

Predicting Human Papilloma Virus Prevalence and Vaccine Policy Effectiveness in Demographic Strata

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Abstract

Human Papilloma Virus (HPV) is a sexually transmitted virus, which can lead to cervical cancer. HPV DNA is found in cervical cancers with types 16, 18, 31 and 45 accounting for more than 75% of cervical cancers. Candidate vaccines have entered phase III testing with the Food and Drug Administration and several drug companies are in licensing arbitration. Once this vaccine becomes available, an effective vaccination strategy is needed. Hughes, Garnett and Anderson have developed a model to predict HPV prevalence and population-level vaccine effectiveness; however, this model does not allow for stratification with time-dependent demographic traits, such as age. With this in mind, we have developed a tool that facilitates predicting HPV prevalence in a variety of demographic settings and allows for quantification of different vaccination policies.

1. Introduction

Human Papilloma Virus (HPV) DNA is found in 99.7% of all cervical cancers with types 16, 18, 31 and 45 accounting for 75% of cervical dysplasia (cancer) [15]. In the United States (US), 13,000 women are diagnosed with cervical dysplasia and 5,000 die annually. By the age 50, 80% of women will have acquired genital HPV infection [13]. Currently, 20 million people are infected with HPV in the U.S. with 5.5 million new cases annually [20]. In 2004, U.S. health care system spent over \$1.6 billion treating HPV symptoms and an additional \$5-6 billion on screening tests, including pap smears.

An effective HPV vaccine would have significant impact on HPV infections and cervical disease. Candidate vaccines finished phase II testing and phase III trials have begun with the Food and Drug Administration [18]. Due to the health

care and human costs associated with this virus, it is vital to have an effective vaccination strategy in place when this vaccine becomes available.

Predictive models are important tools in determining disease transmission dynamics and effective vaccination solutions. Previously, Hughes, Garnett and Anderson have developed a model that predicts HPV prevalence; however, this model does not allow for demographic stratification via time-dependent traits, such as age. With this in mind, we have developed a tool that facilitates predicting HPV prevalence in a variety of demographic settings and allows for various vaccination solutions. These predictive models stratify a population into different subgroups based on sexual mixing patterns. Population demographics and census data are analyzed to extract demographic parameters and youth and adult risk behavior surveys are studied to determine the sexual partner exchange rates for a population [24, 25].

2. Mathematical Models

Newly emerging or re-emerging infectious diseases continue to occur regularly [16]. Identification, treatment and eradication of different infectious diseases can be attributed to the increased understanding of their etiology and pathogenesis. It is ironic that epidemiologists have to take advantage of a disease outbreak in order to collect requisite data to formulate public health policies. While medical research has enhanced the understanding of disease characteristics in an individual, manifestation and spread of infectious diseases in the population remains elusive.

To gain insight into the intricacies of disease dynamics in a specific population, statistical and mathematical models of infectious disease epidemics have been developed [5, 8, 23]. Recent computational disease models facilitate simulation and investigation of different disease

characteristics [1, 22, 23].

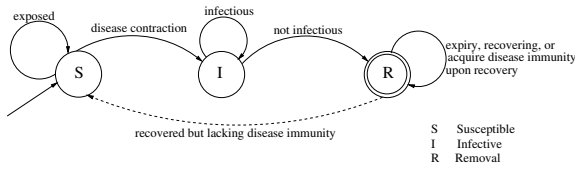


Figure 1. SIR state diagram

2.1. Susceptibles-Infectives-Removals Model

Most mathematical models are based on the principle of interaction between groups of *susceptibles* (S), *exposed* (E) / *infectives* (I), and *recovered/removed* (R) individuals, i.e., the $SIR/SEIR$ model. *Susceptibles* are those individuals in a population who can be infected by the disease. *Infectives* are those individuals who have been infected and are infectious. *Removals* include all individuals that are incapable of transmitting the infection, and are either recovering, fully recovered or expired from the disease.

