Mathematical Analysis of Vaccination Models for the Transmission Dynamics of Oncogenic and Warts-causing HPV Types

by

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Abstract

The thesis uses mathematical modeling and analysis to provide insights into the transmission dynamics of *Human papillomavirus* (HPV), and associated cancers and warts, in a community. A new deterministic model is designed and used to assess the community-wide impact of mass vaccination of new sexually-active susceptible females with the anti-HPV *Gardasil* vaccine. Conditions for the existence and asymptotic stability of the associated equilibria are derived. Numerical simulations show that the use of *Gardasil* vaccine could lead to the effective control of the spread of HPV in the community if the vaccine coverage is at least 78%. The model is extended to include the dynamics of the low- and high-risk HPV types and the combined use of the *Gardasil* and *Cervarix* anti-HPV vaccines. Overall, this study shows that the prospect of the effective community-wide control of HPV using the currently-available anti-HPV vaccines are encouraging.

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Dedication

To my lovely parents, Ali Alsaleh and Laila Alhanfoush, and my brother Hussain Alsaleh.

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Glossary

Abbreviation	Meaning
CIN	Cervical intraepithelial neoplasia
DFE	Disease-free equilibrium
EEP	Endemic equilibrium point
GAS	Globally-asymptotically stable
HPV	*Human papillomavirus*
INM	HPV-related intraepithelial neoplasia in males
LAS	Locally-asymptotically stable
ODE	Ordinary differential equation
STI	Sexually-transmitted infection

Chapter 1

Introduction

This chapter provides a review of some of the key biological and epidemiological features of HPV disease, as well as the associated cancers and warts.

1.1 *Human Papillomavirus* (HPV)

Human papillomavirus (HPV) is a major sexually-transmitted infection (STI) that continues to inflict significant public health burden globally (see, for example, [27, 45, 51, 72, 100]). Genital HPV infection is the commonest STI in Canada and the USA [35, 45, 80, 82]. Currently, 79 million Americans are infected with HPV, and 14 million new HPV infections are recorded in the USA annually [15]. HPV prevalence is higher in women than in men [50, 68, 71, 100], and it is estimated that as many as 75% of sexually-active men and women will have at least one HPV infection in their lifetime [45, 49, 56, 100]. HPV was identified, in 1983, as the causative agent of cervical cancer [45, 46].

Cervical cancer is currently the second most common malignancy among women, and a leading cause of cancer-related death globally [24, 45, 72, 100]. Data shows that up to 250,000 cervical cancer related deaths are recorded globally every year [33, 46], and that about 86% of cervical cancer cases occur in developing countries [100] (see also Table 1.1 and Figures 1.1 and 1.2).

Region	**Cervical cancer cases**	**Deaths**
Africa	80,419	53,334
Americas	80,711	36,125
Asia	312,752	159,774
Europe	54,323	25,102
Oceania	1,595	781
Developing regions	453,321	241,969
Developed regions	76,507	33,159
World (Total)	**529,828**	**275,128**

Table 1.1: Incidence and mortality of cervical cancer by region for the year 2008 [100].

For instance, in the year 2008, about 529,409 new cervical cancer cases and 274,883 related mortality were recorded globally [100]. About 12,000 women in the USA are diagnosed with cervical cancer every year [15]. In Canada, an estimated 1,300 women were diagnosed with cervical cancer in 2009 (with 380 related deaths), corresponding to an annual incidence rate of 7 cases *per* 100,000 women (see Table 1.2) [10, 54]. Cervical cancer ranks as the $12th$ most frequent cancer among women in Canada (it is also the $3rd$ most frequent cancer among Canadian women between the ages of 15 and 45) [54, 100]. Infection with certain HPV types can also cause genital warts, and data from the US Centres for Diseases Control shows that up to 360,000 cases genital warts are recorded in the USA annually [15, 22, 27, 76].

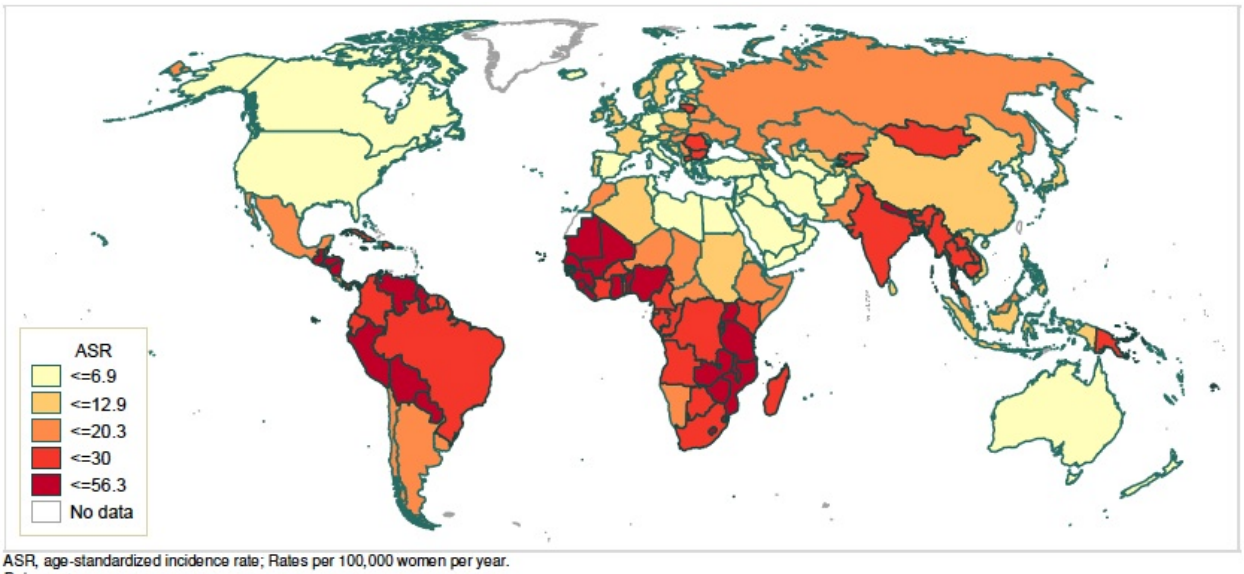


Figure 1.1: World age-standardized* incidence rates of cervical cancer for the year 2008 [100].

* *"age-standardized" rate (ASR) is a method of adjusting the crude (with respect to incidence and mortality) rate to eliminate the effect of differences in population age structures when comparing crude (with respect to incidence and mortality) rates for different periods of time, different geographic areas and/or different population sub-groups [4].*

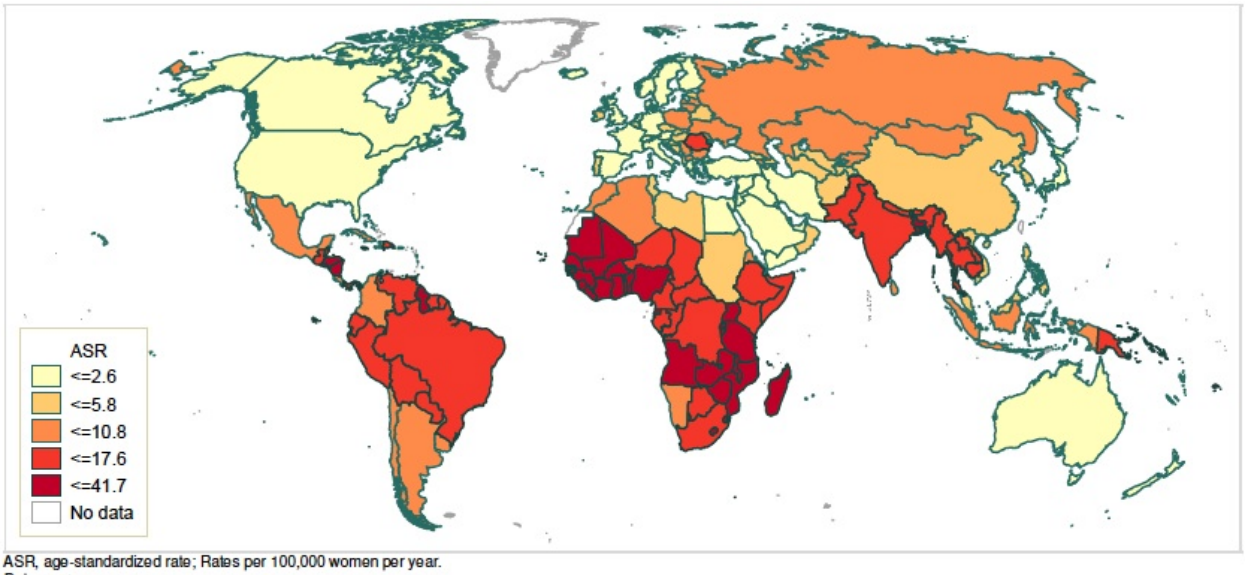


Figure 1.2: World age-standardized mortality rates of cervical cancer for the year 2008 [100].

HPV is caused by over 120 different serotypes [15, 27, 76]. While some of these types cause genital warts only, others can cause diverse cancers [15, 27, 76]. HPV infects squamous

Province	**Estimated new cases**
Newfoundland	20
Prince Edward Island	10
Nova Scotia	50
New Brunswick	30
Quebec	280
Ontario	490
Manitoba	45
Saskatchewan	35
Alberta	160
British Columbia	160
Canada (Total)	**1,300**

Table 1.2: Estimates of new cases of cervical cancer by province in Canada for 2009 [76].

epithelial cells in the cervix, the genital areas of males and females, bladder, mouth, throat, tongue etc. [15, 76, 100]. Transmission of the virus occurs when the virus comes in contact with these areas, allowing it to transfer between epithelial cells. Although genital HPV

infections are very common, especially those caused by the low-risk HPV types (such as, HPV-6 and HPV-11 [18, 51]), they do not (generally) cause any clinical symptoms of HPV (and are cleared up without any treatment within a few years [15, 46, 100]; it is known that in 90% of HPV cases, the body's immune system clears the infection naturally within two years [15]). These low-risk HPV types cause warts (*papillomas*) on the genital areas, which are very common, harmless, non cancerous, and easily treatable [15, 18]. Genital warts usually appear as a small bump or groups of bumps in the genital area (they can be small or large, raised or flat, or shaped like a cauliflower) [22].

Other forms of HPV, particularly those caused by the high-risk types (such as, HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73 and HPV-82), are more problematic [18, 51]. These (high-risk) HPV types cause cervical and other cancers related to the genital areas [15, 18, 22, 51, 76, 100]. The common symptoms of the disease include small bumpy warts on the genitals or anus and itching or burning around the genitals [15, 100].

The incubation period of HPV is typically between 1 month to 2 years [1, 15, 100]. A major challenge associated with the transmission dynamics of HPV is that a high proportion of individuals with genital HPV infections are not detected [15]. Thus, not all people infected with HPV will develop clinical symptoms of HPV, and such latently-infected people (i.e., those with asymptomatic HPV infection) can transmit HPV infection [33, 41, 50]. Numerous factors, such as smoking, weakened immune system or co-infection (or supper infection) with other STIs (or HPV types), affect the risk of developing HPV-related cancer (following infection with the high-risk HPV types) [15, 46, 76].

Although most people clear HPV infection and develop antibody responses, HPV can also employ several strategies to avoid the immune system [41, 49]. In the absence of regression (from pre-cancerous stage to a normal cell situation), pre-cancerous lesions may persist for many years, and may, in some instances, progress to cancer [49, 80, 82, 100]. High-risk HPV types infect genital areas in men and women, and cause flat lesions at these areas.

In women, who do not successfully clear their HPV infection, such lesions can progress to the low-grade cervical intraepithelial neoplasia (denoted by CIN1), and may progress further to higher CIN grades (denoted by CIN2 and CIN3) and cervical cancer if untreated [10, 15, 26, 46, 50, 61, 76]. It has been shown that, without treatment, the incidence of the progression of CIN3 to cervical cancer is about 30% [49, 56]. Figure 1.3 depicts a diagram for the transition of high-risk HPV types through the three CIN stages (CIN1, CIN2 and CIN3) to cancer. It is known that the high-risk HPV-16 and HPV-18 account for over 70% of cervical cancer cases globally [9, 46, 49, 56].

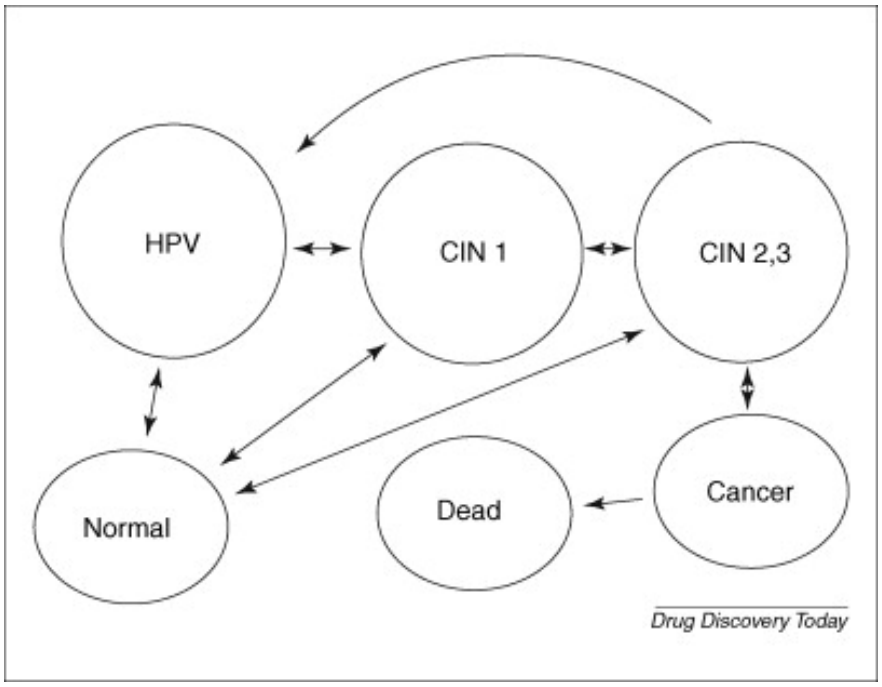


Figure 1.3: A diagram for the transition of high-risk HPV types through the various stages of cervical dysplasia (CIN1, CIN2 and CIN3), cervical cancer, and associated regression [39].

HPV is a circular, double-stranded DNA virus, protected by a capsid protein [17, 22, 66]. It first infects *keratinocyte* stem cells, situated in the basal layer of the epithelium [17, 22, 33]. Consequently, HPV enters the target (normal) cell, uncoats and delivers its DNA into the target cell's nucleus [17, 22, 33, 41, 50]. Upon infection, the virus exploits the replication machinery of the target cell to reproduce several copies of its genome, so that each infected cell contains a low viral load of about 50 copies [17, 22, 66]. The target cells proliferate

and move towards the outer layers of the epithelium (the viruses also proliferate) [17, 22, 66, 74, 94]. At this stage, the viral load has been drastically increased (resulting in the production of thousands of viral particles *per* cell) [17]. As these infected cells approach the surface of the skin, the viral particles are released to infect other target cells [6, 22, 69, 94], continuing the cycle. It is known that HPV-16 and HPV-18 are most frequently associated with cervical cancer (this due to the presence of two viral oncogenes, E6 and E7 genes, which bind to the human p53 tumor suppressor protein [22, 30, 79, 81, 102]. While the E6 protein targets the p53 tumor suppressor for degradation, the E7 protein, on the other hand, inactivates the retinoblastoma susceptibility protein [81]). Figure 1.4 depicts the process of HPV infection in women. Further details about HPV replication cycle can be obtained from [6, 17, 22, 66, 69, 74, 94] (and some of the references therein).

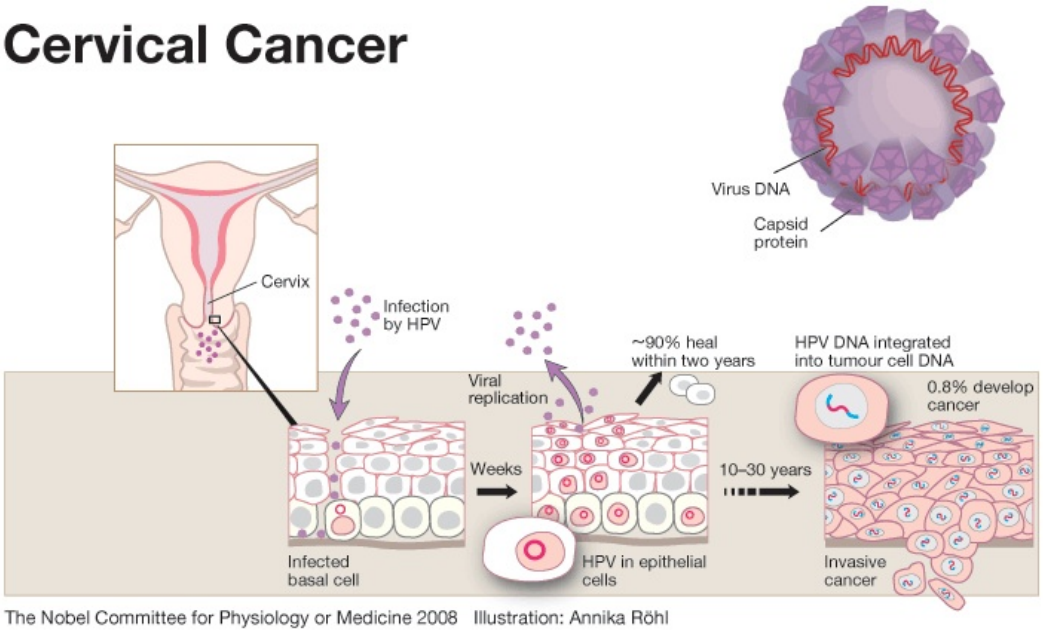


Figure 1.4: HPV infection in women [69].

1.2 Control Strategies

The spread of HPV, and associated cancers and warts, is controlled *via* a number of preventive and therapeutic mechanisms. It is known, first of all, that the use of condoms can

reduce the transmission of HPV between sexual partners [15, 68, 80, 82]. The other main anti-HPV control strategies are described below.

1.2.1 Treatment

Unlike some other STIs, HPV cannot be cured using antibiotics [68]. Treatment against HPV infection depends on the type of the virus the individual is infected with [15, 76, 82]. If the infected person has contracted the low-risk HPV types (which causes genital warts), the resulting (associated) genital warts can be removed using chemical treatment methods (such as, *cryotherapy, podophyllin* and *trichloroacetic acid*) and cream (such as, *Aldara*) [15, 56, 89]. However, it is known that eliminating the visible aspect of the warts will not always eliminate the virus completely, and the warts can re-appear [15, 46, 100]. On the other hand, for individuals infected with the high-risk HPV types (that cause various cancers), treatment will depend on the CIN stage at the time of diagnosis [15, 49, 80]. The associated pre-cancerous HPV do not (in general) cause any noticeable symptoms, and are usually detected through a Pap test (smear) or a colposcopy [15, 22, 33, 41, 50].

1.2.2 Pap screening

Pap screening has proven to be quite effective, particularly in developed nations, in early detection of CIN, and, consequently, reducing cervical cancer incidence and mortality [61]. Pre-cancerous lesions can usually be treated successfully (using, for instance, loop electro-surgical excision procedure, which involves the removal of a cancerous tissue using a wire loop, or using laser therapy [68, 80, 82]). It has recently been recommended that the Pap test be administered every 3 years, starting at age 21 [15, 46, 76, 80]. Furthermore, a positive diagnosis of cervical cancer imply the presence of invasive cancer in the deeper layers of the cervix, and that the cancer has also spread to the uterus. If the cancer is limited to the cervix, it can be treated with the removal of the uterus (*hysterectomy*). However, if it spreads to the anus or other genital areas, it can be treated *via* surgery or radiation therapy

[15, 34, 56, 100].

1.2.3 HPV Vaccine

Two anti-HPV vaccines, namely *Cervarix* and *Gardasil*, have been approved for use to protect new sexually-active males and females against some of the most common HPV types [15, 34, 46, 56, 76]. The *Gardasil* quadrivalent vaccine, produced by Merck Inc., protects against four HPV types (namely, HPV-6, HPV-11, HPV-16 and HPV-18; these are the four commonest HPV types). The *Cervarix* bivalent vaccine, produced by GlaxoSmithKline, targets two high-risk HPV types (namely, HPV-16 and HPV-18) [10, 77]. The two vaccines, administered in a series of three doses over a period of 6 months, are 90-100% effective in preventing HPV infection against the respective HPV types [9, 27, 46, 50, 61, 76, 100]. Both vaccines have been licensed by the Food and Drug Administration of the USA, and the retail price of either vaccine is about USD $130 *per* dose (that is, USD $390 for full series) [15, 34]. It has been reported that both vaccines have side effects, including pain (at the body location where the vaccine is given), fever, dizziness, and nausea [15, 34, 76, 100]. While the *Gardasil* vaccine is approved for both females and males, the *Cervarix* vaccine is only approved for females [76, 77, 100].

1.3 Reproduction Number and Bifurcations

Compartmental mathematical models have been widely used to gain insights into the spread and control of emerging and re-emerging diseases of public health importance, dating back to the pioneering works of Bernoulli in 1760 (see, for instance, [2, 3, 5, 21, 47] and the references therein). The dynamics of these models is typically characterized by a threshold quantity, known as the *basic reproduction number* (denoted by $\mathcal{R}_0$), which measures the average number of new cases a typical infectious individual can generate in a completely-susceptible population [3, 20, 47]. In general, the disease dies out in time if $\mathcal{R}_0 < 1$, and

persists in the community if $\mathcal{R}_0 > 1$. This phenomenon, where the disease-free equilibrium (DFE) and an endemic equilibrium point (EEP) of the model exchange their stability at $\mathcal{R}_0 = 1$, is known as *forward bifurcation* [12, 14, 42, 47, 48, 86]. The epidemiological meaning of the *forward bifurcation* phenomenon is that the requirement $\mathcal{R}_0 < 1$ is (in general) necessary and sufficient for the effective control or elimination of the disease. Figure 1.5 depicts a schematic diagram of forward bifurcation.

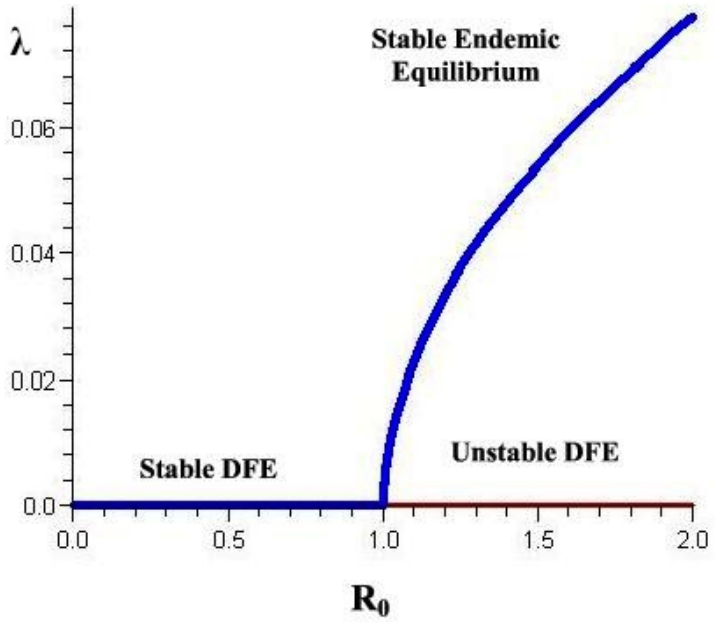


Figure 1.5: Forward bifurcation diagram (where λ is the infection rate).

It is known, in some epidemiological settings, that the requirement $\mathcal{R}_0 < 1$, while necessary, is not sufficient for effective disease control or elimination. This is due to a dynamic phenomenon, known as *backward bifurcation*. This phenomenon results when a stable EEP of the model co-exists with the associated stable DFE when $\mathcal{R}_0 < 1$. Backward bifurcation has been observed in numerous epidemiological studies, such as those in [12, 14, 23, 28, 42, 84, 85, 86]. In a backward bifurcation situation, effective disease control is dependent on the initial sizes of the sub-populations of the model. Consequently, the presence of backward bifurcation in the transmission dynamics of a disease makes the effective control of the disease (in the com-

munity) more difficult. Figure 1.6 depicts a diagram for the backward bifurcation diagram.

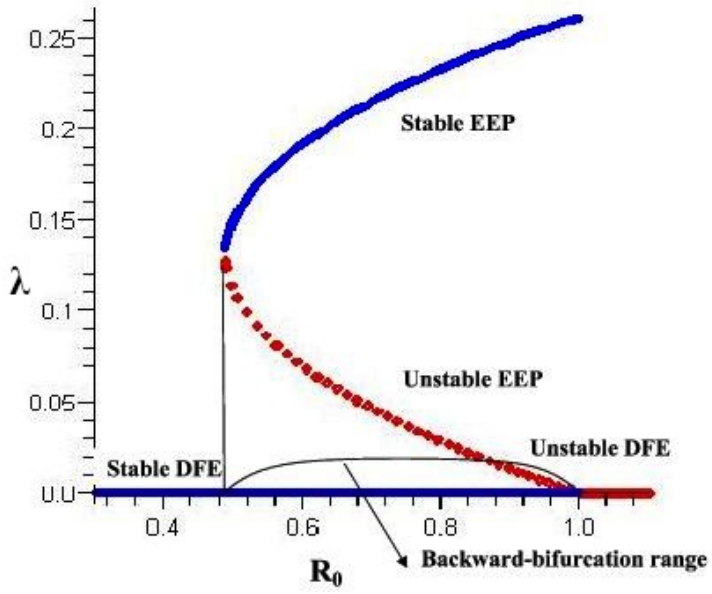


Figure 1.6: Backward bifurcation diagram, showing co-existence of a stable DFE and two branches of endemic equilibria (stable and unstable branch).

1.4 Thesis Outline

The main aim of this thesis is to use mathematical modelling, based on the current knowledge of HPV biology and epidemiology, and rigorous qualitative analysis to gain insights into the transmission dynamics of HPV (and associated cancers and warts) in a community. The models to be developed in this thesis consider only the heterosexual transmission of HPV. The thesis is organized as follows. Some of the basic mathematical preliminaries needed to qualitatively analyze the models to be developed in the thesis are reviewed in Chapter 2. In Chapter 3, an HPV vaccination model (based on using the *Gardasil* vaccine alone in the community) is formulated and rigorously analyzed. In Chapter 4, the model developed in Chapter 3 is extended to include, *inter alia*, the dynamics of the low- and high-risk HPV types and the two anti-HPV vaccines (*Cervarix* and *Gardasil*). The main mathematical

and epidemiological contributions of the thesis, including some areas for future work, are enumerated in Chapter 5.

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

i) What are the main qualitative features of realistic models for the transmission dynamics of HPV (and associated cancers and warts) in a community, in the presence of a mass vaccination program (using the currently-available *Cervarix* and *Gardasil* vaccines) against HPV? In particular, emphasis will be on determining conditions for the existence and asymptotic (both local and global) stability of the associated equilibria of the models, as well as to characterize the various bifurcation types the models may undergo.

ii) Can the singular use of the *Gardasil* vaccine for new sexually-active susceptible women lead to the effective control or elimination of HPV from the community? If yes, what percentage of the new sexually-active susceptible women need to be vaccinated to achieve this result?

iii) What are the qualitative features of a vaccination model for HPV that stratifies the total population in terms of the risk of transmitting infection with the low- and high-risk HPV types?

iv) Does the vaccination of new sexually-active susceptible males have a quantifiable community-wide impact in reducing HPV (and HPV-related) burden?

v) What is the community-wide impact of the combined use of the two anti-HPV vaccines, *Cervarix* and *Gardasil* (for new sexually-active susceptible women)?

Chapter 2

Mathematical Preliminaries

This chapter introduces some of the basis mathematical theories and methodologies relevant to the thesis.

2.1 Equilibria of Autonomous Ordinary Differential Equations (ODEs)

In this thesis, only the systems of *autonomous* ODEs, given by

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

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

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

where f can depend on the independent variable t, are not considered in this thesis.

In both equations (2.1) and (2.2), and throughout this thesis, the over dot represents differentiation with respect to time ($\frac{d}{dt}$), and the right-hand side function, $f \in C^r$ with $r \geq 1$, is called a *vector field* [73].

Definition 2.1. *A point $\bar{x} \in \mathbb{R}^n$ is called an equilibrium point of the autonomous system (2.1) if $f(\bar{x}) = 0$.*

Theorem 2.1. (Fundamental Existence- Uniqueness Theorem [73]). *Let E be an open subset of $\mathbb{R}^n$ containing x_0 and assume that $f \in C^1(E)$. Then, there exists an $a > 0$ such that the initial value problem:*

$$\dot{x} = f(x), \quad x(0) = x_0,$$

has a unique solution $x(t)$ on the interval $[-a, a]$.

Definition 2.2. *The Jacobian matrix of f 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 system (2.1) at the equilibrium $\bar{x}$.*

Definition 2.4. *An equilibrium point $\bar{x}$ of the system (2.1) is called hyperbolic if none of the eigenvalues of $Df(\bar{x})$ has zero real part.*

Definition 2.5. *An equilibrium point that is not hyperbolic is called non-hyperbolic.*

2.2 Hartman-Grobman Theorem

Consider the dynamical system:

$$\begin{aligned} \dot{x} &= f(x), \quad x \in \mathbb{R}^n, \\ \dot{y} &= g(y), \quad y \in \mathbb{R}^n, \end{aligned} \tag{2.3}$$

where $f(x)$ and $g(x)$ are two C^r $(r \geq 1)$ vector fields on $\mathbb{R}^n$.

Definition 2.6. [98]. *The dynamics generated by the vector fields f and g, of the system (2.3), are said to be locally C^k-conjugate ($k \leq r$) if there exists a C^k diffeomorphisim h which takes the orbits of the flow generated by f, $\phi(t,x)$, to the orbits of the flow generated by g, $\psi(t,y)$, preserving orientation and parameterization by time.*

Theorem 2.2. (Hartman-Grobman Theorem [98]). *Consider the $C^r(r \geq 1)$ system*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \tag{2.4}$$

with domain of f to be a large open subset of $\mathbb{R}^n$. Suppose also that the system (2.4) has equilibrium solutions which are hyperbolic. Consider the associated linear system

$$\dot{\xi} = Df(\bar{x})\xi, \quad \xi \in \mathbb{R}^n. \tag{2.5}$$

Then, the flow generated by the system (2.4) is C^0-conjugate to the flow generated by the linearized system (2.5) in a neighborhood of the equilibrium point $x = \bar{x}$.

It should be stated that the Hartman-Grobman Theorem guarantees a homeomorphism between the flow of the non-linear ODE and that of its linearization. In general, near a hyperbolic equilibrium point $\bar{x}$, the non-linear system $\dot{x} = f(x)$ has the same qualitative structure as the linear system $\dot{x} = Ax$, with $A = Df(\bar{x})$ [73].

2.3 Stability Theory

Definition 2.7. [98]. *The equilibrium $\bar{x}$, of the system (2.1), is said to be stable if, given $\epsilon > 0$, there exists a $\delta = \delta(\epsilon) > 0$ such that, for any solution $y(t)$ of the system (2.1) satisfying $|\bar{x} - y(t_0)| < \delta$, $|\bar{x} - y(t)| < \epsilon$ for $t > t_0$ where $t_0 \in \mathbb{R}$.*

Definition 2.8. [98]. *The equilibrium $\bar{x}$, of the system (2.1), 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 the system (2.1) satisfying $|\bar{x} - y(t_0)| < c$, $\lim_{t\to\infty} |\bar{x} - y(t)| = 0$.*

Definition 2.9. *An equilibrium solution which is not stable is said to be unstable.*

The main standard methods for analyzing the stability of the equilibria of the disease transmission models are described below.

2.3.1 Standard linearization

Theorem 2.3. [98]. *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.*

2.3.2 The next generation operator method and $\mathcal{R}_0$

The next generation operator method [19, 95] is used to establish the local asymptotic stability of the disease-free equilibrium (DFE) of a disease transmission model. The notation in [95] is used in this thesis. Suppose the given disease transmission model, with non-negative initial conditions, can be written in terms of the following system:

$$\dot{x}_i = f(x) = F_i(x) - V_i(x),\ i = 1, ..., n, \tag{2.6}$$

where $V_i = V_i^- - V_i^+$ and the functions satisfy Axioms (A1)-(A5) below.

The function $F_i(x)$ represents the rate of appearance of new infections in compartment i, $V_i^+(x)$ represents the rate of transfer of individuals into compartment i, and $V_i^-(x)$ represents the rate of transfer of individuals out of compartment i. Furthermore, the number of individuals in each compartment is given by $x = (x_1, ..., x_n)^t, x_i \geq 0$, and $X_s = \{x \geq 0 \mid x_i = 0,\ i = 1, ..., m\}$ is defined as the disease-free states (non-infected variables of the model).

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

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

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

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

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

Definition 2.10. (M-Matrix). *An $n \times n$ matrix A is called an M-matrix if and only if every off-diagonal entry of the matrix A is non-positive and the diagonal entries are all positive.*

Lemma 2.1. (van den Driessche and Watmough [95]). *If $\bar{x}$ is a DFE of (2.6) and $f_i(x)$ satisfy (A1)-(A5), then the derivatives $DF(\bar{x})$ and $DV(\bar{x})$ are partitioned as*

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

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

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

Further, F is a non-negative matrix, V is a non-singular M-matrix and J_3, 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 [95]). *Consider the disease transmission model given by (2.6) 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 ρ is spectral radius), but unstable if $\mathcal{R}_0 > 1$.*

2.3.3 Krasnoselskii sub-linearity argument

The central idea of the Krasnoselskii sub-linearity argument is to show that the linearized version of the non-linear system $\dot{x} = f(x)$, given by (where $\bar{x}$ is an equilibrium solution of the non-linear system)

$$\dot{Z}(t) = Df(\bar{x})Z,$$

has no solution of the form

$$Z(t) = Z_0 e^{\omega t},$$

with $Z_0 \in \mathbb{C}^n$, $\omega \in \mathbb{C}$ and $Re(\omega) \geq 0$, where $\mathbb{C}$ denotes the complex number (further details about the application of the Krasnoselskii sub-linearity argument to prove the asymptotic stability of an equilibrium of a disease transmission model are available in [31, 32, 91]).

2.4 Center Manifold Theory

An effective way to analyse the qualitative properties of some dynamical systems is to reduce their dimensionality. The Centre Manifold Theory offers a mathematical technique for making such reduction (near an equilibrium point) possible.

Consider the non-linear system (2.1). Further, let,

$$\dot{x} = Ax, \tag{2.7}$$

be the corresponding linearized system, with $A = Df(\bar{x})$, near a hyperbolic equilibrium point $\bar{x}$.

Definition 2.11. [73]. *The stable, unstable, and centre subspaces; respectively, of the linear*

system (2.7) are defined by (where $A \in M_{nn}(\mathbb{R})$)

$$\begin{aligned} E^s &= span\{u_j, v_j; a_j < 0\}, \\ E^u &= span\{u_j, v_j; a_j > 0\}, \\ E^c &= span\{u_j, v_j; a_j = 0\}, \end{aligned}$$

where $w_j = u_j \pm iv_j$ are eigenvectors corresponding to the eigenvalues $\lambda_j = a_j \pm ib_j$.

Remark 2.1. *For a hyperbolic flow of a linear system, $\mathbb{R}^n = E^s \oplus E^u$. These subspaces become manifolds for non-linear ODEs.*

Theorem 2.5. (Stable Manifold Theory [73]). *Let $f \in C^1(E)$, where E is an open subset of $\mathbb{R}^n$ containing the origin, and let ϕ_t be the flow of non-linear system (2.1). Suppose that $f(0) = 0$ and $D(0)$ has k eigenvalues with negative real parts, and $q = n - k$ eigenvalues with positive real parts. Then, there exists a k-dimensional differentiable manifold S tangent to the stable subspace E^s of the linear system (2.7) at 0 such that for all $t \geq 0, \phi_t(S) \subset S$ and for all $x_0 \in S$,*

$$\lim_{t\to\infty} \phi_t(x_0) = 0,$$

and there exists a q-dimensional differentiable manifold U tangent to the unstable subspace E^u of the linear system (2.7) at 0 such that for all $t \geq 0, \phi_t(U) \subset U$ and for all $x_0 \in U$,

$$\lim_{t\to-\infty} \phi_t(x_0) = 0.$$

Definition 2.12. [73]. *Let ϕ_t be the flow of non-linear system (2.1). The global stable and unstable manifolds of (2.7) at 0 are defined, respectively, by*

$$W^s(0) = \bigcup_{t\leq 0} \phi_t(S),$$

and,

$$W^u(0) = \bigcup_{t \geq 0} \phi_t(U).$$

Theorem 2.6. [73]. *Let $f \in C^r(E)$, where E is an open subset of $\mathbb{R}^n$ containing the origin and $r \geq 1$. Suppose that $f(0) = 0$ and that $Df(0)$ has k eigenvalues with negative real parts, j eigenvalues with positive real parts, and $m = n - k - j$ eigenvalues with zero real parts. Then, there exists an $m-$ dimensional centre manifold $W^c(0)$ of class C^r tangent to centre subspace E^c of (2.7) which is invariant under the flow ϕ_t of (2.1).*

Lemma 2.2. *The local centre manifold of the system (2.1) at 0,*

$$W^c_{loc}(0) = \{(x, y) \in \mathbb{R}^m \times \mathbb{R}^k \mid y = h(x) \quad \text{for} \quad |x| < \delta\}, \tag{2.8}$$

for some $\delta > 0$, where $h \in C^r(N_\delta(0))$, $h(0) = 0$ and $Dh(0) = O$ since $W^c(0)$ is tangent to the centre subspace

$$E^c = \{(x, y) \in \mathbb{R}^m \times \mathbb{R}^k \mid y = 0\},$$

at the origin.

Theorem 2.7. (Center Manifold Theory [73]). *Let $f \in C^r(E)$ where E is an open subset of $\mathbb{R}^n$ containing the origin and $r \geq 1$. Suppose that $f(0) = 0$ and that $Df(0)$ has m eigenvalues with zero real parts and k eigenvalues with negative real parts, where $m + k = n$. The system (2.1) then can be written in diagonal form*

$$\begin{aligned} \dot{x} &= Cx + F(x, y), \\ \dot{y} &= Py + G(x, y), \end{aligned}$$

where $(x, y) \in \mathbb{R}^m \times \mathbb{R}^k$, C is a square matrix with m eigenvalues having zero real parts, P is a square matrix with k eigenvalues with negative real parts, and $F(0) = G(0) = 0$, $DF(0) = DG(0) = O$. Furthermore, there exists a $\delta > 0$ and a function $h \in C^r(N_\delta(0))$ that

defines the local centre manifold (2.8) and satisfies

$$Dh(x)[Cx + F(x, h(x))] - Ph(x) - G(x, h(x)) = 0,$$

for $|x| < \delta$*; and the flow on the centre manifold* $W^c(0)$ *is defined by the system of differential equations*

$$\dot{x} = Cx + F(x, h(x)),$$

for all $x \in \mathbb{R}^m$ *with* $|x| < \delta$*.*

Theorem 2.7 can be used to determine the flow near non-hyperbolic equilibrium points [73].

2.5 Bifurcation Theory

Bifurcation theory plays an important role in providing deeper insight into the qualitative dynamics of many phenomena arising in the natural and engineering sciences.

Consider the non-linear autonomous ODE system

$$\dot{x} = f(x, \mu), \quad x \in \mathbb{R}^n, \tag{2.9}$$

where f is a function of time and μ is a scalar parameter.

Definition 2.13. *Bifurcation is defined as a change in the qualitative behaviour of a given dynamical system when an associated parameter is varied.*

Definition 2.14. *The parameter values where bifurcation occurs are called bifurcation values (or bifurcation points).*

There are numerous types of bifurcations, including saddle-node, transcritical, pitchfork, Hopf, and backward bifurcation [44, 47, 73, 98]. The following theorem, which uses Centre Manifold Theory, is used to establish the existence of backward bifurcation phenomenon (for the models in Chapters 3 and 4 of the thesis).

Theorem 2.8. (Castillo-Chavez & Song [11, 14]). *Consider the following general system of ordinary differential equations with a parameter* ϕ

$$\frac{dx}{dt} = f(x,\phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} and \quad f \in \mathbb{C}^2\left(\mathbb{R}^n \times \mathbb{R}\right), \tag{2.10}$$

where 0 is an equilibrium point of the system (that is, $f(0,\phi) \equiv 0$ *for all* ϕ*) and assume*

A.1) $A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ *is the linearization matrix of the system (2.10) around the equilibrium 0 with* ϕ *evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;*

A.2) Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue).

Let f_k *be the k-th component of f and*

$$\begin{aligned} a &= \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ b &= \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \end{aligned}$$

The local dynamics of the system around 0 is totally determined by the signs of a and b.

i) $a > 0, b > 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is locally asymptotically stable and there exists a positive unstable equilibrium; when* $0 < \phi \ll 1$, *0 is unstable and there exists a negative, locally asymptotically stable equilibrium;*

ii) $a < 0, b < 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is unstable; when* $0 < \phi \ll 1$, *0 is locally asymptotically stable equilibrium, and there exists a positive unstable equilibrium;*

iii) $a > 0, b < 0$. *When* $\phi < 0$ *with* $|\phi| \ll 1$, *0 is unstable, and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi \ll 1$, *0 is stable, and a positive unstable equilibrium appears;*

iv) $a < 0, b > 0$. *When* ϕ *changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

Particularly, if $a > 0$ *and* $b > 0$, *then a backward bifurcation occurs at* $\phi = 0$.

2.6 Lyapunov Function Theory

A powerful method for analyzing the stability of an equilibrium point is based on the use of Lyapunov functions.

Definition 2.15. [73]. *A point* $x_0 \in \mathbb{R}^n$ *is called an* $\omega-$*limit point of* $x \in \mathbb{R}^n$, *denoted by* $\omega(x)$, *if there exists a sequence* $\{t_i\}$ *such that*

$$\phi(t_i, x) \to x_0 \quad \text{as} \quad t_i \to \infty.$$

Definition 2.16. [73]. *A point* $x_0 \in \mathbb{R}^n$ *is called an* $\alpha-$*limit point of* $x \in \mathbb{R}^n$, *denoted by* $\alpha(x)$, *if there exists a sequence* $\{t_i\}$ *such that*

$$\phi(t_i, x) \to x_0 \quad \text{as} \quad t_i \to -\infty.$$

Definition 2.17. [73]. *The set of all* $\omega-$*limit points of a flow is called the* $\omega-$*limit set. Similarly, The set of all* $\alpha-$*limit points of a flow is called the* $\alpha-$*limit set.*

Definition 2.18. [98]. *Let* $S \subset \mathbb{R}^n$ *be a set. Then,* S *is said to be invariant under the flow generated by* $\dot{x} = f(x)$ *if for any* $x_0 \in S$ *we have* $\phi(t, x_0) \in S$ *for all* $t \in \mathbb{R}$.

Lemma 2.3. [98]. *A set* $S \subset \mathbb{R}^n$ *is positively-invariant if, for every* $x_0 \in S$, $\phi(t, x_0) \in S$, $\forall$ $t \geq 0$.

Definition 2.19. [98]. *A function* $V : \mathbb{R}^n \to \mathbb{R}$ *is said to be positive-definite if:*

- $V(x) > 0$ *for all* $x \neq 0$,
- $V(x) = 0$ *if and only if* $x = 0$.

Definition 2.20. [98]. *Consider the system (2.1). Let* $\bar{x}$ *be an equilibrium solution of the system (2.1), and let* $V : U \to \mathbb{R}$ *be a* C^1 *function defined on some neighbourhood* U *of* $\bar{x}$ *such that*

i) V *is positive-definite,*

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

Definition 2.21. [98]. *Any function,* V*, that satisfies the conditions (i) and (ii) in Definition 2.20 is called a Lyapunov function.*

Theorem 2.9. (LaSalle's Invariance Principle [44]). *Consider the system (2.1). Let,*

$$S = \{x \in \bar{U} : \dot{V}(x) = 0\} \tag{2.11}$$

and M *be the largest positive invariant set of the system (2.1) in* S*. If* V *is a Lyapunov function on* U *and* $\gamma^+(x_0)$ *is a bounded orbit of the system (2.1) which lies in* S*, then the* $\omega-$*limit set of* $\gamma^+(x_0)$ *belongs to* M*; that is,* $x(t, x_0) \to M$ *as* $t \to \infty$.

Corollary 2.1. *If* $V(x) \to \infty$ *as* $|x| \to \infty$ *and* $\dot{V} \leq 0$ *on* $\mathbb{R}^n$*, then every solution of the system (2.1) is bounded and approaches the largest invariant set* M *of (2.1) in the set where* $\dot{V} = 0$*. In particular, if* $M = \{0\}$*, then the solution* $x = 0$ *is globally-asymptotically stable (GAS).*

2.7 Comparison Theorem

Comparison Theorem is sometimes used to prove the global asymptotic stability of equilibria of dynamical systems. The general idea is to compare the solutions of the non-linear system

$$\dot{x} = f(t, x), \tag{2.12}$$

with those of the differential inequality system

$$\dot{z} \leq f(t, z), \tag{2.13}$$

or,

$$\dot{y} \geq f(t, y), \tag{2.14}$$

on an interval. The technique requires that the system (2.12) has a unique solution. Consider the autonomous system (2.12), where f is a continuously-differentiable function on an open subset $\mathcal{D} \subset \mathbb{R}^n$. Let $\phi_t(x)$ denote the solution of the system (2.12) with initial value x.

Definition 2.22. [87]. *f is said to be of Type K in $\mathcal{D}$ if for each i, $f_i(a) \leq f_i(b)$ for any two points, a and b, in $\mathcal{D}$ satisfying $a \leq b$ and $a_i = b_i$.*

Definition 2.23. [87]. *The subset $\mathcal{D}$ is p-convex if $tx + (1-t)y \in \mathcal{D}$ for all $t \in [0, 1]$ whenever $x, y \in \mathcal{D}$ and $x \leq y$.*

Thus, if $\mathcal{D}$ is a convex set, then it is also p-convex. If $\mathcal{D}$ is a p-convex subset of $\mathbb{R}^n$ and

$$\frac{\partial f_i}{\partial x_j} \geq 0, \quad i \neq j, \quad x \in \mathcal{D}, \tag{2.15}$$

then f is of Type K in $\mathcal{D}$ (i.e., the Type K condition can be identified from the sign structure of the Jacobian matrix of the system (2.12) [87]).

Theorem 2.10. (Comparison Theorem [88]). *Let f be continuous on $\mathbb{R} \times D$ and of Type K. Let $x(t)$ be a solution of (2.12) defined on $[a, b]$. If $z(t)$ is a continuous function on $[a, b]$*

satisfying (2.13) 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 on* $[a, b]$ *satisfying (2.14) on* (a, b)*, with* $y(a) \geq x(a)$*, then* $y(t) \geq x(t)$ *for all* t *in* $[a, b]$*.*

Chapter 3

HPV Model Using the *Gardasil* Vaccine for Females

3.1 Introduction

As stated in Chapter 1, two anti-HPV vaccines are currently available in the market [15, 46, 68, 76, 93, 96]. These vaccines, which are highly-effective against HPV infection (with efficacy of about 90-100% [15, 76, 93, 96]), have been approved for use in a number of countries, including Australia, Canada, USA and some European countries [1, 76, 100]. In this chapter, the quadrivalent *Gardasil* vaccine (which targets the four vaccine-preventable HPV types, namely HPV-6, HPV-11, HPV-16 and HPV-18) will be considered. The vaccine is recommended for females between 9 and 13 years of age (as this is the age range before the onset of sexual activity for most females; the vaccine should be administered to females before they become sexually-active in order to ensure maximum benefit [10, 15, 76]).

In other words, the objective of this chapter is to qualitatively assess the community-wide impact of mass vaccination, of new sexually-active susceptible females using the quadrivalent *Garadsil* vaccine, on the transmission dynamics of the aforementioned four vaccine-preventable HPV types in a community. To achieve this objective, a new deterministic

model, for the heterosexual transmission of HPV community, will be formulated and rigorously analysed, as below.

Although there are many types of cancers associated with HPV infection [10, 15, 26, 46, 50, 76], this chapter considers only cervical cancer (because it is the more predominant of all the HPV-related cancers [10, 15, 33, 34, 35, 45, 46, 50, 76, 77, 97]). Furthermore, it is worth mentioning that a sizeable percentage of HPV-infected females (particularly those who are untreated) develop persistent HPV infection, and become at the greatest risk of developing cervical cancer precursor lesions, causing cell abnormalities (known as cervical intraepithelial neoplasia (CIN)) and cervical cancer [10, 15, 26, 35, 45, 46, 50, 61, 68, 77].

HPV infection affects men as well, causing serious cancers including throat and penile cancers (*albeit* they are less common) [71, 76]. Although some researchers suggest that both females and males should be vaccinated against HPV [46, 76, 77] (while others suggest vaccinating females only is more effective than vaccinating both males and females [9, 40, 41, 68]), this chapter considers the vaccination of females only (in line with the studies reported in [9, 24, 25, 26, 61]). This assumption (of vaccinating only females) is relaxed in Chapter 4, where both new sexually-active susceptible males and females are vaccinated.

3.2 Model Formulation

The model to be constructed is based on the heterosexual transmission dynamics of HPV in a community, subject to the use of mass vaccination of new sexually-active susceptible females (of ages 9 to 13) using the quadrivalent *Gardasil* vaccine. The model assumes homogenous mixing of the sexually-active female and male populations. The total sexually-active population at time t, denoted by $N(t)$, is sub-divided into two gender groups, namely the total female population at time t (denoted by $N_f(t)$) and the total male population at time t (denoted by $N_m(t)$). The total sexually-active female population ($N_f(t)$) is further sub-divided into eight mutually-exclusive compartments of unvaccinated susceptible females

($S_f(t)$), new sexually-active susceptible females vaccinated with the *Gardasil* vaccine ($V_f(t)$), exposed (i.e., latently-infected, and show no clinical symptoms of HPV) females ($E_f(t)$), infected females with clinical symptoms (symptomatic) of HPV ($I_f(t)$), infected females with persistent HPV infection ($P(t)$), infected females with cervical cancer ($C(t)$), infected females who recovered from cervical cancer ($R_c(t)$), and infected females who recovered from infection without developing cervical cancer ($R_f(t)$).

Furthermore, the total sexually-active male population at time t ($N_m(t)$) is sub-divided into susceptible ($S_m(t)$), exposed ($E_m(t)$), infected with clinical symptoms of HPV ($I_m(t)$) and recovered ($R_m(t)$) males. Thus,

$$N(t) = N_f(t) + N_m(t),$$

where,

$$N_f(t) = S_f(t) + V_f(t) + E_f + I_f(t) + P(t) + C(t) + R_c(t) + R_f(t),$$

and,

$$N_m(t) = S_m(t) + E_m + I_m(t) + R_m(t).$$

It should be emphasized that, in this thesis, individuals in the exposed (E_f and E_m) and persistent (P) classes are infected with HPV, and can transmit HPV to susceptible individuals.

