SUBJECT REVIEW

Prophylaxis of Cervical Cancer and Related Cervical Disease: A Review of the Cost-Effectiveness of Vaccination Against Oncogenic HPV Types

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ABSTRACT

BACKGROUND: Vaccines have demonstrated cost-effectiveness in managed care through the prevention of disease. As new vaccines for previously untargeted conditions are developed, pharmacoeconomic modeling is becoming even more critical for the quantification of value in the health care industry. Two recently developed vaccines aimed at prevention of infection from human papillomavirus (HPV) types 16 and 18 have proven to be highly efficacious. HPV 16 and 18 are the 2 most common oncogenic strains of HPV and are responsible for 70% of cervical cancer cases worldwide. Persistent infection with an oncogenic HPV type is a known cause of cervical cancer. Therefore, prevention of cervical cancer via HPV vaccination may have a significant financial impact.

OBJECTIVE: To qualitatively review existing mathematical models of the cost-effectiveness of prophylactic HPV vaccination, with an emphasis on the impact on managed care in the United States.

METHODS: Mathematical models of the cost-effectiveness of HPV vaccination based on U.S. data were reviewed. A search of the PubMed database was conducted using the search terms "HPV," "vaccine," and "cost-effectiveness" for articles published before February 22, 2010. Studies employing mathematical models to estimate the cost-effectiveness of HPV vaccination in healthy subjects from the United States were included. Models based on data or populations from outside of the United States were excluded. Outcomes were measured with incremental cost-effectiveness ratios (ICERs), typically in units of quality-adjusted life expectancy (quality-adjusted life years [QALYs] gained). Most studies included in this review modeled vaccination of a cohort or population of females aged 12 years. Assessment of catch-up vaccination in females (through aged 24 to 26 years) was included in a couple of reports. One study examined vaccination in older females (aged 35, 40, and 45 years). Models typically compared a strategy of HPV vaccination with the current practice of cervical screening (sampling of cervical cells for disease detection) alone.

RESULTS: 11 studies of cost-effectiveness modeling of HPV vaccination were included in this review. A direct quantitative comparison of model results is challenging due to the utilization of different model types as well as differences in variables selected within the same model type. Each model produced a range of cost-effectiveness ratios, dependent on variables included in sensitivity analyses and model assumptions. Sensitivity analyses revealed the lowest ICER to be $997 per QALY gained and the highest ICER to be $12,749,000 per QALY gained. This enormous range highlights the need to clarify what model assumptions are being made. The 2 studies that included modeling of catch-up vaccination scenarios in females older than age 12 years also produced a wide range of ICERs. One study, assuming 90% efficacy, 100% coverage, and lifelong immunity, modeled catch-up vaccination in all females aged 12 to 24 years and yielded an ICER of $4,666 per QALY. If the duration of protection was limited to 10 years, then costs increased to $21,121 per QALY. The other study modeling catch-up HPV vaccination assumed 100% efficacy, 75% coverage, and lifelong immunity. ICERs in this study for outcomes relating to cervical cancer ranged from $43,600 per QALY in the base model vaccinating only 12 year olds with no catch-up vaccination, to $152,700 in a model including catch-up vaccination through age 26 years. Although catch-up to age 21 years resulted in a cost of $120,400 per QALY, the ICER decreased to $101,300 per QALY if model outcomes related to prevention of genital warts were also included. The lone study modeling vaccination in women aged 35 to 45 years resulted in an ICER range of $116,950 to $272,350 per QALY when compared with annual and biennial cytological screening.

Cost-effectiveness was defined as an ICER at or below $100,000 per QALY gained. All models of female adolescent vaccination were able to produce vaccination strategies that would be cost-effective according to this definition in addition to many strategies that would be cost-prohibitive. Variables influential in determining cost-effectiveness of HPV vaccination included the frequency of accompanying cervical screening, the age at which screening is initiated, vaccination efficacy, duration of vaccine protection, and the age range of females to be vaccinated. The actual effectiveness of HPV vaccination in the female population will also depend on levels of vaccine uptake or coverage and compliance in completing all vaccine doses.

CONCLUSION: Clinical studies have shown HPV vaccination to be highly efficacious and potentially lifesaving if administered to females naïve or unexposed to vaccine HPV types. Modeling studies have also shown that HPV vaccination can be cost-effective with an ICER of $100,000 or less per QALY gained if administered to females aged 12 years in the context of cervical screening intervals typically greater than 1 year. Catch-up vaccination through 21 years of age increases the cost per QALY to more than $100,000. Until real-world coverage rates increase, cost-effectiveness modeling of HPV vaccination underestimates the actual cost per QALY.

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What is already known about this subject

- Cervical cancer is the second most common cancer among women worldwide, trailing only breast cancer in incidence and prevalence. Infection with an oncogenic human papillomavirus (HPV) type is the known cause of cervical cancer. Of the 40 HPV types that infect the genital mucosa, 15 are known to be oncogenic (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82). Two vaccines have proven efficacy against types 16 and 18, which account for 70% of cervical cancer cases worldwide.
- While cervical screening with the traditional Papanicolaou test or more recently developed exams such as liquid-based cytology (LBC) or HPV deoxyribonucleic acid (DNA) testing may detect pathology in the cervix, the development of highly efficacious prophylactic HPV vaccines allows for prevention of infection from cancer-causing oncogenic HPV types. Vaccination is therefore considered to be a primary form of prevention for cervical cancer.
- There are presently 2 HPV vaccines (quadrivalent and bivalent) available for use in the United States. Both require 3 intramuscular injections over a course of 6 months to achieve prophylaxis, and the direct vaccine cost excluding administration and medical visits is about $375 per recipient.
- The annual costs of screening and treatment for HPV-related diseases in the United States are estimated to be at least $6 billion. HPV vaccines can potentially provide high value in managed care by providing benefits that may over time offset some of the direct and indirect costs of disease management.

What this review adds

- This is the first qualitative review of cost-effectiveness models of HPV vaccination based solely on U.S. data. All models examined have determined that HPV vaccination in females aged 12 years can be cost-effective in comparison with the current practice, which consists of cervical screening alone beginning no later than 21 years of age.
- Cost-effectiveness models of HPV vaccination may underestimate actual costs due to assumptions about efficacy and coverage (i.e., vaccination rate in the population) that may not be realized in the real world. Efficacy is based on completion of 3 doses, which probably occurs in no more than 75% of females who initiate vaccination. For coverage, Centers for Disease Control and Prevention (CDC) survey data for 2008 showed that only 37% of females between 13-17 years of age and 10% of women between 18-26 years of age had taken at least 1 of the 3 recommended vaccine doses.
- Cost-effectiveness will be lower (more favorable) when the HPV vaccine is universally administered to 12-year-old females. Even with high coverage, the cost per QALY is greater than $100,000 when catch-up HPV vaccination is extended to females aged up to 21 years and more than $150,000 per QALY when extended to females aged up to 26 years. Nevertheless, managed care organizations might consider providing full benefits coverage for the cost of HPV vaccination for all females aged 9 to 26 years, the age range currently recommended for vaccination by the CDC Advisory Committee on Immunization Practices.

In 1999, the Centers for Disease Control and Prevention (CDC) deemed universal vaccinations of children as one of the 10 greatest achievements in public health during the 20th century.[1] In the United States, routine vaccinations have led to the eradication of 2 diseases once considered scourges of society: smallpox and polio. Since 1900, morbidity or disease incidence from 7 other vaccine-preventable diseases (diphtheria, pertussis, tetanus, measles, mumps, rubella, and *Haemophilus influenzae* type b) has also decreased by 95% or better.[1] Vaccination prevents an estimated 3 million deaths annually worldwide, including nearly 1.8 million from hepatitis B and measles combined.[2] Reductions in morbidity and mortality as a result of vaccination have had a significant economic impact as well: in most cases, the savings provided by vaccines far exceed their cost. For example, for every dollar spent on the measles-mumps-rubella, diphtheria-tetanus-acellular pertussis, and *Haemophilus influenzae* type b vaccines, more than $21, $24, and $2 are saved in direct medical costs, respectively.[2] Notably, global savings in direct medical costs related to the eradication of smallpox in 1977 are estimated to exceed $300 million per year.[2]

Managed care organizations should recognize that while vaccines provide optimal value, vaccines continue to be underused and undervalued.[2] This value is derived from the fact that most vaccines provide benefits that exceed both the direct medical and indirect societal costs of disease management, making these agents an obvious choice for implementation in the cost-driven managed care setting.[2] The administration of traditional childhood vaccines has demonstrated substantial cost savings.[2] However, as the paradigm for vaccine use in managed care moves toward prevention of diseases more typical of the adolescent and adult population, the cost offsets may be less obvious. The advent of newer vaccines aimed at previously untargeted infectious agents may require more involved pharmacoeconomic analyses in order to establish definitive value. Thus, complex mathematical models have been employed so that government agencies and health care payers can evaluate whether newer vaccines should be widely administered and subsidized.

