Mathematical Models for Predicting the Epidemiologic and Economic Impact of Vaccination against Human Papillomavirus Infection and Disease

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Infection with human papillomavirus (HPV) is the primary cause of cervical cancer, other anogenital cancers, genital warts, and recurrent respiratory papillomatosis. Clinical studies have demonstrated that a prophylactic HPV vaccine can prevent infection, genital warts, and the precancerous lesions that lead to cervical cancer. Given the absence of data on the long-term effectiveness of HPV vaccination, a number of mathematical models have been developed to provide insight to policy makers by projecting the long-term epidemiologic and economic consequences of vaccination and evaluate alternative vaccination policies. This paper reviews the state of these models. Three types of HPV mathematical models have been reported in the literature: cohort, population dynamic, and hybrid. All have demonstrated that vaccination can significantly reduce the incidence of cervical cancer in the long term. However, only the cohort and hybrid models have evaluated the cost-effectiveness of vaccination strategies for preventing cervical cancer. These models have generally shown that vaccinating females can be cost-effective. None has accounted for the potential benefits of vaccinating the population to reduce the burden of recurrent respiratory papillomatosis and cancers of the vagina, vulva, anus, penis, and head/neck. Given that only the population dynamic model can account for both the direct and indirect (i.e., herd immunity effects) benefits of vaccination in the population, future research should focus on further development of dynamic models by expanding the range of epidemiologic outcomes tracked and including the ability to assess the cost-effectiveness of alternative vaccination policies.

cost-benefit analysis; economics; papillomavirus, human; vaccines

Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; QALY, quality-adjusted life year.

INTRODUCTION

Worldwide, it is estimated that 274,000 women died from cervical cancer in 2002 (1). The cause of cervical cancer is almost 100 percent attributable to genital infection with the human papillomavirus (HPV) (2, 3). HPV infection is also the cause of other anogenital cancers, recurrent respiratory papillomatosis, and genital warts in both men and women (4). Given that HPV is sexually transmitted, the prevalence of HPV infection in the population peaks among persons in their late teens or early twenties during the years following sexual debut (5–7). Up to 70 percent of women will acquire genital HPV infection sometime during their lifetime (8). Most women clear the infection; however, some experience persistent infections that can lead to cervical cancer (9, 10). The progression from persistent infection to cervical cancer typically evolves slowly, often over a period of 20 years or longer (11, 12). During this time, the disease develops through a precancerous stage (i.e., cervical intraepithelial neoplasia (CIN)) that can be detected through regular cytologic screening of the cervix with a Papanicolaou test. If screening confirms an abnormality (i.e., dysplasia), then additional testing and treatment can usually eliminate disease (13). Countries that have adopted organized cervical cancer screening programs have significantly reduced the morbidity and mortality associated with cervical cancer in the population (14–18).

Recently, a number of landmark clinical studies have demonstrated that a prophylactic HPV vaccine can prevent HPV infection (19–22) and disease (22). Given the success of these studies, it is anticipated that an HPV vaccine that
prevents infection, CIN, and genital warts will soon be available (23, 24). While clinical studies are sufficient for vaccine licensure, policy makers will seek additional information that the initial clinical studies cannot provide in order to formulate HPV vaccination guidelines (25, 26). In particular, they will seek information on the long-term epidemiologic and economic consequences of the vaccine (27–30). One source for this information is long-term, follow-up clinical studies. However, given that the results from these long-term studies will not be available when the initial HPV vaccination guidelines are developed, an alternative information source is mathematical models that project the long-term epidemiologic and economic consequences of vaccination. A number of different types of mathematical models have been developed to project the long-term benefits and costs of vaccination and to evaluate alternative HPV vaccination strategies (31–39). These models differ both in their complexity and the questions they answer.

The objective of this paper is to review the state of mathematical modeling (epidemiologic and economic) of HPV disease for evaluating HPV vaccination policies. We begin with a background on mathematical disease modeling. This information is followed by a review of HPV disease models for evaluating vaccination strategies. Specifically, we review the different structures and assumptions used to develop each model, key parameters, strategies evaluated, and main findings. The last section summarizes the similarities and differences among the models and discusses research needs for future model development.

MATHEMATICAL MODELS

Mathematical models have been used for centuries to study the spread and control of infectious diseases; for example, Daniel Bernoulli examined smallpox in 1760, and Ronald Ross investigated malaria in 1908 (40–43). Mathematical models have also been used to evaluate strategies for preventing or managing chronic diseases such as heart disease, diabetes, and cancer (44–47). For instance, with cervical cancer, mathematical models have been used to evaluate screening strategies and develop screening policies (48). The structure of a number of these cervical cancer models has served as the foundation for many of the models developed to evaluate HPV vaccination strategies (48, 49). A simplified, generalized structure of the underlying HPV natural history models can be seen in figure 1a. Generally, these mathematical models simulate the progression of HPV disease by advancing a hypothetical cohort or population through various stages of the disease according to demographic, epidemiologic, and clinical data. We will use this general structure in the following sections as a guide for comparing and contrasting the different types of HPV vaccination mathematical models, which can be divided into three types: cohort, population dynamic, and hybrid. The following describes each of these models in greater depth.

