A Two-Gender Human Papillomavirus Model with an Investigation of the Effects of Male Screening

Cornell Univ., Dept. of Biological Statistics &Computational Biology

Technical Report BU-1621-M

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August 2002

Abstract

The Human Papillomavirus (HPV) is the most common sexually transmitted infection in the United States. Though few of its more than one-hundred strains cause the recognized symptoms of genital warts, numerous high-risk HPV strains are highly correlated with cervical cancer cases. The symptoms of HPV are gender-specific. Men and women exhibit different degrees of infectiousness and varied symptoms of infection from HPV. Men rarely exhibit symptoms and are therefore silent carriers of these carcinogenic agents. In this investigation, we focus on the epidemiological dynamics of a high-risk HPV strain (HPV16) in a heterosexual population. A two-sex model is used to highlight the impact of asymptomatic infectious males on the dynamics of cervical cancer cases in females. Hence, we concentrate on the possible effects of increased HPV detection in males on the spread of HPV16 in a heterosexual population, and on the incidence of cervical cancer cases associated with HPV16.

Contents

1 Introduction

The Human Papillomavirus, HPV, is the most common sexually transmitted infection (STI) in the United States[2]. Over 20 million Americans are currently infected with HPV, and about 5.5 million new cases will be diagnosed this year[20]. Alarmingly, 70 percent of the population has never heard of the disease, but 50 to 75 percent of all Americans will acquire some strain of HPV in their lifetime[2, 7]. Currently, no cure is available for HPV, but its symptoms can be treated and often cured[7, 26].

The diverse HPV family consists of over 100 strains, ranging from those that cause common warts and plantar warts on the hands and feet to those that affect the genitals, each strain infecting different types of epithelial tissue[3]. The approximately 30 strains that do affect the genitals can be further subdivided into two categories: low-risk and high-risk[7]. Biologically, the differences among the low-risk and high-risk strains lie in their varied abilities to integrate their genes into the genome of the host cell. High-risk strains actually amalgamate their genetic code with the host's genome, and experimental evidence seems to show that low-risk strains do not[18]. Two of the HPV's genes, *E6 and E7* act as oncogenes, with products that actually interfere with the cellular proteins that control the cell cycle and DNA repair[1][13]. Viral DNA integration together with other contributing factors such as smoking, unbalanced diet, old age, or infection with additional STIs are sufficient factors for the appearance of cancer caused by HPV[18].

Low-risk strains (e.g., HPV6 and HPV11) can cause genital warts and mild dysplasia[2] but have not been found to cause cancer[7, 27]. In contrast, high-risk strains are associated with cancer[11, 13]. They can cause flat, nearly-invisible growths and moderate to severe dysplasia that may lead to cancer. HPV-linked cancer cases are associated most often with cervical cancer, but the virus has been found in cases of anal, vulval, vaginal, and penile cancer[26]. Numerous strains have been found to be carcinogenic[3][11]. However, HPV16 is the most prominent carcinogenic strain in the United States and throughout the world[26].

The most challenging aspect of diagnosing HPV infection lies in the different degrees of infectiousness and the varied symptoms of each individual. Depending on a person's immune system, symptoms can appear within a week, after a few months, after a number of years, or not at all[5]. The symptoms of HPV (i.e., genital warts and dysplasia) can be treated and cured, but for subclinical HPV (asymptomatic HPV infections), no cure has been found thus far[27]. Since there is no initial HPV test until there are symptoms, most infected individuals are transmitting the virus without knowledge of their infection status.

[1] E6 binds to and induces the degradation of the tumor-suppressing protein p53, and E7 interferes with retinoblastoma tumor suppressor protein pRBr[13].

[2] Abnormal cell growth

[3] HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 69

Clinical tests do exist that can inform individuals of their HPV status. The Digene Hybrid Capture II test is the only test used commercially[2, 6]. The testing process involves taking a tissue sample from the individual and testing the sample for HPV DNA. Currrently, the Digene Hybrid Capture II test is only FDA[4]-approved for use in women. This test is not approved for males because the thick skin of the penis precludes obtaining a good tissue sample, and the test yields a large number of false-negatives[6]. An individual can always be tested for HPV antibodies, but this test does not prove a person is currently infected or infectious, only that they have come into contact with the virus in the past.

Once a person acquires a strain of HPV, it is in his or her body forever, but in 80 percent of HPV cases, the host's immune system is able to suppress the virus within 18 months[7, 18]. When the immune system has the virus under control, the individual becomes no longer infectious, and their symptoms and infectiousness rarely recur. Once the host immune system has suppressed a specific strain, he or she will not be able to be infected with that particular strain again. They could be infected with a different strain, or they could acquire more than one strain of HPV in one sexual encounter. The latter is referred to as superinfection, which occurs in about one-third of HPV cases[7].

Few options exist to prevent contraction of genital HPV. As HPV spreads via skin-to-skin contact, condoms cannot fully prevent a person from transmitting or contracting HPV. Hence, abstinence is the only true means of protection from the virus. Being in a monagamous sexual relationship also reduces the chances of infection[4].

Annual anal, vaginal, and penile exams are important in detecting symptoms that would otherwise go unnoticed. In particular, Papanicoloaou smears (Pap smears) are crucial in early detection of dysplasia. While the exams do not prevent warts or dysplasia from occurring, they can detect them before they progress to more serious health problems such as cervical cancer[1]. Exams also allow for diagnosis and subsequent treatment.

Worldwide, cervical cancer has the second highest mortality among cancers that affect women[25, 27]. In 1990, about 360,000 women were diagnosed with cervical cancer and half of them lost their lives to the disease[17, 15]. In 2002, over 4,000 of the 13,000 women diagnosed with cervical cancer in the U.S. will suffer the same fate[28]. The mortality rate from cervical cancer in America has decreased significantly during the past few decades, mostly because of early diagnosis and intervention due to the Pap smear, but even in countries where screening is often used, cancer remains a serious concern[14]. HPV transmission rates are high, and it has been shown that up to 99 percent of all cases of cervical cancer can be attributed to HPV infections of high-risk strains[2, 17, 27]. Because HPV16 is found in for approximately 50 percent of cervical cancer cases, it is this strain that is the focus of our research[17, 21].