HPV Vaccination Is an Opportunity for Managed Care

Perhaps the most talked about of the newer vaccines are those aimed at prevention of infection from the human papillomavirus (HPV).[3] In the cervix, HPV is typically transmitted through microabrasions that may occur as a result of sexual intercourse.[4] Persistent infection with an oncogenic strain of HPV is the known cause of cervical cancer,[5] the second most common cancer in women worldwide. Of the 40 HPV types that affect the genital area, at least 15 types are known to be oncogenic (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82).[6] The strength of the association between HPV and cervical cancer is at least 10 times greater than the association between smoking and lung cancer.[5] HPV infection is also associated with other genital cancers (e.g., vaginal, vulvar, anal, and penile) as well as non–life-threatening diseases, such as genital warts.

Prophylactic vaccines for cervical cancer target HPV 16 and 18, the most common oncogenic types of HPV. In the United States, there are currently 2 HPV vaccines available for use, quadrivalent HPV vaccine (Gardasil, Merck)[7] and bivalent HPV vaccine (Cervarix with AS04, GlaxoSmithKline).[8] Both vaccines offer protection against HPV types 16 and 18, which are associated with 70% of invasive cervical cancer cases worldwide.[9] Quadrivalent HPV vaccine also protects against nononcogenic HPV types 6 and 11, which are responsible for benign anogenital warts.[7] When administered to females previously unexposed to vaccine HPV types, both HPV vaccines have demonstrated greater than 90% efficacy against the incidence of high-grade precancerous cervical lesions (Table 1).[7,8,10,11] The CDC Advisory Committee on Immunization Practices recommends HPV vaccination for all females aged 11 to 12 years and as young as 9 years.[12] This age recommendation is aimed at vaccinating females before sexual debut. Catch-up vaccination is also recommended for all females aged 13 to 26 years who have not been previously vaccinated.[12]

Since cervical screening only detects neoplastic changes after they have occurred, HPV vaccination is considered to be the primary form of cervical cancer prevention. Because prophylactic HPV vaccination is not effective against infection from all 15 oncogenic HPV types, regular cervical screening is still necessary. However, only about 82% of privately insured women and 65% of women enrolled in Medicaid received a Papanicolaou (Pap) screening test in 2007.[13] This lack of adherence implies that secondary prevention alone is not adequate in addressing the disease burden associated with cervical cancer. Poor screening compliance inevitably results in cervical cancer cases going undetected until later stages when the prognosis is far graver and the disease is more costly to treat.

TABLE 1 Comparison of HPV Vaccine Data

	Quadrivalent HPV[a]	Bivalent HPV[b]
HPV types covered	6, 11, 16, 18	16, 18
Efficacy against high-grade precancerous lesions	98%	92.9%
Duration of antibody response	Vaccine-induced antibody titers to HPV 6, 11, 16, and 18 peaked at month 7 after the initial vaccine dose. Antibody titers declined through month 24, stabilized, and were similar at month 60.[7]	Vaccine-induced antibody titers to HPV 16 and 18 peaked at month 7 after the initial vaccine dose and thereafter reached a plateau that was sustained from month 18 up to month 76.[8] Mathematical modeling estimates duration of antibody response should last at least 20 years.[10]
Cost	Roughly $375 ($125 per dose x 3 doses) in 2008, excluding physician visit or vaccine administration charges.[11]	To be determined
Administration	Intramuscular shoulder injection	Intramuscular shoulder injection
Safety (Phase III studies)	0.8% of individuals who received the vaccine and 1.0% of individuals who received the control reported a serious systemic adverse reaction.[7]	5.3% of individuals who received the vaccine and 5.9% of individuals who received the control reported at least 1 serious adverse event, without regard to causality.[8]

[a]Quadrivalent HPV vaccine (Gardasil, Merck) is effective against oncogenic HPV types 16 and 18 and nononcogenic HPV types 6 and 11, which cause the majority of genital warts.[7]

[b]Bivalent HPV vaccine (Cervarix, GlaxoSmithKline) is effective against oncogenic HPV types 16 and 18.[8]

HPV = human papillomavirus.

Although widespread cervical screening is largely responsible for an approximate 74% decrease in U.S. cervical cancer deaths over the past 50 years,[14] the sensitivity of conventional cytologic cervical screening is only about 50% for detection of moderate to severe precancerous lesions.[15] Use of newer and more expensive liquid-based cytology (LBC) screening has not definitively improved sensitivity.[15] However, the sample collected for LBC may concurrently be used for HPV deoxyribonucleic acid (DNA) testing that may confirm the presence of an oncogenic HPV type. While this combination testing is more sensitive than traditional Pap screening, it is less specific and may lead to more false-positive results and unnecessary follow-up testing.[16] One recent meta-analysis found specificity of traditional cytology in identifying low-grade cervical lesions (96%) to be significantly higher than that of HPV DNA testing (86.5% to 94.7%). It was estimated that the lower sensitivity translated to a false-positive rate of nearly 10%.[17]

Current screening guidelines endorsed by the American Cancer Society recommend beginning screening about 3 years after first vaginal intercourse and no later than age 21 years.[18] Annual screening with the Pap test is recommended, while biannual screening is allowed when using LBC. At 30 years of age, women who have had 3 consecutive normal Pap screens may begin screening every 2 or 3 years. Alternatively, these women may be screened every 3 years in conjunction with HPV DNA testing.[18] The American College of Obstetricians and Gynecologists (ACOG) revised its screening guidelines in December 2009. ACOG now recommends beginning biennial screening at age 21, regardless of sexual history. At age 30, screening every 3 years is recommended for women who have had 3 consecutive negative cytology screenings.[19]

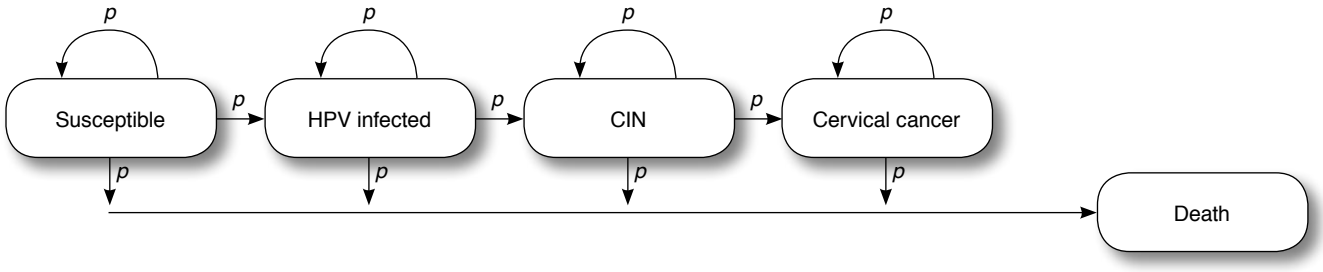
It is estimated that in the United States, 1 in 4 women between the ages of 14 and 59 years is infected with HPV; oncogenic HPV types 16 and 18 have prevalence rates of 1.5% and 0.8%, respectively.[20] An estimated 11,270 new cases and 4,070 deaths still occur annually,[14] and total direct medical costs related to cervical cancer prevention and treatment have been estimated at approximately $6 billion.[21-23] In one health plan in the northwestern United States, nearly two-thirds of these direct costs were allocated to routine screening, with 10% allocated to treatment of invasive cervical cancer, 17% to precancerous lesions, and 9% to follow-up care of false-positive Pap tests.[24] Indirect costs associated with cervical cancer are even higher than direct costs, as more than 75% of the total economic burden of cervical cancer is attributed to decreased productivity, lost future earnings, and other related factors.[25] HPV vaccination may help to diminish the total direct and indirect costs by preventing infection and subsequent development of precancerous lesions and invasive cancer, providing a long-term return on investment by avoiding cervical cancer treatment.

Modeling the Cost-Effectiveness of HPV Vaccination

It can take years to decades for an HPV infection to progress to cervical cancer. Due to this practical limitation, and because cancer incidence cannot be ethically used as an endpoint for vaccine evaluation (i.e., subjects cannot be denied treatment upon detection of cytologic abnormalities or precancerous lesions in order to establish vaccine efficacy against cancer), mathematical modeling is employed to simulate outcomes. Three types of models have been employed: static Markov, transmission dynamic, and hybrid models combining features of both Markov and dynamic models.

Results of HPV vaccine cost-effectiveness studies modeled with U.S. data are summarized in Table 2. These outcomes are typically measured with an incremental cost-effectiveness ratio (ICER), determined by dividing the difference in cost between 2

FIGURE 1 Basic Cohort Model Representation Incorporating HPV Disease Progression to Death



Source: Adapted from Dasbach et al. (2006)[26]
CIN = cervical intraepitelial neoplasia; HPV = human papillomavirus; P = probability of transmission to the next state.

strategies (e.g., HPV vaccination vs. current screening practices) by the difference in health outcomes. Typically, the unit of measurement for the ICER is the difference in life expectancy (life years saved [LYS]) or quality-adjusted life expectancy (including utilities defined on a scale of 0 [death] to 1 [perfect health], quality-adjusted life years [QALY] saved is a measure of disease burden that accounts for years lived in less than perfect health).

