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Cost-Effectiveness of Human Papillomavirus Vaccination and Cervical Cancer Screening in Women Older Than 30 Years in the United States

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Background: Women older than 30 years are the main beneficiaries of improved cervical cancer screening with human papillomavirus (HPV) DNA testing. The role of vaccination against HPV types 16 and 18, which is recommended routinely for preadolescent girls, is unclear in this age group.

Objective: To assess the health and economic outcomes of HPV vaccination in older U.S. women.

Design: Cost-effectiveness analysis with an empirically calibrated model.

Data Sources: Published literature.

Target Population: U.S. women aged 35 to 45 years.

Time Horizon: Lifetime.

Perspective: Societal.

Intervention: HPV vaccination added to screening strategies that differ by test (cytology or HPV DNA testing), frequency, and start age versus screening alone.

Outcome Measures: Incremental cost-effectiveness ratios (2006 U.S. dollars per quality-adjusted life-year [QALY] gained).

Results of Base-Case Analysis: In the context of annual or biennial screening, HPV vaccination of women aged 35 to 45 years ranged from $116 950 to $272 350 per QALY for cytology with HPV DNA testing for triage of equivocal results and from $193 690 to $381 590 per QALY for combined cytology and HPV DNA testing, depending on age and screening frequency.

Results of Sensitivity Analysis: The probability of HPV vaccination being cost-effective for women aged 35 to 45 years was 0% with annual or biennial screening and less than 5% with triennial screening, at thresholds considered good value for money.

Limitation: The natural history of the disease and the efficacy of the vaccine in older women are uncertain.

Conclusion: Given currently available information, the effectiveness of HPV vaccination for women older than 30 years who are screened seems to be small. Compared with current screening that uses sensitive HPV DNA testing, HPV vaccination is associated with less attractive cost-effectiveness ratios in this population than those for other, well-accepted interventions in the United States.

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Organized screening is widely credited with reducing the incidence of cervical cancer, and women in the United States today face an average lifetime risk of 0.7% (1). With the availability of human papillomavirus (HPV) DNA testing, clinical guidelines have been revised to provide several screening options, including cytology every 1 to 3 years with HPV DNA testing for triage of equivocal cytology results and HPV DNA testing in combination with cytology every 2 to 3 years for women older than 30 years (2–4). Previous analyses (5, 6) have reported that these strategies provide greater protection against cervical cancer than cytology-only strategies and good value for resources compared with other public health interventions. As technologies evolve, it is imperative to assess the comparative benefits, risks, and costs of all options in an objective analysis. This principle applies to newer screening tests; novel diagnostic algorithms for women who screen positive; and evolving technologies for primary prevention, such as the HPV vaccine.

In 2006, the U.S. Food and Drug Administration licensed a quadrivalent vaccine that protects against HPV types 16 and 18, 2 of the most common types that cause 70% of cervical cancer, and types 6 and 11, which cause more than 90% of genital warts (7, 8). A bivalent vaccine that targets only HPV types 16 and 18 is expected to be licensed soon. Because of the high efficacy of the vaccines among women without previous exposure to these types (9–13), current guidelines for HPV vaccination in the United States have prioritized covering preadolescent girls before sexual debut (age 11 to 12 years, and as early as 9 years) (14, 15). The recommended upper age limit for a catch-up program, however, has been debated and ranges from 18 (14) to 26 (15) years. In a recent cost-effectiveness analysis (16), a policy of catch-up vaccination in women older than 21 years generally does not provide as much value for money as vaccination of younger girls, even under favorable assumptions of the vaccine.

See also:

Print
Editors' Notes 539
Summary for Patients I-36

Web-Only
Appendix
Appendix Tables
Appendix Figures
Conversion of graphics into slides

Women older than 30 years have been the primary target for improved screening with HPV DNA testing, but they may soon have access to the HPV vaccine. Although they have a greater chance of previous HPV infection than adolescent girls, no commercially available tests can reliably distinguish previous infection. As manufacturers of the vaccines seek approval for vaccinating older women, discussion is mounting about the benefit and costs of vaccinating women up to age 45 years. If approved, current HPV vaccination guidelines will need to be reconsidered, and potentially revised, to provide scientifically based guidance for this population.

Evaluating cervical cancer prevention strategies presents particular challenges because of the long duration of cervical carcinogenesis, the uncertainty in a disease process that is largely unobservable, and the different time points along the disease spectrum at which interventions are applied. Furthermore, clinical studies that compare screening strategies or assess vaccine efficacy mostly rely on surrogate end points, and the observation of these interventions on disease outcomes is decades away. Because of this uncertainty and the inability to compare all potential strategies head-to-head, disease simulation models that synthesize the best available data and ensure consistency with epidemiologic observations are valuable for estimating long-term outcomes of health interventions in a population. When used in a decision-analytic framework, model-based analyses can help assess the incremental benefits and cost-effectiveness of different interventions and inform policy decisions that are being made in the absence of complete information. In anticipation of potential vaccine approval for women older than 30 years, we used an empirically calibrated model to conduct a comparative cost-effectiveness analysis of HPV vaccination of U.S. women up to 45 years of age in the context of available cervical cancer screening.

Context

The U.S. Food and Drug Administration may soon approve vaccination against human papillomavirus (HPV) for women older than 30 years, but the cost-effectiveness of vaccination in this age group is unknown.