The $SIR/SIRS$ state diagram (Figure 1) illustrates the course of a disease in an individual. A susceptible individual may be exposed to a disease pathogen and continue to be in the susceptible state. A susceptible becomes an infective, once the susceptible is able to transmit the pathogen onto others. The recovery state begins once the ability to infect ceases. The individual continues the state of recovery from the disease, or may expire. On full recovery, the individual may acquire full immunity from disease and hence is no longer susceptible (SIR model). The individual reverts to a susceptible on full recovery when lacking disease immunity ($SIRS$ model).

The Kermack-McKendrick Threshold Theorem [6] is the basis for the SIR model. A continuous influx of susceptibles is a requisite for sustained infection in a population. This is the case of endemic diseases, including HPV, that prevail in a community at all times. The model is based on the presumption of a closed population, assuming that the epidemic spreads rapidly enough that the changes brought in by births, deaths, migration and demographic changes are negligible [4].

During the start of a disease epidemic, the total population is susceptible, excluding those that have inherent immunity to the disease. The *index case* is the first infected individual and the infection source. During the infectious period, the infection is transmitted to some susceptibles, who interact with the index case at close proximity to contract the infection. This triggers the cycle of infections progressing through the population. Infectious individuals become

members of the removals category once they cease to be infectious. For the classic SIR model, the total number of susceptibles (S), infectives (I), and removals (R) is constant. New infections occur until the rate of new disease cases, the disease incidence, reaches a peak [6, 7]. Thereafter, the incidence starts to recede due to the decrease in the number of susceptibles, and diminishes eventually. Figure 2 illustrates the temporal flow of the population in each state for the classic SIR model.

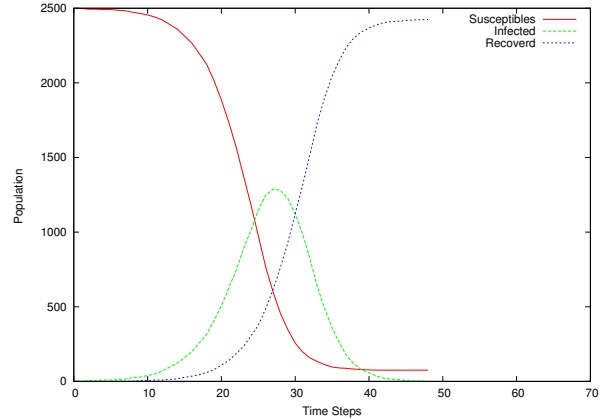


Figure 2. SIR graph

The random mixing of susceptibles and infectives [4] is given by $S * I$. β defines the transmission coefficient based on contact rate and disease infectivity [2]. γ defines the rate of infectives (I) becoming non-infectious. Hence, the average duration of infectivity is $1/\gamma$ [4]. The set of differential equations used in classic SIR model for a closed population are summarized in Eq. 1. The transfer rates of individuals from $S \rightarrow I$ and $I \rightarrow R$ are given by dS/dt and dR/dt respectively. The rate of change of infectives is given by dI/dt .

$$\frac{dS}{dt} = -\beta SI \quad \frac{dI}{dt} = +\beta SI - \gamma I \quad \frac{dR}{dt} = +\gamma I \quad (1)$$

The SIR model provides a simple framework to represent disease prevalence. However, it does not provide sufficient insight into an epidemic composition in order to be used as a policy and planning tool for the allocation of public health resources. The SIR model does not take into account the geography or the demographics of a region.

2.2. Hughes, Garnett and Anderson Model

Hughes, Garnett and Anderson have developed a mathematical model, the HGA model, to predict the endemic prevalence of sexually transmitted diseases [10, 11, 17]. This model describes a set of differential equations, based

on the *SIR* model, that depicts the endemic disease prevalence in a given population. It incorporates the concept of sexual mixing in a population with varying contact rates between individuals. Sexual mixing is defined by interaction of a stratified population in different levels of sexual activity. A sexually active population is determined by those individuals who on average change partners more than once per year.

