Cost-effectiveness of Human Papillomavirus Vaccination in the United States

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We describe a simplified model, based on the current economic and health effects of human papillomavirus (HPV), to estimate the cost-effectiveness of HPV vaccination of 12-year-old girls in the United States. Under base-case parameter values, the estimated cost per quality-adjusted life year gained by vaccination in the context of current cervical cancer screening practices in the United States ranged from $3,906 to $14,723 (2005 US dollars), depending on factors such as whether herd immunity effects were assumed; the types of HPV targeted by the vaccine; and whether the benefits of preventing anal, vaginal, vulvar, and oropharyngeal cancers were included. The results of our simplified model were consistent with published studies based on more complex models when key assumptions were similar. This consistency is reassuring because models of varying complexity will be essential tools for policy makers in the development of optimal HPV vaccination strategies.

In 2000, the Institute of Medicine (IOM) published a report listing 26 candidate vaccines that potentially could be developed and licensed in the first 2 decades of the 21st century (*1*). Included in this list was a candidate vaccine for human papillomavirus (HPV), a virus that can cause cervical and other anogenital cancers, genital warts, and other adverse health outcomes (*1*–*5*). For example, in the United States, HPV types 16 and 18 cause ≈70% of cervical cancer, 80% of anal cancer, and 30% of vaginal and vulvar cancers (*2*–*5*). Furthermore, HPV types 6 and 11 cause >90% of cases of anogenital warts (*5*,*6*). The economic costs of HPV-related genital warts and cervical disease, including screening to prevent cervical cancer, are estimated to be at least $4 billion annually in the United States (*7*,*8*).

In June 2006, the US Food and Drug Administration approved a quadrivalent (HPV 6, 11, 16, 18) vaccine (Gardasil, manufactured by Merck & Co., Inc. [Whitehouse Station, NJ, USA]) for use in girls and women 9–26 years of age (*5*). The efficacy of this vaccine is almost 100% if given to young women before sexual exposure (*3*,*5*,*9*). Also in June 2006, the US Advisory Committee on Immunization Practices recommended routine HPV vaccination for girls 11–12 years of age (*3*). The vaccine series can be initiated in girls as young as 9 years, and catch-up vaccination is recommended for girls and young women of ages 13–26 years who have not received the HPV vaccine previously or who have not completed the full vaccine series (*3*).

In anticipation of the approval of new HPV vaccines, several studies have been conducted to estimate the potential cost-effectiveness of HPV vaccination in the United States in terms of the cost per quality-adjusted life year (QALY) saved (*1*,*9*–*13*). With 1 exception (*1*), these studies applied a Markov model, a decision model, a dynamic transmission model, or a combination thereof (see Dasbach et al. [*14*] for a review of HPV models). To complement these existing studies, we developed a simplified model to estimate the cost-effectiveness of adding HPV vaccination of 12-year-old girls to existing cervical cancer screening practices in the United States. Our approach was similar to that used by IOM (*1*) in that we estimated the potential benefits of HPV vaccination based on current, age-specific incidence rates of HPV-related outcomes. Additionally, our analysis extended the IOM approach to reflect a more current understanding of the vaccine's characteristics and to include the potential benefits of preventing HPV-related anal, vaginal, vulvar, and oropharyngeal cancers.

Methods

Similar to the IOM approach, we used spreadsheet software to build an incidence-based model of the health and economic effects of HPV-related health outcomes in

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the absence of HPV vaccination. We then examined how these effects might change over time because of HPV vaccination, based on factors such as the number of 12-year-old girls vaccinated each year and vaccine efficacy. We adopted a societal perspective and included all direct medical costs (2005 US$) and benefits regardless of who incurred the costs or received the benefits (*15*,*16*). The study question we addressed was "What is the cost per QALY gained by adding vaccination of 12-year-old girls to existing cervical cancer screening practices in the United States?"

Population Model

A hypothetical population of persons 12–99 years of age was created as follows. First, the number of 12-year-old girls was based on recent sex-specific population estimates (*17*). The number of 13-year-old girls was calculated as the product of the number of 12-year-olds and the probability of survival (using recent mortality data) from age 12 years to age 13 years. The number of 14-year-old girls and the number of persons of all subsequent ages through 99 years were calculated in an analogous manner. We assumed that the number of 12-year-olds each year was constant over time so that the age distribution of the population was constant over time as well.

Vaccine Coverage, Efficacy, and Costs

We assumed the HPV vaccine would be administered to 12-year-old girls starting in year 1 and continuing through year 100. We assumed that vaccinated girls would receive the full vaccine series (3 doses) before age 13 years. Vaccination coverage (the percentage of 12-year-old girls vaccinated) was assumed to increase linearly for the first 5 years to 70% and to remain at 70% thereafter (*9*). Vaccination efficacy was assumed to be 100%, on the basis of trials showing high efficacy of prophylactic HPV vaccines against persistent infection and vaccine type–specific cervical intraepithelial neoplasia (CIN) grades 2 and 3 (*3*,*18–21*). The duration of vaccine protection was assumed to be lifelong, and the cost of vaccination was set to $360 per series (*9*).

Adverse Health Outcomes Averted by Vaccination

We examined the following HPV-related health outcomes: cervical cancer; CIN grades 1, 2, and 3; genital warts; and, in some analyses, anal, vaginal, vulvar, and selected oropharyngeal cancers. The age-specific incidence rates of the HPV-related health outcomes were used to estimate the potential reduction in these outcomes that could be obtained through vaccination.

Age-specific cancer incidence rates were derived from 2003 population-based cancer registries that participate in the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER) (*22*,*23*). Together, the 2 cancer registries covered ≈96% of the US population in 2003 (*22*). The cancer incidence rates we applied were conservative because we included only certain morphology (histology) codes, which limited cervical cancers to cervical carcinomas (squamous cell, adenocarcinoma, adenosquamous, and other carcinoma) and which limited all other noncervical cancers to squamous cell carcinomas only (*24*). We did not include in situ cancers from the cancer registries. We limited oropharyngeal cancers to selected sites most commonly associated with HPV (base of tongue, tonsillar, and other oropharyngeal sites as described in the online Technical Appendix, available from www.cdc.gov/EID/content/14/2/244-Techapp.pdf) (*24*).

Age-specific incidence rates of CIN grades 1, 2, and 3, and prevalence rates of genital warts were based on estimates obtained from the literature (*25*,*26*). We used prevalence estimates for genital warts because age-specific incidence estimates were not available (online Technical Appendix).

Cervical Cancer Screening

The incidence rates of CIN and cervical cancers that we applied in our model are those that arise in the context of current cervical cancer screening and sexually transmitted disease prevention activities in the United States. Because these prevention activities are reflected in the incidence rates of CIN and cervical cancer that we applied in our model, no information about these prevention activities (e.g., coverage and frequency of cervical cancer screening) was required in our analysis.

Costs Averted and QALYs Saved by Vaccination

The cervical cancer treatment costs averted by vaccination were calculated each year by multiplying the age-specific number of cervical cancer cases averted by the vaccine in that year by the estimated cost per case of cervical cancer (online Technical Appendix). The number of QALYs saved by preventing cervical cancer was calculated for each year by multiplying the age-specific number of cervical cancer cases averted by the vaccine in that year by the estimated age-specific number of QALYs lost per case of cervical cancer (online Technical Appendix). For other health outcomes (other cancers, CIN 1, CIN 2, CIN 3, and genital warts), the treatment costs averted and QALYs saved by vaccination were estimated in an analogous manner.