Contribution

This analysis assessed the cost-effectiveness of HPV vaccination for women aged 35 to 45 years. It found that vaccination ranged from $116 950 to $381 590 per quality-adjusted life-year gained across various assumptions about how clinicians would screen for cervical cancer and HPV infection in addition to vaccination.

Implication

HPV vaccination for women aged 35 to 45 years costs more per quality-adjusted life-year gained than other well-accepted health care interventions in the United States.

—The Editors

METHODS

Model Overview

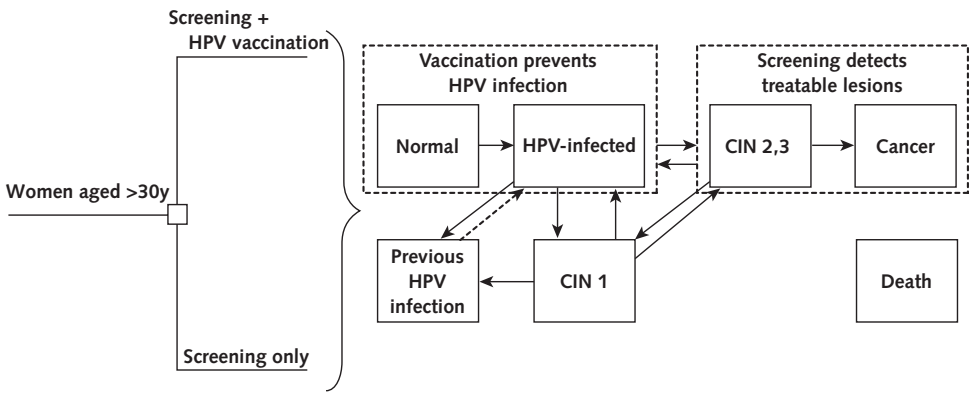
We used a previously developed, individual-based (first-order) Monte Carlo simulation model of the natural history of HPV and cervical disease, as well as primary and secondary preventive interventions (16–18). The model comprises mutually exclusive health states through which women transition over time from entry into the model until death (**Figure 1**). The simulation begins with 9-year-old healthy girls who, each month, can acquire HPV infection, categorized as HPV-16, HPV-18, other high-risk types, and low-risk types. Those with HPV infection can develop precancerous lesions, categorized as cervical intraepithelial neoplasia grade 1 (CIN 1) or grade 2 or 3, and those with CIN 2,3 may develop invasive cancer. Women can clear their HPV infection or lesion, after which they develop a degree of natural immunity that effectively reduces their future risk for same-type infections. Cancer states are stratified by stage (local, regional, or distant) and detection status (undetected, symptom-detected, or screen-detected). Death can occur from all-cause mortality at every health state, with excess cancer-specific mortality from cancer states depending on stage of cancer. Our model accommodates complex cervical cancer prevention strategies and tracks each woman's history (such as vaccination, screening, treatment, and past abnormalities) and resource use.

Using data from epidemiologic studies and cancer registries, we established initial input parameter values for the natural history model (without intervention). Using a likelihood-based approach, we then calibrated our model to fit to empirical data, including age-specific HPV prevalence, age-specific cervical cancer incidence, and HPV type distribution among women with lesions and cancer, primarily from the United States (19–25). We synthesized data from clinical studies and controlled trials to accurately reflect the performance of screening tests and the HPV vaccine (4, 9–13, 26–28). The model structure, parameterization, and calibration are described elsewhere (16–17), and the **Appendix** (available at www.annals.org) provides the data we used for our analysis.

Strategies

We evaluated the cost-effectiveness of vaccinating women of a particular age (for example, 35 years) who had been participating in a specific screening strategy (such as biennial cytology). We intended to simulate a situation in which women would continue with the same screening strategy before and after vaccination. We included screening strategies that are recommended in clinical guidelines, including cytology with HPV DNA testing for triage of equivocal results (cytology with HPV triage) and combined cytology and HPV DNA testing after age 30 years, annu-

Figure 1. **Decision tree and cervical cancer natural history model.**



Women older than 30 years who participate in the U.S. screening program may get vaccinated or continue with screening only. At the start of the analysis, women may reside in any of the mutually exclusive, collectively exhaustive health states denoted by the boxes. Incidence and progression of HPV infection, CIN 1, and CIN 2,3 depend on age and HPV type. Women with previous HPV infection face reduced risks for subsequent type-specific HPV infection because of natural immunity (*dashed arrow*). Not all health states and transitions are shown. CIN = cervical intraepithelial neoplasia (grade 1 or grade 2 or 3); HPV = human papillomavirus.

Table 1. **Cervical Cancer Screening and Cost Parameters**

Variable (Reference)	Input Value
Test characteristics, %	
Cytology (26–28)*	
Sensitivity (CIN 1/CIN 2,3)	70/80
Specificity	95
HPV DNA test (4, 28)†	
Sensitivity (CIN 1/CIN 2,3)	83/93
Specificity	93
Costs, $‡	
HPV vaccine per dose (32–35)§	
Vaccine and wastage	134
Supplies and administration	9
Patient time and transport	24
Screening test (5, 36–39)	
Cytology	32
HPV DNA test‖	49
Office visit	27
Patient time and transport	26
Diagnostic follow-up (5, 36–38)	
Colposcopy	364
Biopsy	53
Office visit	61
Patient time and transport	51
Treatment for CIN 2,3 (5)¶	3438
Treatment for cervical cancer (5)¶	
Local invasive cancer	26 540
Regional invasive cancer	28 430
Distant invasive cancer	45 540

