$  is a  $u_0$ -positive operator, then the cone  $K$  has a unique characteristic vector.

The Krasnoselskii sub-linearity argument [31, 32, 47, 76] is based on showing that the linearization of the non-linear system  $\dot{x} = f(x)$ , given by  $\dot{Z}(t) = Df(\bar{x})Z$  where  $\bar{x}$  is an equilibrium solution of the non-linear system has no solution of the form

$$\bar{Z}(t) = \bar{Z}_0 e^{wt}, \tag{2.4}$$

with  $\bar{Z}_0 = (Z_1, Z_2, \dots, Z_n)$ ,  $Z_i \in \mathbb{C}$ ,  $w \in \mathbb{C}$ , and  $\text{Re}(w) \geq 0$  ( $n$  is the dimension of the associated linearized system). The consequence of this is that all the eigenvalues of the characteristic polynomial associated with the linearized version of  $\dot{x} = f(x)$  will have negative real part (so that the associated equilibrium is locally-asymptotically stable). This technique is used to prove the local asymptotic stability of an equilibrium in Chapter 3.

## 2.7 Uncertainty and Sensitivity Analysis

**Definition 2.19.** [7, 40]. *Uncertainty analysis is a technique for assessing the variability in an outcome variable that arise due to the uncertainty in estimating the input values.*

**Definition 2.20.** [7, 40]. *Sensitivity analysis is concerned with identifying the key input parameters that contribute to the imprecision in the estimate of the output (response) variable. In other words, while uncertainty analysis is focused on assessing the impact of the uncertainties in the parameters of the model being studied on the outcome (simulations of the*

model), sensitivity analysis is based on identifying the key parameters of the model that most influence the outcome (response function) [7].

**Definition 2.21.** [57]. *Latin Hypercube Sampling (LHS) is a statistical method for generating a sample of plausible collections of parameter values from a multidimensional distribution. LHS is an efficient sampling technique, since each sampled value of each of the input parameters is used only once in the computation (of the associated response function) [7].*

**Definition 2.22.** [16]. *The continuous uniform distribution is a family of symmetric probability distributions such that, for each member of the family, all intervals of the same length on the distribution's support have equal probabilities.*

**Definition 2.23.** [79]. *Partial Correlation Coefficient is used to measure the degree of linear relationship between two variables, after adjusting for, or controlling for, the effect of some set of variables.*

**Definition 2.24.** [7, 39, 40, 46]. *Partial Rank Correlation Coefficients (PRCC) are computed for each input parameter (sampled by the LHS scheme) and each output variable to measure the amount of linear relationship between two variables after adjusting for (or controlling for) the effect of some set of variables.*

*PRCC are, typically, obtained via the following steps [7]:*

- i) Choosing an outcome (response) vector for the system (model) being analyzed.*
- ii) Adding the outcome vector as an additional column (column  $K + 1$ ) of the matrix of input values (of the model parameters).*
- iii) Defining the ordinal numbers representing the rank, from 1 to  $N$  (where  $N$  is the number of runs), of each of these columns as the set  $(r_{1i}, r_{2i}, \dots, r_{ki}, R_i)$ , where  $i$  is the run number.*
- iv) Defining a  $(K + 1) \times (K + 1)$  symmetric matrix,  $C = [c_{ij}]$  (where  $\mu$  is the average rank and equals to  $(1 + N)/2$ ), by*

$$c_{ij} = \frac{\sum_{t=1}^N (r_{it} - \mu)(r_{jt} - \mu)}{\sqrt{\sum_{t=1}^N (r_{it} - \mu)^2 \sum_{s=1}^N (r_{js} - \mu)^2}}, \quad i, j = 1, 2, \dots, K.$$

v) Defining the matrix  $B = [b_{ij}] = C^{-1}$  (for the  $c_{i,k+1}$  elements  $R_i$  replaces  $r_{jt}$  and  $r_{js}$  and the leading diagonal elements of  $C$  are all ones).

vi) Finding the PRCC ( $\gamma_i$ ) between the  $i$ th input parameter and the outcome variable using the relation

$$\gamma_i = \frac{-b_{i,K+1}}{\sqrt{b_{ii}b_{K+1,K+1}}}.$$

These steps are followed in the computation of PRCC values of the parameters of the models developed in Chapters 3 and 4.

# Chapter 3

## Basic HPV Transmission Model

### 3.1 Introduction

As stated in Chapter 1, HPV is a major sexually-transmitted disease that induces significant public health and socio-economic burden globally [6, 14, 61, 62, 85]. Furthermore, although 70%–90% of HPV cases (in both females and males) clear their infections naturally [1, 14, 20], females who do not clear their HPV infection (typically those infected with high-risk HPV types, such as HPV-16 and HPV-18 [6, 14, 83]) can develop persistent HPV infection (leading to pre-cancerous *cervical intraepithelial neoplasia* (CIN) and cervical cancer [14, 55, 62, 63]).

The aim of this chapter is to design, and rigorously analyze, a new realistic deterministic model for the transmission dynamics of HPV (and related dysplasia) in a community. The central objective is to gain insight into the qualitative dynamics of the resulting model, *vis-a-vis* determining the conditions for the persistence or effective control (or elimination) of the disease in the community. The new deterministic model to be developed extends many others in the literature. Furthermore, detailed uncertainty and sensitivity analyses (of the parameters of the model that drive the disease transmission process) will be carried out to assess the effect of uncertainties in the estimate of the parameters of the model on the output (and to also identify the key parameters that drive the dynamics of the model). In



particular, Questions 1, 2 and part (a) of Question 3 in Section 1.3 will be addressed in this chapter. It is worth stating that although there are numerous HPV serotypes (low- and high-risk; as stated in Chapter 1) [19, 55], this study lumps them all into one HPV type (since the objective of the thesis is to assess the impact of Pap screening, and Pap screening detects CIN lesions caused by any of the high-risk HPV types).

## 3.2 Model Formulation

The new model for the transmission dynamics of HPV in a community is designed by stratifying the total sexually-active female population at time  $t$  (denoted by  $N_f(t)$ ) into eight mutually-exclusive sub-populations of susceptible females ( $S_f(t)$ ), exposed (asymptomatic; infected but without clinical symptoms of HPV) 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 CIN lesions ( $Q_f(t)$ ), females with cervical cancer ( $C_f(t)$ ), 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

$$N_f(t) = S_f(t) + E_f(t) + I_f(t) + P_f(t) + Q_f(t) + C_f(t) + R_{fc}(t) + R_f(t). \quad (3.1)$$

Similarly, the total sexually-active male population at time  $t$  (denoted by  $N_m(t)$ ) is subdivided into eight mutually-exclusive sub-populations of susceptible males ( $S_m(t)$ ), exposed (asymptomatic; infected but without clinical symptoms of HPV) males ( $E_m(t)$ ), symptomatic males ( $I_m(t)$ ), males with persistent HPV infection ( $P_m(t)$ ), males with INM lesions ( $Q_m(t)$ ), 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,

$$N_m(t) = S_m(t) + E_m(t) + I_m(t) + P_m(t) + Q_m(t) + C_m(t) + R_{mc}(t) + R_m(t). \quad (3.2)$$

It follows from (3.1) and (3.2) that the total sexually-active (heterosexual) population, at time  $t$ , is given by  $N(t) = N_f(t) + N_m(t)$ .

The population of susceptible females ( $S_f(t)$ ) is generated by the recruitment of new sexually-active females (at a rate  $\pi_f$ ). This population is decreased by the acquisition of HPV infection, following effective contact with infected males in the symptomatic ( $I_m$ ) and persistent infection ( $P_m$ ) classes at a rate  $\lambda_m$ , given by (it is assumed, for mathematical convenience, that exposed males ( $E_m$ ) and males with INM ( $Q_m$ ) do not transmit HPV to susceptible females)

$$\lambda_m = \frac{\beta_m c_f(N_m, N_f) (I_m + \theta_m P_m)}{N_m}. \quad (3.3)$$

In (3.3),  $\beta_m$  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,  $\theta_m > 0$  models the assumed variability of the infectiousness of HPV-infected males in the  $P_m$  class in relation to HPV-infected males in the  $I_m$  class. The population of susceptible females is further diminished by natural death (at a rate  $\mu_f$ ; it is assumed that females in all epidemiological compartments suffer natural death at this rate). Thus,

$$\frac{dS_f}{dt} = \pi_f - (\lambda_m + \mu_f)S_f. \quad (3.4)$$

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

$$\frac{dE_f}{dt} = \lambda_m S_f - (\sigma_f + \mu_f)E_f. \quad (3.5)$$

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  $\sigma_f$ ). Members

of this class recover (at a rate  $r_{f1}$ ) and develop persistent HPV infection (at a rate  $\psi_f$ ). It is assumed, in this thesis, that recovery gives permanent immunity against HPV re-infection with the disease (it should be mentioned, however, the re-infection is possible in HPV dynamics, especially with a different HPV strain [28, 78]). This population is further decreased by natural death. Thus,

$$\frac{dI_f}{dt} = \sigma_f E_f - (r_{f1} + \psi_f + \mu_f) I_f. \quad (3.6)$$

The population of females with persistent HPV infection ( $P_f(t)$ ) [61] is generated by the development of persistent HPV infection by symptomatic females (at the rate  $\psi_f$ ). Individuals move out of this class through recovery (at a rate  $r_{f2}$ ), development of CIN lesions (at a rate  $\alpha_f$ ) and natural death. Hence,

$$\frac{dP_f}{dt} = \psi_f I_f - (r_{f2} + \alpha_f + \mu_f) P_f. \quad (3.7)$$

The population of females with CIN lesions ( $Q_f(t)$ ) is generated by the development of CIN lesions by females with persistent HPV infection (at the rate  $\alpha_f$ ). Although there are three multiple CIN stages (based on the size of the associated lesions) [19, 55], they are lumped into one in this thesis, for mathematical convenience (this assumption is relaxed in Chapter 4, where Pap screening is explicitly modeled). Transition out of the CIN class occurs through recovery (at a rate  $r_{f3}$ ), development of cervical cancer (at a rate  $g_f$ ) or natural death. Thus,

$$\frac{dQ_f}{dt} = \alpha_f P_f - (r_{f3} + g_f + \mu_f) Q_f. \quad (3.8)$$

The population of females with cervical cancer ( $C_f(t)$ ) is generated at the rate  $g_f$ . It is decreased by recovery (at a rate  $r_{f4}$ ), natural death and cancer-related mortality (at a rate  $\delta_f$ ). Thus,

$$\frac{dC_f}{dt} = g_f Q_f - (r_{f4} + \mu_f + \delta_f) C_f. \quad (3.9)$$

The population of females who recovered from cervical cancer ( $R_{fc}(t)$ ) is generated at the rate  $r_{f4}$ . Like in other epidemiological classes, females in this class also suffer natural death (at the rate  $\mu_f$ ). Hence,

$$\frac{dR_{fc}}{dt} = r_{f4}C_f - \mu_f R_{fc}. \quad (3.10)$$

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  $I_f$ ,  $P_f$  and  $Q_f$  classes (at the rates  $r_{f1}$ ,  $r_{f2}$  and  $r_{f3}$ , respectively). It is diminished by natural death, so that

$$\frac{dR_f}{dt} = r_{f1}I_f + r_{f2}P_f + r_{f3}Q_f - \mu_f R_f. \quad (3.11)$$

The population of susceptible males ( $S_m(t)$ ) is generated by the recruitment of new sexually-active males (at a rate  $\pi_m$ ). This population is decreased by the acquisition of HPV infection, following effective contact with infected females with clinical symptoms of HPV ( $I_f$ ) or persistent HPV infection ( $P_f$ ), at a rate  $\lambda_f$ , given by (here, too, it is assumed that females in  $E_f$  and  $Q_f$  classes do not transmit HPV to susceptible males)

$$\lambda_f = \frac{\beta_f c_m(N_m, N_f) (I_f + \theta_f P_f)}{N_f}. \quad (3.12)$$

In (3.12),  $\beta_f$  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 (hence,  $\beta_f c_m(N_m, N_f)$  is the effective contact rate for female-to-male transmission of HPV). Furthermore,  $\theta_f > 0$  models the assumed variability of the infectiousness of HPV-infected females in the  $P_f$  class in relation to HPV-infected males in the  $I_f$  class. The population of susceptible males is further diminished by natural death (at a rate  $\mu_m$ ; it is assumed that males in all epidemiological compartments suffer natural death at this rate). Thus,

$$\frac{dS_m}{dt} = \pi_m - (\lambda_f + \mu_m)S_m. \quad (3.13)$$

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

$$\frac{dE_m}{dt} = \lambda_f S_m - (\sigma_m + \mu_m) E_m. \quad (3.14)$$

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  $\sigma_m$ ). It is assumed that members of this class recover (at a rate  $r_{m1}$ ) and develop persistent HPV infection (at a rate  $\psi_m$ ). This population is further decreased by natural death. Thus,

$$\frac{dI_m}{dt} = \sigma_m E_m - (r_{m1} + \psi_m + \mu_m) I_m. \quad (3.15)$$

The population of males with persistent HPV infection ( $P_m(t)$ ) is generated at the rate  $\psi_m$ . Individuals move out of this class through recovery (at a rate  $r_{m2}$ ), development of INM lesions (at a rate  $\alpha_m$ ) and natural death. Hence,

$$\frac{dP_m}{dt} = \psi_m I_m - (r_{m2} + \alpha_m + \mu_m) P_m. \quad (3.16)$$

The population of males with INM lesions ( $Q_m(t)$ ) is generated by the development of INM lesions by males with persistent HPV infection (at the rate  $\alpha_m$ ). Transition out of this class occurs through recovery (at a rate  $r_{m3}$ ), development of HPV-related cancer (at a rate  $g_m$ ) or natural death. Thus,

$$\frac{dQ_m}{dt} = \alpha_m P_m - (r_{m3} + g_m + \mu_m) Q_m. \quad (3.17)$$

The population of males with HPV-related cancer ( $C_m(t)$ ) is generated at the rate  $g_m$ . It is decreased by recovery (at a rate  $r_{m4}$ ) and natural death (it should be mentioned that

since HPV-related cancers, such as penile cancer, are rare in males [81], no mortality due to HPV-related cancer is assumed for males). Thus,

$$\frac{dC_m}{dt} = g_m Q_m - (r_{m4} + \mu_m) C_m. \quad (3.18)$$

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 a rate  $r_{m4}$ ). This population is decreased by natural death (at the rate  $\mu_m$ ). Hence,

$$\frac{dR_{mc}}{dt} = r_{m4} C_m - \mu_m R_{mc}. \quad (3.19)$$

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  $I_m$ ,  $P_m$  and  $Q_m$  classes (at the rates  $r_{m1}$ ,  $r_{m2}$  and  $r_{m3}$ , respectively). It is diminished by natural death, so that

$$\frac{dR_m}{dt} = r_{m1} I_m + r_{m2} P_m + r_{m3} Q_m - \mu_m R_m. \quad (3.20)$$

It is worth stating, from the equations given in  $\{(3.13) - (3.20)\}$ , that the rate of change of the total male population ( $N_m(t)$ ) is given by

$$\frac{dN_m(t)}{dt} = \pi_m - \mu_m N_m(t), \text{ so that } N_m(t) \longrightarrow \frac{\pi_m}{\mu_m}, \text{ as } t \longrightarrow \infty. \quad (3.21)$$

That is, the total male population is asymptotically constant. Furthermore, since the model  $\{(3.4) - (3.11), (3.13) - (3.20) \text{ with } (3.3) \text{ and } (3.12)\}$  is a sex-structured one, the following conservation law of sexual contacts (i.e., the total number of sexual contacts made by males balances that by females) is preserved in the heterosexual community [55]. That is, for the model  $\{(3.4) - (3.11), (3.13) - (3.20) \text{ with } (3.3) \text{ and } (3.12)\}$ ,

$$c_m(N_m, N_f) N_m = c_f(N_m, N_f) N_f. \quad (3.22)$$

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) [26, 55]. Hence, Equation (3.22) can be re-written as

$$c_m(N_m, N_f) = \frac{c_f N_f}{N_m}. \quad (3.23)$$

Consequently, using (3.22) in (3.3) and (3.12), the forces of infection,  $\lambda_m$  and  $\lambda_f$ , are now re-written, respectively, as

$$\lambda_m = \frac{\beta_m c_f (I_m + \theta_m P_m)}{N_m}, \quad \lambda_f = \frac{\beta_f c_f (I_f + \theta_f P_f)}{N_m}. \quad (3.24)$$

Based on the above formulations and assumptions, and using (3.24) for (3.3) and (3.12), it follows that the basic model for the transmission dynamics of HPV (and associated *dysplasia*) in a community is given by the following deterministic system of non-linear differential equations (a flow diagram of the model is depicted in Figure 3.1. The associated state variables and parameters are tabulated in Tables 3.1, and 3.2):

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

(3.25)

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



The basic HPV transmission model (3.25) is an extension of many HPV transmission models in the literature, such as those in [2, 3, 10, 28, 30, 55], by, *inter alia*,

- (i) incorporating the dynamics of exposed females ( $E_f$ ) and males ( $E_m$ ) (this is not included in the models considered in [10, 28, 30, 55]);
- (ii) incorporating the dynamics of individuals (males and females) in the pre-cancerous *intraepithelial neoplasia* stages, as well as the dynamics of HPV-related cancers in males (which are not included in the models considered in [3, 10, 28, 30]; it should, however, be stated that three CIN stages for females are included in [55]);
- (iii) incorporating the dynamics of males with persistent HPV infection (this is not included in the models considered in [3, 10, 28, 30, 55]);
- (iv) incorporating the dynamics of males who recovered from HPV-related cancer (this is not included in the models considered in [3, 10, 28, 30, 55]).

Furthermore, this chapter will contribute by way of providing detailed qualitative analyses of the basic model (3.25).

### 3.2.1 Basic properties

Since the model (3.25) monitors the dynamics of human populations, all its associated parameters and state variables are non-negative for all time  $t \geq 0$ .

**Theorem 3.1.** *Let the initial data be  $S_f(0) > 0$ ,  $E_f(0) \geq 0$ ,  $I_f(0) \geq 0$ ,  $P_f(0) \geq 0$ ,  $Q_f(0) \geq 0$ ,  $C_f(0) \geq 0$ ,  $R_{fc}(0) \geq 0$ ,  $R_f(0) \geq 0$ ,  $S_m(0) > 0$ ,  $E_m(0) \geq 0$ ,  $I_m(0) \geq 0$ ,  $P_m(0) \geq 0$ ,  $Q_m(0) \geq 0$ ,  $C_m(0) \geq 0$ ,  $R_{mc}(0) \geq 0$ ,  $R_m(0) \geq 0$ . Then, the solutions  $(S_f(t), E_f(t), I_f(t), P_f(t), Q_f(t), C_f(t), R_{fc}(t), R_f(t), S_m(t), E_m(t), I_m(t), P_m(t), Q_m(t), C_m(t), R_{mc}(t), R_m(t))$  of the model (3.25) will remain positive for all  $t > 0$ .*

The proof of Theorem 3.1 is given in Appendix A.