It is important to understand that all mathematical models are based on assumptions and predictions that may or may not always be accurate. Therefore, the utility of conclusions drawn by mathematical models is constrained by the need for subsequent validation of these assumptions. Model outcomes of the cost-effectiveness of HPV vaccination are constrained by assumptions of vaccine efficacy, duration of vaccine protection, and level of vaccine coverage in the population among other variables. Although data exist on vaccine efficacy, duration of protection is yet to be determined, and there are uncertainties about how fast vaccine uptake will occur. Therefore, the accuracy of model assumptions and subsequent model outcomes can only be validated over time.

Model Types

Markov models simulate disease progression for a particular cohort (e.g., females aged 11 years) over an expected lifetime (Figure 1).[26] These models are typically probabilistic and linear and follow the susceptible cohort through subsequent disease stages or compartments (e.g., HPV infected, cervical intraepithelial neoplasia, cervical cancer, and death).[26] Probabilistic models allow for events to occur by chance, and the probability that any individual will transition from one compartment to the next is drawn from a probability distribution. Transition probability parameters (*p*), based on established clinical morbidities, are constant over time and determine what proportion of the cohort advances to various disease states during a model cycle.[26] Use of a prophylactic HPV vaccine should reduce the number of patients in the original cohort that will develop HPV infections and lower the proportion of patients developing subsequent HPV-related disease states. The Markov cycles are run until all the members of the original cohort have died, either from HPV-related disease or natural causes, based on the model parameters.[26] The time spent in each stage over the lifetime of the cohort is then used to measure both the survival time and health care costs accrued.[26]

Transmission dynamic models examine a whole population over time.[26] These models are typically deterministic and nonlinear. These models are deterministic in that there is an average rate of transition between disease stages that is the same for each individual at a given time, as opposed to being drawn from a probability distribution for each person. Individuals enter this type of model at birth and exit the model at death. In contrast to cohort models where transition parameters between disease states are constant over time, the parameters in dynamic models can change if HPV prevalence changes. For example, transmission dynamic models can take herd immunity into account, whereby vaccination of a large segment of the population will decrease the transmission parameter between the HPV-susceptible stage and HPV-infected stage by having fewer individuals infected with HPV able to transmit the virus.[26] Since the rate at which individuals become infected is dependent on the number of infectious individuals, this type of model is inherently nonlinear.[27] Although this type of model is more "real world" in that more variables are considered, it is also prone to greater uncertainty based upon an increased number of parameter assumptions that must be made.

Hybrid models combine properties of the Markov and dynamic models. The hybrid model follows a single cohort rather than the whole population but allows for changes in the transmission parameters between disease states over time. In this way, the benefits of herd immunity can be modeled by simulating a decrease in disease transmission over time.

Model Selection

Models included in this review were found by searching the PubMed database using the terms "HPV," "vaccine," and "cost-effectiveness." Only primary research studies focusing on the economic impact of HPV vaccination on cervical cancer that were modeled using U.S. data and published before February 22, 2010, were included in this review. Studies based on data from outside the United States were excluded, as were studies

TABLE 2 Overview of Published HPV Vaccination Cost-Effectiveness Models

Authors/Model Type/Funding	Model Subjects	Vaccine Characteristics	Baseline Screening Characteristics	Cost-Effectiveness Point Estimates	Treatment Comparators	Sensitivity Analyses	Model Assumptions
Kulasingam and Myers (2003)[32] Markov model type Funded by Merck Research Laboratories	100,000 females aged 12 years	70% of oncogenic HPV types (including 16 & 18) 90% efficacy 100% coverage	Biennial Pap screening initiated at age 24 years	$44,889 per LYS	Biennial Pap screening at age 18 years	CE range = $44,889 per LYS to $236,250 per LYS Varied: screening intervals (1, 2, 3, and 5 years); screening initiation age (18, 22, 24, 26, and 30 years); efficacy (25%-100%); duration of protection (2-30 years)	1. Vaccine costs $200 2. Duration of protection 10 years 3. Progression from low- to high-grade cervical lesion not differentially affected by the vaccine 4. Age-specific risks of infection, regression, and disease incidence modeled 5. Future costs and life years discounted at 3% 6. Disutility of precancerous lesions about 1 month, for cancer for 5 years of follow-up
		70% of oncogenic HPV types (including 16 & 18) 90% efficacy 100% coverage	Annual Pap screening initiated at age 18 years	$236,250 per LYS	Annual Pap screening initiated at age 22 years		
Goldie et al. (2004)[33] Markov model type Funded by GlaxoSmithKline Biologicals; NCI	100,000 females aged 12 years	HPV 16/18 90% efficacy 100% coverage Lifelong protection	Current practice: Pap screened 70.5% in last year, 12.6% in last 2 years, 4.3% in last 3 years, and 3.0% in last 5 years; 5.2% never screened	$24,300 per QALY	Current screening practice alone	CE range = $17,200 per QALY to $3,867,500 per QALY Varied: efficacy (70%, 80%, 90%, 100%); duration of protection (5, 10, 15, 20 years or never); proportion of women > 30 years with newly acquired persistent infection versus reactivation of latent infection; frequency of screening, age of initiation, and cost of follow-up	1. Vaccine costs $377 2. 6-month transitions between disease states 3. No cross-protection of the vaccine against nonvaccine HPV types 4. Future costs and life years discounted at 3% 5. Utilities based on previous literature varied "with stage of disease"
		HPV 16/18 100% efficacy 100% coverage Lifelong protection	Current practice	$20,600 per QALY	Current screening practice		
Rogoza et al. (2008)[34] Markov model type Funded by GlaxoSmithKline Biologicals	100,000 females aged 12 years	HPV 6/11/16/18 95% efficacy (vaccine HPV types), 53% efficacy (HPV 31), 88% efficacy (HPV 45) 100% coverage	Current practice: annual screening for females aged 15-89 years, coverage rate 3%-60%	$7,828 per QALY	Current screening practice	CE range = $7,828 per QALY to $79,581 per QALY Varied: screening frequency, diagnostic test costs, screening quality	1. Vaccine costs $474 2. Costs and outcomes discounted 3% 3. Utilities (0.92-0.99 for precancerous lesions; 0.73 for treated cancer; 0.62-0.97 for cancer follow-up)
Goldhaber-Fiebert et al. (2008)[36] Markov model type Funded by NSF; NCI; AHRQ; Harvard Center for Risk Analysis; Bill and Melinda Gates Foundation	1,000,000 females aged 9 years, vaccinated by age 12 years	HPV 16/18 100% efficacy 100% coverage	100% coverage with screening Current screening practice based on "large population-based studies with various levels of screening coverage and frequency for different subpopulations"	$41,000 per QALY with screening every 5 years beginning at age 25 years, HPV DNA testing beginning at age 35 years	Next best strategy defined as screening every 5 years beginning at age 25 and no HPV DNA testing	CE range = $6,000 per QALY to $12,749,000 per QALY Varied: efficacy (75%, 100%); incidence rates of infection; duration (15 years, lifelong); screening frequency (3, 5 years) and initiation age (21, 25 years); screening strategies (Pap with HPV DNA follow-up, HPV DNA with Pap follow-up, or concurrent screening)	1. Vaccine costs $402 2. Costs and outcomes discounted 3% annually 3. Utilities decrease with increasing age 4. Utilities for cancer (0.48-0.68)

TABLE 2 Overview of Published HPV Vaccination Cost-Effectiveness Models (*continued from previous page*)

