Mathematics of HSV-2 Dynamics

by

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Abstract

The thesis is based on using dynamical systems theories and techniques to study the qualitative dynamics of herpes simplex virus type 2 (HSV-2), a sexually-transmitted disease of major public health significance. A deterministic model for the interaction of the virus with the immune system in the body of an infected individual (*in vivo*) is designed first of all. It is shown, using Lyapunov function and LaSalle's Invariance Principle, that the virus-free equilibrium of the model is globally-asymptotically stable whenever a certain biological threshold, known as the *reproduction number*, is less than unity. Furthermore, the model has at least one virus-present equilibrium when the threshold quantity exceeds unity. Using persistence theory, it is shown that the virus will always be present *in vivo* whenever the reproduction threshold exceeds unity. The analyses (theoretical and numerical) of this model show that a future HSV-2 vaccine that enhances cell-mediated immune response will be effective in curtailling HSV-2 burden *in vivo*.

A new single-group model for the spread of HSV-2 in a homogenously-mixed sexually-active population is also designed. The disease-free equilibrium of the model is globally-asymptotically stable when its associated reproduction number is less than unity. The model has a unique endemic equilibrium, which is shown to be globally-stable for a special case, when the reproduction number exceeds unity. The model is extended to incorporate an imperfect vaccine with some therapeutic benefits. Using centre manifold theory, it is shown that the resulting vaccination model undergoes a vaccine-induced backward bifurcation (the epidemiological importance of the phenomenon of backward bifurcation is that the classical requirement of having the reproduction threshold less than unity is, although necessary, no longer sufficient for disease elimination. In such a case, disease elimination depends upon the initial sizes of the sub-populations of the model). Furthermore, it is shown that the use of such an imperfect vaccine could lead to a positive or detrimental population-level impact (depending on the sign of a certain threshold quantity). The model is extended to incorporate the effect of variability in HSV-2 susceptibility due to gender differences. The resulting two-group (sex-structured) model is shown to have essentially the same qualitative dynamics as the single-group model. Furthermore, it is shown that adding periodicity to the corresponding autonomous two-group model does not alter the dynamics of the autonomous two-group model (with respect to the elimination of the disease). The model is used to evaluate the impact of various anti-HSV control strategies.

Finally, the two-group model is further extended to address the effect of risk structure (i.e., risk of acquiring or transmitting HSV-2). Unlike the two-group model described above, it is shown that the risk-structured model undergoes backward bifurcation under certain conditions (the backward bifurcation property can be removed if the susceptible population is not stratified according to the risk of acquiring infection). Thus, one of the main findings of this thesis is that risk structure can induce the phenomenon of backward bifurcation in the transmission dynamics of HSV-2 in a population.

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Dedication

To the memory of my lovely mother (Late - Sufala Rani Podder) and my beloved family (wife - Rita Rani Saha and daughter - Chandrima Podder).

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Glossary

Abbreviation	Meaning
DFE	Disease-free equilibrium
EEP	Endemic equilibrium point
GAS	Globally-asymptotically stable
HSV	Herpes simples virus
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
IVP	Initial-value problem
LAS	Locally-asymptotically stable
ODE	Ordinary differential equation
STD	Sexually-transmitted disease
VFE	Virus-free equilibrium
VPE	Virus-present equilibrium

Chapter 1

Introduction

1.1 Herpes Simplex Virus Type 2 (HSV-2)

HSV-2 is a highly-prevalent sexually-transmitted disease (STD) that causes severe public health burden globally, with the highest prevalence in sub-Saharan Africa and some Asian countries [94]. Approximately 22% of the general population in the United States is infected with HSV-2 [10, 35]. In general, HSV-2 seroprevalence is high in populations whose behavior leads to high risk of acquiring other STDs (some studies show more than 80% HSV seropositivity in sex workers [94]) [6, 27, 51, 63, 68, 90, 92, 94]. Furthermore, data shows that HSV-2 seropositivity is uniformly higher in women than in men, and increases with age [94].

Of the twenty five types of HSV viruses, nine are known to infect humans [69]. Theses are: *Herpes simplex-1* (HSV-1; commonly associated with oral infection), *Herpes simplex-2* (HSV-2; associated with genital infection), *Varicella Zoster virus* (VSV), *Epstein-Barr Virus* (EBV), *Cytomegalovirus* (CMV), *Herpes lymphotropic virus*, *Human herpes virus-7* (HHV-7), *Human herpes virus-8* (HHV-8) and K*aposi's sarcoma-associated herpes virus* (KSHV). Among the nine types that infect humans, only HSV-2 is primarily transmitted sexually (although HSV-1 may also be transmitted sexually

[69]).

HSV-2, a large double-standard DNA virus, targets and infects almost any human cell (such as endothelial cells and fibroblasts) [69]. The virus binds on to the surface of the host cell using its glycoproteins. After binding to the surface of the host cell, the virus then fuses with the plasma membrane of the host cell (using gB) to release some of its proteins into the cytoplasm of the host cell [69]. Subsequently, the virus replicates within the cell (see Figure 1.1), and viral particles are released back into the body of the infected host after the affected cell has disintegrated (following lysis). It is also known that HSV-2 is able to pass through intercellular junctions, thereby spreading from cell-to-cell [69].

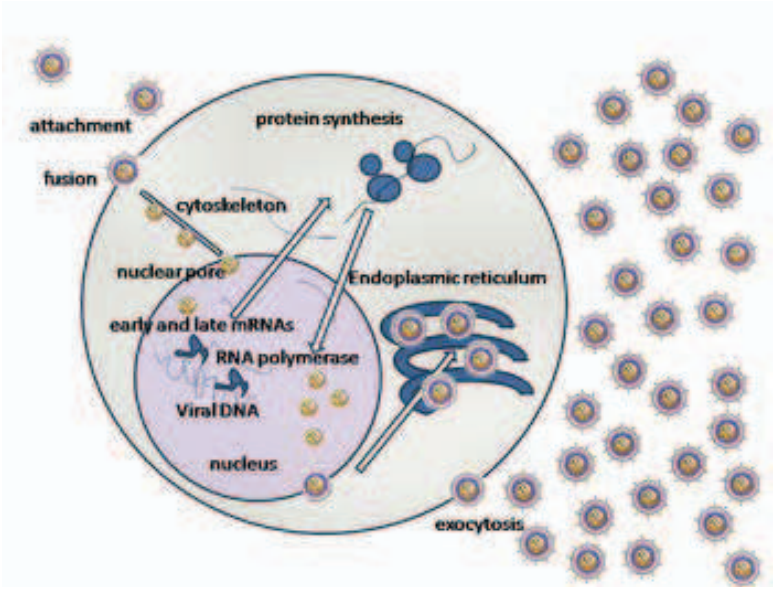


Figure 1.1: Schematic diagram of HSV replication [97].

HSV-2 is most easily transmitted by direct contact with a lesion or body fluid of an infected individual. Transmission may also occur through skin-to-skin contact during periods of asymptomatic shedding [97]. The incubation period is typically between 2 and 20 days [102]. The common symptoms of HSV-2 include itching or pain, followed by sores that appear a few hours to a few days later. The sores, which normally appear

on the genital areas, start out as red bumps that soon turn into red, watery blisters. HSV-2, like HIV, can also be transmitted vertically (from an infected mother to a child) at time of delivery (leading to devastating systemic infection with *encephalitis*). HSV-2 infection is lifelong, and latent infection can re-activate to cause one or more round of disease. Genital herpes is commonly caused by HSV-2 (it can also be caused by HSV-1, but less commonly).

As noted by Corey and Handsfield [24], "a crucial issue in the public health problem of genital herpes is the high proportion of genital HSV infections that are unrecognized by both patients and clinicians. Persons who are HSV-2 seropositive may be symptomatic but nevertheless fail to recognize genital herpes, thereby serving as reservoir for transmission". In other words, not all people infected with HSV-2 will develop symptoms (transmission appeared in about 70% of patients following sexual contact during the periods of asymptomatic viral shedding [65]). As many as 60-70% of people with evidence of HSV-2 infection (as diagnosed by a blood test) have not had symptoms diagnosed as genital herpes [37, 65]. Thus, asymptomatic transmission is an important feature of HSV-2 disease that needs to be taken into consideration in HSV-2 modelling studies.

There is currently no cure for HSV-2. However, the use of condoms is known to offer significant protection against HSV-2 infection, particularly in susceptible women [14, 91]. Similarly, antiviral drugs (such as, *aciclovir (Zovirax)*, *valaciclovir (Valtrex)*, *famciclovir (Famvir)*, *peniciclovir*) can reduce the frequency, duration and severity of outbreaks (antiviral drugs also reduce asymptomatic shedding [12, 52, 59, 77]). Although no suitable anti-HSV-2 vaccine is currently available for use in humans, numerous HSV-2 vaccine studies, have been embarked upon (dating back to the 1920s), and a number of candidate vaccines are undergoing various stages of clinical trials (see, for instance, [5, 10, 50, 57, 74, 80, 87] and some of the references therein).

Data shows that HSV-2 seropositivity is uniformly higher in women than in men

[12, 23, 64, 94]. This may be due to a number of reasons, such as the fact that male-to-female transmission is more likely than female-to-male transmission [23] and the higher rate of disease recurrences in men (which may make them more infectious [12], and, hence, more likely to transmit the disease to their female partners). Furthermore, studies have shown that the majority of HSV-2 infections is largely due to individuals in high-risk populations [25, 34]. These high-risk populations include:

(i) sexually-active females (HSV-2 seropositivity is uniformly higher in females than in males [12, 25, 94]);

(ii) sexually-active adults (especially those who had first intercourse at early age) [34];

(iii) sexually-active adults of lower socio-economic status [25, 34];

(iv) sexually-active individuals with previous history of other STDs [25, 34];

(v) sexually-active individuals with multiple sex partners (this includes elderly people as well) [25, 34];

(vi) sexually-active individuals who do not practice safe sex (e.g., these who do not use condoms consistently) [25].

Figure 1.2 depicts the age- and sex-specific rates of HSV-2 infection in a suburban population in the USA [33] . The figure shows that the relative risk of acquisition of infection is always higher for women than for men. It is also noticeable from Figure 1.2 that, for the 18-49 year age bracket, HSV-2 seropositivity (for both males and females) increases with increasing age (see also Table 1.1 for a data set for HSV-2 seropositivity from Rome, Italy [81]).

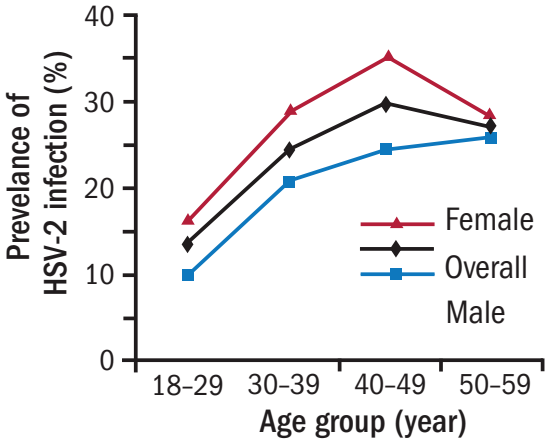


Figure 1.2: Age-specific and sex-specific genital herpes prevalence data for a suburban population [33].

Table 1.1: HSV-2 seroprevalence among various populations in Rome, Italy [81].

	No. of individuals	No. of HSV-2 positive	% HSV-2 positive (95% CI)
Total	673	37	5.5 (3.9-7.5)
Sex			
Males (%)	448	22	4.9 (3.1-7.3)
Females (%)	225	15	6.7 (3.8-10.8)
Age (years)			
1 - 19	168	6	3.6 (1.3 - 7.6)
20 - 29	152	12	7.9 (4.1 - 13.4)
30 - 39	171	7	4.1 (1.7 - 8.3)
40 - 49	98	6	6.1 (2.3 - 12.8)
50 - 99	84	6	7.1 (2.7 - 14.9)
Groups Studied			
Military recruits	156	6	3.8 (1.4 - 8.2)
Outpatients	272	15	5.5 (3.0 - 8.7)
Blood donors	179	11	6.1 (3.1 - 10.7)
Pregnant women	66	5	7.6 (2.5 - 16.8)

1.2 Mathematical Modelling of Infectious Disease

The history of the use of mathematical modelling in disease transmission dates back to the pioneering works of the likes of Daniel Bernoulli, Sir Ronald Ross, Kermack and McKendrick (see, for instance, [2, 3, 8, 43, 53, 54, 73]). The modelling work typically involves the design of models for the transmission dynamics of emerging and re-emerging diseases of public health interest (the models are generally of the forms of

systems of non-linear differential equations), which are then used to evaluate various strategies for controlling the spread of the disease in a population (e.g., vaccination, use of antiviral drugs, quarantine and isolation).

The Kermack-Mckendrick type population-level models are typically designed by splitting the total population at time t, denoted by $N(t)$, into mutually-exclusive compartments (depending on disease status of the individuals in the populations). For instance, $N(t)$ can be divided into compartments for individuals who are susceptible ($S(t)$), infected ($I(t)$) and recovered or removed ($R(t)$), resulting in the classical SIR model. Over the decades, numerous extensions of the Kermack-McKendrick SIR model, incorporating other important epidemiological concepts (such as vaccination, quarantine, isolation, antiviral treatment, periodicity/seasonality considerations), have been designed and used in the mathematical epidemiology literature (see, for instance, [1, 2, 3, 16, 30, 39, 40, 43, 62, 71, 75, 76] and some of the references therein). Some of these models include a class for exposed individuals (denoted by E).

1.3 Motivation and Organization of the Thesis

The central theme of this thesis is to provide deeper qualitative insights into the transmission dynamics and control of HSV-2 *in vivo* (i.e., in the body of an infected host) and in a population. This thesis focuses on the design and mathematical analyses of new and more comprehensive mathematical models for the dynamics of HSV-2 *in vivo* and in a population (it should be mentioned, however, that all the population-level models to be designed are based on a homogenously-mixed heterosexual population). Furthermore, although HSV-2 can be transmitted *via* other means (such as vertical, needle-sharing etc), this thesis considers only sexual mode of HSV-2 transmission. Emphasis is placed on the determination of the existence and stability of associated solutions (equilibria), as well as to characterize the kind of bifurcations the resulting

models will undergo. Knowledge of these dynamical properties is crucial in determining epidemiological thresholds that govern the persistence or elimination of the HSV-2 disease *in vivo* or in the population. Some of the main mathematical and epidemiological questions the thesis seeks to address are:

(a) What kind of dynamics does the virus and the associated host cells exhibit *in vivo*? In particular, what is the impact of cell-mediated and humoral immune responses on HSV-2 dynamics *in vivo*? Under what condition(s) can the virus be cleared from the body of an infected host?

(b) What are the main qualitative features of a single-group model for HSV-2 spread in a homogenously-mixed heterosexual population? What is the impact of an imperfect vaccine on HSV-2 transmission dynamics in a population?

(c) What is the effect of sex-structure (i.e., gender variability) on HSV-2 transmission dynamics in a heterosexual population? What is the role of disease relapse/recurrence on the transmission dynamics of HSV-2 in a population? What is the potential population-level impact of the use of condoms, an imperfect vaccine and antiviral treatment on HSV-2 dynamics?

(d) What is the effect of stratifying the sexually-active heterosexual population in terms of risk of acquiring or transmitting infection on the dynamics of HSV-2 in a population?

The thesis is organized as follows. In Chapter 2, some of the basic mathematical preliminaries, needed to qualitatively analyse the models considered in this thesis, are reviewed. A basic mathematical model for HSV-2 *in vivo* is designed and rigorously analysed in Chapter 3. The model is extended to incorporate the effect of humoral and cell-mediated immune responses. In Chapter 4, a single group model for HSV-2 spread in a homogeneously-mixed heterosexual population is designed. It is extended

to include an imperfect vaccine. A new two-group (sex-structured) model for HSV-2 transmission in a population is designed and analysed in Chapter 5. A non-autonomous version of the model designed in Chapter 5, which accounts for the effect of periodicity on HSV-2 transmission dynamics, is also considered (and qualitatively analysed). The effect of risk structure on HSV-2 transmission dynamics in a population is studied in Chapter 6. Finally, the main contributions of the thesis are summarized in Chapter 7.

Chapter 2

Mathematical Preliminaries

This chapter summarizes some of the main mathematical theories and methodologies relevant to the thesis.

2.1 Equilibria of Linear and Non-linear Systems

Consider the equation

$$\dot{x} = f(x, t; \mu), \quad x \in U \subset \mathbb{R}^n, \quad t \in \mathbb{R}^1, \quad \text{and} \quad \mu \in V \subset \mathbb{R}^p, \tag{2.1}$$

where, U and V are open sets in $\mathbb{R}^n$ and $\mathbb{R}^p$, respectively, and μ is a parameter (and the dot represents differentiation with respect to time). The equation (2.1) is an *ordinary differential equation* (ODE) and the right-hand side function, $f(x, t; \mu)$, is called a *vector field*. ODEs which explicitly depend on time are called *non-autonomous*, while those that are independent of time are called *autonomous*.

Consider the following general autonomous system:

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

Definition 2.1. *An equilibrium solution of the system* (2.2) *is given by* $x = \bar{x} \in \mathbb{R}^n$, *where* $f(\bar{x}) = 0$. *The number* $\bar{x}$ *is called an equilibrium point.*

Theorem 2.1 (Fundamental Existence-Uniqueness Theorem [70])**.** *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 (IVP):*

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

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

Lemma 2.1. [70]. *Let* E *be an open subset of* $\mathbb{R}^n$ *and let* $f : E \to \mathbb{R}^n$. *Then, if* $f \in C^1(E)$, f *is locally Lipschitz on* E.

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

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

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

Definition 2.3. *Let* $x = \bar{x}$ *be an equilibrium solution of* (2.2). *Then,* $\bar{x}$ *is called hyperbolic if none of the eigenvalues of* $Df(\bar{x})$ *have zero real part. An equilibrium point that is not hyperbolic is called non-hyperbolic.*

Definition 2.4. [96]. *The equilibrium* $\bar{x}$ *is said to be stable if given* $\epsilon > 0$, *there exists a* $\delta = \delta(\epsilon) > 0$ *such that, for any solution* $y(t)$ *of* (2.2) *satisfying* $|\bar{x} - y(t_0)| < \delta$, $|\bar{x} - y(t)| < \epsilon$ *for* $t > t_0$, $t_0 \in \mathbb{R}$.

Definition 2.5. [96]. *The equilibrium $\bar{x}$ is said to be asymptotically-stable if (i) it is stable and (ii) there exists a constant $c > 0$ such that, for any solution $y(t)$ of (2.2) satisfying $|\bar{x} - y(t_0)| < c$, then $\lim_{t\to\infty} |\bar{x} - y(t)| = 0$.*

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

Theorem 2.2 ([96])**.** *Suppose all the eigenvalues of $Df(\bar{x})$ have negative real parts. Then the equilibrium solution $x = \bar{x}$ of the system (2.2) is locally-asymptotically stable.*

Definition 2.7. *Let,*

$$\dot{x} = f(x, \mu), \quad x \in \mathbb{R}, \quad \mu \in \mathbb{R}, \tag{2.3}$$

be a one-parameter family of one-dimensional ODEs. An equilibrium solution of (2.3) given by $(x, \mu) = (0, 0)$ is said to undergo bifurcation at $\mu = 0$ if the flow, for μ near zero, and x near zero is not qualitatively the same as the flow near $x = 0$ at $\mu = 0$.

The theorem below is used to prove the presence of backward bifurcation in some of the models developed in the thesis.

Theorem 2.3 (Castillo-Chavez & Song [19])**.** *Consider the following general system of ordinary differential equations with a parameter ϕ*

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \text{ and } f \in \mathbb{C}^2(\mathbb{R}^n \times \mathbb{R}), \tag{2.4}$$

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

A1: *$A = D_x f(0, 0) = \left(\frac{\partial f_i}{\partial x_j}(0, 0)\right)$ is the linearization matrix of the system (2.4) 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;*

A2: *Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue).*

Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0),$$

$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0).$$

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 $\phi = 0$.

2.2 Lyapunov Functions Theory

Definition 2.8. *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*

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

Definition 2.9. *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*

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

Definition 2.10. [96]. *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 2.11. [96]. *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 $x(t, 0, x_0) \in S$ for all $t \in \mathbb{R}$.*

If the region S is restricted to positive times (i.e., $t \geq 0$), then S is a *positively-invariant set*. That is, solutions in a positively-invariant set remain there for all time.

Definition 2.12. *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 2.13. *Consider the following system*

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

Let, $\bar{x}$ be an equilibrium solution of (2.5) 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 $U \backslash \{\bar{x}\}$.*

Any function, V, that satisfies the Conditions (i) and (ii) above is called a *Lyapunov function* [47, 96]. The general Lyapunov Function Theorem is given below.

Theorem 2.4 (LaSalle's Invariance Principle [41])**.** *Consider the following system* (2.5)*. Let,*

$$S = \{x \in \bar{U} : \ \dot{V}(x) = 0\}, \tag{2.6}$$

and M be the largest invariant set of (2.5) *in S. If V is a Lyapunov function on U and $\gamma^+(x_0)$ is a bounded orbit of* (2.5) *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 $t \to \infty$.*

Corolary 2.1. *If $V(x) \to \infty$ as $|x| \to \infty$ and $\dot{V} \leq 0$ on $\mathbb{R}^n$, then every solution of* (2.5) *is bounded and approaches the largest invariant set M of* (2.5) *in the set where $\dot{V} = 0$. In particular, if $M = \{0\}$, then the solution $x = 0$ is globally-asymptotically stable (GAS).*

Theorem 2.5 ([41, 58])**.** *Suppose there is a continuously differentiable, positive definite, and radially unbounded function $V : \mathbb{R}^n \to \mathbb{R}$, such that*

$$\frac{\partial V}{\partial x}(x - \bar{x}) \cdot f(x) = \nabla V(x - \bar{x}) \cdot f(x) \leq W(x) \leq 0, \ \ \forall\, x \in \mathbb{R}^n,$$

where $W(x)$ is any continuous function on U. Then, $\bar{x}$ is a globally-stable equilibrium. The solution $x(t)$ converges to the largest invariant set S contained in $E = \{x \in \mathbb{R}^n : W(x) = 0\}$.

2.3 Comparison Theorem

The use of comparison theorem offers an alternative approach for establishing the global asymptotic stability of equilibria. The methodology entails comparing the solutions of the system of differential equations (assumed to have unique solution)

$$\dot{x} = f(t, x); \tag{2.7}$$

with that of the differential inequality system

$$\dot{z} \leq f(t, z), \tag{2.8}$$

or,

$$\dot{y} \geq f(t, y), \tag{2.9}$$

on an interval. Consider the autonomous system (2.2), where f is continuously differentiable on an open subset $\mathcal{D} \subset \mathbb{R}^n$.

Definition 2.14. *[78]. 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 in $\mathcal{D}$ satisfying $a \leq b$ and $a_i = b_i$.*

Definition 2.15. *[78]. $\mathcal{D}$ 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

$$\frac{\partial f_i}{\partial x_j} \geq 0, \quad i \neq j, \quad x \in \mathcal{D}, \tag{2.10}$$

then f is of Type K in $\mathcal{D}$.

Theorem 2.6 (Comparison Theorem [79])**.** *Let f be continuous on $\mathbb{R} \times D$ and of type K. Let $x(t)$ be a solution of (2.7) defined on $[a, b]$. If $z(t)$ is a continuous function*

on $[a, b]$ *satisfying* (2.8) *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* (2.9) *on* (a, b)*, with* $y(a) \geq x(a)$*, then* $y(t) \geq x(t)$ *for all* t *in* $[a, b]$*.*

2.4 Next Generation Operator Method

The *next generation operator* method [28, 88] is popularly used to compute the associated reproduction number, and also to establish the local asymptotic stability of the associated disease-free equilibrium, of disease transmission models. The formulation in [88] is reproduced below.

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

$$\dot{x}_i = f(x_i) = \mathrm{F}_i(x) - \mathrm{V}_i(x), \quad i = 1, \cdots, n, \tag{2.11}$$

where $\mathrm{V}_i = \mathrm{V}_i^- - \mathrm{V}_i^+$ and the function satisfies the following axioms below. First of all, $X_s = \{x \geq 0 | x_i = 0,\ i = 1, \cdots, m\}$ is defined as the disease-free states (non-infected state variables) of the model, where $x = (x_1, \cdots, x_n)^t, x_i \geq 0$ represents the number of individuals in each compartment of the model.

(A1) if $x \geq 0$, then $\mathrm{F}_i, \mathrm{V}_i^+, \mathrm{V}_i^- \geq 0$ for $i = 1, \cdots, m$.

(A2) if $x_i = 0$, then $\mathrm{V}_i^- = 0$. In particular, if $x \in X_s$ then $\mathrm{V}_i^- = 0$ for $i = 1, \cdots, m$.

(A3) $\mathrm{F}_i = 0$ if $i > m$.

(A4) if $x \in X_s$, then $\mathrm{F}_i(x) = 0$ and $\mathrm{V}_i^+(x) = 0$ for $i = 1, \cdots, m$.

(A5) If $\mathrm{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real part.

In the description above, $\mathrm{F}_i(x)$ represents the rate of appearance of new infections in compartment i; $\mathrm{V}_i^+(x)$ represents the rate of transfer of individuals into compartment

i by all other means, and $\mathrm{V}_i^-(x)$ represents the rate of transfer of individuals out of compartment i. It is assumed that these functions are at least twice continuously-differentiable in each variable [88].

Definition 2.16. ($M-$Matrix). *An $n \times n$ matrix A is an $M-$matrix if and only if every off-diagonal entry of A is non-positive and the diagonal entries are all positive.*

Lemma 2.2. (van den Driessche and Watmough [88]). *If $\bar{x}$ is a DFE of* (2.11) *and $f_i(x)$ satisfy $(A1)-(A5)$, then the derivatives $D\mathrm{F}(\bar{x})$ and $D\mathrm{V}(\bar{x})$ are partitioned as*

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

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

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

Further, F is non-negative, 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 2.7 (van den Driessche and Watmough [88])**.** *Consider the disease transmission model given by* (2.11) *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 the spectral radius), but unstable if $\mathcal{R}_0 > 1$.*

The aforementioned formulation has been extended for use to establish the local stability of the disease-free solution of non-autonomous models for disease transmission [88].

It should be mentioned that, since all the models to be developed in this thesis monitor cell, viral or human populations, all the associated parameters are non-negative. Furthermore, all the numerical simulations in this thesis are carried out using ODE45 (a MATLAB routine).

Chapter 3

Model for HSV-2 Dynamics *in vivo*

3.1 Introduction

Genital herpes, caused by herpes simplex viruses (notably HSV-2), is one of the most prevalent sexually-transmitted diseases globally [6, 27, 51, 63, 68, 71, 90, 92, 94]. Although no cure or suitable vaccine for HSV-2 exist at the present time, it is known that treating HSV-infected individuals with antiviral drugs (such as *aciclovir (Zovirax)*, *valaciclovir (Valtrex)*, *famciclovir (Famvir)*, *peniciclovir*) reduces the frequency, duration and severity of outbreaks [12, 52, 59, 77]. Furthermore, a number of candidate HSV-2 vaccines are undergoing various stages of clinical trials [5, 10, 50, 57, 74, 80, 82, 87]. For instance, several protein subunit candidate vaccines, based on HSV-2 envelope glycoproteins, have reached advanced-phase clinical trials [82]. It is clear, however, that the successful design of such anti-HSV-2 pharmaceutical interventions (antiviral or vaccine) depends on acquiring deeper understanding of the mechanisms of HSV-2 dynamics *in vivo*, as well as the immune response to HSV-2 infection. Consequently, the purpose of this chapter is to provide qualitative insight, *via* the use of mathematical modelling and analyses, into HSV-2 dynamics *in vivo*.

As stated earlier, HSV-2 targets and infects almost any human cell [69]. The virus

binds on to the surface of the host cell using its glycoproteins (*glycoprotein B*, denoted by gB; *glycoprotein C*, denoted by gC; *glycoprotein D*, denoted by gD and *glycoprotein H*, denoted by gH). While the glycoprotein gB is involved in the fusion of the viral membrane with that of the host cell, the glycoproteins gC, gE and gI help the virus escape the associated immune response [69]. Furthermore, when the HSV-2 virion lacks gC, the released virus loses its ability to effectively bind to the surface of the host cell, and the infectivity of the virus is decreased by a factor of 10 [49].

After binding to the surface of the host cell, the virus then fuses with the plasma membrane of the host cell (using gB) to release some of its proteins into the cytoplasm of the host cell [69]. Subsequently, the virus replicates within the cell, and viral particles are released back into the body of the infected host after the affected cell has disintegrated (following lysis). It is also known that HSV-2 is able to pass through intercellular junctions, thereby spreading from cell-to-cell [69].

Upon entering the body, HSV-2 penetrates the nerve cells (primary sensory neurons) in the lower layers of the host's skin tissue and replicates itself in the cell nuclei (thereby destroying the host cells). Following the destruction of the nerve cells, blisters and inflammation develop in the region where the virus was contracted. Towards the end of the visible infection period (typically 3-14 days), viral particles are carried from the skin through the branches of nerve cells to ganglia, where the virus persists in a latent form (until it recurs in an active, visible form) [66]. It is known that stress, strong sunlight and fever can trigger the re-activation of the (latent) virus [69].

Although the dynamics between the immune system and the virus in the body of an infected host is not fully understood, studies have shown that humoral immune response (i.e., the release of antibodies against surface glycoproteins) and cell-mediated immune response (which involves the activation of macrophages, natural killer cells, antigen-specific *cytotoxic T-lymphocytes* (CTLs), and the release of various cytokines in response to HSV-2 infection) are required to fight HSV-2 infection *in vivo*.

The aim of this chapter is to use mathematical modelling and analyses to understand the dynamics of HSV-2 in the body of an infected host. In particular, to assess the impact of cell-mediated and humoral immune responses on HSV-2 dynamics *in vivo*. Although a number of mathematical models have been designed and used to study the transmission dynamics of HSV-2 in human populations (see, for instance, [9, 10, 38, 71, 74]), to the author's knowledge, no other mathematical model for HSV-2 dynamics *in vivo* has so far been published in the literature.

3.2 Model Formulation

The model for HSV-2 dynamics *in vivo* is constructed as follows. Let $H(t)$ represents the density of host healthy (uninfected) cells at time t, $V_C(t)$ represents the density of HSV-2 with gC at time t, $V(t)$ represents the density of HSV-2 without gC at time t, $L_V(t)$ represents the density of HSV-2 that become latent in the neurons (within the nerve cells) at time t, $I(t)$ represents the density of HSV-2-infected cells at time t, $C(t)$ represents the density of CTLs produced by the cell-mediated immune response at time t and $A(t)$ represents the density of HSV-2 specific antibodies produced by the humoral immune response at time t.

It is assumed that healthy host cells are produced at a constant rate Π. These cells become infected, either by the HSV-2 with gC (at a rate β_V) or by the virus without gC (at a reduced rate $\theta\beta_V$, with $0 < \theta < 1$ accounting for the fact that HSV-2 without gC is less likely to infect a healthy cell (due to its reduced ability to bind to the host cell [49]), in comparison to the virus with gC) or by cell-to-cell infection [69] (at a rate β_C). It is assumed that healthy host cells are lost naturally at a rate μ_H (it is assumed that the latent virus (L_V) is not transmitted). Thus,

$$\frac{dH}{dt} = \Pi - \beta_V H V_C - \theta\beta_V H V - \beta_C H I - \mu_H H. \tag{3.1}$$

The rate of change of the density of infected cells is increased by the infection of host cells (as described above). Infected cells are lost due to viral lysis (at a rate γ) and by cell-mediated immune response (at a rate $\rho\epsilon_C$, where $0 < \epsilon_C \leq 1$ is the efficacy of the CTLs to remove infected cells). Hence,

$$\frac{dI}{dt} = \beta_V HV_C + \theta\beta_V HV + \beta_C HI - \gamma I - \rho\epsilon_C CI. \tag{3.2}$$

It is assumed that each infected cell produces N viral particles after its disintegration (following viral lysis). It is further assumed that a proportion, $N_1 \geq 1$, of these (N) viral particles have gC (and are moved to the V_C class) and another proportion, $N_2 \geq 1$, have no gC (and are moved to the V class). The remaining proportion, $N_3 = N - N_1 - N_2$, are assumed to enter the neurons and become latent (and are moved to the L_V class). Thus, the population of viral particles with gC is increased at the aforementioned rate $N_1\gamma$, and by the re-activation of latent viruses (at a rate $\alpha_L(1-\omega)$, where ω represents the fraction of re-activated latent viruses without gC). This population (of viral particles with gC) is reduced by infection of healthy cells by the virus (at the rate β_V), humoral immune response (at a rate $\xi\epsilon_H$, where $0 < \epsilon_H \leq 1$ represents the efficacy of the antibody to neutralize the virus) and natural viral clearance (at a rate μ_V). Thus,

$$\frac{dV_C}{dt} = N_1\gamma I + (1-\omega)\alpha_L L_V - \beta_V HV_C - \xi\epsilon_H V_C A - \mu_V V_C. \tag{3.3}$$

Similarly, the rate of change of the density of viral particles without gC is given by

$$\frac{dV}{dt} = N_2\gamma I + \omega\alpha_L L_V - \theta\beta_V HV - \xi\epsilon_H VA - \mu_V V. \tag{3.4}$$

Latent viruses are generated at the rate $N_3\gamma$, and are reduced due to re-activation (at

the rate α_L) and natural clearance (at a rate μ_L). Thus,

$$\frac{dL_V}{dt} = N_3\gamma I - \alpha_L L_V - \mu_L L_V. \tag{3.5}$$

It is assumed that HSV-specific antibodies (generated from humoral immune response) are produced at a rate proportional to the number of infected cells (given by $\alpha_A I$, where α_A is the production rate of antibodies). Similarly, HSV-specific CTLs are assumed to be produced at a rate proportional to the number of infected cells (given by $\alpha_C I$, where α_C is the production rate of CTLs). The antibodies and CTLs are lost at a rate μ_A and μ_C, respectively. Thus,

$$\frac{dA}{dt} = \alpha_A I - \mu_A A \text{ and } \frac{dC}{dt} = \alpha_C I - \mu_C C. \tag{3.6}$$

In summary, the model for the dynamics of HSV-2 *in vivo*, in the presence of humoral and cell-mediated immune responses, is given by the following system of equations (a flow diagram of the model is given in Figure 3.1, and the associated variables and parameters of the model are described in Table 3.1):

$$\begin{aligned}
\frac{dH}{dt} &= \Pi - \beta_V H V_C - \theta\beta_V H V - \beta_C H I - \mu_H H,\\
\frac{dI}{dt} &= \beta_V H V_C + \theta\beta_V H V + \beta_C H I - \gamma I - \rho\epsilon_C C I,\\
\frac{dV_C}{dt} &= N_1\gamma I + (1-\omega)\alpha_L L_V - \beta_V H V_C - \xi\epsilon_H V_C A - \mu_V V_C,\\
\frac{dV}{dt} &= N_2\gamma I + \omega\alpha_L L_V - \theta\beta_V H V - \xi\epsilon_H V A - \mu_V V,\\
\frac{dL_V}{dt} &= N_3\gamma I - \alpha_L L_V - \mu_L L_V,\\
\frac{dA}{dt} &= \alpha_A I - \mu_A A,\\
\frac{dC}{dt} &= \alpha_C I - \mu_C C.
\end{aligned} \tag{3.7}$$

The model (3.7) incorporates the following main features:

(i) Cell-mediated immune response against HSV-2 infection (at a rate $\rho\epsilon_C$);

(ii) Humoral immune response against HSV-2 infection (at a rate $\xi\epsilon_H$);

(iii) Three viral classes: two infectious (V_C and V; with and without gC, respectively) and one latent (L_V);

(iv) Cell-to-cell transmission of HSV-2 (at a rate β_C);

(v) Re-activation of latent virus (at a rate α_L).

Table 3.1: Description of variables and parameters of the model (3.7).

Variables	Description
$H(t)$	Density of host healthy cells
$V_C(t)$	Density of HSV-2 with glycoprotein (gC)
$V(t)$	Density of HSV-2 without gC
$L_V(t)$	Density of HSV-2 latent in the neurons
$I(t)$	Density of HSV-2 infected cells
$C(t)$	Density of CTLs cells produced by the cell-mediated immune response
$A(t)$	Density of HSV-2 specific antibodies produced by the humoral immune response

Parameter	Description	Assumed Baseline values/hour
Π	Production rate of healthy epithelial cells	Variable
β_V	Effective contact rate between host cells and HSV-2	0.001
β_C	Effective contact rate between host cells and HSV-2 infected cells	0.001
θ	Modification parameter for the reduced ability of HSV-2 without gC to blind to host cells	0.1
γ	Rate of disintegration of infected cells	1
N_1	Proportion of new viral particles with gC	600
N_2	Proportion of new viral particles without gC	200
N_3	Proportion of new viral particles that become latent	200
ρ	Rate of removal of infected cells by CTLs	Variable
ϵ_C	Efficacy of CTLs to remove infected cells	$(0, 1)$
α_A	Rate of production of HSV-2 specific antibodies	0.5
α_C	Rate of production of HSV-2 specific CTLs	0.5
ξ	Rate of neutralization of virus by HSV-2 specific antibodies	Variable
ϵ_H	Efficacy of humoral antibodies	$(0, 1)$
ω	Fraction of re-activated virus assumed to have gC	0.9
α_L	Re-activation rate of latent virus	0.5
$\mu_H; \mu_A;$ $\mu_C; \mu_L$	Clearance rates for compartments $H(t); A(t);$ $C(t); L_V(t)$, respectively	$\frac{1}{10}, \frac{1}{12}, \frac{1}{12}, \frac{1}{15}$
μ_V	Viral clearance rate	$\frac{1}{10}$

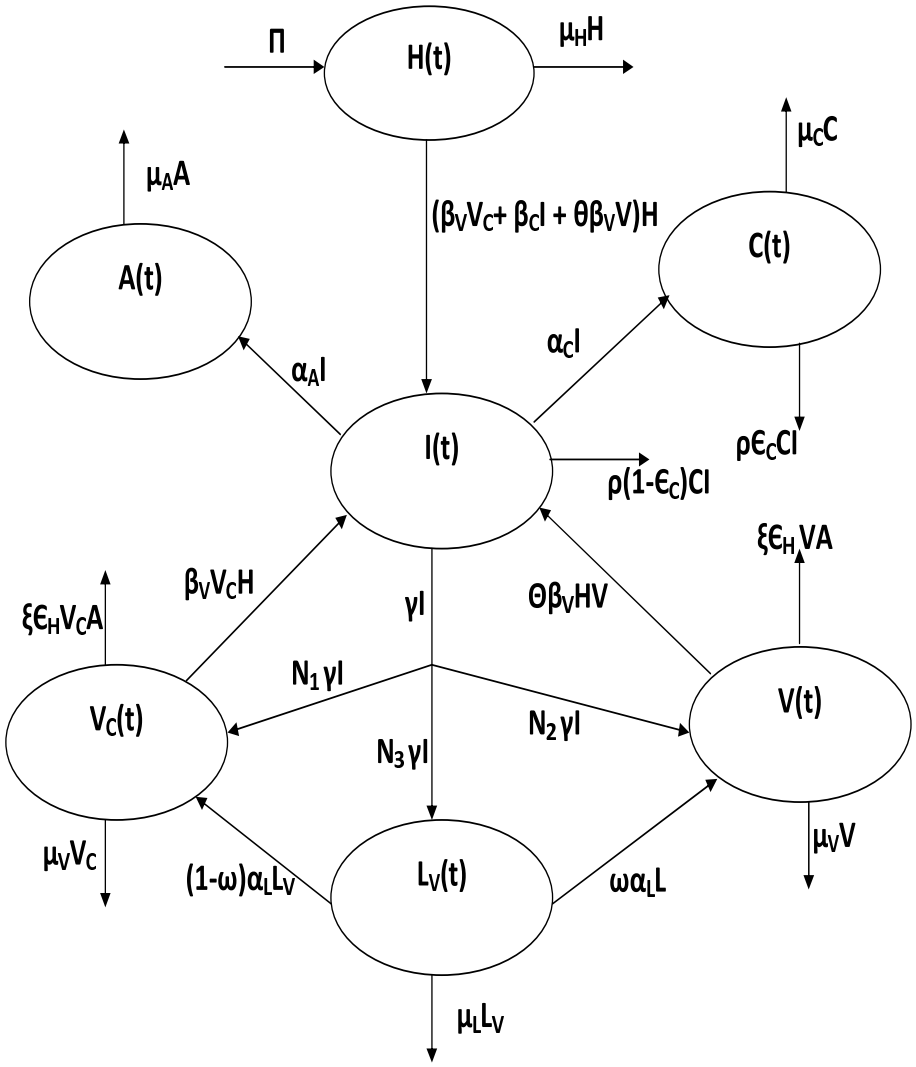


Figure 3.1: Schematic diagram of the model (3.7).

Before analysing the dynamical features of the model (3.7), it is instructive to, first of all, consider a special case of the model in the absence of the cell-mediated and humoral immune responses. The objective is to determine whether such immune responses alter the qualitative dynamics of the model without such responses. This is done below.

3.3 Analysis of Model Without Immune Response

Consider the model (3.7) in the absence of immune response (i.e., consider the model (3.7) with $\rho = \alpha_A = \alpha_C = \xi = 0$). The model (3.7), in the absence of immune response, reduces to the following (reduced model):

$$\begin{aligned}
\frac{dH}{dt} &= \Pi - \lambda_1(t)H(t) - \lambda_2(t)H(t) - \lambda_3(t)H(t) - \mu_H H(t),\\
\frac{dI}{dt} &= \lambda_1(t)H(t) + \lambda_2(t)H(t) + \lambda_3(t)H(t) - \gamma I(t),\\
\frac{dV_C}{dt} &= N_1\gamma I(t) + (1-\omega)\alpha_L L_V(t) - \lambda_1(t)H(t) - \mu_V V_C(t),\\
\frac{dV}{dt} &= N_2\gamma I(t) + \omega\alpha_L L_V(t) - \lambda_2(t)H(t) - \mu_V V(t),\\
\frac{dL_V}{dt} &= N_3\gamma I(t) - k_1 L_V(t),
\end{aligned} \tag{3.8}$$

where,

$$\lambda_1(t) = \beta_V V_C(t), \quad \lambda_2(t) = \theta\beta_V V(t), \quad \lambda_3(t) = \beta_C I(t) \text{ and } k_1 = \mu_L + \alpha_L.$$

3.3.1 Basic Properties

To be biologically meaningful, it is important to prove that the solutions of the reduced model (3.8), with non-negative initial data, will remain non-negative for all time $t > 0$.

Theorem 3.1. *Let the initial data be $H(0) \geq 0$, $I(0) \geq 0$, $V_C(0) \geq 0$, $V(0) \geq 0$ and $L_V(0) \geq 0$. Then, the solutions (H, I, V_C, V, L_V) of the reduced model (3.8) are non-negative for all $t > 0$.*

Proof. Let $T = \sup\{t > 0 : H(t) > 0, I(t) > 0, V_C(t) > 0, V(t) > 0, L_V(t) > 0\}$. Thus, $T > 0$. The first equation of (3.8) can be re-written as:

$$\frac{dH}{dt} + (\lambda(t) + \mu_H)H = \Pi, \quad \textit{where} \quad \lambda(t) = \lambda_1(t) + \lambda_2(t) + \lambda_3(t).$$

Thus,

$$\frac{d}{dt}\left\{H(t)\exp\left[\int_0^T \lambda(u)du + \mu_H T\right]\right\} = \Pi\exp\left[\int_0^T \lambda(u)du + \mu_H T\right],$$

so that,

$$H(T)\exp\left[\int_0^T \lambda(u)du + \mu_H T\right] - H(0) = \int_0^T \Pi\exp\left[\int_0^x \lambda(u)du + \mu_H x\right].$$

Hence,

$$\begin{aligned} H(T) &= H(0)\exp\left\{-\left[\int_0^T \lambda(u)du + \mu_H T\right]\right\} \\ &\quad + \exp\left\{-\left[\int_0^T \lambda(u)du + \mu_H T\right]\right\} \times \int_0^T \Pi\exp\left[\int_0^x \lambda(u)du + \mu_H x\right], \\ &\quad > 0. \end{aligned}$$

Similarly, it can be shown that $I(t) > 0$, $V_C(t) > 0$, $V(t) > 0$ and $L_V(t) > 0$ for all $t > 0$. Hence, all solutions of the reduced model (3.8) remain positive for all non-negative initial conditions, as required. □

Since all the parameters and state variables of the reduced model (3.8) are non-negative for all $t \geq 0$ (Theorem 3.1), it follows from the first equation of (3.8) that

$$\frac{dH}{dt} = \Pi - \lambda_1(t)H - \lambda_2(t)H - \lambda_3(t)H - \mu_H H \leq \Pi - \mu_H H. \tag{3.9}$$

It follows, by comparison theorem (Theorem 2.6), that

$$H(t) \leq H(0)e^{-\mu_H t} + \frac{\Pi}{\mu_H}\left(1 - e^{-\mu_H t}\right).$$

In particular, $H(t) \leq \dfrac{\Pi}{\mu_H}$ if $H(0) \leq \dfrac{\Pi}{\mu_H}$. Consequently, the following biologically-feasible region

$$\mathcal{D} = \left\{(H, I, V_C, V, L_V) \in \mathbb{R}^5_+ : H \leq \Pi/\mu_H, I \geq 0, V_C \geq 0, V \geq 0, L_V \geq 0\right\},$$

is positively-invariant for the reduced model (3.8). In other words, all solutions of the reduced model (3.8), with initial conditions in $\mathcal{D}$, will remain in $\mathcal{D}$ for all $t \geq 0$. It is, therefore, sufficient to consider the solutions of the model in $\mathcal{D}$. In this region, the usual existence, uniqueness and continuation results hold for the model (3.8) (see also [43]). This result, combined with Theorem 3.1, is summarized below.

Lemma 3.1. *The region $\mathcal{D}$ is positively-invariant for the reduced model* (3.8) *with initial conditions in $\mathbb{R}^5_+$.*

Furthermore, it is convenient to define the region:

$$\mathcal{D}_0 = \{(H, I, V_C, V, L_V) \in \mathcal{D} : I = V_C = V = L_V = 0\}.$$

3.3.2 Existence and Stability of Equilibria

The reduced model (3.8) has a virus-free equilibrium (VFE), obtained by setting the right-hand sides of the equations in (3.8) to zero, given by:

$$\mathcal{E}_0 = (H^*, I^*, V_C^*, V^*, L_V^*) = \left(\frac{\Pi}{\mu_H}, 0, 0, 0, 0\right). \tag{3.10}$$

The linear stability of $\mathcal{E}_0$ can be established using the next generation operator method on the system (3.8). Using the notations in [88], the matrices F and Q, for the new infection terms and the remaining transfer terms, are, respectively, given by,

$$F = \begin{bmatrix} \frac{\beta_C \Pi}{\mu_H} & \frac{\beta_V \Pi}{\mu_H} & \frac{\theta \beta_V \Pi}{\mu_H} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

and,

$$Q = \begin{bmatrix} \gamma & 0 & 0 & 0 \\ -N_1\gamma & \dfrac{\beta_V\Pi}{\mu_H} + \mu_V & 0 & -(1-\omega)\alpha_L \\ -N_2\gamma & 0 & \dfrac{\theta\beta_V\Pi}{\mu_H} + \mu_V & -\omega\alpha_L \\ -N_3\gamma & 0 & 0 & k_1 \end{bmatrix}.$$

Thus,

$$\begin{aligned} \mathcal{R}_0 = \rho(FQ^{-1}) = \frac{\beta_C\Pi}{\mu_H\gamma} + \frac{\beta_V\Pi N_1}{\beta_V\Pi + \mu_V\mu_H} + \frac{\beta_V\Pi\theta N_2}{\theta\beta_V\Pi + \mu_V\mu_H} \\ + \frac{\beta_V\alpha_L\Pi N_3[\theta\beta_V\Pi + \mu_V\mu_H\theta\omega + \mu_V\mu_H(1-\omega)]}{k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)}, \end{aligned} \tag{3.11}$$

where ρ is the spectral radius. Hence, using Theorem 2.7, the following result is established.

Lemma 3.2. *The VFE, $\mathcal{E}_0$, of the reduced model* (3.8)*, given by* (3.10)*, is locally-asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The threshold quantity, $\mathcal{R}_0$, is the reproduction number of the reduced model (3.8). It measures the average number of new infected cells produced by a single HSV-2 particle *in vivo* [2, 43, 88]. Lemma 3.2 implies the HSV-2 can be cleared from the body of an infected host (when $\mathcal{R}_0 < 1$) if the initial sizes of the sub-populations of the model (3.8) are in the basin of attraction of the VFE ($\mathcal{E}_0$). To ensure that the viral clearance is independent of the initial sizes of the sub-populations of the model (when $\mathcal{R}_0 < 1$), it is necessary to show that the VFE is globally-asymptotically stable.

Theorem 3.2. *The VFE, $\mathcal{E}_0$, of the reduced model* (3.8)*, is GAS in $\mathcal{D}$ if $\mathcal{R}_0 \leq 1$.*

Proof. Consider the Lyapunov function

$$\mathcal{F} \;=\; f_1I(t) + f_2V_C(t) + f_3V(t) + f_4L_V(t),$$

where,

$$
\begin{aligned}
f_1 &= \beta_C k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H) + \gamma k_1\beta_V\mu_H N_1(\theta\beta_V\Pi + \mu_V\mu_H) \\
&\quad +\gamma k_1\theta\beta_V\mu_H N_2(\beta_V\Pi + \mu_V\mu_H) + \gamma\beta_V\alpha_L\mu_H N_3(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H), \\
f_2 &= k_1\beta_V\mu_H\gamma(\theta\beta_V\Pi + \mu_V\mu_H), \quad f_3 = k_1\theta\beta_V\mu_H\gamma(\beta_V\Pi + \mu_V\mu_H), \\
f_4 &= \beta_V\alpha_L\mu_H\gamma[\theta\beta_V\Pi + \theta\omega\mu_V\mu_H + \mu_V\mu_H(1-\omega)],
\end{aligned}
$$

with Lyapunov derivative given by (where a dot represents differentiation with respect to t)

$$
\begin{aligned}
\dot{\mathcal{F}} &= f_1\dot{I}(t) + f_2\dot{V_C}(t) + f_3\dot{V}(t) + f_4\dot{L_V}(t), \\
&= f_1[\beta_V V_C(t)H(t) + \theta\beta_V V(t)H(t) + \beta_C I(t)H(t) - \gamma I(t)] \\
&+ k_1\beta_V\mu_H\gamma(\theta\beta_V\Pi + \mu_V\mu_H)[N_1\gamma I(t) - \beta_V V_C(t)H(t) - \mu_V V_C(t) + (1-\omega)\alpha_L L_V(t)] \\
&+ k_1\theta\beta_V\mu_H\gamma(\beta_V\Pi + \mu_V\mu_H)[N_2\gamma I(t) - \theta\beta_V V(t)H(t) - \mu_V V(t) + \omega\alpha_L L_V(t)] \\
&+ \beta_V\alpha_L\mu_H\gamma[\theta\beta_V\Pi + \theta\omega\mu_V\mu_H + \mu_V\mu_H(1-\omega)][N_3\gamma I(t) - k_1 L_V(t)],
\end{aligned}
$$

$$= \beta_C k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)[\beta_V V_C(t) + \theta\beta_V V(t) + \beta_C I(t)]H(t)$$

$$+ \gamma k_1\beta_V\mu_H(\theta\beta_V\Pi + \mu_V\mu_H)(N_1 - 1)\beta_V V H(t)$$

$$+ \gamma k_1\beta_V\mu_H N_1(\theta\beta_V\Pi + \mu_V\mu_H)[\theta\beta_V V(t) + \beta_C I(t)]H(t)$$

$$+ \gamma k_1\theta\beta_V\mu_H(\beta_V\Pi + \mu_V\mu_H)(N_2 - 1)\theta\beta_V V_C H(t)$$

$$+ \gamma k_1\theta\beta_V\mu_H N_2(\beta_V\Pi + \mu_V\mu_H)[\beta_V V_C(t) + \beta_C I(t)]H(t)$$

$$+ \gamma\beta_V\alpha_L\mu_H N_3(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)[\beta_V V_C(t) + \theta\beta_V V(t) + \beta_C I(t)]H(t)$$

$$- \gamma k_1\beta_V\mu_H\mu_V(\theta\beta_V\Pi + \mu_V\mu_H)V_C(t) - \gamma k_1\theta\beta_V\mu_H\mu_V(\beta_V\Pi + \mu_V\mu_H)V(t)$$

$$- \gamma k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)\beta_C I(t),$$

$$\leq \beta_C k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)[\beta_V V_C(t) + \theta\beta_V V(t) + \beta_C I(t)]H^*$$

$$+ \gamma k_1\beta_V\mu_H(\theta\beta_V\Pi + \mu_V\mu_H)(N_1 - 1)\beta_V V(t)H^*$$

$$+ \gamma k_1\beta_V\mu_H N_1(\theta\beta_V\Pi + \mu_V\mu_H)[\theta\beta_V V(t) + \beta_C I(t)]H^*$$

$$+ \gamma k_1\theta\beta_V\mu_H(\beta_V\Pi + \mu_V\mu_H)(N_2 - 1)\theta\beta_V V_C(t)H^*$$

$$+ \gamma k_1\theta\beta_V\mu_H N_2(\beta_V\Pi + \mu_V\mu_H)[\beta_V V_C(t) + \beta_C I(t)]H^*$$

$$+ \gamma\beta_V\alpha_L\mu_H N_3(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)[\beta_V V_C(t) + \theta\beta_V V(t) + \beta_C I(t)]H^*$$

$$- \gamma k_1\beta_V\mu_H\mu_V(\theta\beta_V\Pi + \mu_V\mu_H)V_C(t) - \gamma k_1\theta\beta_V\mu_H\mu_V(\beta_V\Pi + \mu_V\mu_H)V(t)$$

$$- \gamma k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)\beta_C I(t),$$

which can be simplified to

$$\begin{aligned}
\dot{\mathcal{F}} &\leq f_1[\beta_V V_C(t) + \theta\beta_V V(t) + \beta_C I(t)]H^* \\
&- \gamma k_1 \beta_V \mu_H(\theta\beta_V\Pi + \mu_V\mu_H)\beta_V V(t)H^* - \gamma k_1\theta\beta_V\mu_H\mu_V(\beta_V\Pi + \mu_V\mu_H)V(t) \\
&- \gamma k_1\beta_V\mu_H\mu_V(\theta\beta_V\Pi + \mu_V\mu_H)V_C(t) - \gamma k_1\theta\beta_V\mu_H(\beta_V\Pi + \mu_V\mu_H)\theta\beta_V V_C(t)H^* \\
&- \gamma k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)\beta_C I(t), \\
&= f_1[\beta_V V_C(t) + \theta\beta_V V(t) + \beta_C I(t)]H^* \\
&- \gamma k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)[\beta_V V_C(t) + \theta\beta_V V(t) + \beta_C I(t)], \\
&= \gamma k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)[\beta_V V_C(t) + \theta\beta_V V(t) \\
&+ \beta_C I(t)]\left[\frac{f_1 H^*}{\gamma k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)} - 1\right], \\
&= \gamma k_1(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)[\beta_V V_C(t) + \theta\beta_V V(t) + \beta_C I(t)](\mathcal{R}_0 - 1), \\
&\leq 0 \ \text{ for } \mathcal{R}_0 \leq 1.
\end{aligned}$$

Since all the model parameters and variables are non-negative for all $t > 0$ (Theorem 3.1), it follows that $\dot{\mathcal{F}} \leq 0$ for $\mathcal{R}_0 \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $V_C(t) = V(t) = I(t) = 0$. Thus, it follows, using the LaSalle's Invariance Principle (Theorem 2.5), that

$$(I(t), V_C(t), V(t)) \to (0, 0, 0) \text{ as } t \to \infty.$$

Hence, for any $\epsilon > 0$ sufficiently small, there exists a $t_a > 0$ such that if $t > t_a$, then

$$I(t) < \epsilon,\ V_C(t) < \epsilon,\ V(t) < \epsilon \text{ and } L_V(t) < \epsilon. \tag{3.12}$$

Consequently, for $t > t_a$ (and noting (3.12)),

$$\begin{aligned}\frac{dH}{dt} &= \Pi - \beta_V V_C(t)H(t) - \theta\beta_V V(t)H(t) - \beta_C I(t)H(t) - \mu_H H(t), \\ &\geq \Pi - [(\beta_V + \theta\beta_V + \beta_C)\epsilon + \mu_H]H(t),\end{aligned}$$

so that, by comparison theorem (Theorem 2.6),

$$\liminf_{t\to\infty} H(t) \geq \frac{\Pi}{[(\beta_V + \theta\beta_V + \beta_C)\epsilon + \mu_H]}. \tag{3.13}$$

Since $\epsilon > 0$ is arbitrarily small, letting $\epsilon \to 0$ in (3.13) gives

$$\liminf_{t\to\infty} H(t) \geq \frac{\Pi}{\mu_H}. \tag{3.14}$$

It should be recalled from Section 3.3.1 that

$$\limsup_{t\to\infty} H(t) \leq \frac{\Pi}{\mu_H}, \tag{3.15}$$

so that, by combining (3.14) and (3.15),

$$\lim_{t\to\infty} H(t) = \frac{\Pi}{\mu_H}.$$

Hence,

$$\lim_{t\to\infty}(H(t), I(t), V_C(t), V(t), L_V(t)) = \left(\frac{\Pi}{\mu_H}, 0, 0, 0, 0\right) = \mathcal{E}_0.$$

Thus, every solution to the equations of the reduced model (3.8), with initial conditions in $\mathcal{D}$, approaches the VFE, $\mathcal{E}_0$, as $t \to \infty$, whenever $\mathcal{R}_0 \leq 1$. □

The biological significance of Theorem 3.2 is that HSV-2 will be cleared from the body of an infected host if the threshold quantity, $\mathcal{R}_0$, can be brought to (and maintained at) a value less than unity (that is, for the reduced model (3.8), $\mathcal{R}_0 \leq 1$ is necessary and sufficient for HSV-2 clearance *in vivo*). Figures 3.2A and B depict the solution profiles of the reduced

model (3.8) for the case when $\mathcal{R}_0 < 1$, showing convergence (of the total healthy epithelial cells and the infected epithelial cells) to the VFE, $\mathcal{E}_0$ (in line with Theorem 3.2).

Let,

$$\mathcal{E}_1 = (H^{**}, I^{**}, V_C^{**}, V^{**}, L_V^{**}),$$

denotes any arbitrary equilibrium of the reduced model (3.8). Furthermore, let

$$\lambda_1^{**} = \beta_V V_C^{**}, \;\; \lambda_2^{**} = \theta\beta_V V^{**} \;\text{ and }\; \lambda_3^{**} = \beta_C I^{**}. \tag{3.16}$$

be the associated *forces of infection* of the reduced model (3.8) at steady-state. To find conditions for the existence of virus-present equilibrium (VPE) (that is, equilibria for which there are HSV-2 particles in the body of the infected host; so that the components I^{**}, V_C^{**}, V^{**} and L_V^{**} are non-zero), the equations in (3.8) are solved in terms of the aforementioned forces of infection at steady-state. Setting the right-hand sides of the reduced model (3.8) to zero gives

$$\begin{aligned}
H^{**} &= \frac{\Pi}{\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**} + \mu_H}, \;\; I^{**} = \frac{\Pi(\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**})}{\gamma(\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**} + \mu_H)}, \\
V_C^{**} &= \frac{\Pi\{(\lambda_1^{**} + \lambda_2^{**})[N_1k_1 + (1-\omega)\alpha_L N_3] + \lambda_2^{**}(1-\omega)\alpha_L N_3 + \lambda_2^{**}k_1(N_1 - 1)\}}{\mu_V k_1(\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**} + \mu_H)}, \\
V^{**} &= \frac{\Pi[(\lambda_1^{**} + \lambda_2^{**})(N_1k_1 + \omega\alpha_L N_3) + \lambda_2^{**}\omega\alpha_L N_3 + \lambda_2^{**}k_1(N_2 - 1)]}{\mu_V k_1(\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**} + \mu_H)}, \\
L_V^{**} &= \frac{\Pi(\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**})N_3}{k_1(\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**} + \mu_H)}.
\end{aligned} \tag{3.17}$$

Substituting (3.17) into the expressions for $\lambda_1^{**}, \lambda_2^{**}$ and λ_2^{**} in (3.16) gives,

$$\lambda_1^{**} = \frac{\beta_V \Pi\{(\lambda_1^{**} + \lambda_2^{**})[N_1 k_1 + (1-\omega)\alpha_L N_3] + \lambda_2^{**}(1-\omega)\alpha_L N_3 + \lambda_2^{**} k_1 (N_1 - 1)\}}{\mu_V k_1 (\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**} + \mu_H)},$$

$$\lambda_2^{**} = \frac{\theta\beta_V \Pi[(\lambda_1^{**} + \lambda_2^{**})(N_1 k_1 + \omega\alpha_L N_3) + \lambda_2^{**}\omega\alpha_L N_3 + \lambda_2^{**} k_1 (N_2 - 1)]}{\mu_V k_1 (\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**} + \mu_H)}, \tag{3.18}$$

$$\lambda_3^{**} = \frac{\beta_C \Pi(\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**})}{\gamma(\lambda_1^{**} + \lambda_2^{**} + \lambda_3^{**} + \mu_H)}.$$

Further simplification of the equations in (3.18) shows that the non-zero (virus-present) equilibria of the reduced model (3.8) satisfy:

$$f(\lambda_1^{**}) = a_0(\lambda_1^{**})^3 + a_1(\lambda_1^{**})^2 + a_2\lambda_1^{**} + a_3 = 0, \tag{3.19}$$

where,

$$\begin{aligned}
a_0 &= \mu_V^2 k_1^4 \beta_V \gamma(1-\theta), \\
a_1 &= k_1^4 \mu_V (1-\theta)(\beta_V \Pi + \mu_H \mu_V)(\beta_C \mu_V + \gamma\beta_V) + k_1^4 \mu_V \gamma\theta\beta_V^2 (\Pi\beta_V + \mu_H\mu_V) N_2 \\
&\quad + k_1^4 \gamma\beta_V^2 \mu_V N_1[\theta\beta_V\Pi + \mu_V\mu_H - (1-\theta)(\beta_V\Pi - \mu_V\mu_H)] + k_1^3 \mu_V\gamma\beta_V^2\alpha_L N_3[\beta_V\theta\Pi \\
&\quad + \mu_V\mu_H(1-\omega) + \theta\omega\mu_H\mu_V - (1-\theta)(1-\omega)(\beta_V\Pi - \mu_V\mu_H)], \\
a_2 &= k_1^2\beta_V[k_1N_1 + (1-\omega)\alpha_L N_3]\{\beta_C k_1 \mu_V(\beta_V\Pi + \mu_V\mu_H)(2\beta_V\theta\Pi - \beta_V\Pi + \mu_V\mu_H) \\
&\quad - \gamma\beta_V k_1\theta(\beta_V\Pi - \mu_V\mu_H)(\beta_V\Pi + \mu_V\mu_H)N_2 - \gamma\beta_V k_1(\beta_V\Pi - \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)N_1 \\
&\quad - k_1\mu_V\mu_H\beta_V^2\gamma\Pi(1-\theta)N_1 - \gamma\beta_V(\beta_V\Pi - \mu_V\mu_H)\alpha_L[\beta_V\theta\Pi + \mu_V\mu_H\theta\omega + \mu_V\mu_H(1-\omega)]N_3 \\
&\quad - \mu_V\mu_H\beta_V^2\gamma\Pi\alpha_L(1-\theta)(1-\omega)N_3 + \gamma\beta_V k_1(\beta_V\Pi + \mu_V\mu_H)[\beta_V\theta\Pi + \mu_V\mu_H(2-\theta)]\}, \\
a_3 &= \beta_V^2 k_1^2 \mu_H\gamma[k_1N_1 + (1-\omega)\alpha_L N_3]^2(\beta_V\Pi + \mu_V\mu_H)(\theta\beta_V\Pi + \mu_V\mu_H)(1 - \mathcal{R}_0).
\end{aligned} \tag{3.20}$$

It can be seen from the expressions in (3.20) that $a_0 > 0$ (since all the model parameters are non-negative, and $0 < \theta < 1$). Furthermore, $a_3 < 0$ whenever $\mathcal{R}_0 > 1$. Thus, the number of possible positive real roots the polynomial (3.19) can have depends on the signs of the coefficients a_1 and a_2. This can be analysed using the Descartes Rule of Signs on the cubic $f(x) = a_0x^3 + a_1x^2 + a_2x + a_3$, given in (3.19) (with $x = \lambda_1^{**}$). The various possibilities for the roots of $f(x)$ are tabulated in Table 3.2.