**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 model (3.25).

*Proof.* Adding the first eight equations of the model (3.25) gives

$$\frac{dN_f}{dt} = \pi_f - \mu_f N_f - \delta_f C_f \leq \pi_f - \mu_f N_f. \quad (3.26)$$

It follows from (3.26) that  $\frac{dN_f}{dt} < 0$  if  $N_f(t) > \frac{\pi_f}{\mu_f}$ . Furthermore, it follows, using Comparison Theorem [51], that

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

so that,  $N_f(t) \leq \frac{\pi_f}{\mu_f}$  if  $N_f(0) \leq \frac{\pi_f}{\mu_f}$ . Similarly, it follows from (3.21) 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  $\mathcal{D}$  is positively-invariant for the model (3.25). 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  $\mathcal{D}$  in finite time, or  $N_f(t)$  approaches  $\frac{\pi_f}{\mu_f}$  and  $N_m(t) \rightarrow \frac{\pi_m}{\mu_m}$  asymptotically [55]. Hence, the region  $\mathcal{D}$  attracts all solutions in  $\mathbb{R}_+^{16}$ .  $\square$

Since the region  $\mathcal{D}$  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 basic model (3.25) in this region [37]).

### 3.3 Asymptotic Stability of Disease-free Equilibrium (DFE)

#### 3.3.1 Local asymptotic stability

The DFE of the basic model (3.25), obtained by setting the right-hand sides of the equations of the model to zero, is given by,

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

As discussed in Chapter 2, the local asymptotic stability of the DFE ( $\mathcal{E}_0$ ) can be established using the next generation operator method [24, 80]. Using the notation in [80], the non-negative matrix  $\mathcal{F}$  (of new infection terms), and the  $M$ -matrix  $\mathcal{V}$  (of the transition terms) associated with the model (3.25), 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 [80] that the *basic reproduction number* of the basic model (3.25) [37], denoted by  $\mathcal{R}_0$ , is given by (where  $\rho$  is the spectral radius of the next generation matrix  $\mathcal{F}\mathcal{V}^{-1}$ )

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\mathcal{R}_m \mathcal{R}_f}, \quad (3.27)$$

with,

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

The result below follows from Theorem 2 of [80].

**Lemma 3.2.** *The DFE,  $\mathcal{E}_0$ , of the model (3.25) 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 (3.25) 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 [37].

### 3.3.2 Interpretation of the basic reproduction number

The basic reproduction number ( $\mathcal{R}_0$ ) can be epidemiologically interpreted as follows. 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  $N_m^* = S_m^* = \frac{\pi_m}{\mu_m}$ )

$$\left(\frac{\mu_m \beta_f c_f \sigma_f}{\pi_m h_1 h_2} + \frac{\mu_m \beta_f c_f \sigma_f \theta_f \psi_f}{\pi_m h_1 h_2 h_3}\right) S_m^* = \frac{\beta_f c_f \sigma_f}{h_1 h_2} \left(1 + \frac{\theta_f \psi_f}{h_3}\right). \quad (3.28)$$

The terms in the left-hand side of (3.28) 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  $\left(\frac{\beta_m c_m S_m^*}{N_m^*}\right)$ , 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  $\left(\frac{\beta_m c_m \theta_m S_m^*}{N_m^*}\right)$ , 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  $S_f^* = \frac{\pi_f}{\mu_f}$ )

$$\left(\frac{\mu_m \beta_m c_m \sigma_m}{\pi_m h_6 h_8} + \frac{\mu_m \beta_m c_m \sigma_m \theta_m \psi_m}{\pi_m h_6 h_7 h_8}\right) S_f^* = \frac{\pi_f \mu_m \beta_m c_m \sigma_m}{\mu_f \pi_m h_6 h_7} \left(1 + \frac{\theta_m \psi_m}{h_8}\right). \quad (3.29)$$

The terms in the left-hand side of (3.29) 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 (3.28) and (3.29) gives the basic reproduction number,  $\mathcal{R}_0$ .

### 3.3.3 Global asymptotic stability

Lemma 3.2 shows that effective disease control (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 has to be established for the DFE ( $\mathcal{E}_0$ ). This is done below.

**Theorem 3.2.** *The DFE,  $\mathcal{E}_0$ , of the model (3.25) is GAS in  $\mathcal{D}$  whenever  $\mathcal{R}_0 < 1$ .*

The proof of Theorem 3.2, based on using a comparison theorem, is given in Appendix B. The epidemiological implication of Theorem 3.2 is that HPV will be eliminated from the community whenever the associated basic reproduction threshold ( $\mathcal{R}_0$ ) is less than unity. Figure 3.2 shows the solution profiles of the basic model (3.25), 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 3.2).

## 3.4 Existence and Stability of Endemic Equilibrium Point (EEP)

In this section, conditions for the existence of endemic equilibria (i.e., equilibria where the infected components of the basic model (3.25) are non-zero) will be explored. Let,

$$\mathcal{E}_1 = (S_f^{**}, E_f^{**}, I_f^{**}, P_f^{**}, Q_f^{**}, C_f^{**}, R_{fc}^{**}, R_f^{**}, S_m^{**}, E_m^{**}, I_m^{**}, P_m^{**}, Q_m^{**}, C_m^{**}, R_{mc}^{**}, R_m^{**}), \quad (3.30)$$

represents an arbitrary EEP of the model (3.25). Furthermore, let

$$\lambda_m^{**} = \frac{\beta_m c_f \mu_m (I_m^{**} + \theta_m P_m^{**})}{\pi_m} \quad \text{and} \quad \lambda_f^{**} = \frac{\beta_f c_f \mu_m (I_f^{**} + \theta_f P_f^{**})}{\pi_m}, \quad (3.31)$$

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  $\frac{\pi_m}{\mu_m}$ ). Solving the equations of the basic model (3.25) at the endemic steady-state gives:

$$\begin{aligned} S_f^{**} &= \frac{\pi_f}{\lambda_m^{**} + \mu_f}, & E_f^{**} &= \frac{\lambda_m^{**} S_f^{**}}{h_1}, & I_f^{**} &= \frac{\sigma_f E_f^{**}}{h_2}, & P_f^{**} &= \frac{\psi_f I_f^{**}}{h_3}, & Q_f^{**} &= \frac{\alpha_f P_f^{**}}{h_4}, \\ C_f^{**} &= \frac{g_f Q_f^{**}}{h_5}, & R_{fc}^{**} &= \frac{r_{f4} C_f^{**}}{\mu_f}, & R_f &= \frac{r_{f1} I_f^{**} + r_{f2} P_f^{**} + r_{f3} Q_f^{**}}{\mu_f}, \\ S_m^{**} &= \frac{\pi_m}{\lambda_f^{**} + \mu_m}, & E_m^{**} &= \frac{\lambda_f^{**} S_m^{**}}{h_6}, & I_m^{**} &= \frac{\sigma_m E_m^{**}}{h_7}, & P_m^{**} &= \frac{\psi_m I_m^{**}}{h_8}, & Q_m^{**} &= \frac{\alpha_m P_m^{**}}{h_9}, \\ C_m^{**} &= \frac{g_m Q_m^{**}}{h_{10}}, & R_{mc}^{**} &= \frac{r_{m4} C_m^{**}}{\mu_m}, & R_m &= \frac{r_{m1} I_m^{**} + r_{m2} P_m^{**} + r_{m3} Q_m^{**}}{\mu_m}. \end{aligned} \quad (3.32)$$

Substituting the expressions in (3.32) into (3.31) gives

$$\lambda_m^{**} = \frac{\beta_m c_f \mu_m \sigma_m (\theta_m \psi_m + h_8) \lambda_f^{**}}{h_6 h_7 h_8 (\lambda_f^{**} + \mu_m)}, \quad (3.33)$$

$$\lambda_f^{**} = \frac{\pi_f \beta_f c_f \mu_m \sigma_f (\theta_f \psi_f + h_3) \lambda_m^{**}}{\pi_m h_1 h_2 h_3 (\lambda_m^{**} + \mu_f)}. \quad (3.34)$$

Substituting (3.33) into (3.34), and simplifying, gives

$$\lambda_f^{**} = \frac{\mu_m [(\mathcal{R}_0)^2 - 1]}{\pi_m h_1 h_2 h_3 [\beta_m c_f \mu_m (\psi_m \sigma_m \theta_m + \sigma_m h_8) + \mu_f h_6 h_7 h_8]}. \quad (3.35)$$

It follows from (3.35) that, since all the parameters of the model (3.25) are positive,  $\lambda_f^{**}$  is positive whenever  $\mathcal{R}_0 > 1$  (so that the basic model (3.25) has a unique EEP whenever  $\mathcal{R}_0 > 1$ ). The components of the unique EEP can then be obtained by substituting (3.35) into the steady-state expressions in (3.32). Furthermore, if  $\mathcal{R}_0 = 1$ , then  $\lambda_f^{**} = 0$  (which



corresponds to the DFE,  $\mathcal{E}_0$ ). For  $\mathcal{R}_0 < 1$ ,  $\lambda_f^{**} < 0$  (which is biologically meaningless). These results are summarized below.

**Theorem 3.3.** *The basic model (3.25) 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 basic model (3.25) will now be explored, for a special case with no disease-induced mortality for the females (i.e.,  $\delta_f = 0$ ). Further, it is convenient to define  $\Delta = \mu_f \mu_m (D_1 D_2 - D_3)$ , where,

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

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 3.4.** *The EEP ( $\mathcal{E}_1$ ) of the model (3.25) is LAS if  $\mathcal{R}_0 > 1$ ,  $\delta_f = 0$  and  $\Delta \neq 0$ .*

The proof of Theorem 3.4, based on using a Krasnoselskii argument [31, 32, 76], is given in Appendix C. The epidemiological implication of Theorem 3.4 is that, for the basic model

(3.25) 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 (3.25) 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 basic model (3.25))

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

with,

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

**Theorem 3.5.** *The unique EEP ( $\mathcal{E}_1$ ) of the basic model (3.25), with  $\theta_m = \theta_f = 0$ , is GAS in  $\mathcal{D} \setminus \mathcal{D}_0$  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 3.5, based on using a nonlinear Lyapunov function of Goh-Volterra type, is given in Appendix D. Theorem 3.5 shows that, for the case of the model (3.25) where individuals with persistent HPV infection do not transmit infection (i.e.,  $\theta_m = \theta_f = 0$ ), the disease 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  $t$ . Figure 3.3 depicts solution profiles of the basic model, showing convergence to the unique EEP ( $\mathcal{E}_1$ ) for the case when  $\mathcal{R}_1 > 1$  (in agreement with Theorem 3.5). 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 model (3.25) suggest that the conditions always hold (all the extensive simulations carried out support this claim).

### 3.5 Uncertainty and Sensitivity Analysis

The basic model (3.25) contains 27 parameters. Hence, uncertainties are expected to 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 model (3.25), a detailed uncertainty analysis, using Latin Hypercube Sampling (LHS) [7, 39, 40, 41, 57, 58], is carried out.

As introduced in Chapter 1, the practical implementation of the LHS technique entails defining each parameter of the basic model (3.25) as a distribution, and, subsequently, generating numerous LHS runs for a given output (which, in this chapter, is the basic reproduction threshold,  $\mathcal{R}_0$ ) [7, 39, 40, 41, 57, 58]. For the purpose of this thesis, and in line with [25, 58, 68], each parameter of the basic model (3.25) is assumed to follow a (continuous) uniform distribution (see Definition 2.22) [16]. Furthermore, sensitivity analysis, using Partial Rank Correlation Coefficients (PRCC) [39, 40, 41], is carried out to determine the key parameters of the model that affect the disease transmission dynamics (i.e., parameters of the basic model (3.25) that most affect the value of the response function,  $\mathcal{R}_0$ ).

Figure 3.4 depicts the box plots of the basic reproduction number ( $\mathcal{R}_0$ ), as a function of the 1000 LHS runs ( $N_R = 1000$ ) carried out, using the baseline parameter values and ranges in Table 3.2. For any given number of runs (i.e., for any value of  $N_R$ ), 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  $\mathcal{R}_0$  [58]. Values for  $\mathcal{R}_0$  plotted beyond the whiskers are classified as outliers. Figure 3.4 shows the distribution of  $\mathcal{R}_0$  lies in the range  $\mathcal{R}_0 \in [2.80, 4.95]$ , with a mean of  $\mathcal{R}_0 = 3.875$  (which is in line with the  $\mathcal{R}_0$  values reported in [30, 55]). Since the distribution of  $\mathcal{R}_0$  exceeds unity, it follows (from Theorem 3.4) that the disease will persist in the population. Thus, this study shows that until an intervention strategy (such as routine Pap screening of sexually-active females) that can reduce (and maintain)  $\mathcal{R}_0$  to a value less than unity is used in the

community, HPV (and associated dysplasia) will always persist in the population.

The effect of HPV transmission by individuals with persistent HPV infection on the cumulative number of new HPV cases for females is assessed by simulating the model (3.25) using the different values of the associated modification parameter for the infectiousness of individuals with persistent infection, relative to those in the  $I_f$  class (denoted by  $\theta_f$ ). The results obtained, depicted in Figure 3.5A, show a marked increase in the cumulative number of new HPV cases with increasing values of the parameter  $\theta_f$ .

Furthermore, it is shown (Figure 3.5B) that HPV transmission by males with persistent infection induces a significant indirect effect on the cumulative number of new female infections (i.e., HPV transmission by males with persistent infection results in the corresponding increase in the cumulative number of new HPV cases in females). Similar results are obtained for the cumulative mortality for females (Figure 3.6) and cumulative new cases for males (Figure 3.7). In other words, these simulations show that HPV transmission by individuals with persistent HPV infection significantly increases the HPV burden (and, by extension, increases the incidence of cervical cancer in females and HPV-related cancers in males) in the community. Furthermore, HPV transmission by those with persistent infection induces an indirect negative effect on the HPV burden of individuals of the opposite gender.

Table 3.3 shows the PRCC values of the parameters of the model (3.25), 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 ( $\mu_f$  and  $\mu_m$ ), the infection probability for females and males ( $\beta_f$  and  $\beta_m$ ), the recruitment rate of new sexually-active individuals ( $\pi_f$  and  $\pi_m$ ), modification parameter for the infectiousness of individuals with persistent infection, relative to those in the corresponding symptomatic class ( $\theta_f$  and  $\theta_m$ ) and the natural recovery rate of infected females ( $r_{f1}$ ). The effect of the aforementioned ten dominant (PRCC-ranked) parameters is further assessed by simulating the basic model (3.25) for the following two scenarios:

- (i) the baseline value of each of the top-ten PRCC-ranked parameters in Table 3.3 is

increased by 10%;

- (ii) the baseline value of each of the top-ten PRCC-ranked parameters in Table 3.3 is decreased by 10%.

It follows from Figure 3.8 that such 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). This figure clearly shows the sensitivity of the outcome of the model's simulations on these parameters. Figures 3.9 and 3.10 also show similar sensitivities of these top-ranked parameters on the cumulative number of cervical cancer (for females) and HPV-related cancers (for males) cases, respectively.

## 3.6 Summary of Chapter

A new deterministic model for the transmission dynamics of HPV (and related dysplasia) in a community is designed and rigorously analyzed in this chapter. Some of the main mathematical and numerical simulation results obtained are summarized below:

- i) The disease-free equilibrium of the basic model (3.25) 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 basic model (3.25) 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 (which is addressed in Chapter 4).
- ii) The basic model (3.25) 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) Numerical simulations of the basic model show that HPV transmission by individuals with persistent infection significantly increases the HPV burden (hence, increase the incidence of cervical cancer in females and HPV-related cancers in males) in the community. Furthermore, HPV transmission by males (females) with persistent HPV infection induces an indirect negative effect on the HPV burden of males (females).
- iv) It is determined (based on the detailed uncertainty and sensitivity analyses carried out in Section 3.5) 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 ( $\mu_f$  and  $\mu_m$ );
  - (c) the infection probability for females and males ( $\beta_f$  and  $\beta_m$ );
  - (d) the recruitment rate of new sexually-active individuals for females and males ( $\pi_f$  and  $\pi_m$ );
  - (e) the modification parameters for the infectiousness of individuals with persistent infection (in relation to those in the respective symptomatic class) ( $\theta_f$  and  $\theta_m$ );
  - (f) the natural recovery rate of infected females ( $r_{f1}$ ).

Items (i) to (iv) above provide answers to Questions 1, 2 and 3 (Part (a)) raised in Section 1.3.

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 3.1: Description of the state variables of the basic HPV model (3.25).

Parameter	Description	Baseline Value <i>per year</i>	Ranges	Ref.
$\pi_f(\pi_m)$	Recruitment rate of new sexually-active females (males)	10000	[9000,11000]	[66]
$\frac{1}{\mu_f}(\frac{1}{\mu_m})$	Average duration of sexual activity for females (males)	65	[59.5,71.5]	[9]
$\beta_m(\beta_f)$	HPV infection probability from males to females (females to males)	0.8/contact (0.7/contact)	[0.72,0.88] [0.63,0.77]	[30]
$c_m(c_f)$	Average number of male (female) sexual partners for females (males) per unit time	2 ( $2 \frac{N_f}{N_m}$ )	[1.8,2.2]	[66]
$\sigma_f(\sigma_m)$	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]	[30]
$\alpha_f(\alpha_m)$	Progression rate from HPV to CIN (INM) for females (males)	0.1	[0.09,0.11]	[29]
$g_f(g_m)$	Progression rate from CIN (INM) to cancer for females (males)	0.08	[0.079, 0.081]	[29]
$r_{f1}(r_{m1})$	Natural recovery rate of infected females (males)	0.495 (0.9)	[0.446,0.545] [0.89, 0.91]	[30]
$r_{f2}(r_{m2})$	Natural recovery rate of females (males) with persistent HPV infection	0.1	[0.09,0.11]	[55]
$r_{f3}(r_{m3})$	Natural recovery rate of females with CIN (males with INM)	0.05	[0.045,0.055]	[60]
$r_{f4}(r_{m4})$	Natural recovery rate of females with cervical cancer (males with HPV-related cancer)	0.76	[0.68,0.84]	[29]
$\theta_f(\theta_m)$	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]	[55]
$\delta_f$	Cancer-induced mortality rate for females	0.01	[0.009,0.011]	[55]

Table 3.2: Description of parameters of the basic HPV model (3.25).  
Notation: "A" denotes "assumed".



