A Cost Analysis of Human Papillomavirus: Individual Education vs. Mass-Media Campaign

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Abstract

Human Papillomavirus (HPV), a common sexually transmitted virus, is a collection of more than 100 viruses, some of which (called "high-risk" oncogenic or carcinogenic HPV) are associated with certain types of cancer. HPV 16 and 18 cause approximately 70% of all cervical cancer. An estimated 11,150 new cases of cervical cancer will develop in the U.S. in 2007. In 2006, the FDA approved the first vaccine to prevent cervical cancer, designated for females ages 9-26, called Gardasil. Studies have indicated Gardasil has a 95-100% success against HPV types 6, 11, 16, and 18. Many studies have shown that there exists a lack of HPV awareness, as well as knowledge of causes, effects and preventive measures. In this study we compare two strategies for controlling the spread of carcinogenic HPV in the population, while minimizing cost. The research is conducted via a cost analysis of a mandatory vaccination policy vs. a mass-media awareness campaign, each individually modeled with a system of differential equations. Mandatory (but not universal) vaccination includes individual-based education at the time of vaccination only, while the mass-media campaign is assumed to be ongoing. In both cases the education influences females to get vaccinated and/or reduce their sexual activity, but is of limited duration. We use qualitative analysis to derive the respective control reproductive numbers, and numerical analysis to obtain the total costs of vaccination, education, high sexual activity, and expected cancer treatment costs for infected females in both models. Our results support the conclustions of a 2005 study analyzing the epidemiology of HPV with a potential vaccination that even in the presence of a vaccine, the infective population will remain large due to a high transmission rate. Our results also support the conclusion that a high transmission rate and a high reproductive rate require a high efficacy and high vaccine coverage to eliminate the epidemic.

1 Introduction

The Human Papillomavirus (HPV), a sexually transmitted virus, infects at least 50% of all sexually active people [11]. The virus is transmitted by genital and skin-to-skin contact, contracted by both males and females. It is unknown whether or not using a condom at time of intercourse will reduce the odds of contracting HPV. HPV is a collection of more than 100 viruses that can be categorized in two groups: low-risk and high-risk viruses [11]. In addition, high-risk HPVs account for 70% of cervical cancer [11]. The high-risk HPV carcinogenic strains integrate their genetic code into the genome of the host cell. Low-risk viruses can cause common warts found on non-genital skin (for example on the hands and feet). In addition genital warts that may cause low-grade cervix cell changes that do not develop into cancer are also due to low-risk HPV [20]. Half a million women each year contract cervical cancer, which claims a quarter of a million lives worldwide [9]. As long as HPV remains endemic, cervical cancer will continue to take a toll on the sexually active population. There is currently no cure for HPV, although some infections go away spontaneously in the early stages, and others can remain asymptomatic for years [11]. There is currently no test for HPV infection among the male population, although a HPV test has been approved by The Food and Drug Administration (FDA) for females [9].

Merck & Co., Inc. designed the first vaccine to combat cervical cancer, Gardasil, in order to prevent HPV 6, 11, 16, and/or 18-related cervical cancer, cervical dysplasias, vulvar or vaginal dysplasias, or genital warts [7]. The vaccine is only effective when given prior to infection of HPV 6, 11, 16 and 18 [10]. However, the FDA approved Gardasil for females in June 2006. Gardasil has a 95–100% effective success rate amongst females between the ages of 9 and 26. Clinical trials have shown no waning in vaccine efficacy over time in the 5 years since tracking began [14].

Public health agencies and state and federal governments are still debating whether to establish a mandatory vaccination policy for HPV. A mandatory vaccination policy ensures that the vaccinated population will not become infected. However, this may lead to behavioral changes to increase sexual activity rates following vaccination because individuals believe they are protected [4]. The increase of sexual activity could then result in an increase of other sexually transmitted infections. On the other hand, a voluntary vaccination policy would yield fewer vaccinated individuals. Thus, while a percentage of the population will be vaccinated, many would remain infectious and offset the results of the vaccination program. The success of such a vaccination program would require an education campaign [4].

For this reason, education campaigns encouraging individuals (in particular, vaccinated women) to lower their sexual activity levels (or abstain altogether) have become an important part of this debate. Texas and other U.S. states are in the process of attempting to implement a mandatory vaccination policy in order to decrease the reproductive rate of the virus in the population [2]. In early 2007, the governor of Texas attempted to implement such a policy by executive order, but the order was struck down, in part because of the objections cited above. The current (2007) Gardasil advertising campaign

sends the message of decreasing sexual activity in addition to aiming to initiate vaccination amongst the female population. Education campaigns targeting sexual activity levels can also affect the spread of HPV itself, to the extent that they reach unvaccinated individuals (including asymptomatic infected individuals unaware of their condition who seek vaccination). A sexually active individual has a higher chance of contracting HPV when the person begins sexual activity at an early age, has many sexual partners, and/or has a sexual partner who has had many partners. Lowering the rate at which individuals contract HPV depends heavily upon their choice of remaining abstinent, limiting the overall number of sexual partners, and choosing a partner that has had no or few sexual partners [11].

This study explores the national potential effects of vaccination and education campaigns on HPV transmission in a sexually active heterosexual population. Using mathematical models, we compare the effects of two strategies for controlling the spread of HPV 6, 11, 16 and 18, in terms of both their direct effects on HPV itself (reproductive number, numbers of cases and deaths, etc.) and an overall cost analysis that incorporates average per capita costs from other STDs (including HPVs not targeted by Gardasil) in order to address the issue of sexual activity levels for those women vaccinated against HPV. One strategy involves a mandatory vaccination policy for USA females in the public school system entering the sixth grade, coupled with an individual-based education campaign applied at the time of vaccination. This study assumes that females entering the sixth grade have not yet become sexually active, hence, the vaccination will have an optimal effect on this female population. The other strategy involves an ongoing mass-media campaign, like the present Gardasil promotion, which encourages females to both seek vaccination and lower their sexual activity level.

The following sections describe our two mathematical models for HPV transmission with vaccination and education, give a qualitative analysis of their behavior, estimate parameter values from the literature in order to make quantitative estimates and cost analyses, and finally draw some conclusions from our comparison.

2 Model Descriptions

Throughout the U.S., states are trying to mandate vaccination with Gardasil to girls in the public school system entering the sixth grade. Therefore, the population in Model 1 will be restricted to a female population consisting of ages 11-26. The population in Model 2 reflects the approved female ages for Gardasil, 9–26. Because Gardasil protects against only 4 strains of HPV (6, 11, 16, and 18), we define our infected class(es) in terms of infections with those strains of HPV only, and do not address directly infections with other STDs or other strains of HPV.

For Model 1, the susceptible S class consists of sexually active females ages 11–26 in non-monogamous relationships. In Model 2, the S class is identical, except we expand the age group to 9–26. The V_E class consists of members of the population who respond to the campaign and get vaccinated with Gardasil as well as reduce their sexual activity. The

vaccinated class V consists of women who are vaccinated but no longer reducing sexual activity. The I class describes women who are infected with one of the 4 strains of HPV prevented by Gardasil. The I_E class are females who are infected (as in the I class), but are also educated. These women may not know they are infected, but they are reducing sexual activity due to the mass-media campaign. In fact these women may attempt to get vaccinated (unaware of their infection). A female may receive the Gardasil vaccination, but the vaccine cannot cure HPV 6, 11, 16, or 18 if the female had the infection prior to vaccination. Even so, if a female has contracted one of the four strains it is best to administer Gardasil, in order to prevent further infection of the remaining three strains. However, they will not move into the V_E or V class in our model because they are already infected with one of the four strains of HPV prevented by Gardasil. The S_E class consists of women who respond to the mass-media campaign by reducing sexual activity, but do not get vaccinated.

Class definitions are summarized in Table 1.

Table 1: Classes

Classes	Description
V	Vaccinated individuals who can no longer infect others
S	Susceptible individuals who are at risk of being infected
I	Individuals who are infected and have the ability to infect others
V_E	Individuals who are both vaccinated and educated
S_E	Individuals who are educated but not vaccinated
I_E	Individuals who are both educated and infected

2.1 Model 1: Individual-Based Education with Mandatory Vaccination

In Model 1, we assume that a mandatory vaccination policy is in place for females entering the 6th grade to be vaccinated with the HPV vaccine Gardasil. Thus, females at this age will go into one of two classes, V_E or S. We assume that a proportion p ($0 < p \leq 1$) of females enter the V_E class where they are vaccinated with Gardasil and then educated at the time of vaccination about risks involved with sexual activity. Although the females who are vaccinated are educated at the time of vaccination, we assume that this education may eventually wear off in the absence of an ongoing mass-media campaign. In this case, the vaccinated girls may not continue to decrease their sexual activity and will move into the vaccinated class V (no longer educated), at a constant per capita rate (the reciprocal of the average duration of education).

However, there will be some females (a proportion $1 - p$) who do not get vaccinated. This would be due to the fact that some females at age 11–12 (entering the 6th grade) are not in the public school system in America, and thus would not be mandated to get the vaccine. The females who do not get vaccinated will then move into the susceptible class S. These individuals may either become infected with one of the four strains of HPV

protected by Gardasil, through sexual activity, or remain susceptible and eventually age out of the population. Finally, since infection with these four strains is assumed to be permanent, infected individuals remain in the I class until they die of natural causes or infection or age out of the population under study. We include an additional death rate due to HPV-related causes (such as cancer).

