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Effectiveness and Cost-Effectiveness of Human Papillomavirus Vaccination Through Age 45 Years in the United States

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Abstract

Background: In the United States, the routine age for human papillomavirus (HPV) vaccination is 11 to 12 years, with catch-up vaccination through age 26 years for women and 21 years for men. U.S. vaccination policy on use of the 9-valent HPV vaccine in adult women and men is being reviewed.

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Reproducible Research Statement: *Study protocol*: A protocol was not published before initiation of the study. The article, Supplement, and technical appendix publicly available on Dr. Brisson's Web site (www.marc-brisson.net/HPVadvise-US.pdf) are designed to provide sufficient information for an interested reader to replicate the analysis. *Statistical code*: Not applicable. *Data set*: Not applicable; this study did not use an analytic data set but used simulated data generated via our model, HPV-ADVISE.

Current author addresses and author contributions are available at Annals.org.

Objective: To evaluate the added population-level effectiveness and cost-effectiveness of extending the current U.S. HPV vaccination program to women aged 27 to 45 years and men aged 22 to 45 years.

Design: The analysis used HPV-ADVISE (Agent-based Dynamic model for VaccInation and Screening Evaluation), an individual-based transmission dynamic model of HPV infection and associated diseases, calibrated to age-specific U.S. data.

Data Sources: Published data.

Target Population: Women aged 27 to 45 years and men aged 22 to 45 years in the United States.

Time Horizon: 100 years.

Perspective: Health care sector.

Intervention: 9-valent HPV vaccination.

Outcome Measures: HPV-associated outcomes prevented and cost-effectiveness ratios.

Results of Base-Case Analysis: The model predicts that the current U.S. HPV vaccination program will reduce the number of diagnoses of anogenital warts and cervical intraepithelial neoplasia of grade 2 or 3 and cases of cervical cancer and noncervical HPV-associated cancer by 82%, 80%, 59%, and 39%, respectively, over 100 years and is cost saving (vs. no vaccination). In contrast, extending vaccination to women and men aged 45 years is predicted to reduce these outcomes by an additional 0.4, 0.4, 0.2, and 0.2 percentage points, respectively. Vaccinating women and men up to age 30, 40, and 45 years is predicted to cost $830 000, $1 843 000, and $1 471 000, respectively, per quality-adjusted life-year gained (vs. current vaccination).

Results of Sensitivity Analysis: Results were most sensitive to assumptions about natural immunity and progression rates after infection, historical vaccination coverage, and vaccine efficacy.

Limitation: Uncertainty about the proportion of HPV-associated disease due to infections after age 26 years and about the level of herd effects from the current HPV vaccination program.

Conclusion: The current HPV vaccination program is predicted to be cost saving. Extending vaccination to older ages is predicted to produce small additional health benefits and result in substantially higher incremental cost-effectiveness ratios than the current recommendation.

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In the United States, human papillomavirus (HPV) vaccine has been recommended for routine vaccination of girls and women since 2006 and boys and men since 2011. The routine age for vaccination is 11 to 12 years, with catch-up vaccination through age 26 for women and 21 years for men (1, 2). In October 2018, the U.S. Food and Drug Administration expanded the approved age range for use of the 9-valent HPV vaccine from 9 through 26 years to 9 through 45 years in women and men (3). The approval was based on safety data as well as the inference of 9-valent vaccine efficacy among women and men from a 4-valent vaccine trial showing 88% efficacy for preventing a combined end point of vaccine-type HPV persistent infection, genital warts, and cervical and other intraepithelial

neoplasias among women aged 27 to 45 years (3). Besides safety and efficacy, another consideration for policy recommendations is the potential for incremental population-level health benefits, as well as the tradeoff between these benefits and the added costs. This study's objective was to use mathematical modeling to estimate the added population-level effectiveness and cost-effectiveness of extending the current U.S. HPV vaccination program to women aged 27 to 45 years and men aged 22 to 45 years. The aim was to inform recommendations of the U.S. Advisory Committee on Immunization Practices (ACIP) on vaccinating women and men through age 45 years (referred to in this report as *mid-adults*) against HPV.