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

Cases	a_0	a_1	a_2	a_3	Number of sign changes	Number of possible positive real roots (endemic equilibrium)
1	+	+	+	-	1	1
2	+	+	-	-	1	1
3	+	-	+	-	3	1,3
4	+	-	-	-	1	1

The result below follows from the various possibilities enumerated in Table 3.2:

Theorem 3.3. *The reduced model* (3.8) *has at least one VPE, of the form* $\mathcal{E}_1$*, whenever* $\mathcal{R}_0 > 1$.

In summary, it is shown that the reduced model (3.8) has a globally-asymptotically stable virus-free equilibrium ($\mathcal{E}_0$) whenever $\mathcal{R}_0 < 1$. It has a unique virus-present equilibrium ($\mathcal{E}_1$) whenever $\mathcal{R}_0 > 1$. The full model (3.7) will now be rigorously analysed.

3.4 Analysis of Model with Immune Response

3.4.1 Basic Properties

The approach in Section 3.3.1 can be used to prove the following result.

Theorem 3.4. *Let the initial data be* $H(0) \geq 0$, $I(0) \geq 0$, $A(0) \geq 0$, $C(0) \geq 0$, $V_C(0) \geq 0$, $V(0) \geq 0$ *and* $L_V(0) \geq 0$. *Then, the solutions* $(H, I, A, C, V_C, V, L_V)$ *of the model* (3.7) *are non-negative for all* $t > 0$.

As in the case of the reduced model (3.8), all the parameters and state variables of the model (3.7) are non-negative for all $t \geq 0$. Using the approach in Section 3.3.1, it can be shown that the region

$$\mathcal{D}_1 = \left\{(H, I, A, C, V_C, V, L_V) \in \mathbb{R}^7_+ : H \leq \Pi/\mu_H, I \geq 0, A \geq 0, C \geq 0, V_C \geq 0, V \geq 0, L_V \geq 0\right\},$$

is positively-invariant for the model (3.7).

3.4.2 Existence and Stability of Equilibria

The VFE of the model (3.7) is given by

$$\mathcal{E}_{01} = (H^*, I^*, A^*, C^*, V_C^*, V^*, L_V^*) = \left(\frac{\Pi}{\mu_H}, 0, 0, 0, 0, 0, 0\right). \tag{3.21}$$

The next generation matrices associated with the model (3.7) (denoted by F_1 and Q_1) are given, respectively, by:

$$F_1 = \begin{bmatrix} \frac{\beta_C \Pi}{\mu_H} & 0 & 0 & \frac{\beta_V \Pi}{\mu_H} & \frac{\theta\beta_V \Pi}{\mu_H} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

and,

$$Q_1 = \begin{bmatrix} \gamma & 0 & 0 & 0 & 0 & 0 \\ -\alpha_A & \mu_A & 0 & 0 & 0 & 0 \\ -\alpha_C & 0 & \mu_C & 0 & 0 & 0 \\ -N_1\gamma & \dfrac{\beta_V\Pi}{\mu_H}+\mu_V & 0 & -(1-\omega)\alpha_L & & \\ -N_2\gamma & 0 & 0 & 0 & \dfrac{\theta\beta_V\Pi}{\mu_H}+\mu_V & -\omega\alpha_L \\ -N_3\gamma & 0 & 0 & 0 & 0 & k_1 \end{bmatrix},$$

so that,

$$\mathcal{R}_{01} = \rho(F_1 Q_1^{-1}) = \mathcal{R}_0. \tag{3.22}$$

Hence, the result below follows from Theorem 2.7.

Lemma 3.3. *The VFE, $\mathcal{E}_{01}$, of the model* (3.7)*, given by* (3.21)*, is LAS if $\mathcal{R}_{01} < 1$, and unstable if $\mathcal{R}_{01} > 1$.*

Theorem 3.5. *The VFE, $\mathcal{E}_{01}$, of the model* (3.7)*, is GAS in $\mathcal{D}_1$ if $\mathcal{R}_{01} < 1$.*

Proof. Consider the model (3.7) with $\mathcal{R}_{01} < 1$. The proof is based on using a comparison theorem (Theorem 2.6) [56, 79]. It is worth noting, first of all, that the equations for the infected components of the model (3.7) can be written in matrix-vector form as:

$$\frac{d}{dt}\begin{pmatrix} I(t) \\ A(t) \\ C(t) \\ V_C(t) \\ V(t) \\ L_V(t) \end{pmatrix} = (F_1 - Q_1)\begin{pmatrix} I(t) \\ A(t) \\ C(t) \\ V_C(t) \\ V(t) \\ L_V(t) \end{pmatrix} - P\begin{pmatrix} I(t) \\ A(t) \\ C(t) \\ V_C(t) \\ V(t) \\ L_V(t) \end{pmatrix}, \tag{3.23}$$

where,

$$P \;=\; [H^* - H(t)]\, F_1 + F_2,$$

with,

$$F_2 = \begin{bmatrix} 0 & 0 & \rho\epsilon_C C & 0 & 0 & 0 \\ 0 & 0 & 0 & \xi\epsilon_H A & \xi\epsilon_H A & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

It should be noted that F_1 and F_2 are non-negative matrices. Furthermore, since $H(t) \leq H^*$ in $\mathcal{D}_1$, it follows that the matrix P is non-negative. Thus, it follows from (3.23) that

$$\frac{d}{dt}\begin{pmatrix} I(t) \\ A(t) \\ C(t) \\ V_C(t) \\ V(t) \\ L_V(t) \end{pmatrix} \leq (F_1 - Q_1)\begin{pmatrix} I(t) \\ A(t) \\ C(t) \\ V_C(t) \\ V(t) \\ L_V(t) \end{pmatrix}. \tag{3.24}$$

Using the fact that the eigenvalues of the matrix $F_1 - Q_1$ all have negative real parts (see the local stability result in Section 3.4.2, where $\rho(F_1 Q_1^{-1}) < 1$ if $\mathcal{R}_{01} < 1$, which is equivalent to $F_1 - Q_1$ having eigenvalues with negative real parts when $\mathcal{R}_{01} < 1$ [88]), it follows that the linearized differential inequality system (3.24) is stable whenever $\mathcal{R}_{01} < 1$. It follows, by comparison theorem (Theorem 2.6), that

$$\lim_{t\to\infty}(I(t), A(t), C(t), V_C(t), V(t), L_V(t)) \to (0, 0, 0, 0, 0, 0).$$

Thus, for any $\epsilon > 0$ sufficiently small, there exists a $t_e > 0$ such that if $t > t_e$, then

$$I(t) < \epsilon,\ A(t) < \epsilon,\ C(t) < \epsilon,\ V_C(t) < \epsilon,\ V(t) < \epsilon \text{ and } L_V(t) < \epsilon. \tag{3.25}$$

Consequently, for $t > t_e$ (and noting (3.25)),

$$\begin{aligned}\frac{dH}{dt} &= \Pi - \beta_V V_C(t)H(t) - \theta\beta_V V(t)H(t) - \beta_C I(t)H(t) - \mu_H H(t), \\ &\geq \Pi - [(\beta_V + \theta\beta_V + \beta_C)\epsilon + \mu_H]H(t),\end{aligned}$$

so that, by comparison theorem (Theorem 2.6),

$$\liminf_{t\to\infty} H(t) \geq \frac{\Pi}{[(\beta_V + \theta\beta_V + \beta_C)\epsilon + \mu_H]}. \tag{3.26}$$

Since $\epsilon > 0$ is arbitrarily small, letting $\epsilon \to 0$ in (3.26) gives

$$\liminf_{t\to\infty} H(t) \geq \frac{\Pi}{\mu_H}, \tag{3.27}$$

and it should be recalled from Section 3.4.1 that

$$\limsup_{t\to\infty} H(t) \leq \frac{\Pi}{\mu_H}. \tag{3.28}$$

Combining (3.27) and (3.28) gives

$$\lim_{t\to\infty} H(t) = \frac{\Pi}{\mu_H}.$$

Hence,

$$\lim_{t\to\infty} (H(t), I(t), A(t), C(t), V_C(t), V(t), L_V(t)) = \left(\frac{\Pi}{\mu_H}, 0, 0, 0, 0, 0, 0\right) = \mathcal{E}_{01}.$$

Thus, every solution to the equations of the model (3.7), with initial conditions in $\mathcal{D}_1$, approaches the VFE, $\mathcal{E}_{01}$, as $t \to \infty$, whenever $\mathcal{R}_{01} < 1$. □

The biological implication of Theorem 3.5 is that HSV-2 will be cleared from the body of an infected host whenever $\mathcal{R}_{01} < 1$.

Let,

$$\mathcal{E}_2 = (H^{***}, I^{***}, A^{***}, C^{***}, V_C^{***}, V^{***}, L_V^{***}),$$

denotes any arbitrary equilibrium of the model (3.7). Furthermore, let

$$\begin{aligned} &\lambda_1^{***} = \beta_V V_C^{***}, \;\; \lambda_2^{***} = \theta\beta_V V^{***}, \;\; \lambda_3^{***} = \beta_C I^{***}, \\ &\lambda_4^{***} = \rho\epsilon_C C^{***} \;\text{ and }\; \lambda_5^{***} = \xi\epsilon_H A^{***}, \end{aligned} \tag{3.29}$$

be the associated forces of infection of the model (3.7) at steady-state. Setting the right-hand sides of the model (3.7) to zero gives

$$\begin{aligned} H^{***} &= \frac{\Pi}{\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H}, \\ I^{***} &= \frac{\Pi(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})}{(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)}, \\ A^{***} &= \frac{\Pi\alpha_A(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})}{\mu_A(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)}, \\ C^{***} &= \frac{\Pi\alpha_C(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})}{\mu_C(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)}, \\ V_C^{***} &= \frac{\Pi\{\gamma(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})[N_1k_1 + (1-\omega)\alpha_L N_3] - \lambda_1^{***}k_1(\gamma + \lambda_4^{***})\}}{k_1(\mu_V + \lambda_5^{***})(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)}, \\ V^{***} &= \frac{\Pi[\gamma(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})(N_1k_1 + \omega\alpha_L N_3) - \lambda_2^{***}k_1(\gamma + \lambda_4^{***})]}{k_1(\mu_V + \lambda_5^{***})(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)}, \\ L_V^{***} &= \frac{\Pi\gamma(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})N_3}{k_1(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)}. \end{aligned} \tag{3.30}$$

Substituting (3.30) into the expression for $\lambda_1^{***}, \lambda_2^{***}, \lambda_3^{***}, \lambda_4^{***}$ and λ_5^{***} in (3.29), gives,

$$\lambda_1^{***} = \frac{\beta_V \Pi\{\gamma(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})[N_1 k_1 + (1-\omega)\alpha_L N_3] - \lambda_1^{***} k_1(\gamma + \lambda_4^{***})\}}{k_1(\mu_V + \lambda_5^{***})(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)},$$

$$\lambda_2^{***} = \frac{\theta\beta_V \Pi[\gamma(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})(N_1 k_1 + \omega\alpha_L N_3) - \lambda_2^{***} k_1(\gamma + \lambda_4^{***})]}{k_1(\mu_V + \lambda_5^{***})(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)},$$

$$\lambda_3^{***} = \frac{\beta_C \Pi(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})}{(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)}, \tag{3.31}$$

$$\lambda_4^{***} = \frac{\rho\epsilon_C \Pi\alpha_C(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})}{\mu_C(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)},$$

$$\lambda_5^{***} = \frac{\xi\epsilon_H \Pi\alpha_A(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***})}{\mu_A(\gamma + \lambda_4^{***})(\lambda_1^{***} + \lambda_2^{***} + \lambda_3^{***} + \mu_H)},$$

so that (following further simplifications) the non-zero equilibria of the model (3.7) satisfy:

$$g(\lambda_4^{***}) = b_0(\lambda_4^{***})^6 + b_1(\lambda_4^{***})^5 + b_2(\lambda_4^{***})^4 + b_3(\lambda_4^{***})^3 + b_4(\lambda_4^{***})^2 + b_5\lambda_4^{***} + b_6 = 0, \tag{3.32}$$

where,

$$\begin{aligned} b_0 &= \beta_V^2 \mu_A^2 \mu_C^3 \theta k_1 \beta_C, \\ b_1 &= k_1 \mu_A \mu_C^2 \beta_V (3\mu_A \gamma\theta\beta_C\beta_V\mu_C + \mu_A\theta\mu_H\rho\epsilon_C\alpha_C\beta_V - \mu_C\xi\epsilon_H\alpha_A\mu_H\beta_C \\ &\quad - \mu_C\xi\epsilon_H\alpha_A\mu_H\theta\beta_C), \end{aligned} \tag{3.33}$$

$$
\begin{aligned}
b_2 = & -\gamma\beta_V^2\mu_A^2 N_1 k_1 \mu_H \rho\epsilon_C\alpha_C\theta\mu_C^2 - \beta_V^2\mu_A^2\mu_C^2\gamma\theta N_2 k_1\mu_H\rho\epsilon_C\alpha_C \\
& - \mu_C^2(\beta_V^2\mu_A^2\gamma\theta\omega\alpha_L\mu_H\rho\epsilon_C\alpha_C + \gamma\beta_V^2\mu_A^2(1-\omega)\alpha_L\mu_H\rho\epsilon_C\alpha_C\theta)N_3 \\
& + \mu_C^2(-2\mu_C\gamma\beta_V\mu_A k_1\xi\epsilon_H\alpha_A\mu_H - \beta_V\mu_A^2 k_1\mu_V\mu_H\rho\epsilon_C\alpha_C \\
& - \mu_V\mu_A^2\mu_H\rho\epsilon_C\alpha_C\theta\beta_V k_1 + \mu_C\xi^2\epsilon_H^2\alpha_A^2\mu_H^2 k_1 + 3\mu_C\gamma^2\beta_V^2\mu_A^2\theta k_1 \\
& - 3\beta_V^2\Pi\mu_A^2\rho\epsilon_C\alpha_C\theta k_1 - 2\mu_C\xi\epsilon_H\alpha_A\mu_H\gamma\theta\beta_V\mu_A k_1)\beta_C \\
& + \mu_C^2(-\beta_V\mu_A k_1\xi\epsilon_H\alpha_A\mu_H^2\rho\epsilon_C\alpha_C + 3\gamma\beta_V^2\mu_A^2\theta k_1\mu_H\rho\epsilon_C\alpha_C \\
& - \xi\epsilon_H\alpha_A\mu_H^2\theta\beta_V\mu_A k_1\rho\epsilon_C\alpha_C),
\end{aligned}
$$

$$
\begin{aligned}
b_3 = & \mu_C[-\mu_V\mu_A^2\mu_H^2\rho^2\epsilon_C^2\alpha_C^2\theta\,\beta_V k_1 - 2\beta_V^2\Pi\mu_A^2\rho^2\epsilon_C^2\alpha_C^2\theta\,k_1\mu_H \\
& + 2\mu_C\beta_C(\Pi\mu_A\rho\epsilon_C\,\alpha_C k_1\xi\epsilon_H\alpha_A\mu_H\beta_V + \xi\epsilon_H\alpha_A\mu_H^2 k_1\mu_V\mu_A\rho\epsilon_C\alpha_C \\
& + \xi\epsilon_H\alpha_A\mu_H\theta\beta_V\mu_A k_1\Pi\rho\epsilon_C\alpha_C) - \mu_C^2\gamma^2\beta_V\mu_A k_1\xi\epsilon_H\alpha_A\mu_H\beta_C \\
& - \mu_C^2\xi\epsilon_H\alpha_A\mu_H\gamma^2\theta\,\beta_V\mu_A k_1\beta_C - 2\mu_C\gamma^2\beta_V^2\mu_A^2(1-\omega)\alpha_L\,N_3\mu_H\rho\epsilon_C\alpha_C\theta \\
& - 2\,\mu_C\gamma^2\beta_V^2\mu_A^2\theta\omega\alpha_L\,N_3\mu_H\rho\epsilon_C\alpha_C + \mu_C\gamma\beta_V\mu_A N_1 k_1\mu_H^2\rho\epsilon_C\alpha_C\xi\epsilon_H\alpha_A \\
& - 6\mu_C\gamma\beta_V^2\mu_A^2\theta\,k_1\beta_C\Pi\rho\epsilon_C\alpha_C - 2\mu_C\gamma^2\beta_V^2\mu_A^2\theta\,N_2 k_1\mu_H\rho\epsilon_C\alpha_C \\
& - 2\mu_C\mu_V\mu_A^2\mu_H\rho\epsilon_C\alpha_C\gamma\theta\beta_V k_1\beta_C + \mu_C\xi\epsilon_H\alpha_A\mu_H^2\gamma\theta\beta_V\mu_A N_2 k_1\rho\epsilon_C\alpha_C \\
& + \mu_C\xi\epsilon_H\alpha_A\mu_H^2\gamma\theta\beta_V\mu_A\omega\alpha_L N_3\rho\epsilon_C\alpha_C - 2\mu_C\xi\epsilon_H\alpha_A\mu_H^2\gamma\theta\beta_V\mu_A k_1\rho\epsilon_C\alpha_C \\
& + \mu_C\gamma\beta_V\mu_A(1-\omega)\alpha_L N_3\mu_H^2\rho\epsilon_C\alpha_C\xi\epsilon_H\alpha_A - 2\,\mu_C\gamma\,\beta_V\mu_A^2 k_1\mu_V\mu_H\rho\epsilon_C\alpha_C\beta_C \\
& + 3\,\mu_C\gamma^2\beta_V^2\mu_A^2\theta\,k_1\mu_H\rho\epsilon_C\alpha_C - 2\mu_C\gamma\beta_V\mu_A k_1\xi\epsilon_H\alpha_A\mu_H^2\rho\epsilon_C\alpha_C \\
& - 2\,\mu_C\gamma^2\beta_V^2\mu_A^2 N_1 k_1\mu_H\rho\epsilon_C\alpha_C\theta - \beta_V\mu_A^2 k_1\mu_V\mu_H^2\rho^2\epsilon_C^2\alpha_C^2 \\
& + \mu_C\xi^2\epsilon_H^2\alpha_A^2\mu_H^3 k_1\rho\epsilon_C\alpha_C + \mu_C^2\gamma^3\beta_V^2\mu_A^2\theta\,k_1\beta_C + \mu_C^2\beta_C\gamma\,k_1\mu_H^2\alpha_A^2\xi^2\epsilon_H^2],
\end{aligned}
$$

$$
\begin{aligned}
b_4 = &-\rho\epsilon_C\mu_C\alpha_C(-2\,\alpha_C\rho\epsilon_C\gamma\,{\beta_V}^2{\mu_A}^2\theta\,\Pi\,k_1\mu_H - \alpha_C\rho\epsilon_C\gamma\,\beta_V{\mu_A}^2k_1\mu_V{\mu_H}^2 \\
&+ \mu_C\gamma^3{\beta_V}^2{\mu_A}^2\theta\,k_1\mu_H - \mu_C\gamma^2\beta_V\mu_Ak_1\xi\epsilon_H\alpha_A{\mu_H}^2)N_1 \\
&- \rho\epsilon_C\mu_C\alpha_C(-\mu_C\xi\epsilon_H\alpha_A{\mu_H}^2\gamma^2\theta\,\beta_V\mu_Ak_1 + \mu_C\gamma^3{\beta_V}^2{\mu_A}^2\theta\,k_1\mu_H \\
&- 2\,\alpha_C\rho\epsilon_C\gamma\beta_V^2\mu_A^2\theta\Pi\,k_1\mu_H - \alpha_C\rho\epsilon_C\mu_V\mu_A^2\mu_H^2\gamma\,\theta\,\beta_Vk_1)N_2 \\
&- \rho\epsilon_C\mu_C\alpha_C(-\alpha_C\rho\epsilon_C\mu_V\mu_A^2\mu_H^2\gamma\theta\beta_V\omega\alpha_L - 2\,\alpha_C\rho\epsilon_C\gamma\beta_V^2\mu_A^2(1-\omega)\alpha_L\mu_H\theta\Pi \\
&- \mu_C\gamma^2\beta_V\mu_A(1-\omega)\alpha_L\mu_H^2\xi\epsilon_H\alpha_A - \alpha_C\rho\epsilon_C\gamma\,\beta_V{\mu_A}^2(1-\omega)\alpha_L\mu_H^2\mu_V \\
&- \mu_C\xi\epsilon_H\alpha_A\mu_H^2\gamma^2\theta\beta_V\mu_A\omega\,\alpha_L + \mu_C\gamma^3\beta_V^2\mu_A^2\theta\omega\alpha_L\mu_H - 2\,\alpha_C\rho\epsilon_C\beta_V^2\Pi\mu_A^2\gamma\,\theta\,\omega\,\alpha_L\mu_H \\
&+ \mu_C\gamma^3\beta_V^2\mu_A^2(1-\omega)\alpha_L\mu_H\theta)N_3 - \rho\epsilon_C\mu_C\alpha_C(-\alpha_C\rho\epsilon_C\mu_V^2\mu_A^2\mu_H^2k_1 \\
&+ \mu_C\xi^2\epsilon_H^2\alpha_A^2\mu_H^2k_1\Pi - 2\,\mu_C\xi\epsilon_H\alpha_A{\mu_H}^2k_1\mu_V\mu_A\gamma + \mu_C\gamma^2\beta_V\mu_A^2k_1\mu_V\mu_H \\
&- 2\,\mu_C\gamma\,\beta_V\mu_Ak_1\xi\epsilon_H\alpha_A\mu_H\Pi + \mu_C\mu_V\mu_A^2\mu_H\gamma^2\theta\,\beta_Vk_1 + 3\,\mu_C\gamma^2\beta_V^2\mu_A^2\theta\,k_1\Pi \\
&- 2\,\mu_C\xi\epsilon_H\alpha_A\mu_H\gamma\,\theta\,\beta_V\mu_Ak_1\Pi - 2\,\alpha_C\rho\epsilon_C\mu_V\mu_A^2\mu_H\theta\,\beta_Vk_1\Pi \\
&- 3\,\alpha_C\rho\epsilon_C\beta_V^2\Pi^2\mu_A^2\theta\,k_1 - 2\alpha_C\rho\epsilon_C\beta_V\Pi\mu_A^2k_1\mu_V\mu_H)\beta_C \\
&- \rho\epsilon_C\mu_C\alpha_C(-\mu_C\gamma^3\beta_V^2\mu_A^2\theta\,k_1\mu_H - \mu_C\xi^2\epsilon_H^2\alpha_A^2\mu_H^3k_1\gamma \\
&+ \mu_C\gamma^2\beta_V\mu_Ak_1\xi\epsilon_H\alpha_A\mu_H^2 + \mu_C\xi\epsilon_H\alpha_A\mu_H^2\gamma^2\theta\,\beta_V\mu_Ak_1 \\
&- 2\,\alpha_C\rho\epsilon_C\xi\epsilon_H\alpha_A\mu_H^3k_1\mu_V\mu_A + 2\,\alpha_C\rho\epsilon_C\mu_V\mu_A^2\mu_H^2\gamma\,\theta\,\beta_Vk_1 \\
&- \alpha_C\rho\epsilon_C\beta_V\Pi\,\mu_Ak_1\xi\epsilon_H\alpha_A\mu_H^2 + 2\,\alpha_C\rho\epsilon_C\gamma\,\beta_V\mu_A^2k_1\mu_V\mu_H^2 \\
&+ 4\,\alpha_C\rho\epsilon_C\gamma\,\beta_V^2\mu_A^2\theta\,\Pi\,k_1\mu_H - \alpha_C\rho\epsilon_C\xi\epsilon_H\alpha_A{\mu_H}^2\theta\,\beta_V\Pi\,\mu_Ak_1),
\end{aligned}
$$

$$
\begin{aligned}
b_5 &= \rho^2\epsilon_C^2\mu_A\alpha_C^2(2\mu_A\gamma^2\beta_V^2\mu_C\theta\,\Pi\,k_1\mu_H - \beta_V\Pi\,k_1\xi\epsilon_H\alpha_A\mu_C\mu_H^2\gamma \\
&+ \mu_A\gamma^2\beta_V\mu_C k_1\mu_V\mu_H^2)N_1 + \rho^2\epsilon_C^2\mu_A\alpha_C^2(2\,\mu_A\gamma^2\beta_V^2\mu_C\theta\,\Pi\,k_1\mu_H \\
&- \mu_C\xi\epsilon_H\alpha_A\mu_H^2\theta\,\beta_V\Pi\,k_1\gamma + \mu_A\mu_V\mu_H^2\gamma^2\theta\,\beta_V k_1\mu_C)N_2 \\
&+ \rho^2\epsilon_C^2\mu_A{\alpha_C}^2(\mu_A\mu_V\mu_H^2\gamma^2\theta\,\beta_V\omega\,\alpha_L\mu_C + \mu_A\gamma^2\beta_V(1-\omega)\alpha_L\mu_H^2\mu_V\mu_C \\
&+ 2\,\mu_A\gamma^2\beta_V^2\mu_C\theta\omega\alpha_L\mu_H\Pi - \mu_C\xi\epsilon_H\alpha_A\mu_H^2\gamma\,\theta\,\beta_V\omega\alpha_L\Pi - \gamma\beta_V(1-\omega)\alpha_L\mu_H^2\xi\epsilon_H\alpha_A\mu_C\Pi \\
&+ 2\,\mu_A\gamma^2\beta_V^2(1-\omega)\alpha_L\mu_H\theta\,\mu_C\Pi)N_3 + \rho^2\epsilon_C^2\mu_A\alpha_C^2(-2\mu_C\xi\epsilon_H\alpha_A\mu_H^2 k_1\mu_V\Pi \\
&- \beta_V\Pi^2 k_1\xi\epsilon_H\alpha_A\mu_C\mu_H + 2\,\mu_A\mu_V\mu_H\gamma\,\theta\,\beta_V k_1\mu_C\Pi - \mu_C\xi\epsilon_H\alpha_A\mu_H\theta\,\beta_V\Pi^2 k_1 \\
&+ 2\,\mu_A\gamma\,\beta_V\mu_C k_1\mu_V\mu_H\Pi + \mu_A\mu_V^2\mu_H^2 k_1\gamma\,\mu_C + 3\,\mu_A\gamma\beta_V^2\mu_C\theta\Pi^2 k_1)\beta_C \\
&+ \rho^2\epsilon_C^2\mu_A\alpha_C^2(\mu_A\alpha_C\rho\epsilon_C\mu_V^2\mu_H^3 k_1 + \mu_A\alpha_C\rho\epsilon_C\mu_V\mu_H^2\theta\,\beta_V\Pi\,k_1 \\
&+ 2\,\mu_C\xi\epsilon_H\alpha_A\mu_H^3 k_1\mu_V\gamma - \mu_A\gamma^2\beta_V\mu_C k_1\mu_V\mu_H^2 + \mu_A\alpha_C\rho\epsilon_C\beta_V^2\Pi^2\theta\,k_1\mu_H \\
&+ \beta_V\Pi\,k_1\xi\epsilon_H\alpha_A\mu_C{\mu_H}^2\gamma + \mu_A\alpha_C\rho\epsilon_C\beta_V\Pi\,k_1\mu_V\mu_H^2 - \mu_A\mu_V\mu_H^2\gamma^2\theta\,\beta_V k_1\mu_C \\
&+ \mu_C\xi\epsilon_H\alpha_A\mu_H^2\theta\,\beta_V\Pi\,k_1\gamma - 2\,\mu_A\gamma^2\beta_V^2\mu_C\theta\Pi\,k_1\mu_H), \\
b_6 &= \rho^3\epsilon_C^2\mu_A^2\alpha_C^3\gamma k_1\mu_H(\mu_H\mu_V + \beta_V\Pi)(\theta\beta_V\Pi + \mu_H\mu_V)(1-\mathcal{R}_{01}).
\end{aligned}
$$

It follows from the expressions for b_i $(i = 0, \cdots, 6)$ in (3.33) that $b_0 > 0$ (since all the model parameters are non-negative). Furthermore, the coefficient $b_6 < 0$ whenever $\mathcal{R}_{01} > 1$. Thus, the number of possible positive real roots the polynomial (3.32) can have depends on the signs of b_1, b_2, b_3, b_4 and b_5. This can be analysed using the Descartes Rule of Signs on the sixth degree polynomial $g(x) = b_0x^6 + b_1x^5 + b_2x^4 + b_3x^3 + b_4x^2 + b_5x + b_6$, given in (3.32) (with $x = \lambda_4^{***}$). A table similar to Table 3.2 can be constructed, from which the following result can be established.

Theorem 3.6. *The model* (3.7) *has at least one VPE, of the form* $\mathcal{E}_2$*, whenever* $\mathcal{R}_{01} > 1$*.*

In summary, the full model (3.7) has the following qualitative features:

(i) It has a GAS VFE, given by $\mathcal{E}_{01}$, whenever $\mathcal{R}_{01} < 1$;

(ii) It has at least one VPE, of the form $\mathcal{E}_2$, whenever $\mathcal{R}_{01} > 1$.

The analyses in Sections 3.3 and 3.4 show that the two models, (3.7) and (3.8), exhibit the same qualitative dynamics (each model has a GAS VFE whenever the associated reproduction number is less than unity; each model has at least one VPE when the associated reproduction number exceeds unity). In other words, adding immune responses to the reduced model (3.8) does not alter its qualitative asymptotic dynamics (with respect to the clearance or persistence of the virus *in vivo*).

3.4.3 Sensitivity Analysis

A sensitivity analysis is carried out on some of the key parameters of the model (3.7) (namely, θ, ω and α_L) to measure their impact on HSV-2 dynamics *in vivo*. This entails computing the partial derivatives of $\mathcal{R}_{01}$ with respect to these parameters. It follows from the expression for $\mathcal{R}_{01}$, given in Section 3.4.2, that

$$\frac{\partial \mathcal{R}_{01}}{\partial \theta} = \frac{\beta_V \Pi \mu_H \mu_V (N_2 k_1 + \omega \alpha_L N_3)}{k_1 (\theta \Pi \beta_V + \mu_V \mu_H)^2} > 0,$$

$$\frac{\partial \mathcal{R}_{01}}{\partial \omega} = -\frac{\beta_V \Pi \mu_H \alpha_L N_3 \mu_V (1-\theta)}{k_1 (\theta \Pi \beta_V + \mu_V \mu_H)(\Pi \beta_V + \mu_V \mu_H)} < 0, \tag{3.34}$$

$$\frac{\partial \mathcal{R}_{01}}{\partial \alpha_L} = \frac{\beta_V \Pi \mu_L N_3 [\theta \Pi \beta_V + \mu_V \mu_H (1-\omega) + \theta \omega \mu_H \mu_V]}{k_1^2 (\theta \Pi \beta_V + \mu_V \mu_H)(\Pi \beta_V + \mu_V \mu_H)} > 0.$$

The expressions in (3.34) show that decreasing the ability of the virus without gC to bind to the host cell (i.e., decreasing θ) and decreasing the re-activation rate for latent viruses (i.e., decreasing α_L) will help reduce the burden of HSV-2 *in vivo* (since they result in a decrease in the reproduction number $\mathcal{R}_{01}$; and a decrease in reproduction number is known to be positively-correlated with a decrease in HSV-2 burden *in vivo*). Furthermore, it follows from (3.34) that increasing the fraction of re-activated latent viruses without gC (i.e., increasing ω) will also reduce the burden of HSV-2 *in vivo*. Overall, the above analyses show that a future HSV-2 vaccine will be effective in reducing HSV-2 burden *in vivo* if it:

(i) reduces the ability of HSV-2 without gC to the bind to host cell (i.e., reduce θ);

(ii) reduces the re-activation rate for HSV-2 (i.e., reduce α_L);

(iii) increases the fraction of re-activated latent HSV-2 without gC (i.e., increase ω).

3.5 Numerical Simulations and Discussions

The model (3.7) with immune response is simulated, using the parameter values given in Table 3.1 (unless otherwise stated), to assess the impact of immune response on HSV-2 dynamics *in vivo*. It should be mentioned that since the model presented in this chapter is completely new (no similar in-host model for HSV-2 dynamics has (yet) been published in the literature to the author's knowledge), appropriate data for estimating the associated parameters are not available at the present time. Thus, the parameter values chosen for the numerical simulations below may not all be realistic biologically (although such uncertainties in parameter values are partially addressed below by considering different effectiveness levels of the immune responses in the simulations, it is prudent to emphasize that the simulation results obtained should be interpreted bearing these uncertainties in mind).

3.5.1 Humoral Immune Response Only Strategy

The model (3.7) is considered in the presence of humoral immune response only (i.e., in the absence of cell-mediated immune response, so that $\rho = \epsilon_C = C = 0$). For simulation purposes, the following levels of effectiveness are considered (arbitrarily):

(i) low effectiveness level of the humoral immune response only strategy ($\xi = 0.05, \epsilon_H = 0.1$);

(ii) moderate effectiveness level of the humoral immune response only strategy ($\xi = 0.5, \epsilon_H = 0.2$);

(iii) high effectiveness level of the humoral immune response only strategy ($\xi = 5, \epsilon_H = 0.3$).

In other words, the effectiveness level is increased (from low to high) based on concomitant increase in the associated rate of humoral immune response (ξ) and efficacy (ϵ_H). For this scenario, the simulation results obtained show a decrease in the total number of infected

cells with increasing effectiveness level of the humoral immune response (Figure 3.3). These simulations show that the low and moderate effectiveness levels of the humoral immune response offer very little, or no, impact in curtailing HSV-2 burden *in vivo* (in fact, the low effective humoral immune response coincides with the worst-case scenario, where no anti-HSV-2 immune response in mounted). However, the high effectiveness level of the humoral immune response strategy results in a significant reduction of HSV-2 burden *in vivo*.

3.5.2 Cell-mediated Immune Response Only Strategy

In this scenario, only cell-mediated immune response is allowed (so that, $\xi = \epsilon_H = A = 0$). Here, too, the following effectiveness levels are considered:

(i) low effectiveness level of the cell-mediated immune response only strategy ($\rho = 0.05, \epsilon_C = 0.1$);

(ii) moderate effectiveness level of the cell-mediated immune response only strategy ($\rho = 0.5, \epsilon_C = 0.3$);

(iii) high effectiveness level of the cell-mediated immune response only strategy ($\rho = 5, \epsilon_C = 0.6$).

Here, too, the effectiveness level is increased (from low to high) based on concomitant increase in the associated rate of cell-mediated immune response (ρ) and efficacy (ϵ_C). Figure 3.4 shows that, while the low effectiveness level of the cell-mediated immune response offers marginal reductions in the number of infected cells, the moderate and high effectiveness levels result in a dramatic reduction of HSV-2 burden *in vivo*. Furthermore, it is clear from Figures 3.3 and 3.4 that each of the three effectiveness levels of the cell-mediated immune response strategy is more competitive than its corresponding effectiveness level for the humoral immune response strategy. In other words, these simulations suggest that the cell-mediated immune response is more effective than the humoral immune response in reducing HSV-2 burden *in vivo*.

3.5.3 Combined Immune Response Strategy

In this section, a combined immune response strategy (where both the humoral and cell-mediated immune responses are mounted) is considered. The following levels of effectiveness are considered for this (combined immune response) strategy:

(i) low effectiveness level of the combined immune response strategy ($\xi = \rho = 0.05, \epsilon_H = \epsilon_C = 0.1$);

(ii) moderate effectiveness level of the combined immune response strategy ($\xi = \rho = 0.5, \epsilon_H = 0.2, \epsilon = 0.3$);

(iii) high effectiveness level of the combined immune response strategy ($\xi = \rho = 5, \epsilon_H = 0.3, \epsilon_C = 0.6$).

Figure 3.5 shows that, while the low and moderate effectiveness levels of the combined immune response strategy essentially coincide with their corresponding levels under the cell-mediated immune response strategy (depicted in Figure 3.4), the high effectiveness level of the combined immune response strategy gives the most reduction in the number of infected cells (in comparison to all other effectiveness levels). Thus, these simulations show the following:

(a) The humoral immune response offers marginal or no impact in reducing HSV-2 burden *in vivo* (except if its effectiveness level is high);

(b) The cell-mediated immune response is always more competitive than the humoral immune response strategy in reducing HSV-2 burden *in vivo*;

(c) The high effectiveness level of the combined immune response strategy offers the greatest reduction of HSV-2 burden *in vivo*.

3.6 Summary

In this chapter, a deterministic model for the dynamics of HSV-2 *in vivo* is designed and rigorously analysed. The main findings of this chapter are itemized below:

(i) The reduced model (3.8), without immune response, has a GAS VFE whenever $\mathcal{R}_0 < 1$ (Theorem 3.2);

(ii) The reduced model (3.8) has at least one VPE, of the form $\mathcal{E}_1$, whenever $\mathcal{R}_0 > 1$ (Theorem 3.3);

(iii) The extended model with immune response (3.7) has a GAS VFE whenever $\mathcal{R}_{01} < 1$ (Theorem 3.5);

(iv) The extended model with immune response (3.7) has at least one VPE, of the form $\mathcal{E}_2$, whenever $\mathcal{R}_{01} > 1$ (Theorem 3.6);

(v) A future HSV-2 vaccine will be effective in reducing HSV-2 burden *in vivo* if it reduces the ability of the virus without glycoprotein C (gC) to bind to the host cell, or if it reduces the re-activation rate of latent HSV-2. Additionally, the vaccine will be effective if it results in an increase in the fraction of re-activated latent viruses without gC.

The mathematical analyses carried out in this chapter showed that the two models, with and without immune responses, have the same qualitative features (pertaining to the clearance or persistence of HSV-2 *in vivo*). Furthermore, numerical simulations of the model (3.7) show that:

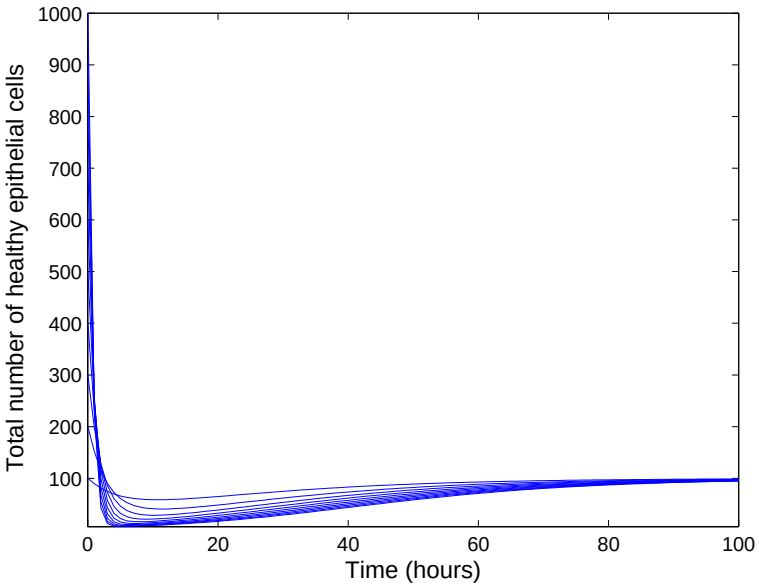
(a) The humoral immune response offers marginal or no impact in reducing HSV-2 burden *in vivo* (except if its effectiveness level is high);

(b) The cell-mediated immune response is more competitive than the humoral immune response strategy in reducing HSV-2 burden *in vivo*;

(c) The high effectiveness level of the combined immune response strategy offers the greatest reduction of HSV-2 burden *in vivo*.

In summary, the main public health finding of this chapter is that, based on the parameter values used in the numerical simulations, a future HSV-2 vaccine that boosts cell-mediated immune response will be effective in reducing HSV-2 disease burden *in vivo*.

(A)



(B)

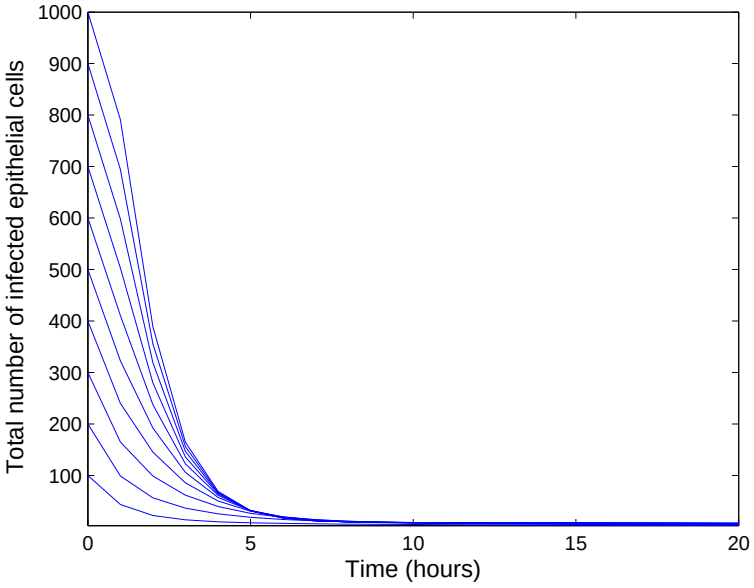


Figure 3.2: Simulations of the reduced model (3.8) using parameter values given in Table 3.1, with $\Pi = 10$ and $N_1 = N_2 = N_3 = 1$ (so that, $\mathcal{R}_0 = 0.88 < 1$) and various initial conditions. (A) Total density of healthy epithelial cells. (B) Total density of infected cells.

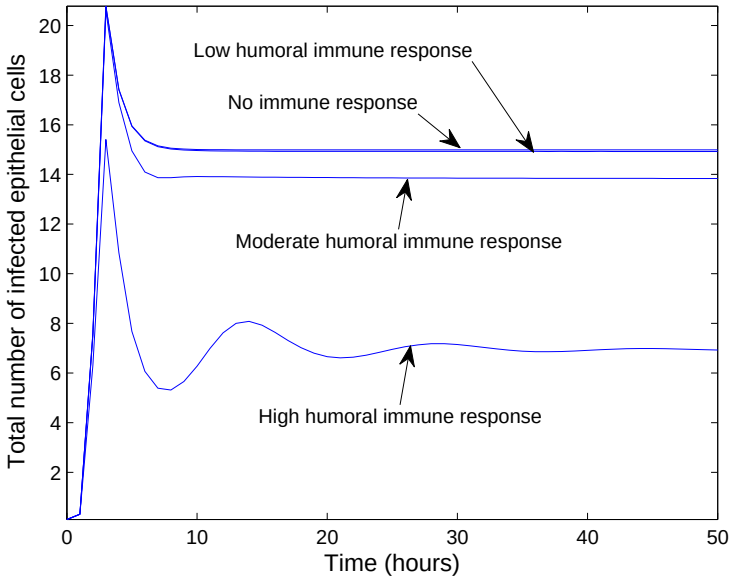


Figure 3.3: Simulations of the extended model (3.7) in the absence of cell-mediated immune response ($\rho = 0$) with different rates ($\xi = 0.05, 0.5, 5$) and efficacy ($\epsilon_H = 0.1, 0.2, 0.3$) of humoral immune response. Plot depicts the total density of the infected epithelial cells as a function of time. Other parameter values used are as given in Table 3.1.

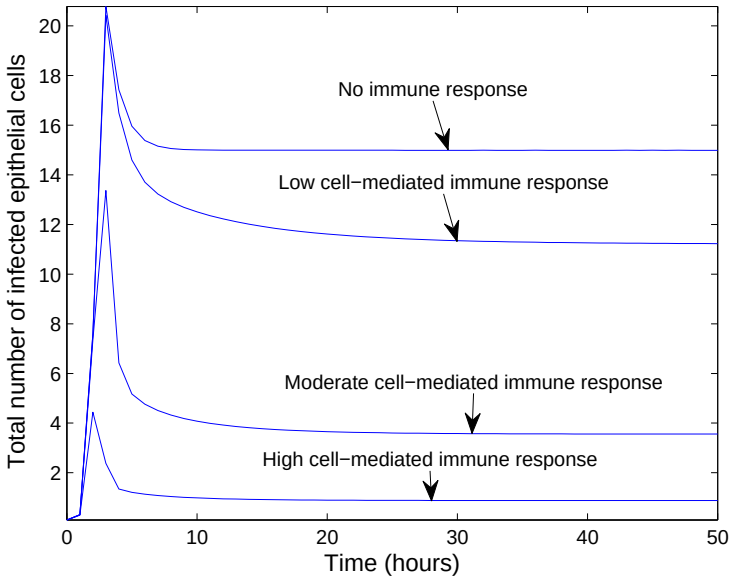


Figure 3.4: Simulations of the extended model (3.7) in the absence of humoral immune response ($\xi = 0$) with different rates ($\rho = 0.05, 0.5, 5$) and efficacy ($\epsilon_C = 0.1, 0.3, 0.6$) of cell-mediated immune response. The plot depicts the total density of the infected epithelial cells as a function of time. Other parameter values used are as given in Table 3.1.

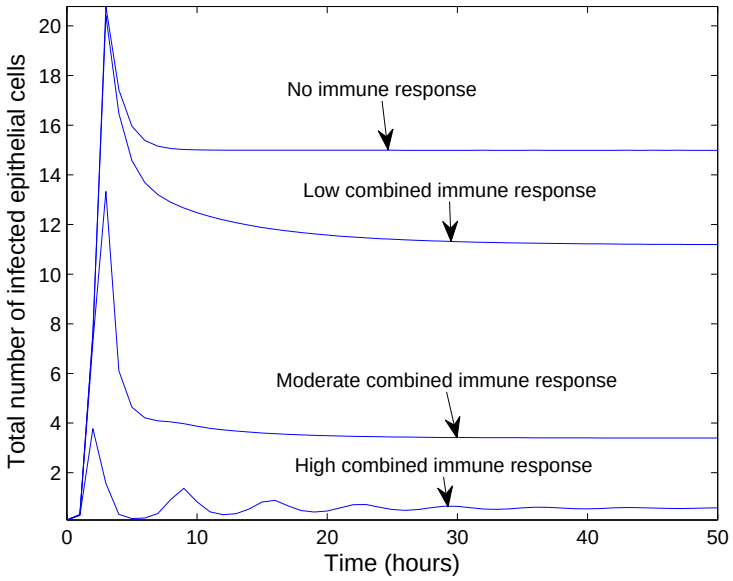


Figure 3.5: Simulations of the extended model (3.7) with combined cell-mediated and humoral immune responses ($\rho = \xi = 0.05, 0.5, 5$) and efficacies ($\epsilon_H = 0.1, 0.2, 0.3$ and $\epsilon_C = 0.1, 0.3, 0.6$). The picture depicts the total density of the infected epithelial cells as a function of time. Other parameter values used are as given in Table 3.1.

Chapter 4

Single Group Model with Vaccination

4.1 Introduction

As stated in Chapter 1, a number of candidate anti-HSV-2 vaccines are undergoing various stages of clinical trials [5, 10, 50, 57, 74, 80, 82, 87], with promising prospects. For instance, some phase 1 and 2 clinical trials showed that humans mount antibody- and T cell-specific responses when they are immunized with HSV-2 gB_2 and gD_2 [57, 74]. Furthermore, a DNA vaccine that encodes gD_2, which is intended to elicit HSV-cellular and humoral immune responses, is in phase 2 trials [50, 74, 80]. Although the concerted global effort to design an effective HSV-2 vaccine is, indeed, promising, it is plausible to expect that any such vaccine will be imperfect (that is, it may not offer full and lasting protection in all vaccinated individuals). The purpose of this chapter is to theoretically assess the potential impact of an imperfect HSV-2 vaccine in a population. The vaccine will be assumed to have some therapeutic benefits (such as, blocking transmission with some efficacy, reducing the transmissibility of break-through infection, slowing onset of symptoms and reducing mortality rate in vaccinated infected individuals).

A few mathematical models, notably by Blower and co-workers (see, for instance, [9,

10, 38, 74]), have been designed and used to gain insight into the transmission dynamics of HSV-2 in a population. Many of these models take the form of deterministic systems of continuous-time differential equations. El-Gohary *et al.* [29] used a stochastic model for the study of optimal stabilization of the steady-states of the genital herpes epidemic. This chapter complements many of the earlier published modelling studies by providing rigorous qualitative analysis of a new realistic mathematical model for HSV-2 transmission dynamics in a homogeneously-mixed heterosexual population. A notable feature of the model is that it allows for disease transmission by asymptomatically-infected individuals (i.e., infected individuals who do not display clinical symptoms of the disease) in addition to including an imperfect HSV-2 vaccine.

4.2 Model Formulation

Before designing the vaccination model, a basic HSV-2 transmission model (without a vaccine) will be formulated (and analysed) first of all. The basic model is designed by sub-dividing the total, homogeneously-mixed, heterosexual, sexually-active population at time t, denoted by $N(t)$, into mutually-exclusive compartments for individuals that are susceptible ($S(t)$), exposed to HSV-2 but show no clinical symptoms of the disease ($E(t)$), infectious (virus-shedding) with clinical symptoms of HSV-2 ($H_u(t)$) and infectious but their infection is quiescent ($Q_u(t)$), so that

$$N(t) = S(t) + E(t) + H_u(t) + Q_u(t).$$

The susceptible population is increased by the recruitment of new sexually-active individuals (assumed susceptible) into the population (at a rate Π). This population is diminished by natural death (at a rate μ) and the acquisition of infection, following effective contact with infectious individuals (in the H_u and Q_u classes), at a rate λ, where,

$$\lambda = \frac{\beta(H_u + \theta Q_u)}{N},$$

is the *force of infection* and β is the effective contact rate. Furthermore, the modification parameter $0 \leq \theta < 1$ accounts for the assumed reduction of infectivity of infectious individuals in the quiescent class (Q_u) in comparison to those in the H_u class (that is, it is assumed that infectious individuals in the quiescent state are less infectious than non-quiescent infectious individuals (in the H_u class), because of their assumed reduced viral load). It is worth emphasizing that the model to be designed is robust enough to allow for disease transmission by individuals in the quiescent state (at the reduced rate $\theta\beta$; such transmission can be relaxed by setting $\theta = 0$). Putting the above assumptions and definitions together gives the following equation for the rate of change of the susceptible population:

$$\frac{dS}{dt} = \Pi - \lambda S - \mu S.$$

The population of exposed humans (that is, newly-infected individuals who have not yet displayed clinical symptoms of the disease) is generated by the infection of susceptible individuals (at the rate λ). It is reduced by the development of clinical symptoms by exposed individuals (at a rate σ) and natural death (at the rate μ). Thus,

$$\frac{dE}{dt} = \lambda S - \sigma E - \mu E.$$

The population of infectious non-quiescent individuals (H_u) is increased by the development of symptoms of exposed individuals (at the rate σ) and by the re-activation of symptoms by individuals in the quiescent state (at a rate r_u). Furthermore, this population is diminished by the acquisition of quiescence status (at a rate q_u), natural death (at the rate μ) and disease-induced death (at a rate δ_u). Thus,

$$\frac{dH_u}{dt} = \sigma E + r_u Q_u - q_u H_u - \mu H_u - \delta_u H_u.$$

Similarly, the rate of change of the population of individuals in the quiescent class (Q_u) is increased by the acquisition of quiescence of individuals in the H_u class (at the rate q_u) and decreases by re-activation of symptoms (at the rate r_u), natural death (at the rate μ) and disease-induced death (at a rate δ_{qu}, where $\delta_{qu} < \delta_u$). This gives

$$\frac{dQ_u}{dt} = q_u H_u - r_u Q_u - \mu Q_u - \delta_{qu} Q_u.$$

Thus, the basic model for the transmission dynamics of HSV-2 in a population is given by the following system of non-linear differential equations [71]:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \lambda S - \mu S, \\
\frac{dE}{dt} &= \lambda S - \sigma E - \mu E, \\
\frac{dH_u}{dt} &= \sigma E + r_u Q_u - q_u H_u - \mu H_u - \delta_u H_u, \\
\frac{dQ_u}{dt} &= q_u H_u - r_u Q_u - \mu Q_u - \delta_{qu} Q_u.
\end{aligned} \tag{4.1}$$

The basic model (4.1) is an extension of the basic (treatment-free) model in [9, 10, 38] and the vaccination-free model in [74], by:

(i) incorporating a compartment for exposed individuals (E);

(ii) adding disease-induced death for infectious individuals (δ_u for individuals in H_u class; and δ_{qu} for those in Q_u class); and

(iii) assuming that quiescent infectious individuals can transmit infection (*albeit* at a lower rate, $\beta\theta$, with $0 < \theta < 1$, in comparison to the non-quiescent infectious individuals).

In addition to the aforementioned extensions, this study contributes to the literature by carrying out a detailed rigorous analysis of the basic model and the extended vaccination model (no such analysis is given in [9, 10, 38, 74]).

4.2.1 Basic Properties

Lemma 4.1. *Let the initial data $S(0) \geq 0$, $E(0) \geq 0$, $H_u(0) \geq 0$ and $Q_u(0) \geq 0$. Then, the solutions (S, E, H_u, Q_u) of the model (4.1) are non-negative for all $t > 0$. Furthermore,*

$$\limsup_{t\to\infty} N(t) \leq \frac{\Pi}{\mu}.$$

Proof. Let $T = \sup\{t > 0 : S, E, H_u, Q_u > 0\}$. Thus, $T > 0$. It follows from the first equation of the differential equation system (4.1) that

$$\frac{d}{dt}\left\{S(t)\exp\left[\int_0^t \lambda(u)du + \mu t\right]\right\} = \Pi\exp\left[\int_0^t \lambda(u)du + \mu t\right].$$

Thus,

$$S(T)\exp\left[\int_0^T \lambda(u)du + \mu T\right] - S(0) = \int_0^T \Pi\exp\left[\int_0^x \lambda(v)dv + \mu x\right]dx,$$

so that,

$$\begin{aligned} S(T) &= S(0)\exp\left[-\int_0^T \lambda(u)du + \mu T\right] + \exp\left[-\int_0^T \lambda(u)du + \mu T\right] \times \\ &\quad \int_0^t \Pi\exp\left[\int_0^x \lambda(v)dv + \mu x\right]dx > 0. \end{aligned}$$

Similarly, it can be shown that $E > 0$, $H_u > 0$ and $Q_u > 0$ for all $t > 0$. Thus, all solutions of the basic model (4.1), with non-negative initial data, remain non-negative for all $t > 0$.

Adding all the equations of the basic model (4.1) gives,

$$\frac{dN(t)}{dt} = \Pi - \mu N(t) - \delta_u H_u(t) - \delta_{qu} Q_u(t). \tag{4.2}$$

Noting that $0 < H_u(t) \leq N(t)$ and $0 < Q_u(t) \leq N(t)$, and considering $\delta = \max\{\delta_u, \delta_{qu}\}$, it follows from (4.2) that

$$\Pi - (\mu + 2\delta)N(t) \leq \frac{dN(t)}{dt} < \Pi - \mu N(t).$$

Thus,

$$\frac{\Pi}{\mu + 2\delta} \leq \liminf_{t\to\infty} N(t) \leq \limsup_{t\to\infty} N(t) \leq \frac{\Pi}{\mu},$$

so that,

$$\limsup_{t\to\infty} N(t) \leq \frac{\Pi}{\mu}, \text{ as required.}$$

□

The above result can also be established using Proposition A.1 in Appendix A of [86].

Consider the biologically-feasible region

$$\mathcal{D} = \left\{(S, E, H_u, Q_u) \in \mathbb{R}^4_+ : S + E + H_u + Q_u \leq \frac{\Pi}{\mu}\right\}.$$

The following steps are followed to establish the positive invariance of $\mathcal{D}$ (i.e., all solutions in $\mathcal{D}$ remain in $\mathcal{D}$ for all $t > 0$). The rate of change of the total population, obtained by adding all the equations in the model (4.1), is given by

$$\frac{dN}{dt} = \Pi - \mu N - \delta_u H_u - \delta_{qu} Q_u. \tag{4.3}$$

It follows that if $N > \Pi/\mu$, then $dN/dt < 0$. Since $dN/dt < \Pi - \mu N$ from (4.3), a standard comparison theorem (Theorem 2.6) can be used to show that $N(t) \leq N(0)e^{-\mu t} + \frac{\Pi}{\mu}(1 - e^{-\mu t})$. In particular, $N(t) \leq \frac{\Pi}{\mu}$ if $N(0) \leq \frac{\Pi}{\mu}$. Thus, every solution of the model (4.1), with initial conditions in $\mathcal{D}$, remains there for all $t > 0$ (that is, the ω-limit sets of the system (4.1) are contained in $\mathcal{D}$). Hence, $\mathcal{D}$ is positively-invariant. This result is summarized below:

Lemma 4.2. *The region $\mathcal{D}$ is positively-invariant for the model* (4.1) *with initial conditions in $\mathbb{R}^4_+$.*

As a consequence of Lemma 4.2, it is sufficient to consider the dynamics of the flow

generated by the basic model (4.1) in $\mathcal{D}$. In this region, the model can be considered epidemiologically and mathematically well-posed [43].

4.2.2 Local Stability of Disease-free Equilibrium (DFE)

The basic model (4.1) has a DFE given by

$$\mathcal{E}_0 = (S^*, E^*, H_u^*, Q_u^*) = \left(\frac{\Pi}{\mu}, 0, 0, 0\right). \tag{4.4}$$

The linear stability of $\mathcal{E}_0$ is studied using the next generation operator technique in [88]. The associated non-negative matrix, F_1, for the new infection terms, and the non-singular M-matrix, Q_1, for the remaining transfer terms, are given, respectively, by

$$F_1 = \begin{pmatrix} 0 & \beta & \beta\theta \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \text{ and } Q_1 = \begin{pmatrix} k_1 & 0 & 0 \\ -\sigma & k_2 & -r_u \\ 0 & -q_u & k_3 \end{pmatrix},$$

where, $k_1 = \sigma + \mu$, $k_2 = q_u + \mu + \delta_u$ and $k_3 = r_u + \mu + \delta_{qu}$. Thus, it follows that [88]

$$\mathcal{R}_0 = \rho(F_1 Q_1^{-1}) = \frac{\beta\sigma(k_3 + \theta q_u)}{k_1(k_2 k_3 - r_u q_u)}. \tag{4.5}$$

It is worth mentioning that $k_2 k_3 - r_u q_u = q_u(\mu + \delta_{qu}) + (\mu + \delta_u)k_3 > 0$, so that $\mathcal{R}_0 > 0$ (since all the parameters of the model are non-negative). Thus, using Theorem 2.7, the following result is established.

Lemma 4.3. *The DFE, $\mathcal{E}_0$, of the basic model* (4.1)*, given by* (4.4)*, is locally-asymptotically stable if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.*

The threshold quantity, $\mathcal{R}_0$, measures the average number of secondary cases generated by a single infected individual in a completely susceptible population [3, 43]. Lemma 4.3 implies that a small influx of infectives would not generate large outbreaks if $\mathcal{R}_0 < 1$. In order for disease elimination to be independent of the initial sizes of the sub-populations of

the model when $\mathcal{R}_0 < 1$, a global asymptotic stability property must be established for the DFE when $\mathcal{R}_0 < 1$. This is explored below.

