MAT5187 Project

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1 Introduction

Human Papillomavirus (HPV) is a double stranded DNA virus [7]. There are over 100 different strains of the virus, subdivided into high and low risk categories[7]. Both types can cause the growth of abnormal cells, but only the high risk strains cause lesions of epithelial cells which may develop into cancer[7]. Globally, the most prevalent strains of HPV are 6, 11, 16 and 18. 6 and 11 are low risk strains which are linked to 90% of all genital warts cases [7, 8]. 16 and 18 are both high risk strains which are associated with 70% of all cervical cancer cases [7, 8]. Most infections affect women and men within the ages of 15 to 25 [6]. In Canada, about 75% of sexually active adults will have at least one HPV infection within their lifetime [2].

Since the virus is very common, widespread and damaging, a lot of resources have already been dedicated to reducing its impact. Cervical cancer screening programs, such as PAP smears, have lead to a reduction in the incidence of cervical cancer [4], although only about 71-85% of women actually get the screening [10] . This approach is quite successful at catching the infection before it turns into cancer, but the next step is to avoid the HPV infection all together. In order to do this, two main strain specific vaccines have been developed to reduce the risk of HPV infections. Gardasil© (Merck & Co.) was approved in 2006 and protects against strains 6, 11, 16 and 18 while Cervarix (GSK©) protects against the two leading cancer causing strains. The vaccines are very effective, with a reported efficacy of $\geq$99% with three doses and $\geq$97% with two doses for Gardasil.

In 2008, every province and territory in Canada began a vaccination program. The common goal of these vaccination programs is to completely eradicate the strains that cause human ailment. In order to reach this goal the federal government provided the provinces and territories with $300 million over 3 years for the HPV immunization programs [9] . Although federally funded, as per all immunization programs in Canada, the vaccination strategy is the responsibility of each province or territory to create and implement. As a result the strategies in each province differ slightly. Table 1 outlines the current provincial of territorial HPV vaccination strategy.

This project aims to determine which provincial vaccination strategy is the most effective at reducing or eliminating the highest number of HPV infections. More specifically, the total number of infected women will be compared while varying the age of vaccination, number of doses and compliance levels. This will be accomplished by creating an ordinary differential equation model which describes the vaccination program and the adult infection dynamics. This project will give practical recommendations for the best provincial strategy based on current compliance rates. This model also aims to determine which measures are important to know in the future in order to have current accurate feedback about the success of the vaccination program.

2 Model

2.1 Flow Diagram

This flow chart depicts the movement of girls (pink), women (red) and men (blue) within the model. The shaded compartments symbolize vaccinated persons while the unshaded are unvaccinated persons. Compartments 'C' are children, 'A' are uninfected female adults, 'I' are infected female adults, while 'N' and 'M' are men. See Table 2 for the description of the other symbols.