Cohort models

The structure of cohort models is typically probabilistic and linear. Often, they are referred to as Markov models (44) or health-state transition models. In a cohort model, the progression of HPV disease is simulated for a single cohort over its expected lifetime, much as a cohort is tracked in a life-table analysis. For example, as shown in figure 1b, the susceptible compartment could start with a hypothetical cohort of 100,000 females aged 11 years. Each period (e.g., year) thereafter, some proportion of this susceptible cohort would advance to the infected compartment, remain in the susceptible compartment, or advance to the dead compartment. The parameter $p_1$, for instance, determines what proportion of the 100,000 females advance to the infected compartment; that is, it represents the probability that a susceptible person becomes infected with HPV over a fixed period of time (e.g., 1 year).

Of the susceptibles who progress to the infected compartment, some will eventually advance in a subsequent period to a precancerous compartment (e.g., CIN) according to the parameter $p_4$. This process is repeated each period until all 100,000 females have advanced to the dead compartment according to the transition probabilities $p_3$, $p_6$, $p_9$, and $p_{11}$. All of the remaining $p_i$ parameters also represent transition probabilities between or within compartments. Once a cohort model run is complete, the time spent in each compartment over the lifetime of the cohort can then be used to measure survival time and health-care costs accrued. Additionally, the proportion of persons who reach each compartment can be used to measure the incidence of key clinical events. Finally, cohort models may include a screening and treatment module that changes the transition probabilities. For a more detailed description of cohort modeling, refer to Beck and Pauker (44) and to Goldie (50).

Six cohort models have been developed to evaluate vaccination strategies. The first cohort model to appear in the literature was developed by the Committee to Study Priorities for Vaccine Development and was published by
the Institute of Medicine (31). This committee represented a group of experts in economic modeling, public health, ethics, epidemiology, immunization policy, infectious diseases, vaccinology, immunology, and clinical medicine commissioned by the Institute of Medicine. The institute published this committee’s model and evaluation as part of a general and preliminary assessment of vaccines for the United States.

The Institute of Medicine’s goal was to prioritize, using cost-effectiveness analysis, the development of vaccines against a number of disparate infectious diseases considered significant threats to public health. The institute did not intend for the evaluation to be the definitive cost-effectiveness analysis for an HPV vaccine. Their model tracked a cohort of 3.8 million girls and boys aged 12 years by using a spreadsheet (Microsoft Excel; Microsoft Corporation, Redmond, Washington) available to the public on the World Wide Web. The model simulated the progression of HPV disease by using the compartments shown in figure 1b. In addition, the model included compartments for genital warts, penile cancer, respiratory papillomatosis, and laryngeal carcinoma. However, the committee did not utilize these last two compartments in their final analyses. The primary output of the model was quality-adjusted life years (QALYs), costs, and cost-effectiveness ratios (i.e., incremental cost per QALY gained). Their analysis assumed that the HPV vaccine would be 100 percent effective with 100 percent coverage. In general, the committee found that HPV vaccination would reduce the cost associated with cervical cancer, penile cancer, and genital warts by $530 million. The committee reported that the cost-effectiveness ratios for HPV vaccination ranged from $4,000 to $6,000 per QALY gained.

Hughes et al. (32) developed the next cohort model to appear in the literature. These authors programmed this model in FORTRAN and limited its scope to epidemiologic outcomes. They explored the effect of a vaccine targeting high-risk HPV types on cervical cancer incidence in a cohort of females aged 16 years. The model tracked this cohort until all were dead by age 75 years. It related the age-specific incidence of HPV infection to the incidence of cervical cancer, and it included four of the five compartments in their final analyses. The primary output of the model was quality-adjusted life years (QALYs), costs, and cost-effectiveness ratios (i.e., incremental cost per QALY gained). Their analysis assumed that the HPV vaccine would be 100 percent effective with 100 percent coverage. In general, the committee found that HPV vaccination would reduce the cost associated with cervical cancer, penile cancer, and genital warts by $530 million. The committee reported that the cost-effectiveness ratios for HPV vaccination ranged from $4,000 to $6,000 per QALY gained.

In 2003, Sanders and Taira (33) published a cohort model that was broader in scope than the Hughes et al. (32) model. The purpose of the Sanders and Taira model was to evaluate both the effectiveness and cost-effectiveness of an HPV vaccine. They developed their model by using the decision tree software package Decision Maker (Pratt Medical Group, Boston, Massachusetts). The model simulated the progression of HPV disease in a cohort of females aged 12 years who either were not vaccinated or were vaccinated against infection with high-risk HPV types. Their analysis assumed that 70 percent of the target cohort would receive the vaccine. Vaccine efficacy against high-risk types was assumed to be 75 percent, with a duration of protection of 10 years. The analysis assumed that the cohort would receive a booster every 10 years. The analysis also assumed that 71 percent of the cohort would receive standard care. Sanders and Taira defined standard care as conventional, biennial, Papanicolaou test screening starting at age 16 years. Hence, the model evaluated two strategies: 1) HPV vaccination plus standard care versus 2) standard care only. In addition, the analysis assumed that those who did not get vaccinated in the vaccination strategy would receive standard care. The model comprised five compartments similar to figure 1b. The structure of the model and progression of disease through the model were based on prior screening models. The model projected the number of cases of HPV, squamous intraepithelial lesions, cervical cancer, and cervical cancer deaths. In addition, it tracked survival, quality-adjusted survival, costs, and cost-effectiveness ratios. Cervical cancer cases and deaths projected by the model matched 2001 Surveillance, Epidemiology, and End Results Program estimates (51) as well as those estimated by the Myers et al. screening model (49). The base-case results of the model showed that, relative to standard care, vaccination of females aged 12 years improved life expectancy by 2.8 days at a cost of $246. The corresponding cost-effectiveness ratios were $32,066 per life year gained and $22,755 per QALY gained. Sanders and Taira also conducted extensive sensitivity analyses. The parameter with the greatest influence on their findings was vaccine efficacy. They concluded that vaccination of girls with an HPV vaccine would be cost-effective when compared with many other generally acceptable health interventions.