METHODS

Vaccination Scenarios Investigated

We examined 4 extended HPV vaccination scenarios (vaccination of women and men up to ages 26, 30, 40, and 45 years) compared with the current recommendation (vaccination of girls and women aged 11 to 26 and boys and men aged 11 to 21 years).

In all the simulations performed, we reproduced historical changes in the U.S. HPV vaccination program as well as vaccination coverage (Supplement Figures 1 and 2, available at Annals.org). Vaccination coverage was modeled by calculating uptake rates (annual percentage of persons reaching series completion). For adolescents aged 13 to 17 years, we reproduced 2- and 3-dose vaccination coverage from National Immunization Survey–Teen from 2007 to 2016 (4–7) (Supplement Figure 2). For persons aged 18 years, given that no data were available, we assumed that uptake rates were the same as those for persons aged 17 years. For women aged 19 to 26 and men aged 19 to 21 years, we assumed 3-dose vaccination with uptake rates of 2.6% and 1.9%, respectively (8), and that the rates remained constant at 2016 values from 2017 onward. For the extended mid-adult vaccination strategies, we also assumed 3-dose uptake rates of 2.6% and 1.9% for women and men, respectively (see Supplement Figure 3, available at Annals.org, for overall coverage over time with mid-adult vaccination). For persons aged 9 to 17 years, we assumed 0% efficacy until the second dose. For adults, the efficacy occurs at dose 3.

Model Structure, Parameters, Calibration, and Validation

For predictions, we used the U.S. version of the HPV-ADVISE (Agent-based Dynamic model for VaccInation and Screening Evaluation) model (9–13). This model was used previously to help inform ACIP recommendations about switching from a 3- to 2-dose HPV vaccine regimen and about the introduction of the 9-valent vaccine (9–11). HPV-ADVISE is an individual-based model of HPV infection and diseases (anogenital warts and cervical, vulvar, vaginal, anal, penile, and oropharyngeal cancer). The model reproduces U.S.-specific data on demographic characteristics, sexual behavior and transmission of HPV, natural history of HPV-associated diseases, medical costs, screening and treatment of cervical lesions and cancer, and vaccination. Persons in the model enter the U.S. simulated population before sexual debut, at age 10 years, at a rate that balances age-specific death rates (our population is thus open and stable). Three risk factors related to HPV transmission and disease are attributed to each person in the model: sex, level of sexual activity (4 levels,

from low to high), and screening behavior for females (5 levels, from frequently to never screened). Transmission of HPV is modeled at the individual level through contacts between infected and susceptible persons. Transmission is thus sex- and age-specific and depends on sexual behavior (for example, number of sexual partners and mixing patterns) and HPV biology and natural history (for example, probability of transmission and natural immunity). Eighteen HPV types are modeled independently (HPV 16, 18, 6, 11, 31, 33, 45, 52, 58, 35, 39, 51, 56, 59, 66, 68, 73, and 82) with respect to transmission, infection, persistence, and disease progression. After clearance, persons may develop same-type natural immunity (that is, same-type reinfection is possible). The transmission–infection model is somewhat similar to a SIRS (susceptible–infected– recovered–susceptible) model taken at the individual level. (See Supplement Figure 4, available at Annals.org, for a visual representation of the modeled natural history.) Of importance, for mid-adult vaccination, the model assumes that HPV vaccines have no therapeutic effects. For an in-depth description of the model structure, parameters, calibration, and validation, see the technical appendix at www.marc-brisson.net/HPVadvise-US.pdf.