Age-specific Estimates of Direct Medical Costs and QALYs Lost per Adverse Health Outcome

The estimated direct medical cost per case of cervical cancer and other HPV-related health outcomes was based on several sources (*7*,*10*,*12*,*26–35*). The age-specific estimates

of the discounted number of QALYs lost per case of an HPV-related heath outcome (e.g., cervical cancer) were based on published estimates of the quality of life without these adverse health outcomes (*36*) and the estimated reduction in quality of life associated with the HPV-related health outcome (*1*,*10*,*12*,*37*) (online Technical Appendix).

Incremental Cost per QALY Gained

Vaccination costs, averted treatment costs, and the number of QALYs saved were calculated for each year over a 100-year period, discounted to present value by using an annual discount rate of 3% (*9*). The incremental cost per QALY gained by adding vaccination to existing cervical cancer screening was calculated as the net cost of vaccination divided by the number of QALYs gained by adding vaccination to existing screening, where the net cost of vaccination is the cost of vaccination minus the treatment costs averted by adding vaccination to existing screening (*16*).

Herd Immunity Scenario

To examine how the estimated cost-effectiveness of vaccination might change if the benefits of herd immunity were included, we assumed an additional effect of the vaccine on nonvaccinated persons, including a reduction in genital warts in men. The online Technical Appendix provides details of the methods and assumptions used to estimate these additional benefits.

Cohort Model

To make our results more comparable to Markov models of an age cohort, we modified our population model to examine the benefits of vaccination of a single cohort of 12-year-old girls over time. Vaccination costs were incurred in the first year only, and the benefits of vaccinating the 12-year-old cohort were calculated through age 99 years. Because Markov models of age cohorts typically do not include transmission dynamics, we did not consider the potential benefits of herd immunity in the cohort model.

Base Case Analyses

Using base-case parameter values (see online Technical Appendix), we estimated the cost-effectiveness of HPV vaccination by using 12 variations of the model. These 12 variations consisted of 4 permutations (including vs. excluding the noncervical cancers and including vs. excluding the benefits of preventing HPV types 6 and 11) of 3 model versions (population model with and without herd immunity, cohort model without herd immunity).

Sensitivity Analyses

We performed sensitivity analyses to examine how changes in the base-case parameter values influenced the estimated cost-effectiveness of vaccination. We first examined how the cost-effectiveness estimates of the population model's herd immunity scenario changed when assumptions about the degree of the effect of herd immunity were changed. The remainder of the sensitivity analyses focused on the population model of the quadrivalent HPV vaccine without the adjustment for herd immunity.

We performed 1-way sensitivity analyses in which we varied 1 set of parameter values while holding other parameters at their base-case values. The parameters we varied included the cost of the vaccine series ($300, $490), vaccine efficacy (95%, 99%), the cost per case of all HPV-related health outcomes (±25% of their base-case values); the discount rate (0%, 5%); the time horizon over which vaccination costs and benefits were assumed to accrue (25 years, 50 years); the incidence rates of health outcomes (±25% of their base-case values for CIN 1, CIN 2, CIN 3, and genital warts, and the lower and upper bound ranges of the 95% confidence interval from the NPCR and SEER data for cancers); the percentage of each health outcome attributable to HPV vaccine types (±20% of their base-case values); and the number of lost QALYs associated with each HPV outcome. We manipulated the last number by varying the reduction in quality of life (±50% of the base-case values) associated with all HPV-related health outcomes and by varying the stage-specific survival probabilities for HPV-related cancers (±2 standard errors). We also performed multiway sensitivity analyses by varying ≥2 sets of these parameter values simultaneously.

The parameters that were varied in the sensitivity analyses comprised almost all of the parameters in the model. Exceptions included duration of vaccine protection (which is difficult to modify in our model without sacrificing the simplicity of our approach), vaccine coverage (which does not affect our results except when herd immunity is assumed), and other parameters such as age-specific death rates, which are not subject to considerable uncertainty.

Comparison to Previous Cost-Effectiveness Studies

We compared our results with previously published estimates of the cost-effectiveness of HPV vaccination. To do so, we modified the parameter inputs to match as closely as possible several key attributes of the models applied in these previous studies (online Technical Appendix).

Results

Under base-case parameter values, the estimated cost per QALY gained by adding vaccination of 12-year-old girls to existing cervical cancer screening was $3,906–$14,723, depending on the type of model applied (cohort vs. population), whether herd immunity effects were assumed, the types of HPV targeted by the vaccine (bivalent vs. quadrivalent), and whether the benefits of preventing other cancers in addition to cervical cancer were included

(Table 1). If all other factors were equal, the estimated cost per QALY gained by vaccination was lower when herd immunity effects were assumed, when protection against HPV types 6 and 11 (rather than just HPV types 16 and 18) was included, and when the benefits of preventing other cancers in addition to cervical cancer were included.

Prevention of HPV-related health outcomes resulted in averted treatment costs and QALYs saved. For example, in the population model of the quadrivalent vaccine (when herd immunity benefits and the benefits of preventing cancers other than cervical were excluded), reductions in CIN, cervical cancer, and genital warts accounted for ≈70%, 19%, and 12% of the averted costs, respectively, and ≈33%, 54%, and 13% of the saved QALYs, respectively.

Sensitivity Analyses

The cost-effectiveness ratios did not change substantially when we modified the assumptions in the population model about the effect of herd immunity. When varying the effect of herd immunity, the cost per QALY gained by vaccination was $3,423–$7,596 for the quadrivalent vaccine and $8,549–$12,354 for the bivalent vaccine, when the benefits of preventing cancers other than cervical were excluded (results not shown).

In the 1-way sensitivity analyses of the population model (excluding assumed herd immunity effects), the discount rate and the time horizon had the greatest effect on the estimated cost per QALY gained (Table 2). When the discount rate was varied from 0% to 5%, the cost per QALY gained ranged from $675 to $24,901 (and from <$0 to $21,966 when other cancers in addition to cervical cancer were excluded). When the time horizon was varied from 25 to 50 years (rather than the base-case value of 100 years), the cost per QALY gained ranged from $21,600 to $81,786 (and from $19,943 to $81,398 when other cancers in addition to cervical cancer were included). Changes in the other sets of parameter values (such as costs and QALYs associated with HPV-related health outcomes) also affected the results, but to a lesser degree than changes in the discount rate and time horizon (Table 2). In the multiway sensitivity analyses, simultaneously changing 2 sets of parameter values resulted in estimated costs per QALY gained of <$0 to $4,606 when parameter values more favorable to vaccination were applied and estimated costs per QALY gained of $17,825 to $36,503 when parameter values less favorable to vaccination were applied (Table 3).

