THE IMPACT OF VACCINATION AND COINFECTION ON HPV AND CERVICAL CANCER

Britnee Crawford and Christopher M. Kribs Zaleta
University of Texas at Arlington
Box 19408
Arlington, TX 76019-0408, USA

Abstract. Understanding the relationship between coinfection with 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 (strain 1, oncogenic) 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 $R_0$ 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 $R_i$ for strain $i$ when strain $j$ is at endemic equilibrium ($i \neq j$). We show that the disease-free equilibrium is locally stable when $R_0 < 1$ and each single strain endemic equilibrium $E_i$ exists when $R_i > 1$. We determine stability of the single strain equilibria using the invasion reproductive numbers. The $R_1, R_2$ parameter space is partitioned into 4 regions by the curves $R_1 = 1$, $R_2 = 1$, $R_1 = 1$, and $R_2 = 1$. 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 strain 2 prevalence 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.

1. Introduction. 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 in the U.S. 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 about 70 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]. In addition, a vaccine called Cervarix marketed by
GlaxoSmithKline which protects against types 16 and 18 has been approved for use in Europe and adopted by the U.K. public health system. Some state legislatures in the U.S. have attempted to implement mandatory vaccination policies for Gardasil for young women, but due to controversy over vaccinating children against sexually transmitted infections, few have been successful. Currently, voluntary 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 percent of women with cervical infections have more than one type of HPV. 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.

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. One study on the dynamics of two viral infections considered cross-immunity and coinfection in an $SI$ model where individuals can be infected with one or both of the two viruses. This study found that even with cross-immunity in both directions, both diseases can be maintained in the population simultaneously, and if immunity is low enough then individual coinfection is possible.

Another study describes effects of two competing flu strains characterized by cross-immunity. Nuño focuses on whether or not a new strain can successfully invade an established strain in the presence of cross-immunity. Again, results indicate that coexistence is possible when cross-immunity is low.

Several studies have been written on vaccination and HPV. One study on a single strain of HPV where vaccination strategies are in effect compared the cost and efficacy of two vaccination strategies: mass vaccination and public education campaigns encouraging voluntary vaccination. A second paper considered coinfection with two strains of HPV, with the possibility of vaccination against either type but not both types. The model uses an $SIR$ infection cycle for each strain as well as the possibility for cross-immunity. Here 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 two cocirculating strains through the lens of scenarios where the strains are competing or synergistic, and concludes that if mass vaccination is implemented against one strain, then due to competition the second strain will take the place of the first in the population. Thus, vaccination may not have an overall positive effect on reducing the prevalence of HPV if strains are competing. However, if instead the strains are mutualistic, the authors found 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.

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 [3, 4, 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. First, 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. A second reason for increased likelihood of HPV coinfections is that the first infection may produce effects which increase a person’s susceptibility to further infection. In a study involving a cohort of Brazilian women, the highest prevalence of HPV coinfection occurred among women with LSIL (low-grade squamous intraepithelial lesions) [4], which is typically caused by viral infection. Although in fact both reasons may come into play, in our study we focus on this 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] than women infected with only one strain. The researchers concluded that the presence of multiple HPV types is associated with poor prognosis in patients with 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. What effect does a second strain of HPV which prevents recovery from cancer due to coinfection with an oncogenic strain 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.

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, females vaccinated for strain 1 but infected with strain 2, females infected with strain 1, or strain 2, or 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.

We also wish to discuss the clinical issues of recovery versus recurrence (latency) for HPV infections. At this point it remains unclear whether a woman actually clears an HPV infection or it becomes latent, as clinical studies have been unable to determine if reappearance of a particular strain of HPV is actually a new infection, or rather 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 question also remains unanswered. Trottier and Franco reviewed studies which address the type-specific immunity of HPV [8], and found 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, with the second peak in the curve suggesting the possibility of reinfection. Given this uncertainty, our study assumes that reinfection with the same type can occur.

A person can enter the vaccinated class in two different ways. A person may enter the population directly into the vaccinated class, due to a mass 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 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. Those who do become so infected then move to the $V_2$ class. The women in the $V_2$ class have strain 2, but cannot contract strain 1. Also, a woman can move from the infected $I_2$ class to the $V_2$ class if she is vaccinated against strain 1. In this study, we also consider voluntary vaccination, at a per capita rate $\phi$ from the $S$ class to the $V$ class (or from $I_2$ to $V_2$). 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, $C_{12}$, or remain in this class until natural mortality. We further note that progression to cervical cancer from $I_{12}$ is due to strain 1.

We assume that a woman can become infected with strain 1 at a rate of $\beta_1$ and infected with strain 2 at a rate of $\beta_2$. Although these infections come from sexual contact with males, we do not consider the population of males in this study. There
have not been many studies on male HPV infection rates. Thus, we assume that the dynamics between males and females in the population will be symmetric. We also assume that the majority in the network of sexual contacts will not be in long-term monogamous relationships, thereby preserving the homogeneity of the system.

For our model, we consider strain 1 to be the oncogenic HPV type 16 and 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 Bachtiary 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 \( I_1 \) 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 (9) as the sum of (1–8).

\[
S' = (1 - p)\Lambda - \phi S - \frac{\beta_2 \hat{I}_2 S}{N} - \frac{\beta_1 \hat{I}_1 S}{N} + \gamma_1 I_1 + \gamma_2 I_2 - \mu S \tag{1}
\]

\[
V' = p\Lambda + \phi S - \frac{\beta_2 \hat{I}_2 V}{N} + \gamma_2 V_2 - \mu V \tag{2}
\]

\[
V_2' = \frac{\beta_2 \hat{I}_2 V}{N} - (\mu + \gamma_2)V_2 + \phi I_2 \tag{3}
\]

\[
I_1' = \frac{\beta_1 \hat{I}_1 S}{N} - k\frac{\beta_2 \hat{I}_2 S}{N} - (\omega + \mu + \gamma_1)I_1 + \alpha C_1 + \gamma_2 I_{12} \tag{4}
\]

\[
I_2' = \frac{\beta_2 \hat{I}_2 S}{N} - \frac{\beta_1 \hat{I}_1 I_1}{N} - (\mu + \gamma_2 + \phi)I_2 + \gamma_1 I_{12} \tag{5}
\]

\[
I_{12}' = k\frac{\beta_2 \hat{I}_2 I_1}{N} + \frac{\beta_1 \hat{I}_1 I_2}{N} - (\mu + \omega + \gamma_1 + \gamma_2)I_{12} \tag{6}
\]

\[
C_1' = \omega I_1 - (\alpha + \mu + \delta)C_1 \tag{7}
\]

\[
C_{12}' = \omega I_{12} - (\mu + \delta)C_{12} \tag{8}
\]

\[
N' = \Lambda - \mu N - \delta(C_1 + C_{12}) \tag{9}
\]

where \( \hat{I}_1 = I_1 + I_{12} \) \( \hat{I}_2 = I_2 + V_2 + I_{12} \). Figure 1 gives a graphical interpretation of equations (1–8).