In the research done by Mandelblatt et al. on the benefits and costs of HPV testing,

[4]Food and Drug Administration

it was determined that most lives being lost to cervical cancer could be reclaimed by using Pap and HPV tests in women simultaneously[14]. Their research did not investigate the effects of screening and treating the male population. Men contribute greatly to the spread of this disease, as their infectiousness is much greater than that of women. They are silent carriers of the carcinogenic agents, and we believe that early detection of HPV in men will also decrease the spread of the virus.

2 Methodology

2.1 Model Assumptions

1. We assume homogeneous mixing in our model, implying that all individuals in our population have identical sexual behavior and that they randomly choose their sexual partners.

2. We assume that immunity to HPV16, once acquired, is permanent. Few recovered individuals experience spontaneous reoccurrence of the virus, where the virus reappears many years, usually decades, after it was acquired by the host and suppressed by the immune system. This can happen because when the immune system is weakened due to smoking, old age, or immuno-deficiency virii[26]. The comparatively small number of people on who regress into the infectious category after recovery leads us to consider this phenomenol insignificant. In addition, the fact that spontaneous reoccurence takes place decades after initial infection means that the individual may have already left the sexually active population by that time.

3. Though we include recruitment into and exit from of our sexually active population, we assume constant male and female population sizes. This is a good assumption for communities with small growth rates and stable age distributions. The dynamics of the disease would, therefore, stabilize before the population size changed significantly. There may be communities where this assumption must be altered (developing countries where the birth rate is very high and where exit from the sexually active population is regularly by means of natural death at a young age), but we do not examine them in this report. Since deaths due to HPV-related cancer are very small as compared to the total number of female deaths in our population (1:500 per year in U.S.[8]), we do not include cancer-related deaths in our model.

4. Chronically infected individuals are assumed to have a different rate of infection than those who are initially infected. The model also integrates the fact that men are proportionally more infectious than women.

5. We use standard incidence as the infection rate. Because we have a constant population, analysis of the same model with mass action would have the same dynamics, with all instances of β in the equations and equilibria being scaled by N^{-1}. We use standard incidence because we define βN to be the total rate of sufficient infectious contacts in the population. Then $\beta N \cdot \frac{I}{N} \cdot \frac{S}{N} = \beta I \frac{S}{N}$ is the rate of sufficient infectious contact between a suseptible and an infectious individual.

6. The model and its analysis focus on the interaction between the two genders, and therefore assumes heterosexual interaction as the only possibility for transmission of the disease. We assume that the two genders have equal population sizes.

7. Our per-individual rate of transmission is assumed to be constant, and a constant screening rate is assumed. Although only a certain percentage of the sexually active population gets tested regularly, we assume that individuals are randomly and homogeneously screened[14]. A constant treatment rate of screened individuals with a certain proportion of success is assumed for those in the initially infected class. The assumption of a constant treatment rate corresponds to the regular frequency of the Pap smears, combined with the treatment that is administered whenever abnormal cells are found.

8. We include a constant treatment rate of chronic individuals similar to the screening-and-treatment for initially infected individuals. Successful treatment imparts strain immunity to the treated individual, while unsuccessfully treated individuals remain in the chronic class. While it is true that individuals might not be sexually active for a few weeks after treatment, the average time spent as a chronically infected individual is so large that the short period of abstinence is considered to be insignificant in comparison.

2.2 Model

In order to describe HPV transmission, we employ a two-sex model with solely heterosexual interaction. In our model, we have reduced important aspects of the disease dynamics to the following. First, a person enters the susceptible classes (S) once he or she becomes sexually active. If and when interaction occurs with someone from the initially infected (I) or the chronically infected (C) classes of the opposite gender, a person becomes infected and goes to the intially infected class. Individuals leave the initially infected class at a constant per-individual rate. As the immune system attempts to clears the virus, a fraction of individuals gain permanent immunity (R), while others progress to chronic infection. Individuals are also screened at a constant per-individual rate, and for a fraction of these individuals, treatment of symptoms is successful and provides permanent immunity to the strain. Once in the

chronic state, a person may be able to fight off the disease with the help of treatment after screening and successful diagnosis. With four stages for each gender, our *SICR* model is a two-gender, heterosexual system drawn in Figure 1.