The population of unvaccinated susceptible females (S_f) is increased by the recruitment of new sexually-active females at a rate $\pi_f(1\text{-}\varphi_f)$, where $0 < \varphi_f \leq 1$ is the fraction of newly-recruited sexually-active females (typically of ages 9 to 13 years [10, 15, 76]) who are vaccinated with the *Gardasil* vaccine. This population is further increased by the loss of infection-acquired immunity by recovered females who did not develop cervical cancer (at a rate ξ_f). Unvaccinated susceptible females acquire HPV infection, following effective contact

with infected males (i.e., those in the E_m and I_m classes), at a rate λ_m, where

$$\lambda_m = \frac{\beta_m c_f\left(N_m, N_f\right)\left(\eta_m E_m + I_m\right)}{N_m}. \tag{3.1}$$

In (3.1), β_m is the probability of infection from males to females *per* contact, and $c_f\left(N_m, N_f\right)$ is the average number of female partners *per* male *per* unit time. Thus, $\beta_m c_f\left(N_m, N_f\right)$ is the effective contact rate (i.e., contact capable of leading to infection) for male-to-female transmission of HPV. Furthermore, η_m (with $0 \leq \eta_m < 1$) is the modification parameter accounting for the assumption that exposed males are less infectious than symptomatically-infected males (in other words, unlike in many other HPV transmission modelling studies (such as those in [9, 24, 25, 26, 61]), the model to be developed in this chapter assumes HPV transmission by exposed individuals). It should be emphasized that a standard incidence formulation is used in (3.1), where the contact rate is assumed to be constant, unlike in the case of the mass action incidence (where the contact rate increases linearly with the total size of the population [47]). It has been shown that using standard incidence function is more suited for modelling human diseases than mass action incidence [58]. The population of unvaccinated susceptible females is further decreased by natural death at a rate μ_f (it is assumed that females in all epidemiological compartments suffer natural death at the rate μ_f). Thus,

$$\frac{dS_f}{dt} = \pi_f(1-\varphi_f) + \xi_f R_f - \lambda_m S_f - \mu_f S_f. \tag{3.2}$$

The population of vaccinated new sexually-active susceptible females with the *Gardasil* vaccine (V_f) is generated by the vaccination of unvaccinated susceptible females (at the rate $\pi_f\varphi_f$), and is decreased by HPV infection (at the reduced rate $\lambda_m(1-\varepsilon_v)$, where $0 < \varepsilon_v \leq 1$ represents the vaccine efficacy against HPV infection) and natural death. As in [10, 15, 46, 76, 77], it is assumed that the *Gardasil* vaccine does not wane for the duration of the HPV dynamics considered (to our knowledge, no evidence of waning *Gardasil* vaccine

protection has been shown in the literature). Thus,

$$\frac{dV_f}{dt} = \pi_f \varphi_f - (1 - \varepsilon_v)\lambda_m V_f - \mu_f V_f. \tag{3.3}$$

The population of exposed females (E_f) is generated by the infection of unvaccinated and vaccinated susceptible females. This population is further increased by the re-infection of recovered females (at a rate $\rho_f \lambda_m$, where $0 \leq \rho_f < 1$ accounts for the assumption that the re-infection of recovered females occur at a rate lower than the primary infection of unvaccinated susceptible females). It is assumed, unlike in some other modelling studies of HPV transmission dynamics (such as those in [9, 24, 25, 26, 61]), that HPV infection does not confer permanent immunity against re-infection. Exposed females develop clinical symptoms of HPV (at a rate σ_f) and suffer natural death. Thus,

$$\frac{dE_f}{dt} = \lambda_m \left[S_f + (1 - \varepsilon_v)V_f\right] + \rho_f \lambda_m R_f - (\sigma_f + \mu_f)E_f. \tag{3.4}$$

The population of infected females with clinical symptoms of HPV (I_f) is generated at the rate σ_f. This population is decreased by recovery (at a rate ψ_f) and natural death. Hence,

$$\frac{dI_f}{dt} = \sigma_f E_f - (\psi_f + \mu_f)I_f. \tag{3.5}$$

The population of infected females with persistent HPV infection (P) is generated when infected females with clinical symptoms of HPV develop persistent HPV infection (at a rate $\psi_f(1-r_f)$, where $0 < r_f \leq 1$ is the fraction of infected females with clinical symptoms of HPV who recover naturally from HPV infection without developing persistent HPV infection). Females with persistent HPV infection move out of this epidemiological class (either through recovery or development of cervical cancer) at a rate α_f, and suffer natural death. Thus,

$$\frac{dP}{dt} = \psi_f(1 - r_f)I_f - (\alpha_f + \mu_f)P. \tag{3.6}$$

It should be mentioned that the model to be developed in this chapter does not not explicitly account for the pre-cancerous CIN stages (*albeit* the P class is assumed to also contain individuals in the CIN stages; individuals in the CIN stages are typically detected using Pap screening [61], which is also not explicitly incorporated in the model to be developed in this chapter, although it is, intuitively, the reason individuals in the persistent infection class are moved to the cancer class). The dynamics of the CIN stages is explicitly modelled in Chapter 4.

The population of females with cervical cancer (C) is generated by the development of cervical cancer by infected females with persistent HPV infection (at a rate $\alpha_f(1-\kappa_f)$, where $0 < \kappa_f \leq 1$ is the fraction of infected females with persistent HPV infection who recovered from HPV infection). This population decreases due to recovery (at a rate γ_f), natural death and disease-induced death (at a rate δ_f). Hence,

$$\frac{dC}{dt} = \alpha_f(1-\kappa_f)P - (\gamma_f + \mu_f + \delta_f)C. \tag{3.7}$$

The class of infected females who recovered from cervical cancer (R_c) is generated at the rate γ_f, and decreases by natural death, so that

$$\frac{dR_c}{dt} = \gamma_f C - \mu_f R_c. \tag{3.8}$$

The population of infected females who recovered from infection without developing cervical cancer (R_f) is generated at the rates $\psi_f r_f$ and $\alpha_f \kappa_f$, respectively. Recovered females acquire HPV re-infection at the rate $\rho_f \lambda_m$. This population is further decreased by the loss of infection-acquired immunity (at the rate ξ_f) and natural death. This gives:

$$\frac{dR_f}{dt} = \psi_f r_f I_f + \alpha_f \kappa_f P - (\rho_f \lambda_m + \xi_f + \mu_f)R_f. \tag{3.9}$$

The population of susceptible males (S_m) is generated by the recruitment of new sexually-

active males (at a rate π_f). It is further increased by the loss of infection-acquired immunity by recovered males (at a rate ξ_m). This population is diminished by infection, following effective contact with infected females, at a rate λ_f, where

$$\lambda_f = \frac{\beta_f c_m\left(N_m, N_f\right)\left(\eta_f E_f + I_f + \theta_p P\right)}{N_f}. \tag{3.10}$$

In (3.10), β_f is the probability of infection from females to males *per* contact, $c_m\left(N_m, N_f\right)$ is the average number of male partners *per* female *per* unit time, η_f $(0 \leq \eta_f < 1)$ is the modification parameter accounting for the assumption that exposed females (i.e., those in the E_f class) are less infectious than symptomatically-infected females (i.e., those in the I_f class), and $\theta_p > 0$ is the modification parameter accounting for the assumption that infected females with persistent HPV infection transmit HPV at a different rate compared to infected females in the I_f class. This population is further decreased by natural death (at a rate μ_m; it is assumed that males in all epidemiological compartments suffer natural death at this rate, μ_m). Thus,

$$\frac{dS_m}{dt} = \pi_m + \xi_m R_m - \lambda_f S_m - \mu_m S_m. \tag{3.11}$$

The population of exposed males (E_m) is generated by the infection of susceptible males (at the rate λ_f) and by the re-infection of recovered males (at a rate $\rho_m \lambda_f$, where $0 \leq \rho_m < 1$ accounts for the assumption that the re-infection of recovered males occur at a rate lower than the primary infection of susceptible males). Exposed males develop clinical symptoms of HPV (at a rate σ_m) and suffer natural death. Thus,

$$\frac{dE_m}{dt} = \lambda_f S_m + \rho_m \lambda_f R_m - (\sigma_m + \mu_m) E_m. \tag{3.12}$$

The population of infected males with clinical symptoms of HPV (I_m) is generated at the

rate σ_m. It is reduced by recovery (at a rate ψ_m) and natural death. Hence,

$$\frac{dI_m}{dt} = \sigma_m E_m - (\psi_m + \mu_m) I_m. \tag{3.13}$$

The population of recovered males (R_m) is generated at the rate ψ_m. It is decreased by re-infection (at the rate $\rho_m \lambda_f$), loss of infection-acquired immunity (at the rate ξ_m) and natural death, so that

$$\frac{dR_m}{dt} = \psi_m I_m - (\rho_m \lambda_f + \xi_m + \mu_m) R_m. \tag{3.14}$$

It should be mentioned that no disease-induced death is assumed for males (although this assumption is justified owing to the fact that penile cancer is rare [46], it will be relaxed in the model to be developed in Chapter 4). Furthermore, no pre-cancerous or cancer stages are considered for males in the model developed in this chapter (this assumption is also relaxed in Chapter 4). It follows from the equations given in {(3.11)-(3.14)} that

$$\frac{dN_m}{dt} = \pi_m - \mu_m N_m, \tag{3.15}$$

so that $N_m(t) \to \frac{\pi_m}{\mu_m}$, as $t \to \infty$.

It is worth mentioning that an important feature of a sex-structured disease transmission model, such as {(3.1)-(3.14)}, is that the total number of sexual contacts females make with males must equal the total number of sexual contacts males make with females (see, for instant, [13, 27, 65, 84, 101]). Thus, the following conservation law (for number of sexual contacts made by males balancing those made by females) must hold:

$$c_m\left(N_m, N_f\right) N_m = c_f\left(N_m, N_f\right) N_f. \tag{3.16}$$

It is assumed that male sexual partners are abundant, so that females can always have enough number of male sexual contacts *per* unit time. Hence, it is assumed that $c_f\left(N_m, N_f\right) = c_f$,

a constant, and $c_m\left(N_m, N_f\right)$ is calculated from the relation

$$c_m\left(N_m, N_f\right) = \frac{c_f N_f}{N_m}. \tag{3.17}$$

Using the constraint (3.17) in (3.1) and (3.10), the infection rates λ_m and λ_f are, now, given, respectively, by

$$\lambda_m = \frac{\beta_m c_f\left(\eta_m E_m + I_m\right)}{N_m} \quad \text{and} \quad \lambda_f = \frac{\beta_f c_f\left(\eta_f E_f + I_f + \theta_p P\right)}{N_m}. \tag{3.18}$$

Based on the above formulations and assumptions (and using (3.18) for (3.1) and (3.10)), the model for the heterosexual transmission of HPV (and associated dysplasia), in a community that implements a mass vaccination campaign against HPV (using the quadrivalent *Gardasil* vaccine), is given by the following deterministic system of non-linear differential equations:

$$
\begin{aligned}
\frac{dS_f}{dt} &= \pi_f(1-\varphi_f) + \xi_f R_f - \frac{\beta_m c_f\left(\eta_m E_m + I_m\right)}{N_m} S_f - \mu_f S_f, \\
\frac{dV_f}{dt} &= \pi_f \varphi_f - (1-\varepsilon_v)\frac{\beta_m c_f\left(\eta_m E_m + I_m\right)}{N_m} V_f - \mu_f V_f, \\
\frac{dE_f}{dt} &= \frac{\beta_m c_f\left(\eta_m E_m + I_m\right)}{N_m}\left[S_f + (1-\varepsilon_v)V_f + \rho_f R_f\right] - (\sigma_f + \mu_f)E_f, \\
\frac{dI_f}{dt} &= \sigma_f E_f - (\psi_f + \mu_f) I_f, \\
\frac{dP}{dt} &= \psi_f(1-r_f) I_f - (\alpha_f + \mu_f) P, \\
\frac{dC}{dt} &= \alpha_f(1-\kappa_f) P - (\gamma_f + \mu_f + \delta_f) C, \\
\frac{dR_c}{dt} &= \gamma_f C - \mu_f R_c, \\
\frac{dR_f}{dt} &= \psi_f r_f I_f + \alpha_f \kappa_f P - \left[\rho_f \frac{\beta_m c_f\left(\eta_m E_m + I_m\right)}{N_m} + \xi_f + \mu_f\right] R_f, \\
\frac{dS_m}{dt} &= \pi_m + \xi_m R_m - \frac{\beta_f c_f\left(\eta_f E_f + I_f + \theta_p P\right)}{N_m} S_m - \mu_m S_m, \\
\frac{dE_m}{dt} &= \frac{\beta_f c_f\left(\eta_f E_f + I_f + \theta_p P\right)}{N_m}\left(S_m + \rho_m R_m\right) - (\sigma_m + \mu_m) E_m, \\
\frac{dI_m}{dt} &= \sigma_m E_m - (\psi_m + \mu_m) I_m, \\
\frac{dR_m}{dt} &= \psi_m I_m - \left[\rho_m \frac{\beta_f c_f\left(\eta_f E_f + I_f + \theta_p P\right)}{N_m} + \xi_m + \mu_m\right] R_m.
\end{aligned}
\tag{3.19}
$$

A flow diagram of the model (3.19) is depicted in Figure 3.1. The state variables and parameters of the model are tabulated in Table 3.1.

The model (3.19) is an extension of the HPV vaccination models in [9, 24, 25, 26, 61], by:

i) including classes for exposed females (E_f) and males (E_m);

ii) allowing for disease transmission by exposed females and males ($\eta_f \neq 0$, $\eta_m \neq 0$);

iii) allowing for the loss of infection-acquired immunity by recovered individuals ($\xi_f \neq 0$, $\xi_m \neq 0$);

iv) allowing for the re-infection of recovered individuals ($\rho_f \neq 0$, $\rho_m \neq 0$).

Furthermore, the model (3.19) extends the vaccination models in [9, 26] by, in addition to Items (i)-(iii) above, including disease-induced mortality ($\delta_f \neq 0$) and a compartment for females with persistent HPV infection (P).

3.2.1 Basic properties

The basic qualitative features of the basic HPV vaccination model (3.19) will be explored. First of all, for the vaccination model (3.19) to be epidemiologically meaningful, it is important to show that all its state variables are non-negative for all time $t > 0$ (i.e., the solutions of the vaccination model (3.19) with non-negative initial data must remain non-negative for all $t > 0$).

Theorem 3.1. *Let the initial data for the vaccination model (3.19) be* $S_f(0) > 0, V_f(0) > 0, E_f(0) \geq 0, I_f(0) \geq 0, P(0) \geq 0, C(0) \geq 0, R_c(0) \geq 0, R_f(0) \geq 0, S_m(0) > 0, E_m(0) \geq 0, I_m(0) \geq 0,$ *and* $R_m(0) \geq 0$. *Then, the solutions* $(S_f(t), V_f(t), E_f(t), I_f(t), P(t), C(t), R_c(t), R_f(t), S_m(t), E_m(t), I_m(t), R_m(t))$ *of the model with positive initial data, will remain positive for all time* $t > 0$.

The proof of Theorem 3.1 is given in Appendix A.

Theorem 3.2. *The closed set*

$$\mathcal{D} = \left\{(S_f, V_f, E_f, I_f, P, C, R_c, R_f, S_m, E_m, I_m, R_m) \in \mathbb{R}^{12}_+ : N_f \leq \frac{\pi_f}{\mu_f}, N_m \leq \frac{\pi_m}{\mu_m}\right\}$$

is positively-invariant and attracting with respect to the model (3.19).

Proof. Adding the first eight equations of the model (3.19) gives:

$$\frac{dN_f}{dt} = \pi_f - \mu_f N_f - \delta_f C \leq \pi_f - \mu_f N_f. \tag{3.20}$$

It follows from (3.20) that $\frac{dN_f}{dt} < 0$ if $N_f(t) > \frac{\pi_f}{\mu_f}$. Thus, using a standard Comparison Theorem (Theorem 2.10; see also [58]),

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

Therefore, $N_f(t) \leq \frac{\pi_f}{\mu_f}$ if $N_f(0) \leq \frac{\pi_f}{\mu_f}$. Similarly, it follows from (3.15) that

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

Hence, $N_m(t) \leq \frac{\pi_m}{\mu_m}$ if $N_m(0) \leq \frac{\pi_m}{\mu_m}$. Thus, $\mathcal{D}$ is positively-invariant. Furthermore, if $N_f(t) > \frac{\pi_f}{\mu_f}$ and $N_m(t) > \frac{\pi_m}{\mu_m}$; then either the solution enters $\mathcal{D}$ in finite time, or $N_f(t)$ approaches $\frac{\pi_f}{\mu_f}$ and $N_m(t)$ approaches $\frac{\pi_m}{\mu_m}$, and the state variables associated with the infected classes of the model approach zero. Hence, $\mathcal{D}$ attracts all solutions in $\mathbb{R}^{12}_+$. □

In the region $\mathcal{D}$, the model (3.19) can be considered as epidemiologically and mathematically well-posed [47].

3.3 Analysis of Vaccination-free Model

Before analyzing the vaccination model (3.19), it is instructive to gain insight into the dynamics of the model (3.19) in the absence of vaccination (i.e., the model (3.19) with $\varphi_f = V_f = 0$). The resulting vaccination-free model is given by

$$
\begin{aligned}
\frac{dS_f}{dt} &= \pi_f + \xi_f R_f - \frac{\beta_m c_f \left(\eta_m E_m + I_m\right)}{N_m} S_f - \mu_f S_f, \\
\frac{dE_f}{dt} &= \frac{\beta_m c_f \left(\eta_m E_m + I_m\right)}{N_m} \left(S_f + \rho_f R_f\right) - (\sigma_f + \mu_f) E_f, \\
\frac{dI_f}{dt} &= \sigma_f E_f - (\psi_f + \mu_f) I_f, \\
\frac{dP}{dt} &= \psi_f (1 - r_f) I_f - (\alpha_f + \mu_f) P, \\
\frac{dC}{dt} &= \alpha_f (1 - \kappa_f) P - (\gamma_f + \mu_f + \delta_f) C, \\
\frac{dR_c}{dt} &= \gamma_f C - \mu_f R_c, \\
\frac{dR_f}{dt} &= \psi_f r_f I_f + \alpha_f \kappa_f P - \left[\rho_f \frac{\beta_m c_f \left(\eta_m E_m + I_m\right)}{N_m} + \xi_f + \mu_f\right] R_f, \\
\frac{dS_m}{dt} &= \pi_m + \xi_m R_m - \frac{\beta_f c_f \left(\eta_f E_f + I_f + \theta_p P\right)}{N_m} S_m - \mu_m S_m, \\
\frac{dE_m}{dt} &= \frac{\beta_f c_f \left(\eta_f E_f + I_f + \theta_p P\right)}{N_m} \left(S_m + \rho_m R_m\right) - (\sigma_m + \mu_m) E_m, \\
\frac{dI_m}{dt} &= \sigma_m E_m - (\psi_m + \mu_m) I_m, \\
\frac{dR_m}{dt} &= \psi_m I_m - \left[\rho_m \frac{\beta_f c_f \left(\eta_f E_f + I_f + \theta_p P\right)}{N_m} + \xi_m + \mu_m\right] R_m,
\end{aligned}
\tag{3.21}
$$

where, now,

$$
N_f(t) = S_f(t) + E_f(t) + I_f(t) + P(t) + C(t) + R_c(t) + R_f(t),
$$

and,

$$
N_m(t) = S_m(t) + E_m(t) + I_m(t) + R_m(t).
$$

For the vaccination-free model (3.21), it can be shown (using the approach in Section 3.2.1) that the following region is positively-invariant and attracting

$$
\mathcal{D}_1 = \left\{(S_f, E_f, I_f, P, C, R_c, R_f, S_m, E_m + I_m, R_m) \in \mathbb{R}_+^{11} : N_f \leq \frac{\pi_f}{\mu_f}, N_m \leq \frac{\pi_m}{\mu_m}\right\},
$$

so that it is sufficient to consider the dynamics of the vaccination-free model (3.21) in $\mathcal{D}_1$.

It is worth noting from (3.15) that $N_m(t) \to \frac{\pi_m}{\mu_m}$ as $t \to \infty$. Consequently, from now on, the total male population at time t (given by $N_m(t)$) will be replaced by its limiting value, $\frac{\pi_m}{\mu_m}$ (since $N_m(t) \to \frac{\pi_m}{\mu_m}$, as $t \to \infty$). In other words, the rest of the analyses in this chapter will be carried out with $N_m(t)$, in (3.19) and (3.21), replaced by its limiting value, $N_m^* = \frac{\pi_m}{\mu_m}$.

3.3.1 Local asymptotic stability of disease-free equilibrium (DFE)

The vaccination-free model (3.21) has a DFE, obtained by setting the right-hand sides of the equations in the model (3.21) to zero, given by

$$\mathcal{E}_0 = (S_f^*, E_f^*, I_f^*, P^*, C^*, R_c^*, R_f^*, S_m^*, E_m^*, I_m^*, R_m^*) = \left(\frac{\pi_f}{\mu_f}, 0, 0, 0, 0, 0, \frac{\pi_m}{\mu_m}, 0, 0\right). \tag{3.22}$$

with,

$$N_f^* = S_f^* = \frac{\pi_f}{\mu_f} \quad \text{and} \quad N_m^* = S_m^* = \frac{\pi_m}{\mu_m}. \tag{3.23}$$

The next generation operator method [95] (see also Section 2.3.2) will be used to explore the local stability of the DFE. The matrices $\mathcal{F}$ (of new infections) and $\mathcal{H}$ (of transfer terms between compartments) evaluated at the DFE ($\mathcal{E}_0$), are given, respectively, by

$$\mathcal{F} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\eta_m \beta_m c_f S_f^*}{N_m^*} & \frac{\beta_m c_f S_f^*}{N_m^*} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \eta_f \beta_f c_f & \beta_f c_f & \theta_p \beta_f c_f & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$\mathcal{H} = \begin{pmatrix} g_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_f & g_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -h_1 & n_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -h_2 & n_2 & 0 & 0 & 0 & 0 \\ 0 & -m_1 & -m_2 & 0 & g_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & g_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\sigma_m & g_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\psi_m & g_6 \end{pmatrix},$$

where,

$$\begin{aligned} g_1 &= \sigma_f + \mu_f,\ g_2 = \psi_f + \mu_f,\ h_1 = \psi_f(1 - r_f),\ h_2 = \alpha_f(1 - \kappa_f),\ n_1 = \alpha_f + \mu_f, \\ n_2 &= \gamma_f + \mu_f + \delta_f,\ m_1 = \psi_f r_f,\ m_2 = \alpha_f \kappa_f,\ g_3 = \xi_f + \mu_f,\ g_4 = \sigma_m + \mu_m, \\ g_5 &= \psi_m + \mu_m,\ g_6 = \xi_m + \mu_m. \end{aligned}$$

It follows from Theorem 2.4 that (where ρ is the spectral radius of $\mathcal{F}\mathcal{H}^{-1}$):

$$\mathcal{R}_0 = \rho\left(\mathcal{F}\mathcal{H}^{-1}\right) = \sqrt{\mathcal{R}_m \mathcal{R}_f}, \tag{3.24}$$

with,

$$\mathcal{R}_m = \frac{\beta_m c_f \mu_m \pi_f}{\pi_m \mu_f g_5}\left(\frac{\eta_m g_5 + \sigma_m}{g_4}\right) \quad \text{and} \quad \mathcal{R}_f = \frac{\beta_f c_f}{g_2}\left[\frac{\eta_f n_1 g_2 + \sigma_f(n_1 + \theta_p h_1)}{n_1 g_1}\right].$$

The result below follows from Theorem 2.4 (or Theorem 2 of [95]).

Theorem 3.3. *The DFE, $\mathcal{E}_0$, of the vaccination-free model (3.21), given by (3.22), is locally-asymptotically stable (LAS) if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The threshold quantity, $\mathcal{R}_0$, is the *basic reproduction number* of the model (3.21) [47]. It represents the average number of secondary HPV infections generated by a typical HPV-

infected person if introduced into a completely-susceptible sexually-active population (or community). It is worth noting that $\mathcal{R}_0$ is an aggregate product of the average number of new HPV cases generated by females (denoted by $\mathcal{R}_f$) and males (denoted by $\mathcal{R}_m$).

Epidemiologically speaking, Theorem 3.3 states that a small influx of infected individuals (males or females) will not generate large HPV outbreaks in the community if $\mathcal{R}_0 < 1$ (in other words, HPV can be effectively controlled in the community if the initial sizes of the sub-populations of the model (3.21) are in the basin of attraction of the DFE, $\mathcal{E}_0$, of the model (3.21)). However, in order for such effective control (or elimination) to be independent of the initial sizes of the sub-populations of the vaccination-free model (3.21), it is necessary to show that the DFE ($\mathcal{E}_0$), of the model (3.21), is globally-asymptotically stable (GAS) if $\mathcal{R}_0 < 1$. This is explored, for a special case, in Section 3.3.5.

3.3.2 Interpretation of the basic reproduction number ($\mathcal{R}_0$)

The reproduction threshold ($\mathcal{R}_0$) can be interpreted as follows. Susceptible females can acquire infection, following effective contacts with either exposed (E_m) or symptomatic males (I_m). The number of female infections generated by exposed males (near the DFE) is given by the product of the infection rate of exposed males $\left(\frac{\beta_m c_f \eta_m S_f^*}{N_m^*}\right)$ and the average duration in the exposed (E_m) class $\left(\frac{1}{\sigma_m+\mu_m} = \frac{1}{g_4}\right)$. Furthermore, the number of female infections generated by symptomatic males (near the DFE) is given by the product of the infection rate of symptomatic males $\left(\frac{\beta_m c_f S_f^*}{N_m^*}\right)$, the probability that an exposed male survives the exposed stage and move to the symptomatic stage $\left(\frac{\sigma_m}{\sigma_m+\mu_m} = \frac{\sigma_m}{g_4}\right)$ and the average duration in the symptomatic (I_m) class $\left(\frac{1}{\psi_m+\mu_m} = \frac{1}{g_5}\right)$. Thus, the average number of new female infections generated by infected males (exposed or symptomatic) is given by (noting that $S_f^* = \frac{\pi_f}{\mu_f}$ and $N_m^* = \frac{\pi_m}{\mu_m}$),

$$\left(\frac{\beta_m c_f \eta_m \mu_m}{\pi_m g_4} + \frac{\beta_m c_f \mu_m \sigma_m}{\pi_m g_4 g_5}\right) S_f^* = \frac{\beta_m c_f \mu_m \pi_f}{\pi_m \mu_f}\left(\frac{\eta_m g_5 + \sigma_m}{g_4 g_5}\right). \tag{3.25}$$

The two terms in the left-hand side (LHS) of (3.25), represent the number of new female infections generated by exposed males (E_m) and the number of new female infections generated by symptomatic males (I_m), respectively.

Similarly, susceptible males acquire HPV infection, following effective contacts with either exposed females (E_f), symptomatic females (I_f) or females with persistent HPV infection (P). The number of male infections generated by exposed females (near the DFE) is the product of the infection rate of exposed females $\left(\frac{\beta_f c_f \eta_f S_m^*}{N_m^*}\right)$ and the average duration in the exposed (E_f) class $\left(\frac{1}{\sigma_f+\mu_f} = \frac{1}{g_1}\right)$. 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 $\left(\frac{\sigma_f}{\sigma_f+\mu_f} = \frac{\sigma_f}{g_1}\right)$ and the average duration in the symptomatic (I_f) class $\left(\frac{1}{\psi_f+\mu_f} = \frac{1}{g_2}\right)$. 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 $\left(\frac{\beta_f c_f \theta_p S_m^*}{N_m^*}\right)$, the probability that an exposed female survives the exposed class and move to the symptomatic stage $\left(\frac{\sigma_f}{\sigma_f+\mu_f} = \frac{\sigma_f}{g_1}\right)$, the proportion of symptomatic females that move to the persistent infection class $\left(\frac{\psi_f(1-r_f)}{\psi_f+\mu_f} = \frac{h_1}{g_2}\right)$ and the average duration in the persistent infection class $\left(\frac{1}{\alpha_f+\mu_f} = \frac{1}{n_1}\right)$. Thus, the average number of new male infections generated by infected females (exposed, symptomatic or those with persistent HPV infection) is given by (noting that $S_m^* = \frac{\pi_m}{\mu_m}$)

$$\left(\frac{\beta_f c_f \eta_f \mu_m}{\pi_m g_1} + \frac{\beta_f c_f \mu_m \sigma_f}{\pi_m g_1 g_2} + \frac{\beta_f c_f \sigma_f \theta_p \mu_m h_1}{\pi_m n_1 g_1 g_2}\right) S_m^* = \beta_f c_f \left(\frac{\eta_f n_1 g_2 + \sigma_f n_1 + \sigma_f \theta_p h_1}{n_1 g_1 g_2}\right). \quad (3.26)$$

The terms in LHS of (3.26), represent the number of new male infections generated by exposed females (E_f), symptomatic (I_f) and females with persistent HPV infection (P).

Since two generations are needed in the female-male-female HPV transmission cycle, the geometric mean of (3.25) and (3.26) gives the *basic reproduction number*, $\mathcal{R}_0$ (interpretation for $\mathcal{R}_0$ is also given in [16, 37, 43] for other epidemiological settings).

3.3.3 Existence and local asymptotic stability of endemic equilibrium point (EEP)

It is instructive to determine the number of possible equilibrium solutions the vaccination-free model (3.21) can have. It is convenient to let

$$\mathcal{E}_1 = (S_f^{**}, E_f^{**}, I_f^{**}, P^{**}, C^{**}, R_c^{**}, R_f^{**}, S_m^{**}, E_m^{**}, I_m^{**}, R_m^{**}), \tag{3.27}$$

be an arbitrary endemic equilibrium of the model (3.21) (an equilibrium where all the infected components of the model are non-zero). Furthermore, let (it should be emphasized that N_m, in (3.21), is now replaced by $\frac{\pi_m}{\mu_m}$)

$$\lambda_m^{**} = \frac{\beta_m c_f \mu_m \left(\eta_m E_m^{**} + I_m^{**}\right)}{\pi_m}, \tag{3.28}$$

and,

$$\lambda_f^{**} = \frac{\beta_f c_f \mu_m \left(\eta_f E_f^{**} + I_f^{**} + \theta_p P^{**}\right)}{\pi_m}, \tag{3.29}$$

be the *force of infection* for males and females at steady- state, respectively.

Solving the equations of the vaccination-free (3.21) at the endemic steady-state gives:

$$\begin{aligned}
S_f^{**} &= \frac{\pi_f + \xi_f R_f^{**}}{\lambda_m^{**} + \mu_f},\ E_f^{**} = \frac{\lambda_m^{**}\left(S_f^{**} + \rho_f R_f^{**}\right)}{g_1},\ I_f^{**} = \frac{\sigma_f E_f^{**}}{g_2}, \\
P^{**} &= \frac{h_1 I_f^{**}}{n_1},\ C^{**} = \frac{h_2 P^{**}}{n_2},\ R_c^{**} = \frac{\gamma_f C^{**}}{\mu_f},\ R_f^{**} = \frac{m_1 I_f^{**} + m_2 P^{**}}{\rho_f \lambda_m^{**} + g_3}, \\
S_m^{**} &= \frac{\pi_m + \xi_m R_m^{**}}{\lambda_f^{**} + \mu_m},\ E_m^{**} = \frac{\lambda_f^{**}\left(S_m^{**} + \rho_m R_m^{**}\right)}{g_4},\ I_m^{**} = \frac{\sigma_m E_m^{**}}{g_5}, \\
R_m^{**} &= \frac{\psi_m I_m^{**}}{\rho_m \lambda_f^{**} + g_6}.
\end{aligned} \tag{3.30}$$

Substituting the expressions in (3.30) into (3.28) and (3.29) gives

$$\lambda_m^{**} = \frac{\lambda_f^{**} z_{11}\left(g_6+\lambda_f^{**}t_{12}\right)}{\left(\lambda_f^{**}\right)^2 z_{12}+\lambda_f^{**}z_{13}+z_{14}}, \tag{3.31}$$

$$\lambda_f^{**} = \frac{\lambda_m^{**} z_{21}\left(g_3+\lambda_m^{**}t_{22}\right)}{\left(\lambda_m^{**}\right)^2 z_{22}+\lambda_m^{**}z_{23}+z_{24}}, \tag{3.32}$$

with,

$$\begin{aligned}
z_{11} &= \beta_m c_f \mu_m \left(\eta_m g_5+\sigma_m\right), \quad t_{12}=\rho_m, \quad z_{12}=t_{12}\left(g_4g_5-\sigma_m\psi_m\right),\\
z_{13} &= g_4g_5\left(g_6+\mu_m t_{12}\right)-\sigma_m\psi_m\left(\xi_m+\mu_m t_{12}\right), \quad z_{14}=g_4g_5g_6\mu_m,\\
z_{21} &= \frac{\beta_f c_f \pi_f \mu_m}{\pi_m}\left(\eta_f n_1 g_2+n_1\sigma_f+\theta_p h_1\sigma_f\right), \quad t_{22}=\rho_f, \quad z_{22}=t_{22}\left[n_1g_1g_2-\sigma_f\left(n_1m_1+h_1m_2\right)\right],\\
z_{23} &= n_1g_1g_2\left(g_3+\mu_f t_{22}\right)-\sigma_f\left(n_1m_1+h_1m_2\right)\left(\xi_f+\mu_f t_{22}\right), \quad z_{24}=n_1g_1g_2g_3\mu_f.
\end{aligned} \tag{3.33}$$

The expressions in (3.33) can be simplified to

$$\begin{aligned}
z_{12} &= t_{12}\mu_m\left(\sigma_m+\psi_m+\mu_m\right)>0,\\
z_{13} &= \mu_m\left[\left(\sigma_m+\psi_m+\mu_m\right)\left(\xi_m+\mu_m t_{12}\right)+\left(\sigma_m+\mu_m\right)\left(\psi_m+\mu_m\right)\right]>0,\\
z_{22} &= t_{22}\mu_f\left(\sigma_f+\psi_f+\mu_f\right)\left(\mu_f+\alpha_f\right)+\sigma_f\psi_f\left(1-r_f\right)\left[\mu_f+\alpha_f\left(1+\kappa_f\right)\right]>0,\\
z_{23} &= \sigma_f\psi_f\left(1-r_f\right)\left\{\xi_f\left[\mu_f+\alpha_f\left(1-\kappa_f\right)\right]+t_{22}\mu_f\left(\alpha_f+\mu_f\right)\right\}\\
&+ \mu_f\left[\mu_f^2\left(\xi_f+\mu_f\right)+\sigma_f\xi_f\left(\alpha_f+\mu_f\right)\right]+\mu_f\left(\sigma_f+\xi_f+\mu_f\right)\left[\alpha_f\left(\psi_f+\mu_f\right)+\mu_f\psi_f\right]\\
&+ t_{22}\mu_f^2\left(\sigma_f+\psi_f+\mu_f\right)\left(\alpha_f+\mu_f\right)>0.
\end{aligned}$$

By substituting (3.32) into (3.31), and simplifying, it follows that the endemic equilibria of the vaccination-free model (3.21) satisfy the following polynomial (in terms of λ_m^{**}),

$$a_0\left(\lambda_m^{**}\right)^4+b_0\left(\lambda_m^{**}\right)^3+c_0\left(\lambda_m^{**}\right)^2+d_0\lambda_m^{**}+e_0=0, \tag{3.34}$$

where,

$$
\begin{aligned}
a_0 &= t_{22}z_{21}\left(t_{22}z_{21}z_{12}+z_{13}z_{22}\right)+z_{14}z_{22}^2,\\[2ex]
b_0 &= 2t_{22}g_3z_{12}z_{21}^2+z_{22}\left(z_{14}z_{23}+g_3z_{13}z_{21}\right)+z_{22}\left(z_{14}z_{23}-g_6g_3z_{11}z_{21}\right)\\
&+ t_{22}z_{21}\left(z_{13}z_{23}-t_{12}t_{22}z_{11}z_{21}\right),\\[2ex]
c_0 &= z_{22}z_{14}z_{24}\left(2-\mathcal{R}_0^2\right)+g_3z_{13}z_{21}z_{23}+g_3z_{21}\left(g_3z_{21}z_{12}-t_{12}t_{22}z_{11}z_{21}\right) \qquad (3.35)\\
&+ t_{22}z_{21}\left(z_{13}z_{23}-t_{12}g_3z_{11}z_{21}\right)+z_{13}\left(z_{14}z_{23}-g_6t_{22}z_{11}z_{21}\right),\\[2ex]
d_0 &= z_{23}z_{14}z_{24}\left(1-\mathcal{R}_0^2\right)+z_{24}\left(g_3z_{13}z_{21}-g_6t_{22}z_{11}z_{21}\right)+g_3z_{21}\left(z_{24}z_{13}-t_{12}g_3z_{11}z_{21}\right),\\[2ex]
e_0 &= z_{11}z_{24}^2\left(1-\mathcal{R}_0^2\right).
\end{aligned}
$$

It follows from (3.35) that the coefficient, a_0, of the quartic (3.34), is always positive (since all the parameters of the model (3.21) are positive). Furthermore, the coefficient, e_0, is positive (negative) if $\mathcal{R}_0$ is less than (greater than) unity. Thus, the number of possible positive real roots the polynomial (3.34) can have depends on the signs of $b_0, c_0,$ and d_0. This can be analysed using the Descartes Rule of Sign for the quartic (3.34). The various possibilities for the number of positive real roots of (3.34) are tabulated in Table 3.2, from which the following result is obtained:

Theorem 3.4. *The vaccination-free model (3.21),*

i) has a unique endemic equilibrium if $\mathcal{R}_0 > 1$ and Cases 1,2,3 and 6 of Table 3.2 hold;

ii) could have more than one endemic equilibria if $\mathcal{R}_0 > 1$ and Cases 4,5,7 and 8 of Table 3.2 hold;

iii) could have two or more endemic equilibria if $\mathcal{R}_0 < 1$ *and Cases 2,3,4,5,6,7 and 8 of Table 3.2 hold.*

We claim the following result, for the local asymptotic stability of a special case of the EEP ($\mathcal{E}_1$) of the model (3.21).

Theorem 3.5. *Consider the vaccination-free model (3.21) with* $\rho_f = \rho_m = 0$ *and that Item (i) of Theorem 3.4 holds. Then, the associated unique endemic equilibrium,* $\mathcal{E}_1$*, of the resulting reduced model, is LAS whenever* $\mathcal{R}_0 > 1$*.*

The proof of Theorem 3.5, based on using a Krasnoselskii sub-linearity argument [31, 32, 91], is given in Appendix B. The result of Theorem 3.5 is numerically illustrated by simulating the model (3.21), using numerous initial conditions and parameter values such that $\mathcal{R}_0 = 6.4887$. The results obtained, depicted in Figure 3.2, show convergence of the solutions to the unique endemic equilibrium, $\mathcal{E}_1$ (in line with Theorem 3.5). The epidemiological implication of this result is that, for this special case (of the model (3.21) with $\rho_f = \rho_m = 0$), HPV will establish itself in the population, when $\mathcal{R}_0 > 1$, if the initial sizes of the sub-populations of the vaccination-free model (3.21) are in the basin of attraction of the unique endemic equilibrium ($\mathcal{E}_1$).

3.3.4 Backward bifurcation analysis

The presence of multiple endemic equilibria of the vaccination-free model (3.21) when $\mathcal{R}_0 < 1$ (as shown in Theorem 3.4 and Table 3.2) suggests the possibility of backward bifurcation, where, typically, the stable DFE ($\mathcal{E}_0$) co-exists with a stable endemic equilibrium ($\mathcal{E}_1$), when the associated basic reproduction number ($\mathcal{R}_0$) is less than unity. The phenomenon of backward bifurcation has been observed in numerous disease transmission models, such as those with imperfect vaccine and exogenous re-infection (see, for instance, [14, 28, 83, 84, 85, 86, 103] and some of the references therein), vector-borne diseases [37] and treatment [104].

We claim the following result (the proof, based on using Centre Manifold Theory, as described in [14], is given in Appendix C).

Theorem 3.6. *The vaccination-free model (3.21) undergoes backward bifurcation at* $\mathcal{R}_0 = 1$ *if the inequality* $\rho_f > \rho_f^c$*, given by (C.6) in Appendix C, holds.*

The backward bifurcation phenomenon is illustrated by simulating the vaccination-free model (3.21) with the following set of parameter values: $\delta_f = 0.0001$, $\xi_f = \xi_m = 0.0012$, $\rho_f = 1.2$, $\rho_m = 0.9855$, $\pi_f = \pi_m = 100$, $\beta_m = 0.35$, $c_m = c_f = 15$, $\mu_f = \mu_m = \frac{1}{75}$, $\kappa_f = 0.895$, $\alpha_f = 0.878$, $\sigma_f = \sigma_m = 0.75$, $\psi_f = \psi_m = 0.8$, $\theta_p = 0.95$ and $\eta_f = \eta_m = 0.9$. With this set of parameter values, the associated bifurcation coefficients, a and b (defined in Appendix C), take the values $a = 0.0182183226 > 0$ and $b = 359.2293164 > 0$.

It should be mentioned that the aforementioned parameter values are chosen only to illustrate the backward bifurcation phenomenon property of the vaccination-free model (and they may not all be realistic epidemiologically; in particular, the parameter ρ_f has to be chosen outside its realistic range $0 \leq \rho_f \leq 1$). As noted by Lipsitch and Murray [60], it is, in general, difficult to illustrate the phenomenon of backward bifurcation using a realistic set of parameter values. Nonetheless, the analyses in Appendix C show that the vaccination-free model (3.21) will undergo backward bifurcation $\mathcal{R}_0 = 1$ if the re-infection parameter for females (ρ_f) exceeds a certain threshold (ρ_f^c). The resulting backward bifurcation diagram is depicted in Figure 3.3.

The epidemiological consequence of the backward bifurcation phenomenon of the vaccination-free model (3.21) is that the effective control of HPV spread in the population (when $\mathcal{R}_0 < 1$) is dependent on the initial sizes of the sub-populations of the model. In other words, the presence of backward bifurcation in the vaccination-free model (3.21) makes the effort to effectively control (or eliminate) HPV spread in the population difficult.

Furthermore, it follows from the analyses in Appendix C that the vaccination-free model (3.21) does not undergo backward bifurcation if recovered females and males do not acquire HPV re-infection (i.e., if $\rho_m = \rho_f = 0$). In such a scenario (i.e., the model (3.21) with

$\rho_m = \rho_f = 0$ and, for computational convenience, $\xi_f = \xi_m = 0$), the backward bifurcation coefficient, a (given by (C.7) in Appendix C), is negative (which excludes backward bifurcation in line with Item (*iv*) of Theorem 2.8 in Chapter 2). Thus, the analyses in Appendix C suggest that the DFE ($\mathcal{E}_0$), of the vaccination-free model (3.21), is GAS if $\mathcal{R}_0 < 1$ and $\rho_m = \rho_f = 0$. This claim is explored below.

3.3.5 Global asymptotic stability of DFE (special case)

To further confirm the absence of backward bifurcation in the vaccination-free model (3.21), for the scenario when $\rho_m = \rho_f = 0$, the global asymptotic stability property of its DFE ($\mathcal{E}_0$), is established below for this special case.

Theorem 3.7. *The DFE, $\mathcal{E}_0$, of the vaccination-free model (3.21), with $\rho_f = \rho_m = 0$, is GAS in $\mathcal{D}_1$ if $\mathcal{R}_0 < 1$.*

The proof of Theorem 3.7, based on using a Comparison Theorem [58], is given in Appendix D. This result is illustrated numerically in Figure 3.4, by simulating the vaccination-free model (3.21) using multiple initial conditions and parameter values such that $\mathcal{R}_0 = 0.3823$ (so that, by Theorem 3.7, the DFE, $\mathcal{E}_0$, of the model (3.21) is GAS). Figure 3.4 shows convergence of the solution profiles to the DFE (in accordance with Theorem 3.7). The epidemiological implication of Theorem 3.7 is that the classical epidemiological requirement of having the associated reproduction number ($\mathcal{R}_0$) less than unity is necessary and sufficient for the elimination of HPV from the community.

In summary, the vaccination-free model (3.21) has the following dynamical features:

i) The model has a LAS DFE whenever $\mathcal{R}_0 < 1$;

ii) The model can have a unique or multiple endemic equilibria when the associated reproduction number ($\mathcal{R}_0$) exceeds unity. For the special case when the model has a unique endemic equilibrium point, this equilibrium is shown to be LAS;

iii) The model undergoes the phenomenon of backward bifurcation at $\mathcal{R}_0 = 1$ if the re-infection parameter for females (ρ_f) exceeds a certain threshold (ρ_f^c);

iv) The re-infection of recovered individuals ($\rho_f \neq 0; \rho_m \neq 0$) causes the phenomenon of backward bifurcation in the vaccination-free model (3.21). It is shown that in the absence of such re-infection (i.e., $\rho_f = \rho_m = 0$), the DFE of the resulting model is GAS in $\mathcal{D}_1$ whenever $\mathcal{R}_0 < 1$.

3.4 Analysis of Vaccination Model

In this section, the full model (3.19) will be rigorously analysed (with the aim of determining whether or not the model (3.19) has certain dynamical features that are absent in the vaccination-free model (3.21)).

3.4.1 Local asymptotic stability of DFE

Consider, now, the full vaccination model (3.19). Its DFE is given by

$$\begin{aligned} \mathcal{E}_0^V &= (S_f^*, V_f^*, E_f^*, I_f^*, P^*, C^*, R_c^*, R_f^*, S_m^*, E_m^*, I_m^*, R_m^*) \\ &= (S_f^*, V_f^*, 0, 0, 0, 0, 0, 0, S_m^*, 0, 0, 0), \end{aligned} \tag{3.36}$$

where, now,

$$S_f^* = \frac{\pi_f(1-\varphi_f)}{\mu_f}, \quad V_f^* = \frac{\pi_f \varphi_f}{\mu_f}, \quad S_m^* = \frac{\pi_m}{\mu_m},$$

with,

$$N_f^* = S_f^* + V_f^* = \frac{\pi_f}{\mu_f} \quad \text{and} \quad N_m^* = S_m^* = \frac{\pi_m}{\mu_m}.$$

The matrices $\mathcal{F}_V$ and $\mathcal{H}_V$, associated with vaccination model (3.19), are given by

$$\mathcal{F}_V = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\beta_m c_f \eta_m}{N_m^*}\left[S_f^* + (1-\varepsilon_v)V_f^*\right] & \frac{\beta_m c_f}{N_m^*}\left[S_f^* + (1-\varepsilon_v)V_f^*\right] & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_f c_f \eta_f & \beta_f c_f & \beta_f c_f \theta_p & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$\mathcal{H}_V = \begin{pmatrix} g_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_f & g_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -h_1 & n_1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -h_2 & n_2 & 0 & 0 & 0 & 0 \\ 0 & -m_1 & -m_2 & 0 & g_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & g_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\sigma_m & g_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\psi_m & g_6 \end{pmatrix},$$

where $g_i (i = 1..., 6)$, n_1, n_2, m_1, m_2 and h_1, h_2 are as defined in Section 3.3.3. Thus, the *vaccination reproduction number*, denoted by $\mathcal{R}_v = \rho\left(\mathcal{F}_V \mathcal{H}_V^{-1}\right)$, is given by

$$\mathcal{R}_v = \sqrt{\mathcal{R}_{vm}\mathcal{R}_{vf}},$$

with (it is worth stating that since $0 < \varepsilon_v \varphi_f < 1$, the threshold quantity $\mathcal{R}_{vf} > 0$),

$$\mathcal{R}_{vm} = \frac{\beta_f \mu_m}{g_5 \pi_m}\left(\frac{\eta_m g_5 + \sigma_m}{g_4}\right) \quad \text{and} \quad \mathcal{R}_{vf} = \frac{\beta_m c_f^2 \pi_f \left(1-\varepsilon_v \varphi_f\right)}{g_2 \mu_f}\left[\frac{\eta_f n_1 g_2 + \sigma_f(n_1+\theta_p h_1)}{n_1 g_1}\right].$$

Thus, the result below follows (from Theorem 2 of [95]).

Theorem 3.8. *The DFE, $\mathcal{E}_0^V$, of the vaccination model (3.19), is LAS if $\mathcal{R}_v < 1$, and unstable if $\mathcal{R}_v > 1$.*

The threshold quantity, $\mathcal{R}_v$, is the *vaccination reproduction number* for the model (3.19). It can be interpreted in the same way as $\mathcal{R}_0$ in Sections 3.3.1 and 3.3.2.

