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Cost-effectiveness of nonavalent HPV vaccination among males aged 22 through 26 years in the United States ☆

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Abstract

Introduction: In the United States, routine human papillomavirus (HPV) vaccination is recommended for females and males at age 11 or 12 years; the series can be started at age 9 years. Vaccination is also recommended for females through age 26 years and males through age 21 years. The objective of this study was to assess the health impact and cost-effectiveness of harmonizing female and male vaccination recommendations by increasing the upper recommended catch-up age of HPV vaccination for males from age 21 to age 26 years.

Methods: We updated a published model of the health impact and cost-effectiveness of 9-valent human papillomavirus vaccine (9vHPV). We examined the cost-effectiveness of (1) 9vHPV for females aged 12 through 26 years and males aged 12 through 21 years, and (2) an expanded program including males through age 26 years.

Results: Compared to no vaccination, providing 9vHPV for females aged 12 through 26 years and males aged 12 through 21 years cost an estimated $16,600 (in 2016 U.S. dollars) per quality-adjusted life year (QALY) gained. The estimated cost per QALY gained by expanding male vaccination through age 26 years was $228,800 and ranged from $137,900 to $367,300 in multi-way sensitivity analyses.

Conclusions: The cost-effectiveness ratios we estimated are not so favorable as to make a strong economic case for recommending expanding male vaccination, yet are not so unfavorable as to preclude consideration of expanding male vaccination. The wide range of plausible results we

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☆The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Conflict of interest

The authors report no conflicts of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.04.071.

obtained may underestimate the true degree of uncertainty, due to model limitations. For example, the cost per QALY might be less than our lower bound estimate of $137,900 had our model allowed for vaccine protection against re-infection. Models that specifically incorporate men who have sex with men (MSM) are needed to provide a more comprehensive assessment of male HPV vaccination strategies.

Keywords

Human papillomavirus; Nonavalent HPV vaccine; Cost-effectiveness; Cost-utility; Disease transmission models; Vaccines

1. Introduction

Human papillomavirus (HPV) infection can cause a range of adverse health outcomes in females and males, including anogenital cancers, oropharyngeal cancer, genital warts, and recurrent respiratory papillomatosis (RRP) [1]. The HPV vaccination program in the United States has been in place for over a decade [2]. The Advisory Committee on Immunization Practices (ACIP) has recommended routine HPV vaccination since 2006 for females and 2011 for males [1–3]. Current ACIP guidance calls for routine HPV vaccination of females and males at age 11 or 12 years (or can be started at age 9 years) [1,3]. ACIP also recommends catch-up vaccination through age 26 years for females and through age 21 years for males [1,3]. Further, ACIP provides additional recommendations through age 26 years for people with immunocompromising conditions, transgender people, and for men who have sex with men [MSM], including men who identify as gay or bisexual [3]. MSM bear a disproportionate burden of HPV-associated genital warts and cancers, particularly anal cancer [4,5].

In 2011, the United States was the first country to include males in the routine HPV vaccination program [6,7]. This decision was based on vaccine clinical trial data, burden of infection and disease, programmatic issues and cost effectiveness, and used the newly implemented ACIP Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process [8,9]. Since that time, additional data have been collected about HPV vaccination coverage in the United States, the percentage of HPV-associated cancers attributable to HPV, and the prevalence of HPV and HPV-associated diseases in males. Although the initial recommendation for males was for a quadrivalent HPV vaccine (4vHPV), a 9-valent vaccine (9vHPV) was licensed in the United States in 2015 and is now the only HPV vaccine available in this country.

ACIP continuously reviews data relevant to vaccination policy as they become available and also considers revisions to existing recommendations based on such data [10]. One common question about existing HPV vaccine recommendations is whether the upper age limit for males should be changed to 26 years [11]. This modification would harmonize the age recommendations for males and females and might facilitate implementation of HPV vaccination recommendations. In addition, expanding catch-up vaccination through age 26 years for all males might help increase the likelihood that men in special risk groups would

be offered HPV vaccination even if they are unaware of or choose not to disclose their risk status in health care settings [12].