In the best and worst case scenarios (when all 6 selected sets of parameters were set to values more favorable and less favorable to vaccination, respectively), the cost per QALY gained was <$0 and $122,976, respectively (<$0 and $115,896 when including other cancers in addition to cervical cancer) (Table 3). However, much of the variation in the best and worst case scenarios was attributable to changes in the discount rate and the time horizon. For example, when the worst case scenario was modified to include a discount rate of 3% (rather than 5%), the estimated cost per QALY gained (when the benefits of preventing cancers other than cervical were excluded) was ≈$75,000 when applying a 50-year time horizon and $41,000 when applying a 100-year time horizon (results not shown).

Comparison with Previous Cost-Effectiveness Studies

Estimates from the simplified model were quite consistent with published estimates (Table 4). The absolute difference between the estimated cost per QALY gained by vaccination as estimated by our simplified model and as estimated by the more complex models did not exceed $4,000.

Discussion

We developed a simple model to estimate the cost-effectiveness of HPV vaccination in the context of current cervical cancer screening in the United States. We found that the cost per QALY gained by adding routine vaccination of 12-year-old girls to existing screening practices ranged from $3,906 to $14,723 under base-case parameter values (depending on the model version we applied) and ranged from <$0 (cost-saving) to $122,976 in the sensitivity analyses when several key parameter values were varied. Our results were consistent with results of published studies based on more complex models, particularly when key assumptions (e.g., vaccine duration, efficacy, and cost) were similar.

Table 1. Estimated cost per QALY gained by adding routine HPV vaccination of 12-y-old girls to existing cervical cancer screening in the United States*

Parameter	Population model		Cohort model;
	No herd immunity, $US	Herd immunity, $US	no herd immunity, $US
Excluding anal, vaginal, vulvar, and oropharyngeal cancers			
Vaccine targets HPV types 6,11,16,18	10,294	5,336	8,593
Vaccine targets HPV types 16,18	14,723	10,318	12,562
Including anal, vaginal, vulvar, and orophayngeal cancers†			
Vaccine targets HPV types 6,11,16,18	8,137	3,906	6,430
Vaccine targets HPV types 16,18	11,602	7,848	9,471

*When applying base-case parameter values to 12 model variations. QALY, quality-adjusted life year; HPV, human papillomavirus.
†The oropharyngeal cancer sites we included were base of tongue, tonsillar, and other sites as described in the online Technical Appendix (available from www.cdc.gov/EID/content/14/2/244-Techapp.pdf).

Table 2. One-way sensitivity analyses: estimated cost per QALY gained by adding routine vaccination of 12-y-old girls to existing cervical cancer screening in the United States*

Parameter or parameter set varied	Values applied in sensitivity analysis	Cost/QALY gained	
		Excluding anal, vaginal, vulvar, oropharyngeal cancers, $US	Including anal, vaginal, vulvar, oropharyngeal cancers, $US
None	NA	10,294	8,137
Vaccine cost per series (base case = $360)	$300, $490	5,811–20,009	4,237–16,587
Vaccine efficacy (base case = 100%)	95%, 99%	10,566–11,710	8,374–9,369
Cost of cervical cancer, CIN 1–CIN 3, genital warts*	Base case ±25%	6,142–14,446	4,332–11,953
Reduction in quality of life due to HPV-related health outcomes	Base case ±50%†	7,720–15,519	6,141–12,135
Incidence rates of cervical cancer, CIN 1–CIN 3, genital warts‡	Base case ±25%†	6,999–16,333	5,181–13,379
% of health outcomes attributable to HPV vaccine types	Base case ±20%	6,014–17,020	4,400–13,987
Discount rate (base case = 3%)	0%, 5%	675–24,901	<0–21,966
Time horizon (base case = 100 y)	25 y, 50 y	21,600–81,786	19,943–81,398

*When key parameter values were varied in the population model of quadrivalent HPV vaccine (excluding herd immunity). QALY, quality-adjusted life year; HPV, human papillomavirus; NA, not applicable; CIN, cervical intraepithelial neoplasia.
†See text and online Technical Appendix (available from www.cdc.gov/EID/content/14/2/244-Techapp.pdf) for details.
‡And, when applicable, anal, vaginal, vulvar, and oropharyngeal cancers.

The simplicity of our approach offers advantages and disadvantages. The main advantage is that it requires substantially fewer assumptions than the more complex Markov and transmission models. For example, there is no need to model the probability of HPV acquisition, the possible progression from HPV infection to disease, the mixing of sex partners, the probability of HPV transmission, and so forth. There also is no need to model cervical cancer screening and sexually transmitted disease prevention activities because these activities are reflected in the incidence rates of HPV-related health outcomes that we applied.

Because we do not model cervical cancer screening directly, however, we are unable to use our model to examine how changes in cervical cancer–screening strategies can affect the cost-effectiveness of HPV vaccination, and vice versa. For example, HPV vaccination is expected to reduce the positive predictive value of abnormal Papanicolaou (Pap) test results (*38*). However, our analysis did not include the loss in quality of life attributable to the initial distress associated with receiving an abnormal Pap result (*39*), regardless of whether it is a false positive. This omission of the lost QALYs due to abnormal Pap test results underestimates the benefits of HPV vaccination because vaccination is expected to offer moderate reductions in the number of abnormal Pap results overall (*38*,*40*). Future changes in screening strategies, such as delayed screening, could also possibly improve the cost-effectiveness of HPV vaccination (*12*).

Another disadvantage of our approach is that it offers only a rough approximation of the cost-effectiveness of HPV

Table 3. Multiway sensitivity analyses: estimated cost per QALY gained by adding routine vaccination of 12-y-old girls to existing cervical cancer screening in the United States*†

Parameter or parameter set varied	Cost per QALY gained	
	Excluding anal, vaginal, vulvar cancers, $US.	Including anal, vaginal, vulvar cancers, $US
Higher cost per case and larger reduction in quality of life for all HPV-related health outcomes	4,606	3,262
Lower cost per case and smaller reduction in quality of life for all HPV-related health outcomes	21,779	17,825
Discount rate = 0%; time horizon = 100 y	675	<0
Discount rate = 5%; time horizon = 50 y	36,503	34,539
Higher percentage of health outcomes attributable to HPV vaccine types; higher incidence of HPV-related health outcomes	3,815	1,882
Lower percentage of health outcomes attributable to HPV vaccine types; lower incidence of HPV-related health outcomes	24,250	20,265
All variables above (best-case scenario)	<0	<0
All variables above (worst-case scenario)	122,976	115,896

*When key parameter values were simultaneously varied in the population model of quadrivalent HPV vaccine (excluding herd immunity). QALY, quality-adjusted life year; HPV, human papillomavirus;
†The lower and upper bound ranges were the same as described in the1-way sensitivity analyses, except for the time horizon, which was varied from 50 y to 100 y.

