

**THE IMPACT OF VACCINATION AND MULTIPLE TYPES OF  
HPV ON CERVICAL CANCER**

by

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To my mother Toni for being an example of  
perseverance and teaching me to never give up.

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## ABSTRACT

### THE IMPACT OF VACCINATION AND MULTIPLE TYPES OF HPV ON CERVICAL CANCER

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Understanding the relationship between multiple strains of human papillomavirus and cervical cancer may play a key role in vaccination strategies for the virus. In this article we formulate a model with two strains of infection and vaccination for one of the strains in order to investigate how multiple strains of HPV and vaccination may affect the number of cervical cancer cases and deaths due to infections with both types of HPV. We calculate the basic reproductive number for both strains independently as well as the basic reproductive number for the system based on  $R_1$  and  $R_2$ . We also compute the *invasion reproductive number*  $\tilde{R}_i$  for strain  $i$  when strain  $j$  is at equilibrium ( $i \neq j$ ). We show that the disease-free equilibrium is locally stable when  $R_0 = \max\{R_1, R_2\} < 1$  and each single strain endemic equilibrium  $E_i$  exists when  $R_i > 1$ . We determine stability of the single strain equilibrium using the invasion reproductive numbers. The  $R_1, R_2$  parameter space is partitioned into 4 regions by the curves  $R_1 = 1, R_2 = 1, \tilde{R}_1 = 1$ , and  $\tilde{R}_2 = 1$ . In each region a different equilibrium is dominant. The presence of strain 2 can increase strain 1 related cancer deaths by more than 100 percent, but can be reduced by more than 90 percent with 50 percent

vaccination coverage. Under certain conditions, we show that vaccination against strain 1 can actually eradicate strain 2.

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# CHAPTER 1

## INTRODUCTION

### 1.1 Background of HPV and Vaccination

Human papillomavirus (HPV) is recognized to be one of the most prevalent sexually transmitted infections. In the National Health and Nutrition Examination Survey in 2003, Dunne et al. estimated the population prevalence of HPV for U.S. females to be approximately 26.8%[17]. There have been over 100 HPV types identified, of which approximately 40 infect the anogenital tract. Of these 40 types, 15 are considered oncogenic or high-risk[20]. Persistent infection with oncogenic HPV types is the primary cause of cervical cancer and its precursor lesions[1]. HPV has been identified in 99.7 percent of all cervical cancers. Thus, we see that persistent infection with high-risk types such as HPV 16, 18, 31, 33, and 45 is considered a necessary step for the development of cervical cancer[7].

Recently, Merck & Co., Inc. introduced the FDA approved quadrivalent vaccine Gardasil to the female population. The vaccine protects against HPV 6, 11, 16, and 18. The first two types listed are considered low-risk and the last two are high-risk, causing almost 90 percent of all cervical cancers. Gardasil is currently approved for use for females ages 9–26, given in three separate injections over a period of six months[6]. Certain legislatures have attempted to implement mandatory vaccination policies for Gardasil for young women, but few have been successful. Currently, vaccination campaigns are underway through television commercials and in print.

Because of the immediate availability of Gardasil, recent interest in coinfections with multiple HPV types has been heightened. It has been observed that 20-30 per-

cent of women with cervical infections have more than one type of HPV[2]. We note that some of these multi-strain infections are not covered by the vaccine. Coinfection can be described as either concurrent or sequential. In this study we consider sequential coinfection where the subject contracts one strain of HPV, then contracts a second strain at a later time. We acknowledge that a female may contract multiple strains of HPV at once, but in this study we focus on sequential acquisition of multiple HPV types.

## 1.2 Literature review of coinfection studies

There are essentially two ways in which strains of infections may interact with one another. Strains may exhibit interdependence or may act completely independently of one another. In broad strokes these interactions may be classified as either competition or mutualism.

In the realm of epidemiology, interdependence among viruses has motivated many mathematical studies. We review several of these studies and describe the ways in which the strains studied interact as well as results obtained.

In a study on dynamics of two viral infections in a population, cross-immunity and coinfection are considered[9]. The model is an  $SI$  model where individuals can be infected with one of the two viruses or infected with both viruses. This study allows for potential cross-immunity in both directions. The results show that both diseases can be maintained in the population simultaneously, and if immunity is low enough then coinfection is possible.

Another study describes effects of two competing flu strains characterized by cross-immunity[22]. Nuño focuses on whether or not strain 2 can successfully invade an established strain 1 in the presence of cross-immunity. Again, results are obtained that coexistence is possible when cross-immunity is low.

We investigate several studies on vaccination and HPV. We first mention a study on a single strain of HPV where vaccination strategies are in effect[18]. This study considers two vaccination strategies: mass vaccination and public education campaigns encouraging voluntary vaccination. Existence of the disease-free equilibrium as well as the endemic equilibrium are established. We also mention a second paper involving vaccination against multiple types of HPV. Two strains are present, and infection with one or both strains is possible[20]. Also, vaccination against either type 1 or type 2 is considered, but not vaccination for both strains. The paper establishes an *SIR* relationship for each strain as well as the possibility for cross-immunity. This model allows for coinfection, where the interaction between the two strains is incorporated by a multiplier that represents cross-immunity or cross-vulnerability. This paper examines the effects of mass vaccination on multiple strains of HPV in the population, examining the scenarios where the strains are competing or synergistic. Results conclude that if mass vaccination is present for one strain, then due to competition the second strain will take the place of strain 1 in the population. Thus, vaccination may not have an overall positive effect on reducing the prevalence of HPV if strains are competing. The second scenario considers that the strains are not competing, but rather the strains are mutualistic. The results show that if mass vaccination is in effect for strain 1, then due to the synergistic relationship between the strains, the vaccine may indirectly reduce the prevalence of strain 2.

We also wish to discuss the clinical issues of recovery versus recurrence (latency) for HPV infections. At this point it is unclear whether a woman actually clears an HPV infection or it becomes latent. In clinical studies, it is still unclear if reappearance of a particular strain of HPV is actually a new infection or a recurrence of the strain from a latent state[2]. Another clinical issue is type-specific immunity. If a woman clears an HPV infection, can she be reinfected with that same strain? This is

still a question that remains unanswered. Trottier, H. and Franco, E.L. review studies in which the type-specific immunity of HPV is addressed.[8]. We see that certain studies observe an age-related decline in prevalence of HPV. One explanation for this is that as women age, they develop type-specific immunity for certain strains which prevent against future infection. Other studies observe a peak in HPV prevalence among women younger than 25 followed by a decline in prevalence until the age of 45 where a second peak in prevalence occurs[19]. This scenario suggests that women may develop an immunity, but it is not lifelong. Thus the second peak in the curve suggests the possibility of reinfection. In our study, we consider these possibilities, but assume that reinfection with the same type can occur.

### 1.3 Motivation for the study

In a study to determine whether HPV infection modifies the risk of acquiring HPV infection with another type, Méndez concludes that subjects with HPV-16 or HPV-18 had 5-7 times higher odds of acquiring a subsequent infection with HPV-58 than subjects who did not have HPV-16 or HPV-18 [16]. From these results and others [4, 3, 5], we conclude that HPV strains are not competing but rather exhibit mutualism.

There are two kinds of reasons why certain women are more likely to contract multiple types of HPV infection. Some women might be predisposed to infections in general, because of lifestyle or lesions. An analysis of a study on a group of Brazilian women suggests that a woman with a history of condyloma may have a greater vulnerability to concurrent infection with multiple strains of HPV [3]. Thus certain women are *a priori* more vulnerable to being infected with any type of HPV. In this situation, infection with multiple strains of HPV would not be uncommon. It has been well established that the most common risk factors for infection with any

HPV are age and number of sexual partners. Many studies have attempted to adjust their findings to account for these factors. In this study, we acknowledge these factors but are considering other causes for a person to have coinfection with multiple strains of HPV.

A second mode for which a woman may become infected with multiple strains of HPV is through the effects of an initial infection. A person who is infected with a particular strain of HPV may actually become more susceptible to infection with other strains of HPV. This vulnerability could be due to something the virus actually does to the body or immune system, thereby increasing a person's susceptibility to other infections. In a study involving a cohort of Brazilian women, the highest prevalence of coinfection was among women with LSIL (low-grade squamous intraepithelial lesion)[4]. In our study we focus on the second reason rather than the first.

Research has shown that women infected with multiple strains of HPV who contract cervical cancer are less likely to recover from cervical cancer[13]. The researchers concluded that the presence of multiple HPV types is associated with poor prognosis in patients with locally advanced cervical cancer. In this study, 7 of the 8 women who did not respond to treatment with radiotherapy had multiple HPV infections. If women infected with multiple strains of HPV are less likely to recover, then an appropriate vaccination coverage may lessen the fatal effects of cervical cancer due to multiple strains of HPV.

In this paper we wish to answer two questions. In the presence of an oncogenic strain of HPV, what effect does a second strain-coinfection with which prevents recovery from cancer have on the number of cervical cancer cases and deaths among U.S. women? Also, what net effect does vaccination have on the number of cervical cancer cases and deaths in this same population? We begin with a description of the model and underlying assumptions in section 2. In section 3, we establish

existence and local stability of single strain equilibria through *invasion reproductive numbers*. We also establish existence of the single strain equilibrium. Section 4 gives the parameter estimation as well as numerical results obtained through simulations, followed by conclusions and discussion in section 5.



## CHAPTER 2

### MODEL

The population in our model is assumed to be U.S. females age 15-59. We choose the lower bound of the age range as 15 because we assume this is the average age for females entering the sexually active population. We consider the following groups in our study: susceptible females at-risk for infection with strain 1 or strain 2, females vaccinated for strain 1 and not infected, females vaccinated for strain 1, but infected with strain 2, females infected with only one strain (strain 1 or strain 2) or infected with both strains, and females with cancer from strain 1 or cancer from strain 1 and 2. We exclude males in this study because we are most interested in the HPV related disease cervical cancer. Because we are interested in the effects of vaccination and coinfection on the cancer cases caused by one of the vaccine-targeted strains, we exclude here all cancer cases caused by strains other than strain 1, including any caused by strain 2.

A person can enter the vaccinated  $V$  class in two different ways. A person may enter the population directly into the vaccinated class, due to a vaccination policy in effect, or a person can move from the susceptible class  $S$  to the vaccinated class due to voluntary vaccination. For our model, we assume that a proportion  $p$  of the population will enter into the vaccinated class perhaps due to a mandatory vaccination policy in effect for girls entering our population at age 15. This class consists of women who are vaccinated for infection 1, but may still contract strain 2. From the vaccinated class, a person may then move to the  $V_2$  class. The women in the  $V_2$  class have strain 2, but cannot contract strain 1. The rate  $\phi$  is the per

capita transition rate from the  $S$  class to the  $V$  class. We consider this transition due to voluntary vaccination. A woman can choose to get vaccinated at any age recommended by the vaccine in effect. The decision can be due to public education campaigns or recommendation by a doctor.

The remaining portion  $1 - p$  enter into the susceptible class. From the  $S$  class, a woman can become infected with either strain 1 or strain 2. We assume that a person can then recover from that infection at a rate of  $\gamma_1$  for strain 1 or  $\gamma_2$  for strain 2. Thus a woman infected with one strain can then either clear (recover from) that strain, or become infected with the other strain (we assume no simultaneous infections by both strains), or else remain in that state until natural death or sexual inactivity. Women infected with strain 1 are assumed to be  $k$  times as vulnerable to infection by strain 2 as uninfected women, where  $k \geq 1$ . Once a woman is infected with strain 1, she may develop cervical cancer due to persistence of the strain, thus moving to  $C_1$ , or she may become infected with strain 2 (as well as the first), thus moving to  $I_{12}$ . From this coinfection class, a woman may then clear either one or both infections, or progress to cervical cancer, or remain in this class until natural mortality. We further note that progression to cervical cancer from  $I_{12}$  is due to strain 1.

For our model, we consider strain 2 to be HPV type 58 or 33. We consider both types for several reasons. We consider HPV-58 as the secondary infection to HPV-16 due to results provided by Méndez et al. Subjects in this study with incident infections of HPV-16 or HPV-18 had 5-7 times higher odds of acquiring HPV-58 [16]. We may also consider HPV-33 as the secondary infection to HPV-16. According to results from a study conducted by Bachtiry et al., HPV-33 was the most common type found in a patient infected with multiple strains of HPV. In fact, the most commonly found coinfection with two HPV types was HPV-16 in combination with HPV-33 [13]. Although we focus on effects on cancer caused by strain 1, we further

assume that women with both strains will have a greater fatality rate from cervical cancer.

We also assume that persons who have cervical cancer due to HPV infection may enter treatment. We assume that in some cases, the treatment will be successful, and the person will enter into remission from the cancer. However, the person may still have presence of HPV DNA in/on the cervix. In this situation, we see the transition from  $C_1$  back to  $I_1$ . We also assume that a woman infected with both strains who gets cervical cancer will not recover from the cancer. Thus, we do not have a transition from  $C_{12}$  back to  $I_{12}$ .