The diagram in Figure 1 summarizes these assumptions.

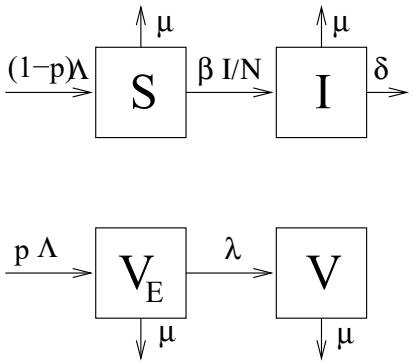

Figure 1: Flow diagram for Model 1

The following are the associated ODE's for Model 1:

$$\frac{dS}{dt} = (1-p)\Lambda - \beta S\frac{I}{N} - \mu S \tag{1}$$

$$\frac{dI}{dt} = \beta S\frac{I}{N} - (\mu+\delta)I \tag{2}$$

$$\frac{dV_E}{dt} = p\Lambda - \lambda V_E - \mu V_E \tag{3}$$

$$\frac{dV}{dt} = \lambda V_E - \mu V \tag{4}$$

2.2 Model 2: Mass-Media Education and Voluntary Vaccination

Model 2 (illustrated in Figure 2) describes the effects of an ongoing mass-media campaign. This campaign is designed to educate females to get vaccinated with Gardasil and also to reduce their sexual activity. This will prevent against other strains of HPV and other STDs not prevented by the vaccine.

The transitions for this model are as follows. We begin with the S class. We assume that some women who respond to the mass-media campaign will get vaccinated and thus move to the V_E class. Because the campaign also encourages women to reduce sexual activity, we can assume that those who get vaccinated will also reduce their sexual activity for at least some time. Once this education "wears off", women may then move to the V class. Movement between the V_E and V classes will continue in both directions due to the fact that the campaign is ongoing and women may get re-educated. We also assume that

some women may be influenced by the public education campaign to lower their sexual activity levels without seeking vaccination (perhaps because they cannot afford the cost of the vaccination series, which at this writing is US$360 [7]); the initiation and waning of this effect causes similar movement between the S and S_E classes. Women who do not get vaccinated may be infected through sexual contact, and move to the I class. There are ongoing transitions between the I and I_E classes due to the fact that education may wear off after some time period. Some women who are not vaccinated but are educated may also be infected through sexual contact, and move to the I_E class. Again, at any stage of the model, women may age out of the population under study or they may die.

Parameters describing transition rates for both models are summarized in Table 2.2.

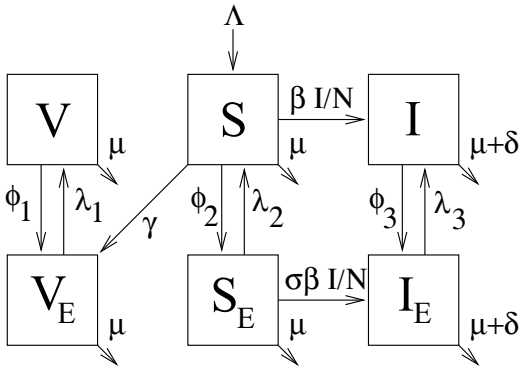

Figure 2: Flow diagram for Model 2

The following are the associated ODE's for Model 2:

$$\frac{dS}{dt} = \Lambda + \lambda_2 S_E - \beta S\frac{I}{N} - \gamma S - \phi_2 S - \mu S \tag{5}$$

$$\frac{dI}{dt} = \beta S\frac{I}{N} + \lambda_3 I_E - \phi_3 I - (\mu + \delta)I \tag{6}$$

$$\frac{dV}{dt} = \lambda_1 V_E - \phi_1 V - \mu V \tag{7}$$

$$\frac{dS_E}{dt} = \phi_2 S - \lambda_2 S_E - \mu S_E - \sigma\beta S_E\frac{I}{N} \tag{8}$$

$$\frac{dI_E}{dt} = \phi_3 I + \sigma\beta S_E\frac{I}{N} - \lambda_3 I_E - (\mu + \delta)I_E \tag{9}$$

$$\frac{dV_E}{dt} = \gamma S + \phi_1 V - \lambda_1 V_E - \mu V_E \tag{10}$$

For simplicity, we are first considering the case where education is 100% effective, so $\sigma = 0$. Thus, $\frac{dS_E}{dt}$ and $\frac{dI_E}{dt}$ can be reduced to the following:

$$\frac{dS_E}{dt} = \phi_2 S - \lambda_2 S_E - \mu S_E \tag{11}$$

$$\frac{dI_E}{dt} = \phi_3 I - \lambda_3 I_E - (\mu + \delta)I_E \tag{12}$$

Table 2: Parameters

Parameters	Description
Λ	Constant birth rate
μ	Per-capita natural death rate
δ	Per-capita death rate due to infection
β	Per-capita rate of infection for susceptible individuals
σ	The reciprocal of the efficiency of education
γ	Rate at which susceptible individuals are being vaccinated due to the mass-media campaign
λ, λ_1	Per-capita rate at which vaccinated individuals lose education
λ_2	Per-capita rate at which susceptible individuals lose education
λ_3	Per-capita rate at which infected individuals lose education
ϕ_1	Per-capita rate at which a vaccinated individual becomes educated again
ϕ_2	Per-capita rate at which a susceptible individual becomes educated but not vaccinated
ϕ_3	Per-capita rate at which an infected individual becomes educated but not vaccinated
p	Proportion vaccination in the mandated vaccination policy
N	Total female population ages 9 - 26

3 Analysis

The vaccinated class and the vaccinated and educated class in Model 1 do not depend on the susceptible class or the infective class. Thus, we can solve for V and V_E explicitly. We find that

$$V_E = \frac{p\Lambda}{\lambda + \mu}(1 - e^{-(\lambda+\mu)t})$$

and

$$V = \frac{\lambda}{\mu}\frac{p\Lambda}{\lambda + \mu}(1 - e^{-(\lambda+\mu)t}).$$

When studying the equilibria we can then look at the system as a system of only two equations involving S and I.

3.1 DFE and R_0 of Model 1

In order to determine whether HPV will invade a population or stabilize over a given region we must investigate the basic reproductive number, R_0, a threshold condition in epidemiology. R_0 represents the affected number of secondary cases caused by a typical infected individual during its infectious period. The reproductive number is computed for both models using the next-generation method, which requires the disease free equilibrium.

For Model 1, we find the disease free equilibrium to be

$$(S, I, V_E, V) = \left(1 - p, 0, p\frac{\mu}{\lambda + \mu}, p\frac{\lambda}{\lambda + \mu}\right)\frac{\Lambda}{\mu}$$

and the reproductive number to be

$$R_0 = \frac{\beta(1 - p)}{\mu + \delta}$$

In order to better understand the meaning of R_0, we look at each part separately; $1 - p$ represents the proportion of individuals who start in the susceptible class, β represents the rate of individuals moving into the infected class, and $\frac{1}{\mu+\delta}$ represents the average infectious period. The disease free equilibrium is locally stable when $R_0 < 1$ and unstable when $R_0 > 1$. Details of these calculations can be found in the Appendix.

3.2 Endemic Equilibrium of Model 1

We then look at the endemic equilibrium, which exists when $R_0 > 1$. For Model 1 we find this to be

$$\left(\frac{\mu + \delta}{\beta}, \frac{\mu}{\beta}(R_0 - 1), p\frac{\mu}{\lambda + \mu}, p\frac{\lambda}{\lambda + \mu}\right)\frac{\Lambda}{\mu}.$$

If $R_0 > 1$ the endemic equilibrium is locally stable. We find this by studying the stability of the two-dimensional system. The stability calculations can be found in the Appendix.

3.3 Global Stability of Model 1

Because the equations for the V and V_E class in Model 1 can be solved explicitly, we are able to view the global behavior of the entire system using only the equations for the S and I classes. By looking at the two-dimensional system, the analysis for global stability can be done using the Poincare-Bendixson Theorem along with Dulac's criterion. By applying the Poincare-Bendixson Theorem, we are able to show that all solutions of the equations for Model 1 tend toward either the disease-free equilibrium or the endemic equilibrium, depending on the value of R_0. It must first be shown that there are no unbounded solutions in this system. We consider the change in the total population for the S and I classes. Using the rates given in Model 1, we have the following equation:

$$N' = (1 - p)\Lambda - \mu N - \delta I.$$

Thus $N' \leq (1 - p)\Lambda - \mu N$. We know then that this differential inequality can be solved explicitly for $N(t)$. We see that $N(t) \leq [N(0) - (1 - p)\frac{\Lambda}{\mu}]e^{-\mu t} + (1 - p)\frac{\Lambda}{\mu}$. Thus, starting at $t = 0$, then $N(t) \leq max(N(0), (1 - p)\frac{\Lambda}{\mu})$. Since we assume that $N = S + I$, by well-posedness $S \geq 0$, $I \geq 0$ for all t, and $N(t)$ is bounded above, then S and I are

individually bounded above as well. Thus there are no unbounded solutions to the system of equations for Model 1.