3.4.2 Existence and local asymptotic stability of EEP

The existence of an EEP of the vaccination model (3.19) is explored below. As in Section 3.3.3, let,

$$\mathcal{E}_1^V = (S_f^{**}, V_f^{**}, E_f^{**}, I_f^{**}, P_f^{**}, C^{**}, R_c^{**}, R_f^{**}, S_m^{**}, E_m^{**}, I_m^{**}, R_m^{**}), \tag{3.37}$$

be an arbitrary endemic equilibrium of the full model (3.19). Furthermore, let λ_m^{**} and λ_f^{**} be given as in (3.31) and (3.32), respectively (see Section 3.3.3). Solving the equations of the model (3.19) at steady-state, in terms of λ_m^{**} and λ_f^{**}, gives

$$\begin{aligned}
S_f^{**} &= \frac{\pi_f\left(1-\varphi_f\right)+\xi_f R_f^{**}}{\lambda_m^{**}+\mu_f},\ V_f^{**} = \frac{\pi_f \varphi_f}{\left(1-\varepsilon_v\right)\lambda_m^{**}+\mu_f},\ E_f^{**} = \frac{\lambda_m^{**}\left[S_f^{**}+(1-\varepsilon_v)V_f^{**}+\rho_f R_f^{**}\right]}{g_1},\\
I_f^{**} &= \frac{\sigma_f E_f^{**}}{g_2},\ P^{**} = \frac{h_1 I_f^{**}}{n_1},\ C^{**} = \frac{h_2 P^{**}}{n_2},\ R_c^{**} = \frac{\gamma_f C^{**}}{\mu_f},\ R_f^{**} = \frac{m_1 I_f^{**}+m_2 P^{**}}{\rho_f \lambda_m^{**}+g_3},\\
S_m^{**} &= \frac{\pi_m+\xi_m R_m^{**}}{\lambda_f^{**}+\mu_m},\ E_m^{**} = \frac{\lambda_f^{**}\left(S_m^{**}+\rho_m R_m^{**}\right)}{g_4},\ I_m^{**} = \frac{\sigma_m E_m^{**}}{g_5},\\
R_m^{**} &= \frac{\psi_m I_m^{**}}{\rho_m \lambda_f^{**}+g_6}.
\end{aligned} \tag{3.38}$$

Using (3.38) in (3.31) and (3.32), and simplifying, gives

$$\lambda_m^{**} = \frac{\lambda_f^{**} z_{11}\left(g_6 + \lambda_f^{**} t_{12}\right)}{\left(\lambda_f^{**}\right)^2 z_{12} + \lambda_f^{**} z_{13} + z_{14}} \quad \text{and} \quad \lambda_f^{**} = \frac{\lambda_m^{**} z_{211}\left[z_{212} + \lambda_m^{**} t_{221} + \left(\lambda_m^{**}\right)^2 z_{213}\right]}{\left(\lambda_m^{**}\right)^3 z_{222} + \left(\lambda_m^{**}\right)^2 z_{223} + \lambda_m^{**} z_{224} + z_{225}}, \tag{3.39}$$

with (where $z_{11}, t_{12}, z_{12}, z_{13}$ and z_{14} are as defined in Section 3.3.3),

$$\begin{aligned}
z_{211} &= \frac{\beta_f c_f \pi_f \mu_m}{\pi_m}\left(\eta_f n_1 g_2 + n_1\sigma_f + \theta_p h_1 \sigma_f\right), \quad t_{221} = \rho_f\mu_f(1-\varepsilon_v\varphi_f) + g_3(1-\varepsilon_v), \\
z_{212} &= g_3\mu_f(1-\varepsilon_v\varphi_f), \quad z_{213} = \rho_f(1-\varepsilon_v), \quad z_{222} = \rho_f(1-\varepsilon_v)\left[n_1 g_1 g_2 - \sigma_f\left(n_1 m_1 + h_1 m_2\right)\right], \\
z_{223} &= (1-\varepsilon_v)\left[n_1 g_1 g_2\left(\rho_f\mu_f + g_3\right) - \sigma_f\left(n_1 m_1 + h_1 m_2\right)\left(\rho_f\mu_f + \xi_f\right)\right] \\
&+ \rho_f\left[n_1 g_1 g_2 - \sigma_f\left(n_1 m_1 + h_1 m_2\right)\right], \\
z_{224} &= (1-\varepsilon_v)\mu_f n_1 g_1 g_2 g_3 + \mu_f n_1 g_1 g_2\left(\rho_f\mu_f + g_3\right) - \sigma_f\left(n_1 m_1 + h_1 m_2\right)\left(\rho_f\mu_f + \xi_f\right), \\
z_{225} &= \mu_f^2 n_1 g_1 g_2 g_3.
\end{aligned} \tag{3.40}$$

Since all the parameters of the vaccination model (3.19) are positive, and $0 < \varepsilon_v < 1$, it can be shown, after some lengthy algebraic manipulations, that all the variables in (3.40) are positive (see Section 3.3.3). Substituting λ_f^{**} into λ_m^{**} in (3.39), and simplifying, it follows that the non-zero equilibria of the vaccination model (3.19) satisfy the following polynomial (in terms of λ_m^{**}),

$$a_2\left(\lambda_m^{**}\right)^6 + b_2\left(\lambda_m^{**}\right)^5 + c_2\left(\lambda_m^{**}\right)^4 + d_2\left(\lambda_m^{**}\right)^3 + e_2\left(\lambda_m^{**}\right)^2 + f_2\lambda_m^{**} + j_2 = 0, \tag{3.41}$$

with,

$$
\begin{aligned}
a_2 &= z_{222}\left(z_{14}z_{222}+z_{13}z_{213}z_{211}\right)+z_{12}z_{213}^2z_{211}^2,\\[2ex]
b_2 &= 2z_{14}z_{223}z_{222}+z_{211}z_{213}\left(z_{13}z_{223}+t_{12}z_{11}z_{211}z_{213}\right)+t_{12}z_{11}^2z_{213}\left(z_{12}+t_{221}\right)\\
&+ z_{222}\left(t_{221}z_{13}z_{211}-g_6z_{11}z_{213}\right),\\[2ex]
c_2 &= z_{12}z_{212}z_{213}z_{211}^2+t_{221}z_{211}^2\left(t_{221}z_{12}+t_{12}z_{11}z_{213}\right)+z_{213}z_{211}^2\left(z_{12}z_{212}+t_{12}t_{221}z_{11}\right)\\
&+ \left(z_{222}+z_{224}\right)\left(z_{14}z_{224}+z_{13}z_{212}z_{211}-t_{221}z_{11}z_{211}z_{212}\right)+z_{223}\left(z_{14}z_{223}+t_{221}z_{13}z_{211}-g_6z_{11}z_{213}\right),\\[2ex]
d_2 &= z_{222}z_{14}z_{225}\left(2-\mathcal{R}_v^2\right)+z_{211}z_{213}\left(z_{13}z_{225}+t_{12}z_{11}z_{211}z_{212}\right)+z_{212}z_{211}^2\left(t_{221}z_{12}+t_{12}z_{11}z_{213}\right)\\
&+ t_{221}z_{211}^2\left(z_{12}z_{212}+t_{12}t_{221}z_{11}\right)+z_{224}\left(z_{14}z_{223}+t_{221}z_{13}z_{211}-g_6z_{11}z_{213}\right)\\
&+ z_{223}\left(z_{14}z_{224}+z_{13}z_{212}z_{211}-g_6t_{211}z_{11}z_{211}\right),\\[2ex]
e_2 &= z_{223}z_{14}z_{225}\left(2-\mathcal{R}_v^2\right)+t_{12}t_{221}z_{211}^2z_{11}z_{212}+z_{211}^2z_{212}\left(z_{12}z_{212}+t_{12}t_{221}z_{11}\right)\\
&+ z_{224}\left(z_{14}z_{224}+z_{212}z_{13}z_{211}-g_6t_{221}z_{11}z_{211}\right)+z_{225}\left(t_{221}z_{13}z_{211}-g_6z_{11}z_{213}\right),\\[2ex]
f_2 &= z_{14}z_{224}z_{225}\left(1-\mathcal{R}_v^2\right)+z_{225}\left(z_{14}z_{224}+z_{13}z_{211}z_{212}-g_6t_{221}z_{11}z_{211}\right)+t_{12}z_{11}z_{211}^2z_{212}^2,\\[2ex]
j_2 &= z_{14}z_{225}^2\left(1-\mathcal{R}_v^2\right).
\end{aligned}
$$

Clearly, the coefficient, a_2, of the polynomial (3.41), is always positive (since all the model parameters are positive). Furthermore, the coefficient, j_2, is positive (negative) if $\mathcal{R}_v$ is less than (greater than) unity. Thus, the number of possible positive real roots the polynomial (3.41) can have depends on the signs of b_2, c_2, d_2, e_2 and f_2. The various possibilities for the

roots of (3.34) are tabulated in Table 3.3.

Theorem 3.9. *The vaccination model (3.19),*

i) has a unique endemic equilibrium if $\mathcal{R}_v > 1$ *and whenever Cases 1,2,3 and 6 of Table 3.3 hold;*

ii) could have more than one endemic equilibrium if $\mathcal{R}_v > 1$ *and whenever Cases 4,5,7,8,11 and 12 of Table 3.3 hold;*

iii) could have two or more endemic equilibrium if $\mathcal{R}_v < 1$ *and whenever Cases 2-12 of Table 3.3 hold.*

Furthermore, as in the case of the vaccination-free model (3.21), the vaccination model (3.19) also undergoes backward bifurcation, as below.

Theorem 3.10. *The vaccination model (3.19) undergoes backward bifurcation at* $\mathcal{R}_v = 1$ *whenever the inequality (E.3), given in Appendix E, is satisfied.*

The proof, based on using Centre Manifold Theory, is given in Appendix E. Here, too, the backward bifurcation property of the vaccination model (3.19) can be removed whenever the re-infection of recovered individuals does not occur (i.e., $\rho_f = \rho_m = 0$). The GAS property of the DFE, $\mathcal{E}_0^V$, of the vaccination model (3.19), is established for this case in Section 3.4.3.

3.4.3 Global asymptotic stability of DFE (special case)

The global asymptotic stability of the DFE, $\mathcal{E}_0^V$, of the vaccination model (3.19) is established for the special case where the re-infection of recovered individuals does not occur (i.e., $\rho_f = \rho_m = 0$).

Theorem 3.11. *The DFE,* $\mathcal{E}_0^V$*, of the vaccination model (3.19), with* $\rho_f = \rho_m = 0$*, is GAS in* $\mathcal{D}$ *if* $\mathcal{R}_v < 1$*.*

The proof of Theorem 3.11, based on using a Lyapunov function, is given in Appendix F.

3.5 Qualitative Assessment of Vaccine Impact

The population-level impact of the anti-HPV mass vaccination program, using the *Gardasil* vaccine, in the community is assessed for the special case of the vaccination model (3.19) with $\rho_f = \rho_m = 0$ (so that the DFE of the resulting model is GAS, in line with Theorem 3.11). It is convenient to re-write the associated *vaccination reproduction number*, $\mathcal{R}_v$, as

$$\mathcal{R}_v^2 = \mathcal{R}_0^2 \left(1 - \varepsilon_v \varphi_f\right), \tag{3.42}$$

where φ_f represents the fraction of females vaccinated at steady-state, ε_v is the vaccine efficacy, and $\mathcal{R}_0$ is *basic reproduction number* for the vaccination-free model (3.21) with $\rho_f = \rho_m = 0$. Thus (noting that $g_i (i = 1..., 6)$, n_1, n_2, m_1, m_2 and h_1, h_2 are as defined in Section 3.3.3),

$$\mathcal{R}_0^2 = \mathcal{R}_v^2 \mid_{\varphi_f = 0} = \frac{\beta_f c_m \beta_m c_f \left(\eta_m g_5 + \sigma_m\right) \left(\eta_f n_1 g_2 + \sigma_f n_1 + \sigma_f \theta_p h_1\right)}{n_1 g_1 g_2 g_4 g_5}.$$

It can be shown from (3.42), by writing $\mathcal{R}_v = \mathcal{R}_v \left(\varphi_f\right)$, that

$$\mathcal{R}_v \left(\varphi_f\right) = \mathcal{R}_0 \sqrt{1 - \varepsilon_v \varphi_f}, \tag{3.43}$$

so that,

$$\frac{\partial \mathcal{R}_v}{\partial \varphi_f} = -\frac{\varepsilon_v \mathcal{R}_0}{2\sqrt{1 - \varepsilon_v \varphi_f}}.$$

Since $0 < \varepsilon_v < 1$, it follows that $\mathcal{R}_v(\varphi_f)$ is a decreasing function of φ_f. Furthermore, there is a unique φ_f^c, such that $\mathcal{R}_v \left(\varphi_f^c\right) = 1$, given by

$$\varphi_f^c = \frac{1}{\varepsilon_v} \left(1 - \frac{1}{\mathcal{R}_0^2}\right).$$

Lemma 3.1. *The DFE, $\mathcal{E}_0^V$, of the vaccination model (3.19), with $\rho_f = \rho_m = 0$, is GAS in*

$\mathcal{D}$ *if* $\varphi_f > \varphi_f^c$, *and unstable if* $\varphi_f < \varphi_f^c$.

Proof. Consider the vaccination model (3.19) with $\rho_f = \rho_m = 0$. Let $\varphi_f > \varphi_f^c$. Then, it follows from (3.42) that $\mathcal{R}_v < 1$. Hence, the result follows from Theorem 3.11 that the DFE, $\mathcal{E}_0^V$ of (3.19) with $\rho_f = \rho_m = 0$, is GAS in $\mathcal{D}$ for this case ($\varphi_f > \varphi_f^c$). □

Figure 3.5 depicts a contour plot of $\mathcal{R}_v$, as a function of the vaccine efficacy (ε_v) and coverage (φ_f). It follows from Figure 3.5 that, with the assumed 90% efficacy of the *Gardasil* vaccine [7, 15, 76, 93, 96], HPV can be effectively controlled or eliminated from the community if at least 78% of the new sexually-active susceptible females in the community are vaccinated (with *Gardasil*) at steady-state.

3.6 Numerical Simulations

The vaccination-free model (3.21) is simulated, first of all, using the parameter values given in Table 3.1 (unless otherwise stated). The following initial conditions were used in the simulations: $S_f(0) = 15,000$, $V_f(0) = 35,000$, $E_f(0) + I_f(0) + P(0) = 5,000$, $C(0) = 1,300$, $S_m(0) = 50,000$, $E_m(0) + I_m(0) = 500$ and $R_c(0) = R_f(0) = R_m(0) = 0$. Figure 3.6 depicts the cumulative number of new cervical cancer cases as a function of time in the absence of vaccination (i.e., $V_f = \varphi_f = 0$). This figure (which represents the worst-case scenario of HPV transmission in the community in the absence of mass vaccination) shows that about 1,700 cervical cancer cases will be recorded over 5 years. Furthermore, up to 262 infected people will die over the same time period (Figure 3.7).

The vaccination model (3.19) is then simulated to determine the impact of mass vaccination of new sexually-active females (using the *Gardasil* vaccine) on the cumulative number of new cervical cancer cases in the community. Figure 3.8 shows a marked decrease in the cumulative number of cases (from 1,700 in Figure 3.6 to about 907) if the *Gardasil* vaccine efficacy is assumed to be 80%. This number further reduces to only 3 cases if the vaccine efficacy is 99% (it should be recalled that the efficacy of the *Gardasil* vaccine is in the range

$90 - 100\%$ [15, 76, 93, 96]; so that the assumption for 80% and 99% efficacy is within a realistic range). The cumulative number of cervical cancer mortality, for various *Gardasil* efficacy, for this case is depicted in Figure 3.9. This figure shows that with an assumed vaccine efficacy of 80%, the cumulative mortality, over 5 years, reduces (in comparison to the worst-case scenario) to about 23 deaths (this number further reduces to 16 deaths if the vaccine efficacy is 99%). It is worth mentioning that the simulations carried out in this chapter are subject to uncertainties in the estimates of the parameter values given in Table 3.1 (the effect of such uncertainties can be assessed by using a sampling technique, such as Latin hypercube sampling, as described in [8, 63]).

In summary, the vaccination model (3.19) has the following dynamical features:

i) The model has a LAS DFE whenever $\mathcal{R}_v < 1$;

ii) The model can have a unique or multiple endemic equilibria when the associated reproduction number ($\mathcal{R}_v$) exceeds unity. For the special case when the model has a unique endemic equilibrium point, this equilibrium is shown to be LAS;

iii) The model undergoes the phenomenon of backward bifurcation at $\mathcal{R}_v = 1$ if the inequality (E.3) holds. It is shown that the re-infection of recovered males and females causes the backward bifurcation phenomenon in this model. In the absence of re-infection of recovered individuals (i.e., $\rho_f = \rho_m = 0$), the DFE of the resulting model was shown to be GAS in $\mathcal{D}$ whenever $\mathcal{R}_v < 1$.

These results show that the vaccination model (3.19) exhibits essentially the same qualitative dynamics (with respect to the existence and stability of the associated equilibria, as well as with respect to the backward bifurcation property) as the vaccination-free model (3.21).

3.7 Summary of the Chapter

A new deterministic model for the transmission dynamics of HPV in a community, where a mass vaccination program using *Gardasil* is administrated for new sexually-active susceptible females, is designed. An essential feature of the resulting HPV vaccination model is that it incorporates the re-infection of, as well as the loss of infection-acquired immunity by, recovered individuals. Both the vaccination-free and vaccination models were rigorously analysed to gain insight into their dynamical features. Some of the main theoretical and epidemiological findings of this chapter are as follows:

i) both the vaccination-free model (3.21) and the vaccination model (3.19) have a globally-asymptotically stable DFE whenever their associated reproduction number is less than unity and no re-infection of recovered individuals occurs (i.e., $\rho_f = \rho_m = 0$);

ii) both models have at least one locally-asymptotically stable EEP whenever their respective reproduction numbers exceed unity for the special case with $\rho_f = \rho_m = 0$;

iii) both models exhibit the phenomenon of backward bifurcation under certain conditions. It is shown that the backward bifurcation phenomenon is caused by the re-infection of recovered individuals;

iv) the cumulative number of cervical cancer cases in the absence of vaccination, which represents the worst-case scenario of HPV transmission in the community, shows that about $1,700$ cervical cancer cases will be recorded over 5 years. Furthermore, up to 262 infected females will die of cervical cancer over the same time period;

v) the impact of mass vaccination of new sexually-active susceptible females (using the *Gardasil* vaccine) on the cumulative number of new cervical cancer cases in the community shows a marked decrease in the number of cases (from $1,700$ in to about 907) if the*Gardasil* vaccine efficacy is assumed to be 80%. This number further reduces to only 3 cases if the *Gardasil* vaccine efficacy is assumed to be 99%;

vi) the cumulative number of cervical cancer mortality shows that with an assumed *Gardasil* vaccine efficacy of 80%, the cumulative mortality, over 5 years, reduces (in comparison to the worst-case scenario) to about 23 deaths (this number further reduces to 16 deaths if the efficacy of the vaccine is assumed to be 99%);

vii) numerical simulations of the vaccination model (3.19) show that the use of the *Gardasil* vaccine (with the assumed efficacy of 90%) can lead to the effective control (or elimination) of the four HPV types (HPV-6, HPV-11, HPV-16 and HPV-18) in the community if at least 78% of the new sexually-active susceptible females are vaccinated at steady-state.

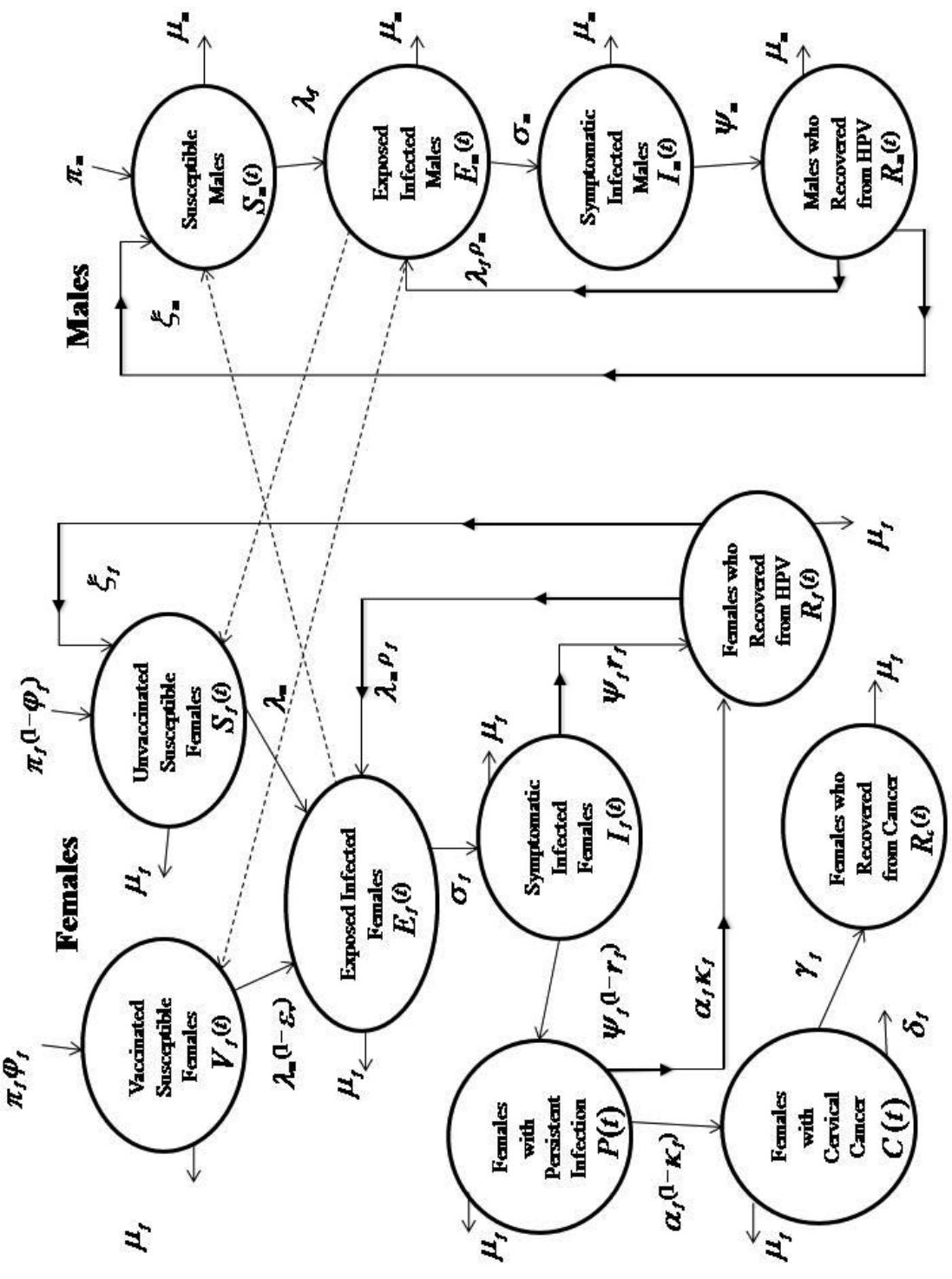


Figure 3.1: Flow diagram of the vaccination model (3.19).

Table 3.1: Description of variables and parameters of the vaccination model (3.19).

Variable	Description
S_f	Population of unvaccinated susceptible females
S_m	Population of susceptible males
V_f	Population of new sexually-active susceptible females vaccinated with the *Gardasil* vaccine
$E_f(E_m)$	Population of exposed females (males)
$I_f(I_m)$	Population of infected females (males) with clinical symptoms of HPV
P	Population of females with persistent infection
C	Population of infected females with cervical cancer
R_c	Population of infected females who recovered from cervical cancer
$R_f(R_m)$	Population females (males) who recovered from HPV
$N_f(N_m)$	Total population of females (males)

Parameter	Description	Nominal value *per* year	Reference
$\pi_f(\pi_m)$	Recruitment rate of new sexually-active females (males)	10000	[61, 75]
β_m (β_f)	Infection probability for females (males)	0.4 (0.5)	[61, 75]
c_f (c_m)	Average number of female (male) sexual partners for males (females)	$2\left(\frac{2N_f(t)}{N_m(t)}\right)$	[61, 75]

Parameter	Description	Nominal value *per* year	Reference
φ_f	Fraction of new sexually-active females vaccinated	0.7	[25, 61]
ε_v	Vaccine (*Gardasil*) efficacy	0.9	[61, 76]
$\mu_f(\mu_m)$	Natural death rate for females (males)	$\frac{1}{65}$	[9, 61]
$\xi_f(\xi_m)$	Rate of loss of infection-acquired immunity for females (males)		Assumed
$\eta_f(\eta_m)$	Modification parameter for infectiousness of exposed individuals in the $E_f(E_m)$ class relative to those in the $I_f(I_m)$ class		Assumed
$\rho_f(\rho_m)$	Re-infection parameter for females (males)		Assumed
$\sigma_f(\sigma_m)$	Rate of development of clinical symptoms of HPV for exposed females (males)		Assumed
$\psi_f(\psi_m)$	Recovery rate of infected females (males)	0.9	[61, 67]
r_f	Fraction of symptomatic females who recover naturally from HPV (but do not develop persistent infection)	0.5	[61]
α_f	Recovery rate of infected females with persistent infection	0.9	[61]
κ_f	Fraction of symptomatic females who recover naturally from persistent infection (but do not develop cervical cancer)		Assumed
γ_f	Recovery rate of females with cervical cancer	0.76	[25, 61]
δ_f	Cancer-induced mortality rate for females	0.001	[61]
θ_p	Modification parameter for the infectiousness of females with persistent infection relative to those in the I_f class	0.9	[61]

Cases	a_0	b_0	c_0	d_0	e_0	$\mathcal{R}_0$	Number of sign changes	Number of possible positive real roots
1	+	+	+	+	+	$\mathcal{R}_0 < 1$	0	0
	+	+	+	+	-	$\mathcal{R}_0 > 1$	1	1
2	+	-	-	-	+	$\mathcal{R}_0 < 1$	2	0,2
	+	-	-	-	-	$\mathcal{R}_0 > 1$	1	1
3	+	+	-	-	+	$\mathcal{R}_0 < 1$	2	0,2
	+	+	-	-	-	$\mathcal{R}_0 > 1$	1	1
4	+	-	+	-	+	$\mathcal{R}_0 < 1$	4	0,2,4
	+	-	+	-	-	$\mathcal{R}_0 > 1$	3	1,3
5	+	-	-	+	+	$\mathcal{R}_0 < 1$	2	0,2
	+	-	-	+	-	$\mathcal{R}_0 > 1$	3	1,3
6	+	+	+	-	+	$\mathcal{R}_0 < 1$	2	0,2
	+	+	+	-	-	$\mathcal{R}_0 > 1$	1	1
7	+	+	-	+	+	$\mathcal{R}_0 < 1$	2	0,2
	+	+	-	+	-	$\mathcal{R}_0 > 1$	3	1,3
8	+	-	+	+	+	$\mathcal{R}_0 < 1$	2	0,2
	+	-	+	+	-	$\mathcal{R}_0 > 1$	3	1,3

Table 3.2: Number of possible positive real roots of (3.34) for $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$.

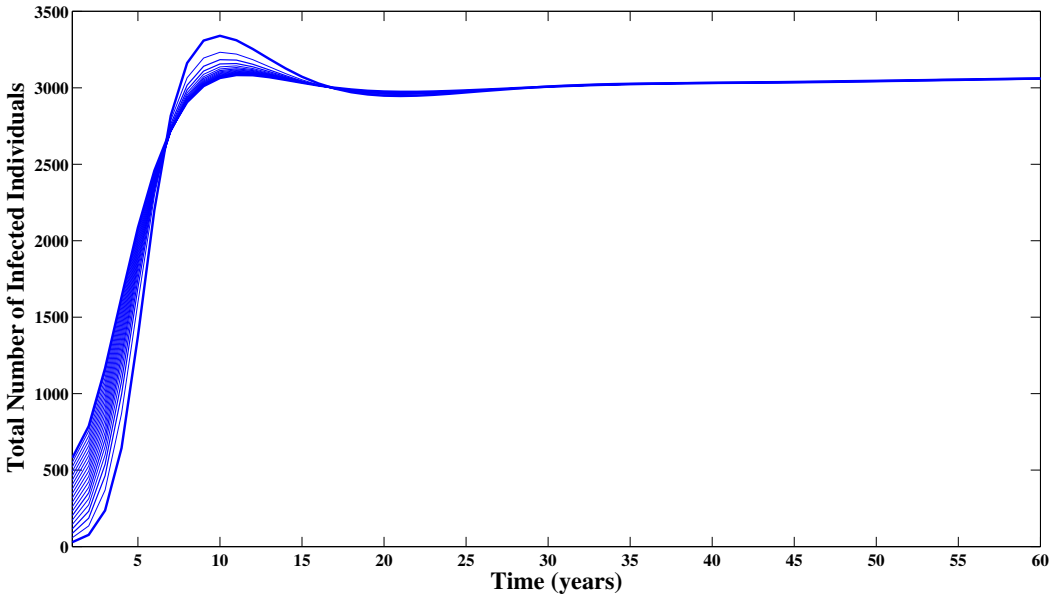


Figure 3.2: Simulations of the vaccination-free model (3.21), showing the total number of infected individuals (females and males) as a function of time using various initial conditions. Parameter values used are as given in Table 3.1, with $\rho_f = \rho_m = 0$, $\xi_f = \xi_m = 0.0012$, $\pi_f = \pi_m = 400$, $\beta_f = 0.8$, $\beta_m = 0.9$, $\kappa_f = 0.7$, $\alpha_f = 0.5$, $\sigma_f = \sigma_m = 0.5$, $\psi_f = \psi_m = 0.5$ and $\eta_f = \eta_m = 0.8$ (so that, $\mathcal{R}_0 = 6.4887 > 1$).

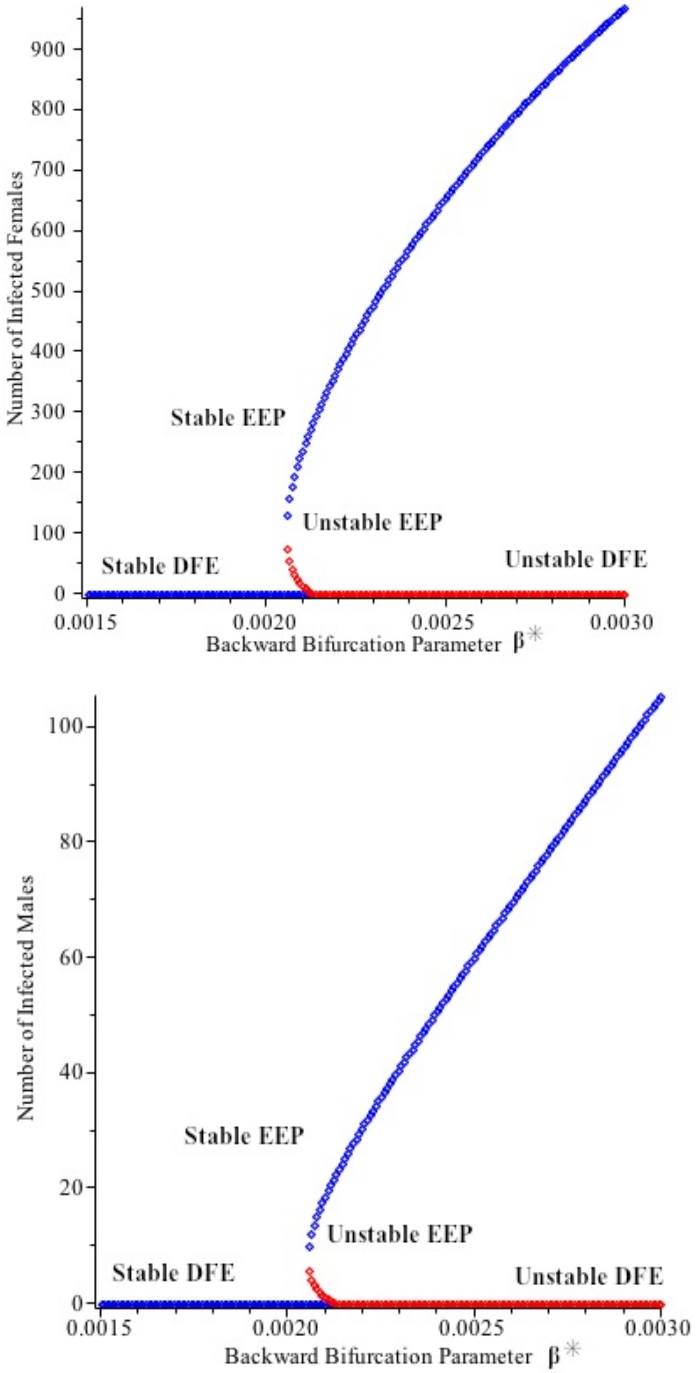


Figure 3.3: Backward bifurcation diagram for the vaccination-free model (3.21), showing the total number of infected individuals (females and males) as a function of the backward bifurcation parameter, β^*. Parameter values used are as given in Table 3.1, with $\xi_f = \xi_m = 0.0012$, $\rho_f = 1.2$, $\rho_m = 0.9855$, $\pi_f = \pi_m = 100$, $\beta_m = 0.35$, $c_m = c_f = 15$, $\mu_f = \mu_m = \frac{1}{75}$, $\kappa_f = 0.895$, $\alpha_f = 0.878$, $\sigma_f = \sigma_m = 0.75$, $\psi_f = \psi_m = 0.8$, $\theta_p = 0.95$ and $\eta_f = \eta_m = 0.9$ (so that, $\mathcal{R}_0 = 1$).

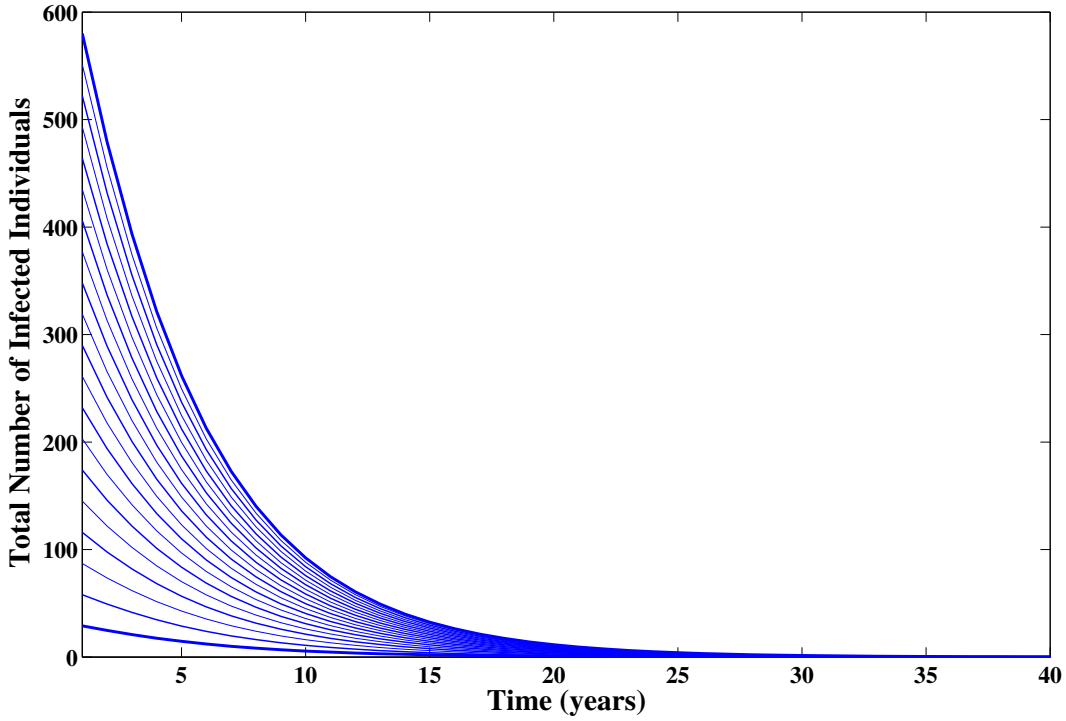


Figure 3.4: Simulations of the vaccination-free model (3.21), showing the total number of infected individuals (females and males) as a function of time using various initial conditions. Parameter values used are as given in Table 3.1, with $\xi_f = \xi_m = 0.1$, $\rho_f = \rho_m = 0$, $\pi_f = \pi_m = 400$, $\beta_f = \beta_m = 0.05$, $\kappa_f = 0.7$, $\gamma_f = 0.22$, $\alpha_f = 0.5$, $\sigma_f = \sigma_m = 0.5$, $\psi_f = \psi_m = 0.5$ and $\eta_f = \eta_m = 0.8$ (so that, $\mathcal{R}_0 = 0.3823 < 1$).

Cases	a_2	b_2	c_2	d_2	e_2	f_2	j_2	$\mathcal{R}_v$	Number of sign changes	Number of possible positive real roots
1	+	+	+	+	+	+	+	$\mathcal{R}_v < 1$	0	0
	+	+	+	+	+	+	-	$\mathcal{R}_v > 1$	1	1
2	+	-	-	-	-	-	+	$\mathcal{R}_v < 1$	2	0,2
	+	-	-	-	-	-	-	$\mathcal{R}_v > 1$	1	1
3	+	+	-	-	-	-	+	$\mathcal{R}_v < 1$	2	0,2
	+	+	-	-	-	-	-	$\mathcal{R}_v > 1$	1	1
4	+	-	+	-	-	-	+	$\mathcal{R}_v < 1$	4	0,2,4
	+	-	+	-	-	-	-	$\mathcal{R}_v > 1$	3	1,3
5	+	-	-	-	-	+	+	$\mathcal{R}_v < 1$	2	0,2
	+	-	-	-	-	+	-	$\mathcal{R}_v > 1$	3	1,3
6	+	+	+	-	-	-	+	$\mathcal{R}_v < 1$	2	0,2
	+	+	+	-	-	-	-	$\mathcal{R}_v > 1$	1	1
7	+	+	-	-	-	+	+	$\mathcal{R}_v < 1$	2	0,2
	+	+	-	-	-	+	-	$\mathcal{R}_v > 1$	3	1,3
8	+	-	+	-	-	+	+	$\mathcal{R}_v < 1$	2	0,2
	+	-	+	-	-	+	-	$\mathcal{R}_v > 1$	3	1,3
9	+	-	+	-	+	+	+	$\mathcal{R}_v < 1$	4	0,2,4
	+	-	+	-	+	+	-	$\mathcal{R}_v > 1$	5	1,3,5
10	+	+	-	+	-	+	+	$\mathcal{R}_v < 1$	4	0,2,4
	+	+	-	+	-	+	-	$\mathcal{R}_v > 1$	5	1,3,5
11	+	+	+	-	+	-	+	$\mathcal{R}_v < 1$	4	0,2,4
	+	+	+	-	+	-	-	$\mathcal{R}_v > 1$	3	1,3
12	+	-	+	-	+	-	+	$\mathcal{R}_v < 1$	6	0,2,4,6
	+	-	+	-	+	-	-	$\mathcal{R}_v > 1$	5	1,3,5

Table 3.3: Number of possible positive real roots of (3.41) for $\mathcal{R}_v < 1$ and $\mathcal{R}_v > 1$.

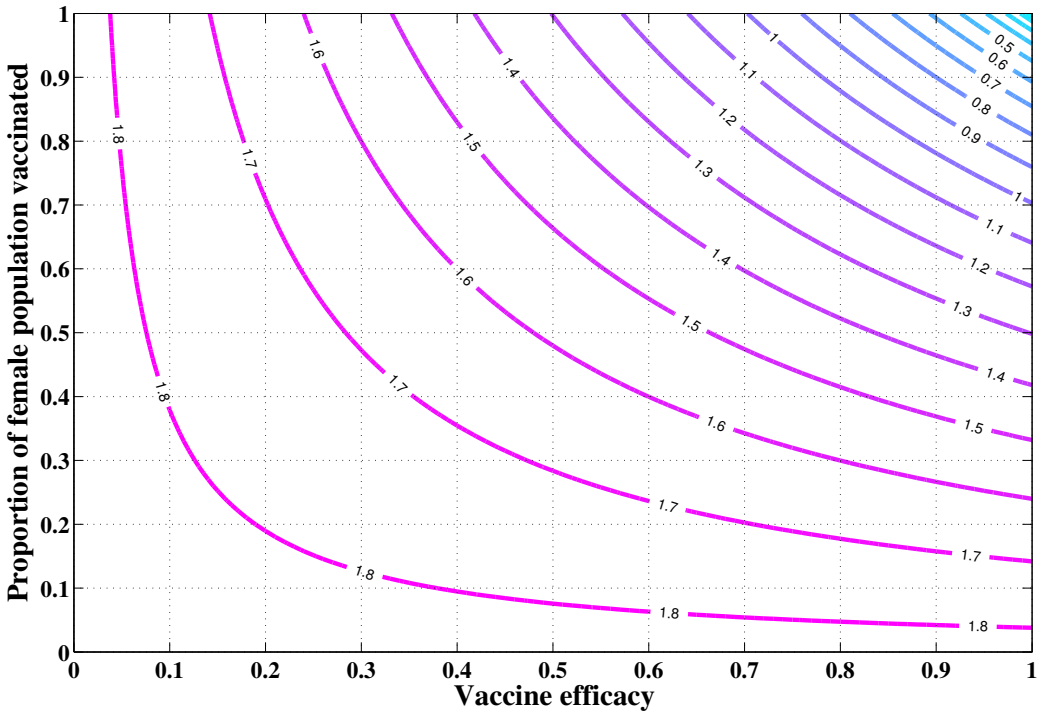


Figure 3.5: Simulations of the vaccination model (3.19), showing a contour plot of $\mathcal{R}_v$ as a function of vaccine efficacy (ε_v) and the fraction of new sexually-active females vaccinated at steady-state (φ_f). Parameter values used are as given in Table 3.1, with $\xi_f = \xi_m = 0.01$, $\rho_f = \rho_m = 0$, $\kappa_f = 0.895$, $\alpha_f = 0.878$, $r_f = 0.887$, $\gamma_f = 0.22$, $\sigma_f = \sigma_m = 0.85$ and $\eta_f = \eta_m = 0.8$ and various values of ε_v and φ_f (with $0 \leq \varepsilon_v, \varphi_f \leq 1$).

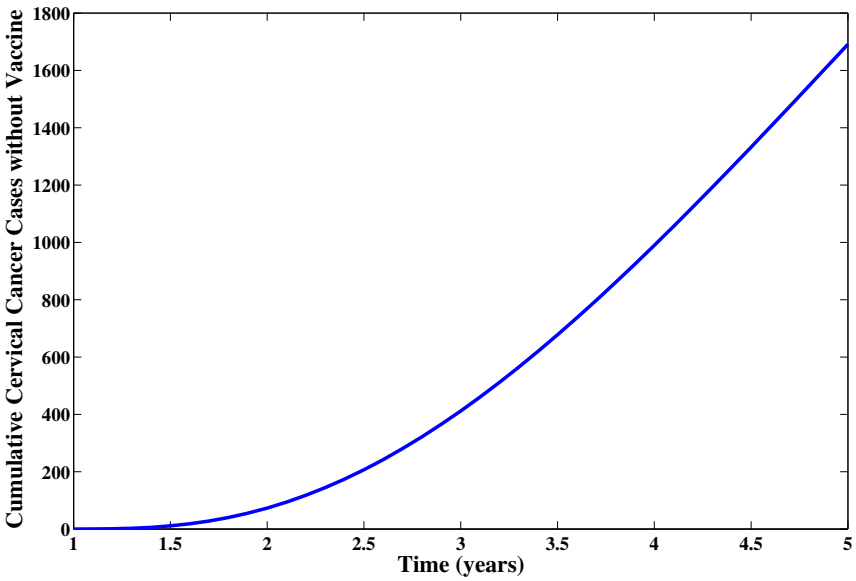


Figure 3.6: Simulation of the vaccination-free model (3.21), showing the cumulative number of cervical cancer cases as a function of time. Parameter values used are as given in Table 3.1, with $\xi_f = \xi_m = 0.012$, $\rho_f = \rho_m = 0.3$, $\kappa_f = 0.7$, $\alpha_f = 0.42$, $\sigma_f = \sigma_m = \psi_f = \psi_m = 0.5$, $\theta_p = 0.9$, $\eta_f = \eta_m = 0.85$ and $\delta_f = 0.001$.

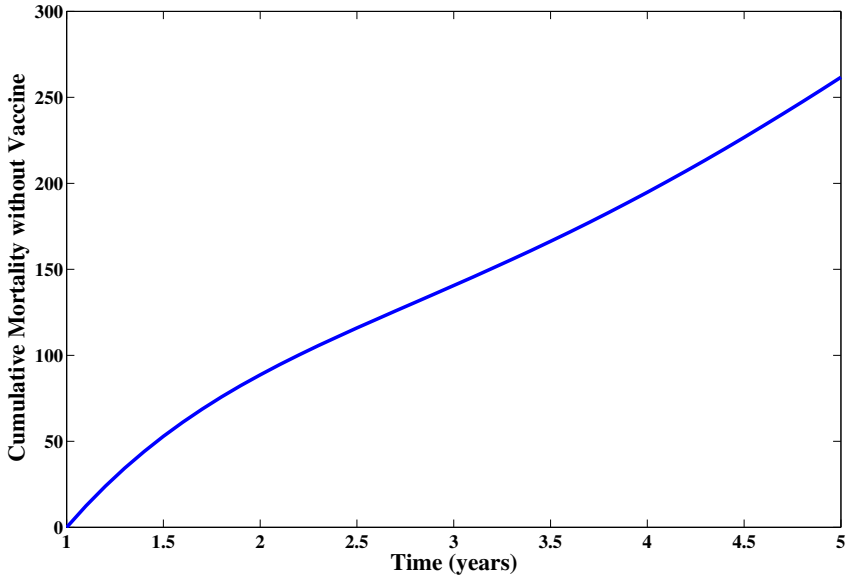


Figure 3.7: Simulation of the vaccination-free model (3.19), showing the cumulative cervical cancer-related mortality as a function of time. Parameter values used are as given in Table 3.1, with $\xi_f = \xi_m = 0.012$, $\rho_f = \rho_m = 0.3$, $\kappa_f = 0.7$, $\alpha_f = 0.42$, $\sigma_f = \sigma_m = \psi_f = \psi_m = 0.5$, $\theta_p = 0.9$, $\eta_f = \eta_m = 0.85$ and $\delta_f = 0.01$.

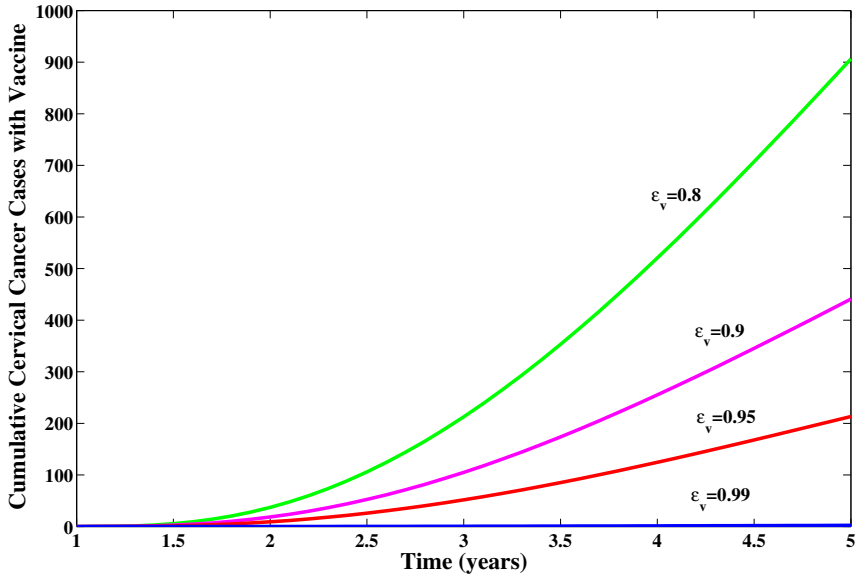


Figure 3.8: Simulation of the vaccination model (3.19), showing the cumulative number of cervical cancer cases as a function of time for various vaccine efficacy levels. Parameter values used are as given in Table 3.1, with $\xi_f = \xi_m = 0.012$, $\rho_f = \rho_m = 0.3$, $\kappa_f = 0.7$, $\alpha_f = 0.42$, $\sigma_f = \sigma_m = \psi_f = \psi_m = 0.5$, $\theta_p = 0.9$, $\eta_f = \eta_m = 0.85$ and $\delta_f = 0.001$.

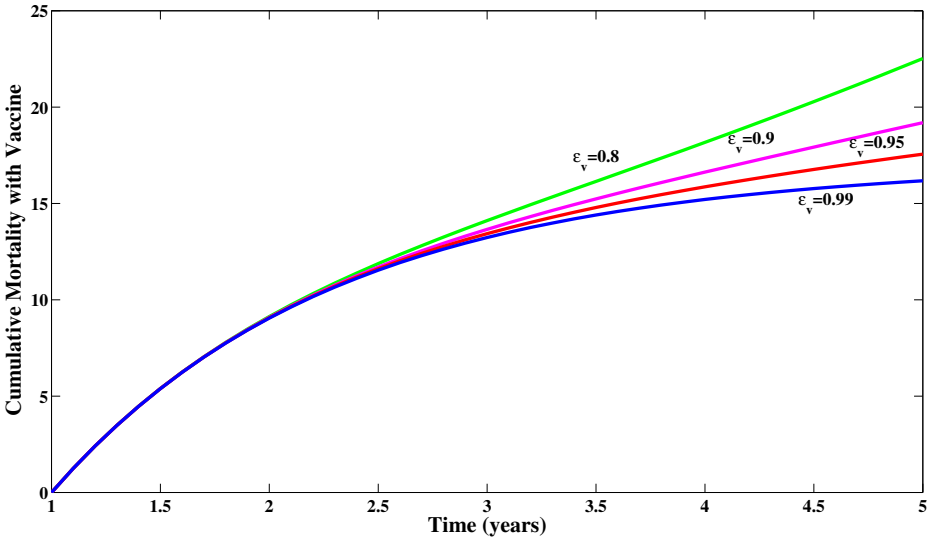


Figure 3.9: Simulation of the vaccination model (3.19), showing the cumulative cervical cancer-related mortality as a function of time for various vaccine efficacy levels. Parameter values used are as given in Table 3.1, with $\xi_f = \xi_m = 0.012$, $\rho_f = \rho_m = 0.3$, $\kappa_f = 0.7$, $\alpha_f = 0.42$, $\sigma_f = \sigma_m = \psi_f = \psi_m = 0.5$, $\theta_p = 0.9$, $\eta_f = \eta_m = 0.85$ and $\delta_f = 0.01$.

Chapter 4

Risk-structured HPV Model with the *Gardasil* and *Cervarix* Vaccines

4.1 Introduction

In this chapter, the vaccination model discussed in Chapter 3 will be extended to account for the dynamics of the low- and high-risk HPV types in the community. For simplicity, only four (of the 120) HPV subtypes, namely HPV-6, HPV-11, HPV-16 and HPV-18, will be considered. HPV-16 and HPV-18 are high-risk, and can persist for many years, causing CIN and cervical cancer if untreated [9, 10, 15, 26, 46, 50, 61, 76]. These (high-risk) HPV types account for 70% of cervical cancer cases globally [9, 46]. Almost all cervical cancer cases are caused by HPV infection (HPV also accounts for 90% of anal cancers, 60% of oropharyngeal cancers, and 40% of vaginal and penile cancers [38, 70]). As stated in Chapter 1, the pre-cancerous CIN stages (lesions) are categorized into the low-grade (denoted by CIN1) and high-grade stages [10, 15, 50, 61, 76]. In line with some other modelling studies for the natural history of HPV [57, 62, 67], the high-grade CIN2 and CIN3 pre-cancerous stages are lumped into a single compartment (for mathematical convenience; denoted by CIN2/3). It should be mentioned that the three CIN stages are considered separately in [25, 61]. In later

stages, the original cancer may spread to areas surrounding the uterus and cervix or near organs such as the bladder or rectum. It may also spread to distant sites in the body through the bloodstream or the lymph nodes [76, 100]. Furthermore, the high-risk HPV types cause pre-cancerous intraepithelial neoplasia in males (also divided into three grades according to severity of the lesions, denoted by INM1 and INM2/3), resulting in various cancers in males (such as anal and penile cancers [29]). The currently-available HPV vaccines (*Gardasil* and *Cervarix*) target these high-risk HPV types.

On the other hand, HPV-6 and HPV-11 are considered low-risk HPV types (since they do not cause cervical cancer; although they do cause genital warts [76, 77]). As stated in Chapter 1, while the bivalent (*Cervarix*) vaccine exclusively targets the high-risk HPV types (HPV-16 and HPV-18), the quadrivalent (*Gardasil*) vaccine targets both the low-risk (HPV-6 and HPV-11) and the high-risk (HPV-16 and HPV-18) HPV types. As stated in Chapter 1, it should be emphasized that the *Cervarix* vaccine is approved for use in females only, while the *Gardasil* vaccine is approved for use in both females and males [76, 77, 100].

Unlike in Chapter 3 (where only the *Gardasil* vaccine is used), both *Gardasil* and *Cervarix* will be used in this chapter. In other words, susceptible females have the option to choose between the *Gardasil* and *Cervarix* vaccines (while susceptible males only have the *Gardasil* vaccine option). Furthermore, in line with the recent recommendations by some Public Health Agencies [46, 76, 77], both females and males will be vaccinated (only females are vaccinated in the model developed in Chapter 3). As in Chapter 3, the vaccines will be given to children of ages 9 to 13 [10, 15, 76] (it should be stated that males and females of ages 13 to 26, who were not vaccinated before, are also be vaccinated [46, 76]). It is worth mentioning that, unlike in [25, 29], no co-infection of HPV types is assumed in this study.