Kulasingam and Myers (34) also published a cohort model in 2003 that was developed by using the decision tree software package DATA (TreeAge Software, Inc., Williamstown, Massachusetts). The objective of their model was to examine the potential health and economic effects of an HPV vaccine in a setting of existing cervical screening. The model simulated the natural history of HPV disease in a cohort of females aged 12 years with and without vaccination for a period up to 85 years of age. The analysis assumed that 100 percent of the cohort would receive a vaccine targeted at 70 percent of oncogenic HPV types including 16 and 18. The efficacy of the vaccine was assumed to be
90 percent, with 10 years’ duration of protection. Their analysis explored in greater depth the role of vaccination alongside established screening and compared three basic strategies: 1) vaccination without conventional cytology-based screening, 2) screening without vaccination, and 3) vaccination followed by screening. The third strategy was expanded to examine screening at different starting ages (i.e., 18–22, 24, 26, and 30 years) as well as differing screening intervals (i.e., 1, 2, 3, and 5 years). The structure of the model was based on the Myers screening cost-effectiveness model (49) and was similar to that shown in figure 1b, except that the HPV, CIN, and cervical cancer compartments were subdivided. Specifically, they represented the HPV compartment as high-risk and low-risk HPV. The CIN compartment was divided into a CIN 1 compartment and a CIN 2/3 compartment. The cancer compartment was divided into four separate ones representing the Federation Internationale de Gynecologie et d’Obstetrique stages of cervical cancer from localized to distant. The primary outcome of interest was a cost-effectiveness ratio expressed as a cost per life-year gained. Other outcomes tracked included HPV, CIN, and cervical cancer incidence, and QALYs. These outcomes were used to establish the validity of the model with natural history data and output from other models. In terms of results, Kulasingam and Myers found that a vaccine that reduced the incidence of oncogenic HPV types during the peak ages of infection could be economically attractive, especially if it allowed for a delay in the onset of screening. Vaccination plus biennial screening starting at age 24 years compared with screening every 3 years starting at age 18 years had the most attractive cost-effectiveness ratio at $44,889 per life-year gained. On the basis of extensive sensitivity analyses, these authors also found that the model results were most influenced by the age at which vaccination started, the HPV types covered, vaccine efficacy, and duration of protection.

The final two cohort models reviewed were developed by Goldie et al. (35, 36). The objective of their first model was to project the impact of a vaccine against persistent HPV-16 and -18 infections on the age-specific incidence of invasive cervical cancer (35). Similar to the previous two models, the Goldie et al. model was built on the foundation of prior cervical cancer screening models. Their analysis simulated the natural history of HPV disease in a cohort of females aged 13 years with and without vaccination over their expected lifetime and assumed that 100 percent of the target cohort would receive the vaccine. The efficacy of the vaccine was assumed to be 90 percent, with a lifetime duration of protection. The model compared three basic strategies: 1) neither screening nor vaccination; 2) cervical cancer screening as practiced in the United States, without vaccination; and 3) vaccination followed by cytology-based screening. All screening strategies were expanded to examine screening at different starting ages (i.e., 18, 21, 25, and 30 years), differing screening intervals (i.e., 1, 2, 3, 4, and 5 years), and differing cytologic tests (i.e., conventional vs. liquid based). The primary outcomes of interest were both epidemiologic (i.e., cases of low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, cervical cancer) and economic (i.e., costs, QALYs, and cost-per-QALY ratios). As with their previous vaccination model, this model demonstrated that HPV vaccination reduced the incidence of the epidemiologic outcomes of interest. From an economic perspective, Goldie et al. concluded that a combined vaccination and screening program could be cost-effective alongside the current screening regimens in the United States as well as under scenarios that delayed screening initiation and/or widened screening intervals. The cost-effectiveness ratio was less than $60,000 per QALY gained for the most effective combined vaccination and screening strategy. Their results were most sensitive to the duration of vaccine efficacy, the patterns of cervical cancer screening, and the natural history of HPV infection in women older than age 30 years.

