ANALYSIS OF CO-INFECTION OF HUMAN IMMUNODEFICIENCY VIRUS WITH HUMAN PAPILLOMAVIRUS

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This dissertation is submitted to the School of Mathematics, Statistics and Computer Science at University of KwaZulu-Natal, Pietermaritzburg, in the fulfilment of the requirements for the degree of Master in Science.

As the candidate's supervisor, I have approved this dissertation for submission.

Signed: Dr. F. Chirove .....

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Dedication

To the Almighty God, to the Holy Spirit and Saviour Jesus Christ.

To my brothers and sisters for their fervent prayers.

Abstract

We formulate a deterministic mathematical model for the co-infection of HPV with HIV without treatment. Mathematical techniques were used to analyze the stability of the models in terms of basic reproduction numbers for disease-free equilibrium point and fixed point theory used for analysis of the endemic equilibrium point. The model incorporating HIV and HPV co-infection sought to investigate the impact of HIV infection in the natural history of HPV infection, and the impact of HPV infection in the natural history of HIV infection, over a period of time. Numerical simulations were carried out to illustrate the trends of progression of HIV and HPV in the case of co-infection. The results from our study showed that when both HIV and HPV infected individuals are active in the system then co-infection grows faster compared to one infection which is active in the system. Our study also showed that when we started with HPV infection in the community and introduces HIV infection after sometime has more impact in the growth of co-infection population compared to start with HIV infection and introduces HPV infection after sometime in the community.

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Chapter 1

INTRODUCTION

1.1 Background information

Human Papillomavirus (HPV) is a DNA virus from the papillomavirus family that affects the human skin and moist membranes of the body. It can affect the throat, mouth, feet, fingers, nails, vulva, vagina, penis, anus and cervix. HPV is mainly transmitted through sexual intercourse or oral sex [1]. HPV is one of the major global health problems. The prevalence of HPV infection in South Africa is estimated to be between 14.6% to 22.3% people of at least 15 years of age are infected with HPV. This means that about 6.9 million people are infected with HPV in South Africa [2]. Globally, between 9% and 14.3%, that is about 630 million people of at least 15 years of age are infected with HPV [3, 4]. HPV is one of the most common sexually transmitted infectious (STIs). The sexually active adults can acquire more than one type at some point in their lifetimes [5, 6]. HPV infection is very high in populations with a high rate of HPV acquisition, such as those who are sexually active, but most of the infections are transient [7].

HPV is classified into two groups namely low-risk and high-risk HPV types. Low-risk HPV types can cause genital warts or very minor cell changes on the cervix and they are not virulent. The low-risk HPV types includes 6, 11, 40, 42, 43, 44, 54, 55, 57, 61, 70, 72, 83 and 84. High-risk HPV types can cause abnormal cells to form on the cervix and they are virulent. The high-risk HPV types includes 16, 18, 26, 31, 33, 34, 35, 39, 45, 51, 53, 56, 58, 59, 66, 68, 73, 80 and 82 [8]. Between 30 and 40 HPV types are transmitted through sexual contact [9]. Individuals can clear HPV through an effective immune response and the body can heal itself naturally. Treatment or vaccination can also be used to clear HPV from an individual's body.

Human Immunodeficiency Virus (HIV) is a retrovirus that fights the immune system. If HIV is in the individual's system, it lowers the number of healthy cells ($CD4^+$ T cells) that the body have to fight against infection [10]. Acquired Immune Deficiency Syndrome (AIDS) is the disease caused by HIV. It is the final stage of HIV infection before an individual dies. At this stage the individuals gets exposed to opportunistic infections such as diarrhoea, cholera, malaria, and tuberculosis. HIV can be transmitted through blood transfusion, unprotected sexual contact, mother to child, and through breast feeding. There are various factors that influence the spread of HIV/AIDS in the community. These include heavy alcohol consumption, drug misuse, poverty and STIs [11–14].

HIV is also an STI where heterosexual transmission is the dominant mode of HIV transmission on both men and women. HIV and AIDS infected individuals do not recover from their infection because there are non curable diseases. There are many ways of prevention and control measures which can be taken in reducing the spread of HIV infections such as the use of condoms, sticking to one partner, avoiding the sharing of needles or syringes with anyone, counseling and testing, and treatment with antiretroviral drugs [15].

HIV/AIDS is also a major public health problem. Heterosexual transmission is the main mode of transmission of HIV in sub-Sahara Africa, a region mostly hit with approximately 74% of the global burden. In this region, 19.9 million people aged 15 years and above are living with HIV and about 1.37 million are newly infected with HIV every year in sub-Sahara Africa. Globally, 26.9 million people of at least 15 years old are living with HIV and 1.55 million people become newly infected with HIV every year [16]. Of the 1.7 million people who die because of AIDS related illness globally, 1.19 million deaths are from sub-Sahara Africa [16].

HIV/HPV co-infection is the infection of individuals with both HIV and HPV infections. Individuals may be first infected with HIV and then infected with HPV or vice versa. Many observational studies involving HIV-positive patients showed a strong and consistent relationship between HIV and HPV [17]. Individuals who are HIV-positive are at high risk of infection with HPV types [18,19]. The increased risk among individuals with HIV/AIDS is consistent with high incidence and persistence of HPV infection [20]. There is evidence showing that high-risk HPV types are associated frequently with HIV-positive individuals [18,21]. Low-risk HPV types were mostly associated with HIV-negative individual population. There are high-risk HPV types which are associated with HIV-negative population and there are also low-risk HPV types which are also associated with HIV-positive population. HPV types associated with the HIV-positive population are HPV type 6, 11, 39, 43, 51 and 53. HPV types 40 and 68 associated with HIV-negative. HPV type 16, 18, 35, 52, 58, 40, 42, 44 and 54 found in both HIV-negative and positive [19].

The population of individuals who are HIV infected have increased susceptibility to HPV infection. Most individuals who are found to be HIV-positive are those with high proportion of multiple

HPV types [4].

1.1.1 Problem statement

The co-infection of HPV with HIV is a significant and growing problem worldwide. Individuals may be infected with HPV first and then with HIV infection or they may get infected with HIV first then with HPV. Individuals can get infected with both infections (HPV and HIV) at the same time. Since HIV infection is an infection that greatly compromises the immune system of an individual, the introduction of an additional infection like HPV can heavily cause a drastic deterioration of the body's immune response to both infections. It is therefore worthy exploring the effects of having both infections prevalent in a community where part of the community is only infected with one of the two infections and part of the community is infected by both infections. Mathematical models are one of the tools that can be used to analyze and understand the interplay of HIV/HPV co-infection. There are rich mathematical theories that can be used to abstract the biological processes and patterns of infectious diseases into mathematical formulations where analysis can be transferred back to the biological explanation.

1.1.2 Aim

The aim of the study is to use mathematical models to understand the co-infection of HIV with HPV and the consequences associated with occurrence of both infections in a community.

1.1.3 Objectives

The specific objectives of the study is to develop a model incorporating HIV/HPV co-infection and analyze it to address the following research questions:

(i) By how much impact does HIV infection impact the progression of HPV infection in a community?

(ii) By how much impact does HPV infection impact the progression of HIV infection in a community,

over a period of time?

1.1.4 Significance of the study

This research may help countries to improve policies on intervention regulating HIV/HPV co-infection since many co-infections change the known dynamics and prognosis of individual infections. The outcomes of this study will help the Government to establish policies, programmes and plans for control of the HPV-HIV co-infection by taking into account of vaccination and treatment.

1.1.5 Scope of the project

The study is divided into six chapters. The first chapter has so far included the introduction to HPV, HIV/AIDS and HIV/HPV co-infection, and statement of the problem, aim, objectives, and significance of the study. In the second chapter, we look at the literature review, where we give the definitions of basic concepts and analytical techniques which are useful in our analysis. In chapter 3, we look at the review of the low-risk and high-risk HPV types models. Chapter 4 contains the co-infection model of HPV with HIV. In chapter 5, we carryout numerical simulations of the co-infection of HPV with HIV model. In chapter 6, we discuss the results from simulations, give possible recommendations and conclusion based on our model results.

Chapter 2

LITERATURE REVIEW

2.1 Introduction

Here we look at the theoretical concepts and definitions of the concepts which we shall use in this study. The techniques give a spectrum over which we are able to ensure the existence of biologically sensible solutions of the model and their behavior over time. We shall also review some mathematical models that were used to model HPV infection and use these as building blocks of the HPV/HIV co-infection model. We shall also discuss the different types of mathematical models used in modelling infectious diseases.

2.2 Preliminary concepts

2.2.1 Basic reproduction number, R_0

The basic reproduction number, R_0, is the average number of secondary infections produced by a typical infective person in a totally susceptible population [22]. To find the threshold R_0, we

assume that there are n compartments of which m are infected, $\overline{x} = (x_1, x_2, ..., x_n)$, where $\overline{x}$ is the disease-free equilibrium (DFE) point and x_i denotes the number or proportion of individuals in the i^{th} compartment. Let $\mathcal{F}_i(\overline{x})$ be the rate of appearance of new infections into compartment i and let $\mathcal{V}_i(\overline{x}) = \mathcal{V}_i^-(\overline{x}) - \mathcal{V}_i^+(\overline{x})$, where $\mathcal{V}_i^+$ is the rate of transfer of individuals into compartment i by all other means and $\mathcal{V}_i^-$ is the rate of transfer of individuals out of the i^{th} compartment. We can form the next generation matrix (operator) FV^{-1} from matrices of partial derivatives of $\mathcal{F}_i$ and $\mathcal{V}_i$ evaluated at $\overline{x}$ [23]. $F = \left[\dfrac{\partial \mathcal{F}_i(\overline{x})}{\partial x_j}\right]$ and $V = \left[\dfrac{\partial \mathcal{V}_i(\overline{x})}{\partial x_j}\right]$, where $i, j = 1, ..., m$. The entries of FV^{-1} give the rate at which infected individuals in x_j produce new infections in x_i, times the average length of time an individual spends in a single visit to compartment j. R_0 is given by the spectral radius (dominant eigenvalue) of the matrix FV^{-1}, that is, $R_0 = \rho(FV^{-1})$.

2.2.2 Bifurcation

A bifurcation is a qualitative change in the nature of the solution of the trajectories due to a parameter change. A bifurcation surface is a surface at which the equilibrium surfaces separate from each other.

A transcritical bifurcation is a bifurcation where there is an exchange of stability between two equilibrium points at a bifurcation point that is the stability is transferred from one equilibrium point to another. In models for infectious diseases the exchange of stability normally occurs between a DFE point and the endemic equilibrium point at $R_0 = 1$, so that the DFE point become unstable and the endemic equilibrium point becomes stable depending continuously on R_0 [24]. A transcritical bifurcation can either be supercritical (forward) or subcritical (backward). In supercritical bifurcation, the disease-free equilibrium point loses its stability when it passes through the bifurcation point and the endemic equilibrium point gains its stability. Thus, a supercritical bifurcation ensures that the

endemic equilibrium point is locally stable when $R_0 > 1$ [12].

A backward bifurcation in epidemic models occurs when there is existence of two sub-critical endemic equilibria for $R_0 < 1$. The initial direction of the bifurcation curve is such that as we move along it from the bifurcation point, R_0 decreases as the level of infection increases. This means that the occurrence of backward bifurcation certainly has an implications for disease control since it is now possible for the disease to spread or multiply even when $R_0 < 1$. There is need to further reduce the R_0 in order to ensure that the disease is eliminated from the population. At least two subcritical endemic equilibria exist for which $R^* < R_0 < 1$, where R^* corresponds to the value of R_0 at which a vertical turning point on the bifurcation curve occurs. Therefore, in order to ensure that the disease is eradicated from the population we require that $R_0 < R^*$ [13, 25–27].

2.2.3 Center manifold theorem

The center manifold theorem provides a technique to analyze a bifurcation or catastrophe. A catastrophe is the sudden jump between DFE point and endemic equilibrium surface. The theory plays a powerful role in the study of non-linear systems when the equilibrium point is not hyperbolic [28]. Under the normal form and with minimum phase assumption, a stabilization technique via the center manifold, would be used to stabilize general affine non-linear control systems. For the case of the non-minimum phase, the results would be obtained by introducing some new tools such as a Lyapunov functions with homogeneous derivative to design the center manifold. For the equilibrium point, the dimensions of such manifolds is determined by the number of roots of the characteristic equation with zero real parts, and for the periodic orbits it is determined by the number of multipliers that lie on the unit circle. Most of the non-linear phenomena have their origin in solutions that are characterized by the zero real part of an eigenvalue of the Jacobian matrix [29].

If we consider a continuous-time system defined by $\dot{x} = f(x)$, x in $\mathbb{R}^n$, where f is a sufficiently smooth vector field on $\mathbb{R}^n$ with $f(0) = 0$, we can find the eigenvalues $\lambda_1, \lambda_2, ..., \lambda_n$ of the Jacobian matrix A of the system evaluated at the equilibrium point $x_0 = 0$ [30]. Suppose the equilibrium point is not hyperbolic and that there are eigenvalues with zero real part. We assume that there are n_+ eigenvalues with $Re(\lambda) > 0$, n_0 eigenvalues with $Re(\lambda) = 0$, and n_- eigenvalues with $Re(\lambda) < 0$. We let T^c denote the linear (generalized) eigenspace of matrix A corresponding to the union of the set of the n_0 eigenvalues and the imaginary axis. The eigenvalues with $Re(\lambda) = 0$ are often called critical, in the eigenspace T^c. We can describe the general center manifold theory using the following theorem:

Theorem 2.2.1. *Castillo-Chavez and Song [29]*

We consider the following system of ordinary differential equations (ODEs) with a parameter ϕ:

$$\frac{\partial x}{\partial t} = f(x, \phi),\ f : \mathbb{R}^n \times \mathbb{R} \longrightarrow \mathbb{R}\ \textbf{\textit{and}}\ f \in C^2(\mathbb{R}^n \times \mathbb{R}). \tag{2.1}$$

It is assumed that $x_0 = \mathbf{0}$ is an equilibrium for system (2.1) for all the parameters values of ϕ, that is

$$f(0, \phi) \equiv 0 \text{ for all } \phi. \tag{2.2}$$

We assume that

(1) $A = D_x f_{(0,0)} = \dfrac{\partial f_i}{\partial x_j}(0, 0)$, $1 \leq i, j \leq n$, is the linearization matrix of the system equation (2.1) around the equilibrium $x_0 = \mathbf{0}$ with ϕ evaluated at 0. We have a simple eigenvalue zero of A and all other eigenvalues of A have negative real parts.

(2) Matrix A has a non-negative right eigenvectors $W = (w_1, w_2, ..., w_n)$ and left eigenvectors $V = (v_1, w_2, ..., w_n)$ corresponding to the zero eigenvalue.

We let f_k be the k^{th} component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0), \qquad b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \phi}(0,0). \tag{2.3}$$

The local stability of the equilibrium point $x_0 = \mathbf{0}$ is determined by the signed of a and b.

(i) $a > 0$, $b > 0$. *When $\phi < 0$ with $|\phi| \ll 1$, $x_0 = \mathbf{0}$ is locally asymptotically stable, and there exists a positive unstable equilibrium; when $0 < \phi \ll 1$, $x_0 = \mathbf{0}$ is unstable and there exists a negative and locally asymptotically stable equilibrium.*

(ii) $a < 0$, $b < 0$. *When $\phi < 0$ with $|\phi| \ll 1$, $x_0 = \mathbf{0}$ is unstable; when $0 < \phi \ll 1$, $x_0 = \mathbf{0}$ is locally asymptotically stable, and there exists a positive unstable equilibrium.*

(iii) $a > 0$, $b < 0$. *When $\phi < 0$ with $|\phi| \ll 1$, $x_0 = \mathbf{0}$ locally asymptotically stable negative equilibrium; when $0 < \phi \ll 1$, $x_0 = \mathbf{0}$ is stable, and a positive unstable equilibrium appears.*

(iv) $a < 0$, $b > 0$. *When ϕ changes from negative to positive, $x_0 = \mathbf{0}$ changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

2.2.4 Fixed point

Let I be a set and let $f : I \longrightarrow I$ be a function that maps I into itself and such a function is often called an operator, a transformation, or a transform on I. A fixed point of f is an element of I_i of I for which $f(I_i) = I_i$ [31]. We use fixed points theory to obtain the existence of the endemic equilibria. We investigate their existence under some specific conditions, where $f(I_i)$ is the disease incidence for stage i, $(i = 1, 2, ..., n)$ and I_i is the infectious class. The non-linear function f is assumed to satisfy the following assumptions:

(i) $f(0) = 0$, $\quad$ (ii) $\quad f'(I_i) > 0$,

(iii) $f''(I_i) < 0$, $\quad$ *and* $\quad$ (iv) $\quad \lim_{I \to +\infty} f(I_i) = C < +\infty$.

The function f is an increasing, bounded and convergent with no change of convexity on a finite interval [32]. Let $\mathbf{y}$ be the solution of $\mathbf{y} = \mathbf{f}(\mathbf{y})$ that is $\mathbf{y}$ which is a fixed point of $\mathbf{f}$. Consider the dynamics of the distances $\mathbf{y^{(v)}} - \mathbf{y}$ between iterates $\mathbf{y^{(v)}}$ and a fixed point $\mathbf{y}$ (v $= 0, 1, 2, ..., n$). If $\mathbf{y^{(v+1)}} = \mathbf{f}(\mathbf{y^{(v)}})$ and $\mathbf{y} = \mathbf{f}(\mathbf{y})$, then

$$\mathbf{y^{(v+1)}} - \mathbf{y} = \mathbf{f}(\mathbf{y^{(v)}}) - \mathbf{f}(\mathbf{y}) = \frac{\partial \mathbf{f}(\mathbf{y})}{\partial \mathbf{y}}(\mathbf{y^{(v)}} - \mathbf{y}) + \mathbf{t.h.o.}$$

The local stability is then governed by the linearization (up to terms of higher order, t.h.o),

$$\mathbf{y^{(v+1)}} - \mathbf{y} = \mathbf{J}(\mathbf{y^{(v)}} - \mathbf{y}),$$

which implies

$$\mathbf{y^{(v)}} - \mathbf{y} = \mathbf{J^v}(\mathbf{y^{(0)}} - \mathbf{y}).$$

Here $\mathbf{J}$ denotes the Jacobian matrix $\mathbf{f_y}$ of the n^2 first order partial derivatives of $\mathbf{f}$, evaluated at $\mathbf{y}$. Then there exists a set of n linearly independent eigenvectors $\mathbf{w^k}$ with eigenvalues μ_{k} such that the initial distance $(\mathbf{y^{(0)}} - \mathbf{y})$ can be written as a linear combination, and $\mathbf{y^{(v)}} - \mathbf{y} = \mathbf{J^v}(\mathbf{y^{(0)}} - \mathbf{y})$ implies

$$\mathbf{y^{(v)}} - \mathbf{y} = \mathbf{J^v} \sum_{\mathbf{k=1}}^{\mathbf{n}} \mathbf{c_k w^k} = \sum_{\mathbf{k=1}}^{\mathbf{n}} \mathbf{c_k J^v w^k} = \sum_{\mathbf{k=1}}^{\mathbf{n}} \mathbf{c_k} \mu_{\mathbf{k}}^{\mathbf{v}} \mathbf{w^k},$$

which shows that convergence $\mathbf{y^{(v)}} \to \mathbf{y}$ can only take place for v $\to \infty$ when $|\mu_{\mathrm{k}}| < 1$ for all k $= 1, 2, ..., n$ [33].

Theorem 2.2.2.

Assume that all eigenvalues μ_k of $\mathbf{J}$ lies inside the unit circle, $|\mu_k| < 1$. Then, locally, the iterates $\mathbf{y^{(v)}}$ converge towards $\mathbf{y}$, which is a stable fixed point. If $|\mu_k| < 1$, then the fixed point is stable. If $|\mu_k| > 1$, then the fixed point is unstable and the iterates $\mathbf{y^{(v)}}$ moves away from $\mathbf{y}$ or it diverges.

2.3 Literature review

Ribassin-Majed et al [6], formulated a deterministic mathematical model for the transmission of HPV 6/11. The purpose of study was to assess the impact of the quadrivalent HPV vaccine on the prevalence of non-oncogenic HPV 6/11 types in French individuals. Quadrivalent HPV vaccine is a four-in-one vaccine used to protect individuals from high-risk HPV types 16/18 and low-risk HPV types 6/11. The transmission of HPV was only through sexual means where vaccination can be used effectively. The vaccinated reproduction number R_v was calculated. The results showed that if $R_v > 1$, the endemic equilibrium point exists and is globally asymptotically stable. If $R_v < 1$, the disease-free equilibrium point exists and is globally asymptotically stable and HPV will die out. Their modeling projected that in 10 years time after the introduction of vaccination, HPV 6/11 prevalence in females would be halved and HPV 6/11 prevalence in males would be reduced by a quarter, assuming a sustained vaccine coverage of 30% among females. However, the study did not include the effects of the vaccine towards high-risk HPV types, which are more virulent than the low-risk HPV types. The impact of the vaccine could be affected by the presence of HIV if it is introduced as a co-infection.

Lee and Tameru et al [1], formulated a mathematical model on HPV and the impact of HPV on cervical cancer. The objective of study was to develop a mathematical model of HPV for African American Women (AAW) in the United States and give quantitative insights into the U.S. prevention and mitigation against cervical cancer. Their model showed that there is a direct relationship between HPV and cervical cancer. Their results exposed the potential to test the effectiveness of new methods of treatment that could be used to reduce the rate of infectivity of HPV and cervical cancer with time. Their research was concentrated on AAW and as a results, the results may not be used to infer the dynamics in men infected with HPV. HPV is one of the sexually transmitted

infection, which can be worsened by other STI diseases such as HIV.

A study by Xiao et al was done on predicting the HIV/AIDS epidemic and measuring the effects of mobility [34]. They formulated a network and compartmental model which enhanced the understanding of the spread and control of HIV in China. They analyzed the spatial characteristics of HIV/AIDS cases, based on the national surveillance system and to addressed the effect of mobility on the HIV/AIDS epidemic in mainland China. HIV-positive individuals who are likely to move from economically developed regions to regions with large numbers of HIV cases, while AIDS individuals move in opposite direction, where individuals have to return to their registered residence to get free antiretroviral treatment.The study focused on high-risk groups only. Low-risk groups may also affect significantly the mobility patterns with time since at any moment they are likely to change their behaviour.

Bhunu et al [11], formulated a mathematical model on the assessing the effects of drug use on the transmission dynamics of HIV/AIDS. Their study was on drug misuse which was recognized to have a significant impact on the spread of HIV/AIDS epidemic.The study was on spread of HIV/AIDS on drug misusers and non-drug users. Drug misusers infected each other through drug injection, while non-drug users infected each other through sexually intercourse. Their theoretical results showed that drug misuse had the capability to increases the spread of HIV transmission through the basic reproduction number. HIV/AIDS is one of the STI's which can co-infect individuals with other STI's such as HPV and so the impact of drug misuse could also be addressed in the case of co-infections.

Auvert et al looked at related study on HIV/HPV co-infection [18]. They formulated a data based model on the association between high risk HPV and HIV acquisition. The objective of their study

was to assess HPV as a risk factor of HIV acquisition among South African Female Sex Workers (FSWs). The study targeted FSWs group which were to be at high-risk of STIs such as HPV and HIV. They found that high-risk HPV was significantly and independently associated with HIV acquisition among South African FSWs. The risk of acquiring HIV infection was significantly increased as a result of multiple high-risk HPV infections. There was no association found in low-risk HPV with HIV acquisition. The study does not include men in the co-infection, while men infect females in the heterosexual transmission of the HIV and HPV co-infection.