Based on our model description and assumptions, we establish the following equations. We note that the population  $N$  is not constant. We therefore derive (2.9) as the sum of (2.1)–(2.8).

$$S' = (1 - p)\Lambda - \phi S - \frac{\beta_2 \tilde{I}_2 S}{N} - \frac{\beta_1 \tilde{I}_1 S}{N} + \gamma_1 I_1 + \gamma_2 I_2 - \mu S \quad (2.1)$$

$$V' = p\Lambda + \phi S - \frac{\beta_2 \tilde{I}_2 V}{N} + \gamma_2 V_2 - \mu V \quad (2.2)$$

$$V_2' = \frac{\beta_2 \tilde{I}_2 V}{N} - (\mu + \gamma_2) V_2 \quad (2.3)$$

$$I_1' = \frac{\beta_1 \tilde{I}_1 S}{N} - k \frac{\beta_2 \tilde{I}_2 I_1}{N} - (\omega + \mu + \gamma_1) I_1 + \alpha C_1 + \gamma_2 I_{12} \quad (2.4)$$

$$I_2' = \frac{\beta_2 \tilde{I}_2 S}{N} - \frac{\beta_1 \tilde{I}_1 I_2}{N} - (\mu + \gamma_2) I_2 + \gamma_1 I_{12} \quad (2.5)$$

$$I_{12}' = \frac{k\beta_2 \tilde{I}_2 I_1}{N} + \frac{\beta_1 \tilde{I}_1 I_2}{N} - (\mu + \omega + \gamma_1 + \gamma_2) I_{12} \quad (2.6)$$

$$C_1' = \omega I_1 - (\alpha + \mu + \delta) C_1 \quad (2.7)$$

$$C_{12}' = \omega I_{12} - (\mu + \delta) C_{12} \quad (2.8)$$

$$N' = \Lambda - \mu N - \delta(C_1 + C_{12}) \quad (2.9)$$

where  $\tilde{I}_1 = I_1 + I_{12}$   $\tilde{I}_2 = I_2 + V_2 + I_{12}$ . Figure 2.1 gives a graphical interpretation of equations (2.1)–(2.8).

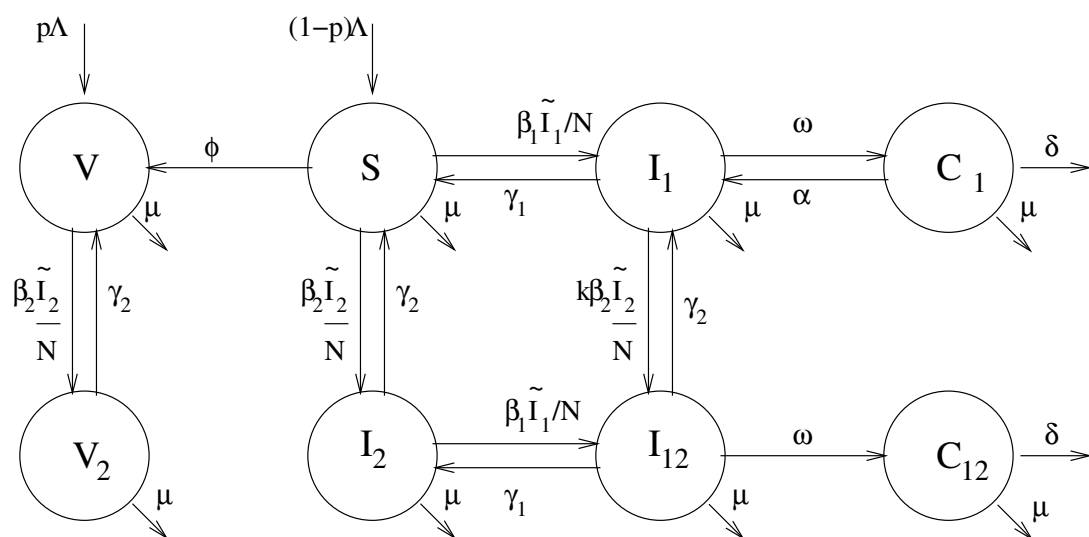


Figure 2.1. Flowchart.

## CHAPTER 3

### ANALYSIS

#### 3.1 DFE and $R_0$

The disease-free equilibrium corresponds to the state of the population when no infection is present. The disease-free equilibrium in proportionalized form is  $E_0 = N^*(s^*, v^*, 0, 0, 0, 0, 0, 0)$ , given by

$$\frac{\Lambda}{\mu} \left( \frac{(1-p)\mu}{\phi + \mu}, \frac{p\mu + \phi}{\phi + \mu}, 0, 0, 0, 0, 0, 0 \right).$$

We note that proportionalized form is obtained by dividing through by the population equilibrium,  $N^*$ . So, for example  $s^* = S^*/N^*$ . We observe that the population dynamics at the DFE consist of two types of flows: the demographic renewal flow and the vaccination flow. The demographic renewal flow is measured by  $\mu$ . Of this flow, we have a proportion  $p$  bringing people into the  $V$  class and the remaining proportion  $1 - p$  bringing people into the  $S$  class. The  $\phi$  flow sends people into  $V$ .

To determine under what conditions infection with strain 1 or strain 2 can persist in the population, we determine the basic reproductive numbers for each infection. The basic reproductive number is a threshold condition defined to be the average number of secondary infections caused by an infected individual. We compute  $R_1$  for strain 1,  $R_2$  for strain 2, and  $R_0$  for the presence of any infection with either strain.

The method used to determine the various reproductive numbers of the diseases in the model is the next-generation operator[10, 13]. Calculations for  $R_0$  are given in Appendix 1. We find  $R_0 = \max\{R_1, R_2\}$ , where

$$R_1 = \frac{\beta_1}{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega} \left( \frac{(1-p)\mu}{\phi + \mu} \right), \quad R_2 = \frac{\beta_2}{\mu + \gamma_2}.$$

We see that  $R_1$  consists of two parts. The first fraction is essentially the rate into the  $I_1$  class versus the rate out of the  $I_1$  class. We note the fraction in the third term of the denominator is only a proportion of the  $\omega$  flow. Recall that  $\omega$  is the rate at which people move from  $I_1$  to  $C_1$ . Thus, the third term in the denominator considers only a proportion of those leaving  $I_1$  to  $C_1$  because the remaining proportion return to  $I_1$  by the  $\alpha$  flow. We consider the second term of  $R_1$ . The effect of the second term is to reduce  $R_1$  by the proportion of the population actually susceptible to infection in the  $S$  class.

$R_2$  can clearly be interpreted as the rate into  $I_2$  divided by the rate out of  $I_2$ .

**Result 1.** *The disease-free equilibrium  $E_0$  is locally asymptotically stable if  $R_0 < 1$  and unstable if  $R_0 > 1$ .*

This result is implied by the construction of  $R_0$  using the next generation operator method.

### 3.2 Endemic Equilibria

Another equilibrium can be found when  $I_2^* = 0$ . In this case, there is no infection with strain 2. This equilibrium, in proportionalized form, is  $E_1 = N^*(s^*, v^*, 0, i_1^*, 0, 0, c_1^*, 0)$ , where

$$s^* = (1-p) \frac{1}{R_1} \frac{\mu}{\mu + \phi}, \quad v^* = p + (1-p) \frac{1}{R_1} \frac{\phi}{\mu + \phi} + (1-p) \left( 1 - \frac{1}{R_1} \right) \frac{\left( \frac{p\delta}{\alpha + \mu + \delta} \right) \omega}{\mu + \left( \frac{\mu + p\delta}{\alpha + \mu + \delta} \right) \omega},$$

$$i_1^* = (1-p) \left(1 - \frac{1}{R_1}\right) \frac{\mu}{\mu + \left(\frac{\mu+p\delta}{\alpha+\mu+\delta}\right) \omega}, \quad c_1^* = (1-p) \left(1 - \frac{1}{R_1}\right) \frac{\left(\frac{\mu}{\alpha+\mu+\delta}\right) \omega}{\mu + \left(\frac{\mu+p\delta}{\alpha+\mu+\delta}\right) \omega},$$

$$N^* = \frac{\Lambda}{\mu + \delta c_1^*}.$$

Note that this equilibrium makes biological sense only when  $R_1 > 1$ . We see that the equilibrium  $E_1$  breaks the population into three parts. The population can be broken into proportions  $p$  and  $1-p$ . The susceptible proportion  $1-p$  can further be broken into two parts:  $\frac{1}{R_1}$  uninfected and  $1 - \frac{1}{R_1}$  infected. The uninfected population can be broken into 2 parts. The infected population is then further subdivided three ways. In  $i_1^*$ , we observe the  $\mu$  term which can be interpreted as staying in the  $I_1$  class until death. We then examine the term  $\frac{\mu}{\alpha+\mu+\delta} \omega$ . We interpret this term as the proportion of those women who move to  $C_1$  who die from natural causes. Essentially, this can be seen as the proportion of those who stay in  $C_1$  until death by natural causes or aging out of the population. The term  $p\frac{\delta}{\alpha+\mu+\omega} \omega$  can be interpreted the following way. We observe first the  $\delta$  term. We interpret this term as those who are taken out of  $C_1$  early, essentially leaving  $C_1$  instead of staying until natural death. The  $p$  term represents those who enter back into the system into the  $V$  class. The equilibrium  $E_1$  is made of these six parts.

The second single-strain equilibrium is found when  $I_1^* = 0$ , where there is no infection with strain 1. The equilibrium value is  $E_2 = N^*(s^*, v^*, v_2^*, 0, i_2^*, 0, 0, 0)$ , where

$$s^* = \frac{1}{R_2} \frac{(1-p)R_2\mu}{R_2\mu + \phi}, \quad v^* = \frac{1}{R_2} \frac{pR_2\mu + \phi}{R_2\mu + \phi},$$

$$i_2^* = \left(1 - \frac{1}{R_2}\right) \frac{(1-p)R_2\mu}{R_2\mu + \phi}, \quad v_2^* = \left(1 - \frac{1}{R_2}\right) \frac{pR_2\mu + \phi}{R_2\mu + \phi}.$$

We note that the total population at  $E_2$  is

$$N^* = \frac{\Lambda}{\mu},$$

as at  $E_0$ . This equilibrium makes biological sense only when  $R_2 > 1$ .

We observe that  $E_2$  breaks the population into two parts,  $\frac{1}{R_2}$  uninfected and  $1 - \frac{1}{R_2}$  infected with strain 2. Of these parts, the population is further broken down into a proportion  $p$  of the demographic renewal flow  $\mu$  to the vaccinated portion of the population as well as all of the  $\phi$  flow. Thus, we see in the non-vaccinated classes the remaining proportion  $1 - p$  of the  $\mu$  flow.

We also mention the possibility of one or more endemic equilibria  $E_3$ . In the end of section 3.3, we will determine existence and stability of this equilibrium numerically in various regions of the parameter space using our parameter estimates from section 4.1.

### 3.3 Stability Analysis

We wish to determine the local stability of each equilibrium  $E_1, E_2, E_3$ . A method to determine stability of equilibrium values is to use the Jacobian evaluated at the specific equilibrium value. However, because of the complexity of the Jacobian matrix for this system, we utilize another method using the *invasion reproductive number*. We do note that the stability for the endemic equilibria are investigated numerically in section 4 using the Jacobian.

The invasion reproductive number has mostly been used in studies where competitive exclusion exists between multiple strains[15, 14]. This quantity represents the average number of secondary infections caused by introducing a person infected with one strain into an environment where a different strain is endemic[14]. The invasion reproductive number measures the ability of a strain to invade while another strain



is present and at equilibrium[15, 14]. In these studies we see that if strain 2 were introduced into a system where strain 1 has attained its equilibrium, strain 2 can persist and invade the population if the invasion reproductive number is greater than 1. But, since our study does not consider competitive exclusion or cross-immunity, we do not see the diminished capacity for invasion of the second strain. However, we are still able to establish the invasion criterion which will allow us to determine local stability of the various single-strain endemic equilibria using the invasion reproductive number. We define the invasion reproductive number  $\tilde{R}_1$  to be the average number of secondary strain 1 infections caused by an infected individual introduced into a population at  $E_2$ . Thus,  $E_2$  may be considered the disease free equilibrium for the reduced system without the presence strain 2.  $\tilde{R}_2$  is defined similarly.

$\tilde{R}_1$  can be found via the next generation operator method at  $E_2$ , where we determine the dominant eigenvalue of the matrix  $M_1 D_1^{-1}$  [10]. This method assumes  $R_2 > 1$  implicitly.

