MODELLING HPV VACCINATION AND SCREENING STRATEGIES TO OPTIMIZE TREATMENT

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Abstract

HPV is a common sexually transmitted infection found worldwide which can lead to serious health effects. While HPV has a high regression rate, if it does progress, it can cause various cancers (i.e. cervical, penile, throat). It is possible to minimize the mal-effects of HPV with tools such as screening, vaccination and treatment. Three sets of compartmental models were developed to study various aspects of HPV infection and progression. The first set of models studies which parameters are relevant in screening and vaccination programs and compares four different programs: a no intervention program, a screening only intervention program, a vaccination only program, and a screening and vaccination program. The second set of models compares various screening programs, including a co-screening program. The purpose of this set of models is to complete a cost analysis on the models, as well as to compare them epidemiologically. The third set of models studies the phenomenon of infection and re-infection with HPV. This chapter includes both single HPV type models and multi-type HPV models. All three sets of models lead to the same conclusions that HPV screening is essential in the minimization of HPV and cervical cancer. Furthermore, both screening and vaccination are essential in lowering the basic reproduction number.

Dedication

To Michael

Acknowledgements

I would like to thank everyone, without whom this work would not have been possible.

To Dr. Jane Heffernan, for your help, patience, and tutelage. Without you, I would not be where I am today. From your guidance in the mathematical biology world during my undergrad years to your support in my graduate years, you have taught me everything I know about mathematical modelling. Your patience from start to finish of my thesis (including multiple revisions), your dedication from halfway across the world, and across the hallway and the way in which you make a pleasant and comfortable work environment have all been factors in the completion of this thesis. You have taught me how to make a math model, make a poster, write a paper, and talk and write with correct English grammar.

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I look forward to working with everyone in future collaborations.

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Abbreviations

HPV	Human papillomavirus
HIV	Human immunodeficiency virus
STI	Sexually transmitted infection
DFE	Disease free equilibrium point
EE	Endemic Equilibrium
LHS	Latin hypercube sampling
PRCC	Partial rank correlation coefficient
ODE	Ordinary differential equations
CIN1	Cervical intraepithelial neoplasia 1
CIN2	Cervical intraepithelial neoplasia 2
CIN3	Cervical intraepithelial neoplasia 3
R_0	Basic reproduction number
ODE	Ordinary differential equations

1 Introduction

Mathematical epidemiology is a field that studies the epidemiology of diseases from a mathematical standpoint. The field stemmed from early childhood diseases, including measles and smallpox [64]. In 1706, Daniel Bernouilli defended the practice of inoculating individuals against small pox. This contributes to the first known result of mathematical epidemiology. However, mathematical epidemiology as it is known today is attributed to P.D. En'ko between the years of 1873 and 1894 and the foundations of mathematical epidemiology with compartmental models is attributed to physicians such as Sir R.A. Ross, W.H. Hamer, A.G. McKendrick and W.O. Kermack between the years of 1900-1935 [7]. Dr. Ross's model of the interaction between mosquitoes and humans in the transmission of malaria received the second Nobel Prize in Medicine. The results of his model were then implemented into society in an attempt to control mosquitoes.

Since the introduction of mathematical epidemiology in the early 20th century, it has been used to study many different diseases including HPV, measles, malaria, tuberculosis, etc. [7]. The results have been applied to health care programs in different parts of the world to understand the evolution and persistence of a disease both within an individual (in-host modelling) and within a population (population level modelling), as well as to answer questions on the projected costs and effectiveness of health programs, and provide program comparison studies [7, 28, 55].

The results of models in mathematical epidemiology have been applied to various settings that have different environmental inputs. An example is third world countries [29]. This thesis in particular will use mathematical epidemiology to study HPV and cervical cancer. It will make use of the statistics and demographics of the third world country, Nepal.

1.1 What is HPV?

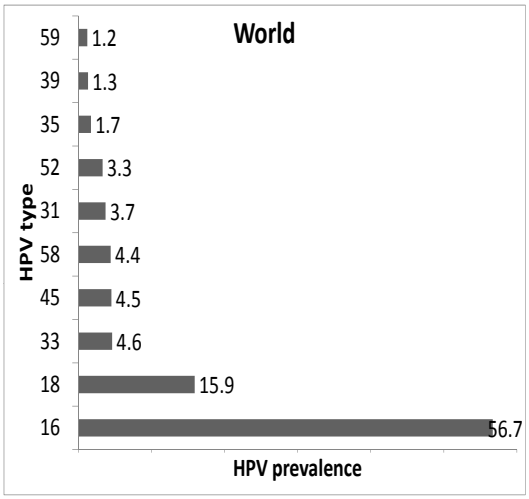
Human papillomavirus (HPV) is a sexually transmitted infection (STI) [52]. There are approximately 200 strains of HPV, where the genomes of about 100 of these strains have been sequenced [4]. Figure 1.1 shows various HPV types by prevalence within the world as well as within third and first world countries. Most HPV types are low risk with 13-18 high risk cancer causing types [4]. While HPV has a high infection rate, it also has a high regression rate [54]. This means that most people will contract HPV at some point in their lifetime, however, it most likely will not progress to cancer. This STI has a worldwide prevalence of over 50% [48].

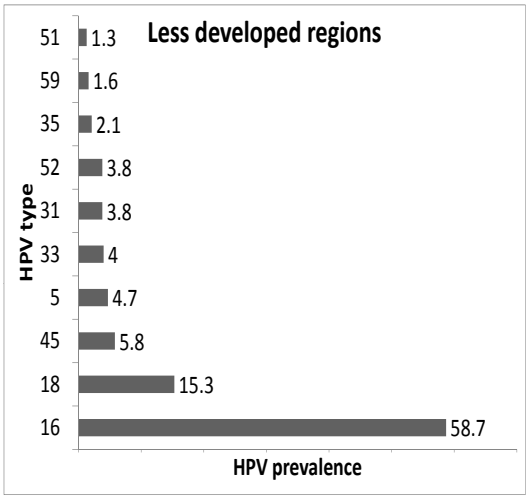
As stated previously, HPV can cause cancer. While it is a necessary cause of cervical cancer, this is not the only cancer caused by HPV [48]. Other cancers include but are not limited to penile, anal and oral cancers [8], however, these are rare in comparison to the prevalence of cervical cancer globally [3]. Cervical cancer is the third most common cancer found amongst women worldwide. Approximately 70% of cervical cancers are caused by HPV types 16/18. These two HPV types are the two most common worldwide, followed by HPV types $31, 33, 35, 45, 52$ and 58, which collectively contribute to approximately 20% of cervical cancers worldwide [8].

There are various stages to HPV/cervical cancer progression. HPV is relatively common and easy to contract. Once contracted, there is a high chance that the HPV infection will regress. However, if it does not, it can progress to a stage 1 pre-cancer called CIN1 and then further progress to CIN2, CIN3 and finally to cancer. There are between 2 and 4 decades between the peak of the infection and the onset of the cancer [6]. The possibility of regression continues throughout the CIN1,CIN2 and CIN3 time-line, however, the chances of regression get smaller the further along the chain the disease progresses [68].

HPV disease progression need not be linear, as once a person is infected, they can jump straight to the CIN2/3 stage [16]. Figure 1.2 illustrates the natural history of an HPV infection.

There are various co-factors that can contribute to infection susceptibility and infection duration of HPV. Table 1.1, adapted from Burchell et al. [9], summarizes the HPV co-factors,





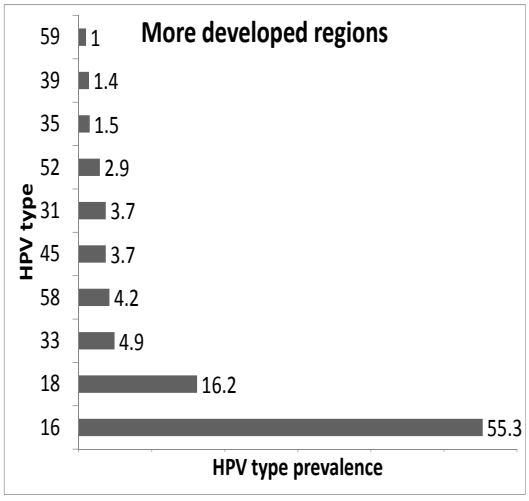


Figure 1.1: HPV types by prevalence in a) the world, b) less developed regions and c) more developed regions [8].

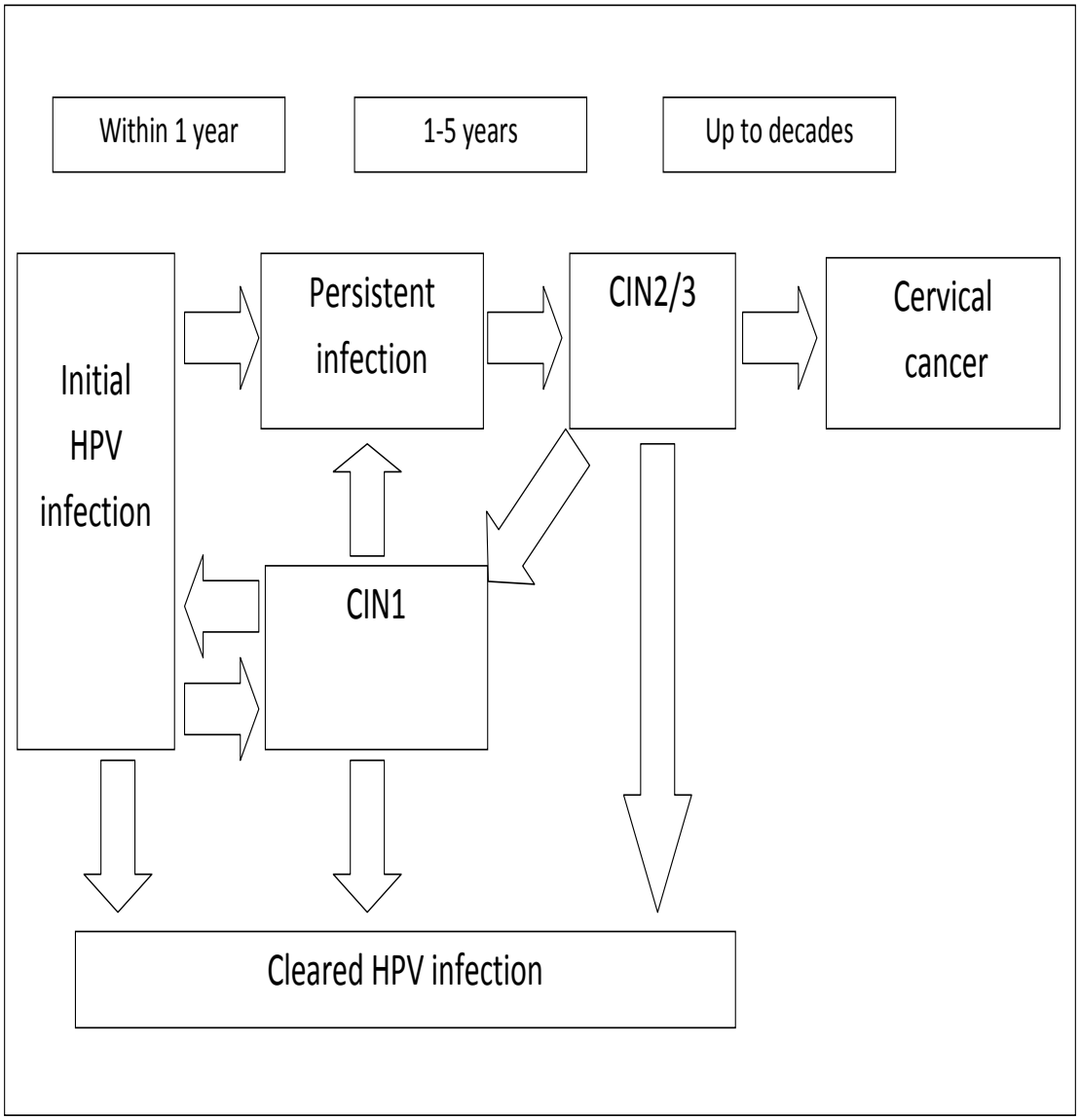


Figure 1.2: Natural history of an HPV infection [3].

Factor	**Effect on susceptibility**	**Effect on duration of infection**	**Prevalence in Nepal**	**Prevalence in Canada**	**Reference**
Earlier age of sexual début	Increase			$\approx 16 - 17$	[9, 31]
Concurrent infection with another STI	Increase	Increase			[9]
Male circumcision	Decrease	Decrease	$< 20\%$	$20 - 80\%$	[9, 19, 79]
Immune suppression, ie. HIV infection	Increase		.5% (HIV prevalence)	.3% (HIV prevalence)	[8, 9]
Hormonal contraceptive	Increase	Increase			[9]
Smoking	Increase	Increase	22.6% women	25.7%	[8, 9, 50]
Total fertility rate	Increase		3.3 (year^{-1})	1.6 (year^{-1})	[8]
Oral contraceptive use	Increase		3.5%	21%	[8]

Table 1.1: Factors affecting the susceptibility and duration of an HPV infection

including co-infection with HIV, smoking and age of sexual début.

There are approximately 2540.9 million women at risk of cervical cancer worldwide. Every year, approximately $527,624$ women are diagnosed with cervical cancer, and approximately $265,653$ women die from it [8]. Having said this, it is not impossible to lower these numbers through techniques such as vaccination, screening and treatment.

1.2 HPV and cervical cancer in Canada and Nepal

In Canada there are approximately 14.92 million woman at risk for cervical cancer over the age of 15. It is estimated that about 9.9% of Canadian women have an HPV infection at any given time, with the most common being HPV types 16 and 18. Approximately 1408 women are diagnosed with cervical cancer per year, of which 503 women die from it. In 2012, there were an estimated 83195 new cases of which 35673 resulted in death. Cervical cancer ranks

the 13th most common cancer amongst women and the 3rd most common cancer for women between the ages of 15 and 44 [8].

As of 2007, there has been a national vaccination program (with Gardasil as the vaccine) in Canada that targets school girls between the ages of $9 - 14$. The coverage of this program is province dependent, but is approximately $50 - 86\%$ [8].

Nepal, a third world country, has a population of approximately 26.5 million people. Of this population, approximately 8.53 million women are at risk for cervical cancer. There are approximately 3504 cases of cervical cancer per year, of which just over half result in death. There is currently no vaccination program in Nepal [8].

1.3 Vaccination, screening and treatment

While there is currently no cure for HPV or its succeeding stages, there are various ways in which an individual can prevent infection and treat infections leading to cancer. These include: vaccination, screening and treatment.

Vaccination

There are currently two vaccines in use, a bivalent vaccine called Cervarix, and a quadrivalent vaccine called Gardasil. Both vaccines are administered in three doses by injection and cost roughly $120 CAD [12]. Cervarix by GlaxoSmithKline protects against HPV types 16 and 18, the most common HPV types causing cervical cancer [21]. Gardasil by Merck & Co protects against four HPV types: $16, 18, 6$, and 11 [21]. There is also a third vaccine, currently in clinical trials. This nonavalent vaccine protects against the following nine strains: $6, 11, 16, 18, 31, 33, 45, 52$, and 58 [20]. Since this vaccine is still in trials, it is currently unknown how much it will cost or what its efficacy will be.

Both Cervarix and Gardasil have been proven thus far to be almost 100% effective in preventing cervical cancer for 9 years following vaccination [15, 77]. This is true as long as the individual does not have a pre-existing infection. If an infected individual is given the vaccine, it will have no impact on their current situation other than to prevent them from re-infection [11]. Although costly, vaccination has proven to be a useful form of prevention

for HPV [24].

It is not completely known how the HPV vaccines work, however, studies suggest that the primary method of fighting HPV is through neutralizing antibodies [17]. Currently, scientists do not know the total extent of protection afforded by either of the two available vaccines [21].

Screening

Effective screening techniques/programs have the capability of preventing cancer, allowing for the early detection and treatment of an HPV or carcinoma infection. While more hands on in terms of the number of visits required, screening has the potential to catch an HPV infection during its progression from HPV to cervical cancer. This is important both clinically and financially.

Clinically, early detection and monitoring of the disease allows for treatment before the onset of cancer. This improves the chances of survival. While it may not be necessary to treat an individual at the HPV infection stage, continuous monitoring of the situation allows treatment if the disease progresses to a more serious stage. On the other hand, if, for example, an individual is screened and found to have pre-cancer CIN3, they may be treated immediately, improving their chances of survival.

Financially, screening is important as treating cancer comes with many costs: treatment, hospitalization, doctor visits, and hospital resources such as beds. For the patient it includes additional costs such as work time missed, and transportation costs. While screening does cost money, over the long run, it may prove to be more economically efficient depending on the screening intervals [51].

There are various types of screening techniques. These range in differences from time spent taking the test, to time spent processing the test, to the cost of the test, to the technology used. Some tests are more simplistic and utilize fewer personnel, or personnel with less training. This is primarily due to the fact that the different tests utilize different biological techniques. Table 1.2 lists a sample of screening techniques and some of their properties.

Screening test	Specificity	Sensitivity	Comments	Reference
HC2 (Qiagen)	68.8−82	78−100	Tests for 13 carcinogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and five low risk types	[18, 61, 72, 80]
APTIMA (Gen Probe)	52.3−92	84.9−99	Can detect the mRNA of 14 high risk types however, it does not indicate which high risk HPV type it identified	[18]
Cobas 4800 (Roche Molecular Systems)	20.9−27.2	92.5−97.2	Can specifically check for HPV 16/18 and check that there are other carcinogenic types present	[73]
Cervista (Hologic)	65.7−72.6	56.6−78.7	Detects DNA from 14 carcinogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68)	[44, 80]
Papillocheck (Greiner Bio-one)	60.2	96.1	PCR based test which detects 24 genotypes: 18 high/probable high risk and 6 low risk types	[69]
Linear array (Roche Molecular Systems)	29.2−36.5	95.8−99.4	Tests for 37 high and low risk HPV types	[73]
Abbot RT PCR (Abbott Laboratories)	24.1−30.7	90.1−95.6	Tests for 14 high risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68)	[73, 78]
Amplicor (Roche Molecular Systems)	18.6−25	96.8−99.8	Tests for 13 high risk carcinogenic types	[73]
PAP smear	97−97.9	26.4−62.3	Detects abnormal cervical cells	[26, 45]
CareHPV (PATH and Qiagen)	96.9−97.9	34.7−70.9	Detects 14 different high risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68)	[45, 62]
VIA	93.9−95.2	9.3−40	Visual inspection of the cervix for abnormal cells using acetic acid	[30, 45]

Table 1.2: HPV screening techniques

Treatment

While vaccination and screening are useful in the prevention and detection of an HPV infection, a patient may still become infected with HPV and have it progress to the cervical cancer stage. If this occurs, then depending on the stage of infection, the patient will undergo a colposcopy, a procedure that enables the gynaecologist to examine the cervix for abnormal cells. Based on the results, the patient may go for further treatment such as chemotherapy, radiation therapy, surgery etc.

There are two types of treatment that focus on treating the affected area. These are ablative and excisional therapies. Ablative treatment includes procedures such as: cryotherapy, or freezing of the area, laser ablation, and cold coagulation. Excisional treatment includes cold knife conization, loop electrosurgical excision procedures (LEEP) and conization, either by laser or electrosurgical needle. Both excisional and ablative methods are said to have similar efficacies of removing the tumour and setting back the disease. Failure rates are reported to be between $5 - 15\%$ [39].

Vaccination, screening and treatment should be considered to help prevent cervical cancer, as well as minimize cancer costs, especially since there are between 2 and 4 decades between the peak of the infection and the onset of the cancer. Hence, an efficient screening technique must be used [6].

1.3.1 Type replacement

HPV types 16 and 18 are the most common HPV types worldwide. This includes both developed and undeveloped regions. Together, they cause 70% of cervical cancers. Figure 1.1 summarizes the prevalence of various HPV types.

It is evident that in more developed regions, once HPV types 16/18 have been eradicated, HPV type 33 can rise as a dominant infecting type. In under-developed regions, HPV type 45 will replace types 16/18 [8]. Both types 33 and 45 are carcinogenic.

Studies by Day and Bauch [5, 53] have examined the idea of type replacement. While this thesis will not model type replacement, it should be considered as future work.

1.4 What is a mathematical model?

Mathematical models are forecasting tools used in various areas of application, including public health. Amongst other things, these models are used to inform health policy, vaccination programs, and help minimize governmental and individual costs. When implementing a new health regime, or when dealing with a new disease, it is important to get an idea of the possible outcomes of implementing a program. These include answering questions such as:

- Will a vaccination program make a significant difference to the outcome of the disease?
- What percentage of the population must be vaccinated in order to eradicate or control a disease?
- If you don't vaccinate a population, what course can you expect the disease to take in the long and short term?
- What is the most cost effective way to treat a disease?

All of these questions are important for policy makers to consider and can be studied using mathematical models. There are different types of models, such as Markov models and deterministic compartmental models; this paper will focus on compartmental models.

A compartmental model examines population classes and their interactions to forecast patterns in population sizes over time. This can be used to identify information concerning possible epidemics such as: start and end times, the magnitude of the epidemics, the amount of people affected etc. An example of a simple compartmental model is the S-I-R model, pioneered by Kermack and McKendrick circa 1927, where "S" represents the susceptible individuals, "I" represents the infected individuals, and "R" represents the recovered or removed individuals [37].

The SIR model is shown in Figure 1.3. Here the β term represents the infection rate as infected individuals (I) interact with susceptible individuals (S). Hence, it impacts the rate of change of both the susceptible individuals as they leave the susceptible compartment, and the infected population as the newly infected individuals enter this compartment. The γ term represents the recovery rate of the infected individuals. This impacts the infected individual's population size, as individuals are removed from the infected compartment, and

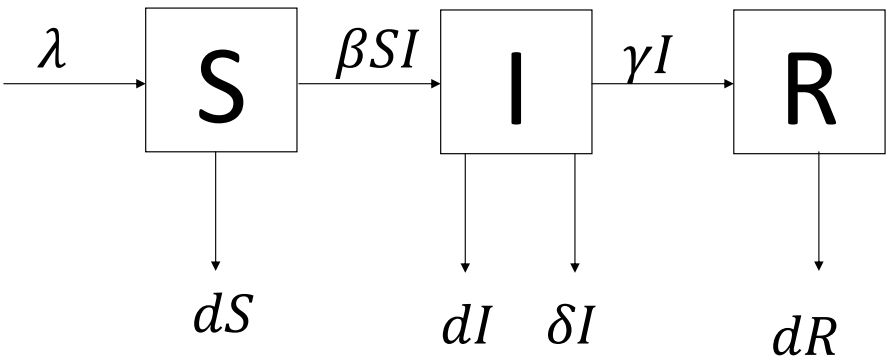


Figure 1.3: Basic SIR model where "S" represents the susceptible population, "I" represents the infected class and "R" represents the recovered class. This compartmental model can be modelled using a system of ODEs as shown in Eq.(1.1).

the recovered individual's population size as they enter this compartment. The δ term represents the disease induced death rate of the infected individuals while the dS, dI, and dR terms represent the number of natural deaths of each class. Finally, the λ term represents the birth rate.

The SIR model shown in Figure 1.3 can be written as:

$$\begin{aligned} S' &= \lambda - \beta SI - dS \\ I' &= \beta SI - \gamma I - \delta I - dI \\ R' &= \gamma I - dR \end{aligned} \tag{1.1}$$

where S', I' and R' represent the rate of change of the susceptible, infected and recovered populations respectively.

The idea of SIR compartmental modelling can be broadened to include any disease stage, for example, individuals who have been exposed to a disease but are not yet infectious and individuals who have been treated for a disease. It can also take into account an individual's gender, age and vaccination status. The model need not be linear, as individuals may skip compartments or approach the same compartment from various sources. Finally, an individual may go backwards in the model, for example, once "recovered", an individual may lose immunity to the disease and may enter the susceptible compartment, or, he/she may recover with life long immunity after the infectious period.

1.4.1 Ordinary Differential Equations

Often, biological phenomena are modelled using compartmental models. These models are composed of systems of differential equations. We employ ordinary differential equations (ODE) in this work. An ODE is an equation representing the rate of change of a certain quantity. In other words,

$$change = inflow - outflow. \tag{1.2}$$

ODEs in compartmental modelling make use of the assumption that individuals mix with each other with an equal probability. This is called a homogeneous mixing assumption. In the SIR model, this is represented by the βSI term. Furthermore, a system of ODEs does not depend on past events. In other words, what happens at time t+1 depends only what

happens at time t. This is referred to as a Markov property.

ODEs can be solved to provide a population size at a certain time, usually a disease free equilibrium point and one infected equilibrium point can be found. However, depending on the parameter values being used, it may be possible to find many infected equilibria.

1.4.2 Basic reproduction numbers

The basic reproduction number (R_0) is defined as the average number of secondary infections generated by a single infectious individual in a totally susceptible population [35]. It is a measure that is used to predict whether or not an epidemic will occur. If $R_0 > 1$ then an epidemic will occur, and if $R_0 < 1$ then the disease will be contained. There are various methods that can be used to calculate R_0. These include but are not limited to: the Jacobian method, the survival function and the next generation method. A review of these methods can be found in Heffernan et al. [35]. This thesis will use the Jacobian and next generation methods. In the Jacobian method, the Jacobian matrix of the system is found. The characteristic polynomial of the Jacobian is calculated and the constant term in the characteristic polynomial is said to be R_0. In the next generation method, two matrices are created. The first matrix, F, contains terms that indicate the rate of appearance of new infections in the model. The matrix V contains terms describing the rate of transfer of individuals into a compartment. The largest eigenvalue of FV^{-1} is the basic reproduction number [35].

The basic reproduction number has been used in disease modelling for various diseases. See articles by Heesterbeek et al. [32, 33], Heffernan et al. [35], and Arino et al. [2], for models in which R_0 has been computed for various diseases such as influenza and West Nile Virus, as well as the various methodologies for calculating the basic reproduction number.

1.4.3 Bifurcations

A bifurcation is a change in the stability of a system. There are many different types of bifurcations including transcritical bifurcations and backward bifurcations (illustrated in Figure 1.4). In disease modelling, a transcritical bifurcation represents the intersection of two curves, one of which is the DFE and the second is the EE. This can be seen in the top panel of Figure 1.4 where the top branches are stable and the bottom branch is unstable. Here, the unstable region of the EE falls in an area which is not biologically viable, and

hence is not shown. The change in stability occurs when $R_0 = 1$.

A backward bifurcation is a bifurcation in which there are a minimum of three equilibria, the stable disease free equilibrium point, a stable endemic equilibrium point and an unstable endemic equilibrium point, when $R_0 < 1$. This is illustrated in Figure 1.4 where E1 represents the stable endemic equilibrium point and E2 represents the unstable endemic equilibrium point.

While a transcritical bifurcation often occurs in disease models, a backward bifurcation will occur when there are two susceptible populations, for example, a non-vaccinated and a vaccinated population [42].

1.4.4 Latin Hypercube Sampling

Latin Hypercube Sampling is a statistical method used to create different parameter sets from various parameter ranges. It was proposed by McKay in 1979 and has since been modified by various researchers to serve a particular purpose in their respective research [59]. Two of these such researchers, Sanchez and Blower, adapted Latin Hypercube Sampling to be applicable to disease modelling, including the modelling of tuberculosis and HIV [66].

The algorithm partitions the range of N variables into M equally probable partitions. M points are taken from the grid, so that there is no overlap in points, creating M different parameter sets.

1.4.5 Sensitivity analysis:

A model may contain many variables, not all of which will be of equal significance, if any at all. Latin Hypercube Sampling, along with partial rank correlation coefficient (PRCC) is used to determine which values play a significant role in the outcome of any particular model. This helps inform the modeller which variables are important to keep in the model, as well as the health care professional which aspects of the proposed health care program to use in order to obtain an optimal result. When performing a PRCC analysis, if $p > |.5|$ then the result is said to be significant [47]. The correlation between the two variables can either be positive or negative, where a positive correlation indicates that an increase (or decrease) in one variable will cause an increase (or decrease) in the second variable, and a negative

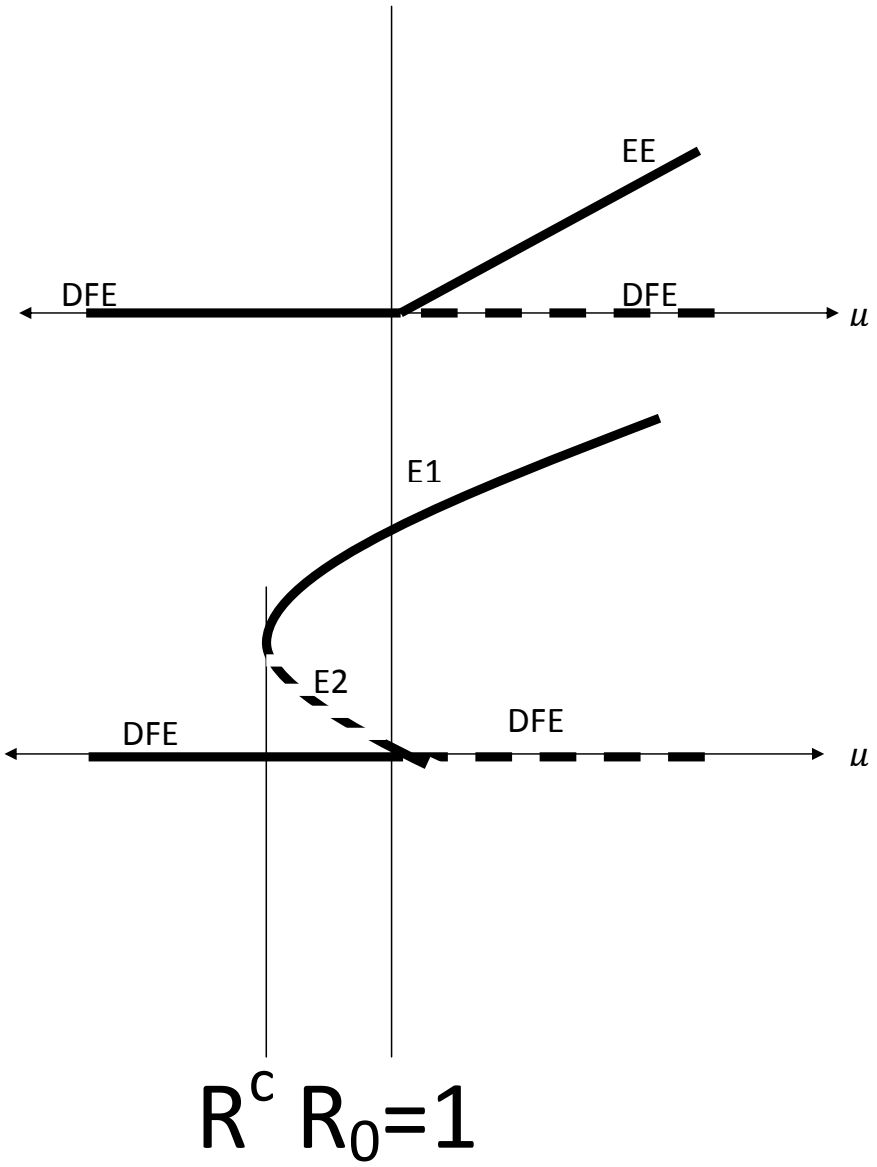


Figure 1.4: Trans-critical (top) and backward bifurcation (bottom) diagrams. The solid line represents a stable solution while the dotted lines represent an unstable solution. The x-axis represents the bifurcation parameter (μ) while the y-axis represents the force of infection.

correlation indicates that an increase in one variable (or a decrease) will cause a decrease in the second variable (or an increase).

1.5 Literature review

There are many articles which discuss various aspects of HPV vaccination and screening programs. These include articles by Garnett et al. [25], Shaban et al. [70], Obeng-Denteh et al. [56] and Lee et al. [46] with respect to the basic reproduction number, as well as, Elbasha et al. [22], Ribassin-Majed et al. [63], Goldie et al. [27], and Dasbach et al. [14] who create mathematical models to study the dynamics of HPV transmission. Some articles that focus on cost analysis include those by Goldie et al. [27], Mandelblatt et al. [49] and Kulasingam et al. [43].

The basic reproduction number for HPV has been determined with a range of $[.070249 - 2.285]$. Various studies have been completed on HPV transmission models. The following summarize the results for the basic reproduction number. Garnett et al. [25], create an SIS model with an R_0 of 1.25. Shaban et al. [70], create a model where the $R_0 = 2.285$, while Obeng-Denteh et al. [56] find $R_0 = 1.66$. Lee et al. [46] on the other hand calculate two different values for the basic reproduction number, one for treated individuals and the second for untreated individuals. Both values are less than one. They calculated these values to be .070249 and .519798 respectively .

Elbasha et al. [22], create a transmission dynamic model that models the cost effectiveness and epidemiological consequences of administering the prophylactic quadrivalent vaccine to girls and boys by age 12. They examined four different scenarios in which boys had a catchup vaccination, girls had a catch up vaccination, both girls and boys had a catchup vaccination and the final scenario where there is no catch up vaccination. They conclude that vaccinating females is the most cost effective, however, vaccinating males as well as females is the most effective in terms of CIN outcome.

Ribassin-Majed et al. [63], examine the effect of the quadrivalent vaccine on the prevalence of HPV types 6/11. They use a non-linear, deterministic model. They conclude that after 10 years, the prevalence of the aforementioned HPV types will be halved in females and reduced by $\frac{1}{4}$ in males so long as there is a 30% vaccine coverage by females. These two

HPV types can be eradicated as long as the vaccine coverage is kept above 12%.

Goldie et al. [27], examine the cost effectiveness of various triage methods making use of a combination of screening techniques combined with vaccination. They focus their model on developing countries. They conclude that incorporating VIA (visual inspection with acetic acid) or DNA testing in one or two visits is the most cost effective strategy.

Dasbach et al. [14], provide three models (cohort, hybrid and population dynamic) that evaluate the effect of vaccination and the cost effectiveness of the vaccine on the propagation of HPV. They conclude that vaccinating females can be cost effective.

Mandelblatt et al. [49], also experiment with various screening strategies to compare costs and benefits. They compare pap smear with HPV testing, pap smear only and HPV testing only. They conclude that co-testing with an HPV test and pap smears "saves additional years of life at reasonable costs compared with pap testing alone".

Kulasingam et al. [43], created a Markov model with the goal of evaluating the benefits and harms of DNA testing as well as cytology as opposed to cytology only.

They conclude that cytological testing every three years followed by co-testing every 5 years results in fewer colposcopies and greater life expectancy than when compared to cytology only.

1.6 Scope of thesis

The purpose of this project is to analyze the various combinations of treatment and screening strategies in order to find the most efficient program to treat HPV victims in Nepal. In this case, efficiency refers to medical outcome, as well as, cost. Deterministic models will be used, as well as, a linear progression of the disease stages.

This will be completed in three sets of models. The first set, found in Chapter 2, consists of four models and examines the significance of various parameters used in screening and vaccination models. These models include:

- A no intervention model.

- A screening only intervention model.
- A vaccination only intervention model.
- Both screening and vaccination as interventions.

The second set of models focuses on various screening techniques, including co-screening. Chapter 3 compares simulations and completes a cost analysis between the various models. This chapter includes the following four models:

- A model in which all infected individuals are treated.
- A model in which only those who may have a carcinogenic type of HPV are treated.
- A co-screening model with HC2 and cobas4800. Individuals are treated if they are HPV 16/18 positive.
- A co-screening model with a pap smear and cobas4800. Indiviudals are treated if they are HPV 16/18 positive.

The final set of models, found in Chapter 4 aims to elucidate the idea of infection versus re-infection with HPV. This is studied through a series of five models, each increasing in complexity. The models that are analyzed include:

- A single HPV-type model with no disease related deaths. In this model, there is no difference between infection and re-infection.
- A single HPV-type model with different compartments for infected and re-infected individuals. In this model, individuals do not die from HPV related disease.
- A model that is the same as the previous model, however, here individuals can die from cancer caused by HPV.
- A model comprised of two types of HPV and multiple infection classes. In this model, individuals do not die from disease related causes.
- A model that is the same as the previous model, however, here individuals can develop cancer, which is assumed to be fatal.

1.7 Methods

This thesis contains three modelling chapters. The methods for all three chapters are recorded here. All the numerical analysis is completed using parameter values for HPV 16.

Compartmental models are created (using a system of ODEs) to model various concepts in the question of HPV infection and its progression to cervical cancer. The models are analyzed through both analytical and numerical methods in order to elucidate various concepts regarding the models and about HPV/cervical cancer, including:

- Equilibrium points
- Stability of the equilibria
- Basic reproduction number
- Simulations
- Sensitivity analysis

1.7.1 Equilibrium points and stability

Conventional methods are used to find and calculate the stability of the equilibrium points. This involves, solving the system of ordinary differential equations to find the equilibrium points, and evaluating the Jacobian of the system at the equilibrium points to find the eigenvalues. If at least one of the eigenvalues is positive, the equilibrium point is said to be unstable or should be further analyzed. If all of the eigenvalues for the equilibrium point are found to be negative, the equilibrium point is said to be stable.

1.7.2 Basic reproduction number

The basic reproduction number is calculated using the next generation method for Chapters 2 and 3 and the Jacobian method is used for Chapter 4. A review of these methods is presented in Heffernan et al. [35]. An example of the next generation method is as follows

for the SEIR model represented by Eq.(1.3):

$$\begin{aligned} S' &= \lambda - dS - \beta IS \\ E' &= \beta IS - dE - \sigma E + \phi I \\ I' &= \sigma E - \phi I - dI - \gamma I + \phi_1 R \\ R' &= \gamma I - dR - \phi_1 R \end{aligned} \tag{1.3}$$

Let:

$$F = \begin{vmatrix} 0 & \beta S + \phi & 0 \\ 0 & 0 & \phi_1 \\ 0 & 0 & 0 \end{vmatrix},$$

$$V = \begin{vmatrix} d+\sigma & 0 & 0 \\ -\sigma & \phi + d + \gamma & 0 \\ 0 & -\gamma & d + \phi_1 \end{vmatrix}.$$

Then the spectral radius of $FV^{-1} = R_0$, where

$$FV^{-1} = \begin{vmatrix} \frac{\sigma(\beta S+\phi)}{(d+\sigma)(\phi+d+\gamma)} & \frac{\beta S+\phi}{\phi+d+\gamma} & 0 \\ \frac{\phi_1\sigma\gamma}{(d+\phi_1)(\phi+d+\gamma)(d+\sigma)} & \frac{\phi_1\gamma}{(d+\phi_1)(\phi+d+\gamma)} & \frac{\phi_1}{d+\phi_1} \\ 0 & 0 & 0 \end{vmatrix}.$$

An example using the Jacobian method for Eq.(1.3) is as follows:

$$J = \begin{vmatrix} -d-\sigma & \beta S + \phi & 0 \\ \sigma & -(\phi + d + \gamma) & \phi_1 \\ 0 & \gamma & -(d + \phi_1) \end{vmatrix}.$$

Solving the constant term of the characteristic polynomial gives: $R_0 = \frac{\phi\gamma}{(d+\phi_1)(\phi+d+\gamma)} \frac{\sigma(\beta S+\phi)}{(d+\sigma)(\sigma+d+\gamma}$.

