MATHEMATICAL MODELS OF THE TRANSMISSION DYNAMICS OF HUMAN PAPILLOMA VIRUS INFECTION

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A dissertation
submitted to the Postgraduate School,
Federal University of Technology, Owerri

In partial Fulfilment of the Requirements for the
Award of Doctor of Philosophy (Ph.D) Degree
in Mathematics

NOVEMBER, 2019

CERTIFICATION

This is to certify that this work "**MATHEMATICAL MODELS OF THE TRANSMISSION DYNAMICS OF HUMAN PAPILLOMA VIRUS INFECTION**" was carried out by Omame Andrew (20154989778), in partial fulfilment for the award of the degree of **Doctor of Philosophy (Ph.D) in Mathematics** in the Department of Mathematics of the Federal University of Technology, Owerri.

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ACKNOWLEDGEMENTS

I would like to thank God for protecting, preserving, and guiding me through out the period of my Ph.D programme.

I would like to immensely appreciate the Vice Chancellor, Prof. Francis C. Eze and the University Management for the Study Fellowship awarded me throughout the period of my study.

I thank my supervisors, Prof. S. C. Inyama, Prof. Daniel Okuonghae and Dr. Godwin Okeke for their mentorship. I wish to sincerely appreciate them for taking out time to go through the work and for the wonderful comments each time. I enjoyed every moment I spent with them. To Dr. R. A. Umana, with whom we started the dissertation, I remain ever-grateful for all his inspiration and encouragement, in ensuring we improve on our research.

I also wish to appreciate the Dean, School of Physical Sciences, Prof C. C. Z. Akaolisa, the Head of Department of Mathematics, Prof. E. N. Erumaka, Prof. A. M. Ette and Dr (Mrs.) E. E. Onugha for their encouragement and support throughout the duration of the Ph.D programme. The immediate past Head, Department of Mathematics, Dr. C. A. Nse has been wonderful beyond words. I equally wish to acknowledge the rigorous effort of the Departmental PG Co-ordinator, Dr. M. C. Obi, who was always on ground in ensuring I presented my seminars and also making sure my work was best enough.

To all my other lecturers and colleagues in the department: Mr. D. E. Mbonu, Dr. (Mrs.) J. U. Chukwuchekwa, Mr. W. I. Osuji, Fr. Celestine Ojike, Mrs. Nneka Ukanwoke, Mr. Araka Nnamdi, Mrs. Chinwe Obi, Mrs. Precious Agigor-Mike, Mr. Ignatius Ngwongwo, Mr. Emeka Godwin, Mr. H. C. Azubuike, Ms. Ashara Precious, Mr. Nzube Ohalete and Dr. Rich U. Ndubuisi, I say a big thank you for their un-equalled support and encouragement throughout the period of my programme.

I won't fail to acknowledge all our Non-academic staff in the Department: Mrs. faith Ajuruchi, Mrs. Ebere Oduma, Ms. Rose Chioma, Mr. Chidi Udodi, Mrs. Joy Nwachukwu, Mrs Ebere Ibe-Nwoko and Mrs. Ogechukwu Anyanwu. Thank you for the encouragement throughout my PhD programme in the Department.

I owe so much gratitude to my Beloved wife, Mary and son, John for the un-equalled support and enabling environment provided for me throughout my PhD programme.

DEDICATION

This work is dedicated to my parents, Mr. Joseph and Mrs. Annah Omame (of blessed memories).

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ABSTRACT

New deterministic models that assess the impact of treatment, condom use, vaccination, vaccine-induced cross-immunity and co-infection with tuberculosis (TB) on the transmission dynamics of human papillomavirus (HPV), are designed and rigorously analyzed. The treatment model includes new compartments for infected females and males treated of HPV symptoms and allows for disease transmission by individuals treated of HPV symptoms. The two-strain model incorporates the dynamics of cross-immunity due to vaccination ($\eta_I \neq 0$, $\eta_p \neq 0$), while some of the new features of the HPV-TB co-infection model include the dynamics of homogeneous transmission of HPV ($\xi_{\mathrm{F}} \neq 0, \xi_{\mathrm{M}} \neq 0$), as well as new compartments for individuals dually infected with HPV and latent(active) TB. The models are shown to exhibit the phenomenon of backward bifurcation when the associated reproduction numbers are less than unity. Numerical simulations of the treatment model reveal that the impact of treatment on effective control of the disease is conditional and depends on the sign of a certain threshold. Furthermore, if condom compliance by males is 70%, then a female vaccine with 45% efficacy is sufficient for effective control of the HPV in a population. Analyses on the two-strain model reveal that vaccination for one strain could lead to significant decrease in the strain not included in the vaccine, while simulations of the co-infection model show that TB-only treatment strategy could significantly bring down the burden of the co-infection of both HPV and TB in a population.

Keywords: HPV, Treatment, Strains, Co-infection, Stability, Simulations.

Chapter 1

Introduction

1.1 Background information

The Human Papilloma Virus (HPV) infection is among the most common sexually transmitted infections (STIs) worldwide (Baseman and Koutsky, 2005; Foreman *et al.,* 2012). There are about 200 HPV types, which are classified into high and low risks HPV, based on their oncogenic potentials (Ault, 2007; Ahmed *et al.*, 2015). Low risk types include types -6, -11, -42, -43, and -44 while types -16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73 and -82 form the high risk HPV types (Ahmed *et al.*, 2015; Kumar *et al.*, 2007). Human Papilloma Virus types (HPV)-16 and -18 are the most common high-risk types and are responsible for the about 70% of global cervical cancer cases. Overall, HPV-16 is the most prevalent type, found in about 54% of cervical cancer cases, and HPV-18 is the second most prominent (Ault, 2007; Smith *et al.*, 2007). Other oncogenic HPV types cause the remaining cancers. Particularly, HPV-45 and -31, being the third and the fourth most prevalent types, are responsible for approximately 10% of cervical cancer cases. Generally, the four HPV types, HPV-16, -18, -45, and -31 all together account for 80% of global cervical cancer cases (Smith *et al.*, 2007; Munoz *et al.*, 2004). The global prevalence of HPV infection is around 11-12%. There is a regional variation in this prevalence around the world, with prevalence highest in Sub-Saharan Africa (24%), Eastern Europe (21%) and Latin America (16%). In Particular, high prevalence is observed in Eastern Africa and the Carribean, where rates exceed 30% (Baseman and Koutsky, 2005; Foreman *et al.,* 2012). Cancer is the major cause of death in developed countries and the second leading cause of death in developing countries (Jemal *et al.,* 2011). Approximately 80% of global cancer cases are attributed to the oncogenic Human Papilloma Virus (HPV) (Ahmed, *et al.*, 2015). Human Papilloma Virus (HPV) infection is responsible for approximately 270,000 cervical cancer deaths and roughly 97,000 cases of other deaths (e.g. anal, oropharyngeal) globally every year (Tota *et al.,* 2011; Murall *et al.,* 2014). Presently in Nigeria, estimates indicate that every year, 14,943 women are diagnosed with cervical cancer and 10,403 die from the disease (Human Papilloma Virus and Related Cancers, Nigeria summary report, Fact Sheet 2018).

HPV transmission occurs most frequently with sexual intercourse but can occur following non-penetrative sexual activity. Genital HPV infection also may be transmitted by nonsexual routes (from a woman to a newborn infant at the time of birth) (Saslow *et al.,* 2012). .Most HPV infections are asymptomatic and result in no clinical symptoms. Clinical manifestations of HPV infection include genital warts, recurrent respiratory papillomatosis, cervical cancer precursors (cervical intraepithelial neoplasia), and cancers, including cervical, anal, vaginal, vulva, penile cancer as well as cancer of the mouth or throat (Saslow *et al.,* 2012). Genital warts appear as flesh-coloured, round bumps of varying sizes. Warts do not cause any symptoms, although the warts can bleed and become painful with intercourse if they are located within the vagina (for women). HPV transmission can be reduced through the use of condom. Recent studies demonstrated a significant reduction among young women after initiation of sexual activity when their partners used condoms consistently and correctly (Winer *et al.,* 2006). Abstaining from sexual activity (i.e. refraining from any genital contact with another individual) is the surest way to prevent genital HPV infection. For those who chose to be sexually active, a monogamous relationship with an uninfected partner is the strategy most likely to prevent future genital HPV infections (Winer *et al.,* 2003). There are currently three major anti-HPV vaccines: the bivalent *Cervarix* vaccine (which targets HPV-16 and -18), the quadrivalent *Gardasil 4* vaccine (which targets the oncogenic HPV types -16 and -18 and the warts causing HPV types -6 and -11) and the recently introduced nonavalent *Gardasil 9* vaccine (which targets the high risk HPV types -16, -18, -31, -33, 45, -52, and -58 and the low risk HPV types -6 and -11) (van Damme *et al.,* 2016). The *Gardasil 4* and *Gardasil 9* vaccines are approved for both females and males while the *Cervarix* vaccine is only approved for females (Public Health Agency of Canada, 2010; Public Health Agency of Canada, 2007; World Health Organization, 2009; Alsaleh and Gumel, 2014b). There are no specific treatment for HPV infection. Medical management depends on treatment of the specific clinical manifestation of the infection (such as genital warts or abnormal cervical cell cytology) (Saslow *et al.,* 2012). The goal of treatment is to remove visible warts and decrease the risk of spreading the virus.

Tuberculosis (TB) caused by *Mycobacterium tuberculosis* (MTB), continues to remain a major cause of global mortality and morbidity, even though it is curable and preventable (Yang *et al.,* 2015; Zhu *et al.,* 2017). Tuberculosis is spread through the air when people who have active TB in their lungs cough, spit, speak, or sneeze. People with latent TB do not spread the disease. Active infection occurs more often in people with immune suppresion, due to infection with other diseases like AIDS, cancer, etc and in those who smoke. The classic symptoms of active TB are a chronic cough with blood-containing mucus, fever, night sweats, and weight loss. It was historically called "consumption" due to the weight loss. Infection of other organs can cause a wide range of symptoms. Diagnosis of active TB is based on chest X-rays, as well as microscopic examination and culture of body fluids. Diagnosis of latent TB relies on the tuberculin skin test (TST) or blood tests. Treatment requires the use of multiple antibiotics over a long period of time. Antibiotic resistance is a growing problem with increasing rates of multiple drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB). A number of factors make people more susceptible to TB infections. The most important risk factor globally is HIV; 13% of all people with TB are infected by the virus. This is a particular problem in sub-Saharan Africa, where rates of HIV are high. Of people without HIV who are infected with tuberculosis, about 5-10% develop active disease during their lifetimes;(Gibson *et al.*, 2005) in contrast, 30% of those coinfected with HIV develop the active disease (Gibson *et al.,* 2005). Tuberculosis is closely linked to both overcrowding and malnutrition, making it one of the principal diseases of poverty (Lawn and Zumla, 2011). Those at high risk thus include: people who inject illicit drugs, inhabitants and employees of locales where vulnerable people gather (e.g. prisons and homeless shelters), medically underprivileged and resource-poor communities, high-risk ethnic minorities, children in close contact with high-risk category patients, and health-care providers serving these patients (Griffit and Kerr, 1996). Tuberculosis prevention and control efforts rely primarily on the vaccination of infants and the detection and appropriate treatment of active cases (Lawn and Zumla, 2011). The World Health Organization (WHO) has achieved some success with improved treatment regimens, and a small decrease in case numbers (Lawn and Zumla, 2011). The only available vaccine as of 2011 is Bacillus Calmette-Guérin (BCG) (McShane, 2011). In children it decreases the risk of getting the infection by 20% and the risk of infection turning into active disease by nearly 60% (Roy *et al.,* 2014). It is the most widely used vaccine worldwide, with more than 90% of all children being vaccinated (Lawn and Zumla, 2011). The immunity it induces decreases after about ten years (Lawn and Zumla, 2011).

1.2 Problem Statement

Human Papilloma Virus (HPV) infection is responsible for almost all cancer cases worldwide. Presently in Nigeria, estimates indicate that every year, a good number of women are diagnosed with cervical cancer and many die from the disease. Despite the threat to life posed by Human Papilloma Virus (HPV) and its contribution in the development of cancers, no mathematical models have been formulated to assess the impact of treatment, condom use, vaccine-derived cross-immunity and co-infection with tuberculosis, on the management and control of the disease.

1.3 Objectives of Study

The general objective of this dissertation is to develop deterministic mathematical models for Human Papilloma Virus (HPV) transmission dynamics that will provide epidemiological and medical insights to current open questions (that is, to assess the impact of condom use and treatment, vaccine-derived cross-immunity and co-infection with tuberculosis, on the general transmission dynamics and control of Human papilloma Virus in a population).

The specific objectives of the study are as follows:

i. To establish the basic properties of the developed models (that is, positivity and boundedness of the solutions of the developed models).

ii. Determine the existence of the equilibrium points of the formulated models (disease-free equilibrium and endemic equilibrium points).

iii. To establish the global asymptotic stability of the equilibrium points using the Lyapunov function method.

iv. To carry out numerical simulations & global sensitivity analyses of the models, using relevant data.

v. To provide robust public health control strategies for HPV management from the qualitative & quantitative results of the formulated models.

1.4 Justification of study

Approximately 80% of global cancer cases are attributed to the oncogenic Human Papilloma Virus (HPV), and many are dying as a result of the disease. Hence, it is very appropriate to develop mathematical models that can proffer ways of eliminating or reducing the burden of the disease, as well as assessing the impact of HPV symptoms treatment, condom-use, vaccine derived cross-immunity and co-infection with tuberculosis on the control and management of HPV infections.

1.5 Scope of study

We shall use mathematical models to examine impact of treatment, condom use and vaccination on the transmission dynamics of human papilloma virus (HPV). We shall examine a case where individuals treated of HPV symptoms can still transmit infections. We shall also consider the co-infection of human papilloma virus and tuberculosis (TB) in a population where dually infected individuals can transmit either HPV or TB but not the mixed infection. In the co-infection model, we assume that transmission of HPV can occur between homosexuals. We want to examine a case where TB treatment is easily available, and clearing of HPV infection can only occur naturally.

Chapter 2

Literature Review

2.1 Conceptual Literature

Epidemiological reports have shown interactions among HPV types (Thomas et al., 2000). Liaw *et al.* (2001) pointed out that women could be susceptible to subsequent infections upon recovery from an initial infection with HPV type, although there may be a reduced risk of getting infected with the same strain (Ho *et al.,* 2002). Studies have recently pointed out that HPV vaccines offer cross-protection against strains that are related (Ault, 2007; de Villers *et al.,* 2004; Jemal *et al.,* 2011). Vaccination against one strain of HPV can confer some cross-protection against other HPV infections (Ault, 2007; de Villers *et al.,* 2004). Ho *et al* (2002) observed that vulnerability to subsequent infection with some HPV types could be reduced by antibodies against other HPV types. Moreover, Ault *et al.* (2007) observed that the bivalent *Cervarix* HPV vaccine which protects primarily against HPV types 16/18, could induce "cross-protection against incident and persistent infection with HPV types 31/45". Harari *et al.* (2016) reported "partial cross-protection by the bivalent human papillomavirus (HPV) vaccine, which targets HPV-16 and HPV-18, against HPV-31, -33, and -45 infection...". These claims were strongly supported by recent findings carried out in Scotland (Kavanagh *et al.,* 2017) and the Netherlands (Woestenberg *et al.,* 2018). There are currently three major anti-HPV vaccines: the bivalent *Cervarix* vaccine (which targets HPV-16 and -18), the quadrivalent *Gardasil* vaccine (which targets the oncogenic HPV types -16 and -18 and the warts causing HPV types -6 and -11) and the recently introduced nonavalent *Gardasil 9* vaccine (which targets the high risk HPV types -16, -18, -31, -33, 45, -52, and -58 and the low risk HPV types -6 and -11) (van Damme *et al.,* 2016). The newly developed nonavalent *Gardasil 9* HPV vaccine, though very effective, may likely be too expensive for poor and developing countries, where cervical cancer continues to remain a major cause of female mortality, and as such the poorest countries may not easily afford it (Brotherton, 2017; Clendinen *et al.,* 2016). Although the costs of the quadrivalent *Gardasil* vaccine and the bivalent *Cervarix* vaccine do not differ much, the "higher cross-protection potential of the bivalent vaccine gives it preference over the quadrivalent vaccine" (Bornstein, 2010). The cross-protection offered by the bivalent *Cervarix* vaccine proves to be effective and lasting in women (Brotherton, 2017). Kudo *et al.* (2018) confirmed this thus: "The bivalent HPV vaccine is highly effective against HPV 16 and 18. Furthermore, significant cross-protection against HPV 31, 45, and 52 was demonstrated and sustained up to 6 years after vaccination. These findings should reassure politicians about the vaccine effectiveness (VE) of bivalent HPV vaccine in a Japanese population". Therefore, the bivalent vaccine's role in the global fight against cervical cancer can not be underestimated (Brotherton, 2017).

Reports indicate that anal HPV infection is more prevalent among men who have sex with men (MSM) than heterosexual men (MSW), and that anal HPV prevalence rates could be much higher in MSM compared to MSW (Nyitray *et al.,* 2011; Goldstone *et al.,* 2011). Clinical data strongly support the claim that HPV infections are common among women who have sex with women (WSW) (Marrazzo *et al.,* 1998; Marrazzo *et al.,* 2001; Gorgos and Marrazzo, 2011). Although only a few people (about five to ten percent) infected with tuberculosis develop the active TB in their lifetime (Zhu *et al.,* 2017), estimates indicate that tuberculosis has infected more than thirty percent of the world's population, with prevalence highest in Africa and Asia (WHO, 2016). Zetola *et al.* (2015) reported most patients with cervical cancer usually record prior TB infection. Zhao *et al.* (2011) pointed out that TB infection is linked with increased vulnerability to infection with oncogenic HPV. TB and cancer usually co-exist, according to epidemiological reports, and the immune suppression caused by cancer or its treatment could bring about the reactivation of latent TB infections (Zetola *et al.,* 2015). Also, "chronic inflammation due to persistent gynecologic TB infection might be a contributing factor in the development of cervical cancer" (Zhao *et al.,* 2011; Zetola *et al.,* 2015).

2.2 Related Literature

Several mathematical models have been developed to analyze interactions among strains of different disease types (Agusto and Gumel, 2013; Alsaleh and Gumel, 2014b; Elbasha and Galvani, 2005; Elbasha *et al.,* 2008; Esteva *et al.,* 2009; Gumel, 2009; Garba and Gumel, 2010; Okuonghae *et al.,* 2015). Gumel (2008) discussed the global dynamics of two strains of avian Influenza model, incorporating the dynamics of both wild and domestic birds and the isolation of individuals with symptoms of both the avian and mutant strains. He showed that the isolation of individuals with the avian strain is more beneficial than isolating those with the mutant strain. Esteva *et al.* (2009) developed and rigorously analyzed a deterministic mathematical model for the dynamics of wild and drug resistant malaria strains. Numerical simulations of their model revealed that for high treatment rates, the resistant strain can dominate, and drive out the wild strain to extinction. In addition, they showed that, when the two strains co-exist, the proportion of individuals with the resistant strain at steady-state decreases with increasing rate of resistance development. Garba and Gumel (2010) discussed the effect of cross-immunity on the dynamics of two strains of Dengue. They assessed the effect of seasonality on the transmission dynamics of dengue, and showed that the oscillation pattern differs between the strains, depending on the degree of the cross-immunity between the strains. Garba *et al.* (2013) discussed the dynamics of two strains of Influenza, where they showed that infection acquired cross-immunity could induce the phenomenon of backward bifurcation. Okuonghae *et al* (2015) studied the dynamics of a vaccination model for two Polio strains. Their model exhibited the phenomenon of competitive exclusion.

A lot of mathematical models have been developed to understand the dynamics of co-infection of two or more diseases (Hussaini *et al.,* 2016; Sharomi *et al.,* 2008; Naresh and Tripathi, 2005; West and Thompson, 1996; Roeger *et al.,* 2009; Bhunu *et al.,* 2009; Bhunu and Mushayabasa, 2013; Okuneye *et al.,* 2017; Mtisi *et al.* 2009; Mukandavire *et al.* 2009; Mushayabasa *et al.,* 2011). Sharomi *et al.,* (2008) considered a mathematical model for the transmission dynamics of HIV/TB co-infection when there is treatment. They observed that the HIV-only treatment strategy could reduce mixed infection cases than the TB-only treatment strategy. Roeger *et al.* (2009) modelled TB and HIV co-infection. They observed that high progression rates from HIV to AIDS may increase the prevalence of HIV. Also, Naresh and Tripathi (2005) studied the dynamics of HIV and TB co-infection. They showed that if the HIV infection is minimized at an early stage through the use of drugs, the progression to AIDS stage could be significantly reduced. The dynamics of HIV/AIDS and TB in the presence of treatment was studied by Bhunu *et al.* (2009). They reported that AIDS-only treatment strategy could bring down the number of latent individuals moving to active TB stage, and that treatment of latent and active TB cases could equally reduce movement to AIDS stage by individuals infected with HIV. Mukandavire *et al.* (2009) formulated and analyzed a co-infection model for HIV and Malaria. They showed that the reduction in sexual activity of individuals with malaria symptoms decreases the number of new cases of HIV and the mixed HIV-malaria infection. Mtisi *et al.* (2009) developed and rigorously analyzed a mathematical model for the co-dynamics of tuberculosis and malaria. They simulated the model to investigate the co-existence of the two diseases when the associated reproduction numbers of the two diseases are greater than unity and equally carried out sensitivity analysis on the main parameters that drive the dynamics of the diseases. Mushayabasa *et al.* (2011) designed a mathematical model to explore the co-interaction of gonorrhea and HIV in the presence of antiretroviral therapy and gonorrhea treatment. They showed that gonorrhea only treatment strategy is highly significant in reducing the co-infection new cases. In another paper, Hussaini *et al* (2016) developed a mathematical model for the transmission dynamics of HIV and Anthroponetic Visceral Leishmaniasis (AVL) co-infection in a population. They showed that the two diseases co-exist, with AVL dominating HIV whenever the reproduction number of each disease is greater than unity. More recently, Nwankwo and Okuonghae (2018) studied the transmission dynamics of HIV Syphilis co-infection when there is treatment for Syphilis. They showed that high treatment rates for primary syphilis (in both singly and dually infected individuals) will result in a significant decrease in the incidence of co-infection of the two diseases in the population. Agusto and Adekunle (2014) developed and analyzed an optimal control model for the co-infection of HIV/AIDS and two strains of tuberculosis. They reported that the most effective control strategy in the fight against HIV/AIDS-TB co-infection is one that combines the prevention of treatment failure in drug-sensitive tuberculosis infectious individuals and the treatment of individuals with drug-resistant tuberculosis. Okuneye *et al.* (2017) developed a deterministic model for the co-infection of Chikungunya-Dengue-Zika in the presence of vaccine for Dengue. Their model incorporated the dynamics of super-infection and the effect of seasonality and local weather variability. Using data relevant to the dynamics of the diseases in Mexico, they showed that the burden of the three diseases increases with increasing mean monthly temperature in the range $[16-29]^oC$, and decreases with increasing mean montly temperature thereafter. Very recently, Bonyah *et al.* formulated and rigoroysly analyzed an optimal control model for the co-infection dengue fever and Zika virus in the presence of treament and prevention efforts. They showed, using numerical simulations that a control strategy that combines effective treatment and prevention of each disease will greatly aid the total control and eradication of the two diseases. Agusto and Gumel (2013) developed and analyzed a deterministic model for the qualitative dynamics of lowly- and highly-pathogenic avian influenza strains. They showed that the re-infection of birds infected with the lowly-pathogenic avian influenza strain induced the phenomenon of backward bifurcation. Numerical simulations of the model revealed that the two strains co-exist (with the lowly-pathogenic avian influenza strain dominating, but not driving out, the highly-pathogenic avian influenza strain to extinction). Of recent, Iboi and Gumel (2018) developed a mathematical model to assess the effect of *Dengvaxia* vaccine on the spread of dengue serotypes. They showed that the model exhibited the phenomenon of backward bifurcation caused by dengue-induced mortality in host population and imperfect vaccine protection

2.3 Specific Literature

A number of mathematical modelling studies have been carried out to understand the transmission dynamics of human papillomavirus disease. Myers *et al.* (2000) developed a nineteen stage Markov model to model a cohort of women between ages 18-85. The model did not include transmission but rather age-specific incidence of HPV. The model predicted age-specific incidence of cervical cancer and connected incidence of HPV to incidence of cervical cancer. Hughes *et al.* (2002) developed a simple ordinary differential equation (ODE) model, based on the on susceptibles, infectious, and recovered (SIR) structure, incorporating compartments for vaccinated and vaccinated-but-infected persons (capturing the possibility of reduced susceptibility and loss of immunity). The model considered three sexual activity levels and distinguished between female-to-male and male-to-female transmission. They observed that vaccinating both gender would lead to a 44% decrease in prevalence while vaccinating only females would result in a 30% decrease. In addition, Hughes et al. (2002) coupled their transmission model to an ODE model of cancer that took into account age-specific risk of disease development. The result of their model showed that reducing HPV prevalence would result in a smaller reduction in cancer incidence and that targeting core groups only would not be an appropriate vaccination strategy. Taira *et al.* (2004) developed a mathematical model for the transmission dynamics of HPV types 16 and 18 that used four sexual activity groups, nine age divisions, and age-based mixing patterns. Economic considerations were taken into account to assess cost per quality-adjusted life-year. They noted that at least 70% vaccination coverage is necessary to attain a very high decrease of cervical cancer cases. Barnabas *et al.* (2006) developed a mathematical model for HPV 16 and progression to cervical cancer. The authors reported that data about sexual activity and number of partner changes was not responsible for the seroprevalence of HPV 16 even with a theoretical maximum of 100 percent transmission rate. Brisson *et al.* (2007) developed a deterministic model of the natural history of HPV to estimate the number of persons that required vaccination and to quantify the impact of uncertainty in model parameters. They used the model to determine the cost-effectiveness of vaccination in Canada. Elbasha *et al.* (2007) developed a heterosexual transmission model for the United States incorporating age and sexual activity together with outcomes of cervical intraepithelial neoplasia, cervical cancer, and genital warts. The analysis suggested that vaccination would reduce incidence of all three outcomes, improve quality of life and survival. A cost effectiveness analysis for the United Kingdom was also carried out by Dasbach *et al.* (2008). Catch-up vaccination model was considered in Elbasha *et al.* (2009). The model in Elbasha *et al.* (2009) was expanded by Elbasha and Dasbach (2010) to include health outcomes for females and males. This study took all anogenital cancers, condylomas, and head and neck cancers into account by using crude assumptions about the natural history and incidence of these outcomes. Gunther *et al.* (2008) developed a deterministic compartmental model of HPV transmission and progression to cervical cancer including progression sub-compartments for loss of immunity, treatment, and progression to cervical cancer. The authors focused on the optimal age to vaccinate girls as a function of duration of immunity. Kim and Goldie (2008) developed a hybrid dynamic transmission model to simulate transmission of HPV 16 and 18 and a stochastic model of progression to cervical cancer. They used likelihood methods to calibrate parameters to demographic and epidemiological data in the United States. Jit *et al.* (2008) performed an economic evaluation of HPV vaccination model. Their model, a dynamic compartmental model similar to those previously discussed, also included genotypes 6 and 11, as well as condylomas having a treatment cost associated with them. Cost parameters were drawn from probability distributions by Monte Carlo Latin-hypercube sampling over a series of simulations. The study found vaccination of young girls to be likely cost effective and that the bivalent and quadrivalent vaccines were of comparable cost-effectiveness. Kulasingam and Myers (2003) developed a mathematical model to assess the potential health and economic impact of including a human papillomavirus vaccine to screening programs. They showed that HPV vaccination together with screening can be cost-effective in the fight against cancer, if the effectiveness of the vaccine is maintained, especially when the incidence of oncogenic HPV is very high. Elbasha (2006) formulated a simple, two sex, SIR compartmental model to assess the impact of vaccination on the control of HPV infection. The expressions for the basic and effective reproduction numbers were derived and the existence, uniqueness and local stability of the disease-free equilibrium and endemic equilibrium were established. However, the global asymptotic stabilities of the disease-free equilibrium or endemic equilibrium were not proved. The global stabilities of the disease-free and endemic equilibria of the model studied in Elbasha (2006) were analyzed rigorously in Elbasha (2008). Elbasha *et al.* (2008) presented a nonlinear, deterministic, age structured, mathematical model of the transmission dynamics of multi-type HPV and disease occurrence in a population classified according to gender and sexual activity. The results of the model in Elbasha *et al.* (2008) were mainly based on numerical simulations. Elbasha and Dasbach (2010) used mathematical population model to assess the public health implication of vaccinating boys and men with the quadrivalent *Gardasil* vaccine, and compared with a program of vaccinating only girls and women. They showed that the strategy that vaccinates only boys and men provides substantial public health benefits and is cost-effective than the strategy that vaccinates only girls and women. Brown and White (2011) explored the role of optimal control in obtaining the most effective vaccination programme for HPV. They showed that vaccinating sexually active susceptible individuals has more impact than vaccinating sexually non-active susceptible individuals. Al-Arydah and Smith (2011) developed a two-sex, age-structured model to describe the vaccination program for an HPV vaccine in childhood (under 13 years) and adult stages. They showed HPV infection can be brought under control if a single age group in one gender are vaccinated. Malik *et al.* (2013) formulated an HPV vaccination model to assess the public health impact of mass vaccination and Pap screening of sexually-active females. Rigorous qualitative analysis of the model reveals that it undergoes the phenomenon of backward bifurcation. It is shown that the backward bifurcation is caused by the imperfect nature of the HPV vaccine or the HPV-induced and cancer-induced mortality in females. It is shown that the disease-free equilibrium is globally-asymptotically stable if the associated reproduction number is less than unity for the case when the disease-induced and cancer-induced mortality is negligible. The model has a unique endemic equilibrium when the reproduction threshold exceeds unity. Alsaleh and Gumel (2014a) designed a two-sex vaccination model for the dynamics of human papillomavirus infection. No disease-induced death was assumed for males and no pre-cancerous or cancer stages are considered for males in the model developed in Alsaleh and Gumel (2014a). The model also incorporated exposed classes for females and males and also assumed transmission of HPV by individuals in the exposed classes. The model in Alsaleh and Gumel (2014a) was shown to undergo the phenomenon of backward bifurcation. Malik et al. (2016) carried out the analysis of the optimal control strategies of an HPV vaccination model, featuring the bivalent *Cervarix* vaccine, the quadrivalent *Gardasil 4* vaccine and the nonavalent *Gardasil 9* vaccine. They considered the situation where the three vaccines are used at the same time and compared with the situation where the bivalent *Cervarix* vaccine and the quadrivalent *Gardasil 4* vaccine were used at the initial stage, and later one or a combination of the two vaccines was replaced by the nonavalent vaccine. Shaban and Mofi (2014) modelled the impact of vaccination and screening on the dynamics of human papilloma virus infection. The model, which is not a two-sex model, incorporated the dynamics of unaware-infected and screened-infected individuals. The reproduction numbers for the vaccination and screening models were derived using the next generation operator method developed by van den Driessche and Watmough (2002). Solis and Gonzalez (2017) developed a mathematical model of the precancer lesions caused by the human papilloma virus. The model was based on a non-linear advection-diffusion-reaction partial differential equation and provided an approach for early diagnosis of human papilloma virus. Al-Arydah and Malik (2017) developed an age-structured model for the transmission dynamics of human papilloma virus, incorporating optimal control analysis. They simulated the model using data relevant to the dynamics of the disease for Toronto population and showed numerically that early and catch up female vaccine program eliminates the disease in both males and females. Lately, Sharomi and Malik (2017) considered an HPV vaccination model to study the impact of vaccine compliance on HPV infection and cervical cancer. They showed that vaccine compliance could reduce the burden of HPV infection and cervical cancer. Sensitivity and uncertainty analyses were also carried out on the model. Solis and Gonzalez (2018) discussed the properties of solutions of an HPV-infected cells model. They proved the existence, uniqueness and stability of solutions for the non-linear advection-diffusion-reaction model for human papilloma virus. Recently, Solis *et al.* (2019) developed mathematical models describing the intercations among immune system. They used the interactions to enumerate possible ways of eradicating human papilloma virus. More recently, Saldana *et al.* (2019) developed and analyzed a vaccination model for HPV with optimal control, incorporating strategies aimed at reducing the spread of the disease through vaccination of susceptibles and screening of infectives. They showed that for the effective control of HPV, vaccination should be administered both before and after the commencement of sexual activities in both females and males. However, higher vaccination rates should be applied at the onset and subsequently reduced. Elbasha and Galvani (2005) considered the effects of vaccination on the prevalence of HPV types when there are interactions among two HPV types. The model was based on the susceptible-infective-removed (SIR) compartmental structure and considered a vaccine that is imperfect. The model in Elbasha and Galvani (2005) assumes that an individual can be infected with both strains at the same time and recovery from both strains confers immunity against infection with either strain. Elbasha *et al.* (2008) considered an HPV transmission model. The analyses of the model were mainly based on numerical simulations. In addition, Alsaleh and Gumel (2014b) considered a vaccination model for the dynamics of high and low risks HPV types. The purpose for the risk structure was to account for the fact that infection with the low-risk HPV types causes genital warts only, while infection with the high-risk types causes cancers. It was shown in Alsaleh and Gumel (2014b), through numerical simulations, that if 70% of the susceptible females and 45% of the susceptible males in the sexually active population are vaccinated with the Gardasil vaccine, then the effective control of the HPV types could be attained.

The purpose of the current study is to extend some of the aforementioned studies by:

i. designing a new and comprehensive sex-structured (male and female) model for the dynamics of human papillomavirus infection, and using the model to assess the public health impact of mass vaccination of sexually-active females and males, condom use by sexually-active individuals and treatment of infected individuals on the dynamics of HPV in a population. We consider a comprehensive model with three strong interventions combined and implemented for HPV control

ii. studying a two-sex, two-strain HPV mathematical model that rigorously assesses the impact of cross-immunity due to vaccination, in a population where two strains co-exist and there is vaccination for one of the strains, which cross-protects against the strain not included in the vaccine.

iii. developing and analyzing a new two-sex, co-infection model for the transmission dynamics of Human Papilloma Virus (HPV) and Tuberculosis (TB) in a population to gain insight into the impact of the spread of each disease on the general transmission dynamics.

These, to the best of our knowledge, we have not seen done by previous researchers.

Chapter 3

Methodology

This chapter introduces some of the key mathematical theories and methodologies relevant to the dissertation.

Definition 3.1. *Consider the system:*

$$\begin{aligned} \dot{x} &= f(x), \quad x \in \mathbb{R}^n, \\ \dot{y} &= g(y), \quad y \in \mathbb{R}^n, \end{aligned} \tag{3.1}$$

where f and g are two $C^r (r \geq 1)$ ODEs defined on $\mathbb{R}^n$. The dynamics generated by the vector field f and g of (3.1) *are said to be locally C^k conjugate $(k \leq r)$ if there exists a C^k diffeomorphism h which takes the orbits of the flow generated by f, $\phi(x, t)$, to the orbits of the flow generated by g, $\psi(t, y)$ preserving orientation and parametrization by time.*

Theorem 3.1 (Hartman and Grobman (Wiggins, 1983))**.** *Consider a $C^r (r \geq 1)$ vector field f and the system*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n, \tag{3.2}$$

with domain of f an open subset of $\mathbb{R}^n$. Suppose also that (3.2) *has equilibrium solutions which are hyperbolic. Consider the associated linear ODE system*

$$\dot{\xi} = Df(\bar{x})\xi, \quad \xi \in \mathbb{R}^n. \tag{3.3}$$

Then the flow generated by (3.2) *is C^0 conjugate to the flow generated by the linearized system* (3.3) *in a neighborhood of the equilibrium point.*

The Hartman-Grobman guarantees that an orbit structure near a hyperbolic equilibrium solution is topologically-equivalent to the orbit structure given by the associated linearized dynamical system.

3.1 Next generation operator method and the basic reproduction number

The next generation operator method (van den Driessche and Watmough, 2002) is used to establish the local asymptotic stability (LAS) of the disease-free equilibrium (DFE) of a disease transmission model. Suppose the given disease transmission model, with non-negative initial conditions, can be written in terms of the following system:

$$\dot{x}_i = f(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), i = 1, ..., n, \tag{3.4}$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ and the functions satisfy Axioms (B1)-(B5) below.

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

B1 If $x \geq 0$, then $\mathcal{F}_i, \mathcal{V}_i^-, \mathcal{F}_i^+ \geq 0$ for $i = 1, ..., m$;

B2 if $x_i = 0$, then $\mathcal{V}_i^- = 0$. In particular, if $x \in X_s$ then $\mathcal{V}_i^- = 0$ for $i = 1, ..., m$;

B3 $\mathcal{F}_i = 0$ if $i > m$;

B4 if $x \in X_s$ then $\mathcal{F}_i(x) = 0$ and $\mathcal{V}_i^+ = 0$ for $i = 1, ..., m$;

B5 if $\mathcal{F}(x)$ is set to zero, then all eigenvalues of $D\mathcal{F}(x_0)$ have negative real parts

Lemma 3.2. (van den Driessche and Watmough, 2002). If $\bar{x}$ is a DFE of (3.4) and $\mathcal{F}_i(x)$ satisfy (B1)-(B5), then the derivatives $D\mathcal{F}(\bar{x})$ and $D\mathcal{V}(\bar{x})$ are partitioned as

$$D\mathcal{F}(\bar{x}) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, \quad D\mathcal{V}(\bar{x}) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix}$$

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

$$F = \frac{\partial \mathcal{F}_i}{\partial x_j}(\bar{x}), \quad V = \frac{\partial \mathcal{V}_i}{\partial x_j}(\bar{x}), \quad \textit{with} \quad 1 \leq i, j \leq m.$$

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

Theorem 3.3. *(van den Driessche and Watmough, 2002). Consider the disease transmission model given by* (3.4) *with $f(x)$ satisfying Axioms (B1)-(B5). If $\bar{x}$ is a DFE of the model, then $\bar{x}$ is locally asymptotically stable (LAS) if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ (where ρ is spectral radius), but unstable if $\mathcal{R}_0 > 1$.*

Theorem 3.4 (Wiggins (1983))**.** *Suppose all the eigenvalues of $Df(\bar{x})$have negative real parts. Then the equilibrium solution $x = \bar{x}$ of the system* (3.4) *is locally asymptotically stable, and unstable if at least one of the eigenvalues has positive real part.*

The following Theorem is used to establish the presence of the backward bifurcation phenomenon for the models considered in this dissertation.

Theorem 3.5 (Castillo-Chavez & Song (2004))**.** *Consider the following system of ordinary differential equations with a parameter ϕ*

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \text{ and } f \in C^2(\mathbb{R}^n \times \mathbb{R}), \tag{3.5}$$

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

- **A1:** *$A = D_x f(0,0) = \left(\frac{\partial f_i}{\partial x_j}(0,0)\right)$ is the linearization matrix of the system* (3.5) *around the equilibrium* 0 *with ϕ evaluated at* 0*. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;*

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

Let f_k be the kth component of f and

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

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

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

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

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

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

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

Theorem 3.6 (Descartes Rule of Signs, Wang(2004))**.** *Let $p(x) = a_0 x^{b_0} + a_1 x^{b_1} + \cdots + a_n x^{b_n}$ denote a polynomial with nonzero real coefficients a_i , where the b_i are integers satisfying $0 \leq b_0 < b_1 < b_2 < \cdots < b_n$. Then the number of positive real zeros of $p(x)$ (counted with multiplicities) is either equal to the number of variations in sign in the sequence $a_0, ..., a_n$ of the coefficients or less than that by an even whole number. The number of negative zeros of $p(x)$ (counted with multiplicities) is either equal to the number of variations in sign in the sequence of the coefficients of $p(-x)$ or less than that by an even whole number.*

3.2 Lyapunov Function Theory

Establishing the global properties of a dynamical system is generally not trivial and the direct Lyapunov method (Dushoff et al., 1998) is one of the most powerful methods. The method requires the construction of an auxiliary function with certain properties, that is a Lyapunov function.

Definition 3.2. *Consider the following system*

$$\dot{x} = f(x), \quad x \in \mathbb{R}^n \tag{3.6}$$

Let, $\bar{x}$ be an equilibrium solution of (3.6) *and let $V : U \to \mathbb{R}$ be a c^1 function defined on some neighborhood U of $\bar{x}$ such that*

i) *V is positive-definite,*

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

Any function, V, that satisfies the Conditions (*i*) and (*ii*) above is called a *Lyapunov function.*

Theorem 3.7 (La Salle's Invariance Principle (La Salle and Lefschetz, 1976))**.** *Consider the following system* (3.6)*. Let,*

$$S = \{x \in \bar{U} : \dot{V} = 0\} \tag{3.7}$$

and M be the largest invariant set of (3.6) *in S. If V is a Lyapunov function on U and $\gamma^+(x_0)$ is a bounded orbit of* (3.6) *which lies in S, then the $\omega -$ limit of set $\gamma^+(x_0)$ belongs to M; that is, $x(t, x_0) \to M$ as $t \to \infty$*

Corollary 3.1. If $V(x) \to \infty$ as $|x| \to \infty$ and $\dot{V} \leq 0$ on $\mathbb{R}^n$, then every solution of (3.6) is bounded and approaches the largest invariant set M of (3.6) in the set where $\dot{V} = 0$. In particular, if $M = \{0\}$, then the solution $x = 0$ is globally-asymptotically stable (GAS)

3.2.1 Construction of Lyapunov functions to prove the GAS of the disease free equilibrium (DFE)

Suppose that there are $n > 0$ disease compartments and $m > 0$ non-disease compartments. Then a general compartmental disease transmission model can be written as

$$\dot{x} = \mathcal{F}(x, y) - \mathcal{V}(x, y), \quad \dot{y} = g(x, y) \tag{3.8}$$

with $g = (g_1, g_2, ..., g_m)^T \in \mathbb{R}^m$, $x = (x_1, x_2, ..., x_n)^T \in \mathbb{R}^n$ and $y = (y_1, y_2, ..., y_m)^T \in \mathbb{R}^m$ represents the populations in disease compartments and non-disease compartments respectively; $\mathcal{F} = (\mathcal{F}_1, \mathcal{F}_2, ..., \mathcal{F}_n)^T$ and $\mathcal{V} = (\mathcal{V}_1, \mathcal{V}_2, ..., \mathcal{V}_n)^T$, where $\mathcal{F}_i$ represents the rate of appearance of new infections in the *ith* disease compartment, $\mathcal{V}_i$ represents the transitions in and out of the *ith* disease compartment, for example, death, recovery, etc. Following van den Driessche and Watmough (2002), define two $n \times n$ matrices

$$F = \frac{\partial \mathcal{F}_i}{\partial x_j}(\bar{x}), \quad V = \frac{\partial \mathcal{V}_i}{\partial x_j}(\bar{x}), \quad with \quad 1 \leq i, j \leq m. \tag{3.9}$$

it is assumed that $F \geq 0$ and $V \geq 0$. Set

$$f(x, y) = (F - V)x - \mathcal{F}(x, y) + \mathcal{V}(x, y) \tag{3.10}$$

Then (3.8) for the disease compartments can be written as

$$\dot{x} = (F - V)(x) - f(x, y) \tag{3.11}$$

Let $\omega^T \geq 0$ be the left eigenvector of the non-negative matrix $V^{-1}F$ corresponding to the eigenvalue $\mathcal{R}_0$. The following result provides a general method to construct a Lyapunov function to prove the GAS of DFE of the system (3.8).

Theorem 3.8 (Shuai and van den Driessche , 2013). *Let F, V and $f(x, y)$ be defined as in* (3.9) *and* (3.10)*, respectively. If $f(x, y) \geq 0$ in $\Gamma \subset \mathbb{R}_+^{n+m}, F \geq 0, V^{-1} \geq 0$ and $\mathcal{R}_0 \leq 1$, then the function $Q = \omega^T V^{-1} x$ is a Lyapunov function for model* (3.8) *on* Γ

3.2.2 Construction of Lyapunov functions to prove the GAS of the endemic equilibrium point (EEP)

The non-linear Lyapunov functions used for studying the global properties of the endemic equilibria are of the Goh-Volterra type (Goh, 1976):

$$W_1(y_1, y_2, ..., y_n) = \sum_{i=1}^{n} c_i (y_i - y_i^{**} - y_i^{**} ln \frac{y_i}{y_i^{**}}). \tag{3.12}$$

Other types of Lyapunov functions that can be used include the quadratic Lyapunov functions (Vargas-De-Leon, 2011):

$$W_2(y_1, y_2, ..., y_n) = \sum_{i=1}^{n} \frac{c_i}{2}(y_i - y_i^{**})^2, \tag{3.13}$$

and composite-Volterra type (Vargas-De-Leon, 2011):

$$W_3(y_1, y_2, ..., y_n) = c\left[\sum_{i=1}^{n}(y_i - y_i^{**}) - \sum_{i=1}^{n} ln\frac{\sum_{i=1}^{n} y_i}{\sum_{i-1}^{n} y_i^{**}}\right] \tag{3.14}$$

3.3 Runge-Kutta method

Let us consider an initial value problem

$$\frac{dy}{dt} = f(t, y(t)) \tag{3.15}$$

$y(t) = (y_1(t), y_2(t), ..., y_n(t))^T$. $f \in [a, b] \times \mathbb{R}^n \to \mathbb{R}^n$, with an initial condition

$$y(0) = y_0 \tag{3.16}$$

We are interested in a numerical approximation of the continuously differentiable solution $y(t)$ of the IVP (3.15)-(3.16) over the interval $t \in [a, b]$. To this aim, we subdivide the interval $[a, b]$ into M subintervals and select the *the mesh points* t_j.

$$t_j = a + jh, \quad j = 0, 1, ..., M, \quad h = \frac{b-a}{M} \tag{3.17}$$

The value h is called a step size. The family of explicit Runge-Kutta (RK) methods of the *mth* stage is given by (Stoer and Bulirsch, 1980)

$$y(t_{n+1}) = y_{n+1} = y_n + h\sum_{i=1}^{m} c_i k_i \tag{3.18}$$

where

$$
\begin{aligned}
k_1 &= f(t_n, y_n), \\
k_2 &= f(t_n + \alpha_2 h, y_n + h\beta_{21} k_1(t_n, y_n)), \\
k_3 &= f(t_n + \alpha_3 h, y_n + h(\beta_{31} k_1(t_n, y_n) + \beta_{32} k_2(t_n, y_n))), \\
&. \\
&. \\
&. \\
k_m &= f(t_n + \alpha_m h, y_n + h \sum_{j=1}^{m-1} \beta_{mj} k_j).
\end{aligned}
$$

To specify a particular method, we need to provide the integer m (the number of stages), and the coefficients α_i (for $i = 1, 2, ..., m$), β_{ij} (for $1 \leq j < i \leq m$), and c_i (for $i = 1, 2, ..., m$). The classical RK method or RK4 method, which corresponds to the case $m = 4$ is the one used by the MATLAB ODE solver, which numerically solves the systems of nonlinear equations in the current study. In general, the accuracy of can be improved by

i. reducing the time step h,

ii. using the method with the higher convergency order

The equations of the models are solved numerically using the the MATLAB ODE45 solver which is based on the fourth order Runge-Kutta method. The stability of the method is well established in May and Noye (1984).

3.4 Formulation of the Treatment model

3.4.1 Model assumptions

The treatment model (3.19) is based on the following assumptions:

i. incorporating the use of condom by both sexually active susceptible females and males;

ii. including compartments for females and males treated of HPV symptoms (T_f and T_m);

iii. allowing for disease transmission by individuals treated of HPV symptoms (that is, those in T_f and T_m classes);

iv. including the dynamics of HPV induced mortality for individuals in the $A_f(A_m)$, $I_f(I_m)$ and $T_f(T_m)$ classes for females(males) (only cancer induced mortality was considered in the model in Alsaleh and Gumel (2014b)).

v. including compartment for males with persistent HPV infection and allowing for disease transmission by males with persistent HPV infection (only females with persistent HPV infection were considered in Alsaleh and Gumel, 2014a)

vi. Including the dynamics of HPV induced death for individuals in the $A_f(A_m), I_f(I_m), P_f(P_m)$ and $T_f(T_m)$ classes for females (males) (only cancer induced mortality was assumed in the model in Alsaleh and Gumel, 2014a).

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

Variable	**Interpretation**
$S_f(S_m)$	Population of susceptible females(males)
$V_f(V_m)$	Population of females (males vaccinated against HPV)
$N_f(N_m)$	total female (male) population
$A_f(A_m)$	Population of asymptomatic females (males)
$I_f(I_m)$	Infectious females (males) showing HPV symptoms
$P_f(P_m)$	Population of females (males) with persistent HPV infection
$R_f(R_m)$	Population of infectious females (males) who have cleared (or recovered naturally) from HPV
$T_f(T_m)$	Infectious females (males) treated of HPV symptoms
$C_f^a(C_m^a)$	Population of females (males) with infected with anal cancer
C_f^c	Population of females infected with cervical cancer
$R_f^a(R_m^a)$	Population of females (males) who have recovered from anal cancer
R_f^c	Population of females who have recovered from cervical cancer
Parameter	**Interpretation**
$f(m)$	Proportion of vaccinated females (males)
$\Lambda_f(\Lambda_m)$	Rate of recruitment for females (males)
$\mu_f(\mu_m)$	Natural mortality rate for females (males)
$\pi_f(\pi_m)$	Vaccine efficacy for females (males)
$\gamma_f(\gamma_m)$	Rate of progression to symptomatic stage for females (males)
$\tau_f(\tau_m)$	Treatment rate for symptomatic females (males)
$\phi_f(\phi_m)$	Transition rate out of $I_f(I_m)$ class for females (males)
$\psi_f(\psi_m)$	Proportion of symptomatic females (males who recover naturally from HPV)
$\kappa_f(\kappa_m)$	Modification parameter that accounts for reduced susceptibility of recovered females (males) relative to susceptible females (males)
$\varepsilon_f(\varepsilon_m)$	Treatment failure rate for females (males)
$\eta_f(\eta_m)$	Fraction of re-infected females (males) who progress to symptomatic stage
$\alpha_f(\alpha_m)$	Transition rate out of $P_f(P_m)$ class for females (males)
$\alpha_f(1-\varphi_f)$	Rate at which females with persistent HPV infection recover naturally from HPV
$\alpha_m(1-\varphi_m)$	Rate at which males with persistent HPV infection recover naturally from HPV
$\alpha_f\varphi_f(1-\omega_f)$	Rate at which females with persistent HPV infection develop cervical cancer
$\delta_f^a(\delta_m^a)$	Anal cancer-induced death rate for females (males)
$\kappa_f^a(\kappa_m^a)$	Rate of recovery from anal cancer for females (males)
κ_f^c	Rate of recovery from cervical cancer for females
$\sigma_f(\sigma_m)$	Modification parameter that accounts for reduced HPV-induced death rate for females (males) treated of HPV symptoms relative to those in the $I_f(I_m)$ class
$\beta_f(\beta_m)$	Effective contact rate for females (males)
$c_f(c_m)$	Condom compliance for females (males)
$\epsilon_f(\epsilon_m)$	Condom efficacy for females (males)
$\theta_{f1}(\theta_{m1})$	Modification parameter that accounts for the infectiousness of individuals in the $A_f(A_m)$ and $T_f(T_m)$ classes relative to those in $I_f(I_m)$ class for females (males)
$\xi_f(\xi_m)$	Modification parameter that accounts for reduced infectiousness of females (males) treated of HPV relative to those in the $A_f(A_m)$ class for females (males)
$\theta_{f2}(\theta_{m2})$	Modification parameter that accounts for the infectiousness of females (males) with persistent HPV infection

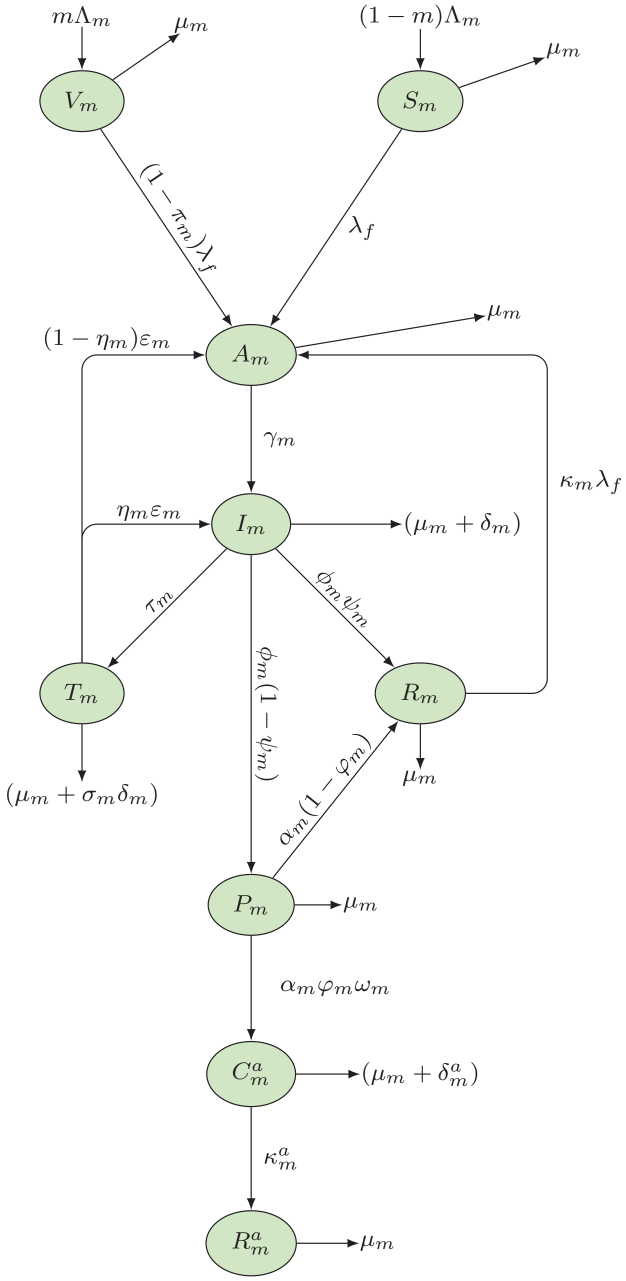


Figure 3.1: Schematic diagram of the male components of the model (3.19)

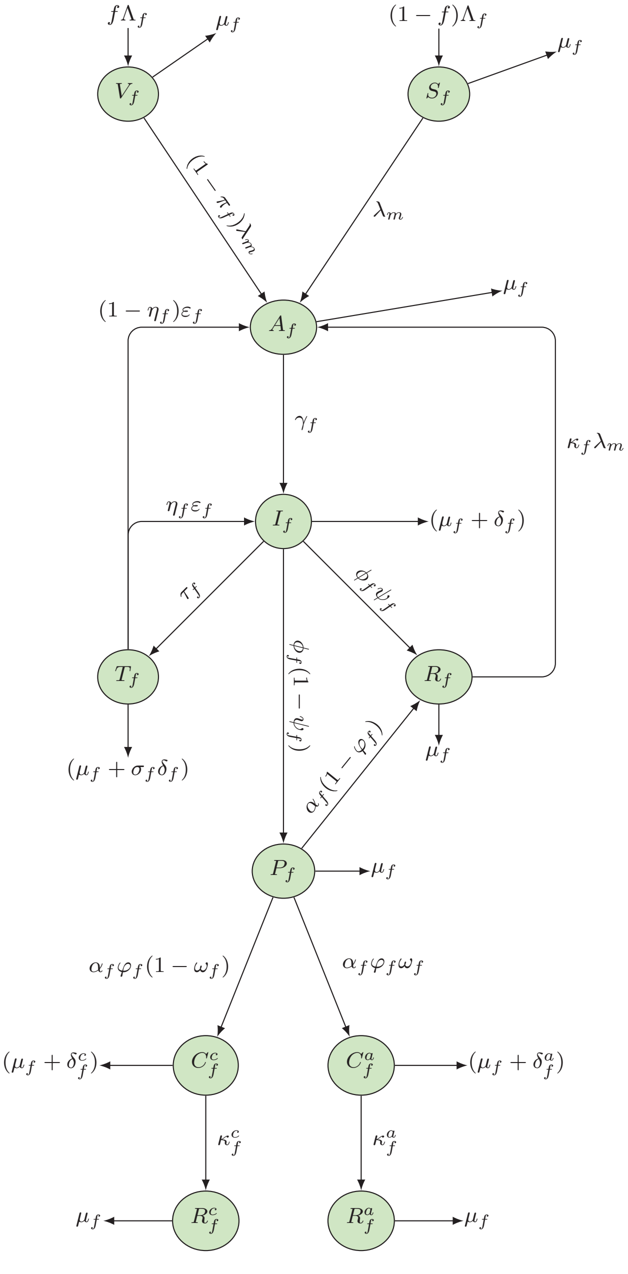


Figure 3.2: Schematic diagram of the female components of the model (3.19)

Combining all these definitions and assumptions, we have that the model for the transmission of HPV in a sexually-active population is given by the following system of differential equations (Table 3.1 describes the associated state variables and parameters in the model (3.19) while Figure 1 gives a flow diagram of the model (3.19)):

$$
\begin{aligned}
\frac{dS_f}{dt} &= (1-f)\Lambda_f - (\lambda_m + \mu_f)S_f,\\
\frac{dV_f}{dt} &= f\Lambda_f - [(1-\pi_f)\lambda_m + \mu_f]V_f,\\
\frac{dA_f}{dt} &= \lambda_m S_f + (1-\pi_f)\lambda_m V_f + \kappa_f\lambda_m R_f + (1-\eta_f)\varepsilon_f T_f - (\gamma_f + \mu_f)A_f,\\
\frac{dI_f}{dt} &= \gamma_f A_f + \eta_f\varepsilon_f T_f - (\phi_f + \tau_f + \delta_f + \mu_f)I_f,\\
\frac{dP_f}{dt} &= \phi_f(1-\psi_f)I_f - (\alpha_f + \mu_f)P_f,\\
\frac{dR_f}{dt} &= \phi_f\psi_f I_f + \alpha_f(1-\varphi_f)P_f - (\mu_f + \kappa_f\lambda_m)R_f,\\
\frac{dT_f}{dt} &= \tau_f I_f - (\sigma_f\delta_f + \varepsilon_f + \mu_f)T_f,\\
\frac{dC_f^a}{dt} &= \alpha_f\varphi_f\omega_f P_f - (\kappa_f^a + \mu_f + \delta_f^a)C_f^a,\\
\frac{dC_f^c}{dt} &= \alpha_f\varphi_f(1-\omega_f)P_f - (\kappa_f^c + \mu_f + \delta_f^c)C_f^c,\\
\frac{dR_f^a}{dt} &= \kappa_f^a C_f^a - \mu_f R_f^a,\\
\frac{dR_f^c}{dt} &= \kappa_f^c C_f^c - \mu_f R_f^c,\\
\frac{dS_m}{dt} &= (1-m)\Lambda_m - (\lambda_f + \mu_m)S_m,\\
\frac{dV_m}{dt} &= m\Lambda_m - [(1-\pi_m)\lambda_f + \mu_m]V_f,\\
\frac{dA_m}{dt} &= \lambda_f S_m + (1-\pi_m)\lambda_f V_f + \kappa_m\lambda_f R_m + (1-\eta_m)\varepsilon_m T_m - (\gamma_m + \mu_m)A_m,\\
\frac{dI_m}{dt} &= \gamma_m A_m + \eta_m\varepsilon_m T_m - (\phi_m + \tau_m + \delta_m + \mu_m)I_m,\\
\frac{dP_m}{dt} &= \phi_m(1-\psi_m)I_m - (\alpha_m + \mu_m)P_m,\\
\frac{dR_m}{dt} &= \phi_m\psi_m I_m + \alpha_m(1-\varphi_m)P_m - (\mu_m + \kappa_m\lambda_f)R_m,\\
\frac{dT_m}{dt} &= \tau_m I_m - (\sigma_m\delta_m + \varepsilon_m + \mu_m)T_m,\\
\frac{dC_m^a}{dt} &= \alpha_m\varphi_m P_m - (\kappa_m^a + \mu_m + \delta_m^a)C_m^a,\\
\frac{dR_m^a}{dt} &= \kappa_m^a C_m^a - \mu_m R_m^a
\end{aligned}
\tag{3.19}
$$

3.4.2 Description of model equations

The total sexually-active population at time t, denoted by $N(t)$, is divided into two classes, namely, the total female population ($N_f(t)$) and the total male population ($N_m(t)$), respectively. The total female population is further subdivided into 11 mutually exclusive compartments: susceptible females ($S_f(t)$), females vaccinated against HPV ($V_f(t)$), infectious females showing no symptoms of HPV ($A_f(t)$), infectious females showing symptoms of HPV ($I_f(t)$), infectious females with persistent HPV infection ($P_f(t)$), infectious females who have cleared (or recovered naturally) from HPV ($R_f(t)$), infectious females treated of HPV symptoms ($T_f(t)$), females infected with anal cancer ($C_f^a(t)$), females infected with cervical cancer ($C_f^c(t)$), females who have recovered from anal cancer ($R_f^a(t)$) and females who have recovered from cervical cancer ($R_f^c(t)$). Similarly, the total male population is subdivided into: susceptible males ($S_m(t)$), males vaccinated against HPV ($V_m(t)$), infectious males showing no symptoms of HPV ($A_m(t)$), infectious males showing symptoms of HPV ($I_m(t)$), infectious males with persistent HPV infection ($P_m(t)$), infectious males who have cleared (or recovered naturally from) HPV ($R_m(t)$), infectious males treated of HPV symptoms ($T_m(t)$), males infected with anal cancer ($C_m^a(t)$) and males who have recovered from anal cancer ($R_m^a(t)$). Thus

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

$$N_f(t) = S_f(t) + V_f(t) + A_f(t) + I_f(t) + P_f(t) + R_f(t) + T_f(t) + C_f^a(t) + C_f^c(t) + R_f^a(t) + R_f^c(t)$$

$$N_m(t) = S_m(t) + V_m(t) + A_m(t) + I_m(t) + P_m(t) + R_m(t) + T_m(t) + C_m^a(t) + R_f^a(t)$$

The population of unvaccinated susceptible females (S_f) is increased by the recruitment of new sexually-active females at a rate $(1 - f)\Lambda_f$ (where f ($0 < f \leq 1$) is the fraction of vaccinated females and λ_f is the recruitment rate for sexually active females). Susceptible females acquire HPV infection following effective contacts with infected males (i.e. those in the A_m, I_m and T_m classes) at a rate λ_m, given by

$$\lambda_m(t) = \frac{\beta_m(1 - c_m\epsilon_m)(I_m + \theta_{m1}A_m + \theta_{m2}P_m + \xi_m\theta_{m1}T_m)}{N_m} \tag{3.20}$$

In (3.20), β_m is the effective contact rate for male-to-female transmission of HPV. It is the product of c_1^f and β_1^m (that is, $\beta_m = c_1^f\beta_1^m$), where β_1^m is the probability of transmitting HPV from male-to-female and c_1^f is the rate at which females acquire new sexual partners. c_m and ϵ_m are the parameters accounting for condom compliance rate and condom efficacy for males respectively. θ_{m1} and θ_{m2} (with $0 \leq \theta_{m1}, \theta_{m2} < 1$) are the modification parameters accounting for the relative infectiousness of asymptomatic males and males with persistent HPV infection compared to symptomatic males. Furthermore, ξ_m is the additional modification parameter accounting for the relative infectiousness of treated males compared to asymptomatic males (it is assumed that treated males can still transmit infection). This population is decreased by natural death at a rate μ_f(natural mortality occurs in all the female compartments at the rate μ_f). Thus,

$$\frac{dS_f}{dt} = (1-f)\Lambda_f - (\lambda_m + \mu_f)S_f,$$

The population of new sexually active susceptible females vaccinated with the quadrivalent *Gardasil* vaccine (V_f) is generated by the vaccination of a fraction, f, of unvaccinated susceptible females with the *Gardasil* vaccine (at the rate $f\Lambda_f$). It is decreased by HPV infection, following effective contacts with males infected with HPV (i.e., those in the A_m, I_m, P_m and T_m classes) at a reduced rate $(1-\pi_f)\lambda_m$, where $0 < \pi_f \leq 1$ represents the efficacy of *Gardasil* vaccine against infection with HPV-16 and -18. This population is decreased by natural death. Thus,

$$\frac{dV_f}{dt} = f\Lambda_f - [(1-\pi_f)\lambda_m + \mu_f]V_f,$$

The population of asymptomatic females with HPV infection (A_f) is generated by the infection of unvaccinated and vaccinated susceptible females with HPV (at the rates λ_m and $(1-\pi_f)\lambda_m$ respectively). This population is increased by the re-infection of recovered females with HPV (at a rate $\kappa_f\lambda_m$, where $0 \leq \kappa_f < 1$ accounts for the assumption that the re-infection of recovered females occur at a rate lower than the rate for primary infection of susceptible females). This population is further increased at the rate $(1-\eta_f)\varepsilon_f$ where $0 < \eta_f \leq 1$ is the fraction of females who fail treatment and develop symptoms. The population is reduced following progression to symptomatic stage at a rate γ_f and natural death. Thus,

$$\frac{dA_f}{dt} = \lambda_m S_f + (1-\pi_f)\lambda_m V_f + \kappa_f\lambda_m R_f + (1-\eta_f)\varepsilon_f T_f - (\gamma_f + \mu_f)A_f,$$

The population of symptomatic females infected with HPV (I_f) is generated by the progression of asymptomatic females infected with HPV at the rate γ_f. The population is further reduced at the rate $\eta_f\varepsilon_f$. The population is decreased by recovery (at a rate ϕ_f), treatment (at a rate τ_f), disease induced death (at a rate δ_f) and natural death. Thus,

$$\frac{dI_f}{dt} = \gamma_f A_f + \eta_f\varepsilon_f T_f - (\phi_f + \tau_f + \delta_f + \mu_f)I_f,$$

The population of females with persistent HPV infection (P_f) is generated by the development of persistent infection by symptomatic females (at a rate $\phi_f(1-\psi_f)$), where $0 < \psi_f \leq 1$ is the fraction of symptomatic females who recovered naturally from HPV infection. This population is decreased through development of anal cancer(at a rate $\alpha_f\varphi_f\omega_f$), cervical cancer (at a rate $\alpha_f\varphi_f(1-\omega_f)$) or recovery (at a rate $\alpha_f(1-\varphi_f)$) and natural death. Thus,

$$\frac{dP_f}{dt} = \phi_f(1-\psi_f)I_f - (\alpha_f + \mu_f)P_f,$$

The population of females who recovered from HPV infection (R_f) is generated by the recovery of symptomatic females(at a rate $\phi_f\psi_f$) and females with persistent HPV infection (at a rate $\alpha_f(1-\varphi_f)$). This population is decreased following re-infection at a rate $\kappa_f\lambda_f$. The population is further decreased by natural death. Thus,

$$\frac{dR_f}{dt} = \phi_f\psi_f I_f + \alpha_f(1-\varphi_f)P_f - (\mu_f + \kappa_f\lambda_m)R_f,$$

The population of females treated of HPV symptoms is generated at the rate τ_f. This population is decreased by treatment failure (at a rate ε_f), disease induced death (at a reduced rate $\sigma_f\delta_f$, where $0 < \sigma_f \leq 1$ is a modification parameter accounting for the assumption that females treated of HPV symptoms suffer disease induced death at a rate lower than that of symptomatic females infected with HPV) and natural death. Thus,

$$\frac{dT_f}{dt} = \tau_f I_f - (\sigma_f\delta_f + \varepsilon_f + \mu_f)T_f,$$

The population of females with anal cancer (C_f^a) is generated by the development of anal cancer by females with persistent HPV infection at the rate $\alpha_f\varphi_f\omega_f$. This population is decreased due to recovery (at a rate κ_f^a), anal cancer induced death (at a rate δ_f^a) and natural death. Thus,

$$\frac{dC_f^a}{dt} = \alpha_f \varphi_f \omega_f P_f - (\kappa_f^a + \mu_f + \delta_f^a) C_f^a,$$

The population of females with cervical cancer (C_f^c) is generated by the development of cervical cancer by females with persistent HPV infection at the rate $\alpha_f \varphi_f (1 - \omega_f)$. This population is decreased due to recovery (at a rate κ_f^c), cervical cancer induced death (at a rate δ_f^c) and natural death. Thus,

$$\frac{dC_f^c}{dt} = \alpha_f \varphi_f (1 - \omega_f) P_f - (\kappa_f^c + \mu_f + \delta_f^c) C_f^c,$$

The population of females who recovered from anal cancer (R_f^a) is generated at the rate κ_f^a and decreases by natural death. Thus,

$$\frac{dR_f^a}{dt} = \kappa_f^a C_f^a - \mu_f R_f^a,$$

The population of females who recovered from cervical cancer (R_f^c) is generated at the rate κ_f^c and decreases by natural death. Thus,

$$\frac{dR_f^c}{dt} = \kappa_f^c C_f^c - \mu_f R_f^c,$$

The population of unvaccinated susceptible males (S_m) is increased by the recruitment of new sexually-active males at a rate $(1 - m)\Lambda_m$ (where m $(0 < m \leq 1)$ is the fraction of vaccinated males and Λ_m is the recruitment rate for sexually active males). Susceptible males acquire HPV infection following effective contacts with infected females (i.e. those in the A_f, I_f and T_f classes) at a rate λ_f, given by

$$\lambda_f(t) = \frac{\beta_f (1 - c_f \epsilon_f)(I_f + \theta_{f1} A_f + \theta_{f2} P_f + \xi_f \theta_{f1} T_f)}{N_f} \tag{3.21}$$

In (3.21), β_f is the effective contact rate for female-to-male transmission of HPV. It is the product of c_1^m and β_1^f (that is, $\beta_f = c_1^m \beta_1^f$), where β_1^f is the probability of transmitting HPV from female-to-male and c_1^m is the rate at which males acquire new sexual partners. c_f and ϵ_f are the parameters accounting for condom compliance rate and condom efficacy for females respectively. θ_{f1} and θ_{f2} (with $0 \leq \theta_{f1}, \theta_{f2} < 1$) are the modification parameters accounting for the relative infectiousness of asymptomatic females and females with persistent HPV infection compared to symptomatic females. Furthermore, ξ_f is the additional modification parameter accounting for the relative infectiousness of treated females compared to asymptomatic females (it is assumed that treated females can still transmit infection). This population is decreased by natural death at a rate μ_m(natural mortality occurs in all the male compartments at the rate μ_m). Thus,

$$\frac{dS_m}{dt} = (1-m)\Lambda_m - (\lambda_f + \mu_m)S_m,$$

The population of new sexually active susceptible males vaccinated with the quadrivalent *Gardasil* vaccine (V_m) is generated by the vaccination of a fraction, m, of unvaccinated susceptible males with the *Gardasil* vaccine (at the rate $f\Lambda_m$). It is decreased by HPV infection, following effective contacts with females infected with HPV (i.e., those in the A_f, I_f, P_f and T_f classes) at a reduced rate $(1-\pi_f)\lambda_f$, where $0 < \pi_m \leq 1$ represents the efficacy of *Gardasil* vaccine against infection with HPV-16 and -18. This population is decreased by natural death. Thus,

$$\frac{dV_m}{dt} = m\Lambda_f - [(1-\pi_m)\lambda_f + \mu_m]V_m,$$

The population of asymptomatic males with HPV infection (A_m) is generated by the infection of unvaccinated and vaccinated susceptible males with HPV (at the rates λ_f and $(1-\pi_m)\lambda_f$ respectively). This population is increased by the re-infection of recovered males with HPV (at a rate $\kappa_m\lambda_f$, where $0 \leq \kappa_m < 1$ accounts for the assumption that the re-infection of recovered males occur at a rate lower than the rate for primary infection of susceptible males). This population is further increased at the rate $(1-\eta_m)\varepsilon_m$ where $0 < \eta_m \leq 1$ is the fraction of males who fail treatment and develop symptoms. The population is reduced following progression to symptomatic stage at a rate γ_m and natural death. Thus,

$$\frac{dA_m}{dt} = \lambda_f S_m + (1-\pi_m)\lambda_f V_m + \kappa_m\lambda_f R_m + (1-\eta_m)\varepsilon_m T_m - (\gamma_m + \mu_m)A_m,$$

The population of symptomatic males infected with HPV (I_m) is generated by the progression of asymptomatic males infected with HPV at the rate γ_m. The population is further at the rate $\eta_m\varepsilon_m$. The population is decreased by recovery (at a rate ϕ_m), treatment (at a rate τ_m), disease induced death (at a rate δ_m) and natural death. Thus,

$$\frac{dI_m}{dt} = \gamma_m A_m + \eta_m \varepsilon_m T_m - (\phi_m + \tau_m + \delta_m + \mu_m) I_m,$$

The population of males with persistent HPV infection (P_m) is generated by the development of persistent infection by symptomatic males (at a rate $\phi_m(1 - \psi_m)$), where $0 < \psi_m \leq 1$ is the fraction of symptomatic males who recovered naturally from HPV infection. This population is decreased either through development of anal cancer (at a rate $\alpha_m \varphi_m \omega_m$) or recovery (at a rate $\alpha_m(1 - \varphi_m)$) and natural death. Thus,

$$\frac{dP_m}{dt} = \phi_m(1 - \psi_m) I_m - (\alpha_m + \mu_m) P_m,$$

The population of males who recovered from HPV infection (R_m) is generated at the rates by the recovery of symptomatic males (at a rate $\phi_m \psi_m$) and males with persistent HPV infection (at a rate $\alpha_m(1 - \varphi_m)$). This population is decreased following the acquisition of re-infection at the rate $\kappa_m \lambda_m$. The population is further decreased by natural death. Thus,

$$\frac{dR_m}{dt} = \phi_m \psi_m I_m + \alpha_m(1 - \varphi_m) P_m - (\mu_m + \kappa_m \lambda_m) R_m,$$

The population of males treated of HPV symptoms is generated at the rate τ_m. This population is decreased by treatment failure (at a rate ε_m), disease induced death (at a reduced rate $\sigma_m \delta_m$, where $0 < \sigma_m \leq 1$ is a modification parameter accounting for the assumption that males treated of HPV symptoms suffer disease induced death at a rate lower than that of symptomatic males infected with HPV) and natural death. Thus,

$$\frac{dT_m}{dt} = \tau_m I_m - (\sigma_m \delta_m + \varepsilon_m + \mu_m) T_m,$$

The population of males with anal cancer (C_m^a) is generated by the development of anal cancer by males with persistent HPV infection at the rate $\alpha_m \varphi_m$. This population is decreased due to recovery (at a rate κ_m^a), anal cancer induced death (at a rate δ_m^a) and natural death. Thus,

$$\frac{dC_m^a}{dt} = \alpha_m \varphi_m P_m - (\kappa_m^a + \mu_m + \delta_m^a) C_m^a,$$

The population of males who recovered from anal cancer (R_m^a) is generated at the rate κ_m^a and decreases by natural death. Thus,

$$\frac{dR_m^a}{dt} = \kappa_m^a C_m^a - \mu_m R_m^a,$$

The model will be studied subject to the group contact constraint given by

$$c_1^m N_m = c_1^f N_f, \tag{3.22}$$

a consistency condition which states that in any small interval of time $[t, t+\Delta t]$, the total number of partnerships formed by females with males must equal total number of partnerships formed by males with females. It is assumed that male sexual partners are abundant, so that females can always have enough number of sexual contacts per unit time. Hence, it is assumed that c_1^f is constant and the rate c_1^m is calculated from the relation $c_1^m = \frac{c_1^f N_f(t)}{N_m(t)}$ (Castillo-Chavez (1989), Castillo-Chavez *et al.* (1989), Castillo-Chavez *et al.* (1997), Dushoff *et al.* (1998), Lajmanovich and Yorke (1976), Nold (1980), Hethcote *et al.* (1982) for discussions on multi-group models).

3.5 Formulation of the Two-strain HPV model

3.5.1 Model assumptions

The two-strain HPV model is based on the following assumptions:

i. incorporating the dynamics of cross-immunity due to vaccination ($\eta_I \neq 0$, $\eta_p \neq 0$) (Ault, 2007). This was not captured in the model in Alsaleh and Gumel (2014b).

ii. allowing for heterogeneity in infectiousness of vaccinated and unvaccinated infected individuals (Bonanni et al., 2009). This feature was not included in the models in Elbasha and Galvani (2005) and Alsaleh and Gumel (2014b).

iii. including compartments for females (males) who recover from one strain and are infected with the other strain, $I_{fij}(I_{mij}), \quad i \neq j$, for females (males), and allowing for disease transmission by individuals who recover from one strain and are infected with the other strain (clinical studies have shown that subsequent infections with other strains are possible after an initial infection with HPV (Ho *et al.*, 2002). This was not incorporated in the model in the risk-structured model in (Alsaleh and Gumel 2014b).

Table 3.2: Description of variables in the model (3.23).

Variable	**Description**
$S_f(S_m)$	Population of susceptible females (males)
V_f	Population of females vaccinated against strain 1
$I_{f\,i}(I_{m\,i}),\ _{i=1,2}$	Population of females (males) infected with strain i
$P_{f\,i,\ i=1,2}$	Population of females with persistent strain i infection
C_f	Population of females with cervical cancer
$R_{f\,i}(R_{m\,i})\ _{i=1,2}$	Population of females (males) who have recovered naturally from strain i
I^p_{f2}	Population of vaccinated females who get infected with strain 2
R^c_f	Population of females who have recovered from cervical cancer
$I_{f\,i\,j}(I_{m\,i\,j})_{i,j=1,2;\,i\neq j}$	Population of females (males) who have recovered from strain i and are infected with strain j
$M_f(M_m)$	Population of females (males) who have recovered from both strains
$N_f(N_m)$	Total female (male) population

Since the model (3.23) monitors human population, it is assumed that all variables and parameters are non-negative.

Table 3.3: Description of parameters in the model (3.23).

Parameter	**Description**
$\Lambda_f(\Lambda_m)$	Recruitment rate for females (males)
f	Proportion of susceptible females vaccinated against strain 1
$\mu_f(\mu_m)$	Natural death rate for females (males)
ξ	Bivalent vaccine efficacy for females
η_I	Modification parameter for cross protection of vaccinated females against incident infection with strain 2
η_p	Modification parameter for cross protection of vaccinated females against persistent infection with strain 2
η_c	Modification parameter for reduced rate of progression to cancer by females with persistent strain 2 infection relative to those with persistent strain 1 infection
$\tau_{f\,i}(\tau_{m\,i})_{,\,i=1,2}$	Recovery rate of females (males) infected with strain i
$\delta_{f\,i}(\delta_{m\,i})_{,\,i=1,2}$	Disease induced death rate for females (males) infected with strain i
$\delta_{f\,i\,j}(\delta_{m\,i\,j})_{\,i,j=1,2;i\neq j}$	HPV induced death rate for females (males) who have recovered from strain i and infected with strain j
δ_{fc}	Cervical cancer induced death rate for females
δ_{f2}^{p}	Disease induced death rate for females in I_{f2}^{p} class
$\varepsilon_i\,,\alpha_i$	Modification parameters for reduced susceptibility of individuals who have recovered naturally from either one or both strains relative to those in the susceptible class
$\tau_{f\,i\,j}(\tau_{m\,i\,j})$	Recovery rate for females (males) who have recovered from strain i and are infected with strain j
$p_i,\ p_{i\,j}$	Proportion of females who recover naturally from HPV and do not progress to persistent HPV infection
q_i	Proportion of females who recover from persistent strain i infection and do not progress to cervical cancer
$\theta_{p\,i,\ i=1,2}$	Modification parameter for the infectiousness of females with persistent strain i infection relative to those in $I_{f1},\ I_{f2},\ I_{f21},\ I_{f12}$ classes
ϕ_p	Modification parameter for the infectiousness of females in I_{f2}^{p} class relative to those in I_{f2} class
π_f	Rate of recovery from cancer for females
κ_{f2}	Transition rate out of P_{f2} class for females

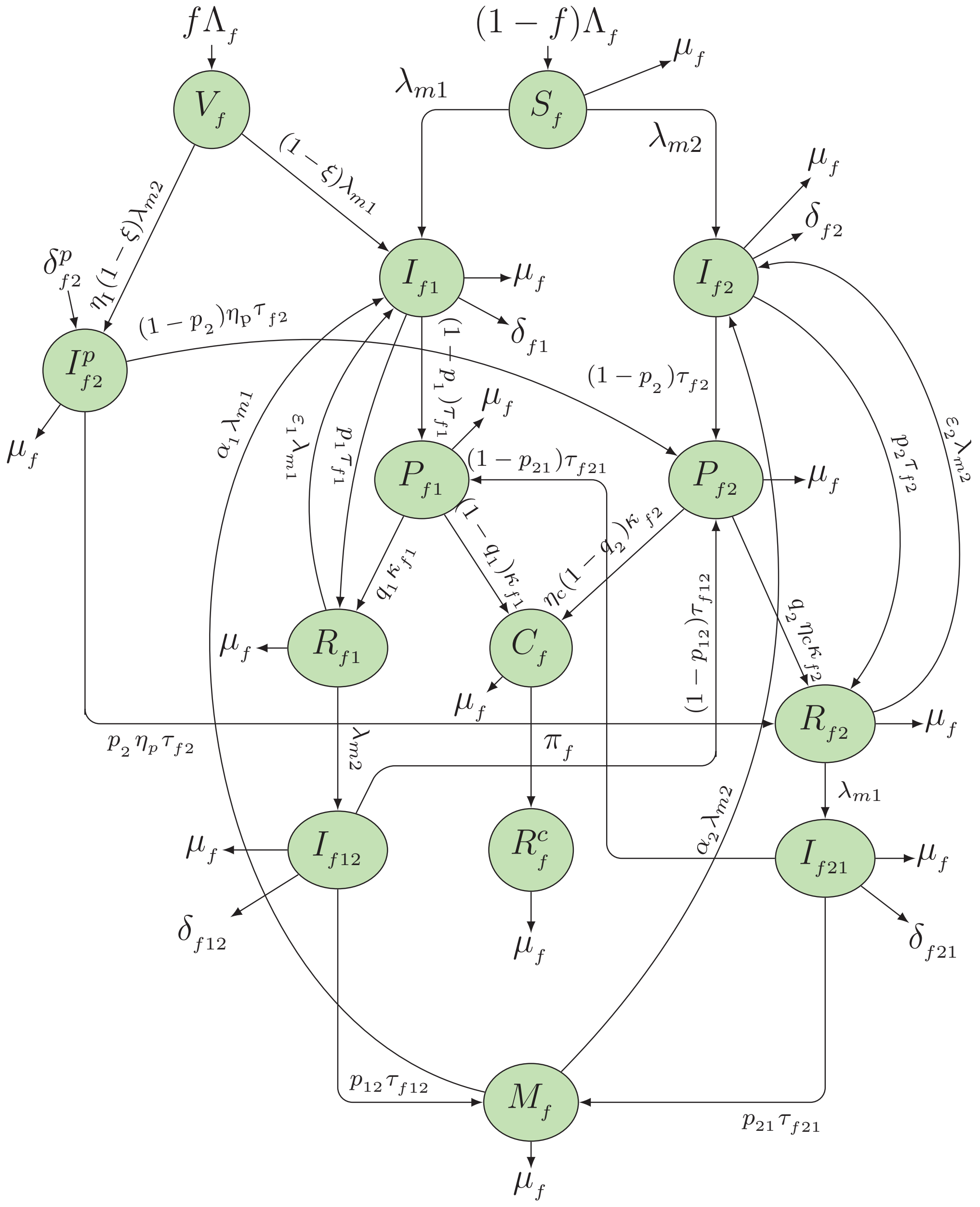


Figure 3.3: Schematic diagram of the female components of the model (3.23)

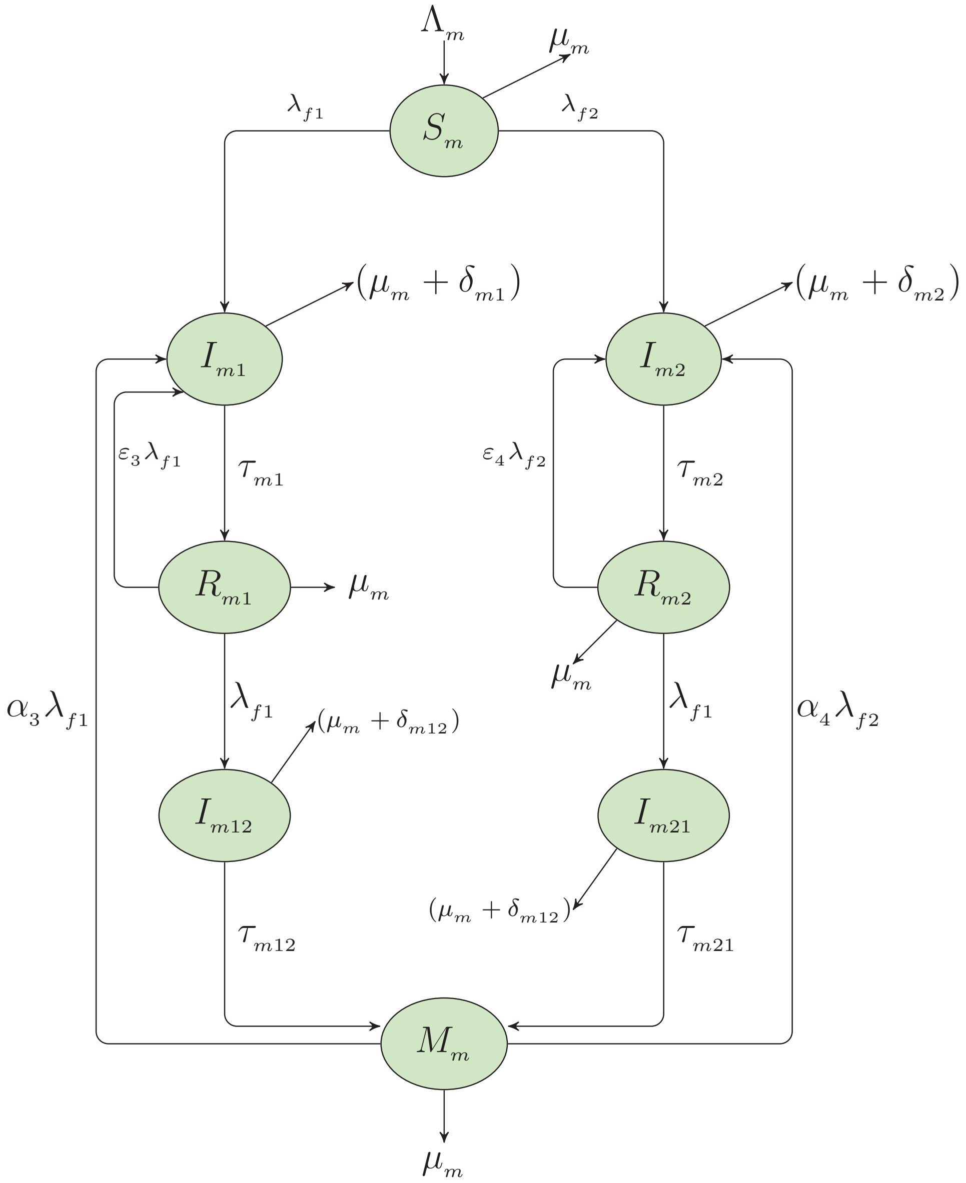


Figure 3.4: Schematic diagram of the male components of the model (3.23)

Combining all these definitions and assumptions, we have that the model for the transmission of HPV in a sexually-active population is given by the following system of differential equations (Table 1 describes the associated state variables and parameters in the model (3.23) while Figures 3.3 and 3.4 give the flow diagrams of the model (3.23)):

$$
\begin{aligned}
\frac{dS_f}{dt} &= (1-f)\Lambda_f - (\lambda_{m1} + \lambda_{m2} + \mu_f)\, S_f \\
\frac{dV_f}{dt} &= f\Lambda_f - [(1-\xi)\lambda_{m1} + \eta_I(1-\xi)\lambda_{m2} + \mu_f]\, V_f \\
\frac{dI_{f1}}{dt} &= (1-\xi)\lambda_{m1}V_f + \lambda_{m1}S_f - (\tau_{f1} + \delta_{f1} + \mu_f)\, I_{f1} + \varepsilon_1\lambda_{m1}R_{f1} + \alpha_1\lambda_{m1}M_f \\
\frac{dP_{f1}}{dt} &= (1-p_1)\tau_{f1}I_{f1} + (1-p_{21})\tau_{f21}I_{f21} - (\kappa_{f1} + \mu_f)\, P_{f1} \\
\frac{dC_f}{dt} &= (1-q_1)\kappa_{f1}P_{f1} + \eta_c(1-q_2)\kappa_{f2}P_{f2} - (\pi_f + \mu_f + \delta_{fc})\, C_f \\
\frac{dR_f^c}{dt} &= \pi_f C_f - \mu_f R_f^c \\
\frac{dR_{f1}}{dt} &= p_1\tau_{f1}I_{f1} + q_1\kappa_{f1}P_{f1} - (\mu_f + \lambda_{m2} + \varepsilon_1\lambda_{m1})\, R_{f1} \\
\frac{dI_{f2}}{dt} &= \lambda_{m2}S_f - (\tau_{f2} + \delta_{f2} + \mu_f)\, I_{f2} + \varepsilon_2\lambda_{m2}R_{f2} + \alpha_2\lambda_{m2}M_f \\
\frac{dI_{f2}^p}{dt} &= \eta_I(1-\xi)\lambda_{m2}V_f - \left(\eta_p\tau_{f2} + \delta_{f2}^p + \mu_f\right) I_{f2}^p \\
\frac{dP_{f2}}{dt} &= (1-p_2)\eta_p\tau_{f2}I_{f2}^p + (1-p_2)\tau_{f2}I_{f2} + (1-p_{12})\tau_{f12}I_{f12} - (\eta_c\kappa_{f2} + \mu_f)\, P_{f2} \\
\frac{dR_{f2}}{dt} &= p_2\eta_p\tau_{f2}I_{f2}^p + p_2\tau_{f2}I_{f2} + q_2\eta_c\kappa_{f2}P_{f2} - (\mu_f + \lambda_{m1} + \varepsilon_2\lambda_{m2})\, R_{f2} \\
\frac{dS_m}{dt} &= \Lambda_m - (\lambda_{f1} + \lambda_{f2} + \mu_m)\, S_m \\
\frac{dI_{m1}}{dt} &= \lambda_{f1}S_m - (\tau_{m1} + \delta_{m1} + \mu_m)I_{m1} + \varepsilon_3\lambda_{f1}R_{m1} + \alpha_3\lambda_{f1}M_m \\
\frac{dR_{m1}}{dt} &= \tau_{m1}I_{m1} - (\mu_m + \lambda_{f2} + \varepsilon_3\lambda_{f1})\, R_{m1} \\
\frac{dI_{m2}}{dt} &= \lambda_{f2}S_m + \varepsilon_4\lambda_{f2}R_{m2} + \alpha_4\lambda_{f2}M_m - (\tau_{m2} + \delta_{m2} + \mu_m)\, I_{m2} \\
\frac{dR_{m2}}{dt} &= \tau_{m2}I_{m2} - (\mu_m + \lambda_{f1} + \varepsilon_4\lambda_{f2})\, R_{m2} \\
\frac{dI_{f12}}{dt} &= \lambda_{m2}R_{f1} - (\tau_{f12} + \delta_{f12} + \mu_f)\, I_{f12} \\
\frac{dI_{f21}}{dt} &= \lambda_{m1}R_{f2} - (\tau_{f21} + \delta_{f21} + \mu_f)\, I_{f21} \\
\frac{dM_f}{dt} &= p_{12}\tau_{f12}I_{f12} + p_{21}\tau_{f21}I_{f21} - (\mu_f + \alpha_1\lambda_{m1} + \alpha_2\lambda_{m2})\, M_f \\
\frac{dI_{m12}}{dt} &= \lambda_{f2}R_{m1} - (\tau_{m12} + \delta_{m12} + \mu_m)\, I_{m12} \\
\frac{dI_{m21}}{dt} &= \lambda_{f1}R_{m2} - (\tau_{m21} + \delta_{m21} + \mu_m)\, I_{m21} \\
\frac{dM_m}{dt} &= \tau_{m12}I_{m12} + \tau_{m21}I_{m21} - (\mu_m + \alpha_3\lambda_{f1} + \alpha_4\lambda_{f2})\, M_m
\end{aligned}
\tag{3.23}
$$

3.5.2 Description of the Model equations

The model is based on the transmission dynamics of two-sex, two-strain HPV infection. In this study, strain 1 is HPV type-16/18 while HPV type-31/45 is considered as strain 2. The total population at time t, denoted by $N(t)$, is subdivided into $N_f(t)$ and $N_m(t)$. $N_f(t)$is further subdivided into susceptible females $(S_f(t))$, females vaccinated with the bivalent vaccine $(V_f(t))$, females infected with strain $i\,(i = 1, 2)$ $(I_{f\,i})$, females with persistent strain $i\,(i = 1, 2)$ $(P_{f\,i})$, females with cancer (C_f), females who have recovered from strain $i\,(i = 1, 2)$ (R_{fi}), females vaccinated with the bivalent vaccine, infected with strain 2, (I^p_{f2}), females who have recovered from cancer (R^c_f) , females who have recovered from strain i and are infected with strain $j(I_{f\,i\,j})$ females who have recovered from both strains $(M_f(t))$. Similarly, $N_m(t)$ is subdivided into susceptible males $(S_m(t))$, males infectious with strain $i\,(i = 1, 2)$ (I_{mi}), males who have recovered from strain $i\,(i = 1, 2)$ $(R_{m\,i})$, males who have recovered from strain i and are infected with strain $j(I_{m\,i\,j})$ Thus

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

$$\begin{aligned} N_f =& S_f + V_f + I_{f1} + P_{f1} + C_f + R^c_f + R_{f1} + I_{f2} + I^p_{f2} + P_{f2} + R_{f2} + I_{f12} + I_{f21} + M_f \\ N_m =& S_m + I_{m1} + R_{m1} + I_{m2} + R_{m2} + I_{m12} + I_{m21} + M_m \end{aligned}$$

The population of unvaccinated susceptible females (S_f) is increased by the recruitment of new sexually-active females at a rate $(1 - f)\Lambda_f$ (where f, with $0 < f \leq 1$, is the fraction of females vaccinated against strain 1). Susceptible females acquire HPV infection following effective contacts with males infected with strain 1 (i.e., those in the I_{m1} and I_{m21} classes) at a rate λ_{m1} and effective contacts with males infected with strain 2 (i.e., those in the I_{m2} and I_{m12} classes) at a rate λ_{m2} given, respectively, by

$$\lambda_{m1} = \frac{\beta_{m1}(I_{m1} + I_{m21})}{N_m} \tag{3.24}$$

and

$$\lambda_{m2} = \frac{\beta_{m2}(I_{m2} + I_{m12})}{N_m} \tag{3.25}$$

In (3.24) and (3.25), β_{m1} and β_{m2} are the effective contact rates for male-to-female transmission of strain 1 and strain 2 infections respectively. β_{m1} is the product of c^f_1 and β^m_1 (that is, $\beta_{m1} = c^f_1\beta^m_1$), while β_{m2} is the product of c^f_1 and β^m_2 (that is, $\beta_{m2} = c^f_1\beta^m_2$), where β^m_1 and β^m_2 denote the probabilities of transmitting strain 1 and strain 2 infections from male-to-female, respectively, and

c_1^f denotes the rate at which females acquire new sexual partners. This population is decreased by natural death at a rate μ_f (natural mortality occurs in all the female epidemiological compartment at the rate μ_f). Thus,

$$\frac{dS_f}{dt} = (1-f)\Lambda_f - (\lambda_{m1} + \lambda_{m2} + \mu_f)\, S_f$$

The population of new sexually active susceptible females vaccinated against strain 1 is generated by the vaccination of a fraction, f, of unvaccinated susceptible females with the *Gardasil* vaccine (at the rate $f\Lambda_f$). It is decreased by HPV infection, following effective contacts with males infected with strain 1 (i.e., those in the I_{m1} and I_{m21} classes) at a reduced rate $(1-\xi)\lambda_{m1}$ and effective contacts with males infected with strain 2 (i.e., those in the I_{m2} and I_{m12} classes) at a reduced rate $\eta_I(1-\xi)\lambda_{m2}$ where $0 < \xi \leq 1$ represents the efficacy of *Gardasil* vaccine against infection with HPV-16 and -18 and η_I is a modification parameter for cross protection against incident infection with strain 2. This population is decreased by natural death. Thus,

$$\frac{dV_f}{dt} = f\Lambda_f - [(1-\xi)\lambda_{m1} + \eta_I(1-\xi)\lambda_{m2} + \mu_f]\, V_f$$

