Impact and Cost-effectiveness of 3 Doses of 9-Valent Human Papillomavirus (HPV) Vaccine Among US Females Previously Vaccinated With 4-Valent HPV Vaccine

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Background. We estimated the potential impact and cost-effectiveness of providing 3-doses of nonavalent human papillomavirus (HPV) vaccine (9vHPV) to females aged 13–18 years who had previously completed a series of quadrivalent HPV vaccine (4vHPV), a strategy we refer to as “additional 9vHPV vaccination.”

Methods. We used 2 distinct models: (1) the simplified model, which is among the most basic of the published dynamic HPV models, and (2) the US HPV-ADVISE model, a complex, stochastic, individual-based transmission-dynamic model.

Results. When assuming no 4vHPV cross-protection, the incremental cost per quality-adjusted life-year (QALY) gained by additional 9vHPV vaccination was $146 200 in the simplified model and $108 200 in the US HPV-ADVISE model ($191 800 when assuming 4vHPV cross-protection). In 1-way sensitivity analyses in the scenario of no 4vHPV cross-protection, the incremental cost per QALY gained by additional 9vHPV vaccination exceeded $100 000 in both models. However, the results varied considerably in sensitivity and uncertainty analyses. Additional 9vHPV vaccination is likely not as efficient as many other potential HPV vaccination strategies, such as increasing primary 9vHPV vaccine coverage.

Conclusions. The average cost per QALY gained by additional 9vHPV vaccination exceeded $100 000 in both models. However, the results varied considerably in sensitivity and uncertainty analyses. Additional 9vHPV vaccination is likely not as efficient as many other potential HPV vaccination strategies, such as increasing primary 9vHPV vaccine coverage.

Keywords. human papillomavirus; vaccine; cost-effectiveness analysis; vaccine impact; disease transmission models.
females aged 13–18 years who had previously completed a 3-dose series of 4vHPV, a strategy we refer to as “additional 9vHPV vaccination.” Information on the costs and benefits of additional 9vHPV vaccination has been requested by the ACIP and other stakeholders. We focused on additional 9vHPV administration to females aged 13–18 years because HPV vaccination is typically more cost-effective in this group than in older females or in males of any age [6, 7].

METHODS

Overview of the Two Models
We used 2 distinct models of multi-type HPV transmission and disease in the United States. The two models fall on opposite ends of the complexity spectrum, as one model (the “simplified model”) is among the most basic of the published dynamic HPV models, whereas the other model (the “US HPV-ADVISE model”) is among the most comprehensive. Both models are dynamic and include indirect impacts of vaccination (ie, herd effects).

US HPV-ADVISE is a stochastic, individual-based transmission-dynamic model of multitype HPV infection and related diseases in a stable, open population. HPV-ADVISE was originally developed for use in Canada but was adapted and recalibrated using US data on sexual behavior, HPV epidemiology, and cervical cancer screening, taken from the literature and population-based data sets [8]. The model includes HPV transmission (18 HPV types, including 6/11/16/18/31/33/45/52/58), natural history of HPV-attributable diseases (anogenital warts and cancers of the cervix, anus, oropharynx, vulva, vagina, and penis), cervical and HPV screening, treatment and follow-up of detected cervical lesions, healthcare costs and quality-adjusted life-years (QALYs), and vaccination. Individuals enter the population prior to the start of sexual activity and are assigned 3 different characteristics to represent heterogeneity in the risk of HPV infection and disease: sex, level of sexual activity (4 levels, from low to high), and cervical screening behavior. For routine cervical screening scenarios, the US HPV-ADVISE model applied 5 screening behavior levels, based on the average interval between routine screening tests: 1 year (10% of women), 2 years (52%), 3–5 years (26%), and ≥5 years (6%), with a fifth and final group consisting of women who are never screened (6%). The US HPV-ADVISE model is written in the C++ programming language and was run on the supercomputer Colosse at Laval University (Quebec, Canada).

An in-depth description of US HPV-ADVISE, including cervical screening parameters, is available at: http://www.marc-brisson.net/HPVadvise-US.pdf.

