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Using mathematical modelling to evaluate human papillomavirus vaccination programs in Canada

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies
in partial fulfillment of the requirements for the degree of Master of Science in Mathematics [1]

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[1]The M.Sc. program is a joint program with Carleton University, administered by the Ottawa-Carleton Institute of Mathematics and Statistics

Abstract

Mathematical models provide unique insights to real-world problems. Within the context of infectious diseases, models are used to explore the dynamics of infections and control mechanisms. Human papillomavirus (HPV) globally infects about 630 million people, many of these infections develop into cancers and genital warts. Vaccines are available to protect against the most prevalent and devastating strains of HPV. The introduction of this vaccine as part of a national immunization program in Canada is a complex decision for policy-makers in which mathematical models can play a key role. We use the current recommendations provided by the World Health Organization to explore the integral role mathematical models have in the decision to incorporate the HPV vaccine within a national immunization program. We then provide a review of the literature discussing the role of mathematical models in the decision to include a vaccine in a national immunization program within the context of the HPV vaccine. Next, we evaluate the current standing of mathematical models used within the context of HPV immunization, to highlight the types of models used, underlying assumptions and general recommendations made about these immunization programs. Then, we create and analyze a model to explore the possibility of bettering the current HPV vaccine strategy in Canada. We focus on the effects of the grade of vaccination and the number of doses required to eradicate the targeted strains of HPV.

Acknowledgements

First and foremost, I'd like to thank my supervisor Dr. Robert Smith? for your continuous guidance and support throughout this work. I have been extremely lucky to have a supervisor who believed in the work and my ability to complete it. Without your encouragement, knowledge and ability to motivate me this would have never happened.

I am particularly grateful to my dad for his unrelenting support and encouragement every step of the way. You were there to remind me that things only *looked* tough, and to celebrate when I finally realized it was really *that* easy all along. You are my rock. Many special thanks go to my sister, Amy, who always makes me think twice about taking life too seriously.

This thesis could not have had such a real-life perspective if it weren't for the internship provided by MITACS with the Public Health Agency of Canada. Not only would I like to thank them for the funding, but mainly for the opportunity to collaborate with those who can put this research to good use. I would like to especially thank Alain Demiers, for his insight to the epidemiology and public health perspective on the HPV vaccine, and Katherine Dinner, for her overwhelming enthusiasm about the project.

I would also like to express my gratitude toward the University of Ottawa Math-Bio team. In particular, thank you to Rachelle Miron, Dr. Frithjof Lutscher and Jeff Musgrave. Without your help and ideas, this thesis just wouldn't be the same.

Lastly, a special thanks goes to Juliein Arino for his helpful observations during the 2012 CMS winter meeting.

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Chapter 1

Introduction

Mathematical modelling uses mathematics to describe real-world phenomena and is useful when investigating questions about these systems. Models can test ideas and make predictions about the real world. They have been used to examine topics in physics, ecology, physiology, chemistry, epidemiology, engineering and population biology, among others. One very insightful application when investigating infectious diseases in particular, is to project the likely outcome of an epidemic based on different public health interventions. We use this application to look into the vaccine against human papillomavirus as a possible intervention against the Canadian HPV pandemic.

We first provide an overview on the human papillomavirus and the vaccine (Chapter 2). This includes a breakdown of viral characteristics that HPV has, how the most widespread strain infects humans, the most common health outcomes caused by specific strains of the disease and how the vaccine works to protect an individual against infection.

In Chapter 3, we give an introduction to how mathematical models have been used and could be used when a nation is deciding whether to add a vaccine to their national immunization program. We use the vaccine introduction guidelines devel-

oped by the World Health Organization as an outline of the decision-making process to include the HPV vaccine within a national immunization program. We highlight steps in this process where mathematical models are useful, and provide examples of such models.

Next, we produce a literature review of the current state of mathematical models exploring HPV vaccination in the literature (Chapter 4). The models are characterized by 10 types (static, dynamic, deterministic, stochastic, discrete, continuous, aggregate, individual-based, SIS and SIR). We explore the underlying assumptions made about HPV, the vaccine and the population included in each model. The scope and conclusions made from each model is summarized. We draw conclusions about the state of HPV vaccine models in the literature.

In Chapter 5, we develop an HPV model specific to Canadian provincial vaccination strategies. We explore the effect on the epidemiology of HPV when vaccinating girls in different grades and giving a different number of doses (two or three). We determine the threshold of eradication, as well as critical vaccine efficacies and probability of infection. Stability analysis shows the relative influence of each parameter on the threshold of eradication. Numerical simulations show the effects of grade of vaccination and number of doses on the eradication of targeted HPV types as well as the amount of time it takes to see the results of the vaccination program.

Chapter 6 concludes with a discussion, conclusion and future work.

Chapter 2

Overview of Human Papillomavirus

Human papillomavirus (HPV) is a double-stranded DNA virus of the papillomavirus family that is capable of infecting humans. HPV is a term that includes hundreds of strains of the virus, subdivided into high- and low-risk groups. These groups are defined by their ability to progress to cancerous lesions (high risk) or not (low risk). The majority of infections are unsuccessful, meaning there are no negative health outcomes caused by the infection. In women, 70% of infections are undetectable in one year and 90% in two years [57]. However, when an infection becomes productive, the health outcomes are numerous and type-dependant. These health outcomes include warts (anogenital, common, flat and genital) and cancer (anal, oral, genital). Table 2.1 outlines several of the most common diseases caused by the indicated HPV types.

This wide variety of health outcomes caused by the same virus (although not the same type) is due largely to the face that each type is able to infect different cells of the body. As such, there is a wide variety of transmission methods HPV employs. These include direct (perinatal, sexual, hands and blood), indirect (contaminated objects) and vertical transmission. HPV 6 and 11 can be vertically transmitted at birth (perinatal), although this is rare; globally, fewer then 2,000 children are born with this infection per year [103]. A risk factor that promotes perinatal transmission is the

presence of genital warts at the time of birth, although the incidence rate is still less than 1% [129]. Genital infections are predominantly acquired through sexual transmission (direct skin-to-skin contact vaginal, penile, oral and anal contact), whether or not the symptoms are present [32, 130]. Some HPV types can be transmitted from direct skin-to-skin contact from other parts of the body, such as hands. HPV has also been suggested to be transmitted through fomites (inanimate objects able to carry infectious diseases), such as towels or underwear [19, 77, 134]. This thesis focuses on the most prevalent sexually-transmitted HPV types, both high and low risk.

2.1 The Life Cycle of a Productive HPV-16 Infection

The process of infection remains largely the same for each HPV type. The main differences between the types are the specific cells they infect. Here, we describe the life cycle of a productive HPV-16 infection in humans.

HPV cannot bind to live tissue and must enter through a lesion in the skin [38]. Once HPV has entered the body, it attaches to a **surface receptor** on a **basal epithelial** cell. [1] The HPV **uncoats** and the **episomal** HPV DNA moves into the nucleus of the cell. There are about 50–100 copies of the viral episome per cell [34]. Naturally, this basal epithelial cell is constantly dividing to replenish the skin cells that are being **sloughed off** on the outer layer of the skin. HPV takes advantage of this constant division and uses cellular proteins already present in the nucleus to replicate the HPV DNA. To make sure that both the cell and the host's immune system do not detect the invasion of the cell, HPV keeps a low **copy number**: about 10-200 copies of HPV DNA per cell. HPV accomplishes this by utilizing the Early 1 and Early 2 (E1 and E2) HPV genes. These genes encode for proteins that serve

[1] Bolded words are defined in the glossary at the end of the chapter

three purposes: 1. maintain viral DNA as an episome (E1), 2. facilitate the correct segregation of genomes during cell division (E2) and 3. viral DNA replication (E1 and E2 form a complex later in this process that allows the genome to be copied, even when the cell is not actively dividing) [149].

The original infected cell in the basal layer has now divided into two daughter cells that both have HPV DNA in them [38]. One stays on the stratum basale (to continue dividing to replace sloughed off cells) while the other moves up to the next level of the epithelium, called the lower stratum spinosum. The cells in the lower stratum spinosum normally stop dividing and begin to **differentiate**. During this differentiation process, the cellular machinery that HPV was using to replicate its genome is no longer available. But HPV has another trick up its sleeve: the E6 and E7 genes. These genes are converted into proteins which stop the cell's double-checking mechanisms for the cell to proceed through the cell cycle. Since these genes override the cell's checkpoints that normally halt cell division, the infected cell now undergoes unregulated cell division. This allows for the viral DNA to be copied, producing several thousand copies per cell [34]. The E1, E2, E4 and E5 genes are also expressed in this level, to a lesser degree than E6 and E7 (see their functions later).

The **transforming protein** made from E6 degrades a cell protein called p53 [38]. Normally, if there is damage to the cell's DNA, p53 is initiated. The p53 protein stops cell growth by halting the cell cycle at the **G1/S checkpoint**, activates DNA repair and induces **apoptosis** if the repair of the DNA is not possible. The E6 protein degrades p53, which allows the cell to continue into the **S phase** of cell division. This is exactly the stage HPV needs the cell to be in to have the DNA replication machinery available. The transforming protein created from E7 plays a similar role. It binds to a cell protein called pRb, which also allows the cell to continue through the S phase of the cell cycle, even though there may be DNA damage, and greatly reduces the chance of the cell initiating apoptosis. As a result of the viral E6 and E7 genes, the

cell is now undergoing unregulated cell division. Note that all of the progeny of this cell will also be infected, because it contains both viral DNA and proteins.

The cell has moved to the upper stratum spinosum (being pushed from the newly created cells below it) and the virus is in the DNA maintenance and proliferation stages of infection [38]. E6 and E7 are still highly expressed and E4 is **upregulated**. E6 and E7 have the same functions as before, so the cell is still continually dividing. The E4 protein disrupts the **cytokeratins**, which affect the assembly of the **cornified envelope** changing the cell and allows it to have an abnormal shape. This allows the virus to exit with ease from the upper epithelial layers. The best time for the virus to modify the cell's shape is at an early stage of the differentiation process, after the cell leaves the stratum basale. One way it does that is through creating keratins. These significant structural changes for the cell can potentially trigger the immune system to detect the infection. E1, E2 and E5 are also expressed, to a much smaller degree. To make sure the cell is not detected and killed by the immune system, the E5 protein inhibits pH-dependent processing of **antigenic peptides** (i.e., the pH of the cell stays normal) [45]. It is typical of a viral infection to alter the pH of the cell when it is infected. By allowing the pH to stay the same, the cell has a much smaller chance of being detected as an infected cell by the body's immune system. E5 also plays a role in enhancing the epidermal growth factor, allowing the cell to grow, proliferate and differentiate faster [38].

As the cell moves to the granular layer, E2 binds to the HPV **upstream regulatory region** and recruits E1, which is a **DNA helicase** [38]. Now, the HPV genome is able to replicate without the cell's machinery (i.e., the cell does not need to be actively dividing anymore for HPV to copy its DNA). Since E1 and E2 are replicating the viral DNA, a higher copy number can be found in the cell (in the 1000s). This is the highest rate of DNA synthesis for the duration of the infection. E4 continues to be highly expressed while E1, E2 and E5 are expressed in lower levels. The virions are now mature and ready to be packaged and released. In preparation for this, the

two late genes L1 and L2 begin to be expressed. The proteins encoded by the two late genes form the viral **capsid**.

In the final layer of the epidermis, the stratum corneum, DNA synthesis becomes less important, and packaging the already-present infectious viral DNA is the main focus [38]. L1 and L2 are greatly expressed. L2 is expressed first and creates the minor coat protein. Soon after, L1 is expressed, encoding the major coat protein. These two proteins are attracted to each other and form the capsid around the infectious viral DNA. This allows for about several thousand new mature virions to be created per cell [34]. These cells are eventually sloughed off, releasing the virions inside of them. At this point the HPV life cycle is complete and the mature virions are ready to infect new cells.

The viral DNA can sometimes be integrated into the cell's DNA (when it is no longer an episome) [38]. If the viral DNA is integrated, and the region encoding for the E2 gene is disrupted, the cell quickly grows out of control. This is because E2 usually controls the amount of E6 and E7 expressed within the cell. When E6 and E7 are uncontrollably expressed, the above-mentioned cell division checkpoints are easily passed, leading to the cell constantly growing, as well as giving the cell an extended lifespan.

All of these changes help to turn the cell cancerous. Having one cancerous cell does not mean the cervical tissue has developed cancer in it. There are several stages of **dysplasia** (also known as neoplasia) before cervical cancer develops [38]. Cervical intraepithelial neoplasia 1 (CIN1) is the first stage. Here, abnormal cells can be seen within the basal third of the epithelium. CIN2 has developed when abnormal cells are confined to the basal $\frac{2}{3}$ of the epithelium and CIN3 when abnormal cells can be seen in more than $\frac{2}{3}$ of the basal epithelial cells. CIN3 is sometimes referred to as cervical carcinoma in situ (CIS). The Bethesda system is an alternative definition of precancerous lesions that use only two categories: low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL).

LSIL generally corresponds to CIN1, while HSIL corresponds to CIN2 and CIN3. A diagnosis of cervical cancer is determined when the abnormal cells break through the basement membrane of the epithelium. This can occur since the abnormal cells are uncontrollably proliferating within a confined space. The cells will not stop dividing, which means the space must accommodate these new cells; the only way to do this is to break through the basement membrane. Within all of these stages, the life cycle of the HPV slightly changes, although the sequence of events remain the same. The only difference is the timing and placement of where the events occur.

2.2 Immunology

HPV has become one of the most common sexually transmitted infections worldwide because it has developed four main traits to thrive in humans. First, HPV has been around for about 100 million years, before the origin of primates [110]. HPV has evolved with humans, and in doing so has developed techniques to avoid the human immune response. Secondly, the HPV genome is very stable has a slow evolution [148]. This is advantageous so the progeny viruses continue to hold the advantageous traits that have allowed HPV to survive for so long. Thirdly, HPV is able to infect humans with persistent infections, which last an average of 8.4, 8.1, 14.0, and 15.1 months for HPV-6, HPV-11, HPV-16, and HPV-18 respectively, which usually present with little to no complications for the host [71]. Lastly, productive HPV infections are able to effectively shed virions to transmit to naive individuals.

The body's reaction to an HPV infection is similar to that of other viruses. Once an **antigen** is detected by the body, there are two immune responses the body can use to defend itself [74]. The first line of defence is the immediate response called the innate immune system. It is non-specific to the **antigen**. This response has no memory associated with it; in other words, the same response will be evoked for any discovered antigen. The major functions of the innate immune system are to

act as a physical and chemical barrier to infectious agents (e.g., hair, mucous, saliva and tears), recruit immune cells to the site of infection through the production of **cytokines**, remove foreign substances through the use of specialized white blood cells, activate the adaptive immune response and induce inflammation stimulated by chemical factors released by injured cells such as macrophages, dendritic cells, interferon α, cytokines and neutrophils) .

The second long-lasting line of defence is the adaptive immune system [74]. This response is typically better than that of the innate response because it is antigen specific and has a memory of antigens it has encountered before, but it takes some time to activate. This system is responsible for recognizing the difference between foreign and non-foreign antigens, to generate the best responses to eliminate specific antigens and develop an immunological memory in the form of antibodies of T-cell receptors that can be called upon quickly in the event of a subsequent infection.

HPV is able to down-regulate the immune responses in several ways. Specific to the innate response, HPV does not provoke an inflammatory response, and there is little to no release of proinflammatory cytokines into the local environment [94]. HPV has the ability to not activate **dendritic cells** when entering an epidermal cell [43, 44]. The exact mechanism is not well known, but there is evidence that **Langerhans cells** are not activated by the uptake of HPV capsids [94]. HPV, like most DNA viruses, has mechanisms to inhibit **interferon** synthesis and receptor signalling. HPV is mostly able to stay out of sight from the immune system because there are no stages of its life cycle where any parts of the virus are circulated in the blood stream, where most of the immunological cells are present. For the entirety of its life cycle, HPV resides in the intraepithelial cells where only small amounts of immune defences are present; HPV has evolved ways to get around the defences that are present. The free-virus particles avoid the vascular and lymphatic channels, which is where most immune responses are activated, by being shed to the surface of the epithelium. HPV does not induce cellular destruction, which is a sign to the

surrounding cells and the rest of the body that a foreign antigen is present within the destroyed cell. Most of the HPV proteins formed (E1, E2, E6 and L2) have been shown to not evoke immune responses in patients with acute or persistent HPV infections, meaning the body doesn't recognize these as foreign objects.

This is not to say there is no immune response to HPV. In fact, for the most part, HPV infections are cleared by an individual's immune system before they have the chance to develop into a productive infection. For women, 50% of high-risk HPV infections are typically cleared within 8 months of the initial infection, 75% are cleared within 12 months of infection and 97% of women clear the infection within 18 months [133]. For men, 70% of high-risk HPV infections are typically cleared within 8 months of the initial infection, 80% are cleared within 12 months and 100% of men clear the infection within 18 months [51]. Clearing an infection does not automatically ensure an individual has immunity. In fact, many couples in the Hernandez study became reinfected with the same type of HPV after clearance, likely because there is a new or continuous source of infection [66]. This clearance of these persistent HPV infections is likely due to the immune system's $CD4^+$ T-helper cells, since patients who are immunocompromised and have low levels of these T-cells are much more likely to develop persistent HPV infections [28, 83, 107]. The biggest immune response is to the viral protein L1. L1 is made up of many different overlapping **epitopes** which is how the immune system detects an antigen. This response can been seen from both naturally acquired infections and vaccine-acquired infections. The natural infection provokes a weak and type-specific response, while the vaccine provokes a stronger response that may also correspond to several types of HPV.

Since the body can detect and clear most HPV infections, the potential to immunize an individual is high. By injecting an individual with something that resembles the HPV L1 protein, their immune system then reacts to this as if it were the actual infection [74]. This way, when the individual comes into contact with a natural infection, the adaptive immune system would already have type-specific memory as-

sociated with HPV, and therefore the infection could theoretically be cleared faster. The HPV vaccine is made out of virus-like particles (VLPs), which mimic the natural virus proteins, most importantly L1 [94]. These VLPs resemble the size and shape of authentic L1 virion proteins, are not infectious or cancer-causing, and have been shown to induce much higher levels of type-specific **neutralizing antibodies** when compared to a natural infection, which are also longer lasting. The current HPV vaccines work well because they evoke a stronger innate and adaptive immune response than a natural infection to the L1 protein. After vaccination, high concentrations of L1 neutralizing antibodies can be detected that remain in high concentration over time. The dose of VLPs in the vaccine is much higher and directly released to the systemic immune responses and therefore can attract the attention of the immune system. The immune responses from the vaccine are more general, corresponding to protection against a larger number of types. Through natural infection, immunity may not provide complete protection over long periods of time, while the vaccine seems to provide a longer-lasting response.

Long-term protection is determined by the memory B cells, which play an important role in long-term protection against a specific infection, since they survive for long periods of time [74]. The role of memory B cells in the immune system is to make antibodies. Each B cell makes only one antibody. The more B cells there are circulating around the blood stream for one type of antibody the faster a new infection can be fought off because of the availability of antibodies. Circulating memory B cells have been detected soon after the HPV bivalent vaccination, suggesting that protection should be sustained for a long period of time [49]. So far, protection provided by the quadrivalent vaccine has been found to last for at least eight years [52, 123]. The protection will last longer if natural re-exposure to the targeted types (including those types that an individual may be been cross-protected against) boost antibody levels. This is still unknown.

2.3 Tables and Figures

Table 2.1 **Overview of ailments related to specific HPV types.** The table outlines eleven of the most common ailments associated with specific HPV types.

Ailment	Related Type(s)	Reference
Anal Lesions	6, 16, 18, 31, 53, 58	[113]
Anogenital Warts	6, 11, 42, 44, others	[88]
Common Warts	2, 7	[128]
Flat Warts	3, 8, 10	[128, 88]
Focal Epithelial Hyperplasia (oral)	13, 32	[128]
Genital Cancers	Highest Risk: 16, 18, 31, 45 Other High-Risk: 33, 35, 39, 51, 52, 56, 58, 59 Likely High-Risk: 26, 53, 66, 68, 73, 82	[88] [88, 100] [100]
Oral Papillomavirus	6, 7, 11, 16, 32	[128]
Oropharyngeal Cancer	16	[62]
Plantar Warts	1, 2, 4, 63	[128]
Recurrent Respiratory Papillomatosis	6, 11	[103]
Verrucous Cyst	59	[79]

2.4 Glossary

Apoptosis: Programmed cell death.

Antigen: Substance that provokes the production of antibodies (immune response).

Antigenic Peptide: A short string of amino acids that the immune system builds antibodies for. When an antigen is attached to an antibody, an immune response is generated to get rid of the infection.

Basal: Furthest layer from the skin surface.

Capsid: The viral structure that holds the genetic material.

Copy Number: The number of copies of DNA within the cell.

Cornified Envelope: The outer layer of cells in the stratum corneum layer that replaces the plasma membrane to provide structure and links between cells to provide strength and waterproofing.

Cytokeratin: Proteins that provide structure for the cell in order to support cytoplasm organization and cellular communication.

Cytokine: Cell signalling protein molecules used for intercellular communication. In the innate immune response, these chemicals are released by an infected cell to notify other cells that it is infected so the susceptible cells may prepare for an impending infection.

Dendritic Cell: Immune cell which serves the main purpose is to present antigen material on the surface of cells.

Differentiate: Become a specialized cell.

DNA Helicase: Unwinds DNA to be translated into RNA.

Dysplasia: Enlargement of tissue caused by the proliferation of abnormal cells.

Epithelium: Skin.

G1/S Checkpoint: Control mechanism of the cell division cycle that halts the process between the G1 phase and S phase.

Episome: Closed circular DNA molecules, replicated in the nucleus.

Epitope: Part of the antigen recognized by the immune system.

Interferon: Proteins made and released by cells in response to a pathogen. These proteins allow for intercellular communication and trigger the immune system to eradicate pathogens or tumours.

Langerhans Cell: A cell found in the epidermis whose main function is to warn the immune system there are pathogens present.

Neutralizing Antibody: Antibody that defends a cell from an antigen by inhibiting or neutralizing its biological effect.

S Phase: Phase of the cell division cycle where the DNA is duplicated to give a copy to each of the daughter cells.

Sloughed Off: Falling off.

Stratum Corneum: The outermost layer of skin cells.

Surface Receptor: Protein on the outer surface of a cell that allows the cell to communicate with the outside world.

Transforming Protein: Transforms a normal cell to a cancerous cell through some mechanism.

Uncoat: The process in which a virus releases its genetic material into the cytoplasm of the cell.

Upstream Regulatory Region: Segment of DNA where some proteins necessary to copy the DNA attach. The genes to be copied are 'downstream' from this sequence.

Upregulate: To produce more of something (usually proteins) in the cell.

Chapter 3

Vaccine Introduction: A Public Health Perspective

Since Edward Jenner's discovery of a smallpox vaccine in 1796, we have been able to successfully eradicate smallpox and rinderpest, and are close to getting rid of polio, guinea worm disease and yaws among others [20]. The vaccine is thus a very important preventative measure against infectious diseases for the health of the global population. It is not the act of creating a vaccine that is effective in protecting individuals, it is the act of vaccination that allows us to decrease the prevalence of a given disease. It is the responsibility of a country's government to create and implement vaccination programs to protect their citizens. This is not an easy task. Overall, one must consider how to fund the program, which vaccine is likely to be most effective, and how to store and deliver the vaccine to the target population among others.

The World Health Organization (WHO) created a document outlining several key issues for a country to consider before introducing a vaccine into their national immunization program [69]. Figure 3.1 outlines the process of vaccine introduction. The first step is to consider policy issues and the second is programmatic issues.

Under policy issues, the governing body must first decide if the disease is in fact a public-health priority. This includes considering the disease burden on the population (incidence, prevalence, hospitalizations, morbidity and mortality) and the perception in the public and medical community about the disease and the vaccine (how safe the vaccine is and the visibility of the disease to influence the acceptance and uptake of the vaccine). The second factor to consider is the current and future possibility of other interventions. It is important to consider the possibility of other vaccines currently available or soon to be available as well as other types of interventions. Once it is decided that a certain vaccine is the right choice for the country, the vaccine safety (efficacy or effectiveness, quality and the risk benefit ratio), and economic and financial issues (cost-effectiveness, the possibility of a future cheaper and more effective vaccine, long-term requirements and budget changes, how to close a funding gap, program costs and financial sustainability) must be evaluated [69].

The programmatic issues that are important to consider are the vaccine formulation and presentation (immunization schedule, number of doses, how many types to protect against), supply availability (current and future), and program strength (private-sector usage, disease surveillance, adverse events, well-managed vaccine stock, phased or countrywide introduction, storage space, vaccine waste, safety equipment, staff training and recording and reporting mechanisms) [69].

There are many advantages of a publicly national immunization program as opposed to a privately offered vaccine. These include a free vaccine for citizens, large coverage, committed, active and well-trained staff, well-monitored storage and distribution, well-functioning and monitored surveillance and a constant evaluation of support from international organizations [78]. On the other hand, a public program generally has little local expertise in complex decision-making, a rapid turnover of health-care workers and senior decision-makers, a lack of resources and expertise in mobilizing the resources, no private sector training and monitoring, limited communication with other sectors and is a fragile system in need of constant help [78].