CIN = cervical intraepithelial neoplasia (grade 1 or grade 2 or 3); HPV = human papillomavirus.
* Sensitivity for detecting CIN 2,3 was calculated as the weighted average of values from 2 recent studies reporting conventional and liquid-based cytology sensitivities using an ASCUS+ threshold (27, 28).
† HPV DNA testing is assumed to be 100% sensitive for the presence and 100% specific for the absence of high-risk HPV types. When this assumption is made, the model generates an implied clinical sensitivity for detecting CIN 1 and CIN 2,3 of 83.0% and 93.0%, respectively, and specificity of 93.0%.
‡ Costs were inflation-adjusted to constant 2006 U.S. dollars by using the medical component of the Consumer Price Index (40).
§ Vaccination assumes 3 doses; the cost per vaccinated individual is $500.
‖ Hybrid Capture II (Qiagen, Valencia, California).
¶ Treatment costs include the cost of procedures, office visits, and the woman's time and transportation.

ally and biennially (2–4). To account for women with less frequent or variable screening histories, we included a scenario that reflects overall current screening practice. We restricted this analysis to those who have ever been screened and assumed 53% are screened annually, 17% every 2 years, 11% every 3 years, and 14% every 5 years (29–31).

We then evaluated a broader array of options that confront women of a particular age (for example, 35 years). We intended to simulate a situation in which these women would consider all available screening options, with and without vaccination. We included currently recommended screening strategies (cytology with HPV triage, with or without a switch to combined cytology and HPV DNA testing at older ages) and promising strategies being evaluated in clinical studies (HPV DNA testing with cytology triage of HPV-positive women at older ages). For all strategies, we assumed women are screened by using cytology with HPV triage before facing the full range of new options.

Vaccination involved the full 3-dose series administered to women at 35, 40, or 45 years. In the base-case analysis, we assumed 100% lifetime efficacy against HPV-16 and HPV-18 among women without previous exposure to these specific types but explored the effect of lower efficacy and waning immunity in sensitivity analyses.

Analysis

We expressed health benefits as reductions in lifetime risk for cervical cancer and gains in quality-adjusted life-years (QALYs), which reflect both morbidity (diminished quality of life due to cervical cancer) and mortality secondary to cervical cancer. Lifetime costs (in 2006 U.S. dollars) included direct medical costs associated with screening, diagnosis, and treatment (such as tests, procedures, and hos-

pitalizations) and vaccination (such as 3 doses at $120 per dose, wastage, supplies, and administration) (**Table 1**) (4, 5, 26–28, 32–40). We included direct nonmedical costs, such as patient time and transportation, for all strategies.

We adopted a societal perspective and discounted costs and benefits by 3% annually (41). After eliminating strategies that were more costly and less effective (strongly dominated) or less costly and less cost-effective (weakly dominated) than an alternative strategy, we calculated incremental cost-effectiveness ratios as the additional cost divided by the additional health benefit associated with one strategy compared with the next less costly strategy.

We conducted sensitivity analyses to explore how results were influenced by uncertainties, such as screening performance, vaccine efficacy and duration, and vaccine cost. We conducted a probabilistic sensitivity analysis by using 50 good-fitting parameter sets.

Role of the Funding Source

This study was supported by the National Cancer Institute, and in part by the Centers for Disease Control and Prevention and the American Cancer Society. The funding sources had no involvement in the design of the study; collection, analysis, or interpretation of the data; or preparation, review, or approval of the finished manuscript.

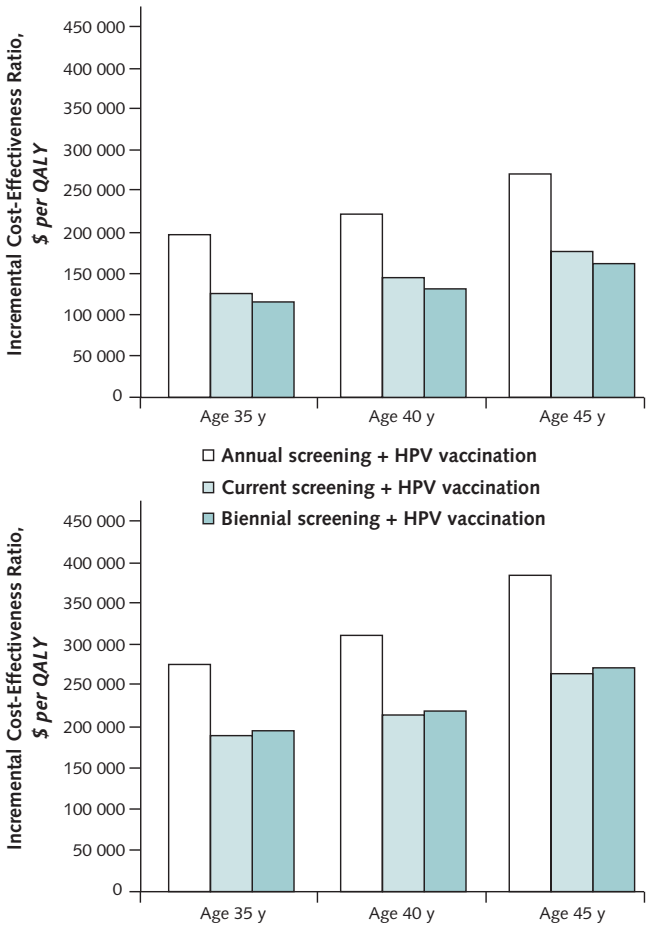
RESULTS

Vaccination of Screened Women

Adding HPV vaccination to screening resulted in gains in quality-adjusted life expectancy, although the incremental gains diminished with age. For example, women who had been screened biennially by using cytology with HPV DNA testing for triage of equivocal results gained 0.0040 QALY (35 hours) when vaccinated at age 35 years and 0.0029 QALY (26 hours) when vaccinated at age 45 years; these results correspond to additional reductions in lifetime cancer risk of 5.4% and 4.2%, respectively. Incremental benefits of vaccination were lower when screening was annual or involved a switch to combined cytology and HPV DNA testing after age 30 years.