Table 4. Summary of previously published models and estimates of the cost per QALY gained by adding routine HPV vaccination of 12-y-old girls to existing cervical cancer screening in the United States*†

Variable	Goldie et al. 2004 (*10*)	Sanders and Taira 2003 (*11*)	Taira et al. 2004 (*13*)	Elbasha et al. 2007 (*9*)
Key assumptions in published models				
Target of HPV vaccine	HPV 16,18	High-risk HPV types	HPV 16,18	HPV 6,11,16,18
Efficacy of vaccine	90%	75%	90%	100%‡
Vaccine cost per series	$393	$300	$300 + $100 booster	$360
Base year of $US	2002	2001	2001	2005
Estimated cost per QALY of vaccination				
Published model estimate	$24,300	$12,700§	$14,600	$3,000
Simplified model estimate	$20,600	$8,700	$17,100	$5,300

*QALY, quality-adjusted life year; HPV, human papillomavirus.
†In all comparisons, the simplified model was modified (as necessary) so that the assumptions regarding the target of the HPV vaccine, vaccine efficacy and cost, vaccine duration of protection (except in the comparison to Taira and colleagues [*13*], as noted in the online Technical Appendix, available from www.cdc.gov/EID/content/14/2/244-Techapp.pdf), and the base year of US$ were consistent with the published models (online Technical Appendix). The simplified model estimate was based on the cohort model in the comparisons with the findings of Goldie et al. (*10*) and Sanders and Taira (*11*) and was based on the population model (assuming transmission effects) in the comparison with the estimates of Taira and colleagues (*13*) and Elbasha and colleagues (*9*).
‡Elbasha and colleagues (*9*) assumed 90% protection against infection with HPV and 100% protection against HPV-related disease.
§To enhance comparability, the published estimate from Sanders and Taira (*11*) was based on their sensitivity analyses when assuming lifetime duration of vaccination, not their base-case estimate of $22,800 when 10-y vaccine duration of protection was assumed.

vaccination and is not suitable for examining strategies such as vaccination of boys and men. In addition, although many of the parameter values and assumptions in our model can be modified with ease, changing the assumption of lifelong duration of protection or examining vaccination at older ages would require the incorporation of assumptions about the incidence and natural history of HPV to account for the probability of acquiring HPV (before vaccination or after vaccine immunity wanes) and the subsequent probability of adverse HPV-attributable health outcomes. However, we can address the issue of waning immunity by assigning a higher cost per vaccination series (as in the sensitivity analyses) to reflect the cost of a booster.

Another limitation of our approach is the uncertainty in the key parameter values, such as the cost and loss in quality of life associated with HPV-related health outcomes, the percentage of health outcomes attributable to each type of HPV targeted by the vaccine, and the incidence of CIN and genital warts. However, our results were fairly robust in response to changes in these key parameter values. For example, when simultaneously varying the costs of HPV-related health outcomes and the loss in QALYs associated with HPV-related health outcomes, we found that the estimated cost per QALY gained by vaccination ranged from $3,262 to $21,779.

Our adjustments for the effect of herd immunity were arbitrary; we simply assumed an additional effect of vaccination in the nonvaccinated population. However, our results did not vary substantially (in absolute terms) when the assumed effect of herd immunity was varied. For example, the estimated cost per QALY gained by quadrivalent vaccination (including herd immunity and excluding the benefits of preventing cancers other than cervical) was $5,336 in the base case and ranged from $3,423 to $7,596 when the adjustments for the effects of herd immunity (including the impact on genital warts in males) were varied. We also note that the benefits to nonvaccinated persons were assumed to occur only in nonvaccinated persons of similar ages to those vaccinated. This restriction may have understated the potential benefits of herd immunity.

Our analysis did not address all of the potential costs and benefits of vaccination. For example, the cost-effectiveness estimates would have been more favorable to vaccination if we had included the potential for cross-protection against high-risk HPV types besides 16 and 18 (*21*); the prevention of anal, vaginal, and vulvar cancer precursor lesions (as demonstrated in the supplemental analysis in the online Technical Appendix); the prevention of other cancers not included in this analysis (such as anal cancer and oropharyngeal cancers in male patients); and the prevention of other HPV-related health outcomes such as recurrent respiratory papillomatosis. Conversely, the cost-effectiveness estimates would have been less favorable to vaccination if we had included the potential for HPV type replacement (i.e., an increase in HPV types not protected against by vaccination), waning immunity, and the possible costs and loss in quality of life associated with adverse side effects of vaccination.

A key finding from this analysis was that the choice of discount rate and time horizon has a substantial influence on the estimated cost-effectiveness of vaccination. Because the costs of HPV vaccination begin to accrue immediately but the full benefits of vaccination are not realized for many years, the cost-effectiveness of vaccination becomes less favorable when higher discount rates are applied or when shorter time horizons are examined.

Another key finding was that the potential benefits of preventing anal, vaginal, vulvar, and oropharyngeal cancers offer nontrivial improvements in the estimated cost-effectiveness of HPV vaccination. The inclusion of these

additional benefits decreased the cost per QALY gained by vaccination by ≈$2,200 (or 21%) in the population model (without herd immunity), by ≈$1,400 (or 27%) in the population model (with herd immunity), and by ≈$2,200 (or 25%) in the cohort model. Future studies that develop better estimates of the cost and loss in quality of life associated with these cancers could more accurately estimate the effects of these additional benefits on the cost-effectiveness of HPV vaccination. Despite the limitations discussed above, our simplified model provides useful estimates of cost-effectiveness of HPV vaccination in the United States. Our results were consistent with previous studies based on more complex models. This consistency is reassuring because models of various degrees of complexity will be essential tools for policy makers in the development of optimal HPV vaccination strategies.

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The Cost-Effectiveness of HPV Vaccination in the United States: Estimates from a Simplified Model

Methods

We adopted a societal perspective and included all direct medical costs and benefits regardless of who incurred the costs or received the benefits (1,2). Indirect costs such as the lost productivity associated with cervical cancer mortality (3) and direct nonmedical costs such as patent travel time were not included in this analysis because previous studies of HPV vaccination cost-effectiveness focused primarily on direct medical costs and because estimates of indirect and direct nonmedical costs are not available for all HPV-related health outcomes. Costs were expressed in 2005 U.S. dollars, except where noted in the comparisons with previous studies.

Vaccine coverage, efficacy and costs

Assumptions regarding vaccine characteristics are summarized in Appendix Table 1. We assumed the HPV vaccine would be administered to 12-year-old girls starting in year 1 and continuing through year 100. We assumed vaccinated girls would receive the full vaccine series (three doses) before age 13 years. Vaccination coverage (the percentage of 12-year-old girls vaccinated) in years 5 through 100 was 70% in the base case (4). We assumed vaccination coverage increased linearly, such that coverage rates in years 1, 2, 3, and 4 were 0.2, 0.4, 0.6, and 0.8 times (respectively) the coverage rates in years 5 through 100 (4). Vaccination efficacy was assumed to be 100%, based on trials showing high efficacy of prophylactic HPV vaccines against persistent infection and vaccine type-specific CIN 2 and 3 (5–9). The duration of vaccine protection was assumed to be lifelong, and the cost of vaccination was set to $360 per series (4).