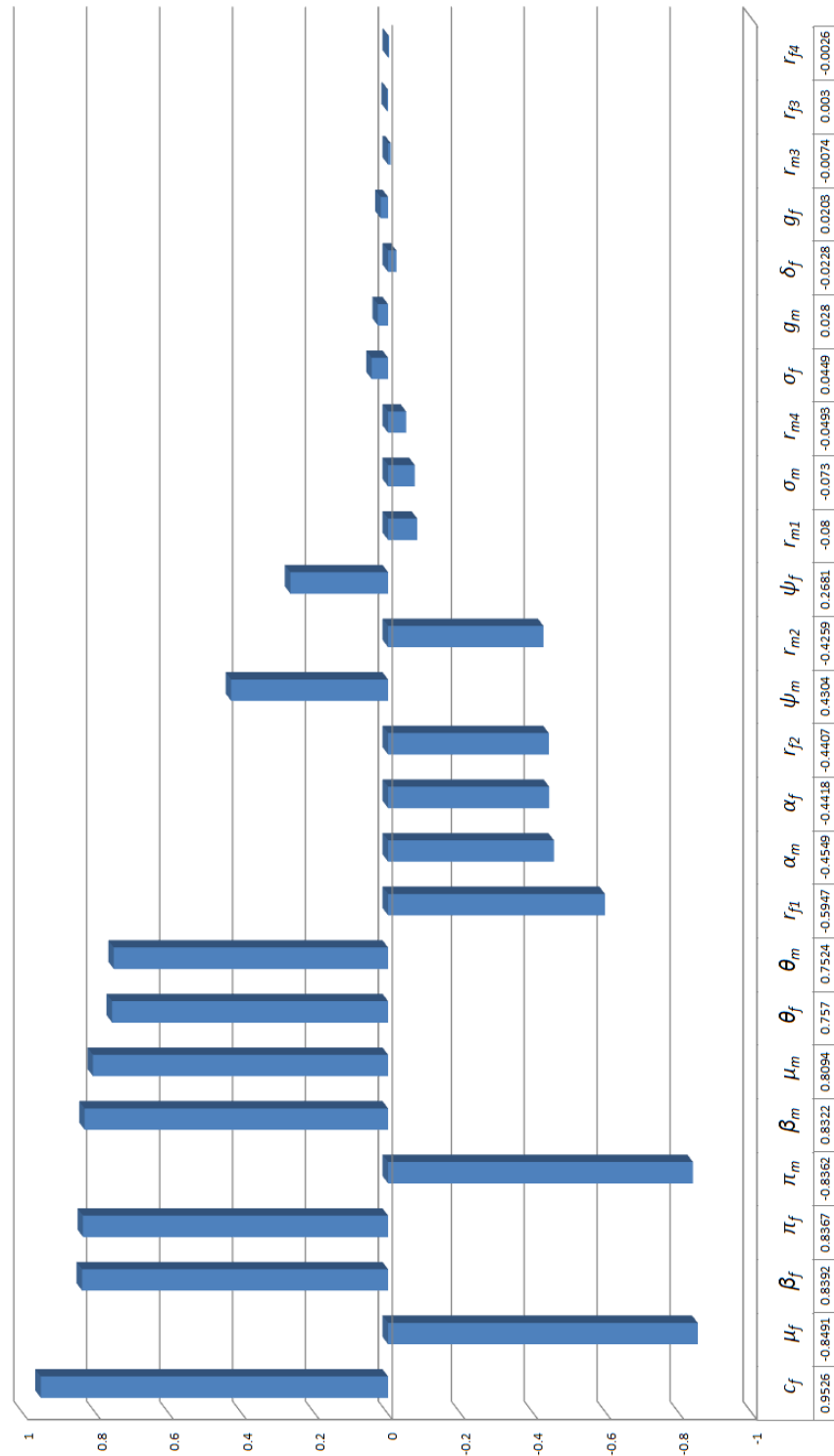


Table 3.3: PRCC values of the parameters of the basic model (3.25) using  $\mathcal{R}_0$  as output. Baseline parameter values and ranges used are as given in Table 3.2.

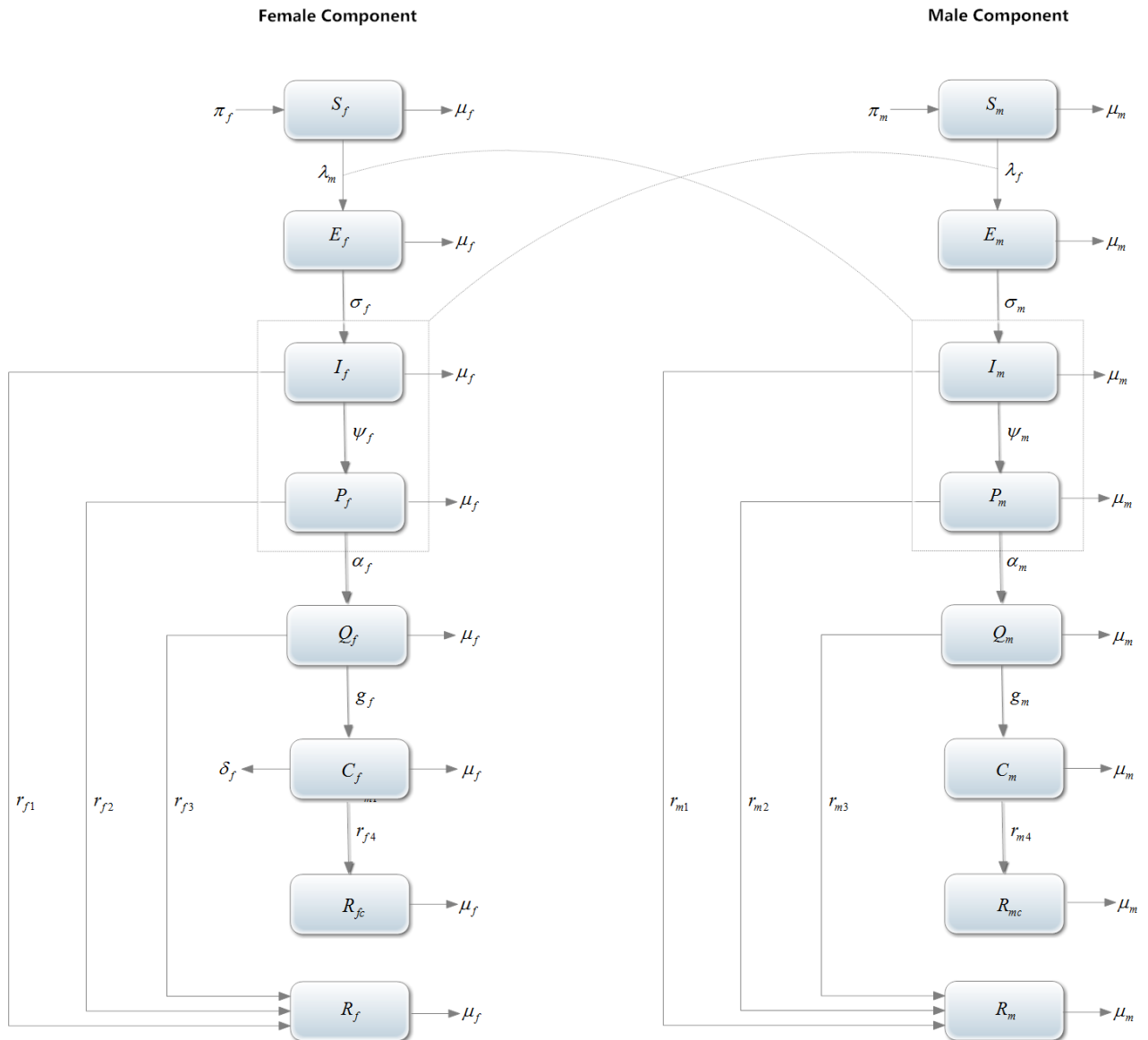


Figure 3.1: Schematic diagram of the basic HPV model (3.25).

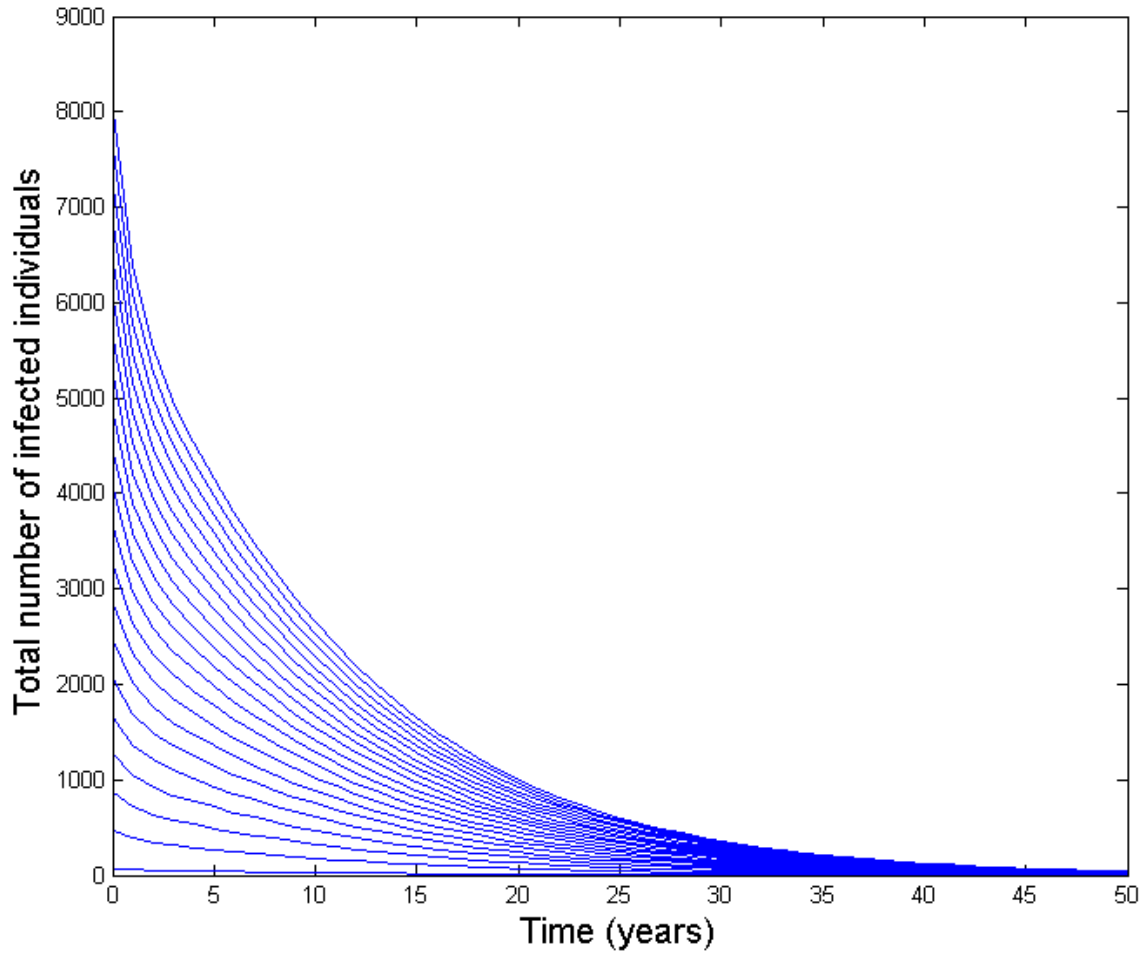


Figure 3.2: Solution profiles of the basic model (3.25), showing the total number of HPV-infected individuals (females and males) as a function of time using various initial conditions. Parameter values used are as given in Table 3.2, with  $c_f = 1$ ,  $\beta_f = 0.2$  and  $\beta_m = 0.2$  (so that,  $\mathcal{R}_0 = 0.5159 < 1$ ).

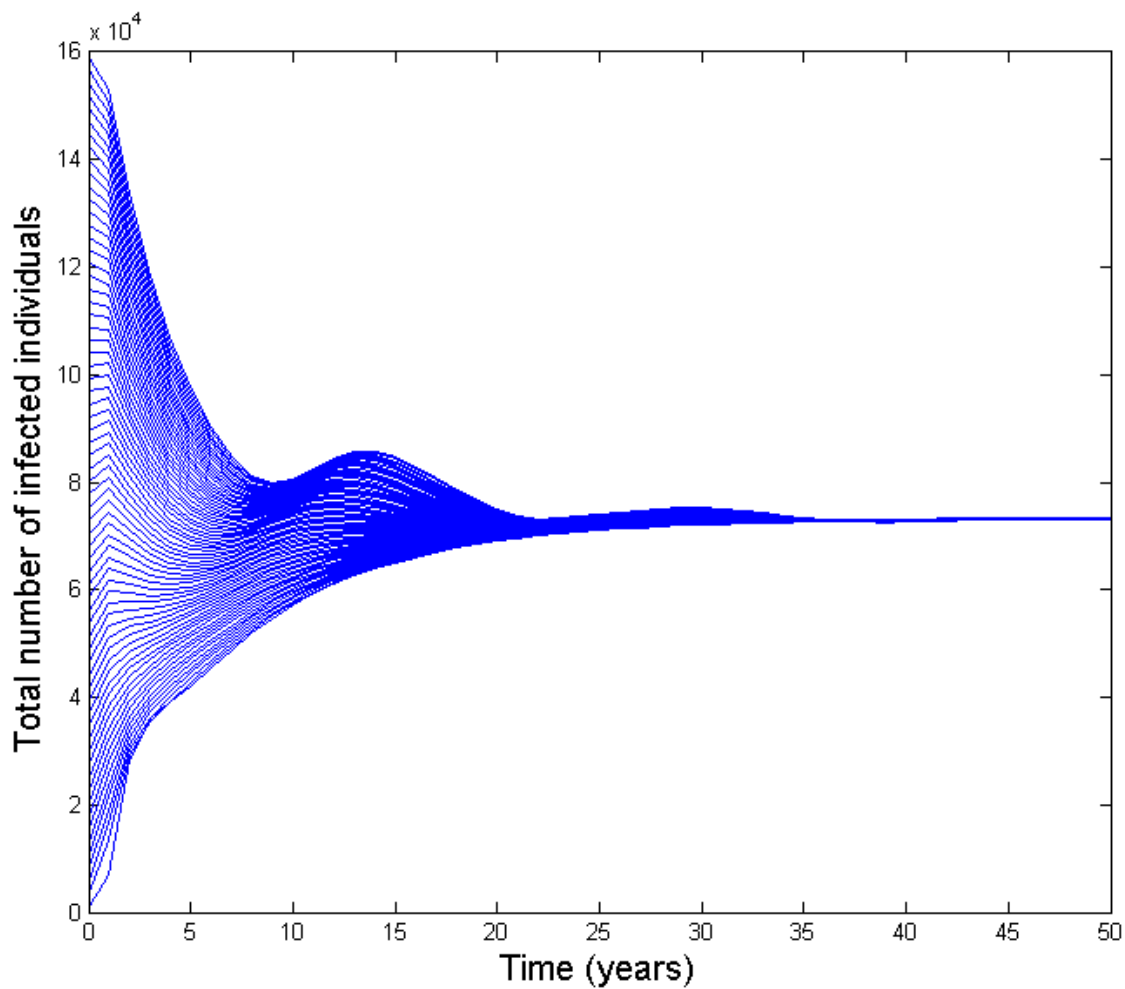


Figure 3.3: Solution profiles of the basic model (3.25), showing the total number of HPV-infected individuals (females and males) with  $\theta_m = \theta_f = 0$  as a function of time using various initial conditions. Parameter values used are as given in Table 3.2, with  $c_f = 3$ ,  $\beta_f = 2.5$  and  $\beta_m = 2.5$  (so that,  $\mathcal{R}_1 = 6.2549 > 1$ ).

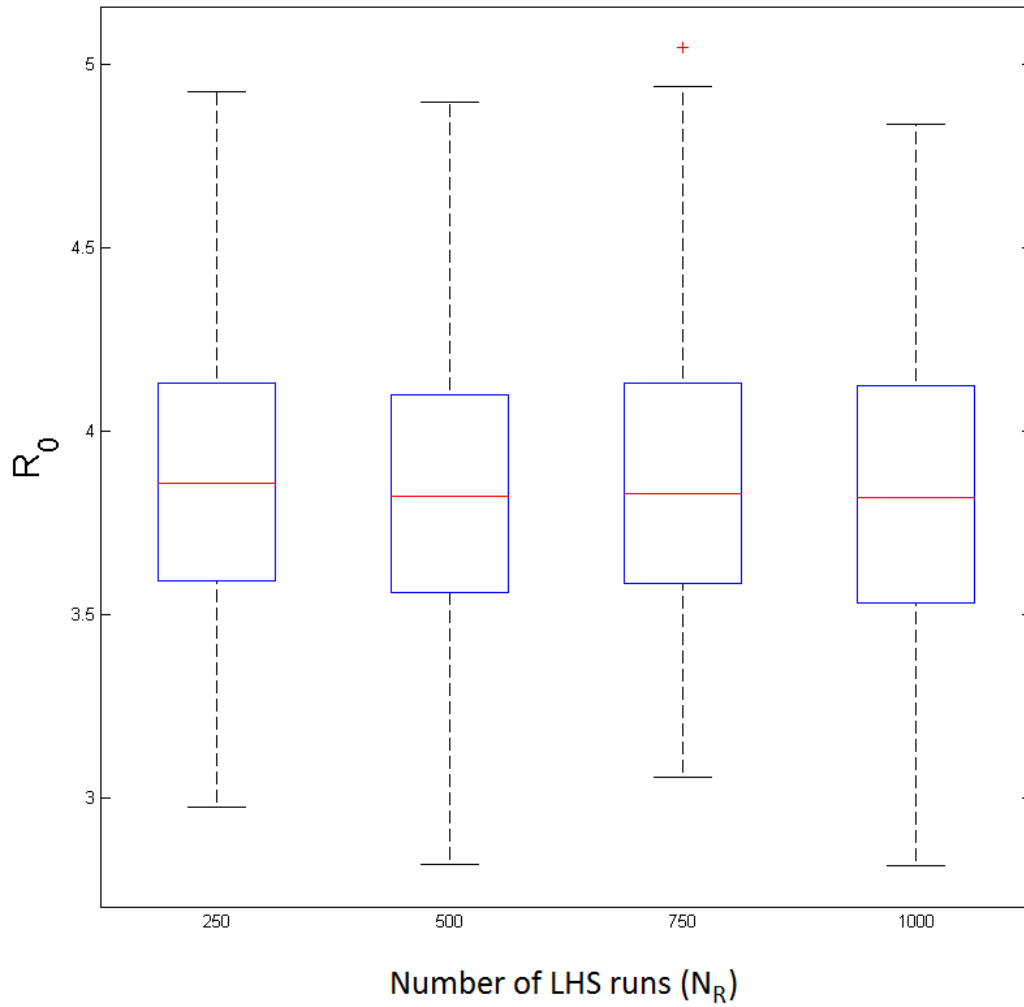


Figure 3.4: Box plot of the basic reproduction number ( $\mathcal{R}_0$ ) as a function of the number of runs ( $N_R$ ) for the basic model (3.25), using the baseline parameter values and ranges given in Table 3.2.