Among women screened annually or biennially using cytology with HPV triage, adding vaccination ranged from $116 950 to $272 350 per QALY gained compared with the corresponding strategies of screening without vaccination, depending on age and screening frequency (**Figure 2**, *top*). For women who switched to combined cytology and HPV DNA testing after age 30 years, the incremental cost-effectiveness ratios were less attractive (higher), ranging from $193 690 to $381 590 per QALY (**Figure 2**, *bottom*). In the context of current U.S. screening patterns, in which women are screened with variable frequency, adding vaccination exceeded $125 000 per QALY regardless of vaccination age or screening strategy. For all scenarios evaluated, the incremental cost-effectiveness of adding vaccination to screening was less attractive (had higher ratios) at older ages.

Figure 2. **Cost-effectiveness of HPV vaccination of screened women, by screening algorithm.**



Ratios for each strategy with vaccination are calculated compared with the corresponding screening strategy without vaccination. All ratios are expressed as cost, in 2006 U.S. dollars, per QALY. HPV = human papillomavirus; QALY = quality-adjusted life-year. **Top.** Ratios for HPV vaccination when screening involves cytology with HPV DNA testing for triage of equivocal results. **Bottom.** Ratios for HPV vaccination when screening involves a switch to combined cytology and HPV DNA testing after age 30 years.

Vaccination and Screening Strategies

When we compared the health and economic outcomes of a range of cervical cancer prevention options facing older women (different tests and frequencies, with and without vaccination), most vaccination strategies were either less efficient (strongly or weakly dominated) than strategies that involved screening alone or had cost-effectiveness ratios above $100 000 per QALY (**Table 2**). For example, the cost-effectiveness of adding vaccination to annual screening for women aged 35 years ranged from nearly $200 000 per QALY (cytology with HPV triage over their lifetime) to more than $400 000 per QALY (cytology with a switch to combined testing). At 2- to 3-year screening intervals, vaccination strategies were either weakly dominated or exceeded $130 000 per QALY; ratios

Table 2. **Cost-Effectiveness of HPV Vaccination and Screening Strategies, by Age and Screening Frequency**

Strategy*	Incremental Cost-Effectiveness Ratio by Screening Frequency, *$ per QALY*†				
	1 Year	2 Years	3 Years	4 Years	5 Years
Women aged 35 y					
Cytology with HPV triage and no vaccination	–	–	–	–	–
Cytology with HPV triage and vaccination	198 362	Not cost-effective	Not cost-effective	Not cost-effective	Not cost-effective
Combined cytology and HPV testing and no vaccination	Not cost-effective	99 315	51 319	35 996	28 366
Combined cytology and HPV testing and vaccination	433 385	193 568	131 832	99 905	78 751
Women aged 45 y					
Cytology with HPV triage and no vaccination	–	–	–	–	–
Cytology with HPV triage and vaccination	272 346	Not cost-effective	Not cost-effective	Dominated	Dominated
Combined cytology and HPV testing and no vaccination	Not cost-effective	102 703	53 631	38 851	27 517
Combined cytology and HPV testing and vaccination	448 989	269 217	186 886	140 658	108 416

HPV = human papillomavirus; QALY = quality-adjusted life-year.
* All screening tests include cytology with HPV DNA testing for triage of equivocal results up to the current age, with either continued cytology screening with HPV triage or switch to combined cytology and HPV DNA testing past the current age. Strategies are listed in order of increasing lifetime costs.
† Strategies that are "dominated" are more costly and less effective than another strategy; strategies that are "not cost-effective" are less costly but less cost-effective than another strategy. Costs are expressed in 2006 U.S. dollars.

fell below $100 000 per QALY with less frequent screening. For women 45 years of age, these ratios were even less attractive. When we considered HPV DNA testing with cytology triage for HPV-positive results instead of combined cytology and HPV DNA testing for screening after vaccination (data not shown), the ratios for vaccination strategies were marginally more attractive but the overall qualitative results were similar.

Sensitivity Analyses

Our general results were not influenced by plausible changes in screening test performance, screening and diagnostic follow-up costs, or the discount rate. Less favorable assumptions about vaccine properties, such as efficacy and duration of protection, resulted in higher (less attractive) cost-effectiveness ratios for the vaccination strategies. For example, when we reduced efficacy to 70% among those not previously exposed to the vaccine types, cost-effectiveness ratios associated with HPV vaccination increased by about 50% across all ages and screening scenarios and exceeded $400 000 per QALY for women aged 45 years. Similarly, cost-effectiveness ratios exceeded $400 000 and $200 000 per QALY for all ages when vaccine protection waned after 5 and 10 years, respectively.

Varying the cost of vaccination modestly influenced the results. When the cost per vaccinated woman was decreased to $250 (corresponding to a cost per dose of $70), adding vaccination to cytology with HPV triage for women aged 35 years decreased to $54 000 per QALY (biennial screening) and $92 000 per QALY (annual screening). When the cost per vaccinated woman was increased to $750, resembling a scenario in which the current costs are underestimated or a booster dose is required, the cost-effectiveness ratios ranged from $180 000 to $600 000 per QALY, depending on age, screening method, and frequency.