4.2 Model Formulation

To formulate the model for the transmission dynamics of the low- and high-risk HPV subtypes in a community, in the presence of mass vaccination (using the *Cervarix* and *Gardasil* vaccines), the total sexually-active female population at time t (denoted by $N_f(t)$) is sub-divided into mutually-exclusive compartments of unvaccinated susceptible females ($S_f(t)$), new sexually-active susceptible females vaccinated with the bivalent *Cervarix* vaccine ($V_f^b(t)$), new sexually-active susceptible females vaccinated with the quadrivalent *Gardasil* vaccine ($V_f^q(t)$), exposed (latently-infected) females with the low-risk HPV types ($E_f^l(t)$), exposed females with the high-risk HPV types ($E_f^h(t)$), infected females with clinical symptoms of the low-risk HPV types ($I_f^l(t)$), infected females with clinical symptoms of the high-risk HPV types ($I_f^l(t)$), infected females with persistent infection with the low-risk HPV types ($P_f^l(t)$), infected females with persistent infection with the high-risk HPV types ($P_f^h(t)$), infected females in the (low-grade) CIN1 stage ($G_{fl}(t)$), infected females in the (high-grade) CIN2/3 stage ($G_{fh}(t)$), infected females with genital warts ($W_f(t)$), infected females with cervical cancer ($C_f^c(t)$), infected females who recovered from cervical cancer ($R_f^c(t)$) and infected females who recovered from HPV infection (and genital warts) without developing cervical cancer ($R_f(t)$), so that (where the indices l and h in G_{fl} and G_{fh} represent, respectively, low- and high-grade CIN, and not low- and high-risk HPV types),

$$\begin{aligned} N_f(t) &= S_f(t) + V_f^b(t) + V_f^q(t) + E_f^i(t) + I_f^i(t) + P_f^i(t) + W_f(t) + G_{fl}(t) + G_{fh}(t) \\ &+ C_f^c(t) + R_f^c(t) + R_f(t), \quad i \in \{l, h\}, \end{aligned} \tag{4.1}$$

where the indices l and h (with exception of those in G_{fl} and G_{fh}) represent low- and high-risk HPV types, respectively. In this study, HPV-6 and HPV-11 are the low-risk HPV types considered, while HPV-16 and HPV-18 are the high-risk HPV types. These HPV types are preventable using the *Cervarix* and *Gardasil* vaccines.

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

sub-divided into mutually-exclusive compartments of unvaccinated susceptible males ($S_m(t)$), new sexually-active susceptible males vaccinated with the quadrivalent *Gardasil* vaccine ($V_m^q(t)$), exposed males with the low-risk HPV types ($E_m^l(t)$), exposed males with the high-risk HPV types ($E_m^h(t)$), infected males with clinical symptoms of the low-risk HPV types ($I_m^l(t)$), infected males with clinical symptoms of the high-risk HPV types ($I_m^h(t)$), infected males with persistent infection with the low-risk HPV types ($P_m^l(t)$), infected males with persistent infection with the high-risk HPV types ($P_m^h(t)$), infected males with genital warts ($W_m(t)$), infected males in the low-grade HPV-related intraepithelial neoplasia INM1 stage ($G_{ml}(t)$), infected males in the high-grade HPV-related intraepithelial neoplasia INM2/3 stage ($G_{mh}(t)$), infected males with HPV-related cancers ($C_m^r(t)$), infected males who recovered from HPV-related cancers ($R_m^c(t)$) and infected males who recovered from HPV (and genital warts) without developing HPV-related cancers ($R_m(t)$). Thus (noting that the indices l and h in G_{ml} and G_{mh} represent, respectively, low- and high-grade INM for males, and not low- and high-risk HPV type),

$$\begin{aligned} N_m(t) &= S_m(t) + V_m^q(t) + E_m^i(t) + I_m^i(t) + P_m^i(t) + W_m(t) + G_{ml}(t) + G_{mh}(t) \\ &+ C_m^r(t) + R_m^c(t) + R_m(t), \quad i \in \{l, h\}. \end{aligned} \tag{4.2}$$

It follows from (4.1) and (4.2) that the total sexually-active (heterosexual) population, at time t, is given by

$$N(t) = N_f(t) + N_m(t).$$

It should be emphasized that, in this chapter, individuals in the exposed (E_f^i and E_m^i) and persistent (P_f^i and P_m^i) classes, with $i \in \{l, h\}$, are infected with HPV, and can transmit HPV to susceptible individuals.

The population of unvaccinated susceptible females (S_f) is increased by the recruitment of new sexually-active females at a rate π_f (a fraction, $1 - \varphi_f^b - \varphi_f^q$, with $0 < \varphi_f^b + \varphi_f^q \leq 1$, of which, is vaccinated; where, φ_f^b is the fraction of unvaccinated susceptible females vaccinated

with the *Cervarix* vaccine, and φ_f^q is the fraction vaccinated with the *Gardasil* vaccine). This population is further increased by the loss of infection-acquired immunity by infected females who recovered without developing cervical cancer (at a rate ξ_f). The population is decreased by infection, following effective contacts with males infected with the high-risk and the low-risk HPV types (i.e., those in the E_m^l, E_m^h, I_m^l, I_m^h, P_m^l and P_m^h classes), at the rates λ_m^l and λ_m^h, given, respectively, by:

$$\lambda_m^l = \frac{\beta_m^l c_f\left(N_m, N_f\right)\left(\eta_m^l E_m^l + I_m^l + \theta_m^l P_m^l\right)}{N_m}, \tag{4.3}$$

$$\lambda_m^h = \frac{\beta_m^h c_f\left(N_m, N_f\right)\left(\eta_m^h E_m^h + I_m^h + \theta_m^h P_m^h\right)}{N_m}. \tag{4.4}$$

In (4.3), β_m^l is the probability of transmission of HPV infection from infected males (with the low-risk HPV types) to susceptible females *per* contact, and $c_f\left(N_m, N_f\right)$ is the average number of female partners *per* male *per* unit time. Thus, $\beta_m^l c_f\left(N_m, N_f\right)$ is the effective contact rate for male-to-female transmission of the low-risk HPV types. Furthermore, η_m^l (with $0 \leq \eta_m^l < 1$) is the modification parameter accounting for the assumption that exposed males with the low-risk HPV types are less infectious than symptomatically-infected males with the low-risk HPV types. Similarly, in (4.4), β_m^h is the probability of transmission of HPV infection from infected males (with the high-risk HPV types) to susceptible females *per* contact, and $\beta_m^h c_f\left(N_m, N_f\right)$ is the effective contact rate for male-to-female transmission of the high-risk HPV types. The parameter η_m^h (with $0 \leq \eta_m^h < 1$) accounts for the assumption that exposed males with the high-risk HPV types are less infectious than symptomatically-infected males with the high-risk HPV types, and $\theta_m^l(\theta_m^h) > 0$ is the modification parameter accounting for the assumption that infected males with persistent infection with the low-risk (high-risk) HPV types transmit HPV at a different rate compared to infected males in the other infected classes ($E_m^l, I_m^l(E_m^h, I_m^h)$). The population of unvaccinated susceptible females is further decreased by natural death (at a rate μ_f; it is assumed that females in all epidemiological compartments suffer natural death at the rate μ_f). Thus,

$$\frac{dS_f}{dt} = (1 - \varphi_f^b - \varphi_f^q)\pi_f + \xi_f R_f - \left(\lambda_m^l + \lambda_m^h\right) S_f - \mu_f S_f. \tag{4.5}$$

The population of new sexually-active susceptible females vaccinated with the bivalent *Cervarix* vaccine (V_f^b) is generated by the vaccination of a fraction, φ_f^b, of unvaccinated susceptible females with the *Cervarix* vaccine (at the rate $\pi_f \varphi_f^b$). It is decreased by HPV infection, following effective contacts with males infected with high-risk HPV types (at the reduced rate $(1 - \varepsilon_b)\lambda_m^h$, where $0 < \varepsilon_b \leq 1$ represents the efficacy of the *Cervarix* vaccine against infection with the high-risk HPV types) and males infected with the low-risk HPV types (at the rate λ_m^l; it should be emphasized that the *Cervarix* vaccine has no efficacy against the low-risk HPV types, HPV-6 and HPV-11 [46, 76, 77]). This population is decreased by natural death. Since there is currently no evidence to the contrary, it is assumed that this vaccine (as well as *Gardasil*) does not wane [10, 15, 46, 76, 77]. Hence,

$$\frac{dV_f^b}{dt} = \varphi_f^b \pi_f - (1 - \varepsilon_b)\lambda_m^h V_f^b - \lambda_m^l V_f^b - \mu_f V_f^b. \tag{4.6}$$

The population of new sexually-active susceptible females vaccinated with the quadrivalent *Gardasil* vaccine (V_f^q) is generated by the vaccination of a fraction, φ_f^q, of unvaccinated susceptible females with the *Gardasil* vaccine (at the rate $\pi_f \varphi_f^q$). It is decreased by HPV infection, following effective contacts with males infected with the low- and high-risk HPV types (at a reduced rate $(1 - \varepsilon_q)\left(\lambda_m^l + \lambda_m^h\right)$, where $0 < \varepsilon_q \leq 1$ represents the efficacy of *Gardasil* vaccine against infection with HPV-6, HPV-11, HPV-16 and HPV-18). This population is decreased by natural death. Thus,

$$\frac{dV_f^q}{dt} = \varphi_f^q \pi_f - (1 - \varepsilon_q)\left(\lambda_m^h + \lambda_m^l\right) V_f^q - \mu_f V_f^q. \tag{4.7}$$

The population of exposed females with the low-risk (high-risk) HPV types ($E_f^l(E_f^h)$) is generated by the infection of unvaccinated and vaccinated susceptible females with the low-

risk HPV types (at the rate $\lambda_m^l(\lambda_m^h)$). This population is further increased by the re-infection of recovered females with the low-risk (high-risk) HPV types (at a rate $\rho_f^l\lambda_m^l(\rho_f^h\lambda_m^h)$, where $0 \leq \rho_f^l(\rho_f^h) < 1$ accounts for the assumption that the re-infection of recovered females with low-risk (high-risk) HPV types occurs at a rate lower than the rate for primary infection of susceptible females). Exposed females develop clinical symptoms of the low-risk (high-risk) HPV types (at a rate $\sigma_f^l(\sigma_f^h)$) and suffer natural death. Thus,

$$\begin{aligned}
\frac{dE_f^l}{dt} &= [S_f + V_b + (1-\varepsilon_q)V_q]\,\lambda_m^l + \rho_f^l\lambda_m^l R_f - (\sigma_f^l + \mu_f)E_f^l, \\
\frac{dE_f^h}{dt} &= [S_f + (1-\varepsilon_b)V_b + (1-\varepsilon_q)V_q]\,\lambda_m^h + \rho_f^h\lambda_m^h R_f - (\sigma_f^h + \mu_f)E_f^h.
\end{aligned} \tag{4.8}$$

The population of infected females with clinical symptoms of the low-risk (high-risk) HPV types ($I_f^l(I_f^h)$) is generated at the rate $\sigma_f^l(\sigma_f^h)$. This population is decreased by recovery (at a rate $\psi_f^l(\psi_f^h)$) and natural death. Hence,

$$\begin{aligned}
\frac{dI_f^l}{dt} &= \sigma_f^l E_f^l - (\psi_f^l + \mu_f)I_f^l, \\
\frac{dI_f^h}{dt} &= \sigma_f^h E_f^h - (\psi_f^h + \mu_f)I_f^h.
\end{aligned} \tag{4.9}$$

The population of females with persistent infection with the low-risk HPV types (P_f^l) is generated by the development of persistent infection, with the low-risk HPV types, by symptomatic females with the low-risk HPV types (at a rate $(1-r_f^l)\psi_f^l$, where $0 < r_f^l \leq 1$ is the fraction of symptomatic females with the low-risk HPV types who recovered from HPV infection without developing genital warts; it is assumed that individuals infected with the low-risk HPV types do not progress to the CIN stages and/or develop cancer [10, 15, 76, 77]). Females with persistent infection with the low-risk HPV types move out of this epidemiological class (either through recovery or development of genital warts) at a rate α_f^l, and suffer natural death. Thus,

$$\frac{dP_f^l}{dt} = (1-r_f^l)\psi_f^l I_f^l - (\alpha_f^l + \mu_f)P_f^l. \tag{4.10}$$

The population of females with persistent infection with the high-risk HPV types (P_f^h) is generated at a rate $(1-r_f^h)\psi_f^h$, where $0 < r_f^h \leq 1$ is the fraction of symptomatic females with the high-risk HPV types who recovered from HPV without progressing to the low-grade CIN1 stage, and by a fraction, $1-(s_{1f}+s_{2f})$, of infected females in the high-grade CIN2/3 stage who develop persistent infection (at a rate $[1-(s_{1f}+s_{2f})]\, z_f$, where s_{1f} and s_{2f}, with $0 \leq s_{1f}+s_{2f} \leq 1$, are the fractions of infected females in the high-grade CIN2/3 stage who naturally recovered from HPV infection, and of infected females in the high-grade CIN2/3 stage who revert to the low-grade CIN1 stage, respectively). Females with persistent infection with the high-risk HPV types move out of this epidemiological class (either through recovery or development of pre-cancerous CIN lesions) at a rate α_f^h, and suffer natural death. Hence,

$$\frac{dP_f^h}{dt} = (1-r_f^h)\psi_f^h I_f^h + [1-(s_{1f}+s_{2f})]\, z_f G_{fh} - (\alpha_f^h + \mu_f)P_f^h.$$

The population of females with genital warts (W_f) is generated when infected females with persistent infection with the low-risk HPV types develop genital warts (at a rate $(1-k_f^l)\alpha_f^l$, where $0 < k_f^l \leq 1$ is the fraction of infected females with persistent low-risk HPV types who recovered from HPV infection). Since genital warts do not cause cervical cancer (or any other type of cancer [76, 100]), it is assumed that genital warts do not cause death in females and males. This population decreases due to recovery (at a rate n_f) and natural death, so that,

$$\frac{dW_f}{dt} = (1-k_f^l)\alpha_f^l P_f^l - (n_f+\mu_f)\, W_f. \tag{4.11}$$

The population of females with the low-grade CIN1 (G_{fl}) is generated when infected females with persistent infection with the high-risk HPV types develop pre-cancerous CIN lesions (at a rate $(1-k_f^h)\alpha_f^h$, where $0 < k_f^h \leq 1$ is the fraction of infected females with persistent infection with the high-risk HPV types who recovered from HPV infection). This population is further increased by the reversion (or regression) of individuals in the high-grade CIN2/3

stage into the low-grade CIN1 stage (at a rate $s_{2f}z_f$). Individuals move out of this class at a rate u_f (due to progression to the high-grade CIN2/3 stage [25, 29, 61, 100], at a rate $(1-d_f)u_f$, or recovery, at a rate $d_f u_f$). It is assumed that individuals in the CIN stages do not suffer disease-induced death (until they develop cervical cancer). Thus,

$$\frac{dG_{fl}}{dt} = (1-k_f^h)\alpha_f^h P_f^h + s_{2f}z_f G_{fh} - (u_f+\mu_f)\,G_{fl}. \tag{4.12}$$

The population of females in the high-grade CIN2/3 stage (G_{fh}) is generated by the progression of infected females with low-grade CIN1 (at the rate $(1-d_f)u_f$, where $0 \leq d_f \leq 1$ is the fraction of infected females in the low-grade CIN1 stage who naturally recovered from HPV infection). Transition out of this class occurs at a rate z_f (where a fraction, $s_{1f}z_f$, recovers; another fraction, $s_{2f}z_f$, reverts to the low-grade CIN1 stage and the remaining fraction, $1-(s_{1f}+s_{2f})$, develops persistent infection). This population is decreased by the development of cervical cancer (at a rate ω_f) and natural death. Hence,

$$\frac{dG_{fh}}{dt} = (1-d_f)u_f G_{fl} - (z_f+\omega_f+\mu_f)\,G_{fh}. \tag{4.13}$$

The population of females with cervical cancer (C_f^c) is generated by the development of cervical cancer by infected females in the high-grade CIN2/3 stage (at the rate ω_f). This population decreases due to recovery (at a rate γ_f), natural death and cancer-induced death (at a rate δ_f), so that

$$\frac{dC_f^c}{dt} = \omega_f G_{fh} - (\gamma_f+\mu_f+\delta_f)C_f^c. \tag{4.14}$$

The population of infected females who recovered from cervical cancer (R_f^c) is generated at the rate γ_f, and decreases by natural death. As in [61], it is assumed that individuals in this class do not acquire HPV infection again (since these individuals require treatment/surgery, which, typically, result in the removal or damage to the cervix and some other normal tissues

around it [68]). Thus,

$$\frac{dR_f^c}{dt} = \gamma_f C_f^c - \mu_f R_f^c. \tag{4.15}$$

The population of infected females who recovered from HPV infection (and genital warts) without developing cervical cancer (R_f) is generated at the rates $r_f^l\psi_f^l$, $r_f^l h\psi_f^h$, $k_f^l\alpha_f^l$, $k_f^h\alpha_f^h$, n_f, $d_f u_f$ and $s_{1f}z_f$, respectively. Recovered females acquire re-infection at the rates $\rho_f^l\lambda_m^l$ and $\rho_f^h\lambda_m^h$. This population is further decreased by the loss of infection-acquired immunity (at the rate ξ_f) and natural death. This gives:

$$\begin{aligned}\frac{dR_f}{dt} &= r_f^l\psi_f^l I_f^l + r_f^h\psi_f^h I_f^h + k_f^l\alpha_f^l P_f^l + k_f^h\alpha_f^h P_f^h + n_f W_f + d_f u_f G_{fl} + s_{1f}z_f G_{fh} \\ &- \left(\rho_f^h\lambda_m^h + \rho_f^l\lambda_m^l\right) R_f - \left(\xi_f + \mu_f\right) R_f. \end{aligned} \tag{4.16}$$

The population of unvaccinated susceptible males (S_m) is generated by the recruitment of new sexually-active males at a rate π_m (a fraction, φ_m^q, of which, is vaccinated with the *Gardasil* vaccine; it is assumed that males are not vaccinated with the *Cervarix* vaccine [76, 77, 100]). It is further increased by the loss of infection-acquired immunity by recovered males (at a rate ξ_m). This population is diminished by infection, following effective contacts with infected females (with both the low-risk and high-risk HPV types), at rates λ_f^l and λ_f^h, where

$$\lambda_f^l = \frac{\beta_f^l c_m\left(N_m, N_f\right)\left(\eta_f^l E_f^l + I_f^l + \theta_f^l P_f^l\right)}{N_f}, \tag{4.17}$$

$$\lambda_f^h = \frac{\beta_f^h c_m\left(N_m, N_f\right)\left(\eta_f^h E_f^h + I_f^h + \theta_f^h P_f^h\right)}{N_f}. \tag{4.18}$$

In (4.17) and (4.18), $\beta_f^l(\beta_f^h)$ is the probability of transmission of HPV infection from infected females with the low-risk (high-risk) HPV types to males *per* contact and $c_m\left(N_m, N_f\right)$ is the average number of male partners *per* female *per* unit time. Furthermore, η_f^l (η_f^h) (with $0 \leq \eta_f^l(\eta_f^h) < 1$) is the modification parameter accounting for the assumption that exposed females with the ow-risk (high-risk) HPV types (i.e., those in the $E_f^l(E_f^h)$ class) are less

infectious than symptomatically-infected females (i.e., those in the $I_f^l(I_f^h)$ class), and $\theta_f^l(\theta_f^h) > 0$ is the modification parameter accounting for the assumption that infected females with persistent infection with the low-risk (high-risk) HPV types transmit HPV at a different rate compared to infected females in the $E_f^l, I_f^l(E_f^h, I_f^h)$ classes. This population is further decreased by natural death (at a rate μ_m; it is assumed that males in all epidemiological compartments suffer natural death at this rate, μ_m). Thus,

$$\frac{dS_m}{dt} = (1-\varphi_m^q)\,\pi_m + \xi_m R_m - \left(\lambda_f^h + \lambda_f^l\right) S_m - \mu_m S_m. \tag{4.19}$$

The population of new sexually-active susceptible males vaccinated with the *Gardasil* vaccine (V_m^q) is generated by the vaccination of the fraction, φ_m^q, of unvaccinated susceptible males (at the rate $\pi_m \varphi_m^q$). It is decreased by HPV infection, following effective contacts with females infected with the high-risk HPV types (at a reduced rate $(1-\varepsilon_q)\lambda_f^h$, where $0 < \varepsilon_q \leq 1$ is the efficacy of the *Gardasil* vaccine) and females infected with the low-risk HPV types (at the rate $(1-\varepsilon_q)\lambda_f^l$). This population is reduced by natural death. Hence,

$$\frac{dV_m^q}{dt} = \varphi_m^q \pi_m - (1-\varepsilon_q)\left(\lambda_f^h + \lambda_f^l\right) V_m^q - \mu_m V_m^q. \tag{4.20}$$

The population of exposed males with the low-risk (high-risk) HPV types ($E_m^l(E_m^h)$) is generated by the infection of unvaccinated and vaccinated susceptible males with the low-risk (high-risk) HPV types (at the rate $\lambda_f^l(\lambda_f^h)$). This population is further increased by the re-infection of recovered males (at a rate $\rho_m^l \lambda_f^l(\rho_m^h \lambda_f^h)$, where $0 \leq \rho_m^l(\rho_m^h) < 1$ also accounts for the assumption that re-infection of recovered females occurs at a rate lower than the primary infection). Exposed males develop clinical symptoms of the low-risk (high-risk) HPV types (at a rate $\sigma_m^l(\sigma_m^h)$) and suffer natural death. Hence,

$$\frac{dE_m^l}{dt} = [S_m + (1-\varepsilon_q)V_m^q]\,\lambda_f^l + \rho_m^l \lambda_f^l R_m - (\sigma_m^l + \mu_m)E_m^l, \tag{4.21}$$

$$\frac{dE_m^h}{dt} = [S_m + (1-\varepsilon_q)V_m^q]\,\lambda_f^h + \rho_m^h \lambda_f^h R_m - (\sigma_m^h + \mu_m)E_m^h. \tag{4.22}$$

The population of infected males with clinical symptoms of the low-risk (high-risk) HPV types ($I_m^l(I_m^h)$) is generated at the rate $\sigma_m^l(\sigma_m^h)$. It is reduced by recovery (at a rate $\psi_m^l(\psi_m^h)$) and natural death. Thus,

$$\frac{dI_m^l}{dt} = \sigma_m^l E_m^l - (\psi_m^l + \mu_m) I_m^l, \tag{4.23}$$

$$\frac{dI_m^h}{dt} = \sigma_m^h E_m^h - (\psi_m^h + \mu_m) I_m^h. \tag{4.24}$$

The population of males with persistent infection with the low-risk HPV types (P_m^l) is generated by the development of persistent infection, with the low-risk HPV types, by symptomatic males with the low-risk HPV types (at a rate $(1 - r_m^l)\psi_m^l$, where $0 < r_m^l \leq 1$ is the fraction of symptomatic males with the low-risk HPV types who recovered from HPV infection without developing genital warts). Males with persistent infection with the low-risk HPV types move out of this epidemiological class (either through recovery or development of genital warts) at a rate α_m^l, and suffer natural death. Thus,

$$\frac{dP_m^l}{dt} = (1 - r_m^l)\psi_m^l I_m^l - (\alpha_m^l + \mu_m) P_m^l. \tag{4.25}$$

The population of males with persistent infection with the high-risk HPV types (P_m^h) is generated at a rate $(1 - r_m^h)\psi_m^h$, where $0 < r_m^h \leq 1$ is the fraction of symptomatic males with the high-risk HPV types who recovered from HPV without progressing to the low-grade INM1 stage, and by a fraction, $1 - (s_{1m} + s_{2m})$, of infected males in the high-grade INM2/3 stage who develop persistent infection (at a rate $[1 - (s_{1m} + s_{2m})]\, z_m$, where s_{1m} and s_{2m}, with $0 \leq s_{1m} + s_{2m} \leq 1$, are the fractions of infected males in the high-grade INM2/3 stage who naturally recovered from HPV infection, and of infected males in the high-grade INM2/3 stage that reverts to the low-grade INM1 stage, respectively). Males with persistent infection with the high-risk HPV types move out of this epidemiological class (either through recovery or development of pre-cancerous lesions) at a rate α_m^h, and suffer natural death. Hence,

$$\frac{dP_m^h}{dt} = (1 - r_m^h)\psi_m^h I_m^h + [1 - (s_{1m} + s_{2m})]\, z_m G_{mh} - (\alpha_m^h + \mu_m) P_m^h.$$

The population of males with genital warts (W_m) is generated when infected males with persistent infection with the low-risk HPV types develop genital warts (at a rate $(1-k_m^l)\alpha_m^l$, where $0 < k_m^l \leq 1$ is the fraction of infected males with low-risk persistent HPV types who recovered from HPV infection). This population decreases due to recovery (at a rate n_m) and natural death, so that,

$$\frac{dW_m}{dt} = (1 - k_m^l)\alpha_m^l P_m^l - (n_m + \mu_m)\, W_m. \tag{4.26}$$

The population of males in the low-grade HPV-related INM1 stage (G_{ml}) is generated when infected males with persistent infection with the high-risk HPV types develop pre-cancerous lesions (at a rate $(1 - k_m^h)\alpha_m^h$, where $0 < k_m^h \leq 1$ is the fraction of infected males with persistent infection with the high-risk HPV types who recovered from HPV infection). This population is further increased by the reversion of individuals in the high-grade HPV-related INM2/3 stage (at a rate $s_{2m}z_m$). Individuals move out of this class at a rate u_m (due to progression to the high-grade INM2/3 stage, at a rate $(1 - d_m)u_m$, or recovery, at a rate $d_m u_m$). It is assumed that individuals in INM stages do not suffer disease-induced death (until they develop HPV-related cancer). Thus,

$$\frac{dG_{ml}}{dt} = (1 - k_m^h)\alpha_m^h P_m^h + s_{2m} z_m G_{mh} - (u_m + \mu_m)\, G_{ml}. \tag{4.27}$$

The population of males in the high-grade HPV-related INM2/3 stage (G_{mh}) is generated by the progression of infected males in the low-grade HPV-related INM1 stage (at the rate $(1 - d_m)u_m$, where $0 \leq d_m \leq 1$ is the fraction of infected males in the low-grade INM1 stage who naturally recovered from HPV infection). Transition out of this class occurs at a rate z_m (where a fraction, $s_{1m}z_m$, recovers; another fraction, $s_{2m}z_m$, reverts to the low-

grade INM1 stage and the remaining fraction, $1-(s_{1m}+s_{2m})$, develops persistent infection). This population is decreased by the development of HPV-related cancer (at a rate ω_m) and natural death. Hence,

$$\frac{dG_{mh}}{dt} = (1-d_m)u_m G_{ml} - (z_m + \omega_m + \mu_m)\, G_{mh}. \tag{4.28}$$

The population of males with HPV-related cancers (C_m^c) is generated by the development of HPV-related cancers by infected males in the high-grade IN2/3 stage (at the rate ω_m). This population decreases due to recovery (at a rate γ_m), natural death and cancer-induced death (at a rate δ_m), so that

$$\frac{dC_m^r}{dt} = \omega_m G_{mh} - (\gamma_m + \mu_m + \delta_m) C_m^r. \tag{4.29}$$

The population of males who recovered from HPV-related cancers (R_m^c) is generated at the rate γ_m, and decreases by natural death, so that

$$\frac{dR_m^c}{dt} = \gamma_m C_m^c - \mu_m R_m^c. \tag{4.30}$$

The population of males who recovered from HPV infection (and genital warts) without developing cancer (R_m) is generated at the rates $r_m^l\psi_m^l, r_m\psi_m^h, k_m^l\alpha_m^l, k_m^h\alpha_m^h, n_m$, $d_m u_m$ and $s_{1m}z_m$. It is decreased by re-infection (at the rates $\rho_m^l\lambda_f^l$ and $\rho_m^h\lambda_f^h$), loss of infection-acquired immunity (at the rate ξ_m) and natural death, so that

$$\begin{aligned} \frac{dR_m}{dt} &= r_m^l\psi_m^l I_m^l + r_f\psi_m^h I_m^h + k_m^l\alpha_m^l P_m^l + k_m^h\alpha_m^h P_m^h + n_m W_m + d_m u_m G_{ml} \\ &+ s_{1m}z_m G_{mh} - \left(\rho_m^h\lambda_f^h + \rho_m^l\lambda_f^l\right) R_m - (\xi_m + \mu_m)\, R_m. \end{aligned} \tag{4.31}$$

It should be emphasized, as in Chapter 3, that the following conservation law for the

model {(4.3)-(4.31)} must hold:

$$c_m\left(N_m, N_f\right) N_m = c_f\left(N_m, N_f\right) N_f. \tag{4.32}$$

Furthermore, it is assumed that male sexual partners are abundant, so that females can always have enough number of male sexual contacts *per* unit time. Hence, $c_f\left(N_m, N_f\right) = c_f$, a constant, and $c_m\left(N_m, N_f\right)$ is calculated from the relation

$$c_m\left(N_m, N_f\right) = \frac{c_f N_f}{N_m}. \tag{4.33}$$

It is assumed, from now on, that the two vaccines (*Gardasil* and *Cervarix*) have the same efficacy (that is, $\varepsilon_b = \varepsilon_q = \varepsilon_v$) [10, 34, 77, 100].

Based on the above formulations and assumptions, and using (4.33) in {(4.3), (4.4), (4.17) and (4.18)}, it follows that the risk-structured model for the transmission dynamics of the low- and high-risk HPV types in a community that adopts mass vaccination (using *Cervarix* and *Gardasil* vaccines) is given by the following deterministic system of 29 non-

linear differential equations:

$$
\begin{aligned}
\frac{dS_f}{dt} &= (1-\varphi_f^b-\varphi_f^q)\pi_f + \xi_f R_f - \left(\lambda_m^h+\lambda_m^l\right) S_f - \mu_f S_f,\\
\frac{dV_f^b}{dt} &= \varphi_f^b\pi_f - (1-\varepsilon_v)\lambda_m^h V_f^b - \lambda_m^l V_f^b - \mu_f V_f^b,\\
\frac{dV_f^q}{dt} &= \varphi_f^q\pi_f - (1-\varepsilon_v)\left(\lambda_m^h+\lambda_m^l\right) V_f^q - \mu_f V_f^q,\\
\frac{dE_f^l}{dt} &= \left[S_f + V_f^b + (1-\varepsilon_v)V_f^q\right]\lambda_m^l + \rho_f^l\lambda_m^l R_f - (\sigma_f^l+\mu_f)E_f^l,\\
\frac{dE_f^h}{dt} &= \left[S_f + (1-\varepsilon_v)V_f^b + (1-\varepsilon_v)V_f^q\right]\lambda_m^h + \rho_f^h\lambda_m^h R_f - (\sigma_f^h+\mu_f)E_f^h,\\
\frac{dI_f^l}{dt} &= \sigma_f^l E_f^l - (\psi_f^l+\mu_f)I_f^l,\\
\frac{dI_f^h}{dt} &= \sigma_f^h E_f^h - (\psi_f^h+\mu_f)I_f^h,\\
\frac{dP_f^l}{dt} &= (1-r_f^l)\psi_f^l I_f^l - (\alpha_f^l+\mu_f)P_f^l,\\
\frac{dP_f^h}{dt} &= (1-r_f^h)\psi_f^h I_f^h + \left[1-(s_{1f}+s_{2f})\right] z_f G_{fh} - (\alpha_f^h+\mu_f)P_f^h,\\
\frac{dW_f}{dt} &= (1-k_f^l)\alpha_f^l P_f^l - (n_f+\mu_f)\,W_f,\\
\frac{dG_{fl}}{dt} &= (1-k_f^h)\alpha_f^h P_f^h + s_{2f} z_f G_{fh} - (u_f+\mu_f)\,G_{fl},\\
\frac{dG_{fh}}{dt} &= (1-d_f)u_f G_{fl} - (z_f+\omega_f+\mu_f)\,G_{fh},\\
\frac{dC_f^c}{dt} &= \omega_f G_{fh} - (\gamma_f+\mu_f+\delta_f)C_f^c,\\
\frac{dR_f^c}{dt} &= \gamma_f C_f^c - \mu_f R_f^c,\\
\frac{dR_f}{dt} &= r_f^l\psi_f^l I_f^l + r_f^h\psi_f^h I_f^h + k_f^l\alpha_f^l P_f^l + k_f^h\alpha_f^h P_f^h + n_f W_f + d_f u_f G_{fl}\\
&+ s_{1f} z_f G_{fh} - \left(\rho_f^h\lambda_m^h + \rho_f^l\lambda_m^l\right) R_f - (\xi_f+\mu_f)\,R_f,
\end{aligned}
\tag{4.34}
$$

$$
\begin{aligned}
\frac{dS_m}{dt} &= (1-\varphi_m^q)\,\pi_m + \xi_m R_m - \left(\lambda_f^h + \lambda_f^l\right) S_m - \mu_m S_m, \\
\frac{dV_m^q}{dt} &= \varphi_m^q \pi_m - (1-\varepsilon_v)\left(\lambda_f^h + \lambda_f^l\right) V_m^q - \mu_m V_m^q, \\
\frac{dE_m^l}{dt} &= \left[S_m + (1-\varepsilon_v)V_m^q\right]\lambda_f^l + \rho_m^l \lambda_f^l R_m - (\sigma_m^l + \mu_m)E_m^l, \\
\frac{dE_m^h}{dt} &= \left[S_m + (1-\varepsilon_v)V_m^q\right]\lambda_f^h + \rho_m^h \lambda_f^h R_m - (\sigma_m^h + \mu_m)E_m^h, \\
\frac{dI_m^l}{dt} &= \sigma_m^l E_m^l - (\psi_m^l + \mu_m)I_m^l, \\
\frac{dI_m^h}{dt} &= \sigma_m^h E_m^h - (\psi_m^h + \mu_m)I_m^h, \\
\frac{dP_m^l}{dt} &= (1-r_m^l)\psi_m^l I_m^l - (\alpha_m^l + \mu_m)P_m^l, \\
\frac{dP_m^h}{dt} &= (1-r_m^h)\psi_m^h I_m^h + \left[1-(s_{1m}+s_{2m})\right] z_m G_{mh} - (\alpha_m^h + \mu_m)P_m^h, \\
\frac{dW_m}{dt} &= (1-k_m^l)\alpha_m^l P_m^l - (n_m + \mu_m)\,W_m, \\
\frac{dG_{ml}}{dt} &= (1-k_m^h)\alpha_m^h P_m^h + s_{2m} z_m G_{mh} - (u_m + \mu_m)\,G_{ml}, \\
\frac{dG_{mh}}{dt} &= (1-d_m)u_m G_{ml} - (z_m + \omega_m + \mu_m)\,G_{mh}, \\
\frac{dC_m^r}{dt} &= \omega_m G_{mh} - (\gamma_m + \mu_m + \delta_m)C_m^r, \\
\frac{dR_m^c}{dt} &= \gamma_m C_m^c - \mu_m R_m^c, \\
\frac{dR_m}{dt} &= r_m^l \psi_m^l I_m^l + r_m^h \psi_m^h I_m^h + k_m^l \alpha_m^l P_m^l + k_m^h \alpha_m^h P_m^h + n_m W_m + d_m u_m G_{ml} \\
&+ s_{1m} z_m G_{mh} - \left(\rho_m^h \lambda_f^h + \rho_m^l \lambda_f^l\right) R_m - (\xi_m + \mu_m)\,R_m.
\end{aligned}
$$

A flow diagram of the model (4.34) is depicted in Figures 4.1 and 4.2. The state variables and parameters of the model are tabulated in Tables 4.1 and 4.2.

It should be mentioned that there is no biological or epidemiological relationship (such as back-and-forth transition or evolution) between the low- and high-risk HPV types. That is, the two HPV risk types (low and high) are independent, and the reason for stratifying the infected population according to the two risk types is to account for the fact that infection

with the low-risk HPV types causes genital warts only, while infection with the high-risk HPV types causes cancers. In other words, the purpose of the risk structure in this study is to account for the heterogeneity of outcomes (cancers or warts) associated with infection with the low- or high-risk HPV types. Another advantage of stratifying the infected population in terms of infection with the low- and high-risk HPV types is that it allows for the realistic assessment of the community-wide impact of the currently-available vaccines (since, for example, the *Cervarix* vaccine only targets the high-risk, HPV-16 and HPV-18, types while the *Gardasil* vaccine targets all the four HPV types considered in this study). Furthermore, it should be emphasized that the risk-structure in this study is not associated with human behaviour (i.e., risky sexual practices), so that there is no back-and-forth transition between the two risk HPV types based on changes in human behaviour.

The 29-dimensional model (4.34) extends the 12-dimensional model (3.19) developed in Chapter 3 by (*inter alia*):

i) stratifying the total population in terms of the dynamics of the low- and high-risk HPV types;

ii) incorporating two anti-HPV vaccines (*Cervarix* and *Gardasil*); only the *Gardasil* vaccine is considered in Chapter 3;

iii) vaccinating both new sexually-active susceptible females and males (only females are vaccinated in Chapter 3);

iv) including the dynamics of individuals with genital warts (W_f, W_m);

v) including the dynamics of individuals in the low- and high-grade pre-cancer (CIN and INM) stages for females and males ($G_{fl}, G_{ml}, G_{fh}, G_{mh}$);

vi) including the dynamics of infected males with HPV-related cancers (C_m^r), cancer-induced mortality for males ($\delta_m \neq 0$), infected males who recovered from HPV-related cancers (R_m^c) and a compartment for males with persistent HPV infection (P_m).

4.2.1 Basic properties

As in Section 3.2.1, the following result holds for the low- and high-risk HPV model (4.34).

Theorem 4.1. *Let the initial data for the model (4.34) be* $S_f(0) > 0, V_f^b(0) > 0, V_f^q(0) > 0, E_f^l(0) \geq 0, E_f^h(0) \geq 0, I_f^l(0) \geq 0, I_f^h(0) \geq 0, P_f^l(0) \geq 0, P_f^h(0) \geq 0, W_f(0) \geq 0, G_{fl}(0) \geq 0, G_{fh}(0) \geq 0, C_f^c(0) \geq 0, R_f^c(0) \geq 0, R_f(0) \geq 0,$ $S_m(0) > 0, V_m^q(0) > 0, E_m^l(0) \geq 0, E_m^h(0) \geq 0, I_m^l(0) \geq 0, I_m^h(0) \geq 0, P_m^l(0) \geq 0, P_m^h(0) \geq 0, W_m(0) \geq 0, G_{ml}(0) \geq 0, G_{mh}(0) \geq 0, C_m^r(0) \geq 0, R_m^c(0) \geq 0$ *and* $R_m(0) \geq 0$. *Then, the solutions* $(S_f(t), V_f^b(t), V_f^q(t), E_f^l(t), E_f^h(t), I_f^l(t), I_f^h(t), P_f^l(t), P_f^h(t), W_f(t), G_{fl}(t), G_{fh}(t), C_f^c(t), R_f^c(t), R_f(t), S_m(t), V_m^q(t), E_m^l(t), E_m^h(t), I_m^l(t), I_m^h(t), P_m^l(t), P_m^h(t), W_m(t), G_{ml}(t), G_{mh}(t), C_m^r(t), R_m^c(t), R_m(t))$ *of the model with positive initial data, will remain positive for all time* $t > 0$.

Theorem 4.1 can be proved using the approach in Appendix A (and the proof is not repeated here). Consider, next, the feasible region

$$\mathcal{D}_r = \mathcal{D}_f \cup \mathcal{D}_m \subset \mathbb{R}_+^{15} \times \mathbb{R}_+^{14},$$

with,

$$\mathcal{D}_f = \left\{ \left(S_f, V_f^b, V_f^q, E_f^l, E_f^h, I_f^l, I_f^h, P_f^l, P_f^h, W_f, G_{fl}, G_{fh}, C_f^c, R_f^c, R_f\right) \in \mathbb{R}_+^{15} : N_f \leq \frac{\pi_f}{\mu_f} \right\},$$

and,

$$\mathcal{D}_m = \left\{ \left(S_m, V_m^q, E_m^l, E_m^h, I_m^l, I_m^h, P_m^l, P_m^h, W_m, G_{ml}, G_{mh}, C_m^c, R_m^c, R_m\right) \in \mathbb{R}_+^{14} : N_m \leq \frac{\pi_m}{\mu_m} \right\}.$$

Using the method described in Section 3.2.1, it can be shown that the region $\mathcal{D}_r$ is positively-invariant and attracting for the model (4.34), so that it is sufficient to consider the dynamics of the model in $\mathcal{D}_r$. This result is summarized below.

Lemma 4.1. *The region* $\mathcal{D}_r = \mathcal{D}_f \cup \mathcal{D}_m \subset \mathbb{R}_+^{15} \times \mathbb{R}_+^{14}$ *is positively-invariant for the model (4.34) with initial conditions in* $\mathbb{R}_+^{29}$.

4.3 Existence and Stability of Equilibria

4.3.1 Local asymptotic stability of DFE

The DFE of the model (4.34) is given by

$$\begin{aligned}
\mathcal{E}_0^r &= (S_f^*, V_f^{b^*}, V_f^{q^*}, E_f^{l^*}, E_f^{h^*}, I_f^{l^*}, I_f^{h^*}, P_f^{l^*}, P_f^{h^*}, W_f^*, G_{fl}^*, G_{fh}^*, C_f^{c^*}, R_f^{c^*}, R_f^*, S_m^*, \\
&\quad V_m^{q^*}, E_m^{l^*}, E_m^{h^*}, I_m^{l^*}, I_m^{h^*}, P_m^{l^*}, P_m^{h^*}, W_m^*, G_{ml}^*, G_{mh}^*, C_m^{r^*}, R_m^{c^*}, R_m^*) \\
&= (S_f^*, V_f^{b^*}, V_f^{q^*}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, S_m^*, V_m^{q^*}, 0, 0, 0, 0, 0, 0, 0, 0, 0, \\
&\quad 0, 0, 0, 0),
\end{aligned} \tag{4.35}$$

with (noting that $\varphi_f^b + \varphi_f^q \leq 1$, so that $S_f^* > 0$),

$$\begin{aligned}
S_f^* &= \frac{\pi_f \left(1 - \varphi_f^b - \varphi_f^q\right)}{\mu_f}, \quad V_f^{b^*} = \frac{\pi_f \varphi_f^b}{\mu_f}, \quad V_f^{q^*} = \frac{\pi_f \varphi_f^q}{\mu_f}, \\
S_m^* &= \frac{\pi_m \left(1 - \varphi_m^q\right)}{\mu_m}, \quad V_m^{q^*} = \frac{\pi_m \varphi_m^q}{\mu_f},
\end{aligned}$$

and,

$$N_f^* = S_f^* + V_f^{b^*} + V_f^{q^*} = \frac{\pi_f}{\mu_f} \quad \text{and} \quad N_m^* = S_m^* + V_m^{q^*} = \frac{\pi_m}{\mu_m}.$$

The associated next generation matrices, $\mathcal{F}_r$ and $\mathcal{H}_r$ (for the new infection terms and the remaining transfer terms in the model (4.34)) are, respectively, given by (it should be mentioned that, for the purpose of the computations in this section, the infected classes of the model (4.34) are ordered as follows: $E_f^l, I_f^l,\ P_f^l, W_f,\ E_f^h, I_f^h,\ P_f^h,\ G_{fl},\ G_{fh},\ C_f^c,$

$E_m^l, I_m^l, P_m^l, W_m, E_m^h, I_m^h, P_m^h, G_{ml}, G_{mh}, C_m^r$):

$$\mathcal{F}_r = \begin{pmatrix} \mathbf{0}_{10\times 10} & \mathcal{F}_1 \\ \mathcal{F}_2 & \mathbf{0}_{10\times 10} \end{pmatrix} \quad \text{and} \quad \mathcal{H}_r = \begin{pmatrix} \mathcal{H}_1 & \mathbf{0}_{10\times 10} \\ \mathbf{0}_{10\times 10} & \mathcal{H}_2 \end{pmatrix},$$

where,

$$\mathcal{F}_1 = \begin{pmatrix} \frac{\beta_m^l c_f \eta_m^l}{N_m^*} p_1 & \frac{\beta_m^l c_f}{N_m^*} p_1 & \frac{\beta_m^l c_f \theta_m^l}{N_m^*} p_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\beta_m^h c_f \eta_m^h}{N_m^*} p_2 & \frac{\beta_m^h c_f}{N_m^*} p_2 & \frac{\beta_m^h c_f \theta_m^h}{N_m^*} p_2 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\mathcal{F}_2 = \begin{pmatrix} \frac{\beta_f^l c_f \eta_f^l}{N_m^*} p_3 & \frac{\beta_f^l c_f}{N_m^*} p_3 & \frac{\beta_f^l c_f \theta_f^l}{N_m^*} p_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\beta_f^h c_f \eta_f^h}{N_m^*} p_4 & \frac{\beta_f^h c_f}{N_m^*} p_4 & \frac{\beta_f^h c_f \theta_f^h}{N_m^*} p_4 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\mathcal{H}_1 = \begin{pmatrix} A_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -b_1 & A_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -b_2 & A_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -b_3 & A_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & A_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -b_5 & A_6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -b_6 & A_7 & 0 & -g_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -b_7 & A_8 & -g_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -b_8 & A_9 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -b_9 & A_{10} \end{pmatrix},$$

$$\mathcal{H}_2 = \begin{pmatrix} D_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -k_1 & D_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_2 & D_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -k_3 & D_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & D_5 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -k_5 & D_6 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -k_6 & D_7 & 0 & -j_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -k_7 & D_8 & -j_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_8 & D_9 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -k_9 & D_{10} \end{pmatrix},$$

with $\mathbf{0}_{10\times 10}$ being the zero matrix of order 10, and

$$
\begin{aligned}
p_1 &= \left[S_f^* + V_f^{b^*} + (1-\varepsilon_v)\, V_f^{q^*}\right] = \frac{\pi_f\left(1-\varepsilon_v\varphi_f^q\right)}{\mu_f},\\
p_2 &= \left[S_f^* + (1-\varepsilon_v)\, V_f^{b^*} + (1-\varepsilon_v)\, V_f^{q^*}\right] = \frac{\pi_f\left[1-\varepsilon_v\left(\varphi_f^b+\varphi_f^q\right)\right]}{\mu_f},\\
p_3 &= \left[S_m^* + V_m^{b^*} + (1-\varepsilon_v)\, V_m^{q^*}\right] = \frac{\pi_m\left(1-\varepsilon_v\varphi_m^q\right)}{\mu_m},\\
p_4 &= \left[S_m^* + (1-\varepsilon_v)\, V_m^{b^*} + (1-\varepsilon_v)\, V_m^{q^*}\right] = \frac{\pi_m\left(1-\varepsilon_v\varphi_m^q\right)}{\mu_m},\\
A_1 &= \sigma_f^l + \mu_f,\ \ b_1 = \sigma_f^l,\ \ A_2 = \psi_f^l + \mu_f,\ \ b_2 = \left(1-r_f^l\right)\psi_f^l,\ \ A_3 = \alpha_f^l + \mu_f,\\
b_3 &= \left(1-k_f^l\right)\alpha_f^l,\ \ A_4 = n_f + \mu_f,\ \ A_5 = \sigma_f^h + \mu_f,\ \ b_5 = \sigma_f^h,\ \ A_6 = \psi_f^h + \mu_f,\\
b_6 &= \left(1-r_f^h\right)\psi_f^h,\ \ A_7 = \alpha_f^h + \mu_f,\ \ g_1 = \left[1-(s_{1f}+s_{2f})\right] z_f,\ \ b_7 = \left(1-k_f^h\right)\alpha_f^h,\\
A_8 &= u_f + \mu_f,\ \ g_2 = s_{2f} z_f,\ \ b_8 = (1-d_f)\, u_f,\ \ A_9 = z_f + \omega_f + \mu_f,\ \ b_9 = \omega_f,\\
A_{10} &= \gamma_f + \mu_f + \delta_f,\ \ D_1 = \sigma_m^l + \mu_m,\ \ k_1 = \sigma_m^l,\ \ D_2 = \psi_m^l + \mu_m,\\
k_2 &= \left(1-r_m^l\right)\psi_m^l,\ \ D_3 = \alpha_m^l + \mu_m,\ \ k_3 = \left(1-k_m^l\right)\alpha_m^l,\ \ D_4 = n_m + \mu_m,\\
D_5 &= \sigma_m^h + \mu_m,\ \ k_5 = \sigma_m^h,\ \ D_6 = \psi_m^h + \mu_m,\ \ k_6 = \left(1-r_m^h\right)\psi_m^h,\ \ D_7 = \alpha_m^h + \mu_m,\\
j_1 &= \left[1-(s_{1m}+s_{2m})\right] z_m,\ \ k_7 = \left(1-k_m^h\right)\alpha_m^h,\ \ D_8 = u_m + \mu_m,\ \ j_2 = s_{2m} z_m,\\
k_8 &= (1-d_m)\, u_m,\ \ D_9 = z_m + \omega_m + \mu_m,\ \ k_9 = \omega_m,\ \ D_{10} = \gamma_m + \mu_m + \delta_m.
\end{aligned}
$$

Thus, it follows from [95] that

$$
\mathcal{R}_0^r = \rho\left(\mathcal{F}_r\mathcal{H}_r^{-1}\right) = \sqrt{\mathcal{R}_{rf}\mathcal{R}_{rm}}, \tag{4.36}
$$

where,

$$
\mathcal{R}_{rf} = \rho\left(\mathcal{F}_1\mathcal{H}_2^{-1}\right) = \max\{\mathcal{R}_{fl}, \mathcal{R}_{fh}\} \quad \text{and} \quad \mathcal{R}_{rm} = \rho\left(\mathcal{F}_2\mathcal{H}_1^{-1}\right) = \max\{\mathcal{R}_{ml}, \mathcal{R}_{mh}\},
$$

with,

$$\mathcal{R}_{fl} = \frac{\beta_m^l c_f \pi_f \mu_m \left(1-\varepsilon_v \varphi_f^q\right) B_1}{\mu_f \pi_m \prod_{i=1}^{3} D_i}, \quad \mathcal{R}_{fh} = \frac{\beta_m^h c_f \pi_f \mu_m \left[1-\varepsilon_v \left(\varphi_f^b + \varphi_f^q\right)\right] (Q_1+Q_2+Q_3)}{\mu_f \pi_m D_5 D_6 Q_4},$$

$$\mathcal{R}_{ml} = \frac{\beta_f^l c_f \left(1-\varepsilon_v \varphi_m^q\right) B_2}{\prod_{i=1}^{3} A_i}, \quad \mathcal{R}_{mh} = \frac{\beta_f^h c_f \left(1-\varepsilon_v \varphi_m^q\right) (Q_5+Q_6+Q_7)}{A_5 A_6 Q_8},$$

and,

$$\begin{aligned}
B_1 &= \eta_m^l D_3 D_2 + k_1 D_3 + \theta_m^l k_2 k_1, \quad Q_1 = \eta_m^h \left(D_6 D_7 D_8 D_9 - k_8 j_2 D_6 D_7 - k_8 k_7 j_1 D_6\right), \\
Q_2 &= k_5 D_7 D_8 D_9 - k_5 k_8 j_2 D_7 - k_5 k_7 k_8 j_1, \quad Q_3 = \theta_m^h \left(k_5 k_6 D_8 D_9 - k_5 k_6 k_8 j_2\right), \\
Q_4 &= D_7 D_8 D_9 - k_8 j_2 D_7 - k_7 k_8 j_1, \quad B_2 = \eta_f^l A_3 A_2 + b_1 A_3 + \theta_f^l b_2 b_1, \\
Q_5 &= \eta_f^h \left(A_6 A_7 A_8 A_9 - b_8 g_2 A_6 A_7 - b_8 b_7 g_1 A_6\right), \quad Q_6 = b_5 A_7 A_8 A_9 - b_5 b_8 g_2 A_7 - b_5 b_7 b_8 g_1, \\
Q_7 &= \theta_f^h \left(b_5 b_6 A_8 A_9 - b_5 b_6 b_8 g_2\right), \quad Q_8 = A_7 A_8 A_9 - b_8 g_2 A_7 - b_7 b_8 g_1.
\end{aligned}$$

It can be shown that the quantities $\mathcal{R}_{fl}, \mathcal{R}_{ml}, \mathcal{R}_{fh}$ and $\mathcal{R}_{mh}$ are positive (see Appendix G), so that the reproduction thresholds, $\mathcal{R}_{rf}$ and $\mathcal{R}_{rm}$ are positive. For mathematical convenience, let (where $\mathcal{R}_l = \mathcal{R}_{fl}\mathcal{R}_{ml}$ and $\mathcal{R}_h = \mathcal{R}_{fh}\mathcal{R}_{mh}$)

$$\mathcal{R}_0^r = \sqrt{\max\{\mathcal{R}_l, \mathcal{R}_h\}}.$$

Consequently, the result below follows from Theorem 2 of [95].