Another study on co-infection of HPV with HIV was done by Baay et al [19], they formulated a baseline model or data based model on HPV in a rural community. The study investigated the HPV prevalence and the impact of HIV co-infection on HPV genotype distribution in a rural community in Zimbabwe, with a high prevalence of HIV infection. They found out that high-risk and low-risk HPV types were associated with HIV-positive women. Low-risk HPV type were also found in HIV-positive and HIV-negative individuals. Their research was on data based model, which only captures the pattern of the infections but does not capture interactive processes that leads to the patterns shown by the data. Mathematical models have the ability to capture both the processes and the patterns.

2.4 Types of mathematical models

Mathematical modelling is the representations of some real world entity and can be in the form of equations or computer codes. The modelling is characterized by assumptions about variables, parameters and functional forms which is the relationship between variables and parameters. Mathematical modelling is a formal practical application of our thought processes expressed in terms of a series of equations, that is, differential equations and stochastic processes. It also plays a great role in

developing scientific understanding of complex biological processes of the epidemic. Mathematical modelling helps us to clearly understand the underlying mechanisms and processes of diseases. It allows us to investigate how the disease spreads in a system as a whole function. Important concepts of infectious diseases such as understanding how the number of new infections at a particular time depends on number of infections and susceptible individuals at existing points in time are also addressed using mathematical models. Mathematical models are classified into the following categories: deterministic, stochastic, spatial, non-spatial, partial differential equations (PDEs), continuous-time and discrete-time models [35, 36].

A deterministic model is a type of mathematical modelling in which outcomes are definitely determined through known relationships among states and events without any room for random variation or measurement error. The assumptions and equations of the deterministic model selected will determine the outcome results. The model processes are often described by differential equations. The models have unique inputs leading to unique outputs for a defined linear models and multiple outputs possible for nonlinear models. The model can be based on the nonlinear dynamics of infection spreading in a population. The model equations can be solved analytically or by numerical methods after discretization, that is, by modification to run on a grid or a mesh and parameterization by setting parameters to account for subgrid processes [35, 37].

A stochastic model is a type of mathematical modelling which presents data or predicts outcomes using ranges of values for variables in the form of probability distributions. The output is represented by a probability distribution, which can be estimated from simulations. Stochastic models are more computationally demanding compared to deterministic models. The stochastic model produces many outcomes, since every iteration produces a different outcome. Many iterations are required for

stochastic models to produce a representative distribution of possible outcomes [35].

Spatial models are used to model diseases that spread within a population by assuming that all individuals within it mix evenly with each other through social or sexual contact. Spatial heterogeneity in populations is important in determining contact patterns between individuals, with potentially profound implications for disease dynamics. Non-spatial models handles the whole population as homogeneous without considering space or any social interactions. Partial differential equations models are used if two or more continuous independent variables are used, for example, time and space, and time and age and comes from a basic balance or conservation law. The conservation law ensures that a particular measurable property of an isolated physical system does not change as the system develops over time [35, 36].

Continuous-time models have more mathematical elegance and can bring more mathematical machinery to bear on the problem which helps in deriving analytically solutions and asymptotic limits [35]. Discrete-time models are used to describe dynamical circumstances in biology and are appropriate when circumstances are defined by discrete time steps [35, 36]. Discrete-time models are more suitable in modeling observed data where measurements are easier to simulate. Discrete-time models are also used to describe the dynamics of various populations and developing methods of optimal control strategies against new infections of diseases [38].

We want to investigate that mathematical models can be useful tools in exploring diseases trends and health consequences of interventions in a population over the time. In our study, we develop a deterministic model represented by the nonlinear ordinary differential equations to describe the heterosexual transmission of the HIV and HPV infections in the population. We have established

so far that HPV as an STI has a potential to complicate diseases dynamics in co-infection scenarios such as in the case of cancer, drug abuse, HIV etc. We shall use this results to investigate HPV effects in case the co-infection is with HIV infection.

Chapter 3

REVIEW OF HUMAN PAPILLOMAVIRUS MODELS

3.1 Introduction

Human Papillomavirus (HPV) is one of the most common sexually transmitted infections in both men and women [39]. As stated earlier, at least 70% of sexually active people acquire HPV infection at some point in their lives [40]. We shall review some mathematical models on HPV information and improvise some of the models using information from the history of HPV. This will set up some precedence towards our study on HPV and HIV co-infection. Mathematical models are important in the study of HPV infection because they are useful tool in simplifying the study of the impact of the processes involved in the spread of HPV. It is important in helping the countries to plan and to predict the health outcomes in the long run [41].

3.2 Basic sex-structured HPV model

We develop a mathematical model for HPV infection stratifying it into sexually active population with the following classes: HPV Susceptibles females (S_w) and males (S_m), HPV Infectious females (I_w) and males (I_m) and HPV Recovered females (R_w) and males (R_m), where subscript w represent females and m represent males. We assume that HPV is spread through heterosexual transmission

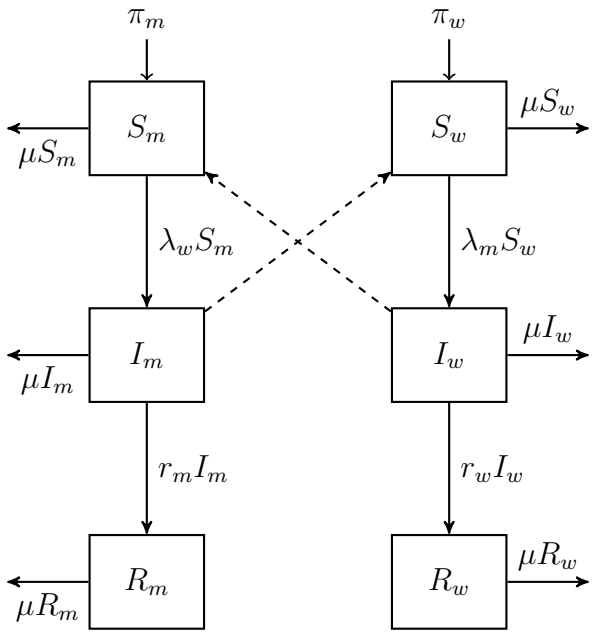

Figure 3.1: Flow chart for the HPV model. The dashed arrows represent cross infection and the solid arrow represent the flow of individuals into and out of the compartment.

only and the probability of an individual acquiring HPV infection is dependent on sexual contact patterns of the distribution of the infection within the population [42]. This means that men can only have sexual contacts with women and vice versa. We therefore assume that recruitment into the susceptible females and males compartments is through sexual maturity and onset of sexual activity. We use constant recruitment rates of π_w and π_m for entry into compartments S_w and S_m respectively. Individuals from susceptible compartments can leave either through natural death at a rate μ or through acquiring HPV infection. Susceptible women acquire HPV infection through a

force of infection $\lambda_m = \beta_w I_m$, $\beta_w = c_w q$, where c_w is the number of male contacts a female makes per unit time and q is the probability of successful HPV infection through a contact. Similarly, a susceptible male acquires infection through a force of infection $\lambda_w = \beta_m I_w$, $\beta_m = c_m q$ where c_m is the number of female contacts a male makes per unit time. $\beta_w = \beta_m$ that is the total average contact rate of females are equals to the total average rage of males. Once infected, women and men enter new compartments I_w and I_m of infectives respectively. They leave these classes either through natural death (at a rate μ) or through recovery at rates r_w and r_m for women and men respectively. Individuals from I_w and I_m can recover from HPV infection naturally and progress to the recovery compartments R_w and R_m (for women and men respectively). Once individuals recover, they acquire immunity to HPV for the entire period of infection [43, 44]. They can only leave the recovery classes through natural death. In this basic model, we assume that there is no regression back to a class once the individual move out of it. This is a simplifying assumption for mathematical tractability so that we can identify the basic dynamics of HPV infection using a basic model. Our HPV model was modified from an aged-structured model of human papillomavirus vaccination [45] and we did not consider vaccination. We collapsed the aged structured model to non aged structured model because one infection in each age group are rely on affected by one type of infection. The model guided by the stated assumptions is given by:

$$\frac{dS_w}{dt} = \pi_w - \lambda_m S_w - \mu S_w, \tag{3.1}$$

$$\frac{dI_w}{dt} = \lambda_m S_w - (\mu + r_w) I_w, \tag{3.2}$$

$$\frac{dR_w}{dt} = r_w I_w - \mu R_w, \tag{3.3}$$

$$\frac{dS_m}{dt} = \pi_m - \lambda_w S_m - \mu S_m, \tag{3.4}$$

$$\frac{dI_m}{dt} = \lambda_w S_m - (\mu + r_m) I_m, \tag{3.5}$$

$$\frac{dR_m}{dt} = r_m I_m - \mu R_m. \tag{3.6}$$

We define N_w as the total female population, N_m as the total male population, $N(t)$ as the total population given by

$$\begin{aligned} N_w(t) &= S_w(t) + I_w(t) + R_w(t), \\ N_m(t) &= S_m(t) + I_m(t) + R_m(t), \\ N(t) &= N_w(t) + N_m(t). \end{aligned}$$

3.2.1 Feasible region

For the system of equations (3.1)-(3.6), we need to prove that all the variables remains non-negative such that the solutions of the systems of equations with positive initial conditions will remain positive for all $t \geq 0$ and that all the solutions are bounded for all $t \geq 0$.

Lemma 3.2.1.

Let $S_w(0) \geq 0$, $I_w(0) \geq 0$, $R_m(0) \geq 0$, $S_m(0) \geq 0$, $I_m(0) \geq 0$, $R_m(0) \geq 0$. The solution $S_w(t)$, $I_w(t)$, $R_w(t)$, $S_m(t)$, $I_m(t)$ and $R_m(t)$ are positively invariant for all $t \geq 0$ in the region

$$\Omega = \{(S_w, I_w, R_w, S_m, I_m, R_m) \in \mathbb{R}_+^6\}.$$

Proof.

For $t \geq 0$ we have from equation (3.1) that

$$\frac{dS_w}{dt} = \pi_w - (\lambda_m + \mu)S_w.$$

This gives

$$\frac{d}{dt}\left[S_w(t)e^{\left(\mu t + \int_0^t \lambda_m(s)ds\right)}\right] = \pi_w e^{\left(\mu t + \int_0^t \lambda_m(s)ds\right)}.$$

The solution is

$$S_w(t)e^{\left(\mu t + \int_0^t \lambda_m(s)ds\right)} = S_w(0) + \int_0^t \pi_w e^{\left(\mu s + \int_0^s \lambda_m(w)d(w)\right)}ds,$$

so that

$$\begin{aligned} S_w(t) &= S_w(0)e^{\left(-(\mu t+\int_0^t \lambda_m(s)ds)\right)} \\ &+ e^{\left(-(\mu t+\int_0^t \lambda_m(s)ds)\right)}\left[\int_0^t \pi_w e^{\left(\mu s+\int_0^s \lambda_m(w)dw\right)}ds\right] > 0. \end{aligned}$$

From equation (3.2), we obtain

$$\begin{aligned} \frac{dI_w}{dt} &\geq -(\mu + r_w)I_w, \\ I_w(t) &\geq I_w(0)e^{-(\mu + r_w)t} \geq 0. \end{aligned}$$

Similarly,

$$\begin{aligned} R_w(t) &\geq R_w(0)e^{-\mu t} \geq 0, \\ S_m(t) &= S_m(0)e^{\left(-(\mu t+\int_0^t \lambda_w(s)ds)\right)} \\ &+ e^{\left(-(\mu t+\int_0^t \lambda_w(s)ds)\right)}\left[\int_0^t \pi_m e^{\left(\mu s+\int_0^s \lambda_w(w)dw\right)}ds\right] > 0, \\ I_m(t) &\geq I_m(0)e^{-(\mu + r_m)t} \geq 0, \\ R_m(t) &\geq R_m(0)e^{-\mu t} \geq 0. \end{aligned}$$

□

Adding the right hand side of system of equations (3.1)-(3.6) we obtain

$$\frac{dN}{dt} = \pi_w + \pi_m - \mu N(t), \tag{3.7}$$

The solution of the differential equation (3.7) is given by

$$N(t) = \frac{\pi_w + \pi_m}{\mu}(1 - e^{-\mu t}) + N_0 e^{-\mu t}.$$

We have $\lim_{t\to\infty} N(t) = \frac{\pi_w + \pi_m}{\mu}$. We then obtain $0 \leq N(t) \leq \frac{\pi_w + \pi_m}{\mu}$. This means that $\frac{\pi_w + \pi_m}{\mu}$ is the upper bound of $N(t)$. Hence all the solutions of equations (3.1)-(3.6) which initiate in $\mathbb{R}^6_+$ are

eventually confined in the region Ω. Clearly, the set Ω is positively invariant with respect to the system of equations (3.1)-(3.6).

3.2.2 Basic reproduction number, R_0

We compute the basic reproduction number R_0 in order to analyze the local and global stability of the disease-free equilibrium point (DFE) and endemic equilibrium point which depends on R_0 values [46]. The basic reproduction number of the model equations (3.1)-(3.6) is computed by using the next generation matrix. We consider a matrix $\mathcal{F}_i$ of the rate of appearances of new infectives into the compartment i, where i representing w for women and m for men, a matrix $\mathcal{V}_i^-$ which is the rate of transfer of infected individuals out the compartment i, a matrix $\mathcal{V}_i^+$ which is the rate of transfer of infected individuals into the compartment i by all other means so that $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ [23].

Now,

$$\mathcal{F} = \begin{pmatrix} \beta_w I_m S_w \\ \\ \beta_m I_w S_m \end{pmatrix}, \quad \mathcal{V}^- = \begin{pmatrix} (\mu + r_w) I_w \\ \\ (\mu + r_m) I_m \end{pmatrix}, \quad \mathcal{V}^+ = \begin{pmatrix} 0 \\ \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} (\mu + r_w) I_w \\ \\ (\mu + r_m) I_m \end{pmatrix}.$$

The DFE is obtained by setting the right hand side of the system of equations (3.1) to (3.6) to zero, given by

$$E_0 \;=\; \left(\frac{\pi_w}{\mu}, \;\; 0, \;\; 0, \;\; \frac{\pi_m}{\mu}, \;\; 0, \;\; 0 \right).$$

The Jacobian matrices F and V of matrices $\mathcal{F}_i$ and $\mathcal{V}_i$ at E_0 are given respectively by:

$$F = \begin{pmatrix} 0 & \beta_w S_w^* \\ \\ \beta_m S_m^* & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \mu + r_w & 0 \\ \\ 0 & \mu + r_m \end{pmatrix},$$

where $S_w^* = \dfrac{\pi_w}{\mu}$ and $S_m^* = \dfrac{\pi_m}{\mu}$. The inverse of matrix V is

$$V^{-1} = \begin{pmatrix} \dfrac{1}{\mu + r_w} & 0 \\ \\ 0 & \dfrac{1}{\mu + r_m} \end{pmatrix},$$

and the next generation matrix defined by FV^{-1} is

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta_w S_w^*}{\mu + r_m} \\ \frac{\beta_m S_m^*}{\mu + r_w} & 0 \end{pmatrix}.$$

The characteristic equation of FV^{-1} is

$$\lambda^2 - \frac{\beta_w \beta_m S_w^* S_m^*}{(\mu + r_m)(\mu + r_w)} = 0,$$

whose roots are

$$\begin{aligned} \lambda &= \pm\sqrt{\left(\frac{\beta_w S_w^*}{\mu + r_m}\right)\left(\frac{\beta_m S_m^*}{\mu + r_w}\right)}, \\ \lambda &= \pm\sqrt{R_w R_m}, \end{aligned}$$

where

$$R_w = \frac{\beta_w \pi_w}{\mu(\mu + r_m)}, \tag{3.8}$$

$$R_m = \frac{\beta_m \pi_m}{\mu(\mu + r_w)}. \tag{3.9}$$

The basic reproduction number is defined as the spectral radius of the next generation matrix FV^{-1} denoted by $R_0 = \rho(FV^{-1})$ is given by

$$R_0 = \sqrt{R_w R_m} \Rightarrow R_0^2 = R_w R_m,$$

where R_w is the number of secondary infections generated by one infected man in a population of susceptible women during his infectious period and R_m is the number of secondary infections generated by a one infected woman in a population of susceptible men during her infectious period.

3.2.3 Endemic equilibrium point

The equilibrium points of the system of equations (3.1)-(3.6) are obtained by setting the right hand sides of differential equations (3.1)-(3.6) to zero.

$$
\begin{aligned}
\pi_w - \lambda_m^* S_w^* - \mu S_w^* &= 0, \\
\lambda_m^* S_w^* - (\mu + r_w) I_w^* &= 0, \\
r_w I_w^* - \mu R_w^* &= 0, \\
\pi_m - \lambda_w^* S_m^* - \mu S_m^* &= 0, \\
\lambda_w^* S_m^* - (\mu + r_m) I_m^* &= 0, \\
r_m I_m^* - \mu R_m^* &= 0,
\end{aligned}
$$

where

$$
\begin{aligned}
\lambda_m^* &= \beta_w I_m^*, \\
\lambda_w^* &= \beta_m I_w^*.
\end{aligned}
$$

If $I_w^* = I_m^* = R_w^* = R_m^* = 0$, then we have the disease-free equilibrium point given in section 3.2.2. If $I_w \neq 0$, $I_m \neq 0$, $R_w \neq 0$ and $R_m \neq 0$, then we have the endemic equilibrium point given by

$$
E_1 = \left(S_w^{**}, \ I_w^{**}, \ R_w^{**}, \ S_m^{**}, \ I_m^{**}, \ R_{**} \right),
$$

where

$$
\begin{aligned}
S_w^{**} &= \frac{\pi_w}{\mu} \left[\frac{\mu(\mu + r_m) R_0^2 + \beta_w \pi_m}{(\beta_w \pi_m + \mu(\mu + r_m)) R_0^2} \right], \\
I_w^{**} &= \frac{\mu^2 (\mu + r_m)(R_0^2 - 1)}{\beta_m (\beta_w \pi_m + \mu(\mu + r_m))}, \\
R_w^{**} &= \frac{\mu r_w (\mu + r_m)(R_0^2 - 1)}{\beta_m (\beta_w \pi_m + \mu(\mu + r_m))}, \\
S_m^{**} &= \frac{\pi_m}{\mu} \left[\frac{\beta_w \pi_m + \mu(\mu + r_m)}{\mu(\mu + r_m) R_0^2 + \beta_w \pi_m} \right], \\
I_m^{**} &= \frac{\mu \pi_m (R_0^2 - 1)}{\mu(\mu + r_m) R_0^2 + \beta_w \pi_m}, \\
R_m^{**} &= \frac{r_m \pi_m (R_0^2 - 1)}{\mu(\mu + r_m) R_0^2 + \beta_w \pi_m}.
\end{aligned}
$$

Clearly, I_w^{**}, I_m^{**}, R_w^{**} and R_m^{**} are positive only when $R_0 > 1$. We summarize the existence of the equilibrium points in the following theorem:

Theorem 3.2.2.

(i) The disease-free equilibrium point exists for all values of R_0.

(ii) The positive endemic equilibrium point exists only for $R_0 > 1$.

3.2.4 Stability analysis of equilibrium points

Theorem 3.2.3.

The disease-free equilibrium point is locally asymptotically stable when $R_0 < 1$.

Proof.

The analysis of the disease free equilibrium point is found by using the matrix $F - V$ [23].

$$F - V = \begin{pmatrix} -(\mu + r_w) & \beta_w S_w^* \\ \beta_m S_m^* & -(\mu + r_m) \end{pmatrix},$$

For stability of the matrix $F - V$, we need to show that $det(F - V) > 0$ and $tr(F - V) < 0$.

$$\begin{aligned} det(F - V) &= (\mu + r_w)(\mu + r_m)(1 - R_0^2) > 0, \\ tr(F - V) &= -((\mu + r_w) + (\mu + r_m)) < 0. \end{aligned}$$

The $det(F - V) > 0$ when $R_0^2 - 1 < 0$, that is $R_0 < 1$. This means that all eigenvalues of $F - V$ have negative real parts when $R_0 < 1$ and the stability of E_0 follows. If $R_0 > 1$, then $det(F - V) < 0$ meaning that at least one of the eigenvalues of $F - V$ has a positive real part and under this condition E_0 becomes unstable. □

Theorem 3.2.4.

The endemic equilibrium point E_1 is locally asymptotically stable when $R_0 > 1$.

Proof.

The Jacobian matrix of the system of equations (3.1)-(3.6) at E_1 is given by

$$J(E_1) = \begin{bmatrix} -(\beta_w I_m^{**} + \mu) & 0 & 0 & 0 & -\beta_w S_w^{**} & 0 \\ \beta_w I_m^{**} & -(\mu + r_w) & 0 & 0 & \beta_w S_w^{**} & 0 \\ 0 & r_w & -\mu & 0 & 0 & 0 \\ 0 & -\beta_m S_m^{**} & 0 & -(\beta_m I_w^{**} + \mu) & 0 & 0 \\ 0 & \beta_m S_m^{**} & 0 & \beta_m I_w^{**} & -(\mu + r_m) & 0 \\ 0 & 0 & 0 & 0 & r_m & -\mu \end{bmatrix}.$$

The eigenvalues of $J(E_1)$ are $\lambda_{1,2} = -\mu < 0$ and the rest are roots of the characteristic equation

$$\lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 = 0, \tag{3.10}$$

where

$$\begin{aligned} b_3 &= (\beta_1 I_m^{**} + \mu) + (\mu + r_w) + (\beta_2 I_w^{**} + \mu) + (\mu + r_m) > 0, \text{ when } R_0 > 1, \\ b_2 &= (\beta_w I_m^{**} + \mu)(\mu + r_w) + (\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu) + (\beta_w I_m^{**} + \mu)(\mu + r_m) \\ &\quad + (\mu + r_w)(\beta_m I_w^{**} + \mu) + (\beta_m I_w^{**} + \mu)(\mu + r_m) > 0, \text{ when } R_0 > 1, \\ b_1 &= (\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)(\mu + r_w) + (\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)(\mu + r_m) \\ &\quad + (\beta_w I_m^{**} + \beta_m I_w^{**})(\mu + r_w)(\mu + r_m) > 0, \text{ when } R_0 > 1, \\ b_0 &= (\beta_w I_m^{**} + \mu)\beta_w\beta_m^2 S_w^{**} S_m^{**} I_w^{**} + \mu\beta_w^2\beta_m S_w^{**} S_m^{**} I_m^{**} > 0 \text{ when } R_0 > 1. \end{aligned}$$

We shall use the Routh-Hurwitz criterion [47, 48] for polynomials of order four to prove the stability of E_1. The following conditions have to be established:

(i) $b_3 > 0$, (ii) $b_1 > 0$, (iii) $b_0 > 0$,

(iv) $b_2 b_3 - b_1 > 0$, (v) $b_1(b_2 b_3 - b_1) - b_3^2 b_0 > 0$.