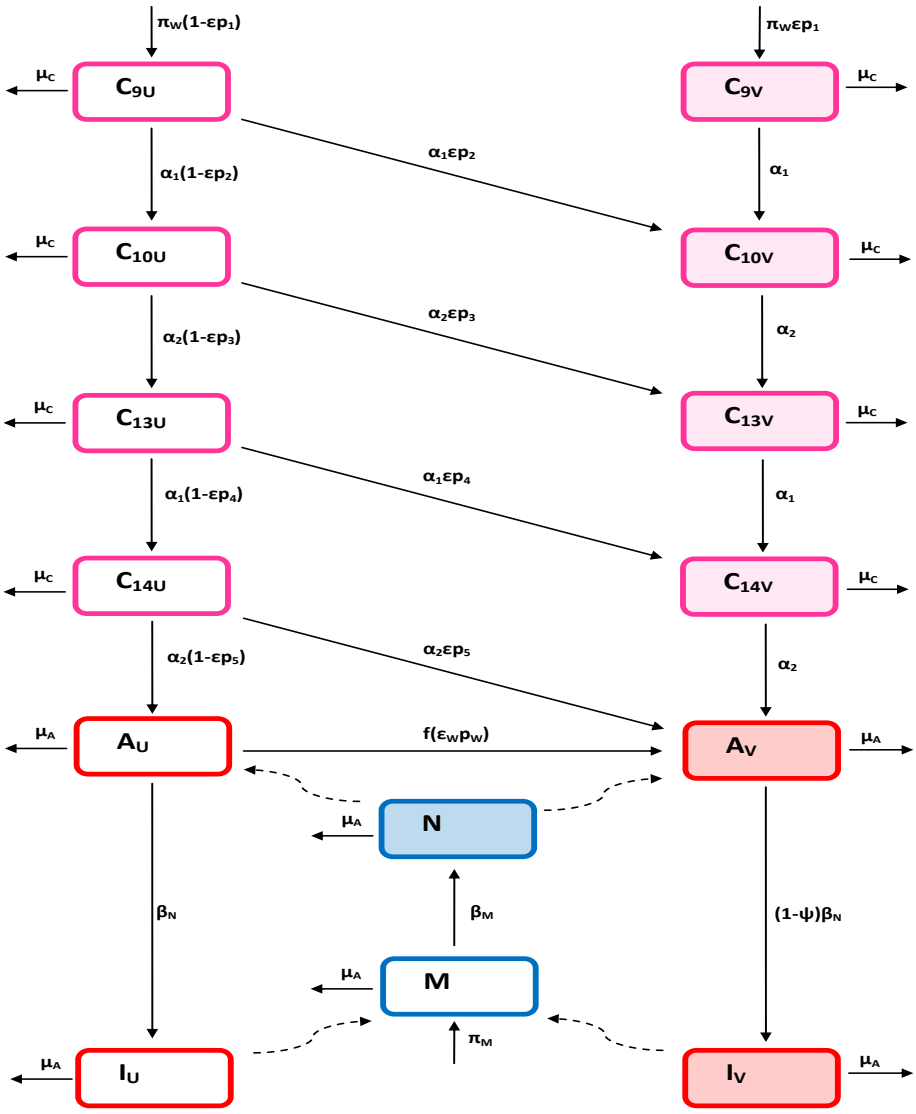

Figure 1: Flow Diagram of Model

2.2 Equations

This general model is composed of 14 general equations, 8 to describe the childhood vaccination strategy and 6 for the disease propagation through adults. The children are broken up into 4 age classes ($\leq$ 9, 10-12, 13 and 14). Within each age class there are vaccinated and unvaccinated children. The adult model is taken from Llamazares and Smith? [8].

Children 9 years old are described as

$$\frac{dC_{9U}}{dt} = \pi_W(1-\epsilon p_1) - \alpha_1 \epsilon p_2 C_{9U} - \alpha_1(1-\epsilon p_2)C_{9U} - \mu_C C_{9U}$$

$$\frac{dC_{9V}}{dt} = \pi_W \epsilon p_1 - \alpha_1 C_{9V} - \mu_C C_{9V}$$

Children between the ages 10-12 are described as

$$\frac{dC_{10U}}{dt} = \alpha_1(1-\epsilon p_2)C_{9U} - \alpha_2(1-\epsilon p_3)C_{10U} - \alpha_2 \epsilon p_3 C_{10U} - \mu_C C_{10U}$$

$$\frac{dC_{10V}}{dt} = \alpha_1 C_{9V} + \alpha_1 \epsilon p_2 C_{9U} - \alpha_2 C_{10V} - \mu_C C_{10V}$$

Children 13 years old are described as

$$\frac{dC_{13U}}{dt} = \alpha_2(1-\epsilon p_3)C_{10U} - \alpha_1(1-\epsilon p_4)C_{13U} - \alpha_1 \epsilon p_4 C_{13U} - \mu_C C_{13U}$$

$$\frac{dC_{13V}}{dt} = \alpha_2 C_{10V} + \alpha_2 \epsilon p_3 C_{10U} - \alpha_1 C_{13V} - \mu_C C_{13V}$$

Children between the ages 14-15 are described as

$$\frac{dC_{14U}}{dt} = \alpha_1(1-\epsilon p_4)C_{13U} - \alpha_2(1-\epsilon p_5)C_{14U} - \alpha_2 \epsilon p_5 C_{14U} - \mu_C C_{14U}$$

$$\frac{dC_{14V}}{dt} = \alpha_1 C_{13V} + \alpha_1 \epsilon p_4 C_{13U} - \alpha_2 C_{14V} - \mu_C C_{14V}$$

