A MATHEMATICAL INVESTIGATION OF THE EFFECTS OF SEXUAL ORIENTATION AND HIV STATUS ON HPV TRANSMISSION AND VACCINATION

By

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Submitted in fulfilment of the requirements for
the degree of Master of Science in Applied Mathematics at the
Nelson Mandela Metropolitan University

2013

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Declaration

In accordance with NMMU Rule G4.6.3, I hereby declare that the dissertation is my own work and that it has not previously been submitted for assessment to another University or for another qualification.

Abstract

The effect of the inclusion of sexual behaviour, particularly three sexual orientation classes, on the transmission dynamics of HPV and cervical cancer incidence was investigated. A comprehensive literature review of mathematical models of HPV transmission and the natural history of cervical cancer was concluded. A mathematical model using ordinary differential equations was developed, which incorporated the three sexual orientation classes, and a sexual mixing algorithm for modelling the transmission dynamics. Reproduction numbers, determined through a simplified version of the developed model, indicated that the bisexual population could form a bridge between the heterosexual and homosexual population. The level of interaction is determined by the selection preferences of a bisexual individual to form a partnership with an individual of the same or opposite sex. The model was simulated, with parameters based on a South African population and HPV type 16/18, to investigate the effects of HIV status, sexual orientation and various vaccination strategies on HPV transmission and cervical cancer incidence. The results indicated that HIV status is a significant factor when determining cervical cancer incidence. The results regarding vaccination strategies agreed with results from the literature review with a two sex before sexual debut and catch up program the most effective, noting that with increased vaccination coverage of females the marginal impact on cervical cancer incidence of this approach diminished.

HPV, vaccination, cervical cancer, mathematical model

Acknowledgments

I would like to thank the people and organisations who have helped and supported me in the writing of this research project.

Firstly I would like to thank NMMU for the Postgraduate Research Bursary which funded my studies.

Secondly I would like to express my appreciation to my supervisor's J.W.Gonsalves and J.Y.T Mugisha for their patience and support. In particular I would like to express my appreciation to J.W.Gonsalves for his continued guidance and encouragement towards my studies.

Thirdly I would like to acknowledge the staff and fellow students of the Mathematics and Applied Mathematics department of NMMU for their continued reassurance.

And finally a thank you to my family and friends, who have been a significant, patient and indispensable source of support.

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Abbreviations

ABBREVIATION	MEANING
AIDS	acquired immunodeficiency syndrome
ART	Active Antiretroviral Therapy
ASSA	Actuarial Society of South Africa
CC	Cervical cancer
CIN	Cervical intraepithelial neoplasia
DFE	Disease Free Equilibrium
DNA	Deoxyribonucleic acid
DVI	Direct Visual Inspection
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique , The International Federation of Gynaecology and Obstetrics
EE	Endemic Equilibrium
HAART	Highly Active Antiretroviral Therapy
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HRHPV	high risk HPV
HSIL	high grade squamous epithelial lesions
ICER	incremental cost effectiveness ratio
LRHPV	low risk HPV
LSIL	low grade squamous epithelial lesions
ODE	Ordinary Differential Equation
PDE	Partial Differential Equation
QALY	Quality of Life Year
SIR	Susceptible-Infective-Recovered
YL	Year Life
YLS	Years of Life Saved

1 Introduction

Human papillomavirus (HPV) is one of the most sexually transmitted infections worldwide. The lifetime risk of a sexually active female being infected with a type of HPV is about 70% [1]. The number of females harbouring HPV DNA worldwide is estimated to be 291 million [2].

Over 100 genotypes of HPV exist, 40 types infect the anogential tract and approximately 18 of these are oncogenic, known as high risk types (hrHPV) [3]–[5]. Most infections are transient, with more than 90% of detected infections are cleared within 2 years [6]. However HPV DNA has been detected in 99.7% of all cervical cancers [7], [8] and persistent HPV infection has been implicated as the cause of squamous intraepithelial lesions and cervical cancer.

Cervical cancer has a devastating impact on women worldwide, with an estimated 530 000 new cases and 274883 deaths in 2008 [9]. Approximately 85% of these cases occur in developing countries. In South Africa an estimated 6000 new cases [10] and 3027 deaths occur annually [4].

Two prophylactic vaccines are commercially available: Ceravix, a bivalent vaccine for HPV types 16 and 18. Gardasil, a quadrilateral vaccine for HPV types 6, 11, 16 and 18 [3], [6], [9]. Infections with HPV type 16 and 18 account for up to 70% of all cervical cancers diagnosed each year [3], with 105 million women worldwide are estimated to have an HPV 16 or 18 infections. HPV types 6 and 11 are associated with 90% of cases of genital warts [5].

Mathematical models of the transmission dynamics of infectious disease provide a framework within which patterns of infection and the disease can be understood and the potential impact of the infections explored. A number of authors have developed mathematical models of the natural history of HPV and cervical cancer to evaluate the effectiveness of various vaccination strategies on cervical cancer incidence. The majority of the models illustrate the potential gains that can be achieved by levels of vaccination strategy effectiveness in a heterosexual population, with the suggestion

of improving models by modelling a heterosexual and homosexual population in the same model.

South Africa has a high prevalence of HIV and HIV has been found to impact the infectiveness and the progression and persistence of HPV related lesions and cancers. A limited number of the models researched have included HIV status when modelling the transmission of HPV. In a country with a high HIV prevalence and HIV positive population models which do not include HIV status could produce biased results particularly concerning short term effectiveness of vaccination and cervical cancer incidence.

1.1 Research Statement

1.1.1 Research Question

Does the inclusion of bisexual, homosexual partnerships and HIV status to heterosexual models provide significant results compared to heterosexual only models when modelling HPV transmission and vaccination strategies.

1.1.2 Objective

The objective of the project was to investigate methods of modelling HPV transmission and the natural history of cervical cancer, in particular methods involving HPV transmission through modelling sexual behaviour such as risk groups and sexual orientation.

1.1.3 Research Aims

This project aims to

1. Investigate previous methods used to model HPV transmission and HPV vaccination strategies in literature.
2. Develop a theoretical dynamic transmission model which includes modelling: (i.) bisexual, homosexual, heterosexual partnerships. (ii.) HIV status in regards to easier acquisition of HPV and faster progression to cervical cancer.
3. Apply the developed model to a South African population.

4. Analyse the developed model to determine whether the developed model with the inclusion of homosexual and bisexual populations produces results which are of significance
5. Investigate the effectiveness of HPV vaccination strategies in a South African population.

1.2 Methodology

A comprehensive literature review of previous models, regarding the natural history of HPV to cervical cancer and HPV transmission, was completed. A theoretical mathematical model on HPV transmission dynamics, with the natural history of HPV and cervical cancer, and the addition of HPV vaccination strategies was developed based on previous models found in literature. The model differs, from the majority of previous models found in literature, through the inclusion of modelling the heterosexual, bisexual and homosexual population in one model, and the inclusion of HIV status. Theoretical analysis was completed on a simplified non age, sexual activity structured model without HIV to determine the impact of sexual orientation on the reproduction number. The model was then simulated with parameters based on a South African population, and with a focus on HPV type 16/18. The model simulations were analysed to determine the effects of the inclusion of sexual orientation on HPV transmission and cervical cancer incidence, additionally vaccination strategies were investigated.

2 Literature Review

2.1 HPV

2.1.1 HPV Epidemiology

Human papillomavirus (HPV) is a double strained DNA virus of the family Papovavridae. HPV infects the epithelial cells in humans, therefore the surfaces of the skin and the moist anogential and upper respiratory tracts [11].

HPV is divided into high (hrHPV) and low risk (lrHPV) subtypes according to their oncogenic potential [12]. High risk HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66, have significant oncogenic potential and can lead to anogential, neck and head cancers. Low risk genotypes have little or no oncogenic potential. Infections with low risk genotypes can cause benign or low grade cervical tissue changes and genital warts. They also cause epithelial growths over the vocal cords of children and adults that require surgical intervention.

There are approximately 40 mucosal genotypes of HPV [11]. Mucosal HPV genotypes are attracted to the moist epithelial cells, therefore the anogential and upper respiratory tracts. Mucosal HPV types are also referred to as anogential HPV types.

Mucosal HPV infection is particularly common in the first few years following first sexual contact, with estimated prevalence rates of 25 to 40% in women up to 20 years of age and 10% for women up to 40 years of age [9]. Transmission of the virus is principally through sexual contact (penetrative and non-penetrative) ([2][8]). Factors that increase the risk of infection include smoking, long term use of contraception pills, HIV and other sexually transmitted infections [13].

Persistent HPV infection has been implicated as the cause of squamous intraepithelial lesions and cervical cancer. High risk HPV types 16 and 18 cause up to 70% of cervical cancers ([5], [14]). Cervical cancer is the most common cancer among women in sub Saharan Africa, where 85% of cervical cancer cases occur ([4], [9], [15]).

2.1.2 HPV and HIV

Women with Human Immunodeficiency Virus (HIV) infection commonly have a broader range of HPV genotypes, often with multiple concurrent HPV infections. HIV disease influences the natural history of HPV by increasing the likelihood of persistent infection, and hastening the period of HPV disease.

HIV positive women were found in studies to be more likely infected with HPV than HIV negative women, regardless of CD4 counts ([16]–[19]). (CD4 counts refer to the number of CD4 molecules within a cubic millimetre). These studies will be discussed in further detail, and will be referred to as the Buonaguro Study [16] and the WIHS Study [17].

In the Buonaguro Study: 39.3% HIV positive women were infected vs. 13.9% HIV negative women. In the WIHS Study: 65.8% HIV positive women were infected vs. 26.2% HIV negative women. The WIHS Study [17] found that women with a CD4 count lower than 200 had detected HPV infection of 75.7%. The probability of subsequent HPV positivity was higher in HIV positive women than HIV negative women. The Buonaguro Study: 43.8% HIV positive women were infected vs. 17.4% HIV negative women. The WIHS Study: 92.9% of HIV positive women with a CD4+ count less than 200, 78.7% of HIV positive women with a CD4 count greater than 500, vs. 47.5% HIV negative women. The WIHS Study found that HPV was more common in women with lower CD4 counts, with hrHPV types 3 times more likely in women of CD4 counts of less than 200 than women with CD4 counts above 500. The WIHS Study also found that HIV positive women were more likely to be infected by multiple HPV types: 42 % for HIV positive women vs. 16% for HIV negative women.

HIV infection interacts with HPV to increase the probability of cervical intraepithelial neoplasia (CIN). HIV positive women were found to have a higher chance of disease than HIV negative women: 6.3 – 12.5 for HIV positive women, vs. 3.7 – 6.8 for HIV negative women [20].

2.1.3 HPV Vaccines

There are two types of vaccinations: prophylactic or therapeutic. Therapeutic vaccines are still being developed and are expected to attack already present HPV infection and HPV related diseases. Current HPV vaccines are designed to be prophylactic which is to prevent infection and the consequent disease.

There are two prophylactic vaccines commercially available: Cervarix® is a bivalent vaccine for HPV types 16 and 18, Gardasil® is quadrivalent vaccine for HPV types 16,18, 6 and 11 [8]. Both vaccines are administered in three doses over a period of six months and have demonstrated efficacy of over 90% against persistent infection due to genotypes 16 or 18 in women who received the 3 doses [8]. Data on efficacy, immunogenicity and safety in women who have already been exposed to a HPV type 16 and 18 is only available for the quadrivalent vaccine which was shown to have no protective effect against cervical intraepithelial neoplasia, grade 2 and 3, in women who had already been infected with before vaccination ([3], [6], [21]).

2.2 Cervical Intraepithelial Neoplasia

Cervical Intraepithelial Neoplasia (CIN) is the dysplasia and abnormal growth of squamous cells on the surface of the cervix. Squamous intraepithelial lesions correspond to the histologic finding of CIN. Three grades of CIN exist; the grades indicate the severity of dysplasia or abnormal growth based on the confined

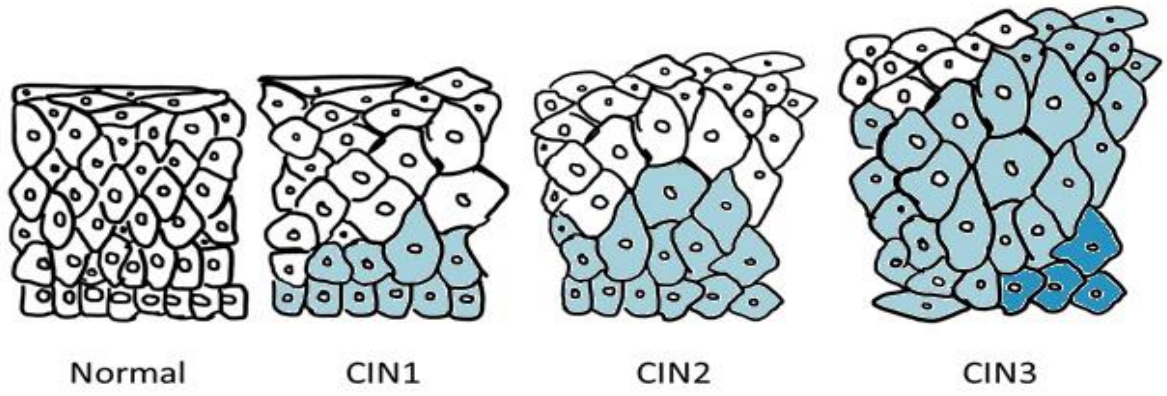


Figure 2-1 Illustration of the progression of cervical intraepithelial neoplasia through histology states. The blue cells are the abnormal cells. CIN1 abnormal cells are shown confined to an area of one third, CIN2 an area of up to two thirds and CIN3 an area greater than two thirds

thickness in the basal epithelium. CIN is cause from persistent infection in the cervix from HPV [12].

HPV infection reaches the basal cells of the squamous cell epithelium (epithelium characterised by its most superficial layer which consists of flat, scale-like cells) of the cervix uteri through micro-lesions. The viral DNA can remain latent for long periods of time. When the viral DNA is activated productive infection in all epithelial layers are initiated which results in low grade squamous epithelial lesions (LSIL) indicating an area of confinement of one third the basal epithelium, corresponding to CIN 1. As cell division occurs more cells in the cervix epithelium are transformed resulting in high grade squamous epithelial lesions (HSIL) indicating an area greater than one third of the basal epithelium, corresponding to CIN2 and CIN3. CIN2 indicates an area of confinement of two thirds and CIN3 indicates an area greater than two thirds the basal epithelium. The Bethesda system uses the cytology LSIL and HSIL for classification [1]. Most CIN left untreated will regress; those which progress to cancer take approximately 15 years.

2.3 Cervical cancer

Cervical cancer staging is an assessment of the disease progression of cervical cancer.

The International Federation of Gynaecology and Obstetrics, bases its staging on clinical examination and proceeds as follows:

Stage 0 Carcinoma in-situ , Carcinoma confined to the surface layer of the cervix

Stage 1 Carcinoma has spread throughout the cervix, but has not spread beyond the cervix

Stage 2 Carcinoma extends beyond the cervix into the upper two thirds of the vagina and nearby tissues, but has not spread beyond the pelvic wall or to the lower third of the vagina

Stage 3 Carcinoma extends to the pelvic wall and lower third of the vagina.

Stage 4 Carcinoma has extended beyond the pelvis and cervical area

2.4 Mathematical Modelling

2.4.1 Introduction

Mathematical models have and can be used to study the spread and control of infectious diseases and are alleged to have started with Bernoulli's models of smallpox [22]. Mathematical models were developed to address those questions that traditional epidemiological methods had failed to provide sufficient understanding. Questions such as: what shall the future incidence of a disease be and what factors could be altered to inhibit or aid transmission of the disease.[22]. Mathematical models are therefore used to evaluate strategies for preventing and managing diseases. Cancer models have been used to evaluate and develop screening strategies and recently HPV vaccination strategies.

Mathematical models are classified in numerous ways, of importance to this work is Infectious Disease Transmission Models, these models are distinguished from the *'curve fitting models'* which determine incidence independent of transmission dynamics [22]. Curve fitting models predate infectious disease modelling and fit functional forms to the series data to characterize the changes in disease incidence over a period of time [22]. They require no assumptions in regard to the transmission dynamics, therefore are frequently used for non-infectious diseases. Infectious disease transmission models can be further classified into sexually transmitted infection (STI) models. In the 1970's STI models began to gain popularity, mainly due to an increase in reported gonorrhoea cases in the USA during the 60's and 70's[22]. STI models are different to other infectious disease models as assumptions about the rate of contact between individuals and the transmission probability per contact can be made whereas others specify an adequate contact rate. The difference is due to STI contacts being easier to describe when compared to other infectious diseases.

Generally mathematical models simulate the progression of HPV by advancing a hypothetical population through stages of the disease according to demographic, epidemiological and clinical data.
In this chapter specific general attributes will be looked at and used to discuss and contrast previous models. The general attributes to be utilized are based on

population behaviour in a model; such as how the population interacts or how the population is simulated.

The section to follow will provide a brief description of the general model types which will be utilized. Leading from this section will be a discussion on the modelling of the natural history of a disease which involves an explanation of the basic theory of the two main model types: cohort and population dynamic, which are the most commonly used when modelling the natural history of HPV. Following each explanation will be a discussion of previous HPV models which fit the type. The definitions and use of separating HPV models into these main categories is based on a review of natural history cervical cancer models by Dasbach *et al* [23]. Additional reviews used include work by Cutts *et al* [6], Wright *et al* [24] and Burchell *et al* [2].

2.4.1.1 General Attributes

Infectious disease models are classified in numerous ways and which differ slightly according to authors, for example Anderson and May classified them according to infection type; distinguishing between micro and macro parasites, additionally distinguishing between direct and indirect transmission types. Hethcote ([25], [26]) distinguished between endemic and epidemic. Models are also distinguished based on incidence used and through compartmental or distributed methods. In order to keep the classifications clear the general attributes and model type definitions used in this work are briefly discussed. These definitions are based on a review by Cutts *et al*. [6]

2.4.1.1.1 Static and Dynamic Models

Static and dynamic models indicate whether the population interacts with itself or not. In a static model the force of infection may change as a function of age or additional individual base factors but it will remain constant over time. This is due to the fact that interactions between individuals are not modelled. In a dynamic model the force of infection is a function of: (i) sexual contact patterns of an individual with others, (ii) transmissibility of infection, and (iii) prevalence of the infection within the population.

2.4.1.1.2 Closed or Open Models

Closed and open models indicate whether the population is allowed to enter the model or not. Closed models, as the name implies, does not allow new entrants into the model over time while open models allow individuals to exit and enter the model over time.

2.4.1.1.3 Individual or Aggregate Models

Individual based / Micro simulation or Aggregate/ Macro simulation models indicate whether the population's behaviour is simulated through reflecting the population as averages or through using each individual's behaviour. Individual based models keep track of the individual behaviours over time with distinct characteristics assigned to each individual of the population being modelled and the events are generated at the individual level. Aggregate models assign individuals to states and the movement between states depends on parameter values at an aggregate level.

2.4.1.1.4 Deterministic or Stochastic Models

Deterministic and Stochastic models indicate whether transition rates are fixed or subject to chance for deterministic model's events occur with fixed parameters whereas stochastic events occur by given probability.

2.4.2 Natural History

The progression of a disease is simulated through advancing a hypothetical cohort or population through various stages of the disease according to demographic, epidemiological and clinical data [23]. The basic compartments for modelling HPV disease progression to cervical cancer are: Susceptible, HPV infected, Cervical intraepithelial neoplasia (CIN) infected, cervical cancer (CC) and cervical cancer survivor (CCS). An additional compartment, recovered from HPV infection, with a natural immunity (Z) is used.

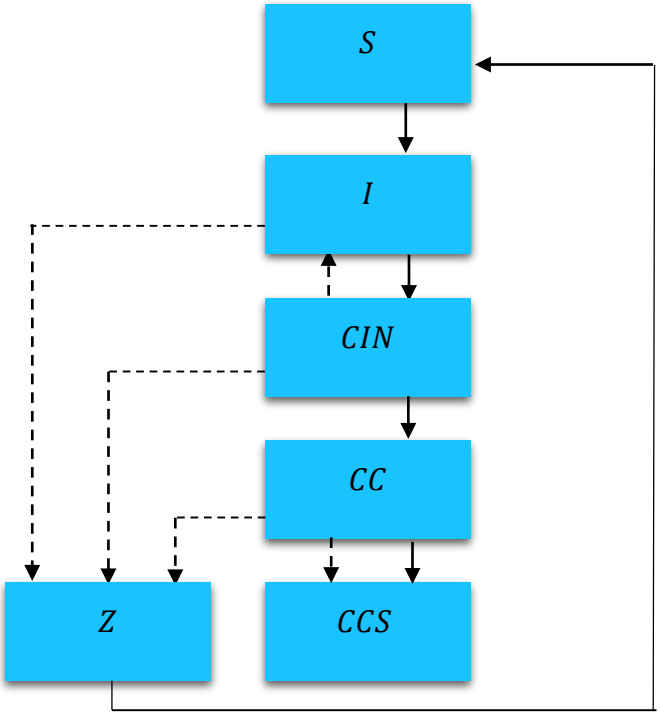


Figure 2-2 Schematic diagram representing the basic natural history of HPV infection .S is the susceptible compartment, I is HPV Infected, CIN indicates cervical intraepithelial neoplasia, CC indicates cervical cancer. CCS indicates cervical cancer survivor. Z indicates individuals who has recovered from HPV infection but who is not susceptible to infection

Modelling the progression can be approached in numerous ways which are catalogued through model types. Model types can be classified according to the general attributes which the models possess.

2.4.2.1 Cohort Models

Cohort Models are commonly referred to as health state transmission models or Markov models, and they simulate a single group over its expected lifetime. Therefore in general they are also classified as closed and static models.

In a cohort model time is associated with the probability of an individual being in a certain compartment during a discrete period of time. The probability is the proportion of the population at risk in a specific period of time. A disease is divided into distinct compartments and based on probabilities the population either progresses to the next compartment, remains in original compartment or progresses

to the dead compartment per the time period. Transitions between states occur once within each cycle or time period. The probabilities of transition may be represented in an *'n x n'* type matrix. The sum of probabilities per period of time must equal 1, therefore the probability of remaining in the original compartment is 1 minus the transition probabilities. The process of transitioning is repeated until the entire population reaches the dead compartment [23].

Once a cohort model is run to completion the survival time and incidence of the key components of the disease can be determined through examining the time spent in each compartment over the lifetime and the percentages of the population which had reached each compartment over the lifetime. For economic evaluation the average amount of time that an individual spends in the various compartments is weighted by a cost which is used to calculate expected costs.

2.4.2.1.1 Cervical cancer Screening Models

2.4.2.1.1.1 Overview

Female cohort model studies were done on cervical cancer screen strategies based on United States, Germany and developing countries population demographics. .Markov cycles were used for modelling the natural history of HPV infection and cervical cancer carcinoma. The effectiveness and cost effectiveness of screening strategies were evaluated. The results indicated that screening was an effective method for cervical cancer mortality and lifetime cervical cancer risk reduction. Limitations to models were: (i) the assumption of a homogeneous population with no risk factors being modelled, the exception being Goldie *et al* [27] where sexual activity and risk factors were assumed to vary, (ii) the population has equal access to healthcare.

In the discussion of results, costs were left in the original studies currency, to aid understanding assume the average for the US dollar to South African Rand (ZAR) was approximately 10.

2.4.2.1.1.2 Models

Myers *et al* [28] investigated the effectiveness and cost effectiveness of screening strategies in Unites States through a cohort of females aged 15 to 85 years. Main

assumptions included HPV acquisition based on age specific incidence rates for all HPV serotypes. The general results indicated baseline prevalence estimates for HPV and LSIL that were lower than adolescent cervical smears study data. Reasons for the difference in include: (i) the entire female population was modelled, not just those who are sexually active, (ii) the incidence, progression and regression estimates are averages for all HPV serotypes. To account for a later sexual debut they moved peak incidence from 20 to 30 years.

Goldie *et al* [29] investigated the cost-effectiveness of screening strategies on a hypothetical previously unscreened cohort of black South African females. The model incorporates states for: (i) cervical disease status,(ii) human papillomavirus (HPV) infection status, and (iii) human immunodeficiency virus (HIV) infection status. Screening strategies evaluated were: (i) three-visit: screening, a diagnostic and then treatment on separate visits, (ii) two-visit: screening, treatment without evaluation on separate visits, and (iii) one-visit: screening and treatment same day. Screening tests used include: (i) direct visual inspection (DVI), (ii) cervical cytology using a conventional Papanicolaou smear, and (iii) HPV DNA testing using a high-risk HPV probe. Main assumptions included: (i) outpatient treatment: cryotherapy; (ii) cryotheraphy:10% receive no benefit and another 10% develop recurrent disease within 1 year ; (iii) cyrotheraphy: 5% have minor ,1% have serious complications; (4) all screen-positive women undergo DVI prior to cryotherapy;(5)10% of screen-positive women have a 4-quadrant lesion or suspicious cancer. General results showed that HPV testing and a two visit strategy produced a 27% cancer incidence reduction. DVI followed by immediate treatment produced a 26% cancer incidence reduction. The most effective strategies with a 3 year frequency DVI was $400 YL gained, and HPV testing $1500YL gained.

Goldie *et al* [30] investigated the cost effectiveness of screening strategies in India, Kenya, Peru, South Africa and Thailand. A previously developed model (insert ref here) was used and fit with the appropriate data and assumptions. The model was used to evaluate two strategies, namely: (i) screening once at age 35 years, and (ii) screening twice at age 35 years and age 40 years. Main assumptions included screening and treatment assumed to occur during the same day. Age specific incidence and cervical cancer death rates as well as sexual behaviour parameters

assumed different for each country. Results indicated that screening at 35 reduced lifetime cervical cancer rate by 25 to 36% and cost less than $500 per year of life saved, two screenings at 35 and 40 further decrease cancer rate by 40% and cost per year of life saved that was less per capita gross domestic product.

Berkhof *et al* [31] investigated the effects of screening on high risk HPV infection and cervical cancer through a cohort of females aged 30 years. In their model the CIN and cervical cancer compartments were subdivided. The CIN compartment is divided into: high risk HPV causing (i) CIN1, (ii) CIN2 and (iii) CIN3 and low risk HPV and other infections caused: (i) CIN1 and (ii) CIN2. Cervical cancer was divided into 2 categories representing the FIGO stages of cervical cancer: (i) FIGO 1 and (ii) FIGO 2 and 3. Main assumptions include cervical cancer cannot develop without persistent high risk HPV infection. CIN1/2 can be caused by low risk HPV infection and other infections, CIN3 is caused by high risk HPV infection only. High risk HPV infection regression can occur before CIN lesion regression. High risk HPV infection is age dependent, CIN progression and regression and high risk HPV infection clearance is not age dependent. Results indicated a lifetime risk for cervical cancer of 2.9% with a peak at age 48 years, this risk dropped to 0.4% when attending cervical screening indicating a 80% reduction. The lifetime risk of females without a high risk HPV infection at age 30 years was 1.6% indicating a 40% reduction.

Siebert *et al* [32] investigated cervical cancer and the effects of screening on cervical cancer using a cohort of females aged 15 years and older. In their study the CIN and cervical cancer compartments were subdivided and additional compartments for benign hysterectomy and cervical cancer survivor included. The CIN compartment was divided into: (i) CIN1, (ii) CIN2 and (iii) CIN3. Cervical cancer was divided into 8 categories representing 4 FIGO stages of cervical cancer, the 4 stages were then subdivided into: (i) diagnosed and treated and (ii) undiagnosed and untreated. They converted Bethesda study data (LSIL, HSIL) into the Munich Nomenclature system (CIN). Main assumptions included assuming that cervical cancer occurred only through progression of CIN states and cervical cancer regression to CIN was not considered, heterogeneity was not implemented in HPV-related cancer development. Treatment was assumed according to German guidelines[32]. Results indicated annual Papanicolaou smear screening could

prevent 98.7% of diagnosed cancer cases and 99.6% of deaths due to cervical cancer in women who would not have been screened or treated previously. Reduction in screening effectiveness would result from extension of the screening interval.

Vijayaraghavan *et al* [33] evaluated the cost effectiveness of cervical cancer screening strategies in a 100 000 female cohort aged 13 years. The strategies evaluated included: (i) no Screening, (ii) Screening (iii) HPV DNA testing and screening, and (iv) co-screening and HPV DNA testing. Screening occurred every 10 years for all strategies starting from the age of 30 years. Each screening and diagnostic test involved a separate clinic visit, except in the co-screening strategy where both HPV and cytology samples were collected during one visit. Screening was discontinued at the age of 55 years. Disease progression were modelled through the basic compartments as discussed in the theory (section 2.4), with CIN and cervical cancer compartment being subdivided and additional compartments for treatment for CIN and cervical cancer added.The CIN compartment was divided into (i) CIN1, (ii) CIN2/3. Cervical cancer was divided into 4 categories representing the FIGO stages of cervical cancer: (i) FIGO 1, (ii) FIGO 2, (iii) FIGO3, and (iv) FIGO4. HIV status was modelled as a factor in HPV infection. Assumptions included rate of HPV infection for HIV positive individuals on ART's to be midway between rate of infection of HIV negative and HIV positive individuals not on treatment. It was also assumed 50% of HIV positive individuals were on ART's. Results indicated a 13-52% reduction in cervical cancer incidence with a R13000-R42000 per QAYL gained.

Chow *et al* [34] studied the effects on economic and epidemiological impact of HPV DNA testing combined with Papanicolaou smear testing with a cohort of females aged 30 years using Taiwan data. Nine screening strategies were evaluated comprising of three screening tools: (i) Papanicolaou smear screening alone, (ii) HPV DNA testing followed by Papanicolaou smear screening, and (iii) HPV DNA testing combined with Papanicolaou smear, and three screening intervals: (i) annually, (ii) every 3 years, (iii) every 5 years. Disease progression was simulated through the basic compartments, as discussed earlier, with the CIN and cervical cancer compartments subdivided. CIN was divided into: (i) CIN1, (ii) CIN2/3. Cervical cancer was divided into number of years infected with maximum 5 years.

Assumptions included no regression for any cervical cancer states, a cured cancer state that can only occur through progression through all cancer states. Results indicated that the most attractive cost effective strategy was HPV DNA testing followed by Papanicolaou smear triage every 3 or 5 years, with an infective cost effective ratio of $1 247 000 per quality adjusted life year (QALY) gained.

Atashi *et al* [35] , using a healthcare software package called TreeAge Pro 2008 , investigated the impact HAART and screening on cervical cancer mortality through a cohort of HIV positive females aged 25 years. Four scenarios were investigated, namely: (i) No HAART and no screening, (ii) HAART and no screening, (iii) HAART and NHNS screening, and (iv) HAART and screening once at aged 35 years. Their model was based on the work of Goldie *et al* [36] with the CIN and cervical cancer compartments subdivided. CIN is divided into LSIL and HSIL. Cervical cancer was divided into 4 categories representing the FIGO stages of cervical cancer. Their assumptions included no regression of cancer states or HIV CD4 count. CIN and Cervical cancer progression occurs in order of the states, skipping does not occur, and progression or regression is not depend on previous history of CIN. Results indicated that the effects of screening and HAART were most sensitive to the rate of progression of CIN, and that screening is an effective method for cervical cancer mortality reduction. The model predicted the risk in lifetime cervical cancer mortality doubled with HAART and screening than in comparison to HAART alone.

2.4.2.1.2 HPV Vaccination Models

2.4.2.1.2.1 Overview

HPV vaccination model studies developed female-only cohort models. Markov cycles were used for modelling the natural history of HPV infection and cervical cancer. The effectiveness and cost effectiveness of HPV vaccination strategies were evaluated. The results indicated that vaccination was an effective method of cervical cancer mortality and lifetime cervical cancer risk reduction. Results were determined to be most sensitive to age at vaccination, duration of vaccine protection, vaccination cost. Limitations to models were: (i) the assumption of a homogeneous population with no risk factors being modelled, the exception being Goldie *et al* [27]where sexual

activity and risk factors were assumed to vary, (ii) the population has equal access to healthcare.

2.4.2.1.2.2 Models

The Institute of Medicine [37] commissioned one of the first cohort models. The effects of HPV vaccination was explored through a cohort of 3.8 million male and female children aged 12 years. Disease progression in the analysis was simulated using the basic compartments approach (see 2.4.2 and Figure 2-2), with additional components for genital warts and penile cancer. Main assumptions included assuming that HPV vaccine effectiveness and coverage was 100%.The models main output was quality adjusted life years (QALY), costs and incremental cost effectiveness ratio (ICER). Results indicated that a HPV vaccine would reduce the costs of genital warts, cervical cancer and penile cancer by $530 million with the cost effective ratios for quality of life gained ranging from $4000 to $6000.