Denote  $M_1 D_1^{-1} =$

$$\begin{pmatrix} \frac{\beta_1 s - k\beta_2 \left(1 - \frac{1}{R_2}\right)}{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega} & \frac{\beta_1 s + \gamma_2}{\mu + \omega + \gamma_1 + \gamma_2} \\ \frac{k\beta_2 \left(1 - \frac{1}{R_2}\right) + \beta_1 i_2}{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega} & \frac{\beta_1 i_2}{\mu + \omega + \gamma_1 + \gamma_2} \end{pmatrix} = \begin{pmatrix} a & b \\ c & d \end{pmatrix}.$$

Then

$$\tilde{R}_1 = \frac{1}{2} \left[ a + d + \sqrt{(a + d)^2 + 4bc} \right], \quad (3.1)$$

where

$$\begin{aligned}
a &= R_1 \frac{\mu + \phi}{R_2 \mu + \phi} \frac{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega}{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega + k\beta_2(1 - \frac{1}{R_2})}, \\
b &= R_1 \frac{\mu + \phi}{R_2 \mu + \phi} \frac{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega}{\mu + \gamma_1 + \gamma_2 + \omega} + \frac{\gamma_2}{\mu + \omega + \gamma_1 + \gamma_2}, \\
c &= R_1 \frac{\mu + \phi}{R_2 \mu + \phi} \frac{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega}{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega + k\beta_2(1 - \frac{1}{R_2})} (R_2 - 1) \\
&\quad + \frac{k\beta_2(1 - \frac{1}{R_2})}{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega + k\beta_2(1 - \frac{1}{R_2})}, \\
d &= R_1 \frac{\mu + \phi}{R_2 \mu + \phi} \frac{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega}{\mu + \gamma_1 + \gamma_2 + \omega} (R_2 - 1).
\end{aligned}$$

Because  $\tilde{R}_1 > a + d$ , we wish to interpret  $a + d$ . We see that  $a$  represents the flow into  $I_1$  from  $S$  where  $d$  represents the flow into  $I_{12}$  from  $I_2$ .

Thus, by construction of  $\tilde{R}_1$  using the next generation operator, we observe the following result.

**Result 2.** *The  $E_2$  equilibrium, which exists when  $R_2 > 1$ , is locally asymptotically stable if  $\tilde{R}_1 < 1$  and unstable if  $\tilde{R}_1 > 1$ .*

We also consider the invasion reproductive number  $\tilde{R}_2$ .  $\tilde{R}_2$  represents the ability of strain 2 to invade a susceptible population at  $E_1$ . Again utilizing the next generation operator method, we compute the dominant eigenvalue of the following matrix:

$$M_2 D_2^{-1} = \begin{pmatrix} R_2 v^* & R_2 v^* & \frac{\beta_2 v^*}{\mu + \omega + \gamma_1 + \gamma_2} \\ R_2 s^* & R_2 s^* + \frac{\beta_1 i_1^*}{\mu + \gamma_2} & \frac{\beta_2 s^* + \gamma_1}{\mu + \omega + \gamma_1 + \gamma_2} \\ k R_2 i_1^* & k R_2 i_1^* + \frac{\beta_1 i_1^*}{\mu + \gamma_2} & \frac{k \beta_2 i_1^*}{(\mu + \omega + \gamma_1 + \gamma_2)} \end{pmatrix}.$$

Because of the complexity of the previous matrix, we compute  $\tilde{R}_2$  numerically using our estimates for the parameters. However, since  $\tilde{R}_2$  is constructed using the next generation operator, we can establish the following result.

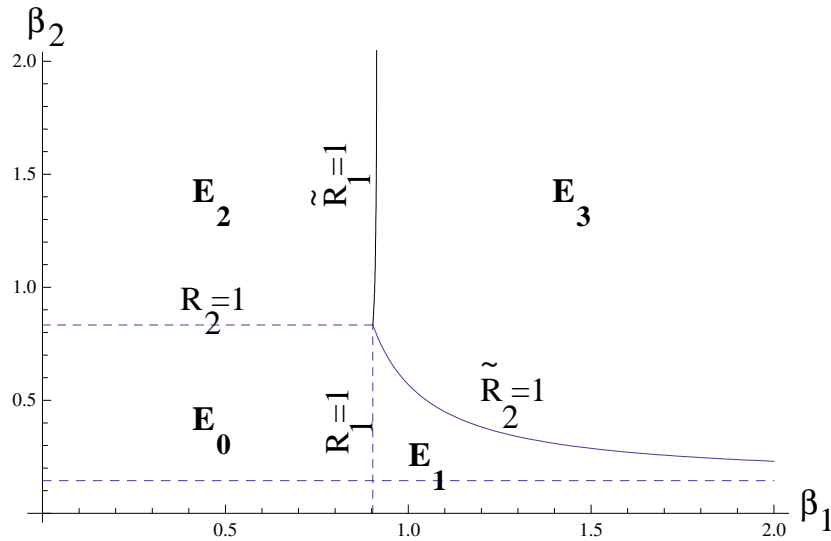


Figure 3.1. Division of the  $\beta_1, \beta_2$  parameter space using  $R_1, R_2, \tilde{R}_1, \tilde{R}_2$ .

**Result 3.** *The equilibrium  $E_1$ , which exists when  $R_1 > 1$ , is locally asymptotically stable if  $\tilde{R}_2 < 1$  and unstable if  $\tilde{R}_2 > 1$ .*

We wish to see how the invasion reproductive numbers  $\tilde{R}_1$  and  $\tilde{R}_2$  interact with the basic reproductive numbers  $R_1$  and  $R_2$ . We use these numbers to separate the  $\beta_1$  and  $\beta_2$  parameter space into four regions where  $E_0, E_1, E_2$  and  $E_3$  exist and are stable, noting that  $E_3$  is the coinfection equilibrium. The graph is given in Figure 3.1.

We see from the figure that the four regions are separated by the lines  $R_1 = 1$ ,  $R_2 = 1$ ,  $\tilde{R}_1 = 1$  and  $\tilde{R}_2 = 1$  as  $\beta_1$  and  $\beta_2$  vary. We conclude that in the lower left hand region, the disease-free equilibrium  $E_0$  is stable. In the upper left region  $E_2$  is stable. In the upper right region,  $E_3$  is stable, and in the lower right region,  $E_1$  is stable.

The graph in Figure 3.1 was generated with  $p, phi = 0$ . For,  $\phi \geq 0$ , the  $\tilde{R}_1 = 1$  curve actually curves to the left. As a result of the construction of the model, we see that those in  $I_2$  do not get vaccinated. Thus, as  $\beta_2 \rightarrow \infty$ , more women are moved

from  $S$  into  $I_2$  faster than women are moved from  $S$  to  $V$ , thereby increasing the region of coinfection when  $\phi \geq 0$ . This, we acknowledge is an aspect of the model, and in further work a vaccination flow from  $I_2$  to  $V_2$  will be considered.

From Result 2 in section 3.2 we conclude that  $E_2$  exists when  $R_2 > 1$  and is locally stable when  $\tilde{R}_1 < 1$ . We note that when  $R_1 < 1$ , either  $E_0$  exists and it stable, or  $E_2$  exists and is stable. So, when  $R_2, R_1 < 1$ ,  $E_0$  exists and is stable, and when  $R_2 > 1, \tilde{R}_1 < 1$ ,  $E_2$  exists and is stable. Because the strain 1 infection rate is independent of strain 2 infection, we can conclude that  $R_1 = 1$  is equivalent to  $\tilde{R}_1 = 1$ . However, the curves  $R_2 = 1$  and  $\tilde{R}_2 = 1$  are not equivalent. It is possible that  $R_2 < 1$  and strain 2 can still persist in the population alongside strain 1 ( $E_3$ ) because of the increased vulnerability of women infected with strain 1. The boundary for  $E_1$  and  $E_3$  is not the same as the boundary for  $E_0$  and  $E_2$ . When  $R_1 > 1$ , strain 1 is endemic which advantages transmission of strain 2. The threshold for persistence of strain 2 is lower then when strain 1 is not endemic. We conclude that there is a range of values for  $R_2$  for which it is possible that vaccination of strain 1 could also cause extinction of strain 2.

Table 3.1. Jacobian matrices used in stability analysis

In order to see the full Jacobian on a single page, we make the following substitutions.  
 $W = N - S$ ,  $X = N - V$ ,  $Y = N - \tilde{I}_2$ ,  $Z = N - \tilde{I}_1$ ,  $y = N - I_2$ ,  $z = N - I_1$ . The full Jacobian is given by

$$\begin{pmatrix} -(\phi + \mu) - \frac{\beta_2 \tilde{I}_2 W}{N^2} - \frac{\beta_1 \tilde{I}_1 W}{N^2} & 0 & -\frac{\beta_2 SY}{N^2} & -\frac{\beta_1 SY}{N^2} + \gamma_1 & -\frac{\beta_2 SY}{N^2} + \gamma_2 & -\frac{\beta_2 SY}{N^2} - \frac{\beta_1 SZ}{N^2} & 0 & 0 \\ \phi & -\frac{\beta_2 \tilde{I}_2 X}{N^2} - \mu & -\frac{\beta_2 VY}{N^2} + \gamma_2 & 0 & -\frac{\beta_2 VY}{N^2} & -\frac{\beta_2 VY}{N^2} & 0 & 0 \\ 0 & \frac{\beta_2 \tilde{I}_2 X}{N^2} & \frac{\beta_2 VY}{N^2} - (\mu + \gamma_2) & 0 & \frac{\beta_2 VY}{N^2} & \frac{\beta_2 VY}{N^2} & 0 & 0 \\ \frac{\beta_1 \tilde{I}_1 W}{N^2} & 0 & -\frac{k\beta_2 I_1 Y}{N^2} & \frac{\beta_1 SZ}{N^2} - \frac{k\beta_2 \tilde{I}_2 z}{N^2} - (\omega + \mu + \gamma_1) & -\frac{k\beta_2 I_1 Y}{N^2} & \frac{\beta_1 SZ}{N^2} - \frac{k\beta_2 I_1 Y}{N^2} + \gamma_2 & \alpha & 0 \\ \frac{\beta_2 \tilde{I}_2 W}{N^2} & 0 & \frac{\beta_2 SY}{N^2} & -\frac{\beta_1 I_2 Z}{N^2} & \frac{\beta_2 SY}{N^2} - \frac{\beta_1 I_1 y}{N^2} - (\mu + \gamma_2) & \frac{\beta_2 SY}{N^2} - \frac{\beta_1 I_1 y}{N^2} + \gamma_1 & 0 & 0 \\ 0 & 0 & \frac{k\beta_2 I_1 Y}{N^2} & \frac{k\beta_2 \tilde{I}_2 z}{N^2} + \frac{\beta_1 I_2 Z}{N^2} & \frac{k\beta_2 I_1 Y}{N^2} + \frac{\beta_1 I_1 y}{N^2} & \frac{k\beta_2 I_1 Y}{N^2} + \frac{\beta_1 I_2 Z}{N^2} - (\mu + \omega + \gamma_1 + \gamma_2) & 0 & 0 \\ 0 & 0 & 0 & \omega & 0 & 0 & -(\alpha + \mu + \delta) & 0 \\ 0 & 0 & 0 & 0 & 0 & \omega & 0 & -(\mu + \delta) \end{pmatrix}.$$

We can eliminate  $V_2, I_2, I_{12}$ , and  $C_{12}$  to obtain the reduced 4th order system.  
 The proportionalized Jacobian  $J(E_1)$ , given by this system where  $i_2^* = 0$ :

$$\begin{pmatrix} -(\phi + \mu) - \beta_1 i_1(1 - s) & 0 & -\beta_2 s & -\beta_1 s(1 - i_1) + \gamma_1 & -\beta_2 s + \gamma_2 & -\beta_2 s - \beta_1 s(1 - i_1) & 0 & 0 \\ \phi & -\mu & -\beta_2 v + \gamma_2 & 0 & -\beta_2 v & -\beta_2 v & 0 & 0 \\ 0 & 0 & \beta_2 v + \gamma_2 & 0 & \beta_2 v & \beta_2 v & 0 & 0 \\ -\beta_1 i_1(1 - s) & 0 & -k\beta_2 i_1 & \beta_1 s(1 - i_1) - (\omega + \mu + \gamma_1) & -k\beta_2 i_1 & \beta_1 s(1 - i_1) - k\beta_2 i_1 + \gamma_2 & \alpha & 0 \\ 0 & 0 & \beta_2 s & 0 & \beta_2 s - \beta_1 i_1 - (\mu + \gamma_2) & \beta_2 s + \gamma_1 & 0 & 0 \\ 0 & 0 & k\beta_2 i_1 & 0 & i_1(k\beta_2 + \beta_1) & k\beta_2 i_1 - (\mu + \omega + \gamma_1 + \gamma_2) & 0 & 0 \\ 0 & 0 & 0 & \omega & 0 & 0 & -(\alpha + \mu + \delta) & 0 \\ 0 & 0 & 0 & 0 & 0 & \omega & 0 & -(\mu + \delta) \end{pmatrix}.$$

Table 3.2. Jacobian matrices used in stability analysis

The proportionalized Jacobian  $J(E_2)$ , where  $i_1^* = 0$ , is given below; we make the substitution  $x_2 = i_2 + v_2$ .