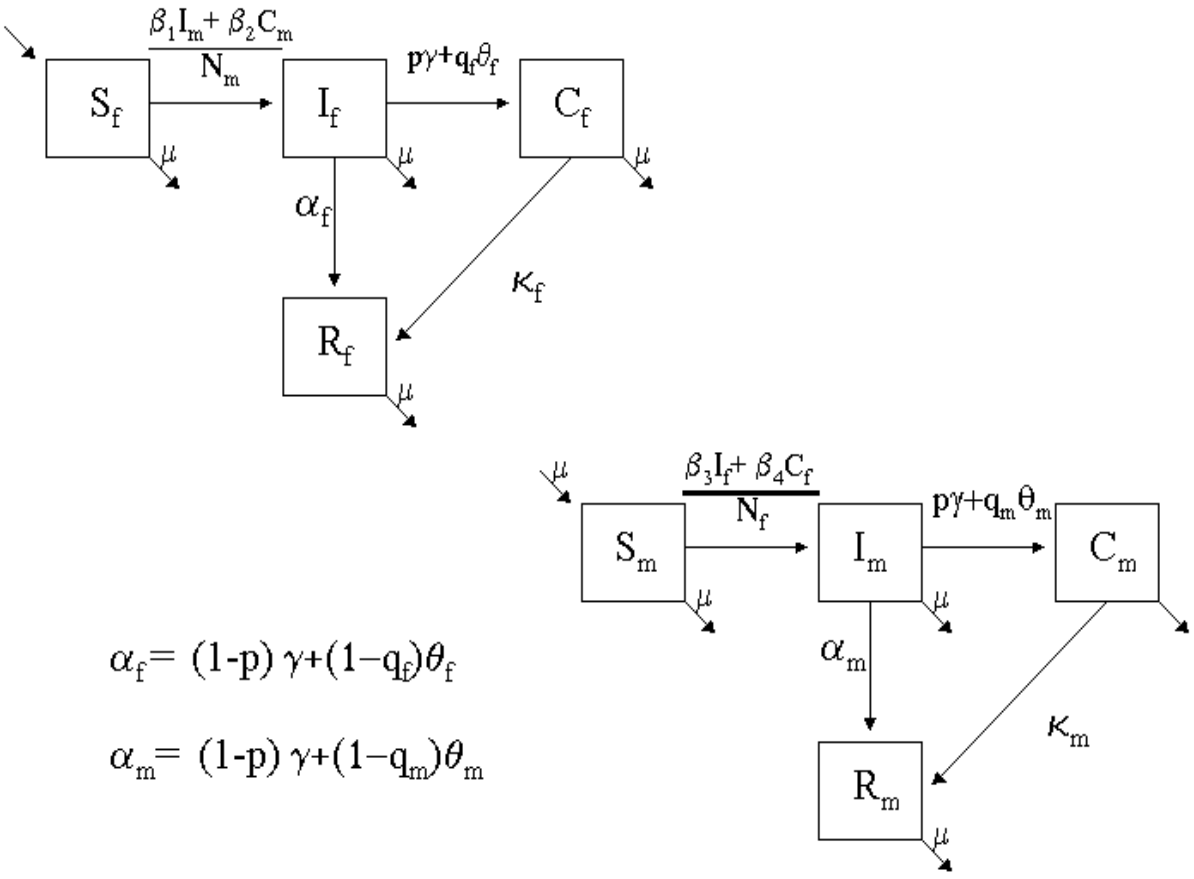

Figure 1: Schematic for the Two-Gender *SICR* Model

The dynamics of our model as represented by the following eight ordinary differential equations, the variables and parameters of which are described in Table 1.

$$\frac{dS_f(t)}{dt} = \mu N_f - \beta_1 S_f \frac{I_m}{N_m} - \beta_2 S_f \frac{C_m}{N_m} - \mu S_f \quad (1)$$

$$\frac{dI_f(t)}{dt} = \beta_1 S_f \frac{I_m}{N_m} + \beta_2 S_f \frac{C_m}{N_m} - I_f[\mu + \gamma + \theta_f] \quad (2)$$

$$\frac{dC_f(t)}{dt} = I_f[p\gamma + \theta_f q_f] - (\mu + \kappa_f) C_f \quad (3)$$

$$\frac{dR_f(t)}{dt} = [(1-p)\gamma + (1-q_f)\theta_f] I_f + \kappa_f C_f - \mu R_f \quad (4)$$

$$\frac{dS_m(t)}{dt} = \mu N_m - \beta_3 S_m \frac{I_f}{N_f} - \beta_4 S_m \frac{C_f}{N_f} - \mu S_m \quad (5)$$

$$\frac{dI_m(t)}{dt} = \beta_3 S_m \frac{I_f}{N_f} + \beta_4 S_m \frac{C_f}{N_f} - I_m[\mu + \gamma + \theta_m] \quad (6)$$

$$\frac{dC_m(t)}{dt} = I_m[p\gamma + \theta_m q_m] - (\mu + \kappa_m) C_m \quad (7)$$

$$\frac{dR_m(t)}{dt} = [(1-p)\gamma + (1-q_m)\theta_m] I_m + \kappa_m C_m - \mu R_m \quad (8)$$

Table 1: Parameter notation and meaning	
S_f	susceptible females
I_f	initially infected females
C_f	chronically infected females
R_f	recovered females
N_f	total female population
S_m	susceptible males
I_m	initially infected males
C_m	chronically infected males
R_m	recovered males
N_m	total male population
γ	natural rate at which individuals leave I_f, I_m
p	proportion of I_f, I_m with failed immune response
$1-p$	proportion of I_f, I_m with successful immune response
β_1	contact rate between S_f and I_m
β_2	contact rate between S_f and C_m
β_3	contact rate between S_m and I_f
β_4	contact rate between S_m and C_f
θ_f	rate at which females I_f are screened and subsequently treated
q_f	proportion of screened women who do not recover with treatment
$1-q_f$	proportion of screened women who recover with treatment
κ_f	treatment-recovery rate of C_f
θ_m	rate at which males in I_m are screened and subsequently treated
q_m	proportion of screened men who do not recover with treatment
$1-q_m$	proportion of screened men who recover with treatment
κ_m	treatment-recovery rate of C_m

3 Expression Analysis

Heesterbeek defines R_0 as the "expected number of secondary cases (new infected individuals) produced by one infectious individual during its entire infectious life in a [totally] susceptible population ... "[23]. In the case of our two-sex model, we expect R_0 to be the expected number of individuals of one gender that one index case in the same gender will cause in an entirely susceptible sexually active population. If each infective individual causes more than one secondary infection during his infectious life-span ($R_0 > 1$), it is intuitive that the epidemic will sustain itself. Likewise, if each infective does not cause more than one secondary infection during his infectious life-span ($R_0 < 1$), the number of infectives in

the population will tend toward zero, i.e., there is no endemic equilibrium. The $R_0 = 1$ threshold is important in the epidemic model, as determining what happens in the model as R_0 crosses that threshold can give insight into how the system is affected by changes in various parameters.

3.1 Disease-Free Equilibrium and R_0

We begin our search for the expression for R_0 by looking at the stability of the disease-free equilibrium (DFE). We expect the disease-free equilibrium to be locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$. By solving for the critical points of the differential equations 1-8, we find that

$$\text{DFE} = (N_f, 0, 0, 0, N_m, 0, 0, 0).$$

We will use the following two lemmas from [24] and [29] to explore the stability of the disease-free equilibrium, first defining the following notation:

$$f^\infty \equiv \limsup_{t\to\infty} f(t).$$

Lemma 3.1 *If $f, g : \Re^+ \to \Re$ are bounded, differentiable functions, then*

$$\limsup_{t\to\infty}(f(t) + g(t)) \leq f^\infty + g^\infty,$$

and if $\lim_{t\to\infty} g(t)$ exists,

$$\limsup_{t\to\infty}(f(t) + g(t)) = f^\infty + \lim_{t\to\infty} g(t).$$

Lemma 3.2 *(Fluctuation Lemma) If $f : \Re^+ \to \Re$ is a bounded, twice differentiable function with bounded second derivative, then there exists a sequence $\{t_m\} \to \infty$ such that*