Hughes *et al* [38] programmed their cohort model in FORTRAN focusing on epidemiological outcomes. The effect of vaccination on high risk types of HPV was explored through a cohort of females aged 16 years. Using the basic compartments approach, they excluded a CIN compartment, included additional compartments for carcinoma *in situ* and cervical cancer. Assumptions included females had a lifespan of 75 years. The prevention of HPV 16/18 would not have an identical effect to that of treatment such as cryotherapy, due to vaccination leaving the transformation zone intact which could therefore result in lesions from high risk HPV types that were not modelled. Results indicated that reduction of HPV16/18 infection led to a proportional but smaller reduction in cervical cancer incidence. They attributed the lower proportion to the effect of other high risk types replacing lesions caused by HPV16/18 and speculated that this effect would not be seen when modelling HPV6/11 and genital lesion incidence.

Sanders and Tiara [39] used a decision tree software package called Decision Maker, to investigate the effect of vaccination through a cohort of females aged 12 years, with the effects of standard care and vaccination combined with standard care being compared. Standard care was described as conventional biennial Papanicolaou (Papanicolaou) smear test screening from the age of 16 years.

Disease progression was simulated using the basic compartments approach. Main assumptions included a 75% vaccine efficiency with a duration of protection of 10 years and a booster prescribed every 10 years. 70% of the cohort would receive the vaccination and it was assumed 71% of the cohort receive standard care. The general results indicated that vaccination of females aged 12 years provided an improved life expectancy with corresponding ICERs of $32066 per YL gained and $22755 per quality adjusted life year (QALY) gained.

Kulasingam and Myers [40], using a decision tree software package called DATA, explored the prospective economic and health effects of HPV vaccination through a cohort of females aged 12 years in a setting of existing cervical screening. Disease progression was simulated using the basic compartments approach discussed earlier with the compartments for HPV, CIN and cervical cancer subdivided. HPV was subdivided into low and high risk HPV types. CIN was split into CIN1 and CIN2/3. Cervical cancer was subdivided into 4 categories representing the FIGO stages of cervical cancer. Various strategies that were evaluated include: (i) vaccination, (ii) screening, and (iii) vaccination and screening. Main assumptions include a 100% vaccination coverage which targets 70% of the oncogenic HPV types with a 10 year lifetime at a cost of $200 per vaccination. The general results indicated that vaccination reduced the incidence during peak ages of infection of oncogenic HPV types and that results were most effected by the age of vaccination. The strategy determined to be the most appealing in terms of the cost-effectiveness ratio was vaccination plus biennial screening, which was begun at the age of 24 years, with $44,889 per life gained.

Goldie *et al* [41] studied the impact of vaccination against persistent HPV16/18 infection on age specific incidence of cervical cancer through a cohort of females aged 13 years. The compartments for HPV, CIN and cervical cancer were subdivided such that HPV was subdivided into transient infection, persistent HPV16/18 infection, persistent high risk type infections and persistent low risk infection. CIN was split into CIN1 and CIN2/3. Cervical cancer was subdivided into 4 categories representing the FIGO stages of cervical cancer. Main assumptions included 100% vaccine coverage of target population, and 50-98% vaccine efficiency with lifetime duration. The general results indicated that a 75% prevention of

HPV16/18 would be associated with 70-83% reduction of cervical cancer cases associated with HPV16/18. It was proposed that similar reductions would occur for low and high grade cervical lesions.

Goldie *et al* [27] explored the cost effectiveness and clinical benefits of HPV vaccination in a population with a cervical cancer screening program through a cohort of 100 000 females aged 13 years. Main assumptions included 100% vaccine coverage of target population and a 90% vaccine efficiency with a lifetime duration. The model was used to evaluate three strategies namely: (i) no screening or vaccination, (ii) screening and no vaccination, and (iii) vaccination and screening. Starting ages, screening intervals and types of screening of the programs were varied in the analysis. Results indicated that vaccination reduced the incidence of cervical cancer, and both low and high grade lesions. Their results were shown to be most sensitive to the vaccine efficiency duration, screening intervals and the natural history of HPV in women aged over 30 years. The strategy determined to be the most appealing in terms of the ICER was screening plus vaccination, the most effective version produced a cost effective ratio less than $60 000 per quality adjusted life year (QALY) gained.

Brisson *et al* [42] investigated the impact on economic and epidemiological effects of HPV vaccination using a cohort of females aged 10 years. Three vaccination strategies were compared namely: (i) bivalent vaccination, (ii) quadrivalent vaccination, and (iii) no vaccination. In this study the CIN compartment was subdivided and an additional compartment for genital warts was introduced. Assumptions included no cross-protection between HPV types, HPV type co-infection occurrence and females could develop life-long immunity following an infection. Prior screening practice remained unaffected by the vaccination strategy. 100% of the aged 12 years female cohort are vaccinated. The vaccination has an efficiency of 95% with a life long duration. The duration of vaccination efficacy was investigated in further analysis. Results indicated that vaccination of females aged 12 years cost effectiveness of CAN$21000 for bivalent vaccine and CAN$31 000 quadrivalent vaccine per quality adjusted life year (QALY) gained. Additional analysis determined results were most sensitive to age at vaccination, duration of vaccine protection, vaccination cost.

Chesson *et al* [43], investigated the impact on epidemiological and economic effects of HPV vaccination on HPV prevalence in an American population, aged 12-99 years with cervical cancer screening practices in place. Assumptions included the 12 year old population remaining constant over time resulting in a constant age distribution. Vaccination of females aged 12 years occurs constantly for 100 years. Vaccination coverage increase linearly for the first 5 years to 70% where it remains at 70%. Vaccination was assumed 100% efficient with a lifelong duration. The models main output was cost per quality adjusted life year (QALY) gained. The general results indicated that under base case parameter values, the estimated cost per quality adjusted life year (QALY) gained by vaccination ranged from $3,906 to $14,723.

2.4.2.2 Population Dynamic Models

Population dynamic models simulate a changing population over time with individuals constantly entering and exiting the model. Thus in general population dynamic models are also classified as open dynamic models.

The population model does not have a natural stopping point like the cohort model, however the majority of models approach a steady state solution after long periods of time [23]. A disease is divided into distinct compartments (as before) and based on rates, dependent on the time period, the population can progress to another compartment. The most important difference is the transmission dynamics of infection. In a population model the progression to infection state is modelled through a force of infection which is time dependent. This allows indirect benefits of vaccination to be taken into account.

All the models discussed in this section, with the exception of [43]–[45] use systems of ordinary equations.

2.4.2.2.1 HPV vaccination models

2.4.2.2.1.1 Overview

The majority of HPV vaccination model studies modelled a heterosexual sexually active population and did not consider bisexual or homosexual individuals in the model, with the exception of Bogaards *et al*[46]. A variety of vaccination strategies were evaluated, and the most common strategies were: (i) female only vaccination, (ii) male and female vaccination, (iii) Adolescents entering the sexually active population only, and (iv) adolescents entering the sexually active population and a catch-up programme. HPV screening was modelled along with vaccination in many of the studies. Results in regards to vaccination strategies indicate that a pre-adolescent vaccination programme in which coverage of females is high produces an insignificant added value of including males compared to a setting where female coverage is low. The marginal impact on the cervical cancer incidence diminished as the coverage of females increased which resulted in less attractive cost-effectiveness ratios. A modest increase in adolescent females was less costly, yet more beneficial, than covering an equal percentage of adolescent males. Some authors indicated the limitation of using a heterosexual population and indicate that homosexual and heterosexual populations should be investigated by modelling them together.

2.4.2.2.1.2 Models

Hughes *et al* [38] explored the impact of HPV vaccination on epidemiological outcomes. Disease progression was modelled through the basic compartments discussed earlier (see 2.4.2 and Figure 2-2), but excluded the CIN and cervical cancer compartments including and subdividing the vaccination compartment. Vaccination was divided into those who are infected through breakthrough infections and those who aren't infected. Main assumptions included assuming that 90% of the targeted population received vaccination, the vaccine had an efficiency of 75% with a 10 year duration effectiveness. The vaccine was assumed to be a monovalent high risk type vaccine with the steady state prevalence of HPV 16 being investigated. Their results indicated that a both sex vaccination program decreased HPV prevalence by 44%, and a female only vaccination program decreased HPV

prevalence by 30%. The authors concluded that a female only vaccination would be 60-75% as efficient as a both sex strategy.

Barnabas and Garnet [45], employing partial differential equations, studied the impact of HPV vaccination in an unscreened developing country population. In this study the CIN compartment was subdivided into CIN1 and CIN2/3. Assumptions included a multivalent HPV vaccine with a 100% efficiency of lifetime duration. The target population was both sexes aged 15 years. The vaccine coverage was varied in analysis. Results indicated a vaccine coverage of 66% produced a cervical cancer incidence reduction of 80%. The authors proposed that vaccinating both sexes offered little benefit when compared to vaccinating women alone for the cervical cancer incidence and a period of 40-60 years would be required for a significant reduction to be appreciated.

Elbasha and Galvani [21] modelled the impact of HPV vaccination and the interaction of two types of HPV was explored. Their model excluded the CIN and cervical cancer compartments and subdivided the other compartments. The susceptible compartment was viewed as susceptible to both types, 16 and 18, of HPV investigated. Infected and immune compartments were divided into (i) Infection with one type and susceptible to another, (ii) Infection with one type and immune to another, (iii) Infection with both types, (iv) immune to one type and susceptible to another, and (v) Immune to both types. Assumptions included immunity on recovery. Vaccination efficiency and duration was varied during analysis, so was the type of HPV the vaccine would target. Results indicated that if infection with an HPV type facilitates subsequent or concurrent infection with another type then HPV vaccination would produce additional results of prevalence reduction of HPV types not included in the vaccination.

Barnabas *et al* [13] investigated the impact of HPV 16 vaccination on HPV 16 cervical cancer incidence ,and the effect of changes in sexual behaviour and smoking on age specific cervical cancer incidence investigated. Smoking was investigated as it was assumed that it could have impacted cervical cancer incidences. Here again the CIN and cervical cancer compartments were subdivided. The CIN compartment was divided into LSIL and HSIL. Cervical cancer was

subdivided into invasive cervical cancer and cervical cancer. Assumptions included vaccination prior to sexual activity at age 15 years and a simple screening and treatment program being in place. A once off change in rates of sexual partner acquisition and age of sexual debut is reflected in the model to account for changes in reported values from surveys. HPV transition and progression rates were converted into transition probabilities. The general results indicated that vaccination of 90% of females before sexual debut would decrease type 16 invasive cervical cancer by 91%. They proposed that vaccination of both sexes provided little impact in comparison to vaccination of females alone. Analysis determined that changes in sexual behaviour and smoking had accounted for, in part, the increase cervical cancer incidence.

Elbasha *et al* ([5], [14], [47], [48]) studied the impact of HPV vaccination on epidemiological and economic outcomes, employing a quadrivalent vaccine in an organised cervical cancer screening setting in the United States. Their results indicated that vaccination produced a substantial reduction in health and economic burden of HPV related diseases. Disease progression was modelled using the basic compartments discussed earlier which have been subdivided and with additional compartments added. The susceptible compartment was viewed as susceptible to both. Infected and immune compartments were divided into: (i) Infection with one type group and susceptible to another, (ii) Infection with one type group and immune to another, (iii) Infection with both type groups, (iv) Immune to one type group and susceptible to another, and (v) Immune to both type groups. It was assumed that vaccination would be provided in conjunction with existing screening programs. Maximum vaccination coverage was assumed to be 70%, the first 5 years of the program results in a linear increase in coverage from 0 to 70%. Various vaccination strategies were evaluated which included: (i) vaccination of females aged 12 years, (ii) vaccination of both sexes aged 12 years, and (iii) vaccination of both sexes aged 12 years together with a catch up program for both sexes aged 12-24 years. The most effective strategy was both sexes with a catch up program which resulted in a reduction of cervical cancer of 91% and a ICER of $46 056 per quality of YL gained. The duration of infection and vaccination coverage was most sensitive to reduction of HPV prevalence. Their model was also used with data from Mexico [47],

indicating the same effective strategy and a reduction in genital warts incidence by 94-98% and $16000 per quality of YL gained.

Llamazares *et al* [49] studied the impact that various HPV vaccination strategies had on epidemiological and economic effects of HPV prevalence in the population. The vaccination strategies evaluated included: (i) childhood only vaccination and (ii) childhood vaccination followed by a supplementary adult vaccination. Disease progression was simulated using three compartments, namely: (i) Child, (ii) Adult, (iii) Infected. All the compartments were subdivided into vaccinated and non-vaccinated. Assumptions included modelling males as age-equivalent cohort sexual partners of adult females, these males would then interact for a finite amount of time. Vaccination occurred before infection could take place in children and vaccination of infected adults was assumed to have no effect. The general results indicated eradication could occur with 81% childhood vaccination, or a 74% childhood vaccination and 20% adult vaccination, or a 55% childhood vaccination and 50% adult vaccination, assuming a 95% vaccine efficiency. Efficiency below 85% results in eradication not being possible.

Crawford *et al* [50] investigated the relationship between co-infection of multiple HPV strains and cervical cancer in an American female population aged 15-59 years. Using the basic compartments approach, omitting the CIN compartment and including a vaccination compartment. The HPV infection, vaccination and cervical cancer compartments were subdivided. Vaccination was divided into (i) vaccinated, and (ii) vaccinated and infected with strain 2. Infected with HPV was divided into 3: (i) infected with strain 1, (ii) infected with strain 2, (iii) infected with both strains. Cervical cancer divided into cervical cancer from: (i) strain 1, (ii) both strains. Main assumptions include excluding cervical cancer cases of strain 2. Females can regress from cervical cancer caused by a single strain but cannot regress when infected with both HPV strains. Females infected with both HPV strains have a higher cancer fatality. Regression from cancer does not mean clearance from HPV infection. The general results indicated that the presence of strain 2 could increase, by over 100%, strain 1 related cervical cancer. A directly proportional relationship with vaccination and strain 2 was determined with 50 percent vaccination coverage producing reduction of strain 2 prevalence by over 90 percent. Additional analysis

indicated that vaccination against strain 1 could eliminate strain 2 under specific conditions.

Bogaards *et al* [46] investigated the epidemiological effect of HPV vaccination on HPV prevalence using a two sex transmission model. They subdivided the CIN and cervical cancer compartments as before with men having only a single infection stage. Assumptions include assuming the equilibrium population, the heterosexual population is evenly distributed, equal sexual activity. The general results indicated that directing vaccination at the sex with the highest pre- vaccination prevalence would result in the greatest reduction of the prevalence.

Ribassin-Majed *et al* [51] investigated the impact of vaccination of HPV 6/11 prevalence's in a French population of both sexes. Disease progression was simulated through the basic compartments approach. Since HPV 6/11 are non-oncogenic the CIN and cervical cancer compartments were omitted. All the compartments were subdivided into vaccinated and not vaccinated sub-compartments. Assumptions included a balance between the entrance to and exit from sexual activity and that the number of men is equals the number of women, therefore a constant population of 500 000 of both sexes is maintained. Vaccinated infected individuals are just as infective as non-vaccinated individuals. Vaccination efficiency is 90% and of lifelong duration. The general results indicated that the prevalence of HPV 6/11 types in females would be reduced by 50% and males by 25% after 10 years for a 30% vaccination coverage of females. Additional analysis inferred that HPV 6/11 types could be eliminated if female vaccination coverage remained above 12%.

2.4.2.2.2 HPV Vaccination and Education Strategies

2.4.2.2.2.1 Overview

A mandatory vaccination programme has been considered in many countries as it ensures the populations is protected, however this may lead to increased sexual activity rates due to vaccination which could result in an increase in sexually transmitted infections not covered by the vaccine. Voluntary vaccination would result in less of the population being vaccinated and reduce the effectiveness of the vaccination programs. Hence education campaigns have also been modelled ([52],

[53]). Mass vaccination and voluntary vaccination were evaluated. In the mass vaccination model the vaccinated class was separate from the other classes whereas in the mass education and voluntary vaccination model the vaccinated class was dependent on the educated individuals that chose to get vaccinated. Results indicated an effective mass education programme would result in fewer infected individuals, and a faster initial result, the costs were also found to be lower. Limitations in the studies involve: (i.) the consideration of the female population only. (ii.) Infections were not based on sexual activity groups (iii.) a heterosexual population was considered only and (iv.) females aged between 9 and 26 were modelled.

2.4.2.2.2.2 Models

Green *et al* [52], using two separate model, studied the impact on economic outcomes of HPV vaccination strategies in an American population. In the first model females aged through 11-26 years were modelled, while in the second model females aged 9-26 years were modelled. The vaccination strategies considered were: (i) mandatory vaccination policy, and (ii) a mass-media awareness campaign. Disease progression for both models was simulated through 4 compartments: (i) susceptible, (ii) infected, (iii) vaccinated with the vaccinated compartment subdivided. The vaccination compartment in the first model is divided into educated and not educated. The second model subdivides the susceptible, infected and vaccinated compartments based on change in behaviour through education and no change in behaviour through education or no education. Their assumptions included that all relationships being non-monogamous and that education results in reduced sexual activity. It was assumed that the effects of education can decrease and therefore educated compartments could regress to non-educated compartments. It was assumed that a proportion of individuals would not get vaccinated in the mandatory policy strategy due to females not attending the public school system. It is assumed individuals in the mass education campaign can regress and progress through the educated and non-educated classes based on education effects decreasing and re-education. Results indicated that even with a vaccination, infection prevalence will remain high with a high transmission rate. To eliminate HPV with a high transmission and reproductive rate requires a high efficacy and vaccination coverage.

2.4.2.2.3 Additional Models

Baussano *et al* [44] using a system of partial integro-differential equations to simulated the influence of the duration of HPV 16 infection on the occurrence of related cervical cancer in a population with a screening program in effect. Using the basic compartment approach (see 2.4.2) with an additional compartment for screening and treatment. Assumptions included 15% of the target population never being screened. Partial immunity for transient HPV16 infections with the probability of lifelong immunity increasing as a function of age. The general results indicated that HPV 16 clearance and progression was inversely proportional to the length of time with infection, the rate of clearance of CIN 2/3 was inversely proportional to age while progression of CIN 2/3 to invasive cervical cancer was directly proportional to the persistence of CIN 2/3.

2.4.3 Transmission

2.4.3.1 Sexual Activity and Partnerships

2.4.3.1.1.1 Overview

The majority of the models in Section 2.4.2.2.1.2 have adapted the Barnabas *et al* [13] models sexual mixing algorithm. The populations were stratified into age, sex, and sexual activity classes with defined roles of partner change specified in the sexual mixing algorithm; this depended on the proportion of sexual partnerships from the opposite sex, from the sexual activity group and the age class in the total sexually active population. The degree of assortative mixing between the age and sexual activity groups is included through mixing parameters and a balancing of supply and demand is taken into account. Limitation's to the models was: (i) only strictly heterosexual or homosexual partnerships were considered, an exception being Bogaards *et al* [46] who investigated (i) the addition of bisexual and homosexual individuals, and (ii) immigration groups and prevalence of HPV infection among recent immigrant as well. The mixing patterns with the local population was not included which could influence the distribution of infection. Results in regards to the effects of sexual activity on HPV and cervical cancer incidence indicated a proportional relationship between the number of sexual partnerships and cervical cancer incidence. The level of heterogeneity was found to be significant in disease

burden with the epidemic shaped more by heterogeneity between sexual activity groups than by age groups.

2.4.3.1.1.2 Models

Muller and Bauch [54] investigated the influence of sexual partnership formation and their dissolutions on HPV transmission. They developed a simple pair model that explicitly included sexual partnership formation and dissolution. They did not model CIN and cervical cancer. Assumptions included a vaccine efficacy of 95%. Their results indicated that not including partnerships could result in biased projections of HPV prevalence, however when transmission rates are calibrated to match the pre-vaccine HPV prevalence, then the projected prevalence with a vaccination does not vary significantly, regardless of whether partnerships are included in the model. The model did have limitations, namely: (i) stochasticity was not included, (ii)A 'core group' of highly sexually active individuals was not included, and (iii) overlapping relationships, sexual risk groups and age structure was excluded. They did acknowledge that a more realistic sexual partnership model could result in a different outcome.

Table 1 Summary of Mathematical Models involving HPV and/or Cervical cancer

AUTHOR(S)	MODEL TYPE	PURPOSE	OUTCOMES	STRATEGIES EVALUATED	KEY ASSUMPTIONS	MAIN FINDINGS
INSTITUTE OF MEDICINE [37]	Cohort, numerical, deterministic	Cost effectiveness criteria to prioritize the development of vaccines against infectious diseases	**Epidemiological:** Genital warts, CIN, CC, Penile Cancer prevalence's; **Economic:** QALYs, costs, cost per QALY gained	(i) Current care (ii) Vaccination and Current care. Females and males aged 12 years, 100% coverage,100% effective, $330 vaccination series cost	Vaccination prevents HPV infection in males and females	Cost per QALY gained for HPV vaccination ranged between $4000 and $6000
HUGHES *ET AL*[38]	Dynamic, numerical, deterministic	Explore population level impact of HPV vaccine	**Epidemiological:** HPV prevalence	Females and males, monovalent, 90% coverage, 75% effective, 10 years protection.	Not age structured, long term impact modelled only , CIN and CC not modelled , steady state prevalence investigated	Female only vaccine 60-75% as efficient as a both sex strategy, while targeting most sexually active less effective
HUGHES *ET AL* [38]	Cohort, numerical, deterministic	Explore population level impact of HPV vaccine	**Epidemiological:** HPV ,CC, Carcinoma *in situ* prevalence's	Females aged 16 years, 60 % effective bivalent vaccine, high risk types, screening	Risk of infection depends on duration of infection, risk of HPV infection depends on age and sexual activity, HPV infection does not regress, time is continuous, Females died by age 75 years	Reduction of HPV16/18 infection led to a proportional but lower reduction in CC incidence. Lower proportion due to the effect of other high risk types replacing lesions; this effect would not be seen when modelling HPV6/11 Screening will remain necessary.
SANDERS AND TIARA[39]	Cohort, numerical, deterministic	Evaluate effectiveness and cost effectiveness of a prophylactic HPV vaccine combined with screening compared to screening alone	**Epidemiological:** Prevalence: HPV infection, Incidence: LSIL, HSIL, CC **Economic:** Cost, life years, QAYLs, cost per YL gained, cost per QALY gained	(i) Screening (from 16 every two years) (ii) vaccination (Females aged 12 years) and screening. High risk types, 70% coverage, 75% efficacy, 10 year protection, , $300 vaccination 10 year boosters, $100 booster	Females can get LSIL,HSIL without HPV infection, progression of disease depends on infection with HPV types, HPV regression is age dependent, monthly Markov cycle	vaccination of females aged 12 years provided an improved life expectancy with corresponding ICERs of $32066 per YL gained and $22755 per QALY gained
KULASINGAM AND MYERS[40]	Cohort, numerical, deterministic	Examine impact on potential health and economic effects of HPV vaccine	**Epidemiological:** Prevalence of HPV infection, Incidences: CIN1,CIN2/3, CC **Economic:** QALYs, cost per YL gained, coat per QALY gained	(i) Vaccination (ii) screening (iii) vaccination and screening. Females aged 12 years, vaccine targeting 70% of oncogenic types, 100% coverage, 10 year protection, $200 vaccine cost	HPV regression is age dependent, annual Markov cycle	Cost per YL gained for vaccination and screening (begun at age 24 years) between $44889 to $236250, vaccination and screening cost effective depending on effectiveness during peak HPV incidence ages
GOLDIE *ET AL*[41]	Cohort, numerical, deterministic	Investigated the impact of a prophylactic vaccine against persistent HPV16/18 infection on age specific incidence of CC	**Epidemiological:** Prevalence's of HPV infection, LSIL, HSIL, CC	Females aged 13 years, HPV 16/18 vaccine, 100% coverage, 50-98% efficacy, no screening	low and high risk HPV infections were modelled, transient HPV infections not impacted by vaccine, semi-annual Markov cycle	HPV16/18 vaccine can reduce HPV16/18 related LSIL, HSIL and CC. 75% prevention of HPV resulted in 70-83% reduction in CC prevalence
GOLDIE *ET AL*[27]	Cohort, numerical, deterministic	Investigated the population level impact of HPV16/18 vaccine through clinical benefits and cost effectiveness	**Epidemiological:** Prevalence of HPV infection, Incidences: LSIL, HSIL, CC **Economic:** cost life years, QALYs, cost per life year gained, cost per QALY gained	(i) Screening (ii) vaccination and screening. Females aged 13 years, HPV 16/18 vaccine, 100% lifetime efficiency and coverage, $377 vaccine cost per series	low and high risk HPV infections were modelled, transient HPV infections not impacted by vaccine, vaccine efficacy and screening intervals varied	Cost per QALY gained $12300 to $60000, screening plus vaccination most cost effective , results most sensitive to vaccine efficacy and screening duration

AUTHOR(S)	MODEL TYPE	PURPOSE	OUTCOMES	STRATEGIES EVALUATED	KEY ASSUMPTIONS	MAIN FINDINGS
ELBASHA AND GALVANI[21]	Dynamic, analytical, numerical, deterministic	Impact of HPV vaccine through investigating HPV type interactions and evaluating whether they affect vaccine efficiency	**Epidemiological:** Prevalence HPV infection	Male and female, high risk types	Analytical modelling, Vaccine efficiency, duration an HPV type vaccine targeted was varied	If HPV type interactions synergistic then mass vaccination may reduce prevalence of types not included in vaccination
GOLDIE *ET AL*[30]	Cohort, numerical, deterministic	Explore cost effectiveness of screening strategies in India, Kenya, Peru, South Africa and Thailand	**Epidemiological:** Prevalence of HPV infection, CC **Economic:** Cost life years, QALYs, cost per YL gained, cost per QALY gained, ICC incidence	Screening once at age 35, Screening twice at age 35 and 40	Age specific incidence rates and CC deaths, sexual behaviour assumed different in each country, monthly increments- dependent on age, HPV status, disease history, screening and treatment could be provided in the same day	Screening at 35 reduced lifetime CC rate by 25 to 36% and cost less than $500 per year of life saved, two screenings at 35 and 40 further decrease cancer rate by 40% and cost per year of life saved that was less than each country's per capita gross domestic product
BARNABAS AND COLLEAGUES [13]	Deterministic, numerical, dynamic	Evaluate population level impact of HPV vaccine and the effect of smoking and sexual behaviour on CC prevalence	**Epidemiological:** Prevalence of HPV infection, LSIL,HSIL and CC	Male and females aged 15 years, 100% effective lifetime protection, simple screening and treatment program in place	Age structured, HPV regression age dependent	Vaccinating men have little benefit in reducing CC, vaccinating 90% females before sexual debut resulted in 91% reduction in CC, smoking and sexual behaviour accounted in part for increase in CC incidence
SIEBERT[32]	Cohort, Deterministic, Numerical	Evaluating the long-term effectiveness of different CC screening tests and strategies screening in the context of German health care	**Epidemiological:** lifetime CC risk, lifetime CC mortality, cancer incidence	Females aged 15 years and older, annual screening starting with age 20 years until end of life	did not implement heterogeneity in HPV-related CC development, CC regression to CIN not considered, treatment occurred according to German guidelines	Annual Screening in female's adherent to screening could prevent 98.7% of diagnosed CC cases and 99.6% of CC deaths. Extending the screening interval resulted in reduced screening effectiveness. Lifetime CC risk of 3.0% and a lifetime CC mortality of 1.0%, with a peak cancer incidence at age 51 years was predicted. Annual screening could prevent 76.9%-94.0% CC cases and 87.3% - 97.7% of CC deaths
KIM *ET AL* [55]	Dynamic, Deterministic, Numerical	Evaluating the cost effectiveness of HPV vaccine in a low resource setting	**Epidemiological:** Prevalence: HPV , Incidences: CIN, CC **Economic:** Lifetime costs, life expectancy, cost-effectiveness ratios	Both sexes aged 12 years, Vaccination occurred before the age of 12 years, coverage was varied, HPV reductions inputted into stochastic model	Vaccine is as effective on males as females, age structured, stochastic model for CC	the added value of including boys will be relatively small in high coverage areas., the marginal impact on CC incidence diminished as coverage in girls increased, while total costs nearly doubled
ELBASHA *ET AL* [14]	Dynamic , Deterministic, numerical	Evaluate the epidemiologic consequences and cost-effectiveness of HPV (6/11/16/18) vaccination strategies	**Epidemiological:** Prevalence: HPV; Incidences: Genital warts ,CC , CIN **Economic:** QALY, QALY gained, ICER	HPV vaccination series cost $360, females aged 12 years, 0-70% linear coverage in first 5 years, catch up program 0-50% in first 5 years thereafter eliminated	Life-long vaccine efficacy, 10 year vaccine efficacy, maximum 70% vaccination coverage, 50% coverage for vaccine catch up	Vaccination females aged 12 reduce the incidence of genital warts (83%) and CC (78%) due to HPV 6/11/16/18, incremental cost-effectiveness ratio (ICER) of augmenting this strategy with a temporary catch-up program

AUTHOR(S)	MODEL TYPE	PURPOSE	OUTCOMES	STRATEGIES EVALUATED	KEY ASSUMPTIONS	MAIN FINDINGS
						for 12- to 24- year-olds was US $4,666 per QALY gained
INSINGA *ET AL* [47]	Deterministic, Dynamic, Numerical	Evaluate the cost effectiveness of HPV vaccination strategies	**Epidemiological:** Prevalence: HPV, Incidences: CC , CIN **Economic:** QALY, QALY gained, ICER	(i) Vaccination of females aged 12 years, (ii) vaccination of both sexes aged 12 years , (iii) vaccination of both sexes aged 12 years and a catch up program for both sexes aged 12-24 years	Vaccination would be provided in conjunction with existing screening programs. Maximum vaccine coverage was assumed to be 70%, the first 5 years of the program results in a linear increase in coverage from 0 to 70%.	reduction in genital warts incidence by 94-98% and $16000 per quality of YL gained
VIJAGIRAGHAVEN *ET AL* [33]	Cohort, numerical, deterministic	Evaluate cost effectiveness of screening strategies in South African setting	**Epidemiological:** Prevalence of HPV, CC **Economic:** Cost, QALYs, ICER, lifetime risk of CC	Strategies evaluated (i) Screening every 10 years from age 30 years, (ii) HPV testing and screening, (ii) Co-screening. Females aged 13 years. HIV status included, assumed 50% of AIDs patients received ART's.	individuals could receive treatment or not, assumed 50% HIV cases receive ART's, HIV positive on ART's HPV risk was indicated as midway between HIV positive no treatment and HIV negative	Screening every 10 years reduced lifetime CC rate by 13-52%, cost per QALY between R13000-R42000
LOUNES *ET AL* [51]	Dynamic, deterministic, numerical	Investigate effect of observed vaccine coverage and low coverage on anal cancer incidence in France	**Epidemiological:** Prevalence: HPV, Incidence: Anal cancer	Sexually active at 14, individuals exit the model at death or age 84, vaccine coverage assumed constant in time: scenario 1 30% female aged 14-19 and 10% females aged 20-24	Male and female aged 14, 90% efficacy of vaccine, lifelong vaccine efficacy, did not assume that individuals who cleared HPV infection developed natural immunity against HPV	Reductions of 55 to 85% HPV 16/18 related anal cancer incidence , Efficacy of HPV vaccination to prevent anal cancers in females decreased dramatically when vaccination coverage was very low
BELLO [53]	Numerical, theoretical	Investigate the population level Cost effectiveness of education and HPV vaccination strategies	**Epidemiological:** Prevalence: HPV **Economic:** ICERs, QALYs	(i) Individual education and compulsory vaccination, (ii) Mass education and vaccination.	Female population aged 9-26, 11-26 years. Educated individuals reduced sexual activity. Education assumed 100% effective	
BRISSON *ET AL* [42]	Deterministic, cohort, numerical	Investigate the effect and cost effectiveness of HPV vaccine strategies	**Epidemiological:** CC incidence **Economic:** QALY gained, ICER, lifetime CC risk	(i) Vaccine, (ii) Screening and vaccination. Females age 12 years, booster vaccination at age 22	No cross protection of HPV types, Co-infection of HPV types can occur, Lifelong immunity after clearing infection, screening and treatment can occur, Cohort females aged 10 years, CAN $295-400 per vaccination series	Female vaccination aged 12 years is cost effective with $25000 QALY, Female vaccination aged 12-20 cost effective analysis $40000 per QALY gained , 90% coverage of females would result in male vaccination not being cost effective
CHESSON *ET AL* [43]	Cohort, Deterministic, Numerical	The population level impact of HPV vaccine on the economic effects of HPV-related health outcomes	**Epidemiological:** Incidences: CIN 1, CIN 2, CIN 3, and genital warts. **Economic:** Vaccination costs, averted treatment costs, and the number of QALYs gained	vaccine efficacy (95%, 99%, 100%),Females aged 12 years through to 99 years	Females vaccinated before aged 13 years, assumed to increase linearly for the first 5 years to 70% and to remain at 70% thereafter. vaccine series cost assumed to be $300 to $490	Vaccination of 12-year-old girls to existing screening practices ranged from $3,906 to $14,723
BAUCH *ET AL* [54]	Deterministic, dynamic, numerical	Investigating the role partnerships have on HPV transmission models and	**Epidemiological:** Prevalence : HPV	Vaccination strategies, to examine how inclusion or exclusion of partnerships	Pair model, heterosexual population, monogamous, pair dynamics have equilibrated in a	Not including partnerships can potentially result in biased projections of HPV prevalence.