4.2.3 Global Stability of DFE

Theorem 4.1. *The DFE, $\mathcal{E}_0$, of the model* (4.1)*, is globally-asymptotically stable in $\mathcal{D}$ if $\mathcal{R}_0 \leq 1$.*

Proof. Consider the Lyapunov function

$$\mathcal{F} \quad = \quad f_1 E + f_2 H_u + f_3 Q_u,$$

where,

$$f_1 \quad = \quad \sigma(k_3 + \theta q_u),\ f_2 = k_1(k_3 + \theta q_u) \text{ and } f_3 = k_1(r_u + \theta k_2),$$

with Lyapunov derivative given by

$$\dot{\mathcal{F}} = f_1 \dot{E} + f_2 \dot{H}_u + f_3 \dot{Q}_u,$$

$$= f_1 \left[\frac{\beta(H_u + \theta Q_u)S}{N} - k_1 E \right] + f_2(\sigma E + r_u Q_u - k_2 H_u) + f_3(q_u H_u - k_3 Q_u),$$

$$= k_1(k_2 k_3 - r_u q_u)\left(\frac{S}{N}\mathcal{R}_0 - 1 \right) H_u + \theta k_1(k_2 k_3 - r_u q_u)\left(\frac{S}{N}\mathcal{R}_0 - 1 \right) Q_u,$$

$$\leq k_1(k_2 k_3 - r_u q_u)(\mathcal{R}_0 - 1)\left(H_u + \theta Q_u\right), \text{ since } S \leq N \text{ in } \mathcal{D}.$$

Thus, $\dot{\mathcal{F}} \leq 0$ if $\mathcal{R}_0 \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $H_u = Q_u = 0$ (it should be recalled that $k_2 k_3 - r_u q_u > 0$). Also, $E \to 0$ as $t \to \infty$ if $H_u = Q_u = 0$ (since $\lambda = \frac{\beta(H_u + \theta Q_u)}{N} = 0$, in this

case). It follows, from the LaSalle's Invariance Principle [58], that

$$(H_u(t), Q_u(t)) \to (0,0) \text{ as } t \to \infty.$$

Thus, for any $\epsilon > 0$ sufficiently small, there exists a $t_a > 0$ such that if $t > t_a$, then

$$E(t) < \epsilon,\ H_u(t) < \epsilon \text{ and } Q_u(t) < \epsilon. \tag{4.6}$$

Consequently, it follows from the equation for $\frac{ds}{dt}$ in (4.1) (and noting the inequalities in (4.6)) that, for $t > t_a$,

$$\frac{dS}{dt} = \Pi - \frac{\beta S(t)[H_u(t) + \theta Q_u(t)]}{N(t)} - \mu S(t) \geq \Pi - \beta(1+\theta)\epsilon - \mu S,$$

so that, by comparison theorem (Theorem 2.6),

$$\liminf_{t\to\infty} S(t) \geq \frac{\Pi - \beta(1+\theta)\epsilon}{\mu}. \tag{4.7}$$

Since $\epsilon > 0$ is arbitrarily small, letting $\epsilon \to 0$ in (4.7) gives

$$\liminf_{t\to\infty} S(t) \geq \frac{\Pi}{\mu}. \tag{4.8}$$

Similarly, it can be shown that

$$\limsup_{t\to\infty} S(t) \leq \frac{\Pi}{\mu}. \tag{4.9}$$

Hence, it follows by combining (4.8) and (4.9) that

$$\lim_{t\to\infty} S(t) = \frac{\Pi}{\mu}.$$

Thus, in summary,

$$\lim_{t\to\infty}(S(t), E(t), H_u(t), Q_u(t)) = \left(\frac{\Pi}{\mu}, 0, 0, 0\right) = \mathcal{E}_0.$$

This proves that every solution to the equations of the reduced model (4.1), with initial conditions in $\mathcal{D}$, approaches the DFE, $\mathcal{E}_0$, as $t \to \infty$, whenever $\mathcal{R}_0 \leq 1$. □

The epidemiological implication of the above result is that HSV-2 will be eliminated from the community if the threshold quantity, $\mathcal{R}_0$, can be brought to (and maintained at) a value less than unity. The result of Theorem 4.1 is illustrated numerically by simulating the model (4.1), for the case when $\mathcal{R}_0 < 1$, using various initial conditions. The solution profiles obtained, depicted in Figure 4.2, show convergence to the DFE ($\mathcal{E}_0$), in line with Theorem 4.1.

4.2.4 Existence and Local Stability of Endemic Equilibria (EEP)

In this section, conditions for the existence of non-zero (endemic) equilibria of the model (4.1) (that is, equilibria for which HSV-2 is endemic in the community) will be determined. Let,

$$\mathcal{E}_1 = (S^{**}, E^{**}, H_u^{**}, Q_u^{**})$$

denotes any arbitrary equilibrium of the model (4.1). The equations in the model (4.1) are then solved in terms of the associated forces of infection at steady-state, namely

$$\lambda^{**} = \frac{\beta(H_u^{**} + \theta Q_u^{**})}{N^{**}}. \tag{4.10}$$

Setting the right-hand sides of the equations in (4.1) to zero gives the following expressions for the state variables of the model (in terms of λ^{**}) :

$$\begin{aligned} S^{**} &= \frac{\Pi}{\lambda^{**}+\mu}, \quad E^{**} = \frac{\lambda^{**}\Pi}{k_1(\lambda^{**}+\mu)}, \quad H_u^{**} = \frac{k_3\sigma\lambda^{**}\Pi}{k_1(k_2k_3 - r_uq_u)(\lambda^{**}+\mu)}, \\ Q_u^{**} &= \frac{q_u\sigma\lambda^{**}\Pi}{k_1(k_2k_3 - r_uq_u)(\lambda^{**}+\mu)}. \end{aligned} \tag{4.11}$$

By substituting the expressions in (4.11) into equation (4.10), and simplifying, it follows that the non-zero equilibria of the model system (4.1) satisfy the following polynomial (in terms of λ^{**}),

$$a_1\lambda^{**} + a_2 = 0, \tag{4.12}$$

where,

$$a_1 = (k_2k_3 - r_uq_u) + \sigma(k_3 + q_u) \quad \text{and} \quad a_2 = 1 - \mathcal{R}_0.$$

The coefficient a_1 is always positive (since $k_2k_3 - r_uq_u > 0$, and all the model parameters are non-negative). The coefficient a_2 is positive (negative) if $\mathcal{R}_0$ is less than (greater than) unity. Thus, the solution $\lambda^{**} = \frac{-a_2}{a_1} < 0$ when $\mathcal{R}_0 < 1$ (hence, the model has no positive real root in this case). Furthermore, when $\mathcal{R}_0 = 1$, the coefficient $a_2 = 0$, and the equation (4.12) reduces to $a_1\lambda^{**} = 0$, with solution $\lambda^{**} = 0$ (corresponding to the DFE, $\mathcal{E}_0$). For the case when $\mathcal{R}_0 > 1$, the coefficient $a_2 < 0$, so that the model has one positive real root (given by $\lambda^{**} = \frac{-a_2}{a_1} > 0$). The components of this endemic equilibrium can then be obtained by substituting the positive root of (4.12) into the expressions in (4.11). These results are summarized below.

Theorem 4.2. *The basic model* (4.1) *has one positive (endemic) equilibrium, of the form* $\mathcal{E}_1$*, whenever* $\mathcal{R}_0 > 1$*, and no positive equilibrium otherwise.*

The local stability of the EEP, $\mathcal{E}_1$, of the basic model (4.1) is considered for the special case when the associated disease-induced mortality is zero (i.e., $\delta_u = \delta_{qu} = 0$). Setting $\delta_u = \delta_{qu} = 0$ in (4.1) gives

$$\frac{dN(t)}{dt} = \Pi - \mu N(t),$$

so that, $N(t) \to \Pi/\mu = N^{**}$ as $t \to \infty$. Using $N = N^{**}$, and the definition $S = N^{**} - E -$

$H_u - Q_u$, in the basic model (4.1), gives the following reduced model:

$$\begin{aligned}
\frac{dE}{dt} &= \frac{\beta(H_u + \theta Q_u)(N^{**} - E - H_u - Q_u)}{N^{**}} - \sigma E - \mu E, \\
\frac{dH_u}{dt} &= \sigma E + r_u Q_u - q_u H_u - \mu H_u, \\
\frac{dQ_u}{dt} &= q_u H_u - r_u Q_u - \mu Q_u.
\end{aligned} \tag{4.13}$$

It can be shown that the reduced system (4.13) has a unique EEP, of the form $\mathcal{E}_1^1 = \mathcal{E}_1|_{(\delta_u=\delta_{qu}=0)} = (E^{**}, H_u^{**}, Q_u^{**})$, whenever $\mathcal{R}_{01} = \mathcal{R}_0|_{(\delta_u=\delta_{qu}=0)} > 1$.

Theorem 4.3. *The unique endemic equilibrium, $\mathcal{E}_1^1$, of the reduced model* (4.13) *is LAS whenever $\mathcal{R}_{01} > 1$.*

Proof. The proof is based on using a Krasnoselskii sub-linearity trick, as described in [84] (see also [31, 32, 44]). Assume, first of all, that the reduced model (4.13) has solution of the form:

$$\bar{\mathbf{Z}}(t) = \bar{\mathbf{Z}}_0 e^{\tau t}, \tag{4.14}$$

with $\bar{\mathbf{Z}}_0 = (Z_1, Z_2, Z_3)$ and $\tau, Z_i \in \mathbb{C}$ $(i = 1, 2, 3)$.

The goal is to show that $Re(\tau) < 0$. Substituting a solution of the form (4.14) into the linearized system of (4.13) (around the equilibrium $\mathcal{E}_1^1$) gives the following system of linear equations:

$$\begin{aligned}
\tau Z_1 &= -\left[\frac{\beta(H_u^{**} + \theta Q_u^{**})}{N^{**}} + k_1\right] Z_1 + \left[\frac{\beta S^{**}}{N^{**}} - \frac{\beta(H_u^{**} + \theta Q_u^{**})}{N^{**}}\right] Z_2 \\
&\quad + \left[\frac{\beta\theta S^{**}}{N^{**}} - \frac{\beta(H_u^{**} + \theta Q_u^{**})}{N^{**}}\right] Z_3, \\
\tau Z_2 &= \sigma Z_1 - k_2 Z_2 + r_u Z_3, \\
\tau Z_3 &= q_u Z_2 - k_3 Z_3.
\end{aligned} \tag{4.15}$$

Solving for Z_3 from the third equation of (4.15), and substituting the result into the remaining

equations of (4.15), and simplifying, gives the equivalent system

$$\begin{aligned}\left\{1+\frac{1}{k_1}\left[\tau+\frac{\beta(H^{**}+\theta Q^{**})}{N^{**}}\right]\right\}Z_1 &= \frac{1}{k_1}\left[\frac{\beta S^{**}}{N^{**}}-\frac{\beta(H_u^{**}+\theta Q_u^{**})}{N^{**}}\right]Z_2\\ &\quad+\frac{1}{k_1}\left[\frac{\beta\theta S^{**}}{N^{**}}-\frac{\beta(H_u^{**}+\theta Q_u^{**})}{N^{**}}\right]Z_3,\\ \left(1+\frac{\tau}{k_2}\right)Z_2 &= \frac{\sigma}{k_2}Z_1+\frac{r_u}{k_2}Z_3,\\ \left(1+\frac{\tau}{k_3}\right)Z_3 &= \frac{q_u}{k_3}Z_2.\end{aligned} \tag{4.16}$$

Adding the first and the third equations of (4.16) and substituting Z_2 from the third equation to the first equation, and moving all the negative terms to their respective left-hand sides, gives:

$$\begin{aligned}Z_1[1+F_1(\tau)]+Z_3[1+F_3(\tau)] &= (M\bar{Z})_1+(M\bar{Z})_3,\\ Z_2[1+F_2(\tau)] &= (M\bar{Z})_2,\end{aligned} \tag{4.17}$$

where,

$$\begin{aligned}F_1(\tau) &= \frac{1}{k_1}\left[\tau+\frac{\beta(H_u^{**}+\theta Q_u^{**})}{N^{**}}\right],\quad F_2(\tau)=\frac{\tau}{k_2},\\ F_3(\tau) &= \frac{\tau}{k_3}+\frac{1}{k_1}\frac{\beta(H_u^{**}+\theta Q_u^{**})}{N^{**}}\left(1+\frac{k_3+\tau}{q_u}\right),\end{aligned} \tag{4.18}$$

with,

$$M=\begin{pmatrix}0 & \frac{\beta S^{**}}{N^{**}k_1} & \frac{\beta\theta S^{**}}{N^{**}k_1}\\ \frac{\sigma}{k_2} & 0 & \frac{r_u}{k_2}\\ 0 & \frac{q_u}{k_3} & 0\end{pmatrix}.$$

The notation $M(\bar{Z})_i$ (with $i=1,2,3$) denotes the ith coordinate of the vector $M(\bar{\mathbf{Z}})$. It should be noted that the matrix M has non-negative entries, and the equilibrium $\mathcal{E}_1^1$ satisfies $\mathcal{E}_1^1 = M\mathcal{E}_1^1$. Furthermore, since the coordinates of $\mathcal{E}_1^1$ are all positive, it follows then that if $\bar{Z}$

is a solution of (4.17), then it is possible to find a minimal positive real number, s, such that

$$| \bar{\mathbf{Z}} | \leq s\mathcal{E}_1^1, \tag{4.19}$$

where, $| \bar{\mathbf{Z}} | = (| Z_1 |, | Z_2 |, | Z_3 |)$ with the lexicographic order and $| \cdot |$ is a norm in $\mathbb{C}$.
As stated above, the goal is to show that $Re(\tau) < 0$. Assume the contrary (i.e., $Re(\tau) \geq 0$). The following two cases are considered.

Case 1: $\tau = 0$

Suppose, first of all, that the complex number, τ, is zero (i.e., τ has zero real and imaginary parts). It follows then that (4.16) is a homogeneous linear system in the variables Z_i ($i = 1, 2, 3$). The determinant of this system corresponds to that of the Jacobian of the system (4.13) evaluated at $\mathcal{E}_1^1$, which is given by

$$\triangle = -\frac{1}{N^{**}}\left[(\beta H_u^{**} + \beta\theta Q_u^{**})(k_2k_3 - r_uq_u) + N^{**}k_1(k_2k_3 - r_uq_u)\left(1 - \frac{S^{**}}{N^{**}}\mathcal{R}_{01}\right)\right]. \tag{4.20}$$

It can be shown that $\frac{S^{**}}{N^{**}} = \frac{1}{\mathcal{R}_{01}}$. Thus (noting from Section 4.2.2 that $k_2k_3 - r_uq_u > 0$),

$$\triangle = -\frac{1}{N^{**}}\left[(\beta H_u^{**} + \beta\theta Q_u^{**})(k_2k_3 - r_uq_u)\right] < 0. \tag{4.21}$$

Consequently, in this case (with $\tau = 0$), the system (4.16) can only have the trivial solution $\bar{\mathbf{Z}} = \bar{\mathbf{0}}$ (which corresponds to the DFE, $\mathcal{E}_0$, of the model (4.1)).

Case 2: $\tau \neq 0$

Consider, now, the case when $\tau \neq 0$. It follows, by assumption, that $Re(\tau) \geq 0$. Thus, $| 1 + F_i(\tau) | > 1$ for $i = 1, 2, 3$. Define $F(\tau) = \min \ | 1 + F_i(\tau) |, \ i = 1, 2, 3$. Then, $F(\tau) > 1$. Therefore, $\frac{s}{F(\tau)} < s$. Since s is a minimal positive real number such that $| \bar{\mathbf{Z}} | \leq s\mathcal{E}_1^1$, it follows that

$$| \bar{\mathbf{Z}} | > \frac{s}{F(\tau)}\mathcal{E}_1^1. \tag{4.22}$$

Taking norms on both sides of the second equation of (4.18), and using the fact that M is non-negative, gives

$$F(\tau) \mid Z_2 \mid \leq M(\mid Z \mid)_2 \leq s(M \mid \mathcal{E}_1^1 \mid)_2 \leq sH_u^{**}. \tag{4.23}$$

Thus, it follows from the inequalities in (4.23) that $\mid Z_2 \mid \leq \frac{s}{F(\tau)} H_u^{**}$, which contradicts (4.22). Hence, $Re(\tau) < 0$, which implies that the equilibrium, $\mathcal{E}_1^1$, is LAS if $\mathcal{R}_{01} > 1$. □

The epidemiological implication of Theorem 4.3 is that the disease will persists in the community if the associated basic reproduction threshold, $\mathcal{R}_{01}$, exceeds unity. Numerical simulations, depicted in Figure 4.3, using numerous initial conditions, show convergence of the solutions to the endemic equilibrium, $\mathcal{E}_1^1$, for the case when $\mathcal{R}_{01} > 1$.

4.2.5 Global Stability of EEP: Special Case

The global stability of the EEP of the basic model (4.1) is considered for the special case where the HSV-2-induced mortality is negligible (so that, $\delta_u = \delta_{qu} = 0$) and individuals in the quiescent state do not re-activate and progress to the symptomatic stage (i.e., $r_u = 0$). Setting $\delta_u = \delta_{qu} = r_u = 0$ in the basic model (4.1), and adding all the equations of the model, gives the following equation for the rate of change of the total population:

$$\frac{dN(t)}{dt} = \Pi - \mu N(t).$$

Thus, $N(t) \to \frac{\Pi}{\mu}$ as $t \to \infty$. Using $N = \frac{\Pi}{\mu}$ (and noting that $\delta_u = \delta_{qu} = r_u = 0$) in the basic model (4.1) gives the following limiting (mass action) system:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \frac{\beta\mu(H_u + \theta Q_u)}{\Pi} S - \mu S, \\
\frac{dE}{dt} &= \frac{\beta\mu(H_u + \theta Q_u)}{\Pi} S - \sigma E - \mu E, \\
\frac{dH_u}{dt} &= \sigma E - q_u H_u - \mu H_u, \\
\frac{dQ_u}{dt} &= q_u H_u - \mu Q_u.
\end{aligned} \tag{4.24}$$

The basic reproduction number of the reduced model (4.24), denoted by $\mathcal{R}_{02}$, is given by

$$\mathcal{R}_{02} = \mathcal{R}_0|_{(\delta_u=\delta_{qu}=r_u=0)} = \frac{\beta\sigma(\mu+\theta q_u)}{\mu(\sigma+\mu)(q_u+\mu)}. \tag{4.25}$$

Using the approach in Section 4.2.4, it can be shown that the reduced system (4.24) has a unique EEP, of the form $\mathcal{E}_2 = \mathcal{E}_1|_{(\delta_u=\delta_{qu}=r_u=0)} = (S^{**}, E^{**}, H_u^{**}, Q_u^{**})$ (where, $S^{**} > 0, E^{**} > 0, H_u^{**} > 0$ and $Q_u^{**} > 0$), whenever $\mathcal{R}_{02} > 1$. It is convenient to define the region:

$$\mathcal{D}_0 = \{(S, E, H_u, Q_u) \in \mathcal{D} : E = H_u = Q_u = 0\}.$$

Theorem 4.4. *The unique EEP, $\mathcal{E}_2$, of the reduced model* (4.24)*, is GAS in $\mathcal{D}\setminus\mathcal{D}_0$ whenever $\mathcal{R}_{02} > 1$.*

Proof. Consider the non-linear Lyapunov function

$$\begin{aligned}\mathcal{F} = &\left(S - S^{**} - S^{**}ln\frac{S}{S^{**}}\right) + \left(E - E^{**} - E^{**}ln\frac{E}{E^{**}}\right) \\ &+ \frac{\beta S^{**}(\theta q_u+\mu)}{\Pi(q_u+\mu)}\left(H_u - H_u^{**} - H_u^{**}ln\frac{H_u}{H_u^{**}}\right) + \frac{\beta S^{**}\theta}{\Pi}\left(Q_u - Q_u^{**} - Q_u^{**}ln\frac{Q_u}{Q_u^{**}}\right),\end{aligned} \tag{4.26}$$

with Lyapunov derivative given by,

$$\begin{aligned}
\dot{\mathcal{F}} &= \left(1-\frac{S^{**}}{S}\right)\dot{S}+\left(1-\frac{E^{**}}{E}\right)\dot{E}+\frac{\beta S^{**}(\theta q_u+\mu)}{\Pi(q_u+\mu)}\left(1-\frac{H_u^{**}}{H_u}\right)\dot{H}_u+\frac{\beta S^{**}\theta}{\Pi}\left(1-\frac{Q_u^{**}}{Q_u}\right)\dot{Q}_u,\\
&= \left(1-\frac{S^{**}}{S}\right)\left[\Pi-\frac{\beta\mu(H_u+\theta Q_u)}{\Pi}S-\mu S\right]+\left(1-\frac{E^{**}}{E}\right)\left[\frac{\beta\mu(H_u+\theta Q_u)}{\Pi}S-\sigma E-\mu E\right]\\
&+ \frac{\beta S^{**}(\theta q_u+\mu)}{\Pi(q_u+\mu)}\left(1-\frac{H_u^{**}}{H_u}\right)(\sigma E-q_uH_u-\mu H_u)+\frac{\beta S^{**}\theta}{\Pi}\left(1-\frac{Q_u^{**}}{Q_u}\right)(q_uH_u-\mu Q_u),\\
&= \frac{2\beta\mu}{\Pi}(H_u^{**}+\theta Q_u^{**})S^{**}+\mu S^{**}(2-\frac{S}{S^{**}}-\frac{S^{**}}{S})-\frac{\beta\mu}{\Pi}(H_u^{**}+\theta Q_u^{**})\frac{(S^{**})^2}{S}-(\mu+\sigma)E\\
&- \frac{\beta\mu}{\Pi}(H_u+\theta Q_u)\frac{SE^{**}}{E}+\frac{\beta\mu}{\Pi}(H_u+\theta Q_u)S^{**}+\frac{\beta\theta q_u}{\Pi}(S^{**}H_u-S^{**}H_u\frac{Q_u^{**}}{Q_u})\\
&+ \frac{\beta\mu\theta S^{**}Q_u^{**}}{\Pi}-\frac{\beta\mu\theta S^{**}Q_u}{\Pi}+\frac{\beta\mu\sigma}{\Pi(q_u+\mu)}(S^{**}E-S^{**}E\frac{H_u^{**}}{H_u})\\
&+ \frac{\beta\theta\sigma q_u}{\Pi(q_u+\mu)}(S^{**}E-S^{**}E\frac{H_u^{**}}{H_u})+\frac{\beta\theta q_u}{\Pi}(S^{**}H_u^{**}-S^{**}H_u)+\frac{\beta\mu S^{**}H_u^{**}}{\Pi}-\frac{\beta\mu S^{**}H_u}{\Pi},\\
&= \mu S^{**}\left(2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\right)+\frac{\beta\mu H_u^{**}S^{**}}{\Pi}\left(3-\frac{S^{**}}{S}-\frac{E}{E^{**}}-\frac{SE^{**}H_u}{S^{**}EH_u^{**}}\right)\\
&+ \frac{\beta\mu\theta Q_u^{**}S^{**}}{\Pi}\left(3-\frac{S^{**}}{S}-\frac{E}{E^{**}}-\frac{SE^{**}Q_u}{S^{**}EQ_u^{**}}\right)+\frac{\beta\mu\sigma}{\Pi(q_u+\mu)}\left(S^{**}E-S^{**}E\frac{H_u^{**}}{H_u}\right)\\
&+ \frac{\beta\sigma\theta q_u}{\Pi(q_u+\mu)}\left(S^{**}E-S^{**}E\frac{H_u^{**}}{H_u}\right)+\frac{\beta\theta q_u}{\Pi}\left(S^{**}H_u^{**}-S^{**}H_u\frac{Q_u^{**}}{Q_u}\right),\\
&= \mu S^{**}\left(2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\right)+\frac{\beta\mu H_u^{**}S^{**}}{\Pi}\left(3-\frac{S^{**}}{S}-\frac{SE^{**}H_u}{S^{**}EH_u^{**}}-\frac{EH_u^{**}}{E^{**}H_u}\right)\\
&+ \frac{\beta\mu\theta Q_u^{**}S^{**}}{\Pi}\left(4-\frac{S^{**}}{S}-\frac{SE^{**}Q_u}{S^{**}EQ_u^{**}}-\frac{EH_u^{**}}{E^{**}H_u}-\frac{H_uQ_u^{**}}{H_u^{**}Q_u}\right).
\end{aligned}$$

In the above calculations, the following relations (obtained from (4.24), at the endemic steady-state $\mathcal{E}_2$) were used:

$$\Pi = \frac{\beta\mu(H_u^{**}+\theta Q_u^{**})S^{**}}{\Pi}+\mu S^{**},\ H_u^{**}=\frac{\sigma E^{**}}{q_u+\mu},\ Q_u^{**}=\frac{q_uH_u^{**}}{\mu},\ \text{and}\ Q_u^{**}=\frac{q_u\sigma E^{**}}{\mu(q_u+\mu)}.$$

Since the arithmetic mean exceeds the geometric mean, it follows then that

$$2-\frac{S}{S^{**}}-\frac{S^{**}}{S}\leq 0,\ 3-\frac{S^{**}}{S}-\frac{SE^{**}H_u}{S^{**}EH_u^{**}}-\frac{EH_u^{**}}{E^{**}H_u}\leq 0,\ 4-\frac{S^{**}}{S}-\frac{SE^{**}Q_u}{S^{**}EQ_u^{**}}-\frac{EH_u^{**}}{E^{**}H_u}-\frac{H_uQ_u^{**}}{H_u^{**}Q_u}\leq 0,$$

so that $\dot{\mathcal{F}}\leq 0$ for $\mathcal{R}_{02}>1$. Thus, by the Lyapunov function $\mathcal{F}$, and the LaSalle's Invariance Principle [58], every solution to the equations in the model (4.24) approaches the unique EEP, $\mathcal{E}_2$, as $t\to\infty$, for $\mathcal{R}_{02}>1$. □

It is worth mentioning that extensive numerical simulations of the basic model (4.1) suggest that the unique endemic equilibrium, $\mathcal{E}_1$, may be globally-asymptotically stable when $\mathcal{R}_0>1$ (hence the following conjecture).

Conjecture: The EEP, $\mathcal{E}_1$, of the basic model (4.1) is globally-asymptotically stable in $\mathcal{D}\backslash\mathcal{D}_0$ whenever $\mathcal{R}_0>1$.

In summary, the basic HSV-2 model (4.1) has a globally-asymptotically stable DFE whenever $\mathcal{R}_0\leq 1$, and a unique EEP if $\mathcal{R}_0>1$. It is shown that the unique EEP of the model (4.1) is globally-asymptotically stable, for the special case when $\delta_u=\delta_{qu}=r_u=0$, whenever $\mathcal{R}_{02}>1$. The basic model (4.1) will now be extended to incorporate an imperfect HSV-2 vaccine, as follows.

4.3 Model With Vaccination

To design the HSV-2 vaccine model, the following new state variables are introduced for the populations of vaccinated individuals ($V(t)$), exposed vaccinated individuals ($E_v(t)$), infectious vaccinated individuals ($H_v(t)$) and quiescent vaccinated infected individuals ($Q_u(t)$). Thus, the total population at time t, denoted by $N(t)$, is now given by:

$$N(t)=S(t)+V(t)+E_u(t)+E_v(t)+H_u(t)+H_v(t)+Q_u(t)+Q_v(t).$$

A fraction, $p\epsilon$, of the new sexually-active (adolescent) individuals recruited at the rate Π is vaccinated (where p is the proportion of these individuals that are vaccinated and ϵ represents the proportion of these vaccinated individuals in whom the vaccine takes). Susceptible individuals are vaccinated at a rate ξ, and the vaccine is assumed to wane at a rate ω. Furthermore, since the vaccine is assumed to be imperfect, vaccinated individuals can acquire break-through infection at a reduced rate $(1-\psi)\lambda_v$, where $0 < \psi < 1$ represents the vaccine efficacy (degree protection against infection). In line with Schwartz and Blower [74], it is assumed that vaccinated individuals have:

(a) shorter average length of viral shedding;

(b) fewer viral shedding episodes; and

(c) lower transmission probability, in comparison to unvaccinated individuals.

The associated force of infection is given by

$$\lambda_v = \frac{\beta[H_u + \eta_1 H_v + \theta(Q_u + \eta_2 Q_v)]}{N},$$

where, $0 < \eta_1, \eta_2 < 1$ are the modification parameters accounting for the vaccine-induced reduction of infectiousness for individuals in the H_v and Q_v classes, respectively, in comparison to unvaccinated infectious individuals (in the H_u and Q_u classes, respectively). Thus, the rates of change of the population of susceptible and vaccinated individuals are given, respectively, by

$$\frac{dS}{dt} = \Pi(1-p\epsilon) - \lambda_v S + \omega V - (\xi + \mu)S,$$

$$\frac{dV}{dt} = \Pi p\epsilon + \xi S - (1-\psi)\lambda_v V - (\omega + \mu)V.$$

The population of exposed vaccinated individuals (E_v) is generated by break-through infection (at the rate $(1-\psi)\lambda_v$) and is decreased by the development of symptoms (at a rate

σ_2) and natural death (at the rate μ), so that

$$\frac{dE_v}{dt} = (1-\psi)\lambda_v V - (\sigma_2 + \mu)E_v.$$

It is assumed that $\sigma_2 < \sigma_1$, to account for the assumption that exposed vaccinated individuals develop clinical symptoms of HSV-2 at a slower rate in comparison to exposed unvaccinated individuals. Infectious vaccinated individuals (in the H_v class) are generated by the progression of exposed vaccinated individuals (at the rate σ_2) and by the re-activation of vaccinated individuals in the quiescent state (at a rate r_v). This population is decreased by progression to quiescence (at a rate q_v), natural death (at the rate μ) and disease-induced death (at a reduced rate $\delta_v < \delta_u$). Thus,

$$\frac{dH_v}{dt} = \sigma_2 E_v + r_v Q_v - (q_v + \mu + \delta_v)H_v.$$

Finally, the population of vaccinated infectious individuals in the quiescent state (Q_v) is increased by the progression to quiescence of infectious vaccinated individuals (at the rate q_v). The rate of change of this population is reduced by re-activation (at the rate r_v), loss of vaccine-induced immunity (at a rate α), natural death (at the rate μ) and disease-induced death (at a rate δ_{qv}). Individuals in the Q_v class who lose their vaccine-induced immunity are moved to the Q_u class (at the rate α [74]). Hence,

$$\frac{dQ_v}{dt} = q_v H_v - (r_v + \alpha + \mu + \delta_{qv})Q_v.$$

Thus, considering the above descriptions, together with the basic model (4.1), the extended vaccination model for the transmission dynamics of HSV-2 in a population is given by the following system of non-linear differential equations [71] (a schematic diagram of the model is depicted in Figure 4.1; the associated variables and parameters of the model are

described in Table 4.1).

$$\begin{aligned}
\frac{dS}{dt} &= \Pi(1-p\epsilon) - \lambda_v S + \omega V - (\xi+\mu)S,\\
\frac{dV}{dt} &= \Pi p\epsilon + \xi S - (1-\psi)\lambda_v V - (\omega+\mu)V,\\
\frac{dE_u}{dt} &= \lambda_v S - (\sigma_1+\mu)E_u,\\
\frac{dE_v}{dt} &= (1-\psi)\lambda_v V - (\sigma_2+\mu)E_v,\\
\frac{dH_u}{dt} &= \sigma_1 E_u + r_u Q_u - (q_u+\mu+\delta_u)H_u,\\
\frac{dH_v}{dt} &= \sigma_2 E_v + r_v Q_v - (q_v+\mu+\delta_v)H_v,\\
\frac{dQ_u}{dt} &= q_u H_u + \alpha Q_v - (r_u+\mu+\delta_{qu})Q_u,\\
\frac{dQ_v}{dt} &= q_v H_v - (r_v+\alpha+\mu+\delta_{qv})Q_v.
\end{aligned} \tag{4.27}$$

In summary, the extended model (4.27) incorporates an imperfect HSV-2 vaccine with the following (assumed) therapeutic characteristics:

(i) it blocks infection with some efficacy;

(ii) it reduces transmissibility in break-through infections;

(iii) it slows development of symptoms in exposed vaccinated individuals; and

(iv) it reduces mortality rate in break-through infections.

The aforementioned vaccine characteristics are in line with the expected characteristics of an ideal HSV-2 vaccine given in [4]. Furthermore, the model (4.27) is an extension of the vaccination model in [74], by:

(a) including two additional compartments for exposed unvaccinated and vaccinated individuals (E_u and E_v);

(b) incorporating disease-induced mortality;

(c) allowing for disease transmission by individuals in the unvaccinated and vaccinated quiescent states (Q_u and Q_v);

(d) incorporating continuous vaccination and cohort vaccination (only the latter is considered in [74]); and

(e) incorporating some therapeutic vaccine characteristics (such as Items (*iii*) and (*iv*) above).

Table 4.1: Description of variables and parameters of the vaccination model (4.27).

Variables	Description	
$S(t)$	Susceptible individuals	
$V(t)$	Vaccinated individuals	
$E_u(t)$	Unvaccinated exposed individuals	
$E_v(t)$	Vaccinated exposed individuals	
$H_u(t)$	Unvaccinated infectious individuals	
$H_v(t)$	Vaccinated infectious individuals	
$Q_u(t)$	Quiescent unvaccinated infectious individuals	
$Q_v(t)$	Quiescent vaccinated infectious individuals	
Parameter	Description	Baseline values/year
Π	Recruitment rate	10000
μ	Natural death rate	$\frac{1}{70}$
β	Contact rate	0.3 [74]
ξ	Vaccination rate of susceptible individuals	0.6
ψ	Efficacy of vaccine	0.6
ω	Waning rate of vaccine	$\frac{1}{15}$ [74]
p	Proportion of new recruited individuals vaccinated	0.5

ϵ	Proportion of recruited susceptible individuals in whom vaccine takes	0.6
σ_1	Progression rate to symptoms development of unvaccinated exposed individuals	$\frac{365}{15}$
σ_2	Progression rate to symptoms development of vaccinated exposed individuals	$\frac{365}{18}$
r_u	Activation rate of unvaccinated infectious individuals in the quiescent state	$\frac{365}{4}$ [74]
r_v	Activation rate of vaccinated infectious individuals in the quiescent state	$\frac{365}{4}$[74]
q_u	Rate at which infectious unvaccinated individuals revert to quiescent state	$\frac{365}{2}$[74]
q_v	Rate at which infectious vaccinated individuals revert to quiescent state	$\frac{365}{3}$[74]
α	Progression rate to quiescent unvaccinated infectious individuals of quiescent infectious vaccinated individuals	$\frac{1}{20}$ [74]
θ	Modification parameter for lower infectiousness of individuals in quiescent class	0.5
η_1, η_2	Modification parameters for reduced infectiousness of vaccinated infectious individuals	0.7,0.6
δ_u, δ_{qu}	Disease-induced death rate for unvaccinated infectious individuals	0.007,0.006
δ_v, δ_{qv}	Disease-induced death rate for vaccinated infectious individuals	0.005,0.004

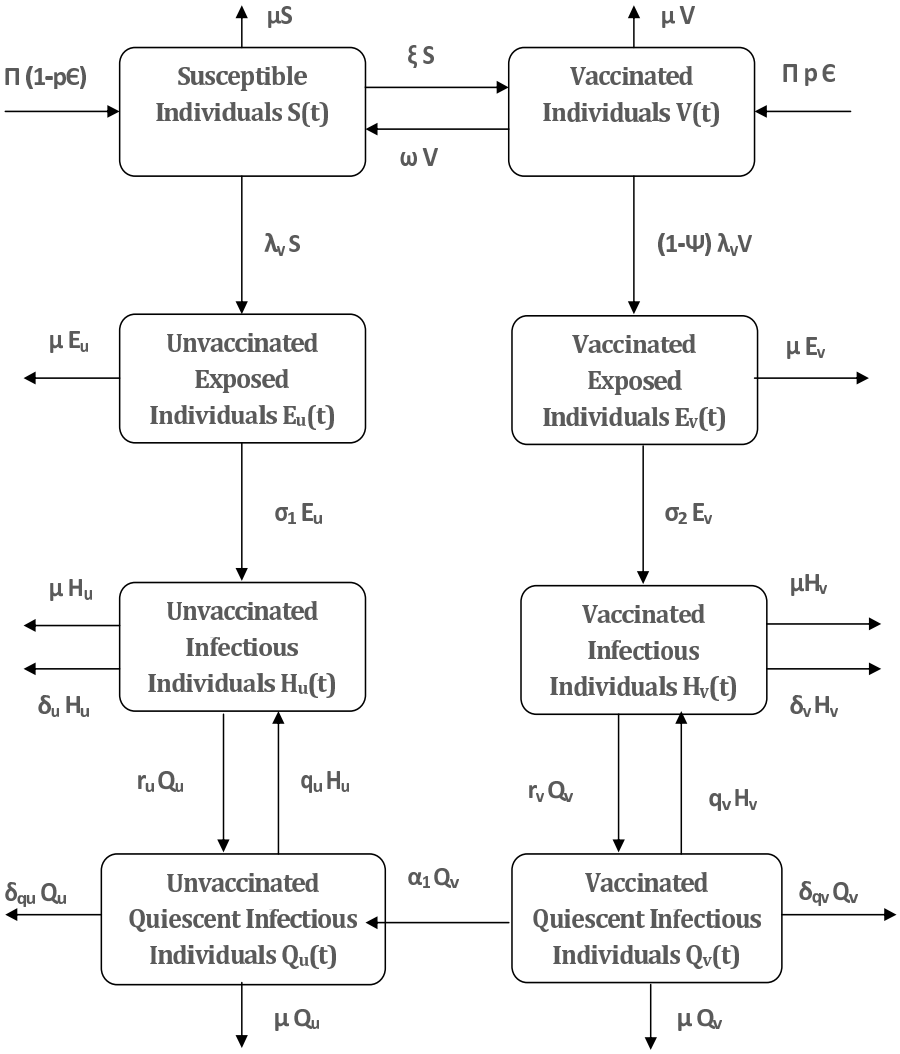


Figure 4.1: Schematic diagram of the HSV-2 vaccination model (4.27).

Furthermore, unlike in [74] and the other aforementioned HSV-2 modeling studies, detailed (rigorous) mathematical analysis of the vaccination model (4.27) will be provided.

4.3.1 Basic Properties

Using the approach in Section 4.2.1, the following biologically-feasible region

$$\begin{aligned}\mathcal{D}_v &= \{(S, V, E_u, E_v, H_u, H_v, Q_u, Q_v) \in \mathbb{R}^8_+ : \\ &\quad S + V + E_u + E_v + H_u + H_v + Q_u + Q_v \leq \Pi/\mu\},\end{aligned}$$

can be shown to be positively-invariant for the vaccination model (4.27). Furthermore, the vaccination model (4.27) has a DFE, given by

$$\begin{aligned}\mathcal{E}_3 &= (S^*, V^*, E_u^*, E_v^*, H_u^*, H_v^*, Q_u^*, Q_v^*) \\ &= \left(\frac{\Pi[(1-p\epsilon)k_{21} + p\epsilon\omega]}{k_{21}\mu + \xi\mu}, \frac{\Pi[(1-p\epsilon)\xi + p\epsilon k_{11}]}{k_{21}\mu + \xi\mu}, 0, 0, 0, 0, 0, 0\right),\end{aligned} \tag{4.28}$$

where, $k_{11} = \xi + \mu$ and $k_{21} = \omega + \mu$. The associated non-negative matrix (F_2) and the non-singular M-matrix (Q_2) are given, respectively, by

$$F_2 = \begin{pmatrix} 0 & 0 & \frac{\beta S^*}{N^*} & \frac{\beta S^* \eta_1}{N^*} & \frac{\beta S^* \theta}{N^*} & \frac{\beta S^* \theta \eta_2}{N^*} \\ 0 & 0 & \frac{\beta(1-\psi)V^*}{N^*} & \frac{\beta(1-\psi)V^*\eta_1}{N^*} & \frac{\beta(1-\psi)V^*\theta}{N^*} & \frac{\beta(1-\psi)V^*\theta\eta_2}{N^*} \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$Q_2 = \begin{pmatrix} k_{31} & 0 & 0 & 0 & 0 & 0 \\ 0 & k_{41} & 0 & 0 & 0 & 0 \\ -\sigma_1 & 0 & k_{51} & 0 & -r_u & 0 \\ 0 & -\sigma_2 & 0 & k_{61} & 0 & -r_v \\ 0 & 0 & -q_u & 0 & k_{71} & -\alpha \\ 0 & 0 & 0 & -q_v & 0 & k_{81} \end{pmatrix},$$

where,

$$\begin{aligned} k_{31} &= \sigma_1 + \mu, \;\; k_{41} = \sigma_2 + \mu, \;\; k_{51} = q_u + \mu + \delta_u, \;\; k_{61} = q_v + \mu + \delta_v, \\ k_{71} &= r_u + \mu + \delta_{qu} \;\text{ and }\; k_{81} = r_v + \alpha + \mu + \delta_{qv}. \end{aligned}$$

It follows then that the associated vaccination reproduction number, denoted by $\mathcal{R}_{vac}$, is given by

$$\mathcal{R}_{vac} = \rho(F_2 Q_2^{-1}) = \frac{k_{31}\sigma_2\beta(1-\psi)V^*A_1 + k_{41}\sigma_1\beta S^*B_1}{N^*k_{31}k_{41}(k_{51}k_{71} - q_u r_u)(k_{61}k_{81} - q_v r_v)}, \tag{4.29}$$

with,

$$A_1 = \alpha q_v(r_u + \theta k_{51}) + (k_{51}k_{71} - q_u r_u)(\eta_1 k_{81} + \theta\eta_2 q_v),\ B_1 = (k_{71} + \theta q_u)(k_{61}k_{81} - q_v r_v).$$

It is worth stating that, in (4.29), $k_{51}k_{71} - q_u r_u = q_u(\delta_{qu} + \mu) + (\delta_u + \mu)k_{71} > 0$ and $k_{61}k_{81} - q_v r_v = q_v(\alpha + \delta_{qv} + \mu) + (\delta_v + \mu)k_{81} > 0$ (so that, $\mathcal{R}_{vac} > 0$). Thus, by Theorem 2.7, the following result is established.

Lemma 4.4. *The DFE, $\mathcal{E}_3$, of the model with vaccination* (4.27)*, given by* (4.28)*, is LAS if $\mathcal{R}_{vac} < 1$, and unstable if $\mathcal{R}_{vac} > 1$.*

The threshold quantity, $\mathcal{R}_{vac}$, measures the average number of secondary cases generated by a single infected individual in a susceptible population where some of the susceptible individuals are vaccinated. Lemma 4.4 implies that a small influx of infectives will not generate large outbreaks if $\mathcal{R}_{vac} < 1$. However, it will be shown, in Section 4.3.2 below, that the classical requirement of the vaccination reproduction number being less than unity becomes only a necessary, but not sufficient, condition for disease elimination.

4.3.2 Endemic Equilibria and Backward Bifurcation

To establish the existence of endemic equilibria of the extended vaccination model (4.27), the following steps are considered. Let, $\mathcal{E}_3 = (S^{**}, V^{**}, E_u^{**}, E_v^{**}, H_u^{**}, H_v^{**}, Q_u^{**}, Q_v^{**})$ represents any arbitrary endemic equilibrium of the vaccination model (4.27). Furthermore, let

$$\lambda_v^{**} = \frac{\beta[H_u^{**} + \eta_1 H_v^{**} + \theta(Q_u^{**} + \eta_2 Q_v^{**})]}{N^{**}} \tag{4.30}$$

(the force of infection of the extended model (4.27) at steady-state). It follows, by solving the equations in (4.27) at steady-state (and substituting the resulting expressions into (4.30)), that the non-zero equilibria of the extended model (4.27) satisfy the following quadratic equation (in terms of λ_v^{**})

$$a_1(\lambda_v^{**})^2 + b_1\lambda_v^{**} + c_1 = 0, \tag{4.31}$$

where,

$$\begin{aligned}
a_1 &= (1-\psi)\Big\{(1-p\epsilon)k_{41}(k_{71}+q_u)(k_{81}k_{61}-r_vq_v)\sigma_1 + p\epsilon k_{31}(k_{81}+q_v)(k_{71}k_{51}-r_uq_u)\sigma_2 \\
&\quad + \alpha k_{31}p\epsilon q_v(k_{51}+r_u)\sigma_2 + (k_{31}p\epsilon + (1-p\epsilon)k_{41})(k_{71}k_{51}+r_uq_u)(k_{81}k_{61}-r_vq_v)\Big\}, \\
b_1 &= -\beta(1-\psi)\Big\{(k_{51}k_{71}-q_ur_u)(\theta\eta_2q_v+\eta_1k_{81})\sigma_2k_{31}p\epsilon \\
&\quad + (k_{61}k_{81}-q_vr_v)(\theta q_u+k_{71})(1-p\epsilon)k_{41}\sigma_1 + p\epsilon k_{31}\sigma_2\alpha q_v(r_u+\theta k_{51})\Big\} \\
&\quad + (1-p\epsilon)\Big\{(k_{61}k_{81}-q_vr_v)k_{21}k_{41}\sigma_1(q_u+k_{71}) + (1-\psi)k_{31}\sigma_2\xi[(k_{51}k_{71}-q_ur_u)(q_v+k_{81}) \\
&\quad + \alpha q_v(k_{51}+r_u)] + (k_{51}k_{71}-q_ur_u)(k_{61}k_{81}-q_vr_v)[k_{31}(1-\psi)(\xi+k_{41})+k_{21}k_{41}]\Big\} \\
&\quad + p\epsilon\Big\{(k_{51}k_{71}-q_ur_u)[(k_{61}k_{81}-q_vr_v)(k_{41}+k_{11}(1-\psi))k_{31} + (1-\psi)(q_v+k_{81})\sigma_2k_{31}k_{11}] \\
&\quad + (k_{61}k_{81}-q_vr_v)[\omega k_{41}\sigma_1(q_u+k_{71}) + k_{41}\omega(k_{51}k_{71}-q_ur_u)] + (1-\psi)(r_u+k_{51})k_{31}\sigma_2\alpha q_vk_{11}\Big\}, \\
c_1 &= k_{31}k_{41}(k_{51}k_{71}-q_ur_u)(k_{61}k_{81}-q_vr_v)[(1-p\epsilon)(\xi+k_{21}) + p\epsilon(\omega+k_{11})](1-\mathcal{R}_{vac}).
\end{aligned}$$

The quadratic equation (4.31) can be analyzed for the possibility of multiple endemic equilibria when $\mathcal{R}_{vac} < 1$. It is worth noting that the coefficient, a_1, is always positive, and c_1 is positive (negative) if $\mathcal{R}_{vac}$ is less than (greater than) unity. Hence, the following result is established:

Theorem 4.5. *The vaccination model* (4.27) *has:*

(i) *a unique endemic equilibrium if* $c_1 < 0 \Leftrightarrow \mathcal{R}_{vac} > 1$*;*

(ii) *a unique endemic equilibrium if* $b_1 < 0$*, and* $c_1 = 0$ *or* $b_1^2 - 4a_1c_1 = 0$*;*

(iii) *two endemic equilibria if* $c_1 > 0$, $b_1 < 0$ *and* $b_1^2 - 4a_1c_1 > 0$*; and*

(iv) *no endemic equilibrium otherwise.*

Thus, it follows from Case (i) of Theorem 4.5 that the vaccination model (4.27) has a unique EEP whenever $\mathcal{R}_{vac} > 1$. Furthermore, Case (*iii*) indicates the possibility of backward bifurcation (where a locally-asymptotically stable DFE co-exists with a locally-asymptotically stable endemic equilibrium when the associated reproduction threshold, $\mathcal{R}_{vac}$ is less than unity, see, for instance, [11, 30, 36, 75]) in the vaccination model (4.27). The epidemiological importance of the phenomenon of backward bifurcation is that the classical requirement of $\mathcal{R}_{vac} < 1$ is, although necessary, no longer sufficient for disease elimination. In such a scenario, disease elimination would depend upon the initial sizes of the sub-populations (state variables) of the model. In other words, the presence of backward bifurcation makes disease elimination more difficult (using the imperfect vaccine).

To check for the possibility of backward bifurcation in the vaccination model (4.27), the discriminant $b_1^2 - 4a_1c_1$ of the equation (4.31) is set to zero, and the result solved for the critical value of $\mathcal{R}_{vac}$, denoted by $\mathcal{R}_{vac}^c$. This gives:

$$\mathcal{R}_{vac}^c = 1 - \frac{b_1^2}{4a_1k_{31}k_{41}(k_{51}k_{71} - q_ur_u)(k_{61}k_{81} - q_vr_v)[(1-p\epsilon)(\xi + k_{21}) + p\epsilon(\omega + k_{11})]},$$

from which it can be shown that backward bifurcation occurs for values of $\mathcal{R}_{vac}$ such that $\mathcal{R}_{vac}^c < \mathcal{R}_{vac} < 1$. This phenomenon is numerically-illustrated by simulating the model (4.27) with the following set of parameter values: $\Pi = 50, \beta = 0.6, p = 0.1, \epsilon = 0.6, \omega = 0.0004, \xi = 0.6, \psi = 0.87, \alpha = 0.009, \mu = 0.008, \delta_u = 0.0009, \delta_v = 0.009, \delta_{qu} = 0.09, \delta_{qv} = 0.009, \sigma_1 = 0.8, \sigma_2 = 0.7, q_u = 0.07, r_u = 50, \eta_1 = 0.02, \eta_2 = 0.09, q_v = 0.04, r_v = 50$ and $\theta = 0.9$ (so that, $0.84 = \mathcal{R}_{vac}^c < \mathcal{R}_{vac} = 0.95 < 1$). It should be stated that the aforementioned parameter values chosen for the numerical simulations may not all be realistic epidemiologically (they are chosen only to illustrate the backward bifurcation phenomenon; the reader may refer to [60] for discussions on whether or not backward bifurcation can occur using a realistic set of parameter values).

The simulation results obtained, depicted in Figure 4.4, show that the model has a disease-free equilibrium (corresponding to $\lambda_v^{**} = 0$) and two endemic equilibria (corresponding to $\lambda_v^{**} = 0.1523686255$ and $\lambda_v^{**} = 0.01420615479$, respectively). One of the endemic equilibria ($\lambda_v^{**} = 0.1523686255$) is LAS, and the other ($\lambda_v^{**} = 0.01420615479$) is unstable (a saddle). The disease-free equilibrium (corresponding to $\lambda_v^{**} = 0$) is LAS. This clearly shows the co-existence of two stable equilibria when $\mathcal{R}_{vac} < 1$, confirming that the extended model (4.27) exhibits backward bifurcation for $\mathcal{R}_{vac}^c < \mathcal{R}_{vac} < 1$.

Thus, in summary, the vaccination model (4.27) exhibits backward bifurcation when Case (*iii*) of Theorem 4.5 holds and $\mathcal{R}_{vac}^c < \mathcal{R}_{vac} < 1$. It should be stated that the backward bifurcation phenomenon of the vaccination model (4.27), described above, is only illustrated numerically. A more rigorous proof, based on using the centre manifold theory [13, 36, 88], is given in Appendix A.

The presence of backward bifurcation in the HSV-2 transmission model (4.27) suggests that the feasibility of controlling or eliminating HSV-2 from a population (using a vaccine) when $\mathcal{R}_{vac} < 1$ could be dependent on the initial sizes of the sub-population of the model (4.27). It is worth mentioning that the vaccination model presented by Schwartz and Blower [74] also exhibits backward bifurcation (*albeit* not shown or discussed in that study). Although backward bifurcation has been established in a number of epidemiological models (such as those in [11, 30, 36, 75] and the references therein), this is (to the author's knowledge) the first time such a phenomenon has been rigorously established in the transmission dynamics of HSV-2 in a population. As is typically the case with vaccination models, the imperfect nature of the vaccine is one cause for the presence of backward bifurcation in disease transmission models. This claim is verified below in the context of the extended model (4.27) .

Consider the vaccination model (4.27) with a perfect vaccine (so that, $\psi = 1$). In this case, the coefficients a_1, b_1 and c_1, of the quadratic (4.31), reduce to $a_1 = 0$, $b_1 > 0$ and $c_1 \geq 0$ whenever $\mathcal{R}_{vac} \leq 1$. Thus, when $\psi = 1$, the quadratic (4.31) becomes linear, with a (unique) solution given by $\lambda_v^{**} = -\frac{c_1}{b_1} \leq 0$ (hence, the model (4.27) has no positive endemic equilibrium in this case). This rules out backward bifurcation phenomenon (since backward

bifurcation requires the presence of multiple endemic equilibria when $\mathcal{R}_{vac} < 1$).

The above fact can also be illustrated in the following alternative way. Setting $\psi = 1$ in the extended model (4.27) gives:

$$\begin{aligned}
\frac{dS}{dt} &= \Pi(1-p\epsilon) - \lambda_v S + \omega V - \xi S - \mu S, \\
\frac{dV}{dt} &= \Pi p\epsilon + \xi S - \omega V - \mu V, \\
\frac{dE_u}{dt} &= \lambda_v S - \sigma_1 E_u - \mu E_u, \\
\frac{dH_u}{dt} &= \sigma_1 E_u + r_u Q_u - q_u H_u - \mu H_u - \delta_u H_u, \\
\frac{dQ_u}{dt} &= q_u H_u - r_u Q_u - \mu Q_u - \delta_{qu} Q_u,
\end{aligned} \tag{4.32}$$

with the associated force of infection now given by

$$\lambda_v = \frac{\beta(H_u + \theta Q_u)}{S + V + E_u + H_u + Q_u}. \tag{4.33}$$

It can be shown that the reproduction number of the model (4.32), with (4.33), is given by

$$\mathcal{R}^1_{vac} = \frac{\beta S^* \sigma_1 (k_{71} + \theta q_u)}{N^* k_{31}(k_{51}k_{71} - r_u q_u)}, \tag{4.34}$$

where $S^* = \frac{\Pi[(1-p\epsilon)k_{21} + p\epsilon\omega]}{k_{21}\mu + \xi\mu}$ and $N^* = \frac{\Pi}{\mu}$. Define the invariant region,

$$\mathcal{D}_2 = \big\{(S, V, E_u, H_u, Q_u) \in \mathbb{R}^5_+ : S + V + E_u + H_u + Q_u \leq \frac{\Pi}{\mu}\big\}, \tag{4.35}$$

for the model (4.32). The DFE of the model (4.32) is given by $\mathcal{E}^1_0 = (S^*, V^*, 0, 0, 0)$, where $V^* = \frac{\Pi[(1-p\epsilon)\xi + p\epsilon k_{11}]}{k_{21}\mu + \xi\mu}$. Furthermore, let $\Phi = \frac{S^*}{N^*}$ (i.e., $\Phi < 1$).

Theorem 4.6. *The DFE, $\mathcal{E}^1_0$, of the model (4.32), with (4.33), is GAS in $\mathcal{D}_2$ whenever $\mathcal{R}^1_{vac} \leq \Phi_1 < 1$.*

Proof. Consider the Lyapunov function

$$\mathcal{F}_1 \quad = \quad g_1 E_u + g_2 H_u + g_3 Q_u,$$

where,

$$g_1 \quad = \quad \sigma_1(k_{71}+\theta q_u),\ g_2 = k_{31}(k_{71}+\theta q_u) \text{ and } g_3 = k_{31}(r_u+\theta k_{51}),$$

with Lyapunov derivative given by

$$\begin{aligned}
\dot{\mathcal{F}}_1 &= g_1\dot{E}_u + g_2\dot{H}_u + g_3\dot{Q}_u, \\
&= g_1\left[\frac{\beta(H_u+\theta Q_u)S}{N} - k_{31}E_u\right] + g_2(\sigma_1 E_u + r_u Q_u - k_{51}H_u) + g_3(q_u H_u - k_{71}Q_u), \\
&= k_{31}(k_{51}k_{71}-r_u q_u)\left(\frac{SN^*}{NS^*}\mathcal{R}^1_{vac}-1\right)H_u + \theta k_{31}(k_{51}k_{71}-r_u q_u)\left(\frac{SN^*}{NS^*}\mathcal{R}^1_{vac}-1\right)Q_u, \\
&\leq k_{31}(k_{51}k_{71}-r_u q_u)\left(\frac{\mathcal{R}^1_{vac}}{\Phi_1}-1\right)(H_u+\theta Q_u), \ \text{ since } S \leq N \text{ in } \mathcal{D}_2.
\end{aligned}$$

Thus, $\dot{\mathcal{F}}_1 \leq 0$ if $\mathcal{R}^1_{vac} \leq \Phi_1 \leq 1$ with $\dot{\mathcal{F}}_1 = 0$ if and only if $H_u = Q_u = 0$ (it should be recalled that $k_{51}k_{71} - r_u q_u > 0$). Furthermore, $E_u \to 0$ as $t \to \infty$ if $H_u = Q_u = 0$ (since $\lambda = \frac{\beta(H_u+\theta Q_u)}{N} = 0$ in this case). It follows, from the LaSalle's Invariance Principle [58], that

$$(H_u(t), Q_u(t)) \to (0,0) \ \text{ as } t \to \infty.$$

Using the similar approach as in Section 4.2.3, it can be shown that

$$\lim_{t\to\infty} S(t) = \frac{\Pi(1-p\epsilon)}{(\xi+\mu)} \text{ and } \lim_{t\to\infty} V(t) = \frac{\Pi(\xi+p\epsilon\mu)}{\mu(\xi+\mu)}.$$

Thus,

$$\lim_{t\to\infty}(S(t), V(t), E_u(t), H_u(t), Q_u(t)) = \left(S^*, V^*, 0, 0, 0\right) = \mathcal{E}^1_0.$$

Hence, every solution to the equations of the reduced model (4.32), with initial conditions in $\mathcal{D}_2$, approaches the DFE, $\mathcal{E}^1_0$, as $t \to \infty$, whenever $\mathcal{R}^1_{vac} \leq \Phi_1 < 1$. □

In summary, it is shown that the use of an imperfect HSV-2 vaccine induces the phenomenon of backward bifurcation in the transmission dynamics of HSV-2 in a population,

and such phenomenon does not occur if the vaccine is 100% effective. Thus, adding vaccination to the basic model (4.1) induces the phenomenon of the backward bifurcation in HSV-2 transmission dynamics (it should be recalled that the basic model (4.1) does not undergo backward bifurcation).

4.3.3 Assessment of Vaccine Impact

In this section, the potential impact of the HSV-2 vaccine is assessed by carrying out sensitivity analysis on the vaccination threshold, $\mathcal{R}_{vac}$. The quantity $\mathcal{R}_{vac}$ is, first of all, expressed as a function of the fraction of susceptible individuals vaccinated at steady-state (given by $\mathcal{P} = \frac{V^*}{N^*}$). That is,

$$\mathcal{R}_{vac} = \mathcal{R}_{vac}(\mathcal{P}) = \frac{\beta k_{31}(1-\psi)\sigma_2 \mathcal{P} A_2 + \beta k_{41}\sigma_1(1-\mathcal{P})B_2}{C_2},$$

where,

$$\begin{aligned} A_2 &= \alpha q_v(r_u + \theta k_{51}) + (k_{51}k_{71} - q_u r_u)(\eta_1 k_{81} + \theta \eta_2 q_v), \\ B_2 &= (k_{71} + \theta q_u)(k_{61}k_{81} - q_v r_v), \\ C_2 &= k_{31}k_{41}(k_{51}k_{71} - q_u r_u)(k_{61}k_{81} - q_v r_v). \end{aligned}$$

Differentiating $\mathcal{R}_{vac}$ partially with respect to $\mathcal{P}$ gives

$$\frac{\partial \mathcal{R}_{vac}}{\partial \mathcal{P}} = -\frac{k_{41}\beta\sigma_1 B_2}{C_2}\Big(1 - \nabla\Big), \tag{4.36}$$

with,

$$\nabla = \frac{k_{31}(1-\psi)\sigma_2 A_2}{k_{41}\sigma_1 B_2}.$$

Since $A_2 > 0, B_2 > 0, C_2 > 0$ (noting that $k_{51}k_{71} - q_u r_u > 0$ and $k_{61}k_{81} - q_v r_v > 0$, as shown in Section 4.3.1) and $\mathcal{R}_{vac} > 0$, it follows from (4.36) that $\frac{\partial \mathcal{R}_{vac}}{\partial \mathcal{P}} < 0$ whenever $\nabla < 1$. That

is, $\mathcal{R}_{vac}$ is a decreasing function of the vaccinated fraction, $\mathcal{P}$, whenever $\nabla < 1$. Furthermore, owing to the fact that a reduction in reproduction number implies reduction in disease burden (measured in terms of generation of new infections, disease-induced mortality, hospitalizations etc.), the above analyses show that a HSV-2 vaccine will have positive population-level impact in reducing disease burden (in the community) whenever $\nabla < 1$, and will not otherwise. This result is summarized below:

Lemma 4.5. *Consider the vaccination model* (4.27). *The vaccine will have:*

(i) *positive population-level impact (i.e., reduce disease burden) if* $\nabla < 1$*;*

(ii) *no population-level impact if* $\nabla = 1$*;*

(iii) *detrimental population-level impact (i.e., increase disease burden) if* $\nabla > 1$.

The above result is illustrated numerically by depicting the total number of infection as a function of time. Figure 4.5A shows the case with $\psi = 0.6$ (corresponding to a vaccine efficacy of 60%) and other parameters chosen such that $\nabla = 0.36 < 1$, from which it is evident that the vaccine has a positive impact, since it reduces the number of infections in comparison to the case when the vaccine is not used. Figure 4.5B depicts the solution profiles obtained for the case when the vaccine efficacy is reduced to 20% (i.e., $\psi = 0.2$) and choosing other parameter values so that $\nabla = 1.48 > 1$. It is clear from these simulations that, for the case $\nabla = 1.48 > 1$, the use of the vaccine increases the number of infections, in relation to the case when the vaccine is not used. It should be emphasized that although the threshold ∇ is a decreasing function of ψ, the vaccine can only have positive impact if its efficacy is high enough (to make $\nabla < 1$).