The simplified model is a deterministic, dynamic model of HPV infection and disease in a stable, open population. The model updates a previous version that was used in 2011 to estimate the impact and cost-effectiveness of 4vHPV in the United States [9]. The updated model is similar in structure to the 2011 version except that it includes the additional HPV types targeted by 9vHPV. The model includes the following HPV-associated health outcomes: anogenital warts; cancers of the cervix, anus, oropharynx, vulva, vagina, and penis; cervical lesions; and recurrent respiratory papillomatosis. One of the key simplifications of the model is that cervical cancer screening is not explicitly modeled but instead is assumed to be reflected in the observed rates of cervical cancer and cervical intraepithelial neoplasia used in the model. The simplified model was developed using Excel (Microsoft, Redmond, Washington). The technical appendix (Supplementary materials) provides a detailed description of the model.

Summary of Study Question, Key Assumptions, and Perspective
The specific study question addressed was as follows: what is the cost-effectiveness of a one-year program of additional 9vHPV vaccination of females aged 13–18 years in the context of an ongoing 9vHPV program for females and males? The general approaches used to estimate the impact and cost-effectiveness of additional 9vHPV vaccination (ie, providing 3 doses of 9vHPV to those previously vaccinated with 3 doses of 4vHPV) are summarized in Table 1 and described in more detail below.

Assumptions regarding vaccine efficacy, cost, and coverage are listed in Table 2. The base-case cost of the 4vHPV and 9vHPV was $145 and $158 per dose, respectively, including administration costs [11]. All costs are reported in 2013 dollars, as described in Supplementary Table 1. Future costs and benefits were discounted at 3% annually.

Efficacy against vaccine types and duration of protection were assumed to be 95% and lifelong, respectively. In some scenarios, the US HPV-ADVISE model included cross-protection for 4vHPV. In such cases, vaccine efficacies of 46.2% against HPV 31, 28.7% against HPV 33, 7.8% against HPV 45, 18.4% against HPV 52, and 5.5% against HPV 58 were used for 4vHPV, based on a recent review [12]. Owing to the uncertainty surrounding 4vHPV efficacy against the 5 additional HPV types, all base-case results for the US HPV-ADVISE model are presented with and without cross-protection for 4vHPV.

We assumed 100% series completion rates with 4vHPV and 9vHPV (ie, everyone who initiated HPV vaccination completed the series with all 3 doses). We assumed that 10% of the entire population of 13–18-year-old girls would receive additional 9vHPV vaccination. This assumption of 10% coverage of the entire population of 13–18-year-old girls is akin to assuming that about 25% of prior 4vHPV recipients aged 13–18 years would also receive 9vHPV, given that almost 40% of 13–18-year-old girls have completed a 3-dose HPV vaccination series [2]. We used a societal perspective and included all vaccination costs, relevant direct medical costs, and gains in quality and length of life without regard to who incurred the costs or who received the benefits.

Summary of Comparison Strategies
US HPV-ADVISE Model
The US HPV-ADVISE model was used to compare the 2 following vaccination scenarios: (1) switching to 9vHPV for
both sexes from the current 4vHPV program for both sexes (comparator) and (2) switching to 9vHPV for both sexes from the current 4vHPV program for both sexes, with 1 year of additional 9vHPV use for females aged 13–18 years who had previously completed a 3-dose series of 4vHPV.

Primary 4vHPV uptake and primary 9vHPV uptake occurred among females and males aged 13–17 years. Vaccine uptake rates were modeled based on the observed age- and sex-specific 3-dose HPV vaccination coverage in the United States from 2007 to 2013 [2]. The uptake rates were assumed to remain constant at 2013 levels from 2014 onward. Under base-case assumptions, the average modeled 3-dose vaccination coverage among 13–17-year-old individuals reaches 46% and 25% in 2017 among girls and boys, respectively. The overall vaccination coverage increases until 2017 (the time it takes for the 2013 cohort of 13-year-old persons to reach 17 years of age) to 62% and 38% in females and males, respectively, by age 17 years. The 1 year of additional 9vHPV vaccination was modeled to occur in 2015, the same year as the modeled switch from 4vHPV to 9vHPV.