Making the decision to introduce a vaccine into a population does not ensure the program will succeed. The program has to be good enough and stay in place long enough to minimize the diseases' effects. It's difficult to choose the right program out of thousands of options for a population, since the results (reduction in disease incidence) are not seen for decades. How can a governing body make the best decision about a vaccine program now without being able to see into the future? Mathematical models may provide some insight to the right choice.

The development of two prophylactic human papillomavirus (HPV) vaccines sparked international interest in preventing the most common sexually transmitted infection [29]. These vaccines are Gardasil™ (Merck & Co.) and Cervarix™ (GlaxoSmithKline). Both vaccines protect against types 16 and 18, which cause 70% of cervical cancers, 80% of anal cancers, 60% of vaginal cancers and 40% of vulvar cancers [35]. Gardasil also protects against types 6 and 11, which account for 90% of genital warts [84]. Now that we have these vaccines, the next question is 'What is the most effective way to incorporate the HPV vaccine into a national immunization program?' Some insight to this problem can be explored though the use of mathematical modelling. While taking into account important epidemiological considerations, we can explore some likely effects of specific decisions made about the national immunization program, without actually imposing them on a population. As information becomes more readily available from clinical and scientific studies, models can be updated and recreated to reflect a more realistic view of HPV and the vaccine, and make updated predictions about the current state of the epidemic.

Models can be useful in several of the outlined key issues to consider when introducing a vaccine to the national immunization program. To use a model and its conclusions appropriately, you must ask a specific question about the immunization program (ex. Will more cases of cervical cancer be prevented with the introduction of the vaccine to 12 or 14 year old girls? Or, is it cost-effective to include vaccinating males?) and create the model using necessary assumptions about the vaccine, popu-

lation or cost. The two primary streams of mathematical models for the HPV vaccine program focus on the vaccine's effect on the level of infection of the virus in the population [139] or the impact made on the levels of cervical intraepithelial neoplasia (CIN, or cancer precursors) or genital warts. This chapter outlines how mathematical models were and could be used when considering adding the HPV vaccine to a national immunization program. Table 4.8 outlines the vaccination strategies used in the countries mentioned in this thesis.

3.1 Public Health Priority and Disease Burden

For a disease to be considered a public-health priority, it must be accepted as such by the public and medical community [69]. The disease must be perceived as a visible problem that must be addressed. The vaccine must be perceived as safe and effective. Investigating what beliefs about the disease and vaccine exist and why they exist will provide insights onto what messages to tell the public and medical communities to promote a higher acceptance of the vaccination program. Another important consideration is the disease burden (including incidence, prevalence, hospitalizations, disability and mortality) that can be prevented by the vaccine.

The most influential social aspects for citizens of the United States relating to the HPV vaccine are the lack of public information, fear, anxiety and confusion around the link between HPV and warts or cancer, a desire to know their status before getting vaccinated, distrust that the government is doing the right thing for the individuals, STD-associated stigma and the cost of the vaccine to patients and/or the amount of insurance coverage a patient has insurance coverage [2, 31, 47, 50, 73, 75, 85, 118, 125, 145, 150]. Knowing this, a game theoretic epidemiological model was created to determine the effect of public perception driven vaccine coverage [6]. They found that a socially optimal target vaccination is 67% coverage for females and 0% for males [6]. However, when adding in the perception that sexual promiscuity will increase with

the introduction of the vaccine, only 32% of female vaccination was socially acceptable [6]. This shows how the public perception can drastically change the coverage of the vaccine. As a policy-maker, it is important to look at this research and others like it to determine the social aspects which must be tackled in order to achieve optimal levels of vaccination.

In order to determine if an HPV vaccination program should be a public-health priority for the United Kingdom, Kohli and colleagues developed a model to estimate the long-term impact of the bivalent vaccine in the United Kingdom [82]. Using age-specific incidence data, HPV type distribution, cervical intraepithelial neoplasia prevalence, and cancer incidence and mortality data from the United Kingdom, the researchers were able to conclude that implementing an HPV vaccination program in the United Kingdom would likely greatly benefit the population. The estimates indicated that vaccinating 12 year-old girls would reduce the prevalence of high-grade precancerous lesions by 66%, and reduce HPV related mortality by 76%.

In Canada, a similar model was used to calculate the number of girls required to vaccinate to prevent diseases and death related to HPV infection [15]. It was estimated that 8 girls would need to get vaccinated to prevent an episode of genital warts, and 324 girls would need to be vaccinated to avoid one case of cervical cancer. Compared to other vaccines, the number needed to vaccinate to prevent one death due to varicella, meningococcal and influenza are 34,000, 21,000 and 5,000 respectively [10]. These predictions show the potential high impact in a country where 75% of sexually active adults will become infected with HPV within their lifetime [29].

Another important measure of how effective the vaccine is likely to be on a population is the infection rates. Swiss researchers developed a model to measure the impact on age-specific infection rated with several possible vaccination scenarios [8]. They concluded that the infection rate would decrease from 9% without vaccination to below 0.5% even with the least effective vaccination scenario [8]. Therefore, including an HPV vaccine with a catch-up program and/or booster should be a public-health

priority for Switzerland.

Finland is yet to implement an HPV vaccine program. In light of this, Barnabas *et al.* consider the effect of vaccination and screening programs on the epidemiology of the country [5]. In order to determine if this should be a public-health priority for Finland, the population demographics considered were the population size, sex and age distribution, and birth and death rates. Without knowing exactly how the vaccine would affect the Finish population, the authors were able to estimate that vaccinating women alone is almost as effective as vaccinating both genders. The authors concluded that HPV vaccination has the potential to make a large impact on cervical cancer incidence in the population: the highest impact occurring with high coverage and long-term initiative. From a purely epidemiological perspective, there is a lot of support for Finland to incorporate the HPV vaccine in their national immunization program.

Mathematical models can be used to help determine whether or not HPV should be a public-health priority. Models can evaluate the effect the public perception of the vaccine, virus, diseases and related issues can have on the coverage rate and financial burden of the program. Policy-makers can then take the most detrimental concerns and implement ways to counter the effect on the HPV vaccine program. Mathematical models can also help policy-makers by determining the current disease burden on the population and predicting the effect of the vaccine on this burden. Researchers can then determine if implementing a program is worth the cost and work.

If the vaccine does not enter the population through the public stream for whatever reason, it is possible for it to be available to citizens privately. This means citizens who choose to get vaccinated may do so at their own financial cost, or that of their insurers. Advantages of private doctors providing immunization include having a designated vaccine provider, a promoter of new vaccines, convenience for patients, a trusted advisor, and a well-connected healthcare advocate. On the other hand, fewer people are likely to receive the vaccine, which can lead to a lower amount of herd im-

munity; there is a high risk of inequality between the rich and poor; there is a higher chance of unrealistic expectations for the program; it is more difficult to monitor the storage, administration and records of those vaccinated; there is less funding available in the private sector; and there is a reliance on each practice communicating with the national immunization program, which may be inconsistent [78].

3.2 Other Interventions

When considering whether to add a vaccine to the national immunization program, it is important to remain open and aware to other therapeutic interventions that impact the same diseases. The infection caused by the targeted HPV types may develop into genital warts and cervical, anal, vaginal and vulvar cancers. The diagnosis of genital warts is generally through visual inspection and may include a biopsy [25]. HPV DNA testing and acetic acid application are also used to detect genital warts, although these tests are not recommended [25].

The general procedure for detecting genital cancer is accomplished by monitoring the virus' progress through the Papanicolaou test (or "pap test"). The pap test is used in screening programs that detect potentially precancerous or cancerous cells by taking a cell sample from a cervix, urethra or anus [64, 109, 141]. This screening program has led to a reduction in the incidence of cervical, vaginal, and vulvar cancer in Canada even though only 71-85% of women actually receive the screening [56, 147]. Genital cancers can also be detected through physical examinations and biopsies of other tissues. Examination approaches to catch anal cancer include the digital rectal examination, a sigmoidoscopy or a high-resolution anoscopy [141]. After detecting genital warts or cancers, specific treatment is given to the patients. These approaches are quite successful at catching the infection before it turns into cancer; however, the downside is that an individual will have a persistent infection in the first place. The HPV vaccine, on the other hand, is designed to protect an individual from ever getting

an infection of the targeted types before physical ailments can develop.

For a country, knowing about and having access to all or some of these alternate intervention strategies, the choice to implement the HPV vaccine becomes convoluted. Not only must the country decide whether to use the vaccine and which of the many possible strategies to implement, but they must also consider how to concurrently use other intervention approaches. There have been many mathematical models developed to study just that.

Canada has had cervical cancer screening programs in place since the 1960s [140]. The recommendation is that all women aged 18 and over should be screened until the age of 69, with slightly different procedures if an individual has an abnormal test result [140]. Considering that one-year participation rates range from 37% in British Columbia and Ontario to 44% in Nova Scotia, introducing an HPV vaccine program in Canada may benefit more of the population [140]. Two separate cost-utility analyses for adding an HPV vaccine program to the existing screening program was performed [15, 140]. Both concluded that adding a vaccine is cost-effective when considering the Quality-Adjusted Life-Years [15, 140].

3.3 Vaccine Efficacy, Quality and Safety

Vaccine efficacy is a measure of the ability of the vaccine to avoid the infection, or related diseases, under optimal conditions whereas the effectiveness of the vaccine describes how well the infection of disease can be avoided under usual circumstances [30]. Generally, these values are determined through clinical trials. The efficacy of both vaccines is estimated to be around 98% [53, 96]. However, since we know that the efficacy is a measure of the impact of the vaccine in an optimal population, it is important for a model to include a range of efficacy values and perform sensitivity analyses to determine the overall impact on the exact efficacy value, as well as see the range of results from the lowest to highest realistic estimate for the efficacy.

Instead of assuming the effectiveness of the vaccine is what the clinical trials claim, Ribassin-Majed and colleagues used epidemiological data from before the introduction of the vaccine and used steady-state estimates taken from a deterministic model to estimate the age-specific incidence of cervical cancer and mortality [119]. These estimates provided by the output of the model were within a 10% range of French published data [119]. The efficacy of the vaccine was back calculated from this information and it was found to be a very low estimate of the vaccine efficacy, 60% [119]. This example outlines the importance of evaluating the efficacy and effectiveness of a vaccine on a specific population. If the population studied includes a higher proportion of HPV-naive individuals (73.6% in the Cervarix trial), the efficacy estimate is likely to be much higher than a more mixed population [53]. It is important to know the population you are trying to protect in order to make a more informed decision about the real impact the vaccine will have. Not only can mathematical models be useful to make the decision to include a vaccine in the national immunization program, but with only five years into the program the Ribassin model was able to indicate the effect the vaccine program has had so far in France.

A unique perspective on the efficacy of the HPV comes from Llamazares and Smith?, who found an expression for the critical efficacy threshold. If the efficacy of the vaccine is below this threshold, then vaccinating 100% of females will not eradicate the targeted types [91]. This threshold consists of the immunogenicity of the vaccine, birth and death rates of the population, rate of viral transmission and the rate which children go from vaccinated to sexually active. The advantages of knowing this threshold are that obtaining most of this information is easy and it is population specific.

A cohort model was used to determine the effectiveness of the quadrivalent HPV vaccine in Canada [142]. They took into consideration the development of squamous cell carcinoma as well as HPV infection and natural immunity for all four targeted types. It was found that vaccinating girls at 12 years old would reduce their lifetime

risk of infection by 21%, cervical intraepithelial neoplasia stage 1 by 24%, cervical intraepithelial neoplasia stage 2 by 49% and squamous cell carcinoma by 61%. These predictions depended greatly on the vaccine efficacy (assumed to be 95%) and the waning of the vaccine. This model provides a great preliminary basis for the effectiveness of the HPV vaccine in Canada. When the vaccine program has been in place for several more years and more data becomes available, this model can be updated and used to better determine the actual effectiveness.

The safety of a vaccine is determined through a risk:benefit ratio. The risks associated with a vaccine are generally considered to be adverse effects of the vaccine. What the adverse effects are can only be determined when a population gets the vaccine. The statistics on the type and frequency of such events are tracked by national programs (such as Canadian Adverse Events Following Immunization Surveillance System in Canada and the Vaccine Adverse Event Reporting System in the United States). Models use this ratio in some cost-effectiveness studies to help determine the quality of life of individuals who are given the vaccine vs. those who are not. These studies are found in the next section.

Mathematical models are useful when determining the vaccine efficacy, effectiveness and safety of a vaccine in a particular population. Policy-makers can use these models and their results to influence choosing the best vaccine for their country and goals.

3.4 Economic and Financial Issues

Mathematical models can be used to determine the cost-effectiveness of vaccines before they are approved. In 2003, while the vaccines were undergoing Phase I clinical trials, several mathematical models were built and analyzed to determine the potential for such a vaccine. A study conducted by Sanders and Taira evaluated the cost-effectiveness of vaccinating adolescent girls against cervical cancer [122]. The

potential vaccine was estimated to be between 35-75% probability of immunity [122]. We know now the probability of immunity is approximately 98% for both vaccines [53, 96], which means this study gives a low estimate on the impact the vaccine could have in the United States. Even so, the vaccine was found to be cost-effective against cervical cancer [122]. A second study was conducted in the same year about the same population, using the same type of model (Markov) and also concluded that HPV vaccination and screening can be cost-effective [87]. However, this model pointed out several important factors that influence how cost-effective the program will be. These include the age of vaccination, duration of vaccine efficacy and cost of vaccination [87]. This is important information for health officials to note because they have the potential to make a program financially sustainable.

As scientists learn more about the vaccine and its implications, mathematical models are able to incorporate the new information and update their conclusions. Realizing the possibility that the vaccines could be used on males, the cost-effectiveness of this new strategy was evaluated [135]. Again, they assessed the end result of a vaccine program as the number of cervical cancer cases. It was found that vaccinating males decreased the number of cervical cancer cases by 2.2% which is significant; however, it is not cost-effective for the United States [135].

A conflicting conclusion was found by Elbasha *et al.*; They found the vaccinating females and males were in fact cost-effective [41]. This difference could be due to the fact that the second study included protection against HPV 6/11, accounting for all of the benefits and costs of vaccinating that were previously unknown and giving different quality of life weights to women with cervical intraepithelial neoplasia.

A third cost-effectiveness study was done in 2011, this time including cervical intraepithelial neoplasia, genital warts, juvenile-onset recurrent respiratory papillomatosis and cervical, vaginal, vulvar, anal, oropharyngeal and penile cancers [26]. It was found that including 12-year-old male vaccination may be cost-effective, if the female vaccination coverage is low. Again, female vaccination should be the priority

because it makes the most financial sense and has the highest epidemiological impact.

In order to determine the cost-effectiveness of adding a human papillomavirus vaccine to the already existing national cervical cancer screening program in Australia, this model evaluated the cost per life-year and quality-adjusted life year of HPV infection with and without vaccination [87]. The authors considered an expensive HPV vaccination program using a full three-dose schedule and a high coverage (between 70-90%). Even so, it was found that adding an HPV vaccine to current cervical cancer interventions is cost-effective for the country. In 2011, the coverage rate of girls completing two doses of the vaccine was 80% and those who completed the entire dose schedule was 73% [58]. These actual coverage rates support the assumptions made by the modellers and validate the results.

It is important not only to determine if it is financially viable to support a catch-up program but what catch-up program is the best to use. Research from the United Kingdom investigated a total of 9900 vaccine-program scenarios [27]. The programs differed from each other by assumptions made about the age-dependent prevalence of HPV infection, the accuracy of cervical screening, the way in which the cervical lesions regress, the length of natural and vaccine immunity, the transmission of HPV, the oncogenic HPV type, partnership transmission and the type of wart, among others. Out of all the scenarios that matched UK data relatively well, it was found that catch-up programs are effective, but only for about the first 30 years. A great realistic and financially stable program for the United Kingdom is to vaccinate 80% of 12-year-old girls over 60 years. This depends on the vaccine immunity being long-lived (either at an average of 20 years or lifelong). If the immunity is short-lived (on an average of 10 years), it is more effective to vaccinate girls at 14. The most important parameter in determining the effect of vaccination is the duration of protection, which is currently being investigated. However, we do know it lasts for at least eight years [52, 123].

The cost-effectiveness of a vaccine can be dramatically influenced by the wealth of the country. The story of a developing country may be very different to that of a

developed country. Cost-effectiveness studies for the HPV vaccine are mostly done in developed countries (Canada, United States, United Kingdom, Italy and France among others) but some developing countries have also been evaluated (Thailand) [136]. In this study, a Markov model was used to evaluate the impact of the quadrivalent vaccine on HPV-related diseases. Even though the vaccine is quite costly, the epidemiological impact of reducing HPV-related deaths by 54% is well worth the money.

Using all types of mathematical models to evaluate the cost-effectiveness state of a country is an important piece of scientific evidence for policy-makers. If a program was deemed to not be cost-effective, it could not be approved by the government. But the research so far shows that the HPV vaccination program is cost-effective for all countries that have been so far considered.

3.5 Vaccine Presentation and Formulation

The most important vaccine presentation and formulation considerations for a country to take into account for the HPV vaccine are the number of doses (two or three with current research), immunization schedule, realistic coverage and whether to vaccinate females or males.

Creating a vaccine depends on a certain amount of guesswork (backed up by scientific evidence), since for most vaccines we do not know the exact mechanism of protection [132]. This makes predicting the optimal age for vaccine administration and the dosing schedule next to impossible to know for every individual on the planet. For Gardasil™, six clinical trials were conducted between 1997 and 2004, and found a three-dose regimen is likely to be the most effective course [144]. Cervarix™ also follows a three-dose schedule. However, there is evidence from the Costa Rica vaccine trial that provided some evidence for an alternate two dose schedule for the bivalent HPV 16/18 vaccine [86]. Although the trial initially intended to provide three doses to

all participants, 11% of those who were considered ended up receiving only two doses while 5% received one. The results of the trial viewed in terms of the number of doses indicated a high efficacy regardless of the dosing schedule. These findings indicate that it may be possible to use fewer doses of the bivalent and maybe the quadrivalent vaccine to inoculate the population against these types of HPV. Of course, this study is not conclusive due to the smaller number of participants who had the two dose schedule and the scope of the study.

Currently, researchers are undergoing clinical trials in Canada and India (among others) aiming to determine the effectiveness of an alternate dosing schedule [37, 72]. More evidence for or against alternative dosing schedules will be discovered from three provinces in Canada (British Columbia, Nova Scotia and Quebec) who have already implemented alternate dosing schedules in their provincial immunization program [40]. Some information we do know about the differences between dosing schedules is that the number of doses given to an individual directly affects the development of immune memory through T and B cells [132]. The question now becomes how much T and B cell response is necessary to develop to invoke a lasting immune response? In terms of the dosing schedule, a team of researchers developed a model to investigate the immune responses of an alternative dosing schedule for three doses [108]. They suggest that the delay between the first and second dose is critical. Although more research is needed to narrow down the optimal dosing and immunization schedule, policy-makers can use this evidence to support a strong HPV vaccine program.

In terms of the optimal age of vaccination, French and colleagues developed a model for a potential vaccination program in Finland. The model includes cervical screening for women every five years beginning at the age of 25 or 30 [48]. Assuming that the age of sexual debut for females is 12, the programs that are explored include vaccinating girls (and possibly boys) at age 12, 15, 18 and 21, as well as catch-up programs which were given at 3, 6, 9 and 12 years after the initial age of vaccination. The most successful program was determined by the greatest reduction in cervical

cancer. The main findings of the study were that vaccinating before sexual debut maximizes the long-term impact of vaccination, including males in the strategy prevented additional cases of cervical cancer but it is much less effective than vaccinating females, and including catch-up programs can speed up the impact and decrease the cumulative number of cervical cancer cases (with the most impact occurring with a 12 year delay). These findings follow the knowledge that immunizing type-naive individuals provokes the strongest immune response to the vaccine, since the immune system has no prior memory of the virus [46].

The coverage of a vaccine is one of the most important determinants of success for a national immunization program. Elbasha and colleagues looked at the epidemiological impacts of an HPV vaccine for females and possibly males in the United States while varying coverage and vaccine immunity length [41]. The authors concluded that the long-term cervical cancer incidence was not strongly influenced by the changes in the degree of vaccine protection but were strongly influenced by the vaccination coverage [41]. Knowing that vaccination coverage is critical to the success of any given HPV vaccine program, efforts can be put into focusing on increasing the coverage. This can be done through initiatives such as national coordinated programs, cancer surveillance for non-targeted HPV types and implementing a school-based immunization program since the coverage is generally much higher than programs that are more opportunistic, clinic-based or primary-care-based [5, 95].

Determining the target population (male or female) is an important part of a national immunization program. Originally, the vaccines were only approved for females but in 2010 the advisory committee on immunization practices recommended the use of the quadrivalent HPV vaccine in males, although not as a routine vaccination [22]. One year later, the advisory committee on immunization practices now recommends that boys should be routinely vaccinated against HPV [24]. Although it is advised, research looking into whether or not immunizing males is worth it must be considered. Several modelling studies have shown that the practice of vaccinating

males and females is cost-effective if the coverage rate for female vaccination is low [26, 27, 87, 135]. Depending on the projected female coverage rate of the HPV vaccine, policy-makers should consider male vaccination. The first country to incorporate male vaccination in their national immunization program is Australia [58].

Mathematical models have been useful so far within the HPV vaccination campaign by finding the optimal number of doses, immunization schedule, coverage rates and target population. As more biological research is conducted and results are published, these models can continue to update their findings. The policy-makers can then adjust their programs in order to continue to maximize the effect the HPV vaccination program can have on the prevalent virus.

3.6 Programmatic Strength and Supply Availability

According to the World Health Organization, the strength of a given vaccine program depends on many factors. These include obtaining the full benefit of the vaccine and a well-managed vaccine stock. In order to obtain the full benefit of the vaccine, sufficient coverage must be obtained and maintained. This is so the full benefit of herd immunity can come into place. Herd immunity describes the effect if a high enough proportion of the population is immune to a disease, the rest of the individuals are protected because the disease can no longer sustain itself with such a small number of susceptible people [115]. Dynamic models have the ability to capture herd immunity and have been used to predict the effect of the HPV vaccine all over the world [5, 8, 27, 41, 91, 119, 139, 140, 143].

To help determine the best use of a vaccine stock, Keeling and Shattock built a model to determine the optimal deployment of a limited vaccine stock in a spatially segregated population to minimize the number of infected cases [76]. This is hopefully

not the case for the HPV vaccine since there is time to plan in order to ensure an adequate stock supply, but this may be the case in poorer countries that cannot afford enough of the vaccine for their population. The authors concluded that, in a situation with a short stockpile of vaccines, real-world vaccination policies need some changes in order to use this optimal vaccination strategy. In order to be proactive, policy-makers should create different policies to put in place in case of a possible vaccine shortage.

Mathematical models are not only effective predictive tools, but they can be used to assess the current state of vaccine programs already in place. They can be used to optimize the program strength in terms of getting the full benefit from the vaccines and evaluating the best way to use a vaccine stock. Future research could include evaluating the functionality of the cold chain vaccine transportation and storage system, disease surveillance and adverse-event recording mechanisms.

3.7 Conclusion

Introducing any vaccine into a national immunization program is a complex decision. The HPV vaccine provides extra complications since there are already programs in place to prevent the same ailments, there is no immediate effect on diseases that develop from an HPV infection (decades pass between being infected and developing cancer), there are large herd immunity and cross immunity effects from the 100's of HPV types, money for health programs is dwindling around the globe and before to the introduction of the vaccine the public knew very little about HPV [47, 80]. Mathematical models can provide valuable insight to many of the important decisions to be made.

Future modelling research that would benefit the decision-making process to include or build the best national HPV vaccine program includes region-specific research about the effect of two and three doses in several populations, the optimal age

of vaccination for girls and boys, the effectiveness of the vaccine, the cross-protection effects of the vaccine on other HPV types, expanding existing models to track a wider range of epidemiological outcomes and validating existing models with new data.

3.8 Figure Captions

Figure 3.1: Key policy and programmatic issues of vaccine introduction. The top green box shows the main policy issues while the bottom blue box shows the main programmatic issues for a nation to evaluate while considering the introduction of a vaccine into the national immunization program. The end results of these considerations are to begin the vaccine introduction to the population or choose to wait and possibly introduce it at a later date. Adapted from [69].