$$\begin{aligned}
 & \begin{pmatrix}
 -(\phi + \mu) - \beta_2 x_2(1-s) & 0 & -\beta_2 s(1-x_2) & -\beta_1 s + \gamma_1 & -\beta_2 s(1-x_2) + \gamma_2 & -\beta_2 s(1-x_2) - \beta_1 s & 0 & 0 \\
 \phi & -\beta_2 x_2(1-v) - \mu & -\beta_2 v(1-x_2) + \gamma_2 & 0 & -\beta_2 v(1-x_2) & -\beta_2 v(1-x_2) & 0 & 0 \\
 0 & \beta_2 x_2(1-v) & \beta_2 v(1-x_2) - (\mu + \gamma_2) & 0 & \beta_2 v(1-x_2) & \beta_2 v(1-x_2) & 0 & 0 \\
 0 & 0 & 0 & \beta_1 s - k\beta_2 x_2 - (\omega + \mu + \gamma_1) & 0 & \beta_1 s - \gamma_2 & \alpha & 0 \\
 \beta_2 x_2(1-s) & 0 & \beta_2 s(1-x_2) & \beta_1 x_2 & \beta_2 s(1-x_2) - (\mu + \gamma_2) & \beta_2 s(1-x_2) - \beta_1 i_2 + \gamma_1 & 0 & 0 \\
 0 & 0 & 0 & k\beta_2 x_2 - \beta_1 i_2 & 0 & \beta_2 i_2 - (\mu + \omega + \gamma_1 + \gamma_2) & 0 & 0 \\
 0 & 0 & 0 & \omega & 0 & 0 & -(\alpha + \mu + \delta) & 0 \\
 0 & 0 & 0 & 0 & 0 & \omega & 0 & -(\mu + \delta)
 \end{pmatrix} \\
 = & \begin{pmatrix}
 -(\phi + \mu) - \beta_2(1 - \frac{1}{R_2})(1-s) & 0 & -\beta_2 s(\frac{1}{R_2}) & -\beta_1 s + \gamma_1 & -\beta_2 s(\frac{1}{R_2}) + \gamma_2 & -\beta_2 s(\frac{1}{R_2}) - \beta_1 s & 0 & 0 \\
 \phi & -\beta_2(1 - \frac{1}{R_2})(1-v) - \mu & -\beta_2 v(\frac{1}{R_2}) + \gamma_2 & 0 & -\beta_2 v(\frac{1}{R_2}) & -\beta_2 v(\frac{1}{R_2}) & 0 & 0 \\
 0 & \beta_2(1 - \frac{1}{R_2})(1-v) & \beta_2 v(\frac{1}{R_2}) - (\mu + \gamma_2) & 0 & \beta_2 v(\frac{1}{R_2}) & \beta_2 v(\frac{1}{R_2}) & 0 & 0 \\
 0 & 0 & 0 & \beta_1 s - k\beta_2(1 - \frac{1}{R_2}) - (\omega + \mu + \gamma_1) & 0 & \beta_1 s - \gamma_2 & \alpha & 0 \\
 \beta_2(1 - \frac{1}{R_2})(1-s) & 0 & \beta_2 s(\frac{1}{R_2}) & \beta_1(1 - \frac{1}{R_2}) & \beta_2 s(\frac{1}{R_2}) - (\mu + \gamma_2) & \beta_2 s(\frac{1}{R_2}) - \beta_1 i_2 + \gamma_1 & 0 & 0 \\
 0 & 0 & 0 & k\beta_2(i_2 + v_2) - \beta_1 i_2 & 0 & \beta_2 i_2 - (\mu + \omega + \gamma_1 + \gamma_2) & 0 & 0 \\
 0 & 0 & 0 & \omega & 0 & 0 & -(\alpha + \mu + \delta) & 0 \\
 0 & 0 & 0 & 0 & 0 & \omega & 0 & -(\mu + \delta)
 \end{pmatrix}
 \end{aligned}$$

## CHAPTER 4

### NUMERICAL APPROXIMATIONS

#### 4.1 Parameters

In this section we estimate the parameters used in our model in order to provide numerical results. All parameter estimates are given in Table 4.1. We assume all rates are *per capita* unless stated otherwise. We consider first  $\Lambda$ , the constant recruitment rate. According to the Population Division of the U.S. Census Bureau, the total population of females age 15-59 in July 1, 2006 was 100,609,815[12]. Dividing this total population by the difference in age for our model, we have a recruitment rate of 2,235,773 females between the age 15-59 in the United States per year. The natural death rate  $\mu$  for the given population is  $1/45yr^{-1}$ . We consider another possible rate of removal from the population,  $\delta$ , the rate of death due to cervical cancer. To determine  $\delta$  we consider results from a paper given by Bachtiry et al.[13]. We will use the formula: (number of cervical cancer cases due to HPV-16)  $\times$  (median survival time) = (woman-months), where this is an estimate of the average woman-months of survival after diagnosis with cervical cancer due to HPV-16. We then compute the number of deaths divided by the number of woman-months to obtain the rate of death due to cervical cancer. Thus using the appropriate numbers from the study, we obtain  $69cases \times 54months = 3726woman - months$ .  $31deaths/3726woman - months = 0.0998yr^{-1} = \delta$ .

To estimate  $\beta_1$ , the infection rate for infection 1, we consider infection 1 to be HPV-16 (the primary infection). Thus, we estimate the infection rate for HPV-16. Several studies have been conducted to determine incidence rates for HPV-16

among other types. Results given by these studies vary in nature. We use results given by Barnabas where a transmission probability of 0.6 per sexual partnership is determined[23]. We further assume the population considered will have an average of 2 sexual partners per year resulting in  $\beta_1 = 1.2yr^{-1}$ .

We estimate  $\beta_2$  using the estimation for  $\beta_1$ . According to a study on multiple strains of HPV in a cohort of Columbian women, the incidence rate of HPV-58 was 0.7 of HPV-16[19]. Thus, we conclude that  $\beta_2 = 0.7\beta_1$ .

The recovery rates for strain 1 and strain 2 are  $\gamma_1$  and  $\gamma_2$ , respectively. Several studies have been conducted to determine average duration of HPV infection. We use results from a study given by Muñoz, where durations of several HPV strains were determined [19]. Durations of HPV-16 and HPV-58 were 13.7 and 14.8 months respectively. We then convert to the appropriate units, obtain rates of  $\gamma_1 = 0.876yr^{-1}$  and  $\gamma_2 = 0.811yr^{-1}$ .

Because we assume that infection with strain 1 affects vulnerability to infection with strain 2, we use a dimensionless parameter  $k$  to describe the factor by which the infection rate for strain 2 increases for individuals infected with strain 1. In particular, since infection with HPV-16 appears to predispose individuals to infection with HPV-58, we take  $k > 1$ . We utilize a study where results concluded women infected with HPV-16 or-18 were 6 times more likely to contract a secondary infection[10]. Thus, for our study, we estimate  $k = 6$ .

We estimate  $\omega$ , rate of developing cancer due to strain 1 infection. According to an article by Khan et al. published in the *Journal of the National Cancer Institute*, the rate of developing cervical cancer due to HPV16 over a 10-year period was 17.2 percent[25]. Thus, we estimate  $\omega = 17.2/10yr = 0.0172yr^{-1}$ .

The rate  $\alpha$  is the cervical cancer remission rate for women with strain 1 only. We will estimate this rate indirectly using the ratio  $\frac{\alpha}{\alpha+\mu+\delta}$ . We consider the proportion



of women who go into remission from cervical cancer, and use this to solve for  $\alpha$  in the previous expression. According to the American Cancer Society, 72 percent of women with cervical cancer will survive at least 5 years [20]. We assume this to be the proportion of women who go into remission from cervical cancer. If a woman survives for at least 5 years after being diagnosed with cervical cancer, we assume that she has gone into remission. Thus solving  $\frac{\alpha}{\alpha+\mu+\delta} = 72$  for  $\alpha$ , we obtain  $\alpha = 0.315yr^{-1}$ .

We consider that a proportion  $p$  of females enter the population directly into the vaccinated class. But, we also consider ongoing vaccination due to public education campaigns or influence by doctors or the medical community. In this situation, we estimate  $\phi$ , the ongoing rate of vaccination. We estimate  $\phi$  by setting up a ratio  $\frac{\phi}{\phi+\mu}$ . We see that this is the proportion of females who get vaccinated voluntarily. According to the CDC, the influenza vaccination coverage for high-risk persons ages 18-49 was 26 percent[24]. Because the human papilloma virus vaccine has been on the market for a short time, we do not have information for current coverage for this vaccine. Thus we estimate the percentage of women who voluntarily get vaccinated for HPV to be the same as the percentage of people who voluntarily get vaccinated for influenza. Setting the ratio above equal to .26 and solving for  $\phi$ , we obtain  $\phi = .007yr^{-1}$ .

## 4.2 Numerical Simulations

We run numerical simulations using our parameter estimates. The simulations were done using Matlab and Mathematica. See the code in Appendix B. In doing these simulations, we wish to examine several scenarios. What effect does the presence of strain 2 in our population have on the number of cervical cancer cases and deaths? Also, if we introduce vaccination into the population, what effect then will this have on the number of cervical cancer cases and deaths? To better answer these questions,

Table 4.1. Model Parameters and Their Values

| Parm.      | Description  | Value               | Units                   | Ref. |
|------------|--|---------------------|-------------------------|------|
| $p$        | Proportion of women who enter the population into the vaccinated class | 0.5                 | -                       |      |
| $\Lambda$  | Constant recruitment rate  | 2,235,773           | <i>people/yr</i>        | [12] |
| $\mu$      | Natural death rate   | 1/44                | $\frac{1}{\text{year}}$ |      |
| $\delta$   | Death rate due to cervical cancer                                      | 0.0998              | <i>1/yr</i>             | [13] |
| $\beta_1$  | Infection rate for infection 1   | 1.2                 | <i>1/yr</i>             | [23] |
| $\beta_2$  | Infection rate for infection 2   | $\frac{7}{10}(1.2)$ | <i>1/yr</i>             | [19] |
| $\gamma_1$ | Recovery rate from infection 1   | 0.876               | <i>1/yr</i>             | [19] |
| $\gamma_2$ | Recovery rate from infection 2   | 0.811               | <i>1/yr</i>             | [19] |
| $\alpha$   | Cervical cancer remission rate for women with strain 1 only            | 0.315               | <i>1/yr</i>             | [20] |
| $\omega$   | Rate of developing cancer due to strain 1 infection                    | 0.0172              | <i>1/yr</i>             | [25] |
| $\phi$     | Rate of ongoing vaccination  | 0.007               | <i>1/yr</i>             | [24] |
| $k$        | Amplification factor   | 6                   | -                       | [16] |

we set up several scenarios. We first consider the population without strain 2. We run a simulation without vaccination, where the reproductive number for strain 1 will be greater than 1, and then a simulation with vaccination which reduces the reproductive number for strain 1 below 1. We then determine the cumulative number of cancer cases and deaths after a time period of 100 years.

We then introduce strain 2 back into the population. The presence of strain 2 will change the dynamics of the population greatly. Strain 2 causes more of the cancer cases to be fatal. We again run the simulation without vaccination and then with vaccination to obtain the number of cervical cancer cases and deaths after the predetermined time period. The results of the simulations can be seen in Table 4.2.

Although the proportions in the table are reasonable, all of the results are higher than expected. There are several reasons why this occurs. Because this is an exponential distribution of lifetimes, we see an overestimate. Since  $\mu$  is  $\frac{1}{45}$ , people

Table 4.2. Effects of the presence of strain 2 and/or vaccination ( $p = 0.5, \phi = 0.007yr^{-1}$ ) on the severity of the strain 1 epidemic and associated cancer over a 100 year period.

| Scenario         | Cumulative No. of Strain 1 Infectives | Cumulative No. Cancer Cases | Cumulative No. Cancer Deaths |
|------------------|---------------------------------------|-----------------------------|------------------------------|
| Without Strain 2 |                                       |                             |                              |
| No Vaccination   | 2,023,500,000                         | 46,502,362                  | 10,314,710                   |
| With Vaccination | 16,394,633                            | 3,863,766                   | 881,325                      |
| With Strain 2    |                                       |                             |                              |
| No Vaccination   | 1,855,800,000                         | 42,240,709                  | 23,970,206                   |
| With Vaccination | 18,378,027                            | 4,308,887                   | 2,019,381                    |

should be removed from the population after 45 years, but in this case some of them are still in the system, thus producing higher final numbers. A second reason for the higher than expected final numbers is that the model allows for people to get reinfected over and over again. We note that this is not unrealistic. The official CDC data count infections differently than we do in this study. Because of the transient nature of HPV and different detection methods, it is difficult to determine whether a person has actually cleared and been reinfected. This overestimate could potentially be avoided by having people recover to a separate  $R$  class rather than moving back and forth from the susceptible to infectious classes. Because we are interested in the effect of strain 2's presence in the population and vaccination present in the population, we use proportional comparisons.