**Dynamic models**

The structure of dynamic models is typically deterministic and nonlinear. Dynamic models differ from cohort models in a number ways. First, they do not track just a single cohort but rather the changing population over time. Hence, individuals constantly enter the model as they are born and exit the model as they die. For instance, the entry of new susceptible individuals into the model is represented by the parameter $\eta$ in figure 1c. Individuals exit the model at the mortality rate $\mu$, which can be compartment specific.
While corresponding parameters exist for parameter $\mu$ in figure 1c with parameters in figure 1b, a corresponding parameter for parameter $\eta$ does not exist. Hence, in a dynamic model, as long as persons are being born, the execution of a dynamic model does not have a natural stopping point, although, for the majority of models, a steady-state solution is usually approached in the long run. In contrast, the execution of a cohort model ends once all in the cohort have died or a prespecified analytical horizon has been reached.

The most significant feature of a dynamic model that differentiates it from a cohort model is the parameter $\lambda$ in figure 1c. This parameter represents the rate at which susceptible individuals become infected over a small period of time (e.g., 1 day). The parameter $\lambda$ is similar to the parameter $p_1$ in figure 1b. However, $p_1$ differs primarily from $\lambda$ in that $p_1$ is fixed with time and does not account for how HPV vaccination reduces the prevalence of HPV infection in the population over time. Reducing the prevalence of HPV infection over time means that susceptible individuals are less likely to become infected because there are fewer persons in the population to infect them with HPV. This indirect benefit of vaccination is referred to as the herd immunity benefits of vaccination (52). As a consequence, cohort models can underestimate the benefits of vaccination in that the indirect benefits of vaccination gained from the herd immunity effects are not accounted for. Additionally, cohort models can also overestimate the benefits of vaccination when the duration of vaccine protection may not be life-long and the progression rates between disease states depend on age. To account for the changing prevalence of HPV infection in the population, the parameter $\lambda$ is measured as a function of time, age, the number of sexually active persons in the population who are infected and not infected, the way they form sexual partnerships, and the transmission probability of HPV infection per partnership. The parameter $\lambda$ thus accounts for the transmission dynamics of HPV infection over time. Finally, similar to parameters $\lambda$ and $\mu$, parameters $\theta$ and $\pi$ in figure 1c have corresponding parameters in figure 2 (e.g., $p_1$ and $p_7$). For a more detailed review of dynamic models, refer to Anderson and May (42) and to Boily and Masse (27). For a more detailed description of the differences between cohort and dynamic models, see Edmunds et al. (53) and Brisson and Edmunds (54).

Three dynamic models have been published to date. Hughes et al. (32) published the first. The objective of their model was to explore the population-level impact of an HPV vaccine. Hughes et al. programmed this model as a series of differential equations and limited its scope to epidemiologic outcomes. They explored the effect of a monovalent high-risk HPV vaccine on the steady-state endemic prevalence of HPV-16 in the population. Their analysis assumed that 90 percent of the target cohort of females would receive a monovalent vaccine. The effectiveness of the vaccine was assumed to be 75 percent, with a duration of protection of 10 years. The model simulated the spread and control of HPV disease in the population by using five compartments: susceptible, infected, immune, effectively vaccinated and have not experienced an infection, and effectively vaccinated but infectious because of a breakthrough infection.

The model did not include a compartment for CIN or cervical cancer. Hughes et al. found that vaccinating both females and males decreased the endemic prevalence of HPV infection in women by 44 percent. They conducted a number of sensitivity analyses. Targeting the vaccine to females reduced the prevalence of HPV in women by only 30 percent. Hughes et al. suggested that a female-only vaccine would likely be 60–75 percent as efficient as a strategy that targets both sexes. Moreover, on the basis of their findings, they concluded that targeting the vaccine toward the most sexually active would be less effective. Because the model equations and inputs were made available in their publication, we were able to replicate their findings (figure 2) and show the importance of the short-term effects of vaccination given that the duration of protection in their model was 10 years.

The second dynamic model was developed by Barnabas and Garnett (38). Their objective was to illustrate the potential epidemiologic impact of an HPV vaccine in an unscreened, developing-world population. They programmed this model as a series of partial differential equations and limited its scope to epidemiologic outcomes. Using this model, they explored the effect of a multivalent HPV vaccine that had 100 percent efficacy against a broad range...
of high-risk HPV types, with lifetime protection. In their model, vaccination targeted males and females 15 years of age. In addition, the authors varied vaccine coverage rates. The model simulated the natural history of HPV disease in the population by using six compartments: susceptible, infected, vaccinated, low-grade squamous intraepithelial lesions, high-grade squamous intraepithelial lesions, and cervical cancer. Barnabas and Garnett found that vaccine coverage of at least 66 percent was needed to decrease cervical cancer by 80 percent. Moreover, a lag phase of 40 and 60 years was necessary to realize significant reductions in precancerous lesions and cervical cancer, respectively. They concluded that vaccinating men in addition to women has little incremental benefit in reducing cervical cancer. Finally, they recommended that HPV control rather than elimination be the first goal of an HPV vaccination program, given that HPV infection can be maintained in the population at low levels by a small number of people with high levels of sexual activity.