Authors/Model Type/Funding	Model Subjects	Vaccine Characteristics	Baseline Screening Characteristics	Cost-Effectiveness Point Estimates	Treatment Comparators	Sensitivity Analyses	Model Assumptions
Sanders and Taira (2003)[37] Markov model type Funded by Stanford Cancer Council	All U.S. females aged 12 years	13 oncogenic HPV types including 16 & 18 75% efficacy 70% coverage	Current standard of care: routine biennial Pap for compliant patients (71% of females) starting at age 16 years	$22,755 per QALY	Biennial screening starting at age 16 years	CE range = $12,682 per QALY to $52,398 per QALY Varied: incidence (0.5-2.0X base case values); duration of protection (3 years – lifetime); efficacy (0%-100%); compliance (30%-100%)	1. Vaccine cost $300, booster cost $100 2. 10-year duration of protection with booster shots 3. Annual infection incidence at age 15 years (10%), peaks at age 19 years (18%). 4. Discounting at 3% 5. No utility decrement for undiagnosed infection or lesion, diagnosed lesions measured at 0.97
Taira et al. (2004)[38] Hybrid model type Funded by SSMMSA; V Foundation; Stanford Cancer Council	All U.S. females aged 12 years accounting for herd immunity	HPV 16/18 90% efficacy 70% coverage	Current practice: biennial Pap for compliant patients (71% of females)	$14,583 per QALY	Current screening practice	CE range = $14,583 per QALY to about $800,000 per QALY Varied: screening intervals (1-4 years); incremental vaccination of males; discount rate (0%-5%); efficacy (10%-90%)	Same assumptions as Sanders and Taira (2003)[37]
	Adding male vaccination	HPV 16/18 90% efficacy 70% coverage	Current practice	$442,039 per QALY	Current screening practice		
Elbasha et al. (2007)[42] Dynamic model type Funded by Merck Research Laboratories	Whole population of U.S. females aged 12 years, catch-up to 24 years	HPV 6/11/16/18 90% efficacy 100% coverage	Current practice: "age-stratified data" used to estimate cytology screening rates	$4,666 per QALY	Current screening practice	CE range= $997 per QALY to $124,063 per QALY Varied: vaccine cost ($300-$500); duration of protection; degree of protection; coverage, cost; target age	1. Vaccine cost $360 2. Costs and QALY discounted at 3% 3. Utility for precancerous lesions (0.87-0.91); for cancer (0.48-0.76); for cancer survivors (0.76)
	Adding male vaccination aged 12-24 years	HPV 6/11/16/18 90% efficacy 100% coverage	Current practice	$45,056 per QALY	Current screening practice		
Chesson et al. (2008)[43] Dynamic model type Funded by CDC	Whole population of U.S. females	HPV 6/11/16/18 100% efficacy 100% coverage	Current practice: not defined, as the incidence rates of cervical disease used in the model occurred in the context of current screening practices	$5,336 per QALY	Current screening practice	CE range= <$0 per QALY to $122,976 per QALY Varied: vaccine cost ($300, $490); efficacy (95%, 99%); discount rate (0%-5%) Duration and coverage not varied	1. Vaccine cost $360 2. Costs and QALY discounted at 3% 3. Age-specific cancer incidence rates from 2003; population-based registries 4. Vaccine coverage rates increased linearly the first 5 years
	Whole population of U.S. females	HPV 16/18 100% efficacy 100% coverage	Current practice	$10,318 per QALY	Current screening practice		

TABLE 2 Overview of Published HPV Vaccination Cost-Effectiveness Models (*continued from previous page*)

Authors/Model Type/Funding	Model Subjects	Vaccine Characteristics	Baseline Screening Characteristics	Cost-Effectiveness Point Estimates	Treatment Comparators	Sensitivity Analyses	Model Assumptions
Kim and Goldie (2008)[44] Dynamic model type Funded by NCI; CDC, ACS, Bill and Melinda Gates Foundation	Whole population of U.S. females vaccinated at age 12 years	HPV 6/11/16/18 100% efficacy 75% coverage	Current practice: starting average age 20 years; either Pap or LBC according to U.S. guidelines; 53% screened annually; 17%, 11%, and 14% screened every 2, 3, 5 years; 5% never screened	$43,600 per QALY	Current screening practice	CE range = $34,900 per QALY to $324,200 per QALY Varied: efficacy (50%-100%); protection against HPV-related disease besides cervical cancer (warts, vaginal, and vulvar cancer); duration (lifelong, 10 years, 10 + booster)	1. Vaccine cost $360; booster cost $250 2. Costs and QALY discounted at 3% 3. Utility for cancer (0.48-0.76); warts (0.91) 4. 75% of targeted population covered within 5 years
	Adding catch-up vaccination to 18 years of age	HPV 6/11/16/18 100% efficacy 75% coverage	Current practice	$97,300 per QALY	Current screening practice		
	Adding catch-up vaccination to 21 years of age	HPV 6/11/16/18 100% efficacy 75% coverage	Current practice	$120,400 per QALY	Current screening practice		
	Adding catch-up vaccination to 26 years of age	HPV 6/11/16/18 100% efficacy 75% coverage	Current practice	$152,700 per QALY	Current screening practice		
Kim and Goldie (2009)[45] Dynamic model type Funded by NCI; CDC; ACS; Bill and Melinda Gates Foundation	Whole population of U.S. females and males vaccinated at age 12 years	HPV 6/11/16/18 Females: 100% efficacy against infection from vaccine-targeted HPV types 75% coverage Males: 85% efficacy against infection from vaccine-targeted HPV types 90% efficacy against disease from vaccine-targeted HPV types 75% coverage	Current practice: starting average age 20 years; either Pap or LBC according to U.S. guidelines; 53% screened annually; 17%, 11%, and 14% screened every 2, 3, 5 years; 5% never screened	$290,290 per QALY	Current screening practice	CE range = $88,930 per QALY to $390,440 per QALY Varied: efficacy (75%-100%); coverage (50%-75%); duration of protection (waning at 20 years – lifetime); protective effects against nonvaccine HPV types (12%-54% efficacy)	1. Vaccine cost $360 2. Costs and QALY discounted at 3% 3. Utility for cancer (0.48 - 0.76); warts (0.91)

TABLE 2 Overview of Published HPV Vaccination Cost-Effectiveness Models (*continued from previous page*)

Authors/Model Type/Funding	Model Subjects	Vaccine Characteristics	Baseline Screening Characteristics	Cost-Effectiveness Point Estimates	Treatment Comparators	Sensitivity Analyses	Model Assumptions
Kim et al. (2009)[46] Dynamic model type Funded by NCI; CDC; ACS	Whole population of U.S. females vaccinated at age 35 years	HPV 6/11/16/18	Current practice: starting average age 20 years; either Pap or LBC according to U.S. guidelines: 53% screened annually; 17%, 11%, and 14% screened every 2, 3, 5 years; 5% never screened	$116,950 per QALY	Biennial screening	CE range = $78,751 per QALY to $448,989 per QALY Varied: efficacy (70%-100%); duration of protection (waning at 5 and 10 years – lifetime); vaccine cost ($250-$750); screening frequency (1-5 years)	1. Vaccine cost $500 2. Costs and QALY discounted at 3%
	Whole population of U.S. females vaccinated at age 45 years	HPV 6/11/16/18	Current practice	$272,350 per QALY	Current screening practice		

ACS = American Cancer Society; AHRQ = Agency for Healthcare Research and Quality; CDC = Centers for Disease Control and Prevention; CE = cost-effectiveness; DHHS = Department of Health and Human Services; DNA = deoxyribonucleic acid; HPV = human papillomavirus; LBC = liquid-based cytology; LYS = life year saved; NCI = National Cancer Institute; NIH = National Institutes of Health; NSF = National Science Foundation; Pap = Papanicolaou; QALY = quality-adjusted life year: SSMMSA = Stanford School of Medicine Medical Scholars Award.

based solely on regional U.S. data. A total of 15 studies met these criteria. A total of 4 studies were excluded. Two excluded studies presented additional data from a previously published model;[28,29] 1 study was excluded because it was based solely on data from Kentucky;[30] and 1 study was excluded because it was focused on the cost-effectiveness of HPV vaccination in the prevention of recurrent respiratory papillomatosis.[31] Because the 11 included studies used varying assumptions in their models, this review is a comparative review rather than a quantitative meta-analysis.

Model Results

Three studies have examined cost-effectiveness of an HPV vaccine administered to a modeled cohort of 100,000 girls at age 12 years.[32-34] Kulasingam and Myers (2003) assumed that their model vaccine offered 10-year protection and was targeted to 70% of oncogenic HPV types, including types 16 and 18.[32] Every female in the cohort was assumed to have been administered the vaccine (100% coverage). The vaccine was assumed to be 90% efficacious and priced at a cost of $200 per series. Compared with biennial screening beginning at age 18 years, a strategy of vaccination at age 12 combined with delayed biennial screening starting at age 24 years resulted in a cost of $44,889 per LYS. By contrast, the strategy of vaccination plus annual screening beginning at age 18 resulted in a cost of $236,250 per LYS. These findings suggest that a delay in cervical screening initiation in addition to a longer interval between screenings would be most cost-effective when vaccinating against HPV.

Goldie et al. (2004) also modeled cost-effectiveness in a cohort of 100,000 females aged 12 years based on a bivalent vaccine protecting against HPV types 16 and 18 only.[33] Cost-effectiveness in this model was measured compared with current U.S. cervical screening practices as determined by data from the CDC's Behavioral Risk Factor Surveillance System[35] (detailed in Table 2). The vaccine in this model was assumed to cover 100% of the target cohort and to have 90% efficacy and lifetime protection, at a cost of $377 per series. Administration of this vaccine would reduce the lifetime incidence of cervical cancer by 58% and would cost $24,300 per QALY gained. When efficacy was set at 100%, the ICER decreased to $20,600 per QALY gained. Model results were most sensitive to changes in duration of vaccine protection, whether persistent HPV infections after age 30 years were newly acquired or reactivations of latent infections, and to variables related to screening (e.g., age at initiation, frequency). The most expensive strategy modeled by Goldie et al. combined vaccination at age 12 years with annual cervical screening and LBC initiated at age 18. This strategy cost more than $3.5 million per QALY compared with the next best strategy, which used the same parameters with annual Pap screening rather than LBC. However, the annual reduction in lifetime risk was only 2% more than biennial screening strategies.