Uninfected adult women are described as

$$\frac{dA_U}{dt} = \alpha_2(1-\epsilon p_5)C_{14U} - f(\epsilon_W p_W)A_U - \mu_A A_U - \beta_N A_U N$$

$$\frac{dA_V}{dt} = \alpha_2 C_{14V} + \alpha_2 \epsilon_W p_5 C_{14U} + f(\epsilon_W p_W)A_U - \mu_A A_V - (1-\psi)\beta_N A_V N$$

Infected adult women are described as

$$\frac{dI_U}{dt} = \beta_U A_U N - \mu_A I_U$$

$$\frac{dI_V}{dt} = (1-\psi)\beta_N A_V N - \mu_A I_V$$

The men are described as

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

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

In this model the population enters the model with birth rate π and exits the model through mortality and leaving rates μ. The children move through age classes with a rate α and the proportion p becomes vaccinated within the age classes which moves them from an unvaccinated class to a vaccinated older class (assuming the vaccine took). The adults have a probability of infection β, a maximal rate of adult vaccination γ and the function f which describes the rate at which unvaccinated women are vaccinated. The vaccine has an immunogenicity of ϵ, efficacy of ψ and attenuation constant c. A summary of the symbols and ranges are given in Table 2.

2.3 Assumptions

For this model, it is assumed that HPV is only heterosexually sexually transmitted, in other words there is no childhood transmission. Female children are considered to be between the ages of 9 and 16, which are the years childhood vaccination can take place (and currently does take place across Canada). It is assumed vaccination only occurs in one year, and the proportion of children vaccinated during other years are negligible. At the age of 16 a child is considered an adult since they are assumed to be sexually active at 16. Both women and men are active in the adult model for 10 years. At 26 women are no longer recommended to get the vaccine [10], and the men move out of the model at the same rate. The disease assumptions are: once a women is infected she cannot become uninfected, the probability of transmission from men to women is higher than the probability of transmission from women to men and the probability of a woman being infected increases as her age increases. The vaccine assumptions are: the vaccine does not wane in children, the vaccine may not protect 100% (this is based on the immunogenicity and the efficacy) and the vaccine does not protect someone who is already infected with the virus.

3 Analysis

3.1 Disease-Free Equilibrium

The Disease-Free Equilibrium is

$$(\overline{C_{9U}}, \overline{C_{9V}}, \overline{C_{10U}}, \overline{C_{10V}}, \overline{C_{13U}}, \overline{C_{13V}}, \overline{C_{14U}}, \overline{C_{14V}}, \overline{A_U}, \overline{A_V}, \overline{I_U}, \overline{I_V}, \overline{M}, \overline{N})$$

where,

$$\overline{C_{9U}} = \frac{\pi_W(1-\epsilon p_1)}{\alpha_1+\mu_C}$$

$$\overline{C_{9V}} = \frac{\pi_W \epsilon p_1}{\alpha_1+\mu_C}$$

$$\overline{C_{10U}} = \frac{\alpha_1(1-\epsilon p_2)C_{9U}}{\alpha_2+\mu_C}$$

$$\overline{C_{10V}} = \frac{\alpha_1 C_{9V} + \alpha_1 \epsilon p_2 C_{9U}}{\alpha_2+\mu_C}$$

$$\overline{C_{13U}} = \frac{\alpha_2(1-\epsilon p_3)C_{10U}}{\alpha_1+\mu_C}$$

$$\overline{C_{13V}} = \frac{\alpha_2 C_{10V} + \alpha_2 \epsilon p_3 C_{10U}}{\alpha_1+\mu_C}$$

$$\overline{C_{14U}} = \frac{\alpha_1(1-\epsilon p_4)C_{13U}}{\alpha_2+\mu_C}$$

$$\overline{C_{14V}} = \frac{\alpha_1 C_{13V} + \alpha_1 \epsilon p_4 C_{13U}}{\alpha_2+\mu_C}$$

$$\overline{A_U} = \frac{\alpha_2(1-\epsilon p_5)C_{14U}}{f(\overline{\epsilon_W}\,\overline{p_5})+\mu_A}$$

$$\overline{A_V} = \frac{\alpha_2 C_{14V} + \alpha_2 \epsilon p_5 C_{14U} + f(\overline{\epsilon_W}\,\overline{p_5})A_U}{\mu_A}$$

$$\overline{I_U} = 0$$

$$\overline{I_V} = 0$$

$$\overline{M} = \frac{\pi_M}{\mu_A}$$

$$\overline{N} = 0$$

and where

$$f = \frac{c\,\overline{\epsilon_W}\,\overline{p_5}}{1-\overline{\epsilon_W}\,\overline{p_5}+\gamma}.$$