3.9 Tables and Figures

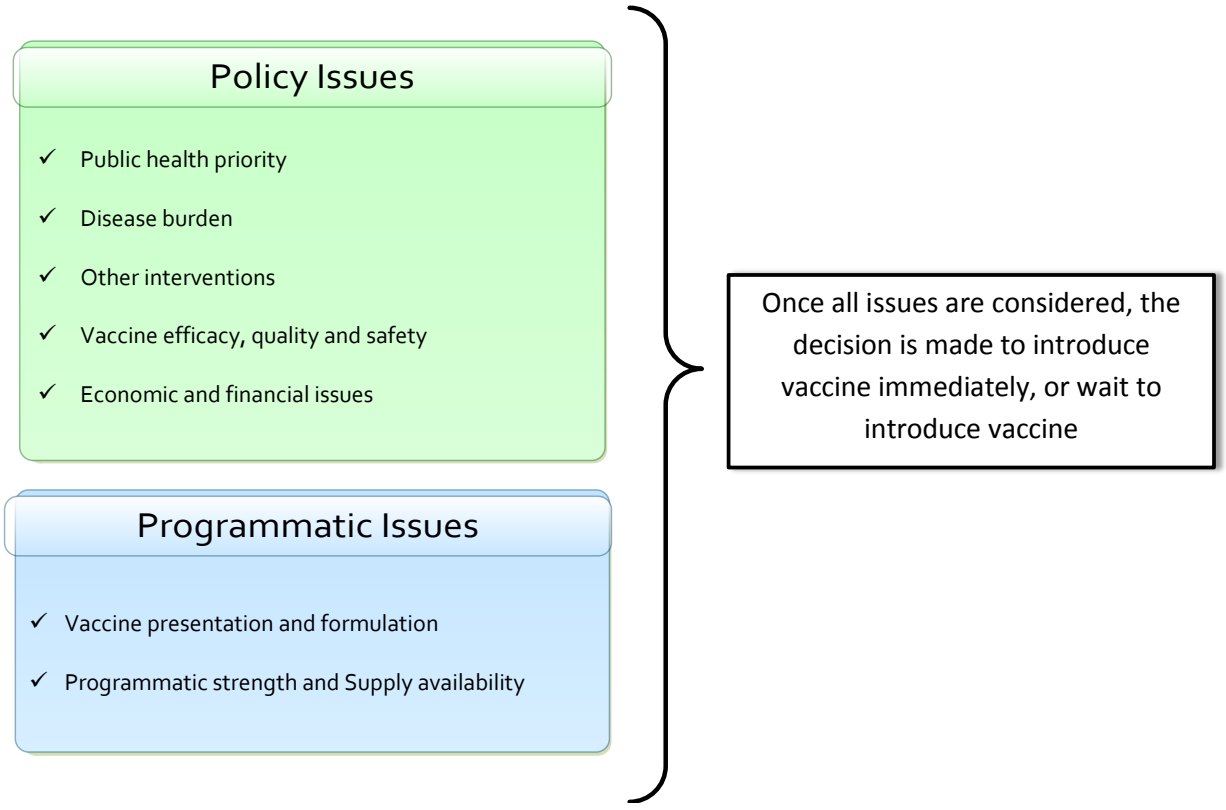

Figure 3.1 Key Policy and Programmatic Issues of Vaccine Introduction.

Chapter 4

Literature Review

4.1 Mathematical Models

Incorporating mathematical models into a decision process is important because they can provide insight to a hypothetical situation (such as a specific HPV vaccination program) at a low cost with much of the information available from research done on the vaccine before it was approved. Models can also provide insight to the likely impact of the vaccine for a specific population. Using a model to look at different situations provides a unique perspective into the future of a decision that would otherwise be unknown. Models are useful for answering specific questions, determining how sensitive a system is to parameter values and establish key parameters which influence the success or failure of a program [13]. Many countries have used the findings from modelling studies to support their decision on including a vaccine in their national immunization program. For example, Canada has used several published mathematical models to assess the financial and epidemiological impact for their country [101].

The choice of model depends on the question asked, important disease dynamics that need to be captured, relevant and available data, experience of the modeller,

time constraints, and the ease of analysis that needs to be done [80]. This section will detail the main types of models used in the context of choosing the best program for the HPV vaccine.

In the context of national HPV immunization programs, there are several types of models that can be useful to give insight to the epidemiological or financial impact of a vaccine program. The base of infectious disease models are classified as SIS (Susceptible, Infected, Susceptible) or SIR (Susceptible, Infected, Removed/Recovered), based on the natural course of infection for HPV. Both types are used for HPV because we still do not know whether there is natural type-specific or cross immunity associated with HPV. Models can be classified as static (at equilibrium) or dynamic (change with respect to time), deterministic (events occur with fixed parameter values) or stochastic (events occur by chance), discrete (time steps) or continuous (continuous in time) and aggregate (change in health states are based on the average of the population) or individual-based (individual behaviour is remembered and can affect future decisions) [13, 80]. This information is shown in Table 4.7. Lastly, through the analysis of these models, many modellers explore an important epidemiological concept called the basic reproductive number. Although this concept is explored by determining thresholds of stability for the disease-free equilibrium, different underlying model assumptions and interpretations of the threshold based on vaccination strategies allow researchers to explore the affect an HPV vaccine would have on a particular population [65, 90]. Table 4.6 outlines which of these properties the 18 models considered use.

When using mathematical models to help make a decision, it is important to remember that models cannot include and account for everything. They are not perfect, since adding more complexity to a model makes it harder to analyze [80]. Certain assumptions must be made about the vaccine program, such as: "Will the program continue to be financially supported and continue in the same fashion?" However, building many models to answer different questions will help give a bigger picture about the future success of vaccine interventions. Because of these pitfalls,

it is important that a government make a decision for a vaccine program based on several distinct models. Understanding these limitations and looking for the model's assumptions will help the reader critically evaluate how useful a specific model is to their situation.

4.2 Base Model

There are two basic models used to describe epidemics. The first is called an SIS model. In this type of model, the population is divided into susceptible (S) or infected (I) individuals. Individuals in this type of model get the disease, then recover without immunity. Many models have used this form [1, 7, 12]. The second basic type is an SIR model. In these models, individuals are classified as susceptible (S), infected (I) or recovered/removed (R). This last class accounts for individuals who have developed immunity (either natural or through vaccination). This base model is used more frequently, perhaps since an SIS model is a special case of an SIR model [5, 7, 8, 12, 27, 68, 91, 142]. Modifications are made to these base models to appropriately describe a specific disease. For HPV, the natural history of an HPV infection is still unknown. Looking at the population level, HPV has a high prevalence of infection in teens and then again in the middle-aged population. There are three main hypotheses that explain the unique pattern. First, the infection could either become latent and reactivate at a later time (i.e., the individual remains latently infected); secondly, the virus could be cleared and the second appearance in the population represents reinfection with the same type; lastly, reinfection could occur with a different type (i.e., there is a possibility of acquiring natural immunity for a certain amount of time) [61]. Since this uncertainty of the natural infection of HPV exists, it is not clear whether an SIS or SIR model is better suited to represent HPV.

The Baussano study explores the effect of using two different base model types (SIS and SIR) when used in the context of HPV vaccination programs [7]. This par-

tial integro-differential age-structured model takes into account screening programs, sexual risk behaviour, the effect of age of infection and age of pre-cancerous lesions on the natural history of cervical cancer in Turin. The vaccine against HPV 16 is given either to girls, or both sexes, before their sexual debut. Three scenarios with both base models were explored. The first was lifelong protection from the vaccine, the second included a vaccine that waned 7 years after vaccination (so that 50% of the initially vaccinated population would still be protected), while the third scenario waned after 14 years. The results showed that the vaccine was more effective using an SIS model than when using an SIR model. This follows from the structure of the model, since an SIR model includes both natural and vaccine immunity against HPV types. This study is important because the natural history of HPV is not yet fully known. This study also helps bring awareness around the fundamental assumptions that mathematical models must make, and provides a better base to understand the conclusions drawn from one type of model to another.

4.3 Type of Model

Static vs. Dynamic

A static model can be seen as taking a snapshot at a single point in time because it describes the structure of a distributed parameter system [21, 92]. For an infectious disease network model, this can be interpreted as the underlying assumption that the number and identity of an individual's contacts remain fixed throughout the outbreak, so the risk of acquiring the disease is constant for each individual [36]. A cervical cancer model may assume that the force of an HPV infection can change as a function of age or other categorizing feature, but it is constant over time for that compartment [80]. Static models are generally used to comparatively assess screening or vaccination strategies [80]. Examples of static models include Monte

Carlo simulations and optimization models [21]. Dynamic models are able to keep track of the changing population between defined compartments over time; in other words, the state variables change over time [21, 33]. Individuals constantly enter (usually by birth) and exit (usually by death) the model, which means the model has no natural stopping point [33]. However, a steady-state solution is generally approached in the long run, which is generally interpreted as the long-term outcome of the intervention strategy. In a dynamic HPV model, the probability of an individual acquiring an infection depends on the sexual contact patterns of an individual, the transmissibility of the considered HPV types and the type-specific prevalence of the infection in the population [80]. One important distinguishing feature for vaccination in static models is that only the individuals who are vaccinated receive any kind of protection against the disease. Thus, static models generally underestimate the benefits of a vaccination program [33]. This differs from dynamic models that take into account the effects of herd immunity and therefore are more suited to answer questions of widespread vaccination [80].

Mathematical models are useful in determining the likelihood of success by using only one type of intervention or many. This success can be measured in financial or epidemiological terms. Of course, since every country has their own resources, these types of models must be specialized to encompass the current and possible future intervention strategies. A Markov model was developed to assess the situation of cervical cancer screening and vaccination in the United States [87]. This model evaluated the incremental cost per life-year gained for vaccination only, screening only and a combination of the two. It was found that adding in vaccination with a 3 or 5 year screening interval was not cost-effective. However, vaccination and a delayed biennial screening program was cost-effective. This study underlines the importance of determining not only whether adding vaccination to screening is effective, but evaluating which vaccination and screening program are most effective. Models have the ability to assess a large number of intervention therapies and can therefore be

useful tools in evaluating the best combination of therapies to use.

An example of a static model is provided by Bergeron *et al.*, who aim to assess the cost-effectiveness of adding a quadrivalent HPV vaccination program to the current screening program in France [9]. The cost-effectiveness is measured by life-year gained and quality-adjusted life-year. This Markov model is considered to be static because it uses (static) transition probabilities to describe how people of a particular gender and age group progress from one disease state to the next. This probability remains constant for each category every time the model is run. This model follows a cohort of females from 14 to 85 years old. Girls at 14 are considered eligible for the vaccine, 80% of whom receive the vaccine. The model includes the natural history of infection, CIN 1, CIN 2, CIN 3, cervical cancer and genital warts. The vaccine is assumed to be 100% effective, reducing the prevalence of CIN 1 by 35%, CIN 2/3 by 55%, cervical cancer by 75% and genital warts by 90%. The vaccine is assumed to provide lifelong immunity; however, the possibility of a booster given to 50% of the originally vaccinated women is explored through sensitivity analyses. Both the program with and the program without the booster are considered to be cost-effective (under €50,000 per quality-adjusted life-year).

Static models can also be used to assess the epidemiological outcomes of different vaccination programs. A static cohort model created by Brisson *et al.* assessed the programs based on calculating the number of women needed to vaccinate to prevent an HPV-related event during their lifetime (as measured by number needed to vaccinate, NNV) [15]. The vaccine was given to 12 year-old girls and was assumed to be 95% efficacious (ranging from 70–100% in sensitivity analyses), with the possibility of lifelong immunity or a waning vaccine (3% per year or within 10 years). The length of protection was found to be highly influential on the results. The HPV types considered are placed in four categories: low risk, 16, 18 and other high risk. It is assumed an individual who is co-infected with one or more HPV types develops a more aggressive infection than someone who is only infected with one type. Lifelong natural immunity

is produced from an infection with HPV 16 or 18. Cervical cancer screening and treatment are included. Brisson and colleagues used an intensive parameter-fitting procedure to identify 209 different parameter sets that reproduce Canadian HPV type-specific data for infection, CIN, cervical cancer and genital warts. The fitting procedure involved searching 10 years of literature for type-specific data to define a range for each parameter, choosing 200,000 parameter sets from the uniformly distributed ranges, and picking the sets that matched their epidemiological data. Using these parameter sets, the NNV was calculating by dividing the size of the vaccinated cohort by the predicted number of HPV-related outcomes prevented by the vaccinated cohort throughout their lifetime. This calculation resulted in estimating the NNV for genital warts as 8, and 324 for cervical cancer with a vaccine that did not wane. For a vaccine that did wane where a booster was available, the NNV for genital warts increased to 14 and 480 for cervical cancer. Compared to three other vaccines, the NNV is 30,000 to prevent one death caused by varicella, 21,000 to prevent one meningococcal-related death and 5,000 to prevent one influenza-related death. The authors conclude that a HPV vaccine will likely significantly reduce the incidence of HPV-related outcomes.

Dynamic models are useful for exploring the effects of different widespread vaccine strategies [80]. A recent model used a dynamic ODE model to estimate the potential impact of vaccination of cervical cancer incidence in France [119]. The population is stratified by age, gender and sexual behaviour. They explore several strategies including the current one (vaccinating 30% of 14 year old girls) and potential strategies (vaccinating younger females, including male vaccination and increasing the coverage rate to 80%). The vaccine is assumed to have 90% lifelong efficacy against HPV 16 and 18. The transmission of HPV 16/18 for each gender depends on the probabilities of infection per partnership (based on sexual behaviour category), the number of sex partners and the proportion of infected individuals in a pool (which depends on age and sexual-behaviour), which is common for dynamic models. This model assumes

that individuals enter the model after sexual debut (at age 14) and the regression of cervical precancerous lesions is due to treatment or spontaneous regression. Since the model focuses on vaccination strategies, cervical screening programs are not included and women who have been previously screened have the same status as those who have not been. The authors conclude that, for France, the most important factor for the vaccine program is increasing the vaccine coverage rate, which may be aided by vaccinating younger girls. They also concluded that adding in male vaccination will moderately help lower the incidence of cervical cancer.

Hughes, Garnett and Koutsky developed two different dynamic models to investigate the population-level impact of a theoretical (at the time) HPV vaccine [68]. The goal of the first model is to explore the effects of sexual mixing (as described by high, medium or low levels) and vaccine characteristics (effectiveness, waning, female-only or both sexes) on the effectiveness of various vaccination strategies using ODEs. The second model, which uses PDEs, focuses on what the reduction in HPV infections due to the vaccine and the potential decreased rate of disease progression means for cervical cancer incidence. The results of these models show that population characteristics (sexual mixing and rate of partner exchange) and vaccine characteristics affect the steady state HPV prevalence. In particular, the heterogeneity of sexual mixing plays a magnified role for a population with lower coverage. As the heterogeneity in the population increases, two things happen: the vaccine coverage needed to eliminate the disease also increases, and the additional benefit of vaccinating men decreases. Another interesting point this model brings to light is the effect of the relative risk of transmission from a vaccinated individual compared to an unvaccinated individual. Under a female-only vaccination program, this parameter plays little to no role, but when including male vaccination this parameter has a larger effect. This could lead to a situation where the prevalence of infection in men is greater than or equal to that in women, providing the transmission is low enough. If a population enters this situation, this switch in prevalence could mean drastic changes to the vaccine program

down the road. The authors make an important distinction between the effect of the vaccine on the prevalence of infection verses related diseases. The model is able to effectively show that, for a vaccine that provides protection for only some high-risk types, the reduction in disease incidence may be less than the reduction in infections since other HPV types may take over the niche. Through these models, the authors were able to provide insight to important population characteristics that could lead to program failure.

4.3.1 Deterministic vs. Stochastic

A model is considered to be deterministic if the future is determined by the present and past states [3]. Each time a simulation is run with the same parameter values and initial conditions, the same result will occur. Models comprised of differential and difference equations are part of this category. The alternative composition of a model is called stochastic. These models allow for different outcomes to occur with the same initial parameter values. A random process that evolves during time is embedded in these models. The behaviour of the model cannot be entirely predicted [21]. A Markov model is an example of a stochastic model. An advantage of including randomness in a model is it builds in the known uncertainty of parameter values. Deterministic models can also take uncertainty of parameters into account by performing a sensitivity analysis, although this is not built into the model.

Deterministic models provide valuable insight to vaccination programs of all types. Before using a model for a specific application, such as an HPV immunization program, it is important to understand the base models in general terms first. A study published in 2011 investigated how a prophylactic vaccine is best divided between males and females in order to lower the population prevalence of infection [12]. They used HPV in the Netherlands as an example to solidify their conclusions. They divided the population based on age and gender while defining the force of infection

based on the sexual activity of an individual and their contact network. This study is unique because it considers the possibility of a male-only vaccination program, and is the first to look at a special case of the model, using the HPV vaccine in a population of men who have sex with men (MSM). The study found that if the objective of the vaccine program is to eliminate the infection from a heterosexual population with as few doses as possible, the best strategy is to focus on vaccinating either males or females. The most effective gender to vaccinate is the one with the highest prevalence before the vaccine program is put into place. Changing the goal of the vaccination program to maximize the reduction of infection in the population is more important when looking at the infection on a population level, verses an individual level. Vaccination of both genders should be considered if less than 40% of females are vaccinated or in a population with a high HIV prevalence. A population with a more heterogeneous sexual contact network leads to a lower degree of herd immunity and a lower impact of vaccination for a given coverage. Deterministic models not only make up the majority of epidemiological-based HPV models, but they are useful in providing insight for both general and specific vaccination programs.

A classic example of a deterministic HPV vaccination model is the French *et al.* PDE model [48]. The purpose of this paper was to explore the effect of age of vaccination (either at 12, 15, 18 or 21 years old), gender to vaccinate (either female-only or female and males) and the potential value of catch-up programs (a one-year program implemented 3, 6, 9 or 12 years after vaccination) on the number of cervical cancer cases in Finland. The researchers considered HPV-16 infection in a population stratified by age, sex and sexual activity classes. Complete natural immunity was achieved for women who cleared the infection. A five-year cervical cancer screening program was included in the model structure. The vaccine was assumed to be 100% efficacious throughout an individual's lifetime and given to 70% of the population. The authors were able to pick up on three general qualitative guidelines for vaccination programs: vaccinating before sexual debut maximizes the

long-term impact of vaccination; catch-up programs can speed up the impact of the program and decrease the cumulative number of cervical cancer cases; and vaccinating males prevents additional cases of cervical cancer, although the proportion is smaller than the associated increase in the fraction vaccinated. These guidelines are common to many models, which shows how essential these factors are to the success of an HPV vaccination program.

Stochastic models are commonly used for cost-effectiveness analysis, but they also have a variety of applications for the HPV vaccine programs. Goldhaber-Fiebert and colleagues developed a model before the vaccine programs were implemented with the intention of determining the current state of knowledge of the natural history of HPV-related cervical cancer, and how screening and/or a vaccination program can improve the incidence of cervical intraepithelial neoplasia and cervical cancer [54]. They developed a stochastic microsimulation model that considers mutually exclusive health states and simulates the transitions of individuals between them. The health states considered in the model are: no infection; infections with low-risk HPV, HPV-16, HPV-18 or other high-risk HPV types, which are further broken up into no CIN, CIN 1 or CIN 2/3; and local, regional or distant cancer, which can be undetected or detected. The model is individual-based, where each female enters the model at 9 years old, prior to sexual debut, and remains in the model until death. Every month, each woman is given a transition probability to be infected and move between the health states that depend on HPV types, age, history of prior infection, type-specific natural immunity, previous treatment for CIN and screening patterns. This model assumes that the regression and clearance rates are equal for HPV 16 and 18, women can move between all CIN states with one type of HPV infection; any HPV infection can be naturally cleared; and once a woman develops cancer, it is assumed she receives treatment and remains in the cancer compartment until her death. The vaccine is assumed to be given to all children prior to age 12, with 100% efficacy and lifelong protection against HPV 16 and 18. For the parameter estimation, it is assumed that

a chi-square distribution is a good approximation for the distribution of the goodness-of-fit scores across simulations. The model is used to predict health outcomes and the uncertainty surrounding cervical cancer screening, HPV-16/18 vaccination and combinations of the two approaches. After an intensive process of model parameterization, calibration and evaluation, 50 good-fitting parameter sets were used to predict the expected reductions in the lifetime risk of cancer. The model predicted a reduction of 76% (69–82%) with annual screening, 69% (60–77%) with biennial screening, 75% (66–88%) with vaccination alone and 89% (83–95%) with vaccination and a 5-year screening program. The advantages of this model are the ability to incorporate multiple HPV types and allowing for a woman's past history of screening and risks to play a role in disease progression. Caution should be taken when using the results of this model because it does not capture herd immunity effects, other cancers and disease outcomes (eg., genital warts) caused by these HPV types, and does not take into consideration the effect of males (both in terms of infections and vaccination).

Another paper published in the same year aimed to develop a general population-based model which could be used to evaluate HPV vaccine programs in different countries, but the parameters and transition probabilities between disease progression states are calibrated to match the United Kingdom [82]. This age-structured Markov model uses three modules to incorporate the natural history of HPV, screening programs and vaccination programs. The high-risk HPV types taken into consideration with this model are 16, 18, 31, 45, 52 and others, while the low-risk types are grouped together. The health states considered are uninfected and disease-free, infected with HPV 16/18, CIN 1–3 and invasive cervical cancer states 1–4. Similar to the last model, this model assumes regression between any of the CIN states is possible; once an individual reaches a state of cancer, the cancer is treated, but the individual remains in the same cancer state for the remainder of their lifetime. The modellers assume that three doses of the vaccine are given to adolescents providing full protection in one year, this protection lasts throughout their entire life, and girls

are vaccinated before they enter the model (and before their sexual debut) at 12 years old. This model assumes screening programs do not change through the course of the simulation and the success of CIN treatment is 90%. Nine scenarios were explored with this model: 1. Base case current (2007) screening practices, with 100% coverage, 95% efficacy for HPV 16/18, 50% for HPV 31 and 90% for HPV 45. 2. Lower efficacy for HPV 16/18. 3. Higher efficacy for HPV 16/18. 4. 80% vaccination coverage. 5. Vaccination of girls at 10 years old. 6. Vaccination of girls at 18 years old. 7. Vaccine waning for HPV 31, 45. 8. Vaccine waning for HPV 31, 45 with a booster after 10 years. 9. Decreased HPV type distribution of HPV 16/18 in cervical cancer. The model estimates that vaccinating 12-year-old females will lead to a 66% reduction of CIN 2/3 prevalence and prevent 77% of cervical-cancer-related deaths. Sensitivity analyses explore the effect of the efficacy varying between 90 and 100%, changing the age of vaccination and adding in a booster vaccine to the program. The success of the vaccine program was found to be most sensitive to the age of vaccination, where the highest probability of program success occurs with a lower age of vaccination.

Some parameters used in models are easy to approximate and interpret. For example, the birth and death rates, and the demographics of a population are generally considered to be good data that is easy to access. Other parameters are difficult to know because they are almost impossible to calculate, like the transmission rate, or are still unknown, like the length of protection from the HPV vaccine. Stochastic models are very useful at providing insight into the effect these quantities have on the outcome of the model. A model developed by Van de Velde, Brisson and Boily aimed to quantify the uncertainty created by the underlying parameter assumptions [142]. The model included HPV infection (divided into low-risk types, 16, 18 and other high-risk types), CIN 1, CIN 2/3 and squamous cell carcinoma. This was accomplished by creating a cohort model and testing 200,000 parameter sets which validate the model to North American epidemiological data (based on the disease states). The parameter sets were found from defining ranges based on published work for all pa-

rameters, and using one combination of parameter values as a set (the combination was found through a uniform distribution of the parameters and using Latin Hypercube Sampling to choose values). They chose 164 parameter sets which accurately predicted the epidemiological data, narrowing down parameter ranges. These results were cross-validated by checking that the parameter sets that were not chosen do not accurately predict the results from the epidemiological data. The results indicate that the duration of protection and rate of acquiring natural immunity to type-specific HPV are the two most influential parameters, while the uncertainty of the model's predictions is most influenced by the efficacy of the vaccine and waning. Current research has still not shown accurate predictions of these parameters, which hinders the ability of mathematical models to predict the outcome of HPV vaccination programs. Still, this model suggests that vaccinating 12-year-old girls would reduce their lifetime risk of HPV infection by 21% (80% credibility interval: 17, 29), CIN 1 by 24% (80% credibility interval: 17, 31), CIN 2 by 49% (80% credibility interval: 36, 60) and squamous cell carcinoma by 61% (80% credibility interval: 47, 73).

4.3.2 Discrete vs. Continuous

Time is an important consideration when looking at an HPV vaccination program. For models, there are two ways to consider time. The first is discrete, where the state variables change only at a countable number of points in time [21]. It is only at these points in time where an event occurs, or there is a change in state. The discrete concept of time resembles everyday life since, in order for change to happen, some time must pass by [111]. This contrasts with a continuous-time model in which the state variables change in a continuous way, and not abruptly from one state to another [21]. Continuous time is often modelled by differential equations or integrals [111]. Both model types have been used within the context of HPV immunization program models.

Discrete models are useful tools to investigate how many people are in which states during a snapshot in time. Depending on the goals of each model, a different time-step may be used even while looking at the same disease. The discrete model by Choi *et al.* uses a time-step of one month because it is more realistic to consider infected individuals moving through disease states (CIN, cervical cancer and genital warts) in months, not years [27]. The goal of this model is to determine the optimal vaccination program to minimize the incidence of CIN, cervical cancer and anogenital warts. The programs differed between the coverage rates (70, 80 or 90%), age of vaccination (12, 13 or 14 years), gender of vaccination and potential catch-up programs. This model breaks up the population according to high-, medium- or low-risk groups for HPV types 16, 18, other high risk types, 6 or 11 (only one type is considered per run). This model finds that the duration of vaccine protection is the key parameter in determining the success of a program. It can be seen through numerical simulations that it is more effective to vaccinate older girls (14 years old) when the vaccine protection is short-lived. However, the model does not take into consideration higher levels of vaccine failure due to prior infection when vaccinating older girls. The model also finds that catch-up programs are only effective for the first 30 years, and male vaccination is helpful only with a small female coverage rate. Type dependent elimination is possible with a vaccine that provides lifelong immunity with 70% coverage rate, although the authors suggest that vaccinating 80% of 12-year-old girls over a period of 60 years will make a substantial impact on cervical cancer reduction.