The population of females infected with strain 1 (I_{f1}) is increased following the infection of unvaccinated susceptible females and vaccinated females at the rates λ_{m1} and $(1-\xi)\lambda_{m1}$ respectively. The population is further increased following the re-infection of females who have recovered from strain 1 and the re-infection of females who have recovered from both strains at the rates $\varepsilon_1\lambda_{m1}$ and $\alpha_1\lambda_{m1}$, respectively (Here, ε_1 and α_1 with, $0 < \varepsilon_1, \alpha_1 \leq 0$, accounts for the assumption that the re-infection of females who have recovered from strain 1 and those who have recovered from both strains occur at a rate lower than the rate for primary infection of susceptible females with strain 1). The population is reduced due to transition out of I_{f1} class at the rate τ_{f1}, disease induced death at the rate δ_{f1} and natural death. Thus,

$$\frac{dI_{f1}}{dt} = (1-\xi)\lambda_{m1}V_f + \lambda_{m1}S_f - (\tau_{f1} + \delta_{f1} + \mu_f)\, I_{f1} + \varepsilon_1\lambda_{m1}R_{f1} + \alpha_1\lambda_{m1}M_f$$

The population of females with persistent strain 1 infection P_{f1} is increased by a fraction $(1-p_1)\tau_{f1}$ and another fraction $(1-p_{21})\tau_{f21}$ of females in the I_{f21} and I_{f1} classes, respectively, who develop persistent HPV infection. The population is decreased due to transition out of P_{f1} class at the rate κ_{f1} and natural death. Thus,

$$\frac{dP_{f1}}{dt} = (1 - p_1)\tau_{f1}I_{f1} + (1 - p_{21})\tau_{f21}I_{f21} - (\kappa_{f1} + \mu_f)\, P_{f1}$$

The population of females with cervical cancer C_f is increased by a fraction $(1 - q_1)\kappa_{f1}$ and another fraction $\eta_c(1 - q_2)\kappa_{f2}$ of females with persistent strain 1 and persistent strain 2 infection who develop cervical cancer (Here, η_c is a modification parameter accounting for the assumption that the progression to cervical cancer by females with persistent strain 2 infection occur at a rate lower than the progression to cervical cancer by females with persistent strain 1 infection). The population is decreased following the treatment of females with cervical cancer at the rate π_f, cancer induced death at the rate δ_{fc} and natural death. Thus,

$$\frac{dC_f}{dt} = (1 - q_1)\kappa_{f1}P_{f1} + \eta_c(1 - q_2)\kappa_{f2}P_{f2} - (\pi_f + \mu_f + \delta_{fc})\, C_f$$

The population of females who have recovered from cervical cancer R_f^c is increased following the treatment of females with cervical cancer at the rate π_f. The population is decreased by natural death. Thus,

$$\frac{dR_f^c}{dt} = \pi_f C_f - \mu_f R_f^c$$

The population of females who have recovered from strain 1 infection R_{f1} is increased by females infected with strain 1 infection and females with persistent strain 1 infection who recover naturally at the rates $p_1\tau_{f1}$ and $q_1\kappa_{f1}$, respectively. The population is reduced due to reinfection with strain 1 (at the reduced rate $\varepsilon_1\lambda_{m1}$) and strain 2 (at the rate λ_{m2}). Thus,

$$\frac{dR_{f1}}{dt} = p_1\tau_{f1}I_{f1} + q_1\kappa_{f1}P_{f1} - (\mu_f + \lambda_{m2} + \varepsilon_1\lambda_{m1})\, R_{f1}$$

The population of females infected with strain 2 (I_{f2}) is increased following the infection of unvaccinated susceptible females at the rate λ_{m2}. The population is further increased following the re-infection of females who have recovered from strain 2 and the re-infection of females who have recovered from both strains at the rates $\varepsilon_2\lambda_{m2}$ and $\alpha_2\lambda_{m2}$, respectively (Here, ε_2 and α_2 with, $0 < \varepsilon_2, \alpha_2 \leq 0$, accounts for the assumption that the re-infection of females who have recovered from strain 2 and those who have recovered from both strains occur at a rate lower than the rate for primary infection of susceptible females with strain 2). The population is reduced due to transition out of I_{f2} class at the rate τ_{f2}, disease induced death at the rate δ_{f2} and natural death. Thus,

$$\frac{dI_{f2}}{dt} = \lambda_{m2}S_f - (\tau_{f2} + \delta_{f2} + \mu_f)\, I_{f2} + \varepsilon_2\lambda_{m2}R_{f2} + \alpha_2\lambda_{m2}M_f$$

The population of vaccinated females with strain infected with strain 2 infection I^p_{f2} is increased following the infection of vaccinated susceptible females at the rate $\eta_I(1-\xi)\lambda_{m2}$. The population is reduced due to transition out of I^p_{f2} class at the rate $\eta_p\tau_{f2}$ (here, η_p is a modification parameter accounting for the cross protection of vaccinated susceptible females against persistent infection with strain 2), disease induced death at the rate δ^p_{f2} and natural death. Thus,

$$\frac{dI^p_{f2}}{dt} = \eta_I(1-\xi)\lambda_{m2}V_f - \left(\eta_p\tau_{f2} + \delta^p_{f2} + \mu_f\right) I^p_{f2}$$

The population of females with persistent strain 2 infection P_{f2} is increased by a fractions $(1-p_2)\eta_p\tau_{f2}$, $(1-p_2)\tau_{f2}$ and $(1-p_{12})\tau_{f12}$ of females in the I^p_{f2}, I_{f2} and I_{f12} classes, respectively, who develop persistent HPV infection. The population is decreased due to transition out of P_{f2} class at the rate $\eta_c\kappa_{f2}$ and natural death. Thus,

$$\frac{dP_{f2}}{dt} = (1-p_2)\eta_p\tau_{f2}I^p_{f2} + (1-p_2)\tau_{f2}I_{f2} + (1-p_{12})\tau_{f12}I_{f12} - (\eta_c\kappa_{f2} + \mu_f)\, P_{f2}$$

The population of females who have recovered from strain 2 infection R_{f2} is increased by females infected with strain 1 infection and females with persistent strain 1 infection who recover naturally at the rates $p_1\tau_{f1}$ and $q_1\kappa_{f1}$, respectively. The population is reduced due to reinfection with strain 1 (at rate λ_{m1}) and strain 2 (at the reduced rate $\varepsilon_2\lambda_{m2}$). Thus,

$$\frac{dR_{f2}}{dt} = p_2\eta_p\tau_{f2}I^p_{f2} + p_2\tau_{f2}I_{f2} + q_2\eta_c\kappa_{f2}P_{f2} - (\mu_f + \lambda_{m1} + \varepsilon_2\lambda_{m2})\, R_{f2}$$

The population of susceptible males (S_m) is increased by the recruitment of new sexually-active males at a rate Λ_m. Susceptible males acquire HPV infection following effective contacts with females infected with strain 1 (i.e., those in the I_{f1} and I_{f21} classes) at a rate λ_{f1} and effective contacts with females infected with strain 2 (i.e., those in the I_{f2}, I^p_{f2} and I_{f12} classes) at a rate λ_{f2} given, respectively, by

$$\lambda_{f1} = \frac{\beta_{f1}(I_{f1} + I_{f21} + \theta_{p1}P_{f1})}{N_f} \tag{3.26}$$

and

$$\lambda_{f2} = \frac{\beta_{f2}(I_{f2} + I_{f12} + \phi_p I_{f2}^p + \theta_{p2} P_{f2})}{N_f} \tag{3.27}$$

In (3.26) and (3.27), β_{f1} and β_{f2} are the effective contact rates for female-to-male transmission of strain 1 and strain 2 infections respectively. β_{f1} is the product of c_1^f and β_1^f (that is, $\beta_{f1} = c_1^m \beta_1^f$), while β_{f2} is the product of c_1^m and β_2^f (that is, $\beta_{f2} = c_1^m \beta_2^f$), where β_1^f and β_2^f denote the probabilities of transmitting strain 1 and strain 2 infections from female-to-male and c_1^m denotes the rate at which males acquire new sexual partners. This population is decreased by natural death at a rate μ_m(natural mortality occurs in all the male epidemiological compartment at the rate μ_m). Thus,

$$\frac{dS_m}{dt} = \Lambda_m - (\lambda_{f1} + \lambda_{f2} + \mu_m) S_m$$

The population of males infected with strain 1 (I_{m1}) is increased following the infection of susceptible males at the rates λ_{f1}. The population is further increased following the re-infection of males who have recovered from strain 1 and the re-infection of males who have recovered from both strains at the rates $\varepsilon_3 \lambda_{f1}$ and $\alpha_3 \lambda_{f1}$, respectively (Here, ε_3 and α_3 with, $0 < \varepsilon_3, \alpha_3 \leq 0$, accounts for the assumption that the re-infection of males who have recovered from strain 1 and those who have recovered from both strains occur at a rate lower than the rate for primary infection of susceptible males with strain 1). The population is reduced due to transition out of I_{m1} class at the rate τ_{m1}, disease induced death at the rate δ_{m1} and natural death. Thus,

$$\frac{dI_{m1}}{dt} = \lambda_{f1} S_m - (\tau_{m1} + \delta_{m1} + \mu_m) I_{m1} + \varepsilon_3 \lambda_{f1} R_{m1} + \alpha_3 \lambda_{f1} M_m$$

The population of males who have recovered from strain 1 infection R_{m1} is increased by males infected with strain 1 infection who recover naturally at the rate τ_{f1}. The population is reduced due to reinfection with strain 1 (at the reduced rate $\varepsilon_3 \lambda_{f1}$) and strain 2 (at the rate λ_{f2}). Thus,

$$\frac{dR_{m1}}{dt} = \tau_{m1} I_{m1} - (\mu_m + \lambda_{f2} + \varepsilon_3 \lambda_{f1}) R_{m1}$$

The population of males infected with strain 2 (I_{m2}) is increased following the infection of susceptible males at the rate λ_{f2}. The population is further increased following the re-infection of males who have recovered from strain 2 and the re-infection of males who have recovered from both strains at the rates $\varepsilon_4 \lambda_{f2}$ and $\alpha_4 \lambda_{f2}$, respectively (Here, ε_4 and α_4 with, $0 < \varepsilon_4, \alpha_4 \leq 0$, accounts for the assumption that the re-infection of males who have recovered from strain 2 and those who have recovered from both strains occur at a rate lower than the rate for primary infection of susceptible males with strain 2). The population is reduced due to transition out of I_{m2} class at the rate τ_{m2}, disease induced death at the rate δ_{m2} and natural death. Thus,

$$\frac{dI_{m2}}{dt} = \lambda_{f2}S_m - (\tau_{m2} + \delta_{m2} + \mu_m)\, I_{m2} + \varepsilon_4\lambda_{f2}R_{m2} + \alpha_4\lambda_{f2}M_m$$

The population of males who have recovered from strain 2 infection R_{m2} is increased by males infected with strain 1 infection who recover naturally at the rate τ_{m1}. The population is reduced due to reinfection with strain 1 (at the rate λ_{m1}) and strain 2 (at the reduced rate $\varepsilon_4\lambda_{f2}$). Thus,

$$\frac{dR_{m2}}{dt} = \tau_{m2}I_{m2} - (\mu_m + \lambda_{f1} + \varepsilon_4\lambda_{f2})\, R_{m2}$$

The population of females who have recovered from strain 1 and are infected with strain 2, I_{f12}, is increased following the re-infection (with strain 2 at the rate λ_{m2}) of females who have recovered naturally from strain 1 infection. This population is decreased following transition out of I_{f12} class at the rate τ_{f12}, disease induced death at the rate δ_{f12} and natural death. Thus

$$\frac{dI_{f12}}{dt} = \lambda_{m2}R_{f1} - (\tau_{f12} + \delta_{f12} + \mu_f)\, I_{f12}$$

The population of females who have recovered from strain 2 and are infected with strain 1, I_{f21}, is increased following the re-infection (with strain 1 at the rate λ_{m1}) of females who have recovered naturally from strain 2 infection. This population is decreased following transition out of I_{f21} class at the rate τ_{f21}, disease induced death at the rate δ_{f21} and natural death. Thus

$$\frac{dI_{f21}}{dt} = \lambda_{m1}R_{f2} - (\tau_{f21} + \delta_{f21} + \mu_f)\, I_{f21}$$

The population of males who have recovered from strain 1 and are infected with strain 2, I_{m12}, is increased following the re-infection (with strain 2 at the rate λ_{f2}) of males who have recovered naturally from strain 1 infection. This population is decreased following recovery from strain 2 at the rate τ_{m12}, disease induced death at the rate δ_{m12} and natural death. Thus

$$\frac{dI_{m12}}{dt} = \lambda_{f2} R_{m1} - \left(\tau_{m12} + \delta_{m12} + \mu_m\right) I_{m12}$$

The population of males who have recovered from strain 2 and are infected with strain 1, I_{m21}, is increased following the re-infection (with strain 1 at the rate λ_{f1}) of males who have recovered naturally from strain 2 infection. This population is decreased following recovery from strain 1 at the rate τ_{m21}, disease induced death at the rate δ_{m21} and natural death. Thus,

$$\frac{dI_{m21}}{dt} = \lambda_{f1} R_{m2} - \left(\tau_{m21} + \delta_{m21} + \mu_m\right) I_{m21}$$

The population of females who have recovered from both strains, M_f, is increased by females in the I_{f12} class who recover from strain 2 at the rate $p_{12}\tau_{f12}$ and females in the I_{f21} class who recover from strain 1 at the rate $p_{21}\tau_{f21}$. The population is reduced following re-infection with strain 1 (at the reduced rate $\alpha_1 \lambda_{m1}$) and re-infection with strain 2 (at the reduced rate $\alpha_2 \lambda_{m2}$). The population is further decreased due to natural death. Thus,

$$\frac{dM_f}{dt} = p_{12}\tau_{f12} I_{f12} + p_{21}\tau_{f21} I_{f21} - \left(\mu_f + \alpha_1 \lambda_{m1} + \alpha_2 \lambda_{m2}\right) M_f$$

The population of males who have recovered from both strains, M_m, is increased by males in the I_{m12} class who recover from strain 2 at the rate τ_{m12} and males in the I_{m21} class who recover from strain 1 at the rate τ_{m21}. The population is reduced following re-infection with strain 1 (at the reduced rate $\alpha_3 \lambda_{f1}$) and re-infection with strain 2 (at the reduced rate $\alpha_4 \lambda_{f2}$). The population is further decreased due to natural death. Thus,

$$\frac{dM_m}{dt} = \tau_{m12} I_{m12} + \tau_{m21} I_{m21} - \left(\mu_m + \alpha_3 \lambda_{f1} + \alpha_4 \lambda_{f2}\right) M_m$$

The model will be studied subject to the group contact constraint given by

$$c_m N_m = c_f N_f, \tag{3.28}$$

3.6 Formulation of the HPV-TB Co-infection model

3.6.1 Model assumptions

The HPV-TB co-infection model is based on the following assumptions:

i. incorporating the dynamics of co-infection of HPV with tuberculosis (Zhao *et al.*, 2011; Zetola *et al.*, 2015),

ii. including the dynamics of homogeneous transmission of HPV ($\xi_{\text{F}} \neq 0, \xi_{\text{M}} \neq 0$) (Marrazzo *et al.,* 1998; Marrazzo *et al.,* 2001; Joseph et al., 2008),

iii. including compartments for infectious individuals dually infected with active TB and HPV (Zetola *et al.,* 2015).

iv. including compartments for infectious individuals dually infected with latent TB and HPV (Zetola *et al.,* 2015),

v. allowing for disease transmission by dually infected individuals,

vi. dually infected individuals can transmit either HPV or TB but not the mixed infection,

vii. including a modification parameter accounting for the increased infectiousness of dually infected individuals.

Table 3.4: Description of variables in the model (3.29).

Variable	**Interpretation**
$S_{F}(S_{M})$	population of susceptible females (males)
V_{HF}	Population of females vaccinated against HPV
$I_{HF}(I_{HM})$	Population of females(males) infected with HPV
$R_{HF}(R_{HM})$	Population of females(males) who have recovered from HPV
P_{HF}	Population of females with persistent HPV infection
C_{F}	Population of females with cervical cancer
R_{F}^{C}	Population of females who have recovered from cervical cancer
$E_{FT}(E_{MT})$	Population of females (males) with latent TB
$I_{FT}(I_{MT})$	Population of females (males) with active TB
$T_{FT}(T_{MT})$	Population of females (males) treated of TB
$I_{HE}^{F}(I_{HE}^{M})$	Population of females (males) dually infected with HPV and latent TB
$I_{HA}^{F}(I_{HA}^{M})$	Population of females (males) dually infected with HPV and active TB
P_{HE}^{F}	Population of females dually infected with persistent HPV and latent TB
P_{HA}^{F}	Population of females dually infected with persistent HPV and active TB
C_{FE}	Population of females dually infected with cervical cancer and latent TB
C_{FA}	Population of females dually infected with cervical cancer and active TB
$N_{HF}(N_{HM})$	Total population of females (males)
N_{H}	Total human population

Table 3.5: Description of parameters in the model (3.29).

Parameter	**Interpretation**
$\Lambda_{\text{F}}(\Lambda_{\text{M}})$	for females (males)
$\mu_{\text{F}}(\mu_{\text{M}})$	Natural death rates for females (males)
f	Proportion of vaccinated females
π_{F}	Vaccine efficacy for females
$\xi_{\text{F}}(\xi_{\text{M}})$	Homosexual contact rate between females (males)
$\phi_i^{\text{F}}(\phi_i^{\text{M}}),\quad i{=}1{,}2{,}3$	Recovery rates from HPV for individuals in the $I_{\text{HF}}(I_{\text{HM}})$, $I_{\text{HE}}^{\text{F}}(I_{\text{HE}}^{\text{M}})$, $I_{\text{HA}}^{\text{F}}(I_{\text{HA}}^{\text{M}})$ classes, respectively, for females (males)
$r_i^{\text{F}}(r_i^{\text{M}})\quad i{=}1{,}2{,}3{,}4$	Recovery rates from TB for individuals in the $I_{\text{FT}}(I_{\text{MT}})$, $I_{\text{HA}}^{\text{F}}(I_{\text{HA}}^{\text{M}})$, P_{HA}^{F}, C_{FA} classes, respectively, for females (males)
$\kappa_i^{\text{F}}\phi_i^{\text{F}}\qquad i{=}1{,}2{,}3$	Fraction of infected females who recovered naturally from HPV (but did not develop persistent HPV infection)
$(1-\kappa_i^{\text{F}})\phi_i^{\text{F}},_{i=1,2,3}$	Fraction of infected females who develop persistent HPV infection
$\rho_{i,\ i=1,2,3}^{\text{F}}$	Transition rates out of P_{HF}, P_{HE}^{F}, P_{HA}^{F} classes for females
$\chi_i^{\text{F}}\rho_{i,\ i=1,2,3}^{\text{F}}$	Rate at which females recover naturally from the persistent infection
$(1-\chi_i^{\text{F}})\rho_{i,}^{\text{F}}$	Rate at which females with persistent HPV infection develop cervical cancer
$\varphi_{\text{F}}(\varphi_{\text{M}})$	Rate of reinfection with HPV for females (males)
$\tau_{i,\ i=1,2,3}^{\text{F}}$	Cervical cancer treatment rates for females in the C_{F}, C_{FE}, C_{FA} classes
$\delta_{\text{HF}}, \delta_{\text{CF}}, \delta_{\text{FT}}$	Disease induced death rates for females singly infected with HPV, cancer and tuberculosis respectively
$\delta_{\text{HM}}, \delta_{\text{MT}}$	Disease induced death rates for males singly infected with HPV and tuberculosis respectively
$\delta_{\text{HF1}}, \delta_{\text{HF2}}, \delta_{\text{FT1}},\ \delta_{\text{FT1}}$	Disease induced death rates for mixed infections for females
$\delta_{\text{HM1}}, \delta_{\text{HM2}}, \delta_{\text{MT1}}$	Disease induced death rates for mixed infections for males
$\sigma_{\text{F}}(\sigma_{\text{M}})$	Rate of reinfection with TB for females (males)
$\psi_i^{\text{F}}(\psi_i^{\text{M}})\ \ i{=}1{,}2{,}3{,}4$	Fraction of newly infected females (males) with active TB
$1-\psi_i^{\text{F}},\ \ i{=}1{,}2{,}3{,}4$	fraction of newly infected females with latent TB
$1-\psi_i^{\text{M}},\quad i{=}1{,}2$	fraction of newly infected males with latent TB
$\varepsilon_i^{\text{F}}(\varepsilon_i^{\text{M}})\ \ i{=}1{,}2{,}3{,}4$	Exogenous re-infection rates to active TB for females (males)
$\gamma_i^{\text{F}}(\gamma_i^{\text{M}})\ \ i{=}1{,}2{,}3{,}4$	Slow progression rate to active TB for females (males)
β_{F}	Effective contact rate for females-to-male transmission of HPV
β_{M}	Effective contact rate for male-to-female transmission of HPV
β_1^{F}	Probability of transmitting HPV from females-to-males
β_1^{M}	Probability of transmitting HPV from males-to-females
ϱ_{M}	Rate at which males acquire new sexual partners
ϱ_{F}	Rate at which females acquire new sexual partners
β_{T}	Effective contact rate for TB transmission
$c_{\text{F}}(c_{\text{M}})$	Condom compliance rate for females (males)
$\epsilon_{\text{F}}(\epsilon_{\text{M}})$	Condom efficacy for females (males)
θ_{T}	Modification parameter for increased infectiousness of dually infected individuals due to TB
ω_{T}	Modification parameter for reduced infectiousness of dually infected individuals with latent TB relative to those with active TB
η_p	Modification parameter for increased infectiousness of dually infected individuals due to HPV
ω_p	Modification parameter for reduced infectiousness of infected females with persistent HPV relative to infected females infected with HPV

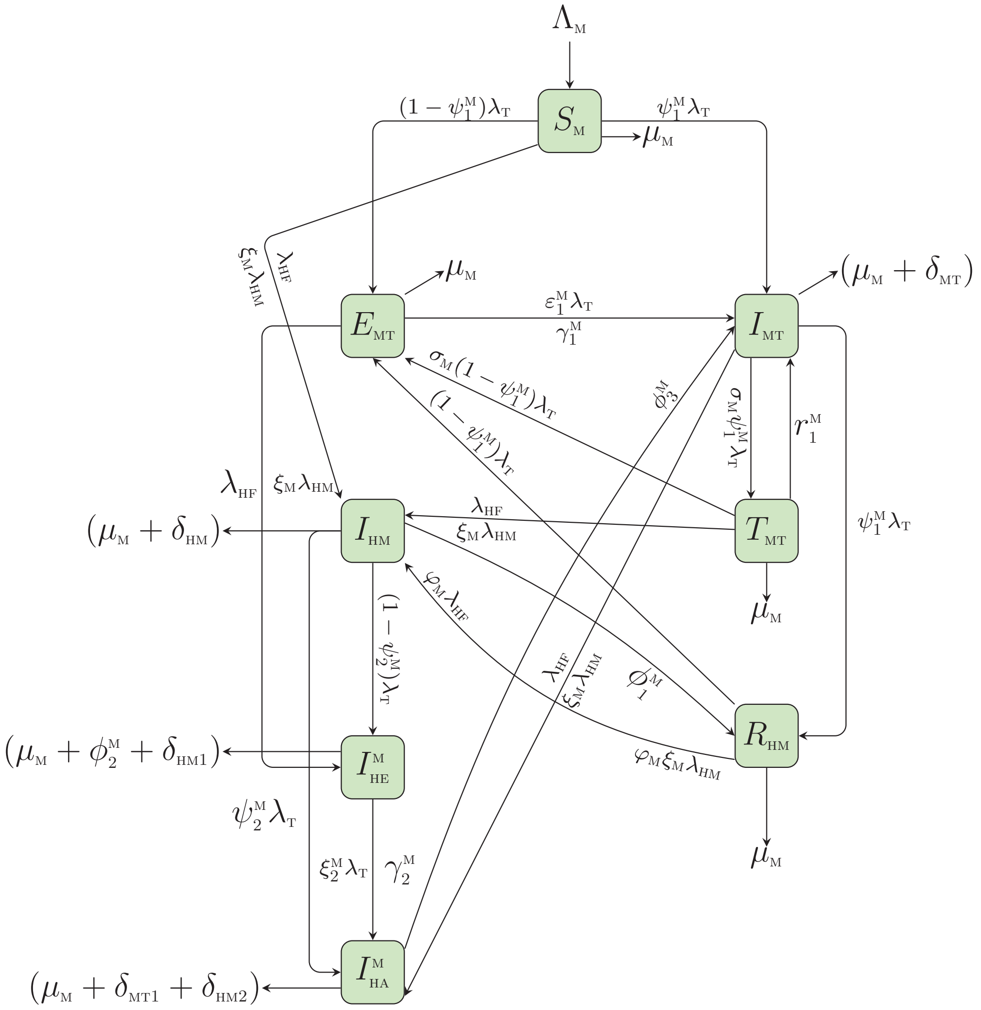


Figure 3.5: Schematic diagram of the male components of the model

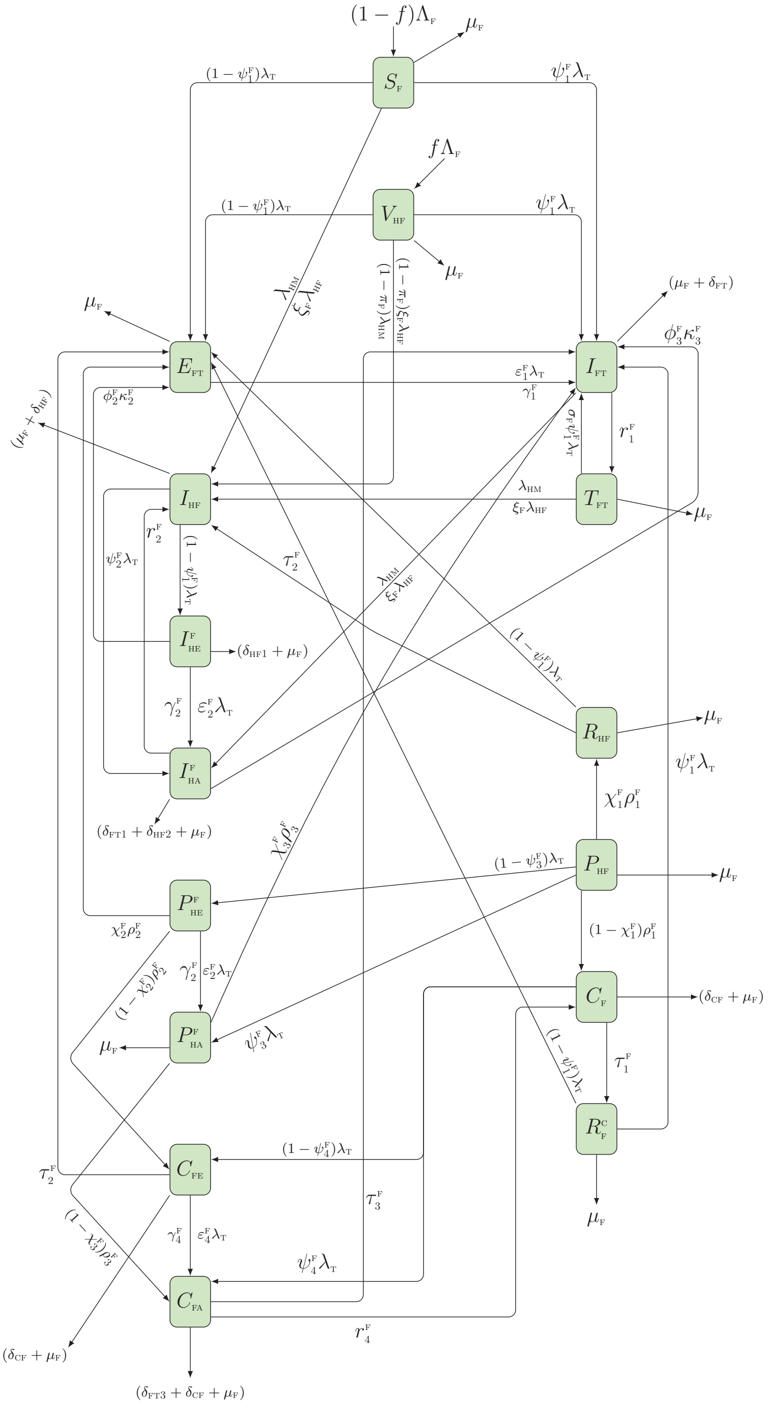


Figure 3.6: Schematic diagram of the female components of the model

Based on the above formulations and assumptions, the HPV-TB model is given by the following deterministic system of non-linear differential equations (flow diagrams of the model are depicted in Figures 3.5 and 3.6, the associated state variables and parameters are described in Table 1):

$$
\begin{aligned}
\frac{dS_{\text{F}}}{dt} &= (1-f)\Lambda_{\text{F}} - (\lambda_{\text{HM}} + \xi_{\text{F}}\lambda_{\text{HF}} + \mu_{\text{F}} + \lambda_{\text{T}})S_{\text{F}}\\
\frac{dV_{\text{HF}}}{dt} &= f\Lambda_{\text{F}} - \left[(1-\pi_{\text{F}})\lambda_{\text{HM}} + (1-\pi_{\text{F}})\xi_{\text{F}}\lambda_{\text{HF}} + (\mu_{\text{F}} + \lambda_{\text{T}})\right] V_{\text{HF}}\\
\frac{dI_{\text{HF}}}{dt} &= (\lambda_{\text{HM}} + \xi_{\text{F}}\lambda_{\text{HF}})S_{\text{F}} + [(1-\pi_{\text{F}})\lambda_{\text{HM}} + (1-\pi_{\text{F}})\xi_{\text{F}}\lambda_{\text{HF}}]V_{\text{HF}} + r_2^{\text{F}}I_{\text{HA}}^{\text{F}} + \lambda_{\text{HM}}T_{\text{FT}} + \xi_{\text{F}}\lambda_{\text{HF}}T_{\text{FT}}\\
&\quad + \varphi_{\text{F}}\lambda_{\text{HM}}R_{\text{HF}} + \varphi_{\text{F}}\xi_{\text{F}}\lambda_{\text{HF}}R_{\text{HF}} - (\phi_1^{\text{F}} + \lambda_{\text{T}} + \mu_{\text{F}} + \delta_{\text{HF}})I_{\text{HF}}\\
\frac{dR_{\text{HF}}}{dt} &= \kappa_1^{\text{F}}\phi_1^{\text{F}}I_{\text{HF}} + \chi_1^{\text{F}}\rho_1^{\text{F}}P_{\text{HF}} - (\varphi_{\text{F}}\lambda_{\text{HM}} + \varphi_{\text{F}}\xi_{\text{F}}\lambda_{\text{HM}} + \mu_{\text{F}} + \lambda_{\text{T}})R_{\text{HF}}\\
\frac{dP_{\text{HF}}}{dt} &= (1-\kappa_1^{\text{F}})\phi_1^{\text{F}}I_{\text{HF}} + r_3^{\text{F}}P_{\text{HA}}^{\text{F}} - (\rho_1^{\text{F}} + \mu_{\text{F}} + \lambda_{\text{T}})P_{\text{HF}}\\
\frac{dC_{\text{F}}}{dt} &= (1-\chi_1^{\text{F}})\rho_1^{\text{F}}P_{\text{HF}} + r_4^{\text{F}}C_{\text{FA}} - (\tau_1^{\text{F}} + \mu_{\text{F}} + \delta_{\text{CF}} + \lambda_{\text{T}})C_{\text{F}}\\
\frac{dR_{\text{F}}^c}{dt} &= \tau_1^{\text{F}}C_{\text{F}} - (\mu_{\text{F}} + \lambda_{\text{T}})R_{\text{F}}^c\\
\frac{dE_{\text{FT}}}{dt} &= (1-\psi_1^{\text{F}})\lambda_{\text{T}}(S_{\text{F}} + V_{\text{HF}} + R_{\text{HF}} + R_{\text{F}}^c + \sigma_{\text{F}}T_{\text{FT}}) + \phi_2^{\text{F}}\kappa_2^{\text{F}}I_{\text{HE}}^{\text{F}} + \chi_2^{\text{F}}\rho_2^{\text{F}}P_{\text{HE}}^{\text{F}} + \tau_2^{\text{F}}C_{\text{FE}}\\
&\quad - (\varepsilon_1^{\text{F}}\lambda_{\text{T}} + \gamma_1^{\text{F}} + \lambda_{\text{HM}} + \xi_{\text{F}}\lambda_{\text{HF}} + \mu_{\text{F}})E_{\text{FT}}\\
\frac{dI_{\text{FT}}}{dt} &= \psi_1^{\text{F}}\lambda_{\text{T}}(S_{\text{F}} + V_{\text{HF}} + R_{\text{HF}} + R_{\text{F}}^c + \sigma_{\text{F}}T_{\text{FT}}) + \varepsilon_1^{\text{F}}\lambda_{\text{T}}E_{\text{FT}} + \gamma_1^{\text{F}}E_{\text{FT}} + \phi_3^{\text{F}}\kappa_3^{\text{F}}I_{\text{HA}}^{\text{F}} + \chi_3^{\text{F}}\rho_3^{\text{F}}P_{\text{HA}}^{\text{F}}\\
&\quad + \tau_3^{\text{F}}C_{\text{FA}} - (r_1^{\text{F}} + \mu_{\text{F}} + \delta_{\text{FT}} + \lambda_{\text{HM}} + \xi_{\text{F}}\lambda_{\text{HF}})I_{\text{FT}}\\
\frac{dT_{\text{FT}}}{dt} &= r_1^{\text{F}}I_{\text{FT}} - (\sigma_{\text{F}}\lambda_{\text{T}} + \lambda_{\text{HM}} + \xi_{\text{F}}\lambda_{\text{HF}} + \mu_{\text{F}})T_{\text{FT}}\\
\frac{dI_{\text{HE}}^{\text{F}}}{dt} &= (1-\psi_2^{\text{F}})\lambda_{\text{T}}I_{\text{HF}} + \lambda_{\text{HM}}E_{\text{FT}} + \xi_{\text{F}}\lambda_{\text{HF}}E_{\text{FT}} - (\varepsilon_2^{\text{F}}\lambda_{\text{T}} + \gamma_2^{\text{F}} + \mu_{\text{F}} + \phi_2^{\text{F}} + \delta_{\text{HF1}})I_{\text{HE}}^{\text{F}}\\
\frac{dI_{\text{HA}}^{\text{F}}}{dt} &= \psi_2^{\text{F}}\lambda_{\text{T}}I_{\text{HF}} + \varepsilon_2^{\text{F}}\lambda_{\text{T}}I_{\text{HE}}^{\text{F}} + \gamma_2^{\text{F}}I_{\text{HE}}^{\text{F}} + \lambda_{\text{HM}}I_{\text{FT}} + \xi_{\text{F}}\lambda_{\text{HF}}I_{\text{FT}} - (r_2^{\text{F}} + \mu_{\text{F}} + \delta_{\text{FT1}} + \delta_{\text{HF2}} + \phi_3^{\text{F}})I_{\text{HA}}^{\text{F}}\\
\frac{dP_{\text{HE}}^{\text{F}}}{dt} &= (1-\psi_3^{\text{F}})\lambda_{\text{T}}P_{\text{HF}} + (1-\kappa_2^{\text{F}})\psi_2^{\text{F}}I_{\text{HE}}^{\text{F}} - (\varepsilon_3^{\text{F}}\lambda_{\text{T}} + \gamma_3^{\text{F}} + \rho_3^{\text{F}} + \mu_{\text{F}})P_{\text{HE}}^{\text{F}}\\
\frac{dP_{\text{HA}}^{\text{F}}}{dt} &= \psi_3^{\text{F}}\lambda_{\text{T}}P_{\text{HF}} + \varepsilon_3^{\text{F}}\lambda_{\text{T}}P_{\text{HE}}^{\text{F}} + \gamma_3^{\text{F}}P_{\text{HE}}^{\text{F}} + (1-\kappa_3^{\text{F}})\phi_3^{\text{F}}I_{\text{HA}}^{\text{F}} - (r_3^{\text{F}} + \delta_{\text{FT2}} + \rho_3^{\text{F}} + \mu_{\text{F}})P_{\text{HA}}^{\text{F}}\\
\frac{dC_{\text{FE}}}{dt} &= (1-\psi_4^{\text{F}})\lambda_{\text{T}}C_{\text{F}} + (1-\chi_2^{\text{F}})\rho_2^{\text{F}}P_{\text{HE}}^{\text{F}} - (\varepsilon_4^{\text{F}}\lambda_{\text{T}} + \gamma_4^{\text{F}} + \delta_{\text{CF}} + \mu_{\text{F}} + \tau_2^{\text{F}})C_{\text{FE}}\\
\frac{dC_{\text{FA}}}{dt} &= \psi_4^{\text{F}}\lambda_{\text{T}}C_{\text{F}} + \varepsilon_4^{\text{F}}\lambda_{\text{T}}C_{\text{FE}} + \gamma_4^{\text{F}}C_{\text{FE}} + (1-\chi_3^{\text{F}})\rho_3^{\text{F}}P_{\text{HA}}^{\text{F}} - (r_4^{\text{F}} + \delta_{\text{FT3}} + \delta_{\text{CF}} + \mu_{\text{F}} + \tau_3^{\text{F}})C_{\text{FA}}
\end{aligned}
\tag{3.29}
$$

$$
\begin{aligned}
\frac{dS_{\mathrm{M}}}{dt} &= \Lambda_{\mathrm{M}} - (\lambda_{\mathrm{HF}} + \xi_{\mathrm{M}}\lambda_{\mathrm{HM}} + \mu_{\mathrm{M}} + \lambda_{\mathrm{T}})S_{\mathrm{M}}\\
\frac{dI_{\mathrm{HM}}}{dt} &= (\lambda_{\mathrm{HF}} + \xi_{\mathrm{M}}\lambda_{\mathrm{HM}})S_{\mathrm{M}} + r_2^{\mathrm{M}} I_{\mathrm{HA}}^{\mathrm{M}} + \lambda_{\mathrm{HF}}T_{\mathrm{MT}} + \xi_{\mathrm{M}}\lambda_{\mathrm{HM}}T_{\mathrm{MT}} + \varphi_{\mathrm{M}}\lambda_{\mathrm{HF}}R_{\mathrm{HM}} + \varphi_{\mathrm{M}}\xi_{\mathrm{M}}\lambda_{\mathrm{HM}}R_{\mathrm{HM}}\\
&\quad - (\phi_1^{\mathrm{M}} + \lambda_{\mathrm{T}} + \mu_{\mathrm{M}} + \delta_{\mathrm{HM}})I_{\mathrm{HM}}\\
\frac{dR_{\mathrm{HM}}}{dt} &= \phi_1^{\mathrm{M}} I_{\mathrm{HM}} - (\varphi_{\mathrm{M}}\lambda_{\mathrm{HF}} + \varphi_{\mathrm{M}}\xi_{\mathrm{M}}\lambda_{\mathrm{HM}} + \mu_{\mathrm{M}} + \lambda_{\mathrm{T}})R_{\mathrm{HM}}\\
\frac{dE_{\mathrm{MT}}}{dt} &= (1 - \psi_1^{\mathrm{M}})\lambda_{\mathrm{T}}(S_{\mathrm{M}} + R_{\mathrm{HM}} + \sigma_{\mathrm{M}}T_{\mathrm{MT}}) + \phi_2^{\mathrm{M}} I_{\mathrm{HE}}^{\mathrm{M}} - (\varepsilon_1^{\mathrm{M}}\lambda_{\mathrm{T}} + \gamma_1^{\mathrm{M}} + \lambda_{\mathrm{HF}} + \xi_{\mathrm{M}}\lambda_{\mathrm{HM}} + \mu_{\mathrm{M}})E_{\mathrm{MT}}\\
\frac{dI_{\mathrm{MT}}}{dt} &= \psi_1^{\mathrm{M}}\lambda_{\mathrm{T}}(S_{\mathrm{M}} + R_{\mathrm{HM}} + \sigma_{\mathrm{M}}T_{\mathrm{MT}}) + \varepsilon_1^{\mathrm{M}}\lambda_{\mathrm{T}}E_{\mathrm{MT}} + \gamma_1^{\mathrm{M}}E_{\mathrm{MT}} + \phi_3^{\mathrm{M}} I_{\mathrm{HA}}^{\mathrm{M}}\\
&\quad - (r_1^{\mathrm{M}} + \mu_{\mathrm{M}} + \delta_{\mathrm{MT}} + \lambda_{\mathrm{HF}} + \xi_{\mathrm{M}}\lambda_{\mathrm{HM}})I_{\mathrm{MT}}\\
\frac{dT_{\mathrm{MT}}}{dt} &= r_1^{\mathrm{M}} I_{\mathrm{MT}} - (\sigma_{\mathrm{M}}\lambda_{\mathrm{T}} + \lambda_{\mathrm{HF}} + \xi_{\mathrm{M}}\lambda_{\mathrm{HM}} + \mu_{\mathrm{M}})T_{\mathrm{MT}}\\
\frac{dI_{\mathrm{HE}}^{\mathrm{M}}}{dt} &= (1 - \psi_2^{\mathrm{M}})\lambda_{\mathrm{T}}I_{\mathrm{HM}} + \lambda_{\mathrm{HF}}E_{\mathrm{MT}} + \xi_{\mathrm{M}}\lambda_{\mathrm{HM}}E_{\mathrm{MT}} - (\varepsilon_2^{\mathrm{M}}\lambda_{\mathrm{T}} + \gamma_2^{\mathrm{M}} + \mu_{\mathrm{M}} + \phi_2^{\mathrm{M}} + \delta_{\mathrm{HM1}})I_{\mathrm{HE}}^{\mathrm{M}}\\
\frac{dI_{\mathrm{HA}}^{\mathrm{M}}}{dt} &= \psi_2^{\mathrm{M}}\lambda_{\mathrm{T}}I_{\mathrm{HM}} + \varepsilon_2^{\mathrm{M}}\lambda_{\mathrm{T}}I_{\mathrm{HE}}^{\mathrm{M}} + \gamma_2^{\mathrm{M}}I_{\mathrm{HE}}^{\mathrm{M}} + \lambda_{\mathrm{HF}}I_{\mathrm{MT}} + \xi_{\mathrm{M}}\lambda_{\mathrm{HM}}I_{\mathrm{MT}} - (r_2^{\mathrm{M}} + \mu_{\mathrm{M}} + \delta_{\mathrm{MT1}} + \delta_{\mathrm{HM2}} + \phi_3^{\mathrm{M}})I_{\mathrm{HA}}^{\mathrm{M}}
\end{aligned}
$$

3.6.2 Description of model equations

The total sexually active population at time t, denoted by $N_{\mathrm{H}}(t)$, is divided into two classes, namely the total female population ($N_{\mathrm{HF}}(t)$) and the total male population ($N_{\mathrm{HM}}(t)$), respectively. The total female population is further subdivided into sixteen mutually-exclusive compartments: Susceptible females ($S_{\mathrm{F}}(t)$), females vaccinated against HPV ($V_{\mathrm{HF}}(t)$), females infected with HPV ($I_{\mathrm{HF}}(t)$), females who have recovered from or cleared HPV infection ($R_{\mathrm{HF}}(t)$), females with persistent HPV infection ($P_{\mathrm{HF}}(t)$), females with cervical cancer ($C_{\mathrm{F}}(t)$), females who have recovered from cervical cancer ($R_{\mathrm{F}}^{\mathrm{c}}(t)$) , females with latent TB ($E_{\mathrm{F}}(t)$), females with active TB infection ($I_{\mathrm{F}}(t)$), females treated of TB ($T_{\mathrm{FT}}(t)$), females dually infected with HPV and latent TB ($I_{\mathrm{HE}}^{\mathrm{F}}(t)$), females dually infected with HPV and active TB $I_{\mathrm{HA}}^{\mathrm{F}}$, females dually infected with persistent HPV and latent TB, ($P_{\mathrm{HE}}^{\mathrm{F}}(t)$) females dually infected with persistent HPV and active ($P_{\mathrm{HA}}^{\mathrm{F}}(t)$), females dually infected with cervical cancer and latent TB ($C_{\mathrm{FE}}(t)$), females dually infected with cervical cancer and active TB ($C_{\mathrm{FA}}(t)$).

Similarly, the total male population is subdivided into eight mutually exclusive compartments: Susceptible males ($S_{\mathrm{M}}(t)$), males infected with HPV ($I_{\mathrm{HM}}(t)$), males who have recovered from or cleared HPV infection ($R_{\mathrm{HM}}(t)$), males with latent TB ($E_{\mathrm{MT}}(t)$), males with active TB ($I_{\mathrm{MT}}(t)$), males treated of TB ($T_{\mathrm{MT}}(t)$), males dually infected with HPV and latent TB ($I_{\mathrm{HE}}^{\mathrm{M}}(t)$), males dually infected with HPV and active TB ($I^{\mathrm{M}}_{\mathrm{HA}}(t)$). Thus

$$N_{\mathrm{H}}(t) = N_{\mathrm{HF}}(t) + N_{\mathrm{HM}}(t)$$

where

$$N_{\mathrm{HF}} = S_{\mathrm{F}} + V_{\mathrm{HF}} + I_{\mathrm{HF}} + R_{\mathrm{HF}} + P_{\mathrm{HF}} + C_{\mathrm{F}} + R^{c}_{\mathrm{F}} + E_{\mathrm{FT}} + I_{\mathrm{FT}} + T_{\mathrm{FT}} + I^{\mathrm{F}}_{\mathrm{HE}} + I^{\mathrm{F}}_{\mathrm{HA}} + P^{\mathrm{F}}_{\mathrm{HE}} + P^{\mathrm{F}}_{\mathrm{HA}} + C_{\mathrm{FE}} + C_{\mathrm{FA}}$$

$$N_{\mathrm{HM}} = S_{\mathrm{M}} + I_{\mathrm{HM}} + R_{\mathrm{HM}} + E_{\mathrm{MT}} + I_{\mathrm{MT}} + T_{\mathrm{MT}} + I^{\mathrm{M}}_{\mathrm{HE}} + I^{\mathrm{M}}_{\mathrm{HA}}$$

The population of susceptible females ($S_{\mathrm{F}}(t)$) is generated by the recruitment of female individuals (at a rate Λ_{F}). A fraction, $0 < f < 1$, of recruited female individuals are vaccinated against HPV. Unvaccinated susceptible females acquire HPV infection following effective contacts with HPV infected male individuals (that is, those in the I_{HM}, $I^{\mathrm{M}}_{\mathrm{HA}}$, $I^{\mathrm{M}}_{\mathrm{HE}}$ classes) at a rate λ_{HM}, and contacts with HPV infected females (that is, those in the (I_{HF}, $I^{\mathrm{F}}_{\mathrm{HA}}$, $I^{\mathrm{F}}_{\mathrm{HE}}$, $P^{\mathrm{F}}_{\mathrm{HA}}$, $P^{\mathrm{F}}_{\mathrm{HE}}$ classes) at a rate $\xi_{\mathrm{F}}\lambda_{\mathrm{HF}}$, Also, unvaccinated susceptible females acquire TB infection following effective contacts with TB infected individuals (that is, those in the $I_{\mathrm{MT}}, I_{\mathrm{FT}}, C_{\mathrm{FA}}, I^{\mathrm{F}}_{\mathrm{HA}}, P^{\mathrm{F}}_{\mathrm{HA}}, I^{\mathrm{M}}_{\mathrm{HA}}$ classes) at a rate λ_{T}, where:

$$\lambda_{\mathrm{HM}} = \frac{\beta_{\mathrm{M}}(1 - c_{\mathrm{M}}\epsilon_{\mathrm{M}})[I_{\mathrm{HM}} + \theta_{\mathrm{T}}(I^{\mathrm{M}}_{\mathrm{HA}} + \omega_{\mathrm{T}} I^{\mathrm{M}}_{\mathrm{HE}})]}{N_{\mathrm{HM}}}, \tag{3.30}$$

$$\lambda_{\mathrm{HF}} = \frac{\beta_{\mathrm{F}}(1 - c_{\mathrm{F}}\epsilon_{\mathrm{F}})[I_{\mathrm{HF}} + \omega_p P_{\mathrm{HF}} + \theta_{\mathrm{T}}(I^{\mathrm{F}}_{\mathrm{HA}} + \omega_{\mathrm{T}} I^{\mathrm{F}}_{\mathrm{HE}} + \omega_p P^{\mathrm{F}}_{\mathrm{HA}} + \omega_{\mathrm{T}}\omega_p P^{\mathrm{F}}_{\mathrm{HE}})]}{N_{\mathrm{HF}}}, \tag{3.31}$$

$$\lambda_{\mathrm{T}} = \frac{\beta_{\mathrm{T}}[I_{\mathrm{MT}} + I_{\mathrm{FT}} + C_{\mathrm{FA}} + \eta_p(I^{\mathrm{F}}_{\mathrm{HA}} + \omega_p P^{\mathrm{F}}_{\mathrm{HA}} + I^{\mathrm{M}}_{\mathrm{HA}})]}{N_{\mathrm{H}}} \tag{3.32}$$

ξ_{F} is a modification parameter which accounts for the transmissibility of HPV from female-to-female. The parameters $\theta_{\mathrm{T}}(\theta_{\mathrm{T}} \geq 1)$ is a modification parameter accounting for the increased infectiousness of dually infected individuals due to tuberculosis, $\omega_{\mathrm{T}}(\omega_{\mathrm{T}} \leq 1)$ is a modification parameter accounting for reduced infectiousness of dually infected individuals due to latent TB. $\eta_p(\eta_p \geq 1)$ is a modification parameter accounting for the increased infectiousness of dually infected individuals due to HPV while $\omega_p(\omega_p \leq 1)$ is a modification parameter accounting for the reduced infectiousness of singly infected and dually infected individuals due to persistent HPV infection. This population is further reduced by natural death (at a rate μ_{F}; natural death occurs in all female epidemiological compartments at this rate). In (3.30), β_{M} is the effective contact rate for male-to-female transmission of HPV infection. β_{M} is the product of ϱ_{F} and β_1^{M} (that is, $\beta_{\text{M}} = \varrho_{\text{F}}\beta_1^{\text{M}}$), where β_1^{M} denotes the probability of transmitting HPV infection from male-to-female, and ϱ_{F} denotes the rate at which females acquire new sexual partners, whereas, In (3.31), β_{F} is the effective contact rate for female-to-male transmission of HPV infection. β_{F} is the product of ϱ_{M} and β_1^{F} (that is, $\beta_{\text{F}} = \varrho_{\text{M}}\beta_1^{\text{F}}$), where β_1^{F} denotes the probability of transmitting HPV infection from female-to-male, and ϱ_{M} denotes the rate at which males acquire new sexual partners. In (3.32), β_{T} denotes the effective contact rate for TB transmission.The parameter $p_{\text{C}}^{\text{F}} = c_{\text{F}}\epsilon_{\text{F}}$ (with $0 < p_{\text{C}}^{\text{F}} < 1$) is the female condom-induced preventability level (it is the product of condom compliance ($0 \leq c_{\text{F}} \leq 1$) and condom efficacy ($0 < \epsilon_{\text{F}} < 1$)) for females, while $p_{\text{C}}^{\text{M}} = c_{\text{M}}\epsilon_{\text{M}}$ (with $0 < p_{\text{C}}^{\text{M}} < 1$) is the male condom-induced preventability level. Marfatis *et al.* (2015) reported that condoms are effective and offers adequate protection (more than 90%) against sexually-transmitted diseases, though condom compliance depends on the behavioural attitude of individuals (Hegamin-Younger *et al.,* 2014). Thus,

$$\frac{dS_{\text{F}}}{dt} = (1-f)\Lambda_{\text{F}} - (\lambda_{\text{HF}} + \xi_{\text{F}}\lambda_{\text{HF}} + \mu_{\text{F}} + \lambda_{\text{T}})S_{\text{F}}$$

The population of females vaccinated against HPV ($V_{\text{HF}}(t)$) is increased by the vaccination of the fraction f, of unvaccinated susceptible females against HPV (at the rate $f\Lambda_{\text{F}}$). The population is reduced following acquisition of HPV from infected male individuals at a rate $(1-\pi_{\text{F}})\lambda_{\text{HM}}$ and from infected female individuals at a rate $(1-\pi_{\text{F}})\xi_{\text{F}}\lambda_{\text{HF}}$, where π_{F} accounts for HPV vaccine efficacy for females. The population is further reduced by the acquisition of TB following effective contacts with individuals infected with TB at rate λ_{T}. Thus,

$$\frac{dV_{\text{HF}}}{dt} = f\Lambda_{\text{F}} - (1-\pi_{\text{F}})\lambda_{\text{HM}}V_{\text{HF}} - (1-\pi_{\text{F}})\xi_{\text{F}}\lambda_{\text{HF}}V_{\text{HF}} - (\mu_{\text{F}} + \lambda_{\text{T}})V_{\text{HF}}$$

The population of female individuals infected with HPV ($I_{\text{HF}}(t)$) is increased by susceptible and vaccinated female individuals infected with HPV at the rate λ_{HM} and $\xi_{\text{F}}\lambda_{\text{HF}}$ as well as $(1-\pi_{\text{F}})\lambda_{\text{HM}}$ and $(1-\pi_{\text{F}})\xi_{\text{F}}\lambda_{\text{HF}}$ respectively. The population is also increased by females dually infected with HPV and active TB who recover from TB at a rate r_2^{F}. It is increased by the infection of females who have recovered from or have been treated of TB. It is further increased following the reinfection of females who have cleared or recovered naturally from HPV at the rate $\varphi_{\text{F}}\lambda_{\text{HM}}$ and $\varphi_{\text{F}}\xi_{\text{F}}\lambda_{\text{HM}}$. This class is reduced following natural recovery from HPV, acquisition of TB, natural death and disease induced death at the rates ϕ_1^{F}, λ_{T}, μ_{F} and δ_{HF} respectively. Thus

$$\frac{dI_{\text{HF}}}{dt} = \lambda_{\text{HM}} S_{\text{F}} + \xi_{\text{F}} \lambda_{\text{HF}} S_{\text{F}} + (1-\pi_{\text{F}})\lambda_{\text{HM}} V_{\text{HF}} + \xi_{\text{F}}\lambda_{\text{HF}} V_{\text{HF}} + r_2^{\text{F}} I_{\text{HA}}^{\text{F}} + \lambda_{\text{HM}} T_{\text{FT}} + \xi_{\text{F}}\lambda_{\text{HF}} T_{\text{FT}} + \varphi_{\text{F}}\lambda_{\text{HM}} R_{\text{HF}} \\ + \varphi_{\text{F}}\xi_{\text{F}}\lambda_{\text{HF}} R_{\text{HF}} - (\phi_1^{\text{F}} + \lambda_{\text{T}} + \mu_{\text{F}} + \delta_{\text{HF}}) I_{\text{HF}}$$

The population of female individuals who have recovered from HPV ($R_{\text{HF}}(t)$) is increased by a fraction $\kappa_1^{\text{F}}\phi_1^{\text{F}}$ of individuals who recover naturally from HPV. It is further increased by a fraction $\chi_1^{\text{F}}\rho_1^{\text{F}}$ of females who recover from persistent HPV infection. This population is reduced following reinfection with HPV at a rate φ_{F} and $\varphi_{\text{F}}\xi_{\text{F}}$, acquisition of TB at rate λ_{T} and natural death at the rate μ_{F}. Thus,

$$\frac{dR_{\text{HF}}}{dt} = \kappa_1^{\text{F}}\phi_1^{\text{F}} I_{\text{HF}} + \chi_1^{\text{F}}\rho_1^{\text{F}} P_{\text{HF}} - (\varphi_{\text{F}}\lambda_{\text{HM}} + \varphi_{\text{F}}\xi_{\text{F}}\lambda_{\text{HF}} + \mu_{\text{F}} + \lambda_{\text{T}})$$

The population of female individuals with persistent HPV infection ($P_{\text{HF}}(t)$) is increased by a fraction $(1-\kappa_1^{\text{F}})$ of infected female individuals who develop persistent HPV infection. It is further increased by female individuals dually infected with persistent HPV and active TB who recover from persistent HPV. This population is reduced following progression out of P_{HF} at a rate ρ_1^{F} acquisition of TB at a rate λ_{T} and natural death at the rate μ_{F}. Thus

$$\frac{dP_{\text{HF}}}{dt} = (1-\kappa_1^{\text{F}})\phi_1^{\text{F}} I_{\text{HF}} + r_3^{\text{F}} P_{\text{HA}}^{\text{F}} - (\rho_1^{\text{F}} + \mu_{\text{F}} + \lambda_{\text{T}}) P_{\text{HF}}$$

The population of females with cervical cancer ($C_{\text{F}}(t)$) is increased by a fraction, $(1-\chi_1^{\text{F}})\rho_1^{\text{F}}$ of females with persistent HPV who develop cervical cancer. It is further increased by females dually infected with cervical cancer and active TB who recover from TB. This population is reduced following treatment, natural death, disease induced death and acquisition of TB at the rates τ_1^{F}, μ_{F}, δ_{CF} and λ_{T} respectively. Thus,

$$\frac{dC_{\text{F}}}{dt} = (1-\chi_1^{\text{F}})\rho_1^{\text{F}} P_{\text{HF}} + r_4^{\text{F}} C_{\text{FA}} - (\tau_1^{\text{F}} + \mu_{\text{F}} + \delta_{\text{CF}} + \lambda_{\text{T}}) C_{\text{F}}$$

The population of female individuals who have recovered from cancer ($R_{\text{F}}^{c}(t)$) is increased by female individuals treated of cervical cancer at the rate τ_1^{F}. It is decreased following acquisition of TB and natural death at the rate λ_{T} and μ_{F} respectively. Thus,

$$\frac{dR^c_{\text{F}}}{dt} = \tau^{\text{F}}_1 C_{\text{F}} - (\mu_{\text{F}} + \lambda_{\text{T}}) R^c_{\text{F}}$$

The population of female individuals with latent TB ($E_{\text{FT}}(t)$), is increased by a fraction, $(1 - \psi^{\text{F}}_1)$ of susceptible females, females vaccinated against HPV and females who have recovered from HPV and females who recover from cervical cancer who acquire TB at the rate λ_{T}. This population is increased by the reinfection of female individuals treated of TB at the rate $\sigma_{\text{F}}\lambda_{\text{T}}$, where σ_{F} is a modification parameter accounting for the reduced susceptibility of treated female individuals relative to susceptible female individuals. This is further increased by female individuals dually infected with HPV and latent TB, females dually infected with persistent HPV and latent TB, and females dually infected with cervical cancer and latent TB who recover from HPV, persistent HPV and cervical cancer respectively. The population is reduced following exogenous re-infection of females with latent TB, progression to active TB, acquisition of HPV from infected males and females, and natural death at the rates ε^{F}_1, λ_{T}, γ^{F}_1, λ_{HM}, $\xi_{\text{F}}\lambda_{\text{HF}}$, and μ_{F} respectively. Thus

$$\begin{aligned} \frac{dE_{\text{FT}}}{dt} &= (1 - \psi^{\text{F}}_1)\lambda_{\text{T}}(S_{\text{F}} + V_{\text{HF}} + R_{\text{HF}} + R^c_{\text{F}} + \sigma_{\text{F}} T_{\text{FT}}) + \phi^{\text{F}}_2 \kappa^{\text{F}}_2 I^{\text{F}}_{\text{HE}} + \chi^{\text{F}}_2 \rho^{\text{F}}_2 P^{\text{F}}_{\text{HE}} + \tau^{\text{F}}_2 C_{\text{FE}} \\ &\quad - (\varepsilon^{\text{F}}_1 \lambda_{\text{T}} + \gamma^{\text{F}}_1 + \lambda_{\text{HM}} + \xi_{\text{F}}\lambda_{\text{HF}} + \mu_{\text{F}}) E_{\text{FT}} \end{aligned}$$

The population of female individuals with active TB ($I_{\text{FT}}(t)$) is increased by a fraction, ψ^{F}_1, of susceptible females, females vaccinated against HPV and females who have recovered from HPV, females who recover from cervical cancer who acquire TB at the rate λ_{T}. This population is increased by the reinfection of female individuals treated of TB at the rate $\sigma_{\text{F}}\lambda_{\text{T}}$ where σ_{F} is a modification parameter accounting for the reduced susceptibility of treated female individuals relative to susceptible female individuals. This is further increased by female individuals dually infected with HPV and active TB, females dually infected with persistent HPV and active TB, and females dually infected with cervical cancer and active TB who recover from HPV, persistent HPV and cervical cancer respectively. The population is further increased by the exogenous re-infection of females with latent TB, progression to active TB by females with latent TB. This population is reduced following recovery from TB, disease induced death, acquisition of HPV from infected males and females and natural death at the rates r^{F}_1, δ_{FT}, λ_{HM}, $\xi_{\text{F}}\lambda_{\text{HF}}$ and μ_{F} respectively.

Thus

$$\begin{aligned}\frac{dI_{\mathrm{FT}}}{dt} &= \psi_1^{\mathrm{F}}\lambda_{\mathrm{T}}(S_{\mathrm{F}} + V_{\mathrm{HF}} + R_{\mathrm{HF}} + R_{\mathrm{F}}^{c} + \sigma_{\mathrm{F}} T_{\mathrm{FT}}) + \varepsilon_1^{\mathrm{F}}\lambda_{\mathrm{T}} E_{\mathrm{FT}} + \gamma_1^{\mathrm{F}} E_{\mathrm{FT}} + \phi_3^{\mathrm{F}}\kappa_3^{\mathrm{F}} I_{\mathrm{HA}}^{\mathrm{F}} \\ &\quad + \chi_3^{\mathrm{F}}\rho_3^{\mathrm{F}} P_{\mathrm{HA}}^{\mathrm{F}} + \tau_3^{\mathrm{F}} C_{\mathrm{FA}} - (r_1^{\mathrm{F}} + \mu_{\mathrm{F}} + \delta_{\mathrm{FT}} + \lambda_{\mathrm{HM}} + \xi_{\mathrm{F}}\lambda_{\mathrm{HF}}) I_{\mathrm{FT}}\end{aligned}$$

The population of females treated of TB ($T_{\mathrm{FT}}(t)$) is increased by the treatment of females with active TB at the rate r_1^{F}. This population is reduced following reinfection of females treated of TB, acquisition of HPV from infected males and females, and natural death at the rates $\sigma_{\mathrm{F}}\lambda_{\mathrm{T}}$, λ_{HM}, $\xi_{\mathrm{F}}\lambda_{\mathrm{HF}}$ and μ_{F}. Thus

$$\frac{dT_{\mathrm{FT}}}{dt} = r_1^{\mathrm{F}} I_{\mathrm{FT}} - (\sigma_{\mathrm{F}}\lambda_{\mathrm{T}} + \lambda_{\mathrm{HM}} + \xi_{\mathrm{F}}\lambda_{\mathrm{HF}} + \mu_{\mathrm{F}}) T_{\mathrm{FT}}$$

The population of females dually infected with HPV and latent TB ($I_{\mathrm{HE}}^{\mathrm{F}}(t)$) is increased by a fraction, $(1 - \psi_2^{\mathrm{F}})$ of females infected with HPV who acquire TB at the rate λ_{T} This population is further increased following acquisition of HPV by females with latent TB at the rates λ_{HM} and $\xi_{\mathrm{F}}\lambda_{\mathrm{HF}}$. This population is reduced by the exogenous reinfection of females dually infected with HPV and latent TB, progression to active TB, natural death, recovery from HPV only and HPV induced death at the rates $\varepsilon_2^{\mathrm{F}}$, λ_{T}, γ_2^{F}, μ_{F}, ϕ_2^{F} and δ_{HF1} respectively. Thus

$$\frac{dI_{\mathrm{HE}}^{\mathrm{F}}}{dt} = (1 - \psi_2^{\mathrm{F}})\lambda_{\mathrm{T}} I_{\mathrm{HF}} + \lambda_{\mathrm{HM}} E_{\mathrm{FT}} + \xi_{\mathrm{F}}\lambda_{\mathrm{HF}} E_{\mathrm{FT}} - (\varepsilon_2^{\mathrm{F}}\lambda_{\mathrm{T}} + \gamma_2^{\mathrm{F}} + \mu_{\mathrm{F}} + \phi_2^{\mathrm{F}} + \delta_{\mathrm{HF1}}) I_{\mathrm{HE}}^{\mathrm{F}}$$

The population of females dually infected with HPV and active TB ($I_{\mathrm{HA}}^{\mathrm{F}}(t)$) is increased by a fraction, ψ_2^{F}, of females infected with HPV who acquire TB at the rate λ_{T}. This population is increased by the exogenous reinfection of females dually infected with HPV and latent TB, and progression to active TB at the rates $\varepsilon_2^{\mathrm{F}}\lambda_{\mathrm{T}}$ and γ_2^{F}respectively. This population is further increased following acquisition of HPV by females with active TB at the rates λ_{HM} and $\xi_{\mathrm{F}}\lambda_{\mathrm{HF}}$. The population is reduced following recovery from TB only, natural death, TB induced death, HPV induced death and recovery from HPV at the rates r_2^{F}, μ_{F}, δ_{FT1}, δ_{HF2} and ϕ_2^{F} respectively. Thus

$$\frac{dI_{\mathrm{HA}}^{\mathrm{F}}}{dt} = \psi_2^{\mathrm{F}}\lambda_{\mathrm{T}} I_{\mathrm{HF}} + \varepsilon_2^{\mathrm{F}}\lambda_{\mathrm{T}} I_{\mathrm{HE}}^{\mathrm{F}} + \gamma_2^{\mathrm{F}} I_{\mathrm{HE}}^{\mathrm{F}} + \lambda_{\mathrm{HM}} I_{\mathrm{FT}} + \xi_{\mathrm{F}}\lambda_{\mathrm{HF}} I_{\mathrm{FT}} - (r_2^{\mathrm{F}} + \mu_{\mathrm{F}} + \delta_{\mathrm{FT1}} + \delta_{\mathrm{HF2}} + \phi_2^{\mathrm{F}}) I_{\mathrm{HA}}^{\mathrm{F}}$$

The population of female individuals with cervical cancer and latent TB ($C_{\mathrm{FE}}(t)$) is increased by a fraction, $(1 - \psi_4^{\mathrm{F}})$, of female individuals with cervical cancer who acquire TB at a rate λ_{T}. It is further increased by a fraction, $(1-\chi_2^{\mathrm{F}})\rho_4^{\mathrm{F}}$, of female individuals dually infected with latent TB and persistent HPV infection who develop cancer. This population is reduced following exogenous reinfection and progression to active TB by female individuals dually infected with cervical cancer and with latent TB at the rates $\varepsilon_4^{\mathrm{F}}\lambda_{\mathrm{T}}$ and γ_4^{F} respectively. It is further reduced following cancer induced death, natural death and recovery from cancer at the rates δ_{CF}, μ_{F} and τ_2^{F} respectively. Thus

$$\frac{dC_{\mathrm{FE}}}{dt} = (1-\psi_4^{\mathrm{F}})\lambda_{\mathrm{T}}C_{\mathrm{F}} + (1-\chi_2^{\mathrm{F}})\rho_4^{\mathrm{F}}P_{\mathrm{HE}}^{\mathrm{F}} - (\varepsilon_4^{\mathrm{F}}\lambda_{\mathrm{T}} + \gamma_4^{\mathrm{F}} + \delta_{\mathrm{CF}} + \mu_{\mathrm{F}} + \tau_2^{\mathrm{F}})$$

The population of female individuals infected with cervical cancer and active TB $(C_{\mathrm{FA}}(t))$ is increased by a fraction, ψ_4^{F} of female individuals with cervical cancer who acquire TB at a rate λ_{T} It is further increased by a fraction $(1-\chi_3^{\mathrm{F}})\rho_3^{\mathrm{F}}$, of female individuals dually infected with active TB and persistent HPV infection who develop cancer. This population is further increased following exogenous reinfection and progression to active TB by female individuals dually infected cervical cancer and with latent TB at the rates $\varepsilon_4^{\mathrm{F}}\lambda_{\mathrm{T}}$ and γ_4^{F} respectively. It is reduced following recovery from TB, TB induced death, cancer induced death, natural death and recovery from cancer at the rates r_2^{F}, δ_{FT1}, δ_{CF}, μ_{F}, and τ_3^{F} respectively. Thus

$$\frac{dC_{\mathrm{FA}}}{dt} = \psi_4^{\mathrm{F}}\lambda_{\mathrm{T}}C_{\mathrm{F}} + \varepsilon_4^{\mathrm{F}}\lambda_{\mathrm{T}}C_{\mathrm{FE}} + \gamma_4^{\mathrm{F}}C_{\mathrm{FE}} + (1-\chi_3^{\mathrm{F}})\rho_3^{\mathrm{F}}P_{\mathrm{HA}}^{\mathrm{F}} - (r_2^{\mathrm{F}} + \delta_{\mathrm{FT1}} + \delta_{\mathrm{CF}} + \mu_{\mathrm{F}} + \tau_3^{\mathrm{F}})C_{\mathrm{FA}}$$

The population of susceptible male individuals S_{M} is increased by the recruitment of sexually active males at the rate Λ_{M}. This population is reduced following effective contacts with HPV infected female and male individuals and natural death at the rates λ_{HF}, $\xi_{\mathrm{M}}\lambda_{\mathrm{HM}}$, and μ_{M} respectively. It is further reduced following effective contacts with TB infected individuals at the rate λ_{T}. ξ_{M} is a modification parameter which accounts for the transmissibility of HPV from male-to-male. Thus

$$\frac{dS_{\mathrm{M}}}{dt} = \Lambda_{\mathrm{M}} - (\lambda_{\mathrm{HF}} + \xi_{\mathrm{M}}\lambda_{\mathrm{HM}} + \mu_{\mathrm{M}} + \lambda_{\mathrm{T}})S_{\mathrm{M}}$$

The population of male individuals infected with HPV $(I_{\mathrm{HM}}(t))$ is increased by susceptible male individuals infected with HPV at the rate λ_{HF} and $\xi_{\mathrm{M}}\lambda_{\mathrm{HM}}$. The population is also increased by males dually infected with HPV and active TB who recover from TB at a rate r_2^{M}. It is increased following the infection of males who have recovered from or have been treated of TB. The population is further increased by the reinfection of males who have naturally recovered from or have cleared

HPV at the rate $\varphi_{M}\lambda_{HF}$ and $\varphi_{M}\xi_{M}\lambda_{HM}$ This population is reduced following natural recovery from HPV, acquisition of TB, natural death and HPV induced death at the rates ϕ_1^{M}, λ_{T}, μ_{M} and δ_{HM} respectively. Thus

$$\begin{aligned}\frac{dI_{HM}}{dt} &= \lambda_{HF}S_{M} + \xi_{M}\lambda_{HM} + r_2^{M}I_{HA}^{M} + \lambda_{HF}T_{MT} + \xi_{M}\lambda_{HM}T_{MT} + \varphi_{M}\lambda_{HF}R_{HM} + \varphi_{M}\xi_{M}\lambda_{HM}R_{HM} \\ &\quad - (\phi_1^{M} + \lambda_{T} + \mu_{M} + \delta_{HM})I_{HM}\end{aligned}$$

The population of male individuals who have recovered from HPV ($R_{HM}(t)$) is increased following natural recovery from HPV at the rate ϕ_1^{M} . It is reduced by the reinfection of males who have recovered naturally from HPV at the rates $\varphi_{M}\lambda_{HF}$ and $\varphi_{M}\xi_{M}\lambda_{HM}$. It is further reduced following natural death effective contacts with individuals infected with TB and at the rates μ_{M} and λ_{T}. Thus

$$\frac{dR_{HM}}{dt} = \phi_1^{M}I_{HM} - (\varphi_{M}\lambda_{HF} + \varphi_{M}\xi_{M}\lambda_{HM} + \mu_{M} + \lambda_{T})R_{HM}$$

The population of male individuals with latent TB ($E_{MT}(t)$) is increased by a fraction, $(1-\psi_1^{M})$, of susceptible males and males who have recovered from HPV who acquire TB at the rate λ_{T}. This population is increased by the reinfection of male individuals treated of TB at the rate $\sigma_{M}\lambda_{T}$ where σ_{M} is a modification parameter accounting for the reduced susceptibility of treated male individuals relative to susceptible male individuals. This is further increased by male individuals dually infected with HPV and latent TB who recover from HPV at the rate ϕ_2^{M}. The population is reduced following exogenous re-infection of males with latent TB, progression to active TB, acquisition of HPV from infected females and males, and natural death at the rates $\varepsilon_1^{M}\lambda_{T}$, γ_1^{M}, λ_{HF}, $\xi_{M}\lambda_{HM}$ and μ_{M} respectively. Thus

$$\frac{dE_{MT}}{dt} = (1-\psi_1^{M})\lambda_{T}(S_{M} + R_{HM} + \sigma_{M}T_{MT}) + \phi_2^{M}I_{HE}^{M} - (\varepsilon_1^{M}\lambda_{T} + \gamma_1^{M} + \lambda_{HF} + \xi_{M}\lambda_{HM} + \mu_{M})E_{MT}$$

The population of male individuals with active TB ($I_{MT}(t)$), is increased by a fraction, ψ_1^{M} of susceptible males, males who have recovered from HPV who acquire TB at the rate λ_{T}, This population is increased by the reinfection of a fraction ψ_1^{M} of male individuals treated of TB at the rate $\sigma_{M}\lambda_{T}$ where σ_{M} is a modification parameter accounting for the reduced susceptibility of treated male individuals relative to susceptible male individuals. This population is further increased by male individuals dually infected with HPV and active TB who recover from HPV. The population is further increased by the exogenous re-infection and progression to active TB by males with latent TB. This population is reduced following recovery from TB, TB induced death, acquisition of HPV from infected females and males and natural death at the rates r_1^{M}, δ_{MT}, λ_{HF}, $\xi_{M}\lambda_{HM}$ and μ_{M} respectively. Thus

$$\frac{dI_{MT}}{dt} = \psi_1^{M}\lambda_{T}(S_{M} + R_{HM} + \sigma_{M}T_{MT}) + \varepsilon_1^{M}\lambda_{T}E_{MT} + \gamma_1^{M}E_{MT} + \phi_3^{M}I_{HA}^{M} - (r_1^{M} + \delta_{MT} + \lambda_{HF} + \xi_{M}\lambda_{HM} + \mu_{M})I_{MT}$$

The population of male individuals who have been treated of TB ($T_{MT}(t)$) is increased following the treatment of male individuals with TB at the rate r_1^{M}. This population is reduced following reinfection with TB, acquisition of HPV from infected males and females and natural death at the rates $\sigma_{M}\lambda_{T}$, λ_{HF}, $\xi_{M}\lambda_{HM}$ and μ_{M} respectively. Thus

$$\frac{dT_{MT}}{dt} = r_1^{M}I_{MT} - (\sigma_{M}\lambda_{T} + \lambda_{HF} + \xi_{M}\lambda_{HM} + \mu_{M})T_{MT}$$

The population of males dually infected with HPV and latent TB ($I_{HE}^{M}(t)$) is increased by a fraction, $(1 - \psi_2^{M})$ of males infected with HPV who acquire TB at the rate λ_{T}. This population is further increased following acquisition of HPV by males with latent TB at the rates λ_{HF} and $\xi_{M}\lambda_{HM}$. This population is reduced by the exogenous reinfection of males dually infected with HPV and latent TB, progression to active TB, natural death, recovery from HPV only and HPV induced death at the rates $\varepsilon_2^{M}\lambda_{T}$, γ_2^{M}, μ_{M}, ϕ_2^{M} and δ_{HM1} respectively. Thus

$$\frac{dI_{HE}^{M}}{dt} = (1 - \psi_2^{M})\lambda_{T}I_{HM} + \lambda_{HF}E_{MT} + \xi_{M}\lambda_{HM}E_{MT} - (\varepsilon_2^{M}\lambda_{T} + \gamma_2^{M} + \mu_{M} + \phi_2^{M} + \delta_{HM1})I_{HE}^{M}$$

The population of males dually infected with HPV and active TB ($I_{HA}^{M}(t)$) is increased by a fraction, ψ_2^{M} of males infected with HPV who acquire TB at the rate λ_{T}. This population is increased by the exogenous reinfection of males dually infected with HPV and latent TB, and progression to active TB at the rates ε_2^{M} and γ_2^{M} respectively. This population is further increased following acquisition of HPV by males with active TB at the rates λ_{HF} and $\xi_{M}\lambda_{HM}$. The population is reduced following recovery from TB only, natural death, TB induced death, HPV induced death and recovery from HPV at the rates r_2^{M}, μ_{M}, δ_{MT1}, δ_{HM2} and ϕ_3^{M}. Thus

$$\frac{dI_{HA}^{M}}{dt} = \psi_2^{M}\lambda_{T}I_{HM} + \varepsilon_2^{M}\lambda_{T}I_{HE}^{M} + \gamma_2^{M}I_{HE}^{M} + \lambda_{HF}I_{MT} + \xi_{M}\lambda_{HM}I_{MT} - (r_2^{M} + \mu_{M} + \delta_{MT1} + \delta_{HM2} + \phi_3^{M})I_{HA}^{M}$$

The population of females dually infected with persistent HPV and latent TB ($P^{\text{F}}_{\text{HE}}(t)$) is increased by a fraction, $(1-\psi^{\text{F}}_3)$ of females infected with persistent HPV who acquire TB at the rate λ_{T}. This population is further increased following progression to persistent HPV stage by a fraction $(1-\kappa^{\text{F}}_1)$ of females dually infected with persistent HPV and latent TB. This population is reduced by the exogenous reinfection of females dually infected with persistent HPV and latent TB, progression to active TB, transition out of ($P^{\text{F}}_{\text{HE}}(t)$) class and natural death at the rates $\varepsilon^{\text{F}}_3\lambda_{\text{T}}$, γ^{F}_3, ρ^{F}_3 and μ_{F} respectively. Thus,

$$\frac{dP^{\text{F}}_{\text{HE}}}{dt} = (1-\psi^{\text{F}}_3)\lambda_{\text{T}}P_{\text{HF}} + (1-\kappa^{\text{F}}_2)\psi^{\text{F}}_2 I^{\text{F}}_{\text{HE}} - (\varepsilon^{\text{F}}_3\lambda_{\text{T}} + \gamma^{\text{F}}_3 + \rho^{\text{F}}_3 + \mu_{\text{F}})P^{\text{F}}_{\text{HE}}$$

The population of females dually infected with persistent HPV and active TB ($P^{\text{F}}_{\text{HA}}(t)$) is increased by a fraction, ψ^{F}_3 of females infected with persistent HPV who acquire TB at the rate λ_{T}. This population is also increased following exogenous re-infection and slow progression to active TB stage by females dually infected with persistent HPV and latent TB ($P^{\text{F}}_{\text{HE}}(t)$) at the rates $\varepsilon^{\text{F}}_3\lambda_{\text{T}}$ and γ^{F}_3, respectively. The population is further increased by a fraction $(1-\kappa^{\text{F}}_3)\phi^{\text{F}}_3$ of females dually infected with HPV and active TB ($I^{\text{F}}_{\text{HA}}(t)$), who develop persistent HPV infection. This population is decreased following recovery from TB, TB-induced death, transition out of ($P^{\text{F}}_{\text{HA}}(t)$) class and natural death at the rates r^{F}_3, δ_{FT2}, ρ^{F}_3 and μ_{F}, respectively. Thus,

$$\frac{dP^{\text{F}}_{\text{HA}}}{dt} = \psi^{\text{F}}_3\lambda_{\text{T}}P_{\text{HF}} + \varepsilon^{\text{F}}_3\lambda_{\text{T}}P^{\text{F}}_{\text{HE}} + \gamma^{\text{F}}_3 P^{\text{F}}_{\text{HE}} + (1-\kappa^{\text{F}}_3)\phi^{\text{F}}_3 I^{\text{F}}_{\text{HA}} - (r^{\text{F}}_3 + \delta_{\text{FT2}} + \rho^{\text{F}}_3 + \mu_{\text{F}})P^{\text{F}}_{\text{HA}}$$

The dynamics of the HPV-only sub-model will be studied subject to the group contact constraint given by

$$\varrho_{\text{M}}N_{\text{HM}} = \varrho_{\text{F}}N_{\text{F}}, \tag{3.33}$$

Chapter 4

Results and Discussion

4.1 Mathematical analysis of the treatment model (3.19)

4.1.1 Basic properties of the Treatment model (3.19)

Positivity and boundedness of solutions

For the model (3.19) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all time (t). In other words, solutions of the model system (3.19) with positive initial data will remain positive for all time $t > 0$.

Theorem 4.1. *Let the initial data be*

$S_f > 0, V_f > 0, A_f > 0, I_f > 0, P_f > 0, R_f > 0, T_f > 0, C_f^a > 0, C_f^c > 0, R_f^a > 0, R_f^c > 0, S_m > 0, V_m > 0, \quad A_m > 0, I_m > 0, P_m > 0, R_m > 0, T_m > 0, C_m^a > 0, R_m^a > 0$

Then the solutions

$(S_f, V_f, A_f, I_f, P_f, R_f, T_f, C_f^a, C_f^c, R_f^a, R_f^c, S_m, V_m, A_m, I_m, P_m, R_m, T_m, C_m^a, R_m^a)$

of the model (3.19) *are positive for all time* $t > 0$.

Proof. Let

$t_1 = \sup\{t > 0 : S_f > 0, V_f > 0, A_f > 0, I_f > 0, P_f > 0, R_f > 0, T_f > 0, C_f^a > 0, C_f^c > 0, R_f^a > 0, R_f^c > 0, S_m > 0, V_m > 0, A_m > 0, I_m > 0, P_m > 0, R_m > 0, T_m > 0, C_m^a > 0, R_m^a > 0 \in [0, t]\}$.

Thus, $t_1 > 0$.

We have, from the first equation of the system (3.19) that

$$\frac{dS_f}{dt} = (1-f)\Lambda_f - (\lambda_m + \mu_f)S_f$$

which can be re-written as

$$\frac{d}{dt}\left\{S_f(t)\exp\left[\int\limits_0^t \lambda_m(u)du + \mu_f t\right]\right\} = (1-f)\Lambda_f \exp\left[\int\limits_0^t \lambda_m(u)du + \mu_f t\right]$$

Hence:

$$\frac{d}{dt}\left\{S_f(t_1)\exp\left[\int\limits_0^{t_1} \lambda_m(u)du + \mu_f t_1\right]\right\} - S_f(0) = (1-f)\Lambda_f \int_0^{t_1} \exp\left[\int\limits_0^{x} \lambda_m(u)du + \mu_f x\right] dx$$

so that

$$\begin{aligned} S_f(t_1) = S_f(0)\exp\left[-\int\limits_0^{t_1} \lambda_m(u)du - \mu_f t_1\right] + \exp\left[-\int\limits_0^{t_1} \lambda_m(u)du - \mu_f t_1\right] \\ \times (1-f)\Lambda_f \int_0^{t_1} \exp\left[\int\limits_0^{x} (\lambda_m(u)du + \mu_f x\right] dx > 0 \end{aligned}$$

Similarly, it can be shown that:

$V_f > 0, A_f > 0, I_f > 0, P_f > 0, R_f > 0, T_f > 0, C_f^a > 0, C_f^c > 0, R_f^a > 0, R_f^c > 0, S_m > 0, V_m > 0, A_m > 0, I_m > 0, P_m > 0, R_m > 0, T_m > 0, C_m^a > 0, R_m^a > 0.$

□

4.1.2 Invariant regions

The model (3.19) will be analyzed in a biologically feasible region as follows. We first show that the system (3.19) is dissipative (that is, all feasible solutions are uniformly-bounded) in a proper subset $\mathcal{D} \subset \Re_+^{20}$. The system (3.19) is split into two parts, namely, the female population (N_f) and the male population (N_m).

Consider the feasible region $\mathcal{D} = \mathcal{D}_f \cup \mathcal{D}_m \subset \Re_+^{11} \times \Re_+^{9}$,

with:

$$\mathcal{D}_f = \Big\{(S_f, V_f, A_f, I_f, P_f, R_f, T_f, C_f^a, C_f^c, R_f^a, R_f^c) \in \mathfrak{R}_+^{11} : S_f + V_f + A_f + I_f + P_f + R_f + T_f + C_f^a + C_f^c \\ + R_f^a + R_f^c \leq \frac{\Lambda_f}{\mu_f}\Big\}$$

and

$$\mathcal{D}_m = \Big\{(S_m, V_m, A_m, I_m, P_m, R_m T_m, C_m^a, R_m^a) \in \mathfrak{R}_+^{9} : S_m + V_m + A_m + I_m + P_m + R_m + T_m + C_m^a \\ + R_m^a \leq \frac{\Lambda_m}{\mu_m}\Big\}$$

The following steps are followed to establish the positive invariance of $\mathcal{D}$ (i.e. solutions in $\mathcal{D}$ remain in $\mathcal{D}$ for all time $t > 0$).

Adding the first eleven and the last nine equations in the differential system (3.19) gives

$$\begin{aligned} \frac{dN_f}{dt} &= \Lambda_f - \mu_f N_f(t) - [\delta_f I_f + \sigma_f \delta_f T_f + \delta_f^a C_f^a + \delta_f^c C_f^c] \\ \frac{dN_m}{dt} &= \Lambda_m - \mu N_m(t) - [\delta_m I_m + \sigma_m \delta_m T_m + \delta_m^a C_m^a] \end{aligned} \tag{4.1}$$

where $\delta_f = \min\{\delta_f, \sigma_f\delta_f, \delta_f^a, \delta_f^c\}$ and $\delta_m = \min\{\delta_m, \sigma_m\delta_m, \delta_m^a\}$.

From (4.1), we have that

$$\begin{aligned} \frac{dN_f}{dt} &\leq \Lambda_f - \mu_f N_f(t), \quad \text{and} \\ \frac{dN_m}{dt} &\leq \Lambda_m - \mu_m N_m(t). \end{aligned}$$

Using the Comparison theorem (Lakshmikantham, et al., 1989), we have that $N_f(t) \leq N_f(0)\mathrm{e}^{-\mu_f t} + \frac{\Lambda_f}{\mu_f}(1 - \mathrm{e}^{-\mu_f t})$ and $N_m(t) \leq N_m(0)\mathrm{e}^{-\mu_m t} + \frac{\Lambda_m}{\mu_m}(1 - \mathrm{e}^{-\mu_m t})$. In particular, $N_f(t) \leq \frac{\Lambda_f}{\mu_f}$ and $N_m(t) \leq \frac{\Lambda_m}{\mu_m}$ if $N_f(0) \leq \frac{\Lambda_f}{\mu_f}$ and $N_m(0) \leq \frac{\Lambda_m}{\mu_m}$ respectively. Thus, the region $\mathcal{D}$ is positively invariant. Hence, it is sufficient to consider the dynamics of the flow generated by the system (3.19) in $\mathcal{D}$. In this region, the model can be considered as being epidemiologically and mathematically well-posed (Hethcote, 2000). Thus, every solution of the model (3.19) with initial conditions in $\mathcal{D}$ remains in $\mathcal{D}$ for all time $t > 0$. Therefore, the $\omega-$limit sets of the system (3.19) are contained in $\mathcal{D}$. This result can be summarized thus.

Lemma 4.2. The region $\mathcal{D} = \mathcal{D}_f \cup \mathcal{D}_m \subset \mathfrak{R}_+^{11} \times \mathfrak{R}_+^{9}$ is positively-invariant for the model (3.19) with initial conditions in $\mathfrak{R}_+^{20}$.

4.1.3 Local stability of Disease-Free Equilibrium (DFE)

The model (3.19) has a DFE, obtained by setting the right-hand sides of the equations in model (3.19) to zero, given by

$$\begin{aligned}\xi_0 &= (S_f^*, V_f^*, A_f^*, I_f^*, P_f^*, R_f^*, T_f^*, C_f^{a*}, C_f^{c*}, R_f^{a*}, R_f^{c*}, S_m^*, V_m^*, A_m^*, I_m^*, P_m^*, R_m^*, T_m^*, C_m^{a*}, R_m^{a*}) \\ &= (S_f^*, V_f^*, 0, 0, 0, 0, 0, 0, 0, 0, 0, S_m^*, V_m^*, 0, 0, 0, 0, 0, 0, 0)\end{aligned} \tag{4.2}$$

with

$$S_f^* = \frac{(1-f)\Lambda_f}{\mu_f}, \quad V_f^* = \frac{f\Lambda_f}{\mu_f}, S_m^* = \frac{(1-m)\Lambda_m}{\mu_m}, \quad \text{and} \quad V_m^* = \frac{m\Lambda_m}{\mu_m}$$

The linear stability of the disease free equilibrium, (ξ_0) can be established using the next generation operator method on the system (3.19). Using the notation in van den Driessche and Watmough (2002), the matrix $\mathcal{F}_i$ (of new infections) and the matrix $\mathcal{V}_i$ (of the transfer of individuals between compartments) are respectively, given by

$$\mathcal{F}_i = \begin{bmatrix} \lambda_m[S_f + (1-\pi_f)V_f] \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ \lambda_f[S_m + (1-\pi_m)V_m] \end{bmatrix}, \quad \mathcal{V}_i = \begin{bmatrix} (\gamma_f + \mu_f)A_f - \kappa_f\lambda_f R_f - (1-\eta_f)\varepsilon_f T_f \\ (\mu_f + \delta_f + \phi_f + \tau_f)I_f - \gamma_f A_f - \eta_f\varepsilon_f T_f \\ (\alpha_f + \mu_f)P_f - \phi_f(1-\psi_f)I_f \\ (\mu_f + \sigma_f\delta_f + \varepsilon_f)T_f - \tau_f I_f \\ (\mu_f + \delta_f^a + \kappa_f^a)C_f^a - \alpha_f\nu_f\omega_f P_f \\ (\mu_f + \delta_f^c + \kappa_f^c)C_f^c - \alpha_f\nu_f(1-\omega_f)P_f \\ (\gamma_m + \mu_m)A_m - \kappa_m\lambda_m R_m - (1-\eta_m)\varepsilon_m T_m \\ (\mu_m + \delta_m + \phi_m + \tau_m)I_m - \gamma_m A_m - \eta_m\varepsilon_m T_m \\ (\alpha_m + \mu_m)P_m - \phi_m(1-\psi_m)I_m \\ (\mu_m + \sigma_m\delta_m + \varepsilon_m)T_m - \tau_m I_m \\ (\mu_m + \delta_m^a + \kappa_m^a)C_m^a - \alpha_m\nu_m P_m \end{bmatrix}$$

The matrices F and V, for the new infection terms and the remaining transfer terms, evaluated at the disease free equilibrium (DFE) are, respectively, given by

$$F = \begin{bmatrix} 0_{6\times 6} & F_{12} \\ F_{21} & 0_{6\times 6} \end{bmatrix},$$

where

$$F_{12} = \begin{bmatrix} \frac{Q_1\theta_{m1}}{N_m^*} & \frac{Q_1}{N_m^*} & \frac{Q_1\theta_{m2}}{N_m^*} & \frac{Q_1\xi_m\theta_{m1}}{N_m^*} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \beta_m(1 - c_m\epsilon_m)$$

$$F_{21} = \begin{bmatrix} \frac{Q_2\theta_{f1}}{N_f^*} & \frac{Q_2}{N_f^*} & \frac{Q_2\theta_{f2}}{N_f^*} & \frac{Q_2\xi_f\theta_{f1}}{N_f^*} & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix} \beta_f(1 - c_f\epsilon_f)$$

$$V = \begin{bmatrix} M_1 & 0 & 0 & -H_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\gamma_f & M_2 & 0 & -H_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -H_3 & M_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\tau_f & 0 & M_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -H_4 & 0 & M_5 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -H_5 & 0 & 0 & M_6 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & M_7 & 0 & 0 & -H_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\gamma_m & M_8 & 0 & -H_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -H_8 & M_9 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\tau_m & 0 & M_{10} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -H_9 & 0 & M_{11} \end{bmatrix}$$

with,

$Q_1 = \frac{(1-f\pi_f)\Lambda_f}{\mu_f}$, $Q_2 = \frac{(1-m\pi_m)\Lambda_m}{\mu_m}$, $M_1 = \gamma_f + \mu_f$, $M_2 = \phi_f + \tau_f + \delta_f + \mu_f$, $M_3 = \alpha_f + \mu_f$, $M_4 = \sigma_f\delta_f + \varepsilon_f + \mu_f$, $M_5 = \kappa_f^a + \delta_f^a + \mu_f$, $M_6 = \kappa_f^c + \delta_f^c + \mu_f$, $M_7 = \gamma_m + \mu_m$, $M_8 = \phi_m + \tau_m + \delta_m + \mu_m$, $M_9 = \alpha_m + \mu_m$, $M_{10} = \sigma_m\delta_m + \varepsilon_m + \mu_m$, $M_{11} = \kappa_m^a + \delta_m^a + \mu_m$, $H_1 = (1-\eta_f)\varepsilon_f$, $H_2 = \eta_f\varepsilon_f$, $H_3 = \phi_f(1-\psi_f)$, $H_4 = \alpha_f\varphi_f\omega_f$, $H_5 = \alpha_f\varphi_f(1-\omega_f)$, $H_6 = (1-\eta_m)\varepsilon_m$, $H_7 = \eta_m\varepsilon_m$, $H_8 = \phi_m(1-\psi_m)$, and $H_9 = \alpha_m\varphi_m\omega_m$

Hence it follows from van den Driessche and Watmough (2002), that the basic reproduction number of the model (3.19) is given by

$$\mathcal{R}_T = \sqrt{\mathcal{R}_{fT}\mathcal{R}_{mT}},$$

where

$$\mathcal{R}_{fT} = \beta_f(1-c_f\epsilon_f)(1-f\pi_f)\left\{\frac{M_3M_4\gamma_f + N_{11}\theta_{f1} + N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1}}{M_3N_{14}}\right\}, \quad \text{and}$$

$$\mathcal{R}_{mT} = \beta_m(1-c_m\epsilon_m)(1-m\pi_m)\left\{\frac{M_9M_{10}\gamma_m + N_{21}\theta_{m1} + N_{22}\theta_{m2} + N_{23}\xi_m\theta_{m1}}{M_9N_{24}}\right\},$$

with,

$$N_{11} = (\alpha_f + \mu_f)\left[(\phi_f + \sigma_f + \mu_f)(\sigma_f + \varepsilon_f + \mu_f) + (\tau_f\sigma_f + \tau_f\mu_f) + (1-\eta_f)\tau_f\varepsilon_f\right],$$

$$N_{12} = \gamma_f\phi_f(1-\psi_f)(\sigma_f\delta_f + \varepsilon_f + \mu_f),$$

$$N_{13} = \gamma_f\tau_f(\alpha_f + \mu_f),$$

$$N_{14} = (\alpha_f + \mu_f)\left[\,(\gamma_f + \mu_f)((\phi_f + \delta_f)(\sigma_f\delta_f + \varepsilon_f + \mu_f) + \mu_f(\sigma_f\delta_f + \varepsilon_f + \mu_f) + \tau_f(\sigma_f\delta_f + \mu_f)) + (1-\eta_f)\mu_f\varepsilon_f\tau_f\,\right],$$

$$N_{21} = (\alpha_m + \mu_m)\left[(\phi_m + \sigma_m + \mu_m)(\sigma_m + \varepsilon_m + \mu_m) + (\tau_m\sigma_m + \tau_m\mu_m) + (1-\eta_m)\tau_m\varepsilon_m\right],$$

$$N_{22} = \gamma_m\phi_m(1-\psi_m)(\sigma_m\delta_m + \varepsilon_m + \mu_m),$$

$$N_{23} = \gamma_m\tau_m(\alpha_m + \mu_m),$$

$$N_{24} = (\alpha_m + \mu_m)\left[\,(\gamma_m + \mu_m)((\phi_m + \delta_m)(\sigma_m\delta_m + \varepsilon_m + \mu_m) + \mu_m(\sigma_m\delta_m + \varepsilon_m + \mu_m) + \tau_m(\sigma_m\delta_m + \mu_m)) + (1-\eta_m)\mu_m\varepsilon_m\tau_m\,\right].$$

Consequently, the following result follows from Theorem 2 of van den Driessche and Watmough

(2002).

Lemma 4.3. The DFE of the treatment model (3.19) is locally asymptotically stable (LAS) whenever $\mathcal{R}_T < 1$, and unstable if $\mathcal{R}_T > 1$

The threshold quantity $\mathcal{R}_T$ is the basic reproduction number for HPV infection. It measures the average number of new HPV infections that can occur when a single infected individual is introduced into a completely susceptible population (van den Driessche and Watmough, 2002; Hethcote, 2000). The quantity $\mathcal{R}_T$ is a composite product of the reproduction numbers for the females ($\mathcal{R}_{fT}$) and males ($\mathcal{R}_{mT}$), respectively. That is, while $\mathcal{R}_{fT}$ measures the average number of new HPV infections in the female population generated by the introduction of an infected female into a completely susceptible female population, $\mathcal{R}_{mT}$ measures the average number of new HPV infections in the male population when a single infected male is introduced into a completely susceptible male population. The epidemiological implication of the above Lemma is that when ($\mathcal{R}_T < 1$) a small influx of HPV-infected persons into the community will not generate large HPV outbreaks, and the disease will die out.