1.7.3 Sensitivity analysis and numerical analysis

In instances where the basic reproduction number, eigenvalues or their stability cannot be calculated due to the complexity of the system, the quantity in question is calculated by substituting parameter values obtained through Latin Hypercube Sampling into the system and then calculating the desired quantity. A sensitivity analysis is run using the parameter values calculated from the Latin Hypercube Sampling parameter sets.

Simulations are run using Matlab's ODE45 function. A separate function is run to provide PRCC plots to measure the significance of each parameter in Chapter 2. The code was created by Simeone Marino in 2007.

2 Single type models

2.1 Introduction

HPV treatment and prevention is a complex matter involving vaccination, screening and treatment. Modelling all of these factors can be difficult to do in a single model, however, understanding the big picture of how all of the prevention and treatment factors work together is an important aspect in the minimization of cervical cancer. This chapter explores the concepts of screening and vaccination by attempting to understand the relative significance of each parameter in relation to the total population sizes through the use of various control strategies in an attempt to minimize HPV infection and its progression to cancer. This is accomplished through the creation and analysis of four sub-models. The first model consists of no intervention, the second of a screening only intervention, the third consists of a vaccination only intervention, and the final model consists of both screening and vaccination.

2.2 Model

The models track individuals in compartments related to susceptible and disease stages. These include both susceptible individuals who are not vaccinated (S), and those who are vaccinated (S_V). All susceptible individuals may become infected. Once infected, the individuals fall into one of three infected classes which are further divided into three stages of disease progression: those who know their infection status (I_n), those who are unaware of their infection status (A_n), and those who are vaccinated and unaware of their infection status (V_n), where n=0,1,2 depending on the disease stage. If an individual's infection does not regress, it may progress to a pre-cancer stage (C_1), or to the cancer stage (C_2).

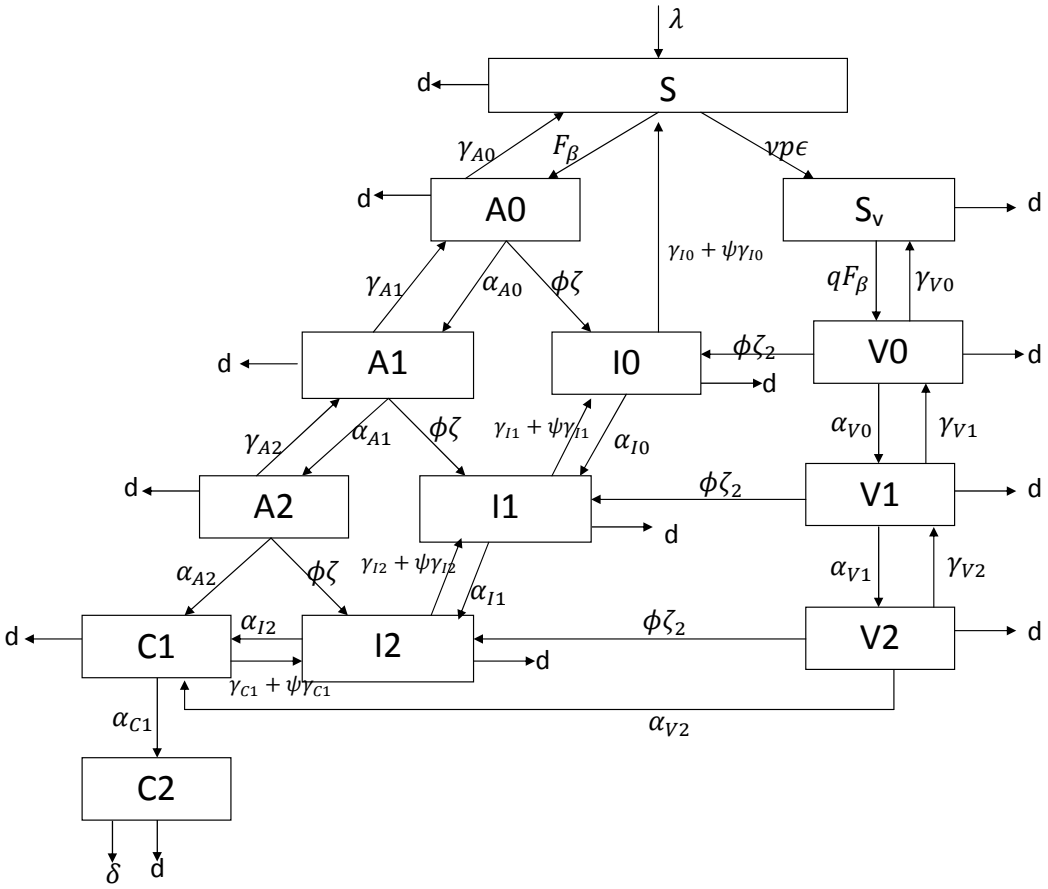


Figure 2.1: Diagram for Eq.s (2.1)-(2.4). This model represents the no intervention case when the screening sensitivity, ϕ, and the vaccine uptake, ρ, are zero. It represents the screening only model when the vaccine uptake, ρ, is zero, and it represents the vaccination only model when the screening sensitivity, ϕ, is zero.

2.2.1 Equations

The systems of equations that represent the four models depicted in Figure 2.1 are presented in Eq.'s (2.1)-(2.4).

The equations that represent the no intervention case are:

$$\begin{aligned}
S' &= \lambda + \gamma_{A0}A_0 + (\gamma_{I0} + \psi\gamma_{I0})I_0 - \tfrac{F_\beta S}{N} - dS \\
A_0' &= \tfrac{F_\beta S}{N} - (\gamma_{A0} + \alpha_{A0} + d)A_0 + \gamma_{A1}A_1 \\
A_1' &= \alpha_{A0}A_0 - (\gamma_{A1} + \alpha_{A1} + d)A_1 + \gamma_{A2}A_2 \\
A_2' &= \alpha_{A1}A_1 - (\gamma_{A2} + \alpha_{A2} + d)A_2 \\
I_0' &= -(\gamma_{I0} + \psi\gamma_{I0} + \alpha_{I0} + d)I_0 + (\gamma_{I1} + \psi\gamma_{I1})I_1 \\
I_1' &= -(\gamma_{I1} + \psi\gamma_{I1} + \alpha_{I1} + d)I_1 + (\gamma_{I2} + \psi\gamma_{I2})I_2 + \alpha_{I0}I_0 \\
I_2' &= -(\gamma_{I2} + \psi\gamma_{I2} + \alpha_{I2} + d)I_2 + (\gamma_{C1} + \psi\gamma_{C1})C_1 + \alpha_{I1}I_1 \\
C_1' &= \alpha_{A2}A_2 + \alpha_{I2}I_2 - (\gamma_{C1} + \psi\gamma_{C1} + \alpha_{C1} + d)C_1 \\
C_2' &= \alpha_{C1}C_1 - (d + \delta)C_2 \\
F_\beta &= \beta((A_0 + A_1 + A_2) + q_I(I_0 + I_1 + I_2))
\end{aligned} \tag{2.1}$$

The equations that represent the screening only case are:

$$\begin{aligned}
S' &= \lambda + \gamma_{A0}A_0 + (\gamma_{I0} + \psi\gamma_{I0})I_0 - \tfrac{F_\beta S}{N} - dS \\
A_0' &= \tfrac{F_\beta S}{N} - (\gamma_{A0} + \alpha_{A0} + \zeta\phi + d)A_0 + \gamma_{A1}A_1 \\
A_1' &= \alpha_{A0}A_0 - (\gamma_{A1} + \alpha_{A1} + \zeta\phi + d)A_1 + \gamma_{A2}A_2 \\
A_2' &= \alpha_{A1}A_1 - (\gamma_{A2} + \alpha_{A2} + \zeta\phi + d)A_2 \\
I_0' &= \zeta\phi(A_0) - (\gamma_{I0} + \psi\gamma_{I0} + \alpha_{I0} + d)I_0 + (\gamma_{I1} + \psi\gamma_{I1})I_1 \\
I_1' &= \zeta\phi(A_1) - (\gamma_{I1} + \psi\gamma_{I1} + \alpha_{I1} + d)I_1 + (\gamma_{I2} + \psi\gamma_{I2})I_2 + \alpha_{I0}I_0 \\
I_2' &= \zeta\phi(A_2) - (\gamma_{I2} + \psi\gamma_{I2} + \alpha_{I2} + d)I_2 + (\gamma_{C1} + \psi\gamma_{C1})C_1 + \alpha_{I1}I_1 \\
C_1' &= \alpha_{A2}A_2 + \alpha_{I2}I_2 - (\gamma_{C1} + \psi\gamma_{C1} + \alpha_{C1} + d)C_1 \\
C_2' &= \alpha_{C1}C_1 - (d + \delta_{C_2})C_2 \\
F_\beta &= \beta(q_A(A_0 + A_1 + A_2) + q_I(I_0 + I_1 + I_2))
\end{aligned} \tag{2.2}$$

The equations that represent the vaccination only case are:

$$\begin{aligned}
S' &= \lambda + \gamma_{A0}A_0 + (\gamma_{I0} + \psi\gamma_{I0})I_0 - \tfrac{F_\beta S}{N} - \nu\rho\epsilon S - dS \\
A_0' &= \tfrac{F_\beta S}{N} - (\gamma_{A0} + \alpha_{A0} + d)A_0 + \gamma_{A1}A_1 \\
A_1' &= \alpha_{A0}A_0 - (\gamma_{A1} + \alpha_{A1} + d)A_1 + \gamma_{A2}A_2 \\
A_2' &= \alpha_{A1}A_1 - (\gamma_{A2} + \alpha_{A2} + d)A_2 \\
I_0' &= -(\gamma_{I0} + \psi\gamma_{I0} + \alpha_{I0} + d)I_0 + (\gamma_{I1} + \psi\gamma_{I1})I_1 \\
I_1' &= -(\gamma_{I1} + \psi\gamma_{I1} + \alpha_{I1} + d)I_1 + (\gamma_{I2} + \psi\gamma_{I2})I_2 + \alpha_{I0}I_0 \\
I_2' &= -(\gamma_{I2} + \psi\gamma_{I2} + \alpha_{I2} + d)I_2 + (\gamma_{C1} + \psi\gamma_{C1})C_1 + \alpha_{I1}I_1 \\
C_1' &= \alpha_{A2}A_2 + \alpha_{I2}I_2 + \alpha_{V2}V_2 - (\gamma_{C1} + \psi\gamma_{C1} + \alpha_{C1} + d)C_1 \\
C_2' &= \alpha_{C1}C_1 - (d + \delta)C_2 \\
S_V' &= \nu\rho\epsilon S + \gamma_{V0}V_0 - \tfrac{qF_\beta S_V}{N} - dS_V \\
V_0' &= \tfrac{qF_\beta S_V}{N} - (\gamma_{V0} + \alpha_{V0} + d)V_0 + \gamma_{V1}V_1 \\
V_1' &= \alpha_{V0}V_0 - (\gamma_{V1} + \alpha_{V1} + d)V_1 + \gamma_{V2}V_2 \\
V_2' &= \alpha_{V1}V_1 - (\gamma_{V2} + \alpha_{V2} + d)V_2 \\
F_\beta &= \beta((A_0 + A_1 + A_2) + q_I(I_0 + I_1 + I_2) + q_V(V_0 + V_1 + V_2))
\end{aligned} \tag{2.3}$$

The equations that represent the screening and vaccination case are:

$$\begin{aligned}
S' &= \lambda + \gamma_{A0}A_0 + (\gamma_{I0} + \psi\gamma_{I0})I_0 - \tfrac{F_\beta S}{N} - \nu\rho\epsilon S - dS \\
A_0' &= \tfrac{F_\beta S}{N} - (\gamma_{A0} + \alpha_{A0} + \zeta\phi + d)A_0 + \gamma_{A1}A_1 \\
A_1' &= \alpha_{A0}A_0 - (\gamma_{A1} + \alpha_{A1} + \zeta\phi + d)A_1 + \gamma_{A2}A_2 \\
A_2' &= \alpha_{A1}A_1 - (\gamma_{A2} + \alpha_{A2} + \zeta\phi + d)A_2 \\
I_0' &= \zeta\phi A_0 + \zeta_2\phi V_0 - (\gamma_{I0} + \psi\gamma_{I0} + \alpha_{I0} + d)I_0 + (\gamma_{I1} + \psi\gamma_{I1})I_1 \\
I_1' &= \zeta\phi A_1 + \zeta_2\phi V_1 - (\gamma_{I1} + \psi\gamma_{I1} + \alpha_{I1} + d)I_1 + (\gamma_{I2} + \psi\gamma_{I2})I_2 + \alpha_{I0}I_0 \\
I_2' &= \zeta\phi A_2 + \zeta_2\phi V_2 - (\gamma_{I2} + \psi\gamma_{I2} + \alpha_{I2} + d)I_2 + (\gamma_{C1} + \psi\gamma_{C1})C_1 + \alpha_{I1}I_1 \\
C_1' &= \alpha_{A2}A_2 + \alpha_{I2}I_2 + \alpha_{V2}V_2 - (\gamma_{C1} + \psi\gamma_{C1} + \alpha_{C1} + d)C_1 \\
C_2' &= \alpha_{C1}C_1 - (d + \delta)C_2 \\
S_V' &= \nu\rho\epsilon S + \gamma_{V0}V_0 - \tfrac{qF_\beta S_V}{N} - dS_V \\
V_0' &= \tfrac{qF_\beta S_V}{N} - (\gamma_{V0} + \alpha_{V0} + \zeta_2\phi + d)V_0 + \gamma_{V1}V_1 \\
V_1' &= \alpha_{V0}V_0 - (\gamma_{V1} + \alpha_{V1} + \zeta_2\phi + d)V_1 + \gamma_{V2}V_2 \\
V_2' &= \alpha_{V1}V_1 - (\gamma_{V2} + \alpha_{V2} + \zeta_2\phi + d)V_2 \\
F_\beta &= \beta((A_0 + A_1 + A_2) + q_I(I_0 + I_1 + I_2) + q_V(V_0 + V_1 + V_2)
\end{aligned} \tag{2.4}$$

Figure 2.1 represents the models used in this chapter. The model as is depicted in its entirety in Figure 2.1 represents the screening and vaccination as interventions model (Eq.(2.4)). The most basic model, corresponding to Eq.(2.1), represents a no intervention model and is obtained when both the screening sensitivity, ϕ, and the vaccine uptake rate, ρ, are zero. When only ρ, the vaccine uptake rate, is zero, the diagram represents the screening only scenario corresponding to Eq.(2.2), and when only ϕ, the screening sensitivity, is zero, the diagram represents the vaccination only scenario, corresponding to Eq.(2.3).

The system of ODEs found in Eq.'s (2.1)-(2.4) include the following assumptions:

- Treatment compartments are not included, rather, treatment can be modelled as an increased rate of regression.
- Individuals regress from the C_1 stage to the I_2 stage as it is assumed that by the time the individual reaches the C_1 stage, they are aware of their disease status.
- The progression rates are such that: $\alpha_{Vi} < \alpha_{Ii} < \alpha_{Ai}$ as the disease progression for individuals who are not vaccinated and do not know their disease status will be higher than those who are vaccinated and know their disease status as they will not practice safe sex and have no protection from the vaccine.
- $q_I > q_V$ as people who are vaccinated will be less likely to pass on HPV.
- Individuals may be screened at any stage of his/her disease.
- Screening has the same sensitivity at any time during the disease progression.
- Individuals are vaccinated before getting infected with HPV.

2.3 Parameters

The variables and parameter descriptions can be found in Tables 2.1 and 2.2. Parameter values are also listed in Table 2.2.

Tables 2.1 and 2.2 provide a comprehensive list of all parameters and variables used in Eq.'s (2.1)-(2.4). Latin Hypercube Sampling was used to sample and provide parameter values for the models. The populations sizes used are representative of those of the female

Variable	Definition
S	Susceptible individuals
A_0	Individuals with HPV, disease status unknown
A_1	Individuals with CIN1 (pre-cancer), disease status unknown
A_2	Individuals with CIN2 (pre-cancer), disease status unknown
C_1	Individuals with CIN3 (pre-cancer), disease status assumed to be known
C_2	Individuals with cancer, disease status known
I_0	Individuals with HPV, disease status known
I_1	Individuals with CIN1 (pre-cancer), disease status known
I_2	Individuals with CIN2 (pre-cancer), disease status known
S_v	Susceptible, vaccinated individuals
V_0	Vaccinated individuals with HPV, disease status unknown
V_1	Vaccinated individuals with CIN1 (pre-cancer), disease status unknown
V_2	Vaccinated individuals with CIN2 (pre-cancer), disease status unknown

Table 2.1: Variables used in Eq.'s (2.1)-(2.4).

population in Nepal. The progression rates (α_n) and the regression rates (γ_n) were obtained from a portion of the ranges found in literature and represent $80-180\%$ boundaries for the mean value used in Latin Hypercube Sampling [16,38]. The boundaries for ρ, the proportion of individuals vaccinated, are $40-180\%$ of the mean value (assumed) and the boundary values for ϵ, the screening efficacy, is $80-105\%$ of the mean value [40]. The screening sensitivity, ϕ, range was calculated as $40-117.5\%$ of the mean value (see Table 1.2), while the added regression rate, ψ [39], and the proportion of individuals screened , ζ and ζ_2 (assumed) represent $95-105\%$ and $40-200\%$ respectively. All ranges fall within accepted ranges found in literature.

Parameter	Description	Range	Source
α_{A0}	Progression rate from HPV to CIN1	[.02-.045](year^{-1})	[16, 38]
α_{I0}	Progression rate from HPV to CIN1	[.016-.036](year^{-1})	[16, 38]
α_{V0}	Progression rate HPV to CIN1	[.012-.027](year^{-1})	[16, 38]
α_{A1}	Progression rate from CIN1 to CIN2	[.0336-.0756](year^{-1})	[38]
α_{I1}	Progression rate from CIN1 to CIN2	[.028-.063](year^{-1})	[38]
α_{V1}	Progression rate from CIN1 to CIN2	[.024-.054](year^{-1})	[38]
α_{A2}	Progression rate from CIN2 to CIN2	[.092-.207](year^{-1})	[38]
α_{I2}	Progression rate from CIN2 to CIN2	[.08-.18](year^{-1})	[38]
α_{V2}	Progression rate from CIN2 to CIN2	[.072-.162](year^{-1})	[38]
α_{C1}	Progression rate from CIN3 to cancer	[.024-.054](year^{-1})	[38]
γ_{A2}	Regression rate from CIN2/3 to CIN1	[.048-.108](year^{-1})	[16]
γ_{I2}	Regression rate from CIN2/3 to CIN1	[.048-.108](year^{-1})	[16]
γ_{V2}	Regression rate from CIN2/3 to CIN1	[.064-.144](year^{-1})	[16]
γ_{A1}	Regression rate from CIN1 to HPV	[.4-.9](year^{-1})	[16]
γ_{I1}	Regression rate from CIN1 to HPV	[.4-.9](year^{-1})	[16]
γ_{V1}	Regression rate from CIN1 to HPV	[.44-.99](year^{-1})	[16]
γ_{A0}	Regression rate from HPV to susceptible	[.16-.36](year^{-1})	[16]
γ_{I0}	Regression rate from HPV to susceptible	[.16-.36](year^{-1})	[16]
γ_{V0}	Regression rate from HPV to susceptible	[.2-.45](year^{-1})	[16]
γ_{C1}	Regression rate from CIN3 to CIN2	.02(year^{-1})	[58]
q_I	Scaling constant	$[.32 - .72]$	assumed
q_V	Scaling constant	$[.16 - .36]$	assumed
ρ	Vaccine uptake	$[.2 - .9]$(year^{-1})	assumed
ϵ	Probability of vaccine success	$[.76 - .9975]$	[40]
β	Infection rate	$[.001 - .8]$(year^{-1})	[16, 41, 71, 74]
ϕ	Screening sensitivity	see Table 1.2	
Cost of screening		$4 - 15$ USD	assumed
d	Natural death rate	68 year^{-1}	[60]
δ	Death due to disease	$\frac{1}{54*12}$(year^{-1})[0-.0998]	[13, 46]
ψ	Added regression rate due to treatment	$[.81 - .945\%]$	[39]
ζ, ζ_2	Proportion of individuals who get screened per year	0-1	assumed
ν	Number of 13 year old girls	$313763/N$	[57]
N	Female population of Nepal	13607013	[57]
q	Scaling constant to account of unknown affect of neutralization antibodies	$[.001 - 1]$	assumed

Table 2.2: Parameters used in Eq.'s (2.1)-(2.4). The subscript represents the population class for which the transition rate is relevant. *Note: These rates are for HPV 16 only.

2.4 Results

2.4.1 Analytical results

2.4.1.1 Equilibrium points

All four models have a disease free equilibrium point and one biologically viable endemic equilibrium point. The disease free equilibrium point for the models in which there is only one susceptible class, ie. for Eq.'s (2.1) and (2.2) is:

$$(S, 0, 0, 0, 0, 0, 0, 0, 0) \quad = \quad (\tfrac{\lambda}{d}, 0, 0, 0, 0, 0, 0, 0, 0) \tag{2.5}$$

and the disease free equilibrium point for Eq.'s (2.3) and (2.4) is:

$$(S, 0, 0, 0, 0, 0, 0, 0, 0, S_v, 0, 0) \quad = \quad (\tfrac{\lambda}{\nu\rho\epsilon+d}, 0, 0, 0, 0, 0, 0, 0, 0, \tfrac{\nu\rho\epsilon\lambda}{d(\nu\rho\epsilon+d)}, 0, 0, 0) \tag{2.6}$$

Eq.'s (2.1)-(2.4) are too complex to calculate the the endemic equilibrium point analytically, hence it will be analyzed numerically.

2.4.1.2 Stability

The Jacobian (J) must be evaluated at the various equilibrium points in order to calculate the stability of the respective equilibrium point. Although not shown in this document for all of the models, the Jacobian was calculated for Eq.'s (2.1)-(2.4) and analyzed to understand the stability conditions of all model equilibria. Eq.'s (2.1)-(2.4) are high in dimension and complexity. In some cases the stability conditions can be found using analytical methods, however, numerical methods are required for much of this study.

Substituting values for the disease free equilibrium point into the Jacobian for Eq.s (2.1)-(2.4) gives the following eigenvalues:

No intervention model, Eq.(2.1)

- $\lambda_1 = -d < 0$ (Entry (1,1) of $J_{(DFE)}$)
- $\lambda_2 = -(d + \delta) < 0$ (Entry (9,9) of $J_{(DFE)}$)

- The third eigenvalue is a polynomial of degree 7. It is too large to calculate numerically, however, it can be related to Eq.(2.7) as was done with $\lambda_{1,2}$.

As the first two eigenvalues are always negative, the stability of the system is dependent on the third eigenvalue.

$$J_{(DFE)} = \begin{vmatrix} -d\,\gamma_{A0} - \frac{\beta q_A S}{N} & -\frac{\beta q_A S}{N} & -\frac{\beta q_A S}{N} & \gamma_{I0} + \gamma_{I0}\psi - \frac{\beta q_I S}{N} & -\frac{\beta q_I S}{N} & -\frac{\beta q_I S}{N} & 0 & 0 \\ 0 & \frac{\beta q_A S}{N} - \gamma_{A0} - \alpha_{A0} - d & \frac{\beta q_A S}{N} + \gamma_{A1} & \frac{\beta q_A S}{N} & \frac{\beta q_I S}{N} & \frac{\beta q_I S}{N} & \frac{\beta q_I S}{N} & 0 & 0 \\ 0 & \alpha_{A0} & -(\gamma_{A1} + \alpha_{A1} + d) & \gamma_{A2} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha_{A1} & -(\gamma_{A2} + \alpha_{A2} + d) & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -(\gamma_{I0} + \psi\gamma_{I0} + \alpha_{I0} + d) & \gamma_{I1} + \psi\gamma_{I1} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \alpha_{I0} & -(\gamma_{I1} + \psi\gamma_{I1} + \alpha_{I1} + d) & \gamma_{I2} + \psi\gamma_{I2} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha_{I1} & -(\gamma_{I2} + \psi\gamma_{I2} + \alpha_{I2} + d) & \gamma_{C1} + \psi\gamma_{C1} & 0 \\ 0 & 0 & 0 & \alpha_{A2} & 0 & 0 & \alpha_{I2} & -(\gamma_{C1} + \psi\gamma_{C1} + \alpha_{C1} + d) & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \alpha_{C1} & -(d + \delta) \end{vmatrix} \tag{2.7}$$

Screening only model, Eq.(2.2)

Calculating the eigenvalues at the disease free equilibrium point of the Jacobian gives:

- $\lambda_1 = 0$
- $\lambda_2 = -d < 0$
- $\lambda_3 = -(d + \delta) < 0$
- $\lambda_4 = -(\gamma_{A2} + \alpha_{A2} + d + \phi\zeta) < 0$
- The last eigenvalues can be calculated from a 5th degree polynomial. It is too difficult to compute λ_{5-9} analytically, hence they will be analyzed numerically in Section 2.4.2.

The stability of Eq.(2.2) depends on the final eigenvalue, as the remaining eigenvalues are negative.

Vaccination only model, Eq.(2.3), and screening and vaccination model, Eq.(2.4)

Eq.'s (2.3) and (2.4) are too large to calculate the eigenvalues explicitly, hence they will be analyzed numerically in Section 2.4.2.

2.4.2 Numerical simulations

2.4.2.1 Simulations

A sample simulation of the four models in this chapter created using a single parameter set generated by Latin Hypercube Sampling is shown in Figure 2.2. The parameters used can be found in Table 6.1 in the appendix. From the simulations, it is possible to compare the various prevention strategies. All models had the initial conditions $S(0) = N$ and $A_0(0) = 1$. The first simulation, the no-intervention model corresponding to Eq.(2.1), agrees with the current data saying that it can take 20-40 years for cancer to manifest [6]. Furthermore, all the intervention programs reduce the cancer incidence compared with the no-intervention model. The models including vaccination cause a steep drop in the susceptible population, however, this is because a proportion of the susceptible population transfer to the susceptible vaccinated class. The vaccination and screening model is the best in terms of minimizing all

of the infected class sizes. Finally, when screening is implemented (versus vaccination), it takes longer for the infected class sizes to increase.

2.4.2.2 Basic reproduction number

Numerical methods were used to calculate R_0. Using the parameter ranges found in Table 2.2, 5000 parameter sets were created using Latin Hypercube Sampling. Of these, only those that satisfied the model assumptions were used. Hence, the basic reproduction number for Eq.(2.1) was calculated using 1708 viable parameter sets. The basic reproduction number for Eq.(2.2) was calculated using 1733 parameter sets. 385 parameter sets were used to calculate the basic reproduction number for Eq.'s (2.3) and (2.4).

Figure 2.3 shows R_0 with respect to various transmission rates, β, for the different models. $R_0 = 1$ when $\beta \approx .2$ year^{-1} for the no intervention model, $\beta \approx .3$ year^{-1} for the screening only model, and $\beta \approx .3$ year^{-1} and $\approx .4$ year^{-1} for the vaccination model and the screening and vaccination model respectively. When the transmission rate, β, is less than the aforementioned values, the DFE will be stable. It will be unstable for all β values larger than the aforementioned values for the respective models. Similarly, for Eq.'s (2.1) and (2.2), the EE will be stable when $R_0 > 1$ and unstable otherwise. See Section 2.4.2.3 for an analysis of the stability at the EE for Eq.'s (2.3) and (2.4).

When $R_0 < 1$, there will be no epidemic. Hence, it should be possible to decrease the transmission rate, β, so that it is less than the threshold rate, (mentioned above) through vaccination and screening practices, as vaccination should prevent an HPV infection while positive screening results should influence the individual to practice safe sex.

2.4.2.3 Stability of the equilibria

Using 5000 LHS parameter sets, 1708 fitted the criteria such that $\alpha_{An} > \alpha_{In}$ for Eq.(2.1), 1733 for Eq.(2.2), and 385 for Eq.'s (2.3) and (2.4). These were used to find the eigenvalues of the Jacobian evaluated at the DFE and to calculate R_0. Figure 2.4 shows R_0 values with respect to the eigenvalues of the system for the LHS filtered parameter sets for all models (Eq.'s (2.1)-(2.4)).

As expected, the DFE is always stable when $R_0 < 1$ (signified by all negative eigenval-

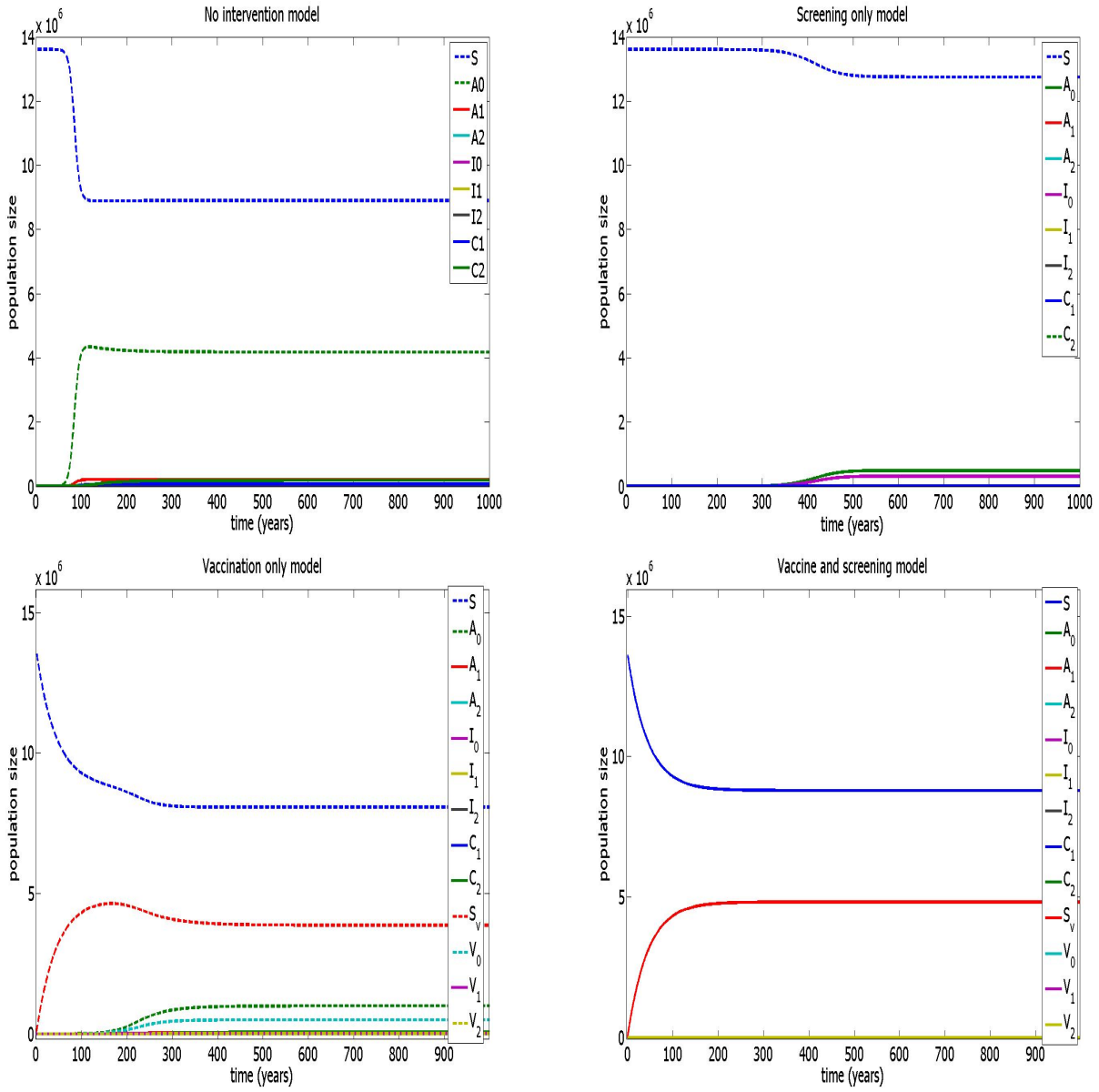


Figure 2.2: Numerical simulations for Eq.'s (2.1)-(2.4), the no-intervention, screening only, vaccination only and screening and vaccination models with the disease free equilibrium and one infected individual as the initial conditions. The x-axis represents the time, measured in years, while the y-axis represents the population size.

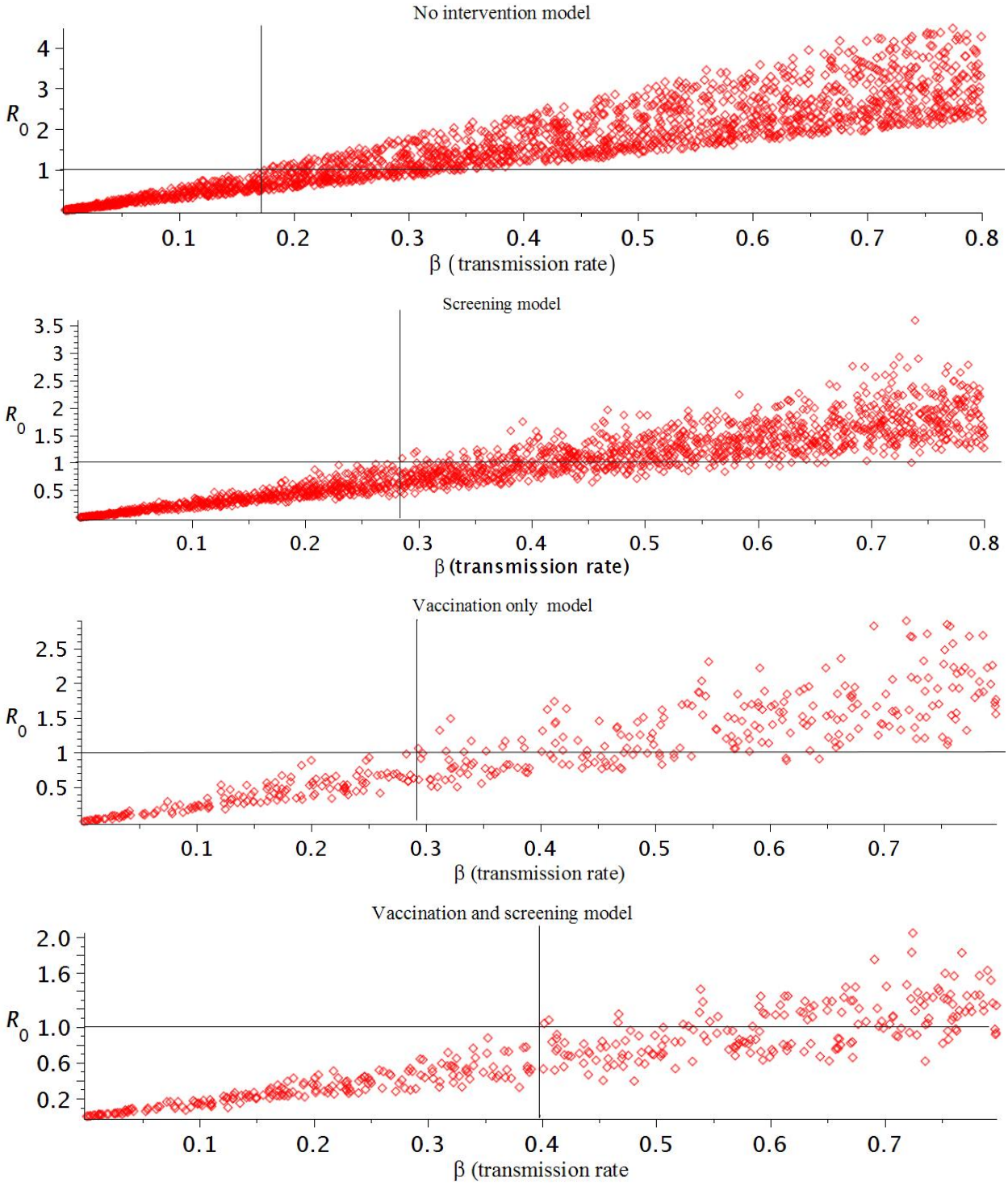


Figure 2.3: R_0 with respect to the transmission rate, β, using multiple parameter sets generated by LHS for Eq.'s (2.1)-(2.4). The no intervention model used 1708 parameter sets, the screening only model used 1733 parameter sets and the vaccination model and vaccination and screening models both used 385 parameter sets. Each point represents R_0 calculated with a different transmission rate, β. The vertical bar depicts $R_0 = 1$

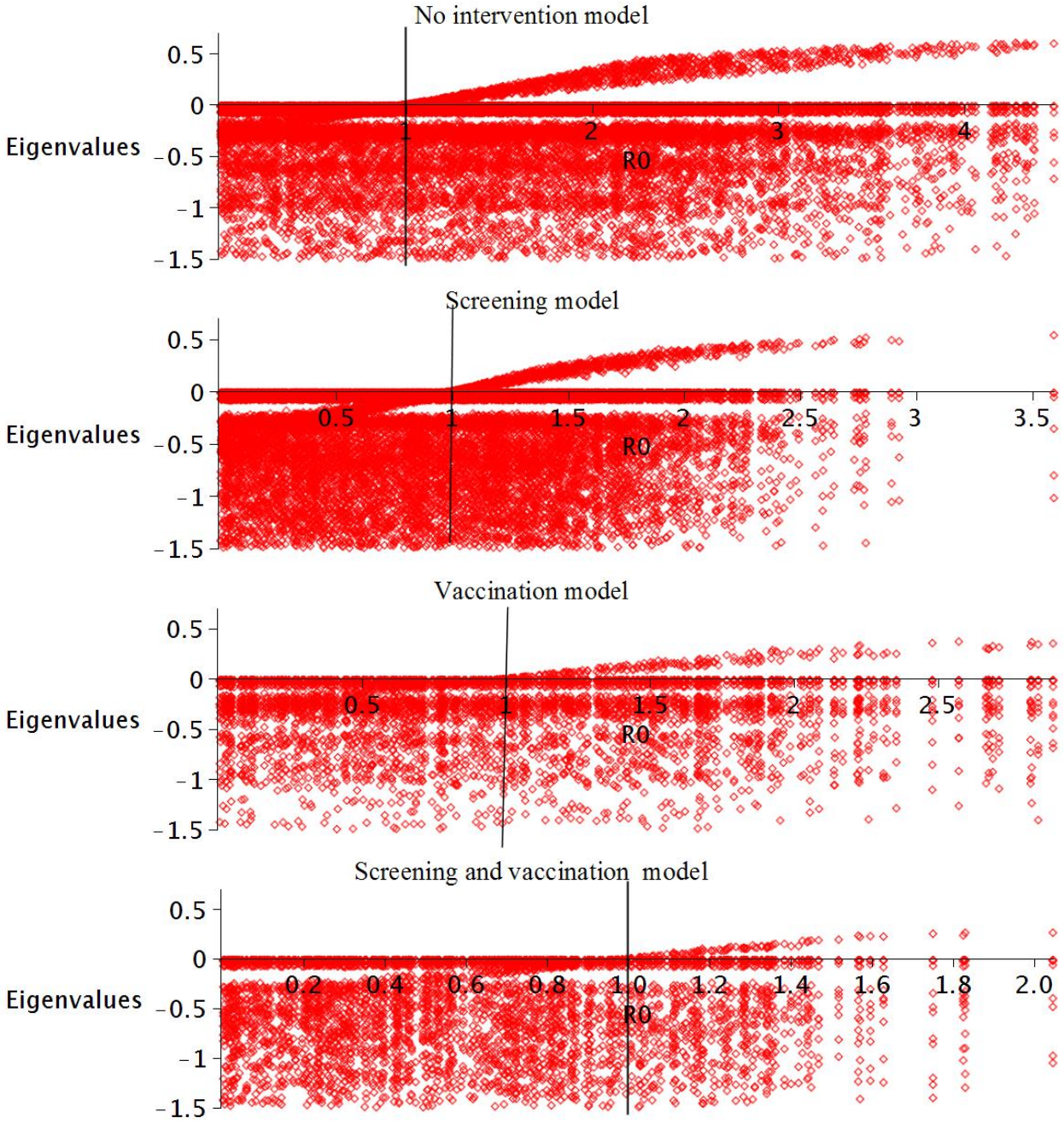


Figure 2.4: Stability of DFE with respect to R_0 for Eq.'s (2.1)-(2.4). The DFE is always stable when $R_0 < 1$. The x-axis represents the basic reproduction number and the y-axis represents the eigenvalues. Each point on the plot represents an eigenvalue. Positive eigenvalues are indicative of an unstable equilibrium point. The vertical bar depicts $R_0 = 1$.

ues). This implies that the final eigenvalue $\lambda_3 < 0$ is equivalent to $R_0 < 1$.