We notice in the results that without vaccination present, the number of cervical cancer cases actually decreases when strain two is introduced into the population. This is because that when strain one is alone in the population, women can develop cervical cancer, but can then recover from that cancer at which point they could conceivably develop it again. Since the model cannot distinguish among individuals

in the same class, this would count as an additional case. However, when strain two is in the population, we have another route to developing cervical cancer. Women can develop cervical cancer from the  $I_{12}$  class, but because the cancer is from a multiple infection with HPV, the cancer cannot be cleared. Thus when strain two is introduced we see that women who enter the  $C_{12}$  class cannot return back into the population. Thus, there are fewer women to get reinfected over time. So, we focus more on the cervical cancer deaths in this situation rather than the number of cases. It is expected that when strain two is in the population (with or without vaccination) cervical cancer deaths will be greater. But, when comparing the scenarios when strain 2 is present without vaccination versus strain 2 present with vaccination we will see cervical cancer cases and deaths reduced by a drastic amount.

Using results found in Table 4.2, we observe the following. First, we examine the results without strain 2. Without a second strain in our system, we see a 92 percent decrease in number of cervical cancer cases when vaccination is introduced into the system. We observe a 92 percent decrease in number of cervical cancer deaths as well. When strain 2 is present in the system, we observe that there is a significant decrease in the number of cervical cancer cases and deaths after 100 years. After 100 years, we see that there is an 88 percent decrease in number of cervical cancer cases if vaccination is present at 50 percent. Also, we observe a 92 percent decrease in number of cervical cancer deaths after this time.

When comparing the effects of the second strain on the system, we observe that without vaccination, there is a 122 percent increase in cervical cancer deaths when strain 2 is entered into the system. If vaccination is present at 50 percent, we see that there is a 129 percent increase in cervical cancer deaths.

We also wish to observe the effect of the vaccination parameters  $p$  and  $\phi$  on cases of strain 1. We view a graph of  $p$  and  $\phi$  versus the number of strain 1 infectives

at the end of 100 years. We solve the system of differential equations over time as  $p$  and  $\phi$  vary. The graph is given in Figure 4.1. We see that the number of strain 1 infectives is essentially zero for most vaccination levels. We see that for values of  $p$  and  $\phi$  as low as 0.2, strain 1 will still be eradicated.

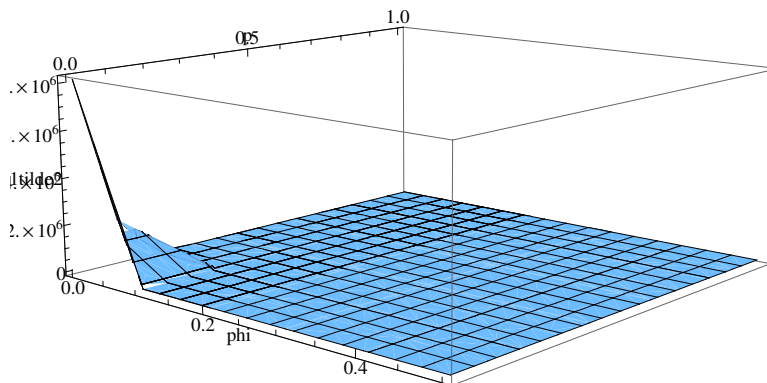


Figure 4.1. Vaccination Parameters vs.  $\tilde{I}_1$ .

We recall that in our model, vaccination is not a possibility for strain 2. However, strain 1 increases a woman's vulnerability of contracting strain 2. We thus wish to examine what effect vaccination for strain 1 will have on strain 2. We examine the graph of the vaccination parameters versus  $\tilde{I}_2$  in Figure 4.2. In the graph we see that  $\tilde{I}_2$  is sustained at the  $E_2$  equilibrium except for values of  $p$  and  $\phi$  near zero. We see from the graph that when  $R_1 < 1$ , strain 2 prevalence remains at 0.8 percent while the prevalence for strain 2 jumps significantly for  $R_1 > 1$ . Because strain 1 contributes so much to the prevalence of strain 2 through secondary infections, for our given parameter estimates vaccination for strain 1 will not eradicate strain 2, but will reduce its prevalence significantly.

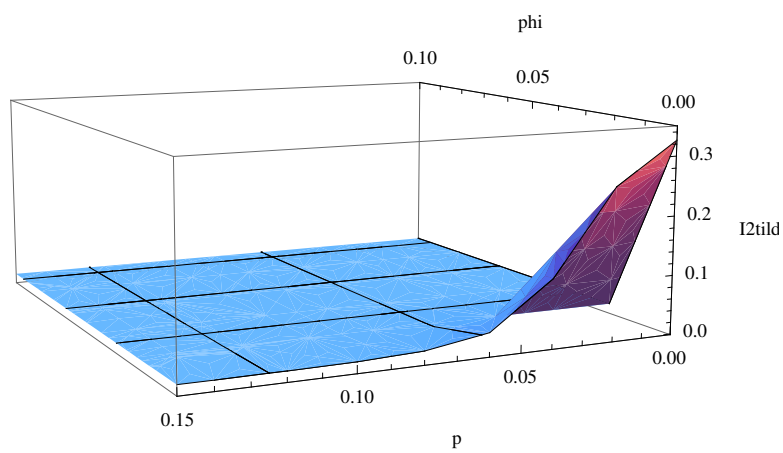


Figure 4.2. Vaccination Parameters vs.  $\tilde{I}_2$ .

## CHAPTER 5

### CONCLUSIONS

The current vaccine Gardasil targets HPV 6, 11, 16, 18, of which the first two account for over 90 percent of all genital warts and the latter two account for 70 percent of all cervical cancers. If there is a mutualistic relationship between HPV as certain studies suggest, then the vaccine may indirectly protect against types not targeted, thereby reducing the prevalence of HPV not targeted in the vaccine. Furthermore, as we have seen women who develop cervical cancer due to persistent multiple HPV infections are less likely to recover from the cancer. If so, then since the vaccine may indirectly protect against types in multiple infections, thus protecting against cervical cancer caused by those infections.

Recall the goal of the study was to investigate the effect of multiple strains of human papillomavirus and vaccination on the number of cervical cancer deaths of female U.S. women. Thus, we construct our model with classes to highlight these effects. We note that in our model the presence of strain one will increase infectivity of strain two. We also recall that women who develop cervical cancer from infection with both strains will not recover from the cancer.

We computed the basic reproductive numbers  $R_1$  and  $R_2$  as well as the invasion reproductive numbers  $\tilde{R}_1$  and  $\tilde{R}_2$ . Together these quantities determine existence and stability for the disease-free and endemic equilibria. Strain 1 persists alone when  $R_1 > 1$ ,  $\tilde{R}_2 < 1$ , and strain 2 persists alone when  $R_2 > 1$ ,  $\tilde{R}_1 < 1$ . We observe that the reproductive number  $R_1$  will be greater than one with the existing estimates we have for the parameters in the absence of vaccination. With a sufficient vaccination

coverage,  $R_1$  can be reduced to less than one so that strain one will eventually be eradicated. However,  $R_2 > 1$  for all values of the vaccination parameters  $p$  and  $\phi$ . Thus, under the conditions given in this study, strain 2 will not be completely eradicated from the population, but its prevalence can be reduced as seen in section 4. We generated a graph to see how the vaccination parameters reduce the prevalence of strain 2 although the vaccine does not directly protect against strain 2. In fact, there are certain scenarios in which  $R_2 < 1 < \hat{k}R_2 = \tilde{R}_2$ . In this case, we see that strain 1 vaccination could actually eradicate strain 2 by reducing the average vulnerability to infection by strain 2.

Two questions were posed in this study. We wish to determine what effect multiple strains of HPV have on the number of cervical cancer cases and deaths. It has been determined that the introduction of a second strain to the system will cause an increase in cervical cancer deaths by more than 100 percent. The second goal was to determine the effects of vaccination for one strain of HPV in a system where infection with multiple strains is possible. Vaccination coverage at approximately 25 percent or greater will result in eradication of strain 1 and eventually the associated cervical cancer cases. Results showed a 92 percent decrease in cervical cancer deaths with vaccination coverage at 50 percent over a period of 100 years.

In the study done by Elbasha and Galvani [20], vaccination against multiple types of HPV was the focus. However, HPV related disease such as cervical cancer were not addressed. In our study we investigated the impacts vaccination have on multiple strains of HPV, but more importantly on cervical cancer cases and deaths caused by infection with HPV. In our study, we also consider more than one vaccination strategy, whereas Elbasha and Galvani consider mass vaccination (vaccination upon entry into the population) only. We discuss how mass vaccination as well as voluntary vaccination play a role in prevalence of both strains. As the decision to



implement mass vaccination is being considered after the release of Gardasil, we acknowledge that this may not be the ultimate direction legislatures may take. For this reason, we consider that voluntary or ongoing vaccination is important to include in the study of HPV infection and cervical cancer.

It is important to mention the uncertainty of the disease cycle of human papillomavirus. Certain studies suggest that once a woman contracts a strain of HPV, once cleared she has lifelong immunity[20]. Other studies may consider that once a strain of HPV is contracted, it cannot be cleared and may become latent but yet still infectious[18]. Because it still is not known whether a woman actually clears an HPV virus or it becomes latent, different studies may choose which scenario provides the most evidence and validity. Thus, we choose to consider that women may contract an HPV virus, it may clear, and they may become reinfected. Many studies previously cited in this paper consider this to be the case.

Our model was created based on the focus of cervical cancer cases and deaths. Thus we did not include a male population in the construction of the model. We also mention that if a vaccine for HPV becomes available for men, then studies could be done to see what effect vaccinating both males and females would have on the prevalence of HPV in general as well as cervical cancer deaths for women. We also mention that we do not have a transition from the  $I_2$  class to the  $V_2$  class. In a further study, a flow from  $I_2$  to  $V_2$  could be considered. Few mathematical studies have been devoted to the study of human papillomavirus and its related diseases. Many more studies need to be done regarding the nature of HPV transmission, persistence, and clearance. Since few studies on HPV involve males, we see this as an area that needs more investigation. In many cases HPV infections in men are symptomless. We realize that the lack of epidemiological information on HPV infections in men is largely due to the fact that mortality related to HPV infection in men is far less common than

in women. However, since the main mode of transmission of genital HPV is through sexual contact, it is necessary to begin to address the disease cycle of HPV in the male population. Due to the uncertainty of several aspects and characteristics of HPV, we realize the difficulty in finding estimates for certain parameters in this study. Specific parameters difficult to estimate are  $\omega$  and  $\alpha$ . Thus, more studies should be done on the development of cervical cancer due to persistent HPV as well as the treatment and recovery rates of cervical cancer.

Although this model was developed specifically for HPV in the female population, we see that the results could extend to other viruses. The model predictions and results could apply to other multi-strain infections exhibiting mutualism in the population.

**APPENDIX A**  
**COMPUTATIONS AND PROOFS**

## A.1 Appendix

### A.1.1 DFE and $R_0$

We compute the disease-free equilibrium by solving the right hand sides of  $S' = 0$  and  $V' = 0$ , obtaining

$$\left( \frac{(1-p)\Lambda}{\phi + \mu}, \frac{\Lambda(p\mu + \phi)}{\mu(\phi + \mu)}, 0, 0, 0, 0, 0, 0 \right)$$

To determine  $R_0$ , we use the next generation operator. We divide the classes into three groups, uninfected, infected but not infectious, and infectious. The uninfected classes are  $X = \{S, V\}$ , infected but not infectious classes  $Y = \{C_1, C_{12}\}$ , and the infected classes  $Z = \{V_2, I_1, I_2, I_{12}\}$ . We first note that

$$C_1^* = \frac{\omega I_1^*}{\alpha + \mu + \delta}, C_{12}^* = \frac{\omega I_{12}}{\mu + \delta}.$$

Computing the Jacobian of  $Z$  at the DFE, we obtain the eigenvalues for

$$M_0 D_0^{-1} = \begin{pmatrix} \frac{\beta V^*}{N} \left( \frac{1}{\mu + \gamma_2} \right) & 0 & \frac{\beta S^*}{N} \left( \frac{1}{\mu + \gamma_2} \right) & 0 \\ 0 & \left( \frac{\beta S^*}{N} - \frac{\mu + \delta}{\alpha + \mu + \delta} \omega \right) \left( \frac{1}{\mu + \gamma_1} \right) & 0 & 0 \\ \frac{\beta V^*}{N} \left( \frac{1}{\mu + \gamma_2} \right) & 0 & \frac{\beta S^*}{N} \left( \frac{1}{\mu + \gamma_2} \right) & 0 \\ \frac{\beta V^*}{N} \left( \frac{1}{\mu + \gamma_2} \right) & \left( \frac{\beta S^*}{N} + \gamma_2 \right) \left( \frac{1}{\mu + \gamma_1} \right) & \left( \frac{\beta S^*}{N} + \gamma_1 \right) \left( \frac{1}{\mu + \gamma_2} \right) & \frac{\gamma_1}{\mu + \gamma_2 + \omega} \end{pmatrix}.$$

The eigenvalues for the corresponding matrix will be  $\{0, 0, R_1, R_2\}$ . Because  $R_0$  is determined to be the dominant eigenvalue found using the next-generation operator,  $R_0 = \max\{R_1, R_2\}$ ,

$$R_1 = \frac{\beta_1}{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega} \left( \frac{(1-p)\mu}{\phi + \mu} \right), R_2 = \frac{\beta_2}{\mu + \gamma_2}.$$

### A.1.2 Single Strain Equilibria

Substituting  $c_1^*$  and  $s^*$  into  $v^*$  for  $E_1$  gives

$$v^* = \left( \frac{1}{\mu} \right) p \left[ \mu + \delta \left( \frac{\mu \omega}{\mu(\alpha + \mu + \delta) + \omega(\mu + p\delta)} \right) \right] + \phi \left[ \frac{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega}{\beta_1} \right].$$

Distributing and simplifying, the following is obtained:

$$v^* = p + \frac{p\delta\omega}{\mu(\alpha + \mu + \delta) + \omega(\mu + p\delta)} + \frac{\phi}{\mu} \left[ \frac{\mu + \gamma_1 + \frac{\mu+\delta}{\alpha+\mu+\delta}\omega}{\beta_1} \right],$$

This  $v^*$  found in section 3.2 is simplified and in terms of  $R_1$ .