3. Qualitative 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 is \( E_0 = \)
(S*, V*, 0, 0, 0, 0, 0, 0), given by
\[ \frac{\Lambda}{\mu} \left( \frac{(1-p)\mu}{\phi + \mu} + \frac{p\mu + \phi}{\phi + \mu} \right). \]

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 (normally without control measures, but we use the term here to distinguish it from other reproductive numbers defined below). 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 matrix method [26]. Calculations for \( R_0 \) are given in Appendix 1. We find \( R_0 = \max\{R_1, R_2\} \), where
\[ R_1 = \frac{\beta_1}{\mu + \gamma_1 + \frac{\mu + \phi}{\alpha + \mu + \omega}} \left( \frac{(1-p)\mu}{\phi + \mu} \right), \quad R_2 = \frac{\beta_2}{\mu + \gamma_2}. \]

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 moving from \( I_1 \) 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 \( I_2 \).
**Theorem 3.1.** 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 matrix method.

We also show that the disease-free equilibrium is globally asymptotically stable under certain conditions by constructing an appropriate Lyapunov function. The proof is given in Appendix 1.

**Theorem 3.2.** The disease-free equilibrium $E_0$ is globally asymptotically stable if $\beta_1 < \mu + \gamma_1$, $\beta_2 < \mu + \gamma_2$, and $\beta_1 + \beta_2 < \mu + \omega$.

### 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

$$N^* = \frac{\Lambda}{\mu + \delta c_1^*} s^* = (1 - p) \frac{1}{R_1} \frac{\mu}{\mu + \phi},$$

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

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

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

Note that this equilibrium makes biological sense only when $R_1 > 1$. We see that the equilibrium $E_1$ breaks the population into several 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. Of those uninfected, we see from the $s^*$ term that a portion of the population remain in that class until death (or aging out of the population), represented by $\frac{\mu}{\mu + \omega}$. Thus, in the $v^*$ term we see the proportion of the uninfected population getting vaccinated, represented by $\frac{\phi}{\mu + \omega}$. 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 $\frac{\mu}{\mu + \phi + \omega}$. 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 $p\frac{\delta}{\mu + \omega}$ 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 are replaced demographically with vaccinated ($V$) individuals.

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

\begin{align*}
  s^* &= \frac{1}{R_2} (1-p) \frac{\mu + \gamma_2 \left(1 - \frac{1}{R_2}\right) \frac{\beta_2}{\beta_2 + \phi}}{(\mu + \phi) \frac{1}{R_2} + (\mu + \gamma_2) \left(1 - \frac{1}{R_2}\right)}, \\
  v^* &= \frac{1}{R_2} \left[p + (1-p) \frac{\phi \frac{1}{R_2} + \gamma_2 \left(1 - \frac{1}{R_2}\right) \frac{\phi + \beta_2 \phi}{\phi + \beta_2}}{(\mu + \phi) \frac{1}{R_2} + (\mu + \gamma_2) \left(1 - \frac{1}{R_2}\right)}\right], \\
  v_2^* &= \left(1 - \frac{1}{R_2}\right) - i_2^*, \quad i_2^* = \left(1 - \frac{1}{R_2}\right) (1-p) \frac{\beta_2}{\beta_2 + \phi} \frac{\mu}{\mu + \phi}.
\end{align*}

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 \(R_2 > 1\).

The \(E_2\) equilibrium can be interpreted term by term similarly to those for \(E_1\) above. The work for \(E_1\) and \(E_2\) is given in Appendix 2.

We also mention the possibility of one or more endemic equilibria \(E_3\), although we only see one in our numerical simulations. 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 coexistence equilibrium is investigated numerically in the next section.

The invasion reproductive number has mostly been used in studies where competitive exclusion exists between multiple strains [14, 15]. 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 [14, 15]. 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 a 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 \(\bar{R}_1\) 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 of strain 2. \(\bar{R}_2\) is defined similarly.

\(\bar{R}_1\) can be found via the next generation matrix method at \(E_2\), where we determine the dominant eigenvalue of the matrix \(F_1V_1^{-1}\) [26]. This method assumes \(R_2 > 1\) implicitly.
As shown in Appendix 3, we find the dominant eigenvalue of $F_1 V_1^{-1}$ is given by

$$
\tilde{R}_1 = R_1 \frac{\mu + \phi}{(1 - p) \mu} \left[ (i_2^* + s^*) \left( \mu + \gamma_1 + \gamma_2 + \frac{\mu + \delta}{\alpha + \mu + \gamma_2} \omega + k \beta_2 (i_2^* + v_2^*) \right) + \frac{\alpha}{\alpha + \mu + \gamma_2} \omega s^* \right],
$$

with $s^*, i_2^*, v_2^*$ as in $E_2$.

We observe a reduction in infectivity because those who contract cancer as a result of coinfection with both strains do not recover back to $I_{12}$. This effectively reduces the infectivity of those with strain 2. Therefore, we can conclude that when $\alpha = 0$, $R_1 = \tilde{R}_1$ (see Appendix 3 for proof).