Stability analysis of the endemic equilibrium point was conducted using numerical methods. 5000 LHS parameter sets were used. Of these, only 1181 gave non-negative population sizes for Eq.(2.1), 818 for Eq.(2.2), 177 for Eq.(2.3) and 107 for Eq.(2.4). It was found that all eigenvalues had negative values corresponding to $R_0 > 1$ for Eq.'s (2.1) and (2.2).

Of the 177 parameter sets used to analyze the stability of Eq (2.3), all of them returned unstable endemic equilibria. ie. one of the 13 eigenvalues for the system was shown to be non-negative, indicating instability of the equilibrium point. A numerical bifurcation analysis was completed on this model. Of the 13 eigenvalues, only one presents a positive value (close to zero), implying that the endemic equilibrium is weakly unstable, hence solutions tend towards stability, creating a transcritical bifurcation. Bifurcation diagrams were created using XPPAUT, a bifurcation diagram software [1].

We now discuss one parameter set as an example that has a small positive eigenvalue for the infected equilibrium. Figure 2.5 shows the bifurcation diagram (top) and R_0 (bottom) for I_0 with respect to β (the transmission rate) for Eq.(2.3) (vaccination only model). Here, $R_0 = 1$ when $\beta \approx .55$ year^{-1} and this corresponds to the appearance of a stable infected equilibrium (top panel).

More complicated dynamics were found for Eq.(2.4), the model incorporating both vaccination and screening. Here, however, of the 107 parameter sets, 88 were shown to be stable and 19 parameter sets were shown to be unstable. A similar bifurcation analysis was completed as that for Eq.(2.3) that resulted in slightly different outcomes. This can be seen in Figure 2.6, which shows a bi-stable, backward bifurcation. This means that R_0^c, which represents the value that indicates eradication of the disease, is less than $R_0 = 1$. In terms of the I_0 population, the endemic equilibrium point has two regions of stability, one in the biologically non-viable area and the second in a biologically viable area. This second stable area changes stability at the node (R_0^c). If a solution lands on the unstable area, it will either move towards the top stable branch (of the EE) or the bottom stable branch of the DFE (as shown in the top corner of the I_0 plot). This however will take a long time. If the solution does not land on the unstable branch, it will move towards one of the stable equilibria. The backward bifurcation means that, in terms of HPV dynamics, a higher level of control must

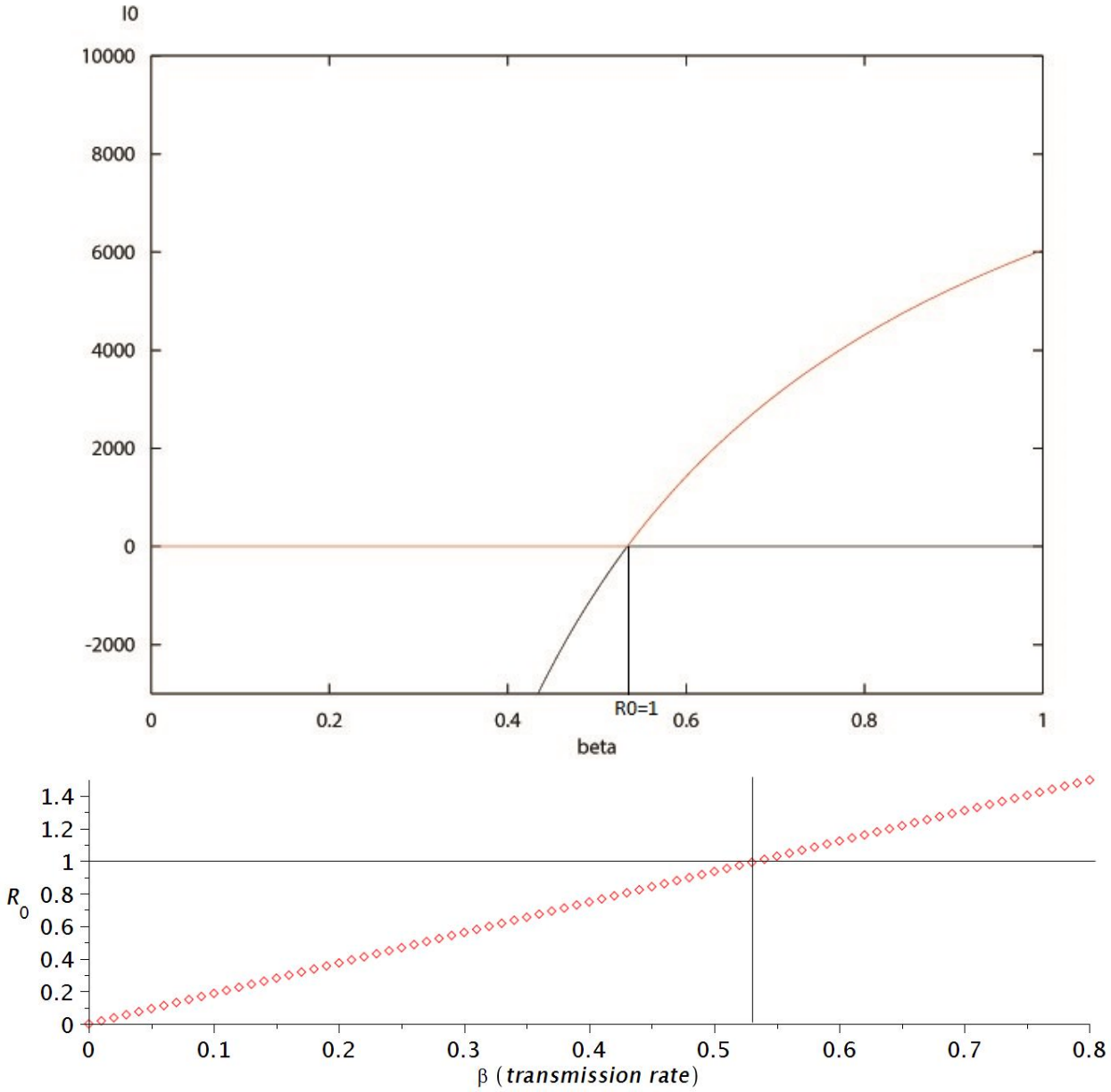


Figure 2.5: Bifurcation diagram for the infected population, I_0, with respect to the transmission rate, β, for a single LHS generated parameter set of the vaccination only model (top panel) (Eq.(2.3)). The top branch represents a stable solution and the bottom branch represents an unstable solution. The bifurcation here is transcritical, however, the unstable endemic equilibrium point has negative values, which are not biologically viable. Hence, the endemic equilibrium only exists when $R_0 \geq 1$, where it is stable, while the DFE always exists. The bottom panel confirms that $R_0 = 1$ when the transmission rate, β, is approximately .55 year^{-1}.

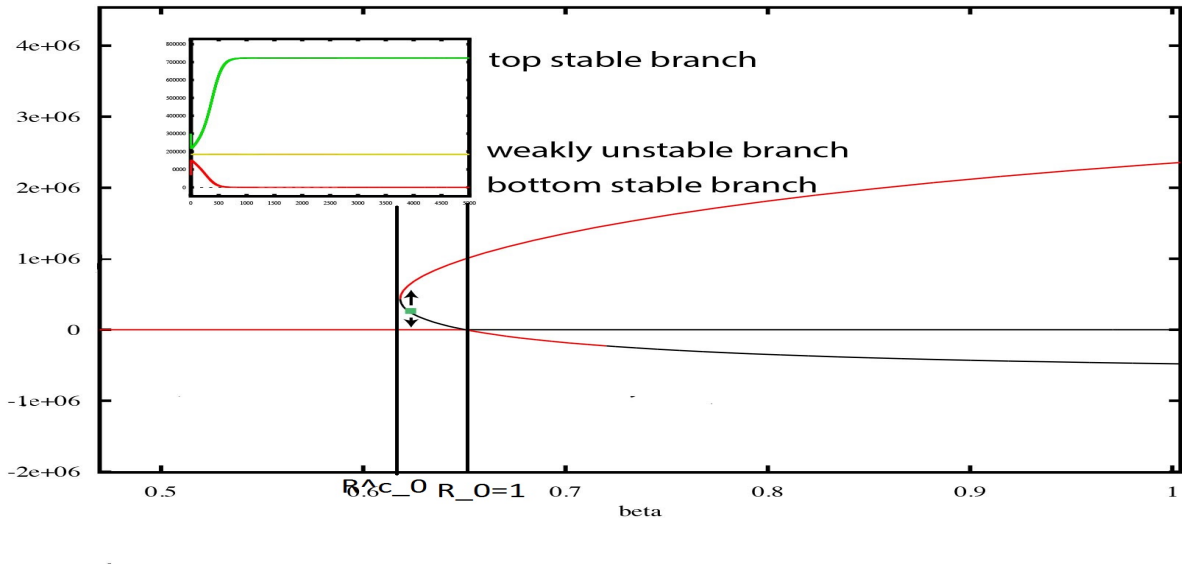


Figure 2.6: Bifurcation diagram for the screened, HPV positive (I_0) class with respect to the transmission rate, β, for Eq.(2.4). A bi-stable, backward bifurcation is shown. Vaccination and screening practices should be implemented to push the solution beyond R_0^c in order to eradicate HPV.

	Positive correlation			Negative correlation		
	HPV (A_0)	HPV (I_0)	Cancer (C_2)	HPV (A_0)	HPV (I_0)	Cancer (C_2)
γ_{I1}	✓					
γ_{A0}				✓	✓	✓
β	✓	✓	✓			

Table 2.3: Significance of the parameters in Eq.(2.1), the no intervention model, corresponding to Figure 2.7.

be applied through screening and vaccination practices to eliminate a possible epidemic. ie. to move to a a parameter space past R_0^c.

2.4.2.4 Sensitivity analysis

PRCC values are used to calculate the significance of a certain parameters. Moreover, they can be used to understand the relative significance of the parameters used in the model in a certain context. The PRCC plots generated in this section relate to the HPV infected (A_0, I_0, and V_0) and cancerous classes (C_2) as the goal of an intervention/prevention program is to prevent HPV infection as well as to minimize its progression to the cancer stage.

All parameter sets generated by LHS that satisfy the model assumptions were used to generate the PRCC plots.

No intervention model, Eq.(2.1)

Figure 2.7 shows the PRCC values for the A_0, I_0, and C_2 populations. Table 2.3 summarizes the parameters that are significant in the model.

β, the transmission rate, is always significant with a positive correlation. Similarly, γ_{A0}, the regression rate from the A_0 compartment to the S compartment, is always significant, however, with a negative correlation. Finally, γ_{I1} has a significant positive correlation, however, only with respect to the A_0 population. In other words, an increase in the transmission rate, β, will cause an increase in the size of the infected and cancerous classes. An increase in the regression rate, γ_{A0}, will cause a decrease in the infected classes (including the cancerous class). Finally, an increase in the regression rate for the I_1 class, will cause an increase in

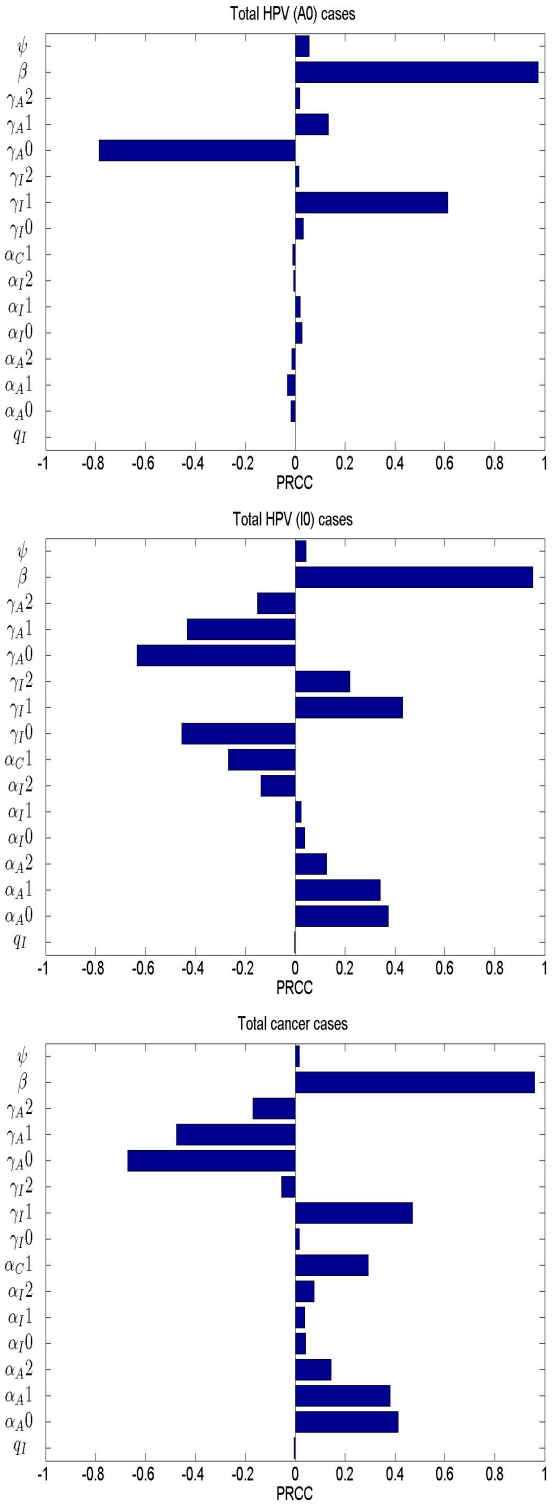


Figure 2.7: PRCC results for the no intervention model (Eq.(2.1)) with respect to the total number of HPV positive and cancer positive cases. A bar whose magnitude is larger than .5 is deemed statistically significant with either a positive correlation to the population size (a bar to the right of the y-axis) or a negative correlation to the population size (a bar to the left of the y-axis).

	Positive correlation			**Negative correlation**		
	HPV (A_0)	HPV (I_0)	Cancer (C_2)	HPV (A_0)	HPV (I_0)	Cancer (C_2)
γ_{A0}				✓	✓	✓
γ_{I0}					✓	
β	✓	✓	✓			
ϕ				✓		✓
ζ				✓		✓

Table 2.4: Significance of the parameters in Eq.(2.2), a screening only model corresponding to Figure 2.8.

the infected population (A_0).

Screening only model, Eq.(2.2)

The PRCC plots for the screening as intervention model can be found in Figure 2.8. Table 2.4 summarizes the PRCC plots. β, the transmission rate, is significant with a positive correlation for all three quantities indicating that an increase or decrease in the transmission rate will cause a similar change in the infected population size. Furthermore, γ_{A0}, the regression rate for individuals from the HPV positive compartment to the susceptible compartment has a negative significance for all three compartments, while γ_{I0} is significant for only the I_0 compartment. Both ϕ, the screening sensitivity, and ζ, the proportion of individuals screened, have a negative significance for the A_0 and C_2 classes. This means that an increase or decrease in the screening sensitivity or amount of individuals screened will have an inverse affect on the A_0 and C_2 classes.

Vaccination only model, Eq. (2.3)

Two cases were studied in order to compare the PRCC results when various initial conditions are implemented:

1. Starting at the DFE and adding $A_0 = 1$ at time 0
2. Starting at $S(0) = N - 1$ and add $A_0 = 1$ at time 0

Figure 2.9 shows the PRCC plots when the initial conditions consist of those found in 2. above. Table 2.5 summarizes the PRCC plots found in Figure 2.9. All the classes have

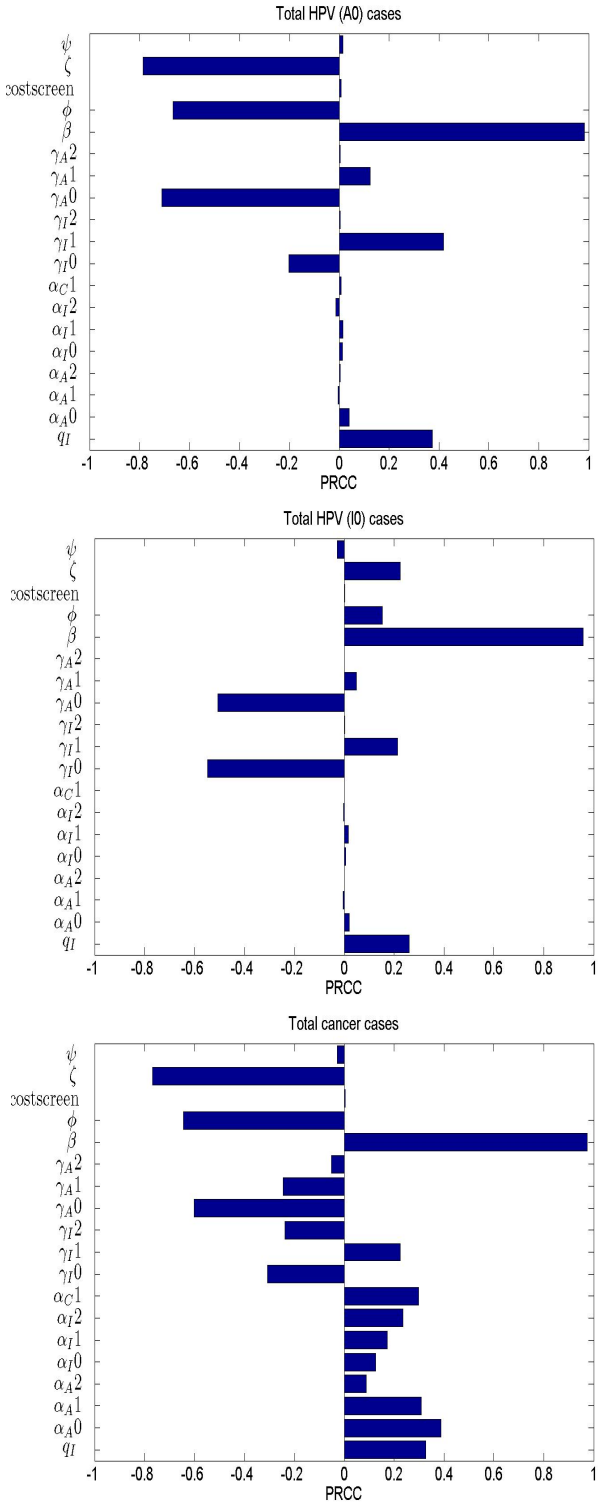


Figure 2.8: PRCC results for the screening only model, Eq.(2.2), with respect to the outcome of the HPV positive and cancer positive cases. A bar whose magnitude is larger than .5 is deemed statistically significant with either a positive correlation to the population size (a bar to the right of the y-axis) or a negative correlation to the population size (a bar to the left of the y-axis).

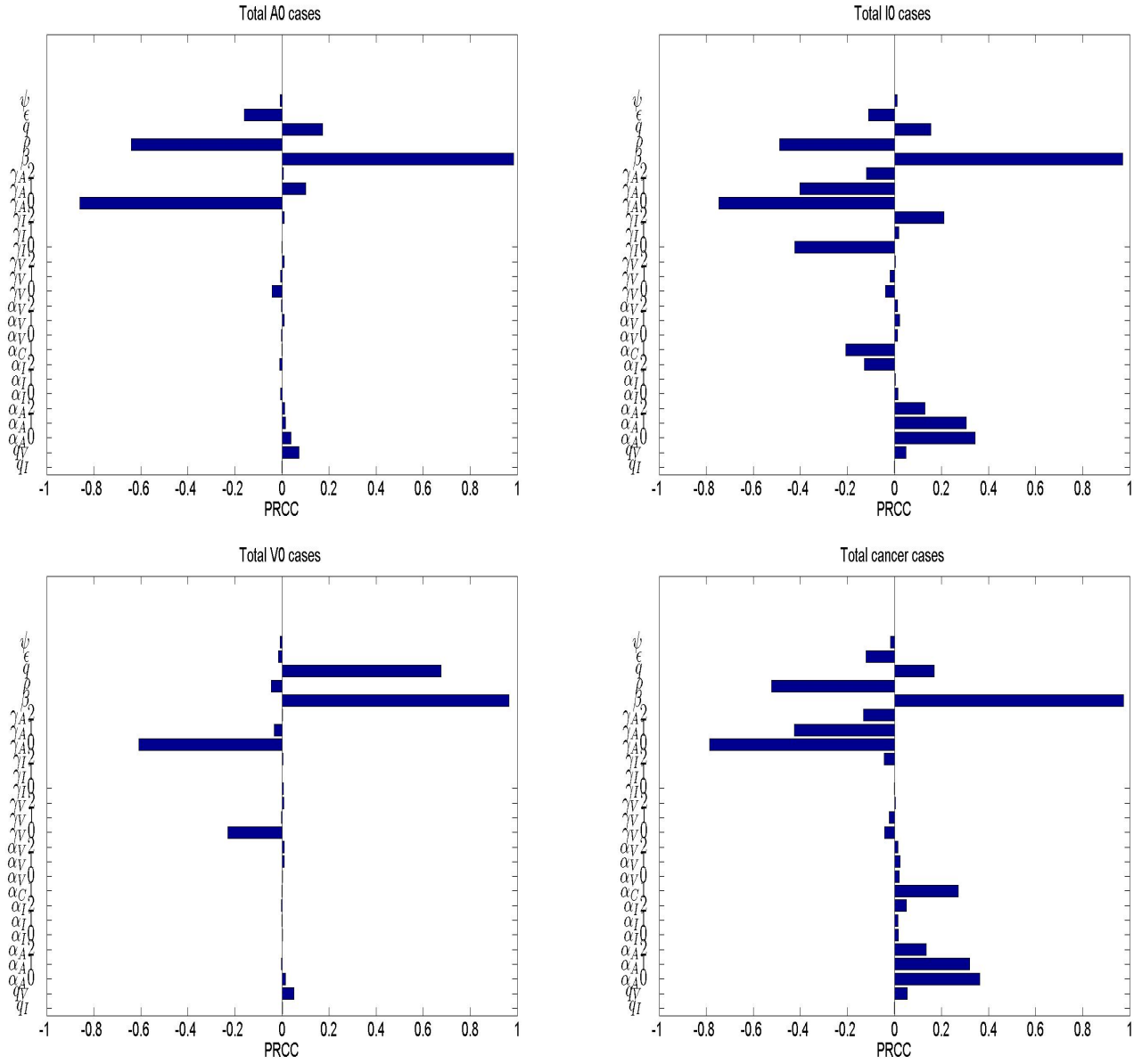


Figure 2.9: PRCC plots for total HPV and cancer cases, when a vaccination program is implemented (Eq.(2.3)). The initial conditions are $S(0) = N - 1$ and $A_0(0) = 1$.

	Positive correlation				**Negative correlation**			
	HPV (A_0)	HPV (I_0)	HPV (V_0)	Cancer (C_2)	HPV (A_0)	HPV (I_0)	HPV (V_0)	Cancer (C_2)
γ_{A0}					✓	✓	✓	✓
β	✓	✓	✓	✓				
ρ					✓			✓
q			✓					

Table 2.5: Summary of parameter significance for Eq.(2.3), where the initial conditions consist of a fully susceptible population, non-vaccinated, with one infected individual.

	Positive correlation				**Negative correlation**			
	HPV (A_0)	HPV (I_0)	HPV (V_0)	Cancer (C_2)	HPV (A_0)	HPV (I_0)	HPV (V_0)	Cancer (C_2)
γ_{V0}							✓	
γ_{I0}						✓		
γ_{A0}					✓		✓	✓
β	✓	✓	✓	✓				
ρ					✓			✓
q			✓					

Table 2.6: Significance of the parameters in the vaccination only model, Eq.(2.3), when the initial conditions are the DFE.

a negative, significant correlation with the regression rate, γ_{A0}, and a positive, significant correlation with the transmission rate, β. In other words, an increase or decrease in the regression rate will have an inverse effect on the size of the A_0, I_0, V_0, and C_2 classes, and an increase or decrease in the transmission rate will have a similar effect on the size of the class in question. Furthermore, both the total HPV positive (A_0) and cancer classes have a significant, negative correlation with ρ, the proportion of individuals who are screened. Hence, a change in ρ will cause an inverse change in the HPV positive (A_0) and cancer classes. q, the scaling coefficient relating to the neutralizing antibodies from the vaccine has a positive, significant, correlation with the total HPV cases for vaccinated individuals, V_0.

When the initial conditions for the simulation are the disease free equilibrium, Figure 2.10 is generated. Table 2.6 is generated based on Figure 2.10.

From Table 2.6 it is possible to see that there is a slight difference in the significance of the parameters when the initial conditions are changed. Here, β, the transmission rate,

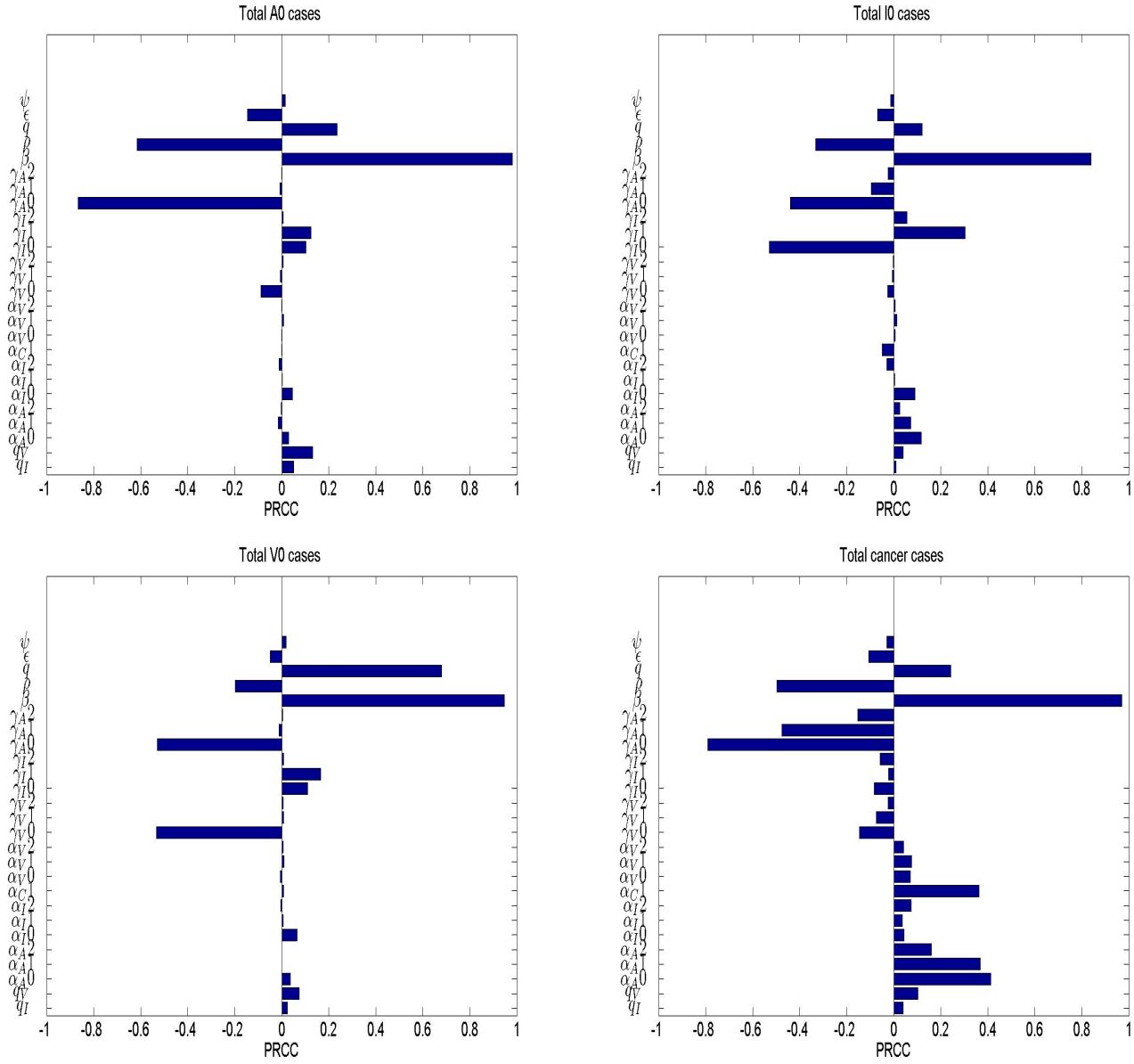


Figure 2.10: PRCC plots for total HPV and cancer cases when a vaccination program (Eq.(2.3)) is implemented and the initial conditions are those of the DFE.

	Positive correlation				Negative correlation			
	HPV (A_0)	HPV (I_0)	HPV (V_0)	Cancer (C_2)	HPV (A_0)	HPV (I_0)	HPV (V_0)	Cancer (C_2)
γ_{A0}					✓			✓
β	✓	✓	✓	✓				
q			✓					
ζ					✓		✓	✓
ϕ					✓			✓

Table 2.7: Summary of the significance of the parameters in the screening and the vaccination model (Eq.(2.4)). Here the initial conditions consist of a fully susceptible, non-vaccinated, population with one infected individual.

is always significant with a positive correlation. ρ, the proportion of individuals who get screened, is significant with a negative correlation in terms of the total A_0 and cancer cases. The regression rate, γ_{A0}, is significant for all quantities other than the total I_0 cases, in which case, the regression rate, γ_{I0}, has a significant negative correlation. Finally, the regression rate, γ_{V0}, is significant in terms of the total V_0 cases.

Screening and vaccination model, Eq.(2.4)

Two cases were studied in order to compare the PRCC results when various initial conditions are implemented:

1. Starting at the DFE and adding $A_0 = 1$ at time 0
2. Starting at $S(0) = N - 1$ and add $A_0 = 1$ at time 0

The PRCC plots for this model, with the initial values $S(0) = N - 1$ and $A_0(0) = 1$ are found in Figure 2.11.

Table 2.7 was generated from Figure 2.11. In this simulation, with these initial conditions, the transmission rate, β, is always significant implying and increase or decrease in the transmission rate will cause a similar change in the respective class size. The regression rate, γ_{A0}, is significant for both the total A_0 and cancer populations. This is similar to the significance of ζ and ϕ, the proportion of individuals screened and the screening sensitivity, however, ζ, the proportion of individuals screened, is also significant with respect to the total V_0 population. The regression rate, γ_{A0}, the proportion of individuals screened, ζ, and the

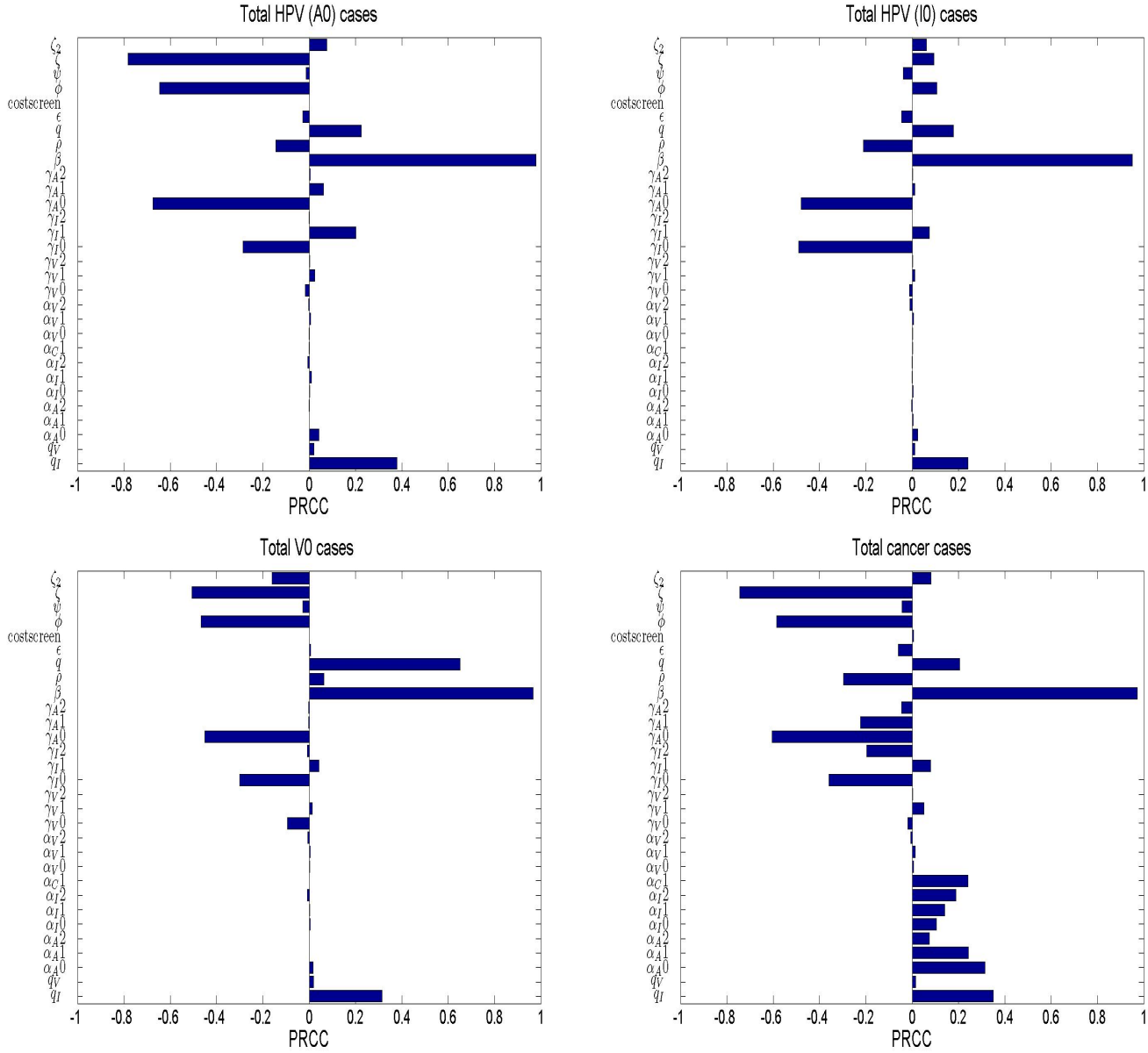


Figure 2.11: PRCC plots for total HPV and cancer cases, when a screening and vaccination program (Eq.(2.4)) is implemented and the initial conditions consists of a totally susceptible, un-vaccinated population with one infected individual.

	Positive correlation				**Negative correlation**			
	HPV (A_0)	HPV (I_0)	HPV (V_0)	Cancer (C_2)	HPV (A_0)	HPV (I_0)	HPV (V_0)	Cancer (C_2)
γ_{I1}	✓							
γ_{I0}						✓		
γ_{A0}					✓			
β	✓	✓	✓	✓				
q			✓					
ζ					✓			✓

Table 2.8: Summary of the significant parameters used in Eq.(2.4), where the initial conditions are the DFE.

screening sensitivity, ϕ, will all have an inverse effect on their respective classes. Finally, as can be expected, q, the added effect of neutralizing antibodies in the vaccine, is significant for the total V_0 population only.

The same analysis can be done when the initial conditions are the disease free equilibrium with one infected individual. These results are shown in Figure 2.12.

Table 2.8 is generated from Figure 2.12. This table is somewhat different from the first table, the main difference being that when the initial conditions are the DFE, the screening sensitivity (ϕ) is not significant.