Theorem 4.2. *The DFE, $\mathcal{E}_0^r$, of the model (4.34), given by (4.35), is LAS if $\mathcal{R}_0^r < 1$, and unstable if $\mathcal{R}_0^r > 1$.*

The threshold quantity, $\mathcal{R}_0^r$, is the *basic reproduction number* [47] for the model (4.34). It represents the average number of secondary HPV infections generated by a typical HPV-infected person if introduced into a susceptible sexually-active population (or community)

where a certain fraction of the new sexually-active individuals is vaccinated. It is worth noting that $\mathcal{R}_0^r$ is an aggregate product of the average number of new HPV cases generated by females (denoted by $\mathcal{R}_{rf}$) and males (denoted by $\mathcal{R}_{rm}$) in a community.

Epidemiologically speaking, Theorem 4.2 states that a small influx of infected individuals (females or males) will not generate large outbreaks of the low- and high-risk HPV types in the community if $\mathcal{R}_0^r < 1$ (in other words, the two HPV types can be effectively controlled in the community if the initial sizes of the sub-populations of the model (4.34) are in the basin of attraction of the DFE, $\mathcal{E}_0^r$, of the model (4.34)). However, in order for such effective control (or elimination) to be independent of the initial sizes of the sub-populations of the model (4.34), it is necessary to show that the DFE ($\mathcal{E}_0^r$), of the model (4.34), is globally-asymptotically stable (GAS) if $\mathcal{R}_0^r < 1$. This is explored, for a special case, in Section 4.3.4.

4.3.2 Existence and local stability of boundary equilibria

The possible non-trivial equilibria of the model (4.34) are:

i) low-risk-only boundary equilibrium (an equilibrium of the model (4.34) with no high-risk HPV types), denoted by $\mathcal{E}_1^l$;

ii) high-risk-only boundary equilibrium (an equilibrium of the model (4.34) with no low-risk HPV types), denoted by $\mathcal{E}_1^h$;

iii) co-existence equilibria (equilibria of the model (4.34) where both the low- and high-risk HPV types co-exist), denoted by $\mathcal{E}_1^r$.

Consider the model (4.34) in the absence of the high-risk HPV types (i.e., the model (4.34) with $V_f^b = E_f^h = I_f^h = P_f^h = G_{fl} = G_{fh} = C_f^c = V_m^b = E_m^h = I_m^h = P_m^h = G_{ml} = G_{mh} = C_m^r = 0$). Furthermore, for computational convenience, let $\eta_m^l = \eta_f^l = \theta_m^l = \theta_f^l = \xi_f = \xi_m = 0$ in the model (4.34). The resulting low-risk-only model is given by (it should be noted that N_m, in the model (4.34), is now replaced by its limiting value, $\frac{\pi_m}{\mu_m}$, since individuals infected

with the low-risk HPV types do not develop or suffer cancer-induced mortality, so that the total male population, $N_m(t)$, remains constant):

$$
\begin{aligned}
\frac{dS_f}{dt} &= (1-\varphi_f^q)\pi_f - \frac{\beta_m^l c_f \mu_m I_m^l}{\pi_m} S_f - \mu_f S_f, \\
\frac{dV_f^q}{dt} &= \varphi_f^q \pi_f - (1-\varepsilon_v)\frac{\beta_m^l \mu_m c_f I_m^l}{\pi_m} V_f^q - \mu_f V_f^q, \\
\frac{dE_f^l}{dt} &= \left[S_f + (1-\varepsilon_v)V_f^q\right]\frac{\beta_m^l c_f \mu_m I_m^l}{\pi_m} + \rho_f^l \frac{\beta_m^l c_f \mu_m I_m^l}{\pi_m} R_f - (\sigma_f^l + \mu_f)E_f^l, \\
\frac{dI_f^l}{dt} &= \sigma_f^l E_f^l - (\psi_f^l + \mu_f) I_f^l, \\
\frac{dP_f^l}{dt} &= (1-r_f^l)\psi_f^l I_f^l - (\alpha_f^l + \mu_f) P_f^l, \\
\frac{dW_f}{dt} &= (1-k_f^l)\alpha_f^l P_f^l - (n_f + \mu_f)\, W_f, \\
\frac{dR_f}{dt} &= r_f^l \psi_f^l I_f^l + k_f^l \alpha_f^l P_f^l + n_f W_f - \rho_f^l \frac{\beta_m^l c_f \mu_m I_m^l}{\pi_m} R_f - \mu_f R_f, \\
\frac{dS_m}{dt} &= (1-\varphi_m^q)\,\pi_m - \frac{\beta_f^l c_f \mu_m I_f^l}{\pi_m} S_m - \mu_m S_m, \\
\frac{dV_m^q}{dt} &= \varphi_m^q \pi_m - (1-\varepsilon_v)\frac{\beta_f^l c_f \mu_m I_f^l}{\pi_m} V_m^q - \mu_m V_m^q, \\
\frac{dE_m^l}{dt} &= [S_m + (1-\varepsilon_v)V_m^q]\frac{\beta_f^l c_f \mu_m I_f^l}{\pi_m} + \rho_m^l \frac{\beta_f^l c_f \mu_m I_f^l}{\pi_m} R_m - (\sigma_m^l + \mu_m)E_m^l, \\
\frac{dI_m^l}{dt} &= \sigma_m^l E_m^l - (\psi_m^l + \mu_m) I_m^l, \\
\frac{dP_m^l}{dt} &= (1-r_m^l)\psi_m^l I_m^l - (\alpha_m^l + \mu_m) P_m^l, \\
\frac{dW_m}{dt} &= (1-k_m^l)\alpha_m^l P_m^l - (n_m + \mu_m)\, W_m, \\
\frac{dR_m}{dt} &= r_m^l \psi_m^l I_m^l + k_m^l \alpha_m^l P_m^l + n_m W_m - \rho_m^l \frac{\beta_f^l c_f \mu_m I_f^l}{\pi_m} R_m - \mu_m R_m.
\end{aligned}
\tag{4.37}
$$

It is convenient to let (with A_1, A_2, D_1, D_2, b_1 and k_1 as defined in Section 4.3.1)

$$
\mathcal{R}_0^l = \mathcal{R}_0^r \,|_{\mathcal{R}_{fh}=\mathcal{R}_{mh}=\eta_m^l=\eta_f^l=\theta_m^l=\theta_f^l=\xi_f=\xi_m=0} = \sqrt{\frac{\beta_m^l c_f^2 \pi_f \mu_m \beta_f^l b_1 k_1 \left(1-\varepsilon_v\varphi_f^q\right)\left(1-\varepsilon_v\varphi_m^q\right)}{\pi_m \mu_f A_1 A_2 D_1 D_2}}.
$$

Furthermore, let

$$\mathcal{E}_1^l = (S_f^{**}, V_f^{q^{**}}, E_f^{l^{**}}, I_f^{l^{**}}, P_f^{l^{**}}, W_f^{**}, R_f^{**}, S_m^{**}, V_m^{q^{**}}, E_m^{l^{**}}, I_m^{l^{**}}, P_m^{l^{**}}, W_m^{**}, R_m^{**}),$$

represents any arbitrary endemic equilibrium of the low-risk-only model (4.37). Define

$$\lambda_m^{l^{**}} = \frac{\beta_m^l c_f \mu_m I_m^{l^{**}}}{\pi_m} \quad \text{and} \quad \lambda_f^{l^{**}} = \frac{\beta_f^l c_f \mu_m I_f^{l^{**}}}{\pi_m}. \tag{4.38}$$

Setting the right-hand sides of the low-risk-only model (4.37) to zero gives the following steady-state expressions:

$$\begin{aligned}
S_f^{**} &= \frac{\pi_f\left(1-\varphi_f^q\right)}{\lambda_m^{l^{**}}+\mu_f}, \;\; V_f^{q^{**}} = \frac{\pi_f \varphi_f^q}{(1-\varepsilon_v)\,\lambda_m^{l^{**}}+\mu_f}, \\
E_f^{l^{**}} &= \frac{\left[S_f^{**}+(1-\varepsilon_v)\,V_f^{q^{**}}\right]\lambda_m^{l^{**}} + \rho_f^l \lambda_m^{l^{**}} R_f^{**}}{A_1}, \;\; I_f^{l^{**}} = \frac{b_1 E_f^{l^{**}}}{A_2}, \;\; P_f^{l^{**}} = \frac{b_2 I_f^{l^{**}}}{A_3}, \\
W_f^{**} &= \frac{b_3 P_f^{l^{**}}}{A_4}, \;\; R_f^{**} = \frac{m_1 I_f^{l^{**}} + m_2 P_f^{l^{**}} + n_f W_f^{**}}{\rho_f^l \lambda_m^{l^{**}} + m_3}, \;\; S_m^{**} = \frac{\pi_m\left(1-\varphi_m^q\right)}{\lambda_f^{l^{**}}+\mu_m}, \\
V_m^{q^{**}} &= \frac{\pi_m \varphi_m^q}{(1-\varepsilon_v)\,\lambda_f^{l^{**}}+\mu_m}, \;\; E_m^{l^{**}} = \frac{\left[S_m^{**}+(1-\varepsilon_v)\,V_m^{q^{**}}\right]\lambda_f^{l^{**}} + \rho_m^l \lambda_f^{l^{**}} R_m^{**}}{D_1}, \\
I_m^{l^{**}} &= \frac{k_1 E_m^{l^{**}}}{D_2}, \;\; P_m^{l^{**}} = \frac{k_2 I_m^{l^{**}}}{D_3}, \;\; W_m^{**} = \frac{k_3 P_m^{l^{**}}}{D_4}, \;\; R_m^{**} = \frac{m_4 I_m^{l^{**}} + m_5 P_m^{l^{**}} + n_m W_m^{**}}{\rho_m^l \lambda_f^{l^{**}} + m_6},
\end{aligned} \tag{4.39}$$

where (with A_i, D_i $(i = 1, ..., 4)$, b_1, b_2, b_3, k_1, k_2 and k_3 as defined in Section 4.3.1),

$$m_1 = r_f^l \psi_f^l, \;\; m_2 = k_f^l \alpha_f^l, \;\; m_4 = r_m^l \psi_m^l \;\text{ and }\; m_5 = k_m^l \alpha_m^l.$$

Substituting (4.39) into the expression for $\lambda_m^{l^{**}}$ and $\lambda_f^{l^{**}}$ in (4.38) gives,

$$\lambda_m^{l^{**}} = \frac{\lambda_f^{l^{**}}\left[a_{02}\left(\lambda_f^{l^{**}}\right)^2 + a_{01}\lambda_f^{l^{**}} + a_0\right]}{a_{33}\left(\lambda_f^{l^{**}}\right)^3 + a_{22}\left(\lambda_f^{l^{**}}\right)^2 + a_{11}\lambda_f^{l^{**}} + a_{00}}, \quad \lambda_f^{l^{**}} = \frac{\lambda_m^{l^{**}}\left[b_{02}\left(\lambda_m^{l^{**}}\right)^2 + b_{01}\lambda_m^{l^{**}} + b_0\right]}{b_{33}\left(\lambda_m^{l^{**}}\right)^3 + b_{22}\left(\lambda_m^{l^{**}}\right)^2 + b_{11}\lambda_m^{l^{**}} + b_{00}}, \tag{4.40}$$

where,

$$
\begin{aligned}
a_{02} &= \frac{\mu_m \beta_m^l c_f k_1 \rho_m^l (1-\varepsilon_v)}{\prod_{i=1}^{2} D_i}, \quad a_{01} = \frac{\mu_m^2 \beta_m^l c_f k_1 \left[(1-\varepsilon_v) + \rho_m^l (1-\varepsilon_q \varphi_m^q)\right]}{\prod_{i=1}^{2} D_i}, \\
a_0 &= \frac{\mu_m^3 \beta_m^l c_f k_1 (1-\varepsilon_v \varphi_m^q)}{\prod_{i=1}^{2} D_i}, \quad a_{33} = \frac{(1-\varepsilon_v)\rho_m^l \left[\prod_{i=1}^{4} D_i - k_1 (m_4 D_3 D_4 + m_5 D_4 k_2 + n_m k_3 k_2)\right]}{\prod_{i=1}^{4} D_i}, \\
a_{22} &= \frac{\mu_m \left\{(1-\varepsilon_v)\prod_{i=1}^{4} D_i + \rho_m^l (2-\varepsilon_v)\left[\prod_{i=1}^{4} D_i - k_1 (m_4 D_3 D_4 + m_5 D_4 k_2 + n_m k_3 k_2)\right]\right\}}{\prod_{i=1}^{4} D_i}, \\
a_{11} &= \frac{\mu_m^2 \left\{(2-\varepsilon_v)\prod_{i=1}^{4} D_i + \rho_m^l \left[\prod_{i=1}^{4} D_i - k_1 (m_4 D_3 D_4 + m_5 D_4 k_2 + n_m k_3 k_2)\right]\right\}}{\prod_{i=1}^{4} D_i}, \qquad (4.41) \\
a_{00} &= \mu_m^3, \quad b_{02} = \frac{\mu_m \pi_f \beta_f^l c_f b_1 \rho_f^l (1-\varepsilon_v)}{\pi_m \prod_{i=1}^{2} A_i}, \quad b_{01} = \frac{\mu_m \mu_f \pi_f \beta_f^l c_f b_1 \left[(1-\varepsilon_v) + \rho_f^l \left(1-\varepsilon_v \varphi_f^q\right)\right]}{\pi_m \prod_{i=1}^{2} A_i}, \\
b_0 &= \frac{\mu_m \mu_f^2 \pi_f \beta_f^l c_f b_1 \left(1-\varepsilon_v \varphi_f^q\right)}{\pi_m \prod_{i=1}^{2} A_i}, \quad b_{33} = \frac{(1-\varepsilon_v)\rho_f^l \left[\prod_{i=1}^{4} A_i - b_1 (m_1 A_3 A_4 + m_2 A_4 b_2 + n_f b_3 b_2)\right]}{\prod_{i=1}^{4} A_i}, \\
b_{22} &= \frac{\mu_f \left\{(1-\varepsilon_v)\prod_{i=1}^{4} A_i + \rho_f^l (2-\varepsilon_v)\left[\prod_{i=1}^{4} A_i - b_1 (m_1 A_3 A_4 + m_2 A_2 b_2 + n_f b_3 b_2)\right]\right\}}{\prod_{i=1}^{4} A_i}, \\
b_{11} &= \frac{\mu_f^2 \left\{(2-\varepsilon_v)\prod_{i=1}^{4} A_i + \rho_f^l \left[\prod_{i=1}^{4} A_i - b_1 (m_1 A_3 A_4 + m_2 A_4 b_2 + n_f b_3 b_2)\right]\right\}}{\prod_{i=1}^{4} A_i}, \quad b_{00} = \mu_f^3.
\end{aligned}
$$

Since all the parameters of the low-risk-only model (4.37) are positive, and $0 < \varepsilon_v, \varphi_m^q, \varphi_f^q \leq 1$, it can be shown, after some lengthy algebraic manipulations, that all the expressions in (4.41) (namely, $a_{02}, a_{01}, a_0, a_{33}, a_{22}, a_{11}, a_{00}, b_{02}, b_{01}, b_0, b_{33}, b_{22}, b_{11}, b_{00}$) are positive. It follows,

by substituting $\lambda_f^{l^{**}}$ into $\lambda_m^{l^{**}}$ in (4.40), and simplifying, that the non-zero (endemic) equilibria of the low-risk-only model (4.37) satisfy the following polynomial (in terms of $\lambda_m^{l^{**}}$):

$$\sum_{i=0}^{9} Y_i \left(\lambda_m^{l^{**}}\right)^{9-i} = 0, \tag{4.42}$$

with Y_i $(i = 0, ..., 9)$ given in Appendix H. Since all the parameters of the low-risk-only model (4.37) are non-negative, it follows from the expressions for Y_i $(i = 0, ..., 9)$ in Appendix H that $Y_0 > 0$ and $Y_9 > 0$ whenever $\mathcal{R}_0^l < 1$. Thus, the number of possible positive real roots the polynomial (4.42) can have depends on the signs of Y_i $(i = 1, ..., 8)$. The various possibilities (using the Descartes Rule of Signs) for the number of positive real roots of (4.42) are tabulated in Table 4.3, from which the following result is obtained.

Theorem 4.3. *The low-risk-only model (4.37) could have 2 or more endemic equilibria if* $\mathcal{R}_0^l < 1$*, and at least one positive endemic equilibrium whenever* $\mathcal{R}_0^l > 1$.

Similar result can be established if the high-risk-only component of the model (4.34) is considered. Consequently, we offer the following conjecture:

Conjecture 4.1. *The model (4.34) could have 2 or more endemic equilibria if* $\mathcal{R}_0^r < 1$*, and at least one positive endemic equilibrium whenever* $\mathcal{R}_0^r > 1$.

The presence of multiple endemic equilibria in the low-risk-only model (4.37) (and, by extension, the risk-structured model (4.34)) when $\mathcal{R}_0^l < 1$ suggests the possibility of backward bifurcation in the model (4.34). This is explored in Section 4.3.3.

Extensive numerical simulations of the model (4.34), using the parameter values in Table 4.2 (unless otherwise stated), were carried out to quantitatively assess the dynamics of the low- and high-risk HPV types in the community, for various scenarios (of the associated reproduction numbers, $\mathcal{R}_l$ and $\mathcal{R}_h$). It should be mentioned that these numerical simulations have to be ran for extended periods of time to reach steady-state (as is evident in some of the plots). Figure 4.3 depicts the simulation results obtained for the case when the reproduction

number of one of the HPV risk type (low or high) is less than unity, while that of the other HPV risk type exceeds unity. This figure shows that the HPV (risk) type with reproduction number less than unity dies out in time, while the HPV (risk) type with reproduction number greater than unity persists. Thus, these simulations suggest that the model (4.34) undergoes competitive exclusion for the case when $\mathcal{R}_i < 1 < \mathcal{R}_j$ (with $i, j = \{l, h\};\ \ i \neq j$), where the HPV (risk) type with the higher reproduction number (greater than unity) drives out (to extinction) the HPV (risk) type with the lower reproduction number (less than unity). This suggests the following conjecture:

Conjecture 4.2. *The model (4.34) has at least one stable low-risk-only (high-risk-only) boundary equilibrium, $\mathcal{E}_1^l(\mathcal{E}_1^h)$, whenever $\mathcal{R}_i < 1 < \mathcal{R}_j$ (with $i, j = \{l, h\};\ \ i \neq j$). In other words, the risk-structured model (4.34) undergoes competitive exclusion, with the HPV risk Type j driving out the HPV risk Type i to extinction, whenever $\mathcal{R}_i < 1 < \mathcal{R}_j$.*

Furthermore, the case when both reproduction numbers ($\mathcal{R}_l$ and $\mathcal{R}_h$) of the model (4.34) exceed unity is simulated. Figure 4.4 shows that the low- and high-risk HPV types co-exist whenever their respective reproduction numbers exceed unity, but the HPV (risk) type with the higher reproduction number dominates the one with the lower reproduction number (but does not drive it to extinction). These simulations suggest the following conjecture:

Conjecture 4.3. *The risk-structured model (4.34) could have at least one stable co-existence endemic equilibria, $\mathcal{E}_1^r$, whenever $1 < \mathcal{R}_i \leq \mathcal{R}_j$ (with $i, j = \{l, h\}$).*

4.3.3 Existence of backward bifurcation

The existence of multiple endemic equilibria when $\mathcal{R}_0^l < 1$ suggests the possibility of backward bifurcation (where, typically, the stable DFE ($\mathcal{E}_0$) co-exists with a stable endemic equilibrium ($\mathcal{E}_1^l$), when the associated basic reproduction number ($\mathcal{R}_0^l$) is less than unity) in the low-risk-only model (4.37).

Theorem 4.4. *The low-risk-only model (4.37) undergoes backward bifurcation at* $\mathcal{R}_0^l = 1$ *under a certain condition, given by (I.5) in Appendix I.*

The proof of Theorem 4.4, based on using Centre Manifold theory [11, 14], is given in Appendix I. Furthermore, it follows from the analyses in Appendix I that the associated bifurcation coefficient, a, is negative whenever the re-infection parameters (ρ_m^l and ρ_f^l) of the model (4.37) are set to zero.

Theorem 4.5. *In the absence of the re-infection of recovered individuals (i.e.,* $\rho_m^l = \rho_f^l = 0$*), the low-risk-only model (4.37) does not undergo backward bifurcation at* $\mathcal{R}_0^l = 1$.

The analyses in Section 4.3.3 and Appendix I (where the low-risk-only model (4.37) is shown not to undergo backward bifurcation in the absence of re-infection) suggest that the DFE of the full risk-structured model (4.34) may be globally-asymptotically stable (GAS) when $\mathcal{R}_0^r < 1$ and $\rho_m^l = \rho_f^l = \rho_m^h = \rho_f^h = 0$. This is explored below.

4.3.4 Global asymptotic stability of DFE (special case)

The global asymptotic stability of the DFE, $\mathcal{E}_0^r$, of the model (4.34), is established for the special case where the re-infection of recovered individuals does not occur (i.e., $\rho_f^l = \rho_m^l = \rho_f^h = \rho_m^h = 0$) and that cancer-induced mortality for males is negligible (so that, $\delta_m = 0$). The following result will be needed in proving the GAS of the DFE, $\mathcal{E}_0^r$.

Lemma 4.2. *The following region*

$$\begin{aligned}\mathcal{D}_r^* \;=\; & \{(S_f, V_f^b, V_f^q, E_f^l, E_f^h, I_f^l, I_f^h, P_f^l, P_f^h, W_f, G_{fl}, G_{fh}, C_f^c, R_f^c, R_f, S_m, V_m^q, \\ & E_m^l, E_m^h, I_m^l, I_m^h, P_m^l, P_m^h, W_m, G_{ml}, G_{mh}, C_m^r, R_m^c, R_m) \in \mathcal{D}_r : \\ & S_f \leq S_f^*, V_f^b \leq V_f^{b^*}, V_f^q \leq V_f^{q^*}, S_m \leq S_m^*, V_m^q \leq V_m^{q^*}\}\end{aligned}$$

is positively-invariant for the model (4.34) with $\xi_f = \xi_m = 0$.

Proof. Consider the risk-structured model (4.34) with $\xi_f = \xi_m = 0$. It then follows from the first equation of (4.34), with $\xi_f = 0$, that

$$\frac{dS_f}{dt} \leq \pi_f(1 - \varphi_f^b - \varphi_f^q) - \mu_f S_f = \mu_f(S_f^* - S_f).$$

Hence,

$$S_f(t) \leq \frac{\pi_f(1 - \varphi_f^b - \varphi_f^q)}{\mu_f} + \left[S_f(0) - \frac{\pi_f(1 - \varphi_f^b - \varphi_f^q)}{\mu_f}\right] e^{-\mu_f t} = S_f^* + \left[S_f(0) - S_f^*\right] e^{-\mu_f t}.$$

Thus, $S_f(t) \leq S_f^*$ if $S_f(0) \leq S_f^*$ as $t \to \infty$. Furthermore, it follows from the sixteenth equation of (4.34), with $\xi_m = 0$, that

$$\frac{dS_m}{dt} \leq \pi_m(1 - \varphi_m^q) - \mu_m S_m = \mu_m(S_m^* - S_m),$$

so that,

$$S_m(t) \leq \frac{\pi_m(1 - \varphi_m^q)}{\mu_m} + \left[S_m(0) - \frac{\pi_m(1 - \varphi_m^q)}{\mu_m}\right] e^{-\mu_m t} = S_m^* + \left[S_m(0) - S_m^*\right] e^{-\mu_m t}.$$

Thus, $S_m(t) \leq S_m^*$ if $S_m(0) \leq S_m^*$ as $t \to \infty$. Similarly, it can be shown that $V_f^b \leq V_f^{b^*}$,$V_f^q \leq V_f^{q^*}$ and $V_m^q \leq V_m^{q^*}$. Hence, the set $\mathcal{D}_r^* \subset \mathcal{D}_r$ is positively-invariant for the model (4.34) with $\xi_f = \xi_m = 0$. □

It is convenient to define,

$$\mathcal{R}_0^r \mid_{\rho_f^l = \rho_m^l = \rho_f^h = \rho_m^h = \delta_m = 0} = \mathcal{R}_{01}^r.$$

Theorem 4.6. *The DFE, $\mathcal{E}_0^r$, of the risk-structured model (4.34) is globally-asymptotically stable (GAS) in $\mathcal{D}_r^*$ if $\mathcal{R}_{01}^r < 1$.*

The proof of Theorem 4.6 is given in Appendix J. The epidemiological consequence of Theorem 4.6 is that both the low- and high-risk HPV types will be eliminated from the

community if $\mathcal{R}_{01}^r < 1$ in the absence of the re-infection of recovered individuals ($\rho_f^l = \rho_m^l = \rho_f^h = \rho_m^h = 0$) and cancer-induced death for males ($\delta_m = 0$). Figure 4.5 illustrates the GAS property of the DFE of the special case of the model (4.34), in line with Theorem 4.6.

4.4 Numerical Simulations

The risk-structured model (4.34) is further simulated, using the parameters in Table 4.2 (unless otherwise stated), to assess the community-wide public health impact of the two vaccines. Figure 4.6A depicts the cumulative number of HPV-related cancers in females and males for the cases where only females, and both females and males, are vaccinated with the *Gardasil* vaccine. This figure shows a significant decrease in the cumulative number of cancer cases if males are (additionally) vaccinated. In particular, while vaccinating females only (at the assumed 70% coverage level) resulted in about 250 cumulative cancer cases over two years, this number reduces to about 100, over the same time period, if both females and males are vaccinated (with 70% *Gardasil* coverage for both). Similar results are obtained for the associated cancer-related mortality. For example, while vaccinating females only (at the rate 70% coverage level) resulted in about 8 cumulative mortality cases over two years, only 2 cancer-related deaths are recorded, over the same time period, if both females and males are vaccinated (Figure 4.6B).

Contour plots of $\mathcal{R}_{01}^r$, as a function of the fraction of females vaccinated with the *Gardasil* vaccine at steady-state (φ_f^q) and the efficacy of the *Gardasil* vaccine (ε_v), are depicted in Figure 4.7. Figure 4.7A shows that, with the assumed 90% efficacy of the *Gardasil* vaccine ($\varepsilon_v = 0.9$), vaccinating 87% of new sexually-active susceptible females will lead to the effective control or elimination of both the low- and high-risk HPV types in the community (since this brings $\mathcal{R}_{01}^r < 1$, which results in the GAS property of the DFE of the model (4.34), in line with Theorem 4.6). It should be emphasized from Figure 4.7A that the current *Gardasil* coverage of the 70% in most communities [9, 26, 46, 61, 76] will not lead to the effective

control of HPV (since it fails, even with the assumed efficacy of 90%, to bring $\mathcal{R}_{01}^{r} < 1$). The case when only females are vaccinated, and both *Cervarix* and *Gardasil* vaccines are used in the community (with efficacy of both vaccines fixed at 90% [9, 10, 15, 26, 46, 61, 76]), is also simulated (Figure 4.7B). It is shown from this figure that, with the assumed 70% *Gardasil* vaccine coverage for females, at least 18% of the remaining new sexually-active susceptible females need to be vaccinated with the *Cervarix* vaccine in order to effectively control the disease. This seems consistent with the 87% *Gardasil* coverage needed for effective control in Figure 4.7A.

Furthermore, a contour plot of $\mathcal{R}_{01}^{r}$, as a function of the fraction of males vaccinated with the *Gardasil* vaccine at steady-state and the fraction of females vaccinated with the *Gardasil* vaccine at steady-state, for the fixed (90%) efficacy of the *Gardasil* vaccine, is depicted in Figure 4.8. This figure shows that if only 70% of the new sexually-active susceptible females are vaccinated with the *Gardasil* vaccine (which is typically the norm [9, 26, 46, 61, 76]), additionally vaccinating 47% of new sexually-active susceptible males will lead to the community-wide elimination of the low- and high-risk HPV types. This is encouraging since, in Figure 4.7A, a large percentage (87%) of new sexually-active females need to be vaccinated to have a realistic chance of effectively controlling the spread of HPV in the community. Hence, this study shows that vaccinating a certain fraction of new sexually-active susceptible males (less than 50%) enhances the likelihood of effectively combatting the spread (or elimination) of HPV in the community (since 70% coverage for new sexually-active females and less than 50% coverage for new sexually-active males, with the *Gardasil* vaccine, seems attainable). In other words, this study supports the recent recommendations, by some public health agencies, to vaccinate sexually-active males [46, 76, 77, 90].

4.5 Summary of the Chapter

A new risk-structured deterministic model for the transmission dynamics of HPV in a population, in the presence of the *Cervarix* and *Gardasil* vaccines (that target the four low- and high-risk HPV types considered in this chapter), is designed. The main theoretical and numerical results obtained are summarized below.

i) the risk-structured model (4.34) has a LAS DFE whenever $\mathcal{R}_0^r < 1$;

ii) the low-risk-only model (4.37) undergoes the phenomenon of backward bifurcation at $\mathcal{R}_0^l = 1$ if Inequality (I.5) holds. It is shown that the re-infection of recovered individuals causes the backward bifurcation property in the model. The low-risk-only model could have one or more endemic equilibria when the associated reproduction number ($\mathcal{R}_0^l$) exceeds unity;

iii) in the absence of the re-infection of recovered individuals (i.e., $\rho_f^l = \rho_m^l = \rho_f^h = \rho_m^h = 0$) and cancer-induced death in males (i.e., $\delta_m = 0$), the DFE of the risk-structured model (4.34) is GAS in $\mathcal{D}_r^*$ whenever $\mathcal{R}_{01}^r < 1$;

iv) with the assumed 90% efficacy of the *Gardasil* vaccine, at least 87% of the new sexually-active females need to be vaccinated to have a realistic chance of effectively controlling the spread of the low- and high-risk HPV types in the community;

v) it is shown that, with the assumed 70% *Gardasil* vaccine coverage for females, at least 18% of the remaining new sexually-active susceptible females need to be vaccinated with the *Cervarix* vaccine in order to effectively control the spread of the low- and high-risk HPV types in the community;

vi) vaccinating a fraction of new sexually-active susceptible males offers beneficial community-wide public health impact. In particular, simulations show that while vaccinating new sexually-active susceptible females only (at the assumed 70% vaccine coverage) resulted in about 250 cumulative cancer cases (in both females and males) over two

years, this number reduces to about 100, over the same time period, if both new sexually-active susceptible males (with 70% *Gardasil* coverage level) and females are vaccinated. Furthermore, while vaccinating females only with the *Gardasil* vaccine (at the 70% coverage level) resulted in about 8 cumulative cancer-related mortality cases over two years, only 2 such deaths are recorded, over the same time period, if both males and females are vaccinated;

vii) if only 70% of the new sexually-active susceptible females are vaccinated with the *Gardasil* vaccine, additionally vaccinating 47% of the new sexually-active susceptible males will lead to the effective community-wide control, or elimination, of the low- and high-risk HPV types. Thus, this study supports the recent recommendations by some public health agencies to vaccine sexually-active males (since doing so offers additional community-wide benefit, *vis-a-vis* the control of the two (risk) HPV types).

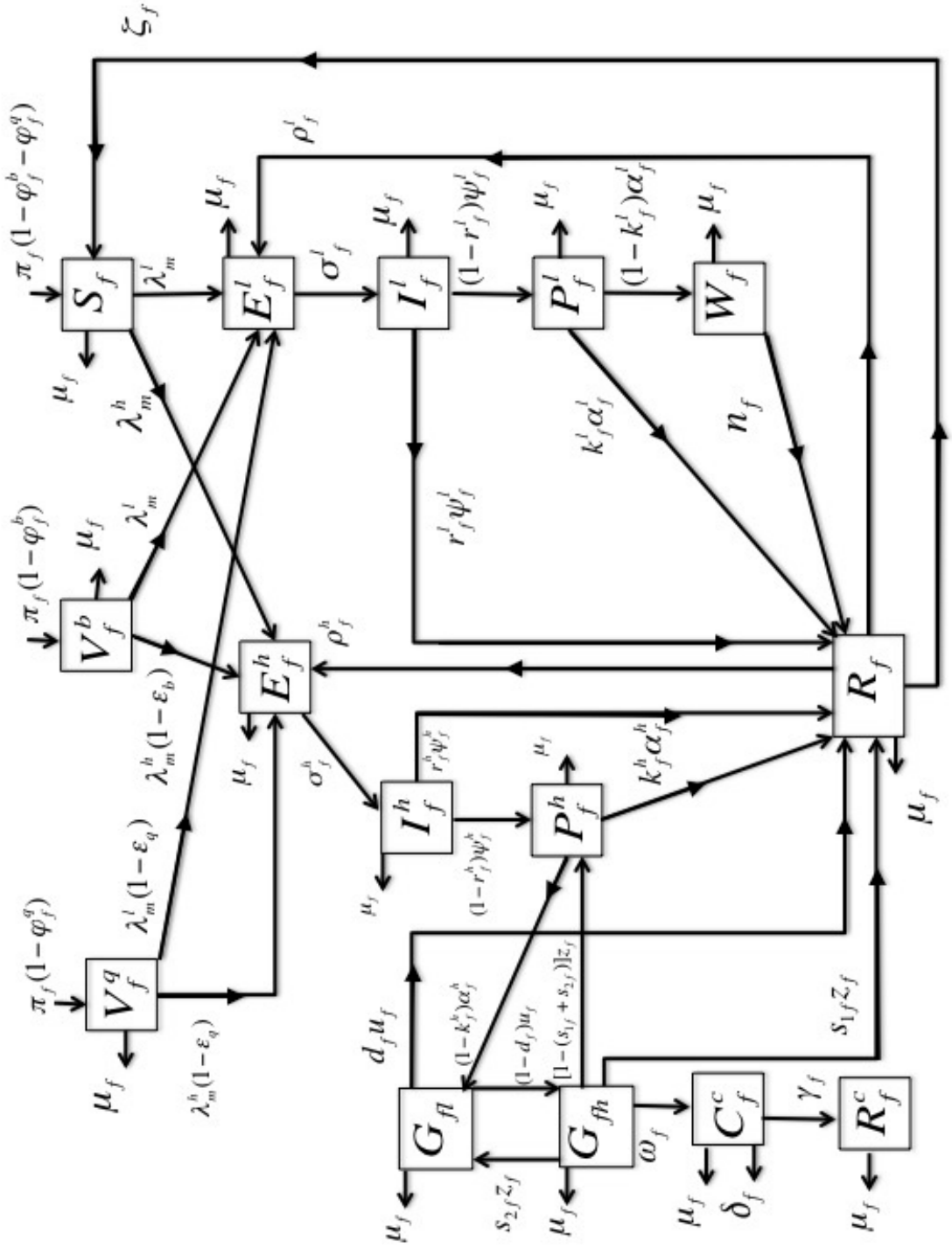


Figure 4.1: Flow diagram of the female component of the model (4.34).

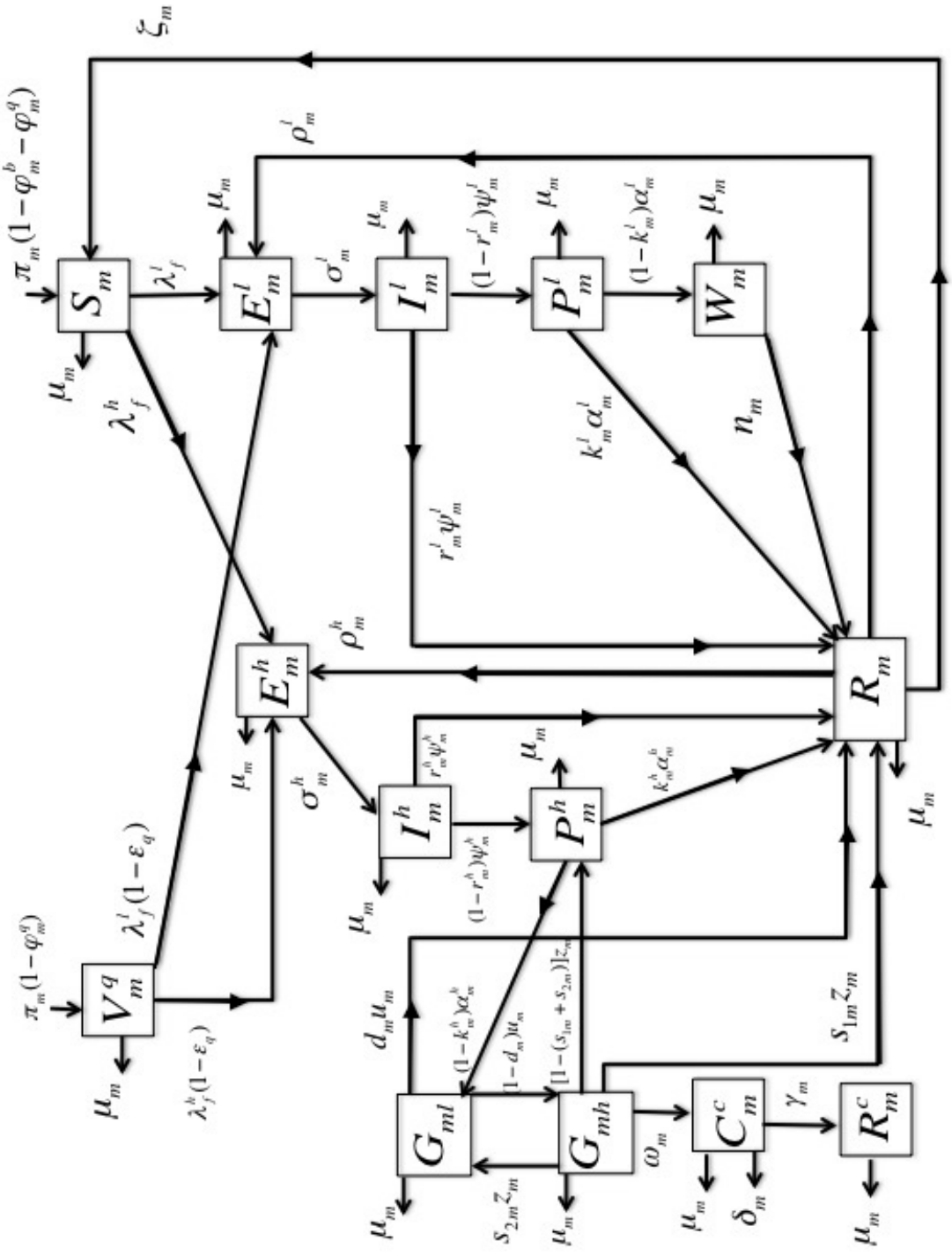


Figure 4.2: Flow diagram of the male component of the model (4.34).

Table 4.1: Description of state variables of the model (4.34).

Variable	Description
$S_f(S_m)$	Population of unvaccinated susceptible females (males)
$E_f^l(E_m^l)$	Population of exposed females (males) infected with the low-risk HPV types
$E_f^h(E_m^h)$	Population of exposed females (males) infected with the high-risk HPV types
$I_f^l(I_m^l)$	Population of infected females (males) with clinical symptoms of the low-risk HPV types
$I_f^h(I_m^h)$	Population of infected females (males) with clinical symptoms of the high-risk HPV types
$V_f^b(V_m^b)$	Population of susceptible females (males) vaccinated with the bivalent *Cervarix* vaccine
$V_f^q(V_m^q)$	Population of susceptible females (males) vaccinated with the quadrivalent *Gardasil* vaccine
$P_f^l(P_m^l)$	Population of infected females (males) with persistent infection with the low-risk HPV types
$P_f^h(P_m^h)$	Population of infected females (males) with persistent infection with the high-risk HPV types
$G_{fl}(G_{ml})$	Population of infected females (males) in the low-grade CIN (INM) stage
$G_{fh}(G_{mh})$	Population of infected females (males) in the high-grade CIN (INM) stage
$W_f(W_m)$	Population of infected females (males) with genital warts
C_f^c	Population of infected females with cervical cancer
C_m^r	Population of infected males with HPV-related cancers
$R_f^c(R_m^c)$	Population of infected females (males) who recovered from HPV-related cancers
$R_f(R_m)$	Population of infected females (males) who recovered from HPV infection
$N_f(N_m)$	Total female (male) population

Table 4.2: Description of the parameters of the model (4.34), where l and h represent the low-risk and high-risk HPV types, respectively.

Parameter	Description	Nominal value *per* year	Reference
$\pi_f(\pi_m)$	Recruitment rate of new sexually-active females (males)	10000	[61, 75]
$\mu_f(\mu_m)$	Average duration of sexual activity for females (males)	$\frac{1}{65}$	[9, 61]
$\beta_m^i(\beta_f^i)$	Infection probability for females (males) with the i-risk HPV types, $i \in \{l, h\}$	0.4 (0.5)	[61, 75]
$c_m(c_f)$	Average number of male (female) sexual partners for females (males) *per* unit time	2 $\left(\frac{2N_f(t)}{N_m(t)}\right)$	[61, 75]
$\xi_f(\xi_m)$	Rate of loss of infection-acquired immunity for females (males)	0.0012	Assumed
$\rho_f^i(\rho_m^i)$	Re-infection parameter for females (males) with i-risk i-risk HPV types, $i \in \{l, h\}$		Assumed
φ_q	Fraction of new sexually-active females (males) vaccinated with the quadrivalent *Gardasil* vaccine	0.7	[7, 25, 61]
φ_b	Fraction of new sexually-active females vaccinated with the bivalent *Cervarix* vaccine	0.2	Assumed
ε_v	Efficacy of the bivalent *Cervarix* vaccine (quadrivalent *Gardasil* vaccine)	0.9	[61, 76]
$\sigma_f^i(\sigma_m^i)$	Rate of symptoms development for exposed females (males) with the i-risk HPV types, $i \in \{l, h\}$	0.5	Assumed
$r_f^i(r_m^i)$	Fraction of symptomatic females (males) with the i-risk HPV types who recover naturally from the i-risk HPV types (but do not develop persistent infection)	0.5	[61]

Parameter	Description	Nominal value *per* year	Reference
$\psi_f^i(\psi_m^i)$	Transition rate out of $I_f^i(I_m^i)$ class for females (males), $i \in \{l, h\}$	0.9	[61]
$k_f^l(k_m^l)$	Fraction of symptomatic females (males) who recovered naturally from persistent infection with the low-risk HPV types (but do not develop genital warts)	0.5	Assumed
$\alpha_f^l(\alpha_m^l)$	Transition rate out of $P_f^l(P_m^l)$ class for females (males)	114	Assumed
$(1-k_f^l)\alpha_f^l$	Rate at which females with low-risk persistent HPV infection develop genital warts	57	[53, 99]
$k_f^h(k_m^h)$	Fraction of symptomatic females (males) who recovered naturally from persistent infection with the high-risk HPV types (but do not develop CIN (INM))	0.5	[61]
$\alpha_f^h(\alpha_m^h)$	Transition rate out of $P_f^h(P_m^h)$ class for females (males)	114	Assumed
$n_f(n_m)$	Recovery rate of infected females (males) with genital warts	87.5	[36, 53, 99]
$d_f(d_m)$	Fraction of infected females (males) with low-grade CIN (INM) who naturally recovered from HPV infection	0.2	Assumed
$u_f(u_m)$	Transition rate out of $G_f^l(G_m^l)$ class for females (males)	17.25	Assumed
$(1-d_f)\,u_f$	Progression rate from CIN1 to CIN2/3 stage	13.8	[52, 53, 55]
$s_{1f}(s_{1m})$	Fraction of infected females (males) with high-grade CIN (INM) who naturally recovered from HPV infection	0.285	Assumed

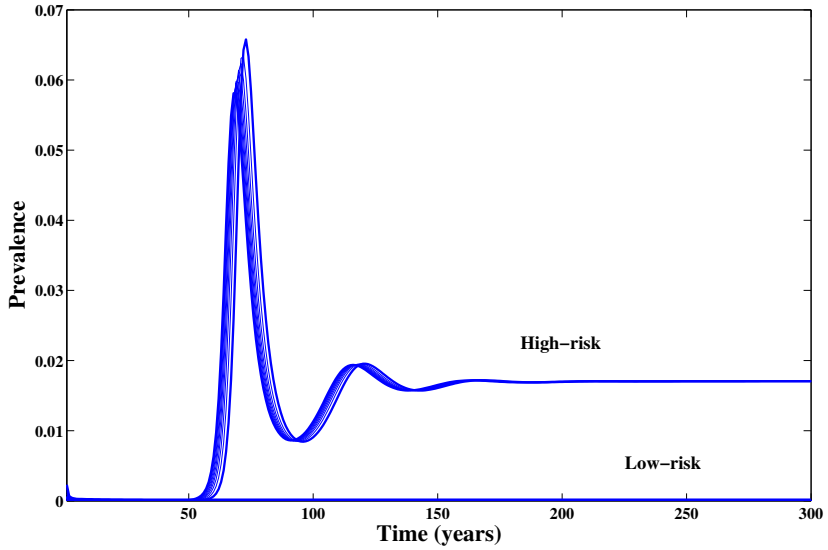
Parameter	Description	Nominal value *per* year	Reference
$s_{2f}(s_{2m})$	Fraction of infected females (males) with high-grade CIN (INM) who regressed to the low-grade CIN (INM) stage	0.2	Assumed
$z_f(z_m)$	Transition rate out of $G_f^h(G_m^h)$ class for females (males)	40.75	[52, 53, 55]
$s_{2f}z_f$	Regression rate from CIN2/3 to CIN1 stage	8.15	[52, 53, 55]
$s_{1f}z_f$	Recovery rate of individuals with CIN2/3 stage	11.6	[52, 53, 55]
$\omega_f(\omega_m)$	Rate of development of cancer for females (males) in high-grade CIN (INM) stages	23.5	[52, 53, 55]
$\gamma_f(\gamma_m)$	Recovery rate of females (males) in the $C_f^c(C_m^r)$ class	0.76	[25, 61]
$\delta_f(\delta_m)$	Cancer-induced mortality rate for females (males)	0.001	[61]
$\eta_f^i(\eta_m^i)$	Modification parameter for infectiousness of exposed individuals in the $E_f^i(E_m^i)$ class for females (males), relative to those in the $I_f^i(I_m^i)$ class, $i \in \{l, h\}$		Assumed
$\theta_f^i(\theta_m^i)$	Modification parameter for the infectiousness of individuals with the i-risk HPV persistent infection relative to those in the $I_f^i, E_f^i(I_m^i, E_m^i)$ class for females (males), $i \in \{l, h\}$		Assumed

$*$ Similar (biological) parameters are used for males and females.

Cases	Y_0	Y_1	Y_2	Y_3	Y_4	Y_5	Y_6	Y_7	Y_8	Y_9	$\mathcal{R}_0^l$	Number of sign changes	Number of possible positive real roots
1	+	+	+	+	+	+	+	+	+	+	$\mathcal{R}_0^l < 1$	0	0
	+	+	+	+	+	+	-	-	-	-	$\mathcal{R}_0^l > 1$	1	1
2	+	-	-	-	-	-	+	+	+	+	$\mathcal{R}_0^l < 1$	2	0,2
	+	-	-	-	-	-	-	-	-	-	$\mathcal{R}_0^l > 1$	1	1
3	+	+	-	-	-	-	+	+	+	+	$\mathcal{R}_0^l < 1$	2	0,2
	+	+	-	-	-	-	-	-	-	-	$\mathcal{R}_0^l > 1$	1	1
4	+	-	+	-	-	-	+	+	+	+	$\mathcal{R}_0^l < 1$	4	0,2,4
	+	-	+	-	-	-	-	-	-	-	$\mathcal{R}_0^l > 1$	3	1,3
5	+	-	-	-	-	+	+	+	+	+	$\mathcal{R}_0^l < 1$	2	0,2
	+	-	-	-	-	+	-	-	-	-	$\mathcal{R}_0^l > 1$	3	1,3
6	+	+	+	-	-	-	+	+	+	+	$\mathcal{R}_0^l < 1$	2	0,2
	+	+	+	-	-	-	-	-	-	-	$\mathcal{R}_0^l > 1$	1	1
7	+	+	-	-	-	+	+	+	+	+	$\mathcal{R}_0^l < 1$	2	0,2
	+	+	-	-	-	+	-	-	-	-	$\mathcal{R}_0^l > 1$	3	1,3
8	+	-	+	-	-	+	+	+	+	+	$\mathcal{R}_0^l < 1$	2	0,2
	+	-	+	-	-	+	-	-	-	-	$\mathcal{R}_0^l > 1$	3	1,3
9	+	-	+	-	+	+	+	+	+	+	$\mathcal{R}_0^l < 1$	4	0,2,4
	+	-	+	-	+	+	-	-	-	-	$\mathcal{R}_0^l > 1$	5	1,3,5
10	+	+	-	+	-	+	+	+	+	+	$\mathcal{R}_0^l < 1$	4	0,2,4
	+	+	-	+	-	+	-	-	-	-	$\mathcal{R}_0^l > 1$	5	1,3,5
11	+	+	+	-	+	-	+	+	+	+	$\mathcal{R}_0^l < 1$	4	0,2,4
	+	+	+	-	+	-	-	-	-	-	$\mathcal{R}_0^l > 1$	3	1,3
12	+	-	+	-	+	-	+	+	+	+	$\mathcal{R}_0^l < 1$	6	0,2,4,6
	+	-	+	-	+	-	-	-	-	-	$\mathcal{R}_0^l > 1$	5	1,3,5
13	+	-	+	-	+	-	+	-	-	-	$\mathcal{R}_0^l < 1$	7	1,3,5,7
	+	-	+	-	+	-	+	+	+	+	$\mathcal{R}_0^l > 1$	6	0,2,4,6
14	+	-	+	-	+	-	+	-	+	+	$\mathcal{R}_0^l < 1$	8	0,2,4,6,8
	+	-	+	-	+	-	+	-	-	-	$\mathcal{R}_0^l > 1$	7	1,3,5,7
15	+	-	+	-	+	-	+	-	+	-	$\mathcal{R}_0^l < 1$	9	1,3,5,7
	+	-	+	-	+	-	+	-	+	+	$\mathcal{R}_0^l > 1$	8	0,2,4,6,8
16	+	+	+	-	+	-	+	-	+	-	$\mathcal{R}_0^l < 1$	7	1,3,5,7
	+	+	+	-	+	-	+	-	+	+	$\mathcal{R}_0^l > 1$	6	0,2,4,6

Table 4.3: Number of possible positive real roots of (4.42) for $\mathcal{R}_0^l < 1$ and $\mathcal{R}_0^l > 1$.