**Theorem 3.3.** 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 matrix method, we compute the dominant eigenvalue of the matrix $F_2 V_2^{-1}$ and obtain the following expression for $\tilde{R}_2$ (see Appendix for calculation of matrices).

$$
\tilde{R}_2 = R_2 \frac{(ki_1^* + s^* + v^*) (\beta_1 i_1^* + \mu + \gamma_2 + \phi + \gamma_1 \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} \right)) + \omega f(s^* + v^*, v^*)}{\beta_1 i_1^* + \mu + \gamma_2 + \phi + \gamma_1 \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} \right) + \omega f(1, 1)},
$$

where $f(x, y) = \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} x + \frac{\beta_1 i_1^*}{\mu + \gamma_2} y$. We can also write $\tilde{R}_2$ as

$$
\tilde{R}_2 = R_2 [(ki_1^* + s^* + v^*) - \omega \theta],
$$

where

$$
\theta = \frac{ki_1^* \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} + \frac{\beta_1 i_1^*}{\mu + \gamma_2} \right) + s^* \beta_1 i_1^* \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} + \gamma_2 + \omega \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} + \frac{\beta_1 i_1^*}{\mu + \gamma_2} \right) \right)}{\beta_1 i_1^* + \mu + \phi + \gamma_1 \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} + \gamma_2 + \omega \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} + \frac{\beta_1 i_1^*}{\mu + \gamma_2} \right) \right)}.
$$

From this view, we can see that $\tilde{R}_2$ is essentially $R_2$ multiplied by a term representing an altered vulnerability to infection with strain 2. This term involves the sum $ki_1^* + s^* + v^*$, which represents those classes in the population vulnerable to infection with strain 2. Furthermore, $\beta_2 (ki_1^* + s^* + v^*)$ can be viewed as the average strain 2 infection rate at $E_1$. We can therefore write $\tilde{R}_2$ as follows:

$$
\tilde{R}_2 = R_2 \bar{k},
$$

where $\bar{k} \leq s^* + v^* + ki_1^*$. Furthermore, $\bar{k} < s^* + v^* + ki_1^*$, with equality only when $\omega = 0$. We see that $\tilde{R}_2 < R_2 (s^* + v^* + ki_1^*)$ because of the cancer process. This process, represented by the $\omega$ flow, essentially removes people from the classes vulnerable to infection with strain 2.

**Theorem 3.4.** 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 2 (values for other parameters are as given in Table 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 $\tilde{R}_1 = 1$ 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 lower right region, $E_1$ is stable, and we conjecture (by numerical investigation of the Jacobian) that in the upper right region $E_3$ exists and is stable.

From Theorem 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 is 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. We note that 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 threshold for dominance of $E_1$ vs. $E_3$ is not the same as the threshold for dominance of $E_0$ vs. $E_2$. We also note that it is slightly more difficult for strain 1 to persist in the presence of strain 2 than by itself, because when strain 2 is present, women with coinfections who develop cancer do not return to an infected class (and hence cannot propagate infection), whereas women with only strain 1 who develop cancer may recover to the infective class $I_1$.

Finally, we observe that if we relax the assumption that no women with coinfection recover from cancer, allowing instead for women in $C_{12}$ to recover at a rate $m\alpha$ ($0 < m < 1$), the reproductive number $R_0$ and the equilibria $E_0$, $E_1$ and $E_2$ remain unchanged, since none of them involve coinfection. The invasion reproductive numbers and $E_3$ are slightly affected, however (see Appendix for some details); in particular, using the parameter estimates derived in the next section, $\tilde{R}_1$ and $\tilde{R}_2$ are seen to vary by no more than 1%, except in the case of mass vaccination alone, in which case $\tilde{R}_2$ increases by up to 11% (for $m = 1$).

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 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 Bachtiary 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 69 cases \( \times \) 54 months = 3726 woman-months. 31 deaths/3726 woman-months = 0.0998/\( 1/45yr^{-1} \) = \( \delta \).

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 Colombian 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, obtaining 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 \([16]\). 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 HPV-16 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 \( \frac{a}{m+\mu+\sigma} = 0.72 \) for \( a \), we obtain \( a = 0.315 yr^{-1} \).

We consider that a proportion \( p \) of females enter the population directly into the vaccinated class. We estimate \( p = 0.5 \) for our simulations representing 50 percent coverage due to mandatory vaccination. However, 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 \( \frac{\Lambda}{\mu} \). 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 papillomavirus 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 \( \phi = .007 yr^{-1} \).

When estimating the initial conditions for the numerical simulations, we will use the population size cited earlier, making \( N(0) = \Lambda/\mu \). It has been stated that currently 1.5% of the U.S. population of women are infected with HPV-16 [17]. Thus, \( I_1(0) = 0.015 * \Lambda/\mu \). Based on a study of multiple types of HPV infection [4], we assume that at present, 0.63% of the U.S. women population is infected with HPV-58, which we will use as strain 2 in our simulation. Thus, \( I_2(0) = .0063 * \Lambda/\mu \). Using the same study, we further estimate that \( I_{12}(0) = .0053 * \Lambda/\mu \). We are not considering any initial vaccinated patients, because we wish to observe how introducing vaccination into the population will affect the HPV and cancer cases. We will also consider that \( C_1(0) = C_{12}(0) = 0 \) because we wish to start counting the number of cancer cases starting when \( t = 0 \) (2009).

4.2. Numerical simulations. Given our parameter estimates, we now 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 will it have on the number of cervical cancer cases and deaths? To better answer these questions, we consider several scenarios: HPV transmission with and without strain 2, with and without mass vaccination, and with and without voluntary (ongoing) vaccination.