3.2 Stability Analysis and the Basic Reproductive Number

The Jacobian matrix was calculated in order to determine the stability of the disease-free equilibrium.
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

$$J^{(1)}_{DFE} = \begin{bmatrix} -\alpha_1\epsilon p_2 - \alpha(1-\epsilon p_2) - \mu_C & 0 & 0 & 0 \\ 0 & -\alpha_1 - \mu_C & 0 & 0 \\ \alpha_1(1-\epsilon p_2) & 0 & -\alpha_2(1-\epsilon p_3) - \alpha_2\epsilon p_3 - \mu_C & 0 \\ \alpha_1\epsilon p_2 & \alpha_1 & 0 & -\alpha_2 - \mu_C \\ 0 & 0 & \alpha_2(1-\epsilon p_3) & 0 \\ 0 & 0 & \alpha_2\epsilon p_3 & \alpha_2 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$J^{(2)}_{DFE} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ -\alpha_1(1-\epsilon p_4) - \alpha_1\epsilon p_4 - \mu_C & 0 & 0 & 0 & 0 & 0 \\ 0 & \alpha_1 - \mu_C & 0 & 0 & 0 & 0 \\ \alpha_1(1-\epsilon p_4) & 0 & -\alpha_2(1-\epsilon p_5) - \alpha_2\epsilon p_5 - \mu_C & 0 & 0 & 0 \\ \alpha_1\epsilon p_4 & \alpha_1 & 0 & -\alpha_2 - \mu_C & 0 & 0 \\ 0 & 0 & \alpha_2(1-\epsilon p_5) & 0 & -f - \mu_A & 0 \\ 0 & 0 & \alpha_2\epsilon p_5 & \alpha_2 & f & -\mu_A \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

$$J^{(3)}_{DFE} = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\beta_N A_U \\ 0 & 0 & 0 & -(1-\psi)\beta_N A_V \\ -\mu_A & 0 & 0 & \beta_N A_U \\ 0 & -\mu_A & 0 & (1-\psi)\beta_N A_V \\ -\beta_M M & -\beta_M M & -\mu_A & 0 \\ \beta_M M & \beta_M M & 0 & -\mu_A \end{bmatrix}.$$

To find stability, the determinant of the matrix was found to be,

$$\begin{aligned} \det(J-\lambda I) =& (-\mu_A-\lambda)^2(-\alpha_2-\mu_C-\lambda)^2(-\alpha_1-\mu_C-\lambda)^2\cdot \\ & (-\alpha_1\epsilon p_2-\alpha_1(1-\epsilon p_2)-\mu_C-\lambda)(-\alpha_2(1-\epsilon p_3)-\alpha_2\epsilon p_3)-\alpha_2\epsilon p_3-\mu_C-\lambda)\cdot \\ & (-\alpha_1(1-\epsilon p_4)-\alpha_1\epsilon p_4-\mu_C-\lambda)(-\alpha_2(1-\epsilon p_5)-\alpha_2\epsilon p_5-\mu_C-\lambda)\det(L) \end{aligned}$$

where

$$L = \begin{bmatrix} -\mu_A-\lambda & 0 & \beta_N A_U \\ 0 & -\mu_A-\lambda & (1-\psi)\beta_N A_V \\ \beta_M M & \beta_M M & -\mu_A-\lambda \end{bmatrix}.$$

Since all of the terms in the determinant (excluding det(L)) are all negative, the stability of the system depends on the largest eigenvalue of L. We must solve the characteristic equation of L,

$$\lambda^3+\alpha\lambda^2+\beta\lambda+\gamma=0$$

where

$$\begin{aligned} \alpha &= 3\mu \\ \beta &= 3\mu_A^2-(1-\psi)\beta_M\beta_N MA_V+\beta_N A_U\beta_M M \\ \gamma &= \mu_A^3-(1-\psi)\mu\beta_M\beta_N MA_V+\mu_A\beta_N A_U\beta_M M \end{aligned}$$