The final dynamic model was developed by Elbasha and Galvani (39). Their objective was to assess the changes in the distribution of HPV types following mass HPV vaccination. These authors developed this model as a system of ordinary differential equations. The model analyzed the transmission of two HPV types and the effects of interactions between them. Like the Hughes et al. model (32), their model focused on only HPV infection and not subsequent HPV disease events such as CIN and cervical cancer. The model simulated the progression of HPV disease in the population by using nine compartments: 1) susceptible to both types, 2–3) infected with one type and susceptible to the other type, 4) infected with both types, 5–6) infected with one type and immune to the other type because of recovery from infection, 7–8) immune against infection with one type because of recovery from infection and susceptible to infection with the other type, and 9) immune to infection with either type because of recovery from infection. The model explored the effect of a perfect as well as an imperfect vaccine on elimination of both HPV types, elimination of only one type with persistence of the other type, and persistence of both types. On the basis of their analytical results and illustration with numerical simulations using the mathematical software package Mathematica (Wolfram, Champaign, Illinois), Elbasha and Galvani found that if infection with one type facilitates concurrent or subsequent infection with another HPV type, then mass HPV vaccination could have the additional benefit of reducing the prevalence of HPV infection for types not covered by the vaccine.

Hybrid models

A hybrid model is a combination of a cohort model and a dynamic model. Earlier, we noted that the parameter \( p_1 \) in a cohort model did not change with time. A hybrid model corrects for this shortcoming by using a dynamic model to estimate how \( p_1 \) would change with time for the cohort of interest. As a result, a hybrid model does not underestimate the indirect benefits of herd immunity for the cohort being simulated. We did not include a figure for the hybrid model in this review because it would be represented by aggregating figures 1b and 1c with an arrow from the model in figure 1c to figure 1b indicating the dependency of \( p_1 \) on \( \lambda \).

Taira et al. (37) developed the only hybrid model in the HPV vaccine literature to our knowledge. Their goal was to evaluate a wide range of vaccine efficacies and population penetrations to understand what is required for a female-only program to achieve sizable benefit and to identify the scenarios in which incremental male vaccination makes sense. To develop their hybrid model, they combined their previous cohort model (33) with a transmission model. The transmission model was developed by using the software package Stella (High Performance Systems, Hanover, New Hampshire). The transmission model provided the long-term HPV infection rates for the cohort being tracked in the cohort model. It consisted of two compartments: susceptible and infected. The transmission model simulated the incidence of HPV infection in the population of females and males aged 12–50 years. The steady-state HPV infection rates predicted by this model were then used in the cohort model, which did not differ from their earlier analysis. Their transmission model predicted that HPV vaccination would reduce the number of cervical cancers due to HPV-16 and -18 in the US population by 95 percent. The cohort model predicted that vaccination of females would have a cost-effectiveness ratio of $14,500 per QALY gained. This estimate was lower than their original figure of $22,500 per QALY gained estimated by using their earlier cohort model that did not account for herd immunity effects. The other interesting result was that vaccinating males and females versus females alone had a significantly higher cost-effectiveness ratio of $440,000 per QALY gained. However, these authors also reported that as vaccination coverage decreased, the incremental cost-effectiveness of vaccinating males in addition to females improved. For example, the cost-effectiveness ratio decreased to less than $50,000 per QALY if vaccination coverage was less than 30 percent. Taira et al. concluded that vaccinating only females can be cost-effective, but vaccinating both females and males is not cost-effective compared with female-only vaccination if vaccine coverage is high.

DISCUSSION

To date, a number of reviews have examined mathematical models for evaluating cervical cancer screening strategies (55–57). This paper extends this work by reviewing a new group of mathematical models that have been built upon these previous screening models in order to evaluate HPV vaccination strategies. The goal of this review was to help the reader understand how these models worked and how they differed both in the research questions they answered and in their conclusions and recommendations. While our work does not represent a formal literature review, we believe we identified all models published at the time of this writing, given how early these models are in their development.

We found many similarities as well as key differences among the models. Table 1 summarizes this information.
TABLE 1. Summary comparison of mathematical models of HPV* disease

