Projected Clinical Benefits and Cost-effectiveness of a Human Papillomavirus 16/18 Vaccine

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Background: **Human papillomavirus (HPV) vaccine may be commercially available in a few years. We explored the clinical benefits and cost-effectiveness of introducing an HPV16/18 vaccine in a population with an organized cervical cancer screening program.** ***Methods:*** **A computer-based model of the natural history of HPV and cervical cancer was used to project cancer incidence and mortality, life expectancy (adjusted and unadjusted for quality of life), lifetime costs, and incremental cost-effectiveness ratios (i.e., the additional cost of a strategy divided by its additional clinical benefit compared with the next most expensive strategy) associated with different cancer prevention policies, including vaccination (initiated at age 12 years), cytologic screening (initiated at 18, 21, 25, 30, or 35 years), and combined vaccination and screening strategies. We assumed that vaccination was 90% effective in reducing the risk of persistent HPV16/18 infections and evaluated alternative assumptions about vaccine efficacy, waning immunity, and risk of replacement with non-16/18 HPV types.** ***Results:*** **Our model showed that the most effective strategy with an incremental cost-effectiveness ratio of less than $60 000 per quality-adjusted life year is one combining vaccination at age 12 years with triennial conventional cytologic screening beginning at age 25 years, compared with the next best strategy of vaccination and cytologic screening every 5 years beginning at age 21 years. This triennial strategy would reduce the absolute lifetime risk of cervical cancer by 94% compared with no intervention. These results were sensitive to alternative assumptions about the underlying patterns of cervical cancer screening, duration of vaccine efficacy, and natural history of HPV infection in older women.** ***Conclusions:*** **Our model predicts that a vaccine that prevents persistent HPV16/18 infection will reduce the incidence of HPV16/18-associated cervical cancer, even in a setting of cytologic screening. A program of vaccination that permits a later age of screening initiation and a less frequent screening interval is likely to be a cost-effective use of health care resources. [J Natl Cancer Inst 2004;96:604–15]**

In countries with organized cervical cancer screening programs, there has been a marked reduction in the incidence of invasive cancer; however, screening and treatment have not been equally accessible to all groups of women *(1–3).* Cost-effective public health strategies to reduce the risk of cervical cancer in these vulnerable groups of women are a priority. From health, economic, and national policy perspectives, among the most pressing concerns are the escalating costs associated with current screening practices. For example, in the United States, more than $6 billion is spent each year on the evaluation and management of low-grade lesions, the majority of which would regress without intervention *(4).*

In the past several years, there have been substantial advances in our understanding of the epidemiology of cervical carcinogenesis and the causal role of oncogenic types of HPV *(5–7).* HPV DNA has been detected in up to 99.7% of all cervical cancers, and infection with one of four types of HPV (i.e., 16, 18, 45, or 31) accounts for approximately 75% of all cervical cancers diagnosed each year *(8,9).* Recent results from a phase II trial of an HPV vaccine showed 100% efficacy over an 18-month period in preventing persistent HPV16 infection and HPV16-specific cervical intraepithelial neoplasia (CIN) *(10).* Larger phase III trials of vaccines targeted against different oncogenic HPV types are underway *(11).* A combined strategy of vaccination for primary prevention of oncogenic HPV infection and cervical cytologic screening for secondary prevention of cervical cancer offers an intriguing option to further reduce the mortality from invasive cervical cancer in the United States, although the potential risks and costs will need to be evaluated.

Cost-effectiveness analysis in the fields of health and medicine provides a tool for evaluating the efficiency of resource utilization for health care interventions by characterizing different interventions in terms of the extra cost per added unit of health benefit conferred. The basic principle of a decision analytic approach is that all consequences of decisions (e.g., individual clinical outcomes, population-based outcomes, and costs) should be identified, measured, and valued (e.g., monetary value of patient time, quality-adjustment of life expectancy). When a decision analysis compares the relationship between the health and economic consequences associated with different public health care interventions, it is considered a cost-effectiveness analysis. To explore the relative costs and benefits of introducing a type-specific HPV vaccine in a population with existing cervical cytologic screening, a number of factors must be explicitly considered. These include, but are not limited to, the age-specific incidence of HPV and the natural history of cervical carcinogenesis; vaccine efficacy, coverage, and acceptability; and cervical cytologic screening practices. No single clinical trial or longitudinal cohort study will be able to consider all of these components. A decision analytic approach using a mathematical

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simulation model can be a useful tool, in conjunction with vaccine efficacy trials, to incorporate data from multiple sources, to extrapolate clinical and economic outcomes beyond the time horizon of a clinical study, to evaluate more strategies than are possible in a single clinical trial, and to assess the relative costs and benefits of alternative policies (screening and/or vaccination) in reducing mortality from cervical cancer *(12–14)*. Building upon the foundation of other cervical cancer models *(15–20)*, we developed a computer-based model to project the clinical benefits and cost-effectiveness of an HPV16/18 vaccine in the setting of an existing cervical cytologic screening program.

METHODS

The Model

We developed a Markov model that was capable of simulating the natural history of HPV infection and cervical carcinogenesis and incorporating the underlying type-specific HPV distribution within each stage of cervical disease. A Markov model is composed of a set of mutually exclusive and collectively exhaustive health states *(14)*. Each person in the model can reside in only one health state at any point in time, and all persons residing in a particular health state are indistinguishable from one another. Transitions occur from one state to another at defined recurring intervals (Markov cycle) of equal length (e.g., monthly or yearly) according to a set of transition probabilities. These probabilities can be made dependent on population characteristics, such as age, sex, and chronic disease, by specifying the probabilities as functions of these characteristics, and they may be constant or time-dependent. A state transition framework is used in which members of a population are allocated and subsequently reallocated into different health states over time. Values are assigned to each health state to reflect the cost and utility of spending one Markov cycle in that state. The contribution of these values to population outcomes (e.g., life expectancy, quality-adjusted life expectancy, and lifetime costs) depends on the length of time spent in each state. By synthesizing data on costs, effects, and quality of life, a Markov model permits comparison of the outcomes associated with different clinical strategies.