The objective of this study was to assess the health impact and cost-effectiveness of expanding male HPV vaccination recommendations to include all males through age 26 years instead of age 21 years. Specifically, we examined the incremental costs and benefits of a 9vHPV program for females and males aged 12 through 26 years compared to a 9vHPV program for females aged 12 through 26 years and males aged 12 through 21 years.

2. Methods

2.1. Study questions addressed

We examined the incremental cost-effectiveness of 9vHPV of males aged 22 through 26 years in the United States, in the context of current vaccination policy. The specific study question we addressed was: What would be the cost-effectiveness of a 9vHPV program for ages 12 through 26 years for all sexes (“expanded scenario”), compared to a 9vHPV program for females aged 12 through 26 years and males aged 12 through 21 years (“comparison scenario”)? In addressing this issue, we also examined the cost-effectiveness of the “comparison scenario” compared to a “no vaccination” scenario. To clarify, the cost-effectiveness of the comparison scenario was calculated versus no vaccination, and the cost-effectiveness of the expanded scenario was calculated versus the comparison scenario.

2.2. Cost-effectiveness ratios

To address the study question, we calculated the incremental cost per quality-adjusted life year (QALY) gained by the expanded scenario (vs. the comparison scenario). The numerator of the incremental cost per QALY ratio was calculated as the projected increase in vaccination costs (costs of vaccination in the expanded scenario minus the costs of vaccination in the comparison scenario) minus the projected increase in averted HPV-associated direct medical costs (medical costs averted in the expanded scenario minus the medical costs averted in the comparison scenario). The denominator of the incremental cost per QALY ratio was the projected gain in the number of QALYs saved by the expanded scenario, and was calculated as the number of QALYs gained in the expanded scenario minus the number of QALYs gained in the comparison scenario. Formally, the calculation of the incremental cost-effectiveness ratio (ICER) can be expressed as:

$$ICER = \frac{\left(V_e - V_c\right) - \left(A_e - A_c\right)}{\left(Q_e - Q_c\right)},$$

where V denotes vaccination costs, A denotes averted direct medical costs, Q denotes QALYs gained, and the subscripts e and c refer to the expanded scenario and the comparison scenario, respectively[13].

2.3. Perspective, scope, time frame, and analytic horizon

We assessed costs from the healthcare system perspective and included all direct medical costs averted by vaccination, without regard to the payer of these costs (e.g., health

insurance, government program, individual patient or family, etc.). Medical costs averted and QALYs gained were accrued by prevention of the following HPV-related health outcomes: anogenital cancers (cervical, vaginal, vulvar, anal, and/or penile), oropharyngeal cancer, cervical intraepithelial neoplasia (CIN), genital warts, and juvenile-onset RRP. We applied a 100-year time horizon. Specifically, the vaccine program was assumed to be in place for 100 years, vaccination costs were incurred in each of the 100 years, and we assessed lifetime costs averted and lifetime QALYs gained for HPV-associated health outcomes that were prevented over the 100-year period. Future costs and QALYs were discounted to present value using a 3% annual discount rate as is commonly recommended for cost-effectiveness studies in the United States [13,14].

2.4. Model description

We applied a deterministic, dynamic, population-based model that has been used previously to examine a range of HPV vaccination strategies in the United States [15,16] and was recently expanded to include the additional five HPV types prevented by 9vHPV [17,18]. For this application of the model, we have updated vaccination coverage and cost assumptions to reflect recent data, and have updated the medical treatment costs to 2016 U.S. dollars using the health care component of the Personal Consumption Expenditures price index (https://www.bea.gov/) [19]. In this section, we provide a brief description of the current model we applied. The technical appendix contains a full description of this model and a complete listing of all model parameter values and sources.