(A)



(B)

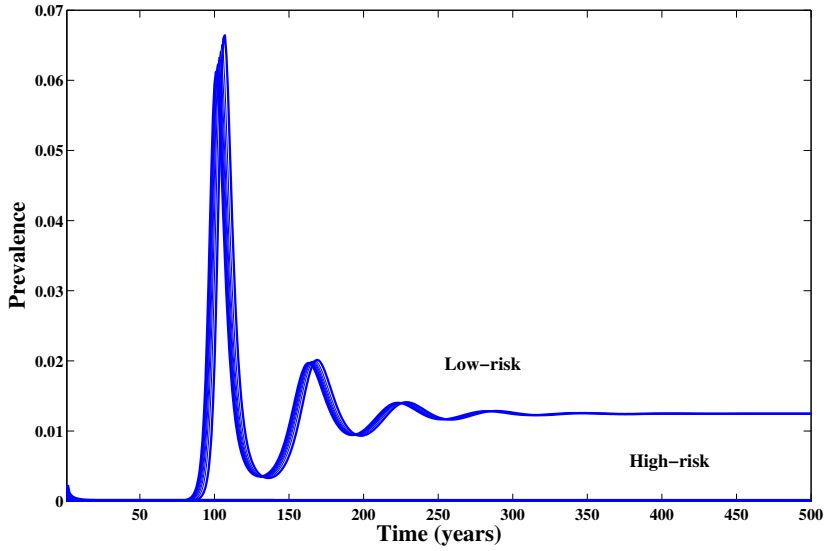
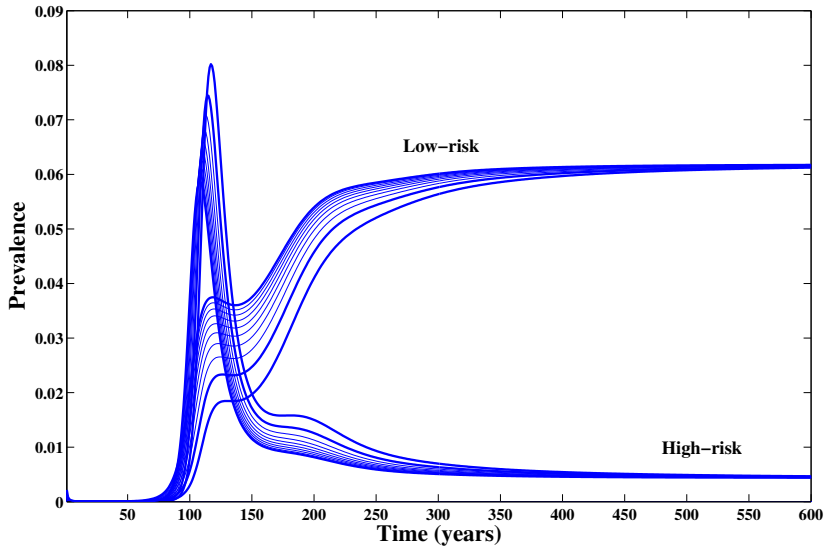


Figure 4.3: HPV prevalence as a function of time for the model (4.34) using various initial conditions. Parameter values used are as given in Table 4.2. (A) $\mathcal{R}_l < 1 < \mathcal{R}_h$ (here, $\rho_f^l = \rho_m^l = 0.2$, $\rho_f^h = \rho_m^h = 0.0001$, $\beta_m^l = \beta_f^l = 0.005$, $\beta_m^h = 0.9$, $\beta_f^h = 0.95875$, $c_f = 32$, $\gamma_f = \gamma_m = 0.22$, $\psi_f^l = \sigma_f^l = 0.1$, $k_f^h = k_m^h = 0.7$, $\eta_f^l = \eta_m^l = 0.8$, $\eta_f^h = \eta_m^h = 0.9$, $\theta_f^l = \theta_m^l = 0.9$ and $\theta_f^h = \theta_m^h = 0.95$; so that $0.1781 = \mathcal{R}_l < 1 < \mathcal{R}_h = 10.5770$ and $\mathcal{R}_0^r = 3.2522$). (B) $\mathcal{R}_h < 1 < \mathcal{R}_l$ (here, $\rho_f^h = \rho_m^h = 0.2$, $\rho_f^l = \rho_m^l = 0.0001$, $\beta_m^l = 0.9$,$\beta_f^l = 0.8$, $\beta_m^h = 0.05$, $\beta_f^h = 0.003$, $c_f = 32$, $\gamma_f = \gamma_m = 0.22$, $\psi_f^l = \sigma_f^l = 0.1$, $k_f^h = k_m^h = 0.7$, $\eta_f^l = \eta_m^l = 0.8$, $\eta_f^h = \eta_m^h = 0.9$, $\theta_f^l = \theta_m^l = 0.9$ and $\theta_f^h = \theta_m^h = 0.95$; so that $0.0310 = \mathcal{R}_h < 1 < \mathcal{R}_l = 5.718$ and $\mathcal{R}_0^r = 2.3899$).

(A)



(B)

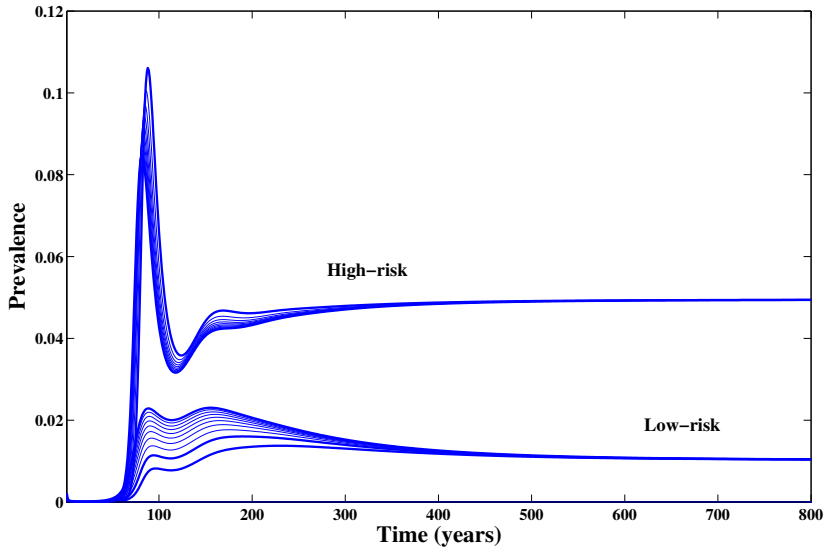


Figure 4.4: HPV prevalence as a function of time for the model (4.34) using various initial conditions. Parameter values used are as given in Table 4.2. (A) $\mathcal{R}_l > \mathcal{R}_h > 1$ (here, $\rho_f^l = \rho_m^l = 0.001$, $\rho_f^h = \rho_m^h = 0.03$, $\beta_m^l = 0.058$, $\beta_f^l = 0.28$, $\beta_m^h = 0.45$, $\beta_f^h = 0.27$, $c_f = 8$, $\gamma_f = 0.7$, $\gamma_m = 0.5$, $\psi_m^l = \psi_m^h = \sigma_m^h = 0.4$, $\sigma_f^l = 0.1$, $k_f^h = k_m^h = 0.7$, $\eta_f^l = \eta_m^l = 0.8$, $\eta_f^h = \eta_m^h = 0.8$, $\theta_f^l = \theta_m^l = 0.9$, $z_f = z_m = 3$, $w_f = w_m = 0.9$, $d_f = d_m = 0.6$, $u_f = u_m = 2$, and $\theta_f^h = \theta_m^h = 0.95$; so that $10.1328 = \mathcal{R}_l > \mathcal{R}_h = 6.3261 > 1$ and $\mathcal{R}_0^r = 3.1832$). (B) $\mathcal{R}_h > \mathcal{R}_l > 1$ (here, $\rho_f^h = \rho_m^h = 0.03$, $\rho_f^l = \rho_m^l = 0.0001$, $\beta_m^l = 0.45$,$\beta_f^l = 0.03$, $\beta_m^h = 0.7$, $\beta_f^h = 0.3$, $c_f = 8$, $\psi_f^l = \sigma_f^l = 0.1$, $k_f^h = k_m^h = 0.7$, $\eta_f^l = \eta_m^l = 0.8$, $\eta_f^h = \eta_m^h = 0.9$, $\theta_f^l = \theta_m^l = 0.9$, $\psi_f^h = \psi_m^h = 0.5$ and $\theta_f^h = \theta_m^h = 0.9$; so that $16.8274 = \mathcal{R}_h > \mathcal{R}_l = 10.9341$ and $\mathcal{R}_0^r = 4.1021$).

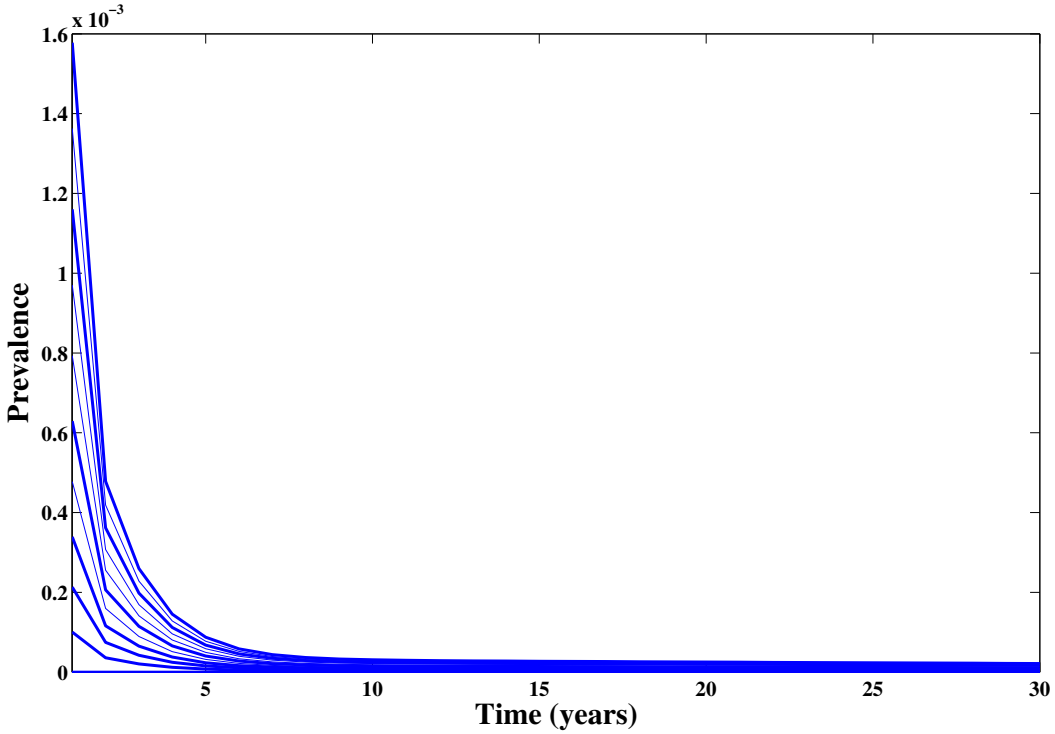
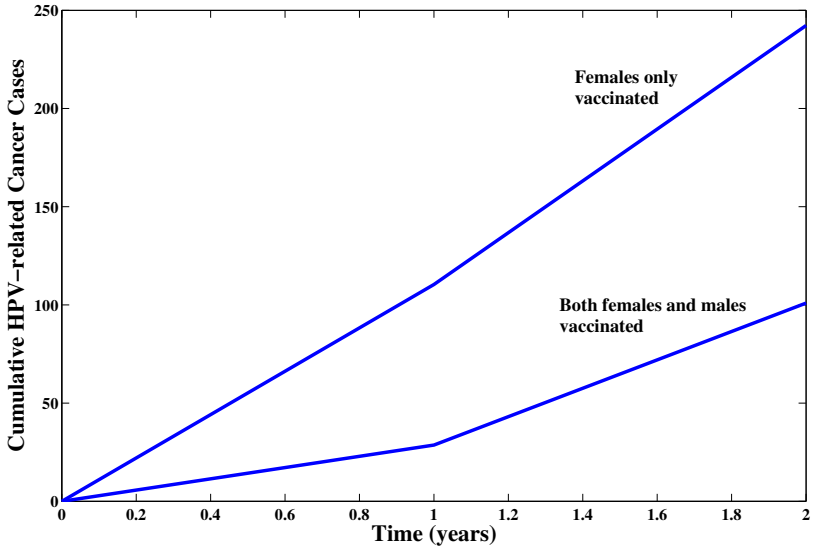


Figure 4.5: HPV prevalence as a function of time for the model (4.34) using various initial conditions. Parameter values used are as given in Table 4.2, with $\rho_f^l = \rho_m^l = \rho_f^h = \rho_m^h = \delta_m = 0$, $\beta_m^l = \beta_f^l = 0.05$, $\beta_m^h = 0.5$, $\beta_f^h = 0.4$, $\eta_f^l = \eta_m^l = 0.7$, $\eta_f^h = \eta_m^h = 0.8$, $\theta_f^l = \theta_m^l = 0.9$ and $\theta_f^h = \theta_m^h = 0.95$ (so that, $0.005 = \mathcal{R}_l < \mathcal{R}_h = 0.2253 < 1$ and $\mathcal{R}_{01}^r = 0.4747 < 1$).

(A)



(B)

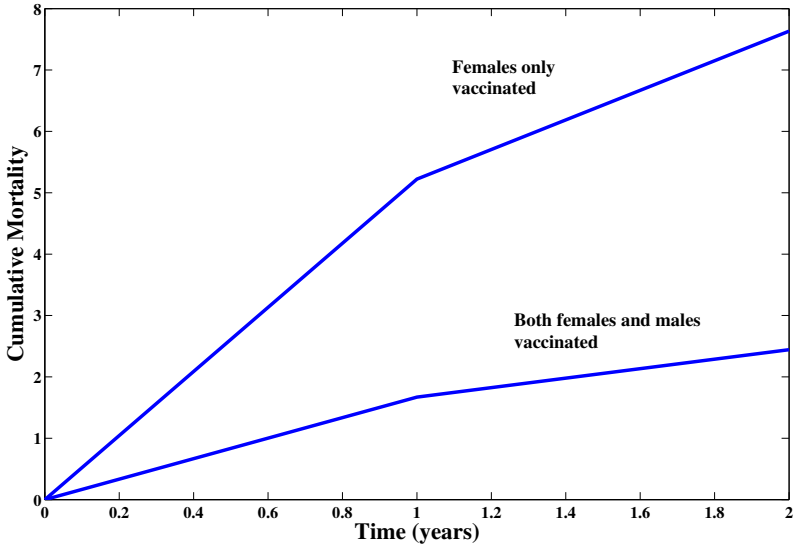
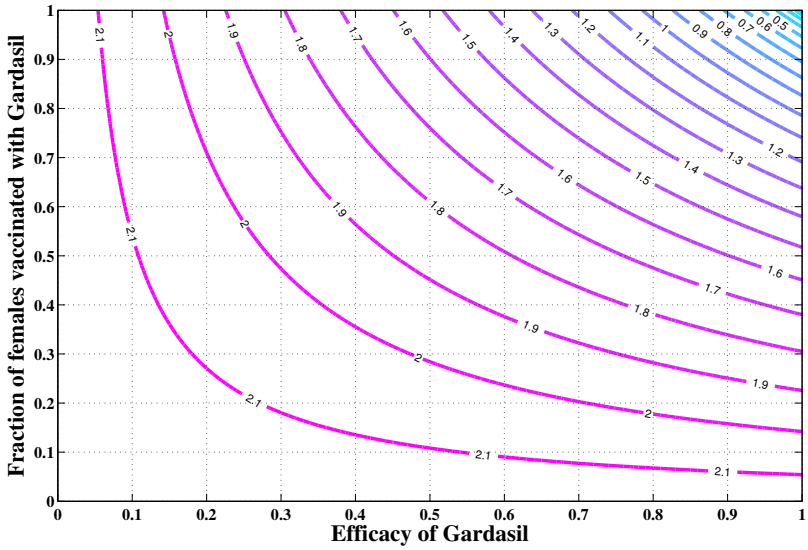


Figure 4.6: Simulation of the model (4.34) using *Gardasil* vaccine. Parameter values used are as given in Table 4.2. (A) Showing the cumulative number of HPV-related cancer cases in both females and males as a function of time for females only vaccinated and both females and males vaccinated (here, $\rho_f^h = \rho_m^h = \rho_f^l = \rho_m^l = 0.0012$, $\beta_m^l = 0.8$, $\beta_f^l = 0.9$, $\beta_m^h = 0.7$, $\beta_f^h = 0.9$, $k_f^h = k_m^h = 0.2$, $\eta_f^l = \eta_m^l = 0.7$, $\eta_f^h = \eta_m^h = 0.8$, $\theta_f^l = \theta_m^l = 0.9$, $\alpha_f^l = \alpha_m^l = 1.4$, $\alpha_f^h = \alpha_m^h = 11.75$ and $\theta_f^h = \theta_m^h = 0.9$). (B) Showing the cumulative number of mortality as a function of time for females only vaccinated and both females and males vaccinated (here, $\rho_f^h = \rho_m^h = \rho_f^l = \rho_m^l = 0.0012$, $\beta_m^l = 0.8$, $\beta_f^l = 0.9$, $\beta_m^h = 0.7$, $\beta_f^h = 0.9$,$k_f^h = k_m^h = 0.2$, $\eta_f^l = \eta_m^l = 0.8$, $\eta_f^h = \eta_m^h = 0.9$, $\theta_f^l = \theta_m^l = 0.9$ and $\theta_f^h = \theta_m^h = 0.9$).

(A)



(B)

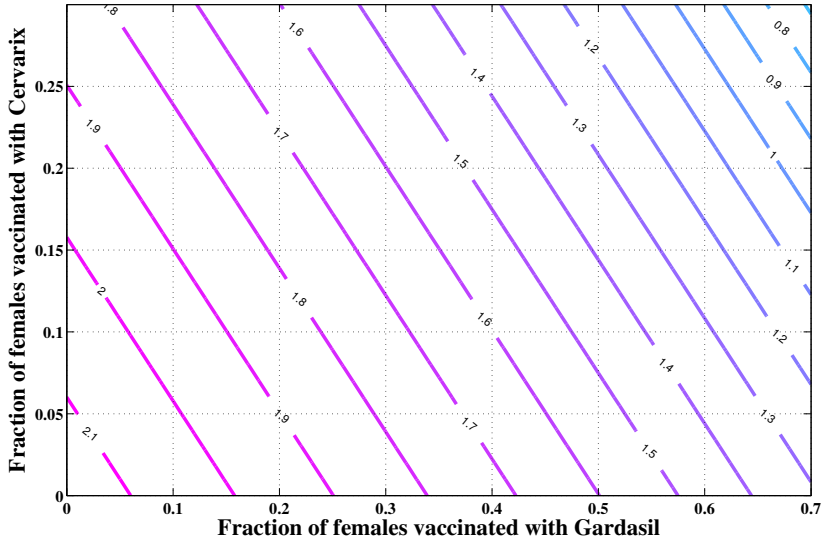


Figure 4.7: Simulations of the model (4.34). Parameter values used are as given in Table 4.2. (A) showing a contour plot of $\mathcal{R}_{01}^r$ as a function of the *Gardasil* vaccine efficacy (ε_q) and the fraction of new sexually-active females vaccinated at steady-state (φ_f^q) with $\rho_f^l = \rho_m^l = \rho_f^h = \rho_m^h = \delta_m = 0$, $\beta_m^l = \beta_f^l = 0.05$, $\beta_m^h = 0.5$, $\beta_f^h = 0.4$, $r_f^l = r_m^l = 0.887$, $\varphi_m^q = 0$, $\eta_f^l = \eta_m^l = \eta_f^h = \eta_m^h = 0.8$ and $\theta_f^l = \theta_m^l = \theta_f^h = \theta_m^h = 0.9$. (B) showing a contour plot of $\mathcal{R}_{01}^r$ as a function of the fraction of new sexually-active females vaccinated with *Gardasil* (φ_f^q) and *Cervarix* (φ_f^b) at steady-state with $\rho_f^l = \rho_m^l = \rho_f^h = \rho_m^h = \delta_m = 0$, $\beta_m^l = \beta_f^l = 0.05$, $\beta_m^h = 0.5$, $\beta_f^h = 0.04$, $r_f^l = r_m^l = 0.887$, $\varphi_m^q = 0$, $\eta_f^l = \eta_m^l = \eta_f^h = \eta_m^h = 0.8$ and $\theta_f^l = \theta_m^l = \theta_f^h = \theta_m^h = 0.9$.

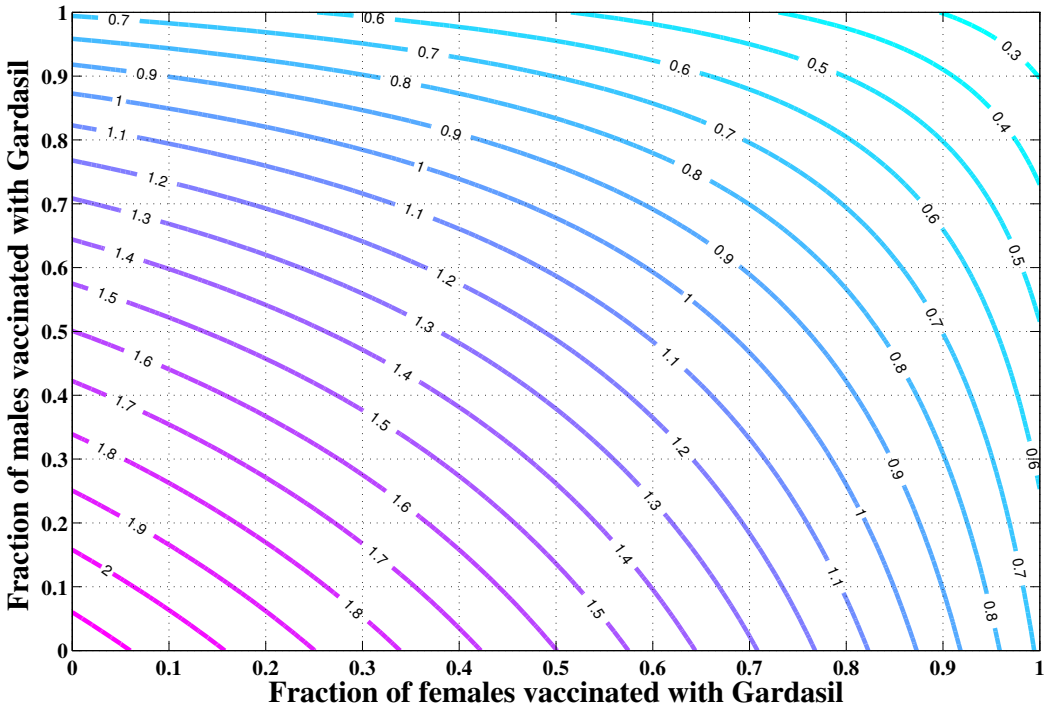


Figure 4.8: Simulations of the model (4.34). Parameter values used are as given in Table 4.2, showing a contour plot of $\mathcal{R}_{01}^r$ as a function the fraction of new sexually-active females vaccinated at steady-state (φ_f^q) and the fraction of new sexually-active males vaccinated at steady-state (φ_m^q) with $\rho_f^l = \rho_m^l = \rho_f^h = \rho_m^h = \delta_m = 0$, $\beta_m^l = \beta_f^l = 0.05$, $\beta_m^h = 0.5$, $\beta_f^h = 0.04$, $r_f^l = r_m^l = 0.887$, $\sigma_m^l = \sigma_f^l = 0.85$, $\eta_f^l = \eta_m^l = \eta_f^h = \eta_m^h = 0.8$ and $\theta_f^l = \theta_m^l = \theta_f^h = \theta_m^h = 0.9$.

Chapter 5

Contributions of the Thesis and Future Work

The thesis contributes in three main categories, namely:

i) **model formulation**: formulation of novel anti-HPV vaccination models, of the form of deterministic systems of non-linear differential equations, for the transmission dynamics of HPV, and the associated cancers and warts, in a community;

ii) **mathematical analysis**: carrying out detailed qualitative (mathematical) analysis of the models developed in the thesis (in particular, finding conditions for the existence and asymptotic stability of the associated equilibria);

iii) **public health**: using the models developed in the thesis to evaluate the impact of the anti-HPV *Cervarix* and *Gardasil* vaccines in combatting the spread of the four chosen HPV-types (HPV-6, HPV-11, HPV-16 and HPV-18).

The specific contributions of the thesis are summarized below.

5.1 Model Formulation

The thesis consists of two new models for HPV transmission dynamics (and the associated cancers and warts) in a community.

i) The first model, given by (3.19), is for the transmission dynamics of HPV (and the associated cancers in females) in a population, in the presence of the *Gardasil* vaccine (which targets the four HPV types, HPV-6, HPV-11, HPV-16 and HPV-18) for new sexually-active susceptible females. Some of the novelties of this model (in relation to the many other HPV transmission models in the literature, including those in [9, 24, 25, 26, 61]) is that it:

   a) includes the dynamics of the exposed (i.e., latently-infected) individuals;

   b) allows for the transmission of HPV by exposed individuals;

   c) allows for the loss of infection-acquired immunity by recovered individuals;

   d) allows for the re-infection of recovered individuals.

   Furthermore, the model (3.19) extends the models in [9, 26] by, additionally, including cancer-induced mortality in females and the dynamics of females with persistent HPV infection.

ii) The second model, given by (4.34), is based on extending the model developed in Chapter 3 to study the transmission dynamics of the low- and high-risk HPV types in the presence of the *Cervarix* and *Gardasil* vaccines. Some of the notable new features of the model (4.34), in relation to the model (3.19), are:

   a) stratifying the entire population in terms of the risk of transmitting either the low-risk (HPV-6 and HPV-11) or the high-risk (HPV-16 and HPV-18) HPV types;

   b) incorporating two anti-HPV vaccines (*Cervarix* and *Gardasil*);

c) allowing for mass vaccination of new sexually-active susceptible males (with the *Gardasil* vaccine);

d) including the dynamics of infected individuals with genital warts;

e) including the dynamics of individuals in the low-grade and high-grade pre-cancer stages (CIN for females and INM for males);

f) including the dynamics of infected males:

   1) with HPV-related cancers;

   2) cancer-induced mortality for males;

   3) infected males who recovered from HPV-related cancers;

   4) a compartment for males with persistent HPV infection.

5.2 Mathematical Analysis

A major contribution of the thesis is the detailed qualitative analyses of (the two models) it contains. Some of the main mathematical results obtained are summarized below.

5.2.1 Chapter 3

The model (3.19), and its vaccination-free version (3.21), are qualitatively analysed. The leading following theoretical results were obtained:

i) it is shown, using the next generation operator method, that each of the two models has a locally-asymptotically stable disease-free equilibrium whenever its associated reproduction number is less than unity;

ii) each of the two models has at least one endemic equilibrium whenever its associated reproduction threshold exceeds unity. For the case when the models have a unique endemic equilibrium, it is shown, using a Krasnoselskii sub-linearity argument, that the unique endemic equilibrium is locally-asymptotically stable;

iii) the two models undergo the phenomenon of backward bifurcation under certain conditions. The backward bifurcation phenomenon, proved using Centre Manifold Theory, is shown to arise due to the re-infection of recovered individuals;

iv) in the absence of the re-infection of recovered individuals, it is shown, using Comparison Theorem and Lyapunov Function theory, that the associated disease-free equilibrium of the two models are globally-asymptotically stable whenever the respective associated reproduction threshold is less than unity;

v) overall, it is shown that the two models (vaccination and vaccination-free models) developed in Chapter 3 have essentially the same qualitative features. Thus, this study shows that adding vaccination to the vaccination-free model (3.21) does not alter its qualitative dynamics with respect to the existence and stability of its associated equilibria, as well as with respect to its backward bifurcation property.

5.2.2 Chapter 4

The model (4.34), and the low-risk-only version (4.37), are qualitatively analysed.

i) Each of the two models has a locally-asymptotically stable disease-free equilibrium whenever its associated reproduction threshold is less than unity;

ii) it is shown that both models have at least one endemic equilibrium whenever the reproduction threshold exceeds unity;

iii) it is shown that the low-risk-only model (4.37) undergoes a re-infection-induced backward bifurcation under certain conditions;

iv) in the absence of the re-infection of recovered individuals and cancer-induced mortality in males, it is shown that the disease-free equilibrium of the model (4.34) is globally-asymptotically stable whenever the associated reproduction threshold is less than unity.

5.3 Public Health

The models developed in this thesis are simulated, using the parameter values in Tables 3.1 and 4.2, to gain quantitative insight into the transmission dynamics of HPV (and related cancers and warts) in a community. Some of the main public health contributions of the thesis, derived from these simulations, are summarized below:

i) the vaccination model in Chapter 3 shows that the mass vaccination of new sexually-active females only, using the *Gardasil* vaccine (with the assumed efficacy of 90%), can lead to effective community-wide control (or elimination) of HPV if at least 78% of the new sexually-active susceptible female population is vaccinated at steady-state. However, the model in Chapter 4 shows that vaccinating new sexually-active susceptible females alone (with the *Gardasil* vaccine) can lead to effective control, or elimination, of HPV from the community if at least 87% of the new sexually-active susceptible females are vaccinated. Unfortunately, however, since the current *Gardasil* coverage in most communities is about 70% [9, 26, 46, 61, 76], this study shows that the singular use of *Gardasil* (with the 70% coverage) is inadequate to lead to the effective control of HPV (since it fails to bring the associated reproduction threshold of the two vaccination models, (3.19) and (4.34), to be less than unity);

ii) vaccinating new sexually-active susceptible males offers beneficial community-wide impact. In particular, simulations show that while vaccinating new sexually-active susceptible females only (at the assumed 70% coverage rate) resulted in about 250 cumulative cancer cases over two years, this number reduces to about 100, over the same time period, if both new sexually-active males (with 70% *Gardasil* coverage) and females are vaccinated. Furthermore, while vaccinating new sexually-active females only with the *Gardasil* vaccine (at the 70% coverage level) resulted in about 8 cumulative mortality cases over two years, only 2 cancer-related deaths are recorded, over the same time period, if both new sexually-active males and females are vaccinated;

iii) if only 70% of the new sexually-active susceptible females are vaccinated with the *Gardasil* vaccine, additionally vaccinating 47% of new sexually-active susceptible males will lead to the community-wide elimination of the low- and high-risk HPV types;

iv) it is shown that, with the assumed 70% *Gardasil* vaccine coverage for new sexually-active females, at least 18% of the remaining unvaccinated susceptible females need to be vaccinated with the *Cervarix* vaccine in order to effectively control the disease.

5.4 Future Work

The work in this thesis can be extended in several directions (in terms of model construction and associated mathematical analyses), such as:

i) including age-structure (since both vaccines are recommended to be administered to individuals in certain age groups [15, 76, 93, 96]);

ii) including other anti-HPV intervention strategies (such as condom use and Pap screening, which are also considered as standard anti-HPV control strategies [15, 27, 61, 76]);

iii) explicitly incorporating the effect of co-infection (of multiple HPV types and/or with other STIs);

iv) carrying out a cost-benefit analysis of implementing the mass vaccination program in a community;

v) vaccination of older susceptible men and women (outside the 9-26 age bracket). The objective is to determine whether vaccinating this age group offers beneficial community-wide impact;

vi) incorporate the homosexual transmission of HPV. This is crucial since HPV can also be transmitted *via* this route. This aspect of HPV transmission dynamics has not yet been addressed in the literature;

vii) modelling the in-host dynamics of HPV;

viii) establishing the global asymptotic stability of the endemic and/or boundary equilibria of the models (mathematical interest). Establishing the global asymptotic stability of a relatively large dynamical system, such as the 29-dimensional model in Chapter 4, is always of significant mathematical interest (since one key objective of mathematical biology research is to develop new mathematical techniques and theories for analysing relatively large systems of non-linear differential equations).

Appendix A

Proof of Theorem 3.1

Proof. Let $t_1 = \sup\{t > 0 : S_f(t) > 0, V_f(t) > 0, E_f(t) > 0, I_f(t) > 0, P(t) > 0, C(t) > 0, R_c(t) > 0, R_f(t) > 0, S_m(t) > 0, E_m(t) > 0, I_m(t) > 0, R_m(t) > 0\} > 0$. It follows from the first equation of the vaccination model (3.19) that

$$\frac{dS_f}{dt} = \pi_f(1-\varphi_f) + \xi_f R_f(t) - \lambda_m(t)S_f(t) - \mu_f S_f(t) \geq \pi_f(1-\varphi_f) - [\lambda_m(t) + \mu_f]\, S_f(t),$$

which can be re-written as,

$$\frac{d}{dt}\left\{S_f(t)\exp\left[\mu_f t + \int_0^t \lambda_m(\tau)\,\mathrm{d}\tau\right]\right\} \geq \pi_f(1-\varphi_f)\exp\left[\mu_f t + \int_0^t \lambda_m(\tau)\,\mathrm{d}\tau\right].$$

Hence,

$$S_f(t_1)\exp\left[\mu_f t_1 + \int_0^{t_1} \lambda_m(\tau)\,\mathrm{d}\tau\right] - S_f(0) \geq \int_0^{t_1} \pi_f(1-\varphi_f)\exp\left[\mu_f y + \int_0^y \lambda_m(\tau)\,\mathrm{d}\tau\right]\mathrm{d}y,$$

so that,

$$
\begin{aligned}
S_f(t_1) &\geq S_f(0)\exp\left[-\mu_f t_1 - \int_0^{t_1}\lambda_m(\tau)\,\mathrm{d}\tau\right] \\
&+ \left\{\exp\left[-\mu_f t_1 - \int_0^{t_1}\lambda_m(\tau)\,\mathrm{d}\tau\right]\right\}\int_0^{t_1}\pi_f(1-\varphi_f)\exp\left[\mu_f y + \int_0^{y}\lambda_m(\tau)\,\mathrm{d}\tau\right]\mathrm{d}y > 0.
\end{aligned}
$$

Similarly, it can be shown that $V_f(t) > 0, E_f(t) \geq 0, I_f(t) \geq 0, P(t) \geq 0, C(t) \geq 0, R_c(t) \geq 0, R_f(t) \geq 0, S_m(t) \geq 0, E_m(t) \geq 0, I_m(t) \geq 0$, and $R_m(t) \geq 0$ for all time $t > 0$. Hence, all solutions remain positive for all non-negative initial conditions. □

Theorem 3.1 can also be proved using the approach given in Appendix A of [92].

Appendix B

Proof of Theorem 3.5

Proof. Consider the vaccination-free model (3.21) with $\rho_f = \rho_m = 0$. The proof of Theorem 3.5 is based on using a Krasnoselskii sub-linearity trick, as given in [91] (see also [31, 32]). The method essentially entails proving that the linearization of the model system (3.21), around the EEP ($\mathcal{E}_1$) of the vaccination-free model (3.21), has no solutions of the form

$$\bar{Z}(t) = \bar{Z}_0 e^{\omega t}, \tag{B.1}$$

with,

$$\bar{Z}_0 = (Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, Z_7, Z_8, Z_9, Z_{10}, Z_{11}), \quad Z_i \in \mathbb{C},\ \omega \in \mathbb{C}, \quad \text{and} \quad Re(\omega) \geq 0.$$

This implies that the eigenvalues of the characteristic polynomial associated with the linearized equations have negative real part (i.e., $Re\,(\omega) < 0$). Then the EEP, $\mathcal{E}_1$, is locally asymptotically stable. For simplicity, consider the special case of the vaccination-free model (3.21) with the probability of re-infection set to zero (so that, $\rho_m = \rho_f = 0$ in (3.21)). The linearized system of (3.21), around the EEP $\mathcal{E}_1$ (with $\rho_m = \rho_f = 0$), gives the following system of linear equations

$$
\begin{aligned}
\omega Z_1 &= -\left[\frac{\beta_m c_f \mu_m \left(\eta_m E_m^{**} + I_m^{**}\right)}{\pi_m} + \mu_f\right] Z_1 + \xi_f Z_7 - \frac{\beta_m c_f \mu_m \eta_m S_f^{**}}{\pi_m} Z_9 - \frac{\beta_m c_f \mu_m S_f^{**}}{\pi_m} Z_{10}, \\
\omega Z_2 &= \frac{\beta_m c_f \mu_m \left(\eta_m E_m^{**} + I_m^{**}\right)}{\pi_m} Z_1 - g_1 Z_2 + \frac{\beta_m c_f \mu_m \eta_m S_f^{**}}{\pi_m} Z_9 + \frac{\beta_m c_f \mu_m S_f^{**}}{\pi_m} Z_{10}, \\
\omega Z_3 &= \sigma_f Z_2 - g_2 Z_3, \\
\omega Z_4 &= h_1 Z_3 - n_1 Z_4, \\
\omega Z_5 &= h_2 Z_4 - n_2 Z_5, \\
\omega Z_6 &= \gamma_f Z_5 - \mu_f Z_6, \\
\omega Z_7 &= m_1 Z_3 + m_2 Z_4 - g_3 Z_7, \\
\omega Z_8 &= -\frac{\beta_f c_f \mu_m \eta_f S_m^{**}}{\pi_m} Z_2 - \frac{\beta_f c_f \mu_m S_m^{**}}{\pi_m} Z_3 - \frac{\beta_f c_f \mu_m \theta_p S_m^{**}}{\pi_m} Z_4 \\
&- \left[\frac{\beta_f c_f \mu_m \left(\eta_f E_f^{**} + I_f^{**} + \theta_p P^{**}\right)}{\pi_m} + \mu_m\right] Z_8 + \xi_m Z_{11}, \\
\omega Z_9 &= \frac{\beta_f c_f \mu_m \eta_f S_m^{**}}{\pi_m} Z_2 + \frac{\beta_f c_f \mu_m S_m^{**}}{\pi_m} Z_3 + \frac{\beta_f c_f \mu_m \theta_p S_m^{**}}{\pi_m} Z_4 + \frac{\beta_f c_f \mu_m \left(\eta_f E_f^{**} + I_f^{**} + \theta_p P^{**}\right)}{\pi_m} Z_8 \\
&- g_4 Z_9, \\
\omega Z_{10} &= \sigma_m Z_9 - g_5 Z_{10}, \\
\omega Z_{11} &= \psi_m Z_{10} - g_6 Z_{11},
\end{aligned}
\tag{B.2}
$$

which is equivalent to the system

$$
\begin{aligned}
\left\{1+\frac{1}{\mu_f}\left[\omega+\frac{\beta_m c_f \mu_m\left(\eta_m E_m^{**}+I_m^{**}\right)}{\pi_m}\right]\right\} Z_1 &= \frac{\xi_f}{\mu_f} Z_7-\frac{\beta_m c_f \mu_m \eta_m S_f^{**}}{\mu_f \pi_m} Z_9 \\
&- \frac{\beta_m c_f \mu_m S_f^{**}}{\mu_f \pi_m} Z_{10}, \\
\left(1+\frac{\omega}{g_1}\right) Z_2 &= \frac{\beta_m c_f \mu_m\left(\eta_m E_m^{**}+I_m^{**}\right)}{g_1 \pi_m} Z_1 \\
&+ \frac{\beta_m c_f \mu_m \eta_m S_f^{**}}{g_1 \pi_m} Z_9+\frac{\beta_m c_f \mu_m S_f^{**}}{g_1 \pi_m} Z_{10}, \\
\left(1+\frac{\omega}{g_2}\right) Z_3 &= \frac{\sigma_f}{g_2} Z_2, \\
\left(1+\frac{\omega}{n_1}\right) Z_4 &= \frac{h_1}{n_1} Z_3, \\
\left(1+\frac{\omega}{n_2}\right) Z_5 &= \frac{h_2}{n_2} Z_4, \\
\left(1+\frac{\omega}{\mu_f}\right) Z_6 &= \frac{\gamma_f}{\mu_f} Z_5, \\
\left(1+\frac{\omega}{g_3}\right) Z_7 &= \frac{m_1}{g_3} Z_3+\frac{m_2}{g_3} Z_4, \\
\left\{1+\frac{1}{\mu_m}\left[\omega+\frac{\beta_f c_f \mu_m\left(\eta_f E_f^{**}+I_f^{**}+\theta_p P^{**}\right)}{\pi_m}\right]\right\} Z_8 &= -\frac{\beta_f c_f \eta_f S_m^{**}}{\pi_m} Z_2-\frac{\beta_f c_f S_m^{**}}{\pi_m} Z_3 \\
&- \frac{\beta_f c_f \theta_p S_m^{**}}{\pi_m} Z_4+\frac{\xi_m}{\mu_m} Z_{11}, \\
\left(1+\frac{\omega}{g_4}\right) Z_9 &= \frac{\beta_f c_f \mu_m \eta_f S_m^{**}}{g_4 \pi_m} Z_2+\frac{\beta_f c_f \mu_m S_m^{**}}{g_4 \pi_m} Z_3 \\
&+ \frac{\beta_f c_f \mu_m \theta_p S_m^{**}}{g_4 \pi_m} Z_4 \\
&+ \frac{\beta_f c_f \mu_m\left(\eta_f E_f^{**}+I_f^{**}+\theta_p P^{**}\right)}{g_4 \pi_m} Z_8, \\
\left(1+\frac{\omega}{g_5}\right) Z_{10} &= \frac{\sigma_m}{g_5} Z_9, \\
\left(1+\frac{\omega}{g_6}\right) Z_{11} &= \frac{\psi_m}{g_6} Z_{10}.
\end{aligned}
\tag{B.3}
$$

Adding the first, ninth, and tenth equations of (B.3), and then adding the second, third, fourth, and eighth equations of (B.3), and finally moving all the negative terms to the left-

hand side (and simplifying) gives the following system:

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

where,

$$
\begin{aligned}
F_1(\omega) &= \frac{1}{\mu_f}\left[\omega + \frac{\beta_m c_f \mu_m \left(\eta_m E_m^{**} + I_m^{**}\right)}{\pi_m}\right], \\
F_2(\omega) &= \frac{1}{g_1}\left(\omega + \frac{g_1 \beta_f c_f \eta_f S_m^{**}}{\pi_m}\right), \\
F_3(\omega) &= \frac{1}{g_2}\left(\omega + \frac{g_2 \beta_f c_f S_m^{**}}{\pi_m}\right), \\
F_4(\omega) &= \frac{1}{n_1}\left(\omega + \frac{n_1 \beta_f c_f \theta_p S_m^{**}}{\pi_m}\right), \\
F_5(\omega) &= \frac{\omega}{n_2}, \\
F_6(\omega) &= \frac{\omega}{\mu_f}, \\
F_7(\omega) &= \frac{\omega}{g_3}, \\
F_8(\omega) &= \frac{1}{\mu_m}\left[\omega + \frac{\beta_f c_f \mu_m \left(\eta_f E_f^{**} + I_f^{**} + \theta_p P^{**}\right)}{\pi_m}\right], \\
F_9(\omega) &= \frac{1}{g_4}\left(\omega + \frac{g_3 \beta_m c_f \mu_m \eta_m S_f^{**}}{\mu_f \pi_m}\right), \\
F_{10}(\omega) &= \frac{1}{g_5}\left(\omega + \frac{g_4 \beta_m c_f \mu_m S_f^{**}}{\mu_f \pi_m}\right), \\
F_{11}(\omega) &= \frac{\omega}{g_6},
\end{aligned}
$$

and,

$$H = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \frac{\xi_f}{\mu_f} & 0 & 0 & 0 & 0 \\ \frac{y_1}{g_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{y_2}{g_1} & \frac{y_3}{g_1} & 0 \\ 0 & \frac{\sigma_f}{g_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{h_1}{n_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{h_2}{n_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\gamma_f}{\mu_f} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{m_1}{g_3} & \frac{m_2}{g_3} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\xi_m}{\mu_m} \\ 0 & \frac{y_4}{g_4} & \frac{y_5}{g_4} & \frac{y_6}{g_4} & 0 & 0 & 0 & \frac{y_7}{g_4} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\sigma_m}{g_5} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\psi_m}{g_6} & 0 \end{pmatrix},$$

with,

$$\begin{aligned} y_1 &= \frac{\beta_m c_f \mu_m \left(\eta_m E_m^{**} + I_m^{**}\right)}{\pi_m}, \quad y_2 = \frac{\beta_m c_f \mu_m \eta_m S_f^{**}}{\pi_m}, \quad y_3 = \frac{\beta_m c_f \mu_m S_f^{**}}{\pi_m}, \\ y_4 &= \frac{\beta_f c_f \mu_m \eta_f S_m^{**}}{\pi_m}, \quad y_5 = \frac{\beta_f c_f \mu_m S_m^{**}}{\pi_m}, \quad y_6 = \frac{\beta_f c_f \mu_m \theta_p S_m^{**}}{\pi_m}, \\ y_7 &= \frac{\beta_f c_f \mu_m \left(\eta_f E_f^{**} + I_f^{**} + \theta_p P^{**}\right)}{\pi_m}. \end{aligned}$$

In the above computations, the notation $H\left(\bar{Z}\right)_i$ (for $i = 1, ..., 11$) denotes the ith coordinate of the vector $H\left(\bar{Z}\right)$. Furthermore, it should be noted that the matrix H has non-negative entries, and the EEP

$$\mathcal{E}_1 = \left(S_f^{**}, E_f^{**}, I_f^{**}, P^{**}, C^{**}, R_c^{**}, R_f^{**}, S_m^{**}, E_m^{**}, I_m^{**}, R_m^{**}\right),$$

satisfies

$$\mathcal{E}_1 = H\mathcal{E}_1. \tag{B.5}$$

To show that $Re\left(\omega\right) < 0$, we consider two cases: $\omega = 0$ and $\omega \neq 0$.

Case 1: $\omega = 0$

Suppose $\omega = 0$. It follows then that (B.2) is a homogeneous linear system. Furthermore, the determinant of (B.2) (with $\omega = 0$) is

$$\Delta = \begin{vmatrix} -y_1-\mu_f & 0 & 0 & 0 & 0 & 0 & \xi_f & 0 & -y_2 & -y_3 & 0 \\ y_1 & -g_1 & 0 & 0 & 0 & 0 & 0 & 0 & y_2 & y_3 & 0 \\ 0 & \sigma_f & -g_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & h_1 & -n_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & h_2 & -n_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_f & -\mu_f & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & m_1 & m_2 & 0 & 0 & -g_3 & 0 & 0 & 0 & 0 \\ 0 & -y_4 & -y_5 & -y_6 & 0 & 0 & 0 & -y_7-\mu_m & 0 & 0 & \xi_m \\ 0 & y_4 & y_5 & y_6 & 0 & 0 & 0 & y_7 & -g_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_m & -g_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \psi_m & -g_6 \end{vmatrix},$$

$$= -(y_1+\mu_f) M_1 + \xi_f M_2 - y_2 M_3 + y_3 M_4, \tag{B.6}$$

where,

$$\begin{aligned} M_1 &= \mu_f n_2 g_3 n_1 g_2 g_5 g_6 \left[g_1 g_4 (\mu_m + y_7) - \mu_m (y_2 + y_4) \right] \\ &- \mu_f n_2 g_3 \mu_m g_6 \left[\sigma_f g_5 y_2 (n_1 y_5 + h_1 y_6) + n_1 \sigma_m g_2 y_3 y_4 + n_1 \sigma_m \sigma_f y_3 y_5 + h_1 \sigma_m \sigma_f y_3 y_6 \right] \\ &- \mu_f n_2 g_3 n_1 g_1 g_2 \sigma_m \xi_m \psi_m y_7, \\ M_2 &= \sigma_f \mu_f n_2 y_1 (n_1 m_1 + h_1 m_2) \left[g_4 g_5 g_6 (\mu_m + y_7) - \sigma_m \xi_m \psi_m y_7 \right], \\ M_3 &= g_5 \mu_m \mu_f n_2 y_1 g_3 g_6 (n_1 g_2 y_4 + h_1 \sigma_f y_6 + n_1 \sigma_f y_5), \\ M_4 &= -\sigma_m \mu_m \mu_f n_2 y_1 g_3 g_6 (n_1 g_2 y_4 + h_1 \sigma_f y_6 + n_1 \sigma_f y_5). \end{aligned} \tag{B.7}$$

It can be shown, by simplifying (B.6) with (B.7), that the determinant, Δ, is non-zero. Hence, for the case that $\omega = 0$, the linear system (B.2) has only the trivial solution $\bar{Z} = 0$. This implies that $\omega \neq 0$.

Case 2: $\omega \neq 0$

Now assume that $\omega \neq 0$ and $Re(\omega) \geq 0$ (assume the contrary to show that $Re(\omega) < 0$). Let $F(\omega) = \min\{|1 + F_i(\omega)|, i = 1, 2, 3, ..., 11\}$. It can be shown from (B.4) that $|1 + F_i(\omega)| > 1$ for all i. Hence, $F(\omega) > 1$. On the other hand, since the coordinates of $\mathcal{E}_1$ are positive, if $\bar{Z}$ is any solution of (B.4), then there exists a minimal positive real number s such that

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

where $\left|\bar{Z}\right| = (|Z_1|, |Z_2|, |Z_3|, |Z_4|, ..., |Z_{11}|)$ and $|.|$ is the norm in $\mathbb{C}$. Therefore, $\frac{s}{F(\omega)} < s$ and the minimality of s implies that $\left|\bar{Z}\right| > \frac{s}{F(\omega)}\mathcal{E}_1$. Since s is the minimal positive real number such that

$$|Z_{11}| \leq sR_m^{**}, \tag{B.8}$$

Taking norms on both side of last equation of (B.4), and using (B.5), (B.8) and the fact that H is nonnegative, gives

$$F(\omega)|Z_{11}| \leq H(|Z|)_{11} \leq sR_m^{**},$$

so that,

$$|Z_{11}| \leq \frac{s}{F(\omega)}R_m^{**} < sR_m^{**},$$

which contradicts the minimality of s. Hence, $Re(\omega) < 0$. This concludes the proof. □

Appendix C

Proof of Theorem 3.6

Proof. The Centre Manifold Theory, as described in [14], will be used to prove Theorem 3.6. It is convenient to, first of all, make the following changes of variables. Let,

$$S_f = x_1, \;\; E_f = x_2, \;\; I_f = x_3, \;\; P = x_4, \;\; C = x_5, \;\; R_c = x_6, \;\; R_f = x_7,$$

and,

$$S_m = x_8, \;\; E_m = x_9, \;\; I_m = x_{10}, \;\; R_m = x_{11}.$$

Furthermore, it should be noted that the total male population, now given by $N_m = x_8 + x_9 + x_{10} + x_{11}$ is replaced by its limiting value $\frac{\pi_m}{\mu_m}$. Hence, the model (3.19) can be re-written in the form:

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \pi_f + \xi_f x_7 - \frac{\beta_m c_f \mu_m \left(\eta_m x_9 + x_{10}\right)}{\pi_m} x_1 - \mu_f x_1, \\
\frac{dx_2}{dt} &= f_2 = \frac{\beta_m c_f \mu_m \left(\eta_m x_9 + x_{10}\right)}{\pi_m} \left(x_1 + \rho_f x_7\right) - g_1 x_2, \\
\frac{dx_3}{dt} &= f_3 = \sigma_f x_2 - g_2 x_3, \\
\frac{dx_4}{dt} &= f_4 = h_1 x_3 - n_1 x_4, \\
\frac{dx_5}{dt} &= f_5 = h_2 x_4 - n_2 x_5, \\
\frac{dx_6}{dt} &= f_6 = \gamma_f x_5 - \mu_f x_6, \\
\frac{dx_7}{dt} &= f_7 = m_1 x_3 + m_2 x_4 - \left[\rho_f \frac{\beta_m c_f \mu_m \left(\eta_m x_9 + x_{10}\right)}{\pi_m} + g_3\right] x_7, \\
\frac{dx_8}{dt} &= f_8 = \pi_m + \xi_m x_{11} - \frac{\beta_f c_f \mu_m (\eta_f x_2 + x_3 + \theta_p x_4)}{\pi_m} x_8 - \mu_m x_8, \\
\frac{dx_9}{dt} &= f_9 = \frac{\beta_f c_f \mu_m (\eta_f x_2 + x_3 + \theta_p x_4)}{\pi_m} \left(x_8 + \rho_m x_{11}\right) - g_4 x_9, \\
\frac{dx_{10}}{dt} &= f_{10} = \sigma_m x_9 - g_5 x_{10}, \\
\frac{dx_{11}}{dt} &= f_{11} = \psi_m x_{10} - \left[\rho_m \frac{\beta_f c_f \mu_m (\eta_f x_2 + x_3 + \theta_p x_4)}{\pi_m} + g_6\right] x_{11}.
\end{aligned}
\tag{C.1}
$$

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

$$J(\mathcal{E}_0) = \begin{pmatrix} -\mu_f & 0 & 0 & 0 & 0 & 0 & \xi_f & 0 & -g_{11} & -g_{12} & 0 \\ 0 & -g_1 & 0 & 0 & 0 & 0 & 0 & 0 & g_{11} & g_{12} & 0 \\ 0 & \sigma_f & -g_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & h_1 & -n_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & h_2 & -n_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \gamma_f & -\mu_f & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & m_1 & m_2 & 0 & 0 & -g_3 & 0 & 0 & 0 & 0 \\ 0 & -g_{13} & -g_{14} & -g_{15} & 0 & 0 & 0 & -\mu_m & 0 & 0 & \xi_m \\ 0 & g_{13} & g_{14} & g_{15} & 0 & 0 & 0 & 0 & -g_4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_m & -g_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \psi_m & -g_6 \end{pmatrix},$$

where,

$$g_{11} = \frac{\eta_m \beta_m c_f \pi_f \mu_m}{\mu_f \pi_m}, \quad g_{12} = \frac{\beta_m c_f \pi_f \mu_m}{\mu_f \pi_m}, \quad g_{13} = \eta_f \beta_f c_f, \quad g_{14} = \beta_f c_f, \quad g_{15} = \theta_p \beta_f c_f.$$

Consider the case when $\mathcal{R}_0 = 1$. Suppose (without loss of generality) that β_f is chosen as a bifurcation parameter. Solving for β_f from $\mathcal{R}_0 = 1$ gives

$$\beta_f = \beta^* = \frac{n_1 g_1 g_2 g_4 g_5 \pi_m \mu_f}{\beta_m c_f^2 \pi_f \mu_m \left(\eta_m g_5 + \sigma_m\right) \left[\eta_f n_1 g_2 + \sigma_f \left(n_1 + \theta_p h_1\right)\right]}. \tag{C.2}$$

The transformed system, (C.1) with $\beta_f = \beta^*$, has a hyperbolic equilibrium point (i.e., the linearization has eigenvalue with zero real part while the other have negative real part).