One measure of the effects of strain 2 and vaccination is given by the reproductive numbers derived in Section 3. These numbers are given in Table 2 for the four vaccination-related scenarios (note that the only effect of the absence of strain 2 on reproductive numbers is to revert the invasion reproductive number \( \hat{R}_1 \) to the basic reproductive number \( R_1 \)). As can be seen in the table, \( \hat{R}_2 \) is naturally unaffected by vaccination. In the scenarios when \( R_1 < 1 \), the equilibrium \( E_1 \) does not exist, and thus we see the negative values for \( \hat{R}_2 \) there. Furthermore, without vaccination and with the estimate for ongoing vaccination only, we expect to see endemic coexistence \( (E_3) \), while mass vaccination only or both types of vaccination can eliminate strain 1.
### Table 1. Model Parameters and Their Values

<table>
<thead>
<tr>
<th>Param.</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Lambda$</td>
<td>Constant recruitment rate</td>
<td>2,235,773</td>
<td>people/yr</td>
<td>[12]</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Natural death rate</td>
<td>1/44</td>
<td>1/yr</td>
<td></td>
</tr>
<tr>
<td>$\delta$</td>
<td>Death rate due to cervical cancer</td>
<td>0.0998</td>
<td>1/yr</td>
<td>[13]</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>Infection rate for infection 1</td>
<td>1.2</td>
<td>1/yr</td>
<td>[23]</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>Infection rate for infection 2</td>
<td>$\frac{7}{1000}$ (1.2)</td>
<td>1/yr</td>
<td>[19]</td>
</tr>
<tr>
<td>$\gamma_1$</td>
<td>Recovery rate from infection 1</td>
<td>0.876</td>
<td>1/yr</td>
<td>[19]</td>
</tr>
<tr>
<td>$\gamma_2$</td>
<td>Recovery rate from infection 2</td>
<td>0.811</td>
<td>1/yr</td>
<td>[19]</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Cervical cancer remission rate for women with strain 1 only</td>
<td>0.315</td>
<td>1/yr</td>
<td>[20]</td>
</tr>
<tr>
<td>$\omega$</td>
<td>Rate of developing cancer due to strain 1 infection</td>
<td>0.0172</td>
<td>1/yr</td>
<td>[25]</td>
</tr>
<tr>
<td>$k$</td>
<td>Amplification factor</td>
<td>6</td>
<td>-</td>
<td>[16]</td>
</tr>
<tr>
<td>$p$</td>
<td>Proportion of women who enter the population into the vaccinated class</td>
<td>0.5</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>$\phi$</td>
<td>Rate of ongoing vaccination</td>
<td>0.007</td>
<td>1/yr</td>
<td>[24]</td>
</tr>
</tbody>
</table>

### Table 2. Reproductive number values under four different vaccination scenarios

<table>
<thead>
<tr>
<th>Repr. No.</th>
<th>No Vaccination</th>
<th>With Vaccination (Both Types)</th>
<th>Mass Vaccination only</th>
<th>Ongoing Vaccination only</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_1$</td>
<td>1.32887</td>
<td>0.505273</td>
<td>0.664434</td>
<td>1.01055</td>
</tr>
<tr>
<td>$\bar{R}_1$</td>
<td>1.32837</td>
<td>0.505085</td>
<td>0.664186</td>
<td>1.01017</td>
</tr>
<tr>
<td>$R_2$</td>
<td>1.00813</td>
<td>1.00813</td>
<td>1.00813</td>
<td>1.00813</td>
</tr>
<tr>
<td>$\bar{R}_2$</td>
<td>2.18021</td>
<td>-1.12118</td>
<td>-0.087277</td>
<td>1.05763</td>
</tr>
</tbody>
</table>

If we wish to consider asynchronous invasion of the two strains, that is, one strain arrives while the other is still establishing itself, then the ability of the later arrival to invade is given by the invasion reproductive number (IRN) for that strain with the transient, rather than equilibrium, population values substituted into the expressions for $R_1$ and $\bar{R}_2$ derived in Section 3. Since the population values vary continuously (from $E_0$ to $E_1$ or $E_2$) as the first-arrived strain establishes itself, the effective IRN for the later arrival varies continuously from its basic value at $E_0$ (i.e., $R_1$ or $R_2$) to the IRN value given in Table 2.

Another measure of the effects of strain 2 and vaccination is given by numerical solutions of system (1–8), which can be used to estimate the numbers of HPV infections and cancer cases and deaths over a certain span of time. We computed numerical solutions for the system under the eight possible combinations of the presence or absence of strain 2, mass (mandatory) vaccination, and ongoing (voluntary) vaccination. Table 3 gives the cumulative numbers of strain 1 infections and cancer cases and deaths after a time period of 50 years. Differences in the results reflect the effectiveness of vaccination in reducing the reproductive number for strain 1 below one, and the fact that the presence of strain 2 causes more cancer cases to be fatal.
### Table 3. Effects of the presence of strain 2 and/or vaccination

\( (\phi = 0.007yr^{-1}) \) on the severity of the strain 1 epidemic and associated cancer over a 50 year period

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Cumulative No. of Strain 1 Infections</th>
<th>Cum. No. of Cancer Cases</th>
<th>Cum. No. of Cancer Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Strain 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Vaccination</td>
<td>836,709,675</td>
<td>15,523,186</td>
<td>3,342,124</td>
</tr>
<tr>
<td>With Vaccination (both types)</td>
<td>107,780,328</td>
<td>2,080,114</td>
<td>474,140</td>
</tr>
<tr>
<td>With Mass Vacc. only</td>
<td>215,948,374</td>
<td>4,125,814</td>
<td>932,616</td>
</tr>
<tr>
<td>With Ongoing Vacc. only</td>
<td>462,111,017</td>
<td>8,659,829</td>
<td>1,896,236</td>
</tr>
<tr>
<td>With Strain 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Vaccination</td>
<td>849,567,516</td>
<td>15,692,747</td>
<td>7,226,491</td>
</tr>
<tr>
<td>With Vaccination (both types)</td>
<td>137,231,798</td>
<td>2,642,113</td>
<td>960,014</td>
</tr>
<tr>
<td>With Mass Vacc. only</td>
<td>251,941,832</td>
<td>4,798,071</td>
<td>1,966,757</td>
</tr>
<tr>
<td>With Ongoing Vacc. only</td>
<td>497,076,740</td>
<td>9,283,705</td>
<td>4,027,205</td>
</tr>
</tbody>
</table>

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 \( \mu = \frac{1}{45yr} \), people should be removed from the population after 45 years, but in this case some of them remain longer 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, the number of cervical cancer cases actually decreases when strain two is introduced into the population. This is because 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 \( I_2 \) 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 \( C_2 \) 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. However, when comparing the scenarios when strain 2 is present without vaccination versus strain 2 present with
vaccination we will expect to see cervical cancer cases and deaths reduced by a drastic amount.