A second SIR-type model looks at the mid- and long-term effects of an HPV 16/18 vaccine on the infection rates [8]. This model uses a time step of one year because it looks at the infection rates, which generally last for 40 or 50 years. The vaccine program takes into account the possibility of a booster (5 years after vaccination, with the opportunity of another at 10 years), a waning vaccine (after 5 or 10 years) and a catch-up program. For Switzerland, the implementation of catch-up programs is always beneficial for the population, and the results of a catch up program compared

to none is more substantial than two catch-up programs compared to each other. The most effective vaccination programs focus on a huge drop in HPV 16/18 prevalence at the beginning of the program, which is due to the catch-up programs. Boosters, on the other hand, are important to use, depending on the length of protection offered by the bivalent vaccine. Infection rates increase for women around the age of 35, so ensuring the population is protected past 35 years of age is an important determinant for the success of an HPV vaccine program.

Continuous models allow for a range of age-dependent effects to be examined simultaneously with the incorporation of the variation in disease outcomes and vaccination status (as opposed to mutually exclusive age groups). Al-arydah and Smith? show this in their age-structured PDE model of HPV vaccination [1]. The aim of the model is to determine if vaccinating one age cohort and one gender can control the infection across other ages and genders. The ages of vaccination considered in the model were under 13 (before sexual debut), or between 13–26, with the likelihood of receiving the vaccine increasing with age. Natural and full lifelong vaccine-acquired protection are included in the model. Addressing the aim of the model, vaccinating a single age can result in eventual control of HPV in all age groups and genders, therefore providing supporting evidence for the currently implemented HPV programs across the globe.

By considering time as a continuous phenomenon, one model addresses the interactions of behavioural and vaccination parameters on the potential success of the HPV vaccine [16]. Brown and White focus on using the effective reproductive value, which serves as a threshold for infection in a not entirely susceptible population. The behavioural parameters taken into consideration are the proportion who decide to become vaccinated, those who are sexually active and the average number of sexual partners per year. With female-only vaccination, as long as the vaccine is sufficiently long-lasting and the coverage is large enough, the infection can be eradicated. This result is shown in many other models, but this paper also adds the average number

of sexual partners per year as a significant influence on the effective threshold. When adding in male vaccination, the possibility of eradication exists for a wider range of parameter values. In terms of allowing the infection to persist within the population, the waning immunity of the vaccine is the parameter that plays the largest role in this disease persistence. Since behaviour is a constantly changing at any point in time, it is important to use continuous time to approximate these changes.

4.3.3 Aggregate vs. Individual-based

The last two categories for HPV models are aggregate or individual-based. Aggregate models consider individuals who are assigned health states, and the movement between these states is taken as an average of the (sub)population [80]. This movement depends on health status or other relevant variables. The model output is based on the number of individuals in each compartment over time. These comprise most of the HPV-related models. It is important to remember that explicit interactions between individuals are not modelled. On the other end of the spectrum, individual-based models are able to keep track of an individual's past behaviours that can influence the future risk of infection or screening schedule for the individual. For example, if a woman has been diagnosed for CIN in the past, she may be more likely to undergo cervical cancer screening more frequently than a woman who has not been diagnosed [80].

Barnabas *et al.* created a model which measures the transmission of HPV 16 per partnership; the value given to represent the transmission is constant for each group defined by age cohort, sexual activity and gender, making it an aggregate model [5]. The model includes low-grade squamous lesions (CIN 1/2), high-grade squamous lesions (CIN 3) and cervical cancer. Along with vaccinating 90% of females against HPV 16, a program for cervical screening is in place every 5 years. The model was used to look at the effects of a combined screening and vaccine program compared to

only one of these programs. Not surprisingly, the authors conclude that a combined method is the most effective way to decrease HPV-related disease prevalence. More importantly, the authors find that vaccinating both males and females had little benefit compared to vaccinating females alone. If Finland can achieve 90% coverage for females before their sexual debut, vaccination with a lifelong 100% efficacious vaccine can decrease cervical cancer incidence by 91%. Although these assumptions are unrealistic, this result underlines the fact that the HPV vaccine is able to positively affect disease prevalence, but it is not the full solution. Protection against other HPV types and screening programs is important for any country to incorporate alongside the vaccination program.

In the second aggregate model, the authors present a model to investigate two questions: 1. What is the potential impact of a quadrivalent HPV vaccine on HPV infection and disease in the United States of America? 2. What is the cost-effectiveness when a quadrivalent HPV vaccine program is added to the current standard practice of care (measured by the incremental cost-effectiveness ratio) [41]? The model included the disease states of CIN, cervical cancer and genital warts. The vaccine was assumed to prevent 90% of infections and have 100% efficacy against related disease. The vaccine program included a coverage rate that could range between 0–75% for the first five years of the program given to girls either before or after their sexual debut (at 12 years of age). Scenarios considered were female-only vaccination, or female and male vaccination with the option of a catch-up program. The results of the model show that the most effective disease-reducing strategy (but most expensive) is including vaccination and screening for both genders. However, the most cost-effective strategy is to vaccinate girls and women with a catch-up program, which could reduce the incidence of genital warts by 83% and cervical cancer by 78%.

Individual-based HPV models provide important insight into the effect of individual behaviours (such as sexual mixing) or individually tailored treatment programs (which is the case for cervical cancer screening) [80]. A model created by Goldhaber-

Fiebert *et al.* investigates the cost-effectiveness of cervical cancer vaccination and DNA testing intervention strategies through individualized treatment programs [55]. The screening varied by age of initiation (either 18, 21 or 25 years old), interval (every 1, 2, 3 or 5 years) and test (one combination of HPV DNA testing and cytological Pap test) [55]. Individuals could change strategies at 25, 30 or 35 years old. The most cost-effective strategies used HPV DNA testing in younger women and PAP tests in older women, which differs from the current practice. By tracking the past history of individual screening and testing for cervical cancer, the authors were able to conjecture about the best practise for the American population.

4.4 R_0

The number R_0 ('basic reproductive number') represents the average number of secondary infections caused by one infectious person in a completely susceptible population. If $R_0 > 1$, each infected person will, on average, cause more than one secondary infection causing the infection to persist in the population. However, if $R_0 < 1$, then the disease will eventually die out without further intervention [65]. Several models explicitly calculated the basic reproductive number. For ODE models, the threshold is usually found by rearranging the largest eigenvalue of the Jacobian matrix, which represents the threshold where the local stability of the disease-free equilibrium changes. Llamarazes and Smith? use this method to determine their R_0, which is dependent on birth and death rates, size of the population, transmission from females to males and males to females, rate of progression of female children to sexual activity, efficacy and immunogenicity of the vaccine, rate of adult vaccination and the coverage for childhood vaccination [91].

A second model also uses this method, but has extended the idea to evaluate the average number of secondary infections in a population that is not completely susceptible [16]. Brown and White define the effective reproductive number ($R_0{}^{\mathrm{e}}$) as

$R_0 \times (1 - p)$ where p is the proportion vaccinated. This is a useful to know for a long-term HPV vaccination program because it can serve as a tool to evaluate the progress of the program by comparing ${R_0}^{\mathrm{e}}$ numbers at different points in time. As a tool, the effective reproductive number is a great concept; however, the simplicity of its definition in this paper neglects individuals who acquire natural type-specific immunity from previous infection, or cross-protection. The modellers use the expression for R_0 to define effective reproductive numbers for a sexually active population, female-only vaccination, and female and male vaccination. The advantage of defining a threshold that depends on the vaccination strategy is the ability to directly compare the values of ${R_0}^{\mathrm{e}}$ under different strategies. Normally, since R_0 is a threshold of stability in mathematical models, comparing the values of R_0 between models or different diseases should be done with caution. Since ${R_0}^{\mathrm{e}}$ is defined from the same disease and model, it is useful to compare the values under different strategies. The results of the model show the most influential parameters on the eradication of the targeted HPV types are the proportion vaccinated, the average rate at which individuals of become sexually active and the average rate at which the protection of the vaccine is lost. The two main distinctions between strategies when including male vaccination are that the infection prevalence in both sexes is the same, since the vaccination rates are equivalent for both sexes and there is a wider range of parameter values that lead to theoretical eradication of the targeted HPV types.

A third ODE model calculates R_0, but extends the idea of the effective reproductive number further (which they call the projected reproductive number), by explicitly including male and female coverage rates in the expression of R_V (as opposed to [16], which compared the values of ${R_0}^{\mathrm{e}}$ with and without male vaccination) [12]. The authors also found the basic reproductive number for heterosexual transmission from women to men and men to women. Through algebraic analysis of how these three basic reproductive numbers change based on parameter values, the authors conclude that one-sex vaccination is more effective than vaccinating both sexes, if the objec-

tive is to eliminate the targeted HPV types. The authors used the basic reproductive number to investigate the case when vaccinating the sex with the highest pre-vaccine HPV prevalence does not achieve the largest reduction in population prevalence. For their model, this occurred under certain conditions dictated by the rate of infection, recovery and transmission. By choosing 10,000 combinations of these parameters that gave $R_0 > 1$, the authors determined that the reduced recovery of infection was the cause of higher pre-vaccine prevalence.

The last model to explicitly determine R_0 is a PDE model [1]. The authors were able to calculate the value of R_0 for child-only, adult-only and a combined program. By considering two limiting vaccination cases, child-only vaccination or adult-only vaccination, the study showed the general R_0 for the model is a composite of the two cases. Using these values, the results of the model show that the most important factors in determining the success of a program is the efficacy and coverage rate. The higher these values are, the greater the program will succeed. Through numerical simulations, the authors concluded that, even in a population with a high prevalence rate, the bivalent vaccine will make a large impact on the prevalence of the infection.

4.5 Discussion and Conclusion

Understanding the underlying assumptions the models make about the vaccine, population and type of model used is important because these can influence the conclusions made by the models. Understanding which assumptions were made will help a reader critically read the outcomes of the models and decide which models best represent a population. The type of model chosen is important to consider. Out of the 18 papers reviewed, the overwhelming majority of research is focused on dynamic (15/18), deterministic (14/18), continuous (13/18) and aggregate models (16/18). Six models incorporated an SIS base while ten used the SIR base, and two papers included one model of each type. The main difference between the two types of models was that

the girls-only programs were more effective with an SIS based model [7].

Recommended strategies for a successful HPV vaccination program using either an SIS or SIR model is to include screening for cervical abnormalities [5, 54, 68] and vaccinating girls before their sexual debut [41, 48, 119]. SIS models also indicate that one of the main focuses of the HPV vaccine program should be to increase the coverage rate [119] and use a vaccine against as many HPV types as possible will reduce the need for treatment against related diseases [68]. SIR models point out that eradication of the targeted types is possible [1, 27], especially with the introduction of adult vaccination [91], although it may be wise for programs to focus on maximizing the reduction of HPV infection prevalence rather then eradication [12]. Including screening programs in models is the most effective way to decrease the differences in outcomes between the two base models; ten papers included screening for HPV (pap smears) and five included treatment for the included disease outcomes (CIN, cervical cancer and/or genital warts).

In terms of male vaccination, SIS models concluded that adding male vaccination is important [119], while only some SIR models recommend male vaccination. Generally speaking, many SIR models concluded that, although male vaccination would have a positive impact of the prevalence of HPV, it is not comparable to female vaccination [5, 16, 27, 41, 48] and is the most effective when less than 40% of females are vaccinated [12]. This gender difference could be due to a higher prevalence seen in females [12], or a high degree of heterogeneity of the sexual contact network [68].

The success of the HPV vaccination programs were most sensitive to the age of vaccination for SIS models [82]. The trend being, a lower the age of vaccination would lead to a more successful program [82]. For SIR models, the most sensitive parameters determining the success of the HPV vaccination program are the duration of protection, which can be compensated for with a booster [8, 15, 16, 27, 142], sexual heterogeneity [12, 68] (higher heterogeneity lowers success of program), efficacy and coverage [1], the proportion of the population not sexually active and the rate of

sexual activity [16]. The duration of protection was the parameter that showed the largest difference in outcomes between the two types of base models [7].

An important aspect of the introduction of a vaccine program is the option of including a catch-up program. Within Canada, ten out of the thirteen provinces/ territories included a catch-up program [101]. Many models support this, since the catch-up programs are shown to speed up the process of protecting the population and decreasing cumulative number of cases [48]. There is, however, controversy about how long these programs should be in place, since there is evidence claiming that catch-up programs are always beneficial [8], but other models suggest they are only effective for first 30 years [27].

Among the hundreds of HPV types, the types of interest are modelled separately, or several types are bunched together and considered as one. Out of the papers reviewed, eight considered low-risk HPV types, of which two considered HPV 6 alone, three looked at HPV 11 alone, and one considered HPV 6 and 11 together. 14 considered high-risk HPV types, of which seven considered HPV 16 alone, four considered HPV 18 alone and four combined HPV 16 and 18 together. Three papers considered types 6, 11, 16 and 18 together. Only one paper failed to mention the specific types looked at in the model, while another paper studied other high-risk types (31, 45 and 52). Three papers included the co-infection of two or more HPV types or groupings. The scope of all of the models thus far have been focused on the vaccine targeted types, so conclusions from these models should not be carried over to non-targeted types.

The vaccine assumptions included within these eighteen models vary in terms of the efficacy assumed for the vaccine, age of vaccination, coverage rate and the possibility of the vaccine waning. The efficacies chosen for these models were 70% [27], 80% [27], 90% [5, 7, 27], 95% [91] and 100% [12]. The age of vaccination for females varied between before sexual debut or entrance of model [5, 16, 41, 54, 82], age 12 [15, 27, 41, 48, 82, 142], 13 [1, 27], 14 [27, 119], 15 [5, 48], 18 [82, 48], 21 [48]

and within the defined adult or sexually active stages within the individual models [1, 68]. Three models chose a constant coverage rate of 70% [48, 82], 30 or 80% [119] and 100% [15]. One model uniquely defined the coverage rate as an increasing function from 0–70% for the first 5 years then the coverage was held constant of 70% for the vaccine program and a similar function was defined for the coverage of the catch-up program, which increased from 0–50% and was held at 50% thereafter [41].

The HPV vaccine may wane, since the duration of protection studies are still ongoing. Evidence shows that the HPV vaccine protects for at least eight years [120]. Waning has been included in several models. Some papers state an average length of time the vaccine protects an individual before they are transferred back to the susceptible compartment, while others specifically include rates. Either way, waning is included by either a constant waning period or exponential decay. Studies have used an average length of time between 5 and 10 years or anywhere between 5 and 100 years [8, 15, 16]. The rates most commonly used have been 3% per year and a constant waning between 7–14 years so that 50% are still protected [7, 15, 142]. Some models have chosen not to include waning [12, 48, 82, 119].

Although the virus initially causes an infection, the disease outcomes that can develop from this infection are plentiful. For the targeted types (HPV 6, 11, 16 and 18), the outcomes of most concern are genital warts, pre-cancer (cervical intraepithelial neoplasia) and cervical cancer. Out of the models considered, eight models looked at HPV infection, five included genital warts, and eleven included cervical intraepithelial neoplasia (CIN) and cervical cancer, of which one used the HSIL/LSIL classification. All of the papers considered only heterosexual transmission of the targeted HPV types; although one paper explores the potential effect of the HPV vaccine in a community of men who have sex with men [12].

Herd immunity accounts for the immunity acquired by a population when a large enough portion of the population is vaccinated. The rest of the population will be protected because they are not likely to come into contact with an infected person.

Twelve of the eighteen models included this important concept. Out of these twelve, only three came up with an expression to represent the basic reproductive number. It represents the number of secondary infections caused by one infectious individual in a completely susceptible population.

Not only should a vaccine program have a purpose and a high likelihood of success, it should also be affordable. Several models developed to evaluate the cost-effectiveness of several vaccine programs showed that vaccinating girls and women is cost effective [41], while vaccinating males is not cost-effective [41]. Some models found that the cost-effectiveness is dependant on vaccine parameters. For example, the HPV vaccination programs are cost-effective if the vaccine protection lasts for at least 20 years (including possible booster), but the efficacy, treatment costs and length of time in each health state do not largely affect the cost-effectiveness of the programs [9].

Recently, new evidence has come to light that shows that a fewer number of doses of the bivalent HPV vaccine may provide adequate protection for individuals. Clinical trials are currently being conducted to test this theory [37]. It is important that modelling research include this information because using fewer than three doses may have a large impact on the epidemiological and financial aspects of the program. Although a lot of work has been done to discover the best way to implement a program, there are still many unanswered questions and ideas to explore.

4.6 Tables and Figures

Table 4.1 **Research objectives and findings of reviewed articles, part 1.** This table summarizes the research objectives and main findings of five out of a total of eighteen models reviewed.

Research Objective	Findings	Reference
• Can vaccinating one age cohort and one gender control the disease across different ages and genders?	• High efficacy vaccine and high coverage determines success • Vaccine is effective even with an initial high number infected • Vaccinating a single cohort can result in eventual control of HPV in all age groups and genders	[1]
• Compare combined effects of screening and vaccination • Estimate the transmission probability of HPV 16 in Finland • Look at the effect of changes in patterns of sexual behaviour and smoking on age-related cancer incidence	• Vaccinating men and women had little benefit from vaccinating women alone • Cover 90% before sexual debut leads to a 91% decrease in cervical cancer incidence • Combination of screening and vaccination is most effective for disease incidence	[5]
• Explore, compare and contrast the consequences of using an SIS vs. SIR model • Explore effect of waning on lifelong cervical cancer risk	• Girls-only vaccination is more effective with some coverage in SIS than SIR • Duration of vaccine protection results in largest difference between model types • Testing women between the ages of 25–60 decreased the differences in cervical cancer cases between model types • A program vaccinating 12 year old girls with a 60-80% coverage rate resulted in an overall cervical cancer risk of $\frac{2}{1000}$ with an SIR model and $\frac{3.5}{1000}$ with an SIS model	[7]
• What are the mid and long-term effects of a waning vaccine, with a possible catch-up program and booster on HPV 16/18 prevalence in Switzerland?	• Catch-up programs are always beneficial • Booster will be useful depending on the length of protection	[8]
• Determine cost-effectiveness of adding HPV vaccination program in adolescent females 14 years of age in addition to the cervical cancer screening program in France	• Screening only: 94% cervical cancer risk and 22% lifetime cancer risk reduced to 33% and 8% with vaccine • For cohort of 370,000 women, the model estimates that 2,245 cervical cancer cases, 531 cervical cancer deaths, 6,278, 6,801, and 8,983 cases of detected CIN 1, 2, and 3 cases, respectively, and 23,105 cases of genital warts could be avoided with vaccination • Vaccination is cost-effective strategy if protection lasts for 20 years or more, even with booster • Cost-effectiveness insensitive to efficacy, treatment costs and length of time in each health state	[9]

Table 4.2 **Research objectives and findings of reviewed articles, part 2.** This table summarizes the research objectives and main findings of four out of a total of eighteen models reviewed.

Research Objective	Findings	Reference
• Is the most effective strategy for reducing prevalence of HPV 16 in a heterosexual population by single gender vaccination or both?	• Vaccinate one gender to eliminate HPV • Vaccinating the sex with the highest prevalence of infection is the most successful • A more heterogeneous sexual contact network leads to a lower degree of herd immunity and lower impact of vaccination at a given coverage • Vaccination programs should focus on maximizing the reduction of HPV infection prevalence rather than elimination • Once routine vaccination of one sex is in place, increasing the coverage in that sex is much more effective in bolstering herd immunity than switching to a two-sex program • Vaccinating males is rarely effective if at least 40% coverage has been achieved among females	[12]
• Calculate the number needed to vaccinate (NNV) in order to prevent one case of included disease results	• If vaccine does not wane, NNV is 8 to prevent one case of genital warts, and 324 to prevent one case of cervical cancer • If vaccine does wane, NNV is 14 to prevent one case of genital warts, and 9080 to prevent one case of cervical cancer, which can be reduced to 480 if a booster is included • Results highly dependant on vaccine protection duration	[15]
• Assess the effect behavioural and vaccination parameters on the potential success of the vaccination program • Judge the impact of male vaccination	• Waning immunity plays large role in allowing infection to persist • R_0^e is affected by proportion of population not sexually active at vaccination and rate of sexual activity • Male vaccination is recommended to decrease the prevalence of infection	[16]
• Determine the optimal vaccine strategy to minimize the prevalence of CIN, cervical cancer and anogenital warts	• Catch-up programs are only effective for first 30 years • Male vaccination is not greatly beneficial • Vaccinating 12-year-old girls with an 80% coverage over 60 years results in substantial cervical cancer reductions (30–82%) and anogenital warts reductions (44–100%) • The targeted types can be eliminated with lifelong immunity and 70% coverage of females • A short-lived vaccine has better success rate if at the same coverage rate 14 year-old girls are vaccinated (vs. 12-year-old) • The duration of protection is the key parameter determining success of the program	[27]

Table 4.3 **Research objectives and findings of reviewed articles, part 3.** This table summarizes the research objectives and main findings of four out of eighteen models reviewed.

Research Objective	Findings	Reference
• What is the potential impact of a quadrivalent HPV vaccine on HPV infection and disease in the US population? • What is the cost-effectiveness of a quadrivalent HPV vaccine program when added to the current standard of care from the perspective of the US health care system?	• Vaccinate girls before their sexual debut • The model predicts an 83% decrease in the prevalence of genital warts and 78% decrease in the prevalence of cervical cancer • Vaccinating girls and women is cost-effective • Adding in vaccination of males is effective in terms of disease prevention, but less cost-effective	[41]
• What is the optimal vaccination program on the prevalence of cervical cancer if the age of vaccination is varied, male vaccination is included and/or there is a catch-up program?	• Vaccinating before sexual debut maximizes the long-term impact of the program • Catch-up programs speed up the process and decrease the cumulative number of cervical cancer cases • Vaccinating males prevents additional cases, although the effect of male vaccination is not comparable to the effect of female vaccination (female having a greater effect)	[48]
• Describe a formal approach to the parameterization, calibration and evaluation of cervical cancer for the United States • Predict health outcomes and uncertainty surrounding the predictions associated with cervical cancer screening, HPV 16/18 vaccination and combinations of vaccination and screening	• Expected reduction in lifetime cancer risk is 76% (69-82%) with annual screening • 69% (60-77%) with biennial screening • 75% (60-88%) with vaccination alone and • 89% (83-85%) with vaccination and a 5 year screening program.	[54]
• What are the effects of sexual mixing and vaccine characteristics on the effectiveness of various vaccination strategies?	• Heterogeneity in levels of sexual activity within the population plays an important role in determining the response to different levels of vaccine coverage • As heterogeneity and coverage increase, the additional benefit from vaccinating men decreases	Model 1 [68]

Table 4.4 **Research objectives and findings of reviewed articles, part 4.** This table summarizes the research objectives and main findings of five out of eighteen models reviewed.

Research Objective	Findings	Reference
• What is the impact of reduced HPV prevalence and change in the rate of progression from infection to disease on cervical cancer incidence?	• If the vaccine gives some protection to only some HPV types, the reduction in disease is less than the reduction in HPV • Using a vaccine that protects against as many types as possible greatly reduces the need for treatments • Pap-smears are not redundant • For a 60% efficacy, there will be a 46% reduction in CIS and 47% reduction in cervical cancer, while the mean age of CIS will increase by 1.2 years, and cervical cancer by 0.6 years	Model 2 [68]
• Estimate age-related probabilities an individual would be in one of the included health states • Develop generic model used to evaluate the vaccine progress in different countries	• Results are sensitive to age of vaccination (lower age corresponds to better results) • Vaccinating a 12-year-old female cohort will lead to a 76% reduction in CIN 2/3 and 76% reduction in cervical-cancer-related deaths	[82]
• Can a childhood-only vaccination program eradicate targeted HPV types? • Should adult vaccination supplement childhood vaccination? • Is eradication possible for vaccines with suboptimal efficacy or immunogenicity?	• Eradication is possible, especially when vaccination program is supplemented with adult vaccination • There is a critical efficacy and immunogenicity threshold below which eradication is not possible	[91]
• Predict the impact of HPV 6/11/16/18 vaccinating by measuring parameter uncertainty	• Duration of protection and natural immunity are most sensitive parameters	[142]
• Asses the impact of vaccination on cervical cancer incidence in France	• Adding male vaccination will moderately help lower the incidence of cervical cancer • Increasing the coverage rate is the most effective way to decrease disease-related deaths • Vaccinating younger girls may improve coverage	[119]

Table 4.5 **Summary comparison of mathematical models related to HPV disease, part 1.** The table gives an overview of the type of model used (static or dynamic, deterministic or stochastic, discrete or continuous, aggregate or individual based, and an SIS or SIR base model), populations traits included (herd immunity, R_0), types of HPV specified (HPV 6, 11, 16, 18, 'high risk' and/or 'low risk') , if co-infection was considered among those types, and the ailments associated with those types specifically included within the model structure. A checkmark indicates that the model has that property. The outlined boxes under the HPV types category indicate these HPV types were considered as one type; in other words, the infected portion of the population was considered to be infected with 'HPV' as opposed to type-specific infection. Table is continued on next page.