$$\lim_{m\to\infty} f(t_m) = \limsup_{t\to\infty} f(t).$$

This sequence satisfies

$$f'(t_m) = 0, \text{ as } m \to \infty.$$

Theorem 3.1 *If*

$$R_0 \equiv \sqrt{\left(\frac{\beta_1}{\mu+\gamma+\theta_m} + \frac{\beta_2}{\mu+\kappa_m}\frac{p\gamma+q_m\theta_m}{\mu+\gamma+\theta_m}\right)\cdot\left(\frac{\beta_3}{\mu+\gamma+\theta_f} + \frac{\beta_4}{\mu+\kappa_f}\frac{p\gamma+q_f\theta_f}{\mu+\gamma+\theta_f}\right)} < 1,$$

then the disease-free equilibrium is globally asymptotically stable. If $R_0 > 1$, the disease-free equilibrium is unstable.

Proof of Theorem 3.1: Let $R_0 < 1$. Choose a sequence $t_m \to \infty$ such that

$$I_f(t_m) \to I_f^\infty, \quad \frac{d}{dt} I_f(t_m) \to 0.$$

From lemma 3.1, equation (2), and the fact that since $N_m = N_f$, $\frac{S_f}{N_m} < 1$ and $\frac{S_m}{N_f} < 1$, we have

$$0 \leq \beta_1 I_m^\infty + \beta_2 C_m^\infty - (\mu + \gamma + \theta_f) I_f^\infty. \tag{9}$$

Similarly, from equations (3, (6), and (7), we have

$$\begin{aligned} 0 &\leq (p\gamma + q_f\theta_f) X_f^\infty - (\mu + \kappa_f) C_f^\infty, & (10)\\ 0 &\leq \beta_2 I_f^\infty + \beta_4 C_f^\infty - (\mu + \gamma + \theta_m) I_m^\infty, & (11)\\ 0 &\leq (p\gamma + q_m\theta_m) X_m^\infty - (\mu + \kappa_m) C_m^\infty. & (12) \end{aligned}$$

We can use equations (10) and (12) to determine

$$\begin{aligned} C_f^\infty &\leq \left(\frac{p\gamma + q_f\theta_f}{\mu + \kappa_f}\right) I_f^\infty, & (13)\\ C_m^\infty &\leq \left(\frac{p\gamma + q_m\theta_m}{\mu + \kappa_m}\right) I_m^\infty, & (14) \end{aligned}$$

and we use the laws of inequalities, expression (9), and expression (11) to find that

$$\begin{aligned} 0 &\leq \beta_1 I_m^\infty + \beta_2 \left(\frac{p\gamma + q_m\theta_m}{\mu + \kappa_m}\right) I_m^\infty - (\mu + \gamma + \theta_f) I_f^\infty, & (15)\\ 0 &\leq \beta_3 I_f^\infty + \beta_4 \left(\frac{p\gamma + q_f\theta_f}{\mu + \kappa_f}\right) I_f^\infty - (\mu + \gamma + \theta_m) I_m^\infty. & (16) \end{aligned}$$

Further algebraic manipulation yields the following.

From inequality (15),

$$\begin{aligned} 0 &\leq \left(\frac{\beta_3 + \beta_4 \frac{p\gamma + q_f\theta_f}{\mu + \kappa_f}}{\mu + \gamma + \theta_f}\right) \left(\beta_1 I_m^\infty + \beta_2 \left(\frac{p\gamma + q_m\theta_m}{\mu + \kappa_m}\right) I_m^\infty - (\mu + \gamma + \theta_f) I_f^\infty\right),\\ 0 &\leq I_m^\infty \left(\frac{\beta_3 + \beta_4 \frac{p\gamma + q_f\theta_f}{\mu + \kappa_f}}{\mu + \gamma + \theta_f}\right) \left(\beta_1 + \beta_2 \left(\frac{p\gamma + q_m\theta_m}{\mu + \kappa_m}\right)\right) - \left(\beta_3 + \beta_4 \frac{p\gamma + q_f\theta_f}{\mu + \kappa_f}\right) I_f^\infty. \quad (17) \end{aligned}$$

Adding expressions (16) and (17) we have

$$\begin{aligned}
0 &\leq I_m^\infty\left[\left(\frac{\beta_3(\mu+\kappa_f)+\beta_4(p\gamma+q_f\theta_f)}{(\mu+\kappa_f)(\mu+\gamma+\theta_f)}\right)\left(\frac{\beta_1(\mu+\kappa_m)+\beta_2(p\gamma+q_m\theta_m)}{\mu+\kappa_m}\right)-(\mu+\gamma+\theta_m)\right],\\
0 &\leq I_m^\infty\left[\left(\frac{\beta_3(\mu+\kappa_f)+\beta_4(p\gamma+q_f\theta_f)}{(\mu+\kappa_f)(\mu+\gamma+\theta_f)}\right)\left(\frac{\beta_1(\mu+\kappa_m)+\beta_3(p\gamma+q_m\theta_m)}{(\mu+\kappa_m)(\mu+\gamma+\theta_m)}\right)-1\right].
\end{aligned}$$

From our definition of R_0, we can write

$$0 \leq I_m^\infty(R_0^2-1),$$

but since $I_m^\infty \geq 0$ and $R_0^2-1<0$,

$$\begin{aligned}
I_m^\infty(R_0^2-1) &\leq 0,\\
I_m^\infty &= 0, \quad \text{and}\\
I_m(t) &\to 0, \quad t\to\infty.
\end{aligned}$$

By expression (15) we have that

$$I_f(t)\to 0, \quad t\to\infty.$$

Furthermore, from inequalities (13) and (14) we have

$$\begin{aligned}
C_m(t)\to 0, \quad t\to\infty,\\
C_f(t)\to 0, \quad t\to\infty.
\end{aligned}$$