In our model, the natural history of disease was modeled as a sequence of 6-month transitions among mutually exclusive health states (Fig. 1). These states were defined by use of five general categories of HPV infection (persistent HPV16/18, persistent high-risk non-16/18 HPV types, persistent low-risk HPV types, transient low-risk or high-risk HPV types, and no HPV), three categories of cervical disease (no neoplasia or cancer, cervical intraepithelial neoplasia 1 [CIN1], and cervical intraepithelial neoplasia 2,3 [CIN2,3]), and three categories of invasive cervical cancer (local, regional, and distant) *(21,22)*. Studies that have examined the risk of cervical neoplasia associated with persistent HPV infection have defined "persistence" in a variety of ways *(23–30)*. We stratified the HPV sector of health states into categories that were consistent with the classification used in the main clinical studies from which the parameter estimates for the incidence of HPV were derived *(23,30,31)*. The HPV stratum reflecting persistent high-risk types of HPV was further stratified into two groups (one to represent HPV16 or HPV18 and the other to represent high-risk non-16 or non-18 HPV types, including 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

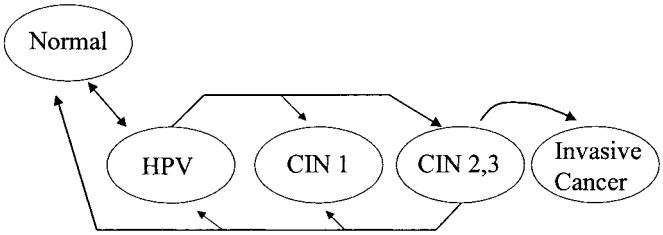

Fig. 1. Simple schematic of model. Model simulates the natural history of human papillomavirus (HPV) infection and cervical carcinogenesis while incorporating the underlying type-specific HPV distribution within each stage of cervical disease, by use of a sequence of 6-month transitions among mutually exclusive health states. Health states are defined by use of five general categories of HPV infection (persistent HPV16/18, persistent high-risk non-16/18 HPV types, persistent low-risk HPV types, transient low-risk or high-risk HPV types, and no HPV), three categories of cervical disease (no neoplasia or cancer, cervical intraepithelial neoplasia 1 [CIN1], and cervical intraepithelial neoplasia 2,3 [CIN2,3]), and three categories of invasive cervical cancer (local, regional, and distant). The probabilities governing each of these transitions are conditional on the type of HPV infection. HPV infections may be persistent or transient. Persistent infection with a high-risk type is necessary for invasive cervical cancer. Transient infection with any HPV type may be accompanied by the development of CIN1, and vaccination prior to sexual activity prevents 90% of persistent infection with HPV16/18.

The HPV stratum reflecting persistent low-risk types included women with all other HPV types.

The time horizon of the analysis incorporated a woman's entire lifetime and was divided into equal 6-month increments, referred to as Markov cycles, during which women "transitioned" from one health state to another. The model assumed a cohort of 100 000 adolescent girls subjected to age-dependent probabilities of acquiring and clearing HPV infection starting at age 13 years. Women with either transient or persistent HPV infection could develop histopathologic cervical changes, and those with CIN1 or with CIN2,3 could progress, regress, or stay the same. The probabilities governing each of these transitions were conditional on the type of HPV infection. We assumed that only women with persistent HPV infections developed CIN2,3 and invasive cancer. In each cycle, women with invasive cancer could develop symptoms or progress to the next stage of cancer. We assumed that symptomatic women with invasive cancer received stage-specific treatment for their disease and were subject to the corresponding stage-specific survival rates. From every health state and in every cycle, women faced competing all-cause mortality risks *(32)*.

Adding Vaccination to Current Cervical Cancer Screening in the United States

We first conducted an analysis to estimate the clinical benefits and costs associated with the introduction of an HPV16/18 vaccine in the setting of cervical cancer screening and conservatively assumed that vaccination would not alter current screening practice. We based initial estimates for screening behavior on data from the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System, which estimated that 5.2% of women had never been screened and that 70.5% of those women who had received a Papanicolaou (Pap) test had received it in the last year. An additional 12.6%, 4.3%, and 3.0% of women reported receiving a Pap test within the last 2 years, 3 years, and 5 years, respectively *(33)*. We assumed that

9.6% of women were screened more than 5 years ago. The model was then calibrated to the lifetime risk of cervical cancer reported in the National Cancer Institute's Surveillance, Epidemiology, and End Results Program *(34)*. The model was used to evaluate the cost-effectiveness of an HPV16/18 vaccine and to explore the impact of changes in 1) vaccine efficacy, defined as a reduction in the probability of acquiring a persistent HPV16/18 infection; 2) vaccine coverage, defined as the proportion of the cohort that receive three doses of vaccine (actual coverage) and the proportion of the cohort fully immunized (effective coverage); and 3) duration of vaccine efficacy, defined as the period before waning immunity.

Primary and Secondary Cervical Cancer Prevention Strategies

We then assessed the costs and clinical benefits associated with a variety of hypothetical cervical cancer control policies consisting of a primary prevention component (i.e., vaccination) and/or a secondary cervical cancer prevention component (i.e., cervical cytologic screening starting at a specific age and conducted at a specific frequency). We evaluated screening intervals of 1–5 years with conventional and liquid-based cytology initiated at age 18, 21, 25, 30, or 35 years. To permit comparison of our findings with previously published cost-effectiveness analyses of cervical cancer screening *(16–20,35–39)*, we assumed 100% compliance with vaccination and screening but varied these estimates widely in sensitivity analyses.

Assumptions

For strategies that incorporated cytologic screening, we made the following assumptions: 1) All women with abnormal Pap test results, which were classified as a low-grade squamous intraepithelial lesion (LSIL) or above, received colposcopy and a biopsy examination *(40)*. 2) Women with a cytologic screening result of atypical squamous cells of uncertain significance underwent HPV DNA testing (using either the residual sample from a liquid-based cytology specimen or, for conventional cytology, a sample co-collected at the time of the initial screening) *(41)*. 3) Women with a conventional cytologic screening result of atypical squamous cells of uncertain significance were managed with immediate colposcopy or repeat cytologic screening in 6 months. 4) Colposcopy and biopsy examination accurately determined the true underlying histology of the cervix. 5) All women with histologically confirmed CIN2,3 or worse were treated appropriately. 6) Women with histologically confirmed CIN1 were not treated but were monitored every 6 months until they regressed to normal or progressed to CIN2,3.

For strategies that incorporated vaccination, we made the following assumptions for the base case: 1) All (100%) of the adolescent cohort would be successfully vaccinated at age 12 years (actual coverage) before their first exposure to HPV. 2) All 12-year-olds would have received three doses of the vaccine and would be fully immunized by age 13 years (effective coverage). 3) Among women successfully vaccinated, the probability of acquiring persistent infection with HPV16/18 would be reduced by 90% (efficacy). 4) Recipients of an effective vaccine were subjected to the competing risks associated with acquisition of other types of HPV (replacement). 5) Vaccination would have no impact on HPV16/18 infections that were destined to be transient and no effect on any non-HPV16/18 infections (cross-protection). *(6)* Finally, immunity would not wane over time. Because of the obvious uncertainty as to the real-world performance of a prophylactic vaccine against HPV16/18, we explored the implications of alternative assumptions to each of those used in the base case.