<table>
<thead>
<tr>
<th>Author(s) (reference no.)</th>
<th>Type</th>
<th>Purpose</th>
<th>Outcomes</th>
<th>Strategies evaluated</th>
<th>Key assumptions</th>
<th>Outcomes validated</th>
<th>Main findings</th>
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<tbody>
<tr>
<td>Institute of Medicine (31)</td>
<td>Cohort, numerical, deterministic</td>
<td>To prioritize, using cost-effectiveness criteria, the development of vaccines against a number of disparate infectious diseases considered significant threats to public health</td>
<td>Genital warts, CIN*, cervical cancer, penile cancer, QALYs,* costs, cost per QALY gained</td>
<td>Current care vs. vaccination + current care, females and males aged 12 years, 100% coverage, 100% effective, $330 vaccine series cost</td>
<td>Vaccination prevents HPV infection in males and females.</td>
<td>Cost per QALY gained for HPV vaccination ranged from $4,000 to $6,000.</td>
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<tr>
<td>Hughes et al. (32)</td>
<td>Dynamic, numerical, deterministic</td>
<td>To explore the population-level impact of an HPV vaccine</td>
<td>HPV prevalence</td>
<td>Females and males, monovalent, 90% coverage, 75% effective, 10 years of protection, age at vaccination not specified</td>
<td>Not age-structured; risk of HPV infection depends on age and sexual activity; examined only the long-term impact of vaccination.</td>
<td>Female-only vaccine would likely be 60–75% as efficient as a strategy that targets both sexes; targeting the vaccine toward the most sexually active is less effective.</td>
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<tr>
<td>Hughes et al. (32)</td>
<td>Cohort, numerical, deterministic</td>
<td>To explore the population-level impact of an HPV vaccine</td>
<td>Carcinoma in situ, ICC*</td>
<td>Females aged 16 years, bivalent high-risk types, 60% effective, screening</td>
<td>Risk of infection depends on duration of infection (not a Markov model); risk of HPV infection depends on age and sexual activity; HPV infection does not regress; time is a continuous variable.</td>
<td>60% reduction in high-risk HPV leads to a smaller reduction in carcinoma in situ (46%) and ICC (47%) because some of the HPV-associated lesions that are avoided are replaced by lesions caused by other high-risk types; reductions in the incidence of genital warts proportionate to the reduction in infection can be expected if a vaccine also prevented HPV-6 and -11; screening programs will still likely be necessary because vaccination will not eliminate all cervical cancers.</td>
<td></td>
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<tr>
<td>Sanders and Taira (33)</td>
<td>Cohort, numerical, deterministic</td>
<td>To evaluate the effectiveness and cost-effectiveness of a prophylactic HPV vaccine</td>
<td>Cost, life years, QALYs, cost per life year gained, cost per QALY gained</td>
<td>Screening (biennial Papanicolaou starting at age 16 years) vs. vaccination + screening; females aged 12 years; high-risk types, 70% coverage, 75% efficacy, 10-year protection, boosters every 10 years; $300 vaccine cost for the series in 2001 US dollars; $100 per dose for booster</td>
<td>Females can get LSIL* or HSIL* without HPV infection; progression of disease depends on infection with low- or high-risk type; regression of HPV infection is age dependent; monthly Markov cycle.</td>
<td>Cervical cancer</td>
<td></td>
</tr>
</tbody>
</table>

* LSIL: Low-grade squamous intra-epithelial lesion; HSIL: High-grade squamous intra-epithelial lesion; ICC: Invasive carcinoma of the cervix.
<table>
<thead>
<tr>
<th>Author(s) and Reference</th>
<th>Study Type, Model Type</th>
<th>Objective</th>
<th>HPV Infection, CIN, Cervical Cancer, Cost, Life Years, QALYs, Cost per Life Year Gained, Cost per QALY Gained</th>
<th>Methodology</th>
<th>Health Impact and Cost-Effectiveness</th>
<th>Cost per Life Year Gained for HPV Vaccination</th>
<th>Vaccine Strategy and Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kulasingam and Myers (34)</td>
<td>Cohort, numerical, deterministic</td>
<td>To examine the potential health and economic effects of an HPV vaccine in a setting of existing screening</td>
<td>HPV infection, ICC, cost, cervical cancer, life years, QALYs, cost per life year, cost per QALY, cost per QALY gained</td>
<td>Conventional cytology; vaccination vs. screening (conventional cytology, 1–5-year intervals starting between ages 18 and 30 years) vs. vaccination + screening; females aged 12 years; vaccine targeting 70% of oncogenic HPV types, 100% coverage, 90% efficacy, 10-year protection; $200 vaccine cost for the series in 2002 US dollars</td>
<td>Regression of HPV infection is age dependent; annual Markov cycle.</td>
<td>Cost per life year gained for biennial vaccination at age 24 years ranged from $44,889 to $236,250; vaccination for HPV in combination with screening can be a cost-effective health intervention, but it depends on maintaining effectiveness during the ages of peak oncogenic HPV incidence; identifying optimal age for vaccination should be a top research priority.</td>
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<td>Goldie et al. (35)</td>
<td>Cohort, numerical, deterministic</td>
<td>To project the impact of a prophylactic vaccine against persistent HPV-16/-18 infection on the age-specific incidence of ICC</td>
<td>HPV infection, LSIL, HSIL, ICC</td>
<td>Females aged 12 years, bivalent HPV-16/-18, 100% coverage, 50–98% efficacy, no screening</td>
<td>Tracks low-risk and high-risk HPV infections; vaccination does not impact transient HPV infections; examined the effect of cross-protection; examined the effect of latent infections reactivating; semiannual Markov cycle.</td>
<td>A prophylactic vaccine that prevents persistent HPV-16/-18 infection can be expected to significantly reduce HPV-16/-18–related LSIL, HSIL, and cervical cancer; important priorities for future research and public health policy include understanding the heterogeneity of vaccine response, the effect of type-specific vaccination on other HPV types, and the degree to which vaccination effect persists over time.</td>
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<tr>
<td>Goldie et al. (36)</td>
<td>Cohort, numerical, deterministic</td>
<td>To explore the clinical benefits and cost-effectiveness of introducing an HPV-16/-18 vaccine in a population with an organized screening program</td>
<td>HPV infection, LSIL, HSIL, ICC, cost, life years, QALYs, cost per life year gained, cost per QALY gained</td>
<td>Screening (conventional and liquid-based cytology, and HPV testing, 1–5-year intervals starting between ages 18 and 35 years) vs. vaccination + screening; females aged 12 years; bivalent (HPV-16/-18), 100% coverage, 90% efficacy, lifetime protection; $377 vaccine cost per series in 2002 US dollars</td>
<td>Model tracks low-risk and high-risk HPV infections; vaccination does not impact transient HPV infections; transient infections can cause CIN1; examined the effect of cross-protection; examined the effect of latent infections reactivating; semiannual Markov cycle.</td>
<td>Cervical cancer</td>
<td>Cost per QALY gained for HPV vaccination ranged from $12,300 to $4,863,000; a vaccine that prevents persistent HPV-16/-18 infection will reduce the incidence of HPV-16/-18–associated cervical cancer, even in a setting of cytologic screening; a program that permits a later age at screening initiation and a less frequent screening interval is likely to be a cost-effective use of healthcare resources.</td>
</tr>
</tbody>
</table>
### TABLE 1. Continued