In fact, the threshold value of the vaccine efficacy (denoted by ψ_c) needed to ensure positive population-level vaccine impact can be obtained by setting $\nabla = 1$ and solving for ψ_c. Doing so gives

$$\psi_c = 1 - \frac{P_1}{P_2}, \tag{4.37}$$

where $P_1 = k_{41}\sigma_1 B_2$ and $P_2 = k_{31}\sigma_2 A_2$ (it should be noted that the Condition $P_1 < P_2$ is needed to ensure that $0 < \psi_c < 1$). Thus, the following result is established:

Lemma 4.6. *An imperfect HSV-2 vaccine will have:*

(i) *positive population-level impact if* $\psi > \psi_c$;

(ii) *no population-level impact if* $\psi = \psi_c$; *and*

(iii) *negative population-level impact if* $\psi < \psi_c$.

Alternatively, the vaccine impact can be measured by re-writing $\mathcal{R}_{vac}$ as

$$\mathcal{R}_{vac} = \mathcal{R}_0\left[1 - \frac{V^*}{N^*}\left(1 - \frac{\mathcal{R}_0^{vac}}{\mathcal{R}_0}\right)\right], \tag{4.38}$$

where,

$$\mathcal{R}_0 = \frac{\beta\sigma(k_{71} + \theta q_u)}{k_{31}(k_{51}k_{71} - r_u q_u)}, \tag{4.39}$$

is the *basic reproduction number* (defined in Section 4.2.2), and

$$\mathcal{R}_0^{vac} = \frac{\beta(1-\psi)\sigma_2(\eta_1 k_{81} + \theta\eta_2 q_v)}{k_{41}(k_{61}k_{81} - q_v r_v)}, \tag{4.40}$$

is the reproduction number when every individual in the population is vaccinated (it should be recalled that $k_{51}k_{71} - r_u q_u > 0$ and $k_{61}k_{81} - q_v r_v > 0$, so that $\mathcal{R}_0$ and $\mathcal{R}_0^{vac}$ are non-negative). Using the notation in [9, 30], it follows from (4.38) that the associated *vaccination impact factor*, denoted by ϕ (with $0 < \phi < 1$), is given by

$$\phi = \frac{V^*}{N^*}\left(1 - \frac{\mathcal{R}_0^{vac}}{\mathcal{R}_0}\right). \tag{4.41}$$

It should be noted from (4.41) that if $\mathcal{R}_0^{vac} < \mathcal{R}_0$, then the impact factor, ϕ, is positive. Hence, vaccination will reduce the reproduction number ($\mathcal{R}_{vac}$), and, therefore, the vaccine will have positive population-level impact. On the other hand, if $\mathcal{R}_0^{vac} > \mathcal{R}_0$, then $\phi < 0$.

In this case, vaccination will have negative population-level impact (by increasing disease burden). If $\phi = 0$, then $\mathcal{R}_0^{vac} = \mathcal{R}_0$; and the vaccine will have no population-level impact in this case. These results are summarized below.

Theorem 4.7. *The use of an imperfect HSV-2 vaccine will have:*

(i) positive population-level impact in the community if $\phi > 0$ *(*$\mathcal{R}_0^{vac} < \mathcal{R}_0$*);*

(ii) no population-level impact if $\phi = 0$ *(*$\mathcal{R}_0^{vac} = \mathcal{R}_0$*); and*

(iii) negative population-level impact in the community if $\phi < 0$ *(*$\mathcal{R}_0^{vac} > \mathcal{R}_0$*).*

Figure 4.5A shows that when $\phi = 0.78 > 0$, the vaccine will have a positive impact, while Figure 4.5B shows that the vaccine will be detrimental (increase total infection) when $\phi = -0.05 < 0$. It should be stated that not all of the parameter values used in these simulations are obtained from epidemiological data/studies (and some may not be completely realistic; hence, it is likely that, with a complete set of realistic parameter values, the case where $\nabla > 1$ or $\phi < 0$ would not arise. In other words, it is most probably the case that the vaccine will always have positive impact if all the parameter values used in the simulations are realistic).

Contour plots of $\mathcal{R}_{vac}$, as a function of the fraction of individuals vaccinated at steady-state ($\mathcal{P} = \frac{V^*}{N^*}$) and vaccine efficacy ($\psi$), are depicted in Figure 4.6, using a reasonable set of parameter values (mostly within the ranges given in [74]). It is clear from Figure 4.6 that effective HSV-2 control or elimination is feasible if the vaccine efficacy (ψ) and the fraction of susceptible individuals vaccinated at steady-state ($\mathcal{P}$) are high enough (at least 80% each), since such a combination can reduce $\mathcal{R}_{vac}$ to values less than unity and elimination results for values of $\mathcal{R}_{vac} < 1$ outside the backward bifurcation range ($\mathcal{R}_{vac}^c < \mathcal{R}_{vac} < 1$). On the other hand, disease elimination is not possible if the vaccination efficacy is low (less than 60%) irrespective of the size of the fraction of susceptible individuals vaccinated at steady state.

It is worth stating that Schwartz and Blower [74] showed, using a reasonable ranges of parameter values (taking into account uncertainties in these ranges, based on using Latin

Hypercube Sampling technique), that the use of an imperfect vaccine could induce a modest reduction in incidence of infection in the USA (estimating a reduction of more than 1 million infections within a decade of its introduction). Overall, the theoretical and numerical analyses in this chapter suggest that the prospect of effectively controlling the spread of HSV-2 in a population, using an imperfect vaccine with a reasonably high efficacy, is promising.

4.4 Summary

A basic deterministic model for the transmission dynamics of HSV-2 in a population is designed in this chapter. The basic model is extended to incorporate an imperfect HSV-2 vaccine, with some therapeutic characteristics. Rigorous mathematical analyses are carried out to gain insights into the qualitative dynamics of the two models. Some of the main mathematical and epidemiological findings of this chapter include the following:

(i) The model without vaccination has a globally-asymptotically stable disease-free equilibrium whenever its associated reproduction number is less than unity (Theorem 4.1). It has a unique endemic equilibrium if the associated reproduction number is greater than unity (Theorem 4.2). The endemic equilibrium is shown to be locally- and globally-asymptotically stable for a special case (Theorems 4.3 and 4.4);

(ii) The model with vaccination undergoes the phenomenon of backward bifurcation when the associated reproduction number is less than unity. The presence of this phenomenon, which does not arise if the vaccine is 100% effective, implies that the effort to effectively combat the spread of HSV-2 in a population, using an imperfect vaccine, could be dependent on the initial sizes of the sub-populations of the model;

(iii) An imperfect HSV-2 vaccine could have positive, no, or negative population-level impact depending on whether or not a certain threshold quantity (∇) is less than, equal to, or greater than unity (Theorem 4.5), respectively. This result is also expressed in terms of a "*vaccine impact factor*", ϕ (Theorem 4.6);

(iv) Numerical simulations suggest that disease elimination is possible if the vaccine efficacy and the fraction of individuals vaccinated at steady-state are high enough (at least 80% each).

It should be mentioned that the single-group models presented in this chapter did not incorporate the role of sex structure in HSV-2 transmission dynamics. In other words, the single-group models, (4.1) and (4.27), are limited to some epidemiological settings, such as studying HSV-2 transmissions in populations with one-to-one gender ratio or equal average rates of sexual activity between the sexes. A new model that incorporates sex structure (and, therefore, more realistic) is designed in Chapter 5.

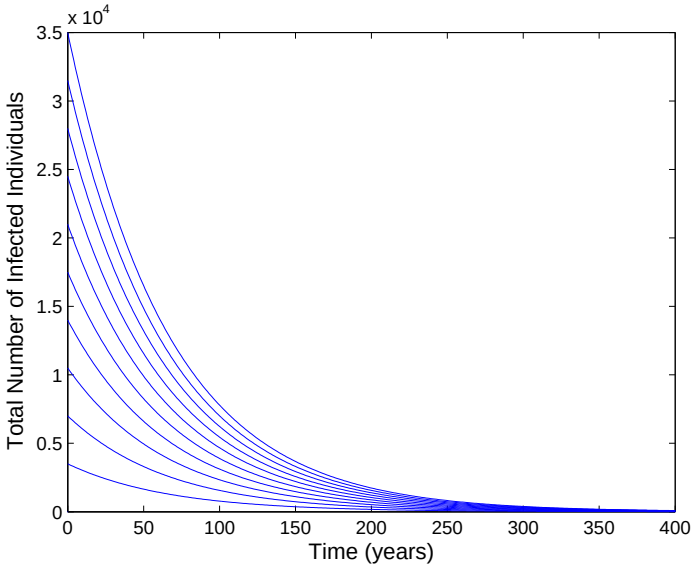


Figure 4.2: Simulations of the basic model (4.1) showing the total number of infected individuals ($E + H_u + Q_u$) as a function of time using the parameters in Table 4.1, with $\beta = 0.01, \mu = \frac{1}{60}$ and $\sigma = \frac{365}{15}$ (so that, $\mathcal{R}_0 = 0.34 < 1$).

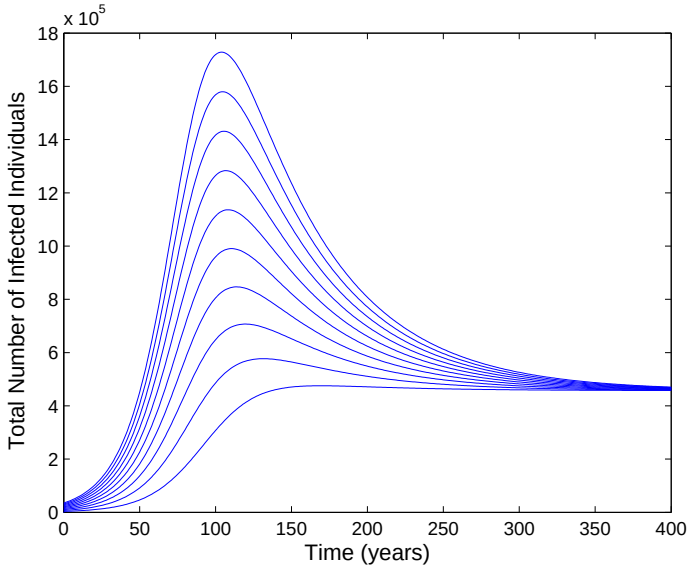


Figure 4.3: Simulations of the basic model (4.1) showing the total number of infected individuals ($E + H_u + Q_u$) as a function of time using the parameters in Table 4.1, with $\beta = 0.1, \mu = \frac{1}{60}, r_u = 0, \delta_u = 0, \delta_{qu} = 0$ and $\sigma = \frac{365}{15}$ (so that, $\mathcal{R}_{01} = 4.20 > 1$).

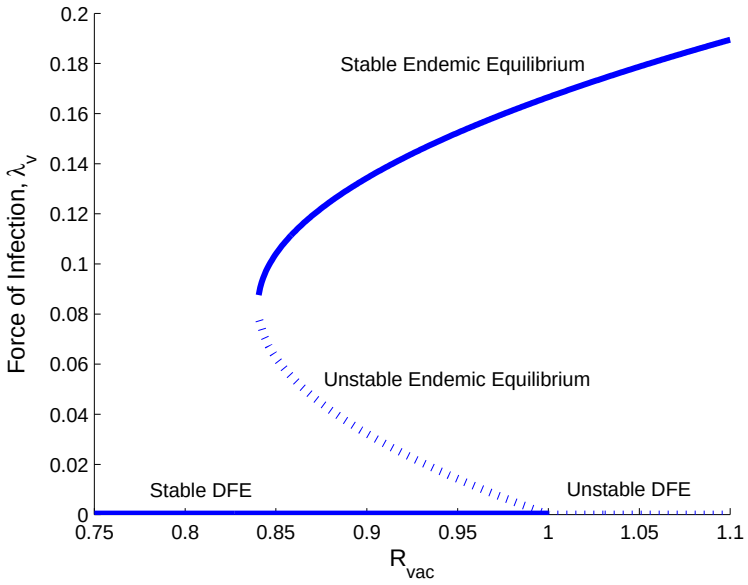
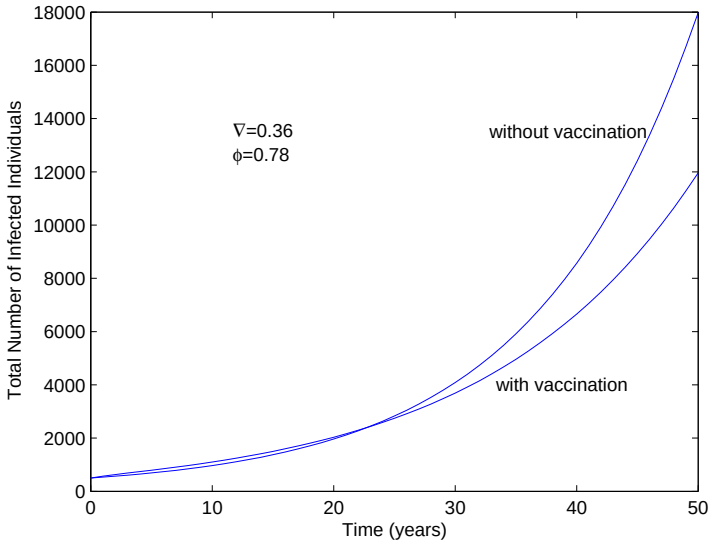


Figure 4.4: Simulations of the vaccination model (4.27) showing the backward bifurcation phenomenon. Parameter values used are as given in Section 4.3.2.

(A)



(B)

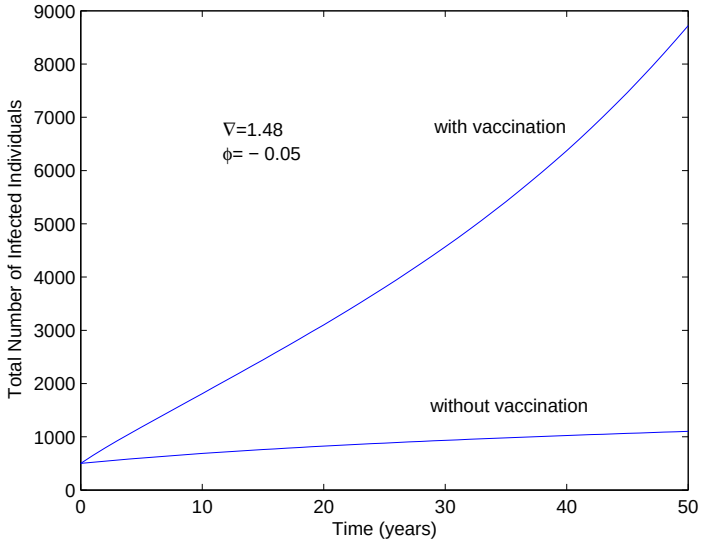


Figure 4.5: Simulations of the vaccination model (4.27) showing the total number of infected individuals ($E_u + E_v + H_u + H_v + Q_u + Q_v$) as a function of time in the presence or absence of vaccination. (A) $\nabla = 0.36 < 1$ and $\phi = 0.78 > 0$ ($\mathcal{R}_{vac} = 1.19, \mathcal{R}_0 = 9.69$ and $\mathcal{R}_0^{vac} = 4.23$). (B) $\nabla = 1.48 > 1$ and $\phi = -0.05 < 0$ (using $\epsilon = 0.3, \psi = 0.2, \sigma_1 = \frac{1}{150}, \sigma_2 = \frac{1}{180}, \eta_1 = 4, \eta_2 = 2, \mathcal{R}_{vac} = 3.25, \mathcal{R}_0 = 3.09$ and $\mathcal{R}_0^{vac} = 4.39$). All other parameters are as given in Table 4.1.

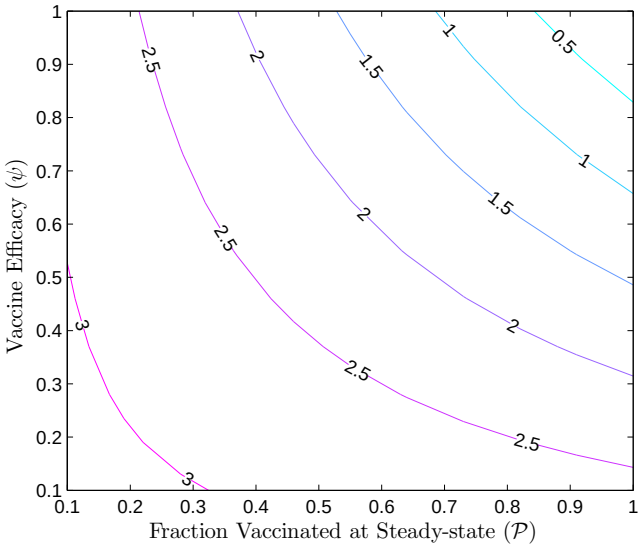


Figure 4.6: Simulations of the vaccination model (4.27) showing contour plots of $\mathcal{R}_{vac}$ as a function of the fraction of individuals vaccinated at steady-state ($\mathcal{P} = \frac{V^*}{N^*}$) and vaccine efficacy ($\psi$) with $\beta = 0.1$. All other parameters are as given in Table 4.1.

Chapter 5

Two-group Model

5.1 Introduction

An important biological feature of HSV-2 disease is the fact that seropositivity is uniformly higher in women than in men [12, 23, 64, 94]. This is attributed to a number of reasons, such as the fact that male-to-female transmission is more likely than female-to-male transmission [23] and the higher rate of disease recurrences in men (which may make them more infectious; and, therefore, more likely to infect their female partners) [12]. Hence, as stated in Chapter 4, realistic models for HSV-2 transmission dynamics in a population should incorporate such heterogeneity in susceptibility due to gender variability (i.e., sex structure). Consequently, the aim of this chapter is to model the transmission dynamics of HSV-2 in a sex-structured heterosexual population. The deterministic model to be designed, which is an extension of the model (4.1), will be used to evaluate the impact of various intervention strategies, such as the use of condoms, antiviral drugs and an imperfect HSV-2 vaccine. As stated in Chapter 1, condoms are known to offer significant protection against HSV-2 infection, particularly in susceptible women [14, 91]. Similarly, antiviral drugs (such as, *aciclovir (Zovirax)*, *valaciclovir (Valtrex)*, *famciclovir (Famvir)*, *peniciclovir*) can reduce the frequency, duration and severity of outbreaks [12, 52, 59, 77]. Furthermore, a number of candidate HSV-2 vaccines are undergoing various stages of clinical trials.

Thus, it is significant to evaluate the impact of the aforementioned pharmaceutical and non-pharmaceutical interventions in curtailing the spread of HSV-2 in a sexually-active sex-structured population. In addition to evaluating the impact of the control strategies, the objective of this chapter is to determine whether or not adding sex structure to the basic HSV-2 model (4.1) affects the qualitative dynamics of the single-group model (4.1).

5.2 Model Formulation

The total sexually-active population at time t, denoted by $N(t)$, is sub-divided into two groups, namely, the total male population ($N_m(t)$) and the total female population ($N_f(t)$). The total male population is further sub-divided into four mutually-exclusive compartments for males that are susceptible ($S_m(t)$), exposed to HSV-2 but show no clinical symptoms of the disease ($E_m(t)$), infectious (virus-shedding) with clinical symptoms of HSV-2 ($H_m(t)$) and infectious, whose infection is quiescent ($Q_m(t)$), so that

$$N_m(t) = S_m(t) + E_m(t) + H_m(t) + Q_m(t).$$

Similarly, the total female population is further sub-divided into four mutually-exclusive compartments for females that are susceptible ($S_f(t)$), exposed to HSV-2 but show no clinical symptoms of the disease ($E_f(t)$), infectious (virus-shedding) with clinical symptoms of HSV-2 ($H_f(t)$) and infectious, whose infection is quiescent ($Q_f(t)$), so that

$$N_f(t) = S_f(t) + E_f(t) + H_f(t) + Q_f(t).$$

The model to be considered consists of the following system of differential equations [72]:

$$\begin{aligned}
\frac{dS_m}{dt} &= \Pi_m - \lambda_f S_m - \mu S_m, \\
\frac{dE_m}{dt} &= \lambda_f S_m - (\sigma_m + \mu) E_m, \\
\frac{dH_m}{dt} &= \sigma_m E_m + r_m Q_m - (q_m + \mu + \delta_1) H_m, \\
\frac{dQ_m}{dt} &= q_m H_m - (r_m + \mu + \delta_2) Q_m, \\
\frac{dS_f}{dt} &= \Pi_f - \lambda_m S_f - \mu S_f, \\
\frac{dE_f}{dt} &= \lambda_m S_f - (\sigma_f + \mu) E_f, \\
\frac{dH_f}{dt} &= \sigma_f E_f + r_f Q_f - (q_f + \mu + \delta_1) H_f, \\
\frac{dQ_f}{dt} &= q_f H_f - (r_f + \mu + \delta_2) Q_f.
\end{aligned} \tag{5.1}$$

In (5.1), the parameters Π_m and Π_f represent the recruitment rate of males and females into the sexually-active population, respectively. Susceptible males acquire HSV-2 infection following effective contact with infectious females at a rate λ_f, given by

$$\lambda_f = \frac{\beta_f c_m (H_f + \eta_f Q_f)}{N_f}, \tag{5.2}$$

where β_f is the probability of infection (from females to males) *per* contact and c_m is the average number of male sexual partners (for females) *per* unit time. Similarly, susceptible females acquire HSV-2 infection following effective contact with infectious males at a rate λ_m (the reader may refer to [43] on the derivation of the infection rates, λ_f and λ_m), where

$$\lambda_m = \frac{\beta_m c_f (H_m + \eta_m Q_m)}{N_m}, \tag{5.3}$$

with c_f and β_m having similar definitions as c_m and β_f (it is, however, assumed that $\beta_m > \beta_f$ since females are more susceptible to HSV-2 infection than males [94]). Unlike in many other HSV-2 modelling studies (including those in [10, 74]), it is assumed that infected individuals in the quiescent state (i.e., those in the Q_m and Q_f classes) can indeed transmit infection.

The modification parameters $0 < \eta_m, \eta_f < 1$ account for the assumption that quiescent individuals transmit infection at a slower rate than the corresponding infected individuals with clinical symptoms of the disease (in the H_m and H_f classes), due to their assumed reduced viral load (it is assumed that viral load is positively correlated with infectiousness). Individuals in each epidemiological compartment suffer natural death at a rate μ.

Newly-infected individuals move to the exposed class $E_m(E_f)$ at the rate $\lambda_f(\lambda_m)$ for males (females). Exposed individuals develop symptoms at a rate $\sigma_m(\sigma_f)$ for males (females). Quiescent individuals re-activate (relapse) their infection (and become symptomatic) at a rate $r_m(r_f)$ for males (females), and move to the corresponding $H_m(H_f)$ class. Individuals with clinical symptoms of the disease become quiescent at a rate $q_m(q_f)$ for males (females). The parameters δ_1 and δ_2 represent the disease-induced death for individuals with symptoms (in H_m or H_f class) and those in quiescent state (in Q_m or Q_f class), respectively. It is assumed that $\delta_2 \leq \delta_1$.

The model (5.1) is an extension of the one-group HSV-2 transmission model presented by Podder and Gumel [71], by considering a two-group (males/females) structure (that takes into account the differential susceptibility to HSV-2 infection between the two genders). It should be mentioned that although numerous two-sex models have been published in the literature (see, for instance, [17, 20, 22, 21, 40, 45, 48, 83]), no such model has so far been published in the context of the transmission dynamics of HSV-2 in a population.

The main objective of the current study is to determine whether or not adding sex structure to the single-group HSV-2 model presented in [71] alters its qualitative (equilibrium) dynamics. It is worth mentioning that an important feature of a sex-structured model is that the total number of sexual contacts females make with males must equal the total number of sexual contacts males make with females. Thus, the following group contact constraint must hold (see also [16, 17, 98]) :

$$c_m N_m = c_f N_f. \tag{5.4}$$

It is assumed that male sexual partners are abundant, so that females can always have enough

number of sexual contacts per unit time. Hence, it is assumed that c_f is constant (and c_m is calculated from the relation $c_m = \frac{c_f N_f}{N_m}$) (see, for instance, [15, 18, 16, 17, 46, 55, 67, 95, 100] for further discussions on multi-group models). Using the constraint (5.4) in (5.2) and (5.3), the basic model (5.1) can be re-written as:

$$\begin{aligned}
\frac{dS_m}{dt} &= \Pi_m - \frac{\beta_f c_f}{N_m}(H_f + \eta_f Q_f)S_m - \mu S_m,\\
\frac{dE_m}{dt} &= \frac{\beta_f c_f}{N_m}(H_f + \eta_f Q_f)S_m - (\sigma_m + \mu)E_m,\\
\frac{dH_m}{dt} &= \sigma_m E_m + r_m Q_m - (q_m + \mu + \delta_1)H_m,\\
\frac{dQ_m}{dt} &= q_m H_m - (r_m + \mu + \delta_2)Q_m,\\
\frac{dS_f}{dt} &= \Pi_f - \frac{\beta_m c_m}{N_f}(H_m + \eta_m Q_m)S_f - \mu S_f,\\
\frac{dE_f}{dt} &= \frac{\beta_m c_m}{N_f}(H_m + \eta_m Q_m)S_f - (\sigma_f + \mu)E_f,\\
\frac{dH_f}{dt} &= \sigma_f E_f + r_f Q_f - (q_f + \mu + \delta_1)H_f,\\
\frac{dQ_f}{dt} &= q_f H_f - (r_f + \mu + \delta_2)Q_f.
\end{aligned} \tag{5.5}$$

The two-group HSV-2 transmission model (5.5) is an extension of the single-group HSV-2 model (4.1), by incorporating sex-structure. In other words, the model (5.5) relaxes the assumption (in (4.1)) that every sexually-active individual has the same likelihood of acquiring HSV-2 infection (this assumption seems unrealistic, since data shows that HSV-2 seropositivity is uniformly higher in women than in men [12, 23, 64, 94]).

The model (5.5) will now be analysed for its basic properties.

5.2.1 Basic Properties

Using the approach in Section 4.2.1, the following result can be proven.

Theorem 5.1. *Denote* $x_i(t) = (S_i(t), E_i(t), H_i(t), Q_i(t)), \quad i = m, f$. *Let the initial data* $(x_m(0), x_f(0)) > 0$. *Then the solutions* $(x_m(t), x_f(t))$ *of the basic model* (5.5) *are positive for*

all $t > 0$. Furthermore,

$$\limsup_{t\to\infty} N_m(t) \leq \frac{\Pi_m}{\mu},\ \limsup_{t\to\infty} N_f(t) \leq \frac{\Pi_f}{\mu}.$$

Define the region:

$$\begin{aligned}\mathcal{D} &= \Bigg\{(S_m, E_m, H_m, Q_m, S_f, E_f, H_f, Q_f) \in \mathbb{R}^8_+ : \\ &\quad S_m + E_m + H_m + Q_m \leq \frac{\Pi_m}{\mu},\ \ S_f + E_f + H_f + Q_f \leq \frac{\Pi_f}{\mu}\Bigg\}.\end{aligned}$$

The following result can also be shown using the approach in Section 4.2.1.

Lemma 5.1. *The region $\mathcal{D}$ is positively-invariant for the basic model* (5.5) *with initial conditions in $\mathbb{R}^8_+$.*

5.3 Existence and Stability of Equilibria

5.3.1 Local Stability of DFE

The DFE of the model (5.5) is given by

$$\mathcal{E}_0 = (S_m^*, E_m^*, H_m^*, Q_m^*, S_f^*, E_f^*, H_f^*, Q_f^*) = \left(\frac{\Pi_m}{\mu}, 0, 0, 0, \frac{\Pi_f}{\mu}, 0, 0, 0\right). \tag{5.6}$$

Using the notations in [88], the next generation matrices F and V, associated with the model (5.5), are, respectively, given by,

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 & \beta_f c_f & \eta_f \beta_f c_f \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_m c_m & \eta_m \beta_m c_m & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \quad \text{and} \quad V = \begin{pmatrix} m_1 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_m & m_2 & -r_m & 0 & 0 & 0 \\ 0 & -q_m & m_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & m_{11} & 0 & 0 \\ 0 & 0 & 0 & -\sigma_f & m_{21} & -r_f \\ 0 & 0 & 0 & 0 & -q_f & m_{31} \end{pmatrix},$$

with, $m_1 = \sigma_m + \mu$, $m_2 = q_m + \mu + \delta_1$, $m_3 = r_m + \mu + \delta_2$, $m_{11} = \sigma_f + \mu$, $m_{21} = q_f + \mu + \delta_1$ and $m_{31} = r_f + \mu + \delta_2$. Hence, it follows that

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\mathcal{R}_m \mathcal{R}_f}, \tag{5.7}$$

where,

$$\mathcal{R}_m = \frac{\beta_f c_f \sigma_m (m_3 + \eta_m q_m)}{m_1(m_2 m_3 - q_m r_m)}, \tag{5.8}$$

and,

$$\mathcal{R}_f = \frac{\beta_m c_m \sigma_f (m_{31} + \eta_f q_f)}{m_{11}(m_{21} m_{31} - q_f r_f)}. \tag{5.9}$$

It should be mentioned that, in (5.8) and (5.9), $m_2 m_3 - q_m r_m = q_m(\mu + \delta_2) + m_3(\mu + \delta_1) > 0$ and $m_{21} m_{31} - q_f r_f = q_f(\mu + \delta_2) + m_{31}(\mu + \delta_1) > 0$. Consequently, it follows from Theorem 2.7 that:

Lemma 5.2. *The DFE of the model* (5.5)*, given by* (5.6)*, is locally-asymptotically stable whenever* $\mathcal{R}_0 < 1$*, and unstable if* $\mathcal{R}_0 > 1$*.*

The threshold quantity, $\mathcal{R}_0$, is the aggregate (geometric) product of the average number of new cases generated by females (denoted by $\mathcal{R}_f$) and males (denoted by $\mathcal{R}_m$). It measures the average number of secondary cases generated by a single infectious male (female) in a completely susceptible population [3, 43]. The epidemiological implication of Lemma 5.2 is that a small influx of infectious individuals will not generate large outbreaks in the population if $\mathcal{R}_0 < 1$. In order for disease elimination to be independent of the initial sizes of the sub-populations of the model when $\mathcal{R}_0 < 1$, a global asymptotic stability property must be established for the DFE ($\mathcal{E}_0$) of the model when $\mathcal{R}_0 < 1$. This is explored below.

5.3.2 Global Stability of DFE

Theorem 5.2. *The DFE,* $\mathcal{E}_0$*, of the basic model* (5.5)*, is GAS in* $\mathcal{D}$ *if* $\mathcal{R}_0 \leq 1$*.*

Proof. Consider the Lyapunov function

$$\mathcal{F} = f_1 E_m + f_2 H_m + f_3 Q_m + f_4 E_f + f_5 H_f + f_6 Q_f,$$

where,

$$\begin{aligned} f_1 &= \Phi_2\Phi_3\mathcal{R}_0\sigma_m m_{11},\ f_2 = \Phi_2\Phi_3\mathcal{R}_0 m_1 m_{11},\ f_3 = \Phi_2\mathcal{R}_0 m_1 m_{11}(r_m + \eta_m m_2), \\ f_4 &= \Phi_3\Phi_4\beta_f c_f \sigma_m\sigma_f,\ f_5 = \Phi_3\Phi_4\beta_f c_f\sigma_m m_{11},\ f_6 = \Phi_3\beta_f c_f\sigma_m m_{11}(r_f + \eta_f m_{21}), \end{aligned}$$

with,

$$\Phi_1 = m_2 m_3 - q_m r_m,\ \Phi_2 = m_{21}m_{31} - q_f r_f,\ \Phi_3 = m_3 + \eta_m q_m \text{ and } \Phi_4 = m_{31} + \eta_f q_f.$$

The Lyapunov derivative of $\mathcal{F}$ is given by

$$\begin{aligned} \dot{\mathcal{F}} &= f_1\dot{E_m} + f_2\dot{H_m} + f_3\dot{Q_m} + f_4\dot{E_f} + f_5\dot{H_f} + f_6\dot{Q_f}, \\ &= f_1\left[\frac{\beta_f c_f}{N_m}(H_f + \eta_f Q_f)S_m - m_1 E_m\right] + f_2(\sigma_m E_m + r_m Q_m - m_2 H_m) + f_3(q_m H_m - m_3 Q_m) \\ &+ f_4\left[\frac{\beta_m c_m}{N_f}(H_m + \eta_m Q_m)S_f - m_{11}E_f\right] + f_5(\sigma_f E_f + r_f Q_f - m_{21}H_f) + f_6(q_f H_f - m_{31}Q_f), \\ &= \Phi_2\Phi_3 m_{11}c_f\sigma_m\frac{\lambda_f N_f}{c_m}\left(\frac{S_m}{N_m}\mathcal{R}_0 - 1\right) + \Phi_1\Phi_2 m_1 m_{11}\mathcal{R}_0\frac{\lambda_m N_m}{\beta_m c_f}\left(\frac{S_f}{N_f}\mathcal{R}_0 - 1\right), \\ &\leq \Phi_2\Phi_3 m_{11}c_f\sigma_m\frac{\lambda_f N_f}{c_m}\left(\mathcal{R}_0 - 1\right) + \Phi_1\Phi_2 m_1 m_{11}\mathcal{R}_0\frac{\lambda_m N_m}{\beta_m c_f}\left(\mathcal{R}_0 - 1\right), \\ &\quad \text{since } S_m \leq N_m \text{ and } S_f \leq N_f \text{ in } \mathcal{D}. \end{aligned}$$

Thus, $\dot{\mathcal{F}} \leq 0$ if $\mathcal{R}_0 \leq 1$ with $\dot{\mathcal{F}} = 0$ if and only if $E_m = H_m = Q_m = E_f = H_f = Q_f = 0$. It follows, from the LaSalle's Invariance Principle [58], that

$$(E_m, H_m, Q_m, E_f, H_f, Q_f) \to (0,0,0,0,0,0) \text{ as } t \to \infty.$$

Thus, for any $\epsilon > 0$ sufficiently small, there exists a $t_1 > 0$ such that if $t > t_1$, then

$$E_m < \epsilon,\ H_m < \epsilon,\ Q_m < \epsilon,\ E_f < \epsilon,\ H_f < \epsilon \text{ and } Q_f < \epsilon. \tag{5.10}$$

Now, it follows from the equations for S_m and S_f in (5.5) that for $t > t_1$ (and noting (5.10))

$$\begin{aligned}
\frac{dS_m}{dt} &= \Pi_m - \lambda_f(t)S_m(t) - \mu S_m(t) \geq \Pi_m - c_f\beta_f(1+\eta_f)\epsilon - \mu S_m(t), \\
\frac{dS_f}{dt} &= \Pi_f - \lambda_m(t)S_f(t) - \mu S_f(t) \geq \Pi_f - c_m\beta_m(1+\eta_m)\epsilon - \mu S_m(t).
\end{aligned}$$

Thus, by comparison theorem,

$$\liminf_{t\to\infty} S_m(t) \geq \frac{\Pi_m - c_f\beta_f(1+\eta_f)\epsilon}{\mu},\ \liminf_{t\to\infty} S_f(t) \geq \frac{\Pi_f - c_m\beta_m(1+\eta_m)\epsilon}{\mu}. \tag{5.11}$$

Since $\epsilon > 0$ is arbitrarily small, letting $\epsilon \to 0$ in (5.11) gives

$$\liminf_{t\to\infty} S_m(t) \geq \frac{\Pi_m}{\mu} \text{ and } \liminf_{t\to\infty} S_f(t) \geq \frac{\Pi_f}{\mu}. \tag{5.12}$$

Similarly, it can be shown that

$$\limsup_{t\to\infty} S_m(t) \leq \frac{\Pi_m}{\mu} \text{ and } \limsup_{t\to\infty} S_f(t) \leq \frac{\Pi_f}{\mu}. \tag{5.13}$$

Hence, it follows from (5.12) and (5.13) that

$$\lim_{t\to\infty} S_m(t) = \frac{\Pi_m}{\mu} \text{ and } \lim_{t\to\infty} S_f(t) = \frac{\Pi_f}{\mu}.$$

Thus,

$$\begin{aligned}
&\lim_{t\to\infty} (S_m(t), E_m(t), H_m(t), Q_m(t), S_f(t), E_f(t), H_f(t), Q_f(t)) \\
= &\left(\frac{\Pi_m}{\mu}, 0, 0, 0, \frac{\Pi_f}{\mu}, 0, 0, 0\right) = \mathcal{E}_0.
\end{aligned}$$

□

The epidemiological implication of Theorem 5.2 is that the classical epidemiological requirement of $\mathcal{R}_0 \leq 1$ is necessary and sufficient for the elimination of HSV-2 from the community.

5.3.3 Existence and Stability of Endemic Equilibria

The existence of an EEP of the model (5.5) is considered for the special case where the associated disease-induced mortality is negligible (so that, $\delta_1 = \delta_2 = 0$). Setting $\delta_1 = \delta_2 = 0$ in the model (5.5), and adding all the equations of the model, gives the following equations for the rate of change of the total male and female populations, respectively:

$$\frac{dN_m(t)}{dt} = \Pi_m - \mu N_m(t) \text{ and } \frac{dN_f(t)}{dt} = \Pi_f - \mu N_f(t).$$

Thus, $N_m(t) \to \frac{\Pi_m}{\mu}$ and $N_f(t) \to \frac{\Pi_f}{\mu}$ as $t \to \infty$. Using $N_m = \frac{\Pi_m}{\mu}$ and $N_f = \frac{\Pi_f}{\mu}$ (and noting that $\delta_1 = \delta_2 = 0$) in the basic model (5.5) gives the following reduced or limiting (mass action) system:

$$\begin{aligned}
\frac{dS_m}{dt} &= \Pi_m - \frac{\beta_f c_f \mu}{\Pi_m}(H_f + \eta_f Q_f)S_m - \mu S_m,\\
\frac{dE_m}{dt} &= \frac{\beta_f c_f \mu}{\Pi_m}(H_f + \eta_f Q_f)S_m - p_1 E_m,\\
\frac{dH_m}{dt} &= \sigma_m E_m + r_m Q_m - p_2 H_m,\\
\frac{dQ_m}{dt} &= q_m H_m - p_3 Q_m,\\
\frac{dS_f}{dt} &= \Pi_f - \frac{\beta_m c_m \mu}{\Pi_f}(H_m + \eta_m Q_m)S_f - \mu S_f,\\
\frac{dE_f}{dt} &= \frac{\beta_m c_m \mu}{\Pi_f}(H_m + \eta_m Q_m)S_f - p_{11} E_f,\\
\frac{dH_f}{dt} &= \sigma_f E_f + r_f Q_f - p_{21} H_f,\\
\frac{dQ_f}{dt} &= q_f H_f - p_{31} Q_f,
\end{aligned} \tag{5.14}$$

where, $p_1 = \sigma_m + \mu$, $p_2 = q_m + \mu$, $p_3 = r_m + \mu$, $p_{11} = \sigma_f + \mu$, $p_{21} = q_f + \mu$ and $p_{31} = r_f + \mu$.

To obtain conditions for the existence of non-zero (endemic) equilibria of the mass action

model (5.14), it is convenient to let

$$\mathcal{E}_1 = (S_m^{**}, E_m^{**}, H_m^{**}, Q_m^{**}, S_f^{**}, E_f^{**}, H_f^{**}, Q_f^{**}),$$

denotes any arbitrary equilibrium of the mass action model (5.14). The equations in the model (5.14) are then solved in terms of the associated forces of infection (λ_{f1} and λ_{m1}) at steady-state (obtained from (5.2) and (5.3) at steady-state), namely

$$\lambda_{f1}^{**} = \frac{\beta_f c_f \mu (H_f^{**} + \eta_f Q_f^{**})}{\Pi_m} \text{ and } \lambda_{m1}^{**} = \frac{\beta_m c_m \mu (H_m^{**} + \eta_m Q_m^{**})}{\Pi_f}. \tag{5.15}$$

It follows that the basic reproduction number associated with the reduced model (5.14), denoted by $\mathcal{R}_1$, is given by

$$\mathcal{R}_1 = \mathcal{R}_0|_{(\delta_1=\delta_2=0)} = \sqrt{\frac{\beta_m \beta_f c_m c_f \sigma_m \sigma_f (p_3 + \eta_m q_m)(p_{31} + \eta_f q_f)}{p_1 p_{11} (p_2 p_3 - q_m r_m)(p_{21} p_{31} - q_f r_f)}},$$

where, $p_2 p_3 - q_m r_m = \mu(q_m + p_3) > 0$ and $p_{21} p_{31} - q_f r_f = \mu(q_f + p_{31}) > 0$.

Setting the right-hand sides of the equations in (5.14) to zero gives the following expressions for the state variables of the model (in terms of λ_{f1}^{**} and λ_{m1}^{**}):

$$\begin{aligned}
S_m^{**} &= \frac{\Pi_m}{\lambda_{f1}^{**} + \mu},\ E_m^{**} = \frac{\lambda_{f1}^{**} \Pi_m}{p_1(\lambda_{f1}^{**} + \mu)},\ H_m^{**} = \frac{p_3 \sigma_m \lambda_{f1}^{**} \Pi_m}{p_1(p_2 p_3 - r_m q_m)(\lambda_{f1}^{**} + \mu)},\ Q_m^{**} = \frac{B_1 \lambda_{f1}^{**} \Pi_m}{\lambda_{f1}^{**} + \mu}, \\
S_f^{**} &= \frac{\Pi_f}{\lambda_{m1}^{**} + \mu},\ E_f^{**} = \frac{\lambda_{m1}^{**} \Pi_f}{p_{11}(\lambda_{m1}^{**} + \mu)},\ H_f^{**} = \frac{p_{31} \sigma_f \lambda_{m1}^{**} \Pi_f}{p_{11}(p_{21} p_{31} - r_f q_f)(\lambda_{m1}^{**} + \mu)},\ Q_f^{**} = \frac{B_2 \lambda_{m1}^{**} \Pi_f}{\lambda_{m1}^{**} + \mu},
\end{aligned} \tag{5.16}$$

where,

$$B_1 \quad = \quad \frac{k_3 \sigma_m}{p_1(p_2 p_3 - r_m q_m)} \text{ and } B_2 = \frac{p_{31} \sigma_f}{p_{11}(p_{21} p_{31} - r_f q_f)}. \tag{5.17}$$

By substituting the expressions in (5.16) (and noting (5.17)) into equation (5.15), and simplifying, it follows that the non-zero equilibria of the model system (5.14) satisfy the following

polynomial (in terms of λ_{f1}^{**}):

$$a_1\lambda_{f1}^{**} + a_2 = 0, \tag{5.18}$$

where,

$$a_1 = p_{31}g_1B_1\Pi_m p_3 + p_{31}g_2B_1\Pi_m\eta_m q_m + p_{31}\mu p_3,$$

and,

$$a_2 \;\; = \;\; \mu^2 p_1 p_{11}(p_2p_3 - r_m q_m)(p_{21}p_{31} - r_f q_f)(1 - \mathcal{R}_1^2),$$

with, $g_1 = \frac{\beta_f c_f \mu}{\Pi_m}$ and $g_2 = \frac{\beta_m c_m \mu}{\Pi_f}$.

Clearly, the coefficient, a_1, of the linear equation (5.18), is always positive (since all the model parameters are positive). Furthermore, since $p_2p_3 - r_m q_m > 0$ and $p_{21}p_{31} - r_f q_f > 0$, it follows that the coefficient a_2 is positive (negative) if $\mathcal{R}_1$ is less than (greater than) unity. Thus, the unique solution of (5.18), given by $\lambda_{f1}^{**} = \frac{-a_2}{a_1}$, is negative whenever $\mathcal{R}_1 < 1$ (so that the model has no positive real root in this case). When $\mathcal{R}_1 = 1$, the coefficient $a_2 = 0$, and the equation (5.18) reduces to $a_1\lambda_{f1}^{**} = 0$ (with solution $\lambda_{f1}^{**} = 0$; corresponding to the DFE, $\mathcal{E}_0$). For the case when $\mathcal{R}_1 > 1$, the coefficient $a_2 < 0$, so that the model has one positive real root, given by $\lambda_{f1}^{**} = \frac{-a_2}{a_1} > 0$ (the components of this endemic equilibrium, for the case $\mathcal{R}_1 > 1$, can then be obtained by substituting the positive root of (5.18) into the expressions in (5.16)). These results are summarized below.

Lemma 5.3. *The reduced model* (5.14) *has one positive (endemic) equilibrium, of the form* $\mathcal{E}_1$*, whenever* $\mathcal{R}_1 > 1$*, and no positive equilibrium otherwise.*

The local stability property of the unique endemic equilibrium ($\mathcal{E}_1$) of the reduced model (5.14) is now explored. For mathematical convenience, the substitutions $S_m = N_m^{**} - E_m -$

$H_m - Q_m$ and $S_f = N_f^{**} - E_f - H_f - Q_f$ will be used in (5.14), giving

$$\begin{aligned}
\frac{dE_m}{dt} &= \frac{\beta_f c_f}{N_m^{**}}(H_f + \eta_f Q_f)(N_m^{**} - E_m - H_m - Q_m) - p_1 E_m,\\
\frac{dH_m}{dt} &= \sigma_m E_m + r_m Q_m - p_2 H_m,\\
\frac{dQ_m}{dt} &= q_m H_m - p_3 Q_m,\\
\frac{dE_f}{dt} &= \frac{\beta_m c_m}{N_f^{**}}(H_m + \eta_m Q_m)(N_f^{**} - E_f - H_f - Q_f) - p_{11} E_f,\\
\frac{dH_f}{dt} &= \sigma_f E_f + r_f Q_f - p_{21} H_f,\\
\frac{dQ_f}{dt} &= q_f H_f - p_{31} Q_f.
\end{aligned} \tag{5.19}$$

Theorem 5.3. *The unique endemic equilibrium, $\mathcal{E}_1$, of the model* (5.19) *is LAS whenever* $\mathcal{R}_1 > 1$.

The proof of Theorem 5.3 is given in Appendix B.

The global stability of the EEP ($\mathcal{E}_1$) of the model (5.14) is considered for the special case where quiescent individuals do not transmit infection (i.e., $\eta_f = \eta_m = 0$) or re-activate their infection (i.e., $r_m = r_f = 0$). Substituting $\eta_f = \eta_m = r_m = r_f = 0$ in (5.14) gives the following system:

$$\begin{aligned}
\frac{dS_m}{dt} &= \Pi_m - \frac{\beta_f c_f \mu}{\Pi_m} H_f S_m - \mu S_m,\\
\frac{dE_m}{dt} &= \frac{\beta_f c_f \mu}{\Pi_m} H_f S_m - p_1 E_m,\\
\frac{dH_m}{dt} &= \sigma_m E_m - p_2 H_m,\\
\frac{dQ_m}{dt} &= q_m H_m - p_3 Q_m,\\
\frac{dS_f}{dt} &= \Pi_f - \frac{\beta_m c_m \mu}{\Pi_f} H_m S_f - \mu S_f,\\
\frac{dE_f}{dt} &= \frac{\beta_m c_m \mu}{\Pi_f} H_m S_f - p_{11} E_f,\\
\frac{dH_f}{dt} &= \sigma_f E_f - p_{21} H_f,\\
\frac{dQ_f}{dt} &= q_f H_f - p_{31} Q_f.
\end{aligned} \tag{5.20}$$

The reproduction number associated with the system (5.20) is given by

$$\mathcal{R}_2 = \mathcal{R}_1|_{(\eta_m=\eta_f=r_m=r_f=0)} = \sqrt{\frac{\beta_m\beta_f c_m c_f \sigma_m \sigma_f}{p_1 p_{11} p_2 p_{21}}}. \tag{5.21}$$

Using the approach in Section 5.3.3, it can be shown that the reduced system (5.20) has a unique EEP, of the form

$$\mathcal{E}_2 = (S^{**}_{m1}, E^{**}_{m1}, H^{**}_{m1}, Q^{**}_{m1}, S^{**}_{f1}, E^{**}_{f1}, H^{**}_{f1}, Q^{**}_{f1})$$

(where, $S^{**}_{m1} > 0, E^{**}_{m1} > 0, H^{**}_{m1} > 0, Q^{**}_{m1} > 0, S^{**}_{f1} > 0, E^{**}_{f1} > 0, H^{**}_{f1} > 0,$ and $Q^{**}_{m1} > 0$), whenever $\mathcal{R}_2 > 1$. It is convenient to define the region:

$$\mathcal{D}_0 = \{(S_m, E_m, H_m, Q_m, S_f, E_f, H_f, Q_f) \in \mathcal{D} : H_m = Q_m = H_f = Q_f = 0\}.$$

Theorem 5.4. *The unique EEP, $\mathcal{E}_2$, of the reduced model* (5.20) *is GAS in $\mathcal{D} \setminus \mathcal{D}_0$ whenever $\mathcal{R}_2 > 1$.*

Proof. It should be noted from the system (5.20), first of all, that the variables Q_m and Q_f do not feature in any of the other equations of the model. Hence, these variables can be (temporarily) removed from the analysis of the system (5.20), by considering a sub-system of the model (5.20) without the equations for $\frac{dQ_m}{dt}$ and $\frac{dQ_f}{dt}$. Furthermore, consider the non-linear Lyapunov function

$$\begin{aligned}\mathcal{F} = &\left(S_m - S^{**}_{m1} - S^{**}_{m1} ln\frac{S_m}{S^{**}_{m1}}\right) + \left(E_m - E^{**}_{m1} - E^{**}_{m1} ln\frac{E_m}{E^{**}_{m1}}\right) \\ &+ \frac{\sigma_m + \mu}{\sigma_m}\left(H_m - H^{**}_{m1} - H^{**}_{m1} ln\frac{H_m}{H^{**}_{m1}}\right) + \frac{g_1 H^{**}_{f1} S^{**}_{m1}}{g_2 H^{**}_{m1} S^{**}_{f1}}\left(S_f - S^{**}_{f1} - S^{**}_{f1} ln\frac{S_f}{S^{**}_{f1}}\right) \\ &+ \frac{g_1 H^{**}_{f1} S^{**}_{m1}}{g_2 H^{**}_{m1} S^{**}_{f1}}\left(E_f - E^{**}_{f1} - E^{**}_{f1} ln\frac{E_f}{E^{**}_{f1}}\right) + \frac{g_1 H^{**}_{f1} S^{**}_{m1}}{g_2 H^{**}_{m1} S^{**}_{f1}}\frac{\sigma_f + \mu}{\sigma_f}\left(H_m - H^{**}_{m1} - H^{**}_{m1} ln\frac{H_m}{H^{**}_{m1}}\right),\end{aligned} \tag{5.22}$$

where, g_1 and g_2 are as defined in Section 5.3.3. Thus, the Lyapunov derivative of $\mathcal{F}$ is given

by

$$
\begin{aligned}
\dot{\mathcal{F}} &= \left(1-\frac{S^{**}_{m1}}{S_m}\right)\dot{S_m}+\left(1-\frac{E^{**}_{m1}}{E_m}\right)\dot{E_m} \\
&+ \frac{\sigma_m+\mu}{\sigma_m}\left(1-\frac{H^{**}_{m1}}{H_m}\right)\dot{H_m}+\frac{g_1H^{**}_{f1}S^{**}_{m1}}{g_2H^{**}_{m1}S^{**}_{f1}}\Bigg[\left(1-\frac{S^{**}_{f1}}{S_f}\right)\dot{S_f} \\
&+ \left(1-\frac{E^{**}_{f1}}{E_f}\right)\dot{H_f}+\frac{\sigma_f+\mu}{\sigma_f}\left(1-\frac{H^{**}_{f1}}{H_f}\right)\dot{H_f}\Bigg] \\
&= \left(1-\frac{S^{**}_{m1}}{S_m}\right)\left(\Pi_m-\frac{\beta_fc_f\mu}{\Pi_m}H_fS_m-\mu S_m\right)+\left(1-\frac{E^{**}_{m1}}{E_m}\right)\left(\frac{\beta_fc_f\mu}{\Pi_m}H_fS_m-p_1E_m\right) \\
&+ \frac{\sigma_m+\mu}{\sigma_m}\left(1-\frac{H^{**}_{m1}}{H_m}\right)\left(\sigma_mE_m-p_2H_m\right)+\frac{g_1H^{**}_{f1}S^{**}_{m1}}{g_2H^{**}_{m1}S^{**}_{f1}}\Bigg[\left(1-\frac{S^{**}_{f1}}{S_f}\right)\left(\Pi_f-\frac{\beta_mc_m\mu}{\Pi_f}H_mS_f-\mu S_f\right) \\
&+ \left(1-\frac{E^{**}_{f1}}{E_f}\right)\left(\frac{\beta_mc_m\mu}{\Pi_f}H_mS_f-p_{11}E_f\right)+\frac{\sigma_f+\mu}{\sigma_f}\left(1-\frac{H^{**}_{f1}}{H_f}\right)\left(\sigma_fE_f-p_{21}H_f\right)\Bigg] \\
&= \mu S^{**}_{m1}\left(2-\frac{S^{**}_{m1}}{S_m}-\frac{S_m}{S^{**}_{m1}}\right)+g_1H^{**}_{f1}S^{**}_{m1}\left(2-\frac{S^{**}_{m1}}{S_m}+\frac{H_f}{H^{**}_{f1}}-\frac{S_mH_fE^{**}_{m1}}{S^{**}_{m1}H^{**}_{f1}E_m}-\frac{E_m}{E^{**}_{m1}}\right) \\
&+ \frac{g_1H^{**}_{f1}S^{**}_{m1}}{g_2H^{**}_{m1}S^{**}_{f1}}\Bigg[\mu S^{**}_{f1}\left(2-\frac{S^{**}_{f1}}{S_f}-\frac{S_f}{S^{**}_{f1}}\right)+g_2H^{**}_{m1}S^{**}_{f1}\left(2-\frac{S^{**}_{f1}}{S_f}+\frac{H_m}{H^{**}_{m1}}-\frac{S_fH_mE^{**}_{f1}}{S^{**}_{f1}H^{**}_{f1}E_f}-\frac{E_f}{E^{**}_{f1}}\right)\Bigg] \\
&= \mu S^{**}_{m1}\left(2-\frac{S^{**}_{m1}}{S_m}-\frac{S_m}{S^{**}_{m1}}\right)+\frac{g_1H^{**}_{f1}S^{**}_{m1}}{g_2H^{**}_{m1}S^{**}_{f1}}\mu S^{**}_{f1}\left(2-\frac{S^{**}_{f1}}{S_f}-\frac{S_f}{S^{**}_{f1}}\right) \\
&+ g_1H^{**}_{f1}S^{**}_{m1}\left(6-\frac{S^{**}_{m1}}{S_m}-\frac{S_mH_fE^{**}_{m1}}{S^{**}_{m1}H^{**}_{f1}E_m}-\frac{S^{**}_{f1}}{S_f}-\frac{S_fH_mE^{**}_{f1}}{S^{**}_{f1}H^{**}_{f1}E_f}-\frac{E_mH^{**}_{m1}}{E^{**}_{m1}H_m}-\frac{E_fH^{**}_{f1}}{E^{**}_{f1}H_f}\right).
\end{aligned}
$$

It should be stated that, in the above calculations, the following relations (obtained from (5.20) at the endemic steady-state, $\mathcal{E}_2$) have been used:

$$
\begin{aligned}
\Pi_m &= \frac{\beta_fc_f\mu H^{**}_{m1}S^{**}_{m1}}{\Pi_m}+\mu S^{**}_{m1},\ \ \Pi_f=\frac{\beta_mc_m\mu H^{**}_{f1}S^{**}_{f1}}{\Pi_f}+\mu S^{**}_{f1}, \\
(\sigma_m+\mu)E^{**}_{m1} &= \frac{\beta_fc_f\mu S^{**}_{m1}}{\Pi_m},\ \ (\sigma_f+\mu)E^{**}_{f1}=\frac{\beta_mc_m\mu S^{**}_{f1}}{\Pi_f}, \\
(q_m+\mu)H^{**}_{m1} &= \sigma_mE^{**}_{m1},\ \ (q_m+\mu)H^{**}_{m1}=\sigma_mE^{**}_{m1}.
\end{aligned}
$$

Since the arithmetic mean exceeds the geometric mean, it follows then that

$$\begin{aligned} 2 \quad & -\frac{S_{m1}^{**}}{S_m} - \frac{S_m}{S_{m1}^{**}} \leq 0, \quad 2 - \frac{S_{f1}^{**}}{S_f} - \frac{S_f}{S_{f1}^{**}} \leq 0, \\ 6 \quad & -\frac{S_{m1}^{**}}{S_m} - \frac{S_m H_f E_{m1}^{**}}{S_{m1}^{**} H_{f1}^{**} E_m} - \frac{S_{f1}^{**}}{S_f} - \frac{S_f H_m E_{f1}^{**}}{S_{f1}^{**} H_{f1}^{**} E_f} - \frac{E_m H_{m1}^{**}}{E_{m1}^{**} H_m} - \frac{E_f H_{f1}^{**}}{E_{f1}^{**} H_f} \leq 0, \end{aligned}$$

so that $\dot{\mathcal{F}} \leq 0$ whenever $\mathcal{R}_2 > 1$. Thus, $\mathcal{F}$ is a Lyapunov function of the sub-system of the model (5.20) without the equations for $\frac{dQ_m}{dt}$ and $\frac{dQ_f}{dt}$. It then follows, by the LaSalle's Invariance Principle [58], that

$$\begin{aligned} &\lim_{t\to\infty} S_m(t) = S_m^{**}, \quad \lim_{t\to\infty} E_m(t) = E_m^{**}, \quad \lim_{t\to\infty} H_m(t) = H_m^{**}, \\ &\lim_{t\to\infty} S_f(t) = S_f^{**}, \quad \lim_{t\to\infty} E_f(t) = E_f^{**}, \quad \lim_{t\to\infty} H_f(t) = H_f^{**}. \end{aligned} \tag{5.23}$$

It is clear from (5.23) that $\limsup_{t\to\infty} E_m = E_m^{**}$. Thus, for sufficiently small $\kappa > 0$, there exists a constant $\tau > 0$ such that $\limsup_{t\to\infty} E_m \leq E_m^{**} + \kappa$ for all $t > \tau$. It follows from the fourth equation of the model (5.20) that, for $t > \tau$,

$$\dot{Q}_m \leq q_m(H_m^{**} + \kappa) - p_3 Q_m.$$

Thus, by comparison theorem (Theorem 2.6),

$$Q_m^{\infty} = \limsup_{t\to\infty} Q_m \leq \frac{q_m(H_m^{**} + \kappa)}{p_3}, \tag{5.24}$$

so that, by letting $\kappa \to 0$ in (5.24)

$$Q_m^{\infty} = \limsup_{t\to\infty} Q_m \leq \frac{q_m H_m^{**}}{p_3}. \tag{5.25}$$

Similarly (by using $\liminf_{t\to\infty} H_m = H_m^{**}$), it can be shown that

$$Q_{m\infty} = \liminf_{t\to\infty} Q_m \geq \frac{q_m H_m^{**}}{p_3}. \tag{5.26}$$

Thus, it follows from (5.25) and (5.26) that

$$Q_{m\infty} \geq \frac{q_m H_m^{**}}{p_3} \geq Q_m^{\infty}.$$

Hence,

$$\lim_{t\to\infty} Q_m = \frac{q_m(H_m^{**})}{p_3} = Q_m^{**}. \tag{5.27}$$

Similarly, it can be shown that

$$\lim_{t\to\infty} Q_f = \frac{q_f(H_f^{**})}{p_{31}} = Q_f^{**}. \tag{5.28}$$

Thus, by combining (5.23), (5.27) and (5.28), it follows that every solution to the equations of the model (5.20), with $\eta_m = \eta_f = r_m = r_f = 0$ and initial conditions in $\mathcal{D} \setminus \mathcal{D}_0$ approaches $\mathcal{E}_2$ as $t \to \infty$, for $\mathcal{R}_2 > 1$. □

In summary, the basic two-group HSV-2 model (5.5) has the following qualitative properties:

(i) it has a GAS DFE whenever the reproduction threshold ($\mathcal{R}_0$) is less than unity (Theorem 5.2);

(ii) the model with $\delta_1 = \delta_2 = 0$ has a unique endemic equilibrium ($\mathcal{E}_1$) whenever the associated reproduction number ($\mathcal{R}_1$) exceeds unity (Lemma 5.3). The unique endemic equilibrium is LAS when it exists (Theorem 5.3);

(iii) the EEP of the model with $\delta_1 = \delta_2 = 0$ is GAS for the special case when quiescent individuals do not transmit infection (i.e., $\eta_f = \eta_m = 0$) and also do not re-activate and progress to the symptomatic stage (i.e., $r_m = r_f = 0$), whenever the associated reproduction threshold ($\mathcal{R}_2$) exceeds unity (Theorem 5.4).

These results are generally consistent with those reported in Chapter 4 [71], for the single group HSV-2 transmission model (4.1). In other words, adding sex-structure to the single-group HSV-2 model (4.1) does not alter the main qualitative (equilibrium) dynamics of the

single sex model (it is worth recalling that the basic single-group model (4.1) has a GAS DFE whenever its associated reproduction threshold is less than unity, and it has an endemic equilibrium whenever the threshold exceeds unity. This endemic equilibrium was shown to be GAS for a special case).