For each strategy, we tracked clinical events (e.g., HPV infection), life expectancy–adjusted and unadjusted for quality of life, and costs (expressed in 2002 U.S. dollars) accrued by this hypothetical cohort throughout their lifetimes. Following the recommendations of the Panel on Cost-Effectiveness in Health and Medicine *(14)*, we adopted a societal perspective and expressed clinical benefits as quality-adjusted life years gained to reflect both the gains in longevity and quality of life associated with effective interventions to prevent cervical cancer. Future costs and life years were discounted at an annual rate of 3%. The results of a cost-effectiveness analysis are summarized by use of an incremental cost-effectiveness ratio. In this ratio, all health outcomes associated with a particular strategy (compared with an alternative) are included in the denominator, and all costs or changes in use of resources with a particular strategy (compared with an alternative) are included in the numerator. The incremental cost-effectiveness ratio for a strategy is computed in reference to the next most effective option after eliminating strategies that are dominated (i.e., strategies that are more costly and less effective than other options) and strategies that are ruled out by extended (weak) dominance (i.e., strategies that have higher incremental cost-effectiveness ratios than more effective options).

Statistical issues in cost-effectiveness studies are different from those that arise in experiments or other data analyses. Rather than testing hypotheses using traditional statistical significance as a criterion, model-based evaluation studies aim to portray the scope and nature of the uncertainties that surround the estimates of costs, benefits, and cost-effectiveness ratios that they produce through the use of a sensitivity analysis *(14)*. In a sensitivity analysis, some critical component in the calculation is varied over a plausible range, and the cost-effectiveness ratio is recalculated. The resulting difference in the ratio provides some indication of how sensitive the results might be to a change in that parameter. We conducted extensive sensitivity analyses to evaluate the stability of our conclusions over a wide range of parameter estimates and structural assumptions.

Data

Selected data are shown in Table 1 *(42–97)*. Transition probabilities required by the model that were not available from primary data were obtained by use of calibration methods described elsewhere *(15–19)*. We assessed the face validity of the model by projecting a series of intermediate-term and long-term outcomes for which there were suitable data in the absence of screening (e.g., age-specific cervical cancer incidence and stage distribution of invasive disease) *(74,75)*. Using published data to establish the range of HPV types within LSIL, high-grade SIL (HSIL), and cancer *(1,9,38,41,66–71)*, we calibrated the model to the best available data on age-specific HPV infection, LSIL, HSIL, and cancer *(34,46–50,63–65)*. Model corroboration was assessed by comparing the predicted outcomes in the setting of screening at different intervals with those of other published analyses *(19,20)*. Estimates for the sensitivity and specificity of cervical cytologic screening were obtained from large clinical

Table 1. Selected model variables: baseline values and ranges used in sensitivity analysis*

Variable	Base case	Range
Incidence and clearance of HPV infection *(42–50)*†		
Normal to persistent HPV DNA		
Age <35 y	0.010–0.030	†
Age ≥35 y	0.002–0.006	†
Normal to transient HPV DNA		
Age <35 y	0.030–0.070	†
Age ≥35 y	0.002–0.010	†
HPV DNA to normal		
Age <35 y	0.100–0.460	†
Age ≥35 y	0.100–0.460	†
Natural history of CIN *(51–71)*		
HPV DNA to CIN1		
Age <35 y	0.030–0.060	†
Age ≥35 y	0.007–0.015	†
HPV DNA to CIN2,3		
Age <35 y	0.001–0.006	†
Age ≥35 y	0.004–0.025	†
CIN1 to CIN2,3‡		
Age <35 y	0.008–0.050	†
Age ≥35 y	0.037–0.220	†
CIN2,3 to invasive cancer‡		
Age <35 y	0.001–0.002	†
Age 35–64 y	0.006–0.012	†
Age ≥65 y	0.001–0.020	†
CIN1 to HPV	0.440–0.540	†
CIN1 to normal	0.110–0.540	†
CIN2,3 to HPV	0.010–0.030	†
CIN2,3 to normal	0.001–0.003	†
Natural history of invasive cervical cancer§ *(2,72–75)*		
Probability of progression		
Stage I to Stage II	0.1500	0.1125–0.1875
Stage II to Stage III	0.1600	0.1200–0.2000
Stage III to Stage IV	0.2252	0.1689–0.2815
Probability of developing symptoms		
Stage I	0.0750	0.0563–0.0938
Stage II	0.1125	0.0844–0.1406
Stage III	0.3000	0.2250–0.3750
Stage IV	0.4500	0.3375–0.5625
Probability of survival at 5 years		
Stage I	0.84	0.63–0.98
Stage II	0.66	0.49–0.83
Stage III	0.38	0.28–0.48
Stage IV	0.11	0.08–0.14
Vaccine characteristics *(10,11)*		
Vaccine efficacy, %	90	50–100
Age at vaccination, y	12	12–15
Vaccine coverage, %	100	50–100
Screening test characteristics *(76–87)*‖		
Sensitivity of liquid-based cytology, %	84	69–88
Specificity of liquid-based cytology, %	88	77–93
Sensitivity of conventional cytology, %	66	34–86
Specificity of conventional cytology, %	97	88–99
Vaccination costs, $U.S. *(88–90)*¶		
Vaccination series	377	188–565
Patient time cost	16	8–24
Costs of cervical cancer screening and treatment, $U.S. *(91–95)*		
Screening costs		
Conventional cytology#	15–51	12–75
Liquid-based cytology#	28–64	20–80
HPV DNA test (Hybrid Capture 2)	49	30–200
Office visit	22	11–50
Patient time cost	21	11–200
Diagnostic and treatment costs, $U.S.**		
Colposcopy and biopsy	436	200–600
CIN1	1264	800–1706
CIN2,3	2833	1500–3275
Stage I	21 533	16 150–26 916
Stage II	23 046	17 285–28 808
Stage III	27 067	20 300–33 834
Stage IV	36 912	27 684–46 140
Health-related quality of life *(88,96,97)*††		
Quality weights for detected invasive cancer		
Stage I	0.65	0.49–0.81
Stage II	0.56	0.42–0.70
Stage III	0.56	0.42–0.70
Stage IV	0.48	0.36–0.60
Quality weights after treatment for invasive cancer		
Stage I	0.97	0.73–0.99
Stage II	0.90	0.68–0.98
Stage III	0.90	0.68–0.98
Stage IV	0.62	0.47–0.78

*Selected parameter values used for the baseline analysis are shown. Range for each parameter indicates the upper and lower bound for each value used in sensitivity analysis. In a sensitivity analysis, some critical component in the calculation is varied over a plausible range, and the cost-effectiveness ratio is recalculated. The resulting difference in the ratio provides some indication of how sensitive the results might be to a change in that parameter. Clinical estimates (base case and range) are reported as 6-month probabilities unless otherwise noted. HPV = human papillomavirus; CIN = cervical intraepithelial neoplasia.