We conducted a probabilistic sensitivity analysis that used 50 parameter sets with good fit to the epidemiologic data and estimated the probability that adding vaccination to screening is cost-effective according to lower- and upper-bound cost-effectiveness thresholds. For women 35 years of age, adding vaccination to annual or biennial screening with combined cytology and HPV DNA testing resulted in cost-effectiveness ratios that exceeded $100 000 per QALY in all 50 simulations. Adding vaccination yielded ratios greater than $100 000 per QALY in 96% and 72% of simulations that involved 3-year and 4-year screening, respectively, and none of these scenarios resulted in ratios that were less than $50 000 per QALY across the 50 simulations. Across these same frequencies, 100% of simulations resulted in ratios higher than $100 000 per QALY for vaccination and screening of women 45 years of age compared with screening alone.

DISCUSSION

The availability of accurate HPV diagnostics, new screening strategies, and a preventive vaccine against HPV-16 and HPV-18 holds great promise for cervical cancer prevention in the United States. Model-based decision analyses of how best to use these new options alone or synergistically can provide insight for policy deliberations and professional guidelines and aid in identifying research priorities. Although previous analyses (16, 42, 43) have evaluated the HPV vaccine in the context of catch-up programs up to age 26 years, to our knowledge, our study is the first to assess routine use of the vaccine in older U.S. women. Consistent with the consensus that the value of HPV vaccination diminishes with increasing age of vaccination (16, 43–45), we found that HPV vaccination provides nominal benefits in the context of current screening recommendations and practice among women aged 35 to 45 years. Considering that the lifetime risk for cervical

cancer in the United States is less than 1% (1), the absolute risk reductions that HPV vaccination provides this age group are low. Likewise, the incremental cost-effectiveness ratios associated with adding vaccination to screening, given currently available information, exceeded $100 000 per QALY in most instances. These results were stable even when we evaluated new, promising screening algorithms that used HPV DNA testing with cytology triage, which is expected to have a higher positive predictive value than cytology alone in a vaccinated population (46).

No universal criterion defines a threshold cost-effectiveness ratio below which an intervention is considered good value for money. Unlike some countries, the United States has not adopted an absolute cost-effectiveness threshold. Instead, informal heuristics have been cited, including the cost-effectiveness ratio associated with renal dialysis through the Medicare entitlement program (which ranges from $55 000 to $108 500 per QALY [47–50]) and those associated with such widely adopted interventions as diabetes care, knee replacement, and mammography screening (all generally below $100 000, and often below $50 000, per QALY [51–53]). Shiroiwa and colleagues (54) measured thresholds in selected countries and estimated a willingness-to-pay threshold per QALY of $62 000 in the United States. On the basis of this information we feel that $50 000 to $100 000 per QALY gained is a reasonable benchmark for cost-effectiveness in the United States, although societal willingness to pay more than $100 000 per QALY may be based on other considerations. Using this threshold range, our results suggest that HPV vaccination in older women does not represent good value for resources expended, which implies that more health can be gained by investing in alternative interventions, such as screening previously unscreened women.

The vaccine's effect in an older population is influenced in part by the level of exposure to the vaccine-targeted HPV types. Clinical trials (55, 56) report that most female participants up to age 26 years were not exposed to any vaccine type at enrollment and would therefore stand to benefit completely from the vaccine; however, because the trials excluded women with more than 4 sexual partners, it is unclear whether the sample is representative of the general U.S. population with respect to exposure status or how these data extend to women up to 45 years of age. To explore the uncertainty in the natural history of the disease, including previous exposure to HPV, we conducted a probabilistic analysis with 50 distinct parameter sets that fit well to the empirical data on HPV and cervical disease in the United States. The probability of HPV vaccination being cost-effective for screened women aged 35 to 45 years was low at a threshold of $100 000 per QALY, even at extended screening intervals.

Our analysis captures the average health and economic effect of the interventions over an entire population and is intended primarily to inform the comparative effectiveness of health services, a priority recently highlighted in the American Recovery and Reinvestment Act of 2009 (57). Despite its policy focus, our analysis can also provide insights into clinical decision making for women with particular screening histories who may benefit differentially from vaccination and screening. Specifically, we provide estimates of the potential added value of vaccination compared with the counterfactual scenario (continuation of screening without vaccination) and with new strategies involving revised screening algorithms and testing options (such as HPV DNA testing with cytology triage). Although we found that, on average, HPV vaccination does not provide good value among older women from a population perspective, some women may benefit from the vaccine (such as the 1% to 2% of women with no sexual partner by age 35 to 45 years who may then become sexually active). Because no test can conclusively specify a woman's infection history, decisions about vaccination should involve information about her risk for HPV exposure (number of sexual partners) and particular screening history (adherence and frequency), as well as her preferences.

Our study has limitations, including uncertainty in the natural history of cervical disease, particularly among older women. As noted by Goldie and colleagues (58), whether an HPV infection detected later in life is newly acquired or reemergent, having been acquired years before, will influence the vaccine's effect; however, this determination is subject to much uncertainty and debate. Our probabilistic analysis attempts to explore plausible scenarios of natural history uncertainties while maintaining a good fit to the data available from empirical studies. Also, vaccine efficacy data that use HPV infection and cervical disease end points are available for only 5 years and have only recently been presented for older women (59, 60). In our analysis, we assumed that women up to age 45 years fully adhered to the 3-dose vaccine series and that the vaccine conferred complete lifelong protection on those not previously exposed to the vaccine types. Given these optimistic assumptions, our results are a best-case scenario; to the extent that efficacy is lower or of shorter duration, cost-effectiveness ratios for vaccination strategies may be even less attractive than those we present.