Applying Dulac's criterion to the system allows us to rule out any periodic orbits. The computations for Dulac's criterion can be seen in the Appendix.

Thus, we have ruled out unbounded solutions and limit cycles. Then by the Poincare-Bendixson Theorem, all solutions to the system will tend toward an equilibrium. Thus, we can conclude that each locally stable equilibrium is in fact globally stable.

3.4 DFE and R_0 of Model 2

For Model 2, the disease free equilibrium is

$$(S^*, 0, V^*, S_E^*, 0, V_E^*)$$

where

$$\frac{S^*}{N} = \frac{\mu}{\mu + \gamma + \frac{\mu}{\lambda_2+\mu}\phi_2}, \frac{V^*}{N} = \frac{\lambda_1}{\lambda_1 + \phi_1 + \mu}\frac{\gamma}{\mu + \gamma + \frac{\mu}{\lambda_2+\mu}\phi_2},$$

$$\frac{S_E^*}{N} = \frac{\frac{\mu}{\lambda_2+\mu}\phi_2}{\mu + \gamma + \frac{\mu}{\lambda_2+\mu}\phi_2}, \frac{V_E^*}{N} = \frac{\phi_1 + \mu}{\lambda_1 + \phi_1 + \mu}\frac{\gamma}{\mu + \gamma + \frac{\mu}{\lambda_2+\mu}\phi_2},$$

and

$$N = \frac{\Lambda}{\mu}.$$

The corresponding reproductive number, R_0 is

$$\frac{S^*}{N}\frac{\beta}{\mu + \delta + \frac{\mu+\delta}{\mu+\delta+\lambda_3}\phi_3}.$$

The disease free equilibrium breaks the model into three flows: demographic renewal, education, and vaccination. Demographic renewal is associated with rate μ and contributes to the S class, education is associated with rate $\frac{\mu}{\lambda_3+\mu}\phi_2$ and contributes to the S_E class, and vaccination is associated with rate γ and contributes to the V and V_E classes.

We then look at each part of R_0 separately in order to better understand its meaning. $\frac{S^*}{N}$ represents the proportion of susceptible individuals, β represents the rate of individuals entering the infected class, and $\mu + \delta + \frac{\mu+\delta}{\mu+\delta+\lambda_3}\phi_3$ represents the rate of individuals moving out of the infected class. $\frac{\mu+\delta}{\mu+\delta+\lambda_3}$ represents the proportion of individuals who leave the infected class via education, who do not re-enter it. The disease free equilibrium is stable when $R_0 < 1$ and unstable when $R_0 > 1$.

3.5 Endemic Equilibrium of Model 2

For Model 2, the endemic equilibrium is

$$(S^*, I^*, V^*, S_E^*, I_E^*, V_E^*)$$

where,

$$\frac{S^*}{N} = \frac{(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)}{\beta(\lambda_3+\mu+\delta)},$$

$$\frac{I^*}{N} = \frac{\mu(\lambda_3+\mu+\delta)}{(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)} - \frac{(\gamma+\mu)(\lambda_2+\mu)+\phi_2\mu}{\beta(\lambda_2+\mu)},$$

$$\frac{V^*}{N} = \frac{\lambda_1\gamma(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)}{\mu\beta(\lambda_1+\mu+\phi_1)(\lambda_3+\mu+\delta)}, \frac{S_E^*}{N} = \frac{\phi_2(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)}{\beta(\lambda_2+\mu)(\lambda_3+\mu+\delta)},$$

$$\frac{I_E^*}{N} = \frac{\phi_3}{\lambda_3+\mu+\delta}\left[\frac{\mu(\lambda_3+\mu+\delta)}{(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)} - \frac{(\gamma+\mu)(\lambda_2+\mu)+\phi_2\mu}{\beta(\lambda_2+\mu)}\right],$$

$$\frac{V_E^*}{N} = \left[1+\frac{\phi_1\lambda_1}{\mu(\lambda_1+\phi_1+\mu)}\right]\left[\frac{\gamma(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)}{\beta(\lambda_1+\mu)(\lambda_3+\mu+\delta)}\right].$$

This equilibrium exists when $R_0 > 1$. Due to the complex nature of the system of differential equations for Model 2, we were unable to determine the local stability of the endemic equilibrium. For future work, the Routh Hurwitz criteria is a potential method of determining the stability.

3.6 Global Stability of Model 2

We attempt to establish global stability of the disease-free equilibrium for Model 2 using a Lyapunov function. We assume the Lyapunov function $W = I + I_E$. Then, $W = 0$ at the DFE, $W > 0$ elsewhere, and

$$\frac{dW}{dt} = \beta(S+\sigma S_E)\frac{I}{N} - (\mu+\delta)(I+I_E) < [\beta-(\mu+\delta)](I+I_E).$$

This implies that if $\frac{\beta}{\mu+\delta} < 1$, then $W = (I+I_E) \to 0$ as $t \to \infty$ (in particular $dW/dt < 0$ when $W > 0$). Thus, the disease-free equilibrium is globally stable for $R_0 < \frac{\beta}{\mu+\delta} < 1$. (Numerical analysis suggests that the DFE is globally stable even if $\frac{\beta}{\mu+\delta} < R_0 < 1$.)

4 Parameter Estimation

In this section we review certain studies and data on the parameters of our two models.

Λ: Since our models are only concerned with the female population, our birth rate, Λ, depends on the population of females ages 9-26 [21]. Taking that total population,

we divided that number by the difference of the age group. This gave us a birth rate of 2,162,846 females between 9-26 in the US per year.

μ: In order to determine the natural death rate, μ, we simply divide 1 by the total difference of the female age group we are interested in, giving us a rate of $1/17$ year^{-1}.

δ: Once an individual is infected with HPV 16 and 18, it is very likely that individual will develop cervical cancer which, if untreated, can lead to death. According to data from the National Cancer Institute [28] from 2000-2004, 5.7% of females between the ages of 20-34 had cervical cancer at some point during this period. Since the data is inconsistent in years, we assume that the number of cervical cancer cases in 2004 is equivalent to the number in 2007. As our models are restricted to females between 9-26, we multiply 5.7% by 7/15 in order to give us the percentage of females between ages 9-26 who die due to cervical cancer. The appropriate number we derive is 2.66% or a total of 532 cancer cases from 2000-2004 in the US population, which is a total period of 5 years. In order to calculate the number of deaths per year we divide 532 by 5, giving us 106 deaths per year. To estimate the number of deaths per HPV case, we use the following formula: (number of deaths per year/cervical cancer cases per year)$\times$(proportion of cervical cancer cases per HPV case). We plug in the appropriate numbers; $(106/11150) \times (250726/1194373)$. This gives us the number of deaths per HPV case. We then solve the equation $\frac{\delta}{\mu+\delta} =$ (deaths per HPV case) for δ, giving us an an estimated rate of 1.18×10^{-4} deaths per year due to cervical cancer.

β: We estimate the rate of infection based on the infection rate of HPV 16, since its prevalence is very high. According to a study in 2002 [23], the prevalence is 48%, and the infection rate is 5.9 infections per 1000 woman-months. We then multiply the infection rate by 12 and divide by 1000 to calculate the infection rate per year, 0.0708 year^{-1}.

$\lambda, \lambda_1, \lambda_2, \lambda_3$: To determine λ, we use the results from Strong [26] to create an exponential fit graph. We take the rate in weeks given by the exponential fit and multiply it by 52 to provide the rate per year, 4.576 year^{-1}. For simplicity, we assume that $\lambda = \lambda_1 = \lambda_2 = \lambda_3$.

ϕ_1, ϕ_2, ϕ_3: A study was conducted in the effectiveness of mass-media campaigns on reducing drinking and driving and alcohol-involved crashes [17]. 17% was the most consistent equilibrium value for the proportion of individuals who actually learned and responded to the campaign. We decided to use 17% as the proportion of individuals who were educated by the HPV mass-media campaign. We find ϕ through the equation, $0.17 = \frac{\phi}{\phi+\mu+\lambda}$, where $\frac{\phi}{\phi+\mu+\lambda}$ represents the proportion of individuals educated by the mass-media campaign at equilibrium. We then solve this equation, given μ and λ, for ϕ, giving us the rate at which an individual becomes educated due to the campaign, 0.937 year^{-1}. For simplicity, we are assuming that $\phi_1 = \phi_2 = \phi_3$.

γ: According to the CDC, the vaccination coverage for influenza after a mass-media campaign was 26% among high-risk 18 to 26 year olds [25]. Assuming that the population would have the same reaction towards a mass-media campaign, we consider 26% as the HPV vaccination coverage level. We then use the equation, $0.26 = \frac{\gamma}{\mu+\gamma+\frac{\mu}{\mu+\lambda_2}\phi_2}$ where the right hand side of the equation represents the proportion of individuals in the vaccinated

classes at the disease free equilibrium. Given μ, λ_2, and ϕ_2, we then solve this equation for γ, providing the rate in which people are vaccinated due to a mass-media campaign, 0.0245 year^{-1}.