†Plausible range was established with age-specific values where indicated. HPV infection was categorized as persistent high-risk HPV16/18, persistent high-risk non-16/18 HPV, persistent low-risk types, and any type of transient HPV. Details of point estimates for each age group available from authors on request.

‡Persistent HPV infection was assumed to be necessary for progression to CIN2,3 and invasive cancer.

§Probabilities for progression through cancer stages and for development of stage-specific symptoms imputed through previously described methods *(17–19,72–75)*.

‖Estimates for sensitivity conditional on age and cervical lesion severity were used in sensitivity analyses.

¶The vaccination series includes three doses (estimated at $100 each, based on the assumptions made by the Institute of Medicine) *(88)*, as well as three brief clinic visits, surveillance, and educational costs.

#Costs reflect a weighted average of normal and abnormal cytologic smears.

**Aggregate costs reflect the sum of the costs of the procedure, office visit, and woman's time.

††Age-related quality weights (weights for each health state were multiplied by the time spent in the state and then summed to calculate the number of quality-adjusted life years) for noncancer states were based on published data from the Health Utilities Index (Mark II Scoring System) and ranged from 0.92 in women aged 25–34 years to 0.74 in women older than 85 years.

trials and recent comprehensive reviews *(76–87)*. Because of the uncertainty in screening test performance after the introduction of a type-specific vaccine, we varied these parameters over a wide plausible range in a sensitivity analysis.

Selected costs are shown in Table 1 *(88–95)*. We assumed that vaccination required the costs of three brief clinic visits, surveillance and educational costs, and patient (or parent) time costs. We assumed that all adolescents and their parents would require a 10-minute pre-vaccination counseling session with a registered nurse or nurse practitioner. Data from the U.S. Bureau of Labor Statistics were used to assign a cost for the time

required from each provider *(90)*. To account for inflation, all costs were converted to 2002 U.S. dollars by use of the Medical Care Component of the Consumer Price Index *(95)*. We included the costs of additional booster doses in sensitivity analyses.

Direct medical costs for screening and treatment were derived from previously published data *(16,91–94)*. Costs of invasive cancer were obtained from published results, including a report from the Agency for Health Care Policy and Research *(50)* that used data from the Medstat MarketScan database. The time spent undergoing screening was derived from a prospective study of time costs associated with cervical cancer screening *(94)*, and previously published data incorporating transportation costs were used in sensitivity analyses.

Selected quality weights are shown in Table 1 *(88,96,97)*. Quality weights for each health state, which ranged from 0 to 1, where a weight of 1 corresponds to perfect health and a weight of 0 corresponds to a health state judged equivalent to death, were multiplied by the time spent in the state and then summed to calculate the number of quality-adjusted life years. Age-specific quality weights were used for noncancer states, as recommended by the Panel on Cost-Effectiveness in Health and Medicine *(14,96)*. The quality weights for the time spent in cancer health states were derived from utility estimates by the Committee to Study Priorities for Vaccine Development (Institute of Medicine) *(88)* and varied with stage of disease. The plausible ranges for these quality weights were established by use of the lowest and highest values reported in the literature *(88,96,97)*. Sensitivity analyses were conducted to evaluate the impact of quality-of-life decrements associated with receiving an abnormal cytologic screening result.

RESULTS

Model Validity

In the absence of screening, the absolute lifetime risk of cervical cancer predicted by the model is 3.64%. The age-specific incidence of cervical cancer peaks at an age of 48 years at a rate of 81.2 cases of cervical cancer per 100 000 women. The model predicts that 65% of all cancers are caused by HPV16/18, 26% are caused by non-16/18 HPV types, and 9% are preceded by persistent infections with low-risk HPV types.

Impact of an HPV16/18 Vaccine on LSIL and HSIL With Current Cervical Cancer Screening

Fig. 2 shows the impact of introducing an HPV16/18 vaccine in the setting of current cervical cancer screening on the age-specific prevalence of LSIL and HSIL. The reduction in total cases of LSIL and HSIL (caused by any type of HPV) is a function of the proportion of lesions attributable to HPV16/18 and the efficacy of the vaccine. Because the proportion of HSIL attributable to HPV16/18 is greater than the proportion of LSIL attributable to HPV16/18, there is a greater reduction in the projected age-specific prevalence of HSIL than LSIL. In the presence of an organized screening program, the model predicts that the absolute difference in the prevalence of HSIL will be relatively small because HSIL is already a relatively rare event.

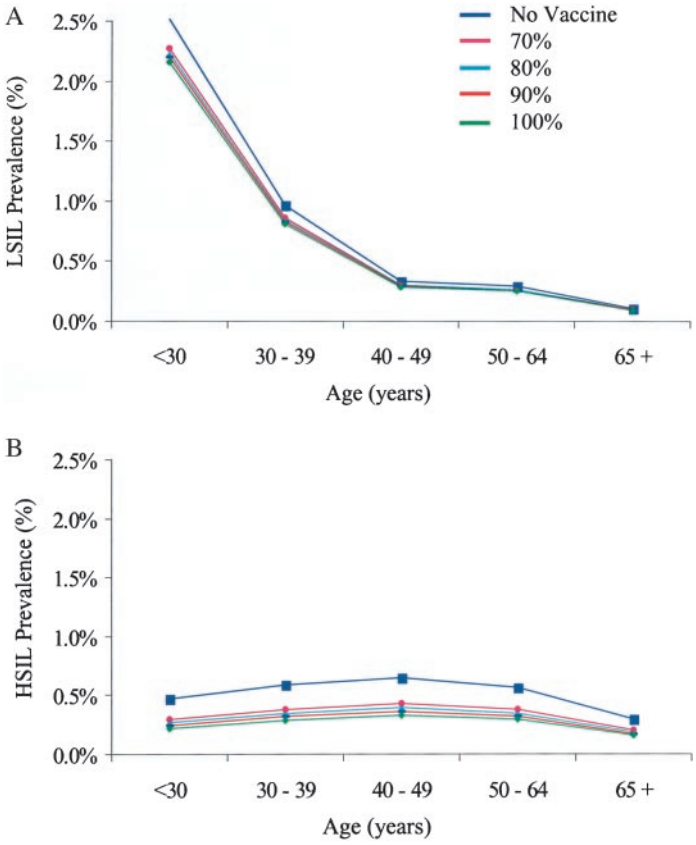

Fig. 2. Impact of an human papillomavirus (HPV) 16/18 vaccine on low-grade squamous intraepithelial lesion (LSIL) and high-grade SIL (HSIL). The impact of introducing an HPV16/18 vaccine, in the setting of current cervical cancer screening, on the age-specific prevalence of LSIL (**A**) and HSIL (**B**) is shown. The reduction in total cases of LSIL and HSIL (caused by any type of HPV) is a function of both the proportion of lesions attributable to HPV16/18 and the vaccine efficacy.