Finally, Rogoza et al. (2008) analyzed cost-effectiveness in the

same cohort of 100,000 females aged 12 years given a quadrivalent vaccine protecting against nononcogenic HPV types 6 and 11 in addition to oncogenic types 16 and 18.[34] This vaccine was estimated to have 100% coverage, 95% efficacy, and lifetime protection. Sensitivity analyses related to properties of the vaccine were not conducted for this model. The vaccine was also modeled to have some protective efficacy for nonvaccine HPV types: efficacy against HPV 31 was set at 53%, and efficacy against HPV 45 was set at 88%. HPV 31 and 45 combined are associated with another 7% of cervical cancer cases.[9] Compared with current U.S. screening practices, vaccination in this model resulted in a cost per QALY gained of $7,828.

Goldhaber-Fiebert et al. (2008) used a Markov model to estimate cost-effectiveness of HPV vaccination in a larger cohort of 1 million females 9 years of age who were to be vaccinated by age 12 years.[36] Their model also allowed for individual variation in life history to be accounted for. Rather than using population-based averages to determine transition probabilities between disease states (i.e., between HPV infection and cervical intraepitelial neoplasia [CIN]), this model simulated all possible individual clinical pathways. In their model, the whole cohort was assumed to be vaccinated by age 12, and the vaccine was assumed to be 100% effective against HPV 16 and 18 with lifelong duration of protection. The model also simulated the effects of varying the starting age of cervical screening and screening frequency interval. If this cohort began 5-year interval cervical screening at age 25, switching to HPV DNA testing at age 35, the cost per QALY gained was $41,000 compared with a strategy with the same screening parameters but without the switch to HPV DNA testing. Switching to HPV testing at age 30 increased the ICER to $126,000 per QALY, while increasing screening frequency to a 3-year interval increased ICER to $188,000 per QALY. The most expensive vaccination strategy (more than $12 million per QALY) included annual Pap screening at age 18 years that switched to LBC at 25 years of age.

Sanders and Taira (2003) measured cost-effectiveness of HPV vaccination in 2 ways: in a Markov model following a cohort of all U.S. 12 year olds[37] and also in a hybrid model that accounted for disease transmission rate changes due to herd immunity.[38] The authors modeled a vaccine that was 75% efficacious against a set of 13 oncogenic HPV types including HPV 16 and 18. This model also assumed 70% coverage, 10-year protection (at a cost of $300 per series) with booster injections every 10 years (at a cost of $100 per booster). In the cohort model, compared with biennial Pap screening beginning at age 16 years, the addition of HPV vaccination resulted in an incremental cost per QALY gained of $22,755. Vaccine efficacy was shown to be the parameter with the greatest influence on cost-effectiveness. For example, at 35% efficacy, cost-effectiveness increased to $52,398 per QALY.

Taira et al. (2004) amended this cohort model to include changes in HPV prevalence resulting from widespread immunization (herd immunity) as well as to model the cost-effectiveness of male vaccination.[38] In this hybrid model, the vaccine had 90% efficacy against HPV 16 and 18, with 70% coverage. The inclusion of herd immunity (as well as the increase in efficacy) decreased the cost per QALY gained to $14,583. When the hybrid model was altered to include male vaccination, the cost per QALY gained jumped to $442,039. Although males may also develop penile and anal cancers as a result of HPV infection, the incidence rates are much lower compared with cervical cancer. For example, about 1 in 100,000 men infected with HPV will develop penile cancer, and 2,100 cases of anal cancer are diagnosed in men annually.[39,40] By comparison, 94% of all HPV-related cancers affect women.[41] Therefore, the cost-effectiveness of vaccinating males will largely result from the indirect benefits of increasing herd immunity. Taira et al. found that vaccinating males would decrease cancer incidence only slightly for such a high cost.[38]

Transmission dynamic models have also simulated the effects of HPV vaccination in the whole U.S. female population. Elbasha et al. (2007) examined the cost-effectiveness of a vaccine protecting against infection from HPV types 16, 18, 6, and 11.[42] Vaccine efficacy against incident infection was set at 90%, and efficacy against HPV-related disease was 100%. Vaccine cost was set at $360 for the 3-dose series and produced lifelong protection. Coverage of 12-year-old females increased from 0% to 70% over the first 5 years and was set at 70% thereafter. Coverage in a catch-up vaccination program for those aged 12 to 24 years increased from 0% to 50% over the first 5 years and was then eliminated from the model. Compared with current practice, female-only vaccination before age 12 with the catch-up program resulted in a cost of $4,666 per QALY gained. However, if duration of protection was limited to 10 years, then costs increased to $21,121 per QALY. The most effective strategy in terms of disease reduction included the additional vaccination of boys and men with lifelong protection at a cost of $45,056 per QALY. Limiting duration of protection to 10 years while vaccinating males and females increased costs to $54,928 per QALY.

Chesson et al. (2008) also examined the cost-effectiveness of the same quadrivalent HPV vaccine as well as a bivalent vaccine (protecting against HPV 16 and 18 only) using a dynamic model.[43] In this study, efficacy was assumed to be 100% against HPV infection and disease. Although no catch-up vaccination was modeled, the coverage of 12 year olds, vaccine cost, and duration of protection were the same as the Elbasha et al. study detailed above.[42] Chesson et al. found that a vaccine targeting HPV 16, 18, 6, and 11, or only HPV 16 and 18, resulted in estimated costs of $5,336 and $10,318 per QALY gained respectively when examining cervical abnormalities (i.e., not including anal, vaginal, vulvar, and oropharyngeal cancers), compared with existing cervical cancer screening.[43] Sensitivity analyses produced a worst-case scenario cost-effectiveness estimate of $122,976 per QALY, including parameters such as a lower incidence of HPV-related diseases and a smaller reduction in quality of life resulting from HPV-related diseases.

Kim and Goldie (2008) also utilized a dynamic model with some modifications to allow for individual variations in behavior to examine cost-effectiveness of a vaccine targeting HPV 16, 18, 6, and 11.[44] In addition to evaluating population dynamics that varied transmission rates over time, this model also allowed for differences in individual history (e.g., vaccination, screening,

treatment, and past abnormalities) thereby accommodating complexities in screening strategies. Kim and Goldie examined the cost-effectiveness of vaccinating all 12 year olds alone, as well as the cost-effectiveness of adding catch-up vaccinations through ages 18, 21, and 26 years.[44] Coverage was assumed to be 75% within the first 5 years, at a coverage rate of 25% per year. In the base-case scenario, efficacy was assumed to be 100% with lifelong duration of protection. Compared with current screening practices, vaccination of 12 year olds alone resulted in a cost of $43,600 per QALY gained for outcomes solely related to cervical cancer (i.e., not including genital warts). A number of sensitivity analyses were conducted by the authors, including evaluation of the assumption of duration of protection. If duration of protection was limited to 10 years, costs increased to $144,100 per QALY. Use of a booster shot at 10 years resulted in an ICER of $83,300 per QALY. Under the base assumption of lifelong protection, ICERs increased incrementally when extending the age range of females to be vaccinated: to $97,300 per QALY for catch-up through age 18; $120,400 through age 21; and $152,700 through age 26. Vaccinations of all age ranges were more cost-effective if prevention against nonvaccine HPV types were included. Studies of both HPV vaccines have demonstrated some level of cross-protection against nonvaccine oncogenic HPV types.[7,8]

Kim and colleagues (2009) also used this model to examine cost-effectiveness of HPV vaccination in 2 other populations: all 12 year olds including boys and women aged 35 to 45 years.[45,46] In the analyses of 12 year olds, vaccination of girls at 75% coverage with 100% lifelong efficacy against infection and disease related to HPV 16 and 18 resulted in an ICER of $40,310 per QALY compared with current screening practices for outcomes related to cervical disease.[45] Vaccinating 12-year-old boys at 75% coverage with lifelong 85% efficacy against HPV 16/18 infection and 90% efficacy against HPV 16/18-related disease increased the ICER to $290,290 per QALY for cervical disease outcomes. When HPV 16/18-related noncervical male and female cancer outcomes were added into the model (50% vaccine efficacy), the ICER for vaccinating girls only decreased to $27,370 per QALY, while the addition of male vaccination resulted in a cost of $164,580 per QALY. When lower efficacy, waning immunity, or higher vaccine costs were assumed, the incremental cost of vaccinating boys consistently exceeded $250,000 per QALY.[45] A strategy vaccinating older women was also modeled and found to not be cost-effective (more than $100,000 per QALY).[46] Neither HPV vaccine has been indicated for use for women older than 26 years of age.[12] In the model of HPV vaccination in older females, women aged 35, 40, and 45 years were given the complete 3-dose series. The cost-effectiveness of vaccination was compared with a baseline of women practicing annual or biennial screening and also with the more variable and infrequent screening rate of current practice. Compared with annual or biennial screening, vaccination with 100% lifetime efficacy resulted in an ICER range from $116,950 to $272,350 per QALY gained. Compared with current screening practice, vaccination at any age resulted in ICERs of more than $125,000 per QALY.[46]