Type of Model Used										Population Trait		HPV Types							Associated Ailments				
Static	Dynamic	Deterministic	Stochastic	Discrete	Continuous	Aggregate	Individual	SIS	SIR	Herd Immunity	R_0	HPV 6	HPV 11	HPV 16	HPV 18	Low Risk	High Risk	Co-infection	Infection	Genital Warts	CIN	Cervical Cancer	Reference
	✓	✓			✓	✓			✓					✓	✓								[1]
	✓	✓				✓			✓					✓							✓	✓	[5]
	✓	✓			✓	✓		✓	✓	✓				✓							✓	✓	[7]
	✓		✓	✓			✓		✓					✓	✓				✓				[8]
✓		✓		✓		✓		✓				✓	✓	✓	✓				✓	✓	✓	✓	[9]
	✓	✓			✓	✓		✓	✓	✓	✓			✓					✓				[12]
✓		✓			✓	✓			✓					✓	✓	✓	✓	✓	✓	✓	✓	✓	[15]
	✓	✓			✓	✓		✓		✓	✓	✓	✓	✓	✓				✓				[16]
	✓		✓	✓		✓			✓	✓		✓	✓	✓	✓		✓			✓	✓	✓	[27]
	✓	✓			✓	✓			✓	✓		✓	✓	✓	✓			✓		✓	✓	✓	[41]
	✓	✓			✓	✓			✓	✓			✓								✓	✓	[48]

Table 4.6 **Summary comparison of mathematical models related to HPV disease, part 2.** The table gives an overview of the type of model used (static or dynamic, deterministic or stochastic, discrete or continuous, aggregate or individual based, and an SIS or SIR base model), populations traits included (herd immunity, R_0), types of HPV specified (HPV 6, 11, 16, 18, 'high risk' and/or 'low risk') , if co-infection was considered among those types, and the ailments associated with those types specifically included within the model structure. A checkmark indicates that the model has that property. The outlined boxes under the HPV types category indicate these HPV types were considered as one type; in other words, the infected portion of the population was considered to be infected with 'HPV' as opposed to type-specific infection.

	Type of Model Used										Population Trait		HPV Types							Associated Ailments				
	Static	Dynamic	Deterministic	Stochastic	Discrete	Continuous	Aggregate	Individual	SIS	SIR	Herd Immunity	R_0	HPV 6	HPV 11	HPV 16	HPV 18	Low Risk	High Risk	Co-infection	Infection	Genital Warts	CIN	Cervical Cancer	Reference
	✓			✓	✓			✓	✓						✓	✓	✓	✓		✓		✓	✓	[54]
		✓	✓			✓	✓			✓	✓							✓						Model 1 [68]
		✓	✓			✓	✓		✓		✓							✓				✓	✓	Model 2 [68]
	✓			✓	✓		✓		✓															[82]
		✓	✓			✓	✓			✓	✓	✓								✓				[91]
		✓	✓			✓	✓		✓		✓				✓	✓							✓	✓	[119]
		✓		✓		✓	✓			✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	[142]
		✓	✓			✓	✓		✓		✓	✓	✓	✓	✓	✓	✓	✓		✓				This thesis
Total	**4**	**15**	**14**	**5**	**5**	13	**17**	**2**	**9**	**12**	**12**	**4**	**6**	**7**	**14**	**11**	**4**	**7**	**3**	**9**	**5**	**11**	**11**	**19**

Table 4.7 **Model types.** The table gives a brief overview of the 10 categories used to define the model type for the eighteen reviewed articles. Each category is partnered with another (as denoted by option 1 and option 2) to show that a model can only be considered in one of these options. A short definition of the category is included.

Option 1	*Definition*	*Option 2*	*Definition*
Static	At equilibrium	**Dynamic**	Change with respect to time
Deterministic	Events occur with fixed parameter values	**Stochastic**	Events occur by chance
Discrete	Transitions between states occur at specific time intervals	**Continuous**	Transitions between states occur at a random but distributed amount of time
Aggregate	Change in health is based on the average of the population	**Individual-based**	Individual behaviour is remembered and can affect future decisions
SIS	Susceptible Infected Susceptible (no natural immunity)	**SIR**	Susceptible Infected Recovered (natural immunity)

Table 4.8 **Examples of currently implemented programs around the world.** The table outlines six countries, chosen as examples used within Chapter 4, and their HPV vaccination programs. The programs are defined as public or private based on where the funding comes from. The target age, number of doses given and coverage rates indicated show the most current data available at time of publishing.

Country	*Public or Private*	*Target Age*	*Doses*	*Coverage*
United Kingdom	Public [95]	12–13	3	84–92 % [4, 104]
Australia	Public [95]	12–13	3	71% [70]
France	Private [95]	14	3	24 % [39]
United States	Private [95]	11–12	3	32 % [23]
Canada	Both [95]	9–14	2 or 3	49–86 % [105, 127]
Switzerland	Both [95]	10–14	2	–

Chapter 5

The Model

Abstract

Background: The human papillomavirus (HPV) infection is the most common sexually transmitted infection, which is linked to several cancers and genital warts. Out of hundreds of strains, HPV types 6 and 11, which are linked to 90% of genital warts, and types 16 and 18, which cause 70% of cervical cancer, are currently vaccinated against across Canada. Depending on the province, the quadrivalent vaccine is given to girls in grades 4 through 10 with either a two or three dose schedule.

Methods: We use a mathematical model to investigate the influence of quadrivalent vaccine programs, which differ by the grade of vaccination and number of doses given, the prevalence of HPV 6, 11, 16 and 18. We address the following research questions: 1. Does the grade at which the girls are vaccinated and the number of doses given (two or three) significantly affect the outcome of the program? 2. What coverage rate must the provinces reach in order to reduce the impact of HPV on the Canadian population? 3. What are the implications of vaccinating with two or three doses?

Results: The model suggests the grade of vaccination does not make a significant difference to the outcome of the public vaccination program under the assumption

that the vaccine is just as efficacious for girls in either grade. The number of doses given does not make a significant difference to the outcome of the public vaccination program. The most significant factor in the success of these programs is the coverage rate of children and adults.

Conclusions: Since girls in higher grades are more likely to have had their sexual debut, increasing their chance of being infected with HPV, we recommend that provinces vaccinate as early as possible to avoid vaccine failure due to previous infection. We also recommend that the main focus of the program should be on obtaining a large enough coverage rate for children and/or adults in order to achieve the desired outcome with either a two or three doses of the vaccine.

Keywords: Human Papillomavirus, vaccine, Canada, mathematical model, ordinary differential equations

5.1 Introduction

Human papillomavirus (HPV) is the most common sexually transmitted virus, infecting 75% of the sexually active Canadian population [29, 66]. It can cause cancer of the cervix, vulva, oropharynx, penis and anus, as well as genital warts [81, 91, 101]. Until recently, there were no medical interventions against HPV infections except monitoring the virus' progress through the Papanicolaou test (or "Pap test") and treating the ailments that developed. The pap test is a screening tool which detects potentially precancerous or cancerous cells by taking a cell sample from a woman's cervix [64]. This screening tool has led to a reduction in the incidence of cervical cancer even though only 71–85% of women actually receive the screening [56, 147]. This approach is quite successful at catching the infection before it turns into cancer, but the next preventative measure is to stop the infection from occurring at all. A possible solution to this problem was found in 2006 when the vaccine Gardasil™

(Merck & Co.) was approved for use in Canada [17]. Four years later, the second HPV vaccine, Cervarix^{TM} (GlaxoSmithKline), was approved. In 2007, the Canadian federal government provided the provinces and territories with $300 million to spend over 3 years for the HPV immunization programs [117].

By 2009, every province and territory in Canada had an HPV vaccination program in place [89]. The creation and implementation of the programs is the responsibility of the individual provinces and territories. This results in eight distinct strategies throughout Canada, which can be seen in Table 5.1. Some provinces may have based their decision about which grade to vaccinate and how many doses to give out by looking at pre-existing vaccine programs (ex. Hepatitis B and the tetanus, diphtheria and pertussis vaccine) since this strategy was used in other countries [131]. This way, the province can utilize allocated resources by adding the HPV vaccine to the pre-existing programs [60]. Other provinces may have decided to vaccinate female children as young as possible, since the vaccine is most effective on those who have never been infected with the virus, and younger children are less likely to have encountered it before [89]. These strategies vary in the number of doses of the quadrivalent vaccine given (only two doses in British Columbia and Quebec and three doses administered elsewhere), the grade of the girls who are given the vaccine (ranging from 4 to 10) and the coverage rate (49-86% within the first two years of the program) [89]. Although the reality of these programs differ between provinces, they all share a common goal of reducing the impact of HPV on the Canadian population [102]. This is measured through the morbidity and mortality rates of HPV [102]. The hope with this vaccine is that we do not have to immunize 100% of the population; we must only immunize enough people to reach a level of herd immunity.

There have been a number of mathematical models since the vaccine's introduction assessing its impact on several populations. In terms of the cost effectiveness of the vaccine, Brown and White used an optimal control model for vaccinating adolescent females and males in the United Kingdom [16]. Brisson used a cohort model to

estimate how many girls need to be vaccinated to prevent cervical cancer and genital warts in Canada [15]. In terms of the disease impact on a population, Barnabas *et al.* developed a transmission model to measure the impact of vaccinating against HPV-16 in Finland for both women and men [5]. Although it does consider the effects caused by HPV later in life, this model neglects to consider herd immunity. There are current clinical trials in British Columbia looking at the effect of taking two or three doses of the quadrivalent vaccine [37]. This trial will provide valuable information about the levels of protection provided by two or three doses. Llamazares and Smith? developed an epidemiological model that includes a widespread childhood vaccination program and voluntary adult vaccination [91]. The model is used as a preliminary investigation to determine whether provincial healthcare programs in Canada should fund adult HPV vaccination. The authors were able to determine a threshold of eradication for the targeted types of HPV, and critical efficacy and immunogenicity levels such that eradication is not possible at any coverage rate.

In this chapter, we develop a mathematical model to explore the current vaccination strategies across Canada, as well as potential alternative strategies. These strategies are defined by the number of doses given, the grade of the girls the vaccine is given to and the coverage rate achieved. Our model will provide similar insight into the effectiveness of two and three doses of the quadrivalent vaccine. This model also provides insight into what the programs should look like in order to achieve a desired outcome. This model provides a unique perspective in its evaluation of the provincial programs based on the grade of vaccination, number of doses given and the necessary coverage rate. We address the following research questions: 1. Does the grade at which the girls are vaccinated and the number of doses given (two or three) significantly affect the outcome of the program? 2. What coverage rate must the provinces reach in order to reduce the impact of HPV on the Canadian population? 3. What are the implications of vaccinating with two or three doses? This model is an extension of one created by Llamazares and Smith? [91]. The current model includes

childhood vaccination strategies, standard incidence to describe a larger population and a more realistic view of the natural history of the HPV infection by including possible clearance of the infection.

This paper is organized as follows. Section 5.2 gives the model description and equations. Section 5.3 details the analysis of the model. Section 5.4 gives the expressions for critical thresholds of efficacy and probability of protection. Section 5.5 explores how the parameters were estimated, the results on the infection when varying the grade, dosage and coverage rate, how long the until the results of a vaccine program will be seen and the sensitivity analysis of the model. Section 5.6 discusses the implications.

5.2 The Model

Our model is composed of 19 equations, 13 that describe the childhood vaccination strategy and 6 that describe the disease propagation through adults. The female children are broken up into seven grades (4 through 10). Within each appropriate grade class, there are unvaccinated (C_{iU} where $4 \leq i \leq 10$) and vaccinated female children (C_{iV} where $4 \leq i \leq 10$). In the adult portion of the model, women are broken up into unvaccinated uninfected susceptible women (A_U), vaccinated uninfected susceptible women (A_V), unvaccinated and infected women (I_U) or vaccinated infected women (I_V). Men are considered either uninfected susceptible (M) or infected (N).

For this model, it is assumed that HPV is only heterosexually transmitted. Sexual partnerships are not included [99]. Female children are in grades 4 through 10, which are the years childhood vaccination can take place. It is assumed that vaccination only occurs in one year, and the proportion of female children vaccinated during other years are negligible. Both women and men are active in the adult model for approximately 10 years because the vaccine is not recommended for women over the age of 26 [147]. The rate at which the HPV infection is cleared is independent

of previous infection status. The probability of transmission from women to men is higher than the probability of transmission from men to women [66].

The assumptions made about the vaccine are that the vaccine does not wane in children, it may not protect 100% (this is based on the probability of protection and the efficacy) and the vaccine does not protect someone who is already infected with the virus [14, 67]. The difference between a two and three dose schedule is the efficacy of the vaccine. Lastly, we do not consider disease-induced death since it does not play a role in removing sexually active individuals from the pool that we are considering (complications due to HPV such as cervical cancer are generally seen much later in life) [42, 124, 147].

5.2.1 Equations

Girls in grade 4 (approx. 9 years old) are described as

$$\frac{dC_4}{dt} = \pi_W - (1 + \mu_C)C_4.$$

Girls in grade 5 (approx. 10 years old) are described as

$$\frac{dC_{5U}}{dt} = (1 - \epsilon p_4)C_4 - (1 + \mu_C)C_{5U}$$
$$\frac{dC_{5V}}{dt} = \epsilon p_4 C_4 - (1 + \mu_C)C_{5V}.$$

Girls in grade 6 (approx. 11 years old) are described as

$$\frac{dC_{6U}}{dt} = (1 - \epsilon p_5)C_{5U} - (1 + \mu_C)C_{6U}$$
$$\frac{dC_{6V}}{dt} = \epsilon p_5 C_{5U} + C_{5V} - (1 + \mu_C)C_{6V}.$$

Girls in grade 7 (approx. 12 years old) are described as

$$\frac{dC_{7U}}{dt} = (1 - \epsilon p_6)C_{6U} - (1 + \mu_C)C_{7U}$$
$$\frac{dC_{7V}}{dt} = \epsilon p_6 C_{6U} + C_{6V} - (1 + \mu_C)C_{7V}.$$

Girls in grade 8 (approx. 13 years old) are described as

$$\frac{dC_{8U}}{dt} = (1 - \epsilon p_7)C_{7U} - (1 + \mu_C)C_{8U}$$
$$\frac{dC_{8V}}{dt} = \epsilon p_7 C_{7U} + C_{7V} - (1 + \mu_C)C_{8V}.$$

Girls in grade 9 (approx. 14 years old) are described as

$$\frac{dC_{9U}}{dt} = (1 - \epsilon p_8)C_{8U} - (1 + \mu_C)C_{9U}$$
$$\frac{dC_{9V}}{dt} = \epsilon p_8 C_{8U} + C_{8V} - (1 + \mu_C)C_{9V}.$$

Girls in grade 10 (approx. 15 years old) are described as

$$\frac{dC_{10U}}{dt} = (1 - \epsilon p_9)C_{9U} - (1 + \mu_C)C_{10U}$$
$$\frac{dC_{10V}}{dt} = \epsilon p_9 C_{9U} + C_{9V} - (1 + \mu_C)C_{10V}.$$

Uninfected adult women are described as

$$\frac{dA_U}{dt} = (1-\phi_U)C_{10U} + \xi_U I_U - f(\epsilon_W p_W)A_U - \frac{\beta_W A_U N}{\male} - \mu_A A_U$$
$$\frac{dA_V}{dt} = (1-\phi_V)C_{10V} + \xi_V I_V + f(\epsilon_W p_W)A_U - \frac{(1-\psi)\beta_W A_V N}{\male} - \mu_A A_V.$$

Infected adult women are described as

$$\frac{dI_U}{dt} = \phi_U C_{10U} + \frac{\beta_W A_U N}{\male} - \xi_U I_U - \mu_A I_U$$
$$\frac{dI_V}{dt} = \phi_V C_{10V} + \frac{(1-\psi)\beta_W A_V N}{\male} - \xi_V I_V - \mu_A I_V.$$

Uninfected men are described as

$$\frac{dM}{dt} = \pi_M - \frac{\beta_M I_U M}{\female} - \frac{\beta_M I_V M}{\female} - \mu_A M$$

Infected men are described as

$$\frac{dN}{dt} = \frac{\beta_M I_U M}{\female} + \frac{\beta_M I_V M}{\female} - \xi_M N - \mu_A N.$$

where

$$f = \frac{c\epsilon_W p_W}{1-\epsilon_W p_W + \gamma}$$

$$\female = C_4 + C_{5U} + C_{5V} + C_{6U} + C_{6V} + C_{7U} + C_{7V} + C_{8U} + C_{8V} + C_{9U} + C_{9V} + C_{10U} + C_{10V} + A_U + A_V + I_U + I_V$$

and

$$\male = M + N.$$

A girl enters the model unvaccinated in grade 4 through a constant rate π_W. At any grade between 4 and 10, a proportion of the girls become vaccinated at rate ϵp_i (where p_i is the proportion of girls given the vaccine in grade i, and ϵ represents the vaccine efficacy for girls). When the girls enter grade 11, a proportion of unvaccinated girls $(1 - \phi_U)$ grow up to become unvaccinated women (A_U), while the rest of the unvaccinated girls (ϕ_U) are categorized as infected unvaccinated women (I_U) because they have had a previous infection with any of the four targeted types. A proportion of vaccinated girls $(1 - \phi_V)$ either grow up to become vaccinated women (A_V), while the rest of the vaccinated girls (ϕ_V) are categorized as infected vaccinated women (I_V) to account for a proportion of girls who have contracted at least one of the targeted types before receiving the vaccine. Once in the adult stage (grade 11 to around the age of 26), all of the disease propagation takes place. Once the girl reaches grade 11 she is considered a woman, and assumed to be sexually active. Unvaccinated adult women (A_U) can become vaccinated at rate $f(\epsilon_W p_W)$, where ϵ_W is the efficacy of the vaccine for adult women and p_W is the proportion of women who get the vaccine. Unvaccinated adult women become infected (I_U) at rate β_W when coming into contact with an infected man (N). Vaccinated adult women (A_V) can also become infected (I_V) at rate (1- $\psi)\beta_W$, where ψ represents the ability of the vaccine to protect against all targeted types i.e. to those women who have no previous infection with the targeted types of HPV. Men enter the model as susceptible (M) through a constant rate π_M, and stay in the model for approximately 10 years. Unvaccinated susceptible men (M) can become infected by contacting an infected woman (I_U or I_V) with a rate β_M. Each compartment also includes a natural death rate, μ_C or μ_A, depending on child or adult status. The flow diagram is illustrated in Figure 5.3. Parameter descriptions, ranges and sample values can be found in Table 5.2.

The model is comprised of ordinary differential equations (ODEs), which make some assumptions about the population. First, the populations within the compartments are exponentially distributed. This means that, on average, most people spend

one year (time step) in the child age classes and 10 years in the adult compartments. However, there is a (small) proportion of people who spend longer or shorter time in those compartments. This is why the model considers grade of vaccination as opposed to age of vaccination: everyone is guaranteed to age one year every year, but some students are held back or skip grades. Second, our total population size is not constant, since

$$\begin{aligned} N' &= \pi_W + \pi_M \\ &\quad - \mu_C(C_4 + C_{5U} + C_{5V} + C_{6U} + C_{6V} + C_{7U} + C_{7V} + C_{8U} + C_{8V} + C_{9U} + C_{9V} \\ &\quad + C_{10U} + C_{10V}) - \mu_A(A_U + A_V + I_U + I_V). \end{aligned}$$

If it were, then the population size over time would exponentially increase or decrease, meaning the population size would eventually be infinite, or die out. Neither of these scenarios are realistic. It is not possible for human population growth to always be exponentially increasing due to limiting resources (i.e., food, water, space etc.). If the total human population were zero, then there is no reason to study the effects of the HPV vaccine. The changing total population size allows the model to more realistically model the population considered. Since the model describes the disease dynamics over a large population (population of a given Canadian province), we assume a standard incidence of transmission. This indicates that, for each contact, there is a probability β that the contact will lead to infection. For an infection spread from men to women, the probability of transmission of β_W. This probability is multiplied by the number of susceptible females (A_U) and the proportion of infected males ($\frac{N}{\sigma^{\prime}}$). This gives the rate at which infections are spread from infected men to susceptible women.

5.3 Analysis

We analyze the model by first determining the disease-free equilibrium then determining its stability by looking at the characteristic polynomial found through the determinant of the Jacobian matrix and applying the Routh–Hurwitz stability criterion. We then calculate the basic reproductive number, R_0.

5.3.1 Stability of Disease-Free Equilibrium

The disease-free equilibrium occurs when there are no infected individuals (i.e. when $I_U = I_V = N = 0$).

The disease-free equilibrium is
$(\overline{C_4}, \overline{C_{5U}}, \overline{C_{5V}}, \overline{C_{6U}}, \overline{C_{6V}}, \overline{C_{7U}}, \overline{C_{7V}}, \overline{C_{8U}}, \overline{C_{8V}}, \overline{C_{9U}}, \overline{C_{9V}}, \overline{C_{10U}}, \overline{C_{10V}}, \overline{A_U}, \overline{A_V}, \overline{I_U}, \overline{I_V}, \overline{M}, \overline{N})$,
where

$$\overline{C_{4U}} = \frac{\pi_W}{1+\mu_C}$$

For $4 \leq i \leq 10$,

$$\overline{C_{iU}} = \frac{(1-\epsilon p_{(i-1)})\overline{C_{(i-1)U}}}{1+\mu_C} \qquad \overline{C_{iV}} = \frac{\epsilon p_{(i-1)}\overline{C_{(i-1)U}} + \overline{C_{(i-1)V}}}{1+\mu_C}$$

$$\overline{A_U} = \frac{(1-\phi_U)\overline{C_{10U}}}{f(\overline{\epsilon_W}\,\overline{p_W}) + \mu_A} \qquad \overline{A_V} = \frac{f(\overline{\epsilon_W}\,\overline{p_W})\overline{A_U} + (1-\phi_V)\overline{C_{10V}}}{\mu_A}$$

$$\overline{I_U} = 0 \qquad \overline{I_V} = 0$$

$$\overline{M} = \frac{\pi_M}{\mu_A} \qquad \overline{N} = 0.$$

The Jacobian matrix was calculated in order to determine the stability of the disease-free equilibrium. According to stability theory of ordinary differential equa-

tions, if all of the eigenvalues (λ) of the Jacobian at the disease-free equilibrium have negative real parts, then the disease-free equilibrium is stable.

The Jacobian matrix for this model evaluated at the disease-free equilibrium is $J_{DFE} = [J^{(1)}_{DFE}|J^{(2)}_{DFE}|J^{(3)}_{DFE}]$, where

$$J^{(1)}_{DFE} = \begin{bmatrix} -(1+\mu_C) & 0 & 0 & 0 & 0 & 0 \\ (1-\epsilon p_4) & -(1+\mu_C) & 0 & 0 & 0 & 0 \\ \epsilon p_4 & 0 & -(1+\mu_C) & 0 & 0 & 0 \\ 0 & (1-\epsilon p_5) & 0 & -(1+\mu_C) & 0 & 0 \\ 0 & \epsilon p_5 & 1 & 0 & -(1+\mu_C) & 0 \\ 0 & 0 & 0 & 1-\epsilon p_6 & 0 & -(1+\mu_C) \\ 0 & 0 & 0 & \epsilon p_6 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & (1-\epsilon p_7) \\ 0 & 0 & 0 & 0 & 0 & \epsilon p_7 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$J^{(2)}_{DFE} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ -(1+\mu_C) & 0 & 0 & 0 & 0 & 0 \\ 0 & -(1+\mu_C) & 0 & 0 & 0 & 0 \\ 1 & 0 & -(1+\mu_C) & 0 & 0 & 0 \\ 0 & (1-\epsilon p_8) & 0 & -(1+\mu_C) & 0 & 0 \\ 0 & \epsilon p_8 & 1 & 0 & -(1+\mu_C) & 0 \\ 0 & 0 & 0 & (1-\epsilon p_9) & 0 & -(1+\mu_C) \\ 0 & 0 & 0 & \epsilon p_9 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1-\phi_U \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \phi_U \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

$$
J_{DFE}^{(3)} = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-(1-\mu_C) & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -f-\mu_A & 0 & \xi_U & 0 & 0 & \frac{-\beta_W A_V}{\male} \\
1-\phi_V & f & -\mu_A & 0 & \xi_V & 0 & \frac{-(1-\psi)\beta_W A_V}{\male} \\
0 & 0 & 0 & -\xi_U-\mu_A & 0 & 0 & \frac{\beta_W A_U}{\male} \\
\phi_V & 0 & 0 & 0 & -\xi_V-\mu_A & 0 & \frac{(1-\psi)\beta_W A_V}{\female} \\
0 & 0 & 0 & \frac{-\beta_M M}{\female} & \frac{-\beta_M M}{\female} & -\mu_A & \xi_M \\
0 & 0 & 0 & \frac{\beta_M M}{\female} & \frac{\beta_M M}{\female} & 0 & -\xi_M-\mu_A
\end{bmatrix}.
$$

The characteristic polynomial of the Jacobian is

$$
\det(J-\lambda I) = (-\mu_A-\lambda)^2(-1-\mu_C-\lambda)^{13}(-f(\epsilon_W p_W)-\mu_A-\lambda)\det(L),
$$

where

$$
L = \begin{bmatrix}
-\xi_U-\mu_A-\lambda & 0 & \frac{\beta_W \overline{A_U}}{\male} \\
0 & -\xi_V-\mu_A-\lambda & \frac{(1-\psi)\beta_W \overline{A_V}}{\male} \\
\frac{\beta_M \overline{M}}{\female} & \frac{\beta_M \overline{M}}{\female} & -\xi_M-\mu_A-\lambda
\end{bmatrix}.
$$

Solving det(L)=0, we get

$$
\lambda^3 + \alpha\lambda^2 + \omega\lambda + \rho = 0, \tag{5.3.1}
$$

where

$$\alpha = 3\mu_A + \xi_U + \xi_V + \xi_M$$

$$\omega = 3\mu_A^2 + \xi_U\xi_V + \xi_U\xi_M + \xi_V\xi_M + 2\mu_A(\xi_U + \xi_V + \xi_M) - \frac{(1-\psi)\beta_W\beta_M\,\overline{A_V}}{♀} - \frac{\beta_W\beta_M\overline{A_U}}{♀}$$

$$\rho = \mu_A^3 + \mu_A^2(\xi_U + \xi_V + \xi_M) + \mu_A(\xi_U\xi_V + \xi_U\xi_M + \xi_V\xi_M) - \frac{(1-\psi)\beta_W\beta_M\,\overline{A_V}}{♀}(\mu_A + \xi_U) - \frac{\beta_W\beta_M\overline{A_U}}{♀}(\mu_A + \xi_V)$$

In order to determine the stability of the disease-free equilibrium in the linearized system we use the Routh–Hurwitz stability criterion. This criterion determines whether the roots of the characteristic polynomial have negative real parts. If they do, the equilibrium is locally stable, since the solutions in the form $e^{\lambda t}$ are bounded.