Cost-effectiveness of an HPV16/18 Vaccine With Current Cervical Cancer Screening

Table 2 shows the discounted costs, quality-adjusted life expectancy, and the estimated lifetime risk of cervical cancer associated with the introduction of a type-specific HPV vaccine (ranging in efficacy from 70% to 100%) in the setting of current cervical cancer screening practice in the United States. If we conservatively assume that vaccination would not alter screening practice, an HPV16/18 vaccine ranging in efficacy from 70% to 100% would reduce the lifetime risk of cancer by 46%–66% (i.e., the absolute lifetime risk would be reduced from 0.86% to 0.30%–0.47%), compared with current screening. The incremental cost-effectiveness ratio of an HPV16/18 vaccine would vary from $20 600 per quality-adjusted life year with a vaccine that prevents 100% of persistent HPV16/18 infections to $33 700 per quality-adjusted life year with a vaccine that prevents 70% of persistent HPV16/18 infections.

Cost-effectiveness of Primary and Secondary Cervical Cancer Prevention Strategies

We then assessed the costs and clinical benefits associated with three basic strategies, including 1) no vaccination and no screening, 2) no vaccination and cytologic screening, and 3)

Table 2. Discounted costs, quality-adjusted life expectancy, lifetime risk of cancer, and incremental cost-effectiveness of vaccination in the setting of current screening in the United States, by varying vaccine efficacy*

Screening strategy	Total lifetime costs, $U.S.	Incremental costs, $U.S.	Quality adjusted life expectancy, QALY	Lifetime risk of cancer, %	Cost-effectiveness ratio, $U.S./QALY†
Current screening program	1111	—	25.9815	0.86	—
Vaccination at 70% efficacy	1421	310	25.9907	0.47	33 700
Vaccination at 80% efficacy	1409	298	25.9921	0.41	28 100
Vaccination at 90% efficacy	1400	289	25.9934	0.36	24 300
Vaccination at 100% efficacy	1384	274	25.9948	0.30	20 600

*Average per woman lifetime costs, quality-adjusted life expectancy, and the estimated lifetime risk of cervical cancer associated with the introduction of a type-specific HPV vaccine (ranging in efficacy from 70% to 100%) in the setting of current cervical cancer screening practice in the United States. Each vaccination strategy is being compared with the current screening program in the United States. Costs have been rounded to the nearest whole dollar. QALY = quality-adjusted life year.

†The difference in cost divided by the difference in quality-adjusted life expectancy for each strategy compared with the current screening program.

vaccination and cytologic screening. The discounted costs, quality-adjusted life expectancy, and reduction in lifetime risk of cancer associated with each of the potential 80 cervical cancer prevention strategies were calculated (data available from authors upon request). The non-dominated strategies (i.e., strategies that were more effective and less costly or that were more effective and more cost-effective than all other options) are shown in Table 3. Strategies shown differ by type of cytologic screening (e.g., conventional versus liquid-based screening, age at which screening is initiated, frequency of screening, and use of vaccination [90% efficacy] as an adjunct to cytologic screening). The most effective strategy with an incremental cost-effectiveness ratio of less than $60 000 per quality-adjusted life year is one combining vaccination at age 12 years with triennial conventional cytologic screening beginning at age 25 years, which would reduce the lifetime risk of cancer by 94% compared with no intervention. Increasing screening frequency with either liquid-based or conventional cytologic screening to an annual basis provides an additional reduction in the lifetime risk of cancer of less than 2% compared with biennial strategies, yet is accompanied by an appreciable increase in costs. For example, vaccination at age 12 years with annual liquid-based cytologic screening starting at age 18 years costs more than U.S.$3.5 million per quality-adjusted life year, compared with the next best non-dominated strategy of vaccination at age 12 years with annual conventional cytologic screening starting at age 18 years.

Impact of Vaccine Efficacy on Cost-effectiveness of Cervical Cancer Prevention Strategies

Table 4 presents the reduction in lifetime risk of cervical cancer, quality-adjusted life expectancy, and total lifetime costs associated with the non-dominated cervical cancer control strategies for four hypothetical HPV16/18 vaccines that vary in efficacy from 70% to 100%. Strategies that would reduce the lifetime risk of cervical cancer by less than 85% are not shown

Table 3. Discounted costs, quality-adjusted life expectancy, reduction of lifetime risk of cervical cancer, and cost-effectiveness of different cervical cancer prevention policies*

Strategy	Cytology type	Age at screening initiation, y	Screening interval, y	Lifetime costs, $U.S.	Quality-adjusted life expectancy, QALYs	Reduction in lifetime cancer risk, %	Cost-effectiveness, ($U.S./QALY)†
No intervention	—	—	—	235	25.9112	—	—
Screening only	Conventional	35	5	386	25.9607	67.4	3100
Screening only	Conventional	30	5	443	25.9696	71.4	6400
Screening only	Conventional	25	5	526	25.9765	73.9	12 100
Screening/vaccine	Conventional	30	5	748	25.9893	88.9	17 200
Screening/vaccine	Conventional	25	5	828	25.9919	89.8	31 200
Screening/vaccine	Conventional	21	5	896	25.9930	89.7	57 400
Screening/vaccine‡	Conventional	25	3	1030	25.9953	94.0	58 500
Screening/vaccine	Conventional	21	3	1144	25.9967	95.4	83 000
Screening/vaccine	Conventional	21	2	1450	25.9986	96.6	164 400
Screening/vaccine	Conventional	18	2	1581	25.9990	96.8	280 200
Screening/vaccine	Liquid-based	18	2	2314	26.0002	98.0	617 900
Screening/vaccine	Conventional	18	1	2581	26.0006	98.5	771 300
Screening/vaccine	Liquid-based	18	1	3992	26.0009	99.0	3 867 500

*Average per woman lifetime costs, quality-adjusted life expectancy, and reduction in lifetime risk of cervical cancer associated with three basic cervical cancer prevention strategies: 1) no vaccination and no screening, 2) no vaccination and cytologic screening, and 3) vaccination and cytologic screening. Strategies differ by type of cytologic screening (e.g., conventional versus liquid-based screening, age at which screening is initiated, frequency of screening, and use of vaccination with 90% efficacy as an adjunct to cytologic screening). Strategies shown are the most efficient strategies (i.e., non-dominated) of a total of 80 strategies evaluated. Strategies that were dominated were either less effective and more costly (i.e., strongly dominated) or more costly and less cost-effective (i.e., weakly dominated) than the strategies shown. Vaccine efficacy was defined as prevention of 90% of persistent human papillomavirus 16/18 (HPV16/18) infections. Costs have been rounded to the nearest whole dollar. QALY = quality-adjusted life-year.

†The difference in cost divided by the difference in quality-adjusted life expectancy for each strategy compared with the next best strategy. All strategies are assumed to be equally available.