Table 3: Parameter Estimations

Parameters	Estimations
Λ	$2,162,846$ people per year
μ	$1/17$ year^{-1}
δ	0.000118 year^{-1}
β	0.0708 year^{-1}
σ	0
γ	0.0245 year^{-1}
λ	4.576 year^{-1}
ϕ	0.937 year^{-1}
p	0.95
N	$36,768,382$ people per year

5 Cost Analysis

The number of American HPV infections each year is 6.2 million [10]. By 2007 an estimated 7,805 HPV cases in the U.S.A will develop into cervical cancer [8]. Gardasil has a cost of $360 for the total amount of the 3 series vaccinations. Reducing sexual activity will help decrease the rate of HPV infection and the overall infection of other sexually transmitted diseases (STD). The expected costs per case of STD are as follows: syphilis, $6,000; gonorrhea, $166; chlamydia, $270; and genital herpes, $93 [1, 18]. According to the National Cancer Institute, Medicare reported spending an average $21,486.90 per individual for cervical cancer treatment[17, 18]. Note that the accurate price of cervical cancer treatment may be higher, since most U.S. commercial insurances could pay up to 120-150% of Medicare. In addition, the average cost of treating warts caused by HPV strains 6 and 11 is an estimated $523.16 per person[18, 19]. We estimate that a six month national mass-media campaign would cost about $34.9 million in 2007 dollars [29].

The components of our cost analysis will be C_1, the total vaccination cost, C_2, the total HPV infection cost, C_3, the total sexual activity cost, and C_4, the total cost of education. We expect that the mandatory vaccination campaign will result in more females vaccinated but also more females infected. This is due to the length of time it will take to vaccinate the large population. For the mass-media campaign, we expect there to be fewer vaccinated females but also fewer infected females. This is because the mass-media education will begin taking effect immediately. We also expect there to be more highly sexually active individuals in the mass-media campaign. This is because the effects of the education will wear off. Thus, depending on the proportions of these numbers, one campaign will cost more than the other.

We will calculate the total overall cost of HPV control and high sexual activity using

three shadow classes, L_{V_E}, L_I, and L_S. The first shadow class, L_{V_E}, will calculate the vaccination cost by counting the number of people who become vaccinated. The equation to compute this for Model 1 is

$$\frac{dL_{V_E}}{dt} = p\Lambda$$

and for Model 2 is

$$\frac{dL_{V_E}}{dt} = \gamma S$$

We then use the equation

$$C_1 = C_V L_{V_E}(T)$$

to calculate the total vaccination cost in $[0, T]$ where T is the final time when the epidemic is over ($I < 1$) and C_V is the cost per vaccination ($360).

The second shadow class, L_I, will calculate the HPV infection cost associated with the strains of HPV that we are studying, which lead to cases of cervical cancer and genital warts. Thus, the cost of one case of HPV will incorporate costs of cervical cancer and genital warts. The equation to compute this for Model 1 is

$$\frac{dL_I}{dt} = \beta S \frac{I}{N}$$

and for Model 2 is

$$\frac{dL_I}{dt} = \beta(S + \sigma S_E)\frac{I}{N}$$

We then use the equation

$$C_2 = C_I L_I(T)$$

to calculate the total HPV infection cost in $[0, T]$ where C_I is the average cost of one case of HPV ($22,010.06).

The third shadow class, L_S, will calculate the cost of high sexual activity. Highly sexually active individuals are more likely to contract another sexually transmitted disease. Thus, the cost of one person's high sexual activity will incorporate costs of treatment for chlamydia, gonorrhea, syphilis, and genital herpes. The equation to compute this for Model 1 is

$$\frac{dL_S}{dt} = \mu S + (\mu + \delta)I + \mu V$$

and for Model 2 is

$$\frac{dL_S}{dt} = (\mu + \frac{\mu}{\mu + \lambda_2}\phi_2)S + (\mu + \delta + \frac{\mu + \delta}{\mu + \delta + \lambda_3}\phi_3)I + (\mu + \frac{\mu}{\mu + \lambda_1}\phi_1)V$$

We then use the equation

$$C_3 = C_S L_S(T)$$

to calculate the total sexual activity cost in $[0, T]$ where C_S is the average cost of one person's high sexual activity ($6,529).

The last component of the cost function is the total cost of education in $[0, T]$ which we denote $C_4 = C_E T$, where C_E is the cost per year of a mass-media campaign of intensity

equal to that in [27] which generates the value for ϕ. For Model 1, the education is given by the administrator of the vaccination enduring a very small cost; thus, we are assuming that $C_E = 0$ for Model 1.

The total cost, C_T, is the sum of each of the components. That is,

$$C_T = C_1 + C_2 + C_3 + C_4.$$

For Model 1, we found this time T to be 272 years, and for Model 2, we found the time to be 624 years. The code used to calculate these times and for the graph below can be found in the Appendix.

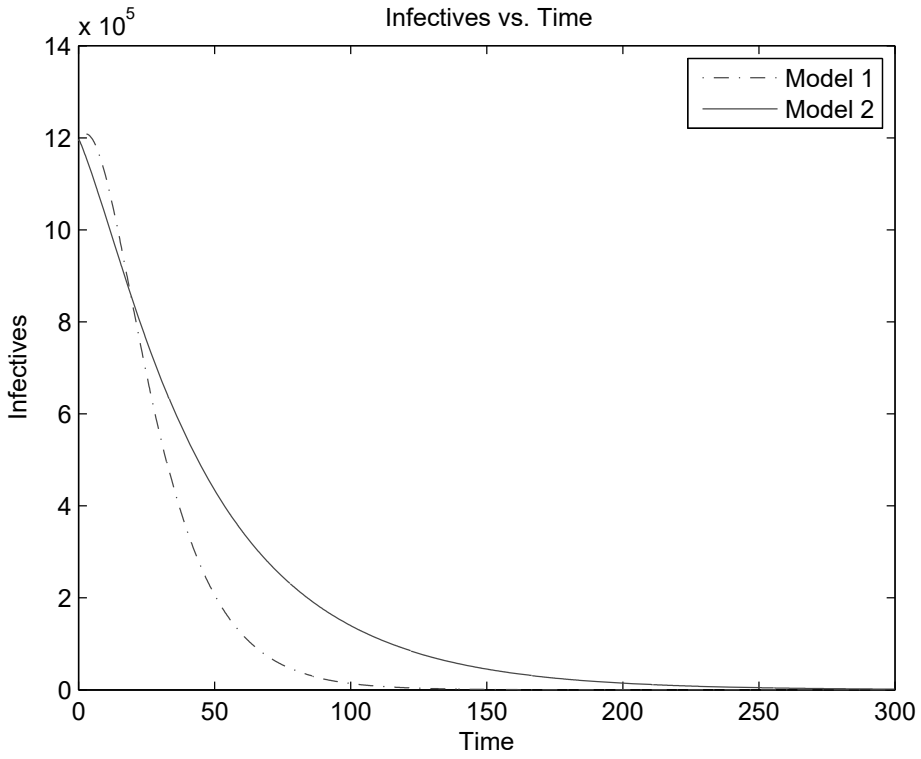

Figure 3: Infectives vs. Time for Models 1 and 2

After determining the number of years after which HPV is completely eradicated, we are able to calculate the costs of vaccination, HPV treatment, sexually transmitted diseases, and education for both models. The cost associated with the vaccinated and educated population in our mandated vaccination policy model is significantly high, \$201 billion. The cost of HPV treatment for 6, 11, 16, and 18 is higher for the mass-media campaign because fewer people are vaccinated, thus the disease continues to grow along with the cost providing a total amount of \$49 billion for treatment. The mandated vaccination policy has about half of Model 2's infectious population, hence, the cost of HPV in Model 1 yields about half of Model 2's treatment cost giving a total of \$24 billion for Model

1. Because the sexually active population in our mass-media model does not decrease to a lower level than Model 1's, we have a high cost of $8.8 trillion for Model 2. The cost for the sexually active population in the mandated vaccination policy, susceptible to sexually transmitted diseases, is $3.8 trillion. The last cost that plays an important role in completing our total cost for each model is the cost of education. For the mandated vaccination policy model, we assume that individuals become educated at the same time they are vaccinated, therefore the cost of education is 0. For our mass-media campaign, according to [29], a typical campaign costs about $69.8 million per year in 2007 dollars. Having found all of the individual costs for vaccination, HPV treatment, sexually transmitted diseases treatment, and education, we are able to calculate the total cost for each model. The total cost for the mandated vaccination policy model is $\$4 \times 10^{12}$, ($4 trillion), over the 272 years, and for the mass-media campaign policy is $\$9 \times 10^{12}$, ($9 trillion), over the 624 years.

6 Discussion

Though the cost of the mass-media campaign is much greater (more than twice), we look at the final values of the shadow classes, the number vaccinated and educated, the number infected, and the number sexually active, to better understand these costs. The values of these shadow classes at our final time, T, for each model respectively are as follows:

Model 1: $L_{V_E} = 558$ million, $L_I = 1.13$ million, $L_S = 581$ million

Model 2: $L_{V_E} = 349$ million, $L_I = 2.24$ million, $L_S = 1.34$ billion.