AUTHOR(S)	MODEL TYPE	PURPOSE	OUTCOMES	STRATEGIES EVALUATED	KEY ASSUMPTIONS	MAIN FINDINGS
		evaluating when modelling partnerships is necessary		affects projected prevalence, the dynamics of the pair model can be explored for a range of possible values of the separation rate	population where infection and vaccination are introduced, track the time evolution of partnerships and disease prevalence with or without vaccination	When transmission rates are calibrated to match empirical pre-vaccine HPV prevalence, the projected prevalence under a vaccination program does not vary significantly, regardless of whether partnerships are included
DIAZ *ET AL* [56]	Stochastic, individual based, numerical	Investigate the impact of HPV vaccination strategies and screening strategies in India	**Epidemiological:** Prevalence: HPV, Incidences CC **Economic:** life expectancy gains, cost-effectiveness ratios	Individual girls representative of a single birth cohort enter the model at age 9, before sexual debut,	70 % vaccine coverage, Individual girls representative of a single birth cohort enter the model at age 9, before sexual debut,	70% vaccine coverage resulted in 44 % reduction in lifetime CC risk, combined approach of pre-adolescent vaccination and screening three times per lifetime after age 30, both at 70% coverage, provided a mean cancer reduction of 56–63%, depending on the specific screening strategy
CHOW *ET AL* [34]	Cohort, numerical, deterministic	Investigating the impact and cost effectiveness of HPV DNA testing with screening in a population in Taiwan	**Epidemiological:** prevalence: HPV infection Incidence: CIN and CC **Economic:** QALY gained, cost effective ratio	Nine screening strategies were evaluated comprising of three screening tools: (i) Papanicolaou smear alone, (ii) HPV DNA testing followed by Papanicolaou smear triage, and (iii) HPV DNA testing combined with Papanicolaou smear, and three screening intervals: (i) annually, (ii) every 3 years, (iii) every 5 years.	No regression of CC states, maximum of 5 year CC infection	Most cost effective strategy was HPV DNA testing followed by Papanicolaou smear triage every 3 or 5 years, cost effective ratio of $1 247 000 per QALY
BERKHOF *ET AL* [31]	Cohort, deterministic, numerical	Investigating the population level impact on the effects of screening on HPV prevalence and CC incidence	**Epidemiological:** Prevalence : HPV infection Incidence: CIN,CC, Lifetime CC risk	Females screening from age 30 years, 5 year intervals, 80% compliance rate.	CC cannot develop without persistent high risk HPV type infection, CIN3 caused by high risk type infection only, 50% of non-compliers to screening have never been screened	Lifetime CC risk 2.9%, peak at 48 years, 80% reduction with screening. 40% reduction of HPV high risk type infection with screening
ELBASHA *ET AL* [5]	Deterministic, dynamic, numerical	Evaluate the epidemiologic consequences and cost effectiveness of vaccination strategies in a setting of organized CC screening in the United States	**Epidemiological:** prevalence: HPV infection Incidence: CIN and CC **Economic:** QALY gained, cost effective ratio	Coverage increase linearly from 0% to 70% during the first 5 years of the program and remain at 70% thereafter, catch-up program would increase linearly from 0% up to 50% during the first 5 years and then drop to 0% after 5 years, 70% of adolescents vaccinated before they turn 12	equal access to health care, sexual debut age 12 years ,male population in the model is always at a steady-state, vaccine efficacy 90%, vaccine does not affect natural course of disease,	HPV vaccine can: (i) substantially reduce the incidence of disease, (ii) increase survival among females, (iii) improve quality of life for both males and females, (iv) be cost-effective when with females age 12–24 years ,(v) be cost-effective both sex vaccination before age 12 with a 12 to 24 years of age catch-up program .ICER for catch-up vaccination of females age 12–24 is $4,666, and the most

AUTHOR(S)	MODEL TYPE	PURPOSE	OUTCOMES	STRATEGIES EVALUATED	KEY ASSUMPTIONS	MAIN FINDINGS
						effective strategy of vaccinating both sexes had an ICER of $45,056.
BARNABAS ET AL [57]	Deterministic, dynamic, numerical	estimate the transmission probability of the virus, to look at the effect of changes in patterns of sexual behaviour and smoking on age-specific trends in cancer incidence, and to explore the impact of HPV 16 vaccination	**Epidemiological:** Prevalence of HPV infection, Incidences: CIN1,CIN2/3, CC	100% efficiency, lifelong protection, Vaccination coverage altered. Vaccination at age 15 years. Screening: Aged 30 years, 49% of eligible women are screened, aged 40–55 years, 72% of eligible women are screened. screened age groups were 30–60 y, using cytological Papanicolaou smear screening, and the screening interval was 5 y	HPV 16 accounted for 56% of CC incidence, hysterectomy rate 20%, 0.6 transmission probability,	Changes in sexual behaviour and smoking accounted, in part, for the increase seen in CC incidence in 35- to 39-y-old women from 1990 to 1999. At both low (10% in opportunistic immunisation) and high (90% in a national immunisation programme) coverage of the adolescent population, vaccinating women and men had little benefit over vaccinating women alone
GOLDIE *ET AL* [58]	Cohort, deterministic, numerical	Evaluating the population level impact and cost effectiveness of HPV vaccination strategies in Asia Pacific Region	**Epidemiological:** Prevalence of HPV, Lifetime cancer risk **Economic:** DALYs , ICERs	Screening females aged 30 years onwards, 3 times, pre-adolescent vaccination	population-based and epidemiologic data for 25 countries in Asia	cost- effective if the cost per vaccinated girl is less than I$10-I$25
GOLD-HABER *ET AL* [59]	Stochastic, dynamic, numerical	Investigating population level impact of CC screening strategies	**Epidemiological:** Prevalence: HPV, CIN1, CIN2/3 , Incidence: CC	5 screening scenarios: (i) no screening and screening using cervical cytology at 4 levels of intensity: every (ii) 1, (iii)2,(iv) 3, (v) 5 years ,from ages 18 to 70	age 9 prior to sexual debut, symptomatic women cancer receive stage-specific treatment	expected reductions in lifetime risk of cancer with annual or biennial screening were 76%, reduction from vaccination alone was 75%, although it ranged from 60% to 88%, vaccination combined with every-5-year screening, reduction of 89% and range of 83% to 95%
BOGAARDS *ET AL* [46]	Dynamic, deterministic, qualitative	Investigating the population level impact of HPV vaccination	**Epidemiological:** Prevalence: HPV	Vaccination of sex with highest HPV incidence	Population in demographic equilibrium, sexes have a similar degree of natural immunity, and that the probability of male-to-female transmission is the same as that of female-to-male transmission	Increasing preadolescent female's vaccination is more effective in reducing HPV infection than including males in existing vaccination programs.
GREEN *ET AL* [52]	Cohort, deterministic, numerical, qualitative	Evaluating the population level effectiveness of mass education an individual education strategies on HPV	**Epidemiological:** Prevalence: HPV **Economic:** ICERs, QALYs	(i) mandatory vaccination policy females in grade 6, individual education (ii) ongoing mass-media campaign, optional vaccination	Educated individuals reduce sexual activity, females vaccinated in grade 6 have no prior sexual activity, effects of education can be lost	even in the presence of a vaccine, the infective population will remain large due to a high transmission rate. Their results also support the conclusion that a high transmission rate and a high reproductive rate require a high efficacy and high vaccine coverage to eliminate the epidemic
BOOT *ET AL* [60]	Cohort,	Evaluating the population	**Epidemiological:**	Females only, 80% vaccine	Vaccine: no reduced trans-	10–12-year-old girls most

AUTHOR(S)	MODEL TYPE	PURPOSE	OUTCOMES	STRATEGIES EVALUATED	KEY ASSUMPTIONS	MAIN FINDINGS
	deterministic, numerical	level impact of vaccinating pre-adolescent females	Prevalence HPV, Incidence: CC, CC mortality. **Economic:** ICERs, QALYs	efficiency, no effects on the screening	mission, no cross protection, and no impact on non-CCs, 60% of the CCs can be avoided with HPV-16/18 vaccination, while in reality~75% of all CCs cases in The Netherlands	effective with a catch up program up to the age 15 years – due to limited sexual activity. Basic : vaccination of preadolescent females would require D€ 24,000/LYG, less than the Dutch gross domestic product (GDP) per capita
BARNABAS *ET AL* [44]	Dynamic, Deterministic, Numerical	Investigate the influence of duration of infection an precancerous lesions	**Epidemiological:** Prevalence: HPV , Incidence: CIN1,CIN2+,CC	local organized CC screening program (females aged 25 to 65 years, every 3 years)	Average probability per partnership 40%, clearance of lesions independent of age, developing lifelong immunity dependent on age, sexual debut after age 15 years	suggest that an exclusive role of women's age in shaping the rate of progression to cancer is unlikely
ELBASHA *ET AL* [61]	Dynamic, Deterministic, Theoretical	Investigate the global stability of a two sex HPV transmission model	basic and effective reproduction numbers and a measure of vaccine impact	Evaluated reproduction number under vaccine coverage percentages	susceptible-infective-removed (SIR) compartmental structure	if the effective reproduction number is greater than unity, there is a locally unstable infection-free equilibrium and a unique, globally asymptotically stable endemic equilibrium. If the effective reproduction number is less than unity, the infection-free equilibrium is globally asymptotically stable, and HPV will be eliminated
KOROSTIL ET AL [62]	Bayesian statistical model, theoretical	explore the ability of an extension to the class of adaptive Markov chain Monte Carlo algorithms to incorporate a forward projection simulation strategy for the ordinary differential equation state trajectories ,(HPV-6, HPV-11) transmission and vaccination impact	probability of transmission, HPV incubation period, duration of infection, duration of genital warts treatment, duration of immunity, the probability of sero-conversion	stochastic mixing matrix framework, explore the ability of an extension to the class of adaptive Markov chain Monte Carlo algorithms to incorporate a forward projection simulation strategy for the ordinary differential equation state trajectories	(HPV-6, HPV-11) stochastic mixing matrix framework, aged 15-59, constant over time	the predictive performance under the Bayesian framework can be directly interpreted as the predictive distribution of the model, providing advantages for the proposed Bayesian estimation approach in interpretation of the results
AL-ARYDAH ET AL [63]	Deterministic, theoretical, numerical	Investigating the population level impact of HPV vaccination strategies	**Epidemiological:** Prevalence: HPV	HPV vaccination program for a vaccine targeting HPV types 16 and 18 in both childhood and adult stages. (i) vaccinating all children but no adults and (ii) vaccinating all adults but no children	Females/Males enter at aged 13 years, vaccination does not occur past 26 years,	vaccinating a single age cohort in one sex can result in eventual control of the disease across all age groups

3 Mathematical Model

This chapter describes the mathematical model developed. The chapter begins with a Table 2 Description of subscripts and variables, and parameters (Table 2 and 3 respectively). The demographic section of the model is briefly discussed followed by the description of the epidemiological model. The specific equations used in each compartment are then described, based on the natural history of HPV progression to cervical cancer. The chapter ends with the description the HPV transmission mixing matrix and the force of infection.

Table 2 Description of subscripts and variables

SYMBOL	DESCRIPTION
SUBSCRIPTS	
g,g'	Sex where g sex, g' sex opposite of sex g
f,m	Sex where f is for female and m is for male
i,j	Age groups
k,l	Sexual activity groups
r,t	Sexual orientation groups
h	HIV status
s	Stage of CIN or cervical cancer
VARIABLES	
λ_{gikr}^{h}	Force of HPV infection
$\varkappa_{gikr}^{h}$	Force of HIV infection
S_{gikr}^{h}	Susceptible to HPV
I_{gikr}^{h}	Infected with HPV
Z_{gikr}^{h}	Recovered and partial immune to HPV infection
V_{gikr}^{h}	Vaccinated from HPV and susceptible to HPV
W_{gikr}^{h}	Vaccinated from HPV and infected with HPV
X_{gikr}^{h}	Vaccinated from HPV and recovered and partially immune to HPV infection
CIN_{gikr}^{hs}	Infected with CIN and HPV
CC_{gikr}^{hs}	Infected with cervical cancer and HPV
CCS_{gikr}^{h}	Cervical cancer survivor
N_{gikr}^{h}	Number of individuals

Table 3 Description of parameters

PARAMETER SYMBOL	DESCRIPTION NAME
DEMOGRAPHIC PARAMETERS	
μ_{gi}	Natural mortality ; sex g , age i
μ_{CCfi}^{hs}	Cervical cancer related death rate ; age i , HIV status h, cervical cancer state s dependent
Λ_{gikr}^{h}	Rate of population growth ; sex g , age i, HIV status h, sexual activity k, sexual orientation r dependent
$band_i$	Number of years within age group i
d_{gi}	transmission from age group i to age group $i+1$; sex g , age i dependent
BEHAVIOURAL PARAMETERS	
c_{gik}	average rate of sexual partner change ; sex g , age i, sexual activity k dependent
ω_{g2}	proportion of partnerships that are of a heterosexual nature for bisexuals ; sex g dependent
ψ_{gikjl}	probability of mixing ; sex g , age i, sexual activity k dependent
ε_1, ε_2	mixing parameters between age and sexual activity groups
BIOLOGICAL PARAMETERS	
RATES	
$1/\sigma_{lgi}^{h}$	Mean duration of recovery from HPV infection ; sex g , age i, HIV status h dependent
χ_{gi}^{h}	rate of removal from sexually active population due to HIV progression to AIDS ; sex g, age i , HIV status h dependent
χ_{gi}^{h}	rate of removal from sexually active population due to HIV progression to AIDS ; sex g, age i , HIV status h dependent
PROBABILITIES	
$\beta_{gg'}$	HPV transmission probability per partnership from an individual sex g' to individual sex g ; sex g and type of partnership dependent
β_{gg}	HPV transmission probability per partnership from individual sex g to an individual sex g ; ; sex g and type of partnership dependent
$\beta_{gg'}^{+}$	HIV transmission probability per partnership from an individual sex g' to individual sex g ; sex g and type of partnership dependent
β_{gg}^{+}	HIV transmission probability per partnership from individual sex g to an individual sex g ; sex g and type of partnership dependent
σ_{HPVgi}^{h}	probability of recovery from HPV infection ; sex g, age i , HIV status h dependent
σ_{CINgi}^{hs}	probability of regression from CIN stage s; sex g, age i , HIV status h, CIN state s dependent

σ_{CCgi}^{hs}	probability of regression of CC state s or no cancer or HPV infection ; sex g, age i , HIV status h, CC state s dependent
ρ_{lgi}^{hs}	probability of progression from HPV to CIN state s; sex g, age i , HIV status h, CIN state s dependent
ρ_{CINgi}^{hs}	probability of progression between CIN state s to higher state (i.e. CIN1 to CIN2/3, CIN2/3 to CC) ; sex g, age i , HIV status h, CIN state s dependent
ρ_{CCgi}^{hs}	probability of progression of CC state s to an adjacent higher state ; sex g, age i , HIV status h, CC state s dependent
PERCENTAGES	
κ^{s}	percentage regressing from CIN state s to normal ; CIN state s dependent
κ_{l}^{s}	percentage regressing from CIN state s to HPV infection ; CIN state s dependent
κ_{CIN}^{s}	percentage regressing from CIN2/3 to state s; CIN state s dependent
ϕ_{gi}	percentage of individual vaccinated on entry into sexual active , sex g , age i ; sex g, age i dependent
ϑ_{gi}	percentage vaccinated in sex g , age group i; sex g, age i dependent
VACCINATION EFFECTS	
$\pi_{\sigma l}$	Effect of vaccination on regression of HPV infection
$\pi_{\sigma Z}$	Effect of vaccination on waning immunity
π_{λ}	Effect of vaccination on Force of infection
$\pi_{\rho l}$	Effect of vaccination on HPV infection transmission
$\pi_{\sigma CIN}^{s}$	Effect of vaccination on regression of CIN state s

3.1 The demographic model

The demographic model is based on the model described and used by Elbasha *et al* [5] which was a modified version of the initial boundary value problem for age-dependent population growth described by Hethcote [64].

The population is divided into n age groups defined by the age interval $[a_{i-1}, a_i]$. The integral of the age distribution function from a_{i-1} to a_i is used to determine the number of individuals at time t in the age interval $[a_{i-1}, a_i]$. It is assumed the population has reached a steady state distribution with exponential growth or

decay of the form e^{qt}. Individuals are transferred between consecutive age groups at an age and sex specific per capita rate per year. This transfer rate was given by Hethcote [64] to be:

$$d_{gi} = \frac{\mu_{gi} + q}{e^{band_i(\mu_{gi}+q)} - 1}$$

where $band_i$ is the number of years an individual remains in an age group i; μ_{gi} is the age and sex specific per capita death rate and q is the annual growth rate.

The annual growth rate is required to satisfy the modified age-group form of the Lokta characteristic equations ([21], [64]).

$$\Lambda_{gikr} = \left(d_{gi} + \mu_{gi} + q\right) N_{gikr}(0)$$

where N_{gikr} indicates the total population of sex g, age i, sexual orientation r, sexual activity k.

The modelled population consists of male and females aged 10 to 64, who are divided into five year age groups. The population is limited to the range of 10-64 by the presumed absence of sexual activity in people under the age of 10 years old and the low sexual activity rate in people over the age of 64. The age limit is chosen to fit data available on the South African population. The five year age group is a commonly used method for reporting survey results and is used in the literature and survey, reports and clinical trials providing data to the model [65]–[70].

The population is divided into additional compartments based on:

1. Sexual orientation represented by *r* with: (i) *r=1* indicating heterosexual, (ii) *r=2* indicating bisexual, and (iii) *r=3* indicating homosexual,
2. HIV status represented by h with: (i) a negative sign or lack of sign indicating HIV negative, and (ii) a positive sign indicating HIV positive,
3. Sexual activity groups represented by *k* with: (i) no sexual activity, (ii) low sexual activity, and (iii) high sexual activity. The sexual activity groups are defined according to the sex, sexual activity, and age specific rate of sexual partnership change per unit time c_{gki}.

New additions enter the sexually active population at a rate Λ^h_{gikr} which is sex g, age i, sexual orientation r, sexual activity k, and HIV status h specific. Individuals die at a per capita rate μ_{gi} which is sex g,and age i specific. Individuals are transferred between age groups at a rate d_{gi}. Individuals are transferred between the HIV positive and negative classes through HIV infection at a rate λ^h_{gikr} which is sex, sexual activity, sexual orientation, time, and age dependent. The HIV infected population is reduced by progression to AIDS through a transition probability χ_{gi}. It is assumed individuals who have progressed to AIDs are not sexually active. It is additionally assumed that cervical cancer survivors do not contribute to the disease progression of the population. Individuals are removed from all compartments through a natural mortality per capita rate μ_{gi}. Females with cervical cancer have an additional mortality rate μ^{hs}_{CCf1}.

The demographic model is given by the equations:

$$\dot{N}^h_{m1kr} = \Lambda^h_{m1kr} - \left(d_{m1} + \mu_{m1} + \chi^h_{m1}\right)N^h_{m1kr} \quad (2.a)$$

$$\dot{N}^h_{f1kr} = \Lambda^h_{f1kr} - \sum_s \mu^{hs}_{CCf1} CC^{hs}_{f1kr} - \left(d_{f1} + \mu_{f1} + \chi^h_{f1}\right)N^h_{f1kr} \quad (2.b)$$

$$\dot{N}^h_{mikr} = d_{\mathrm{m}(i-1)} N^h_{\mathrm{m}(i-1)kr} - \left(d_{mi} + \mu_{mi} + \chi^h_{mi}\right)N^h_{mikr} \quad (2.c)$$

$$\dot{N}^h_{fikr} = d_{\mathrm{f}(i-1)} N^h_{\mathrm{f}(i-1)kr} - \sum_s \mu^{hs}_{CCfi} CC^{hs}_{fikr} - \left(d_{fi} + \mu_{fi} + \chi^h_{fi}\right)N^h_{fikr} \quad (2.d)$$

where $i > 2;\ d_{gn} = 0$

All parameters and variables are defined in the text and additionally in tables Table 2 and Table 3, shown at the beginning on this chapter on page35.

3.2 The epidemiological model

The epidemiological model is described in Figure 3-1. Assumptions include No cervical screening or treatment scenarios and CIN and CC are only HPV type specific cases. Each compartment is described and equations given in the sections to follow.

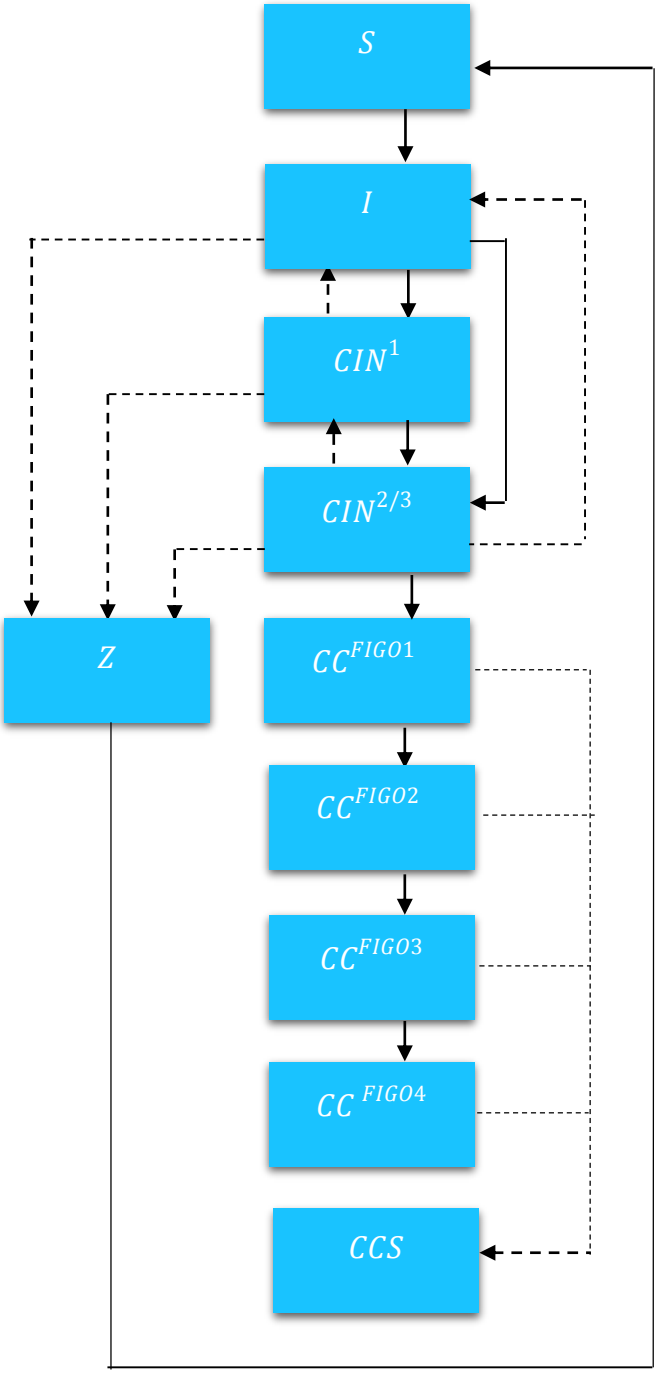


Figure 3-1 Schematic diagram representing the natural history of HPV infection and cervical cancer to be followed in the mathematical model. HPV infection can be acquired at a rate known as the Force of Infection. A HPV infected individual can either recover from HPV or progress to HPV caused CIN. A CIN1 infected individual can either progress to a higher state of CIN or lesions can regress. A CIN2/3 infected individual can either regress to CIN1 or complete regression of CIN. Regression of CIN can involve clearance of HPV infection or not. A CIN2/3 infected individual can additional progress to cervical cancer. CC is characterised by the FIGO system, it is assumed that an individual cannot skip cervical cancer states, therefore progression involves going to a higher state, all cervical cancer states can regress to the state CCS. Z indicates recovery from HPV infection but an individual who is not susceptible due to a natural immunity that can wane and result in becoming susceptible.

3.2.1 HPV Susceptible Individuals

New additions to the sexually active population enter into the uninfected with HPV and susceptible to HPV compartment at a rate Λ^{h}_{gikr}. A percentage ϕ_{gi} of these individuals are vaccinated on entry and move to the HPV susceptible vaccination compartment, the remaining proportion move to the HPV susceptible compartment. The model assumes a proportion ϑ_{gi} of individuals in other age groups and epidemiological classes are vaccinated and therefore move into the vaccinated compartments. Individuals in susceptible classes acquire HPV infection at a rate λ^{h}_{gikr} which is sex, sexual activity, sexual orientation, HIV status, age, and time dependent.

The ODE's for this compartment are:

$$\dot{S}^{-}_{g1kr} = \left(1-\phi_{g1}\right)\Lambda^{-}_{g1kr} + \sigma^{-}_{Zg1}Z^{-}_{g1kr} - \left(\lambda^{-}_{g1kr} + \vartheta_{g1} + \varkappa_{g1kr} + d_{g1} + \mu_{g1}\right)S^{-}_{g1kr} \quad (3.a)$$

$$\dot{S}^{+}_{g1kr} = \left(1-\phi_{g1}\right)\Lambda^{+}_{g1kr} + \varkappa_{g1kr}S^{-}_{g1kr} + \sigma^{+}_{Zg1}Z^{+}_{g1kr} - \left(\lambda^{+}_{g1kr} + \vartheta_{g1} + d_{g1} + \mu_{g1} + \chi_{g1}\right)S^{+}_{g1kr} \quad (3.b)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f,m$

$$\dot{S}^{-}_{gikr} = \left(1-\phi_{gi}\right)\Lambda^{-}_{gikr} + \sigma^{-}_{Zgi}Z^{-}_{gikr} + d_{g(i-1)}S^{-}_{g(i-1)kr} - \left(\lambda^{-}_{gikr} + \vartheta_{gi} + \varkappa_{gikr} + d_{gi} + \mu_{gi}\right)S^{-}_{gikr} \quad (3.c)$$

$$\dot{S}^{+}_{gikr} = \left(1-\phi_{gi}\right)\Lambda^{+}_{gikr} + \varkappa_{gikr}S^{-}_{gikr} + \sigma^{+}_{Zgi}Z^{+}_{gikr} + d_{g(i-1)}S^{+}_{g(i-1)kr} - \left(\lambda^{+}_{gikr} + \vartheta_{gi} + d_{gi} + \mu_{gi} + \chi_{gi}\right)S^{+}_{gikr} \quad (3.d)$$

where $i = 2,\ldots 11,;\ k = 1,2,3;\ r = 1,2,3;\ g = f,m$

3.2.1.1 HPV Vaccinated

The vaccination induced immunity can wane therefore individuals can move to the susceptible compartments at a rate σ^{h}_{Zgi}, which is sex, age and HIV status dependent. It is assumed vaccination will not confer any therapeutic benefits to individuals who are already HPV infected during vaccination, therefore vaccinated individuals who experience a breakthrough infection enter the Infectious vaccinated compartment at a rate λ^{h}_{gikr}. Individuals who are vaccinated have a decreased probability of becoming HPV infected, the effect of vaccination on becoming HPV infected is determined by π_{λ}.

The ODE's for this compartment are:

$$\dot{V}^{-}_{g1kr} = \phi_{g1}\Lambda^{-}_{g1kr} + \vartheta_{g1}S^{-}_{g1kr} + \pi_{\sigma Z}\sigma^{-}_{Zg1}X^{-}_{g1kr} - \left(\pi_{\lambda}\lambda^{-}_{g1kr} + \varkappa_{g1kr} + d_{g1} + \mu_{g1}\right)V^{-}_{g1kr} \quad (3.e)$$

$$\dot{V}^{+}_{g1kr} = \phi_{g1}\Lambda^{+}_{g1kr} + \vartheta_{g1}S^{+}_{g1kr} + \varkappa_{g1kr}V^{-}_{g1kr} + \pi_{\sigma Z}\sigma^{+}_{Zg1}X^{+}_{g1kr} - \left(\pi_{\lambda}\lambda^{+}_{g1kr} + d_{g1} + \mu_{g1} + \chi_{g1}\right)V^{+}_{g1kr} \quad (3.f)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f,m$

$$\dot{V}^{-}_{gikr} = \phi_{gi}\Lambda^{-}_{gikr} + \vartheta_{gi}S^{-}_{gikr} + \pi_{\sigma Z}\sigma^{-}_{Zgi}X^{-}_{gikr} + d_{g(i-1)}V^{-}_{g(i-1)kr} - \left(\pi_{\lambda}\lambda^{-}_{gikr} + \varkappa_{gikr} + d_{gi} + \mu_{gi}\right)V^{-}_{gikr} \quad (3.g)$$

$$\dot{V}^{+}_{gikr} = \phi_{gi}\Lambda^{+}_{gikr} + \vartheta_{gi}S^{+}_{gikr} + \varkappa_{gikr}V^{-}_{gikr} + \pi_{\sigma Z}\sigma^{+}_{Zgi}X^{+}_{gikr} + d_{g(i-1)}V^{+}_{g(i-1)kr} - \left(\pi_{\lambda}\lambda^{+}_{gikr} + d_{gi} + \mu_{gi} + \chi_{gi}\right)V^{+}_{gikr} \quad (3.h)$$

where $i = 2,\ldots 11,;\ k = 1,2,3;\ r = 1,2,3;\ g = f,m$

3.2.2 HPV Infected Individuals

When HPV transmission occurs HPV susceptible individuals enter the HPV infected compartment. Females additionally enter if their HPV type caused CIN spontaneously regresses at a probability σ^{hs}_{CINgi}, but are still infected with percentage κ^{s}_{I}. Individuals leave this compartment and enter the recovered and partially immune compartment when the infectious period for HPV ends. HPV infection is resolved at a per capita rate σ^{h}_{Igi}. Individuals can develop CIN at a rate ρ^{hs}_{Igi}. It is assumed vaccination will not confer any therapeutic benefits to individuals who are already HPV infected during vaccination therefore individuals who are vaccinated leave this compartment and enter the infected but vaccinated compartment.

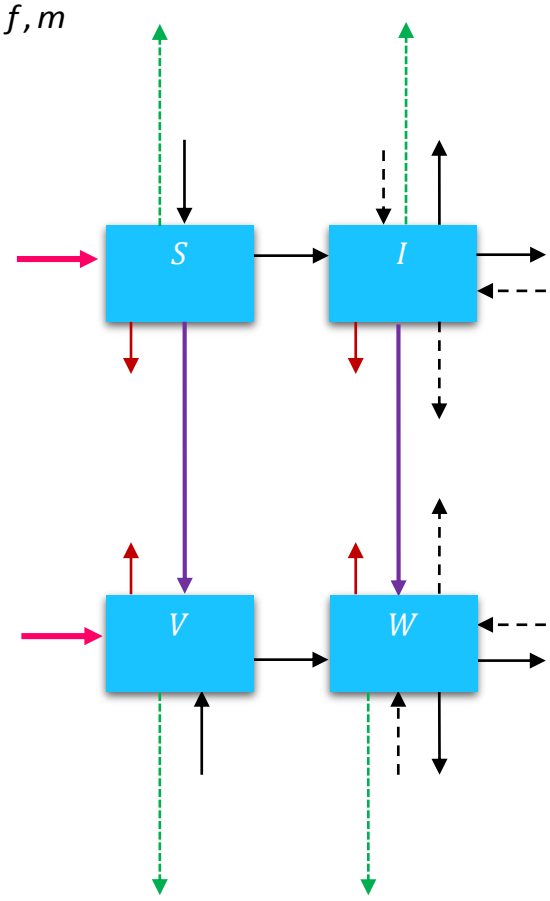


Figure 3-2 Diagram of a simplified schematic of the Susceptible and Infective compartments. The pink line indicates new additions to the sexually active population. The green line represents the effect of HIV transmission, the red lines the natural mortality. The purple lines indicate vaccination. The black lines indicate progression to a higher state of disease severity, whereas the dotted black line indicates regression to a state of lower severity..