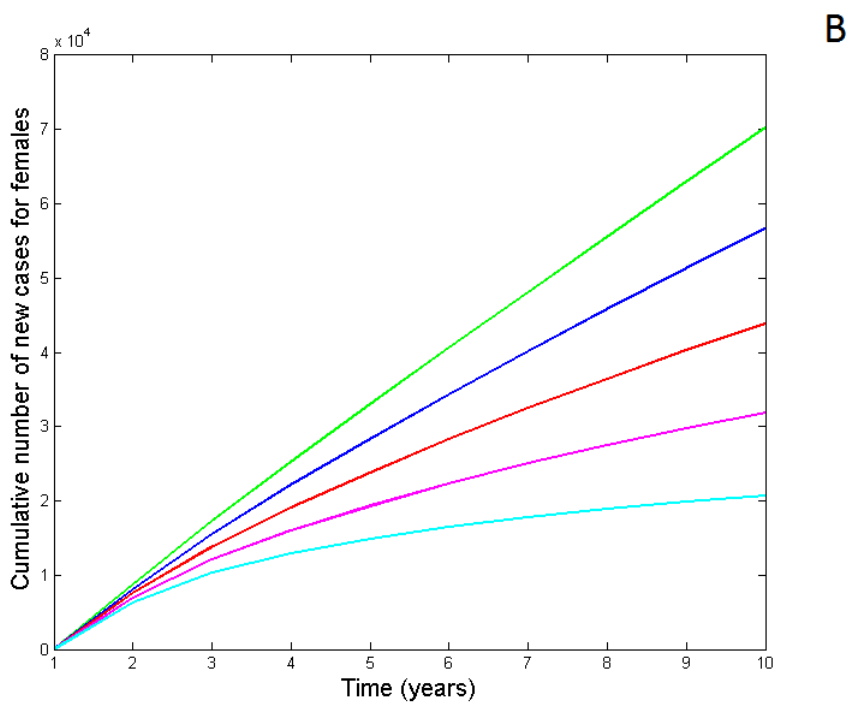
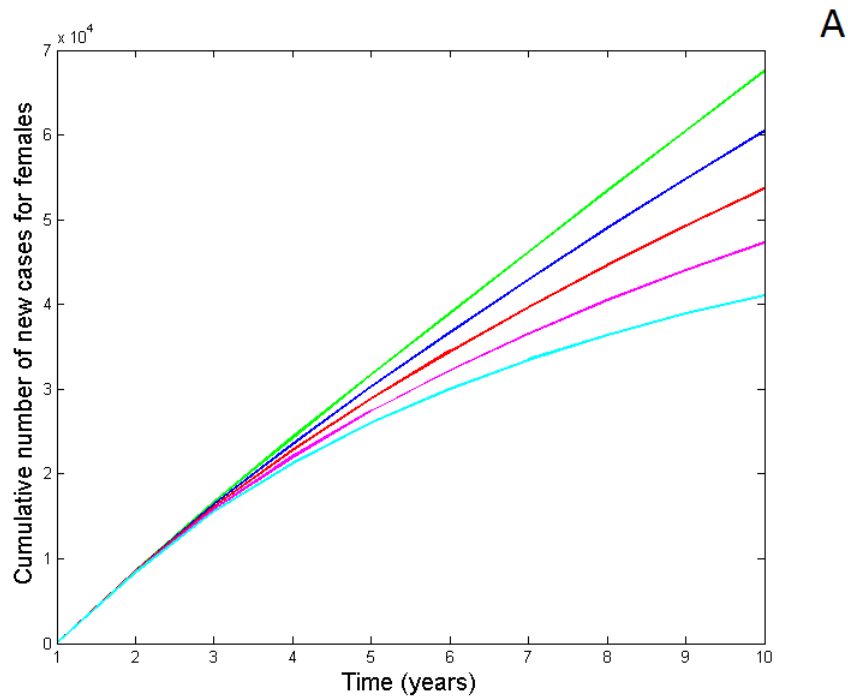


Figure 3.5: Simulations of the basic model (3.25), showing the cumulative number of new HPV cases for females, as a function of time, for various values of  $\theta_f$  and  $\theta_m$ . Parameter values used are as given in Table 3.2 with (A) green color:  $\theta_f = 1$ ; blue color:  $\theta_f = 0.75$ ; red color:  $\theta_f = 0.5$ ; magenta color:  $\theta_f = 0.25$ ; cyan color:  $\theta_f = 0$ . (B) green color:  $\theta_m = 1$ ; blue color:  $\theta_m = 0.75$ ; red color:  $\theta_m = 0.5$ ; magenta color:  $\theta_m = 0.25$ ; cyan color:  $\theta_m = 0$ .

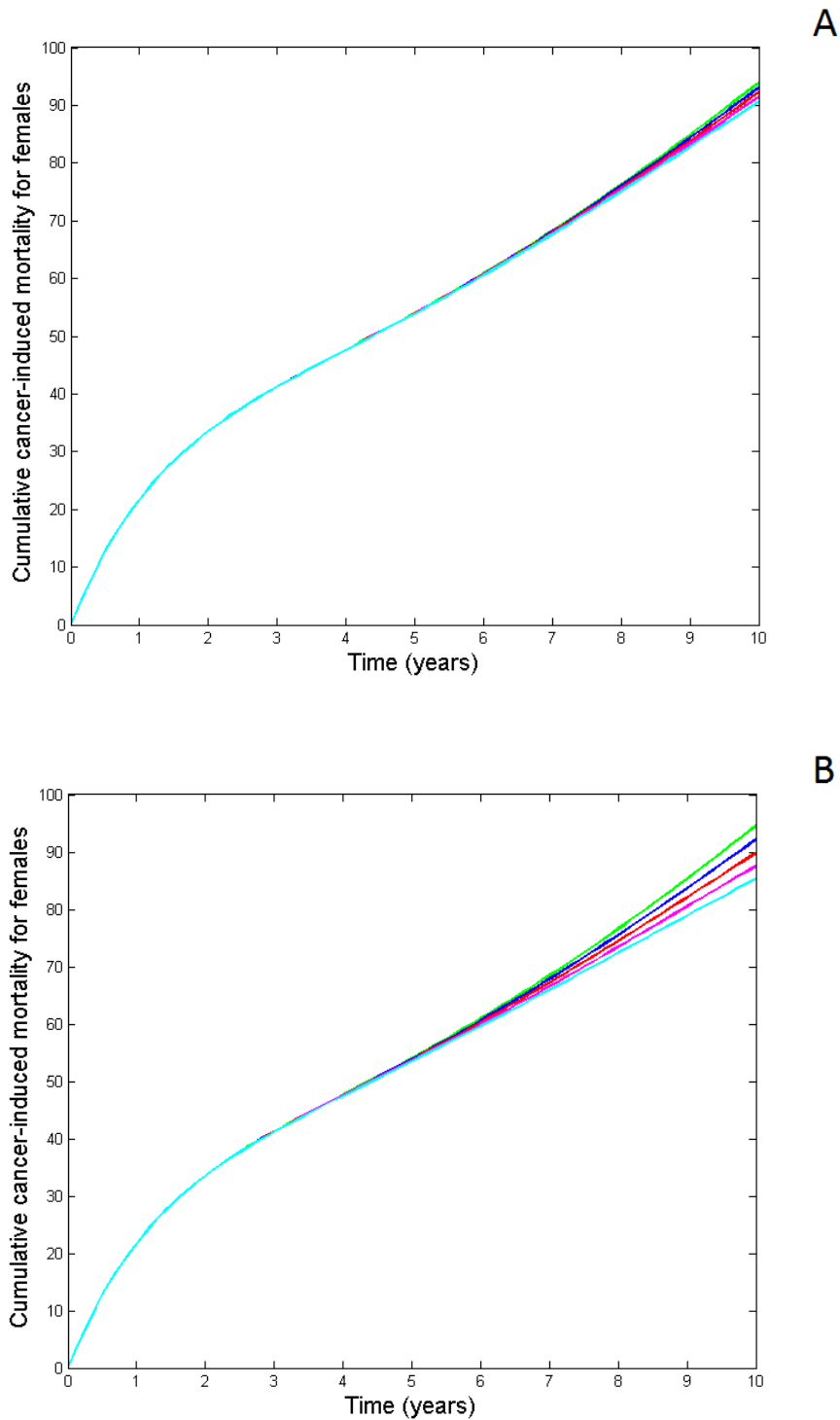


Figure 3.6: Simulations of the basic model (3.25), showing the cumulative number of cancer-induced mortality for females, as a function of time, for various values of  $\theta_f$  and  $\theta_m$ . Parameter values used are as given in Table 3.2 with (A) green color:  $\theta_f = 1$ ; blue color:  $\theta_f = 0.75$ ; red color:  $\theta_f = 0.5$ ; magenta color:  $\theta_f = 0.25$ ; cyan color:  $\theta_f = 0$ . (B) green color:  $\theta_m = 1$ ; blue color:  $\theta_m = 0.75$ ; red color:  $\theta_m = 0.5$ ; magenta color:  $\theta_m = 0.25$ ; cyan color:  $\theta_m = 0$ .

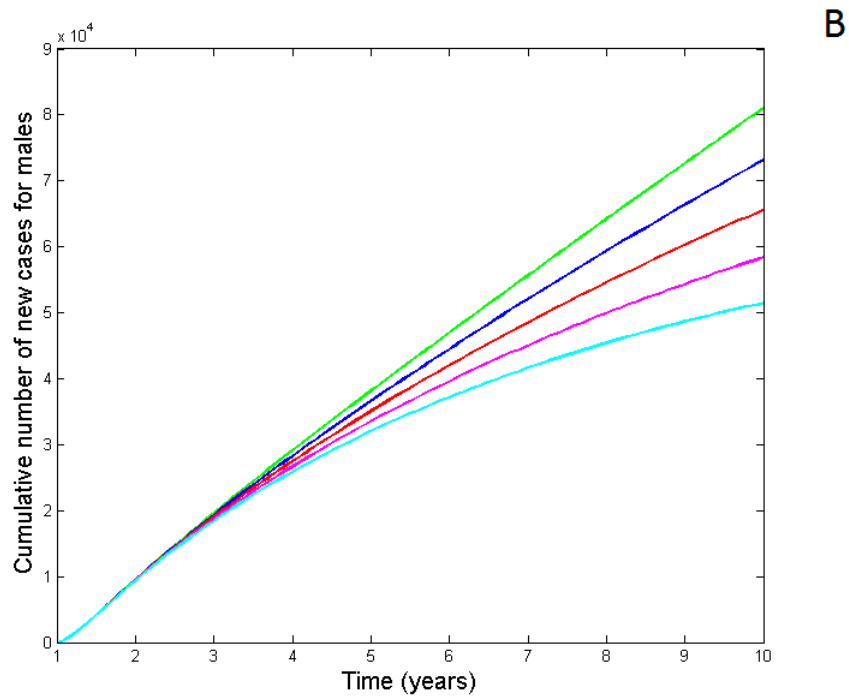
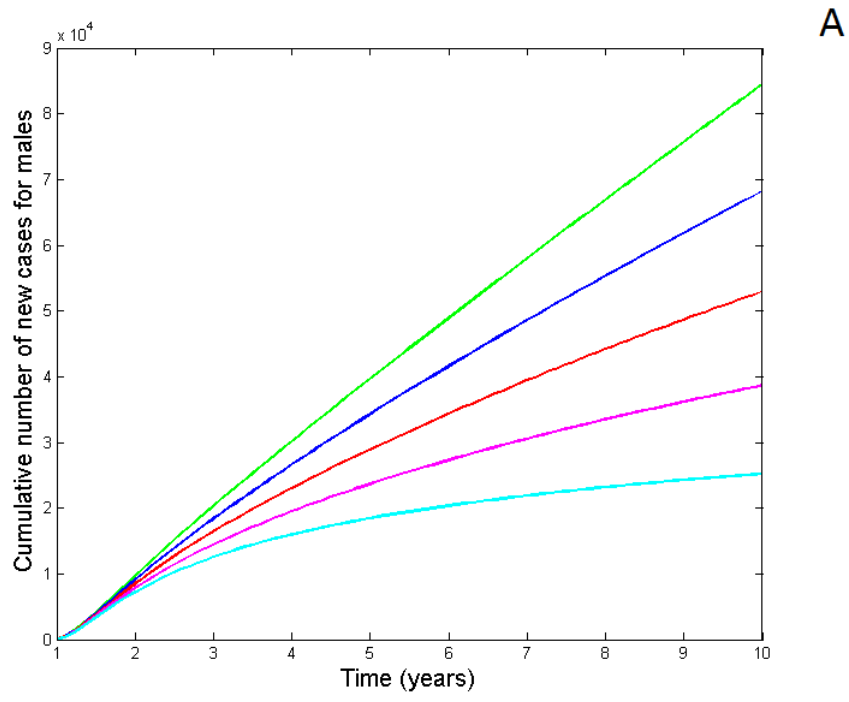


Figure 3.7: Simulations of the basic model (3.25), showing the cumulative number of new HPV cases for males, as a function of time, for various values of  $\theta_m$  and  $\theta_f$ . Parameter values used are as given in Table 3.2 with (A) green color:  $\theta_f = 1$ ; blue color:  $\theta_f = 0.75$ ; red color:  $\theta_f = 0.5$ ; magenta color:  $\theta_f = 0.25$ ; cyan color:  $\theta_f = 0$ . (B) green color:  $\theta_m = 1$ ; blue color:  $\theta_m = 0.75$ ; red color:  $\theta_m = 0.5$ ; magenta color:  $\theta_m = 0.25$ ; cyan color:  $\theta_m = 0$ .



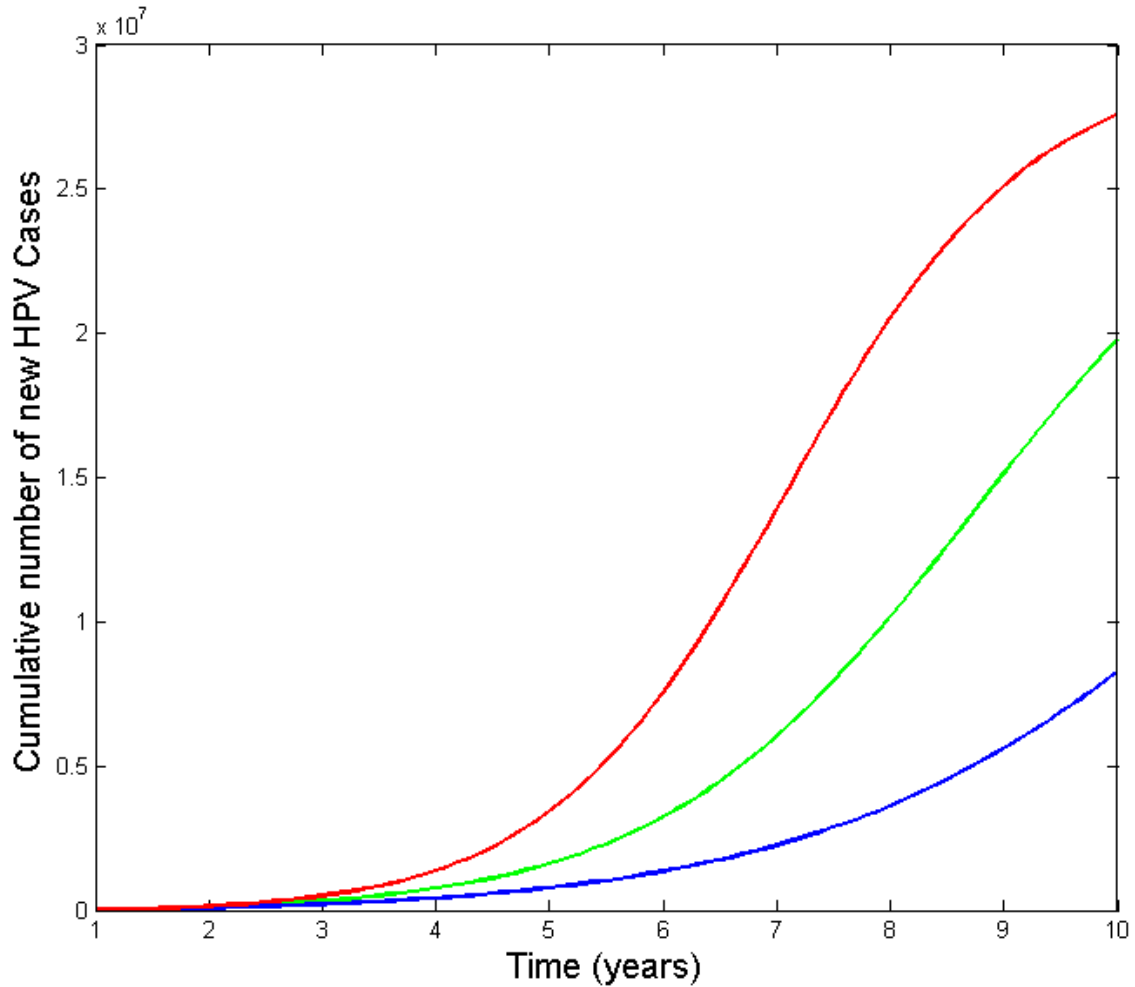


Figure 3.8: Simulations of the basic model (3.25), showing the cumulative number of new HPV cases (for females and males) as a function of time. Parameter values used are as given in Table 3.2 (with the top ten ranked parameters modified accordingly). Green color: baseline parameters as in Table 3.2 ( $\mathcal{R}_0 = 3.8607$ ). Blue color: top-ten PRCC-ranked parameters in Table 3.3 decreased by 10% ( $\mathcal{R}_0 = 2.9771$ ). Red color: top-ten PRCC-ranked parameters in Table 3.3 increased by 10% ( $\mathcal{R}_0 = 4.8612$ ).