We find  $s^*$  by setting the right hand side of  $S^*/N^* = 0$ , obtaining

$$(1-p) \left( \mu + \delta \frac{\omega}{\alpha + \mu + \delta} \right) i_1^* - \phi s^* - \beta_1 i_1^* s^* + \gamma_1 i_1^* - \mu s^* = 0.$$

Simplifying, we obtain

$$(1-p)\mu - (\mu + \phi)s^* = \left( \beta_1 s^* - \gamma_1 - (1-p)\omega \frac{\delta}{\alpha + \mu + \delta} \right) i_1^*.$$

Simplifying and putting in terms of  $R_1$ , we obtain the  $s^*$  and  $i_1^*$  from section 3.2. Also,  $c_1^* = C_1^*/N^*$  is found by solving the right hand side of  $C_1^* = 0$ , obtaining

$$c_1^* = \frac{\omega i_1^*}{\alpha + \mu + \delta}.$$

Substituting  $i_1^*$  into the numerator, we obtain  $c_1^*$  in section 3.2.

To find the equilibrium  $E_2$ , we use the following equations,

$$S' + V'|_{I_1=0} = \Lambda - \beta_2 \tilde{I}_2 \left( \frac{S+V}{N} \right) + \gamma_2 (I_2 + V_2) - \mu (S+V)$$

and

$$I_2' + V_2'|_{I_1=0} = \beta_2 \tilde{I}_2 \left( \frac{S+V}{N} \right) - (\mu + \gamma_2) (I_2 + V_2).$$

Setting the right hand sides of each equation to zero and dividing by  $N^*$ , we obtain the proportionalized  $E_2 = s^*, v^*, v_2^*, 0, i_2^*, 0, 0, 0$  below.

$$s^* = \frac{1}{R_2} \frac{(1-p)R_2\mu}{R_2\mu + \phi}, \quad v^* = \frac{1}{R_2} \frac{pR_2\mu + \phi}{R_2\mu + \phi},$$

$$i_2^* = \left( 1 - \frac{1}{R_2} \right) \frac{(1-p)R_2\mu}{R_2\mu + \phi}, \quad v_2^* = \left( 1 - \frac{1}{R_2} \right) \frac{pR_2\mu + \phi}{R_2\mu + \phi}.$$

### A.1.3 Stability Analysis

The full Jacobian matrix for the system, and the full proportionalized Jacobians at the two single-strain equilibria  $E_1$  and  $E_2$ , are given in Table 3.1 and 3.2.

The reduced proportionalized Jacobian for stability/instability of  $E_1$ :

$$\begin{pmatrix} -(\phi + \mu) - \beta_1 i_1(1 - s) & 0 & -\beta_1 s(1 - i_1) + \gamma_1 & 0 \\ \phi & -\mu & 0 & 0 \\ -\beta_1 i_1(1 - s) & 0 & \beta_1 s(1 - i_1) - (\omega + \mu + \gamma_1) & \alpha \\ 0 & 0 & \omega & -(\alpha + \mu + \delta) \end{pmatrix}$$

The reduced proportionalized Jacobian for stability/instability of  $E_2$  is given below.

We make the substitution  $x_2 = i_2 + v_2$  in order for the matrix to fit on one page.

$$\begin{pmatrix} -(\phi + \mu) - \beta_2 x_2(1 - s) & 0 & -\beta_2 s(1 - x_2) & -\beta_2 s(1 - x_2) + \gamma_2 \\ \phi & -\beta_2 x_2(1 - v) - \mu & -\beta_2 v(1 - x_2) + \gamma_2 & -\beta_2 v(1 - x_2) \\ 0 & \beta_2 x_2(1 - v) & \beta_2 v(1 - x_2) - \beta_2 \left(\frac{1}{R_2}\right) & \beta_2 v(1 - x_2) \\ \beta_2 x_2(1 - s) & 0 & \beta_2 s(1 - x_2) & \beta_2 s(1 - x_2) - \beta_2 \left(\frac{1}{R_2}\right) \end{pmatrix}$$

Substituting  $(i_2^* + v_2^*) = 1 - 1/R_2$  and  $1 - (i_2^* + v_2^*) = 1/R_2$  into the above matrix, we obtain:

$$\begin{pmatrix} -(\phi + \mu) - \beta_2(1 - \frac{1}{R_2})(1 - s) & 0 & -\beta_2 s(\frac{1}{R_2}) & -\beta_2 s(\frac{1}{R_2}) + \gamma_2 \\ \phi & -\beta_2(1 - \frac{1}{R_2})(1 - v) - \mu & -\beta_2 v(\frac{1}{R_2}) + \gamma_2 & -\beta_2 v(\frac{1}{R_2}) \\ 0 & \beta_2(1 - \frac{1}{R_2})(1 - v) & \beta_2 v(\frac{1}{R_2}) - \beta_2 \left(\frac{1}{R_2}\right) & \beta_2 v(\frac{1}{R_2}) \\ \beta_2(1 - \frac{1}{R_2})(1 - s) & 0 & \beta_2 s(\frac{1}{R_2}) & \beta_2 s(\frac{1}{R_2}) - \beta_2 \left(\frac{1}{R_2}\right) \end{pmatrix}$$

We utilize the next generation operator method in computing the invasion reproductive number  $\tilde{R}_1$ , where  $E_2$  is considered the disease-free equilibrium. We separate the population into 3 groups. The first group will be the infectious classes  $Z = \{I_1, I_{12}\}$ , the infected but noninfectious classes  $Y = \{C_1, C_{12}\}$ , and the uninfected classes  $X = \{S, V, V_2, I_2\}$ .

We solve the  $Y$  classes in terms of the infected classes  $Z$  to obtain

$$C_1 = \frac{\omega I_1}{\alpha + \mu + \delta} \quad C_{12} = \frac{\omega I_{12}}{\mu + \delta}.$$

We next compute the proportionalized Jacobian for  $Z$ , obtaining

$$\begin{aligned}
J &= M_1 - D_1 \\
&= \begin{pmatrix} \beta_1 s - k\beta_2 \left(1 - \frac{1}{R_2}\right) & \beta_1 s + \gamma_2 \\ k\beta_2 \left(1 - \frac{1}{R_2}\right) + \beta_1 i_2 & \beta_1 i_2 \end{pmatrix} - \begin{pmatrix} \mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega & 0 \\ 0 & \mu + \omega + \gamma_1 + \gamma_2 \end{pmatrix}, \\
M_1 D_1^{-1} &= \begin{pmatrix} \frac{\beta_1 s - k\beta_2 \left(1 - \frac{1}{R_2}\right)}{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega} & \frac{\beta_1 s + \gamma_2}{\mu + \omega + \gamma_1 + \gamma_2} \\ \frac{k\beta_2 \left(1 - \frac{1}{R_2}\right) + \beta_1 i_2}{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega} & \frac{\beta_1 i_2}{\mu + \omega + \gamma_1 + \gamma_2} \end{pmatrix}.
\end{aligned}$$

The dominant eigenvalue then is given in (3.1).

We now consider  $E_1$  as the disease-free equilibrium for our system. We will use the next-generation operator method to determine the invasion reproductive number  $\tilde{R}_2$  for the system. The infectious classes are  $Z = \{V_2, I_2, I_{12}\}$ , infected but not infectious class  $Y = \{C_{12}\}$ , and the uninfected classes  $X = \{S, V, I_1, C_1\}$ . We first solve for  $C_{12}$  in terms of the infected classes  $Z^*$ :

$$C_{12} = \frac{\omega I_{12}}{\mu + \delta}.$$

We then compute the proportionalized Jacobian of  $Z$  at the disease-free equilibrium  $i_1$ , obtaining

$$\begin{pmatrix} \beta_2 v - (\mu + \gamma_2) & \beta_2 v & \beta_2 v \\ \beta_2 s & \beta_2 s - (\mu + \gamma_2) + \beta_1 i_1 & \beta_2 s + \gamma_1 \\ k\beta_2 i_1 & k\beta_2 i_1 + \beta_1 i_1 & -(\mu + \omega + \gamma_1 + \gamma_2) \end{pmatrix}.$$

Next we split the Jacobian into 2 parts,  $J = M_2 - D_2$  where  $M_2$  consists of the nonnegative terms, and  $D_2$  consists of the negative terms along the diagonal.

$$J = \begin{pmatrix} \beta_2 v & \beta_2 v & \beta_2 v \\ \beta_2 s & \beta_2 s + \beta_1 i_1 & \beta_2 s + \gamma_1 \\ k\beta_2 i_1 & k\beta_2 i_1 + \beta_1 i_1 & k\beta_2 i_1 \end{pmatrix} - \begin{pmatrix} (\mu + \gamma_2) & 0 & 0 \\ 0 & (\mu + \gamma_2) & 0 \\ 0 & 0 & (\mu + \omega + \gamma_1 + \gamma_2) \end{pmatrix}.$$

Thus, the invasion reproductive number at  $E_1$  will be  $\rho(M_2D_2^{-1})$ , where  $\rho$  is the dominant eigenvalue of the matrix  $M_2D_2^{-1}$ . We have

$$M_2D_2^{-1} = \begin{pmatrix} \frac{\beta_2v}{\mu+\gamma_2} & \frac{\beta_2v}{\mu+\gamma_2} & \frac{\beta_2v}{\mu+\omega+\gamma_1+\gamma_2} \\ \frac{\beta_2s}{\mu+\gamma_2} & \frac{\beta_2s+\beta_1i_1}{\mu+\gamma_2} & \frac{\beta_2s+\gamma_1}{\mu+\omega+\gamma_1+\gamma_2} \\ \frac{k\beta_2i_1}{\mu+\gamma_2} & \frac{k\beta_2i_1+\beta_1i_1}{\mu+\gamma_2} & \frac{k\beta_2i_1}{(\mu+\omega+\gamma_1+\gamma_2)} \end{pmatrix}.$$

Simplifying,

$$M_2D_2^{-1} = \begin{pmatrix} R_2v & R_2v & \frac{\beta_2v}{\mu+\omega+\gamma_1+\gamma_2} \\ R_2s & R_2s + \frac{\beta_1i_1}{\mu+\gamma_2} & \frac{\beta_2s+\gamma_1}{\mu+\omega+\gamma_1+\gamma_2} \\ kR_2i_1 & kR_2i_1 + \frac{\beta_1i_1}{\mu+\gamma_2} & \frac{k\beta_2i_1}{(\mu+\omega+\gamma_1+\gamma_2)} \end{pmatrix}.$$

Again, we can simplify by letting  $b_1 = \frac{\beta_1}{\beta_2}$ , thus  $\frac{\beta_1i_1}{\mu+\gamma_2} = b_1R_2i_1$  and  $h = \frac{\mu+\gamma_2}{\mu+\gamma_2+\gamma_1+\omega} < 1$ .