‡Cost-effectiveness ratios are often placed in context by comparisons with interventions that are widely mandated. As such, a cost-effectiveness ratio of less than $75 000 per quality-adjusted life year gained would be considered good value for resources (i.e., a cost-effective intervention) in the United States *(14)*.

Table 4. Discounted costs, quality-adjusted life expectancy, reduction in cancer incidence, and incremental cost-effectiveness of selected cervical cancer prevention policies for vaccine efficacy varying from 70% to 100%*

Strategy	Cytology type	Age at screening initiation, y	Screening interval, y	Total average lifetime costs, $U.S.	Quality-adjusted life expectancy, QALYs	Reduction in lifetime cancer risk, %	Cost-effectiveness ratio, $U.S./QALY)†
No screening/no vaccine	—	—	—	235	25.9112	—	—
Vaccine with 100% efficacy							
Screening/vaccine‡	Conventional	35	5	679	25.9888	89.6	12 300‡
Screening/vaccine	Conventional	30	5	738	25.9916	90.9	21 400
Screening/vaccine	Conventional	25	5	818	25.9936	91.6	38 800
Screening/vaccine	Conventional	25	3	1020	25.9965	95.1	70 900
Screening/vaccine	Conventional	21	3	1133	25.9976	95.3	103 700
Screening/vaccine	Conventional	18	2	1438	25.9991	97.2	201 800
Screening/vaccine	Conventional	18	2	1568	25.9994	98.1	354 200
Screening/vaccine	Liquid-based	18	2	2301	26.0004	98.3	766 300
Screening/vaccine	Conventional	18	1	2567	26.0007	98.8	963 400
Screening/vaccine	Liquid-based	18	1	3977	26.0010	99.2	4 863 000
Vaccine with 90% efficacy							
Screening/vaccine§	Conventional	30	5	748	25.9893	88.9	17 300§
Screening/vaccine	Conventional	25	5	828	25.9919	89.8	31 200
Screening/vaccine	Conventional	21	5	896	25.9930	89.7	57 400
Screening/vaccine	Conventional	25	3	1030	25.9953	94.0	58 500
Screening/vaccine	Conventional	21	3	1144	25.9967	95.4	83 000
Screening/vaccine	Conventional	21	2	1450	25.9986	96.6	164 400
Screening/vaccine	Conventional	18	2	1581	25.9990	96.8	280 200
Screening/vaccine	Liquid-based	18	2	2314	26.0002	98.0	617 900
Screening/vaccine	Conventional	18	1	2581	26.0006	98.5	771 300
Screening/vaccine	Liquid-based	18	1	3992	26.0009	99.0	3 867 500
Vaccine with 80% efficacy							
Screening/vaccine‖	Conventional	30	5	758	25.9870	86.9	22 200‖
Screening/vaccine	Conventional	25	5	839	25.9901	88.0	26 200
Screening/vaccine	Conventional	21	5	907	25.9915	88.1	47 900
Screening/vaccine	Conventional	25	3	1040	25.9942	92.9	50 000
Screening/vaccine	Conventional	21	3	1154	25.9958	93.2	69 500
Screening/vaccine	Conventional	21	2	1461	25.9980	95.9	138 800
Screening/vaccine	Conventional	18	2	1592	25.9986	96.0	232 400
Screening/vaccine	Liquid-based	18	2	2327	26.0000	97.6	518 400
Screening/vaccine	Conventional	18	1	2595	26.0004	98.3	645 800
Screening/vaccine	Liquid-based	18	1	4007	26.0009	98.9	3 205 600
Vaccine with 70% efficacy							
Screening/vaccine¶	Conventional	25	3	1050	25.9931	91.7	52 200¶
Screening/vaccine	Conventional	21	3	1165	25.9950	92.2	59 900
Screening/vaccine	Conventional	21	2	1472	25.9975	95.3	120 400
Screening/vaccine	Conventional	18	2	1604	25.9982	95.4	199 100
Screening/vaccine	Liquid-based	18	2	2339	25.9998	97.2	446 800
Screening/vaccine	Conventional	18	1	2609	26.0003	98.0	556 300
Screening/vaccine	Liquid-based	18	1	4022	26.0008	98.7	2 748 000

*Average per woman lifetime costs, quality-adjusted life expectancy, and reduction in lifetime risk of cervical cancer associated with the non-dominated cervical cancer control strategies for four hypothetical HPV16/18 vaccines that vary in efficacy from 70% to 100% are shown. Strategies shown reflect the non-dominated options among a total of 320 strategies evaluated (80 for each vaccine efficacy). Strategies that were dominated were either less effective and more costly (i.e., strongly dominated) or more costly and less cost-effective (i.e., weakly dominated) than the strategies shown. Not shown are strategies that would reduce the lifetime risk of cervical cancer by less than 85% because these would imply less protection against cervical cancer than current cervical cancer screening practice. Costs have been rounded to the nearest whole dollar. QALY = quality-adjusted life year.

†The difference in cost divided by the difference in quality-adjusted life expectancy or life expectancy for each strategy compared with the next best strategy. All strategies are assumed to be equally available.

‡The next best non-dominated comparator (data not shown) used to calculate the incremental cost-effectiveness ratio was conventional screening every 5 years starting at age 30 years without vaccination (total costs = $443; total QALYs = 25.9696).

§The next best non-dominated comparator (data not shown) used to calculate the incremental cost-effectiveness ratio was conventional screening every 5 years starting at age 25 years without vaccination (total costs = $526; total QALYs = 25.9765).

‖The next best non-dominated comparator (data not shown) used to calculate the incremental cost-effectiveness ratio was conventional screening every 5 years starting at age 21 years without vaccination (total costs = $597; total QALYs = 25.9798).

¶The next best non-dominated comparator (data not shown) used to calculate the incremental cost-effectiveness ratio was conventional screening every 3 years starting at age 21 years without vaccination (total costs = $845; total QALYs = 25.9891).

because these strategies would imply less protection against cervical cancer than current cervical cancer screening practice. The reduction in lifetime risk of cervical cancer varies from 67% to 99%, depending on vaccine efficacy, screening frequency, and age at which screening is begun. Provided that the vaccine is at least 70% effective, vaccination at age 12 years combined with cytologic screening every 3 years beginning at age 25 years is more effective than our current screening program, provides a

92% reduction in cervical cancer incidence, and costs approximately $50 000 per quality-adjusted life year. As a general rule, with more effective vaccines, less frequent cytologic screening produced equivalent protection against cancer. For example, with a vaccine that prevents 100% of persistent HPV16/18 infections, the same level of cancer protection may be obtained (92% reduction in lifetime cancer risk), but screening frequency may be decreased to every 5 years rather than every 3 years.