Discussion and Limitations

Whether or not females will choose to be vaccinated may depend on their awareness of the benefits and risks of HPV vaccination. Given that most infections resolve without intervention, Haug (2009) questioned the necessity of HPV vaccination, concluding that the HPV infection "does not appear to be very harmful."[47] Haug also states that it is impossible to determine in which females HPV infection will persist, leading to disease progression, and in which females the infection will regress. These arguments raise the issue of the clinical value of HPV vaccination. However, HPV is a common infection in U.S. females,[20] and natural immune responses are not reliably protective against infection.[48] Although 91% of HPV infections regress within 2 years,[49] for women with persistent HPV 16 or 18 infection the risk of developing precancerous lesions is 169 times greater than for those who are uninfected.[50] HPV vaccination targets the 2 most common HPV types associated with approximately 3 out of every 4 cases of cervical cancer in the United States.[9] Furthermore, the vaccines may provide additional protection against nonvaccine HPV types that are phylogenetically related to HPV 16 and 18.[7,8]

Assumptions about the HPV vaccine affect modeling estimates of the cost-effectiveness of HPV vaccination. Efficacy rate, duration of protection, and rates of vaccine coverage or uptake are critical variables that will impact the cost-effectiveness of HPV vaccination. Most models assumed vaccine characteristics of 90% or 100% efficacy against vaccine HPV types, consistent with the currently available data from the controlled clinical trials for the 2 HPV vaccines. Phase III studies of quadrivalent HPV vaccine revealed 98% protection against high-grade precancerous lesions,[7] whereas for bivalent HPV vaccine 93% efficacy has been demonstrated in females naïve to HPV 16 and 18 who completed the 3-dose vaccine series.[8] However, while these studies have demonstrated high vaccine efficacy rates, it must be kept in mind that patients and their providers must be compliant with prescribing and receiving the vaccination regimen to achieve these high vaccination protection rates. Initial data suggest that adolescents may often not receive the vaccine when eligible and that when the vaccine regimen is started, only 58% to 75% of patients complete the entire 3 injection series.[51,52] If fewer patients complete the entire vaccination series than what was estimated by a cost-effectiveness model, the "real world" cost per QALY results would be worse than what was predicted by the model.

Based on clinical trials, HPV vaccination is efficacious against the occurrence of precancerous lesions, which suggests that vaccination is likely to be effective. However, real-world effectiveness of the vaccine will be contingent upon actual levels of vaccine coverage, compliance, and duration of protection. One assumption common to all models is a high level of vaccine coverage (at least 70% of the target population is assumed to receive the vaccination). However, recent CDC survey data reveal that only 37% of females between 13-17 years of age[53] and 10% of women between 18-26 years of age had taken at least 1 of the 3 recommended vaccine doses.[54] Until coverage levels increase in the target population, cost-effectiveness model estimates may underestimate

actual costs. Unfortunately, no model has estimated the cost-effectiveness of vaccination with coverage levels at 37% or lower. Therefore, the modeling of beneficial effects from herd immunity is only speculative until vaccine uptake increases. Regarding vaccine compliance, not everyone who initiates the vaccine series completes all 3 doses or completes all doses in the recommended 6-month time frame,[55] and it is presently unknown how noncompliance affects vaccine efficacy and duration of protection.

Concerns over vaccine safety may be contributing to the low coverage rates observed thus far. Yet, a recent analysis of the quadrivalent vaccine found that the overall rates of adverse events were not greater after HPV vaccination compared with background rates following other types of vaccination.[56] However, a disproportionate number of syncope and venous thrombolic events were observed after HPV vaccination. The venous thrombolic events reported fell within a large time window post-vaccination, and 90% of subjects reported having pre-existing risk factors. As such, venous thrombolic events were not clearly linked to vaccination. For the bivalent vaccine, local reactions (pain, redness, swelling) were reported more frequently after vaccine injection compared with control injection.[8] However, incidence of new onset autoimmune diseases was comparable between vaccine and control groups.[8] Among females aged 10 through 25 years, 6.4% of subjects who received the bivalent vaccine and 7.2% of subjects who received the control reported at least 1 adverse event (without regard to causality) during a 7.4 year follow-up period.[8]

For questions regarding duration of protection, most models assumed that the vaccine provided either 10-year or lifetime protection. At this time, the minimum antibody titer level that confers protective efficacy has not been determined. For the quadrivalent HPV vaccine, titers specific to vaccine HPV types (6, 11, 16, 18) peaked at month 7 after the initial vaccine dose, declined through month 24, and stabilized at levels above baseline. Anti-HPV titers remained similar at month 60.[7] For the bivalent HPV vaccine, antibody titers for both HPV 16 and 18 peaked at month 7 after the initial dose and reached a plateau that was sustained from month 18 through month 76.[8] A recent mathematical model of the immunological data from the bivalent HPV vaccine predicts that antibody titers above baseline may be observed 20 years post-vaccination.[10] It is presently unknown if model assumptions of duration of protection will be validated. Until long-term studies of efficacy have been completed, the use of ICERs based on the conservative estimate of 10-year protection may be warranted rather than the use of ICERs based on lifetime protection.

Other model assumptions that impacted cost-effectiveness were the inclusion or exclusion of herd immunity effects, the amount of discounting assumed, and the setting of disease-related utilities. The major shortcoming of studies using Markov models is the exclusion of herd immunity effects. The inclusion of herd effects in hybrid and dynamic models should decrease modeled ICERs, although the specific contribution of herd immunity is difficult to quantify across models with different assumptions. The closest comparison that can be made among the studies currently examined is between the Markov model of Sanders and Taira[37] and the Taira et al. hybrid model.[38] The hybrid model added herd immunity to the original Markov model, resulting in a decrease of about $8,000 per QALY. However, the direct comparison is complicated by the fact that Taira et al. assumed 90% efficacy while Sanders and Taira assumed 75% efficacy.[37,38] Although some models varied the discount rate of future costs in sensitivity analyses, all models set discounting of the base case analysis at 3%. By contrast, the quality of life utility scores for cervical disease progression varied across studies. Again, it is difficult to isolate the singular effect of these different utility scores on the ICERs across studies.

Typically, an intervention is deemed cost-effective if the ICER is within or below the range of $50,000 to $100,000 per QALY gained.[57] By this standard, all models presented above have determined that HPV vaccination in females can be a cost-effective intervention in comparison with the current practice of cervical screening alone. However, broad ranges of ICERs were produced from sensitivity analyses. The highest estimates typically resulted from vaccination strategies that included annual cervical screening initiated at age 18 years. The Kim and Goldie model was especially useful as the authors incorporated several additional variables, including vaccination, screening, treatment, past abnormalities, and the implications of catch-up vaccinations.[44] Including these additional variables makes the results more "real world" and may explain why the cost per QALY results for certain patient subgroups were often higher than $100,000 per QALY gained (e.g., $120,000 per QALY for vaccination catch-up for women through 21 years of age).

Cervical screening is still a necessary preventive procedure, as the currently developed HPV vaccines do not protect against all oncogenic HPV types. However, HPV vaccination may allow for potential revisions in the current screening guidelines.[32,36] Although it is beyond the scope of this review to recommend revisions to current screening guidelines, cervical screening is most inefficient in younger women, when HPV infections are most likely to be transient, and 1 report suggests that screening should not begin until age 25.[58] If widespread HPV vaccination could decrease the incidence of oncogenic HPV infection during the peak ages of infection (late adolescence and early adulthood),[20] it may be feasible to begin screening later and/or increase the interval between screenings. For example, Goldhaber-Fiebert et al. estimated in their model that screening alone every 3 years beginning at 25 years of age would decrease cervical cancer risk by 71%.[36] Vaccination in combination with these screening parameters was estimated to decrease cervical cancer risk by 93%. Increasing the interval between screenings to every 5 years still resulted in a decrease in cervical cancer risk of 91%-92%, at a substantial cost savings. However, in this model, vaccination was assumed to have 100% efficacy against infection with HPV 16 and 18 with a lifetime duration of protection.[36] Therefore, the reduction in cervical cancer risk and the cost savings may be lower than estimated, as efficacy is not 100% and duration is yet to be determined.