To account for the substantial uncertainty around sexual behavior and natural history of HPV and associated diseases, we identified several parameter sets that simultaneously fit 776 U.S. data target points for sexual behavior, HPV epidemiology, and screening taken from the literature and population-based data sets (for data sources, see the technical appendix at www.marc-brisson.net/HPVadvise-US.pdf). For model predictions, we identified the 50 best-fitting parameter sets by using least squares. The model was calibrated to prevaccination infection and disease data before 2007. As postvaccination surveillance data become available, model predictions are validated against them. (Supplement Figures 5 and 6, available at Annals.org, show examples of model fit to U.S. data on sexual behavior and prevaccination HPV epidemiology; Supplement Figure 7, available at Annals.org, shows model validation using postvaccination surveillance data.) For the economic parameters, we used previously published data on health care resource use, direct medical costs (Supplement Table 1, available at Annals.org) (8, 14–24), and quality-adjusted life-year (QALY) weights. For vaccine parameters, we used a cost per dose of $225 for the 9-valent vaccine for adults (including administration fees) and 95% vaccine efficacy with lifelong duration (Supplement Table 1). We varied key assumptions in sensitivity analyses. We also conducted sensitivity analyses on the natural history parameters. Taking into account the results of a recent meta-analysis by Beachler and colleagues (25) and considering that natural immunity was likely to have an impact on the results, we produced model simulations comparing the parameter sets with a 40% or less probability of developing natural immunity after clearance with those with a greater than 40% probability. As a result of the model calibration process, the 22 parameter sets with lower probability of developing natural immunity after clearance also have faster progression to cervical lesions than the 28 parameter sets with higher natural immunity (such as an average median time from infection to cervical intraepithelial neoplasia of grade 1 [CIN1] of 10 vs. 15 months, and average median time from infection to CIN3 of 32 vs. 36 months; see Supplement Table 2, available at Annals.org).

Before producing the model predictions for the extended-age vaccination scenarios, we conducted model validation. A key driver of the potential for additional benefits of mid-adult

vaccination is the number of new HPV infections that occur in these age groups and whether these infections lead to HPV-associated diseases. We therefore examined the cumulative proportion of the age of acquisition of HPV infection that causes cervical cancer (in the absence of vaccination and screening) (Supplement Figure 8, available at Annals.org). Our model predicts that 50% of cervical cancer cases are caused by an HPV infection acquired before the ages of 19 to 21 years, which is consistent with predictions from other models (26, 27). However, our model predicts a smaller percentage of cervical cancer cases due to HPV infections acquired after age 30 years (26, 27). We also verified that HPV-ADVISE was repro-ducing pre- and postvaccination empirical data not used in model calibration (Supplement Figures 7 and 9, available at Annals.org) (28).

Model Outcomes

For population-level effectiveness, our main outcome was the number of HPV-associated outcomes averted. For the economic analysis, our main outcome was cost per QALY gained. We performed the economic analysis by using a health care sector perspective (see Supplement Table 3, available at Annals.org, for the impact inventory for the health care perspective), a 3% annual discount rate for future costs and benefits (as used for U.S. vaccination programs [29]), and a 100-year time horizon. All costs are in 2018 U.S. dollars. Base-case model predictions are presented by using the median results from the 50 best-fitting parameter sets identified during model calibration to consider variability due to uncertainty in sexual behavior, HPV infection, and progression of HPV-related diseases.

Role of the Funding Source

Coauthors from the Centers for Disease Control and Prevention (CDC) contributed to designing the study, interpreting the findings, and editing the manuscript.

RESULTS

Under current recommendations and base-case assumptions, HPV vaccination is predicted to prevent 32 million diagnoses of anogenital warts, 13 million diagnosed cases of CIN2/3, 653 000 cervical cancer cases, and 769 000 cases of noncervical HPV-associated cancer over 100 years in the United States (Figure 1; Supplement Table 4 [available at Annals.org]; and Supplement Figure 10, A [available at Annals.org]). These numbers correspond to an 82%, 80%, 59%, and 39% reduction in anogenital wart diagnoses, diagnosed CIN2/3 cases, cervical cancer cases, and cases of noncervical HPV-associated cancer, respectively, over 100 years (Figure 1 and Supplement Table 2). In contrast, extending vaccination through age 45 years for women and men is predicted to reduce the number of anogenital wart diagnoses, diagnosed CIN2/3 cases, and cases of cervical cancer and noncervical HPV-associated cancer by an additional 0.4, 0.4, 0.2, and 0.2 percentage points, respectively (vs. current vaccination) (Figure 1; Supplement Table 4; and Supplement Figure 10, B). Supplement Figure 11 (available at Annals.org) shows the percentage of change in the incidence of the infection.