For our cubic characteristic polynomial (5.3.1), we have four Routh–Hurwitz conditions that must all be satisfied in order for the disease-free equilibrium to be locally stable.

1. $\alpha > 0$
2. $\rho > 0$
3. $\omega > 0$
4. $\alpha \cdot \omega > \rho$

The first condition is satisfied, since $\alpha = 3\mu_a + \xi_U + \xi_V + \xi_M$ and all of the parameters are positive.

The second condition must be satisfied since, if $\rho < 0$, then we are guaranteed to have at least one positive real root of the characteristic polynomial. If $\rho = 0$, then we have a non-hyperbolic fixed point and must use stability theory to determine the stability of the disease-free equilibrium. We determine stability for the case when $\rho = 0 + \delta > 0$ (where δ is a small positive perturbation). We show that $\omega > 0$ and $\alpha\omega > 0$ in order to satisfy the Routh–Hurwitz criterion.

We define

$$\diamondsuit = \xi_U + \xi_V + \xi_M$$
$$\heartsuit = \xi_U\xi_V + \xi_U\xi_M + \xi_V\xi_M$$

Setting $\rho = 0 + \delta$ and rearranging the original expression of ρ, we find

$$\frac{(1-\psi)\beta_W\beta_M\overline{A_V}}{\varphi} = \frac{1}{\mu_A+\xi_U}\left[\mu_A^3+\mu_A^2+\mu_A\heartsuit-\frac{\beta_W\beta_M\overline{A_U}}{\varphi}(\mu_A+\xi_V)-\delta\right]$$

Substituting this into ω, we have

$$\omega = 3\mu_A^2+2\mu_A\diamondsuit+\heartsuit-\frac{1}{\mu_A+\xi_U}\left[\mu_A^3+\mu_A^2+\mu_A\heartsuit-\frac{\beta_W\beta_M\overline{A_U}}{\varphi}(\mu_A+\xi_V)-\delta\right]-\frac{\beta_W\beta_M\overline{A_U}}{\varphi}.$$

Simplifying the expression $\omega > 0$, we find

$$(\mu_A+\xi_U)\left(3\mu_A^2+2\mu_A\diamondsuit+\heartsuit\right)+\frac{\beta_W\beta_M\overline{A_U}}{\varphi}(\mu_A+\xi_V)+\delta >$$
$$\mu_A^3+\mu_A^2\diamondsuit+\mu_A\heartsuit+\frac{\beta_W\beta_M\overline{A_U}}{\varphi}(\mu_A+\xi_U)$$

$$3\mu_A^3+2\mu_A^2\diamondsuit+\mu_A\heartsuit+3\mu_A^2\xi_U+2\mu_A\xi_U\diamondsuit+\xi_U\heartsuit+(\mu_A+\xi_V)\frac{\beta_W\beta_M\overline{A_U}}{\varphi}+\delta>$$
$$\mu_A^3+\mu_A^2\diamondsuit+\mu_A\heartsuit+(\mu_A+\xi_U)\frac{\beta_W\beta_M\overline{A_U}}{\varphi}$$

$$2\mu_A^3+\mu_A^2\diamondsuit+3\mu_A\xi_U+2\mu_a\xi_U\diamondsuit+\xi_U\heartsuit+(\mu_A+\xi_V)\frac{\beta_W\beta_M\overline{A}_U}{\varphi}+\delta >$$
$$(\mu_A+\xi_U)\frac{\beta_W\beta_M\overline{A}_U}{\varphi}$$

$$(\mu_A+\xi_V)\frac{\beta_W\beta_M\overline{A}_U}{\varphi} > (\mu_A+\xi_U)\frac{\beta_W\beta_M\overline{A}_U}{\varphi}$$

which is true if

$$\xi_V > \xi_U.$$

This is equivalent to the condition

$$\frac{1}{\xi_V} < \frac{1}{\xi_U}.$$

Since $\omega > 0$ (strictly positive) when $\rho = 0$, $\omega > 0$ when $\rho = 0 + \delta$.
Since $\alpha > 0$, $\omega > 0$ because

$$\begin{aligned}\omega \approx & \frac{\beta_W \beta_M \overline{A_U}}{\varphi} \left(\frac{\mu_A + \xi_V}{\mu_A + \xi_U}\right) \\ & - \frac{1}{\mu_A + \xi_U}[(\mu_A + \xi_U)(3\mu_A^2 + \xi_U\xi_V + \xi_U\xi_M + \xi_V\xi_M + 2\mu_A(\xi_U + \xi_V + \xi_M)) \\ & - \mu_A^3 - \mu_A^2(\xi_U + \xi_V + \xi_M) - \mu_A(\xi_U\xi_V + \xi_U\xi_M + \xi_V\xi_M)] > 0.\end{aligned}$$

When $\rho = 0^+$, the Routh–Hurwitz conditions are satisfied, all roots have a negative real part, and our system is stable at the disease-free equilibrium. Since $\alpha > 0$ and $\omega > 0$ when $\rho = 0^+$, then $\rho \approx 0$ is our threshold of stability.

For the case when $\rho > 0$, the disease-free equilibrium is stable as long as $\alpha > 0$ (given) $\omega > 0$, $\rho > 0$ and $\alpha\omega > \rho$. Using numerical simulations, we determine the stability based on $\beta = \beta_W\beta_M$ since the transmission probabilities highly influence the location of the stable regions. This analysis can be seen in Figure 5.2. Figure 5.2A shows the scenario before vaccination while Figure 5.2B shows the scenario with 100% children and 100% adult vaccination. Note that the grade of childhood vaccination does not change the results. The region of stability does not significantly change depending on the efficacies (ϵ_C and ϵ_W) or the probability of protection (Ψ). In Figure 5.2, ρ is represented by the solid red line while $\alpha\omega$ is represented by the dashed blue line. When $\rho > 0$, $\alpha\omega > 0$. Since $\alpha > 0$, then $\omega > 0$. This satisfies the first Routh–Hurwitz stability criterion that $\alpha > 0$, $\omega > 0$ and $\rho > 0$.

The disease-free equilibrium is stable only if $\rho > 0$ and $\alpha\omega > \rho$ (the region in the inset graph). The value of β^* indicated on the inset graph shows the threshold of transmission between a stable and unstable disease-free equilibrium. These values change depending on the coverage rate. As long as $\beta < \beta^*$ when $\rho > 0$, then the stability of the system remains the same as the case when $\rho = 0 + \delta$. This shows that we can use ρ as a threshold of stability. This threshold is discussed in greater detail in section 5.3.2.

We have not ruled out the existence of backwards bifurcations. Figure 5.1 depicts a backwards bifurcation. That is to say, it is possible for multiple stable equilibria to coexist for $R_0 < 1$ [90]. This is important, because it means there is a possibility that the disease will still persist even if $R_0 < 1$. If a backwards bifurcation does exist, then this means there are at least two thresholds which determine stability. Hence, an

endemic disease is only eradicated if the R_0 threshold is positive and smaller than the others. If another threshold, R_a exists such that $R_a < R_0 < 1$, the outcome depends on the initial conditions. If a perturbation from the initial conditions are fairly small, then the system will approach the disease-free equilibrium, meaning the disease will be eradicated. If the initial conditions are large, then the system will approach the endemic equilibrium and the disease will persist, even if $R_0 < 1$.

5.3.2 Basic Reproductive Number

The basic reproductive number R_0 represents the average number of secondary infections caused by one infectious person in a completely susceptible population. If $R_0 > 1$, each infected person will, on average, cause more than one secondary infection causing the infection to persist in the population. However, if $R_0 < 1$, then the disease will eventually die out without further intervention [65]. In other words, this threshold is the point where the disease-free equilibrium changes stability. From the analysis in section 5.3.1, the R_0 threshold is

$$R_0 = \frac{\beta_W \beta_M ((1-\psi)(\mu_A + \xi_U)\overline{A_V} + (\mu_A + \xi_V)\overline{A_U})}{♀\mu_A({\mu_A}^2 + \mu_A(\xi_U + \xi_V + \xi_M) + (\xi_U\xi_V + \xi_V\xi_M + \xi_V\xi_M))},$$

where $\overline{A_U}$ and $\overline{A_V}$ are the values at the disease-free equilibrium.

Knowing this threshold is significant, since it will tell us which parameters are involved in shifting the disease from persistence to eradication. This threshold is also used to determine which parameters have the greatest influence on R_0 which in turn gives us insight into the most effective intervention strategies (section 5.5.7).

5.4 Critical Thresholds

There is a critical vaccine efficacy for both children (ϵ^*) and women (ϵ^*_W), and a critical probability of protection (ψ) that serves for a threshold where, even with 100% vaccination, the targeted types of HPV can not be eradicated in the population. These values are determined by first setting $R_0 = 1$ and rearranging for the desired parameter. In order to simplify the expression for R_0, we rewrite the equilibrium values for our population in a general form. Note that here k^* represents the grade of childhood vaccination.

For $4 \leq k \leq 10$, we find

$$\overline{C_{kU}} = \frac{\pi_W}{(1+\mu_C)^{k-3}} \qquad \text{for } k \leq k^*$$

$$\overline{C_{kU}} = \frac{\pi_W(1-\epsilon p_{k-1})}{(1+\mu_C)^{k-3}} \qquad \text{for } k > k^*$$

$$\overline{C_{kV}} = 0 \qquad \text{for } k \leq k^*$$

$$\overline{C_{kV}} = \frac{\pi_W \epsilon}{(1+\mu_C)^{k-3}} \qquad \text{for } k > k^*$$

$$\overline{A_U} = \frac{\pi_W}{(f(p_W\epsilon_W)+\mu_A)(1-\mu_C)^7}$$

$$\overline{A_V} = \frac{\pi_W f}{(f(p_W\epsilon_W)+\mu_A)(1-\mu_C)^7}.$$

To determine the expression for ϵ^*, we look at only childhood vaccination (i.e. no adult vaccination), which we get by setting $p_W = 0$. Since childhood vaccination only occurs during one year, then

$$p_k = \begin{cases} 1 & \text{when } k = k^* \\ 0 & \text{when } k \neq k^*. \end{cases}$$

Rearranging the expression $R_0 = 1$ and solving for ϵ^*, we find

$$\epsilon^* = \frac{♀\mu_A^2(1-\mu_C)^7(\mu_A^2 + \mu_A(\xi_U+\xi_V+\xi_M) + \xi_U\xi_V + \xi_U\xi_M + \xi_V\xi_M)}{\beta_W\beta_M\pi_W((1-\psi)(\mu_A+\xi_U) - (\mu_A+\xi_V))}.$$

Noticing that $♀' \neq 0$ (i.e. ♀ is not constant), we construct the following inequality from the definition of ♀. We know that

$$\pi_W - \mu_A ♀ \leq ♀' \leq \pi_M - \mu_C ♀$$
$$♀_L = \frac{\pi_W}{\mu_C} \leq \overline{♀} \leq \frac{\pi_W}{\mu_A} = ♀_U.$$

This statement indicates that the size of the female population at equilibrium ($\overline{♀}$) is dictated by the size of the female population when there are only women ($♀_W$) and when there are only girls ($♀_G$). This allows us to bound ϵ^* between

$$\epsilon^*(♀_W) \leq \epsilon^*(\overline{♀}) \leq \epsilon^*(♀_G).$$

If $\epsilon < \epsilon^*(\text{♀}_W)$, then 100% coverage rate of girls will not work since $R_0 > 1$. If $\epsilon > \epsilon^*(\text{♀}_G)$, then with a sufficient coverage rate it is possible for female-only vaccine intervention to eradicate the targeted types of HPV. If ϵ is between the bounds, we cannot accurately predict the outcome of the vaccine intervention.

Using a similar strategy, the critical adult efficacy is

$$\epsilon_W^* = \frac{\mu_A(1+\gamma)(\beta_W\beta_M\pi_W\xi_V + \mu_A(1+\mu_C)^7 D)}{\beta_W\beta_M\pi_W(c+\mu_A(\mu_A+\xi_U)) - \mu_A^2(1+\mu_C)^7 D},$$

where D is the denominator of R_0. ϵ_W^* is bounded between

$$\epsilon_W^*(\text{♀}_W) \leq \epsilon_W^*(\overline{\text{♀}}) \leq \epsilon_W^*(\text{♀}_G).$$

The interpretation of ϵ_W^* is similar to that of ϵ^*.

Just as the critical efficacies were found by allowing $R_0 = 1$ and solving for the desired threshold value, the critical protection rate (ψ^*) is

$$\psi^* = 1 + \frac{\beta_W\beta_M(\mu_A+\xi_U)\overline{A_U} - D}{\beta_W\beta_M(\mu_A+\xi_V)\overline{A_V}}$$

which is bounded between

$$\psi^*(\text{♀}_W) \leq \psi^*(\overline{\text{♀}}) \leq \psi^*(\text{♀}_G).$$

The interpretation of ψ^* is similar to that of ϵ^*.

5.5 Numerical Simulations

All of the numerical simulations were completed using Matlab®. The ODEs were solved using the built-in ode45 solver.

5.5.1 Transmission

Figure 5.2A shows the region of stability for when no vaccination is present. If the actual measured transmission probability in Canada is below $\beta^* = 0.34$ then the disease would be eradicated without any intervention. Since HPV is an endemic throughout the world and has not become eradicated, we conclude that the actual transmission parameters must be greater than 0.34 (assuming all other parameters used in the simulation are correct).

Figure 5.2B shows the region of stability for 100% childhood and 100% adult vaccination. As long as the actual transmission is lower than $\beta^* = 0.69$, then the introduction of the vaccine has the ability to eradicate HPV. However, if the actual β is above 0.69 then even 100% vaccination cannot eradicate HPV. These values allow us to estimate a range of likely transmission values, which are currently unknown.

5.5.2 Estimation of Parameters

transmission found in Hernandez *et al.* [66] was multiplied by 112, which is the average number of times 18-29 year olds have sex per year [114]. The transmission parameters used in the model were calculated by

The probability of protection, ϕ, was estimated by including the transmission of the targeted HPV types and an estimate for the proportion of girls who become sexually active before grade 11 (30%) [121]. Assuming all of the sexually active girls came into contact with someone able to transmit one of the targeted HPV types, the infection for this grade class would spread at a rate of 30% $\times$ β, giving a range of $0 \leq \phi \leq 0.3$.

The recovery rate was found by determining the average infectious period for both high and low risk types of HPV ($\frac{1}{\xi}$) and solving for ξ [98, 146].

5.5.3 Varying Grade

We looked at the significance of vaccinating girls at different ages by constructing a box plot as seen in Figure 5.4. For a specific grade, the coverage rate was varied between 0 and 100%. In Figures 5.4A and 5.4B, the efficacy was held constant to represent two (95-97%) and three (97-99%) doses, respectively. In Figure 5.4C, the efficacy was varied between two and three doses, and all other parameters were varied among their ranges as seen in Table 5.2. Latin Hypercube Sampling was used to sample parameter values from the given ranges in Table 5.2 using a uniform distribution. Latin Hypercube sampling is a statistical sampling method in which parameters are assigned a range of values, and a distribution of plausible collections of these parameter values are created [11]. R_0 was calculated 1000 times (diamonds) per grade. Note that only one grade (or adult) is considered during each run; for example, a box plot representing grade 4 only takes into account vaccinating girls in grade 4, and does not include vaccinating any other grade or adults. The thick red horizontal lines and the number indicated above them represent the median value of R_0, while the box indicates the location of the upper and lower quartiles.

Comparing the median values in Figures 5.4A, 5.4B and 5.4C, we notice that when girls are between grade 4 and 10, the values are all between 0.62 and 0.69 whereas the median R_0 is always above one for adult vaccination regardless of the number of doses given. The upper quartile values and lower quartile values also follow

the trend where the children vaccination values are all in the same range which is significantly smaller than when adult vaccination occurs.

Figure 5.5 shows similar results. Vaccinating any grade will, on average, lead to theoretical eradication (since $R_0 < 1$). Conversely, if only adults are vaccinated, the mean R_0 is above one and HPV persists in the population.

5.5.4 Varying Dosage

Comparing Figures 5.4A and 5.4B, we notice that the R_0 values are generally smaller in the case of three doses (panel C), which is expected since the vaccine is less effective on a two dose schedule. However the difference is minimal. The same trends seen in panel A and B of Figure 5.4 are also seen in Figure 5.4C, which suggests the number of doses given does not make a significant difference for the outcome. This can also be validated by Figure 5.6 which shows a low correlation of ϵ and ϵ_W to R_0.

Figure 5.5 shows the minute difference in the mean R_0 when using a two-dose verses a three-dose regime. The regime that leads to the lowest mean R_0 switches, showing no clear trend between the regimes. Either regime could lead to theoretical eradication (if children are vaccinated).

5.5.5 Varying Coverage Rate

The coverage rate desired in order to eliminate the targeted high risk types of HPV can be seen in Figure 5.8. Above the curves is the region where $R_0 < 1$ and the targeted types are theoretically eradicated, whereas below the lines is the region where the disease persists in the population. The curves indicate when $R_0 = 1$ for either two doses (dashed red line) or three doses (solid black line). As expected, the curve for two doses is higher than three since the efficacy for two doses is slightly lower.

A childhood-only vaccination program can theoretically eradicate the targeted types of HPV with either two or three doses, as long as the appropriate coverage rate is achieved (Figure 5.8). A province that provides two doses must vaccinate at least 78% of girls, while a province with a three-dose schedule must vaccinate at least of 76% of girls. However, if adult vaccination is included, the burden of vaccinating children decreases. For example, if 30% of adult women are vaccinated, then 65% of girls with a two-dose regimen, while 63% of girls with a three-dose regime would require vaccination to eradicate the targeted types of HPV (blue dashed box). Note that these curves do not change with the grade of childhood vaccination.

5.5.6 Time of Eradication

It has been shown that it is possible, through a female-only vaccination program, to eradicate the targeted types of HPV, but how long will it take to do so? Figure 5.9

shows the timecourse of HPV with different doses and coverage rates. The blue thick line labelled "no vaccination" shows the outcome of the number of infected women over time without vaccination. As expected, the proportion of infected individuals remains at the current Canada-wide level, about 75% [29]. The red dashed lines represent a two-dose schedule, whereas the black solid curves represent the outcomes with a three-dose schedule. Looking at the two middle curves that indicate a constant 70% level of childhood vaccination, the proportion of infected females equilibrates at about 16.5% with three doses and 19% with two doses after 100 years. The lower curves show the effect of a 70% childhood coverage rate and 30% adult vaccination coverage. With a three-dose program, the level of infection reaches 2.59% after 100 years, while the two-dose schedule reaches 2.56% after the same amount of time. Notice that the most significant reduction in the number of infected women should happen within the first 50 years.

5.5.7 Sensitivity to Variations

Since the true value of each parameters may fluctuate, we explore the sensitivity of R_0 to the parameter values in Table 5.2 using Latin Hypercube sampling.This in turn allows us to use partial rank correlation coefficients to rank the parameters in terms of their influence on R_0, be it a positive or negative influence. Figure 5.6 shows the partial rank correlation coefficient sensitivity analysis on R_0. The parameters were varied for 1000 runs. Here, R_0 is most sensitive to the transmission of HPV from men to women, β_W, and from women to men, β_M. The next influential parameter is ψ. Notice that the coverage rate (p_i, where, $4 \leq i \leq 10$, and p_W) and vaccine efficacy (ϵ and ϵ_W) do not significantly affect the value of R_0. Figure 5.5 shows the output of the Latin Hypercube sampling for the two significantly influential parameters and the next closest (ψ).

5.6 Discussion and Conclusion

Based on the results of the model, we conclude that, as long as vaccination occurs before sexual debut, it is possible to eradicate the targeted HPV types. We also determine that the grade of vaccination before sexual debut, does not make a significant difference on the prevalence of the targeted HPV types for the Canadian population. Comparing Figures 5.4A, 5.4B and 5.4C, we observe that the average value of R_0 is always below one when children are vaccinated, while the average value of R_0 is above one when only adult women are vaccinated, independent of the number of doses given. While looking only at childhood-only vaccination, there does not to seem to be a large difference between the grades. From a mathematical standpoint, it is easy to understand why the grade of vaccination does not matter in the model, since there is no impact in terms of the disease dynamics, whether girls are vaccinated in grade 4 or

10. The large jump is due to the change in vaccine effectiveness for those previously exposed to the considered HPV types, as well as the possibility of over-vaccinating women, since they are considered within the model for 10 years whereas children are only vaccinated within a single year. This is important to determine because it shows there are likely no underlying grade-dependent trends. However, from an epidemiological standpoint, we know that the vaccine has little to no impact on those individuals who have a previous infection with a targeted type. Therefore, public vaccination strategies should choose the grade of vaccination based on epidemiological and vaccination-program limitations.

Assuming that the number of does given only changes the efficacy of the vaccine, the evidence from this model suggests that the number of doses given does not significantly change the outcome of the vaccine strategy. Figure 5.8 shows that the possibility of eradication of the targeted HPV types exists with either two or three doses, independent of the grade the childhood vaccine is given in. This evidence follows the findings by several clinical studies that suggest that two doses of the bivalent vaccine may protect just as well as three doses [37, 86, 101]. Even with a large range for the efficacy (using efficacies much smaller than reported values), the outcome of the vaccine program barely differs (Figure 5.9). The higher the coverage rate, the higher the success of the vaccine program (Figure 5.8). Based on this evidence, we suggest each province choose the number of doses based on cost or ease of program implementation, as long as an appropriate coverage rate is matched to achieve the desired level of infection in the community.

The value R_0 is mainly affected by the ability of the targeted HPV types to transmit, the ability of the vaccine to prevent the infection, how quickly infected individuals clear the virus, the population dynamics, and the number of individuals in each compartment. The most effective way to decrease R_0 is to decrease the transmission of the targeted types of HPV. This could be done through the use of condoms, abstinence or increasing the heterogeneity of the sexual contact network of the population [68, 127]. Since HPV has been infecting humans for millions of years and has not been eradicated, the real transmission probability in the Canadian population must be greater than 34%. By studying the critical transmission value for 100% childhood and adult vaccination, we know that if the actual transmission probability is greater than 69%, then even with 100% vaccine coverage the targeted HPV types could not be eradicated. Looking at the stability of the disease-free equilibrium based on the probability of transmission is reasonable since the transmission parameters are the only two parameters which significantly impact the value of the basic reproductive number, as shown by the sensitivity analysis.

Using sample values in Table 5.2, and calculating $♀_L$ and $♀_U$ based on $\pi_W = 100$, $\psi^* = 0.6592$. This indicates that if $\psi \leq 0.6592$, then even with a 100% coverage rate, there is no possibility of eradication of the targeted HPV types. Realistic values of ψ are likely much higher (around 0.75–1), since the vaccine has a very high efficacy

and therefore very low failure rate in the general population [86].

The estimates for high-risk HPV types were used for numerical simulations in order to depict the worst realistic outcomes of the vaccine. The results may be an overestimate for how well the low-risk types transmit, as well as an overestimate on the proportion of people who need to be vaccinated in order to eradicate the targeted HPV types.

We chose the estimates for the efficacies (ϵ and ϵ_W) based on clinical evidence of both the bivalent and quadrivalent vaccine. Obviously, a single vaccine program will only use either the bivalent or quadrivalent vaccine. Since this model does not differentiate between different HPV types, and the efficacies for either vaccine do not largely differ, the numerical results hold for either vaccine. Through sensitivity analysis, using larger ranges of the efficacy than observed for either vaccine, we see in Figure 5.6 that it is not important to narrow down the range of efficacies since neither ϵ nor ϵ_W affect the value of R_0 significantly. In order to estimate the efficacy of a two-dose schedule of the quadrivalent vaccine, we used the efficacy of the bivalent vaccine from the Costa Rica clinical trial [86]. This model should be updated once better data is available for the efficacy and effectiveness of a two-dose quadrivalent HPV vaccine.