From equations (4) and (8) we find that

$$\begin{aligned}
R_f^\infty &\leq \frac{1}{\mu}\Big(\big((1-p)\gamma+(1-q_f)\theta_f\big)I_f^\infty+\kappa_f C_f\Big)=0,\\
R_m^\infty &\leq \frac{1}{\mu}\Big(\big((1-p)\gamma+(1-q_m)\theta_m\big)I_m^\infty+\kappa_m C_m\Big)=0,
\end{aligned}$$

so

$$\begin{aligned}
R_f(t)\to 0, \quad t\to\infty,\\
R_m(t)\to 0, \quad t\to\infty.
\end{aligned}$$

Finally, because we have constant population in both gender classes, we know that

$$\begin{aligned}
S_f(t)=N_f-I_f(t)-C_f(t)-R_f(t)\to N, \quad t\to\infty,\\
S_m(t)=N_m-I_m(t)-C_m(t)-R_m(t)\to N, \quad t\to\infty.
\end{aligned}$$

Hence, the DFE is globally asymptotically stable when $R_0 < 1$.
Let $R_0 > 1$. Because we have constant population in both gender classes, we can analyze the dynamics of I_f, I_m, C_f, C_m, R_f, and R_m, and we will have determined the dynamics for the entire system. The Jacobian of our system evaluated at the DFE is

$$J = \begin{pmatrix} -(\mu+\gamma+\theta_f) & \beta_1\frac{N_f}{N_m} & 0 & \beta_2\frac{N_f}{N_m} & 0 & 0 \\ \beta_3\frac{N_m}{N_f} & -(\mu+\gamma+\theta_m) & \beta_4\frac{N_m}{N_f} & 0 & 0 & 0 \\ p\gamma+q_f\theta_f & 0 & -(\mu+\kappa_f) & 0 & 0 & 0 \\ 0 & p\gamma+q_m\theta_m & 0 & -(\mu+\kappa_m) & 0 & 0 \\ (1-p)\gamma+(1-q_f)\theta_f & 0 & \kappa_f & 0 & -\mu & 0 \\ 0 & (1-p)\gamma+(1-q_m)\theta_m & 0 & \kappa_m & 0 & -\mu \end{pmatrix}.$$

In order to determine the stability of the DFE for $R_0 > 1$, we look at the eigenvalues of this matrix. If we find any to be positive, we know that the DFE is not stable. The characteristic equation of J is

$$y(\lambda) = (\lambda+\mu)^2(\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4),$$

where

$$\begin{aligned} a_1 &= F+f+T+t, \\ a_2 &= Ff+FT+Ft+fT+ft+Tt-\beta_1\beta_3, \\ a_3 &= FfT+Fft+fTt-(\beta_1\beta_3(F+f)+\beta_1\beta_4G+\beta_2\beta_3g), \\ a_4 &= FfTt-(\beta_1\beta_3Ff+\beta_2\beta_3Fg+\beta_1\beta_4fG+\beta_2\beta_4gG), \\ T &= \mu+\theta_f+\gamma, \\ t &= \mu+\theta_m+\gamma, \\ F &= \mu+\kappa_f, \\ f &= \mu+\kappa_m, \\ G &= p\gamma+q_f\theta_f, \\ g &= p\gamma+q_m\theta_m. \end{aligned}$$

Because $\lambda_1, \lambda_2 = -\mu$ are two eigenvalues of the Jacobian, from the Routh-Hurwitz criteria[10], we know that all the roots of the above quartic will be negative if and only if the following inequalities are true:

$$\begin{aligned} a_1 &> 0, \\ a_3 &> 0, \\ a_4 &> 0, \\ a_1 a_2 a_3 &> a_3^2 + a_1^2 a_4. \end{aligned}$$

However, when $R_0 > 1$,

$$\begin{aligned} a_4 &= FfTt\left(1 - \frac{(\beta_1 f + \beta_2 g)(\beta_2 F + \beta_4 G)}{FfTt}\right) \\ &= FfTt(1 - R_0^2) < 0, \\ \Rightarrow a_4 &< 0. \end{aligned}$$

Thus, not all of the eigenvalues of the Jacobian evaluated at the disease-free equilbrium are negative, and the DFE is unstable for $R_0 > 1$. □

3.2 Interpretation of the Reproductive Number

In order to better analyze the reproductive number we look at each term with the square root. The first expression is the contribution by the male gender. $\beta_1, \beta_2, \beta_3, \beta_4$ are contact rates as described in Table 1. The fraction $\frac{1}{\mu+\gamma+\theta_m}$ is the average amount of time that the males spend in the initial infected class. The fraction $\frac{1}{\mu+\kappa_m}$ is the average amount of time that the males spend in the chronic class. The fraction $\frac{p\gamma+q_m\theta_m}{\mu+\gamma+\theta_m}$ is the proportion of males that continue be infected and become part of the chronic class. Due to the symmetry of the model, the contribution by the expression by females in the system is similar, and comprises of the second half of the expression for R_0 .

3.3 Disease Endemic Equilibrium

Having now determined the dynamics of the disease-free equilibrium for $R_0 < 1$ and $R_0 > 1$, we turn our attention to the endemic equilibria. We solve our original set of differential equations for the critical points, and we find one unique endemic equilibrium (DEE).

$$\text{DEE} = (S_f^*, I_f^*, C_f^*, R_f^*, S_m^*, I_m^*, C_m^*, R_m^*),$$

where

$$S^*_f = \frac{N_f[{R_0}^2(\mu+\theta_m+\gamma)(\mu+\kappa_m)+\beta_1(\mu+\kappa_m)+\beta_2(p\gamma+q_m\theta_m)]}{{R_0}^2[\beta_2(p\gamma+q_m\theta_m)+\beta_1(\mu+\kappa_m)+(\mu+\theta_m+\gamma)(\mu+\kappa_m)],} \quad (18)$$

$$S^*_m = \frac{N_m[{R_0}^2(\mu+\theta_f+\gamma)(\mu+\kappa_f)+\beta_3(\mu+\kappa_f)+\beta_4(p\gamma+q_f\theta_f)]}{{R_0}^2[\beta_4(p\gamma+q_f\theta_f)+\beta_3(\mu+\kappa_f)+(\mu+\theta_f+\gamma)(\mu+\kappa_f)],} \quad (19)$$