Our model employs three important simplifying features that distinguish it from other, more complex HPV models in the literature. First, our model does not explicitly account for the pathologic transition from HPV acquisition to HPV-associated disease. Without modeling the natural history of HPV infections in individuals, our model approximates the percentage reduction in HPV-associated outcomes based on the percentage reduction in cumulative HPV acquisition at the population level. For example, suppose that as a result of the HPV vaccination program, cumulative lifetime acquisition of HPV 16 among 45-year-old women in year 25 of the HPV vaccination program was 50% lower than it would have been in the absence of vaccination. In this example, the incidence of HPV 16-associated cervical cancer among this birth cohort of 45-year-old women would be calculated by the model to be approximately 50% lower than it would have been in the absence of vaccination.

The second simplifying feature is the approach used to model HPV transmission dynamics. In our model, all people who have not yet acquired a given HPV type are subject each year to a sex-and age-specific probability of acquiring the given HPV type, and each year these probabilities are adjusted in accordance with sex- and age-specific reductions in HPV in the population due to HPV vaccination.

The third simplifying feature of our model is that we do not explicitly account for cervical cancer screening, and therefore cannot assess the impact of potential changes in cervical cancer screening strategies. Instead, cervical cancer screening was incorporated indirectly in the model, through our use of the observed rates of CIN and cervical cancer that have occurred in the context of current and historical cervical cancer screening practices in the United States. Our model thus allows for an assessment of the impact and cost-effectiveness

of HPV vaccination strategies in a scenario in which rates of CIN and cervical cancer detection are assumed to have leveled off just prior to the onset of the HPV vaccination program. For example, the cervical cancer rates we apply in our model are based on 2006–2010 data, and we assume these cervical cancer rates would remain constant over the 100-year time horizon of our model in the absence of an HPV vaccination program.

2.5. Vaccine characteristics

We assumed that a complete series of 9vHPV would provide lifelong, 95% vaccine efficacy against each of the nine vaccine types of HPV (Table 1) [20]. For ease of comparison of the vaccination strategies and interpretation of the cost-effectiveness results, we assumed every person vaccinated would complete the recommended vaccine series (2 doses for those initiating vaccination through age 14 years, and 3 doses for those initiating vaccination at age 15 years or older.) The base-case vaccine cost per 3-dose series, including administration costs, was $522 (range: $372–$669, see Table 1). We applied age- and sex-specific annual probabilities of vaccination based on estimated U.S. HPV vaccination coverage rates [21–23], as described in the technical appendix. Briefly, we examined a base case coverage scenario, along with lower and higher scenarios. The base case coverage scenario reflects the coverage that will be achieved if current uptake rates continue.

2.6. Other parameter values

Our model incorporated numerous other parameters, such as age- and sex-specific incidence rates of HPV-associated health outcomes in the absence of vaccination, the percent of health outcomes attributable to each of the nine HPV vaccine types, and the lifetime direct medical costs and number of QALYs lost per case of each HPV-associated outcome included in our model. The technical appendix provides a complete listing and documentation of all of the model parameters. For illustrative purposes, selected parameter values are presented in Table 2.

2.7. Sensitivity analyses

We conducted one-way sensitivity analyses to examine how the cost-effectiveness results would change when we varied one parameter (such as vaccine cost) or one set of parameters (such as the number of QALYs lost per case of each health outcome) at a time, holding all other parameters to their base case values. We also conducted probabilistic sensitivity analyses, consisting of 5000 model simulations, to examine how the cost-effectiveness of 9vHPV vaccination strategies would change when numerous parameter values were varied simultaneously (see technical appendix for details).

3. Results

3.1. HPV-associated cancers averted by vaccination (not discounted)

Table 3 shows the estimated number of HPV-associated cancers averted by vaccination. Under base case coverage assumptions, an estimated 1,449,200 HPV-associated cancers would be averted over 100 years under the comparison scenario of routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 26 years for females and 21 years for males, compared to no vaccination. The expanded

scenario of including males through age 26 years would avert an additional 6200 cancers over 100 years versus the comparison scenario.