4.1.4 Analysis of the reproduction number

Impact of Treatment

Using the threshold parameter, $\mathcal{R}_T$, we wish to determine the effect of the treatment rates of individuals on the control of HPV in the population. Recall that

$$\mathcal{R}_T = \sqrt{\mathcal{R}_{fT}\mathcal{R}_{mT}}$$

Carrying out the partial derivatives of $\mathcal{R}_T$ (with respect to τ_f and τ_m) we have that

$$\begin{aligned}\frac{\partial \mathcal{R}_T}{\partial \tau_f} &= \frac{\partial}{\partial \tau_f}(\sqrt{\mathcal{R}_{fT}\mathcal{R}_{mT}}) = \sqrt{\mathcal{R}_{mT}}\frac{\partial}{\partial \tau_f}\sqrt{\mathcal{R}_{fT}} + \sqrt{\mathcal{R}_{fT}}\frac{\partial}{\partial \tau_f}\sqrt{\mathcal{R}_{mT}} \\ &= \sqrt{\mathcal{R}_{mT}}\frac{\partial}{\partial \tau_f}\sqrt{\mathcal{R}_{fT}}\end{aligned}$$

Also, we have that

$$\frac{\partial \mathcal{R}_T}{\partial \tau_m} = \sqrt{\mathcal{R}_{fT}}\frac{\partial}{\partial \tau_m}\sqrt{\mathcal{R}_{mT}}$$

Thus, $\frac{\partial \mathcal{R}_T}{\partial \tau_f} > 0(< 0)$ and $\frac{\partial \mathcal{R}_T}{\partial \tau_m} > 0(< 0)$ if $\frac{\partial}{\partial \tau_f}\sqrt{\mathcal{R}_{fT}} > 0(< 0)$ and $\frac{\partial}{\partial \tau_m}\sqrt{\mathcal{R}_{mT}} > 0(< 0)$, respectively. Moreover,

$$\begin{aligned}
\frac{\partial}{\partial \tau_f}\sqrt{\mathcal{R}_{fT}} &= \frac{1}{2\sqrt{\mathcal{R}_{fT}}}\frac{\partial \mathcal{R}_{fT}}{\partial \tau_f} = \frac{\beta_1^m c_1^f(1-c_m\epsilon_m)(1-f\pi_f)}{2\sqrt{\mathcal{R}_{fT}}}\frac{\partial}{\partial \tau_f}\left\{\frac{M_3M_4\gamma_f + N_{11}\theta_{f1} + N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1}}{M_3N_{14}}\right\} \\
&= \frac{\beta_1^m c_1^f(1-c_m\epsilon_m)(1-f\pi_f)}{2M_3\sqrt{\mathcal{R}_{fT}}}\left\{\frac{-M_3M_4\gamma_f N_{14}'}{N_{14}^2} + \frac{(N_{14}N_{11}'\theta_{f1} - N_{11}\theta_{f1}N_{14}')}{N_{14}^2}\right. \\
&\left. + \frac{N_{14}N_{12}'\theta_{f2} - N_{12}\theta_{f2}N_{14}'}{N_{14}^2} + \frac{N_{14}N_{13}'\xi_f\theta_{f1} - N_{13}\xi_f\theta_{f1}N_{14}'}{N_{14}^2}\right\} \\
&= \frac{\beta_1^m c_1^f(1-c_m\epsilon_m)(1-f\pi_f)}{2M_3N_{14}^2\sqrt{\mathcal{R}_{fT}}}\Big\{ -\gamma_f M_3M_4 + N_{14}(N_{11}'\theta_{f1} + N_{12}'\theta_{f2} + N_{13}'\xi_f\theta_{f1}) - N_{14}'(N_{11}\theta_{f1} \\
&+ N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1})\Big\}
\end{aligned} \tag{4.3}$$

Suppose

$$\Delta_f = -\gamma_f M_3M_4 + N_{14}(N_{11}'\theta_{f1} + N_{12}'\theta_{f2} + N_{13}'\xi_f\theta_{f1}) - N_{14}'(N_{11}\theta_{f1} + N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1}),$$

where $N_{11}' = (\alpha_f + \mu_f)\left[(\sigma_f + \mu_f) + (1-\eta_f)\varepsilon_f\right]$, $N_{12}' = 0$, $N_{13}' = \gamma_f(\alpha_f + \mu_f)$, and

$$N_{14}' = (\alpha_f + \mu_f)\left[\,(\gamma_f + \mu_f)(\sigma_f\delta_f + \mu_f) + (1-\eta_f)\mu_f\varepsilon_f\,\right].$$

we have that

$$\frac{\partial \mathcal{R}_T}{\partial \tau_f} = \frac{\beta_1^m c_1^f(1-c_m\epsilon_m)(1-f\pi_f)\sqrt{\mathcal{R}_{mT}}}{2M_3N_{14}^2\sqrt{\mathcal{R}_{fT}}}\Delta_f. \tag{4.4}$$

Also,

$$\frac{\partial \mathcal{R}_T}{\partial \tau_m} = \frac{\beta_1^f c_1^m(1-c_f\epsilon_f)(1-m\pi_m)\sqrt{\mathcal{R}_{fT}}}{2M_9N_{24}^2\sqrt{\mathcal{R}_{mT}}}\Delta_m. \tag{4.5}$$

where,

$$\Delta_m = -\gamma_m M_9M_{10} + N_{24}(N_{21}'\theta_{m1} + N_{22}'\theta_{m2} + N_{23}'\xi_m\theta_{m1}) - N_{24}'(N_{21}\theta_{m1} + N_{22}\theta_{m2} + N_{23}\xi_m\theta_{m1}),$$

$$N_{21}' = (\alpha_m + \mu_m)\left[(\sigma_m + \mu_m) + (1-\eta_m)\varepsilon_m\right], \quad N_{22}' = 0, \quad N_{23}' = \gamma_m(\alpha_m + \mu_m), \quad \textit{and}$$

$$N_{24}' = (\alpha_m + \mu_m)\left[\,(\gamma_m + \mu_m)(\sigma_m\delta_m + \mu_m) + (1-\eta_m)\mu_m\varepsilon_m\,\right].$$

From (4.4) and (4.5), we have that

$$\frac{\partial \mathcal{R}_T}{\partial \tau_f} < 0 \quad \text{if and only if} \quad \Delta_f < 0 \quad \text{and} \quad \frac{\partial \mathcal{R}_T}{\partial \tau_m} < 0 \quad \text{if and only if} \quad \Delta_m < 0.$$

Thus, the treatment of infectious individuals will result in a reduction in the value of the reproduction number ($\mathcal{R}_T$) (and, consequently, the disease burden in the community) if and only if the threshold quantity $\Delta_H = \max\{\Delta_f, \Delta_m\} < 0$. On the other hand, if $\Delta_H = \max\{\Delta_f, \Delta_m\} > 0$, then the use of treatment alone, as a control strategy against HPV, will have a negative impact on the disease burden in the population. However, if $\Delta_H = 0$, then use of treatment alone will have no impact on the disease burden in the population. This result is summarized below:

Lemma 4.4. The use of treatment will have positive (negative) impact if $\Delta_H < 0 (> 0)$ and no impact if $\Delta_f = \Delta_m = 0$.

The result in Lemma (4.4) indicates that the effectiveness of the treatment strategy is largely dependent on Δ_H.

4.1.5 Impact of condom use

We shall in this section explore the impact of condom use on the control of HPV in the population. Computing the partial derivatives of the threshold parameter, $\mathcal{R}_T$, with respect to the condom parameters (c_f, c_m, ϵ_f and ϵ_m) we have:

$$\frac{\partial \mathcal{R}_T}{\partial c_f} = -\frac{\beta_1^f c_1^m \epsilon_m (1 - m\pi_m)\sqrt{\mathcal{R}_{fT}}}{2\sqrt{\mathcal{R}_{mT}}} \left\{ \frac{M_9 M_{10}\gamma_m + N_{21}\theta_{m1} + N_{22}\theta_{m2} + N_{23}\xi_m\theta_{m1}}{M_9 N_{24}} \right\} < 0, \quad (4.6a)$$

$$\frac{\partial \mathcal{R}_T}{\partial c_m} = -\frac{\beta_1^m c_1^f \epsilon_f (1 - f\pi_f)\sqrt{\mathcal{R}_{mT}}}{2\sqrt{\mathcal{R}_{fT}}} \left\{ \frac{M_3 M_4\gamma_f + N_{11}\theta_{f1} + N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1}}{M_3 N_{14}} \right\} < 0, \quad (4.6b)$$

$$\frac{\partial \mathcal{R}_T}{\partial \epsilon_f} = -\frac{\beta_1^f c_1^m c_m (1 - m\pi_m)\sqrt{\mathcal{R}_{fT}}}{2\sqrt{\mathcal{R}_{mT}}} \left\{ \frac{M_9 M_{10}\gamma_m + N_{21}\theta_{m1} + N_{22}\theta_{m2} + N_{23}\xi_m\theta_{m1}}{M_9 N_{24}} \right\} < 0, \quad (4.6c)$$

$$\frac{\partial \mathcal{R}_T}{\partial \epsilon_m} = -\frac{\beta_1^m c_1^f c_f (1 - f\pi_f)\sqrt{\mathcal{R}_{mT}}}{2\sqrt{\mathcal{R}_{fT}}} \left\{ \frac{M_3 M_4\gamma_f + N_{11}\theta_{f1} + N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1}}{M_3 N_{14}} \right\} < 0. \quad (4.6d)$$

Clearly, the partial derivatives in (4.66) are unconditionally negative. This shows that condom use in the population (by both sexually active males and females) will always result in a reduction in the value of the reproduction number $\mathcal{R}_T$ regardless of the values of the other parameters in the expressions on the right-hand sides of (4.6a)–(4.6d)

4.1.6 Impact of vaccine

Here, we shall determine the impact of vaccination on the control of HPV in the population. Computing the partial derivatives of $\mathcal{R}_T$ with respect to the vaccine parameters (f, m, π_f and π_m) gives:

$$\frac{\partial \mathcal{R}_T}{\partial f} = -\frac{\beta_1^m c_1^f \pi_f (1 - c_m\epsilon_m)\sqrt{\mathcal{R}_{mT}}}{2\sqrt{\mathcal{R}_{fT}}}\left\{\frac{M_3M_4\gamma_f + N_{11}\theta_{f1} + N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1}}{M_3N_{14}}\right\} < 0 \tag{4.7a}$$

$$\frac{\partial \mathcal{R}_T}{\partial m} = -\frac{\beta_1^f c_1^m \pi_m (1 - c_f\epsilon_f)\sqrt{\mathcal{R}_{fT}}}{2\sqrt{\mathcal{R}_{mT}}}\left\{\frac{M_9M_{10}\gamma_m + N_{21}\theta_{m1} + N_{22}\theta_{m2} + N_{23}\xi_m\theta_{m1}}{M_9N_{24}}\right\} < 0 \tag{4.7b}$$

$$\frac{\partial \mathcal{R}_T}{\partial \pi_f} = -\frac{f\beta_1^m c_1^f (1 - c_m\epsilon_m)\sqrt{\mathcal{R}_{mT}}}{2\sqrt{\mathcal{R}_{fT}}}\left\{\frac{M_3M_4\gamma_f + N_{11}\theta_{f1} + N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1}}{M_3N_{14}}\right\} < 0 \tag{4.7c}$$

$$\frac{\partial \mathcal{R}_T}{\partial \pi_m} = -\frac{m\beta_1^f c_1^m (1 - c_f\epsilon_f)\sqrt{\mathcal{R}_{fT}}}{2\sqrt{\mathcal{R}_{mT}}}\left\{\frac{M_9M_{10}\gamma_m + N_{21}\theta_{m1} + N_{22}\theta_{m2} + N_{23}\xi_m\theta_{m1}}{M_9N_{24}}\right\} < 0 \tag{4.7d}$$

If we increase the fraction of vaccinated sexually active female (f), there will always be a corresponding decrease in the value of the reproduction number $\mathcal{R}_T$. Similarly, if we increase the efficacy of the female vaccine (π_f) and male vaccine (π_m), there will always be a corresponding decrease in the value of the reproduction number $\mathcal{R}_T$ (as shown in (4.7a)–(4.7d)). These analyses have shown that condom use and vaccination will always have a positive impact on HPV control unlike concentrating on treatment alone.

4.1.7 Existence and stability of Endemic Equilibrium of the Treatment model (3.19)

To establish the existence of endemic equilibria of model (3.19), let

$$\xi_e = (\ S_f^{**}, V_f^{**}, A_f^{**}, I_f^{**}, P_f^{**}, R_f^{**}, T_f^{**}, C_f^{a**}, C_f^{c**}, R_f^{a**}, R_f^{c**}, S_m^{**}, V_m^{**}, A_m^{**}, I_m^{**}, P_m^{**}, R_m^{**}, T_m^{**}, C_m^{a**}, R_m^{a**}\ )$$

represents any arbitrary endemic equilibrium of the model (that is, an endemic equilibrium in which at least one of the infected components is non-zero). Furthermore, let

$$\lambda_f^{**} = \frac{\beta_f(1 - c_f\epsilon_f)(I_f^{**} + \theta_{f1}A_f^{**} + \theta_{f2}P_f^{**} + \xi_f\theta_{f1}T_f^{**})}{N_f^{**}} \tag{4.8}$$

and

$$\lambda_m^{**} = \frac{\beta_m(1-c_m\epsilon_m)(I_m^{**}+\theta_{m1}A_m^{**}+\theta_{m2}P_m^{**}+\xi_m\theta_{m1}T_m^{**})}{N_m^{**}} \tag{4.9}$$

be the forces of infection for females and males, respectively, at steady-state. Solving the model (3.19) at steady-state gives:

$$\begin{aligned}
S_f^{**} &= \frac{(1-f)\Lambda_f}{(\mu_f+\lambda_m^{**})}, \quad V_f^{**} = \frac{f\Lambda_f}{[\mu_f+(1-\pi_f)\lambda_m^{**}]}\\
I_f^{**} &= \frac{\gamma_f M_3 M_4 \lambda_m^{**}[(1-\pi_f)\lambda_m^{**}+(1-f\pi_f)\mu_f](\mu_f+k_f\lambda_m^{**})}{c_{21}\lambda_m^{**3}+c_{22}\lambda_m^{**2}+c_{23}\lambda_m^{**}+c_{24}}\\
P_f^{**} &= \frac{H_3 I_f^{**}}{M_3} = \frac{H_3 M_4 \gamma_f \Lambda_f \lambda_m^{**}[(1-\pi_f)\lambda_m^{**}+(1-f\pi_f)\mu_f](\mu_f+k_f\lambda_m^{**})}{c_{21}\lambda_m^{**3}+c_{22}\lambda_m^{**2}+c_{23}\lambda_m^{**}+c_{24}}\\
T_f^{**} &= \frac{\tau_f I_f^{**}}{M_4} = \frac{M_3 \gamma_f \tau_f \Lambda_f \lambda_m^{**}[(1-\pi_f)\lambda_m^{**}+(1-f\pi_f)\mu_f](\mu_f+k_f\lambda_m^{**})}{c_{21}\lambda_m^{**3}+c_{22}\lambda_m^{**2}+c_{23}\lambda_m^{**}+c_{24}}\\
R_f^{**} &= \frac{H_{12}I_f^{**}+H_{10}P_f^{**}}{(\mu_f+k_f\lambda_f^{**})} = \frac{(M_3H_{12}+H_3H_{10})M_4\gamma_f\Lambda_f\lambda_f^{**}[(1-\pi_f)\lambda_f^{**}+(1-f\pi_f)\mu_f]}{c_{21}\lambda_m^{**3}+c_{22}\lambda_m^{**2}+c_{23}\lambda_m^{**}+c_{24}}\\
A_f^{**} &= \frac{\lambda_m^{**}S_f^{**}+(1-\pi_f)\lambda_m^{**}V_f^{**}+H_1T_f^{**}+k_f\lambda_m^{**}R_f^{**}}{M_1} = \frac{(M_2M_4-H_2\tau_f)I_f^{**}}{\gamma_f M_4}\\
C_f^{a**} &= \frac{H_4P_f^{**}}{M_5} = \frac{H_3H_4M_4\gamma_f\Lambda_f\lambda_m^{**}[(1-\pi_f)\lambda_m^{**}+(1-f\pi_f)\mu_f](\mu_f+k_f\lambda_m^{**})}{M_5\left(c_{21}\lambda_m^{**3}+c_{22}\lambda_m^{**2}+c_{23}\lambda_m^{**}+c_{24}\right)}\\
R_f^{a**} &= \frac{k_f^aC_f^{a**}}{\mu_f} = \frac{H_3H_4M_4k_f^a\gamma_f\Lambda_f\lambda_m^{**}[(1-\pi_f)\lambda_m^{**}+(1-f\pi_f)\mu_f](\mu_f+k_f\lambda_m^{**})}{\mu_f M_5\left(c_{21}\lambda_m^{**3}+c_{22}\lambda_m^{**2}+c_{23}\lambda_m^{**}+c_{24}\right)}\\
C_f^{c**} &= \frac{H_5P_f^{**}}{M_6} = \frac{H_3H_5M_4\gamma_f\Lambda_f\lambda_m^{**}[(1-\pi_f)\lambda_m^{**}+(1-f\pi_f)\mu_f](\mu_f+k_f\lambda_m^{**})}{M_6\big(c_{21}\lambda_m^{**3}+c_{22}\lambda_m^{**2}+c_{23}\lambda_m^{**}+c_{24}\big)}\\
R_f^{c**} &= \frac{k_f^cC_f^{c**}}{\mu_f} = \frac{H_3H_5M_4\gamma_f\Lambda_f k_f^c\lambda_m^{**}[(1-\pi_f)\lambda_m^{**}+(1-f\pi_f)\mu_f](\mu_f+k_f\lambda_m^{**})}{\mu_f M_6(c_{21}\lambda_m^{**3}+c_{22}\lambda_m^{**2}+c_{23}\lambda_m^{**}+c_{24}}
\end{aligned} \tag{4.10}$$

$$
\begin{aligned}
S_m^{**} &= \frac{(1-m)\Lambda_m}{(\mu_m+\lambda_f^{**})}, \quad V_m^{**} = \frac{m\Lambda_m}{[\mu_m+(1-\pi_m)\lambda_f^{**}]} \\
I_m^{**} &= \frac{\gamma_m M_9 M_{10}\lambda_f^{**}[(1-\pi_m)\lambda_f^{**}+(1-m\pi_m)\mu_m](\mu_m+k_m\lambda_f^{**})}{k_{21}\lambda_f^{**3}+k_{22}\lambda_f^{**2}+k_{23}\lambda_f^{**}+k_{24}} \\
P_m^{**} &= \frac{H_8 I_m^{**}}{M_9} = \frac{H_8 M_{10}\gamma_m\Lambda_m\lambda_f^{**}[(1-\pi_m)\lambda_f^{**}+(1-m\pi_m)\mu_m](\mu_m+k_m\lambda_f^{**})}{k_{21}\lambda_m^{**3}+k_{22}\lambda_f^{**2}+k_{23}\lambda_f^{**}+k_{24}} \\
T_m^{**} &= \frac{\tau_m I_m^{**}}{M_{10}} = \frac{M_9\gamma_m\tau_m\Lambda_m\lambda_f^{**}[(1-\pi_m)\lambda_f^{**}+(1-m\pi_m)\mu_m](\mu_m+k_m\lambda_f^{**})}{k_{21}\lambda_f^{**3}+k_{22}\lambda_f^{**2}+k_{23}\lambda_f^{**}+k_{24}} \\
R_m^{**} &= \frac{H_{12}I_m^{**}+H_{11}P_m^{**}}{(\mu_m+k_m\lambda_f^{**})} = \frac{(M_9H_{12}+H_8H_{11})M_{10}\gamma_m\Lambda_m\lambda_f^{**}[(1-\pi_m)\lambda_f^{**}+(1-m\pi_m)\mu_m]}{k_{21}\lambda_f^{**3}+k_{22}\lambda_f^{**2}+k_{23}\lambda_f^{**}+k_{24}} \\
A_m^{**} &= \frac{\lambda_f^{**}S_m^{**}+(1-\pi_m)\lambda_f^{**}V_m^{**}+H_6T_m^{**}+k_m\lambda_f^{**}R_m^{**}}{M_7} = \frac{(M_8M_{10}-H_7\tau_m)I_m^{**}}{\gamma_m M_{10}} \\
C_m^{a**} &= \frac{H_9P_m^{**}}{M_{11}} = \frac{H_8H_9M_{10}\gamma_m\Lambda_m\lambda_f^{**}[(1-\pi_m)\lambda_f^{**}+(1-m\pi_m)\mu_m](\mu_m+k_m\lambda_f^{**})}{M_{11}\left(k_{21}\lambda_f^{**3}+k_{22}\lambda_f^{**2}+k_{23}\lambda_f^{**}+C_{24}\right)} \\
R_m^{a**} &= \frac{k_m^aC_m^{a**}}{\mu_m} = \frac{H_8H_9M_{10}k_m^a\gamma_m\Lambda_m\lambda_f^{**}[(1-\pi_m)\lambda_m^{**}+(1-m\pi_m)\mu_m](\mu_m+k_m\lambda_m^{**})}{\mu_mM_{11}\left(k_{21}\lambda_f^{**3}+k_{22}\lambda_f^{**2}+k_{23}\lambda_f^{**}+k_{24}\right)}
\end{aligned}
\tag{4.11}
$$

where

$$\begin{aligned}
c_{21} &= (1-\pi_f)\kappa_f[M_1M_3(M_2M_4 - H_2\tau_f) - (M_3H_2 + H_3H_{10})\gamma_f M_4 - M_3H_1\gamma_f\tau_f] \\
&= (1-\pi_f)\,\kappa_f\big[\alpha_f\phi_f\gamma_f\varphi_f\,(1-\psi_f)\,(\sigma_f\delta_f + \xi_f + \mu_f) + (1-\eta_f)\,(\alpha_f+\mu_f)\,\tau_f\xi_f\mu_f \\
&+ \gamma_f\phi_f\psi_f\mu_f\,(\sigma_f\delta_f + \xi_f + \mu_f) + \gamma_f\,(\alpha_f+\mu_f)\,(\delta_f+\mu_f)\,(\sigma_f\delta_f + \xi_f + \mu_f) \\
&+ \mu_f\,(\alpha_f+\mu_f)\,(\phi_f+\delta_f+\mu_f)\,(\sigma_f\delta_f + \xi_f\mu_f) + \tau_f\,(\gamma_f+\mu_f)\,(\alpha_f+\mu_f)\,(\sigma_f\delta_f+\mu_f)\,\big] \\
c_{22} &= (1-\pi_f)\mu_f[M_3M_4(M_2M_4 - H_2\tau_f) - M_3H_1\gamma_f\tau_f] + (2-\pi_f)\mu_f[M_1M_3\kappa_f(M_3M_4 - H_2\tau_f) \\
&- (M_3H_2 + H_3H_{10})\gamma_f\kappa_f M_4 - M_3H_1\gamma_f\tau_f\kappa_f] \\
&= (1-\pi_f)(\alpha_f+\mu_f)\mu_f[(\gamma_f+\mu_f)(\phi_f+\delta_f)(\sigma_f\delta_f+\xi_f+\mu_f) + \mu_f(\gamma_f+\mu_f)(\sigma_f\delta_f+\xi_f+\mu_f) \\
&+ \tau_f(\gamma_f+\mu_f)(\sigma_f\delta_f+\mu_f) + (1-\eta_f)\mu_f\xi_f\tau_f] + (2-\pi_f)\mu_f\kappa_f[\alpha_f\phi_f\gamma_f\varphi_f(1-\psi_f) \\
&\times (\sigma_f\delta_f+\xi_f+\mu_f) + (1-\eta_f)(\alpha_f+\mu_f)\tau_f\xi_f\mu_f + \gamma_f\phi_f\psi_f\mu_f(\sigma_f\delta_f+\xi_f+\mu_f) + \gamma_f(\alpha_f+\mu_f) \\
&\times (\delta_f+\mu_f)(\sigma_f\delta_f+\xi_f+\mu_f) + \mu_f(\alpha_f+\mu_f)(\phi_f+\delta_f+\mu_f)(\sigma_f\delta_f+\xi_f+\mu_f) \\
&+ \tau_f(\gamma_f+\mu_f)(\alpha_f+\mu_f)(\sigma_f\delta_f+\mu_f)] \\
c_{23} &= (2-\pi_f)\mu_f^2[M_1M_3(M_2M_4 - H_2\tau_f) - M_3H_7\gamma_f\tau_f] + \mu_f^2\kappa_f[M_1M_3(M_2M_4 - H_2\tau_f) \\
&- (M_3H_{12} + H_3H_{10})\gamma_f M_4 - H_1M_3\gamma_f\tau_f] \\
&= (2-\pi_f)\mu_f^2(\alpha_f+\mu_f)[(\gamma_f+\mu_f)(\phi_f+\delta_f)(\sigma_f\delta_f+\xi_f+\mu_f) + \mu_f(\gamma_f+\mu_f) \\
&\times (\sigma_f\delta_f+\xi_f+\mu_f) + \tau_f(\gamma_f+\mu_f)(\sigma_f\delta_f+\mu_f) + (1-\eta_f)\mu_f\xi_f\tau_f] + \mu_f^2\kappa_f[\alpha_f\phi_f\gamma_f\varphi_f \\
&\times (1-\psi_f)(\sigma_f\delta_f+\xi_f+\mu_f) + (1-\eta_f)(\alpha_f+\mu_f)\tau_f\xi_f\mu_f + \gamma_f\phi_f\varphi_f\mu_f(\sigma_f\delta_f+\xi_f+\mu_f) \\
&+ \gamma_f(\alpha_f+\mu_f)(\delta_f+\mu_f)(\sigma_f\delta_f+\xi_f+\mu_f) + \mu_f(\alpha_f+\mu_f)(\phi_f+\delta_f+\mu_f)(\sigma_f\delta_f+\xi_f+\mu_f) \\
&+ \tau_f(\gamma_f+\mu_f)(\alpha_f+\mu_f)(\sigma_f\delta_f+\mu_f)] \\
c_{24} &= \mu_f^3M_3[M_1(M_2M_4 - H_2\tau_f) - H_1\gamma_f\tau_f] \\
&= \mu_f(\alpha_f+\mu_f)[(\gamma_f+\mu_f)(\phi_f+\delta_f)(\sigma_f\delta_f+\xi_f+\mu_f) + \mu_f(\gamma_f+\mu_f) \\
&\times (\sigma_f\delta_f+\xi_f+\mu_f) + \tau_f(\gamma_f+\mu_f)(\sigma_f\delta_f+\mu_f) + (1-\eta_f)\mu_f\xi_f\tau_f]
\end{aligned}$$

$$
\begin{aligned}
k_{21} &= (1-\pi_m)\kappa_m[M_7M_9(M_8M_{10}-H_7\tau_m)-(M_9H_7+H_8H_{11})\gamma_mM_{10}-M_9H_6\gamma_m\tau_m] \\
&= (1-\pi_m)\,\kappa_m\big[\alpha_m\phi_m\gamma_m\varphi_m\,(1-\psi_m)\,(\sigma_m\delta_m+\xi_m+\mu_m)+(1-\eta_m)\,(\alpha_m+\mu_m)\,\tau_m\xi_m\mu_m \\
&+\gamma_m\phi_m\psi_m\mu_m\,(\sigma_m\delta_m+\xi_m+\mu_m)+\gamma_m\,(\alpha_m+\mu_m)\,(\delta_m+\mu_m)\,(\sigma_m\delta_m+\xi_m+\mu_m) \\
&+\mu_m\,(\alpha_m+\mu_m)\,(\phi_m+\delta_m+\mu_m)\,(\sigma_m\delta_m+\xi_m\mu_m)+\tau_m\,(\gamma_m+\mu_m)\,(\alpha_m+\mu_m)\,(\sigma_m\delta_m+\mu_m)\,\big] \\
k_{22} &= (1-\pi_m)\mu_m[M_9M_{10}(M_8M_{10}-H_7\tau_m)-M_9H_6\gamma_m\tau_m]+(2-\pi_m)\mu_m[M_7M_9\kappa_m(M_9M_{10}-H_7\tau_m) \\
&-(M_9H_7+H_8H_{11})\gamma_m\kappa_mM_{10}-M_9H_6\gamma_m\tau_m\kappa_m] \\
&= (1-\pi_m)(\alpha_m+\mu_m)\mu_m[(\gamma_m+\mu_m)(\phi_m+\delta_m)(\sigma_m\delta_m+\xi_m+\mu_m)+\mu_m(\gamma_m+\mu_m)(\sigma_m\delta_m+\xi_m+\mu_m) \\
&+\tau_m(\gamma_m+\mu_m)(\sigma_m\delta_m+\mu_m)+(1-\eta_m)\mu_m\xi_m\tau_m]+(2-\pi_m)\mu_m\kappa_m[\alpha_m\phi_m\gamma_m\varphi_m(1-\psi_m) \\
&\times(\sigma_m\delta_m+\xi_m+\mu_m)+(1-\eta_m)(\alpha_m+\mu_m)\tau_m\xi_m\mu_m+\gamma_m\phi_m\psi_m\mu_m(\sigma_m\delta_m+\xi_m+\mu_m) \\
&+\gamma_m(\alpha_m+\mu_m)(\delta_m+\mu_m)(\sigma_m\delta_m+\xi_m+\mu_m)+\mu_m(\alpha_m+\mu_m)(\phi_m+\delta_m+\mu_m)(\sigma_m\delta_m+\xi_m+\mu_m) \\
&+\tau_m(\gamma_m+\mu_m)(\alpha_m+\mu_m)(\sigma_m\delta_m+\mu_m)] \\
k_{23} &= (2-\pi_m)\mu_m^2[M_7M_9(M_8M_{10}-H_7\tau_m)-M_9H_7\gamma_m\tau_m]+\mu_m^2\kappa_m[M_7M_9(M_8M_{10}-H_7\tau_m) \\
&-(M_9H_{13}+H_8H_{11})\gamma_mM_{10}-H_6M_9\gamma_m\tau_m] \\
&= (2-\pi_m)\mu_m^2(\alpha_m+\mu_m)[(\gamma_m+\mu_m)(\phi_m+\delta_m)(\sigma_m\delta_m+\xi_m+\mu_m)+\mu_m(\gamma_m+\mu_m) \\
&\times(\sigma_m\delta_m+\xi_m+\mu_m)+\tau_m(\gamma_m+\mu_m)(\sigma_m\delta_m+\mu_m)+(1-\eta_m)\mu_m\xi_m\tau_m]+\mu_m^2\kappa_m[\alpha_m\phi_m\gamma_m\varphi_m \\
&\times(1-\psi_m)(\sigma_m\delta_m+\xi_m+\mu_m)+(1-\eta_m)(\alpha_m+\mu_m)\tau_m\xi_m\mu_m+\gamma_m\phi_m\varphi_m\mu_m(\sigma_m\delta_m+\xi_m+\mu_m) \\
&+\gamma_m(\alpha_m+\mu_m)(\delta_m+\mu_m)(\sigma_m\delta_m+\xi_m+\mu_m)+\mu_m(\alpha_m+\mu_m)(\phi_m+\delta_m+\mu_m)(\sigma_m\delta_m+\xi_m+\mu_m) \\
&+\tau_m(\gamma_m+\mu_m)(\alpha_m+\mu_m)(\sigma_m\delta_m+\mu_m)] \\
k_{24} &= \mu_m^3M_9[M_7(M_8M_{10}-H_7\tau_m)-H_6\gamma_m\tau_m] \\
&= \mu_m(\alpha_m+\mu_m)[(\gamma_m+\mu_m)(\phi_m+\delta_m)(\sigma_m\delta_m+\xi_m+\mu_m)+\mu_m(\gamma_m+\mu_m) \\
&\times(\sigma_m\delta_m+\xi_m+\mu_m)+\tau_m(\gamma_m+\mu_m)(\sigma_m\delta_m+\mu_m)+(1-\eta_m)\mu_m\xi_m\tau_m]
\end{aligned}
$$

with,

$H_{10}=\alpha_f(1-\varphi_f)$, $H_{11}=\alpha_m(1-\varphi_m)$.

Substituting (4.10) and (4.11) in (4.8) and (4.9), and simplifying, gives

$$
\lambda_f^{**}=\frac{\lambda_m^{**}[d_{03}(\lambda_m^{**})^2+d_{02}\lambda_m^{**}+d_{01}]}{d_{33}(\lambda_m^{**})^3+d_{22}(\lambda_m^{**})^2+d_{11}\lambda_m^{**}+d_{00}} \tag{4.12}
$$

and

$$\lambda_m^{**} = \frac{\lambda_f^{**}[g_{03}(\lambda_f^{**})^2 + g_{02}\lambda_f^{**} + g_{01}]}{g_{33}(\lambda_f^{**})^3 + g_{22}(\lambda_f^{**})^2 + g_{11}\lambda_f^{**} + g_{00}} \tag{4.13}$$

By substituting (4.12) into (4.13), we have that the positive (endemic) equilibria of the model (3.19) satisfy the following polynomial (in terms of λ_m):

$$s_1(\lambda_m^{**})^9 + s_2(\lambda_m^{**})^8 + s_3(\lambda_m^{**})^7 + s_4(\lambda_m^{**})^6 + s_5(\lambda_m^{**})^5 + s_6(\lambda_m^{**})^4 + s_7(\lambda_m^{**})^3 + s_8(\lambda_m^{**})^2 + s_9\lambda_m^{**} + s_{10} = 0 \tag{4.14}$$

where the coefficients of (4.14) are given in **Appendix A** . The components of the EEP are then obtained by solving for λ_m^{**} from the polynomial (4.14), and substituting the positive values of λ_m^{**} into the expressions in (4.11) [noting the coefficients in Appendix A]. Furthermore, it follows from Appendix A, that the coefficient s_1, is always positive and s_{10} is positive (negative) if $\mathcal{R}_T$ is less (greater) than unity. Using the Descartes Rule of Signs (Wang, 2004), the following result can be deduced.

Theorem 4.5. *The treatment model* (3.19) *with* $\delta_f = \delta_f^a = \delta_f^c = \delta_m = \delta_m = \delta_m^a = 0$ *could have two or more endemic equilibria if* $\mathcal{R}_T < 1$*, and at least one positive endemic equilibrium whenever* $\mathcal{R}_T > 1$

The first part of Theorem 4.5 suggests the possibility of backward bifurcation in the treatment model (3.19) with negligible disease-induced deaths (i.e., $\delta_f = \delta_f^a = \delta_f^c = \delta_m = \delta_m = \delta_m^a = 0$) when $\mathcal{R}_T < 1$. The phenomenon of backward bifurcation, which has been observed in numerous disease transmission dynamics (for instance, in Gumel (2012) as well as in Iboi and Okuonghae (2016)), is typically characterized by the coexistence of a stable DFE and a stable endemic equilibrium when the associated reproduction number of the model is less than unity. The public health implication of backward bifurcation is that the classical requirement of having the the basic reproduction number less than unity, while necessary, is no longer sufficient for effective control of the disease in the population. Such control measures will now be dependent on the initial sizes of the sub-population of the model (3.19).

4.1.8 Backward Bifurcation Analysis of the Treatment model (3.19)

It is instructive to characterize the type of bifurcation the model (3.19) may undergo. We claim the following result.

Theorem 4.6. *The model* (3.19) *exhibits backward bifurcation at* $\mathcal{R}_T = 1$ *whenever a bifurcation coefficient, denoted by a (given by* (4.17)*), is positive.*

Proof:

Proof. Suppose

$$\xi_e = \big(S_f^{**}, V_f^{**}, A_f^{**}, I_f^{**}, P_f^{**}, R_f^{**}, T_f^{**}, C_f^{a**}, C_f^{c**}, R_f^{a**}, R_f^{c**}, S_m^{**}, V_m^{**}, A_m^{**}, I_m^{**}, P_m^{**}, R_m^{**},$$
$$T_m^{**}, C_m^{a**}, R_m^{a**}\big)$$

represents any arbitrary endemic equilibrium of the model (that is, an endemic equilibrium in which at least one of the infected components is non-zero). The existence (or otherwise) of backward bifurcation will be explored using the Centre Manifold Theory (Carr, 1981, Castillo-Chavez and Song, 2004). To apply this theory, it is necessary to carry out the following change of variables.

Let $S_f = x_1$, $V_f = x_2$, $A_f = x_3$, $I_f = x_4$, $P_f = x_5$, $R_f = x_6$, $T_f = x_7$, $C_f^a = x_8$, $C_f^c = x_9$, $R_f^a = x_{10}$, $R_f^c = x_{11}$

$$S_m = x_{12},\ V_m = x_{13},\ A_m = x_{14},\ I_m = x_{15},\ P_m = x_{16},\ R_m = x_{17},\ T_m = x_{18},\ C_m^a = x_{19},\ R_m^a = x_{20}$$

so that

$$N = \sum_{i=1}^{20} x_i.$$

Further, using the vector notation

$$X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}, x_{11}, x_{12}, x_{13}, x_{14}, x_{15}, x_{16}, x_{17}, x_{18}, x_{19}, x_{20})^T$$

the model (3.19) can be re-written in the form

$$\frac{dX}{dt} = F = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10}, f_{11}, f_{12}, f_{13}, f_{14}, f_{15}, f_{16}, f_{17}, f_{18}, f_{19}, f_{20})^T$$

as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} &\equiv f_1 = (1-f)\,\Lambda_f - (\lambda_m + \mu_f)\,x_1\\
\frac{dx_2}{dt} &\equiv f_2 = f\Lambda_f - \left[(1-\pi_f)\lambda_m + \mu_f\right]x_2\\
\frac{dx_3}{dt} &\equiv f_3 = \lambda_m x_1 + (1-\pi_f)\,\lambda_m x_2 + \kappa_f\lambda_m x_6 + (1-\eta_f)\,\varepsilon_f x_7 - (\gamma_f + \mu_f)\,x_3\\
\frac{dx_4}{dt} &\equiv f_4 = \gamma_f x_3 + \eta_f\varepsilon_f x_7 - (\phi_f + \tau_f + \delta_f + \mu_f)\,x_4\\
\frac{dx_5}{dt} &\equiv f_5 = \phi_f\,(1-\psi_f)\,x_4 - (\alpha_f + \mu_f)\,x_5\\
\frac{dx_6}{dt} &\equiv f_6 = \phi_f\psi_f x_4 + \alpha_f\,(1-\varphi_f)\,x_5 - (\mu_f + \kappa_f\lambda_m)\,x_6\\
\frac{dx_7}{dt} &\equiv f_7 = \tau_f x_4 - (\sigma_f\delta_f + \varepsilon_f + \mu_f)\,x_7\\
\frac{dx_8}{dt} &\equiv f_8 = \alpha_f\varphi_f\omega_f x_5 - \left(\kappa_f^a + \mu_f + \delta_f^a\right)x_8\\
\frac{dx_9}{dt} &\equiv f_9 = \alpha_f\varphi_f\,(1-\omega_f)\,x_5 - \left(\kappa_f^c + \mu_f + \delta_f^c\right)x_9\\
\frac{dx_{10}}{dt} &\equiv f_{10} = \kappa_f^a x_8 - \mu_f x_{10}\\
\frac{dx_{11}}{dt} &\equiv f_{11} = \kappa_f^c x_9 - \mu_f x_{11}\\
\frac{dx_{12}}{dt} &\equiv f_{12} = (1-m)\,\Lambda_m - (\lambda_f + \mu_m)\,x_{12}\\
\frac{dx_{13}}{dt} &\equiv f_{13} = m\Lambda_m - \left[(1-\pi_m)\lambda_f + \mu_m\right]x_{13}\\
\frac{dx_{14}}{dt} &\equiv f_{14} = \lambda_f x_{12} + (1-\pi_m)\,\lambda_f x_{13} + \kappa_m\lambda_f x_{17} + (1-\eta_m)\,\varepsilon_m x_{18} - (\gamma_m + \mu_m)\,x_{14}\\
\frac{dx_{15}}{dt} &\equiv f_{15} = \gamma_m x_{14} + \eta_m\varepsilon_m x_{18} - (\phi_m + \tau_m + \delta_m + \mu_m)\,x_{15}\\
\frac{dx_{16}}{dt} &\equiv f_{16} = \phi_m\,(1-\psi_m)\,x_{15} - (\alpha_m + \mu_m)\,x_{16}\\
\frac{dx_{17}}{dt} &\equiv f_{17} = \phi_m\psi_m x_{15} + \alpha_m\,(1-\varphi_m)\,x_{16} - (\mu_m + \kappa_m\lambda_f)\,x_{17}\\
\frac{dx_{18}}{dt} &\equiv f_{18} = \tau_m x_{15} - (\sigma_m\delta_m + \varepsilon_m + \mu_m)\,x_{18}\\
\frac{dx_{19}}{dt} &\equiv f_{19} = \alpha_m\varphi_m x_{16} - \left(\kappa_m^a + \mu_m + \delta_m^a\right)x_{19}\\
\frac{dx_{20}}{dt} &\equiv f_{20} = \kappa_m^a x_{19} - \mu_m x_{20}
\end{aligned}
\tag{4.15}
$$

where

$$
\lambda_f = \frac{\beta_f\,(1-c_f\epsilon_f)\,(x_4 + \theta_{f1}x_3 + \theta_{f2}x_5 + \xi_f\theta_{f1}x_7)}{\sum_{i=1}^{11} x_i},
$$

$$
\lambda_m = \frac{\beta_m\,(1-c_m\epsilon_m)\,(x_{15} + \theta_{m1}x_{14} + \theta_{m2}x_{16} + \xi_m\theta_{m1}x_{18})}{\sum_{i=12}^{20} x_i}
$$

$$J(\xi_0) = \begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix} \tag{4.16}$$

where

$$J_{11} = \begin{bmatrix}
-\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -M_1 & 0 & 0 & 0 & H_1 & 0 & 0 & 0 & 0 \\
0 & 0 & \gamma_f & -M_2 & 0 & 0 & H_2 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & H_3 & -M_3 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \phi_f\psi_f & H_{10} & -\mu_f & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \tau_f & 0 & 0 & -M_4 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & H_4 & 0 & 0 & -M_5 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & H_5 & 0 & 0 & 0 & -M_6 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \kappa_f^a & 0 & -\mu_f & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \kappa_f^c & 0 & -\mu_f
\end{bmatrix}$$

$$J_{12} = \begin{bmatrix}
0 & 0 & -\theta_{m1}x_1^* & -x_1^* & -\theta_{m2}x_1^* & 0 & -\theta_{m1}\xi_m x_1^* & 0 & 0 \\
0 & 0 & -\theta_{m1}(1-\pi_f)x_2^* & -(1-\pi_f)x_2^* & -\theta_{m2}(1-\pi_f)x_2^* & 0 & -\theta_{m1}\xi_m(1-\pi_f)x_2^* & 0 & 0 \\
0 & 0 & \theta_{m1}X_1^* & X_1^* & \theta_{m2}X_1^* & 0 & \theta_{m1}\xi_m X_1^* & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix} \frac{\beta_m(1-c_f\epsilon_f)}{N_m^*}$$

$$J_{21} = \begin{bmatrix} 0 & 0 & -\theta_{f1}x_{12}^* & -x_{12}^* & -\theta_{f2}x_{12}^* & 0 & -\theta_{f1}\xi_f x_{12}^* & 0 & 0 & 0 & 0 \\ 0 & 0 & -\theta_{f1}(1-\pi_m)x_{13}^* & -(1-\pi_m)x_{13}^* & -\theta_{f2}(1-\pi_m)x_{13}^* & 0 & -\theta_{f1}\xi_f(1-\pi_m)x_{13}^* & 0 & 0 & 0 & 0 \\ 0 & 0 & \theta_{f1}X_2^* & X_2^* & \theta_{f2}X_2^* & 0 & \theta_{f1}\xi_f X_2^* & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \frac{\beta_f(1-c_f\epsilon_f)}{N_f^*}$$

$$J_{22} = \begin{bmatrix} -\mu_m & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu_m & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -M_7 & 0 & 0 & 0 & H_6 & 0 & 0 \\ 0 & 0 & \gamma_m & -M_8 & 0 & 0 & H_7 & 0 & 0 \\ 0 & 0 & 0 & H_8 & -M_9 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \phi_m\psi_m & H_{11} & -\mu_m & 0 & 0 & 0 \\ 0 & 0 & 0 & \tau_m & 0 & 0 & -M_{10} & 0 & 0 \\ 0 & 0 & 0 & 0 & H_9 & 0 & 0 & -M_{11} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \kappa_m^a & -\mu_m \end{bmatrix}$$

It can be shown that the Jacobian of (4.16) has a right eigenvector (associated with the zero eigenvalue) given by

$$\mathbf{w} = [\omega_1, \omega_2, \omega_3, \omega_4, \omega_5, \omega_6, \omega_7, \omega_8, \omega_9, \omega_{10}, \omega_{11}, \omega_{12}, \omega_{13}, \omega_{14}, \omega_{15}, \omega_{16}, \omega_{17}, \omega_{18}, \omega_{19}, \omega_{20}]^T$$

where,

$$-\mu_f\omega_1 - \frac{\theta_{m1}\beta_m^*(1-c_m)x_1^*}{N_m^*}\omega_{14} - \frac{\beta_m^*(1-c_m)x_1^*}{N_m^*}\omega_{15} - \frac{\theta_{m2}\beta_m^*(1-c_m)x_1^*}{N_m^*}\omega_{16} - \frac{\theta_{m1}\xi_m\beta_m^*(1-c_m)x_1^*}{N_m^*}\omega_{18} = 0$$

$$-\mu_f\omega_2 - \frac{\theta_{m1}\beta_m^*(1-c_m)(1-\pi_f)x_2^*}{N_m^*}\omega_{14} - \frac{\beta_m^*(1-c_m)(1-\pi_f)x_2^*}{N_m^*}\omega_{15} - \frac{\theta_{m2}\beta_m^*(1-c_m)(1-\pi_f)x_2^*}{N_m^*}\omega_{16} - \frac{\theta_{m1}\xi_m\beta_m^*(1-c_m)(1-\pi_f)x_2^*}{N_m^*}\omega_{18} = 0$$

$$-M_1\omega_3 + H_1\omega_7 + \frac{\theta_{m1}\beta_m^*(1-c_m)X_1^*}{N_m^*}\omega_{14} + \frac{\beta_m^*(1-c_m)X_1^*}{N_m^*}\omega_{15} + \frac{\theta_{m2}\beta_m^*(1-c_m)X_1^*}{N_m^*}\omega_{16} - \frac{\theta_{m1}\xi_m\beta_m^*(1-c_m)X_1^*}{N_m^*}\omega_{18} = 0$$

$$\gamma_f\omega_3 - M_2\omega_4 + H_2\omega_7 = 0$$

$$H_3\omega_4 - M_3\omega_5 = 0$$

$$\phi_f \psi_f \omega_4 + H_{10}\omega_5 - \mu_f \omega_6 = 0$$

$$\tau_f \omega_4 - M_4 \omega_7 = 0$$

$$H_4 \omega_5 - M_5 \omega_8 = 0$$

$$H_5 \omega_5 - M_6 \omega_9 = 0$$

$$\kappa_f^a \omega_8 - \mu_f \omega_{10} = 0$$

$$\kappa_f^c \omega_9 - \mu_f \omega_{11} = 0$$

$$-\tfrac{\theta_{f1}\beta_f(1-c_f)x_{12}^*}{N_f^*}\omega_3 - \tfrac{\beta_f(1-c_f)x_{12}^*}{N_f^*}\omega_4 - \tfrac{\theta_{f2}\beta_f(1-c_f)x_{12}^*}{N_f^*}\omega_5 - \tfrac{\theta_{f1}\xi_f\beta_f(1-c_f)x_{12}^*}{N_f^*}\omega_7 - \mu_m \omega_{12} = 0$$

$$-\tfrac{\theta_{f1}\beta_f(1-c_f)(1-\pi_m)x_{13}^*}{N_f^*}\omega_3 - \tfrac{\beta_f(1-c_f)(1-\pi_m)x_{13}^*}{N_f^*}\omega_4 - \tfrac{\theta_{f2}\beta_f(1-c_f)(1-\pi_m)x_{13}^*}{N_f^*}\omega_5 - \tfrac{\theta_{f1}\xi_f\beta_f(1-c_f)(1-\pi_m)x_{13}^*}{N_f^*}\omega_7 - \mu_m \omega_{13} = 0$$

$$\tfrac{\theta_{f1}\beta_f(1-c_f)X_2^*}{N_f^*}\omega_3 + \tfrac{\beta_f(1-c_f)X_2^*}{N_f^*}\omega_4 + \tfrac{\theta_{f2}\beta_f(1-c_f)X_2^*}{N_f^*}\omega_5 - \tfrac{\theta_{f1}\xi_f\beta_f(1-c_f)X_2^*}{N_f^*}\omega_7 - M_7\omega_{14} + H_6\omega_{18} = 0$$

$$\gamma_m \omega_{14} - M_8 \omega_{15} + H_7 \omega_{18} = 0$$

$$H_8 \omega_{15} - M_9 \omega_{16} = 0$$

$$\phi_m \psi_m \omega_{15} + H_{11}\omega_{16} - \mu_m \omega_{17} = 0$$

$$\tau_m \omega_{15} - M_{10}\omega_{18} = 0$$

$$H_9 \omega_{16} - M_{11}\omega_{19} = 0$$

$$\kappa_m^a \omega_{19} - \mu_m \omega_{20} = 0$$

Solving, we obtain

$$
\begin{aligned}
\omega_1 &= \frac{-\beta_f(1-c_f\epsilon_f)\beta_m^*(1-c_m\epsilon_m)x_1^*X_2^*K_1K_2\omega_3}{\mu_f N_f^* N_m^* M_3M_9(M_2M_4-H_2\tau_f)N_{24}} < 0,\\
\omega_2 &= \frac{-\beta_m^*\beta_f(1-c_m\epsilon_m)(1-c_f\epsilon_f)K_1K_2(1-\pi_f)x_1^*X_2^*\omega_3}{\mu_f N_f^* N_m^* M_3M_9(M_2M_4-H_2\tau_f)N_{24}} < 0,\\
\omega_3 &= \omega_3 > 0, \quad \omega_4 = \frac{\gamma_f M_4\omega_3}{M_2M_4-H_2\tau_f} > 0, \quad \omega_5 = \frac{\gamma_f H_3 M_4\omega_3}{M_3(M_2M_4-H_2\tau_f)} > 0,\\
\omega_6 &= \frac{(\gamma_f H_{12}M_3M_4+\gamma_f H_3H_{10}M_4)\omega_3}{M_3(M_2M_4-H_2\tau_f)} > 0, \quad \omega_7 = \frac{\gamma_f\tau_f\omega_3}{M_2M_4-H_2\tau_f}, \quad \omega_8 = \frac{\gamma_f H_3H_4M_4\omega_3}{M_3M_5(M_2M_4-H_2\tau_f)} > 0,\\
\omega_9 &= \frac{\gamma_f H_3H_5M_4\omega_3}{M_3M_6(M_2M_4-H_2\tau_f)} > 0, \quad \omega_{10} = \frac{\gamma_f K_f^a H_3H_4M_4\omega_3}{\mu_f M_3M_5(M_2M_4-H_2\tau_f)} > 0,\\
\omega_{11} &= \frac{\gamma_f \kappa_f^c H_3H_5M_4\omega_3}{\mu_f M_3M_6(M_2M_4-H_2\tau_f)}, \quad \omega_{12} = -\frac{1}{\mu_m}\left\{\frac{\beta_f(1-c_f\epsilon_f)x_{12}^*K_1\omega_3}{(M_2M_3M_4-H_2M_3\tau_f)N_f^*}\right\} < 0,\\
\omega_{13} &= -\frac{1}{\mu_m}\left\{\frac{\beta_f(1-c_f\epsilon_f)(1-\pi_m)x_{13}^*K_1\omega_3}{M_3(M_2M_4-H_2\tau_f)N_f^*}\right\} < 0, \quad \omega_{14} = \frac{\beta_f(1-c_f\epsilon_f)K_1(M_8M_{10}-H_7\tau_m)X_2^*\omega_3}{N_f M_3(M_2M_4-H_2\tau_f)N_{24}} > 0,\\
\omega_{15} &= \frac{\beta_f(1-c_f\epsilon_f)K_1X_2^*M_{10}\gamma_m\omega_3}{N_f^*M_3(M_2M_4-H_2\tau_f)N_{24}} > 0, \quad \omega_{16} = \frac{\beta_f(1-c_f\epsilon_f)K_1X_2^*M_{10}\gamma_m H_8\omega_3}{N_f^*M_3M_9(M_2M_4-H_2\tau_f)N_{24}} > 0,\\
\omega_{17} &= \frac{\beta_f(1-c_f\epsilon_f)K_1X_2^*(\gamma_m H_{13}M_9M_{10}+\gamma_m H_8H_{11}M_{10})\omega_3}{\mu_m N_f^*M_3M_9(M_2M_4-H_2\tau_f)N_{24}} > 0, \quad \omega_{18} = \frac{\beta_f(1-c_f\epsilon_f)K_1X_2^*\tau_m\gamma_m\omega_3}{N_f^*M_3(M_2M_4-H_2\tau_f)N_{24}} > 0,\\
\omega_{19} &= \frac{\beta_f(1-c_f\epsilon_f)K_1X_2^*\gamma_m H_8H_9M_{10}\omega_3}{N_f^*M_3M_9M_{11}(M_2M_4-H_2\tau_f)N_{24}} > 0, \quad \omega_{20} = \frac{\beta_f(1-c_f\epsilon_f)K_1X_2^*\gamma_m K_m^a H_8H_9M_{10}\omega_3}{\mu_m M_9M_{11}(M_2M_4-H_2\tau_f)N_{24}} > 0.
\end{aligned}
$$

Furthermore, $J(\xi_0)|_{\beta_m=\beta_m^*}$ has a corresponding left eigenvector (associated with the zero eigenvalue) given by

$$v = [\nu_1,\nu_2,\nu_3,\nu_4,\nu_5,\nu_6,\nu_7,\nu_8,\nu_9,\nu_{10},\nu_{11},\nu_{12},\nu_{13},\nu_{14},\nu_{15},\nu_{16},\nu_{17},\nu_{18},\nu_{19},\nu_{20}]$$

where,

$$-M_1\nu_3 + \gamma_f\nu_4 + \tfrac{\theta_{f1}\beta_f(1-c_f)X_2^*}{N_f^*}\nu_{14} = 0$$

$$-M_2\nu_4 + H_3\nu_5 + \tau_f\nu_7 + \tfrac{\beta_f(1-c_f)X_2^*}{N_f^*}\nu_{14} = 0$$

$$-M_3\nu_5 + \tfrac{\theta_{f2}\beta_f(1-c_f)X_2^*}{N_f^*}\nu_{14} = 0$$

$$H_1\nu_3 + H_2\nu_4 - M_4\nu_7 + \tfrac{\theta_{f1}\xi_f\beta_f(1-c_f)X_2^*}{N_f^*}\nu_{14} = 0$$

$$\tfrac{\theta_{m1}\beta_m^*(1-c_m)X_1^*}{N_m^*}\nu_3 - M_7\nu_{14} + \gamma_m\nu_{15} = 0$$

$$\tfrac{\beta_m^*(1-c_m)X_1^*}{N_m^*}\nu_3 - M_8\nu_{15} + H_8\nu_{16} + \tau_m\nu_{18} = 0$$

$$\tfrac{\theta_{m2}\beta_m^*(1-c_m)X_1^*}{N_m^*}\nu_3 - M_9\nu_{16} = 0$$

$$\tfrac{\xi_m\theta_{m1}\beta_m^*(1-c_m)X_1^*}{N_m^*}\nu_3 + H_6\nu_{14} + H_7\nu_{15} - M_{10}\nu_{18} = 0$$

Solving, gives components of the left eigenvector of $J(\xi_0)|_{\beta_m=\beta_m^*}$, $\mathbf{v} = (\nu_1, \nu_2, ..., \nu_{20})$, satisfying $\mathbf{v}.\mathbf{w} = 1$ as follows:

$$\begin{aligned}
\nu_3 &= \nu_3 > 0\\
\nu_4 &= \frac{\Big\{\tau_f M_3 M_9[H_1 N_{24} N_f^* N_m^* + \theta_{f1}\xi_f\Phi] + [\Phi M_4(H_3\theta_{f2} + M_9)]\Big\}}{N_f^* N_m^* M_3 M_9 N_{24}}\nu_3 > 0\\
\nu_5 &= \frac{\theta_{f2}\beta_f\beta_m(1-c_f\epsilon_f)(1-c_m\epsilon_m)K_2X_1^*X_2^*}{N_f^*N_m^*M_3M_9N_{24}}\nu_3 > 0\\
\nu_7 &= \frac{\Big\{M_2M_3M_9[H_1N_{24}N_f^*N_m^* + \theta_{f1}\xi_f\beta_f\beta_m(1-c_f\epsilon_f)(1-c_m\epsilon_m)K_2X_1^*X_2*] + \Phi H_2(H_3\theta_{f2}+M_9)\Big\}}{N_f^*N_m^*M_3M_9N_{24}}\nu_3 > 0\\
\nu_{14} &= \frac{\beta_m^*(1-c_m\epsilon_m)K_2X_1^*}{N_m^*M_9N_{24}}\nu_3 > 0\\
\nu_{15} &= \frac{\beta_m^*(1-c_m\epsilon_m)X_1^*\Big\{(M_9M_{10} + H_8M_{10}\theta_{m2} + \xi_m\theta_{m1}\tau_mM_9)N_{24}H_6\tau_mK_2\Big\}}{N_m^*M_9N_{24}}\nu_3 > 0\\
\nu_{16} &= \frac{\theta_{m2}\beta_m^*(1-c_m\epsilon_m)X_1^*}{M_9N_m^*}\nu_3 > 0\\
\nu_{18} &= \frac{\beta_m^*(1-c_m\epsilon_m)X_1^*\Big\{H_7(M_9H_8\theta_{m2})N_{24} + \xi_m\theta_{m1}M_8M_9N_{24} + M_8K_6K_2\Big\}}{N_m^*M_9N_{24}(M_8M_{10} - H_7\tau_m)}\nu_3 > 0
\end{aligned}$$

where,

$$X_1^* = x_1^* + \{1-\pi_f\}x_2^*, \quad X_2^* = x_{12}^* + \{1-\pi_m\}x_{13}^*, \quad \Phi = \beta_f\beta_m(1-c_f\epsilon_f)(1-c_m\epsilon_m)K_2X_1^*X_2^*,$$

$$K_1 = M_3M_4\gamma_f + N_{11}\theta_{f1} + N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1}, \quad K_2 = M_9M_{10}\gamma_m + N_{21}\theta_{m1} + N_{22}\theta_{m2} + N_{23}\xi_m\theta_{m1}$$

$$M_2M_4 - H_2\tau_f = (\phi_f + \delta_f + \mu_f)(\sigma_f\delta_f + \varepsilon_f + \mu_f) + \tau_f(\sigma_f\delta_f + \mu_f) + (1-\eta_f)\varepsilon_f\tau_f > 0$$

$$M_7M_8 - H_7\tau_m = (\phi_m + \delta_m + \mu_m)(\sigma_m\delta_m + \varepsilon_m + \mu_m) + \tau_m(\sigma_m\delta_m + \mu_m) + (1-\eta_m)\varepsilon_m\tau_m > 0$$

Consider the case when $\mathcal{R}_T = 1$. Suppose, further, that β_m is chosen as a bifurcation parameter. Solving for $\beta_m = \beta_m^*$ from $\mathcal{R}_T = 1$ gives

$$\beta_m = \beta_m^* = \frac{N_fN_mM_3M_9N_{14}N_{24}}{\beta_f(1-c_f\epsilon_f)(1-c_m\epsilon_m)S_f^*S_m^*K_1K_2}$$

We have, based on Theorem 4.1 in Castillo-Chavez and Song (2004), by computing the non-zero partial derivatives of $F(x)$(evaluated at the disease free equilibrium, DFE (ε_0)) that the associated bifurcation coefficients defined by a and b, are given by

$$a = \sum_{k,i,j=1}^{n} \nu_k \omega_i \omega_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \quad \text{and} \quad b = \sum_{k,i=1}^{n} \nu_k \omega_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_S^*}(0,0),$$

are computed to be

$$\begin{aligned}
a = & \frac{-2\beta_m^*(1-c_m\epsilon_m)(\theta_{m1}\omega_{14}+\omega_{15}+\theta_{m2}\omega_{16}+\xi_m\theta_{m1}\omega_{18})\nu_3}{N_m^{*2}} \Big\{ (\omega_{12}+\omega_{13})X_1^* - \kappa_f\omega_6 N_m^* + n_2 X_1^* \\
& - (\omega_1 + (1-\pi_f)\omega_2)N_m^* \Big\} - \frac{2\beta_f(1-c_f\epsilon_f)}{N_f^{*2}}(\theta_{f1}\omega_3+\omega_4+\theta_{f2}\omega_5+\xi_f\theta_{f1}\omega_7)\nu_{14} \Big\{ (\omega_1+\omega_2)X_2^* - \kappa_m\omega_{17}N_f^* \\
& + n_1 X_2^* - (\omega_{12} + (1-\pi_m)\omega_{13})N_f^* \Big\} \\
= & \frac{-2N_{14}\omega_3\nu_3}{(M_2M_4 - H_2\tau_f)(1-f\pi_f)N_f^*N_m^*} \Big\{ (\omega_{12}+\omega_{13})X_1^* - \kappa_f\omega_6 N_m^* + n_2X_1^* - (\omega_1+(1-\pi_f)\omega_2)N_m^* \Big\} \\
& + \frac{-2N_{14}\omega_3\nu_3}{(M_2M_4 - H_2\tau_f)(1-m\pi_m)N_f^*N_m^*} \Big\{ (\omega_1+\omega_2)X_2^* - \kappa_m\omega_{17}N_f^* + n_1X_2^* - (\omega_{12}+(1-\pi_m)\omega_{13})N_f^* \Big\}
\end{aligned} \tag{4.17}$$

$$n_1 = \sum_{i=3}^{11} \omega_i, \ \ n_2 = \sum_{i=14}^{20} \omega_i$$

$$b = \sum_{k,i=1}^{20} \nu_k \omega_i \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) = \frac{(1-c_m\epsilon_m)\left[x_1^* + (1-\pi_f)x_2^*\right]}{N_m^*}\nu_3\left(\theta_{m1}\omega_{14}+\omega_{15}+\theta_{m2}\omega_{16}+\theta_{m1}\xi_m\omega_{18}\right) > 0$$

Since the bifurcation coefficient b is positive, it follows from Theorem 4.1 in Castillo-Chavez and Song (2004), that the model (3.19), or the transformed model (4.15), will undergo a backward bifurcation if the backward bifurcation coefficient, a, given by (4.17) is positive. □

The associated backward bifurcation diagram is depicted in Figure 4.1).

4.1.9 Non-existence of backward bifurcation

Theorem 4.7. *In the absence of re-infection for recovered females and males as well as imperfect vaccine* ($\kappa_f = \kappa_m = 0, \pi_f = \pi_m = 1$)*, the model* (3.19) *does not undergo backward bifurcation.*

Proof. Consider the model (3.19) with $\kappa_f = \kappa_m = 0, \pi_f = \pi_m = 1$. The expression for the backward bifurcation coefficient, a, given as (4.17) (and noting that all parameters of the model

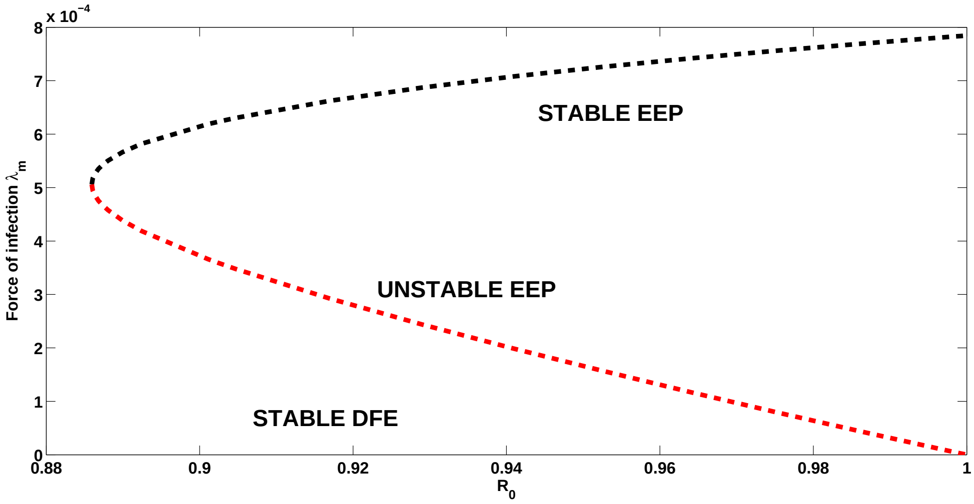


Figure 4.1: Bifurcation diagram for the model (3.19). Parameter values used are: $\beta_f = 1.76, \beta_m = 1.65, \kappa_f = \kappa_m = 15, \pi_f = 0.8, \pi_m = 0.7$. All other parameters as in Table 4.1

(3.19) are positive), reduces to:

$$a = \frac{-2N_{14}\omega_3\nu_3}{(M_2M_4 - H_2\tau_f)}\left\{\frac{n_2}{N_m^*} + \frac{n_1}{N_f^*} + \Big(\frac{1}{N_f^*} - \frac{1}{x_1^*}\Big)\omega_1 + \Big(\frac{1}{N_m^*} - \frac{1}{x_{12}^*}\Big)\omega_{12}\right\} < 0$$

since $N_f^* > x_1^*$ and $N_m^* > x_{12}^*$, then $(\frac{1}{N_f^*} - \frac{1}{x_1^*}) < 0$ and $(\frac{1}{N_m^*} - \frac{1}{x_{12}^*}) < 0$, and noting, that $n_1 > 0$ and $n_2 > 0$ while $\omega_1 < 0$ and $\omega_{12} < 0$. Hence, it follows from Theorem 4.1 in Castillo-Chavez and Song (2004), that the model (3.19) does not undergo a backward bifurcation if $\kappa_f = \kappa_m = 0, \pi_f = \pi_m = 1$. □

Hence, this study shows that the reinfection of recovered individuals and imperfect vaccine induce backward bifurcation in the HPV transmission model. A global asymptotic stability result is established below for the DFE of the model for this scenario (to completely rule out backward bifurcation in this case).

4.1.10 Global Asymptotic Stability: Special Case $\kappa_f = \kappa_m = 0, \pi_f = \pi_m = 1$

Theorem 4.8. *Consider the model* (3.19) *with* $\kappa_f = \kappa_m = 0, \pi_f = \pi_m = 1$. *The DFE, given by* (4.2), *is GAS in* $\mathcal{D}$ *whenever* $\mathcal{R}_T \leq 1$

Proof. Consider the linear Lyapunov function

$$\mathcal{L} = b_1A_f + b_2I_f + b_3P_f + b_4T_f + b_5A_m + b_6I_m + b_7P_m + b_8T_m$$

where,

$$
\begin{aligned}
b_1 &= \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_1 K_2}{N_f^* N_m^* M_3 M_9 N_{14} N_{24}}, \quad b_3 = \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_2 \theta_{f2}}{N_f^* N_m^* M_3 M_9 N_{24}} \\
b_2 &= \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_2 \left[M_1 M_3 M_4 + H_1 M_3 \tau_f \theta_{f1} + H_3 M_1 M_4 \theta_{f2} + M_1 M_3 \tau_f \xi_f \theta_{f1}\right]}{N_f^* N_m^* M_3 M_9 N_{14} N_{24}} \\
b_4 &= \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_2 \left[M_3(H_2 M_1 + H_1\gamma_f) + H_1 M_3 \tau_f \theta_{f1} + H_3(H_2 M_1 + H_1 \gamma_f)\theta_{f2} + M_1 M_2 M_3 \xi_f \theta_{f1}\right]}{N_f^* N_m^* M_3 M_9 N_{14} N_{24}} \\
b_5 &= \frac{K_2 \mathcal{R}_T}{M_9 N_{24}}, \quad b_6 = \frac{M_7 M_9 M_{10} + H_6 M_9 \tau \theta_{m1} + H_8 M_7 M_{10} \theta_{m2} + M_7 M_9 \tau_m \xi_m \theta_{m1}}{M_9 N_{24}} \\
b_7 &= \frac{\theta_{m2} \mathcal{R}_T}{M_9}, \quad b_8 = \frac{\left[M_9(H_7 M_7 + H_6 \gamma_m) + H_6 M_8 M_9 \theta_{m1} + H_8(H_7 M_7 + H_6\gamma_m)\theta_{m2} + M_7 M_8 M_9 \xi_m \theta_{m1}\right] \mathcal{R}_T}{M_9 N_{24}}
\end{aligned}
$$

$$K_1 = M_3 M_4 \gamma_f + N_{11}\theta_{f1} + N_{12}\theta_{f2} + N_{13}\xi_f\theta_{f1}, \quad K_2 = M_9 M_{10}\gamma_m + N_{21}\theta_{m1} + N_{22}\theta_{m2} + N_{23}\xi_m\theta_{m1}$$

with the Lyapunov derivative $\cdots$

$$\dot{\mathcal{L}} = b_1 \dot{A}_f + b_2 \dot{I}_f + b_3 \dot{P}_f + b_4 \dot{T}_f + b_5 \dot{A}_m + b_6 \dot{I}_m + b_7 \dot{P}_m + b_8 \dot{T}_m$$

$$
\begin{aligned}
\dot{\mathcal{L}} =& \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_1 K_2}{N_f^* N_m^* M_3 M_9 N_{14} N_{24}} \Big[\lambda_m S_f + H_1 T_f - M_1 A_f\Big] \\
&+ \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_2 [M_1 M_3 M_4 + H_1 M_3 \tau_f \theta_{f1} + H_3 M_1 M_4 \theta_{f2} + M_1 M_3 \tau_f \xi_f \theta_{f1}]}{N_f^* N_m^* M_3 M_9 N_{14} N_{24}} \Big[\gamma_f A_f + H_2 T_f - M_2 I_f\Big] \\
&+ \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_2 \theta_{f2}}{N_f^* N_m^* M_3 M_9 N_{24}} \Big[H_3 I_f - M_3 P_f\Big] \\
&+ \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_2 \Big[M_3(H_2 M_1 + H_1\gamma_f) + H_1 M_2 M_3 \theta_{f1} + H_3(H_2 M_1 + H_1\gamma_f)\theta_{f2} M_1 M_2 M_3 \xi_f \theta_{f1}\Big]}{N_f^* N_m^* M_3 M_9 N_{14} N_{24}} \Big[\tau_f I_f - M_4 T_f\Big] \\
&+ \frac{K_2 \mathcal{R}_T}{M_9 N_{24}} \Big[\lambda_f S_m + H_6 T_m - M_7 A_m\Big] \\
&+ \frac{\Big[M_7 M_9 M_{10} + H_6 M_9 \tau_m \theta_{m1} + H_8 M_7 M_{10} \theta_{m2} + M_7 M_9 \tau_m \xi_m \theta_{m1}\Big] \mathcal{R}_T}{M_9 N_{24}} \Big[\gamma_m A_m + H_7 T_m - M_8 I_m\Big] \\
&+ \frac{\theta_{m2} \mathcal{R}_T}{M_9} \Big[H_8 I_m - M_9 P_m\Big] \\
&+ \frac{\Big[M_9(H_7 M_7 + H_6\gamma_m) + H_6 M_8 M_9 \theta_{m1} + H_8(H_7 M_7 + H_6\gamma_m)\theta_{m2} M_7 M_8 M_9 \xi_m \theta_{m1}\Big] \mathcal{R}_T}{M_9 N_{24}} \Big[\tau_m I_m - M_{10} T_m\Big]
\end{aligned}
$$

$$
\begin{aligned}
\dot{\mathcal{L}} =& \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_1 K_2 \lambda_m S_f}{N_f^* N_m^* M_3 M_9 N_{14} N_{24}} - \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_2 \Big(\theta_{f1} A_f + I_f + \theta_{f2} P_f + \xi_f \theta_{f1} T_f\Big)}{N_f^* N_m^* M_9 N_{24}} \\
&+ \frac{K_2 \mathcal{R}_T \lambda_f S_f}{M_9 N_{24}} - \mathcal{R}_T \Big(\theta_{m1} A_m + I_m + \theta_{m2} P_m + \xi_m \theta_{m1} T_m\Big) \\
=& \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_1 K_2 \lambda_m S_f}{N_f^* N_m^* M_3 M_9 N_{14} N_{24}} - \mathcal{R}_T \Big(\theta_{m1} A_m + I_m + \theta_{m2} P_m + \xi_m \theta_{m1} T_m\Big) \\
&+ \frac{K_2 \mathcal{R}_T \lambda_f S_m}{M_9 N_{24}} - \frac{\beta_1^f c_1^f (1-c_f\epsilon_f) S_f^* S_m^* K_2 \Big(\theta_{f1} A_f + I_f + \theta_{f2} P_f + \xi_f \theta_{f1} T_f\Big)}{N_f^* N_m^* M_9 N_{24}}
\end{aligned}
$$

Applying the definition of the forces of infection in (3.20) and (3.21) and the group constraint in (3.22), we have that

$$
\begin{aligned}
\dot{\mathcal{L}} &\leq \frac{\mathcal{R}_T \lambda_m N_f}{c_1^m \beta_1^m (1 - c_m \epsilon_m)} (\frac{\mathcal{R}_T S_f}{N_f} - 1) + \frac{K_2 \lambda_f N_m}{M_9 N_{24}} (\frac{\mathcal{R}_T S_m}{N_m} - 1) \\
&\leq \frac{\mathcal{R}_T \lambda_m N_f}{c_1^m \beta_1^m (1 - c_m \epsilon_m)} (\mathcal{R}_T - 1) + \frac{K_2 \lambda_f N_m}{M_9 N_{24}} (\mathcal{R}_T - 1)
\end{aligned}
$$

□

Since all the model parameters and variables are non-negative, we have that $\dot{\mathcal{L}} \leq 0$ for $\mathcal{R}_T \leq 1$ (it should be noted that $\frac{S_f}{N_f} < 1, \frac{S_m}{N_m} < 1 \quad \text{and} \quad \frac{S_f^* S_m^*}{N_f^* N_m^*} < 1$) with $\dot{\mathcal{L}} = 0$ if and only if $I_f = A_f = P_f = T_f = I_m = A_m = P_m = T_m = 0$. Hence, $\mathcal{L}$ is a Lyapunov function on $\mathcal{D}$. Thus, using the La Salle Invariance Principle (La Salle and Lefschetz (1976)), $I_f \to 0, A_f \to 0, P_f \to 0, T_f \to 0, I_m \to 0, A_m \to 0, P_m \to 0, T_m \to 0$ as $t \to \infty$. Substituting $I_f = A_f = P_f = T_f = I_m = A_m = P_m = T_m = 0$ in (3.19) shows that $R_f \to 0, C_f^a \to 0, C_f^c \to 0, R_f^a \to 0, R_f^c \to 0, S_f \to S_f^*, V_f \to V_f^*, R_m \to 0, C_m^a \to 0, R_m^a \to 0, S_m \to S_m^*, V_m \to V_m^*$ as $t \to \infty$. Thus, every solution to the equations of the model (3.19) with $\kappa_f = \kappa_m = 0, \pi_f = \pi_m = 1$, with initial conditions in $\mathcal{D}$, approaches the DFE ξ_0 as $t \to 0$ whenever $\mathcal{R} \leq 1$. The epidemiological significance of the above result is that, in the absence of re-infection for recovered females and males as well as imperfect vaccine for females and males ($\kappa_f = \kappa_m = 0, \pi_f = \pi_m = 1$), HPV will be eliminated from the population if the reproduction threshold $\mathcal{R}_{\mathcal{T}} < \infty$.

4.2 Basic properties of the two-strain HPV model (3.23)

4.2.1 Positivity and boundedness of solutions

For the model (3.23) to be epidemiologically meaningful, it is important to prove that all its state variables are non-negative for all time . In other words, solutions of the model system (3.23) with positive initial data will remain positive for all time $t > 0$.

Theorem 4.9. *Let the initial data* $S_f > 0, V_f > 0, I_{f1} > 0, P_{f1} > 0, C_f > 0, R_f^c > 0, R_{f1} > 0, I_{f2} > 0, I_{f2}^p > 0, P_{f2} > 0, R_{f2} > 0, S_m > 0, I_{m1} > 0, R_{m1} > 0, I_{m2} > 0, R_{m2} > 0, I_{f12} > 0, I_{f21} > 0, M_f > 0, I_{m12} > 0, I_{m21} > 0, M_m > 0$
Then the solutions
$(S_f, V_f, I_{f1}, P_{f1}, C_f, R_f^c, R_{f1}, I_{f2}, I_{f2}^p, P_{f2}, R_{f2}, S_m, I_{m1}, R_{m1}, I_{m2}, R_{m2}, I_{f12}, I_{f21}, M_f, I_{m12}, I_{m21}, M_m)$ *of the model* (3.23) *are positive for all time* $t > 0$. *Furthermore,*

$\lim_{t\to 0} \sup N_f(t) \leq \frac{\Lambda_f}{\mu_f}$ *and* $\lim_{t\to 0} \sup N_m(t) \leq \frac{\Lambda_m}{\mu_m}$

Proof.

$$\text{Let} \quad t_1 = \sup\Big\{S_f(0) > 0, V_f(0) > 0, I_{f1}(0) > 0, P_{f1}(0) > 0, C_f(0) > 0, R_f^c(0) > 0,$$
$$R_{f1}(0) > 0, I_{f2}(0) > 0, I_{f2}^p(0) > 0, P_{f2}(0) > 0, R_{f2}(0) > 0, S_m(0) > 0, I_{m1}(0) > 0,$$
$$R_{m1}(0) > 0, I_{m2} > 0, R_{m2} > 0, I_{f12} > 0, I_{f21} > 0, M_f > 0, I_{m12} > 0, I_{m21} > 0, M_m > 0 \in [0, t]\Big\}$$

Thus, $t_1 > 0$. From the first equation of the system (3.23), we have that

$$\frac{dS_f}{dt} = (1-f)\Lambda_f - (\lambda_{m1} + \lambda_{m2} + \mu_f)\, S_f$$

which can be re-written as

$$\frac{d}{dt}\left\{S_f(t)\exp\left[\int_0^{t_1} (\lambda_{m1}(u) + \lambda_{m2}(u))\, du + \mu_f t\right]\right\} = (1-f)\,\Lambda_f \exp\left[\int_0^{t_1} (\lambda_{m1}(u) + \lambda_{m2}(u))\, du + \mu_f t\right]$$

Hence,

$$\frac{d}{dt}\left\{S_f(t_1)\exp\left[\int_0^{t_1} (\lambda_{m1}(u) + \lambda_{m2}(u)) du + \mu_f t_1\right]\right\} - S_f(0) = (1-f)\Lambda_f \int_0^{t_1} \exp\left[\int_0^{y} (\lambda_{m1}(u) + \lambda_{m2}(u)) du + \mu_f y\right] dy$$

so that

$$S_f(t_1) = S_f(0)\exp\left[-\int_0^{t_1} (\lambda_{m1}(u) + \lambda_{m2}(u))\, du + \mu_f t_1\right] + \exp\left[-\int_0^{t_1} (\lambda_{m1}(u) + \lambda_{m2}(u))\, du + \mu_f t_1\right]$$
$$\times (1-f)\,\Lambda_f \int_0^{t_1} \exp\left[\int_0^{y} (\lambda_{m1}(u) + \lambda_{m2}(u))\, du + \mu_f y\right] dy > 0$$

Similarly, it can be shown that $V_f(0) > 0, I_{f1}(0) > 0, P_{f1}(0) > 0, C_f(0) > 0, R_f^c(0) > 0, R_{f1}(0) > 0, I_{f2}(0) > 0, I_{f2}^p(0) > 0, P_{f2}(0) > 0, R_{f2}(0) > 0, S_m(0) > 0, I_{m1}(0) > 0, R_{m1}(0) > 0, I_{m2} > 0, R_{m2} > 0, I_{f12} > 0, I_{f21} > 0, M_f > 0, I_{m12} > 0, I_{m21} > 0, M_m > 0$

Adding the female compartments and the male compartments in the differential system (3.23) respectively gives

$$\frac{dN_f}{dt} = \Lambda_f - \mu_f N_f(t) - \left[\delta_{f1} I_{f1} + \delta_{fc} C_f + \delta_{f2} I_{f2} + \delta_{f2}^p I_{f2}^p + \delta_{f12} I_{f12} + \delta_{f21} I_{f21}\right]$$

$$\frac{dN_m}{dt} = \Lambda_m - \mu_m N_m(t) - [\delta_{m1}I_{m1} + \delta_{m2}I_{m2} + \delta_{m12}I_{m12} + \delta_{m21}I_{m21}]$$

We have that,

$$\Lambda_f - (\mu_f + 6\delta_f)N_f \leq \frac{dN_f}{dt} < \Lambda_f - \mu_f N_f,$$

$$\Lambda_m - (\mu_m + 4\delta_m)N_m \leq \frac{dN_m}{dt} < \Lambda_m - \mu_m N_m$$

Where

$\delta_f = \min\{\delta_{f1}, \delta_{fc}, \delta_{f2}, \delta^p_{f2}, \delta_{f12}, \delta_{f21}\}$,

$\delta_m = \min\{\delta_{m1}, \delta_{m2}, \delta_{m12}, \delta_{m21}\}$,

Thus,

$$\frac{\Lambda_f}{\mu_f + 6\delta_f} \leq \lim_{t\to\infty} \ \inf \ N_f(t) \leq \lim_{t\to\infty} \ \sup \ N_f(t) \leq \frac{\Lambda_f}{\mu_f},$$

$$\frac{\Lambda_m}{\mu_m + 4\delta_m} \leq \lim_{t\to\infty} \ \inf \ N_m(t) \leq \lim_{t\to\infty} \ \sup \ N_m(t) \leq \frac{\Lambda_m}{\mu_m},$$

so that

$\lim_{t\to\infty} \ \sup \ N_f(t) \leq \frac{\Lambda_f}{\mu_f}$ and $\lim_{t\to\infty} \ \sup \ N_m(t) \leq \frac{\Lambda_m}{\mu_m}$

as required. □ □

4.2.2 Invariant regions

The two-strain model will be analyzed in a biologically feasible region as follows. We first show that the system (3.23) is dissipative (that is, all feasible solutions are uniformly-bounded in a proper subset $\mathcal{D} \subset \mathcal{R}^{22}_+$). The system (3.23) is split into two parts, namely the female population (N_f)

(with $N_f = S_f + V_f + I_{f1} + P_{f1} + C_f + R^c_f + R_{f1} + I_{f2} + I^p_{f2} + P_{f2} + R_{f2} + I_{f12} + I_{f21} + M_f$) and the male population (N_m)

(with $N_m = S_m + I_{m1} + R_{m1} + I_{m2} + R_{m2} + I_{m12} + I_{m21} + M_m$) Consider the feasible region

$$\mathcal{D} = \mathcal{D}_f \cup \mathcal{D}_m \subset \mathcal{R}^{14}_+ \times \mathcal{R}^8_+,$$

with

$$\mathcal{D}_f = \Bigg\{(S_f, V_f, I_{f1}, P_{f1}, C_f, R_f^c, R_{f1}, I_{f2}, I_{f2}^p, P_{f2}, R_{f2}, I_{f12}, I_{f21}, M_f) \in \mathcal{R}_+^{14} :$$
$$S_f + V_f + I_{f1} + P_{f1} + C_f + R_f^c + R_{f1} + I_{f2} + I_{f2}^p + P_{f2} + R_{f2} + I_{f12} + I_{f21} + M_f \leq \frac{\Lambda_f}{\mu_f}\Bigg\}$$

and

$$\mathcal{D}_m = \Bigg\{(S_m, I_{m1}, R_{m1}, I_{m2}, R_{m2}, I_{m12}, I_{m21}, M_m) \in \mathcal{R}_+^{8} : S_m + I_{m1} + R_{m1} + I_{m2} + R_{m2} + I_{m12}$$
$$+ I_{m21} + M_m \leq \frac{\Lambda_m}{\mu_m}\Bigg\}$$

The following steps are followed to establish the positive invariance of $\mathcal{D}$ (i.e. solutions in $\mathcal{D}$ remain in $\mathcal{D}$ for all time $t \geq 0$). From (3.23), we have that

$$\frac{dN_f}{dt} \leq \Lambda_f - \mu_f N_f(t),$$
$$\frac{dN_m}{dt} \leq \Lambda_m - \mu_m N_m(t)$$

Using the Comparison theorem (Lakshmikantham, et al., 1989), we have that $N_f(t) \leq N_f(0)e^{-\mu_f t} + \frac{\Lambda_f}{\mu_f}(1 - e^{-\mu_f t})$ and $N_f(t) \leq N_f(0)e^{-\mu_f t} + \frac{\Lambda_f}{\mu_f}(1 - e^{-\mu_f t})$.

In particular, $N_f(t) \leq \frac{\Lambda_f}{\mu_f}$ and $N_f(t) \leq \frac{\Lambda_f}{\mu_f}$ if $N_f(0) \leq \frac{\Lambda_f}{\mu_f}$ and $N_m(0) \leq \frac{\Lambda_m}{\mu_m}$, respectively.

Thus, the region $\mathcal{D}$ is positively-invariant. Hence, it is sufficient to consider the dynamics of the flow generated by (3.23) in $\mathcal{D}$. In this region, the model can be considered as been epidemiologically and mathematically well-posed (Hethcote, 2000). Thus, every solution of the model (3.23) with initial conditions in $\mathcal{D}$ remains in $\mathcal{D}$ for all time $t \geq 0$. Therefore, the $\omega-$limit sets of the system (3.23) are contained in $\mathcal{D}$. Thus result is summarized thus.

Lemma 4.10. The region $\mathcal{D}$=$\mathcal{D}_f$∪$\mathcal{D}_M$⊂ $\mathcal{R}_+^{14} \times \mathcal{R}_+^{8}$ is positively-invariant for the two-strain HPV model (3.23) with initial conditions in $\mathcal{R}_+^{22}$

4.3 Existence and stability of equilibrium of the model (3.23)

4.3.1 Local stability of disease-free equilibrium (DFE)

The model (3.23) has a DFE, obtained by setting the right-hand sides of the equations in the model (3.23) to zero, given by

$$\begin{aligned}\xi_0 &= \left(S_f^*, V_f^*, I_{f1}^*, P_{f1}^*, C_f^*, R_f^{c*}, R_{f1}^*, I_{f2}^*, I_{f2}^{p*}, P_{f2}^*, R_{f2}^*, S_m^*, I_{m1}^*, R_{m1}^*, I_{m2}^*, R_{m2}^*, I_{f12}^*, I_{f21}^*, M_f^*, I_{m12}^*, I_{m21}^*, M_m^*\right)\\ &= \left(S_f^*, V_f^*, 0, 0, 0, 0, 0, 0, 0, 0, 0, S_m^*, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0\right)\end{aligned}$$

with,

$$S_f^* = \frac{(1-f)\Lambda_f}{\mu_f}, \quad V_f^* = \frac{f\Lambda_f}{\mu_f}, \quad S_m^* = \frac{\Lambda_m}{\mu_m}$$

The linear stability of the disease free equilibrium, ξ_0 can be established using the next generation operator method on the system (3.23). Using the notation in van den Driessche and Watmough (2002), the matrix $\mathcal{F}_i$ (of new infections) and the matrix $\mathcal{V}_i$ (of the transfer of individuals between compartments) are respectively, given by

$$\mathcal{F}_i = \begin{bmatrix} \lambda_{m1}[S_f + (1-\xi_f)V_f] \\ 0 \\ 0 \\ \lambda_{m2}S_f \\ \eta_I(1-\xi)\lambda_{m2}V_f \\ 0 \\ \lambda_{f1}S_m \\ \lambda_{f2}S_m \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad \mathcal{V}_i = \begin{bmatrix} K_1 I_{f1} - \varepsilon_1\lambda_{m1}R_{f1} - \alpha_1\lambda_{m1}M_f \\ K_2 P_{f1} - (1-p_1)\tau_{f1}I_{f1} - (1-p_{21})\tau_{f21}I_{f21} \\ K_3 C_f - G_3 P_{f1} - \eta_c(1-q_2)\kappa_{f2}P_{f2} \\ K_4 I_{f2} - \varepsilon_2\lambda_{m2}R_{f2} - \alpha_2\lambda_{m2}M_f \\ (\eta_p\tau_{f2} + \delta_{f2}^p + \mu_f)I_{f2}^p \\ K_6 P_{f2} - G_5 I_{f2}^p - G_6 I_{f2} - G_7 I_{f12} \\ K_7 I_{m1} - \varepsilon_3\lambda_{f1}R_{m1} - \alpha_3\lambda_{f1}M_m \\ K_8 I_{m2} - \varepsilon_4\lambda_{f2}R_{m2} - \alpha_4\lambda_{f2}M_m \\ K_9 I_{f12} - \lambda_{m2}R_{f1} \\ K_{10} I_{f21} - \lambda_{m1}R_{f2} \\ K_{11} I_{m12} - \lambda_{f2}R_{m1} \\ K_{12} I_{m21} - \lambda_{f1}R_{m2} \end{bmatrix}$$

The matrices F and V, for the new infection terms and the remaining transfer terms, evaluated at the disease free equilibrium (DFE) are, respectively, given by

$$F = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{m1}Q_1}{N_m^*} & 0 & 0 & 0 & 0 & \frac{\beta_{m1}Q_1}{N_m^*} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{m2}S_f^*}{N_m^*} & 0 & 0 & \frac{\beta_{m2}S_f^*}{N_m^*} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{m2}S_f^*}{N_m^*} & 0 & 0 & \frac{\beta_{m2}Q_2}{N_m^*} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_{f1}S_m^*}{N_f^*} & \frac{\beta_{f1}\theta_{p1}S_m^*}{N_f^*} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{f1}S_m^*}{N_f^*} & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{f2}S_m^*}{N_f^*} & \frac{\beta_{f2}\phi_p S_m^*}{N_f^*} & \frac{\beta_{f2}\theta_{p2}S_m^*}{N_f^*} & 0 & 0 & \frac{\beta_{f2}S_m^*}{N_f^*} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} K_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -G_1 & K_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -G_2 & 0 & 0 \\ 0 & 0 & K_3 & 0 & 0 & -G_4 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & K_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & K_5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -G_6 & -G_5 & K_6 & 0 & 0 & -G_7 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & K_7 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & K_8 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & K_9 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & K_{10} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & K_{11} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & K_{12} \end{bmatrix}$$

where,

$$
\begin{aligned}
&Q_1 = S_f^* + (1-\xi)V_f^* = \frac{(1-f\xi)\Lambda_f}{\mu_f}, \quad Q_2 = (1-\xi)\eta_I V_f^* = \frac{(1-\xi)f\eta_I\Lambda_f}{\mu_f} \\
&K_1 = \tau_{f1} + \delta_{f1} + \mu_f, \quad K_2 = \kappa_{f1} + \mu_f, \quad K_3 = \pi_f + \mu_f + \delta_{fc}, \quad K_4 = \tau_{f2} + \delta_{f2} + \mu_f, \\
&K_5 = \eta_p\tau_{f2} + \delta_{f2}^p + \mu_f, \quad K_6 = \eta_c\kappa_{f2} + \mu_f, \quad K_7 = \tau_{m1} + \delta_{m1} + \mu_m, \\
&K_8 = \tau_{m2} + \delta_{m2} + \mu_m, \quad K_9 = \tau_{f12} + \delta_{f12} + \mu_m, \quad K_{10} = \tau_{f21} + \delta_{f21} + \mu_f, \\
&K_{11} = \tau_{m12} + \delta_{m12} + \mu_m, \quad K_{12} = \tau_{m21} + \delta_{m21} + \mu_m, \quad G_1 = (1-p_1)\tau_{f1}, \\
&G_2 = (1-p_{21})\tau_{f21}, \quad G_3 = (1-q_1)\kappa_{f1}, \quad G_4 = \eta_c(1-q_2)\kappa_{f2}, \quad G_5 = (1-p_2)\eta_p\tau_{f2}, \\
&G_6 = (1-p_2)\tau_{f2}, \quad G_7 = (1-p_{12})\tau_{f12}, \quad G_8 = p_2\eta_p\tau_{f2}, \quad G_9 = q_2\eta_c\kappa_{f2}, \\
&G_{10} = p_{12}\tau_{f12}, G_{11} = p_{21}\tau_{f21}
\end{aligned}
$$

Hence, it follows from van den Driessche and Watmough (2002) that the basic reproduction number of the model (3.23), denoted by $\mathcal{R}_0$, is given by (where ρ is the spectral radius) $\mathcal{R}_0 = \rho(FV^{-1}) = \max\{\mathcal{R}_{01}, \mathcal{R}_{02}\}$ where $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$ are the associated reproduction numbers for strain 1 and strain 2, respectively, given by

$$
\mathcal{R}_{01} = \sqrt{\frac{\beta_{f1}\beta_{m1}(K_2 + G_1\theta_{p1})(1-f\xi)}{K_1K_2K_7}}, \quad \mathcal{R}_{02} = \sqrt{\frac{\beta_{f2}\beta_{m2}(K_6 + G_6\theta_{p2})}{K_4K_6K_8}}
$$

The result below follows from Theorem 2 in van den Driessche and Watmough (2002).

Lemma 4.11. The DFE (ξ_0) of the model (3.23) is locally asymptotically stable (LAS) if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

The threshold quantity, $\mathcal{R}_0 = \max\ \{\mathcal{R}_{01}, \mathcal{R}_{02}\}$, is the basic reproduction number of the disease (Anderson and May, 1982; Anderson and May, 1991 and Hethcote, 2000). It represents the average number of secondary cases generated by a typical infected individual (with strain 1 or strain 2) in a completely susceptible population (van den Driessche and Watmough, 2002). The epidemiological implication of Lemma 4.11 is that when $\mathcal{R}_0$ is less than unity, a small flux of strain 1- or strain 2-infected individual into the community will not generate large outbreak, and the disease will die out. In other words, the disease can be effectively controlled in the community if the initial sizes of the sub-populations of the model (3.23) are in the basin of attraction of the DFE (ξ_0).