The HGA model allows arbitrary vaccination in segments of the population, ϕ_{kl} with gender k and strata l ; vaccine coverage can be targeted in high-risk sub-groups or spread across the entire population. The vaccine efficacy in the general population is yet unknown; however, the model has encapsulated the needed functionality to vary the vaccine efficacy (ψ). The model also incorporates other characteristics, such as time-line until the vaccine ceases to be effective ($1/\sigma$), relative risk of transmission from a vaccinated individual compared with an unvaccinated individual (r) and infectious period of non-vaccinated ($1/\gamma$) and vaccinated ($1/\alpha\gamma$) individuals.

The basis for interaction in the HGA model is uniform mixing of heterosexual contacts. The age range of the sexually active population is modeled from 15 to 30; however, this range ($1/\mu$) can be varied depending on the demographics of a region. The HGA model assumes uniform mixing; however, the parameter, ϵ , determines the population proportion that interacts with individuals of the opposite sex in disparate demographic and sexual activity subgroups. The parameter ρ_{lm} generates contacts occurring within an individuals activity group (l) and the contacts ($N_m c_m$) made outside of the individuals activity group (m). The mixing ranges from assortative to random ($0 \leq \epsilon \leq 1$).

Several disease characteristics are vital for accurate portrayal of disease propagation, including infectivity and infectious period. HPV is highly virulent with more than 30 strains that are sexually transmittable. The transmission risk from an infectious individual to a susceptible of the opposite gender differs by gender. The transmission risk (β) from male to female is 80% and for female to male is 70%. The transmission risk is derived from a binomial distribution, $1 - (1 - \gamma)^\alpha$, over the average number of sex acts with a partner (α) and γ is the risk of being infected in one sex act [3]. An infected individual is infectious with the disease for approximately 1.5 years [14].

The HGA model allows for population stratification by demographic traits that are time-independent (e.g., race, ethnicity or income). Each demographic group is also divided into sexual activity classes (ω) defined by contact rates (c). At every time step, individuals age into the model as either susceptible ($1 - \phi$) or vaccinated (ϕ) and a portion of individuals (μ) age-out of each state. Susceptibles become infectious at a rate of λ and the vaccinated individuals become infectious at a rate of $\psi\lambda$. Infectious and

vaccinated infectious individuals recover at rates of γ and $\alpha\gamma$, respectively. Additionally, the vaccine ceases to be effective in a portion of the vaccinated individuals (σ). The HGA model is illustrated in Figure 3.

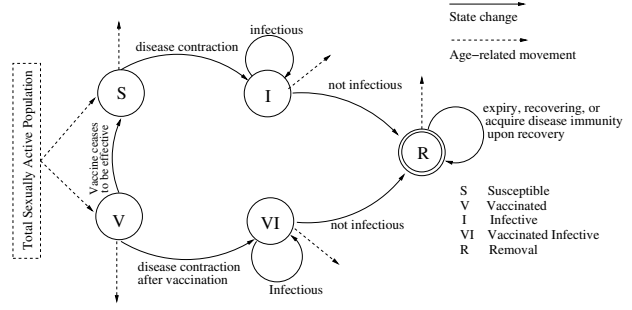


Figure 3. HGA Model State Diagram

2.3. Temporal Model

We have developed a *temporal* model that is time-dependent and stratifies the population via age. The temporal model predicts endemic prevalence of HPV by continually *aging-in* new susceptibles and *aging-out* a proportion (v) of each sexual activity class iteratively. Each class maintains a constant population size and the age range in each activity class is uniform.

3. Predicting Prevalence by Demographics

We extend the mathematical model to support multiple-demographic subgroups. This is critical for determining effective vaccination strategies. Surveys conducted by the Centers for Disease Control and Prevention Youth Risk Behavior Surveillance [24, 25] are incorporated in our demographically stratified model. These surveys state that reported sexual activity varies by age and demographics. Our model illustrates temporal population flow and is described by a set of linear difference equations. A key component of these models is the infectivity of HPV (λ_{kl}) of an infectious individual of gender k in activity group l to a susceptible of the opposite sex. We define infectivity (Equation 2) as a binomial probability over the transmission risk in each demographic subgroup (\sum_m) as determined by the mixing parameter (ρ_{lm}).