By the same reasoning as Llamazares and Smith? [8], stability will occur if

$$\mu_A^2-\beta_N\beta_M M[A_U+(1-\psi)A_V]>0.$$

Since this expression describes the stability of the system, the basic reproductive number comes from rearranging the expression to give a threshold of

$$1<\frac{\beta_N\beta_M M[A_U+(1-\psi)A_V]}{\mu^2}$$

Rearranging this expression, we find the basic reproductive number is

$$R_0 = \frac{\beta_N \beta_M M[A_U + (1-\psi)A_V]}{\mu^2}$$

3.3 Sensitivity Analysis

Partial rank correlation coefficient was used to look more deeply into the relationship between the variables [1] and the R_0 with the rangers reported in Table 2. The output of a typical sample is seen in Figure 2.

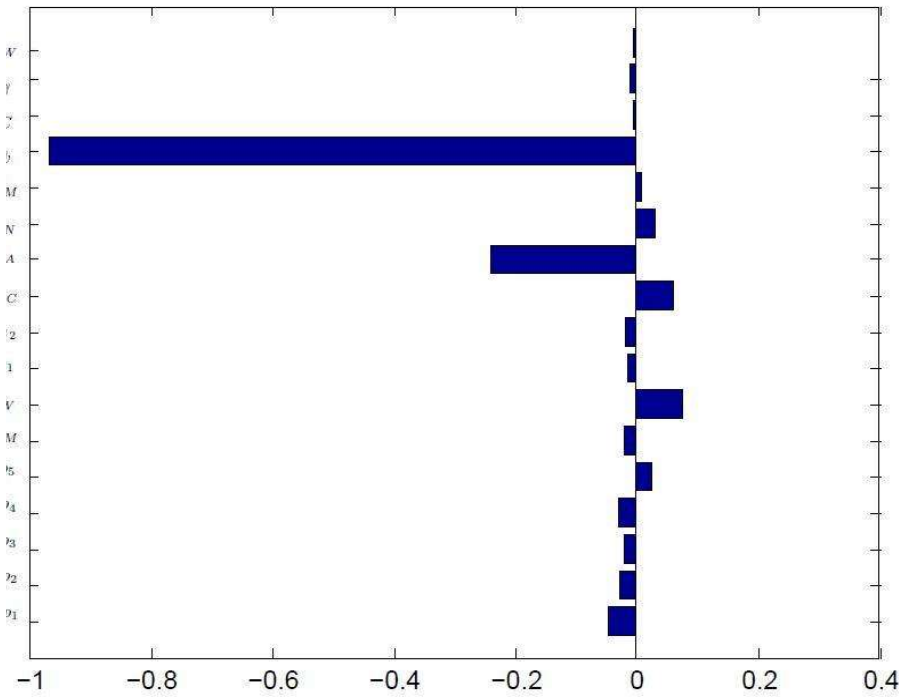

Figure 2: Partial Rank Correlation Coefficient sensitivity analysis on R_0 between all parameters.

The two most influential parameters are ψ, the vaccine efficacy, and μ_A, the adult removal rate. Unfortunately, there are no control measures to influence ψ or μ_A. It is, however, important to look more closely at ψ since it may change over time within an individual. The sensitivity graph, as seen in Figure 3, depending on the value of ψ the R_0 threshold can be brought below one, indicating the disease will die out of the population.