**Simplified Model**
To use the simplified model, we assumed that the incidence of health outcomes related to HPV 6, 11, 16, and 18 would be the same regardless of whether there was a program of additional 9vHPV vaccination. Thus, the prevention of health outcomes related to HPV 6, 11, 16, and 18 was ignored when calculating the marginal benefits of additional 9vHPV vaccination.

### Table 1. Summary of Modeling Approaches and Strategies Evaluated

| Characteristic | US HPV-ADVISE Model* | Simplified Model* |
|----------------|-----------------------|------------------|
| General approach | Switch to 9vHPV vaccination from 4vHPV vaccination, with 1-year additional 9vHPV vaccination of prior 4vHPV recipients | Provision of 9vHPV to prior 4vHPV recipients was modeled as a 1-year program to provide a hypothetical 5vHPV |
| Time horizon, y | 100 | 100 |
| Annual discount rate, % | 3 | 3 |
| Additional 9vHPV vaccination program length, y | 1 | 1 |
| Sex, age (in y) of additional 9vHPV vaccination program | Females, 13–18 | Females, 13–18 |
| Comparison scenario | Primary HPV vaccination of both sexes, ages 13–18 y; switch from 4vHPV to 9vHPV in 2015 | Primary 9vHPV receipt by both sexes, ages 12–18 y |
| Additional 9vHPV vaccination scenario | Same as comparison scenario, with additional 9vHPV vaccination among females aged 13–18 y; additional 9vHPV vaccination occurs in 2015 | Same as comparison scenario, except that coverage of females aged 13–18 y is higher in year 1; the additional females vaccinated (vs the comparison scenario) correspond to those who receive additional 9vHPV vaccination |

The “additional 9vHPV vaccination” strategy refers to administration of 3 doses of 9vHPV to females aged 13–18 years who had previously completed a 3-dose series of 4vHPV.

Abbreviations: HPV, human papillomavirus; 4vHPV, quadrivalent human papillomavirus vaccine; 5vHPV, hypothetical 5-valent human papillomavirus vaccine; 9vHPV, nonavalent human papillomavirus vaccine.

### Table 2. Human Papillomavirus (HPV) Vaccine Characteristics and Coverage Rates

| Vaccine Characteristics | Base Case Value (Range of Values Applied in Analyses) |
|-------------------------|-----------------------------------------------------|
|                         | US HPV-ADVISE | Simplified Model |
| Efficacy against vaccine types, %* | 95 | 95 [10] |
| Duration of vaccine protection | Lifelong | Lifelong |
| Cost per dose of 4vHPV (including administration), $ | 145 [11] | Not applicable |
| Cost per dose of 9vHPV (including administration), $ | 158 (145–171) [11] | 158 (145–171) [11] |
| Primary 9vHPV coverage (3 doses) among females aged 13–17 y, % | 46 (33–48) | 46 (38–80) |
| Primary 9vHPV coverage (3 doses) among males aged 13–17 y, % | 25 (16–25) | 29 (14–80) |
| Percent of all females aged 13–18 y who receive additional 9vHPV vaccination, % | 10 (10–30) | 10 (1–30) |

The “additional 9vHPV vaccination” strategy refers to administration of 3 doses of 9vHPV to females aged 13–18 years who had previously completed a 3-dose series of 4vHPV.

Abbreviations: 4vHPV, quadrivalent human papillomavirus vaccine; 9vHPV, nonavalent human papillomavirus vaccine.

* In some scenarios, the US HPV-ADVISE model included cross-protection for 4vHPV. In such cases, vaccine efficacies of 46.2% against HPV 31, 28.7% against HPV 33, 7.8% against HPV 45, 18.4% against HPV 52, and 5.5% against HPV 58 were used for 4vHPV, based on a recent review [12].