Other Sensitivity Analyses

Results were most sensitive to alternative assumptions about the 1) duration of vaccine efficacy; 2) proportion of persistent HPV in women older than 30 years attributable to newly acquired HPV infection versus reactivation of infection acquired in earlier adulthood; and 3) underlying frequency of cervical cancer screening, age at which screening is initiated, and cost of following women with atypical cytologic screening results and low-grade lesions. Results were less sensitive to plausible changes in the natural history parameters, screening test characteristics, cervical cancer mortality, and costs.

Although the clinical benefits of vaccination diminish proportionally with decreasing vaccination coverage, the incremental cost-effectiveness ratio of vaccination in the base case was not sensitive to plausible changes in vaccine costs because the unvaccinated proportion of the cohort did not accrue the costs of vaccination. In contrast, the cost-effectiveness of vaccination strategies improved as screening coverage decreased (i.e., as the proportion of the population never screened was increased). For example, the incremental cost-effectiveness ratio of adding a vaccine with 90% efficacy against persistent HPV infections to current screening practice in the United States is less than $25 000 per quality-adjusted life year. Adding this same vaccine to a hypothetical screening program in which all women comply with every scheduled screening session exceeds $50 000 per quality-adjusted life year.

In strategies that combined vaccination and screening, the choice of conventional versus liquid-based cytologic screening depends mainly on their relative costs and test characteristics. For example, when the cost of conventional cytologic screening is doubled, vaccination combined with liquid-based cytologic screening is preferred. When the sensitivity of conventional cytologic screening is reduced to less than 50%, liquid-based cytologic screening is preferred. Our cost-effectiveness results are stable over a wide plausible range of vaccination costs; however, when total per person vaccination costs (including initial dose, office visits, counseling, and booster doses) exceed $1000, strategies that combine vaccination with screening are dominated by strategies that rely on screening alone. Results are sensitive to the costs (both monetary costs and decrements in quality of life) associated with the workup of positive screening test results, including costs attributable to workup after false-positive cytologic results, equivocal cytologic results, and LSIL results. The incremental cost-effectiveness ratios of vaccination strategies become more attractive as the costs and/or quality-of-life decrements attributable to screening increase.

We evaluated the impact of waning (i.e., vaccine efficacy wanes after 5, 10, 15, or 20 years) on the effectiveness of a vaccine that prevents 90% of persistent HPV16/18 infections (Fig. 3). As the proportion of persistent HPV infections attributable to new (versus latent or previously acquired) infections is varied from 75% to 50% to 25%, the relative effect of waning is markedly attenuated. When we evaluated the cost-effectiveness of different policies under these three assumptions, we found that a policy that combines vaccination and screening costs less than $100 000 per quality-adjusted life year, provided that the proportion of persistent HPV infections attributable to new (versus latent) infection was equal to or less than 75%.

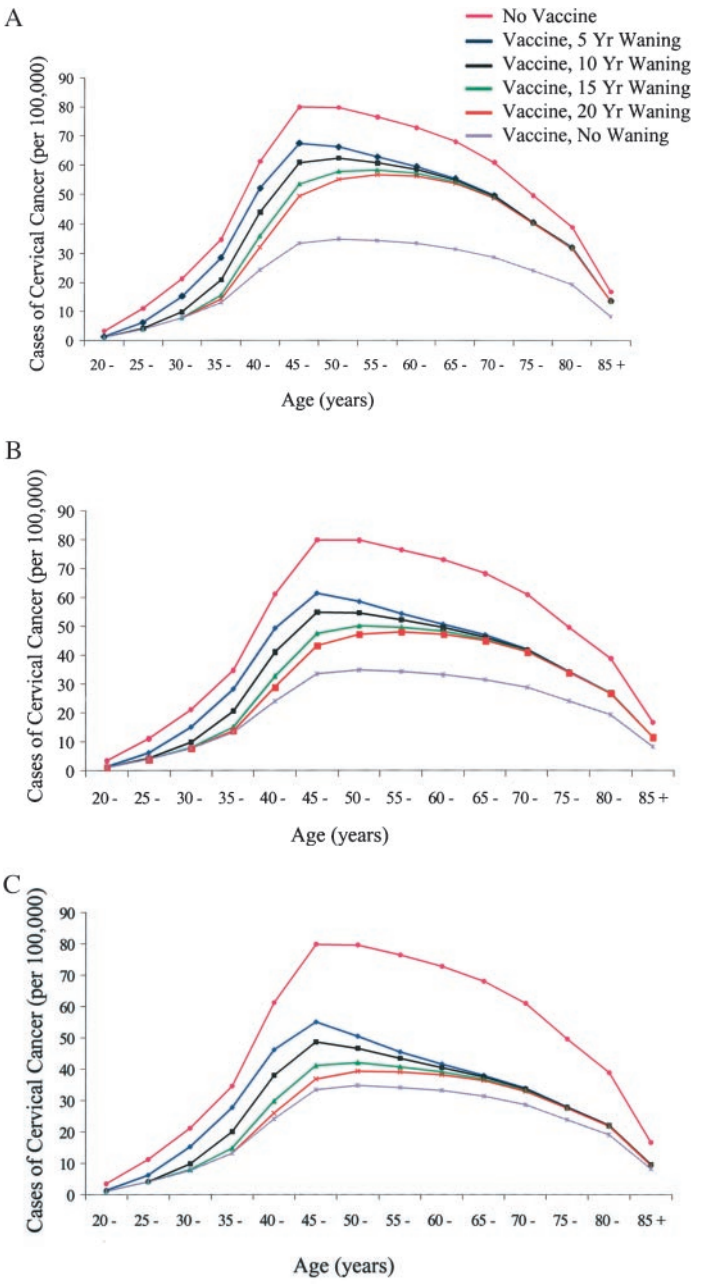

Fig. 3. Sensitivity analysis of vaccination waning. The impact of waning (i.e., vaccine efficacy wanes after 5, 10, 15, or 20 years) on the effectiveness of a vaccine that prevents 90% of persistent human papillomavirus (HPV) 16/18 infections is shown. As the proportion of persistent HPV infection attributable to new (versus latent or previously acquired) infections is varied from 75% (**A**), to 50% (**B**), and to 25% (**C**), the relative effect of waning is markedly attenuated.

Discussion

This analysis was motivated by the prospect that an HPV vaccine may be commercially available in the next several years

(10,11,98–104). Our results indicate that the addition of an HPV 16/18 vaccine to current cervical cancer screening in the United States has the potential to be a cost-effective use of health care resources. Our model, like other reports *(105–107),* predicts that a type-specific HPV vaccine will reduce, but not eliminate, the risk of cervical cancer. Moreover, because data on the long-term effectiveness of vaccination, duration of immunity, and impact of type-specific vaccination on other HPV types will not be available for several decades, it is unlikely that serious consideration would be given to replacing organized screening programs with vaccination. However, it is plausible that a comprehensive cervical cancer prevention program that includes both a primary prevention (vaccination) and secondary prevention (screening) component could provide distinct advantages over the status quo. For example, it has been well documented that screening is not equally accessible to all groups of women and that most cases of invasive cervical cancer occur in women who have not been screened at regular intervals *(108).* In addition, previous cost-effectiveness analyses have consistently reported that annual cervical cytologic screening, compared with screening every 2 or 3 years, results in very small gains in life expectancy (e.g., hours) yet is accompanied by enormous incremental costs.