4.3.2 Backward bifurcation analysis of the full two-strain HPV model

It is instructive to characterize the type of bifurcation the model (3.23) may undergo. We claim the following result:

Theorem 4.12. *The model* (3.23) *exhibits backward bifurcation at* $\mathcal{R}_0 = 1$ *whenever a bifurcation coefficient, denoted by a (given by* (4.19)*), is positive.*

Proof Suppose

$$\xi_e = (S_f^{**}, V_f^{**}, I_{f1}^{**}, P_{f1}^{**}, C_f^{**}, R_f^{c**}, R_{f1}^{**}, I_{f2}^{**}, I_{f2}^{p**}, P_{f2}^{**}, R_{f2}^{**}, S_m^{**}, I_{m1}^{**}, R_{m1}^{**}, I_{m2}^{**}, R_{m2}^{**}, I_{f12}^{**}, I_{f21}^{**}, M_f^{**}, I_{m12}^{**},$$
$$I_{m21}^{**}, M_m^{**})$$

represents any arbitrary endemic equilibrium of the model (that is, an endemic equilibrium in which at least one of the infected components is non-zero). The existence (or otherwise) of backward bifurcation will be explored using the Centre Manifold Theory Castillo-Chavez and Song (2004). To apply this theory, it is necessary to carry out the following change of variables. Let

$$S_f = x_1, V_f = x_2, I_{f1} = x_3, P_{f1} = x_4, C_f = x_5, R_f^c = x_6, R_{f1} = x_7, I_{f2} = x_8, I_{f2}^p = x_9,$$
$$P_{f2} = x_{10}, R_{f2} = x_{11}, S_m = x_{12}, I_{m1} = x_{13}, R_{m1} = x_{14}, I_{m2} = x_{15}, R_{m2} = x_{16}, I_{f12} = x_{17},$$
$$I_{f21} = x_{18}, M_f = x_{19}, I_{m12} = x_{20}, I_{m21} = x_{21}, M_m = x_{22}$$

so that

$$N = \sum_{i=1}^{22} x_i.$$

Further, using the vector notation

$$X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10}, x_{11}, x_{12}, x_{13}, x_{14}, x_{15}, x_{16}, x_{17}, x_{18}, x_{19}, x_{20}, x_{21}, x_{22})^T$$

the model (3.23) can be re-written in the form

$$\frac{dX}{dt} = f = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10}, f_{11}, f_{12}, f_{13}, f_{14}, f_{15}, f_{16}, f_{17}, f_{18}, f_{19}, f_{20}, f_{21}, f_{22})^T$$

as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} &\equiv f_1 = (1-f)\Lambda_f - \left(\lambda_{m1} + \lambda_{m2} + \mu_f\right) x_1 \\
\frac{dx_2}{dt} &\equiv f_2 = f\Lambda_f - \left[(1-\xi)\lambda_{m1} + \eta_I(1-\xi)\lambda_{m2} + \mu_f\right] x_2 \\
\frac{dx_3}{dt} &\equiv f_3 = (1-\xi)\lambda_{m1}x_2 + \lambda_{m1}x_1 + \varepsilon_1\lambda_{m1}x_7 + \alpha_1\lambda_{m1}x_{19} - (\tau_{f1} + \delta_{f1} + \mu_f)x_3 \\
\frac{dx_4}{dt} &\equiv f_4 = (1-p_1)\tau_{f1}x_3 + (1-p_{21})\tau_{f21}x_{18} - (\kappa_{f1} + \mu_f)x_4 \\
\frac{dx_5}{dt} &\equiv f_5 = (1-q_1)\kappa_{f1}x_4 + \eta_c(1-q_2)\kappa_{f2}x_{10} - (\pi_f + \mu_f + \delta_{fc})x_5 \\
\frac{dx_6}{dt} &\equiv f_6 = \pi_f x_5 - \mu_f x_6 \\
\frac{dx_7}{dt} &\equiv f_7 = p_1\tau_{f1}x_3 + q_1\kappa_{f1}x_4 - \left(\mu_f + \lambda_{m2} + \varepsilon_1\lambda_{m1}\right) x_7 \\
\frac{dx_8}{dt} &\equiv f_8 = \lambda_{m2}x_1 + \varepsilon_2\lambda_{m2}x_{11} + \alpha_2\lambda_{m2}x_{19} - (\tau_{f2} + \delta_{f2} + \mu_f)x_8 \\
\frac{dx_9}{dt} &\equiv f_9 = \eta_I(1-\xi)\lambda_{m2}x_2 - (\eta_p\tau_{f2} + \delta_{f2}^{p} + \mu_f)x_9 \\
\frac{dx_{10}}{dt} &\equiv f_{10} = (1-p_2)\eta_p\tau_{f2}x_9 + (1-p_2)\tau_{f2}x_8 + (1-p_{12})\tau_{f12}x_{17} - (\eta_c\kappa_{f2} + \mu_f)x_{10} \\
\frac{dx_{11}}{dt} &\equiv f_{11} = p_2\eta_p\tau_{f2}x_9 + p_2\tau_{f2}x_8 + q_2\eta_c\kappa_{f2}x_{10} - \left(\lambda_{m1} + \varepsilon_2\lambda_{m2} + \mu_f\right) x_{11} \\
\frac{dx_{12}}{dt} &\equiv f_{12} = \Lambda_m - \left(\lambda_{f1} + \mu_m + \lambda_{f2}\right) x_{12} \\
\frac{dx_{13}}{dt} &\equiv f_{13} = \lambda_{f1}x_{12} + \varepsilon_3\lambda_{f1}x_{14} + \alpha_3\lambda_{f1}x_{22} - (\tau_{m1} + \delta_{m1} + \mu_m)x_{13} \\
\frac{dx_{14}}{dt} &\equiv f_{14} = \tau_{m1}x_{13} - \left(\lambda_{f2}x_{14} + \varepsilon_3\lambda_{f1}x_{14} + \mu_m\right) x_{14} \\
\frac{dx_{15}}{dt} &\equiv f_{15} = \lambda_{f2}x_{12} + \varepsilon_4\lambda_{f2}x_{16} + \alpha_4\lambda_{f2}x_{22} - (\tau_{m2} + \delta_{m2} + \mu_m)x_{15} \\
\frac{dx_{16}}{dt} &\equiv f_{16} = \tau_{m2}x_{15} - \left(\mu_m + \lambda_{f1} + \varepsilon_4\lambda_{f2}\right) x_{16} \\
\frac{dx_{17}}{dt} &\equiv f_{17} = \lambda_{m2}x_7 - \left(\tau_{f12} + \delta_{f12} + \mu_f\right) x_{17} \\
\frac{dx_{18}}{dt} &\equiv f_{18} = \lambda_{m1}x_{11} - \left(\tau_{f21} + \delta_{f21} + \mu_f\right) x_{18} \\
\frac{dx_{19}}{dt} &\equiv f_{19} = p_{12}\tau_{f12}x_{17} + p_{21}\tau_{f21}x_{18} - \left(\mu_f + \alpha_1\lambda_{m1} + \alpha_2\lambda_{m2}\right) x_{19} \\
\frac{dx_{20}}{dt} &\equiv f_{20} = \lambda_{f2}x_{14} - \left(\tau_{m12} + \delta_{m12} + \mu_m\right) x_{20}
\end{aligned}
\tag{4.18}
$$

$$
\begin{aligned}
\frac{dx_{21}}{dt} &\equiv f_{21} = \lambda_{f1}x_{16} - \left(\tau_{m21} + \delta_{m21} + \mu_m\right) x_{21} \\
\frac{dx_{22}}{dt} &\equiv f_{22} = \tau_{m12}x_{20} + \tau_{m21}x_{21} - \left(\mu_m + \alpha_3\lambda_{f1} + \alpha_4\lambda_{f2}\right) x_{22}
\end{aligned}
$$

where,

$$\begin{aligned}
\lambda_{f1} &= \frac{\beta_{f1}(x_3 + x_{18} + \theta_{p1}x_4)}{\sum_{i=1}^{11} x_i + \sum_{i=17}^{19} x_i} \\
\lambda_{f2} &= \frac{\beta_{f2}(x_8 + x_{17} + \phi_p x_9 + \theta_{p2}x_{10})}{\sum_{i=1}^{11} x_i + \sum_{i=17}^{19} x_i} \\
\lambda_{m1} &= \frac{\beta_{m1}(x_{13} + x_{21})}{\sum_{i=12}^{16} x_i + \sum_{i=20}^{22} x_i} \\
\lambda_{m2} &= \frac{\beta_{m2}(x_{15} + x_{20})}{\sum_{i=12}^{16} x_i + \sum_{i=20}^{22} x_i}
\end{aligned}$$

Without loss of generality, consider the case when $\mathcal{R}_{01} = 1$. Suppose, further, that β_{f1} is chosen as a bifurcation parameter. Solving for $\beta_{f1} = \beta_{f1}^*$ from $\mathcal{R}_{01} = 1$ gives

$$\beta_{f1} = \beta_{f1}^* = \frac{K_1 K_2 K_7}{\beta_{m1}\left(K_2 + G_1\theta_{p1}\right)\left(1 - f\xi\right)}$$

The Jacobian of the transformed system (4.18), evaluated at the DFE (ξ_0) with $\beta_{f1} = \beta_{f1}^*$, is given by

$$J(\xi_0)|_{\beta_{f1}=\beta_{f1}^*} = \begin{bmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{bmatrix}$$

where

$$J_{11} = \begin{bmatrix}
-\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -K_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & G_1 & -K_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -K_3 & 0 & 0 & 0 & 0 & G_4 & 0 \\
0 & 0 & 0 & 0 & 0 & -\mu_f & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & p_1\tau_{f1} & q_1\kappa_{f1} & 0 & 0 & -\mu_f & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -K_4 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -K_5 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & G_6 & G_5 & -K_6 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & p_2\tau_{f2} & G_8 & G_9 & -\mu_f
\end{bmatrix}$$

$$J_{12} = \begin{bmatrix} 0 & \frac{-\beta_{m1}x_1^*}{N_m^*} & 0 & \frac{-\beta_{m2}x_1^*}{N_m^*} & 0 & 0 & 0 & 0 & \frac{-\beta_{m2}x_1^*}{N_m^*} & \frac{-\beta_{m1}x_1^*}{N_m^*} & 0 \\ 0 & \frac{-\beta_{m1}(1-\xi)x_2^*}{N_m^*} & 0 & \frac{-\beta_{m2}\eta_I(1-\xi)x_2^*}{N_m^*} & 0 & 0 & 0 & 0 & \frac{-\beta_{m2}\eta_I(1-\xi)x_2^*}{N_m^*} & \frac{-\beta_{m2}(1-\xi)x_2^*}{N_m^*} & 0 \\ 0 & \frac{\beta_{m1}X_1^*}{N_m^*} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{m2}X_1^*}{N_m^*} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & G_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{m2}x_1^*}{N_m^*} & 0 & 0 & 0 & 0 & \frac{\beta_{m2}x_1^*}{N_m^*} & 0 & 0 \\ 0 & 0 & 0 & \frac{\beta_{m2}\eta_I(1-\xi)x_2^*}{N_m^*} & 0 & 0 & 0 & 0 & \frac{\beta_{m2}\eta_I(1-\xi)x_2^*}{N_m^*} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & G_7 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$J_{21} = \begin{bmatrix} 0 & 0 & \frac{-\beta_{f1}x_{12}^*}{N_f^*} & \frac{-\beta_{f1}\theta_{p1}x_{12}^*}{N_f^*} & 0 & 0 & 0 & \frac{-\beta_{f2}x_{12}^*}{N_f^*} & \frac{-\beta_{f2}\phi_p x_{12}^*}{N_f^*} & \frac{-\beta_{f2}\theta_{p2}x_{12}^*}{N_f^*} & 0 \\ 0 & 0 & \frac{\beta_{f1}x_{12}^*}{N_f^*} & \frac{\beta_{f1}\theta_{p1}x_{12}^*}{N_f^*} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{f2}x_{12}^*}{N_f^*} & \frac{\beta_{f2}\phi_p x_{12}^*}{N_f^*} & \frac{\beta_{f2}\theta_{p2}x_{12}^*}{N_f^*} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$J_{22} = \begin{bmatrix} -\mu_m & 0 & 0 & 0 & 0 & \frac{-\beta_{f2}x_{12}^*}{N_f^*} & \frac{-\beta_{f1}x_{12}^*}{N_f^*} & 0 & 0 & 0 & 0 \\ 0 & -K_7 & 0 & 0 & 0 & 0 & \frac{\beta_{f1}x_{12}^*}{N_f^*} & 0 & 0 & 0 & 0 \\ 0 & \tau_{m1} & -\mu_m & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -K_8 & 0 & \frac{\beta_{f2}x_{12}^*}{N_f^*} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \tau_{m2} & -\mu_m & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -K_9 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -K_{10} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & G_{10} & G_{11} & -\mu_f & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -K_{11} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -K_{12} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \tau_{m12} & \tau_{m21} & -\mu_m \end{bmatrix}$$

where, $N_f^* = x_1^* + x_2^*$, $N_m^* = x_{12}^*$, $X_1^* = x_1^* + (1-\xi)x_2^*$.

It can be shown that the Jacobian of (3.23) has a right eigenvector (associated with the zero eigenvalue) given by

$$w = [\omega_1, \omega_2, \omega_3, \omega_4, \omega_5, \omega_6, \omega_7, \omega_8, \omega_9, \omega_{10}, \omega_{11}, \omega_{12}, \omega_{13}, \omega_{14}, \omega_{15}, \omega_{16}, \omega_{17}, \omega_{18}, \omega_{19}, \omega_{20}, \omega_{21}, \omega_{22}]^T$$

with,

$$-\mu_f\omega_1 - \frac{\beta_{m1}x_1^*}{N_m^*}\omega_{13} - \frac{\beta_{m2}x_1^*}{N_m^*}\omega_{15} = 0$$

$$-\mu_f\omega_2 - \frac{\beta_{m1}(1-\xi)x_2^*}{N_m^*}\omega_{13} - \frac{\beta_{m2}\eta_I(1-\xi)x_2^*}{N_m^*}\omega_{15} = 0$$

$$-K_1\omega_3 + \frac{\beta_{m1}X_1^*}{N_m^*}\omega_{13} = 0$$

$$G_3\omega_4 - K_3\omega_5 + G_4\omega_{10} = 0$$

$$\pi\omega_5 - \mu_f\omega_6 = 0$$

$$p_1\tau_{f1}\omega_3 + q_1\kappa_{f1}\omega_4 - \mu_f\omega_7 = 0$$

$$-K_4\omega_8 + \frac{\beta_{m2}x_1^*}{N_m^*}\omega_{15} = 0$$

$$-K_5\omega_9 + \frac{\beta_{m2}\eta_I(1-\xi)x_2^*}{N_m^*}\omega_{15} = 0$$

$$G_6\omega_8 + G_5\omega_9 - K_6\omega_{10} = 0$$

$$p_2\tau_{f2}\omega_8 + G_8\omega_9 + G_9\omega_{10} - \mu_f\omega_{11} = 0$$

$$-\tfrac{\beta^*_{f1}x^*_{12}}{N^*_f}\omega_3 - \tfrac{\beta^*_{f1}\theta_{p1}x^*_{12}}{N^*_f}\omega_4 - \tfrac{\beta_{f2}x^*_{12}}{N^*_f}\omega_8 - \tfrac{\beta_{f2}\phi_p x^*_{12}}{N^*_f}\omega_9 - \tfrac{\beta_{f2}\theta_{p2}x^*_{12}}{N^*_f}\omega_{10} - \mu_m\omega_{12} = 0$$

$$\tfrac{\beta^*_{f1}x^*_{12}}{N^*_f}\omega_3 + \tfrac{\beta^*_{f1}\theta_{p1}x^*_{12}}{N^*_f}\omega_4 - K_7\omega_{13} = 0$$

$$\tau_{m1}\omega_{13} - \mu_m\omega_{14} = 0$$

$$\tfrac{\beta_{f2}x^*_{12}}{N^*_f}\omega_8 + \tfrac{\beta_{f2}\phi_p x^*_{12}}{N^*_f}\omega_9 + \tfrac{\beta_{f2}\theta_{p2}x^*_{12}}{N^*_f}\omega_{10} - K_8\omega_{15} = 0$$

$$\tau_{m2}\omega_{15} - \mu_m\omega_{16} = 0$$

where,

$$\begin{aligned}
\omega_1 &= -\frac{1}{\mu_f}\left\{\frac{K_1x^*_1\omega_3}{N^*_f(1-f\xi)} + \frac{\beta_{m2}x^*_1\omega_{15}}{N^*_m}\right\}, \quad \omega_2 = -\frac{1}{\mu_f}\left\{\frac{K_1(1-\xi)x^*_2\omega_3}{N^*_f(1-f\xi)} + \frac{\beta_{m2}\eta_I(1-\xi)x^*_2\omega_{15}}{N^*_m}\right\}, \\
\omega_3 &= \omega_3 > 0, \quad \omega_4 = \frac{G_1\omega_3}{K_2}, \quad \omega_5 = \frac{G_1G_3\omega_3}{K_2K_3} + \frac{G_4\beta_{m2}\big\{G_6K_5x^*_1 + G_5K_4\eta_I(1-\xi)x^*_2\big\}\omega_{15}}{K_3K_4K_5K_6N^*_m}, \\
\omega_6 &= \frac{\pi_fG_1G_3\omega_3}{\mu_fK_2K_3} + \frac{\pi_fG_4\beta_{m2}\big\{G_6K_5x^*_1 + G_5K_4\eta_I(1-\xi)x^*_2\big\}\omega_{15}}{\mu_fK_3K_4K_5K_6N^*_m}, \quad \omega_7 = \frac{(p_1\tau_{f1}K_2 + q_1\kappa_{f1}G_1)\omega_3}{\mu_fK_2}, \\
\omega_8 &= \frac{\beta_{m2}x^*_1\omega_{15}}{K_4N^*_m}, \quad \omega_9 = \frac{\beta_{m2}\eta_I(1-\xi)x^*_2}{K_5N^*_m}, \quad \omega_{10} = \frac{\beta_{m2}\big\{G_6K_5x^*_1 + G_5K_4\eta_I(1-\xi)x^*_2\big\}\omega_{15}}{K_4K_5K_6N^*_m}, \\
\omega_{11} &= \frac{\beta_{m2}\big\{(p_2\tau_{f2}K_5K_6 + G_6G_9K_5)x^*_1 + (G_8K_4K_6 + G_5G_9K_4)\eta_I(1-\xi)x^*_2\big\}\omega_{15}}{\mu_fK_4K_5K_6N^*_m}, \\
\omega_{12} &= -\frac{1}{\mu_m}\left\{\frac{K_1K_2K_7x^*_{12}\omega_3}{\beta_{m1}N^*_f(1-f\xi)} + \frac{\beta_{f2}\beta_{m2}\big\{K_5(K_6+\theta_{p2}G_6)x^*_1 + K_4(K_6\phi_p + \theta_{p2}G_5)\eta_I(1-\xi)x^*_2\big\}\omega_{15}}{K_4K_5K_6N^*_f}\right\} \\
\omega_{13} &= \frac{\beta^*_{f1}x^*_{12}(K_2+\theta_{p1}G_1)\omega_3}{K_2K_7N^*_f}, \quad \omega_{14} = \frac{\tau_{m1}K_1x^*_{12}\omega_3}{\beta_{m1}\mu_m(1-f\xi)N^*_f}, \quad \omega_{15} = \omega_{15} > 0, \quad \omega_{16} = \frac{\tau_{m2}\omega_{15}}{\mu_m}
\end{aligned}$$

Furthermore, (3.23) has a corresponding left eigenvector (associated with the zero eigenvalue) given by

$$v = [\nu_1, \nu_2, \nu_3, \nu_4, \nu_5, \nu_6, \nu_7, \nu_8, \nu_9, \nu_{10}, \nu_{11}, \nu_{12}, \nu_{13}, \nu_{14}, \nu_{15}, \nu_{16}, \nu_{17}, \nu_{18}, \nu_{19}, \nu_{20}, \nu_{21}, \nu_{22}]$$

where,

$$-K_1\nu_3 + G_1\nu_4 + \tfrac{\beta^*_{f1}x^*_{12}}{N^*_f}\nu_{13} = 0$$

$$-K_2\nu_4 + \tfrac{\beta^*_{f1}\theta_{p1}x^*_{12}}{N^*_f}\nu_{13} = 0$$

$$-K_4\nu_8 + G_6\nu_{10} + \tfrac{\beta_{f2}x_{12}^*}{N_f^*}\nu_{15} = 0$$

$$-K_5\nu_9 + G_5\nu_{10} + \tfrac{\beta_{f2}\phi_p x_{12}^*}{N_f^*}\nu_{15} = 0$$

$$-K_6\nu_{10} + \tfrac{\beta_{f2}\theta_{p2}x_{12}^*}{N_f^*}\nu_{15} = 0$$

$$\tfrac{\beta_{m1}X_1^*}{N_m^*}\nu_3 - K_7\nu_{13} = 0$$

$$\tfrac{\beta_{m2}x_1^*}{N_m^*}\nu_8 + \tfrac{\beta_{m1}\eta_I(1-\xi)x_2^*}{N_m^*}\nu_9 - K_8\nu_{15} = 0$$

$$G_7\nu_{10} + \tfrac{\beta_{f2}x_{12}^*}{N_f^*}\nu_{15} - K_9\nu_{17} = 0$$

$$G_2\nu_4 + \tfrac{\beta_{f1}^*x_{12}^*}{N_f^*}\nu_{13} - K_{10}\nu_{18} = 0$$

$$\tfrac{\beta_{m2}x_1^*}{N_m^*}\nu_8 + \tfrac{\beta_{m1}\eta_I(1-\xi)x_2^*}{N_m^*}\nu_9 - K_{11}\nu_{20} = 0$$

$$\tfrac{\beta_{m1}X_1^*}{N_m^*}\nu_3 - K_{12}\nu_{21} = 0$$

Solving, gives

$$\nu_3 = \nu_3 > 0, \quad \nu_4 = \frac{\theta_{p1}\nu_3}{(K_2 + \theta_{p1}G_1)}, \quad \nu_8 = \frac{\beta_{f2}x_{12}^*\nu 15(K_6 + \theta_{p2}G_6)}{K_4K_6N_f^*}, \quad \nu_9 = \frac{\beta_{f2}x_{12}^*\nu 15(K_6 + \theta_{p2}G_6)}{K_5K_6N_f^*},$$
$$\nu_{10} = \frac{\beta_{f2}\theta_{p2}x_{12}^*\nu_{15}}{K_6N_f^*}, \quad \nu_{13} = \frac{\beta_{m1}X_1^*\nu_3}{K_7N_m^*}, \quad \nu_{17} = \frac{\beta_{f2}x_{12}^*\nu 15(K_6 + \theta_{p2}G_6)}{K_6K_9N_f^*}, \quad \nu_{18} = \frac{(\theta_{p1}G_2 + K_1K_2)\nu_3}{K_{10}(K_2 + \theta_{p1}G_1)},$$
$$\nu_{20} = \frac{\beta_{f2}\beta_{m2}\big\{(K_6 + \theta_{p2}G_6)x_1^* + (\phi_pK_6 + \theta_{p2}G_5)\eta_I(1-\xi)x_2^*\big\}\nu_{15}}{K_4K_5K_6K_{11}N_f^*}, \quad \nu_{21} = \frac{\beta_{m1}X_1^*\nu_3}{K_{12}N_m^*}$$

Based on Theorem 4.1 in Castillo-Chavez and Song (2004), and by computing the non-zero partial derivatives of $F(x)$(evaluated at the disease free equilibrium, DFE (ξ_0)), we have that the associated bifurcation coefficients defined by a and b, are given by

$$a = \sum_{k,i,j=1}^{n} \nu_k\omega_i\omega_j\frac{\partial^2 f_k}{\partial x_i\partial x_j}(0,0) \quad \text{and} \quad b = \sum_{k,i=1}^{n} \nu_k\omega_i\frac{\partial^2 f_k}{\partial x_i\partial\beta_S^*}(0,0),$$

are computed to be

$$\begin{aligned} a = &-\frac{2\beta_{m1}\nu_3\omega_{13}}{N_m^{*2}}\left\{\omega_{12}X_1^* - \varepsilon_1\omega_7 N_m^* + (\omega_{13}+\omega_{14}+\omega_{15}+\omega_{16})X_1^* - \{\omega_1 + (1-\xi)\omega_2\}N_m^*\right\} \\ &- \frac{2\beta_{m2}\nu_8\omega_{15}}{N_m^{*2}}\left\{\omega_{12}x_1^* - \varepsilon_2\omega_{11}N_m^* + (\omega_{13}+\omega_{14}+\omega_{15}+\omega_{16})x_1^* - \omega_1 N_m^*\right\} \\ &- \frac{2\beta_{m2}\eta_I(1-\xi)\nu_9\omega_{15}}{N_m^{*2}}\left\{\omega_{12}x_2^* + (\omega_{13}+\omega_{14}+\omega_{15}+\omega_{16})x_2^* - \omega_2 N_m^*\right\} \\ &- \frac{2\beta_{f1}^*(\omega_3+\theta_{p1}\omega_4)\nu_{13}}{N_f^{*2}}\left\{\{\omega_1+\omega_2\}x_{12}^* - \varepsilon_3\omega_{14}N_f^* + n_1 x_{12}^* - \omega_{12}N_f^*\right\} \\ &- \frac{2\beta_{f2}(\omega_8+\phi_p\omega_9+\theta_{p2}\omega_{10})\nu_{15}}{N_f^{*2}}\left\{\{\omega_1+\omega_2\}x_{12}^* - \varepsilon_4\omega_{16}N_f^* + n_1 x_{12}^* - \omega_{12}N_f^*\right\} \end{aligned} \tag{4.19}$$

Which is further simplified to give

$$\begin{aligned} a = &-\frac{2K_1\nu_3\omega_3}{N_m^* X_1^*}\left\{\omega_{12}X_1^* - \varepsilon_1\omega_7 N_m^* + (\omega_{13}+\omega_{14}+\omega_{15}+\omega_{16})X_1^* - \{\omega_1 + (1-\xi)\omega_2\}N_m^*\right\} \\ &- \frac{2\beta_{m2}\beta_{f2}(K_6+\theta_{p2}G_6)\nu_{15}\omega_{15}}{K_4K_6N_m^*N_f^*}\left\{\omega_{12}X_1^* - \varepsilon_2\omega_{11}N_m^* + (\omega_{13}+\omega_{14}+\omega_{15}+\omega_{16})x_1^* - \omega_1 N_m^*\right\} \\ &- \frac{2\beta_{m2}\beta_{f2}\eta_I(1-\xi)\nu_{15}\omega_{15}}{K_5K_6N_m^*N_f^*}\left\{\omega_{12}x_{12}^* + (\omega_{13}+\omega_{14}+\omega_{15}+\omega_{16})x_2^* - \omega_2 N_m^*\right\} \\ &- \frac{2K_1\nu_3\omega_3}{N_m^*N_f^*}\left\{\{\omega_1+\omega_2\}x_{12}^* - \varepsilon_3\omega_{14}N_f^* + n_1 x_{12}^* - \omega_{12}N_f^*\right\} \\ &- \frac{2\beta_{f2}\beta_{m2}\left\{K_5(K_6+\theta_{p2}G_6)x_1^* + K_5(\phi_pK_6+\theta_{p2}G_5)\eta_I(1-\xi)x_2^*\right\}\nu_{15}\omega_{15}}{K_4K_5K_6N_m^*N_f^{*2}} \\ &\times\left\{\{\omega_1+\omega_2\}x_{12}^* - \varepsilon_4\omega_{16}N_f^* + n_1 x_{12}^* - \omega_{12}N_f^*\right\} \end{aligned}$$

and

$$b = \frac{x_{12}^*}{N_f^*}\nu_{13}\left(\omega_3 + \theta_{p1}\omega_4 + \omega_{18}\right) > 0$$

Here,

$$n_1 = \omega_3+\omega_4+\omega_5+\omega_6+\omega_7+\omega_8+\omega_9+\omega_{10}+\omega_{11}$$

Since the bifurcation coefficient b is positive, it follows from Theorem 4.1 in Castillo-Chavez and Song (2004) that the model (3.23), or the transformed model (4.18), will undergo a backward bifurcation if the backward bifurcation coefficient, a, given by (4.19) is positive.

4.3.3 Non-existence of backward bifurcation of the full two-strain HPV model

Theorem 4.13. *In the absence of re-infection of recovered individuals with the same strain as well as imperfect vaccine* ($\varepsilon_1 = \varepsilon_2 = \varepsilon_3 = \varepsilon_4 = 0, \xi = 1$)*, the model* (3.23) *does not undergo backward bifurcation.*

Proof. Consider the model (3.23) with $\varepsilon_1 = \varepsilon_2 = \varepsilon_3 = \varepsilon_4 = 0$ and $\xi = 1$. The expression for the backward bifurcation coefficient, a, given as (4.19) (and noting that all parameters of the model (3.23) are positive), reduces to:

$$\begin{aligned} a = &- 2K_7\omega_3\nu_3\Bigg\{\frac{1}{N_m^*}(\omega_{13}+\omega_{14}+\omega_{15}+\omega_{16}) + \frac{1}{N_f^*}(\omega_3+\omega_4+\omega_5+\omega_6+\omega_7+\omega_8+\omega_9+\omega_{10}+\omega_{11}) \\ &+ \omega_1\Big(\frac{1}{N_f^*} - \frac{1}{x_1^*}\Big)\Bigg\} - \frac{2\beta_{m2}\beta_{f2}(K_2+\theta_{p2}G_6)\omega_{15}\nu_{15}}{K_4K_6N_f^*}\Bigg\{\frac{x_1^*}{N_m^*}(\omega_{13}+\omega_{14}+\omega_{15}+\omega_{16}) + \omega_1\Big(\frac{x_1^*}{N_f^*} - 1\Big) \\ &+ \frac{x_1^*}{N_f^*}(\omega_3+\omega_4+\omega_5+\omega_6+\omega_7+\omega_8+\omega_9+\omega_{10}+\omega_{11})\Bigg\} < 0, \end{aligned}$$

since $N_f^* > x_1^*$, then $\left(\frac{1}{N_f^*} - \frac{1}{x_1^*}\right) < 0$, and $\left(\frac{x_1^*}{N_f^*} - 1\right) < 0$, and also noting, that $(\omega_{13}+\omega_{14}+\omega_{15}+\omega_{16}) > 0$ and $(\omega_3+\omega_4+\omega_5+\omega_6+\omega_7+\omega_8+\omega_9+\omega_{10}+\omega_{11}) > 0$ while $\omega_1 < 0$. Hence, it follows from Theorem 4.1 in Castillo-Chavez and Song (2004) that the model (3.23) does not undergo a backward bifurcation if $\varepsilon_1 = \varepsilon_2 = \varepsilon_3 = \varepsilon_4 = 0$ and $\xi = 1$. $\square$

Hence, this study shows that the reinfection of recovered individuals with the same strain and imperfect vaccine induce backward bifurcation in a two-strain HPV model with cross-immunity. It is worthy of note, that the phenomenon of backward bifurcation was not captured in the multi-strain HPV models with cross-immunity in Elbasha and Galvani (2005) and Elbasha *et al.* (2008). To the authors' knowledge, we have been able to show, for the first time, that an imperfect HPV vaccine (that partially cross-protects against incident infection with strains not covered by the vaccine) and re-infection of recovered individuals with the same strain could induce backward bifurcation in a two-sex, two-strain vaccination model for HPV.

Remark: It is interesting to note that, in the absence of re-infection of recovered individuals with the same strain, if we set the cross-immunity parameter η_I to zero, backward bifurcation still persists due to the presence of an imperfect vaccine, ξ. However, setting $\xi = 1$, rules out the possibility of backward bifurcation in the model (3.23). This implies that, in the absence of re-infection of recovered individuals with the same strain, the over-riding parameter inducing backward bifurcation is the imperfect vaccine, though it has been established that cross-immunity due to infection induced the phenomenon of backward bifurcation in a two-strain model (Garba *et al.*, 2013; Garba and Gumel, 2010).

A global asymptotic stability result is established below for the DFE of the model for this scenario (to completely rule out backward bifurcation in this case).

4.3.4 Global asymptotic stability of the DFE of the two-strain HPV model: special case $\varepsilon_1 = \varepsilon_2 = \varepsilon_3 = \varepsilon_4 = 0, \xi = 1$

Theorem 4.14. *Consider the model* (3.23) *with* $\varepsilon_1 = \varepsilon_2 = \varepsilon_3 = \varepsilon_4 = 0$ *and* $\xi = 1$. *The DFE, given by* (4.2), *is GAS in* $\mathcal{D}$ *whenever* $\mathcal{R}_0 \leq 1$

Proof. Consider the Lyapunov function

$$\mathcal{L} = H_1 I_{f1} + H_2 P_{f1} + H_3 I_{f21} + H_4 I_{m1} + H_5 I_{m21} + H_6 I_{f2} + H_7 P_{f2} + H_8 I_{f12} + H_9 I_{m2} + H_{10} I_{m12}$$

whose coefficients are to be determined based on the approach illustrated in Shuai and van den Driessche (2013).

Corrsponding to the infected classes of the two-strain model (3.23), we assume a *Peron* eigenvector, as follows

$$w^T = \big(\omega_1, \omega_2, 0, \omega_4, \omega_5, \omega_6, \omega_7, \omega_8, \omega_9, \omega_{10}, \omega_{11}, \omega_{12}\big)$$

Evaluating $V^{-1}F$, we obtain

$$\begin{pmatrix}
0 & 0 & 0 & 0 & 0 & 0 & \frac{Q_1\beta_{m1}}{K_1N_m} & 0 & 0 & 0 & 0 & \frac{Q_1\beta_{m1}}{K_1N_m} \\
0 & 0 & 0 & 0 & 0 & 0 & \frac{G_1Q_1\beta_{m1}}{K_1K_2N_m} & 0 & 0 & 0 & 0 & \frac{G_1Q_1\beta_{m1}}{K_1K_2N_m} \\
0 & 0 & 0 & 0 & 0 & 0 & \frac{G_1G_3Q_1\beta_{m1}}{K_1K_2K_3N_m} & \frac{G_4G_6S_f\beta_{m2}}{K_3K_4K_6N_m} & 0 & 0 & \frac{G_4G_6S_f\beta_{m2}}{K_3K_4K_6N_m} & \frac{G_1G_3Q_1\beta_{m1}}{K_1K_2K_3N_m} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{S_f\beta_{m2}}{K_4N_m} & 0 & 0 & \frac{S_f\beta_{m2}}{K_4N_m} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{G_6S_f\beta_{m2}}{K_4K_6N_m} & 0 & 0 & \frac{G_6S_f\beta_{m2}}{K_4K_6N_m} & 0 \\
\frac{S_m\beta_{f1}}{K_7N_f} & \frac{S_m\beta_{f1}\theta_{p1}}{K_7N_f} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{S_m\beta_{f1}}{K_7N_f} & 0 & 0 \\
0 & 0 & 0 & \frac{S_m\beta_{f2}}{K_8N_f} & \frac{S_m\beta_{f2}\phi_p}{K_8N_f} & \frac{S_m\beta_{f2}\theta_{p2}}{K_8N_f} & 0 & 0 & \frac{S_m\beta_{f2}}{K_8N_f} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{pmatrix}$$

Evaluating $\omega^T V^{-1} F = \mathcal{R}_0 w^T$, we obtain the following equations:

$$\begin{aligned}
\frac{S_m^*\beta_{f1}}{N_f K_7}\omega_7 &= \mathcal{R}_{01}\omega_1 \\
\frac{S_m^*\beta_{f1}\theta_{p1}}{N_f K_7}\omega_7 &= \mathcal{R}_{01}\omega_2 \\
\frac{S_m^*\beta_{f2}}{N_f K_8}\omega_8 &= \mathcal{R}_{02}\omega_4 \\
\frac{S_m^*\beta_{f2}\phi_p}{N_f K_8}\omega_8 &= \mathcal{R}_{02}\omega_5 \\
\frac{S_m^*\beta_{f2}\theta_{p2}}{N_f^* K_8}\omega_8 &= \mathcal{R}_{02}\omega_6 \\
\frac{Q_1\beta_{m1}}{N_m^* K_1}\omega_1 + \frac{G_1Q_1\beta_{m1}}{K_1K_2N_m^*}\omega_2 + \frac{G_1G_3Q_1\beta_{m1}}{K_1K_2K_3N_m^*}\omega_3 &= \mathcal{R}_{01}\omega_7 \\
\frac{G_4G_6S_f^*\beta_{m2}}{K_3K_4K_6N_m^*}\omega_3 + \frac{S_f^*\beta_{m2}}{K_4N_m^*}\omega_4 + \frac{G_6S_f^*\beta_{m2}}{K_4K_6N_m^*}\omega_6 &= \mathcal{R}_{02}\omega_8 \\
\frac{S_m^*\beta_{f2}}{N_f K_8}\omega_8 &= \mathcal{R}_{02}\omega_9 \\
\frac{S_m^*\beta_{f1}}{N_f K_7}\omega_7 &= \mathcal{R}_{01}\omega_{10} \\
\frac{G_4G_6S_f^*\beta_{m2}}{K_3K_4K_6N_m^*}\omega_3 + \frac{S_f^*\beta_{m2}}{K_4N_m^*}\omega_4 + \frac{G_6S_f^*\beta_{m2}}{K_4K_6N_m^*}\omega_6 &= \mathcal{R}_{02}\omega_{11} \\
\frac{Q_1\beta_{m1}}{N_m^* K_1}\omega_1 + \frac{G_1Q_1\beta_{m1}}{K_1K_2N_m^*}\omega_2 + \frac{G_1G_3Q_1\beta_{m1}}{K_1K_2K_3N_m^*}\omega_3 &= \mathcal{R}_{01}\omega_{12}
\end{aligned} \tag{4.20}$$

Solving, we obtain

$$w^T = \left(\frac{S_m^*\beta_{f1}}{N_f^*K_7}, \frac{S_m^*\beta_{f1}\theta_{p1}}{N_fK_7}, 0, \frac{S_m^*\beta_{f2}}{N_f^*K_8}, 0, \frac{S_m^*\beta_{f2}\theta_{p2}}{N_f^*K_8}, \mathcal{R}_{01}, \mathcal{R}_{02}, \frac{S_m^*\beta_{f2}}{N_f^*K_8}, \frac{S_m^*\beta_{f1}}{N_f^*K_7}, \mathcal{R}_{02}, \mathcal{R}_{01}\right)$$

The coefficients of the Lyapunov function are obtained from the non-zero components of the matrix $\omega^T V^{-1}$, where

$$V^{-1} = \begin{pmatrix} \frac{1}{K_1} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{G_1}{K_1K_2} & \frac{1}{K_2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{G_2}{K_2K_{10}} & 0 & 0 \\ \frac{G_1G_3}{K_1K_2K_3} & \frac{G_3}{K_2K_3} & \frac{1}{K_3} & \frac{G_4G_6}{K_3K_4K_6} & 0 & \frac{G_4}{K_3K_6} & 0 & 0 & \frac{G_4G_7}{K_3K_6K_9} & \frac{G_2G_3}{K_2K_3K_{10}} & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{K_4} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{\mu_f} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{G_6}{K_4K_6} & 0 & \frac{1}{K_6} & 0 & 0 & \frac{G_7}{K_6K_9} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{K_7} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{K_8} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{K_9} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{K_{10}} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{K_{11}} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{K_{12}} \end{pmatrix}$$

The coefficients are given as:

$$H_1 = \frac{(K_2 + \theta_{p1}G_1)\beta_{f1}^f c_f S_f^*}{K_1K_2K_7N_f^*}, \quad H_2 = \frac{\theta_{p1}\beta_{f1}^f c_f S_f^*}{K_2K_7N_f^*}, \quad H_3 = \frac{(K_2 + \theta_{p1}G_2)\beta_{f1}^f c_f S_f^*}{K_2K_7K_{10}N_f^*}, \quad H_4 = \frac{\mathcal{R}_{01}}{K_7}$$
$$H_5 = \frac{\mathcal{R}_{01}}{K_{12}}, \quad H_6 = \frac{(K_6 + \theta_{p2}G_6)\beta_{f2}^f c_f}{K_4K_6K_8}, \quad H_7 = \frac{\theta_{p2}\beta_{f2}^f c_f}{K_6K_8}, \quad H_8 = \frac{(K_6 + \theta_{p2}G_7)\beta_{f2}^f c_f}{K_6K_8K_9}$$
$$H_9 = \frac{\mathcal{R}_{02}}{K_8}, \quad H_{10} = \frac{\mathcal{R}_{02}}{K_{11}}$$

The Lyapunov function is thus given by:

$$\begin{aligned}\mathcal{L} = {} & \frac{(K_2 + \theta_{p1}G_1)\beta_{f1}^f c_f S_f^*}{K_1K_2K_7N_f^*} I_{f1} + \frac{\theta_{p1}\beta_{f1}^f c_f S_f^*}{K_2K_7N_f^*} P_{f1} + \frac{(K_2 + \theta_{p1}G_2)\beta_{f1}^f c_f S_f^*}{K_2K_7K_{10}N_f^*} I_{f21} + \frac{\mathcal{R}_{01}}{K_7} I_{m1} + \frac{\mathcal{R}_{01}}{K_{12}} I_{m21} \\ & + \frac{(K_6 + \theta_{p2}G_6)\beta_{f2}^f c_f}{K_4K_6K_8} I_{f2} + \frac{\theta_{p2}\beta_{f2}^f c_f}{K_6K_8} P_{f2} + \frac{(K_6 + \theta_{p2}G_7)\beta_{f2}^f c_f}{K_6K_8K_9} I_{f12} + \frac{\mathcal{R}_{02}}{K_8} I_{m2} + \frac{\mathcal{R}_{02}}{K_{11}} I_{m12}\end{aligned}$$

with Lyapunov derivative

$$\begin{aligned}\dot{\mathcal{L}} = {} & \frac{(K_2 + \theta_{p1}G_1)\beta_{f1}^f c_f S_f^*}{K_1K_2K_7N_f^*} \dot{I}_{f1} + \frac{\theta_{p1}\beta_{f1}^f c_f S_f^*}{K_2K_7N_f^*} \dot{P}_{f1} + \frac{(K_2 + \theta_{p1}G_2)\beta_{f1}^f c_f S_f^*}{K_2K_7K_{10}N_f^*} \dot{I}_{f21} + \frac{\mathcal{R}_{01}}{K_7} \dot{I}_{m1} + \frac{\mathcal{R}_{01}}{K_{12}} \dot{I}_{m21} \\ & + \frac{(K_6 + \theta_{p2}G_6)\beta_{f2}^f c_f}{K_4K_6K_8} \dot{I}_{f2} + \frac{\theta_{p2}\beta_{f2}^f c_f}{K_6K_8} \dot{P}_{f2} + \frac{(K_6 + \theta_{p2}G_7)\beta_{f2}^f c_f}{K_6K_8K_9} \dot{I}_{f12} + \frac{\mathcal{R}_{02}}{K_8} \dot{I}_{m2} + \frac{\mathcal{R}_{02}}{K_{11}} \dot{I}_{m12}\end{aligned}$$

Substituting the expressions for $\dot{I}_{f1}$, $\dot{P}_{f1}$ and $\dot{I}_{m1}$ from (3.23), we have that

$$\begin{aligned}
\dot{\mathcal{L}} = {} & \frac{(K_2+\theta_{p1}G_1)\beta^f_{f1}c_f S^*_f}{K_1K_2K_7N^*_f}[\lambda_{m1}S_f+\alpha_1\lambda_{m1}M_f-K_1I_{f1}]+\frac{\theta_{p1}\beta^f_{f1}c_fS^*_f}{K_2K_7N^*_f}[G_1I_{f1}-K_2P_{f1}]\\
&+\frac{(K_2+\theta_{p1}G_2)\beta^f_{f1}c_fS^*_f}{K_2K_7K_{10}N^*_f}[\lambda_{m1}R_{f2}-K_{10}I_{f21}]+\frac{\mathcal{R}_{01}}{K_7}[\lambda_{f1}S_m+\alpha_3\lambda_{f1}M_m-K_7I_{m1}]+\frac{\mathcal{R}_{01}}{K_{12}}[\lambda_{f1}R_{m2}-K_{12}I_{m21}]\\
&+\frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f}{K_4K_6K_8}[\lambda_{m2}S_f+\alpha_2\lambda_{m2}M_f-K_4I_{f2}]+\frac{\theta_{p2}\beta^f_{f2}c_f}{K_6K_8}[G_6I_{f2}-K_6P_{f2}]\\
&+\frac{(K_6+\theta_{p2}G_7)\beta^f_{f2}c_f}{K_6K_8K_9}[\lambda_{m2}R_{f1}-K_9I_{f12}]+\frac{\mathcal{R}_{02}}{K_8}[\lambda_{f2}S_m+\alpha_4\lambda_{f2}M_m-K_8I_{m2}]+\frac{\mathcal{R}_{02}}{K_{11}}[\lambda_{f2}R_{m1}-K_{11}I_{m12}]
\end{aligned}$$

Since it is assumed that recovery from one strain does not confer any cross-protection or cross-enhancement against infection with the other strain, the dynamics of the disease for individuals in compartments I_{ij} and I_j are the same for males and females respectively. Hence, we can do the following substitutions

$$G_2=G_1,\quad G_7=G_6,\quad K_9=K_4,\quad K_{10}=K_1,\quad K_{11}=K_8,\quad K_{12}=K_7,$$

so that

$$\begin{aligned}
\dot{\mathcal{L}} = {} & \frac{(K_2+\theta_{p1}G_1)\beta^f_{f1}c_f S^*_f}{K_1K_2K_7N^*_f}[\lambda_{m1}S_f+\alpha_1\lambda_{m1}M_f-K_1I_{f1}]+\frac{\theta_{p1}\beta^f_{f1}c_fS^*_f}{K_2K_7N^*_f}[G_1I_{f1}-K_2P_{f1}]\\
&+\frac{(K_2+\theta_{p1}G_1)\beta^f_{f1}c_fS^*_f}{K_2K_7K_1N^*_f}[\lambda_{m1}R_{f2}-K_1I_{f21}]+\frac{\mathcal{R}_{01}}{K_7}[\lambda_{f1}S_m+\alpha_3\lambda_{f1}M_m-K_7I_{m1}]+\frac{\mathcal{R}_{01}}{K_7}[\lambda_{f1}R_{m2}-K_7I_{m21}]\\
&+\frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f}{K_4K_6K_8}[\lambda_{m2}S_f+\alpha_2\lambda_{m2}M_f-K_4I_{f2}]+\frac{\theta_{p2}\beta^f_{f2}c_f}{K_6K_8}[G_6I_{f2}-K_6P_{f2}]\\
&+\frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f}{K_6K_8K_4}[\lambda_{m2}R_{f1}-K_4I_{f12}]+\frac{\mathcal{R}_{02}}{K_8}[\lambda_{f2}S_m+\alpha_4\lambda_{f2}M_m-K_8I_{m2}]+\frac{\mathcal{R}_{02}}{K_8}[\lambda_{f2}R_{m1}-K_8I_{m12}]
\end{aligned}$$

which can be simplified to

$$\begin{aligned}
\dot{\mathcal{L}} = {} & \frac{(K_2+\theta_{p1}G_1)\beta^f_{f1}c_fS^*_f\lambda_{m1}(S_f+\alpha_1M_f+R_{f2})}{K_1K_2K_7N^*_f}+\frac{\mathcal{R}_{01}\lambda_{f1}(S_m+\alpha_3M_m+R_{m2})}{K_7}\\
&-I_{f1}\left[\frac{(K_2+\theta_{p1}G_1)\beta^f_{f1}c_fS^*_f}{K_2K_7N^*_f}-\frac{\theta_{p1}G_1\beta^f_{f1}c_fS^*_f}{K_2K_7N^*_f}\right]-P_{f1}\left[\frac{\theta_{p1}\beta^f_{f1}c_fS^*_f}{K_7N^*_f}\right]-\frac{(K_2+\theta_{p1}G_1)\beta^f_{f1}c_fS^*_f}{K_2K_7N^*_f}I_{f21}-\mathcal{R}_{01}I_{m1}\\
&+\frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f\lambda_{m2}(S_f+\alpha_2M_f+R_{f1})}{K_4K_6K_8}+\frac{\mathcal{R}_{02}\lambda_{f2}(S_m+\alpha_4M_m+R_{m1})}{K_8}\\
&-I_{f2}\left[\frac{(K_4+\theta_{p2}G_6)\beta^f_{f2}c_f}{K_4K_8}-\frac{\theta_{p2}G_6\beta^f_{f2}c_f}{K_4K_8}\right]-P_{f2}\left[\frac{\theta_{p2}\beta^f_{f2}c_f}{K_8}\right]-\frac{(K_4+\theta_{p2}G_6)\beta^f_{f2}c_f}{K_4K_8}I_{f12}-\mathcal{R}_{02}I_{m2}
\end{aligned}$$

Since $S_f+\alpha_1M_f+R_{f2}\le N_f$, $S_f+\alpha_2M_f+R_{f1}\le N_f$, $S_m+\alpha_3M_m+R_{m2}\le N_m$ and $S_m+\alpha_4M_m+R_{m1}\le N_m$, it then follows that,

$$\begin{aligned}
\dot{\mathcal{L}} \le {} & \frac{(K_2+\theta_{p1}G_1)\beta^f_{f1}c_fS^*_f\lambda_{m1}N_f}{K_1K_2K_7N^*_f}+\frac{\mathcal{R}_{01}\lambda_{f1}N_m}{K_7}-\frac{\beta^f_{f1}c_fI_{f1}}{K_7N^*_f}-P_{f1}\left[\frac{\theta_{p1}\beta^f_{f1}c_fS^*_f}{K_7N^*_f}\right]-\frac{\beta^f_{f1}c_fI_{f21}}{K_7N^*_f}-\mathcal{R}_{01}I_{m1}\\
&+\frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f\lambda_{m2}N_f}{K_4K_6K_8}+\frac{\mathcal{R}_{02}\lambda_{f2}N_m}{K_8}-\frac{\beta^f_{f2}c_fI_{f2}}{K_8}-P_{f2}\left[\frac{\theta_{p2}\beta^f_{f2}c_f}{K_8}\right]-\frac{\beta^f_{f2}c_fI_{f12}}{K_8}-\mathcal{R}_{02}I_{m2}
\end{aligned}$$

Applying the group constraint in (3.28) and the definition of the forces of infection in (3.24) - (3.27), we have that

$$\begin{aligned}\dot{\mathcal{L}} &= \frac{(K_2+\theta_{p1}G_1)\beta^f_{f1}c_fS^*_f\lambda_{m1}N_f}{K_1K_2K_7N^*_f} - \frac{\mathcal{R}_{01}\lambda_{m1}N_f}{c_m\beta^m_{m1}} + \frac{\mathcal{R}_{01}\lambda_{f1}N_m}{K_7} - \frac{S^*_f\lambda_{f1}N_m}{K_7N^*_f} \\ &+ \frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f\lambda_{m2}S_f}{K_4K_6K_8} - \frac{\mathcal{R}_{02}\lambda_{m2}N_f}{c_m\beta^m_{m2}} + \frac{\mathcal{R}_{02}\lambda_{f2}N_m}{K_8} - \frac{\lambda_{f2}N_m}{K_8} \\ \dot{\mathcal{L}} &\leq \frac{\mathcal{R}_{01}\lambda_{m1}N_f}{c_m\beta^m_{m1}}\left(\mathcal{R}_{01}-1\right) + \frac{\lambda_{f1}N_m}{K_7}\left(\mathcal{R}_{01}-1\right) \qquad \left(\text{since} \quad \frac{S^*_f}{N^*_f} < 1\right) \\ &+ \frac{\mathcal{R}_{02}\lambda_{m2}N_f}{c_m\beta^m_{m2}}\left(\mathcal{R}_{02}-1\right) + \frac{\lambda_{f2}N_m}{K_8}\left(\mathcal{R}_{02}-1\right)\end{aligned}$$

Since all the model parameters and variables are non-negative, we have that $\dot{\mathcal{L}} \leq 0$ for $\mathcal{R}_0 \leq 1$ with $\dot{\mathcal{L}} = 0$ if and only if $I_{f1} = P_{f1} = I_{f21} = I_{m1} = I_{m21} = 0$. Hence, $\mathcal{L}$ is a Lyapunov function on $\mathcal{D}$. Thus, using the La Salle's Invariance Principle (La Salle and Lefschetz, 1976), $I_{f1} \to 0, P_{f1} \to 0, I_{f21} \to 0, I_{m1} \to 0$ and $I_{m21} \to 0$ as $t \to \infty$. Substituting $I_{f1} = P_{f1} = I_{f21} = I_{m1} = I_{m21} = 0$ in (3.23) shows that $C_f \to 0, R^c_f \to 0, R_{f1} \to 0, S_f \to S^*_f, V_f \to V^*_f, R_{m1} \to 0, S_m \to S^*_m$ as $t \to \infty$. Thus, every solution to the equations of the model (3.23) with $\varepsilon_1 = \varepsilon_2 = \varepsilon_3 = \varepsilon_4 = 0, \xi = 1$, with initial conditions in $\mathcal{D}$, approaches the DFE ξ_0 as $t \to 0$ whenever $\mathcal{R}_0 \leq 1$. □

4.4 Existence and stability of boundary equilibria

The existence and stability of boundary equilibria of the model (3.23) is now investigated for a special case when the disease-induced death rates are assumed to be negligible (that is, $\delta_{f1} = \delta_{f2} = \delta^p_{f2} = \delta_{f12} = \delta_{f21} = \delta_{m1} = \delta_{m2} = \delta_{m12} = \delta_{m21} = \delta_{fc} = 0$). This is fitting in places like Northern America, Western Europe, Australia and New Zealand where the average annual HPV and cancer mortality rates are less than 4 persons per 100,000 of the population (Foreman *et al.* 2012; HPV and Related Diseases Report, 2017). It should be noted that setting $\delta_{f1} = \delta_{f2} = \delta^p_{f2} = \delta_{f12} = \delta_{f21} = \delta_{m1} = \delta_{m2} = \delta_{m12} = \delta_{m21} = \delta_{fc} = 0$ in (3.23) gives $N_f \to \frac{\Lambda_f}{\mu_f}$ and $N_m \to \frac{\Lambda_m}{\mu_m}$ as $t \to \infty$.

We will now explore the existence and stability of the positive boundary equilibria. Let,

$$\begin{aligned} \lambda^{**}_{f1} &= \frac{\beta_{f1}\mu_f\left(I^{**}_{f1} + I^{**}_{f21} + \theta_{p1}P^{**}_{f1}\right)}{\Lambda_f} \quad \text{and} \quad \lambda^{**}_{m1} = \frac{\beta_{m1}\mu_m(I^{**}_{m1} + I^{**}_{m21})}{\Lambda_m} \\ \lambda^{**}_{f2} &= \frac{\beta_{f2}\mu_f\left(I^{**}_{f2} + I^{**}_{f12} + \phi_p I^{p**}_{f2} + \theta_{p2}P^{**}_{f2}\right)}{\Lambda_f} \quad \text{and} \quad \lambda^{**}_{m2} = \frac{\beta_{m2}\mu_m(I^{**}_{m2} + I^{**}_{m12})}{\Lambda_m} \end{aligned} \tag{4.21}$$

be the forces of infection for strain 1 and strain 2, respectively, at the endemic steady-state.

The equilibria of the model (3.23) can then be obtained by finding the fixed points of the equation

$$X = \Phi(X) = \begin{pmatrix} \theta_1(\lambda^{**}_1, \lambda^{**}_2) \\ \theta_2(\lambda^{**}_1, \lambda^{**}_2) \end{pmatrix}, \quad \text{where} \quad X = \begin{pmatrix} \lambda^{**}_1 \\ \lambda^{**}_2 \end{pmatrix} \tag{4.22}$$

with,

$\lambda^{**}_1 = \lambda^{**}_{f1} + \lambda^{**}_{m1}, \quad \lambda^{**}_2 = \lambda^{**}_{f2} + \lambda^{**}_{m2}$

4.4.1 Strain 1-only sub-model

In the absence of strain 2, (obtained by setting $I_{f2} = I^p_{f2} = P_{f2} = R_{f2} = I_{f12} = I_{f21} = M_f = I_{m2} = R_{m2} = I_{m12} = I_{m21} = M_m = 0$ in the model (3.23)), the strain 1-only sub-model with

$\delta_{f1} = \delta_{m1} = \delta_{fc} = 0$ is given by:

$$\begin{aligned}
\frac{dS_f}{dt} &= (1-f)\Lambda_f - (\lambda_{m1} + \mu_f)\, S_f \\
\frac{dV_f}{dt} &= f\Lambda_f - (1-\xi)\lambda_{m1} V_f - \mu_f V_f \\
\frac{dI_{f1}}{dt} &= (1-\xi)\lambda_{m1} V_f + \lambda_{m1} S_f - K_1 I_{f1} + \varepsilon_1 \lambda_{m1} R_{f1} \\
\frac{dP_{f1}}{dt} &= G_1 I_{f1} - K_2 P_{f1} \\
\frac{dC_f}{dt} &= G_3 P_{f1} - K_3 C_f \\
\frac{dR^c_f}{dt} &= \pi_f C_f - \mu_f R^c_f \\
\frac{dR_{f1}}{dt} &= p_1 \tau_{f1} I_{f1} + q_1 \kappa_{f1} P_{f1} - (\mu_f + \varepsilon_1 \lambda_{m1})\, R_{f1} \\
\frac{dS_m}{dt} &= \Lambda_m - (\lambda_{f1} + \mu_m)\, S_m \\
\frac{dI_{m1}}{dt} &= \lambda_{f1} S_m - K_7 I_{m1} + \varepsilon_3 \lambda_{f1} R_{m1} \\
\frac{dR_{m1}}{dt} &= \tau_{m1} I_{m1} - (\mu_m + \varepsilon_3 \lambda_{f1})\, R_{m1}
\end{aligned} \tag{4.23}$$

where now

$$\lambda_{f1} = \frac{\beta_{f1}(I_{f1} + \theta_{p1} P_{f1})}{N_f}, \quad \lambda_{m1} = \frac{\beta_{m1} I_{m1}}{N_m}$$

with

$$\begin{aligned}
N_f &= S_f + V_f + I_{f1} + P_{f1} + C_f + R^c_f + R_{f1}, \quad \text{and} \\
N_m &= S_m + I_{m1} + R_{m1}
\end{aligned}$$

Consider the regions:

$$\mathcal{D}_1 = \mathcal{D}_1^f \cup \mathcal{D}_1^m$$

with

$$\begin{aligned}
\mathcal{D}_1^f &= \left\{ (S_f, V_f, I_{f1}, P_{f1}, C_f, R^c_f, R_{f1}) \in \mathfrak{R}^7_+ : N_f \leq \frac{\Lambda_f}{\mu_f} \right\}, \text{and} \\
\mathcal{D}_1^m &= \left\{ (S_m, I_{m1}, R_{m1}) \in \mathfrak{R}^3_+ : N_m \leq \frac{\Lambda_m}{\mu_m} \right\}
\end{aligned}$$

The region $\mathcal{D}_1$ is positively invariant.

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

The strain 1-only sub-model (4.23) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\begin{aligned} \xi_{01} =& (S_f^*, V_f^*, I_{f1}^*, P_{f1}^*, C_f^*, R_f^{c*}, R_{f1}^*, S_m^*, I_{m1}^*, R_{m1}^*) \\ =& (\frac{(1-f)\Lambda_f}{\mu_f}, \frac{f\Lambda_f}{\mu_f}, 0, 0, 0, 0, 0, \frac{\Lambda_m}{\mu_m}, 0, 0) \end{aligned} \tag{4.24}$$

The linear stability of ξ_{01} will be investigated using the next generation operator method on the system (4.23) (van den Driessche and Watmough, 2002). The matrices F_{01} (for the new infection terms) and V_{01} (for the remaining transition terms) associated with the Strain 1-only sub-model (4.23) are given, respectively, by (noting that $S_f^* = \frac{(1-f)\Lambda_f}{\mu_f}$, $V_f^* = \frac{f\Lambda_f}{\mu_f}$, $N_f^* = \frac{\Lambda_f}{\mu_f}$, $S_m^* = N_m^* = \frac{\Lambda_m}{\mu_m}$ at the DFE ξ_{01})

$$F_{01} = \begin{bmatrix} 0 & 0 & 0 & \frac{\beta_{m1}(S_f^*+(1-\xi)V_f^*)}{N_m^*} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\beta_{f1}S_m^*}{N_f^*} & \frac{\theta_{p1}\beta_{f1}S_m^*}{N_f^*} & 0 & 0 \end{bmatrix} \tag{4.25}$$

$$V_{01} = \begin{bmatrix} K_1 & 0 & 0 & 0 \\ -G_1 & K_2 & 0 & 0 \\ 0 & -G_3 & K_3 & 0 \\ 0 & 0 & 0 & K_7 \end{bmatrix} \tag{4.26}$$

The associated basic reproduction number of the Strain 1-only sub-model (4.23), denoted by $\mathcal{R}_{01} = \rho(F_{01}V_{01}^{-1})$, is given by

$$\mathcal{R}_{01} = \sqrt{\frac{\beta_{f1}\beta_{m1}(K_2 + G_1\theta_{p1})(1 - f\xi)}{K_1K_2K_7}}$$

where ρ represents the spectral radius of $F_{01}V_{01}^{-1}$. Using Theorem 2 of van den Driessche and Watmough (2002), the following result is established.

Lemma 4.15. The DFE, ξ_{01}, of the Strain 1-only sub-model (4.23) is locally asymptotically stable (LAS) if $\mathcal{R}_{01} < 1$, and unstable if $\mathcal{R}_{01} > 1$.

4.4.3 Strain 1-only boundary equilibrium (ξ_{e1})

Setting $\lambda_{f2} = \lambda_{m2} = 0$ in (3.23) gives the following general form of the strain 1-only boundary equilibrium (denoted by ξ_{e1})

$$\xi_{e1} = \left(S_f^{**}, V_f^{**}, I_{f1}^{**}, P_{f1}^{**}, C_f^{**}, R_f^{c**}, R_{f1}^{**}, 0, 0, 0, 0, S_m^{**}, I_{m1}^{**}, R_{m1}^{**}, 0, 0, 0, 0, 0, 0, 0, 0\right)$$

(It should be noted here that N_f^{**} and N_m^{**} are replaced with their limiting values $\frac{\Lambda_f}{\mu_f}$ and $\frac{\Lambda_m}{\mu_m}$ respectively, as all disease induced death rates are assumed zero). It should be noted that setting $\delta_{f1} = \delta_{m1} = \delta_{fc} = 0$ in (4.23) gives $N_f \to \frac{\Lambda_f}{\mu_f}$ and $N_m \to \frac{\Lambda_m}{\mu_m}$ as $t \to \infty$. Let $\bar{\beta}_{f1} = \frac{\mu_f \beta_{f1}}{\Lambda_f}$ and $\bar{\beta}_{m1} = \frac{\mu_m \beta_{m1}}{\Lambda_m}$ so that

$$\lambda_{f1} = \bar{\beta}_{f1}(I_{f1} + \theta_{p1} P_{f1}) \tag{4.27}$$

and

$$\lambda_{m1} = \bar{\beta}_{m1} I_{m1} \tag{4.28}$$

Define

$$\begin{aligned} \lambda_{f1}^{**} &= \frac{\beta_{f1}\mu_f \left(I_{f1}^{**} + \theta_{p1} P_{f1}^{**}\right)}{\Lambda_f} \\ \lambda_{m1}^{**} &= \frac{\beta_{m1}\mu_m I_{m1}^{**}}{\Lambda_m} \end{aligned} \tag{4.29}$$

Setting the right hand sides of model (4.23) to zero gives the steady state solutions

$$
\begin{aligned}
S_f^{**} &= \frac{(1-f)\,\Lambda_f}{(\lambda_{m1}^{**}+\mu_f)}, \quad V_f^{**} = \frac{f\Lambda_f}{[(1-\xi)\,\lambda_{m1}^{**}+\mu_f]},\\
I_{f1}^{**} &= \frac{\big\{(1-\xi)\Lambda_f(\lambda_{m1}^{**})^2+(1-\xi f)\Lambda_f\mu_f\lambda_{m1}^{**}\big\}K_2(\mu_f+\varepsilon_1\lambda_{m1}^{**})}{C_1(\lambda_{m1}^{**})^3+C_2(\lambda_{m1}^{**})^2+C_3\lambda_{m1}^{**}+C_4},\\
P_{f1}^{**} &= \frac{\big\{(1-\xi)\Lambda_f(\lambda_{m1}^{**})^2+(1-\xi f)\Lambda_f\mu_f\lambda_{m1}^{**}\big\}G_1(\mu_f+\varepsilon_1\lambda_{m1}^{**})}{C_1(\lambda_{m1}^{**})^3+C_2(\lambda_{m1}^{**})^2+C_3\lambda_{m1}^{**}+C_4},\\
R_{f1}^{**} &= \frac{\big\{(1-\xi)\Lambda_f(\lambda_{m1}^{**})^2+(1-\xi f)\Lambda_f\mu_f\lambda_{m1}^{**}\big\}(G_1+K_2)}{C_1(\lambda_{m1}^{**})^3+C_2(\lambda_{m1}^{**})^2+C_3\lambda_{m1}^{**}+C_4},\\
C_f^{**} &= \frac{\big\{(1-\xi)\Lambda_f(\lambda_{m1}^{**})^2+(1-\xi f)\Lambda_f\mu_f\lambda_{m1}^{**}\big\}G_1G_3(\mu_f+\varepsilon_1\lambda_{m1}^{**})}{K_3\big\{C_1(\lambda_{m1}^{**})^3+C_2(\lambda_{m1}^{**})^2+C_3\lambda_{m1}^{**}+C_4\big\}},\\
R_f^{c**} &= \frac{\big\{(1-\xi)\Lambda_f(\lambda_{m1}^{**})^2+(1-\xi f)\Lambda_f\mu_f\lambda_{m1}^{**}\big\}G_1G_3\pi_f(\mu_f+\varepsilon_1\lambda_{m1}^{**})}{\mu_fK_3\big\{C_1(\lambda_{m1}^{**})^3+C_2(\lambda_{m1}^{**})^2+C_3\lambda_{m1}^{**}+C_4\big\}},\\
S_m^{**} &= \frac{\Lambda_m}{(\mu_m+\lambda_{f1}^{**})}, \quad I_{m1}^{**} = \frac{\Lambda_m\lambda_{f1}^{**}(\mu_m+\varepsilon_3\lambda_{f1}^{**})}{D_1(\lambda_{f1}^{**})^2+D_2\lambda_{f1}^{**}+D_3}\\
R_{m1}^{**} &= \frac{\tau_{m1}\Lambda_m\lambda_{f1}^{**}}{D_1(\lambda_{f1}^{**})^2+D_2\lambda_{f1}^{**}+D_3}
\end{aligned}
\tag{4.30}
$$

where,

$$C_1 = (1-\xi)\varepsilon_1\big\{(1-p_1)(1-q_1)\tau_{f1}\kappa_{f1}+(1-p_1)\tau_{f1}\mu_f+(\delta_{f1}+\mu_f)(\kappa_{f1+\mu_f})\big\}>0$$

$$C_2 = (1-\xi)K_1K_2\mu_f+(2-\xi)\mu_f\varepsilon_1\big\{(1-p_1)(1-q_1)\tau_{f1}\kappa_{f1}+(1-p_1)\tau_{f1}\mu_f+(\delta_{f1}+\mu_f)(\kappa_{f1+\mu_f})\big\}>0$$

$$
\begin{aligned}
C_3 &= (2-\xi)\mu_f^2(\tau_{f1}+\delta_{f1}+\mu_f)(\kappa_{f1}+\mu_f)+\mu_f^2\varepsilon_1\big\{(1-p_1)(1-q_1)\tau_{f1}\kappa_{f1}+(1-p_1)\tau_{f1}\mu_f\\
&\quad+(\delta_{f1}+\mu_f)(\kappa_{f1+\mu_f})\big\}>0
\end{aligned}
$$

$$D_1=\varepsilon_3(K_7+\tau_{m1}), \quad D_2=\mu_m(K_7+\varepsilon_3+\tau_{m1}\varepsilon_3), \quad D_3=\mu_m^2K_7$$

Substituting the above expressions into (4.29) gives

$$
\begin{aligned}
\lambda_{f1}^{**} &= \frac{\lambda_{m1}^{**}\,[b_{02}(\lambda_{m1}^{**})^2+b_{01}\lambda_{m1}^{**}+b_0]}{[b_{33}(\lambda_{m1}^{**})^3+b_{22}(\lambda_{m1}^{**})^2+b_{11}\lambda_{m1}^{**}+b_{00}]},\\
\lambda_{m1}^{**} &= \frac{\lambda_{f1}^{**}\left(c_{02}\lambda_{f1}^{**}+c_{01}\right)}{c_{22}(\lambda_{f1}^{**})^2+c_{11}\lambda_{f1}^{**}+c_{00}}
\end{aligned}
\tag{4.31}
$$

where,

$$
\begin{aligned}
b_0 &= \beta_{f1}\Lambda_f\mu_f^2(1-\xi f)(K_2\mu_f+\theta_{p1}\mu_f G_1),\\
b_{01} &= \beta_{f1}\Lambda_f\mu_f(1-\xi)(K_2\mu_f+\theta_{p1}\mu_f G_1)+\beta_{f1}\Lambda_f\mu_f^2(1-\xi)(K_2\varepsilon_1+\theta_{p1}G_1\varepsilon_1),\\
b_{02} &= \beta_{f1}\Lambda_f\mu_f(1-\xi)(K_2\varepsilon_1+\theta_{p1}G_1\varepsilon_1),\\
b_{00} &= K_1K_2\Lambda_f\mu_f^3,\\
b_{11} &= (2-\xi)\Lambda_f\mu_f^2(\tau_{f1}+\delta_{f1}+\mu_f)(\kappa_{f1}+\mu_f)+\Lambda_f\mu_f^2\varepsilon_1\big\{(1-p_1)(1-q_1)\tau_{f1}\kappa_{f1}+(1-p_1)\tau_{f1}\mu_f\\
&\quad+(\delta_{f1}+\mu_f)(\kappa_{f1+\mu_f})\big\}>0\\
b_{22} &= (1-\xi)\Lambda_f\mu_f(\tau_{f1}+\delta_{f1}+\mu_f)(\kappa_{f1}+\mu_f)+(2-\xi)\Lambda_f\mu_f\varepsilon_1\big\{(1-p_1)(1-q_1)\tau_{f1}\kappa_{f1}+(1-p_1)\tau_{f1}\mu_f\\
&\quad+(\delta_{f1}+\mu_f)(\kappa_{f1}+\mu_f)\big\}>0\\
b_{33} &= (1-\xi)\Lambda_f\varepsilon_1\big\{(1-p_1)(1-q_1)\tau_{f1}\kappa_{f1}+(1-p_1)\tau_{f1}\mu_f(\delta_{f1}+\mu_f)(\kappa_{f1}+\mu_f)\big\}>0\\
c_{00} &= \Lambda_m\mu_m^2K_7,\ \ c_{11}=\Lambda_m\mu_mK_7+\Lambda_m\mu_mK_7\varepsilon_3+\Lambda_m\mu_m\tau_{m1}\varepsilon_3,\ \ c_{22}=\varepsilon_3\Lambda_m(K_7+\tau_{m1})\\
c_{01} &= \beta_{m1}\Lambda_m\mu_m^2,\ \ c_{02}=\beta_{m1}\Lambda_m\mu_m\varepsilon_3
\end{aligned}
\tag{4.32}
$$

Since all the parameters of the model (4.23) are positive and $0<\xi\le 1$, we have that all the expressions in (4.32) are positive.

$$
H_1(\lambda_{m1}^{**})^6+H_2(\lambda_{m1}^{**})^5+H_3(\lambda_{m1}^{**})^4+H_4(\lambda_{m1}^{**})^3+H_5(\lambda_{m1}^{**})^2+H_6\lambda_{m1}^{**}+H_7=0 \tag{4.33}
$$

with

$$
\begin{aligned}
H_1 &= b_{02}^2 c_{22} + c_{11} b_{02} b_{33} + c_{00} b_{33}^2 > 0\\
H_2 &= 2b_{01} b_{02} c_{22} + c_{11} b_{02} b_{22} + c_{11} b_{01} b_{33} + 2c_{00} b_{22} b_{33} - b_{02}^2 c_{02} - b_{02} c_{01} b_{33},\\
H_3 &= 2b_0 b_{02} c_{22} + b_{01}^2 c_{22} + c_{11} b_{02} b_{11} + c_{11} b_{01} b_{22} + c_{11} b_0 b_{33} + 2c_{00} b_{11} b_{33}\\
&\quad + c_{00} b_{22}^2 - 2b_{01} b_{02} c_{02} - b_{02} c_{01} b_{22} - b_{01} c_{01} b_{33},\\
H_4 &= 2b_0 b_{01} c_{22} + b_{00} b_{02} c_{11} + b_{01} b_{11} c_{11} + b_0 b_{22} c_{11} - 2b_0 b_{02} c_{02} - b_{01}^2 c_{02}\\
&\quad - b_{02} b_{11} c_{01} - b_{01} b_{22} c_{01} + b_{00} b_{33} c_{00}(2 - \mathcal{R}_{01}^2)\\
H_5 &= (b_{01} c_{11} - b_{02} c_{01}) b_{00} + (b_{11} c_{11} - 2b_{01} c_{02}) b_0 + (b_{11} c_{00} - b_{01} c_{01}) b_{11} + b_{00} c_{00} b_{22}(2 - \mathcal{R}_{01}^2)\\
H_6 &= b_0 b_{00} c_{11} - b_0^2 c_{02} - b_{00} b_{01} c_{01} + 2b_{00} b_{11} c_{00}(1 - \mathcal{R}_{01}^2)\\
H_7 &= b_{00}^2 c_{00}(1 - \mathcal{R}_{01}^2) > 0 \quad \text{if} \quad \mathcal{R}_{01} < 1
\end{aligned}
\tag{4.34}
$$

The components of the EEP are then obtained by solving for λ_{m1}^{**} from the polynomial (4.33), and substituting the positive values of λ_{m1}^{**} into the expressions in (4.30) [noting (4.32)]. Furthermore, it follows from (4.34) that the coefficient H_1, is always positive and H_7 is positive (negative) if $\mathcal{R}_{01}$ is less (greater) than unity. The following results can be deduced.

Theorem 4.16. *The Strain 1-only sub-model* (4.23) *with* $\delta_{f1} = \delta_{m1} = \delta_{fc} = 0$ *has:*

(i) six or four endemic equilibria if $H_2 < 0, H_3 > 0, H_4 < 0, H_5 > 0, H_6 < 0$ *and* $\mathcal{R}_{01} < 1$,

(ii) four or two endemic equilibria if $H_2 > 0, H_3 < 0, H_4 > 0, H_5 < 0, H_6 > 0$ *and* $\mathcal{R}_{01} < 1$,

(iii) two endemic equilibria if $H_2 > 0, H_3 > 0, H_4 < 0, H_5 < 0, H_6 > 0$ *and* $\mathcal{R}_{01} < 1$

(iv) no endemic equilibrium otherwise, if $\mathcal{R}_{01} < 1$,

The first three items of Theorem 4.16 ((i) - (iii)) suggest the possibility of backward bifurcation in the strain 1-only sub-model (4.23) with negligible disease-induced deaths (i.e., $\delta_{f1} = \delta_{m1} = \delta_{fc} = 0$) when $\mathcal{R}_{01} < 1$.

4.4.4 Backward bifurcation analysis of strain-1 only sub-model

It is instructive to characterize the type of bifurcation the model (4.23) may undergo. We claim the following result:

Theorem 4.17. *The model* (4.23) *exhibits backward bifurcation at* $\mathcal{R}_{01} = 1$ *whenever a bifurcation coefficient, denoted by a (given by* (4.36)*), is positive.*

Proof:

Proof. Suppose

$$\xi_{e1} = \left(S_f^{**}, V_f^{**}, I_{f1}^{**}, P_{f1}^{**}, C_f^{**}, R_f^{c**}, R_{f1}^{**}, 0, 0, 0, 0, S_m^{**}, I_{m1}^{**}, R_{m1}^{**}, 0, 0, 0, 0, 0, 0, 0, 0\right)$$

represents any arbitrary endemic equilibrium of the strain 1-only model (that is, an endemic equilibrium in which at least one of the infected components is non-zero). The existence (or otherwise) of backward bifurcation will be explored using the Centre Manifold Theory Castillo-Chavez and Song (2004). To apply this theory, it is necessary to carry out the following change of variables.

$$S_f = x_1,\ V_f = x_2,\ I_{f1} = x_3,\ P_{f1} = x_4,\ C_f = x_5,\ R_f^c = x_6,\ R_{f1} = x_7,\ S_m = x_8,\ I_{m1} = x_9,\ R_{m1} = x_{10}$$

so that

$$N = \sum_{i=1}^{10} x_i$$

Further, using the vector notation

$$X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10})^T$$

the model (4.23) can be re-written in the form

$$\frac{dX}{dt} \equiv f = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10})^T$$

as follows:

$$
\begin{aligned}
\frac{dx_1}{dt} &\equiv f_1 = (1-f)\Lambda_f - (\lambda_{m1} + \mu_f)\, x_1 \\
\frac{dx_2}{dt} &\equiv f_2 = f\Lambda_f - [(1-\xi)\lambda_{m1} + \mu_f]\, x_2 \\
\frac{dx_3}{dt} &\equiv f_3 = \lambda_{m1}x_1 + (1-\xi)\lambda_{m1}x_2 + \varepsilon_1\lambda_{m1}x_7 - (\tau_{f1} + \delta_{f1} + \mu_f)x_3 \\
\frac{dx_4}{dt} &\equiv f_4 = (1-p_1)\tau_{f1}x_3 - (\kappa_{f1} + \mu_f)x_4 \\
\frac{dx_5}{dt} &\equiv f_5 = (1-q_1)\kappa_{f1}x_4 - (\pi_f + \mu_f + \delta_{fc})x_5 \\
\frac{dx_6}{dt} &\equiv f_6 = \pi_f x_5 - \mu_f x_6 \\
\frac{dx_7}{dt} &\equiv f_7 = p_1\tau_{f1}x_3 + q_1\kappa_{f1}x_4 - \mu_f x_7 - \varepsilon_1\lambda_{m1}x_7 \\
\frac{dx_8}{dt} &\equiv f_8 = \Lambda_m - (\lambda_{f1} + \mu_m)\, x_8 \\
\frac{dx_9}{dt} &\equiv f_9 = \lambda_{f1}x_8 + \varepsilon_3\lambda_{f1}x_{10} - (\tau_{m1} + \delta_{m1} + \mu_m)x_9 \\
\frac{dx_{10}}{dt} &\equiv f_{10} = \tau_{m1}x_9 - \mu_m x_{10} - \varepsilon_3\lambda_{f1}x_{10}
\end{aligned}
\tag{4.35}
$$

where

$$
\begin{aligned}
\lambda_{f1} &= \frac{\beta_{f1}(x_3 + \theta_{p1}x_4)}{\sum_{i=1}^{7} x_i} \\
\lambda_{m1} &= \frac{\beta_{m1}x_9}{\sum_{i=8}^{10} x_i}
\end{aligned}
$$

Without loss of generality, consider the case when $\mathcal{R}_{01} = 1$. Suppose, further, that β_{f1} is chosen as a bifurcation parameter. Solving for $\beta_{f1} = \beta_{f1}^*$ from $\mathcal{R}_{01} = 1$ gives

$$
\beta_{f1} = \beta_{f1}^* = \frac{K_1K_2K_7}{\beta_{m1}\,(K_2 + G_1\theta_{p1})\,(1 - f\xi)}
$$

The Jacobian of the transformed system (4.35), evaluated at the DFE (ξ_{01}) with $\beta_{f1} = \beta_{f1}^*$, is given by

$$J(\xi_{01})|_{\beta_{f1}=\beta_{f1}^*} = \begin{bmatrix} -\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{-\beta_{m1}x_1^*}{N_m^*} & 0 \\ 0 & -\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & \frac{-\beta_{m1}(1-\xi)x_2^*}{N_m^*} & 0 \\ 0 & 0 & -K_1 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{m1}X_1^*}{N_m^*} & 0 \\ 0 & 0 & G_1 & -K_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & G_3 & -K_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \pi_f & -\mu_f & 0 & 0 & 0 & 0 \\ 0 & 0 & p_1\tau_{f1} & q_1\kappa_{f1} & 0 & 0 & -\mu_f & 0 & 0 & 0 \\ 0 & 0 & \frac{-\beta_{f1}^*x_8^*}{N_f^*} & \frac{-\beta_{f1}^*\theta_{p1}x_8^*}{N_f^*} & 0 & 0 & 0 & -\mu_m & 0 & 0 \\ 0 & 0 & \frac{\beta_{f1}^*x_8^*}{N_f^*} & \frac{\beta_{f1}^*\theta_{p1}x_8^*}{N_f^*} & 0 & 0 & 0 & 0 & -K_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \tau_{m1} & -\mu_m \end{bmatrix}$$

where, $N_f^* = x_1^* + x_2^*$, $N_m^* = x_8^*$, $X_1^* = x_1^* + (1-\xi)x_2^*$.

It can be shown that the Jacobian of (4.35) has a right eigenvector (associated with the zero eigenvalue) given by

$$w = [\omega_1, \omega_2, \omega_3, \omega_4, \omega_5, \omega_6, \omega_7, \omega_8, \omega_9, \omega_{10}]^T$$

where,

$$-\mu_f\omega_1 - \frac{\beta_{m1}x_1^*}{N_m^*}\omega_9 = 0$$

$$-\mu_f\omega_2 - \frac{\beta_{m1}(1-\xi)x_2^*}{N_m^*}\omega_9 = 0$$

$$-K_1\omega_3 - \frac{\beta_{m1}X_1^*}{N_m^*}\omega_9 = 0$$

$$G_1\omega_3 - K_2\omega_4 = 0$$

$$G_3\omega_4 - K_3\omega_5 = 0$$

$$\pi_f\omega_5 - \mu_f\omega_6 = 0$$

$$p_1\tau_{f1}\omega_3 + q_1\kappa_{f1}\omega_4 - \mu_f\omega_7 = 0$$

$$-\frac{\beta_{f1}x_8^*}{N_f^*}\omega_3 - \frac{\beta_{f1}\theta_{p1}x_8^*}{N_f^*}\omega_4 - \mu_m\omega_8 = 0$$

$$\frac{\beta_{f1}x_8^*}{N_f^*}\omega_3 + \frac{\beta_{f1}\theta_{p1}x_8^*}{N_f^*}\omega_4 - K_7\omega_9 = 0$$

$$\tau_{m1}\omega_9 - \mu_m\omega_{10}$$

Solving, gives

$$\begin{aligned}
&\omega_1 = -\frac{\beta_{m1}x_1^*\omega_9}{\mu_f N_m^*}, \quad \omega_2 = -\frac{\beta_{m1}(1-\xi)x_2^*\omega_9}{\mu_f N_m^*}, \quad \omega_3 = \frac{\beta_{m1}X_1^*\omega_9}{K_1 N_m^*}, \quad \omega_4 = \frac{\theta_{p1}G_1\beta_{m1}X_1^*\omega_9}{K_1K_2N_m^*},\\
&\omega_5 = \frac{\theta_{p1}G_1G_3\beta_{m1}X_1^*\omega_9}{K_1K_2K_3N_m^*}, \quad \omega_6 = \frac{\pi_f\theta_{p1}G_1G_3\beta_{m1}X_1^*\omega_9}{\mu_f K_1K_2K_3N_m^*}, \quad \omega_7 = \frac{\beta_{m1}X_1^*(p_1\tau_{f1}K_2 + q_1\kappa_{f1}G_1)\omega_9}{\mu_f K_1K_2N_m^*}\\
&\omega_8 = -\frac{K_7X_1^*\omega_9}{\mu_m(1-f\xi)}, \quad \omega_9 = \omega_9 > 0, \quad \omega_{10} = \frac{\tau_{m1}\omega_9}{\mu_m}
\end{aligned}$$

Furthermore, (4.35) has a corresponding left eigenvector (associated with the zero eigenvalue) given by

$$v = [\nu_1, \nu_2, \nu_3, \nu_4, \nu_5, \nu_6, \nu_7, \nu_8, \nu_9, \nu_{10}]$$

where,

$$-K_1\nu_3 + G_1\nu_4 + \tfrac{\beta_{f1}^* x_8^*}{N_f^*}\nu_9 = 0$$

$$-K_2\nu_4 + \tfrac{\beta_{f1}^*\theta_{p1}x_8^*}{N_f^*}\nu_9 = 0$$

$$\tfrac{\beta_{m1}X_1^*}{N_m^*}\nu_3 - K_7\nu_9 = 0$$

Solving, gives

$$\nu_3 = \frac{\beta_{f1}^* x_8^*(K_2 + \theta_{p1}G_1)\nu_9}{K_1K_2N_f^*}, \quad \nu_4 = \frac{\beta_{f1}^*\theta_{p1}x_8^*\nu_9}{K_2N_f^*}, \quad \nu_9 = \nu_9 > 0$$

Based on Theorem 4.1 in Castillo-Chavez and Song (2004), and by computing the non-zero partial derivatives of $F(x)$(evaluated at the disease free equilibrium, DFE (ξ_{01})), we have that the associated bifurcation coefficients defined by a and b, are given by

$$a = \sum_{k,i,j=1}^{n} \nu_k\omega_i\omega_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \quad \text{and} \quad b = \sum_{k,i=1}^{n} \nu_k\omega_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_S^*}(0,0),$$

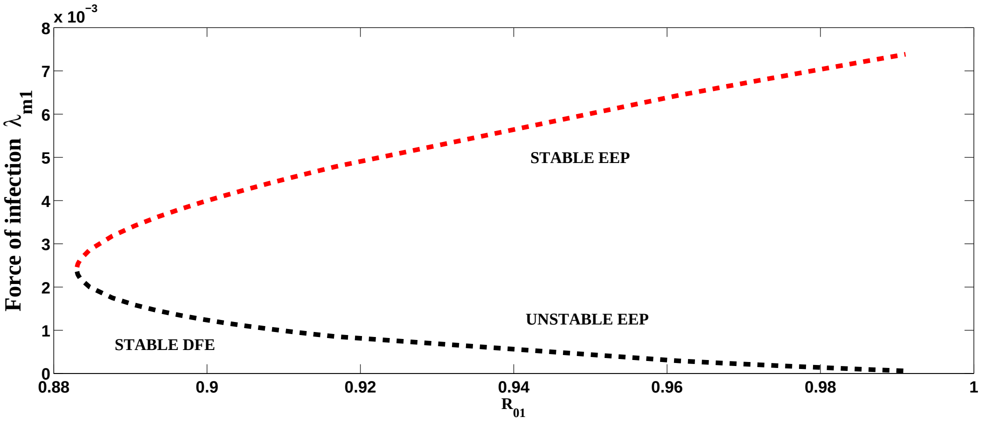


Figure 4.2: Bifurcation diagram for the model (4.23). Parameter values used are: $\beta_{f1} = 0.7422, \beta_{m1} = 0.88, \varepsilon_1 = \varepsilon_3 = 10, \pi_f = 0.0000009$. All other parameters as in Table 4.4

are computed to be

$$\begin{aligned} a &= -\frac{2\beta_{m1}\omega_9\nu_3}{N_m^{*2}}\Big\{\omega_8 X_1^* - \varepsilon_1\omega_7 N_m^* + (\omega_9+\omega_{10})X_1^* - \{\omega_1 + (1-\xi)\omega_2\}N_m^*\Big\} \\ &\quad - \frac{2\beta_{f1}^*(\omega_3+\theta_{p2}\omega_4)\nu_9}{N_f^{*2}}\Big\{\{\omega_1+\omega_2\}x_8^* - \varepsilon_3\omega_{10}N_f^* + (\omega_3+\omega_4+\omega_5+\omega_6+\omega_7)x_8^* - \omega_8 N_f^*\Big\} \\ &= -\frac{2K_7\omega_9\nu_9}{N_m^* X_1^*}\Big\{\omega_8 X_1^* - \varepsilon_1\omega_7 N_m^* + (\omega_9+\omega_{10})X_1^* - \{\omega_1 + (1-\xi)\omega_2\}N_m^*\Big\} \\ &= -\frac{2K_7 x_1^*\omega_9\nu_9}{N_f^* N_m^* X_1^*}\Big\{\{\omega_1+\omega_2\}x_8^* - \varepsilon_3\omega_{10}N_f^* + (\omega_3+\omega_4+\omega_5+\omega_6+\omega_7)x_8^* - \omega_8 N_f^*\Big\} \end{aligned} \tag{4.36}$$

$$b = \frac{x_8^*}{N_f^*}\nu_9\left(\omega_3 + \theta_{p1}\omega_4\right) > 0$$

Since the bifurcation coefficient b is positive, it follows from Theorem 4.1 in Castillo-Chavez and Song (2004), that the model (4.23), or the transformed model (4.35), will undergo a backward bifurcation if the backward bifurcation coefficient, a, given by (4.36) is positive. ☐ ☐

The associated backward bifurcation diagram is depicted in Figure 4.2).

4.4.5 Non-existence of backward bifurcation

Theorem 4.18. *In the absence of re-infection of recovered individuals with strain 1 as well as imperfect vaccine ($\varepsilon_1 = \varepsilon_3 = 0, \xi = 1$), the model* (4.23) *does not undergo backward bifurcation.*

Proof. Consider model (4.23). Setting $\varepsilon_1 = \varepsilon_3 = 0$ and $\xi = 1$, the expression for the backward bifurcation coefficient, a, given as (4.36) (and noting that all parameters of the model (4.23) are positive), reduces to:

$$a = -2K_7\omega_9\nu_9\left\{\frac{1}{N_m^*}(\omega_9+\omega_{10}) + \frac{1}{N_f^*}(\omega_3+\omega_4+\omega_5+\omega_6+\omega_7) + \omega_1\Big(\frac{1}{N_f^*} - \frac{1}{x_1^*}\Big)\right\} < 0,$$

since $N_f^* > x_1^*$, then $\left(\frac{1}{N_f^*} - \frac{1}{x_1^*}\right) < 0$, and noting, that $(\omega_9+\omega_{10}) > 0$ and $(\omega_3+\omega_4+\omega_5+\omega_6+\omega_7) > 0$ while $\omega_1 < 0$. Hence, it follows from Theorem 4.1 in Castillo-Chavez and Song (2004), that the model (4.23) does not undergo a backward bifurcation if $\varepsilon_1 = \varepsilon_3 = 0$ and $\xi = 1$. $\square$

Hence, this study shows that the reinfection of recovered individuals with strain 1 and imperfect vaccine induce backward bifurcation in the strain-1 only sub-model. A global asymptotic stability result is established below for the DFE of the model for this scenario (to completely rule out backward bifurcation in this case).

Theorem 4.19. *In the absence of re-infection of recovered individuals with strain 1 and imperfect vaccine (i.e. $\varepsilon_1 = \varepsilon_3 = 0, \xi = 1$), the DFE of the strain 1-only sub-model* (4.23)*, given by ξ_{01}, is GAS in $\mathcal{D}$ whenever $\mathcal{R}_{01}|_{\xi=1} = \bar{\mathcal{R}}_{01} \le 1$.*

Proof. Consider the model (3.23) with strain 1-only (i.e., let $\mathcal{R}_{02} < 1$, so that strain 2 dies out) given by (4.23). Also, let $\varepsilon_1 = \varepsilon_3 = 0, \xi = 1$. Further, let us consider the Lyapunov function:

$$\mathcal{L}_1 = \frac{(K_2+\theta_{p1}G_1)\beta_{f1}^f c_f S_f^*}{K_1K_2K_7N_f^*} I_{f1} + \frac{\theta_{p1}\beta_{f1}^f c_f S_f^*}{K_2K_7N_f^*} P_{f1} + \frac{\bar{\mathcal{R}}_{01}}{K_7} I_{m1}$$

with Lyapunov derivative

$$\dot{\mathcal{L}}_1 = \frac{(K_2+\theta_{p1}G_1)\beta_{f1}^f c_f S_f^*}{K_1K_2K_7N_f^*} \dot{I}_{f1} + \frac{\theta_{p1}\beta_{f1}^f c_f S_f^*}{K_2K_7N_f^*} \dot{P}_{f1} + \frac{\bar{\mathcal{R}}_{01}}{K_7} \dot{I}_{m1}$$

Substituting the expressions for $\dot{I}_{f1}$, $\dot{P}_{f1}$ and $\dot{I}_{m1}$ from (4.23), we have that

$$\begin{aligned}
\dot{\mathcal{L}}_1 &= \frac{(K_2+\theta_{p1}G_1)\beta_{f1}^f c_f S_f^*}{K_1K_2K_7N_f^*}[\lambda_{m1}S_f - K_1I_{f1}] + \frac{\theta_{p1}\beta_{f1}^f c_f S_f^*}{K_2K_7N_f^*}[G_1I_{f1} - K_2P_{f1}] + \frac{\bar{\mathcal{R}}_{01}}{K_7}[\lambda_{f1}S_m - K_7I_{m1}] \\
&= \frac{(K_2+\theta_{p1}G_1)\beta_{f1}^f c_f S_f^* \lambda_{m1}S_f}{K_1K_2K_7N_f^*} + \frac{\bar{\mathcal{R}}_{01}\lambda_{f1}S_m}{K_7} \\
&\quad - I_{f1}\left[\frac{(K_2+\theta_{p1}G_1)\beta_{f1}^f c_f S_f^*}{K_2K_7N_f^*} - \frac{\theta_{p1}G_1\beta_{f1}^f c_f S_f^*}{K_2K_7N_f^*}\right] - P_{f1}\left[\frac{\theta_{p1}\beta_{f1}^f c_f S_f^*}{K_7N_f^*}\right] - \bar{\mathcal{R}}_{01}I_{m1}
\end{aligned}$$

which can be further simplified into

$$\dot{\mathcal{L}}_1 = \frac{(K_2+\theta_{p1}G_1)\beta_{f1}^{f}c_fS_f^{*}\lambda_{m1}S_f}{K_1K_2K_7N_f^{*}} + \frac{\bar{\mathcal{R}}_{01}\lambda_{f1}S_m}{K_7} - \frac{\beta_{f1}^{f}c_fS_f^{*}(I_{f1}+\theta_{p1}P_{f1})}{K_7N_f^{*}} - \bar{\mathcal{R}}_{01}I_{m1}$$

Applying the group constraint in (3.28) and the definition of the forces of infection in (3.24) - (3.27), we have that

$$\begin{aligned}
\dot{\mathcal{L}}_1 &= \frac{(K_2+\theta_{p1}G_1)\beta_{f1}^{f}c_fS_f^{*}\lambda_{m1}S_f}{K_1K_2K_7N_f^{*}} - \frac{\bar{\mathcal{R}}_{01}\lambda_{m1}N_f}{c_m\beta_{m1}^{m}} + \frac{\bar{\mathcal{R}}_{01}\lambda_{f1}S_m}{K_7} - \frac{S_f^{*}\lambda_{f1}N_m}{K_7N_f^{*}} \\
\dot{\mathcal{L}}_1 &\le \frac{\bar{\mathcal{R}}_{01}\lambda_{m1}N_f}{c_m\beta_{m1}^{m}}\left(\frac{\bar{\mathcal{R}}_{01}S_f}{N_f}-1\right) + \frac{\lambda_{f1}N_m}{K_7}\left(\frac{\bar{\mathcal{R}}_{01}S_m}{N_m}-1\right) \qquad \left(\text{since } \frac{S_f^{*}}{N_f^{*}}<1\right) \\
&\le \frac{\bar{\mathcal{R}}_{01}\lambda_{m1}N_f}{c_m\beta_{m1}^{m}}\left(\bar{\mathcal{R}}_{01}-1\right) + \frac{\lambda_{f1}N_m}{K_7}\left(\bar{\mathcal{R}}_{01}-1\right) \qquad \left(\text{since } \frac{S_f}{N_f}<1, \text{and} \frac{S_m}{N_m}<1\right)
\end{aligned}$$

Since all the model parameters and variables are non-negative, we have that $\dot{\mathcal{L}}_1 \le 0$ for $\mathcal{R}_{01} \le 1$ with $\dot{\mathcal{L}}_1 = 0$ if and only if $I_{f1} = P_{f1} = I_{m1} = 0$. Hence, $\mathcal{L}_1$ is a Lyapunov function on $\mathcal{D}_1$. Thus, using the La Salle Invariance Principle (La Salle and Lefschetz, 1976), $I_{f1} \to 0, P_{f1} \to 0$ and $I_{m1} \to 0$ as $t \to \infty$. Substituting $I_{f1} = P_{f1} = I_{m1} = 0$ in (4.23) shows that $C_f \to 0, R_f^c \to 0, R_{f1} \to 0, S_f \to S_f^{*}, V_f \to V_f^{*}, R_{m1} \to 0, S_m \to S_m^{*}$ as $t \to \infty$. Thus, every solution to the equations of the model (4.23) with $\varepsilon_1 = \varepsilon_3 = 0, \xi = 1$, with initial conditions in $\mathcal{D}_1$, approaches the DFE ξ_{10} as $t \to \infty$ whenever $\bar{\mathcal{R}}_{01} \le 1$. □

Also, the following result can be proven.

Theorem 4.20. *In the absence of re-infection of recovered individuals with strain 2 (i.e.* $\varepsilon_2 = \varepsilon_4 = 0$*), the DFE of the strain 2-only sub-model* (4.43)*, given by* ξ_{02}*, is GAS in* $\mathcal{D}$ *whenever* $\mathcal{R}_{02} \le 1$.