The ODE's for this compartment are:

$$\dot{I}^{-}_{g1kr} = \lambda^{-}_{g1kr} S^{-}_{g1kr} + \sum_{s} \kappa^{s}_{l} \sigma^{-s}_{CINg1} CIN^{-s}_{g1kr} - \left(\sigma^{-}_{HPVgi} \sigma^{-}_{lg1} + \vartheta_{g1} + \varkappa_{g1kr} + \sum_{s} \rho^{-s}_{lg1} + d_{g1} + \mu_{g1} \right) I^{-}_{g1kr} \quad (4.a)$$

$$\dot{I}^{+}_{g1kr} = \lambda^{+}_{g1kr} S^{+}_{g1kr} + \varkappa_{g1kr} I^{-}_{g1kr} + \sum_{s} \kappa^{s}_{l} \sigma^{+s}_{CINg1} CIN^{+s}_{g1kr} - \left(\sigma^{+}_{HPVgi} \sigma^{+}_{lg1} + \vartheta_{g1} + \sum_{s} \rho^{+s}_{lg1} + d_{g1} + \mu_{g1} + \chi_{g1} \right) I^{+}_{g1kr} \quad (4.b)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f, m$

$$\dot{I}^{-}_{gikr} = \lambda^{-}_{gikr} S^{-}_{gikr} + \sum_{s} \kappa^{s}_{l} \sigma^{-s}_{CINgi} CIN^{-s}_{gikr} + d_{g(i-1)} I^{-}_{g(i-1)kr} - \left(\sigma^{-}_{HPVgi} \sigma^{-}_{lgi} + \vartheta_{gi} + \varkappa_{gikr} + \sum_{s} \rho^{-s}_{lgi} + d_{gi} + \mu_{gi} \right) I^{-}_{gikr} \quad (4.c)$$

$$\dot{I}^{+}_{gikr} = \lambda^{+}_{gikr} S^{+}_{gikr} + \varkappa_{gikr} I^{-}_{gikr} + \sum_{s} \kappa^{s}_{l} \sigma^{+s}_{CINgi} CIN^{+s}_{gikr} + d_{g(i-1)} I^{+}_{g(i-1)kr} - \left(\sigma^{+}_{HPVgi} \sigma^{+}_{lgi} + \vartheta_{gi} + \sum_{s} \rho^{+s}_{lgi} + d_{gi} + \mu_{gi} + \chi_{gi} \right) I^{+}_{gikr} \quad (4.d)$$

where $i = 2, \ldots 11, ;\ k = 1, 2, 3;\ r = 1, 2, 3;\ g = f, m$

3.2.2.1 HPV Vaccinated

Vaccination is assumed to effect HPV transmission and regression of HPV and HPV Type caused CIN. The effect of vaccination on becoming infected with HPV is determined by π_{λ} .The effects of vaccination on CIN regression and HPV regression are determined by $\pi^{s}_{\sigma CIN}$,and $\pi_{\sigma l}$ respectively.

The ODE's for this compartment are:

$$\dot{W}^{-}_{g1kr} = \pi_{\lambda} \lambda^{-}_{g1kr} V^{-}_{g1kr} + \vartheta_{g1} I^{-}_{g1kr} + \sum_{s} \pi^{s}_{\sigma CIN} \kappa^{s}_{l} \sigma^{-s}_{CINg1} VCIN^{-s}_{g1kr} - \left(\pi_{\sigma l} \sigma^{-}_{HPVgi} \sigma^{-}_{lg1} + \varkappa_{g1kr} + \sum_{s} \rho^{-s}_{lg1} + d_{g1} + \mu_{g1} \right) W^{-}_{g1kr} \quad (5.a)$$

$$\dot{W}^{+}_{g1kr} = \pi_{\lambda} \lambda^{+}_{g1kr} V^{+}_{g1kr} + \varkappa_{g1kr} W^{-}_{g1kr} + \vartheta_{g1} I^{+}_{g1kr} + \sum_{s} \pi^{s}_{\sigma CIN} \kappa^{s}_{l} \sigma^{+s}_{CINg1} VCIN^{+s}_{g1kr} - \left(\pi_{\sigma l} \sigma^{+}_{HPVgi} \sigma^{+}_{lg1} + \sum_{s} \rho^{+s}_{lg1} + d_{g1} + \mu_{g1} + \chi_{g1} \right) W^{+}_{g1kr} \quad (5.b)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f,m$

$$\dot{W}^{-}_{gikr} = \pi_{\lambda}\lambda^{-}_{gikr}V^{-}_{gikr} + \vartheta_{gi}I^{-}_{gikr} + \sum_{s}\pi^{s}_{\sigma CIN}\kappa^{s}_{I}\sigma^{-s}_{CINgi}VCIN^{-s}_{gikr} + d_{g(i-1)}W^{-}_{g(i-1)kr} - \left(\pi_{\sigma I}\sigma^{-}_{HPVgi}\sigma^{-}_{Igi} + \varkappa_{gikr} + \sum_{s}\rho^{-s}_{Igi} + d_{gi} + \mu_{gi}\right)W^{-}_{gikr} \quad (5.c)$$

$$\dot{W}^{+}_{gikr} = \pi_{\lambda}\lambda^{+}_{gikr}V^{+}_{gikr} + \varkappa_{gikr}W^{-}_{gikr} + \vartheta_{gi}I^{+}_{gikr} + \sum_{s}\pi^{s}_{\sigma CIN}\kappa^{s}_{I}\sigma^{+s}_{CINgi}VCIN^{+s}_{gikr} + d_{g(i-1)}W^{+}_{g(i-1)kr} - \left(\pi_{\sigma I}\sigma^{+}_{HPVgi}\sigma^{+}_{Igi} + \sum_{s}\rho^{+s}_{Igi} + d_{gi} + \mu_{gi} + \chi_{gi}\right)W^{+}_{gikr} \quad (5.d)$$

where $i = 2,\ldots 11,;\ k = 1,2,3;\ r = 1,2,3;\ g = f,m$

3.2.3 HPV Recovered and Partially Immune Individuals

Individuals enter the partially immune category when HPV infection is resolved or when recovered from CIN and having resolved HPV infection. It is assumed that immunity derived from natural infection can be temporary and that individuals in the partial immune category eventually move to the susceptible compartment at a rate σ^{h}_{Zgi}.

The ODE's for this compartment are:

$$\dot{Z}^{-}_{g1kr} = \sigma^{-}_{HPVgi}\sigma^{-}_{Ig1}I^{-}_{g1kr} + \sum_{s}\kappa^{s}\sigma^{-s}_{CINg1}CIN^{-s}_{g1kr} - \left(\vartheta_{g1} + \sigma^{-}_{Zg1} + \varkappa_{g1kr} + d_{g1} + \mu_{g1}\right)Z^{-}_{g1kr} \quad (6.a)$$

$$\dot{Z}^{+}_{g1kr} = \sigma^{+}_{HPVgi}\sigma^{+}_{Ig1}I^{+}_{g1kr} + \varkappa^{h}_{g1kr}Z^{-}_{g1kr} + \sum_{s}\kappa^{s}\sigma^{+s}_{CINg1}CIN^{+s}_{g1kr} - \left(\vartheta_{g1} + \sigma^{+}_{Zg1} + d_{g1} + \mu_{g1} + \chi_{g1}\right)Z^{+}_{g1kr} \quad (6.b)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f,m$

$$\dot{Z}^{-}_{gikr} = \sigma^{-}_{HPVgi}\sigma^{-}_{Igi}I^{-}_{gikr} + \sum_{s}\kappa^{s}\sigma^{-s}_{CINgi}CIN^{-s}_{gikr} + d_{g(i-1)}Z^{-}_{g(i-1)kr} - \left(\vartheta_{gi} + \sigma^{-}_{Zgi} + \varkappa_{gikr} + d_{gi} + \mu_{gi}\right)Z^{-}_{gikr} \quad (6.c)$$

$$\dot{Z}^{+}_{gikr} = \sigma^{+}_{HPVgi}\sigma^{+}_{Igi}I^{+}_{gikr} + \varkappa^{h}_{gikr}Z^{-}_{gikr} + \sum_{s}\kappa^{s}\sigma^{+s}_{CINgi}CIN^{+s}_{gikr} + d_{g(i-1)}Z^{+}_{g(i-1)kr} - \left(\vartheta_{gi} + \sigma^{+}_{Zgi} + d_{gi} + \mu_{gi} + \chi_{gi}\right)Z^{+}_{gikr} \quad (6.d)$$

where $i = 2,\ldots 11,;\ k = 1,2,3;\ r = 1,2,3;\ g = f,m$

3.2.3.1 HPV Vaccinated

The ODE's for this compartment are:

$$\dot{X}^{-}_{g1kr} = \pi_{\sigma I}\sigma^{-}_{HPVgi}\sigma^{-}_{Ig1}W^{-}_{g1kr} + \vartheta_{g1}Z^{-}_{g1kr} + \sum_{s}\pi^{s}_{\sigma CIN}\kappa^{s}\sigma^{-s}_{CINg1}VCIN^{-s}_{g1kr} - \left(\pi_{\sigma Z}\sigma^{-}_{Zg1} + \varkappa_{g1kr} + d_{g1} + \mu_{g1}\right)X^{-}_{g1kr} \quad (7.a)$$

$$\dot{X}^{+}_{g1kr} = \pi_{\sigma I}\sigma^{+}_{HPVgi}\sigma^{+}_{Ig1}W^{+}_{g1kr} + \vartheta_{g1}Z^{+}_{g1kr} + \varkappa^{h}_{g1kr}X^{-}_{g1kr} + \sum_{s}\pi^{s}_{\sigma CIN}\kappa^{s}\sigma^{+s}_{CINg1}VCIN^{+s}_{g1kr} - \left(\pi_{\sigma Z}\sigma^{+}_{Zg1} + d_{g1} + \mu_{g1} + \chi_{g1}\right)X^{+}_{g1kr} \quad (7.b)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f,m$

$$\dot{X}^{-}_{gikr} = \pi_{\sigma I}\sigma^{-}_{HPVgi}\sigma^{-}_{Igi}W^{-}_{gikr} + \vartheta_{gi}Z^{-}_{gikr} + \sum_{s}\pi^{s}_{\sigma CIN}\kappa^{s}\sigma^{-s}_{CINgi}VCIN^{-s}_{gikr} + d_{g(i-1)}X^{-}_{g(i-1)kr} - \left(\pi_{\sigma Z}\sigma^{-}_{Zgi} + \varkappa_{gikr} + d_{gi} + \mu_{gi}\right)X^{-}_{gikr} \quad (7.c)$$

$$\dot{X}^{+}_{gikr} = \pi_{\sigma I}\sigma^{+}_{HPVgi}\sigma^{+}_{Igi}W^{+}_{gikr} + \vartheta_{gi}Z^{+}_{gikr} + \varkappa^{h}_{gikr}X^{-}_{gikr} + \sum_{s}\pi^{s}_{\sigma CIN}\kappa^{s}\sigma^{+s}_{CINgi}VCIN^{+s}_{gikr} + d_{g(i-1)}X^{+}_{g(i-1)kr} - \left(\pi_{\sigma Z}\sigma^{+}_{Zgi} + d_{gi} + \mu_{gi} + \chi_{gi}\right)X^{+}_{gikr} \quad (7.d)$$

where $i = 2,\ldots 11,;\ k = 1,2,3;\ r = 1,2,3;\ g = f,m$

3.2.4 Cervical Intraepithelial Neoplasia

HPV type caused CIN is divided into two compartments based on the grade of CIN. CIN1 indicates grade 1 and CIN2/3 indicates a combined compartment for CIN grade 2 and 3. See section 2.2 for an explanation of the grades of CIN. Only CIN caused from persistent HPV infection is modelled. CIN infected individuals increase through progression of HPV infection at a probability ρ^{hs}_{Igi} and progression from a lower CIN state at a probability ρ^{hs}_{CINgi}. CIN infected individuals are removed from their CIN states through progression to a higher CIN state ρ^{hs}_{CINgi} or regression of their CIN σ^{hs}_{CINgi}.

3.2.4.1 CIN1

The ODE's for this compartment are:

$$\dot{CIN}^{-1}_{g1kr} = \rho^{-1}_{lg1} I^{-}_{g1kr} + \kappa^{1}_{CIN}\sigma^{-2}_{CINg1} CIN^{-2}_{g1kr} - \left(\sigma^{-1}_{CINg1} + \rho^{-1}_{CINg1} + \mathcal{H}_{g1kr} + \vartheta_{g1} + d_{g1} + \mu_{g1}\right) CIN^{-1}_{g1kr} \quad (8.a)$$

$$\dot{CIN}^{+1}_{g1kr} = \rho^{+1}_{lg1} I^{+}_{g1kr} + \mathcal{H}_{g1kr} CIN^{-1}_{g1kr} + \kappa^{1}_{CIN}\sigma^{+2}_{CINg1} CIN^{+2}_{g1kr} - \left(\sigma^{+1}_{CINg1} + \rho^{+1}_{CINg1} + \vartheta_{g1} + d_{g1} + \mu_{g1} + \chi_{g1}\right) CIN^{+1}_{g1kr} \quad (8.b)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f, m$

$$\dot{CIN}^{-1}_{gikr} = \rho^{-1}_{lgi} I^{-}_{gikr} + \kappa^{1}_{CIN}\sigma^{-2}_{CINgi} CIN^{-2}_{gikr} + d_{g(i-1)} CIN^{-1}_{g(i-1)kr} - \left(\sigma^{-1}_{CINgi} + \rho^{-1}_{CINgi} + \mathcal{H}_{gikr} + \vartheta_{gi} + d_{gi} + \mu_{gi}\right) CIN^{-1}_{gikr} \quad (8.c)$$

$$\dot{CIN}^{+1}_{gikr} = \rho^{+1}_{lgi} I^{+}_{gikr} + \mathcal{H}_{gikr} CIN^{-1}_{gikr} + \kappa^{1}_{CIN}\sigma^{+2}_{CINgi} CIN^{+2}_{gikr} + d_{g(i-1)} CIN^{+1}_{g(i-1)kr} - \left(\sigma^{+1}_{CINgi} + \rho^{+1}_{CINgi} + \vartheta_{gi} + d_{gi} + \mu_{gi} + \chi_{gi}\right) CIN^{+1}_{gikr} \quad (8.d)$$

where $i = 2,\ldots 11,; k = 1,2,3;\ r = 1,2,3;$
$g = f, m$

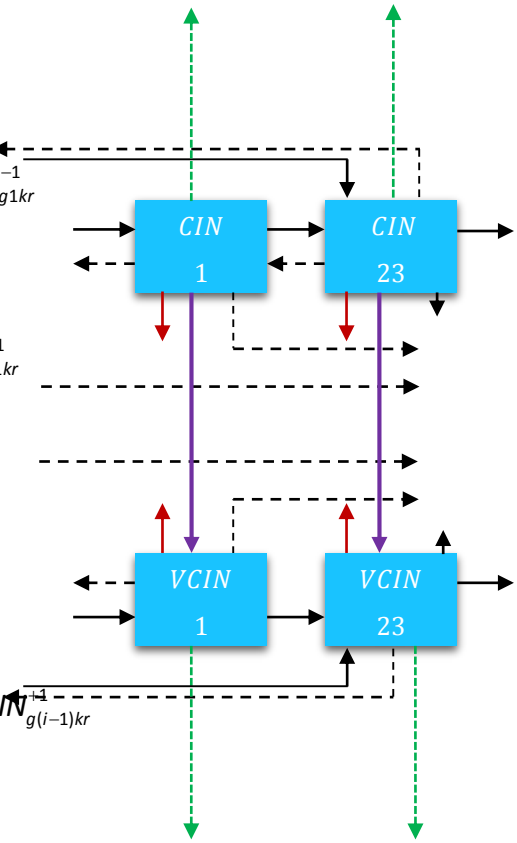


Figure 3-3 Diagram of a simplified schematic of the CIN compartments. The green line represents the effect of HIV transmission, the red lines the natural mortality. The purple lines indicate vaccination. The black lines indicate progression to a higher state of disease severity, whereas the dotted black line indicates regression to a state of lower severity..

3.2.4.1.1 HPV Vaccinated

The ODE's for this compartment are:

$$\dot{VCIN}^{-1}_{g1kr} = \rho^{-1}_{lg1} W^{-}_{g1kr} + \pi^{s}_{\sigma CIN}\kappa^{1}_{CIN}\sigma^{-2}_{CIN1} VCIN^{-2}_{g1kr} + \vartheta_{g1} CIN^{-1}_{g1kr} - \left(\pi^{s}_{\sigma CIN}\sigma^{-1}_{CIN1} + \rho^{-1}_{CIN1} + \mathcal{H}_{g1kr} + d_{g1} + \mu_{g1}\right) VCIN^{-1}_{g1kr} \quad (8.e)$$

$$\dot{VCIN}^{+1}_{g1kr} = \rho^{+1}_{lg1} W^{+}_{g1kr} + \mathcal{H}_{g1kr} VCIN^{-1}_{g1kr} + \pi^{s}_{\sigma CIN}\kappa^{1}_{CIN}\sigma^{+2}_{CIN1} VCIN^{+2}_{g1kr} + \vartheta_{g1} CIN^{-1}_{g1kr} - \left(\pi^{s}_{\sigma CIN}\sigma^{+1}_{CIN1} + \rho^{+1}_{CIN1} + d_{g1} + \mu_{g1} + \chi_{g1}\right) VCIN^{+1}_{g1kr} \quad (8.f)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f, m$

$$\dot{VCIN}^{-1}_{gikr} = \rho^{-1}_{lgi} W^{-}_{gikr} + \pi^{s}_{\sigma CIN}\kappa^{1}_{CIN}\sigma^{-2}_{CINi} VCIN^{-2}_{gikr} + d_{g(i-1)} VCIN^{-1}_{g(i-1)kr} + \vartheta_{gi} CIN^{-1}_{gikr} - \left(\pi^{s}_{\sigma CIN}\sigma^{-1}_{CINi} + \rho^{-1}_{CINi} + \mathcal{H}_{gikr} + d_{gi} + \mu_{gi}\right) VCIN^{-1}_{gikr} \quad (8.g)$$

$$\dot{VCIN}^{+1}_{gikr} = \rho^{+1}_{lgi} W^{+}_{gikr} + \mathcal{H}_{gikr} VCIN^{-1}_{gikr} + \pi^{s}_{\sigma CIN}\kappa^{1}_{CIN}\sigma^{+2}_{CINi} VCIN^{+2}_{gikr} + d_{g(i-1)} VCIN^{+1}_{g(i-1)kr} + \vartheta_{gi} CIN^{-1}_{gikr} - \left(\pi^{s}_{\sigma CIN}\sigma^{+1}_{CINi} + \rho^{+1}_{CINi} + d_{gi} + \mu_{gi} + \chi_{gi}\right) VCIN^{+1}_{gikr} \quad (8.h)$$

where $i = 2,\ldots 11,; k = 1,2,3;\ r = 1,2,3;\ g = f, m$

3.2.4.2 CIN2/3

The ODE's for this compartment are:

$$\dot{CIN}^{-2}_{g1kr} = \rho^{-2}_{lg1} I^{-}_{g1kr} + \rho^{-1}_{CINg1} CIN^{-1}_{g1kr} - \left(\sigma^{-2}_{CIN1} + \rho^{-2}_{CINg1} + \varkappa_{g1kr} + \vartheta_{g1} + d_{g1} + \mu_{g1}\right) CIN^{-2}_{g1kr} \quad (8.i)$$

$$\dot{CIN}^{+2}_{g1kr} = \rho^{+2}_{lg1} I^{+}_{g1kr} + \rho^{+1}_{CIN1} CIN^{+1}_{g1kr} + \varkappa_{g1kr} CIN^{-2}_{g1kr} - \left(\sigma^{+2}_{CIN1} + \rho^{+2}_{CIN1} + \vartheta_{g1} + d_{g1} + \mu_{g1} + \chi_{g1}\right) CIN^{+2}_{g1kr} \quad (8.j)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f, m$

$$\dot{CIN}^{-2}_{gikr} = \rho^{-2}_{lgi} I^{-}_{gikr} + \rho^{-1}_{CINgi} CIN^{-1}_{gikr} + d_{g(i-1)} CIN^{-2}_{g(i-1)kr} - \left(\sigma^{-2}_{CINgi} + \rho^{-2}_{CINgi} + \varkappa_{gikr} + \vartheta_{gi} + d_{gi} + \mu_{gi}\right) CIN^{-2}_{gikr} \quad (8.k)$$

$$\dot{CIN}^{+2}_{gikr} = \rho^{+2}_{lgi} I^{+}_{gikr} + \rho^{+1}_{CINgi} CIN^{+1}_{gikr} + \varkappa_{gikr} CIN^{-2}_{gikr} + d_{g(i-1)} CIN^{+2}_{g(i-1)kr} - \left(\sigma^{+2}_{CINgi} + \rho^{+2}_{CINgi} + \vartheta_{gi} + d_{gi} + \mu_{gi} + \chi_{gi}\right) CIN^{+2}_{gikr} \quad (8.l)$$

where $i = 2,\ldots 11,; k = 1,2,3;\ r = 1,2,3;\ g = f, m$

3.2.4.2.1 HPV Vaccinated

The ODE's for this compartment are:

$$\dot{VCIN}^{-2}_{g1kr} = \rho^{-2}_{lg1} W^{-}_{g1kr} + \rho^{-1}_{CINg1} VCIN^{-1}_{g1kr} + \vartheta_{g1} CIN^{-2}_{g1kr} - \left(\pi^{2}_{\sigma CIN} \sigma^{-2}_{CINg1} + \rho^{-2}_{CINg1} + \varkappa_{g1kr} + d_{g1} + \mu_{g1}\right) VCIN^{-2}_{g1kr} \quad (8.m)$$

$$\dot{VCIN}^{+2}_{g1kr} = \rho^{+2}_{lg1} W^{+}_{g1kr} + \rho^{+1}_{CINg1} VCIN^{+1}_{g1kr} + \varkappa_{g1kr} VCIN^{-2}_{g1kr} + \vartheta_{g1} CIN^{+2}_{g1kr} - \left(\pi^{2}_{\sigma CIN} \sigma^{+2}_{CINg1} + \rho^{+2}_{CINg1} + d_{g1} + \mu_{g1} + \chi_{g1}\right) VCIN^{+2}_{g1kr} \quad (8.n)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f, m$

$$\dot{VCIN}^{-2}_{gikr} = \rho^{-2}_{lgi} W^{-}_{gikr} + \rho^{-1}_{CINgi} VCIN^{-1}_{gikr} + d_{g(i-1)} VCIN^{-2}_{g(i-1)kr} + \vartheta_{gi} CIN^{-2}_{gikr} - \left(\pi^{2}_{\sigma CIN} \sigma^{-2}_{CINgi} + \rho^{-2}_{CINgi} + \varkappa_{gikr} + d_{gi} + \mu_{gi}\right) VCIN^{-2}_{gikr} \quad (8.o)$$

$$\dot{VCIN}^{+2}_{gikr} = \rho^{+2}_{lgi} W^{+}_{gikr} + \rho^{+1}_{CINgi} VCIN^{+1}_{gikr} + \varkappa_{gikr} VCIN^{-2}_{gikr} + d_{g(i-1)} VCIN^{+2}_{g(i-1)kr} + \vartheta_{gi} CIN^{+2}_{gikr} - \left(\pi^{2}_{\sigma CIN} \sigma^{+2}_{CINgi} + \rho^{+2}_{CINgi} + d_{gi} + \mu_{gi} + \chi_{gi}\right) VCIN^{+2}_{gikr} \quad (8.p)$$

where $i = 2,\ldots 11,; k = 1,2,3;\ r = 1,2,3;\ g = f, m$

3.2.5 Cervical Cancer

HPV type caused cervical cancer is modelled. It is assumed that once individuals have had cancer they do not re-enter the other compartments of the model,

therefore cervical cancer is not separated into compartments based on vaccination. It is also assumed that cervical cancer does not regress to lower cervical cancer states and cervical cancer progression cannot skip states. Females with cervical cancer have an additional mortality rate μ_{CCf1}^{hs}.

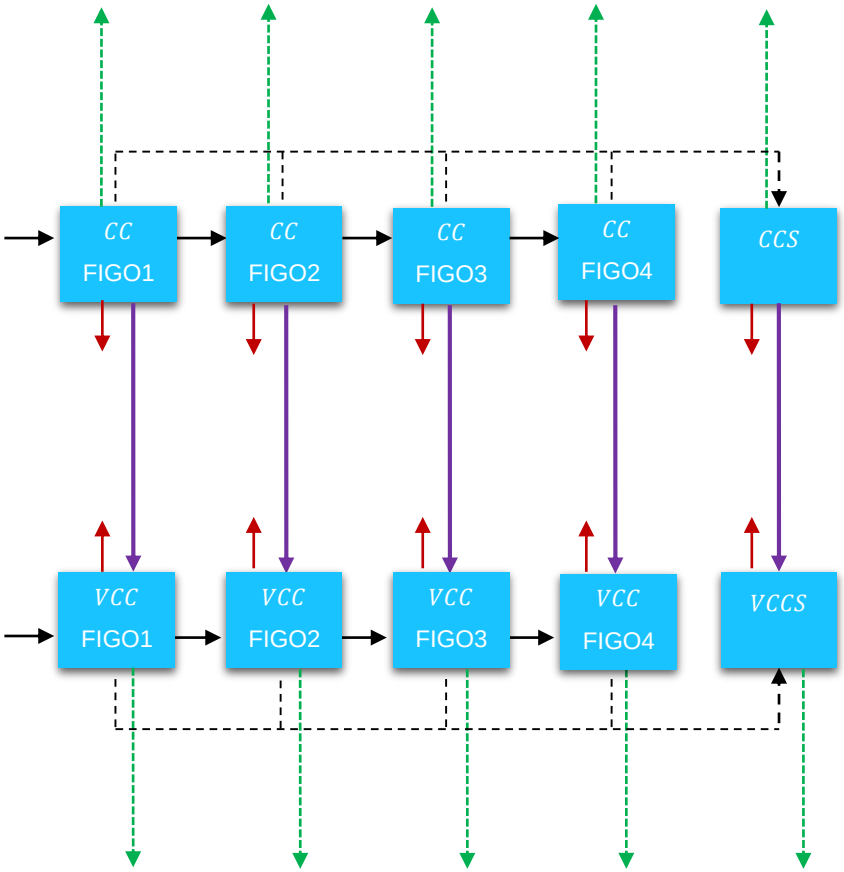


Figure 3-4 Diagram of a simplified schematic of the CC and CCS compartments. The green line represents the effect of HIV transmission, the red lines the natural mortality. The purple lines indicate vaccination. The black lines indicate progression to a higher state of disease severity, whereas the dotted black line indicates regression to CCS.

The ODE's for this compartment are:

$$\begin{aligned} \dot{CC}_{g1kr}^{-s} &= \rho_{CINg1}^{-2}\left(CIN_{g1kr}^{-2} + VCIN_{g1kr}^{-2}\right) + \rho_{CCg1}^{-(s+1)} CC_{g1kr}^{-(s+1)} \\ &\quad -\left(\varkappa_{g1kr} + \rho_{CCg1}^{-s} + d_{g1} + \mu_{g1} + \sigma_{CCg1}^{-s} + \mu_{CCg1}^{-s}\right) CC_{g1kr}^{-s} \end{aligned} \tag{9.a}$$

$$\begin{aligned} \dot{CC}_{g1kr}^{+s} &= \rho_{CINg1}^{+2}\left(CIN_{g1kr}^{+2} + VCIN_{g1kr}^{+2}\right) + \rho_{CCg1}^{+(s+1)} CC_{g1kr}^{+(s+1)} + \varkappa_{g1kr} CC_{g1kr}^{-s} \\ &\quad -\left(d_{g1} + \mu_{g1} + \rho_{CCg1}^{+s} + \sigma_{CCg1}^{+s} + \mu_{CCg1}^{+s} + \chi_{g1}\right) CC_{g1kr}^{+s} \end{aligned} \tag{9.b}$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f,m$

$$\dot{CC}^{-s}_{gikr} = \rho^{-2}_{CINgi}\left(CIN^{-2}_{gikr} + VCIN^{-2}_{gikr}\right) + \rho^{-(s+1)}_{CCgi} CC^{-(s+1)}_{gikr} + d_{g(i-1)} CC^{-s}_{g(i-1)kr} - \left(\varkappa_{gikr} + \rho^{-s}_{CCgi} + d_{gi} + \sigma^{-s}_{CCgi} + \mu_{gi} + \mu^{-s}_{CCgi}\right) CC^{-s}_{gikr} \quad (9.c)$$

$$\dot{CC}^{+s}_{gikr} = \rho^{+2}_{CINgi}\left(CIN^{+2}_{gikr} + VCIN^{+2}_{gikr}\right) + \rho^{+(s+1)}_{CCgi} CC^{+(s+1)}_{gikr} + \varkappa_{gikr} CC^{-s}_{gikr} + d_{g(i-1)} CC^{+s}_{g(i-1)kr} - \left(d_{gi} + \mu_{gi} + \rho^{+s}_{CCgi} + \sigma^{+s}_{CCgi} + \mu^{+s}_{CCgi} + \chi_{gi}\right) CC^{+s}_{gikr} \quad (9.d)$$

where $i = 2,\ldots 11,; k = 1,2,3;\ r = 1,2,3;\ g = f, m$

3.2.6 Cervical Cancer Survivor

An individual which recovers from cervical cancer enters the cervical cancer survivor compartment. An individual can recover from cervical cancer via any of the cervical cancer states. Individuals in the cervical cancer survivor state are assumed to never leave the state and have no effect on the rest of the population. The ODE's for this compartment are:

$$\dot{CCS}^{-}_{g1kr} = \sum_{a=1}^{4} \sigma^{-a}_{CCg1} CC^{-a}_{g1kr} - \left(\varkappa_{g1kr} + d_{g1} + \mu_{g1}\right) CCS^{-}_{g1kr} \quad (10.a)$$

$$\dot{CCS}^{+}_{g1kr} = \varkappa_{g1kr} CCS^{-}_{g1kr} + \sum_{a=1}^{4} \sigma^{+a}_{CCg1} CC^{+a}_{g1kr} - \left(d_{g1} + \mu_{g1}\right) CCS^{+}_{g1kr} \quad (10.b)$$

where $k = 1,2,3;\ r = 1,2,3;\ g = f, m$

$$\dot{CCS}^{-}_{gikr} = \sum_{a=1}^{4} \sigma^{-a}_{CCgi} CC^{-a}_{gikr} + d_{g(i-1)} CCS^{-}_{g(i-1)kr} - \left(\varkappa_{gikr} + d_{gi} + \mu_{gi}\right) CCS^{-}_{gikr} \quad (10.c)$$

$$\dot{CCS}^{+}_{gikr} = \varkappa_{gikr} CCS^{-}_{gikr} + \sum_{a=1}^{4} \sigma^{+a}_{CCgi} CC^{+a}_{gikr} + d_{g(i-1)} CCS^{+}_{g(i-1)kr} - \left(d_{gi} + \mu_{gi}\right) CCS^{+}_{gikr} \quad (10.d)$$

where $i = 2,\ldots 11,; k = 1,2,3;\ r = 1,2,3;\ g = f, m$

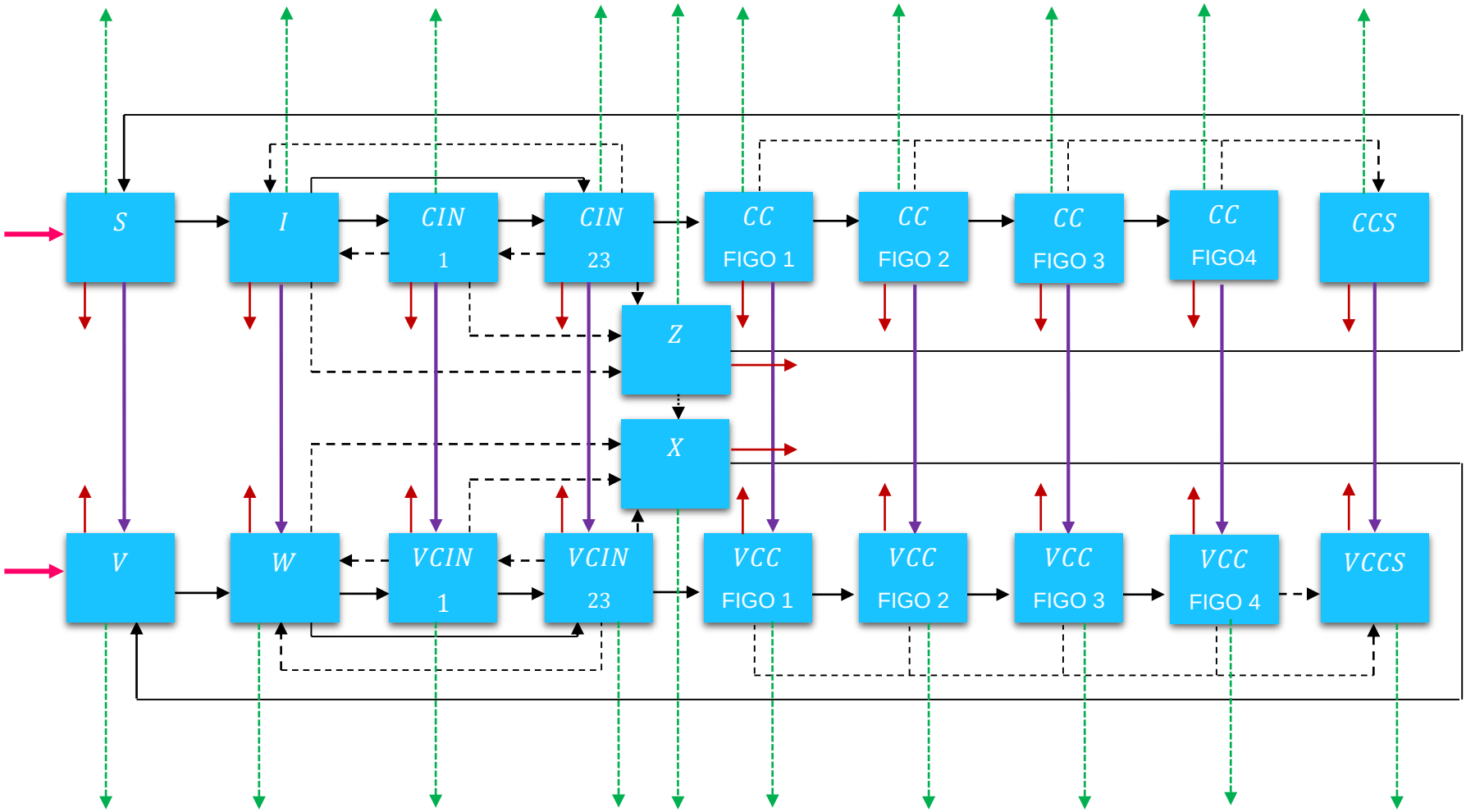


Figure 3-5 A simplified schematic diagram of the HIV negative compartments of the transmission and natural history of HPV and Cervical cancer model. The green arrows indicate transmission due to HIV infection, the red arrow indicate mortality, and the solid black arrows indicate progression of the disease to a state of higher severity and progression from immune to susceptible. The black dotted line indicates regression of the disease to states of less severity. The purple line indicates vaccination. The pink line indicates new entries into the sexually active population. Symbols are intentionally left off the diagram to produce a clearer image.