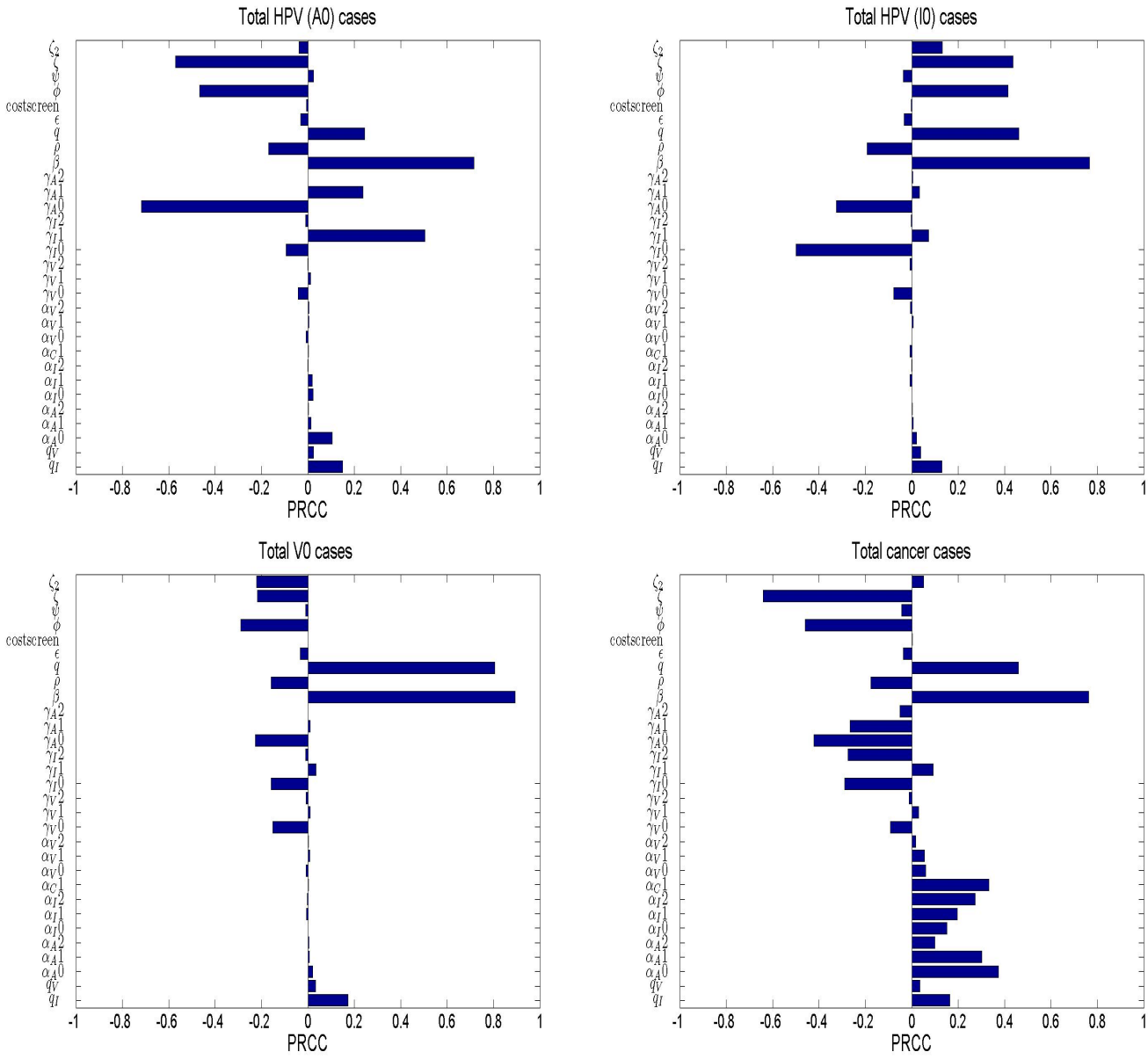


Figure 2.12: PRCC plots for total HPV and cancer cases, when a screening and vaccination program (Eq.(2.4)) is implemented with the initial values being the DFE.

2.5 Discussion

Four models were analyzed with the goal of understanding which parameters are the most important in the question of screening and vaccination in order to minimize the effects of HPV. These include no intervention, screening only intervention, vaccination only intervention, and both screening and vaccination as intervention models. Two aspects were analyzed for each scenario: analytical information, including the equilibria and their stability with respect to the basic reproduction ratio, and PRCC plots.

Table 2.9 summarizes the data with respect to the analytical part of the analysis. Briefly, the implementation of either screening or vaccination into a totally susceptible population will decrease the basic reproductive number for the same transmission rate, β. In other words, the implementation of either of these techniques will allow for a higher transmission rate before causing an epidemic. This is followed by the logical conclusion that the implementation of both screening **and** vaccination will further increase the accepted transmission rate before creating an epidemic. These results are logical.

All of the models follow the expected stability of the disease free equilibrium point with respect to the basic reproduction number. All of the disease free equilibrium points are stable when $R_0 < 1$. The endemic equilibrium points, however, do not all initially follow the expected stability outcomes. While the no intervention case and the screening only case present a stable endemic equilibrium point, implying a forwards bifurcation, both models involving vaccination are not as straight forward. A numerical bifurcation analysis was completed on these models using the set of 5000 parameter sets created by Latin Hypercube Sampling.

Eq.(2.3) produces 13 eigenvalues of which one is positive but close to 0, suggesting a weak instability. However, if the initial conditions of the system are those of the endemic equilibrium, the solution will plateau, indicating a stable solution. Hence, it is fair to conclude from the bifurcation analysis that the endemic equilibria of the system are stable, presenting a trans-critical bifurcation.

Eq.(2.4) takes a different course. Figure 2.6 shows a backward bifurcation. This means that in order to prevent an epidemic, more control in terms of screening and vaccination

	β **s.t.** $R_0 = 1$	**DFE stable when** $R_0 < 1$	**EE stable**
No intervention model	$\approx .2$	✓	✓
Screening only model	$\approx .3$	✓	✓
Vaccination only model	$\approx .3$	✓	✓(weak instability)
Screening and vaccination model	$\approx .4$	✓	✓ (bistability)

Table 2.9: Summary of analytical results for Eq.'s (2.1)-(2.4).

must be implemented so that the $R_0^c < R_0$. This is interesting as it implies that the addition of vaccination to a population will influence the epidemiology in such a drastic way. Hence, it is possible to conclude that the incorporation of a vaccine into a population will only be successful in eradicating disease if enough individuals are vaccinated, such that the critical value, R_0^c is surpassed.

The parameters deemed significant by the PRCC analysis are summarized in Table 2.10. These parameters were deemed significant with respect to the outcomes in the HPV infected (A_0, I_0, and V_0) populations as well as the cancerous population (C_2), as the goal of a screening/vaccination program is to prevent infection with HPV and to minimize cervical cancer through screening and treatment practices.

Table 2.10 shows some expected and unexpected trends. Keeping in mind which population classes were studied, one would expect the progression terms, α_n, to be significant for at least the total number of cancer cases (this is accounted for in the F_β term in the A_0 and V_0 quantities). However, there is no significance for these variables in any of the models. Rather, the only progression rate that is significant is the transmission rate, β, (found in the F_β term). This is the main trend that occurs over all four models.

In terms of the models incorporating vaccination, two trials were run. One using the disease

	Positive significance				Negative significance			
	A_0	I_0	V_0	C_2	A_0	I_0	V_0	C_2
No intervention								
γ_{I1}	✓		N/A				N/A	
γ_{A0}					✓	✓		✓
β	✓	✓		✓				
Screening only								
γ_{A0}			N/A		✓	✓	N/A	✓
γ_{I0}						✓		
β	✓	✓		✓				
ϕ					✓			✓
ζ					✓			✓
Vaccine only								
γ_{A0}					✓ ✓	✓	✓ ✓	✓ ✓
β	✓ ✓	✓ ✓	✓ ✓	✓ ✓				
ρ					✓ ✓			✓ ✓
q			✓ ✓					
γ_{V0}							✓	
γ_{I0}						✓		
Vaccine and screening								
γ_{I1}	✓							
γ_{I0}						✓ ✓		
γ_{A0}					✓ ✓			✓
β	✓ ✓	✓ ✓	✓ ✓	✓ ✓				
q			✓ ✓					
ζ					✓ ✓		✓	✓ ✓
ϕ					✓			✓

Table 2.10: Summary of the PRCC results for Eq.'s (2.1)-(2.4). Analysis using the DFE as the initial conditions are shown in red.

free equilibrium point as the initial conditions and the other starting at $S(0) = N - 1$ and $A_0(0) = 1$. While the PRCC results were very similar between the two runs, there were some differences. These are summarized in the following list:

- With respect to the I_0 class, the regression rate, γ_{A0}, is only significant when the initial conditions are those where $S = N$.
- The regression rate, γ_{V0}, has a negative significance in relation to the total HPV positive, vaccinated (V_0) population when the initial conditions are those of the DFE.
- The regression rate, γ_{I0}, has a negative significance with respect to the total HPV positive (I_0) population when the initial conditions are the DFE.

With respect to the screening and vaccination model the following differences between the two runs were found:

- The regression rate, γ_{A0}, has a negative significance with respect to the cancer class when the initial conditions are $S = N$
- The screening sensitivity, ϕ, is only significant when $S = N$ with respect to the HPV positive (A_0) and cancer quantities.
- The regression rate γ_{I1} has a positive significance only when the initial conditions are those of the DFE.

These results are significant as it shows that the various initial conditions will have a slight difference on the outcome of the simulation in terms of parameter significance. This is an important result as it relates to the socio-economic state of the region in question. If one were to implement a vaccination/screening program into a more developed country such as Canada, the initial conditions would be different than those of a developing country such as Nepal, where a very low percentage of individuals will be vaccinated at the start of the program.

The second aspect to consider is that of the type of program implemented. The above four models represent three different possible programs. For example, in a screening only program, screening will be significant to minimizing the effects of HPV (and likewise for vaccination programs where, q, the effect of the vaccine's neutralizing antibodies, and ρ, the vaccine uptake, are significant). However, it is not so clear what will be the most significant

aspect in a mixed strategy program. Here, the screening sensitivity, ϕ, and the proportion of individuals screened, ζ, are significant. Both of these parameters are related to screening. Here ρ, the vaccine uptake, is not significant at all. However, q, the effect of the neutralizing antibodies is significant (less so than the screening parameters).

To conclude, while a mixed strategy is clearly beneficial in terms of lowering R_0, it is important to understand the individual factors that contribute to this reduction in R_0. From this study, both screening and vaccination play a part in minimizing the effects of HPV. While vaccination prevents HPV infection, it is costly and most effective before infection. Screening itself does not prevent or lower the effects of HPV. However, the knowledge that the individual is infected will enable him/her to treat the infection, decreasing the severity of the lesion in question, which, in turn increases the regression rate. This is important as it will cause an immediate response in the health care system, while the effects of vaccination will only be seen much later.

3 Co-screening models

3.1 Introduction

HPV treatment and prevention is a complicated matter with many different aspects. This chapter will examine various screening techniques, including that of co-screening, which means re-screening individuals whose initial screening results are positive.

There are many different methods for screening of HPV and its progressive stages. Each method has a specific sensitivity and specificity. This allows for the chance of false positives and false negatives. See Table 1.2 in Section 1.3 for a list of various screening methods and their properties.

Different countries employ different screening guidelines. These guidelines can vary throughout the country by province or state. Table 3.1 summarizes the screening programs for a selection of countries.

While a screening method may result in an HPV positive reading, sometimes it may be more cost efficient and clinically efficient to perform a second test to confirm this result, instead of treating the individual straight away [36]. The first test would be a general test whereas the second one would be a more specific test. This way only individuals with a high risk type of HPV will receive treatment. This decreases the chance of treating false positives which can be a costly exercise both in terms of money and resources. Various models have been used to examine the effect/logic of double testing individuals who test positive the first time. These include articles by Goldie et al. [27], Mandelblatt et al. [49], and Kulasingam et al. [43].

This chapter contains four different models to study the concept of co-screening, ie. re-screening and treating individuals who were screened positive with a "basic" screening test,

from a costing point of view, as well as, analytically and epidemiologically.

A set of parameters from the ranges found in Table 2.2 in Section 2.3 will be used to conduct numerical simulations (and can be found in Table 6.2 in the appendix). One of the purposes of the chapter is to compare the various screening techniques. Hence, the model ignores variation in the screening sensitivity, ϕ, by keeping it constant.

	Country	Age to screen	Screening strategy	Repetitions of screening	Comments
North America	United States	From 30 years old	Co-testing with PAP/ cytology (HC2)	Every 5 years	
			Cytology	Every 3 years	
	Canada (Ontario)	From 30 years of age	HPV test followed by cytology if the first test is positive	Every five years if HPV test is negative until age of 65	
		21-29 years old	Cytology	Every three years	
Europe	Italy	From 30 years of age	HPV testing for management of ASC-US		
			HPV testing as a follow up after treatment of CIN2/3 as screening instead of cytology		For positive screening, HPV tests or cytology are to be used as a follow up test
	Spain	From the age of 35 years	Co-testing	Every 5 years	
Asia	China		Pap smear or VIA		There is no country wide cervical cancer screening program. There have been various pilot projects such as the ones mentioned here
	India		VIA or HPV screening		There is no country wide cervical cancer screening program. There have been various pilot projects such as the ones mentioned here
Afirca	South Africa	From 30 years of age	HPV DNA testing or cytology (where they exist and are functional)	Every 10 years	

Table 3.1: Screening guidelines in selected countries [10]

3.2 Model

The models track individuals in compartments related to susceptible and disease stages. The disease stages include infected individuals who are unaware of their disease status (A_n), as well as individuals who are aware of their disease status through screening (I_n). In the case that an individual's infection does not regress, it may progress to the pre-cancer (CIN3) stage (C_1 compartment) or to the cancer compartment (C_2).

3.2.1 Equations

The equations that represent the screen and treat model are:

$$\begin{aligned}
S' &= \lambda + \gamma_{A0}A_0 - \tfrac{F_\beta S}{N} - dS \\
A_0' &= \tfrac{F_\beta S}{N} + \gamma_{A1}A_1 - (\gamma_{A0} + \alpha_{A0} + \phi\zeta + d)A_0 \\
A_1' &= \alpha_{A0}A_0 + \gamma_{A2}A_2 - (\gamma_{A1} + \alpha_{A1} + \phi\zeta + d)A_1 \\
A_2' &= \alpha_{A1}A_1 - (\gamma_{A2} + \alpha_{A2} + \phi\zeta + d)A_2 \\
C_1' &= \alpha_{A2}A_2 - (\alpha_{C1} + \gamma_{C1} + d)C_1 \\
C_2' &= \alpha_{C1}C_1 - (d + \delta)C_2 \\
I_{0p}' &= \phi\zeta A_0 - (\kappa + d)I_{0p} \\
I_{1p}' &= \phi\zeta A_1 - (\kappa + d)I_{1p} \\
I_{2p}' &= \phi\zeta A_2 - (\kappa + d)I_{2p} + \gamma_{C1}C_1 \\
R' &= (I_{0p} + I_{1p} + I_{2p})\kappa - dR \\
\\
F_\beta &= \beta((A_0 + A_1 + A_2) + q_{Ip}(I_{0p} + I_{1p} + I_{2p}))
\end{aligned} \tag{3.1}$$

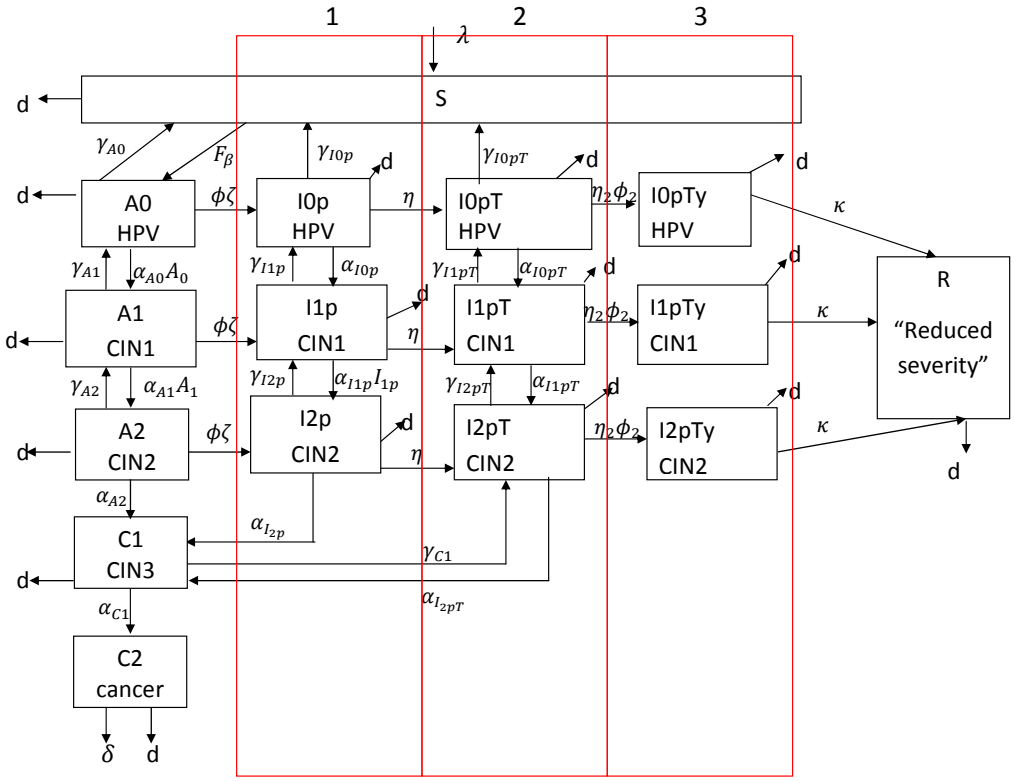


Figure 3.1: Flow diagram for Eq.'s (3.1)-(3.4). This diagram summarizes four different models. The first model, corresponding to Eq.(3.1), consists of the base model (unboxed) as well as the enclosed space 1. The second model, corresponding to Eq.(3.2) consists of the base model as well as the enclosed spaces 1 and 2. The third model, corresponding to Eq.(3.3) consists of the base model as well as enclosed spaces 1,2,and 3. Finally,in the last model, the base model is used as well as the enclosed spaces 1 and 3, however, here, the compartments in box 1 are entitled I_{npap} instead of I_{np}.

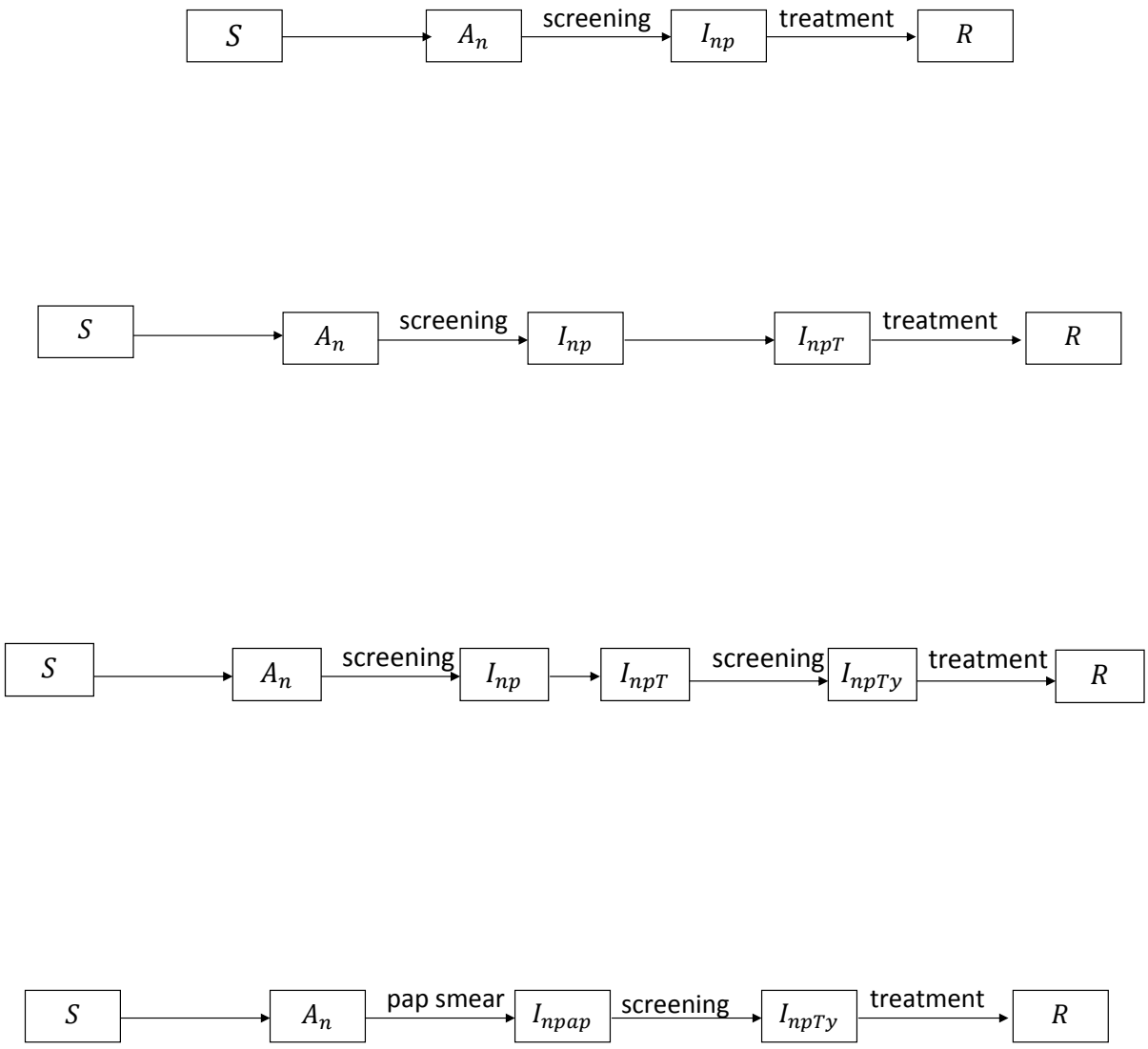


Figure 3.2: This figure summarizes Eq.'s (3.1)-(3.4). The top panel represents the model involving a single screening test where all individuals who are screened positive are treated. The second panel represents the model in which there is a single screening event where all individuals infected with a carcinogenic type of HPV are treated. The third panel represents the co-screening model where the first test is HC2 followed by cobas4800 for all positively screened individuals. The final panel represents the co-screening model where the first screening event uses a pap smear followed by cobas4800 for all positively screened individuals

The equations that represent the model in which only those individuals who have a high risk type of HPV are treated are:

$$
\begin{aligned}
S' &= \lambda + \gamma_{A0}A_0 + \gamma_{I0p}I_{0p} - \tfrac{F_\beta S}{N} - dS \\
A_0' &= \tfrac{F_\beta S}{N} + \gamma_{A1}A_1 - (\gamma_{A0} + \alpha_{A0} + \zeta\phi + d)A_0 \\
A_1' &= \alpha_{A0}A_0 + \gamma_{A2}A_2 - (\gamma_{A1} + \alpha_{A1} + \phi\zeta + d)A_1 \\
A_2' &= \alpha_{A1}A_1 - (\gamma_{A2} + \alpha_{A2} + \phi\zeta + d)A_2 \\
C_1' &= \alpha_{A2}A_2 + \alpha_{I2p}I_{2p} - (\alpha_{C1} + \gamma_{C1} + d)C_1 \\
C_2' &= \alpha_{C1}C_1 - (d + \delta)C_2 \\
I_{0p}' &= \phi\zeta A_0 + \gamma_{I1p}I_{1p} - (\gamma_{I0p} + \alpha_{I0p} + \eta + d)I_{0p} \\
I_{1p}' &= \phi\zeta A_1 + \gamma_{I2p}I_{2p} + \alpha_{I0p}I_{0p} - (\gamma_{I1p} + \alpha_{I1p} + \eta + d)I_{1p} \\
I_{2p}' &= \phi\zeta A_2 + \alpha_{I1p}I_{1p} - (\gamma_{I2p} + \alpha_{I2p} + \eta + d)I_{2p} \\
I_{0pT}' &= \eta I_{0p} - (\kappa + d)I_{0pT} \\
I_{1pT}' &= \eta I_{1p} - (\kappa + d)I_{1pT} \\
I_{2pT}' &= \eta I_{2p} + \gamma_{C1}C_1 - (\kappa + d)I_{2pT} \\
R' &= (I_{0pT} + I_{1pT} + I_{2pT})\kappa - dR
\end{aligned}
\qquad (3.2)
$$

$$
\begin{aligned}
F_\beta = \; & \beta((A_0 + A_1 + A_2) + q_I p(I_{0p} + I_{1p} + I_{2p}) \\
& + q_{IpT}(I_{0pT} + I_{1pT} + I_{2pT}))
\end{aligned}
$$

The equations that represent the model in which there is co-screening with HC2 and cobas4800 are:

$$
\begin{aligned}
S' &= \lambda + \gamma_{A0}A_0 + \gamma_{I0p}I_{0p} + \gamma_{I0pT}I_{0pT} - \tfrac{F_\beta S}{N} - dS \\
A_0' &= \tfrac{F_\beta S}{N} + \gamma_{A1}A_1 - (\gamma_{A0} + \alpha_{A0} + \zeta\phi + d)A_0 \\
A_1' &= \alpha_{A0}A_0 + \gamma_{A2}A_2 - (\gamma_{A1} + \alpha_{A1} + \phi\zeta + d)A_1 \\
A_2' &= \alpha_{A1}A_1 - (\gamma_{A2} + \alpha_{A2} + \phi\zeta + d)A_2 \\
C_1' &= \alpha_{A2}A_2 + \alpha_{I2p}I_{2p} + \alpha_{I2pT}I_{2pT} - (\alpha_{C1} + \gamma_{C1} + d)C_1 \\
C_2' &= \alpha_{C1}C_1 - (d + \delta)C_2 \\
I_{0p}' &= \phi\zeta A_0 + \gamma_{I1p}I_{1p} - (\gamma_{I0p} + \alpha_{I0p} + \eta + d)I_{0p} \\
I_{1p}' &= \phi\zeta A_1 + \gamma_{I2p}I_{2p} + \alpha_{I0p}I_{0p} - (\gamma_{I1p} + \alpha_{I1p} + \eta + d)I_{1p} \\
I_{2p}' &= \phi\zeta A_2 + \alpha_{I1p}I_{1p} - (\gamma_{I2p} + \alpha_{I2p} + \eta + d)I_{2p} \\
I_{0pT}' &= \eta I_{0p} + \gamma_{I1pT}I_{1pT} - (\gamma_{I0pT} + \alpha_{I0pT} + \eta_2\phi_2 + d)I_{0pT} \\
I_{1pT}' &= \eta I_{1p} + \gamma_{I2pT}I_{2pT} + \alpha_{I0pT}I_{0pT} - (\gamma_{I1pT} + \alpha_{I1pT} + \eta_2\phi_2 + d)I_{1pT} \\
I_{2pT}' &= \eta I_{2p} + \alpha_{I1pT}I_{1pT} + \gamma_{C1}C_1 - (\gamma_{I2pT} + \alpha_{I2pT} + \eta_2\phi_2 + d)I_{2pT} \\
I_{0pTy}' &= \eta_2\phi_2 I_{0pT} - (\kappa + d)I_{0pTy} \\
I_{1pTy}' &= \eta_2\phi_2 I_{1pT} - (\kappa + d)I_{1pTy} \\
I_{2pTy}' &= \eta_2\phi_2 I_{2pT} - (\kappa + d)I_{2pTy} \\
R' &= (I_{0pTy} + I_{1pTy} + I_{2pTy})\kappa - dR
\end{aligned}
\tag{3.3}
$$

$$
\begin{aligned}
F_\beta = {} & \beta((A_0 + A_1 + A_2) + q_I p(I_{0p} + I_{1p} + I_{2p}) + q_{IpT}(I_{0pT} + I_{1pT} + I_{2pT}) \\
& + q_{IpTy}(I_{0pTy} + I_{1pTy} + I_{2pTy}))
\end{aligned}
$$

The equations that represent co-testing with a pap smear and cobas4800 are:

$$\begin{aligned}
S' &= \lambda + \gamma_{A0}A_0 + \gamma_{I0pap}I_{0pap} - \tfrac{F_\beta S}{N} - dS \\
A_0' &= \tfrac{F_\beta S}{N} + \gamma_{A1}A_1 - (\gamma_{A0} + \alpha_{A0} + \zeta\phi_{1a} + d)A_0 \\
A_1' &= \alpha_{A0}A_0 + \gamma_{A2}A_2 - (\gamma_{A1} + \alpha_{A1} + \phi_{1a}\zeta + d)A_1 \\
A_2' &= \alpha_{A1}A_1 - (\gamma_{A2} + \alpha_{A2} + \phi_{1b}\zeta + d)A_2 \\
C_1' &= \alpha_{A2}A_2 + \alpha_{I2pap}I_{2pap} - (\alpha_{C1} + \gamma_{C1} + d)C_1 \\
C_2' &= \alpha_{C1}C_1 - (d + \delta)C_2 \\
I_{0pap}' &= \phi_{1a}\zeta A_0 + \gamma_{I1pap}I_{1pap} - (\gamma_{I0pap} + \alpha_{I0pap} + \phi_2\eta + d)I_{0pap} \\
I_{1pap}' &= \phi_{1a}\zeta A_1 + \gamma_{I2pap}I_{2pap} + \alpha_{I0pap}I_{0pap} - (\gamma_{I1pap} + \alpha_{I1pap} + \phi_2\eta + d)I_{1pap} \\
I_{2pap}' &= \phi_{1b}\zeta A_2 + \alpha_{I1pap}I_{1pap} - (\gamma_{I2pap} + \alpha_{I2pap} + \phi_2\eta + d)I_{2pap} \\
I_{0pTy}' &= \phi_2\eta I_{0pap} - (\kappa + d)I_{0pTy} \\
I_{1pTy}' &= \phi_2\eta I_{1pap} - (\kappa + d)I_{1pTy} \\
I_{2pTy}' &= \phi_2\eta I_{2pap} + \gamma_{C1}C_1 - (\kappa + d)I_{2pTy} \\
R' &= (I_{0pTy} + I_{1pTy} + I_{2pTy})\kappa - dR \\
F_\beta &= \beta((A_0 + A_1 + A_2) + q_I p(I_{0pap} + I_{1pap} + I_{2pap}) + q_{IpT}(I_{0pTy} + I_{1pTy} + I_{2pTy}))
\end{aligned} \tag{3.4}$$

Figure 3.1 represents the flow diagram for four different models, each of which represents a different screening scenario. The unboxed area is common to Eq.'s (3.1)-(3.4). Each model is summarized in Figure 3.2.

The first model, which involves treating all infected individuals (Eq.(3.1)) corresponds to Section 1 in Figure 3.1. Eq.(3.2) corresponds to Sections 1 and 2 of Figure 3.1 and involves treating only those individuals who have a carcinogenic type of HPV. These individuals know their disease status through one screening event. The third model, corresponding to Eq.(3.3) and Sections 1,2, and 3 on Figure 3.1, involves co-screening infected individuals with HC2 and cobas4800 screening tests. Only high risk individuals are treated. Eq.(3.4) corresponds to Sections 1 and 3 on Figure 3.1. This model consists of co-screening with a pap smear, as well as, cobas4800. Only high risk individuals are treated.

Eq.'s (3.1)-(3.4) include the following assumptions:

- A 10% screening rate, ϕ.

- The general screening test is HC2 with a sensitivity of 90.4%. This test tests for both high and low risk HPV types.
- The specific screening test is cobas4800 (with a sensitivity of 89.9%) as it has the capability to specifically check for HPV types 16/18.
- The sensitivity of the pap smear for HPV and CIN1 is: 45% and 69% for CIN2.
- $q_{Ip} = q_{IpT} = q_{IpTy}$. Since all of the individuals in these classes are diligent enough to get screened, it is assumed that there will be little difference in how they act once they know their infection status.

3.3 Parameters

The variables and parameters that will be used in this chapter can be found in Table 3.2. These include multiple infected stages, $A_n, I_{np}, I_{npT}, I_{npTy}, I_{npap}$, and C_n, as well as, a susceptible class, S. The different I_n classes represent a different "infection status", however, all of the I_n classes are aware of their infection status. The A_n class is unaware of their infection status. The "R" class, the reduced severity class, represents individuals who have been treated and whose infection is therefore less severe.

A set of parameters created by LHS will be used to calculate the stability of the equilibria as well as the basic reproduction number. These ranges can be found in Table 3.2. The simulations will be run using a fixed parameter set chosen from the LHS set of parameters created with the ranges in Table 3.2. These can be found in Table 6.2 in the appendix. Additional parameters used in the cost analysis can be found in Table 3.2. As costs of these tests differ depending on location, they will be represented here as parameters in US dollars. S represents the cost of a pap smear, T, the cost of treatment, P the cost of a general screening test and Q, the cost of a typing test.

3.4 Results

Numerical and analytical results are presented. Numerical results were run using parameter sets created with Latin Hypercube Sampling, except for the simulations, in which a fixed parameter set was used. Parameter values from Table 3.2 were considered.

Term	Definition	Range	Reference
T	Cost of treating the lesion ($)		
P	Cost of a general screening test (assumed to be HC2)($)		
Q	Cost of a more specific, typing test (assumed to be Cobas 4800) ($)		
S	Cost of a pap smear ($)		
S	Susceptible individuals		
A_n	Infected individuals whose disease status is unknown		
I_{np}	Infected individuals who know their "infected" status through one screening event		
I_{npT}	Proportion of the infected individuals who have a high risk type of HPV		
I_{npTy}	Proportion of the infected population with HPV type 16/18		
I_{npap}	Individuals who are aware of their infection status through screening with a pap smear		
C_1	Individuals with pre-cancer, CIN3		
C_2	Individuals with cancer		
R	Individuals who were treated for HPV and are therefore in a "reduced severity" state		
$q_{Ip}, q_{IpT}, q_{IpTy}$	Scaling constant	$[.32 - .72]$	assumed
β	Infection rate	$[.001 - .8](\text{year}^{-1})$	[16, 41, 71, 74]
$\phi, \phi_2, \phi_{1a}, \phi_{1b}$	Screening sensitivity	see Table 1.2	
Cost of screening		$4 - 15$ USD	assumed
d	Natural death rate	68 year^{-1}	[60]
δ	Death due to disease	$\frac{1}{54*12}\text{year}^{-1}$[0-.0998]	[13, 46]
ζ	Proportion of individuals who get screened per year	$0 - 1$ (year^{-1})	assumed
N	Female population of Nepal	13607013	[57]
q	Scaling constant to account for the unknown effect of neutralization antibodies	$[.001 - 1]$	assumed
η, η_2	Proportion of individuals who have a high risk type of HPV	$0 - 1$	assumed
κ	Regression rate due to treatment	$.81 - .945$	[39]
α_n	Progression rate	see Table 2.2	
γ_n	regression rate	see Table 2.2	

Table 3.2: Table of variables used in Eq.'s (3.1)-(3.4).

3.4.1 Analytical results

3.4.1.1 Equilibrium points

Eq.'s (3.1)-(3.4) have the same DFE:

$$(S, A_n, I_{np}, I_{npT}, I_{npTy}, I_{npap}, C_1, C_2, R) = (\tfrac{\lambda}{d}, 0, 0, 0, 0, 0, 0, 0, 0) \tag{3.5}$$

Eq.'s (3.1)-(3.4) are high dimensional, and do not lead to analytical determination of the endemic equilibrium. The endemic equilibrium will be determined numerically.

The stability of the DFE and the endemic equilibrium point is too complex to analyze analytically, hence they will both be analyzed numerically.

3.4.2 Numerical simulations

3.4.2.1 Simulations

A parameter set (found in Table 6.2) generated by Latin Hypercube Sampling, and deemed significant by a correlation plot was used to simulate the model. Throughout all the simulations, the proportion of individuals screened, ζ, was varied to see the effect of screening uptake on the epidemiology of HPV. The following ζ values were used: 1 (everyone gets screened), .5 (half the infected class gets screened), .1 (ten percent of the infected class gets screened), .05 (five percent of the infected class gets screened) and 0 (no one is screened). Figures 3.4- 3.7 show the simulations for the S, A_0, I_{0p}, I_{0pT}, R, and C_2 groups.

In terms of the susceptible simulations, as the S class population decreases, so does the proportion of individuals screened, ζ. Furthermore, when $\zeta \neq 1$, the simulations result in oscillations that decrease in size as ζ decreases. Similar trends can be seen in the HPV positive (A_0) class. In the I_0 and R simulations, there is overlap between the simulations using the intermediate ζ values. Furthermore, ζ values of 0 and 1 give rise to roughly the same population sizes in the I_0 simulations. In terms of the cancerous population, the population size gets larger as the proportion of individuals screened, ζ, gets smaller.

Eq.(3.3) is similar to Eq.'s (3.1) and (3.2), however, there is a greater overlap in the simulations for $\zeta = .5$ and those for $\zeta = .1$ and .05 in the I_{0p}, I_{0pT} and I_{0pTy} classes. Furthermore,

the simulations for the aforementioned classes follow the same trends. The population sizes for I_{0p} are larger than the corresponding population sizes for the I_{0pT} and I_{0pTy} classes, which are the same.

Although the simulations for Eq.(3.4), found in Figure 3.7, are quantitatively similar to the simulations for Eq.(3.2) which can be found in Figure 3.5, the results are different. While the susceptible class follows the same trends in terms of the order of the population size ($\zeta = 1$ gives the largest population size, etc.), there is a larger dip when $\zeta = 1$. Furthermore, there is a larger gap in the population size between the simulations when $\zeta = 1$ and $\zeta = .5$. In the A_0 simulation, there is a larger difference in the population size between the $\zeta = 1$ and $\zeta = .5$ simulations. There is overlap between all the simulations in the I_{0pap} and I_{0pTy} classes. At the equilibrium point however, the same trend is present in the two simulations where the population sizes range in size from largest to smallest for $\zeta = .1, .5, .05, 1$ and 0 respectively. This shows that while the screening program implemented will cause similar end results, they will impact the solutions for the intermediate years (time from implementation until time to the endemic equilibrium) in different ways. As it can take a long time for a system to reach an equilibrium, it is important to choose a screening program based on the short term results, as well as, the long term results.

The cancerous population simulation is the same as that for the previous models, however, there is a larger discrepancy between population sizes at the endemic equilibrium when $\zeta = .1$ and $\zeta = .5$. The most significant difference in the "R" class simulations is that in this model, the population size when the model is run for $\zeta = .5$ is in between that of when $\zeta = .1$ and $\zeta = .05$. Furthermore, the end result of the simulation when $\zeta = 1$ is much larger than in the other models.