5.4 Model in Periodic Environment

In this section, the effect of "periodicity" on the transmission dynamics of HSV-2 in a sex-structured population will be qualitatively assessed. The case for periodicity in HSV-2 transmission dynamics in a sexually-active population stems from the fact that HSV-2 infection is lifelong, and latent infection can re-activate. This re-activation can occur regularly, producing a relapse period of infectiousness [10, 89]. The frequency and amplitude (severity) of recurrence (relapse) of HSV-2 vary greatly, depending on the individual and various environmental factors including stress (both physical and mental) [42]. To incorporate such time varying recurrence, it is assumed that the associated transmission and relapse parameters of the model (5.5) are periodic (i.e., $\beta_m = \beta_m(t)$, $\beta_f = \beta_f(t)$, $r_m = r_m(t)$ and $r_f = r_f(t)$). It should, however, be mentioned that (at the moment) there is no clear epidemiological evidence in favor or against this (periodicity) assumption in this context.

Using the aforementioned definitions for β_m, β_f, r_m and r_f in the model (5.5) gives the following non-autonomous, sex-structured, two-group model for HSV-2 transmission in a

population:

$$\begin{aligned}
\frac{dS_m}{dt} &= \Pi_m - \frac{\beta_f(t)c_f}{N_m}(H_f + \eta_f Q_f)S_m - \mu S_m,\\
\frac{dE_m}{dt} &= \frac{\beta_f(t)c_f}{N_m}(H_f + \eta_f Q_f)S_m - (\sigma_m + \mu)E_m,\\
\frac{dH_m}{dt} &= \sigma_m E_m + r_m(t)Q_m - (q_m + \mu + \delta_1)H_m,\\
\frac{dQ_m}{dt} &= q_m H_m - [r_m(t) + \mu + \delta_2]Q_m,\\
\frac{dS_f}{dt} &= \Pi_f - \frac{\beta_m(t)c_m}{N_f}(H_m + \eta_m Q_m)S_f - \mu S_f,\\
\frac{dE_f}{dt} &= \frac{\beta_m(t)c_m}{N_f}(H_m + \eta_m Q_m)S_f - (\sigma_f + \mu)E_f,\\
\frac{dH_f}{dt} &= \sigma_f E_f + r_f(t)Q_f - (q_f + \mu + \delta_1)H_f,\\
\frac{dQ_f}{dt} &= q_f H_f - [r_f(t) + \mu + \delta_2]Q_f.
\end{aligned} \tag{5.29}$$

The objective is to determine whether or not adding periodicity to the autonomous two-group model (5.5) alters its qualitative dynamics (particularly with respect to the elimination of the disease).

5.4.1 Basic Properties

It is convenient to define the regions:

$$\begin{aligned}
X = \{&(S_m, E_m, H_m, Q_m, S_f, E_f, H_f, Q_f) \in \mathbb{R}^8_+ :\\
&S_m + E_m + H_m + Q_m \leq N_m \text{ and } S_f + E_f + H_f + Q_f \leq N_f\},\\
X_0 = &(S^0_m, E^0_m, H^0_m, Q^0_m, S^0_f, E^0_f, H^0_f, Q^0_f),
\end{aligned}$$

and the function,

$$g \equiv g(S_m, E_m, H_m, Q_m, S_f, E_f, H_f, Q_f).$$

Lemma 5.4. *The non-autonomous model* (5.29) *has a unique and bounded solution with the*

initial data X_0, where $X_0 \in X$. Further, the compact set

$$\mathcal{D} = \left\{ (S_m, E_m, H_m, Q_m, S_f, E_f, H_f, Q_f) \in X : N_m \leq \frac{\Pi_m}{\mu} \text{ and } N_f \leq \frac{\Pi_f}{\mu} \right\},$$

is positively-invariant and attracts all positive orbits in X.

Proof. Following [61], let $g \in (\mathbb{R}^8_+, \mathbb{R})$ be defined by:

$$g = \begin{cases} 0, & (S_m, E_m, H_m, Q_m, S_f, E_f, H_f, Q_f) = (0,0,0,0,0,0,0,0); \\ \dfrac{\beta_f c_f (H_f + \eta_f Q_f) S_m}{S_m + E_m + H_m + Q_m}, & (S_m, E_m, H_m, Q_m) \in \mathbb{R}^4_+ \setminus \{(0,0,0,0)\}; \\ \dfrac{\beta_m c_m (H_m + \eta_m Q_m) S_f}{S_f + E_f + H_f + Q_f}, & (S_f, E_f, H_f, Q_f) \in \mathbb{R}^4_+ \setminus \{(0,0,0,0)\}. \end{cases}$$

Hence, the function g is continuous and globally lipschitz on $\mathbb{R}^8_+$. It follows, from Theorem 5.2.1 of [78], that the non-autonomous model (5.29) has a unique non-negative local solution $(S_m, E_m, H_m, Q_m, S_f, E_f, H_f, Q_f)$ with

$$\begin{aligned} & (S_m(0), E_m(0), H_m(0), Q_m(0), S_f(0), E_f(0), H_f(0), Q_f(0)) \\ = \; & (S^0_m, E^0_m, H^0_m, Q^0_m, S^0_f, E^0_f, H^0_f, Q^0_f) \in \mathbb{R}^8_+. \end{aligned}$$

Adding the first four equations of the model (5.29) gives

$$\frac{dN_m}{dt} = \Pi_m - \mu N_m - \delta_1 H_m - \delta_2 Q_m \leq \Pi_m - \mu N_m,$$

from which it is clear that the associated linear differential equation,

$$\frac{dN_m}{dt} = \Pi_m - \mu N_m,$$

has a unique equilibrium $N^*_m = \dfrac{\Pi_m}{\mu}$, which is globally-asymptotically stable. Thus, it can be shown, using comparison theorem [56], that $N_m(t)$ is bounded. Similarly, it can be shown that $N_f(t)$ is bounded. Hence, the solution of the model (5.29) exists globally on the interval $[0, \infty)$. □

5.4.2 Stability of DFE

The disease-free equilibrium solution of the system (5.29) is the same as $\mathcal{E}_0$, given in (5.6). The equations for the rates of change of the infected components $(E_m, H_m, Q_m, E_f, H_f, Q_f)$ of the linearized version of the system (5.29) at the DFE ($\mathcal{E}_0$) are given by

$$\begin{aligned}
\frac{dE_m}{dt} &= \beta_f(t)c_f(H_f + \eta_f Q_f) - (\sigma_m + \mu)E_m,\\
\frac{dH_m}{dt} &= \sigma_m E_m + r_m(t)Q_m - (q_m + \mu + \delta_1)H_m,\\
\frac{dQ_m}{dt} &= q_m H_m - [r_m(t) + \mu + \delta_2]Q_m,\\
\frac{dE_f}{dt} &= \beta_m(t)c_m(H_m + \eta_m Q_m) - (\sigma_f + \mu)E_f,\\
\frac{dH_f}{dt} &= \sigma_f E_f + r_f(t)Q_f - (q_f + \mu + \delta_1)H_f,\\
\frac{dQ_f}{dt} &= q_f H_f - [r_f(t) + \mu + \delta_2]Q_f.
\end{aligned}$$

Using the notation in Wang and Zhao [93], the matrix $F(t)$ (of new infection terms) and the M- matrix $V(t)$ (of the remaining transition terms) associated with the non-autonomous model (5.29) are given, respectively, by

$$F(t) = \begin{pmatrix}
0 & 0 & 0 & 0 & \beta_f(t)c_f & \eta_f\beta_f(t)c_f\\
0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0\\
0 & \beta_m(t)c_m & \eta_m\beta_m(t)c_m & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix},$$

and,

$$V(t) = \begin{pmatrix} m_1 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_m & m_2 & -r_m(t) & 0 & 0 & 0 \\ 0 & -q_m & m_3 & 0 & 0 & 0 \\ 0 & 0 & 0 & m_{11} & 0 & 0 \\ 0 & 0 & 0 & -\sigma_f & m_{21} & -r_f(t) \\ 0 & 0 & 0 & 0 & -q_f & m_{31} \end{pmatrix},$$

with, $m_1 = \sigma_m + \mu$, $m_2 = q_m + \mu + \delta_1$, $m_3 = r_m(t) + \mu + \delta_2$, $m_{11} = \sigma_f + \mu$, $m_{21} = q_f + \mu + \delta_1$ and $m_{31} = r_f(t) + \mu + \delta_2$.

As in [93], let Φ_M be the monodromy matrix of the linear $\omega-$ periodic system

$$\frac{dZ}{dt} = M(t)Z,$$

and $\rho(\Phi_M(\omega))$ be the spectral radius of $\Phi_M(\omega)$. It is convenient to define

$$Y(t,s), \;\; t \geq s,$$

as the evolution operator of the linear $\omega-$ periodic system

$$\frac{dy}{dt} = -V(t)\; y.$$

That is, for each $s \in \mathbb{R}$, the associated 6×6 matrix, $Y(t,s)$, satisfies:

$$\frac{dY(t,s)}{dt} = -V(t)Y(t,s) \;\; \forall t \geq s, \;\; Y(s,s) = I.$$

Furthermore, in line with Wang and Zhao [93], it is assumed that $\phi(s)$ ($\omega-$periodic in s) is the initial distribution of infectious individuals. That is, $F(s)\phi(s)$ is the rate at which new infections are produced by infected individuals who were introduced into the population at time s [93]. Since $t \geq s$, it follows then that $Y(t,s)F(s)\phi(s)$ represents the distribution of

those infected individuals who were newly-infected at time s and, remain infected at time t.

Thus, the cumulative distribution of new infections at time t, produced by all infected individuals ($\phi(s)$) introduced at a prior time $s = t$, is given by

$$\psi(t) = \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da.$$

Let $\mathbb{C}_\omega$ be the ordered Banach space of all $\omega-$periodic functions from $\mathbb{R}$ to $\mathbb{R}^6_+$, with maximum norm $\|.\|$ and positive cone

$$\mathbb{C}^+_\omega = \{\phi \in \mathbb{C}_\omega : \phi(t) \geq 0, \forall\ t \in \mathbb{R}\}.$$

Following Wang and Zhao [93], define a linear operator $L : \mathbb{C}_\omega \to \mathbb{C}_\omega$ by

$$(L\phi)(t) = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da\ \ \forall\ \ t \in \mathbb{R},\ \ \phi \in \mathbb{C}_\omega. \tag{5.30}$$

The associated reproduction ratio (denoted by $\mathcal{R}_p$) is given by the spectral radius of L (that is, $\mathcal{R}_p = \rho(L)$ [93]). The quantity $\mathcal{R}_p$ measures the average number of new HSV-2 cases generated by a single infectious individual in a completely susceptible population. Methods for computing $\mathcal{R}_p$ for non-autonomous systems have been developed by a number of authors (see, for instance, [7, 93]). The method in [93] will be used in this thesis. First of all, it is shown in Appendix C that the system (5.29) satisfies Assumptions A1-A7 in [93]. Thus, using Theorem 2.2 in [93], the following result is established.

Lemma 5.5. *The DFE of the model non-autonomous* (5.29)*, given by* (5.6)*, is LAS whenever* $\mathcal{R}_p < 1$*, and unstable if* $\mathcal{R}_p > 1$*.*

Theorem 5.5. *The DFE,* $\mathcal{E}_0$*, of the non-autonomous model* (5.29)*, given by* (5.6)*, is GAS in* $\mathcal{D}$ *whenever* $\mathcal{R}_p < 1$*.*

The proof of Theorem 5.5 is given in Appendix D.

The epidemiological implication of Theorem 5.5 is that, as in the case of the autonomous two-group model (5.5), HSV-2 will be eliminated from the community if the associated reproduction number ($\mathcal{R}_p$) is brought to (and maintained at) a value less than unity. Thus, the analyses in this section show that adding periodicity to the corresponding autonomous model (5.5) does not alter the dynamics of the autonomous model (5.5) (with respect to disease elimination). The basic model (5.1) will now be extended to incorporate the effect of three control strategies on the transmission dynamics of HSV-2 in a population.

5.5 Autonomous Model with Intervention Strategies

To extend the basic autonomous model (5.1) to include three intervention strategies (namely, the use of an imperfect vaccine, condoms and antiviral treatment), the following 16 new state variables are introduced:

(i) unvaccinated exposed males and females ($E_{mu}(t)$ and $E_{fu}(t)$, respectively),

(ii) vaccinated exposed males and females ($E_{mv}(t)$ and $E_{fv}(t)$, respectively),

(iii) unvaccinated infectious males and females ($H_{mu}(t)$ and $H_{fu}(t)$, respectively),

(iv) vaccinated infectious males and females ($H_{mv}(t)$ and $H_{fv}(t)$, respectively),

(v) unvaccinated quiescent infected males and females ($Q_{mu}(t)$ and $Q_{fu}(t)$, respectively),

(vi) vaccinated quiescent infected males and females ($Q_{mv}(t)$ and $Q_{fv}(t)$, respectively),

(vii) unvaccinated treated infected males and females ($T_{mu}(t)$ and $T_{fu}(t)$, respectively),

(viii) vaccinated treated infected males and females ($T_{mv}(t)$ and $T_{fv}(t)$, respectively).

Thus, the total male and female populations at time t (denoted by $N_{me}(t)$ and $N_{fe}(t)$, respectively), are now given by

$$\begin{aligned} N_{me}(t) &= S_m(t) + V_m(t) + E_{mu}(t) + E_{mv}(t) + H_{mu}(t) \\ &+ H_{mv}(t) + Q_{mu}(t) + Q_{mv}(t) + T_{mu}(t) + T_{mv}(t), \end{aligned}$$

and,

$$\begin{aligned} N_{fe}(t) &= S_f(t) + V_f(t) + E_{fu}(t) + E_{fv}(t) + H_{fu}(t) \\ &+ H_{fv}(t) + Q_{fu}(t) + Q_{fv}(t) + T_{fu}(t) + T_{fv}(t). \end{aligned}$$

A fraction $p_m\epsilon_m(p_f\epsilon_f)$, of the new sexually-active (adolescent) males (females) recruited at the rate $\Pi_m(\Pi_f)$ is vaccinated (where $p_m(p_f)$ is the proportion of these individuals that are vaccinated and $\epsilon_m(\epsilon_f)$ represents the proportion of these vaccinated individuals in whom the vaccine takes). Susceptible males (females) are vaccinated at a rate $\xi_m(\xi_f)$, and the vaccine is assumed to wane at a rate $\omega_m(\omega_f)$. The use of condoms is incorporated using the term $(1-\nu_1 c)$ in the male population (and $(1-\nu_2 c)$ in the female population), where $0 < \nu_1 < 1$ $(0 < \nu_2 < 1)$ is the condom efficacy and $0 < c < 1$ represents the compliance in condom use. Furthermore, since the vaccine is assumed to be imperfect, vaccinated males (females) can acquire break-through infection at a reduced rate, $(1-\psi)(1-\nu_1 c)\lambda_{fe}$ for males and $(1-\psi)(1-\nu_2 c)\lambda_{me}$ for females (where $0 < \psi < 1$ represents the vaccine efficacy against infection).

Following Schwartz and Blower [74], it is assumed that vaccinated individuals have:

(a) shorter average length of viral shedding;

(b) fewer viral shedding episodes; and

(c) lower transmission probability, in comparison to unvaccinated individuals.

Furthermore, following [4], it is assumed that the imperfect HSV-2 vaccine offers the following therapeutic benefits (to vaccinated individuals):

(i) it blocks infection with some efficacy;

(ii) it reduces transmissibility in break-through infections;

(iii) it slows development of symptoms in exposed vaccinated individuals;

(iv) it reduces mortality rate in break-through infections.

The populations of exposed vaccinated males (E_{mv}) and females (E_{fv}) are generated by break-through infection (at the rate $(1-\psi)(1-\nu_1 c)\lambda_{fe}$ and $(1-\psi)(1-\nu_2 c)\lambda_{me}$, respectively) and are decreased by the development of symptoms (at the rates σ_{mv} and σ_{fv}, respectively). Here, it is assumed that $\sigma_{mv} < \sigma_{mu}$ and $\sigma_{fv} < \sigma_{fu}$, to account for the assumption that exposed vaccinated individuals develop clinical symptoms of HSV-2 at a slower rate in comparison to exposed unvaccinated individuals.

Infectious vaccinated individuals (H_{mv} and H_{fv}) are generated by the progression of exposed vaccinated individuals (at the rates σ_{mv} and σ_{fv}, respectively) and by the re-activation of vaccinated individuals in the quiescent states (at the rates r_{mv} and r_{fv}, respectively). Vaccinated infectious males (females) are treated at a rate $\gamma_{hmv}(\gamma_{hfv})$, while unvaccinated infectious males (females) are treated at a rate $\gamma_{hmu}(\gamma_{hfu})$. These populations are further decreased by progression to quiescence (at the rates q_{mv} and q_{fv}, respectively), and disease-induced death (at a reduced rate, $\delta_v < \delta_u$).

The populations of vaccinated infectious individuals in the quiescent states (Q_{mv}, Q_{fv}) are increased by the progression to quiescence of infectious vaccinated individuals (at the rates q_{mv} and q_{fv}, respectively). These populations are reduced by re-activation (at the rates r_{mv} and r_{fv}, respectively), loss of vaccine-induced immunity (at the rates α_m and α_f, respectively), treatment (at the rates γ_{qmv} and γ_{qfv}, respectively) and disease-induced death (at a rate δ_{qv}). Individuals in the Q_{mv} and Q_{fv} classes who lose their vaccine-induced immunity are moved to the respective Q_{mu} and Q_{fu} classes (at the rates α_m and α_f, respectively [74]). Natural death occurs in all epidemiological classes at a rate μ.

The associated forces of infection are given by

$$\begin{aligned}\lambda_{fe} &= \frac{\beta_f c_m (H_{fu} + \eta_1 H_{fv} + \eta_2 Q_{fu} + \eta_3 Q_{fv} + \eta_4 T_{fu} + \eta_5 T_{fv})}{N_{fe}}, \\ \lambda_{me} &= \frac{\beta_m c_f (H_{mu} + \eta_1 H_{mv} + \eta_2 Q_{mu} + \eta_3 Q_{mv} + \eta_4 T_{mu} + \eta_5 T_{mv})}{N_{me}},\end{aligned} \tag{5.31}$$

where, $0 < \eta_5 < \eta_4 < \eta_3 < \eta_2 < \eta_1 < 1$ are the modification parameters that account for the vaccine-induced reduction of infectiousness of vaccinated infected individuals in comparison to unvaccinated infectious individuals.

Thus, considering the above descriptions and assumptions, together with the basic model (5.1), the extended autonomous model for the transmission dynamics of HSV-2 in a sex-structured population is given by the following system of non-linear differential equations (the associated parameters of the model are described in Table 5.1).

$$
\begin{aligned}
\frac{dS_m}{dt} &= \Pi_m(1-p_m\epsilon_m) + \omega_m V_m - \lambda_{fe}(1-\nu_1 c)S_m - k_1 S_m,\\
\frac{dV_m}{dt} &= \Pi_m p_m \epsilon_m + \xi_m S_m - \lambda_{fe}(1-\nu_1 c)(1-\psi)V_m - k_2 V_m,\\
\frac{dE_{mu}}{dt} &= \lambda_{fe}(1-\nu_1 c)S_m - k_3 E_{mu},\\
\frac{dE_{mv}}{dt} &= \lambda_{fe}(1-\nu_1 c)(1-\psi)V_m - k_4 E_{mv},\\
\frac{dH_{mu}}{dt} &= \sigma_{mu}E_{mu} + r_{mu}Q_{mu} - k_5 H_{mu},\\
\frac{dH_{mv}}{dt} &= \sigma_{mv}E_{mv} + r_{mv}Q_{mv} - k_6 H_{mv},\\
\frac{dQ_{mu}}{dt} &= q_{mu}H_{mu} + \alpha_m Q_{mv} - k_7 Q_{mu},\\
\frac{dQ_{mv}}{dt} &= q_{mv}H_{mv} - k_8 Q_{mv},\\
\frac{dT_{mu}}{dt} &= \gamma_{hmu}H_{mu} + \gamma_{qmu}Q_{mu} - k_9 T_{mu},\\
\frac{dT_{mv}}{dt} &= \gamma_{hmv}H_{mv} + \gamma_{qmv}Q_{mv} - k_{10} T_{mv},\\
\frac{dS_f}{dt} &= \Pi_f(1-p_f\epsilon_f) + \omega_f V_f - \lambda_{me}(1-\nu_2 c)S_f - k_{11} S_f,\\
\frac{dV_f}{dt} &= \Pi_f p_f \epsilon_f + \xi_f S_f - \lambda_{me}(1-\nu_2 c)(1-\psi)V_f - k_{12} V_f,\\
\frac{dE_{fu}}{dt} &= \lambda_{me}(1-\nu_2 c)S_f - k_{13} E_{fu},\\
\frac{dE_{fv}}{dt} &= \lambda_{me}(1-\nu_2 c)(1-\psi)V_f - k_{14} E_{fv},\\
\frac{dH_{fu}}{dt} &= \sigma_{fu}E_{fu} + r_{fu}Q_{fu} - k_{15} H_{fu},\\
\frac{dH_{fv}}{dt} &= \sigma_{fv}E_{fv} + r_{fv}Q_{fv} - k_{16} H_{fv},\\
\frac{dQ_{fu}}{dt} &= q_{fu}H_{fu} + \alpha_f Q_{fv} - k_{17} Q_{fu},\\
\frac{dQ_{fv}}{dt} &= q_{fv}H_{fv} - k_{18} Q_{fv},\\
\frac{dT_{fu}}{dt} &= \gamma_{hfu}H_{fu} + \gamma_{qfu}Q_{fu} - k_{19} T_{fu},\\
\frac{dT_{fv}}{dt} &= \gamma_{hfv}H_{fv} + \gamma_{qfv}Q_{fv} - k_{20} T_{fv},
\end{aligned}
\tag{5.32}
$$

where, $k_1 = \xi_m + \mu$, $k_2 = \omega_m + \mu$, $k_3 = \sigma_{mu} + \mu$, $k_4 = \sigma_{mv} + \mu$, $k_5 = q_{mu} + \gamma_{hmu} + \mu + \delta_u$, $k_6 = q_{mv} + \gamma_{hmv} + \mu + \delta_v$, $k_7 = r_{mu} + \gamma_{qmu} + \mu + \delta_{qu}$, $k_8 = r_{mv} + \alpha_m + \gamma_{qmv} + \mu + \delta_{qv}$, $k_9 = \mu + \delta_{tu}$, $k_{10} = \mu + \delta_{tv}$, $k_{11} = \xi_f + \mu$, $k_{12} = \omega_f + \mu$, $k_{13} = \sigma_{fu} + \mu$, $k_{14} = \sigma_{fv} + \mu$, $k_{15} = q_{fu} + \gamma_{hfu} + \mu + \delta_u$, $k_{16} = q_{fv} + \gamma_{hfv} + \mu + \delta_v$, $k_{17} = r_{fu} + \gamma_{qfu} + \mu + \delta_{qu}$, $k_{18} = r_{fv} + \alpha_f + \gamma_{qfv} + \mu + \delta_{qv}$, $k_{19} = \mu + \delta_{tu}$ and $k_{20} = \mu + \delta_{tv}$.

The extended two-group HSV-2 transmission model (5.32), subject to the constraint condition (5.4), will now be analysed to gain insight into its qualitative properties.

Table 5.1: Description of parameters of the vaccination model (5.32).

Parameter	Description	Baseline Values/Year
Π_m, Π_f	Recruitment rates for male and female	10000 (Assumed)
μ	Natural death rate	$\frac{1}{70}$ [71]
β_m, β_f	Infection probabilities for males/females	0.5 and 0.4, resp. (Assumed)
$c_m(c_f)$	Average number of male(female) sexual partners	
	for females(males) per unit time	2 (Assumed)
ξ_m, ξ_f	Vaccination rate of susceptible males and females	0.6 [71]
ψ	Efficacy of vaccine	0.6 [71]
ω_m, ω_f	Waning rate of vaccine for males and females	$\frac{1}{15}$ [71, 74]
p_m, p_f	Proportion of new recruited males and	
	females vaccinated	0.5 (Assumed)
ϵ_m, ϵ_f	Proportion of vaccinated males and females	
	in whom the vaccine takes	0.6 [71]
$\nu(\nu = \nu_1 = \nu_2)$	Condom efficacy	0.87 [26]
c	Condom compliance	0.6 (Assumed)
σ_{mu}, σ_{fu}	Progression rate to symptoms development of	
	unvaccinated exposed males and females	$\frac{365}{15}$ [71]

σ_{mv}, σ_{fv}	Progression rate to symptoms development of vaccinated exposed males and females	$\frac{365}{18}$ [71]
r_{mu}, r_{fu}	Activation rate of unvaccinated infectious males and females in the quiescent state	$\frac{365}{4}$ [71, 74]
r_{mv}, r_{fv}	Activation rate of vaccinated infectious males and females in the quiescent state	$\frac{365}{4}$ [71, 74]
q_{mu}, q_{fu}	Rate at which infectious unvaccinated males and females revert to quiescent state	$\frac{365}{2}$ [71, 74]
q_{mv}, q_{fv}	Rate at which infectious vaccinated males and females revert to quiescent state	$\frac{365}{3}$ [71, 74]
α_m, α_f	Progression rate to quiescent unvaccinated infectious males and females of quiescent infectious vaccinated individuals	$\frac{1}{20}$ [71, 74]
η_1, η_3, η_4	Modification parameters for reduced infectiousness of vaccinated infectious individuals	0.4,0.1 and 0.001, resp.
η_2, η_5	Modification parameters for reduced infectiousness of unvaccinated infectious individuals	0.2 and 0.01, resp.
$\gamma_{hmu}, \gamma_{hmv}$	Treatment rates for H_{mu} and H_{mv}, respectively	Variable
$\gamma_{qmu}, \gamma_{qmv}$	Treatment rates for Q_{mu} and Q_{mv}, respectively	Variable
$\gamma_{hfu}, \gamma_{hfv}$	Treatment rates for H_{fu} and H_{fv}, respectively	Variable
$\gamma_{qfu}, \gamma_{qfv}$	Treatment rates for Q_{fu} and Q_{fv}, respectively	Variable
δ_u, δ_{qu}	Disease-induced death rate for unvaccinated infectious individuals	0
δ_v, δ_{qv}	Disease-induced death rate for vaccinated infectious individuals	0

5.5.1 Basic Properties

Using similar approach as in the basic model (5.5), the following biologically-feasible region

$$\Gamma_e = \Gamma_{me} \cup \Gamma_{fe} \in \mathbb{R}^{10}_+ \times \mathbb{R}^{10}_+,$$

where,

$$\begin{aligned}\Gamma_{me} &= \{(S_m, V_m, E_{mu}, E_{mv}, H_{mu}, H_{mv}, Q_{mu}, Q_{mv}, T_{mu}, T_{mv}) \in \mathbb{R}^{10}_+ : \\ &\quad S_m + V_m + E_{mu} + E_{mv} + H_{mu} + H_{mv} + Q_{mu} + Q_{mv} + T_{mu} + T_{mv} \leq \Pi_m/\mu\},\end{aligned}$$

$$\begin{aligned}\Gamma_{fe} &= \{(S_f, V_f, E_{fu}, E_{fv}, H_{fu}, H_{fv}, Q_{fu}, Q_{fv}, T_{fu}, T_{fv}) \in \mathbb{R}^{10}_+ : \\ &\quad S_f + V_f + E_{fu} + E_{fv} + H_{fu} + H_{fv} + Q_{fu} + Q_{fv} + T_{fu} + T_{fv} \leq \Pi_f/\mu\},\end{aligned}$$

can be shown to be positively-invariant for the extended model (5.32) with the contact constraint (5.4). Furthermore, the model (5.32) has a DFE, given by

$$\begin{aligned}\mathcal{E}_{02} =& \Bigg(S^*_m, V^*_m, E^*_{mu}, E^*_{mv}, H^*_{mu}, H^*_{mv}, Q^*_{mu}, Q^*_{mv}, T^*_{mu}, T^*_{mv}, \\ & S^*_f, V^*_f, E^*_{fu}, E^*_{fv}, H^*_{fu}, H^*_{fv}, Q^*_{fu}, Q^*_{fv}, T^*_{fu}, T^*_{fv} \Bigg) \\ =& \Bigg(\frac{\Pi_m[p_m\epsilon_m\omega_m + k_2(1-p_m\epsilon_m)]}{k_1k_2 - \xi_m\omega_m}, \frac{\Pi_m[k_1p_m\epsilon_m + \xi_m(1-p_m\epsilon_m)]}{k_1k_2 - \xi_m\omega_m}, 0, 0, 0, 0, \\ & 0, 0, 0, 0, \frac{\Pi_f[p_f\epsilon_f\omega_f + k_{12}(1-p_f\epsilon_f)]}{k_{11}k_{12} - \xi_f\omega_f}, \frac{\Pi_f[k_{11}p_f\epsilon_f + \xi_f(1-p_f\epsilon_f)]}{k_{11}k_{12} - \xi_f\omega_f}, 0, 0, 0, 0, 0, 0, 0, 0 \Bigg),\end{aligned} \tag{5.33}$$

where, $1 - p_m\epsilon_m > 0$, $1 - p_f\epsilon_f > 0$, $1 - \psi > 0$, $k_1k_2 - \xi_m\omega_m = \xi_m\mu + \mu k_2 > 0$ and $k_{11}k_{12} - \xi_f\omega_f = \xi_f\mu + \mu k_{12} > 0$.

Using the constraint (5.4) in (5.32), it can be shown that the associated next generation matrices, F_e and V_e, are given, respectively, by

$$F_e = \begin{pmatrix} \mathbf{0}_{8\times8} & F_1 \\ F_2 & \mathbf{0}_{8\times8} \end{pmatrix}, \; V_e = \begin{pmatrix} V_1 & \mathbf{0}_{8\times8} \\ \mathbf{0}_{8\times8} & V_2 \end{pmatrix},$$

where,

$$F_1 = \begin{pmatrix} \mathbf{0}_{2\times2} & (F_{11})_{2\times6} \\ \mathbf{0}_{6\times2} & \mathbf{0}_{6\times6} \end{pmatrix}, \quad F_2 = \begin{pmatrix} \mathbf{0}_{2\times2} & (F_{21})_{2\times6} \\ \mathbf{0}_{6\times2} & \mathbf{0}_{6\times6} \end{pmatrix},$$

and,

$$F_{11} = \begin{pmatrix} \beta_1 & \beta_1\eta_1 & \beta_1\eta_2 & \beta_1\eta_3 & \beta_1\eta_4 & \beta_1\eta_5 \\ \beta_2 & \beta_2\eta_1 & \beta_2\eta_2 & \beta_2\eta_3 & \beta_2\eta_4 & \beta_2\eta_5 \end{pmatrix}, \; F_{21} = \begin{pmatrix} \beta_3 & \beta_3\eta_1 & \beta_3\eta_2 & \beta_3\eta_3 & \beta_3\eta_4 & \beta_3\eta_5 \\ \beta_4 & \beta_4\eta_1 & \beta_4\eta_2 & \beta_4\eta_3 & \beta_4\eta_4 & \beta_4\eta_5 \end{pmatrix},$$

$$V_1 = \begin{pmatrix} k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & k_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_{mu} & 0 & k_5 & 0 & -r_{mu} & 0 & 0 & 0 \\ 0 & -\sigma_{mv} & 0 & k_6 & 0 & -r_{mv} & 0 & 0 \\ 0 & 0 & -q_{mu} & 0 & k_7 & -\alpha_m & 0 & 0 \\ 0 & 0 & 0 & -q_{mv} & 0 & k_8 & 0 & 0 \\ 0 & 0 & -\gamma_{hmu} & 0 & -\gamma_{qmu} & 0 & k_9 & 0 \\ 0 & 0 & 0 & -\gamma_{hmv} & 0 & -\gamma_{qmv} & 0 & k_{10} \end{pmatrix},$$

$$V_4 = \begin{pmatrix} k_{13} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & k_{14} & 0 & 0 & 0 & 0 & 0 & 0 \\ -\sigma_{fu} & 0 & k_{15} & 0 & -r_{fu} & 0 & 0 & 0 \\ 0 & -\sigma_{fv} & 0 & k_{16} & 0 & -r_{fv} & 0 & 0 \\ 0 & 0 & -q_{fu} & 0 & k_{17} & -\alpha_f & 0 & 0 \\ 0 & 0 & 0 & -q_{fv} & 0 & k_{18} & 0 & 0 \\ 0 & 0 & -\gamma_{hfu} & 0 & -\gamma_{qfu} & 0 & k_{19} & 0 \\ 0 & 0 & 0 & -\gamma_{hfv} & 0 & -\gamma_{qfv} & 0 & k_{20} \end{pmatrix},$$

with,

$$\begin{aligned} \beta_1 &= \frac{(1-\nu_1 c)\beta_f c_f S_m^*}{N_{me}^*},\ \beta_2 = \frac{(1-\nu_1 c)(1-\psi)\beta_f c_f V_m^*}{N_{me}^*}, \\ \beta_3 &= \frac{(1-\nu_2 c)\beta_m c_m S_f^*}{N_{fe}^*},\ \beta_4 = \frac{(1-\nu_2 c)(1-\psi)\beta_m c_m V_f^*}{N_{fe}^*}. \end{aligned}$$

It follows then that the associated effective reproduction number for the model (5.32) with (5.4), denoted by $\mathcal{R}_c$, is given by

$$\mathcal{R}_c = \rho(F_e V_e^{-1}) = \sqrt{\mathcal{R}_{me}\mathcal{R}_{fe}},$$

where,

$$\mathcal{R}_{me} = \frac{A}{k_3 k_4 k_9 k_{10} A_3 A_5} \text{ and } \mathcal{R}_{fe} = \frac{B}{k_{13} k_{14} k_{19} k_{20} A_2 A_4},$$

with,

$$
\begin{aligned}
A &= \beta_1\sigma_{mu}k_4k_{10}A_5A_7 + \beta_2\sigma_{mv}k_3k_9A_3A_{10} + \beta_2\sigma_{mv}\alpha_m q_{mv}k_3k_{10}A_{11},\\
B &= \beta_3\sigma_{fu}k_{14}k_{20}A_4A_6 + \beta_4\sigma_{fv}k_{13}k_{19}A_2A_8 + \beta_4\sigma_{fv}\alpha_f q_{fv}k_{13}k_{20}A_9,\\
A_2 &= k_{15}k_{17} - q_{fu}r_{fu} > 0,\ A_3 = k_5k_7 - q_{mu}r_{mu} > 0,\\
A_4 &= k_{16}k_{18} - q_{fv}r_{fv} > 0,\ A_5 = k_6k_8 - q_{mv}r_{mv} > 0,\\
A_6 &= k_{17}k_{19} + \gamma_{hfu}\eta_4k_{17} + \eta_4\gamma_{qfv}q_{fu} + \eta_2q_{fu}k_{19},\\
A_7 &= k_7k_9 + \gamma_{hmu}\eta_4k_7 + \eta_4\gamma_{qmu}q_{mu} + \eta_2q_{mu}k_9,\\
A_8 &= q_{fv}\eta_3k_{20} + \eta_1k_{18}k_{20} + \eta_5\gamma_{hfv}k_{18} + \eta_5q_{fv}\gamma_{qfv},\\
A_9 &= r_{fu}k_{19} + \eta_4\gamma_{qfu}k_{15} + \eta_4\gamma_{hfu}r_{fu} + \eta_2k_{15}k_{19},\\
A_{10} &= \eta_5\gamma_{hmv}k_8 + q_{mv}\eta_3k_{10} + \eta_1k_8k_{10} + q_{mv}\eta_5\gamma_{qmv},\\
A_{11} &= \eta_4\gamma_{qmu}k_5 + r_{mu}\eta_4\gamma_{hmu} + r_{mu}k_9 + \eta_2k_5k_9.
\end{aligned}
$$

Thus, by Theorem 2.7, the following result is established.

Lemma 5.6. *The DFE ($\mathcal{E}_{02}$) of the extended autonomous model* (5.32) *with the contact constraint* (5.4)*, given by* (5.33)*, is LAS whenever $\mathcal{R}_c < 1$, and unstable if $\mathcal{R}_c > 1$.*

It should be mentioned that, like in the case of the single group HSV-2 vaccination model (4.27), the extended sex-structured model (5.32) (with (5.4)) can be shown to undergo a vaccine-induced backward bifurcation (this phenomenon is not established here, for the model (5.32), to avoid repetition). It will, however, be shown (in Section 5.5.2 below) that the model (5.32), with the constraint (5.4), has a globally-stable DFE for a special case (ruling out backward bifurcation for this particular special case).

5.5.2 Global Stability of DFE: Special Case

Let, $\delta_u = \delta_v = \delta_{qu} = \delta_{qv} = \delta_{tu} = \delta_{tv} = \delta$. The global asymptotic stability property of the DFE ($\mathcal{E}_{02}$) of the model (5.32) (with (5.4)) will be explored for the special case where the disease-induced mortality is negligible (so that, $\delta = 0$). Setting $\delta = 0$ in (5.32) leads

to $N_{me} = N^*_{me} \to \Pi_m/\mu$ and $N_{fe} = N^*_{fe} \to \Pi_f/\mu$ as $t \to \infty$. Furthermore, the forces of infection, λ_{fe} and λ_{me}, given in (5.31), now reduce to λ_{fec} and λ_{mec}, where (it should be noted that the constraint (5.4) is used in (5.34))

$$\begin{aligned}\lambda_{fec} &= \frac{\beta_f c_f[H_{fu} + \eta_1 H_{fv} + \eta_2 Q_{fu} + \eta_3 Q_{fv} + \eta_4 T_{fu} + \eta_4 T_{fv}]}{N^*_{me}},\\ \lambda_{mec} &= \frac{\beta_m c_m[H_{mu} + \eta_1 H_{mv} + \eta_2 Q_{mu} + \eta_3 Q_{mv} + \eta_4 T_{mu} + \eta_4 T_{mv}]}{N^*_{fe}}.\end{aligned} \tag{5.34}$$

Let, $\mathcal{R}_{ce} = \mathcal{R}_c|_{\delta=0}$. Furthermore, define

$$\begin{aligned}\Gamma_1 = \Bigg\{\Big(&S_m, V_m, E_{mu}, E_{mv}, H_{mu}, H_{mv}, Q_{mu}, Q_{mv}, T_{mu}, T_{mv}, S_f, V_f, E_{fu}, E_{fv},\\ &H_{fu}, H_{fv}, Q_{fu}, Q_{fv}, T_{fu}, T_{fv}\Big) \in \Gamma_e : S_m \le S^*_m, V_m \le V^*_m, S_f \le S^*_f, V_f \le V^*_f\Bigg\}.\end{aligned} \tag{5.35}$$

Theorem 5.6. *The DFE of the model* (5.32)*, with* (5.4) *and* (5.34)*, given by* $\mathcal{E}_{02}$*, is GAS in* Γ_1 *if* $\mathcal{R}_{ce} < 1$.

Proof. First need to prove that the set Γ_1 is positively-invariant and attracts all solutions in Γ_e, and then use a comparison argument. It can be seen from the first equation of the system (5.32) (where, now, $N_{me}(t) = N^*_{me} = \frac{\Pi_m}{\mu}$ and $N_{fe}(t) = N^*_{fe} = \frac{\Pi_f}{\mu}$) that

$$\begin{aligned}\frac{dS_m}{dt} &= \Pi_m(1 - p_m\epsilon_m) + \omega_m V_m - \lambda_{fec}(1 - \nu_1 c)S_m - (\xi_m + \mu)S_m,\\ &\le \Pi_m(1 - p_m\epsilon_m) + \omega_m V_m - (\xi_m + \mu)S_m,\\ &\le \Pi_m(1 - p_m\epsilon_m) + \omega_m(\Pi_m/\mu - S_m - E_{mu} - E_{mv} - H_{mu}\\ &- H_{mv} - Q_{mu} - Q_{mv} - T_{mu} - T_{mv}) - (\xi_m + \mu)S_m,\\ &\le \Pi_m(1 - p_m\epsilon_m) + \omega_m\Pi_m/\mu - (\omega_m + \xi_m + \mu)S_m,\\ &= (\omega_m + \xi_m + \mu)(S^*_m - S_m).\end{aligned}$$

Hence,

$$S_m(t) \le S^*_m - [S^*_m - S_m(0)]e^{-(\omega_m + \xi_m + \mu)t}.$$

It follows that either $S_m(t)$ approaches S_m^* asymptotically, or there is some finite time after which $S_m(t) \leq S_m^*$ [75]. Finally, it follows from the second equation of (5.32) that

$$\begin{aligned}
\frac{dV_m}{dt} &= \Pi_m p_m \epsilon_m + \xi_m S_m - \lambda_{fec}(1-\nu_1 c)(1-\psi)V_m - (\omega_m + \mu)V_m, \\
&\leq \Pi_m p_m \epsilon_m + \xi_m S_m - (\omega_m + \mu)V_m, \\
&\leq \Pi_m p_m \epsilon_m + \xi_m(\Pi_m/\mu - V_m - E_{mu} - E_{mv} - H_{mu} \\
&- H_{mv} - Q_{mu} - Q_{mv} - T_{mu} - T_{mv}) - (\omega_m + \mu)V_m, \\
&\leq \Pi_m p_m \epsilon_m + +\xi_m(\Pi_m/\mu) - (\omega_m + \xi_m + \mu)V_m, \\
&= (\omega_m + \xi_m + \mu)(V_m^* - V_m).
\end{aligned}$$

Thus,

$$V_m(t) \leq V_m^* - [V_m^* - V_m(0)]e^{-(\omega_m + \xi_m + \mu)t}.$$

Hence, it follows that either $V_m(t)$ approaches V_m^* asymptotically, or there is some finite time after which $V_m(t) \leq V_m^*$. Similarly, it can be shown that $S_f(t) \leq S_f^*$ and $V_f(t) \leq V_f^*$. Thus, the set Γ_1 is positively-invariant and attracting for the model (5.32), with (5.4) and (5.34). Define:

$$\begin{aligned}
Y = \Big(& S_m, V_m, E_{mu}, E_{mv}, H_{mu}, H_{mv}, Q_{mu}, Q_{mv}, T_{mu}, T_{mv}, \\
& S_f, V_f, E_{fu}, E_{fv}, H_{fu}, H_{fv}, Q_{fu}, Q_{fv}, T_{fu}, T_{fv} \Big).^T
\end{aligned}$$

The equations for the infected components of (5.32), with (5.4) and (5.34), can then be re-written as:

$$\frac{dY}{dt} = (F_e - V_{e1} - U)\, Y,$$

where, $V_{e1} = V_e|_{\delta=0}$ and the matrices F_e and V_e are as defined in Section 5.5.1. The matrix

U is given by

$$U = \begin{pmatrix} \mathbf{0}_{8\times 8} & U_1 \\ U_2 & \mathbf{0}_{8\times 8} \end{pmatrix},$$

where,

$$U_1 = \begin{pmatrix} \mathbf{0}_{2\times 2} & U^{11}_{2\times 6} \\ \mathbf{0}_{6\times 2} & \mathbf{0}_{6\times 6} \end{pmatrix}, \quad U_2 = \begin{pmatrix} \mathbf{0}_{2\times 2} & U^{21}_{2\times 6} \\ \mathbf{0}_{6\times 2} & \mathbf{0}_{6\times 6} \end{pmatrix},$$

and,

$$U^{11} = \begin{pmatrix} \alpha_1 & \alpha_1\eta_1 & \alpha_1\eta_2 & \alpha_1\eta_3 & \alpha_1\eta_4 & \alpha_1\eta_5 \\ \alpha_2 & \alpha_2\eta_1 & \alpha_2\eta_2 & \alpha_2\eta_3 & \alpha_2\eta_4 & \alpha_2\eta_5 \end{pmatrix}, \; U^{21} = \begin{pmatrix} \alpha_3 & \alpha_3\eta_1 & \alpha_3\eta_2 & \alpha_3\eta_3 & \alpha_3\eta_4 & \alpha_3\eta_5 \\ \alpha_4 & \alpha_4\eta_1 & \alpha_4\eta_2 & \alpha_4\eta_3 & \alpha_4\eta_4 & \alpha_4\eta_5 \end{pmatrix},$$

with, $\alpha_1 = (1-\nu_1 c)\beta_f c_f \frac{S^*_m}{N^*_{me}}(1-\frac{S_m}{S^*_m})$, $\alpha_2 = (1-\nu_1 c)(1-\psi)\beta_f c_f \frac{V^*_m}{N^*_{me}}(1-\frac{V_m}{V^*_m})$,
$\alpha_3 = (1-\nu_2 c)\beta_m c_m \frac{S^*_f}{N^*_{fe}}(1-\frac{S_f}{S^*_f})$ and $\alpha_4 = (1-\nu_2 c)(1-\psi)\beta_m c_m \frac{V^*_f}{N^*_{fe}}(1-\frac{V_f}{V^*_f})$.

Since $S_m \leq S^*_m$, $V_m \leq V^*_m$, $S_f \leq S^*_f$ and $V_f \leq V^*_f$ (for all $t \geq 0$) in Γ_1, it follows that the matrix U is non-negative. Thus,

$$\frac{dY}{dt} \leq (F_e - V_{e1})\, Y. \tag{5.36}$$

Furthermore, if $\mathcal{R}_{ce} < 1$, then $\rho(F_e V_{e1}^{-1}) < 1$ (from the local stability result given in Lemma 5.6, which is equivalent to $F_e - V_{e1}$ having all its eigenvalues in the left-half plane [88]). It follows that the linearized differential inequality system (5.36) is stable whenever $\mathcal{R}_{ce} < 1$. Consequently, by comparison theorem [56], it follows that

$$(E_{mu}, E_{mv}, H_{mu}, H_{mv}, Q_{mu}, Q_{mv}, T_{mu}, T_{mv}) \rightarrow (0,0,0,0,0,0,0,0),$$

and,

$$(E_{fu}, E_{fv}, H_{fu}, H_{fv}, Q_{fu}, Q_{fv}, T_{fu}, T_{fv}) \quad \rightarrow \quad (0,0,0,0,0,0,0,0).$$

Using similar argument as in the proof of Theorem 5.2, it follows that

$$\begin{aligned} & \lim_{t\to\infty}(S_m(t), E_{mu}(t), E_{mv}(t), H_{mu}(t), H_{mv}(t), Q_{mu}(t), Q_{mv}(t), T_{mu}(t), T_{mv}(t), \\ & S_f(t), E_{fu}(t), E_{fv}(t), H_{fu}(t), H_{fv}(t), Q_{fu}(t), Q_{fv}(t), T_{fu}(t), T_{fv}(t)) \\ = & \left(\frac{\Pi_m}{\mu}, 0,0,0,0,0,0,0,0, \frac{\Pi_f}{\mu}, 0,0,0,0,0,0,0,0, \right) = \mathcal{E}_{02}. \end{aligned}$$

Furthermore, since Γ_1 is positively-invariant, it follows that every solution to the equations of the model (5.32), with (5.4) and (5.34), approaches the DFE, $\mathcal{E}_{02}$, as $t \to \infty$ whenever $\mathcal{R}_{ce} < 1$. □

The epidemiological implication of Theorem 5.6 is that HSV-2 can be eliminated from the community if the three intervention strategies (namely, the use of a vaccine, condoms and drug treatment) can bring (and maintain) the associated threshold quantity, $\mathcal{R}_{ce}$, to a value less than unity.

5.5.3 Existence of EEP: Special Case

The existence of endemic equilibria of the model (5.32) with (5.4), is considered for the special case with $\delta = 0$, so that the associated forces of infection of the model are given by λ_{fec} and λ_{mec} in (5.34). Let,

$$\begin{aligned} \mathcal{E}_3 = & \Big(S_m^{**}, V_m^{**}, E_{mu}^{**}, E_{mv}^{**}, H_{mu}^{**}, H_{mv}^{**}, Q_{mu}^{**}, Q_{mv}^{**}, T_{mu}^{**}, T_{mv}^{**}, \\ & S_f^{**}, V_f^{**}, E_{fu}^{**}, E_{fv}^{**}, H_{fu}^{**}, H_{fv}^{**}, Q_{fu}^{**}, Q_{fv}^{**}, T_{fu}^{**}, T_{fv}^{**} \Big), \end{aligned} \tag{5.37}$$

represents any arbitrary equilibrium of the model (5.32), with (5.4) and (5.34). The expressions for λ_{fec} and λ_{mec} at steady-state are given by:

$$\begin{aligned}\lambda^{**}_{fec1} =& \frac{\beta_f c_f \mu \left(H^{**}_{fu} + \eta_1 H^{**}_{fv} + \eta_2 Q^{**}_{fu} + \eta_3 Q^{**}_{fv} + \eta_4 T^{**}_{fu} + \eta_4 T^{**}_{fv} \right)}{\Pi_m}, \\ \lambda^{**}_{mec1} =& \frac{\beta_m c_m \mu \left(H^{**}_{mu} + \eta_1 H^{**}_{mv} + \eta_2 Q^{**}_{mu} + \eta_3 Q^{**}_{mv} + \eta_4 T^{**}_{mu} + \eta_4 T^{**}_{mv} \right)}{\Pi_f}.\end{aligned} \tag{5.38}$$

Using the approach in Section 5.3.3, it can be shown (after some tedious algebraic manipulations) that the non-zero equilibria of the model (5.32) with (5.4) and (5.34) satisfy

$$b_1(\lambda^{**}_{mec1})^4 + b_2(\lambda^{**}_{mec1})^3 + b_3(\lambda^{**}_{mec1})^2 + b_4(\lambda^{**}_{mec1}) + b_5 = 0, \tag{5.39}$$

where,

$$\begin{aligned} b_1 &= C_5 D_3^2 + C_4 g_1 D_{16} D_3 + C_3 g_1^2 D_{16}^2, \\ b_2 &= 2C_3 g_1^2 D_{16} D_{17} - g_1^2 g_2 C_{16} D_{16}^2 + C_4 g_1 D_{16} D_4 - g_1 g_2 C_{17} D_3 D_{16} + C_4 g_1 D_1 7 D_3 + 2C_5 D_3 D_4, \\ b_3 &= -2g_1^2 g_2 C_{16} D_{16} D_{17} + C_3 g_1^2 D_{17}^2 + C_4 g_1 D_{17} D_4 - g_1 g_2 C_{17} D_3 D_{17} \\ &+ 2C_5 D_3 D_5 + C_5 D_4^2 + C_4 g_1 D_{16} D_5 - g_1 g_2 C_{17} D_4 D_{16}, \\ b_4 &= 2C_5 D_4 D_5 - g_1^2 g_2 C_{16} D_{17}^2 - g_1 g_2 C_{17} D_5 D_{16} + C_4 g_1 D_{17} D_5 - g_1 g_2 C_{17} D_4 D_{17}, \\ b_5 &= D_5 C_5^2 \left[1 - (\mathcal{R}_{ce})^2 \right]. \end{aligned} \tag{5.40}$$

The expressions for the C_i's and D_i's in (5.40) are given in Appendix E.

In (5.40), $b_1 > 0$. Since $C_5 > 0$ and $D_5 > 0$, it follows that $b_5 < 0$ if $\mathcal{R}_{ce} > 1$. Thus, using the Descartes Rule of Signs, the polynomial (5.39) has at least one positive root. Hence, the following result is established.

Theorem 5.7. *The extended model* (5.32)*, with* (5.4) *and* (5.34)*, has at least one (positive) endemic equilibrium, of the form* $\mathcal{E}_3$*, whenever* $\mathcal{R}_{ce} > 1$*.*

Theorem 5.7 shows the existence of at least one endemic equilibrium when $\mathcal{R}_{ce} > 1$. The

global asymptotic stability of this equilibrium is explored for a special case below.

5.5.4 Global Stability of EEP: Special Case

Define,

$$\begin{aligned}\mathcal{D}_1 &= \Big\{\Gamma_1 : S_m = V_m = E_{mu} = E_{mv} = H_{mu} = H_{mv} = Q_{mu} = Q_{mv} \\ &= T_{mu} = T_{mv} = S_f = V_f = E_{fu} = E_{fv} = H_{fu} = H_{fv} = Q_{fu} = Q_{fv} = T_{fu} = T_{fv} = 0\Big\}.\end{aligned}$$

Furthermore, let,

$$\begin{aligned}sign(S_m - S_m^{**}) &= sign(V_m - V_m^{**}) = sign(E_{mu} - E_{mu}^{**}) = sign(E_{mv} - E_{mv}^{**}) \\ &= sign(H_{mu} - H_{mu}^{**}) = sign(H_{mv} - H_{mv}^{**}) = sign(Q_{mu} - Q_{mu}^{**}) \\ &= sign(Q_{mv} - Q_{mv}^{**}) = sign(T_{mu} - T_{mu}^{**}) = sign(T_{mv} - T_{mv}^{**}) \\ &= sign(S_f - S_f^{**}) = sign(V_f - V_f^{**}) = sign(E_{fu} - E_{fu}^{**}) \\ &= sign(E_{fv} - E_{fv}^{**}) = sign(H_{fu} - H_{fu}^{**}) = sign(H_{fv} - H_{fv}^{**}) \\ &= sign(Q_{fu} - Q_{fu}^{**}) = sign(Q_{fv} - Q_{fv}^{**}) = sign(T_{fu} - T_{fu}^{**}) = sign(T_{fv} - T_{fv}^{**}).\end{aligned} \tag{5.41}$$

Theorem 5.8. *The EEP, $\mathcal{E}_3$, of the extended model* (5.32)*, with* (5.4) *and* (5.34)*, is GAS in $\Gamma_1 \setminus \mathcal{D}_1$ whenever $\mathcal{R}_{ce} > 1$ and Condition* (5.41) *holds.*

Proof. Let $\mathcal{R}_{ce} > 1$, so that (by Theorem 5.7) an EEP of the form, $\mathcal{E}_3$, exists for the model (5.32). Furthermore, let Condition (5.41) holds. Consider the Lyapunov function (Lyapunov functions of this type have been used in the literature, such as in [99])

$$\begin{aligned}G &= |S_m - S_m^{**}| + |V_m - V_m^{**}| + |E_{mu} - E_{mu}^{**}| + |E_{mv} - E_{mv}^{**}| + |H_{mu} - H_{mu}^{**}| \\ &+ |H_{mv} - H_{mv}^{**}| + |Q_{mu} - Q_{mu}^{**}| + |Q_{mv} - Q_{mv}^{**}| + |T_{mu} - T_{mu}^{**}| + |T_{mv} - T_{mv}^{**}| \\ &+ |S_f - S_f^{**}| + |V_f - V_f^{**}| + |E_{fu} - E_{fu}^{**}| + |E_{fv} - E_{fv}^{**}| + |H_{fu} - H_{fu}^{**}| \\ &+ |H_{fv} - H_{fv}^{**}| + |Q_{fu} - Q_{fu}^{**}| + |Q_{fv} - Q_{fv}^{**}| + |T_{fu} - T_{fu}^{**}| + |T_{fv} - T_{fv}^{**}|.\end{aligned}$$

The right derivative, D^+G, of G along the solutions of (5.32), is given by

$$
\begin{aligned}
D^+G = {} & sign(S_m - S_m^{**})\Big[\omega_m(V_m - V_m^{**}) - \lambda_{fec}(1-\nu_1 c)S_m + \lambda_{fec}^{**}(1-\nu_1 c)S_m^{**} - K_1(S_m - S_m^{**})\Big] \\
& + sign(V_m - V_m^{**})\Big[\xi_m(S_m - S_m^{**}) - \lambda_{fec}(1-\nu_1 c)(1-\psi)V_m + \lambda_{fec}^{**}(1-\nu_1 c)(1-\psi)V_m^{**} \\
& - K_2(V_m - V_m^{**})\Big] + sign(E_{mu} - E_{mu}^{**})\Big[\lambda_{fec}(1-\nu_1 c)S_m - \lambda_{fec}^{**}(1-\nu_1 c)S_m^{**} - K_3(E_{mu} - E_{mu}^{**})\Big] \\
& + sign(E_{mv} - E_{mv}^{**})\Big[\lambda_{fec}(1-\nu_1 c)(1-\psi)V_m - \lambda_{fec}^{**}(1-\nu_1 c)(1-\psi)V_m^{**} - K_4(E_{mv} - E_{mv}^{**})\Big] \\
& + sign(H_{mu} - H_{mu}^{**})\Big[\sigma_{mu}(E_{mu} - E_{mu}^{**}) + r_{mu}(Q_{mu} - Q_{mu}^{**}) - K_5(H_{mu} - H_{mu}^{**})\Big] \\
& + sign(H_{mv} - H_{mv}^{**})\Big[\sigma_{mv}(E_{mv} - E_{mv}^{**}) + r_{mv}(Q_{mv} - Q_{mv}^{**}) - K_6(H_{mv} - H_{mv}^{**})\Big] \\
& + sign(Q_{mu} - Q_{mu}^{**})\Big[q_{mu}(H_{mu} - H_{mu}^{**}) + \alpha_m(Q_{mv} - Q_{mv}^{**}) - K_7(Q_{mu} - Q_{mu}^{**})\Big] \\
& + sign(Q_{mv} - Q_{mv}^{**})\Big[q_{mv}(H_{mv} - H_{mv}^{**}) - K_8(Q_{mv} - Q_{mv}^{**})\Big] \\
& + sign(T_{mu} - T_{mu}^{**})\Big[\gamma_{hmu}(H_{mu} - H_{mu}^{**}) + \gamma_{qmu}(Q_{mu} - Q_{mu}^{**}) - \mu(T_{mu} - T_{mu}^{**})\Big] \\
& + sign(T_{mv} - T_{mv}^{**})\Big[\gamma_{hmv}(H_{mv} - H_{mv}^{**}) + \gamma_{qmv}(Q_{mv} - Q_{mv}^{**}) - \mu(T_{mv} - T_{mv}^{**})\Big] \\
& + sign(S_f - S_f^{**})\Big[\omega_f(V_f - V_f^{**}) - \lambda_{mec}(1-\nu_2 c)S_f + \lambda_{mec}^{**}(1-\nu_2 c)S_f^{**} - K_9(S_f - S_f^{**})\Big] \\
& + sign(V_f - V_f^{**})\Big[\xi_f(S_f - S_f^{**}) - \lambda_{mec}(1-\nu_2 c)(1-\psi)V_f + \lambda_{mec}^{**}(1-\nu_2 c)(1-\psi)V_f^{**} \\
& - K_{10}(V_f - V_f^{**})\Big] \\
& + sign(E_{fu} - E_{fu}^{**})\Big[\lambda_{mec}(1-\nu_2 c)S_f - \lambda_{mec}^{**}(1-\nu_2 c)S_f^{**} - K_{11}(E_{fu} - E_{fu}^{**})\Big] \\
& + sign(E_{fv} - E_{fv}^{**})\Big[\lambda_{mec}(1-\nu_2 c)(1-\psi)V_f - \lambda_{mec}^{**}(1-\nu_2 c)(1-\psi)V_f^{**} - K_{12}(E_{fv} - E_{fv}^{**})\Big] \\
& + sign(H_{fu} - H_{fu}^{**})\Big[\sigma_{fu}(E_{fu} - E_{fu}^{**}) + r_{fu}(Q_{fu} - Q_{fu}^{**}) - K_{13}(H_{fu} - H_{fu}^{**})\Big] \\
& + sign(H_{fv} - H_{fv}^{**})\Big[\sigma_{fv}(E_{fv} - E_{fv}^{**}) + r_{fv}(Q_{fv} - Q_{fv}^{**}) - K_{14}(H_{fv} - H_{fv}^{**})\Big] \\
& + sign(Q_{fu} - Q_{fu}^{**})\Big[q_{fu}(H_{fu} - H_{fu}^{**}) + \alpha_f(Q_{fv} - Q_{fv}^{**}) - K_{15}(Q_{fu} - Q_{fu}^{**})\Big] \\
& + sign(Q_{fv} - Q_{fv}^{**})\Big[q_{fv}(H_{fv} - H_{fv}^{**}) - K_{16}(Q_{fv} - Q_{fv}^{**})\Big]
\end{aligned}
$$

$$
\begin{aligned}
&+ \quad sign(T_{fu} - T_{fu}^{**})\Big[\gamma_{hfu}(H_{fu} - H_{fu}^{**}) + \gamma_{qfu}(Q_{fu} - Q_{fu}^{**}) - \mu(T_{fu} - T_{fu}^{**})\Big] \\
&+ \quad sign(T_{fv} - T_{fv}^{**})\Big[\gamma_{hfv}(H_{fv} - H_{fv}^{**}) + \gamma_{qfv}(Q_{fv} - Q_{fv}^{**}) - \mu(T_{fv} - T_{fv}^{**})\Big],
\end{aligned}
$$

where, $K_1 = \xi_m + \mu$, $K_2 = \omega_m + \mu$, $K_3 = \sigma_{mu} + \mu$, $K_4 = \sigma_{mv} + \mu$, $K_5 = q_{mu} + \gamma_{hmu} + \mu$, $K_6 = q_{mv} + \gamma_{hmv} + \mu$, $K_7 = r_{mu} + \gamma_{qmu} + \mu$, $K_8 = r_{mv} + \alpha_m + \gamma_{qmv} + \mu$, $K_9 = \xi_f + \mu$, $K_{10} = \omega_f + \mu$, $K_{11} = \sigma_{fu} + \mu$, $K_{12} = \sigma_{fv} + \mu$, $K_{13} = q_{fu} + \gamma_{hfu} + \mu$, $K_{14} = q_{fv} + \gamma_{hfv} + \mu$, $K_{15} = r_{fu} + \gamma_{qfu} + \mu$ and $K_{16} = r_{fv} + \alpha_f + \gamma_{qfv} + \mu$.