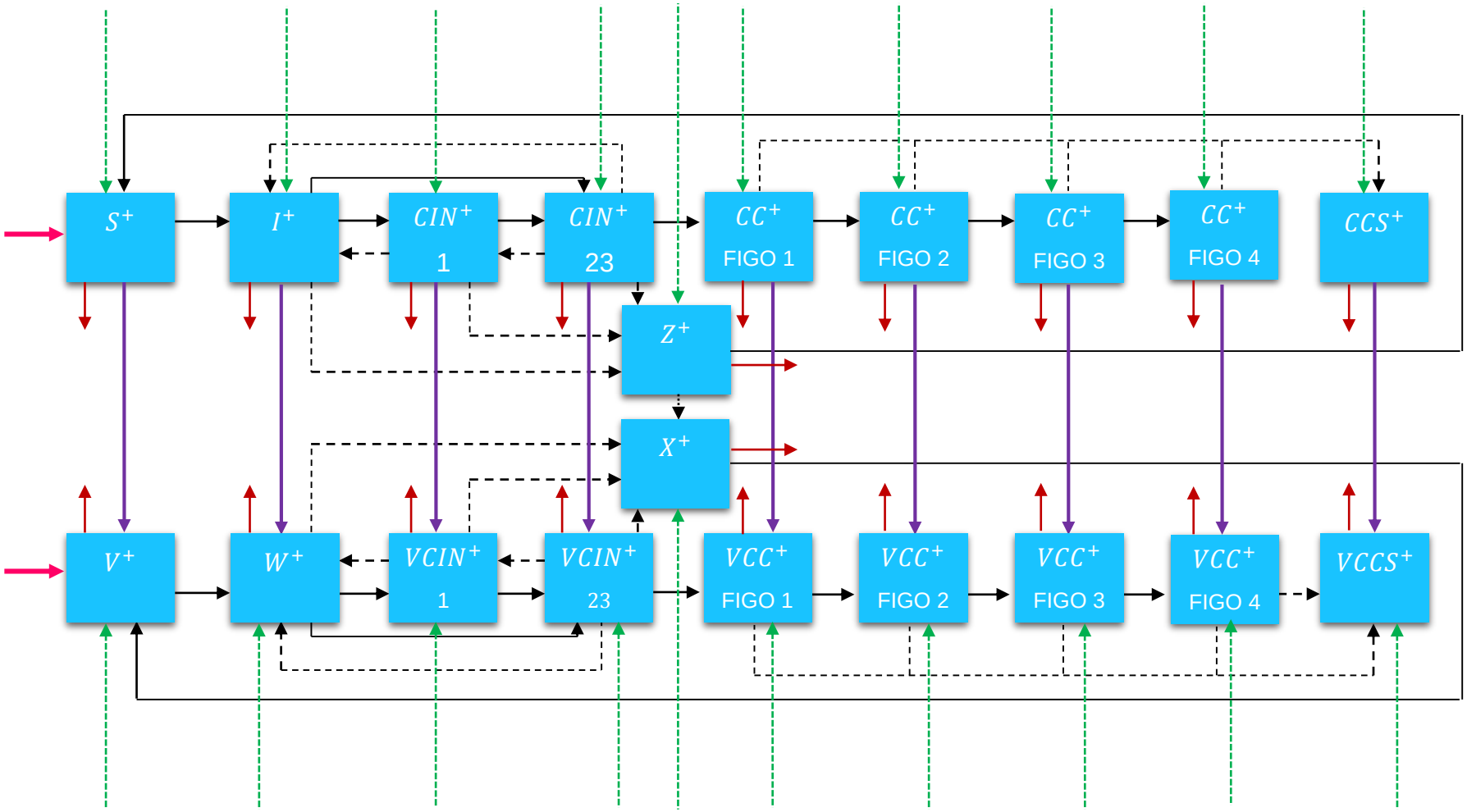


Figure 3-6 A simplified schematic diagram of the HIV positive compartments of the transmission and natural history of HPV and Cervical cancer model. The green arrows indicate transmission due to HIV infection, the red arrow indicate mortality, and the solid black arrows indicate progression of the disease to a state of higher severity and progression from immune to susceptible. The black dotted line indicates regression of the disease to states of less severity. The purple line indicates vaccination. The pink line indicates new entries into the sexually active population. Symbols are intentionally left off the diagram to produce a clearer image.

3.3 Mixing preferences

The way partnerships are formed is governed by the probability matrix. The probability matrix is based on Barnanbas *et al* [45] and Elbasha *et al* [21]. Each cell in the probability matrix represents the probability that an individual of sex, sexual activity and age class have a sexual activity and age class specific partner. In generating the mixing matrix the parameters ε_1 ε_2 depict the degree of the assortative mixing between age and sexual activity groups. Mixing can range between fully assortative and fully proportionate by altering ε between 0 and 1.

It is assumed that sexual orientation only plays a role in the number of available partners and sex of partners. Orientation will not have any other influence in partnership.

Note that since it is assumed that sexual orientations only influence in partnership formation is the available partner, therefore the probability that individuals associated mainly with their sexual orientation groups is not accounted for in the mixing matrix. This approach is similar to Bogaards *et al* [46]

$$\psi_{gik1jl} = (1-\varepsilon_1)\delta_{ij} + \varepsilon_1 \frac{\sum_a c_{g'ja}\left(N_{g'ja1}(0) + \omega_{g'2}N_{g'ja2}(0)\right)}{\sum_u \sum_a c_{g'ua}\left(N_{g'ua1}(0) + \omega_{g'2}N_{g'ua2}(0)\right)} + (1-\varepsilon_2)\delta_{kl} + \varepsilon_2 \frac{c_{g'jl}\left(N_{g'jl1}(0) + \omega_{g'2}N_{g'jl2}(0)\right)}{\sum_u \sum_a c_{g'ua}\left(N_{g'ua1}(0) + \omega_{g'2}N_{g'ua2}(0)\right)} \quad (11.a)$$

$$\psi_{gik3jl} = (1-\varepsilon_1)\delta_{ij} + \varepsilon_1 \frac{\sum_a c_{gja}\left(N_{gja3}(0) + (1-\omega_{g2})N_{gja2}(0)\right)}{\sum_u \sum_a c_{gua}\left(N_{gua3}(0) + (1-\omega_{g2})N_{gua2}(0)\right)} + (1-\varepsilon_2)\delta_{kl} + \varepsilon_2 \frac{c_{gjl}\left(N_{gjl3}(0) + (1-\omega_{g2})N_{gjl2}(0)\right)}{\sum_u \sum_a c_{gua}\left(N_{gua3}(0) + (1-\omega_{g2})N_{gua2}(0)\right)} \quad (11.b)$$

$$
\begin{aligned}
\psi_{gik2jl} &= (1-\varepsilon_1)\delta_{ij} \\
&+\varepsilon_1\left(\frac{\sum_a\left(c_{g'ja}\left(N_{g'ja1}(0)+\omega_{g'2}N_{g'ja2}(0)\right)\right)}{\sum_u\sum_a\left(c_{g'ua}\left(N_{g'ua1}(0)+\omega_{g'2}N_{g'ua2}(0)\right)\right)}+\right. \\
&\left.\frac{\sum_a\left(c_{gja}\left(N_{gja3}(0)+(1-\omega_{g2})N_{gja2}(0)\right)\right)}{\sum_u\sum_a\left(c_{gua}\left(N_{gua3}(0)+(1-\omega_{g2})N_{gua2}(0)\right)\right)}\right)+(1-\varepsilon_2)\delta_{kl} \\
&+\varepsilon_2\left(\frac{c_{g'jl}\left(N_{g'jl1}(0)+\omega_{g'2}N_{g'jl2}(0)\right)}{\sum_u\sum_a c_{g'ua}\left(N_{g'ua1}(0)+\omega_{g'2}N_{g'ua2}(0)\right)}+\right. \\
&\left.\frac{c_{gjl}\left(N_{gjl3}(0)+(1-\omega_{g2})N_{gjl2}(0)\right)}{\sum_u\sum_a c_{gua}\left(N_{gua3}(0)+(1-\omega_{g2})N_{gua2}(0)\right)}\right)
\end{aligned}
\qquad (11.c)
$$

where $\sum_u$ indicates the sum of all age groups from 1 to 11

$\sum_a$ indicates the sum of all sexual activity groups 1 to 3

The supply and demand of partnerships should be satisfied by the model. Homosexual and bisexual partnerships with individuals of the same sex guarantee a balance.

The heterosexual relationships formula's to ensure balancing is based on Elbasha *et al* [21] .

Heterosexual relationships require:

$c_{gik}\psi_{g'ikjl}\left(N_{gki1}+\omega_{g2}N_{gki2}\right)=c_{g'jl}\psi_{g'jlik}\left(N_{g'lj1}+\omega_{g'2}N_{g'lj2}\right)$ to hold. To accomplish this mean rates of sexual partnership is specified as functions of the initial imbalance in supply and demand, and it is assumed that both sexes equally adjust to supply and demand. This produces the equation:

$$
c_{gikjl}=c_{gik}\left(\frac{c_{g'jl}\psi_{g'jlik}\left(N_{g'lj1}(0)+\omega_{g'2}N_{g'lj2}(0)\right)}{c_{gik}\psi_{g'ikjl}\left(N_{gki1}(0)+\omega_{g2}N_{gki2}(0)\right)}\right)^{0.5}
$$

Removal of individuals from the population due to cervical cancer deaths and progression of HIV to AIDS cause an imbalance in supply and demand. To rectify

this, mixing patterns will be assumed fixed in time and partnership rates will vary over time, therefore:

$$c_{gikjl} = c_{gik}\left(\frac{c_{g'jl}\psi_{g'jlik}\left(N_{g'lj1}(t)+\omega_{g'2}N_{g'lj2}(t)\right)}{c_{gik}\psi_{g'ikjl}\left(N_{gki1}(t)+\omega_{g2}N_{gki2}(t)\right)}\right)^{0.5} \quad (11.d)$$

3.4 HPV Force of Infection

The HPV force of infection is the rate at which susceptible individuals acquire infection with the specific HPV type modelled (per capita force of infection). The force of infection is sex, sexual activity, age and time dependent. The rate at which individuals of sex, sexual activity group, sexual orientation, age class at time *t* acquire infection of the HPV type modelled depends on the number of partnerships, the way they form partnerships with individuals, the fraction of infected intercourse partners, and the transmission probability per partnership.

The force of infection is based on Elbasha *et al* [21], with modifications to include bisexual and homosexual partnerships. The force of infection is given by:

$$\lambda^{h}_{mik1} = \beta_{mf}\sum_{j}\sum_{l} c_{mikjl}\Psi_{mikjl}\sum_{h}\left(\frac{\left(\left(\sum_{s}\left(CIN^{hs}_{fik1}+VCIN^{hs}_{fik1}+CC^{hs}_{fik1}\right)+I^{h}_{fik1}+W^{h}_{fik1}\right)\right)}{\left(N_{fjl1}+\omega_{f2}N_{fjl2}\right)}\right.$$
$$\left.+\frac{\omega_{f2}\left(\sum_{s}\left(CIN^{hs}_{fik2}+VCIN^{hs}_{fik2}+CC^{hs}_{fik2}\right)+I^{h}_{fik2}+W^{h}_{fik2}\right)}{\left(N_{fjl1}+\omega_{f2}N_{fjl2}\right)}\right) \quad (12.a)$$

$$\lambda^{h}_{mik3} = \beta_{mm}\sum_{j}\sum_{l} c_{mikjl}\Psi_{mikjl}\sum_{h}\left(\frac{\left(\left(I^{h}_{mik3}+W^{h}_{mik3}\right)\right)}{\left(N_{mjl3}+(1-\omega_{m2})N_{mjl2}\right)}+\frac{(1-\omega_{m2})\left(I^{h}_{mik2}+W^{h}_{mik2}\right)}{\left(N_{mjl3}+(1-\omega_{m2})N_{mjl2}\right)}\right) \quad (12.b)$$

$$\lambda^{h}_{fik1} = \beta_{fm}\sum_{j}\sum_{l} c_{fikjl}\Psi_{fikjl}\sum_{h}\left(\frac{\left(\left(I^{h}_{mik1}+W^{h}_{mik1}\right)\right)}{\left(N_{mjl1}+\omega_{m2}N_{mjl2}\right)}+\frac{\omega_{m2}\left(I^{h}_{mik2}+W^{h}_{mik2}\right)}{\left(N_{mjl1}+\omega_{m2}N_{mjl2}\right)}\right) \quad (12.c)$$

$$\lambda^{h}_{fik3} = \beta_{ff} \sum_{j}\sum_{l} c_{fikjl}\Psi_{fikjl} \sum_{h} \left(\frac{\left(\left(\sum_{s} \left(CIN^{hs}_{fik3} + VCIN^{hs}_{fik3} + CC^{hs}_{fik3} \right) + I^{h}_{fik3} + W^{h}_{fik3} \right) \right)}{\left(N_{fjl3} + (1-\omega_{f2}) N_{fjl2} \right)} \right.$$

$$\left. + \frac{\left(1-\omega_{f2}\right)\left(\sum_{s} \left(CIN^{hs}_{fik2} + VCIN^{hs}_{fik2} + CC^{hs}_{fik2} \right) + I^{h}_{fik2} + W^{h}_{fik2} \right)}{\left(N_{fjl3} + \left(1-\omega_{f2}\right) N_{fjl2} \right)} \right) \tag{12.d}$$

$$\lambda^{h}_{gik2} = \omega_{g2}\lambda^{h}_{gik1} + \left(1-\omega_{g2}\right)\lambda^{h}_{gik3} \tag{12.e}$$

3.5 HIV Force of Infection

The HIV force of infection is the rate at which HIV susceptible individuals acquire infection with the HIV (per capita force of infection). The force of infection is sex, sexual activity, age and time dependent. The HIV force of infection follows a similar structure to the HPV force of infection. Therefore, the rate at which individuals of sex, sexual activity group, sexual orientation, age class at time *t* acquire HIV infection depends on the number of partnerships, the way they form partnerships with individuals, the fraction of infected sex partners, and the transmission probability per partnership.

The force of infection is given by:

$$\mathcal{H}^{h}_{gik1} = \beta^{+}_{gg'} \sum_{j}\sum_{l} \frac{c_{gikjl}\Psi_{gikjl}\left(N^{+}_{g'ik1} + \omega_{g'2} N^{+}_{g'ik2} \right)}{\sum_{h}\left(N^{h}_{g'jl1} + \omega_{g'2} N^{h}_{g'jl2} \right)} \tag{13.a}$$

$$\mathcal{H}^{h}_{gik3} = \beta^{+}_{gg} \sum_{j}\sum_{l} \frac{c_{gikjl}\Psi_{gikjl}\left(N^{+}_{gik3} + \left(1-\omega_{g2}\right) N^{+}_{gik2} \right)}{\sum_{h}\left(N^{h}_{gjl3} + \left(1-\omega_{g2}\right) N^{h}_{gjl2} \right)} \tag{13.b}$$

$$\mathcal{H}^{h}_{gik2} = \omega_{g2}\mathcal{H}^{h}_{gik1} + \left(1-\omega_{g2}\right)\mathcal{H}^{h}_{gik3} \tag{13.c}$$

4 A brief introduction to model analysis[1]

4.1 Reproduction number

The basic reproduction number ([71]–[73]) is the expected number of secondary infections produced by an index case in a completely susceptible population, therefore it a measure of how an infection will spread through a population. The basic reproduction number gives a sharp threshold which completely determines the global dynamics. If the reproduction number is less than one the disease will dissipate and die out, this is due to the infected population decreasing in every generation. If the reproduction number is greater than one, the infected population will replace itself for every generation and therefore the infection will spread.

The basic reproduction number estimates the threshold behaviour therefore as the disease begins to spread, the parameters influencing the spread will alter and the reproduction number will not be the best measure of how the infection spreads [74]. However since in many models the peak prevalence of infected individuals and final epidemic size are functions of the reproduction number it is still a useful measure of the infection spread ([71]–[73]).

4.1.1 The next generation matrix

The next generation matrix $\bar{G}$ is the square matrix where the ijth element of the matrix is the expected number of secondary infections of type i caused by a single infected individual of type j, with the assumption that the population of type I is entirely susceptible ([72]–[74]).

The next generation matrix can be written as ([72]–[74]):

$$\bar{G} = \bar{F}\bar{U}^{-1}$$

where

$$\bar{F} = \left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j} \right]$$

[1] All theory reproduced from references [71] - [75]

$$\bar{U}^{-1} = \left[\frac{\partial \mathcal{U}_i(x_0)}{\partial x_j} \right]$$

with

$\mathcal{F}_i$ New infections in the i[th] infection compartment

$\mathcal{U}_i$ Transition terms in the i[th] infection compartment

x_0 Disease Free Equilibrium, DFE

The basic reproduction number is then defined as the spectral radius of the matrix: $R_0 = \rho\left(\bar{F}\bar{U}^{-1}\right)$ [72]. The spectral radius is the dominant eigenvalue.

4.2 Disease Free Equilibrium Stability

4.2.1 Compartmental Disease Model

Individuals are characterized by a single discrete state variable and are sorted into compartments by this state. An individual is in the infected compartment if they are infected with the disease which is being investigated.

The model can be described as:

Suppose there is *n* infection compartments and *m* uninfected compartments. A general compartmental disease transmission model can be written as [74]:

$$\dot{\bar{x}} = \bar{\mathcal{F}}(x, y) - \bar{\mathcal{U}}(\mathrm{x}, \mathrm{y}) \text{ and } \dot{\bar{y}} = \bar{f}(x, y) \qquad (1.a)$$

with

$$\bar{f} = (\mathrm{f}_1, \mathrm{f}_2, \mathrm{f}_3, ..., \mathrm{f}_m)^T$$

where

$\bar{x} = (\mathrm{x}_1, \mathrm{x}_2, \mathrm{x}_3, ..., \mathrm{x}_n)^T \in \mathbb{R}^n$,Population in infected compartments

$\bar{y} = (\mathrm{y}_1, \mathrm{y}_2, \mathrm{y}_3, ..., \mathrm{y}_m)^T \in \mathbb{R}^m$,Population in the uninfected compartments

$\mathcal{F}_i$,New infections in the *i[th]* infection compartment

$\mathcal{U}_i$,Transition terms in the i[th] infection compartment

Note that the decomposition of the dynamics of $\mathcal{F}$ and $\mathcal{U}$ depend on the epidemiological interpretations of a model.

A well-posed model has a solution that exists, is unique and behaviour changes with the initial conditions. For well-posedness of the model and the existence of DFE, the following assumptions are made [72]:

1. $\mathcal{F}_i(0,y)=0 \quad \mathcal{U}_i(0,y)=0$ for all $y \geq 0$,and $i=1,2,...,n$

   This ensures that the disease free set is invariant

2. $\mathcal{F}_i(\mathrm{x},y) \geq 0$ for all $x,y \geq 0$,and $i=1,2,...,n$

   Represents the new infections

3. $\mathcal{U}_i(\mathrm{x},y) \leq 0$ whenever $x_i=0$,and $i=1,2,...,n$

   Represents the net outflow from compartment *i* and must be negative when the compartment is empty.

4. $\sum_{i=1}^{n} \mathcal{U}_i(\mathrm{x},y) \geq 0$ for all $x,y \geq 0$ *and* $i=1,2,...,n$

   Represents the outflow from all infected compartment

5. $\dot{\bar{y}} = \bar{f}(0,y)$ has a unique equilibrium $y=y_0>0$

   Which is locally asymptotically stable with the DFE.

To use the definition of the next generation matrix (see 4.1.1), define two *nxn* matrices [72], using assumption 1:

$$\bar{F}=\left[\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}\right], \bar{U}=\left[\frac{\partial \mathcal{U}_i(x_0)}{\partial x_j}\right]$$

This implies that the equations for the infection compartments are decoupled from the other equations of the model and can be written as:

$$\dot{\bar{x}} = \left(\bar{F} - \bar{U}\right)\bar{x} \qquad \text{(1.b)}$$

the linear stability of the system (1.a) is completely determined by the linear stability of $\left(\bar{F} - \bar{U}\right)$ in (1.b) by Assumption 5.

4.2.2 Local Stability

If the reproduction number $R_0 = \rho\left(\bar{F}\bar{U}^{-1}\right)$ is consistent with the differential equation model, then the DFE is locally asymptotically stable if $R_0 < 1$ and unstable otherwise, proven by the lemma's and theorem to follow.

Lemma 1 [72]

If A has the Z sign pattern, then $A^{-1} \geq 0$ *if and only if A is a non-singular M-matrix*

A sign pattern is a matrix whose entries come from the set $\{+, -, 0\}$. For a real matrix A, sgn(A) is the sign pattern having entries that are the signs of the corresponding entries in A [72]. An M-matrix is a Z-matrix with eigenvalues whose real parts are positive [72].

From assumptions 1 and 2 it follows that each entry of $\bar{F}$ is nonnegative. From assumptions 1 and 3 if follows that the diagonal elements of $\bar{U}$ are negative or zero. Therefore $\bar{U}$ has a Z sign pattern. Assumption 1 and 4 ensures that the column sums of $\bar{U}$ are positive or zero, together with the sign pattern, implies that $\bar{U}$ is a M-matrix (ref here)

Assume $\bar{U}$ is non-singular $\bar{U}^{-1} \geq 0$,therefore by Lemma 1, $\bar{G} = \bar{F}\bar{U}^{-1}$ is also non-negative.

Lemma 2 [72]

If $\bar{F}$ *is non-negative and* $\bar{U}$ *is non-singular M matrix, then* $R_0 = \rho\left(\bar{F}\bar{U}^{-1}\right) < 1$ *if and only if all eigenvalues of* $\left(\bar{F} - \bar{U}\right)$ *have negative real parts.*

Theorem 1 [72], [75]

Consider the model given by (1.a). The disease free equilibrium of (1.a) is locally asymptotically stable if $R_0 < 1$ *but unstable if* $R_0 > 1$*, where* R_0 *is defines as* $R_0 = \rho\left(\bar{F}\bar{U}^{-1}\right)$. For proof see [75]

4.2.3 Global Stability

The sharp threshold property [75] is when the basic reproduction number gives a sharp threshold that completely determines the global dynamics of the model.

A general compartmental disease transmission model given by (1.a) has the sharp threshold property if R_0, given by: $R_0 = \rho\left(\bar{F}\bar{U}^{-1}\right)$ is such that the DFE is global asymptotically stable for $R_0 < 1$. There is an unique endemic equilibrium EE that is globally asymptotically stable in the interior of the feasible region for $R_0 < 1$ [72].

4.2.3.1 A matrix-theoretic method to construct a Lyapunov function

Lyapunov functions are used to establish global stability results for biological models. Constructing a Lyapunov function is generally difficult, with no universal method available. A graph theoretic method is used in this study and the approach used to construct the Lyapunov function for this system approach will be described. This method and the approach is from [75]

To begin to construct the Lyapunov function:

Set $f(x,y) = (\bar{F} - \bar{U})x - \bar{\mathcal{F}}(x,y) + \bar{\mathcal{U}}(x,y)$ (1.c)

with the disease compartments written as (1.a).

Assume $f(0,y) = 0$,the DFE.

Let $\varpi^T \geq 0$ be the left eigenvector of the non-negative matrix $\bar{U}^{-1}\bar{F}$ which corresponds to eigenvalue $\rho\left(\bar{U}^{-1}\bar{F}\right) = \rho\left(\bar{F}\bar{U}^{-1}\right) = R_0$.

The following theorem provides a general method to construct a Lyapunov function for the system (1.a).

Theorem 2 [75]

Let $\bar{F}, \bar{U}$ *and* $f(x,y)$ *be defined as the system: (1.a),and (1.c). If* $f(x,y) \geq 0$ *in* $\Gamma \subset \mathbb{R}_{+}^{n+m}$, $\bar{F} \geq 0$, $\bar{U}^{-1} \geq 0$ *, and* $R_0 \leq 1$*, then the function* $Q = \bar{\varpi}^T \bar{U}^{-1} \bar{x}$ *is a Lyapunov function for the system on* Γ*.*

Proof (see [75])

The Lyapunov function created in Theorem 2 can be used to prove the global stability of the DFE and uniform persistence.

Theorem 3 [75]

Let $\bar{F}, \bar{U}$ *and* $f(x,y)$ *be defined by the system :* (1.a),(1.c)*. Let* $\Gamma \subset \mathbb{R}_{+}^{n+m}$ *be compact such that* $(0, y_0) \in \Gamma$ *and* Γ *is positively invariant with respect to* (1.a)*. Suppose that* $f(x,y) \geq 0$ *with* $f(x, y_0) = 0$ *in* Γ, $\bar{F} \geq 0$, $\bar{U}^{-1} \geq 0$ *and* $\bar{U}^{-1}\bar{F}$ *is irreducible. Assume that the disease free system* $\dot{\bar{y}} = \bar{f}(0, y)$ *has a unique equilibrium* $y = y_0 > 0$ *that is globally asymptotically stable in* $\mathbb{R}_{+}^{m}$*. Then the following holds for* (1.a)*: If* $R_0 < 1$ *then the DFE is globally asymptotically stable in* Γ*.*

Proof (see [75]).

5 Theoretical Analysis

5.1 Basic SIRS

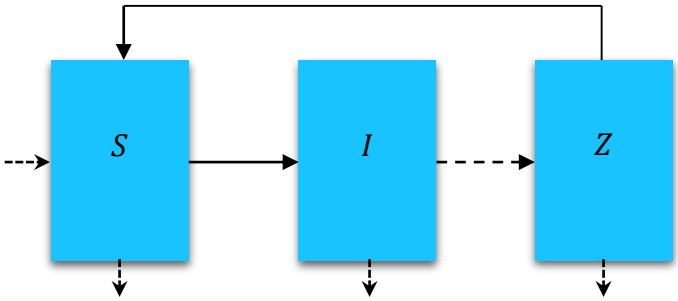


Figure 5-1 The population of susceptible individuals is increased by recruitment of new sexually active individuals into the population by a recruitment rate. The susceptible population is further increased by the loss of infection acquired immunity of the recovered individuals. Susceptible individuals acquire HPV infection at a rate known as the force of infection. The population of infected individuals is increased by the population of susceptible individuals that acquire infection. The infected population is decreased through recovery of HPV infection at a recovery rate. The population of recovered and immune individuals Z is increased by infected individuals that recover. The recovered population decreases through waning immunity. All stages are further decreased by the natural mortality rate.

5.1.1 Equations for the Model

The ODE's for the model are:

$$\dot{S}_g = \Lambda_g + \sigma_{Zg} Z_g - \left(\lambda_g + \mu_g\right) S_g \tag{1.a}$$

$$\dot{I}_g = \lambda_g S_g - \left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right) I_g \tag{1.b}$$

$$\dot{Z}_g = \sigma_{HPV}\sigma_{Ig} I_g - \left(\sigma_{Zg} + \mu_g\right) Z_g \tag{1.c}$$

It follows from the equations (1.a)-(1.c) that

$$\dot{N}_g = \Lambda_g - \mu_g N_g \tag{1.d}$$

where $N_g = S_g + I_g + Z_g$

5.1.1.1 Force of infection: Heterosexual population only

$$\lambda_g = c_g \beta_{gg'} \frac{I_{g'}}{N_{g'}} \tag{2.a}$$

where $\beta_{g,g'}$ is the probability of disease transmission per partnership between an infected individual in sex class g' and a susceptible individual in the opposite sex class g, c_g is the mean number of sexual partnerships for an individual of group g per unit time t. $c_g\beta_{g,g'}$ is the effective contact rate and $I_{g'}/N_{g'}$ is the probability that the contact is with an infected individual.

5.1.1.2 Force of infection: Homosexual population only

$$\lambda_g = c_g\beta_{gg}\frac{I_g}{N_g} \qquad (2.b)$$

where $\beta_{g,g}$ is the probability of disease transmission per partnership between an infected individual in sex class g and a susceptible individual in the same sex class g, c_g is the mean number of sexual partnerships for an individual of class g per unit time t. $c_g\beta_{g,g}$ is the effective contact rate and I_g/N_g is the probability that the contact is with an infected individual.

5.1.1.3 Force of infection: Bisexual population only

$$\lambda_{gI2} = \beta_{gg'}c_g\omega_{g2}\frac{\left(I_{g'2}\right)}{\left(N_{g'2}\right)} + \beta_{gg}c_g\left(1-\omega_{g2}\right)\frac{\left(I_{g2}\right)}{\left(N_{g2}\right)} \qquad (2.c)$$

where $\beta_{g,g}$ is the probability of disease transmission per partnership between an infected individual in sex class g and a susceptible individual in the same sex class g, $\beta_{g,g'}$ is the probability of disease transmission per partnership between an infected individual in sex class g' and a susceptible individual in the opposite sex class g, c_g is the mean number of sexual partnerships for an individual of class g per unit time t, ω_{g2} is the proportion of sexual partnerships of a heterosexual nature. $\beta_{gg'}c_g\omega_{g2}$, $\beta_{gg}c_g\left(1-\omega_{g2}\right)$ is the effective contact rate for heterosexual and homosexual relationships, respectively. I_g/N_g, $I_{g'}/N_{g'}$ is the probability that the contact is with an infected individual.

For the model to be epidemiologically meaningful all the state variables must be non-negative for all time. The model can be shown to satisfy:

Theorem 4: Let the initial population states be positive, then the solutions of the model with positive initial data must be nonnegative for all time. [21]

Theorem 5: The closed set is positively invariant and attracting with respect to the model. [21]

The proof for Theorem 5 with respect to this model are shown in APPENDIX A1.

5.1.2 Disease Free Equilibrium

The DFE is when the infective and recovered populations are zero. Thus, the DFE point is $E^0 = \left(S_g^0, 0, 0, S_{g'}^0, 0, 0\right)$.

with $S_g^0 = \frac{\Lambda_g}{\mu_g}$ and $N_g^0 = S_g^0$.

5.1.3 Local Asymptotical Stability of the Disease Free Equilibrium

The disease free equilibrium is locally asymptotically stable if $R_o < 1$ and unstable if $R_o > 1$.

5.1.3.1 Reproduction numbers

The Next Generation matrix approach (see 4.1.1) was used to determine the reproduction numbers for the various sexual orientation populations. The calculations to determine the reproduction number can be seen in APPENDIX **Error! Reference source not found.**, All calculations were carried out with the aid of Matlab R2012B [76]. The assumptions applied in calculating the reproduction number was based on Elbasha *et al* [61] .