3.2. QALYs gained and costs averted by vaccination, and cost-effectiveness

Table 4 shows the discounted values for the estimated number of QALYs gained and costs averted by vaccination. Over the 100-year time horizon, the comparison scenario resulted in estimated costs of about $19.2 billion and a gain of 1.2 million QALYs, compared to no vaccination. The expanded scenario would result in additional costs of about $1.5 billion and a gain of 6000 QALYs over 100 years, versus the comparison scenario. The cost per QALY gained by the comparison scenario was $16,600 (versus no vaccination). The expanded scenario would cost an estimated $228,800 per QALY gained (versus the comparison scenario).

3.3. Sensitivity analyses

In the one-way sensitivity analyses, the cost per QALY gained by expanding male vaccination through age 26 years ranged from $146,600 to $296,800 (Table 5). The lowest cost per QALY gained was obtained when applying upper bound values for the number of QALYs lost per health outcome, and the highest cost per QALY gained was obtained when applying the upper bound value for the cost of the vaccine series. In multiway sensitivity analyses (Table 5), estimates of the cost per QALY gained by the expanded scenario (vs. the comparison scenario) ranged from $137,900 to $367,300 in the 5th and 95th percentiles of the simulations, respectively.

4. Discussion

We used an existing model of 9vHPV vaccination strategies to examine the incremental costs and benefits of increasing the upper recommended catch-up age of HPV vaccination for all males from age 21 to age 26 years. We estimated that expanding catch-up vaccination recommendations for males in this age range would cost an estimated $230,000 per QALY gained under base case assumptions. Further, we found a wide range of plausible results in sensitivity analyses. However, the comparison scenario of routine vaccination of adolescents with catch-up through age 26 years for females and 21 years for males was estimated to cost $16,600 per QALY gained (compared to no vaccination). Although the expanded scenario was not as cost-efficient as the comparison scenario, including older males in the recommendation would increase the costs of vaccination by less than 5% in our base case coverage scenario.

Cost-effectiveness studies can help to inform vaccine recommendations [24]. Regarding the question of whether it would be cost-effective to expand male catch-up vaccination through age 26 years, however, our cost-effectiveness estimates do not provide clear and unambiguous guidance. There is no official cost per QALY threshold established by ACIP or the U.S. government to determine cost-effectiveness. The cost-effectiveness ratios we estimated are not so favorable as to make a strong economic case for expanding male vaccination recommendations, yet are not so unfavorable as to preclude consideration of expanding male vaccination recommendations. Furthermore, although we performed

sensitivity analyses to illustrate how our results would change when key assumptions were varied, the range of values we report for the cost per QALY gained may not reflect the true degree of uncertainty around our results given the limitations of our model.

One key limitation that might have led to an overestimation of the cost per QALY gained by vaccinating older males is that we did not account for the possibility that vaccination could provide protection against previously-acquired but cleared HPV types. Our model assumes 100% lifelong natural immunity, such that there is no type-specific benefit to vaccination after person acquires a given HPV type. For example, in our model, a person who had already acquired HPV 6 and 16 at the time of vaccination would not benefit in terms of protection against HPV 6 and 16, but would benefit in terms of protection against the other seven vaccine types. If vaccination does provide protection against reinfection, the cost-effectiveness of vaccination of young adults could be more favorable than we estimated [25,26]. For example, the cost per QALY gained by expanding a 1-year, 4vHPV vaccine catch-up program in Norway for females through age 26 years (instead of through 24 years) ranged from $83,000 to $272,000 (in 2010 U.S. dollars, assuming a cost of $150 for each of the 3 doses) when assumptions were varied regarding the degree of vaccine protection against reinfection [25].