Since the mass-media campaign took 2.29 times as long as the mandatory vaccination policy, we divide both sets of numbers by their respective final times to get the average numbers per year. The new values are as follows:

Model 1: $L_{V_E} = 2.05$ million per year, $L_I = 4.2$ thousand per year, $L_S = 2.14$ million per year

Model 2: $L_{V_E} = 559$ thousand per year, $L_I = 3.6$ thousand per year, $L_S = 2.15$ million per year.

As expected, the mandatory vaccination policy causes more females to become vaccinated and educated per year. However, the numbers of infected and sexually active for both models are relatively equal. The differences one would expect in these numbers are not seen because of the small estimated efficiency of the mass-media campaign.
If we raise the efficiency of the campaign to 50%, we are able to see the expected results. We recalculate ϕ and γ with 50% efficiency. The new values, $\phi = 4.576$ year^{-1} and $\gamma = 0.0706$ year^{-1}, are substituted into the model and a new time, 294 years, is calculated from the graph below. The code used to find this time and the code for the graph below can be found in the Appendix.

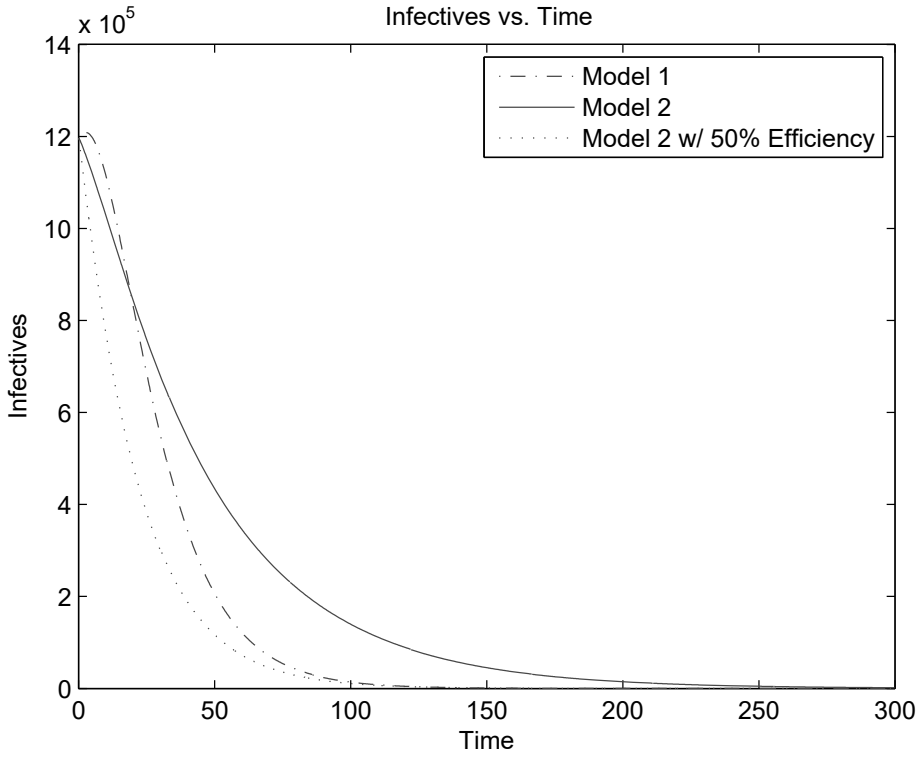

Figure 4: Infectives vs. Time for Model 1, Model 2, and Model 2 with 50% Efficiency

Using the final time, T, in the cost equations, we find that the total cost for Model 2 with 50% efficiency to be \$4.24 trillion. This cost is only 1.05 times the cost of Model 1. Thus, the cost of a mandatory vaccination policy and the cost of a mass-media campaign with 50% efficiency are relatively comparable. The difference between these two models, then, must come in the final values of the shadow classes. The values of the shadow classes in the new Model 2 with 50% efficiency at time T are:
$L_{V_E} = 244$ million, $L_I = 347$ thousand, $L_S = 633$ million.

The new final time for Model 2 with 50% efficiency is 1.08 times the final time of Model 1. Dividing the values of Model 2 with 50% efficiency by its respective final time, our new values of Model 2 with 50% efficiency are:
$L_{V_E} = 762$ thousand, $L_I = 1.18$ thousand, $L_S = 2.15$ million.

As expected, the mandatory vaccination policy (Model 1) yields many more vaccinated individuals. Also, the numbers of sexually active individuals are relatively equal. The main difference can be seen in the number of infectives. There are about 3.52 times as many total infectives in Model 1 as in Model 2 with 50% effective education. Thus, the trade off between mandatory vaccination and a highly (50%) effective mass-media campaign is that while the mandatory vaccination policy will result in 2.47 times as many vaccinated individuals, it will also result in 3.52 times as many infected individuals, enduring approximately the same cost.

We now look at the graphs of the infection as a whole to see what occurs in each model.

According to [21] the US female population between the ages 9-26 is 36.8 million and approximately 1.2 million are currently infected with HPV 6, 11, 16, and 18 [30].

In the graph of Model 1, Figure 4, one can see that our population starts with about 1.2 million infectives. Within the first several years, we can see that there is a slight increase in the number of infectives. This is because the proportion of people becoming vaccinated is not large enough to reduce the reproductive number to less than 1. After a while, there are enough people vaccinated that R_0 becomes less than 1, and the number of infectives decreases. This causes a rapid decrease because after 17 years, all of the infectives age out of our population model and almost everyone is vaccinated. The decrease in our graph shows that the mandated vaccination policy is playing a vital role in reducing the number of infectives at a rapid rate. After approximately 100 years, the population of infectives reduces to the thousands and gradually decreases from there.

In the graph of Model 2, Figure 4, one can see that the mass-media campaign has a strong effect on the population within the first 200 years. The number of infectives decreases very rapidly during this time. After approximately 200 years, the number of infectives decreases less rapidly.

The graph of Model 2 with 50% efficiency, Figure 4, is similar to that of Model 2; however, the effects of the mass-media campaign can be seen much earlier. There is a very strong effect in the first 100 years, as opposed to 200 years. After this time, the number of infectives decreases much less rapidly.

Based on the Model 2 graphs in Figure 4, one can see that the efficiency of the campaign is a very important factor in determining how quickly the disease will be eliminated. Though both the graph of Model 1 and the graph of Model 2 with 50% efficiency end around the same time, the slight increase in the number infectives evident in the beginning of the mandatory vaccination policy is avoided by the mass-media campaign, which affects a large number of females almost immediately.

Looking at the graph of cost vs. time, one can see which method would be the least costly in the beginning, as well as the end. In Figure 5, the costs all appear to be very close near the origin. As time goes on, however, they begin to separate, indicating that the Model 2 solutions would be less costly. Model 2 with 50% efficiency is less costly than Model 2 with less efficacy, since Model 2 has a much longer time. If the campaigns were to run for the same amount of time, however, it would be difficult to distinguish from this graph which would be least costly. For this we look at the graph of time 0 to 300. From this graph, one can see that Model 2 with 50% efficiency costs slightly less than Model 2. The code for these graphs can be found in the Appendix.