3.4.2.2 Basic reproduction number

Numerical methods were used to calculate R_0. Using the parameter ranges found in Table 3.2, 5000 parameter sets were created using Latin Hypercube Sampling. Figure 3.3 shows R_0 with respect to various transmission rates, β, for the different models. $R_0 = 1$ when $\beta \approx .25$, .2, .25 and .2 year^{-1} for Eq.'s (3.1), (3.2), (3.3) and (3.4) respectively, indicating that the type of screening program implemented will have similar effects on the basic reproduction number.

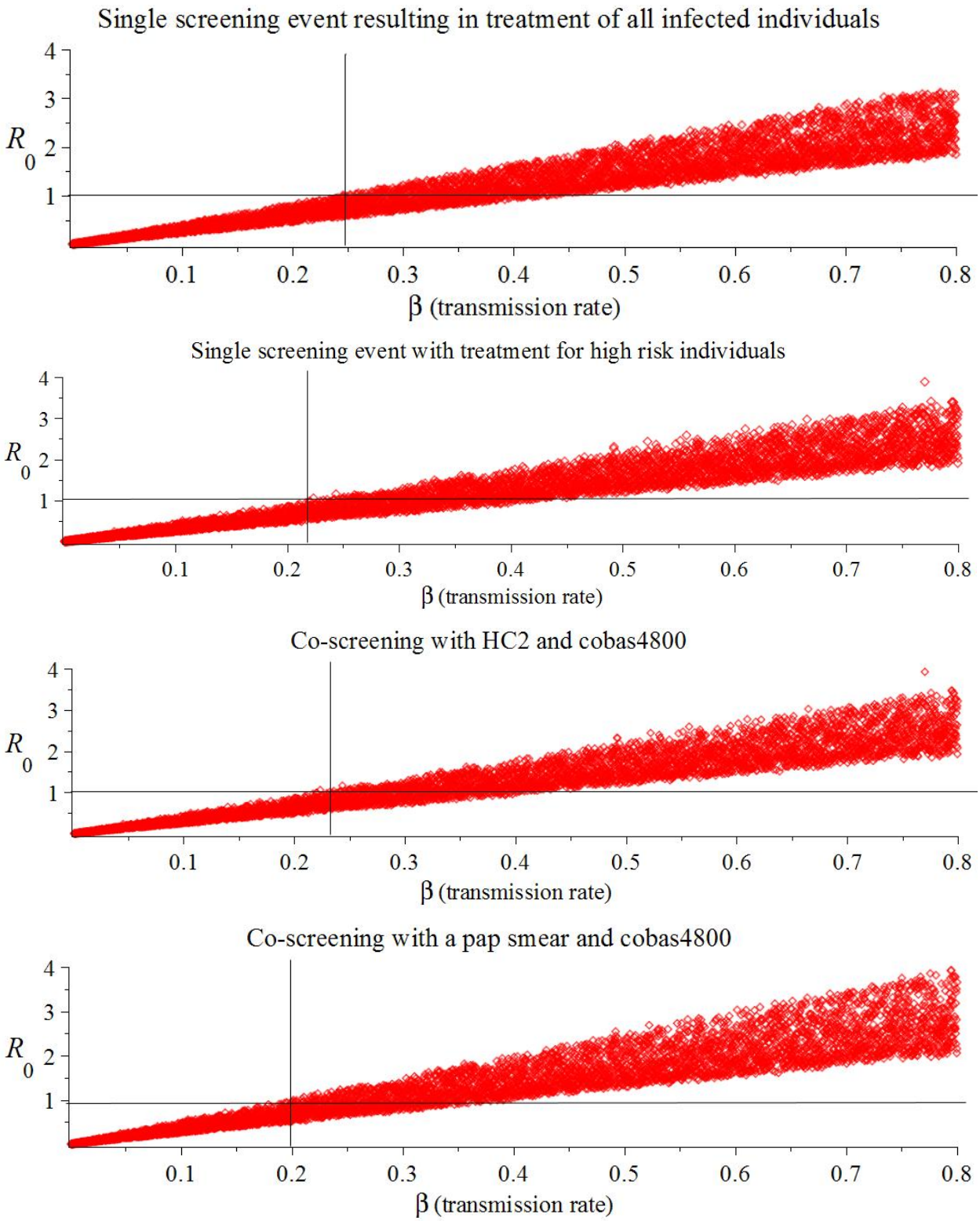


Figure 3.3: Basic reproduction number of 5000 different parameter sets with respect to the transmission rate, β, for Eq.(3.1)-(3.4). The x-axis represents the various transmission rates used to calculate the basic reproduction number. An epidemic will be avoided when $R_0 < 1$. The vertical bar depicts where $R_0 = 1$.

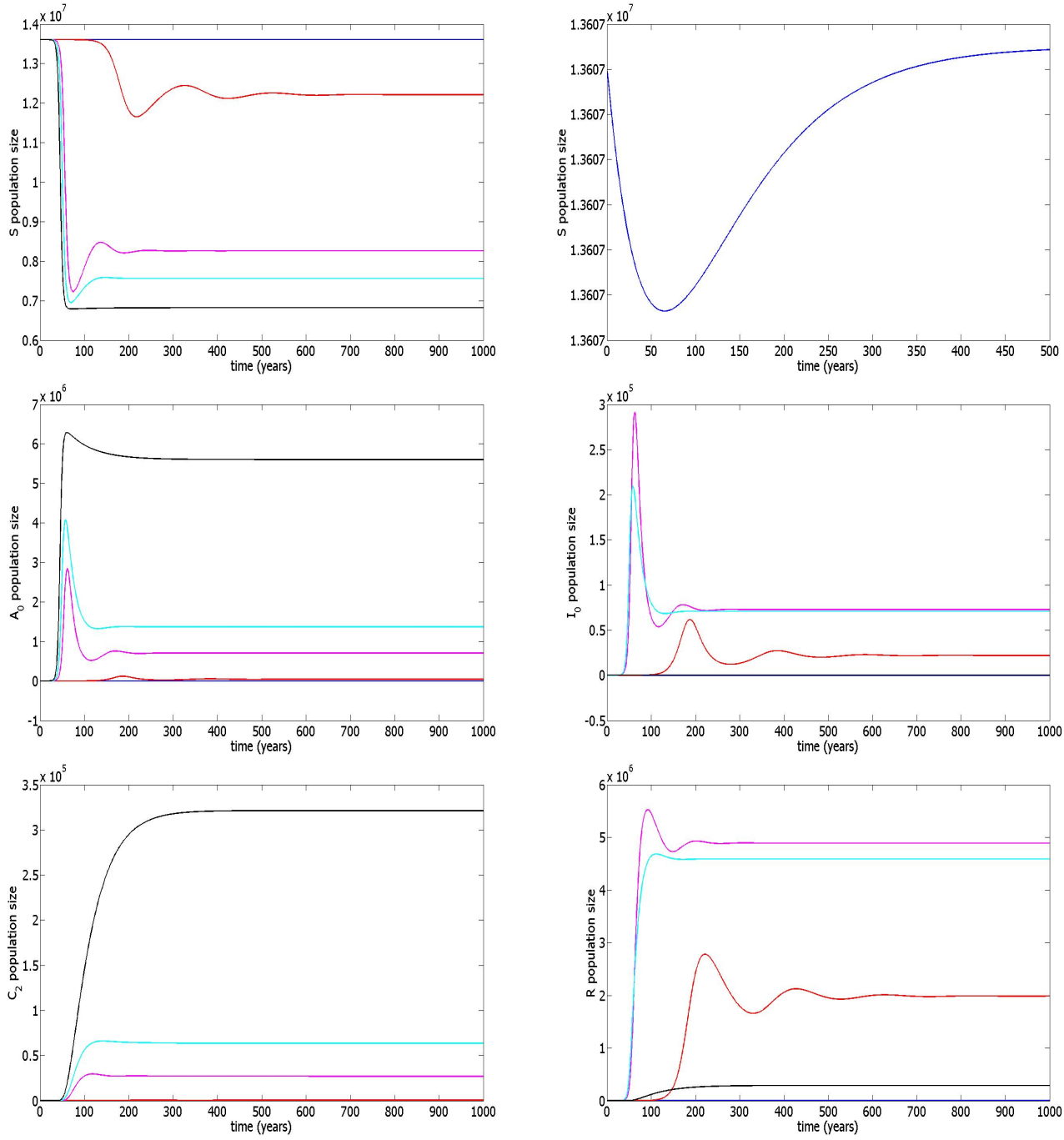


Figure 3.4: Simulations of Eq.(3.1), with a fixed parameter set where all HPV positive individuals are screened. ζ, the proportion of individuals screened, was varied for each of the five simulations.— : $\zeta = 1$, —: $\zeta = .5$, —: $\zeta = .1$, —:$\zeta = .05$ and — $\zeta = 0$.

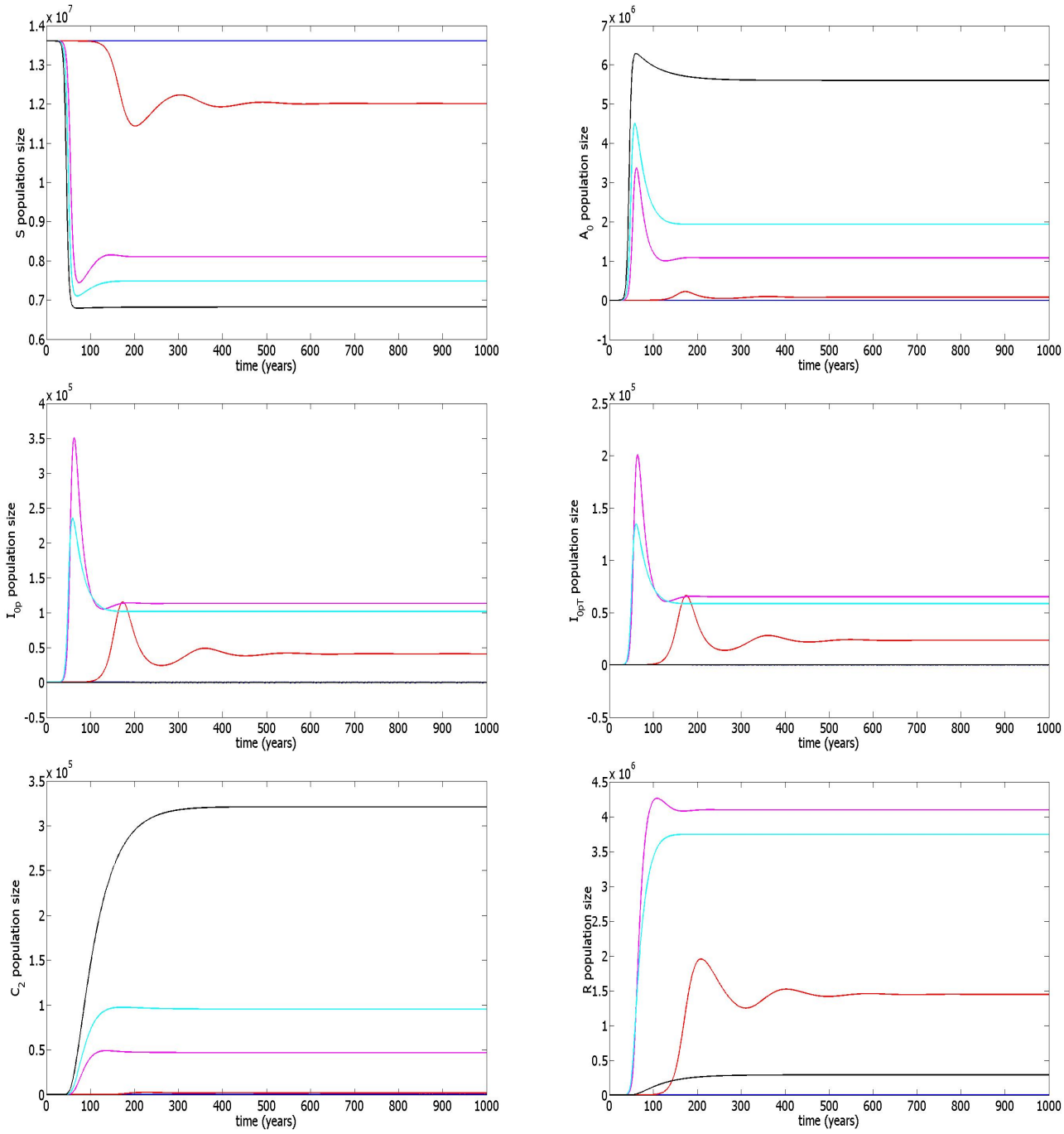


Figure 3.5: Simulation of Eq.(3.2), with a fixed parameter set where only high risk individuals are screened. ζ was varied for each of the five simulations. — : $\zeta = 1$, —: $\zeta = .5$, —: $\zeta = .1$, —:$\zeta = .05$ and — $\zeta = 0$.

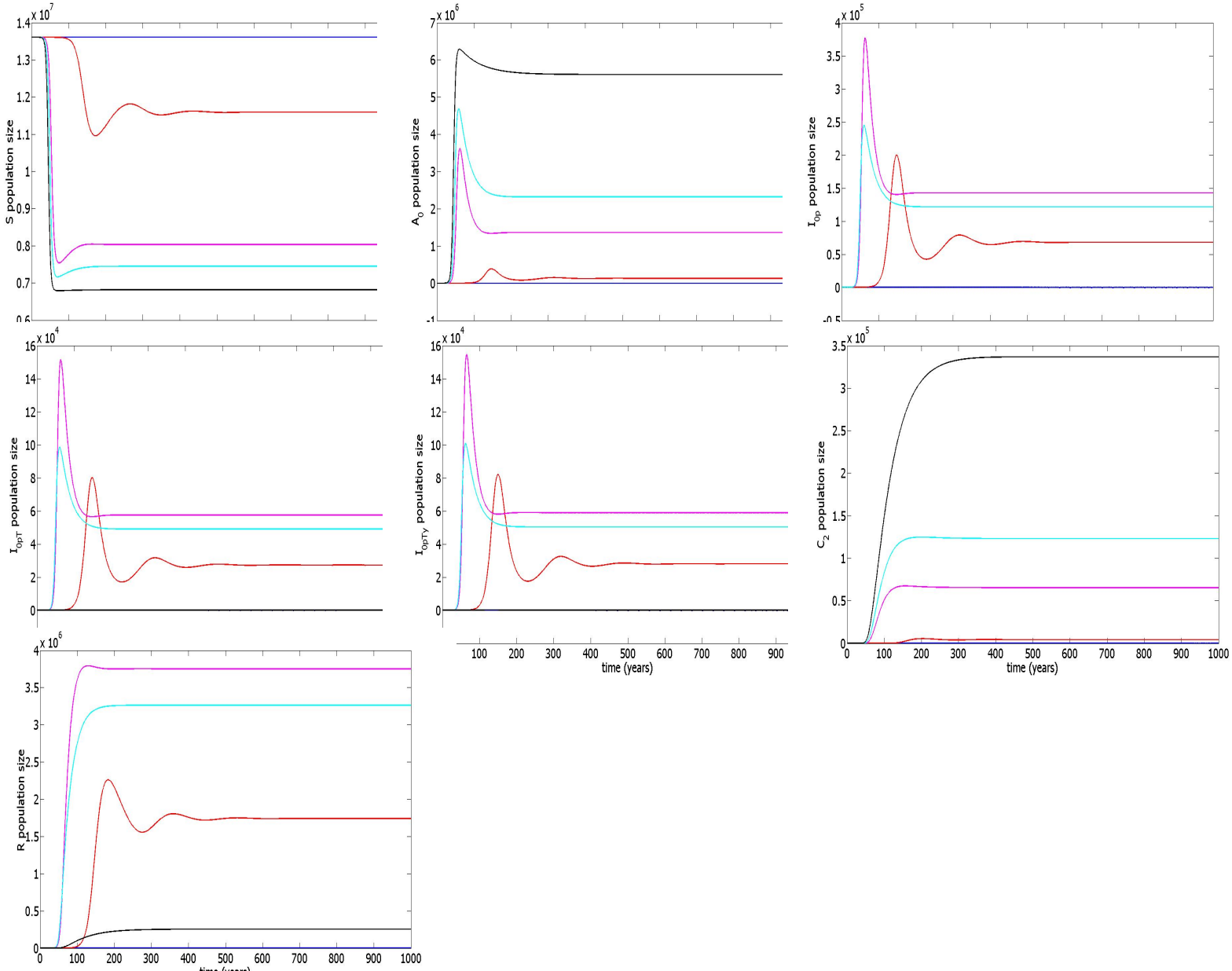


Figure 3.6: Simulation of Eq. (3.3) with a fixed parameter set when co-screening with HC2 and cobas4800 is used. ζ was varied for each of the five simulations. — : $\zeta = 1$, —: $\zeta = .5$, —: $\zeta = .1$, —:$\zeta = .05$ and — $\zeta = 0$.

3.4.2.3 Stability of the equilibria

5000 parameter sets (in which the screening sensitivity was kept constant) were used to analyze the stability of the DFE and the endemic equilibrium point for Eq.'s (3.1)-(3.4). Only those parameters that provided a biologically viable endemic equilibrium point were used.

Figure 3.8 shows the disease free equilibrium point with respect to the basic reproduction number for all four models. The disease free equilibrium point is stable when $R_0 < 1$ and unstable otherwise.

With respect to the endemic equilibrium point, 2920 parameter sets were used to test the stability of Eq.(3.1), 3025 parameter sets were used to test the stability of Eq.(3.2) and 3056 and 3186 parameter sets were used to test the stability of Eq.'s (3.3) and (3.4) respectively. All four models had a stable endemic equilibrium point.

3.4.2.4 Cost analysis

The cost of implementing each program must take two points into consideration:

- The cost of the screening test
- The cost of treating the individual

These costs will differ depending on the country in question, hence a direct cost comparison cannot be completed.

The first model, in which all infected individuals are treated includes the cost of one screening event and treatment. The total cost (denoted by "$cost_{M1}$") can be represented as:

$$cost_{M1} = P\zeta(A_0 + A_1 + A_2) + T(I_{0p} + I_{1p} + I_{2p}) \tag{3.6}$$

Similar to Eq.(3.1), Eq.(3.2) also only consists of one screening event and treatment, however, here, not all infected individuals are treated. Rather, only those who have a high risk type of HPV are treated. Hence, the total cost (denoted by "$cost_{M2}$") of the prevention/screening plan can be represented as:

$$\begin{aligned} cost_{M2} &= P\zeta(A_0 + A_1 + A_2) + T(I_{0pT} + I_{1pT} + I_{2pT}) \\ &= P\zeta(A_0 + A_1 + A_2) + T\eta(I_{0p} + I_{1p} + I_{2p}) \end{aligned} \tag{3.7}$$

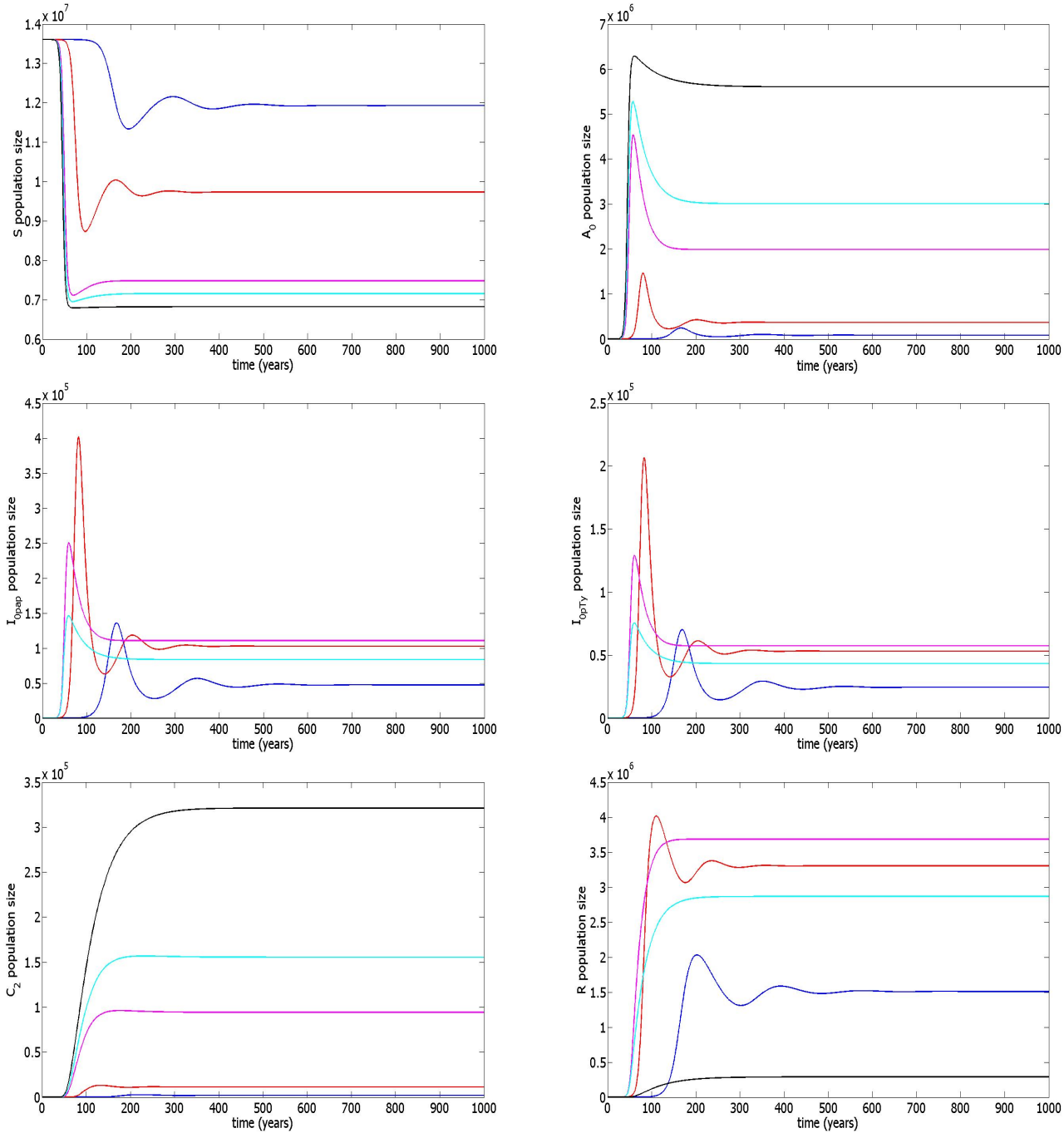


Figure 3.7: Simulation of Eq.(3.4) with a fixed parameter set when co-screening with a pap smear and cobas4800 is used. ζ was varied for each of the five simulations. — : $\zeta = 1$, —: $\zeta = .5$, —: $\zeta = .1$, —:$\zeta = .05$ and — $\zeta = 0$.

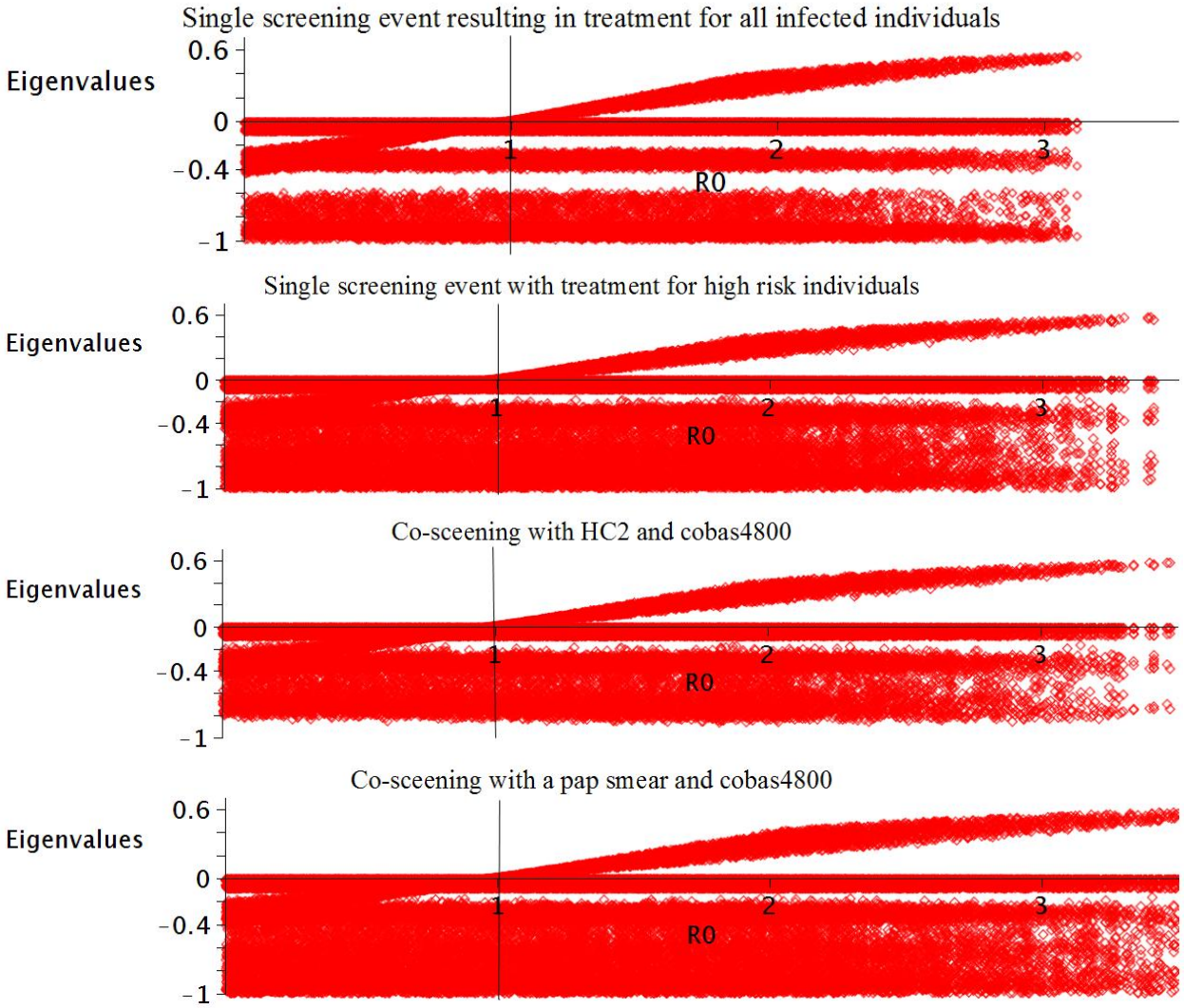


Figure 3.8: Stability of the disease free equilibrium point with respect to the basic reproduction number for Eq.'s (3.1)-(3.4). 5000 parameter sets were used.The x-axis represents the basic reproduction number, while the y-axis represents the eigenvalues of the system. Positive eigenvalues are indicative of an unstable system. The vertical bar depicts $R_0 = 1$.

The final two models, corresponding to Eq.(3.3) and (3.4) both use co-screening (with different sets of screening tests). Hence, the costing here consists of two screening events and treatment. The total cost (denoted by "$cost_{M3}$" and "$cost_{M4}$" respectively) can be written as:

$$\begin{aligned} cost_{M3} &= P\zeta(A_0 + A_1 + A_2) + Q(I_{0pT} + I_{1pT} + I_{2pT}) + T(I_{0pTy} + I_{1pTy} + I_{2pTy}) \\ &= P\zeta(A_0 + A_1 + A_2) + Q\eta(I_{0p} + I_{1p} + I_{2p}) + T(I_{0pTy} + I_{1pTy} + I_{2pTy}) \end{aligned} \tag{3.8}$$

and the cost of Eq.(3.4) can be written as:

$$cost_{M4} = S\zeta(A_0 + A_1 + A_2) + Q(I_{0pap} + I_{1pap} + I_{2pap}) + T(I_{0pTy} + I_{1pTy} + I_{2pTy}) \tag{3.9}$$

A cost comparison of Eq.'s (3.1) and (3.4) is not simple, as most of the parameters are unknown. Tables 3.3 and 3.4 summarize the cost comparison in terms of the relative magnitude of the costing parameters.

The cost comparisons depend on the comparison of various costing parameters, for example, whether or not Q, the cost of a typing test, is larger or smaller than T, the cost of treatment. An example of this can be seen in Figure 3.9, where the HPV prevention plans are implemented at the endemic equilibrium for a fixed set of parameters for Eq.'s (3.1) and (3.2).

Other considerations that influence the cost of the screening program implemented include the amount of individuals infected and the proportion of individuals who have a high risk type of HPV.

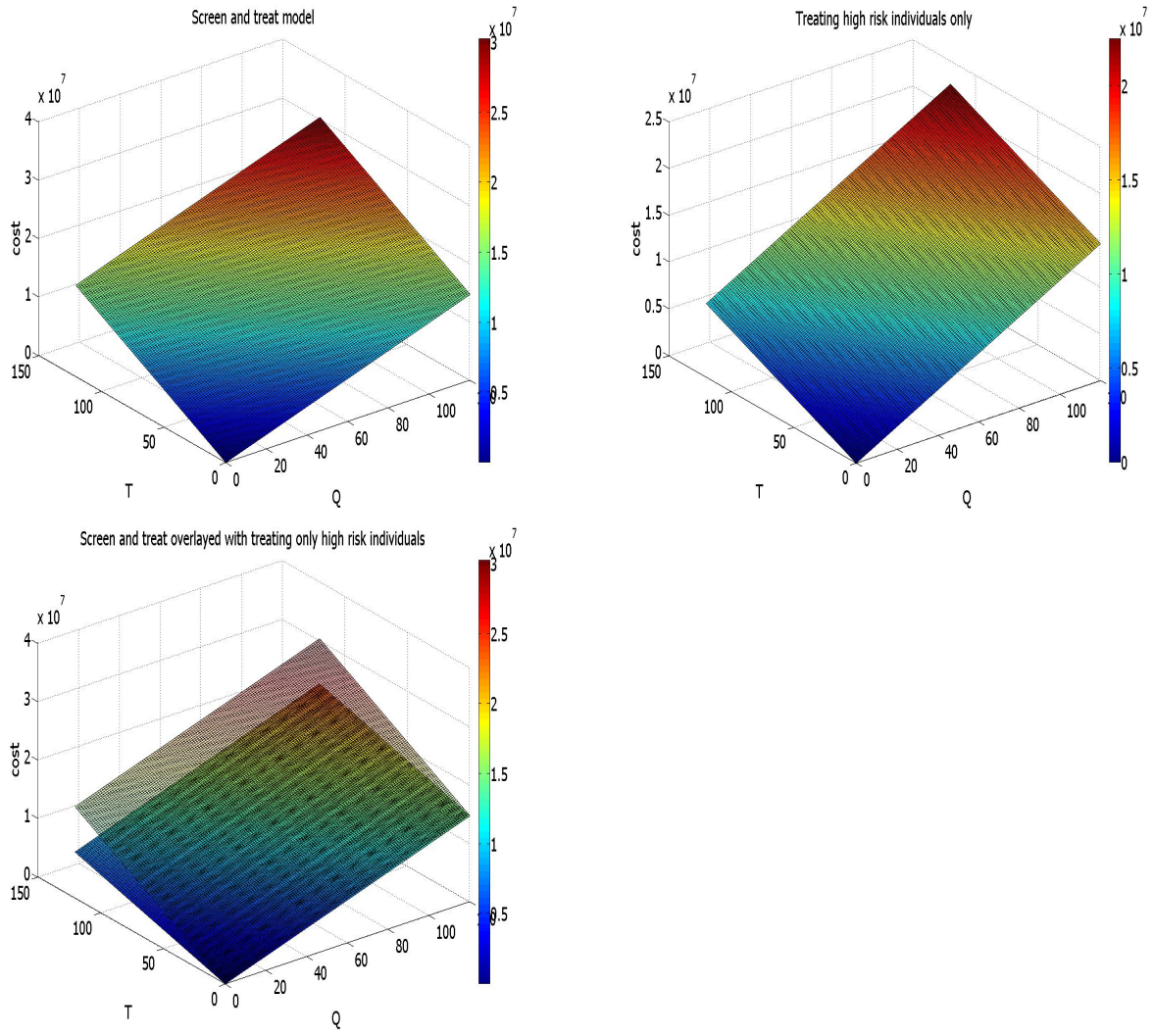


Figure 3.9: Comparison of the screen and treat model (Eq.(3.1)) versus treating high risk individuals only (Eq.(3.2)) in terms of the implementation costs.

Eq.(3.1) vs. Eq.(3.2)		
The model in which only high risk individuals are treated (Eq.(3.2)) will always be less expensive to implement		
Eq.(3.2) vs. Eq.(3.3)		
$Q = T$	$Q < T$	$Q > T$
If $Y > 0$ then $cost_{M3} > cost_{M2}$, otherwise, $cost_{M3} = cost_{M2}$	If $Y = 0$ then $cost_{M3} > cost_{M2}$, otherwise, the relative costs depend on the relationship between T and $\frac{\eta X(T-Q)}{Y}$	$cost_{M3} > cost_{M2}$
Eq.(3.1) vs. Eq.(3.3)		
$Q = T$	$Q < T$	$Q > T$
The relative costs depend on the relationship between Y and $X(1-\eta)$	The relative costs depend on the relationship between T and $\frac{X}{Y}(T - Q\eta)$	The relative costs depend on the relationship between Q and $\frac{T}{\eta}(1 - \frac{Y}{X})$

Table 3.3: Comparison of costs of the models including the following scenarios: screen and treat (Eq.(3.1)), screen and treat only high risk individuals (Eq.(3.2)), and co-screening with HC2 and cobas4800 (Eq.(3.3)). Here, $X = \sum_{n=0}^{2} I_{np}, Y = \sum_{n=0}^{2} I_{npTy}$.

<table>
<tr><td colspan="4">Eq.(3.1) vs. Eq.(3.4)</td></tr>
<tr><td colspan="4">If $P = S$</td></tr>
<tr><td colspan="2">If $Q = T$</td><td colspan="2">If $Q \neq T$</td></tr>
<tr><td>If $Z = X$</td><td>If $Z < X$</td><td>If $Z = X$</td><td>If $Z < X$</td></tr>
<tr><td>$cost_{M4} > cost_{M1}$</td><td>Depends on the size of TZ in relation to $T(X - Y)$</td><td>$cost_{M4} > cost_{M1}$</td><td>Depends on the size of Z in relation to $\frac{T}{Q}(X-Y)$</td></tr>
<tr><td colspan="4">If $P < S$</td></tr>
<tr><td colspan="2">If $Z = X$</td><td colspan="2">If $Z < X$</td></tr>
<tr><td>If $Q \geq T$</td><td>If $Q < T$</td><td>$Q = T$</td><td>$Q \neq T$</td></tr>
<tr><td>$cost_{M4} > cost_{M1}$</td><td>Depends on parameter sizes</td><td>$cost_{M4} > cost_{M1}$</td><td>Depends on parameter sizes</td></tr>
<tr><td colspan="4">If $P > S$</td></tr>
<tr><td colspan="4">Depends on the size of QZ in relation to $\zeta A(P - S) + T(X - Y)$</td></tr>
<tr><td colspan="4">Eq.(3.4) vs. Eq.(3.3)</td></tr>
<tr><td colspan="4">If $P = S$</td></tr>
<tr><td colspan="2">If $Z = X$</td><td colspan="2">If $X > Z$</td></tr>
<tr><td colspan="2">$cost_{M4} > cost_{M3}$</td><td colspan="2">Depends on the size of ηX with respect to Z</td></tr>
<tr><td colspan="4">If $P < S$</td></tr>
<tr><td colspan="2">If $Z = X$</td><td colspan="2">If $X > Z$</td></tr>
<tr><td colspan="2">$cost_{M4} > cost_{M3}$</td><td colspan="2">Depends on parameter sizes</td></tr>
<tr><td colspan="4">If $P > S$</td></tr>
<tr><td colspan="2">If $Z = X$</td><td colspan="2">If $X > Z$</td></tr>
<tr><td colspan="4">Depends on parameter sizes</td></tr>
<tr><td colspan="4">Eq.(3.4) vs. Eq.(3.2)</td></tr>
<tr><td colspan="4">If $P = S$</td></tr>
<tr><td colspan="2">$Q = T$</td><td colspan="2">$Q \neq T$</td></tr>
<tr><td>If $Z = X$</td><td>If $Z < X$</td><td>If $Z = X$</td><td>If $Z < X$</td></tr>
<tr><td>$cost_{M4} > cost_{M2}$</td><td>Depends on parameter sizes</td><td>If $Q < T$ then it depends on parameter sizes. Otherwise, $cost_{M4} > cost_{M2}$</td><td>Depends on the magnitude of η</td></tr>
<tr><td colspan="4">$P < S$</td></tr>
<tr><td colspan="2">$Q = T$</td><td colspan="2">$Q \neq T$</td></tr>
<tr><td>If $Z = X$</td><td>If $Z < X$</td><td>If $Z = X$</td><td>If $Z < X$</td></tr>
<tr><td>$cost_{M4} > cost_{M2}$</td><td>Depends on the magnitude of η</td><td colspan="2">Depends on the magnitude of η</td></tr>
<tr><td colspan="4">$P > S$</td></tr>
<tr><td colspan="2">$Q = T$</td><td colspan="2">$Q \neq T$</td></tr>
<tr><td>If $Z = X$</td><td>If $Z < X$</td><td>If $Z = X$</td><td>If $Z < X$</td></tr>
<tr><td colspan="4">Depends on the magnitude of η</td></tr>
</table>

Table 3.4: Comparison of costs of Eq.'s (3.1)-(3.3) with the co-screening model using a pap smear and cobas4800 (Eq.(3.4)). Here, $X = \sum_{n=0}^{2} I_{np}, Y = \sum_{n=0}^{2} I_{npTy}, A = \sum_{n=0}^{2} A_n$ and $Z = \sum_{n=0}^{2} I_{npap}$.

3.5 Discussion

This chapter is comprised of four different models. The first model, corresponding to Eq.(3.1) is a simple model where everyone who is aware that they are infected (after one screening event) is treated, regardless of HPV type. In the second model corresponding to Eq.(3.2), only those individuals who have a carcinogenic type of HPV receive treatment. The third and least simplistic model, corresponding to Eq.(3.3) involves co-screening with HC2 and cobas4800 and treating only those individuals who have HPV types 16/18. The final model, corresponding to Eq.(3.4) uses a general pap smear to test individuals initially and a more specific test (cobas4800) to find and treat those individuals with HPV types 16/18. Each prevention plan gives rise to a different overall cost that is both model dependent and country dependent. The goal of this chapter is to compare screening techniques, both epidemiologically and through a cost analysis.