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Type</th>
<th>Purpose</th>
<th>Outcomes</th>
<th>Strategies evaluated</th>
<th>Key assumptions</th>
<th>Outcomes validated</th>
<th>Main findings</th>
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<tbody>
<tr>
<td>Taira et al. (37)</td>
<td>Hybrid, numerical, deterministic</td>
<td>To evaluate a wide range of vaccine efficacies and population penetrations to understand what is required for a female-only program to achieve a sizable benefit and to identify the scenarios in which incremental male vaccination makes sense</td>
<td>HPV prevalence, cervical cancer, cost, life years, QALYs, cost per life year gained, cost per QALY gained</td>
<td>Females aged 12 years, bivalent high-risk types, 90% efficacy, 10-year protection, boosters at age 22 years, 70% coverage, 71% biennial Papanicolaou test starting at age 16 years, catch-up vaccination at ages 24–30 years, $300 vaccine cost for the series, $100 per dose for booster</td>
<td>Transmission model is age structured but limited to HPV infection; females can get LSIL or HSIL without HPV infection; progression of disease depends on infection with low- or high-risk type; regression of HPV infection is age dependent; HPV infection can become dormant and cause lesions and cancer; persons who clear an HPV infection are at risk for reinfection; monthly Markov cycle in cohort model.</td>
<td>HPV, cervical cancer</td>
<td>Cost per QALY gained for HPV vaccination ranged from $14,583 to $442,039; a vaccine that protects against HPV-16/-18 could be cost-effective and can substantially reduce cervical cancer rates; including males in a vaccination program is generally not cost-effective compared with female-only vaccination when coverage rates are high.</td>
</tr>
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| Barnabas and Garnett (38) | Dynamic, numerical, deterministic | To illustrate the potential epidemiologic impact of an HPV vaccine by using a mathematical model | Prevalence of HPV infection, LSIL, HSIL, and cervical cancer | Females and males aged 15 years; all HPV types as a single pathogen; 100% effective; lifetime protection; 100% coverage; developing-country setting, no screening; catch-up vaccination at ages 24–30 years | Age structured; regression of HPV infection is age dependent; examined short- and long-term impact of vaccination. | HPV, cervical cancer | HPV control rather than elimination should be the first goal of vaccine programs; vaccinating men has little benefit in reducing cervical cancer; vaccine coverage of at least 66% is needed to substantially decrease the incidence of cervical cancer; a lag phase of 40 and 60 years is necessary to realize significant reductions in precancerous lesions and cervical cancer, respectively; HPV vaccination improves survival. |

| Elbasha and Galvani (39) | Dynamic, analytical | To explore how interactions between HPV types enhance or diminish the effectiveness of HPV vaccination | Prevalence of HPV infection | Women and men, bivalent high-risk types | Analytical modeling. | * HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; QALYs, quality-adjusted life years; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions. |

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* HPV, human papillomavirus; CIN, cervical intraepithelial neoplasia; QALYs, quality-adjusted life years; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions.
One area in which the models differed was in the questions they answered. Five of the models focused on only the long-term epidemiologic consequences of HPV vaccination (32, 35, 38, 39). Of the five, only three examined the impact of vaccination on cervical cancer (32, 35, 38). The other two focused on the impact of HPV vaccination on the prevalence of HPV infection in the population. Two of the models examined the effect of interaction between types on epidemiologic outcomes (35, 39). Only one model considered the impact of vaccination on genital warts (31). This model was also the only one to examine the benefits of HPV vaccination to males. In terms of results, all models predicted that HPV vaccination would result in a reduction in HPV infection and/or a reduction in cervical precancers and cancer. The magnitudes of these reductions were most influenced by the duration of protection conferred by the vaccine, the effectiveness of vaccination, the effectiveness of screening, whether or not HPV types interacted, and the duration of follow-up examined by the model.

In addition to projecting epidemiologic outcomes, five of the models examined the long-term economic consequences of HPV vaccination (31, 33, 34, 36, 37). None of these models were dynamic. A consistent finding across these five models was that vaccinating females can be cost-effective (58). The cost-effectiveness of vaccination further improved if vaccination was used to delay the start of or widen the interval for cervical cancer screening. Also influential in the cost-effectiveness analyses were the duration of vaccine protection, vaccine effectiveness, vaccination cost, the health utilities used to estimate QALYs, and whether or not males were vaccinated.