Adverse health outcomes averted by vaccination

We examined the following HPV-related health outcomes: cervical cancer; cervical intraepithelial neoplasias (CIN) grades 1, 2, or 3; genital warts; and in some analyses, anal, vaginal, vulvar, and selected oropharyngeal cancers. Estimates of the age-specific incidence rates of these health outcomes (Appendix Table 2) in the absence of vaccination were used to estimate the potential reduction in these outcomes that could be obtained through vaccination. For example, the number of cervical cancer cases averted by the vaccine in a given year t for a given age group i was estimated as: $R_i\ (P_i/100{,}000)(A_{16} + A_{18})EC_{i,t}$, where R_i is the rate of cervical

cancer (per 100,000) in age group i, P_i is the number of females in age group i, A_{16} and A_{18} are the percentages of cervical cancer attributable to HPV 16 and HPV 18, respectively, E is vaccine efficacy, and $C_{i,t}$ is the coverage of vaccination in age group i in year t (the percentage of persons in age group i in year t who were vaccinated at age 12). The number of cases of other health outcomes (other cancers, CIN 1, CIN 2, CIN 3, and genital warts) averted by vaccination was estimated in a manner analogous to that for cervical cancer.

The estimated percentage of cervical cancer attributable to HPV 16 and 18 (as well as the fraction of other health outcomes attributable to various HPV types) was based on several sources (10–26)(Appendix Table 3). We assumed that the proportion of cancers attributable to HPV types 16 and 18, respectively, was 76% and 7% for anal cancer, 28% and 4% for vaginal cancer, 29% and 3% for vulvar cancer, and 31% and 1% for the selected oropharyngeal cancers we included in this analysis (Appendix Table 3). These attributable proportions for anal, vaginal, and vulvar cancers were selected such that the proportion attributable to HPV 16 and 18 was consistent with a recent review of the burden of HPV-related cancers (19), and the impact of HPV 16 relative to HPV 18 was consistent with a range of published estimates (11–18,20). The attributable proportions for the selected oropharyngeal cancers were based on a review indicating HPV prevalence of 35.6% in oropharyngeal squamous cell carcinomas (SCCs), with HPV 16 and HPV 18 accounting for 86.7% and 2.8% of the HPV-positive oral SCCs, respectively (26). We assumed that the proportion of CIN 2 attributable to HPV vaccine types was the same as that of CIN 3, as the source study for this information (23) did not provide different estimates for CIN 2 and CIN 3. This assumption may have caused a slight overestimation of the role of HPV 16 and 18 in CIN 2 and a slight underestimation of the role of HPV 16 and 18 in CIN 3.

Age-specific incidence rates of anal, cervical, vaginal, vulvar, and oropharyngeal cancers were derived from 2003 population-based cancer registries that participate in the Centers for Disease Control and Prevention's National Program of Cancer Registries (NPCR) and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program (27,28). Together, the two cancer registries covered ≈96% of the United States population in 2003 (27). SEER*Stat software was used to calculate incidence rates and 95% confidence intervals (29). Because the estimates of the percentage of each cancer attributable to HPV vaccine types (described above) were based on overall site and not on morphology, we expect

that our application of these estimated attributable fractions will be conservative given that the cancer incidence rates we applied were limited (based on morphology) to those more likely to be HPV-related (30). That is, we limited cervical cancers to include cervical carcinomas (squamous cell, adenocarcinomas, adenosquamous, and other carcinoma) and we limited all other non-cervical cancers to include squamous cell carcinomas only (30). Further, we limited oropharyngeal cancers to selected sites more commonly associated with HPV (base of tongue, tonsillar, and other oropharyngeal sites), using the following International Classification of Diseases for Oncology (ICD-O-3) codes: 019, 024, 090, 091, 098, 099, 142, 028, 102, 108, 109, 140, and 148 (30,31).

Age-specific incidence rates of CIN grades 1, 2, and 3, and prevalence rates of genital warts were based on estimates obtained from the literature (32,33). Prevalence rates of genital warts in persons aged 65 years and older were adjusted as follows. Rates for persons aged 65 to 69 years were assumed to be as estimated by Insinga and colleagues (33) for ages 65 years and older. The decrease in prevalence from the 60- to 64-year age group to the 65- to 69-year age group was applied to all subsequent age groups, such that genital warts prevalence after age 65 years declined steadily with age. We used prevalence estimates for genital warts because age-specific incidence estimates were not available. In the study from which the prevalence estimates were obtained (33), the mean duration of genital warts episodes was ≈3 months, suggesting that these annual prevalence rates may be similar to annual incidence rates. In the absence of vaccination, our model predicts ≈486,000 new cases of genital warts each year, which is consistent with published estimates ranging from 250,000 to 1,000,000 (34).

Costs averted and QALYs saved by vaccination

The cervical cancer treatment costs averted by vaccination were calculated each year by multiplying the age-specific number of cervical cancer cases averted by the vaccine in that year (as described above) by the estimated cost per case of cervical cancer. The estimated cost per case of cervical cancer and other HPV-related health outcomes was based on several sources (33–45)(Appendix Table 1). The cost per case of genital warts we applied was based three published estimates (33–35) and was reduced by 25% to account for the possibility that genital warts cases might go untreated (34). We estimated the cost per case of vaginal and vulvar cancers under the assumption that the ratio of these costs to the cost of anal cancer (43) was

similar to the ratio of these costs as reported in a study of the potential costs averted by HPV vaccination in British Columbia (44). The cost of oropharyngeal cancers was based on average Medicare payments among persons with head and neck cancers in the first year of illness minus the average Medicare payments among matched comparison patients (45).

The number of QALYs saved by preventing cervical cancer was calculated for each year by multiplying the age-specific number of cervical cancer cases averted by the vaccine in that year by the estimated age-specific number of QALYs lost per case of cervical cancer (described below and summarized in Appendix Table 4). For other health outcomes (other cancers, CIN 1, CIN 2, CIN 3, and genital warts), the treatment costs averted and QALYs saved by vaccination were estimated in an analogous manner.

Age-specific estimates of QALYs lost per adverse health outcome

The age-specific estimates of the discounted number of QALYs lost per case of cervical cancer and other cancers, CIN 1, CIN 2, CIN 3, and genital warts were based on published estimates of the quality of life without adverse these health outcomes (46) and the estimated reduction in quality of life associated with these HPV-related health outcomes (38,41,47,48), as described below.

Cervical cancer was assumed to lead to one of six outcomes, based on three possible stages at diagnosis (local, regional, or distant) and two possible survival outcomes (survival or death). For survivors, the relative loss in quality of life associated with treatment and followup was 0.27 for 4 months for local cancer, 0.37 for 3 years for regional cancer, and 0.45 for 3 years for distant cancer; with subsequent lifelong relative losses in quality of life of 0.07 for local cancer, 0.1 for regional cancer, and 0.24 for distant cancer. For non-survivors, a relative loss in quality of life (0.36 for local cancer, 0.41 for regional cancer, and 0.45 for distant cancer) was assumed for 3 years, followed by death. The quality weights described above, and the estimated durations of these reductions in quality of life, were based on previously published estimates (41,47,48). Based on SEER data, the distributions of cervical cancer stage at diagnosis (local, regional, distant) we applied were: 64%, 29%, and 7%, respectively, for women under 50 years of age and 40%, 46%, and 14%, respectively, for women 50 years of age and older. For women 41–49 years of age, we used a linear combination of these two distributions to allow for a gradual change with age in the distribution of cancer stage at diagnosis. We applied probabilities

of survival for local, regional, and distant cervical cancer of 0.94, 0.64, and 0.20, respectively, for women under 50 years of age and 0.87, 0.50, and 0.09, respectively, for women 50 years of age and older.