Thus, the matrix in simplified form is,

$$M_2D_2^{-1} = R_2 \begin{pmatrix} v & v & v h \\ s & s + b_1i_1 & s h + \frac{\gamma_1}{R_2} \\ ki_1 & ki_1 + b_1i_1 & k h i_1 \end{pmatrix}$$



**APPENDIX B**  
**CODE FOR NUMERICAL SIMULATIONS**

### Definition of Parameters

$$p=0;$$

$$\text{Lambda}=2235773;$$

$$\text{mu}=1/45;$$

$$\text{delta}=.0998;$$

$$g1=.876;$$

$$g2=.811;$$

$$\text{alpha}=.315;$$

$$\text{omega}=.0172;$$

$$\text{phi}=.007;$$

$$k=6;$$

### Reproductive Numbers and Equilibria

$$\begin{aligned} R1[b1\_]&:=b1/(\text{mu}+g1+((\text{mu}+\text{delta})/(\text{alpha}+\text{mu}+\text{delta}))^*\text{omega}) \\ &(1-p)^*\text{mu})/(\text{phi}+\text{mu}) \\ R2[b2\_]&:=b2/(\text{mu}+g2) \\ \text{thematrix}[b1\_ , b2\_]&:=\{\{R2[b2]^*v1[b1], R2[b2]^*v1[b1], (b2^*v1[b1])/ \\ &(\text{mu}+\text{omega}+g1+g2)\}, \{R2[b2]^*s1[b1], R2[b2]^*s1[b1]+(b1^*i1[b1])/(\text{mu}+g2), \\ &(b2^*s1[b1]+g1)/(\text{mu}+\text{omega}+g1+g2)\}, \{k^*R2[b2]^*i1[b1], k^*R2[b2]^*i1[b1]+ \\ &(b1^*i1[b1])/(\text{mu}+g2), (k^*b2^*i1[b1])/(\text{mu}+\text{omega}+g1+g2)\}\} \\ d[b1\_ , b2\_]&:=\text{Max}[\text{Re}[\text{Eigenvalues}[\text{thematrix}[b1, b2]]]] \\ R2\text{tilde}[b1\_ , b2\_]&:=d[b1, b2] \\ \text{theothermatrix}[b1\_ , b2\_]&:= \\ &\{\{(b1^*s2[b2]-k^*b2^*(1-1/R2[b2]))/(\text{mu}+g1+((\text{mu}+\text{delta})/(\text{alpha}+\text{mu}+\text{delta}))^*\text{omega}, \\ &(b1^*s2[b2]+g2)/(\text{mu}+\text{omega}+g1+g2)\}, \{(k^*b2^*(1-1/R2[b2])+b1^*i2[b2])/(\text{mu}+g1+ \\ &((\text{mu}+\text{delta})/(\text{alpha}+\text{mu}+\text{delta}))^*\text{omega}), (b1^*i2[b2])/(\text{mu}+\text{omega}+g1+g2)\}\} \\ \text{num}&:=\text{mu}+g1+((\text{mu}+\text{delta})/(\text{alpha}+\text{mu}+\text{delta})) \text{omega} \end{aligned}$$

```

den:=mu+g1+g2+omega

theothermatrix2[b1_,b2_] := {{R1[b1] ((mu+phi)/(R2[b2] mu+phi)) ( num/
(num+k b2 (1-1/R2[b2]))) , R1[b1] ((mu+phi)/(R2[b2] mu+phi)) (num/den)+g2/den},
{R1[b1] ((mu+phi)/(R2[b2] mu+phi)) (num/(num+k b2 (1-1/R2[b2]))) (R2[b2]-1)+(k b2
(1-1/R2[b2]))/(num+k b2 (1-1/R2[b2])), R1[b1] ((mu+phi)/(R2[b2] mu+phi)) (num/den)
(R2[b2]-1)}}

e[b1_,b2_] := Max[Re[Eigenvalues[theothermatrix[b1,b2]]]]
f[b1_,b2_] := Max[Re[Eigenvalues[theothermatrix2[b1,b2]]]]
R1tilde[b1_,b2_] := e[b1,b2]
R1tilde2[b1_,b2_] := f[b1,b2]
s1[b1_] := (((1 - p)*mu)/(mu + phi))*(1/R1[b1])
v1[b1_] := p+(1-p) (1/R1[b1])(phi/(phi+mu))+ (1-p) (1-1/R1[b1])
((omega*p delta)/(alpha+mu+delta))/((mu+(mu+p delta)
omega)/(alpha+mu+delta))
i1[b1_] := (1-p) (1-1/R1[b1]) (mu/(mu+((mu+p delta) omega)/(alpha+mu+
delta)))
c1[b1_] := (1-p)(1-1/R1[b1])*((omega mu)/(alpha+mu+delta))/
(mu+((mu+p delta) omega)/(alpha+mu+delta))
NNstar1[b1_] := Lambda/(mu+delta c1[b1])
E1[b1_] = {s1[b1],v1[b1],0,i1[b1],0,0,c1[b1],0}
s2[b2_] := (1/R2[b2])*((1-p)*R2[b2]*mu)/(R2[b2]*mu+phi)
v2[b2_] := (1/R2[b2])* (p*R2[b2]*mu+phi)/(R2[b2]*mu+phi)
i2[b2_] := (1-1/R2[b2])*((1-p)*R2[b2]*mu)/(R2[b2]*mu+phi)
v22[b2_] := (1-1/R2[b2])* (p*R2[b2]*mu+phi)/(R2[b2]*mu+phi)
NNstar2 := Lambda/mu

```

```

E3[b1_,b2_] := NSolve[{nn == S + V + V2 + I1 + I2 + I12 + C1 + C12, (1 - p) * Lambda -
(phi + mu) * S - (b2 * (I2 + I12 + V2) * S) / nn - (b1 * (I1 + I12) * S) / nn + g1 * I1 + g2 * I2 == 0,
p * Lambda + phi * S - (b2 * (I2 + I12 + V2) * V) / nn + g2 * V2 - mu * V == 0,
(b2 * (I2 + V2 + I12) * V) / nn - (mu + g2) * V2 == 0,
(b1 * (I1 + I12) * S) / nn - (k * b2 * (I2 + I12 + V2) * I1) / nn - (omega + mu + g1) * I1 + alpha *
C1 + g2 * I12 == 0,
(b2 * (I2 + I12 + V2) * S) / nn - (b1 * (I1 + I12) * I2) / nn - (mu + g2) * I2 + g1 * I12 == 0,
(k * b2 * (I2 + V2 + I12) * I1) / nn + (b1 * (I1 + I12) * I2) / nn - (mu + omega + g1 + g2) * I12 == 0,
omega * I1 - (alpha + mu + delta) * C1 == 0,
omega * I12 - (mu + delta) * C12 == 0}, {S, V, V2, I1, I2, I12, C1, C12, nn}];

```

```

posE3[b1_, b2_] := Select[{S, V, V2, I1, I2, I12, C1, C12, nn} /. E3[b1, b2],
(Im#[[1]] == 0. && Im#[[2]] == 0. && Im#[[3]] == 0. && Im#[[4]] == 0. &&
Im#[[5]] == 0. && Im#[[6]] == 0. && Im#[[7]] == 0. && Im#[[8]] == 0. &&
Im#[[9]] == 0. && Re#[[1]] >= 0. && Re#[[2]] >= 0. && Re#[[3]] >= 0. &&
Re#[[4]] >= 0. && Re#[[5]] >= 0. && Re#[[6]] >= 0. && Re#[[7]] >= 0. &&
Re#[[8]] >= 0. && Re#[[9]] >= 0. &)]

```

```

E2[b2_] := {s2[b2], v2[b2], v22[b2], 0, i2[b2], 0, 0, 0}

```

### The General Jacobian

```

genJac[seq_, veq_, v2eq_, i1eq_, i2eq_, i12eq_, c1eq_, c12eq_, b1_, b2_] :=
{{-(phi + mu) - (b2 * (i2eq + i12eq +
v2eq) * (1 - seq)) - (b1 * (i1eq + i12eq) * (1 - seq)), 0, -(b2 * seq * (1 - (i2eq + v2eq + i12eq))),
-(b1 * seq * (1 - (i1eq + i12eq))) + g1,
-(b2 * seq * (1 - (i2eq + v2eq + i12eq))) + g2,
-(b2 * seq * (1 - (i2eq + i12eq + v2eq))) - (b1 *
seq * (1 - (i1eq + i12eq))), 0, 0},
{phi, -(b2 * (i2eq + i12eq + v2eq) * (1 - veq)) - mu, -(b2 * veq * (1 - (i1eq + i12eq + v2eq)))}

```

```

+g2, 0, -(b2*veq*(1-(i2eq+v2eq+i12eq))), -(b2*veq*(1-(i2eq+v2eq+i12eq))), 0,
0},
{0, b2*(i2eq+i12eq+v2eq)*(1-veq), b2*veq*(1-(i2eq+i12eq+v2eq))-(mu+g2), 0,
b2*veq*(1-(i2eq+i12eq+v2eq)), b2*veq*(1-(i2eq+i12eq+v2eq)), 0, 0},
{b1*(i1eq+i12eq)*(1-seq), 0, -(k*b2*i1eq*(1-(i2eq+i12eq+v2eq))), b1*seq*(1-
(i1eq+i12eq))-(k*b2*(i2eq+i12eq+v2eq)*(1-i1eq))-(omega+mu+g1), -(k*b2*
i1eq*(1-(i2eq+v2eq+i12eq))), b1*seq*(1-(i1eq+i12eq+v2eq))-
(k*b2*i1eq*(1-(i2eq+ v2eq+i12eq)))+g2, alpha, 0},
{b2*(i2eq+v2eq+i12eq)*(1-seq), 0, b2*seq*(1- (i2eq+i12eq+v2eq)),
-(b1*i2eq*(1-(i1eq+i12eq))), b2*seq*(1-(i2eq+i12eq+v2eq))-
(b1*(i1eq+i12eq)*(1-i2eq))-(mu+g2), b2*seq*(1-(i2eq+i12eq+v2eq))-(b1*
i2eq*(1-(i1eq+i12eq)))+g1, 0, 0},
{0,0, k*b2*i1eq*
(1-(i2eq+v2eq+i12eq)), k*b2*(i2eq+v2eq+i12eq)*(1-i1eq)+(b1*i2eq*
(1-(i1eq+i12eq))), k*b2*i1eq*
(1-(i2eq+v2eq+i12eq))+(b1*(i1eq+i12eq)*(1-i2eq)),
k*b2*i1eq*(1-(i2eq+v2eq+i12eq))+b1*i2eq*(1-(i1eq+i12eq))-(mu+omega+
g1+g2),
0,0},
{0, 0, 0, omega, 0, 0, -(alpha+mu+delta), 0},{0, 0, 0, 0, 0, omega, 0, -(mu+delta)}}

```

**Code used to generate the graph in Figure 3.1**

```

b1crit=b1/.Solve[R1[b1]==1,b1][[1]]
b2crit=b2/.Solve[R2[b2]==1,b2][[1]]
R1is1=Plot[b2crit,b1,0,b1crit,PlotStyle Dashing[{0.01,0.01}],
AxesLabel {b1,b2}]

```

```

R2is1=ParametricPlot[{b1crit,b2},{b2,0,b2crit},PlotStyle->
Dashing[{0.01,0.01}], AxesLabel {b1,b2}]
R2tildeis1=Plot[(mu+g2)/(s1[b1]+v1[b1]+k i1[b1]),{b1,b1crit,2}]
R1tildeis1=ContourPlot[R1tilde2[b1,b2],{b1,0.0000001,2.5},{b2,b2crit,5},
ContourShading False,Contours {1},PlotPoints20]
NiceGraph=Show[R1is1,R2is1,R2tildeis1,R1tildeis1,ASYMP,
ASYMP2,PlotRange {{0,2},{0,2}}]

```

### The ODEs

```

odes:={S'[t]==(1-p) Lambda-phi S[t]-(B2 (I2[t]+V2[t]+I12[t]) S[t])/NN[t]-(B1
(I1[t]+I12[t]) S[t])/NN[t]+g1 I1[t]+g2 I2[t]-mu S[t],
V'[t]==p Lambda+phi S[t]-(B2 (I2[t]+V2[t]+I12[t]) V[t])/NN[t]+g2 V2[t]-mu V[t],
V2'[t]==(B2 (I2[t]+V2[t]+I12[t]) V[t])/NN[t]-(mu+g2) V2[t],
I1'[t]==(B1 (I1[t]+I12[t]) S[t])/NN[t]-(k B2 (I2[t]+V2[t]+I12[t]) I1[t])/NN[t]-(omega+
mu+g1) I1[t]+alpha C1[t]+g2 I12[t],
I2'[t]==(B2 (I2[t]+V2[t]+I12[t]) S[t])/NN[t]-(B1 (I1[t]+I12[t]) I2[t])/NN[t]-(mu+g2)
I2[t]+g1 I12[t],I12'[t]==(k B2 (I2[t]+V2[t]+I12[t]) I1[t])/NN[t]+(B1 (I1[t]+I12[t])
I2[t])/NN[t]-(mu+omega+g1+g2) I12[t],
C1'[t]==omega I1[t]-(alpha+mu+delta) C1[t],
C12'[t]==omega I12[t]-(mu+delta) C12[t],
NN'[t]==Lambda-mu NN[t]-delta (C1[t]+C12[t]),S[0]==S0,V[0]==V0,V2[0]==V20,
I1[0]==I10,I2[0]==I20,I12[0]==I120,C1[0]==C10,C12[0]==C120,NN[0]==NN0}

Clear[p]

Clear[phi]

phitop=1/2;

phistep=.1;

pstep=.1;