We did not consider the effects of reduced HPV transmission attributable to vaccinating older women and therefore excluded herd immunity benefits. We also did not include the vaccine's potential cross-protective effects against other high-risk HPV infections or the benefits related to other HPV-associated conditions, such as other anogenital, oral, and oropharyngeal cancer; the natural histories of these conditions and the contribution of HPV types 16 and 18 are far less certain, and vaccine efficacy data on these outcomes are limited. Previous cost-effectiveness studies that included some or all of these factors (16, 61) suggest that their inclusion does not offset the diminished efficacy among older women.

We did not incorporate the risks for adverse events or diminished quality of life from vaccination (such as side effects) or screening (such as overtreatment). Even though small risks for minor adverse events from either intervention will probably be outweighed by the overall average benefits at the population level, studies should incorporate all risks and costs associated with a vaccination program as data become available. We also assumed that a woman's screening interval would not change after vaccination; because a woman's particular history of vaccine-type HPV exposure—and therefore her level of vaccine protection—cannot be known with certainty in clinical practice, we assumed that extending a woman's screening interval without more information would be unjustifiable. Finally, this analysis is not relevant for women who have never been screened, who may represent up to 5% of screening-eligible women in the United States (29–31). Both vaccination and screening will probably have beneficial effects in this population, but the magnitude of benefit from either approach will depend on such important factors as previous exposure to vaccine-targeted HPV types and adherence to the 3 necessary doses and screening visits.

In summary, our results indicate that HPV vaccination of older women who participate in the U.S. screening program provides much lower benefits than vaccination of preadolescent girls and does not provide good health value for the resources invested, compared with well-accepted health interventions in the United States. This analysis should be revisited as more information becomes available on the natural history of HPV and the vaccine's effect in older women.

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Appendix: First-Order Monte Carlo Simulation Model

Details of the individual-based (first-order) Monte Carlo simulation model structure, assumptions, and calibration are documented elsewhere (16–17). In brief, the model simulates individual women from age 9 until death, reflects detailed heterogeneities (such as history of screening and treatment), and tracks individual-level expenditures. The model is stochastic and is therefore inherently able to capture variability in outcomes as well as uncertainty in the parameters. All HPV types are represented, categorized as HPV-16, HPV-18, other (non–HPV-16 or HPV-18) high-risk types, and low-risk types. Incidence of HPV is a function of age and individual-level characteristics but does not explicitly change over time in response to sexual activity and population prevalence. We wrote and solved equations for the model in C++.

Model Calibration

Our model calibration is an extensive, iterative, and evolving process that requires comprehensive literature reviews, synthesis of primary and secondary data, consultations with epidemiologists and clinical experts, and explorations of the influence of uncertain parameters and assumptions in the model. The purpose of multiparameter calibration is to identify candidate sets of parameter values that, when used simultaneously in the model, achieve good fit to data that are observed in the real world.

We established baseline input parameter values for the natural history model by using data from epidemiologic studies in the published literature (1, 62–79). Because we cannot observe the entire natural course of cervical cancer through empirical studies, we leveraged multiple epidemiologic studies that investigated different phases along the disease spectrum to either directly or indirectly inform our model inputs. The parameter search ranges (**Appendix Table 1**) are purposefully wide to accommodate varied data sources from different populations and study designs.

We performed more than 1 million model simulations in the absence of any vaccination or screening intervention. For each simulation, we randomly selected 1 value for each of the uncertain parameters from a uniform distribution over the identified plausible range, creating a unique natural history parameter set. For each parameter set, we scored model outcomes according to their overall fit with calibration targets that were based primarily on data from epidemiologic studies and cancer registries in the United States (**Appendix Table 2**) (19–25).

We specified likelihood functions for all calibration targets and assumed that each followed an independent normal distribution. For each of the 1 million parameter sets, we computed a composite goodness-of-fit score by summing over the individual log likelihood measures of all targets. We selected the best-fitting set for the base-case analysis and a sample of 50 good-fitting sets for probabilistic sensitivity analysis.

Appendix Table 3 provides information on the types of data that we used in the analysis, including those used to inform baseline parameter values, parameter ranges, calibration targets, screening test performance, and vaccine efficacy. For example, HPV prevalence among women 25 to 29 years of age is an output of the model that is a function of HPV incidence and clearance, which are inputs of the model. As **Appendix Table 3** indicates, we used information from prospective natural history studies with large sample sizes, long-term follow-up, and close repeated measures (62–67) to estimate HPV incidence and clearance rates that served as baseline inputs or parameter search ranges. However, we obtained the cross-sectional estimates of HPV prevalence from a different data source, in this case a large population-based survey in the United States (19), and compared them against the model-predicted outcomes. Of note, one of the strengths of a model-based analysis is the ability to synthesize multiple sources of data regardless of study design.

The model calibration exercise enables a flexible yet rigorous process by which we can vary each input parameter across a plausible range of values and identify candidate sets of input values that, when used together in the model, achieve a good fit to the observed data. **Appendix Figures 1** to **3** illustrate model fits to empirical data.