$$\lambda_{kl} = 1 - \left(1 - \beta_k \sum_m \left[\rho_{lm} \frac{I_{k'm} + rVI_{k'm}}{N_{k'm}} \right] \right)^{c_l} \quad (2)$$

3.1. Temporal Model

Our temporal model combines demographic groups of different age ranges with sexual activity classes. Due to stratification of the population by age, individuals that *age-out* of each demographic subgroup must *age-in* to the next contiguous age group. Individuals in the last age group exit the sexually active population. The *susceptibles* are described by the difference equations for the first n activity groups in Eq. 3 and remaining activity groups in Eq. 4.

$$\Delta S_{kl} = .5\mu(1 - \phi_{kl}) \frac{\omega_l}{\sum_{i=1}^n \omega_i} \eta - (\lambda_{kl} + v)S_{kl} + \sigma V_{kl} \quad (3)$$

The change in *susceptibles* (ΔS_{kl}) of gender k and activity group l for the first age group's n activity classes in Eq. 3 contains three main components. Unvaccinated ($1 - \phi$) individuals in the first activity classes ($\omega_l / \sum_n \omega_n$) of the sexually active population become susceptible. Susceptibles also age-in to the next contiguous age-group (v) and become infectious with infectivity λ . Finally, vaccinated individuals in which the vaccine ceases to be effective become susceptible (σ).

$$\Delta S_{kl} = (1 - \phi_{kl})vS_{k(l-n)} - (\lambda_{kl} + v)S_{kl} + \sigma V_{kl} \quad (4)$$

The change in *susceptibles* (ΔS_{kl}) for the remaining $l - n$ activity groups are described in Eq. 4. A proportion of *susceptibles* who are unvaccinated ($1 - \phi$) age-in (v) from the preceeding age group ($S_{k(l-n)}$). Similarly, susceptibles age-in to the next contiguous age-group (v) and become infectious with infectivity λ . Finally, vaccinated individuals in which the vaccine ceases to be effective become susceptible (σ).

The *infectious*, *removed*, *vaccinated* and *vaccinated-infectious* individuals in the temporal model are quantified similarly. Individuals in the $l - n$ groups flow into the next contiguous age group and same activity class. This model is mathematically described in Appendix (A.1, A.2).

4. Tool Interface

We have created an application interface to the HGA and temporal models. Our application interface facilitates quantification of the effectiveness of different vaccination policies. This tool, illustrated in Figure 4, accepts the necessary vaccine, disease and demographic parameters of HPV to predict the endemic prevalence in a demographically stratified population.

Our tool allows the user to choose to stratify the population (Figure 5(a)) by age or other demographic and to define the number of demographic groups and sexual activity subgroups. Sexual activity subgroup proportions can be

predefined (0.03, 0.15 and 0.82) for each group or the user can define the proportions. The user can also choose to input model parameters with a configuration file or use the application interface. The configuration page (Figure 5(c)) displays the model variables the user can change, such as the population count, transmission risk, duration of inclusion in the sexually active population, vaccine efficacy, etcetera. Our tool also allows the user to input information about contact/partner change rates and proportions of each demographic and sexual activity subgroup (Figure 5(b)). The user can specify the vaccine coverage for each demographic and sexual activity subgroup. Our tool produces the HPV prevalence and temporal flow of the population in each state for the chosen demographic stratification and allows quantification of the effectiveness of different vaccination strategies.

5. Integrating Demographics

Through population stratification by demographics and analysis of risk behavior surveys, effective vaccination strategies can be defined for a given geographic area. Demographic analysis is critical for appropriate and effective policies in regions with different demographics, including high-risk communities such as youth or minority groups. These models incorporate different demographic parameters that are critical to determine the most effective vaccination strategy for a population.

Denton County, Texas population demographics, obtained from the U.S. Census in 2000 is used in our analysis. Table 1 describes Denton County population demographics by age and race.