Our base-case results predict that the current recommended HPV vaccination strategy in the United States is cost saving and would produce substantial QALY gains (Table 1). On the

other hand, the median incremental cost per QALY gained of vaccinating women and men through ages 30, 40, and 45 years is $830 000, $1 843 000, and $1 471 000 (vs. current vaccination), respectively. Furthermore, 90% of model simulations produce incremental cost-effectiveness ratios (ICERs) greater than $124 000, $382 000, and $463 000 per QALY gained for vaccination through ages 30, 40, and 45 years, respectively (vs. current vaccination) (Table 1; Figure 2, *top*; and Supplement Figure 12 [available at Annals.org]).

Cost-effectiveness results are most sensitive to natural immunity after infection, rate of progression to cervical lesions, and assumptions about historical vaccination coverage and vaccine efficacy (Table 2). The 22 parameter sets (of 50) with the lowest probability of natural immunity after clearance in females and fastest progression to cervical lesions produce substantially higher benefits and lower ICERs of mid-adult vaccination (vs. the 28 parameter sets with higher natural immunity and slower progression), mainly because they reproduce a natural history in which a relatively greater proportion of CIN2/3 and cervical cancer cases are the result of infection among mid-adults (Table 2 and Figure 2, *bottom*). Lower historical coverage and vaccine efficacy produce lower mid-adult vaccination ICERs, because they induce smaller herd effects under the current vaccination strategy; thus, they provide a greater potential for benefit from mid-adult vaccination (Table 2).

DISCUSSION

Our results suggest that the current vaccination strategy in the United States will substantially reduce HPV-associated diseases and is cost saving, whereas vaccinating mid-adult women and men through age 45 years is predicted to produce small additional reductions in HPV-associated diseases and ICERs above $463 000 per QALY gained in 90% of base-case simulations (median, $1.5 million per QALY gained). The ICERs for mid-adult vaccination are highly sensitive to assumptions about the natural history of HPV, historical vaccination coverage, and vaccine efficacy.

To our knowledge, this is the first published study to examine the cost-effectiveness of vaccinating mid-adult women and men against HPV, taking into account herd effects. However, Kim and colleagues (30) examined the cost-effectiveness of vaccinating women aged 35 to 45 years against HPV by using a mathematical model without herd effects. The authors predicted that HPV vaccination for women aged 35 to 45 years with annual or biennial cervical screening would cost between $117 000 and $382 000 per QALY gained. Lower ICERs are to be expected in the absence of herd effects, because this leaves more room for additional effects from mid-adult vaccination. Our results, along with those of 4 other health economic models, were used as part of the evidence base that informed the August 2019 ACIP recommendation on expanding HPV vaccination to mid-adults. Although quantitative differences exist among model predictions, all models estimated that the cost-effectiveness of the current vaccination program in the United States ranges from cost saving to $35 000 per QALY gained. All models except 1 concluded that in the context of the existing vaccination program, expanding vaccination through age 45 years would produce relatively small additional health benefits and relatively high cost-effectiveness ratios (31).

Our analysis has 4 main strengths. First, HPV-ADVISE was calibrated to highly stratified U.S. data to represent country-specific sexual behavior, HPV epidemiology, health care resource use, and cervical cancer screening. Second, the model was validated with pre- and postvaccination data not used during the calibration process. Our short-term predictions are consistent with postvaccination data from the United States (Supplement Figure 7) (28) and Australia (32). Third, predictions were made by using the 50 best-fitting parameter sets to capture uncertainty in the natural history of HPV infection and associated diseases, as well as variability in sexual behavior data. Our cost-effectiveness predictions have large variability, indicating that the results are highly sensitive to sexual behavior and natural history assumptions. The small predicted QALY gains from mid-adult vaccination probably contribute to the large variability in the cost-effectiveness predictions, given that the QALY gains represent the denominator of the ICERs. Using only 1 or a few parameter sets might provide decision makers with a false sense of security in the results. Finally, extensive sensitivity analyses were performed.