Eigenvectors of $J(\mathcal{E}_0)\mid_{\beta_f=\beta^*}$:

Let $J(\mathcal{E}_0)\mid_{\beta_f=\beta^*} = J_{\beta^*}$. In order to apply the method described in [14], the following computations are necessary. The matrix J_{β^*} has a left eigenvector (associated with the zero

eigenvalue) given by,

$$\boldsymbol{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}]^T,$$

with,

$$\begin{aligned} v_1 &= 0, \;\; v_2 = \frac{\sigma_f v_3 + \eta_f \beta^* c_f v_9}{g_1}, \;\; v_3 = \frac{h_1 v_4 + \beta^* c_f v_9}{g_2}, \;\; v_4 = \frac{\theta_p \beta^* c_f v_9}{n_1}, \;\; v_5 = 0, \\ v_6 &= 0, \;\; v_7 = 0, \;\; v_8 = 0, \;\; v_9 = v_9 > 0, \;\; v_{10} = \frac{\beta_m c_f \mu_m \pi_f v_2}{g_4 \pi_m \mu_f}, \;\; v_{11} = 0. \end{aligned}$$

Furthermore, the matrix J_{β^*} has a right eigenvector (associated with the zero eigenvalue) given by,

$$\boldsymbol{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}, w_{11}]^T,$$

where,

$$\begin{aligned} w_1 &= \frac{\xi_f w_7}{\mu_f} - \frac{\beta_m c_f \mu_m \pi_f \left(\eta_m w_9 + w_{10}\right)}{\mu_f^2 \pi_m}, \;\; w_2 = \frac{\beta_m c_f \mu_m \pi_f \left(\eta_m w_9 + w_{10}\right)}{g_1 \pi_m \mu_f}, \;\; w_3 = \frac{\sigma_f w_2}{g_2}, \\ w_4 &= \frac{\sigma_f h_1 w_2}{g_2 n_1}, \;\; w_5 = \frac{h_2 w_4}{n_2}, \;\; w_6 = \frac{h_2 \gamma_f w_4}{n_2 \mu_f}, \;\; w_7 = \frac{m_1 w_3 + m_2 w_4}{g_3}, \\ w_8 &= \frac{\xi_m w_{11}}{\mu_m} - \frac{\beta^* c_f \left(\eta_f w_2 + w_3 + \theta_p w_4\right)}{\mu_m}, \;\; w_9 = w_9 > 0, \;\; w_{10} = \frac{\sigma_m w_9}{g_5}, w_{11} = \frac{\psi_m w_{10}}{g_6}. \end{aligned}$$

Computations of bifurcation coefficients, a and b:

It follows from Theorem 2.8 of Chapter 2 that, for the system (C.1), the associated non-zero partial derivatives of C.1 (at the DFE, $\mathcal{E}_0$) are given by

$$
\begin{aligned}
\frac{\partial^2 f_1}{\partial x_9 \partial x_{10}} &= \frac{\eta_m \beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f} + \frac{\beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}, \quad \frac{\partial^2 f_2}{\partial x_9 \partial x_{10}} = -\frac{\eta_m \beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f} - \frac{\beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}, \\
\frac{\partial^2 f_9}{\partial x_2 \partial x_{11}} &= -\frac{\eta_f \beta^* c_f \mu_m}{\pi_m} + \frac{\rho_m \eta_f \beta^* c_f \mu_m}{\pi_m}, \quad \frac{\partial^2 f_9}{\partial x_3 \partial x_{11}} = -\frac{\beta^* c_f \mu_m}{\pi_m} + \frac{\rho_m \beta^* c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_9}{\partial x_4 \partial x_{11}} &= -\frac{\theta_p \beta^* c_f \mu_m}{\pi_m} + \frac{\rho_m \theta_p \beta^* c_f \mu_m}{\pi_m}, \quad \frac{\partial^2 f_{11}}{\partial x_2 \partial x_{11}} = -\frac{\rho_m \eta_f \beta^* c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_{11}}{\partial x_3 \partial x_{11}} &= -\frac{\rho_m \beta^* c_f \mu_m}{\pi_m}, \quad \frac{\partial^2 f_{11}}{\partial x_4 \partial x_{11}} = -\frac{\rho_m \theta_p \beta^* c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_7}{\partial x_7 \partial x_9} &= -\frac{\rho_f \eta_m \beta_m c_f \mu_m}{\pi_m}, \quad \frac{\partial^2 f_7}{\partial x_7 \partial x_{10}} = -\frac{\rho_f \beta_m c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_2}{\partial x_7 \partial x_9} &= \frac{\rho_f \eta_m \beta_m c_f \mu_m}{\pi_m}, \quad \frac{\partial^2 f_2}{\partial x_7 \partial x_{10}} = \frac{\rho_f \beta_m c_f \mu_m}{\pi_m}, \qquad \text{(C.3)} \\
\frac{\partial^2 f_2}{\partial x_9 \partial x_9} &= -2\frac{\eta_m \beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}, \quad \frac{\partial^2 f_2}{\partial x_{10} \partial x_{10}} = -2\frac{\beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}, \quad \frac{\partial^2 f_2}{\partial x_1 \partial x_{10}} = \frac{\beta_m c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_1}{\partial x_9 \partial x_9} &= 2\frac{\eta_m \beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}, \quad \frac{\partial^2 f_1}{\partial x_{10} \partial x_{10}} = 2\frac{\beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}, \quad \frac{\partial^2 f_1}{\partial x_1 \partial x_{10}} = -\frac{\beta_m c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_1}{\partial x_8 \partial x_9} &= \frac{\partial^2 f_1}{\partial x_9 \partial x_{11}} = \frac{\eta_m \beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}, \quad \frac{\partial^2 f_1}{\partial x_1 \partial x_9} = -\frac{\eta_m \beta_m c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_2}{\partial x_8 \partial x_9} &= \frac{\partial^2 f_2}{\partial x_9 \partial x_{11}} = -\frac{\eta_m \beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}, \quad \frac{\partial^2 f_2}{\partial x_1 \partial x_9} = \frac{\eta_m \beta_m c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_8}{\partial x_2 \partial x_9} &= \frac{\partial^2 f_8}{\partial x_2 \partial x_{10}} = \frac{\partial^2 f_8}{\partial x_2 \partial x_{11}} = \frac{\eta_f \beta^* c_f \mu_m}{\pi_m}, \quad \frac{\partial^2 f_8}{\partial x_3 \partial x_9} = \frac{\partial^2 f_8}{\partial x_3 \partial x_{10}} = \frac{\partial^2 f_8}{\partial x_3 \partial x_{11}} = \frac{\beta^* c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_8}{\partial x_4 \partial x_9} &= \frac{\partial^2 f_8}{\partial x_4 \partial x_{10}} = \frac{\partial^2 f_8}{\partial x_4 \partial x_{11}} = \frac{\theta_p \beta^* c_f \mu_m}{\pi_m}, \quad \frac{\partial^2 f_9}{\partial x_2 \partial x_9} = \frac{\partial^2 f_9}{\partial x_2 \partial x_{10}} = -\frac{\eta_f \beta^* c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_9}{\partial x_3 \partial x_9} &= \frac{\partial^2 f_9}{\partial x_3 \partial x_{10}} = -\frac{\beta^* c_f \mu_m}{\pi_m}, \quad \frac{\partial^2 f_9}{\partial x_4 \partial x_9} = \frac{\partial^2 f_9}{\partial x_4 \partial x_{10}} = -\frac{\theta_p \beta^* c_f \mu_m}{\pi_m}, \\
\frac{\partial^2 f_1}{\partial x_8 \partial x_{10}} &= \frac{\partial^2 f_1}{\partial x_{10} \partial x_{11}} = \frac{\beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}, \quad \frac{\partial^2 f_2}{\partial x_8 \partial x_{10}} = \frac{\partial^2 f_2}{\partial x_{10} \partial x_{11}} = -\frac{\beta_m c_f \mu_m^2 \pi_f}{\pi_m^2 \mu_f}.
\end{aligned}
$$

It follows from the expressions in (C.3), and Theorem 2.8 of Chapter 2, that

$$\begin{aligned} a &= \sum_{k,i,j=1}^{11} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\ &= \frac{2c_f\mu_m}{\mu_f^2\pi_m^2}\left[A_1 v_2\left(\eta_m w_9 + w_{10}\right) + A_2 v_9\left(\eta_f w_2 + w_3 + \theta_p w_4\right)\right] \\ &- \frac{2c_f\mu_m}{\mu_f^2\pi_m^2}\left[B_1 v_2\left(\eta_m w_9 + w_{10}\right) + B_2 v_9\left(\eta_f w_2 + w_3 + \theta_p w_4\right) + B_3\right], \end{aligned} \tag{C.4}$$

with,

$$\begin{aligned} A_1 &= \beta_m\left[\pi_m\mu_f\left(\xi_f + \mu_f\rho_f\right)w_7 + \beta^*\pi_f\mu_f c_f\left(\eta_f w_2 + w_3 + \theta_p w_4\right)\right], \\ A_2 &= \beta^*\pi_m\mu_f^2\rho_m w_{11}, \\ B_1 &= \beta_m\pi_f\left[\mu_f\left(\xi_m w_{11} + \mu_m\left(w_9 + w_{11}\right)\right) + c_f\mu_m\left(\eta_m w_9 + w_{10}\right)\right], \\ B_2 &= \beta^*\pi_m\mu_f^2\left(w_9 + w_{10} + w_{11}\right), \\ B_3 &= \beta_m\pi_f\mu_m\mu_f v_2 w_{10}\left(w_9 + w_{10}\right), \end{aligned}$$

and,

$$b = \sum_{k,i=1}^{11} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(0,0) = c_f v_9\left(\eta_f w_2 + w_3 + \theta_p w_4\right) > 0.$$

It is evident from (C.4) that the bifurcation coefficient, a, is positive whenever

$$Q_1 > Q_2, \tag{C.5}$$

where,

$$\begin{aligned} Q_1 &= A_1 v_2\left(\eta_m w_9 + w_{10}\right) + A_2 v_9\left(\eta_f w_2 + w_3 + \theta_p w_4\right), \\ Q_2 &= B_1 v_2\left(\eta_m w_9 + w_{10}\right) + B_2 v_9\left(\eta_f w_2 + w_3 + \theta_p w_4\right) + B_3. \end{aligned}$$

Thus, it follows from Theorem 2.8, that the vaccination-free model (3.21) undergoes backward bifurcation whenever Inequality (C.5) holds. □

The inequality (C.5) can be expressed in terms of the re-infection parameter for recovered females, ρ_f, as

$$\rho_f > \rho_f^c, \tag{C.6}$$

where,

$$\begin{aligned}\rho_f^c &= \frac{B_1}{\beta_m \pi_m \mu_f^2} + \frac{B_2 v_9 \left(\eta_f w_2 + w_3 + \theta_p w_4\right)}{v_2 \left(\eta_m w_9 + w_{10}\right) \beta_m \pi_m \mu_f^2} + \frac{B_3}{v_2 \left(\eta_m w_9 + w_{10}\right) \beta_m \pi_m \mu_f^2} \\ &- \frac{A_2 v_9 \left(\eta_f w_2 + w_3 + \theta_p w_4\right)}{v_2 \left(\eta_m w_9 + w_{10}\right) \beta_m \pi_m \mu_f^2} - \frac{\beta^* \pi_f c_f \left(\eta_f w_2 + w_3 + \theta_p w_4\right)}{\pi_m \mu_f} - \frac{\xi_f}{\mu_f} > 0.\end{aligned}$$

Thus, this study shows that the vaccination-free model (3.21) undergoes backward bifurcation whenever the re-infection parameter for females (ρ_f) exceeds a certain threshold (ρ_f^c). Models with re-infection, such as those for the transmission dynamics of *mycobacterium tuberculosis* [14, 60, 86], are known to undergo backward bifurcation. It is instructive, therefore, to check whether or not the re-infection of recovered individuals in the model (3.21) induces the phenomenon of backward bifurcation in the model. This is explored below.

C.1 Effect of Re-infection of Recovered Individuals on Backward Bifurcation

It is worth exploring the possible effect the re-infection of recovered individuals may have on the backward bifurcation property of the vaccination-free model (3.21). Setting $\rho_f = \rho_m = 0$ (and, for computational convenience, $\xi_f = \xi_m = 0$) in (C.5) shows that

$$a = \frac{2 c_f \mu_m}{\mu_f^2 \pi_m^2} \left[\left(A_{11} - B_{11}\right) v_2 - B_{22} v_9 \left(\eta_f w_2 + w_3 + \theta_p w_4\right)\right], \tag{C.7}$$

with,

$$\begin{aligned}
A_{11} &= \beta^*\mu_f\beta_m\pi_f c_f\left(\eta_f w_2 + w_3 + \theta_p w_4\right)\left(\eta_m w_9 + w_{10}\right), \\
B_{11} &= \beta^*\pi_f\mu_m\left[\left(\eta_m w_9 + w_{10}\right)\left(\beta^* c_f\left(\eta_m w_9 + w_{10}\right) + \mu_f\left(w_9 + w_{10}\right)\right) + \mu_f w_{10} w_{11}\right], \\
B_{22} &= \mu_f^2\pi_m\beta^*\left(w_9 + w_{10} + w_{11}\right).
\end{aligned}$$

Using the value of β^* from (C.2) gives (here the eigenvectors v_9 and w_9 are given the value unity)

$$\begin{aligned}
A_{11} - B_{11} &= -\frac{\pi_f^2\mu_m\left(\sigma_m + \mu_m\right)}{\pi_m c_f\mu_f\left(\psi_m + \mu_m\right)\left(\eta_m\psi_m + \eta_m\mu_m + \sigma_m\right)}\left[\eta_m\mu_f\psi_m\left(\mu_m\psi_m + 2\mu_m^2 + 2\beta_m c_f\sigma_m\right)\right. \\
&+ \beta_m c_f\eta_m\psi_m\mu_m\left(2\eta_m\mu_m + \eta_m\psi_m + 2\sigma_m\right) + \eta_m\mu_m^2\left(\beta_m c_f\mu_m\eta_m + \mu_m\mu_f + 2\beta_m c_f\sigma_m\right) \\
&+ \left.\sigma_m\left(\beta_m c_f\mu_m\sigma_m + 2\mu_f\sigma_m\psi_m + \eta_m\mu_m\mu_f\psi_m + \mu_m\mu_f\psi_m + \mu_f\mu_m^2\right)\right] < 0, \\
B_{22} &= \frac{\pi_f^2\mu_m\left(\sigma_m + \mu_m\right)^2}{\pi_m c_f} > 0. \qquad \text{(C.8)}
\end{aligned}$$

Hence, it follows from (C.7), with (C.8), that the bifurcation coefficient $a < 0$ for the vaccination-free model (3.21) with $\rho_f = \rho_m = \xi_f = \xi_m = 0$. Thus, it follows from Item (iv) of Theorem 2.8 of Chapter 2 that the vaccination-free model (3.21) does not undergo backward bifurcation in the absence of re-infection and loss of infection-acquired immunity ($\rho_f = \rho_m = \xi_f = \xi_m = 0$). This fact can further be illustrated by substituting $\rho_f = \rho_m = 0$ in the quartic (3.34) in Section 3.4.2. Doing so shows that the non-zero equilibria of the model (3.21), with $\rho_f = \rho_m = 0$, reduces to

$$a_1\lambda_m^{**} - b_1 = 0, \qquad \text{(C.9)}$$

where,

$$
\begin{aligned}
a_1 &= \frac{\beta_f c_f \pi_f \mu_m}{\pi_m} \left(\eta_f n_1 g_2 + n_1 \sigma_f + \theta_p h_1 \sigma_f\right) g_3 \mu_m \left[\left(\sigma_m + \psi_m + \mu_m\right) \xi_m + \left(\sigma_m + \mu_m\right)\left(\psi_m + \mu_m\right)\right] \\
&+ \mu_m g_4 g_5 g_6 \xi_f \sigma_f \psi_f \left(1 - r_f\right)\left[\mu_f + \alpha_f\left(1 - \kappa_f\right)\right] + \mu_f \left[\mu_f^2 \left(\xi_f + \mu_f\right) + \sigma_f \xi_f \left(\alpha_f + \mu_f\right)\right] \\
&+ \mu_f \left(\sigma_f + \xi_f + \mu_f\right)\left[\alpha_f \left(\psi_f + \mu_f\right) + \mu_f \psi_f\right],
\end{aligned}
$$

$$
b_1 = \mu_f \mu_m n_1 g_1 g_2 g_3 g_4 g_5 g_6 \left(\mathcal{R}_0^2 - 1\right).
$$

It is clear from (C.9) that the coefficient $a_1 > 0$ and $b_1 > 0$ for $\mathcal{R}_0 > 1$ (furthermore, $b_1 < 0$ if $\mathcal{R}_0 < 1$). Thus, the linear system (C.9) has a unique positive solution, given by $\lambda_m^{**} = \frac{b_1}{a_1}$, whenever $\mathcal{R}_0 > 1$ (the linear system has no positive endemic equilibrium when $\mathcal{R}_0 < 1$).

Lemma C.1. *The vaccination-free model (3.21), with $\rho_f = \rho_m = 0$, has a unique endemic equilibrium whenever $\mathcal{R}_0 > 1$, and no endemic equilibrium whenever $\mathcal{R}_0 < 1$.*

The absence of endemic equilibria in (C.9) when $\mathcal{R}_0 < 1$ suggests that the phenomenon backward bifurcation is not possible in the vaccination-free model (3.21), when $\rho_f = \rho_m = 0$ (since backward bifurcation requires the existences of multiple endemic equilibria when $\mathcal{R}_0 < 1$). Thus, it can be concluded from the analyses in this Appendix (and Theorem 3.7) that the backward bifurcation property of the vaccination-free model (3.21) is caused by the re-infection of recovered individuals.

Appendix D

Proof of Theorem 3.7

Proof. Consider the vaccination-free model (3.21) in the absence of re-infection (i.e., $\rho_f = \rho_m = 0$). The proof is based on using a Comparison Theorem (see Theorem 2.10). The equations for the infected components of the vaccination-free model (3.21), with $\rho_f = \rho_m = 0$, can be re-written as (it should be noted the system (D.1) satisfies the Type K condition [87], as discussed in Section 2.7):

$$\frac{d}{dt}\begin{pmatrix} E_f(t) \\ I_f(t) \\ P(t) \\ C(t) \\ R_f(t) \\ E_m(t) \\ I_m(t) \\ R_m(t) \end{pmatrix} = (\mathcal{F}-\mathcal{H})\begin{pmatrix} E_f(t) \\ I_f(t) \\ P(t) \\ C(t) \\ R_f(t) \\ E_m(t) \\ I_m(t) \\ R_m(t) \end{pmatrix} - J\begin{pmatrix} E_f(t) \\ I_f(t) \\ P(t) \\ C(t) \\ R_f(t) \\ E_m(t) \\ I_m(t) \\ R_m(t) \end{pmatrix}, \tag{D.1}$$

where the matrices $\mathcal{F}$ and $\mathcal{H}$ are as defined in Section 3.3.1, and

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

with,

$$J_1 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & \frac{\eta_m \beta_m c_f \pi_f \mu_m}{\mu_f \pi_m} & \frac{\beta_m c_f \pi_f \mu_m}{\mu_f \pi_m} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$J_2 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \eta_f \beta_f c_f & \beta_f c_f & \theta_p \beta_f c_f & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

It should be noted that J_1 and J_2 are non-negative matrices. Furthermore, since,

$$S_f(t) \leq N_f(t) \leq \frac{\pi_f}{\mu_f} \quad \text{and} \quad S_m(t) \leq N_m(t) \leq \frac{\pi_m}{\mu_m} \quad (\text{for all t} \geq 0 \text{ in } \mathcal{D}_1),$$

it follows that,

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

so that J is a non-negative matrix. It follows from (D.1) that

$$\frac{d}{dt}\begin{pmatrix} E_f(t) \\ I_f(t) \\ P(t) \\ C(t) \\ R_f(t) \\ E_m(t) \\ I_m(t) \\ R_m(t) \end{pmatrix} \leq (\mathcal{F}-\mathcal{H}) \begin{pmatrix} E_f(t) \\ I_f(t) \\ P(t) \\ C(t) \\ R_f(t) \\ E_m(t) \\ I_m(t) \\ R_m(t) \end{pmatrix}. \tag{D.2}$$

Using the fact that the eigenvalues of the matrix $\mathcal{F}-\mathcal{H}$ all have negative real parts (see local stability result in Section 3.3.1, where $\rho(\mathcal{F}\mathcal{H}^{-1}) < 1$ if $\mathcal{R}_0 < 1$, which is equivalent to $\mathcal{F}-\mathcal{H}$ having eigenvalues with negative real parts when $\mathcal{R}_0 < 1$), it follows that the linearized differential inequality system (D.2) is stable whenever $\mathcal{R}_0 < 1$. Thus, it follows, by Comparison Theorem [58] (see also Theorem 2.10), that

$$\lim_{t\to\infty}(E_f(t), I_f(t), P(t), C(t), E_m(t), I_m(t)) \to (0,0,0,0,0,0)\,.$$

Substituting $E_f = I_f = P = C = I_m = E_m = 0$ into the first and eighth equations of the vaccination-free model (3.21) gives $S_f(t) \to S_f^*$ and $S_m(t) \to S_m^*$ as $t \to \infty$ for $\mathcal{R}_0 < 1$. Thus,

$$\lim_{t\to\infty}(S_f(t), E_f(t), I_f(t), P(t), C(t), R_c(t), R_f(t), S_m(t), E_m(t), I_m(t), R_m(t)) = \mathcal{E}_0,$$

so that the DFE, $\mathcal{E}_0$, of the vaccination-free model (3.21) is GAS in $\mathcal{D}_1$ whenever $\mathcal{R}_0 < 1$ and $\rho_f = \rho_m = 0$. □

Appendix E

Proof of Theorem 3.10

Proof. The proof of Theorem 3.10 is also based on using Centre Manifold Theory, as shown in Appendix C. Solving for β_f from $\mathcal{R}_v = 1$ gives

$$\beta_f = \beta^* = \frac{n_1 g_1 g_2 g_4 g_5 \pi_m \mu_f}{\beta_m c_f^2 \pi_f \mu_m \left(\eta_m g_5 + \sigma_m\right)\left[\eta_f n_1 g_2 + \sigma_f \left(n_1 + \theta_p h_1\right)\right]\left(1 - \varepsilon_v \varphi_f\right)}. \tag{E.1}$$

Eigenvectors of $J(\mathcal{E}_0^V)\,|_{\beta_f=\beta^*}$:

For the system (3.19), it can be shown that the associated matrix $J(\mathcal{E}_0^V)\,|_{\beta_f=\beta^*} = J_{\beta^*}^V$ has a left eigenvector (associated with the zero eigenvalue) given by,

$$\boldsymbol{v} = \left[v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12}\right]^T,$$

with,

$$\begin{aligned}
v_1 &= 0, \quad v_2 = 0, \quad v_3 = \frac{\beta^* c_f \left(\sigma_f n_1 + \sigma_f h_1 \theta_p + n_1 g_2 \eta_f\right) v_{10}}{n_1 g_1 g_2}, \quad v_4 = \frac{\beta^* c_f (n_1 + \theta_p h_1) v_{10}}{n_1 g_2}, \\
v_5 &= \frac{\theta_p \beta^* c_f v_{10}}{n_1}, \quad v_6 = 0, \quad v_7 = 0, \quad v_8 = 0, \quad v_9 = 0, \quad v_{10} = v_{10} > 0, \\
v_{11} &= \frac{\beta_m c_f \mu_m \pi_f (1 - \varepsilon_v \varphi_f) v_3}{g_5 \pi_m \mu_f}, \quad v_{12} = 0.
\end{aligned}$$

Furthermore, $J^V_{\beta^*}$ has a right eigenvector (associated with the zero eigenvalue) given by,

$$\boldsymbol{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}, w_{11}, w_{12}]^T,$$

where,

$$\begin{aligned}
w_1 &= \frac{\xi_f w_8}{\mu_f} - \frac{\beta_m c_f \mu_m \pi_f (1-\varphi_f)(\eta_m w_{10} + w_{11})}{\mu_f^2 \pi_m}, \quad w_2 = -\frac{\beta_m c_f \mu_m \pi_f \varphi_f (1-\varepsilon_v)(\eta_m w_{10} + w_{11})}{\mu_f^2 \pi_m}, \\
w_3 &= \frac{\beta_m c_f \mu_m \pi_f (\sigma_m + \eta_m g_5)(1-\varepsilon_v \varphi_f) w_{10}}{\mu_f \pi_m g_1 g_5}, \quad w_4 = \frac{\sigma_f w_3}{g_2}, \quad w_5 = \frac{h_1 w_4}{n_1}, \quad w_6 = \frac{h_1 h_2 w_4}{n_1 n_2}, \\
w_7 &= \frac{\gamma_f w_6}{\mu_f}, \quad w_8 = \frac{m_1 w_4 + m_2 w_5}{g_3}, \quad w_9 = \frac{\xi_m w_{12}}{\mu_m} - \frac{\beta^* c_f (\eta_f w_3 + w_4 + \theta_p w_5)}{\mu_m}, \\
w_{10} &= w_{10} > 0, \quad w_{11} = \frac{\sigma_m w_{10}}{g_5}, \quad w_{12} = \frac{\psi_m w_{11}}{g_6}.
\end{aligned}$$

Computations of bifurcation coefficients, a and b:

For the model (3.19), it can be shown that the associated bifurcation coefficients, a and b are given, respectively, by

$$\begin{aligned}
a &= \sum_{k,i,j=1}^{12} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \\
&= \frac{2 c_f \mu_m}{\mu_f^2 \pi_m^2} \left[A_{111} v_3 (\eta_m w_{10} + w_{11}) + A_{222} v_{10} (\eta_f w_3 + w_4 + \theta_p w_5) \right], \qquad \text{(E.2)} \\
&- \frac{2 c_f \mu_m}{\mu_f^2 \pi_m^2} \left[B_{111} v_3 (\eta_m w_{10} + w_{11}) + B_{222} v_{10} (\eta_f w_3 + w_4 + \theta_p w_5) \right],
\end{aligned}$$

and,

$$b = \sum_{k,i=1}^{12} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(0,0) = c_f v_{10} (\eta_f w_3 + w_4 + \theta_p w_5) > 0.$$

In (E.2),

$$\begin{aligned}
A_{111} &= \beta_m \left[\pi_m \mu_f \left(\xi_f + \mu_f \rho_f\right) w_8 + \beta^* \mu_f c_f \pi_f \left(1 - \varepsilon_v \varphi_f\right) \left(\eta_f w_3 + w_4 + \theta_p w_5\right)\right] \\
&+ \beta_m^2 c_f \mu_m \pi_f \varphi_f \left(\eta_m w_{10} + w_{11}\right), \\
A_{222} &= \beta^* \pi_m \mu_f^2 \rho_m w_{12}, \\
B_{111} &= \beta_m \mu_f \pi_f \left(1 - \varepsilon_v \varphi_f\right) \left[\xi_m w_{12} + \mu_m \left(w_{10} + w_{11} + w_{12}\right)\right] + \beta_m^2 c_f \mu_m \pi_f \left(\eta_m w_9 + w_{10}\right), \\
B_{222} &= \beta^* \pi_m \mu_f^2 \left(w_{10} + w_{11} + w_{12}\right).
\end{aligned}$$

Hence, it follows from Theorem 2.8 that the vaccination model (3.19) undergoes backward bifurcation at $\mathcal{R}_v = 1$ if the bifurcation parameter a, given in (E.2), is positive. It is evident from (E.2) that $a > 0$ whenever

$$Q_3 > Q_4, \tag{E.3}$$

where,

$$\begin{aligned}
Q_3 &= A_{111} v_3 \left(\eta_m w_{10} + w_{11}\right) + A_{222} v_{10} \left(\eta_f w_3 + w_4 + \theta_p w_5\right), \\
Q_4 &= B_{111} v_3 \left(\eta_m w_{10} + w_{11}\right) + B_{222} v_{10} \left(\eta_f w_3 + w_4 + \theta_p w_5\right).
\end{aligned}$$

□

E.1 Non-existence of Backward Bifurcation

Consider the vaccination model (3.19) in the absence of re-infection ($\rho_f = \rho_m = 0$). Setting $\rho_f = \rho_m = 0$ (and, for simplicity, $\xi_f = \xi_m = 0$) into the expression for the bifurcation coefficient, a in (E.2), and using β^* for β_f in (E.1), shows that (here, the eigenvectors v_{10}

and w_{10} are given the value unity)

$$a = -\frac{2\beta_m c_f \mu_m \left(\sigma_m + \mu_m\right)\left(\eta_m \psi_m + \eta_m \mu_m + \sigma_m\right)\left[1 - \varepsilon_v \varphi_f \left(2 - \varepsilon_v\right)\right]}{\pi_m \mu_f \left(\mu_m + \psi_m\right)\left(1 - \varepsilon_v \varphi_f\right)} - \frac{2\left(\sigma_m + \mu_m\right)^2}{\pi_m} < 0. \tag{E.4}$$

It should be stated that, in (E.4), $0 \leq \varepsilon_v, \varphi_f \leq 1$. Hence, it follows from (E.4), that the bifurcation coefficient, $a < 0$, for the vaccination model (3.19) with $\rho_f = \rho_m = \xi_f = \xi_m = 0$. Thus, it follows from Item (iv) of Theorem 2.8 that the vaccination model (3.19) does not undergo backward bifurcation in the absence of re-infection.

Appendix F

Proof of Theorem 3.11

Proof. Consider the vaccination model (3.19) with $\rho_f = \rho_m = 0$ and $\mathcal{R}_v < 1$. Furthermore, consider the following Lyapunov function (where g_1, g_2, g_4, g_5, n_1 and h_1 are as defined in Section 3.3.3):

$$\begin{aligned}\mathcal{L} &= \frac{\beta_f c_f \left(\eta_f n_1 g_2 + \sigma_f n_1 + \theta_p \sigma_f h_1\right)\left(\eta_m g_5 + \sigma_m\right)}{n_1 g_1 g_2 g_4 \mathcal{R}_v^2} E_f + \frac{\beta_f c_f \left(n_1 + \theta_p h_1\right)\left(\eta_m g_5 + \sigma_m\right)}{n_1 g_2 g_4 \mathcal{R}_v^2} I_f \\ &+ \frac{\beta_f c_f \theta_p \left(\eta_m g_5 + \sigma_m\right)}{n_1 g_4} P + \frac{\left(\eta_m g_5 + \sigma_m\right)}{g_4} E_m + I_m,\end{aligned}$$

with Lyapunov derivative (where, as in Chapter 2, the dot denotes the differentiation with respect to t) given by

$$\begin{aligned}\dot{\mathcal{L}} &= \frac{\beta_f c_f \left(\eta_f n_1 g_2 + \sigma_f n_1 + \theta_p \sigma_f h_1\right)\left(\eta_m g_5 + \sigma_m\right)}{n_1 g_1 g_2 g_4 \mathcal{R}_v^2} \dot{E}_f + \frac{\beta_f c_f \left(n_1 + \theta_p h_1\right)\left(\eta_m g_5 + \sigma_m\right)}{n_1 g_2 g_4 \mathcal{R}_v^2} \dot{I}_f \\ &+ \frac{\beta_f c_f \theta_p \left(\eta_m g_5 + \sigma_m\right)}{n_1 g_4} \dot{P} + \frac{\left(\eta_m g_5 + \sigma_m\right)}{g_4} \dot{E_m} + \dot{I_m},\end{aligned}$$

so that,

$$\begin{aligned}
\dot{\mathcal{L}} &= \frac{\beta_f c_f \left(\eta_f n_1 g_2 + \sigma_f n_1 + \theta_p \sigma_f h_1\right)\left(\eta_m g_5 + \sigma_m\right)}{n_1 g_1 g_2 g_4 \mathcal{R}_v^2}\left\{\frac{\beta_m c_f \left(\eta_m E_m + I_m\right)}{N_m}\left[S_f + (1-\varepsilon_v)V_f\right] - g_1 E_f\right\} \\
&+ \frac{\beta_f c_f \left(n_1 + \theta_p h_1\right)\left(\eta_m g_5 + \sigma_m\right)}{n_1 g_2 g_4 \mathcal{R}_v^2}\left(\sigma_f E_f - g_2 I_f\right) + \frac{\beta_f c_f \theta_p \left(\eta_m g_5 + \sigma_m\right)}{n_1 g_4}\left(h_1 I_f - n_1 P\right) \\
&+ \frac{\left(\eta_m g_5 + \sigma_m\right)}{g_4}\left[\frac{\beta_f c_f \left(\eta_f E_f + I_f + \theta_p P\right)}{N_m} S_m - g_4 E_m\right] + \left(\sigma_m E_m - g_5 I_m\right).
\end{aligned}$$

Since $S_f(t) + V_f(t) \leq N_f(t) \leq \frac{\pi_f}{\mu_f}$, $S_m(t) \leq N_m(t) \leq \frac{\pi_m}{\mu_m}$ for all t in $\mathcal{D}$, and $0 < \varepsilon_v < 1$, it follows that

$$\begin{aligned}
\dot{\mathcal{L}} &\leq \left[-\frac{\beta_f c_f \left(\eta_f n_1 g_2 + \sigma_f n_1 + \theta_p \sigma_f h_1\right)\left(\eta_m g_5 + \sigma_m\right)}{n_1 g_1 g_2 g_4 \mathcal{R}_v^2} g_1 + \frac{\beta_f c_f \left(n_1 + \theta_p h_1\right)\left(\eta_m g_5 + \sigma_m\right)}{n_1 g_2 g_4 \mathcal{R}_v^2}\sigma_f\right] E_f \\
&+ \left[-\frac{\beta_f c_f \left(n_1 + \theta_p h_1\right)\left(\eta_m g_5 + \sigma_m\right)}{n_1 g_2 g_4 \mathcal{R}_v^2} g_2 + \frac{\beta_f c_f \theta_p \left(\eta_m g_5 + \sigma_m\right)}{n_1 g_4} h_1\right] I_f \\
&+ \left[-\frac{\beta_f c_f \left(\eta_m g_5 + \sigma_m\right)}{g_4} + \frac{\beta_f c_f \left(\eta_m g_5 + \sigma_m\right)}{g_4 \mathcal{R}_v^2}\right]\left(\eta_f E_f + I_f\right) \\
&+ \left[-g_5 + \frac{\beta_m c_f^2 \pi_f \mu_m \left(\eta_m g_5 + \sigma_m\right)\left(\eta_f n_1 g_2 + \sigma_f n_1 + \sigma_f \theta_p h_1\right)\left(1 - \varepsilon_v \varphi_f\right)}{n_1 g_1 g_2 g_4 \pi_m \mu_f \mathcal{R}_v^2}\right]\left(\eta_m E_m + I_m\right) \\
&+ \left[-\frac{\beta_f c_f \theta_p \left(\eta_m g_5 + \sigma_m\right)}{n_1 g_4} n_1 + \frac{\beta_f c_f \theta_p \left(\eta_m g_5 + \sigma_m\right)}{g_4}\right] P,
\end{aligned}$$

$$\dot{\mathcal{L}} = \frac{\eta_f \beta_f c_f \left(\eta_m g_5 + \sigma_m\right)}{g_4 \mathcal{R}_v^2} \left(\mathcal{R}_v^2 - 1\right) E_f + \frac{\beta_f c_f \left(\eta_m g_5 + \sigma_m\right)\left(n_1 + \theta_p h_1\right)}{n_1 g_4 \mathcal{R}_v^2} \left(\mathcal{R}_v^2 - 1\right) I_f$$

$$+ \quad g_5 \left(\mathcal{R}_v^2 - 1\right)\left(\eta_m E_m + I_m\right) < 0 \quad \text{for} \quad \mathcal{R}_v^2 < 1.$$

Since all the model parameters are non-negative, it follows that $\dot{\mathcal{L}} < 0$ if $\mathcal{R}_v^2 < 1$. Hence, it follows from the LaSalle's Invariance Principle [59] that every solution of the vaccination model (3.19), with $\rho_f = \rho_m = 0$ and initial conditions in $\mathcal{D}$, converges to the DFE, $\mathcal{E}_0^V$, as $t \to \infty$. That is, $(E_f(t), I_f(t), P(t), C(t), E_m(t), I_m(t)) \to (0, 0, 0, 0, 0, 0)$ as $t \to \infty$. Substituting $E_f = I_f = P = C = I_m = E_m = 0$ in the first, second and ninth equations of the vaccination model (3.19) gives $S_f(t) \to S_f^*$, $V_f(t) \to V_f^*$ and $S_m(t) \to S_m^*$ as $t \to \infty$ for $\mathcal{R}_v < 1$. Thus,

$$\lim_{t\to\infty} (S_f(t), V_f(t), E_f(t), I_f(t), P(t), C(t), R_c(t), R_f(t), S_m(t), E_m(t), I_m(t), R_m(t)) = \mathcal{E}_0^V,$$

so that, the DFE, $\mathcal{E}_0^V$, of the vaccination model (3.19) is GAS in $\mathcal{D}$ whenever $\mathcal{R}_v < 1$ and $\rho_f = \rho_m = 0$. □

Appendix G

Positivity of $\mathcal{R}_{fl}, \mathcal{R}_{ml}, \mathcal{R}_{fh}$ and $\mathcal{R}_{mh}$

Recall from Section 4.3.1 (with all the associated variables as defined in Section 4.3.1) that

$$\begin{aligned}
\mathcal{R}_{fl} &= \frac{\beta_m^l c_f \pi_f \mu_m \left(1-\varepsilon_v \varphi_f^q\right) B_1}{\mu_f \pi_m D_1 D_2 D_3}, \quad \mathcal{R}_{fh} = \frac{\beta_m^h c_f \pi_f \mu_m \left[1-\varepsilon_v \left(\varphi_f^b + \varphi_f^q\right)\right] (Q_1+Q_2+Q_3)}{\mu_f \pi_m D_5 D_6 Q_4}, \\
\mathcal{R}_{ml} &= \frac{\beta_f^l c_f \left(1-\varepsilon_v \varphi_m^q\right) B_2}{A_1 A_2 A_3}, \quad \mathcal{R}_{mh} = \frac{\beta_f^h c_f \left(1-\varepsilon_q \varphi_m^q\right) (Q_5+Q_6+Q_7)}{A_5 A_6 Q_8}.
\end{aligned}$$

The following steps are taken to prove that the quantities above are positive. It can be shown that:

$$B_1 = \eta_m^l D_3 D_2 + k_1 D_3 + \theta_m^l k_2 k_1 > 0,$$

$$\begin{aligned}
Q_1 &= \eta_m^h \left(D_6 D_7 D_8 D_9 - k_8 j_2 D_6 D_7 - k_8 k_7 j_1 D_6\right) \\
&= \eta_m^h D_6 \left(\omega_m + \mu_m\right)\left(u_m + \mu_m\right)\left(\alpha_m^h + \mu_m\right) \\
&+ \eta_m^h D_6 z_m \mu_m \left(\alpha_m^h + \mu_m\right) + \eta_m^h D_6 d_m u_m z_m \left(\alpha_m^h + s_{2m}\mu_m\right) + \eta_m^h D_6 u_m z_m \mu_m \left(1-s_{2m}\right) \\
&+ \eta_m^h D_6 u_m z_m \left(1-d_m\right) \alpha_m^h \left[s_{1m}\left(1-k_m^h\right) + k_m^h \left(1-s_{2m}\right)\right] > 0,
\end{aligned}$$

$$
\begin{aligned}
Q_2 &= k_5 D_7 D_8 D_9 - k_5 k_8 j_2 D_7 - k_5 k_7 k_8 j_1 = k_5 \left(\omega_m + \mu_m\right)\left(u_m + \mu_m\right)\left(\alpha_m^h + \mu_m\right) \\
&+ k_5 z_m \mu_m \left(\alpha_m^h + \mu_m\right) + k_5 d_m u_m z_m \left(\alpha_m^h + s_{2m}\mu_m\right) + k_5 u_m z_m \mu_m \left(1 - s_{2m}\right) \\
&+ k_5 u_m z_m \left(1 - d_m\right)\alpha_m^h \left[s_{1m}\left(1 - k_m^h\right) + k_m^h \left(1 - s_{2m}\right)\right] > 0,
\end{aligned}
$$

$$
\begin{aligned}
Q_3 &= \theta_m^h \left(k_5 k_6 D_8 D_9 - k_5 k_6 k_8 j_2\right) \\
&= \theta_m^h k_5 k_6 \left(\omega_m + \mu_m\right)\left(u_m + \mu_m\right) + \theta_m^h k_5 k_6 z_m u_m \left(1 - s_{2m}\right) \\
&+ \theta_m^h k_5 k_6 z_m \left(d_m u_m s_{2m} + \mu_m\right) > 0,
\end{aligned}
$$

$$
\begin{aligned}
Q_4 &= D_7 D_8 D_9 - k_8 j_2 D_7 - k_7 k_8 j_1 \\
&= \left(\omega_m + \mu_m\right)\left(u_m + \mu_m\right)\left(\alpha_m^h + \mu_m\right) + z_m \mu_m \left(\alpha_m^h + \mu_m\right) \\
&+ d_m u_m z_m \left(\alpha_m^h + s_{2m}\mu_m\right) + u_m z_m \mu_m \left(1 - s_{2m}\right) \\
&+ u_m z_m \left(1 - d_m\right)\alpha_m^h \left[s_{1m}\left(1 - k_m^h\right) + k_m^h \left(1 - s_{2m}\right)\right] > 0,
\end{aligned}
$$

$$
B_2 = \eta_f^l A_3 A_2 + b_1 A_3 + \theta_f^l b_2 b_1 > 0,
$$

$$
\begin{aligned}
Q_5 &= \eta_f^h \left(A_6 A_7 A_8 A_9 - b_8 g_2 A_6 A_7 - b_8 b_7 g_1 A_6\right) \\
&= \eta_f^h A_6 \left(\omega_f + \mu_f\right)\left(u_f + \mu_f\right)\left(\alpha_f^h + \mu_f\right) \\
&+ \eta_f^h A_6 z_f \mu_f \left(\alpha_f^h + \mu_f\right) + \eta_f^h A_6 d_f u_f z_f \left(\alpha_f^h + s_{2f}\mu_f\right) + \eta_f^h A_6 u_f z_f \mu_f \left(1 - s_{2f}\right) \\
&+ \eta_f^h A_6 u_f z_f \left(1 - d_f\right)\alpha_f^h \left[s_{1f}\left(1 - k_f^h\right) + k_f^h \left(1 - s_{2f}\right)\right] > 0,
\end{aligned}
$$

$$
\begin{aligned}
Q_6 &= b_5 A_7 A_8 A_9 - b_5 b_8 g_2 A_7 - b_5 b_7 b_8 g_1 \\
&= b_5 \left(\omega_f + \mu_f\right)\left(u_f + \mu_f\right)\left(\alpha_f^h + \mu_f\right) \\
&+ b_5 z_f \mu_f \left(\alpha_f^h + \mu_f\right) + b_5 d_f u_f z_f \left(\alpha_f^h + s_{2f}\mu_f\right) + b_5 u_f z_f \mu_f \left(1 - s_{2f}\right) \\
&+ b_5 u_f z_f \left(1 - d_f\right)\alpha_f^h \left[s_{1f}\left(1 - k_f^h\right) + k_f^h \left(1 - s_{2f}\right)\right] > 0,
\end{aligned}
$$

$$
\begin{aligned}
Q_7 &= \theta_f^h \left(b_5 b_6 A_8 A_9 - b_5 b_6 b_8 g_2\right) \\
&= \theta_f^h b_5 b_6 \left(\omega_f + \mu_f\right)\left(u_f + \mu_f\right) + \theta_f^h b_5 b_6 z_f u_f \left(1 - s_{2f}\right) \\
&+ \theta_f^h b_5 b_6 z_f \left(d_f u_f s_{2f} + \mu_f\right) > 0,
\end{aligned}
$$

$$
\begin{aligned}
Q_8 &= A_7 A_8 A_9 - b_8 g_2 A_7 - b_7 b_8 g_1 \\
&= \left(\omega_f + \mu_f\right)\left(u_f + \mu_f\right)\left(\alpha_f^h + \mu_f\right) + z_f \mu_f \left(\alpha_f^h + \mu_f\right) \\
&+ d_f u_f z_f \left(\alpha_f^h + s_{2f}\mu_f\right) + u_f z_f \mu_f \left(1 - s_{2f}\right) \\
&+ u_f z_f \left(1 - d_f\right)\alpha_f^h \left[s_{1f}\left(1 - k_f^h\right) + k_f^h \left(1 - s_{2f}\right)\right] > 0.
\end{aligned}
$$

Thus,

$$
\mathcal{R}_{fl} > 0, \;\; \mathcal{R}_{ml} > 0, \;\; \mathcal{R}_{fh} > 0 \;\text{ and }\; \mathcal{R}_{mh} > 0.
$$

Appendix H

Coefficients of the Polynomial (4.42)

$$
\begin{aligned}
Y_0 &= b_{02}^3 a_{33} + a_{02}a_{22}b_{02}b_{33} + b_{33}^3 a_{00} + b_{33}^2 b_{02}a_{11} > 0,\\[2ex]
Y_1 &= 2b_{22}b_{33}\left(a_{00}b_{33} + a_{11}b_{02}\right) + b_{33}^2\left(b_{22}a_{00} - b_{02}a_0 + b_{01}a_{11}\right) + a_{02}a_{22}\left(b_{02}b_{22} + b_{01}b_{33}\right) + 2b_{02}^2 b_{01}a_{33}\\
&+ b_{02}b_{33}\left(b_{01}a_{22} - b_{02}a_{01}\right) + b_{02}^2\left(b_{01}a_{33} - b_{02}a_{02}\right),\\[2ex]
Y_2 &= b_{02}^2\left(b_0 a_{33} - b_{01}a_{02}\right) + 2b_{02}b_{01}\left(b_{01}b_{33} - b_{02}a_{02}\right) + b_{02}b_{33}\left(2b_0 b_{02} + b_{01}^2\right) + b_{02}b_{33}\left(b_0 a_{22} - b_{01}a_{01}\right)\\
&+ a_{02}a_{22}\left(b_{02}b_{11} + b_{01}b_{22} + b_0 b_{33}\right) + \left(b_{02}b_{22} + b_{01}b_{33}\right)\left(b_{01}a_{22} - b_{02}a_{01}\right)\\
&+ \left(2b_{11}b_{33} + b_{22}^2\right)\left(a_{00}b_{33} + a_{11}b_{02}\right) + 2b_{33}b_{22}\left(b_{22}a_{00} - b_{02}a_0 + b_{01}a_{11}\right)\\
&+ b_{33}^2\left(b_{11}a_{00} + b_0 a_{11} - b_{01}a_0\right),\\[2ex]
Y_3 &= -b_{02}^2 b_0 a_{02} + 2b_{02}b_{01}\left(b_0 a_{33} - b_{01}a_{02}\right) + \left(b_{02}b_0 + b_{01}^2 + b_0 b_{02}\right)\left(b_{01}a_{33} - b_{02}a_{02}\right) - a_{01}b_0 b_{02}b_{33}\\
&+ 2b_0 b_{01}b_{02}a_{33} + a_{02}a_{22}\left(b_{02}b_{00} + b_{01}b_{11} + b_0 b_{22}\right) + 2b_{22}b_{33}\left(a_{11}b_0 + a_{00}b_{11} - b_{01}a_0\right)\\
&+ \left(b_{01}a_{22} - b_{02}a_{01}\right)\left(b_{02}b_{11} + b_{01}b_{22} + b_0 b_{33}\right) + \left(a_{00}b_{33} + a_{11}b_{02}\right)\left(2b_{33}b_{00} + 2b_{22}b_{11}\right)\\
&+ \left(b_0 a_{22} - b_{01}a_{01}\right)\left(b_{02}b_{22} + b_{01}b_{33}\right) + \left(b_{22}a_{00} - b_{02}a_0 + b_{01}a_{11}\right)\left(2b_{33}b_{11} + b_{22}^2\right)\\
&+ b_{33}^2\left(a_{00}b_{00} - a_0 b_0\right),
\end{aligned}
$$

$$
\begin{aligned}
Y_4 &= -2b_0a_{02}b_{02}b_{01} + \left(2b_0b_{02} + b_{01}^2\right)(b_0a_{33} - b_{01}a_{02}) + 2b_0b_{01}(b_{01}a_{33} - a_{02}b_{02}) + a_{02}a_{22}b_{01}b_{00} \\
&+ a_{02}a_{22}b_0b_{11} + (b_{01}a_{22} - b_{02}a_{01})(b_{02}b_{00} + b_{01}b_{11} + b_0b_{22}) - a_{01}b_0(b_{02}b_{22} + b_{01}b_{33}) \\
&+ (b_0a_{22} - b_{01}a_{01})(b_{02}b_{11} + b_{01}b_{22} + b_0b_{33}) + (a_{00}b_{33} + a_{11}b_{02})\left(2b_{22}b_{00} + b_{11}^2\right) \\
&+ (b_{22}a_{00} - a_0b_{02})(2b_{22}b_{11} + 2b_{33}b_{00}) + (a_{11}b_0 + a_{00}b_{11} - b_{01}a_0)\left(2b_{11}b_{33} + b_{22}^2\right) \\
&+ 2b_{22}b_{33}(a_{00}b_{00} - a_0b_0)\,,
\end{aligned}
$$

$$
\begin{aligned}
Y_5 &= -2b_0a_{02}\left(2b_0b_{02} + b_{01}^2\right) + b_{01}^2(b_{01}a_{33} - a_{02}b_{02}) + 2b_0b_{01}(b_0a_{33} - b_{01}a_{02}) + 2b_{00}b_{11}a_{00}b_{33} \\
&+ 2b_{00}b_{11}a_{11}b_{02} + (b_{01}a_{22} - b_{02}a_{01})(b_{01}b_{00} + b_0b_{11}) - a_{01}b_0(b_{02}b_{11} + b_{01}b_{22} + b_0b_{33}) \\
&+ (b_{22}a_{00} - a_0b_{02} + b_{01}a_{11})\left(2b_{00}b_{22} + b_{11}^2\right) + (b_0a_{22} - b_{01}a_{01})(b_{02}b_{00} + b_{01}b_{11} + b_0b_{22}) \\
&+ (a_{11}b_0 + a_{00}b_{11} - b_{01}a_0)(2b_{00}b_{33} + 2b_{22}b_{11}) + (a_{00}b_{00} - a_0b_0)\left(2b_{11}b_{33} + b_{22}^2\right)\,,
\end{aligned}
$$

$$
\begin{aligned}
Y_6 &= -2b_0^2b_{01}a_{02} + b_{01}^2(b_0a_{33} - b_{01}a_{02}) + b_0b_{00}(b_{01}a_{22} - b_{02}a_{01}) + (b_0a_{22} - b_{01}a_{01})(b_{01}b_{00} + b_0b_{11}) \\
&+ 2b_{00}b_{11}(b_{22}a_{00} - a_0b_{02} + b_{01}a_{11}) + b_{00}^2(a_{00}b_{33} + a_{11}b_{02}) - b_0^2a_{01}b_{00} - b_{01}a_0\left(2b_{22}b_{00} + b_{11}^2\right) \\
&+ (a_{11}b_0 + b_{11}a_{00})\left(2b_{22}b_{00} + b_{11}^2\right) + (a_{00}b_{00} - a_0b_0)(2b_{33}b_{00} + 2b_{22}b_{11})\,,
\end{aligned}
$$

$$
\begin{aligned}
Y_7 &= -b_0a_{02}b_{01}^2 + b_0b_{00}(b_0a_{22} - b_{01}a_{01}) - a_{01}b_0(b_{01}b_{00} + b_0b_{11}) + 2b_{00}b_{11}(a_{00}b_{11} - b_{01}a_0 + a_{11}b_0) \\
&+ b_{00}^2(b_{22}a_{00} - a_0b_{02} + b_{01}a_{11}) + (a_{00}b_{00} - a_0b_0)\left(2b_{22}b_{00} + b_{11}^2\right)\,,
\end{aligned}
$$

$$
Y_8 = -a_{01}b_0^2b_{00} + b_{00}^2(a_{11}b_0 + a_{00}b_{11} - a_0b_{01}) + 2b_{00}b_{11}(a_{00}b_{00} - a_0b_0)\,,
$$

$$
Y_9 = b_{00}^3a_{00}\left[1 - \left(\mathcal{R}_0^l\right)^2\right] > 0 \quad \left(\text{if } \mathcal{R}_0^l < 1\right).
$$

Appendix I

Proof of Theorem 4.4

Proof. The Centre Manifold Theory, as described in [14], will be used to prove Theorem 4.4. It is convenient to use the change of variables:

$$\begin{aligned} S_f &= x_1,\ V_f^q = x_2,\ E_f^l = x_3,\ I_f^l = x_4,\ P_f^l = x_5,\ W_f = x_6,\ R_f = x_7,\ S_m = x_8, \\ V_m^q &= x_9,\ E_m^l = x_{10},\ I_m^l = x_{11},\ P_m^l = x_{12},\ W_m = x_{13},\ R_m = x_{14}. \end{aligned} \tag{I.1}$$

Let $\hat{f} = [f_1, ..., f_{14}]$ denote the vector field of the low-risk-only model (4.37) in the notation (I.1), so that the low-risk-only model (4.37) is re-written in the form:

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1 = (1-\varphi_f^q)\pi_f - \frac{\beta_m^l c_f \mu_m x_{11} x_1}{\pi_m} - \mu_f x_1, \\
\frac{dx_2}{dt} &= f_2 = \varphi_f^q \pi_f - (1-\varepsilon_v)\frac{\beta_m^l c_f \mu_m x_{11} x_2}{\pi_m} - \mu_f x_2, \\
\frac{dx_3}{dt} &= f_3 = \left[x_1 + (1-\varepsilon_v)x_2 + \rho_f^l x_7\right]\frac{\beta_m^l c_f \mu_m x_{11}}{\pi_m} - A_1 x_3, \\
\frac{dx_4}{dt} &= f_4 = \sigma_f^l x_3 - A_2 x_4, \\
\frac{dx_5}{dt} &= f_5 = b_2 x_4 - A_3 x_5, \\
\frac{dx_6}{dt} &= f_6 = b_3 x_5 - A_4 x_6, \\
\frac{dx_7}{dt} &= f_7 = m_1 x_4 + m_2 x_5 + n_f x_6 - \rho_f^l \frac{\beta_m^l c_f \mu_m x_{11} x_7}{\pi_m} - \mu_m x_7, \\
\frac{dx_8}{dt} &= f_8 = (1-\varphi_m^q)\,\pi_m - \frac{\beta_f^l c_f \mu_m x_3 x_8}{\pi_m} - \mu_m x_8, \\
\frac{dx_9}{dt} &= f_9 = \varphi_m^q \pi_m - (1-\varepsilon_v)\frac{\beta_f^l c_f \mu_m x_3 x_9}{\pi_m} - \mu_m x_9, \\
\frac{dx_{10}}{dt} &= f_{10} = \left[x_8 + (1-\varepsilon_v)x_9 + \rho_m^l x_{14}\right]\frac{\beta_f^l c_f \mu_m x_3}{\pi_m} - D_1 x_{10}, \\
\frac{dx_{11}}{dt} &= f_{11} = \sigma_m^l x_{10} - D_2 x_{11}, \\
\frac{dx_{12}}{dt} &= f_{12} = k_2 x_{11} - D_3 x_{12}, \\
\frac{dx_{13}}{dt} &= f_{13} = k_3 x_{13} - D_4 x_{13}, \\
\frac{dx_{14}}{dt} &= f_{14} = m_4 x_{11} + m_5 x_{12} + n_m x_{13} - \rho_m^l \frac{\beta_f^l c_f \mu_m x_3 x_{14}}{\pi_m} - \mu_m x_{14},
\end{aligned}
\tag{I.2}
$$

where A_i, D_i $(i = 1, ..., 4)$, b_j, k_j $(j = 1, ..., 3)$ and m_1, m_2, m_4, m_5 are defined in Sections 4.3.1 and 4.3.2.