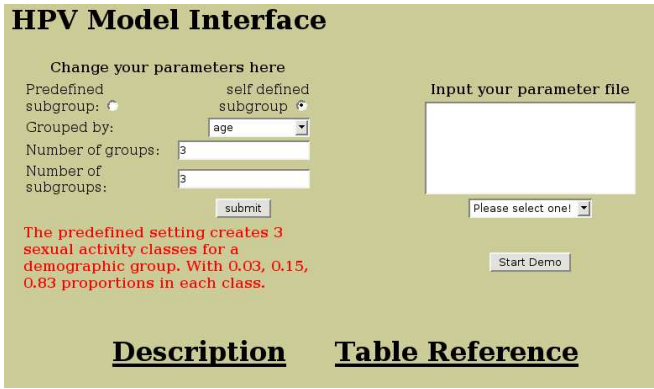
Table 1. U.S. Census Data for Denton County

| Demographic | Males | Females |
|--------------------|--------|---------|
| Population by age | | |
| 15-19 | 15,923 | 15,579 |
| 20-24 | 17,106 | 18,478 |
| 25-29 | 19,237 | 19,193 |
| Population by race | | |
| White | 35,980 | 37,809 |
| Hispanic | 9,559 | 7,583 |
| African-American | 3,406 | 4,112 |
| Other | 3,321 | 3,746 |
| Total | 52,266 | 53,250 |

5.1. Sexual Mixing Patterns

Sexual mixing characteristics differ in varied demographic groups. Sexual activity rates also vary by age and by race [19, 24]. Data obtained from the Youth Risk Behavior Surveillance: National College Health Risk Behav-

Figure 4. HPV Tool Interface



(a) Interface Start page

| group | subgroup | contact | proportion |
|-------|----------|---------|------------|
| 1 | a | 8 | 0.0089 |
| 1 | b | 2.5 | 0.0447 |
| 1 | c | 1 | 0.2444 |
| 2 | a | 9 | 0.0101 |
| 2 | b | 3 | 0.0506 |
| 2 | c | 1.25 | 0.2763 |
| 3 | a | 9.5 | 0.0110 |
| 3 | b | 3.5 | 0.0548 |
| 3 | c | 1.5 | 0.2993 |

(b) Contact rates and proportions can be defined for each group

| | |
|---|-------|
| Age range for each group: | 5 |
| Degree of group mixing(0 to 1): | 0.5 |
| Relative risk of transmission: | |
| female-male: | 0.7 |
| male-female: | 0.8 |
| Average time infectious(years): | 1.5 |
| Average time in sexually active population(years): | 15 |
| Number of males: | 52266 |
| Number of females: | 52260 |
| Percentage of vaccinated initially infected: | 0.00 |
| Percentage of unvaccinated initially infected: | 0.001 |
| Duration of simulation(years): | 50 |
| Duration of Vaccine Efficacy(years): | 10 |
| Relative susceptibility to infection of vaccinated vs unvaccinated: | .25 |
| Relative risk of transmission of vaccine with breakthrough vs unvaccinated: | 1.0 |
| Recovery rate from breakthrough infection compared with unvaccinated: | 1.0 |

(c) Configuration page, displays parameters the user can change

ior Survey [24] indicate students aged greater than or equal to 25 years (97.8%) were more likely to report sexual intercourse in their lifetime than students aged 18-24 years (79.9%). African-American students (92.8%) were more likely than White (86.7%) and Hispanic (85.2%) students to report sexual activity. Sexual activity classes for our models were created artificially to reflect this data. The sexual activity class proportions in the demographic groups are 3%, 15% and 82%. The activity class proportions and contact rates for stratification by age and race are in Table 2.