Some limitations and several uncertainties also are related to the analysis. First, the long-term herd effects on mid-adult women and men from vaccinating younger cohorts remain uncertain. If our model overestimates the herd effects of the current program, vaccinating mid-adult women and men might produce greater benefits and lower ICERs than predicted. However, our model reproduces short-term postvaccination herd effects (Supplement Figure 7). Furthermore, we examined a scenario assuming no herd effects from teens and young adults and found that even under this extreme scenario, vaccinating 80% of women and men at age 30 years would cost $184 000 per QALY gained (Supplement Table 5, available at Annals.org). Second, considerable uncertainty also exists about the level of natural immunity after infection and the rate of progression from infection to lesions. When parameter sets with the lowest natural immunity levels and fastest progression from infection to CIN1/2/3 were used, vaccinating mid-adults through age 30 years (vs. current vaccination) produced greater benefits and lower ICERs than predictions from all parameter sets. Third, the distribution of ages at which cancer-causing infections are acquired is unknown. If causal infections occur at a later age than forecasted by our model, mid-adult vaccination might yield greater benefits and lower ICERs than predicted. However, studies have reported that new infections occurring later in life may be cleared as quickly as those occurring at a younger age; some found an equal or smaller risk for progression to CIN2+ lesions (33, 34). More work is needed to better understand the natural history of HPV and cervical cancer, particularly among adults older than 26 years. Fourth, more than half of new cervical cancer cases in the United States occur among under- or never-screened women (35). These women also may be less likely to receive mid-adult vaccination (36). If this is the case, mid-adult vaccination would provide fewer benefits and higher ICERs than predicted by our model, because we assume no relationship between screening and vaccination uptake. Finally, future vaccine prices and potential changes in vaccine schedules (such as the number of doses given) are unknown. In the sensitivity analysis, we examined a scenario in which HPV vaccination is extended to mid-adults with a 2-dose regimen (assuming that 2 and 3 doses provide the same protection). However, this scenario only reduces the ICER for vaccinating mid-adults up to 30 years to $545 900 per QALY gained.

In conclusion, our results suggest that the current vaccination program in the United States will substantially reduce HPV-associated diseases and is cost saving, whereas vaccinating mid-adult women and men through age 30, 40, or 45 years is predicted to produce small additional reductions in HPV-associated diseases and to result in substantially higher ICERs than the current program. Future research priorities should include estimating the herd effects produced by the current U.S. HPV vaccination program (that is, the reduction of HPV-associated outcomes in unvaccinated mid-adult women and men) and the percentage of HPV-associated disease burden due to acquisition of infection after age 26 years, and identifying subgroups of women and men in the United States who would benefit most from mid-adult vaccination.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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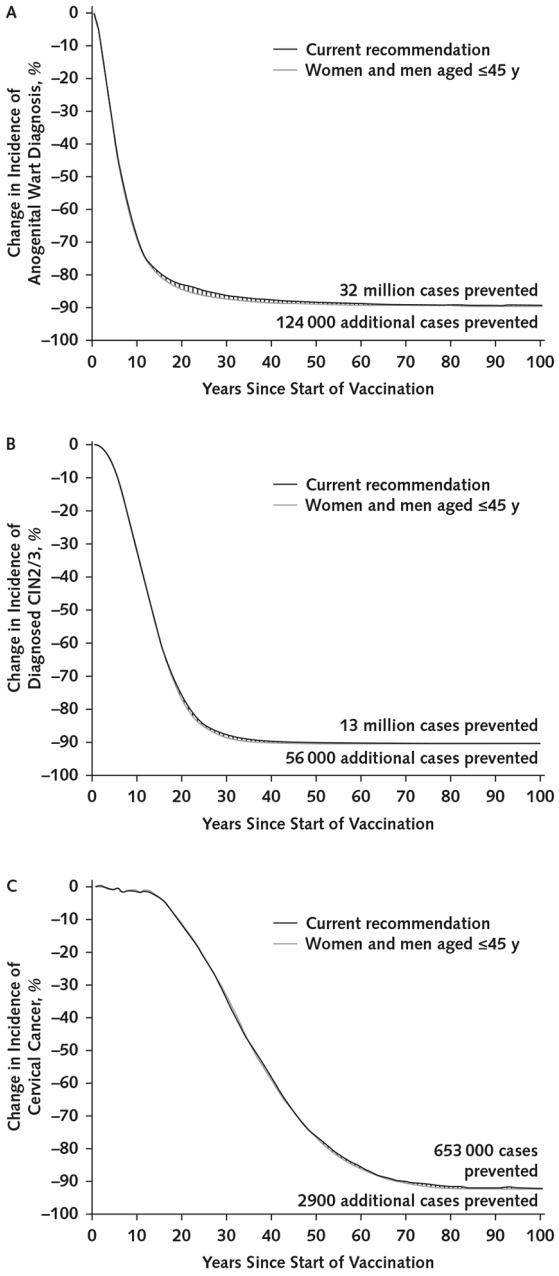