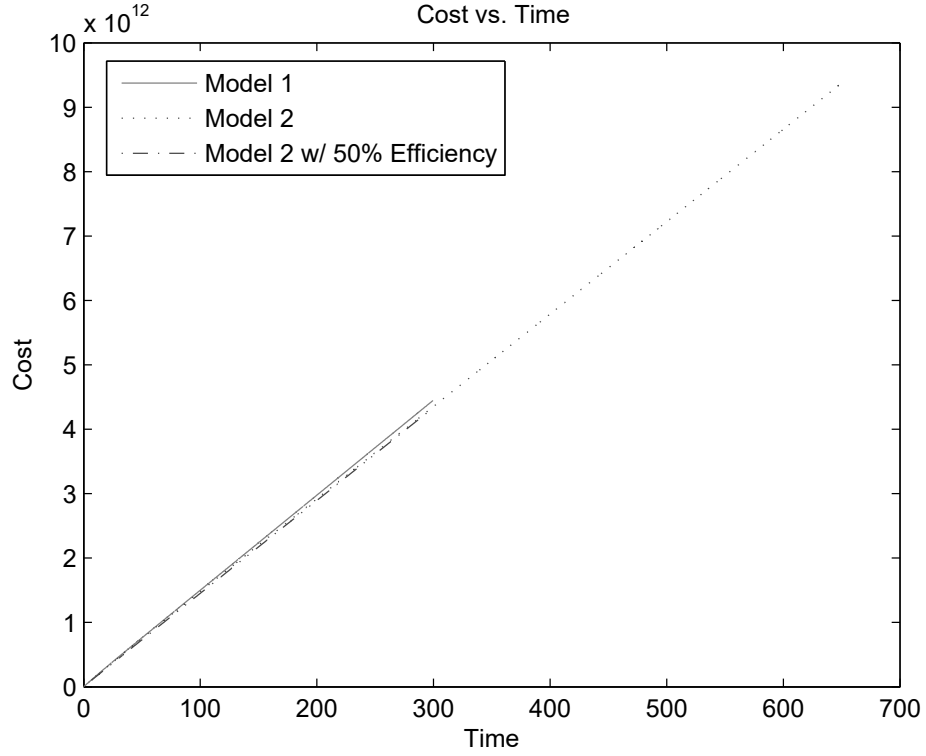

Figure 5: Cost vs. Time

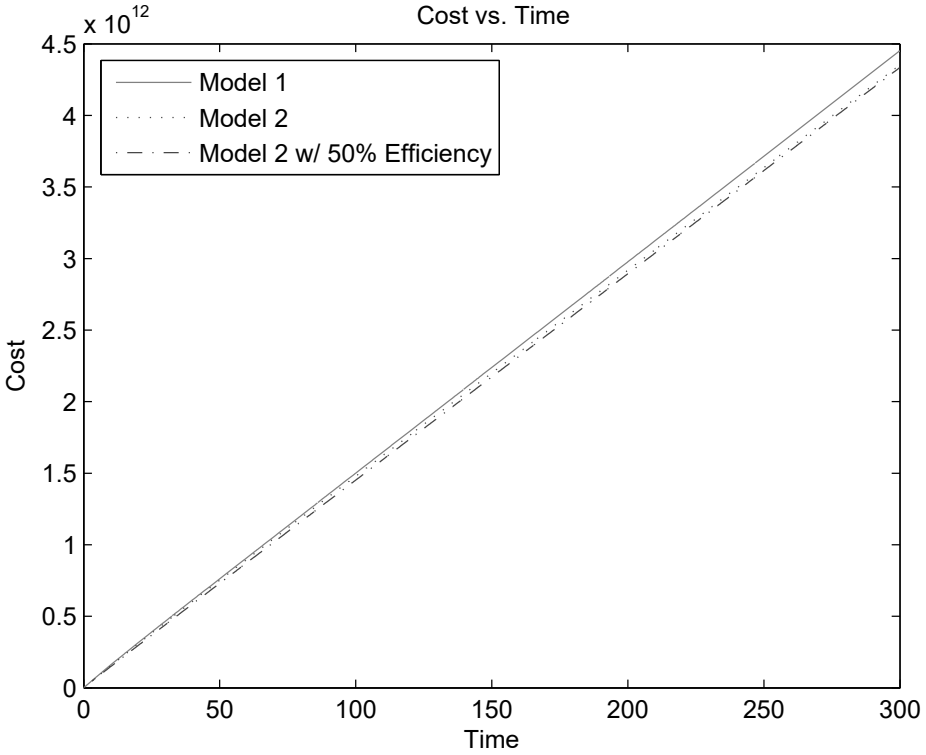

Figure 6: Cost vs. Time

Throughout this paper, we analyze the difference in costs between a mass-media campaign and a mandated vaccination policy. Using each individual model, we were able to create shadow classes for the susceptible, infected and vaccinated and educated (V_E) classes. This enables us to keep an accurate count of how many individuals enter those classes. We then use these counts to calculate our costs. By solving a system of differential equations, we are able to determine when the number of infectives is less than one, thus giving our final time. Using this final time we estimate the total costs for each model, for the total number of years it takes in order for HPV to be eradicated. Although it may seem that the final time is large for both the mandated vaccination policy and both mass-media campaigns, we have to take into account many factors. The model is specifically designed for females between the ages of 9 and 26. Our restricted population restrains us from having a faster time to eradicate HPV. Another factor to consider is that many HPV infections may go undetected unless regular screening is being practiced. There may be greater or fewer HPV cases than what we have concluded. Our parameter values can also be adjusted to more accurate estimations.

A study conducted in 2005 analyzed the epidemiology of HPV with a potential vaccination [22]. In this study, the authors show that even with a vaccine the infective population remains large due to a high transmission rate. It is stated within this study that a high transmission rate and a high reproductive rate requires a high efficacy and high vaccine coverage to eliminate the infection. As mentioned before, although our final time at which the infection is eliminated may seem large it is also an appropriate estimation considering the age population chosen and the high transmission rate.

In the future, we hope to explore the case in which σ is greater than 0. In this case, education is not 100% effective; therefore, educated susceptibles can also become infected. We initially set σ to 0 due to time constrictions. We also hope to include a sensitivity analysis which will help us optimize the tolerance of our parameters and help to compare different results. Additionally, we hope to expand our female population to include all females in the U.S. By doing so, a rough estimate of when HPV may be eliminated within the U.S. could be calculated, therefore making the model created useful for the future.

7 Acknowledgements

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8 Appendix

8.1 Disease Free Equilibrium of Model 1

The disease free equilibrium (DFE), denoted by (S_0, I_0, V_{E0}, V_0) is found by setting the right hand side of each of the equations, $\frac{dS}{dt}$, $\frac{dI}{dt}$, $\frac{dV_E}{dt}$, and $\frac{dV}{dt}$, to 0 and solving for S, I, V_E, and V respectively. Doing this we find

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

8.2 Reproductive Number of Model 1

Using the DFE found for Model 1, we can then find the reproductive number, R_0. To do this, we use the next-generation matrix method with

$$\mathcal{F} = [0 \quad \beta S\tfrac{I}{N} \quad 0 \quad 0],$$

and

$$\mathcal{V} = [-(1-p)\Lambda + \beta S\tfrac{I}{N} + \mu S \quad (\mu+\delta)I \quad -p\Lambda + \lambda V_E + \mu V_E \quad -\lambda V_E + \mu V].$$

We take differentiate of each of these matrices and take the 1×1 submatrices which correspond to the 1 infective class. This gives us $\mathbf{F}$ and $\mathbf{V}$. R_0 is then the dominant eigenvalue of $(\mathbf{F}) \times (\mathbf{V})^{-1}$. We find that

$$R_0 = \frac{(1-p)\beta}{\mu+\delta}.$$

8.3 Endemic Equilibrium of Model 1

The endemic equilibrium (EE) is found in a similar way to how the DFE was found. In the endemic case, however, I can not be 0. This gives,

$$EE = \left(\frac{\mu+\delta}{\beta}, (1-p) - \frac{\mu+\delta}{\beta}, p\frac{\mu}{\lambda+\mu}, p\frac{\lambda}{\lambda+\mu} \right) \frac{\Lambda}{\mu}$$

where

$$(1-p) - \frac{\mu+\delta}{\beta} = \frac{\mu}{\beta}(R_0 - 1).$$

8.4 Global Stability of Model 1

We first look at the local stability of the endemic equilibrium. For this we compute the jacobian (J) of $\frac{dS}{dt}$ and $\frac{dI}{dt}$ with respect to S and I.

$$J = \begin{bmatrix} -(\frac{\beta I}{N} + \mu) & -\frac{\beta S}{N} \\ \frac{\beta I}{N} & \frac{\beta S}{N} - (\mu+\delta) \end{bmatrix}.$$

Substituting our values for S and I from the endemic equililbrium,

$$J(EE) = \begin{bmatrix} -(\frac{\beta}{N}\frac{\Lambda(R_0-1)}{\beta} + \mu) & -\frac{\beta}{N}\frac{(\mu+\delta)N}{\beta} \\ \frac{\beta}{N}\frac{\Lambda(R_0-1)}{\beta} & \frac{\beta}{N}\frac{(\mu+\delta)N}{\beta} - (\mu+\delta) \end{bmatrix}.$$

After simplifying,

$$J(EE) = \begin{bmatrix} -(\frac{\Lambda(R_0-1)}{N} + \mu) & -(\mu+\delta) \\ \frac{\Lambda(R_0-1)}{N} & 0 \end{bmatrix}.$$

If $R_0 > 1$, then $trace(J) = -(\frac{\Lambda(R_0-1)}{N} + \mu) < 0$, and $det(J) = -(-(\mu+\delta)\frac{\Lambda(R_0-1)}{N}) > 0$. Thus, the endemic equilibrium is locally asymptotically stable for $R_0 > 1$.

We then use Dulac's Criterion to rule out the possibility of a limit cycle or periodic orbit.
Given $S' = \frac{dS}{dt}$ and $I' = \frac{dI}{dt}$, we will show that

$$\frac{\partial(BS')}{\partial S} + \frac{\partial(BI')}{\partial I} < 0$$

where $B(S,I) = \frac{1}{SI}$ and B is a continuous and differentiable function on the invariant subspace $S > 0, I > 0$.

$$BS' = \frac{1}{SI}\left[(1-p)\Lambda - \frac{\beta SI}{N} - \mu S\right] = \frac{(1-p)\Lambda}{SI} - \frac{\beta}{N} - \frac{\mu}{I}$$

$$BI' = \frac{1}{SI}\left[\frac{\beta SI}{N} - (\mu+\delta)I\right] = \frac{\beta}{N} - \frac{\mu+\delta}{S}.$$

Then,

$$\frac{\partial(BS')}{\partial S} + \frac{\partial(BI')}{\partial I} = -\frac{(1-p)\Lambda I}{(SI)^2} < 0$$

Since

$$\frac{\partial(BS')}{\partial S} + \frac{\partial(BI')}{\partial I} < 0,$$

there are no limit cycles.