Clearly $b_3 > 0$, $b_1 > 0$ and $b_0 > 0$ when $R_0 > 1$. It remains to prove conditions (iv) and (v). The expression for condition (iv) after manipulations and simplification is given by

$$
\begin{aligned}
b_2 b_3 - b_1 \;=\;& (\beta_w I_m^{**} + \mu)^2(\mu + r_w) + (\beta_w I_m^{**} + \mu)^2(\beta_m I_w^{**} + \mu) + (\beta_1 I_m^{**} + \mu)^2(\mu + r_m) \\
&+(\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)(\mu + r_w) + (\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)(\mu + r_m) \\
&+(\beta_w I_m^{**} + \mu)(\mu + r_w)^2 + (\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)(\mu + r_w) + (\beta_w I_m^{**} + \mu)(\mu + r_w)(\mu + r_m) \\
&+(\beta_m I_w^{**} + \mu)(\mu + r_w)^2 + (\beta_m I_w^{**} + \mu)(\mu + r_m)(\mu + r_w) + (\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)^2 \\
&+(\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)(\mu + r_m) + (\beta_m I_2^{**} + \mu)^2(\mu + r_w) + (\beta_m I_w^{**} + \mu)^2(\mu + r_m) \\
&+2\mu(\mu + r_w)(\mu + r_m) + (\beta_w I_m^{**} + \mu)(\mu + r_m)^2 + (\beta_m I_w^{**} + \mu)(\mu + r_m)^2 > 0, \text{when } R_0 > 1.
\end{aligned}
$$

The condition (v) after simplification is given by $b_1(b_3 b_2 - b_1) - b_3^2 b_0 =$

$$
\begin{aligned}
&(\beta_w I_m^{**} + \mu)^3(\beta_m I_w^{**} + \mu)(\mu + r_w)^2 + (\beta_w I_m^{**} + \mu)^3(\beta_m I_w^{**} + \mu)^2(\mu + r_w) \\
&+(\beta_w I_m^{**} + \mu)^2(\beta_m I_w^{**} + \mu)^2(\mu + r_w)^2 + (\beta_w I_m + \mu)^2(\beta_m I_w^{**} + \mu)^2(\mu + r_m)(\mu + r_w) \\
&+(\beta_w I_m^{**} + \mu)^2(\beta m I_w^{**} + \mu)(\mu + r_w)^3 + (\beta_w I_m^{**} + \mu)^2(\beta_m I_w^{**} + \mu)^2(\mu + r_w)^2 \\
&+(\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)^2(\mu + r_w)^3 + (\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)^2(\mu + r_m)(\mu + r_w)^2 \\
&+(\beta_w I_m^{**} + \mu)^2(\beta_m I_w^{**} + \mu)^3(\mu + r_w) + (\beta_w I_m^{**} + \mu)^2(\beta_m I_w^{**} + \mu)^2(\mu + r_m)(\mu + r_w) \\
&+(\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)^3(\mu + r_w)^2 + 2\mu(\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)(\mu + r_w)^2(\mu + r_m) \\
&+(\beta_w I_m^{**} + \mu)(\beta_m I_w + \mu)^2(\mu + r_w)(\mu + r_m)^2 + (\beta_w I_m^{**} + \mu)^3(\beta_m I_w^{**} + \mu)^2(\mu + r_m) \\
&+(\beta_1 I_m^{**} + \mu)^3(\beta_2 I_w^{**} + \mu)(\mu + r_m)^2 + (\beta_w I_m^{**} + \mu)^2(\beta_m I_w^{**} + \mu)^2(\mu + r_m)^2 \\
&+(\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)^2(\mu + r_m)(\mu + r_w)^2 \\
&+(\beta_w I_m^{**} + \mu)(\beta_m I_w^{**} + \mu)(\mu + r_w)(\mu + r_m)^2 + (\beta_w I_m^{**} + \beta_m I_w^{**})^2(\mu + r_m)^3(\mu + r_w)
\end{aligned}
$$

$$+(\beta_w I_m^{**}+\mu)^2(\beta_m I_w^{**}+\mu)^3(\mu+r_m)+(\beta w I_m^{**}+\mu)^2(\beta_m I_w+\mu)^2(\mu+r_m)^2$$

$$+(\beta_w I_m^{**}+\mu)(\beta_m I_w^{**}+\mu)^3(\mu+r_m)(\mu+r_w)+(\beta_w I_m^{**}+\mu)(\beta_m I_w^{**}+\mu)^3(\mu+r_m)^2$$

$$+(\beta_w I_w+\mu)^2(\beta_m I_w^{**}+\mu)(\mu+r_m)^3+(\beta_w I_m^{**}+\mu)(\beta_m I_w^{**}+\mu)^2(\mu+r_m)^3$$

$$+(\beta_w I_m^{**}+\beta_m I_w^{**})(\beta_w I_m^{**}+\mu)^2(\beta_m I_w^{**}+\mu)(\mu+r_m)(\mu+r_w)$$

$$+(\beta_w I_m^{**}+\beta_m I_w^{**})(\beta_w I_m^{**}+\mu)(\mu+r_m)^2(\mu+r_w)+\mu\beta_m I_w^{**}(\mu+r_w)^2(\mu+r_m)^2$$

$$+\mu(\beta_w I_m^{**}+\mu)^3(\mu+r_w)(\mu+r_m)+2\beta_w I_m^{**}\beta_m I_w^{**}(\beta_w I_m^{**}+\mu)(\mu+r_m)^2(\mu+r_w)$$

$$+(\beta_w I_m^{**}+\beta_m I_w^{**})(\beta_m I_w^{**}+\mu)(\mu+r_w)^3(\mu+r_m)+(\beta_m I_w^{**})^2(\mu+r_m)^2(\mu+r_w)^2$$

$$+(\beta_w I_m^{**}+\beta_m I_w^{**})(\beta_w I_m^{**}+\mu)(\beta_m I_w^{**}+\mu)^2(\mu+r_w)(\mu+r_m)$$

$$+(\beta_w I_m^{**}+\beta_m I_w^{**})(\beta_m I_w^{**}+\mu)^2(\mu+r_w)^2(\mu+r_m)+(\beta_w I_m^{**}+\beta_m I_w^{**})^2(\mu+r_m)^3(\mu+r_w)$$

$$+(\beta_w I_m^{**}+\beta_m I_w^{**})(\beta_m I_w^{**}+\mu)^2(\mu+r_m)^2(\mu+r_w)+(\beta_w I_m^{**})^2(\mu+r_w)^3(\mu+r_m)$$

$$+\beta_w I_m^{**}\beta_m I_w^{**}(\beta_w I_m^{**}+\mu)^2(\mu+r_m)(\mu+r_w)+2\mu^2(\beta_w I_m^{**}+\mu)(\mu+r_m)(\mu+r_w)^2$$

$$+\mu(\beta_w I_m^{**}+\mu)^2(\beta_m I_w^{**}+\mu)^2(\mu+r_w)(\mu+r_m)+\mu^2(\beta_m I_w^{**}+\mu)^2(\mu+r_w)(\mu+r_m)$$

$$+(\beta_w I_m^{**}+\beta_m I_w^{**})(\beta_w I_m^{**}+\mu)^2(\mu+r_w)^2(\mu+r_m)+2\mu(\beta_w I_m^{**}+\mu)^2(\mu+r_w)(\mu+r_m)^2$$

$$+2\mu^2(\beta_w I_m^{**}+\mu)(\beta_m I_w^{**}+\mu)(\mu+r_w)(\mu+r_m)+\mu\beta_m I_w^{**}(\mu+r_w)^2(\mu+r_m)^2$$

$$+2(\beta_w I_m^{**})^2(\beta_m I_w^{**}+\mu)(\mu+r_m)(\mu+r_w)^2+(\beta_w I_m^{**})^2(\mu+r_m)^2(\mu+r_w)^2$$

$$+2\mu^2(\beta_m I_w^{**}+\mu)(\mu+r_w)(\mu+r_m)^2+(\beta_m I_w^{**})^2(\mu+r_m)^3(\mu+r_w)>0, \text{when } R_0>1.$$

Since all the Routh-Hurwitz criterion conditions are satisfied when $R_0 > 1$, then all the eigenvalues of the Jacobian matrix $J(E_1)$ are negative or have negative real parts when $R_0 > 1$. This proves that E_1 is locally asymptotically stable when $R_0 > 1$. □

3.3 HPV model incorporating Low-risk and High-risk HPV types

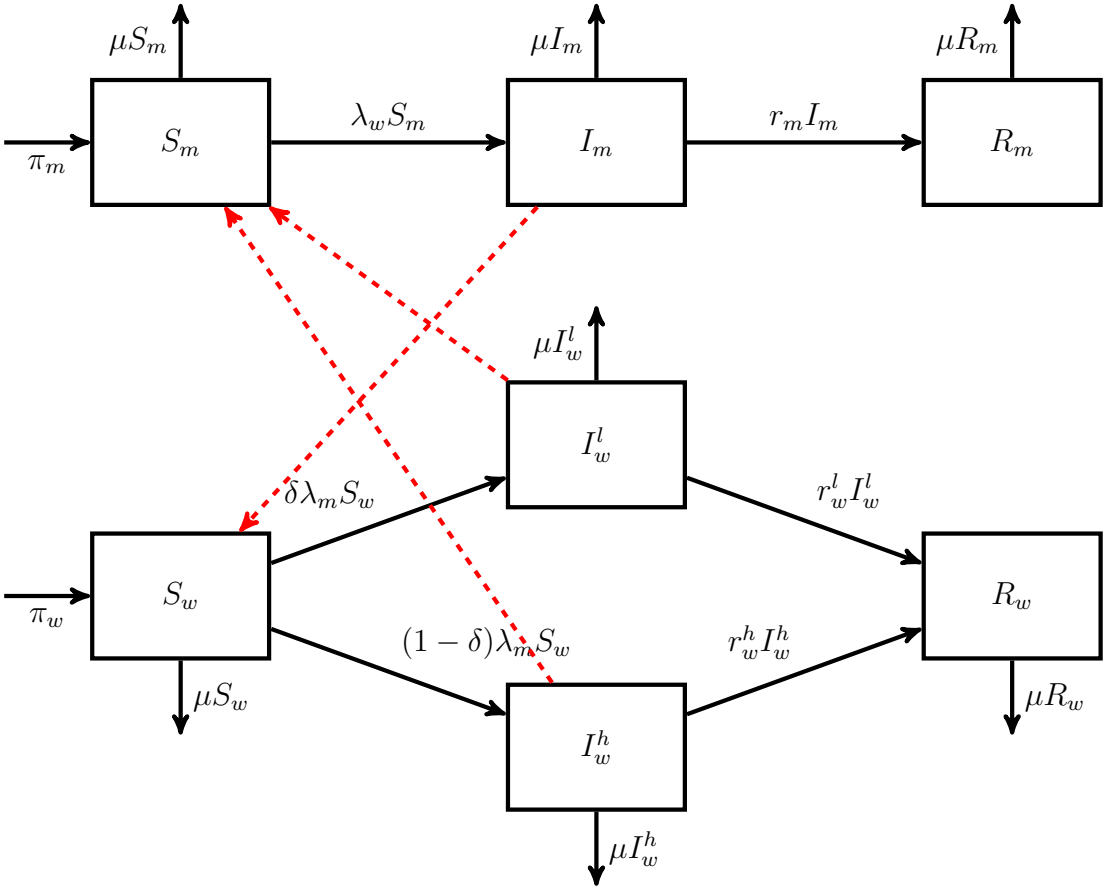

Figure 3.2: Flow chart for the low-risk and high-risk HPV types. The dashed arrows represent cross infection and the solid arrow represent the flow of individuals into and out of the compartment.

More than half of sexually active people are infected with more than one or more HPV types at some point in their lives [49]. Low-risk and high-risk HPV types are found in females population, while man harbor all types of HPV but there are difficult to diagnose. Most men with HPV don't have any symptoms and so diagnosing HPV in men is difficult compared with women [50] We develop the population for the HPV epidemic into the following classes: susceptibles (S_w) and (S_m), infectious

women with low-risk (I_w^l) HPV and infectious women with high-risk (I_w^h) HPV , infectious men (I_m) with low or high-risk HPV and recovered women (R_w) and recovered men (R_m). We use constant recruitment of π_w and π_m for entry into compartment S_w and S_m respectively. Susceptible women are infected by the low risk HPV and high risk HPV with a force of infection $\lambda_m = \beta_w I_m$. Similarly, susceptible men acquire infection through a force of infection $\lambda_w = \beta_m(I_w^l + b_w I_w^h)$, where $b_w \geq 1$. The assumption that $b_w \geq 1$ ensures that high-risk HPV infected women have a higher likelihood of infecting susceptible man than low-risk HPV infected women. Once infected, women progress to the compartments I_w^l and I_w^h of infectives, while men progress to I_m. δ is the proportion of S_w that are infected by low HPV, where $0 \leq \delta \leq 1$. Individuals from (I_w^l) and (I_w^h) join the recovery class R_w through recovery rates r_w^l and r_w^h respectively. Individuals from I_m progress to R_m through recovery rate r_m. Both low-risk and high-risk HPV infected individuals can recover through acquiring natural immunity [1]. Individuals from recovery classes R_w and R_m leave the classes through natural death μ. In this model, we assume that there is no regression back to a class once the individuals move out of it. The non-linear system of ordinary differential equations (ODEs) that represent our compartmental structure is given as

$$\frac{dS_w}{dt} = \pi_w - \beta_w I_m S_w - \mu S_w, \tag{3.11}$$

$$\frac{dI_w^l}{dt} = \delta\beta_w I_m S_w - (r_w^l + \mu) I_w^l, \tag{3.12}$$

$$\frac{dI_w^h}{dt} = (1-\delta)\beta_w I_m S_w - (r_w^h + \mu) I_w^h, \tag{3.13}$$

$$\frac{dR_w}{dt} = r_w^l I_w^l + r_w^h I_w^h - \mu R_w, \tag{3.14}$$

$$\frac{dS_m}{dt} = \pi_m - \beta_m(I_w^l + b_w I_w^h) S_m - \mu S_m, \tag{3.15}$$

$$\frac{dI_m}{dt} = \beta_m(I_w^l + b_w I_w^h) S_m - (r_m + \mu) I_m, \tag{3.16}$$

$$\frac{dR_m}{dt} = r_m I_m - \mu R_m. \tag{3.17}$$

The total population is governed by the following differential equation

$$\frac{dN}{dt} = \pi_w + \pi_m - \mu N(t).$$

3.3.1 Positivity and boundness of solutions of the model

The feasible region of system of equations (3.11)-(3.17) is is defined by

$$\begin{aligned}\Omega &= \{(S_w, I_w^l, I_w^h, R_w, S_m, I_m, R_m) \in \mathbb{R}_+^7 : S_w \geq 0, I_w^l \geq 0, \\ &\quad I_w^h \geq 0, R_w \geq 0, S_m \geq 0, I_m \geq 0, R_m \geq 0, N \leq \frac{\pi_w + \pi_m}{\mu}\}.\end{aligned}$$

We need to prove that the feasible region Ω is positively invariant and the solutions of feasible region are bounded in the following lemma.

Lemma 3.3.1.

Given that the initial conditions of systems of equations (3.11)-(3.17) are $S_w(0) > 0$, $I_w^l(0) > 0$, $I_w^h(0) > 0$, $R_w(0) > 0$, $S_m(0) > 0$, $I_m(0) > 0$ *and* $R_m(0) > 0$, *the solutions of* $S_w(t)$, $I_w^l(t)$, $I_w^h(t)$, $R_w(t)$, $S_m(t)$, $I_m(t)$ *and* $R_m(t)$ *are non-negative for all* $t > 0$.

Proof.

The positivity of solutions of system of equation (3.11)-(3.17) is similar to that of the model in section 3.2.1 except noting in this case,

$$\begin{aligned}I_w^l(t) &\geq I_w^l(0)e^{-(r_w^l + \mu)t} \geq 0, \\ I_w^h(t) &\geq I_w^h(0)e^{-(r_w^h + \mu)t} \geq 0.\end{aligned}$$

The boundedness of solutions also follows from the proof in section 3.2.1. □

3.3.2 The disease free equilibrium point (DFE)

The disease free equilibrium is given by

$$E_0 = \left(\frac{\pi_w}{\mu}, 0, 0, 0, \frac{\pi_m}{\mu}, 0, 0\right).$$

3.3.3 Basic reproduction number

We calculate the reproduction number using the equations from the system of equations (3.11)-(3.17) that models infectious classes. The extracted infectious classes equations are given as:

$$\begin{aligned}
\frac{dI_w^l}{dt} &= \delta\beta_w I_m S_w - (r_w^l + \mu) I_w^l, \\
\frac{dI_w^h}{dt} &= (1-\delta)\beta_w I_m S_w - (r_w^h + \mu) I_w^h, \\
\frac{dI_m}{dt} &= \beta_m (I_w^l + b_w I_w^h) S_m - (r_m + \mu) I_m.
\end{aligned}$$

We first have to obtain the matrices $\mathcal{F}_i$ and $\mathcal{V}^-{}_i - \mathcal{V}^+{}_i = \mathcal{V}_i$, where $i = 1, 2, 3$.

Now,

$$\mathcal{F}_i = \begin{pmatrix} \delta\beta_w I_m S_w \\ (1-\delta)\beta_w I_m S_w \\ \beta_m (I_w^l + b_w I_w^h) \end{pmatrix}, \quad \mathcal{V}_i = \begin{pmatrix} (r_w^l + \mu) I_w^l \\ (r_w^h + \mu) I_w^h \\ (r_m + \mu) I_m \end{pmatrix}.$$

We also need to compute $F = \dfrac{\partial(\mathcal{F}(E_0))}{\partial x_i}$, $V = \dfrac{\partial(\mathcal{V}(E_0))}{\partial x_i}$ and V^{-1}. For the system equations (3.11)-(3.17) that models the infectious classes, we obtain that

$$F = \begin{pmatrix} 0 & 0 & \delta\beta_w \dfrac{\pi_w}{\mu} \\ 0 & 0 & (1-\delta)\beta_w \dfrac{\pi_w}{\mu} \\ \beta_m \dfrac{\pi_m}{\mu} & \beta_m b_w \dfrac{\pi_m}{\mu} & 0 \end{pmatrix}, \quad V = \begin{pmatrix} (r_w^l + \mu) & 0 & 0 \\ 0 & (r_w^h + \mu) & 0 \\ 0 & 0 & (r_m + \mu) \end{pmatrix},$$

$$V^{-1} = \begin{pmatrix} \frac{1}{r_w^l+\mu} & 0 & 0 \\ 0 & \frac{1}{r_w^h+\mu} & 0 \\ 0 & 0 & \frac{1}{r_m+\mu} \end{pmatrix}.$$

R_0 is given by the spectral radius of the matrix FV^{-1} [51], so that

$$FV^{-1} = \begin{pmatrix} 0 & 0 & \frac{\delta\beta_w\pi_w}{\mu(r_m+\mu)} \\ 0 & 0 & \frac{(1-\delta)\beta_w\pi_w}{\mu(r_m+\mu)} \\ \frac{\beta_m\pi_m}{\mu(r_w^l+\mu)} & \frac{\beta_m b_w\pi_m}{\mu(r_w^h+\mu)} & 0 \end{pmatrix}.$$

The entries of FV^{-1} can be explained as follows:

$\frac{\delta\beta_w\pi_w}{\mu(r_m+\mu)}$ is the average number of women with low-risk HPV types infected by singe man.
$\frac{(1-\delta)\beta_w\pi_w}{\mu(r_m+\mu)}$ is the average number of women with high-risk HPV types infected by singe man.
$\frac{\beta_m\pi_m}{\mu(r_w^l+\mu)}$ is the average number of men with HPV cases which are infected by a single woman with low-risk HPV types.

$\frac{\beta_m\pi_m}{\mu(r_w^h+\mu)}$ is the average number of men with HPV cases which are infected by a single woman with high-risk HPV types.

The characteristic equation is obtained by solving the equation $|FV^{-1} - \lambda I_3| = 0$, where I_3 is a 3×3 identity matrix to obtain

$$-\lambda\left(\lambda^2 - \frac{\beta_w\beta_m b_w\pi_w\pi_m(1-\delta)(r_w^l+\mu) + \delta\beta_w\beta_m\pi_w\pi_m(r_w^h+\mu)}{\mu^2(r_w^l+\mu)(r_w^h+\mu)(r_m+\mu)}\right) = 0.$$

Thus, the spectral radius $\rho(FV^-)$ is given by

$$R_0 = \sqrt{\frac{\beta_w\beta_m\pi_w\pi_m\left(b_w(1-\delta)(r_w^l+\mu) + \delta(r_w^h+\mu)\right)}{\mu^2(r_w^l+\mu)(r_w^h+\mu)(r_m+\mu)}}, \tag{3.18}$$

which can be written as

$$R_0 = \sqrt{R_w(\delta R_m^l + (1-\delta)R_m^h)}.$$

$R_m^l = \dfrac{\beta_m \pi_m}{\mu(r_w^l + \mu)}$, $R_m^h = \dfrac{b_w \beta_m \pi_m}{\mu(r_w^h + \mu)}$ and $R_w = \dfrac{\beta_w \pi_w}{\mu(r_{mw} + \mu)}$. R_m^l is the reproduction number for men who were infected by women with low-risk HPV types, R_m^h is the reproduction number for men who were infected by women with high-risk HPV types and R_w is the reproduction number for women who were infected by man.

3.3.4 Analysis of R_0

We examine the effects of reproduction numbers R_w, R_m^l, R_m^h and δ on R_0 by computing the partial derivatives of R_0 with respect to R_w, R_m^l, R_m^h and δ.

$$\frac{\partial R_0}{\partial R_w} = \frac{1}{2}\sqrt{\frac{\delta R_m^l + (1-\delta)R_m^h}{R_w}} > 0.$$

R_0 is an increasing function of threshold value R_w. The increase in the reproduction number for women will results in the increase of the basic reproduction number R_0. The partial derivative of R_0 with respect to R_m^l is given by

$$\frac{\partial R_0}{\partial R_m^l} = \frac{1}{2}\sqrt{\frac{R_w}{\delta R_m^l + (1-\delta)R_m^h}} > 0.$$

The increase in the reproduction number for men who are infected by women with low-risk HPV types will results in the increase of the basic reproduction number. The partial derivative of R_0 with respect to R_m^h is given by

$$\frac{\partial R_0}{\partial R_m^h} = \frac{1-\delta}{2}\sqrt{\frac{R_w}{\delta R_m^l + (1-\delta)R_m^h}} > 0.$$

The increase in the reproduction number for men are infected by women with high risk HPV types will yield an increase of the basic reproduction number. The derivative of R_0 with respect to δ and is given by

$$\frac{\partial R_0}{\partial \delta} = \frac{1}{2}\frac{R_w(R_m^l - R_m^h)}{R_0}.$$

We observe the following

(i) If $R_m^l \geq R_m^h$, then $\dfrac{\partial R_0}{\partial \delta} \geq 0$.

(ii) If $R_m^l < R_m^h$, then $\dfrac{\partial R_0}{\partial \delta} < 0$.

When R_m^l is above the threshold R_m^h, then the increase in δ will increase the basic reproduction number. When R_m^l is less than the threshold R_m^h, the increase in δ result in the decrease of the basic reproduction number.

3.3.5 The endemic equilibrium point

The endemic equilibrium solutions can be obtained from equating the right hand side of the system (3.11)-(3.17) to zero, i.e. denoted by

$$E_1 = (S_w^{**}, I_w^{l**}, I_w^{**}, R_w^{**}, S_m^{**}, I_m^{**}, R_m^{**})$$

where

$$\begin{aligned}
S_w^{**} &= \frac{\pi_w}{\mu}\left(\frac{d+a}{aR_0^2+d}\right), \\
I_w^{l**} &= \frac{a\delta\pi_w(R_0^2-1)}{(aR_0^2+d)(r_w^l+\mu)}, \\
I_w^{h**} &= \frac{a\pi_w(1-\delta)(R_0^2-1)}{(aR_0^2+d)(r_w^h+\mu)}, \\
R_w^{**} &= \frac{\mu\pi_w\left(r_w^l\delta(r_w^h+\mu)+r_w^h(1-\delta)(r_w^l+\mu)\right)(R_0^2-1)}{aR_0^2+d}, \\
S_m^{**} &= \frac{\pi_m(aR_0^2+d)(d+a)}{ad(R_0^2-1)(\mu aR_0^2+d)}, \\
I_m^{**} &= \frac{a\mu(R_0^2-1)}{\beta_w(d+a)}, \\
R_m^{**} &= \frac{ar_m(R_0^2-1)}{\beta_w(d+a)},
\end{aligned}$$

and

$$\begin{aligned}
a &= \mu(r_w^l+\mu)(r_w^h+\mu), \\
d &= \beta_m\pi w\left[\delta(r_w^h+\mu)+b_w(1-\delta)(r_w^l+\mu)\right].
\end{aligned}$$

The equilibrium point exists and is unique when $R_0 > 1$.

3.3.6 Stability analysis of equilibrium points

Theorem 3.3.2.

The DFE is locally asymptotically stable when $R_0 > 1$ and unstable when $R_0 < 1$.