The 3 studies modeling cost-effectiveness of HPV vaccination in males produced mixed results. Compared with the cost-prohibitive projections (more than $400,000 per QALY) of the Taira et al. model,[38] cost estimates of vaccinating males in the Elbasha et al.[42] study were much lower (approximately $50,000 per QALY). Differences in the modeled vaccines and model assumptions may have contributed to this large disparity. The study vaccine in the model described by Taira et al. did not protect against HPV types 6 and 11,[38] responsible for genital warts, and included higher utility scores for precancerous lesions compared with the Elbasha et al. model.[42] The most recent model including male vaccination, by Kim and Goldie, found that male vaccination was not cost-effective under most scenarios.[45] The addition of male vaccination fell below the $100,000 per QALY threshold only when high, lifelong vaccine efficacy against all HPV-related diseases, including other noncervical cancers and genital warts, was included, or if lower efficacy was modeled with lower coverage or lower vaccine costs.[45] Further clinical and modeling studies should be conducted before conclusions can be drawn about the cost-effectiveness of male vaccination. Data on the clinical efficacy of quadrivalent HPV vaccine in males show that the vaccine is 76% effective against the incidence of external genital lesions and 80% effective against the incidence of genital warts.[7]

Elbasha et al. and Kim and Goldie were the only investigators to model the costs of catch-up vaccination.[42,44] In addition to modeling the whole population of 12-year-old females and males, respectively, the Elbasha et al. model included catch-up vaccination up through age 24 years.[42] In females only compared with current screening practices, the Elbasha et al. model produced a relatively low ICER of less than $5,000 per QALY.[42] Kim and Goldie's ICER estimates were much higher by comparison.[44] One factor contributing to this disparity is the lower vaccine coverage rate modeled by Kim and Goldie (75% compared with 100%).[42,44] Kim and Goldie examined female vaccination of 12 year olds with catch-up through 26 years of age, matching the catch-up range of current CDC recommendations.[44] Although their results suggested that vaccination of all 12-year-old females can be cost-effective ($43,600 per QALY compared with current screening practice), catch-up vaccination becomes more expensive as older cohorts are added. Assuming lifelong immunity, adding catch-up vaccination through age 18, 21, and 26 years increased the ICER to approximately $100,000 per QALY, $120,000 per QALY, and $150,000 per QALY, respectively. These estimates decreased if cross-protection against nonvaccine HPV types was included in the model. The inclusion of cross-protection lowered the costs of catch-up vaccination through age 21 years to just over $100,000 per QALY. Although this model did not support catch-up vaccination through the CDC's recommended age of 26 years from a cost-effectiveness perspective, the clinical risk of HPV infection and disease progression remains lifelong. The only study to examine vaccination in older females found that HPV vaccination was not cost-effective for women 35 to 45 years of age.[46] For this age range, the probability of HPV vaccination being cost-effective for women was 0% with biennial screening and less than 5% with triennial screening.[46]

Above and beyond the costs of vaccination, the implications of HPV vaccine-derived protection affect the primary goal of disease prevention in managed health care. Although covering the costs of HPV vaccination may be initially cost-prohibitive for managed care organizations, coverage of HPV vaccination and cervical screening should result in noticeable improvements in clinical outcomes, which should over the long term lead to some cost offsets. As health plans continue to expand and meet the changing needs of their customers and society, financial implications must be weighed against clinical benefit to arrive at the best decisions. Economic models are necessary for managed care organizations to evaluate the different options and design benefits to include in their health plans.[59] Plan stakeholders have different options for approaching the issue of HPV vaccine coverage. Full coverage of these products under a standard vaccination benefit is 1 option, as is a "nonstandard" vaccination benefit where health plan members pay a portion (e.g., 20%) of the costs for vaccines deemed optional (e.g., rotavirus, palivizumab, and HPV vaccine).[59] Given available cost-effectiveness data, full coverage may be the more appropriate option, and this option has already been adopted by at least 1 managed care organization.[59]

The direct cost of HPV vaccine ($375) is high compared with other vaccines and may be prohibitively expensive for a large percentage of females. Therefore, full coverage should help to increase HPV vaccine uptake, thereby increasing herd immunity effects. However, these financial incentives must be accompanied by public health initiatives that help to educate the public about the consequences of HPV infection as well as the benefits of HPV vaccination. Although the cost-effectiveness of HPV vaccination may be questionable above the age of 21 years, to best meet the goal of disease prevention, managed care organizations might extend full coverage to all females between 9 and 26 years to encourage vaccination according to the schedule recommended by the CDC.

Conclusion

Comprehensive health benefits coverage of vaccines has been a mainstay of virtually all managed care benefits and has proven to be a wise investment from clinical, societal, and economical perspectives. As newer vaccines come to market that are targeted to morbidity more than mortality, quantification of disease burden and modeling of the cost-effectiveness of intervention options are becoming more important when determining how best to allocate scarce health care dollars. Although the current models predict cost-effectiveness of HPV vaccination, emerging clinical data for quadrivalent HPV vaccine and bivalent HPV vaccine may require revisions in ICER estimates to reflect demonstrated long-term efficacy. Models will underestimate actual costs per QALY if real-world vaccination series completion rates do not match those of controlled clinical trials or if coverage of HPV vaccination is less than assumed.

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REFERENCES

1. Centers for Disease Control and Prevention (CDC). Impact of vaccines universally recommended for children—United States, 1990-1998. *MMWR Morb Mortal Wkly Rep.* 1999;48(12):243-48. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00056803.htm. Accessed March 14, 2010.

2. Ehreth J. The global value of vaccination. *Vaccine*. 2003;21(7-8):596-600.

3. Centers for Disease Control and Prevention, Department of Health and Human Services. Report to Congress: prevention of genital human papillomavirus infection. January 2004. Available at: http://www.cdc.gov/std/HPV/2004HPV%20report.pdf. Accessed March 14, 2010.

4. Stanley M, Lowy DR, Frazer I. Chapter 12: Prophylactic HPV vaccines: underlying mechanisms. *Vaccine*. 2006;24(Suppl 3):S106-S13.

5. Bosch FX, Lorincz A, Muñoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol.* 2002;55(4):244-65. Available at: http://jcp.bmj.com/cgi/reprint/55/4/244. Accessed March 14, 2010.

6. Muñoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med.* 2003;348(6):518-27. Available at: http://content.nejm.org/cgi/reprint/348/6/518.pdf. Accessed March 14, 2010.

7. Merck & Co. Highlights of prescribing information. Gardasil (human papillomavirus quadrivalent [types 6, 11, 16, and 18] vaccine, recombinant] suspension for intramuscular injection Revised October 2009. Available at: http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf. Accessed March 14, 2010.

8. GlaxoSmithKline. Highlights of prescribing information. Cervarix (human papillomavirus bivalent [types 16 and 18] vaccine, recombinant]) suspension for intramuscular injection. Revised October 2009. Available at: http://us.gsk.com/products/assets/us_cervarix.pdf. Accessed March 14, 2010.

9. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer.* 2007;121(3):621-32. Available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/114205264/PDFSTART. Accessed March 14, 2010.

10. David MP, Van Herck K, Hardt K, et al. Long-term persistence of anti-HPV-16 and -18 antibodies induced by vaccination with the AS04-adjuvanted cervical cancer vaccine: modeling of sustained antibody responses. *Gynecol Oncol.* 2009;115(3 Suppl):S1-S6.

11. Centers for Disease Control and Prevention. HPV vaccine information for young women. June 26, 2008. Available at: http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine-young-women.htm. Accessed March 14, 2010.

12. Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices. ACIP provisional recommendations for HPV vaccine. December 1, 2009. Available at: http://www.cdc.gov/vaccines/recs/provisional/downloads/hpv-vac-dec2009-508.pdf. Accessed March 14, 2010.

13. National Committee for Quality Assurance. The state of health care quality 2008. Updated April 23, 2009. Available at: http://www.ncqa.org/Portals/0/Newsroom/SOHC/SOHC_08.pdf. Accessed March 14, 2010.

14. American Cancer Society. What are the key statistics about cervical cancer? Last revised January 19, 2010. Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_cervical_cancer_8.asp?sitearea=. Accessed March 14, 2010.

15. Wright TC, Jr. Cervical cancer screening in the 21st century: is it time to retire the PAP smear? *Clin Obstet Gynecol.* 2007;50(2):313-23. Available at: http://www.quimiolab.com/pdf/104-wright_07.pdf. Accessed March 14, 2010.

16. Myers E, Huh WK, Wright JD, Smith JS. The current and future role of screening in the era of HPV vaccination. *Gynecol Oncol.* 2008;109(Suppl 2):S31-S39.

17. Koliopoulos G, Arbyn M, Martin-Hirsch P, Kyrgiou M, Prendiville W, Paraskevaidis E. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: a systematic review and meta-analysis of non-randomized studies. *Gynecol Oncol.* 2007;104(1):232-46.

18. American Cancer Society. American Cancer Society guidelines for the early detection of cancer. Last revised May 21, 2009. Available at: http://www.cancer.org/docroot/ped/content/ped_2_3x_acs_cancer_detection_guidelines_36.asp. Accessed March 14, 2010.

19. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 109: Cervical cytology screening. *Obstet Gynecol.* 2009;114(6):1409-20.

20. Dunne EF, Unger ER, Sternberg M, et al. Prevalence of HPV infection among females in the United States. *JAMA.* 2007;297(8):813-19. Available at: http://jama.ama-assn.org/cgi/content/full/297/8/813. Accessed March 14, 2010.

21. Insinga RP, Dasbach EJ, Elbasha EH. Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US: analytic framework and review of the literature. *Pharmacoeconomics*. 2005;23(11):1107-22.

22. Mahdavi A, Monk BJ. Vaccines against human papillomavirus and cervical cancer: promises and challenges. *Oncologist*. 2005;10(7):528-38. Available at: http://theoncologist.alphamedpress.org/cgi/reprint/10/7/528. Accessed March 14, 2010.

23. Eltoum IA, Roberson J. Impact of HPV testing, HPV vaccine development, and changing screening frequency on national Pap test volume: projections from the National Health Interview Survey (NHIS). *Cancer.* 2007;111(1):34-40. Available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/114099805/PDFSTART. Accessed March 14, 2010.

24. Insinga RP, Glass AG, Rush BB. The health care costs of cervical human papillomavirus-related disease. *Am J Obstet Gynecol.* 2004;191(1):114-20.

25. Max W, Rice DP, Sung H-Y, Michel M, Breuer W, Zhang X. The economic burden of gynecologic cancers in California, 1998. *Gynecol Oncol.* 2003;88(2):96-103.

26. Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. *Epidemiol Rev.* 2006;28:88-100.

27. Brisson, M, Edmunds, WJ. Economic evaluation of vaccination programs: the impact of herd-immunity. *Med Decis Making.* 2003;23(1):76-82.

28. Elbasha EH, Dasbach EJ, Insinga RP, Haupt RM, Barr E. Age-based programs for vaccination against HPV. *Value Health.* 2009;12(5):697-707. [epub 2009 March 10]

29. Elbasha EH, Dasbach EJ, Insinga RP. A multi-type HPV transmission model. *Bull Math Biol.* 2008;70(8):2126-76.

30. Prasad SR, Hill R. Cost-benefit analysis on the HPV vaccine in Medicaid-enrolled females of the Appalachian region of Kentucky. *J Ky Med Assoc.* 2008;106(6):271-76

31. Chesson HW, Forhan SE, Gottlieb SL, Markowitz LE. The potential health and economic benfits of preventing recurrent respiratory pappillomatosis through quadrivalent human papillomavirus vaccination. *Vaccine.* 2008;25(35):4513-18.

32. Kulasingam SL, Myers ER. Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA.* 2003;290(6):781-89. Available at: http://jama.ama-assn.org/cgi/reprint/290/6/781. Accessed March 14, 2010.

33. Goldie SJ, Kohli M, Grima D, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *J Natl Cancer Inst.* 2004;96(8):604-15. Available at: http://jnci.oxfordjournals.org/cgi/reprint/96/8/604. Accessed March 14, 2010.

34. Rogoza RM, Ferko N, Bentley J, et al. Optimization of primary and secondary cervical cancer prevention strategies in an era of cervical cancer vaccination: a multi-regional health economic analysis. *Vaccine.* 2008;26 (Suppl 5):F46-F58.

35. Centers for Disease Control and Prevention. Behavioral risk factor surveillance system. 2009. Available at: http://www.cdc.gov/brfss/. Accessed March 14, 2010.

36. Goldhaber-Fiebert JD, Stout NK, Salomon JA, Kuntz KM, Goldie SJ. Cost-effectiveness of cervical cancer screening with human papillomavirus DNA testing and HPV-16,18 vaccination. *J Natl Cancer Inst.* 2008;100(5):308-20. Available at: http://jnci.oxfordjournals.org/cgi/reprint/100/5/308. Accessed March 14, 2010.

37. Sanders GD, Taira AV. Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerg Infect Dis.* 2003;9(1):37-48. Available at: http://www.cdc.gov/ncidod/eid/vol9no1/02-0168.htm. Accessed March 14, 2010.

38. Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. *Emerg Infect Dis.* 2004;10(11):1915-23. Available at: http://www.cdc.gov/ncidod/eid/vol10no11/04-0222.htm. Accessed March 14, 2008.

39. American Cancer Society. What are the key statistics about penile cancer? Last revised October 7, 2009. Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_penile_cancer_35.asp?rnav=cri. Accessed March 14, 2010.

40. American Cancer Society. What are the key statistics about anal cancer? Last revised August 17, 2009. Available at: http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_Anal_Cancer_47.asp?sitearea=. Accessed March 14, 2010.

41. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer.* 2006;118(12):3030-44. Available at: http://www3.interscience.wiley.com/cgi-bin/fulltext/112226580/PDFSTART. Accessed March 14, 2010.

42. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis.* 2007;13(1):28-41. Available at: http://www.cdc.gov/ncidod/eid/13/1/pdfs/28.pdf. Accessed March 14, 2010.

43. Chesson HW, Ekwueme DU, Saraiya M, Markowitz LE. Cost-effectiveness of human papillomavirus vaccination in the United States. *Emerg Infect Dis.* 2008;14(2):244-51. Available at: http://www.cdc.gov/eid/content/14/2/244.htm. Accessed March 14, 2010.

44. Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. *N Engl J Med.* 2008;359(8):821-32. Available at: http://content.nejm.org/cgi/reprint/359/8/821.pdf. Accessed March 14, 2010.

45. Kim JJ, Goldie SJ. Cost effectiveness analysis of including boys in a human papillomavirus vaccination programme in the United States. *BMJ.* 2009:339, b3884. Available at: http://www.bmj.com/cgi/reprint/339/oct08_2/b3884. Accessed March 14, 2010.

46. Kim JJ, Ortendahl J, Goldie SJ. Cost-effectiveness of human papillomavirus vaccination and cervical cancer screening in women older than 30 years in the United States. *Ann Intern Med.* 2009;151(8):538-45.

47. Haug C. The risks and benefits of HPV vaccination. *JAMA.* 2009;302 (7):795-96.

48. Viscidi RP, Schiffman M, Hildesheim A et al. Seroreactivity to human papillomavirus (HPV) types 16, 18, or 31 and risk of subsequent HPV infection: results from a population-based study in Costa Rica. *Cancer Epidemiol Biomarkers Prev.* 2004;13(2):324-27.

49. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med.* 1998;338(7):423-28. Available at: http://content.nejm.org/cgi/reprint/338/7/423.pdf. Accessed March 14, 2010.

50. Trottier H, Mahmud S, Lindsay L et al. Persistence of an incident human papillomavirus infection and timing of cervical lesions in previously unexposed young women. *Cancer Epidemiol Biomarkers Prev.* 2009;18(3):854-62.

51. Dempsey AF, Cohn LM, Dalton VK, Ruffin MT. Human papillomavirus vaccine utilization: experiences of the first year. Presentation at: 43rd National Immunization Conference, March 2009; Dallas, TX. Abstract 53. Available at: http://cdc.confex.com/cdc/nic2009/webprogram/Paper17969.html. Accessed March 14, 2010.

52. Neubrand TP, Breitkopf CR, Rupp R, Breitkopf D, Rosenthal SL. Factors associated with completion of the human papillomavirus vaccine series. *Clin Pediatr (Phila).* 2009;48(9):966-69. [epub 2009 May 29]

53. Centers for Disease Control and Prevention(CDC). National, state, and local area vaccination coverage among adolescents aged 13-17 years—United States, 2008. *MMWR Morb Mort Weekly Rep.* 2009;58(36):997-1001. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5836a2.htm. Accessed March 14, 2010.

54. Jain N, Euler GL, Shefer A, Lu P, Yankey D, Markowitz L. Human papillomavirus (HPV) awareness and vaccination initiation among women in the United States, National Immunization Survey-Adult 2007. *Prev Med.* 2009;48(5):426-31.

55. Neubrand TP, Breitkopf CR, Rupp R, Breitkopf D, Rosenthal SL. Factors associated with completion of the human papillomavirus vaccine series. *Clin Pediatr (Phila).* 2009;48(9):966-69.

56. Slade BA, Leidel L, Vellozzi C, et al. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. *JAMA.* 2009;302(7):750-57. Available at: http://jama.ama-assn.org/cgi/reprint/302/7/750. Accessed March 14, 2010.

57. Rascati KL. The $64,000 question—what is a quality-adjusted life-year worth? *Clin Ther.* 2006;28(7):1042-43.

58. Ronco G, Arbyn M, Segnan N. Cervical screening according to age and HPV status. *BMJ.* 2009;339:b3005.

59. Cannon HE. Pharmacy management of vaccines. *J Manag Care Pharm.* 2007;13(7 Suppl B):S7-S11. Available at: http://www.amcp.org/data/jmcp/pages%207-11.pdf.