* In both models, the age- and sex-specific annual probabilities of vaccination applied in the base case were calculated based on the basis of reported HPV coverage rates in the United States as described in the technical appendices (Supplementary materials). When these age-specific probabilities of receiving vaccination were applied in the models, primary HPV vaccine 3-dose coverage rates among ages 13–17 reached a plateau of 28% for males and 46% for females in the simplified model and 25% for males and 46% for females in the US HPV-ADVISE model.
9vHPV administration. Thus, the prevention of health outcomes related to HPV 6, 11, 16, and 18 was ignored when calculating the marginal benefits of additional 9vHPV vaccination. Specifically, we examined the cost-effectiveness of a hypothetical pentavalent HPV vaccine (5vHPV) targeted against HPV 31/33/45/52/58. To approximate the scenario in which there was primary 9vHPV uptake but no additional 9vHPV vaccination, we established a comparison scenario in which 5vHPV was administered to 12-year-old girls and boys each year from years 1 through 100 of the vaccine program. In all years, females and males aged 13–18 years were also eligible for 5vHPV if not previously vaccinated. To approximate a scenario in which there was a 1-year program of additional 9vHPV vaccination, we examined an alternate scenario that was identical to the comparison scenario except that 5vHPV coverage among females aged 13–18 years was 10 percentage points higher in year 1 of the vaccine program. The additional females vaccinated in this alternate scenario versus the comparison scenario correspond to females provided with additional 9vHPV vaccination. For these additional females vaccinated, the cost per series of 5vHPV was set to $158 per dose, the assumed cost per dose of 9vHPV. As with the US HPV-ADVISE model, vaccine uptake rates in the simplified model were based on the observed age- and sex-specific 3-dose HPV vaccination coverage in the United States. Under base-case assumptions, the average modeled vaccination coverage among 13–17-year-old persons reaches 46% and 29% in 2017 among girls and boys, respectively.

Sensitivity Analyses (Both Models)

We conducted 1-way sensitivity analyses for both models, in which we varied the vaccine-related assumptions such as cost and coverage, as well as health economic parameters. Each parameter was varied one at a time from its lower bound to its upper bound value, while holding all other parameters at their base case values.

Our sensitivity analyses also included an optimistic scenario in which only 2 doses of 9vHPV would be needed for previous recipients of 4vHPV. In this 2-dose scenario, we did not vary any of our assumptions about the efficacy or duration of protection against the additional HPV types yielded by 9vHPV; rather, we assumed that the only difference in the 2-dose scenario is that the cost of the third dose of 9vHPV would not be incurred.

In addition, we conducted uncertainty analyses for the US HPV-ADVISE model. We present parametric uncertainty of the US HPV-ADVISE model predictions as the mean and 10th and 90th percentiles of simulation results, using 50 parameter sets identified through calibration (referred to as 80% uncertainty intervals [UIs]) as described in the technical appendix (Supplementary materials).

RESULTS

If no 4vHPV cross-protection was assumed, the simplified model predicted that additional 9vHPV vaccination of 950,270 females would save 2,680 QALYs at an incremental cost (vaccination costs minus averted direct medical costs) of $392 million, yielding a cost per QALY gained of $1,462,000 (Table 3). If no 4vHPV cross-protection was assumed, the US HPV-ADVISE model predicted that additional 9vHPV vaccination of 1,065,000 females would save 3,900 QALYs at an incremental cost of $422 million, yielding a cost per QALY gained of $1,082,000. When 4vHPV cross-protection was assumed, the US HPV-ADVISE model predicted that additional 9vHPV vaccination would save 2,240 QALYs at an incremental cost of $430 million, yielding a cost per QALY gained of $1,918,000.