Proof.

To establish the local stability of DFE at E_0, we use the Jacobian of the model evaluated at E_0. The Jacobian matrix for the system (3.11)-(3.17) is given by:

$$J = \begin{pmatrix} -(\beta_w I_m^* + \mu) & 0 & 0 & 0 & 0 & -\beta_w S_w^* & 0 \\ \delta\beta_w I_m^* & -(r_w^l + \mu) & 0 & 0 & 0 & \delta\beta_w S_w^* & 0 \\ (1-\delta)\beta_w I_m^* & 0 & -(r_w^h + \mu) & 0 & 0 & (1-\delta)\beta_w S_w^* & 0 \\ 0 & r_w^l & r_w^h & -\mu & 0 & 0 & 0 \\ 0 & -\beta_m S_m^* & -\beta_m b_w S_m^* & 0 & -(\beta_m(I_w^{l*} + b_w I_w^{h*}) + \mu) & 0 & 0 \\ 0 & \beta_m S_m^* & \beta_m b_w S_m^* & 0 & \beta_m(I_w^{l*} + b_w I_w^{h*}) & -(r_m + \mu) & 0 \\ 0 & 0 & 0 & 0 & 0 & r_m & -\mu \end{pmatrix}.$$

The DFE is locally asymptotically stable if and only if all the roots of the characteristic equation are negative or have negative real parts. Therefore either $-(\mu + \lambda)^4 = 0$ i.e. $\lambda_{1,2,3,4} = -\mu$ or

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{3.19}$$

where

$$\begin{aligned} a_1 &= (r_w^l + \mu) + (r_w^h + \mu) + (r_m + \mu), \\ a_2 &= (r_w^l + \mu)(r_w^h + \mu) + (r_w^l + \mu)(r_m + \mu) + (r_w^h + \mu)(r_m + \mu) - \frac{\beta_m\beta_w\pi_m\pi_w}{\mu^2}(b_w(1-\delta) + \delta), \\ a_3 &= (r_w^l + \mu)(r_w^h + \mu)(r_m + \mu)(1 - R_0^2). \end{aligned}$$

We analyze the roots of the characteristic equation (3.19) using Routh Hurwitz criterion to test the stability of the DFE, so we need to show that $a_1 > 0$, $a_3 > 0$ and $a_1a_2 - a_3 > 0$. The first inequality is automatically satisfied. The second inequality, $a_3 > 0$, holds if and only if $R_0^2 < 1$, i.e $R_0 < 1$.

We rewrite a_2 in terms of R_0 by considering

$$\begin{aligned}(r_w^l + \mu)(r_m + \mu) &= (r_w^l + \mu)(r_m + \mu)(1 - R_0^2) + (r_w^l + \mu)(r_m + \mu)R_0^2,\\ (r_w^h + \mu)(r_m + \mu) &= (r_w^h + \mu)(r_m + \mu)(1 - R_0^2) + (r_w^h + \mu)(r_m + \mu)R_0^2.\end{aligned}$$

Now,

$$\begin{aligned}a_2 &= (r_w^l + \mu)(r_w^h + \mu) + (r_w^l + \mu)(r_m + \mu) + (r_w^h + \mu)(r_m + \mu) - \frac{\beta_m\beta_w\pi_m\pi_w}{\mu^2}(b_w(1 - \delta) + \delta),\\ &= (r_w^l + \mu)(r_w^h + \mu) + \left((r_w^l + \mu) + (r_w^h + \mu)\right)(r_m + \mu)(1 - R_0^2)\\ &\quad + \left(\delta(r_w^h + \mu)R_m^l + (1 - \delta)(r_w^l + \mu)R_m^h\right)(r_m + \mu)R_w, > 0, \text{ when } R_0^2 < 1 \Rightarrow R_0 < 1.\end{aligned}$$

Therefore

$$\begin{aligned}a_1a_2 - a_3 &= (r_w^l + \mu)^2(r_w^h + \mu) + (r_w^l + \mu)(r_w^h + \mu)^2 + (r_w^l + \mu)(r_w^h + \mu)(r_m + \mu)\\ &\quad +(r_w^l + \mu)^2(r_m + \mu)(1 - R_0^2) + ((r_w^l + \mu) + (r_w^h + \mu))(r_m + \mu)^2(1 - R_0^2)\\ &\quad +((r_w^l + \mu) + (r_w^h + \mu))(r_m + \mu)(r_w^h + \mu)(1 - R_0^2)\\ &\quad +(\delta(r_w^h + \mu)R_m^l + (1 - \delta)(r_w^l + \mu)R_m^h)(r_m + \mu)(r_w^l + \mu)R_w\\ &\quad +(\delta(r_w^h + \mu)R_m^l + (1 - \delta)(r_w^l + \mu)R_m^h)(r_m + \mu)(r_w^h + \mu)R_w\\ &\quad +(\delta(r_w^h + \mu)R_m^l + (1 - \delta)(r_w^l + \mu)R_m^h)(r_m + \mu)^2R_w > 0, \text{when } R_0^2 < 1 \Rightarrow R_0 < 1.\end{aligned}$$

Since all the Routh-Hurwitz criterion conditions are satisfied when $R_0^2 < 1 \Rightarrow R_0 < 1$, then all the eigenvalues of the Jacobian matrix $J(E_0)$ are negative or have negative real parts when $R_0 < 1$. This proves that E_0 is locally asymptotically stable when $R_0 < 1$. □

Theorem 3.3.3.

The endemic equilibrium point E_1 is locally asymptotically stable for $R_0 > 1$.

Proof.

Let β_w be the bifurcation parameter so that when $R_0 = 1$ the endemic and disease-free equilibrium points coalesce. When $R_0 = 1$, then

$$\beta_w = \beta_w^* = \frac{\mu^2(r_w^l + \mu)(r_w^h + \mu)(r_m + \mu)}{\beta_m \pi_m \pi_w (b_w(1-\delta)(r_w^l + \mu) + \delta(r_w^h + \mu))}. \tag{3.20}$$

The characteristic equation of the Jacobian matrix when $R_0 = 1$ becomes:

$$-\lambda(\lambda + \mu)^4(\lambda^2 + b_1\lambda + b_2) = 0, \quad \text{where} \quad \lambda_1 = 0, \quad \lambda_{2,3,4,5} = -\mu$$

and

$$\lambda^2 + b_1\lambda + b_2 = 0,$$

where

$$\begin{aligned} b_1 &= (r_w^l + \mu) + (r_w^h + \mu) + (r_m + \mu), \\ b_2 &= (r_w^l + \mu)(r_w^h + \mu) + \left(\delta(r_w^h + \mu)R_m^l + (1-\delta)(r_w^l + \mu)R_m^h\right)(r_m + \mu)R_w. \end{aligned}$$

$$\lambda_6 = -\left(\frac{b_1}{2}\right) - \sqrt{\left(\frac{b_1}{2}\right)^2 - b_2},$$

$$\lambda_7 = -\left(\frac{b_1}{2}\right) + \sqrt{\left(\frac{b_1}{2}\right)^2 - b_2}.$$

$\lambda_{6,7}$ are the eigenvalues which are either negative or have negative real parts. We obtain a simple eigenvalue $\lambda_1 = 0$ and all other eigenvalues are negative or have negative real parts at $R_0 = 1$. This means that we can use center manifold theory which is associated with $\lambda_1 = 0$ to establish the stability of the endemic equilibrium point [29].

We denote

$$W = (w_1, w_2, w_3, w_4, w_5, w_6, w_7)^\top$$

as the right eigenvector associated with the zero eigenvalue $\lambda_1 = 0$, where $\top$ is the transpose. To find W, we use

$$(J(E_0, \beta_w^*))W = \mathbf{0},$$

where $J(E_0, \beta_w^*)$ is the Jacobian matrix at the disease free equilibrium point when $R_0 = 1$, where $\mathbf{0}$ is the zero vector. We solve the system of equations

$$\begin{aligned}
-\mu w_1 - \frac{\beta_w^* \pi_w}{\mu} w_6 &= 0, \\
-(r_w^l + \mu) w_2 + \frac{\delta \beta_w^* \pi_w}{\mu} w_6 &= 0, \\
-(r_w^h + \mu) w_3 + \frac{(1-\delta) \beta_w^* \pi_w}{\mu} w_6 &= 0, \\
r_w^l w_2 + r_w^h w_3 - \mu w_4 &= 0, \\
-\frac{\beta_m \pi_m}{\mu} w_2 - \frac{\beta_m b_w \pi_m}{\mu} w_3 - \mu w_5 &= 0, \\
\frac{\beta_m \pi_m}{\mu} w_2 + \frac{\beta_m b_w \pi_m}{\mu} w_3 - (r_m + \mu) w_6 &= 0, \\
r_m w_6 - \mu w_7 &= 0,
\end{aligned}$$

to yield

$$W = \left(-\frac{\beta_w^* \pi_w}{\mu^2}, \frac{\delta \beta_w^* \pi_w}{\mu (r_w^l + \mu)}, \frac{(1-\delta) \beta_w^* \pi_w}{\mu (r_w^h + \mu)}, \frac{\beta_w^* \pi_w \left(r_w^l \delta (r_w^h + \mu) + r_w^h (1-\delta)(r_w^l + \mu) \right)}{\mu^2 (r_w^l + \mu)(r_w^h + \mu)}, -\frac{r_m + \mu}{\mu}, 1, \frac{r_m}{\mu} \right)^\top.$$

We denote the left eigenvector by $V = (v_1, v_2, v_3, v_4, v_5, v_6, v_7)^\top$. To find V, we use

$$V^\top (J(E_0, \beta_w^*)) = 0,$$

i.e

$$\begin{aligned}
-\mu v_1 &= 0 \\
-(r_w^l + \mu) V_2 + r_w^l v_4 - \frac{\beta_m \pi_m}{\mu} v_5 + \frac{\beta_m \pi_m}{\mu} v_6 &= 0, \\
-(r_w^h + \mu) V_3 + r_w^h v_4 - \frac{\beta_m b_w \pi_m}{\mu} v_5 + \frac{\beta_m b_w \pi_m}{\mu} v_6 &= 0, \\
-\mu v_4 &= 0, \\
-\mu v_5 &= 0, \\
-\frac{\beta_w^* \pi_w}{\mu} v_1 - \frac{\delta \beta_w^* \pi_w}{\mu} v_2 + \frac{(1-\delta) \beta_w^* \pi_w}{\mu} v_3 - (r_m + \mu) v_6 + r_m v_7 &= 0, \\
-\mu v_7 &= 0.
\end{aligned}$$

We obtain

$$V = \left(0, \frac{\beta_m \pi_m}{\mu(r_w^l + \mu)}, \frac{\beta_m b_w \pi_m}{\mu(r_w^h + \mu)}, 0, 0, 1, 0\right)^\top.$$

Introducing the change of variables $x_1 = S_w$, $x_2 = I_w^l$, $x_3 = I_w^h$, $x_4 = R_w$, $x_5 = S_m$, $x_6 = I_m$ and $x_7 = R_m$ and letting $X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7)^\top$, the equations (3.11)-(3.17) can be rewritten in the form $\frac{dX}{dt} = F(X)$, with $F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7)^\top$, as follows:

$$\begin{aligned}
\frac{dx_1}{dt} = f_1 &= \pi_w - \beta_w x_6 x_1 - \mu x_1, \\
\frac{dx_2}{dt} = f_2 &= \delta\beta_w x_6 x_1 - (r_w^l + \mu)x_2, \\
\frac{dx_3}{dt} = f_3 &= (1-\delta)\beta_w x_6 x_1 - (r_w^h + \mu)x_3, \\
\frac{dx_4}{dt} = f_4 &= r_w^l x_2 + r_w^h x_3 - \mu x_4, \\
\frac{dx_5}{dt} = f_5 &= \pi_m - \beta_m(x_2 + b_w x_3)x_5 - \mu x_5, \\
\frac{dx_6}{dt} = f_6 &= \beta_m(x_2 + b_w x_3)x_5 - (r_m + \mu)x_6, \\
\frac{dx_7}{dt} = f_7 &= r_m x_6 - \mu x_7.
\end{aligned}$$

The bifurcation coefficients, a and b are defined as

$$a = \sum_{k,i,j=1}^{7} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(E_0), \tag{3.21}$$

$$b = \sum_{k,i=1}^{7} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_w}(E_0). \tag{3.22}$$

Now, the non-zero partial derivatives of F at E_0 are given by

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_6} = \frac{\partial^2 f_2}{\partial x_6 \partial x_1} = \delta\beta_w^*, \qquad \frac{\partial^2 f_3}{\partial x_1 \partial x_6} = \frac{\partial^2 f_3}{\partial x_6 \partial x_1} = (1-\delta)\beta_w^*,$$
$$\frac{\partial^2 f_6}{\partial x_2 \partial x_5} = \frac{\partial^2 f_6}{\partial x_5 \partial x_2} = \beta_m, \qquad \frac{\partial^2 f_6}{\partial x_3 \partial x_5} = \frac{\partial^2 f_6}{\partial x_5 \partial x_3} = b_w\beta_m.$$

To obtain a, we substitute the expressions above of the partial derivatives into equation (3.21). We

get

$$\begin{aligned} a &= 2v_2w_1w_6\frac{\partial^2 f_2}{\partial x_1\partial x_6} + 2v_3w_1w_6\frac{\partial^2 f_3}{\partial x_1\partial x_6} + 2v_6w_2w_5\frac{\partial^2 f_6}{\partial x_2\partial x_5} + 2v_6w_3w_5\frac{\partial^2 f_6}{\partial x_3\partial x_5} \\ &= -2\frac{\beta_w^*}{\mu}\beta_w^*\frac{\beta_m\pi_m\pi_w(\delta(r_w^h+\mu)+b_w(1-\delta)(r_w^l+\mu))}{\mu^2(r_w^l+\mu)(r_w^h+\mu)} \\ &\quad -2\beta_w^*\beta_m\pi_w(r_m+\mu)\frac{(\delta(r_w^h+\mu)+b_w(1-\delta)(r_w^l+\mu))}{\mu^2(r_w^l+\mu)(r_w^h+\mu)} \\ &= -2(r_m+\mu)\left(\frac{\beta w^*}{\mu}+\frac{r_m+\mu}{\pi_w}\right) < 0. \end{aligned}$$

For b, we take the partial derivatives of F that are non-zero partial derivatives at E_0 which are

$$\frac{\partial 2f_2}{\partial x_6\partial\beta_w^*} = \delta x_1^*, \frac{\partial 2f_3}{\partial x_6\partial\beta_w^*} = (1-\delta)x_1^*. \tag{3.23}$$

Substituting the expressions (3.23) into equation (3.22) we have

$$\begin{aligned} b &= v_2w_6\frac{\partial^2 f_2}{\partial x_6\partial\beta_w^*} + v_3w_6\frac{\partial^2 f_3}{\partial x_6\partial\beta_w^*}, \\ &= \frac{\beta_m\pi_m\pi_w(\delta(r_w^h+\mu)+b_w(1-\delta)(r_w^l+\mu))}{\mu^2(r_w^l+\mu)(r_w^h+\mu)} > 0. \end{aligned}$$

Since $a < 0$ and $b > 0$, it follows that the system will undergo a transcritical bifurcation at $R_0 = 1$. The type of transcrital bifurcation exhibited is supercritical bifurcation. In a supercritical bifurcation there is an exchange of stability between the disease free equilibrium point and the endemic equilibrium point that ensures that the endemic equilibrium point is locally asymptotically stable when $R_0 > 1$ [12]. □

3.3.7 Summary

We managed to obtain the disease- free equilibrium point. Using Routh Hurwitz criterion conditions, we proved that it is locally asymptotically stable when $R_0 < 1$. We managed to obtain the positivity of endemic equilibrium point when $R_0 > 1$. Using the center manifold theorem, the stability of endemic equilibrium point was locally asymptotically stable when $R_0 > 1$.

We review some mathematical models on dynamics of HPV information. The model incorporated states for HPV infection, low and high-risk HPV types to analyse the natural history of HPV infection in men and women. HPV infection was used as a building block in the HPV-HIV co-infection. We collapsed the two-sex model from the HPV model into one-sex model in the HPV-HIV co-infection model because we assuming that the progression and infection of the disease is the same in males and females. We concentrate more on individuals who are at high risk of HPV which is the most important risk factor which associated with HIV. We adopt the HIV/AIDS models from other researchers to review and analyse the natural history of HIV infection [11, 34, 52, 53]. This will help us in set up of some precedence towards the analysis of our study on HPV-HIV co-infection model.

Chapter 4

MODEL FOR CO-INFECTION OF HPV WITH HIV

4.1 Introduction

HPV and Human Immunodeficiency Virus (HIV) infection are sexually transmitted infections, and there is evidence that the two infections are often found together [17]. Further evidence showed that high risk HPV types are associated in patients with HIV infection and the acquired immunodeficiency syndrome (AIDS) [21]. We collapsed the two-sex model from the HPV model into one-sex model in the HPV-HIV co-infection model because we assuming that the progression and infection of the disease is the same in males and females. We build up the core model of HPV-HIV co-infection using the review of HPV model in chapter 3 and also the review of HIV/AIDS models from other studies [11, 34, 52, 53]. In this study, we seek to investigate the effects of the co-infection of HIV with HPV and also by address the following research questions:

(i) By how much impact does HIV infection impact the natural history of HPV infection?

(ii) By how much impact does HPV infection impact the natural history of HIV infection,

over a period of time?

4.2 Model formulation

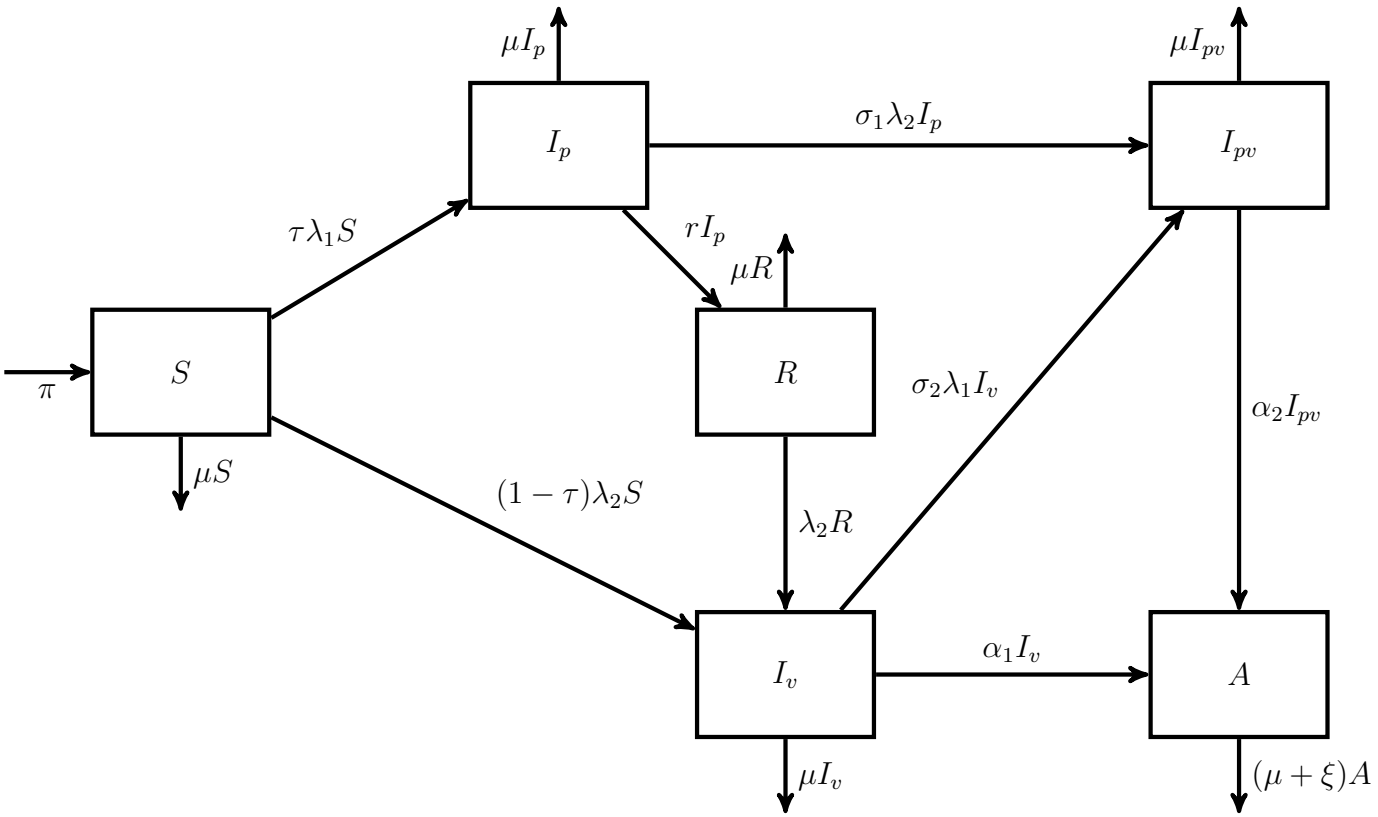

Figure 4.1: Flow chart for the co-infection of HPV with HIV. The arrow represent the flow of individuals into and out of the compartment.

We develop a mathematical model of the co-infection of HPV with HIV infection by considering the following compartments: susceptible individuals (S) who are vulnerable to both HPV and HIV, infectious individuals with HPV infection only (I_p), infectious individuals with HIV infection only (I_v), infectious individuals with both HPV and HIV infection (I_{pv}), AIDS individuals (A) and individuals

recovered from HPV (R) but susceptible to HIV. We consider recruitment into the susceptible class through sexual maturity since the two infections are mostly found in sexually active and mature individuals. We use constant recruitment π for entry into the susceptible compartment S. Individuals leave the susceptible compartment either through natural death (at a rate μ) or through infection by HPV or HIV and/or AIDS individuals. We assume that a susceptible individual can become infected with HPV with a force of infection $\lambda_1 = \beta_1 I_p$. τ is the proportion of susceptible individuals that are infected by HPV only. We assume that $0 < \tau < 1$ so that at any particular moment, individuals are either infected with HIV and/ or with HPV. The susceptible individuals are also infected by HIV individuals with a force of infection $\lambda_2 = \beta_2(I_v + \rho_1 I_{pv} + \rho_2 A)$. β_1 is the rate of infection of susceptible individuals by the infected HPV population and β_2 is the rate of infection of susceptible individuals by the HIV infected population. Thus, β_1 is the probability of HPV transmission per sexual contact and β_2 is the probability of HIV transmission per sexual contact. We assume that infection from individuals co-infected with both HPV and HIV have a higher probability of generating more new infections relative to infections coming from HIV individuals only, so that $\rho_1 > 1$. ρ_1 is the modification factor of transmission rate for co-infection of HPV with HIV, in the HIV transmission rate. We assume that the AIDS individuals have the highest probability of generating new HIV infections compared to HIV infected individuals and co-infected individuals. Thus, $\rho_2 > 1$ and $\rho_2 > \rho_1 > 1$. Where ρ_2 is the modification factor of transmission rate for AIDS in the HIV transmission rate. Individuals infected with HPV only will progress to the I_p compartment while those infected with HIV only will move to the I_v compartment. Individuals from I_p compartment progress to R through natural recovery from HPV at a rate r and also progressing to the co-infected class I_{pv} with a force of infection $\lambda_3 = \sigma_1 \lambda_2$. We assume that $\sigma_1 > 1$, since HPV infected individuals are at a higher risk of getting HIV infection. Individuals from I_v compartment progresses to AIDS (A) at a progression rate α_1, or through HPV infection with a force of infection $\lambda_4 = \sigma_2 \lambda_1$. Since

several studies showed that HIV positive individuals are at higher risk of HPV infection compared to HIV negative individuals [21,54], we assume that $\sigma_2 > 1$. Individuals from I_{pv} compartment move to join AIDS class (A) through progression rate α_2. We assume that individuals from I_{pv} class progress to the HIV class after recovery from HPV and that the time taken to recover from HPV is small due to the effects of HIV. $\frac{1}{\alpha_1}$ is the average time spent by individuals in I_v and $\frac{1}{\alpha_2}$ is the average time spent by individuals in I_{pv}. Individuals in I_v are assumed to stay longer in their class than those in I_{pv}. This means that $\frac{1}{\alpha_1} > \frac{1}{\alpha_2}$ i.e $\alpha_2 > \alpha_1$. Individuals from A moves out of the compartment through natural death (at a rate μ) or through the mortality associated with AIDS related illness (at a rate ξ). R leaves the compartment through natural death (at a rate μ)or through progression to the I_v class. Based on our model description and assumptions, we establish the following system of non-linear ordinary differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \pi - \tau\lambda_1 S - (1-\tau)\lambda_2 S - \mu S, && (4.1)\\
\frac{dI_p}{dt} &= \tau\lambda_1 S - \sigma_1\lambda_2 I_p - (\mu + r)I_p, && (4.2)\\
\frac{dI_v}{dt} &= (1-\tau)\lambda_2 S - \sigma_2\lambda_1 I_v - (\mu + \alpha_1)I_v + \lambda_2 R, && (4.3)\\
\frac{dI_{pv}}{dt} &= \sigma_1\lambda_2 I_p + \sigma_2\lambda_1 I_v - (\mu + \alpha_2)I_{pv}, && (4.4)\\
\frac{dA}{dt} &= \alpha_1 I_v + \alpha_2 I_{pv} - (\mu + \xi)A, && (4.5)\\
\frac{dR}{dt} &= rI_p - (\mu + \lambda_2)R. && (4.6)
\end{aligned}$$

The total population is given by $N(t) = S + I_p + I_v + I_{pv} + A + R$.