We used a similar approach to calculate the lost QALYs attributable to other cancers. For each cancer, we applied the same stage-specific quality weights as for cervical cancer, but applied cancer-specific distributions of the stage at diagnosis (local, regional, or distant) and cancer-specific, stage-specific survival probabilities. The distributions of stage at diagnosis (local, regional, or distant) we applied were: 56%, 35%, and 9% for anal cancer; 38%, 37%, and 25% for vaginal cancer; 60%, 35%, and 5% for vulvar cancer; and 17%, 69%, and 13% for oropharyngeal cancers. These distributions were applied to all age groups. The survival probabilities we applied for local, regional, and distant cancer were: 0.86, 0.65, and 0.26 for anal cancer; 0.79, 0.41, and 0.32 for vaginal cancer; 0.91, 0.55, 0.23 for vulvar cancer; and 0.58, 0.51, and 0.25 for oropharyngeal cancers, based on 5-year survival probabilities obtained from SEER data. For vaginal cancer diagnosed in the regional stage, the survival probability we applied (0.41) reflects the upper bound value suggested by the SEER data. We used this higher value so that the relative change in survival probability across cancer stages (local, regional, and distant) for vaginal cancer was consistent with that of the other cancers.

CIN 1 was assumed to cause a relative loss in quality of life of 0.03 for 18 months, with no effect thereafter (47). CIN 2 was assumed to cause a relative loss in quality of life of 0.07 for 18 months, with no effect thereafter, based on estimates of the impact of CIN 1 (47) and the relative impact of CIN 2 to CIN 1 on quality of life (38). CIN 3 was assumed to cause a relative loss in quality of life of 0.2 for 4 months and 0.03 for 2 years, and with no effect thereafter (47).

For genital warts in females, the relative loss of quality of life and the duration of such loss were assumed to be one of the following four scenarios: 0.05 loss for 3 months, 0.1 loss for 6 months, 0.15 loss for 3 months, or 0.15 loss for 6 months, with probability 0.475, 0.475, 0.025, and 0.025, respectively (47). For genital warts in males, the relative loss of quality of life and the duration of such loss were assumed to be one of the following four scenarios: 0.1 loss for 3 months, 0.1 loss for 6 months, 0.15 loss for 3 months, or 0.15 loss for 6 months, with probability 0.475, 0.475, 0.025, and 0.025, respectively (47).

We used these estimates of the impact of HPV-related health outcomes (cervical cancer, CIN 1, 2, and 3, and genital warts) on quality of life to estimate the QALYs lost per case of each health outcome. For example, as noted above, CIN 1 was assumed to cause a relative loss in quality of life of 0.03 for 18 months. For a 20-year-old female, the number of lost QALYs associated with CIN 1 was calculated as $0.03(Q_{20}/2) + 0.03(Q_{21}S_{20})/(1+r)$, where Q_t denotes the expected quality of life for a female at age t years in the absence of genital warts, r is the discount rate, and S_{20} is the probability that a 20-year-old female would survive to at least age 21 years. The first 6 months of lost quality of life were assumed to occur at age 20 (the Q_{20} term is divided by 2 to reflect 6 months of lost quality of life rather than 1 year) and the final 12 months of lost quality of life were assumed to occur at age 21. The lost quality of life at age 21 was adjusted to reflect the probability of survival to age 21 and discounted to present value at the time of onset of the health outcome (in this case, age 20). For other ages, and for other health outcomes (cervical cancer and other cancers, CIN 2, CIN 3, and genital warts), the age-specific estimates of the QALYs lost per health outcome were calculated in an analogous manner. The resulting age-specific estimates of the number of lost QALYs associated with these health outcomes, under the assumptions described above, are summarized in Appendix Table 4.

Cost per QALY gained

Vaccination costs, averted treatment costs, and the number of QALYs saved were calculated for each year over a 100-year time period, discounted to present value using an annual discount rate of 3% (49). The cost per QALY gained by vaccination was calculated as (V-A)/Q, where V is the cost of vaccination, A is the averted treatment costs due to vaccination, and Q is the number of QALYs saved due to vaccination (50).

Herd immunity scenario

To examine how the estimated cost-effectiveness of vaccination might change if the benefits of herd immunity were included, we assumed an additional impact of the vaccine on non-vaccinated persons, including a reduction in genital warts in males. For each health outcome in females (cervical and other cancers, CIN 1, CIN 2, CIN 3, and genital warts), we assumed that the number of cases averted in non-vaccinated females in a given age group would be equal to the number of cases averted in vaccinated females in that age group multiplied by the percentage of females in that age group not vaccinated multiplied by an adjustment factor F ($0 \leq F \leq 1$). For

example, the number of cases of cervical cancer averted through herd immunity in age group i in year t was calculated as $R_i(P_i/100{,}000)(A_{16} + A_{18})EC_{i,t}(1-C_{i,t})F$.

Vaccination of females would be expected to reduce genital warts in males as well. In the herd immunity scenario, we assumed the percentage reduction in genital warts in males was M ($0<M<1$) times the overall percentage reduction in genital warts in females.

We applied 0.5 as the base case value of M, which is consistent with, but slightly more conservative, than the 0.56 relative reduction in male HPV prevalence (as compared to the reduction in female HPV prevalence) predicted by a population-level transmission model of female HPV vaccination (51). We also applied 0.5 as the base case value of F, due to a lack of available estimates for this parameter value. The implication of this assumption is as follows. With 70% coverage and 100% efficacy, the direct impact of vaccination in our model is a 70% reduction in health outcomes attributable to the HPV vaccine types in females. When herd immunity benefits are included, using the adjustment factor $F = 0.5$, the population-level impact would be an 80.5% reduction in health outcomes attributable to the HPV vaccine types in females. The uncertainty associated with the adjustment factors F and M is addressed later in the sensitivity analyses.

Cohort model

To make our results more comparable to Markov models of an age cohort, we modified our population model to examine the benefits of vaccination of a single cohort of 12-year-old girls over time. Vaccination costs were incurred in the first year only, and the benefits of vaccinating the 12-year-old cohort were calculated through age 99 years. The benefits of vaccination (averted treatment costs and QALYs saved) were calculated as in the main analysis described above. Because Markov models of age cohorts typically do not include transmission dynamics, we did not consider the potential benefits of herd immunity in the cohort model.

Base case parameter values

Base case parameter values are summarized in Appendix Tables 1–4. Using these base case parameter values, we estimated the cost-effectiveness of HPV vaccination under 12 variations of the model (Appendix Table 5). These 12 variations consisted of 4 permutations (including versus excluding anal, vaginal, vulvar, and oropharyngeal cancers; and including

versus excluding the benefits of preventing HPV types 6 and 11) of 3 model versions (the population model with and without herd immunity; and the cohort model without herd immunity).

Sensitivity analyses

We performed sensitivity analyses to examine how changes in the base case parameter values influenced the estimated cost-effectiveness of vaccination. We first examined how the estimated cost-effectiveness estimates of the population model's herd immunity scenarios (model variations 5 and 6 in Appendix Table 5, which exclude anal, vaginal, vulvar, and oropharyngeal cancers) changed under varying assumptions about the impact of herd immunity (F) and the relative impact (M) of female vaccination on genital warts in males compared to females (F = M = 0.25, F = M = 0.75). The remainder of the sensitivity analyses focused on the population model of the quadrivalent HPV vaccine without the adjustment for herd immunity (model variations 1 and 3 in Appendix Table 5).