With respect to this last strategy, only one of the five models examined the cost-effectiveness of vaccinating males and females versus females only (37). This model found that vaccinating males along with females would not be a cost-effective strategy for reducing cervical cancer in women if vaccine coverage was high. Given that this finding was generated by using a hybrid model, the results generalize only to the female cohort evaluated by the model and do not account for the complete herd immunity benefits of vaccination in the entire female population. Moreover, given that some HPV vaccines may benefit men and women by preventing genital warts (22), accounting for this benefit is likely to improve the cost-effectiveness of vaccination for the general population.

Besides developing future models that account for all the direct and indirect (i.e., herd immunity) benefits of vaccination to the general population, researchers can improve future models by conducting further validation work (i.e., internal, convergent, and external) (59–61). Most of the models reviewed reported some level of validation. In terms of the cohort models, all used cross-sectional, population-based, epidemiologic data instead of population-based, longitudinal cohort data for internal validation. Utilizing cross-sectional data may be acceptable if cohort and period effects remain constant over time in the population. However, a number of studies have shown that there are significant cohort (e.g., sexual behavior) and period (e.g., screening) effects in cross-sectional, age-specific cervical cancer incidence data (14, 18). As a result, the model validation work may need to account for the changing cohort and period effects when model output is compared with the epidemiologic data (29). One approach for handling this task is to utilize cervical cancer and precancer registry data available in various Nordic countries (62) and Canada (63) to follow birth cohorts longitudinally and examine the cumulative incidence of HPV disease events. In terms of dynamic models, cross-sectional data from these registries would also be useful for internal validation. However, adjustments for period and cohort effects may also be necessary. Another type of validation (i.e., convergent) that should be considered for future models would be formal comparisons of output from independently developed models using reference case inputs, assumptions, and strategies. For example, in the diabetes field, researchers have organized annual conferences to compare output from independently developed diabetes disease mathematical models using reference case inputs, assumptions, and strategies (64). A final type of validation or model checking is the ability to replicate results by disclosing the model equations. The Hughes et al. (32) model was the most transparent in this regard. Given that Hughes et al. included their differential equations and inputs in their paper, we were able to replicate their findings, as shown in figure 2. This type of independent replication can be more challenging with cohort and hybrid models.

A number of the models identified parameters that were highly influential, yet lacking in evidence. These parameters included duration of vaccine protection, reactivation of infection, HPV type interaction, transmission of infection, and health utilities. Clearly, data on the duration of vaccine protection will not be available for some time. However, in the interim, antibody decay statistical models (65) could be developed by using longitudinal, epidemiologic, and clinical trial data to better quantify this parameter. The assumption of reactivation of infection after it has apparently cleared also remains an outstanding issue (66). Better data on this issue could inform whether the models should assume that persons who clear an infection can or cannot reactivate infection or be reinfected with the same HPV type. Long-term follow-up studies of the vaccine clinical trials should provide some insights into these issues. Additional data could also be useful to learn whether HPV types interact (67). The evidence to date is mixed (68–72). Data from the vaccine clinical trials should also be able to provide insights regarding HPV-type interaction. The one parameter that clinical trial data will not be able to provide information for is the transmission probability per sexual contact. No empirical data exist on transmission probabilities for HPV infection used to estimate λ in figure 1e (73). Hence, epidemiologic studies of disease transmission are necessary. Lastly, few studies have collected health utility data for the HPV disease states tracked in these models. Given the influence that utility data have on the cost-effectiveness ratios, it will be important that more studies be conducted. Of particular interest will be country-specific studies to help adapt these models to other populations.

Another area for further research is to apply these models to evaluate the benefits of vaccination for populations underserved by screening (e.g., the developing world).
Given that the burden of cervical cancer in these populations is high (74), results from these models can be instrumental for developing policy that can facilitate introduction of vaccination by addressing economic issues. In particular, the ability of these models to examine the economics of vaccination allows policy makers to determine over what cost range vaccination will be cost-effective for specific countries. For example, Goldie et al. (75) used cost-effectiveness analysis to identify cost-effective cervical cancer screening strategies in five developing countries by using criteria developed by the Commission on Macroeconomics and Health for the World Health Organization.

Finally, the scope of the models reviewed was limited to cervical cancer, CIN, and genital warts. HPV infection has also been associated with cancers of the anus, penis, vagina, vulva, and head and neck, as well as recurrent respiratory papillomatosis (4). None of the models accounted for these other HPV diseases in their analyses. As evidence becomes available for modeling the potential effects of vaccination on these other HPV conditions, future models will need to broaden their scope and incorporate these conditions as compartments into their structure. Other important considerations for future model development include the need for modeling separate versus combined HPV types as well as stochastic sensitivity analyses.

In summary, we reviewed the state of mathematical modeling of HPV disease for evaluating HPV vaccination policies. We found three types of HPV mathematical models in our review of the literature: cohort, population dynamic, and hybrid. These models differed both in their complexity and in the questions they answered. Of the models developed, cohort models were the most complete, whereas dynamic models were still in early development. Future research in the field should focus on further development of population dynamic models by expanding the range of epidemiologic outcomes tracked, accounting for the economic consequences of HPV vaccination, including the ability to assess the cost-effectiveness of alternative HPV vaccination policies, and conducting more epidemiologic studies to inform model parameters and structure and support model validation.

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REFERENCES