4.2.1 Feasible region

For the system of equations (4.1)-(4.6), we need to prove for the positivity invariant and the bounded of all the solutions of the system of equations with positive initial conditions will remain positive for

all $t \geq 0$. We define the feasible region to be

$$\Omega = \{(S, I_p, I_v, I_{pv}, A, R) \in \mathbb{R}^6_+ : S \geq 0, I_p \geq 0, I_v \geq 0, I_{pv} \geq 0, A \geq 0, R \geq 0, N \leq \frac{\pi}{\mu}\}.$$

Lemma 4.2.1.

The feasible region Ω is positively invariant.

Proof.

The positivity of solutions of systems of equations (4.1) to (4.6) is already shown in section 3.2.1

The rate of change of the total population, obtained by adding equations (4.1) to (4.6), is given by:

$$\begin{aligned} \frac{dN}{dt} &= \pi - \mu N - \xi A \\ &\leq \pi - \mu N. \end{aligned} \tag{4.7}$$

The solution of differential equation (4.7) is given by

$$N(t) \leq N(0)e^{-\mu t} + \frac{\pi}{\mu}[1 - e^{-\mu t}].$$

As $t \to \infty$, $0 \leq N(t) \leq \frac{\pi}{\mu}$. The $\lim_{t\to\infty} N(t) = \frac{\pi}{\mu}$. This means that $\frac{\pi}{\mu}$ is the upper bound of $N(t)$. □

4.2.2 Disease free equilibrium point

The disease free equilibrium point is given by

$$E_0 = \left(\frac{\pi}{\mu}, 0, 0, 0, 0, 0\right).$$

4.2.3 Basic reproduction number R_0

We first have to obtain the matrices $\mathcal{F}_i$ and $\mathcal{V}_i^- - \mathcal{V}_i^+ = \mathcal{V}_i$.

$$\mathcal{F}_i = \begin{pmatrix} \tau\lambda_1 S \\ (1-\tau)\lambda_2 S + \lambda_2 R \\ \sigma_1\lambda_2 I_p + \sigma_2\lambda_1 I_v \\ 0 \end{pmatrix}, \quad \mathcal{V}_i = \begin{pmatrix} (\mu+r)I_p + \sigma_1\lambda_2 I_p \\ (\mu+\alpha_1)I_v + \sigma_2\lambda_1 I_v \\ (\mu+\alpha_2)I_{pv} \\ (\mu+\xi)A - \alpha_1 I_v - \alpha_2 I_{pv} \end{pmatrix}.$$

The matrices, $F = D(\mathcal{F}(E_0))$, $V = D(\mathcal{V}(E_0))$, V^{-1} and FV^{-1}, are given by

$$F = \begin{pmatrix} \frac{\tau\beta_1\pi}{\mu} & 0 & 0 & 0 \\ 0 & \frac{(1-\tau)\beta_2\pi}{\mu} & \frac{(1-\tau)\beta_2\rho_1\pi}{\mu} & \frac{(1-\tau)\beta_2\rho_2\pi}{\mu} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} (\mu+r) & 0 & 0 & 0 \\ 0 & (\mu+\alpha_1) & 0 & 0 \\ 0 & 0 & (\mu+\alpha_2) & 0 \\ 0 & -\alpha_1 & -\alpha_2 & (\mu+\xi) \end{pmatrix},$$

$$V^{-1} = \begin{pmatrix} \frac{1}{\mu+r} & 0 & 0 & 0 \\ 0 & \frac{1}{\mu+\alpha_1} & 0 & 0 \\ 0 & 0 & \frac{1}{\mu+\alpha_2} & 0 \\ 0 & \frac{\alpha_1}{(\mu+\alpha_1)(\mu+\xi)} & \frac{\alpha_2}{(\mu+\alpha_2)(\mu+\xi)} & \frac{1}{\mu+\xi} \end{pmatrix},$$

$$FV^{-1} = \begin{pmatrix} \frac{\tau\beta_1\pi}{\mu(\mu+r)} & 0 & 0 & 0 \\ 0 & \frac{(1-\tau)\beta_2\pi((\mu+\xi)+\alpha_1\rho_2)}{\mu(\mu+\alpha_1)(\mu+\xi)} & \frac{(1-\tau)\beta_2\pi(\rho_1(\mu+\xi)+\alpha_2\rho_2)}{\mu(\mu+\alpha_2)(\mu+\xi)} & \frac{(1-\tau)\beta_2\rho_2\pi}{\mu(\mu+\xi)} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Remark 4.2.1. *(1)* $\dfrac{\tau\beta_1\pi}{\mu(\mu+r)}$ *is the number of HPV cases that are caused by a single HPV individual.*

(2) $\dfrac{(1-\tau)\beta_2\pi((\mu+\xi)+\alpha_1\rho_2)}{\mu(\mu+\alpha_1)(\mu+\xi)}$ *is the number of HIV cases that are caused by a single HIV individual.*

(3) $\dfrac{(1-\tau)\beta_2\pi(\rho_1(\mu+\xi)+\alpha_2\rho_2)}{\mu(\mu+\alpha_2)(\mu+\xi)}$ *is the number of HIV cases that are caused by a single co-infected individual.*

(4) $\dfrac{(1-\tau)\beta_2\rho_2\pi}{\mu(\mu+\xi)}$ *is the number of HIV cases that are caused by a single AIDS individual.*

The characteristic equation of FV^{-1} is given by $|FV^{-1}-\lambda I|=0$ which yields

$$\lambda^2\left(\frac{\tau\beta_1\pi}{\mu(\mu+r)}-\lambda\right)\left(\frac{(1-\tau)\beta_2\pi((\mu+\xi)+\alpha_1\rho_2)}{\mu(\mu+\alpha_1)(\mu+\xi)}-\lambda\right)=0.$$

Thus, the spectral radius $\rho(FV^{-1})$ is given by

$$R_0=\max\{R_p,R_v\},$$

where

$$\begin{aligned} R_p &= \left(\frac{\tau\beta_1\pi}{\mu}\right)\left(\frac{1}{\mu+r}\right), \\ R_v &= \left(\frac{(1-\tau)\beta_2\pi}{\mu}\right)\left(\frac{1}{\mu+\alpha_1}\right)+\rho_2\left(\frac{(1-\tau)\beta_2\pi}{\mu}\right)\left(\frac{\alpha_1}{\mu+\alpha_1}\right)\left(\frac{1}{\mu+\xi}\right). \end{aligned} \tag{4.8}$$

$R_v=R_{vv}+R_{va}$, where $R_{vv}=\left(\dfrac{(1-\tau)\beta_2\pi}{\mu}\right)\left(\dfrac{1}{\mu+\alpha_1}\right)$ and $R_{va}=\rho_2\left(\dfrac{(1-\tau)\beta_2\pi}{\mu}\right)\left(\dfrac{\alpha_1}{\mu+\alpha_1}\right)\left(\dfrac{1}{\mu+\xi}\right)$. R_{vv} is the reproduction number due to HIV infected individuals and R_{va} is the reproduction number due to AIDS individuals.

The terms R_p and R_v from the co-infection model coincide with single-infection basic reproduction numbers for HPV and HIV when $\tau=1$ and $\tau=0$ respectively. The overall co-infection basic reproduction number, R_0, is given by the maximum of R_p and R_v where R_p is the reproduction number for the HPV infection and R_v is the reproduction number for the HIV infection.

4.2.4 Analysis of R_0

We want to look at the influences of parameters on the basic reproduction number R_0. We compute the partial derivative of R_0 with respect to the parameters. We shall start by carrying out the analysis on the reproduction number of HPV (R_p) i.e. differentiating R_p with respect to τ, β_1 and r respectively. The following partial derivatives are obtained

$$\begin{aligned}
\frac{\partial R_p}{\partial \tau} &= \frac{\beta_1 \pi}{\mu(\mu + r)} > 0, \\
\frac{\partial R_p}{\partial \beta_1} &= \frac{\tau \pi}{\mu(\mu + r)} > 0, \\
\frac{\partial R_p}{\partial r} &= -\frac{\tau \beta_1 \pi}{\mu(\mu + r)^2} < 0.
\end{aligned}$$

When either the proportion of susceptible that are infected with HPV (τ) and HPV infection transmission probability per sexual contact (β_1) are increased keeping other parameters at baseline levels then the reproduction number of HPV (R_p) increases. This implies that they increase the endemicity of the co-infection. The increase in HPV recovery rate (r) decreases value of threshold (R_p).

We take the partial derivatives of the reproduction number of HIV (R_v) with respect to τ, β_2, ρ_2, ξ and α_1 respectively. We obtain

$$\begin{aligned}
\frac{\partial R_v}{\partial \tau} &= -\frac{\beta_2 \pi[(\mu + \xi) + \rho_2 \alpha_1]}{\mu(\mu + \alpha_1)(\mu + \xi)} < 0, \\
\frac{\partial R_v}{\partial \beta_2} &= \frac{(1 - \tau)\pi[(\mu + \xi) + \rho_2 \alpha_1]}{\mu(\mu + \alpha_1)(\mu + \xi)} > 0, \\
\frac{\partial R_v}{\partial \rho_2} &= \frac{(1 - \tau)\beta_2 \alpha_1 \pi}{\mu(\mu + \alpha_1)(\mu + \xi)} > 0, \\
\frac{\partial R_v}{\partial \xi} &= -\frac{(1 - \tau)\beta_2 \rho_2 \alpha_1 \pi}{\mu(\mu + \alpha_1)(\mu + \xi)^2} < 0, \\
\frac{\partial R_v}{\partial \alpha_1} &= \frac{(1 - \tau)\beta_2 \pi[\rho_2 \mu - (\mu + \xi)]}{\mu(\mu + \alpha_1)^2(\mu + \xi)}.
\end{aligned}$$

From the partial derivatives above, an increase in the HIV infection transmission probability per sexual contact (β_2) and the modification of transmission rate for AIDS (ρ_2) will results in an increase in the reproduction number of HIV (R_v) which increases the endemicity of HIV in the community.

While the increase in τ and the death rate due to AIDS (ξ) will result in a reduction in the threshold R_v and reduces the endemicity of the HIV in the community. The effects of the progression rate from HIV to AIDS (α_1) is determined by $\frac{\rho_2\mu}{\mu+\xi}-1$. When $\frac{\rho_2\mu}{\mu+\xi}>1$ which means α_1 will increase the threshold R_v, while when $\frac{\rho_2\mu}{\mu+\xi}<1$ will result in the reduction of R_v. $R_p > R_v$ means that there are more individuals who are infected with HPV compared with HIV and these individuals are at risk of getting infected by HIV. The HPV infection reproduction number can be increased when the rate of infection of susceptibles individuals increases and as a result the number of individuals infected with HPV increases. The scenario can be made worse when the rate of recovery from HPV infection is low. In this case a lot of the HPV infected individuals spend more time in the I_p class where there are at high risk of contracting HIV. If $R_v > R_p$, then there are more individuals who are infected with HIV than HPV. The key processes responsible for increasing R_v are the increase in rate of HIV infection β_2, the increase progression from HIV infected class to the AIDS class and the increase in the intensity of infection by the AIDS individuals relative to other infectious classes. The scenario can be made worse when the death rate due to AIDS is low and the proportion of those getting infected with HPV is reduced.

The terms in the next generation can be explained as follows:

(i) $\frac{1}{\mu+r}$ is the average times an individual spends in the infected class I_p.

(ii) $\frac{1}{\mu+\alpha_1}$ is the average times an individual spends in the infected I_v.

(iii) $\frac{1}{\mu+\xi}$ is the average times an individual spends in the AIDS class A.

(iv) $\frac{\alpha_1}{\mu+\alpha_1}$ is the proportion of HIV individuals who develop AIDS by progressing from compartment I_v to compartment A.

(v) $\left(\frac{\alpha_1}{\mu+\alpha_1}\right)\left(\frac{1}{\mu+\xi}\right)$ is the proportion of HIV individuals who develop AIDS by progressing

from compartment I_v to compartment A by the average times an individual spends in the AIDS class A.

4.2.5 Stability analysis of the disease free equilibrium

Theorem 4.2.2.

The disease-free equilibrium point E_0 of the model (4.1) to (4.6) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof.

To establish the local stability of E_0, we use the Jacobian matrix of the model evaluated at disease free equilibrium (E_0). Stability of this equilibrium point is then determined based on the eigenvalues of the matrix for system (4.1) to (4.6) is given by $J(E_0) =$

$$\begin{pmatrix} -\mu & -(\mu+r)R_p & -\frac{(\mu+\alpha_1)(\mu+\xi)}{((\mu+\xi)+\rho_2\alpha_1)}R_v & -\rho_1\frac{(\mu+\alpha_1)(\mu+\xi)}{((\mu+\xi)+\rho_2\alpha_1)}R_v & -\rho_2\frac{(\mu+\alpha_1)(\mu+\xi)}{((\mu+\xi)+\rho_2\alpha_1)}R_v & 0 \\ 0 & (\mu+r)(R_p-1) & 0 & 0 & 0 & 0 \\ 0 & 0 & (\mu+\alpha_1)(\frac{(\mu+\xi)}{((\mu+\xi)+\rho_2\alpha_1)}R_v-1) & \rho_1\frac{(\mu+\alpha_1)(\mu+\xi)}{((\mu+\xi)+\rho_2\alpha_1)}R_v & \rho_2\frac{(\mu+\alpha_1)(\mu+\xi)}{((\mu+\xi)+\rho_2\alpha_1)}R_v & 0 \\ 0 & 0 & 0 & -(\mu+\alpha_2) & 0 & 0 \\ 0 & 0 & \alpha_1 & \alpha_2 & -(\mu+\xi) & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu \end{pmatrix}.$$

The eigenvalues obtained from the characteristic polynomial of the matrix $J(E_0)$ are given by

$$\begin{aligned} \lambda_{1,2} &= -\mu < 0, \qquad \lambda_3 = -(\mu+\alpha_2) < 0, \\ \lambda_4 &= -(\mu+r)(1-R_p) < 0, \text{when } R_p < 1, \end{aligned}$$

and

$$\lambda^2 + a_1\lambda + a_2 = 0,$$

where

$$a_1 = [(\mu+\xi)+(\mu+\alpha_1)[1-\frac{\mu+\xi}{\mu+\xi+\rho_2\alpha_1}R_v]] > 0, \text{ when } R_v < 1 \text{ since } 0 < \frac{\mu+\xi}{\mu+\xi+\rho_2\alpha_1} < 1,$$

$$a_2 = (\mu+\alpha_1)(\mu+\xi)(1-R_v) > 0, \text{ when } R_v < 1.$$

Now,

$$\lambda_5 = -\frac{a_1}{2} - \sqrt{\left(\frac{a_1}{2}\right)^2 - a_2} < 0,$$

$$\lambda_6 = -\frac{a_1}{2} + \sqrt{\left(\frac{a_1}{2}\right)^2 - a_2} < 0, \text{when } R_v < 1.$$

$\lambda_5 < 0$ and $\lambda_6 < 0$ when $R_v < 1$. Since all the eigenvalues have negative real parts when both $R_p < 1$ and $R_v < 1$, the disease-free equilibrium point (E_0) is locally asymptotically stable if and only if $R_0 < 1$ and unstable when $R_0 > 1$. □

Remark 4.2.2.

For $R_0 > 1$, the following scenarios should hold

(i) $R_p < 1$ and $R_v > 1$. In this case, $a_2 > 0$ making at least one eigenvalue to be positive. The disease-free equilibrium point becomes a saddle point, which renders it unstable. This is a scenario where HIV is the dominant infection in the co-infection.

(ii) $R_p > 1$ and $R_v < 1$. We also have at least one eigenvalue positive. Again, the equilibrium point is a saddle point where HPV infection progress but HIV infection is suppressed.

(iii) $R_p > 1$ and $R_v > 1$. We have at least two positive eigenvalues and both HIV and HPV infections are prevalent.

4.2.6 Endemic equilibrium point

We define

$$G^{**} = \beta_1 I_p^{**}, \tag{4.9}$$

$$H^{**} = \beta_2(I_v^{**} + \rho_1 I_{pv}^{**} + \rho_2 A^{**}). \tag{4.10}$$

The system of equations (4.1) to (4.6) at endemic equilibrium point can be simplified in terms of G^{**} and H^{**} to give

$$E_1 = (S^{**}, I_p^{**}, I_v^{**}, I_{pv}^{**}, A^{**}, R^{**}),$$

where

$$S^{**} = \frac{\pi}{\tau G^{**} + (1-\tau)H^{**} + \mu}, \tag{4.11}$$

$$I_p^{**} = \frac{\tau G^{**}\pi}{(\sigma_1 H^{**} + (\mu + r))(\tau G^{**} + (1-\tau)H^{**} + \mu)}, \tag{4.12}$$

$$I_v^{**} = \frac{\pi K_0 H^{**}}{(\mu + H^{**})(\sigma_2 G^{**} + (\mu + \alpha_1))(\sigma_1 H^{**} + (\mu + r))(\tau G^{**} + (1-\tau)H^{**} + \mu)} \tag{4.13}$$

$$I_{pv}^{**} = \frac{\pi G^{**} H^{**}[\tau\sigma_1(\mu + H^{**})(\sigma_2 G^{**} + (\mu + \alpha_1)) + \sigma_2 K_0]}{K_1(\mu + H^{**})(\sigma 2G^{**} + (\mu + \alpha_1))(\tau G^{**} + (1-\tau)H^{**} + \mu)}, \tag{4.14}$$

$$A^{**} = \frac{\pi H^{**}[K_0[\alpha_1(\mu + \alpha_2) + \alpha_2\sigma_2 G^{**}] + \alpha_2\tau\sigma_1 G^{**}(\mu + H^{**})(\sigma_2 G^{**} + (\mu + \alpha_1))]}{K_1(\mu + \xi)(\mu + H^{**})(\sigma_2 G^{**} + (\mu + \alpha_1))(\tau G^{**} + (1-\tau)H^{**} + \mu)}, \tag{4.15}$$

$$R^{**} = \frac{r\tau G^{**}\pi}{(\sigma_1 H^{**} + (\mu + r))(\tau G^{**} + (1-\tau)H^{**} + \mu)}, \tag{4.16}$$

and

$$K_0 = (1-\tau)(\mu + H^{**})(\sigma_1 H^{**} + (\mu + r)) + r\tau G^{**},$$

$$K_1 = (\mu + \alpha_2)(\sigma_1 H^{**} + (\mu + r)).$$

The positive endemic equilibrium of system (4.1)-(4.6) can be obtained by solving for the fixed points of G^{**} and H^{**} in equations (4.9) and (4.10) and substituting the results into equations (4.11)-(4.16) [53, 55, 56]. The expressions of G^{**} and H^{**} are given by

$$G^{**} = \frac{\tau\beta_1\pi G^{**}}{(\sigma_1 H^{**} + (\mu + r))(\tau G^{**} + (1-\tau)H^{**} + \mu)}, \tag{4.17}$$

$$H^{**} = \frac{\beta_2 \pi H^{**}[K_0(\mu+\alpha_2)[(\mu+\xi)+\rho_2\alpha_1] + K_2 G^{**}]}{K_1(\mu+\xi)(\mu+H^{**})(\sigma_2 G^{**}+(\mu+\alpha_1))(\tau G^{**}+(1-\tau)H^{**}+\mu)}, \tag{4.18}$$

where $K_2 = (\rho_1(\mu+\xi)+\rho_2\alpha_2)[\sigma_2 K_0 + \tau\sigma_1(\mu+H^{**})(\sigma_2 G^{**}+(\mu+\alpha_1))]$.

We define

$$\begin{pmatrix} G^{**} \\ \\ H^{**} \end{pmatrix} = f(G,H) = \begin{pmatrix} f_1(G,H) \\ \\ f_2(G,H) \end{pmatrix},$$

where $f_1(G,H)$ and $f_2(G,H)$ are defined as the right hand sides of equations (4.17) and (4.18) respectively. Clearly, $G^{**}=0$ and $H^{**}=0$ is a fixed point of $f_1(G,H)$ and $f_2(G,H)$ which corresponds to the disease free equilibrium point E_0. We proceed to derive conditions which show that f has a unique nonzero fixed point corresponding to the positive endemic equilibrium point whose coordinates are the equations (4.1)-(4.6). For a fixed $H>0$, we consider the real valued function

$$f_1^H(G) = \frac{\tau\beta_1\pi G}{(\sigma_1 H+(\mu+r))(\tau G+(1-\tau)H+\mu)}.$$

Since $f_1^H(0)=0$ and $\lim_{G\to\infty} f_1^H(G) = \dfrac{\beta_1\pi}{\sigma_1 H+(\mu+r)} < \infty$, then $0 \le f_1^H(G) < \infty$. This means that $f_1^H(G)$ is bounded for all fixed $H>0$.

Now

$$\begin{aligned} \frac{\partial f_1^H(G)}{\partial G} &= \frac{\tau\beta_1\pi[(1-\tau)H+\mu]}{(\sigma_1 H+(\mu+r))(\tau G+(1-\tau)H+\mu)^2} > 0, \\ \frac{\partial^2 f_1^H(G)}{\partial G^2} &= -\frac{2\tau^2\beta_1\pi[(1-\tau)H+\mu]}{(\sigma_1 H+(\mu+r))(\tau G+(1-\tau)H+\mu)^3} < 0. \end{aligned}$$

This shows that $f_1^H(G)$ is an increasing concave down function which has no change in convexity [32]. Thus, there exist a unique positive G^{**} such that $f_1^H(G^{**}) = G^{**}$.

Substituting G^{**} into the function $f_2(G,H)$ yields the function

$$f_2^{G^{**}}(H) = \frac{\beta_2\pi H[K_0(\mu+\alpha_2)[(\mu+\xi)+\rho_2\alpha_1] + G^{**}K_2]}{K_1(\mu+\xi)(\mu+H)(\sigma_2 G^{**}+(\mu+\alpha_1))(\tau G^{**}+(1-\tau)H+\mu)}.$$

$$
\begin{aligned}
f_2^{G^{**}}(0) &= 0 \text{ and} \\
\lim_{H\to\infty} f_2^{G^{**}}(H) &= \frac{\sigma_1(1-\tau)(\mu+\alpha_2)[(\mu+\xi)+\rho_2\alpha_1]+\sigma_1\sigma_2G^{**}(1-\tau)[\rho_1(\mu+\xi)+\rho_2\alpha_2]}{\sigma_1(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2G^{**}+(\mu+\alpha_1))} < \infty.
\end{aligned}
$$

Thus, $0 \leq f_2^{G^{**}}(H) < \infty$.