Proof. Consider the Lyapunov function

$$\mathcal{L}_2 = \frac{(K_6+\theta_{p2}G_6)\beta_{f2}^{f}c_f}{K_4K_6K_8}I_{f2} + \frac{\theta_{p2}\beta_{f2}^{f}c_f}{K_6K_8}P_{f2} + \frac{\mathcal{R}_{02}}{K_8}I_{m2}$$

with Lyapunov derivative

$$\dot{\mathcal{L}}_2 = \frac{(K_6+\theta_{p2}G_6)\beta_{f2}^{f}c_f}{K_4K_6K_8}\dot{I}_{f2} + \frac{\theta_{p2}\beta_{f2}^{f}c_f}{K_6K_8}\dot{P}_{f2} + \frac{\mathcal{R}_{02}}{K_8}\dot{I}_{m2}$$

Substituting the expressions for $\dot{I}_{f2}$, $\dot{P}_{f2}$ and $\dot{I}_{m2}$ from (4.23), we have that

$$\begin{aligned}
\dot{\mathcal{L}}_2 &= \frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f}{K_4K_6K_8}[\lambda_{m2}S_f - K_4I_{f2}] + \frac{\theta_{p2}\beta^f_{f2}c_f}{K_6K_8}[G_6I_{f2} - K_6P_{f2}] + \frac{\mathcal{R}_{02}}{K_8}[\lambda_{f2}S_m - K_8I_{m2}] \\
&= \frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f\lambda_{m2}S_f}{K_4K_6K_8} + \frac{\mathcal{R}_{02}\lambda_{f2}S_m}{K_8} \\
&\quad - I_{f2}\left[\frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f}{K_6K_8} - \frac{\theta_{p2}G_6\beta^f_{f2}c_f}{K_6K_8}\right] - P_{f2}\left[\frac{\theta_{p2}\beta^f_{f2}c_f}{K_8}\right] - \mathcal{R}_{02}I_{m2}
\end{aligned}$$

which can be further simplified into

$$\dot{\mathcal{L}}_2 = \frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f\lambda_{m2}S_f}{K_4K_6K_8} + \frac{\mathcal{R}_{02}\lambda_{f2}S_m}{K_8} - \frac{\beta^f_{f2}c_f(I_{f2}+\theta_{p2}P_{f2})}{K_8} - \mathcal{R}_{02}I_{m2}$$

Applying the group constraint in (3.28) and the definition of the forces of infection in (3.24) - (3.27), we have that

$$\begin{aligned}
\dot{\mathcal{L}}_2 &= \frac{(K_6+\theta_{p2}G_6)\beta^f_{f2}c_f\lambda_{m2}S_f}{K_4K_6K_8} - \frac{\mathcal{R}_{02}\lambda_{m2}N_f}{c_m\beta^m_{m2}} + \frac{\mathcal{R}_{02}\lambda_{f2}S_m}{K_8} - \frac{\lambda_{f2}N_m}{K_8} \\
\dot{\mathcal{L}}_2 &\leq \frac{\mathcal{R}_{02}\lambda_{m2}N_f}{c_m\beta^m_{m2}}\left(\frac{\mathcal{R}_{02}S_f}{N_f} - 1\right) + \frac{\lambda_{f2}N_m}{K_8}\left(\frac{\mathcal{R}_{02}S_m}{N_m} - 1\right) \\
&\leq \frac{\mathcal{R}_{02}\lambda_{m2}N_f}{c_m\beta^m_{m2}}(\mathcal{R}_{02}-1) + \frac{\lambda_{f2}N_m}{K_8}(\mathcal{R}_{02}-1) \qquad \left(\text{since } \frac{S_f}{N_f} < 1, \text{and} \frac{S_m}{N_m} < 1\right)
\end{aligned}$$

Since all the model parameters and variables are non-negative, we have that $\dot{\mathcal{L}}_2 \leq 0$ for $\mathcal{R}_{02} \leq 1$ with $\dot{\mathcal{L}}_2 = 0$ if and only if $I_{f2} = P_{f2} = I_{m2} = 0$. Hence, $\mathcal{L}_2$ is a Lyapunov function on $\mathcal{D}_2$. Thus, using the La Salle Invariance Principle (La Salle and Lefschetz (1976)), $I_{f2} \to 0, P_{f2} \to 0$ and $I_{m2} \to 0$ as $t \to \infty$. Substituting $I_{f2} = P_{f2} = I_{m2} = 0$ in (4.43) shows that $C_f \to 0, R^c_f \to 0, R_{f2} \to 0, S_f \to S^*_f, R_{m2} \to 0, S_m \to S^*_m$ as $t \to \infty$. Thus, every solution to the equations of the model (4.43) with $\epsilon_2 = \epsilon_4 = 0$, with initial conditions in $\mathcal{D}_2$, approaches the DFE ξ_{20} as $t \to \infty$ whenever $\mathcal{R}_{02} \leq 1$. □ □

Theorem 4.21. *In the absence of re-infection of recovered individuals with the same strain (i.e.* $\varepsilon_1 = \varepsilon_3 = 0$*), the model* (3.23) *with* $\delta_{f1} = \delta_{m1} = \delta_{fc} = 0, \xi = 1$*, has a unique strain 1-only boundary equilibrium,* ξ_{e1}*, whenever* $\mathcal{R}_{02} < 1 < \mathcal{R}_{01}|_{\xi=1} = \bar{\mathcal{R}}_{01} \leq 1$

Proof. In the absence of re-infection of recovered individuals with the same strain and imperfect vaccine (i. e. $\varepsilon_1 = \varepsilon_3 = 0, \xi = 1$), the polynomial (4.33) reduces to

$$\bar{H}_5(\lambda_{m1}^{**})^2 + \bar{H}_6\lambda_{m1}^{**} + \bar{H}_7 = 0 \tag{4.37}$$

with,

$$\begin{aligned}
\bar{H}_5 &= \Lambda_f\mu_f^2(\tau_{f1}+\mu_f)(\kappa_{f1}+\mu_f)[\beta_{f1}\Lambda_m\Lambda_f\mu_f^2\bar{K}_7(1-f)(\bar{K}_2\mu_f+\theta_{p1}\mu_f G_1)+\Lambda_m\Lambda_f\mu_m^2\mu_f^2 ...\\
&\quad\times(\tau_{f1}+\mu_f)(\kappa_{f1}+\mu_f)\bar{K}_7] > 0,\\
\bar{H}_6 &= \beta_{f1}\Lambda_f^2\Lambda_m\mu_f^5\mu_m\bar{K}_1\bar{K}_2\bar{K}_7(1-f)(\bar{K}_2\mu_f+\theta_{p1}\mu_f G_1)+2\Lambda_f^2\Lambda_m\mu_f^5\mu_m^2\bar{K}_1\bar{K}_2\bar{K}_7 ...\\
&\quad\times(\tau_{f1}+\mu_f)(\kappa_{f1}+\mu_f)(1-\bar{\mathcal{R}}_{01}^2),\\
\bar{H}_7 &= \Lambda_m\Lambda_f^2\mu_f^6\mu_m^2\bar{K}_2\bar{K}_2\bar{K}_7(1-\bar{\mathcal{R}}_{01}^2) < 0, \quad \text{if} \quad \bar{\mathcal{R}}_{01} > 1
\end{aligned} \tag{4.38}$$

We have from (4.37) and (4.38) that, irrespective of the sign of $\bar{H}_6$, the quadratic (4.37) has a unique positive solution whenever $\bar{\mathcal{R}}_{01} > 1$. In addition, it should be pointed out that for the equilibrium ξ_{e1} to exist, it is necessary that strain 2 dies out asymptotically (i.e. $\mathcal{R}_{02} < 1$, in line with Theorem 4.20). Hence, the model (3.23) has a unique strain 1-only boundary equilibrium, ξ_{e1}, whenever $\mathcal{R}_{02} < 1 < \bar{\mathcal{R}}_{01}$. □

□

Theorem 4.22. *In the absence of re-infection of recovered individuals with the same strain and imperfect vaccine (i.e. $\varepsilon_1 = \varepsilon_3 =, \xi = 1$), the unique strain 1-only boundary equilibrium, ξ_{e1}, of the model* (3.23)*, with $\delta_{f1} = \delta_{m1} = \delta_{fc} = 0$ is globally asymptotically stable (GAS) in $\mathcal{D}\setminus\mathcal{D}_{01}$ whenever $\mathcal{R}_{02} < 1 < \bar{\mathcal{R}}_{01} = \mathcal{R}_{01}|_{\xi=1}$, where*

$$\mathcal{D}_{01} = \left\{(S_f, V_f, I_{f1}, P_{f1}, C_f, R_f^c, R_{f1}, S_m, I_{m1}, R_{m1}) \in \mathcal{D}_1 : I_{f1} = P_{f1} = C_f = R_f^c = R_{f1} = I_{m1} = 0\right\}$$

Proof. Consider the model (4.23) with (4.27) and (4.28), $\varepsilon_1 = \varepsilon_3 = 0$ and $\mathcal{R}_{01} > 1$, so that the associated unique endemic equilibrium exists. Also, consider the non-linear Lyapunov function of the Goh-Volterra type (Goh, 1976):

$$\begin{aligned}\mathcal{V}_1 = (K_2+\theta_{p1}G_1)\bar{\beta}_{f1}S_m^{**}\Bigg[S_f - S_f^{**} - S_f^{**}\ln\left(\frac{S_f}{S_f^{**}}\right) + V_f - V_f^{**} - V_f^{**}\ln\left(\frac{V_f}{V_f^{**}}\right) \\ + I_{f1} - I_{f1}^{**} - I_{f1}^{**}\ln\left(\frac{I_{f1}}{I_{f1}^{**}}\right)\Bigg] + K_1\theta_{p1}\bar{\beta}_{f1}S_m^{**}\Bigg[P_{f1} - P_{f1}^{**} - P_{f1}^{**}\ln\left(\frac{P_{f1}}{P_{f1}^{**}}\right)\Bigg] \\ K_1K_2\Bigg[S_m - S_m^{**} - S_m^{**}\ln\left(\frac{S_m}{S_m^{**}}\right) + I_{m1} - I_{m1}^{**} - I_{m1}^{**}\ln\left(\frac{I_{m1}}{I_{m1}^{**}}\right)\Bigg]\end{aligned}$$

with Lyapunov derivative,

$$\begin{aligned}\dot{\mathcal{V}}_1 = (K_2+\theta_{p1}G_1)\bar{\beta}_{f1}S_m^{**}\left[\left(1-\frac{S_f^{**}}{S_f}\right)\dot{S}_f + \left(1-\frac{V_f^{**}}{V_f}\right)\dot{V}_f + \left(1-\frac{I_{f1}^{**}}{I_{f1}}\right)\dot{I}_{f1}\right] \\ + K_1\theta_{p1}\bar{\beta}_{f1}S_m^{**}\left[\left(1-\frac{P_{f1}^{**}}{P_{f1}}\right)\dot{P}_{f1}\right] + K_1K_2\left[\left(1-\frac{S_m^{**}}{S_m}\right)\dot{S}_m + \left(1-\frac{I_{m1}^{**}}{I_{m1}}\right)\dot{I}_{m1}\right]\end{aligned} \tag{4.39}$$

Substituting the derivatives in (4.23) into $\dot{\mathcal{V}}_1$, we have

$$\begin{aligned}\dot{\mathcal{V}}_1 &= (K_2+\theta_{p1}G_1)\bar{\beta}_{f1}S_m^{**}\left[\left(1-\frac{S_f^{**}}{S_f}\right)((1-f)\Lambda_f - (\bar{\beta}_{m1}I_{m1}+\mu_f)S_f) + \left(1-\frac{V_f^{**}}{V_f}\right)(f\Lambda_f - \mu_f V_f)\right. \\ &\left.+\left(1-\frac{I_{f1}^{**}}{I_{f1}}\right)(\bar{\beta}_{m1}I_{m1}S_f - K_1I_{f1})\right] + K_1\theta_{p1}\bar{\beta}_{f1}S_m^{**}\left[\left(1-\frac{P_{f1}^{**}}{P_{f1}}\right)(G_1I_{f1} - K_2P_{f1})\right] \\ &+ K_1K_2\left[\left(1-\frac{S_m^{**}}{S_m}\right)\left(\Lambda_m - \left(\bar{\beta}_{f1}(I_{f1}+\theta_{p1}P_{f1}) + \mu_m\right)S_m\right)\right. \\ &\left.+\left(1-\frac{I_{m1}^{**}}{I_{m1}}\right)(\bar{\beta}_{f1}(I_{f1}+\theta_{p1}P_{f1})S_m - K_7I_{m1})\right]\end{aligned} \tag{4.40}$$

Observe from model (4.23) that, at steady state,

$$\begin{aligned}(1-f)\Lambda_f = \left(\bar{\beta}_{m1}I_{m1}^{**}+\mu_f\right)S_f^{**}, \quad f\Lambda_f = \mu_f V_f^{**}, \quad \bar{\beta}_{m1}I_{m1}S_f^{**} = K_1I_{f1}^{**}, \\ G_1I_{f1}^{**} = K_2P_{f1}^{**}, \quad \Lambda_m = \left(\bar{\beta}_{f1}(I_{f1}^{**}+\theta_{p1}P_{f1}^{**})+\mu_m\right)S_m^{**}, \quad \bar{\beta}_{f1}(I_{f1}^{**}+\theta_{p1}P_{f1}^{**})S_m^{**} = K_7I_{m1}^{**}\end{aligned} \tag{4.41}$$

Substituting the expressions in (4.41) into (4.40) gives

$$\begin{aligned}\dot{\mathcal{V}}_1 = {} & (K_2+\theta_{p1}G_1)\bar{\beta}_{f1}S_m^{**}\Bigg[\left(1-\frac{S_f^{**}}{S_f}\right)(\bar{\beta}_{m1}I_{m1}^{**}S_f^{**}+\mu_f S_f^{**}-\bar{\beta}_{m1}I_{m1}S_f-\mu_f S_f)\\ & +\left(1-\frac{V_f^{**}}{V_f}\right)(\mu_f V_f^{**}-\mu_f V_f)+\left(1-\frac{I_{f1}^{**}}{I_{f1}}\right)(\bar{\beta}_{m1}I_{m1}S_f-K_1I_{f1})\Bigg]\\ & +K_1\theta_{p1}\bar{\beta}_{f1}S_m^{**}\Bigg[\left(1-\frac{P_{f1}^{**}}{P_{f1}}\right)(G_1I_{f1}-K_2P_{f1})\Bigg]\\ & +K_1K_2\Bigg[\left(1-\frac{S_m^{**}}{S_m}\right)(\bar{\beta}_{f1}I_{f1}^{**}S_m^{**}+\bar{\beta}_{f1}\theta_{p1}P_{f1}^{**}S_m^{**}+\mu_m S_m^{**}-\bar{\beta}_{f1}I_{f1}S_m-\bar{\beta}_{f1}\theta_{p1}P_{f1}S_m-\mu_m S_m)\\ & +\left(1-\frac{I_{m1}^{**}}{I_{m1}}\right)(\bar{\beta}_{f1}I_{f1}S_m+\bar{\beta}_{f1}\theta_{p1}P_{f1}S_m-K_7I_{m1})\Bigg]\end{aligned}$$

which can be simplified to

$$\begin{aligned}\dot{\mathcal{V}}_1 = {} & (K_2+\theta_{p1}G_2)\bar{\beta}_{f1}\mu_f S_m^{**}S_f^{**}\left(2-\frac{S_f^{**}}{S_f}-\frac{S_f}{S_f^{**}}\right)+K_1K_2\mu_m S_m^{**}\left(2-\frac{S_m^{**}}{S_m}-\frac{S_m}{S_m^{**}}\right)\\ & +K_1K_2\bar{\beta}_{f1}I_{f1}^{**}S_m^{**}\left(4-\frac{S_f^{**}}{S_f}-\frac{S_m^{**}}{S_m}-\frac{I_{m1}I_{f1}^{**}S_f}{I_{m1}^{**}I_{f1}S_f^{**}}-\frac{I_{f1}I_{m1}^{**}S_m}{I_{f1}^{**}I_{m1}S_m^{**}}\right)\\ & +K_1K_2\bar{\beta}_{f1}\theta_{p1}P_{f1}^{**}S_m^{**}\left(5-\frac{S_f^{**}}{S_f}-\frac{S_m^{**}}{S_m}-\frac{I_{m1}I_{f1}^{**}S_f}{I_{m1}^{**}I_{f1}S_f^{**}}-\frac{I_{m1}^{**}P_{f1}S_m}{I_{m1}P_{f1}^{**}S_m^{**}}-\frac{I_{f1}P_{f1}^{**}}{I_{f1}^{**}P_{f1}}\right)\end{aligned} \tag{4.42}$$

Finally, since arithmetic mean is greater that geometric mean, the following inequalities from (4.42) hold:

$$\begin{gathered}\left(2-\frac{S_f^{**}}{S_f}-\frac{S_f}{S_f^{**}}\right)\leq 0, \quad \left(2-\frac{S_m^{**}}{S_m}-\frac{S_m}{S_m^{**}}\right)\leq 0\\ \left(4-\frac{S_f^{**}}{S_f}-\frac{S_m^{**}}{S_m}-\frac{I_{m1}I_{f1}^{**}S_f}{I_{m1}^{**}I_{f1}S_f^{**}}-\frac{I_{f1}I_{m1}^{**}S_m}{I_{f1}^{**}I_{m1}S_m^{**}}\right)\leq 0\\ \left(5-\frac{S_f^{**}}{S_f}-\frac{S_m^{**}}{S_m}-\frac{I_{m1}I_{f1}^{**}S_f}{I_{m1}^{**}I_{f1}S_f^{**}}-\frac{I_{m1}^{**}P_{f1}S_m}{I_{m1}P_{f1}^{**}S_m^{**}}-\frac{I_{f1}P_{f1}^{**}}{I_{f1}^{**}P_{f1}}\right)\leq 0\end{gathered}$$

Thus, $\dot{\mathcal{V}}_1 \leq 0$ for $\bar{\mathcal{R}}_{01} > 1$. Hence, $\mathcal{V}_1$ is a Lyapunov function in $\mathcal{D}\diagdown\mathcal{D}_{01}$ and it follows from the La Salle's Invariance principle (La Salle and Lefschetz, 1976), that every solution to the equations of the model (4.23) with (4.27), and initial conditions in $\mathcal{D}\diagdown\mathcal{D}_{01}$ approaches the associated unique endemic equilibrium ξ_{e1}, of the model as $t \to \infty$ for $\bar{\mathcal{R}}_{01} > 1$. □

4.4.6 Strain 2-only sub-model

The Strain 2-only sub-model (is obtained by setting $V_f = I_{f1} = P_{f1} = R_{f1} = I_{f2}^p = I_{f12} = I_{f21} = M_f = I_{m1} = R_{m1} = I_{m12} = I_{m21} = M_m = 0$ in the model (3.23)) is given by:

$$
\begin{aligned}
\frac{dS_f}{dt} &= \Lambda_f - (\lambda_{m2} + \mu_f)\, S_f \\
\frac{dI_{f2}}{dt} &= \lambda_{m2} S_f - K_4 I_{f2} + \varepsilon_2 \lambda_{m2} R_{f2} \\
\frac{dP_{f2}}{dt} &= G_6 I_{f2} - K_6 P_{f2} \\
\frac{dC_f}{dt} &= G_4 P_{f2} - K_3 C_f \\
\frac{dR_f^c}{dt} &= \pi_f C_f - \mu_f R_f^c \\
\frac{dR_{f2}}{dt} &= p_2 \tau_{f2} I_{f2} + q_2 \eta_c \kappa_{f2} P_{f2} - (\mu_f + \varepsilon_2 \lambda_{m2})\, R_{f2} \\
\frac{dS_m}{dt} &= \Lambda_m - (\lambda_{f2} + \mu_m)\, S_m \\
\frac{dI_{m2}}{dt} &= \lambda_{f2} S_m + \varepsilon_4 \lambda_{f2} R_{m2} - K_8 I_{m2} \\
\frac{dR_{m2}}{dt} &= \tau_{m2} I_{m2} - (\mu_m + \varepsilon_4 \lambda_{f2})\, R_{m2}
\end{aligned}
\tag{4.43}
$$

where now

$$\lambda_{f2} = \frac{\beta_{f2}(I_{f2} + \theta_{p2} P_{f2})}{N_f}, \quad \lambda_{m2} = \frac{\beta_{m2} I_{m2}}{N_m}$$

with

$$
\begin{aligned}
N_f &= S_f + I_{f2} + P_{f2} + C_f + R_f^c + R_{f2}, \quad \text{and} \\
N_m &= S_m + I_{m2} + R_{m2}
\end{aligned}
$$

Consider the regions:

$$\mathcal{D}_2 = \mathcal{D}_2^f \cup \mathcal{D}_2^m$$

with

$$
\begin{aligned}
\mathcal{D}_2^f &= \left\{ (S_f, I_{f2}, P_{f2}, C_f, R_f^c, R_{f2}) \in \Re_+^6 : N_f \le \frac{\Lambda_f}{\mu_f} \right\}, \text{and} \\
\mathcal{D}_2^m &= \left\{ (S_m, I_{m2}, R_{m2}) \in \Re_+^3 : N_m \le \frac{\Lambda_m}{\mu_m} \right\}
\end{aligned}
$$

The region $\mathcal{D}_2$ is positively invariant.

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

The Strain 2-only sub-model (4.43) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\begin{aligned}\xi_{02} =&(S_f^*, I_{f2}^*, P_{f2}^*, C_f^*, R_f^{c*}, R_{f2}^*, S_m^*, I_{m2}^*, R_{m2}^*)\\ =&(\frac{\Lambda_f}{\mu_f}, 0, 0, 0, 0, 0, \frac{\Lambda_m}{\mu_m}, 0, 0)\end{aligned} \tag{4.44}$$

The linear stability of ξ_{02} will be investigated using the next generation operator method on the system (4.43) (van den Driessche and Watmough, 2002). The matrices F_{02} (for the new infection terms) and V_{02} (for the remaining transition terms) associated with the Strain 2-only sub-model (4.43) are given, respectively, by (noting that $S_f^* = N_f^* = \frac{\Lambda_f}{\mu_f}$, $S_m^* = N_m^* = \frac{\Lambda_m}{\mu_m}$ at the DFE ξ_{02})

$$F_{02} = \begin{bmatrix} 0 & 0 & 0 & \frac{\beta_{m2} S_f^*}{N_m^*} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\beta_{f2} S_m^*}{N_f^*} & \frac{\theta_{p2}\beta_{f2} S_m^*}{N_f^*} & 0 & 0 \end{bmatrix} \tag{4.45}$$

$$V_{02} = \begin{bmatrix} K_1 & 0 & 0 & 0 \\ -G_1 & K_2 & 0 & 0 \\ 0 & -G_3 & K_3 & 0 \\ 0 & 0 & 0 & K_7 \end{bmatrix} \tag{4.46}$$

The associated basic reproduction number of the Strain 2-only sub-model (4.43), denoted by $\mathcal{R}_{02} = \rho(F_{02}V_{02}^{-1})$, is given by

$$\mathcal{R}_{02} = \sqrt{\frac{\beta_{f2}\beta_{m2}(K_6 + G_6\theta_{p2})}{K_4 K_6 K_8}}$$

where ρ represents the spectral radius of $F_{02}V_{02}^{-1}$. Using Theorem 2 of van den Driessche and Watmough (2002), the following result is established.

Lemma 4.23. The DFE, ξ_{02}, of the Strain 2-only sub-model (4.43) is locally asymptotically stable (LAS) if $\mathcal{R}_{02} < 1$, and unstable if $\mathcal{R}_{02} > 1$.

4.4.8 Strain 2-only boundary equilibrium (ξ_{e2})

Setting $\lambda_{f1} = \lambda_{m1} = 0$ in (3.23) gives the following general form of the strain 2-only boundary equilibrium (denoted by ξ_{e2})

$$xi_{e2} = \left(S_f^{**}, 0, 0, 0, C_f^{**}, R_f^{c**}, 0, I_{f2}^{**}, 0, P_{f2}^{**}, R_{f2}^{**}, S_m^{**}, 0, 0, I_{m2}^{**}, R_{m2}^{**}, 0, 0, 0, 0, 0, 0\right)$$

(It should be noted here that N_f^{**} and N_m^{**} are replaced with their limiting values $\frac{\Lambda_f}{\mu_f}$ and $\frac{\Lambda_m}{\mu_m}$ respectively, as all disease induced death rates are assumed zero). It should be noted that setting $\delta_{f2} = \delta_{m2} = \delta_{fc} = 0$ in (4.43) gives $N_f \to \frac{\Lambda_f}{\mu_f}$ and $N_m \to \frac{\Lambda_m}{\mu_m}$ as $t \to \infty$. Let $\bar{\beta}_{f2} = \frac{\mu_f \beta_{f2}}{\Lambda_f}$ and $\bar{\beta}_{m2} = \frac{\mu_m \beta_{m2}}{\Lambda_m}$ so that

$$\lambda_{f2} = \bar{\beta}_{f2}(I_{f2} + \theta_{p2} P_{f2}) \tag{4.47}$$

and

$$\lambda_{m2} = \bar{\beta}_{m2} I_{m2} \tag{4.48}$$

Define

$$\begin{aligned} \lambda_{f2}^{**} &= \frac{\beta_{f2}\mu_f \left(I_{f2}^{**} + \theta_{p2} P_{f2}^{**}\right)}{\Lambda_f}, \\ \lambda_{m2}^{**} &= \frac{\beta_{m2} I_{m2}^{**} \mu_m}{\Lambda_m} \end{aligned} \tag{4.49}$$

Setting the right hand sides of model (4.43) to zero gives the steady state solutions

$$\begin{aligned}
S_f^{**} &= \frac{\Lambda}{(\lambda_{m2}^{**} + \mu_f)}, \quad I_{f2}^{**} = \frac{K_6 \Lambda_f \left(\varepsilon_2 \lambda_{m2}^{**2} + \mu_f \lambda_{m2}^{**}\right)}{(\mu_f + \lambda_{m2}^{**}) \left[\lambda_{m2}^{**} \left(K_4 K_6 \varepsilon_2 - K_6 p_2 \tau_{f2} \varepsilon_2 + G_6 G_9 \varepsilon_2\right) + K_4 K_6 \mu_f\right]}, \\
R_{f2}^{**} &= \frac{\Lambda_f \left(\varepsilon_2 \lambda_{m2}^{**2} + \mu_f \lambda_{m2}^{**}\right) \left(K_6 p_2 \tau_{f2} + G_6 G_9\right)}{(\mu_f + \lambda_{m2}^{**}) (\mu_f + \varepsilon_2 \lambda_{m2}^{**}) \left[\lambda_{m2}^{**} \left(K_4 K_6 \varepsilon_2 - K_6 p_2 \tau_{f2} \varepsilon_2 + G_6 G_9 \varepsilon_2\right) + K_4 K_6 \mu_f\right]} \\
P_{f2}^{**} &= \frac{G_6 \Lambda_f \left(\varepsilon_2 \lambda_{m2}^{**2} + \mu_f \lambda_{m2}^{**}\right)}{(\mu_f + \lambda_{m2}^{**}) \left[\lambda_{m2}^{**} \left(K_4 K_6 \varepsilon_2 - K_6 p_2 \tau_{f2} \varepsilon_2 + G_6 G_9 \varepsilon_2\right) + K_4 K_6 \mu_f\right]}, \\
C_f^{**} &= \frac{G_4 G_6 \Lambda_f \left(\varepsilon_2 \lambda_{m2}^{**2} + \mu_f \lambda_{m2}^{**}\right)}{(\mu_f + \lambda_{m2}^{**}) K_3 \left[\lambda_{m2}^{**} \left(K_4 K_6 \varepsilon_2 - K_6 p_2 \tau_{f2} \varepsilon_2 + G_6 G_9 \varepsilon_2\right) + K_4 K_6 \mu_f\right]}, \\
R_f^{c**} &= \frac{G_4 G_6 \Lambda_f \pi_f \left(\varepsilon_2 \lambda_{m2}^{**2} + \mu_f \lambda_{m2}^{**}\right)}{\mu_f K_3 (\mu_f + \lambda_{m2}^{**}) \left[\lambda_{m2}^{**} \left(K_4 K_6 \varepsilon_2 - K_6 p_2 \tau_{f2} \varepsilon_2 + G_6 G_9 \varepsilon_2\right) + K_4 K_6 \mu_f\right]}, \\
S_m^{**} &= \frac{\Lambda_m}{\left(\lambda_{f2}^{**} + \mu_m\right)}, \quad I_{m2}^{**} = \frac{\Lambda_m \lambda_{f2}^{**} \left(\varepsilon_4 \lambda_{f2}^{**} + \mu_m\right)}{\left[(K_8 \varepsilon_4 - \tau_{m2} \varepsilon_4) \lambda_{f2}^{**2} + (K_8 \mu_m + K_8 \mu_m \varepsilon_4 - \tau_{m2} \mu_m \varepsilon_4) \lambda_{f2}^{**} + K_8 \mu_m^2\right]} \\
R_{m2}^{**} &= \frac{\tau_{m2} \lambda_{f2}^{**} \Lambda_m}{\left[(K_8 \varepsilon_4 - \tau_{m2} \varepsilon_4) \lambda_{f2}^{**2} + (K_8 \mu_m + K_8 \mu_m \varepsilon_4 - \tau_{m2} \mu_m \varepsilon_4) \lambda_{f2}^{**} + K_8 \mu_m^2\right]}
\end{aligned} \tag{4.50}$$

Substituting the above expressions into (4.49), gives

$$\begin{aligned}
\lambda_{f2}^{**} &= \frac{h_{02}\lambda_{m2}^{**2} + h_{01}\lambda_{m2}^{**}}{h_{22}\lambda_{m2}^{**2} + h_{11}\lambda_{m2}^{**} + h_{00}}, \\
\lambda_{m2}^{**} &= \frac{j_{02}\lambda_{f2}^{**2} + j_{01}\lambda_{f2}^{**}}{j_{22}\lambda_{f2}^{**2} + j_{11}\lambda_{f2}^{**} + j_{00}}
\end{aligned} \tag{4.51}$$

where,

$$\begin{aligned}
h_{02} &= \beta_{f2}\mu_f\varepsilon_2(K_6 + \theta_{p2}G_6), \quad h_{01} = \beta_{f2}\mu_f^2(K_6 + \theta_{p2}G_6), \\
h_{22} &= K_4K_6\varepsilon_2 - \varepsilon_2(K_6p_2\tau_{f2} + G_6G_9), \\
h_{11} &= K_4K_6\mu_f + K_4K_6\mu_f\varepsilon_2 - \mu_f\varepsilon_2(K_2p_2\tau_{f2} + G_6G_9), \\
h_{00} &= K_4K_6\mu_f^2, \\
j_{02} &= \beta_{m2}\mu_m\varepsilon_4, \quad j_{01} = \beta_{m2}\mu_m^2, \quad j_{22} = K_8\varepsilon_4 - \tau_{m2}\varepsilon_4, \\
j_{11} &= K_8\mu_m + K_8\mu_m\varepsilon_4 - \tau_{m2}\mu_m\varepsilon_4, \quad j_{00} = K_8\mu_m^2
\end{aligned} \tag{4.52}$$

$$Y_1(\lambda_{m2}^{**})^4 + Y_2(\lambda_{m2}^{**})^3 + Y_3(\lambda_{m2}^{**})^2 + Y_4\lambda_{m2}^{**} + Y_5 = 0 \tag{4.53}$$

with

$$\begin{aligned}
Y_1 &= h_{02}^2j_{22} + h_{02}h_{22}j_{11} + h_{22}^2j_{00} > 0 \\
Y_2 &= 2h_{01}h_{02}j_{22} + h_{02}h_{11}j_{11} + h_{01}h_{22}j_{11} + 2h_{11}h_{22}j_{00} - h_{02}^2j_{02} - h_{02}h_{22}j_{01}, \\
Y_3 &= h_{01}^2j_{22} + h_{02}h_{00}j_{11} + h_{01}h_{11}j_{11} + h_{11}^2j_{00} - 2h_{01}h_{02}j_{02} - h_{02}h_{11}j_{01} + h_{00}h_{22}j_{00}(2 - \mathcal{R}_{02}^2) \\
Y_4 &= h_{00}h_{01}j_{11} - h_{01}^2j_{02} - h_{02}h_{00}j_{01} + h_{00}h_{11}j_{00}(1 - \mathcal{R}_{02}^2), \\
Y_5 &= h_{00}^2j_{00}(1 - \mathcal{R}_{02}^2) > 0 \quad \text{if} \quad \mathcal{R}_{02} < 1
\end{aligned} \tag{4.54}$$

The components of the EEP are then obtained by solving for λ_{m2}^{**} from the polynomial (4.53), and substituting the positive values of λ_{m2}^{**} into the expressions in (4.50) [noting (4.32)]. Furthermore, it follows from (4.54) that the coefficient Y_1, is always positive and Y_5 is positive (negative) if $\mathcal{R}_{02}$ is less (greater) than unity. The following results can be deduced.

Theorem 4.24. *The Strain 2-only sub-model* (4.43) *with* $\delta_{f2} = \delta_{m2} = \delta_{fc} = 0$ *has:*

(i) four or two endemic equilibria if $Y_2 < 0, Y_3 > 0, Y_4 < 0$ *and* $\mathcal{R}_{02} < 1$,

(ii) two endemic equilibria if Y_3 is of the same sign as Y_2 or Y_4 and $\mathcal{R}_{02} < 1$,

(iii) two endemic equilibria if $Y_2 > 0, Y_3 < 0, Y_4 > 0$ and $\mathcal{R}_{02} < 1$,

(iv) no endemic equilibrium otherwise, if $\mathcal{R}_{02} < 1$,

Items (i)-(iii) of Theorem 4.24 suggest the possibility of backward bifurcation in the Strain 1-only sub-model (4.43) with negligible disease-induced deaths (i.e., $\delta_{f2} = \delta_{m2} = \delta_{fc} = 0$) when $\mathcal{R}_{02} < 1$.

4.4.9 Backward bifurcation analysis of strain-2 only sub-model

It is instructive to characterize the type of bifurcation the model (4.43) may undergo. We claim the following result:

Theorem 4.25. *The model* (4.43) *exhibits backward bifurcation at $\mathcal{R}_{02} = 1$ whenever a bifurcation coefficient, denoted by a (given by* (4.56)*), is positive.*

Proof:

Proof. Suppose

$$\xi_e = \left(S_f^{**}, 0, 0, 0, C_f^{**}, R_f^{c**}, 0, I_{f2}^{**}, 0, P_{f2}^{**}, R_{f2}^{**}, S_m^{**}, 0, 0, I_{m2}^{**}, R_{m2}^{**}, 0, 0, 0, 0, 0, 0\right)$$

represents any arbitrary endemic equilibrium of the strain 2-only model (that is, an endemic equilibrium in which at least one of the infected components is non-zero). The existence (or otherwise) of backward bifurcation will be explored using the Centre Manifold Theory (van den Driessche and Watmough, 2002; Castillo-Chavez and Song, 2004 and Carr, 1981). To apply this theory, it is necessary to carry out the following change of variables.

$$S_f = x_1,\ I_{f2} = x_2,\ P_{f2} = x_3,\ C_f = x_4,\ R_f^c = x_5,\ R_{f2} = x_6,\ S_m = x_7,\ I_{m2} = x_8,\ R_{m2} = x_9$$

so that

$$N = \sum_{i=1}^{9} x_i$$

Further, using the vector notation

$$X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9)^T$$

the model (4.43) can be re-written in the form

$$\frac{dX}{dt} \equiv f = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9)^T$$

as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &\equiv f_1 = \Lambda_f - (\lambda_{m2} + \mu_f)\, x_1 \\
\frac{dx_2}{dt} &\equiv f_2 = \lambda_{m2} x_1 + \varepsilon_2 \lambda_{m2} x_6 - (\tau_{f2} + \delta_{f2} + \mu_f)\, x_2 \\
\frac{dx_3}{dt} &\equiv f_3 = (1 - p_2)\tau_{f2} x_2 - (\eta_c \kappa_{f2} + \mu_f) x_3 \\
\frac{dx_4}{dt} &\equiv f_4 = \eta_c (1 - q_2)\kappa_{f2} x_3 - (\pi_f + \mu_f + \delta_{fc}) x_4 \\
\frac{dx_5}{dt} &\equiv f_5 = \pi_f x_4 - \mu_f x_5 \\
\frac{dx_6}{dt} &\equiv f_6 = p_2 \tau_{f2} x_2 + q_2 \eta_c \kappa_{f2} x_3 - (\mu_f + \varepsilon_2 \lambda_{m2})\, x_6 \\
\frac{dx_7}{dt} &\equiv f_7 = \Lambda_m - (\lambda_{f2} + \mu_m)\, x_7 \\
\frac{dx_8}{dt} &\equiv f_8 = \lambda_{f2} x_7 + \varepsilon_4 \lambda_{f2} x_9 - (\tau_{m2} + \delta_{m2} + \mu_m)\, x_8 \\
\frac{dx_9}{dt} &\equiv f_9 = \tau_{m2} x_8 - (\mu_m + \varepsilon_4 \lambda_{f2})\, x_9
\end{aligned} \tag{4.55}$$

$$\begin{aligned}
\lambda_{f2} &= \frac{\beta_{f2}(x_2 + \theta_{p2} x_3)}{\sum_{i=1}^{6} x_i} \\
\lambda_{m2} &= \frac{\beta_{m2} x_8}{\sum_{i=7}^{9} x_i}
\end{aligned}$$

Without loss of generality, consider the case when $\mathcal{R}_{02} = 1$. Suppose, further, that β_{f2} is chosen as a bifurcation parameter. Solving for $\beta_{f2} = \beta_{f2}^*$ from $\mathcal{R}_{02} = 1$ gives

$$\beta_{f2} = \beta_{f2}^* = \frac{K_4 K_6 K_8}{\beta_{m2}\,(K_6 + G_6 \theta_{p2})}$$

The Jacobian of the transformed system (4.55), evaluated at the DFE (ξ_{02}) with $\beta_{f2} = \beta_{f2}^*$, is given by

$$J(\xi_{02})|_{\beta_{f2}=\beta_{f2}^*} = \begin{bmatrix} -\mu_f & 0 & 0 & 0 & 0 & 0 & 0 & \frac{-\beta_{m2}x_1^*}{N_m^*} & 0 \\ 0 & -K_4 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{m2}x_1^*}{N_m^*} & 0 \\ 0 & G_6 & -K_6 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & G_4 & -K_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \pi_f & -\mu_f & 0 & 0 & 0 & 0 \\ 0 & p_2\tau_{f2} & G_9 & 0 & 0 & -\mu_f & 0 & 0 & 0 \\ 0 & \frac{-\beta_{f2}x_7^*}{N_f^*} & \frac{-\beta_{f2}\theta_{p2}x_7^*}{N_f^*} & 0 & 0 & 0 & -\mu_m & 0 & 0 \\ 0 & \frac{\beta_{f2}x_7^*}{N_f^*} & \frac{\beta_{f2}\theta_{p2}x_7^*}{N_f^*} & 0 & 0 & 0 & 0 & -K_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \tau_{m2} & -\mu_m \end{bmatrix}$$

where, $N_f^* = x_1^*$, $N_m^* = x_7^*$

It can be shown that the Jacobian of (4.55) has a right eigenvector (associated with the zero eigenvalue) given by

$$w = [\omega_1, \omega_2, \omega_3, \omega_4, \omega_5, \omega_6, \omega_7, \omega_8, \omega_9]^T$$

where,

$$-\mu_f\omega_1 - \tfrac{\beta_{m2}x_1^*}{N_m^*}\omega_8 = 0$$

$$-K_4\omega_2 + \tfrac{\beta_{m2}x_1^*}{N_m^*}\omega_8 = 0$$

$$G_6\omega_2 - K_6\omega_3 = 0$$

$$G_4\omega_3 - K_3\omega_4 = 0$$

$$\pi_f\omega_4 - \mu_f\omega_5 = 0$$

$$p_2\tau_{f2}\omega_2 + G_9\omega_3 - \mu_f\omega_6 = 0$$

$$-\tfrac{\beta_{f2}x_7^*}{N_f^*}\omega_2 - \tfrac{\beta_{f2}\theta_{p2}x_7^*}{N_f^*}\omega_3 - \mu_m\omega_7 = 0$$

$$\tfrac{\beta_{f2}x_7^*}{N_f^*}\omega_2 + \tfrac{\beta_{f2}\theta_{p2}x_7^*}{N_f^*}\omega_3 - K_8\omega_8 = 0$$

$$\tau_{m2}\omega_8 - \mu_m\omega_9 = 0$$

Solving, gives

$$\omega_1 = -\frac{\beta_{m2}x_1^*\omega_8}{\mu_f N_m^*}, \quad \omega_2 = \frac{\beta_{m2}x_1^*\omega_8}{K_4 N_m^*}, \quad \omega_3 = \frac{G_6\beta_{m2}x_1^*\omega_8}{K_4K_6N_m^*}, \quad \omega_4 = \frac{G_4G_6\beta_{m2}x_1^*\omega_8}{K_3K_4K_6N_m^*},$$
$$\omega_5 = \frac{\pi_f G_4G_6\beta_{m2}x_1^*\omega_8}{\mu_f K_3K_4K_6N_m^*}, \quad \omega = \frac{\beta_{m2}x_1^*(K_2p_2\tau_{f2} + G_6G_9)\omega_8}{K_4K_6\mu_f N_m^*}, \quad \omega_7 = -\frac{\beta_{f2}\beta_{m2}(K_6 + \theta_{p2}G_6)\omega_8}{\mu_m K_4K_6},$$
$$\omega_8 = \omega_8 > 0, \quad \omega_9 = \frac{\tau_{m2}\omega_8}{\mu_m}$$

Furthermore, (4.55) has a corresponding left eigenvector (associated with the zero eigenvalue) given by

$$v = [\nu_1, \nu_2, \nu_3, \nu_4, \nu_5, \nu_6, \nu_7, \nu_8, \nu_9]$$

where,

$$-K_4\nu_2 + G_6\nu_3 + \tfrac{\beta_{f2}^*x_7^*}{N_f^*}\nu_8 = 0$$

$$-K_6\nu_3 + \tfrac{\beta_{f2}^*\theta_{p2}x_7^*}{N_f^*}\nu_8 = 0$$

$$\tfrac{\beta_{m2}x_1^*}{N_m^*}\nu_2 - K_8\nu_8 = 0$$

Solving, gives

$$\nu_2 = \frac{K_8x_7^*\nu_8}{\beta_{m2}N_f^*}, \quad \nu_3 = \frac{\beta_{f2}\theta_{p2}x_7^*\nu_8}{K_6N_f^*}, \quad \nu_8 = \nu_8 > 0$$

Based on Theorem 4.1 in Castillo-Chavez and Song (2004), and by computing the non-zero partial derivatives of $F(x)$(evaluated at the disease free equilibrium, DFE (ξ_{02})) we have that the associated bifurcation coefficients defined by a and b, are given by

$$a = \sum_{k,i,j=1}^{n} \nu_k\omega_i\omega_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \quad \text{and} \quad b = \sum_{k,i=1}^{n} \nu_k\omega_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_S^*}(0,0),$$

are computed to be

$$\begin{aligned}
a = &-\frac{2\beta_{m2}\omega_8\nu_2}{N_m^{*2}}\Big\{\omega_7x_1^* - \varepsilon_2\omega_6N_m^* + (\omega_8+\omega_9)x_1^* - \omega_1N_m^*\Big\} \\
&- \frac{2\beta_{f2}^*(\omega_2+\theta_{p2}\omega_3)\nu_8}{N_f^{*2}}\Big\{\omega_1x_7^* - \varepsilon_4\omega_9N_f^* + (\omega_2+\omega_3+\omega_4+\omega_5+\omega_6)x_7^* - \omega_7N_f^*\Big\} \qquad (4.56) \\
= &-\frac{2K_8\omega_8\nu_8}{N_f^*N_m^*}\Big\{ - \varepsilon_2\omega_6N_m^* + (\omega_8+\omega_9)x_1^* - \varepsilon_4\omega_9N_f^* + (\omega_2+\omega_3+\omega_4+\omega_5+\omega_6)x_7^*\Big\}
\end{aligned}$$

$$\begin{aligned} b &= \sum_{k,i=1}^{9} \nu_k \omega_i \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \\ &= \frac{x_7^*}{N_f^*} \nu_8 \left(\omega_2 + \theta_{p1}\omega_3\right) > 0 \end{aligned}$$

Since the bifurcation coefficient b is positive, it follows from Theorem 4.1 in Castillo-Chavez and Song (2004), that the model (4.43), or the transformed model (4.55), will undergo a backward bifurcation if the backward bifurcation coefficient, a, given by (4.56) is positive. ☐ ☐

4.4.10 Non-existence of backward bifurcation

Theorem 4.26. *In the absence of re-infection of recovered individuals with strain 2 ($\varepsilon_2 = \varepsilon_4 = 0$), the sub-model* (4.43) *does not undergo backward bifurcation.*

Proof. Consider the sub-model (4.43) with $\varepsilon_2 = \varepsilon_4 = 0$. The expression for the backward bifurcation coefficient, a, given as (4.56) (and noting that all parameters of the model (4.43) are positive), reduces to:

$$a == -\frac{2K_8\omega_8\nu_8}{N_f^* N_m^*}\left\{(\omega_8+\omega_9)x_1^* + (\omega_2+\omega_3+\omega_4+\omega_5+\omega_6)x_7^*\right\} < 0,$$

since we have that $(\omega_8+\omega_9) > 0$ and $(\omega_2+\omega_3+\omega_4+\omega_5+\omega_6) > 0$. Hence, it follows from Theorem 4.1 in Castillo-Chavez and Song (2004), that the model (4.43) does not undergo a backward bifurcation if $\varepsilon_2 = \varepsilon_4 = 0$. ☐

Theorem 4.27. *The unique endemic equilibrium (EEP) of the Strain 2-only sub-model* (4.43) *is globally asymptotically stable in $\mathcal{D}_2 \setminus \mathcal{D}_{20}$ whenever $\mathcal{R}_{02} > 1$ and $\varepsilon_2 = \varepsilon_4 = 0$*

Proof. Consider the model (4.43) with (4.47) and (4.48), $\varepsilon_2 = \varepsilon_4 = 0$ and $\mathcal{R}_{02} > 1$, so that the associated unique endemic equilibrium exists. Also, consider the non-linear Lyapunov function of the Goh-Volterra type (Goh, 1976):

$$\begin{aligned} \mathcal{V}_2 &= (K_6+\theta_{f2}G_1)\bar{\beta}_{f2}S_m^{**}\left[S_f - S_f^{**} - S_f^{**}\ln\left(\frac{S_f}{S_f^{**}}\right) + I_{f2} - I_{f2}^{**} - I_{f2}^{**}\ln\left(\frac{I_{f2}}{I_{f2}^{**}}\right)\right] \\ &+ K_4\theta_{p2}\bar{\beta}_{f2}S_m^{**}\left[P_{f2} - P_{f2}^{**} - P_{f2}^{**}\ln\left(\frac{P_{f2}}{P_{f2}^{**}}\right)\right] + K_4K_6\left[S_m - S_m^{**} - S_m^{**}\ln\left(\frac{S_m}{S_m^{**}}\right)\right. \\ &\left. + I_{m2} - I_{m2}^{**} - I_{m2}^{**}\ln\left(\frac{I_{m2}}{I_{m2}^{**}}\right)\right] \end{aligned}$$

with Lyapunov derivative,

$$\begin{aligned}\dot{\mathcal{V}}_1 &= (K_6+\theta_{p2}G_1)\bar{\beta}_{f2}S_m^{**}\left[\left(1-\frac{S_f^{**}}{S_f}\right)\dot{S}_f+\left(1-\frac{I_{f2}^{**}}{I_{f2}}\right)\dot{I}_{f2}\right]+K_4\theta_{p2}\bar{\beta}_{f2}S_m^{**}\left[\left(1-\frac{P_{f2}^{**}}{P_{f2}}\right)\dot{P}_{f2}\right]\\&\quad+K_4K_6\left[\left(1-\frac{S_m^{**}}{S_m}\right)\dot{S}_m+\left(1-\frac{I_{m2}^{**}}{I_{m2}}\right)\dot{I}_{m2}\right]\end{aligned} \tag{4.57}$$

Substituting the derivatives in (4.43) into $\dot{\mathcal{V}}_1$, we have

$$\begin{aligned}\dot{\mathcal{V}}_1 &= (K_6+\theta_{p2}G_1)\bar{\beta}_{f2}S_m^{**}\left[\left(1-\frac{S_f^{**}}{S_f}\right)(\Lambda_f-(\bar{\beta}_{m2}I_{m2}+\mu_f)S_f)\right.\\&\quad\left.+\left(1-\frac{I_{f2}^{**}}{I_{f2}}\right)(\bar{\beta}_{m2}I_{m2}S_f-K_4I_{f2})\right]+K_4\theta_{p2}\bar{\beta}_{f2}S_m^{**}\left[\left(1-\frac{P_{f2}^{**}}{P_{f2}}\right)(G_1I_{f2}-K_6P_{f2})\right]\\&\quad+K_4K_6\left[\left(1-\frac{S_m^{**}}{S_m}\right)\left(\Lambda_m-\left(\bar{\beta}_{f2}(I_{f2}+\theta_{p2}P_{f2})+\mu_m\right)S_m\right)\right.\\&\quad\left.+\left(1-\frac{I_{m2}^{**}}{I_{m2}}\right)(\bar{\beta}_{f2}(I_{f2}+\theta_{p2}P_{f2})S_m-K_8I_{m2})\right]\end{aligned} \tag{4.58}$$

Observe from model (4.43) that, at steady state,

$$\begin{aligned}\Lambda_f &= \left(\bar{\beta}_{m2}I_{m2}^{**}+\mu_f\right)S_f^{**},\quad \bar{\beta}_{m2}I_{m2}S_f^{**}=K_4I_{f2}^{**},\\G_1I_{f2}^{**}&=K_6P_{f2}^{**},\quad \Lambda_m=\left(\bar{\beta}_{f2}(I_{f2}^{**}+\theta_{p2}P_{f2}^{**})+\mu_m\right)S_m^{**},\quad \bar{\beta}_{f2}(I_{f2}^{**}+\theta_{p2}P_{f2}^{**})S_m^{**}=K_8I_{m2}^{**}\end{aligned} \tag{4.59}$$

Substituting the expressions in (4.59) into (4.58) gives

$$\begin{aligned}\dot{\mathcal{V}}_1 &= (K_6+\theta_{p2}G_1)\bar{\beta}_{f2}S_m^{**}\left[\left(1-\frac{S_f^{**}}{S_f}\right)(\bar{\beta}_{m2}I_{m2}^{**}S_f^{**}+\mu_fS_f^{**}-\bar{\beta}_{m2}I_{m2}S_f-\mu_fS_f)\right.\\&\quad\left.+\left(1-\frac{I_{f2}^{**}}{I_{f2}}\right)(\bar{\beta}_{m2}I_{m2}S_f-K_4I_{f2})\right]+K_4\theta_{p2}\bar{\beta}_{f2}S_m^{**}\left[\left(1-\frac{P_{f2}^{**}}{P_{f2}}\right)(G_1I_{f2}-K_6P_{f2})\right]\\&\quad+K_4K_6\left[\left(1-\frac{S_m^{**}}{S_m}\right)(\bar{\beta}_{f2}I_{f2}^{**}S_m^{**}+\bar{\beta}_{f2}\theta_{p2}P_{f2}^{**}S_m^{**}+\mu_mS_m^{**}-\bar{\beta}_{f2}I_{f2}S_m-\bar{\beta}_{f2}\theta_{p2}P_{f2}S_m-\mu_mS_m)\right.\\&\quad\left.+\left(1-\frac{I_{m2}^{**}}{I_{m2}}\right)(\bar{\beta}_{f2}I_{f2}S_m+\bar{\beta}_{f2}\theta_{p2}P_{f2}S_m-K_8I_{m2})\right]\end{aligned}$$

which can be simplified to

$$\begin{aligned}\dot{\mathcal{V}}_2 &= (K_6+\theta_{p2}G_6)\bar{\beta}_{f2}\mu_f S_m^{**}S_f^{**}\left(2-\frac{S_f^{**}}{S_f}-\frac{S_f}{S_f^{**}}\right)+K_4K_6\mu_m S_m^{**}\left(2-\frac{S_m^{**}}{S_m}-\frac{S_m}{S_m^{**}}\right)\\ &+K_4K_6\bar{\beta}_{f2}I_{f2}^{**}S_m^{**}\left(4-\frac{S_f^{**}}{S_f}-\frac{S_m^{**}}{S_m}-\frac{I_{m2}I_{f2}^{**}S_f}{I_{m2}^{**}I_{f2}S_f^{**}}-\frac{I_{f2}I_{m2}^{**}S_m}{I_{f2}^{**}I_{m2}S_m^{**}}\right)\\ &+K_4K_6\bar{\beta}_{f2}\theta_{p2}P_{f2}^{**}S_m^{**}\left(5-\frac{S_f^{**}}{S_f}-\frac{S_m^{**}}{S_m}-\frac{I_{m2}I_{f2}^{**}S_f}{I_{m2}^{**}I_{f2}S_f^{**}}-\frac{I_{m2}^{**}P_{f2}S_m}{I_{m2}P_{f2}^{**}S_m^{**}}-\frac{I_{f2}P_{f2}^{**}}{I_{f2}^{**}P_{f2}}\right)\end{aligned}\tag{4.60}$$

Finally, since arithmetic mean is greater that geometric mean, the following inequalities from (4.60) hold:

$$\left(2-\frac{S_f^{**}}{S_f}-\frac{S_f}{S_f^{**}}\right)\le 0,\quad \left(2-\frac{S_m^{**}}{S_m}-\frac{S_m}{S_m^{**}}\right)\le 0$$

$$\left(4-\frac{S_f^{**}}{S_f}-\frac{S_m^{**}}{S_m}-\frac{I_{m2}I_{f2}^{**}S_f}{I_{m2}^{**}I_{f2}S_f^{**}}-\frac{I_{f2}I_{m2}^{**}S_m}{I_{f2}^{**}I_{m2}S_m^{**}}\right)\le 0$$

$$\left(5-\frac{S_f^{**}}{S_f}-\frac{S_m^{**}}{S_m}-\frac{I_{m2}I_{f2}^{**}S_f}{I_{m2}^{**}I_{f2}S_f^{**}}-\frac{I_{m2}^{**}P_{f2}S_m}{I_{m2}P_{f2}^{**}S_m^{**}}-\frac{I_{f2}P_{f2}^{**}}{I_{f2}^{**}P_{f2}}\right)\le 0$$

Thus, $\dot{\mathcal{V}}_2 \le 0$ for $\mathcal{R}_{02} > 1$. Hence, $\mathcal{V}_2$ is a Lyapunov function in $\mathcal{D}_2$ and it follows from the La Salle's Invariance principle (La Salle and Lefschetz, 1976), that every solution to the equations of the model (4.43) with (4.47) and (4.48), and initial conditions in $\mathcal{V}_2\diagdown\mathcal{V}_{20}$ approaches the associated unique endemic equilibrium ξ_{10}, of the model as $t\to\infty$ for $\mathcal{R}_{02} > 1$. □

4.5 Basic properties of the HPV-TB co-infection model (3.29)

4.5.1 Positivity and boundedness of solutions

For the model (3.29) to be epidemiologically meaningful, it is important to prove that all its state variables are non- negative for all time. In other words, solutions of the model system (3.29) with positive initial data will remain positive for all time $t > 0$.

Theorem 4.28. *Let the initial data be*

$S_{\text{F}}(0) > 0, V_{\text{HF}}(0) > 0, I_{\text{HF}}(0) > 0, R_{\text{HF}}(0) > 0, P_{\text{HF}}(0) > 0, C_{\text{F}}(0) > 0, R^c_{\text{F}}(0) > 0, E_{\text{FT}}(0) > 0,$
$I_{\text{FT}}(0) > 0, T_{\text{FT}}(0) > 0, I^{\text{F}}_{\text{HE}}(0) > 0, I^{\text{F}}_{\text{HA}}(0) > 0, P^{\text{F}}_{\text{HE}}(0) > 0, P^{\text{F}}_{\text{HA}}(0) > 0, C_{\text{FE}}(0) > 0, C_{\text{FA}}(0) > 0,$
$S_{\text{M}}(0) > 0, I_{\text{HM}}(0) > 0, R_{\text{HM}}(0) > 0, E_{\text{MT}}(0) > 0, I_{\text{MT}}(0) > 0, T_{\text{MT}}(0) > 0, I^{\text{M}}_{\text{HE}}(0) > 0, I^{\text{M}}_{\text{HA}}(0) > 0.$
Then the solutions
$(S_{\text{F}}, V_{\text{HF}}, I_{\text{HF}}, R_{\text{HF}}, P_{\text{HF}}, C_{\text{F}}, R^c_{\text{F}}, E_{\text{FT}}, I_{\text{FT}}, T_{\text{FT}}, I^{\text{F}}_{\text{HE}}, I^{\text{F}}_{\text{HA}}, P^{\text{F}}_{\text{HE}}, P^{\text{F}}_{\text{HA}}, C_{\text{FE}},$

$C_{\text{FA}}, S_{\text{M}}, I_{\text{HM}}, R_{\text{HM}}, E_{\text{MT}}, I_{\text{MT}}, T_{\text{MT}}, I^{\text{M}}_{\text{HE}}, I^{\text{M}}_{\text{HA}})$ *of the model* (3.29) *are positive for all time* $t > 0$.
Furthermore, $\limsup\limits_{t\to 0} N_{\text{M}}(t) \le \dfrac{\Lambda_{\text{M}}}{\mu_{\text{M}}}$ *and* $\limsup\limits_{t\to 0} N_{\text{F}}(t) \le \dfrac{\Lambda_{\text{F}}}{\mu_{\text{F}}}$

Proof. Let $t_1 = \sup\{S_{\text{F}}(0) > 0, V_{\text{HF}}(0) > 0, I_{\text{HF}}(0) > 0, R_{\text{HF}}(0) > 0, P_{\text{HF}}(0) > 0, C_{\text{F}}(0) > 0, R^c_{\text{F}}(0) > 0, E_{\text{FT}}(0) > 0, I_{\text{FT}}(0) > 0, T_{\text{FT}}(0) > 0, I^{\text{F}}_{\text{HE}}(0) > 0,$
$I^{\text{F}}_{\text{HA}}(0) > 0, P^{\text{F}}_{\text{HE}}(0) > 0, P^{\text{F}}_{\text{HA}}(0) > 0, C_{\text{FE}}(0) > 0, C_{\text{FA}}(0) > 0, S_{\text{M}}(0) > 0, I_{\text{HM}}(0) > 0, R_{\text{HM}}(0) > 0, E_{\text{MT}}(0) > 0, I_{\text{MT}}(0) > 0, T_{\text{MT}}(0) > 0, I^{\text{M}}_{\text{HE}}(0) > 0, I^{\text{M}}_{\text{HA}}(0) > 0 \in [0, t]\}$
Thus, $t_1 > 0$. From the first equation of the system (3.29), we have that

$$\frac{dS_{\text{F}}}{dt} = (1 - f)\Lambda_{\text{F}} - (\lambda_{\text{HM}} + \xi_{\text{F}}\lambda_{\text{HF}} + \mu_{\text{F}} + \lambda_{\text{T}})S_{\text{F}}$$

which can be re-written as

$$\frac{d}{dt}\left\{S_{\text{F}}(t)\exp\left[\int_0^{t_1}(\lambda_{\text{HM}}(u) + \xi_{\text{F}}\lambda_{\text{HF}}(u) + \lambda_{\text{T}}(u))du + \mu_{\text{F}}t\right]\right\}$$
$$= (1 - f)\Lambda_{\text{F}}\exp\left[\int_0^{t_1}(\lambda_{\text{HM}}(u) + \xi_{\text{F}}\lambda_{\text{HF}}(u)\lambda_{\text{T}}(u))du + \mu_{\text{F}}t\right]$$

Hence:

$$\frac{d}{dt}\left\{S_{\text{F}}(t_1)\exp\left[\int\limits_0^{t_1}(\lambda_{\text{HM}}(u)+\xi_{\text{F}}\lambda_{\text{HF}}(u)+\lambda_{\text{T}}(u))du+\mu_{\text{F}}t_1\right]\right\}-S_{\text{F}}(0)$$
$$=(1-f)\Lambda_{\text{F}}\int_0^{t_1}\exp\left[\int\limits_0^{x}(\lambda_{\text{HM}}(u)+\xi_{\text{F}}\lambda_{\text{HF}}(u)+\lambda_{\text{T}}(u))du+\mu_{\text{F}}x\right]dx$$

so that

$$S_{\text{F}}(t_1)=S_{\text{F}}(0)\exp\left[-\int\limits_0^{t_1}(\lambda_{\text{HM}}(u)+\xi_{\text{F}}\lambda_{\text{HF}}(u)+\lambda_{\text{T}}(u))du+\mu_{\text{F}}t_1\right]$$
$$+\exp\left[-\int\limits_0^{t_1}(\lambda_{\text{HM}}(u)+\xi_{\text{F}}\lambda_{\text{HF}}(u)+\lambda_{\text{T}}(u))du+\mu_{\text{F}}t_1\right]$$
$$\times(1-f)\Lambda_{\text{F}}\int_0^{t_1}\exp\left[\int\limits_0^{x}(\lambda_{\text{HM}}(u)+\xi_{\text{F}}\lambda_{\text{HF}}(u)+\lambda_{\text{T}}(u))du+\mu_{\text{F}}x\right]dx>0$$

Similarly, it can be shown that:

$V_{\text{HF}}(0)>0, I_{\text{HF}}(0)>0, R_{\text{HF}}(0)>0, P_{\text{HF}}(0)>0, C_{\text{F}}(0)>0, R^c_{\text{F}}(0)>0, E_{\text{FT}}(0)>0, I_{\text{FT}}(0)>0, T_{\text{FT}}(0)>0, I^{\text{F}}_{\text{HE}}(0)>0, I^{\text{F}}_{\text{HA}}(0)>0, P^{\text{F}}_{\text{HE}}(0)>0, P^{\text{F}}_{\text{HA}}(0)>0, C_{\text{FE}}(0)>0, C_{\text{FA}}(0)>0, S_{\text{M}}(0)>0, I_{\text{HM}}(0)>0, R_{\text{HM}}(0)>0, E_{\text{MT}}(0)>0, I_{\text{MT}}(0)>0, T_{\text{MT}}(0)>0, I^{\text{M}}_{\text{HE}}(0)>0, I^{\text{M}}_{\text{HA}}(0)>0.$

□

4.5.2 Invariant Regions

The Co-infection model (3.29) will be analyzed in a biologically feasible region as follows. We first show that the system (3.29) is dissipative (that is, all feasible solutions are uniformly-bounded in a proper subset $\mathcal{D}\subset\mathfrak{R}^{24}_{+}$). The system (3.29) is split into two parts, namely the male population (N_{M}) (with $N_{\text{M}}=S_{\text{M}}+I_{\text{HM}}+R_{\text{HM}}+E_{\text{MT}}+I_{\text{MT}}+T_{\text{MT}}+I^{\text{M}}_{\text{HE}}+I^{\text{M}}_{\text{HA}}$) and the female population, (N_{F}) (with $N_{\text{F}}=S_{\text{F}}+V_{\text{HF}}+I_{\text{HF}}+R_{\text{HF}}+P_{\text{HF}}+C_{\text{F}}+R^c_{\text{F}}+E_{\text{FT}}+I_{\text{FT}}+T_{\text{FT}}+I^{\text{F}}_{\text{HE}}+I^{\text{F}}_{\text{HA}}+P^{\text{F}}_{\text{HE}}+P^{\text{F}}_{\text{HA}}+C_{\text{FE}}+C_{\text{FA}}$). Consider the feasible region $\mathcal{D}=\mathcal{D}_{\text{F}}\cup\mathcal{D}_{\text{M}}\subset\mathfrak{R}^{16}_{+}\times\mathfrak{R}^{8}_{+}$,

with:

$\mathcal{D}_{\text{F}}=\{(S_{\text{F}},V_{\text{HF}},I_{\text{HF}},R_{\text{HF}},P_{\text{HF}},C_{\text{F}},R^c_{\text{F}},E_{\text{FT}},I_{\text{FT}},T_{\text{FT}},I^{\text{F}}_{\text{HE}},I^{\text{F}}_{\text{HA}},P^{\text{F}}_{\text{HE}},P^{\text{F}}_{\text{HA}},C_{\text{FE}},C_{\text{FA}}))\in\mathfrak{R}^{16}_{+}:$
$S_{\text{F}}+V_{\text{HF}}+I_{\text{HF}}+R_{\text{HF}}+P_{\text{HF}}+C_{\text{F}}+R^c_{\text{F}}+E_{\text{FT}}+I_{\text{FT}}+T_{\text{FT}}+I^{\text{F}}_{\text{HE}}+I^{\text{F}}_{\text{HA}}+P^{\text{F}}_{\text{HE}}+P^{\text{F}}_{\text{HA}}+$
$C_{\text{FE}}+C_{\text{FA}})\leq\dfrac{\Lambda_{\text{F}}}{\mu_{\text{F}}}\Big\}$

and

$\mathcal{D}_{\text{M}} = \{S_{\text{M}}, I_{\text{HM}}, R_{\text{HM}}, E_{\text{MT}}, I_{\text{MT}}, T_{\text{MT}}, I^{\text{M}}_{\text{HE}}, I^{\text{M}}_{\text{HA}} \in \mathfrak{R}^{8}_{+} :$

$S_{\text{M}} + I_{\text{HM}} + R_{\text{HM}} + E_{\text{MT}} + I_{\text{MT}} + T_{\text{MT}} + I^{\text{M}}_{\text{HE}} + I^{\text{M}}_{\text{HA}} \leq \dfrac{\Lambda_{\text{M}}}{\mu_{\text{M}}}\Big\}$

The following steps are followed to establish the positive invariance of $\mathcal{D}$ (i.e. solutions in $\mathcal{D}$ remain in $\mathcal{D}$ for all time $t \geq 0$). Adding the first sixteen and the last eight equations in the differential system (3.29) gives

$$\begin{aligned}
\frac{dN}{dt} &= \Lambda_{\text{F}} - \mu_{\text{F}} N_{\text{F}}(t) - [\delta_{\text{HF}} I_{\text{HF}} + \delta_{\text{CF}} I_{\text{F}} + \delta_{\text{FT}} I_{\text{FT}} + \delta_{\text{HF1}} I^{\text{F}}_{\text{HE}} + (\delta_{\text{FT}} + \delta_{\text{HF2}}) I^{\text{F}}_{\text{HA}} \\
&\quad + \delta_{\text{FT1}} P^{\text{F}}_{\text{HA}} + \delta_{\text{CF}} C_{\text{FE}} + (\delta_{\text{FT3}} + \delta_{\text{CF}}) C_{\text{FA}}] \\
\frac{dN_{\text{M}}}{dt} &= \Lambda_{\text{M}} - \mu N_{\text{M}}(t) - [\delta_{\text{HM}} I_{\text{HM}} + \delta_{\text{MT}} I_{\text{MT}} + \delta_{\text{HM 1}} I^{\text{M}}_{\text{HE}} + \delta_{\text{MT}} I^{\text{M}}_{\text{HA}} + \delta_{\text{HM2}} I^{\text{M}}_{\text{HA}}]
\end{aligned} \tag{4.61}$$

From (4.61), we have that

$$\begin{aligned}
\Lambda_{\text{F}} - (\mu_{\text{F}} + 10\delta_{\text{F}}) N_{\text{F}} \leq \frac{dN_{\text{F}}}{dt} < \Lambda_{\text{F}} - \mu_{\text{F}} N_{\text{F}} \\
\Lambda_{\text{M}} - (\mu_{\text{M}} + 5\delta_{\text{M}}) N_{\text{M}} \leq \frac{dN_{\text{M}}}{dt} < \Lambda_{\text{M}} - \mu_{\text{M}} N_{\text{M}}
\end{aligned}$$

Where $\delta_{\text{F}} = \min\{\delta_{\text{HF}}, \delta_{\text{CF}}, \delta_{\text{FT}}, \delta_{\text{HF1}}, \delta_{\text{HF2}}, \delta_{\text{FT1}}, \delta_{\text{CF}}, \delta_{\text{FT3}}, \delta_{\text{CF}},\}$ and $\delta_{\text{M}} = \min\{\delta_{\text{HM}}, \delta_{\text{MT}}, \delta_{\text{HM1}}, \delta_{\text{MT1}}\}$. Using the Comparison theorem (Lakshmikantham, et al., 1989), we have that $N_{\text{F}}(t) \leq N_{\text{F}}(0)\text{e}^{-\mu_F t} + \dfrac{\Lambda_{\text{F}}}{\mu_{\text{F}}}(1 - \text{e}^{-\mu_F t})$ and $N_{\text{M}}(t) \leq N_{\text{M}}(0)\text{e}^{-\mu_M t} + \dfrac{\Lambda_{\text{M}}}{\mu_{\text{M}}}(1 - \text{e}^{-\mu_M t})$. In particular, $N_{\text{F}}(t) \leq \dfrac{\Lambda_{\text{F}}}{\mu_{\text{F}}}$ and $N_{\text{M}}(t) \leq \dfrac{\Lambda_{\text{M}}}{\mu_{\text{M}}}$ if $N_{\text{F}}(0) \leq \dfrac{\Lambda_{\text{F}}}{\mu_{\text{F}}}$ and $N_{\text{M}}(0) \leq \dfrac{\Lambda_{\text{M}}}{\mu_{\text{M}}}$ respectively. Thus, the region $\mathcal{D}$ is positively invariant. Hence, it is sufficient to consider the dynamics of the flow generated by (3.29) in $\mathcal{D}$. In this region, the model can be considered as been epidemiologically and mathematically well-posed (Hethcote, 2000). Thus, every solution of the model (3.29) with initial conditions in $\mathcal{D}$ remains in $\mathcal{D}$ for all time $t \geq 0$. Therefore, the $\omega-$limit sets of the system (3.29) are contained in $\mathcal{D}$. Thus result is summarized thus.

Lemma 4.29. The region $\mathcal{D} = \mathcal{D}_{\text{F}} \cup \mathcal{D}_{\text{M}} \subset \mathfrak{R}^{16}_{+} \times \mathfrak{R}^{8}_{+}$ is positively-invariant for the co-infection model (3.29) with initial conditions in $\mathfrak{R}^{24}_{+}$.

4.5.3 Existence and stability of Equilibrum

HPV-only sub-model

The HPV-only sub-model is (obtained by setting $E_{\text{FT}} = I_{\text{FT}} = T_{\text{FT}} = I^{\text{F}}_{\text{HE}} = I^{\text{F}}_{\text{HA}} = P^{\text{F}}_{\text{HE}} = P^{\text{F}}_{\text{HA}} = C_{\text{FE}} = C_{\text{FA}} = E_{\text{MT}} = I_{\text{MT}} = T_{\text{MT}} = I^{\text{M}}_{\text{HE}} = I^{\text{M}}_{\text{HA}} = 0$ in the model (3.29)) given by:

$$
\begin{aligned}
\frac{dS_{\text{F}}}{dt} &= (1-f)\Lambda_{\text{F}} - \left(\lambda_{\text{HM}} + \xi_{\text{F}}\lambda_{\text{HF}} + \mu_{\text{F}}\right) S_{\text{F}} \\
\frac{dV_{\text{HF}}}{dt} &= f\Lambda_{\text{F}} - (1-\pi_{\text{F}})\lambda_{\text{HM}}V_{\text{HF}} - (1-\pi_{\text{F}})\xi_{\text{F}}\lambda_{\text{HF}}V_{\text{HF}} - \mu_{\text{F}}V_{\text{HF}} \\
\frac{dI_{\text{HF}}}{dt} &= (1-\pi_{\text{F}})\lambda_{\text{HM}}V_{\text{HF}} + (1-\pi_{\text{F}})\xi_{\text{F}}\lambda_{\text{HF}}V_{\text{HF}} + \lambda_{\text{HM}}S_{\text{F}} + \xi_{\text{F}}\lambda_{\text{HF}}S_{\text{F}} - (\phi^{\text{F}}_1 + \delta_{\text{HF}} + \mu_{\text{F}})I_{\text{HF}} + \varphi_{\text{F}}\lambda_{\text{HM}}R_{\text{HF}} + \varphi_{\text{F}}\xi_{\text{F}}\lambda_{\text{HF}}R_{\text{HF}} \\
\frac{dP_{\text{HF}}}{dt} &= (1-\kappa^{\text{F}}_1)\phi^{\text{F}}_1 I_{\text{HF}} - (\rho^{\text{F}}_1 + \mu_{\text{F}})P_{\text{HF}} \\
\frac{dC_{\text{F}}}{dt} &= (1-\chi^{\text{F}}_1)\rho^{\text{F}}_1 P_{\text{HF}} - (\tau^{\text{F}}_1 + \delta_{\text{CF}} + \mu_{\text{F}})C_{\text{F}} \\
\frac{dR^{\text{C}}_{\text{F}}}{dt} &= \tau^{\text{F}}_1 C_{\text{F}} - \mu_{\text{F}}R^{\text{C}}_{\text{F}} \\
\frac{dR_{\text{HF}}}{dt} &= \kappa^{\text{F}}_1\phi^{\text{F}}_1 I_{\text{HF}} + \chi^{\text{F}}_1\rho^{\text{F}}_1 P_{\text{HF}} - \left(\mu_{\text{F}} + \varphi_{\text{F}}\lambda_{\text{HM}} + \varphi_{\text{F}}\xi_{\text{F}}\lambda_{\text{HF}}\right) R_{\text{HF}} \\
\frac{dS_{\text{M}}}{dt} &= \Lambda_{\text{M}} - \left(\lambda_{\text{HF}} + \xi_{\text{M}}\lambda_{\text{HM}} + \mu_{\text{M}}\right) S_{\text{M}} \\
\frac{dI_{\text{HM}}}{dt} &= \lambda_{\text{HF}}S_{\text{M}} + \xi_{\text{M}}\lambda_{\text{HM}}S_{\text{M}} - (\phi^{\text{M}}_1 + \delta_{\text{HM}} + \mu_{\text{M}})I_{\text{HM}} + \varphi_{\text{M}}\lambda_{\text{HF}}R_{\text{HM}} + \varphi_{\text{M}}\xi_{\text{M}}\lambda_{\text{HM}}R_{\text{HM}} \\
\frac{dR_{\text{HM}}}{dt} &= \phi^{\text{M}}_1 I_{\text{HM}} - \left(\mu_{\text{M}} + \varphi_{\text{M}}\lambda_{\text{HF}} + \varphi_{\text{M}}\xi_{\text{M}}\lambda_{\text{HM}}\right) R_{\text{HM}}
\end{aligned}
\tag{4.62}
$$

where now,

$$
\begin{aligned}
\lambda_{\text{HF}} =& \frac{\beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})(I_{\text{HF}} + \omega_p P_{\text{HF}})}{N_{\text{HF}}} \\
\lambda_{\text{HM}} =& \frac{\beta_{\text{M}}(1-c_{\text{M}}\epsilon_{\text{M}})I_{\text{HM}}}{N_{\text{HM}}}
\end{aligned}
$$

with

$$
\begin{aligned}
N_{\text{HF}} =& S_{\text{F}} + V_{\text{HF}} + I_{\text{HF}} + P_{\text{HF}} + C_{\text{F}} + R^{\text{C}}_{\text{F}} + R_{\text{HF}} \\
N_{\text{HM}} =& S_{\text{M}} + I_{\text{HM}} + R_{\text{HM}}
\end{aligned}
$$

4.5.4 Local asymptotic stability of disease-free equilibrium (DFE) of the HPV-only sub-model

The HPV-only sub-model (4.62) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\begin{aligned}\xi_{0\text{H}} =&(S_{\text{F}}^{*}, V_{\text{HF}}^{*}, I_{\text{HF}}^{*}, P_{\text{HF}}^{*}, C_{\text{F}}^{*}, R_{\text{F}}^{c*}, R_{\text{HF}}^{*}, S_{\text{M}}^{*}, I_{\text{HM}}^{*}, R_{\text{HM}}^{*}) \\ =&\Big(\frac{(1-f)\Lambda_{\text{F}}}{\mu_{\text{F}}}, \frac{f\Lambda_{\text{F}}}{\mu_{\text{F}}}, 0, 0, 0, 0, 0, \frac{\Lambda_{\text{M}}}{\mu_{\text{M}}}, 0, 0\Big)\end{aligned} \tag{4.63}$$

The linear stability of $\xi_{0\text{H}}$ will be investigated using the next generation operator method on the system (4.62) (van den Driessche and Watmough, 2002). The matrices F (for the new infection terms) and V (for the remaining transition terms) associated with the HPV-only sub-model (4.62) are given, respectively, by (noting that $S_{\text{F}}^{*} = \frac{(1-f)\Lambda_{\text{F}}}{\mu_{\text{F}}}$, $V_{\text{HF}}^{*} = \frac{f\Lambda_{\text{F}}}{\mu_{\text{F}}}$, $N_{\text{HF}}^{*} = \frac{\Lambda_{\text{F}}}{\mu_{\text{F}}}$, $S_{\text{HM}}^{*} = N_{\text{HM}}^{*} = \frac{\Lambda_{\text{M}}}{\mu_{\text{M}}}$ at the DFE $\xi_{0\text{H}}$)

$$F_{\text{H}} = \begin{bmatrix} \frac{\beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})\{S_{\text{F}}^{*}+(1-\pi_{\text{F}})V_{\text{HF}}^{*}\}\xi_{\text{F}}}{N_{\text{HF}}^{*}} & \frac{\beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})\{S_{\text{F}}^{*}+(1-\pi_{\text{F}})V_{\text{HF}}^{*}\}\xi_{\text{F}}}{N_{\text{HF}}^{*}} & 0 & \frac{\beta_{\text{M}}(1-c_{\text{M}}\epsilon_{\text{M}})\{S_{\text{F}}^{*}+(1-\pi_{\text{F}})V_{\text{HF}}^{*}\}}{N_{\text{HM}}^{*}} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\beta_{\text{F}}^{*}(1-c_{\text{F}}\epsilon_{\text{F}})S_{\text{M}}^{*}}{N_{\text{HF}}^{*}} & \frac{\omega_{p}\beta_{\text{F}}^{*}(1-c_{\text{F}}\epsilon_{\text{F}})S_{\text{M}}^{*}}{N_{\text{HF}}^{*}} & 0 & \frac{\beta_{\text{M}}(1-c_{\text{M}}\epsilon_{\text{M}})S_{\text{M}}^{*}\xi_{\text{M}}}{N_{\text{HM}}^{*}} \end{bmatrix} \tag{4.64}$$

$$V_{\text{H}} = \begin{bmatrix} Q_1 & 0 & 0 & 0 \\ -D_1 & Q_2 & 0 & 0 \\ 0 & -D_2 & Q_3 & 0 \\ 0 & 0 & 0 & Q_{12} \end{bmatrix} \tag{4.65}$$

We have that the associated basic reproduction number of the HPV-only sub-model (4.62), denoted by $\mathcal{R}_{0H} = \rho(F_H V_H^{-1})$ (where ρ represents the spectral radius of $F_H V_H^{-1}$), is given by

$$\begin{aligned}\mathcal{R}_{0H} &= \frac{1}{2}\Big(\mathcal{R}_{\text{MM}} + \mathcal{R}_{\text{FF}}\Big) + \frac{1}{2}\sqrt{\mathcal{R}_{\text{MM}}^{2} + \mathcal{R}_{\text{FF}}^{2} + 4\mathcal{R}_{\text{FM}}^{2} - 2\mathcal{R}_{\text{FM}}\xi_{\text{M}}\xi_{\text{F}}} \\ &= \frac{1}{2}\Big(\mathcal{R}_{\text{MM}} + \mathcal{R}_{\text{FF}}\Big) + \frac{1}{2}\sqrt{\Big(\mathcal{R}_{\text{MM}} - \mathcal{R}_{\text{FF}}\Big)^{2} + 4\mathcal{R}_{\text{FM}}^{2}}\end{aligned}$$

where,

$$\begin{aligned}
\mathcal{R}_{\text{MM}} &= \frac{\beta_{\text{M}}(1 - c_{\text{M}}\epsilon_{\text{M}})\xi_{\text{M}}}{Q_{12}}, \\
\mathcal{R}_{\text{FF}} &= \frac{(1 - f\pi_{\text{F}})\beta_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})(Q_2 + \omega_p D_1)\xi_{\text{F}}}{Q_1 Q_2}, \\
\mathcal{R}_{\text{FM}} &= \sqrt{\frac{\beta_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})\beta_{\text{M}}(1 - c_{\text{M}}\epsilon_{\text{M}})(Q_2 + D_1\omega_p)(1 - f\pi_{\text{F}})}{Q_1 Q_2 Q_{12}}}
\end{aligned}$$

with,

$$Q_1 = (\phi_1^{\text{F}} + \delta_{\text{HF}} + \mu_{\text{F}}), \quad Q_2 = (\rho_1^{\text{F}} + \mu_{\text{F}}), \quad Q_{12} = (\phi_1^{\text{M}} + \delta_{\text{HM}} + \mu_{\text{M}}), \quad D_1 = (1 - \kappa_1^{\text{F}})\phi_1^{\text{F}}$$

It should be noted that $\mathcal{R}_{\text{MM}}$ is the reproduction number for the male-male transmission of HPV, $\mathcal{R}_{\text{FF}}$ is the reproduction number for the female-female transmission of HPV and $\mathcal{R}_{\text{FM}}$ is the reproduction number for the male-female-male transmission of HPV.
Using Theorem 2 of van den Driessche and Watmough (2002), the following result is established.

Lemma 4.30. The DFE, ξ_{0H}, of the HPV-only sub-model (4.62) is locally asymptotically stable (LAS) if $\mathcal{R}_{0H} < 1$, and unstable if $\mathcal{R}_{0H} > 1$.

4.5.5 Analysis of the reproduction number $\mathcal{R}_{0\text{H}}$

Impact of condom use and vaccine

Using the threshold parameter, $\mathcal{R}_{0\text{H}}$, we wish to determine the effect of condom use and vaccination on the control of HPV in the population. We have that the reproduction number of the HPV-only sub-model is given by:

$$\begin{aligned}
\mathcal{R}_{0\text{H}} &= \frac{1}{2}\Big(\mathcal{R}_{\text{MM}} + \mathcal{R}_{\text{FF}}\Big) + \frac{1}{2}\sqrt{\mathcal{R}_{\text{MM}}^2 + \mathcal{R}_{\text{FF}}^2 + 4\mathcal{R}_{\text{FM}}^2 - 2\mathcal{R}_{\text{FM}}\xi_{\text{M}}\xi_{\text{F}}} \\
&= \frac{1}{2}\Big(\mathcal{R}_{\text{MM}} + \mathcal{R}_{\text{FF}}\Big) + \frac{1}{2}\sqrt{\Big(\mathcal{R}_{\text{MM}} - \mathcal{R}_{\text{FF}}\Big)^2 + 4\mathcal{R}_{\text{FM}}^2}
\end{aligned}$$

Differentiating $\mathcal{R}_{0\text{H}}$ partially with respect to the condom parameters c_{F} and c_{F} we obtain,

$$\frac{\partial \mathcal{R}_{0\text{H}}}{\partial c_{\text{F}}} = \frac{\partial \mathcal{R}_{0\text{H}}}{\partial \mathcal{R}_{\text{FF}}}\frac{\partial \mathcal{R}_{\text{FF}}}{\partial c_{\text{F}}} + \frac{\partial \mathcal{R}_{0\text{H}}}{\partial \mathcal{R}_{\text{FM}}}\frac{\partial \mathcal{R}_{\text{FM}}}{\partial c_{\text{F}}}, \quad \frac{\partial \mathcal{R}_{0\text{H}}}{\partial c_{\text{M}}} = \frac{\partial \mathcal{R}_{0\text{H}}}{\partial \mathcal{R}_{\text{MM}}}\frac{\partial \mathcal{R}_{\text{MM}}}{\partial c_{\text{M}}} + \frac{\partial \mathcal{R}_{0\text{H}}}{\partial \mathcal{R}_{\text{FM}}}\frac{\partial \mathcal{R}_{\text{FM}}}{\partial c_{\text{M}}}$$

which gives

$$\begin{aligned}\frac{\partial \mathcal{R}_{0\mathrm{H}}}{\partial c_{\mathrm{F}}} &= -\frac{(1-f\pi_{\mathrm{F}})\beta_{\mathrm{F}}\epsilon_{\mathrm{F}}\xi_{\mathrm{F}}(Q_2+\omega_p D_1)}{2Q_1Q_2} - \frac{\beta_{\mathrm{F}}\beta_{\mathrm{M}}\epsilon_{\mathrm{F}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})(Q_2+\omega_p D_1)(1-f\pi_{\mathrm{F}})}{Q_1Q_2Q_{12}\sqrt{\Big(\mathcal{R}_{\mathrm{MM}}-\mathcal{R}_{\mathrm{FF}}\Big)^2+4\mathcal{R}_{\mathrm{FM}}^2}} \\ &\quad + \frac{\beta_{\mathrm{F}}\epsilon_{\mathrm{F}}\xi_{\mathrm{F}}(1-f\pi_{\mathrm{F}})(Q_2+\omega_p D_1)(\mathcal{R}_{\mathrm{MM}}-\mathcal{R}_{\mathrm{FF}})}{Q_1Q_2\sqrt{\Big(\mathcal{R}_{\mathrm{MM}}-\mathcal{R}_{\mathrm{FF}}\Big)^2+4\mathcal{R}_{\mathrm{FM}}^2}},\end{aligned} \tag{4.66}$$

$$\begin{aligned}\frac{\partial \mathcal{R}_{0\mathrm{H}}}{\partial c_{\mathrm{M}}} &= -\frac{\beta_{\mathrm{M}}\epsilon_{\mathrm{M}}\xi_{\mathrm{M}}(Q_2+\omega_p D_1)}{2Q_2} - \frac{\beta_{\mathrm{F}}\beta_{\mathrm{M}}\epsilon_{\mathrm{M}}(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})(Q_2+\omega_p D_1)}{Q_1Q_2Q_{12}\sqrt{\Big(\mathcal{R}_{\mathrm{MM}}-\mathcal{R}_{\mathrm{FF}}\Big)^2+4\mathcal{R}_{\mathrm{FM}}^2}} \\ &\quad - \frac{\beta_{\mathrm{M}}\epsilon_{\mathrm{M}}\xi_{\mathrm{M}}(\mathcal{R}_{\mathrm{MM}}-\mathcal{R}_{\mathrm{FF}})}{Q_{12}\sqrt{\Big(\mathcal{R}_{\mathrm{MM}}-\mathcal{R}_{\mathrm{FF}}\Big)^2+4\mathcal{R}_{\mathrm{FM}}^2}},\end{aligned} \tag{4.67}$$

Likewise, differentiating $\mathcal{R}_{0\mathrm{H}}$ partially with respect to the vaccine efficacy parameter π_{F}, we obtain,

$$\frac{\partial \mathcal{R}_{0\mathrm{H}}}{\partial \pi_{\mathrm{F}}} = \frac{\partial \mathcal{R}_{0\mathrm{H}}}{\partial \mathcal{R}_{\mathrm{FF}}}\frac{\partial \mathcal{R}_{\mathrm{FF}}}{\partial \pi_{\mathrm{F}}} + \frac{\partial \mathcal{R}_{0\mathrm{H}}}{\partial \mathcal{R}_{\mathrm{FM}}}\frac{\partial \mathcal{R}_{\mathrm{FM}}}{\partial \pi_{\mathrm{F}}},$$

which gives,

$$\begin{aligned}\frac{\partial \mathcal{R}_{0\mathrm{H}}}{\partial \pi_{\mathrm{F}}} &= -\frac{f\beta_{\mathrm{F}}\xi_{\mathrm{F}}(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})(Q_2+\omega_p D_1)}{2Q_1Q_2} - \frac{f\beta_{\mathrm{F}}\beta_{\mathrm{M}}(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})(Q_2+\omega_p D_1)}{Q_1Q_2Q_{12}\sqrt{\Big(\mathcal{R}_{\mathrm{MM}}-\mathcal{R}_{\mathrm{FF}}\Big)^2+4\mathcal{R}_{\mathrm{FM}}^2}} \\ &\quad + \frac{\beta_{\mathrm{F}}\epsilon_{\mathrm{F}}\xi_{\mathrm{F}}(1-f\pi_{\mathrm{F}})(Q_2+\omega_p D_1)(\mathcal{R}_{\mathrm{MM}}-\mathcal{R}_{\mathrm{FF}})}{2Q_1Q_2\sqrt{\Big(\mathcal{R}_{\mathrm{MM}}-\mathcal{R}_{\mathrm{FF}}\Big)^2+4\mathcal{R}_{\mathrm{FM}}^2}},\end{aligned} \tag{4.68}$$

4.5.6 Simulations of the HPV-only sub-model (4.62)

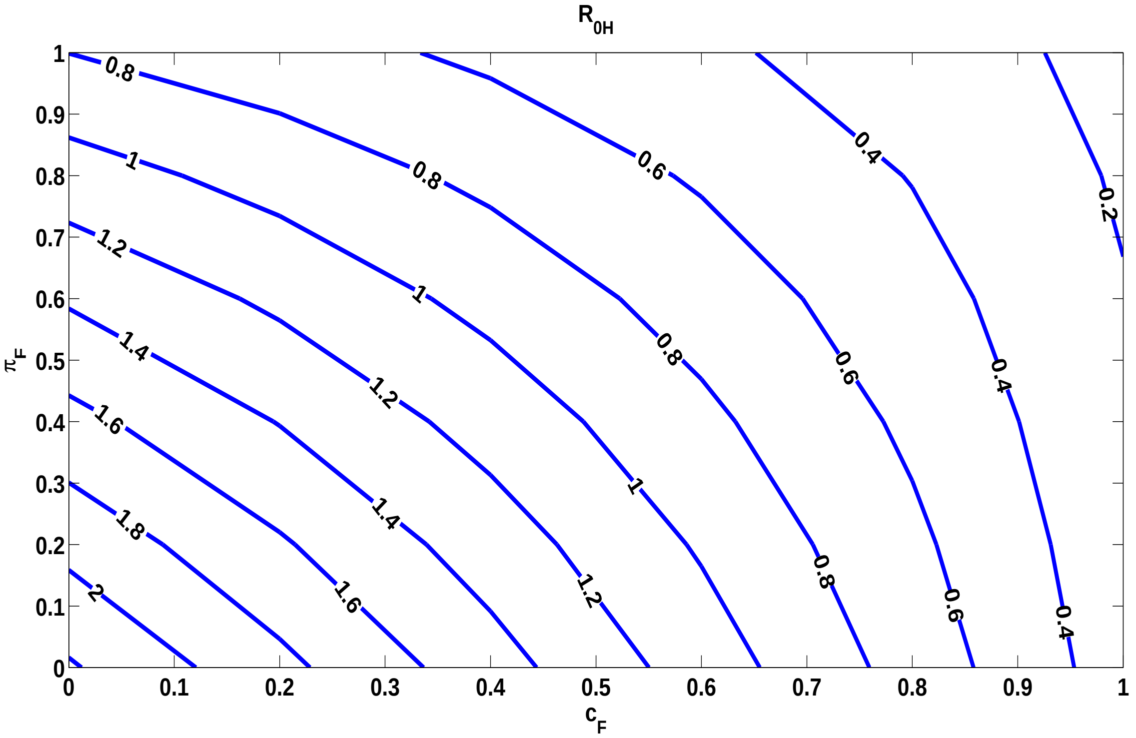


Figure 4.3: A contour plot of $\mathcal{R}_{0\mathrm{H}}$ as a function of HPV vaccine efficacy for females (π_{F}) and condom compliance for females (c_{F}). Here, $\xi_{\mathrm{F}} = 2, \xi_{\mathrm{M}} = 0$. All other parameters as in Table 4.7

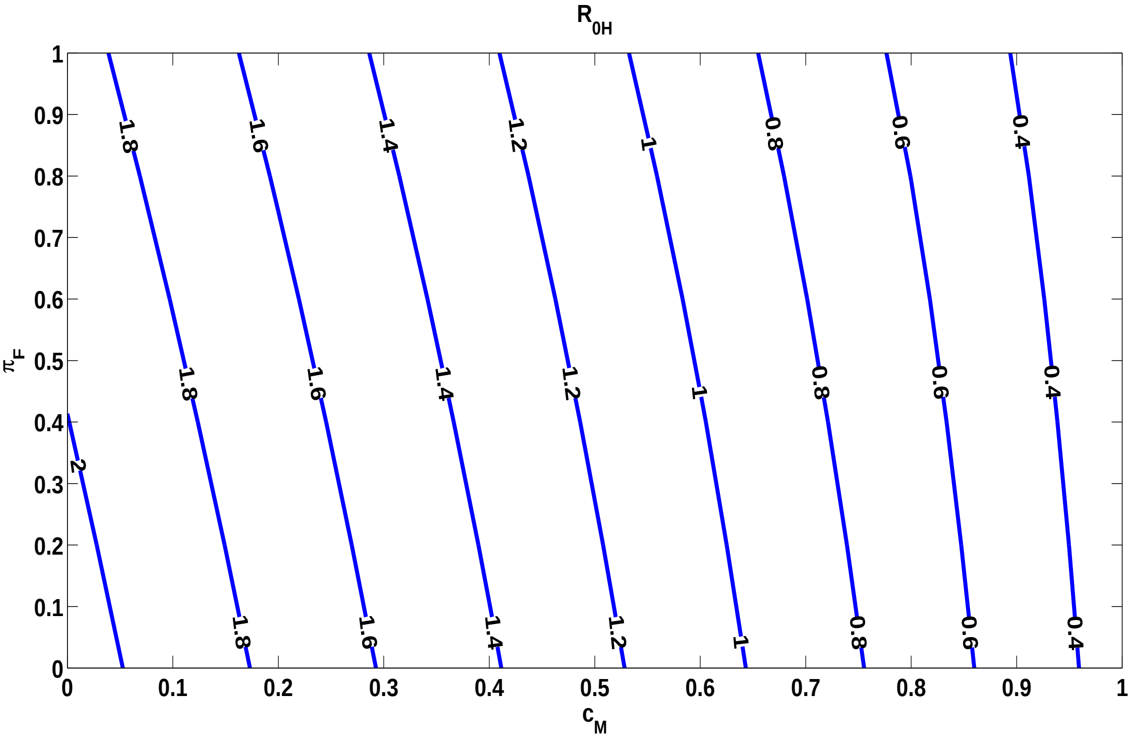


Figure 4.4: A contour plot of $\mathcal{R}_{0\mathrm{H}}$ as a function of HPV vaccine efficacy for females (π_{F}) and condom compliance for males (c_{M}). Here, $\xi_{\mathrm{F}} = 0, \xi_{\mathrm{M}} = 2.0$. All other parameters as in Table 4.7

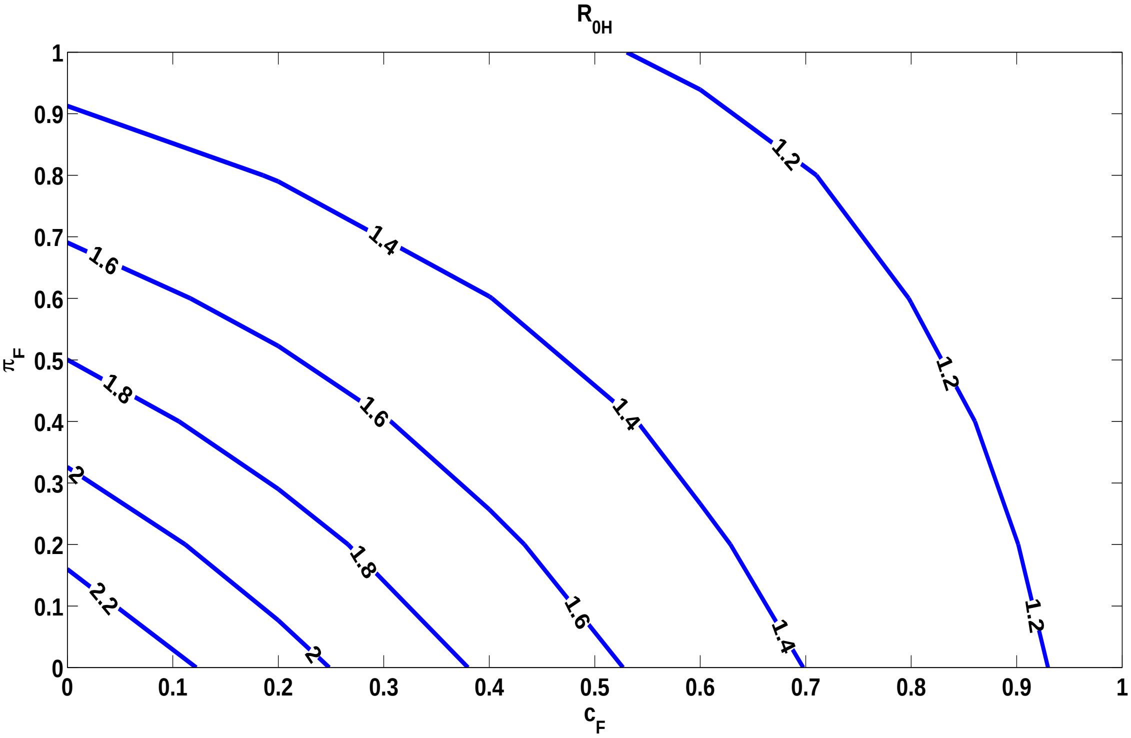


Figure 4.5: A contour plot of $\mathcal{R}_{0\mathrm{H}}$ as a function of HPV vaccine efficacy for females (π_{F}) and condom compliance for females (c_{F}). Here, $\xi_{\mathrm{F}} = 2, \xi_{\mathrm{M}} = 0$. All other parameters as in Table 4.7

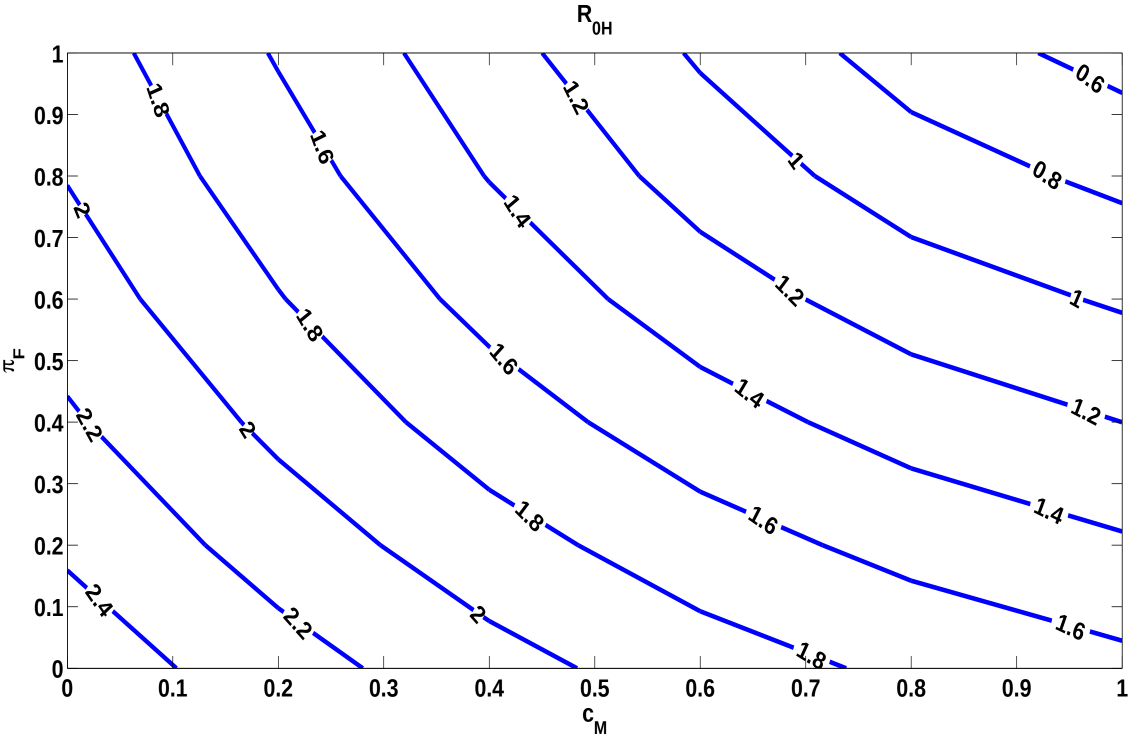


Figure 4.6: A contour plot of $\mathcal{R}_{0\mathrm{H}}$ as a function of HPV vaccine efficacy for females (π_{F}) and condom compliance for males (c_{M}). Here, $\xi_{\mathrm{F}} = 0, \xi_{\mathrm{M}} = 2.0$. All other parameters as in Table 4.7

A contour plot of the reproduction number $\mathcal{R}_{0\mathrm{H}}$, as a function of female *Cervarix* vaccine efficacy (π_{F}) and condom compliance (c_{F}) for females (when there are only bisexual females and heterosexual males), depicted in Figure 4.3 is plotted using the baseline values of the parameters in Table 4.7. This plot reveals that, with 40% condom compliance by the female population, administering a female vaccine (with 50% efficacy) is sufficient for effective control of HPV. However, similar plot carried out in Figure 4.5 (when there are both bisexual females and males), shows that the maximum level of condom compliance by females is insufficient for the elimination of HPV in the population (since $\mathcal{R}_{0\mathrm{H}}$ is always greater than unity).