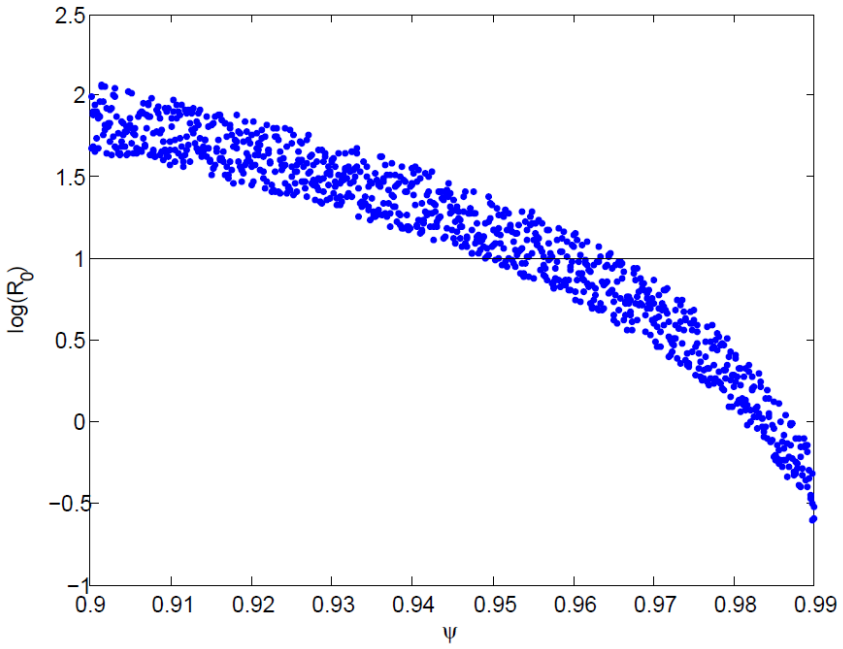

Figure 3: The effect of ψ on the R_0 as seen through the partial rank correlation coefficient.

Notice in Figure 3 the R_0 crosses the threshold of 1 when the efficacy is within the range of 94.5-96.5% ie. with an efficacy close to or within that range the disease will potentially be eradicated or persist in the population.

4 Numerical Simulations

The numerical simulations were performed using the $Matlab^{©}$ program.

4.1 Constant Efficacy

These simulations explore the idea that each province has fixed compliance rates, which were determined by the proportion of eligible females who voluntarily received the vaccine before the provincial strategies were put in place [3]. These rates are seen in Table 1. Apart from the compliance level, the number of doses and age of vaccination are also taken into account and compared.

Figure 4 shows the total number of infected women through time (in years) The number of doses does not affect the outcome. Eradication is possible with a

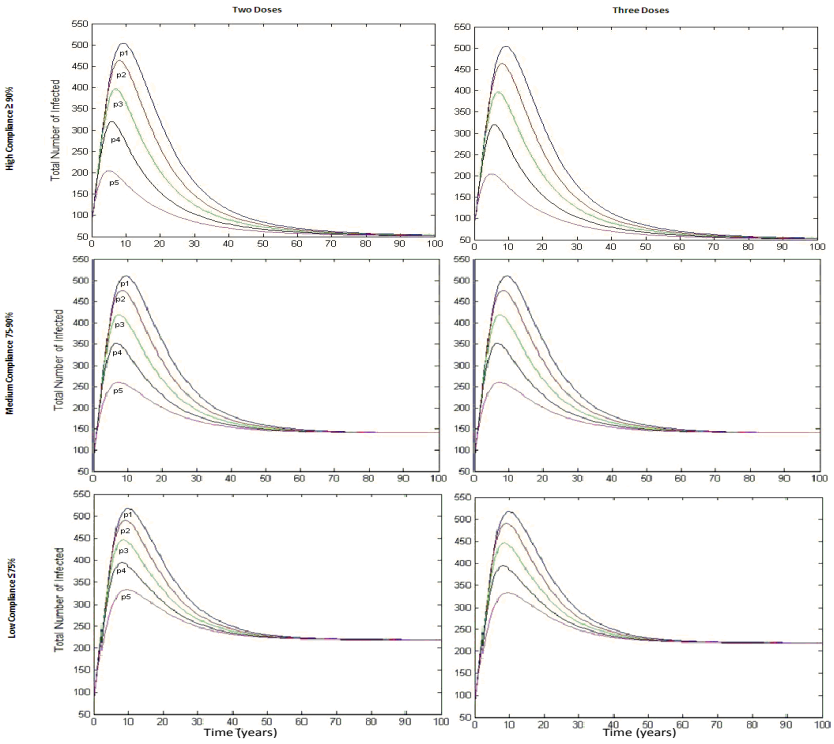

Figure 4: This illustrates the total number of infected women when the efficacy of the vaccine is not influenced by age through the higher probability of infections.

high level of compliance. As compliance decreases the total number of infected at equilibrium increases. Independently of the age of vaccination and doses, the number of infected women at equilibrium are the same.