Let

$$
f_2^{G^{**}}(H) = \frac{\beta_2\pi H[\psi_1H^2+\psi_2H+\psi_3]}{\psi_4H^3+\psi_5H^2+\psi_6H+\psi},
$$

where

$$
\begin{aligned}
\psi_1 &= \sigma_1(1-\tau)(\mu+\alpha_2)[(\mu+\xi)+\rho_2\alpha_1]+\sigma_1\sigma_2G^{**}(1-\tau)[\rho_1(\mu+\xi)+\rho_2\alpha_2], \\
\psi_2 &= (1-\tau)(\mu+\alpha_2)[\mu\sigma_1+(\mu+r)][(\mu+\xi)+\rho_2\alpha_1]+\sigma_2G^{**}(1-\tau)[\mu\sigma_1 \\
&+ (\mu+r)][\rho_1(\mu+\xi)+\rho_2\alpha_2]+\tau\sigma_1G^{**}(\sigma_2G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2], \\
\psi_3 &= \sigma_2G^{**}[\mu(1-\tau)(\mu+r)+r\tau G^{**}](\rho_1(\mu+\xi)+\rho_2\alpha_2)+\mu\tau\sigma_1G^{**}(\sigma_2G^{**} \\
&+ (\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2]+[\mu(1-\tau)(\mu+r)+r\tau G^{**}](\mu+\alpha_2)[(\mu+\xi)+\rho_2\alpha_1], \\
\psi_4 &= \sigma_1(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2G^{**}+(\mu+\alpha_1)), \\
\psi_5 &= (\mu+\xi)(\mu+\alpha_2)(\sigma_2G^{**}+(\mu+\alpha_1))[\mu\sigma_1(1-\tau)+\mu\sigma_1+\sigma_1\tau G^{**}+(1-\tau)(\mu+r)], \\
\psi_6 &= [\mu^2\sigma_1+\mu\sigma_1\tau G^{**}+\mu(1-\tau)(\mu+r)+(\mu+r)(\tau G^{**}+\mu)](\mu+\xi)(\mu+\alpha_2)(\sigma_2G^{**}+(\mu+\alpha_1)), \\
\psi_7 &= \mu(\mu+r)(\tau G^{**}+\mu)(\mu+\xi)(\mu+\alpha_2)(\sigma_2G^{**}+(\mu+\alpha_1)).
\end{aligned}
$$

The partial derivative of $f_2^{G^{**}}(H)$ with respect to H is given by $\frac{\partial f_2^{G^{**}}(H)}{\partial H} =$

$$
\frac{\beta_2\pi[(\psi_1\psi_5-\psi_2\psi_4)H^4+2(\psi_1\psi_6-\psi_3\psi_4)H^3+(3\psi_1\psi_7+\psi_2\psi_6-\psi_3\psi_5)H^2+2\psi_2\psi_7H+\psi_3\psi_7]}{(\psi_4H^3+\psi_5H^2+\psi_6H+\psi_7)^2}.
$$

$\frac{\partial f_2^{G^{**}}(H)}{\partial H} > 0$ when

$$
(i)\ \frac{\rho_1\alpha_1}{\alpha_2} > 1, \tag{4.19}
$$

$$
(ii)\ (\mu+\alpha_1) < 1, \tag{4.20}
$$

The conditions (i) and (ii) hold if

$(a)\ \psi_1\psi_5 - \psi_2\psi_4 > 0 \qquad (b)\ \psi_1\psi_6 - \psi_3\psi_4 > 0 \qquad (c)\ \psi_2\psi_6 - \psi_3\psi_5 > 0.$

The detailed calculation of positivity of condition (a) are given in appendix **A1** where condition (a) reduces to

$$\sigma_1^2\tau G^{**}(1-\tau)(\mu+\alpha_2)(\mu+\xi)(\sigma_1 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1][\alpha_2-\alpha_1] > 0,$$

since $\alpha_2 > \alpha_1$.

The detailed calculation of positivity of condition (b) are given in appendix **A2** where condition (b) reduces to

$$\mu\sigma_1 G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2][\mu\sigma_2-\sigma_1\tau(\mu+\alpha_1)] > 0.$$

We require that $\mu\sigma_2 - \sigma_1\tau(\mu+\alpha_1) > 0$, that is $\dfrac{\mu\sigma_2}{\tau(\mu+\alpha_1)} > 1$, where $(\mu+\alpha_1) < 1$.

The detailed calculation of positivity of condition (c) are given in appendix **A3** and condition (c) holds if the following expressions are positive. We require $\mu(\rho_1-1)+(\rho_1\alpha_1-\alpha_2) > 0$, therefore $\rho_1 > 1$ and $\dfrac{\rho_1\alpha_1}{\alpha_2} > 1$.

We also require that $\dfrac{\mu\sigma_2}{\tau} > (\mu+\alpha_1)$ and $\dfrac{\mu\sigma_2}{\tau} > \dfrac{\sigma_1}{1-\tau} > 1$ and these inequalities reduces to $(\mu+\alpha_1) < 1$.

Condition (c) holds if the inequalities (4.19) and (4.20) holds.

Clearly conditions (a), (b) and (c) reduces to conditions (i) and (ii), which are necessary for $\dfrac{\partial f_2^{G^{**}}}{\partial H}(H) > 0$.

The second partial derivative of $f_2^{G^{**}}(H)$ with respect to H is given by

$$\frac{\partial^2 f_2^{G^{**}}(H)}{\partial H^2} = -\frac{2\beta_2\pi[a_1H^6+a_2H^5+a_3H^4+a_4H^3+a_5H^2+a_6H+a_7]}{(\psi_4H^3+\psi_5H^2+\psi_6H+\psi_7)^3} < 0,$$

where

$$
\begin{aligned}
a_1 &= \psi_4(\psi_1\psi_5 - \psi_2\psi_4),\\
a_2 &= 3\psi_4(\psi_1\psi_6 - \psi_3\psi_4),\\
a_3 &= 2\psi_4(3\psi_1\psi_7 + \psi_2\psi_6 - \psi_3\psi_5) + \psi_4(\psi_2\psi_6 - \psi_3\psi_5),\\
a_4 &= 7\psi_7(\psi_1\psi_5 + \psi_2\psi_4) + 3\psi_5(\psi_2\psi_6 - \psi_3\psi_5) - \psi_6(\psi_1\psi_6 - \psi_3\psi_4),\\
a_5 &= 6\psi_3\psi_4\psi_7 + 3\psi_7(\psi_2\psi_5 - \psi_1\psi_6),\\
a_6 &= 3\psi_7(\psi_3\psi_4 - \psi_1\psi_7) > 0, \text{ (see appendix } \mathbf{A5)},\\
a_7 &= \psi_7(\psi_3\psi_6 - \psi_2\psi_7) > 0, \text{ (see appendix } \mathbf{A6)}.
\end{aligned}
$$

$\frac{\partial^2 f_2^{G^{**}}(H)}{\partial H^2} < 0$ when $a_1 > 0$, $a_2 > 0$, $a_3 > 0$, $a_4 > 0$ and $a_5 > 0$.

If the conditions in inequalities (4.19) and (4.20) holds then $a_1 > 0$, $a_2 > 0$ and $a_3 > 0$.

$a_4 > 0$, if in an addition to condition in inequalities (4.19) and (4.20),

$$\frac{3\psi_5(\psi_2\psi_6 - \psi_3\psi_5)}{\psi_6(\psi_1\psi_6 - \psi_3\psi_4)} > 1. \tag{4.21}$$

$a_5 > 0$, when inequality (4.19) hold, see appendix **A4**.

This shows that $f_2^{G^{**}}(H)$ is an increasing concave down function which has no change of convexity. Thus, there exist a unique positive H^{**} such that $f_2^{G^{**}}(H^{**}) = H^{**} > 0$, when conditions (4.19), (4.20) and (4.21) are satisfied.

(G^{**}, H^{**}) is a fixed point of f which corresponds to an endemic state E^{**} of the model. For stability of (G^{**}, H^{**}), we require that $|f'(G^{**}, H^{**})| < 1$ and for instability we require that $|f'(G^{**}, H^{**})| > 1$.

The Jacobian of f at (G^{**}, H^{**}) is given by

$$J^{**} = \begin{pmatrix} \frac{\partial f_1(G,H)}{\partial G}\big|_{(G^{**},H^{**})} & \frac{\partial f_1(G,H)}{\partial H}\big|_{(G^{**},H^{**})} \\ \frac{\partial f_2(G,H)}{\partial G}\big|_{(G^{**},H^{**})} & \frac{\partial f_2(G,H)}{\partial H}\big|_{(G^{**},H^{**})} \end{pmatrix},$$

where

$$\frac{\partial f_1(G,H)}{\partial H}|_{(G^{**},H^{**})} = -\frac{\tau\beta_1\pi G^{**}[\sigma_1(\tau G^{**}+(1-\tau)H^{**}+\mu)+(1-\tau)(\sigma_1 H^{**}+(\mu+r))]}{(\sigma_1 H^{**}+(\mu+r))^2(\tau G^{**}+(1-\tau)H^{**}+\mu)^2} < 0.$$

Let

$$f_2(G^{**},H^{**}) = \frac{\beta_2\pi H^{**}[\phi_1 G^{**2}+\phi_2 G^{**}+\phi_3]}{\phi_4 G^{**2}+\phi_5 G^{**}+\phi_6},$$

where

$$\begin{aligned}
\phi_1 &= \sigma_2\tau[r+\sigma_1(\mu+H^{**})][\rho_1(\mu+\xi)+\rho_2\alpha_2],\\
\phi_2 &= [\rho_1(\mu+\xi)+\rho_2\alpha_2][\sigma_2(1-\tau)(\mu+H^{**})(\sigma_1 H^{**}+(\mu+r))\\
&+ \tau\sigma_1(\mu+H^{**})(\mu+\alpha_1)]+r\tau(\mu+\alpha_2)[(\mu+\xi)+\rho_2\alpha_1],\\
\phi_3 &= K_1(1-\tau)(\mu+H^{**})[(\mu+\xi)+\rho_2\alpha_1],\\
\phi_4 &= \tau\sigma_2 K_1(\mu+\xi)(\mu+H^{**}),\\
\phi_5 &= K_1(\mu+\xi)(\mu+H^{**})[\sigma_2(1-\tau)H^{**}+\mu\sigma_2+\tau(\mu+\alpha_1)],\\
\phi_6 &= K_1(\mu+\alpha_1)(\mu+\xi)(\mu+H^{**})((1-\tau)H^{**}+\mu).
\end{aligned}$$

The partial derivative of $f_2(G,H)$ with respect to G is given by

$$\frac{\partial f_2}{\partial G}|_{(G^{**},H^{**})} = \frac{\beta_2\pi H[(\phi_1\phi_5-\phi_2\phi_4)G^2+2(\phi_1\phi_6-\phi_3\phi_4)G+(\phi_2\phi_6-\phi_3\phi_5)]}{(\phi_4 G^2+\phi_5 G+\phi_6)^2} > 0.$$

$\frac{\partial f_2}{\partial G}|(G^{**},H^{**}) > 0$ when

$$(i)\ \frac{\rho_1\alpha_1}{\alpha_2} > 1, \tag{4.22}$$

$$(ii)\ \frac{\sigma_1\alpha_1}{(1-\tau)\alpha_2} > 1. \tag{4.23}$$

$\frac{\partial f_2^{H^{**}}}{\partial G} > 0$, when the following conditions holds.

(a) $\phi_1\phi_5-\phi_2\phi_4 > 0$,

(b) $\phi_1\phi_6 - \phi_3\phi_4 > 0$,

(c) $\phi_2\phi_6 - \phi_3\phi_5 > 0$.

From condition (a)

$$\begin{aligned}\phi_1\phi_5 - \phi_2\phi_4 &= \tau\mu\sigma_2^2 K_1(\mu + H^{**})^2(\mu+\xi)[\rho_1(\mu+\xi) + \rho_2\alpha_2][\sigma_1 - (1-\tau)] \\ &+ r\tau^2\sigma_2 K_1(\mu+\xi)^2(\mu + H^{**})[\rho_1(\mu+\alpha_1) - (\mu+\alpha_2)] > 0.\end{aligned}$$

Since $\sigma_1 > 1$ and $(1-\tau) < 1$, $\sigma_1 - (1-\tau) > 0$.

Since $\rho_1 > 1$, $\rho_1(\mu+\alpha_1) - (\mu+\alpha_2) > 0$, reduces to $\mu(\rho_1 - 1) > 0$, and $\dfrac{\rho_1\alpha_1}{\alpha_2} > 1$.

From condition (b), we have

$$\begin{aligned}\phi_1\phi_6 - \phi_3\phi_4 &= \mu\sigma_2\tau K_1(\mu+\xi)^2(\mu+H^{**})^2[\sigma_1(\mu+\alpha_1) - (1-\tau)(\mu+\alpha_2)] \\ &+ \tau\sigma_1\sigma_2 K_1 H^{**}(1-\tau)(\mu+\xi)^2(\mu+H^{**})^2[\rho_1(\mu+\alpha_1) - (\mu+\alpha_2)] \\ &+ r\tau\sigma_2 K_1 H^{**}(1-\tau)(\mu+\xi)^2(\mu+H^{**})[\rho_1(\mu+\alpha_1) - (\mu+\alpha_2)] \\ &+ r\tau\mu\sigma_2 K_1\rho_2(\mu+\xi)(\mu+H^{**})[\alpha_2(\mu+\alpha_1) - \alpha_1(\mu+\alpha_2)].\end{aligned}$$

Condition (b) holds if $\dfrac{\rho_1\alpha_1}{\alpha_2} > 1$ and $\dfrac{\sigma_1\alpha_1}{(1-\tau)\alpha_2} > 1$.

Condition (c) is given by

$$\begin{aligned}\phi_2\phi_6 - \phi_3\phi_5 &= \sigma_2 K_1 H^{**}(1-\tau)^2(\mu+H^{**})^2(\mu+\xi)^2(\sigma_1 H^{**} + (\mu+r))[\rho_1(\mu+\alpha_1) - (\mu+\alpha_2)] \\ &+ \mu\sigma_2 K_1(1-\tau)(\mu+\xi)^2(\mu+H^{**})^2(\sigma_1 H^{**} + (\mu+r))[\rho_1(\mu+\alpha_1) - (\mu+\alpha_2)] \\ &+ \tau\sigma_1 K_1 H^{**}(1-\tau)(\mu+\alpha_1)(\mu+\xi)^2(\mu+H^{**})^2[\rho_1(\mu+\alpha_1) - (\mu+\alpha_2)].\end{aligned}$$

Condition (c) holds if $\dfrac{\rho_1\alpha_1}{\alpha_2} > 1$. The eigenvalues from the Jacobian matrix are given by the characteristic equation

$$\lambda^2 - \lambda\left(\frac{\partial f_1}{\partial G} + \frac{\partial f_2}{\partial H}\right)\Big|_{(G^{**},H^{**})} + \left(\frac{\partial f_1}{\partial G}\frac{\partial f_2}{\partial H} - \frac{\partial f_1}{\partial H}\frac{\partial f_2}{\partial G}\right)\Big|_{(G^{**},H^{**})} = 0. \tag{4.24}$$

Since $\frac{\partial f_1}{\partial G}|_{(G^{**},H^{**})} > 0$ and $\frac{\partial f_2}{\partial H}|_{(G^{**},H^{**})} > 0$, then $\left(\frac{\partial f_1}{\partial G} + \frac{\partial f_2}{\partial H}\right)|_{(G^{**},H^{**})} > 0$ when $\frac{\rho_1\alpha_1}{\alpha_2} > 1$ and $(\mu + \alpha_1) < 1$.

$\frac{\partial f_1}{\partial H}|_{(G^{**},H^{**})} < 0$ and $\frac{\partial f_2}{\partial G}|_{(G^{**},H^{**})} > 0$, then $\left(\frac{\partial f_1}{\partial G}\frac{\partial f_2}{\partial H} - \frac{\partial f_1}{\partial H}\frac{\partial f_2}{\partial G}\right)|_{(G^{**},H^{**})}$, yields

$$\frac{A\tau\beta_1\pi[(1-\tau)H^{**}+\mu](\phi_4G^{**2}+\phi_5G^{**}+\phi_6)^2(\sigma_1H^{**}+(\mu+r)) + BC(\psi_4H^{**3}+\psi_5H^{**2}+\psi_6H^{**}+\psi_7)^2}{(\sigma_1H^{**}+(\mu+r))^2(\tau G^{**}+(1-\tau)H^{**}+\mu)^2(\psi_4H^{**3}+\psi_5H^{**2}+\psi_6H^{**}+\psi_7)^2(\phi_4G^{**2}+\phi_5G^{**}+\phi_6)^2},$$

such that $\left(\frac{\partial f_1}{\partial G}\frac{\partial f_2}{\partial H} - \frac{\partial f_1}{\partial H}\frac{\partial f_2}{\partial G}\right)|_{(G^{**},H^{**})} > 0$, where

$$\begin{aligned}
A &= \beta_2\pi[(\psi_1\psi_5 - \psi_2\psi_4)H^{**4} + 2(\psi_1\psi_6 - \psi_3\psi_4)H^{**3} + (3\psi_1\psi_7 + \psi_2\psi_6 - \psi_3\psi_5)H^{**2} \\
&+ 2\psi_2\psi_7H^{**} + \psi_3\psi_7], \\
B &= \beta_2\pi H^{**}[(\phi_1\phi_5 - \phi_2\phi_4)G^{**2} + 2(\phi_1\phi_6 - \phi_3\phi_4)G^{**} + (\phi_2\phi_6 - \phi_3\phi_5)], \\
C &= \tau\beta_1\pi G^{**}[\sigma_1(\tau G^{**} + (1-\tau)H^{**} + \mu) + (1-\tau)(\sigma_1H^{**} + (\mu + r))].
\end{aligned}$$

$\left(\frac{\partial f_1}{\partial G}\frac{\partial f_2}{\partial H} - \frac{\partial f_1}{\partial H}\frac{\partial f_2}{\partial G}\right)|_{(G^{**},H^{**})} > 0$ when $\frac{\rho_1\alpha_1}{\alpha_2} > 1$, $\frac{\sigma_1\alpha_1}{(1-\tau)\alpha_2} > 1$ and $(\mu + \alpha_2) < 1$.

The characteristic equation (4.24) has two positive eigenvalues which are given by

$$D_1 = \frac{1}{2}\left[\left(\frac{\partial f_1}{\partial G} + \frac{\partial f_2}{\partial H}\right) + \sqrt{\left(\frac{\partial f_1}{\partial G} - \frac{\partial f_2}{\partial H}\right)^2 + 4\frac{\partial f_1}{\partial H}\frac{\partial f_2}{\partial G}}\right],$$

and

$$D_2 = \frac{1}{2}\left[\left(\frac{\partial f_1}{\partial G} + \frac{\partial f_2}{\partial H}\right) - \sqrt{\left(\frac{\partial f_1}{\partial G} - \frac{\partial f_2}{\partial H}\right)^2 + 4\frac{\partial f_1}{\partial H}\frac{\partial f_2}{\partial G}}\right].$$

The fact that $det(J^{**}) > 0$ implies that

$$\begin{aligned}
\left|\frac{\partial f_1}{\partial G} + \frac{\partial f_2}{\partial H}\right| &> \sqrt{\left(\frac{\partial f_1}{\partial G} - \frac{\partial f_2}{\partial H}\right)^2 + 4\frac{\partial f_1}{\partial H}\frac{\partial f_2}{\partial G}}, \\
\left(\frac{\partial f_1}{\partial G} + \frac{\partial f_2}{\partial H}\right)^2 &> \left(\frac{\partial f_1}{\partial G} - \frac{\partial f_2}{\partial H}\right)^2 + 4\frac{\partial f_1}{\partial H}\frac{\partial f_2}{\partial G}, \\
\frac{\partial f_1}{\partial G}\frac{\partial f_2}{\partial H} - \frac{\partial f_1}{\partial H}\frac{\partial f_2}{\partial G} &> 0.
\end{aligned}$$

Thus, both $D_1 > 0$ and $D_2 > 0$. Since $D_1 = \rho(J(G^{**}, H^{**}))$ is the dominant eigenvalue of the Jacobian matrix, then the fixed point (G^{**}, H^{**}) is locally asymptotically stable when the dominant eigenvalue $D_1 < 1$ and unstable when $D_1 > 1$. We summarize this result in the following theorem.

Theorem 4.2.3.

The endemic equilibrium point E_1 is locally asymptotically stable if $D_1 < 1$ and unstable if $D_1 > 1$.

Remark 4.2.3.

When the fixed point $(G^{**}, H^{**}) = (0, 0)$, then

$D_1 = \frac{1}{2}\left[(R_p + R_v) + \sqrt{(R_p - R_v)^2}\right] = R_p$, *thus $D_1 = R_p$ and the fixed point is stable when $R_p < 1$ and unstable when $R_p > 1$, while*

$D_2 = \frac{1}{2}\left[(R_p + R_v) - \sqrt{(R_p - R_v)^2}\right] = R_v$, *thus, $D_2 = R_v$, and the equilibrium point is stable when $R_v < 1$ and unstable when $R_v > 1$. Since $\frac{\partial f_1}{\partial G}|_{(0,0)} = R_p$, $\frac{\partial f_2}{\partial H}|_{(0,0)} = R_v$, $\frac{\partial f_1}{\partial H}|_{(0,0)} = 0$ and $\frac{\partial f_2}{\partial G}|_{(0,0)} = 0$. Therefore when $(G^{**}, H^{**}) = (0, 0)$ then $D_i = R_0 = max\{R_p, R_v\}$, where the equilibrium point is stable when $R_0 < 1$ and unstable when $R_0 > 1$.*

4.2.7 Summary

The positivity of the endemic equilibrium point is obtained by showing that f has a unique non-zero fixed point. Since $0 < f_1^H(G) < \infty$, $\frac{\partial f_1^H(G)}{\partial G} > 0$ and $\frac{\partial^2 f_1^H(G)}{\partial G^2} < 0$, which shows that there exist a unique positive G^{**}, such that $f_1^H(G^{**}) = G^{**} > 0$. While $0 < f_2^{G^{**}}(H) < \infty$, $\frac{\partial f_2^{G^{**}}(H)}{\partial H} > 0$ and $\frac{\partial^2 f_2^{G^{**}}(H)}{\partial H^2} < 0$, which shows that there exist unique positive H^{**}, such that $f_2^{G^{**}}(H^{**}) = H^{**} > 0$. The stability of (G^{**}, H^{**}) is asymptotically stable when $D_i < 1$, where $i = 1, 2$ and unstable when $D_i > 1$.

Chapter 5

NUMERICAL SIMULATIONS

5.1 Introduction

In this chapter, we are going to enhance the understanding of the theoretical results by carrying out numerical simulations of a co-infection of HPV with HIV system of equations (4.1)-(4.6). We use the parameter values from authentic literature which are suitable to represent our model situations. Numerical results will help to draw important conclusions and to also give an understanding of the effects of HIV infection alone, HPV infection alone as well as both infections in the community. We illustrate the simulation results using graphs which shows the trends of each of the variables over a period of time.