8.5 Disease Free Equilibrium of Model 2

The disease free equilibrium (DFE), denoted by $(S_0, I_0, V_0, S_{E0}, I_{E0}, V_{E0})$ is found by setting the right hand side of each of the equations, $\frac{dS}{dt}$, $\frac{dI}{dt}$, $\frac{dV}{dt}$, $\frac{dS_E}{dt}$, $\frac{dI_E}{dt}$, $\frac{dV_E}{dt}$, to 0 and solving for S, I, V, S_E, I_E and V_E respectively, substituting where necessary. Doing this we find

$$DFE = N\left(\frac{\mu}{\mu+\gamma+\frac{\mu}{\mu+\lambda_2}\phi_2}, 0, \frac{\lambda_1}{\mu+\phi_1+\lambda_1}\frac{\gamma}{\mu+\gamma+\frac{\mu}{\mu+\lambda_2}\phi_2},\right.$$

$$\frac{\frac{\mu}{\mu+\lambda_2}\phi_2}{\mu+\gamma+\frac{\mu}{\mu+\lambda_2}\phi_2}, 0, \frac{\mu+\phi_1}{\mu+\phi_1+\lambda_1}\frac{\gamma}{\mu+\gamma+\frac{\mu}{\mu+\lambda_2}\phi_2}\Bigg).$$

8.6 Reproductive Number of Model 2

Using the DFE found for Model 2, we can then find the reproductive number, R_0. To do this, we use the next-generation matrix method, with

$$\mathcal{F} = [\beta S\tfrac{I}{N} \quad 0 \quad 0 \quad 0 \quad 0 \quad 0],$$

and

$$\mathcal{V} = \big[[-\lambda_3 I_E + (\mu+\delta+\phi_3)I \quad -\phi_3 I + (\mu+\delta+\lambda_3)I_E \quad -\Lambda - \lambda_2 S_E + \beta S\tfrac{I}{N} + (\mu+\gamma+\phi_2)S]$$

$$[-\phi_2 S + (\mu+\lambda_2)S_E \quad -\lambda_1 V_E + (\mu+\phi_1)V \quad -\gamma S - \phi_1 V + (\lambda_1+\mu)V_E]\big].$$

We differentiate of each of these matrices and take the 1×1 submatrices. This gives us $\mathbf{F}$ and $\mathbf{V}$. R_0 is then the dominant eigenvalue of $(\mathbf{F})\times(\mathbf{V})^{-1}$. We find that

$$R_0 = \frac{S^*}{N}\frac{\beta}{\mu+\delta+\frac{\mu+\delta}{\mu+\delta+\lambda_3}\phi_3}.$$

8.7 Endemic Equilibrium of Model 2

The endemic equilibrium (EE) is found in a similar way to how the DFE was found. In the endemic case, however, I can not be 0. This gives,

$$EE = N\Bigg(\frac{(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)}{\beta(\lambda_3+\mu+\delta)}, \frac{\mu(\lambda_3+\mu+\delta)}{(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)} - \frac{(\gamma+\mu)(\lambda_2+\mu)+\phi_2\mu}{\beta(\lambda_2+\mu)},$$

$$\frac{\lambda_1\gamma(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)}{\mu\beta(\lambda_2+\mu)(\lambda_3+\mu+\delta)}, \frac{\phi_2(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)}{\beta(\lambda_2+\mu)(\lambda_3+\mu+\delta)},$$

$$\frac{\phi_3}{\lambda_3+\mu+\delta}\left[\frac{\mu(\lambda_3+\mu+\delta)}{(\mu+\gamma)(\phi_3+\mu+\delta+\lambda_3)} - \frac{(\gamma+\mu)(\lambda_2+\mu)+\phi_2\mu}{\beta(\lambda_2+\mu)}\right],$$

$$\left[1+\frac{\phi_1\lambda_1}{\mu(\lambda_1+\phi_1+\mu)}\right]\left[\frac{\gamma(\mu+\delta)(\phi_3+\mu+\delta+\lambda_3)}{\beta(\lambda_1+\mu)(\lambda_3+\mu+\delta)}\right]\Bigg).$$

8.8 Final Time for Model 1

We first put the differential equations, S, I, V_E, V, L_{V_E}, L_I, and L_S, into a vector.

```
%HPV1.m
function dx = HPV1(t,x)
```

```
%S in system is x(1)
%I in system is x(2)
%VE in system is x(3)
%V in system is x(4)
%LVE in system is x(5)
% LI in system is x(6)
%LS in system is x(7)

global p N Lambda mu beta delta lambda

dx=[(1-p)*Lambda-(beta*x(1)*(x(2)/N))-mu*x(1);
beta*x(1)*(x(2)/N)-(mu+delta)*x(2);
p*Lambda-lambda*x(3)-mu*x(3);
lambda*x(3)-mu*x(4);
p*Lambda;
beta*x(1)*(x(2)/N);
mu*x(1)+mu*x(4)+(mu+delta)*x(2)];
```

We then solve this system of equations using the ordinary differential equation solver and plot the solution against time.

```
%plotHPV12.m

clear;
global p N Lambda mu beta delta lambda

tf=300;
N=36768382;
Lambda= 2162846;
mu=1/17;
beta=.0708;
delta=.000118;
lambda=4.576;
p=.95;
R0=((beta)*(1-p))/(mu+delta)
tspan=[0,tf];

y0=[35574009; 1194373; 0; 0; 0; 0; 0];

[t, z]=ode45('HPV1',tspan, y0);
plot(t,z(:,2),'r')
```

We look for the point where the number of infectives is less than 1. For Model 1, this time is 272 years.

8.9 Final Time for Model 2

We first put the equations for S, I, V, SE, IE, VE, L_{V_E}, L_I, and L_S, into a vector.

```
%HPV2.m

function dx=HPV2(t,x)

%S in system is x(1)
%I in system is x(2)
%V in system is x(3)
%SE in system is x(4)
%IE in system is x(5)
%VE in system is x(6)
%LVE in system is x(7)
%LI in system is x(8)
%LS in system is x(9)

global Lambda mu delta beta gamma lambda lambda1 lambda2 lambda3 phi1 phi2
phi3 N

dx=[Lambda+lambda2*x(4)-beta*x(1)*(x(2)/N)-gamma*x(1)-phi2*x(1)-mu*x(1);
beta*x(1)*(x(2)/N)+lambda3*x(5)-phi3*x(2)-(mu+delta)*x(2);
lambda1*x(6)-phi1*x(3)-mu*x(3);
phi2*x(1)-lambda2*x(4)-mu*x(4);
phi3*x(2)-lambda3*x(5)-(mu+delta)*x(5);
gamma*x(1)+phi1*x(3)-lambda1*x(6)-mu*x(6);
gamma*x(1);
beta*(x(1)*(x(2)/N));
(mu+(mu/(mu+lambda2))*phi2)*
x(1)+(mu+delta+((mu+delta)/(mu+delta+lambda3))*phi3)*x(2)+
(mu+(mu/(mu+lambda1))*phi1)*x(3)];
```

We then solve this system of equations using the ordinary differential equation solver and plot the solution against time.

```
%plotHPV2.m

clear;
global Lambda mu delta beta gamma lambda lambda1 lambda2 lambda3 phi1 phi2
phi3 N

tf=650;
N=36768382;
Lambda= 2162846;
mu=1/17;
gamma=.0245;
```

```
beta=.0708;
delta=.000118;
lambda=4.576;
lambda1=4.576;
lambda2=4.576;
lambda3=4.576;
phi1=.937;
phi2=.937;
phi3=.937;
p=.95;
R0=(mu/(mu+gamma+(mu/(lambda2+mu))*phi2))*
(beta/mu+delta+((mu+delta)/(mu+delta+lambda3))*phi3)

y0=[35574009; 1194373; 0; 0; 0; 0; 0; 0; 0];

tspan=[0,tf];
p=.95;
```
$[t, z] = ode45('HPV2', tspan, y0);$
```
plot(t,z(:,2)+z(:,5),'r')
```

We again look for the point where the number of infectives is less than 1. For Model 2, this time is 624 years.