$$I^*_f = \frac{\mu N_f(\mu+\kappa_f)({R_0}^2-1)}{(\mu+\kappa_f)(\mu+\gamma+\theta_f){R_0}^2+\beta_3(\mu+\kappa_f)+\beta_4(p\gamma+q_f\theta_f),} \quad (20)$$

$$I^*_m = \frac{\mu N_m(\mu+\kappa_m)({R_0}^2-1)}{(\mu+\kappa_m)(\mu+\gamma+\theta_m){R_0}^2+\beta_1(\mu+\kappa_m)+\beta_2(p\gamma+q_m\theta_m),} \quad (21)$$

$$C^*_f = \frac{\mu N_f(p\gamma+q_f\theta_f)({R_0}^2-1)}{(\mu+\gamma+\theta_f)(\mu+\kappa_f){R_0}^2+\beta_3(\mu+\kappa_f)+\beta_4(p\gamma+q_f\theta_f),} \quad (22)$$

$$C^*_m = \frac{\mu N_m(p\gamma+q_m\theta_m)({R_0}^2-1)}{(\mu+\gamma+\theta_m)(\mu+\kappa_m){R_0}^2+\beta_1(\mu+\kappa_m)+\beta_2(p\gamma+q_m\theta_m),} \quad (23)$$

$$R^*_f = \frac{N_f[\gamma(\mu+\kappa_f)+\theta_f(\mu+\kappa_f)-\mu(p\gamma+q_f\theta_f)]({R_0}^2-1)}{(\mu+\theta_f+\gamma)(\mu+\kappa_f){R_0}^2+\beta_3(\mu+\kappa_f)+\beta_4(p\gamma+q_f\theta_f),} \quad (24)$$

$$R^*_m = \frac{N_m[\gamma(\mu+\kappa_m)+\theta_m(\mu+\kappa_m)-\mu(p\gamma+q_m\theta_m)]({R_0}^2-1)}{(\mu+\theta_m+\gamma)(\mu+\kappa_m){R_0}^2+\beta_1(\mu+\kappa_m)+\beta_2(p\gamma+q_m\theta_m),}. \quad (25)$$

As R_0 increases from the $R_0 = 1$ threshold, the endemic equilibrium values for all the I, C, and R classes go from being always negative to being always positve, and the endemic values for S_m and S_f become less than N_m and N_f, respectively. This represents the existence of a forward bifurcation, as shown in Figure 2. We are unable to prove local stability for the endemic equilibrium, though, as can be seen in section 4, our endemic equilibrium seems to be stable.

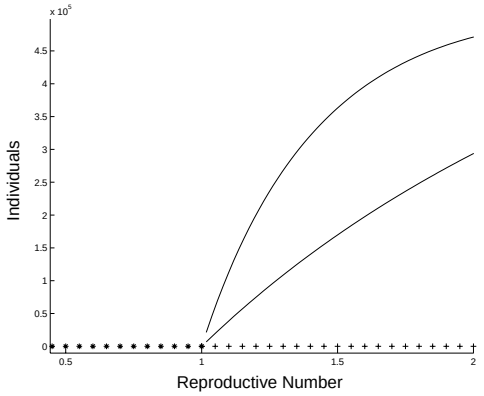

Figure 2: A bifurcation diagram showing the appearance of initially infected males (upper curve) and initially infected females (lower curve) in the positive domain at $R_0 = 1$. The DFE is unstable for $R_0 > 1$ and stable for $R_0 < 1$. Other non-susceptible classes appear at the same threshold values but are not shown.

4 Simulations

Table 2: Parameter Values for Simulations

Parameter	Value	Units
N_f	93088389^a	individuals
N_m	93088389^a	individuals
γ	$.69^b$	time^{-1}
p	$.2^b$	unitless
β_1	2	time^{-1}
β_2	1.2	time^{-1}
β_3	1.33	time^{-1}
β_4	.80	time^{-1}
θ_f	1^c	time^{-1}
q_f	$.1^c$	unitless
κ_f	.1	time^{-1}
θ_m	.2	time^{-1}
q_m	.1	unitless
κ_m	0	time^{-1}

[a] U.S. Census Bureau.
[b] HPV Hotline, American Social Health Association.
[c] Journal of American Medical Association, 2002.

The complexity of our endemic equilibrium makes it difficult to analyze its stability. However, we were able to use simulations done in Matlab[5] to predict stability. Figure 3 represents a portion of the simulations run. Each simulation was run using the same parameter values (see Table 2) but varying initial conditions (see Appendix). By inspecting the simulations, we note a definite tendency toward our expected endemic equilibrium values in every class. Though this does not prove stability of the DEE, it does suggest that the system is strongly attracted to the DEE when $R_0 > 1$.

5 Discussion

The main goal of our research was to determine the effects that male screening and treatment have on the dynamics of HPV16 transmission in our population. Figure 4 shows the relationship between R_0 and the screening and treatment rates of males and females. With a fixed female screening and treatment rate (θ_f), increasing male screening and treatment (θ_m) lowers R_0. We can conclude that increased male screening and treatment will decrease the number of secondary infections caused by an individual. Unfortunately as we further examine Figure 4, we see that even with screening and treating males five times a year ($\theta_m = 5$), R_0 does not decrease below unity. Therefore, no biologically realistic values of θ_m are large enough to drive the endemic to extinction. If we allow both genders, treatment and screening rates to increase, we see that R_0 can be driven to a, but R_0 is still not driven below unity for all biologically feasible θ_f and θ_m values. Though the disease cannot be driven to extinction with this approach, since R_0 does decrease, the incidence of infection in women will also become less frequent with increased treatment. Because the number of deaths per year due to cervical cancer is highly correlated to the number of individuals infected, this lowering of the reproductive number should reduce the number of cervical cancer deaths per year.

6 Future Work

In the future, we would like to complete analysis of stability of the DEE for $R_0 > 1$. Our method for proving the stability for the DFE when $R_0 < 1$ could be used for other models with a chronic state, perhaps to analyze a multiple-strain model of a disease like HPV.

Using this model to investigate the effects of a preventive vaccine for HPV could be informative. The effect of the vaccine could be represented in the model in three different ways:

[5]MATLAB is a registered trademark of *The Math Works, Inc.*, All Rights Reserved.