Therefore, in our first analysis, we sought to estimate the costs and clinical benefits associated with the introduction of a type-specific HPV vaccine in the setting of current cervical cancer screening as practiced in the United States. If we conservatively assume that vaccination would not alter screening behavior, an HPV16/18 vaccine ranging in efficacy from 70% to 100% would reduce the lifetime risk of cancer by 46%–66% compared with current screening practices. Provided the vaccine prevents at least 70% of persistent HPV16/18 infections, the incremental cost-effectiveness ratio of an HPV16/18 vaccine was well below $50 000 compared with that for current screening practices.

Recommendations for cervical cancer screening are likely to be modified in the next several years as enhanced cytologic methods evolve, new technology is developed, and the ability to test for high-risk types of HPV DNA is refined *(109–111).* In this context, it is important to define the conditions under which combined vaccination and screening efforts may be cost-effective. In our second analysis, we thus explored the costs and clinical benefits associated with a variety of hypothetical cervical cancer control policies consisting of primary prevention with vaccination and/or secondary prevention with screening. Our general results indicated that strategies that combine vaccination with cytologic screening were more cost-effective than strategies relying only on cytologic screening. If one imposed a minimum threshold of clinical effectiveness (e.g., the reduction in cervical cancer risk over a woman's lifetime must be at least equivalent to or greater than that in our current screening program), then the best balance between costs and benefits appeared to be triennial screening starting at age 25 years with vaccination at age 12 years. These general results supporting the cost-effectiveness of a combined vaccination and screening program, provided that screening may be initiated at a later age and conducted less frequently, are similar to those reported in a recent analysis that used an independent model *(107).*

Results were sensitive to alternative assumptions about the underlying patterns of cervical cancer screening, the duration of vaccine efficacy, and the natural history of HPV in women older than 30 years. The relative value of vaccination-induced protection against cervical cancer (compared with screening-induced protection against cervical cancer) was greater in the presence of more aggressive strategies for low-grade lesions that are likely to regress without intervention when a substantial proportion of high-risk women were not screened and when screening practices were inefficient (e.g., annual cytologic screening). There is a greater reduction in the projected age-specific prevalence of HSIL than of LSIL because a greater proportion of overall LSIL is associated with non-16/18 HPV types compared with HSIL. The implication of what will potentially be very minor reductions in LSIL within a screened community is that the economic benefits of potentially averted procedures will only be realized in the context of altered practice patterns that permit LSIL to be less aggressively managed and screening to be conducted less frequently.

Assumptions about the relative proportion of persistent HPV infections in women older than 30 years attributable to new exposure and acquisition of HPV, as opposed to reactivation of latent or previously acquired HPV, also have a major impact on the projected clinical effects of waning of vaccine efficacy. At one extreme, if the majority of cervical cancer in 50-year-old women is a result of new HPV infections that are acquired after age 25 or 30 years, administering a vaccine to a 12-year-old girl that wanes after 10 or 15 years will have a dramatically reduced impact on the prevention of cervical cancer. At the other extreme, if the majority of cervical cancers are caused by reactivation of latent or previously acquired HPV, then an HPV16/18 vaccine administered to a 12-year-old girl that is effective during the 10–15 years that she is at the highest risk for incident HPV infections may still have a substantial effect on the risk of cervical cancer. We felt it prudent to present the projected cost-effectiveness results for both of these extreme assumptions. The need for better data to inform these assumptions is highlighted by the dramatic differences in the relative effects of waning as the proportion of persistent HPV infection attributable to new (versus latent or previously acquired) infections is varied. Despite the uncertainty, we did find that, provided the proportion of persistent HPV infection attributable to new (versus latent) infections was equal to or less than 75%, a policy that combines vaccination and screening was still attractive.

There are a number of limitations to this exploratory analysis. First, if the proportion of cervical cancers caused by HPV16/18 is higher than we assumed in our base case, we may have underestimated the benefits of vaccination. Second, we did not explicitly model the natural history of multiple HPV infections. Therefore, vaccination against HPV16/18 in our model appeared to reduce the overall total number of HPV infections, although the lifetime risk of non-16/18 HPV infections appeared to increase marginally because women effectively vaccinated against HPV16/18 were then at risk for acquiring other HPV types. It will be important to better elucidate the natural history of multiple infections, the effect on the natural history of other HPV types when vaccine targets are effectively eliminated, and whether HPV DNA assays used for cervical cancer screening will need to be modified as a result of a vaccine program that alters the type-specific HPV prevalence over time. Third, we did not consider any potential cross-protection from other HPV types; if this occurs, we may have underestimated the benefits of vaccination. Fourth, we have implicitly assumed that the majority of persistent HPV infections in older women represent reac-

tivation of latent or previously acquired HPV. A better understanding of what proportion of persistent HPV infections that eventually lead to cancer are a result of reactivation of latent or previously acquired HPV as opposed to new incident infections acquired later in life will substantially affect the clinical and economic consequences of waning immunity in vaccinated women. Fifth, our model cannot be used to assess the impact of HPV vaccination of both men and women on the dynamics of viral transmission and will therefore underestimate the impact of factors such as herd immunity *(105,112,113).* Sixth, long-term vaccine efficacy is uncertain, and there are heterogeneities in vaccine response that we did not include in the absence of empiric data *(114).* Clinical trials may provide information on some of these parameters, facilitating cost-effectiveness analyses in the future. Finally, data are needed about patient and parent preferences, likelihood of vaccine acceptability, and behavioral response (e.g., screening behavior) to an intervention that is only partially protective against cervical cancer; we were unable to assess these issues in this analysis *(115).*

Although a decision analytic approach using mathematical simulation modeling cannot replace clinical trial–based evaluation of vaccine efficacy, model-based analyses can provide qualitative and quantitative insight into the relative importance of different parameters, can help to prioritize and to guide the design of future clinical studies, and can provide information on the potential cost-effectiveness of different policy alternatives. Our analysis, intended to be an exploration of the potential cost-effectiveness of an HPV16/18 vaccine, suggests that a prophylactic vaccine that prevents at least 70% of persistent HPV16/18 infections should substantially reduce HPV16/18-associated SIL and cervical cancer, even in a setting of established cytologic screening. A combined program of vaccination and screening that permits a later age of screening initiation and a less frequent screening interval will likely be a cost-effective use of limited health care resources.

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NOTES

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