4.2 Variable Efficacy

These simulations looks at the importance of the impact of the vaccine while taking into account the biologically significant impact on the vaccine efficacy if a proportion of the population is already infected with HPV. As previously stated in the assumptions, the vaccine has no effect on an individual who is infected with HPV. In order to incorporate this effect, the vaccine efficacy, or the reduction in the incidence of the disease from the vaccine, decreases as the age of vaccination increases, since there is a higher probability of a woman already being infected with the virus. Figure 5 shows the output of sample simulations.

In Figure 5, notice the disease is never eradicated within the time frame, the

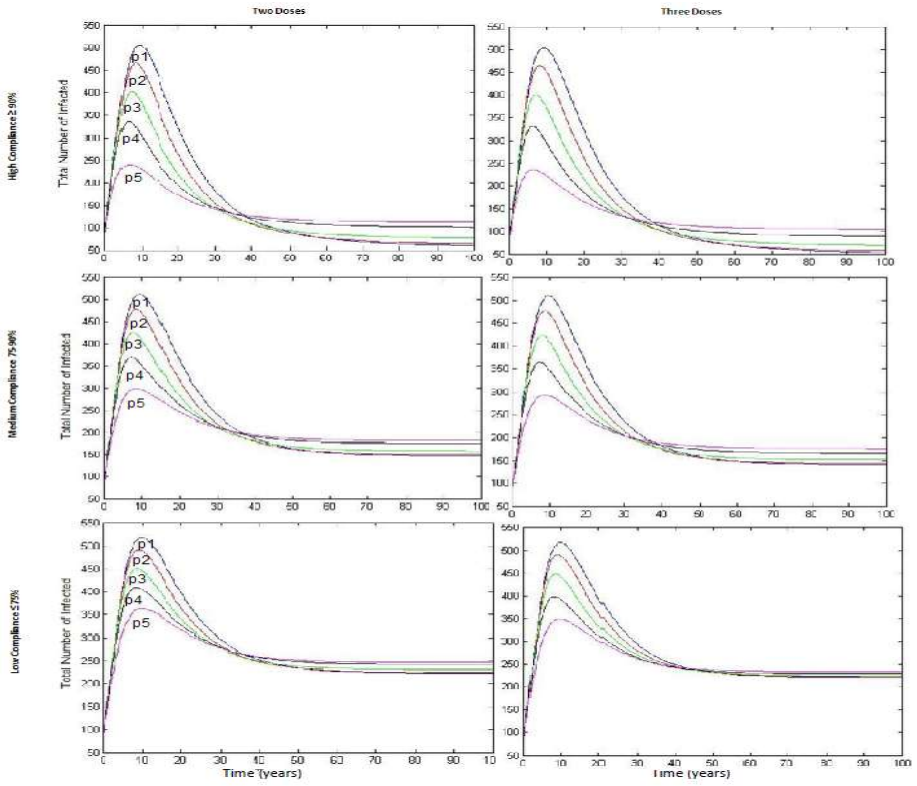

Figure 5: This illustrates the total number of infected women with the efficacy of the virus is influenced by age through the higher probability of infections.

number of doses does effect the outcome of the number of infected women, the equilibrium is different for each vaccinated age group and there is a switch of the optimal strategy.

5 Discussion

Looking at Figure 4, there are a few interesting dynamics to point out. The first being the prominent humps at the beginning of the infection. The humps are due to the initial conditions. Initially there is a much lower proportion of infected persons than currently observed in the population, so the hump is the conditions 'catching up' to the values observed. The peak occurs around the time the initial population is aged out, which is also supported by the 'catching up' logic. The difference in the height of the hump related to the age of vaccination is due to the number of infected people in the model. When

an early vaccination strategy (p1) is in place, a higher number of unvaccinated people go through the model because the same number of children start in each age class; compared to a late vaccination strategy (p5) where all of the girls initially in the model will be vaccinated by the time they reach the adult stage. With these simulations the best vaccination strategy is a high compliance, two doses and vaccinating children when they are older.