It follows, after some algebraic manipulations and taking into account Condition (5.41), that

$$
\begin{aligned}
D^+G &= -\mu\Big\{|S_m - S_m^{**}| + |V_m - V_m^{**}| + |E_{mu} - E_{mu}^{**}| + |E_{mv} - E_{mv}^{**}| + |H_{mu} - H_{mu}^{**}| \\
&+ |H_{mv} - H_{mv}^{**}| + |Q_{mu} - Q_{mu}^{**}| + |Q_{mv} - Q_{mv}^{**}| + |T_{mu} - T_{mu}^{**}| + |T_{mv} - T_{mv}^{**}| \\
&+ |S_f - S_f^{**}| + |V_f - V_f^{**}| + |E_{fu} - E_{fu}^{**}| + |E_{fv} - E_{fv}^{**}| + |H_{fu} - H_{fu}^{**}| \\
&+ |H_{fv} - H_{fv}^{**}| + |Q_{fu} - Q_{fu}^{**}| + |Q_{fv} - Q_{fv}^{**}| + |T_{fu} - T_{fu}^{**}| + |T_{fv} - T_{fv}^{**}|\Big\} = -\mu G.
\end{aligned}
$$

Thus, $\lim_{t\to\infty} G(t) = 0$. Hence, the equilibrium, $\mathcal{E}_3$, of the extended model (5.32), with (5.4) and (5.34), is GAS in $\Gamma_1 \setminus \mathcal{D}_1$ whenever $\mathcal{R}_{ce} > 1$ and Condition (5.41) holds. □

It should be stated that Condition (5.41) seems somewhat restrictive, but it is necessary for the proof to work using the Lyapunov function chosen. In summary, the extended model (5.32), with (5.4) and (5.34), has the following qualitative properties:

(i) it has a LAS DFE whenever the reproduction threshold ($\mathcal{R}_c$) is less than unity (Theorem 5.6). The DFE is GAS if the associated epidemiological threshold ($\mathcal{R}_{ce}$) is less than unity for the special case when the disease-induced death is negligible (Theorem 5.6);

(ii) it has at least one (positive) endemic equilibrium whenever the associated reproduction number ($\mathcal{R}_{ec}$) exceeds unity, for the case when the disease-induced death is zero (Theorem 5.7). An endemic equilibrium is GAS in $\Gamma_1 \setminus \mathcal{D}_1$ for a special case (Theorem 5.8).

5.6 Numerical Simulations

The extended model (5.32), subject to (5.4) and (5.34), is numerically-simulated, using the parameter values given in Table 5.1 (unless otherwise stated), to evaluate the impact of the various intervention strategies discussed earlier. The following initial conditions were used in the simulations: $S_m(0) = S_f(0) = 500,000$, $V_m(0) = V_f(0) = 500$, $E_{mu}(0) = E_{mv}(0) = E_{fu}(0) = E_{fv}(0) = 100$, $H_{mu}(0) = H_{mv}(0) = Q_{mu}(0) = Q_{mv}(0) = H_{fu}(0) = H_{fv}(0) = Q_{fu}(0) = Q_{fv}(0) = 10$, and $T_{mu}(0) = T_{mv}(0) = T_{fu}(0) = T_{fv}(0) = 10$.

The effect of condom use and treatment is monitored by simulating the extended model in the absence of vaccination. Figure 5.1A shows that, for low treatment rates and 87% condom efficacy (estimated in [26]), a condom compliance of at least 90% is needed to effectively control the disease (i.e., make $\mathcal{R}_{ce} < 1$; it should be noted from Theorem 5.6 that, for the full model (5.32), the requirement $\mathcal{R}_{ce} < 1$ is necessary and sufficient for disease elimination). On the other hand, if the treatment rates are increased (e.g., by two-fold), the condom compliance needed for effective disease control reduces to about 70% (see Figure 5.1B). However, if a vaccine is added to the combined treatment/condom strategy, it is shown (Figure 5.2) that even for relatively low treatment and vaccination rates, the disease will be eliminated regardless of the level of condom compliance (since all the $\mathcal{R}_{ce}$ contours in Figure 5.2 are less than unity; and Theorem 5.6 guarantees HSV-2 elimination if $\mathcal{R}_{ce} < 1$).

More simulations are carried out to evaluate the impact of the targeted use of the vaccination program administered as a sole intervention (i.e., in the absence of condom use and drug treatment). For instance, if only susceptible females are vaccinated, the simulations show that over 12,000 new female infections will be averted over a period of ten years (Figure 5.3A). This figure further shows an indirect benefit for the male population (since equally high number of new infections in the male population is averted). Similar situation is observed if only susceptible males are vaccinated (Figure 5.3B). Thus, these simulations show that (based on the parameter values used in the simulations) vaccinating one sex group induces an indirect benefit (preventing new cases) in the other sex group. It is worth noting from Figure 5.3B that even if only males are vaccinated, more new cases of females are averted in

comparison to the new cases of males averted. This may be due to the fact that females are more susceptible to infection than males ($\beta_m > \beta_f$).

5.7 Summary

A deterministic model for the transmission dynamics of HSV-2 in a sex-structured population, which incorporates the effect of three intervention strategies (namely: the use of an imperfect vaccine, condoms and drug treatment), is designed and qualitatively analysed. The main theoretical findings of this chapter are:

(i) The basic model (without any of the three interventions), given by (5.5), has a globally-asymptotic stable disease-free equilibrium whenever the associated reproduction threshold ($\mathcal{R}_0$) is less than or equal to unity (Theorem 5.2). This model has a unique endemic equilibrium, which is shown to be globally-asymptotically stable for a special case, when the reproduction threshold exceeds unity (Theorem 5.4);

(ii) The non-autonomous model (5.29) has a GAS DFE whenever the associated reproduction threshold ($\mathcal{R}_p$) is less than unity (Theorem 5.5);

(iii) The extended model (that incorporates the use of condom, drug treatment and an imperfect vaccine) has a GAS DFE whenever its associated reproduction threshold ($\mathcal{R}_{ce}$) is less than unity, for a special case when the disease-induced mortality is negligible (Theorem 5.6). It has at least one EEP when $\mathcal{R}_{ce} > 1$ (Theorem 5.7). It is shown that the model has a GAS EEP, for a special case (Theorem 5.8).

Numerical simulations of the extended model (5.32), subject to (5.4) and (5.34), reveal the following:

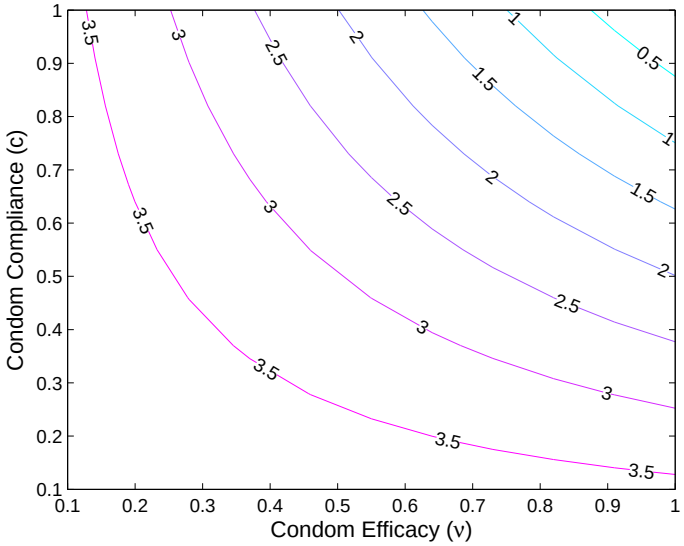
(a) For low treatment rates, very high condom compliance (at least 90%) will be required to effectively control the spread of the disease in the absence of vaccination. The level of condom compliance required for effective disease control reduces if the treatment rates are increased;

(b) The combined use of vaccination, treatment and condoms will be very effective in curtailing (or eliminating) HSV-2 in (from) the population even if the vaccination and treatment rates are low;

(c) Using vaccination as a singular control strategy, the targeted vaccination of one sex group (only) induces an indirect benefit in the other sex group. Under this vaccine-only strategy, more new cases of females are prevented than new cases of males regardless of which sex group is targeted for vaccination (i.e., regardless of which sex group is vaccinated).

Overall, the analyses in this chapter suggest that adding sex structure to the single-group HSV-2 transmission model (4.1) does not alter its main equilibrium dynamics (pertaining to the persistence or elimination of the disease). Furthermore, adding periodicity to the corresponding autonomous model (5.5) does not alter the dynamics of the autonomous model (5.5), with respect to the elimination of the disease. Finally, the prospect of effectively controlling the spread of HSV-2 in a population, using an imperfect vaccine, drug treatment and condoms, is bright.

(A)



(B)

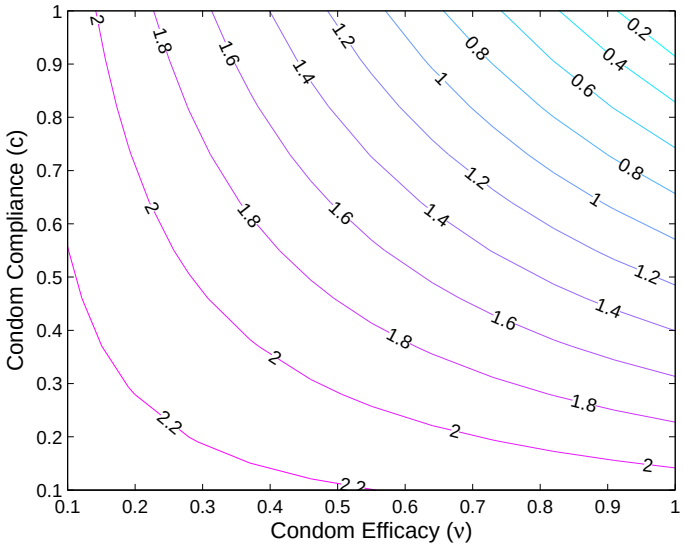


Figure 5.1: Simulations of the extended model (5.32) (with (5.4) and (5.34)) in the absence of vaccination. Contour plots of $\mathcal{R}_{ce}$ as a function of condom efficacy (ν) and compliance (c). Parameter values used are as given in Table 5.1, with $\beta_m = 0.5$ and $\beta_f = 0.4$, set the vaccination parameters to zero. (A) Low treatment rates ($\gamma_{hmu} = \gamma_{hmv} = \gamma_{hfu} = \gamma_{hfv} = \gamma_{qmu} = \gamma_{qmv} = \gamma_{qfu} = \gamma_{qfv} = 0.1$). (B) Relatively high treatment rates ($\gamma_{hmu} = \gamma_{hmv} = \gamma_{hfu} = \gamma_{hfv} = \gamma_{qmu} = \gamma_{qmv} = \gamma_{qfu} = \gamma_{qfv} = 0.2$).

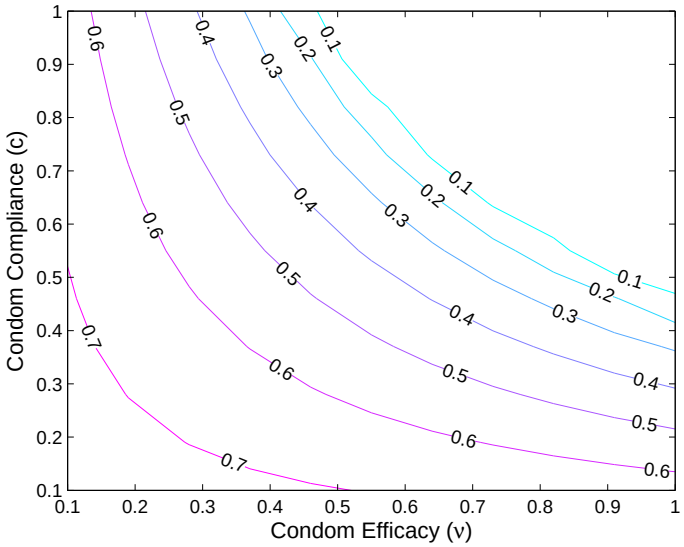
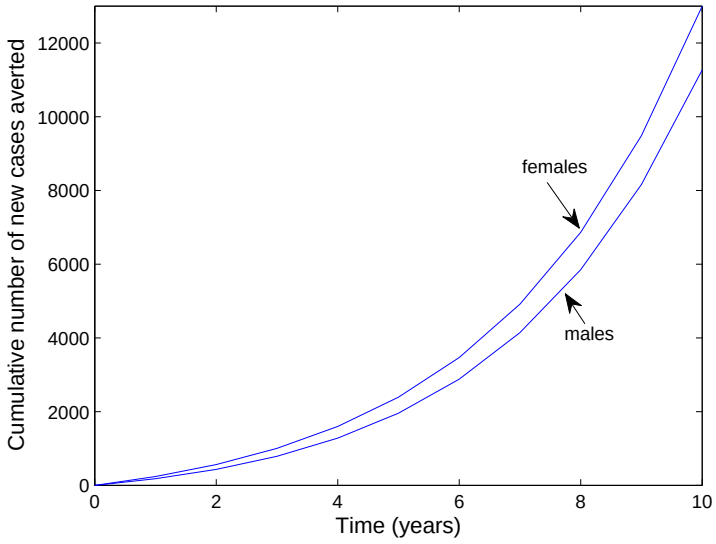


Figure 5.2: Simulations of the extended model (5.32) (with (5.4) and (5.34)). Contour plots of $\mathcal{R}_{ce}$ as a function of condom efficacy (ν) and compliance (c). Parameter values used are as given in Table 5.1, with $\epsilon_m = \epsilon_f = \psi_m = \psi_f = \xi_m = \xi_f = 0.3, \gamma_{hmu} = \gamma_{hmv} = \gamma_{hfu} = \gamma_{hfv} = \gamma_{qmu} = \gamma_{qmv} = \gamma_{qfu} = \gamma_{qfv} = 0.2$.

(A)



(B)

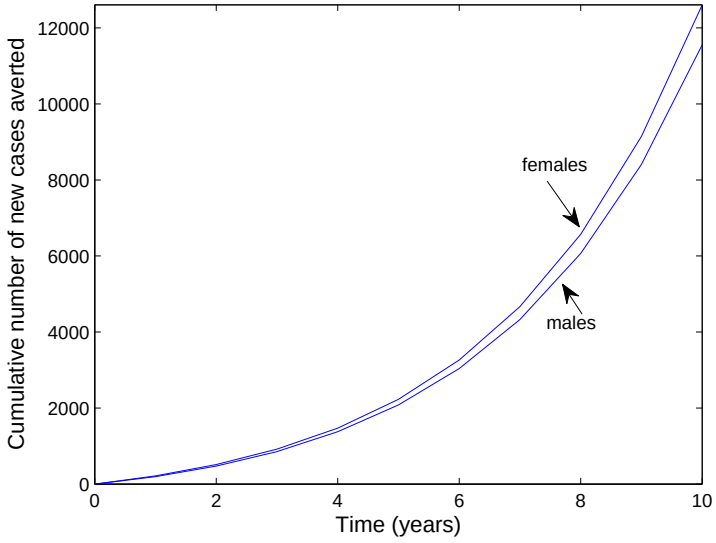


Figure 5.3: Simulations of the extended model (5.32) (with (5.4) and (5.34)) in the absence of treatment and condom use, measuring the impact of targeted vaccination strategies. Cumulative number of new cases averted as a function of time. Parameter values used are as given in Table 5.1, with $\gamma_{hmu} = \gamma_{hmv} = \gamma_{hfu} = \gamma_{hfv} = \gamma_{qmu} = \gamma_{qmv} = \gamma_{qfu} = \gamma_{qfv} = \nu = c = 0$. (A) Only susceptible females are vaccinated. (B) Only susceptible males are vaccinated.

Chapter 6

Two-group Model with Risk Structure

6.1 Introduction

In this chapter, the two-sex model, given by (5.1), is extended to include the effect of risk structure (defined in terms of the risk of acquiring or transmitting HSV-2 infection) on the transmission dynamics of HSV-2 in a population. The motivation for including such heterogeneity stems from the fact that majority of HSV-2 infections are generated by individuals in high-risk populations, such as [12, 25, 34, 94]:

(i) sexually-active females (HSV-2 seropositivity is uniformly higher in females than in males);

(ii) sexually-active adults (especially those who had first intercourse at early age);

(iii) sexually-active adults of lower socio-economic status;

(iv) sexually-active individuals with previous history of other STDs;

(v) sexually-active individuals with multiple sex partners (this includes elderly people as well);

(vi) sexually-active individuals who do not practice safe sex (e.g., these who do not use condoms consistently).

The objective of this chapter is to determine whether or not stratifying the entire sexually-active heterosexual population in terms of their risk of acquiring or transmitting HSV-2 infection will alter the qualitative dynamics of the equivalent non-stratified two-group HSV-2 model (5.5) considered in Chapter 5.

6.2 Model Formulation

The total sexually-active population at time t, denoted by $N(t)$, is divided into two groups, namely the total male population (denoted by $N_m(t)$) and the total female population (denoted by $N_f(t)$). The total male population is further sub-divided into eight mutually-exclusive compartments of low-risk susceptible males ($S_{ml}(t)$), high-risk susceptible males ($S_{mh}(t)$), low-risk males exposed to HSV-2 but with no clinical symptoms of the disease ($E_{ml}(t)$), high-risk males exposed to HSV-2 but show no clinical symptoms of the disease ($E_{mh}(t)$), low-risk infectious males with clinical symptoms of HSV-2 ($H_{ml}(t)$), high-risk infectious (virus-shedding) males with clinical symptoms of HSV-2 ($H_{mh}(t)$), low-risk infectious males, whose infection is quiescent ($Q_{ml}(t)$) and high-risk infectious males, whose infection is quiescent ($Q_{mh}(t)$).

Similarly, the total female population is sub-divided into low-risk susceptible females ($S_{fl}(t)$), high-risk susceptible females ($S_{fh}(t)$), low-risk females exposed to HSV-2 but with no clinical symptoms of the disease ($E_{fl}(t)$), high-risk females exposed to HSV-2 but with no clinical symptoms of the disease ($E_{fh}(t)$), low-risk infectious females with clinical symptoms of HSV-2 ($H_{fl}(t)$), high-risk infectious females with clinical symptoms of HSV-2 ($H_{fh}(t)$), low-risk infectious females whose infection is quiescent ($Q_{fl}(t)$) and high-risk infectious females

whose infection is quiescent ($Q_{fh}(t)$). Thus, $N(t) = N_m(t) + N_f(t)$, where,

$$\begin{aligned} N_m(t) &= S_{ml}(t) + S_{mh}(t) + E_{ml}(t) + E_{mh}(t) + H_{ml}(t) + H_{mh}(t) + Q_{ml}(t) + Q_{mh}(t), \\ N_f(t) &= S_{fl}(t) + S_{fh}(t) + E_{fl}(t) + E_{fh}(t) + H_{fl}(t) + H_{fh}(t) + Q_{fl}(t) + Q_{fh}(t). \end{aligned}$$

In other words, the model to be developed stratifies the total population in terms of risk of acquisition and transmission of HSV-2 infection. Furthermore, for mathematical tractability, this study lumps all individuals in the various risk groups, defined by Items (i) to (vi) of Section 6.1, as high-risk (that is, all individuals that fall under the Categories (i) to (vi) in Section 6.1 are considered as high-risk, while the remaining sexually-active members of the community are considered low-risk). It is worth clarifying that "exposed individuals" are those who are newly-infected with the disease but have not shown clinical symptoms of the disease.

The susceptible populations (for both males and females) are increased by the recruitment of new sexually-active individuals (assumed susceptible) into the population at a rate Π_m and Π_f for the male and female populations, respectively. A fraction p_m (p_f) of the newly-recruited sexually-active individuals is assumed to be in the high-risk group for the male (female) populations, while the remaining fraction, $1-p_m$ ($1-p_f$), is considered to be in the low-risk class for the male (female) population. Susceptible males (both low- and high-risk) acquire HSV-2 infection and become exposed, following effective contact with infected females (i.e., those in the H_{fl}, H_{fh}, Q_{fl} and Q_{fh} classes), at a rate λ_f, given by $\lambda_f(t) = \lambda_{fl}(t)+\lambda_{fh}(t)$, where,

$$\lambda_{fl}(t) = \frac{c_m\beta_f[H_{fl}(t) + \eta_f Q_{fl}(t)]}{N_f(t)} \text{ and } \lambda_{fh}(t) = \frac{\zeta_f c_m\beta_f[H_{fh}(t) + \eta_f Q_{fh}(t)]}{N_f(t)}, \tag{6.1}$$

with $\lambda_{fl}(t)$ and $\lambda_{fh}(t)$ representing the *forces of infection* associated with HSV-2 transmission by low-risk and high-risk infected females, respectively.

Similarly, susceptible females (both low- and high-risk) acquire HSV-2 infection following effective contact with males (i.e., those in the H_{ml}, H_{mh}, Q_{ml} and Q_{mh} classes) at a rate λ_m,

given by $\lambda_m(t) = \lambda_{ml}(t) + \lambda_{mh}(t)$, where,

$$\lambda_{ml}(t) = \frac{c_f\beta_m[H_{ml}(t) + \eta_m Q_{ml}(t)]}{N_m(t)} \text{ and } \lambda_{mh}(t) = \frac{\zeta_m c_f\beta_m[H_{mh}(t) + \eta_m Q_{mh}(t)]}{N_m(t)}, \quad (6.2)$$

with $\lambda_{ml}(t)$ and $\lambda_{mh}(t)$ representing the *forces of infection* associated with HSV-2 transmission by low-risk and high-risk infected males, respectively.

In (6.1) and (6.2), $\beta_m(\beta_f)$ is the probability of HSV-2 infection *per* contact from male-to-female (female-to-male). It is assumed that $\beta_m > \beta_f$, since females are more susceptible to HSV-2 infection than males [25]. The terms c_m and c_f represent the rates at which males and females acquire new sexual partners *per* unit time, respectively. Thus, $c_f\beta_m$ and $c_m\beta_f$ represent the effective contact rates for male-to-female and female-to-male transmission of HSV-2, respectively. Unlike in other modeling studies for HSV-2 (such as those in [71]), this study assumes that infected individuals in the quiescent state (i.e., those in the Q_{ml}, Q_{mh}, Q_{fl} and Q_{fh} classes) can transmit infection. The modification parameters $0 < \eta_m, \eta_f < 1$ account for the assumption that quiescent individuals transmit infection at a slower rate than the corresponding infected individuals with clinical symptoms of the disease (in the H_{ml}, H_{mh}, H_{fl} and H_{fh} classes), due to their assumed reduced viral load (it is assumed that viral load is positively correlated with infectiousness). Furthermore, the modification parameters $\zeta_m > 1$ and $\zeta_f > 1$ account for the assumed increase in the relative infectiousness of individuals in the high-risk group in comparison to those in the low-risk group for the male and female populations, respectively.

It is assumed that susceptible individuals can change their risk status, by switching from low- to high-risk status and *vice versa*. Susceptible males (females) switch from low- to high-risk status at a rate ξ_1^m (ξ_1^f), and switch from high- to low-risk status at a rate ξ_2^m (ξ_2^f), respectively. Newly-infected individuals in any group move to the corresponding exposed classes $E_{ml}; E_{mh}$ ($E_{fl}; E_{fh}$) at the rates $\lambda_{fl}; \theta_m\lambda_f$ ($\lambda_m; \theta_f\lambda_m$) for males (females). The parameters $\theta_m \geq 1$ and $\theta_f \geq 1$ account for the fact that high-risk uninfected individuals are more susceptible to HSV-2 infection than those in the low-risk susceptible group. Exposed individuals (either in the low- or high-risk group) develop symptoms at a rate σ_m (σ_f) for

males (females). Exposed individuals change their risk status from low- to high-risk at a rate ξ_3^m (ξ_3^f) for males (females), and switch from high- to low-risk at a rate ξ_4^m (ξ_4^f), for males (females), respectively.

Infectious individuals (both low- and high-risk) become quiescent at a rate q_m (q_f) for males (females). Infectious individuals switch from low- to high-risk status at a rate ξ_5^m (ξ_5^f) for males (females), and switch from high- to low-risk status at a rate ξ_6^m (ξ_6^f) for males (females), respectively. Quiescent individuals (both low- and high-risk) re-activate (relapse) their infection (and become symptomatic) at a rate $r_{ml}; r_{mh}$ ($r_{fl}; r_{fh}$) for males (females), and move to the corresponding $H_{ml}; H_{mh}$ ($H_{fl}; H_{fh}$) classes. Quiescent individuals switch from low- to high-risk status at a rate ξ_7^m (ξ_7^f) for males (females), and switch from high- to low-risk status at a rate ξ_8^m (ξ_8^f) for males (females), respectively. Furthermore, natural mortality occurs in all classes at a rate μ. The parameters δ_1 and δ_2 represent the disease-induced death for individuals (both males and females) with symptoms in low-risk (H_{ml}, H_{fl}), and in high-risk (H_{mh}, H_{fh}) groups, respectively. Similarly, δ_3 and δ_4 represent the disease-induced mortality rate for low-risk quiescent individuals (in the Q_{ml} and Q_{fl} classes) and high-risk quiescent individuals (in the Q_{mh} and Q_{fh} classes), respectively.

Combining all these definitions and assumptions, it follows that the risk-structured, two-sex, model for the transmission dynamics of HSV-2 in a sexually-active population is given by the following system of differential equations (the associated variables and parameters of the model are described in Table 6.1):

$$
\begin{aligned}
\frac{dS_{ml}}{dt} &= (1-p_m)\Pi_m + \xi_2^m S_{mh}(t) - \lambda_f(t)S_{ml}(t) - (\xi_1^m + \mu)S_{ml}(t),\\
\frac{dS_{mh}}{dt} &= p_m\Pi_m + \xi_1^m S_{ml}(t) - \theta_m\lambda_f(t)S_{mh}(t) - (\xi_2^m + \mu)S_{mh}(t),\\
\frac{dE_{ml}}{dt} &= \lambda_f(t)S_{ml}(t) + \xi_4^m E_{mh}(t) - (\xi_3^m + \sigma_m + \mu)E_{ml}(t),\\
\frac{dE_{mh}}{dt} &= \theta_m\lambda_f(t)S_{mh}(t) + \xi_3^m E_{ml}(t) - (\xi_4^m + \sigma_m + \mu)E_{mh}(t),\\
\frac{dH_{ml}}{dt} &= \sigma_m E_{ml}(t) + r_{ml}Q_{ml}(t) + \xi_6^m H_{mh}(t) - (\xi_5^m + q_m + \mu + \delta_1)H_{ml}(t),\\
\frac{dH_{mh}}{dt} &= \sigma_m E_{mh}(t) + r_{mh}Q_{mh}(t) + \xi_5^m H_{ml}(t) - (\xi_6^m + q_m + \mu + \delta_2)H_{mh}(t),\\
\frac{dQ_{ml}}{dt} &= q_m H_{ml}(t) + \xi_8^m Q_{mh}(t) - (\xi_7^m + r_{ml} + \mu + \delta_3)Q_{ml}(t),\\
\frac{dQ_{mh}}{dt} &= q_m H_{mh}(t) + \xi_7^m Q_{ml}(t) - (\xi_8^m + r_{mh} + \mu + \delta_4)Q_{mh}(t),\\
\frac{dS_{fl}}{dt} &= (1-p_f)\Pi_f + \xi_2^f S_{fh}(t) - \lambda_m(t)S_{fl}(t) - (\xi_1^f + \mu)S_{fl}(t),\\
\frac{dS_{fh}}{dt} &= p_f\Pi_f + \xi_1^f S_{fl}(t) - \theta_f\lambda_m(t)S_{fh}(t) - (\xi_2^f + \mu)S_{fh}(t),\\
\frac{dE_{fl}}{dt} &= \lambda_m(t)S_{fl}(t) + \xi_4^f E_{fh}(t) - (\xi_3^f + \sigma_f + \mu)E_{fl}(t),\\
\frac{dE_{fh}}{dt} &= \theta_f\lambda_m(t)S_{fh}(t) + \xi_3^f E_{fl}(t) - (\xi_4^f + \sigma_f + \mu)E_{fh}(t),\\
\frac{dH_{fl}}{dt} &= \sigma_f E_{fl}(t) + r_{fl}Q_{fl}(t) + \xi_6^f H_{fh}(t) - (\xi_5^f + q_f + \mu + \delta_1)H_{fl}(t),\\
\frac{dH_{fh}}{dt} &= \sigma_f E_{fh}(t) + r_{fh}Q_{fh}(t) + \xi_5^f H_{fl}(t) - (\xi_6^f + q_f + \mu + \delta_2)H_{fh}(t),\\
\frac{dQ_{fl}}{dt} &= q_f H_{fl}(t) + \xi_8^f Q_{fh}(t) - (\xi_7^f + r_{fl} + \mu + \delta_3)Q_{fl}(t),\\
\frac{dQ_{fh}}{dt} &= q_f H_{fh}(t) + \xi_7^f Q_{fl}(t) - (\xi_8^f + r_{fh} + \mu + \delta_4)Q_{fh}(t).
\end{aligned}
\tag{6.3}
$$

In summary, the risk-structured HSV-2 model (6.3) is constructed based on the following key assumptions:

(i) Quiescent individuals (in the Q_{ml}, Q_{mh}, Q_{fl} and Q_{fh} classes) can transmit infection (this assumption is also made in [71]);

(ii) High-risk susceptible individuals acquire infection at a faster rate than low-risk susceptible individuals (with the associated parameters $\theta_m > 1$ and $\theta_f > 1$ for males and females, respectively);

(iii) High-risk infected individuals transmit infection at a faster rate than the corresponding low-risk infected individuals (with the associated parameters $\zeta_m > 1$ and $\zeta_f > 1$ for males and females, respectively);

(iv) All individuals can change their risk status, by switching from low- to high-risk status and *vice-versa*.

The model (6.3) is an extension of the sex-structured HSV-2 transmission model (5.5), by incorporating risk-structure into the model (this entails adding eight new epidemiological compartments to the model (5.5). As in Section 5.2, the following group contact constraint must hold:

$$c_m N_m = c_f N_f. \tag{6.4}$$

Furthermore, it is also assumed that male sexual partners are abundant, so that females can always have enough number of sexual contacts *per* unit time (i.e., c_f is constant, and c_m is calculated from the relation $c_m = \frac{c_f N_f}{N_m}$, as discussed in Section 5.2).

Table 6.1: Variables and parameters of the risk-structured model (6.3).

Variables	Description
$S_{ml}(t); S_{mh}(t)$	Population of low- and high-risk susceptible males
$S_{fl}(t); S_{fh}(t)$	Population of low- and high-risk susceptible females
$E_{ml}(t); E_{mh}(t)$	Population of low- and high-risk exposed males
$E_{fl}(t); E_{fh}(t)$	Population of low- and high-risk exposed females
$H_{ml}(t); H_{mh}(t)$	Population of low- and high-risk infectious males
$H_{fl}(t); H_{fh}(t)$	Population of low- and high-risk infectious females
$Q_{ml}(t); Q_{mh}(t)$	Population of low- and high-risk quiescent males
$Q_{fl}(t); Q_{fh}(t)$	Population of low- and high-risk quiescent females

Parameter	Description
$\Pi_m; \Pi_f$	Recruitment rates for males and females
$p_m; p_f$	Fraction of recruited individuals that are high-risk for males and females
$\beta_m; \beta_f$	Probability of transmission for males and females
$c_m; c_f$	Average number of new sexual partners for males and females per unit time
$\zeta_m; \zeta_f$	Modification parameters for relative infectiousness of high-risk individuals in comparison to low-risk
$\eta_m; \eta_f$	Modification parameters for infectiousness of infectious individuals in relation to exposed individuals
μ	Natural death rate
$\sigma_m; \sigma_f$	Progression rates to symptoms development of exposed males and females
$r_{ml}; r_{fl}$	Activation rate of low-risk infectious males and females in the quiescent state
$r_{mh}; r_{fh}$	Activation rate of high-risk infectious males and females in the quiescent state
$q_m; q_f$	Rate at which infectious males and females revert to their quiescent states
$\theta_m; \theta_f$	Modification parameters for increased HSV-2 susceptibility by males and females in high-risk
$\xi_i^m; \xi_i^f$ $(i = 1, 3, 5, 7)$	Rate of behavioral change from low- to high-risk
$\xi_j^m; \xi_j^f$ $(j = 2, 4, 6, 8)$	Rate of behavioral change from high- to low-risk
$\delta_1; \delta_2$	Disease-induced death rate for infectious individuals
$\delta_3; \delta_4$	Disease-induced death rate for quiescent individuals

6.2.1 Basic Properties

The following result can be proven (using the approach in Section 4.2.1 or in Appendix A of [86]).

Theorem 6.1. *Let* $x_{il}(t) = (S_{il}(t), E_{il}(t), H_{il}(t), Q_{il}(t))$ *and* $x_{ih}(t) = (S_{ih}(t), E_{ih}(t), H_{ih}(t), Q_{ih}(t))$ *for* $i = m, f$. *Let the initial data* $(x_{ml}(0), x_{fl}(0), x_{mh}(0), x_{fh}(0)) > 0$. *Then the solutions* $(x_{ml}(t), x_{mh}(t), x_{fl}(t), x_{fh}(t))$, *of the basic model* (6.3), *are positive for all* $t > 0$. *Furthermore,*

$$\limsup_{t\to\infty} N_m(t) \leq \frac{\Pi_m}{\mu} \text{ and } \limsup_{t\to\infty} N_f(t) \leq \frac{\Pi_f}{\mu}.$$

The risk-structured HSV-2 model (6.3) will be analyzed in a biologically-feasible region as follows. Consider the region

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

with,

$$\begin{aligned}\mathcal{D}_m &= \Bigg\{(S_{ml}, S_{mh}, E_{ml}, E_{mh}, H_{ml}, H_{mh}, Q_{ml}, Q_{mh}) \in \mathbb{R}^8_+ : \\ &\qquad S_{ml} + S_{mh} + E_{ml} + E_{mh} + H_{ml} + H_{mh} + Q_{ml} + Q_{mh} \leq \frac{\Pi_m}{\mu}\Bigg\},\end{aligned}$$

and,

$$\begin{aligned}\mathcal{D}_f &= \Bigg\{(S_{fl}, S_{fh}, E_{fl}, E_{fh}, H_{fl}, H_{fh}, Q_{fl}, Q_{fh}) \in \mathbb{R}^8_+ : \\ &\qquad S_{fl} + S_{fh} + E_{fl} + E_{fh} + H_{fl} + H_{fh} + Q_{fl} + Q_{fh} \leq \frac{\Pi_f}{\mu}\Bigg\}.\end{aligned}$$

Adding the first eight and the last eight equations of the model (6.3) gives

$$\frac{dN_m}{dt} \leq \Pi_m - \mu N_m(t) \text{ and } \frac{dN_f}{dt} \leq \Pi_f - \mu N_f(t). \tag{6.5}$$

A comparison theorem (Theorem 2.6) can then be used to show that

$$N_m(t) \leq N_m(0)e^{-\mu t} + \frac{\Pi_m}{\mu}\left(1 - e^{-\mu t}\right) \text{ and } N_f(t) \leq N_f(0)e^{-\mu t} + \frac{\Pi_f}{\mu}\left(1 - e^{-\mu t}\right).$$

In particular,

$$N_m(t) \leq \frac{\Pi_m}{\mu} \text{ if } N_m(0) \leq \frac{\Pi_m}{\mu} \text{ and } N_f(t) \leq \frac{\Pi_f}{\mu} \text{ if } N_f(0) \leq \frac{\Pi_f}{\mu}.$$

This result is summarized below.

Lemma 6.1. *The region $\mathcal{D}$ is positively-invariant for the model* (6.3) *with initial conditions in* $\mathbb{R}^{16}_+$.

6.3 Existence and Stability of Equilibria

6.3.1 Local Stability of DFE

The DFE of the model (6.3) is given by

$$\begin{aligned}\mathcal{E}_0 =&(S^*_{ml}, S^*_{mh}, E^*_{ml}, E^*_{mh}, H^*_{ml}, H^*_{mh}, Q^*_{ml}, Q^*_{mh}, S^*_{fl}, S^*_{fh}, E^*_{fl}, E^*_{fh}, H^*_{fl},\\ & H^*_{fh}, Q^*_{fl}, Q^*_{fh}) = \left(S^*_{ml}, S^*_{mh}, 0, 0, 0, 0, 0, 0, S^*_{fl}, S^*_{fh}, 0, 0, 0, 0, 0, 0\right),\end{aligned} \tag{6.6}$$

where,

$$\begin{aligned} S^*_{ml} &= \frac{\Pi_m[p_m\xi^m_2 + k_2(1-p_m)]}{k_1k_2 - \xi^m_1\xi^m_2},\ S^*_{mh} = \frac{\Pi_m[\xi^m_1(1-p_m) + k_1p_m]}{k_1k_2 - \xi^m_1\xi^m_2},\\ S^*_{fl} &= \frac{\Pi_f[p_f\xi^f_2 + k_{12}(1-p_f)]}{k_{11}k_{12} - \xi^f_1\xi^f_2}, \quad S^*_{fh} = \frac{\Pi_f[\xi^f_1(1-p_f) + k_{11}p_f]}{k_{11}k_{12} - \xi^f_1\xi^f_2},\end{aligned}$$

with $k_1 = k_2 = \mu$, $k_3 = k_4 = \sigma_m + \mu$, $k_5 = q_m + \mu + \delta_1$, $k_6 = q_m + \mu + \delta_2$, $k_7 = r_{ml} + q_m + \mu + \delta_3$, $k_8 = r_{mh} + q_m + \mu + \delta_4$, $k_{11} = k_{12} = \mu$, $k_{13} = k_{14} = \sigma_f + \mu$, $k_{15} = q_f + \mu + \delta_1$, $k_{16} = q_f + \mu + \delta_2$, $k_{17} = r_{fl} + q_f + \mu + \delta_3$, $k_{18} = r_{fh} + q_f + \mu + \delta_4$.

Using the notations in [88], the matrices F and V, for the new infection terms and the remaining transfer terms, are, respectively, given by (where $\mathbf{0}_{m\times n}$ represents a zero matrix with m rows and n columns),

$$F = \begin{pmatrix} \mathbf{0}_{6\times 6} & F_1 \\ F_2 & \mathbf{0}_{6\times 6} \end{pmatrix}, \; V = \begin{pmatrix} V_1 & \mathbf{0}_{6\times 6} \\ \mathbf{0}_{6\times 6} & V_4 \end{pmatrix},$$

where,

$$F_1 = \begin{pmatrix} (F_{11})_{2\times 6} \\ \mathbf{0}_{4\times 6} \end{pmatrix}, \quad F_2 = \begin{pmatrix} (F_{21})_{2\times 6} \\ \mathbf{0}_{4\times 6} \end{pmatrix},$$

and,

$$F_{11} = \begin{pmatrix} 0 & 0 & \frac{S^*_{ml}}{N^*_m} & \frac{S^*_{ml}\zeta_f}{N^*_m} & \frac{S^*_{ml}\eta_f}{N^*_m} & \frac{S^*_{ml}\zeta_f\eta_f}{N^*_m} \\ 0 & 0 & \frac{\theta_m S^*_{mh}}{N^*_m} & \frac{\theta_m S^*_{mh}\zeta_f}{N^*_m} & \frac{\theta_m S^*_{mh}\eta_f}{N^*_m} & \frac{\theta_m S^*_{mh}\zeta_f\eta_f}{N^*_m} \end{pmatrix} c_f\beta_f,$$

$$F_{21} = \begin{pmatrix} 0 & 0 & \frac{S^*_{fl}}{N^*_f} & \frac{S^*_{fl}\zeta_m}{N^*_f} & \frac{S^*_{fl}\eta_m}{N^*_f} & \frac{S^*_{fl}\zeta_m\eta_m}{N^*_f} \\ 0 & 0 & \frac{\theta_f S^*_{fh}}{N^*_f} & \frac{\theta_f S^*_{fh}\zeta_m}{N^*_f} & \frac{\theta_f S^*_{fh}\eta_m}{N^*_f} & \frac{\theta_f S^*_{fh}\zeta_m\eta_m}{N^*_f} \end{pmatrix} c_m\beta_m,$$

$$V_1 = \begin{pmatrix} k_3+\sigma_m & -\xi^m_4 & 0 & 0 & 0 & 0 \\ -\xi^m_3 & k_4+\sigma_m & 0 & 0 & 0 & 0 \\ -\sigma_m & 0 & k_5+q_m & -\xi^m_6 & -r_{ml} & 0 \\ 0 & -\sigma_m & -\xi^m_5 & k_6+q_m & 0 & -r_{mh} \\ 0 & 0 & -q_m & 0 & k_7+r_{ml} & -\xi^m_8 \\ 0 & 0 & 0 & -q_m & -\xi^m_7 & k_8+r_{mh} \end{pmatrix},$$

$$V_4 = \begin{pmatrix} k_{13}+\sigma_f & -\xi_4^f & 0 & 0 & 0 & 0 \\ -\xi_3^f & k_{14}+\sigma_f & 0 & 0 & 0 & 0 \\ -\sigma_f & 0 & k_{15}+q_f & -\xi_6^f & -r_{fl} & 0 \\ 0 & -\sigma_f & -\xi_5^f & k_{16}+q_f & 0 & -r_{fh} \\ 0 & 0 & -q_f & 0 & k_{17}+r_{fl} & -\xi_8^f \\ 0 & 0 & 0 & -q_f & -\xi_7^f & k_{18}+r_{fh} \end{pmatrix}.$$

Thus,

$$\mathcal{R}_0 = \rho(FV^{-1}) = \sqrt{\mathcal{R}_m \mathcal{R}_f}, \tag{6.7}$$

where,

$$\mathcal{R}_m = \mathcal{R}_{ml} + \mathcal{R}_{mh}, \quad \mathcal{R}_f = \mathcal{R}_{fl} + \mathcal{R}_{fh}, \tag{6.8}$$

with,

$$\begin{aligned} \mathcal{R}_{ml} &= \frac{c_m\beta_m\sigma_m(S^*_{ml}A_{11} + \theta_m S^*_{mh}A_{21})}{(S^*_{ml}+S^*_{mh})A}, \quad \mathcal{R}_{mh} = \frac{c_m\beta_m\sigma_m(S^*_{ml}A_{12} + \theta_m S^*_{mh}A_{22})}{(S^*_{ml}+S^*_{mh})A}, \\ \mathcal{R}_{fl} &= \frac{c_f\beta_f\sigma_f(S^*_{fl}B_{11} + \theta_f S^*_{fh}B_{21})}{(S^*_{fl}+S^*_{fh})B}, \quad \mathcal{R}_{fh} = \frac{c_f\beta_f\sigma_f(S^*_{fl}B_{12} + \theta_f S^*_{fh}B_{22})}{(S^*_{fl}+S^*_{fh})B}, \end{aligned} \tag{6.9}$$

and,

$$\begin{aligned} A_{11} &= (\sigma_m q_m + \sigma_m k_6 + q_m k_4 + k_4 k_6 + \xi_3^m \xi_6^m)(k_7 k_8 - \xi_7^m \xi_8^m) + \sigma_m r_{ml}(k_6 k_8 + r_{mh} k_6) \\ &+ q_m r_{ml}(\sigma_m k_8 + \xi_3^m \xi_8^m) + r_{mh} r_{ml}(k_4 k_6 + \xi_6^m \xi_3^m) + r_{ml} k_8 (q_m k_4 + k_4 k_6 + \xi_6^m \xi_3^m) \\ &+ r_{mh} k_7 (\sigma_m k_6 + k_4 k_6 + \xi_6^m \xi_3^m) + \eta_m q_m^2 (\sigma_m k_{18} + \xi_3^m \xi_8^m + k_4 k_8) + \eta_m q_m [k_6(\sigma_m r_{mh} \\ &+ k_4 k_8 + \sigma_m k_8) + k_4(r_{mh} k_6 + \xi_5^m \xi_8^m) + (\xi_3^m \xi_6^m r_{mh} + \sigma_m \xi_5^m \xi_8^m)], \end{aligned}$$

$$
\begin{aligned}
A_{12} &= \zeta_m(\xi_5^m\sigma_m + \xi_5^m k_4 + \xi_3^m q_m + k_5\xi_3^m)(k_7k_8 - \xi_7^m\xi_8^m) + \zeta_m q_m r_{mh}(\xi_3^m k_7 + \xi_5^m k_7 \\
&+ \xi_7^m\sigma_m + \xi_7^m k_4) + \zeta_m\sigma_m r_{ml}(\xi_5^m k_8 + \xi_5^m r_{mh}) + \zeta_m(r_{ml}k_8 + r_{mh}k_7 + r_{ml}r_{mh})(\xi_5^m k_4 + \xi_3^m k_5) \\
&+ \zeta_m\eta_m q_m^2(\xi_7^m k_4 + \xi_3^m k_7 + \xi_7^m\sigma_m) + \zeta_m\eta_m q_m[(k_4 + \sigma_m)(\xi_5^m k_7 + \xi_7^m k_6) \\
&+ r_{ml}(\xi_3^m k_5 + \xi_5^m\sigma_m + \xi_5^m k_4) + \xi_3^m(k_5k_7 + \xi_6^m\xi_7^m)],
\end{aligned}
$$

$$
\begin{aligned}
A_{21} &= (\sigma_m\xi_6^m + \xi_6^m k_3 + q_m\xi_4^m + \xi_4^m k_6)(k_7k_8 - \xi_7^m\xi_8^m) + (r_{ml}k_8 + r_{mh}k_7 + r_{mh}r_{ml}) \\
&(\xi_4^m k_6 + \xi_6^m k_3 + \xi_6^m\sigma_m) + q_m r_{ml}(\xi_8^m k_3 + \xi_4^m k_8 + \xi_8^m\sigma_m) + \eta_m q_m^2(\xi_4^m k_8 + \xi_8^m\sigma_m + k_3\xi_8^m) \\
&+ \eta_m q_m[\sigma_m(\xi_6^m k_8 + \xi_6^m r_{mh} + k_5\xi_8^m) + r_{mh}(\xi_6^m k_3 + \xi_4^m k_6) + \xi_4^m(k_6k_8 + \xi_5^m\xi_8^m) + k_3(\xi_6^m k_8 + \xi_8^m k_5)],
\end{aligned}
$$

$$
\begin{aligned}
A_{22} &= \zeta_m(q_m k_3 + \sigma_m k_5 + k_3k_5 + \xi_4^m\xi_5^m + \sigma_m q_m)(k_7k_8 - \xi_7^m\xi_8^m) + \zeta_m q_m r_{mh}(k_3k_7 + \xi_4^m\xi_7^m + \sigma_m k_7) \\
&+ \zeta_m(r_{ml}k_8 + r_{mh}k_7 + r_{mh}r_{ml})(\xi_4^m\xi_5^m + k_3k_5 + k_5\sigma_m) + \zeta_m\eta_m q_m^2(\xi_4^m\xi_7^m + k_3k_7 + \sigma_m k_7) \\
&+ \zeta_m\eta_m q_m[(k_3k_5 + \xi_4^m\xi_5^m + k_5\sigma_m)(k_7 + r_{ml}) + \xi_7^m(\xi_6^m k_3 + \xi_4^m k_6 + \sigma_m\xi_6^m)],
\end{aligned}
$$

$$
\begin{aligned}
B_{11} &= (\sigma_f q_f + \sigma_f k_{16} + q_f k_{14} + k_{14}k_{16} + \xi_3^f\xi_6^f)(k_{17}k_{18} - \xi_7^f\xi_8^f) + \sigma_f r_{fl}(k_{16}k_{18} + r_{fh}k_{16}) \\
&+ q_f r_{fl}(\sigma_f k_{18} + \xi_3^f\xi_8^f) + r_{fh}r_{fl}(k_{14}k_{16} + \xi_6^f\xi_3^f) + r_{fl}k_{18}(q_f k_{14} + k_{14}k_{16} + \xi_6^f\xi_3^f) \\
&+ r_{fh}k_{17}(\sigma_f k_{16} + k_{14}k_{16} + \xi_6^f\xi_3^f) + \eta_f q_f^2(\sigma_f k_{18} + \xi_3^f\xi_8^f + k_{14}k_{18}) \\
&+ \eta_f q_f[k_{16}(\sigma_f r_{fh} + k_{14}k_{18} + \sigma_f k_{18}) + k_{14}(r_{fh}k_{16} + \xi_5^f\xi_8^f) + (\xi_3^f\xi_6^f r_{fh} + \sigma_f\xi_5^f\xi_8^f)],
\end{aligned}
$$

$$
\begin{aligned}
B_{12} &= \zeta_f(\xi_5^f\sigma_f + \xi_5^f k_{14} + \xi_3^f q_f + k_{15}\xi_3^f)(k_{17}k_{18} - \xi_7^f\xi_8^f) + \zeta_f q_f r_{fh}(\xi_3^f k_{17} + \xi_5^f k_{17} + \xi_7^f\sigma_f + \xi_7^f k_{14}) \\
&+ \zeta_f\sigma_f r_{fl}(\xi_5^f k_{18} + \xi_5^f r_{fh}) + \zeta_f(r_{fl}k_{18} + r_{fh}k_{17} + r_{fl}r_{fh})(\xi_5^f k_{14} + \xi_3^f k_{15}) \\
&+ \zeta_f\eta_f q_f^2(\xi_7^f k_{14} + \xi_3^f k_{17} + \xi_7^f\sigma_f) + \zeta_f\eta_f q_f[(k_{14} + \sigma_f)(\xi_5^f k_{17} + \xi_7^f k_{16}) + r_{fl} \\
&(\xi_3^f k_{15} + \xi_5^f\sigma_f + \xi_5^f k_{14}) + \xi_3^f(k_{15}k_{17} + \xi_6^f\xi_7^f)],
\end{aligned}
$$

$$
\begin{aligned}
B_{21} &= (\sigma_f\xi_6^f + \xi_6^f k_{13} + q_f\xi_4^f + \xi_4^f k_{16})(k_{17}k_{18} - \xi_7^f\xi_8^f) + (r_{fl}k_{18} + r_{fh}k_{17} + r_{fh}r_{fl}) \\
&\quad (\xi_4^f k_{16} + \xi_6^f k_{13} + \xi_6^f\sigma_f) + q_f r_{fl}(\xi_8^f k_{13} + \xi_4^f k_{18} + \xi_8^f\sigma_f) + \eta_f q_f^2(\xi_4^f k_{18} + \xi_8^f\sigma_f + k_{13}\xi_8^f) \\
&+ \eta_f q_f[\sigma_f(\xi_6^f k_{18} + \xi_6^f r_{fh} + k_{15}\xi_8^f) + r_{fh}(\xi_6^f k_{13} + \xi_4^f k_{16}) + \xi_4^f(k_{16}k_{18} + \xi_5^f\xi_8^f) + k_{13}(\xi_6^f k_{18} + \xi_8^f k_{15})],
\end{aligned}
$$

$$
\begin{aligned}
B_{22} &= \zeta_f(q_f k_{13} + \sigma_f k_{15} + k_{13}k_{15} + \xi_4^f\xi_5^f + \sigma_f q_f)(k_{17}k_{18} - \xi_7^f\xi_8^f) + \zeta_f q_f r_{fh}(k_{13}k_{17} + \xi_4^f\xi_7^f + \sigma_f k_{17}) \\
&+ \zeta_f(r_{fl}k_{18} + r_{fh}k_{17} + r_{fh}r_{fl})(\xi_4^f\xi_5^f + k_{13}k_{15} + k_{15}\sigma_f) + \zeta_f\eta_f q_f^2(\xi_4^f\xi_7^f + k_{13}k_{17} + \sigma_f k_{17}) \\
&+ \zeta_f\eta_f q_f[(k_{13}k_{15} + \xi_4^f\xi_5^f + k_{15}\sigma_f)(k_{17} + r_{fl}) + \xi_7^f(\xi_6^f k_{13} + \xi_4^f k_{16} + \sigma_f\xi_6^f)],
\end{aligned}
$$

$$
\begin{aligned}
A &= [(k_3k_4 - \xi_3^m\xi_4^m) + \sigma_m(\sigma_m + k_3 + k_4)]\Big[(k_7k_8 - \xi_7^m\xi_8^m)(k_5k_6 - \xi_5^m\xi_6^m) \\
&+ (k_5k_6 - \xi_5^m\xi_6^m)(r_{ml}r_{mh} + k_8r_{ml} + k_7r_{mh}) + q_m r_{mh}(k_6k_7 - \xi_6^m\xi_7^m) \\
&+ q_m r_{ml}(k_5k_8 - \xi_5^m\xi_8^m) + (k_7k_8 - \xi_7^m\xi_8^m)(q_m^2 + q_m k_5 + q_m k_6)\Big], \\
B &= [(k_{13}k_{14} - \xi_3^f\xi_4^f) + \sigma_f(\sigma_f + k_{13} + k_{14})]\Big[(k_{17}k_{18} - \xi_7^f\xi_8^f)(k_{15}k_{16} - \xi_5^f\xi_6^f) \\
&+ (k_{15}k_{16} - \xi_5^f\xi_6^f)(r_{fl}r_{fh} + k_{18}r_{fl} + k_{17}r_{fh}) + q_f r_{fh}(k_{16}k_{17} - \xi_6^f\xi_7^f) \\
&+ q_f r_{fl}(k_{15}k_{18} - \xi_5^f\xi_8^f) + (k_{17}k_{18} - \xi_7^f\xi_8^f)(q_f^2 + q_f k_{15} + q_f k_{16})\Big].
\end{aligned}
$$

It should be mentioned that, in the above expressions, $k_3k_4 - \xi_3^m\xi_4^m > 0$, $k_6k_7 - \xi_6^m\xi_7^m > 0$, $k_5k_6 - \xi_5^m\xi_6^m > 0$, $k_5k_8 - \xi_5^m\xi_8^m > 0$, $k_7k_8 - \xi_7^m\xi_8^m > 0$, $k_{16}k_{17} - \xi_6^f\xi_7^f > 0$, $k_{13}k_{14} - \xi_3^f\xi_4^f > 0$, $k_{15}k_{16} - \xi_5^f\xi_6^f > 0$, $k_{15}k_{18} - \xi_5^f\xi_8^f > 0$, and $k_{17}k_{18} - \xi_7^f\xi_8^f > 0$ (so that, $\mathcal{R}_m > 0$, $\mathcal{R}_f > 0$ and $\mathcal{R}_0 > 0$). Consequently, it follows from Theorem 2.7 that:

Lemma 6.2. *The DFE of the model* (6.3)*, given by* (6.6)*, is locally-asymptotically stable whenever* $\mathcal{R}_0 < 1$*, and unstable if* $\mathcal{R}_0 > 1$*.*

The threshold quantity ($\mathcal{R}_0$) has the same interpretation as given for the corresponding quantity for the model (5.5).

6.3.2 Existence of Endemic Equilibria

To determine the number of possible equilibrium solutions the model (6.3) can have, it is convenient to let

$$\mathcal{E}_1 = (S^{**}_{ml}, S^{**}_{mh}, E^{**}_{ml}, E^{**}_{mh}, H^{**}_{ml}, H^{**}_{mh}, Q^{**}_{ml}, Q^{**}_{mh}, S^{**}_{fl}, S^{**}_{fh}, E^{**}_{fl}, E^{**}_{fh}, H^{**}_{fl}, H^{**}_{fh}, Q^{**}_{fl}, Q^{**}_{fh}),$$

be any arbitrary equilibrium of the model. Furthermore, let

$$\begin{aligned} \lambda^{**}_m &= \frac{c_f \beta_m [H^{**}_{ml} + \zeta_m H^{**}_{mh} + \eta_m Q^{**}_{ml} + \zeta_m \eta_m Q^{**}_{mh}]}{N^{**}_m}, \\ \lambda^{**}_f &= \frac{c_m \beta_f [H^{**}_{fl} + \zeta_f H^{**}_{fh} + \eta_f Q^{**}_{fl} + \zeta_f \eta_f Q^{**}_{fh}]}{N^{**}_f}, \end{aligned} \tag{6.10}$$

be the associated forces of infection for males and females, respectively, at steady-state. To find conditions for the existence of equilibria of the model (6.3) for which HSV-2 infection is endemic in the population (i.e., the components of E^{**}_{ml}, E^{**}_{mh}, H^{**}_{ml}, H^{**}_{mh}, Q^{**}_{ml}, Q^{**}_{mh}, E^{**}_{fl}, E^{**}_{fh}, H^{**}_{fl}, H^{**}_{fh}, Q^{**}_{fl}, Q^{**}_{fh} are non-zero), the equations in (6.3) are solved in terms of the aforementioned forces of infection at steady-state.

Setting the right-hand sides of the model (6.3) to zero gives

$$\begin{aligned} S_{ml} &= \frac{\Pi_m (m_{10}\lambda_f + m_{11})}{m_{00}\lambda_f^2 + m_{01}\lambda_f + m_{02}}, \qquad S_{mh} = \frac{\Pi_m (m_{20}\lambda_f + m_{21})}{m_{00}\lambda_f^2 + m_{01}\lambda_f + m_{02}}, \\ E_{ml} &= \frac{\Pi_m \lambda_f (m_{30}\lambda_f + m_{31})}{(m_{00}\lambda_f^2 + m_{01}\lambda_f + m_{02})A_1}, \quad E_{mh} = \frac{\Pi_m \lambda_f (m_{40}\lambda_f + m_{41})}{(m_{00}\lambda_f^2 + m_{01}\lambda_f + m_{02})A_1}, \\ H_{ml} &= \frac{\Pi_m \sigma_m \lambda_f (m_{50}\lambda_f + m_{51})}{(m_{00}\lambda_f^2 + m_{01}\lambda_f + m_{02})A}, \quad H_{mh} = \frac{\Pi_m \sigma_m \lambda_f (m_{60}\lambda_f + m_{61})}{(m_{00}\lambda_f^2 + m_{01}\lambda_f + m_{02})A}, \\ Q_{ml} &= \frac{\Pi_m \sigma_m \lambda_f (m_{70}\lambda_f + m_{71})}{(m_{00}\lambda_f^2 + m_{01}\lambda_f + m_{02})A}, \quad Q_{mh} = \frac{\Pi_m \sigma_m \lambda_f (m_{80}\lambda_f + m_{81})}{(m_{00}\lambda_f^2 + m_{01}\lambda_f + m_{02})A}, \end{aligned} \tag{6.11}$$

$$S_{fl} = \frac{\Pi_f(n_{10}\lambda_m + n_{11})}{n_{00}\lambda_m^2 + n_{01}\lambda_m + n_{02}}, \qquad S_{fh} = \frac{\Pi_f(n_{20}\lambda_m + n_{21})}{n_{00}\lambda_m^2 + n_{01}\lambda_m + n_{02}},$$

$$E_{fl} = \frac{\Pi_f\lambda_m(n_{30}\lambda_m + n_{31})}{(n_{00}\lambda_m^2 + n_{01}\lambda_m + n_{02})B_1}, \quad E_{fh} = \frac{\Pi_f\lambda_m(n_{40}\lambda_m + n_{41})}{(n_{00}\lambda_m^2 + n_{01}\lambda_m + n_{02})B_1},$$

$$H_{fl} = \frac{\Pi_f\sigma_f\lambda_m(n_{50}\lambda_m + n_{51})}{(n_{00}\lambda_m^2 + n_{01}\lambda_m + n_{02})B}, \quad H_{fh} = \frac{\Pi_f\sigma_f\lambda_m(n_{60}\lambda_m + n_{61})}{(n_{00}\lambda_m^2 + n_{01}\lambda_m + n_{02})B},$$

$$Q_{fl} = \frac{\Pi_f\sigma_f\lambda_m(n_{70}\lambda_m + n_{71})}{(n_{00}\lambda_m^2 + n_{01}\lambda_m + n_{02})B}, \quad Q_{fh} = \frac{\Pi_f\sigma_f\lambda_m(n_{80}\lambda_m + n_{81})}{(n_{00}\lambda_m^2 + n_{01}\lambda_m + n_{02})B},$$

where,

$A_1 = [(k_3k_4 - \xi_3^m\xi_4^m) + \sigma_m(\sigma_m + k_3 + k_4)]$ and $B_1 = [(k_{13}k_{14} - \xi_3^f\xi_4^f) + \sigma_f(\sigma_f + k_{13} + k_{14})]$,

with $m_{ij} > 0$ and $n_{ij} > 0$ (but not reported here since their expressions are too lengthy).

Substituting (6.11) into the expressions for λ_m^{**} and λ_f^{**} in (6.10) gives:

$$\lambda_m^{**} = \frac{A_1\sigma_m\beta_m c_f(p_{11}\lambda_f + p_{12})\lambda_f}{p_{13}\lambda_f^2 + p_{14}\lambda_f + p_{15}} \text{ and } \lambda_f^{**} = \frac{B_1\sigma_f\beta_f c_m(p_{21}\lambda_m + p_{22})\lambda_m}{p_{23}\lambda_m^2 + p_{24}\lambda_m + p_{25}}, \qquad (6.12)$$

where,

$$
\begin{aligned}
p_{11} &= (m_{50} + \zeta_m m_{60} + \eta_m q_m m_{70} + \zeta_m \eta_m q_m m_{80}), \;\; p_{12} = m_{51} + \zeta_m m_{61} + \eta_m q_m m_{71} \\
&+ \zeta_m \eta_m q_m m_{81}, \\
p_{13} &= Am_{30} + Am_{40} + \sigma_m A_1 m_{50} + \sigma_m A_1 m_{60} + \sigma_m q_m A_1 m_{70} + \sigma_m q_m A_1 m_{80}, \\
p_{14} &= A_1 Am_{10} + A_1 Am_{20} + Am_{31} + Am_{41} + \sigma_m A_1 m_{51} + \sigma_m A_1 m_{61} + \sigma_m q_m A_1 m_{71} \\
&+ \sigma_m q_m A_1 m_{81}, \\
p_{15} &= A_1 A(m_{11} + m_{21}), \;\; p_{25} = B_1 B(n_{11} + n_{21}), \\
p_{21} &= (n_{50} + \zeta_f n_{60} + \eta_f q_f n_{70} + \zeta_f \eta_f q_f n_{80}), \;\; p_{22} = n_{51} + \zeta_f n_{61} + \eta_f q_f n_{71} + \zeta_f \eta_f q_f n_{81} \\
p_{23} &= Bn_{30} + Bn_{40} + \sigma_f B_1 n_{50} + \sigma_f B_1 n_{60} + \sigma_f q_f B_1 n_{70} + \sigma_f q_f B_1 n_{80}, \\
p_{24} &= B_1 Bn_{10} + B_1 Bn_{20} + Bn_{31} + Bn_{41} + \sigma_f B_1 n_{51} + \sigma_f B_1 n_{61} + \sigma_f q_f B_1 n_{71} \\
&+ \sigma_f q_f B_1 n_{81},
\end{aligned}
$$

so that the non-zero equilibria of the model (6.3) satisfy:

$$\sum_{i=0}^{4} a_i \, (\lambda_m^{**})^{4-i} = 0. \tag{6.13}$$

The coefficient $a_0 > 0$ (but is not reported here, because its expression is too lengthy). Furthermore, a_i $(i = 1, \cdots, 3)$ may be positive or negative (the coefficients, a_i with $i = 1, \cdots, 3$, are also not reported here for the same reason), and

$$a_4 = A_1^2 A^2 B_1 B(m_{11} + m_{21})^2 (n_{11} + n_{21})(1 - \mathcal{R}_0^2). \tag{6.14}$$

It follows from (6.14) that $a_4 > 0$ whenever $\mathcal{R}_0 < 1$. Thus, the number of possible real roots the polynomial (6.13) can have depends on the sign of a_i $(i = 1, \cdots, 3)$. Using the Descartes Rule of Signs on the equation (6.13), the various possibilities for the roots are tabulated in Table 6.2.