Numerical methods were used to analyze the basic reproduction number and the stability of the disease free and endemic equilibrium of Eq.'s (3.1)-(3.4). All four models follow the expected stability of a forward, transcritical bifurcation, which means that all four models' disease free equilibrium points are stable when $R_0 < 1$, and unstable otherwise. The endemic equilibrium point for all four models is stable.

Table 3.5 summarizes the outcomes of the analytical analysis for all four models. The required transmission rate, β, so that $R_0 = 1$ is relatively similar throughout the four models (for a 10% screening rate). Although this screening rate may or may not be realistic, the result is significant as it shows that implementation of any screening program regardless of the strategy will cause similar effects in the outcome of the predicted R_0. There is, however, no consensus in literature on the value for the basic reproduction number. As mentioned in Section 1.4.2, some authors calculate it to be greater than 1 while others calculate it to be

	Screen and treat model (Eq.(3.1))	**Treatment of high risk individuals only (Eq.(3.2))**	**Co-screening with HC2 and cobas4800 (Eq.(3.3))**	**Co-screening with a pap smear and cobas4800 (Eq.(3.4))**
β	$\approx .25$	$\approx .2$	$\approx .25$	$\approx .2$

Table 3.5: Summary of the transmission rates, β, when $R_0 = 1$ for Eq.'s (3.1)-(3.4).

	Cost of screening
$cost_{M1}$	$P\zeta(A_0 + A_1 + A_2) + T(I_{0p} + I_{1p} + I_{2p})$
$cost_{M1}alt$	$P\zeta(A_0 + A_1 + A_2) + T(I_{1p} + I_{2p})$
$cost_{M2}$	$P\zeta(A_0 + A_1 + A_2) + T\eta(I_{0p} + I_{1p} + I_{2p})$
$cost_{M2}alt$	$P\zeta(A_0 + A_1 + A_2) + T\eta(I_{1p} + I_{2p})$
$cost_{M3}$	$P\zeta(A_0 + A_1 + A_2) + Q\eta(I_{0p} + I_{1p} + I_{2p}) + T(I_{0pTy} + I_{1pTy} + I_{2pTy})$
$cost_{M3}alt$	$P\zeta(A_0 + A_1 + A_2) + Q\eta(I_{1p} + I_{2p}) + T(I_{1pTy} + I_{2pTy})$
$cost_{M4}$	$S\zeta(A_0 + A_1 + A_2) + Q(I_{0pap} + I_{1pap} + I_{2pap}) + T(I_{0pTy} + I_{1pTy} + I_{2pTy})$
$cost_{M4}alt$	$S\zeta(A_0 + A_1 + A_2) + Q(I_{1pap} + I_{2pap}) + T(I_{1pTy} + I_{2pTy})$

Table 3.6: Summary of the cost functions for Eq.'s (3.1)-(3.4). $cost_{M1}$ represents the cost function for Eq.(3.1), $cost_{M2}$ represents the cost function for Eq.(3.2), $cost_{M3}$ represents the cost function for Eq.(3.3), and $cost_{M4}$ represents the cost function for Eq.(3.4). The $cost_{Mn}alt$ equations represent the cost functions when HPV positive individuals are not treated.

less than 1, implying no epidemic. From this set of models, it is possible to observe that when a screening program is implemented, the proportion of individuals who progress to the cancer stage is relatively low, leading to the implication of no epidemic.

With every screening program comes additional costs, a summary of which can be found in Table 3.6. Once screened, it is up to the discretion of the specialist together with the patient in question to decide whether the resulting infection is worth treating. HPV has a high regression rate, although, the further it progresses, the smaller the chances are of the infection regressing [68]. Hence, if a patient was to be screened and found to have HPV, they may or may not choose to treat it. These models however, assume that everyone gets treated, regardless of the stage of HPV progression. An alternative cost function can be found in Table 3.6 which assumes that individuals are only treated if they are found to have progressed from the HPV positive stage to the CIN1 or a later stage. Table 3.6 summarizes the cost functions as they pertain to this thesis, denoted by $cost_{Mn}$, where n=1 denotes the screen and treat model, n=2 denotes the model in which only high risk individuals are treated, n=3 denotes the model in which co-screening with HC2 and cobas4800 are used and n=4 denotes the model in which co-screening with a pap smear and cobas4800 are used. The alternative cost functions, also found in Table 3.6, do not include individuals infected with HPV and is denoted by "$cost_{Mn}alt$".

Clearly, for a specific screening program, not treating individuals infected with HPV will

be cheaper than treating all infected individuals. However, if these individuals happen to progress to a pre-cancer stage (which is relatively unlikely), this can become more costly, as treating individuals at this stage of their infection will only reduce the severity of the infection rather than get rid of it. Furthermore, an infection can then metastasize, spreading to other regions of the body which will involve additional screening and treatment costs. Secondly, the further along an infection progresses, the smaller the chance is of regressing. Hence, it may be more cost effective to treat an individual before they progress too far in order to reduce the severity of the lesion and increase the chances of regression.

To summarize, each of the models will be cost efficient depending on the parameter values used. As each country's economy is different, it is difficult to predict the costs of the various screening tests. For this reason, it is difficult to determine which model will be the most cost efficient. Hence, the models should be examined in a specific context with a specific set of parameters to be able to fully understand their cost dynamics.

The final part of this discussion will revolve around the topic of the model simulations in Section 3.4.2.1. There are two main goals when considering the simulations. These include minimizing the total HPV positive and cancerous populations as well as maximizing the "reduced severity" and susceptible populations. When trying to achieve these goals, it is important to keep in mind both the possible long term and short term outcomes of the proposed program as each model produces various differences in the simulations over time. Finally, in order to optimize the screening program implemented it is crucial to choose a screening program based on a realistic screening rate, ϕ. Hence, the simulations where $\phi = 1$ should be disregarded in terms of their epidemiological outcome, as a 100% screening rate is unrealistic.

4 Re-infection with multiple HPV types models

4.1 Introduction

There is much debate over the topic of HPV infection and re-infection, both in terms of re-infection with the same genotype (type) of HPV, as well as, with different types of HPV [75]. While it is agreed upon that an individual who has seemingly cleared their infection, in other words is asymptomatic or has no visual infection, can get infected again, there is no consensus on the method of their re-infection [75]. One possibility is that the initial infection is always present, however in a latent form. Hence, the individual is not being re-infected with HPV, rather, the infection is switching from the latent to active form. The second opinion is that the individual does completely clear the infection but is not left with sufficient antibodies to fight off a second round of HPV infection after sexual intercourse with a carrier [75]. There is further debate regarding the rate of re-infection. Trottier et al. [75] conclude that rates of infection and re-infection are comparable, while Safaeian et al. [65] conclude that higher titers of HPV 16 and HPV 18 antibodies (due to infection) will decrease the re-infection rate (50% and 64% respectively) regardless of sexual activity [65]. Alternatively, Trottier et al. [75] conclude that new sexual partners increase re-infection rates. Hence,it is hypothesized that an individual who has seemingly cleared their infection and is re-infected with HPV has a lowered immunity.

The purpose of this chapter is to study the concept of initial infections with HPV with respect to subsequent infections with HPV, both with the same and different types of HPV. This will be accomplished by starting with a simple, single type model and expanding this model to include multiple HPV types.

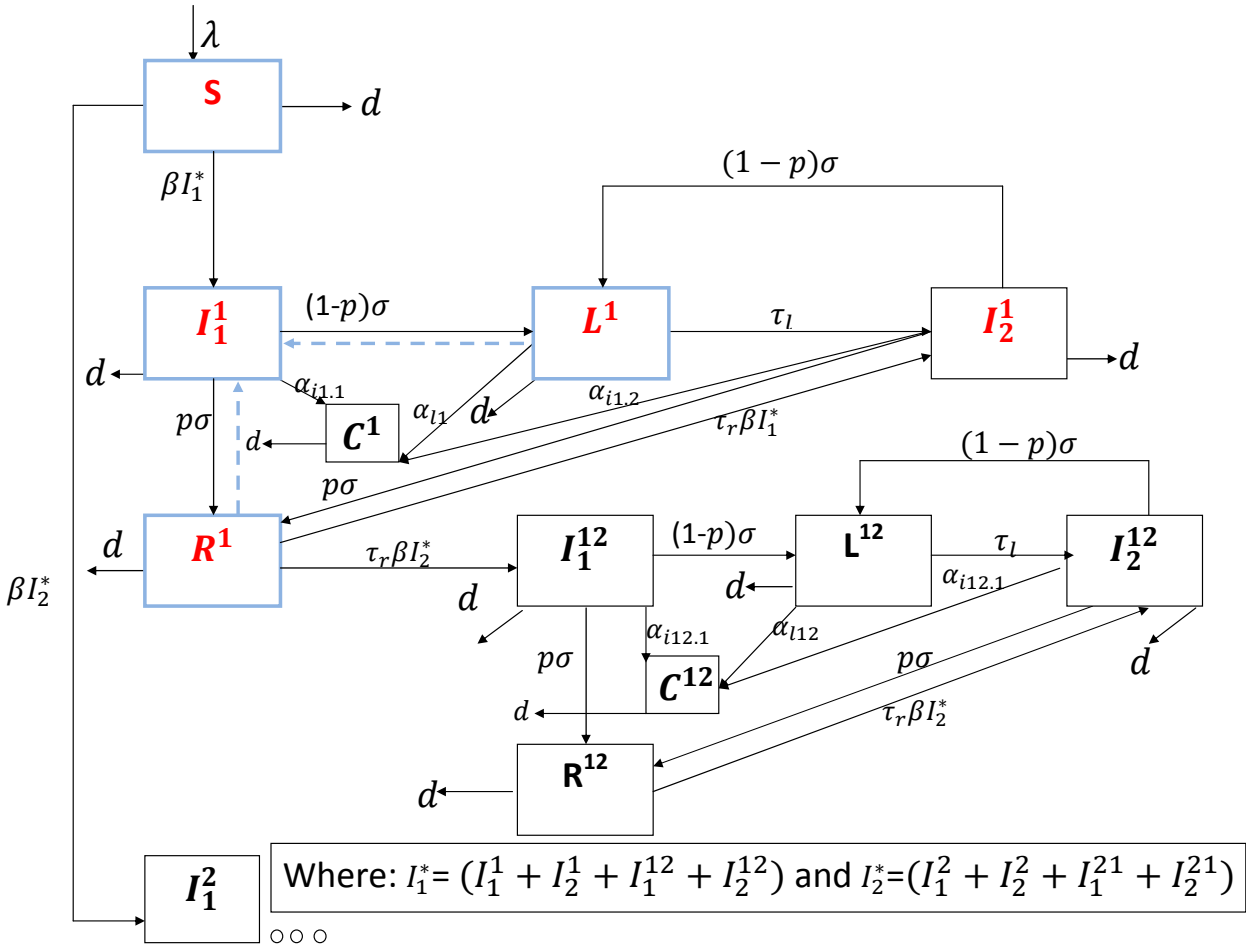


Figure 4.1: Flow diagram for Eq.'s (4.1)-(4.5), the models incorporating re-infection with multiple HPV types. The blue compartments represent a base case model in which there is no difference in compartments between the initial infection and individuals who have been infected multiple times. The red represents a model in which infection and re-infection are differentiated between. The red model with the addition of the C^1 class represents a model in which individuals can progress to the cancer stage. The red,blue and black portions (excluding the C^n classes) represent the first multi-type model, and the entire diagram represents a multi type model in which individuals can progress to the cancer stage.

4.2 Model

The models are composed of the basic compartmental states of susceptible (S), infected (I), recovered (R)(should be thought of as cleared), latently infected (L) and cancerous (C). Here, the infected compartment is representative of all of the HPV disease progression stages. Infected individuals can either clear their infection (R) or the infection can go into latency (L). Both recovered and latently infected individuals can become re-infected with HPV (I_2^n).

4.2.1 Equations

This chapter involves five different models, each growing in complexity to examine the phenomenon of re-infection with HPV.
The base case scenario in which there is no differentiation between infection and re-infection can be represented as follows:

$$\begin{aligned} S' &= \lambda - \tfrac{\beta}{N} S I_1^1 - dS \\ I_1^{1\prime} &= \tfrac{\beta}{N} I_1^1(\tau_r R + S) - \sigma I_1^1 + \tau_l L - dI_1^1 \\ R^{1\prime} &= p\sigma I_1^1 - \tau_r \tfrac{\beta}{N} R I_1^1 - dR \\ L^{1\prime} &= (1-p)\sigma I_1^1 - \tau_l L - dL \end{aligned} \tag{4.1}$$

The equations that represent the single-type model in which in which there is a differentiation between infected and re-infected individuals are:

$$\begin{aligned} S' &= \lambda - \tfrac{\beta}{N} S(I_1^1 + I_2^1) - dS \\ I_1^{1\prime} &= \tfrac{\beta}{N} S(I_1^1 + I_2^1) - \sigma I_1^1 - dI_1^1 \\ I_2^{1\prime} &= \tau_l L^1 + \tau_r \tfrac{\beta}{N} R^1(I_1^1 + I_2^1) - \sigma I_2^1 - dI_2^1 \\ R^{1\prime} &= p\sigma I_1^1 - \tau_r \tfrac{\beta}{N} R^1(I_1^1 + I_2^1) + p\sigma I_2^1 - dR^1 \\ L^{1\prime} &= (1-p)\sigma I_1^1 - \tau_l L^1 + (1-p)\sigma I_2^1 - dL^1 \end{aligned} \tag{4.2}$$

The equations that represent the single type model in which individuals can progress to the cancer stage are:

$$\begin{aligned}
S' &= \lambda - \tfrac{\beta}{N} S(I_1^1 + I_2^1) - dS \\
I_1^{1\prime} &= \tfrac{\beta}{N} S(I_1^1 + I_2^1) - \sigma I_1^1 - \alpha_{i1.1} I_1^1 - dI_1^1 \\
I_2^{1\prime} &= \tau_l L^1 + \tau_r \tfrac{\beta}{N} R^1 (I_1^1 + I_2^1) - \sigma I_2^1 - \alpha_{i1.2} I_2^1 - dI_2^1 \\
R^{1\prime} &= p\sigma I_1^1 - \tau_r \tfrac{\beta}{N} R^1 (I_1^1 + I_2^1) + p\sigma I_2^1 - dR^1 \\
L^{1\prime} &= (1-p)\sigma I_1^1 - \tau_l L^1 + (1-p)\sigma I_2^1 - \alpha_{l1} L^1 - dL^1 \\
C' &= \alpha_{i1.2} I_2^1 + \alpha_{i1.1} I_1^1 + \alpha_{l1} L^1 - dC
\end{aligned} \tag{4.3}$$

The equations for the multi-type model are:

$$\begin{aligned}
S' &= \lambda - S(\tfrac{\beta}{N}(I_1^* + I_2^*) + d) \\
I_1^{1\prime} &= \tfrac{\beta}{N} S I_1^* - I_1^1(\sigma + d) \\
I_2^{1\prime} &= \tau_l L^1 + \tau_r \tfrac{\beta}{N} R^1 I_1^* - I_2^1(\sigma + d) \\
R^{1\prime} &= p\sigma I_1^1 + p\sigma I_2^1 - R^1(\tau_r \tfrac{\beta}{N}(I_1^* + I_2^*) + d) \\
L^{1\prime} &= (1-p)\sigma I_1^1 - L^1(\tau_l + d) + (1-p)\sigma I_2^1 \\
I_1^{12\prime} &= I_2^* \tau_r \tfrac{\beta}{N} R^1 - I_1^{12}(\sigma + d) \\
L^{12\prime} &= (1-p)\sigma I_1^{12} + (1-p)\sigma I_2^{12} - L^{12}(\tau_l + d) \\
I_2^{12\prime} &= \tau_l L^{12} + \tau_r \tfrac{\beta}{N} R^{12} I_2^* - I_2^{12}(\sigma + d) \\
R^{12\prime} &= p\sigma I_1^{12} + p\sigma I_2^{12} - R^{12}(\tau_r \tfrac{\beta}{N} I_2^* + d) \\
I_1^{2\prime} &= \tfrac{\beta}{N} S I_2^* - I_1^2(\sigma + d) \\
I_2^{2\prime} &= \tau_l L^2 + \tau_r \tfrac{\beta}{N} R^2 I_2^* - I_2^2(\sigma + d) \\
R^{2\prime} &= p\sigma I_1^2 + p\sigma I_2^2 - R^2(\tau_r \tfrac{\beta}{N}(I_1^* + I_2^*) + d) \\
L^{2\prime} &= (1-p)\sigma I_1^2 + (1-p)\sigma I_2^2 - L^2(\tau_l + d) \\
I_1^{21\prime} &= \tau_r \tfrac{\beta}{N} R^2 I_2^* - I_1^{21}(\sigma + d) \\
L^{21\prime} &= (1-p)\sigma I_1^{21} + (1-p)\sigma I_2^{21} - L^{21}(\tau_l + d) \\
I_2^{21\prime} &= \tau_r \tfrac{\beta}{N} R^{21} I_1^* - I_2^{21} d + \tau_l L^{21} - \sigma I_2^{21} \\
R^{21\prime} &= p\sigma I_1^{21} + p\sigma I_2^{21} - R^{21}(\tau_r \tfrac{\beta}{N} I_1^* + d) \\
&where: \\
I_1^* &= I_1^1 + I_2^1 + I_1^{21} + I_2^{21} \\
I_2^* &= I_1^2 + I_2^2 + I_1^{12} + I_2^{12}
\end{aligned} \tag{4.4}$$

The final multi-type model in which individuals can progress to the cancer stage can be represented as follows:

$$
\begin{aligned}
S' &= \lambda - S(\tfrac{\beta}{N}(I_1^* + I_2^*) + d) \\
I_1^{1\prime} &= \tfrac{\beta}{N} S I_1^* - I_1^1(\sigma + \alpha_{i1.1} + d) \\
I_2^{1\prime} &= \tau_l L^1 + \tau_r \tfrac{\beta}{N} R^1 I_1^* - I_2^1(\sigma + \alpha_{i1.2} + d) \\
R^{1\prime} &= p\sigma I_1^1 + p\sigma I_2^1 - R^1(\tau_r \tfrac{\beta}{N}(I_2^* + I_1^*) + d) \\
L^{1\prime} &= (1-p)\sigma I_1^1 - L^1(\tau_l + \alpha_{l1} + d) + (1-p)\sigma I_2^1 \\
C^{1\prime} &= \alpha_{i1.1} I_1^1 + \alpha_{l1} L^1 + \alpha_{i1.2} I_2^1 - dC^1 \\
I_1^{12\prime} &= \tau_r \tfrac{\beta}{N} R^1 I_2^* - I_1^{12}(\sigma + \alpha_{i12.1} + d) \\
L^{12\prime} &= (1-p)\sigma I_1^{12} + (1-p)\sigma I_2^{12} - L^{12}(\tau_l + \alpha_{l12} + d) \\
I_2^{12\prime} &= \tau_l L^{12} + \tau_r \tfrac{\beta}{N} R^{12} I_2^* - I_2^{12}(\sigma + \alpha_{i12.2} + d) \\
R^{12\prime} &= p\sigma I_1^{12} + p\sigma I_2^{12} - R^{12}(\tau_r \tfrac{\beta}{N} I_2^* + d) \\
C^{12\prime} &= \alpha_{i12.1} I_1^{12} + \alpha_{l12} L^{12} + \alpha_{i12.2} I_2^{12} - dC^{12} \\
I_1^{2\prime} &= \tfrac{\beta}{N} S I_2^* - I_1^2(\sigma + \alpha_{i2.1} + d) \\
I_2^{2\prime} &= \tau_l L^2 + \tau_r \tfrac{\beta}{N} R^2 I_2^* - I_2^2(\sigma + \alpha_{i2.2} + d) \\
R^{2\prime} &= p\sigma I_1^2 + p\sigma I_2^2 - R^2(\tau_r \tfrac{\beta}{N}(I_2^* + I_1^*) + d) \\
L^{2\prime} &= (1-p)\sigma I_1^2 + (1-p)\sigma I_2^2 - L^2(\tau_l + \alpha_{l2} + d) \\
C^{2\prime} &= \alpha_{i2.1} I_1^2 + \alpha_{l2} L^2 + \alpha_{i2.2} I_2^2 - dC^2 \\
I_1^{21\prime} &= \tau_r \tfrac{\beta}{N} R^2 I_2^* - I_1^{21}(\sigma + \alpha_{i21.1} + d) \\
L^{21\prime} &= (1-p)\sigma I_1^{21} + (1-p)\sigma I_2^{21} - L^{21}(\tau_l + \alpha_{l21} + d) \\
I_2^{21\prime} &= \tau_r \tfrac{\beta}{N} R^{21} I_1^* - I_2^{21}(\alpha_{i21.2} + d + \sigma) + \tau_l L^{21} \\
R^{21\prime} &= p\sigma I_1^{21} + p\sigma I_2^{21} - R^{21}(\tau_r \tfrac{\beta}{N} I_1^* + d) \\
C^{21\prime} &= \alpha_{i21.1} I_1^{21} + \alpha_{l21} L^{21} + \alpha_{i21.2} I_2^{21} - dC^{21} \\
&where: \\
I_1^* &= I_1^1 + I_2^1 + I_1^{21} + I_2^{21} \\
I_2^* &= I_1^2 + I_2^2 + I_1^{12} + I_2^{12}
\end{aligned}
\tag{4.5}
$$

Figure 4.1 represents the models used in this chapter. Eq.(4.1) represents the model used as a base case model. This model includes only one infected compartment and is represented by the blue boxes as well as the dotted blue lines. Eq.(4.2) corresponds to the compartments in Figure 4.1 in which the class name is written in red. These represent the second model in which the re-infected class is differentiated from the infected class. This model and the C^1 compartment make up the third model, corresponding to Eq.(4.3). It differs from the

previous model in that individuals can transfer to the cancer class, which is assumed to be fatal. Eq.(4.4) corresponds to Figure 4.1 as it is presented excluding the C^1 and C^{12} classes. This is the first model that takes multiple HPV types into consideration. The final model, corresponding to Eq.(4.5) includes the model as is shown in Figure 4.1. In this model, individuals can transfer to the cancer class after being infected with any type of HPV.

The system of ODE's found in Eq.'s (4.1)-(4.5) employ the following assumptions:

- "Re-infected" individuals consist of both those individuals who have cleared their infection and developed a second infection, as well as, those whose infection has re-activated after a period of latency.
- The model assumes a probability p of a full recovery, implying a probability $(1-p)$ of the disease going into latency.
- The same reduced rate of re-infection and re-activation (τ).
- The progression rate to cancer (α_n) is assumed to be the same from all infected stages.
- The cancer stage is assumed to be fatal.

4.3 Parameters

Table 4.1 describes the variables used in Eq.(4.1)-(4.5). The nomenclature throughout the chapter works as follows: the subscript indicates the infection time (ie. 2 means that this is the second time that the individual has been infected) and the superscript indicates the HPV type that the individual is infected with.

As the mechanism of re-infection is unknown, τ, the decreased rate of infection, is assumed to be the same for all new infections. Furthermore, as the method of re-infection is unknown, we assume a that an individual's infection will clear with a probability p, and will go into latency with a probability $1-p$.

Term	Definition	Value	Reference
S	Susceptible population		
I_i	Population infected with HPV for the $I^(th)$ time		
I_i^k	Population infected with HPV type k for the $i^(th)$ time		
I_i^{kj}	Population infected first with HPV type k and then with type j for the $i^(th)$ time		
R^k	Population recovered from HPV type k		
R^{kj}	Recovered population who was infected first with HPV type k and then with type j		
L^k	Population with latent infection from HPV type k		
L^{kj}	Population with latent infection who was infected first with HPV type k and then with type j		
C	Population with cancer		
C^k	Population with cancer, who as infected with HPV type k		
C^{kj}	Population with cancer who was infected first with HPV type k and then with type j		
β	Infection rate	$0 - .8$ (year^{-1})	[16, 41, 71, 74]
$\alpha_{ij.k}$	Progression rate (to cancer) from infected stage, HPV type j,time being infected, k	$0.0001 - .5$ (year^{-1})	inferred
α_{lj}	Progression rate (to cancer)from latent stage, HPV type j	$0 - 1$(year^{-1})	inferred
σ	Recovery rate	$0.1 - 1$ (year^{-1})	inferred
τ_l	Decreased rate of reinfection from latent stage	$50\%[.3 - .6]$	[65]
τ_r	Decreased rate of reinfection from recovered stage	$50\%[.3 - .6]$	[65]
p	Probability of full recovery	$0.1 - 1$	

Table 4.1: Variables and parameters used in Eq.'s (4.1)-(4.5).

4.4 Results

4.4.1 Analytical results

4.4.1.1 Basic reproduction number

*Note: the α term is only included in the models that include the cancer stage.

Single type models, Eq.'s (4.1)-(4.3)

The Jacobian method was used to calculate R_0.

$R_0 = \frac{\beta S}{N(\sigma+\alpha_{i1.1}+d)} + \frac{(1-p)\sigma\tau_l}{(\tau_l+\alpha_{l1}+d)(\sigma+\alpha_{i1.2}+d)}$.

The assumption that $\alpha_{i1.1} = \alpha_{l1} = \alpha_{i1.2} = \alpha$ causes R_0 to become:

$R_0 = \frac{\beta S}{N(\sigma+\alpha+d)} + \frac{(1-p)\sigma\tau_l}{(\tau_l+\alpha+d)(\sigma+\alpha+d)}$. The disease will be contained when $R_0 < 1$.

Biologically, R_0 can be interpreted as follows: $\frac{\beta S}{N(\sigma+\alpha_{i1.1}+d)}$ represents the newly infected individuals by a previously infected individual in his lifetime. Here, the lifetime is determined by $\frac{1}{\sigma+\alpha_{i1.1}+d}$, where σ represents the individual's duration in the infected compartment before recovering or moving to the latently infected compartment, $\alpha_{i1.1}$ is the duration of the individual in the infected compartment before moving to the cancer compartment and d is the duration of the individual in the infected compartment before dying by natural causes.

The second term, $\frac{(1-p)\sigma\tau}{(\tau+\alpha_{l1}+d)(\sigma+\alpha_{i1.2}+d)}$, represents the movement of individuals from the infected stage to the latently infected stage $((1-p)\sigma)$ in their lifetime $(\sigma + \alpha_{i1.2} + d)$ and to the second infected stage (τ_l), in their lifetime $(\tau_l + \alpha_{l1} + d)$.

Multi-type models, Eq.'s (4.4) and (4.5)

Although the models differentiate between the progression rates of infected and latently infected individuals to cancer, the following simplifying assumption will be made:
$\alpha_{i21.1} = \alpha_{l21} = \alpha_{i21.2} = \alpha_{i2.1} = \alpha_{l2} = \alpha_{i2.2} = \alpha_{i12.1} = \alpha_{l12} = \alpha_{i12.2} = \alpha_{i1.1} = \alpha_{l1} = \alpha_{i1.2} = \alpha$.

Using the Jacobian method, the basic reproduction number was calculated to be:

$$R_0 = \frac{1}{2}\frac{(1-p)^4\sigma^4\tau^4}{(\tau+d+\alpha)^4(\sigma+d+\alpha)^4(\frac{\beta S}{N(\sigma+d+\alpha)}+2\frac{(1-p)\sigma\tau}{(\tau+d+\alpha)(\sigma+d+\alpha)})(\frac{(1-p)\sigma\tau}{(\tau+d+\alpha)(\sigma+d+\alpha)}\frac{\beta S}{N(\sigma+d+\alpha)}+\frac{(1-p)^2\sigma^2\tau^2}{(\tau+d+\alpha)^2(\sigma+d+\alpha)^2}+1)}$$
$$+\frac{1}{2}\frac{\frac{\beta S}{N(\sigma+d+\alpha)}(1-p)^2\sigma^2\tau^2}{N(\sigma+d+\alpha)^2(\tau+d+\alpha)^2(\frac{(1-p)\sigma\tau}{(\tau+d+\alpha)(\sigma+d+\alpha)}\frac{\beta S}{N(\sigma+d+\alpha)}+\frac{(1-p)^2\sigma^2\tau^2}{(\sigma+d+\alpha)^2(\tau+d+\alpha)^2}+1)}$$
$$+\frac{3(1-p)^2\sigma^2\tau^2}{(\sigma+d+\alpha)^2(\tau+d+\alpha)^2(\frac{\beta S}{N(\sigma+d+\alpha)}+\frac{2(1-p)\sigma\tau}{(\tau+d+\alpha)(\sigma+d+\alpha)})(\frac{\beta S}{N(\sigma+d+\alpha)}\frac{(1-p)\sigma\tau}{(\sigma+d+\alpha)(\tau+d+\alpha)}+\frac{(1-p)^2\sigma^2\tau^2}{(\tau+d+\alpha)^2(\sigma+d+\alpha)^2}+1)}$$
$$+\frac{1}{2}\frac{(\frac{\beta S}{N(\sigma+d+\alpha)})^2+\frac{\beta S}{N(\sigma+d+\alpha)}\frac{6(1-p)\sigma\tau}{(\sigma+d+\alpha)(\tau+d+\alpha)}+1}{(\frac{\beta S}{N(\sigma+d+\alpha)}+\frac{2(1-p)\sigma\tau}{(\sigma+d+\alpha)(\tau+d+\alpha)})(\frac{\beta S}{N(\sigma+d+\alpha)}\frac{(1-p)\sigma\tau}{(\sigma+d+\alpha)(\tau+d+\alpha)}+\frac{(1-p)^2\sigma^2\tau^2}{(\sigma+d+\alpha)^2(\tau+d+\alpha)^2}+1)}.$$

This represents the number of newly infected individuals by an infected individual in a totally susceptible population. This R_0 is a polynomial of four terms. Although interpreting an R_0 of this complexity is beyond the scope of this thesis, each individual term can be interpreted in the following way:

- $\frac{\beta S}{N(\sigma+d+\alpha)}$
  where:
  - βS represents the infection of a susceptible individual
  - $\frac{1}{\sigma+d+\alpha}$ represents the infected individual's lifetime: σ represents the amount of time they spend in the infected class before moving to the latent or recovered classes. d represents their natural death rate and $\frac{1}{\alpha}$ represents the time before progressing to the cancer stage.
- $\frac{\tau_l}{\tau_l+d+\alpha}$
  where:
  - τ_l represents the flow of individuals from the latently infected compartment to an infected compartment.
  - $\frac{1}{\tau_l+d+\alpha}$ represents the individual's lifetime before leaving the latently infected compartment ($\frac{1}{\tau_l}$), natural death ($\frac{1}{d}$) or progression to the cancer stage ($\frac{1}{\alpha}$).
- $\frac{(1-p)\sigma}{\sigma+d+\alpha}$
  where:
  - $(1-p)\sigma$ represents the flow of individuals from an infected compartment to a latently infected compartment.
  - $\frac{1}{\sigma+d+\alpha}$ represents the individual's lifetime:$\frac{1}{\sigma}$ represents the time it takes for an individual to move to the latently infected class or the recovered class, $\frac{1}{d}$ represents

the individual's lifetime before death by natural causes and $\frac{1}{\alpha}$ represents the average time it takes to move to the cancer compartment.

The basic reproduction number consists of infection terms from both the infected stage and the latently infected stage and is heavily dependent on the regression rate, σ, and the transmission rate, β.

4.4.1.2 Equilibrium points

The disease free equilibrium point is the same throughout the five models. It is:

$$(S, I_i^{kj}, R^{kj}, L^{kj}, C^{kj}) \quad = \quad (\tfrac{\lambda}{d}, 0, 0, 0, 0) \tag{4.6}$$

The endemic equilibrium point for the single-type, single infection model (Eq.(4.1)) can be written as: $(S*, R*, L*)$ where:

- $S* = \frac{\lambda}{\frac{\beta I_1^{1\prime}}{N}+d}$
- $R* = \frac{p\sigma I_1^{1\prime}}{\frac{\tau_r \beta I_1^{1\prime}}{N}+d}$
- $L* = \frac{(1-p)\sigma I_1^{1\prime}}{\tau_l+d}$
  where:
- $I_1^{1\prime} = I_1^1(\frac{\beta}{N}(\frac{\lambda}{\frac{\beta I_1^1}{N}+d} + \frac{\tau_r p\sigma I_1^1}{\frac{\tau_r \beta I_1^{1\prime}}{N}+d}) - (\sigma+d) + \frac{\tau_l(1-p)\sigma}{(\tau_l+d)})$.

The endemic equilibrium point for the single type models in which infection and re-infection are differentiated between (Eq.'s (4.2) and (4.3)) is $(S*, R^1*, L^1*, C*)$, where:

- $S* = \frac{\lambda}{\frac{\beta}{N}(I_1^{1\prime}+I_2^{1\prime})+d}$
- $R^1* = \frac{p\sigma(I_1^{1\prime}+I_2^{1\prime})}{\tau_r \frac{\beta}{N}(I_1^{1\prime}+I_2^{1\prime})+d}$
- $L^1* = \frac{(1-p)\sigma(I_1^{1\prime}+I_2^{1\prime})}{\tau_l+\alpha_{l1}+d}$
- $C* = \frac{1}{d}(\alpha_{i1.2} I_2^{1\prime} + \alpha_{i1.1} I_1^{1\prime} + \alpha_{l1}\frac{(1-p)\sigma(I_1^{1\prime}+I_2^{1\prime})}{\tau+\alpha_{l1}+d})$
  where:
- $I_1^{1\prime} = \frac{\beta}{N}\frac{\lambda}{\frac{\beta}{N}(I_1^{1\prime}+I_2^{1\prime})+d}(I_1^{1\prime}+I_2^{1\prime}) - I_1^{1\prime}(\sigma+\alpha_{i1.1}+d)$

- $I_2^{1\prime} = \frac{\tau_l(1-p)\sigma(I_1^{1\prime}+I_2^{1\prime})}{\tau_l+\alpha_l+d} + \frac{\tau_r\beta p\sigma(I_1^{1\prime}+I_2^{1\prime})^2}{N(\tau_r\frac{\beta}{N}(I_1^{1\prime}+I_2^{1\prime})+d)} - I_2^{1\prime}(\sigma+\alpha_{i1.2}+d)$

The endemic equilibrium point for the multi-type models (Eq.'s (4.4) and (4.5)) is:
$(S*, R^1*, L^1*, C^1*, L^{12}*, R^{12}*, C^{12}*, R^2*, L^2*, C^2*, L^{21}*, R^{21}*, C^{21}*)$,
where:

- $S* = \frac{\lambda}{\frac{\beta}{N}(I_1^*+I_2^*)+d}$
- $R^1* = \frac{p\sigma(I_1^{1\prime}+I_2^{1\prime})}{\tau_r\frac{\beta}{N}(I_2^*+I_1^*)+d}$
- $L^1* = \frac{(1-p)\sigma(I_1^{1\prime}+I_2^{1\prime})}{\tau_l+\alpha_{l1}+d}$
- $C^1* = \frac{\alpha_{i1.1}I_1^{1\prime}+\alpha_{l1}L^{1\prime}+\alpha_{i1.2}I_2^{1\prime}}{d}$
- $L^{12}* = \frac{(1-p)\sigma(I_1^{12\prime}I_2^{12\prime})}{\tau_l+\alpha_{l12}+d}$
- $R^{12}* = \frac{p\sigma(I_1^{12\prime}+I_2^{12\prime})}{\tau_r\frac{\beta}{N}I_2^*+d}$
- $C^{12}* = \frac{\alpha_{i12.1}I_1^{12\prime}+\alpha_{l12}L^{12\prime}+\alpha_{i12.2}I_2^{12\prime}}{d}$
- $R^2* = \frac{p\sigma(I_1^{2\prime}+I_2^{2\prime})}{\tau_r\frac{\beta}{N}(I_2^*+I_1^*)+d}$
- $L^2* = \frac{(1-p)\sigma(I_1^{2\prime}+I_2^{2\prime})}{\tau_l+\alpha_{l2}+d}$
- $C^2* = \frac{\alpha_{i2.1}I_1^{2\prime}+\alpha_{l2}L^{2\prime}+\alpha_{i2.2}I_2^{2\prime}}{d}$
- $L^{21}* = \frac{(1-p)\sigma(I_1^{21\prime}I_2^{21\prime})}{\tau_l+\alpha_{l21}+d}$
- $R^{21}* = \frac{p\sigma(I_1^{21\prime}+I_2^{21\prime})}{\tau_r\frac{\beta}{N}I_1^*+d}$
- $C^{21}* = \frac{\alpha_{i21.1}I_1^{21\prime}+\alpha_{l21}L^{21\prime}+\alpha_{i21.2}I_2^{21\prime}}{d}$

  where:

- $I_1^{1\prime} = \frac{\beta}{N}\frac{\lambda I_1^*}{\frac{\beta}{N}(I_1^*+I_2^*)+d} - I_1^{1\prime}(\sigma+\alpha_{i1.1}+d)$
- $I_2^{1\prime} = \tau_l\frac{(1-p)\sigma(I_1^{1\prime}+I_2^{1\prime})}{\tau_l+\alpha_{l1}+d} + \tau_r\frac{\beta}{N}\frac{I_1^*p\sigma(I_1^{1\prime}+I_2^{1\prime})}{\frac{\tau_r\beta}{N}(I_1^*+I_2^*)+d} - I_2^{1\prime}(\sigma+\alpha_{i1.2}+d)$
- $I_1^{12\prime} = \tau_r\frac{\beta}{N}\frac{I_2^*p\sigma(I_1^{1\prime}+I_2^{1\prime})}{\tau_r\frac{\beta}{N}(I_2^*+I_1^*)+d)} - I_1^{12}(\sigma+\alpha_{i12.1}+d)$

- $I_2^{12\prime} = \frac{\tau_l(1-p)\sigma(I_1^{12\prime}+I_2^{12\prime})}{\tau_l+\alpha_{l12}+d} + \frac{\tau_r\frac{\beta}{N}I_2^*p\sigma(I_1^{12\prime}+I_2^{12\prime})}{\tau_r\frac{\beta}{N}I_2^*+d} - I_2^{12}(\sigma+\alpha_{i12.2}+d)$
- $I_1^{2\prime} = \frac{\beta}{N}\frac{\lambda I_2^*}{\frac{\beta}{N}(I_1^*+I_2^*)+d} - I_1^{2\prime}(\sigma++\alpha_{i2.1}+d)$
- $I_2^{2\prime} = \frac{\tau_l(1-p)\sigma(I_1^{2\prime}+I_2^{2\prime})}{\tau_l+\alpha_{l2}+d} + \frac{\tau_r\beta}{N}\frac{I_2^*p\sigma(I_1^{2\prime}+I_2^{2\prime})}{\frac{\tau_r\beta}{N}(I_1^*+I_2^*)+d} - I_2^{2\prime}(\sigma+\alpha_{i2.2}+d)$
- $I_1^{21\prime} = \frac{\tau_r\frac{\beta}{N}I_2^*p\sigma(I_1^{2\prime}+I_2^{2\prime})}{\tau_r\frac{\beta}{N}(I_2^*+I_1^*)+d} - I_1^{21\prime}(\sigma+\alpha_{i21.1}+d)$
- $I_2^{21\prime} = \frac{\tau_l(1-p)\sigma(I_1^{21\prime}+I_2^{21\prime})}{\tau_l+\alpha_{l21}+d} + \frac{\tau_r\frac{\beta}{N}I_1^*p\sigma(I_1^{21\prime}+I_2^{21\prime})}{\tau_r\frac{\beta}{N}I_1^*+d} - I_2^{21\prime}(\sigma+\alpha_{i21.2}+d)$

*note that the C^{jk} and α terms are only applicable in the models in which individuals can progress to the cancer stage.