A contour plot of the reproduction number $\mathcal{R}_{0\mathrm{H}}$, as a function of female *Cervarix* vaccine efficacy (π_{F}) and condom compliance (c_{M}) for males (when there are only bisexual males and heterosexual females), depicted in Figure 4.4, plotted using the baseline values of the parameters in Table 4.7, shows that with the assumed 90% Cervarix vaccine efficacy for females, about 55% condom compliance by males is required for effective control or elimination of HPV in the population. Moreover, similar plot carried out when there are both bisexual females and males in the population reveals that with the assumed 90% Cervarix vaccine efficacy for females, about 65% condom compliance level is required by males for the elimination of HPV in the population (Figure 4.6).

TB Only sub-model

$$
\begin{aligned}
\frac{dS_{\mathrm{F}}}{dt} &= \Lambda_{\mathrm{F}} - \left(\mu_{\mathrm{F}} + \lambda_{\mathrm{T}}\right) S_{\mathrm{F}} \\
\frac{dE_{\mathrm{FT}}}{dt} &= \left(1 - \psi_1^{\mathrm{F}}\right) \lambda_{\mathrm{T}} \left(S_{\mathrm{F}} + \sigma_{\mathrm{F}} T_{\mathrm{FT}}\right) - \left(\varepsilon_1^{\mathrm{F}} \lambda_{\mathrm{T}} + \gamma_1^{\mathrm{F}} + \mu_{\mathrm{F}}\right) E_{\mathrm{FT}} \\
\frac{dI_{\mathrm{FT}}}{dt} &= \psi_1^{\mathrm{F}} \lambda_{\mathrm{T}} \left(S_{\mathrm{F}} + \sigma_{\mathrm{F}} T_{\mathrm{FT}}\right) + \varepsilon_1^{\mathrm{F}} \lambda_{\mathrm{T}} E_{\mathrm{FT}} + \gamma_1^{\mathrm{F}} E_{\mathrm{FT}} - \left(r_1^{\mathrm{F}} + \mu_{\mathrm{F}} + \delta_{\mathrm{FT}}\right) I_{\mathrm{FT}} \\
\frac{dT_{\mathrm{FT}}}{dt} &= r_1^{\mathrm{F}} I_{\mathrm{FT}} - \left(\sigma_{\mathrm{F}} \lambda_{\mathrm{T}} + \mu_{\mathrm{F}}\right) T_{\mathrm{FT}} \\
\frac{dS_{\mathrm{M}}}{dt} &= \Lambda_{\mathrm{M}} - \left(\mu_{\mathrm{M}} + \lambda_{\mathrm{T}}\right) S_{\mathrm{M}} \\
\frac{dE_{\mathrm{MT}}}{dt} &= (1 - \psi_1^{\mathrm{M}}) \lambda_{\mathrm{T}} \left(S_{\mathrm{M}} + \sigma_{\mathrm{M}} T_{\mathrm{MT}}\right) - (\varepsilon_1^{\mathrm{M}} \lambda_{\mathrm{T}} + \gamma_1^{\mathrm{M}} + \mu_{\mathrm{M}}) E_{\mathrm{MT}} \\
\frac{dI_{\mathrm{MT}}}{dt} &= \psi_1^{\mathrm{M}} \lambda_{\mathrm{T}} \left(S_{\mathrm{M}} + \sigma_{\mathrm{M}} T_{\mathrm{MT}}\right) + \varepsilon_1^{\mathrm{M}} \lambda_{\mathrm{T}} E_{\mathrm{MT}} + \gamma_1^{\mathrm{M}} E_{\mathrm{MT}} - \left(r_1^{\mathrm{M}} + \mu_{\mathrm{M}} + \delta_{\mathrm{MT}}\right) I_{\mathrm{MT}} \\
\frac{dT_{\mathrm{MT}}}{dt} &= r_1^{\mathrm{M}} I_{\mathrm{MT}} - \left(\sigma_{\mathrm{M}} \lambda_{\mathrm{T}} + \mu_{\mathrm{M}}\right) T_{\mathrm{MT}}
\end{aligned} \tag{4.69}
$$

$$
\lambda_{\mathrm{T}} = \frac{\beta_{\mathrm{T}} \left(I_{\mathrm{MT}} + I_{\mathrm{FT}}\right)}{\left(N_{\mathrm{F}} + N_{\mathrm{M}}\right)}
$$

4.5.7 Local asymptotic stability of disease-free equilibrium (DFE) of the TB-only sub-model

The TB-only sub-model (4.69) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$
\begin{aligned}
\xi_{0\mathrm{T}} =& (S_{\mathrm{F}}^*, E_{\mathrm{FT}}^*, I_{\mathrm{FT}}^*, T_{\mathrm{FT}}^*, S_{\mathrm{M}}^*, E_{\mathrm{MT}}^*, I_{\mathrm{MT}}^*, T_{\mathrm{MT}}^*) \\
=& \Big(\frac{\Lambda_{\mathrm{F}}}{\mu_{\mathrm{F}}}, 0, 0, 0, \frac{\Lambda_{\mathrm{M}}}{\mu_{\mathrm{M}}}, 0, 0, 0\Big)
\end{aligned} \tag{4.70}
$$

The linear stability of $\xi_{0\mathrm{T}}$ will be investigated using the next generation operator method on the system (4.69) (van den Driessche and Watmough, 2002). The matrices F (for the new infection terms) and V (for the remaining transition terms) associated with the TB-only sub-model (4.69) are given, respectively, by (noting that $S_{\mathrm{F}}^* = N_{\mathrm{F}}^* = \frac{\Lambda_{\mathrm{F}}}{\mu_{\mathrm{F}}}$, $S_{\mathrm{M}}^* = N_{\mathrm{M}}^* = \frac{\Lambda_{\mathrm{M}}}{\mu_{\mathrm{M}}}$ at the DFE $\xi_{0\mathrm{T}}$)

$$
F_{\mathrm{T}} = \begin{bmatrix}
0 & \frac{\beta_{\mathrm{T}}\left(1-\psi_1^{\mathrm{F}}\right)S_{\mathrm{F}}^*}{N_{\mathrm{F}}^*+N_{\mathrm{M}}^*} & 0 & 0 \\
0 & \frac{\beta_{\mathrm{T}}\psi_1^{\mathrm{F}}S_{\mathrm{F}}^*}{N_{\mathrm{F}}^*+N_{\mathrm{M}}^*} & 0 & 0 \\
0 & 0 & 0 & \frac{\beta_{\mathrm{T}}\left(1-\psi_1^{\mathrm{M}}\right)S_{\mathrm{M}}^*}{N_{\mathrm{F}}^*+N_{\mathrm{M}}^*} \\
0 & 0 & 0 & \frac{\beta_{\mathrm{T}}\psi_1^{\mathrm{M}}S_{\mathrm{F}}^*}{N_{\mathrm{F}}^*+N_{\mathrm{M}}^*}
\end{bmatrix} \tag{4.71}
$$

$$V_{\mathrm{T}} = \begin{bmatrix} Q_4 & 0 & 0 & 0 \\ \gamma_1^{\mathrm{F}} & Q_5 & 0 & 0 \\ 0 & 0 & Q_{13} & 0 \\ 0 & 0 & \gamma_1^{\mathrm{M}} & Q_{14} \end{bmatrix} \tag{4.72}$$

We have that the associated basic reproduction number of the TB-only sub-model (4.69), denoted by $\mathcal{R}_{0\mathrm{H}} = \rho(F_{\mathrm{T}}V_{\mathrm{T}}^{-1})$ (where ρ represents the spectral radius of $F_{\mathrm{T}}V_{\mathrm{T}}^{-1}$), is given by

$$\mathcal{R}_{0T} = \frac{\beta_{\mathrm{T}}(\mu_{\mathrm{M}} + \mu_{\mathrm{F}})}{(\Lambda_{\mathrm{F}} + \Lambda_{\mathrm{M}})} \left(\frac{\Lambda_F[\gamma_1^F(1-\psi_1^F) + Q_4\psi_1^F]}{\mu_F Q_4 Q_5} + \frac{\Lambda_M[\gamma_1^M(1-\psi_1^M) + Q_{13}\psi_1^M]}{\mu_M Q_{13} Q_{14}} \right)$$

where

$$Q_4 = (\gamma_1^{\mathrm{F}} + \mu_{\mathrm{F}}), \quad Q_5 = (r_1^{\mathrm{F}} + \delta_{\mathrm{FT}} + \mu_{\mathrm{F}}) \quad Q_{13} = (\gamma_1^{\mathrm{M}} + \mu_{\mathrm{M}}) \quad Q_{14} = (r_1^{\mathrm{M}} + \delta_{\mathrm{MT}} + \mu_{\mathrm{M}}),$$

Using Theorem 2 of van den Driessche and Watmough (2002), the following result is established.

Lemma 4.31. The DFE, $\xi_{0\mathrm{T}}$, of the TB-only sub-model (4.69) is locally asymptotically stable (LAS) if $\mathcal{R}_{0\mathrm{T}} < 1$, and unstable if $\mathcal{R}_{0\mathrm{T}} > 1$.

4.5.8 Local stability of disease-free equilibrium (DFE) of the Full model

The model (3.29) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$\xi_0 = (S_{\mathrm{F}}^*, V_{\mathrm{HF}}^*, I_{\mathrm{HF}}^*, R_{\mathrm{HF}}^*, P_{\mathrm{HF}}^*, C_{\mathrm{F}}^*, R_{\mathrm{F}}^{c*}, E_{\mathrm{FT}}^*, I_{\mathrm{FT}}^*, T_{\mathrm{FT}}^*, I_{\mathrm{HE}}^{\mathrm{F}*}, I_{\mathrm{HA}}^{\mathrm{F}*}, P_{\mathrm{HE}}^{\mathrm{F}*}, P_{\mathrm{HA}}^{\mathrm{F}*}, C_{\mathrm{FE}}^*,$

$C_{\mathrm{FA}}^*, S_{\mathrm{M}}^*, I_{\mathrm{HM}}^*, R_{\mathrm{HM}}^*, E_{\mathrm{MT}}^*, I_{\mathrm{MT}}^*, T_{\mathrm{MT}}^*, I_{\mathrm{HE}}^{\mathrm{M}*}, I_{\mathrm{HA}}^{\mathrm{M}*})$

$= (S_{\mathrm{F}}^*, V_{\mathrm{HF}}^*, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, S_{\mathrm{M}}^*, 0, 0, 0, 0, 0, 0, 0, 0)$

with $S_{\mathrm{F}}^* = \dfrac{(1-f)\Lambda_{\mathrm{F}}}{\mu_{\mathrm{F}}}, \quad V_{\mathrm{HF}}^* = \dfrac{f\Lambda_{\mathrm{F}}}{\mu_{\mathrm{F}}}, \quad S_{\mathrm{M}}^* = \dfrac{\Lambda_{\mathrm{M}}}{\mu_{\mathrm{M}}}$

The linear stability of the disease free equilibrium, ε_0 can be established using the next generation operator method (van den Driessche and Watmough, 2002) on the system (3.29). Using the notation in van den Driessche and Watmough (2002), the matrices F and V, for the new infection terms and the remaining transfer terms, evaluated at the disease free equilibrium (DFE) are, respectively, given by

$$F = \begin{bmatrix} F_1 & F_2 \\ F_3 & F_4 \end{bmatrix}, \qquad V = \begin{bmatrix} V_1 & V_2 \\ V_3 & V_4 \end{bmatrix}$$

where:

$$F_1 = \begin{bmatrix}
\frac{A_2\beta_f(1-c_\mathrm{F}\epsilon_\mathrm{F})}{N^*_\mathrm{HF}} & 0 & 0 & 0 & 0 & \frac{A_2\beta_f(1-c_\mathrm{F}\epsilon_\mathrm{F})\theta_\mathrm{T}\omega_\mathrm{T}}{N^*_\mathrm{HF}} & \frac{A_2\beta_f(1-c_\mathrm{F}\epsilon_\mathrm{F})\theta_\mathrm{T}}{N^*_\mathrm{HF}} & \frac{A_2\beta_f(1-c_\mathrm{F}\epsilon_\mathrm{F})\theta_\mathrm{T}\omega_\mathrm{T}\omega_p}{N^*_\mathrm{HF}} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & \frac{A_3(1-\psi_1^\mathrm{F})\beta_T}{N^*} & 0 & \frac{A_3(1-\psi_1^\mathrm{F})\beta_T\eta_p}{N^*} & 0 \\
0 & 0 & 0 & 0 & \frac{A_3\psi_1^\mathrm{F}\beta_T}{N^*} & 0 & \frac{A_3\psi_1^\mathrm{F}\beta_T\eta_p}{N^*} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}$$

$$F_2 = \begin{bmatrix}
\frac{A_2\beta_f(1-c_\mathrm{F}\epsilon_\mathrm{F})\theta_\mathrm{T}\omega_p}{N^*_\mathrm{HF}} & 0 & 0 & \frac{A_1\beta_\mathrm{M}(1-c_\mathrm{M}\epsilon_\mathrm{M})}{N^*_{HM}} & 0 & 0 & \frac{A_2\beta_m(1-c_\mathrm{M}\epsilon_\mathrm{M})\theta_\mathrm{T}}{N^*_{HM}} & \frac{A_2\beta_m(1-c_\mathrm{M}\epsilon_\mathrm{M})\theta_\mathrm{T}\omega_\mathrm{T}}{N^*_{HM}} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{A_3(1-\psi_1^\mathrm{F})\beta_\mathrm{T}\eta_p\omega_p}{N*} & 0 & \frac{A_3(1-\psi_1^\mathrm{F})\beta_\mathrm{T}}{N^*} & 0 & 0 & \frac{A_3(1-\psi_1^\mathrm{F})\beta_\mathrm{T}}{N^*} & 0 & \frac{A_3(1-\psi_1^\mathrm{F})\beta_\mathrm{T}\eta_p}{N^*} \\
\frac{A_3\psi_1^\mathrm{F}\beta_\mathrm{T}\eta_p\omega_p}{N^*} & 0 & \frac{A_3\psi_1^\mathrm{F}\beta_\mathrm{T}}{N^*} & 0 & 0 & \frac{A_3\psi_1^\mathrm{F}\beta_\mathrm{T}}{N^*} & 0 & \frac{A_3\psi_1^\mathrm{F}\beta_\mathrm{T}\eta_p}{N^*} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}$$

$$F_3 = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{\beta_\mathrm{F}(1-c_\mathrm{F}\epsilon_\mathrm{F})S^*_\mathrm{M}}{N^*_\mathrm{HF}} & 0 & 0 & 0 & 0 & \frac{\beta_\mathrm{F}(1-c_\mathrm{F}\epsilon_\mathrm{F})\theta_\mathrm{T}\omega_\mathrm{T}S^*_\mathrm{M}}{N^*_\mathrm{HF}} & \frac{\beta_\mathrm{F}(1-c_\mathrm{F}\epsilon_\mathrm{F})\theta_\mathrm{T}S^*_\mathrm{M}}{N^*_\mathrm{HF}} & \frac{\beta_\mathrm{F}(1-c_\mathrm{F}\epsilon_\mathrm{F})\theta_\mathrm{T}\omega_\mathrm{T}\omega_pS^*_\mathrm{M}}{N^*_\mathrm{HF}} \\
0 & 0 & 0 & 0 & \frac{(1-\psi_1^\mathrm{M})\beta_\mathrm{T}S^*_\mathrm{M}}{N^*} & 0 & \frac{(1-\psi_1^\mathrm{M})\beta_\mathrm{T}\eta_pS^*_\mathrm{M}}{N^*} & 0 \\
0 & 0 & 0 & 0 & \frac{\psi_1^\mathrm{M}\beta_\mathrm{T}S^*_\mathrm{M}}{N^*} & 0 & \frac{\psi_1^\mathrm{M}\beta_\mathrm{T}\eta_pS^*_\mathrm{M}}{N^*} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0
\end{bmatrix}$$

$$F_4 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\beta_{\mathrm{F}}(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})\theta_{\mathrm{T}}\omega_p S^*_{\mathrm{M}}}{N^*_{\mathrm{HF}}} & 0 & 0 & \frac{\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})\xi_{\mathrm{M}} S^*_{\mathrm{M}}}{N^*_{\mathrm{HF}}} & 0 & 0 & \frac{\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})\xi_{\mathrm{M}}\theta_{\mathrm{T}}\omega_{\mathrm{T}} S^*_{\mathrm{M}}}{N^*_{\mathrm{HF}}} & \frac{\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})\xi_{\mathrm{M}}\theta_{\mathrm{T}} S^*_{\mathrm{M}}}{N^*_{\mathrm{HF}}} \\ \frac{(1-\psi_1^{\mathrm{M}})\beta_{\mathrm{T}}\eta_p\omega_p S^*_{\mathrm{M}}}{N^*} & 0 & \frac{(1-\psi_1^{\mathrm{M}})\beta_{\mathrm{T}} S^*_{\mathrm{M}}}{N^*} & 0 & 0 & \frac{(1-\psi_1^{\mathrm{M}})\beta_{\mathrm{T}} S^*_{\mathrm{M}}}{N^*} & 0 & \frac{(1-\psi_1^{\mathrm{M}})\beta_{\mathrm{T}}\eta_p S^*_{\mathrm{M}}}{N^*} \\ \frac{\psi_1^{\mathrm{M}}\beta_{\mathrm{T}}\eta_p\omega_p S^*_{\mathrm{M}}}{N^*} & 0 & \frac{\psi_1^{\mathrm{M}}\beta_{\mathrm{T}} S^*_{\mathrm{M}}}{N^*} & 0 & 0 & \frac{\psi_1^{\mathrm{M}}\beta_{\mathrm{T}} S^*_{\mathrm{M}}}{N^*} & 0 & \frac{\psi_1^{\mathrm{M}}\beta_{\mathrm{T}}\eta_p S^*_{\mathrm{M}}}{N^*} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V_1 = \begin{bmatrix} Q_1 & 0 & 0 & 0 & 0 & 0 & -r_2^{\mathrm{F}} & 0 \\ -D_1 & Q_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -D_2 & Q_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & Q_4 & 0 & -D_3 & 0 & -D_4 \\ 0 & 0 & 0 & -\gamma_1^{\mathrm{F}} & Q_5 & 0 & -D_5 & 0 \\ 0 & 0 & 0 & 0 & 0 & Q_6 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\gamma_2^{\mathrm{F}} & Q_7 & 0 \\ 0 & 0 & 0 & 0 & 0 & -D_7 & 0 & Q_8 \end{bmatrix}$$

$$V_2 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -r_3^{\mathrm{F}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -r_4^{\mathrm{F}} & 0 & 0 & 0 & 0 & 0 \\ 0 & -\tau_2^{\mathrm{F}} & 0 & 0 & 0 & 0 & 0 & 0 \\ -D_6 & 0 & -\tau_3^{\mathrm{F}} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V_3 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & -D_8 & -\gamma_3^{F} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -D_9 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V_4 = \begin{bmatrix} Q_9 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & Q_{10} & 0 & 0 & 0 & 0 & 0 & 0 \\ -D_{10} & -\gamma_4^{F} & Q_{11} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & Q_{12} & 0 & 0 & 0 & -r_2^{M} \\ 0 & 0 & 0 & 0 & Q_{13} & 0 & -\phi_2^{M} & 0 \\ 0 & 0 & 0 & 0 & -\gamma_1^{M} & Q_{14} & 0 & -\phi_3^{M} \\ 0 & 0 & 0 & 0 & 0 & 0 & Q_{15} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \gamma_2^{M} & Q_{16} \end{bmatrix}$$

Where:

$$A_1 = \frac{(1 - f\pi_{\text{F}})\Lambda_{\text{F}}}{\mu_{\text{F}}}, \quad A_2 = \frac{(1 - f\pi_{\text{F}})\xi_{\text{F}}\Lambda_{\text{F}}}{\mu_{\text{F}}} \quad A_3 = \frac{\Lambda_{\text{F}}}{\mu_{\text{F}}}$$

$$Q_1 = (\phi_1^{\text{F}} + \delta_{\text{HF}} + \mu_{\text{F}}), \quad Q_2 = (\rho_1^{\text{F}} + \mu_{\text{F}}), \quad Q_3 = (\tau_1^{\text{F}} + \delta_{\text{CF}} + \mu_{\text{F}}), \quad Q_4 = (\gamma_1^{\text{F}} + \mu_{\text{F}}),$$

$$Q_5 = (r_1^{\text{F}} + \delta_{\text{FT}} + \mu_{\text{F}}), \quad Q_6 = (\gamma_2^{\text{F}} + \delta_{\text{HF1}} + \phi_2^{\text{F}} + \mu_{\text{F}}), \quad Q_7 = (r_2^{\text{F}} + \delta_{\text{FT1}} + \delta_{\text{HF2}} + \phi_3^{\text{F}} + \mu_{\text{F}})$$

$$Q_8 = (\gamma_3^{\text{F}} + \rho_2^{\text{F}}\mu_{\text{F}}), \quad Q_9 = (r_3^{\text{F}} + \delta_{\text{FT2}} + \rho_3^{\text{F}}\mu_{\text{F}}), \quad Q_{10} = (\gamma_4^{\text{F}} + \delta_{\text{CF}} + \tau_2^{\text{F}} + \mu_{\text{F}})$$

$$Q_{11} = (r_4^{\text{F}} + \delta_{\text{FT3}} + \delta_{\text{CF}} + \tau_3^{\text{F}} + \mu_{\text{F}}), \quad Q_{12} = (\phi_1^{\text{M}} + \delta_{\text{HM}} + \mu_{\text{M}}), \quad Q_{13} = (\gamma_1^{\text{M}} + \mu_{\text{M}})$$

$$Q_{14} = (r_1^{\text{M}} + \delta_{\text{MT}} + \mu_{\text{M}}), \quad Q_{15} = (\gamma_2^{\text{M}} + \phi_2^{\text{M}} + \delta_{\text{HM1}} + \mu_{\text{M}}), \quad Q_{16} = (r_2^{\text{M}} + \delta_{\text{MT1}} + \delta_{\text{HM2}} + \phi_2^{\text{M}} + \mu_{\text{M}})$$

$$D_1 = (1 - \kappa_1^{\text{F}})\phi_1^{\text{F}}, \quad D_2 = (1 - \chi_1^{\text{F}})\rho_1^{\text{F}}, \quad D_3 = \phi_2^{\text{F}}\rho_2^{\text{F}}, \quad D_4 = \chi_2^{\text{F}}\rho_2^{\text{F}}$$

$$D_5 = \phi_3^{\text{F}}\kappa_3^{\text{F}}, \quad D_6 = \chi_3^{\text{F}}\rho_3^{\text{F}}, \quad D_7 = (1 - \kappa_2^{\text{F}})\phi_2^{\text{F}}, \quad D_8 = (1 - \kappa_3^{\text{F}})\phi_3^{\text{F}}, \quad D_9 = (1 - \chi_2^{\text{F}})\phi_2^{\text{F}},$$

$$D_{10} = (1 - \chi_3^{\text{F}})\rho_3^{\text{F}}$$

Hence, the basic reproduction number of the model (3.29), denoted by $\mathcal{R}_0$, is given by $\mathcal{R}_0 = \max\{\mathcal{R}_{0H}, \mathcal{R}_{0T}\}$ where $\mathcal{R}_{0H}$ and $\mathcal{R}_{0T}$ are the associated reproduction numbers for HPV transmission and TB transmission, respectively, given by

$$\begin{aligned}\mathcal{R}_{0H} &= \frac{1}{2}\Big(\mathcal{R}_{\text{MM}} + \mathcal{R}_{\text{FF}}\Big) + \frac{1}{2}\sqrt{\mathcal{R}_{\text{MM}}^2 + \mathcal{R}_{\text{FF}}^2 + 4\mathcal{R}_{\text{FM}}^2 - 2\mathcal{R}_{\text{FM}}\xi_{\text{M}}\xi_{\text{F}}} \\ &= \frac{1}{2}\Big(\mathcal{R}_{\text{MM}} + \mathcal{R}_{\text{FF}}\Big) + \frac{1}{2}\sqrt{\Big(\mathcal{R}_{\text{MM}} - \mathcal{R}_{\text{FF}}\Big)^2 + 4\mathcal{R}_{\text{FM}}^2}\end{aligned}$$

where,

$$\begin{aligned}\mathcal{R}_{\text{MM}} &= \frac{\beta_{\text{M}}(1 - c_{\text{M}}\epsilon_{\text{M}})\xi_{\text{M}}}{Q_{12}}, \\ \mathcal{R}_{\text{FF}} &= \frac{(1 - f\pi_{\text{F}})\beta_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})(Q_2 + \omega_p D_1)\xi_{\text{F}}}{Q_1 Q_2}, \\ \mathcal{R}_{\text{FM}} &= \sqrt{\frac{\beta_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})\beta_{\text{M}}(1 - c_{\text{M}}\epsilon_{\text{M}})(Q_2 + D_1\omega_p)(1 - f\pi_{\text{F}})}{Q_1 Q_2 Q_{12}}}\end{aligned}$$

with,

$$Q_1 = (\phi_1^{\text{F}} + \delta_{\text{HF}} + \mu_{\text{F}}), \quad Q_2 = (\rho_1^{\text{F}} + \mu_{\text{F}}), \quad Q_{12} = (\phi_1^{\text{M}} + \delta_{\text{HM}} + \mu_{\text{M}}), \quad D_1 = (1 - \kappa_1^{\text{F}})\phi_1^{\text{F}}$$

$$\mathcal{R}_{0T} = \frac{\beta_{\text{T}}(\mu_{\text{M}} + \mu_{\text{F}})}{(\Lambda_{\text{F}} + \Lambda_{\text{M}})}\left(\frac{\Lambda_F[\gamma_1^F(1 - \psi_1^F) + Q_4\psi_1^F]}{\mu_F Q_4 Q_5} + \frac{\Lambda_M[\gamma_1^M(1 - \psi_1^M) + Q_{13}\psi_1^M]}{\mu_M Q_{13} Q_{14}}\right)$$

where

$$Q_4 = (\gamma_1^{\text{F}} + \mu_{\text{F}}), \quad Q_5 = (r_1^{\text{F}} + \delta_{\text{FT}} + \mu_{\text{F}}) \quad Q_{13} = (\gamma_1^{\text{M}} + \mu_{\text{M}}) \quad Q_{14} = (r_1^{\text{M}} + \delta_{\text{MT}} + \mu_{\text{M}}),$$

Using Theorem 2 of van den Driessche and Watmough (2002), the following result is established.

Lemma 4.32. The DFE, ξ_0, of the HPV-TB co-infection model (3.29) is locally asymptotically stable (LAS) if $\mathcal{R}_0 < 1$, and unstable if $\mathcal{R}_0 > 1$.

4.5.9 Interpretation of the basic reproduction number $\mathcal{R}_0$

There are two components in the reproduction number $\mathcal{R}_0$, that is the $\mathcal{R}_{0\text{H}}$ and $\mathcal{R}_{0\text{T}}$. They can be interpreted as follows:

1. **Interpretation of $\mathcal{R}_{0\text{H}}$:** This is the threshold quantity associated with the transmission of HPV among sexually active individuals. It also has three sub-components, $\mathcal{R}_{\text{MM}}$, $\mathcal{R}_{\text{FF}}$, and $\mathcal{R}_{\text{FM}}$ which can be interpreted thus. $\mathcal{R}_{\text{MM}}$ is the quantity associated with the male-to-male transmission of HPV. It is the product of the rate at which males acquire HPV infection from males $\beta_{\text{M}}(1 - c_{\text{M}}\epsilon_{\text{M}})\xi_{\text{M}}$ and the average duration in the I_{HM} class $\left(\frac{1}{\phi_1^{\text{M}}+\delta_{\text{HM}}+\mu_{\text{M}}}\right)$. The threshold quantity $\mathcal{R}_{\text{FF}}$ is associated with the female-to-female transmission of HPV. It is the sum of the female infections generated by HPV-infected females and persistent HPV-infected females. The number of female infections generated by HPV-infected females is the product of the rate of infection of susceptible and vaccinated females $\frac{\xi_{\text{F}}\beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})[S_{\text{F}}^{**}+(1-\pi_{\text{F}})V_{\text{HF}}^*]}{N_{\text{HF}}^*}$ and the average duration in the I_{HF} stage $\left(\frac{1}{\phi_1^{\text{F}}+\delta_{\text{HF}}+\mu_{\text{F}}}\right)$. he number of female infections generated by persistent HPV-infected females is the product of the infection rate of susceptible and vaccinated females by persistent HPV-infected females $\frac{\omega_p\xi_{\text{F}}\beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})[S_{\text{F}}^{*}+(1-\pi_{\text{F}})V_{\text{HF}}^*]}{N_{\text{HF}}^*}$, the probability that an infected female survives the HPV infection stage and moves to the persistent HPV infection stage $\left(\frac{(1-\kappa_1^{\text{F}})\phi_1^{\text{F}}}{\phi_1^{\text{F}}+\delta_{\text{HF}}+\mu_{\text{F}}}\right)$ and the average duration in the persistent infection stage $\left(\frac{1}{\rho_1^{\text{F}}+\mu_{\text{F}}}\right)$. The threshold quantity $\mathcal{R}_{\text{FM}}$ is associated with the female-to-male-to-female transmission of HPV. It can be re-written as $\mathcal{R}_{\text{FM}} = \sqrt{\mathcal{R}_{0\text{F}}.\mathcal{R}_{0\text{M}}}$, with

$$\begin{aligned}
\mathcal{R}_{0\text{F}} &= \frac{\beta_{\text{M}}(1 - c_{\text{M}}\epsilon_{\text{M}})[S_{\text{F}}^* + (1 - \pi_{\text{F}})V_{\text{HF}}^*]}{(\phi_1^{\text{M}} + \delta_{\text{HM}} + \mu_{\text{M}})N_{\text{HF}}^*}, \\
\mathcal{R}_{0\text{M}} &= \frac{\beta_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})[(\rho_1^{\text{F}} + \mu_{\text{F}}) + (1 - \kappa_1^{\text{F}})\phi_1^{\text{F}}\omega_p]S_{\text{M}}^*}{(\phi_1^{\text{F}} + \delta_{\text{HF}} + \mu_{\text{F}})(\rho_1^{\text{F}} + \mu_{\text{F}})N_{\text{HM}}^*}.
\end{aligned}$$

$\mathcal{R}_{\text{FM}}$ is the geometric mean of $\mathcal{R}_{0\text{F}}$ and $\mathcal{R}_{0\text{M}}$, where $\mathcal{R}_{0\text{F}}$ is the average number of new cases of female HPV infections generated by an average infected male and $\mathcal{R}_{0\text{M}}$ is the average number of new cases of male HPV infections generated by an average infected female. $\mathcal{R}_{0\text{F}}$ is the product of the infection rate of susceptible and vaccinated females by HPV-infected males $\frac{\beta_{\text{M}}(1-c_{\text{M}}\epsilon_{\text{M}})[S^*_{\text{F}}+(1-\pi_{\text{F}})V^*_{\text{HF}}]}{N^*_{\text{HF}}}$ and the average duration in the infected stage I_{HM} $\left(\frac{1}{\phi^{\text{M}}_1+\delta_{\text{HM}}+\mu_{\text{M}}}\right)$. $\mathcal{R}_{0\text{M}}$ is the sum of the male infections generated by HPV-infected females and persistent HPV-infected females. The number of male infections generated by HPV-infected females is the product of the infection rate of susceptible males by HPV-infected females $\frac{\beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})S^*_{\text{M}}}{N^*_{\text{HM}}}$ and the average duration in the infected stage I_{HF} $\left(\frac{1}{\phi^{\text{F}}_1+\delta_{\text{HF}}+\mu_{\text{F}}}\right)$. The number of male infections generated by persistent HPV-infected females is the product of the infection rate of susceptible males by persistent HPV-infected females $\frac{\beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})\omega_p S^*_{\text{M}}}{N^*_{\text{HM}}}$, the probability that an infected female survives the HPV infection stage and moves to the persistent HPV infection stage $\left(\frac{(1-\kappa^{\text{F}}_1)\phi^{\text{F}}_1}{\phi^{\text{F}}_1+\delta_{\text{HF}}+\mu_{\text{F}}}\right)$ and the average duration in the persistent HPV infection stage $\left(\frac{1}{\rho^{\text{F}}_1+\mu_{\text{F}}}\right)$.

2. **Interpretation of $\mathcal{R}_{0\text{T}}$**: This is the threshold quantity associated with the transmission of TB among individuals. It is the average number of new TB cases generated by TB infected individuals. It can be re-written as $\mathcal{R}_{0\text{T}} = \sqrt{\mathcal{R}_{\text{FT}}.\mathcal{R}_{\text{MT}}}$, with

$$\begin{aligned}
\mathcal{R}_{\text{FT}} &= \frac{\beta_{\text{T}}}{(N^*_{\text{HF}}+N^*_{\text{HM}})}\left(\frac{(S^*_{\text{F}}+V^*_{\text{HF}})[\gamma^{\text{F}}_1(1-\psi^{\text{F}}_1)+(\gamma^{\text{F}}_1+\mu_{\text{F}})\psi^{\text{F}}_1]}{(\gamma^{\text{F}}_1+\mu_{\text{F}})(r^{\text{F}}_1+\delta_{\text{FT}}+\mu_{\text{F}})}\right),\\
\mathcal{R}_{\text{MT}} &= \frac{\beta_{\text{T}}}{(N^*_{\text{HF}}+N^*_{\text{HM}})}\left(\frac{S^*_{\text{M}}[\gamma^{\text{M}}_1(1-\psi^{\text{M}}_1)+(\gamma^{\text{M}}_1+\mu_{\text{M}})\psi^{\text{M}}_1]}{(\gamma^{\text{M}}_1+\mu_{\text{M}})(r^{\text{M}}_1+\delta_{\text{MT}}+\mu_{\text{M}})}\right),
\end{aligned}$$

where,

$\mathcal{R}_{\text{FT}}$ is the average number of new female TB cases and $\mathcal{R}_{\text{MT}}$ is the average number of new male TB cases generated by TB infected individuals. $\mathcal{R}_{\text{FT}}$ is the sum of the number of new latent TB cases and the number of new active TB cases for females. The number of new latent TB cases for females $\frac{\beta_{\text{T}}}{(N^*_{\text{HF}}+N^*_{\text{HM}})}\left(\frac{(S^*_{\text{F}}+V^*_{\text{HF}})[\gamma^{\text{F}}_1(1-\psi^{\text{F}}_1)]}{(\gamma^{\text{F}}_1+\mu_{\text{F}})(r^{\text{F}}_1+\delta_{\text{FT}}+\mu_{\text{F}})}\right)$, is the product of the infection rate for susceptible females by TB infected individuals $\frac{\beta_{\text{T}}(S^*_{\text{F}}+V^*_{\text{HF}})}{N_{\text{HF}}+N_{\text{HM}}}$, the probability that a latent TB infected female survives the latent stage and moves to the active TB stage, $\frac{\gamma^{\text{F}}_1}{\gamma^{\text{F}}_1+\mu_{\text{F}}}$, the fraction of newly infected females with latent TB, $(1-\psi^{\text{F}}_1)$ and the average duration in the active TB stage for females, $\frac{1}{(r^{\text{F}}_1+\delta_{\text{FT}}+\mu_{\text{F}})}$. The number of new female active TB cases, $\frac{\beta_{\text{T}}}{(N^*_{\text{HF}}+N^*_{\text{HM}})}\left(\frac{(S^*_{\text{F}}+V^*_{\text{HF}})\psi^{\text{F}}_1}{(r^{\text{F}}_1+\delta_{\text{FT}}+\mu_{\text{F}})}\right)$, is the product of the infection rate for susceptible females by TB infected individuals, $\frac{\beta_{\text{T}}(S^*_{\text{F}}+V^*_{\text{HF}})}{(N^*_{\text{HF}}+N^*_{\text{HM}})}$, the fraction of newly infected females with active TB, (ψ^{F}_1)

and the average duration in the active TB stage for females, $\frac{1}{(r_1^{F}+\delta_{FT}+\mu_F)}$. The threshold quantity $\mathcal{R}_{MT}$ is interpreted in a similar manner as $\mathcal{R}_{FT}$.

4.5.10 HPV-only sub-model (with heterogeneous transmission route)

The HPV-only sub-model (with heterogeneous transmission route only) is (obtained by setting $E_{FT} = I_{FT} = T_{FT} = I_{HE}^{F} = I_{HA}^{F} = P_{HE}^{F} = P_{HA}^{F} = C_{FE} = C_{FA} = E_{MT} = I_{MT} = T_{MT} = I_{HE}^{M} = I_{HA}^{M} = 0$ and $\xi_F = \xi_M = 0$ in the model (3.29)) given by:

$$\begin{aligned}
\frac{dS_F}{dt} &= (1-f)\Lambda_F - (\lambda_{HM} + \mu_F)\, S_F \\
\frac{dV_{HF}}{dt} &= f\Lambda_F - (1-\pi_F)\lambda_{HM} V_{HF} - \mu_F V_{HF} \\
\frac{dI_{HF}}{dt} &= (1-\pi_F)\lambda_{HM} V_{HF} + \lambda_{HM} S_F - Q_1 I_{HF} + \varphi_F \lambda_{HM} R_{HF} \\
\frac{dP_{HF}}{dt} &= D_1 I_{HF} - Q_2 P_{HF} \\
\frac{dC_F}{dt} &= D_2 P_{HF} - Q_3 C_F \\
\frac{dR_F^{C}}{dt} &= \tau_1^{F} C_F - \mu_F R_F^{C} \\
\frac{dR_{HF}}{dt} &= \kappa_1^{F}\phi_1^{F} I_{HF} + \chi_1^{F}\rho_1^{F} P_{HF} - (\mu_F + \varphi_F\lambda_{HM})\, R_{HF} \\
\frac{dS_M}{dt} &= \Lambda_M - (\lambda_{HF} + \mu_M)\, S_M \\
\frac{dI_{HM}}{dt} &= \lambda_{HF} S_M - Q_{12} I_{HM} + \varphi_M \lambda_{HF} R_{HM} \\
\frac{dR_{HM}}{dt} &= \phi_1^{M} I_{HM} - (\mu_M + \varphi_M\lambda_{HF})\, R_{HM}
\end{aligned} \tag{4.73}$$

where now,

$$\begin{aligned}
\lambda_{HF} =& \frac{\beta_F(1-c_F\epsilon_F)(I_{HF} + \omega_p P_{HF})}{N_{HF}} \\
\lambda_{HM} =& \frac{\beta_M(1-c_M\epsilon_M)I_{HM}}{N_{HM}}
\end{aligned} \tag{4.74}$$

with

$$\begin{aligned}
N_{HF} =& S_F + V_{HF} + I_{HF} + P_{HF} + C_F + R_F^{C} + R_{HF} \\
N_{HM} =& S_M + I_{HM} + R_{HM}
\end{aligned}$$

Consider the regions

$$\mathcal{D}_{0H} = \mathcal{D}_{0H}^{F} \cup \mathcal{D}_{0H}^{M}$$

where

$$\begin{aligned}\mathcal{D}^{\text{F}}_{0\text{H}} =&(S^{**}_{\text{F}}, V^{**}_{\text{HF}}, I^{**}_{\text{HF}}, P^{**}_{\text{HF}}, C^{**}_{\text{F}}, R^{c**}_{\text{F}}, R^{**}_{\text{HF}}) \in \mathfrak{R}^7_+ : N_{\text{HF}} \leq \frac{\Lambda_{\text{F}}}{\mu_{\text{F}}}\\ \mathcal{D}^{\text{M}}_{0\text{H}} =&(S^{**}_{\text{M}}, I^{**}_{\text{HM}}, R^{**}_{\text{HM}}) \in \mathfrak{R}^3_+ : N_{\text{HM}} \leq \frac{\Lambda_{\text{M}}}{\mu_{\text{M}}}\end{aligned}$$

It can be shown as in section 4.5.2, that the region $\mathcal{D}_{0H}$ is positively invariant.

4.5.11 Local asymptotic stability of disease-free equilibrium (DFE) of the HPV-only sub-model(with heterogeneous transmission route)

The HPV-only sub-model (4.73) has a DFE, obtained by setting the right-hand sides of the equations in the model to zero, given by

$$\begin{aligned}\xi_{0\text{H}} =&(S^{*}_{\text{F}}, V^{*}_{\text{HF}}, I^{*}_{\text{HF}}, P^{*}_{\text{HF}}, C^{*}_{\text{F}}, R^{c*}_{\text{F}}, R^{*}_{\text{HF}}, S^{*}_{\text{M}}, I^{*}_{\text{HM}}, R^{*}_{\text{HM}})\\ =&(\frac{(1-f)\Lambda_{\text{F}}}{\mu_{\text{F}}}, \frac{f\Lambda_{\text{F}}}{\mu_{\text{F}}}, 0, 0, 0, 0, 0, \frac{\Lambda_{\text{M}}}{\mu_{\text{M}}}, 0, 0)\end{aligned} \tag{4.75}$$

The linear stability of $\xi_{0\text{H}}$ will be investigated using the next generation operator method on the system (4.73) (van den Driessche and Watmough, 2002). The matrices F (for the new infection terms) and V (for the remaining transition terms) associated with the HPV-only sub-model (4.73) are given, respectively, by (noting that $S^*_{\text{F}} = \frac{(1-f)\Lambda_{\text{F}}}{\mu_{\text{F}}}$, $V^*_{\text{HF}} = \frac{f\Lambda_{\text{F}}}{\mu_{\text{F}}}$, $N^*_{\text{HF}} = \frac{\Lambda_{\text{F}}}{\mu_{\text{F}}}$, $S^*_{\text{M}} = N^*_{\text{HM}} = \frac{\Lambda_{\text{M}}}{\mu_{\text{M}}}$ at the DFE $\xi_{0\text{H}}$)

$$F_{\text{H}} = \begin{bmatrix} 0 & 0 & 0 & \frac{\beta_{\text{M}}(1-c_{\text{M}}\epsilon_{\text{M}})(S^*_{\text{F}}+(1-\pi_{\text{F}})V^*_{\text{HF}}))}{N^*_{\text{HM}}} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\beta^*_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})S^*_{\text{M}}}{N^*_{\text{HF}}} & \frac{\omega_p\beta^*_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})S^*_{\text{M}}}{N^*_{\text{HF}}} & 0 & 0 \end{bmatrix} \tag{4.76}$$

$$V_{\text{H}} = \begin{bmatrix} Q_1 & 0 & 0 & 0 \\ -D_1 & Q_2 & 0 & 0 \\ 0 & -D_2 & Q_3 & 0 \\ 0 & 0 & 0 & Q_{12} \end{bmatrix} \tag{4.77}$$

We have that the associated basic reproduction number of the HPV-only sub-model (4.73), denoted by $\mathcal{R}_{0\text{H}}|_{\xi_\text{F}=\xi_\text{M}=0} = \rho(F_{\text{H}}V_{\text{H}}^{-1})$, is given by

$$\mathcal{R}_{0\text{H}}|_{\xi_\text{F}=\xi_\text{M}=0} = \sqrt{\frac{\beta_\text{F}(1-c_\text{F}\epsilon_\text{F})\beta_\text{M}(1-c_\text{M}\epsilon_\text{M})(Q_2+D_1\omega_p)(1-f\pi_{\text{F}})}{Q_1Q_2Q_{12}}}$$

where ρ represents the spectral radius of $F_{\text{H}}V_{\text{H}}^{-1}$. Using Theorem 2 of van den Driessche and Watmough (2002), the following result is established.

Lemma 4.33. The DFE, $\xi_{0\text{H}}$, of the HPV-only sub-model (with heterogeneous transmission route) (4.73) is locally asymptotically stable (LAS) if $\mathcal{R}_{0\text{H}}|_{\xi_\text{F}=\xi_\text{M}=0} < 1$, and unstable if $\mathcal{R}_{0\text{H}}|_{\xi_\text{F}=\xi_\text{M}=0} > 1$.

4.5.12 Existence of Endemic Equilibrium of the HPV-only sub-model (4.73)

Let an arbitrary equilibrium point of the HPV-only sub-model be denoted by

$$\xi_{eH} = (S_{\text{F}}^{**}, V_{\text{HF}}^{**}, I_{\text{HF}}^{**}, P_{\text{HF}}^{**}, C_{\text{F}}^{**}, R_{\text{F}}^{\text{C}^{**}}, R_{\text{HF}}^{**}, S_{\text{M}}^{**}, I_{\text{HM}}^{**}, R_{\text{HM}}^{**})$$

The steady state solutions of equations of the sub-model

$$\begin{aligned}
S_{\text{F}}^{**} &= \frac{(1-f)\,\Lambda_{\text{F}}}{(\lambda_{\text{HM}}^{**}+\mu_{\text{F}})}, \quad V_{\text{HF}}^{**} = \frac{f\Lambda_{\text{F}}}{[(1-\pi_{\text{F}})\,\lambda_{\text{HM}}^{**}+\mu_{\text{F}}]},\\
I_{\text{HF}}^{**} &= \frac{\big\{(1-\pi_{\text{F}})\Lambda_{(}\lambda_{\text{HM}}^{**})^2+(1-f\pi_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}\lambda_{\text{HM}}^{**}\big\}Q_2(\mu_{\text{F}}+\varphi_{\text{F}}\lambda_{\text{HM}}^{**})}{G_1(\lambda_{\text{HM}}^{**})^3+G_2(\lambda_{\text{HM}}^{**})^2+G_3\lambda_{\text{HM}}^{**}+G_4},\\
P_{\text{HF}}^{**} &= \frac{\big\{(1-\pi_{\text{F}})\Lambda_{\text{F}}(\lambda_{\text{HM}}^{**})^2+(1-f\pi_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}\lambda_{\text{HM}}^{**}\big\}D_1(\mu_{\text{F}}+\varphi_{\text{F}}\lambda_{\text{HM}}^{**})}{G_1(\lambda_{\text{HM}}^{**})^3+G_2(\lambda_{\text{HM}}^{**})^2+G_3\lambda_{\text{HM}}^{**}+G_4},\\
R_{\text{HF}}^{**} &= \frac{\big\{(1-\pi_{\text{F}})\Lambda_{\text{F}}(\lambda_{\text{HM}}^{**})^2+(1-f\pi_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}\lambda_{\text{HM}}^{**}\big\}(D_1+Q_2)}{G_1(\lambda_{\text{HM}}^{**})^3+G_2(\lambda_{\text{HM}}^{**})^2+G_3\lambda_{\text{HM}}^{**}+G_4},\\
C_{\text{F}}^{**} &= \frac{\big\{(1-\pi_{\text{F}})\Lambda_{\text{F}}(\lambda_{\text{HM}}^{**})^2+(1-f\pi_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}\lambda_{\text{HM}}^{**}\big\}D_1D_2(\mu_{\text{F}}+\varphi_{\text{F}}\lambda_{\text{HM}}^{**})}{Q_3\big\{G_1(\lambda_{\text{HM}}^{**})^3+G_2(\lambda_{\text{HM}}^{**})^2+G_3\lambda_{\text{HM}}^{**}+G_4\big\}},\\
R_{\text{F}}^{\text{C}^{**}} &= \frac{\big\{(1-\pi_{\text{F}})\Lambda_{\text{F}}(\lambda_{\text{HM}}^{**})^2+(1-f\pi_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}\lambda_{\text{HM}}^{**}\big\}D_1D_2\pi_f(\mu_{\text{F}}+\varphi_{\text{F}}\lambda_{\text{HM}}^{**})}{\mu_{\text{F}}Q_3\big\{G_1(\lambda_{\text{HM}}^{**})^3+G_2(\lambda_{\text{HM}}^{**})^2+G_3\lambda_{\text{HM}}^{**}+G_4\big\}},\\
S_{\text{M}}^{**} &= \frac{\Lambda_{\text{M}}}{(\mu_{\text{M}}+\lambda_{\text{HF}}^{**})}, \quad I_{\text{HM}}^{**} = \frac{\Lambda_{\text{M}}\lambda_{\text{HF}}^{**}(\mu_{\text{M}}+\varphi_{\text{M}}\lambda_{\text{HF}}^{**})}{H_1(\lambda_{\text{HF}}^{**})^2+H_2\lambda_{\text{HF}}^{**}+H_3}\\
R_{\text{HM}}^{**} &= \frac{\phi_1^{\text{M}}\Lambda_{\text{M}}\lambda_{\text{HF}}^{**}}{H_1(\lambda_{\text{HF}}^{**})^2+H_2\lambda_{\text{HF}}^{**}+H_3}
\end{aligned} \tag{4.78}$$

where,

$$
\begin{aligned}
G_1 &= (1-\pi_{\text{F}})\varphi_{\text{F}}\big\{(1-\kappa_1^{\text{F}})(1-\chi_1^{\text{F}})\phi_1^{\text{F}}\rho_1^{\text{F}} + (1-\kappa_1^{\text{F}})\phi_1^{\text{F}}\mu_{\text{F}} + (\delta_{\text{HF}}+\mu_{\text{F}})(\rho_1^{\text{F}}+\mu_{\text{F}})\big\} > 0\\
G_2 &= (1-\pi_{\text{F}})Q_1\mu_{\text{F}}Q_2 + (2-\pi_{\text{F}})\mu_{\text{F}}\varphi_{\text{F}}\big\{(1-\kappa_1^{\text{F}})(1-\chi_1^{\text{F}})\phi_1^{\text{F}}\rho_1^{\text{F}} + (1-\kappa_1^{\text{F}})\phi_1^{\text{F}}\mu_{\text{F}} + (\delta_{\text{HF}}+\mu_{\text{F}})(\rho_1^{\text{F}}+\mu_{\text{F}})\big\} > 0\\
G_3 &= (2-\pi_{\text{F}})\mu_{\text{F}}^2(\phi_1^{\text{F}}+\delta_{\text{HF}}+\mu_{\text{F}})(\rho_1^{\text{F}}+\mu_{\text{F}}) + \mu_{\text{F}}^2\varphi_{\text{F}}\big\{(1-\kappa_1^{\text{F}})(1-\chi_1^{\text{F}})\phi_1^{\text{F}}\rho_1^{\text{F}} + (1-\kappa_1^{\text{F}})\phi_1^{\text{F}}\mu_{\text{F}}\\
&\quad + (\delta_{\text{HF}}+\mu_{\text{F}})(\rho_1^{\text{F}}+\mu_{\text{F}})\big\} > 0\\
H_1 &= \varphi_{\text{M}}(Q_{12}+\phi_1^{\text{M}}), \quad H_2 = \mu_{\text{M}}(Q_{12}+\varphi_{\text{M}}+\phi_1^{\text{M}}\varphi_{\text{M}}), \quad H_3 = \mu_{\text{M}}^2 Q_{12}
\end{aligned}
$$

Substituting the above expressions into the forces of infection (4.74), at steady state, gives

$$
\begin{aligned}
\lambda_{\text{HF}}^{**} &= \frac{\lambda_{\text{HM}}^{**}\left[\alpha_{02}(\lambda_{\text{HM}}^{**})^2+\alpha_{01}\lambda_{\text{HM}}^{**}+\alpha_0\right]}{\left[\alpha_{33}(\lambda_{\text{HM}}^{**})^3+\alpha_{22}(\lambda_{\text{HM}}^{**})^2+\alpha_{11}\lambda_{\text{HM}}^{**}+\alpha_{00}\right]},\\
\lambda_{\text{HM}}^{**} &= \frac{\lambda_{\text{HF}}^{**}\left(\delta_{02}\lambda_{\text{HF}}^{**}+\delta_{01}\right)}{\delta_{22}(\lambda_{\text{HF}}^{**})^2+\delta_{11}\lambda_{\text{HF}}^{**}+\delta_{00}}
\end{aligned}
\tag{4.79}
$$

where,

$$
\begin{aligned}
\alpha_0 &= \beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}^2(1-f\pi_{\text{F}})(\mu_{\text{F}}Q_2+\omega_p\mu_{\text{F}}G_1),\\
\alpha_{01} &= \beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}(1-\pi_{\text{F}})(\mu_{\text{F}}Q_2+\omega_p\mu_{\text{F}}G_1) + \beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}^2(1-\pi_{\text{F}})(Q_2\varphi_{\text{F}}+\omega_p G_1\varphi_{\text{F}}),\\
\alpha_{02} &= \beta_{\text{F}}(1-c_{\text{F}}\epsilon_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}(1-\pi_{\text{F}})(Q_2\varphi_{\text{F}}+\omega_p G_1\varphi_{\text{F}}),\\
\alpha_{00} &= Q_1Q_2\Lambda_{\text{F}}\mu_{\text{F}}^3,\\
\alpha_{11} &= (2-\pi_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}^2(\phi_1^{\text{F}}+\delta_{\text{HF}}+\mu_{\text{F}})(\rho_1^{\text{F}}+\mu_{\text{F}}) + \Lambda_{\text{F}}\mu_{\text{F}}^2\varphi_{\text{F}}\big\{(1-\kappa_1^{\text{F}})(1-\chi_1^{\text{F}})\phi_1^{\text{F}}\rho_1^{\text{F}} + (1-\kappa_1^{\text{F}})\phi_1^{\text{F}}\mu_{\text{F}}\\
&\quad + (\delta_{\text{HF}}+\mu_{\text{F}})(\rho_1^{\text{F}}+\mu_{\text{F}})\big\} > 0\\
\alpha_{22} &= (1-\pi_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}(\phi_1^{\text{F}}+\delta_{\text{HF}}+\mu_{\text{F}})(\rho_1^{\text{F}}+\mu_{\text{F}}) + (2-\pi_{\text{F}})\Lambda_{\text{F}}\mu_{\text{F}}\varphi_{\text{F}}\big\{(1-\kappa_1^{\text{F}})(1-\chi_1^{\text{F}})\phi_1^{\text{F}}\rho_1^{\text{F}} + (1-\kappa_1^{\text{F}})\phi_1^{\text{F}}\mu_{\text{F}}\\
&\quad + (\delta_{\text{HF}}+\mu_{\text{F}})(\rho_1^{\text{F}}+\mu_{\text{F}})\big\} > 0\\
\alpha_{33} &= (1-\pi_{\text{F}})\Lambda_{\text{F}}\varphi_{\text{F}}\big\{(1-\kappa_1^{\text{F}})(1-\chi_1^{\text{F}})\phi_1^{\text{F}}\rho_1^{\text{F}} + (1-\kappa_1^{\text{F}})\phi_1^{\text{F}}\mu_{\text{F}}(\delta_{\text{HF}}+\mu_{\text{F}})(\rho_1^{\text{F}}+\mu_{\text{F}})\big\} > 0\\
\delta_{00} &= \Lambda_{\text{M}}\mu_{\text{M}}^2Q_{12}, \;\; \delta_{11} = \Lambda_{\text{M}}\mu_{\text{M}}Q_{12} + \Lambda_{\text{M}}\mu_{\text{M}}Q_{12}\varphi_{\text{M}} + \Lambda_{\text{M}}\mu_{\text{M}}\phi_1^{\text{M}}\varphi_{\text{M}}, \;\; \delta_{22} = \varphi_{\text{M}}\Lambda_{\text{M}}(Q_{12}+\phi_1^{\text{M}})\\
\delta_{01} &= \beta_{\text{M}}(1-c_{\text{M}}\epsilon_{\text{M}})\Lambda_{\text{M}}\mu_{\text{M}}^2, \;\; \delta_{02} = \beta_{\text{M}}(1-c_{\text{M}}\epsilon_{\text{M}})\Lambda_{\text{M}}\mu_{\text{M}}\varphi_{\text{M}}
\end{aligned}
\tag{4.80}
$$

Since all the parameters of the sub-model (4.73) are positive and $0 < \pi_{\text{F}} \leq 1$, we have that all the expressions in (4.80) are positive.

$$\Phi_1(\lambda^{**}_{\text{HM}})^6 + \Phi_2(\lambda^{**}_{\text{HM}})^5 + \Phi_3(\lambda^{**}_{\text{HM}})^4 + \Phi_4(\lambda^{**}_{\text{HM}})^3 + \Phi_5(\lambda^{**}_{\text{HM}})^2 + \Phi_6\lambda^{**}_{\text{HM}} + \Phi_7 = 0 \tag{4.81}$$

with

$$\begin{aligned}
\Phi_1 &= \alpha_{02}^2\delta_{22} + \delta_{11}\alpha_{02}\alpha_{33} + \delta_{00}\alpha_{33}^2 > 0\\
\Phi_2 &= 2\alpha_{01}\alpha_{02}\delta_{22} + \delta_{11}\alpha_{02}\alpha_{22} + \delta_{11}\alpha_{01}\alpha_{33} + 2\delta_{00}\alpha_{22}\alpha_{33} - \alpha_{02}^2\delta_{02} - \alpha_{02}\delta_{01}\alpha_{33},\\
\Phi_3 &= 2\alpha_{0}\alpha_{02}\delta_{22} + \alpha_{01}^2\delta_{22} + \delta_{11}\alpha_{02}\alpha_{11} + \delta_{11}\alpha_{01}\alpha_{22} + \delta_{11}\alpha_{0}\alpha_{33} + 2\delta_{00}\alpha_{11}\alpha_{33}\\
&\quad + \delta_{00}\alpha_{22}^2 - 2\alpha_{01}\alpha_{02}\delta_{02} - \alpha_{02}\delta_{01}\alpha_{22} - \alpha_{01}\delta_{01}\alpha_{33},\\
\Phi_4 &= 2\alpha_{0}\alpha_{01}\delta_{22} + \alpha_{00}\alpha_{02}\delta_{11} + \alpha_{01}\alpha_{11}\delta_{11} + \alpha_{0}\alpha_{22}\delta_{11} - 2\alpha_{0}\alpha_{02}\delta_{02} - \alpha_{01}^2\delta_{02}\\
&\quad - \alpha_{02}\alpha_{11}\delta_{01} - \alpha_{01}\alpha_{22}\delta_{01} + \alpha_{00}\alpha_{33}\delta_{00}(2 - \bar{\mathcal{R}}_{0\text{H}}^2)\\
\Phi_5 &= (\alpha_{01}\delta_{11} - \alpha_{02}\delta_{01})b_{00} + (\alpha_{11}\delta_{11} - 2\alpha_{01}\delta_{02})\alpha_{0} + (\alpha_{11}\delta_{00} - \alpha_{01}\delta_{01})\alpha_{11} + \alpha_{00}\delta_{00}\alpha_{22}(2 - \bar{\mathcal{R}}_{0\text{H}}^2)\\
\Phi_6 &= \alpha_{0}\alpha_{00}\delta_{11} - \alpha_{0}^2\delta_{02} - \alpha_{00}\alpha_{01}\delta_{01} + 2\alpha_{00}\alpha_{11}\delta_{00}(1 - \bar{\mathcal{R}}_{0\text{H}}^2)\\
\Phi_7 &= \alpha_{00}^2\delta_{00}(1 - \bar{\mathcal{R}}_{0\text{H}}^2) > 0 \quad \text{if} \quad \bar{\mathcal{R}}_{0\text{H}} < 1
\end{aligned} \tag{4.82}$$

The components of the EEP are obtained upon solving for λ^{**}_{HM} from the polynomial (4.81), and substituting the positive values of λ^{**}_{HM} into the expressions in (4.78) [noting (4.80)]. In addition, it follows from (4.82) that the coefficient Φ_1, is always positive and Φ_7 is positive (negative) if $\bar{\mathcal{R}}_{0\text{H}}$ is less (greater) than unity. The following results can be deduced.

Theorem 4.34. *The HPV-only sub-model* (4.73) *with* $\delta_{\text{HF}} = \delta_{\text{HM}} = \delta_{\text{CF}} = 0$ *has:*

(i) six or four endemic equilibria if $\Phi_2 < 0, \Phi_3 > 0, \Phi_4 < 0, \Phi_5 > 0, \Phi_6 < 0$ *and* $\bar{\mathcal{R}}_{0\text{H}} < 1$*,*

(ii) four or two endemic equilibria if $\Phi_2 > 0, \Phi_3 < 0, \Phi_4 > 0, \Phi_5 < 0, \Phi_6 > 0$ *and* $\bar{\mathcal{R}}_{0\text{H}} < 1$*,*

(iii) two endemic equilibria if $\Phi_2 > 0, \Phi_3 > 0, \Phi_4 < 0, \Phi_5 < 0, \Phi_6 > 0$ *and* $\bar{\mathcal{R}}_{0\text{H}} < 1$

(iv) no endemic equilibrium otherwise, if $\bar{\mathcal{R}}_{0\text{H}} < 1$*,*

The first three items of Theorem 4.34 ((i) - (iii)) suggest the possibility of backward bifurcation in the HPV-only sub-model (4.73) with negligible disease-induced deaths (i.e., $\delta_{\text{HF}} = \delta_{\text{HM}} = \delta_{\text{CF}} = 0$)

when $\bar{\mathcal{R}}_{0\mathrm{H}} < 1$. In the next sub-section, we shall explore the existence of the phenomenon of backward bifurcation in sub-model (4.73).

4.5.13 Backward Bifurcation Analysis of the HPV-only sub-model (with heterogeneous transmission route)

It is instructive to characterize the type of bifurcation the model (4.73) may undergo. We claim the following result:

Theorem 4.35. *The model* (4.73) *exhibits backward bifurcation at* $\mathcal{R}_{0\mathrm{H}}|_{\xi_\mathrm{F}=\xi_\mathrm{M}=0} = 1$ *whenever a bifurcation coefficient, denoted by a (given by* (4.84)*), is positive.*

proof Suppose $\xi_\mathrm{E} = (S_\mathrm{F}^{**}, V_\mathrm{HF}^{**}, I_\mathrm{HF}^{**}, P_\mathrm{HF}^{**}, C_\mathrm{F}^{**}, R_\mathrm{F}^{c**}, R_\mathrm{HF}^{**}, S_\mathrm{M}^{**}, I_\mathrm{HM}^{**}, R_\mathrm{HM}^{**})$ represents any arbitrary endemic equilibrium of the HPV (with heterogeneous transmission route) only sub-model (that is, an endemic equilibrium in which at least one of the infected components is non-zero). The existence (or otherwise) of backward bifurcation will be explored using the Centre Manifold Theory (Castillo-Chavez and Song, 2004). To apply this theory, it is necessary to carry out the following change of variables.

$$S_\mathrm{F} = x_1,\ V_\mathrm{HF} = x_2,\ I_\mathrm{HF} = x_3,\ P_\mathrm{HF} = x_4,\ C_\mathrm{F} = x_5,\ R_\mathrm{F}^\mathrm{c} = x_6,\ R_\mathrm{HF} = x_7,\ S_\mathrm{M} = x_8,\ I_\mathrm{HM} = x_9,\ R_\mathrm{HM} = x_{10}$$

so that

$$N = \sum_{i=1}^{10} x_i$$

Further, using the vector notation

$$X = (x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8, x_9, x_{10})^T$$

the model (4.73) can be re-written in the form

$$\frac{dX}{dt} \equiv f = (f_1, f_2, f_3, f_4, f_5, f_6, f_7, f_8, f_9, f_{10})^T$$

as follows:

$$\begin{aligned}
\frac{dx_1}{dt} &\equiv f_1 = (1-f)\Lambda_{\text{F}} - \left(\lambda_{\text{HM}} + \mu_{\text{F}}\right) x_1\\
\frac{dx_2}{dt} &\equiv f_2 = f\Lambda_{\text{F}} - \left[(1-\pi_{\text{F}})\lambda_{\text{HM}} + \mu_{\text{F}}\right] x_2\\
\frac{dx_3}{dt} &\equiv f_3 = \lambda_{\text{HM}} x_1 + (1-\pi_{\text{F}})\lambda_{\text{HM}} x_2 + \varphi_{\text{F}}\lambda_{\text{HM}} x_7 - Q_1 x_3\\
\frac{dx_4}{dt} &\equiv f_4 = D_1 x_3 - Q_2 x_4\\
\frac{dx_5}{dt} &\equiv f_5 = D_2 x_4 - Q_3 x_5\\
\frac{dx_6}{dt} &\equiv f_6 = \tau_1^{\text{F}} x_5 - \mu_{\text{F}} x_6\\
\frac{dx_7}{dt} &\equiv f_7 = \kappa_1^{\text{F}}\phi_1^{\text{F}} x_3 + \chi_1^{\text{F}}\rho_1^{\text{F}} x_4 - \mu_{\text{F}} x_7 - \varphi_{\text{F}}\lambda_{\text{HM}} x_7\\
\frac{dx_8}{dt} &\equiv f_8 = \Lambda_{\text{M}} - \left(\lambda_{\text{HF}} + \mu_{\text{M}}\right) x_8
\end{aligned} \tag{4.83}$$

$$\begin{aligned}
\frac{dx_9}{dt} &\equiv f_9 = \lambda_{\text{HF}} x_8 + \varphi_{\text{M}}\lambda_{\text{HF}} x_{10} - Q_{12} x_9\\
\frac{dx_{10}}{dt} &\equiv f_{10} = \phi_1^{\text{F}} x_9 - \mu_{\text{M}} x_{10} - \varphi_{\text{M}}\lambda_{\text{HF}} x_{10}
\end{aligned}$$

where

$$\begin{aligned}
\lambda_{\text{HF}} &= \frac{\beta_{\text{F}}^*(1-c_{\text{F}}\epsilon_{\text{F}})(x_3+\omega_p x_4)}{\sum_{i=1}^{7} x_i}\\
\lambda_{\text{HM}} &= \frac{\beta_{\text{M}}(1-c_{\text{M}}\epsilon_{\text{M}})x_9}{\sum_{i=8}^{10} x_i}
\end{aligned}$$

Without loss of generality, consider the case when $\mathcal{R}_{0\text{H}} = 1$. Suppose, further, that β_{F} is chosen as a bifurcation parameter. Solving for $\beta_{\text{F}} = \beta_{\text{F}}^*$ from $\mathcal{R}_{0\text{H}} = 1$ gives

$$\beta_{\text{F}} = \beta_{\text{F}}^* = \frac{Q_1 Q_2 Q_{12}}{\beta_{\text{M}}(1-c_{\text{M}}\epsilon_{\text{M}})(1-c_{\text{F}}\epsilon_{\text{F}})\left(Q_2+\omega_p D_1\right)\left(1-f\pi_{\text{F}}\right)}$$

The Jacobian of the transformed system (4.83), evaluated at the DFE (ξ_0) with $\beta_{\text{F}} = \beta_{\text{F}}^*$, is given by

$$J(\xi_0)|_{\beta_{\mathrm{F}}=\beta_{\mathrm{F}}^*}=\begin{bmatrix} -\mu_{\mathrm{F}} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \frac{-\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})x_1^*}{N_{\mathrm{HM}}^*} & 0 \\ 0 & -\mu_{\mathrm{F}} & 0 & 0 & 0 & 0 & 0 & 0 & \frac{-\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})(1-\pi_{\mathrm{F}})x_2^*}{N_{\mathrm{HM}}^*} & 0 \\ 0 & 0 & -Q_1 & 0 & 0 & 0 & 0 & 0 & \frac{\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})X_1^*}{N_{\mathrm{HM}}^*} & 0 \\ 0 & 0 & D_1 & -Q_2 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & D_3 & -Q_3 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \tau_1^{\mathrm{F}} & -\mu_{\mathrm{F}} & 0 & 0 & 0 & 0 \\ 0 & 0 & \kappa_1^{\mathrm{F}}\phi_1^{\mathrm{F}} & \chi_1^{\mathrm{F}}\rho_1^{\mathrm{F}} & 0 & 0 & -\mu_{\mathrm{F}} & 0 & 0 & 0 \\ 0 & 0 & \frac{-\beta_{\mathrm{F}}^*(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})x_8^*}{N_{\mathrm{HF}}^*} & \frac{-\beta_{\mathrm{F}}^*(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})\omega_p x_8^*}{N_{\mathrm{HF}}^*} & 0 & 0 & 0 & -\mu_{\mathrm{M}} & 0 & 0 \\ 0 & 0 & \frac{\beta_{\mathrm{F}}^*(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})x_8^*}{N_{\mathrm{HF}}^*} & \frac{\beta_{\mathrm{F}}^*(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})\omega_p x_8^*}{N_{\mathrm{HF}}^*} & 0 & 0 & 0 & 0 & -Q_{12} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \phi_1^{\mathrm{M}} & -\mu_{\mathrm{M}} \end{bmatrix}$$

where, $N_{\mathrm{HF}}^* = x_1^* + x_2^*$, $N_{\mathrm{HM}}^* = x_8^*$, $X_1^* = x_1^* + (1-\pi_{\mathrm{F}})x_2^*$.

It can be shown that the Jacobian of (4.83) has a right eigenvector (associated with the non-zero eigenvalue) given by

$$w = [\omega_1, \omega_2, \omega_3, \omega_4, \omega_5, \omega_6, \omega_7, \omega_8, \omega_9, \omega_{10}]^T$$

where,

$$\begin{aligned}
\omega_1 &= -\frac{\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})x_1^*\omega_9}{\mu_{\mathrm{F}}N_{\mathrm{HM}}^*}, \quad \omega_2 = -\frac{\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})(1-\pi_{\mathrm{F}})x_2^*\omega_9}{\mu_{\mathrm{F}}N_{\mathrm{HM}}^*}, \quad \omega_3 = \frac{\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})X_1^*\omega_9}{Q_1N_{\mathrm{HM}}^*}, \\
\omega_4 &= \frac{\omega_p D_1\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})X_1^*\omega_9}{Q_1Q_2N_{\mathrm{HM}}^*}, \quad \omega_5 = \frac{\omega_p D_1 D_2\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})X_1^*\omega_9}{Q_1Q_2Q_3N_{\mathrm{HM}}^*}, \\
\omega_6 &= \frac{\pi_{\mathrm{F}}\omega_p D_1 D_2\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})X_1^*\omega_9}{\mu_f Q_1Q_2Q_3N_{\mathrm{HM}}^*},, \quad \omega_7 = \frac{\beta_{\mathrm{M}}(1-c_{\mathrm{M}}\epsilon_{\mathrm{M}})X_1^*(\kappa_1^{\mathrm{F}}\phi_1^{\mathrm{F}}Q_2 + \chi_1^{\mathrm{F}}\rho_1^{\mathrm{F}}D_1)\omega_9}{\mu_{\mathrm{F}}Q_1Q_2N_{\mathrm{HM}}^*}, \\
\omega_8 &= -\frac{Q_{12}X_1^*\omega_9}{\mu_{\mathrm{M}}(1-f\pi_{\mathrm{F}})}, \quad \omega_9 = \omega_9 > 0, \quad \omega_{10} = \frac{\phi_1^{\mathrm{M}}\omega_9}{\mu_{\mathrm{M}}}
\end{aligned}$$

Furthermore, (4.83) has a corresponding left eigenvector (associated with the zero eigenvalue) given by

$$v = [\nu_1, \nu_2, \nu_3, \nu_4, \nu_5, \nu_6, \nu_7, \nu_8, \nu_9, \nu_{10}]$$

where,

$$\nu_3 = \frac{\beta_{\mathrm{F}}^*(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})x_8^*(Q_2+\omega_p D_1)\nu_9}{Q_1Q_2N_{\mathrm{HF}}^*}, \quad \nu_4 = \frac{\beta_{\mathrm{F}}^*(1-c_{\mathrm{F}}\epsilon_{\mathrm{F}})\omega_p x_8^*\nu_9}{Q_2N_{\mathrm{HF}}^*}, \quad \nu_9 = \nu_9 > 0$$

We have, based on Theorem 4.1 in Castillo-Chavez and Song (2004), by computing the non-zero partial derivatives of $F(x)$(evaluated at the disease free equilibrium, DFE (ξ_0)) that the associated

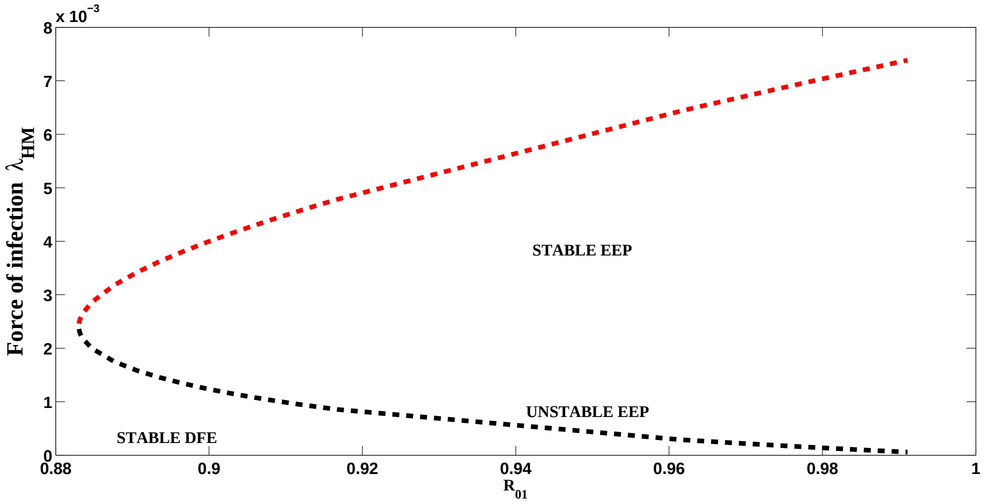


Figure 4.7: Bifurcation diagram for the sub-model (4.73). Parameter values used are: $\beta_{\rm F} = 0.7422, \beta_{\rm M} = 0.88, \varphi_{\rm F} = \varphi_{\rm M} = 12, \pi_{\rm F} = 0.000000009$. All other parameters as in Table 4.7

bifurcation coefficients defined by a and b, are given by

$$a = \sum_{k,i,j=1}^{n} \nu_k \omega_i \omega_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(0,0) \quad \text{and} \quad b = \sum_{k,i=1}^{n} \nu_k \omega_i \frac{\partial^2 f_k}{\partial x_i \partial \beta^*_{\rm F}}(0,0),$$

are computed to be

$$\begin{aligned} a = & -\frac{2\beta_{\rm M}(1-c_{\rm M}\epsilon_{\rm M})\omega_9\nu_3}{N^{*2}_{\rm HM}}\left\{\omega_8 X_1^* - \varphi_{\rm F}\omega_7 N^*_{\rm HM} + (\omega_9+\omega_{10})X_1^* - \{\omega_1 + (1-\pi_{\rm F})\omega_2\}N^*_{\rm HM}\right\} \\ & - \frac{2\beta^*_{\rm F}(1-c_{\rm F}\epsilon_{\rm F})(\omega_3+\omega_p\omega_4)\nu_9}{N^{*2}_{\rm HF}}\left\{\{\omega_1+\omega_2\}x_8^* - \varphi_{\rm M}\omega_{10}N^*_{\rm HF} + (\omega_3+\omega_4+\omega_5+\omega_6+\omega_7)x_8^* - \omega_8 N^*_{\rm HF}\right\} \\ = & -\frac{2Q_{12}\omega_9\nu_9}{N^*_{\rm HM}X_1^*}\left\{\omega_8 X_1^* - \varphi\omega_7 N^*_{\rm HM} + (\omega_9+\omega_{10})X_1^* - \{\omega_1+(1-\pi_{\rm F})\omega_2\}N^*_{\rm HM}\right\} \\ = & -\frac{2Q_{12}x_1^*\omega_9\nu_9}{N^*_{\rm HF}N^*_{\rm HM}X_1^*}\left\{\{\omega_1+\omega_2\}x_8^* - \varphi_{\rm M}\omega_{10}N^*_{\rm HF} + (\omega_3+\omega_4+\omega_5+\omega_6+\omega_7)x_8^* - \omega_8 N^*_{\rm HF}\right\} \end{aligned} \tag{4.84}$$

$$b = \frac{x_8^*}{N^*_{\rm HF}}\nu_9\left(\omega_3 + \omega_p\omega_4\right) > 0$$

Since the bifurcation coefficient b is positive, we have, based on Theorem 4.1 in Castillo-Chavez and Song (2004), that the model (4.73), or the transformed model (4.83), will undergo a backward bifurcation if the backward bifurcation coefficient, a, given by (4.84) is positive. The associated backward bifurcation diagram is depicted in Figure 4.7). The epidemiological significance of Theorem 4.35 is that the condition $\mathcal{R}_{0\rm H} < 1$ for the elimination of HPV, though necessary, is no longer sufficient. Therefore, the reproduction number must be further reduced to a much smaller value than one for the disease-free equilibrium to be locally-asymptotically stable.

4.5.14 Non-existence of backward bifurcation of the HPV only sub-model (with heterogeneous transmission route)

Theorem 4.36. *In the absence of re-infection of recovered individuals with HPV as well as imperfect vaccine* ($\varphi_{\text{F}} = \varphi_{\text{M}} = 0, \pi_{\text{F}} = 1$)*, the HPV only sub-model (with heterogeneous transmission route only)* (4.73) *does not undergo backward bifurcation.*

Proof. Consider the HPV only sub-model (with heterogeneous transmission route only) (4.73). Setting $\varphi_{\text{F}} = \varphi_{\text{M}} = 0, \pi_{\text{F}} = 1$, the expression for the backward bifurcation coefficient, a, given as (4.84) (and noting that all parameters of the model (4.73) are positive), reduces to:

$$a = -2Q_{12}\omega_9\nu_9\left\{\frac{1}{N_M^*}(\omega_9+\omega_{10}) + \frac{1}{N_F^*}(\omega_3+\omega_4+\omega_5+\omega_6+\omega_7) + \omega_1\left(\frac{1}{N_F^*} - \frac{1}{x_1^*}\right)\right\} < 0,$$

since $N_F^* > x_1^*$, then $\left(\frac{1}{N_F^*} - \frac{1}{x_1^*}\right) < 0$, and noting, that $(\omega_9+\omega_{10}) > 0$ and $(\omega_3+\omega_4+\omega_5+\omega_6+\omega_7) > 0$ while $\omega_1 < 0$. Hence, based on Theorem 4.1 in Castillo-Chavez and Song (2004), we have that the model (4.62) does not undergo a backward bifurcation if $\varphi_{\text{F}} = \varphi_{\text{M}} = 0$ and $\pi_{\text{F}} = 1$. $\square$

Hence, this study shows that the reinfection of recovered individuals and imperfect vaccine induce backward bifurcation in the HPV-only sub-model. A global asymptotic stability result is established below for the DFE of the model for this scenario (to completely rule out backward bifurcation in this case).

4.6 Global Asymptotic Stability of the disease-free equilibrium (DFE) of the HPV-only sub-model (with heterogeneous transmission route): Special Case $\varphi_{\text{F}} = \varphi_{\text{M}} = 0, \pi_{\text{F}} = 1$

Theorem 4.37. *Consider the model* (4.73) *with* $\varphi_{\text{F}} = \varphi_{\text{M}} = 0, \pi_{\text{F}} = 1$. *The DFE is GAS in* $\mathcal{D}_H$ *whenever* $\bar{\mathcal{R}}_{0\text{H}} = \mathcal{R}_{0\text{H}}|_{\xi_{\text{F}}=\xi_{\text{M}}=0} \leq 1$

Proof. Consider the Lyapunov function

$$\mathcal{L} = \frac{(Q_2 + \omega_p D_1)\beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*}{N_{\text{HF}}^*} I_{\text{HF}} + \frac{Q_1 \omega_p \beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*}{N_{\text{HF}}^*} P_{\text{HF}} + Q_1 Q_2 \bar{\mathcal{R}}_{0\text{H}} I_{\text{HM}}$$

with Lyapunov derivative

$$\dot{\mathcal{L}} = \frac{(Q_2 + \omega_p D_1)\beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*}{N_{\text{HF}}^*} \dot{I}_{\text{HF}} + \frac{Q_1 \omega_p \beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*}{N_{\text{HF}}^*} \dot{P}_{\text{HF}} + Q_1 Q_2 \bar{\mathcal{R}}_{0\text{H}} \dot{I}_{\text{HM}}$$

Substituting the expressions for $\dot{I}_{\text{HF}}$, $\dot{P}_{\text{HF}}$ and $\dot{I}_{\text{HM}}$ from (3.29), we have that

$$\begin{aligned}
\dot{\mathcal{L}} &= \frac{(Q_2 + \omega_p D_1)\beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*}{N_{\text{HF}}^*}[\lambda_{\text{HM}} S_{\text{F}} - Q_1 I_{\text{HF}}] + \frac{Q_1 \omega_p \beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*}{N_{\text{HF}}^*}[D_1 I_{\text{HF}} - Q_2 P_{\text{HF}}] \\
&\quad + Q_1 Q_2 \bar{\mathcal{R}}_{0\text{H}}[\lambda_{\text{HF}} S_{\text{M}} - Q_{12} I_{\text{HM}}] \\
&= \frac{(Q_2 + \omega_p D_1)\beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^* \lambda_{\text{HM}} S_{\text{F}}}{N_{\text{HF}}^*} + Q_1 Q_2 \bar{\mathcal{R}}_{0\text{H}} \lambda_{\text{HF}} S_{\text{M}} \\
&\quad - I_{\text{HF}}\left[\frac{Q_1(Q_2 + \omega_p D_1)\beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*}{N_{\text{HF}}^*} - \frac{Q_1 \omega_p D_1 \beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*}{N_{\text{HF}}^*}\right] - P_{\text{HF}}\left[\frac{Q_1 Q_2 \omega_p \beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*}{N_{\text{HF}}^*}\right] \\
&\quad - Q_1 Q_2 Q_{12} \bar{\mathcal{R}}_{0\text{H}} I_{\text{HM}}
\end{aligned}$$

which can be further simplified into

$$\begin{aligned}
\dot{\mathcal{L}} &= \frac{(Q_2 + \omega_p D_1)\beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^* \lambda_{\text{HM}} S_{\text{F}}}{N_{\text{HF}}^*} + Q_1 Q_2 \bar{\mathcal{R}}_{0\text{H}} \lambda_{\text{HF}} S_{\text{M}} - \frac{Q_1 Q_2 \beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^*(I_{\text{HF}} + \omega_p P_{\text{HF}})}{N_{\text{HF}}^*} \\
&\quad - Q_1 Q_2 Q_{12} \bar{\mathcal{R}}_{0\text{H}} I_{\text{HM}}
\end{aligned}$$

Applying the group constraint in (3.22), we have that

$$\begin{aligned}
\dot{\mathcal{L}} &= \frac{(Q_2 + \omega_p D_1)\beta_1^{\text{F}} \varrho_{\text{F}}(1 - c_{\text{F}}\epsilon_{\text{F}})S_{\text{F}}^* \lambda_{\text{HM}} S_{\text{F}}}{N_{\text{HF}}^*} - \frac{Q_1 Q_2 Q_{12} \bar{\mathcal{R}}_{0\text{H}} \lambda_{\text{HM}} N_{\text{HF}}}{\varrho_{\text{M}} \beta_1^{\text{M}}(1 - c_{\text{M}}\epsilon_{\text{M}})} + Q_1 Q_2 \bar{\mathcal{R}}_{0\text{H}} \lambda_{\text{HF}} S_{\text{M}} - \frac{Q_1 Q_2 S_{\text{F}}^* \lambda_{\text{HF}} N_{\text{HM}}}{N_{\text{HF}}^*} \\
\dot{\mathcal{L}} &\leq \frac{Q_1 Q_2 Q_{12} \bar{\mathcal{R}}_{0\text{H}} \lambda_{\text{HM}} N_{\text{HF}}}{\varrho_{\text{M}} \beta_1^{\text{M}}(1 - c_{\text{M}}\epsilon_{\text{M}})}\left(\frac{\bar{\mathcal{R}}_{0\text{H}} S_{\text{F}}}{N_{\text{HF}}} - 1\right) + Q_1 Q_2 \lambda_{\text{HF}} N_{\text{HM}}\left(\frac{\bar{\mathcal{R}}_{0\text{H}} S_{\text{M}}}{N_{\text{HM}}} - 1\right) \qquad \left(\text{since} \quad \frac{S_{\text{F}}^*}{N_{\text{HF}}^*} < 1\right) \\
&\leq \frac{Q_1 Q_2 Q_{12} \bar{\mathcal{R}}_{0\text{H}} \lambda_{\text{HM}} N_{\text{HF}}}{\varrho_{\text{M}} \beta_1^{\text{M}}(1 - c_{\text{M}}\epsilon_{\text{M}})}\left(\bar{\mathcal{R}}_{0\text{H}} - 1\right) + Q_1 Q_2 \lambda_{\text{HF}} N_{\text{HM}}\left(\bar{\mathcal{R}}_{0\text{H}} - 1\right) \qquad \left(\text{since} \quad \frac{S_{\text{F}}}{N_{\text{HF}}} < 1, \text{and} \frac{S_{\text{M}}}{N_{\text{HM}}} < 1\right)
\end{aligned}$$

Since all the model parameters and variables are non-negative, we have that $\dot{\mathcal{L}} \leq 0$ for $\bar{\mathcal{R}}_{0\text{H}} \leq 1$ with $\dot{\mathcal{L}} = 0$ if and only if $I_{\text{HF}} = P_{\text{HF}} = I_{\text{HM}} = 0$. Hence, $\mathcal{L}$ is a Lyapunov function on $\mathcal{D}_H$. Thus, using the La Salle's Invariance Principle (La Salle and Lefschetz, 1976), $I_{\text{HF}} \to 0, P_{\text{HF}} \to 0$ and $I_{\text{HM}} \to 0$ as $t \to \infty$. Substituting $I_{\text{HF}} = P_{\text{HF}} = I_{\text{HM}} = 0$ in (3.29) shows that $C_{\text{F}} \to 0, R_{\text{F}}^{\text{C}} \to 0, R_{\text{HF}} \to 0, S_{\text{F}} \to$

$S^*_{\text{F}}, V_{\text{HF}} \to V^*_{\text{HF}}, R_{\text{HM}} \to 0, S_{\text{M}} \to S^*_{\text{M}}$ as $t \to \infty$. Thus, every solution to the equations of the sub-model (4.73) with $\varphi_{\text{F}} = \varphi_{\text{M}} = 0, \pi_{\text{F}} = 1$, with initial conditions in $\mathcal{D}_{\text{H}}$, approaches the DFE as $t \to 0$ whenever $\mathcal{R}_{0H} \leq 1$. $\square$

GAS of EEP of the HPV-only sub-model (with heterosexual transmission route only): special case($\varphi_{\mathbf{F}} = \varphi_{\mathbf{M}} = \delta_{\mathbf{HF}} = \delta_{\mathbf{CF}} = \delta_{\mathbf{HM}} = 0, \pi_{\mathbf{F}} = 1$)

The HPV-only sub-model (with heterogeneous transmission route only) endemic equilibrium (denoted by ξ_{eH}) is given by

$$\xi_{eH} = (S^{**}_{\text{F}}, V^{**}_{\text{HF}}, I^{**}_{\text{HF}}, P^{**}_{\text{HF}}, C^{**}_{\text{F}}, R^{\text{C}**}_{\text{F}}, R^{**}_{\text{HF}}, 0,0,0,0, S^{**}_{\text{M}}, I^{**}_{\text{HM}}, R^{**}_{\text{HM}}, 0,0,0,0,0,0,0,0)$$

(It should be noted here that N^{**}_{HF} and N^{**}_{HM} are replaced with their limiting values $\frac{\Lambda_{\text{F}}}{\mu_{\text{F}}}$ and $\frac{\Lambda_{\text{M}}}{\mu_{\text{M}}}$ respectively, as all disease induced death rates are assumed zero). It should be noted that setting $\delta_{\text{HF}} = \delta_{\text{CF}} = \delta_{\text{HM}} = 0$ in (4.73) gives $N_{\text{HF}} \to \frac{\Lambda_{\text{F}}}{\mu_{\text{F}}}$ and $N_{\text{HM}} \to \frac{\Lambda_{\text{M}}}{\mu_{\text{M}}}$ as $t \to \infty$. Let $\bar{\beta}_{\text{F}} = \frac{\mu_{\text{F}}\beta_{\text{F}}}{\Lambda_{\text{F}}}$ and $\bar{\beta}_{\text{M}} = \frac{\mu_{\text{M}}\beta_{\text{M}}}{\Lambda_{\text{M}}}$ so that

$$\lambda_{\text{HF}} = \bar{\beta}_{\text{F}}(I_{\text{HF}} + \omega_p P_{\text{HF}}) \quad \text{and} \quad \lambda_{\text{HM}} = \bar{\beta}_{\text{M}} I_{\text{HM}} \tag{4.85}$$

Theorem 4.38. *Consider the sub-model* (4.73) *with* $\varphi_{\text{F}} = \varphi_{\text{M}} = 0, \pi_{\text{F}} = 1$. *The model is GAS in* $\mathcal{D}_H \backslash \mathcal{D}_{0H}$ *whenever* $\bar{\mathcal{R}}_{0\text{H}} = \mathcal{R}_{0\text{H}}|_{\xi_{\text{F}}=\xi_{\text{M}}=0} > 1$, *where*

$$\mathcal{D}_{0H} = \left\{ (S_{\text{F}}, V_{\text{HF}}, I_{\text{HF}}, P_{\text{HF}}, C_{\text{F}}, R^{\text{C}}_{\text{F}}, R_{\text{HF}}, S_{\text{M}}, I_{\text{HM}}, R_{\text{HM}}) \in \mathcal{D}_H : I_{\text{HF}} = P_{\text{HF}} = C_{\text{F}} = R^{\text{C}}_{\text{F}} = R_{\text{HF}} = I_{\text{HM}} = 0 \right\}$$

Proof. Consider the model (4.62) with (4.85) and $\varphi_{\text{F}} = \varphi_{\text{M}} = 0$, $\pi_{\text{F}} = 1$ and $\bar{\mathcal{R}}_{0\text{H}} > 1$, so that the associated unique endemic equilibrium exists. Also, consider the non-linear Lyapunov function of the Goh-Volterra type:

$$\begin{aligned}\mathcal{L} = (Q_2 + \omega_p D_1)\bar{\beta}_{\text{F}} S^{**}_{\text{M}} & \left[S_{\text{F}} - S^{**}_{\text{F}} - S^{**}_{\text{F}} \ln\left(\frac{S_{\text{F}}}{S^{**}_{\text{F}}}\right) + V_{\text{HF}} - V^{**}_{\text{HF}} - V^{**}_{\text{HF}} \ln\left(\frac{V_{\text{HF}}}{V^{**}_{\text{HF}}}\right) \right. \\ & \left. + I_{\text{HF}} - I^{**}_{\text{HF}} - I^{**}_{\text{HF}} \ln\left(\frac{I_{\text{HF}}}{I^{**}_{\text{HF}}}\right) \right] + Q_1 \omega_p \bar{\beta}_{\text{F}} S^{**}_{\text{M}} \left[P_{\text{HF}} - P^{**}_{\text{HF}} - P^{**}_{\text{HF}} \ln\left(\frac{P_{\text{HF}}}{P^{**}_{\text{HF}}}\right) \right] \\ & Q_1 Q_2 \left[S_{\text{M}} - S^{**}_{\text{M}} - S^{**}_{\text{M}} \ln\left(\frac{S_{\text{M}}}{S^{**}_{\text{M}}}\right) + I_{\text{HM}} - I^{**}_{\text{HM}} - I^{**}_{\text{HM}} \ln\left(\frac{I_{\text{HM}}}{I^{**}_{\text{HM}}}\right) \right]\end{aligned}$$

with Lyapunov derivative,

$$\begin{aligned}\dot{\mathcal{L}} &= (Q_2+\omega_p D_1)\bar{\beta}_{\text{F}} S_{\text{M}}^{**}\left[\left(1-\frac{S_{\text{F}}^{**}}{S_{\text{F}}}\right)\dot{S}_{\text{F}}+\left(1-\frac{V_{\text{HF}}^{**}}{V_{\text{HF}}}\right)\dot{V}_{\text{F}}+\left(1-\frac{I_{\text{HF}}^{**}}{I_{\text{HF}}}\right)\dot{I}_{\text{HF}}\right]\\ &\quad + Q_1\omega_p\bar{\beta}_{\text{F}} S_{\text{M}}^{**}\left[\left(1-\frac{P_{\text{HF}}^{**}}{P_{\text{HF}}}\right)\dot{P}_{\text{HF}}\right]+Q_1Q_2\left[\left(1-\frac{S_{\text{M}}^{**}}{S_{\text{M}}}\right)\dot{S}_{\text{M}}+\left(1-\frac{I_{\text{HM}}^{**}}{I_{\text{HM}}}\right)\dot{I}_{\text{HM}}\right]\end{aligned} \tag{4.86}$$

Substituting the derivatives in (4.62) into $\dot{\mathcal{L}}$, we have

$$\begin{aligned}\dot{\mathcal{L}} &= (Q_2+\omega_p D_1)\bar{\beta}_{\text{F}} S_{\text{M}}^{**}\Bigg[\left(1-\frac{S_{\text{F}}^{**}}{S_{\text{F}}}\right)((1-f)\Lambda_f-(\bar{\beta}_{\text{M}} I_{\text{HM}}+\mu_{\text{F}})S_{\text{F}})+\left(1-\frac{V_{\text{HF}}^{**}}{V_{\text{HF}}}\right)(f\Lambda_{\text{F}}-\mu_{\text{F}}V_{\text{HF}})\\ &\quad+\left(1-\frac{I_{\text{HF}}^{**}}{I_{\text{HF}}}\right)(\bar{\beta}_{\text{M}} I_{\text{HM}} S_{\text{F}}-Q_1 I_{\text{HF}})\Bigg]+Q_1\omega_p\bar{\beta}_{\text{F}} S_{\text{M}}^{**}\left[\left(1-\frac{P_{\text{HF}}^{**}}{P_{\text{HF}}}\right)(D_1 I_{\text{HF}}-Q_2 P_{\text{HF}})\right]\\ &\quad+Q_1Q_2\Bigg[\left(1-\frac{S_{\text{M}}^{**}}{S_{\text{M}}}\right)\left(\Lambda_m-\left(\bar{\beta}_{\text{F}}(I_{\text{HF}}+\omega_p P_{\text{HF}})+\mu_m\right)S_{\text{M}}\right)\\ &\quad+\left(1-\frac{I_{\text{HM}}^{**}}{I_{\text{HM}}}\right)(\bar{\beta}_{\text{F}}(I_{\text{HF}}+\omega_p P_{\text{HF}})S_{\text{M}}-Q_{12} I_{\text{HM}})\Bigg]\end{aligned} \tag{4.87}$$

Observe from model (4.62) that, at steady state,

$$\begin{aligned}(1-f)\Lambda_{\text{F}} &= \left(\bar{\beta}_{\text{M}} I_{\text{HM}}^{**}+\mu_{\text{F}}\right)S_{\text{F}}^{**},\quad f\Lambda_{\text{F}}=\mu_{\text{F}} V_{\text{HF}}^{**},\quad \bar{\beta}_{\text{M}} I_{\text{HM}} S_{\text{F}}^{**}=Q_1 I_{\text{HF}}^{**},\\ D_1 I_{\text{HF}}^{**} &= Q_2 P_{\text{HF}}^{**},\quad \Lambda_{\text{M}}=\left(\bar{\beta}_{\text{F}}(I_{\text{HF}}^{**}+\omega_p P_{\text{HF}}^{**})+\mu_{\text{M}}\right)S_{\text{M}}^{**},\quad \bar{\beta}_{\text{F}}(I_{\text{HF}}^{**}+\omega_p P_{\text{HF}}^{**})S_{\text{M}}^{**}=Q_{12} I_{\text{HM}}^{**}\end{aligned} \tag{4.88}$$

Substituting the expressions in (4.88) into (4.87) gives

$$\begin{aligned}\dot{\mathcal{L}} &= (Q_2+\omega_p D_1)\bar{\beta}_{\text{F}} S_{\text{M}}^{**}\Bigg[\left(1-\frac{S_{\text{F}}^{**}}{S_{\text{F}}}\right)(\bar{\beta}_{\text{M}} I_{\text{HM}}^{**} S_{\text{F}}^{**}+\mu_f S_{\text{F}}^{**}-\bar{\beta}_{\text{M}} I_{\text{HM}} S_{\text{F}}-\mu_{\text{F}} S_{\text{F}})\\ &\quad+\left(1-\frac{V_{\text{HF}}^{**}}{V_{\text{HF}}}\right)(\mu_{\text{F}} V_{\text{HF}}^{**}-\mu_{\text{F}} V_{\text{HF}})+\left(1-\frac{I_{\text{HF}}^{**}}{I_{\text{HF}}}\right)(\bar{\beta}_{\text{M}} I_{\text{HM}} S_f-Q_1 I_{\text{HF}})\Bigg]\\ &\quad+Q_1\omega_p\bar{\beta}_{\text{F}} S_{\text{M}}^{**}\left[\left(1-\frac{P_{\text{HF}}^{**}}{P_{\text{HF}}}\right)(D_1 I_{\text{HF}}-Q_2 P_{\text{HF}})\right]\\ &\quad+Q_1Q_2\Bigg[\left(1-\frac{S_{\text{M}}^{**}}{S_{\text{M}}}\right)(\bar{\beta}_{\text{F}} I_{\text{HF}}^{**} S_m^{**}+\bar{\beta}_{\text{F}}\omega_p P_{\text{HF}}^{**} S_{\text{M}}^{**}+\mu_{\text{M}} S_{\text{M}}^{**}-\bar{\beta}_{\text{F}} I_{\text{HF}} S_{\text{M}}-\bar{\beta}_{\text{F}}\omega_p P_{\text{HF}} S_{\text{M}}-\mu_{\text{M}} S_{\text{M}})\\ &\quad+\left(1-\frac{I_{\text{HM}}^{**}}{I_{\text{HM}}}\right)(\bar{\beta}_{\text{F}} I_{\text{HF}} S_{\text{M}}+\bar{\beta}_{\text{F}}\omega_p P_{\text{HF}} S_{\text{M}}-Q_{12} I_{\text{HM}})\Bigg]\end{aligned}$$

which can be simplified to

$$
\begin{aligned}
\dot{\mathcal{L}} &= (Q_2+\omega_p D_2)\bar{\beta}_{\text{F}}\mu_{\text{F}} S_{\text{M}}^{**} S_{\text{F}}^{**}\left(2-\frac{S_{\text{F}}^{**}}{S_{\text{F}}}-\frac{S_{\text{F}}}{S_{\text{F}}^{**}}\right)+(Q_2+\omega_p D_2)\bar{\beta}_{\text{F}}\mu_{\text{F}} S_{\text{M}}^{**} V_{\text{HF}}^{**}\left(2-\frac{V_{\text{HF}}^{**}}{V_{\text{HF}}}-\frac{V_{\text{HF}}}{V_{\text{HF}}^{**}}\right)\\
&\quad + Q_1 Q_2 \mu_{\text{M}} S_{\text{M}}^{**}\left(2-\frac{S_{\text{M}}^{**}}{S_{\text{M}}}-\frac{S_{\text{M}}}{S_{\text{M}}^{**}}\right)+Q_2\bar{\beta}_{\text{F}}\bar{\beta}_{\text{M}} I_{\text{HM}}^{**} S_{\text{M}}^{**} S_{\text{F}}^{**}\left(4-\frac{S_{\text{F}}^{**}}{S_{\text{F}}}-\frac{S_{\text{M}}^{**}}{S_{\text{M}}}-\frac{I_{\text{HM}} I_{\text{HF}}^{**} S_{\text{F}}}{I_{\text{HM}}^{**} I_{\text{HF}} S_{\text{F}}^{**}}-\frac{I_{\text{HF}} I_{\text{HM}}^{**} S_{\text{M}}}{I_{\text{HF}}^{**} I_{\text{HM}} S_{\text{M}}^{**}}\right)\\
&\quad + \omega_p D_2 \bar{\beta}_{\text{F}}\bar{\beta}_{\text{M}} I_{\text{HM}}^{**} S_{\text{M}}^{**} S_{\text{F}}^{**}\left(5-\frac{S_{\text{F}}^{**}}{S_{\text{F}}}-\frac{S_{\text{M}}^{**}}{S_{\text{M}}}-\frac{I_{\text{HM}} I_{\text{HF}}^{**} S_{\text{F}}}{I_{\text{HM}}^{**} I_{\text{HF}} S_{\text{F}}^{**}}-\frac{I_{\text{HM}}^{**} P_{\text{HF}} S_{\text{M}}}{I_{\text{HM}} P_{\text{HF}}^{**} S_{\text{M}}^{**}}-\frac{I_{\text{HF}} P_{\text{HF}}^{**}}{I_{\text{HF}}^{**} P_{\text{HF}}}\right)
\end{aligned}
\tag{4.89}
$$

Finally, since arithmetic mean is greater than geometric mean, the following inequalities from (4.89) hold:

$$
\begin{aligned}
\left(2-\frac{S_{\text{F}}^{**}}{S_{\text{F}}}-\frac{S_{\text{F}}}{S_{\text{F}}^{**}}\right)\le 0,\quad \left(2-\frac{S_{\text{M}}^{**}}{S_{\text{M}}}-\frac{S_{\text{M}}}{S_{\text{M}}^{**}}\right)&\le 0\\
\left(4-\frac{S_{\text{F}}^{**}}{S_{\text{F}}}-\frac{S_{\text{M}}^{**}}{S_{\text{M}}}-\frac{I_{\text{HM}} I_{\text{HF}}^{**} S_{\text{F}}}{I_{\text{HM}}^{**} I_{\text{HF}} S_{\text{F}}^{**}}-\frac{I_{\text{HF}} I_{\text{HM}}^{**} S_{\text{M}}}{I_{\text{HF}}^{**} I_{\text{HM}} S_{\text{M}}^{**}}\right)&\le 0\\
\left(5-\frac{S_{\text{F}}^{**}}{S_{\text{F}}}-\frac{S_{\text{M}}^{**}}{S_{\text{M}}}-\frac{I_{\text{HM}} I_{\text{HF}}^{**} S_{\text{F}}}{I_{\text{HM}}^{**} I_{\text{HF}} S_{\text{F}}^{**}}-\frac{I_{\text{HM}}^{**} P_{\text{HF}} S_{\text{M}}}{I_{\text{HM}} P_{\text{HF}}^{**} S_{\text{M}}^{**}}-\frac{I_{\text{HF}} P_{\text{HF}}^{**}}{I_{\text{HF}}^{**} P_{\text{HF}}}\right)&\le 0
\end{aligned}
$$

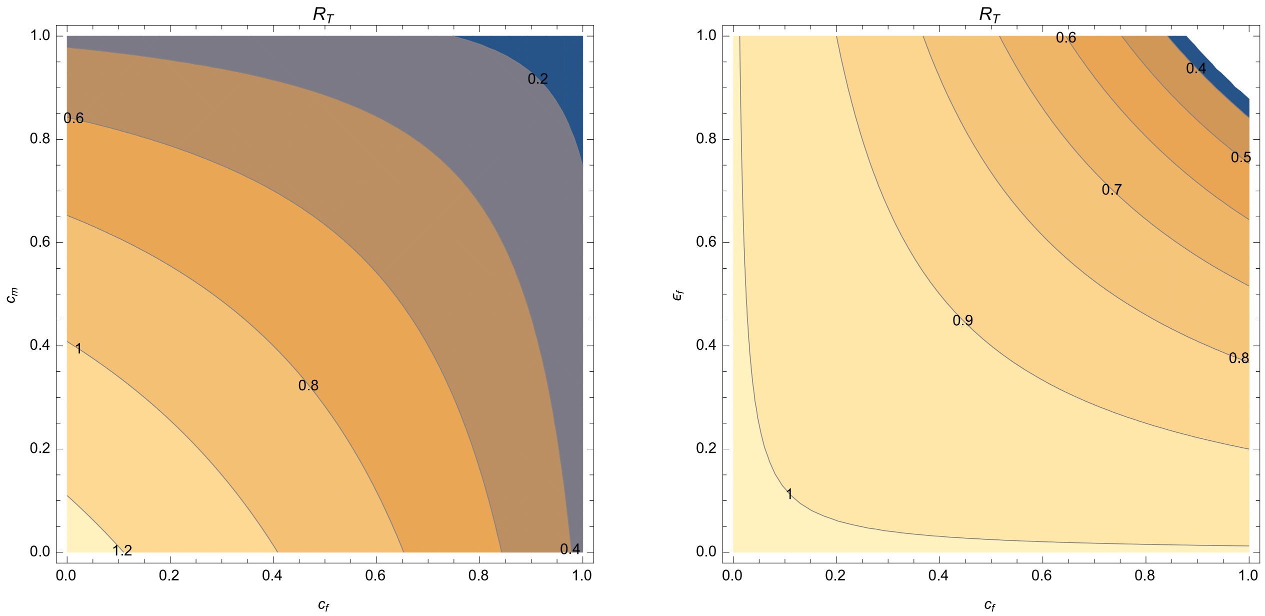
Thus, $\dot{\mathcal{L}} \le 0$ for $\bar{\mathcal{R}}_{0\text{H}} > 1$. Hence, $\mathcal{L}$ is a Lyapunov function in $\mathcal{D}_H$ and based on the La Salle's Invariance principle (La Salle and Lefschetz, 1976), we have that every solution to the equations of the sub-model (4.73) with (4.85) and initial conditions in $\mathcal{D}_H \setminus \mathcal{D}_{0H}$ approaches the associated unique endemic equilibrium ξ_{eH}, of the model as $t \to \infty$ for $\bar{\mathcal{R}}_{0\text{H}} > 1$. □

4.7 Simulations of the Treatment model (3.19)

The model (3.19) is now numerically simulated using the parameter estimates in Table 4.1 (unless otherwise stated), to assess the potential impact of various control strategies on the transmission dynamics of HPV in the population (South Africa). Demographic parameters relevant to South Africa were chosen. Specifically, since the total population of sexually active susceptible females and males (15-64 years) in South Africa are estimated to be 17,827,279 and 17,901,625 respectively, at disease free equilibrium, $\frac{\Lambda_f}{\mu_f} = 17,827,279$ and $\frac{\Lambda_m}{\mu_m} = 17,901,625$ (CIA World Factbook, South Africa Demographics Profile (2018)). In South Africa, the life expectancy for females and males are estimated at 64.6 years and 61.6 years, respectively (CIA World Factbook, South Africa Demographics Profile (2018)).