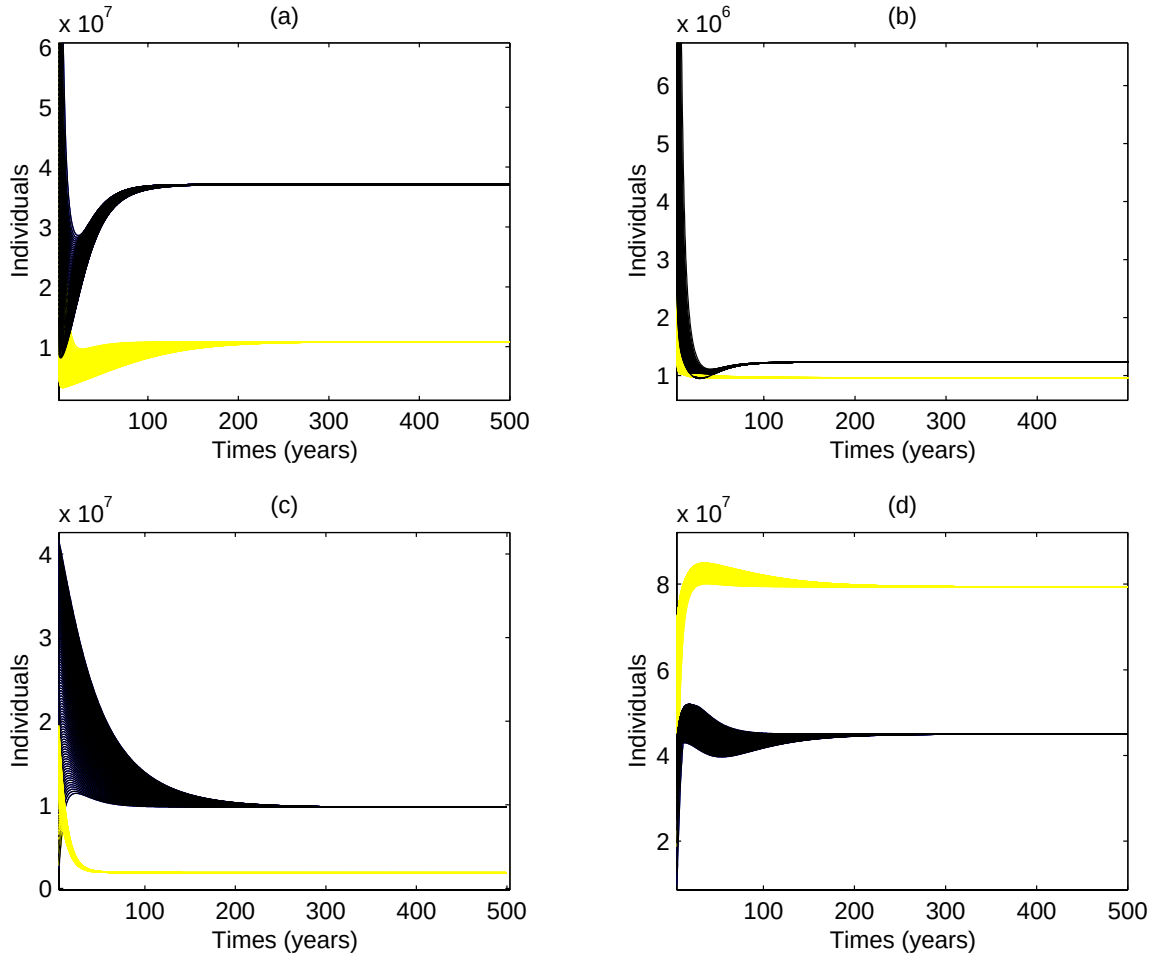

Figure 3: The dynamics of 500 simulations run with the same parameters and different initial values for all classes ((a) S-classes, (b) I-classes, (c) C-classes, (d) R-classes), demonstrating the tendency toward the expected equilibrium values. Black represents the male classes; grey represents the female classes. Note that the female recovered class has a greater number of individuals than the male recovered class, but only in this class does this relationship occur. This is due to the high infectiousness of males, as well as the lack of screening and treatment for the male I- and C-classes.

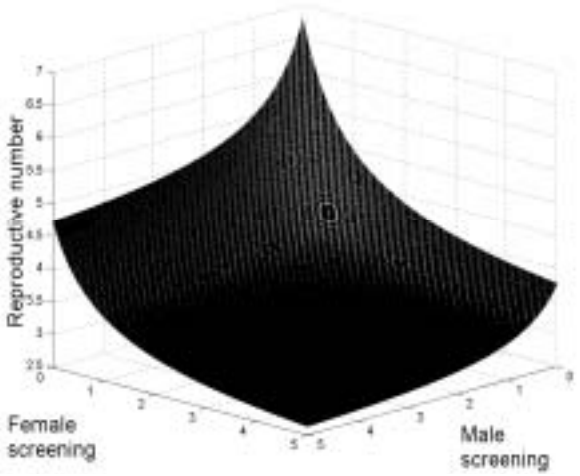

Figure 4: The reproductive number R_0 with respect to θ_m and θ_f, decreasing as both screening and treatment rates increase.

1) A change in the rate at which susceptible individuals are infected

2) Susceptible individuals moving into the recovered class as they are vaccinated

3) Modifying the model so susceptible individuals go to a "vaccinated" class from which they could become susceptible again if the effects of the vaccine wear off.

We could also show the effects of a therapeutic vaccine on the general population using this model. Instead of preventing an individual from initially contracting the virus, the therapeutic vaccines that are currently under development (such as those for HIV) would be given to individuals who are already infected in order to reduce their infectiousness to others[22]. This would affect the rate at which a vaccinated individual's partners become infected and could be analyzed after adding certain changes to our model.

To better reflect reality, age structure could be incorporated into the model, as people of certain ages tend to have different sexual behavior. This, in turn, would lead individuals in different age classes to have a greater or lesser effect on the system.

The model could also be modified to include a "core group" of individuals who are at a much higher risk of contracting and transmitting HPV. The changes in the dynamics of the population resulting from the treatment of the core group could be analyzed.