We chose a model comprised of ordinary differential equations since there are numerous analytical techniques for ODEs, especially for disease models. This includes calculating R_0, which is a technique not widely used for other types of models but is an important epidemiological concept. Our population can be divided into compartments and the flow of people between those compartments do not necessarily occur in discrete time steps. For example, children in grade school typically move up a grade per year, but there are some students who skip grades and some who are held back. Ordinary differential equations are thus a good approximation for this behaviour. Considering the model is comprised of 19 equations, it is perhaps a bit surprising that the characteristic polynomial was third order. This simplicity can be explained through having only three infected states (unvaccinated women, vaccinated women and men) with not very much overlap between them.

It is important to note that our model has several limitations. In terms of vaccination programs, the model does not include catch-up programs unless included in the initial population conditions. Our model does not allow for the vaccine program to differ amongst individuals. Each person receiving the vaccine with either two or three doses must complete the regimen within one year. The possibility of male vaccination is not included, although it is now approved by Health Canada [29, 101, 102]. The model does not differentiate between HPV 6, 11, 16 or 18 or include any other HPV types. We assume the vaccine does not wane. This model also does not include immigrating (infectious) adults. From the base adult model, we assume that men who have sexual relations with women in the sexually active cohort (i.e. women who are eligible for adult vaccination) do not continue to find new partners in this

age group as time goes on. The sexually active cohorts of men and women are linked only for the time (approximately 10 years) that adult women are sexually active and eligible for vaccination [91].

This thesis considers the number of HPV infections within the population. More specifically, it does not consider the vaccine's effect on the secondary causes of HPV infection, namely cancer and warts. Future research could explore the type-specific effects of the vaccine on targeted and non-targeted types of HPV or the impact the vaccination programs across Canada have on secondary illnesses linked to the targeted types of HPV, such as cancer and genital warts. Future research could also explore the age-dependent effects of vaccination through differently structured models (such as discrete-time dynamical systems).

Since the provincial vaccination programs are already in place and each province has chosen their dosing schedule (although it is possible they may change), we recommend that all of the provinces focus on increasing their coverage rate for both the public vaccination of girls and privately vaccinated women to at least 80%. This number is realistic for many provinces, since several provinces have already reached this criterion in 2009 (Quebec, Nova Scotia, Newfoundland and PEI). For the other provinces who need to increase their coverage rate, it may be accomplished by creating public-education campaigns or may involve making protocols similar to vaccines necessary to attend school such as that for Hepatitis B [97, 105].

Our model suggests the grade of vaccination does not affect the outcome of the vaccination program. Therefore, we suggest provinces vaccinate girls as early as possible to avoid vaccine failure due to previous infection. We also recommend that the number of doses should be chosen and the main focus should be on obtaining a large enough coverage rates for children and/or adults in order to achieve the desired outcome (eradication of HPV 6, 11, 16 and 18 or a lower infected population).

5.7 Figure Captions

Figure 5.1 Backwards bifurcations. Figure 5.1 shows the effects of backwards bifurcations. The solid curve indicate stable equilibria, while dashed curves indicate unstable equilibria. (a) A backward bifurcation at $R_0 = 1$ may result in persistence of the disease when $R_0 < 1$. There is a point R_a <1 such that the endemic equilibrium exists for $R_a < R_0 < 1$ and a third, unstable, equilibrium also exists. Hence, the disease-free equilibrium is only globally stable if $0 < R_0 < R_a$. (b) Backward bifurcations at other points may also affect the outcome. Although the disease persists for all $R_0 > 1$ and is eradicated when $R_0 < 1$ (due to the transcritical bifurcation at $R_0 = 1$), there is a region $R_m < R_0 < R_n$, where three equilibria coexist. In this region, the outcome depends on the initial conditions. Reprinted from [90] with permission.

Figure 5.2 Stability when $\rho > 0$. Figure 5.2A shows the scenario with no vaccination which contrasts with Figure 5.2B which shows the scenario with 100% child and 100% adult vaccination. The dashed line represents $\alpha\omega$ and the solid line represents ρ. These are the two conditions which determine the stability of the disease-free equilibrium for our system. The disease-free equilibrium is stable in the region where the dashed line is above the solid line and when the solid line is above zero. This region is shown in more detail in the inset graph. We compare these conditions to $\beta = \beta_W \beta_M$ since these parameters always show up in this fashion, we combined them into one parameter for simplification. The β^* value indicated in the inset graphs are the critical β values which determine when the disease-free equilibrium become unstable. Since Figure A includes no vaccination, this β^* indicates that the actual value of β within the Canadian population must be at least 0.34 since HPV is an epidemic and has not been eradicated. Since Figure B depicts the scenario with 100% childhood and 100% adult vaccination, if the actual β exceeds 0.69, then even with 100% vaccination we cannot eradicate HPV since the disease-free equilibrium is always unstable.

Figure 5.3: The Model. Movement of individuals through childhood vaccination programs and the infection cycle as adults. Girls from grades 4 through 10 (pink, C_i) can be vaccinated (shaded) depending on the proportion vaccinated (p_i) and the efficacy of the vaccine (ϵ). Once the girls turn 16 (approximately grade 11), they enter adulthood as women (purple) where they are introduced and may become infected (dashed) with HPV. Unvaccinated women (A_U) can become vaccinated (f) or become infected (I_U) with the probability (β_W) when they meet an infected man (N). Vaccinated adult women (A_V) can also become infected (I_V), but with a reduced transmissibility, due to the failure of the vaccine (ψ). Unvaccinated men (M) become infected upon contact with infected women, with a transmission probability β_W. The mortality rate for children is μ_C and the leaving rate of adults is μ_A.

Figure 5.4: Effect of Grade and Dose. R_0 values based on the grade of vaccination and the number of doses. Panel A represents the effects of two doses, panel B three doses and panel C a combination of either dosing schedule. The grade of vaccination is controlled by forcing $p_i = 0$ except for the given grade. The number of doses are defined by different ranges of ϵ and ϵ_W. The horizontal line represents the threshold for eradication, $R_0 = 1$, while the numbers at the top of the graphs indicate the median values. For a children-only program, the median R_0 is always below 1 (i.e. HPV 6, 11, 16 and 18 is theoretically eradicated), independent of the number of doses given. This contrasts with an adult-only vaccination program, where the median R_0 is always above 1 (i.e. the disease will persist). Not only does the eradication threshold trend take place but the difference in the values are large: the median when vaccinating girls is in the range of 0.6–0.7 whereas adults are close to 1. All other parameters used the sample values in Table 5.2.

Figure 5.5: Effect of Mean R_0 Values Based on the Grade of Vaccination. For each grade of vaccination, the mean R_0 was calculated from a run of 1000 parameters chosen using Latin Hypercube sampling. The number of doses are defined by different ranges of ϵ and ϵ_W. The red solid line indicates the threshold $R_0 = 1$. The dosing program (either two or three doses) that lead to the lowest mean R_0 is not consistent, nor does it show a grade-related trend. This indicates that there is no obvious trend in children between theoretical eradication, grade of vaccination and number of doses given. For a children-only program, the mean R_0 is always below 1 (i.e. HPV 6, 11, 16 and 18 are theoretically eradicated), independent of the number of doses given. This contrasts with an adult-only vaccination program, where the median R_0 is always above 1 (i.e. the disease will persist).

Figure 5.6: Partial Rank Correlation Coefficients. Partial rank correlation coefficient sensitivity analysis on R_0 for all parameters. Here, R_0 is most sensitive to the transmission of HPV from men to women, β_W, and from women to men, β_M. R_0 is also sensitive to ψ. All ranges are as in Table 5.2.

Figure 5.7: Latin Hypercube Sampling Output. Latin Hypercube sampling output for the three most influential parameters on R_0. Each graph shows the sampled parameter values from the given range on the horizontal axis and its degree of correlation between the sampled value and the value of R_0. Panel A shows the correlation of β_M while panel B shows β_M. These two parameters are considered to significantly affect the value of R_0. The increasing trend seen in both panel A and B indicates a high degree of correlation between the values of each β and their influence on R_0. Panel C shows the next most influential parameter, the probability of protection (ψ), although it it not considered to be significant. This can be visualized

by the weak trend between ψ and the degree of correlation.

Figure 5.8: Thresholds of Eradication. Thresholds of eradication for targeted types of HPV dependent on coverage rates of children and adults. The three-dose curve assumes a childhood efficacy of 99% and an adult efficacy of 80.9%. The two-dose curve assumes a childhood efficacy of 97% and an adult efficacy of 84.1%. Other parameters are given in Table 5.2. If no adult vaccination is undertaken, then a childhood vaccination program must cover 75% with three doses and 78% with two doses. If30% of adults are vaccinated, then the eradication of targeted types can be achieved with only 63% of girls vaccinated with three doses or 65% with two doses.

Figure 5.9: Timecourse of Infection. Timecourse dynamics among a community where initial conditions are taken to be equilibrium values of an existing infection before the vaccine programs began, 75% of adult males and females. If there is no vaccine introduced, the proportion of women infected remains at 75%. However, if a 70% childhood vaccination program is introduced, the proportion of infected women is reduced to 19% with three doses and 16.5% with two doses. If this program is extended with a 30% coverage rate for women, the proportion of infected women then declines to 2.56% with two doses and 1.72% with three doses after 100 years. All parameters are as in Figure 5.8.

5.8 Tables and Figures

Table 5.1 Overview of Provincial Vaccination Programs

Strategy	*Province(s)*	*Grade*	*Doses*	*Coverage Rate*	*Reference*
1	NWT	4	3	unknown	—
2	QU	4, 9	2, 1(last)	81-86%	[127]
3	AB	5	3	50-60%	[127]
4	BC	6,9	2	62%	[127, 105]
5	NL	6,9	3	85%	[127]
6	MB	6	3	52-61%	[127]
6	NU	6	3	unknown	—
6	PE	6	3	85%	[127]
6	SK	6	3	58-66%	[127]
6	YK	6	3	unknown	—
7	NS	7	3	85%	[127, 59]
7	NB	7	3	unknown	—
8	ON	8	3	49- 59%	[127, 138, 116]

Table 5.2 List of Parameters and State Variables

Parameter	*Description*	*Range*	*Sample Value*	*Reference*
C_{iU}	Unvaccinated child in grade i	*(State Variable)*		
A_U	Unvaccinated adult women	*(State Variable)*		
C_{iV}	Vaccinated child in grade i	*(State Variable)*		
A_V	Vaccinated adult women	*(State Variable)*		
I_U	Uninfected adult women	*(State Variable)*		
I_V	Infected adult women	*(State Variable)*		
M	Uninfected men	*(State Variable)*		
N	Infected men	*(State Variable)*		
π_W, π_M	Birth rate for women, men	0–100 year^{-1}	100	[91]
μ_C	Mortality rate for children	1/50–1/90 year^{-1}	1/90	$\frac{1}{\text{avg. time in compartment}}$
μ_A	Leaving rate for adults	1/12–1/8 year^{-1}	1/10	$\frac{1}{\text{avg. time in compartment}}$
ϵ	Vaccine efficacy in female children	93.3–99.8% 2 doses	0.97	[81]
		93.3-99.8% 3 doses	0.99	[81]
ϵ_W	Vaccine efficacy in adult women	50.2–96.3% 2 doses	.809	[63, 81, 86, 101, 137, 112]
		71.1–87.7% 3 doses	.841	[63, 81, 86, 101, 137, 112]
p_i, where $9 \leq i \leq 14$	Proportion of children vaccinated within the corresponding grade	0–100%		[105, 116, 127, 138]
p_W*	Proportion of previously unvaccinated adult women vaccinated	0–100%		[105, 116, 127, 138]
β_W	Probability of infection of a woman by an infected man	0–1 year^{-1}	0.77	[66]
β_M	Probability of infection of a man by an infected woman	0–1 year^{-1}	0.77	[66]
$\beta = \beta_W \beta_M$	Overall transmission	0–1 year^{-2}	0.6	
$\phi_{U,V}$	Proportion of infected girls at 15 unvaccinated, vaccinated	0–0.3 year^{-1}	0.1	[121]
ψ	Probability of protection against all targeted types	0.6592–1%	0.8	ψ^*
$\xi_{U,V,M}$	Recovery rate for unvaccinated women, vaccinated women, men	1/2- 4/3 year^{-1}	2/3	[98, 146]
c	Attenuation constant	0–0.3 year^{-1}	0.15	[91]
γ	Maximal possible rate of adult vaccination	0–0.2	0.1	[91]
$f(\overline{\epsilon}, \overline{p}) = \frac{c\,\overline{\epsilon_W}\,\overline{p_{10}}}{1 - \overline{\epsilon_W}\,\overline{p_{10}} + \gamma}$	Rate at which unvaccinated women are vaccinated			[91]