5.1.3.1.1 Reproduction number: Heterosexual population only

The reproduction number of the heterosexual population was determined to be:

$$R_0^1 = \sqrt{R_{0m}^1 R_{0f}^1} \qquad (3.a)$$

where

$$R_{0m}^{1} = \frac{\left(c_m \beta_{mf}\right)}{\left(\sigma_{HPV}\sigma_{1m} + \mu_m\right)} \quad (3.b)$$

$$R_{0f}^{1} = \frac{\left(c_f \beta_{fm}\right)}{\left(\sigma_{HPV}\sigma_{If} + \mu_f\right)} \quad (3.c)$$

The reproduction number shows that infection depends on interaction with the opposite sex. The reproduction number is a geometric mean because a female will infect a male, and a male will infect a female. Therefore for a male to infect a male, infection is required to go through female.

The reproduction number matches the reproduction number determined by Elbasha *et al* [61].

5.1.3.1.2 Reproduction number: Homosexual population only

The reproduction number of the homosexual population was determined to be:

$$R_0^3 = R_{0f}^3 + R_{0m}^3 \quad (4.a)$$

Where

$$R_{0f}^{3} = \frac{\beta_{ff} c_f}{\left(\sigma_{HPV}\sigma_{If} + \mu_{\mathrm{f}}\right)} \quad (4.b)$$

$$R_{0m}^{3} = \frac{\beta_{mm} c_m}{\left(\sigma_{HPV}\sigma_{\mathrm{Im}} + \mu_m\right)} \quad (4.c)$$

The reproduction number demonstrates that infection for a homosexual population depends on the interaction with the same sex. Two reproduction numbers are determined, one for each sex class. This is because a female individual will only infect another female individual, and a male individual will only infect another male individual, therefore no geometric mean is observed.

5.1.3.1.3 Reproduction number: Bisexual population only

The reproduction number of the bisexual population was determined to be:

$$R_0^2 = \frac{1}{2}\left(\frac{\left(\left(1-\omega_{g'}\right)\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)\beta_{g'g}c_{g'} - \left(1-\omega_g\right)\left(\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)\beta_{gg}c_g\right)^2}{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)^2\left(\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)^2} \right.$$
$$\left. +4\left(\frac{\omega_g\beta_{g'g}c_g}{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\right)\left(\frac{\omega_{g'}\beta_{gg'}c_{g'}}{\left(\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)}\right)\right)^{\frac{1}{2}} \qquad (5.a)$$
$$+\frac{\left(1-\omega_g\right)\beta_{gg}c_g}{2\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}+\frac{\left(1-\omega_{g'}\right)\beta_{g'g}c_{g'}}{2\left(\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)}$$

The reproduction number demonstrates that infection for a bisexual population depends on the interactions with the same and the opposite sex. The reproduction number is a combination of a geometric mean due to the interaction of sex classes for infection. A bisexual individual can be infected by either a male or a female, the male or female that caused the infection could have been infected by either a homosexual type partnership or heterosexual type partnership.

The bisexual reproduction number can be rewritten in terms of the homosexual and heterosexual only reproduction numbers:

$$R_0^2 = \frac{1}{2}\sqrt{\left(\left(1-\omega_g\right)\left(R_{0g}^3\right)+\left(1-\omega_{g'}\right)\left(R_{0g'}^3\right)\right)^2+4\left(\omega_g R_{0g}^1\right)\left(\omega_{g'}R_{0g'}^1\right)} \qquad (5.b)$$
$$+\frac{1}{2}\left(\left(1-\omega_g\right)R_{0g}^3+\left(1-\omega_{g'}\right)R_{0g'}^3\right)$$

One can reduce the bisexual reproduction number to either the only heterosexual or only homosexual reproduction numbers by setting ω_g to 0 or 1.

5.1.4 Global Stability of the Disease Free Equilibrium

Complete calculations to determine the global stability can be found in Elbasha *et al* [61] and will not be repeated here. Alternatively using the matrix theoretic approach discussed in 4.2.3.1, and Theorem 3 global stability can be determined. The model is globally asymptotically stable for $R_0 < 1$.

5.2 Basic SIRS with Vaccination

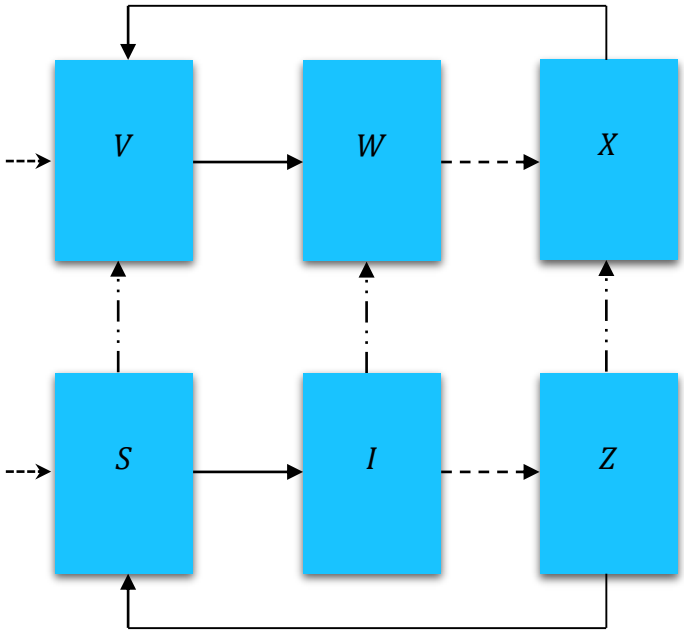


Figure 5-2 The population of susceptible individuals is increased by recruitment of new sexually active individuals into the population by a recruitment rate. The susceptible population is further increased by the loss of infection acquired immunity of the recovered individuals. Susceptible individuals acquire HPV infection at a rate known as the force of infection. The population of infected individuals is increased by the population of susceptible individuals that acquire infection. The infected population is decreased through recovery of HPV infection at a recovery rate. The population of recovered and immune individuals is increased by infected individuals that recover. The recovered population decreases through waning immunity. All stages are further decreased by the natural mortality rate. Each SIR compartment is subdivided into vaccinated and not vaccinated, individuals are removed from the SIR unvaccinated compartments at a percentage of the population vaccinated.

5.2.1 Equations for the Model

The ODE's for the model are:

$$\dot{S}_g = \left(1-\phi_g\right)\Lambda_g + \sigma_\vartheta V_g + \sigma_{Zg} Z_g - \left(\lambda_g + \vartheta_g + \mu_g\right) S_g \tag{1.a}$$

$$\dot{I}_g = \lambda_g S_g + \sigma_\vartheta W_g - \left(\sigma_{HPVg}\sigma_{Ig} + \vartheta_g + \mu_g\right) I_g \tag{1.b}$$

$$\dot{Z}_g = \sigma_{HPVg}\sigma_{Ig} I_g + \sigma_\vartheta X_g - \left(\vartheta_g + \sigma_{Zg} + \mu_g\right) Z_g \tag{1.c}$$

$$\dot{V}_g = \phi_g \Lambda_g + \vartheta_g S_g + \pi_{\sigma Z} \sigma_{Zg} X_g - \left(\pi_\lambda \lambda_g + \sigma_\vartheta + \mu_g\right) V_g \quad (1.d)$$

$$\dot{W}_g = \pi_\lambda \lambda_g V_g + \vartheta_g I_g - \left(\pi_{\sigma I} \sigma_{HPVg} \sigma_{Ig} + \sigma_\vartheta + \mu_g\right) W_g \quad (1.e)$$

$$\dot{X}_g = \pi_{\sigma I} \sigma_{HPVg} \sigma_{Ig} W_g + \vartheta_g Z_g - \left(\pi_{\sigma Z} \sigma_{Zg} + \sigma_\vartheta + \mu_g\right) X_g \quad (1.f)$$

It follows from the equations (1.a)-(1.f) that

$$\dot{N}_g = \Lambda_g - \mu_g N_g \quad (1.g)$$

where $N_g = S_g + I_g + Z_g + V_g + W_g + X_g$

5.2.1.1 Force of Infection: Heterosexual population only

$$\lambda_g = \beta_{gg'} c_g \frac{I_{g'} + W_{g'}}{N_{g'}} \quad (1.h)$$

where $\beta_{gg'}$ is the probability of disease transmission per partnership between an infected individual in sex class g' and a susceptible individual in the opposite sex class g, c_g is the mean number of sexual partnerships for an individual of group g per unit time t. $c_g \beta_{gg'}$ is the effective contact rate and $\left(I_{g'} + W_{g'}\right) / N_{g'}$ is the probability that the contact is with an infected individual.

5.2.1.2 Force of Infection: Homosexual population only

$$\lambda_g = \beta_{gg} c_g \frac{I_g + W_g}{N_g} \quad (1.i)$$

where β_{gg} is the probability of disease transmission per partnership between an infected individual in sex class g and a susceptible individual in the same sex class g, c_g is the mean number of sexual partnerships for an individual of class g per unit time t. $c_g \beta_{gg}$ is the effective contact rate and $\left(I_g + W_g\right) / N_g$ is the probability that the contact is with an infected individual.

5.2.1.3 Force of Infection: Bisexual population only

$$\lambda_{g2} = \omega_{g2}\beta_{gg'}c_g \frac{\omega_{g'2}\left(I_{g'} + W_{g'}\right)}{\left(\omega_{g'2}N_{g'}\right)} + \left(1-\omega_{g2}\right)\beta_{gg}c_g \frac{\left(1-\omega_{g2}\right)\left(I_g + W_g\right)}{\left(\left(1-\omega_{g2}\right)N_g\right)} \qquad (1.j)$$

where $\beta_{g,g}$ is the probability of disease transmission per partnership between an infected individual in sex class g and a susceptible individual in the same sex class g, $\beta_{g,g'}$ is the probability of disease transmission per partnership between an infected individual in sex class g' and a susceptible individual in the opposite sex class g, c_g is the mean number of sexual partnerships for an individual of class g per unit time t, ω_{g2} is the proportion of sexual partnerships of a heterosexual nature. $\beta_{gg'}c_g\omega_{g2}, \beta_{gg}c_g\left(1-\omega_{g2}\right)$ is the effective contact rate for heterosexual and homosexual relationships, respectively. The probability that the contact is with an infected individual is determined by $\left(I_g + W_g\right)/N_g$,and $\left(I_{g'} + W_{g'}\right)/N_{g'}$.

For the model to be epidemiologically meaningful all the state variables must be non-negative for all time. The model can be shown to satisfy:

Theorem 4: Let the initial population states be positive, then the solutions of the model with positive initial data must be nonnegative for all time [21] .

Theorem 5: The closed set is positively invariant and attracting with respect to the model [21] .

The proof for Theorem 5 with respect to this model is shown in APPENDIX A2.

5.2.2 Disease Free Equilibrium

The DFE point is $E^0 = \left(S_g^0, 0, 0, \mathrm{V}_g^0, 0, 0, S_{g'}^0, 0, 0, \mathrm{V}_{g'}^0, 0, 0\right)$

with $S_g^0 = \frac{\left(1-\phi_g\right)\Lambda_g}{\left(\vartheta_g + \mu_g\right)}$, $V_g^0 = \frac{\Lambda_g\left(\vartheta_g + \phi_g\mu_g\right)}{\mu_g\left(\vartheta_g + \mu_g\right)}$ and $N_g{}^0 = S_g^0 + V_g^0 = \frac{\Lambda_g}{\mu_g}$.

5.2.3 Local Asymptotical Stability of the Disease Free Equilibrium

The DFE is locally asymptotically stable if $R_o < 1$ and unstable if $R_o > 1$.

5.2.3.1 Reproduction number

The Next Generation matrix approach (see 4.1.1) was used to determine the reproduction numbers for the various sexual orientation populations. All calculations to determine the reproduction number can be seen in APPENDIX A2, all calculations were performed with the aid of Matlab R2012B [76]. Once again the assumptions applied in calculating the reproduction number was based on Elbasha *et al* [61] .

5.2.3.1.1 Reproduction number: Heterosexual population only

The reproduction number of the heterosexual population was determined to be:

$$R_0^{1V} = \sqrt{R_{0m}^{1V} R_{0f}^{1V}} \tag{2.a}$$

where

$$R_{0g}^{1V} = \frac{\left(c_g \beta_{g,g'}\right)}{\left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right)}\left(1 - \phi_g\left(1 - \pi_\lambda \frac{\left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig} + \mu_g\right)}\right)\right) \tag{2.b}$$

Recalling the reproduction number for the heterosexual population without vaccination that was determined from the basic SIR version:

$$R_0^1 = \sqrt{R_{0m}^1 R_{0f}^1} \tag{3.a}$$

Where

$$R_{0m}^1 = \frac{\left(c_m \beta_{mf}\right)}{\left(\sigma_{HPV}\sigma_{1m} + \mu_m\right)} \tag{3.b}$$

$$R_{0f}^1 = \frac{\left(c_f \beta_{fm}\right)}{\left(\sigma_{HPV}\sigma_{If} + \mu_f\right)} \tag{3.c}$$

Therefore the effective reproduction number with vaccination is described as:

$$R_{0g}^{1V} = R_{0g}^1\left(vaccineimpact_g\right) \tag{2.c}$$

where $vaccineimpact_g = 1-\phi_g\left(1-\pi_\lambda \frac{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\right)$ (2.d)

5.2.3.1.2 Reproduction number: Homosexual population only

The reproduction number of the homosexual population was determined to be:

$$R_0^{3V} = R_{0f}^{3V} + R_{0m}^{3V} \tag{3.a}$$

where

$$R_{0g}^{3V} = \frac{\left(c_g\beta_{gg}\right)}{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\left(1-\phi_g\left(1-\pi_\lambda \frac{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\right)\right) \tag{3.b}$$

Recalling the reproduction number for the homosexual population without vaccination that was determined from the basic SIR version:

$$R_0^3 = R_{0f}^3 + R_{0m}^3 \tag{4.a}$$

where

$$R_{0f}^3 = \frac{\beta_{ff}c_f}{\left(\sigma_{HPV}\sigma_{If}+\mu_{\mathrm{f}}\right)} \tag{4.b}$$

$$R_{0m}^3 = \frac{\beta_{mm}c_m}{\left(\sigma_{HPV}\sigma_{\mathrm{Im}}+\mu_m\right)} \tag{4.c}$$

Therefore the effective reproduction number with vaccination is described as

$$R_{0g}^{3V} = R_{0g}^3\left(vaccineimpact_g\right) \tag{3.c}$$

where $vaccineimpact_g = 1-\phi_g\left(1-\pi_\lambda \frac{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\right)$ (3.d)

The reproduction number matches the reproduction number determined by Elbasha *et al* [61] .

5.2.3.1.3 Reproduction number: Bisexual population only

The effective reproduction number with vaccination for a bisexual population only can be written in terms of the effective reproduction numbers of the heterosexual only and homosexual only populations as:

$$R_0^{2V} = \frac{1}{2}\sqrt{\left(\left(1-\omega_g\right)\left(R_{0g}^{3V}\right)+\left(1-\omega_{g'}\right)\left(R_{0g'}^{3V}\right)\right)^2+4\left(\omega_g R_{0g}^{1V}\right)\left(\omega_{g'}R_{0g'}^{1V}\right)} + \frac{1}{2}\left(\left(1-\omega_g\right)R_{0g}^{3V}+\left(1-\omega_{g'}\right)R_{0g'}^{3V}\right) \quad (4.a)$$

5.2.4 Global Stability of the disease free equilibrium

Complete calculations to determine the global stability can be found in Elbasha *et al* [61] and will not be repeated here. Alternatively using the matrix theoretic approach discussed in 4.2.3.1 and Theorem 3 global stability is determined. The model is globally asymptotically stable for $R_o < 1$.

6 Model Simulations

In this section, the numerical results were obtained by simulating the model. All model equations and inputs were programmed in Matlab R2012B [76]. The predictive quality of the model was accessed through comparison to available data. Epidemiological outputs included the prevalence of HPV, and the incidence of CIN and cervical cancer.

6.1 Demographic Model

The initial population distribution was taken from estimates by Dorrington [77] and Statistics South Africa, [66] Natural mortality rates were taken from the initial assumptions for the ASSA2008 model [78] , and a growth rate of 0.5 was used [69]. The model produced a close fit to estimates provided by Statistics South Africa [66] and Dorrington [77] for the years 2002 to 2013, as seen in Figure 6-1 and Figure 6-2 Total Population projections for 2002-2013 with comparisons to Statistics SA [66]and alternative estimates by Dorrington [77] , using Dorrington estimates as initial population produced a closer fit, as to be expected. An additional comparison of the model with the estimates, based by age groups, can be found in APPENDIX B.

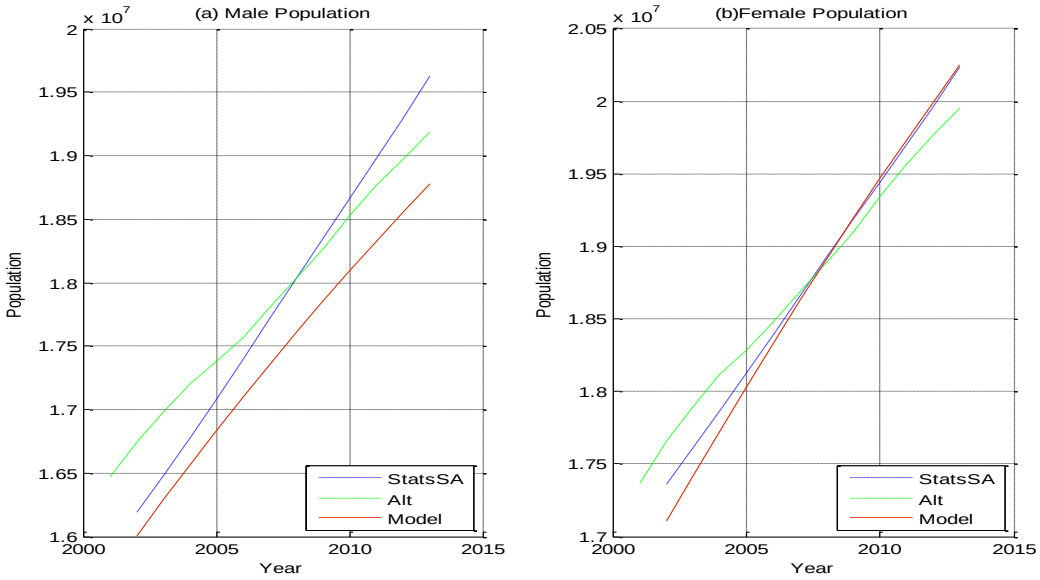


Figure 6-1 Total Population projections for 2002-2013(HIV status not modelled) with comparisons to Statistics SA [66]*and alternative estimates by Dorrington* [77] *, using Statisitcs SA estimates as initial population.*

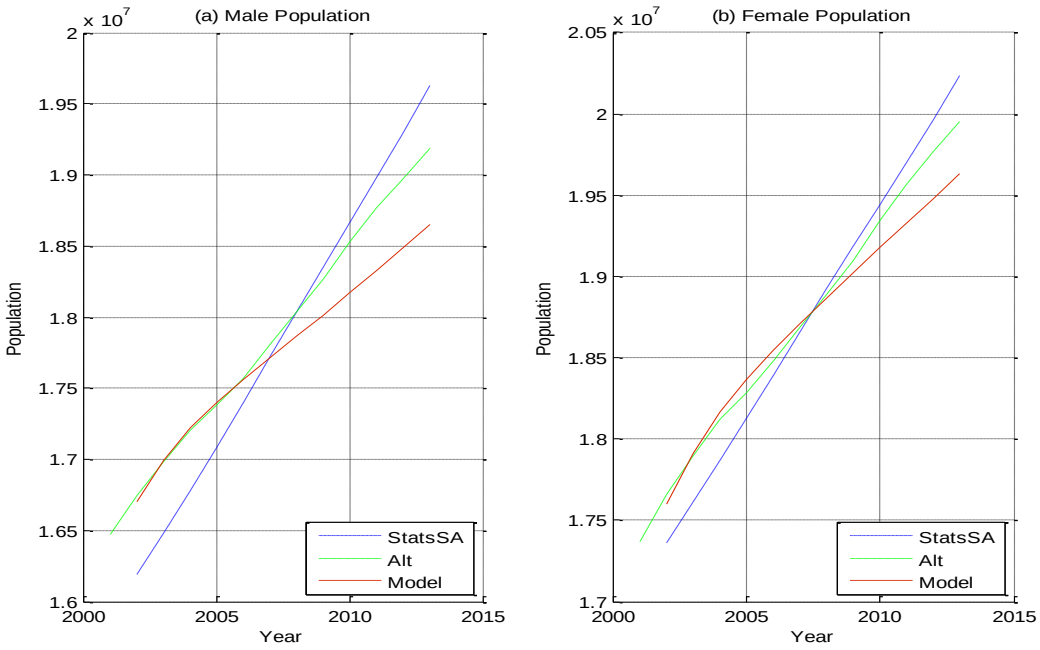


Figure 6-2 Total Population projections for 2002-2013 with comparisons to Statistics SA [66]*and alternative estimates by Dorrington* [77] *, using Dorrington estimates as initial population*

6.2 Epidemiological Model

6.2.1 Model Inputs

Initial prevalence's of the population who are HPV type infected was taken from Richter *et al* [10], see APPENDIX C or the table of values. The initial prevalence's of the population who are HIV positive was taken from HSRC survey data [79], [80]. Additional model inputs not discussed can be found in APPENDIX C .

6.2.2 Progression of HPV to Cervical Cancer

Table 4 and Table 5, were taken from Vijayaraghavan *et al* [33] and Myers *et al* [28]. Additional resources are indicated in the tables. HIV status was determined to increase the probability of disease progression by a factor. The effects of HIV on HPV progression , found in Table 6 Effects of HIV on model parameters, were taken from Vijayaraghavan *et al* [33].Natural immunity from HPV infection was assumed to be of life long duration, with a transmission probability per partnership 0.7 and 0.8, for female to male and male to female, respectively.

Table 4 Parameters used for model HPV progression and regression to cervical cancer

SYMBOL		VALUE	
PROBABILITY OF PROGRESSION %			[33]
ρ_{lgi}^{-1}	HPV Infection to CIN1	8.1 [b]	[81]
ρ_{lgi}^{-2}	HPV Infection to CIN2	0.56 [b]	[28]
ρ_{CINgi}^{-1}	CIN1 to CIN2	1.7-5.7[a]	[28]
ρ_{CINgi}^{-2}	CIN2 to CC1	3.8 [b]	
PROBABILITY OF DISEASE REGRESSION %			[33]
σ_{HPVgi}^{-}	Of HPV	3.3-37.3[a]	
σ_{CINgi}^{-1}	Of CIN1	2.7-14.2[a]	
σ_{CINgi}^{-2}	Of CIN2/3	3.7-5.8[a]	[28]
PERCENTAGE REGRESSING %			[33]
κ_{l}^{1}	CIN1 to HPV infection	10	
κ_{l}^{2}	CIN2 to HPV infection	5	
κ_{CIN}^{1}	CIN2 to CIN1	50	

[a] indicates the range of values used

[b] where only one value is indicated there was insufficient data for age specific values though the model caters for it.

Table 5 Parameters used to model cervical cancer progression

NATURAL HISTORY OF CC	
Probability of progression % [27]	
Stage 1 to stage 2	43.7
Stage 2 to stage 3	53.5
Stage 3 to stage 4	68.3
Probability of survival of 5 years % [27][33]	
Stage 1	85
Stage 2	55
Stage 3	41
Stage 4	12

Table 6 Effects of HIV on model parameters

EFFECT OF HIV ON HPV AND CIN [82] [33]	
PROGRESSION	
HPV INFECTION TO CIN1	3.34
HPV INFECTION TO CIN2/3	3.34
CIN1 TO CIN2/3	2.3
CIN2/3	1
REGRESSION	
HPV INFECTION	0.84
CIN1	0.33
CIN2/3	0

6.2.3 Transmission Probability

To explore the effect of transmission of HPV , a transmission probability of 0.8 for male to female and 0.7 for female to male per partnership was applied. It is assumed that male to male transmission is identical to male to female transmission and female to female transmission is half that of female to male transmission. This is due to transmission being higher when skin is irritated, more likely due to penetrative intercourse. (This does not discount penetrative intercourse in female to female transmission, but does assume a lower source of irritation and that sex toys are not shared)

6.2.3.1Sexual Activity

The population is divided into 3 risk groups: low, med and high, based on sexual activity. The rates in acquisition of sexual partnerships was adjusted from partner acquisition rates in Johnson [22]. The rates were for high risk short term partnerships. It was assumed that the proportion of individuals who responded to survey's ([79], [80]) as having two or more current partners consist of the proportion of the population who are high risk. Therefore the average of the proportion of the population who engage in multiple sexual partnerships per time period are assumed to be risk group 3. Where the percentage of the population in

the high risk group exceed the percentage of high risk age specific population the rates are adjusted by the percentage difference. The proportion of individuals in risk group 1 is determined through the proportion of the population who responded in survey to having no current partnerships for the past year. Risk group 2 have partner acquisition rates which are a combination of risk group 1 and 3. A fraction (0.25) of the rates for the high risk partnerships used for individuals. Risk group 2 was adjusted in a similar manner to risk group 3 with additional by sight adjustments to match HIV incidence and prevalence. A table of the data discussed can be found in APPENDIX B. The mixing parameter between age groups was set to 0.8 and between sexual activity groups as 0.2.

6.3 Model Outcomes

6.3.1 Bisexual and Homosexual Population

The transmission of HPV requires only skin-to-skin contact, therefore sexual transmission can occur by direct genital-to-genital or digital-genital contact. Genital HPV types have even been identified on human fingers ([83], [84]). Studies have also found that the majority of women who have intercourse with women (53%-99%) have had sex with men, and many (21%-30%) continue to have sexual relationships with men ([83], [84]).

To investigate sexual orientation a strictly heterosexual population was compared with a population where 5% or 10% of the population consisted of homosexuals and bisexuals. These percentages were then further analysed by splitting the bisexual and homosexual percentages into 0.25/0.75,0.5/0.5 and 0.75/0.25 proportions. See figure 6-3.

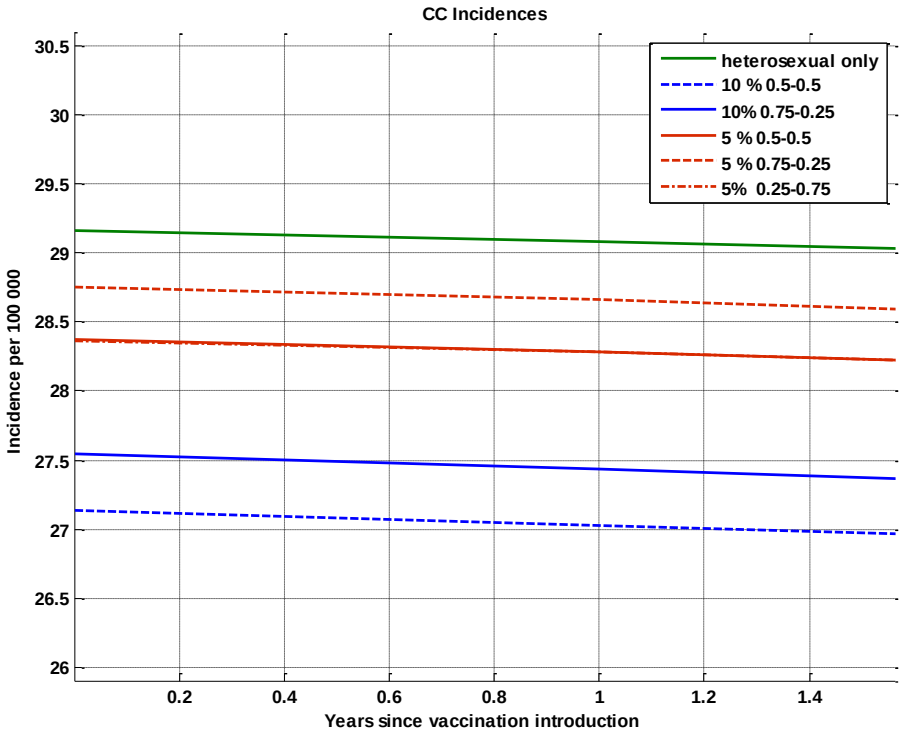


Figure 6-3 The effect on cervical cancer incidence when modelling mixed orientations. The dotted lines and solid lines indicate a 5% and 10% population, identifying as bisexual or homosexual, respectively. Additionally the percentage is split 25-75,50-50 and 75-25 between bisexual and homosexual, as indicated in the legend.

The results indicated that a lower proportion of the population identifying as bisexual produced a lower cervical cancer incidence. This is due to the decreased probability in female to female transmission compared to male to female transmission. Figure 6-4 The effect of including bisexual and homosexual partnerships to the cervical incidence ratedemonstrates the sensitivity of the proportion of the population identifying as homosexual or bisexual, and the proportion of partnerships they have preference towards. When the bisexual population is of a larger proportion the preference towards heterosexual or homosexual partnerships is significant. In the figure higher homosexual orientated partnerships produce a substantial decrease in the cervical cancer incidence. This result is understandable due to the fact that HPV female to female transmission probability was set to half female to male transmission.

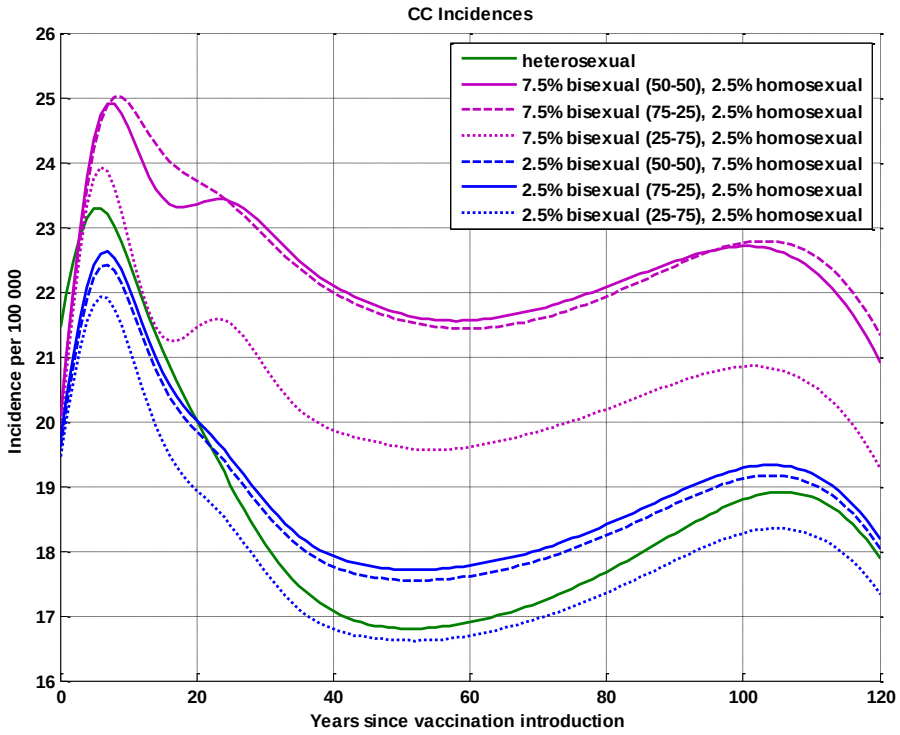


Figure 6-4 The effect of including bisexual and homosexual partnerships to the cervical incidence rate

6.3.2 HIV status

To determine the effect HIV status has on the cervical cancer incidence the population is modelled both with and without HIV status risk factors and with. The average incidence without HIV status is approximately 5 per 100 000. In the case of HIV status ,and the added effects on transmission and progression parameters due to HIV status, the incidence is approximately 18 per 100 000. This figure supports the assumed cervical cancer incidence of 30 per 100 000 as HPV 16/18 accounts for 60 to 70% of all cervical cancer cases.

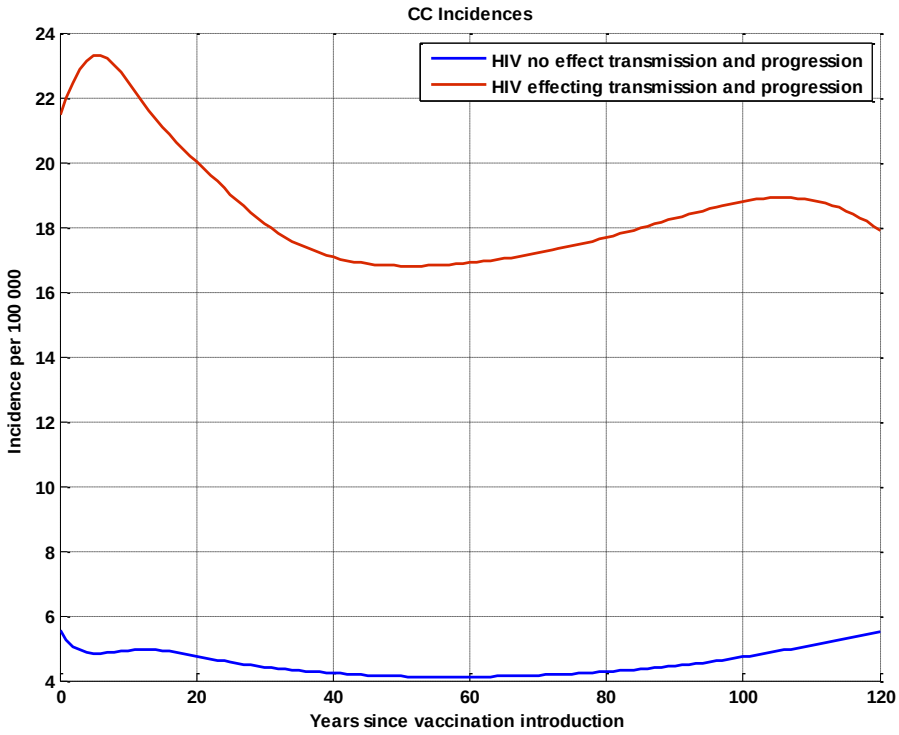


Figure 6-5 Comparison in the cervical cancer incidence when including HIV status effects on HPV transmission and disease progression

6.3.3 Impact of Vaccination

Vaccination with HPV16/18 vaccine was investigated in a population with no cervical cancer screening program. Four main vaccination strategies were examined, namely: (i) Adolescent females before sexual debut, (ii) Adolescent females before sexual debut and a female catch up program for ages up to 25, (iii) Adolescent males before sexual debut, and (iv) Adolescent males and females before sexual debut and a female catch up program for ages up to 25.