Using results found in Table 3, we observe the following. First, we examine the results without strain 2. Without a second strain in our system, we see a 87 percent decrease in number of cervical cancer cases when both ongoing vaccination and mandatory vaccination policies are in effect. We also observe a 86 percent decrease in number of cervical cancer deaths. When strain 2 is present in the system, we observe that vaccination causes a significant decrease in the number of cervical cancer cases and deaths after 50 years. After 50 years, we see that there is a 70 percent decrease in number of cervical cancer cases if vaccination is present at 50 percent. Also, we observe a 73 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 116 percent increase in cervical cancer deaths when strain 2 is entered into the system. If vaccination is present at 50 percent, we see that the presence of strain 2 causes a 110 percent increase in cervical cancer deaths.

We notice that the decrease in cervical cancer cases and deaths is greater if mass vaccination is in effect versus ongoing vaccination. However, we note that the mass vaccination is set at 50 percent coverage.

In Figure 3, we include two time-series graphs of new HPV cases over a 50 year time period to observe the effects of vaccination on the number of new strain 1 HPV infections.

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 infections present at the end of 100 years. We solve the system of differential equations numerically over time as \( p \) and \( \phi \) vary. The graph is given in Figure 4. We see that
the number of strain 1 infections is essentially zero for most vaccination levels. We see that for values of $p$ as low as 0.2 strain 1 will still be eradicated.

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 5. 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.

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 $R_2 < 1 < k\tilde{R}_2 = \tilde{R}_2$. 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 diseases such as cervical cancer were not addressed. In our study we investigated the impact vaccination has 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. 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 after 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.

Few mathematical studies have been devoted to the study of human papillo-
mavirus 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 asymptomatic. We realize that the lack of epidemiologi-

cal 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 param-
eters 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 structure and
results could apply to other multi-strain infections exhibiting mutualism in the
population.

REFERENCES

Predictors of cervical confection with multiple human papillomavirus types, Cancer Epidemi-
ology, Biomarkers and Prevention, 12 (2003), 1029–1037.
Occurrence of cervical infection with multiple human papillomavirus types is associated with
age and cytologic abnormalities, Sexually Transmitted Diseases, 30 (2003), 581–587.
human papillomavirus (HPV) type 16 DNA detection by polymerase chain reaction and its
association with acquisition and persistence of other HPV types, Journal of Infectious
[6] Merck & Co., Inc. GARDASIL [Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18)
Recombinant Vaccine] (2006), Merck & Co., Inc, Whitehouse Station, NJ 08889, USA
27 (2005), S3–S9.
[8] H. Trottier and E. Franco, The epidemiology of genital human papillomavirus infection, Vac-
population with applications to hantavirus, Mathematical Biosciences, 186 (2003), 191–217.


Appendix A. Appendix.

A.1. DFE and $R_0$.

A.1.1. $R_0$. We compute the disease-free equilibrium by solving the right hand sides of $S' = 0$ and $V' = 0$, obtaining

$$\begin{pmatrix} (1-p) \Lambda, \Lambda (p \mu + \phi) \overline{\phi + \mu}, \overline{(p \phi + \mu)}, \overline{0}, 0, 0, 0, 0, 0 \end{pmatrix}.$$  

The reproductive number $R_0$ is computed using the next generation matrix method. We separate the terms in the equations into two vectors, $\mathcal{F}_0$ and $\mathcal{V}_0$. The entries in the $\mathcal{F}_0$ vector consist of the terms in the equations representing new infections (with strain 1 or 2), while the entries in the $\mathcal{V}_0$ consist of the remaining terms. We write the vectors as $\mathcal{F}_0 \mathcal{V}_0$, where

$$\mathcal{F}_0^T = \begin{pmatrix} 0, 0, \beta_2 \tilde{I}_2 V_N, \beta_1 \tilde{I}_1 S, \beta_2 \tilde{I}_2 S, k \beta_2 \tilde{I}_2 I_1, \beta_1 \tilde{I}_1 I_2, 0, 0 \end{pmatrix},$$

$$\mathcal{V}_0 = \begin{pmatrix} -(1-p) \Lambda + \phi S + \frac{\beta_2 I_2 V}{N} + \frac{\beta_1 I_1 S}{N} - \gamma_1 I_1 - \gamma_2 I_2 + \mu S \\ -p \Lambda - \phi S + \frac{\beta_2 I_2 V}{N} - \gamma_2 V_2 + \mu V \\ (\mu + \gamma_2) V_2 - \phi I_2 \\ \frac{k \beta_2 I_2 I_1}{N} + (\omega + \mu + \gamma_1) I_1 - \alpha C_1 - \gamma_2 I_{12} \\ \frac{\beta_1 I_1 I_2}{N} + (\mu + \gamma_1 + \gamma_2) I_2 - \gamma_1 I_{12} \\ (\mu + \omega + \gamma_1 + \gamma_2) I_{12} \\ -\omega I_1 + (\alpha + \mu + \delta) C_1 \\ -\omega I_{12} + (\mu + \delta) C_{12} \end{pmatrix}.$$  

We then compute the Jacobians of $\mathcal{F}_0$ and $\mathcal{V}_0$ obtaining the following matrices:

$$F_0 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_2 V^* & 0 & \beta_2 V^* & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_1 S^* & 0 & \beta_1 S^* & 0 & 0 & 0 & 0 \\ 0 & \beta_2 S^* & 0 & \beta_2 S^* & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V_0 = \begin{pmatrix} \phi + \mu & 0 & \beta_2 S^* & \beta_1 S^* - \gamma_1 & \beta_2 S^* - \gamma_2 & \beta_1 S^* & 0 & 0 \\ -\phi & \mu & \beta_2 V^* - \gamma_2 & 0 & \beta_2 V^* & \beta_2 V^* & 0 & 0 \\ 0 & 0 & \mu + \gamma_2 & 0 & -\phi & 0 & 0 & 0 \\ 0 & 0 & \omega + \mu + \gamma_1 & 0 & -\gamma_2 - \alpha & 0 & 0 & 0 \\ 0 & 0 & 0 & \mu + \gamma_2 + \phi & -\gamma_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \zeta & 0 & 0 & 0 \\ 0 & 0 & 0 & -\omega & 0 & \eta & 0 & 0 \\ 0 & 0 & 0 & 0 & -\omega & 0 & \mu + \delta & 0 \end{pmatrix}.$$
where $\zeta = \mu + \omega + \gamma_1 + \gamma_2$, $\eta = \alpha + \mu + \delta$. We then compute $F_0V_0^{-1}$, obtaining:

$$\begin{pmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \frac{\beta_1v^*}{\mu + \gamma_2} & \frac{\beta_1v^*}{\mu + \gamma_2} & \frac{\beta_1v^*}{\mu + \gamma_2} & A_2 & 0 & 0 \\
0 & 0 & \frac{\beta_2s^*}{\mu + \gamma_2} & 0 & \frac{\beta_2s^*}{\mu + \gamma_2} & 0 & 0 & 0 \\
0 & 0 & 0 & \frac{\beta_2s^*}{\mu + \gamma_2} & \frac{\beta_2s^*(\gamma_2 + \mu + \omega)}{\gamma_2 + \mu + \omega} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\end{pmatrix},$$

where $\rho = \mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta}\omega$, $A_1 = \alpha(\gamma_1 + \mu) + (\mu + \delta)(\gamma_1 + \mu + \omega)$, $A_2 = \frac{\mu + \gamma_1 + \gamma_2}{\mu + \gamma_2 + \omega}$, and $A_3 = (\alpha + \mu + \delta)A_2 + (\mu + \delta)(1 - A_2)s^*$. The eigenvalues for $F_0V_0^{-1}$ are $\{0,0,0,0,0,0,1,1\}$. Because $R_0$ is determined to be the dominant eigenvalue for the matrix, we conclude $R_0 = \max\{R_1, R_2\}$.

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

### A.1.2. Global Stability of DFE

We also show that disease-free equilibrium is globally asymptotically stable under certain conditions. By constructing the Lyapunov function, $L = V_2 + I_1 + I_{12} + I_2 + C_1$, we can see that $L = 0$ for all values except at the disease-free equilibrium, where $L = 0$. We first wish to show that $\frac{dL}{dt} < 0$.

$$\frac{dL}{dt} = \frac{\beta_2I_2V}{N} - (\mu + \gamma_2)V_2 + \phi I_2 + \frac{\beta_1I_1S}{N} - k\frac{\beta_2I_2I_1}{N} - (\omega + \mu + \gamma_1)I_1 + \alpha C_1$$

$$+ \gamma_2I_{12} + \frac{\beta_2I_2S}{N} - \frac{\beta_1I_1I_2}{N} - (\mu + \gamma_2 + \phi)I_2 + \gamma_1I_{12} + \omega I_1 - (\alpha + \mu + \delta)C_1$$

$$= \frac{\beta_1(I_1 + I_{12})S}{N} + \frac{\beta_2(I_2 + I_{12} + V_2)(V + S)}{N}$$

$$+ (\mu + \gamma_1)I_1 - (\mu + \gamma_2)(I_2 + V_2) - (\mu + \delta)C_1 - (\mu + \omega)I_{12}$$

Thus, if $\beta_1 < \mu + \gamma_1$, $\beta_2 < \mu + \gamma_2$, and $\beta_1 + \beta_2 < \mu + \omega$, then $\frac{dL}{dt} \leq 0$. Thus $L(t) \to 0$. We also need to show that $C_{12} \to 0$. We have

$$\frac{dC_{12}}{dt} = \omega I_{12} - (\mu + \delta)C_{12}.$$
is globally asymptotically stable. This system has a single equilibrium,
\[
\left\{ \frac{(1 - p)\Lambda}{\mu + \phi}, \frac{\Lambda}{\mu + \phi} \right\} \frac{p \mu + \phi}{\mu + \phi}.
\]
By the Poincaré-Bendixson Theorem, we know that all solutions to the system tend toward an equilibrium, grow unbounded, or tend to a limit cycle. We know that the solutions to the system are bounded. We have
\[
N' = \Lambda - \mu N.
\]
The solutions to this system are bounded by max\{\frac{\Lambda}{\mu}, N_0\}.
To show that this equilibrium is g.a.s., we must show there are no periodic orbits. By using Dulac’s criterion, we see that for \(g(S, V) = 1\),
\[
\frac{\partial}{\partial S} (g(S, V) [(1 - p)\Lambda - (\mu + \phi)S]) + \frac{\partial}{\partial V} (g(S, V) [p\Lambda + \phi S - \mu V]) = -2\mu - \phi \leq 0.
\]
Since this sum is strictly negative, we can conclude that the solutions to this system do not tend toward a limit cycle (no period orbits).
Therefore, we can conclude that the disease-free equilibrium is globally asymptotically stable.

A.2. Single strain equilibria. To find the strain 1 equilibria, \(E_1\), we first set \(\frac{dC_1}{dt} = 0\) and proportionalize to obtain
\[
c^*_1 = \left( \frac{\omega}{\alpha + \mu + \delta} \right) i^*_1.
\]
We then set \(\frac{dI_1}{dt} = 0\) and use the previous equation to obtain the following (in proportionalized form):
\[
\beta_1 i^*_1 - (\omega + \mu + \gamma_1) i^*_1 + \left( \frac{\alpha}{\alpha + \mu + \delta} \right) i^*_1 = 0
\]
\[
\left( \beta_1 i^*_1 - (\omega + \mu + \gamma_1) + \frac{\alpha}{\alpha + \mu + \delta} \right) i^*_1 = 0
\]
Thus, we conclude that either \(i^*_1 = 0\) or \(\beta_1 i^*_1 - (\omega + \mu + \gamma_1) + \frac{\alpha}{\alpha + \mu + \delta} = 0\).
Therefore,
\[
s^* = \left( \frac{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega}{\beta_1} \right).
\]
Substituting \(c^*_1\) and \(s^*\) into \(v^*\) for \(E_1\) gives
\[
v^* = \left( \frac{1}{\mu} \right) p \left[ \mu + \delta \left( \frac{\omega}{\mu(\alpha + \mu + \delta) + \omega(\mu + p\delta)} \right) + \phi \left[ \frac{\mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \delta} \omega}{\beta_1} \right] \right].
\]
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

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

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. Thus, we substitute the expression for \( i_1^* \) into the expression for \( c_1^* = \frac{\alpha}{\alpha + \mu + \delta} \omega i_1^* \) to obtain the \( c_1^* \) found in section 3.2.