1-Way Sensitivity Analyses

In 1-way sensitivity analyses, the cost per QALY gained by additional 9vHPV vaccination ranged from $70,300 to $182,000 in the simplified model (Table 4). The quality of life assumptions had the greatest impact on the results, as the $70,300 and $182,000 estimates were obtained when the upper bound values and lower bound values, respectively, for the number of QALYs lost per health outcome were assumed. In the 1-way sensitivity analyses for the US HPV-ADVISE model, the average cost per

Table 3. Base Case Results: Incremental Costs, Quality-Adjusted Life-Years (QALYs) Gained, and Cost per QALY Gained by Additional Nonavalent Human Papillomavirus Vaccine (9vHPV) Vaccination Among Females Aged 13–18 Years

| Model                  | Females Provided With Additional 9vHPV Vaccination, No. | Incremental Cost, $ × 10^6 (80% UI)^a | Incremental Gain in QALYs, $ × 1000 (80% UI)^b,c | Incremental Cost per QALY, $ (80% UI)^d,e |
|------------------------|---------------------------------------------------------|----------------------------------------|---------------------------------------------------|---------------------------------------------|
| Simplified model, no 4vHPV cross-protection | 950,270                                                | 392                                    | 2.68                                              | 146,200                                     |
| US HPV-ADVISE, no 4vHPV cross-protection   | 1,065,000                                              | 422 (220–685)^d                        | 3.90 (~31.1 to 29.1)^e                           | 108,200 (8700 to 390,000)^f,g               |
| US HPV-ADVISE, with 4vHPV cross-protection | 1,065,000                                              | 430 (274–580)^d                        | 2.24 (~33.8 to 40.7)^d                           | 191,800 (8400 to 60,000)^f,g                |

The "additional 9vHPV vaccination" strategy refers to administration of 3 doses of 9vHPV to females aged 13–18 years who had previously completed a 3-dose series of 4vHPV. Abbreviation: 4vHPV, quadrivalent human papillomavirus vaccine.

^a Costs reported in 2013 dollars.

^b The cost and QALY values reported in this table were discounted at 3% annually.

^c The incremental cost per QALY of a 1-year program of additional 9vHPV vaccination for females aged 13–18 years was calculated in the context of an ongoing primary 9vHPV vaccination program and was compared to the same ongoing primary 9vHPV vaccination program in which there was no additional 9vHPV vaccination.

^d The 80% uncertainty interval (UI) reflects the 10th and 90th percentiles of model results based on the 50 best-fitting parameter sets in the US HPV-ADVISE model.

^e The cost per QALY gained by additional 9vHPV vaccination was assigned a value of $0 in simulations in which there were no health benefits observed for additional 9vHPV vaccination.
### Table 4. Incremental Cost per Quality-Adjusted Life-Year (QALY) Gained by Additional Nonavalent Human Papillomavirus Vaccine (9vHPV) Vaccination Among Females Aged 13–18 Years When Varying Selected Parameter Values: Sensitivity Analyses

| Parameter Varied | Simplified Model, $ | US HPV-ADVISE Model, $(80% UI) |
|------------------|----------------------|---------------------------------|
| None (base case) | 146 200              | 108 200 (8700 to 10 800)        |
| Lower cost per 9vHPV dose ($145) | 132 400 | 97 600 (6600 to 70 600) |
| Higher cost per 9vHPV dose ($171) | 160 100 | 114 900 (9400 to 98 900) |
| Lower primary vaccine coverage scenario | 124 800 | 100 700 (7500 to 10 500) |
| Higher primary vaccine coverage scenario | 150 900 | 114 200 (8800 to 11 200) |
| Lower healthcare cost scenarioa | 155 400 | 117 300 (13 400 to 117 300) |
| Higher healthcare cost scenarioa | 135 800 | 97 700 (1200 to 100 600) |
| Lower quality of life impact scenarioa | 182 000 | 114 900 (9500 to 114 900) |
| Higher quality of life impact scenarioa | 70 300 | 101 500 (7200 to 101 500) |
| Lower additional 9vHPV coverage scenario | 144 600 | n/a |
| Higher additional 9vHPV coverage scenario | 150 000 | 109 400 (22 800 to 109 400) |
| 2-dose 9vHPV scenariob | 90 200 | 65 100 (2800 to 65 100) |

The “additional 9vHPV vaccination” strategy refers to administration of 3 doses of 9vHPV to females aged 13–18 years who had previously completed a 3-dose series of 4vHPV. Abbreviation: 4vHPV, quadrivalent human papillomavirus vaccine.