Table 2. Sexual Mixing Parameters

| Dem. Trait | Activity class ratio (ω) | | | Contact rate (c) | | |
|----------------|-----------------------------------|--------|--------|----------------------|------|------|
| | High | Mod. | Low | High | Mod. | Low |
| HGA model | | | | | | |
| White | 0.0168 | 0.0840 | 0.4595 | 9 | 3.25 | 1.25 |
| Hispanic | 0.0073 | 0.0366 | 0.1999 | 8.5 | 3 | 1.25 |
| Black | 0.0041 | 0.0205 | 0.1122 | 10 | 4 | 1.5 |
| Other | 0.0018 | 0.0089 | 0.0484 | 9 | 3 | 1.4 |
| Temporal model | | | | | | |
| 15-19 | 0.0089 | 0.0447 | 0.2444 | 8 | 2.5 | 1 |
| 20-24 | 0.0101 | 0.0506 | 0.2763 | 9 | 3 | 1.25 |
| 25-29 | 0.0110 | 0.0548 | 0.2993 | 9.5 | 3.5 | 1.5 |

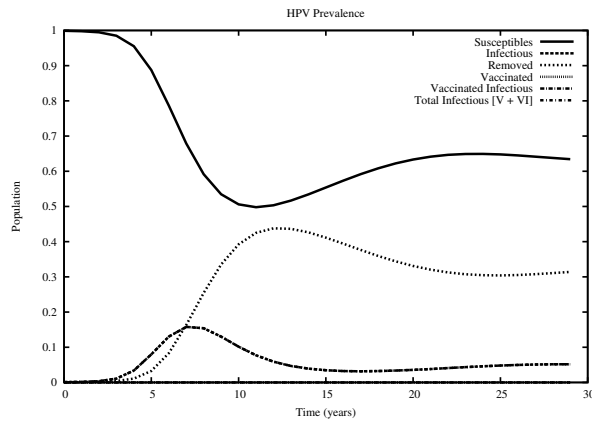
6. Results

Experiments are performed on both models utilizing the same disease and vaccine parameters and different demo-

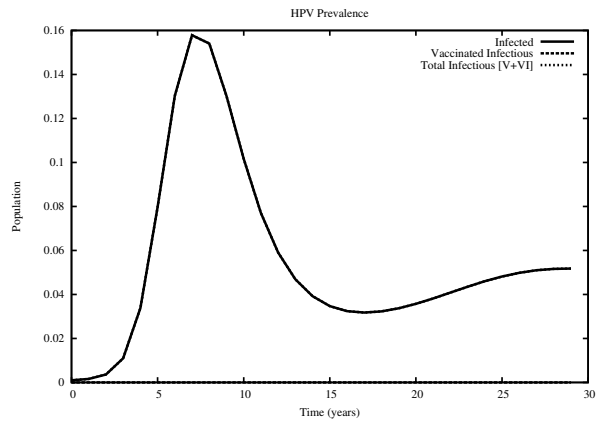
graphics¹. Figure 5 illustrates the temporal model popu-

¹Population demographics are obtained from the U.S. Census data in 2000 and the disease and vaccine parameters are the initial values in the HGA model [17]