Screening Assumptions

All strategies included routine cervical cancer screening with conventional or liquid-based cytology, beginning at an average age of 20 years, on the basis of U.S. guidelines that recommend that screening start 3 years after sexual debut (2, 3, 80). Women with cytology results of atypical squamous cells of undetermined significance were managed by using triage HPV DNA testing; those who tested positive for high-risk types of HPV received colposcopy or biopsy, whereas those who tested negative returned to routine screening. Women with positive cytology results (or positive HPV DNA results, in the combined strategy) were referred for colposcopy or biopsy; those with histologically confirmed CIN 1 were not treated but monitored every 6 to 12 months until they had 3 consecutive negative screening tests. Women who received a positive diagnosis of CIN 2,3 or invasive cancer were treated according to standard guidelines (81). Women with any confirmed abnormality, even if treated successfully for CIN, were screened annually until they received 3 consecutive negative results.

On the basis of cervical cancer screening patterns reported for U.S. women (29–31), we assumed that current screening practice involved 53% of women being screened annually, 17% every 2 years, 11% every 3 years, 14% every 5 years, and 5% not being screened. According to the 2005 National Health Interview Survey (29), 9% of women had not been screened at all in the past 6 years; we split that group into 5% who are never screened in their lifetime and assumed the remaining 4% are screened every 5 years. The survey also indicated that 9% of women were screened less than triennially, and we assumed that all of those women are screened every 5 years.

Appendix Table 1. **Parameter Baseline Values, Search Range, and Calibrated Values for Best-Fitting Set**

Variable (Reference)	Baseline Value*	Parameter Search Range†	Best-Fitting Parameter Set
HPV incidence (62–67)			
HPV-16	0.0001–0.0100	0.1–8.0	4.747
HPV-18	0.0001–0.0100	0.1–8.0	1.760
HPV other high-risk	0.0001–0.0100	0.1–8.0	4.563
HPV low-risk	0.0001–0.0100	0.1–8.0	6.844
Progression of HPV incidence to CIN 1 (66–71)			
HPV-16	0.0047–0.0085	0.1–6.0	3.738
HPV-18	0.0047–0.0085	0.1–6.0	1.136
HPV other high-risk	0.0047–0.0085	0.1–6.0	2.745
HPV low-risk	0.0046–0.0054	0.1–6.0	0.398
Proportion of women with HPV who transition directly to CIN 2,3			
HPV-16	0.10	0.1–1.0	0.619
HPV-18	0	0–0.10	0.007
HPV other high-risk	0	0–0.10	0.055
HPV low-risk	0	0–0.10	0.028
Progression of CIN 1 to CIN 2,3 (72–77)			
HPV-16	0.0001–0.0039	0.1–6.0	1.927
HPV-18	0.0001–0.0039	0.1–6.0	4.552
HPV other high-risk	0.0001–0.0039	0.1–6.0	2.645
HPV low-risk	0.00001–0.0008	0.1–6.0	0.421
Progression of CIN 2,3 to invasive cancer (1, 66, 67)			
HPV-16	0.00001–0.0060	0.5–6.0	4.808
HPV-18	0.00001–0.0060	0.5–6.0	2.973
HPV other high-risk	0.00001–0.0060	0.5–4.0	1.719
HPV clearance (66, 67, 78)			
HPV-16	0.0305	0.5–8.0	6.732
HPV-18	0.0305	0.5–8.0	7.959
HPV other high-risk	0.0305	0.5–8.0	7.731
HPV low-risk	0.0305	0.5–8.0	4.057
Regression of CIN 1 (66, 67, 71, 72)‡			
HPV-16	0.0305	0.5–6.0	3.412
HPV-18	0.0305	0.5–6.0	4.234
HPV other high-risk	0.0305	0.5–6.0	2.764
HPV low-risk	0.0305	0.5–6.0	3.055
Regression of CIN 2,3 (66, 67, 71, 72)§			
HPV-16	0.0014–0.0065	0.5–6.0	5.668
HPV-18	0.0014–0.0065	0.5–6.0	5.932
HPV other high-risk	0.0014–0.0065	0.5–6.0	4.868
HPV low-risk	0.0014–0.0065	0.5–6.0	2.560
Probability that a woman develops an immune response after first HPV infection and clearance			
Any high-risk type	1.0	0.95–1.0	0.998
Reduction in HPV incidence, conditional on immune response (79)			
HPV-16	1.0	0.4–1.0	0.755
HPV-18	1.0	0.4–1.0	0.698
HPV other high-risk	1.0	0–0.5	0.334
Progression of invasive cancer stages (1, 66, 67)‖			
Local to regional	0.020	NA	NA
Regional to distant	0.025	NA	NA
5-year cervical cancer survival rate (1)‖			
Local	0.92	NA	NA
Regional	0.56	NA	NA
Distant	0.17	NA	NA
Annual probability of symptom detection (1)‖			
Local	0.19	NA	NA
Regional	0.60	NA	NA
Distant	0.90	NA	NA

CIN = cervical intraepithelial neoplasia (grade 1 or grade 2 or 3); HPV = human papillomavirus; NA = not applicable.
* Baseline values of parameters before calibration are monthly probabilities unless otherwise noted; the range represents age-specific probabilities.
† Values are factors that were multiplied to the baseline probability.
‡ 70% of women with CIN 1 have regression to normal and 30% to HPV.
§ 70% of women with CIN 2,3 have regression to normal, 15% to HPV, and 15% to CIN 1.
‖ These parameters were not included in the model calibration process.