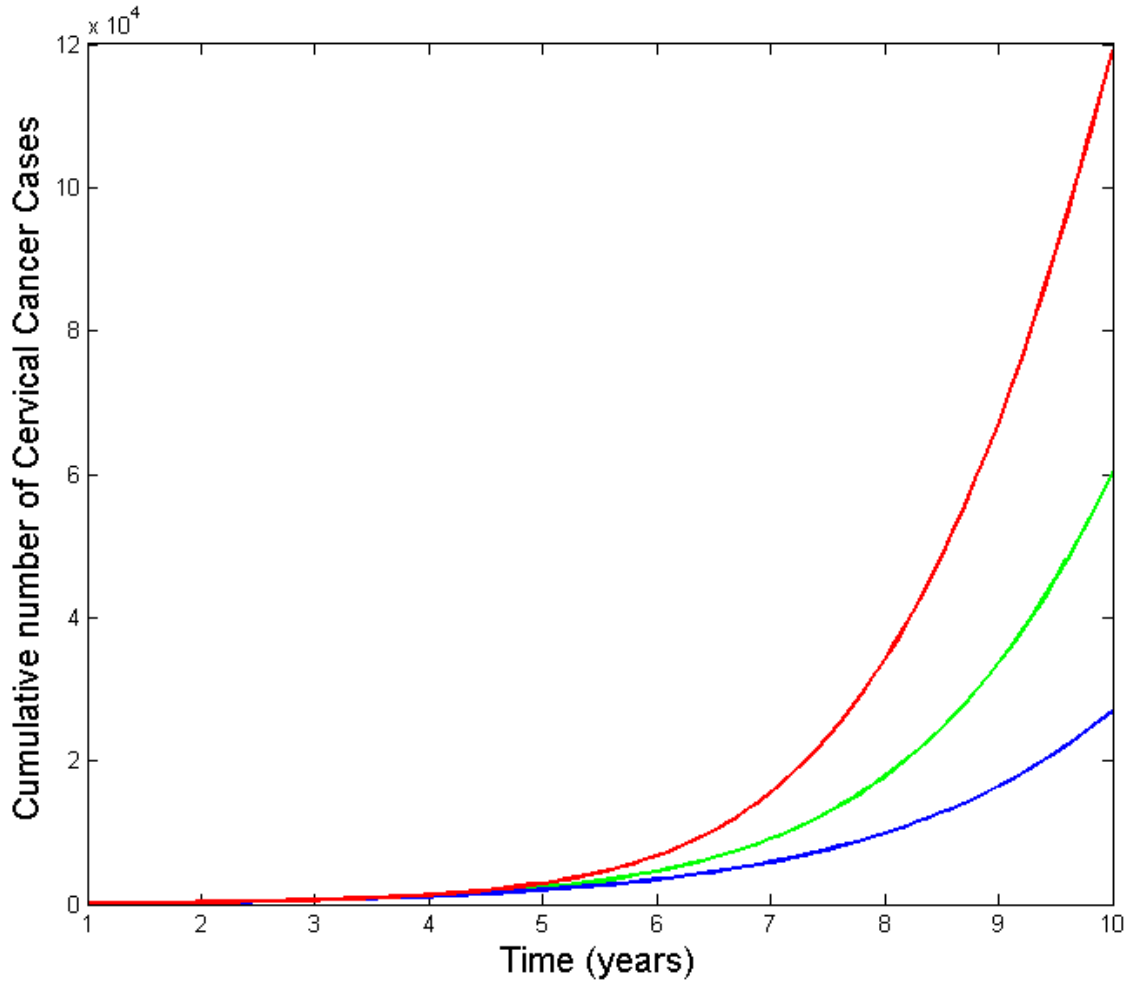


Figure 3.9: Simulations of the basic model (3.25), showing the cumulative number of cervical cancer cases in females, as a function of time. Parameter values used are as given in Table 3.2 (with the top ten PRCC-ranked parameters modified accordingly). Green color: baseline parameters as in Table 3.2 ( $\mathcal{R}_0 = 3.8607$ ). Blue color: top-ten PRCC-ranked parameters in Table 3.3 decreased by 10% ( $\mathcal{R}_0 = 2.9771$ ). Red color: top-ten PRCC-ranked parameters in Table 3.3 increased by 10% ( $\mathcal{R}_0 = 4.8612$ ).

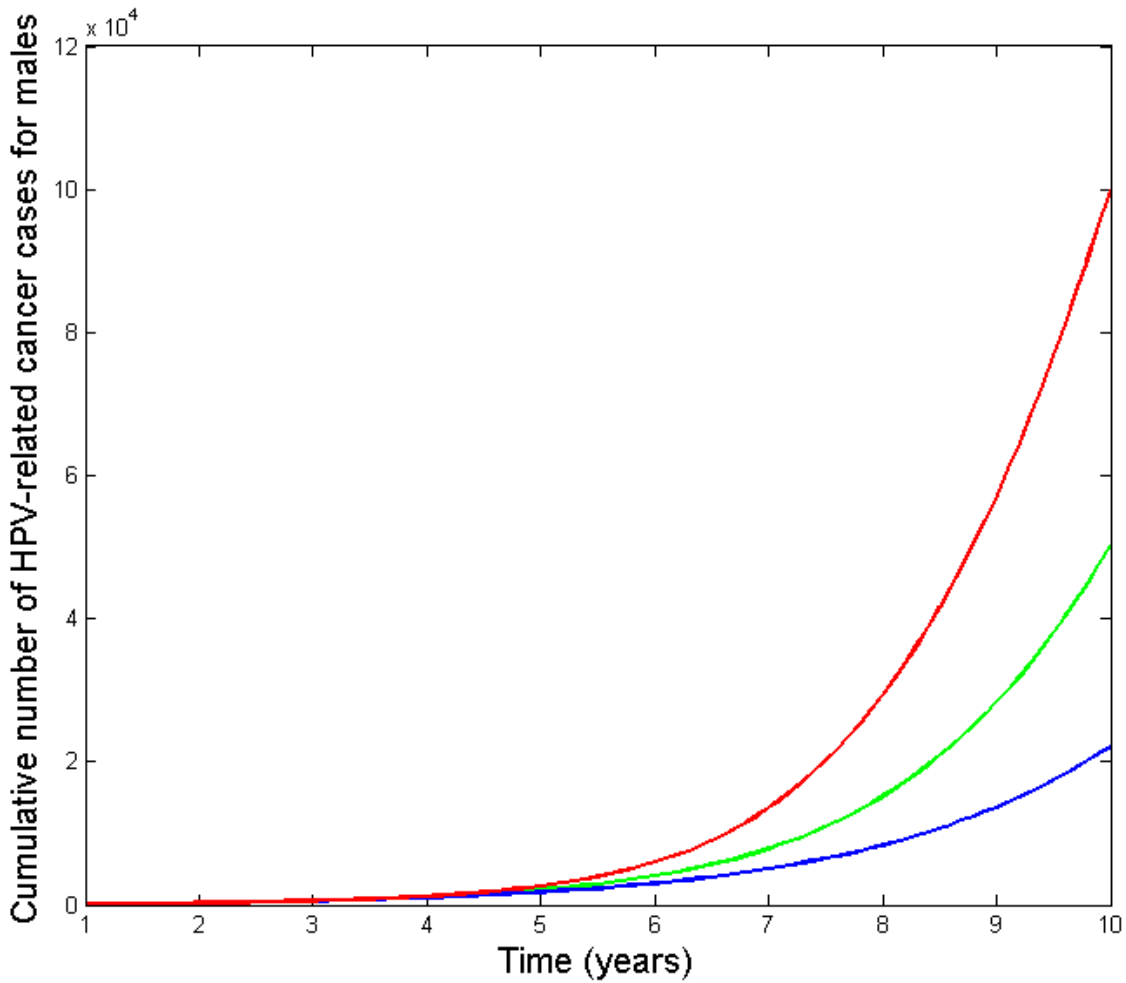


Figure 3.10: Simulations of the basic model (3.25), showing the cumulative number of HPV-related cancer cases for males as a function of time. Parameter values used are as given in Table 3.2 (with the top ten PRCC-ranked parameters modified accordingly). Green color: baseline parameters as in Table 3.2 ( $\mathcal{R}_0 = 3.8607$ ). Blue color: top-ten PRCC-ranked parameters in Table 3.3 decreased by 10% ( $\mathcal{R}_0 = 2.9717$ ). Red color: top-ten PRCC-ranked parameters in Table 3.3 increased by 10% ( $\mathcal{R}_0 = 4.8612$ ).

# Chapter 4

## Model with Pap Screening

### 4.1 Introduction

In this Chapter, the basic HPV transmission model developed in Chapter 3 will be extended and used to assess the community-wide impact of Pap screening on HPV transmission dynamics (and associated dysplasia) in the community. As stated in Chapter 1, the main objective of Pap screening is the early detection of abnormal cells (i.e., pre-cancerous CIN lesions) in females. Once detected, the 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 [15, 63, 69]). 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 [63]. Regular Pap screening is known to significantly decrease the incidence of cervical cancer [35, 54].

Furthermore, owing to the relatively low coverage rates of the two licensed anti-HPV vaccines (as discussed in Chapter 1), as well as their associated side-effects and high costs [13, 54, 77], Pap screening remains the most realistic option for controlling the spread of HPV in most populations (particularly, in developing nations). The aim of this chapter is to develop, and rigorously analyze, a new model for theoretically assessing the impact of

Pap screening on curtailing the spread of HPV (and related dysplasia) in a community. The model to be designed is based on extending the basic model (3.25). The new model will be used to answer Questions 3 (Part (b)), 4 and 5 raised in Section 1.3.

## 4.2 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

$$\begin{aligned}
 N_f(t) &= S_f(t) + E_f(t) + I_f(t) + P_f(t) + L_{fu}(t) + L_{fd}(t) + H_{fu}(t) + H_{fd}(t) \\
 &+ C_{fu}(t) + C_{fd}(t) + R_{fc}(t) + R_f(t).
 \end{aligned} \tag{4.1}$$

Similarly, the total sexually-active male population at time  $t$  (denoted by  $N_m(t)$ ) is subdivided 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,

$$N_m(t) = S_m(t) + E_m(t) + I_m(t) + P_m(t) + L_m(t) + H_m(t) + C_m(t) + R_{mc}(t) + R_m(t). \quad (4.2)$$

It follows from (4.1) and (4.2) 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 4.1; the associated state variables and parameters are tabulated in Tables 4.1, 4.2 and 4.3):

$$\begin{array}{l}
\left. \begin{array}{l}
\frac{dS_f}{dt} = \pi_f + \xi_f R_f - (\lambda_m + \mu_f) S_f, \\
\frac{dE_f}{dt} = \lambda_m S_f - (\sigma_f + \mu_f) E_f, \\
\frac{dI_f}{dt} = \sigma_f E_f - (\psi_f + \mu_f) I_f, \\
\frac{dP_f}{dt} = (1 - b_f) \psi_f I_f + d_{f2} g_f L_{fu} + q_{f4} z_f H_{fu} - (\alpha_f + \mu_f) P_f, \\
\frac{dL_{fu}}{dt} = (1 - k_f) \alpha_f P_f + q_{f2} z_f H_{fu} - (g_f + \mu_f) L_{fu}, \\
\frac{dL_{fd}}{dt} = d_{f3} g_f L_{fu} - (r_1 + \mu_f) L_{fd}, \\
\frac{dH_{fu}}{dt} = [1 - (d_{f1} + d_{f2} + d_{f3})] g_f L_{fu} + j_{f2} \gamma_f C_{fu} - (z_f + \mu_f) H_{fu}, \\
\frac{dH_{fd}}{dt} = q_{f3} z_f H_{fu} - (r_2 + \mu_f) H_{fd}, \\
\frac{dC_{fu}}{dt} = [1 - (q_{f1} + q_{f2} + q_{f3} + q_{f4})] z_f H_{fu} - (\gamma_f + \mu_f + \delta_{fu}) C_{fu}, \\
\frac{dC_{fd}}{dt} = j_{f1} \gamma_f C_{fu} - (r_3 + \mu_f + \delta_{fd}) C_{fd}, \\
\frac{dR_{fc}}{dt} = [1 - (j_{f1} + j_{f2})] \gamma_f C_{fu} + r_3 C_{fd} - \mu_f R_{fc}, \\
\frac{dR_f}{dt} = b_f \psi_f I_f + k_f \alpha_f P_f + d_{f1} g_f L_{fu} + r_1 L_{fd} + q_{f1} z_f H_{fu} + r_2 H_{fd} - (\xi_f + \mu_f) R_f,
\end{array} \right\} \text{Females} \\
\left. \begin{array}{l}
\frac{dS_m}{dt} = \pi_m + \xi_m R_m - (\lambda_f + \mu_m) S_m, \\
\frac{dE_m}{dt} = \lambda_f S_m - (\sigma_m + \mu_m) E_m, \\
\frac{dI_m}{dt} = \sigma_m E_m - (\psi_m + \mu_m) I_m, \\
\frac{dP_m}{dt} = (1 - b_m) \psi_m I_m + d_{m2} g_m L_m + q_{m3} z_m H_m - (\alpha_m + \mu_m) P_m, \\
\frac{dL_m}{dt} = (1 - k_m) \alpha_m P_m + q_{m2} z_m H_m - (g_m + \mu_m) L_m, \\
\frac{dH_m}{dt} = [1 - (d_{m1} + d_{m2})] g_m L_m + j_m \gamma_m C_m - (z_m + \mu_m) H_m, \\
\frac{dC_m}{dt} = [1 - (q_{m1} + q_{m2} + q_{m3})] z_m H_m - (\gamma_m + \mu_m) C_m, \\
\frac{dR_{mc}}{dt} = (1 - j_m) \gamma_m C_m - \mu_m R_{mc}, \\
\frac{dR_m}{dt} = b_m \psi_m I_m + k_m \alpha_m P_m + d_{m1} g_m L_m + q_{m1} z_m H_m - (\xi_m + \mu_m) R_m.
\end{array} \right\} \text{Males}
\end{array} \tag{4.3}$$

The derivation of the equations for the Pap screening model (4.3) is described in Appendix E. The model (4.3) is an extension of the basic HPV transmission model (3.25) developed in Chapter 3, by

- (a) adding Pap screening for females (no Pap screening was considered in the basic model (3.25));
- (b) incorporating multiple CIN ( $L_{fu}$ ,  $L_{fd}$ ,  $H_{fu}$  and  $H_{fd}$ ) and INM ( $L_m$  and  $H_m$ ) stages (a single CIN and INM stage was considered in the basic model (3.25)). Two cancer classes ( $C_{fu}$  and  $C_{fd}$ ) for undetected and detected females with cervical cancer, are also added (only one cancer class for females is considered in the basic model (3.25));
- (c) allowing for HPV transmission by individuals (females and males) in the exposed classes as well as those in the various *intraepithelial neoplasia* stages (these were not considered in the basic model (3.25));
- (d) allowing for the loss of infection-acquired immunity by recovered individuals (these were not considered in the basic model (3.25));
- (e) allowing for 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 (for both females and males) to persistent infection (these were not considered in the basic model (3.25)).

Furthermore, the Pap screening model (4.3) is an extension of many of the HPV models that (also) incorporate Pap screening in the literature, such as those in [2, 3, 10, 28, 30, 55], 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 [10, 28, 30, 55]);



- (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, 10, 28, 30, 55]; it should, however, be stated that three CIN stages for females are included in the model developed in [55]);
- (iii) allowing for the loss of infection-acquired immunity by recovered individuals (this is not included in the models considered in [10, 28, 30, 55]);
- (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, 10, 28, 30, 55]); 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, 10, 28, 30, 55]).

### 4.2.1 Basic properties

The following result can be proved using the approach in Appendix A.

**Theorem 4.1.** *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 Pap screening model (4.3), with positive initial data, will remain positive for all time  $t > 0$ .*

Furthermore, using the approach in Section 3.2.1, the following result can be established for the Pap screening model (4.3).

**Lemma 4.1.** *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 (4.3).

Hence, it is sufficient to study the dynamics of the Pap screening model (4.3) in the invariant region  $\mathcal{D}_s$  [37].

## 4.3 Asymptotic Stability of DFE

### 4.3.1 Local asymptotic stability

The DFE of the Pap screening model (4.3) is given by,

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

Using the next generation operator method (as in Chapter 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  $n$ ),

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

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

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

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

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 [80] that the *effective reproduction number* (i.e., reproduction number of the model in the presence of Pap screening) of the model (4.3) is given by

$$\mathcal{R}_{0s} = \rho(FV^{-1}) = \sqrt{\mathcal{R}_f \mathcal{R}_m}, \quad (4.4)$$

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,

$$\begin{aligned}
A_1 &= \beta_m c_f \pi_f \mu_m (a_3 b_3 c_{10} h_{15} \sigma_m \theta_m + a_3 b_4 c_{11} h_{13} \sigma_m \theta_m - a_3 h_{13} h_{14} h_{15} \sigma_m \theta_m + a_4 b_3 c_9 \eta_m h_{11} h_{15} \\
&\quad - a_4 b_4 c_8 c_{11} \eta_m h_{11} + a_4 c_8 \eta_m h_{11} h_{14} h_{15} + b_3 c_{10} \eta_m h_{11} h_{12} h_{15} + b_4 c_{11} \eta_m h_{11} h_{12} h_{13} \\
&\quad - \eta_m h_{11} h_{12} h_{13} h_{14} h_{15} + a_4 b_3 c_9 h_{15} \sigma_m - a_4 b_4 c_8 c_{11} \sigma_m + a_4 c_8 h_{14} h_{15} \sigma_m + b_3 c_{10} h_{12} h_{15} \sigma_m \\
&\quad + b_4 c_{11} h_{12} h_{13} \sigma_m - h_{12} h_{13} h_{14} h_{15} \sigma_m), \\
A_2 &= \mu_f \pi_m h_{10} h_{11} (a_4 b_3 c_9 h_{15} - a_4 b_4 c_8 c_{11} + a_4 c_8 h_{14} h_{15} + b_3 c_{10} h_{12} h_{15} + b_4 c_{11} h_{12} h_{13} \\
&\quad - h_{12} h_{13} h_{14} h_{15}), \\
B_1 &= \beta_f c_f (a_1 b_1 c_3 h_8 \sigma_f \theta_f + a_1 b_2 c_5 h_4 \sigma_f \theta_f - a_1 h_4 h_6 h_8 \sigma_f \theta_f + a_2 b_1 c_2 \eta_f h_2 h_8 - a_2 b_2 c_1 c_5 \eta_f h_2 \\
&\quad + a_2 c_1 \eta_f h_2 h_6 h_8 + b_1 c_3 \eta_f h_2 h_3 h_8 + b_2 c_5 \eta_f h_2 h_3 h_4 - \eta_f h_2 h_3 h_4 h_6 h_8 + a_2 b_1 c_2 h_8 \sigma_f \\
&\quad - a_2 b_2 c_1 c_5 \sigma_f + a_2 c_1 h_6 h_8 \sigma_f + b_1 c_3 h_3 h_8 \sigma_f + b_2 c_5 h_3 h_4 \sigma_f - h_3 h_4 h_6 h_8 \sigma_f), \\
B_2 &= (a_2 b_1 c_2 h_8 - a_2 b_2 c_1 c_5 + a_2 c_1 h_6 h_8 + b_1 c_3 h_3 h_8 + b_2 c_5 h_3 h_4 - h_3 h_4 h_6 h_8) h_1 h_2,
\end{aligned}$$

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 [80].

**Lemma 4.2.** *The DFE,  $\mathcal{E}_{0s}$ , of the Pap screening model (4.3) is LAS if  $\mathcal{R}_{0s} < 1$ , and unstable if  $\mathcal{R}_{0s} > 1$ .*

As in Chapter 3, the epidemiological consequence of Lemma 4.2 is that the use of Pap screening in the community could lead to the effective control (or elimination) of HPV (when  $\mathcal{R}_{0s} < 1$ ) if the initial sizes of the sub-populations of the Pap screening model (4.3) are in the basin of attraction of the DFE ( $\mathcal{E}_{0s}$ ). 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 [37].

### 4.3.2 Global asymptotic stability

Consider the Pap screening model (4.3). The global asymptotic stability property of its DFE ( $\mathcal{E}_{0s}$ ) is established below.