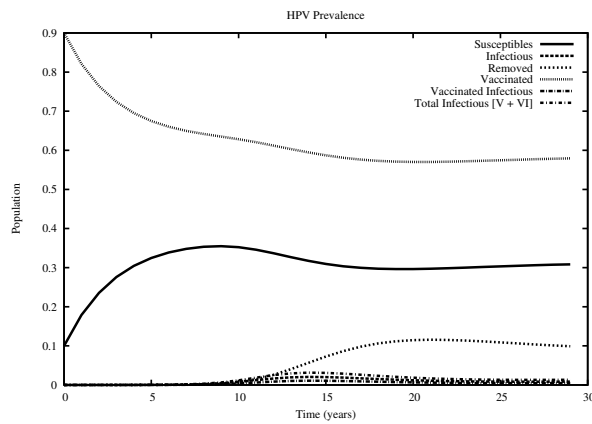
Figure 5. Temporal Model



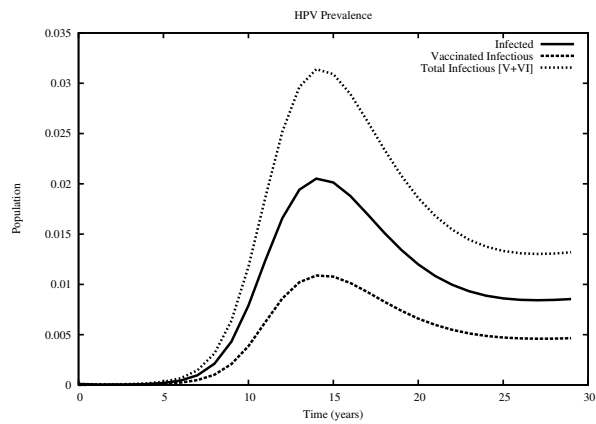
(a) No vaccine coverage: all states



(b) No vaccine coverage: infectious proportion



(c) 90% vaccine coverage: all states



(d) 90% vaccine coverage: infectious proportion

lation distribution with no vaccine coverage and 90% vaccine coverage. Endemic prevalence with no vaccination coverage is the baseline to measure the impact of vaccination. The baseline for the temporal model is displayed in Fig. 6(b). The potential impact on endemic prevalence by targeting vaccine coverage in certain sub-groups is analyzed. The effect of a vaccination policy is measured against a steady state endemic prevalence with no vaccine coverage and the average of male and female benefits; this comparison is the resulting vaccination benefit. The resulting endemic prevalence of various vaccination strategies are shown in Table 3.

The HGA model evaluates an endemic prevalence of 3.8% and 3.9% for males and females, respectively². High-

²The baseline endemic prevalence for the two models vary due to evaluations with different demographic parameters and contact rates.

risk groups account for 13.7% of the population, when demographically stratified by race. Targeting vaccination of both males and females in high-risk groups (7.89%) is significantly lower than vaccination targeting the total population (47.4%). Vaccine coverage targeting females in high-risk groups (2.56%) is significantly less effective than targeting all females (48.7%).

The temporal model evaluates an endemic prevalence of 4.7% and 5.0% for males and females, respectively. Vaccine coverage targeting both males and females, ages 15-19 (48.0%) is less effective than targeting the total population (70.0%). Vaccinating females, ages 15-19 (26.6%) has lower impact than targeting all females in the population (39.9%). Although full vaccine coverage in the population would be desirable, costs associated with the vaccine makes it infeasible [20].

Table 3. Steady State Endemic Prevalence of HPV in the Population

| Vaccination Policy | Male(M) | Female(F) |
|-------------------------------------|---------|-----------|
| HGA model | | |
| No vaccination policy | 0.038 | 0.039 |
| M & F | 0.020 | 0.020 |
| F | 0.030 | 0.027 |
| High-risk* M & F | 0.035 | 0.037 |
| High-risk* F | 0.037 | 0.038 |
| Spread targeting [†] M & F | 0.033 | 0.035 |
| Spread targeting [†] F | 0.036 | 0.036 |
| Temporal model | | |
| No vaccination policy | 0.047 | 0.050 |
| Vaccinate M & F | 0.014 | 0.015 |
| Vaccinate F | 0.033 | 0.025 |
| Vaccinate ages 15-19 M & F | 0.025 | 0.026 |
| Vaccinate ages 15-19 F | 0.038 | 0.033 |
| Vaccinate ages 20-24 M & F | 0.029 | 0.031 |
| Vaccinate ages 20-24 F | 0.040 | 0.036 |
| Vaccinate ages 25-29 M & F | 0.038 | 0.040 |
| Vaccinate ages 25-29 F | 0.044 | 0.043 |

* Targetting vaccination of African-Americans

[†] Vaccine coverage 90% for African-Americans and 10% for all other groups

Through analysis of predictive endemic prevalence of HPV types in Denton County, we show that targeting vaccination at age group 15-19 will have a 48.0% decrease in the prevalence compared to targeting high-risk minority groups with a decrease in prevalence of 7.89%³. It should be noted that the contact rates for each group are created artificially; however, the variance in contact rates is in line with published reports [12, 24].