4.4.1.3 Stability

To determine the stability of the system, one must first find the Jacobian and then evaluate the Jacobian at the equilibrium point. Substituting in the disease free equilibrium point and calculating the characteristic polynomial gives the following eigenvalues for the single-type models represented by Eq.'s (4.1)-(4.3). Note that the α terms are only applicable in the models including the cancer stage, namely, Eq.(4.3). Eq.(4.1) only consists of λ_{1-4} and Eq.'s (4.2) and (4.3) consists of λ_{1-5}.

- $\lambda_{1,2} = -d < 0$
- $\lambda_{3,4} = -\frac{1}{2}(((\sigma+\alpha_{i1.1}+d)+(\tau_l+\alpha_l+d)-\frac{\beta S}{N})\pm$
  $\sqrt{((\sigma+\alpha_{i1.1}+d)+(\tau_l+\alpha_{l1}+d)-\frac{\beta S}{N})^2+4(-(\sigma+\alpha_{i1.1}+d)(\tau_l+\alpha_{l1}+d)+(1-p)\sigma\tau_l+}$

  $\overline{(\tau_l+\alpha_{l1}+d)\frac{\beta S}{N}}))$
  $= -\frac{1}{2}((\sigma+\alpha+d)+(\tau_l+\alpha+d)-\frac{\beta S}{N})$

  $\pm\sqrt{((\sigma+\alpha+d)+(\tau_l+\alpha+d)-\frac{\beta S}{N})^2+4(1-R_0)(\sigma+\alpha+d)(\tau_l+\alpha+d))}$
- $\lambda_5 = -(\sigma+\alpha_{i1.1}+d) < 0$

Since $d > 0$, $\lambda_{1,2} < 0$. $\lambda_5 < 0$ as both σ and $d > 0$.
The calculations for the stability of $\lambda_{3,4}$ are as follows:

$\left|(\tau_l+\alpha+d)+(\sigma+\alpha+d)-\frac{\beta S}{N}\right| = \sqrt{((\tau_l+\alpha+d)+(\sigma+\alpha+d)-\frac{\beta S}{N})^2}$. Therefore, if $4((\tau_l+\alpha+d)\frac{\beta S}{N}-(\tau_l+\alpha+d)(\sigma+\alpha+d)+(1-p)\sigma\tau_l) > 0$ the square root term will be larger than the non-square root term. This happens when $(\tau_l+\alpha+d)\frac{\beta S}{N}+(1-p)\sigma\tau_l > (\tau_l+\alpha+d)(\sigma+\alpha+d)$, in other words, when $\frac{(1-p)\sigma\tau_l}{(\tau_l+\alpha+d)(\sigma+\alpha+d)} + \frac{\beta S}{N(\sigma+\alpha+d)} = R_0 > 1$. When $R_0 > 1$, then $\lambda_3 < 0$ and $\lambda_4 > 0$ causing the the equilibrium point to be unstable. However, when $R_0 < 1$, and the non-root term is negative, then $\lambda_{3,4} < 0$ and when it's positive then $\lambda_{3,4} > 0$. To conclude, the disease free equilibrium point is stable, provided that $R_0 < 1$ and $\frac{\beta S}{N} < (\tau_l+\alpha_l+d)+(\sigma+\alpha_{i1.1}+d)$.

Numerical methods will be used to analyze the endemic equilibrium point.

The eigenvalues for Eq.'s (4.4) and (4.5) are:

- $\lambda_{1,2,3,4,5} = -d < 0$
- $\lambda_{6,7,8,9} = -(\sigma+\alpha+d) < 0$
- $\lambda_{10,11,12,13} = -\frac{1}{2}(((\tau_l+\alpha+d)+(\sigma+\alpha+d))$
  $\pm\sqrt{((\tau_l+\alpha+d)+(\sigma+\alpha+d))^2+4((1-p)\sigma\tau_l-(\tau_l+\alpha+d)(\sigma+\alpha+d))})$
- $\lambda_{14,15,16,17} = -\frac{1}{2}(((\tau_l+\alpha+d)+(\sigma+\alpha+d)-\frac{\beta S}{N})$
  $\pm\sqrt{((\tau_l+\alpha+d)+(\sigma+\alpha+d)-\frac{\beta S}{N})^2+4((\tau_l+\alpha+d)\frac{\beta S}{N}+(1-p)\sigma\tau_l-}$
  $\overline{(\tau_l+\alpha+d)(\sigma+\alpha+d)))}$

If in λ_{10-13}, $(1-p)\sigma\tau_l < (\tau_l+\alpha+d)(\sigma+\alpha+d) \rightarrow \frac{(1-p)\sigma\tau_l}{(\tau_l+\alpha+d)(\sigma+\alpha+d)} < 1$ then $\lambda_{10-13} < 0$. Similarly, for λ_{14-17}, the eigenvalue will be negative if $(\tau_l+\alpha+d)\frac{\beta S}{N}+(1-p)\sigma\tau_l < (\tau_l+\alpha+d)(\sigma+\alpha+d) \rightarrow \frac{\beta S}{N(\sigma+\alpha+d)}+\frac{(1-p)\sigma\tau_l}{(\tau_l+\alpha+d)(\sigma+\alpha+d)} < 1$ AND $\frac{\beta S}{N} < (\tau_l+\alpha+d)+(\sigma+\alpha+d)$.

Note that the α terms only apply to Eq.(4.5)

4.4.2 Numerical simulations

4.4.2.1 Simulations

1000 LHS parameter sets were used to examine the population sizes at the endemic equilibrium point for Eq.'s (4.1)-(4.5).

Base case model, Eq.(4.1)

The relationship between the various populations with respect to the transmission rate, β, and the regression rate, σ, is illustrated in its entirety in Figure 4.2 for Eq.(4.1). Figure 4.3 represents sub-plots of Figure 4.2. The susceptible population is always the largest. Furthermore, the recovered population and the infected population represent the second largest group depending on the independent variable. The infected and latently infected populations are close to equal in population size depending on the independent variable. Varying the regression rate, σ, causes a larger change on the infected population size compared to varying the transmission rate, β. This is important as it means that in terms of a screening or vaccination program, one should concentrate on increasing the regression rate, as it will have a larger impact on the infected population size than decreasing the transmission rate. This can be accomplished through screening and treatment practices.

Single-type models, Eq.'s (4.2) and (4.3)

Figures 4.4-4.5 represent the population sizes at the endemic equilibrium point for Eq.(4.2) while Figures 4.6-4.7 represent the population sizes at the endemic equilibrium point for Eq.(4.3). The figures illustrate this with respect to the various regression (σ) and transmission (β) rates used. The following trends are evident from the numerical analysis: for the most part, the re-infected population is larger than the population of individuals who have only been infected once. Varying the regression rate, σ, causes a larger change in the infected population's size than varying the transmission rate, β. Furthermore, there is a more dramatic change in the infected population's size when varying the regression rate, σ, than in the re-infected population's size.

In the simulation of 1000 parameter sets, 687 of them resulted in all non-negative population sizes for Eq.(4.2) and 296 resulted in non-negative population sizes for Eq.(4.3). There were only five population sets in which $I_1^1* > I_2^1*$.

The consequences of these results are that it is more efficient to vary the regression rate, through screening and treatment practices, than it is to vary the transmission rate through vaccination practices. Furthermore, it is important to model HPV infection and re-infection in future models as opposed to just a single infection, as the re-infected class is larger than

the infected class.

Multi-type models, Eq.'s (4.4) and (4.5)

Figures 4.8-4.10 represent the population sizes at the endemic equilibrium point for Eq.(4.4) while Figures 4.11-4.13 represent the population sizes at the endemic equilibrium point for Eq.(4.5). All of the aforementioned figures present the following trends:

- At the endemic equilibrium point, a re-infected population (in these cases, I_2^1*) represents the largest population size for any given transmission rate, β, or regression rate, σ.
- There is a larger change in the population size when the regression rate, σ, is varied than when the transmission rate, β, is varied.

As mentioned in Section 4.4.2.2, there exists equilibrium points at certain parameter sets that were shown to be unstable. As the only parameters which can biologically be altered are the regression rate and the infection rate, the unstable equilibrium points were studied with respect to these two parameters only. Figures 4.14 and 4.15 illustrate this point.

In order to understand the instability in Eq.'s (4.4) and (4.5), perturbations were applied to various sets of stable and unstable endemic equilibria. The solutions returned to their pre-perturbation equilibrium, implying a stable equilibria for both the stable and unstable equilibrium points. This leads to the conclusion that the instability in the system is due to numerical error, possibly due to the size and complexity of the model.

One final point about Figure 4.15 is that there are two solutions for a single parameter set. However, it is difficult to differentiate the stable population set from the unstable population set. The aforementioned stability test confirmed that **all** of the population sets were stable, indicating that the results of this model confirm those of the previous models.

4.4.2.2 Stability of the endemic equilibria

Latin Hypercube Sampling (1000 runs) was used to create 1000 sets of parameters. Since it is only realistic to examine populations that are non-negative in size, the parameter sets created by LHS were fed into the solution of the system and the non-negative population

sets were used to calculate the eigenvalues of the system. The Jacobian was calculated 687 times for Eq.'s (4.1) and (4.2), 296 times for Eq.(4.3) and 177 and 591 times for Eq.'s (4.4) and (4.5) respectively, as only the parameter sets where $(S*, I_1^1*, R*, L*) \geq 0$ were used. All of the eigenvalues for the uninfected equilibrium point were negative for Eq.'s (4.1)-(4.3), indicating stability. However, the endemic equilibrium point for Eq.'s (4.4) and (4.5) were shown to be unstable. A perturbation was applied to the unstable solutions. All solutions returned to their pre-perturbation point, indicating that the instability is due to numerical error, and the endemic equilibrium is in fact, stable.

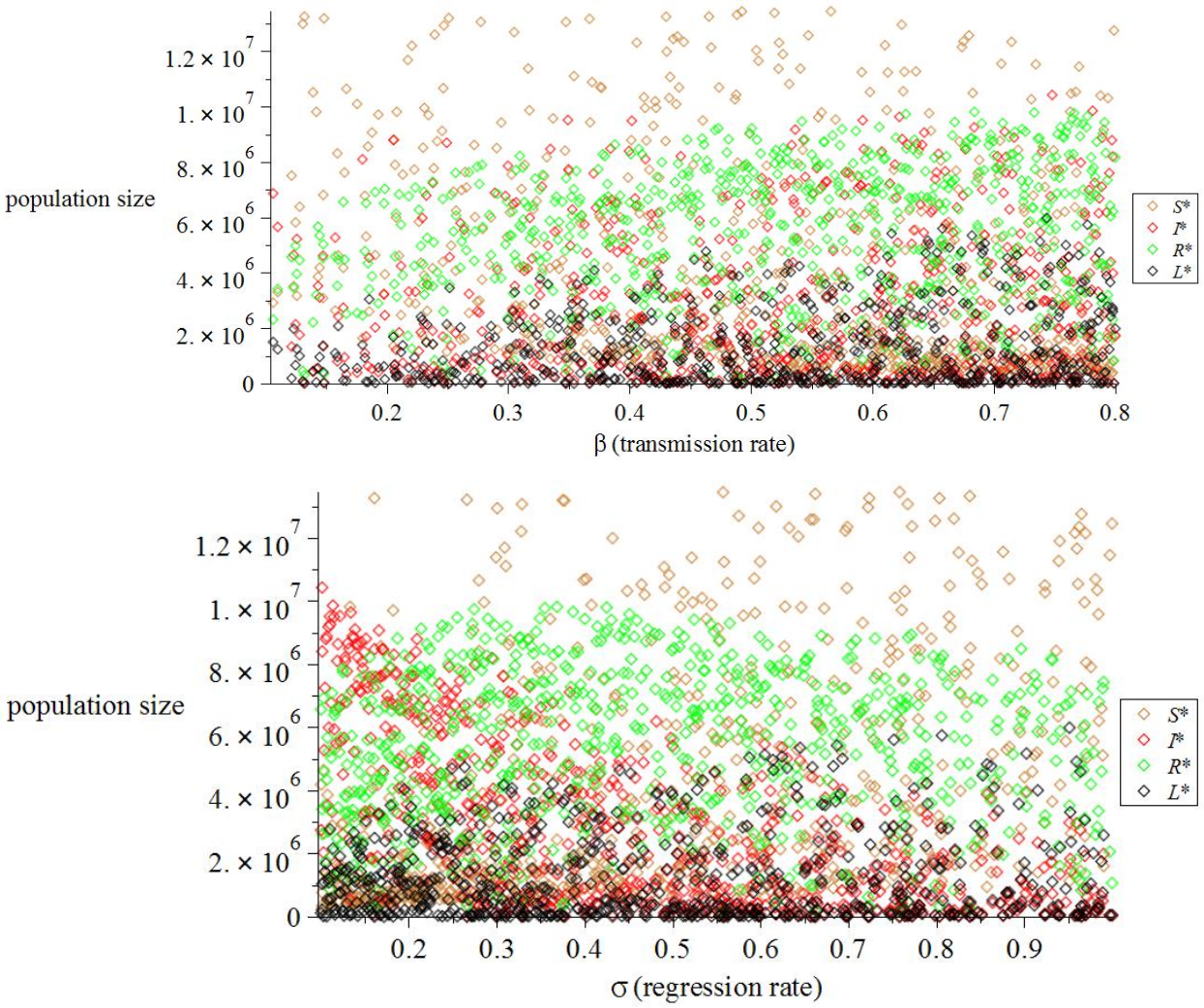


Figure 4.2: Endemic equilibrium population sizes with respect to the transmission rate, β (top), and the regression rate, σ (bottom), for Eq.(4.1), the base case model.

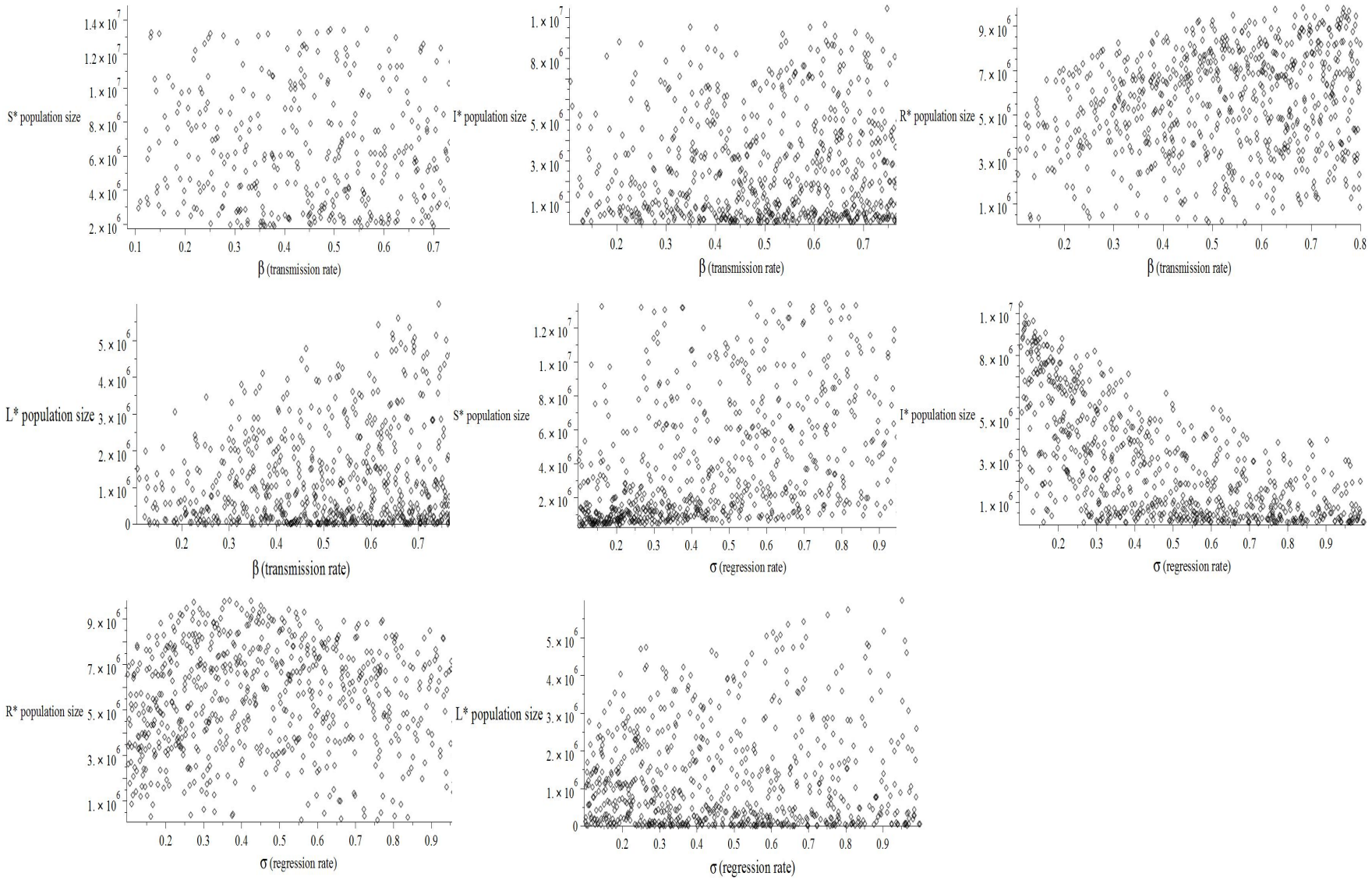


Figure 4.3: Endemic equilibrium population sizes with respect to the transmission rate, β, and the regression rate, σ, for Eq.(4.1), the base case model.

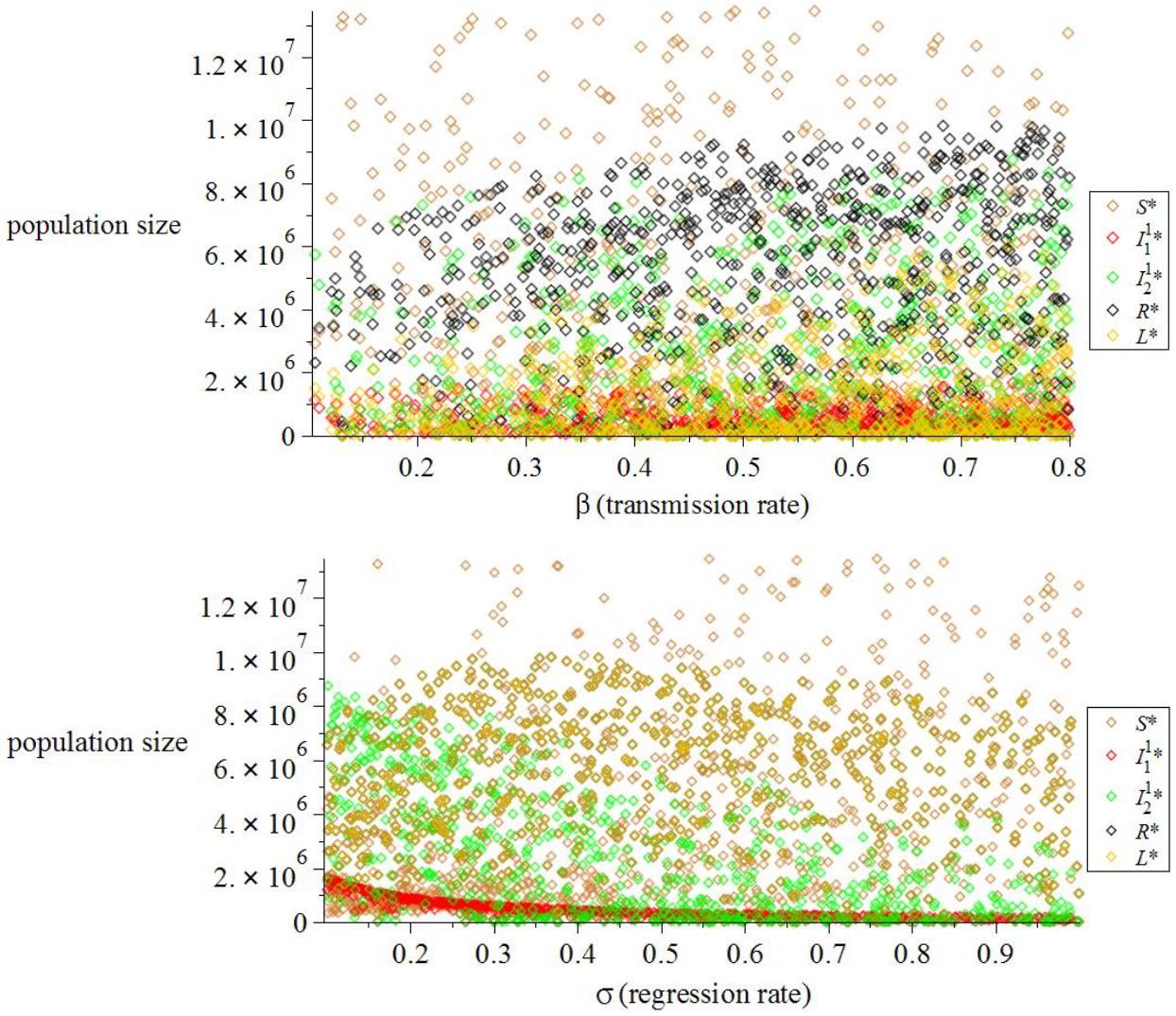


Figure 4.4: Endemic equilibrium population sizes with respect to the transmission rate, β (top), and the regression rate, σ (bottom), for Eq.(4.2), the single type model with no cancer stage.

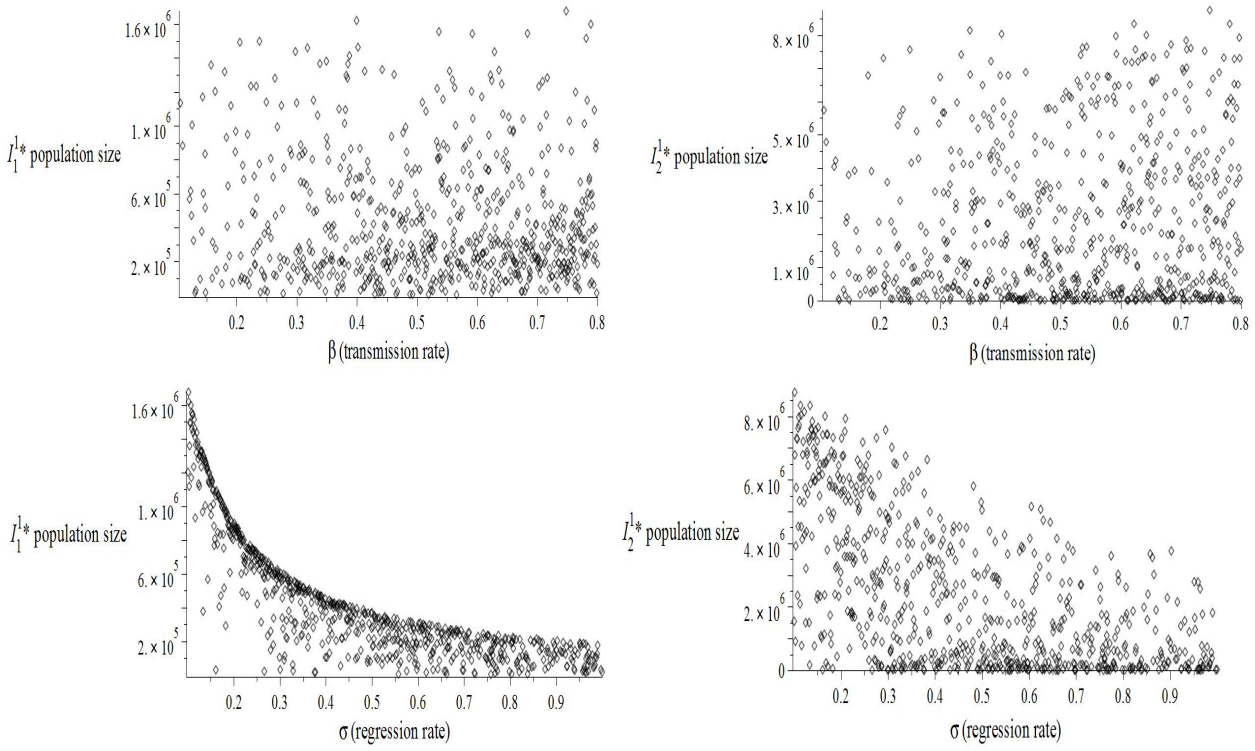


Figure 4.5: Endemic equilibrium population sizes with respect to the transmission rate, β (top), and the regression rate, σ (bottom), for Eq.(4.2), the single type model with no cancer stage. The sub-plots represent the I_1^1 and I_2^1 population sizes.

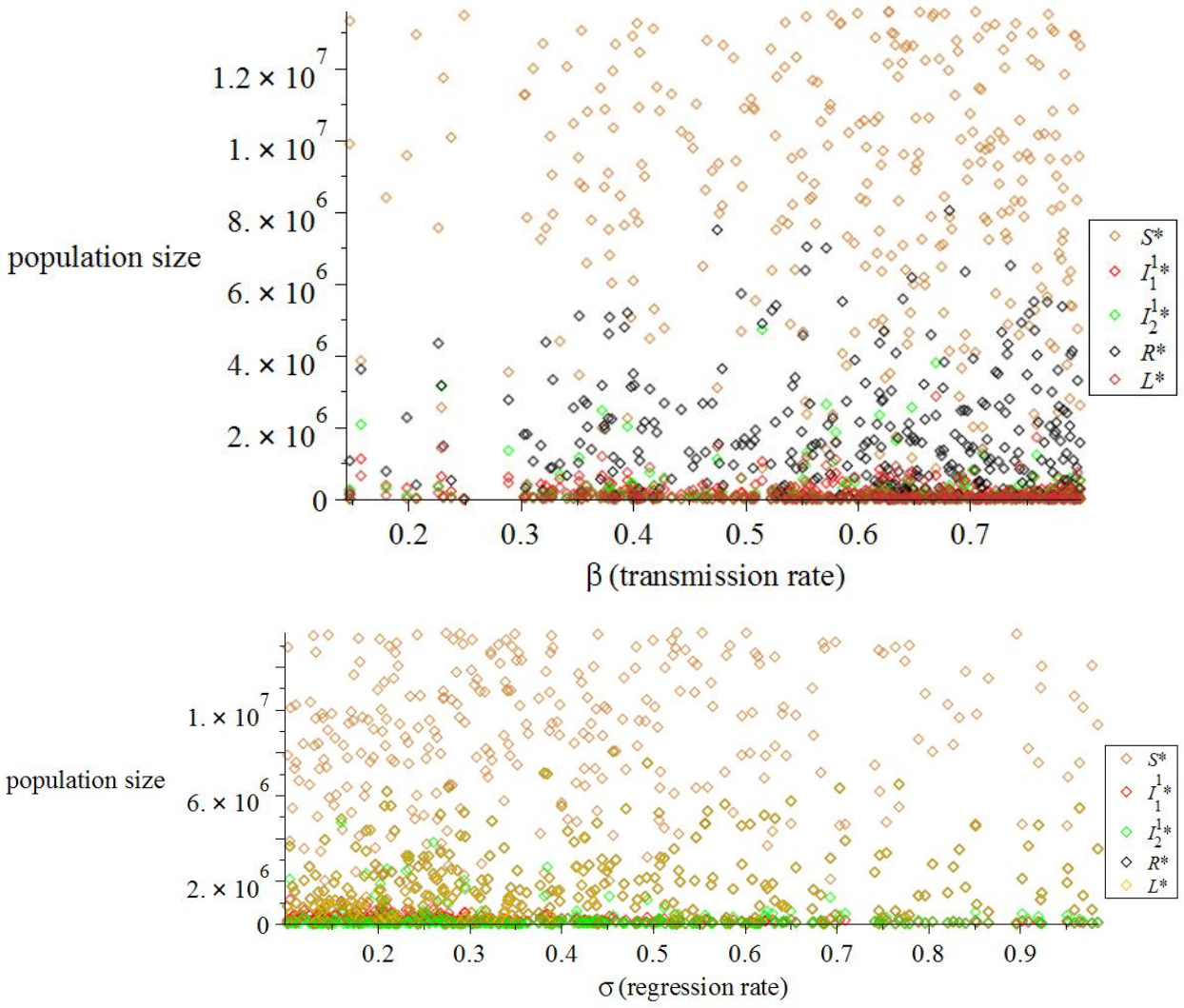


Figure 4.6: Endemic equilibrium populations sizes with respect to the transmission rate, β (top), and the regression rate, σ (bottom), for Eq.(4.3), the single type model with a cancer stage.

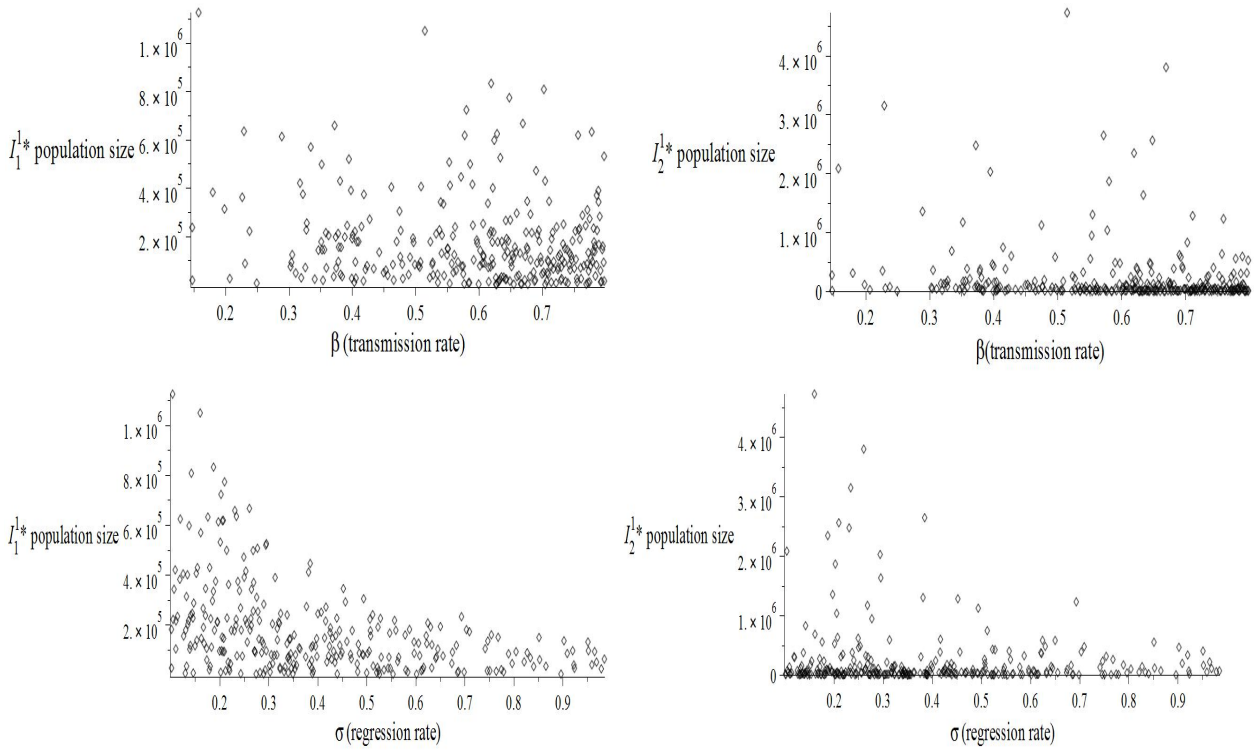


Figure 4.7: Endemic equilibrium population sizes with respect to the transmission rate, β (top), and the regression rate, σ (bottom), for Eq.(4.3), the single type model with a cancer stage. These sub-plots represent the I_1^1 and the I_2^1 population sizes.

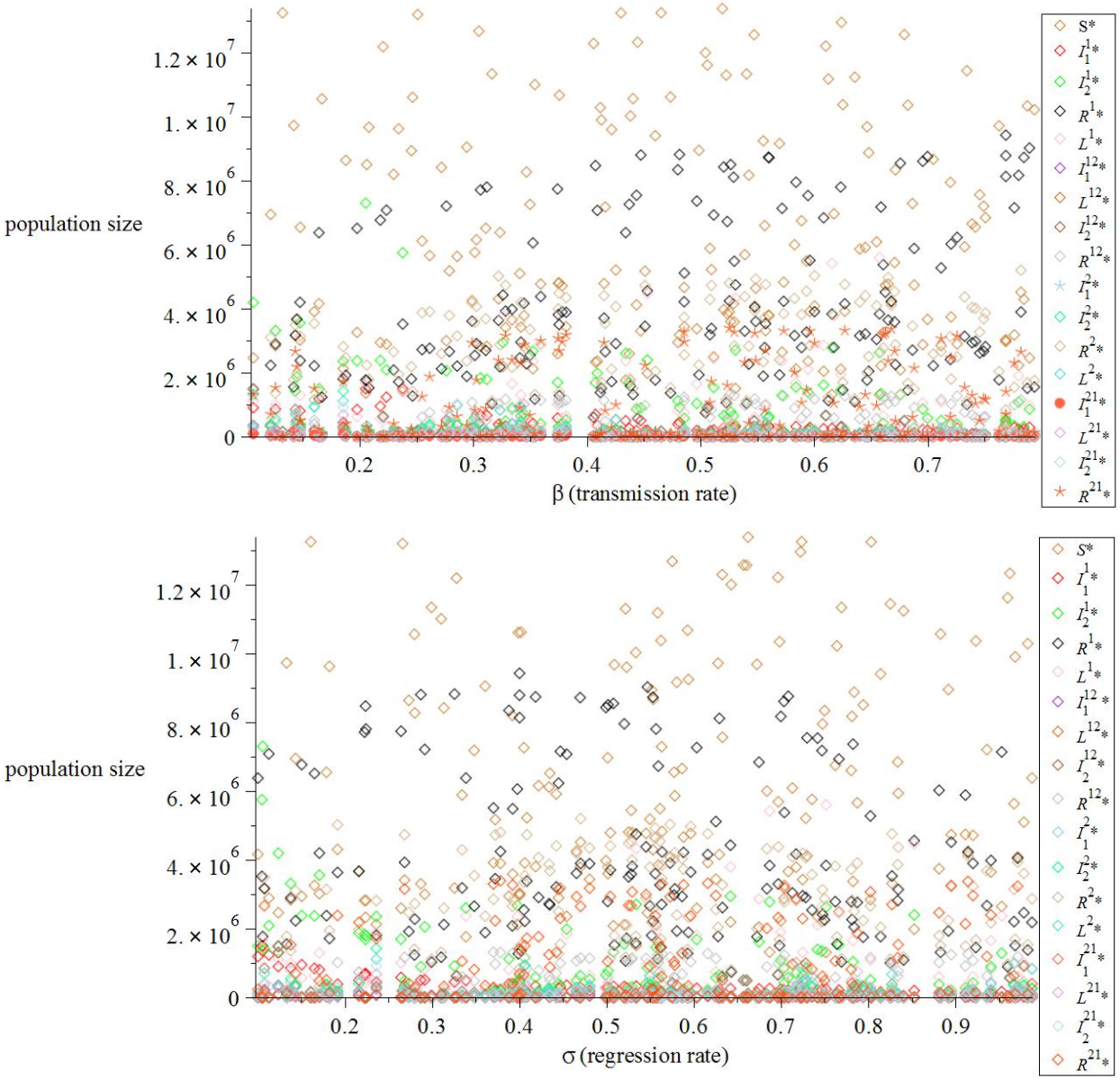


Figure 4.8: Endemic equilibrium population sizes with respect to the transmission rate, β (top), and the regression rate, σ (bottom), for Eq.(4.4), the multi-type, no cancer model.