```

```

I1tilde=ConstantArray[0,{Round[phitop/phistep+1],Round[1/pstep+1]]
Clear[p]
Clear[phi]
phitop=1/4;
phistep=.05;
pstep=.1;
pcountmax=Round[1/pstep];
phicountmax=Round[phitop/phistep];
I1tilde2=ConstantArray[0,{(pcountmax+1)*(phicountmax+1),3}];
For[phicount=0, phicount≤ phicountmax,phicount++,
For[pcount=0,pcount≤ pcountmax,pcount++,phi=phicount*phistep;
p=pcount*pstep;
ans=NDSolve[odes,{S,V,V2,I1,I2,I12,C1,C12,NN},{t,0,100}];
i1=(((I1[v]+I12[v])/ .ans)/ .{v→99});
I1tilde2[[phicount*(pcountmax+1)+pcount+1]]={phi,p,i1[[1]]};];
ListPlot3D[I1tilde2,PlotRange→ All,AxesLabel→ {phi,p,I1tilde2}]

```

## MATLAB Code

### Simulations Run Without Strain 2

```

% No strain 2⇒x(3),x(5),x(6),x(8) do not exist
function dx=HPV2(t,x)
%S in system is x(1)
%V in system is x(2)
%V2 in system is x(3)
%I1 in system is x(4)

```

```

%I2 insystem is x(5)
%I12 in system is x(6)
%C1 in system is x(7)
%C12 in system is x(8)

global p Lambda beta1 beta2 gamma1 gamma2 phi alpha omega k mu delta
N=x(1)+x(2)+x(3)+x(4)+x(5)+x(6)+x(7)+x(8); x(3)=0; x(5)=0; x(6)=0; x(8)=0;

dx=[(1-p)*Lambda-(phi+mu)*x(1)-(beta2*(x(3)+x(5)+x(6))*x(1))/N-(beta1*
(x(4)+x(6))*x(1))/N+gamma1*x(4)+gamma2*x(5);
p*Lambda+phi*x(1)-(beta2*(x(3)+x(5)+x(6))*x(2))/N+gamma2*x(3)-mu*x(2);
(beta2*(x(3)+x(5)+x(6))*x(2))/N-(mu+gamma2)*x(3);
(beta1*(x(4)+x(6))*x(1))/N-k*(beta2*(x(3)+x(5)+x(6))*x(4))/N-(omega+mu+
gamma1)*x(4)+alpha*x(7)+ gamma2*x(6);
(beta2*(x(3)+x(5)+x(6))*x(1))/N-(beta1*(x(4)+x(6))*x(5))/N-(mu+gamma2)*x(5)
+gamma1*x(6);
(k*beta2*(x(3)+x(5)+x(6))*x(4))/N+(beta1*(x(4)+x(6))*x(5))/N-(mu+omega+
gamma1+gamma2)*x(6);
omega*x(4)-(alpha+mu+delta)*x(7);
omega*x(6)-(mu+delta)*x(8);
omega*(x(4)+x(6));
delta*(x(7)+x(8)); beta1*(x(4)+x(6))*(x(1)+x(5))/N];

```

### Simulations Run With Strain 2

```

function dx=HPV2(t,x)
%S in system is x(1)
% V in system is x(2)
%V2 in system is x(3)

```



```

%I1 in system is x(4)
%I2 in system is x(5)
%I12 in system is x(6)
%C1 in system is x(7)
%C12 in system is x(8)

global p Lambda beta1 beta2 gamma1 gamma2 phi alpha omega k mu delta
N=x(1)+x(2)+x(3)+x(4)+x(5)+x(6)+x(7)+x(8);
dx=[(1-p)*Lambda-(phi+mu)*x(1)-(beta2*(x(3)+x(5)+x(6))*x(1))/N-(beta1*
(x(4)+x(6))*x(1))/N+gamma1*x(4)+gamma2*x(5);
p*Lambda+phi*x(1)-(beta2*(x(3)+x(5)+x(6))*x(2))/N+gamma2*x(3)-mu*x(2);
(beta2*(x(3)+x(5)+x(6))*x(2))/N-(mu+gamma2)*x(3);
(beta1*(x(4)+x(6))*x(1))/N-k*(beta2*(x(3)+x(5)+x(6))*x(4))/N-(omega+mu+
gamma1)*x(4)+alpha*x(7)+ gamma2*x(6);
(beta2*(x(3)+x(5)+x(6))*x(1))/N-(beta1*(x(4)+x(6))*x(5))/N-(mu+gamma2)*x(5)
+gamma1*x(6);
(k*beta2*(x(3)+x(5)+x(6))*x(4))/N+(beta1*(x(4)+x(6))*x(5))/N-(mu+omega+
gamma1+gamma2)*x(6);
omega*x(4)-(alpha+mu+delta)*x(7);
omega*x(6)-(mu+delta)*x(8);
omega*(x(4)+x(6));
delta*(x(7)+x(8)); beta1*(x(4)+x(6))*(x(1)+x(5))/N];

```

### ODE Solver Using Parameter Estimates

The parameter estimates can be changed to consider no vaccination, or 50 percent vaccination coverage as stated in the numerical simulation section.

```

tf = 100; p = .5; Lambda = 2235773; mu = 1/44; beta1 = 1.2; beta2 = (11/14)*beta1;
gamma1=.709; gamma2=.816; alpha = .315; omega = .0172; phi = 007; k = 6; delta

```

```
= .0998;  
R1 =beta1/(mu+gamma1+((mu+delta)/(alpha+mu+delta))*omega)*((1-p)*mu)/  
(phi+mu)  
R2 = beta2/(mu+gamma2)  
tspan = [0,tf];% y0 = [50304907;0;0;1509146;0;500000;0;0;0;0;0]  
%choose initial condition for I1 based on study where currently 1.5% of  
population is infected with HPV16  
[t,z]=ode45('HPV2',tspan,y0);  
plot(t,z(:,4)+z(:,6),'y',t,z(:,5)+z(:,6),'b',t,z(:,7),'g',t,z(:,8),'r')
```

## REFERENCES

- [1] Bosch, F.X., Lorincz, A., Munoz, Meijer, C.J., Shah, K.V.. The Causal Relation Between Human Papillomavirus and Cervical Cancer. *Journal of Clinical Pathology*, 55(2002) 244.
- [2] Moscicki, A., Schiffman, M., Kjaer, S., Villa, L.L.. Chapter 5: Updating the Natural History of HPV and Anogenital Cancer. *Vaccine*, 24S2(2006) 42–51.
- [3] Rousseau M., Abrahamowicz M., Villa L.L, Costa, M.C., Rohan, T.E., and Franco, E.L..Predictors of Cervical Coinfection with Multiple Human Papillomavirus Types. *Cancer Epidemiology, Biomarkers and Prevention* 12 (2003) 1029–1037.
- [4] Marie-Claude Rousseau, Luisa L. Villa, Maria Cecillia Costa, Michal Abrahamowicz, Thomas E. Rohan, and Eduardo Franco. Occurrence of Cercical Infection with Multiple Human Papillomavirus Types is Associated with Age and Cytologic Abnormalities. *Sexually Transmitted Diseases* 30 (2003) 581–587.
- [5] Liaw K.L., Hildesheim, A., Burk R., Gravitt P., Wacholder S. et al. A prospective study of human papillomavirus (HPV) type 16 DNA detection by polymerase chain reaction and its association with acquisition and persistence of other HPV types. *J. Infect. Dis*, 183 (2001) 8–15.
- [6] Merck & Co., Inc. GARDASIL [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine] (2006), Merck & Co., Inc, Whitehouse Station, NJ 08889, USA  
  
(<http://today.reuters.co.uk/news/articleinvesting.aspx?view=PR&symbol=MRK.N&storyID=285300+09-May-2007+BW&type=qcna>).

- [7] Moscicki, A., Impact of HPV Infection in Adolescent Populations. *Journal of Adolescent Health*, 27(2005) S3–S9.
- [8] Trottier, H., Franco, E. The epidemiology of genital human papillomavirus infection. *Vaccine*, 24S1 (2006) 4–15.
- [9] Allen, L., Langlais, M., Phillips, C.J. The Dynamics of Two Viral Infections in a Single Host Population with Applications to Hantavirus, *Mathematical Biosciences* 186 (2003) 191–217.
- [10] O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz, On the definition and the computation of the basic reproduction ratio  $R_0$  in models for infectious diseases in heterogeneous population, *J Math Biol* 28 (1990) 365–382.
- [11] Castillo-Chávez, C., Z. Feng and W. Huang, On the computation of  $R_0$  and its role on global stability, in *Mathematical Approaches for Emerging and Reemerging Infectious Diseases: An Introduction*, ed. Carlos Castillo-Chavez, Sally Blower, Pauline van den Driessche, Denise Kirschner and Abdul-Aziz Yakubu (IMA Vol. 125). Berlin: Springer-Verlag, 2002. pp. 224–250.
- [12] U.S. Census Bureau, Table 1: Annual Estimates of the Population by Five-Year Age Groups and Sex for the United States: April 1, 2000 to July 1, 2006 (NC-EST2006-01)(2007), 25 March 2008, (<http://www.census.gov/popest/national/asrh/NC-EST2006-sa.html>).
- [13] Bachtiry, B., Obermair, A., Dreier, B., Birner, P., Breitenecker, G., Knocke, T.H., Selzer, E., Pötter. Impact of Multiple HPV Infection on Response to Treatment and Survival in Patients Receiving Radical Radiotherapy for Cervical Cancer. *Int. J. Cancer* 102(2002) 237–243.
- [14] Zhang, P., Sandland, G.J., Zhilan, F., Xu, D., Minchella, D.J., Evolutionary Implications for Interactions Between Multiple Strains of Host and Parasite, *Journal of Theoretical Biology*. 248(2007) 225–240.

- [15] Porco, T.C. and Blower, S.M., Designing HIV vaccination policies: subtypes and cross-immunity. *Interfaces* 28/3 (1998),167–190
- [16] Méndez, F., Muñoz, N. Posso, H., Molano, M., Moreno, V., J.C. van den Bruele, A., Ronderos, M., Meijer, C., Muñoz, A.. Cervical Coinfection with Human Papillomavirus (HPV) Types and Possible Implications for the Prevention of Cervical Cancer by HPV Vaccines. *The Journal of Infectious Diseases* 192(2005) 1158–1165.
- [17] Dunne, EF., Unger, ER., Sternberg, M. et al. Prevalence of HPV infection among females in the United States, *JAMA*. 297(2007) 813–819.
- [18] Green A., Nieves, Y., Enrigue, C., Kribs-Zaleta, C., Crawford, B. A Cost Analysis of Human Papillomavirus: Individual Education vs. Mass-Media Campaign, *MTBI Technical Report MTBI-04-03M*,2007
- [19] Muñoz, N., Méndez, F., Posso, H., Molano, M., J.C. van den Brule, A., Ronderos, M., Meijer, C., Muñoz, A.. Incidence, Duration, and Determinants of Cervical Human Papillomavirus Infection in a Cohort of Colombian Women with Normal Cytological Results. *The Journal of Infectious Diseases*. 190(2004) 2077–2087.
- [20] Elbasha, E.H., Galvani, A.P. Vaccination Against Multiple HPV Types. *Mathematical Biosciences*, 197(2005) 88–117.
- [21] American Cancer Society. Cancer Facts and Figures 2006. 2006,25 March 2008, (<http://www.cancer.org/downloads/STT/CAFF2006PWSecured.pdf>).
- [22] Nuño M.,Chowell G., Wang X., Castillo-Chavez C., On the Role of Cross-Immunity and Vaccines on the Survival of Less Fit Flu Strains.,*Theoretical Population Biology*,71 (2007) 20–29.
- [23] Barnabas, R.V., Laukkanen, P., Koskela, P., Kontula, O., Lehtinen, M., Garnett, G.P. Epidemiology of HPV 16 and Cervical Cancer in Finland and the Poten-

tial Impact of Vaccination: Mathematical Modelling Analyses. *PLOS Medicine*, 3(2006)624–632.

- [24] Centers for Disease Control and Prevention (CDC), Estimates of Influenza Vaccination Target Population Sizes in 2006 and Recent Vaccine Uptake Levels (2006), 25 March 2008, (<http://www.cdc.gov/flu/professionals/vaccination/pdf/targetpopchart.pdf>)
- [25] Khan, M.J., Castle, P.E., Lorincz, A.T., Wacholder, S., Sherman, M., Scott, D.R., Rush, B.B., Glass, A.G., Schiffman, M.. The Elevated 10-Year Risk of Cervical Cancer in Women With the Human Papillomavirus (HPV) Type 16 or 18 and the Possible Utility of Type-Specific HPV Testing in Clinical Practice. *Journal of the National Cancer Institute*, 97 (2005) 1072–1079.

## **BIOGRAPHICAL STATEMENT**

Britnee A. Crawford was born in Plano, Texas in 1983. She received her B.S. degree from Dallas Baptist University in 2005 and her M.S. degree from The University of Texas at Arlington in 2008, all in Mathematics. In 2005, she joined Grace Preparatory Academy in Arlington, Texas as a secondary math teacher teaching Pre-calculus and Calculus. Her current research interests are in the field of mathematical biology and epidemiology. She is currently pursuing her Ph.D from The University of Texas at Arlington