The Jacobian of the system (I.2) at the DFE ($\mathcal{E}_0^l$) is given by

$$J^l(\mathcal{E}_0^l) = \begin{pmatrix} -\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -U_1 & 0 & 0 & 0 \\ 0 & -\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -U_2 & 0 & 0 & 0 \\ 0 & 0 & U_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & U_3 & 0 & 0 & 0 \\ 0 & 0 & \sigma_f^l & U_5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & b_2 & U_6 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & b_3 & U_7 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & m_1 & m_2 & n_f & -\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -U_8 & 0 & 0 & 0 & -\mu_m & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -U_9 & 0 & 0 & 0 & 0 & -\mu_m & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & U_{10} & 0 & 0 & 0 & 0 & 0 & U_{11} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sigma_m^l & U_{12} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_2 & U_{13} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_3 & U_{14} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & m_4 & m_5 & n_m & -\mu_m \end{pmatrix},$$

where,

$$\begin{aligned} U_1 &= \frac{\beta_m^l c_f \pi_f \mu_m \left(1-\varphi_f^q\right)}{\mu_f \pi_m}, \ U_2 = \frac{\beta_m^l c_f \pi_f \mu_m \varphi_f^q \left(1-\varepsilon_v\right)}{\mu_f \pi_m}, \ U_3 = \frac{\beta_m^l c_f \pi_f \mu_m \left(1-\varepsilon_q \varphi_f^q\right)}{\pi_m}, \\ U_4 &= -A_1, \ U_5 = -A_2, \ U_6 = -A_3, \ U_7 = -A_4, \ U_8 = \beta^* c_f \left(1-\varphi_m^q\right), \\ U_9 &= \beta^* c_f \varphi_m^q \left(1-\varepsilon_v\right), \ U_{10} = \beta^* c_f \left(1-\varepsilon_v \varphi_m^q\right), \ U_{11} = -D_1, \ U_{12} = -D_2, \\ U_{13} &= -D_3, \ U_{14} = -D_4. \end{aligned}$$

Consider the case when $\mathcal{R}_0^l = 1$. Suppose, further, that β_f^l is chosen as a bifurcation parameter. Solving for β_f^l from $\mathcal{R}_0^l = 1$ gives

$$\beta_f^l = \beta^* = \frac{A_1 A_2 D_1 D_2 \pi_m \mu_f}{\beta_m^l c_f^2 \pi_f \mu_m \left(1-\varepsilon_v \varphi_f^q\right)\left(1-\varepsilon_v \varphi_m^q\right) k_1 b_1}. \tag{I.3}$$

Here, too, the transformed system, (I.2) with $\beta_f^l = \beta^*$, has a hyperbolic equilibrium point.

Eigenvectors of $J^l(\mathcal{E}_0^l)\mid_{\beta_f^l=\beta^*}$:

It can be shown that the Jacobian of (I.2) at $\beta_f^l = \beta^*$ (denoted by $J_{\beta^*}^l$) has a left eigenvector (associated with the zero eigenvalue) given by,

$$\boldsymbol{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12}, v_{13}, v_{14}]^T,$$

with,

$$\begin{aligned}
v_1 &= 0, \;\; v_2 = 0, \;\; v_3 = \frac{\sigma_f^l v_4}{A_1}, \;\; v_4 = \frac{\beta^* c_f \left(1-\varepsilon_v \varphi_m^q\right) v_{10}}{A_2}, \;\; v_5 = 0, \;\; v_6 = 0, \;\; v_7 = 0, \;\; v_8 = 0, \\
v_9 &= 0, \;\; v_{10} = v_{10} > 0, \;\; v_{11} = \frac{\beta_m^l c_f \mu_m \pi_f \left(1-\varepsilon_v \varphi_f^q\right) v_3}{D_2 \pi_m \mu_f}, \;\; v_{12} = 0, \;\; v_{13} = 0, \;\; v_{14} = 0.
\end{aligned}$$

Furthermore, the matrix $J_{\beta^*}^l$ has a right eigenvector (associated with the zero eigenvalue) given by,

$$\boldsymbol{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}, w_{11}, w_{12}, w_{13}, w_{14}]^T,$$

where,

$$\begin{aligned}
w_1 &= -\frac{\beta_m^l c_f \mu_m \pi_f \left(1-\varphi_f^q\right) w_{11}}{\mu_f^2 \pi_m}, \;\; w_2 = -\frac{\beta_m^l c_f \mu_m \pi_f \left(1-\varepsilon_v\right) \varphi_f^q w_{11}}{\pi_m \mu_f^2}, \\
w_3 &= \frac{\beta_m^l c_f \mu_m \pi_f \left(1-\varepsilon_v \varphi_f^q\right) w_{11}}{A_1 \pi_m \mu_f}, \;\; w_4 = \frac{\sigma_f^l w_3}{A_2}, \;\; w_5 = \frac{b_2 w_4}{A_3}, \;\; w_6 = \frac{b_3 w_5}{A_4}, \\
w_7 &= \frac{m_1 w_4 + m_2 w_5 + n_f w_6}{\mu_f}, \;\; w_8 = -\frac{\beta^* c_f \left(1-\varphi_m^q\right) w_4}{\mu_m}, \\
w_9 &= -\frac{\beta^* c_f \left(1-\varepsilon_v\right) \varphi_m^q w_4}{\mu_m}, \;\; w_{10} = w_{10} > 0, \;\; w_{11} = \frac{\sigma_m^l w_{10}}{D_2}, \;\; w_{12} = \frac{k_2 w_{11}}{D_3}, \\
w_{13} &= \frac{k_3 w_{12}}{D_4}, \;\; w_{14} = \frac{m_4 w_{11} + m_5 w_{12} + n_m w_{13}}{\mu_m}.
\end{aligned}$$

Thus, using Theorem 2.8, the bifurcation coefficients, a and b, can be computed.

Computations of bifurcation coefficients, a and b:

It can be shown, by computing the non-zero partial derivatives of the model (I.2) at the DFE ($\mathcal{E}_0^l$) and simplifying, that

$$a = \sum_{k,i,j=1}^{14} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) = \frac{2c_f}{\mu_f^2 \pi_m^2}\left(M_{11} - M_{22}\right), \tag{I.4}$$

and,

$$b = \sum_{k,i=1}^{14} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*}(0,0) = c_f v_{10} w_4 \left(1 - \varepsilon_v \varphi_m^q\right) > 0.$$

where,

$$\begin{aligned}
M_{11} &= v_3 w_7 w_{11} \rho_f^l \beta_m^l \mu_m \mu_f^2 \pi_m + v_{10} w_4 w_{14} \rho_m^l \beta^* \mu_m \mu_f^2 \pi_m + v_3 w_{11}^2 \beta_m^l \mu_m^2 \pi_f \mu_f \varepsilon_v \varphi_f^q \\
&+ v_3 w_4 w_{11} \beta^* c_f \beta_m^l \mu_m \pi_f \mu_f \left(1 - \varepsilon_v \varphi_f^q\right) + v_3 w_{11}^2 \beta_m^{l^2} c_f \mu_m^2 \pi_f \varepsilon_v \varphi_f^q \left(2 - \varepsilon_v\right),
\end{aligned}$$

$$\begin{aligned}
M_{22} &= v_3 w_{11}^2 \beta_m^{l^2} c_f \mu_m^2 \pi_f + v_3 w_{11}^2 \beta_m^l \mu_m^2 \pi_f \mu_f + v_3 w_4 w_{11} \beta^* c_f \beta_m^l \mu_m \pi_f \mu_f \varphi_m^q \varepsilon_v \left(1 - \varepsilon_v \varphi_f^q\right) \\
&+ v_3 w_{10} w_{11} \beta_m^l \mu_m^2 \pi_f \mu_f \left(1 - \varepsilon_v \varphi_f^q\right) + v_3 w_{11} w_{12} \beta_m^l \mu_m^2 \pi_f \mu_f \left(1 - \varepsilon_v \varphi_f^q\right) \\
&+ v_3 w_{11} w_{13} \beta_m^l \mu_m^2 \pi_f \mu_f \left(1 - \varepsilon_v \varphi_f^q\right) + v_3 w_{11} w_{14} \beta_m^l \mu_m^2 \pi_f \mu_f \left(1 - \varepsilon_v \varphi_f^q\right) \\
&+ v_{10} w_4^2 \beta^{*^2} c_f \pi_m \mu_f^2 \varphi_m^q \varepsilon_v^2 \left(1 - \varphi_m^q\right) + v_{10} w_4 w_{10} \beta^* \pi_m \mu_f^2 \mu_m \left(1 - \varepsilon_v \varphi_m^q\right) \\
&+ v_{10} w_4 w_{11} \beta^* \pi_m \mu_f^2 \mu_m \left(1 - \varepsilon_v \varphi_m^q\right) + v_{10} w_4 w_{12} \beta^* \pi_m \mu_f^2 \mu_m \left(1 - \varepsilon_v \varphi_m^q\right) \\
&+ v_{10} w_4 w_{13} \beta^* \pi_m \mu_f^2 \mu_m \left(1 - \varepsilon_v \varphi_m^q\right) + v_{10} w_4 w_{14} \beta^* \pi_m \mu_f^2 \mu_m \left(1 - \varepsilon_v \varphi_m^q\right).
\end{aligned}$$

Thus, the result below follows from Theorem 2.8.

Theorem I.1. *The transformed model (I.2) (or, equivalently, the model (4.37)) undergoes a backward bifurcation at $\mathcal{R}_0^l = 1$ if the bifurcation coefficient a, given by (I.4), is positive.*

□

It is clear from the expression for the bifurcation coefficient, a, given by (I.4), that $a > 0$ whenever (since all the low-risk-only model parameters are positive)

$$M_{11} > M_{22}. \tag{I.5}$$

Furthermore, consider the low-risk-only model (4.37) in the absence of re-infection ($\rho_f^l = \rho_m^l = 0$). Setting $\rho_f^l = \rho_m^l = 0$ into the expression for the bifurcation coefficient, a in (I.4), and using β^* for β_f^l in (I.3), shows that (here, the eigenvectors v_{10} and w_{10} are given the value unity)

$$
\begin{aligned}
a &= -\frac{2\left(\sigma_m^l+\mu_m\right)}{\mu_f\pi_m\left(\psi_m^l+\mu_m\right)\left(1-\varepsilon_v\varphi_f^q\right)^2}\left[\varepsilon_v\sigma_m^l\varphi_f^q\psi_m^l\mu_m\left(2-\varepsilon_v\varphi_f^q\right)+\varepsilon_v\sigma_m^l\varphi_f^q\mu_m^2\left(2-\varepsilon_v\varphi_f^q\right)\right] \\
&- \frac{2\left(\sigma_m^l+\mu_m\right)}{\mu_f\pi_m\left(\psi_m^l+\mu_m\right)\left(1-\varepsilon_v\varphi_f^q\right)^2}\left[\varepsilon_v\sigma_m^{l^2}\varphi_f^q\left(\psi_m^l+\mu_m\right)\left(2-\varepsilon_v\varphi_f^q\right)+\mu_f\mu_m\sigma_m^{l^2}\left(1-\varepsilon_v\varphi_f^q\right)\right] \\
&- \frac{2\mu_m\sigma_m^l\left(\sigma_m^l+\mu_m\right)\left(n_m+\mu_m\right)\psi_m^l}{\pi_m\mu_f\left(\psi_m^l+\mu_m\right)\left(\alpha_m^l+\mu_m\right)\left(n_m+\mu_m\right)}\left[r_m^l\left(\alpha_m^l+\mu_m\right)+k_m^l\alpha_m^l\left(1-r_m^l\right)\right] \\
&- \frac{2\mu_m\sigma_m^l\left(\sigma_m^l+\mu_m\right)}{\pi_m\mu_f\left(\psi_m^l+\mu_m\right)\left(\alpha_m^l+\mu_m\right)\left(n_m+\mu_m\right)}\left[n_m\left(1-r_m^l\right)\psi_m^l\left(1-k_m^l\right)\alpha_m^l\right] \\
&- \frac{2\left(\sigma_m^l+\mu_m\right)}{\mu_f\pi_m\left(\psi_m^l+\mu_m\right)\left(1-\varepsilon_v\varphi_f^q\right)^2}\left[\mu_f\mu_m\sigma_m^l\psi_m^l\left(1-\varepsilon_v\varphi_f^q\right)+\mu_f\sigma_m^{l^2}\psi_m^l\left(1-\varepsilon_v\varphi_f^q\right)\right] \\
&- \frac{2\left(\sigma_m^l+\mu_m\right)}{\mu_f\pi_m\left(\psi_m^l+\mu_m\right)\left(1-\varepsilon_v\varphi_f^q\right)^2}\left[\beta_m^l\mu_m\sigma_m^{l^2}c_f\left(1-\varepsilon_v\varphi_f^q\right)+\mu_f\mu_m^2\sigma_m^l\left(1-\varepsilon_v\varphi_f^q\right)^2\right] \\
&- \frac{2\sigma_m^l\varphi_m^q\varepsilon_v\left(\sigma_m^l+\mu_m\right)^2\left(1-\varphi_m^q\right)}{\pi_m\mu_f^2\left(1-\varepsilon_v\varphi_m^q\right)^2}-\frac{2\mu_m\sigma_m^l\left(\sigma_m^l+\mu_m\right)}{\pi_m\mu_f}\left[1+\frac{1}{\left(\psi_m^l+\mu_m\right)}\right] \\
&- \frac{2\mu_m\sigma_m^l\left(\sigma_m^l+\mu_m\right)\left(1-r_m^l\right)\psi_m^l}{\pi_m\mu_f\left(\psi_m^l+\mu_m\right)\left(\alpha_m^l+\mu_m\right)}\left[1+\frac{\left(1-k_m^l\right)\alpha_m^l}{\left(n_m+\mu_m\right)}\right]<0. \qquad \text{(I.6)}
\end{aligned}
$$

It should be stated that, in (I.6), $0 \leq \varepsilon_v, \varphi_f^q, \varphi_m^q \leq 1$. Hence, it follows from (I.6), that the bifurcation coefficient, $a < 0$, for the low-risk-only model (4.37) with $\rho_f^l = \rho_m^l = 0$. Thus, it follows from Item (iv) of Theorem 2.8 that the low-risk-only model (4.37) does not undergo backward bifurcation in the absence of re-infection.

Appendix J

Proof of Theorem 4.6

Proof. Consider the model (4.34) with $\rho_f^l = \rho_m^l = \rho_f^h = \rho_m^h = \delta_m = 0$. The proof is based on using a Comparison Theorem. The equations for the infected components of the model (4.34) can be written as (it should be mentioned that system (J.1) satisfies the Type K condition discussed in Chapter 2):

$$\frac{d}{dt}\begin{pmatrix} E_f^l(t) \\ I_f^l(t) \\ P_f^l(t) \\ W_f^l(t) \\ E_f^h(t) \\ I_f^h(t) \\ P_f^h(t) \\ G_{fl}(t) \\ G_{fh}(t) \\ C_f^c(t) \\ E_m^l(t) \\ I_m^l(t) \\ P_m^l(t) \\ W_m(t) \\ E_m^h(t) \\ I_m^h(t) \\ P_m^h(t) \\ G_{ml}(t) \\ G_{mh}(t) \\ C_m^r(t) \end{pmatrix} = (\mathcal{F}_r - \mathcal{H}_r)\begin{pmatrix} E_f^l(t) \\ I_f^l(t) \\ P_f^l(t) \\ W_f^l(t) \\ E_f^h(t) \\ I_f^h(t) \\ P_f^h(t) \\ G_{fl}(t) \\ G_{fh}(t) \\ C_f^c(t) \\ E_m^l(t) \\ I_m^l(t) \\ P_m^l(t) \\ W_m(t) \\ E_m^h(t) \\ I_m^h(t) \\ P_m^h(t) \\ G_{ml}(t) \\ G_{mh}(t) \\ C_m^r(t) \end{pmatrix} - \mathcal{J}_r\begin{pmatrix} E_f^l(t) \\ I_f^l(t) \\ P_f^l(t) \\ W_f^l(t) \\ E_f^h(t) \\ I_f^h(t) \\ P_f^h(t) \\ G_{fl}(t) \\ G_{fh}(t) \\ C_f^c(t) \\ E_m^l(t) \\ I_m^l(t) \\ P_m^l(t) \\ W_m(t) \\ E_m^h(t) \\ I_m^h(t) \\ P_m^h(t) \\ G_{ml}(t) \\ G_{mh}(t) \\ C_m^r(t) \end{pmatrix}, \tag{J.1}$$

where the matrices $\mathcal{F}_r$ and $\mathcal{H}_r$ are as defined in Section 4.3.1, and

$$
\begin{aligned}
\mathcal{J}_r &= \left[\frac{S_f^* + V_f^{b^*} + (1-\varepsilon_v)\,V_f^{q^*}}{N_m^*} - \frac{S_f + V_f^q + (1-\varepsilon_v)\,V_f^q}{N_m^*}\right]\mathcal{J}_{1r} \\
&+ \left[\frac{S_f^* + (1-\varepsilon_v)\,V_f^{b^*} + (1-\varepsilon_v)\,V_f^{q^*}}{N_m^*} - \frac{S_f + (1-\varepsilon_v)\,V_f^q + (1-\varepsilon_v)\,V_f^q}{N_m^*}\right]\mathcal{J}_{2r} \\
&+ \left[\frac{S_m^* + (1-\varepsilon_v)\,V_m^{q^*}}{N_m^*} - \frac{S_m + (1-\varepsilon_v)\,V_m^q}{N_m^*}\right](\mathcal{J}_{3r} + \mathcal{J}_{4r}),
\end{aligned}
$$

where,

$$
\mathcal{J}_{1r} = \begin{pmatrix} \mathbf{0}_{10\times 10} & \mathcal{J}_1 \\ \mathbf{0}_{10\times 10} & \mathbf{0}_{10\times 10} \end{pmatrix}, \quad \mathcal{J}_{2r} = \begin{pmatrix} \mathbf{0}_{10\times 10} & \mathcal{J}_2 \\ \mathbf{0}_{10\times 10} & \mathbf{0}_{10\times 10} \end{pmatrix},
$$

$$
\mathcal{J}_{3r} = \begin{pmatrix} \mathbf{0}_{10\times 10} & \mathbf{0}_{10\times 10} \\ \mathcal{J}_3 & \mathbf{0}_{10\times 10} \end{pmatrix} \quad \text{and} \quad \mathcal{J}_{4r} = \begin{pmatrix} \mathbf{0}_{10\times 10} & \mathbf{0}_{10\times 10} \\ \mathcal{J}_4 & \mathbf{0}_{10\times 10} \end{pmatrix},
$$

with,

$$
\mathcal{J}_1 = \begin{pmatrix}
\beta_m^l c_f \eta_m^l & \beta_m^l c_f & \beta_m^l c_f \theta_m^l & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix},
$$

$$\mathcal{J}_2 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_m^h c_f \eta_m^h & \beta_m^h c_f & \beta_m^h c_f \theta_m^h & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$\mathcal{J}_3 = \begin{pmatrix} \beta_f^l c_f \eta_f^l & \beta_f^l c_f & \beta_f^l c_f \theta_f^l & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

and,

$$\mathcal{J}_4 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \beta_f^h c_f \eta_f^h & \beta_f^h c_f & \beta_f^h c_f \theta_f^h & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

It should be noted that $\mathcal{J}_{1r}, \mathcal{J}_{2r}, \mathcal{J}_{3r}$, and $\mathcal{J}_{4r}$, are non-negative matrices. Furthermore, since

$$S_f(t) \leq S_f^*(t), \;\; V_f^b(t) \leq V_f^{b^*}(t), \;\; V_f^q(t) \leq V_f^{q^*}(t),$$

and,

$$S_m(t) \leq S_m^*(t), \;\; V_m^q(t) \leq V_m^{q^*}(t),$$

(for all t ≥ 0 in $\mathcal{D}_{\mathrm{r}}^*$), the matrix $\mathcal{J}_r$ is non-negative. Thus, it follows from (J.1) that

$$\frac{d}{dt}\begin{pmatrix} E_f^l(t) \\ I_f^l(t) \\ P_f^l(t) \\ W_f^l(t) \\ E_f^h(t) \\ I_f^h(t) \\ P_f^h(t) \\ G_{fl}(t) \\ G_{fh}(t) \\ C_f^c(t) \\ E_m^l(t) \\ I_m^l(t) \\ P_m^l(t) \\ W_m(t) \\ E_m^h(t) \\ I_m^h(t) \\ P_m^h(t) \\ G_{ml}(t) \\ G_{mh}(t) \\ C_m^r(t) \end{pmatrix} \leq (\mathcal{F}_r - \mathcal{H}_r) \begin{pmatrix} E_f^l(t) \\ I_f^l(t) \\ P_f^l(t) \\ W_f^l(t) \\ E_f^h(t) \\ I_f^h(t) \\ P_f^h(t) \\ G_{fl}(t) \\ G_{fh}(t) \\ C_f^c(t) \\ E_m^l(t) \\ I_m^l(t) \\ P_m^l(t) \\ W_m(t) \\ E_m^h(t) \\ I_m^h(t) \\ P_m^h(t) \\ G_{ml}(t) \\ G_{mh}(t) \\ C_m^r(t) \end{pmatrix}. \tag{J.2}$$

Using the fact that the eigenvalues of the matrix $\mathcal{F}_r - \mathcal{H}_r$ all have negative real parts (see local stability result in Section 4.3.1, where $\rho(\mathcal{F}_r\mathcal{H}_r^{-1}) < 1$ if $\mathcal{R}_{01}^r < 1$, which is equivalent to $\mathcal{F}_r - \mathcal{H}_r$ having eigenvalues with negative real parts when $\mathcal{R}_{01}^r < 1$), it follows that the linearized differential inequality system (J.2) is stable whenever $\mathcal{R}_{01}^r < 1$. Thus, it follows,

by Comparison Theorem [58] (see also Theorem 2.10), that

$$\begin{aligned}&\lim_{t\to\infty}\ (E_f^l(t), I_f^l(t), P_f^l(t), W_f^l(t), E_f^h(t), I_f^h(t), P_f^h(t), G_{fl}(t), G_{fh}(t), C_f^c(t), E_m^l(t),\\ &I_m^l(t), P_m^l(t), W_m(t), E_m^h(t), I_m^h(t), P_m^h(t), G_{ml}(t), G_{mh}(t), C_m^r(t))\\ &= (0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0).\end{aligned}$$

Substituting $E_f^l = I_f^l = P_f^l = W_f^l = E_f^h = I_f^h = P_f^h = G_{fl} = G_{fh} = C_f^c = E_m^l = I_m^l = P_m^l = W_m = E_m^h = I_m^h = P_m^h = G_{ml} = G_{mh} = C_m^r = 0$ into the equations of the model (4.34) gives $S_f(t) \to S_f^*, V_f^b(t) \to V_f^{b^*}, V_f^q(t) \to V_f^{q^*}$, $S_m(t) \to S_m^*$ and $V_m^q(t) \to V_m^{q^*}$, as $t \to \infty$ for $\mathcal{R}_{01}^r < 1$. Thus,

$$\begin{aligned}&\lim_{t\to\infty}\ (S_f(t), V_f^b(t), V_f^q(t), E_f^l(t), I_f^l(t), P_f^l(t), W_f^l(t), E_f^h(t), I_f^h(t), P_f^h(t), G_{fl}(t),\\ &G_{fh}(t), C_f^c(t), S_m(t), V_m^q(t), E_m^l(t), I_m^l(t), P_m^l(t), W_m(t), E_m^h(t),\\ &I_m^h(t), P_m^h(t), G_{ml}(t), G_{mh}(t), C_m^r(t)) = \mathcal{E}_0^r,\end{aligned}$$

so that the DFE, $\mathcal{E}_0^r$, of the model (4.34) is GAS in $\mathcal{D}_r^*$ whenever $\mathcal{R}_{01}^r < 1$. □

Bibliography

[1] American University. (2011). *Sexually Transmitted Diseases (STDs)*. www.american.ca. Accessed: 15 January 2013.

[2] Anderson, R. M., & May, R. M., eds. (1982). *Population of Biology of Infectious Diseases*. Springer-Verlage, Berlin, Heidelberg: New York.

[3] Anderson, R. M., & May, R. M., eds. (1991). *Infectious Diseases of Humans: Dynamics and Control*. Oxford Univ, Press, London: New York.

[4] Australian Institute of Health and Welfare. (2013). http://www.aihw.gov.au. Accessed: 20 March 2013.

[5] Bernoulli, D. (1766). Essai D'une Nouvelle Analyse De La Mortalité Causée Par La Petite Vérole. *Mém. Math. Phys. Acad. Roy. Sci.*, Paris.

[6] Bellanger, S., Tan, C. L., Xue, Y. Z., Teissier, S., & Thierry, F. (2011). Tumor Suppressor or Oncogene? A critical Role of the Human Papillomavirus (HPV) E2 Protein in Cervical Cancer Progression. *Am J Cancer Res.*, **1**(3): 373-389.

[7] Brisson, M., Van de Velde, N. & Boily, M. C. (2011). Different Population-level Vaccination Effectiveness for HPV Types 16, 18, 6 and 11. *Sex. Transm. Infect.*, **87**: 41-43.

[8] Blower, S. M., & Dowlatabadi, H. (1994). Sensitivity and Uncertainty Analysis of Complex Models of Disease Transmission: An HIV Model, As An Example. *Int. Stat. Rev.*, **62**: 229-243.

[9] Brown, V. L., & White, K. A. J. (2011). The Role of Optimal Control in Assessing the Most Cost-effective Implementation of a Vaccination Programme: HPV as a Case Study. *Math. Biosci.,* **231**: 126-134.

[10] Canadian Cancer Society. (2010). http://www.cancer.ca. Accessed: 10 September 2012.

[11] Carr, J. (1981). *Applications of Centre Manifold Theory*. Springer-Verlag, New York.

[12] Castillo-Chavez, C., Cooke, K., Huang, W., & Levin, S. A. (1989). Results on the Dynamics for Models for the Sexual Transmission of the Human Immunodeficiency Virus. *Appl. Math. Letters*, **2**: 327-331.

[13] Castillo-Chavez, C., Huang, W., & Li, J. (1997). The Effects of Females' Susceptibility on the Co-existence of Multiple Pathogen Strains of Sexually Transmitted Diseases. *J. Math. Biol.*, **35**: 503-522.

[14] Castillo-Chavez, C., & Song, B. (2004). Dynamical Models of Tuberculosis and Their Applications. *Math. Biosci. Engrg.,* **1**(2): 361-404.

[15] Centres for Disease Control and Prevention. (2012). *Sexually Transmitted Diseases (STDs)*. http://www.cdc.gov. Accessed: 15 November 2012.

[16] Chowell, G., Diaz-Duenas, P., Miller, J. C., Alcazar-Velazco, A., Hyman, J. M., Fenimore, P. W., & Castillo Chavez, C. (2007). Estimation of the Reproduction Number of Dengue Fever from Spatial Epidemic Data. *Mathematical Biosciences*, **208**(2): 571-589.

[17] Davidson College. (2006). http://www.bio.davidson.edu. Accessed: 23 March 2013.

[18] de Villiers, E.-M., Fauquet, C., Broker, T. R., Bernard, H.-V. & zur Hausen, H. (2004). Classification of Papillomaviruses. *Virology*. **324**: 17-27.

[19] Diekmann, O., Heesterbeek, J. A. P., & Metz, J. A. J. (1990). On the Definition and the Computation of the Basic Reproduction Ratio $\mathcal{R}_0$ in Models for Infectious Diseases in Heterogeneous Populations. *J. Math. Biol.*, **28**(4): 365-382.

[20] Dietz, K. (1975). Transmission and Control of Arboviurs Disease, In Epidemiology, K. L. Cook, ed. *SIAM*, Philadelphia.

[21] Dietz, K., & Heesterbeek, J. A. P. (2002). Daniel Bernoulli's Epidemiological Model Revisited. *Mathematical Biosciences*, **180**: 1-21.

[22] Doorbar, J. (2005). The Papillomavirus Life Cycle. *Review. Virology*, **32**: 7-15.

[23] Dushoff, J., Wenzhang, H., & Castillo-Chavez, C. (1998). Backwards Bifurcations and Catastrophe in Simple Models of Fatal Diseases. *J. Math. Biol.*, **36**: 227-248.

[24] Elbasha, E. H., Dasbach, E. J., & Insinga, R. P. (2008). A Multi-Type HPV Transmission Model. *Bull. Math. Biol.,* **70**(8): 2126-2176.

[25] Elbasha, E. H., Dasbach, E. J., & Insinga, R. P. (2007). Model For Assessing Human Papilomavirus Vaccination Strategies. *Emerg Infect Dis.,* **13**(1): 28- 41.

[26] Elbasha, E. H., & Galvani, A. P. (2005). Vaccination Against Multiple HPV Types. *Math. Biosci.,* **197**(1): 88-117.

[27] Elbasha, E. H. (2008). Global Stability of Equilibria in a Two-Sex HPV Vaccination Model. *Bull. Math. Biol.,* **70**: 894-909.

[28] Elbasha, E. H., & Gumel, A. B. (2006). Theoretical Assessment of Public Health Impact of Imperfect Prophylactic HIV-1 Vaccines with Therapeutic Benefits. *Bull. Math. Biol.,* **68**: 577-614.

[29] Elbasha, E. H., & Dasbach, E. J. (2010). Impact of Vaccinating Boys and Men Against HPV in the United States. *Vaccine*, *28*: 6858-6867.

[30] Escobar Ospina, M. E., & Perdomo, J. G. (2012). A growth Model of Human Papillomavirus Type 16 Designed From Cellular Automata and Agent-based Models. *Artif. Intell. Med.*, **57**(1):31-47.

[31] Esteva, L., Gumel, A. B., & de Leon, C. V. (2009). Qualitative Study of Transmission Dynamics of Drug-Resistant Malaria. *Math. Comput. Modelling,* **50**: 611-630.

[32] Esteva, L., & Vergas, C. (2000). Influence of Vertical and Mechanical Transmission on the Dynamics of Dengue Disease. *Math Biosci.,* **167**: 51-64.

[33] Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., & Parkin, D. M. (2010). Estimates of Worldwide Burden of Cancer in 2008: GLOBOCAN 2008. *Int. J. Cancer,* **127**(12): 2893-2917.

[34] Food and Drug Administration. (2010). *FDA Approves New Vaccine for Prevention of Cervical Cancer.* http://www.fda.gov. Accessed: 5 December 2012.

[35] Franco, E. L., Duarte-Franco, E. & Ferenczy, A. (2001). Cervical Cancer: Epidemiology, Prevention and The Role of Human Papillomavirus Infection. *CMAJ.,* **164**(7): 1017-1025.

[36] Friedman-Kien, A. (1995). Management of Condylomata Acuminata with Alferon N Injection, Interferon Alfa-n3 (Human Leukocyte Derived). *Am J Obstet Gynecol.*, **172**: 1359-1368.

[37] Garba, S. M., Gumel, A. B., & Abu Bakar, M. R. (2008). Backward Bifurcations in Dengue Transmission Dynamics. Math. *Biosci.,* **215**: 11-25.

[38] Gillison, M. L., Chaturvedi, A. K., &Lowy, D. R. (2008). HPV Prophylactic Vaccines and the Potential Prevention of Noncervical Cancers in Both Men and Women. *Cancer*, **113**(10): 3036-3046.

[39] Goldberg Arnold, R. J. (2007). Cost-effectiveness Analysis: Should It Be Required for Drug Registration and Beyond? *Drug Discovery Today*, **12**(22): 960-965.

[40] Goldie, S. J., Goldhaber-Fiebert, J. D., & Garnett, G. P. (2006) Chapter 18: Public Health Policy for Cervical Cancer Prevention; the Role of Decision Science, Economic Evaluation and Mathematical Modelling. *Vaccine,* **24**(3): 155-163

[41] Goldie, S. J., Kim, J. J., & Myers, E. (2006) Chapter 19: Cost-effectiveness of Cervical Cancer Screening. *Vaccine,* **24**(3): 164-170.

[42] Gumel, A. B. (2012). Causes of Backward Bifurcations in Some Epidemiological Models. *J. Math. Anal. Appl.*, **395**(1): 355-365.

[43] Gumel, A. B., McCluskey, Connell C., & van den Driessche, P. (2006). Mathematical Study of a Staged-progression HIV Model with Imperfect Vaccine. *Bull. Math. Biol.,* **68** (8): 2105-2128.

[44] Hale, J. K. (1969). *Ordinary Differential Equations*. New York: John Wiley and Sons.

[45] Hausen, H. (2002). Papillomaviruses and Cancer: From Basic Studies to Clinical Application. *Nature Publishing Group,* **2**: 342-350.

[46] Health Canada. (2010). http://www.hc-sc.gc.ca. Accessed: 19 July 2012.

[47] Hethcote, H. W. (2000). The Mathematics of Infectious Diseases. *SIAM Review,* **42**(4): 599-653.

[48] Hethcote, H. W., & van Ark, J. W. (1987). Epidemiology Models for Heterogeneous Population: Proportionate Mixing, Parameter Estimation, and Immunization Programs.*Math. Biosci.*, **84**: 85-118.

[49] Holowaty, P., Miller, A. B., Rohan, T., & To, T. (1999). Natural History of Dysplasia of the Uterine Cervix. *J Natl Cancer Inst.*, **91**: 252-258.

[50] IARC Working Group. (2007). Human Papillomaviruses: IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. *Lyon, France: International Agency for Research on Cancer,* **90**: 23-476.

[51] Insinga, R., Glass, A. & Rush, B. (2004). The Healthcare Costs of Cervical Human Papillomavirus-related Disease. *Am. J. Obstet. Gynecol.,* **191**: 114-120.

[52] Insinga, R. P. (2007). The Natural History of Low-grade Cervical Intraepithelial Neoplasia. Manuscript in preparation.

[53] Insinga, R. P., Dasbach, E. J., & Elbasha, E. H. (2009). Epidemiologic Natural History and Clinical Management of Human Papillomavirus (HPV) Disease: a Critical and Systematic Review of the Literature in the Development of an HPV Dynamic Transmission Model. *BMC Infectious Diseases*, **9**(119): 1-26.

[54] Institute of Health Economics. (2009). *Human Papillomavirus (HPV): Testing in Alberta*. http://www.ihe.ca. Accessed: 2 January 2013.

[55] Kataja, V., Syrjanen, K., Mantyjarvi, R., et al. (1989). Prospective Follow-up of Cervical HPV Infections: Life Table Analysis of Histopathological, Cytological and Colposcopic Data. *Eur. J. Epidemiol.,* **5**: 1-7.

[56] Kei, K., Katsuyuki, A., Satoko, K., Shiro, K., & Tomoyuki, F. (2012). Therapeutic Human Papillomavirus (HPV) Vaccines: A Novel Approach. *Virol J.*, **6**: 264-269.

[57] Kim, J. J., Wright, T. C., & Goldie, S. J. (2002). Cost-effectiveness of Alternative Triage Strategies for Atypical Squamous Cells of Undetermined Significance. *JAMA*, **287**:2382-2390.

[58] Lakshmikantham, V., Leela, S., & Martynyuk, A. A. (1989). *Stability Analysis of Nonlinear Systems*. Marcel Dekker Inc.: New York and Basel.

[59] LaSalle, J. P. (1976). The stability of dynamical systems. Regional Conference Series in Applied Mathematics, *SIAM*, Philadelphia.

[60] Lipsitch, M. & Murray, M. B. (2003). Multiple Equilibria: Tuberculosis Transmission Require Unrealistic Assumption. *Theor. Popul. Biol.,* **63**(2): 169-170.

[61] Malik, M. T., Reimer, J., Gumel, A. B., Elbasha, E. H., & Mahmud, S. M. (2013). The Impact of an Imperfect Vaccine and Pap Cytology Screening on the Transmission

of Human Papillomavirus and Occurrence of Associated Cervical Dysplasia and Cancer. *Math. Biosci. Engrg.* To appear.

[62] Mandelblatt, J. S., Lawrence, W. F., Womack, S. M., et al. (2002). Benefits and Costs of Using HPV Testing to Screen for Cervical Cancer. *JAMA*, **287**:2372-2381.

[63] McLeod, R. G., Brewster, J. F., Gumel, A. B., & Slonowsky, D. A. (2006). Sensitivity and Uncertainty Analyses for a SARS Model With Time-varying Inputs and Outputs. *Math. Biosci. Eng.*, **3**(3): 527-544.

[64] MicrobiologyBytes. (2009). http://www.microbiologybytes.com/virology. Accessed: 13 March 2013.

[65] Mukandavire, Z., & Garira, W. (2007). Age and Sex Structured Model for Assessing the Demographic Impact of Mother-to-child Transmission of HIV/AIDS. *Bull. Math. Biol.*, **69**(6): 2061-2092.

[66] Muller, M., & Demeret, C. (2012). The HPV E2-Host Protein-Protein Interactions: A Complex Hijacking of the Cellular Network. *Virol J.*, **6**: 173-189.

[67] Myers, E. R. et al. (2000). Mathematical Model for the Natural History of Human Papillomavirus Infection and Cervical Carcinogenesis. *Am. J. Epidemiol.,* **151**(12): 1158-1171.

[68] National Cancer Institute. (2011). *Human Papillomavirus (HPV) Vaccines.* http://www.cancer.gov. Accessed: 19 December 2012.

[69] Onco Health Corp. (2013). http://oncohealthcorp.com/technology. Accessed: 13 March 2013.

[70] Oxford Journals. (2012). *Annual Report to the Nation on the Status of Cancer,1975-2009, Featuring the Burden and Trends in Human Papillomavirus (HPV)-Associated Can-*

cers and HPV Vaccination Coverage Levels. http://jnci.oxfordjournals.org. Accessed: 18 February 2013.

[71] Palefsky, J. M. (2010). Human Papillomavirus-Related Disease in Men: Not Just a Women Issue. *Journal of Adolescent Health,* **46**: 12-19.

[72] Parkin, D., Bray, F., Ferlay, J. & Pisani, P. (2005). Global Cancer Statistics. *Cancer J. Clin.,* **55**: 74-108.

[73] Perko, L. (2001). *Differential Equations and Dynamical Systems*. New York: Springer.

[74] Physicians' Research Network, Inc. (2013). http://www.prn.org. Accessed: 10 March 2013.

[75] Podder, C. N., & Gumel, A. B. (2009). Transmission Dynamics of a Two-sex Model for Herpes Simplex Virus Type2. *Can. Math. Quarterly.,* **17**(2): 339-386.

[76] Public Health Agency of Canada. (2010). Human Papillomavirus. *HPV Purple Paper (bds)*. http://www.phac-aspc.gc.ca/std-mts/hpv-vph/fact-faits-eng.php. Accessed: 11 October 2012.

[77] Public Health Agency of Canada. (2007). *Statement on Human Papillomavirus Vaccine.* http://www.publichealth.gc.ca. Accessed: 5 December 2012.

[78] Roche Molecular Systems Inc. (2013). http://www.hpv16and18.com. Accessed: 15 March 2013.

[79] Spangle, J. M., & Munger, K. (2013). The HPV16 E6 Oncoprotein Causes Prolonged Receptor Protein Tyrosine Kinase Signaling and Enhances Internalization of Phosphorylated Receptor Species. *PLoS. Pathog.*, **9**(3): e1003237. doi: 10.1371/journal.ppat.1003237

[80] Saslow, D. et al. (2012). American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Screening Guidelines for

the Prevention and Early Detection of Cervical Cancer. *Am. J. Clin. Pathol.*, **137**: 516-542.

[81] Seavey, S. E., Holubar, M., Saucedo, L. J., & Perry, M. E. (1999). The E7 Oncoprotein of Human Papillomavirus Type 16 Stabilizes p53 through a Mechanism Independent of p19ARF. *J. Virol.*, **73**(9): 7590-7598.

[82] Severini, A., Jiang, Y., Brassard, P., Morrison, H., Demers, A. A., Oguntuase, E., Al-Rushdi, M., Preston, F., Ratnam, S., & Mao, Y. (2013). Type-specific Prevalence of Human Papillomavirus in Women Screened for Cervical Cancer in Labrador, Canada. *Int J Circumpolar Health*, **72**: doi: 10.3402/ijch.v72i0.19743.

[83] Sharomi, O., & Gumel, A. B. (2011). Mathematical Dynamical Analysis of a Sex-Structured Chlamydia Trachomatis Transmission Model with Time Delay. *Nonlinear Anal. Real World Appl.,* **12**(2): 837-866.

[84] Sharomi, O., & Gumel, A. B. (2009). Re-infection-induced Backward Bifurcation in the Transmission Dynamics of Chlamydia Trachomatis. *Journal of Mathematical Analysis and Applications,* **356**(1): 96-118.

[85] Sharomi, O., Podder, C. N., Gumel, A. B., Elbasha, E. H., & Watmough. J. (2007). Role of Incidence Function in Vaccine-induced Backward Bifurcation in Some HIV Models. *Bull. Math. Biol.,* **210**(2): 436-463.

[86] Sharomi, O., Podder, C. N., Gumel, A. B., & Song, B. (2008). Mathematical Analysis of the Transmission Dynamics of HIV/TB Co-infection in the Presence of Treatment. *Math. Biosci. Engg.,* **5**(1): 145-174.

[87] Smith, H. L. (1995). *Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems*. Mathematical Surveys and Monographs. American Mathematical Society; Providence. **41**.

[88] Smith, H. L., & Waltman, P. (1995). *The Theory of the Chemostat*. Cambridge University Press.

[89] Stanford University. (2005). http://www.stanford.edu. Accessed: 14 March 2013.

[90] Statistics Canada. (2012). www.statcan.gc.ca. Accessed: 20 January 2013.

[91] Thieme, H. R., & Hethcote, H. W. (1985). Stability of the Endemic Equilibrium in Epidemic Models with Subpopulations. *Math. Biosci.,* **75**: 205-227.

[92] Thieme, H.R. (2003). Mathematics in Population Biology. Princeton University Press; Princeton, NJ.

[93] The GlaxoSmithKline Vaccine HPV-007 Study Group. (2009). Sustained Efficacy and Immunogenicity of the Human Papillomavirus (HPV)-16/17 ASO4-adjuvanted Vaccine: Analysis of a Randomised Placebo-controlled Trial up to 6.4 Years. *Lancet,* **374**: 1975-1985.

[94] University of Bristol. (2006). http://www.bristol.ac.uk. Accessed: 1 March 2013.

[95] van den Driessche, P., & Watmough, J. (2005). Reproduction Numbers and Sub-Threshold Endemic Equilibria for Compartmental Models of Disease Transmission. *Math. Biosci.* **180**: 29-48.

[96] Villa, L. L., Costa, R. L., Petta, C. A., Andrade, R. P., Paavonen, J., & Iversen, O-E., et al. (2006). High Sustained Efficacy of a Prophylactic Quadrivalent Human Papillomavirus Types 6/11/16/18 virus-like Particle Vaccine Through 5 Years of Follow-up. *British Journal of Cancer,* **95**(11): 1459-1466.

[97] Walboomers, J. M. M., Jacobs, M. V., & Manos, M. M. et al. (1999). Human Papillomavirus is a Necessary Cause of Invasive Cervical Cancer Worldwide. *J. Pathol.,* **189**(1): 12-19.

[98] Wiggins, S. (1983). *Introduction to Applied Nonlinear Dynamical Systems and Chaos.* New York: Springer- Verlag.

[99] Winer, R. L., Kiviat, N. B., Hughes, J. P., et al. (2005). Development and Duration of Human Papillomavirus Lesions, After Initial Infection. *J Infect Dis.*, **191**: 731-738.

[100] World Health Organization. (2009). Accessed: 11 January 2013.

[101] Xiaodong, L., Hethcote, H. W., & van den Driessche, P. (1993). An Epidemiological Model for HIV/AIDS with Proportional Recruitment. *Math. Biosci.*, **118**: 181-195.

[102] Yew, C. W., Lee, P., Chan, W. K., Lim, V. K., Tay, S. K., Tan, T. M., & Deng, L. W. (2011). A Novel MLL5 Isoform That Is Essential to Activate E6 and E7 Transcription in HPV16/18-associated Cervical Cancers. *Cancer Res.*, **71**(21): 6696-6707.

[103] Zhang, X. & Liu, X. (2009). Backward Bifurcation and Global Dynamics of an SIS Epidemic Model with General Incidence Rate and Treatment. *Nonlinear Anal: Real World Appl.,* **10**: 565-575.

[104] Zhang, X. & Liu, X. (2008). Backward Bifurcation of an Epidemic Model with Saturated Treatment Function. *J. Math. Anal. Appl.,* **348**: 433-443.