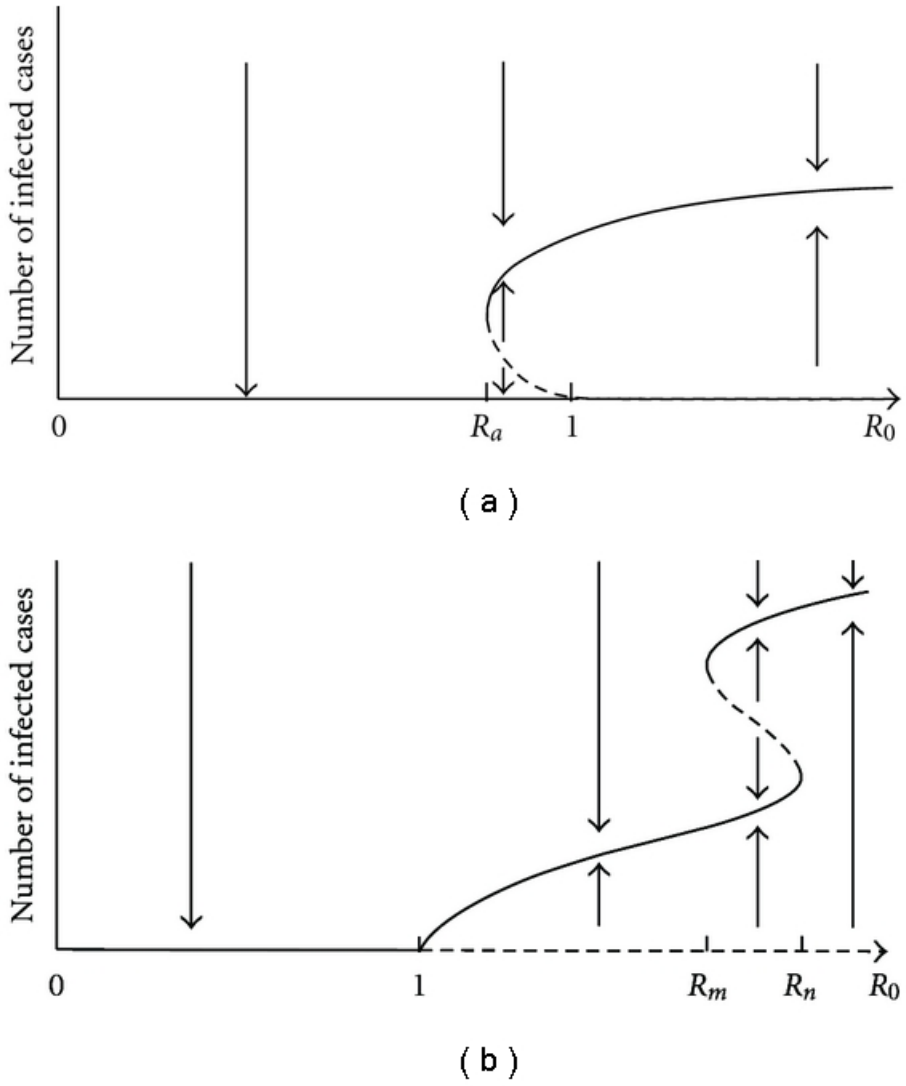

Figure 5.1 Backwards Bifurcations

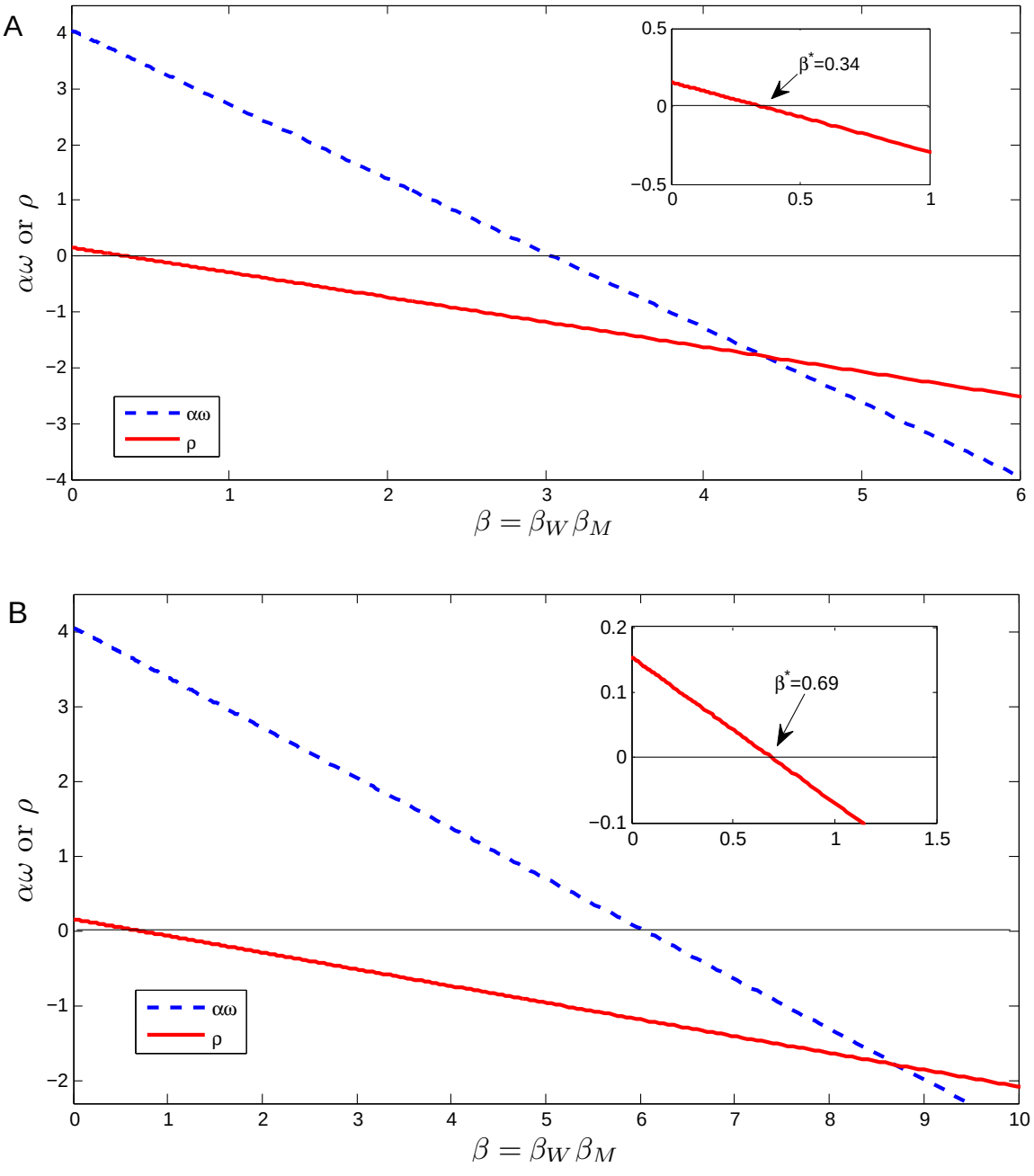

Figure 5.2 Stability when $\rho > 0$

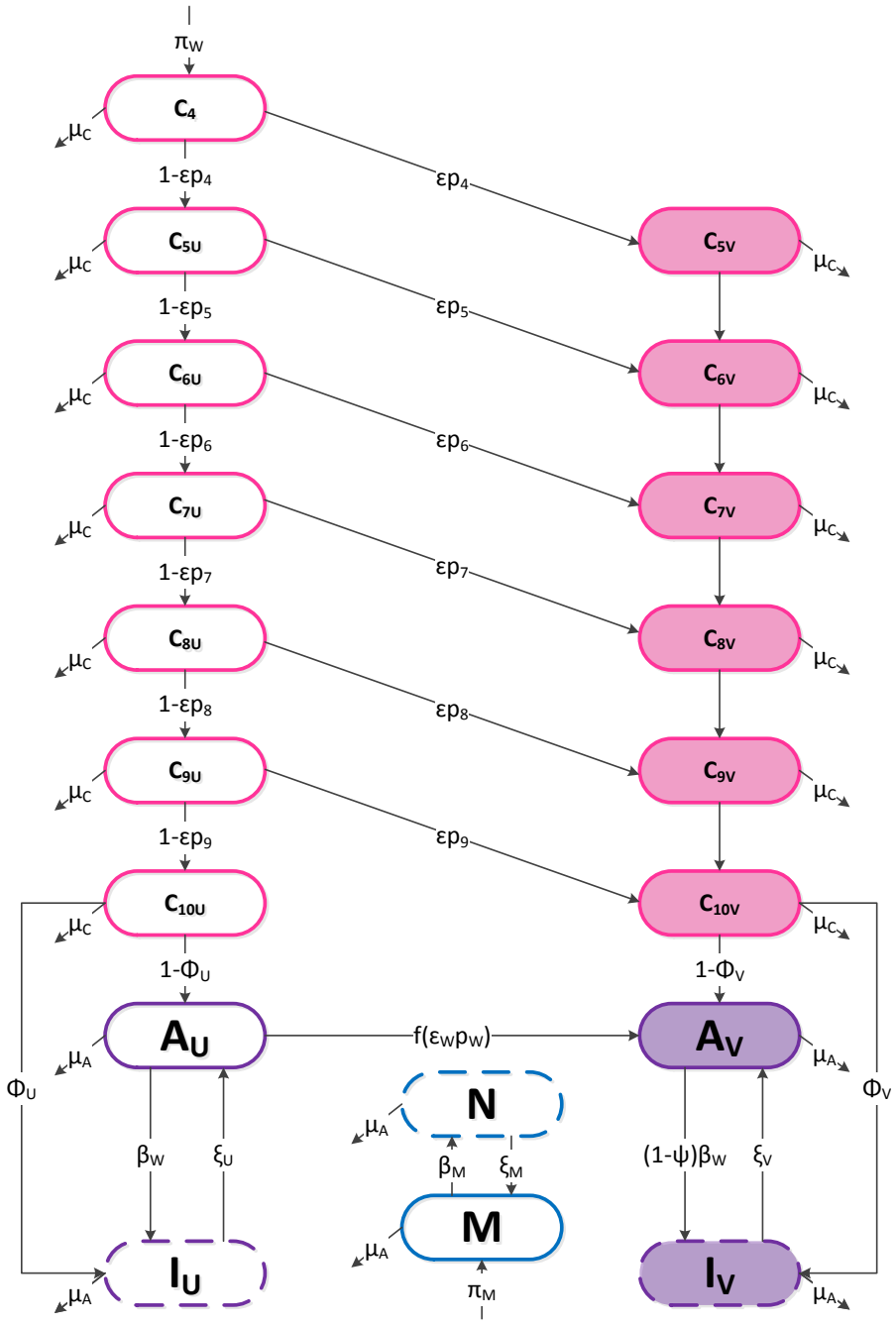

Figure 5.3 The Model

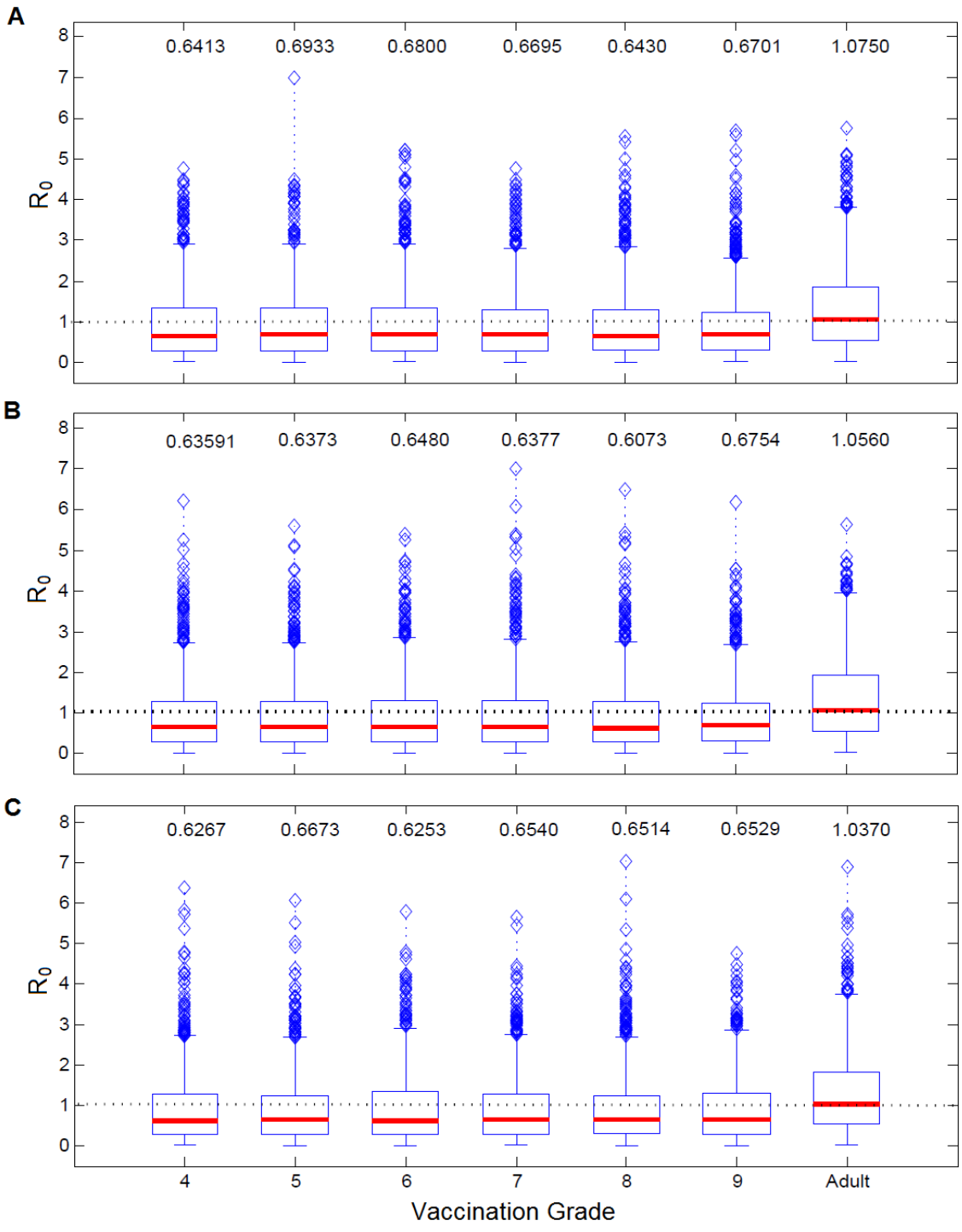

Figure 5.4 Effect of Grade of Vaccination and Dose

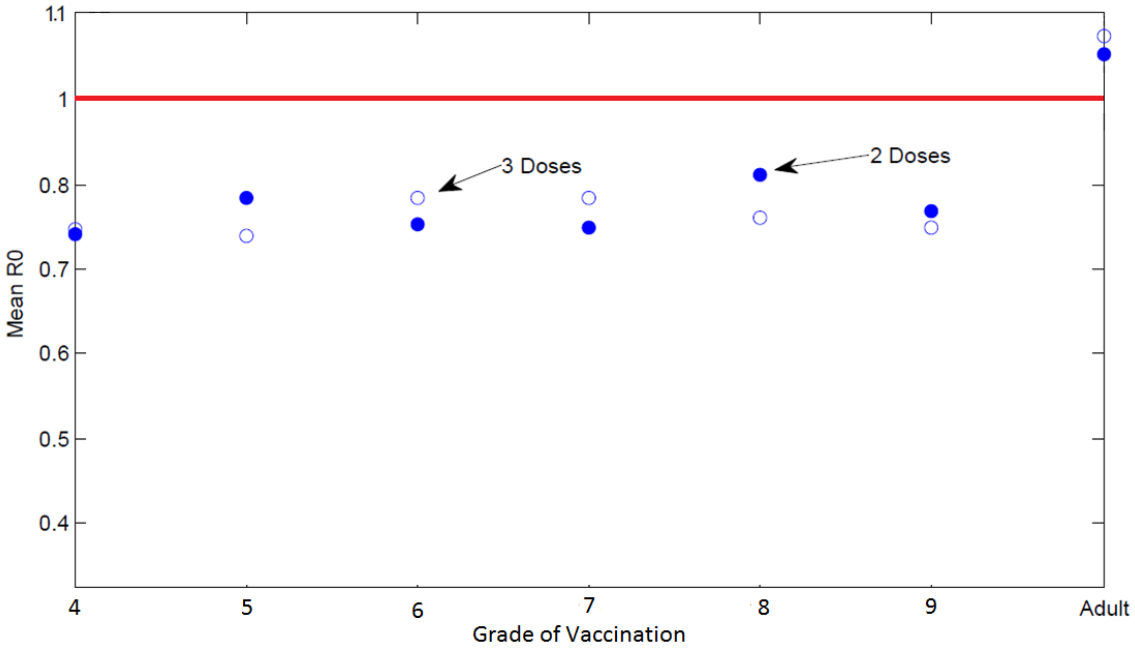

Figure 5.5 Effect of Mean R_0 Vales Based on the Grade of Vaccination

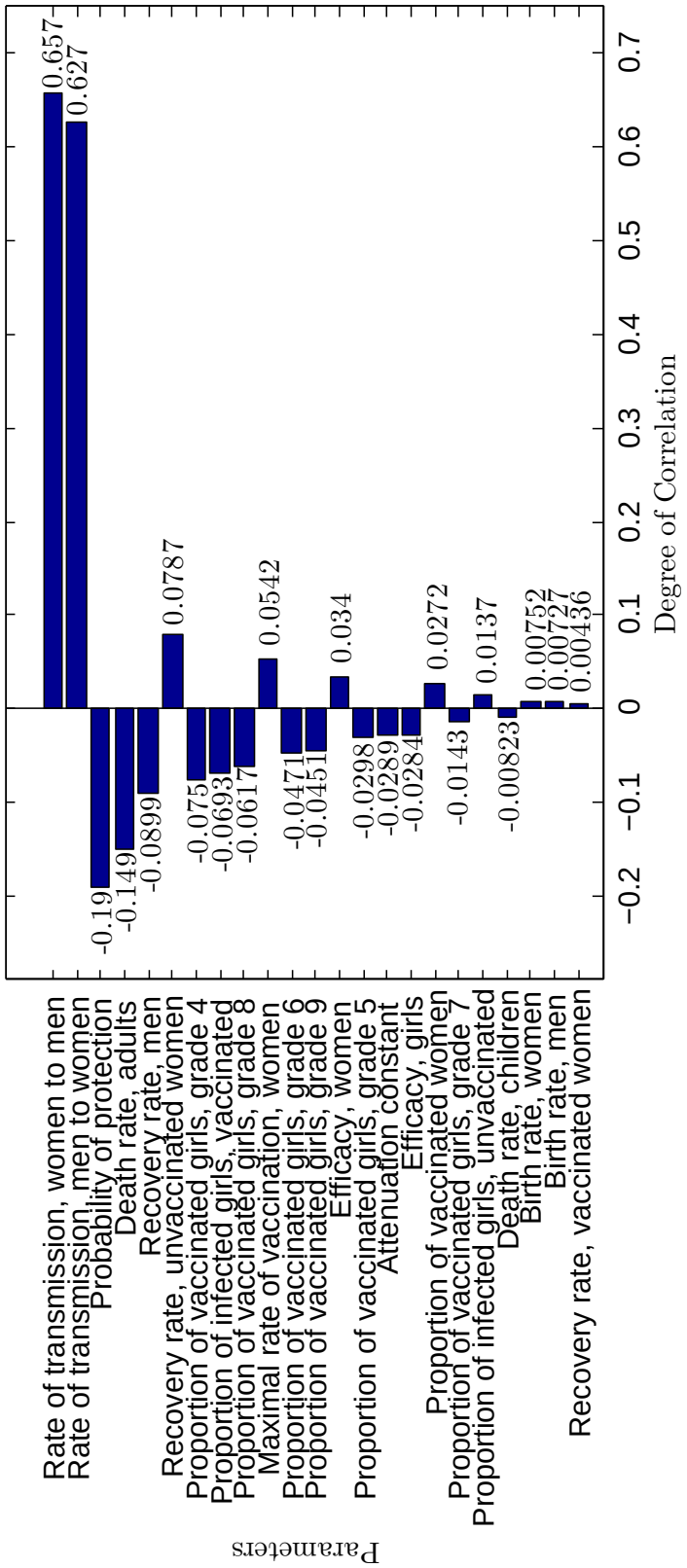

Figure 5.6 Thresholds of Eradication

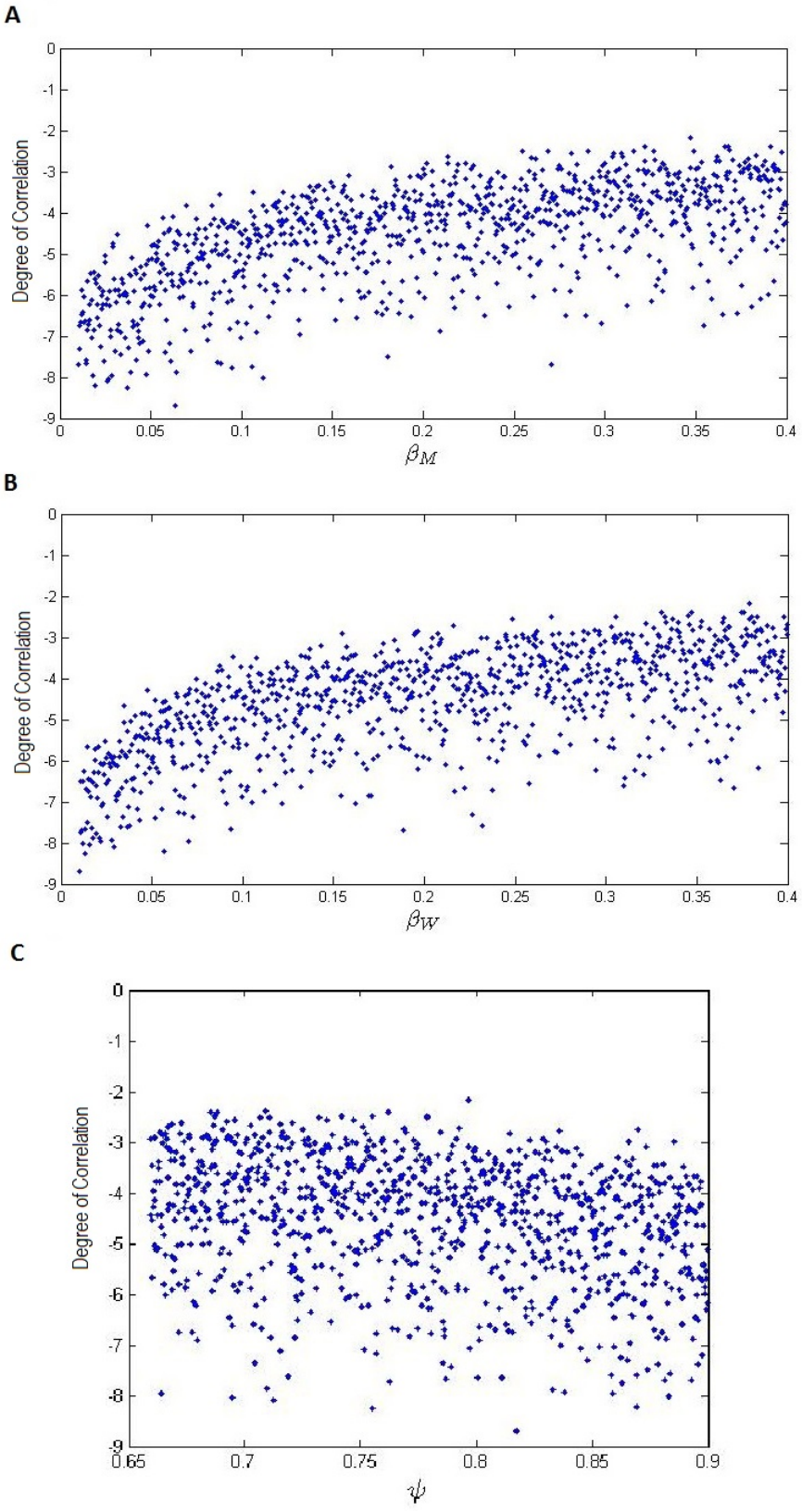

Figure 5.7 Latin Hypercube Sampling Output

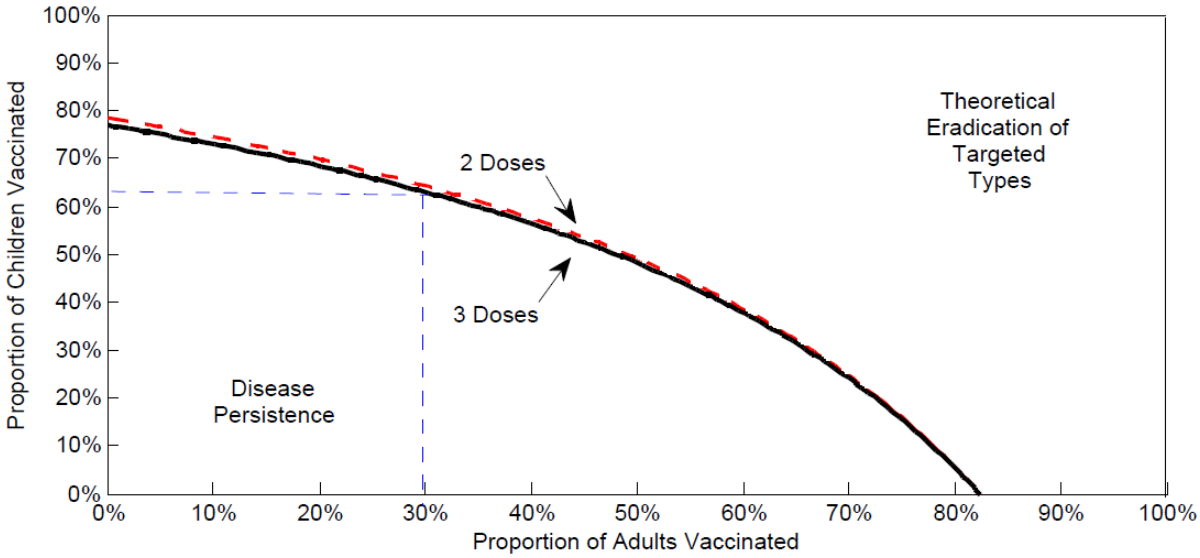

Figure 5.8 Children and Adult Coverage Rate Required to Achieve Eradication

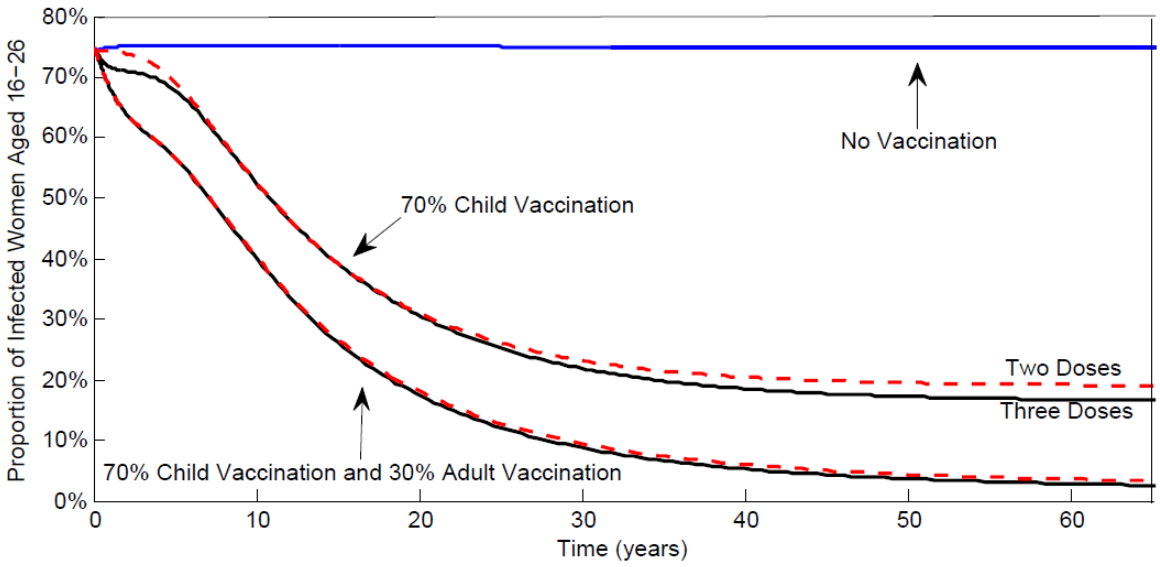

Figure 5.9 Telecourse of Infection

Chapter 6

Discussion, conclusion and future work

Mathematical models are important because they are able to investigate the likely possible future outcomes of different scenarios in a real-world system. Three different aspects of mathematical models were explored within the context of HPV vaccination. The first was how models could be used to introduce HPV as a part of a national immunization program, using the guidelines produced by the World Health Organization. The second was a literature review of the current mathematical models on HPV vaccination. The third characteristic considered was a model developed to explore the various HPV vaccination strategies in Canada, based on grade of vaccination and the number of doses given.

In order to emphasize how useful mathematical models are, we consider the guidelines to adding a vaccine to a national immunization program, published by the World Health Organization. An overview of this decision-making process, about the inclusion of a vaccine in a national immunization program, is discussed within the context of HPV. For many of the steps involved in this decision, examples of mathematical models that have been used or could be used were explored. In particular, models are useful to assess the amount of disease preventable with a vaccine based on the public perception of the disease and disease burden before the introduction of the vaccination program. Models can also investigate the likelihood of success for a vaccination program verses other interventions to combat HPV. The vaccine efficacy, quality and safety in a specific population can be evaluated to provide evidence for one intervention to reach the disease prevention goals for the population. Cost-effectiveness models provide necessary insight to the ability of the intervention to affect the disease on a population based on the financial constraints applied by the country. Examples of how models have been used to investigate the optimal vaccine presentation, formulation, vaccine program strength and supply availability were provided.

The next aspect of HPV models was a literature review, which was focused on the types of mathematical models already produced within the context of HPV vaccination strategies. The majority of models were dynamic, deterministic, continuous and aggregate models. In order for an HPV vaccination program to be successful, the majority of papers recommended to combine it with a cervical-cancer-screening program. For developed countries, this strategy appears to be cost-effective. Increasing the coverage rate and number of HPV types that are covered by the vaccine will aid a higher success rate for a given HPV vaccination program.

Six models incorporated an SIS base, ten used the SIR base and two papers included one model of each type. The difference in recommendations between SIS and SIR type models for male vaccination was that SIS models concluded what male vaccination should be included while only some SIR models concluded that male vaccination is an important aspect of a successful HPV vaccine program. The main reasoning behind this is because male vaccination usually only made a profound impact on HPV prevalence if the prevalence before vaccination was higher in males, or there was a low coverage ($<40\%$) of females. This could be due to female-only vaccination having a higher effect on SIS models when compared to SIR models. Catch-up programs were a controversial topic throughout the literature, although they were found to be helpful for the most part.

Within the last couple of years, there is new evidence that suggests a fewer number of doses may also protect individuals against the targeted HPV types. Research is needed to model how giving a fewer number of doses may affect the end result of an HPV vaccination program. Although many countries have already started an HPV vaccination program, determining the optimal age of vaccination is still largely unknown. Investigating the effects of this factor on vaccination programs is an important piece missing in the field.

In order to solidify how important modelling research is to the abundance of HPV vaccination research and to advance scientific research in a new direction by considering the number of doses, an epidemiological model was developed and analyzed. Although the HPV vaccine is already part of each provincial immunization program, this model provides insight to what changes could be made to these programs to allow for greater success. The system took into account the grade of vaccination and number of doses given to eligible girls in Canada. A stability analysis was performed to predict the long-term behaviour of the epidemic. Several thresholds were calculated, giving insight to the range of parameters which promote the eradication of the four targeted HPV types. In particular, the threshold of eradication (R_0) and critical thresholds for the childhood efficacy, adult efficacy and protection rate were determined. At these critical thresholds, 100% coverage of children or adults could not eradicate the targeted types. The threshold of eradication was used to look at the significance of vaccinating different grades, of which there was little to no significance. The number of doses did have an effect on the long-term outcome of a vaccination

program, although a small change in the coverage rate of female vaccination could counteract the effect. Sensitivity analysis provided insight to the most significant parameters for eradication, the two which described the transmission of the virus.

6.1 Conclusion

Mathematical models provide a unique and necessary view into the world of vaccination. They are able to guide decisions about whether to include a vaccine within a national immunization program by providing future epidemiological, financial and logistical predictions based on current knowledge on the subject. So far, developed mathematical models have provided insight in recommending that the programs should focus on increasing the female coverage rate, combining the vaccination program with screening programs and including male vaccination only when a higher prevalence of the targeted types are found in males or when female coverage is low. The development and analysis of a system of ordinary differential equations describing the HPV vaccination programs across Canada was completed. Analysis included stability analysis, calculation of several thresholds of eradication and sensitivity analysis. The developed model on HPV vaccination programs in Canada provided evidence that vaccinating girls in any grade with either two or three doses can lead to the theoretical eradication of the targeted types, providing a high enough coverage rate can be achieved. The grade of vaccination does not make a significant difference to the outcome of the public vaccination program under the assumption that the vaccine is just as efficacious for girls in either grade. The number of doses given foes not make a significant difference to the outcome of the public vaccination program. The most significant factor in the success of these programs is the coverage rate of children and adults.

The work completed throughout this thesis is important because it expands the current knowledge of HPV vaccination research by specifically considering the grade of vaccination and number of doses within the model. The general public has a large influence on the success of the program. Without evidence supporting the reasons policy-makers have created a vaccination strategy and are choosing to implement it in such a way, it is hard to convince the public to even start or follow through with the program. This thesis also addresses the knowledge gap about HPV vaccine programs between scientists, policy-makers and the general public. These are the three most important stakeholders determining the success of a vaccination program. Until now, the number of doses considered has only been within the context of cost-effectiveness evaluations. This research took the first look at the effects of using two or three doses on the epidemiology of the HPV pandemic in Canada from a mathematical perspective. This is significant because policy is being created and implemented at the time of publishing in British Columbia and Quebec for the use of two doses for the public vaccination programs [18]. The grade of vaccination is important to explore

for the public HPV vaccination programs in Canada for two main reasons. The first is epidemiology. It is important to know throughout course of public vaccination programs the likely effects of factors that can be controlled by policy-makers and health professionals (for example, grade of vaccination, dosing, coverage rate and budget). This way, the most efficient program can be created within the constraints of current knowledge. Secondly, the HPV vaccines have been typically marketed to the public as a vaccine against cervical cancer caused by a sexually transmitted disease. Since the vaccine is given to young girls, it is difficult for many parents and caregivers to even consider that their daughter (or, soon, son) is at risk of an HPV infection. Since cervical cancer is not an immediate consequence of an HPV infection, it is difficult to persuade expensive medical interventions for the prevention of something there is a small chance of occurring for each individual. However, on a population level, cervical cancer is a strain on our health-care system. From a health and financial perspective, there is a lot of evidence supporting the strategy of preventing HPV infections through this vaccine rather then treating the disease consequences caused by HPV.

6.2 Future Work

Mathematical modelling studies allow for a unique and in-depth comprehension of a variety of topics in infectious diseases. For the HPV vaccine in particular, models are useful at answering specific questions about different populations. These models can then make recommendations for the implementation of the vaccine that will likely provide the highest amount of success for the population. Each model is able to take into account the goals for the population (which may differ from region to region) and specifics of a vaccination program that each region deems reasonable. As more data becomes available about the efficacy and immunogenicity of the vaccine in different populations, modelling should keep up to date with these findings and update their models as necessary.

6.2.1 Male vaccination

The option to add male vaccination began in 2011, when a quadrivalent HPV vaccine was approved for the use in males between the ages of 9 and 26. This opportunity allows for provincial vaccination programs with a wider variety of options to vaccinate the population in order to reach their goals. Studying the effect of adding in male vaccination to the general population will be a valuable research topic for modellers and public-health communities alike. Before the option was given to vaccinate males, communities of men who have sex with men (MSM) are less affected by the herd immunity offered by the HPV vaccine. Adding male vaccination provides an

opportunity for all individuals in a population to benefit from an HPV vaccine; and mathematical modelling can provide insight into what the benefit may be.

6.2.2 Dosing Schedule

Apart from a different number of doses, alternate dosing schedules are being considered by health professionals [93, 106]. Possible advantages of these alternate schedules include easier access for remote communities or low-resource countries, better immune response and protection, lower costs or increased coverage. Using mathematical models to explore the possibilities of these dosing schedules in different populations will provide an interesting challenge to modellers and useful results for public-health professionals.

6.2.3 Age of Vaccination

More evidence is required to determine the population-specific optimal age(s) of vaccination. Modelling research conducted thus far has mainly focused on vaccinating a single age cohort defined by a certain age (typically between 12 and 15), or considered to be before the girls' sexual debut [1, 5, 15, 27, 48, 41, 82, 119, 142]. From a public-health perspective, the age of vaccination for a sexually transmitted disease could determine the difference between the success and failure of a vaccination program. More work is needed to determine the optimal age of the HPV vaccine within a population.

6.2.4 Sexual Activity

Sexual activity is included in models either by groups defining risk behaviour in some way (eg., sexual mixing and partner exchange) [5, 7, 12, 16, 33, 41, 48, 68, 119]. Although modelling human behaviour is a difficult task, the field of behaviour modelling and prediction is becoming an increasingly deep field of research. Crossing ideas between this field and epidemiological modelling could bolster some interesting results. Sexual debut is typically defined at one age where all girls are considered to be susceptible to sexually transmitted HPVs. Although this is done to simplify the model, it is not realistic. Modelling sexual debut in a more realistic way would be an interesting and insightful modelling project.

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