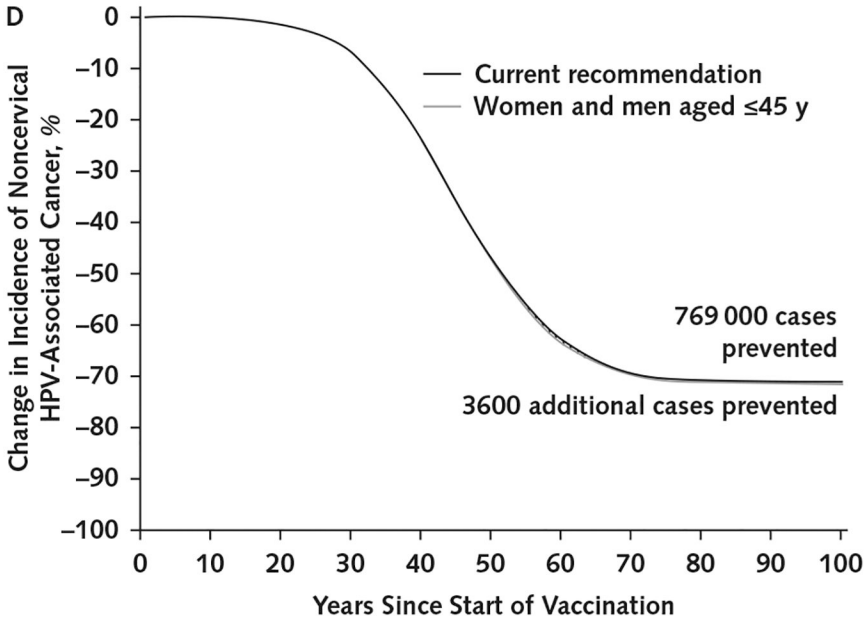

Figure 1.

Percent age of change in incidence under the current U.S. HPV vaccine recommendation and extended vaccination of women and men up to age 45 years for different outcomes. Base-case assumptions. The term *cases prevented* refers to the number of cases prevented in the United States over 100 years. Model predictions are represented as the median of the 50 best-fitting parameter sets. CIN2/3 = cervical intraepithelial neoplasia grade 2 or 3; HPV = human papillomavirus. A. Anogenital wart diagnoses (*vertical lines* between the curves represent the incremental benefit between the 2 strategies). B. Diagnosed CIN2/3. C. Cervical cancer. D. Noncervical HPV-associated cancer.