We performed one-way sensitivity analyses in which we varied one set of parameter values while holding other parameters at their base case values. The parameters varied included the cost of the vaccine series ($300, $490); vaccine efficacy (95%, 99%); the cost per case of all HPV-related health outcomes (±25% of their base case values); the discount rate (0%, 5%); the time horizon over which vaccination costs and benefits were assumed to accrue (25 years, 50 years); the incidence rates of health outcomes (±25% of their base case values for CIN1, CIN 2, CIN 3, and genital warts, and the lower and upper bound ranges of the 95% confidence interval from the NPCR and SEER data for cancers); the percentage of each health outcome attributable to HPV vaccine types (±20% of their base case values); and the loss in quality of life associated with each HPV-related outcome, which was manipulated by varying the reduction in quality of life (±50% of their base case values) associated with all HPV-related health outcomes and by varying the survival probabilities for HPV-related cancers (±2 standard errors). We also performed multi-way sensitivity analyses by varying two or more sets of these parameter values simultaneously.

Comparison with previous cost-effectiveness studies

To compare our results with previously published estimates, we modified the parameter inputs to match as closely as possible several key attributes of the models applied in these

previous studies. Specifically, we used our cohort analyses when comparing our results to that of published Markov models and used our population model with assumed herd immunity effects when comparing our results to those of transmission models, and we closely followed the other models in their assumptions regarding vaccine price, efficacy, coverage, and duration of protection; base year in which costs were reported; and HPV types targeted by the vaccine (bivalent or quadrivalent).

In our comparison to the Markov model of Goldie et al. (41), we applied our cohort model, adjusted two parameter values (vaccine efficacy = 0.9, vaccine cost = $393), and calculated the cost per QALY gained in 2002 U.S. dollars. We focused only on the benefits of preventing HPV 16 and 18, and excluded herd immunity effects and the benefits of preventing anal, vaginal, vulvar, and oropharyngeal cancers.

In our comparison to the Markov model of Sanders and Taira (52), we applied our cohort model, set vaccine cost to $300, and calculated the cost-per-QALY gained in 2001 U.S. dollars. Sanders and Taira examined a vaccine with 75% efficacy against high risk HPV types. To mirror this assumption in our model, we assumed 100% efficacy against HPV 16 and 18 but changed the percent of cervical cancer attributable to HPV 16 and 18 from 70% to 75%. We adjusted the percentage of CIN 1, CIN 2, and CIN 3 attributable to HPV 16 and 18 by the same proportion. We focused only on the benefits of preventing HPV 16 and 18, and excluded herd immunity effects and the benefits of preventing anal, vaginal, vulvar, and oropharyngeal cancers. Finally, to make the comparison more valid, we compared our results to Sanders and Taira's estimated cost per QALY of $12,700 when assuming lifetime duration of protection, rather than their base case estimate of $22,800 when assuming 10 years duration of vaccine protection.

In our comparison to the transmission model of Taira et al. (53), we applied our population model (with herd immunity included), adjusted two parameter values (vaccine efficacy = 0.9, vaccine cost = $374), and calculated the cost per QALY gained in 2001 U.S. dollars. The $374 cost was chosen to reflect the $300 cost of the vaccine series and the discounted cost of the $100 booster required 10 years after the initial series as assumed by Taira and colleagues. We were unable to match the assumption of Taira and colleagues of waning vaccine protection 10 years after the booster. Thus, in this comparison, the initial vaccine series and booster shot were assumed to provide lifetime protection in our simplified model as opposed

to 20 years protection in the model by Taira and colleagues. We focused only on the benefits of preventing HPV 16 and 18 and excluded the benefits of preventing anal, vaginal, vulvar, and oropharyngeal cancers.

In our comparison to the transmission model of Elbasha et al. (4), we applied our population model and calculated the cost per QALY gained in 2005 U.S. dollars. We included the benefits of protection against HPV 6,11,16 and 18 and the benefits of herd immunity, but excluded the benefits of preventing anal, vaginal, vulvar, and oropharyngeal cancers.

Because our simplified approach does not directly incorporate cervical cancer screening activities (which instead are reflected in the incidence rates of CIN and cervical cancer we applied), we did not compare our model results to those of Kulasingam and Myers (38), who examined the cost-effectiveness of vaccination in the context of various cervical cancer screening strategies.

Additional analysis and results: Anal, vaginal, and vulvar cancer precursor lesions

As a supplement to the main analyses, we also examined how the estimated cost-effectiveness of vaccination might change when including the potential impact of vaccination on the incidence of anal, vaginal and vulvar cancer precursor lesions. The inclusion of these additional health outcomes is problematic due to the lack of information available on the treatment cost and quality of life impacts of these health outcomes. However, to obtain a rough approximation of the potential impact of the inclusion of these precursor lesions on our results, we estimated the vaccine impact (treatment costs averted and QALYs saved) on anal, vaginal, and vulvar cancer precursor lesions as described below. We note, however, that the anal, vaginal, and vulvar cancer precursor lesions were included only in this supplemental analysis, and were not included in the results reported elsewhere.

The treatment cost averted by preventing anal, vaginal, and vulvar cancer precursor lesions was calculated as $(\theta_1/\theta_2)\times\theta_3\times\sigma$, where θ_1 is the averted costs associated with cervical cancer precursor lesions (CIN 1–3), θ_2 is the averted cost of cervical cancer, θ_3 is the averted cost of anal, vaginal, and vulvar cancers, and σ is an adjustment factor. That is, we assumed the ratio of the averted costs of anal, vaginal, and vulvar cancer precursor lesions to the averted costs of

anal, vaginal, and vulvar cancers would be equal to the ratio of the averted costs of cervical cancer precursor lesions to the averted costs of cervical cancer, multiplied by an adjustment factor (σ). We first used an adjustment factor of 0.5, as the ratio of the cost of precursor lesions to the cost of cancer may be lower for anal, vaginal, and vulvar cancers than for cervical cancer, because screening (which can increase the number of precursor lesions detected and reduce the incidence of cancer) is more common for cervical cancer than for anal, vaginal, or vulvar cancers. We also applied an adjustment factor of 1.0 to examine the sensitivity of the results to this adjustment. The number of QALYs saved by preventing anal, vaginal, and vulvar cancer precursor lesions was estimated in an analogous manner.

As reported in the main text, when applying the population model without assuming herd immunity, the estimated cost per QALY averted by a quadrivalent vaccine was $8,137 when including anal, vaginal, vulvar, and oropharyngeal cancers. When anal, vaginal and vulvar cancer precursor lesions were also included as described above, the estimated cost per QALY was $6,754 (when $\sigma = 0.5$) and $5,447 (when $\sigma = 1.0$).