Figure 5, shows some very similar traits to Figure 4 although there are some key differences. The first main difference is the switching of the optimal strategy the age strategies between 30-50 years. The second difference is the equilibrium levels of the total number of infected women are different when children are vaccinated at different times. These concepts can be explained by the relationship between ψ and R_0. When the strategy is to vaccinate younger children (p1) the efficacy is higher, allowing the R_0 to always be lower than the age of children vaccinated being higher, with a lower efficacy. This result is supported by the large effect ψ has on the R_0 seen from the sensitivity analysis. This explain the long term outcome of Figure 5, and the short term pattern is Another key difference is the number of doses. This time having three doses slightly decreases the long term number of infected women. And as before, the more people who are vaccinated, the better the outcome is. Comparing the proportion of women infected against the number of doses and the compliance, the compliance has a greater effect on decreasing the number of infected persons. These observations allow us to conclude that the best long term strategy when the efficacy crosses some threshold within the age classes in the population is three doses, a high compliance and to vaccinate girls while they are young.

6 Conclusions

While creating a mathematical model which aims to describe a biological situation, in order to reach a biologically relevant conclusion it is important to consistently refer back to what is happening in the biological world. The dynamics between the compartments are all based on how HPV spreads and most of the assumptions built into the model are for the biology. The parameter values are harder to all based on previous knowledge of HPV or similar viruses, or estimated to create biologically plausible situations. It's important to remember what's happening with the biology because it can drastically change the out come of the model. This can be observed in the difference between the conclusions when a simplified version of the model is simulated (when the change in efficacy is not taken into consideration) compared to when a more in depth understanding of the biology is fit into the model. This being said, for this model it is very important to know the effect of the vaccine on a population level when children are vaccinated during different ages.

Using this model as a guide to optimize provincial HPV vaccination strategies, the best strategy overall is to vaccinate early, a lot of people and two or three doses. The dosage does not dramatically decrease the number of infected people allowing the recommendation for provinces, such as Ontario and Alberta,

with low compliance rates to focus on vaccinating more people with two doses than three. In provinces with medium or high compliance rates, such as Quebec and Nova Scotia, the recommendation is to vaccinate early and focus on keeping high compliance rates and if the budget allows for three doses and a high compliance rate, this is the best case scenario.

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7 Tables

Table 1: Age of Vaccination, Doses and Compliance Rates by Province [3, 5]

Province or Territory	*Age of Vaccination*	*Number of Doses*	*ComplianceRates*
NT	9 (Grade 4)	3	
AB, YK	10 (Grade 5)	3	50-55% (AB)
MB, NL, NU, PE, SK	11 (Grade 6)	3	50-55% (MB) 80% (PEI)
BC	11 (Grade 6)	3	65.7%
NB, NS	12 (Grade 7)	3	80% (NS)
ON	13 (Grade 8)	3	49%
QU	9 (Grade 4) & 14 (Grade 9)	2	84-87%

Table 2: Description of Symbols

Parameter	*Definition*	*Range*
C_{iU}	Unvaccinated child in age class i	
A_U	Unvaccinated adult women	
C_{iV}	Vaccinated child in age class i	
A_V	Vaccinated adult women	
I_U	Uninfected adult women	
I_V	Infected adult women	
M	Uninfected men	
N	Infected men	
π_W, π_M	Birth rate for women, men	0-100 per year
$\alpha_{1,2}$	Rate of movement between age classes of children	1/8-1
ϵ_C	Vaccine immunogenicity in children	75-100%
ϵ_W	Vaccine immunogenicitly in adult women	60-100%
μ_C	Mortality rate for children	1/140-1/9 $years^{-1}$
μ_A	Leaving rate for adults	1/8-1 $years^{-1}$
β_N	Probability of infection of a woman by an infected man	0-0.00112
β_M	Probability of infection of a man by an infected woman	0-0.0006
p_1	Proportion of vaccinated children brought into age class 9	0-100%
p_2	Proportion of previously unvaccinated children in age class 9 vaccinated	0-100%
p_3	Proportion of previously unvaccinated children in age class 10 vaccinated	0-100%
p_4	Proportion of previously unvaccinated children in age class 13 vaccinated	0-100%
p_5	Proportion of previously unvaccinated children in age class 14 vaccinated	0-100%
p_W	Proportion of previously unvaccinated adult women vaccinated	0-100%
ψ	Vaccine efficacy	90-99%
c	Attenuation constant	0-0.3 $years^{-1}$
γ	Maximal possible rate of adult vaccination	0-0.2
$f(\overline{\epsilon}, \overline{p}) = \frac{c\,\overline{\epsilon_W}\,\overline{p_5}}{1-\overline{\epsilon_W}\,\overline{p_5}+\gamma}$	Rate at which unvaccinated women are vaccinated	