To find the equilibrium \( E_2 \), we use the following equations,

\[
S' + V'|_{i_1 = 0} = \Lambda - \beta_2 i_2 \left( \frac{S + V}{N} \right) + \gamma_2 (I_2 + V_2) - \mu (S + V)
\]

and

\[
I'_2 + V'_2|_{i_1 = 0} = \beta_2 i_2 \left( \frac{S + V}{N} \right) - (\mu + \gamma_2) (I_2 + V_2).
\]

Setting the right hand sides of each equation to zero and dividing by \( N^* \), we obtain the following proportionalized expressions:

\[
i^*_2 + v^*_2 = 1 - \frac{\mu + \gamma_2}{\beta_2} = 1 - \frac{1}{R_2},
\]

\[
s^* + v^* = \frac{1}{R_2}.
\]

By setting the right hand side of \( S' = 0 \), we obtain the following proportionalized expression for \( s^* \)

\[
s^* = \frac{(1 - p) \mu + \gamma_2 i_2}{\mu + \phi + \beta_2 (i^*_2 + v^*_2)}.
\]

Substituting this expression into the right hand side of \( I'_2 = 0 \), we obtain the following:

\[
i^*_2 + v^*_2 = \frac{(\mu + \gamma_2 + \phi)(\mu + \phi)i^*_2}{\beta_2 ((1 - p) \mu - (\mu + \phi)i^*_2)}.
\]

By replacing the left hand side of the former equation with \( 1 - \frac{1}{R_2} \), we obtain the expression for \( i^*_2 \).

A.2.1. Invasion Reproductive Numbers. We utilize the next generation matrix method in computing the invasion reproductive number \( R_1 \), where \( E_2 \) is considered the disease-free equilibrium.

We first note that we only consider the equations representing those classes infected with strain 1, \( I'_1, I'_2, C'_1, C'_2 \).

We separate the terms in the equations into two vectors \( F_1 \) and \( V_1 \). The entries in the \( F_1 \) matrix consist of the terms in the equations representing new infections with strain 1. The entries in the \( V_1 \) matrix consist of the remaining terms, where we write the matrices as \( F_1 - V_1 \). Thus we have

\[
F_1 - V_1 = \begin{pmatrix}
\frac{\beta_1 i_1 s}{N} & \frac{k\beta_2 i_2 I_1}{N} & (\omega + \mu + \gamma_1)I_1 - \alpha C_1 - \gamma_2 I_{12} \\
\beta_1 i_1 I_1 & -k\beta_2 i_2 I_1 & + (\mu + \omega + \gamma_1 + \gamma_2)I_{12} \\
0 & 0 & -\omega I_1 + (\alpha + \mu + \delta)C_1 \\
0 & 0 & -\omega I_{12} + (\mu + \delta)C_{12}
\end{pmatrix}.
\]
Computing the Jacobians of each matrix at the equilibrium $E_2$ and proportion-alizing, we obtain the following matrices for $F_1$ and $V_1$.

\[
F_1 = \begin{pmatrix}
\beta_1 s^* & \beta_1 s^* & 0 & 0 \\
\beta_1 i_2^* & \beta_1 i_2^* & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
\]

and

\[
V_1 = \begin{pmatrix}
k\beta_2(i_2^* + v_2^*) + (\omega + \mu + \gamma_1) & -\gamma_2 & -\alpha & 0 \\
-k\beta_2(i_2^* + v_2^*) & \mu + \omega + \gamma_1 + \gamma_2 & 0 & 0 \\
-\omega & 0 & \alpha + \mu + \delta & 0 \\
0 & -\omega & 0 & \mu + \delta
\end{pmatrix}
\]

We determine the dominant eigenvalue of the matrix determined by $F_1V_1^{-1}$ to be the invasion reproductive number $\tilde{R}_1$ given by

\[
\tilde{R}_1 = \frac{\beta_1}{\rho} \left[ \frac{(i_2^* + s^*) \left( \mu + \gamma_1 + \gamma_2 + \frac{\mu + \delta}{\alpha + \mu + \gamma_1 + \omega} \omega + k\beta_2(i_2^* + v_2^*) \right) + \frac{\alpha}{\alpha + \mu + \omega} \omega s^*}{\mu + \gamma_1 + \gamma_2 + \omega + k\beta_2(i_2^* + v_2^*) \frac{\mu + \gamma_1 + \gamma_2 + \omega}{\mu + \gamma_1 + \omega + k\beta_2(i_2^* + v_2^*)}} \right],
\]

where $\rho = \mu + \gamma_1 + \frac{\mu + \delta}{\alpha + \mu + \gamma_1 + \omega} \omega$. The second factor (in square brackets) gives the effective vulnerability of the population to infection by strain 1 (replacing $(1-p)\frac{\mu}{\mu + \phi}$ in $R_1$).

If we allow women with coinfection to recover at a reduced rate $ma$ ($0 < m < 1$), via a flow of $maC_{12}$ from $C_{12}$ to $I_{12}$, then $R_1$ is given instead by

\[
\tilde{R}_1 = \frac{\beta_1}{\rho} \left[ \frac{(i_2^* + s^*) \left( \mu + \gamma_1 + \gamma_2 + \frac{\mu + \delta}{\alpha + \mu + \gamma_1 + \omega} \omega + k\beta_2(i_2^* + v_2^*) \right) + M \frac{\alpha}{\alpha + \mu + \omega} \omega s^*}{\mu + \gamma_1 + \gamma_2 + \omega + k\beta_2(i_2^* + v_2^*) \left[ 1 + M \frac{\mu}{\mu + \gamma_1 + \omega + \beta_2(i_2^* + v_2^*)} \right]} \right],
\]

where $M = (1-m)\frac{\mu + \delta}{\alpha m + \mu + \delta}$.