8.10 Graph of Models 1 and 2

Using the files HPV1.m and HPV2.m from above, we create a new file, models1and2.m in which we solve the differential equations and plot the graphs of Model 1 and of Model 2 on the same graph.

```
%models1and2.m

clear;
global Lambda mu delta beta gamma lambda lambda1 lambda2 lambda3 phi1 phi2
phi3 N

tf1=300;
tf2=650;
N=36768382;
Lambda= 2162846;
mu=1/17;
gamma=.0245;
beta=.0708;
delta=.000118;
lambda=4.576;
lambda1=4.576;
lambda2=4.576;
```

```
lambda3=4.576;
phi1=.937;
phi2=.937;
phi3=.937;
p=.95;
R01=((beta)*(1-p))/(mu+delta)
R02=(mu/(mu+gamma+(mu/(lambda2+mu))*phi2))*
(beta/mu+delta+((mu+delta)/(mu+delta+lambda3))*phi3)

tspan1=[0,tf1];
y0=[35574009; 1194373; 0; 0; 0; 0; 0];
[t,z] = ode45('HPV1',tspan1,y0);
plot(t,z(:,2),'r')

tspan2=[0,tf2];
a0=[35574009; 1194373; 0; 0; 0; 0; 0; 0; 0];
[t,b] = ode45('HPV2',tspan2,a0);
hold on
plot(t,b(:,2)+b(:,5),':')
```

8.11 Final Time for Model 2 with 50% efficiency

We first put the equations for S, I, V, SE, IE, VE, L_{V_E}, L_I, and L_S, into a vector.

```
%HPV2.m

function dx=HPV2(t,x)

%S in system is x(1)
%I in system is x(2)
%V in system is x(3)
%SE in system is x(4)
%IE in system is x(5)
%VE in system is x(6)
%LVE in system is x(7)
%LI in system is x(8)
%LS in system is x(9)

global Lambda mu delta beta gamma lambda lambda1 lambda2 lambda3 phi1 phi2
phi3 N

dx=[Lambda+lambda2*x(4)-beta*x(1)*(x(2)/N)-gamma*x(1)-phi2*x(1)-mu*x(1);
beta*x(1)*(x(2)/N)+lambda3*x(5)-phi3*x(2)-(mu+delta)*x(2);
lambda1*x(6)-phi1*x(3)-mu*x(3);
phi2*x(1)-lambda2*x(4)-mu*x(4);
phi3*x(2)-lambda3*x(5)-(mu+delta)*x(5);
gamma*x(1)+phi1*x(3)-lambda1*x(6)-mu*x(6);
```

```
gamma*x(1);
beta*(x(1)*(x(2)/N));
(mu+(mu/(mu+lambda2))*phi2)*x(1)+(mu+delta+
((mu+delta)/(mu+delta+lambda3))*phi3)*x(2)+
(mu+(mu/(mu+lambda1))*phi1)*x(3)];
```

We then solve this system of equations using the ordinary differential equation solver and plot the solution against time.

```
%plotHPV250.m

clear;
global Lambda mu delta beta gamma lambda lambda1 lambda2 lambda3 phi1 phi2
phi3 N

tf=650;
N=36768382;
Lambda= 2162846;
mu=1/17;
gamma=.0706;
beta=.0708;
delta=.000118;
lambda=4.576;
lambda1=4.576;
lambda2=4.576;
lambda3=4.576;
phi1=4.576;
phi2=4.576;
phi3=4.576;
p=.95;
R0=(mu/(mu+gamma+(mu/(lambda2+mu))*phi2))*
(beta/mu+delta+((mu+delta)/(mu+delta+lambda3))*phi3)

y0=[35574009; 1194373; 0; 0; 0; 0; 0; 0; 0];
tspan=[0,tf];
p=.95;
```

$[t, z] = ode45('HPV2', tspan, y0);$

```
plot(t,z(:,2)+z(:,5),'r')
```

We again look for the point where the number of infectives is less than 1. For Model 2 with 50% efficiency, this time is 294 years.

8.12 Graph of all Three Models

Using the files HPV1.m and HPV2.m from above (with some modifications), we create a new file, models3.m in which we solve the differential equations and plot the graphs of

Model 1, Model 2, and Model 2 with 50% efficiency on the same graph.

```
%models3.m

clear;
global Lambda mu delta beta gamma gamma2 lambda lambda1 lambda2 lambda3 phi1
phi2 phi3 phi12 phi22 phi32 N

tf1=300;
tf2=650;
tf3=650;
N=36768382;
Lambda= 2162846;
mu=1/17;
gamma=.0245;
gamma2=.0706;
beta=.0708;
delta=.000118;
lambda=4.576;
lambda1=4.576;
lambda2=4.576;
lambda3=4.576;
phi1=.937;
phi2=.937;
phi3=.937;
phi12=4.576;
phi22=4.576;
phi32=4.576;
p=.95;
R01=((beta)*(1-p))/(mu+delta)
R02=(mu/(mu+gamma+(mu/(lambda2+mu))*phi2))*
(beta/mu+delta+((mu+delta)/(mu+delta+lambda3))*phi3)
R0250=(mu/(mu+gamma2+(mu/(lambda2+mu))*phi22))*
(beta/mu+delta+((mu+delta)/(mu+delta+lambda3))*phi32)

tspan1=[0,tf1];
y0=[35574009; 1194373; 0; 0; 0; 0; 0];
[t, z] = ode45('HPV1', tspan1, y0);
plot(t,z(:,2),'b')

tspan2=[0,tf2];
a0=[35574009; 1194373; 0; 0; 0; 0; 0; 0; 0];
[t, b] = ode45('HPV2', tspan2, a0);
hold on
plot(t,b(:,2)+b(:,5),'r:')

tspan=[0,tf3];
c0=[35574009; 1194373; 0; 0; 0; 0; 0; 0; 0];
```

$[t, d] = ode45('HPV22', tspan, c0);$
```
hold on
plot(t,d(:,2)+d(:,5),'b')
```

8.13 Graph of Cost vs. Time

Using the files HPV1.m and HPV2.m from above (with some modifications), we create a new file, time.m in which we solve the differential equations and plot the graphs of cost vs. time for Model 1, Model 2, and Model 2 with 50% efficiency on the same graph.

```
%time.m

clear;
global Lambda mu delta beta gamma gamma2 lambda lambda1 lambda2 lambda3 phi1
phi2 phi3 phi12 phi22 phi32 N Cv Ci Cs Ce

tf1=300;
tf2=650;
tf3=650;
N=36768382;
Cv=360;
Ci=22010.06;
Cs=6529;
Ce=69800000;
Lambda= 2162846;
mu=1/17;
gamma=.0245;
gamma2=.0706;
beta=.0708;
delta=.000118;
lambda=4.576;
lambda1=4.576;
lambda2=4.576;
lambda3=4.576;
phi1=.937;
phi2=.937;
phi3=.937;
phi12=4.576;
phi22=4.576;
phi32=4.576;
p=.95;
R01=((beta)*(1-p))/(mu+delta)
R02=(mu/(mu+gamma+(mu/(lambda2+mu))*phi2))*
(beta/mu+delta+((mu+delta)/(mu+delta+lambda3))*phi3)
R0250=(mu/(mu+gamma2+(mu/(lambda2+mu))*phi22))*
(beta/mu+delta+((mu+delta)/(mu+delta+lambda3))*phi32)
```

```
tspan1=[0,tf1];
y0=[35574009; 1194373; 0; 0; 0; 0; 0];
[t, z] = ode45('HPV1', tspan1, y0);
plot(t,Cv*z(:,5)+Ci*z(:,6)+Cs*z(:,7)+Ce*t),'r')

tspan2=[0,tf2];
a0=[35574009; 1194373; 0; 0; 0; 0; 0; 0; 0];
[t, b] = ode45('HPV2', tspan2, a0);
hold on
plot(t,Cv*b(:,7)+Ci*b(:,8)+Cs*b(:,9)+Ce*t,':')

tspan=[0,tf3];
c0=[35574009; 1194373; 0; 0; 0; 0; 0; 0; 0];
[t, d] = ode45('HPV22', tspan, c0);
hold on
plot(t,Cv*d(:,7)+Ci*d(:,8)+Cs*d(:,9)+Ce*t,'-.')
```

8.14 Second Graph of Cost vs. Time

This is the same as the first graph of cost vs. time, but with time only through 300.

```
%time2.m

clear;
global Lambda mu delta beta gamma gamma2 lambda lambda1 lambda2 lambda3 phi1
phi2 phi3 phi12 phi22 phi32 N Cv Ci Cs Ce

tf1=300;
tf2=300;
tf3=300;
N=36768382;
Cv=360;
Ci=22010.06;
Cs=6529;
Ce=69800000;
Lambda= 2162846;
mu=1/17;
gamma=.0245;
gamma2=.0706;
beta=.0708;
delta=.000118;
lambda=4.576;
lambda1=4.576;
lambda2=4.576;
lambda3=4.576;
phi1=.937;
phi2=.937;
```

```
phi3=.937;
phi12=4.576;
phi22=4.576;
phi32=4.576;
p=.95;
R01=((beta)*(1-p))/(mu+delta)
R02=(mu/(mu+gamma+(mu/(lambda2+mu))*phi2))*
(beta/mu+delta+((mu+delta)/(mu+delta+lambda3))*phi3)
R0250=(mu/(mu+gamma2+(mu/(lambda2+mu))*phi22))*
(beta/mu+delta+((mu+delta)/(mu+delta+lambda3))*phi32)

tspan1=[0,tf1];
y0=[35574009; 1194373; 0; 0; 0; 0; 0];
[t,z] = ode45('HPV1',tspan1,y0);
plot(t,Cv*z(:,5)+Ci*z(:,6)+Cs*z(:,7)+Ce*t),'r')

tspan2=[0,tf2];
a0=[35574009; 1194373; 0; 0; 0; 0; 0; 0; 0];
[t,b] = ode45('HPV2',tspan2,a0);
hold on
plot(t,Cv*b(:,7)+Ci*b(:,8)+Cs*b(:,9)+Ce*t,':')

tspan=[0,tf3];
c0=[35574009; 1194373; 0; 0; 0; 0; 0; 0; 0];
[t,d] = ode45('HPV22',tspan,c0);
hold on
plot(t,Cv*d(:,7)+Ci*d(:,8)+Cs*d(:,9)+Ce*t,'-.')
```

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