6.3.3.1 Impact of HPV16/18 vaccine on CIN1 and CIN2/3

Figure 6-6 Effects of vaccination of CIN incidence, with female population targeted on entry to sexually active population (homosexual population only)

shows the impact of introducing a HPV16/18 vaccine on CIN1 and CIN2/3. CIN1 showed a significant impact with vaccination over a short time period. Literature indicates that CIN2/3 should show a higher impact due to CIN2/3 association with

HPV type 16/18 [27]. It should be noted that only HPV type16/18 induced CIN was modelled and these results do not contradict the literature.

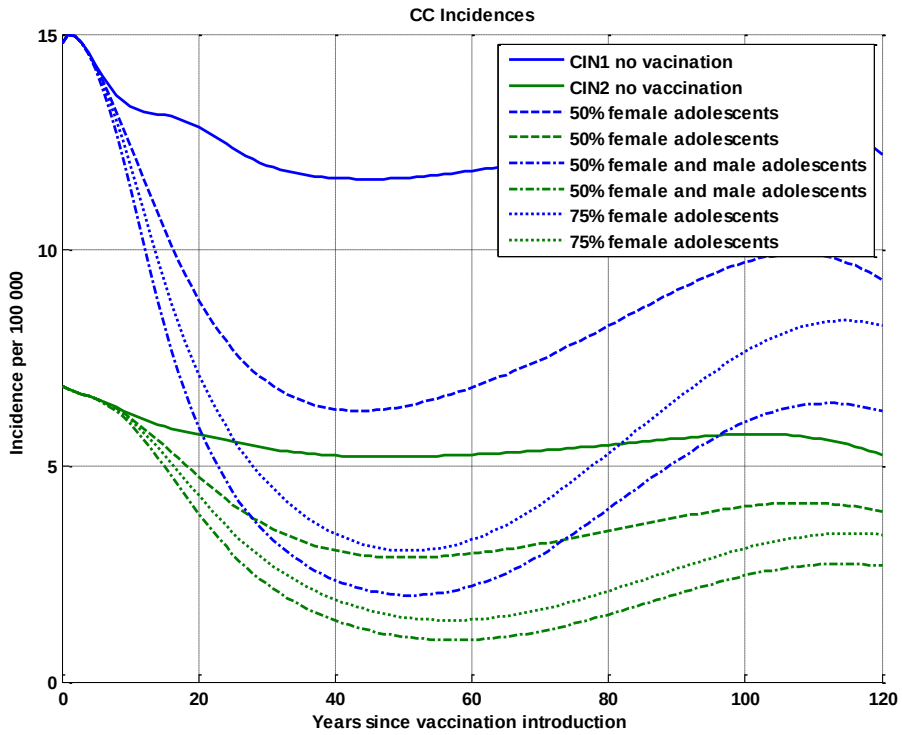


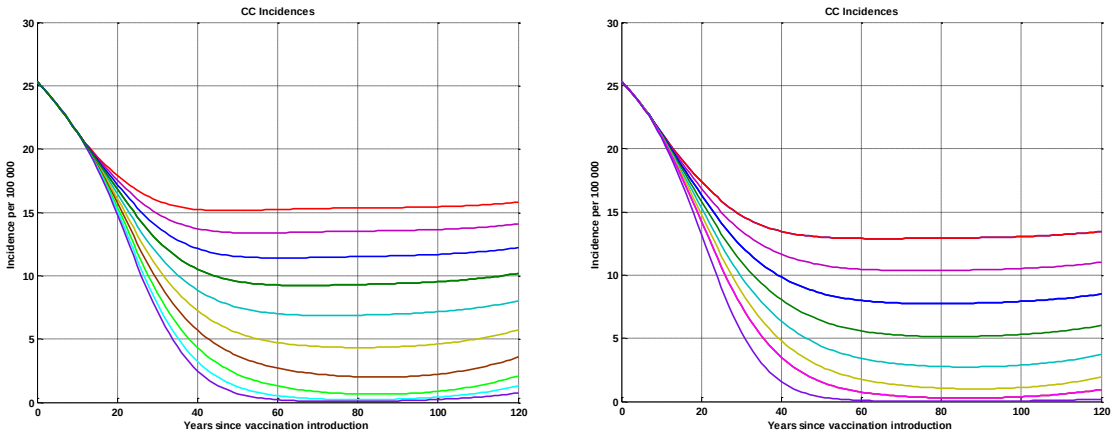
Figure 6-6 Effects of vaccination of CIN incidence, with female population targeted on entry to sexually active population (homosexual population only)

6.3.4 Impact of HPV16/18 Vaccine on Cervical Cancer Incidence

Cervical cancer incidence was determined to be on average 18 per 100 000 in the heterosexual population model and 20 per 100 000 in the population of 5% bisexual and 5% homosexual, when HPV is assumed to have no waning immunity. This is lower than the reported average of 30 per 100 000 for cervical cancer, however HPV16/18 is determined to cause between 60 and 70% of cervical cancer cases [85] therefore it is within the correct range.

Results (see figures 6-7 to 6-10) showed that the most effective vaccination strategy was adolescent males and females before sexual debut and a female catch up program for ages up to 25. However when vaccination coverage of females is high it produces an insignificant added value of including males

compared to a setting where female vaccination coverage is low. The marginal impact on the cervical cancer incidence, by a both sex adolescent on sexual debut vaccination strategy with a both sex catch up program, diminished as the coverage of females increased.



(a) (b)

Figure 6-8 The effects of vaccination coverage on adolescent females entering the sexually active population. In increments of 10% coverage. The lines in the graph represent in descending order an increase in vaccination. The top most line is 10 % while the bottom most line is 90% coverage. The graph illustrates the delay in the effect of vaccination coverage on cervical cancer incidence.

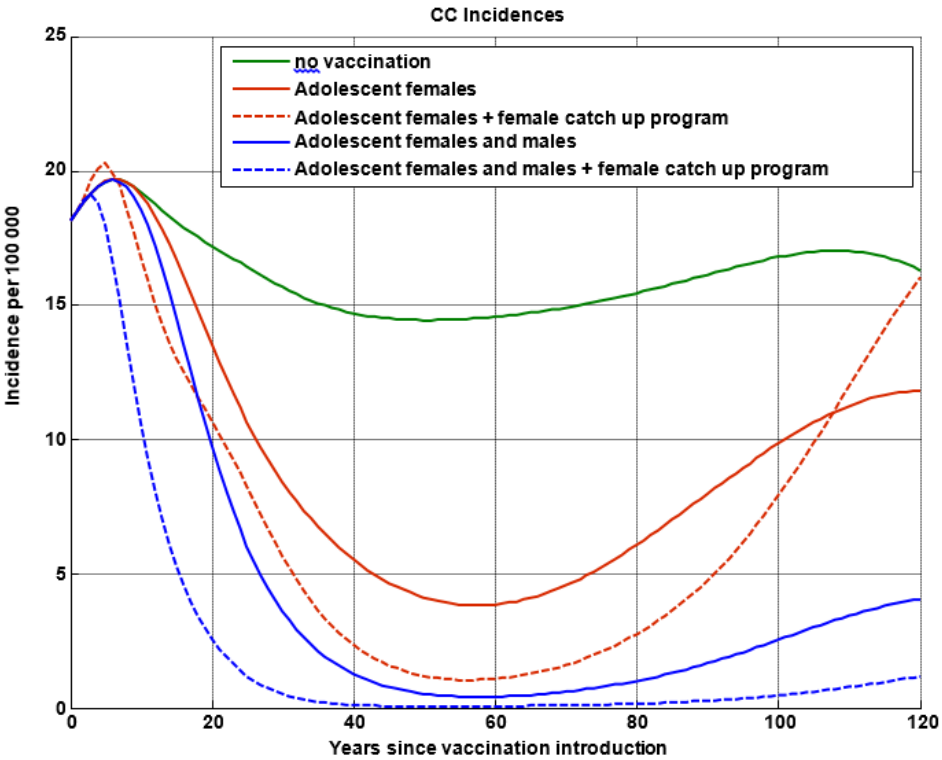


Figure 6-7 The effects of vaccination on Cervical cancer incidence. 50% of the populations targeted receive vaccination. (5% bisexual 5% homosexual population model)

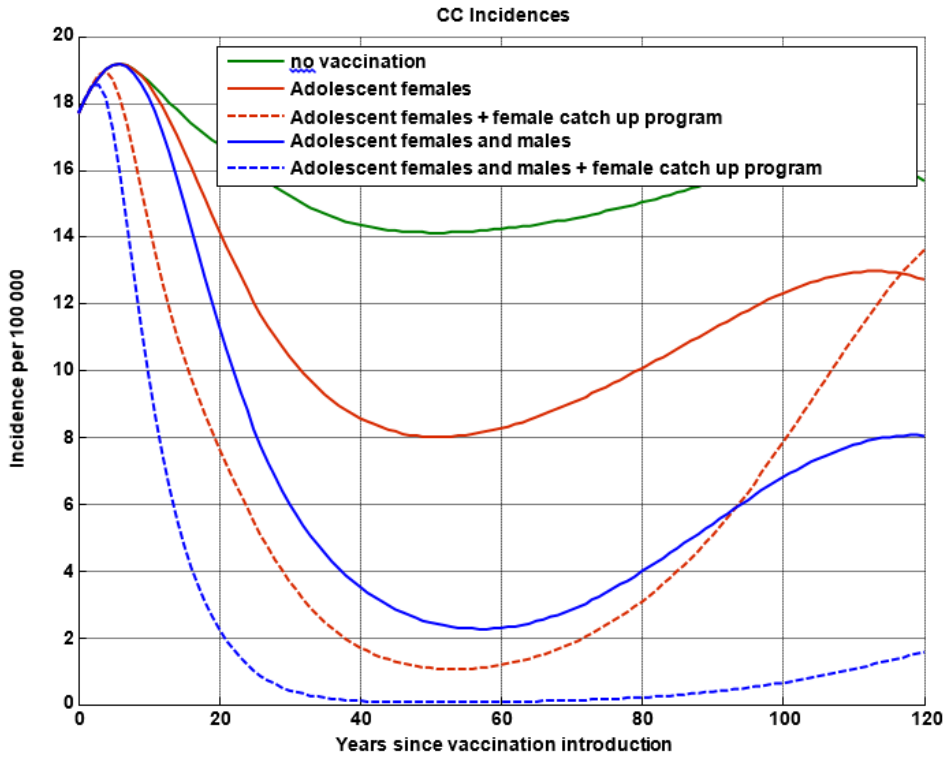


Figure 6-9 The effects of vaccination on cervical cancer incidence. 50% of the populations targeted receive vaccination. (heterosexual population model)

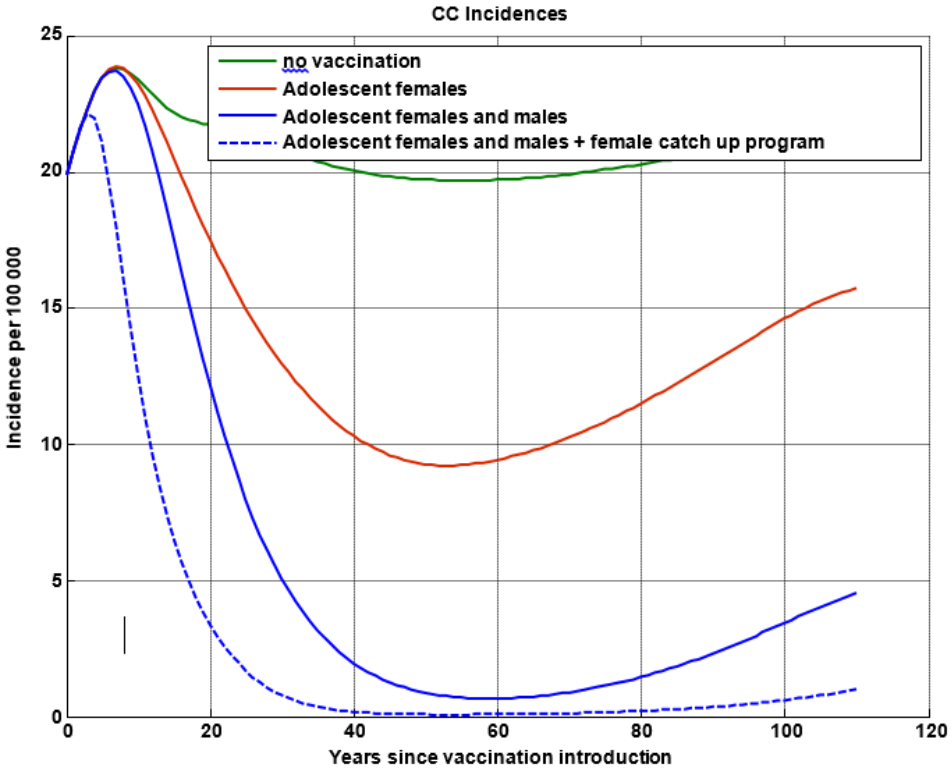


Figure 6-10 The effects of vaccination on Cervical cancer incidence. 75% of the populations targeted receive vaccination. (heterosexual population model)

7 Discussion and Conclusion

In this project an extensive review of literature in regards to modelling HPV transmission and the natural history of HPV transmission to HPV type caused cervical cancer was completed. Literature indicated two main approaches, a cohort model approach and a population dynamic approach. The models were used to investigate different screening strategies, and more recently HPV vaccination strategies on a population. Four main vaccination strategies were investigated, vaccinating: (i) Adolescent females before sexual debut, (ii) Adolescent females before sexual debut and a female catch up program up to the age of 265, (iii) Adolescent male and female before sexual debut, and (iv) Adolescent male and females before sexual debut and a female catch up program up to the age 25 years. The results indicated that screening was an effective method of cervical cancer mortality and lifetime cervical cancer risk reduction with the most effective strategy determined to be vaccinating adolescent males and females before sexual debut and a catch up program.

An important limitation to the cohort models was the assumption of a homogeneous population with no risk factors being modelled, the exception being Goldie *et al* [41] where sexual activity and risk factors were assumed to vary. The majority of the population dynamic models used a sexual mixing algorithm adapted from Barnabas *et al* [13].In their approach populations were stratified into age, sex, and sexual activity classes with defined roles of partner change specified in a sexual mixing algorithm. The algorithm depended on the proportion of sexual partnerships from the opposite sex, from the sexual activity group and the age class in the total sexually active population. The degree of assortative mixing between the age and sexual activity groups is included through mixing parameters and a balancing of supply and demand is taken into account. Results in regards to the effects of sexual activity on HPV and cervical cancer incidence indicated a proportional relationship between the number of sexual partnerships and cervical cancer incidence. The level of heterogeneity was found to be significant in disease burden, with the epidemic shaped more by heterogeneity between sexual activity groups than by age groups. An important limitation to the models was the

modelling of a heterosexual population only, an exception being Bogaards *et al* [46] who investigated the addition of bisexual and homosexual individuals.
A mathematical model of HPV transmission and the natural history of HPV type caused cervical cancer, using ordinary differential equations, was developed. The model incorporated the three sexual orientation classes, and a sexual mixing algorithm for modelling the transmission dynamics. The model was based on that by Elbasha *et al* [5], [14].

Theoretical analysis was performed to determine the effects of sexual orientation classes on the reproduction number. This was achieved through a simplified SIR version of the model developed, see Chapter 5. The reproduction numbers indicated that the bisexual population could form a bridge between the heterosexual and homosexual population. This indicated that an effect on one sexual orientation class could affect the other class dependent on the level of interaction of that class with the bisexual population. The level of interaction is determined by the selection preferences of a bisexual individual to form a partnership with the same or opposite sex.

The model was simulated to investigate the effects of HIV status, sexual orientation and various vaccination strategies on HPV transmission and cervical cancer incidence. Model input parameters were based on the South African population where data was available, and from global literature resources where South African data was not available. Vaccination strategies evaluated were: (I) Adolescent females before sexual debut, (ii) Adolescent females before sexual debut and a female catch up program for ages up to 25, : (Iii) Adolescent males before sexual debut, (iv) Adolescent males and females before sexual debut and a female catch up program for ages up to 25. Results, similar to those appearing in the literature, indicated that the best approach is a both sex adolescent on sexual debut vaccination strategy with sex a female catch up program. However when vaccination coverage of females is high including males has an insignificant affected as compared to a when female vaccination coverage is low. The marginal impact on the cervical cancer incidence, by a both sex adolescent on sexual debut vaccination strategy with sex female catch up program, diminished as the coverage of females increased.

HIV status was determined in literature to increase the probability of HPV transmission and the probability of HPV disease progression. This argument was supported in this study, see figure 6-5, and is especially true for South Africa. The incidence rate increased significantly when including the effects of HIV status on progression. Sexual orientation was investigated through comparison to a strictly heterosexual population with a population with 5 and 10% identifying as homosexual or bisexual. The 5 and 10% were further analysed through splitting the percentage into bisexual and homosexual proportions of 0.25/0.75, 0.50/0.50 and 0.75/0.25. The results indicated that a smaller bisexual population produced a lower cervical cancer incidence. . The relationship between the bisexual population and HPV transmission and cervical cancer incidence is determined by the selection preferences of a bisexual individual to form a partnership with an individual of the same or opposite sex.

The model has numerous limitations. One of the main limitations includes the lack of incorporating immigration, South Africa has a large annual migration population which could influence the transmission dynamics and prevalence of HPV due to the immigrated population consisting of a proportion of 'new' invectives. The model also does not incorporate screening practices or medical treatment. The HIV compartment is not subdivided to include all the HIV stages, HIV stages produced varying levels of infectiveness and different stages would have different effects on progression and regression of HPV to cervical cancer progression. The model has a limited number of sexual activity class and individuals cannot leave their sexual activity class based on behavioural change. The complexity of the model and the lack of extensive sexual behaviour data was another limitation, the complexity of the model reduced the ability for an effective theoretical analysis.

The model could be extended to incorporate the limitations discussed. An immigration entry for each age group together with a, screening and treatment program could be incorporated. The HIV compartment can be extended to include HIV stages. The sexual activity classes could be extended to include less general classes based on type of partnership and not just sexual activity level. Finally, a rate of transmission between the sexual activity classes could be incorporated to

model the effects of changing behaviour as an individual ages or responds to an education program.

Glossary[2]

WORD	MEANING
ANOGENTIAL	involving the genital organs and the anus
BIVALENT	conferring immunity to two diseases or two serotypes
CD4	a large glycoprotein that is found especially on the surface of helper T cells, that is the receptor for HIV
CERVIX	The neck of the uterus
CYROTHERAPHY	the local or general use of low temperatures in medical therapy
CYTOLOGY	the structure, function, multiplication, pathology, and life history of cells
EPITHELIUM	Layers of cells that line hollow organs and glands and make up the outer surface of the body.
GENOTYPES	all or part of the genetic constitution of an individual or group
HISTOLOGY	structure or organization of tissue
IMMUNOGENCITY	the quality or state of being immunogenic
IMMUNOGENIC	relating to or producing an immune response
ONCOGENIC	tending to cause tumours
PAPANICOLAOU SMEAR	cells are collected from the outer opening of the cervix and examined under a microscope.
PERSISTENT	remaining infective for a relatively long time in a vector after an initial period of incubation
PROPHYLATIC	guarding from or preventing the spread or occurrence of disease or infection
QUADRILATERAL	conferring immunity to four diseases or four serotypes
SEROTYPE	a group of intimately related microorganisms distinguished by a common set of antigens
SQUAMOUS CELL EPITHELIUM	epithelium characterised by its most superficial layer consisting of flat, scale-like cells
TRANSIENT	existing temporarily
UTERUS	female reproductive organ located in the pelvis
VACCINE EFFICACY	the effectiveness of the vaccine

[2] [86]

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APPENDIX A1

Basic Properties

Theorem 4: Let the initial population states be positive, then the solutions of the model with positive initial data must be nonnegative for all time. Proof (See [21])

Theorem 5: The closed set is positively invariant and attracting with respect to the model.

Proof follows Elbasha *et al* (See [21]):

$$D = \{(\mathrm{S_g}, \mathrm{I_g}, \mathrm{Z_g}, \mathrm{S_{g'}}, \mathrm{I_{g'}}, \mathrm{Z_{g'}}) \in \mathbb{R}^6_+, \mathrm{N_g} \leq \frac{\Lambda_g}{\mu_g} \text{ and } \mathrm{N_{g'}} \leq \frac{\Lambda_{g'}}{\mu_{g'}}\}$$

It follows from the equations (1.a)-(1.d),in Chapter 5, that

$$\dot{N}_g = \Lambda_\mathrm{g} - \mu_g N_g$$

This implies that $\dot{N}_g < 0$ if $\frac{\Lambda_\mathrm{g}}{\mu_g} < N_g$

$$N_g(0)e^{\mu_g(0)} = N_g(0)$$

And $\frac{\Lambda_\mathrm{g}}{\mu_g} e^{\mu_g(0)} = \frac{\Lambda_\mathrm{g}}{\mu_g}$

Therefore

$$N_g(0)e^{\mu_g(0)} = N_g(0) \leq \frac{\Lambda_\mathrm{g}}{\mu_g} e^{\mu_g(0)} = \frac{\Lambda_\mathrm{g}}{\mu_g}$$

Which gives

$$N_g(0) \leq \frac{\Lambda_\mathrm{g}}{\mu_g}$$

For t>0:

$$N_g(\mathrm{t})e^{\mu_g(\mathrm{t})} \leq \frac{\Lambda_\mathrm{g}}{\mu_g} e^{\mu_g(\mathrm{t})}$$

Subtracting $N_g(0)$ from $N_g(\mathrm{t})e^{\mu_g(\mathrm{t})}$:

$$N_g(\mathrm{t})e^{\mu_g(\mathrm{t})} - N_g(0) \leq \frac{\Lambda_\mathrm{g}}{\mu_g} + \frac{\Lambda_\mathrm{g}}{\mu_g} e^{\mu_g(\mathrm{t})}$$

Dividing through by $e^{\mu_g(t)}$:

$$N_g(t) \le N_g(0)e^{-\mu_g(t)} + \frac{\Lambda_g}{\mu_g}e^{-\mu_g(t)} + \frac{\Lambda_g}{\mu_g}e^{\mu_g(t)}e^{-\mu_g(t)}$$

$$N_g(t) \le N_g(0)e^{-\mu_g(t)} + (1-e^{-\mu_g(t)})\frac{\Lambda_g}{\mu_g}$$

Which implies if $N_g(0) \le \frac{\Lambda_g}{\mu_g}$ then $N_g(t) \le \frac{\Lambda_g}{\mu_g}$

Similarly done for g'.

Therefore positively invariant.

If $N_g > \frac{\Lambda_g}{\mu_g}$ (for both sexes) then either the solution enters D in a finite time or approaches $\frac{\Lambda_g}{\mu_g}$. The infected population state variables approach zero.

Therefore D attracts all the solutions.

Calculation of Reproduction number

The next generation method was used to determine the reproduction number and examine the local stability of the DFE. The next generation matrix $\bar{G}$ is given by: $\bar{G} = \bar{F}\bar{V}^{-1}$, therefore in order to utilize the next generation method two matrices are required. A matrix $\bar{F}$ for new infections and a matrix $\bar{V}$ for transfers between the compartments.

Calculation of the reproduction numbers was done with the aid of Matlab 2012. The assumptions applied in calculating the reproduction number was based on Elbasha *et al* [61] .

Heterosexual Population only

The matrix $\bar{F}$ for new infections and $\bar{V}$ for transfer between the compartments evaluated at the DFE and accounting for only the infected states for a heterosexual population only are:

$$\bar{F} = \begin{bmatrix} 0 & \left(c_g \beta_{gg'} \frac{S_g^0}{N_{g'}^0}\right) \\ \left(c_{g'} \beta_{g'g} \frac{S_{g'}^0}{N_g^0}\right) & 0 \end{bmatrix} \qquad \bar{V} = \begin{bmatrix} \left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right) & 0 \\ 0 & \left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right) \end{bmatrix}$$

Substituting the DFE points, $S_g^0 = \frac{\Lambda_g}{\mu_g}$ and $N_g^0 = S_g^0$, produces:

$$\bar{F} = \begin{bmatrix} 0 & \left(c_g \beta_{gg'} \frac{\mu_{g'}\Lambda_g}{\mu_g \Lambda_{g'}}\right) \\ \left(c_{g'} \beta_{g'g} \frac{\mu_g \Lambda_{g'}}{\mu_{g'}\Lambda_g}\right) & 0 \end{bmatrix} \qquad \bar{V} = \begin{bmatrix} \left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right) & 0 \\ 0 & \left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right) \end{bmatrix}$$

Without the loss of generality the population is expressed as a fraction of their sex by assuming:

$$\Lambda_g = \mu_g$$

$$\bar{F} = \begin{bmatrix} 0 & \left(c_g \beta_{gg'}\right) \\ \left(c_{g'} \beta_{g'g}\right) & 0 \end{bmatrix} \qquad \bar{V} = \begin{bmatrix} \left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right) & 0 \\ 0 & \left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right) \end{bmatrix}$$

The spectral radii of : $\left(\bar{F}\bar{U}^{-1}\right)$ is:

$$\rho\left(\bar{F}\bar{U}^{-1}\right) = \sqrt{\frac{\left(c_{g'} \beta_{g'g}\right)}{\left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right)} \frac{\left(c_g \beta_{gg'}\right)}{\left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right)}}$$

Homosexual Population only

The matrix $\bar{F}$ for new infections and $\bar{V}$ for transfer between the compartments evaluated at the DFE and accounting for only the infected states for a heterosexual population only are:

$$\bar{F} = \begin{bmatrix} \left(c_g \beta_{gg}\right) & 0 \\ 0 & \left(c_{g'} \beta_{g'g'}\right) \end{bmatrix} \qquad \bar{U} = \begin{bmatrix} \left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right) & 0 \\ 0 & \left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right) \end{bmatrix}$$

The spectral radii of : $\left(\bar{F}\bar{U}^{-1}\right)$ is:

$$\rho\left(\bar{F}\bar{U}^{-1}\right) = \frac{\left(c_g \beta_{gg}\right)}{\left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right)} \text{ or } \frac{\left(c_{g'} \beta_{g'g'}\right)}{\left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right)}$$

Bisexual Population only

The matrix $\bar{F}$ for new infections and $\bar{V}$ for transfer between the compartments evaluated at the DFE and accounting for only the infected states for a heterosexual population only are:

$$\bar{F} = \begin{bmatrix} \left(\left(1-\omega_g\right)c_g \beta_{gg}\right) & \left(\omega_g c_g \beta_{gg'} \frac{S_g^0}{N_{g'}^0}\right) \\ \left(\omega_{g'} c_{g'} \beta_{g'g} \frac{S_{g'}^0}{N_g^0}\right) & \left(\left(1-\omega_{g'}\right)c_{g'} \beta_{g'g'}\right) \end{bmatrix} \qquad \bar{U} = \begin{bmatrix} \left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right) & 0 \\ 0 & \left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right) \end{bmatrix}$$

Substituting the DFE points, $S_g^0 = \frac{\Lambda_g}{\mu_g}$ and $N_g^0 = S_g^0$, and without the loss of generality assuming the population is expressed as a fraction of their sex: $\Lambda_g = \mu_g$

$$\bar{F} = \begin{bmatrix} \left(\left(1-\omega_g\right)c_g \beta_{gg}\right) & \left(\omega_g c_g \beta_{gg'} \frac{\mu_{g'}\Lambda_g}{\mu_g \Lambda_{g'}}\right) \\ \left(\omega_{g'} c_{g'} \beta_{g'g} \frac{\mu_g \Lambda_{g'}}{\mu_{g'}\Lambda_g}\right) & \left(\left(1-\omega_{g'}\right)c_{g'} \beta_{g'g'}\right) \end{bmatrix} \qquad \bar{U} = \begin{bmatrix} \left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right) & 0 \\ 0 & \left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right) \end{bmatrix}$$

Which results in:

$$\bar{F} = \begin{bmatrix} \left(\left(1-\omega_g\right)c_g \beta_{gg}\right) & \left(\omega_g c_g \beta_{gg'}\right) \\ \left(\omega_{g'} c_{g'} \beta_{g'g}\right) & \left(\left(1-\omega_{g'}\right)c_{g'} \beta_{g'g'}\right) \end{bmatrix} \qquad \bar{U} = \begin{bmatrix} \left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right) & 0 \\ 0 & \left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right) \end{bmatrix}$$

The spectral radii of : $\left(\bar{F}\bar{U}^{-1}\right)$ is:

$$\rho\left(\bar{F}\bar{U}^{-1}\right)=\frac{1}{2}\left(\frac{\left(\left(1-\omega_{g'}\right)\left(\sigma_{HPV}\sigma_{Ig}+\mu_{g}\right)\beta_{g'g}c_{g'}-\left(1-\omega_{g}\right)\left(\sigma_{HPV}\sigma_{\mathrm{I}g'}+\mu_{g'}\right)\beta_{gg}c_{g}\right)^{2}}{\left(\sigma_{HPV}\sigma_{Ig}+\mu_{g}\right)^{2}\left(\sigma_{HPV}\sigma_{\mathrm{I}g'}+\mu_{g'}\right)^{2}}\right.$$

$$\left.+4\left(\frac{\omega_{g}\beta_{g'\mathrm{g}}c_{g}}{\left(\sigma_{HPV}\sigma_{Ig}+\mu_{g}\right)}\right)\left(\frac{\omega_{g'}\beta_{gg'}c_{g'}}{\left(\sigma_{HPV}\sigma_{\mathrm{I}g'}+\mu_{g'}\right)}\right)\right)^{\frac{1}{2}}$$

$$+\frac{\left(1-\omega_{g}\right)\beta_{gg}c_{g}}{2\left(\sigma_{HPV}\sigma_{Ig}+\mu_{g}\right)}+\frac{\left(1-\omega_{g'}\right)\beta_{g'g}c_{g'}}{2\left(\sigma_{HPV}\sigma_{\mathrm{I}g'}+\mu_{g'}\right)}$$

APPENDIX A2
Basic Properties

Theorem 4: Let the initial population states be positive, then the solutions of the model with positive initial data must be nonnegative for all time.

Proof (See[21])

Theorem 5: The closed set is positively invariant and attracting with respect to the model.

Proof follows Elbasha *et al* (See [21]):

$$D=\{(\mathrm{S_g},\mathrm{I_g},\mathrm{Z_g},\mathrm{V_g},\mathrm{W_g},\mathrm{X_g},\mathrm{S_{g'}},\mathrm{I_{g'}},\mathrm{Z_{g'}},\mathrm{V_{g'}},\mathrm{W_{g'}},\mathrm{X_{g'}})\in\mathbb{R}_{+}^{12},\mathrm{N_g}\leq\frac{\Lambda_g}{\mu_g}\,\mathrm{and}\,\mathrm{N_{g'}}\leq\frac{\Lambda_{g'}}{\mu_{g'}}\}$$

It follows from the equations (1.a)-(1.g), in Chapter 5, that

$$\dot{N}_g=\Lambda_{\mathrm{g}}-\mu_g N_g$$

Which implies $\dot{N}_g<0$ if $\frac{\Lambda_{\mathrm{g}}}{\mu_g}<N_g$

(Using comparison)

$$N_g(0)e^{\mu_g(0)}=N_g(0)$$

And $\frac{\Lambda_{\mathrm{g}}}{\mu_g}e^{\mu_g(0)}=\frac{\Lambda_{\mathrm{g}}}{\mu_g}$

Therefore

$$N_g(0)e^{\mu_g(0)}=N_g(0)\leq\frac{\Lambda_{\mathrm{g}}}{\mu_g}e^{\mu_g(0)}=\frac{\Lambda_{\mathrm{g}}}{\mu_g}$$

Which gives:

$$N_g(0)\leq\frac{\Lambda_{\mathrm{g}}}{\mu_g}$$

For any t >0:

$$N_g(\mathrm{t})e^{\mu_g(\mathrm{t})}\leq\frac{\Lambda_{\mathrm{g}}}{\mu_g}e^{\mu_g(\mathrm{t})}$$

Subtracting $N_g(0)$ from $N_g(t)e^{\mu_g(t)}$:

$$N_g(t)e^{\mu_g(t)} - N_g(0) \leq \frac{\Lambda_g}{\mu_g} + \frac{\Lambda_g}{\mu_g} e^{\mu_g(t)}$$

Dividing through by $e^{\mu_g(t)}$:

$$N_g(t) \leq N_g(0)e^{-\mu_g(t)} + \frac{\Lambda_g}{\mu_g} e^{-\mu_g(t)} + \frac{\Lambda_g}{\mu_g} e^{\mu_g(t)} e^{-\mu_g(t)}$$

$$N_g(t) \leq N_g(0)e^{-\mu_g(t)} + (1 - e^{-\mu_g(t)}) \frac{\Lambda_g}{\mu_g}$$

Which implies if $N_g(0) \leq \frac{\Lambda_g}{\mu_g}$ then $N_g(t) \leq \frac{\Lambda_g}{\mu_g}$

Similarly done for g'. Therefore positively invariant.