Table 6.2: Number of possible positive real roots of (6.13).

Cases	a_0	a_1	a_2	a_3	a_4	Number of sign changes	Number of possible positive real roots (endemic equilibrium)
1	+	+	+	+	+ (for $\mathcal{R}_0 < 1$)	0	0
2	+	+	+	-	+ (for $\mathcal{R}_0 < 1$)	2	0,2
3	+	+	-	-	+ (for $\mathcal{R}_0 < 1$)	2	0,2
4	+	+	-	+	+ (for $\mathcal{R}_0 < 1$)	2	0,2
5	+	-	-	-	+ (for $\mathcal{R}_0 < 1$)	2	0,2
6	+	-	+	+	+ (for $\mathcal{R}_0 < 1$)	2	0,2
7	+	-	+	-	+ (for $\mathcal{R}_0 < 1$)	4	0,2,4
8	+	-	-	+	+ (for $\mathcal{R}_0 < 1$)	2	0,2
9	+	+	+	+	- (for $\mathcal{R}_0 > 1$)	1	1
10	+	+	+	-	- (for $\mathcal{R}_0 > 1$)	1	1
11	+	+	-	-	- (for $\mathcal{R}_0 > 1$)	1	1
12	+	+	-	+	- (for $\mathcal{R}_0 > 1$)	3	1,3
13	+	-	-	-	- (for $\mathcal{R}_0 > 1$)	1	1
14	+	-	+	+	- (for $\mathcal{R}_0 > 1$)	3	1,3
15	+	-	+	-	- (for $\mathcal{R}_0 > 1$)	3	1,3
16	+	-	-	+	- (for $\mathcal{R}_0 > 1$)	3	1,3

The following result is established (the endemic equilibria of the model (6.3) are obtained by substituting the positive solutions of (6.13) into (6.3)) from the various possibilities enumerated in Table 6.2:

Theorem 6.2. *The model* (6.3) *could have no, two or four endemic equilibria if* $\mathcal{R}_0 < 1$, *and at least one endemic equilibrium whenever* $\mathcal{R}_0 > 1$.

The existence of multiple endemic equilibria when $\mathcal{R}_0 < 1$ (in Theorem 6.2) suggests the possibility of backward bifurcation in the model (6.3), when the associated reproduction number ($\mathcal{R}_0$) is less than unity. This is explored below, using centre manifold theory [13]. Let, for mathematical convenience,

$$S_{ml} = x_1, S_{mh} = x_2, E_{ml} = x_3, E_{mh} = x_4, H_{ml} = x_5, H_{mh} = x_6, Q_{ml} = x_7, Q_{mh} = x_8,$$
$$S_{fl} = x_9, S_{fh} = x_{10}, E_{fl} = x_{11}, E_{fh} = x_{12}, H_{fl} = x_{13}, H_{fh} = x_{14}, Q_{fl} = x_{15}, Q_{fh} = x_{16}.$$

Thus,

$$N_m = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8, \quad N_f = x_9 + x_{10} + x_{11} + x_{12} + x_{13} + x_{14} + x_{15} + x_{16}.$$

Further, by using vector notation $X = (x_1, x_2, \cdots, x_{16})^T$, and $\mathcal{F} = (f_1, f_2, \cdots, f_{16})^T$, the

model (6.3) can be written in the form $\frac{dX}{dt} = \mathcal{F}X$, as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} &= (1-p_m)\Pi_m + \xi_2^m x_2 - \lambda_f(t)x_1 - (\xi_1^m + \mu)x_1,\\
\frac{dx_2}{dt} &= p_m\Pi_m + \xi_1^m x_1 - \theta_m\lambda_f(t)x_2 - (\xi_2^m + \mu)x_2,\\
\frac{dx_3}{dt} &= \lambda_f(t)x_1 + \xi_4^m x_4 - (\xi_3^m + \sigma_m + \mu)x_3,\\
\frac{dx_4}{dt} &= \theta_m\lambda_f(t)x_2 + \xi_3^m x_3 - (\xi_4^m + \sigma_m + \mu)x_4,\\
\frac{dx_5}{dt} &= \sigma_m x_3 + r_{ml}x_7 + \xi_6^m x_6 - (\xi_5^m + q_m + \mu + \delta_1)x_5,\\
\frac{dx_6}{dt} &= \sigma_m x_4 + r_{mh}x_8 + \xi_5^m x_5 - (\xi_6^m + q_m + \mu + \delta_2)x_6,\\
\frac{dx_7}{dt} &= q_m x_5 + \xi_8^m x_8 - (\xi_7^m + r_{ml} + \mu + \delta_3)x_7,\\
\frac{dx_8}{dt} &= q_m x_6 + \xi_7^m x_7 - (\xi_8^m + r_{mh} + \mu + \delta_4)x_8,\\
\frac{dx_9}{dt} &= (1-p_f)\Pi_f + \xi_2^f x_{10} - \lambda_m(t)x_9 - (\xi_1^f + \mu)x_9,\\
\frac{dx_{10}}{dt} &= p_f\Pi_f + \xi_1^f x_9 - \theta_f\lambda_m(t)x_{10} - (\xi_2^f + \mu)x_{10},\\
\frac{dx_{11}}{dt} &= \lambda_m(t)x_9 + \xi_4^f x_{12} - (\xi_3^f + \sigma_f + \mu)x_{11},\\
\frac{dx_{12}}{dt} &= \theta_f\lambda_m(t)x_{10} + \xi_3^f x_{11} - (\xi_4^f + \sigma_f + \mu)x_{12},\\
\frac{dx_{13}}{dt} &= \sigma_f x_{11} + r_{fl}x_{15} + \xi_6^f x_{14} - (\xi_5^f + q_f + \mu + \delta_1)x_{13},\\
\frac{dx_{14}}{dt} &= \sigma_f x_{12} + r_{fh}x_{16} + \xi_5^f x_{13} - (\xi_6^f + q_f + \mu + \delta_2)x_{14},\\
\frac{dx_{15}}{dt} &= q_f x_{13} + \xi_8^f x_{16} - (\xi_7^f + r_{fl} + \mu + \delta_3)x_{15},\\
\frac{dx_{16}}{dt} &= q_f x_{14} + \xi_7^f x_{15} - (\xi_8^f + r_{fh} + \mu + \delta_4)x_{16},
\end{aligned}
\tag{6.15}
$$

with,

$$\begin{aligned}
\lambda_f &= \lambda_{fl} + \lambda_{fh}, \;\; \lambda_m = \lambda_{ml} + \lambda_{mh}, \\
\lambda_{fl} &= \frac{c_f \beta_f (x_{13} + \eta_f x_{15})}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8}, \\
\lambda_{fh} &= \frac{\zeta_f c_f \beta_f (x_{14} + \eta_f x_{16})}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8}, \\
\lambda_{ml} &= \frac{c_m \beta_m (x_5 + \eta_m x_7)}{x_9 + x_{10} + x_{11} + x_{12} + x_{13} + x_{14} + x_{15} + x_{16}}, \\
\lambda_{mh} &= \frac{\zeta_m c_m \beta_m (x_6 + \eta_f x_8)}{x_9 + x_{10} + x_{11} + x_{12} + x_{13} + x_{14} + x_{15} + x_{16}}.
\end{aligned}$$

The Jacobian of the system (6.15), at the associated DFE ($\mathcal{E}_0$), is given by

$$J(\mathcal{E}_0) = \begin{bmatrix} J_1 & J_2 \\ J_3 & J_4 \end{bmatrix},$$

where,

$$J_1 = \begin{bmatrix}
-k_1 & \xi_2^m & 0 & 0 & 0 & 0 & 0 & 0 \\
\xi_1^m & -k_2 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -k_3 & \xi_4^m & 0 & 0 & 0 & 0 \\
0 & 0 & \xi_3^m & -k_4 & 0 & 0 & 0 & 0 \\
0 & 0 & \sigma_m & 0 & -k_5 & \xi_6^m & r_{ml} & 0 \\
0 & 0 & 0 & \sigma_m & \xi_5^m & -k_6 & 0 & r_{mh} \\
0 & 0 & 0 & 0 & q_m & 0 & -k_7 & \xi_8^m \\
0 & 0 & 0 & 0 & 0 & q_m & \xi_7^m & -k_8
\end{bmatrix},$$

$$J_2 = \begin{bmatrix} 0 & 0 & 0 & 0 & -\Phi_1 & -\zeta_f\Phi_1 & -\nu_f\Phi_1 & -\zeta_f\nu_f\Phi_1 \\ 0 & 0 & 0 & 0 & -\Phi_2 & -\zeta_f\Phi_2 & -\nu_f\Phi_2 & -\zeta_f\nu_f\Phi_2 \\ 0 & 0 & 0 & 0 & \Phi_1 & \zeta_f\Phi_1 & \nu_f\Phi_1 & \zeta_f\nu_f\Phi_1 \\ 0 & 0 & 0 & 0 & \Phi_2 & \zeta_f\Phi_2 & \nu_f\Phi_2 & \zeta_f\nu_f\Phi_2 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$J_3 = \begin{bmatrix} 0 & 0 & 0 & 0 & -\Phi_3 & -\zeta_m\Phi_3 & -\nu_m\Phi_3 & -\zeta_m\nu_m\Phi_3 \\ 0 & 0 & 0 & 0 & -\Phi_4 & -\zeta_m\Phi_4 & -\nu_m\Phi_4 & -\zeta_m\nu_m\Phi_4 \\ 0 & 0 & 0 & 0 & \Phi_3 & \zeta_m\Phi_3 & \nu_m\Phi_3 & \zeta_m\nu_m\Phi_3 \\ 0 & 0 & 0 & 0 & \Phi_4 & \zeta_m\Phi_4 & \nu_m\Phi_4 & \zeta_m\nu_m\Phi_4 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$J_4 = \begin{bmatrix} -k_{11} & \xi_2^f & 0 & 0 & 0 & 0 & 0 & 0 \\ \xi_1^f & -k_{12} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -k_{13} & \xi_4^f & 0 & 0 & 0 & 0 \\ 0 & 0 & \xi_3^f & -k_{14} & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma_f & 0 & -k_{15} & \xi_6^f & r_{fl} & 0 \\ 0 & 0 & 0 & \sigma_f & \xi_5^f & -k_{16} & 0 & r_{fh} \\ 0 & 0 & 0 & 0 & q_f & 0 & -k_{17} & \xi_8^f \\ 0 & 0 & 0 & 0 & 0 & q_f & \xi_7^f & -k_{18} \end{bmatrix},$$

with,

$$\Phi_1 = \frac{c_f\beta_f x_1^*}{x_1^*+x_2^*},\ \Phi_2 = \frac{\theta_m c_f\beta_f x_2^*}{x_1^*+x_2^*},\ \Phi_3 = \frac{c_m\beta_m x_9^*}{x_9^*+x_{10}^*},\ \Phi_3 = \frac{\theta_m c_m\beta_m x_9^*}{x_9^*+x_{10}^*},$$

and, $x_1^* = S_{ml}^*,\ x_2^* = S_{mh}^*,\ x_9^* = S_{fl}^*, x_{10}^* = S_{fh}^*$ are as defined before. It can be shown, from $J(\mathcal{E}_0)$, that (as in Section 6.3.1):

$$\mathcal{R}_0 = \sqrt{c_f c_m \beta_f \beta_m \sigma_f \sigma_m Z_1 Z_2}, \tag{6.16}$$

where,

$$Z_1 = \frac{x_1^*(A_{11}+A_{12}) + \theta_m x_2^*(A_{21}+A_{22})}{(x_1^*+x_2^*)A},$$

$$Z_2 = \frac{x_9^*(B_{11}+B_{12}) + \theta_f x_{10}^*(B_{21}+B_{22})}{(x_9^*+x_{10}^*)B},$$

with, $A_{11}, A_{12}, A_{21}, A_{22}, B_{11}, B_{12}, B_{21}, B_{22}, A$ and B as defined in Section 6.3.

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

$$\beta_m = \beta^* = \frac{1}{c_f c_m \beta_f \sigma_f \sigma_m Z_1 Z_2}. \tag{6.17}$$

It should be noted that the transformed system (6.15), with $\beta_m = \beta^*$, has a hyperbolic equilibrium point (i.e., the linearized system has a simple eigenvalue with zero real part). Hence, the centre manifold theory [13] can be used to analyse the dynamics of (6.15) near $\beta_m = \beta^*$. In particular, to apply Theorem 2.3, the following computations are necessary.

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

It can be shown that the Jacobian of (6.15) at $\beta_m = \beta^*$ (denoted by J_{β^*}) has a left eigenvector

(associated with the zero eigenvalue), given by

$$\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12}, v_{13}, v_{14}, v_{15}, v_{16}],$$

where,

$$v_1 = 0, \;\; v_2 = 0, \;\; v_3 = \frac{\sigma_m(\xi_3^m v_6 + k_4 v_5)}{k_3 k_4 - \xi_3^m \xi_4^m}, \;\; v_4 = \frac{\sigma_m(\xi_4^m v_5 + k_3 v_6)}{k_3 k_4 - \xi_3^m \xi_4^m}, \;\; v_5 = \frac{\xi_5^m a_2 + k_6 a_1}{k_5 k_6 - \xi_5^m \xi_6^m},$$

$$v_6 = \frac{\xi_6^m a_1 + k_5 a_2}{k_5 k_6 - \xi_5^m \xi_6^m}, \;\; v_7 = \frac{\xi_7^m a_4 + k_8 a_3}{k_7 k_8 - \xi_7^m \xi_8^m}, \;\; v_8 = \frac{\xi_8^m a_3 + k_7 a_4}{k_7 k_8 - \xi_7^m \xi_8^m}, \;\; v_9 = 0, \;\; v_{10} = 0,$$

$$v_{11} = \frac{\sigma_f(\xi_3^f v_{14} + k_{14} v_{13})}{k_{13} k_{14} - \xi_3^f \xi_4^f}, \;\; v_{12} = \frac{\sigma_f(\xi_4^f v_{13} + k_{13} v_{14})}{k_{13} k_{14} - \xi_3^f \xi_4^f}, \;\; v_{13} = \frac{\xi_5^f a_6 + k_{16} a_5}{k_{15} k_{16} - \xi_5^f \xi_6^f},$$

$$v_{14} = \frac{\xi_6^f a_5 + k_{15} a_6}{k_{15} k_{16} - \xi_5^f \xi_6^f}, \;\; v_{15} = \frac{\xi_7^f a_8 + k_{18} a_7}{k_{17} k_{18} - \xi_7^f \xi_8^f}, \;\; v_{16} = \frac{\xi_8^f a_7 + k_{17} a_8}{k_{17} k_{18} - \xi_7^f \xi_8^f},$$

with,

$$\begin{aligned}
a_1 &= q_m v_7 + \Phi_3 v_{11} + \Phi_4 v_{12}, \;\; a_2 = q_m v_8 + \zeta_m \Phi_3 v_{11} + \zeta_m \Phi_4 v_{12}, \\
a_3 &= r_{ml} v_5 + \nu_m \Phi_3 v_{11} + \nu_m \Phi_4 v_{12}, \;\; a_4 = r_{mh} v_6 + \zeta_m \nu_m \Phi_3 v_{11} + \zeta_m \nu_m \Phi_4 v_{12}, \\
a_5 &= \Phi_1 v_3 + \Phi_2 v_4 + q_f v_{15}, \;\; a_6 = \zeta_f \Phi_1 v_3 + \zeta_f \Phi_2 v_4 + q_f v_{16}, \\
a_7 &= \nu_f \Phi_1 v_3 + \nu_f \Phi_2 v_4 + r_{fl} v_{13}, \;\; a_8 = \zeta_f \nu_f \Phi_1 v_3 + \zeta_f \nu_f \Phi_2 v_4 + r_{fh} v_{14}.
\end{aligned}$$

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

$$\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}, w_{11}, w_{12}, w_{13}, w_{14}, w_{15}, w_{16}]^T,$$

where,

$$w_1 = -\frac{k_2b_1+b_2\xi_2^m}{k_1k_2-\xi_1^m\xi_2^m},\ \ w_2=-\frac{k_1b_2+b_1\xi_1^m}{k_1k_2-\xi_1^m\xi_2^m},\ \ w_3=\frac{k_4b_1+b_2\xi_4^m}{k_3k_4-\xi_3^m\xi_4^m},\ \ w_4=\frac{k_3b_2+b_1\xi_3^m}{k_3k_4-\xi_3^m\xi_4^m},$$

$$w_5 = \frac{k_6b_3+b_4\xi_6^m}{k_5k_6-\xi_5^m\xi_6^m},\ \ w_6=\frac{k_5b_4+b_3\xi_5^m}{k_5k_6-\xi_5^m\xi_6^m},\ \ w_7=\frac{k_8b_5+b_6\xi_8^m}{k_7k_8-\xi_7^m\xi_8^m},\ \ w_8=\frac{k_7b_6+b_5\xi_7^m}{k_7k_8-\xi_7^m\xi_8^m},$$

$$w_9 = -\frac{k_{12}b_7+b_8\xi_2^f}{k_{11}k_{12}-\xi_1^f\xi_2^f},\ \ w_{10}=-\frac{k_{11}b_8+b_7\xi_1^f}{k_{11}k_{12}-\xi_1^f\xi_2^f},\ \ w_{11}=\frac{k_{14}b_7+b_8\xi_4^f}{k_{13}k_{14}-\xi_3^f\xi_4^f},\ \ w_{12}=\frac{k_{13}b_8+b_7\xi_3^f}{k_{13}k_{14}-\xi_3^f\xi_4^f},$$

$$w_{13} = \frac{k_{16}b_9+b_{10}\xi_6^f}{k_{15}k_{16}-\xi_5^f\xi_6^f},\ \ w_{14}=\frac{k_{15}b_{10}+b_9\xi_5^f}{k_{15}k_{16}-\xi_5^f\xi_6^f},\ \ w_{15}=\frac{k_{18}b_{11}+b_{12}\xi_8^f}{k_{17}k_{18}-\xi_7^f\xi_8^f},\ \ w_{16}=\frac{k_{17}b_{12}+b_{11}\xi_7^f}{k_{17}k_{18}-\xi_7^f\xi_8^f},$$

with,

$$b_1 = \Phi_1w_{13}+\zeta_f\Phi_1w_{14}+\nu_f\Phi_1w_{15}+\zeta_f\nu_f\Phi_1w_{16},\ \ b_2=\Phi_2w_{13}+\zeta_f\Phi_2w_{14}+\nu_f\Phi_2w_{15}+\zeta_f\nu_f\Phi_2w_{16},$$

$$b_3 = \sigma_mw_3+r_{ml}w_7, b_4=\sigma_mw_4+r_{mh}w_8,\ \ b_5=q_mw_5,\ \ b_6=q_mw_6,$$

$$b_7 = \Phi_3w_5+\zeta_m\Phi_3w_6+\nu_m\Phi_3w_7+\zeta_m\nu_m\Phi_3w_8,\ \ b_8=\Phi_4w_5+\zeta_m\Phi_4w_6+\nu_m\Phi_4w_7+\zeta_m\nu_m\Phi_4w_8,$$

$$b_9 = \sigma_fw_{11}+r_{fl}w_{15},\ \ b_{10}=\sigma_fw_{12}+r_{fh}w_{16},\ \ b_{11}=q_fw_{13},\ \ b_{12}=q_fw_{14}.$$

It should be mentioned that all the eigenvectors ($\mathbf{v}$ and $\mathbf{w}$, with the exception of w_1, w_2, w_9 and w_{10}) are non-negative (see Section 6.3.1).

Computation of bifurcation coefficients a and b

By computing the non-zero partial derivatives of $\mathcal{F}$ at the DFE ($\mathcal{E}_0$), it can be shown, after some algebraic manipulations, that the associated backward bifurcation coefficient, a [19], is

given by:

$$
\begin{aligned}
a &= \sum_{k,i,j=1}^{16} v_k w_i w_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j}, \\
&= \frac{1}{(x_1+x_2)^2}\Big\{2c_f\beta_f(w_{13}+w_{14}\zeta_f+w_{15}\nu_f+w_{16}\zeta_f\nu_f) \\
&\big[(v_3w_1-v_4w_7\theta_m-v_4w_8\theta_m-v_4w_4\theta_m-v_4w_1\theta_m-v_4w_6\theta_m-v_4w_3\theta_m-v_4w_5\theta_m)x_2 \\
&+(-v_3w_4-v_3w_6-v_3w_7-v_3w_8-v_3w_5+v_4w_2\theta_m-v_3w_2-v_3w_3)x_1\big]\Big\} \\
&-\frac{1}{(x_9+x_{10})^2}\Big\{2c_m\beta_m(w_6\zeta_m+w_7\nu_m+w_8\zeta_m\nu_m+w_5) \\
&\big[(v_{12}w_{12}\theta_f+v_{12}w_{13}\theta_f+v_{12}w_{14}\theta_f-v_{11}w_9+v_{12}w_9\theta_f+v_{12}w_{15}\theta_f+v_{12}w_{16}\theta_f+v_{12}w_{11}\theta_f)x_{10} \\
&+(v_{11}w_{10}+v_{11}w_{14}+v_{11}w_{15}+v_{11}w_{11}+v_{11}w_{13}+v_{11}w_{16}-v_{12}w_{10}\theta_f+v_{11}w_{12})x_9\big]\Big\}.
\end{aligned}
\tag{6.18}
$$

Furthermore, it can be shown that the bifurcation coefficient, b [19], is given by:

$$
b = \sum_{i=1}^{16} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*} = \frac{1}{x_9+x_{10}} c_m(w_5+w_6\zeta_m+w_7\nu_m+w_8\zeta_m\nu_m)(v_{11}x_9+v_{12}\theta_f x_{10}) > 0.
$$

Since the coefficient b is always positive, it follows from Theorem 2.3 that the system (6.15) will undergo backward bifurcation if $a > 0$. This result is summarized below.

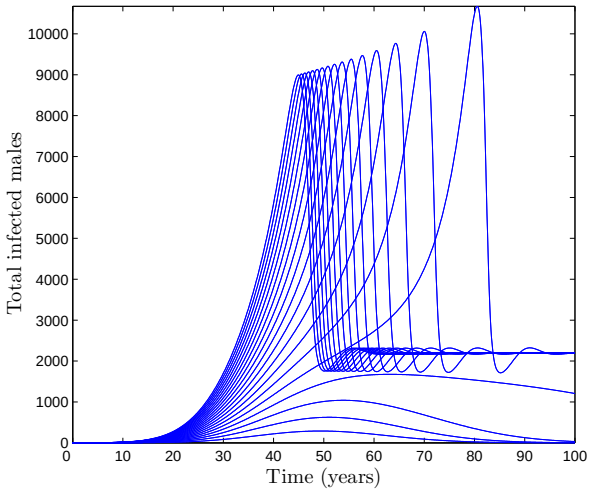
Theorem 6.3. *The transformed model* (6.15)*, or equivalently* (6.3)*, exhibits backward bifurcation at* $\mathcal{R}_0 = 1$ *whenever the bifurcation coefficient,* a*, given in* (6.18)*, is positive.*

The result of Theorem 6.3 is illustrated numerically by simulating the model (6.3) with the following set of parameter values: $\mu = \frac{1}{10000}, \eta_m = 5, \eta_f = 5, \Pi_m = 1000, \Pi_f = 1000, \beta_m = 0.0265, \beta_f = 0.02, \delta_1 = 0, \delta_2 = 10, \sigma_m = 1, \sigma_f = 1, q_m = 1, q_f = 1, r_{mh} = 1, r_{fh} = 1, r_{ml} = 1, r_{fl} = 1, \xi_1^m = 0.001, xi_2^m = 0.001, \xi_3^m = 0.001, \xi_4^m = 10, \xi_5^m = 10, \xi_6^m = 10, \xi_7^m = 10, \xi_8^m = 10, \xi_1^f = 0.001, \xi_2^f = 0.001, \xi_3^f = 0.001, \xi_4^f = 10, \xi_5^f = 10, \xi_6^f = 10, \xi_7^f = 10, \xi_8^f = 10, p_m = 0.99, p_f = 0.99, \theta_m = 2, \theta_f = 2, \zeta_m = 5.1, \zeta_f = 5.1, c_m = 5, c_f = \frac{c_m N_m(t)}{N_f(t)}$ (so that, $\mathcal{R}_0 = 0.91$). The simulations show that, for the case when $\mathcal{R}_0 < 1$, the profiles can converge to either the DFE or and an endemic equilibrium point, depending on the initial sizes of the sub-populations of the model (owing to the phenomenon of backward bifurcation). It is

worth stating that like in the simulation of the vaccination model (4.27), the aforementioned parameter values are chosen only to illustrate the backward bifurcation phenomenon of model (6.3), and may not all be realistic epidemiologically.

Figure 6.1A shows convergence to the DFE and the EEP for the total infected male population when $\mathcal{R}_0 < 1$ (it should be mentioned that the simulations have to be run for a long period of time in order for the backward bifurcation phenomenon to be clearly captured). A similar plot, for the total infected female population, is depicted in Figure 6.1B. The epidemiological consequence of this result is that the effective control of HSV-2 in a population (when $\mathcal{R}_0 < 1$) is dependent on the initial sizes of the sub-populations of the model (the disease would persist if the number is high, and can be eliminated otherwise).

(A)



(B)

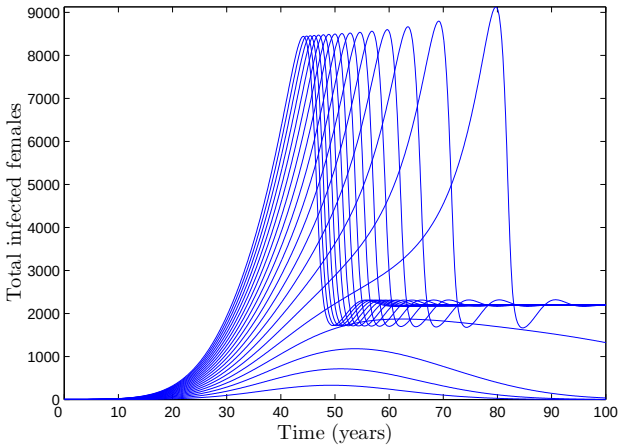


Figure 6.1: Simulations of the model (6.3) showing the total number of infected (A) males and (B) females as a function of time, using various initial conditions. Parameter values used are: $\mu = \frac{1}{10000}, \eta_m = 5, \eta_f = 5, \Pi_m = 1000, \Pi_f = 1000, \beta_m = 0.0265, \beta_f = 0.02, \delta_1 = 0, \delta_2 = 10, \sigma_m = 1, \sigma_f = 1, q_m = 1, q_f = 1, r_{mh} = 1, r_{fh} = 1, r_{ml} = 1, r_{fl} = 1, \xi_1^m = 0.001, xi_2^m = 0.001, \xi_3^m = 0.001, \xi_4^m = 10, \xi_5^m = 10, \xi_6^m = 10, \xi_7^m = 10, \xi_8^m = 10, \xi_1^f = 0.001, \xi_2^f = 0.001, \xi_3^f = 0.001, \xi_4^f = 10, \xi_5^f = 10, \xi_6^f = 10, \xi_7^f = 10, \xi_8^f = 10, p_m = 0.99, p_f = 0.99, \theta_m = 2, \theta_f = 2, \zeta_m = 5.1, \zeta_f = 5.1, c_m = 5$ and $c_f = \frac{c_m N_m(t)}{N_f(t)}$ (so that, $\mathcal{R}_0 = 0.91$).

It should be recalled that the equivalent two-group HSV-2 model (5.5), which was not

stratified according to risk of acquiring or transmitting infection, does not exhibit backward bifurcation. Thus, the analyses in this chapter shows that adding risk structure to the model (5.5) causes a new dynamical feature (backward bifurcation) in the transmission dynamics of HSV-2 in a population. It is instructive, therefore, to determine the "cause" or "causes" of the backward bifurcation property of the risk-structured model (6.3). This is considered below.

6.4 Effect of Risk of Susceptibility: Reduced Model

The risk-structured model (6.3) is considered for the case where the susceptible individuals are not stratified according to their risk of acquiring HSV-2 infection (that is, every susceptible male or female is equally likely to be infected as every other susceptible male or female, respectively). It should be mentioned that the exposed and infected classes (E, H and Q) are still stratified according to their risk (low or high) of transmitting HSV-2 infection.

Let $S_m(t)$ and $S_f(t)$ represent the population of susceptible males and females at time t, respectively. Furthermore, Π_m (Π_f) represents the *per* capita recruitment of sexually-active males (females) into the population. Let ν_m (ν_f) represent the fraction of new infected males (females) who are in the low-risk category, and the remaining fraction, $1-\nu_m$ ($1-\nu_f$), is in the high-risk category. It follows that the rates of change of the susceptible male and female populations are given by

$$\frac{dS_m}{dt} = \Pi_m - \lambda_f(t)S_m(t) - \mu S_m(t) \text{ and } \frac{dS_f}{dt} = \Pi_f - \lambda_m(t)S_f(t) - \mu S_f(t), \tag{6.19}$$

where, $\lambda_m(t)$ and $\lambda_f(t)$ are as defined before. Combining the HSV-2 model (6.3) with (6.19), it follows that the reduced model for HSV-2 transmission dynamics, in the absence of risk structure in the susceptible populations, is given by

$$
\begin{aligned}
\frac{dS_m}{dt} &= \Pi_m - \lambda_f(t)S_m(t) - \mu S_m(t),\\
\frac{dE_{ml}}{dt} &= \nu_m\lambda_f(t)S_m(t) + \xi_4^m E_{mh}(t) - (\xi_3^m + \sigma_m + \mu)E_{ml}(t),\\
\frac{dE_{mh}}{dt} &= (1-\nu_m)\lambda_f(t)S_m(t) + \xi_3^m E_{ml}(t) - (\xi_4^m + \sigma_m + \mu)E_{mh}(t),\\
\frac{dH_{ml}}{dt} &= \sigma_m E_{ml}(t) + r_{ml}Q_{ml}(t) + \xi_6^m H_{mh}(t) - (\xi_5^m + q_m + \mu + \delta_1)H_{ml}(t),\\
\frac{dH_{mh}}{dt} &= \sigma_m E_{mh}(t) + r_{mh}Q_{mh}(t) + \xi_5^m H_{ml}(t) - (\xi_6^m + q_m + \mu + \delta_2)H_{mh}(t),\\
\frac{dQ_{ml}}{dt} &= q_m H_{ml}(t) + \xi_8^m Q_{mh}(t) - (\xi_7^m + r_{ml} + \mu + \delta_3)Q_{ml}(t),\\
\frac{dQ_{mh}}{dt} &= q_m H_{mh}(t) + \xi_7^m Q_{ml}(t) - (\xi_8^m + r_{mh} + \mu + \delta_4)Q_{mh}(t),\\
\frac{dS_f}{dt} &= \Pi_f - \lambda_m(t)S_f(t) - \mu S_f(t),\\
\frac{dE_{fl}}{dt} &= \nu_f\lambda_m(t)S_f(t) + \xi_4^f E_{fh}(t) - (\xi_3^f + \sigma_f + \mu)E_{fl}(t),\\
\frac{dE_{fh}}{dt} &= (1-\nu_f)\lambda_m(t)S_f(t) + \xi_3^f E_{fl}(t) - (\xi_4^f + \sigma_f + \mu)E_{fh}(t),\\
\frac{dH_{fl}}{dt} &= \sigma_f E_{fl}(t) + r_{fl}Q_{fl}(t) + \xi_6^f H_{fh}(t) - (\xi_5^f + q_f + \mu + \delta_1)H_{fl}(t),\\
\frac{dH_{fh}}{dt} &= \sigma_f E_{fh}(t) + r_{fh}Q_{fh}(t) + \xi_5^f H_{fl}(t) - (\xi_6^f + q_f + \mu + \delta_2)H_{fh}(t),\\
\frac{dQ_{fl}}{dt} &= q_f H_{fl}(t) + \xi_8^f Q_{fh}(t) - (\xi_7^f + r_{fl} + \mu + \delta_3)Q_{fl}(t),\\
\frac{dQ_{fh}}{dt} &= q_f H_{fh}(t) + \xi_7^f Q_{fl}(t) - (\xi_8^f + r_{fh} + \mu + \delta_4)Q_{fh}(t).
\end{aligned}
\tag{6.20}
$$

6.4.1 Basic Properties

As in Section 4.2.1, the following result can be proven for the model (6.20).

Theorem 6.4. *Denote* $x_{il}(t) = (E_{il}(t), H_{il}(t), Q_{il}(t))$ *and* $x_{ih}(t) = (E_{ih}(t), H_{ih}(t), Q_{ih}(t))$ *for* $i = m, f$. *Let the initial data* $(S_m(0), S_f(0), x_{ml}(0), x_{fl}(0), x_{mh}(0), x_{fh}(0)) > 0$. *Then the solutions* $(S_m(t), S_f(t), x_{ml}(t), x_{mh}(t), x_{fl}(t), x_{fh}(t))$ *of the reduced model* (6.20) *are positive*

for all $t > 0$. *Furthermore,*

$$\limsup_{t\to\infty} N_m(t) \leq \frac{\Pi_m}{\mu} \quad \text{and} \quad \limsup_{t\to\infty} N_f(t) \leq \frac{\Pi_f}{\mu}.$$

Consider the feasible region

$$\mathcal{D}_r = \mathcal{D}_{mr} \cup \mathcal{D}_{fr} \subset \mathbb{R}_+^7 \times \mathbb{R}_+^7,$$

with,

$$\begin{aligned}\mathcal{D}_{mr} &= \Bigg\{(S_m, E_{ml}, E_{mh}, H_{ml}, H_{mh}, Q_{ml}, Q_{mh}) \in \mathbb{R}_+^7 : \\ &\qquad S_m + E_{ml} + E_{mh} + H_{ml} + H_{mh} + Q_{ml} + Q_{mh} \leq \frac{\Pi_m}{\mu}\Bigg\},\end{aligned}$$

and,

$$\begin{aligned}\mathcal{D}_{fr} &= \Bigg\{(S_f, E_{fl}, E_{fh}, H_{fl}, H_{fh}, Q_{fl}, Q_{fh}) \in \mathbb{R}_+^7 : \\ &\qquad S_f + E_{fl} + E_{fh} + H_{fl} + H_{fh} + Q_{fl} + Q_{fh} \leq \frac{\Pi_f}{\mu}\Bigg\}.\end{aligned}$$

Using the same approach as in Section 4.2.1, it can be shown that the region $\mathcal{D}_r$ is positively-invariant for the model (6.20).

6.4.2 Existence and Stability of Equilibria

The DFE of the model (6.20) is given by

$$\begin{aligned}\mathcal{E}_2 = (S_m^*, E_{ml}^*, E_{mh}^*, H_{ml}^*, H_{mh}^*, Q_{ml}^*, Q_{mh}^*, S_{fl}^*, S_{fh}^*, E_{fl}^*, E_{fh}^*, H_{fl}^*, \\ H_{fh}^*, Q_{fl}^*, Q_{fh}^*) = \left(\frac{\Pi_m}{\mu}, 0, 0, 0, 0, 0, 0, \frac{\Pi_f}{\mu}, 0, 0, 0, 0, 0, 0\right).\end{aligned} \tag{6.21}$$

The next generation matrices, F_r and V, associated with the reduced model (6.20), are given, respectively, by

$$F_r = \begin{pmatrix} \mathbf{0}_{6\times 6} & F_{r1} \\ F_{r2} & \mathbf{0}_{6\times 6} \end{pmatrix},$$

where,

$$F_{r1} = \begin{pmatrix} (F_{r11})_{2\times 6} \\ \mathbf{0}_{4\times 6} \end{pmatrix}, \quad F_{r2} = \begin{pmatrix} (F_{r21})_{2\times 6} \\ \mathbf{0}_{4\times 6} \end{pmatrix},$$

and,

$$F_{r11} = \begin{pmatrix} 0 & 0 & \nu_m & \nu_m\zeta_f & \nu_m\eta_f & \nu_m\zeta_f\eta_f \\ 0 & 0 & (1-\nu_m) & (1-\nu_m)\zeta_f & (1-\nu_m)\eta_f & (1-\nu_m)\zeta_f\eta_f \end{pmatrix} c_f\beta_f,$$

$$F_{r21} = \begin{pmatrix} 0 & 0 & \nu_f & \nu_f\zeta_m & \nu_f\eta_m & \nu_f\zeta_m\eta_m \\ 0 & 0 & (1-\nu_f) & (1-\nu_f)\zeta_m & (1-\nu_f)\eta_m & (1-\nu_f)\zeta_m\eta_m \end{pmatrix} c_m\beta_m,$$

with the matrix V as defined in Section 6.3. Thus,

$$\mathcal{R}_r = \rho(F_r V^{-1}) = \sqrt{\mathcal{R}_{rm}\mathcal{R}_{rf}}, \tag{6.22}$$

where,

$$\begin{aligned} \mathcal{R}_{rm} &= \frac{c_m\beta_m\sigma_m}{A}[\nu_m A_{11} + (1-\nu_m)A_{21} + \nu_m A_{12} + (1-\nu_m)A_{22}], \\ \mathcal{R}_{rf} &= \frac{c_f\beta_f\sigma_f}{B}[\nu_f B_{11} + (1-\nu_f)B_{21} + \nu_f B_{12} + (1-\nu_f)B_{22}], \end{aligned} \tag{6.23}$$

with, $A_{11}, A_{12}, A_{21}, A_{22}, B_{11}, B_{12}, B_{21}, B_{22}, A$ and B as defined in Section 6.3. Thus, this result follows from Theorem 2.7.

Lemma 6.3. *The DFE of the reduced model* (6.20)*, given by* (6.21)*, is LAS whenever* $\mathcal{R}_r < 1$*, and unstable if* $\mathcal{R}_r > 1$*.*

It should be stated that the epidemiological thresholds, $\mathcal{R}_r$, $\mathcal{R}_{rm}$ and $\mathcal{R}_{rf}$, have similar definitions as $\mathcal{R}_0$, $\mathcal{R}_m$ and $\mathcal{R}_f$, respectively.

Theorem 6.5. *The reduced model* (6.20) *does not undergo backward bifurcation at* $\mathcal{R}_r = 1$*.*

The proof is given in Appendix F.

In other words, Theorem 6.5 shows that the absence of risk of susceptibility to HSV-2 infection (within the male and female populations) removes the backward bifurcation property of the risk-structured model (6.3) (eventhough infected individuals are stratified according to their risk of transmission of infection). This result is further emphasized by proving the global asymptotic stability property of the DFE ($\mathcal{E}_2$) of the reduced model (6.20) below.

Theorem 6.6. *The DFE of the reduced model* (6.20)*, given by* $\mathcal{E}_2$*, is GAS in* $\mathcal{D}_r$ *if* $\mathcal{R}_r < 1$*.*

Proof. The proof is based on using a comparison theorem (Theorem 2.6) [56]. Let,

$$Y = \Big(E_{ml}, E_{mh}, H_{ml}, H_{mh}, Q_{ml}, Q_{mh} E_{fl}, E_{fh}, H_{fl}, H_{fh}, Q_{fl}, Q_{fh}\Big),^T$$

so that the equations for the infected components of (6.20) can be re-written as:

$$\frac{dY}{dt} = (F_r - V - U)\, Y,$$

where the matrices F_r and V are as defined above, and the matrix U is given by

$$U \;=\; \begin{pmatrix} \mathbf{0}_{6\times 6} & U_1 \\ U_2 & \mathbf{0}_{6\times 6} \end{pmatrix},$$

with,

$$U_1 = \begin{pmatrix} (U_{11})_{2\times 6} \\ \mathbf{0}_{4\times 6} \end{pmatrix}, \quad U_2 = \begin{pmatrix} (U_{21})_{2\times 6} \\ \mathbf{4}_{6\times 6} \end{pmatrix},$$

$$U_{11} = \begin{pmatrix} 0 & 0 & \nu_m & \nu_m\zeta_f & \nu_m\eta_f & \nu_m\zeta_f\eta_f \\ 0 & 0 & (1-\nu_m) & (1-\nu_m)\zeta_f & (1-\nu_m)\eta_f & (1-\nu_m)\zeta_f\eta_f \\ & & & & & \end{pmatrix} c_f\beta_f\left(1-\frac{S_m}{N_m}\right),$$

and,

$$U_{21} = \begin{pmatrix} 0 & 0 & \nu_f & \nu_f\zeta_m & \nu_f\eta_m & \nu_f\zeta_m\eta_m \\ 0 & 0 & (1-\nu_f) & (1-\nu_f)\zeta_m & (1-\nu_f)\eta_m & (1-\nu_f)\zeta_m\eta_m \end{pmatrix} c_m\beta_m\left(1-\frac{S_f}{N_f}\right).$$

Since $S_m < N_m$ and $S_f < N_f$ (for all $t \geq 0$) in $\mathcal{D}_r$, it follows that the matrix U is non-negative. Thus,

$$\frac{dY}{dt} \leq (F_r - V)\, Y. \tag{6.24}$$

Furthermore, if $\mathcal{R}_r < 1$, then $\rho(F_r V^{-1}) < 1$ (from the local stability result given in Lemma 6.3, which is equivalent to $F_r - V$ having all its eigenvalues in the left-half plane [88]). It follows that the linearized differential inequality system (6.24) is stable whenever $\mathcal{R}_r < 1$. Consequently, by comparison theorem, it follows that

$$(E_{ml}, E_{mh}, H_{ml}, H_{mh}, Q_{ml}, Q_{mh}) \quad \rightarrow \quad (0,0,0,0,0,0),$$

and,

$$(E_{fl}, E_{fh}, H_{fl}, H_{fh}, Q_{fl}, Q_{fh}) \quad \rightarrow \quad (0,0,0,0,0,0).$$

Thus, for any $\epsilon > 0$ sufficiently small, there exists a $t_1 > 0$ such that if $t > t_1$, then

$$\begin{aligned} &E_{ml} < \epsilon,\ E_{mh} < \epsilon,\ H_{ml} < \epsilon,\ H_{mh} < \epsilon,\ Q_{ml} < \epsilon,\ Q_{mh} < \epsilon, \\ &E_{fl} < \epsilon,\ E_{fh} < \epsilon,\ H_{fl} < \epsilon,\ H_{fh} < \epsilon,\ Q_{fl} < \epsilon \text{ and } Q_{fh} < \epsilon. \end{aligned} \tag{6.25}$$

It follows from the equations for S_m and S_f in (6.20), noting (6.25), that

$$\frac{dS_m}{dt} = \Pi_m - \lambda_f(t)S_m(t) - \mu S_m(t) \geq \Pi_m - c_f\beta_f(1+\eta_f)(1+\zeta_f)\epsilon - \mu S_m(t),$$

$$\frac{dS_f}{dt} = \Pi_f - \lambda_m(t)S_f(t) - \mu S_f(t) \geq \Pi_f - c_m\beta_m(1+\eta_m)(1+\zeta_m)\epsilon - \mu S_m(t).$$

Thus, using comparison theorem,

$$\begin{aligned} \liminf_{t\to\infty} S_m(t) &\geq \frac{\Pi_m - c_f\beta_f(1+\eta_f)(1+\zeta_f)\epsilon}{\mu}, \\ \liminf_{t\to\infty} S_f(t) &\geq \frac{\Pi_f - c_m\beta_m(1+\eta_m)(1+\zeta_m)\epsilon}{\mu}. \end{aligned} \tag{6.26}$$

Since $\epsilon > 0$ is arbitrary, letting $\epsilon \to 0$ in (6.26) gives

$$\liminf_{t\to\infty} S_m(t) \geq \frac{\Pi_m}{\mu} \text{ and } \liminf_{t\to\infty} S_f(t) \geq \frac{\Pi_f}{\mu}.$$

Similarly, it can be shown that

$$\limsup_{t\to\infty} S_m(t) \leq \frac{\Pi_m}{\mu} \text{ and } \limsup_{t\to\infty} S_f(t) \leq \frac{\Pi_f}{\mu}.$$

Thus,

$$\lim_{t\to\infty} S_m(t) = \frac{\Pi_m}{\mu} \text{ and } \lim_{t\to\infty} S_f(t) = \frac{\Pi_f}{\mu},$$

and,

$$\lim_{t\to\infty}(S_m(t), E_{ml}(t), E_{mh}(t), H_{ml}(t), H_{mh}(t), Q_{ml}(t), Q_{mh}(t), S_f(t),$$
$$E_{fl}(t), E_{fh}(t), H_{fl}(t), H_{fh}(t), Q_{fl}(t), Q_{fh}(t))$$

$$= \left(\frac{\Pi_m}{\mu}, 0, 0, 0, 0, 0, 0, \frac{\Pi_f}{\mu}, 0, 0, 0, 0, 0, 0\right) = \mathcal{E}_2.$$

Hence, every solution to the equations of the reduced model (6.20), with initial conditions in $\mathcal{D}_r$, approaches the DFE, $\mathcal{E}_2$, as $t \to \infty$ whenever $\mathcal{R}_r < 1$. □

As in Section 6.3.2, the number of possible endemic equilibria of the reduced model (6.20) is explored by letting

$$\mathcal{E}_3 = (S_m^{**}, E_{ml}^{**}, E_{mh}^{**}, H_{ml}^{**}, H_{mh}^{**}, Q_{ml}^{**}, Q_{mh}^{**}, S_f^{**}, E_{fl}^{**}, E_{fh}^{**}, H_{fl}^{**}, H_{fh}^{**}, Q_{fl}^{**}, Q_{fh}^{**}),$$

be any arbitrary equilibrium of the reduced model (6.20). Further, let

$$\begin{aligned} \lambda_{rm}^{**} &= \frac{c_f\beta_m[H_{ml}^{**} + \zeta_m H_{mh}^{**} + \eta_m Q_{ml}^{**} + \zeta_m\eta_m Q_{mh}^{**}]}{N_m^{**}}, \\ \lambda_{rf}^{**} &= \frac{c_m\beta_f[H_{fl}^{**} + \zeta_f H_{fh}^{**} + \eta_f Q_{fl}^{**} + \zeta_f\eta_f Q_{fh}^{**}]}{N_f^{**}}, \end{aligned} \tag{6.27}$$

be the associated forces of infection for males and females, respectively, at steady-state. Setting the right-hand sides of the reduced model (6.20) to zero gives:

$$\begin{aligned} &S_m^{**} = \frac{\Pi_m}{\lambda_{rf}^{**} + k_1}, \quad E_{ml}^{**} = \frac{\Pi_m\lambda_{rf}^{**}m_1}{(\lambda_{rf}^{**} + k_1)m_{00}}, \quad E_{mh}^{**} = \frac{\Pi_m\lambda_{rf}^{**}m_2}{(\lambda_{rf}^{**} + k_1)m_{00}}, \quad H_{ml}^{**} = \frac{\Pi_m\sigma_m\lambda_{rf}^{**}m_3}{(\lambda_{rf}^{**} + k_1)m_{00}m_{01}}, \\ &H_{mh}^{**} = \frac{\Pi_m\sigma_m\lambda_{rf}^{**}m_4}{(\lambda_{rf}^{**} + k_1)m_{00}m_{01}}, \quad Q_{ml}^{**} = \frac{\Pi_m\sigma_m q_m\lambda_{rf}^{**}m_5}{(\lambda_{rf}^{**} + k_1)m_{00}m_{01}}, \quad Q_{mh}^{**} = \frac{\Pi_m\sigma_m q_m\lambda_{rf}^{**}m_6}{(\lambda_{rf}^{**} + k_1)m_{00}m_{01}}, \end{aligned} \tag{6.28}$$

$$\begin{aligned} &S_f^{**} = \frac{\Pi_f}{\lambda_{rm}^{**} + k_{11}}, \quad E_{fl}^{**} = \frac{\Pi_f\lambda_{rm}^{**}n_1}{(\lambda_{rm}^{**} + k_{11})n_{00}}, \quad E_{fh}^{**} = \frac{\Pi_f\lambda_{rm}^{**}n_2}{(\lambda_{rm}^{**} + k_{11})n_{00}}, \quad H_{fl}^{**} = \frac{\Pi_f\sigma_f\lambda_{rm}^{**}n_3}{(\lambda_{rm}^{**} + k_{11})n_{00}n_{01}}, \\ &H_{fh}^{**} = \frac{\Pi_f\sigma_f\lambda_{rm}^{**}n_4}{(\lambda_{rm}^{**} + k_{11})n_{00}n_{01}}, \quad Q_{fl}^{**} = \frac{\Pi_f\sigma_f q_f\lambda_{rm}^{**}n_5}{(\lambda_{rm}^{**} + k_{11})n_{00}n_{01}}, \quad Q_{fh}^{**} = \frac{\Pi_f\sigma_f q_f\lambda_{rm}^{**}n_6}{(\lambda_{rm}^{**} + k_{11})n_{00}n_{01}}, \end{aligned} \tag{6.29}$$

with $m_{ij} > 0$, $n_{ij} > 0$, $m_k > 0$ and $n_k > 0$ (but not reported here since their expressions are too lengthy). Substituting (6.28) and (6.29) into the expressions for λ_{rm}^{**} and λ_{rf}^{**} in (6.27) gives,

$$\begin{aligned}
\lambda_{rm}^{**} &= \frac{(m_3 + \zeta_m m_4 + \eta_m q_m m_5 + \zeta_m \eta_m q_m m_6)\lambda_{rf}^{**}\sigma_m \beta_m c_f}{m_1^2 \lambda_{rf}^{**} + (m_2 m_1 + \sigma_m m_3 \sigma_m m_4 + q_m \sigma_m m_5 + q_m \sigma_m m_6)\lambda_{rf}^{**} + m_{00} m_1}, \\
\lambda_{rf}^{**} &= \frac{(n_3 + \zeta_f n_4 + \eta_f q_f n_5 + \zeta_f \eta_f q_f n_6)\lambda_{rm}^{**}\sigma_f \beta_f c_m}{n_1^2 \lambda_{rm}^{**} + (n_2 n_1 + \sigma_f n_3 \sigma_f n_4 + q_f \sigma_f n_5 + q_f \sigma_f n_6)\lambda_{rm}^{**} + n_{00} n_1}.
\end{aligned} \tag{6.30}$$

It follows from (6.30) that the endemic equilibria of the reduced model system (6.20) satisfy:

$$\lambda_{rf}^{**}(a_2 \lambda_{rf}^{**} + a_1) = 0, \tag{6.31}$$

where,

$$\begin{aligned}
a_2 = \{&[(n_1^2 m_6 + n_2 n_1 m_6)\beta_m c_f \sigma_m + (n_3 m_6 + q_f n_5 m_6 + q_f n_6 m_6 + n_4 m_6)\beta_m c_f \sigma_m \sigma_f]\zeta_m \\
&+ (n_2 n_1 m_5 + n_1^2 m_5)\beta_m c_f \sigma_m + (n_4 m_5 + q_f n_5 m_5 + n_3 m_5 + q_f n_6 m_5)\beta_m c_f \sigma_m \sigma_f\} q_m \eta_m \\
&+ (n_0 n_1 m_6 + n_0 n_1 m_5)\sigma_m q_m + n_0 n_1 m_2 m_1 + [(n_2 n_1 m_4 + n_1^2 m_4)\beta_m c_f \sigma_m \\
&+ (q_f n_5 m_4 + n_3 m_4 + n_4 m_4 + q_f n_6 m_4)\beta_m c_f \sigma_m \sigma_f]\zeta_m + [(n_1^2 m_3 + n_2 n_1 m_3)\beta_m c_f \\
&+ n_0 n_1 m_4 + n_0 n_1 m_3]\sigma_m + (q_f n_5 m_3 + n_4 m_3 + n_3 m_3 + q_f n_6 m_3)\beta_m c_f \sigma_m \sigma_f + n_0 n_1 m_1^2 > 0, \\
a_1 = {} & n_0 n_1 m_0 m_1 [1 - (\mathcal{R}_r)^2].
\end{aligned}$$

Equation (6.31) has two solutions, namely $\lambda_{rf}^{**} = 0$ (which corresponds to the DFE, $\mathcal{E}_2$) and $\lambda_{rf}^{**} = \frac{-a_1}{a_2}$. The coefficient a_2 is always positive, and the coefficient a_1 is positive (negative) if $\mathcal{R}_r$ is less than (greater than) unity. Thus, the coefficients of the quadratic (6.31) are positive whenever $\mathcal{R}_r < 1$ (hence, the model has no positive real root in this case). For the case when $\mathcal{R}_r > 1$, the coefficient $a_1 < 0$, so that the model has one positive real root (given by $\lambda_{rf}^{**} = \frac{-a_1}{a_2} > 0$) in this case. For the case when $\mathcal{R}_r = 1$, the coefficient $a_1 = 0$ and $\lambda_{rf}^{**} = 0$ (which corresponds to the DFE, $\mathcal{E}_2$). These results are summarized below.

Theorem 6.7. *The reduced model* (6.20) *has one positive (endemic) equilibrium, of the form*

$\mathcal{E}_3$, whenever $\mathcal{R}_r > 1$, and no positive equilibrium otherwise.

Theorem 6.7 shows the existence of a unique endemic equilibrium when $\mathcal{R}_r > 1$. The global asymptotic stability of this equilibrium is explored for a special case below.

6.4.3 Global Stability of EEP: Special Case

Define,

$$\begin{aligned}\mathcal{D}_1 &= \Big\{\mathcal{D}_{mr} \cup \mathcal{D}_{fr} : S_m = E_{ml} = E_{mh} = H_{ml} = H_{mh} = Q_{ml} \\ &= Q_{mh} = S_f = E_{fl} = E_{fh} = H_{fl} = H_{fh} = Q_{fl} = Q_{fh} = 0\Big\}.\end{aligned}$$

Furthermore, let,

$$\begin{aligned}sign(S_m - S_m^{**}) &= sign(E_{ml} - E_{ml}^{**}) = sign(E_{mh} - E_{mh}^{**}) = sign(H_{ml} - H_{ml}^{**}) \\ &= sign(H_{mh} - H_{mh}^{**}) = sign(Q_{ml} - Q_{ml}^{**}) = sign(Q_{mh} - Q_{mh}^{**}) \\ &= sign(S_f - S_f^{**}) = sign(E_{fl} - E_{fl}^{**}) = sign(E_{fh} - E_{fh}^{**}) \\ &= sign(H_{fl} - H_{fl}^{**}) = sign(H_{fh} - H_{fh}^{**}) = sign(Q_{fl} - Q_{fl}^{**}) = sign(Q_{fh} - Q_{fh}^{**}).\end{aligned} \tag{6.32}$$

Theorem 6.8. *The EEP, $\mathcal{E}_3$, of the reduced model* (6.20)*, is GAS in $\mathcal{D}_{mr} \cup \mathcal{D}_{fr} \setminus \mathcal{D}_1$ whenever $\mathcal{R}_r > 1$ and Condition* (6.32) *holds.*

Proof. Consider the Lyapunov function (as in Section 5.5.4)

$$\begin{aligned}G &= |S_m - S_m^{**}| + |E_{ml} - E_{ml}^{**}| + |E_{mh} - E_{mh}^{**}| + |H_{ml} - H_{ml}^{**}| + |H_{mh} - H_{mh}^{**}| \\ &+ |Q_{ml} - Q_{ml}^{**}| + |Q_{mh} - Q_{mh}^{**}| + |S_f - S_f^{**}| + |E_{fl} - E_{fl}^{**}| + |E_{fh} - E_{fh}^{**}| \\ &+ |H_{fl} - H_{fl}^{**}| + |H_{fh} - H_{fh}^{**}| + |Q_{fl} - Q_{fl}^{**}| + |Q_{fh} - Q_{fh}^{**}|.\end{aligned}$$

The right derivative, D^+G, of G along the solutions of (6.20), is given by

$$
\begin{aligned}
D^+G = {} & sign(S_m - S_m^{**})\Big[-\lambda_f S_m + \lambda_f^{**} S_m^{**} - \mu(S_m - S_m^{**})\Big] \\
& + sign(E_{ml} - E_{ml}^{**})\Big[\lambda_f \nu_m S_m - \lambda_f^{**}\nu_m S_m^{**} + \xi_4^m(E_{mh} - E_{mh}^{**}) - m_1(E_{ml} - E_{ml}^{**})\Big] \\
& + sign(E_{mh} - E_{mh}^{**})\Big[\lambda_f(1-\nu_m) S_m - \lambda_f^{**}(1-\nu_m) S_m^{**} + \xi_3^m(E_{ml} - E_{ml}^{**}) - m_2(E_{mh} - E_{mh}^{**})\Big] \\
& + sign(H_{ml} - H_{ml}^{**})\Big[\sigma_m(E_{ml} - E_{ml}^{**}) + r_{ml}(Q_{ml} - Q_{ml}^{**}) + \xi_6^m(H_{mh} - H_{mh}^{**}) - m_3(H_{ml} - H_{ml}^{**})\Big] \\
& + sign(H_{mh} - H_{mh}^{**})\Big[\sigma_m(E_{mh} - E_{mh}^{**}) + r_{mh}(Q_{mh} - Q_{mh}^{**}) + \xi_5^m(H_{ml} - H_{ml}^{**}) - m_4(H_{mh} - H_{mh}^{**})\Big] \\
& + sign(Q_{ml} - Q_{ml}^{**})\Big[q_m(H_{ml} - H_{ml}^{**}) + \xi_8^m(Q_{mh} - Q_{mh}^{**}) - m_5(Q_{ml} - Q_{ml}^{**})\Big] \\
& + sign(Q_{mh} - Q_{mh}^{**})\Big[q_m(H_{mh} - H_{mh}^{**}) + \xi_7^m(Q_{ml} - Q_{ml}^{**}) - m_6(Q_{mh} - Q_{mh}^{**})\Big] \\
& + sign(S_f - S_f^{**})\Big[-\lambda_m S_f + \lambda_m^{**} S_f^{**} - \mu(S_f - S_f^{**})\Big] \\
& + sign(E_{fl} - E_{fl}^{**})\Big[\lambda_m \nu_f S_f - \lambda_m^{**}\nu_f S_f^{**} + \xi_4^f(E_{fh} - E_{fh}^{**}) - m_7(E_{fl} - E_{fl}^{**})\Big] \\
& + sign(E_{fh} - E_{fh}^{**})\Big[\lambda_m(1-\nu_f) S_f - \lambda_m^{**}(1-\nu_f) S_f^{**} + \xi_3^f(E_{fl} - E_{fl}^{**}) - m_8(E_{fh} - E_{fh}^{**})\Big] \\
& + sign(H_{fl} - H_{fl}^{**})\Big[\sigma_f(E_{fl} - E_{fl}^{**}) + r_{fl}(Q_{fl} - Q_{fl}^{**}) + \xi_6^f(H_{fh} - H_{fh}^{**}) - m_9(H_{fl} - H_{fl}^{**})\Big] \\
& + sign(H_{fh} - H_{fh}^{**})\Big[\sigma_f(E_{fh} - E_{fh}^{**}) + r_{fh}(Q_{fh} - Q_{fh}^{**}) + \xi_5^f(H_{fl} - H_{fl}^{**}) - m_{10}(H_{fh} - H_{fh}^{**})\Big] \\
& + sign(Q_{fl} - Q_{fl}^{**})\Big[q_f(H_{fl} - H_{fl}^{**}) + \xi_8^f(Q_{fh} - Q_{fh}^{**}) - m_{11}(Q_{fl} - Q_{fl}^{**})\Big] \\
& + sign(Q_{fh} - Q_{fh}^{**})\Big[q_f(H_{fh} - H_{fh}^{**}) + \xi_7^f(Q_{fl} - Q_{fl}^{**}) - m_{12}(Q_{fh} - Q_{fh}^{**})\Big]
\end{aligned}
$$

where, $m_1 = \xi_3^m + \sigma_m + \mu$, $m_2 = \xi_4^m + \sigma_m + \mu$, $m_3 = \xi_5^m + q_m + \mu + \delta_1$, $m_4 = \xi_6^m + q_m + \mu + \delta_2$, $m_5 = \xi_7^m + r_{ml} + \mu + \delta_3$, $m_6 = \xi_8^m + r_{ml} + \mu + \delta_4$, $m_7 = \xi_3^f + \sigma_f + \mu$, $m_8 = \xi_4^f + \sigma_f + \mu$, $m_9 = \xi_5^f + q_f + \mu + \delta_1$, $m_{10} = \xi_6^f + q_f + \mu + \delta_2$, $m_{11} = \xi_7^f + r_{fl} + \mu + \delta_3$ and $m_{12} = \xi_8^f + r_{fl} + \mu + \delta_4$.