Due to potential differences by sex in immunity after natural infection, assumptions about natural immunity could particularly impact the estimated cost-effectiveness of male vaccination, since a larger percentage of females than males develop antibody after infection and antibody after natural infection might be more protective against reinfection in females compared with males [27]. Thus, the cost per QALY gained by vaccinating males aged 22 through 26 years could be notably lower than we estimated if vaccination provides protection against previously-acquired but cleared HPV types.

One key limitation that might have led to an underestimation of the cost per QALY gained by expanding male vaccination recommendations is that our model does not stratify by risk behavior. Although the incidence rates we applied for HPV-associated health outcomes in males are population-level estimates that include special populations such as MSM, our model does not specifically account for these special populations. Our comparison strategy was defined as vaccination of females through age 26 years and males through age 21 years. This comparison strategy was based on the current vaccination approach but does not precisely match the current ACIP recommendations for HPV vaccine for older males. The current recommendations already call for HPV vaccination through age 26 years for MSM and transgender persons, as well as men with certain immunocompromising conditions [3]. To the extent that some males aged 22 through 26 years who are at higher risk for HPV-associated health outcomes are already included in the current guidelines, our model might have overestimated the potential benefits of expanding HPV vaccination recommendations to include all males through age 26 years. However, HPV vaccine uptake has been low among men aged 22 through 26 years, even among men in this age range for whom vaccination is recommended [28]. For example, among MSM aged 22 through 26 years participating in the National HIV Behavioral Surveillance (NHBS) system, self-reported coverage with at least one HPV vaccine dose was 16.2% in 2014 [28].

More precise estimates of the impact and cost-effectiveness of HPV vaccination, particularly male vaccination strategies, could be obtained by expanding existing models or developing new models to specifically incorporate MSM. Such models could also assess the impact and cost-effectiveness of interventions to increase vaccination coverage among MSM in the United States. A model of HPV epidemic trajectories in MSM in Australia, for example, found that a targeted HPV vaccination program for young MSM could be cost-effective, even in a setting where young boys are vaccinated [29].

For simplification, we assumed that everyone who initiated HPV vaccination would complete the series. Our model is not well-suited for accounting for the potential costs and benefits of those who initiate but do not complete the vaccine series. Additional limitations of our model are described and discussed in more detail elsewhere [16,18,30,31]. Although our model is subject to important limitations and is relatively simple in its structure, the model has provided estimates of the health benefits and cost-effectiveness of HPV vaccination that are consistent with the estimates of more complex models [17,32].

Population-level health benefits of HPV vaccination have been documented in the United States, including significant declines in HPV vaccine-type prevalence, anogenital warts, and cervical precancers following vaccine introduction [33–38]. Numerous modeling studies have shown that the HPV vaccination program in the United States has a favorable cost-effectiveness profile [15,16,18,39–43]. However, most of these studies focus on the cost-effectiveness of vaccination of young adolescents and do not consider adults in their early twenties. The contribution of this study was to provide approximations of the potential health impact and cost-effectiveness of harmonizing HPV vaccine recommendations by expanding the vaccine program to include males as well as females through age 26 years.

Finally, we note that cost-effectiveness information is but one of many factors that ACIP is asked to consider when developing vaccine recommendations. Other important considerations include burden of disease, vaccine safety and efficacy, and programmatic and implementation issues [24].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

HPV vaccine efficacy, cost, and coverage assumptions in the model.

Vaccine characteristic	Lower bound	Base case	Upper bound
Efficacy and cost			
Type-specific vaccine efficacy [20]	85%	95%	100%
Cost of 3-dose series including administration[a]	$372	$522	$669
Annual probability of vaccination			
Females, 12 years[b]	29.5%	29.5%	56.4%
Females 13–18 years	7.7%	12.9%	14.3%
Females 19–26 years	1.5%	2.6%	2.9%
Males, 12 years[b]	24.9%	24.9%	48.7%
Males 13–18 years	1.7%	9.7%	14.2%
Males 19–21/26 years[c]	0.3%	1.9%	2.8%

Vaccine duration of protection was assumed to be lifelong.