**Theorem 4.2.** *The DFE,  $\mathcal{E}_{0s}$ , of the Pap screening model (4.3) is GAS in  $\mathcal{D}_s$  whenever  $\mathcal{R}_{0s} < 1$ .*

*Proof.* The proof of Theorem 4.2 is given in Appendix F. □

The epidemiological implication of Theorem 4.2 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 down (and maintain) the associated effective reproduction threshold ( $\mathcal{R}_{0s}$ ) to a value less than unity. Figure 4.2 shows solution profiles of the model (4.3) converging to the DFE ( $\mathcal{E}_{0s}$ ) when  $\mathcal{R}_{0s} < 1$  (in line with Theorem 4.2).

## 4.4 Uncertainty and Sensitivity Analysis

As in Chapter 3, the effect of uncertainties in the estimates of the parameter values of the Pap screening model (4.3) is accounted for using Latin Hypercube Sampling (based on the baseline parameter values and ranges tabulated in Tables 4.2 and 4.3). Furthermore, sensitivity analysis is carried out using PRCC.

Figure 4.3 depicts the box plots of the effective reproduction number ( $\mathcal{R}_{0s}$ ), as a function of the LHS runs carried out ( $N_R = 1000$ ), from which it is evident that the distribution of  $\mathcal{R}_{0s}$ , for the Pap screening model (4.3), lies in the range  $\mathcal{R}_{0s} \in [1.45, 2.70]$  (which is in line with those reported in [22, 30, 55]). Thus, although Pap screening reduces the range of the basic reproduction number ( $\mathcal{R}_0$ ) of the basic HPV transmission model (3.25) (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  $\mathcal{R}_{0s} > 1$ , and the disease will persist in this case). Table 4.4 depicts the PRCC values of the parameters of the Pap screening model (4.3), from which it is clear that the most dominant parameters (that govern the dynamics of the Pap screening model (4.3), 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 ( $\beta_m$  and  $\beta_f$ ), the recruitment rate of new sexually-active individuals ( $\pi_f$  and  $\pi_m$ ), the average duration of sexual activity ( $\mu_f$  and  $\mu_m$ ) and the transition rate out of the  $I_f(I_m)$  class ( $\psi_f(\psi_m)$ ).

The effect of the aforementioned eleven dominant (PRCC-ranked) parameters is further assessed by simulating the Pap screening model (4.3) for the following two scenarios:

- (i) the baseline value of each of the top-eleven PRCC-ranked parameters in Table 4.4 is increased by 10%;
- (ii) the baseline value of each of the top-eleven PRCC-ranked parameters in Table 4.4 is decreased by 10%.

It follows from Figure 4.4 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 4.5 and 4.6 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 in the pre-cancerous stages (both CIN and INM) on the dynamics of HPV is assessed by simulating the Pap screening model (4.3) in the presence, and absence, of such transmission. Figure 4.7 shows that HPV transmission by individuals with CIN and INM increases (in the long run) the cumulative number of

HPV cases. Thus, these simulations suggest 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 4.8. 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 4.2 and 4.3 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 4.2).

Finally, the effect of Pap screening on the cumulative number of cervical cancer cases is assessed by simulating the model (4.3) with different values of the fraction of females with CIN detected. Figure 4.9 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.

## 4.5 Summary of Chapter

A new deterministic model for the transmission dynamics of HPV and related cancers in a community, where Pap cytology screening is administered for females, is designed. The resulting 21-dimensional Pap screening model extends numerous other HPV transmission models in the literature by, for instance, incorporating the dynamics of individuals (females and males) in the pre-cancerous (CIN and INM) and cancerous stages. Furthermore, it



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) The disease-free equilibrium of the Pap screening model (4.3) 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 Pap screening could reduce (and maintain) the associated reproduction number ( $\mathcal{R}_{0s}$ ) to a value less than unity.
- ii) The parameters 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 ( $\beta_f$  and  $\beta_m$ );
  - (d) the recruitment rate of new sexually-active individuals ( $\pi_f$  and  $\pi_m$ );
  - (e) the average duration of sexual activity ( $\mu_f$  and  $\mu_m$ );
  - (f) the average duration of sexual activity and the transition rate out of the  $I_f$  ( $I_m$ ) class ( $\psi_f(\psi_m)$ ).
- iii) Numerical simulations of the Pap screening model (4.3) 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.

Items (i) to (iii) provide answers to Questions 3 (Part (b)), 4 and 5 raised in Section 1.3.

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 4.1: Description of the state variables of the Pap screening model (4.3).

Parameter	Description	Baseline Value <i>per year</i>	Ranges	Ref.
$\pi_f(\pi_m)$	Recruitment rate of new sexually-active females (males)	10000	[9000,11000]	[66]
$\frac{1}{\mu_f}(\frac{1}{\mu_m})$	Average duration of sexual activity for females (males)	65	[59.5,71.5]	[9]
$\beta_m(\beta_f)$	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]	[66]
$\xi_f(\xi_m)$	Rate of loss of infection-acquired immunity for females (males)	0.5	[0.45,0.55]	[49]
$\sigma_f(\sigma_m)$	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]	[71]
$\psi_f(\psi_m)$	Transition rate out of the $I_f$ ( $I_m$ ) class for females (males)	0.5	[0.45,0.55]	[30]
$k_f(k_m)$	Fraction of symptomatic females (males) who recover naturally from persistent infection with HPV	0.5	[0.45,0.55]	[55]
$\alpha_f(\alpha_m)$	Transition rate out of the $P_f$ ( $P_m$ ) class for females (males)	0.25	[0.2,0.3]	[29]
$d_{f1}(d_{m1})$	Fraction of infected females (males) with low-grade low-grade CIN (INM ) who recover naturally from HPV infection	0.04	[0.01,0.1]	[55]
$d_{f2}(d_{m2})$	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]	[29]
$d_{f3}$	Fraction of females with low-grade CIN who is detected	0.64	[0.6,0.7]	[55]
$g_f(g_m)$	Transition rate out of $L_{fu}$ ( $L_m$ ) class for females (males)	1.18	[1,1.5]	[55]
$r_1$	Recovery rate of detected females with low-grade CIN	0.13	[0.1,0.2]	[60]
$q_{f1}(q_{m1})$	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]	[55]
$q_{f2}(q_{m2})$	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]	[60]

Table 4.2: Description of parameters of the Pap screening model (4.3). Notation: "A" denotes "assumed".

Parameter	Description	Baseline Value <i>per year</i>	Ranges	Ref.
$q_{f3}$	Fraction of females with high-grade CIN 2/3 who is detected	0.47	[0.4,0.55]	[55]
$q_{f4}(q_{m3})$	Regression rate from the $H_{fu}$ ( $H_m$ ) class to $P_f$ ( $P_m$ ) class	0.17	[0.1,0.25]	[43]
$z_f(z_m)$	Transition rate out of the $H_{fu}$ ( $H_m$ ) class for females (males)	2.08	[2,2.2]	[55]
$r_2$	Recovery rate of detected females with high-grade CIN 2/3	0.13	[0.1,0.2]	[60]
$j_{f1}$	Fraction of females with cervical cancer who is detected	0.62	[0.5,0.7]	[52]
$j_{f2}(j_m)$	Fraction of females (males) with cervical (HPV-related) cancer who revert to the $H_{fu}$ ( $H_m$ ) class	0.23	[0.15,0.3]	[29]
$\gamma_f(\gamma_m)$	Transition rate out of the $C_{fu}$ ( $C_m$ ) class for females (males)	1.31	[1.2,1.4]	[52]
$r_3$	Recovery rate of females with detected cancer	0.75	[0.65,0.85]	[29]
$\eta_f(\eta_m)$	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]	[55]
$\theta_{fh}(\theta_{mh})$	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])	[55]

Table 4.3: Description of parameters of the Pap screening model (4.3) continued. Notation: "A" denotes "assumed".

Parameter	PRCC value	Parameter	PRCC value
$c_f$	0.9123	$r_2$	0.0348
$b_m$	-0.8571	$\sigma_m$	-0.0340
$b_f$	-0.8494	$g_f$	-0.0300
$\beta_f$	0.8133	$k_f$	-0.0274
$\beta_m$	0.8128	$j_{f1}$	-0.0269
$\pi_m$	-0.7373	$\xi_f$	0.0262
$\pi_f$	0.7281	$d_{f3}$	0.0223
$\mu_f$	-0.7258	$\xi_m$	-0.0200
$\mu_m$	0.7098	$r_1$	0.0192
$\psi_m$	-0.6151	$\delta_{fd}$	0.0182
$\psi_f$	-0.5868	$\theta_{fh}$	0.0178
$\alpha_m$	-0.4380	$j_{f2}$	0.0173
$\alpha_f$	-0.4110	$\eta_m$	0.0166
$\theta_m$	0.2732	$d_{f1}$	-0.0152
$\theta_f$	0.2257	$d_{m1}$	-0.0141
$d_{m2}$	0.1199	$\delta_{fu}$	0.0123
$q_{m3}$	0.0986	$z_m$	-0.0101
$\eta_f$	0.0984	$\gamma_m$	-0.0090
$d_{f2}$	0.0773	$z_f$	-0.0068
$g_m$	0.0690	$q_{f3}$	-0.0066
$j_m$	0.0668	$\gamma_f$	0.0059
$q_{f4}$	-0.0563	$\sigma_f$	0.0051
$k_m$	-0.0473	$\theta_{mh}$	-0.0028
$r_3$	0.0472	$q_{f1}$	0.0010
$q_{m1}$	0.0376	$q_{f2}$	0.0007
$q_{m2}$	-0.0355		

Table 4.4: PRCC values of the parameters of the Pap screening model (4.3), using  $\mathcal{R}_{0s}$  as output. Baseline parameter values and ranges used are as given in Tables 4.2 and 4.3.

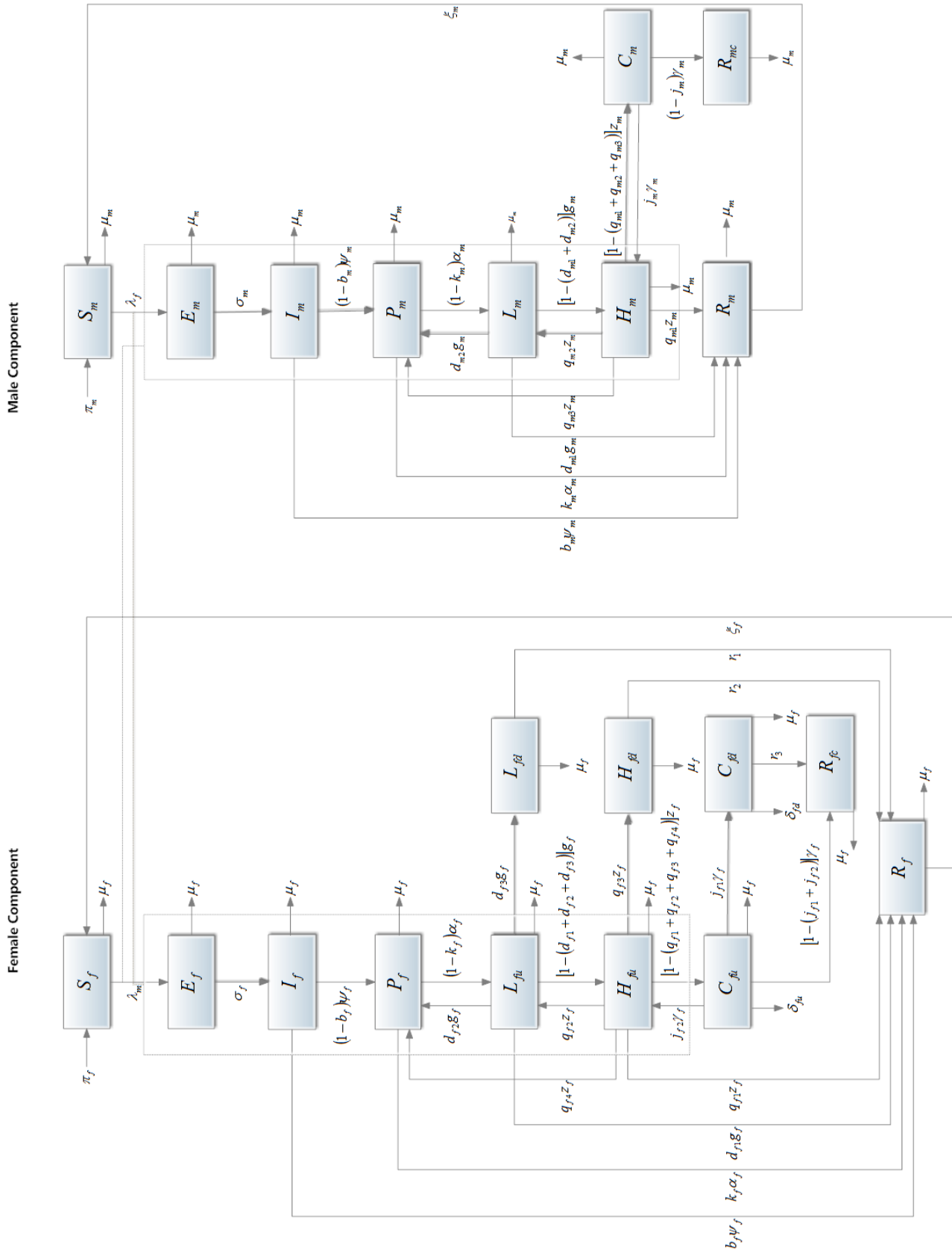


Figure 4.1: Schematic diagram of the Pap screening model (4.3).

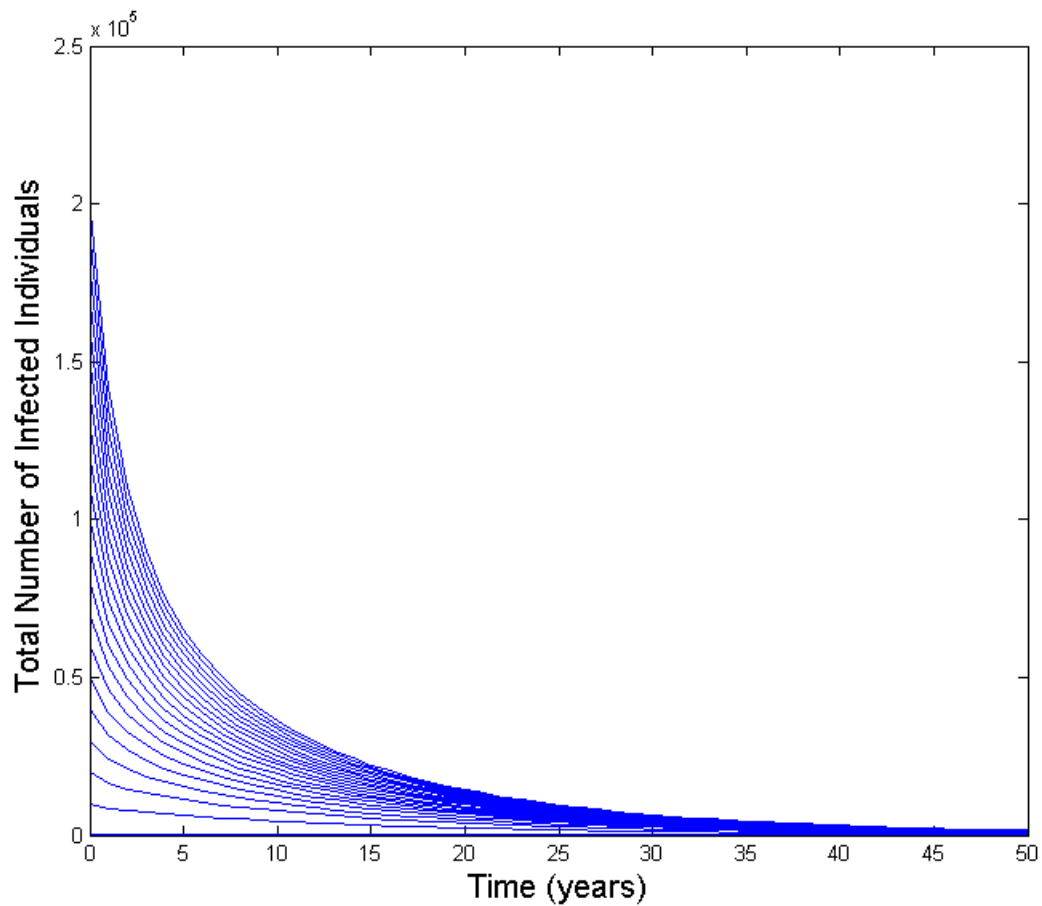


Figure 4.2: Solution profiles of the Pap screening model (4.3), showing the total number of HPV-infected individuals (females and males) as a function of time, using various initial conditions. Parameter values used are as given in Tables 4.2 and 4.3, with  $c_f = 1.3$ ,  $\beta_m = 0.25$  and  $\beta_f = 0.25$  (so that,  $\mathcal{R}_{0s} = 0.8111 < 1$ ).



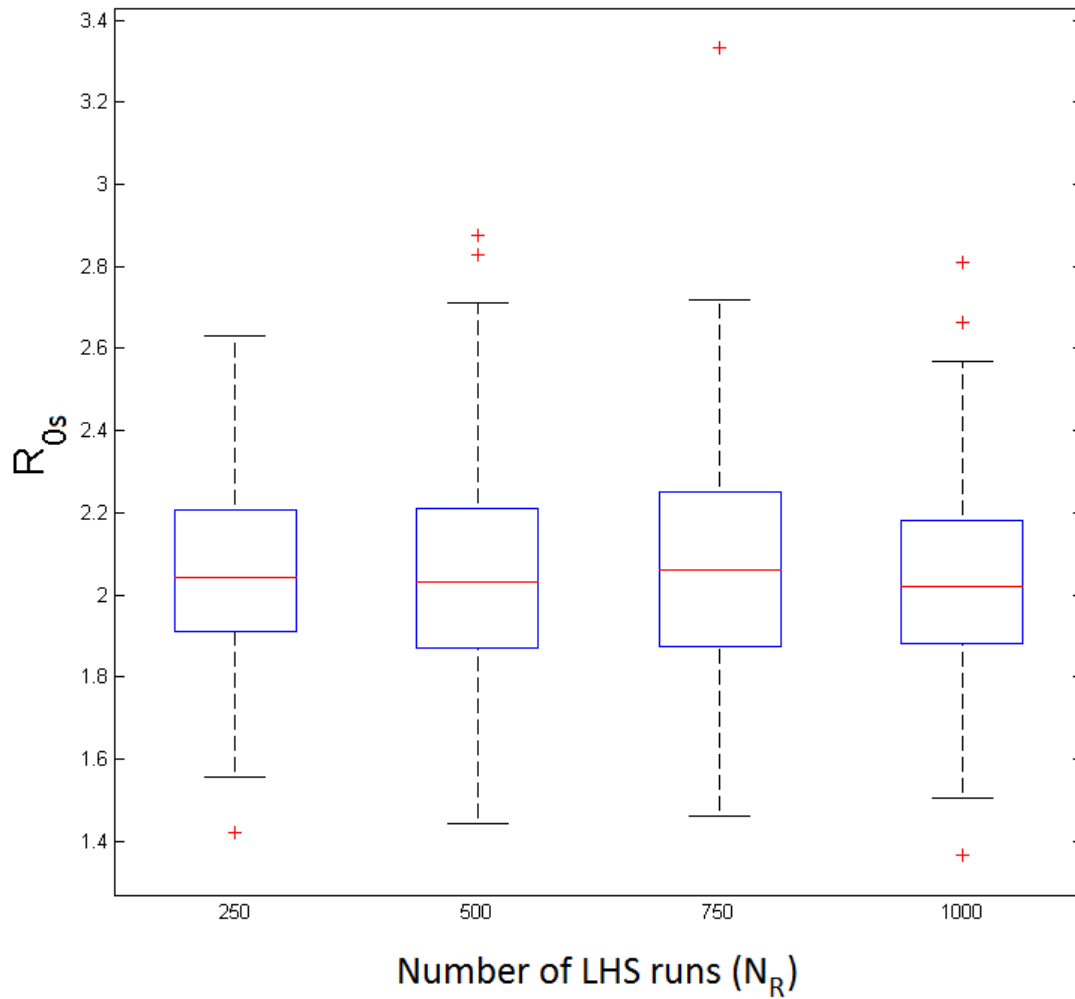


Figure 4.3: Box plot of the effective reproduction number ( $\mathcal{R}_{0s}$ ) as a function of the number of runs ( $N_R$ ) for the Pap screening model (4.3), using the parameter values and ranges given in Tables 4.2 and 4.3.