7 Acknowledgements

This research has been partially supported by grants given by the National Science Foundation, National Security Agency, and the Sloan Foundation (through the Cornell-Sloan National Pipeline Program in the Mathematical Sciences). Substantial financial and moral support was also provided by the Office of the Provost of Cornell University, the College of Agriculture and Life Sciences (CALS), and the Department of Biological Statistics and Computational Biology. The authors are solely responsible for the views and opinions expressed in this research; it does not necessarily reflect the ideas and/or opinions of the funding agencies and/or Cornell University.

The authors are very grateful to Carlos Hernández, Baojun Song, and Danielle Lyles for their assistance throughout the course of this research. We would like to thank Paul Hurtado, Chris Kribs-Zaleta, and Laura Jones for advice at important times during the project. We are also thankful to Steve Wirkus, Carlos Castillo-Chavez, and the MTBI community. In addition, the authors would like to give a special thanks to Guarionex Jordan-Salivia for his support.

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Appendix – MatLab[5] files

```
function dx=HPVsim(t,x)

%Sf in system is x(1)
%If in system is x(2)
%Cf in system is x(3)
%Rf in system is x(4)
%Sm in system is x(5)
%Im in system is x(6)
%Cm in system is x(7)
%Rm in system is x(8)

global beta1 beta2 beta3 beta4 mu gamma theta1 theta2 kappa1 kappa2 q1 q2 p N

dx=[mu*N-x(1).*((beta1*x(6)+beta2*x(7))/(N))-mu.*x(1);
    x(1).*((beta1*x(6)+beta2*x(7))/(N))-(gamma+theta1+mu)*x(2);
    x(2)*(p*gamma+q1*theta1)-(mu+kappa1)*x(3);
    ((1-p)*gamma+(1-q1)*theta1)*x(2)+kappa1*x(3)-mu*x(4);
    mu*N-x(5).*((beta3*x(2)+beta4*x(3))/(N))-mu.*x(5);
    x(5).*((beta3*x(2)+beta4*x(3))/(N))-(gamma+theta2+mu)*x(6);
    x(6)*(p*gamma+q2*theta2)-(mu+kappa2)*x(7);
    ((1-p)*gamma+(1-q2)*theta2)*x(6)+kappa2*x(7)-mu*x(8)];
%%%%%%%%%%%%%%%%%%%%%%

function y=plotHPV(tf)
global beta1 beta2 beta3 beta4 mu gamma q1 p N theta1 theta2 kappa1 kappa2 q2

beta1=2;
beta2 = 1.2;
q1 = .1;
q2=0.1;
kappa1 = 0.1000;
kappa2=0;
n=93088389;
N=93088389;
mu =1/50;
gamma = 0.6900;
```

```
theta1 =1;
theta2=.2;
k=kappa2;
K=kappa1;
beta3 =2/3*2;
beta4 = 2/3*1.2;
R0=(beta1*mu+beta1*k+beta2*p*gamma+beta2*q2*theta2)*(beta3*mu+beta3*K+beta4*p*gamma+
beta4*q1*theta1)/((mu+theta1+gamma)*(mu+theta2+gamma)*(mu+k)*(mu+K));
p=.2;
tspan=[0,tf];
for i=1:100
    j=i*130004

x0=[N-6*j;3*j;2*j;j;N-6*j;2*j;3*j;j];
[t,z]=ode45('HPVsim',tspan,x0);

subplot(221),plot(t,z(:,1),'y')
subplot(221), xlabel('Times (years)')
subplot(221), ylabel('Individuals')
hold on
subplot(221),plot(t,z(:,5),'b')
subplot(221),title('(a)')

subplot(222),plot(t,z(:,2),'y')
subplot(222), xlabel('Times (years)')
subplot(222), ylabel('Individuals')
hold on
subplot(222),plot(t,z(:,6),'b')
subplot(222),title('(b)')

subplot(223),plot(t,z(:,3),'y')
subplot(223), xlabel('Times (years)')
subplot(223), ylabel('Individuals')
hold on
subplot(223),plot(t,z(:,7),'b')
subplot(223),title('(c)')

subplot(224),plot(t,z(:,4),'y')
```

```
subplot(224), xlabel('Times (years)')
subplot(224), ylabel('Individuals')
hold on
subplot(224),plot(t,z(:,8),'b')
subplot(224),title('(d)')

end
%%%%%%%%%%%%%%%%%%%%%%%

function y=plotHPV2(tf)
global beta1 beta2 beta3 beta4 mu gamma q1 p N theta1 theta2 kappa1 kappa2 q2


beta1=2;
beta2 = 1.2;
q1 = .1;
q2=0.1;
kappa1 = 0.1000;
kappa2=0;
n=93088389;
N=93088389;
mu =1/50;
gamma = 0.6900;
theta1 =1;
theta2=.2;
k=kappa2;
K=kappa1;
beta3 =2/3*2;
beta4 = 2/3*1.2;
R0=(beta1*mu+beta1*k+beta2*p*gamma+beta2*q2*theta2)*(beta3*mu+beta3*K+beta4*p*gamma+
beta4*q1*theta1)/((mu+theta1+gamma)*(mu+theta2+gamma)*(mu+k)*(mu+K));
p=.2;

tspan=[0,tf];
for i=1:100
    j=i*130004

x0=[N-6*j;3*j;2*j;j;N-6*j;2*j;3*j;j];
```

```
[t,z]=ode45('HPVsim',tspan,x0);
figure(1);
plot(t,z(:,1),'b');
hold on
figure(2)
plot(t,z(:,2),'r');
hold on
figure(3)
plot(t,z(:,3),'g');
hold on
figure(4)
plot(t,z(:,4),'y');
hold on
figure(5)
plot(t,z(:,5),'b');
hold on
figure(6)
plot(t,z(:,6),'m');
hold on
figure(7)
plot(t,z(:,7),'k');
hold on
figure(8)
plot(t,z(:,8),'c');
hold on
end
legend('Sf','If','Cf','Rf','Sm','Im','Cm','Rm');
xlabel('T(In years)');
ylabel('I(t)');
title('Stability of Endemic Equilibrium');
hold on
```