It follows, after some algebraic manipulations and taking into account Condition (6.32), that

$$\begin{aligned}
D^+G &= -\mu\Big[|S_m - S_m^{**}| + |E_{ml} - E_{ml}^{**}| + |E_{mh} - E_{mh}^{**}| + |H_{ml} - H_{ml}^{**}| + |H_{mh} - H_{mh}^{**}| \\
&+ |Q_{ml} - Q_{ml}^{**}| + |Q_{mh} - Q_{mh}^{**}| + |S_f - S_f^{**}| + |E_{fl} - E_{fl}^{**}| + |E_{fh} - E_{fh}^{**}| \\
&+ |H_{fl} - H_{fl}^{**}| + |H_{fh} - H_{fh}^{**}| + |Q_{fl} - Q_{fl}^{**}| + |Q_{fh} - Q_{fh}^{**}|\Big] \\
&- \delta_1\Big[|H_{ml} - H_{ml}^{**}| + |H_{fl} - H_{fl}^{**}|\Big] - \delta_2\Big[|H_{mh} - H_{mh}^{**}| + |H_{fh} - H_{fh}^{**}|\Big] \\
&- \delta_3\Big[|Q_{ml} - Q_{ml}^{**}| + |Q_{fl} - Q_{fl}^{**}|\Big] - \delta_4\Big[|Q_{fl} - Q_{fl}^{**}| + |Q_{fh} - Q_{fh}^{**}|\Big] \\
&= -\mu G - \delta_1\Big[|H_{ml} - H_{ml}^{**}| + |H_{fl} - H_{fl}^{**}|\Big] - \delta_2\Big[|H_{mh} - H_{mh}^{**}| + |H_{fh} - H_{fh}^{**}|\Big] \\
&- \delta_3\Big[|Q_{ml} - Q_{ml}^{**}| + |Q_{fl} - Q_{fl}^{**}|\Big] - \delta_4\Big[|Q_{fl} - Q_{fl}^{**}| + |Q_{fh} - Q_{fh}^{**}|\Big].
\end{aligned}$$

Thus, $\lim_{t\to\infty} G(t) = 0$. Hence, the equilibrium, $\mathcal{E}_3$, of the reduced model (6.20) is GAS in $\mathcal{D}_{mr} \cup \mathcal{D}_{fr} \setminus \mathcal{D}_1$ whenever $\mathcal{R}_r > 1$ and Condition (6.32) holds. □

6.5 Summary

The main theoretical findings of this chapter are itemized below.

(i) The model (6.3) exhibits the phenomenon of backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium, when the associated reproduction number ($\mathcal{R}_0$) is less than unity (Theorem 6.3);

(ii) The backward bifurcation property of the model (6.3) can be removed if the susceptible individuals (both males and females) are not stratified according to risk of acquiring infection (Theorem 6.5). That is, the backward bifurcation phenomenon of the model (6.3) is removed if every susceptible male (female) is equally likely to acquire HSV-2 infection as every other susceptible male (female). Hence, this study shows that the backward bifurcation phenomenon of the risk-structured model (6.3) arises due to the stratification of the susceptible male and female populations in terms of risk of acquiring HSV-2 infection;

(iii) The DFE of the reduced model (6.20), which does not stratify the susceptible population based on risk of acquiring HSV-2 infection, is GAS if the associated reproduction number ($\mathcal{R}_r$) is less than unity (Theorem 6.6). This model has a unique endemic equilibrium if $\mathcal{R}_r > 1$ (Theorem 6.7). The endemic equilibrium is GAS for a special case (Theorem 6.8).

In summary, it is shown in this chapter that adding risk-structure to the two group HSV-2 transmission model (5.5) alters the qualitative dynamics of the risk-free model (5.5) (by inducing the phenomenon of backward bifurcation of the model). It is shown that the backward bifurcation property of the risk-structured model presented in this chapter arises due to the stratification of the susceptible male and female populations in terms of risk of acquiring HSV-2 infection.

Chapter 7

Summary of Contributions and Future Work

The main contributions of this thesis can be classified into three main categories namely:

(1) Formulation of new realistic mathematical models for the transmission dynamics of HSV-2 *in vivo* and in a population-level;

(2) Rigorous mathematical (dynamical) analysis of the resulting deterministic systems of non-linear differential equations;

(3) Public health contributions (by giving qualitative and quantitative insights into the mechanisms of disease spread *in vivo* as well as in a population; together with the assessment of various anti-HSV control strategies).

7.1 Model Formulation

The thesis consists of six new models for HSV-2 dynamics (two for *in-host* dynamics, and four for population-level dynamics). These are summarized below.

(i) A new deterministic model for HSV-2 *in vivo* is designed in Chapter 3. This model was extended to incorporate the effect of cell-mediated and humoral immune responses

against HSV-2 spread *in vivo*.

(ii) A single-group model for HSV-2 spread in a heterosexual homogeneously-mixed population is designed in Chapter 4. It is extended to include an imperfect vaccine.

(iii) A new two-group (sex-structured) model, which extends the basic model (in Chapter 4), is designed in Chapter 5. It was further extended to incorporate the effect of various anti-HSV-2 control strategies.

(vi) The two-group model in Chapter 5 is extended, in Chapter 6, to incorporate the effect of risk structure (by stratifying the entire sexually-active population based on risk of acquiring or transmitting HSV-2 infection) on the transmission dynamics of HSV-2 in a population.

7.2 Mathematical Analysis

This thesis further contributes by giving detailed qualitative analyses (using a robust collection of non-linear dynamical systems theories and techniques) of all the new models developed in the thesis (which are relatively large). Some of the main mathematical results obtained are summarized below.

Chapter 3

In this chapter, the new deterministic model designed for HSV-2 dynamics *in vivo* is rigorously analysed. It is shown, using Lyapunov function theory and LaSalle's Invariance Principle, that the model has a globally-asymptotically stable virus-free equilibrium whenever the associated reproduction threshold is less than unity. Furthermore, the model has at least one virus-present equilibrium whenever the associated reproduction threshold exceeds unity. The extended model, which incorporates immune responses, is also shown to exhibit similar dynamics. The results in this chapter show, for the first time, that HSV-2 exhibits the classical threshold dynamics *in vivo* (with a GAS VFE whenever $\mathcal{R}_0 < 1$; and at least

one VPE whenever $\mathcal{R}_0 > 1$).

Chapter 4

A new mathematical model for the transmission dynamics of HSV-2, which takes into account disease transmission by infected individuals in the quiescent state and an imperfect HSV-2 vaccine, is designed and qualitatively analyzed. In the absence of vaccination, it is shown (using Lyapunov function theory and LaSalle's Invariance Principle) that the model has a globally-asymptotically stable disease-free equilibrium point whenever the associated reproduction number is less than unity. Furthermore, this model has a unique endemic equilibrium whenever the reproduction number exceeds unity. Using a non-linear Lyapunov function, it is shown that the unique endemic equilibrium is globally-asymptotically stable (for a special case) when the associated reproduction threshold is greater than unity. On the other hand, it is shown (using centre manifold theory) that the extended model with vaccination undergoes a vaccine-induced backward bifurcation, where the stable disease-free equilibrium co-exists with a stable endemic equilibrium when the reproduction threshold is less than unity. Threshold analysis of the vaccination model reveals that the use of an imperfect HSV-2 vaccine could have positive or negative population-level impact (in reducing disease burden).

Chapter 5

In this chapter, the two-group model is shown to have a globally-asymptotically stable disease-free equilibrium whenever the associated reproduction threshold is less than unity. It has a unique endemic equilibrium, which is shown to be globally-asymptotic stable for a special case, when the reproduction threshold exceeds unity. The extended model (which incorporates an imperfect vaccine, condoms and drug treatment) has a globally-asymptotic stable disease-free equilibrium whenever its associated reproduction threshold is less than unity. Furthermore, it is shown that the extended model has at least one endemic equilibrium when the threshold exceeds unity. This endemic equilibrium is globally-asymptotically stable under certain conditions.

Chapter 6

The qualitative analysis of the new risk-structured model (that stratifies the entire population based on risk of acquiring or transmitting infection), using centre manifold theory, reveals that it exhibits the phenomenon of backward bifurcation. On the other hand, a reduced version of the model, which does not stratify the susceptible population based on risk of acquiring HSV-2 infections, is shown to have a globally-asymptotically stable disease-free equilibrium when the associated reproduction threshold is less than unity. The reduced model has a unique endemic equilibrium when the associated reproduction number exceeds unity, and the endemic equilibrium is globally-asymptotically stable for a special case. It is shown that adding risk-structure to the two group HSV-2 transmission model (5.5) studied in Chapter 5 alters the qualitative dynamics of the risk-free model (5.5) (by inducing the phenomenon of backward bifurcation of the model). Furthermore, it is also shown that the backward bifurcation property of the risk-structured model presented in this chapter arises due to the stratification of the susceptible male and female populations in terms of risk of acquiring HSV-2 infection.

7.3 Public Health

Some of the main public health contributions of the thesis are summarized below.

7.3.1 Effect of Immune Responses

The analysis of the in-host model in Chapter 3 reveals that cell-mediated immune response is more effective than humoral immune response in reducing HSV-2 burden *in vivo*. Furthermore, it is shown that a future HSV-2 vaccine that boosts cell-mediated immune response will be quite effective in reducing HSV-2 burden *in vivo*.

7.3.2 Effect of Vaccination as a Singular Intervention

(i) A future HSV-2 vaccine will be effective in reducing HSV-2 burden *in vivo* if it reduces the ability of the virus without glycoprotein C (gC) to bind to the host cell, or if it reduces the re-activation rate of latent HSV-2. Additionally, the vaccine will be effective if it results in an increase in the fraction of re-activated latent viruses without gC;

(ii) A future HSV-2 vaccine could lead to effective disease control or elimination if the vaccine efficacy and the fraction of susceptible individuals vaccinated at steady-state are high enough (at least 80% each);

(iii) The targeted vaccination of one sex group (only) induces an indirect benefit in the other sex group.

7.3.3 Effect of Combined Interventions

(i) For low treatment rates, very high condom compliance (at least 90%) will be required to effectively control the spread of the disease in the absence of vaccination. The level of condom compliance required for effective disease control reduces if the treatment rates are increased;

(ii) The combined use of vaccination, treatment and condoms will be very effective in curtailing (or eliminating) HSV-2 in (from) the population even if the vaccination and treatment rates are low.

7.4 Future Work

The thesis can be extended in several directions, both in terms of model construction and associated mathematical analysis. These include:

(i) Establishing the global dynamics of the endemic equilibria of the models (without considering special cases);

(ii) Extending the *in-host* model presented in Chapter 3 to further assess the potential impact of a future HSV-2 vaccine;

(iii) Using separate sub-groups for each of the risk groups considered in Chapter 6 (instead of lumping all individuals in the various high-risk groups as "high-risk");

(iv) Carrying out detailed uncertainty and sensitivity analysis in the models (to study the effect of such uncertainties on some of the simulation results obtained);

(v) Studying the interaction between HSV-2 and other STDs (particularly HIV). This is especially relevant since it is known that HSV-2 infection can increase the risk of acquiring and transmission of other infectious diseases (such as HIV);

(vi) Investigating the impact of other modes of HSV-2 transmission (such as mother-to-child and needle-sharing).

Appendices

Appendix A: Backward Bifurcation in Model (4.27)

As in Section 6.3.2, let

$$S = x_1, V = x_2, E_u = x_3, E_v = x_4, H_u = x_5, H_v = x_6, Q_u = x_7, Q_v = x_8,$$

so that,

$$N = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8.$$

Further, by using vector notation $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8)^T$, the vaccination model (4.27) can be written in the form $\frac{dX}{dt} = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8)^T$, as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &= f_1 = \Pi(1 - p\epsilon) - \frac{\beta[x_5 + \eta_1 x_6 + \theta(x_7 + \eta_2 x_8)]x_1}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8} + \omega x_2 - (\xi + \mu)x_1,\\
\frac{dx_2}{dt} &= f_2 = \Pi p\epsilon + \xi x_1 - \frac{\beta[x_5 + \eta_1 x_6 + \theta(x_7 + \eta_2 x_8)](1 - \psi)x_2}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8} - (\omega + \mu)x_2,\\
\frac{dx_3}{dt} &= f_3 = \frac{\beta[x_5 + \eta_1 x_6 + \theta(x_7 + \eta_2 x_8)]x_1}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8} - (\sigma_1 + \mu)x_3,\\
\frac{dx_4}{dt} &= f_4 = (1 - \psi)\frac{\beta[x_5 + \eta_1 x_6 + \theta(x_7 + \eta_2 x_8)]x_2}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7 + x_8} - (\sigma_2 + \mu)x_4,\\
\frac{dx_5}{dt} &= f_5 = \sigma_1 x_3 + r_u x_7 - (q_u + \mu + \delta_u)x_5,\\
\frac{dx_6}{dt} &= f_6 = \sigma_2 x_4 + r_v x_8 - (q_v + \mu + \delta_v)x_6,\\
\frac{dx_7}{dt} &= f_7 = q_u x_5 + \alpha x_8 - (r_u + \mu + \delta_{qu})x_7,\\
\frac{dx_8}{dt} &= f_8 = q_v x_6 - (r_v + \alpha + \mu + \delta_{qv})x_8.
\end{aligned} \tag{A.1}$$

The Jacobian of the system (A.1), at the associated DFE $\mathcal{E}_3$, is given by $J(\mathcal{E}_3) = \begin{bmatrix} R_{8\times 5} & S_{8\times 3} \end{bmatrix}$, where,

$$R = \begin{pmatrix} -(\xi+\mu) & \omega & 0 & 0 & -\frac{\beta x_1^*}{x_1^*+x_2^*} \\ \xi & -(\omega+\mu) & 0 & 0 & -\frac{\beta(1-\psi)x_2^*}{x_1^*+x_2^*} \\ 0 & 0 & -(\sigma_1+\mu) & 0 & \frac{\beta x_1^*}{x_1^*+x_2^*} \\ 0 & 0 & 0 & -(\sigma_2+\mu) & \frac{\beta(1-\psi)x_2^*}{x_1^*+x_2^*} \\ 0 & 0 & \sigma_1 & 0 & -(q_u+\delta_u+\mu) \\ 0 & 0 & 0 & \sigma_2 & 0 \\ 0 & 0 & 0 & 0 & q_u \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$S = \begin{pmatrix} -\frac{\beta x_1^*\eta_1}{x_1^*+x_2^*} & -\frac{\beta\theta x_1^*}{x_1^*+x_2^*} & -\frac{\beta\theta\eta_2 x_1^*}{x_1^*+x_2^*} \\ -\frac{\beta\eta_1(1-\psi)x_2^*}{x_1^*+x_2^*} & -\frac{\beta\theta(1-\psi)x_2^*}{x_1^*+x_2^*} & -\frac{\beta\theta\eta_2(1-\psi)x_2^*}{x_1^*+x_2^*} \\ \frac{\beta x_1^*\eta_1}{x_1^*+x_2^*} & \frac{\beta\theta x_1^*}{x_1^*+x_2^*} & \frac{\beta\theta\eta_2 x_1^*}{x_1^*+x_2^*} \\ \frac{\beta\eta_1(1-\psi)x_2^*}{x_1^*+x_2^*} & \frac{\beta\theta(1-\psi)x_2^*}{x_1^*+x_2^*} & \frac{\beta\theta\eta_2(1-\psi)x_2^*}{x_1^*+x_2^*} \\ 0 & r_u & 0 \\ -(q_v+\delta_v+\mu) & 0 & r_v \\ 0 & -(r_u+\mu+\delta_{qu}) & \alpha \\ q_v & 0 & -(r_v+\alpha+\mu+\delta_{qv}) \end{pmatrix}.$$

Consider the case when $\mathcal{R}_{vac}$, given in (4.29), equals unity. Suppose, further, that β is chosen as a bifurcation parameter. Solving for β from $\mathcal{R}_{vac} = 1$ in (4.29) gives

$$\beta^* = \beta = \frac{N^* k_{31}k_{41}(k_{51}k_{71} - q_u r_u)(k_{61}k_{81} - q_v r_v)}{k_{31}\sigma_2(1-\psi)V^* A_1 + k_{41}\sigma_1 S^* B_1}, \tag{A.2}$$

where, $k_{31}, k_{41}, k_{51}, k_{61}, k_{71}, k_{81}, A_1, B_1, S^*, V^*$ and N^* are defined in Section 4.3.1. It should be noted that the transformed system (A.1), with $\beta = \beta^*$, has a hyperbolic equilibrium point (i.e., the linearized system has a simple eigenvalue with zero real part). Hence, the centre manifold theory [13] can be used to analyse the dynamics of (A.1) near $\beta = \beta^*$. In order to apply Theorem 2.3 to prove the backward bifurcation phenomenon of the system (A.1) (or, equivalently, (4.27)), the following computations are necessary.

Eigenvectors of $J(\mathcal{E}_3)\Big|_{\beta=\beta^*}$

It can be shown that the Jacobian of (A.1) at $\beta = \beta^*$ (denoted by J_{β^*}) has a right eigenvector (associated with the zero eigenvalue), given by $\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8]^T$, where

$$\begin{aligned}
w_1 &= w_1, \;\; w_2 = \frac{(\xi+\mu)w_1 + m_1 w_5 + m_1\eta_1 w_6 + \theta m_1 w_7 + \theta m_1\eta_2 w_8}{\omega}, \\
w_3 &= \frac{m_1 w_5 + m_1\eta_1 w_6 + \theta m_1 w_7 + \theta m_1\eta_2 w_8}{\sigma_1+\mu}, \;\; w_4 = \frac{n_1 w_5 + n_1\eta_1 w_6 + \theta n_1 w_7 + \theta n_1\eta_2 w_8}{\sigma_2+\mu}, \\
w_5 &= w_5 > 0, \;\; w_6 = \frac{(r_v+\alpha+\mu+\delta_{qv})w_8}{q_v}, \;\; w_7 = \frac{q_u w_5 + \alpha w_8}{r_u+\mu+\delta_{qu}}, \;\; w_8 = w_8 > 0,
\end{aligned}$$

with, $m_1 = \frac{\beta^* x_1^*}{x_1^*+x_2^*}, n_1 = \frac{\beta^*(1-\psi)x_2^*}{x_1^*+x_2^*}$.

Further, J_{β^*} has a left eigenvector $\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8]$ (associated with the zero eigenvalue), where

$$\begin{aligned}
v_1 &= 0, \;\; v_2 = 0, \;\; v_3 = v_3 > 0, \;\; v_4 = v_4 > 0, \;\; v_5 = \frac{(\sigma_1+\mu)v_3}{\sigma_1}, \\
v_6 &= \frac{(\sigma_2+\mu)v_4}{\sigma_2}, \;\; v_7 = \frac{\theta m_1 v_3 + \theta n_1 v_4 + r_u v_5}{r_u+\mu+\delta_{qu}}, \\
v_8 &= \frac{r_v v_6 + \alpha v_7 + \theta m_1\eta_2 v_3 + \theta n_1\eta_2 v_4}{r_v+\alpha+\mu+\delta_{qv}}.
\end{aligned}$$

Computation of a :

Starting with the expression (from Theorem 2.3)

$$a = \sum_{k,i,j=1}^{8} v_k w_i w_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j},$$

it can be shown, after some algebraic manipulations, that

$$a = \frac{1}{(S^* + V^*)^2}[2\beta^*(M_1 + M_2)(\theta\eta_2 w_8 + w_6\eta_1 + w_5 + w_7\theta)], \tag{A.3}$$

with,

$$\begin{aligned} M_1 &= -S^* v_3(w_2 + w_3 + w_4 + w_5 + w_6 + w_7 + w_8) + S^* w_2(1-\psi)v_4 \\ M_2 &= -V^*(1-\psi)v_4(w_1 + w_3 + w_4 + w_5 + w_6 + w_7 + w_8) + V^* w_1 v_3. \end{aligned}$$

and S^* and V^* are defined in Section 4.3.1.

Computation of b :

Substituting the vectors $\mathbf{v}$ and $\mathbf{w}$ and the respective partial derivatives (at the DFE, $\mathcal{E}_3$) into

$$b = \sum_{i=1}^{8} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*},$$

gives,

$$b = \frac{1}{S^* + V^*}[V^*(1-\psi)v_4 + S^* v_3](\theta\eta_2 w_8 + w_6\eta_1 + w_5 + w_7\theta) > 0.$$

Since the coefficient b is always positive, it follows (using Theorem 2.3) that the system (A.1) will undergo backward bifurcation if $a > 0$. This result is summarized below.

Theorem 7.1. *The model* (A.1) *(or, equivalently,* (4.27)*) exhibits backward bifurcation at* $\mathcal{R}_{vac} = 1$ *whenever the bifurcation coefficient, a, given by* (A.3)*, is positive.*

Appendix B: Proof of Theorem 5.3

Proof. As in Section 4.2.4, the objective is to show that the system (5.19), around the equilibrium $\mathcal{E}_1$, has no solutions of the form

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

with $\bar{\mathbf{Z}}_0 \in \mathbb{C}^6 \setminus \{0\}$, $\tau \in \mathbb{C}$, $Z_i \in \mathbb{C}$ and $\mathrm{Re}(\tau) \geq 0$. The consequence of this is that the eigenvalues of the characteristic polynomial associated with the linearized method will have negative real part; in which case, the unique endemic equilibrium, $\mathcal{E}_1$, is LAS.

Linearizing the model (5.19) around the endemic equilibrium, $\mathcal{E}_1$, gives

$$\begin{aligned}
\frac{dE_m}{dt} &= -(\alpha_1 + p_1)E_m - \alpha_1 H_m - \alpha_1 Q_m + \alpha_2 H_f + \alpha_2 \eta_f Q_f, \\
\frac{dH_m}{dt} &= \sigma_m E_m + r_m Q_m - p_2 H_m, \\
\frac{dQ_m}{dt} &= q_m H_m - p_3 Q_m, \\
\frac{dE_f}{dt} &= \alpha_3 H_m + \alpha_3 \eta_m Q_m - (\alpha_4 + p_{11})E_f - \alpha_4 H_f - \alpha_4 Q_f, \\
\frac{dH_f}{dt} &= \sigma_f E_f + r_f Q_f - p_{21} H_f, \\
\frac{dQ_f}{dt} &= q_f H_f - p_{31} Q_f,
\end{aligned} \tag{B.2}$$

where,

$$\alpha_1 = \frac{\beta_f c_f}{N_m^{**}}(H_f^{**} + \eta_f Q_f^{**}),\ \alpha_2 = \frac{\beta_f c_f S_m^{**}}{N_m^{**}},\ \alpha_3 = \frac{\beta_m c_m S_f^{**}}{N_f^{**}},\ \alpha_4 = \frac{\beta_m c_m S_f^{**}}{N_f^{**}}(H_m^{**} + \eta_m Q_m^{**}).$$

Substituting a solution of the form (B.1) into the linearized system of (B.2), around the

equilibrium $\mathcal{E}_1$, gives the following linear system

$$\begin{aligned}
\tau Z_1 &= -(\alpha_1 + p_1)Z_1 - \alpha_1 Z_2 - \alpha_1 Z_3 + \alpha_2 Z_5 + \alpha_2 \eta_f Z_6, \\
\tau Z_2 &= \sigma_m Z_1 + r_m Z_3 - p_2 Z_2, \\
\tau Z_3 &= q_m Z_2 - p_3 Z_3, \\
\tau Z_4 &= \alpha_3 Z_2 + \alpha_3 \eta_m Z_3 - (\alpha_4 + p_{11})Z_4 - \alpha_4 Z_5 - \alpha_4 Z_6, \\
\tau Z_5 &= \sigma_f Z_4 + r_f Z_6 - p_{21} Z_5, \\
\tau Z_6 &= q_f Z_5 - p_{31} Z_6.
\end{aligned} \tag{B.3}$$

Firstly, all the negative terms in the second, third, fifth and sixth equations of system (B.3) are moved to their respective left-hand sides and then substituted some of the results into the remaining equations of the system. Finally, all the negative terms of the remaining (first and fourth) equations are moved to the right-hand sides. These algebraic manipulations result in the following system:

$$\begin{aligned}
Z_1[1 + F_1(\tau)] + Z_3[1 + F_3(\tau)] &= (M\bar{Z})_1 + (M\bar{Z})_3, \\
Z_2[1 + F_2(\tau)] &= (M\bar{Z})_2, \\
Z_4[1 + F_4(\tau)] + Z_6[1 + F_6(\tau)] &= (M\bar{Z})_4 + (M\bar{Z})_6, \\
Z_5[1 + F_5(\tau)] &= (M\bar{Z})_5,
\end{aligned} \tag{B.4}$$

where,

$$\begin{aligned}
F_1(\tau) &= \frac{\tau + \alpha_1}{p_1}, \quad F_2(\tau) = \frac{\tau}{p_2}, \\
F_3(\tau) &= \frac{\tau}{p_3} + \frac{\alpha_1(p_3 + \tau)}{p_1 p_3 q_m}, \\
F_4(\tau) &= \frac{\tau + \alpha_4}{p_{11}}, \quad F_5(\tau) = \frac{\tau}{p_{21}}, \\
F_6(\tau) &= \frac{\tau}{p_{31}} + \frac{\alpha_4(p_{31} + \tau)}{p_{11} p_{31} q_f},
\end{aligned} \tag{B.5}$$

with,

$$M = \begin{pmatrix} 0 & 0 & 0 & 0 & \frac{\alpha_2}{p_1} & \frac{\alpha_2\eta_f}{p_1} \\ \frac{\sigma_m}{p_2} & 0 & \frac{r_m}{p_2} & 0 & 0 & 0 \\ 0 & \frac{q_m}{p_3} & 0 & 0 & 0 & 0 \\ 0 & \frac{\alpha_3}{p_{11}} & \frac{\alpha_3\eta_m}{p_{11}} & 0 & 0 & 0 \\ \frac{\sigma_f}{p_{21}} & 0 & \frac{r_f}{p_{21}} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{q_f}{p_{31}} & 0 \end{pmatrix}.$$

In the above computations, the notation $M(\bar{Z})_i$ (for $i = 1, \cdots, 6$) denotes the ith coordinate of the vector $M(\bar{\mathbf{Z}})$. It should further be noted that the matrix M has non-negative entries, and the equilibrium $\mathcal{E}_1$ satisfies $\mathcal{E}_1 = M\mathcal{E}_1$. Furthermore, since the coordinates of $\mathcal{E}_1$ are all positive, it follows then that if $\bar{Z}$ is a solution of (B.4), then it is possible to find a minimal positive real number s such that

$$|| \bar{\mathbf{Z}} || \leq s\mathcal{E}_1, \tag{B.6}$$

where, $|| \bar{\mathbf{Z}} || = (|| Z_1 ||, \cdots, || Z_6 ||)$ with the lexicographic order, and $|| \cdot ||$ is a norm in $\mathbb{C}$.

The main goal is to show that $\mathrm{Re}(\tau) < 0$. Assume the contrary (i.e., $\mathrm{Re}(\tau) \geq 0$). The following two cases are considered.

Case 1: $\tau = 0$

Suppose $\tau = 0$. Then, (B.3) is a homogeneous linear system in the variables Z_i ($i = 1, \cdots, 6$). The determinant of the system (B.3) corresponds to that of the Jacobian of the system (B.2)

evaluated at $\mathcal{E}_1$, which is given by

$$\begin{aligned}\triangle = &\left\{\frac{\beta_m\beta_f c_m c_f}{N_m^* N_f^{**}}\Big[\sigma_m(q_m+p_3)+(p_2p_3-q_mr_m)\Big]\Big[\sigma_f(q_f+p_{31})+(p_{21}p_{31}-q_fr_f)\Big](H_f^{**}+\eta_f Q_f^{**})\right.\\ &\left.+\frac{\beta_m c_m}{N_f^{**}}p_1(p_2p_3-q_mr_m)\Big[\sigma_f(q_f+p_{31})+(p_{21}p_{31}-q_fr_f)\Big]\right\}(H_m^{**}+\eta_m Q_m^{**})\\ &+\frac{\beta_f c_f}{N_m^{**}}p_{11}(p_{21}p_{31}-q_fr_f)\Big[\sigma_m(q_m+p_3)+(p_2p_3-q_mr_m)\Big](H_f^{**}+\eta_f Q_f^{**})\\ &+p_1p_{11}(p_2p_3-q_mr_m)(p_{21}p_{31}-q_fr_f)\left(1-\frac{S_m^{**}S_f^{**}}{N_m^{**}N_f^*}\mathcal{R}_1\right).\end{aligned} \tag{B.7}$$

By solving (5.19) at the endemic steady-state ($\mathcal{E}_1$), and using the first and fourth equations of (5.19), it can be shown that

$$\frac{S_m^{**}S_f^{**}}{N_m^{**}N_f^{**}}=\frac{1}{\mathcal{R}_1^2}.$$

Hence, since $p_2p_3-q_mr_m>0$ and $p_{21}p_{31}-q_fr_f>0$, it follows from (B.7) that $\triangle>0$. Consequently, the system (B.3) can only have the trivial solution $\bar{\mathbf{Z}}=\bar{\mathbf{0}}$ (which corresponds to the DFE, $\mathcal{E}_0$ of the system).

Case 2: $\tau\neq 0$

Consider, now, the case $\tau\neq 0$. Since, by assumption, $\mathrm{Re}(\tau)\geq 0$, it follows that $\mid 1+F_i(\tau)\mid>1$ for all i. Let, $F(\tau)=\min\mid 1+F_i(\tau)\mid$ (for $i=1,\cdots,6$). Then, $F(\tau)>1$. Hence, $\frac{s}{F(\tau)}<s$. The minimality of s implies that $\parallel\bar{\mathbf{Z}}\parallel>\frac{s}{F(\tau)}\mathcal{E}_1$. On the other hand, taking norms of both sides of the second equation of (B.3), and using the fact that the matrix M is non-negative, gives

$$F(\tau)\parallel Z_2\parallel\leq M(\parallel Z\parallel)_2\leq s(M\parallel\mathcal{E}_1\parallel)_2\leq sH_m^{**}. \tag{B.8}$$

Then, it follows from the above inequality that $\parallel Z_2\parallel\leq\frac{s}{F(\tau)}H_m^{**}$, which contradicts $\mathrm{Re}(F_i(\tau))\geq 0$. Hence, $\mathrm{Re}(\tau)<0$, so that the endemic equilibrium, $\mathcal{E}_1$, is LAS if $\mathcal{R}_1>1$. □

Appendix C: Verification of Assumptions A1-A7 in [93]

Following the notation as in [93], system (5.5) can be re-written as follows:

$$\frac{d}{dt}x(t) = \mathcal{F}(t, x(t)) - \mathcal{V}(t, x(t)) = f(t, x(t)), \tag{C.1}$$

where,

$$x = \begin{pmatrix} S_m \\ E_m \\ H_m \\ Q_m \\ S_f \\ E_f \\ H_f \\ Q_f \end{pmatrix}, \ \mathcal{F} = \begin{pmatrix} 0 \\ \frac{\beta_f c_f S_m (H_f + \eta_f Q_f)}{N_m} \\ \sigma_m E_m + r_m(t) Q_m \\ q_m H_m \\ 0 \\ \frac{\beta_m c_m S_f (H_m + \eta_m Q_m)}{N_f} \\ \sigma_f E_f + r_f(t) Q_f \\ q_f H_f \end{pmatrix},$$

and,

$$\mathcal{V} = \begin{pmatrix} -\Pi_m + \frac{\beta_f c_f S_m (H_f + \eta_f Q_f)}{N_m} + \mu S_m \\ (\sigma_m + \mu) E_m \\ (q_m + \mu + \delta_1) H_m \\ (r_m(t) + \mu + \delta_2) Q_m \\ -\Pi_f + \frac{\beta_m c_m S_f (H_m + \eta_m Q_m)}{N_f} + \mu S_f \\ (\sigma_f + \mu) E_f \\ (q_f + \mu + \delta_1) H_f \\ (r_f(t) + \mu + \delta_2) Q_f \end{pmatrix}.$$

Further, let,

$$\mathcal{V}^+ = \begin{pmatrix} \Pi_m \\ 0 \\ 0 \\ 0 \\ \Pi_f \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

and

$$\mathcal{V}^- = \begin{pmatrix} \frac{\beta_f c_f S_m (H_f + \eta_f Q_f)}{N_m} + \mu S_m \\ (\sigma_m + \mu) E_m \\ (q_m + \mu + \delta_1) H_m \\ (r_m(t) + \mu + \delta_2) Q_m \\ \frac{\beta_m c_m S_f (H_m + \eta_m Q_m)}{N_f} + \mu S_f \\ (\sigma_f + \mu) E_f \\ (q_f + \mu + \delta_1) H_f \\ (r_f(t) + \mu + \delta_2) Q_f \end{pmatrix}.$$

It is clear that $\mathcal{V} = \mathcal{V}^- - \mathcal{V}^+$. The function $\mathcal{F}$, $\mathcal{V}^+$ and $\mathcal{V}^-$ satisfy the following:

(A1) For each $1 \leq i \leq 8$, $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^+(t,x)$ and $\mathcal{V}_i^-(t,x)$ are non-negative, continuous on $\mathbb{R} \times \mathbb{R}_+^8$ and continuously differentiable with respect to x, (since each function denotes a direct non-negative transfer of individuals).

(A2) By assumption (note that it is assumed that some of the model parameters are $\omega-$periodic functions), there exists a real number $\omega > 0$, such that $\mathcal{F}_i(t,x)$, $\mathcal{V}_i^+(t,x)$ and $\mathcal{V}_i^-(t,x)$ are $\omega-$periodic in t.

(A3) If $x_i = 0$, then $\mathcal{V}_i^- = 0$ for $i = 2, 3, 4, 6, 7, 8$.

(A4) $\mathcal{F}_i = 0$ for $i = 1, 5$.

(A5) Define $x_s = \{x \geq 0 : x_i = 0 \ \text{for} i = 2, 3, 4, 6, 7, 8\}$. Thus, if $x \in X_s$, then $\mathcal{F}_i = \mathcal{V}_i^- = 0$ for $i = 2, 3, 4, 6, 7, 8$. System (5.5) has a disease-free periodic solution $x^* = \left(\frac{\Pi_m}{\mu}, 0, 0, 0, \frac{\Pi_f}{\mu}, 0, 0, 0\right)$. Define a 2×2 matrix

$$M(t) = \left(\frac{\partial f_i(t, x^*)}{\partial x_j}\right)_{i,j=1,5}.$$

It follows from (C.1), and the definitions of matrices $\mathcal{F}$ and $\mathcal{V}$, that

$$M(t) = \begin{bmatrix} -\mu & 0 \\ 0 & -\mu \end{bmatrix}.$$

(A6) Since $M(t)$ is a diagonalizable matrix with negative eigenvalues, then $\rho(\Phi_M(\omega)) < 1$.

(A7) Similarly, $-V(t)$ is a diagonalizable matrix with negative eigenvalues. Hence, $\rho(\Phi_- V(\omega)) < 1$.

Appendix D: Proof of Theorem 5.5

Proof. It follows from Lemma 5.5 that the DFE, $\mathcal{E}_0$, of the system (5.29) is asymptotically-stable if $\mathcal{R}_p < 1$. Using the fact that $S_m(t) \leq N_m(t)$ and $S_f(t) \leq N_f(t)$ for all $t \geq 0$ in $\mathcal{D}$, the infected compartments of the system (5.29) can be re-written in terms of the following differential inequality system (see also [93]):

$$\begin{aligned}
\frac{dE_m}{dt} &\leq \beta_f c_f (H_f(t) + \eta_f Q_f) - (\sigma_m + \mu) E_m, \\
\frac{dH_m}{dt} &= \sigma_m E_m + r_m(t) Q_m - (q_m + \mu + \delta_1) H_m, \\
\frac{dQ_m}{dt} &= q_m H_m - (r_m(t) + \mu + \delta_2) Q_m, \\
\frac{dE_f}{dt} &\leq \beta_m c_m (H_m + \eta_m Q_m) - (\sigma_f + \mu) E_f, \\
\frac{dH_f}{dt} &= \sigma_f E_f + r_f(t) Q_f - (q_f + \mu + \delta_1) H_f, \\
\frac{dQ_f}{dt} &= q_f H_f - (r_f(t) + \mu + \delta_2) Q_f.
\end{aligned} \tag{D.1}$$

The equations in (D.1), with equality used in place of the inequality, can be re-written in terms of the next generation matrices $F(t)$ and $V(t)$ defined in Section 5.4.2, as follows:

$$\frac{dW}{dt} = [F(t) - V(t)]W(t). \tag{D.2}$$

It follows from Lemma 2.1 in [101] that there exists a positive $\omega-$periodic function, $w(t)$, such that $W(t) = e^{\vartheta t}w(t)$, with $\vartheta = \frac{1}{\omega}ln\rho[\phi_{F-V}(\omega)]$, is a solution of (D.2). By Theorem 2.2 in [93], $\mathcal{R}_0 < 1$ implies that $\rho[\phi_{F-V}(\omega)] < 1$. Hence, ϑ is a negative constant. Thus, $W(t) \to 0$ as $t \to \infty$. This implies that the trivial solution of system (D.2), given by $W(t) = 0$, is GAS. For any non-negative initial solution $(E_m(0), H_m(0), Q_m(0), E_f(0), H_f(0), Q_f(0))^T$, of the system (D.2), there exists a sufficiently large $M^* > 0$, such that

$$(E_m(0), H_m(0), Q_m(0), E_f(0), H_f(0), Q_f(0))^T \leq M^* w(0).$$

Thus, by comparison theorem (Theorem 2.6), it follows that

$$(E_m, H_m, Q_m, E_f, H_f, Q_f)^T \leq M^* W(t) \text{ for all } t > 0,$$

where, $M^*W(t)$ is also a solution of (D.2).

Hence,

$$\lim_{t\to\infty}\Big(E_m(t), H_m(t), Q_m(t), E_f(t), H_f(t), Q_f(t)\Big) \to (0, 0, 0, 0, 0, 0).$$

Finally, by Theorem 1.2 in [85], it follows that $S_m(t) \to \frac{\Pi_m}{\mu}$ and $S_f(t) \to \frac{\Pi_f}{\mu}$as $t \to \infty$. Hence,

$\lim_{t\to\infty}(S_m(t)E_m(t), H_m(t), Q_m(t), S_f(t), E_f(t), H_f(t), Q_f(t)) \to \mathcal{E}_0$, whenever $\mathcal{R}_0 < 1$. $\square$

Appendix E: Definitions for Terms in Equation (5.40)

$$
\begin{aligned}
C_1 &= \Pi_m(1-\psi)(1-\nu_1 c)(1-p_m\epsilon_m),\ \ C_2 = \Pi_m\omega_m p_m\epsilon_m + \Pi_m k_2(1-p_m\epsilon_m),\\
C_3 &= (1-\nu_1 c)^2(1-\psi),\ \ C_4 = (1-\nu_1 c)k_2 + (1-\nu_1 c)(1-\psi)k_1,\\
C_5 &= k_1k_2 - \omega_m\xi_m,\ \ C_6 = \Pi_m p_m\epsilon_m(1-\nu_1 c),\ \ C_7 = \Pi_m p_m\epsilon_m k_1 + \Pi_m\xi_m(1-p_m\epsilon_m),\\
C_8 &= \frac{1-\nu_1 c}{k_3},\ \ C_9 = \frac{(1-\psi)(1-\nu_1 c)}{k_4},\ \ C_{10} = \frac{\sigma_{mv}K_8}{K_6K_8 - q_{mv}r_{mv}},\\
C_{11} &= \frac{\sigma_{mu}K_7}{K_5K_7 - q_{mu}r_{mu}},\ \ C_{12} = \frac{r_{mu}\alpha_m q_{mv}}{K_8(K_5K_7 - q_{mu}r_{mu})},\\
C_{15} &= \frac{\Pi_m}{\mu}(k_1k_2 - \xi_m\omega_m),\ \ C_{17} = \frac{\Pi_m\mathcal{R}_m(k_1k_2 - \xi_m\omega_m)}{\mu\beta_f c_f},\\
C_{16} &= C_8C_{11}C_1 + C_9C_{10}C_{12}C_6 + \eta_1C_9C_{10}C_6 + \frac{q_{mu}}{K_7}\eta_2(C_8C_{11}C_1 + C_9C_{10}C_{12}C_6)\\
&+ \frac{\eta_2\alpha_m q_{mv}}{K_7K_8}C_9C_{10}C_6 + \frac{\eta_3 q_{mv}}{K_8}C_9C_{10}C_6 + \frac{\eta_4\gamma_{hmu}}{K_9}(C_8C_{11}C_1\\
&+ C_9C_{10}C_{12}C_6) + \frac{\eta_4\gamma_{qmu}q_{mu}}{K_7K_9}(C_8C_{11}C_1 + C_9C_{10}C_{12}C_6)\\
&+ \frac{\eta_4\gamma_{qmu}\alpha_m q_{mv}}{K_7K_8K_9}C_9C_{10}C_6 + \frac{\eta_5\gamma_{hmv}}{K_{10}}C_9C_{10}C_6 + \frac{\eta_5\gamma_{qmv}q_{mv}}{K_8K_{10}}C_9C_{10}C_6,
\end{aligned}
$$

$$
\begin{aligned}
D_1 &= \Pi_f(1-\psi)(1-\nu_2 c)(1-p_f\epsilon_f),\ \ D_2 = \Pi_f\omega_f p_f\epsilon_f + \Pi_f K_{12}(1-p_f\epsilon_f),\\
D_3 &= (1-\nu_2 c)^2(1-\psi),\ \ D_4 = (1-\nu_2 c)K_{12} + (1-\nu_2 c)(1-\psi)k_{11},\\
D_5 &= k_{11}k_{12} - \omega_f\xi_f,\ \ D_6 = \Pi_f p_f\epsilon_f(1-\nu_2 c),\ \ D_7 = \Pi_f p_f\epsilon_f k_{11} + \Pi_f\xi_f(1-p_f\epsilon_f),\\
D_8 &= \frac{1-\nu_2 c}{k_{13}},\ \ D_9 = \frac{(1-\psi)(1-\nu_2 c)}{k_{14}},\ \ D_{20} = \frac{\sigma_{fv}K_{18}}{K_{16}K_{18} - q_{fv}r_{fv}},\\
D_{11} &= \frac{\sigma_{fu}K_{17}}{K_{15}K_{17} - q_{fu}r_{fu}},\ \ D_{12} = \frac{r_{fu}\alpha_f q_{fv}}{K_{18}(K_{15}K_{17} - q_{fu}r_{fu})},\\
D_{15} &= \frac{\Pi_f}{\mu}(k_{11}k_{12} - \xi_f\omega_f),\ \ D_{17} = \frac{\Pi_f\mathcal{R}_f(k_{11}k_{12} - \xi_f\omega_f)}{\mu\beta_m c_m},
\end{aligned}
$$

$$
\begin{aligned}
D_{16} &= D_8D_{11}D_1 + D_9D_{10}D_{12}D_6 + \eta_1 D_9D_{10}D_6 + \frac{q_{fu}}{K_{17}}\eta_2(D_8D_{11}D_1 + D_9D_{10}D_{12}D_6) \\
&+ \frac{\eta_2\alpha_f q_{fv}}{K_{17}K_{18}}D_9D_{10}D_6 + \frac{\eta_3 q_{fv}}{K_{18}}D_9D_{10}D_6 + \frac{\eta_4\gamma_{hfu}}{K_{19}}(D_8D_{11}D_1 \\
&+ D_9D_{10}D_{12}D_6) + \frac{\eta_4\gamma_{qfu}q_{fu}}{K_{17}k_{19}}(D_8D_{11}D_1 + D_9D_{10}D_{12}D_6) \\
&+ \frac{\eta_4\gamma_{qfu}\alpha_f q_{fv}}{K_{17}K_{18}K_{19}}D_9D_{10}D_6 + \frac{\eta_5\gamma_{hfv}}{K_{20}}D_9D_{10}D_6 + \frac{\eta_5\gamma_{qfv}q_{fv}}{K_{18}K_{20}}D_9D_{10}D_6,
\end{aligned}
$$

with, $K_5 = q_{mu}+\gamma_{hmu}+\mu$, $K_6 = q_{mv}+\gamma_{hmv}+\mu$, $K_7 = r_{mu}+\gamma_{qmu}+\mu$, $K_8 = r_{mv}+\alpha_m+\gamma_{qmv}+\mu$, $K_9 = \mu$, $k_{10} = \mu$, $K_{15} = q_{fu} + \gamma_{hfu} + \mu$, $K_{16} = q_{fv} + \gamma_{hfv} + \mu$, $K_{17} = r_{fu} + \gamma_{qfu} + \mu$, $K_{18} = r_{fv} + \alpha_f + \gamma_{qfv} + \mu$, $K_{19} = \mu$ and $K_{20} = \mu$.

Appendix F: Proof of Theorem 6.5

Proof. As in Section 6.3.2, let

$$
\begin{aligned}
&S_m = x_1, E_{ml} = x_2, E_{mh} = x_3, H_{ml} = x_4, H_{mh} = x_5, Q_{ml} = x_6, Q_{mh} = x_7, \\
&S_f = x_8, E_{fl} = x_9, E_{fh} = x_{10}, H_{fl} = x_{11}, H_{fh} = x_{12}, Q_{fl} = x_{13}, Q_{fh} = x_{14}.
\end{aligned}
$$

Thus,

$$
N_m = x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7, \quad N_f = x_8 + x_9 + x_{10} + x_{11} + x_{12} + x_{13} + x_{14}.
$$

Further, by using vector notation $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}, x_{11}, x_{12}, x_{13}, x_{14}),^T$ and $\mathcal{F} = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10}, f_{11}, f_{12}, f_{13}, f_{14}),^T$ the reduced model (6.20) can be written in the form

$$
\frac{dX}{dt} = \mathcal{F}X,
$$

as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} &= \Pi_m - \lambda_f(t)x_1 - \mu x_1,\\
\frac{dx_2}{dt} &= \nu_m\lambda_f(t)x_1 + \xi_4^m x_3 - (\xi_3^m + \sigma_m + \mu)x_2,\\
\frac{dx_3}{dt} &= (1-\nu_m)\lambda_f(t)x_1 + \xi_3^m x_2 - (\xi_4^m + \sigma_m + \mu)x_3,\\
\frac{dx_4}{dt} &= \sigma_m x_2 + r_{ml}x_6 + \xi_6^m x_5 - (\xi_5^m + q_m + \mu + \delta_1)x_4,\\
\frac{dx_5}{dt} &= \sigma_m x_3 + r_{mh}x_7 + \xi_5^m x_4 - (\xi_6^m + q_m + \mu + \delta_2)x_5,\\
\frac{dx_6}{dt} &= q_m x_5 + \xi_8^m x_7 - (\xi_7^m + r_{ml} + \mu + \delta_3)x_6,\\
\frac{dx_7}{dt} &= q_m x_6 + \xi_7^m x_6 - (\xi_8^m + r_{mh} + \mu + \delta_4)x_7,\\
\frac{dx_8}{dt} &= \Pi_f - \lambda_m(t)x_8 - \mu x_8,\\
\frac{dx_9}{dt} &= \nu_f\lambda_m(t)x_8 + \xi_4^f x_{10} - (\xi_3^f + \sigma_f + \mu)x_9,\\
\frac{dx_{10}}{dt} &= (1-\nu_f)\lambda_m(t)x_8 + \xi_3^f x_9 - (\xi_4^f + \sigma_f + \mu)x_{10},\\
\frac{dx_{11}}{dt} &= \sigma_f x_9 + r_{fl}x_{13} + \xi_6^f x_{12} - (\xi_5^f + q_f + \mu + \delta_1)x_{11},\\
\frac{dx_{12}}{dt} &= \sigma_f x_{10} + r_{fh}x_{14} + \xi_5^f x_{11} - (\xi_6^f + q_f + \mu + \delta_2)x_{12},\\
\frac{dx_{13}}{dt} &= q_f x_{11} + \xi_8^f x_{14} - (\xi_7^f + r_{fl} + \mu + \delta_3)x_{13},\\
\frac{dx_{14}}{dt} &= q_f x_{12} + \xi_7^f x_{13} - (\xi_8^f + r_{fh} + \mu + \delta_4)x_{14},
\end{aligned}
\tag{F.1}
$$

with,

$$
\begin{aligned}
\lambda_{rf} &= \lambda_{rfl} + \lambda_{rfh},\ \ \lambda_{rm} = \lambda_{rml} + \lambda_{rmh},\\
\lambda_{rfl} &= \frac{c_f\beta_f(x_{11} + \eta_f x_{13})}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7},\\
\lambda_{rfh} &= \frac{\zeta_f c_f\beta_f(x_{12} + \eta_f x_{14})}{x_1 + x_2 + x_3 + x_4 + x_5 + x_6 + x_7},\\
\lambda_{rml} &= \frac{c_m\beta_m(x_4 + \eta_m x_6)}{x_8 + x_9 + x_{10} + x_{11} + x_{12} + x_{13} + x_{14}},\\
\lambda_{rmh} &= \frac{\zeta_m c_m\beta_m(x_5 + \eta_f x_7)}{x_8 + x_9 + x_{10} + x_{11} + x_{12} + x_{13} + x_{14}}.
\end{aligned}
$$

The Jacobian of the system (F.1), at the associated DFE ($\mathcal{E}_2$), is given by

$$J_r(\mathcal{E}_2) = \begin{bmatrix} J_{r1} & J_{r2} \\ J_{r3} & J_{r4} \end{bmatrix},$$

with,

$$J_{r1} = \begin{bmatrix} -k_1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_3 & \xi_4^m & 0 & 0 & 0 & 0 \\ 0 & \xi_3^m & -k_4 & 0 & 0 & 0 & 0 \\ 0 & \sigma_m & 0 & -k_5 & \xi_6^m & r_{ml} & 0 \\ 0 & 0 & \sigma_m & \xi_5^m & -k_6 & 0 & r_{mh} \\ 0 & 0 & 0 & q_m & 0 & -k_7 & \xi_8^m \\ 0 & 0 & 0 & 0 & q_m & \xi_7^m & -k_8 \end{bmatrix},$$

$$J_{r2} = \begin{bmatrix} 0 & 0 & 0 & -\Phi_{r1} & -\zeta_f\Phi_{r1} & -\nu_f\Phi_{r1} & -\zeta_f\nu_f\Phi_{r1} \\ 0 & 0 & 0 & \Phi_{r2} & \zeta_f\Phi_{r2} & \nu_f\Phi_{r2} & \zeta_f\nu_f\Phi_{r2} \\ 0 & 0 & 0 & \Phi_{r3} & \zeta_f\Phi_{r3} & \nu_f\Phi_{r3} & \zeta_f\nu_f\Phi_{r3} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$J_{r3} = \begin{bmatrix} 0 & 0 & 0 & -\Phi_{r11} & -\zeta_m\Phi_{r11} & -\nu_m\Phi_{r11} & -\zeta_m\nu_m\Phi_{r11} \\ 0 & 0 & 0 & \Phi_{r21} & \zeta_m\Phi_{r21} & \nu_m\Phi_{r21} & \zeta_m\nu_m\Phi_{r21} \\ 0 & 0 & 0 & \Phi_{r31} & \zeta_m\Phi_{r31} & \nu_m\Phi_{r31} & \zeta_m\nu_m\Phi_{r31} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

$$J_{r4} = \begin{bmatrix} -k_{11} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -k_{13} & \xi_4^f & 0 & 0 & 0 & 0 \\ 0 & \xi_3^f & -k_{14} & 0 & 0 & 0 & 0 \\ 0 & \sigma_f & 0 & -k_{15} & \xi_6^f & r_{fl} & 0 \\ 0 & 0 & \sigma_f & \xi_5^f & -k_{16} & 0 & r_{fh} \\ 0 & 0 & 0 & q_f & 0 & -k_{17} & \xi_8^f \\ 0 & 0 & 0 & 0 & q_f & \xi_7^f & -k_{18} \end{bmatrix},$$

where,

$$\begin{aligned} \Phi_{r1} &= c_f\beta_f,\ \Phi_{r2} = \nu_m c_f\beta_f,\ \Phi_{r3} = (1-\nu_m)c_f\beta_f, \\ \Phi_{r11} &= c_m\beta_m,\ \Phi_{r21} = \nu_f c_m\beta_m,\ \Phi_{r31} = (1-\nu_f)c_m\beta_m. \end{aligned}$$

It can be shown, from $J(\mathcal{E}_2)$, that (as in Section 6.3):

$$\mathcal{R}_r = \sqrt{c_f c_m \beta_f \beta_m \sigma_f \sigma_m Z_{r1} Z_{r2}}, \tag{F.2}$$

where,

$$\begin{aligned} Z_{r1} &= \frac{\nu_m(A_{11}+A_{12}) + (1-nu_m)(A_{21}+A_{22})}{A}, \\ Z_{r2} &= \frac{\nu_f(B_{11}+B_{12}) + (1-nu_f)(B_{21}+B_{22})}{B}, \end{aligned}$$

with, $A_{11}, A_{12}, A_{21}, A_{22}, B_{11}, B_{12}, B_{21}, B_{22}, A$ and B as defined in Section 6.3.

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

$$\beta_m = \beta^* = \frac{1}{c_f c_m \beta_f \sigma_f \sigma_m Z_{r1} Z_{r2}}. \tag{F.3}$$

Eigenvectors of $J_r(\mathcal{E}_2)\Big|_{\beta_m=\beta^*}$

It can be shown that the Jacobian of (F.1) at $\beta_m = \beta^*$ (denoted by $J_{r\beta^*}$) has a left eigenvector

(associated with the zero eigenvalue) given by

$$\mathbf{v} = [v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9, v_{10}, v_{11}, v_{12}, v_{13}, v_{14}],$$

where,

$$\begin{aligned}
v_1 &= 0, \;\; v_2 = \frac{\sigma_m(\xi_3^m v_5 + k_4 v_4)}{k_3 k_4 - \xi_3^m \xi_4^m}, \;\; v_3 = \frac{\sigma_m(\xi_4^m v_4 + k_3 v_5)}{k_3 k_4 - \xi_3^m \xi_4^m}, \;\; v_4 = \frac{\xi_5^m a_2 + k_6 a_1}{k_5 k_6 - \xi_5^m \xi_6^m}, \\
v_5 &= \frac{\xi_6^m a_1 + k_5 a_2}{k_5 k_6 - \xi_5^m \xi_6^m}, \;\; v_6 = \frac{\xi_7^m a_4 + k_8 a_3}{k_7 k_8 - \xi_7^m \xi_8^m}, \;\; v_7 = \frac{\xi_8^m a_3 + k_7 a_4}{k_7 k_8 - \xi_7^m \xi_8^m}, \;\; v_8 = 0, \\
v_9 &= \frac{\sigma_f(\xi_3^f v_{12} + k_{14} v_{11})}{k_{13} k_{14} - \xi_3^f \xi_4^f}, \;\; v_{10} = \frac{\sigma_f(\xi_4^f v_{11} + k_{13} v_{12})}{k_{13} k_{14} - \xi_3^f \xi_4^f}, \;\; v_{11} = \frac{\xi_5^f a_6 + k_{16} a_5}{k_{15} k_{16} - \xi_5^f \xi_6^f}, \\
v_{12} &= \frac{\xi_6^f a_5 + k_{15} a_6}{k_{15} k_{16} - \xi_5^f \xi_6^f}, \;\; v_{13} = \frac{\xi_7^f a_8 + k_{18} a_7}{k_{17} k_{18} - \xi_7^f \xi_8^f}, \;\; v_{14} = \frac{\xi_8^f a_7 + k_{17} a_8}{k_{17} k_{18} - \xi_7^f \xi_8^f},
\end{aligned}$$

with,

$$\begin{aligned}
a_1 &= q_m v_6 + \Phi_{r21} v_9 + \Phi_{r31} v_{10}, \;\; a_2 = q_m v_7 + \zeta_m \Phi_{r21} v_9 + \zeta_m \Phi_{r31} v_{10}, \\
a_3 &= r_{ml} v_7 + \nu_m \Phi_{r21} v_9 + \nu_m \Phi_{r31} v_{10}, \;\; a_4 = r_{mh} v_5 + \zeta_m \nu_m \Phi_{r21} v_9 + \zeta_m \nu_m \Phi_{r31} v_{10}, \\
a_5 &= \Phi_{r2} v_2 + \Phi_{r3} v_3 + q_f v_{13}, \;\; a_6 = \zeta_f \Phi_{r2} v_2 + \zeta_f \Phi_{r3} v_3 + q_f v_{14}, \\
a_7 &= \nu_f \Phi_{r2} v_2 + \nu_f \Phi_{r3} v_3 + r_{fl} v_{11}, \;\; a_8 = \zeta_f \nu_f \Phi_{r2} v_2 + \zeta_f \nu_f \Phi_{r3} v_3 + r_{fh} v_{12}.
\end{aligned}$$

Further, $J_{r\beta^*}$ has a right eigenvector (associated with the zero eigenvalue)

$$\mathbf{w} = [w_1, w_2, w_3, w_4, w_5, w_6, w_7, w_8, w_9, w_{10}, w_{11}, w_{12}, w_{13}, w_{14}]^T,$$

where,

$$
\begin{aligned}
w_1 &= -\frac{1}{k_1}(\Phi_{r1}w_{11} + \zeta_f\Phi_{r1}w_{12} + \nu_f\Phi_{r1}w_{13} + \zeta_f\nu_f\Phi_{r1}w_{14}),\\
w_2 &= \frac{k_4b_1 + b_2\xi_4^m}{k_3k_4 - \xi_3^m\xi_4^m},\ \ w_3 = \frac{k_3b_2 + b_1\xi_3^m}{k_3k_4 - \xi_3^m\xi_4^m},\ \ w_4 = \frac{k_6b_3 + b_4\xi_6^m}{k_5k_6 - \xi_5^m\xi_6^m},\\
w_5 &= \frac{k_5b_4 + b_3\xi_5^m}{k_5k_6 - \xi_5^m\xi_6^m},\ \ w_6 = \frac{k_8b_5 + b_6\xi_8^m}{k_7k_8 - \xi_7^m\xi_8^m},\ \ w_7 = \frac{k_7b_6 + b_5\xi_7^m}{k_7k_8 - \xi_7^m\xi_8^m},\\
w_8 &= -\frac{1}{k_{11}}(\Phi_{r11}w_4 + \zeta_m\Phi_{r11}w_5 + \nu_m\Phi_{r11}w_6 + \zeta_m\nu_m\Phi_{r11}w_7),\\
w_9 &= \frac{k_{14}b_7 + b_8\xi_4^f}{k_{13}k_{14} - \xi_3^f\xi_4^f},\ \ w_{10} = \frac{k_{13}b_8 + b_7\xi_3^f}{k_{13}k_{14} - \xi_3^f\xi_4^f},\ \ w_{11} = \frac{k_{16}b_9 + b_{10}\xi_6^f}{k_{15}k_{16} - \xi_5^f\xi_6^f},\\
w_{12} &= \frac{k_{15}b_{10} + b_9\xi_5^f}{k_{15}k_{16} - \xi_5^f\xi_6^f},\ \ w_{13} = \frac{k_{18}b_{11} + b_{12}\xi_8^f}{k_{17}k_{18} - \xi_7^f\xi_8^f},\ \ w_{14} = \frac{k_{17}b_{12} + b_{11}\xi_7^f}{k_{17}k_{18} - \xi_7^f\xi_8^f},
\end{aligned}
$$

with,

$$
\begin{aligned}
b_1 &= \Phi_{r2}w_{11} + \zeta_f\Phi_{r2}w_{12} + \nu_f\Phi_{r2}w_{13} + \zeta_f\nu_f\Phi_{r2}w_{14},\\
b_2 &= \Phi_{r3}w_{11} + \zeta_f\Phi_{r3}w_{12} + \nu_f\Phi_{r3}w_{13} + \zeta_f\nu_f\Phi_{r3}w_{14},\\
b_3 &= \sigma_m w_2 + r_{ml}w_6, b_4 = \sigma_m w_3 + r_{mh}w_7,\ \ b_5 = q_m w_4,\ \ b_6 = q_m w_5,\\
b_7 &= \Phi_{r21}w_4 + \zeta_m\Phi_{r21}w_5 + \nu_m\Phi_{r21}w_6 + \zeta_m\nu_m\Phi_{r21}w_7,\\
b_8 &= \Phi_{r31}w_4 + \zeta_m\Phi_{r31}w_5 + \nu_m\Phi_{r31}w_6 + \zeta_m\nu_m\Phi_{r31}w_7,\\
b_9 &= \sigma_f w_9 + r_{fl}w_{13},\ \ b_{10} = \sigma_f w_{10} + r_{fh}w_{14},\ \ b_{11} = q_f w_{11},\ \ b_{12} = q_f w_{12}.
\end{aligned}
$$

Computation of coefficients a and b : It can be shown, after some algebraic manipulations, that

$$
\begin{aligned}
a &= \sum_{k,i,j=1}^{14} v_k w_i w_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j}, \\
&= -\Bigg\{ \frac{2c_f\beta_f}{x_1^{**}}(w_2+w_3+w_4+w_5+w_6+w_7)(w_{14}\zeta_f\nu_f + w_{12}\nu_f + w_{11} + w_{13}\nu_f)[v_3(1-\nu_m)+v_2\nu_m] \\
&+ \frac{2c_m\beta_m}{x_8^{**}}(w_4 + w_5\zeta_m + w_6\nu_m + w_5 + w_7\zeta_m\nu_m)(w_9+w_{10}+w_{11}+w_{12}+w_{13}+w_{14}) \\
&[\nu_f v_9 + v_{10}(1-\nu_f)] \Bigg\} < 0.
\end{aligned}
$$

Furthermore, it can be shown that:

$$
b = \sum_{i=1}^{14} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*} = c_m[\nu_f v_9 + v_{10}(1-\nu_f)](w_4 + w_5\zeta_m + w_6\nu_m + w_7\zeta_m\nu_m) > 0.
$$

Since the coefficient a is negative, and b is always positive, it follows (by Theorem 2.3) that the system (F.1) will not undergo backward bifurcation. □

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