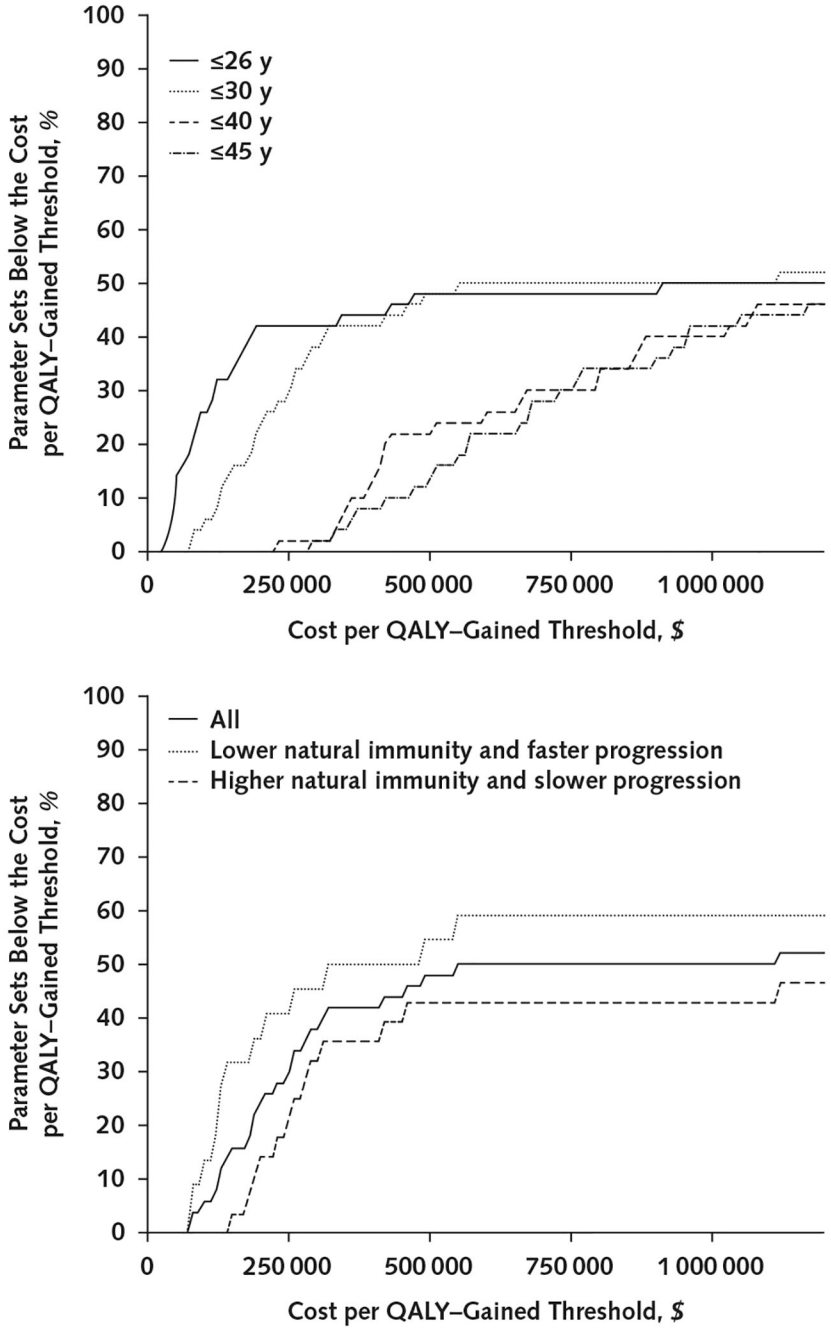

Figure 2.

Cost-effectiveness acceptability curves: percentage of the parameter sets in which the estimated incremental cost per QALY gained by mid-adult vaccination (vs. current vaccination) is equal to or less than a given cost per QALY–gained threshold.

We separated the 50 parameter sets into those with lower probability of natural immunity after clearance in women (≤40% vs. >40%) and faster progression to CIN1/2/3 (e.g., average median time from infection to CIN1, 10 vs. 15 months; average median time from infection to CIN3, 32 vs. 36 months) (22 of 50 parameter sets) and those with higher natural immunity and slower progression (28 of 50 parameter sets). CIN1/2/3 = cervical

intraepithelial neoplasia of grade 1, 2, or 3; QALY = quality-adjusted life-year. **Top.** Base-case analysis for all age scenarios of vaccination in mid-adult women and men. **Bottom.** Sensitivity analysis of natural history parameters for vaccination through age 30 years.

Table 1.

ICERs for Mid-adult Vaccination [*]

Vaccination Strategy	Additional Cost, *$ (million)* [†]	QALYs Gained, *n (thousand)* [†]	ICER vs. Current Recommendation, *$ per QALY gained* [‡]		Cost-Effectiveness Frontier ICER vs. Nondominated Strategy, *$ per QALY gained* [‡]	
			Median	10th-90th Percentile [§]	Median	10th-90th Percentile [§]
Current recommendation	0	0				
Women and men aged ≤26 y	1400	-//	-	44 000 to -	Dominated [¶]	
Women and men aged ≤30 y	3700	5	830 000	124 000 to -	830 000	124 000 to -
Women and men aged ≤40 y	10 800	6	1 843 000	382 000 to -	Extended dominated	
Women and men aged ≤45 y	15 000	10	1 471 000	463 000 to -	1 746 000 [**]	415 000 to -

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[*] Base-case assumptions: mid-adult vaccine uptake rates, 2.6% and 1.9% for women and men, respectively; 9-valent cost per dose, $205 up to age 18 years and $225 in persons aged 19 to 45 y; vaccine efficacy, 95%; discount rate, 3%; time horizon, 100 y; U.S. population. Model predictions are represented as the median of model predictions generated by the 50 best-fitting parameter sets.