7. Related Work

Most work in modeling infectious disease epidemics is mathematically inspired and based on differential equations and SIR/SEIR (Susceptible, Exposed, Infectious, Recovered) model [5]. Differential equation SIR modeling relies on the assumption of constant population and neglects population demographics [8, 9]. They fail to consider individual interaction processes and assume homogeneous population. Both partial and ordinary differential equation models are deterministic in nature and neglect the stochastic or probabilistic behavior [21]. Nevertheless, these models have been shown to be effective in regions of small population [21]. Modeling sexually transmitted diseases with differential equations has been developed [3, 11] and incorporates sexual activity classes with broad population interaction.

³The decrease in HPV prevalence of targeting age group 15-19 over targeting high-risk minority groups was found to be statistically significant, using a paired t-test ($p < 0.001$)

Markov models have been developed that are capable of simulating the natural history of HPV and type specific stages of cervical carcinogenesis [14, 15]. Improved Markov models simulate high-and-low risk HPV infection. They are capable simulating non-persist and persistent HPV infections that leads to cervical carcinogenesis [18]. Cost-effectiveness analysis has been performed on the benefits of a HPV vaccine implementing decision and Markov models [20]. The differential equation and Markov models ignore specific demographics and approach modeling at population-level [10, 17].

8. Conclusion

Our tool focuses on predicting HPV transmission in heterogeneous populations and measures the effectiveness of a HPV vaccine. Both models, HGA and temporal, vaccinate target demographic subgroups and simulate assortative population interaction. The HGA model incorporates time-independent demographics such as race, ethnicity and income. Our temporal model stratifies a population by time-dependent demographics such as age. Measuring the effectiveness of vaccine coverage on a specific age group illustrates a beneficial age to begin vaccination.

By modeling multiple local regions incorporating sub-population demographics, the cost-effectiveness of a HPV vaccine can be increased. Simulating these scenarios is critical for determining appropriate and effective policies and what-if analysis. Information available such as risk-behavior surveys for adults and youth and demographic data are processed by our model to prioritize demographic subgroups for vaccination. Targeted vaccination strategies reduces the incidence and prevalence of cervical disease, thereby enhancing the health of the general population.

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A. Mathematical Description of Demographic Models

A.1. Population Equations

The following describe the number of individuals in the population as described in the HGA model:

$$\eta = \sum_k \sum_l N_{kl}$$

$$N_{kl} = S_{kl} + I_{kl} + R_{kl} + V_{kl} + VI_{kl}$$

A.2. Temporal model

The following equations describe the change in state for the first n sexual activity classes in the temporal model:

$$\Delta S_{kl} = .5\mu(1 - \phi_{kl}) \frac{\omega_l}{\sum_{i=1}^n \omega_i} \eta - (\lambda_{kl} + v)S_{kl} + \sigma V_{kl}$$

$$\Delta I_{kl} = \lambda_{kl}S_{kl} - (\gamma + v)I_{kl}$$

$$\Delta R_{kl} = \gamma I_{kl} + \alpha\gamma VI_{kl} - vR_{kl}$$

$$\Delta V_{kl} = .5\mu\phi_{kl} \frac{\omega_l}{\sum_{i=1}^n \omega_i} \eta - (v + \sigma + \psi\lambda_{kl})V_{kl}$$

$$\Delta VI_{kl} = \psi\lambda_{kl}V_{kl} - (v + \alpha\gamma)VI_{kl}$$

The following equations describe the change in state for the remaining $l-n$ sexual-activity groups in temporal model:

$$\Delta S_{kl} = (1 - \phi_{kl})vS_{k(l-n)} - (\lambda_{kl} + v)S_{kl} + \sigma V_{kl}$$

$$\Delta I_{kl} = vI_{k(l-n)} + \lambda_{kl}S_{kl} - (\gamma + v)I_{kl}$$

$$\Delta R_{kl} = vR_{k(l-n)} + \gamma I_{kl} + \alpha\gamma VI_{kl} - vR_{kl}$$

$$\Delta V_{kl} = vV_{k(l-n)} + \phi_{kl}vS_{k(l-n)} - (v + \sigma + \psi\lambda_{kl})V_{kl}$$

$$\Delta VI_{kl} = vVI_{k(l-n)} + \psi\lambda_{kl}V_{kl} - (v + \alpha\gamma)VI_{kl}$$