Appendix Table 2. Calibration Target Data*

Calibration Target (Reference)	Mean Value (SD)	
	Low-Risk HPV	High-Risk HPV
Prevalence of HPV infection among women, by age (19)		
14–19 y	0.145 (0.015)	0.188 (0.027)
20–24 y	0.325 (0.054)	0.295 (0.041)
25–29 y	0.223 (0.040)	0.150 (0.036)
30–39 y	0.200 (0.038)	0.179 (0.026)
40–49 y	0.153 (0.019)	0.149 (0.013)
50–59 y	0.175 (0.038)	0.078 (0.011)
	Mean Value (SD)	
HPV type distribution (20–24)		
Among women with CIN 1		
HPV-16 and -18	0.304 (0.051)	
HPV other high-risk	0.491 (0.051)	
Among women with CIN 2,3		
HPV-16	0.346 (0.051)	
HPV-18	0.090 (0.046)	
HPV other high-risk	0.510 (0.051)	
Among women with invasive cancer		
HPV-16	0.551 (0.051)	
HPV-18	0.220 (0.051)	
Incidence rate of invasive cancer per 100 000 women, by age (25)		
20–24 y	2.6 (1.4)	
25–29 y	13.5 (5.4)	
30–34 y	28.9 (7.8)	
35–39 y	36.4 (8.1)	
40–44 y	45.1 (8.1)	
45–49 y	46.1 (8.2)	
50–54 y	50.9 (9.9)	
55–59 y	54.4 (7.8)	
60–64 y	61.2 (11.3)	
65–69 y	66.4 (14.2)	
70–74 y	65.4 (15.5)	
75–79 y	63.1 (19.4)	

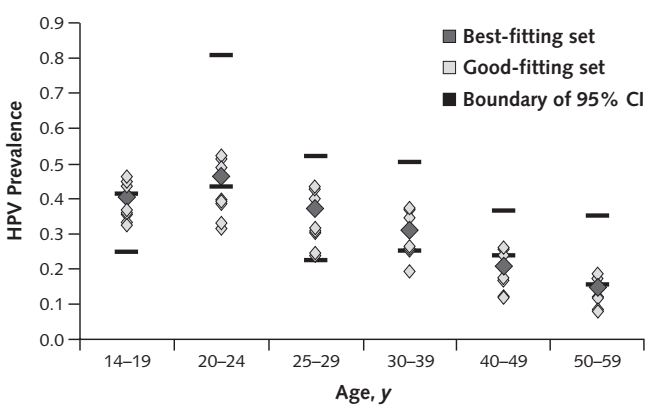
CIN = cervical intraepithelial neoplasia (grade 1 or grade 2 or 3); HPV = human papillomavirus.
* All target data were assumed to follow normal distributions.

Appendix Table 3. Information on Data Sources for Key Model Variables

Variable	Data Source*
Natural history parameters	
HPV incidence, clearance, and progression	B, M, X
CIN 1 progression and regression	B, M, R
CIN 2,3 progression and regression†	B, D, M, R
Natural immunity after same type of infection and clearance	B, X
Cancer progression, survival, and symptom detection	D, M
Calibration targets	
HPV prevalence	D
HPV type distribution	C, M, R
Cancer incidence	D
Screening test performance	
Cytology	A, C, M, R
HPV DNA test	A, C, R
Vaccine efficacy	A

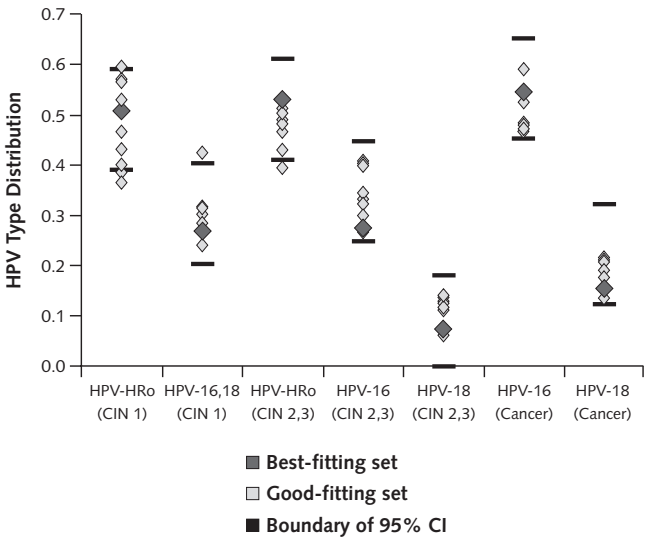
A = randomized, controlled trial; B = prospective cohort study; C = case–control study or study of sensitivity and specificity of diagnostic test; CIN = cervical intraepithelial neoplasia (grade 1 or grade 2 or 3); D = cross-sectional study; HPV = human papillomavirus; M = meta-analysis, decision analysis, or cost-effectiveness study; R = review article or consensus report; X = medical opinion.
* Classification of study types is based on reference 2.
† Progression and regression of CIN 2,3 are largely unobservable and therefore primarily inferred from model calibration.

Appendix Figure 1. Model fit to HPV prevalence.



HPV = human papillomavirus.

Appendix Figure 2. **Model fit to HPV type distribution among women with CIN and invasive cancer.**



CIN = cervical intraepithelial neoplasia (grade 1 or grade 2 or 3); HPV = human papillomavirus; HRo = other (non–HPV-16 or HPV-18) high-risk HPV types.

Appendix Figure 3. **Model fit to cervical cancer incidence.**