5.1.1 Parameter estimations

In this section, we estimate the parameters used in the system of equations (4.1)-(4.6) in order to carry out numerical simulations. The parameter values are given in Table 5.1. The parameter π which represents the constant recruitment rate, models the inflow of uninfected population into a

risk susceptible sexually mature and active community. The population recruited into the community must be at least 15 years old. This parameter is estimated based on the HPV and HIV transmission data in the heterosexual community. We use HPV data from HPV Information Center of South Africa of 2010 where the total population of males and females who are aged 15 years and above was 32,773,000 [2]. $\pi = 642,608$ was the population aged 15 years and above in South Africa per year. We estimate the natural death, calculated as the reciprocal of life expectancy. The life expectancy of South Africa is estimated to be in the range $[50, 53]$ years [2]. Thus $\mu \in \left[\frac{1}{53}, \frac{1}{50}\right]$ per year. β_1 is the infectivity rates of successful HPV transmission per sexual contact, and is in the interval $[0, 5]$ per year [6]. The rate at which susceptible individuals are infected by HPV is given by τ, which is governed by $0 < \tau < 1$. The natural recovery rate from HPV infection is estimated to be in the range $0.036 \leq r \leq 1.6$ per year $[1, 57]$. β_2, the infectivity rates of successful HIV transmission per sexual contact is assumed to be in the interval $\beta_2 \in (0, 1)$ per year [56]. The rate of progression of HIV infected individuals to AIDS is $\alpha_1 = 0.116$ [34]. $\frac{1}{\alpha_1}$ is the average time spent by individuals in I_v and $\frac{1}{\alpha_2}$ is the average time spent by individuals in I_{pv}. Individuals in I_v are assumed to stay longer in their class than those in I_{pv}. This means that $\frac{1}{\alpha_1} > \frac{1}{\alpha_2}$ i.e $\alpha_2 > \alpha_1$. The death rate due to AIDS is given by ξ and assumes a value of $\xi = 0.43$ per year [2].

When estimating the initial values for the numerical simulations, we use the total population of South Africa of population aged 15 years and above using 2010 population. The initial population is given by the range [14.6%, 22.3%] of south African population aged 15 years and above are infected with HPV [2]. Thus, $I_p(0) = 0.21 \times 32,773,000 = 6,882,330$. Estimated number of adults population of South Africa with 15 years and above living with HIV is given by the range [4,700,000, 6,200,000] [2]. Thus, $I_v(0) = 5,400,000$. We consider the initial population of co-infection of HPV with HIV to be zero, of AIDS to be zero and of recovered from HPV to be zero. Thus, $I_{pv}(0) = A(0) = R(0) = 0$.

The susceptible population is then calculated as $S(0) = N(0) - (I_p(0) + I_v(0)) = 20,490,670$.

5.1.2 Simulations

Parameter values used in this study are given in the Table 5.1. In order to get insight on the predictions of our theoretical results and make projection of public healthy interests, we carry out numerical simulations using the hybrid Runge-Kutta method of order 4 and 5 using MATLAB. We seek to address the following hypotheses:

(i) By how much impact does HIV infection impact the natural history of HPV infection,

(ii) By how much impact does HPV infection impact the natural history of HIV infection,

over a period of 20 years. We would like to examine first the effects of considering that the recovered individuals from HPV are careful not to indulge in risk of sexual activities again and thus will not be at risk of contracting HIV. Figure 5.1-5.5 shows the dynamics of co-infection of HPV with HIV reflecting this scenario.

Table 5.1: Variables and parameters for HIV and HPV co-infection

Parameter	Description	Estimated value/range	Reference
π	Human recruitment rate	642,608 $\mathbf{yr}^{-1}$	[2]
τ	Proportion of susceptible that are infected with HPV	$0 < \tau < 1$ $\mathbf{yr}^{-1}$	see text
β_1	HPV infection transmission probability per sexual contact	[0, 5] $\mathbf{yr}^{-1}$	[6]
β_2	HIV infection transmission probability per sexual contact	$0 \leq \beta_2 \leq 1$ $\mathbf{yr}^{-1}$	[56]
r	Rate recovery from HPV infection	[0.036, 1.6] $\mathbf{yr}^{-1}$	[1, 57]
σ_1	Progression rate of HIV infection to co-infection class	$\sigma_1 > 1$ $\mathbf{yr}^{-1}$	see text
σ_2	Progression rate of HPV infection to co-infection class	$\sigma_2 > 1$ $\mathbf{yr}^{-1}$	see text
ξ	Death rate due to AIDS	0.43 $\mathbf{yr}^{-1}$	[2]
α_1	Rate of progression from HIV to AIDS	0.116 $\mathbf{yr}^{-1}$	[34]
α_2	Rate of progression from co-infection to AIDS	$\alpha_2 > 0.116$ $\mathbf{yr}^{-1}$	see text
μ	Natural death rate	$\frac{1}{51}$ $\mathbf{yr}^{-1}$	[2]
ρ_1	Modification factor of transmission rate for co-infection	$\rho_1 > 1$ $\mathbf{yr}^{-1}$	see text
ρ_2	Modification factor of transmission rate for AIDS	$\rho_2 > \rho_1$ $\mathbf{yr}^{-1}$	see text

Figure 5.1-5.5 shows the simulation results which illustrate the dynamics of HPV-HIV co-infections. Figure 5.1 is the control of our simulation results which shows the effects of both infections at the

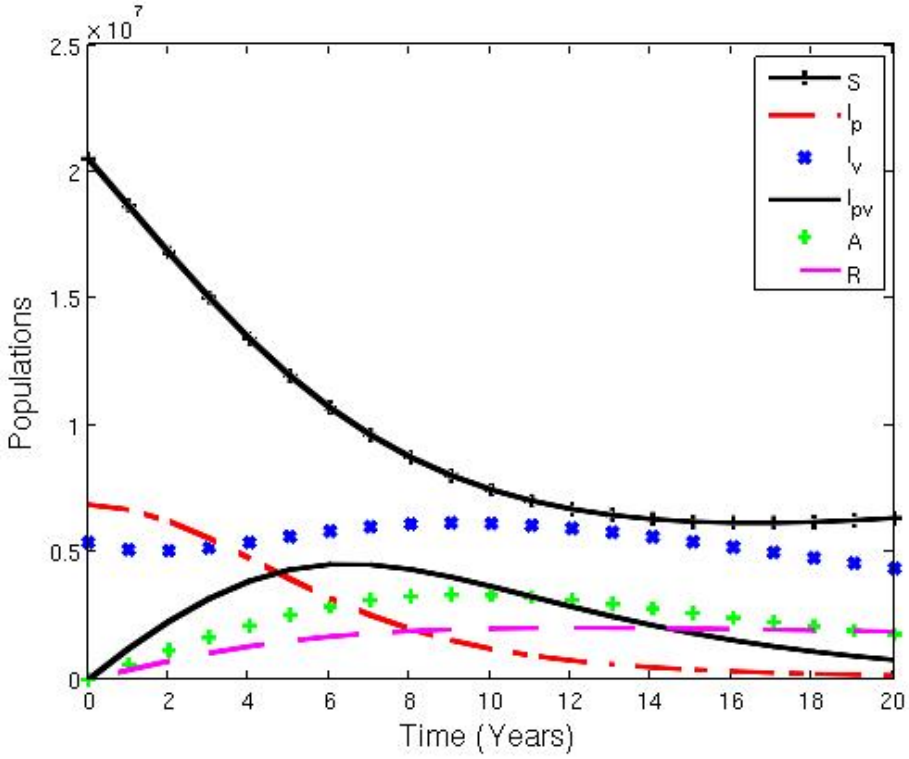

Figure 5.1: HIV and HPV infections dynamics when both infections are introduced at the same time.Using the parameters: $\pi = 642608$, $\beta_1 = 1.7 \times 10^{-8}$, $\beta_2 = 1.6 \times 10^{-8}$, $\tau = 0.45$, $\sigma_1 = 1.015$, $\sigma_2 = 1.09$, $r = 0.056$, $\rho_1 = 1.112$, $\rho_2 = 1.12$, $\alpha_1 = 0.116$, $\alpha_2 = 0.2$, $\xi = 0.43$, $\mu = 0.01961$

same time. In figure 5.2 and 5.3 illustrate the effects when we start with one infection and introduce another infection after 2 years. The effects will show the changes after 2 years. We acknowledge that using different times of introducing co-infection may lead to changes in the peaks but the qualitative nature of the curves will be maintained. In figure 5.2, HPV infection is a predominant in the system while HIV infection is not participating in the system of HPV-HIV co-infection. In figure 5.4, HPV individuals were presents in the system but HPV infection were not participating in the co-infection of HPV with HIV.

Figure 5.1 illustrates the scenario of introducing both infections (HPV and HIV) in the system at the same time. The HIV only population generally increases slowly to peak around 10 years after which it decreases steadily. The co-infection population increases to peak earlier than the HIV only population peaks within 6 to 8 years and decreases slowly until reaches its equilibrium. The suscep-

tibles population decreases significantly until it reaches its equilibrium. The HPV only population decreases slowly within 4 to 6 years and decreases rapidly when the co-infection population reaches its peak. The AIDS population steadily increases to peak within 8 to 9 years and there after it decreases gradually. The recovered individuals grows slowly over time.

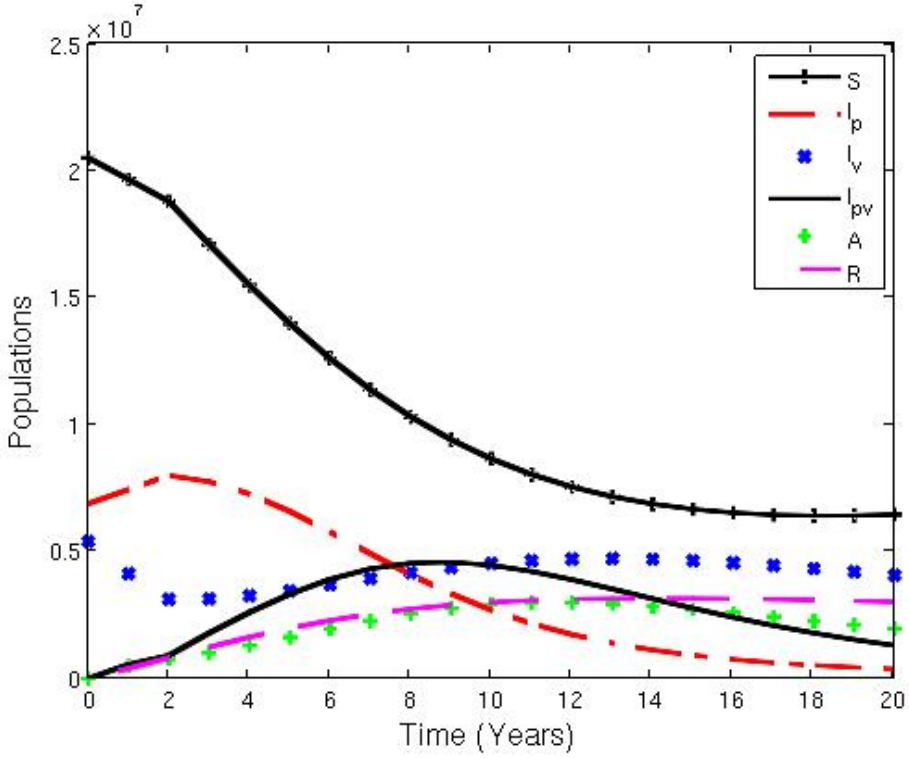

Figure 5.2: Simulation graph results showing the trends of compartments when we starts by switching off HIV infection and switch on after 2 years, i.e $\beta_2 = 0$ and $\sigma_1 = 0$. Using the parameters given in figure 5.1.

In Figure 5.2, we examine the effects of introducing HIV infection into a predominantly HPV infection. We introduce HIV infection hypothetically 2 years after HPV infection has established in the community. HIV infection will controlling the dynamics of the HPV-HIV co-infection. Initially, the susceptible population decreases steadily within the first 2 years but sharply when HIV infection is introduced. The HIV only population decreases rapidly within 2 years but there after slightly increases reach its peak around 12 years after which it decreases slowly to finally reach its equilibrium. Within the first 2 years, HIV individuals were present in the system but HIV infection were

not participating in the co-infection. The peak of HIV only population is delayed compared to the scenario in Figure 5.1. In the initial stage of HPV only population, we observe a slight increase in HPV infections because HPV infection is the only infection dominating in the system. After 2 years when HIV infection becomes active, HPV only population decreases slowly within 8 to 10 years and further decreases when the co-infection population reaches its peak. The co-infection population initially increases slowly within the first 2 years but increases faster after HIV is active in the population. The AIDS population increases slowly before 2 years, and there after increases to a peak around 12 years. The recovered individuals increases slowly before and after 2 years. In this case, we observe that the co-infection can rise above the HIV only population, the recovered population grows to levels above the AIDS population.

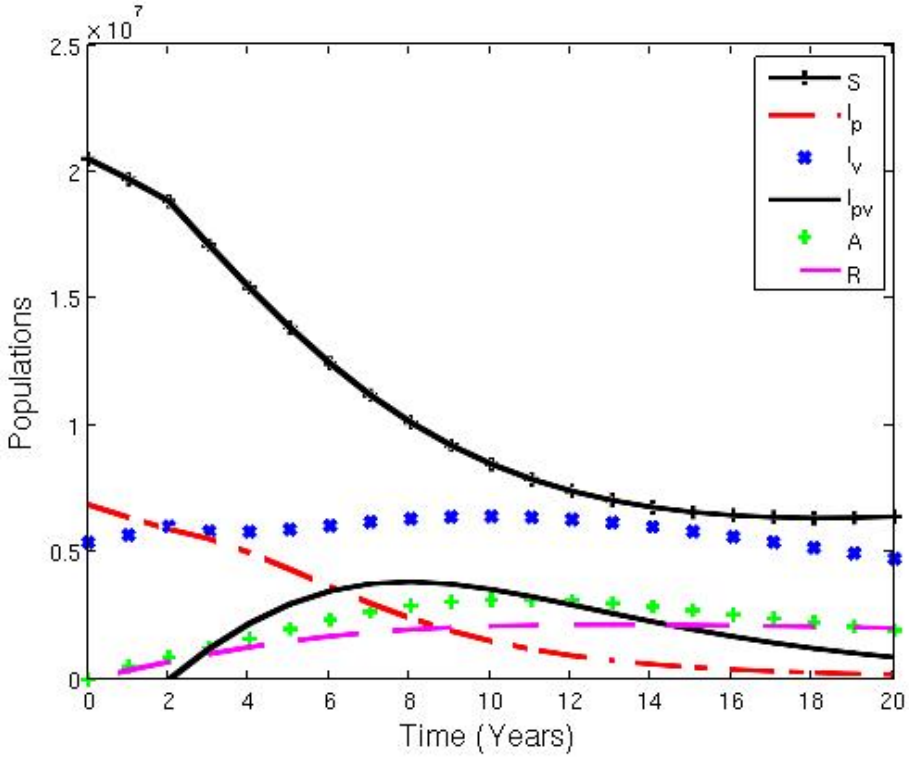

Figure 5.3: Simulation graph results shows the effects of starting by switching off HPV infection and switch on after 2 years, i.e $\beta_1 = 0$ and $\sigma_1 = 0$. Using the parameters given in figure 5.1.

Figure 5.3 shows the effects of introducing HPV infection after 2 years into the community pre-

dominantly HIV infected. The graph shows the distribution of individuals before and after 2 years in all classes. The dynamics will be controlled by HPV infection. The susceptible population decreases slowly within 2 years and thereafter faster decreases faster. The HIV only population increases within 2 years, after which it slightly drops due to the introduction of HPV and then increases slowly again until it takes its peak within 10 to 12 years. HPV only population decreases continuously before and after 2 years. HPV individuals were also present within the first 2 years, but HPV infection were not participating in the co-infection. After 2 years, the co-infection population increases but to levels below the HIV only population. The AIDS population increases to levels above the recovered population. In this case the HIV only population reaches an equilibrium that is higher than the equilibrium in Figure 5.1 and 5.2.

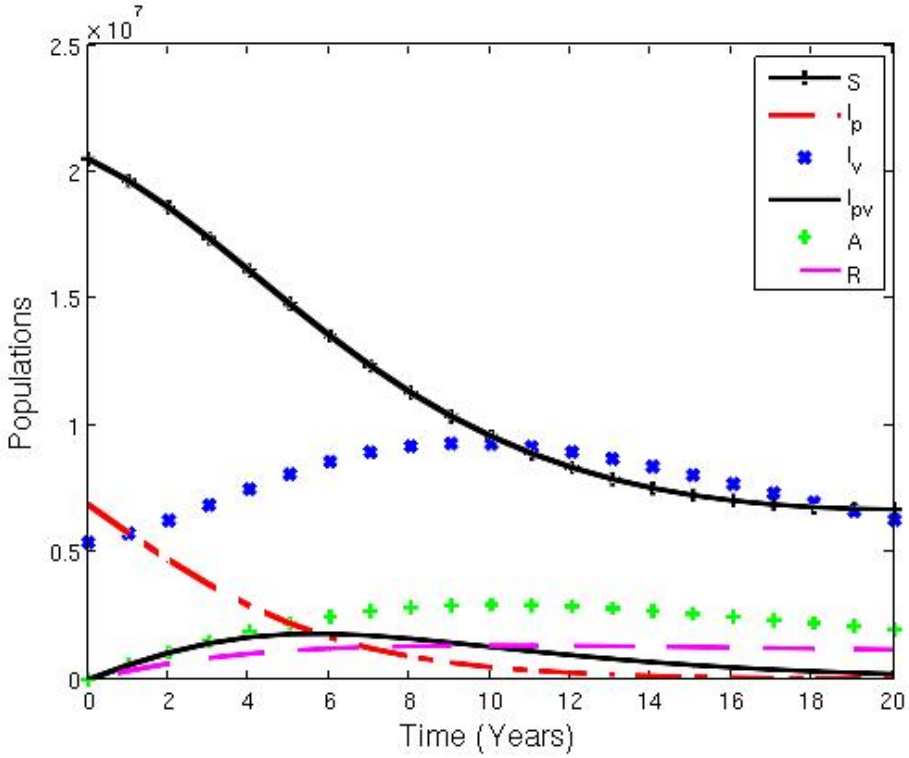

Figure 5.4: Shows the impact of HIV alone, i.e by taking $\beta_1 = 0$. Using the parameters given in figure 5.1.

Figure 5.4 illustrates the impact of dominant HIV infection in the system by taking HPV infec-

tion transmission probability per sexual contact to be zero after HIV infection has once established itself in the community. The HPV population rapidly decreases and ultimately diminishes to zero. HPV population were present in the system but HPV infection were not active in the co-infection. The susceptible population gradually decreases while the HIV only population increases more than the case in Figure 5.1, 5.2 and 5.3. The co-infection population does not grow to higher levels than those in Figure 5.1, 5.2 and 5.3.

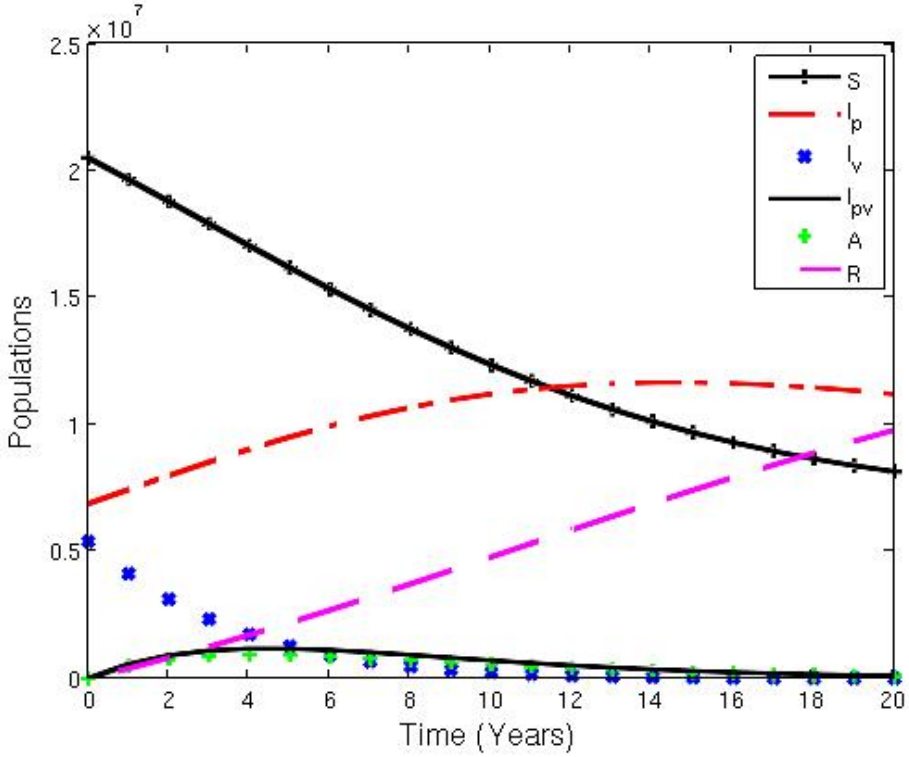

Figure 5.5: The impact of HPV alone i.e when $\beta_2 = 0$. Using the parameters given in figure 5.1.

Figure 5.5 illustrate the impact of dominant HPV infection in the system by switching off HIV infection, after HPV infection has once establish itself in the community. We observe an increase in HPV only population and recovered population over time whilst the susceptible population decreases slowly with time. HIV and AIDS population diminishes within a short time period. HIV population were there in the system but HIV infection were not active in the co-infection. The co-infection

population grows as much as the case when HIV infection only in the system.

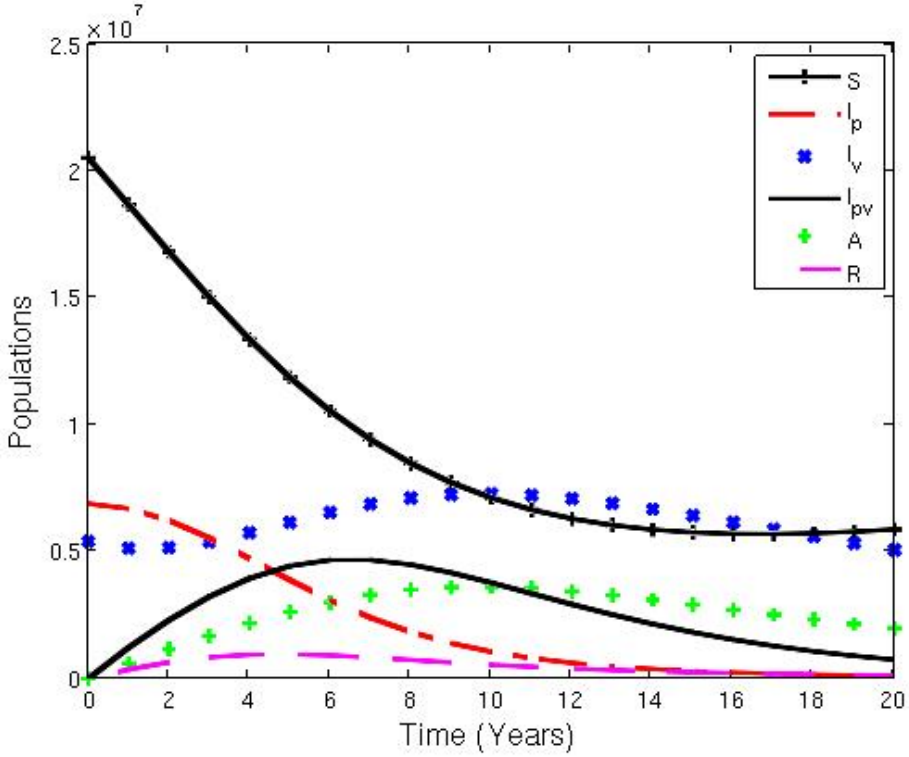

Figure 5.6: HIV and HPV infections dynamics when both infections are introduced at the same time.Using the parameters given in figure 5.1.

We proceed to investigate the scenario where recovered individuals from HPV participate in the HIV dynamics. In this case, recovering from HPV does not protect an individual from contracting HIV infection. Figures 5.6-5.10 exhibit various cases of this scenario.