- Costs reported in 2013 dollars. Cost and quality of life assumptions are summarized in Supplementary Tables 1 and 2 in the supplementary content and described in detail in the technical appendices (Supplementary materials).
- In this optimistic scenario, we assumed that only 2 doses of 9vHPV would be needed to achieve 95% efficacy and lifetime duration of protection against the additional HPV types in 9vHPV.

QALY gained by additional 9vHPV vaccination ranged from $97 600 to $118 900 when no 4vHPV cross-protection was assumed and from $114 200 to $210 400 when 4vHPV cross-protection was assumed. When it was assumed that additional 9vHPV vaccination required only 2 doses instead of 3 doses, the cost per QALY gained was $90 200 in the simplified model and $65 100 in the US HPV-ADVISE model if no 4vHPV cross-protection was assumed and $116 700 in the US HPV-ADVISE model when 4vHPV cross-protection was assumed.

### Uncertainty Analysis (US HPV-ADVISE Model)

Under base case assumptions, the 80% uncertainty intervals for the cost per QALY gained by additional 9vHPV vaccination ranged from < $10 000 to $108 200 (8700 to 10 800) in the US HPV-ADVISE model. However, these lower bound and upper bound values were observed in model simulations in which chance fluctuations in population-level benefits of vaccination made additional 9vHPV vaccination appear much more effective or much less effective than could reasonably be expected. Further, it is important to note that the average cost-effectiveness ratio from the 50 parameter sets is robust. Although results can vary substantially from one simulation to the next, the cost-effectiveness predictions based on the average of the simulations across the 50 parameter sets are stable.

Although we examined additional 9vHPV vaccination in the context of an ongoing primary 9vHPV vaccination program, the cost-effectiveness ratios for additional 9vHPV vaccination were calculated in relation to an otherwise identical strategy without additional 9vHPV vaccination. The cost per QALY gained by additional 9vHPV vaccination might be much higher than we calculated when compared to other viable vaccination strategies, such as an intervention to increase primary 9vHPV vaccine coverage.

We made several simplifying assumptions in our analysis. One key assumption that was favorable to additional 9vHPV vaccination was that additional 9vHPV vaccination would produce the same efficacy against HPV 31/33/45/52/58 as 9vHPV vaccination among those without previous HPV vaccination. In

DISCUSSION

Previous studies have shown that a primary 9vHPV program is a cost-saving alternative to a primary 4vHPV program in the United States, on the assumption that 9vHPV costs about $13 more per dose than 4vHPV [8, 11, 13]. Not surprisingly, our analyses suggest that additional 9vHPV vaccination among previous 4vHPV recipients will be less cost-effective than primary 9vHPV uptake among those not previously vaccinated. A main reason for this relative difference in cost-effectiveness is that the incremental costs of the vaccination strategies differ. Whereas changing from a primary 4vHPV program to a primary 9vHPV program incurs a marginal cost of $13 per dose (the difference in the cost of 9vHPV and 4vHPV in our base case) per person vaccinated, a program of additional 9vHPV vaccination incurs a marginal cost of about $158 per dose per person vaccinated.

The cost per QALY gained by additional 9vHPV vaccination varied substantially in the uncertainty analyses. Under base case assumptions, the 80% uncertainty intervals for the cost per QALY gained by additional 9vHPV vaccination ranged from < $10 000 to $108 200 (8700 to 10 800) in the US HPV-ADVISE model. However, these lower bound and upper bound values were observed in model simulations in which chance fluctuations in population-level benefits of vaccination made additional 9vHPV vaccination appear much more effective or much less effective than could reasonably be expected. Further, it is important to note that the average cost-effectiveness ratio from the 50 parameter sets is robust. Although results can vary substantially from one simulation to the next, the cost-effectiveness predictions based on the average of the simulations across the 50 parameter sets are stable.