If $N_g > \frac{\Lambda_g}{\mu_g}$ (for both sexes) then either the solution enters D in a finite time or approaches $\frac{\Lambda_g}{\mu_g}$. The infected population state variables approach zero. Therefore D attracts all the solutions.

Calculation of Reproduction numbers

Calculation of reproduction numbers in Chapter 5 was done with the aid of Matlab 2012. The assumptions applied in calculating the reproduction number was based on Elbasha [61] .

Heterosexual Population only

Using the next generation method to examine the local stability of the DFE. The matrices $\bar{F}$ (New infections) and $\bar{V}$ (transfer between the compartments) evaluated at the DFE and accounting for only the infected states are given, respectively, by:

$$\bar{F} = \begin{bmatrix} 0 & c_g \beta_{g,g'} \frac{S^0_{g}}{N_{g'}} & 0 & c_g \beta_{g,g'} \frac{S^0_{g}}{N_{g'}} \\ c_{g'} \beta_{g',g} \frac{S^0_{g'}}{N_g} & 0 & c_{g'} \beta_{g',g} \frac{S^0_{g'}}{N_g} & 0 \\ 0 & \pi_\lambda c_g \beta_{g,g'} \frac{V^0_{g}}{N_{g'}} & 0 & \pi_\lambda c_g \beta_{g,g'} \frac{V^0_{g}}{N_{g'}} \\ \pi_\lambda c_{g'} \beta_{g',g} \frac{V^0_{g'}}{N_g} & 0 & \pi_\lambda c_{g'} \beta_{g',g} \frac{V^0_{g'}}{N_g} & 0 \end{bmatrix}$$

$$\bar{U} = \begin{bmatrix} \left(\sigma_{HPVg}\sigma_{Ig} + \vartheta_g + \mu_g\right) & 0 & 0 & 0 \\ 0 & \left(\sigma_{HPVg'}\sigma_{Ig'} + \vartheta_{g'} + \mu_{g'}\right) & 0 & 0 \\ -\vartheta_g & 0 & \left(\pi_{\sigma I}\sigma_{HPVg}\sigma_{Ig} + \mu_g\right) & 0 \\ 0 & -\vartheta_{g'} & 0 & \left(\pi_{\sigma I}\sigma_{HPVg'}\sigma_{Ig'} + \mu_{g'}\right) \end{bmatrix}$$

Substituting in the Disease Free Equilibrium values:

The DFE point is $E^0 = \left(S^0_g, 0, 0, \mathrm{V}^0_g, 0, 0, S^0_{g'}, 0, 0, \mathrm{V}^0_{g'}, 0, 0\right)$.

With

$$S^0_g = \frac{\left(1-\phi_g\right)\Lambda_g}{\left(\vartheta_g + \mu_g\right)} \tag{4.b}$$

$$V^0_g = \frac{\Lambda_g\left(\vartheta_g + \phi_g\mu_g\right)}{\mu_g\left(\vartheta_g + \mu_g\right)} \tag{4.c}$$

And $\dot{N} = \Lambda - \mu N$

$$N_g{}^0 = S^0_g + V^0_g = \frac{\Lambda_g}{\mu_g}$$

$$\overline{F} = \begin{bmatrix} 0 & c_g \beta_{g,g'} \dfrac{\left(1-\phi_g\right)\Lambda_g}{\left(\vartheta_g+\mu_g\right)} \dfrac{\mu_{g'}}{\Lambda_{g'}} & 0 & c_g \beta_{g,g'} \dfrac{\left(1-\phi_g\right)\Lambda_g}{\left(\vartheta_g+\mu_g\right)} \dfrac{\mu_{g'}}{\Lambda_{g'}} \\ c_{g'} \beta_{g',g} \dfrac{\left(1-\phi_{g'}\right)\Lambda_{g'}}{\left(\vartheta_{g'}+\mu_{g'}\right)} \dfrac{\mu_g}{\Lambda_g} & 0 & c_{g'} \beta_{g',g} \dfrac{\left(1-\phi_{g'}\right)\Lambda_{g'}}{\left(\vartheta_{g'}+\mu_{g'}\right)} \dfrac{\mu_g}{\Lambda_g} & 0 \\ 0 & \pi_\lambda c_g \beta_{g,g'} \dfrac{\Lambda_g\left(\vartheta_g+\phi_g\mu_g\right)}{\mu_g\left(\vartheta_g+\mu_g\right)} \dfrac{\mu_{g'}}{\Lambda_{g'}} & 0 & \pi_\lambda c_g \beta_{g,g'} \dfrac{\Lambda_g\left(\vartheta_g+\phi_g\mu_g\right)}{\mu_g\left(\vartheta_g+\mu_g\right)} \dfrac{\mu_{g'}}{\Lambda_{g'}} \\ \pi_\lambda c_{g'} \beta_{g',g} \dfrac{\Lambda_{g'}\left(\vartheta_{g'}+\phi_{g'}\mu_{g'}\right)}{\mu_{g'}\left(\vartheta_{g'}+\mu_{g'}\right)} \dfrac{\mu_g}{\Lambda_g} & 0 & \pi_\lambda c_{g'} \beta_{g',g} \dfrac{\Lambda_{g'}\left(\vartheta_{g'}+\phi_{g'}\mu_{g'}\right)}{\mu_{g'}\left(\vartheta_{g'}+\mu_{g'}\right)} \dfrac{\mu_g}{\Lambda_g} & 0 \end{bmatrix}$$

$$\overline{U} = \begin{bmatrix} \left(\sigma_{HPVg}\sigma_{Ig}+\vartheta_g+\mu_g\right) & 0 & 0 & 0 \\ 0 & \left(\sigma_{HPVg'}\sigma_{Ig'}+\vartheta_{g'}+\mu_{g'}\right) & 0 & 0 \\ -\vartheta_g & 0 & \left(\pi_{\sigma I}\sigma_{HPVg}\sigma_{Ig}+\mu_g\right) & 0 \\ 0 & -\vartheta_{g'} & 0 & \left(\pi_{\sigma I}\sigma_{HPVg'}\sigma_{Ig'}+\mu_{g'}\right) \end{bmatrix}$$

For simplicity it is assumed that:

$$\mu_g = \mu_{g'} = \mu$$

$$\Lambda_g = \Lambda_{g'}$$

$$\sigma_{Ig} = \sigma_I$$

$$\vartheta_g = 0$$

And without the loss of generality express the population as a fraction of their sex by assuming:

$$\Lambda_g = \mu_g$$

This results in the equilibrium points:

$$S_g^0 = \left(1 - \phi_g\right)$$

$$V_g^0 = \phi_g$$

And

$$\overline{F} = \begin{bmatrix} 0 & c_g \beta_{g,g'} \left(1-\phi_g\right) & 0 & c_g \beta_{g,g'} \left(1-\phi_g\right) \\ c_{g'} \beta_{g',g} \left(1-\phi_{g'}\right) & 0 & c_{g'} \beta_{g',g} \left(1-\phi_{g'}\right) & 0 \\ 0 & \pi_\lambda c_g \beta_{g,g'} \phi_g & 0 & \pi_\lambda c_g \beta_{g,g'} \phi_g \\ \pi_\lambda c_{g'} \beta_{g',g} \phi_{g'} & 0 & \pi_\lambda c_{g'} \beta_{g',g} \phi_{g'} & 0 \end{bmatrix}$$

$$\overline{U} = \begin{bmatrix} \left(\sigma_{HPV}\sigma_I + \mu\right) & 0 & 0 & 0 \\ 0 & \left(\sigma_{HPV}\sigma_I + \mu\right) & 0 & 0 \\ 0 & 0 & \left(\pi_{\sigma I}\sigma_{HPV}\sigma_I + \mu\right) & 0 \\ 0 & 0 & 0 & \left(\pi_{\sigma I}\sigma_{HPV}\sigma_I + \mu\right) \end{bmatrix}$$

The spectral radii of : $\left(\overline{F}\overline{U}^{-1}\right)$ is

$$\rho\left(\overline{F}\overline{U}^{-1}\right) = \left(\frac{\left(c_g \beta_{gg'}\right)}{\left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right)} \left(1 - \phi_g \left(1 - \pi_\lambda \frac{\left(\sigma_{HPV}\sigma_{Ig} + \mu_g\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig} + \mu_g\right)}\right)\right) \times \right.$$

$$\left. \frac{\left(c_{g'} \beta_{g'g}\right)}{\left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right)} \left(1 - \phi_{g'} \left(1 - \pi_\lambda \frac{\left(\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig'} + \mu_{g'}\right)}\right)\right)\right)^{\frac{1}{2}}$$

Similarly the matrices $\bar{F}$ (New infections) and $\bar{U}$ (transfer between the compartments) evaluated at the DFE and accounting for only the infected states for the homosexual and bisexual population are determined to be:

Homosexual Population only

The spectral radii of : $\left(\bar{F}\bar{U}^{-1}\right)$ is

$$\rho\left(\bar{F}\bar{U}^{-1}\right)=\frac{\left(c_g\beta_{gg}\right)}{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\left(1-\phi_g\left(1-\pi_\lambda\frac{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\right)\right)$$

Bisexual Population only

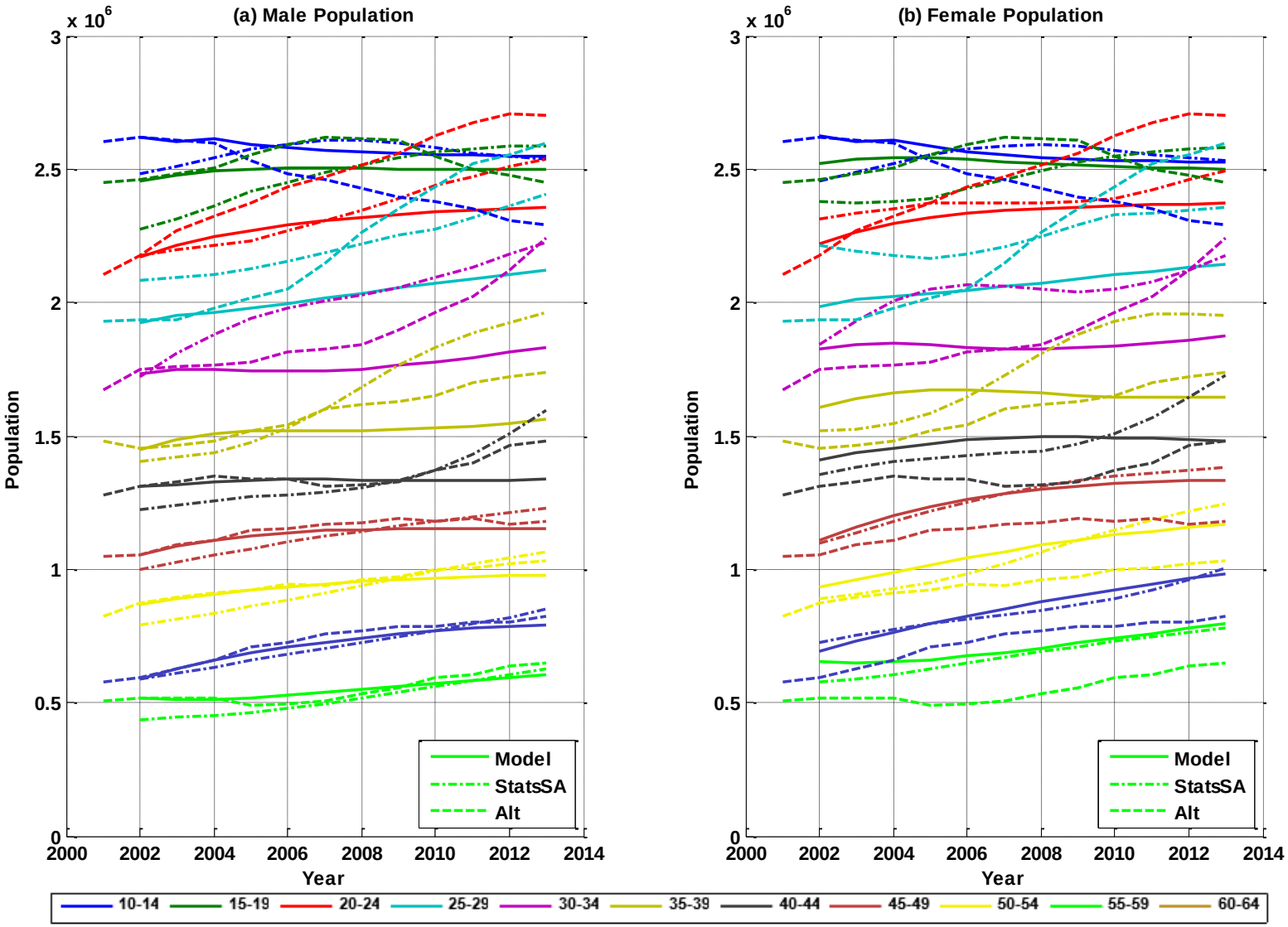
The spectral radii of : $\left(\bar{F}\bar{U}^{-1}\right)$ is

$$\rho\left(\bar{F}\bar{U}^{-1}\right)=\frac{1}{2}\left(\begin{array}{l}\left(1-\omega_g\right)\left(R_{0g}^3\right)\left(1-\phi_g\left(1-\pi_\lambda\frac{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\right)\right)\\+\left(1-\omega_{g'}\right)\left(R_{0g'}^3\right)\left(1-\phi_{g'}\left(1-\pi_\lambda\frac{\left(\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)}\right)\right)\end{array}\right)^2$$

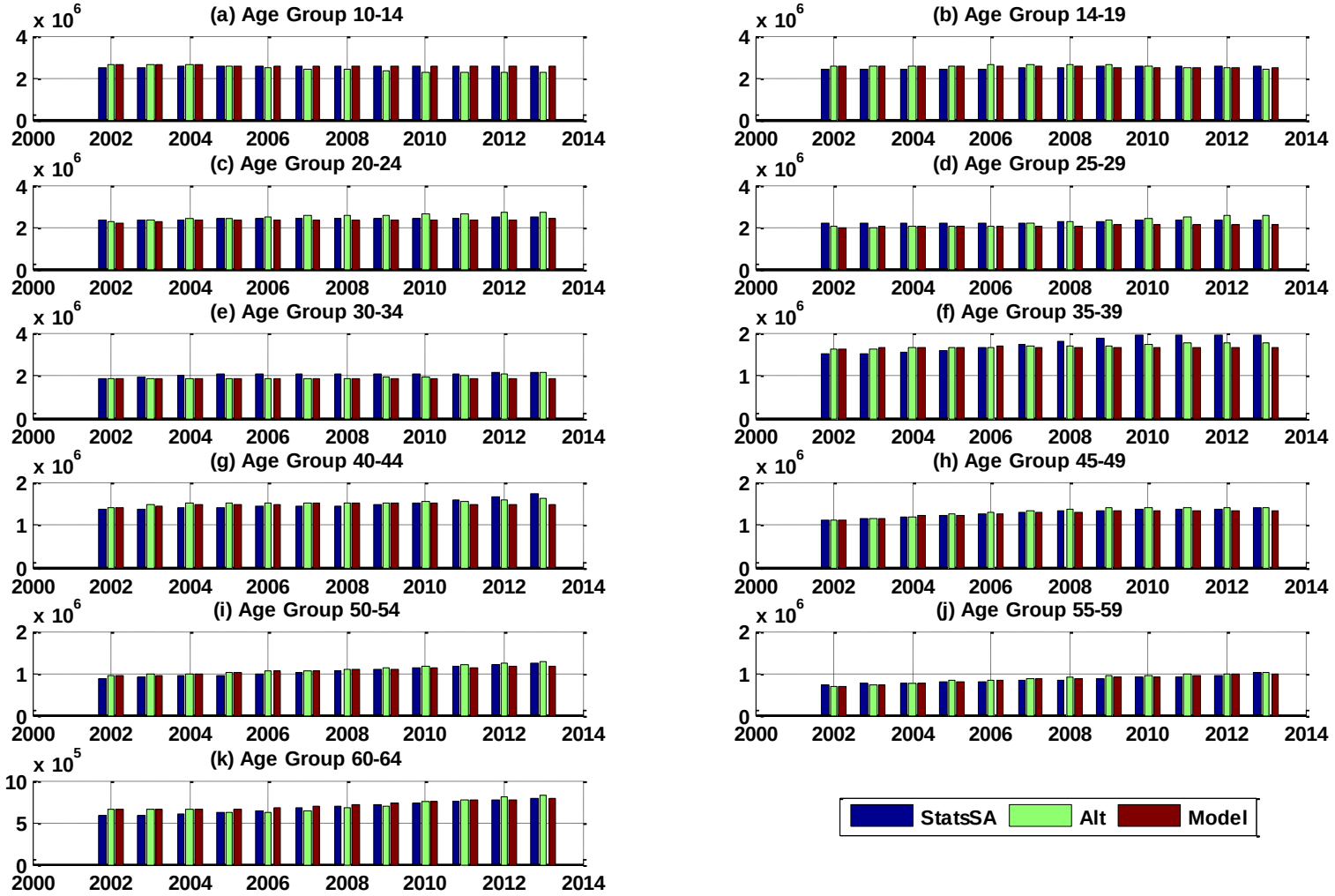
$$+4\left(\omega_gR_{0g}^1\right)\left(1-\phi_g\left(1-\pi_\lambda\frac{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\right)\right)\left(\omega_{g'}R_{0g'}^1\right)\left(1-\phi_{g'}\left(1-\pi_\lambda\frac{\left(\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)}\right)\right)\Bigg)^{\frac{1}{2}}$$

$$+\frac{1}{2}\left(\begin{array}{l}\left(1-\omega_g\right)R_{0g}^3\left(1-\phi_g\left(1-\pi_\lambda\frac{\left(\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig}+\mu_g\right)}\right)\right)\\+\left(1-\omega_{g'}\right)R_{0g'}^3\left(1-\phi_{g'}\left(1-\pi_\lambda\frac{\left(\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)}{\left(\pi_{\sigma I}\sigma_{HPV}\sigma_{Ig'}+\mu_{g'}\right)}\right)\right)\end{array}\right)$$

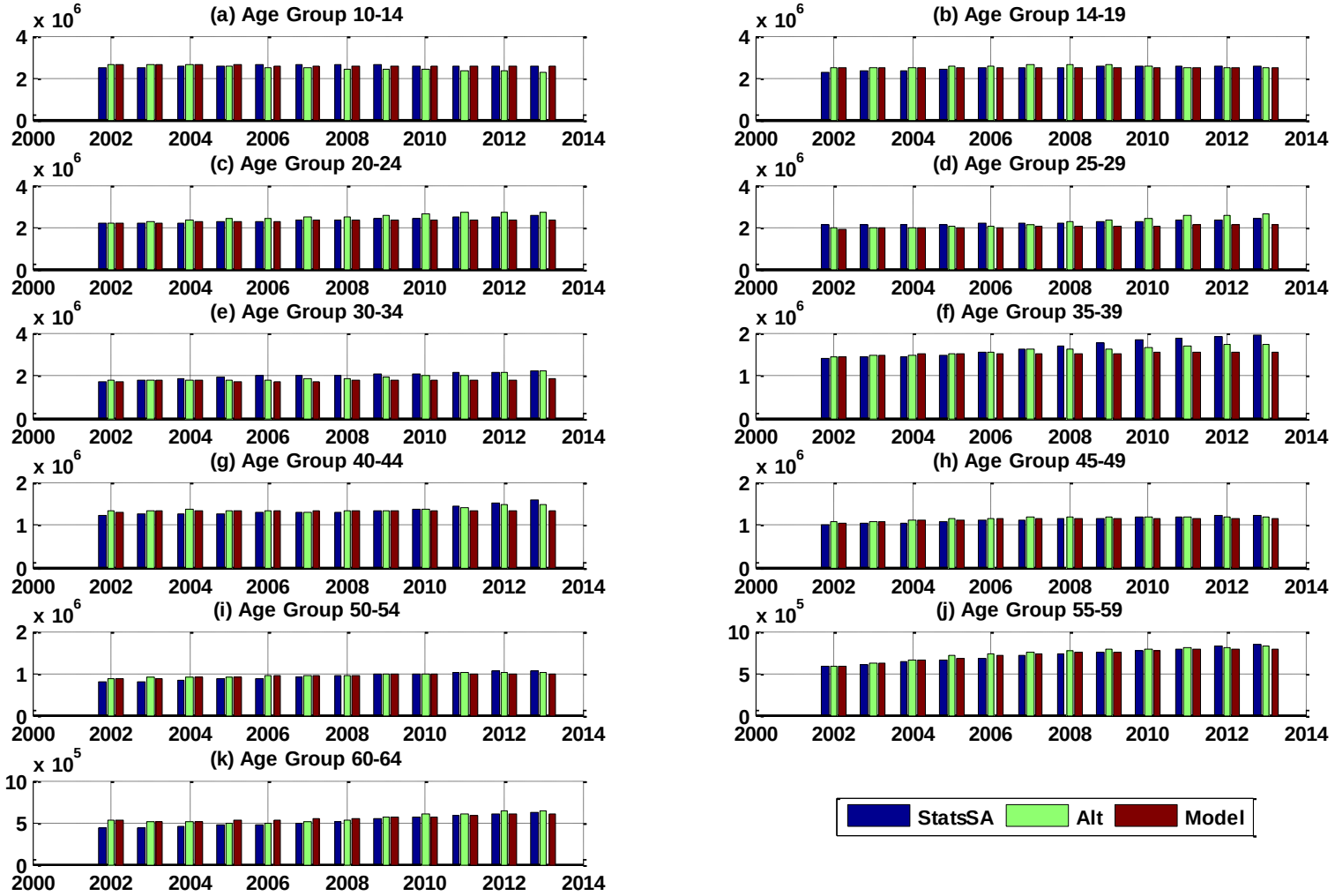
APPENDIX B



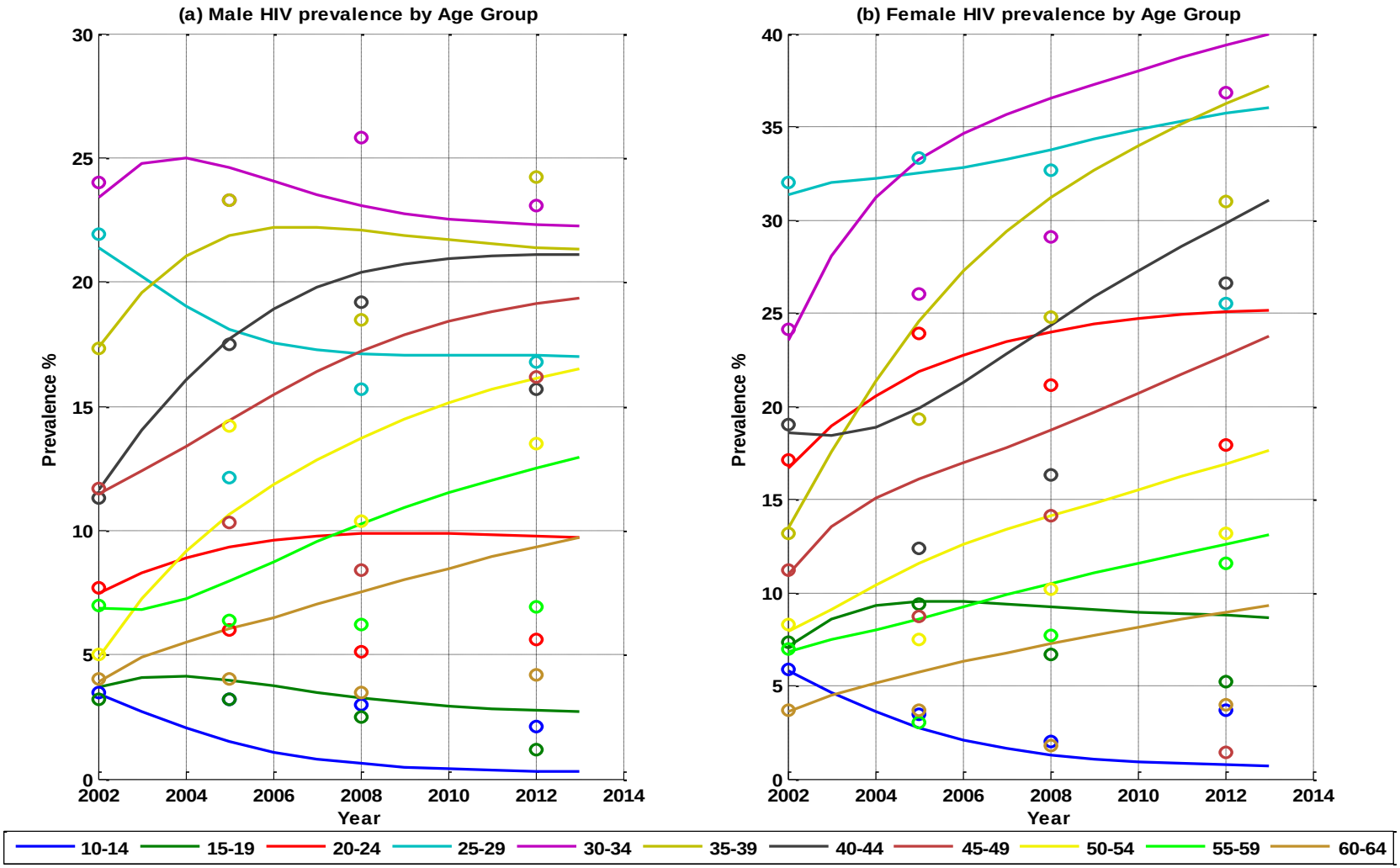
APPENDIX B Figure 1 Population projections by Age Group 2002-2013 with comparisons to Statistics SA [66] and alternative estimates by Dorrington [79]



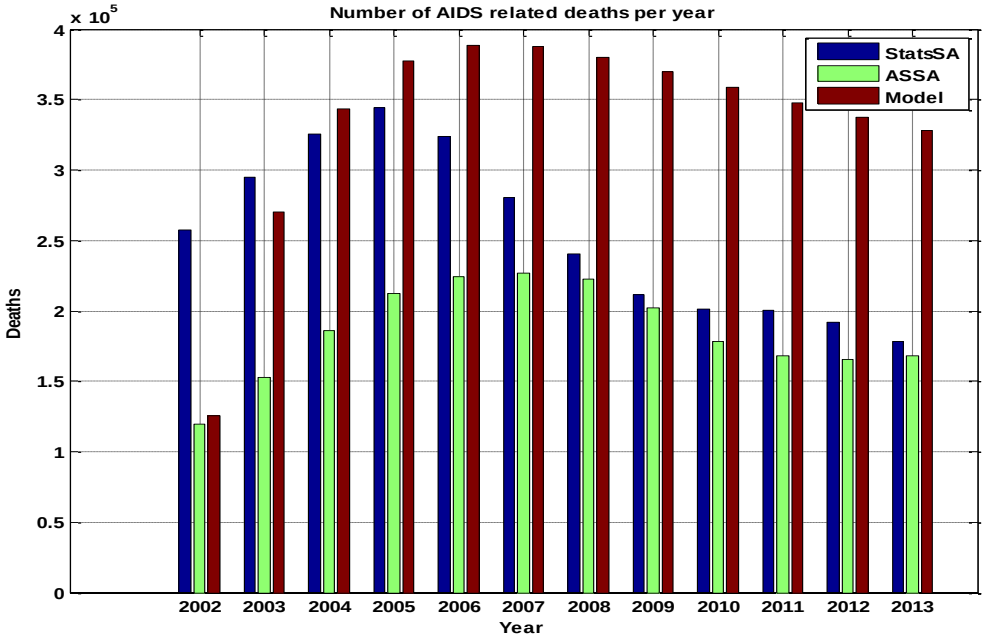
APPENDIX B Figure 2 Female population projections by Age Group 2002-2013 (HIV status not modelled) with comparisons to Statistics SA [66]and alternative estimates by Dorrington [79]



APPENDIX B Figure 3 Male population projections by Age Group 2002-2013 (HIV status not modelled) with comparisons to Statistics SA [66]and alternative estimates by Dorrington [79]



APPENDIX B Figure 4 Comparison of HIV prevalence estimates by age groups for the year 2002-2013, with prevalence values from the HSRC [79]



APPENDIX B Figure 5 Comparison of the AIDs related deaths per year 2002-2013 with comparisons to Statistics SA [66]and ASSA2008

APPENDIX C

APPENDIX C Table 1 Sexual Behaviour data used to determine rate of partner acquisition

AGE GROUPS	ANNUAL RATE OF SHORT TERM PARTNER ACQUISITION[68]		REPORTED CURRENT PARTNERSHIP [79]					
			Females			Males		
	Male	Female	0	1	2+	0	1	2+
10-14	0.6	1.4						
15-19	7.3	14.6	62.6	33.5	2.9	64.1	26.6	8.2
20-24	15.9	23.3	25.4	69.9	3.8	19.2	55.8	24.0
25-29	20.6	21.5	16.3	77.6	4.0	8.2	67.7	23.7
30-34	20.8	15.2	16.1	80.1	2.4	8.5	72.1	19.1
35-39	18.0	9.2	15.0	81.0	1.4	5.3	81.4	11.3
40-44	14.0	5.0	18.7	77.8	1.3	8.2	81.1	7.3
45-49	10.2	2.5	34.6	62.8	0.6	7.8	79.4	8.9
50-54	7.1	1.2				18.1	72.8	7.7
55-59	4.7	0.5				18.4	75.2	2.7
60-64	3.0	0.2						

APPENDIX C Table 2 3 HPV, CIN1, CIN2/3 and Cervical cancer age-specific prevalence percentage data

HPV AGE-SPECIFIC PREVALENCE PERCENTAGE[10]				CYTOLOGICAL ABNORMALITY AGE-SPECIFIC PREVALENCE PERCENTAGE		
AGE GROUPS	HPV16+	HPV18+	HPV16/18	LSIL	HSIL	Cervical carcinoma
<25	17	8	24	5.9	8.8	0
25-29	15.1	9.7	22	4.2	9	0.5
30-34	18	9.9	24.5	4.3	15.7	0.4
35-39	14	8.4	21.4	2.3	11.8	0
40-44	14.1	6.3	18.5	2.8	12.6	0.9
45-49	10.6	6.7	15.6	1.7	1.7	2.2
50-54	10.3	5.5	13.7	2.7	6	0
≥55	8.4	8.4	15.6	1.1	3.3	0

APPENDIX C Table 4 Additional model inputs

PARAMETER	DESCRIPTION
SYMBOL	**NAME**
DEMOGRAPHIC PARAMETERS	
μ_{gi}	0.00045-0.01970, 0.00178-0.04371 [78]
μ_{CCfi}^{hs}	0.038-0.683 [28]
$band_i$	5
q	0.5
BEHAVIOURAL PARAMETERS	
ω_{g2}	0.5
ε_1, ε_2	0.2,0.8
BIOLOGICAL PARAMETERS	
RATES	
$1/\sigma_{lgi}^{h}$	1.2 [5], [28], [33]
σ_{Zgi}^{h}	0
χ_{gi}^{h}	1/9, 1/7
,PROBABILITIES	
$\beta_{gg'}$	0.7,0.8 [5]
β_{gg}	0.35,0.8
$\beta_{gg'}^{+}$	0.1,0.2
β_{gg}^{+}	0.01,0.2
VACCINATION EFFECTS	
$\pi_{\sigma I}$	1
$\pi_{\sigma Z}$	1
π_{λ}	0.1 (Assuming 90% vaccine efficancy)
$\pi_{\rho I}$	1
$\pi_{\sigma ClN}^{s}$	1