[†] Versus current recommendation (the current recommendation is cost saving vs. no vaccination).

[‡] ICERs are estimated as the median over the 50 best-fitting parameters sets, not median costs divided by median QALYs gained.

[§] The 10th and 90th percentiles were generated by using the 50 best-fitting parameter sets.

[//] A dash (–) means that no median gains in QALYs could be measured because of small incremental gains and the population size of the model.

[¶] "Women and men aged ≤26 y" is more costly and does not result in measurable median gains in QALYs compared with "Current recommendation."

[**] "Women and men aged ≤40 y" is a less efficient use of resources than "Women and men aged ≤45 y" (extended dominance), because the ICER for the former exceeds that for the latter. Thus in the frontier analysis, "Women and men aged ≤45 y" is compared with "Women and men aged ≤30 y."

Table 2.

Sensitivity Analysis: ICERs for Vaccination Through Age 30 Years Versus Current Recommendation [*]

Sensitivity Analysis	ICER, *$ per QALY gained*		
	All Parameter Sets (*N* = 50)	**Lower Immunity and Faster Progression (*n* = 22)[†]**	**Higher Immunity and Slower Progression (*n* = 28)[†]**
Base case[‡]	830 000	404 000	2 308 000
Vaccination of mid-adult women only	–[§]	601 000	-
High mid-adult coverage	747 000	507 000	1 487 000
Low historical vaccination coverage[‖]	336 000	318 000	410 000
Stopping mid-adult catch-up after 40 y	616 000	296 000	1 697 000
Switching to a 2-dose regimen for all ages	546 000	261 000	1 492 000
Low vaccine efficacy[¶]	481 000	366 000	835 000
Vaccination cost per dose[**]			
$176	644 000	310 000	1 775 000
$235	867 000	423 000	2 417 000
Maximum health care costs[††]	821 000	395 000	2 253 000
Maximum disease burden[††]	753 000	317 000	1 211 000
Disutility in cervical cancersurvivors[‡‡]	499 000	276 000	658 000
Discount rate			
1.5%	479 000	307 000	699 000
0%	327 000	275 000	389 000
50-ytime horizon	932 000	449 000	2 054 000

CDC = Centers for Disease Control and Prevention; CIN1/2/3 = cervical intraepithelial neoplasia grades 1, 2, and 3; HPV = human papillomavirus; HPV-ADVISE = Agent-based Dynamic model for VaccInation and Screening Evaluation; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

[*] Discount rate, 3%; time horizon, 100 y. Model predictions are represented as the median estimate generated by the 50 best-fitting parameter sets.

[†] We separated the 50 parameter sets into the parameter sets with lower probability of natural immunity after clearance in women (≤40% vs. >40%, on the basis of Beachler and colleagues [25]) and faster progression to CIN1/2/3 (e.g., average median time from infection to CIN1, 10 vs. 15 mo; average median time from infection to CIN3, 32 vs. 36 mo) (22 of 50 parameter sets) and those with higher natural immunity and slower progression (28 of 50 parameter sets).

[‡] Base case: mid-adult vaccine uptake rates, 2.6% and 1.9% for women and men, respectively; 9-valent cost per dose, $225 in persons aged 19 to 45 y; vaccine efficacy, 95%.

[§] A dash (–) means that no median gains in QALYs could be measured because of small incremental gains and the population size of the model.

‖75% of base-case vaccination uptake rates for historical coverage.

¶Vaccine efficacy is assumed to be 85% (vs. base-case vaccine efficacy of 95%) against persistent infections for all HPV types included in the vaccine.

**Vaccination costs are based on the CDC vaccine price list as of 1 August 2018 (www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/index.html) and include the cost of vaccine administration.

††Maximum estimates from the U.S. literature (see Supplement Table 1[available at Annals.org] for health care costs used and the HPV-ADVISE technical appendix [available at www.marc-brisson.net/HPVadvise-US.pdf] for detailed QALY weights and case fatality).

‡‡We assumed an average 0.24 annual disutility (vs. none in the base case) for life after cervical cancer survival, on the basis of Elbasha and colleagues (22).

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