The annual probability of vaccination was calculated from U.S. HPV vaccination coverage rates [21–23], as described in the technical appendix.

[a]Vaccine cost per dose was assumed to be $116.22 (public cost) and $193.63 (private sector cost) based on CDC vaccine price list for adults (https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/) as of March 5, 2017. The cost of administration per dose was assumed to be $8 public and $29 private [44]. The base case value reflects an average of the public and private costs, and the range was calculated using the public costs (lower bound) and the private costs (the upper bound). The cost of a 2-dose series was assumed to be two-thirds that of a 3-dose series.

[b]For simplicity, vaccination at age 12 years in our model incorporates vaccination series that occur from ages 9 through 12 years.

[c]The age cutoff for males was either 21 or 26 years, depending on the scenario examined.

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Table 2

Examples of parameter values used in model: incidence, cost per case, and number of quality-adjusted life years (QALYs) lost per case of HPV-associated health outcomes for selected sex and age groups.

Health outcome	Selected sex and age group (years) to whom the parameter values in this table apply[a]	Incidence per 100,000[a]	Cost per case[a]	Number of QALYs lost per case[a]
Selected examples for females				
Genital warts	Females, 15–19	223	$660	0.024
CIN 1	Females, 25–29	297	$1340	0.007
CIN 2/3	Females, 30–34	243	$2470	0.01
Cervical cancer	Females, 55–59	12.2	$42,000	5.97
Anal cancer	Females, 70–74	5.3	$39,200	2.86
Vaginal cancer	Females, 55–59	0.8	$29,300	6.59
Vulvar cancer	Females, 80–84	10.6	$25,500	1.88
Oropharyngeal cancer	Females, 55–59	4.1	$46,700	6.05
Selected examples for males				
Genital warts	Males, 20–24	236	$660	0.024
Penile cancer	Males, 55–59	1.2	$21,400	4.41
Anal cancer	Males, 70–74	2.8	$39,200	2.96
Oropharyngeal cancer	Males, 60–64	24.8	$46,700	4.02
Selected example for children				
RRP	Both sexes, 0–18	0.735	$144,200	1.05

Costs are reported in 2016 U.S. dollars. CIN: cervical intraepithelial neoplasia. RRP: recurrent respiratory papillomatosis.

Cancer incidence assumptions were based on data from CDC's National Program of Cancer Registries (NPCR) and NCI's Surveillance, Epidemiology, and End Results (SEER) program for 2006–2010, which cover approximately 94.8% of the U.S. population. A range of sources were used for the incidence of the other health outcomes (CIN, genital warts, and RRP) [45–50], costs [45,51,52], and quality of life assumptions [49,53–57].

[a]This table includes selected age groups and corresponding parameter values for the outcomes in column 1, whereas the model applied age-specific values for all age groups and for both sexes (where applicable). See the technical appendix for a complete description of all model parameter values, ranges, and sources.

Table 3

Base case estimates of health impact: Estimated number of HPV-associated cancers averted by vaccination over 100-year vaccination program (not discounted).

Subgroup examined	Comparison scenario (females 12–26 years, males 12–21 years)	Expanded scenario (females & males, 12–26 years)	Incremental benefit of expanded scenario
Cancers averted in females	957,400	958,700	1300
Cancers averted in males	491,700	496,600	4900
Total cancers averted	1,449,200	1,455,400	6200

These outcomes were not discounted and have been rounded to the nearest 100. The first column of results shows the number of cancers averted by the comparison scenario of routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 26 years for females and 21 years for males (vs. no vaccination). The second column of results shows the number of cancers averted by the expanded scenario of routine 9vHPV vaccination of 12-year-old females and males with catch-up vaccination through age 26 years for females and males. The third column of results shows the incremental benefits of expanding male catch-up vaccination recommendations through age 26 years (instead of through age 21 years) and was calculated as the number of cancers averted by the expanded scenario minus the number of cancers averted by the comparison scenario.