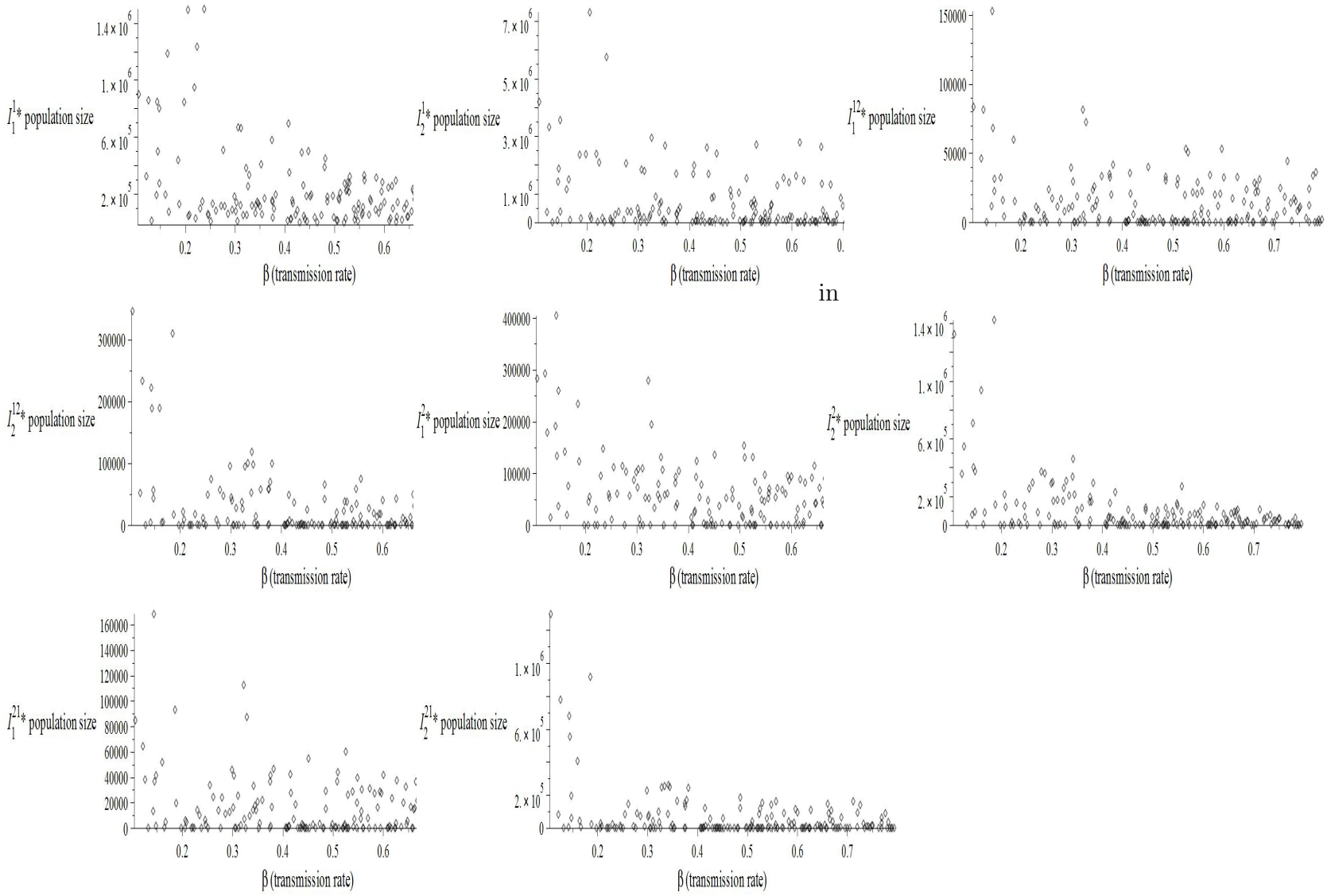


Figure 4.9: Endemic equilibrium population sizes with respect to the transmission rate, β, for Eq.(4.4), the multi-type, no cancer model.

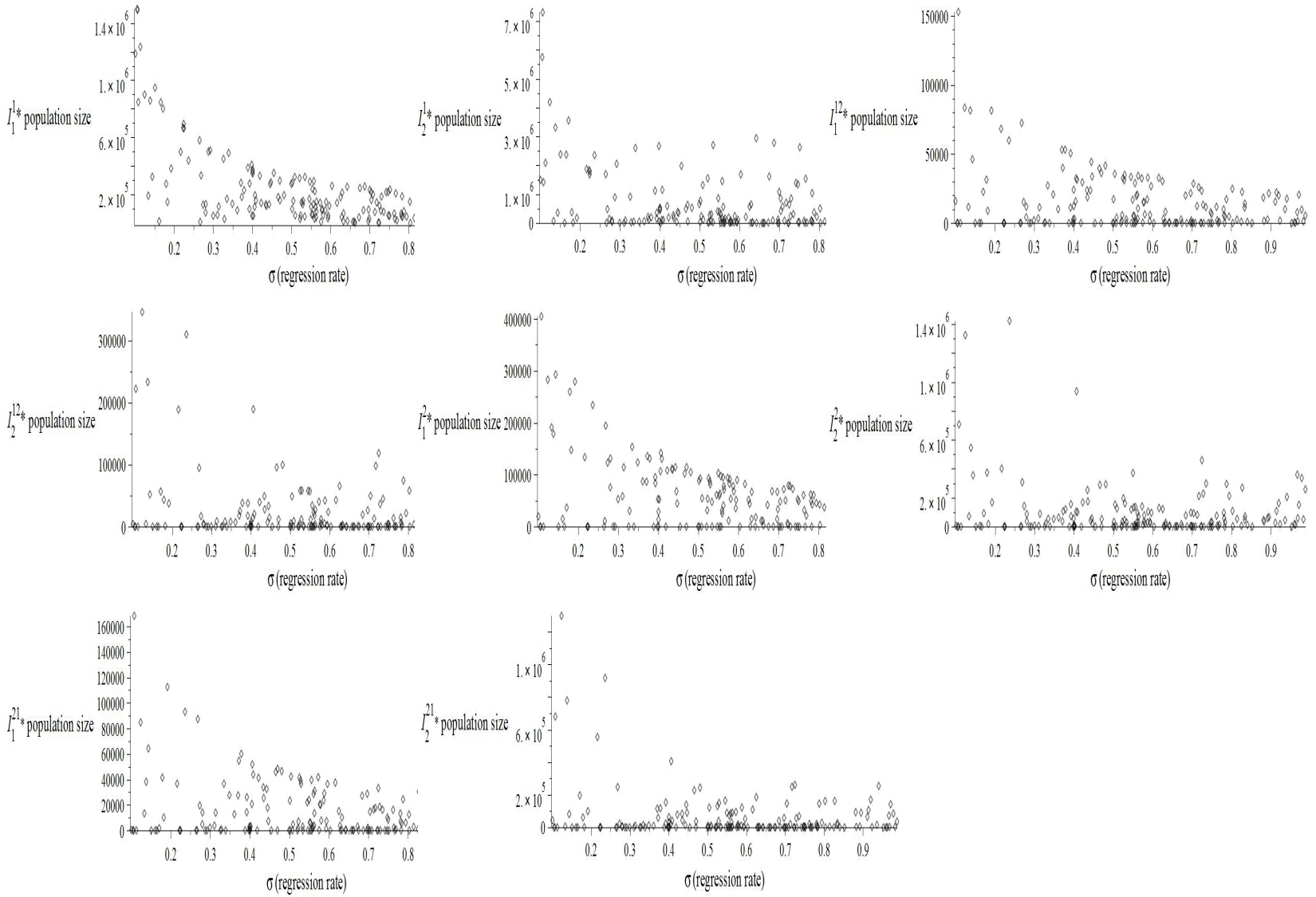


Figure 4.10: Endemic equilibrium population sizes with respect to the regression rate, σ, for the I_i^{kj} classes in Eq.(4.4), the multi-type, no cancer model.

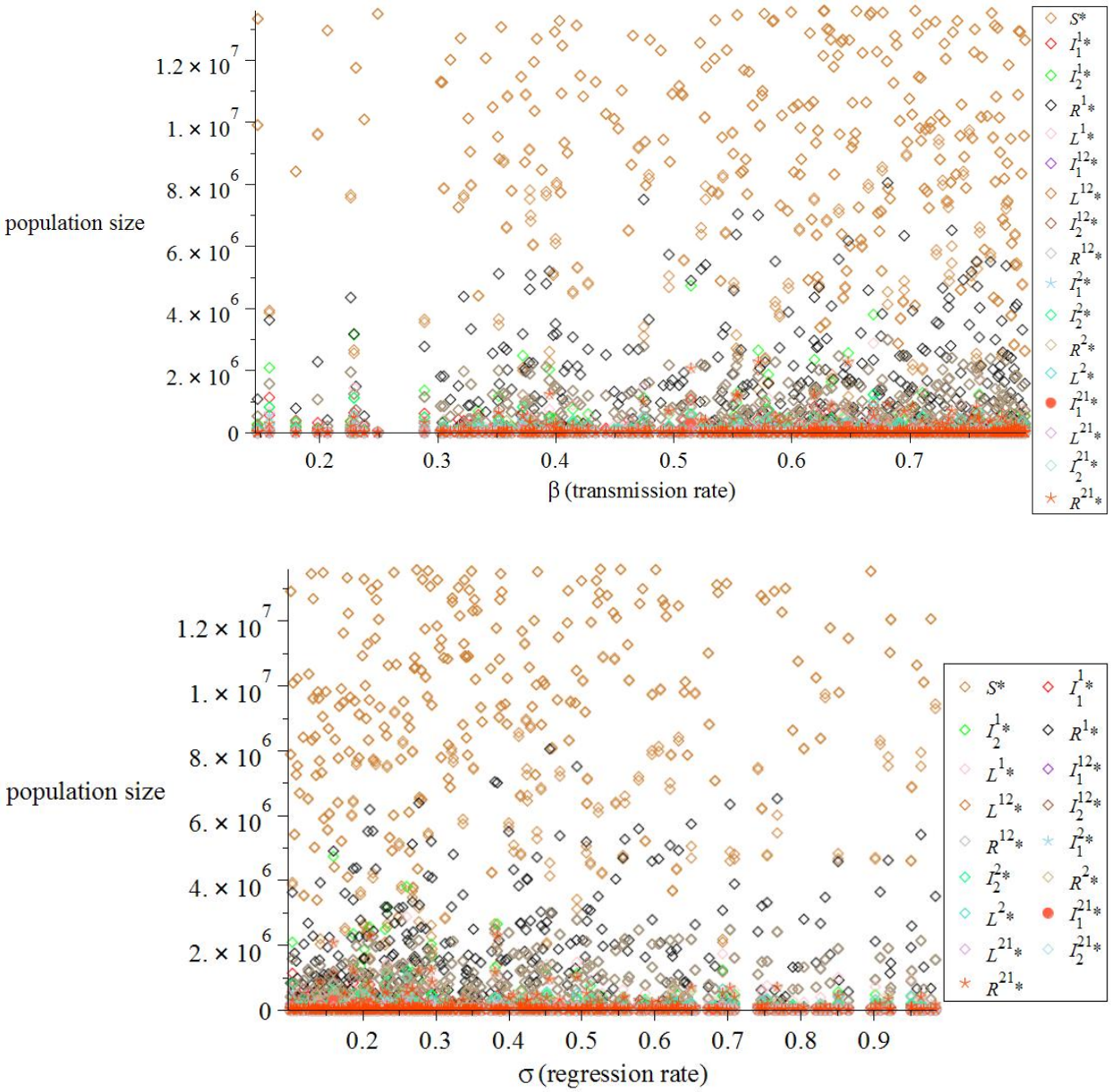


Figure 4.11: Endemic equilibrium population sizes with respect to the transmission rate, β (top), and the regression rate, σ (bottom), for Eq.(4.5), the multi-type model with a cancer stage.

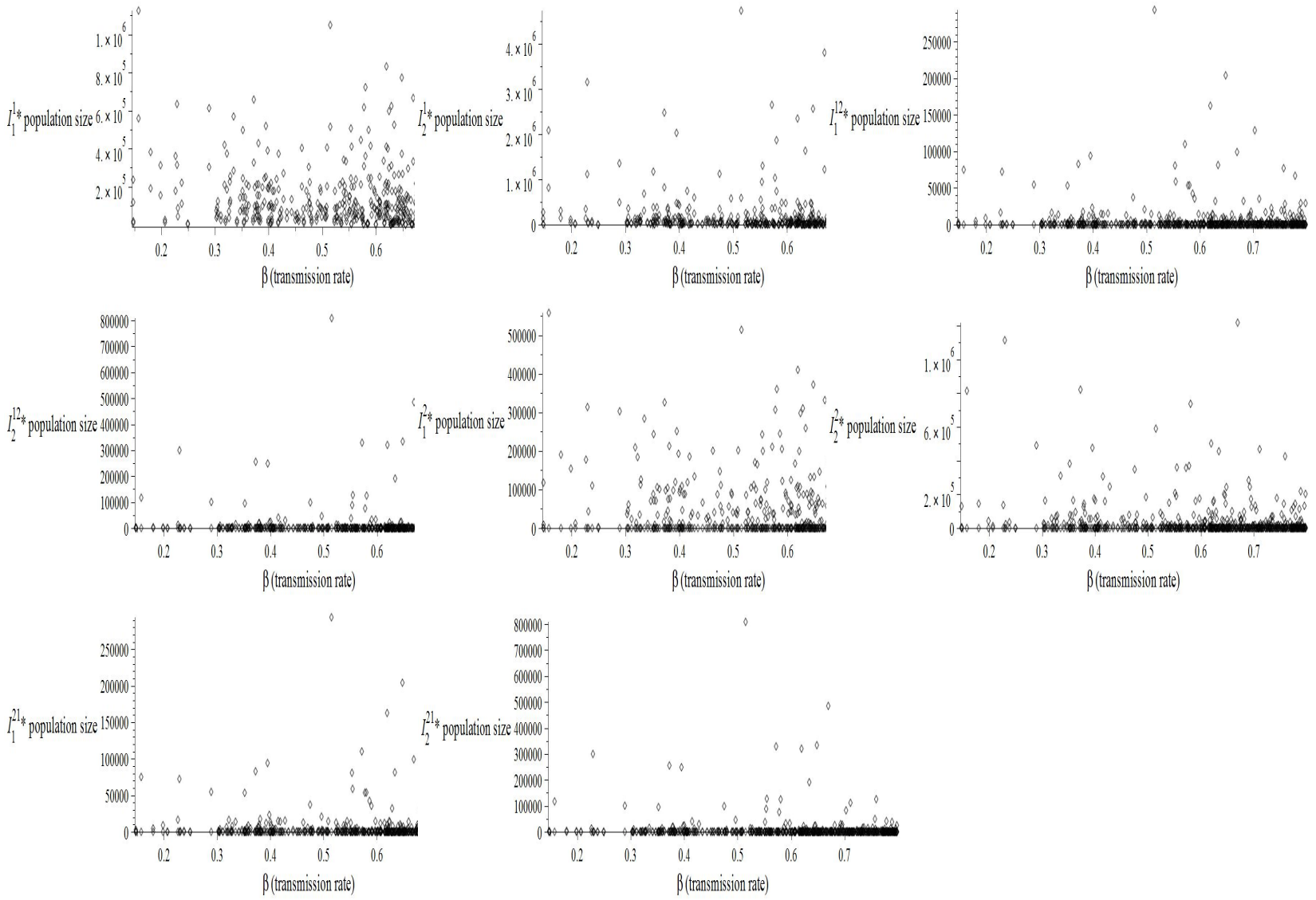


Figure 4.12: Endemic equilibrium population sizes with respect to the transmission rate, β, for the I_i^{kj} classes with respect to Eq.(4.5), the multi-type model including a cancer stage.

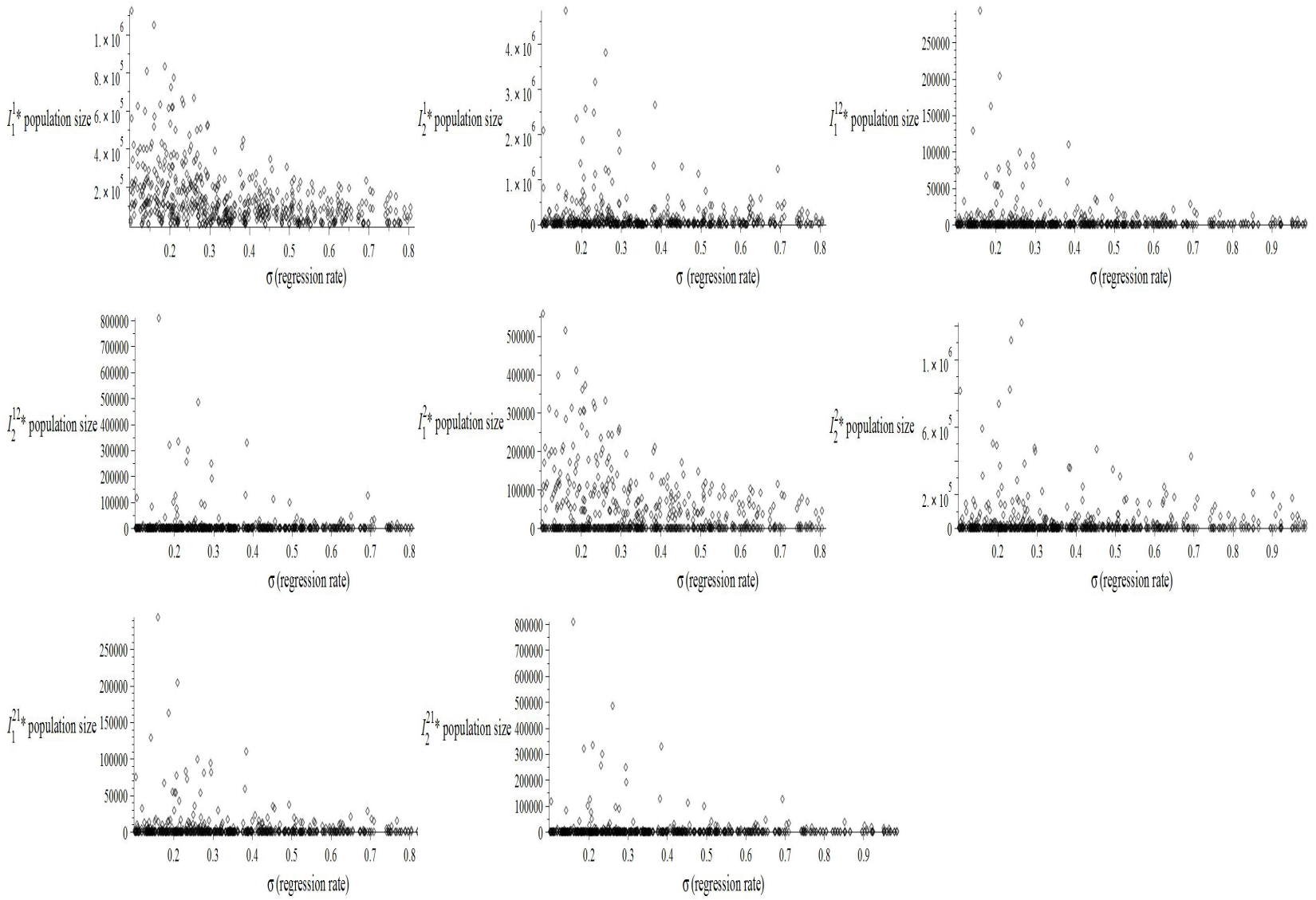


Figure 4.13: Endemic equilibrium population sizes with respect to the regression rate, σ for the I_i^{kj} classes with respect to Eq.(4.5), the multi-type model including the cancer stage.

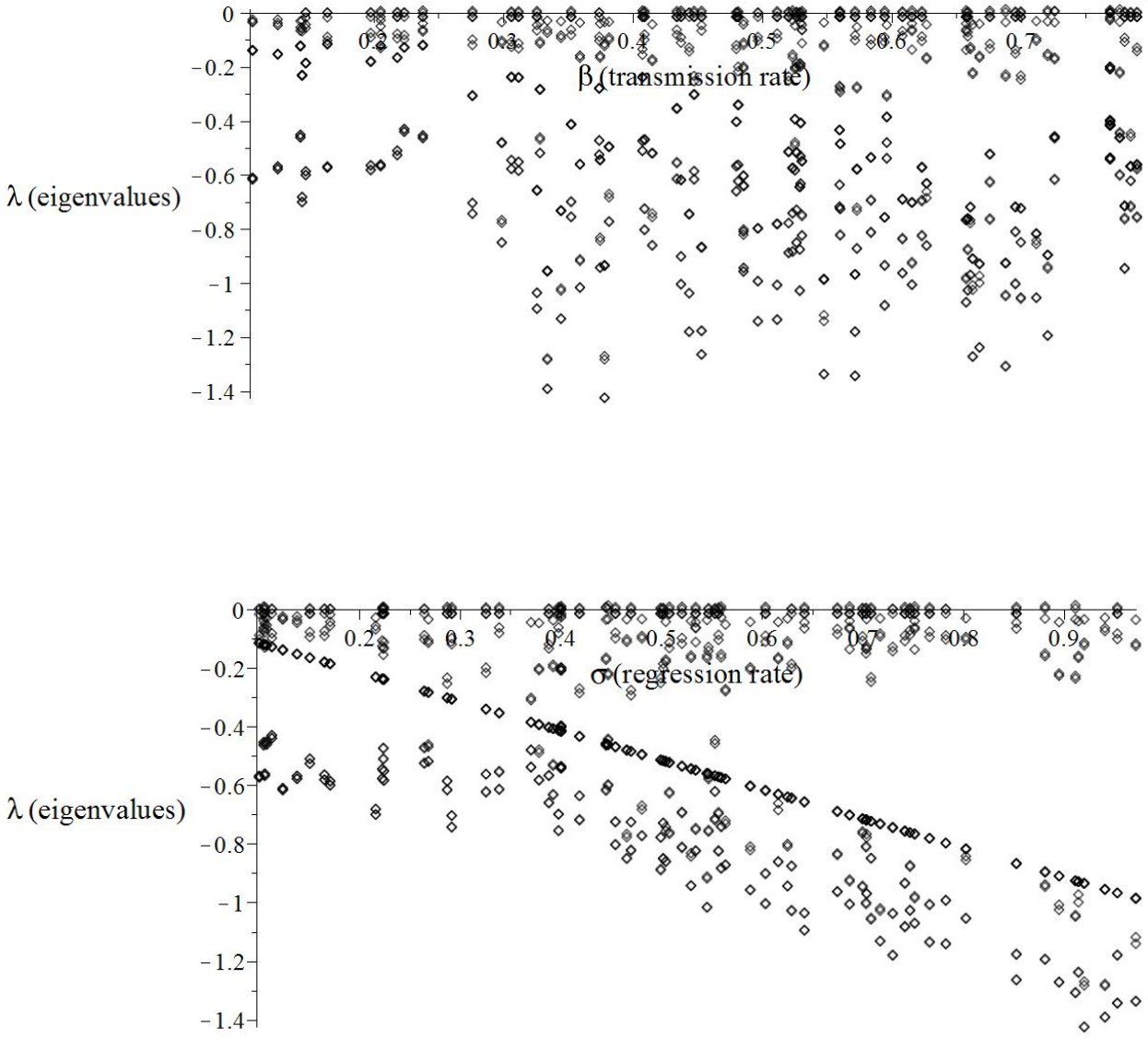


Figure 4.14: Instability of Eq.(4.4), the multi-type model, with respect to the transmission rate, β (top), and the regression rate, σ (bottom), at the endemic equilibrium point.

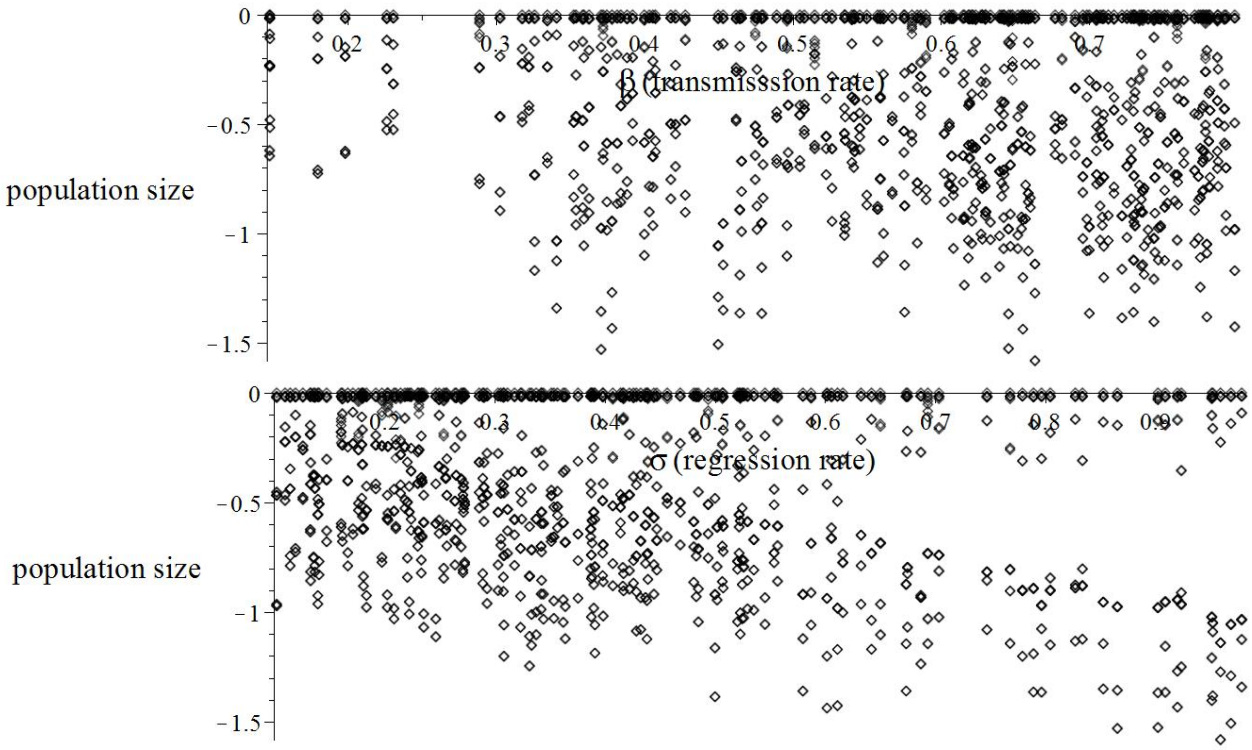


Figure 4.15: Instability of Eq.(4.5), the multi-type model with a cancer stage with respect to the transmission rate, β (top), and the regression rate, σ (bottom).

4.5 Discussion

Five models were created and analyzed to better understand the concept of infection with HPV versus "re-infection" with HPV. Each model increased in complexity with the first three models (Eq.'s (4.1)-(4.3)) being single genotype models and the final two (Eq.'s (4.4) and (4.5)) including two types of HPV. Various aspects were analyzed, including R_0, the equilibria and their stability, and the relative population sizes at the endemic equilibria.

The type reproduction number was considered for this chapter, however, while it is useful in order to single out a specific target to control in order to accomplish the larger goal of minimizing the spread of the disease [34], it does not make sense to use it for Eq.'s (4.1)-(4.5). The mode of "re-infection" is currently not known which makes it difficult to target individuals who fit either into the latent compartment or the recovered compartment. Therefore, instead of computing the type reproduction number, the basic reproduction number was computed.

There are two aspects of HPV progression that can be controlled. These are the regression rate (σ) and the transmission rate (β). The regression rate can be controlled through treatment such as excision, or cryotherapy. It is important to note, that treatment will not cure HPV, rather it will decrease the severity of the infection. Control of the transmission rate, β, is possible through safe sex practices, vaccination and the knowledge that an individual carries HPV. By decreasing the transmission rate or increasing the regression rate, it is possible to decrease the basic reproduction number. This is in agreement with the numerical results from Eq.'s (4.1)-(4.5).

All of the models have a disease free equilibrium point, the stability of which is dependent on β, the transmission rate. The single-type models' disease free equilibrium points can easily be related to their R_0. While it may be possible to do this for the multi-type models, it is beyond the scope of this thesis.

As previously mentioned, altering the regression rate and transmission rate will influence R_0, which in turn influences the stability of the disease free equilibrium point. This points to two important points in the minimization of the HPV viral spread:

1. An important aspect in the minimization of the infection and re-infection with HPV

is minimizing the infection rate.

2. A second important aspect in the minimization of the infection and re-infection of HPV is increasing the regression and clearance rates.

Both of these points are becoming more and more applicable as biotechnology advances. There are currently two vaccines available for public use (and a third in trials). These will greatly lower the transmission rate, β. Additionally, safe sex practices should be taught and practised. Use of condoms as well as monogamy is an additional way to lower the β value [23]. Corresponding to both points above is screening. Once an individual is aware that he/she has HPV (through screening), it is more likely that they will practice safe sex or receive treatment, thus lowering the β value.

There are various treatment options such as excision which should be used to increase the regression rate, σ. However, regular screening would aid in the knowledge of the existence of the tumour, thus enabling an individual to treat it. It is important to keep in mind that treatment does not cure HPV, rather, it decreases the severity of the lesion. While this could be a good thing, as the less severe the lesion is, the higher chance it has of regressing, it does not mean that the person is necessarily healthier. There is a possibility that there are lesions in other parts of the anatomy that cannot or have not been detected.

While not much can be learned from the base case model (Eq.(4.1)) with respect to the infection and re-infection debate, it is possible to observe that the change in population size over an increasing regression rate, σ, is larger than the change in population size over a decreasing transmission rate, β. This implies that changing the regression rate through screening and treatment will be more beneficial than increasing the transmission rate.

Eq.(4.2) follows the same trend for both the I_1^1* and I_2^1* classes. Furthermore, an increase in the regression rate has a more defined effect on the I_1^1* class than it does on the I_2^1* class. This suggests that increasing the regression rate will have a larger effect on a population that is infected for the first time. It also means that the compartment of individuals who are infected for a second time will always be larger than those infected for the first time. This trend is similar for all five models, however, for Eq.'s (4.4)-(4.5), it is not seen to the same degree for all eight infected classes.

Similar trends can be observed throughout Eq.'s (4.1)-(4.5).

In terms of the relative population sizes with respect to the infected populations, the I_2^1* class is always the largest population. This is followed by the I_1^1* class, however, the latter is not much larger than the remaining infected populations which are more or less of a similar size. This shows that individuals are most likely to become re-infected with their original HPV type. Furthermore, this shows that it is not necessary to include every combination of infection/re-infection of HPV types when modelling HPV. Rather, one should include infection with the original type, as well as, re-infection with the original type. From these results we can conclude that it is more relevant to model re-infection with the same type than with different HPV types.

This makes sense as the re-infected compartment includes individuals whose latent infection has become active again. These individuals will have the same type of HPV as their "original" type. Hence, it is not surprising that the largest re-infected population is one that has the same type of HPV as the original infection type.

One difference between the the multi-type models and the single-type models is the stability of the endemic equilibrium points. In Eq.'s (4.1)-(4.3), the endemic equilibrium points are always stable. However, in Eq.'s (4.4) and (4.5), the endemic equilibrium points appear to be unstable. Although the eigenvalues for the system are positive, they are very close to zero, which leads to two possible conclusions:

- The perceived instability is due to numerical error which indicates that the system at the endemic equilibrium point is stable, similar to the first three models.
- The instability of the endemic equilibrium point is real. Having said this, there are still a few transmission and regression rates that are stable, and which have the largest population as a recovered population, which again, leads to the same conclusions as the first three models.

A stability analysis was conducted on Eq.'s (4.4) and (4.5) from which it is possible to make the same conclusions as those of Eq.'s (4.1)-(4.3), indicating that the instability is due to numerical error.

Eq.'s (4.1)-(4.5) play an important role in the big picture of understanding the dynamics of HPV, as well as, in the way that we model HPV in general. Multiple infection models can be complicated to create and analyze. Hence, from this set of models, we can conclude that it is not necessary to model multiple types of HPV. This is important financially, as it means that in the case that an individual is re-infected with HPV, it is feasible to assume that the re-infecting type is the same as the original infection type, which bypasses the costs of screening.

There is much uncertainty regarding re-infection/re-activation with the HPV virus. These models help show the importance of prevention and treatment practices. It is important to use this knowledge to ensure an appropriate public health plan to deal with HPV.

5 Conclusions

HPV has a high transmission rate and a high regression rate. This can lead to the conclusion contraction of HPV is not such a serious matter, especially since there are relatively few carcinogenic types. While this last statement is true, it is misleading, as, if a high risk type of HPV causes an infection that does happen to progress, it can have serious ramifications such as cancer. Clearly, cancer affects the well being of the patient and their family, but it can also be costly to treat, both in terms of resources and financially. Hence, it is beneficial to all parties involved to try to minimize the effects of HPV both through prevention and through treatment.

Prevention and treatment programs have been implemented in many countries and have been shown to make a difference in cervical cancer prevalence. It has been shown that since the implementation of cervical cytology circa 1949, cervical cancer rates have been reduced by $60 - 90\%$ after three years of implementation [67]. The vaccines for HPV are fairly new (within the last decade) making conclusions about their efficacy relatively difficult [76]. This is made even more difficult as it can take 20-40 years to see the effects of an HPV infection [6]. Hence one benefit of screening is that it causes instant effects in the individual's health as well as the overall health of a population, while it can take up to four decades to see the effects of implementing a vaccination program.

The idea of screening versus vaccination corresponds to the results of this thesis in almost every model. Chapter 2 examines the significance of the various aspects used in both a screening and vaccination program. Two things become evident from the results of this chapter:

1. The basic reproduction number is reduced when either a vaccination or a screening (or both) program is implemented into a completely susceptible population.

2. The PRCC plots indicate that screening sensitivity and uptake are more significant in

the minimization of cancer than that of vaccination.

Furthermore, Chapter 3 shows that regardless of the screening program implemented, there will be a similar effect on the basic reproduction number.

Chapter 4 cements the idea of the importance of screening as it shows that there is a larger change in the infected population size with an increase in the regression rate (related to screening), compared to a decrease in the transmission rate (related to vaccination).

Hence, it is fair to conclude that the effects of a screening program are large and instant.

Combining the results of Chapters 3 and 4 implies the following: if it is safe to assume that an individual who has been re-infected with HPV has the same type as their original infection, then from a costing point of view, if a typing test is more expensive than a general test, it is not necessary to use a typing test. Rather, it is important to establish that individuals who have previously been infected, are indeed, re-infected. This can be accomplished through a general screening test

While vaccination is important too, the current vaccines protect against up to 9 high risk HPV types only. While they do offer protection against the most common HPV types, there are still many high risk types which can only be caught and treated through screening.

The cost of implementing a screening and/or vaccination program will vary depend on the program implemented and the country in question. However, Chapter 4 shows that individuals who are re-infected with HPV are likely to be infected with the original HPV type. This is important as it means that in low income countries, it may be advisable to skip a typing test assuming that the individual who has been infected multiple times is infected with their original HPV type. Hence, if their original HPV infection was with a low risk HPV type, then there is no point to treating them when they are re-infected.

To conclude, two main topics were examined in this thesis, numerical results such as those of screening and/or vaccination programs and analytical results such as the basic reproduction number. The basic reproduction number is less important than the other aspects in the screening-vaccination program debate as it is debatable what the actual R_0 is. Some studies conclude that it is larger than 1 while other studies conclude that it is less than one. What

all studies do agree on is that implementation of a screening-vaccination program will reduce the basic reproduction number. Hence, it is important, especially in developing countries to implement a screening-vaccination program, as the costs of treating cancer, both mentally and financially, can be greater than the cost of a screening program.

5.0.1 Future work

Treatment and prevention of HPV is a sizeable topic and difficult to model with a single model. Hence components of the prevention/treatment program should be analyzed individually as was done in this thesis. However, each component leaves a plethora of work to be modelled. This includes but is not limited to the topics discussed below.

It has been shown that vaccination does play a part in the minimization of cancer, as it prevents individuals from being infected with certain types of HPV. However, a cost analysis should be completed to understand if the long term benefits of the vaccine will justify the costs of the vaccine.

Having said this, an analysis, both in terms of cost and from an epidemiological point of view should be completed to understand how vaccinating males will effect the outcomes of these models. Males are a major source of transmission, and by targeting them as well as females, one should be able to further reduce the prevalence of cancer caused by HPV.

Chapter 4 examines the concept of infection and re-infection with respect to HPV. This set of models should be expanded to incorporate the tracking of individuals who are re-infected from the latent class versus those who are re-infected from the recovered class. Doing this should be able to shed more light on the concept of re-infection, as well as help to understand whether individuals are generally re-infected with their original HPV type or not.

Furthermore, a sensitivity analysis should be completed on the transmission rate, β, and the regression rate, σ, to confirm the results found in Chapter 4. A cost analysis should be considered too, as both prevention and treatment can be pricey and require professional administration, although prevention may require less professional training than treatment as it can be administered by a local GP.

One final topic of discussion is that of type replacement. In the successful eradication of HPV types 16/18, the next prevalent HPV type will take its place. Studies should be conducted as to examine what the best way to deal with type replacement and mutation is.

HPV can be a serious virus, and with the advent of new technology, including vaccines, there is much to learn. Epidemiological modelling can help inform policy makers, as well as biologists as to the mechanism of transmission and infection.

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6 Appendix

Parameter	Value
q_I	0.542967837631601
q_V	0.204890651199993
α_{A0}	0.0268740801188195 (year^{-1})
α_{A1}	0.0488320922689987 (year^{-1})
α_{A2}	0.136188399191519 (year^{-1})
α_{I0}	0.0171946749370184 (year^{-1})
α_{I1}	0.0288935517694315 (year^{-1})
α_{I2}	0.131978515929929 (year^{-1})
α_{C1}	0.0453153046387752 (year^{-1})
α_{V0}	0.0214328598671292 (year^{-1})
α_{V1}	0.0509953092464185 (year^{-1})
α_{V2}	0.0972134180564544 (year^{-1})
γ_{V0}	0.328863980677454 (year^{-1})
γ_{V1}	0.481859598015195 (year^{-1})
γ_{V2}	0.104291113066865 (year^{-1})
γ_{I0}	0.258380260700360 (year^{-1})
γ_{I1}	0.830242977472094 (year^{-1})
γ_{I2}	0.0786649443042148 (year^{-1})
γ_{C1}	.02(year^{-1})
γ_{A0}	0.348396211517799(year^{-1})
γ_{A1}	0.511231079519821 (year^{-1})
γ_{A2}	0.0984113101456231(year^{-1})
β	0.527216463327684(year^{-1})
ρ	0.433642122805760(year^{-1})
q	0.990032562034885
ϵ	0.806184405659902
ϕ	0.471613576241770
ψ	0.891803578133610 (year^{-1})
ζ	0.664310970748574(year^{-1})
ζ_2	0.795819583971955(year^{-1})
η	0.448538976348080

Table 6.1: Parameters used in the simulations for Eq.'s (2.1)-(2.4).

Parameter	Value
$q_{Ip} = q_{IpT} = q_{IpTy}$	0.359086208048564
α_{A0}	0.033017864169859 (year^{-1})
α_{A1}	0.073274891225565(year^{-1})
α_{A2}	0.196182244734854(year^{-1})
α_{I0p}	0.030665827414585(year^{-1})
α_{I1p}	0.044397713496558(year^{-1})
α_{I2p}	0.158402397571585(year^{-1})
α_{C1}	0.024068695670569(year^{-1})
γ_{A0}	0.358600801514842(year^{-1})
γ_{A1}	0.667245411708137(year^{-1})
γ_{A2}	0.072536569882527(year^{-1})
γ_{I0p}	0.349893263494934(year^{-1})
γ_{I1p}	0.702039463929003(year^{-1})
γ_{I2p}	0.102806505320276(year^{-1})
γ_{C1}	.02(year^{-1})
β	0.710588712556604(year^{-1})
κ	0.860110434299079(year^{-1})
η	0.504147544669074(year^{-1})
η_2	1(year^{-1})
ϕ	0.904
ϕ_2	.898
ϕ_{1a}	.45
ϕ_{1b}	.69
ζ	$1, .5, .1, .05, 0$(year^{-1})

Table 6.2: Parameters used in the simulations for Eq.'s (3.1)-(3.4).