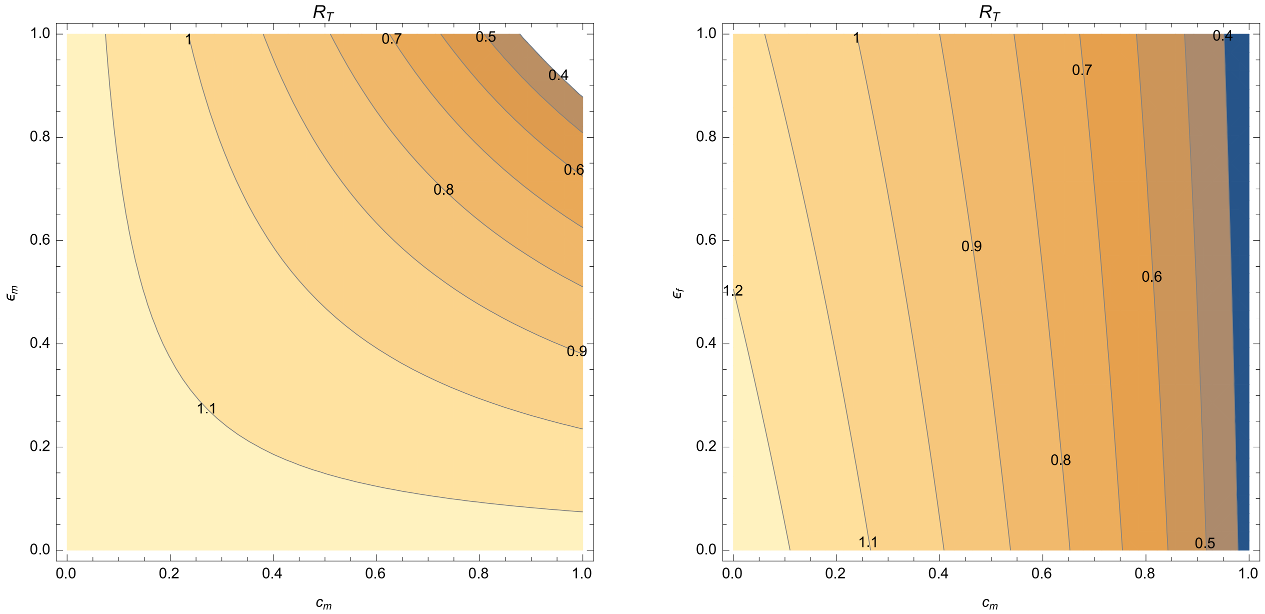
4.7.1 Uncertainty and sensitivity analysis of the Treatment model

The model (3.19) has forty seven (47) parameters, and uncertainties are expected to arise in the estimates of their values used in the numerical simulations. Following Blower and Dowlatabadi (1994), we perform a Latin Hypercube Sampling (LHS) on the parameters that appear in the expression for the reproduction number, $\mathcal{R}_T$ and the infected classes. For the sensitivity analysis, a Partial Rank Correlation Coefficient (PRCC) was calculated between values of the parameters in the response function and the values of the response function derived from the sensitivity analysis. A total of 1,000 simulations (of the model (3.19)) *per* LHS run were carried out. Using the basic reproduction number, $\mathcal{R}_T$, as the response function, it is observed in Table 4.2 that the top four PRCC-ranked parameters are the effective contact rate for female to male transmission of HPV, β_f, fraction of vaccinated females, f, the effective contact rate for male to female transmission of HPV, β_m and fraction of vaccinated males, m. It is important to note that the profile of $\mathcal{R}_T$ as a function of condom compliance for males (c_m) and condom compliance for females (c_f), as depicted in Figure 4.8(a), shows that if the condom compliance by males (females) is 40%, a little or no compliance is required for females (males) to eliminate HPV from the population (this drives $\mathcal{R}_T$ below unity, which results in the GAS property of the DFE of the model (3.19), in line with Theorem 4.8). $\mathcal{R}_T$ as a function of condom efficacy for females (ϵ_f) and condom compliance for females (c_f), as depicted in Figure 4.8(b), shows that if the condom efficacy for females is



(a) A contour plot of $\mathcal{R}_T$ as a function of condom compliance for males (c_m) and condom compliance for females (c_f)

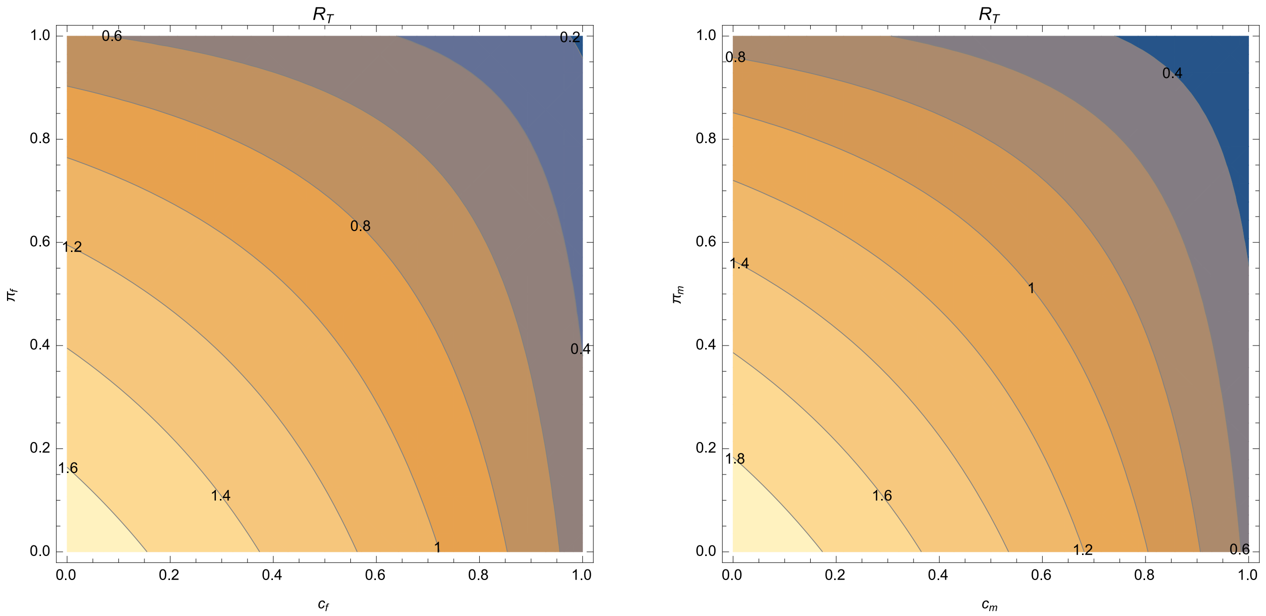
(b) A contour plot of $\mathcal{R}_T$ as a function of condom efficacy for females (ϵ_f) and condom compliance for females (c_f)



(c) A contour plot of $\mathcal{R}_T$ as a function of condom efficacy for males (ϵ_m) and condom compliance for males (c_m)

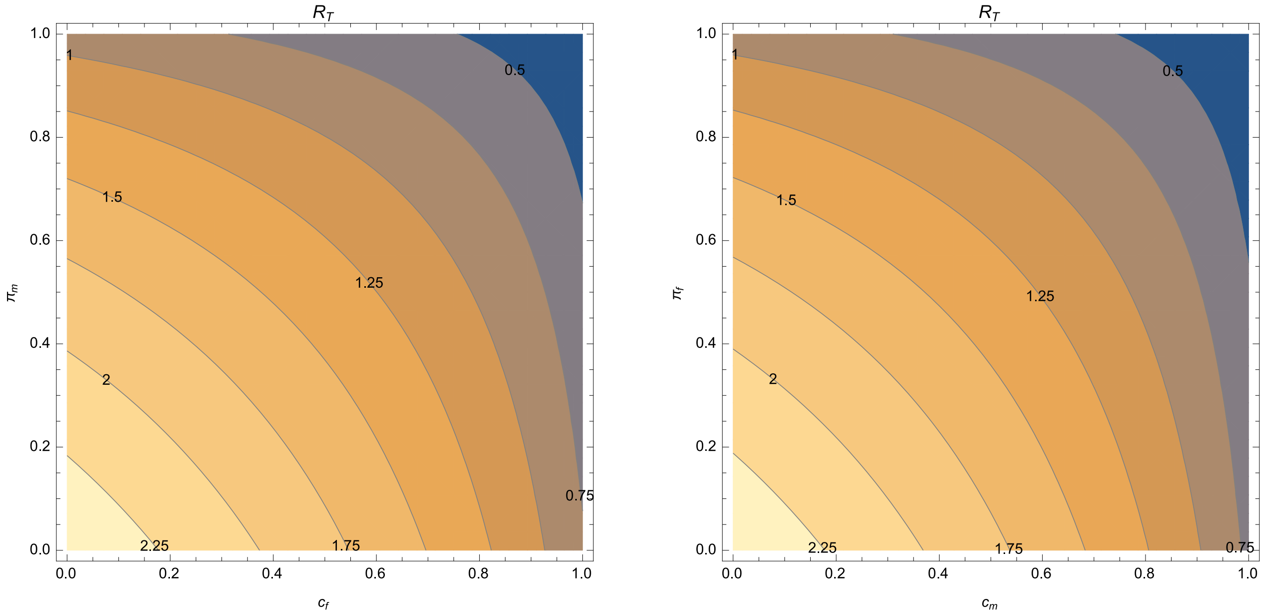
(d) A contour plot of $\mathcal{R}_T$ as a function of condom efficacy for females (ϵ_f) and condom compliance for males (c_m)

Figure 4.8: Simulations of the model (3.19) showing the contour plots. Parameter values used are: $\beta_f = 2.5, \beta_m = 2.5, \kappa_f = \kappa_m = 0.3$. All other parameters as in Table 4.1



(a) A contour plot of $\mathcal{R}_T$ as a function of vaccine efficacy for females (π_f) and condom compliance for females (c_f)

(b) A contour plot of $\mathcal{R}_T$ as a function of vaccine efficacy for males (π_m) and condom compliance for males (c_m)



(c) A contour plot of $\mathcal{R}_T$ as a function of vaccine efficacy for males (π_m) and condom compliance for females (c_f)

(d) A contour plot of $\mathcal{R}_T$ as a function of vaccine efficacy for females (π_f) and condom compliance for males (c_m)

Figure 4.9: Simulations of the model (3.19) showing various contour plots. Parameter values used are: $\beta_f = 2.0, \beta_m = 2.0, \kappa_f = \kappa_m = 0.3$. All other parameters as in Table 4.1

Table 4.1: Baseline values and ranges of the parameters of the model (3.19).

Parameter	Baseline value	Range(*per* year)	Reference
μ_f	0.0162	[0.0100,0.2000]	SA Demo. Pro. (2018)
μ_m	0.0155	[0.0100,0.2000]	SA Demo. Pro. (2018)
Λ_f	271369	[250000, 280000]	SA Demo. Pro. (2018)
Λ_m	266208	[250000, 280000]	SA Dem. Pro. (2018)
β_f	1.0	[0.4,3.0]	Malik *et al.*(2013)
β_m	0.8	[0.3,2.5]	Malik *et al.*(2013)
c_f	0.2	[0.1,1.0]	Mukandavire et al (2007)
c_m	0.4	[0.1,1.0]	Mukandavire et al (2007)
$\epsilon_f(\epsilon_m)$	0.92	[0.1, 1.0]	Mukandavire et al (2007)
$\theta_{f1}(\theta_{m1})$	0.8	[0.7, 0.9]	Alsaleh and Gumel (2014b)
$\theta_{f2}(\theta_{m2})$	0.9	[0.5, 0.95]	Malik *et al.*(2013)
$f(m)$	0.87	[0.5,0.9]	HPV and Related Cancers, SA (2018)
$\pi_f(\pi_m)$	0.9	[0.9,1]	Malik *et al.* (2013)
$\delta_f(\delta_m)$	0.001	[0.0005,0.002]	Malik *et al.* (2013)
$\gamma_f(\gamma_m)$	0.5	[0.3,0.7]	Alsaleh and Gumel (2014b)
$\phi_f(\phi_m)$	0.9	[0.7,0.9]	Malik *et al.* (2013)
$\alpha_f\alpha_m$	114	[110,120]	Alsaleh and Gumel (2014a)
$\tau_f(\tau_m)$	0.9	[0.5,2.5]	Assumed
$\psi_f(\psi_m)$	0.99	[0.5,1]	Myers *et al.* (2000)
$\kappa_f(\kappa_m)$	0.3	[0.1,0.5]	Alsaleh and Gumel (2014b)
δ_f^c	0.001	[0.0005,0.002]	Malik *et al.* (2013)
ω_f	0.01	[0.005,0.02]	Assumed
$\delta_f^a(\delta_m^a)$	0.001	[0.0005,0.002]	Malik *et al.* (2013)
$\kappa_f^a(\kappa_m^a)$	0.76	[0.56,0.96]	Elbasha et al (2007), Malik *et al.* (2013)
κ_f^c	0.76	[0.56,0.96]	Elbasha *et al.* (2007), Malik *et al.* (2013)
$\eta_f(\eta_m)$	0.9	[0.1,1.0]	Assumed
$\varepsilon_f(\varepsilon_m)$	0.01	[0.005,0.02]	Assumed
$\sigma_f(\sigma_m)$	0.8	[0.2,0.90]	Assumed
$\varphi_f(\varphi_m)$	0.5	[0.1,0.9]	Assumed
$\xi_f(\xi_m)$	0.001	[0.005,0.10]	Assumed

Table 4.2: Partial rank correlation coefficients (PRCC) for $\mathcal{R}_T$ and each input parameter variable

Input parameter	PRCC($\mathcal{R}_T$)	Input parameter	PRCC($\mathcal{R}_T$)
β_f	**0.5056**	β_m	**0.5006**
f	**-0.5024**	m	**-0.5017**
c_f	-0.2762	c_m	-0.26777
ϵ_f	-0.2590	ϵ_m	-0.2667
μ_f	-0.2409	μ_m	-0.2230
γ_f	-0.1800	γ_m	-0.1881
π_f	-0.0754	π_m	-0.0841
τ_f	-0.1740	τ_m	-0.1553
θ_{f1}	0.0540	θ_{m1}	0.0520
ξ_f	0.0075	ξ_m	0.0586
δ_f	-0.0062	δ_m	-0.0021
ϕ_f	-0.0057	ϕ_m	-0.0143
ε_f	0.0390	ε_m	-0.0153
θ_{f2}	-0.0038	θ_{m2}	-0.0030
α_f	-0.0393	α_m	-0.0008
σ_f	0.0012	σ_m	-0.0188
η_f	-0.0267	η_m	-0.0029
ψ_f	0.0029	ψ_m	0.0101

60%, then 40% condom compliance is required for females for the effective control or elimination of HPV in the population (since this brings $\mathcal{R}_T$ below unity, which results in the GAS property of the DFE of the model (3.19), in line with Theorem 4.8)to drive $\mathcal{R}_T$ below unity. In addition, it is noteworthy to note that if condom compliance by females is below 30%, then condom efficacy for females, no matter how high, is not sufficient to drive $\mathcal{R}_T$ below unity. In Figure 4.8(c), the profile of $\mathcal{R}_T$ as a function of condom efficacy for males (ϵ_m) and condom compliance for males (c_m) is given. The figure shows that with 40% male condom efficacy, condom compliance of about 60% by males is required to drive the reproduction number, $\mathcal{R}_T$ below unity. The profile of $\mathcal{R}_T$ as a function of condom efficacy for females (ϵ_f) and condom compliance for males (c_m), depicted in Figure 4.8(d), shows that if the condom compliance by males is 40%, then female condom efficacy, no matter how small, is sufficient to drive $\mathcal{R}_T$ below unity.

The profile of $\mathcal{R}_T$ as a function of vaccine efficacy for females (π_f) and condom compliance for females (c_f), as depicted in Figure 4.9(a), shows that if the vaccine efficacy for females is 75%, then a little condom compliance by females is required to drive $\mathcal{R}_T$ below unity. If condom compliance by males is 80%, as depicted in Figure 4.9(b), then vaccine efficacy for females, no matter how small is enough to drive $\mathcal{R}_T$ below unity. The contour plot of $\mathcal{R}_T$ as a function of vaccine efficacy for males (π_m) and condom compliance for females (c_f), as depicted in Figure 4.9(c), shows that if the condom compliance for females is 75%, then a male vaccine with 45%

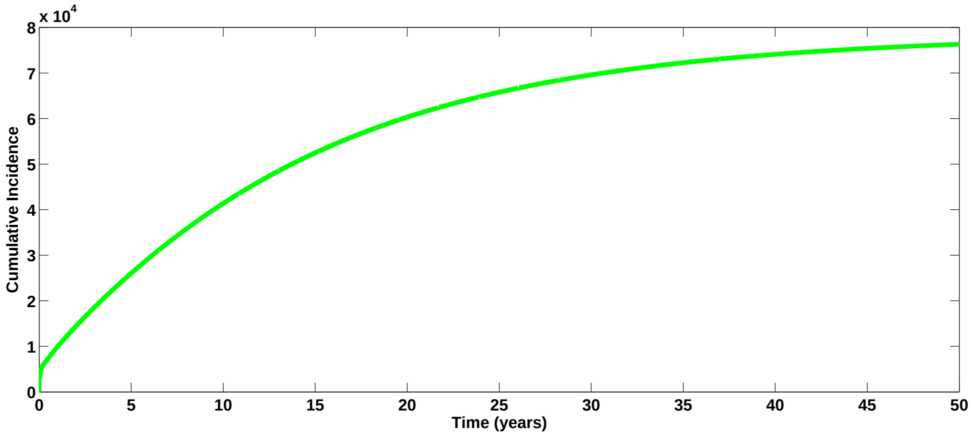


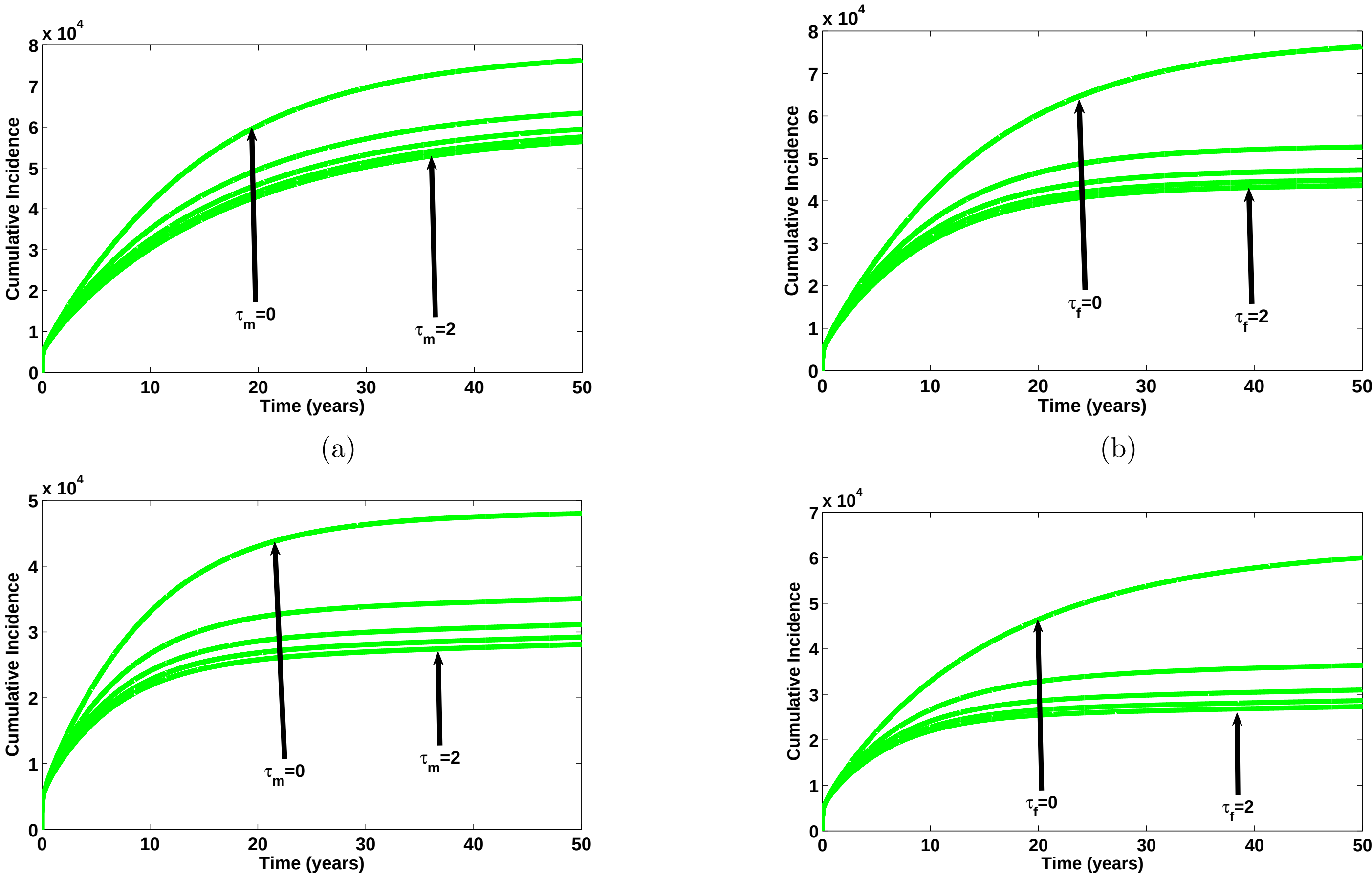
Figure 4.10: Simulations of the model (3.19) showing the cumulative number of new cases of HPV when there is none of the control strategies. $\beta_f = 0.3, \beta_m = 0.25, c_f = c_m = 0, \epsilon_f = \epsilon_m = 0, f = m = \pi_f = \pi_m = 0, \tau_f = \tau_m = \varepsilon_f = \varepsilon_m = \xi_f = \xi_m = \sigma_f = \sigma_m = 0$. All other parameters as in Table 4.1

efficacy is required to drive $\mathcal{R}_T$ below unity. The profile of $\mathcal{R}_T$ as a function of vaccine efficacy for females (π_f) and condom compliance for males (c_m), as depicted in Figure 4.9(d), shows that if the condom compliance rate by males is 75%, then a female vaccine with about 40% efficacy is sufficient to drive $\mathcal{R}_T$ below unity.

Alsaleh and Gumel (2014a) reported that with 90% vaccine efficacy, vaccinating 78–88% of new sexually active females could lead to the effective control of the four Gardasil-preventable HPV types. Again, the study in Alsaleh and Gumel (2014b) revealed that 70% vaccine coverage for susceptible females, vaccinating 45% (34–56%) of new sexually active males would lead to effective control of HPV in the community. Numerical simulations of the current study showed that, with the parameter values used, if the vaccine efficacy for males is 75%, then about 40% condom compliance is required by females to eliminate the disease in the population. Also, if condom compliance by males is 70%, then a female vaccine with 45% efficacy is sufficient for effective control of the disease. Moreover, with 80% condom efficacy for males, a female condom with 55% efficacy is required to eliminate HPV from the population.

4.7.2 Treatment-only strategy

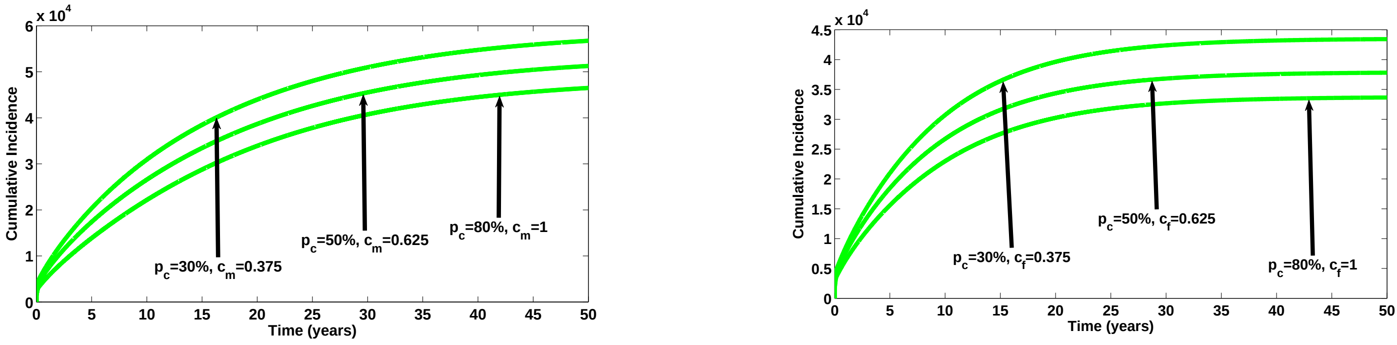
Consider the scenario where treatment is the only available control measure, as depicted in Figures 4.11(a)-(d). It is observed that increasing treatment leads to a decrease in the cumulative number of new HPV cases in the population. However, a higher population level impact is observed when both males and females are treated than when either males only or females only are treated.



(a) (b)

(c) (d)

Figure 4.11: Simulations of the model (3.19) showing the impact of treatment-only on the cumulative number of new cases of HPV. In (a) $\tau_f = 0$ and τ_m is varied from 0 to 2, (b) $\tau_m = 0$ and τ_f is varied from 0 to 2, (c) $\tau_f = 0.9$ and τ_m is varied from 0 to 2, (d) $\tau_m = 0$ and τ_f is varied from 0 to 2. $\beta_f = 0.3, \beta_m = 0.25, c_f = c_m = 0, \epsilon_f = \epsilon_m = 0, f = m = \pi_f = \pi_m = 0$. All other parameters as in Table 4.1



(a)

(b)

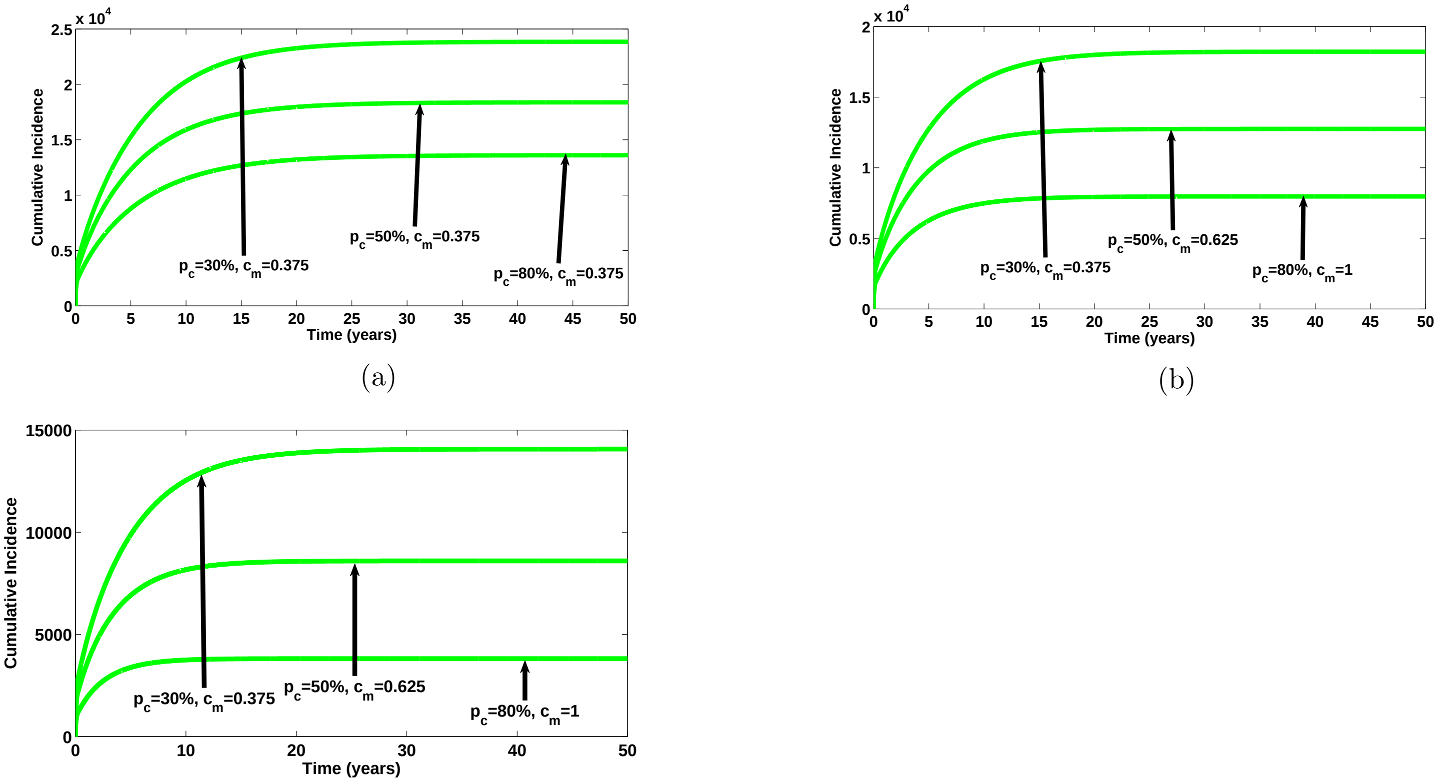
Figure 4.12: Simulations of the model (3.19) showing the impact of (a) male-only condom use (Condom preventability for male p_c is varied from 30% to 80%) and (b)female-only condom use (Condom preventability for female p_c is varied from 30% to 80%) on the cumulative number of new cases of HPV. Parameter values used are: $\beta_f = 0.3, \beta_m = 0.25, f = m = \pi_f = \pi_m = 0, \tau_f = \tau_m = \varepsilon_f = \varepsilon_m = \xi_f = \xi_m = \sigma_f = \sigma_m = 0$. All other parameters as in Table 4.1

4.7.3 Condom-only strategy

The simulations of the model (3.19) showing the impact of condom-use by male-only and female-only respectively, on the cumulative number of new HPV cases, depicted in Figures 4.12a and 4.12b, show that male-only condom use can have more beneficial effect in reducing disease burden in the population than female-only condom-use. Again, Figures 4.13a-c depict the simulations of the model (3.19) showing the impact of condom use by both females and males on the cumulative number of new HPV cases. The condom preventability for males p_c is varied from 30% to 80% while the condom compliance for females by females c_f is varied from 0 to 1. It is observed from the figures that increasing condom preventability for males and condom compliance by females can reduce the burden of HPV in the population, with the highest reduction in disease burden recorded when condom preventability for males $p_c = 80\%$ and condom compliance by females 100%.

4.7.4 Vaccination-only strategy

The simulations of the model (3.19) showing the impact of vaccination only on the cumulative number of new HPV cases, depicted in Figures 4.14 (a)-(d), show that, though vaccination can reduce the burden of the disease in the population, vaccinating both sexually active susceptible males and females can induce a more beneficial effect than vaccinating only sexually active susceptible males or only sexually active susceptible females. It is worthy of note, comparing Treatment only strategy, condom only strategy and vaccination only strategy, to observe that, treatment

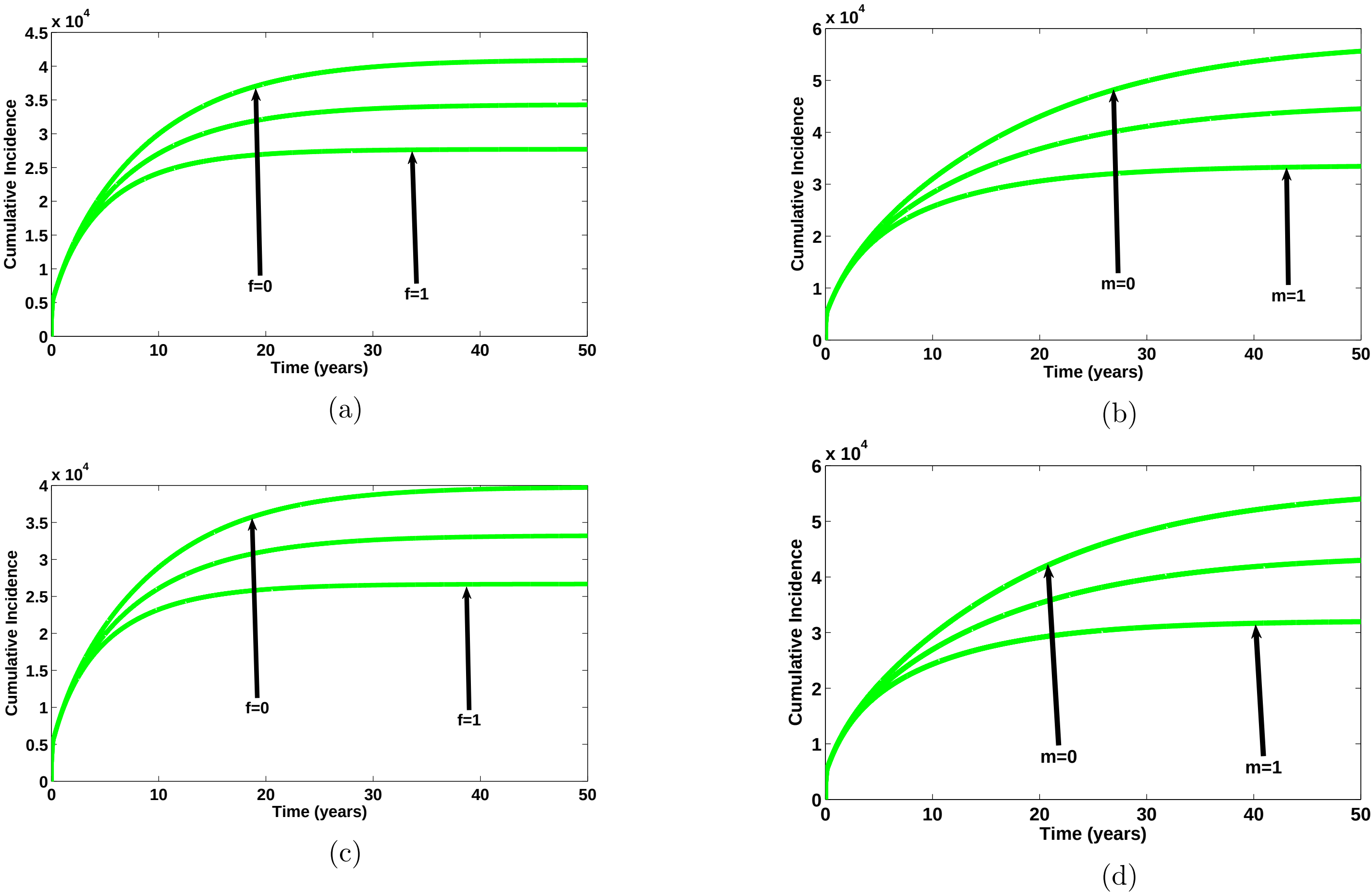


(a)

(b)

(c)

Figure 4.13: Simulations of the model (3.19) showing the Impact of condom-use (by both males and females) on the cumulative new cases of HPV. In (a) $c_f = 0.375$, (b) $c_f = 0.625$ (c) $c_f = 1.0$ while condom preventability for male p_c is varied from 30% to 80% in each case. $\beta_f = 0.3, \beta_m = 0.25, f = m = \pi_f = \pi_m = 0, \tau_f = \tau_m = \varepsilon_f = \varepsilon_m = \xi_f = \xi_m = \sigma_f = \sigma_m = 0$. All other parameters as in Table 4.1



(a) (b)

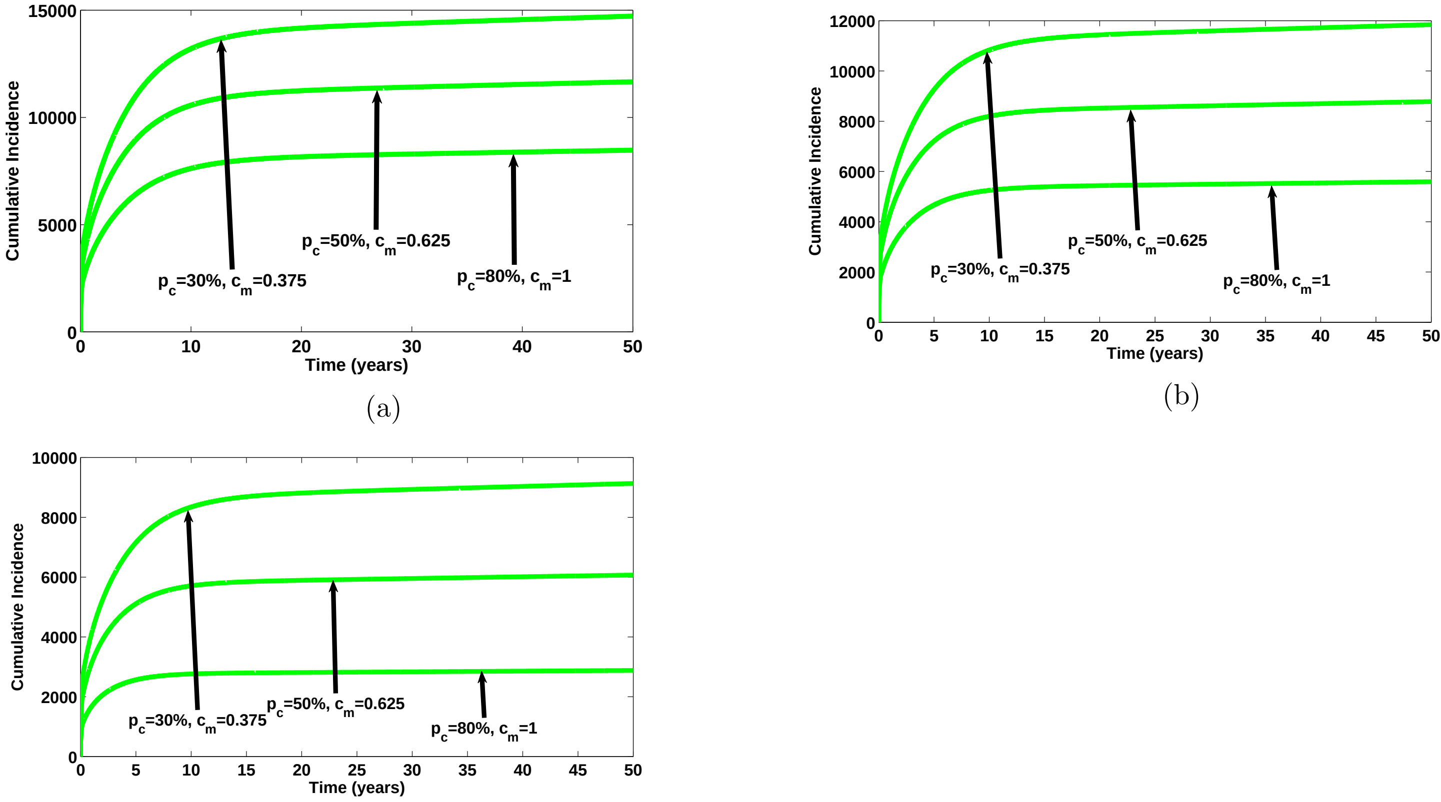
(c) (d)

Figure 4.14: Simulations of the model (3.19) showing the impact of vaccination-only on the cumulative number of new cases of HPV. In (a) $m = 0$ while f is varied from 0 to 1, (b) $f = 0$ while m is varied from 0 to 1, (c) $m = 0.87$ while f is varied from 0 to 1, (d) $f = 0.87$ while m is varied from 0 to 1. $\beta_f = 0.3, \beta_m = 0.25$, $c_f = c_m = \epsilon_f = \epsilon_m = 0, \tau_f = \tau_m = \varepsilon_f = \varepsilon_m = \xi_f = \xi_m = \sigma_f = \sigma_m = 0$. All other parameters as in Table 4.1

only strategy and condom-only strategy have more population level impact than vaccination only strategy.

4.7.5 Condom-treatment strategy

The simulations of the model (3.19) showing the impact of condom-treatment only strategy on the cumulative number of new HPV cases, depicted in Figures 4.15 - 4.17, reveal a decrease in disease burden in the population with increase in treatment rates (as expected), condom preventability for males and condom compliance for females; with the highest decline recorded (in Figure 4.17) when condom preventability for males, p_c is 80%, condom compliance by females, c_f is 100% and treatment rates, τ_f and τ_m are four times baseline values.

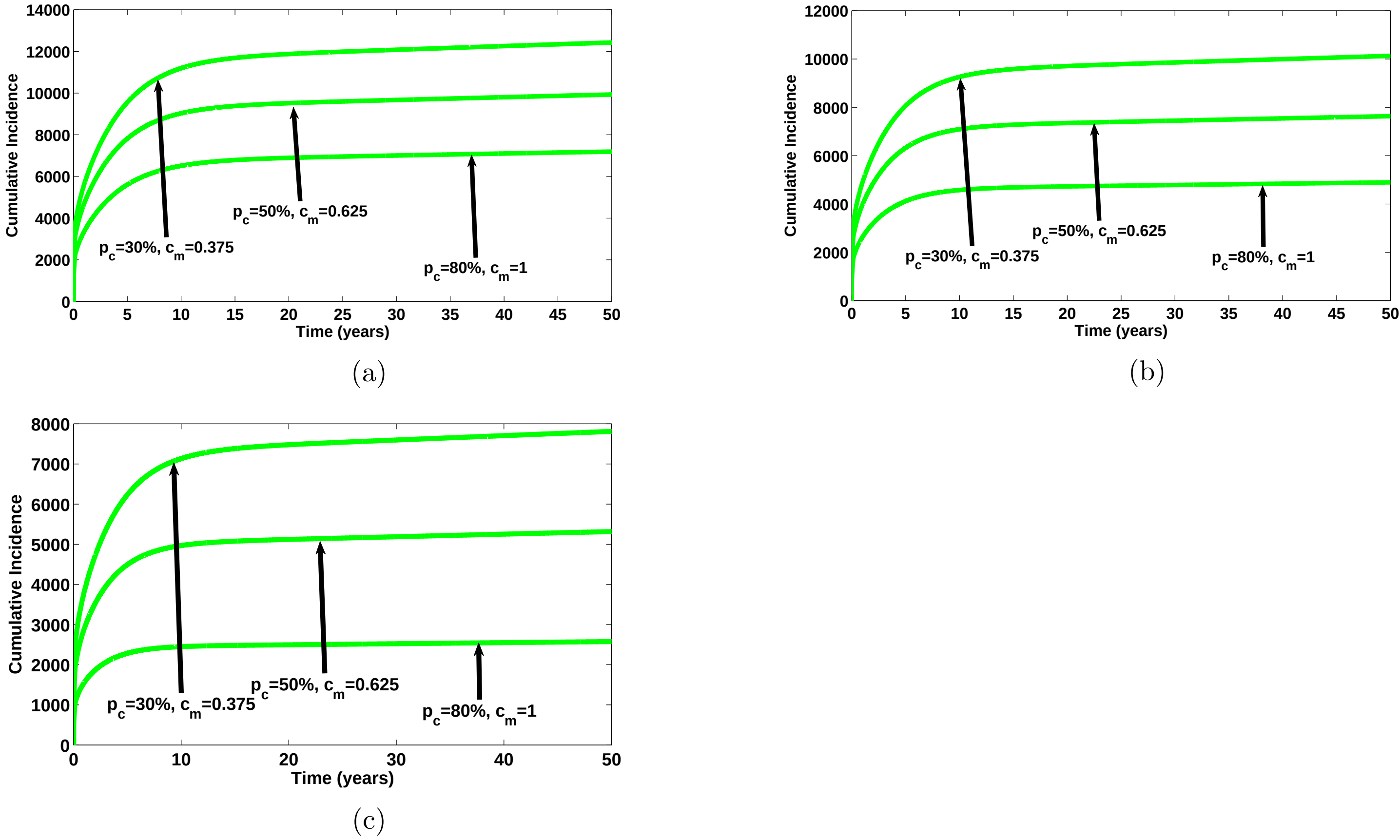


(a)

(b)

(c)

Figure 4.15: Simulations of the model (3.19) showing the impact of condom-treatment strategy on the cumulative number of new HPV cases. Here, treatment rates are at baseline values while in (a) $c_f = 0.375$, (b) $c_f = 0.625$, (c) $c_f = 1.0$ and condom preventability p_c is varied from 30% to 80% in each case. $\beta_f = 0.3, \beta_m = 0.25, f = m = \pi_f = \pi_m = 0$. All other parameters as in Table 4.1

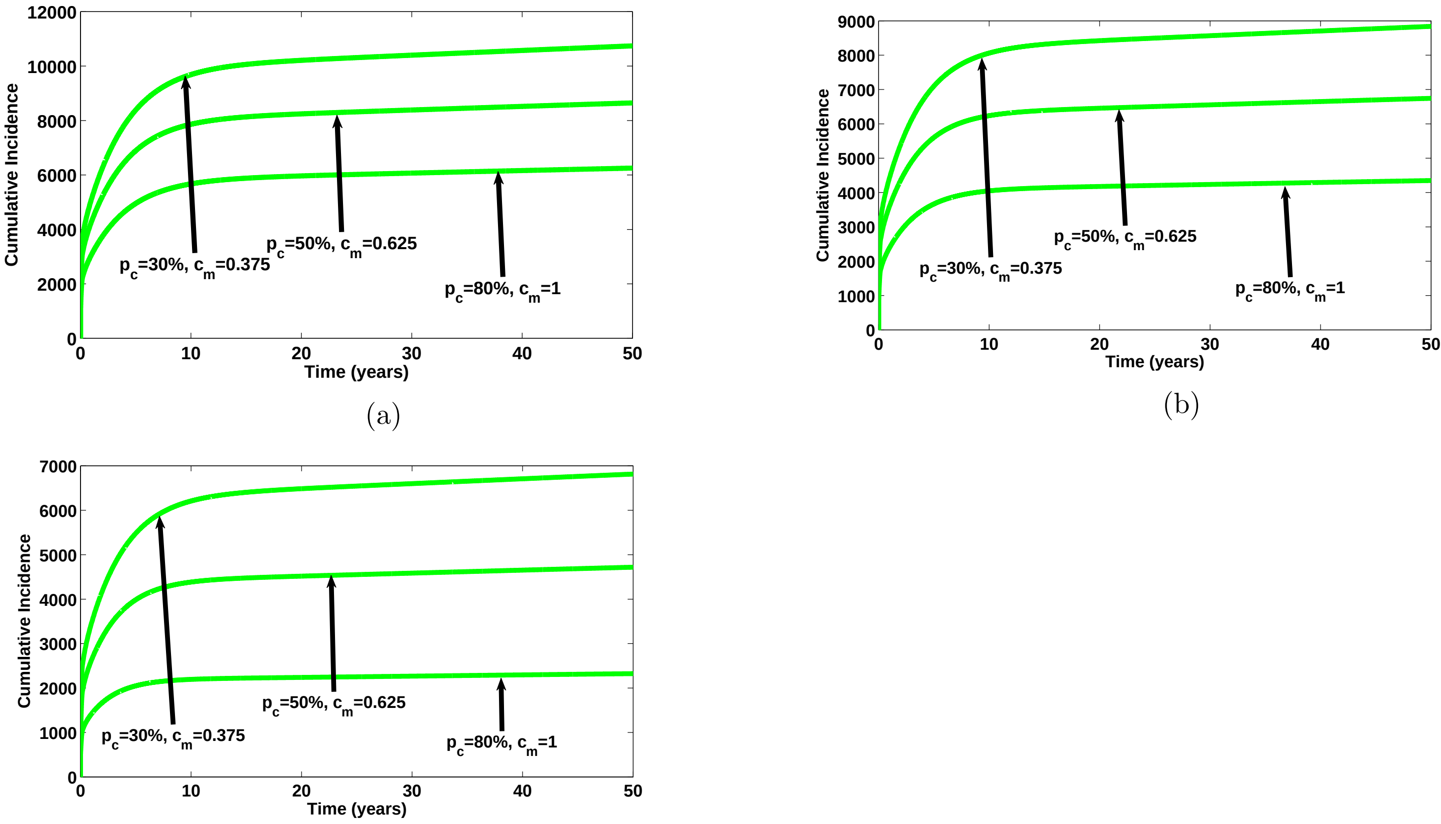


(a)

(b)

(c)

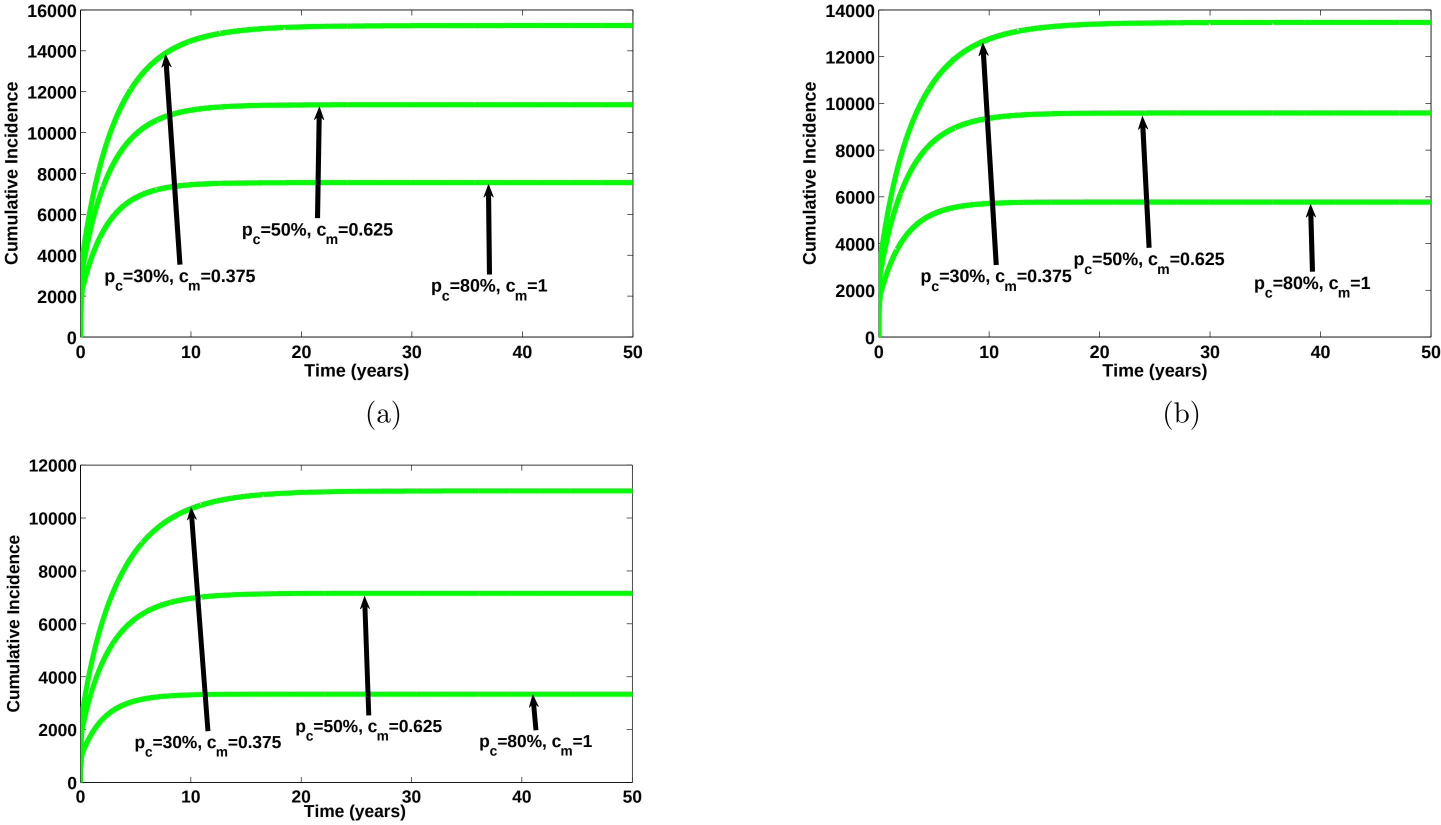
Figure 4.16: Simulations of the model (3.19) showing the impact of condom-treatment strategy on the cumulative number of new HPV cases. Here, treatment rates are twice baseline values while in (a) $c_f = 0.375$, (b) $c_f = 0.625$, (c) $c_f = 1.0$ and condom preventability p_c is varied from 30% to 80% in each case. $\beta_f = 0.3, \beta_m = 0.25, f = m = \pi_f = \pi_m$. All other parameters as in Table 4.1



(a) (b)

(c)

Figure 4.17: Simulations of the model (3.19) showing the impact of condom-treatment strategy on the cumulative number of new HPV cases. Here, treatment rates are four times baseline values while in (a) $c_f = 0.375$, (b) $c_f = 0.625$, (c) $c_f = 1.0$ and condom preventability p_c is varied from 30% to 80% in each case. $\beta_f = 0.3, \beta_m = 0.25, f = m = \pi_f = \pi_m$. All other parameters as in Table 4.1



(a)

(b)

(c)

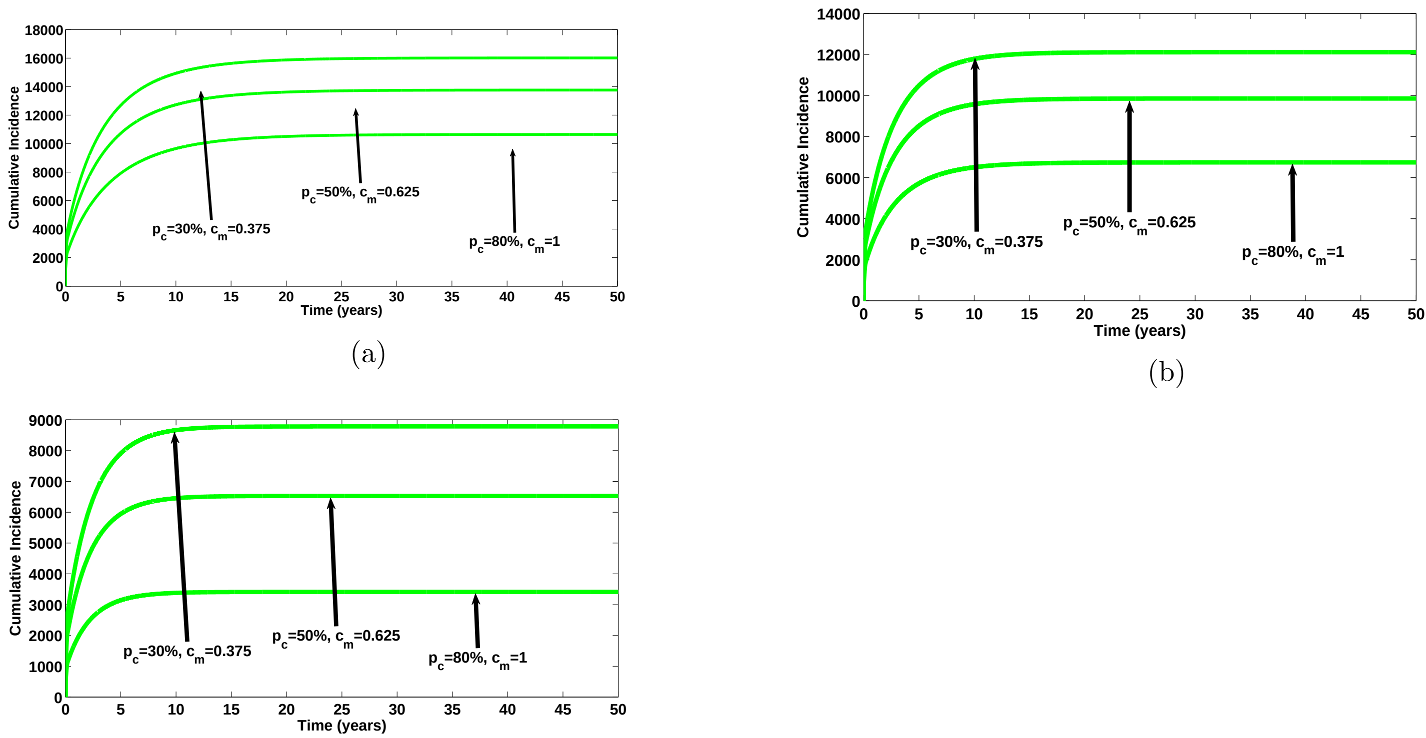
Figure 4.18: Simulations of the model (3.19) showing the impact of condom-vaccination strategy on the cumulative number of new HPV cases. Here, $m = 0$, $f = 0.87$ while in (a) $c_f = 0.375$, (b) $c_f = 0.625$, (c) $c_f = 1.0$ and condom preventability p_c is varied from 30% to 80% in each case. $\beta_f = 0.3, \beta_m = 0.25, \tau_f = \tau_m = \xi_f = \xi_m = \varepsilon_f = \varepsilon_m = \sigma_f = \sigma_m = 0$. All other parameters as in Table 4.1

4.7.6 Condom-vaccination strategy

The simulations of the model (3.19) showing the impact of condom-vaccination strategy on the cumulative number of new HPV cases, depicted in Figures 4.18 - 4.20, show a decrease in disease burden in the population with increasing condom preventability for males, p_c, condom compliance by females, c_f and vaccination of both sexually active males and females. It is interesting to note that the highest reduction in disease burden is recorded (in Figure 4.20) when condom preventability for males, p_c is 80%, condom compliance by females, c_f is 100% and 87% of both sexually active susceptible males and females are vaccinated.

4.7.7 Treatment-vaccination strategy

The simulations of the model (3.19) showing the impact of treatment-vaccination only on the cumulative number of new HPV cases, depicted in Figures 4.21 - 4.24, show a decrease in disease

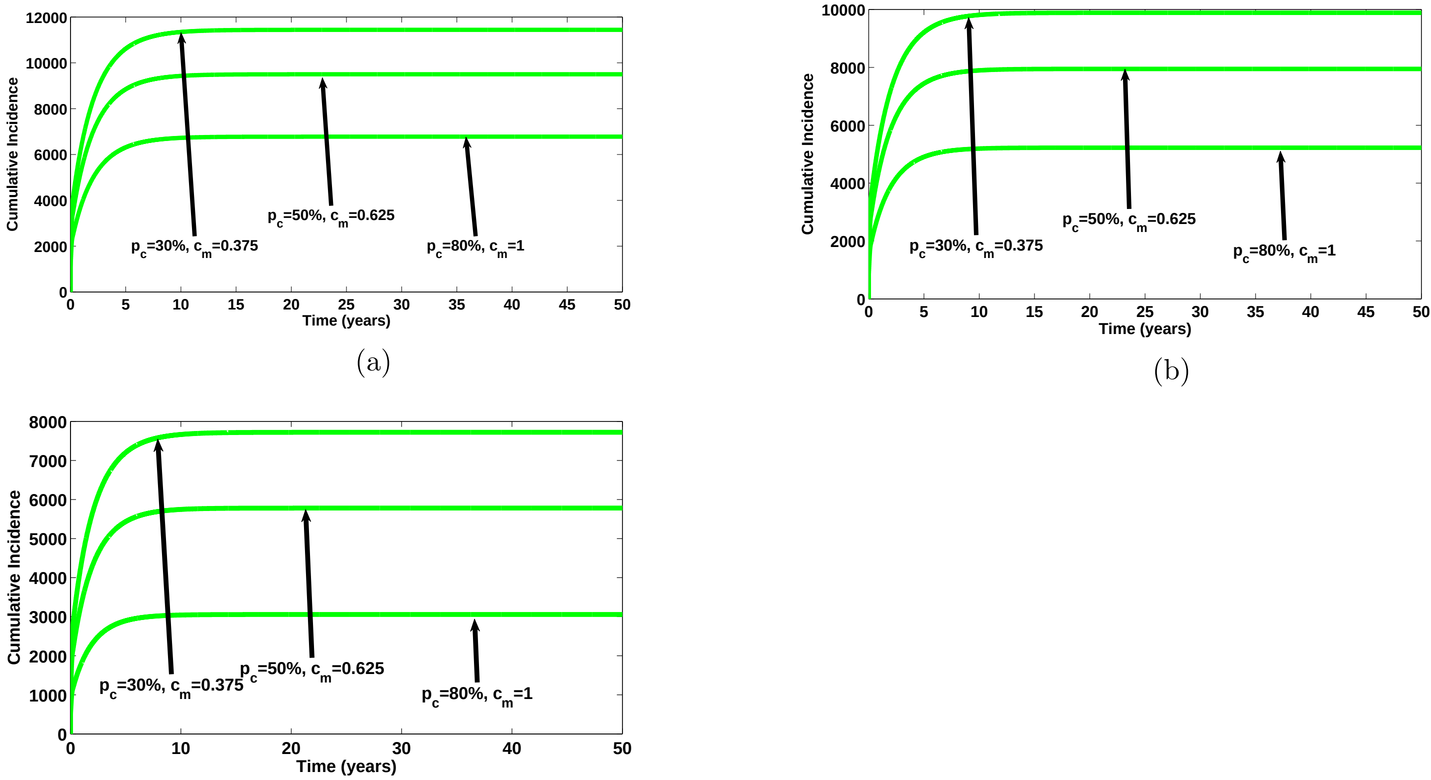


(a)

(b)

(c)

Figure 4.19: Simulations of the model (3.19) showing the impact of condom-vaccination strategy on the cumulative number of new HPV cases. Here, $m = 0.87$, $f = 0$ while in (a) $c_f = 0.375$, (b) $c_f = 0.625$, (c) $c_f = 1.0$ and condom preventability p_c is varied from 30% to 80% in each case. $\beta_f = 0.3, \beta_m = 0.25, \tau_f = \tau_m = \xi_f = \xi_m = \varepsilon_f = \varepsilon_m = \sigma_f = \sigma_m = 0$. All other parameters as in Table 4.1

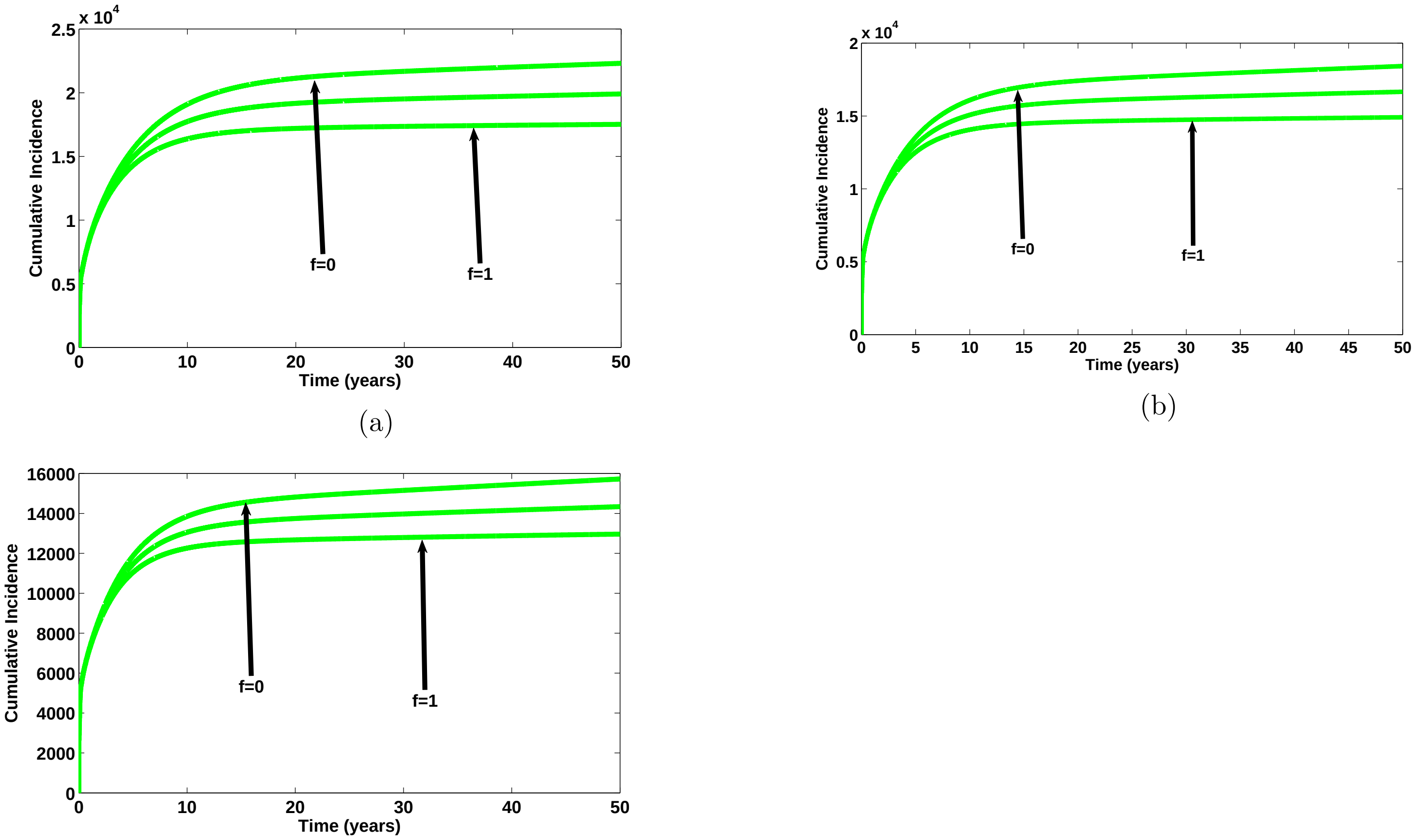


(a)

(b)

(c)

Figure 4.20: Simulations of the model (3.19) showing the impact of condom-vaccination strategy on the cumulative number of new HPV cases. Here, $m = 0.87$, $f = 0.87$ while in (a) $c_f = 0.375$, (b) $c_f = 0.625$, (c) $c_f = 1.0$ and condom preventability p_c is varied from 30% to 80% in each case. $\beta_f = 0.3, \beta_m = 0.25, \tau_f = \tau_m = \xi_f = \xi_m = \varepsilon_f = \varepsilon_m = \sigma_f = \sigma_m = 0$. All other parameters as in Table 4.1



(a) (b)

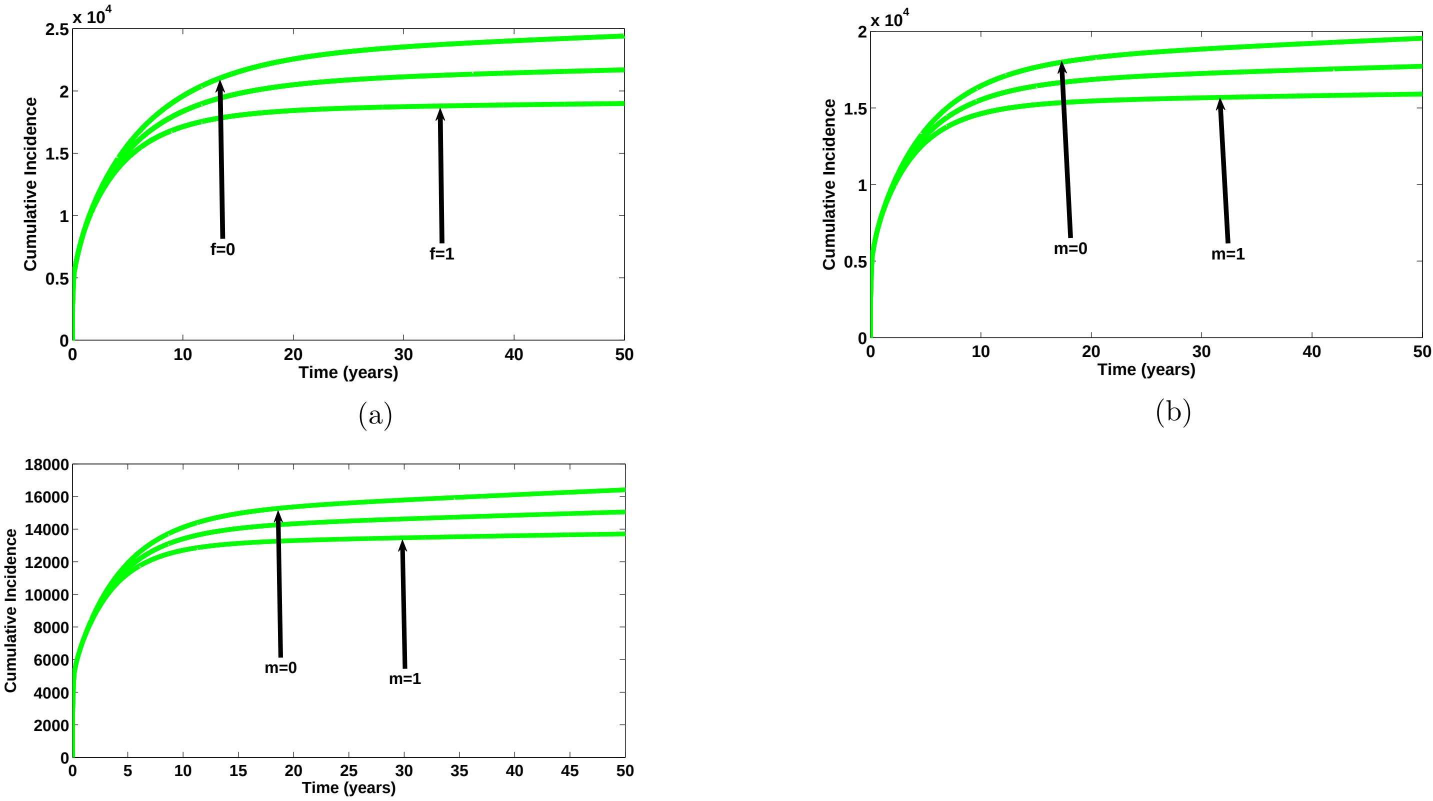
(c)

Figure 4.21: Simulations of the model (3.19), showing the impact of treatment and vaccination on the cumulative number of new HPV cases. Here, $\beta_f = 0.3, \beta_m = 0.25$, $m = 0, c_f = c_m = \epsilon_f = \epsilon_m = 0$. In (a) treatment rates are at baseline values, (b) treatment rates are twice baseline values and (c) treatment rates are four times baseline values. The proportion of vaccinated females (f) is varied from 0 to 1. All other parameters as in Table 4.1

burden in the population with increase in treatment rates and proportion of vaccinated sexually active susceptible males and females; with the highest reduction in disease burden recorded (in Figure 4.24) when treatment rates are four times baseline values and 87% of sexually active susceptible females or males are vaccinated. Comparing condom-treatment only strategy, condom-vaccination only strategy and treatment-vaccination only strategy in Figures 4.17, 4.20 and 4.24 respectively, shows that condom-treatment only strategy has more population-level impact than condom-vaccination only and treatment-vaccination only strategies.

4.7.8 Universal strategy

The simulations of the model (3.19) showing the impact of the universal strategy (where all the control strategies are present) on the cumulative number of new HPV cases, depicted in Figures 4.25 - 4.27, show a decrease in disease burden in the population with increase in treatment rates,

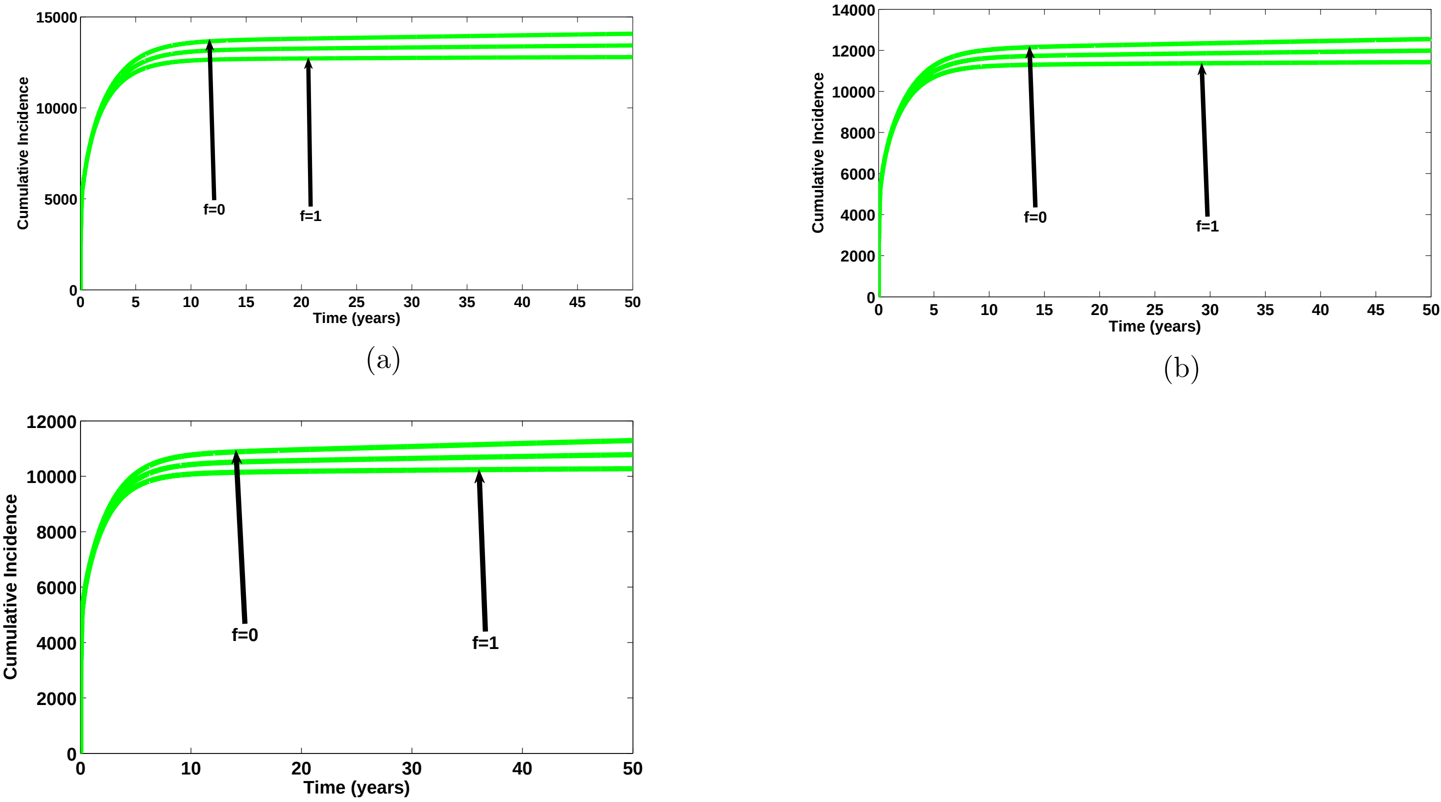


(a)

(b)

(c)

Figure 4.22: Simulations of the model (3.19), showing the impact of treatment and vaccination on the cumulative number of new HPV cases. Here, $\beta_f = 0.3, \beta_m = 0.25,\ f = 0, c_f = c_m = \epsilon_f = \epsilon_m = 0$. In (a) treatment rates are at baseline values, (b) treatment rates are twice baseline values and (c) treatment rates are four times baseline values. The proportion of vaccinated males (m) is varied from 0 to 1. All other parameters as in Table 4.1

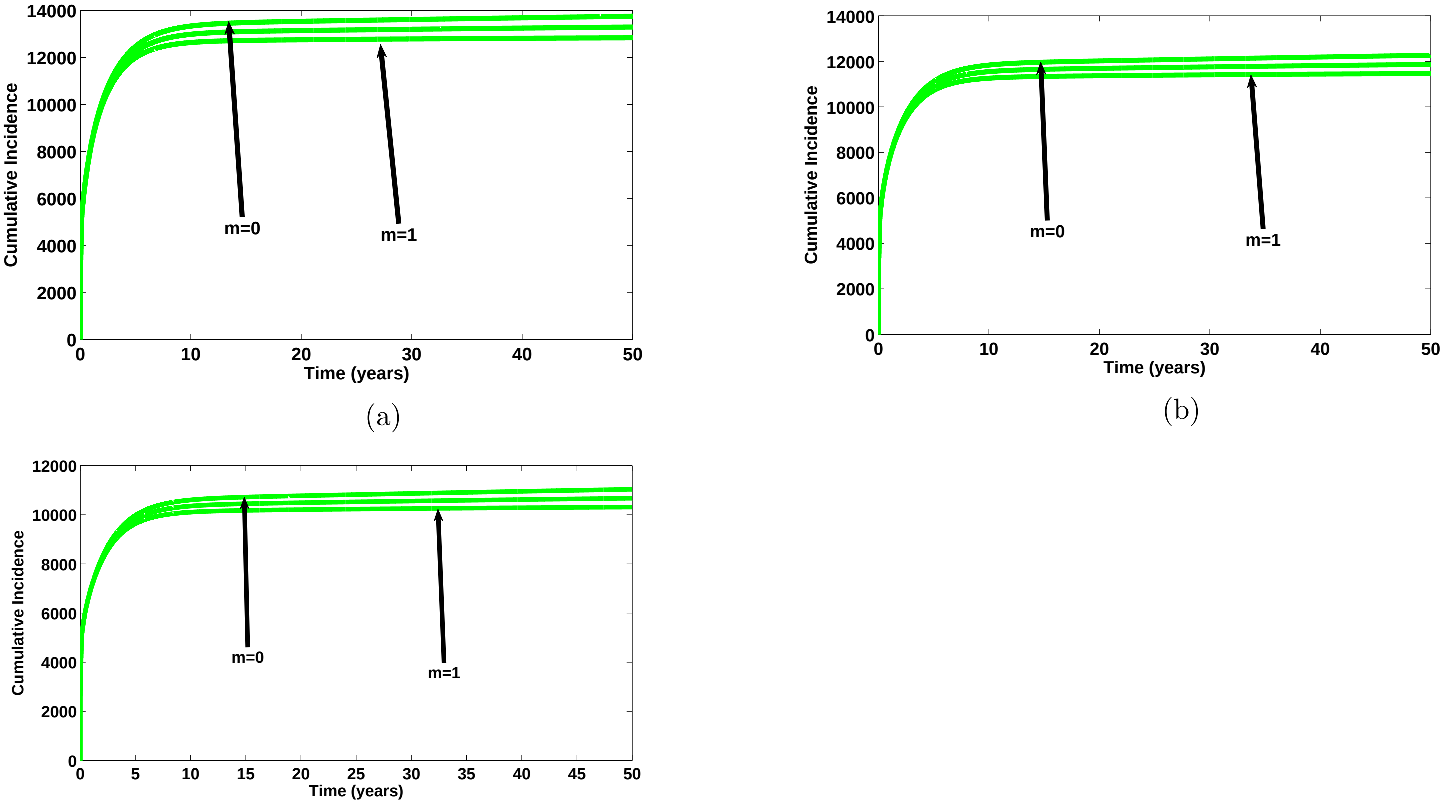


(a)

(b)

(c)

Figure 4.23: Simulations of the model (3.19), showing the impact of treatment and vaccination on the cumulative number of new HPV cases. Here, $\beta_f = 0.3, \beta_m = 0.25$, $m = 0.87, c_f = c_m = \epsilon_f = \epsilon_m = 0$. In (a) treatment rates are at baseline values, (b) treatment rates are twice baseline values and (c) treatment rates are four times baseline values. The proportion of vaccinated females (f) is varied from 0 to 1. All other parameters as in Table 4.1

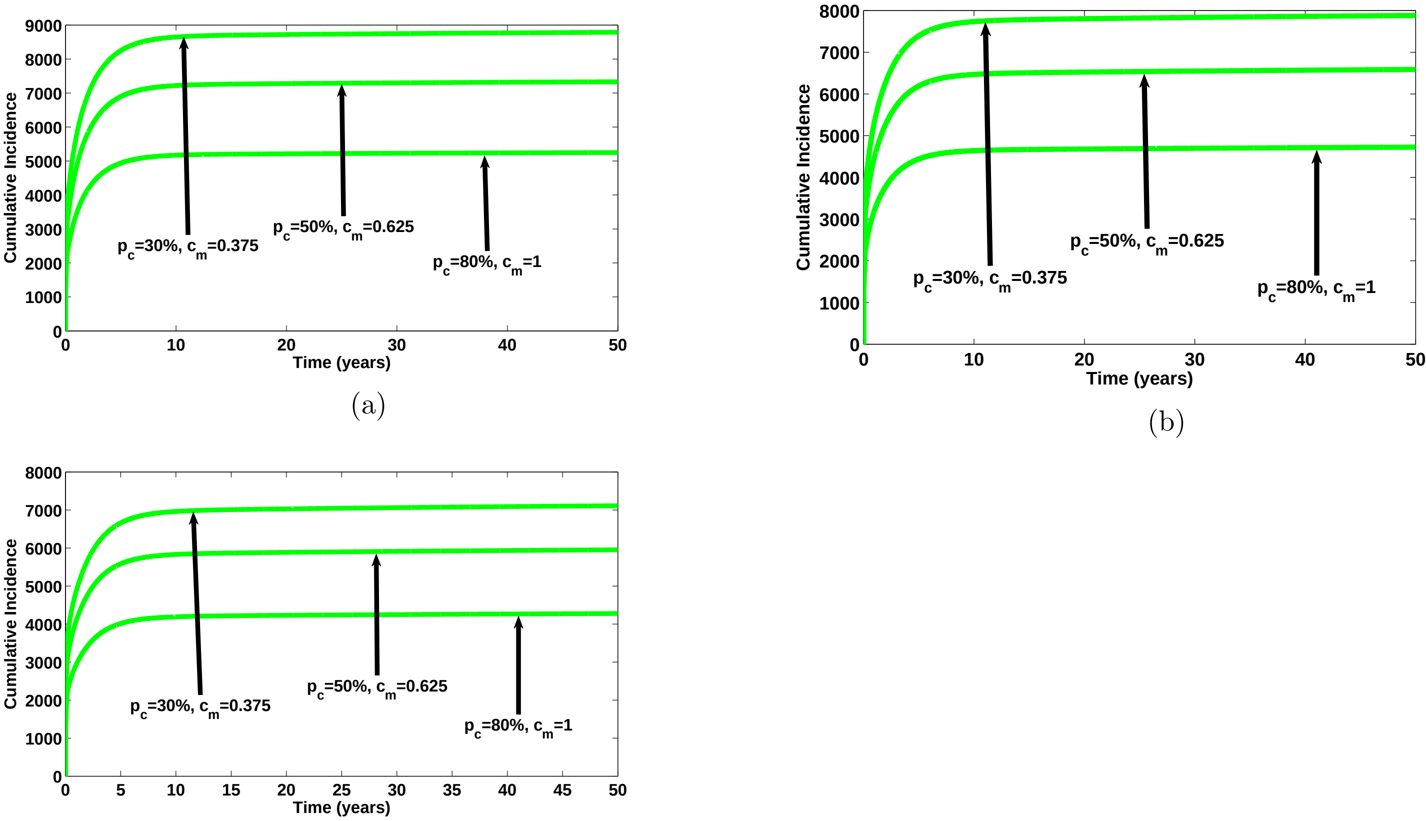


(a)

(b)

(c)

Figure 4.24: Simulations of the model (3.19), showing the the impact of treatment and vaccination on cumulative number of new HPV cases. Here, $\beta_f = 0.3, \beta_m = 0.25,\ f = 0.87, c_f = c_m = \epsilon_f = \epsilon_m = 0$. In (a) treatment rates are at baseline values, (b) treatment rates are twice baseline values and (c) treatment rates are four times baseline values. The proportion of vaccinated males (m) is varied from 0 to 1. All other parameters as in Table 4.1



(a)

(b)

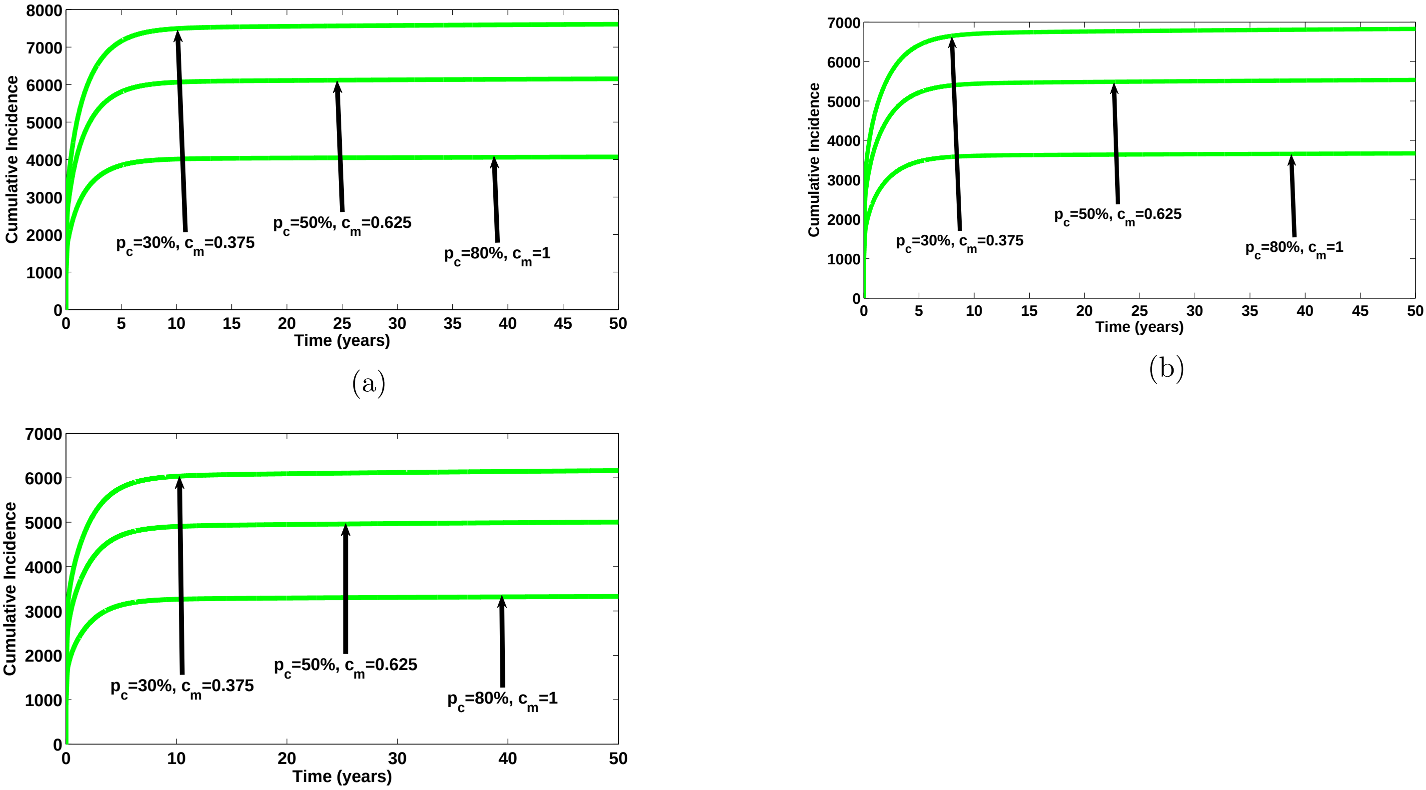
(c)

Figure 4.25: Simulations of the model (3.19), showing the cumulative number of new HPV cases. Here, $\beta_f = 0.3, \beta_m = 0.25$, $f = 0.87$, $m = 0.87$, $c_f = 0.375$. Condom preventability p_c is varied from 30% to 80%. (a) Treatment rates at baseline, (b)twice treatment rates and (c) four times treatment rates. All other parameters as in Table 4.1

increase in condom compliance by both sexually active susceptible males and females, proportion of vaccinated sexually active susceptible males and females. The highest population level impact is observed (in Figure 4.27) when condom preventability for males, p_c, is 80%, condom-compliance by females, c_f, is 100% and treatment rates, τ_f and τ_m, are four times baseline values.