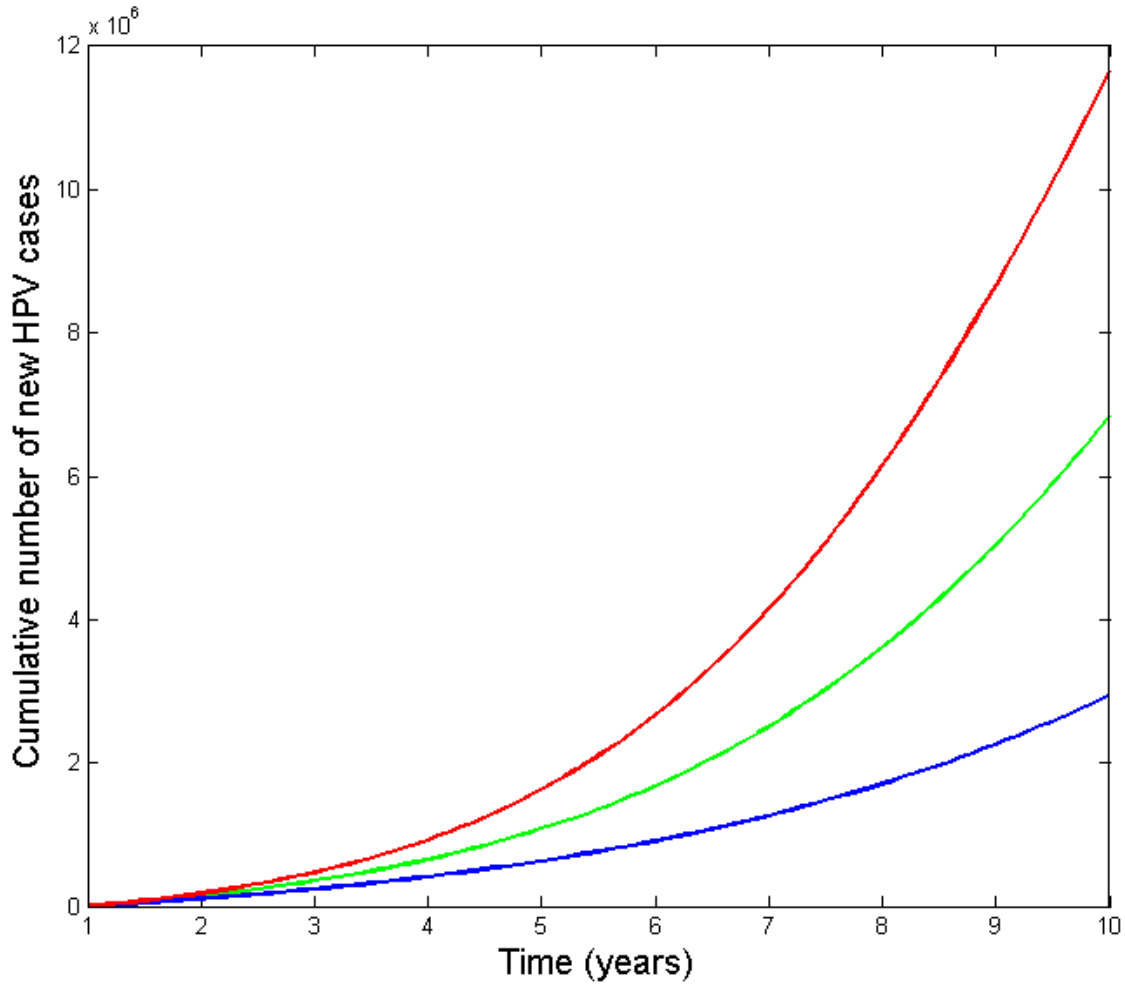


Figure 4.4: Simulations of the Pap screening model (4.3), showing the cumulative number of new HPV cases (for females and males) as a function of time. Parameter values used are as given in Tables 4.2 and 4.3 (with the top eleven ranked parameters modified accordingly). Green color: baseline parameters as in Tables 4.2 and 4.3 ( $\mathcal{R}_{0s}=2.1019$ ). Blue color: top-eleven PRCC-ranked parameters in Table 4.4 decreased by 10% ( $\mathcal{R}_{0s}=1.8537$ ). Red color: top-eleven PRCC-ranked parameters in Table 4.4 increased by 10% ( $\mathcal{R}_{0s}=2.1734$ ).

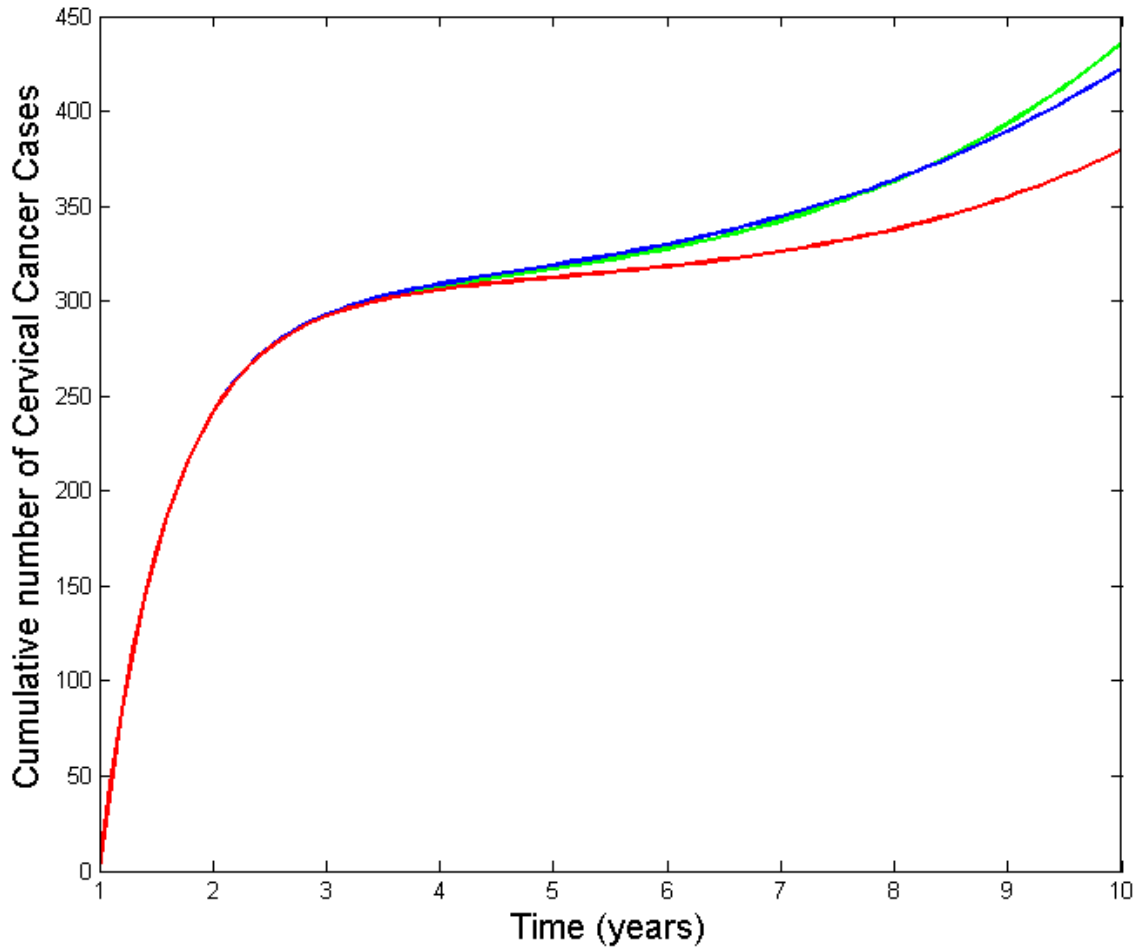


Figure 4.5: Simulations of the Pap screening model (4.3), showing the cumulative number of cervical cancer cases as a function of time. Parameter values used are as given in Tables 4.2 and 4.3 (with the top eleven PRCC-ranked parameters modified accordingly). Green color: baseline parameters as in Tables 4.2 and 4.3 ( $\mathcal{R}_{0s}=2.1019$ ). Blue color: top-eleven PRCC-ranked parameters in Table 4.4 decreased by 10% ( $\mathcal{R}_{0s}=1.8537$ ). Red color: top-eleven PRCC-ranked parameters in Table 4.4 increased by 10% ( $\mathcal{R}_{0s}=2.1734$ ).

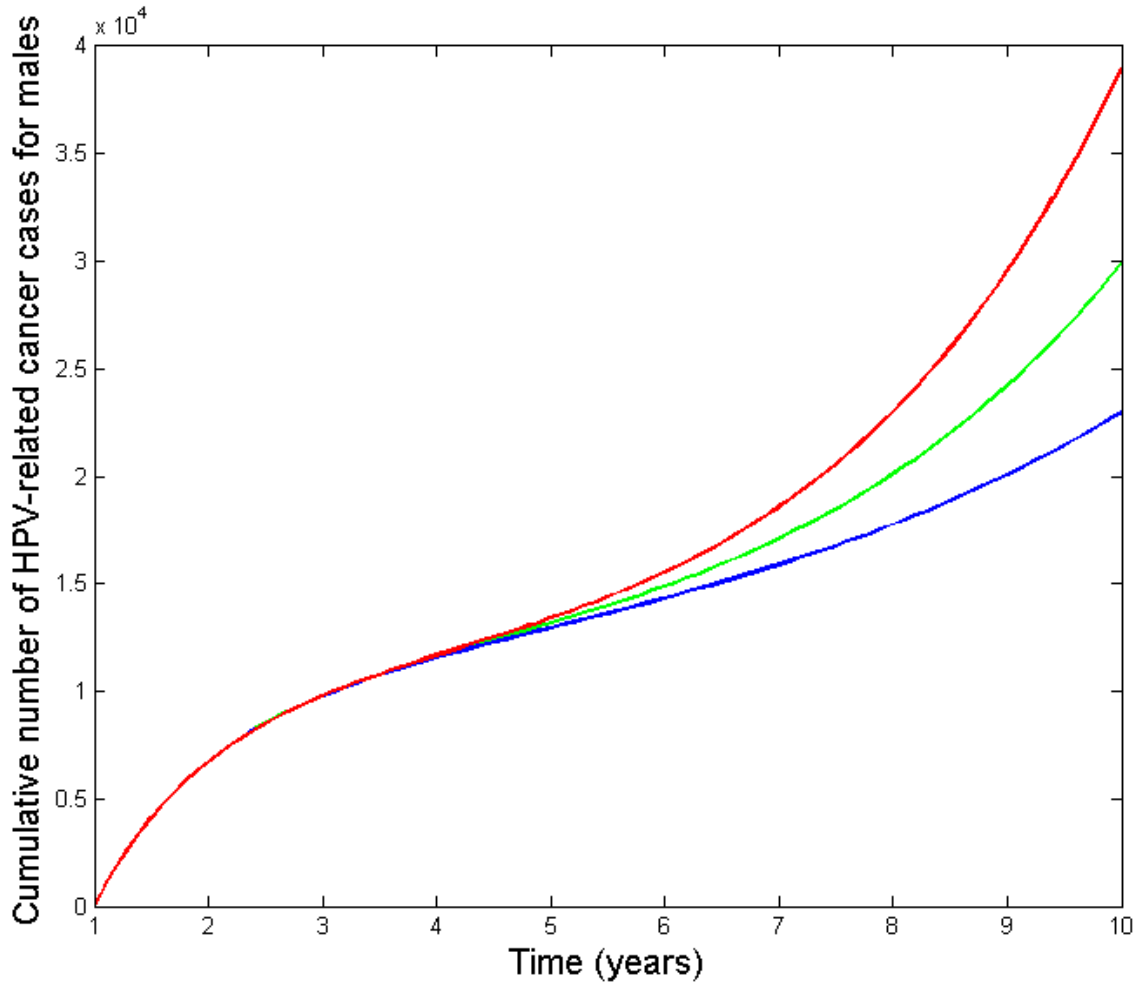


Figure 4.6: Simulations of the Pap screening model (4.3), showing the cumulative number of HPV-related cancer cases for males as a function of time. Parameter values used are as given in Tables 4.2 and 4.3 (with the top eleven PRCC-ranked parameters modified accordingly). Green color: baseline parameters as in Tables 4.2 and 4.3 ( $\mathcal{R}_{0s}=2.1019$ ). Blue color: top-eleven PRCC-ranked parameters in Table 4.4 decreased by 10% ( $\mathcal{R}_{0s}=1.8537$ ). Red color: top-eleven PRCC-ranked parameters in Table 4.4 increased by 10% ( $\mathcal{R}_{0s}=2.1734$ ).

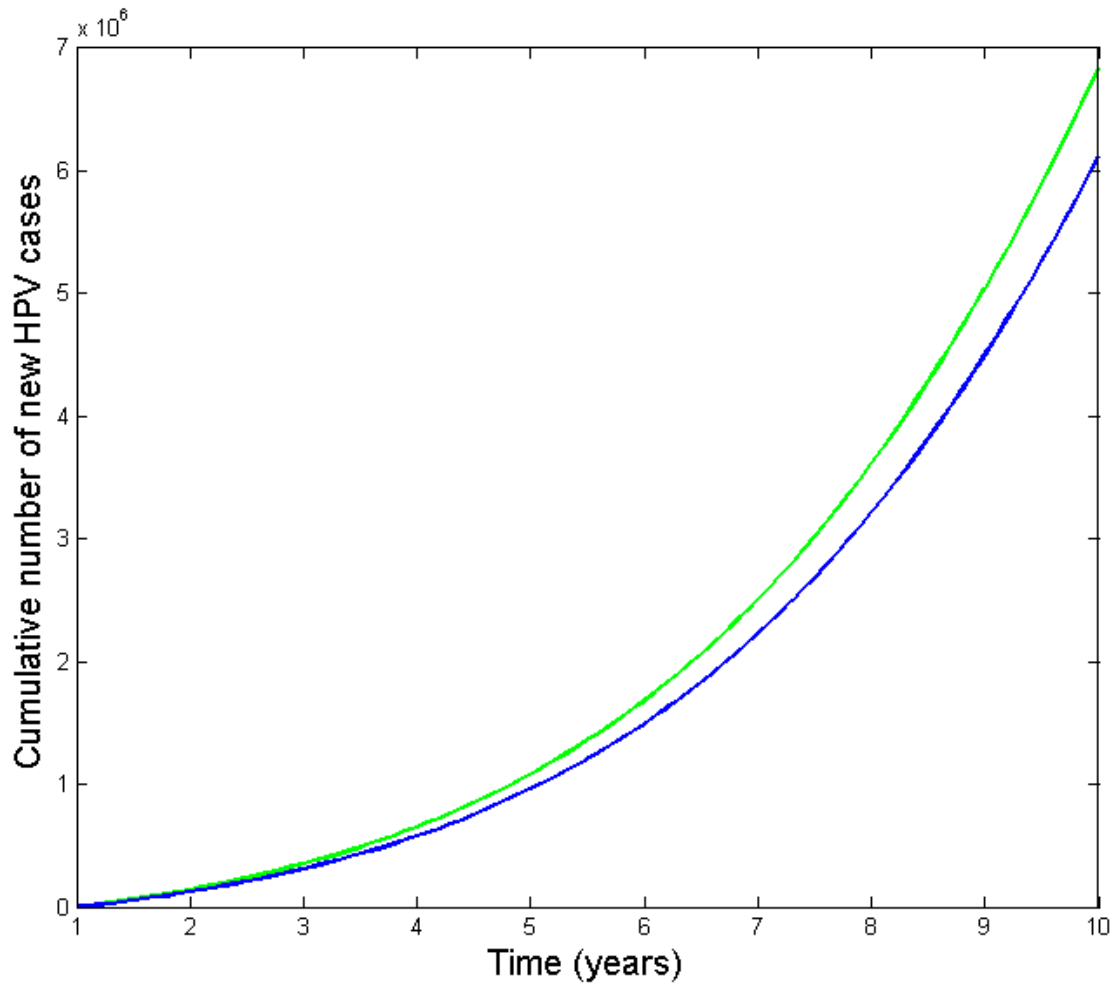


Figure 4.7: Simulations of the Pap screening model (4.3), showing the cumulative number of new HPV cases (for females and males) as a function of time in the presence (green color) and absence (blue color) of the HPV transmission by individuals in the pre-cancerous stages (both CIN and INM). Parameter values used are as given in Tables 4.2 and 4.3 ( $\mathcal{R}_{0s} = 2.1019 > 1$ ).