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the one study conducted of additional 9vHPV vaccination, HPV 31/33/45/52/58 geometric mean titers (GMTs) in females who received 9vHPV after completing a 3-dose 4vHPV series were 25%–63% of the GMTs of HPV vaccine–naïve females in other 9vHPV studies [5]. It is not clear whether this indicates that there would be lower efficacy against the 5 additional types. In addition, we did not include quality of life losses due to mild or moderate adverse events of vaccination. Additional 9vHPV vaccination might have appeared relatively less favorable than we estimated had we included these adverse events, as females who received 3 doses of 9vHPV after having received 4vHPV had higher rates of injection-site swelling and erythema than 9vHPV recipients who had not previously received 4vHPV [5].

We focused on additional 9vHPV vaccination of females aged 13–18 years. Estimates of the cost per QALY gained by additional vaccination of females aged >18 years or males of any age would be higher than the cost per QALY estimates we presented for females aged 13–18 years, given that male HPV vaccination is typically less cost-effective than female HPV vaccination and that HPV vaccination becomes less cost-effective as the age at vaccination increases beyond 18 years [6,7]. In the base case, we assumed lifetime duration of protection for 4vHPV and 9vHPV. This assumption was potentially unfavorable to additional 9vHPV vaccination if the duration of 4vHPV protection is not lifelong and if additional 9vHPV vaccination among previous 4vHPV recipients would increase the duration of protection against HPV 6, 11, 16, and 18. We modeled cost-effectiveness for females aged 13–18 years and did not consider any additional subgroup-specific analyses. Future modeling studies are needed to examine the impact and cost-effectiveness of additional 9vHPV vaccination among groups at higher risk of HPV-associated disease.

A main strength of our study was the use of 2 distinct HPV models. The US HPV-ADVISE model is an adaptation of the HPV-ADVISE model developed for Canada, which has been used in numerous publications [14–20]. In adapting the model to the United States, multiple parameter sets were identified that produced acceptable fits to >750 prespecified target data points, including data on demographic characteristics, sexual behavior and HPV transmission, natural history of disease, and cervical cancer screening and treatment outcomes [8]. The simplified model is an expanded version of the 4vHPV model that has been used to examine the cost-effectiveness of various HPV vaccination strategies in the United States [9,21]. Despite vast differences in model structure, both the simplified model and US HPV-ADVISE produced comparable estimates of the cost-effectiveness of additional 9vHPV vaccination in the United States. Additional limitations of the 2 models we used, as well as limitations of HPV models in general, are described in detail elsewhere [9,14–17,21,22].

We found a wide range of plausible estimates for the cost-effectiveness of additional 9vHPV vaccination. The high degree of variability in our results arises primarily because of the relatively small incremental benefits per person receiving additional 9vHPV vaccination. Because of the variability in our results, our findings do not allow for firm conclusions as to whether additional 9vHPV vaccination can be considered cost-effective by conventional standards. Similarly, we cannot rule out the possibility that additional 9vHPV vaccination might be highly cost-ineffective, with a cost per QALY approaching infinity. In the base case, we assumed that additional vaccination would consist of 3 doses of 9vHPV. Unsurprisingly, the cost per QALY gained by additional 9vHPV vaccination was lower in the optimistic scenario in which we assumed that a 2-dose schedule of additional vaccination would provide the same benefits as a 3-dose schedule. An immunogenicity study of 9vHPV 2-dose schedules is ongoing, and data from this trial might allow the inference of efficacy with a 2-dose schedule [23].

Current vaccine recommendations in the United States allow for the use of 9vHPV to continue or complete the series for those who initiated the series with another HPV vaccine [1,24]. Use of 9vHPV to continue or complete the series has also been suggested in a recent publication [25]. We did not examine such scenarios, however, and instead limited our analysis of additional 9vHPV vaccination to females who had previously completed the 3-dose series of 4vHPV.

While a primary 9vHPV program is cost-saving as compared to a primary 4vHPV program in the United States [8,11,13], the cost per QALY gained by providing additional 9vHPV vaccination for those who have already completed an HPV vaccine series likely exceeds $100 000 in the base case and is potentially much higher. Additional 9vHPV vaccination is likely not as efficient as many other potential HPV vaccination strategies, such as increasing primary 9vHPV coverage.

**Supplementary Data**

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the author, so questions or comments should be addressed to the author.

**Notes**

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