It is interesting to note, comparing all the various control strategies, that the universal strategy has the highest population-level impact.

It is also imperative to state that the simulations carried out in this work are subject to uncertainties in the estimates of the parameter values given in Table 4.2 (the effect of such uncertainties was assessed by using the Latin Hypercube sampling technique) and the above conclusions are based on the parameter values used for obtaining the plots in Table 4.1.

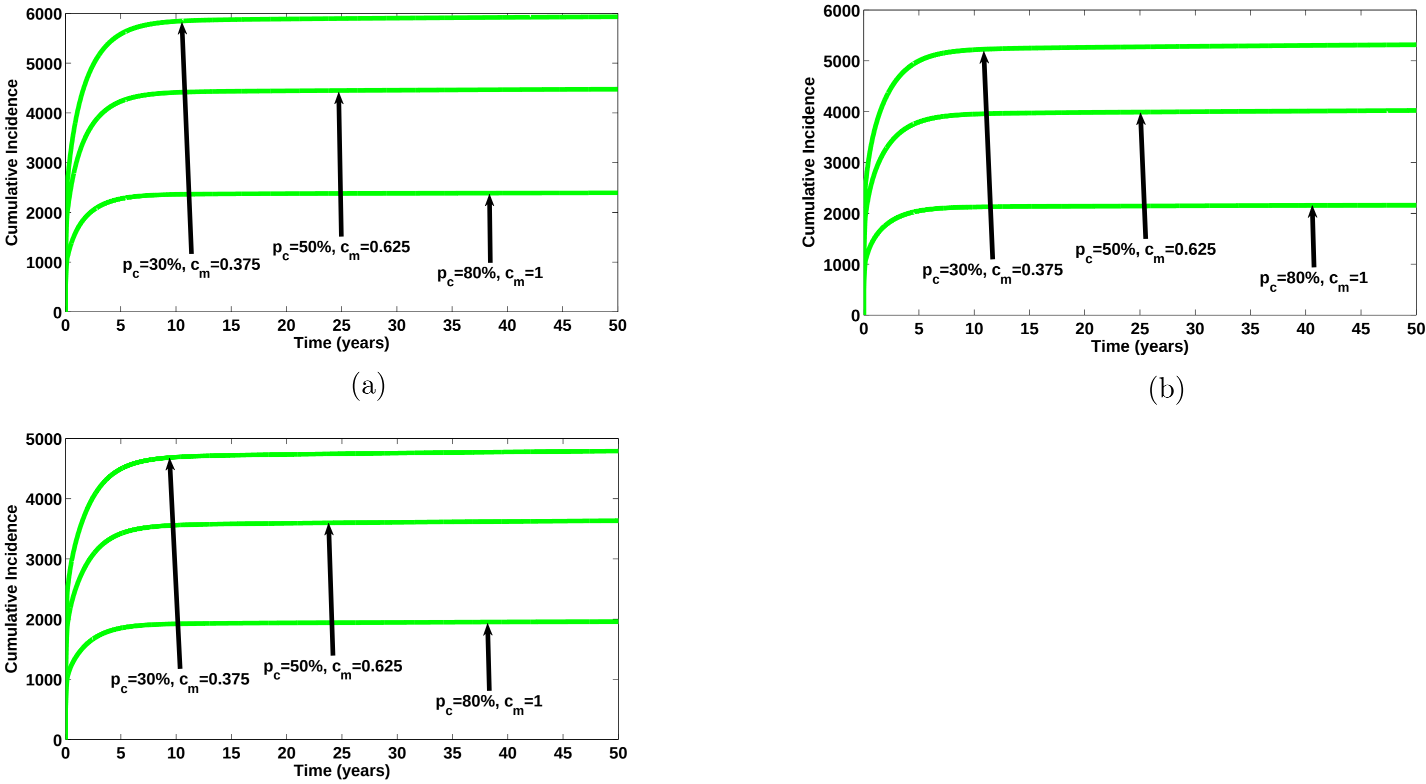


(a)

(b)

(c)

Figure 4.26: Simulations of the model (3.19), showing the cumulative number of new HPV cases. Here, $\beta_f = 0.3, \beta_m = 0.25$, $f = 0.87$, $m = 0.87$, $c_f = 0.625$. Condom preventability p_c is varied from 30% to 80%. (a) Treatment rates at baseline, (b)twice treatment rates and (c) four times treatment rates. All other parameters as in Table 4.1



(a)

(b)

(c)

Figure 4.27: Simulations of the model (3.19), showing the cumulative number of new HPV cases. Here, $\beta_f = 0.3, \beta_m = 0.25,\ f = 0.87,\ m = 0.87,\ c_f = 1.0$. Condom preventability p_c is varied from 30% to 80%. (a) Treatment rates at baseline, (b)twice treatment rates and (c) four times treatment rates. All other parameters as in Table 4.1

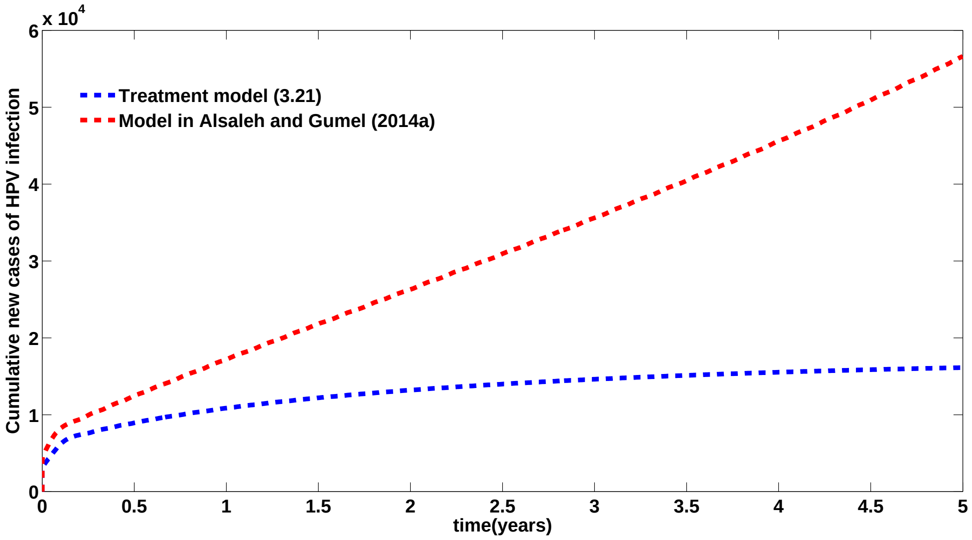


Figure 4.28: Cumulative new cases of HPV infection using model (3.19) and the model in Alsaleh and Gumel (2014a). Parameter values used are: $\beta_1^f = 0.5, \beta_1^m = 0.5$. All other parameters as in Table 4.1

The cumulative new cases of HPV infection, using the parameters in Table 4.1, as shown in Figures 4.28 and 4.29 compares the model (3.19) with the models in Alsaleh and Gumel (2014a) and Malik *et al.* (2013), respectively. There is a reduction in the cumulative new cases of HPV using the model (3.19) compared to the simulations using the models in Alsaleh and Gumel (2014a) and Malik *et al.* (2013). This is as a result of the control strategies included in our model.

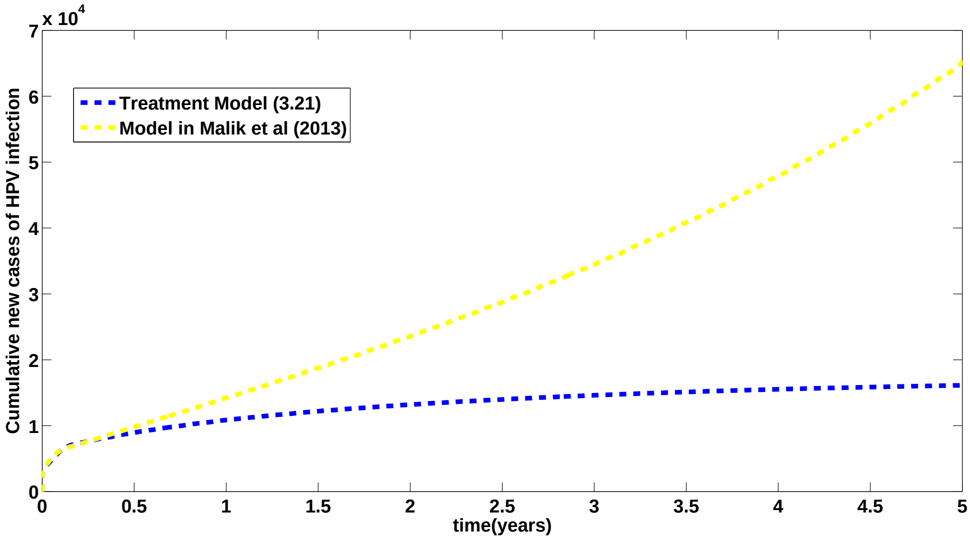


Figure 4.29: Cumulative new cases of HPV infection using model (3.19) and the model in Malik *et al.* (2013). Parameter values used are: $\beta_1^f = 0.5, \beta_1^m = 0.5$. All other parameters as in Table 4.1

4.8 Simulations of the Two-strain HPV model (3.23)

4.8.1 Uncertainty and sensitivity analysis

We now carry out a Latin Hypercube Sampling (LHS) on the parameters of the model, to ascertain the effect of these uncertainties and to determine the parameter(s) that have the greatest impact on the transmission dynamics of Human Papilloma Virus. For the sensitivity analysis, a Partial Rank Correlation Coefficient (PRCC) was calculated between values of the parameters in the response function and the values of the response function derived from the sensitivity analysis. Using the reproduction numbers $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$ as response functions, we have from Table 4.3, that the top PRCC-ranked parameters are: the effective contact rates, β_{f1} (β_{m1}) and β_{f2} (β_{m2}) for strain 1 and strain 2 respectively, the fraction of females vaccinated against strain 1 f, the vaccine efficacy, ξ, the treatment rates, τ_{f1} (τ_{m1}) and τ_{f2} (τ_{m2}) for strain 1 and strain 2. respectively as well as the demographic parameters, μ_f and μ_m.

Parameters	$\mathcal{R}_{01}$	$\mathcal{R}_{02}$
μ_f	**-0.5377**	**-0.7109**
μ_m	**-0.5396**	**-0.6937**
ε_1	0.0076	–
ε_2	–	-0.0014
ε_3	-0.0187	–
ε_4	–	0.0313
p_1	-0.0014	–
p_2	–	-0.0597
ξ	**-0.5644**	–
q_1	0.0905	–
q_2	–	-0.0325
π_f	-0.0105	-0.0319
τ_{f1}	**-0.8511**	–
τ_{m1}	**-0.8542**	–
δ_{f1}	-0.0137	–
κ_{f1}	-0.0042	–
κ_{f2}	–	0.0315
δ_{m1}	-0.0210	–
δ_{fc}	0.0385	0.0551
f	**-0.9600**	–
β_{f2}	–	**0.6088**
β_{m2}	–	**0.9470**
η_c	–	-0.0128
δ_{f2}	–0.0137	-0.0298
δ_{m2}	–	-0.0346
τ_{f2}	–	**-0.9285**
τ_{m2}	–	**-0.9324**
θ_{p1}	0.0142	–
θ_{p2}	–	0.0187
β_{f1}	**0.5001**	–
β_{m1}	**0.8835**	–

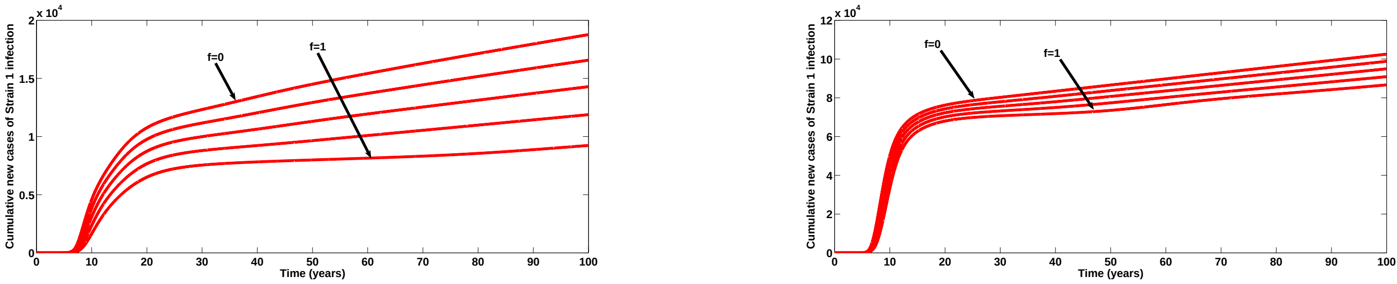
Table 4.3: Partial rank correlation coefficients (PRCC) for $\mathcal{R}_{01}$ and $\mathcal{R}_{02}$ and each input parameter variable

4.8.2 Numerical simulations

We now simulate the model (3.23) numerically using the parameter estimates in Table 4.4 (unless otherwise stated), to assess the potential impact of various targeted control strategies on the transmission dynamics of HPV in the population. Demographic parameters relevant to Nigeria were chosen. Specifically, since the total population of sexually active susceptible females and males (15-64 years) in Nigeria are estimated to be 50,697,439, and 52,862,042 respectively, at disease free equilibrium, $\frac{\Lambda_f}{\mu_f} = 50,697,439$ and $\frac{\Lambda_m}{\mu_m} = 52,862,042$ (HPV and Related Cancers NG (2018), Nigeria Demographics Profile, 2018). In Nigeria, the life expectancy for females and males are estimated at 55 years and 52.8 years, respectively (Nigeria Demographics Profile, 2018). Hence we have that $\mu_f = 0.0182$ and $\mu_m = 0.0189$, so that $\Lambda_f = 922693$ and $\Lambda_m = 9999073$ per year.

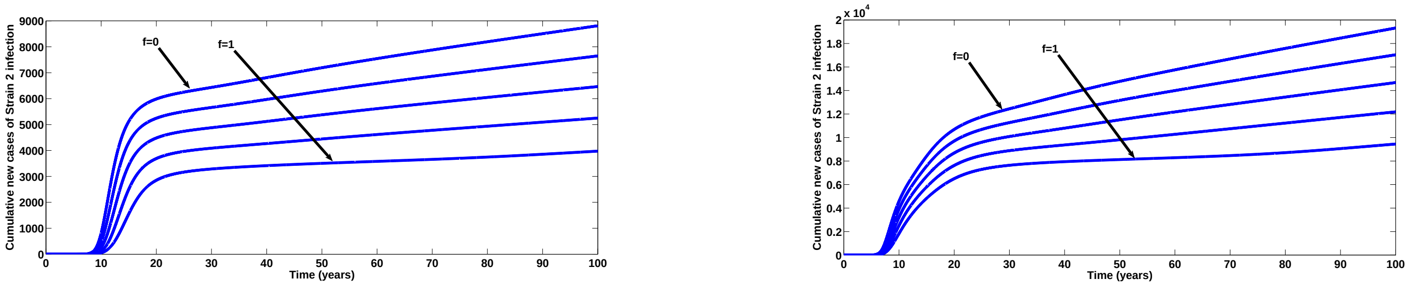
Table 4.4: Baseline values and ranges of the parameters of the model (3.23).

Parameter	value	Range(*per* year)	Reference
μ_f	0.0182	[0.0100,0.2000]	CIA World Factbook, NG Demo. Pro. (2018)
μ_m	0.0189	[0.0100,0.2000]	CIA World Factbook, NG Demo. Pro. (2018)
Λ_f	922693	[900000, 1000000]	CIA World Factbook, NG Demo. Pro. (2018)
Λ_m	999073	[900000, 1000000]	CIA World Factbook, NG Demo. Pro. (2018)
$\beta_1^f(\beta_2^f)$	0.5	[0.4,0.6]	Alsaleh and Gumel (2014a)
$\beta_1^m(\beta_2^m)$	0.4	[0.3,0.5]	Alsaleh and Gumel (2014a)
c_f	2	[1,5]	Malik *et al.*(2013)
$\eta_I(\eta_p)$	0.5	[0.5,1.0]	Inferred from Ault (2007)
η_c	0.5	[0.5,1.0]	Inferred from Ault (2007)
ϕ_p	0.7	[0.5,1.0]	Assumed
$\varepsilon_1(\varepsilon_2)$	0.2	[0.1, 1.0]	Inferred from Ho *et al.* (2002)
$\varepsilon_3(\varepsilon_4)$	0.3	[0.1, 1.0]	Inferred from Ho *et al.* (2002)
$\theta_{p1}(\theta_{p2})$	0.9	[0.7, 0.9]	Malik *et al.*(2013), Alsaleh and Gumel (2014a)
f	0.80	[0.5,0.9]	Assumed
ξ	0.9	[0.9,1]	Malik *et al.*(2013)
$\delta_{f1}(\delta_{m1})$	0.001	[0.0005,0.002]	Alsaleh and Gumel (2014a)
$\delta_{f12}(\delta_{m12})$	0.001	[0.0005,0.002]	Alsaleh and Gumel (2014a)
$\delta_{f2}(\delta_{m2})$	0.001	[0.0005,0.002]	Alsaleh and Gumel (2014a)
$\delta_{f21}(\delta_{m21})$	0.001	[0.0005,0.002]	Alsaleh and Gumel (2014a)
δ_{f2}^p	0.01	[0.005,0.002]	Assumed
$\gamma_f(\gamma_m)$	0.5	[0.3,0.7]	Alsaleh and Gumel (2014a)
$\phi_f(\phi_m)$	0.9	[0.7,0.9]	Malik *et al.*(2013)
$\kappa_{f1}(\kappa_{f2})$	114	[110,120]	Alsaleh and Gumel (2014b)
$\tau_{f1}(\tau_{f2})$	0.9	[0.5,2.5]	Malik *et al.*(2013)
$\tau_{f21}(\tau_{f12})$	0.9	[0.5,2.5]	Malik *et al.*(2013)
$\tau_{m1}(\tau_{m2})$	0.9	[0.5,2.5]	Malik *et al.*(2013)
$\tau_{m21}(\tau_{m12})$	0.9	[0.5,2.5]	Malik *et al.*(2013)
$\kappa_{f1}(\kappa_{f2})$	0.3	[0.1,0.5]	Alsaleh and Gumel (2014a)
δ_f^c	0.01	[0.005,0.002]	Malik *et al.*(2013)
ω_f	0.01	[0.005,0.02]	Assumed
π_f	0.76	[0.56,0.96]	Elbasha et al (2007),Malik *et al.*(2013)
α_1	0.4	[0.1,1.0]	Inferred from Ho *et al.* (2002)
α_2	0.5	[0.1,1.0]	Inferred from Ho *et al.* (2002)
α_3	0.3	[0.1,1.0]	Inferred from Ho *et al.* (2002)
α_4	0.2	[0.1,1.0]	Inferred from Ho *et al.* (2002)
$p_1(p_2)$	0.5	[0.1,1.0]	Assumed
$q_1(q_2)$	0.3	[0.1,1.0]	Assumed
$p_{12}(p_{21})$	0.5	[0.1,1.0]	Assumed



(a) (b)

Figure 4.30: Effect of f on the cumulative new cases of Strain 1 infection. (a) Here, $\beta_{f1} = 3.5, \beta_{m1} = 3.5$, (b) Here, $\beta_{f1} = 4.0, \beta_{m1} = 4.0$. All other parameters as in Table 4.4

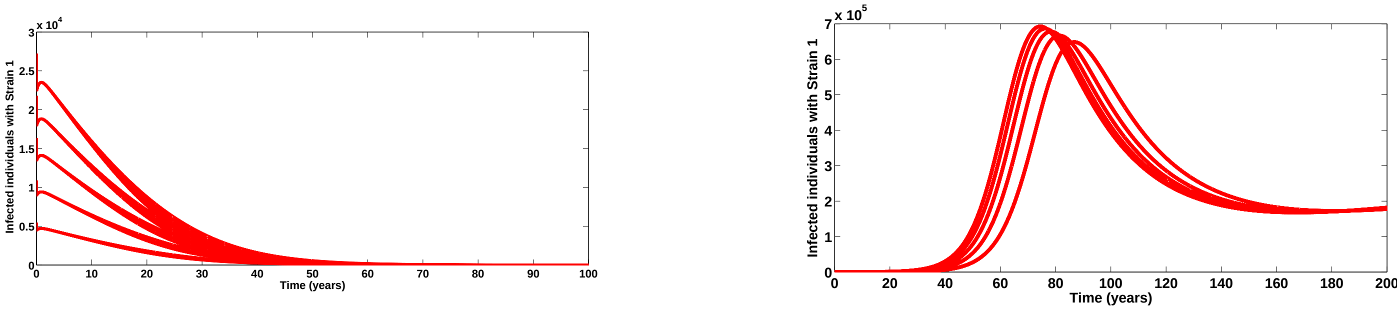


(a) (b)

Figure 4.31: Effect of f on the cumulative new cases of Strain 2 infection. (a) Here, $\beta_{f2} = 3.5, \beta_{m2} = 3.5$, (b) Here, $\beta_{f2} = 4.0, \beta_{m2} = 4.0$. All other parameters as in Table 4.4

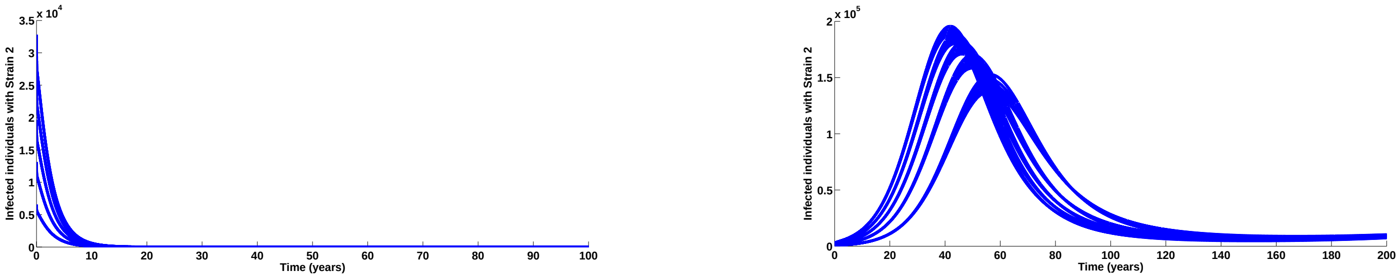
Numerical simulations for the cases $\mathcal{R}_{01} < 1$ and $\mathcal{R}_{01} > 1$, depicted in Figure 4.32, shows that strain 1 dies out when $\mathcal{R}_{01} < 1$ and persists at steady state when $\mathcal{R}_{01} > 1$. Similar conclusions are reached for the cases $\mathcal{R}_{02} < 1$ and $\mathcal{R}_{02} > 1$. Numerical simulations for the case $\mathcal{R}_{01} > 1 > \mathcal{R}_{02}$ ($\mathcal{R}_{02} > 1 > \mathcal{R}_{01}$), depicted in Figure 4.34 show that the strain with the lower reproduction number dies out over time while the strain with the higher reproduction number drives the other to extinction. Thus, the model (3.23) (for the case when vaccination against one strain confers partial cross-immunity against incident and persistent infection with the other strain ($\eta_I \neq 0, \eta_p \neq 0$)) exhibits competitive exclusion. (The two-strain HPV model in Alsaleh and Gumel (2014b) and the two-strain Polio model in Okuonghae et al (2015) also exhibit competitive exclusion).

The effect of the fraction of vaccinated females, f, on the cumulative new cases of strain 1 and strain 2 infections, depicted in Figures 4.30 and 4.31, respectively, show a decrease in the cumulative new cases of strain 1 infection with increasing fraction of vaccinated females, as expected. Also, increasing the fraction of vaccinated females leads to a corresponding decrease in the cumulative new cases of strain 2 infection.



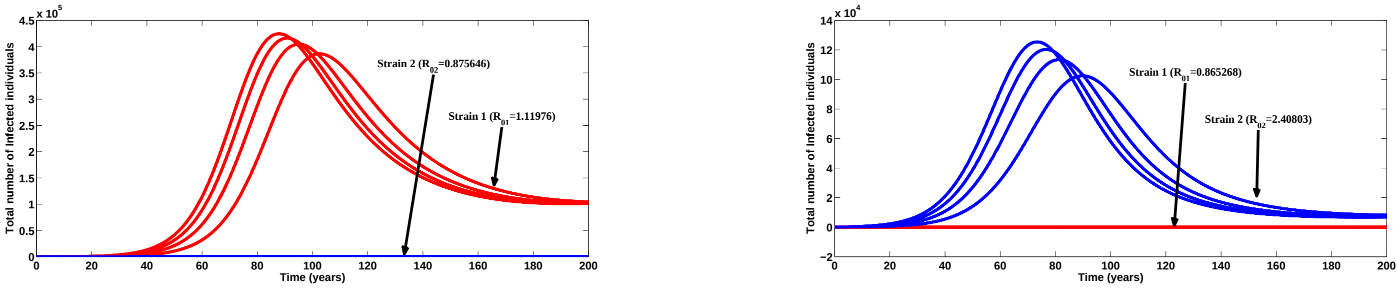
(a) (b)

Figure 4.32: Infected individuals with Strain 1 at different initial conditions. (a) Here, $\beta_{f1} = \beta_{m1} = 1.7$, so that $\mathcal{R}_{01} = 0,865268 < 1$ (b) Here, $\beta_{f1} = \beta_{m1} = 2.1$, so that $\mathcal{R}_{01} = 1.06886 > 1$. All other parameters as in Table 4.4



(a) (b)

Figure 4.33: Infected individuals with Strain 2 at different initial conditions. (a) Here, $\beta_{f2} = \beta_{m2} = 0.8$, so that $\mathcal{R}_{02} = 0.875646 < 1$ (b) Here, $\beta_{f2} = \beta_{m2} = 2.2$, so that $\mathcal{R}_{02} = 2.40803 > 1$. All other parameters as in Table 4.4



(a) (b)

Figure 4.34: Simulations of the model (3.23) showing the total number of infected individuals at different initial conditions. (a) Here, $\beta_{f1} = \beta_{m1} = 2.2$ and $\beta_{f2} = \beta_{m2} = 0.8$ (so that $\mathcal{R}_{01} = 1.11976 > 1 > \mathcal{R}_{02} = 0.875646$). (b) Here, $\beta_{f1} = \beta_{m1} = 1.7$ and $\beta_{f2} = \beta_{m2} = 2.2$ (so that $\mathcal{R}_{01} = 0.865268 < 1 < \mathcal{R}_{02} = 2.40803$). All other parameters as in Table 4.4

4.9 Simulations of the HPV-TB Co-infection model (3.29)

4.9.1 Uncertainty and sensitivity analysis

We carry out a Latin Hypercube Sampling (LHS) on the parameters that appear in the expression for the reproduction numbers, $\mathcal{R}_{0\mathrm{T}}$ and $\mathcal{R}_{0\mathrm{H}}$, respectively (Blower and Dowlatabadi, 1994). For the sensitivity analysis, a Partial Rank Correlation Coefficient (PRCC) was computed between values of the parameters in the response function and the values of the response function derived from the sensitivity analysis. We carried out a total of 1,000 simulations of the model (3.29) *per* LHS run. Using the reproduction numbers $\mathcal{R}_{0\mathrm{T}}$ and $\mathcal{R}_{0\mathrm{H}}$ as response functions, it follows from Tables 4.5 and 4.6, that the top PRCC-ranked parameters with respect to the reproduction number $\mathcal{R}_{0\mathrm{H}}$, are the effective contact rate for HPV transmission from female to male β_{F}, the fraction of females vaccinated against HPV f, condom efficacy for females ϵ_{F}, condom compliance for males c_{M} and the recovery rate from HPV for males in the I_{HM} class, while the only parameter that strongly influences the dynamics of TB in the population is the effective contact rate for TB transmission β_{T}

Parameters	$\mathcal{R}_{0\mathrm{H}}$
β_{M}	**0.8559**
ϵ_{M}	**-0.7243**
ξ_{M}	**0.7957**
c_{M}	**-0.7173**
ϕ_1^{M}	**-0.6407**
β_{F}	**0.5010**
f	**-0.5104**
τ_1^{F}	0.0180
ρ_1^{F}	-0.0152
κ_1^{F}	-0.0220
χ_1^{F}	-0.0202
ϕ_1^{F}	-0.2334
φ_{F}	-0.0094
φ_{M}	0.0179
δ_{HF}	-0.0025
δ_{HM}	-0.0085
δ_{CF}	-0.0097
ω_{P}	0.0076
π_{F}	-0.0810
ϵ_{F}	-0.2816
c_{F}	-0.2577
ξ_{F}	0.2223
μ_{F}	-0.0785
μ_{M}	-0.29657

Table 4.5: Partial rank correlation coefficients (PRCC) values for the parameters of the model that appear in the reproduction number $\mathcal{R}_{0\mathrm{H}}$, using the reproduction number as the response function.

Parameters	$\mathcal{R}_{0\mathrm{T}}$
β_{T}	**0.6534**
ψ_1^{F}	0.2961
ψ_1^{M}	0.3456
$\varepsilon_1^{\mathrm{F}}$	-0.0136
$\varepsilon_1^{\mathrm{M}}$	0.0476
σ_{F}	0.0215
σ_{M}	0.0224
r_1^{F}	-0.3743
r_1^{M}	0.0142
γ_1^{F}	0.1650
γ_1^{M}	0.1851
δ_{FT}	-0.0727
δ_{MT}	-0.0642
μ_{F}	-0.3735
μ_{M}	-0.3395

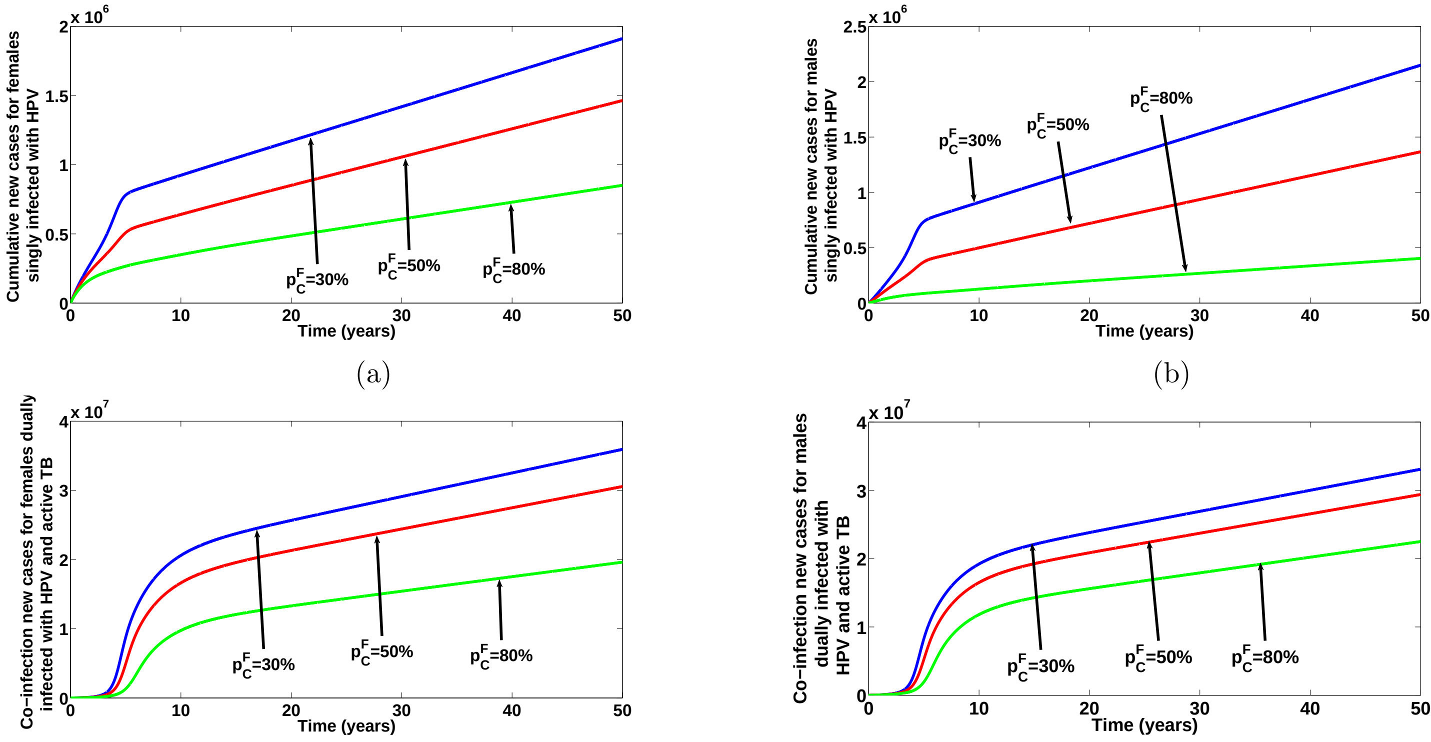
Table 4.6: Partial rank correlation coefficients (PRCC) values for the parameters of the model that appear in the reproduction number $\mathcal{R}_{0\mathrm{T}}$, using the reproduction number as the response functions.

4.9.2 Numerical simulations

We now simulate the model (3.29) numerically using the parameter estimates in Table 4.7 (unless otherwise stated), to assess the potential impact of various targeted control strategies on the transmission dynamics of HPV in the population. Demographic parameters relevant to the Shanxi Province in China were chosen. Specifically, since the total population of sexually active susceptible females and males (15-64 years) in the Shanxi Province of China are estimated to be 12,850,804 and 13,544,652 respectively, at disease free equilibrium, $\frac{\Lambda_F}{\mu_F} = 12,850,804$ and $\frac{\Lambda_M}{\mu_M} = 13,544,652$ (Shanxi Demographics Data (2015),China Demographics Profile, 2018). In China, the life expectancy for females and males are estimated at 78 years and 73.6 years, respectively (China Demographics Profile, 2018). Hence we have that $\mu_F = 0.0128$ and $\mu_M = 0.0136$, so that $\Lambda_F = 164490$ and $\Lambda_M = 184207$ per year. Using the expressions for the basic reproduction numbers, $\mathcal{R}_{0T}$ and $\mathcal{R}_{0H}$, corresponding to TB and HPV respectively, we calculate the threshold condition for the elimination of the two diseases in Shanxi Province, in China. The parameter values used are as given in Table 4.7. We obtain $\mathcal{R}_{0T} = 1.57524$, and $\mathcal{R}_{0H} = 1.62118$, resulting in $\mathcal{R}_0 = max\{\mathcal{R}_{0T}, \mathcal{R}_{0H}\} = 1.62118$. As seen, the HPV reproduction number is higher than the TB reproduction number in Shanxi Province in China. So the basic reproduction number is influenced by the HPV disease burden in the population.

Table 4.7: Baseline values and ranges of the parameters of the model (3.29).

Parameter	value	Range(*per* year)	Reference
μ_{F}	0.0128	[0.0100,0.2000]	China Demographics Profile (2018)
μ_{M}	0.0136	[0.0100,0.2000]	China Demographics Profile (2018)
Λ_{F}	164490	[150000, 200000]	China Demographics Profile (2018)
Λ_{M}	184207	[150000, 200000]	China Demographics Profile (2018)
β_1^{F}	0.5	[0.5,0.6]	Malik *et al.* (2013)
β_1^{M}	0.4	[0.3,0.5]	Malik *et al.* (2013)
c_1^{F}	2.0	[1,5]	Malik *et al.* (2013)
c_{F}	0.2	[0.1,1.0]	Mukandavire *et al.* (2007)
c_{M}	0.4	[0.1,1.0]	Mukandavire *et al.* (2007)
$\epsilon_{\text{F}}(\epsilon_{\text{M}})$	0.92	[0.1, 1.0]	Mukandavire *et al.* (2007)
θ_{T}	1.2	[1.0, 2.0]	Assumed
ω_p	0.9	[0.5, 0.95]	Malik *et al.* (2013)
ω_{T}	0.9	[0.5, 0.95]	Malik *et al.* (2013)
η_p	1.2	[1.0, 2.0]	Assumed
f	0.70	[0.5,0.9]	Levin *et al.* (2015)
β_{T}	2	[1,2]	Assumed
π_{F}	0.9	[0.9,1]	Malik *et al.* (2013)
$\phi_1^{\text{F}}, \phi_2^{\text{F}}(\phi_1^{\text{M}}, \phi_2^{\text{M}})$	0.9	[0.5,1.0]	Malik *et al.* (2013), Myers *et al.* (2000)
$\phi_3^{\text{F}}(\phi_3^{\text{M}})$	0.9	[0.5,1.0]	Malik *et al.* (2013), Myers *et al.* (2000)
$r_1^{\text{F}}, r_2^{\text{F}}, r_3^{\text{F}}, r_4^{\text{F}}$	2.0	[1,2]	Agusto and Adekunle (2014)
$r_1^{\text{M}}, r_2^{\text{M}}$	2.0	[1,2]	Agusto and Adekunle (2014)
κ_1^{F}	0.5	[0.1,1.0]	Malik *et al.* (2013)
$\kappa_2^{\text{F}}, \kappa_3^{\text{F}}$	0.5	[0.1,1.0]	Malik *et al.* (2013)
ρ_1^{F}	114	[110,120]	Alsaleh and Gumel (2014b)
$\rho_2^{\text{F}}, \rho_3^{\text{F}}$	114	[110,120]	Alsaleh and Gumel (2014a)
χ_1^{F}	0.895	[0.5,1.0]	Alsaleh and Gumel (2014a)
$\chi_2^{\text{F}}, \chi_3^{\text{F}}$	0.895	[0.5,1.0]	Alsaleh and Gumel (2014a)
$\varphi_{\text{F}}(\varphi_{\text{M}})$	0.2	[0.1,1.0]	Alsaleh and Gumel (2014a)
τ_1^{F}	0.76	[0.5,1.0]	Elbasha *et al.* (2007), Malik *et al.* (2013)
$\tau_2^{\text{F}}, \tau_3^{\text{F}}$	0.76	[0.5,1.0]	Elbasha *et al.* (2007), Malik *et al.* (2013)
$\delta_{\text{HF}}(\delta_{\text{HM}})$	0.001	[0.0005,0.002]	Malik *et al.* (2013)
δ_{CF}	0.001	[0.0005,0.002]	Malik *et al.* (2013)
$\delta_{\text{FT}}(\delta_{\text{MT}})$	0.365	[0.1,0.5]	Borgdoff (2004), Okuonghae and Omosigho (2011)
$\delta_{\text{HF1}}, \delta_{\text{HF2}}(\delta_{\text{HM1}}, \delta_{\text{HM2}})$	0.001	[0.0005,0.002]	Assumed
$\delta_{\text{FT1}}, \delta_{\text{FT2}}(\delta_{\text{MT1}})$	0.365	[0.1,0.5]	Assumed
$\sigma_{\text{F}}(\sigma_{\text{M}})$	0.2	[0.1,0.5]	Borgdoff (2004), Okuonghae and Omosigho (2011)
$\psi_1^{\text{F}}(\psi_1^{\text{M}})$	0.7	[0.1,1.0]	Sharomi *et al.* (2008)
$\psi_2^{\text{F}}, \psi_3^{\text{F}}, \psi_3^{\text{M}}$	0.7	[0.1,1.0]	Sharomi *et al.* (2008)
$\gamma_1^{\text{F}}(\gamma_1^{\text{M}})$	0.05	[0.005,0.05]	Blower *et al.* (1995), Cohen *et al.* (2007)
$\gamma_2^{\text{M}}, \gamma_2^{\text{F}}, \gamma_3^{\text{F}}, \gamma_4^{\text{F}}$	0.05	[0.005,0.05]	Blower *et al.* (1995), Cohen *et al.* (2007)
$\varepsilon_1^{\text{F}}(\varepsilon_1^{\text{M}})$	1.5	[1.5,3.5]	Okuonghae and Aihie (2008)
$\varepsilon_2^{\text{M}}\varepsilon_2^{\text{F}}, \varepsilon_3^{\text{F}}, \varepsilon_4^{\text{F}}$	1.5	[1.5,3.5]	Okuonghae and Aihie (2008)
$\xi_{\text{F}}(\xi_{\text{M}})$	2	[1,3]	Gorgos and Marrazzo (2011), Nyitray *et al.* (2011)
$\zeta_1^{\text{F}}(\zeta_1^{\text{M}})$	1.3	[1,3]	Inferred from Zhao *et al.* (2011)
$\zeta_2^{\text{F}}(\zeta_2^{\text{M}})$	1.7	[1,3]	Inferred from Zhao *et al.* (2011)
α_{F}	1.3	[1,3]	Inferred from Zetola *et al.* (2015)



(a) (b) (c) (d)

Figure 4.35: Plots of the cumulative new cases for individuals singly infected with HPV (Figures 4.35a and 4.35b) and co-infection new cases for individuals dually infected with HPV and active TB (Figures 4.35c and 4.35d), at different *condom preventability* levels for females, *viz* $p_c^{\text{F}} = 30\%(\mathcal{R}_{0\text{H}} = 1.67771)$, $p_c^{\text{F}} = 50\%(\mathcal{R}_{0\text{H}} = 1.61225)$, $p_c^{\text{F}} = 80\%(\mathcal{R}_{0\text{H}} = 1.53114)$ and $(\mathcal{R}_{0\text{T}} = 9.90526)$. Here, $\beta_{\text{T}} = 2.0$, $\beta_{\text{F}} = \beta_{\text{M}} = 1.0, \xi_{\text{F}} = \xi_{\text{M}} = 2.0, r_1^{\text{F}} = r_2^{\text{F}} = r_3^{\text{F}} = r_4^{\text{F}} = r_1^{\text{M}} = r_2^{\text{M}} = 0$. All other parameters as in Table 4.7

4.9.3 HPV vaccination/Condom use-only strategy

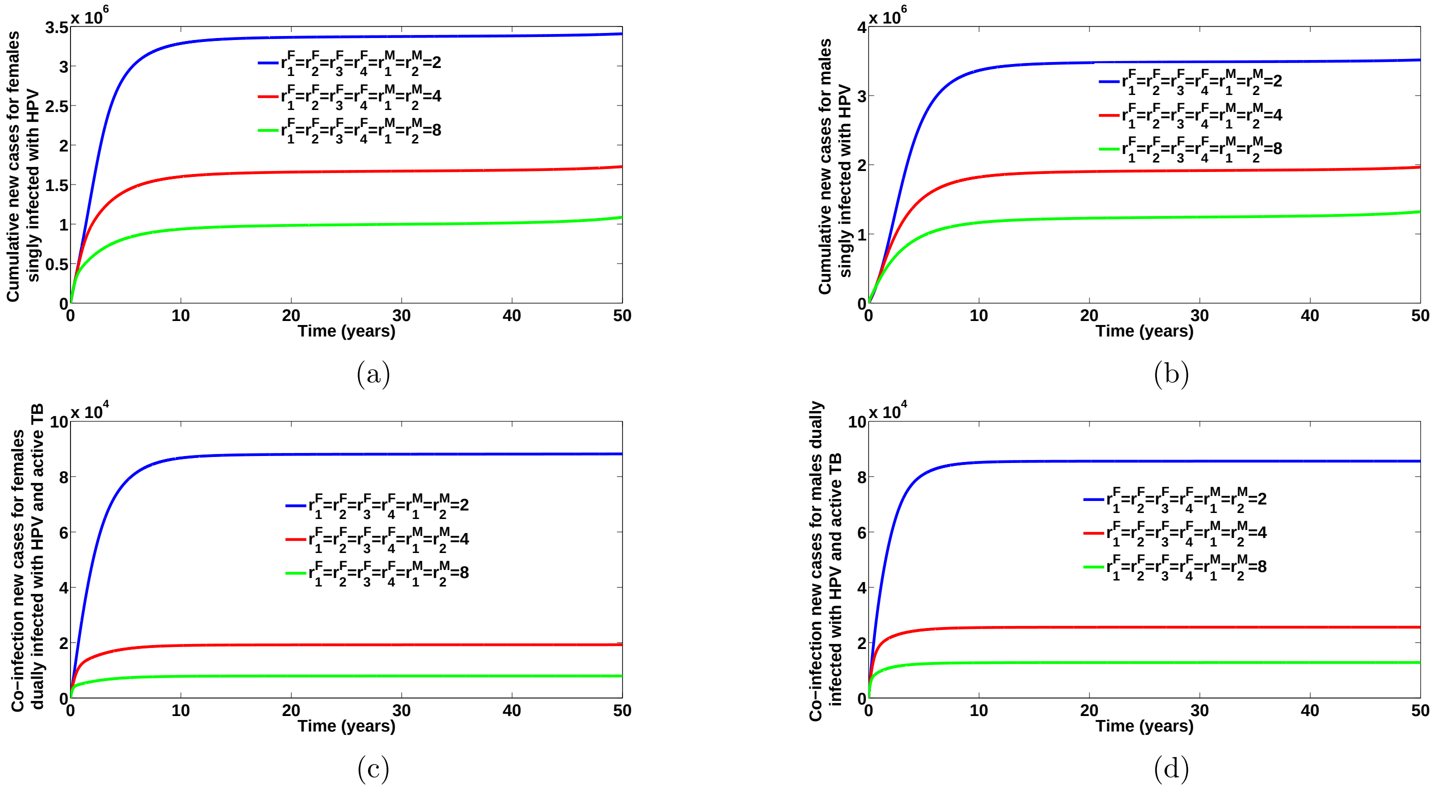
Simulations of the co-infection model (3.29) when HPV vaccination/condom use-only strategy is administered are given in Figures 4.35a-4.35d. The associated basic reproductions are both greater than one, though TB associated basic reproduction number ($\mathcal{R}_{0\text{T}} = 9.90526$) is greater, thereby driving the co-endemicity of the two diseases. The vaccination rate , f and the vaccine efficacy, π_{F}, are at baseline values while the condom preventability level for females is varied from from 30% to 80%. The TB treatment rates for singly and dually infected individuals are set to zero (that is, $r_1^{\text{F}} = r_2^{\text{F}} = r_3^{\text{F}} = r_4^{\text{F}} = r_1^{\text{M}} = r_2^{\text{M}} = 0$). From the figures, it is observed that increasing the condom preventability for sexually active susceptible females leads to a resultant decrease in the number of individuals singly infected with HPV and individuals dually infected with HPV and active TB (even when there is no treatment for the TB infected individuals).

4.9.4 TB treatment-only strategy

Simulations of the co-infection model (3.29) when TB treatment-only strategy is administered are given in Figures 4.36-4.37. The HPV associated basic reproduction number ($\mathcal{R}_{0\mathrm{H}} = 3.2874$) is greater than the TB associated reproduction number, thereby driving the co-endemicity of the two diseases. The vaccination and condom parameters are set to zero ($f = \pi_{\mathrm{F}} = c_{\mathrm{F}} = c_{\mathrm{M}} = \epsilon_{\mathrm{F}} = \epsilon_{\mathrm{M}} = 0$). The TB treatment rates for singly and dually infected individuals are varied (that is, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 2.0(\mathcal{R}_{0\mathrm{T}} = 1.57524)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 4.0(\mathcal{R}_{0\mathrm{T}} = 0.85561)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 8.0(\mathcal{R}_{0\mathrm{T}} = 0.447144)$).

Figure 4.38 depicts the simulations of the cumulative new cases for individuals singly infected with HPV (Figures 4.38a and 4.38b) and co-infection new cases for individuals dually infected with HPV and active TB (Figures 4.38c and 4.38d), at different treatment rates for singly and dually infected individuals with active TB. The simulations of the co-infection new cases for individuals infected with persistent HPV and active TB (Figure 4.40a) and co-infection new cases for individuals dually infected with cervical cancer and active TB, depicted in Figure 4.40b, respectively.

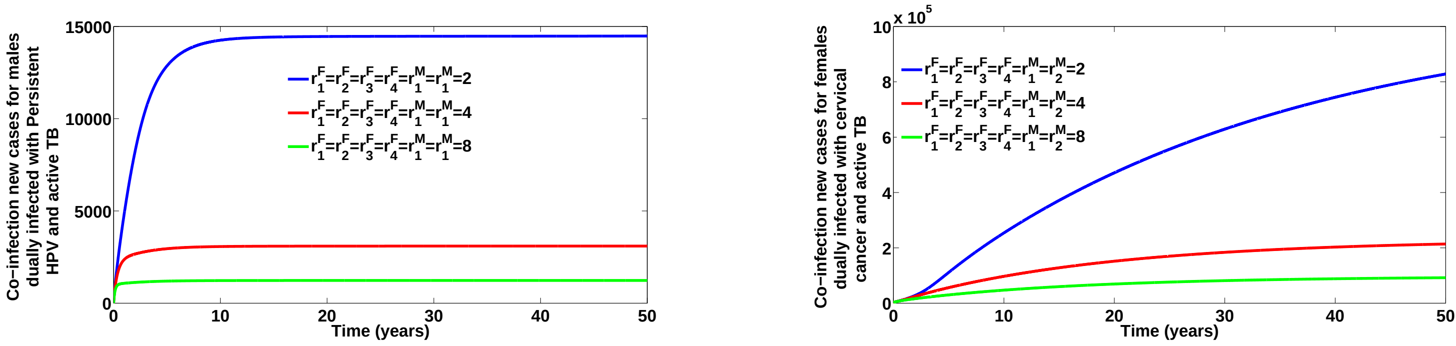
The plots reveal that increasing treatment rates for individuals with active TB cases could bring down the incidence of HPV as well as co-infection new cases of mixed infections among individuals with HPV and TB (even when there is little or no HPV vaccination and condom use by sexually active susceptible individuals). This is consistent with the claim that TB infection is linked with increased susceptibility to infection with oncogenic HPV/cervical cancer [**?**]. Therefore, to reduce susceptibility to Oncogenic HPV/cervical cancer, focus should be on treating TB cases.



(a) (b)

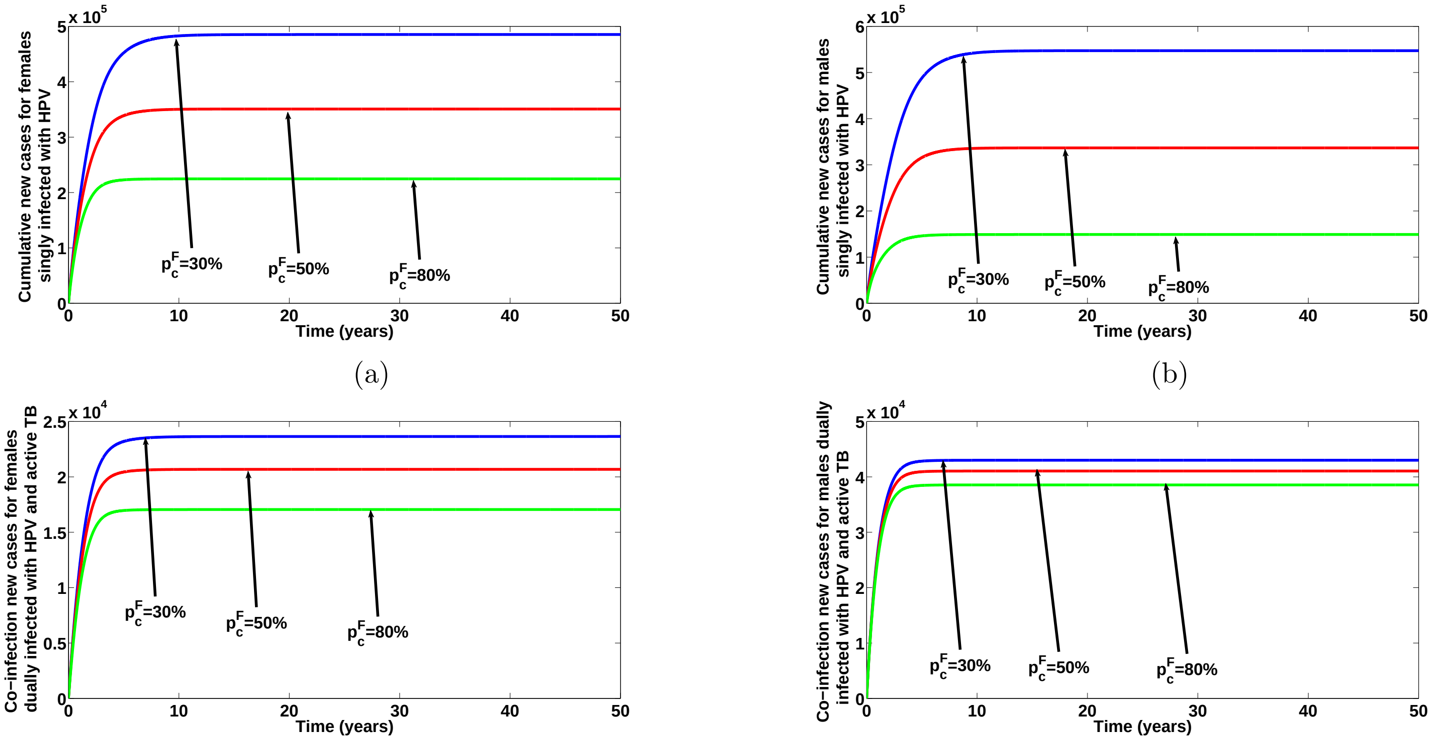
(c) (d)

Figure 4.36: Plots of the cumulative new cases for individuals singly infected with HPV (Figures 4.36a and 4.36b) and co-infection new cases for individuals dually infected with HPV and active TB (Figures 4.36c and 4.36d), at different treatment rates for individuals with active TB, *viz* $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 2.0(\mathcal{R}_{0\mathrm{T}} = 1.57524)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 4.0(\mathcal{R}_{0\mathrm{T}} = 0.85561)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 8.0(\mathcal{R}_{0\mathrm{T}} = 0.447144)$ and $(\mathcal{R}_{0\mathrm{H}} = 3.2874)$. Here, $\beta_{\mathrm{T}} = 2.0$, $\beta_{\mathrm{F}} = \beta_{\mathrm{M}} = 1.0, \xi_{\mathrm{F}} = \xi_{\mathrm{M}} = 2.0, f = \pi_{\mathrm{F}} = c_{\mathrm{F}} = c_{\mathrm{M}} = \epsilon_{\mathrm{F}} = \epsilon_{\mathrm{M}} = 0$. All other parameters as in Table 4.7



(a) (b)

Figure 4.37: Plots of the co-infection new cases for females dually infected with persistent HPV and active TB (Figure 4.37a) and co-infection new cases for females dually infected with cervical cancer and active TB (Figure 4.37b), at different treatment rates for individuals with active TB, *viz* $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 2.0(\mathcal{R}_{0\mathrm{T}} = 1.57524)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 4.0(\mathcal{R}_{0\mathrm{T}} = 0.85561)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 8.0(\mathcal{R}_{0\mathrm{T}} = 0.447144)$ and $(\mathcal{R}_{0\mathrm{H}} = 3.2874)$. Here, $\beta_{\mathrm{T}} = 2.0$, $\beta_{\mathrm{F}} = \beta_{\mathrm{M}} = 1.0, \xi_{\mathrm{F}} = \xi_{\mathrm{M}} = 2.0, f = \pi_{\mathrm{F}} = c_{\mathrm{F}} = c_{\mathrm{M}} = \epsilon_{\mathrm{F}} = \epsilon_{\mathrm{M}} = 0$. All other parameters as in Table 4.7



(a) (b)

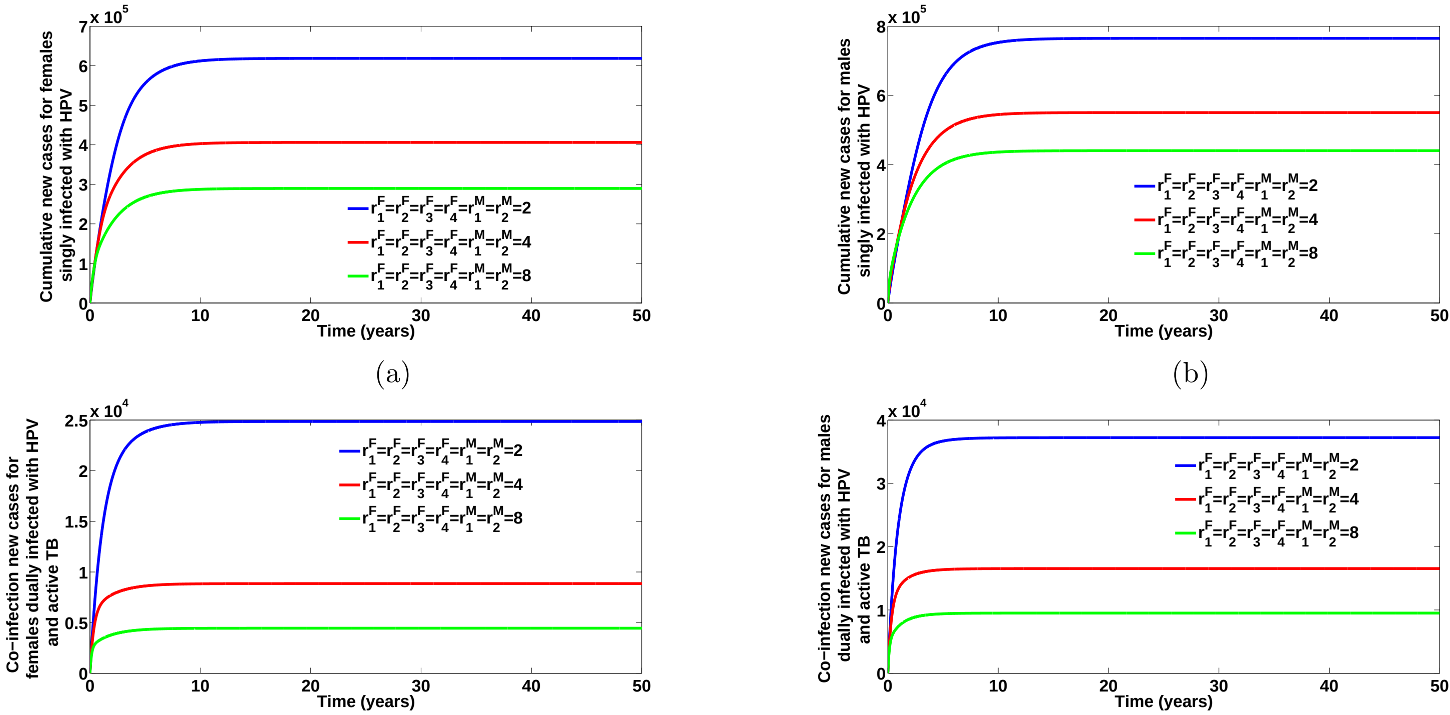
(c) (d)

Figure 4.38: Plots of the cumulative new cases for individuals singly infected with HPV (Figures 4.38a and 4.38b) and co-infection new cases for individuals dually infected with HPV and active TB (Figures 4.38c and 4.38d), at different *condom preventability* levels for females, *viz* $p_c^{\mathrm{F}} = 30\%(\mathcal{R}_{0\mathrm{H}} = 1.67771)$, $p_c^{\mathrm{F}} = 50\%(\mathcal{R}_{0\mathrm{H}} = 1.61225)$, $p_c^{\mathrm{F}} = 80\%(\mathcal{R}_{0\mathrm{H}} = 1.53114)$ and $(\mathcal{R}_{0\mathrm{T}} = 1.57524)$. Here, $\beta_{\mathrm{T}} = 2.0$, $\beta_{\mathrm{F}} = \beta_{\mathrm{M}} = 1.0, \xi_{\mathrm{F}} = \xi_{\mathrm{M}} = 2.0, \epsilon_{\mathrm{F}} = 0.80, \epsilon_{\mathrm{M}} = 0.80$. All other parameters as in Table 4.7

4.9.5 Universal strategy

Simulations of the co-infection model (3.29) when all the control strategies for both HPV and TB are administred are given in Figures 4.38 - 4.41. Figure 4.38 depicts the simulations of the cumulative new cases for individuals singly infected with HPV (Figures 4.38a and 4.38b) and co-infection new cases for individuals dually infected with HPV and active TB (Figures 4.38c and 4.38d), at different condom preventability levels, p_{C}^{F}, (for females). The figure shows that, with increasing condom preventability levels for sexually active susceptible females (from 30% to 80%), there is a decrease in the cumulative new cases for individuals infected with HPV and a corresponding decrease in the co-infection new cases for individuals infected with HPV and active TB.

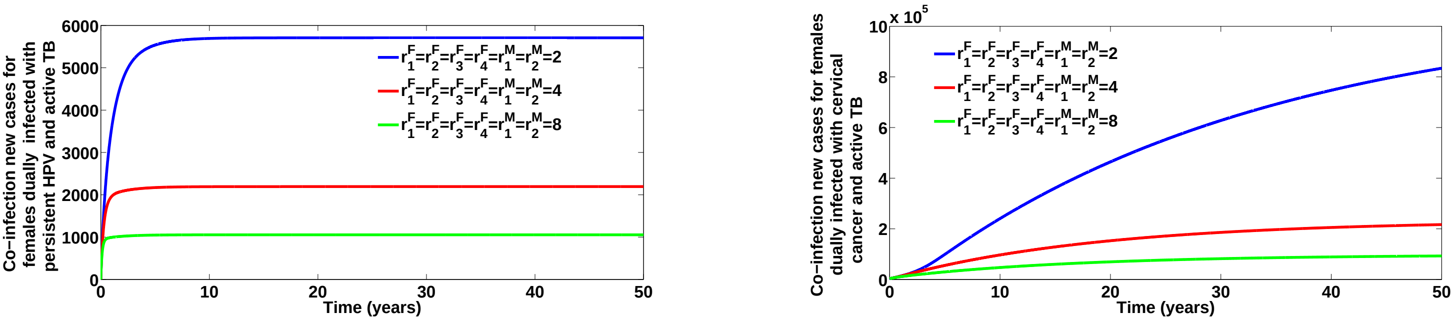
The simulations of the cumulative new cases for individuals infected with HPV (Figures 4.39a and 4.39b) and co-infection new cases for individuals dually infected with HPV and TB, depicted in Figures 4.39c and 4.39d, reveal that increasing treatment rates for individuals with active TB



(a) (b)

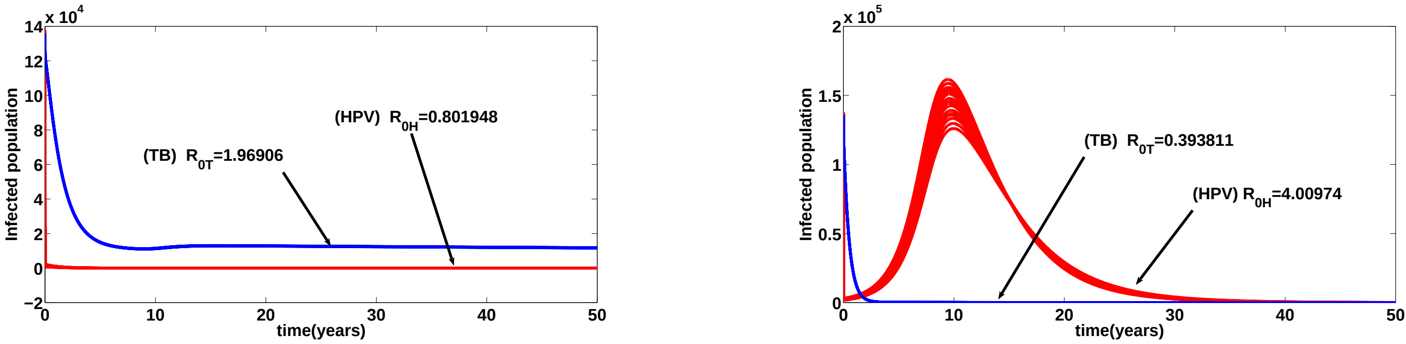
(c) (d)

Figure 4.39: Plots of the cumulative new cases for individuals singly infected with HPV (Figures 4.39a and 4.39b) and co-infection new cases for individuals dually infected with HPV and active TB (Figures 4.39c and 4.39d), at different treatment rates for individuals with active TB, *viz* $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 2.0(\mathcal{R}_{0\mathrm{T}} = 1.57524)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 4.0(\mathcal{R}_{0\mathrm{T}} = 0.85561)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 8.0(\mathcal{R}_{0\mathrm{T}} = 0.447144)$ and $(\mathcal{R}_{0\mathrm{H}} = 1.72942)$. Here, $\beta_{\mathrm{T}} = 2.0$, $\beta_{\mathrm{F}} = \beta_{\mathrm{M}} = 1.0, \xi_{\mathrm{F}} = \xi_{\mathrm{M}} = 2.0, \epsilon_{\mathrm{F}} = 0.80, \epsilon_{\mathrm{M}} = 0.80$. All other parameters as in Table 4.7



(a) (b)

Figure 4.40: Plots of the co-infection new cases for females dually infected with persistent HPV and active TB (Figure 4.40a) and co-infection new cases for females dually infected with cervical cancer and active TB (Figure 4.40b), at different treatment rates for individuals with active TB, *viz* $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 2.0(\mathcal{R}_{0\mathrm{T}} = 1.57524)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 4.0(\mathcal{R}_{0\mathrm{T}} = 0.85561)$, $r_1^{\mathrm{F}} = r_2^{\mathrm{F}} = r_3^{\mathrm{F}} = r_4^{\mathrm{F}} = r_1^{\mathrm{M}} = r_2^{\mathrm{M}} = 8.0(\mathcal{R}_{0\mathrm{T}} = 0.447144)$ and $(\mathcal{R}_{0\mathrm{H}} = 1.72942)$. Here, $\beta_{\mathrm{T}} = 2.0$, $\beta_{\mathrm{F}} = \beta_{\mathrm{M}} = 1.0, \xi_{\mathrm{F}} = \xi_{\mathrm{M}} = 2.0, \epsilon_{\mathrm{F}} = 0.80, \epsilon_{\mathrm{M}} = 0.80$. All other parameters as in Table 4.7



(a) (b)

Figure 4.41: Simulations of the co-infection model (3.29) showing the total number of infected individuals at different initial conditions. (a) Here, $\beta_{\mathrm{T}} = 2.5$, $\beta_{\mathrm{F}} = \beta_{\mathrm{M}} = 0.4, \xi_{\mathrm{F}} = \xi_{\mathrm{M}} = 2.0$ (so that $\mathcal{R}_{0\mathrm{T}} = 1.96906 > 1 > \mathcal{R}_{0\mathrm{H}} = 0.801948$). (b) Here, $\beta_{\mathrm{T}} = 0.5$, $\beta_{\mathrm{F}} = \beta_{\mathrm{M}} = 2.0, \xi_{\mathrm{F}} = \xi_{\mathrm{M}} = 2.0$ (so that $\mathcal{R}_{0\mathrm{H}} = 4.00974 > 1 > \mathcal{R}_{0\mathrm{T}} = 0.393811$). All other parameters as in Table 4.7

cases could bring down the incidence of HPV as well as co-infection new cases of mixed infections among individuals with HPV and TB. This is consistent with the claim that TB infection is linked with increased susceptibility to infection with oncogenic HPV (Zhao *et al.*, 2011). Therefore, to reduce susceptibility to Oncogenic HPV, focus should be on treating TB cases.

The simulations of the co-infection new cases for individuals infected with persistent HPV and active TB (Figure 4.40a) and co-infection new cases for individuals dually infected with cervical cancer and active TB, depicted in Figure 4.40b, respectively, reveal that increasing treatment rates for individuals with active TB cases could bring down the incidence of mixed infections with persistent HPV and active TB and as well decrease the co-infection new cases of mixed infections among individuals with cervical cancer and active TB. As reported in the introduction, Zetola *et al.* (2015) confirmed that prior TB infection is highly prevalent among patients with cervical cancer. Again, Zhao *et al* (2011) pointed out that TB infection is linked with increased susceptibility to infection with oncogenic HPV. Therefore, if we focus on treating TB cases, among individuals with mixed infections, it can lead to significant decrease in the co-infection new cases.

Moreover, simulations of the co-infection model (3.29) at different initial conditions, depicted in Figures 4.41(a) and 4.41(b) show that for the case when $\mathcal{R}_{0\mathrm{T}} > 1 > \mathcal{R}_{0\mathrm{H}}$, TB dominates and drives HPV to extinction. However, for the case when $\mathcal{R}_{0\mathrm{H}} > 1 > \mathcal{R}_{0\mathrm{T}}$, both diseases die out asymptotically over time.

Chapter 5

Conclusion and Recommendations

5.1 Conclusion

A new two-sex deterministic treatment and vaccination model for Human Papilloma Virus (HPV) was designed and qualitatively analyzed. The model (3.19) was shown to have a locally asymptotically stable DFE whenever the associated basic reproduction number ($\mathcal{R}_T$) is less than unity. The model was also shown to undergo the phenomenon of backward bifurcation, where the stable DFE co-exists with one stable endemic equilibrium when the associated reproduction number was less than unity. The analyses showed that the phenomenon of backward bifurcation was caused by the imperfect vaccine as well as the re-infection of individuals who recover from a previous infection. Moreover, analyses of the treatment model showed that the use of treatment could have a positive population-level impact on the dynamics of the disease, depending on a certain epidemiological threshold. Simulations of the study showed that, with the parameter values used, if the vaccine efficacy for males was 75%, then about 40% condom compliance was required by females to eliminate the disease in the population. Also, if condom compliance by males was 70%, then a female vaccine with 45% efficacy was sufficient for effective control of the disease.

Also, a new two-sex vaccination model for the transmission dynamics of two strains of HPV (type-16/18 and type-31/45) was designed and rigorously analyzed. The model (3.23) was shown to have a locally asymptotically stable disease free equilibrium whenever the basic reproduction number ($\mathcal{R}_0$) was less than unity. The model was also shown to undergo the phenomenon of backward bifurcation, where the stable disease free equilibrium co-exists with one stable endemic equilibrium when the associated reproduction number was less than unity. The analyses showed that the phenomenon of backward bifurcation was caused by the imperfect vaccine as well as the re-infection of individuals who recovered from a previous infection with the same strain. Furthermore, the existence and stability of the boundary equilibrium of the the strain 1-only sub-model was investigated. It was shown rigorously that the strain 1-only sub-model undergoes backward bifurcation in the due to re-infection of recovered individuals and the presence of an imperfect vaccine. In the absence of re-infection of recovered individuals and imperfect vaccine for females, the DFE of the strain 1-only sub-model was shown to be globally asymptotically stable when the associated reproduction number was less than one. Moreover, numerical simulations of the model that the bivalent *Cervarix* vaccine offered high protection not only against the most prevalent HPV types -16 and -18, but also against other oncogenic types like HPV-31 and -45.

Finally, a new sex-structured co-infection model for the transmission dynamics of HPV and TB in a population was developed and analyzed to assess the impact of the spread of each disease on the general transmission dynamics. The HPV-only sub-model (with heterosexual transmission route only) was shown to undergo the phenomenon of backward bifurcation when the associated reproduction number of the HPV-only sub-model (denoted by $\mathcal{R}_{0\text{H}}|_{\xi_\text{F}=\xi_\text{M}=0}$) was less than unity. The global asymptotic stability of the infection free and endemic equilibria of the HPV-only sub-model (with heterosexual transmission route only) was proved using the method of Lyapunov functions. Uncertainty and sensitivity analyses of the full model, using data relevant to the dynamics of the two diseases in Shanxi Province in rural China, showed that the top ranked parameters that drive the HPV infection (with respect to the associated response function, $\mathcal{R}_{0\text{H}}$) were the effective contact rate for HPV transmission from males to females, β_M, condom efficacy for males, ϵ_M, condom compliance rate for males, c_M, homosexual contact rate between males, ξ_M, the HPV recovery rate for males, ϕ_M , the effective contact rate for HPV transmission from females to males, β_F and the fraction of females vaccinated against HPV, f. In addition, the top ranked parameter that affect TB dynamics (with respect to the response function $\mathcal{R}_{0\text{T}}$) was the TB transmission rate β_T. In addition, simulations of the HPV-TB model reveal that increasing treatment rates for individuals with active TB in the singly and dually infected stages could bring down the burden of HPV (when the infection was caused by dually infected individuals), and increasing the condom preventability for females could significantly lead to reduction in the cumulative new TB cases (when the infection was caused by dually infected individuals).

5.2 Recommendations

Based on the results from the study, we make the following recommendations:

i. Proper condom usage and compliance by sexually active individuals should be encouraged, especially in middle-income and low-income countries, where the government may not be able to afford the cost of National HPV vaccination programme, as means of eliminating the disease.

ii. For effective control and prevention of oncogenic HPV types and cervical cancer, this study recommends wide vaccination of susceptible females with the bivalent *Cervarix* vaccine, especially in a population where HPV type-16/18 and type-31 and -45 are co-circulating.

iii. We recommend proper and adequate treatment for individuals infected with Tuberculosis (TB), as a means of bringing down the burden of Human papilloma virus (HPV) as well as burden of the co-infection of HPV and TB in a population where the two diseases are endemic.

   The models in this dissertation can be extended in numerous ways:

   i incorporating the effect of co-infection with other sexually transmitted infections like Chlamydia Trachomatis, Syphilis, and so on.

   ii carrying out optimal control analysis of the developed models

   iii proving the global stabilities of the infection free and endemic equilibria for the full models (instead of considering special cases)

5.3 Contributions to knowledge

The contributions of the first model (3.19) are as follows: incorporating the use of condom by both sexually active susceptible females and males; including compartments for infected females and males treated of HPV symptoms and allowing for disease transmission by individuals treated of HPV symptoms and including HPV induced mortality for individuals in the $A_f(A_m)$, $I_f(I_m)$ and $T_f(T_m)$ classes for females(males). Numerical simulations of the model (3.19) showed that, with the parameter values used, if the vaccine efficacy for a vaccine administered to males is 75%, then about 40% condom compliance is required by females to eliminate the disease in the population, where condom compliance by males is 40%. Also, if condom compliance by males is 70%, then a female vaccine with 45% efficacy is sufficient for effective control of the disease, if 20% of females use condoms.

Also, some of the new features of the second model (3.23) include: incorporating the dynamics of cross-immunity due to vaccination ($\eta_I \neq 0$, $\eta_p \neq 0$); allowing for heterogeneity in infectiousness of vaccinated and unvaccinated females with strain 2 (HPV type-31/45) and including compartments for females (males) who recover from one strain and are infected with the other strain, $I_{fij}(I_{mij}), \quad i \neq j$, for females (males), and allowing for disease transmission by individuals who recover from one strain and are infected with the other strain. Moreover, numerical simulations of the second model (3.23) showed that increasing the fraction of females vaccinated against a particular strain could significantly bring down the burden of the strain not included in the vaccine.

Finally, some of the novelties of the third model (3.29) are as follows: incorporating the dynamics of co-infection of HPV with tuberculosis; including the dynamics of homogeneous transmission of HPV ($\xi_{\text{F}} \neq 0, \xi_{\text{M}} \neq 0$) and including a modification parameters accounting for the increased infectiousness of dually infected individuals; allowing for increased susceptibility to HPV by TB infected individuals ($\zeta_1^{\text{F}} \neq 0, \zeta_1^{\text{M}} \neq 0, \zeta_2^{\text{F}} \neq 0, \zeta_2^{\text{M}} \neq 0$). In addition, simulations of the HPV-TB model reveal that increasing treatment rates for individuals with active TB in the singly and dually infected stages could bring down the burden of HPV and the co-infection new cases and increasing the condom preventability for females could significantly lead to reduction in the cumulative co-infection new cases of the two diseases in a population.

5.4 Publications from the Dissertation

Publications from the dissertation include Omame *et al* (2018), Omame *et al* (2020a) and Omame *et al.* (2020b).

Appendix A: Coefficients of the polynomial (4.14)

$$s_1 = d_{33}g_{03}^2 + d_{03}d_{22}g_{03}g_{33} + d_{00}g_{33}^2 + d_{11}g_{03}g_{33}^2 > 0$$

$$\begin{aligned} s_2 = {} & 3d_{33}g_{02}g_{03}^2 + 2d_{22}g_{02}g_{03}g_{33} + d_{22}g_{03}^2g_{33} + 2d_{11}g_{03}g_{22}g_{33} + d_{11}g_{02}g_{33}^2 + 3d_{00}g_{22}g_{33}^2 - d_{03}g_{03}^3 - d_{02}g_{03}^2g_{33} \\ & - d_{01}g_{03}g_{33}^2 \end{aligned}$$

$$\begin{aligned} s_3 = {} & 3d_{33}g_{02}^2g_{03} + 3d_{33}g_{01}g_{03}^3 + d_{22}g_{02}^2g_{33} + 2d_{22}g_{01}g_{03}g_{33} + 2d_{22}g_{02}g_{03}g_{22} + d_{22}g_{03}^2g_{22} + d_{11}g_{03}g_{22}^2 \\ & + 2d_{11}g_{03}g_{11}g_{33} + 2d_{11}g_{02}g_{22}g_{33} + d_{11}g_{01}g_{33}^2 + 3d_{00}g_{22}^2g_{33} + 3d_{00}g_{11}g_{33}^2 - 3d_{03}g_{02}g_{03}^2 - 2d_{02}g_{02}g_{03}g_{33} \\ & - d_{02}g_{03}^2g_{22} - 2d_{01}g_{03}g_{22}g_{33} - d_{01}g_{02}g_{33}^2 \end{aligned}$$

$$\begin{aligned} s_4 = {} & d_{33}g_{02}^2 + 6d_{33}g_{01}g_{02}g_{03} + 2d_{22}g_{01}g_{02}g_{33} + d_{22}g_{02}^2g_{22} + 2d_{22}g_{01}g_{03}g_{22} + 2d_{22}g_{02}g_{03}g_{11} + d_{22}g_{03}^2g_{11} \\ & + 2d_{11}g_{01}g_{22}g_{33} + d_{00}g_{22}^2 + 6d_{00}g_{11}g_{22}g_{33} - 3d_{03}g_{02}^2g_{03} - 3d_{03}g_{01}g_{03} - d_{02}g_{02}^2g_{33} - 2d_{02}g_{01}g_{03}g_{33} \\ & - 2d_{02}g_{02}g_{03}g_{22} - d_{02}g_{03}^2g_{11} - d_{01}g_{03}g_{22}^2 - 2d_{01}g_{03}g_{11}g_{33} - 2d_{01}g_{02}g_{22}g_{33} + d_{00}g_{00}g_{33}^2(3 - \mathcal{R}_T^2) \end{aligned}$$

$$\begin{aligned} s_5 = {} & 3d_{33}g_{01}g_{02}^2 + 3d_{33}g_{01}^2g_{03} + d_{22}g_{01}^2g_{33} + 2d_{22}g_{01}g_{02}g_{22} + d_{22}g_{02}^2g_{11} + 2d_{22}g_{01}g_{03}g_{11} + 2d_{22}g_{02}g_{03}g_{00} \\ & + d_{22}g_{00}g_{03}^2 + d_{11}g_{03}g_{11}^2 + 2d_{11}g_{00}g_{03}g_{22} + 2d_{11}g_{02}g_{11}g_{22} + 2d_{11}g_{00}g_{02}g_{33} + d_{11}g_{01}g_{22}^2 + 2d_{11}g_{01}g_{11}g_{33} \\ & + 3d_{00}g_{11}g_{22}^2 + 3d_{00}g_{11}^2g_{33} - d_{03}g_{02}^3 - 6d_{03}g_{01}g_{02}g_{03} - 2d_{02}g_{01}g_{02}g_{33} - d_{02}g_{02}^2g_{22} - 2d_{02}g_{01}g_{03}g_{22} \\ & - 2d_{02}g_{02}g_{03}g_{11} - d_{02}g_{03}^2g_{00} - 2d_{01}g_{03}g_{11}g_{22} - 2d_{01}g_{03}g_{00}g_{33} - d_{01}g_{02}g_{22}^2 - 2d_{01}g_{02}g_{11}g_{33} \\ & + 2d_{00}g_{00}g_{22}g_{33}(3 - \mathcal{R}_T^2) \end{aligned}$$

$$\begin{aligned} s_6 = {} & 3d_{33}g_{01}^2g_{02} + d_{22}g_{01}^2g_{22} + 2d_{22}g_{01}g_{02}g_{11} + d_{22}g_{02}^2g_{00} + 2d_{22}g_{01}g_{00}g_{03} + 2d_{11}g_{00}g_{03}g_{11} + d_{11}g_{02}g_{11}^2 \\ & + 2d_{11}g_{02}g_{00}g_{22} + 2d_{11}g_{01}g_{11}g_{22} + 2d_{11}g_{01}g_{00}g_{33} + 3d_{00}g_{11}^2g_{22} - 3d_{03}g_{01}g_{02}^2 - 3d_{03}g_{01}^2g_{03} - d_{02}g_{01}^2g_{33} \\ & - 2d_{02}g_{01}g_{02}g_{22} - d_{02}g_{02}^2g_{11} - 2d_{02}g_{01}g_{03}g_{11} - 2d_{02}g_{02}g_{00}g_{03} - d_{01}g_{03}g_{11}^2 - 2d_{01}g_{00}g_{03}g_{22} \\ & - 2d_{01}g_{02}g_{11}g_{22} - 2d_{01}g_{00}g_{02}g_{33} + d_{00}g_{00}g_{22}^2(3 - \mathcal{R}_T^2) + 2d_{00}g_{00}g_{11}g_{33}(3 - \mathcal{R}_T^2) \end{aligned}$$

$$\begin{aligned} s_7 = {} & d_{33}g_{01}^3 + d_{22}g_{01}^2g_{11} + 2d_{22}g_{00}g_{01}g_{02} + d_{11}g_{00}^2g_{03} + 2d_{11}g_{02}g_{00}g_{11} + d_{11}g_{01}g_{11}^2 + 2d_{11}g_{00}g_{01}g_{22} + d_{00}g_{11}^3 \\ & - 3d_{03}g_{01}^2g_{02} - d_{02}g_{01}^2g_{22} - 2d_{02}g_{01}g_{02}g_{11} - d_{02}g_{02}^2g_{00} - 2d_{02}g_{01}g_{03}g_{00} - 2d_{01}g_{03}g_{00}g_{11} - d_{01}g_{02}g_{11}^2 \\ & - 2d_{01}g_{02}g_{00}g_{22} + 2d_{00}g_{00}g_{11}g_{22}(3 - \mathcal{R}_T^2) + d_{00}g_{00}^2g_{33}(3 - 2\mathcal{R}_T^2) \end{aligned}$$

$$\begin{aligned} s_8 = {} & d_{22}g_{01}^2g_{00} + d_{11}g_{02}g_{00}^2 + 2d_{11}g_{01}g_{00}g_{11} + d_{00}g_{00}g_{11}^2(3 - \mathcal{R}_T^2) + d_{00}g_{00}^2g_{22}(3 - 2\mathcal{R}_T^2) - d_{03}g_{01}^3 - d_{02}g_{01}^2g_{11} \\ & - 2d_{02}g_{01}g_{00}g_{02} - d_{01}g_{00}^2g_{03} - 2d_{01}g_{00}g_{02}g_{11} \end{aligned}$$

$$s_9 = d_{11}g_{01}g_{00}^2 + d_{00}g_{00}^2g_{11}(3 - 2\mathcal{R}_T^2) - d_{02}g_{01}^2g_{00} - d_{01}g_{00}^2g_{02}$$

$$s_{10} = d_{00}g_{00}^3(1 - \mathcal{R}_T^2)$$

$$
\begin{aligned}
d_{03} &= \beta_f(1-c_f\epsilon_f)\gamma_f M_3M_4\kappa_f\Lambda_f\mu_f\bigl[\gamma_f M_3M_4 + M_3\theta_{f1}(M_2M_4 - H_2\tau_f) + \gamma_f M_4H_3\theta_{f2} \\
&\quad + \gamma_f M_3\xi_f\theta_{f1}\tau_f\bigr] \\
d_{02} &= \beta_f(1-c_f\epsilon_f)\mu_f\bigl[\gamma_f M_3M_4 + M_3\theta_{f1}(M_2M_4 - H_2\tau_f) + \gamma_f M_4H_3\theta_{f2} \\
&\quad + \gamma_f M_3\xi_f\theta_{f1}\tau_f\bigr]\bigl[\gamma_f M_3M_4\kappa_f(1-f\pi_f)\Lambda_f\mu_f + \gamma_f M_3M_4\Lambda_f\mu_f(1-\pi_f)\bigr] \\
d_{01} &= \beta_f(1-c_f\epsilon_f)\gamma_f M_3M_4\Lambda_f\mu_f^3(1-f\pi_f)\bigl[\gamma_f M_3M_4 + M_3\theta_{f1}(M_2M_4 - H_2\tau_f) \\
&\quad + \gamma_f M_4H_3\theta_{f2} + \gamma_f M_3\xi_f\theta_{f1}\tau_f\bigr] \\
d_{33} &= \Lambda_f\gamma_f\kappa_f M_3M_4(1-\pi_f)\bigl[M_1M_3(M_2M_4 - H_2\tau_f) - (M_3H_{12} + H_3H_{10})\gamma_f M_4 \\
&\quad - M_3H_1\gamma_f\tau_f\bigr] \\
d_{22} &= \Lambda_f\gamma_f M_3M_4\Biggl[\mu_f(1-\pi_f)M_3\bigl[M_1(M_2M_4 - H_2\tau_f) - H_1\gamma_f\tau_f\bigr] \\
&\quad + (2-\pi_f)\mu_f\kappa_f\bigl[M_1M_3(M_2M_4 - H_2\tau_f) - (M_3H_{12} + H_3H_{10})\gamma_f M_4 - M_3H_1\gamma_f\tau_f\bigr]\Biggr] \\
d_{11} &= \Lambda_f\gamma_f M_3M_4\Biggl[(2-\pi_f)\mu_f^2M_3\bigl[M_1(M_2M_4 - H_2\tau_f) - H_1\gamma_f\tau_f\bigr] + \mu_f^2\kappa_f\bigl[M_1M_3(M_2M_4 \\
&\quad - H_2\tau_f) - (M_3H_{12} + H_3H_{10})\gamma_f M_4 - M_3H_1\gamma_f\tau_f\bigr]\Biggr] \\
d_{00} &= \Lambda_f\gamma_f M_3^2M_4\mu_f^3\bigl[M_1(M_2M_4 - H_2\tau_f) - H_1\gamma_f\tau_f\bigr]
\end{aligned}
$$

$$
\begin{aligned}
g_{03} &= \beta_m(1-c_m\epsilon_m)\gamma_m M_9 M_{10}\kappa_m\Lambda_m\mu_m\big[\gamma_m M_9 M_{10} + M_9\theta_{m1}(M_8 M_{10} - H_7\tau_m) + \gamma_m M_{10} H_8\theta_{m2} \\
&\qquad + \gamma_m M_9\xi_m\theta_{m1}\tau_m\big] \\
g_{02} &= \beta_m(1-c_m\epsilon_m)\mu_m\big[\gamma_m M_9 M_{10} + M_9\theta_{m1}(M_8 M_{10} - H_7\tau_m) + \gamma_m M_{10} H_8\theta_{m2} \\
&\qquad + \gamma_m M_9\xi_m\theta_{m1}\tau_m\big]\big[\gamma_m M_9 M_{10}\kappa_m(1-m\pi_m)\Lambda_m\mu_m + \gamma_m M_9 M_{10}\Lambda_m\mu_m(1-\pi_m)\big] \\
g_{01} &= \beta_m(1-c_m\epsilon_m)\gamma_m M_9 M_{10}\Lambda_m\mu_m^3(1-m\pi_m)\big[\gamma_m M_9 M_{10} + M_9\theta_{m1}(M_8 M_{10} - H_7\tau_m) \\
&\qquad + \gamma_m M_{10} H_8\theta_{m2} + \gamma_m M_9\xi_m\theta_{m1}\tau_m\big] \\
g_{33} &= \Lambda_m\gamma_m\kappa_m M_9 M_{10}(1-\pi_m)\big[M_7 M_9(M_8 M_{10} - H_7\tau_m) - (M_9 H_{13} + H_8 H_{11})\gamma_m M_{10} \\
&\qquad - M_9 H_6\gamma_m\tau_m\big] \\
g_{22} &= \Lambda_m\gamma_m M_9 M_{10}\Big[\mu_m(1-\pi_m)M_9\big[M_7(M_8 M_{10} - H_7\tau_m) - H_6\gamma_m\tau_m\big] \\
&\qquad + (2-\pi_m)\mu_m\kappa_m\big[M_7 M_9(M_8 M_{10} - H_7\tau_m) - (M_9 H_{13} + H_8 H_{11})\gamma_m M_{10} - M_9 H_6\gamma_m\tau_m\big]\Big] \\
g_{11} &= \Lambda_m\gamma_m M_9 M_{10}\Big[(2-\pi_m)\mu_m^2 M_9\big[M_7(M_8 M_{10} - H_7\tau_m) - H_6\gamma_m\tau_m\big] + \mu_m^2\kappa_m\big[M_7 M_9(M_8 M_{10} \\
&\qquad - H_7\tau_m) - (M_9 H_{13} + H_8 H_{11})\gamma_m M_{10} - M_9 H_6\gamma_m\tau_m\big]\Big] \\
g_{00} &= \Lambda_m\gamma_m M_9^2 M_{10}\mu_m^3\big[M_7(M_8 M_{10} - H_7\tau_m) - H_6\gamma_m\tau_m\big]
\end{aligned}
$$

$$
\begin{aligned}
M_2 M_4 - H_2\tau_f &= (\phi_f + \delta_f + \mu_f)(\sigma_f\delta_f + \varepsilon_f + \mu_f) + \tau_f(\sigma_f\delta_f + \mu_f) + (1-\eta_f)\varepsilon_f\tau_f > 0 \\
M_7 M_8 - H_7\tau_m &= (\phi_m + \delta_m + \mu_m)(\sigma_m\delta_m + \varepsilon_m + \mu_m) + \tau_m(\sigma_m\delta_m + \mu_m) + (1-\eta_m)\varepsilon_m\tau_m > 0
\end{aligned}
$$

$$
\begin{aligned}
&M_1(M_2 M_4 - H_2\tau_f) - H_1\gamma_f\tau_f = (\alpha_f + \mu_f)\,[\,(\gamma_f + \mu_f)((\phi_f + \delta_f)(\sigma_f\delta_f + \varepsilon_f + \mu_f) \\
&+ \mu_f(\sigma_f\delta_f + \varepsilon_f + \mu_f) + \tau_f(\sigma_f\delta_f + \mu_f)) + (1-\eta_f)\mu_f\varepsilon_f\tau_f\,] > 0 \\
&M_7(M_8 M_{10} - H_7\tau_m) - H_6\gamma_m\tau_m = (\alpha_m + \mu_m)\,[\,(\gamma_m + \mu_m)((\phi_m + \delta_m)(\sigma_m\delta_m + \varepsilon_m + \mu_m) \\
&+ \mu_m(\sigma_m\delta_m + \varepsilon_m + \mu_m) + \tau_m(\sigma_m\delta_m + \mu_m)) + (1-\eta_m)\mu_m\varepsilon_m\tau_m\,] > 0
\end{aligned}
$$

$$
\begin{aligned}
&[M_1 M_3(M_2 M_4 - H_2\tau_f) - (M_3 H_{12} + H_3 H_{10})\gamma_f M_4 - H_1 M_3\gamma_f\tau_f] \\
&= [\alpha_f\phi_f\gamma_f\varphi_f(1-\psi_f)(\sigma_f\delta_f + \xi_f + \mu_f) + (1-\eta_f)(\alpha_f + \mu_f)\tau_f\xi_f\mu_f + \gamma_f\phi_f\varphi_f\mu_f(\sigma_f\delta_f + \xi_f + \mu_f) \\
&+ \gamma_f(\alpha_f + \mu_f)(\delta_f + \mu_f)(\sigma_f\delta_f + \xi_f + \mu_f) + \mu_f(\alpha_f + \mu_f)(\phi_f + \delta_f + \mu_f)(\sigma_f\delta_f + \xi_f + \mu_f) \\
&+ \tau_f(\gamma_f + \mu_f)(\alpha_f + \mu_f)(\sigma_f\delta_f + \mu_f)] > 0
\end{aligned}
$$

$$[M_7M_9(M_8M_{10} - H_7\tau_m) - (M_9H_{13} + H_8H_{11})\gamma_m M_{10} - H_6M_9\gamma_m\tau_m]$$

$$= [\alpha_m\phi_m\gamma_m\varphi_m(1-\psi_m)(\sigma_m\delta_m + \xi_m + \mu_m) + (1-\eta_m)(\alpha_m + \mu_m)\tau_m\xi_m\mu_m + \gamma_m\phi_m\varphi_m\mu_m(\sigma_m\delta_m$$

$$+ \xi_m + \mu_m) + \gamma_m(\alpha_m + \mu_m)(\delta_m + \mu_m)(\sigma_m\delta_m + \xi_m + \mu_m) + \mu_m(\alpha_m + \mu_m)(\phi_m + \delta_m + \mu_m)(\sigma_m\delta_m$$

$$+ \xi_m + \mu_m) + \tau_m(\gamma_m + \mu_m)(\alpha_m + \mu_m)(\sigma_m\delta_m + \mu_m)] > 0$$

where,

$H_{12} = \phi_f\psi_f$, $H_{13} = \phi_m\psi_m$.

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