In Figures 5.6-5.9, we observe the occurrence of higher peaks in HIV only population, co-infection and AIDS population than in Figure 5.1-5.4 respectively. In Figures 5.6-5.9, the recovered population do not grow as much as in Figures 5.1- 5.4. No significant differences are observed in the dynamics of susceptible populations and HPV only populations. This means that the recovered class has a significant contribution towards the growth of HIV population, co-infection population and the AIDS population.

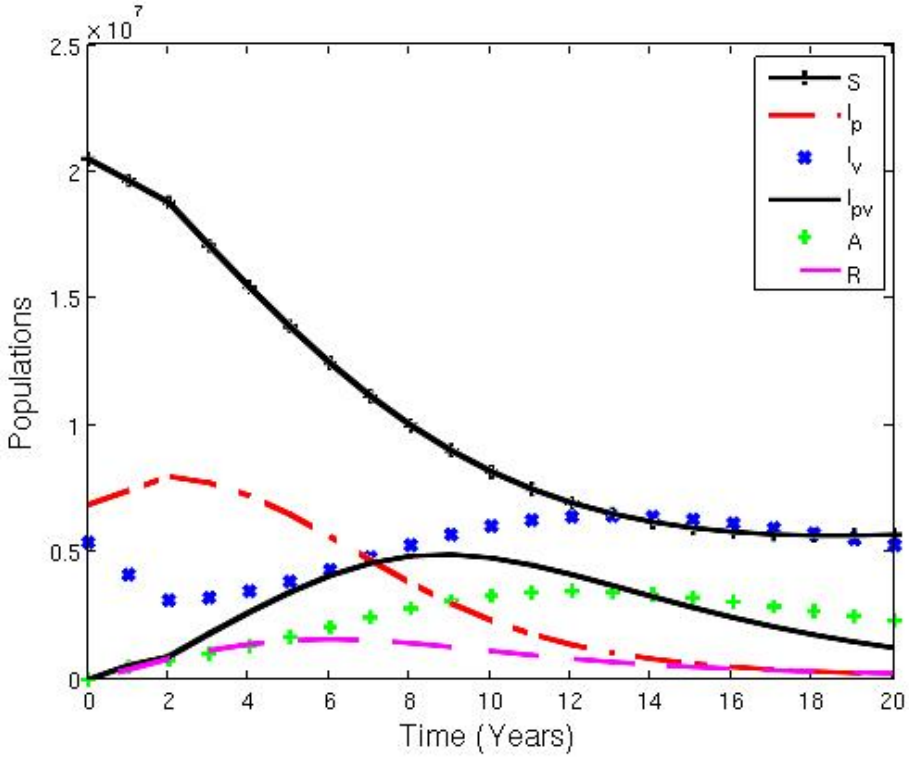

Figure 5.7: Simulation graph results showing the trends of compartments when we starts by switching off HIV infection and switch on after 2 years, i.e $\beta_2 = 0$ and $\sigma_1 = 0$. using parameters given in figure 5.1.

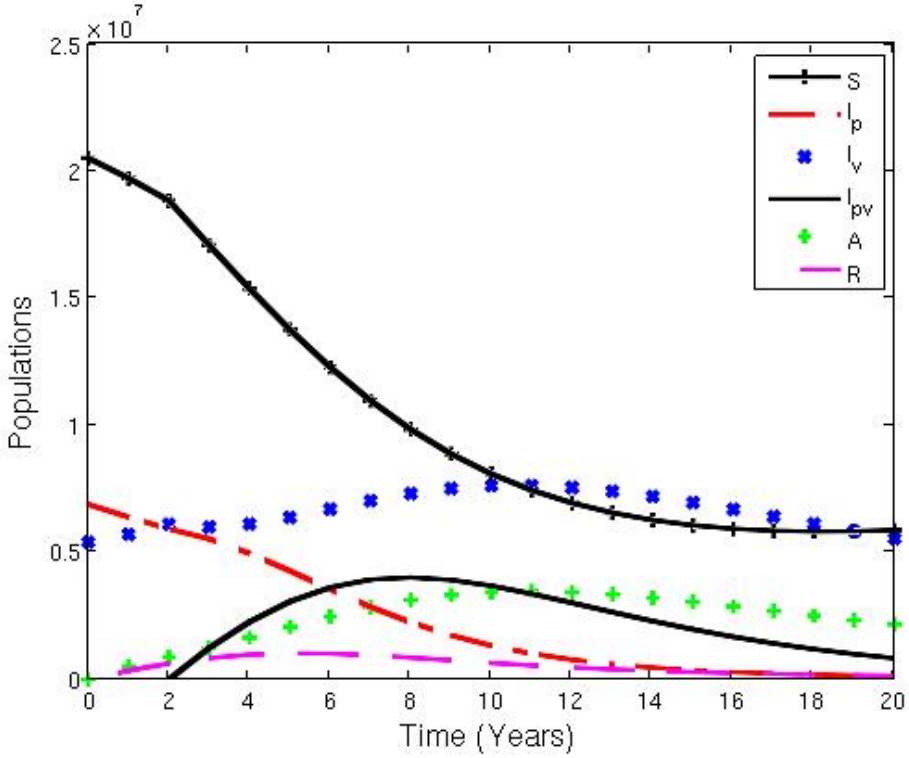

Figure 5.8: Simulation graph results shows the effects of starting by switching off HPV infection and switch on after 2 years, i.e $\beta_1 = 0$ and $\sigma_1 = 0$. Using the parameters given in figure 5.1.

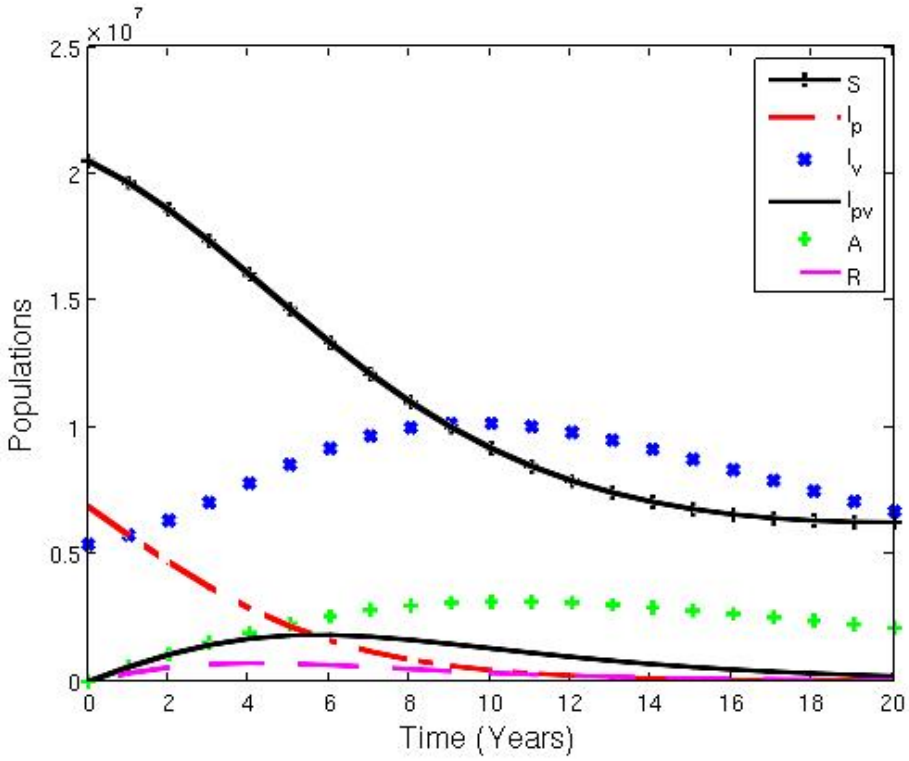

Figure 5.9: Shows the impact of HIV alone, i.e by taking $\beta_1 = 0$. Using the parameters given in figure 5.1.

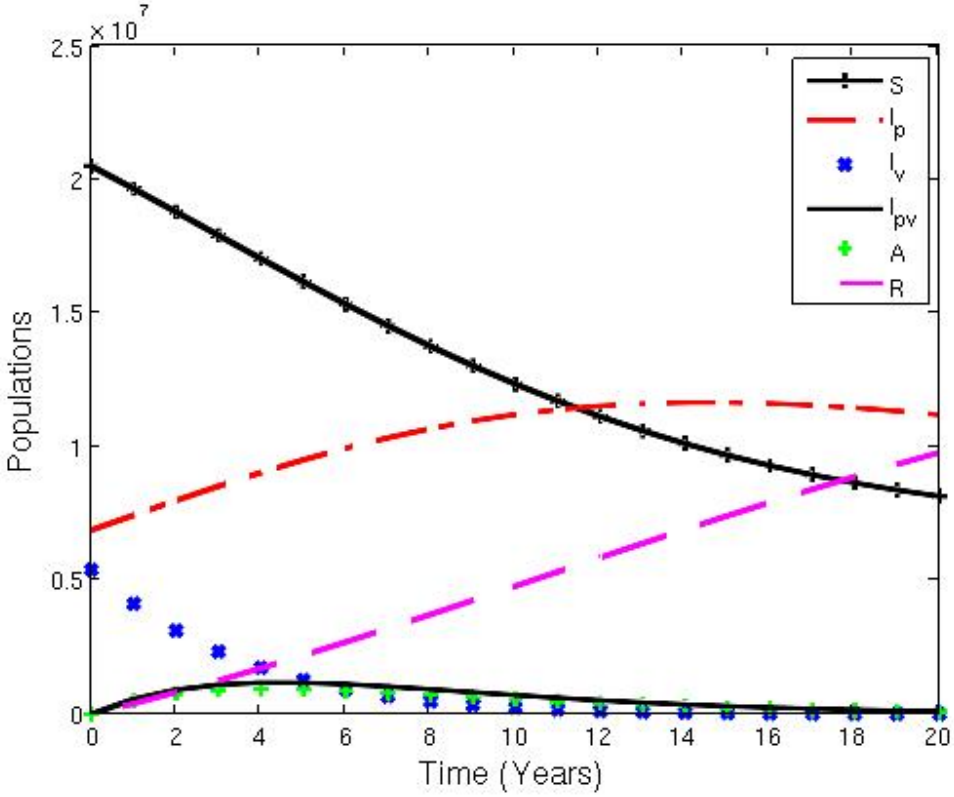

Figure 5.10: The impact of HPV alone i.e when $\beta_2 = 0$. Using the parameters given in figure 5.1.

Chapter 6

CONCLUSION AND RECOMMENDATION

6.1 Conclusion

We first reviewed the HPV model. We managed to obtain the basic reproduction number for HPV model. The model had two equilibrium points which are DFE point and endemic equilibrium point. The disease-free equilibrium point were existed and locally asymptotically stable when $R_0 < 1$. The existence of positivity endemic equilibrium point and their asymptotically stable were proved using the center manifold theory. Our results showed that when $R_0 < 1$, it is possible for HPV infection to die out from the community and when $R_0 > 1$, then HPV infection becomes endemic in the sense that it will persist into the community. We observed that the increases in the reproduction number for women (R_w), the reproduction number for men who were infected by women with low-risk HPV types (R_m^l) and the reproduction number for men who were infected by women with high-risk HPV types (R_m^h), results in the increase of basic reproduction number (R_0). The increase in the basic reproduction number will result in the persistence of HPV infection in the community.

We formulated the model for co-infection of HPV with HIV using the reviewed models of HPV as building blocks. We first analyzed the mathematical model. We obtained the basic reproduction number with two contributing components that is the reproduction number for HPV infection (R_p)

and reproduction number for HIV infection R_v. The basic reproduction number was shown to be the maximum of the reproduction number for HPV and the reproduction number due to HIV. Our basic reproduction number does not include parameters from the co-infection class. We identified the parameters which had an influence in the basic reproduction number of HIV and HPV co-infection. We showed that the increase in the probability of successful HPV transmission per sexual contact and the proportion at which susceptible individuals are infected by HPV will increase in reproduction number for HPV and if we increased rate of recovery from HPV then reproduction number for HPV decreases. If we increased the probability of successful HIV transmission per sexual contact and the contribution of AIDS individuals towards successful transmission of HIV then, the reproduction number due to HIV increases. Furthermore, the increase in the proportion of susceptible individuals infected by HPV and the increase in the death rate due to AIDS results in the decrease of the reproduction number due to HIV. When the reproduction number for HPV is greater than the reproduction number due to HIV, we observed a rise in numbers of individuals from HPV population. This suggests that these HPV infected individuals remains at high risk of being infected with HIV. The recovered individuals from HPV would be at high risk of being infected with HIV, since they become susceptible to HIV infection. We showed that the DFE point of the co-infection of HPV with HIV exist and locally asymptotically stable when $R_0 < 1$ that is when $R_p < 1$ and $R_v < 1$. We proved the positivity of endemic equilibrium point of the co-infection model using fixed point theory. The condition for stability for the endemic equilibrium point could not be expressed in terms of the basic reproduction number since the equilibrium point could not be expressed in close form. However, we managed to express the condition in terms of other parameters D_1 and D_2. The parameters D_1 and D_2 reduces to R_p and R_v at the $(0, 0)$ fixed point. This gave us an insight that D_1 and D_2 are closely related to the basic reproduction number of the model and hence one can infer that $D < 1$ may imply that $R_0 > 1$. The fixed point theory was beneficial to our model analysis

in that it ensured the existence of a unique positive fixed point corresponding to a unique endemic equilibrium point qualitatively. It is important in modelling of infectious diseases to determine the existence and uniqueness of solutions in biologically feasible regions as this ensures one of the possible trends of the infection from one basin of attraction of the system equilibrium point to another.

Our numerical analysis of HIV and HPV co-infection using the South African data produced several interesting observations. In the scenario where the recovered individuals from HPV were careful not to indulge in risky sexual activities and thus not at risk of contracting HIV, we observed the continuous increase of recovered population leading few cases of HIV, co-infected and AIDS individuals. This suggests that behavioral change from individuals without HIV infection does an impact of reducing the prevalence of HIV, co-infected and AIDS population. We observed that when both HIV and HPV infected individuals are active in the system then the co-infection population grows faster. We also observed that when one infection is active in the system then the co-infection population will be at low level.

In the scenario where the recovered individuals from HPV participates in the HIV dynamics or when they are susceptible to HIV infection, we observed high peaks in HIV population, which had an impact in the growth of co-infection population and AIDS population. The participation of recovered population in the HIV dynamics promotes the high rise the HIV population, co-infection and AIDS population compared to where the recovered individuals from HPV were not participating in risky sexual activities.

If we consider the scenario where we start by switching off HIV infection and the progression rate of HIV infection to co-infection population and introduce the HIV infection after 2 years then we

observed a higher peak in co-infection than if we introducing both infection at the same time. After introducing HIV infection, there are more individuals who are infected with HPV, and the HPV population would be at high risk of being infected with HIV. This will increase the burden for HIV infection and cause the increase in the co-infection population. If we switched off HPV infection from the community and introducing it after sometime a lower peak in co-infection was obtained compared to where both infections are introduced at the same time results. After introducing HPV infection, the HIV population slightly decreases but peaks up again.

6.2 Recommendation

Our results showed that without intervention the burden of both HIV and HPV is compounded to levels worse than when the two infection occur as single infections in the community. From the base of this study, we intend to build up this study for future work by applying the vaccination and treatment strategies. However, there are available interventions strategies such as vaccination against HPV. The vaccines reduce the burden of HPV infected population in the community and increases the number of recovered individuals [58], but will not protect the individuals from HIV infection. HPV individuals and recovered individuals from HPV can be protected from HIV infection by educating them on sticking to one partner who are HIV uninfected, abstinence from sexual activities, use of condoms and contraceptives [59]. These will reduce the burden of HIV population and reduce the number of co-infected individuals. Individuals with HIV infection need treatment which will induces the immune response such as use of antiretroviral (ART) drugs. These can significantly prolong the HIV infected population's lives and also to stay safe and healthy in HIV population class and reduce the progression rate to co-infection population and AIDS population as well as reducing the infectiousness of individuals.

Individuals with co-infection of HPV and HIV, may need to be considered for a combination of both HPV and HIV interventions simultaneously. However, due care should be taken when considering this strategy since the administration of more than one intervention (vaccine and ARV treatment) may result in one strategy rendering the other strategy useless. Some strategy suggests that multikine treatments showed eliminated a number of HPV strains in the case of co-infection treatment [60].

Our model had several limitations. We did not include any treatment and prevention measures in our co-infection of HPV with HIV model. HPV can be curable and there are prevention measures which can be used to prevent from HIV infection such as condom use. We did not include some processing as regression of recovered individuals into HPV population and also regression into susceptible population, which could bring other realistic and exciting observations and predictions on HIV/HPV co-infection. However, we believe our model managed to expose potential dangers of HIV/HPV co-infection guided by the basic assumptions on the model construction.

Appendix

A1

$$\begin{aligned}
\psi_1\psi_5 - \psi_2\psi_4 &= \sigma_1^2\tau G^{**}(1-\tau)(\mu+\alpha_2)(\mu+\xi)(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1](\alpha_2-\alpha_1) \\
&+ \mu\sigma_1^2(1-\tau)(\mu+\alpha_2)^2(\mu+\xi)(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+xi)+\rho_2\alpha_1]] \\
&+ \mu\sigma_1^2\sigma_2 G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \sigma_1^2\tau G^{**}(1-\tau)(\mu+\alpha_2)^2(\mu+\xi)(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&> 0, \text{ since } \alpha_2 > \alpha_1.
\end{aligned}$$

A2

$$\begin{aligned}
\psi_1\psi_6 - \psi_3\psi_4 &= \mu\tau\sigma_1^2 G^{**}(1-\tau)(\mu+\alpha_2)^2(\mu+\xi)(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\sigma_1 G^{**}(1-\tau)(\mu+\alpha_2)(\mu+\xi)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2][\mu\sigma_2-\sigma_1\tau(\mu+\alpha_1)] \\
&+ \mu\sigma_1\tau(1-\tau)(\mu+\alpha_2)^2(\mu+\xi)(\mu+r)(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\sigma_1\sigma_2\tau G^{**}(1-\tau)(\mu+\alpha_2)(\mu+r)(\mu+\xi)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_1^2(1-\tau)(\mu+\alpha_2)^2(\mu+\xi)(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\sigma_1(1-\tau)^2(\mu+\alpha_2)^2(\mu+\xi)(\mu+r)(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\sigma_1\sigma_2 G^{**}(1-\tau)^2(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1\tau G^{**}(1-\tau)(\mu+\alpha_2)^2(\mu+\xi)(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\sigma_1\sigma_2\tau G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&> 0, \text{ when } (\mu+\alpha_1) < 1.
\end{aligned}$$

A3

$$
\begin{aligned}
\psi_2\psi_6 - \psi_3\psi_5 &= \mu^3\sigma_1^2(1-\tau)(\mu+\alpha)^2(\mu+\xi)(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu^2\sigma_1(1-\tau)^2(\mu+r)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu^2\sigma_1\tau G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\tau G^{**}(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu(1-\tau)(\mu+r)^2(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu^2\sigma_1\sigma_2 G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_1\sigma_2\tau G^{**2}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_2\tau G^{**2}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_2 G^{**}(1-\tau)(\mu+r)^2(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1\sigma_2\tau^2 G^{**3}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_1\tau G^{**}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_1\tau(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ r\sigma_1\tau^2 G^{**2}(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\sigma_1\tau^2 G^{**2}(\mu+\xi)(\mu+\alpha_2)(\mu+\alpha_1)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ r\mu\sigma_1\tau G^{**}(\mu+\xi)^2(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\mu(\rho_1-1)+(\rho_1\alpha_1-\alpha_2)] \\
&+ r\mu^2\sigma_1\rho_2\tau G^{**}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\alpha_2-\alpha_1] \\
&+ \mu^2\sigma_1^2 G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2][\mu\sigma_2-\tau(\mu+\alpha_1)] \\
&+ r\tau G^{**2}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2][\mu\sigma_2(1-\tau)-\tau\sigma_1] \\
&> 0, \text{ when } \frac{\rho_1\alpha_1}{\alpha_2} > 1,\ \mu\sigma_2-\tau(\mu+\alpha_1) > 0 \text{ and } \mu\sigma_2(1-\tau)-\tau\sigma_1 > 0.
\end{aligned}
$$

A4

$$
\begin{aligned}
\psi_2\psi_5 - \psi_1\psi_6 &= \mu^2\sigma_1^2(1-\tau)^2(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\sigma_1(1-\tau)^2(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu^2\sigma_1^2\sigma_2 G^{**}(1-\tau)^2(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1\sigma_2 G^{**}(1-\tau)^2(\mu+r)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1^2\tau G^{**2}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1^2\tau G^{**}(\mu+\xi)(\mu+\alpha_2)(\mu+\alpha_1)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1^2\tau G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\sigma_1^2\sigma_2\tau G^{**2}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \sigma_1^2\tau^2 G^{**2}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))^2[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ (1-\tau)^2(\mu+r)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \sigma_2 G^{**}(1-\tau)^2(\mu+r)^2(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \sigma_1\tau G^{**}(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))^2[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1^2\sigma_2\tau^2 G^{**2}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1^2\tau G^{**}(1-\tau)(\mu+\xi)^2(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\mu(\rho_1-1)+(\rho_1\alpha_1-\alpha_2)] \\
&+ \mu^2\sigma_1^2\rho_2\tau G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\alpha_2-\alpha_1] \\
&+ \mu\sigma_1\sigma_2\tau G^{**}(\mu+r)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&> 0, \text{ since } \rho_1 > 1 \text{ and } \frac{\alpha_2}{\alpha_1} > 1 \text{ and when } \frac{\rho_1\alpha_1}{\alpha_2} > 1.
\end{aligned}
$$

A5

$$
\begin{aligned}
\psi_3\psi_5 - \psi_1\psi_7 &= \mu^2\sigma_1\sigma_2 G^{**}(1-\tau)^2(\mu+r)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ r\mu\sigma_1\sigma_2\tau G^{**2}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_1^2\tau G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))^2[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_1(1-\tau)^2(\mu+r)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ r\mu\sigma_1\tau G^{**}(1-\tau)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ r\mu\sigma_1\sigma_2 G^{**}(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_1^2\tau G^{**}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))^2[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ r\sigma_1\sigma_2\tau^2 G^{**3}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1^2\tau^2 G^{**2}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))^2[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ r\sigma_1\tau^2 G^{**2}(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ \mu\sigma_2 G^{**}(1-\tau)^2(\mu+r)^2(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ r\sigma_2\tau G^{**2}(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu\sigma_1\tau G^{**}(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))^2[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu(1-\tau)^2(\mu+r)^2(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ r\tau G^{**}(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&> 0.
\end{aligned}
$$

A6

$$
\begin{aligned}
\psi_3\psi_6 - \psi_2\psi_7 &= r\mu^2\sigma_1\sigma_2\tau^2 G^{**2}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^3\sigma_1^2\tau G^{**}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))^2[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ r\mu^2\sigma_1\tau G^{**}(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ r\mu\sigma_1\sigma_2\tau^2 G^{**3}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_1^2\tau^2 G^{**2}(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))^2[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_2 G^{**}(1-\tau)^2(\mu+r)^2(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ r\mu\sigma_2\tau G^{**2}(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2\sigma_1\tau G^{**}(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))^2[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ \mu^2(1-\tau)^2(\mu+r)^2(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ r\mu\tau G^{**}(1-\tau)(\mu+r)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ r\sigma_2\tau G^{**2}(\mu+r)(\tau G^{**}+\mu)(\mu+\xi)(\mu+\alpha_2)(\sigma_2 G^{**}+(\mu+\alpha_1))[\rho_1(\mu+\xi)+\rho_2\alpha_2] \\
&+ r\tau G^{**}(\mu+r)(\tau G^{**}+\mu)(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&+ r\mu\sigma_1\tau^2 G^{**2}(\mu+\xi)(\mu+\alpha_2)^2(\sigma_2 G^{**}+(\mu+\alpha_1))[(\mu+\xi)+\rho_2\alpha_1] \\
&> 0.
\end{aligned}
$$

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