Table 4

Base case estimates of cost-effectiveness: Discounted incremental costs, incremental quality-adjusted life years (QALY) gained, and cost effectiveness (incremental cost per QALY gained) of 9vHPV vaccination strategies.

Item estimated	Comparison scenario (females 12–26 years, males 12–21 years)	Expanded scenario (females & males, 12–26 years)
Vaccination costs ($ millions)	38,354	39,918
Direct medical costs averted ($ millions)	19,175	19,256
Number of QALYs gained	1,154,000	1,160,000
Incremental cost ($ millions)	19,180	1483
Incremental gain in QALYs	1,154,000	6000
Incremental cost per QALY gained (S/QALY)	16,600	228,800

QALY: quality-adjusted life year. All future costs and QALYs were discounted at 3% annually. The cost-effectiveness of the comparison scenario was calculated vs. no vaccination. The cost-effectiveness of the expanded scenario was calculated vs. the comparison scenario.

Table 5

Sensitivity analyses: incremental cost per quality-adjusted life year (QALY) gained by expanding HPV vaccination recommendations for all males through age 26 years when varying one or more parameter values.

Parameter varied	Cost per QALY gained by expanded scenario versus comparison scenario[a]
None (base case)	$228,800
One-way sensitivity analyses	
More QALYs lost per health outcome[b]	$146,600
Lower vaccine price per series ($372)	$159,400
Higher % of disease due to HPV vaccine types[b]	$186,800
Higher coverage scenario[b]	$207,400
Lower coverage scenario[b]	$208,800
Higher incidence rates of health outcomes[b]	$210,100
Higher medical cost per health outcome[b]	$223,100
Higher vaccine efficacy (100%)	$226,200
Lower medical cost per health outcome[b]	$235,000
Lower vaccine efficacy (85%)	$235,500
Lower incidence rates of health outcomes[b]	$243,700
Lower % of disease due to HPV vaccine types[b]	$275,100
Fewer QALYs lost per health outcome[b]	$279,600
Higher vaccine price per series ($669)	$296,800
Multi-way sensitivity analyses	
5th and 95 percentiles of Monte Carlo simulations	$137,900–$367,300

In the multi-way sensitivity analyses, for each of 5000 simulations, four sets of parameter values were varied (medical cost per case of each health outcome, number of QALYs lost per case of each health outcome, the incidence rates of the health outcomes in the absence of vaccination, and the percentages of the health outcomes attributable to the HPV vaccine types); vaccine cost, vaccination coverage, and vaccine efficacy assumptions were held at their base case values.

[a]This table shows the incremental cost effectiveness of a 9vHPV program for ages 12 through 26 years for all sexes (“expanded scenario”) compared to a 9vHPV program for females aged 12 through 26 years and males aged 12 through 21 years (“comparison scenario”).

[b]These parameters reflect sets of parameter values rather than individual values. For example, vaccination coverage includes the six age- and sex-specific probabilities of vaccination shown in Table 1. As another example, the medical cost per health outcome includes the costs of all health outcomes in the analysis. When varying a parameter set, all parameter values in the set were varied together such that all

were set to their lower bound value or all were set to their upper bound value. For example, when varying the medical cost per health outcome, the costs for all health outcomes were simultaneously set to their lower bound values or simultaneously set to their upper bound values. That is, we did not examine scenarios in which the cost per case of one outcome (e.g., cervical cancer) was set to its lower bound value while the cost per case of another health outcome (e.g., penile cancer) was set to its upper bound value. See the technical appendix for the ranges applied for the incidence rates of the health outcomes, the medical costs and number of QALYs lost per health outcome, and the percent of each health outcome attributable to the HPV vaccine types.