**Proof that if $\alpha = 0$, then $R_1 = \tilde{R}_1$:**

We can see that when $\alpha = 0$, $R_1 = \frac{\beta_1}{\mu + \gamma_1 + \omega} \left( \frac{(1-p)\mu}{\mu + \phi} \right)$ implies $\frac{\beta_1}{\mu + \gamma_1 + \omega} = \frac{\mu + \phi}{\mu(1-p)} R_1$. Then

\[
\tilde{R}_1 = \frac{\beta_1}{\mu(1-p)} \left[ \frac{(i_2^* + s^*) \left( \mu + \gamma_1 + \omega + \gamma_2 + k\beta_2(i_2^* + v_2^*) \right)}{\mu + \gamma_1 + \omega + \gamma_2 + k\beta_2(i_2^* + v_2^*)} \right]
\]

\[
= \frac{\beta_1}{\mu + \gamma_1 + \omega} (i_2^* + s^*)
\]

\[
= R_1 \frac{\mu + \phi}{\mu(1-p)} \left[ \frac{1}{R_2} \left( 1 - \frac{1}{R_2} \right) \frac{\mu + \gamma_2 \left( 1 - \frac{1}{R_2} \right)}{\beta_2 + \phi} \right] + \left( 1 - \frac{1}{R_2} \right) (1-p) \frac{\beta_2}{\beta_2 + \phi}
\]

\[
= R_1 \left[ \frac{1}{R_2} \left( \mu + \phi + \gamma_2 \left( 1 - \frac{1}{R_2} \right) \frac{\beta_2}{\beta_2 + \phi} \right) + \left( 1 - \frac{1}{R_2} \right) \beta_2 + \phi \right]
\]
\[
R_1 \frac{1}{\rho_2} (\mu + \phi) + \left( 1 - \frac{1}{\rho_2} \right) \frac{\beta_2}{\rho_2 + \phi} \left( \mu + \gamma_2 + \frac{1}{\rho_2} \phi \right) \\
R_1 \frac{1}{\rho_2} (\mu + \phi) + \left( 1 - \frac{1}{\rho_2} \right) \frac{\beta_2}{\rho_2 + \phi} \left( \mu + \gamma_2 + \frac{1 + \phi}{\rho_2} \right) \\
R_1 \frac{1}{\rho_2} (\mu + \phi) + \left( 1 - \frac{1}{\rho_2} \right) \frac{\beta_2}{\rho_2 + \phi} \left( \mu + \gamma_2 \right) \left( 1 + \frac{\phi}{\rho_2} \right) \\
R_1 \frac{1}{\rho_2} (\mu + \phi) + \left( 1 - \frac{1}{\rho_2} \right) \frac{\beta_2}{\rho_2 + \phi} \left( \mu + \gamma_2 \right) \left( 1 - \frac{1}{\rho_2} \right) \\
R_1.
\]

To determine \( R_2 \), we follow a similar procedure as seen previously using the next generation matrix approach. The \( F_2 \) matrix is given by the new infection terms in the equations \( V'_2, I'_2, C'_{12} \), and the \( V_2 \) matrix consists of the remainder of the terms in those equations. We obtain

\[
F_2 \quad V_2 = \begin{pmatrix}
\frac{\beta_1 I V}{N} \\
\frac{\beta_1 I S}{N} \\
\frac{k \beta_2 I_1 I_2}{N} \\
0
\end{pmatrix}
- \begin{pmatrix}
(\mu + \gamma_2) V_2 - \phi I_2 \\
(\mu + \gamma_2 + \phi) I_2 - \gamma_1 I_{12} \\
(\mu + \omega + \gamma_1 + \gamma_2) I_{12} \\
-\omega I_{12} + (\mu + \delta) C_{12}
\end{pmatrix}.
\]

We then compute the Jacobians of \( F_2 \) and \( V_2 \) at \( E_2 \) (proportionalized) to obtain

\[
F_2 = \begin{pmatrix}
\beta_2 v^* & \beta_2 v^* & \beta_2 v^* & 0 \\
\beta_2 s^* & \beta_2 s^* & \beta_2 s^* & 0 \\
k \beta_2 i_1^* & k \beta_2 i_1^* & k \beta_2 i_1^* & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
\]

and

\[
V_2 = \begin{pmatrix}
\mu + \gamma_2 & -\phi & 0 & 0 \\
\beta_1 i_1^* + \mu + \gamma_2 + \phi & -\gamma_1 & 0 \\
0 & \beta_1 i_1^* + \mu + \gamma_2 + \phi & -\omega & \mu + \delta \\
0 & 0 & 0 & \mu + \delta
\end{pmatrix}.
\]

We then find the dominant eigenvalue of \( F_2 V_2^{-1} \) to be

\[
\tilde{R}_2 = R_2 \frac{(k_i^* + s^* + v^*) \left( \beta_1 i_1^* + \mu + \gamma_2 + \phi + \gamma_1 \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} \right) \right) + \omega f(s^* + v^*, v^*)}{\beta_1 i_1^* + \mu + \gamma_2 + \phi + \gamma_1 \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} \right) + \omega f(1, 1)}.
\]

where \( f(x, y) = \frac{x + \gamma_1}{\mu + \gamma_2} \). An alternate form of \( \tilde{R}_2 \) can be written to clearly see that \( \tilde{R}_2 = \tilde{k} R_2 \), where \( \tilde{k} < k_i^* + s^* + v^* \). This alternate form is given below:

\[
\tilde{R}_2 = R_2 [(k_i^* + s^* + v^*) - \omega \delta], \quad \text{where}
\]
If we allow women with coinfections to recover from cancer at a per capita rate $m\alpha (0 < m < 1)$, the value of $R_2$ becomes instead

$$R_2 \frac{(k_i^s + s^* + v^*) \left( \mu + \gamma_1 \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} \right) + \gamma_2 + \phi + \beta_1 i_1^s \right) + \frac{\mu + \phi}{\alpha\gamma_1 + \mu + \phi} \omega f(s^* + v^*, v^*)}{\mu + \gamma_1 \left( \frac{\mu + \gamma_2 + \phi}{\mu + \gamma_2} \right) + \gamma_2 + \phi + \beta_1 i_1^s + \frac{\mu + \phi}{\alpha\gamma_1 + \mu + \phi} \omega f(1, 1)}.$$