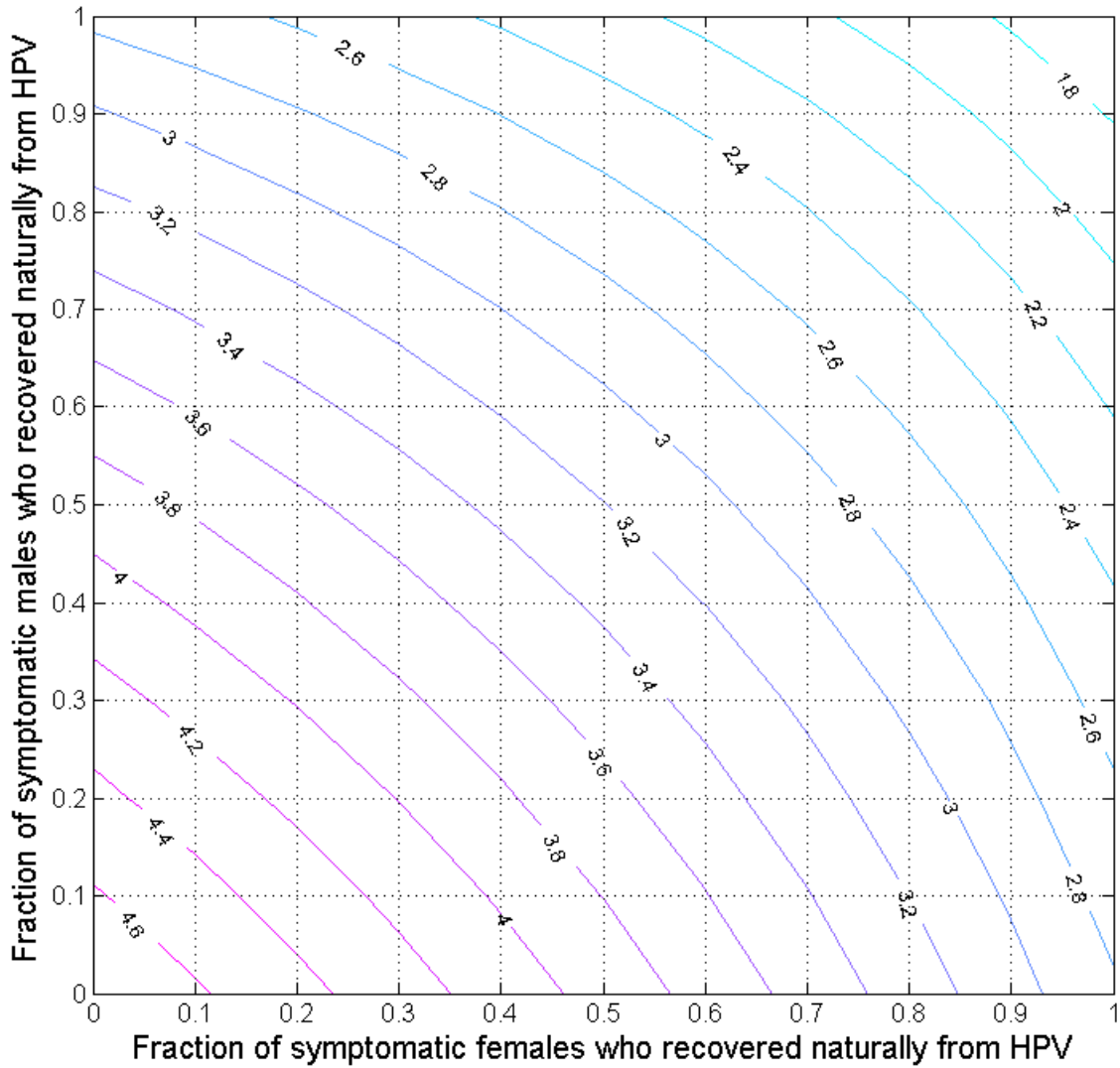


Figure 4.8: Simulations of the Pap screening model (4.3), showing a counter plot of  $\mathcal{R}_{0s}$ , as a function of the fraction of symptomatic females who recovered naturally from HPV ( $b_f$ ) and the fraction of symptomatic males who recovered naturally from HPV ( $b_m$ ). Parameter values used are as given in Tables 4.2 and 4.3.

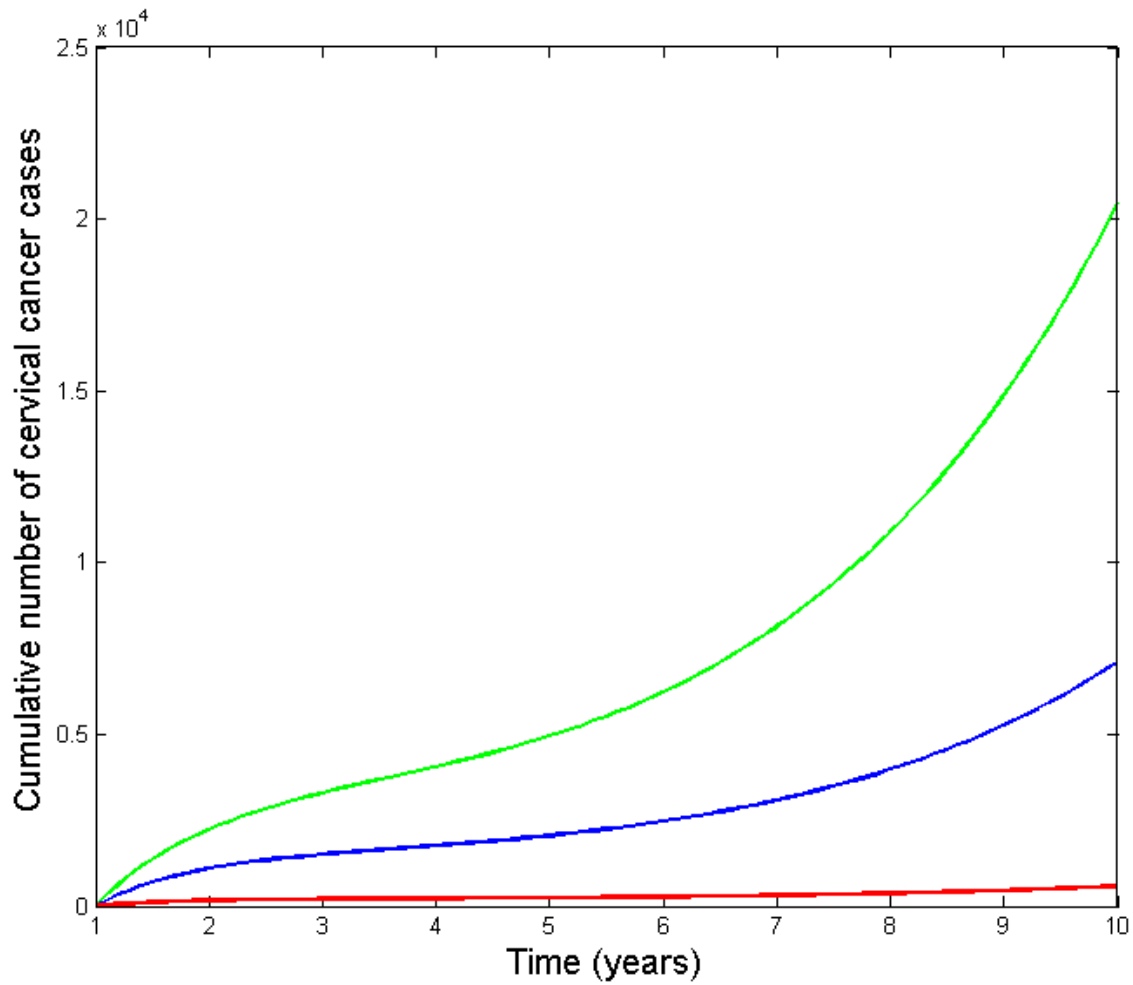


Figure 4.9: Simulations of the Pap screening model (4.3), showing the cumulative number of cervical cancer cases for females as a function of time. Green color: 0% of females with CIN detected ( $\mathcal{R}_{0s}=2.1201$ ). Blue color: 25% of females with CIN detected ( $\mathcal{R}_{0s}=2.1118$ ). Red color: 50% of females with CIN detected ( $\mathcal{R}_{0s}=2.1051$ ).

# Appendix A

## Proof of Theorem 3.1

*Proof.* Let

$$t_1 = \sup \{ t > 0 : S_f(0) > 0, E_f(0) \geq 0, I_f(0) \geq 0, P_f(0) \geq 0, Q_f(0) \geq 0, C_f(0) \geq 0, \\ R_{fc}(0) \geq 0, R_f(0) \geq 0, S_m(0) > 0, E_m(0) \geq 0, I_m(0) \geq 0, P_m(0) \geq 0, \\ Q_m(0) \geq 0, C_m(0) \geq 0, R_{mc}(0) \geq 0, R_m(0) \geq 0 \} > 0.$$

The first equation of the basic model (3.25) 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,

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



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  $E_f(t) \geq 0$ ,  $I_f(t) \geq 0$ ,  $P_f(t) \geq 0$ ,  $Q_f(t) \geq 0$ ,  $C_f(t) \geq 0$ ,  $R_{fc}(t) \geq 0$ ,  $R_f(t) \geq 0$ ,  $S_m(t) \geq 0$ ,  $E_m(t) \geq 0$ ,  $I_m(t) \geq 0$ ,  $P_m(t) \geq 0$ ,  $Q_m(t) \geq 0$ ,  $C_m(t) \geq 0$ ,  $R_{mc}(t) \geq 0$  and  $R_m(t) \geq 0$  for all time  $t > 0$ . Hence, all solutions of the basic model (3.25) remain positive for all non-negative initial conditions.  $\square$

# Appendix B

## Proof of Theorem 3.2

*Proof.* The proof is based on using a Comparison Theorem [51]. It is worth mentioning, first of all, that since the off-diagonal entries of the Jacobian matrix of the infected components of the basic model (3.25), at the DFE ( $\mathcal{E}_0$ ), are non-negative, the system (3.25) satisfies the Type K condition [51]. Hence, comparison theorem can be used.

Let  $\mathcal{R}_0 < 1$  (so that the DFE,  $\mathcal{E}_0$ , of the basic model (3.25) is LAS, in line with Lemma 3.2). The infected components of the model (3.25) can be re-written as:

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

where,

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

where the matrices  $\mathcal{F}$  and  $\mathcal{V}$  are as defined in Section 3.3, 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,

$$\mathcal{J}_1 = \begin{pmatrix} 0 & \frac{\beta_m c_f \pi_f \mu_m}{\pi_m \mu_f} & \frac{\beta_m c_f \theta_m \pi_f \mu_m}{\pi_m \mu_f} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \quad \mathcal{J}_2 = \begin{pmatrix} 0 & \beta_f c_f & \beta_f c_f \theta_f & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

It is worth noting that  $J_1$  and  $J_2$  are non-negative matrices. Furthermore, since, for all  $t \geq 0$  in  $\mathcal{D}$ ,  $S_f(t) \leq N_f(t) \leq \frac{\pi_f}{\mu_f}$  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

$$\frac{d\mathbf{x}}{dt} \leq (\mathcal{F} - \mathcal{V})\mathbf{x}. \quad (\text{B.2})$$

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 [51],

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

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 (3.25) shows that  $S_f(t) \rightarrow S_f^*$  and  $S_m(t) \rightarrow S_m^*$  as  $t \rightarrow \infty$  (for  $\mathcal{R}_0 < 1$ ). Thus,

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

□

# Appendix C

## Proof of Theorem 3.4

*Proof.* Let  $\mathcal{R}_0 > 1$  (so that the unique EEP ( $\mathcal{E}_1$ ) of the basic model (3.25) exists, by Theorem 3.3),  $\delta_f = 0$  (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 (3.25)):

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

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 [31, 32, 76]

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

with  $\bar{Z}_0 = (Z_1, Z_2, \dots, Z_{14})$ ,  $Z_i \in \mathbb{C}$ ,  $w \in \mathbb{C}$ , and  $\text{Re}(w) \geq 0$ . 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

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

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

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

where,

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

with,

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

It should be noted that the notation  $H(\bar{Z})_i$  (with  $i = 1, \dots, 14$ ) denotes the  $i$ th 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  $|\bar{Z}| = (|Z_1|, \dots, |Z_9|)$ , and  $|\cdot|$  is a norm in  $\mathbb{C}$ . The task ahead is to show that  $\text{Re}(w) < 0$ . It will be proved by contradiction. Assume the first case  $w = 0$  then, (C.3) is a homogeneous linear system in the variables  $Z_i$  ( $i = 1, \dots, 14$ ). The determinant of this system corresponds to that of the Jacobian of the system (C.1), evaluated at  $\mathcal{E}_1$ , given by,  $\Delta = \mu_f \mu_m (D_1 D_2 - D_3)$ . It should be recalled that  $\Delta \neq 0$  (Theorem 3.4). 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  $\operatorname{Re}(F_i(w)) \geq 0$  ( $i = 1, \dots, 14$ ) since, by assumption,  $\operatorname{Re} w \geq 0$ . It means that  $|1 + F_i(w)| > 1$  for all  $i$ . Now, by defining  $F(w) = \min|1 + F_i(w)|$ ,  $i = 1, \dots, 14$ , 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 fourth 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,  $\operatorname{Re} w < 0$ . Hence, the unique endemic equilibrium ( $\mathcal{E}_1$ ) of the model (3.25) is LAS whenever  $\mathcal{R}_0 > 1$ ,  $\delta_f = 0$  and  $\Delta \neq 0$ .  $\square$

# Appendix D

## Proof of Theorem 3.5

*Proof.* Consider the basic model (3.25), with  $\mathcal{R}_1 > 1$  (so that its unique EEP ( $\mathcal{E}_1$ ) exists, by Theorem 3.3). 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 (3.25). 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 basic model (3.25):

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

where,

$$\begin{aligned}
b_1 &= \frac{\beta_m c_f \mu_m S_f^{**} I_m^{**}}{\sigma_f \pi_m E_f^{**}}, & b_2 &= \frac{\beta_m c_f \mu_m S_f^{**} I_m^{**}}{\psi_f \pi_m I_f^{**}}, & b_3 &= \frac{\beta_m c_f \mu_m S_f^{**} I_m^{**}}{\alpha_f \pi_m P_f^{**}}, & b_4 &= \frac{\beta_m c_f \mu_m S_f^{**} I_m^{**}}{g_f \pi_m Q_f^{**}}, \\
b_5 &= \frac{\beta_f c_f \mu_m S_m^{**} I_f^{**}}{\sigma_m \pi_m E_m^{**}}, & b_6 &= \frac{\beta_f c_f \mu_m S_m^{**} I_f^{**}}{\psi_m \pi_m I_m^{**}}, & b_7 &= \frac{\beta_f c_f \mu_m S_m^{**} I_f^{**}}{\alpha_m \pi_m P_m^{**}}, & b_8 &= \frac{\beta_f c_f \mu_m S_m^{**} I_f^{**}}{g_m \pi_m Q_m^{**}}.
\end{aligned}$$

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

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

The following relations, at the endemic steady-state (obtained from the associated sub-model

of the model (3.25)), will be used to simplify (D.2):

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

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,

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

Substituting  $(I_f(t), P_f(t), Q_f(t), I_m(t), P_m(t), Q_m(t)) = (I_f^{**}, P_f^{**}, Q_f^{**}, I_m^{**}, P_m^{**}, Q_m^{**})$  into the model (3.25) shows that  $(R_{fc}(t), R_f(t), R_{mc}(t), R_m(t)) \rightarrow (R_{fc}^{**}, R_f^{**}, R_{mc}^{**}, R_m^{**})$  as  $t \rightarrow \infty$ . Hence, the unique endemic equilibrium of the basic model (3.25), with  $\theta_m = \theta_f = 0$ , is GAS in  $\mathcal{D} \setminus \mathcal{D}_0$  whenever  $\mathcal{R}_1 > 1$ ,  $S_f(t) \leq S_f^{**}$  and  $S_m(t) \leq S_m^{**}$  for all  $t$ .  $\square$

# Appendix E

## Description of the Pap Screening

### Model (4.3)

The population of susceptible females ( $S_f(t)$ ) is generated by the recruitment of new sexually-active females (at a rate  $\pi_f$ ). 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  $\xi_f$ ). 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  $\lambda_m$ , given by

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

In (E.1),  $\beta_m$  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  $\mu_f$ ; it is assumed that females in all epidemiological compartments suffer natural death at this rate). Thus,

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

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

$$\frac{dE_f}{dt} = \lambda_m S_f - (\sigma_f + \mu_f) E_f. \quad (\text{E.3})$$

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  $\sigma_f$ ). 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,

$$\frac{dI_f}{dt} = \sigma_f E_f - (\psi_f + \mu_f) I_f. \quad (\text{E.4})$$

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,

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

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,

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

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,

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

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,

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

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,

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

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  $\gamma_f$  (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  $\delta_{fu}$ ). Thus,

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

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  $\delta_{fd}$ ). Hence,

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

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  $\mu_f$ ). Hence,

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

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  $\xi_f$ ) and natural death, so that

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

The population of susceptible males ( $S_m(t)$ ) is generated by the recruitment of new sexually-active males (at a rate  $\pi_m$ ). 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  $\xi_m$ ). 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  $\lambda_f$ , given by

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

In (E.14),  $\beta_f$  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  $\mu_m$ ; it is assumed that males in all epidemiological compartments suffer natural death at this rate). Thus,

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

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

$$\frac{dE_m}{dt} = \lambda_f S_m - (\sigma_m + \mu_m) E_m. \quad (\text{E.16})$$

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  $\sigma_m$ ). 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,

$$\frac{dI_m}{dt} = \sigma_m E_m - (\psi_m + \mu_m) I_m. \quad (\text{E.17})$$

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,

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

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,

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

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,

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

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  $\gamma_m$  (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 [81], no

mortality due to HPV-related cancer is assumed for males). Thus,

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

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,

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

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  $\xi_m$ ) and natural death, so that

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

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

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

Furthermore, since the model  $\{(E.2) - (E.23)\}$  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 [55]. Hence, for the model  $\{(E.2) - (E.23)\}$ ,

$$c_m(N_m, N_f) N_m = c_f(N_m, N_f) N_f. \quad (\text{E.25})$$

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, (E.25) can be re-written as

$$c_m(N_m, N_f) = \frac{c_f N_f}{N_m}. \quad (\text{E.26})$$

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 (E.25) in (E.1) and (E.14), the force of infections,  $\lambda_m$  and  $\lambda_f$ , are now re-written, respectively, as

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

# Appendix F

## Proof of Theorem 4.2

*Proof.* The proof is based on using a Comparison Theorem [51]. As in Appendix B, it can be shown that the system (4.3) 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 4.2). The infected components of the model (4.3) can be re-written as:

$$\frac{d\mathbf{x}_s}{dt} = (\mathcal{F}_s - \mathcal{V}_s)\mathbf{x}_s - J_s\mathbf{x}_s, \quad (\text{F.1})$$

where,

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

with the matrices  $\mathcal{F}_s$  and  $\mathcal{V}_s$  are as defined in Section 4.3, 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,

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

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

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 (F.1), that

$$\frac{d\mathbf{x}_s}{dt} \leq (\mathcal{F}_s - \mathcal{V}_s)\mathbf{x}_s. \quad (\text{F.2})$$

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 4.2), it follows that the linear differential inequality system (F.2) is stable whenever  $\mathcal{R}_{0s} < 1$ . Hence, by Comparison Theorem [51],

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

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 (4.3) shows that  $S_f(t) \rightarrow S_f^*$  and  $S_m(t) \rightarrow S_m^*$  as  $t \rightarrow \infty$  (for  $\mathcal{R}_{0s} < 1$ ). Thus,

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

□

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