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Table 1: Base case values of vaccine characteristics, treatment costs, and other parameters

Parameter	Base case value	Source
Vaccine characteristics		
Vaccine efficacy	100%	(5–9)
Duration of vaccine protection	Lifetime	(4)
Vaccine coverage	70%	(4)*
Vaccine cost per series	$360	(4)
Treatment cost per case		
Genital warts	$425	(33–35)*
CIN 1	$1,739	(36,38–42)
CIN 2	$3,233	(36,38–42)
CIN 3	$3,671	(36,38–42)
Cervical cancer	$31,120	(37–42)
Anal cancer	$29,206	(43)
Vaginal cancer	$24,837	(43,44)*
Vulvar cancer	$20,468	(43,44)*
Oropharyngeal cancers	$34,098	(45)*
Herd immunity adjustment factors*		
F (females)	0.5	Assumed
M (males)	0.5	Assumed
Other		
Discount rate, annual	3%	(49)
Time horizon	100 y	Assumed

CIN: cervical intraepithelial neoplasia.
Treatment cost estimates reflect the expected, discounted lifetime costs, and were updated to 2005 U.S. dollars using the medical care component of the consumer price index.
*See text for more details.

Table 2: Age specific incidence rates of cervical and other cancers, CIN 1, CIN2, CIN 3, and prevalence rates of genital warts (per 100,000) applied in the model

Age	Cervical cancer	CIN 1	CIN 2	CIN 3	Genital warts (females)	Genital warts (males)	Anal cancer	Vaginal cancer	Vulvar cancer	Oropharyngeal cancers
12–14	0	0	0	0	43	41	0	0	0	0
15–19	0*	160	80	30	287	65	0	0	0*	0
20–24	1.3	510	320	130	620	293	0	0*	0*	0*
25–29	5.8	140	380	410	394	501	0*	0*	0.2	0*
30–34	11.3	240	140	180	265	388	0*	0*	0.4	0.2
35–39	13.5	240	140	180	199	252	0.6	0.2	0.9	0.4
40–44	15.3	120	50	50	139	189	1.5	0.3	1.8	1.0
45–49	13.7	120	50	50	144	128	2.6	0.4	2.2	1.7
50–54	12.6	70	40	10	92	118	3.4	0.6	2.5	2.5
55–59	13.4	70	40	10	86	86	4.3	0.7	2.6	3.5
60–64	12.2	40	10	0	76	100	5.0	0.7	3.3	4.5
65–69	12.3	40	10	0	55	87	4.4	1.6	4.4	5.2
70–74	11.3	20	0	10	40	76	5.6	1.4	5.8	5.2
75–79	10.5	20	0	10	29	66	5.6	1.9	8.0	4.3
80–84	10.7	0	0	0	21	57	5.4	2.3	9.7	4.0
85–89	9.0	0	0	0	15	50	5.5	3.2	11.7	2.9
90–94	9.0	0	0	0	11	43	5.5	3.2	11.7	2.9
95–99	9.0	0	0	0	8	38	5.5	3.2	11.7	2.9

CIN: cervical intraepithelial neoplasia. Cancer incidence rates were obtained from NPCR and SEER data (see appendix text). Oropharyngeal cancer sites included base of tongue, tonsillar, and other sites as described elsewhere in this appendix. The CIN incidence rates and genital warts prevalence rates were obtained from studies by Insinga and colleagues (32,33). The prevalence rates of genital warts in persons over age 65 y were adjusted as described elsewhere in this appendix. We assumed a rate of 0 for CIN in the 12- to 14-y age group.
*Cancer case counts are suppressed and incidence rates are not calculated if fewer than 16 cases. We assumed a rate of 0 in these instances.

Table 3: Estimated percentages of health outcomes attributable to various HPV types

Health outcome	HPV 6,11	HPV 16	HPV 18	Source
Genital warts	90.0%	0%	0%	(10,24,25)
CIN 1	6.3%	19.4%	9.2%	(22)
CIN 2	0%	45.8%	10.0%	(23) *
CIN 3	0%	45.8%	10.0%	(23) *
Cervical cancer	0%	58.0%	12.0%	(10,19,21)
Anal cancer	0%	76.0%	7.0%	(11,12,14,17,19,20) *
Vaginal cancer	0%	28.0%	4.0%	(13,14,16,19) *
Vulvar cancer	0%	29.0%	3.0%	(14–16,18,19) *
Oropharyngeal cancers	0%	31%	1%	(26) *

*See appendix text for more details.

Table 4: Expected number of discounted lifetime quality-adjusted life years (QALYs) lost as a result of HPV-related health outcomes, by age group

Age	Cervical cancer	CIN 1	CIN 2	CIN 3	Genital warts (females)	Genital warts (males)	Anal cancer	Vaginal cancer	Vulvar cancer	Oropharyngeal cancers
12–14	6.6	0.04	0.10	0.12	0.03	0.04	8.1	12.6	7.6	13.8
15–19	6.4	0.04	0.09	0.11	0.03	0.04	7.9	12.2	7.4	13.3
20–24	6.1	0.04	0.09	0.11	0.03	0.04	7.5	11.7	7.1	12.8
25–29	5.8	0.04	0.09	0.11	0.03	0.04	7.2	11.1	6.8	12.2
30–34	5.5	0.04	0.09	0.11	0.03	0.04	6.8	10.5	6.4	11.5
35–39	5.1	0.04	0.09	0.11	0.03	0.03	6.3	9.8	6.0	10.7
40–44	5.4	0.04	0.09	0.11	0.03	0.03	5.8	9.0	5.5	9.8
45–49	6.4	0.04	0.09	0.11	0.03	0.03	5.3	8.2	5.0	8.9
50–54	6.5	0.04	0.09	0.11	0.03	0.03	4.7	7.3	4.5	8.0
55–59	5.7	0.04	0.08	0.10	0.03	0.03	4.2	6.4	3.9	7.0
60–64	4.9	0.03	0.08	0.10	0.03	0.03	3.6	5.5	3.4	6.0
65–69	4.1	0.03	0.08	0.10	0.03	0.03	3.0	4.6	2.8	5.0
70–74	3.2	0.03	0.08	0.09	0.03	0.03	2.4	3.6	2.3	4.0
75–79	2.5	0.03	0.07	0.08	0.02	0.03	1.8	2.8	1.7	3.0
80–84	1.8	0.03	0.07	0.08	0.02	0.03	1.4	2.0	1.3	2.2
85–89	1.3	0.03	0.07	0.08	0.02	0.03	1.0	1.5	0.9	1.6
90–94	1.0	0.03	0.07	0.08	0.02	0.03	0.8	1.1	0.8	1.3
95–99	0.4	0.02	0.06	0.07	0.02	0.03	0.4	0.5	0.3	0.5

CIN: cervical intraepithelial neoplasia. See appendix text for details.

Table 5: Description of 12 model variations estimated using base case parameter values

Variation	Type of model	Herd immunity included?	Anal, vaginal, vulvar, and oropharyngeal cancers included?	Protection against HPV 6–11 included?
1	Population	No	No	Yes
2	Population	No	No	No
3	Population	No	Yes	Yes
4	Population	No	Yes	No
5	Population	Yes	No	Yes
6	Population	Yes	No	No
7	Population	Yes	Yes	Yes
8	Population	Yes	Yes	No
9	Cohort	No	No	Yes
10	Cohort	No	No	No
11	Cohort	No	Yes	Yes
12	Cohort	No	Yes	No